**BOSTON MEDICAL CENTER**

# Phase III trial of high-dose melphalan and stem cell transplantation vs high-dose melphalan and Bortezomib and stem cell transplantation in patients with AL amyloidosis




PRINCIPAL INVESTIGATOR:

Vaishali Sanchorawala, M.D.
Section of Hematology and Oncology
Boston Medical Center
One Boston Medical Center Place / FGH-1
Boston, MA 02118
617-638-7017
Vaishali.sanchorawala@bmc.org

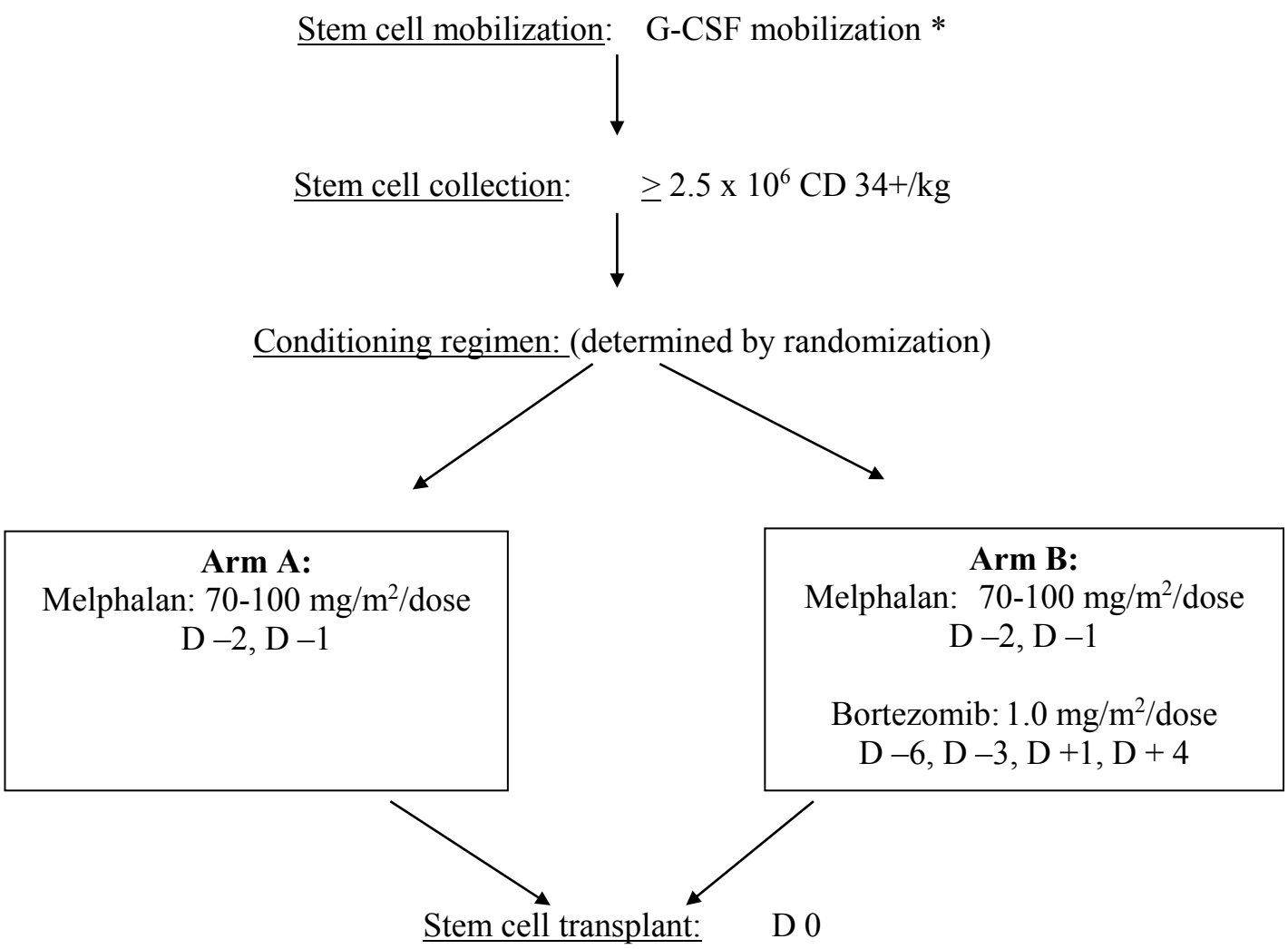
CO-INVESTIGATORS:

