A Phase I Study of Melphalan, Bendamustine, and Carfilzomib for Autologous Hematopoietic Stem Cell Transplantation in Patients with Multiple Myeloma

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1. Background and Rationale

Multiple myeloma is characterized by malignant plasma cell proliferation with hematologic and renal manifestations and bone destruction. With a median age at diagnosis of 70 years, the disease accounts for 1% of cancer-related death in the Western Countries. Conventional therapy is not curative but improves the quality of life. High-dose therapy does improve outcomes of the disease and is safe with less than 3% treatment-related mortality.

Single autologous blood and marrow transplantation *(ABMT) versus conventional therapy.* The Intergroupe Fancophone du Myelome (IFM) 90 study was the first to establish, in a randomized trial, the superiority of high dose therapy with ABMT in comparison to standard therapy in patients up to the age of 65 years with newly diagnosed multiple myeloma. The complete remission (CR) rate, event-free survival (EFS), and overall survival (OS) increased significantly. While 2 additional trials using no or low-dose total body irradiation (TBI) in the conditioning regimen showed survival benefit, 3 trials employing busulfan and high-dose TBI as conditioning regimen failed to do so. The IFM 95 study indeed demonstrated the negative impact of high-dose radiation therapy as part of the conditioning regimen. The randomized study showed equal response rate and duration but increased toxicity and lower OS in a high-dose melphalan and TBI arm compared to a high-dose melphalan only-arm. Taken together, the studies established high-dose melphalan conditioning followed by autologous transplantation rescue as the standard of care in multiple myeloma.

Single versus tandem ABMT*.* In a randomized trial comparing single to two ABMT, the IFM 94 study showed improved EFS and OS. However, the benefit was limited to patients who failed to achieve at least a very good partial remission (VGPR) defined by > 90% reduction in the M-spike. Out of 5 additional randomized trials comparing single to tandem ABMT, 3 studies reported survival benefit. Therefore, tandem ABMT is a reasonable option for patients who demonstrate less than VGPR after the first ABMT.

Early versus late ASCT*.* Three randomized trials compared early ASCT as opposed to ASCT as salvage therapy at relapse and showed similar OS.[16-18] In one study, OS was not different but EFS improved from 13 to 39 months along with increased average time without symptoms and reduced toxicities and discontinuation of therapy.

ASCT versus continuation of novel standard therapy*.* The role of ASCT in multiple myeloma has been questioned after the introduction of modern more effective standard therapies. In a randomized trial, the outcomes of patients receiving lenalidomide-based induction therapy followed by either ASCT or the combination of melphalan, thalidomide, and prednisone were studied. At 2 years; ASCT reduced the risk of disease progression by 50%. With a short follow-up of 2 years, OS was comparable between the two arms. The benefit of ASCT is currently being compared to continuation of bortezomib-based therapy in 2 large randomized studies.

Role of maintenance therapy*.* In a meta-analysis, a median of 1 year of thalidomide maintenance after ASCT was associated with decreased risk of progression and death at a price of substantial toxicity leading 52% of patients to discontinue treatment. Tested in two studies, a median of 2 years of lenalidomide after ASCT resulted in decreased risk of progression in both studies and the risk of death in one study. Hematologic toxicity was significant and more concerning the incidence of second primary cancer was 8%. Bortezomib was compared to thalidomide as maintenance therapy after ASCT in one study. The median duration of therapy was 2 years for bortezomib and 1 year for thalidomide. The near CR and CR rate was improved in the bortezomib arm with reduced risk of progression. It is notable that the benefit in many of these studies was limited to patients with residual disease after ASCT suggesting that the benefit was not related to maintenance but to the consolidation effect.

Role of allogeneic transplantation*.* Myelo-ablative allogeneic SCT was rapidly abandoned as treatment for multiple myeloma because of excessive toxicity and a risk of treatment-related mortality as high as 53% in one trial. Studies comparing ASCT followed by reduced-intensity allogeneic SCT have yielded conflicting results. The studies differed substantially in term of inclusion criteria and conditioning regimen. At this point, the major question about the role that reduced-intensity allogeneic SCT remains unanswered and its use must be limited to clinical trials.

