

SCRIMM 23 – A Phase II Study for the Evaluation of Bendamustine, Bortezomib and Dexamethasone (BBD) in the First-Line Treatment of Patients with Multiple Myeloma Who Are Not Candidates for High Dose Chemotherapy

Fast Facts

Bendamustine and Bortezomib provided.

CTC v4; RECIST n/a; AJCC Staging book n/a

Inclusion Criteria

1. Patients must meet the Durie and Salmon criteria for initial diagnosis of multiple myeloma (Appendix A).
2. Previously histologically confirmed, multiple myeloma with indication for therapy including one of the following:
 - a. Hemoglobin <10 g/dl or 2 g/dl below normal
 - b. Serum calcium > 11.5 mg/dl
 - c. Creatinine >2 mg/dl
 - d. Lytic bone lesions or severe osteopenia
 - e. Extramedullary plasmacytomas
3. Patients should not be considered candidates for high dose therapy/autologous stem cell transplantation due to coexistent medical conditions, advanced age, poor performance status, refusal of high dose chemotherapy or other reasons as judged by the patient and/or physician.
4. ECOG Performance Status 0-2. (Appendix B).
5. WBC \geq 3000/ μ L; ANC \geq 1000/ μ L; platelets \geq 50,000/ μ L (patients with platelets \geq 30,000/ μ L are eligible if thrombocytopenia is felt to be due to extensive bone marrow involvement with myeloma).
6. Patients must have measurable disease requiring systemic therapy. At least one of the three following measurements defines measurable disease:
 - a. Serum M-protein \geq 1 g/dl (\geq 10 g/l)
 - b. Urine M-protein \geq 200 mg/24 hrs
 - c. Serum free light chain assay: involved free light chain level \geq 10 mg/dl (\geq 100 mg/l) provided the serum free light chain ratio is abnormal
7. Patients must be accessible for treatment and follow-up procedures.
8. Male or female patients 18 years of age or older.
9. Women of childbearing potential (WOCBP) must have a negative serum pregnancy or urine pregnancy test with a sensitivity of at least 50 mIU/mL \leq 7 days prior to start of treatment. Female patient is either postmenopausal for at least 1 year before the screening visit, is surgically sterilized or if they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing the informed consent form through 30 days after the last dose of study drug(s), or agree to completely abstain from heterosexual intercourse.
10. Male patients, even if surgically sterilized, (i.e., status post vasectomy) must agree to 1 of the following: practice effective barrier contraception during the entire study treatment period and for 3 months after the end of treatment, or completely abstain from heterosexual intercourse.
11. Patients must be able to understand the nature of this study and give voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time by the without prejudice to future medical care.

Exclusion Criteria

1. Previous treatment with any systemic therapy for multiple myeloma. Prior treatment with corticosteroids (not exceeding the total equivalent of 160 mg of dexamethasone over a 2-week period) or radiation therapy will not disqualify the patient.
2. Patients requiring concurrent localized radiotherapy are not eligible. Two weeks must have elapsed since the date of the last radiotherapy treatment.
3. Patients with \geq NCI CTCAE v4.0 grade 2 peripheral neuropathy \leq 14 days prior to study enrollment.
4. Treatment with investigational agent(s) outside of this trial, or \leq 14 days prior to the start of this trial.
5. Active infection requiring or infection requiring intravenous antibiotic treatment at the time of accrual.
6. Known to be HIV positive (HIV test is not required for participation in the trial).
7. Patients with New York Heart Association (NYHA) class III/IV heart failure or any of the following:
 - History of uncontrolled or symptomatic angina.

- History of arrhythmias requiring medications. or clinically significant, with the exception of asymptomatic atrial fibrillation requiring anticoagulation
 - Electrocardiographic evidence of acute ischemia or active conduction system abnormalities
 - Myocardial infarction < 6 months from study entry
 - Uncontrolled or symptomatic congestive heart failure
 - Ejection fraction below the institutional normal limit
 - Any other cardiac condition that, in the opinion of the treatment physician, would make this protocol unreasonably hazardous for the patient
 - Uncontrolled hypertension (systolic blood pressure [BP]>180 or diastolic BP >100mm Hg) or uncontrolled cardiac arrhythmias.
 - Prior to study entry, any ECG abnormality at Screening must be documented by the investigator as not medically relevant.
8. Other serious medical conditions or psychiatric illness that would potentially interfere with patient participation in this trial.
 9. A second malignancy, other than basal cell carcinoma of the skin or in situ carcinoma of the cervix, unless the tumor was treated with curative intent at least 2 years previously or low-risk prostate cancer after curative therapy.
 10. Known hypersensitivity to bortezomib, boron, or mannitol.
 11. Female patient is pregnant or lactating, or if applicable, had a positive serum pregnancy test during the screening period, or a positive urine pregnancy test on Day 1 before the first dose of study drug. Confirmation that WOCBP are not pregnant must be established by a negative β -human chorionic gonadotropin (β -hCG) pregnancy test ≤ 7 days prior to start of treatment. Pregnancy testing is not required for postmenopausal or surgically sterilized women.

Pre-Study Parameters

1. History and physical including weight, vital signs, neurological exam, BSA, ECOG performance status and concomitant medication review
2. Laboratory tests including CBC with 3 part differential and platelets; CMP including fasting glucose, LDH, uric acid, phosphate; PT/PTT/INR, serum β -HCG or urine pregnancy test for women of child bearing potential
3. Chest x-ray
4. Disease assessment: bone marrow aspiration/biopsy; skeletal survey; serum free light chain; serum immunoglobulin G, A, M; serum β -2 microglobulin; SPEP and immunofixation; UPEP and immunofixation

Treatment

Drug	Dose	Route	Days	Frequency
Bendamustine	80 mg/m ²	IV	1, 2	q 28 days
Bortezomib	1.3 mg/m ²	IV	1, 8, 15	q 28 days
Dexamethasone	20 mg	PO	1, 2, 8, 9, 15, 16	q 28 days

Reevaluate every 4 weeks.

Continue until progression, intolerable toxicity, total of eight cycles or CR + 2 cycles. Patients who achieve a response during treatment may continue on with maintenance therapy.

Maintenance

Drug	Dose	Route	Days	Frequency
Bortezomib	1.3 mg/m ²	IV	1, 15	q 28 days
Dexamethasone	20 mg	PO	1, 15	q 28 days

Patients continue with maintenance therapy until progressive disease or unacceptable toxicity.