Karen Quillen, MD
Director of Blood Bank
Boston Medical Center
One Boston Medical Center Place / Blood Bank
Boston, MA 02118
617-638-7828
Karen.Quillen@bmc.org

Mark Sloan, MD
Section of Hematology and Oncology
Boston Medical Center
One Boston Medical Center Place / FGH-1
Boston, MA 02118
617-638-2367
Mark.Sloan@bmc.org

Cindy Varga, MD
Section of Hematology and Oncology
Boston Medical Center
One Boston Medical Center Place / FGH-1
Boston, MA 02118
617-638- 6428
Cindy.Varga@bmc.org

**SCHEMA**




* Plerixafor allowed per institutional guidelines.

## 1.0 OBJECTIVES

### 1.1 Primary Objective

1.1.1 To determine hematologic response of high-dose melphalan and stem cell transplantation with the addition of bortezomib to the conditioning regimen compared to standard high-dose melphalan and stem cell transplantation

### 1.2 Secondary Objectives

1.2.1 To determine the toxicities, overall survival, and organ response of high-dose melphalan and stem cell transplantation with the addition of bortezomib to the conditioning regimen compared to standard high-dose melphalan and stem cell transplantation

1.2.2 To prospectively examine anxiety, depression, and their potential mediators and moderators over the course of high-dose melphalan and stem cell transplantation with and without bortezomib

## 2.0 BACKGROUND

AL amyloidosis is a rare complex multisystem disease related to plasma cell dyscrasia. In this disease, clonal plasma cells produce light chains which get mis-folded, and get deposited as amyloid fibrils in various organs and tissues leading to organ dysfunction and organ failure and death[1]. Unfortunately, due to its rarity and complexity, there is no standard of care for treatment of this rare disease.

High-dose melphalan and stem cell transplantation (HDM/SCT) was initially studied in the late 1990s after its success in myeloma at Boston Medical Center and has been an effective treatment for selected patients with AL amyloidosis. It has been shown in several reports from our center as well as other centers that HDM/SCT can improve survival and lead to hematologic and clinical remissions[2].

Recently, Boston Medical Center reported on long-term outcome of HDM/SCT in patients with AL amyloidosis and the 19-year survival in this report was 25%. Hematologic complete response (CR) as defined by the international consensus criteria occurred in 34% at 6 months; by intention-to-treat analysis. Our experience treating more than 600 patients suggests that clinical outcomes following HDM/SCT correlate with the attainment of a CR. This report also demonstrates that the median survival of patients who achieve a CR is > 12.8 years compared to 6 years for those who do not ($p<0.001$) and that clinical improvement in affected organ systems occurs in 2/3 of patients achieving a hematologic CR compared to only 1/3 of those who do not ($p<0.001$). There are similar differences with respect to improvements in performance status and quality of life[3,4].

Because hematologic CR is such a critical determinant of treatment outcome following HDM/SCT, a pilot study was performed to evaluate whether incorporation of bortezomib in the conditioning regimen would increase the hematologic CR rates. A synergistic effect between bortezomib and melphalan has been demonstrated in vitro and in vivo. Furthermore, the toxicity of these two drugs is different. Thus, the combination of bortezomib and HDM was a logical approach to study. Ten patients with AL amyloidosis were treated on this study and hematologic CR was achieved by 66% of patients; by intention-to-treat analysis. This pilot study demonstrated that the addition of Bortezomib to conditioning regimen for

HDM/SCT produced a high hematologic responses and organ responses without additional toxicities[5].

Therefore, we propose a randomized phase III clinical trial of HDM/SCT vs addition of bortezomib to HDM regimen prior to SCT for patients with AL amyloidosis who are eligible to receive stem cell transplantation. This would be a practice changing if phase III trial proves HDM-Bor conditioning to be superior to HDM alone conditioning prior to SCT.