ASCT with enhanced conditioning regimens*.* Bortezomib in combination with ASCT has been studied by the IFM. Bortezomib was administered on days -6, -3, +1 and +4 and was not associated with delayed recovery of blood counts.

A high VGPR was noted. Since VGPR response is a surrogate marker for improved survival, the authors concluded that the addition of bortezomib to melphalan as part of the conditioning regimen was safe and promising. Furthermore, the safety of adding bendamustine (another drug active on multiple myeloma) to melphalan was explored in a phase I study. The dose of bendamustine was escalated in 6 cohorts to 125 mg/m^2 and 100 mg/m^2 on two consecutive days without reaching maximum tolerated dose. An impressive CR of 50% in 18 evaluable patients was reported.

Carfilzomib. Carfilzomib is a new proteasome inhibitor that has shown single-agent activity in relapsed refractory multiple myeloma and gained FDA approval in that setting. It is primarily metabolized via peptidase and epoxide hydrolase and is unlikely to affect exposure of other drugs. Given at a dose of 20 mg/m^2 for the first cycle and 27 mg/m^2 thereafter, the incidence of grade 3 peripheral neuropathy was low at < 1%.[31] Other serious side effects, including cardiac arrest and failure, pulmonary hypertension, hepatic, and renal toxicity were rare. With the exception of hematologic toxicities, no other grade 3 or 4 toxicity occurred in > 3-5% of 526 patients enrolled in clinical trials. The safety profile and lack of drug interaction makes carfilzomib an attractive candidate to be added to the combination of melphalan and bendamustine. Although there is no direct comparison, carfilzomib is preferred over bortezomib as it lacks peripheral neuropathy toxicity making it more appealing in this setting.

Carfilzomib in combination with bendamustine. The combination has not been studied. A study combining bortezomib and bendamustine showed the drugs can be safely administered in full doses with no unexpected side effects[86].

In aggregate, the above data suggest that ASCT represent today's gold standard in terms of treatment of multiple myeloma. Our approach is to perform early ASCT and to reserve tandem transplant to patients who fail to achieve VGPR. In patients with residual disease after the second ASCT, we consider bortezomib maintenance. We consider early reduced-intensity allogeneic SCT in young patients with very poor cytogenetics such as del17 and t (4;14) and in patients who relapse after exhausting ASCT options. Unfortunately, most patients with multiple myeloma ultimately progress and die from their disease, underlying an abiding need to explore new therapies and combinations. In this study, we explore the safety of the addition of carfilzomib to a combination of melphalan and bendamustine as preparatory regimen before ASCT in a standard phase I design.

2. Study Design

2.1. Study overview: This is a phase I clinical trial. Patients with a diagnosis of multiple myeloma undergoing ASCT will receive a preparative regimen of melphalan, bendamustine, and carfilzomib (see Appendix A). They will receive a cycle of carfilzomib at 20 mg/m^2 on days -29, -28, -22, -21, -15, and -14. Thereafter, patients will receive a fixed dose of melphalan on day -1 and bendamustine on days -2 and -1. Patients will also receive a dose of carfilzomib on days -2, -1, and +5. The dose will be determined by in which cohort (cohort 1, cohort 2, 2B, or cohort 3B) the patient is enrolled. Cohort 1 and 2 have already been satisfied and will not enroll any further patients. Cohorts 2B and 3B will receive a dose of carfilzomib 20 mg/m^2 and 27 mg/m^2 respectively (see Appendix A). Three patients will be initially enrolled in each cohort. If dose-limiting toxicity (DLT) occurs in 1 out of 3 patients, 3 additional patients will be enrolled at that same dose level. Dose escalation will be permitted if DLT does not occur in more than 0 out of 3 or 1 out of 6 patients. No dose escalation will be permitted if DLT occurs in ≥ 33% of patients. Six additional patients will be enrolled at the highest dose level associated with < 33% incidence of DLT to further ascertain the safety at that dose level. The DLT is defined as:

1. Absence of neutrophil engraftment by day +22,
2. Absence of platelet engraftment by day +35,
3. Any grade 4 GI toxicity or any ≥ grade 3 non-hematologic toxicity, as defined by the Common Toxicity Criteria.[84], which is deemed by the DSMB as probably related to the study protocol.