We recently completed and closed X05292 clinical trial of 2 cycles of induction with bortezomib and dexamethasone followed by HDM-Bortezomib/SCT. Thirty five patients with new diagnosis of AL amyloidosis were enrolled in this clinical trial from Jan 2010 to Aug 2013. The preliminary data suggests high hematologic responses with high CR rates of 67% in this clinical trial. However, 2 cycles of induction with twice a week of bortezomib and dexamethasone led to dose modifications and without additional benefit in improving hematologic responses than pilot study of HDM-Bor/SCT. Therefore, the current trial design would exclude the 2 cycles of induction treatment with Bortezomib and dexamethasone.

Currently, there is a phase III randomized clinical trial of MLN 9708 vs physician choice treatment for relapsed patients with AL amyloidosis is ongoing, C16011. However, this proposed trial would not compete with enrollment on C16011. The eligibility and inclusion criteria to participate in both these trials would be different and the subjects relapsing or not responding on this proposed clinical trial should be able to enroll on C16011 trial.

While there have been a number of studies prospectively investigating the course of anxiety and depression in patients with hematological malignancies undergoing SCT [6,7], there are no studies of these kind with AL amyloidosis patients undergoing HDM/SCT. Investigating the course of anxiety and depression may be important as studies with heterogeneous cancer and SCT regimens have found that elevated depressive symptoms after transplant may be associated with decreased survival[8,9] and that psychiatric morbidity is associated with longer hospitalization duration for SCT. Indeed, only limited research exists for anxiety and depression in AL amyloidosis[10-12].

## 3.0 DRUG INFORMATION

### 3.1 Bortezomib (Velcade™)

#### 3.1.1 Pharmacology

Mechanism of Action: Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitinproteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death.

#### 3.1.2 Adverse Effects

| Adverse Events with Possible Relationship to PS-341 (Bortezomib, Velcade) (CTCAE 4.0 Term) [n= 2084] | | |
|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | |
| Anemia | | |
| CARDIAC DISORDERS | | |
| | | Heart failure |
| GASTROINTESTINAL DISORDERS | | |
| | Abdominal pain | |
| Constipation | | |
| Diarrhea | | |
| | Dyspepsia | |
| | Gastrointestinal hemorrhage[2] | |
| | | Gastrointestinal perforation[3] |
| | Ileus | |
| Nausea | | |
| Vomiting | | |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | |
| | Chills | |
| | Edema limbs | |
| Fatigue | | |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | |
| Fever | | |
| INFECTIONS AND INFESTATIONS | | |
| Infection[4] | | |
| INVESTIGATIONS | | |
| | Neutrophil count decreased | |
| Platelet count decreased | | |
| | Weight loss | |
| METABOLISM AND NUTRITION DISORDERS | | |
| Anorexia | | |
| | Dehydration | |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | |
| | Arthralgia | |
| | Back pain | |
| | Bone pain | |
| | Musculoskeletal and connective tissue disorder - Other (muscle spasms) | |
| | Myalgia | |
| | Pain in extremity | |
| NERVOUS SYSTEM DISORDERS | | |
| | Dizziness | |
| | Headache | |
| | | Leukoencephalopathy |
| | Neuralgia | |
| | Paresthesia | |

| | | |
|---|---|---|
| Peripheral motor neuropathy | | |
| Peripheral sensory neuropathy | | |
| | | Reversible posterior leukoencephalopathy syndrome |
| PSYCHIATRIC DISORDERS | | |
| | Anxiety | |
| | Insomnia | |
| RENAL AND URINARY DISORDERS | | |
| | | Acute kidney injury |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | |
| | | Adult respiratory distress syndrome |
| | Cough | |
| | Dyspnea | |
| | Pharyngeal mucositis | |
| | | Pulmonary hypertension |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | |
| | Rash maculo-papular | |
| VASCULAR DISORDERS | | |
| | Hypotension | |

1 This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision.

2 Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

3 Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

4 Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

**Also reported on PS-341 (bortezomib, Velcade) trials but with the relationship to PS-341 (bortezomib, Velcade) still undetermined:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Blood and lymphatic system disorders - Other (hematocrit low); Blood and lymphatic system disorders - Other (lymphadenopathy); Disseminated intravascular coagulation; Febrile neutropenia; Hemolytic uremic syndrome; Leukocytosis

**CARDIAC DISORDERS** - Acute coronary syndrome; Asystole; Atrial fibrillation; Atrial flutter; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (cardiac amyloidosis); Cardiac disorders - Other (cardiomegaly); Chest pain - cardiac; Left ventricular systolic dysfunction; Mobitz type I; Myocardial infarction; Palpitations; Pericardial effusion; Pericardial tamponade; Pericarditis; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular arrhythmia; Ventricular fibrillation; Ventricular tachycardia

**EAR AND LABYRINTH DISORDERS** - External ear inflammation; Hearing impaired; Tinnitus

**ENDOCRINE DISORDERS** – Hypothyroidism

**EYE DISORDERS** - Blurred vision; Conjunctivitis; Dry eye; Extraocular muscle paresis; Eye disorders - Other (chalazion); Eye disorders – Other (choroidal effusion); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (retinal hemorrhage with bilateral vision impairment); Keratitis; Watering eyes
**GASTROINTESTINAL DISORDERS** - Abdominal distension; Ascites; Bloating; Colitis; Dry mouth; Duodenal ulcer; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (colonic wall thickening); Gastrointestinal disorders - Other (early satiety); Gastrointestinal disorders - Other (eructation); Gastrointestinal disorders - Other (ileitis); Gastrointestinal disorders - Other (ischemic bowel); Gastrointestinal disorders - Other (mouth/tongue ulceration); Gastrointestinal disorders - Other (retching); Gastrointestinal pain; Gingival pain; Hemorrhoids; Mucositis oral; Oral pain; Pancreatitis; Small intestinal obstruction; Typhlitis
**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Edema face; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (catheter related
complication);General disorders and administration site conditions - Other (hepato-renal syndrome); Hypothermia; Injection site reaction; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS
**HEPATOBILIARY DISORDERS** - Hepatic failure; Hepatobiliary disorders - Other (hepatitis); Hepatobiliary disorders - Other (portal vein thrombosis); Hepatobiliary disorders - Other (VOD)
**IMMUNE SYSTEM DISORDERS** - Allergic reaction; Anaphylaxis; Cytokine release syndrome
**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Bruising; Fall; Fracture; Vascular access complication
**INVESTIGATIONS** - Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Creatinine increased; Ejection fraction decreased; GGT increased; INR increased; Investigations – Other (albumin); Investigations - Other (BUN); Investigations - Other (low chloride); Investigations - Other (pancytopenia); Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain; White blood cell decreased
**METABOLISM AND NUTRITION DISORDERS** - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia); Tumor lysis syndrome
**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Arthritis; Avascular necrosis; Buttock pain; Chest wall pain; Generalized muscle weakness; Joint range of motion decreased; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder – Other (cramping); Osteonecrosis of jaw
**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Tumor pain
**NERVOUS SYSTEM DISORDERS** - Acoustic nerve disorder NOS; Akathisia; Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Edema cerebral;
Encephalopathy; Facial muscle weakness; Facial nerve disorder; Hypersomnia; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Memory impairment; Nervous system disorders – Other (autonomic neuropathy); Nervous system disorders - Other (Bell's palsy); Nervous system disorders - Other (cranial palsy); Nervous system disorders - Other (dysautonomia); Nervous system disorders - Other (L sided facial droop); Nervous system disorders - Other (paralysis); Nervous system disorders - Other (polyneuropathy); Nervous system disorders - Other (spinal cord compression); Nervous system disorders - Other (tongue paralysis); Presyncope; Seizure; Somnolence; Stroke; Syncope; Tremor; Vasovagal reaction
**PSYCHIATRIC DISORDERS** - Agitation; Confusion; Delirium; Depression; Personality change; Psychosis

**RENAL AND URINARY DISORDERS** - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Hematuria; Proteinuria; Renal and urinary disorders - Other (bilateral hydronephrosis); Renal and urinary disorders - Other (calculus renal); Renal and urinary disorders - Other (glomerular nephritis proliferative); Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain
**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Allergic rhinitis; Aspiration; Atelectasis; Bronchopulmonary hemorrhage; Bronchospasm; Epistaxis; Hiccups; Hypoxia; Laryngeal edema; Mediastinal hemorrhage; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumonitis; Postnasal drip; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (obstructive airways disease); Respiratory, thoracic and mediastinal disorders - Other (pleurisy); Respiratory, thoracic and mediastinal disorders - Other (respiratory distress); Respiratory, thoracic and mediastinal disorders - Other (tachypnea); Tracheal mucositis; Tracheal stenosis; Voice alteration
**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Alopecia; Bullous dermatitis; Dry skin; Erythema multiforme; Erythroderma; Hyperhidrosis; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (angioedema); Skin and subcutaneous tissue disorders – Other (leukoclastic vasculitis); Skin and subcutaneous tissue disorders – Other (Skin lesion NOS); Urticaria
**VASCULAR DISORDERS** - Capillary leak syndrome; Flushing; Hematoma; Hypertension; Thromboembolic event; Vascular disorders - Other (trach site); Vasculitis
**Note**: PS-341 (bortezomib; Velcade) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Pregnancy and Lactation: Pregnancy Category D. It is not knownwhether bortezomib is excreted in human milk.

Drug Interactions: Closely monitor patients receiving bortezomib in combination with strong CYP3A4 inhibitors. Concomitant use of strong CYP3A4 inducers is not recommended. Due to potential drug interactions, a complete patient medication list should be screened prior to initiation of bortezomib.

### 3.1.3 Storage & Stability

Please refer to the current FDA-approved package insert for storage, stability and special handling information.

### 3.1.4 Supply

VELCADE (bortezomib) for Injection is commercially available. Each single dose vial contains 3.5 mg of bortezomib as a sterile lyophilized powder. Inactive ingredient: 35 mg mannitol, USP.

## 4.0 ELIGIBILITY CRITERIA

1. Histological diagnosis of primary systemic (AL) amyloidosis based on:
    a. Deposition of amyloid material by Congo red stain showing characteristic apple green birefringence, **AND**…
    b. evidence of a clonal plasma cell dyscrasia with monoclonal protein in the serum or urine by immunofioxation electrophoresis studies **AND/OR** abnormal serum free light chain assay **AND/OR** clonal plasma cells in the bone marrow exam demonstrated by immunohistochemistry, flow cytometry or in situ hybridization **AND**…
    c. evidence of organ involvement other than carpal tunnel syndrome. Patients with senile, secondary, localized, dialysis-related or familial amyloidosis are not

eligible. Confirmation of tissue diagnosis at all sites of organ dysfunction is encouraged, but not required.

2. Patients must be $\geq$ 18 years of age.

3. Patients must have a performance status of 0-2 by ECOG criteria

4. Patients must have LVEF $\geq$ 45% by ECHO within 60 days of enrollment

5. Patients with recent (< 6 months) myocardial infarction, congestive heart failure, NYHA class III/IV or arrhythmia which are refractory to medical therapy are ineligible.

6. Prior chemotherapy with alkylating agent allowed only if no evidence of Myelodysplastic Dysplastic Syndrome (MDS) morphologically or cytogenetically. Total cumulative dose of oral melphalan must be < 300 mg. Patients should not have received any cytotoxic therapy < 4 weeks prior to registration and should have fully recovered from the effects of such therapy.

7. Patients must not have overt multiple myeloma (>30% bone marrow plasmacytosis and, extensive (>2) lytic lesions and hypercalcemia).

8. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.

9. Patients must not be HIV positive.

10. Pulmonary Function Tests must show DLCO $\geq$ 50%.

11. Pregnant or nursing women may not participate. Women and men of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.

12. All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

13. Patients must not have known hypersensitivity to bortezomib.

## 5.0 **TREATMENT PLAN**

5.1.1 Stem cell mobilization: G-CSF alone mobilization

Stem cell collection > 2.5 x $10^6$ CD 34+/kg

Conditioning regimen:

**Randomization**:

**Arm A**
Melphalan 70-100 mg/$m^2$/dose D –2, D –1

**Arm B**
Melphalan 70-100 mg/$m^2$/dose D –2, D –1

Bortezomib 1.0 mg/$m^2$/dose D –6, D –3, D +1, D + 4

Stem cell transplant D 0

5.5 Criteria for Removal from Protocol Treatment:

5.5.1 Discontinuation of transplant procedure for any reason

5.5.2 Inadequate stem cell collection < 2.5

5.5.3 Complications of stem cell mobilization regimen which are not reversible with medical management

5.5.4 Unacceptable toxicity.

5.5.5 The patient may withdraw from the study at any time for any reason.

5.5.6 Development of overt multiple myeloma.

5.5.7 Completion of all protocol therapy.

5.5.8 Determination by the treating physician that further protocol treatment will not be in the best interest of the patient.

5.6 All patients will be followed by standard transplant protocol at 6 months, 1 year, then annually until death.

## 6.0 **DOSAGE MODIFICATIONS**

N/A

## 7.0 STUDY CALENDAR

The following testing will be performed per institutional standard for transplant patients.

| REQUIRED STUDIES | PRE STUDY * | Transplant *f* | F/U # |
|---|---|---|---|
| **PHYSICAL** | | | |
| History & Physical Exam | X | | X |
| Weight & Performance Status | X | | X |
| Toxicity Notation | | | X |
| | | | |
| **LABORATORY-Serum** | | | |
| CBC with Differential | X | | X |
| BUN / Serum Creatinine / Glucose | X | | X |
| Bili / Alb / Alp / SGOT / SGPT / Amy / TP / LD | X | | X |
| AST/ALT/COR/CRP | X | | X |
| Na / K / Cl / CO2 / chol / CK / Ca | X | | X |
| IRN / Mg / P / Trig / Uric/ TSH | X | | X |
| β-2 Microglobulin / C-reactive protein | X | | X |
| SPEP / GAM / KAPLAM / IFEP | X | | X |
| VITB12 / FOL / ESR / RETICB | X | | X |
| PTB/ PTT/ DIMER/ INR/ Factor X | X | | X |
| FLC | X | | X |
| BNP/Tropinin I | X | | X |
| Hep B Surface AG, Hep B Core AB, Hep C AB | X | | |
| AHIV - 1+2 | X | | |
| | | | |
| **LABORATORY-Urine** | | | |
| UA | X | | X |
| UTP24 / UCR24 / UKAP / ULAM | X | | X |
| UPEP / UIFEP / TV | X | | X |
| | | | |
| PATHOLOGY | | | |
| BM aspiration / biopsy | X | | X≠ |
| Fat aspirate | X | | |
| | | | |
| **X-RAYS AND SCANS** | | | |
| EKG / CXR | X | | X |
| Echocardiogram | X | | X |
| PFT's | X | | |
| CPST ♥ | X | | |
| | | | |
| **OPTIONAL SUB-STUDY** | | | |
| Questionnaires▲ | X▲ | X▲ | X▲ |
| | | | |
| **TREATMENT** | | | |
| High-Dose Melphalan with AuSCT +/- Bortezomib | | X | |

*f* Testing during treatment should be done per institutional standard and as clinically indicated, including toxicity evaluations. The following routine labs should be obtained until neutrophil and platelet engraftment (~14 days) **Daily**: electrolytes, BUN, creatinine, glucose, CBCd; **Mon & Thurs**: Bili, ALP, GGT, ALT, ALB, Ca, Mg, Phos, INR/PTT, clot to blood bank

\# Follow-up evaluations for disease response will take place at 6 months, one year and annually thereafter.

* Tests are recommended for good medical practice and only those listed in the eligibility criteria are required by the protocol.

♥ If clinically indicated at physician's discretion

≠ If needed to evaluate response.

▲ If patient consents to the optional sub-study, questionnaires will be completed at pre-study (any time after consent, but prior to mobilization), D-1 (any time between D-2 and D+4), discharge (± 7d), and at 6m follow-up (± 1m). See Section 8.0 for questionnaire details.

## 8.0 **OPTIONAL QUESTIONNAIRES**

If the patient consents to the optional sub-study, the following questionnaires will be completed at all four time points detailed in Section 7.0:

- Sociodemographic Questionnaire
  - Patients will be asked to self-report educational attainment and estimated income.
- State-Trait Anxiety Inventory (STAI-Y)[13]
  - A 20 item, 4-point measure of state anxiety. It has been shown to reliably assess aspects of anxiety symptoms and has been used to diagnose clinical anxiety.
- Center for Epidemiologic Studies Depression Scale Revised (CES-D) [14]
  - A 20 item, 4-point measure of depressive symptoms. It has been shown to reliably assess aspects of depressive symptoms.
- Satisfaction with Life Scale [15]
  - A 5 item, 7-point self-report rating scale designed to assess life satisfaction as a cognitive domain of subjective wellbeing.
- Coping Strategy Indicator (CSI)[16]
  - A 33 item, 3-point self-report rating scale designed to assess 3 basic modes of coping. The original version requires patients to identify a stressful event that has occurred within the last 6 months and then answer the items based on how they coped with their event. In this study, "coping with AL amyloidosis and your stem cell transplantation" will be specified as the event.
- Distress Intolerance Index (DII) [17]
  - A 10 item, 5-point self-report scale derived from the Anxiety Sensitivity Index, Frustration Discomfort Scale and the Distress Tolerance Scale designed to assess the ability withstand negative somatic and emotional states.
- Medical Outcomes Study (MOS) 36-item Short Form General Health Survey (SF-36)[18]
  - A 36 item questionnaire that assess 8 scales of health status that can be combined into composite scores physical and mental health. SF-36 has good reliability and validity in a variety of diseases, and has been suggested to be the most appropriate assessment for quality of life for AL amyloidosis[4].

These questionnaires can be completed with the assistance of the study team and interpreter services if necessary. Any assistance should be noted.

## 9.0 **CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS**

### 9.1 Primary

#### 9.1.1 Hematologic Response:

**CR** Negative serum and urine immunofixation electrophoresis, normal serum free light chain ratio

**VGPR** dFLC <40 mg/L, dFLC = difference in involved and uninvolved serum free light-chain levels

**PR** dFLC reduction >50%, dFLC = difference in involved and uninvolved serum free light-chain levels

**SD** Meets neither criteria for CR, VGPR, PR or PD

**PD** From CR, an increase in serum M-protein to > 0.5 g/dL, an increase in the urine M-protein to > 200 mg/day, or an increase in the serum monoclonal free light chain by > 10 mg/dL (100 mg/L). From VGPR, PR or SD, an increase in the serum M-protein from the lowest level by > 50%, as long as the absolute magnitude of this increase is > 0.5 g/dL; or an increase in the urine M-protein from the lowest level by 50%, as long as the absolute magnitude of this increase is > 200 mg/day; or an increase in the serum or urine monoclonal free light chain by > 50% from the lowest level, as long as the absolute magnitude is > 10 mg/dL (100 mg/L).

9.2 Secondary

9.2.1 Organ Response:

A subject will be said to have had an organ response in an involved organ if *any* of the following criteria are met:

**Kidney:** 50% reduction in 24-hour urine protein excretion in the absence of progressive renal insufficiency (defined as a 25% increase in serum creatinine, as long as that is ≥ to an absolute increase of 0.5 mg/dL). In the case of nephrotic syndrome: a decrease in proteinuria to < 1g/24h and an improvement in one of 2 extrarenal features – normalization of serum albumin or resolution of edema and/or discontinuation of diuretics in response to improvement in edema.

**Heart**: ≥ 2 mm reduction in the interventricular septal (IVS) thickness by echocardiogram, improvement of ejection fraction by ≥ 20% (echocardiogram must be performed at the same institution), or decrease in 2 NYHA classes without increase in diuretic need (see Appendix E for class definitions).

**Liver:** ≥ 50% decrease in normalization of an initially elevated alkaline phosphatase level or reduction in the size of the liver by at least 3 cm (determined by clinical exam).

**Neuropathy:** While neurotoxicity is acceptable for determining organ involvement, it will not be adequate for assessing organ response; organ response will be indeterminable for subjects in which neurotoxicity is the only site of organ involvement.

**Gastrointestinal Tract:** While GI involvement is acceptable for determining organ involvement, it will not be adequate for assessing organ response: organ

response will be indeterminable for subjects in which GI is the only site of organ involvement.

9.2.2 Tolerability

9.2.3 Survival at 1 and 2 years

## 10.0 STATISTICAL CONSIDERATIONS

- Estimated accrual 2-3/month
- Accrual in similar clinical trial: X-05292 accrued 35 patients from Jan 2010 to Aug 2013

- Expected Hem CR with HDM/SCT: 34%, Expected Hem CR with Bor-HDM/SCT: 65%
- Design: Type I error alpha=0.05, power 80%
- Randomized phase III design

Accrual Goal

The accrual goal for this trial is 64 subjects, 32 subjects per arm. If unacceptable toxicity or treatment related mortality in the first 5 patients exceeds 25%, the study will be terminated early.

Optional Sub-Study: As this is an observational study, the sample size is limited to the enrollment on the main treatment study. Similar studies investigating psychosocial factors in SCT have had sample sizes ranging anywhere between 20 to 320 subjects[19].

## 11.0 REFERENCES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