2.2. Data Safety Monitoring Board: In order to ensure patient safety, a data safety monitoring board will meet to review patient data. This board will include the principal investigator, the sub-investigators, and an independent reviewer(s). The board will convene after the requirements for each cohort have been satisfied –

meaning the cohort has enrolled three patients, each patient has undergone their transplant course, and all adverse events have been collected through the day of discharge from their transplant admission. No further patient enrollment into the current cohort nor dose escalation will be permitted until the safety monitoring board has convened, reviewed all data, and reached a decision regarding the safety of resuming the study or not. The safety monitoring board will generate a report of their decision to continue or suspend enrollment, and this report will be given to the investigational review board and kept on file. Only after these actions are met and if the study is deemed appropriate to continue, enrollment can again commence.

2.3. Objectives

1. Primary objective**:** Define the maximum tolerated dose of carfilzomib administered in combination with melphalan and bendamustine in the setting of ASCT for multiple myeloma.
2. Secondary objective**:** Find the response rate of the combination of melphalan, bendamustine, and carfilzomib as a conditioning regimen in patients with multiple myeloma undergoing ASCT.

2.4. Setting: The research will be conducted at Spectrum Health Butterworth Campus, which will include the Adult Blood and Marrow Transplantation (ABMT) outpatient clinic and the adult oncology inpatient unit.

2.5. Accrual: Allowing for dropout, no more than 26 patients will be enrolled in the study.

2.6. Hypothesis: We hypothesize that the addition of carfilzomib to a conditioning regimen of melphalan and bendamustine in the setting of ASCT for multiple myeloma is feasible and safe.

2.7. End Points and Definitions

1. **Engraftment of Neutrophils:** ANC recovery is defined as an absolute neutrophil count (ANC) of ≥ 0.5 x 10^9/L for three consecutive laboratory values obtained on different days. The day used as neutrophil engraftment is the date of the first of three laboratory values. [80]
2. **Engraftment of Platelets:** Platelet engraftment is defined as a platelet count ≥ 20 x 10^9/L for 3 consecutive measurements obtained on different days. The patient must not have received a platelet infusion for seven consecutive days prior to the first day being considered. The day used as platelet engraftment is the date of the first of three laboratory values. [80]
3. **Graft Failure:** Graft failure includes failure to achieve neutrophil engraftment by day 22.

3. Eligibility: The PI, physician or advanced practice provider (APP) will evaluate all eligible patients for inclusion. Patients must meet all of the following inclusion criteria and none of the exclusion criteria.

3.1. Inclusion Criteria

1. Diagnosis of multiple myeloma
2. At least 2 x 10^6 CD34+ cells/kg have been collected from the patient and cryopreserved for ASCT
3. Age ≥ 18 years
4. Karnofsky score ≥ 70% (see Appendix B)
5. No evidence of progressive bacterial, viral, or fungal infection
6. Absolute neutrophil count ≥ 1x10^3/L
7. Platelet count ≥ 50x10^3/L
8. Hemoglobin ≥ 8 g/dL
9. Creatinine clearance > 50 mL/min
10. Total bilirubin, ALT, and AST < 2 x the upper limit of normal
11. Alkaline phosphatase ≤ 250 IU/L
12. Left Ventricular Ejection Fraction (LVEF) ≥ 45%
13. Adjusted Carbon Monoxide Diffusing Capacity (DLCO) ≥ 60%
14. Negative HIV serology
15. Recovered from toxicity of previous chemotherapy (excludes grade 1 neurotoxicity and hematological toxicity)

16. Patients with a pre-transplant disease status consistent with a very good partial response (VGPR), partial response (PR), stable disease (SD), progressive disease (PD), or relapse from complete remission (CR).

3.2. Exclusion Criteria:

1. Patients who are refractory to carfilzomib. Refractory is defined as disease progression while on carfilzomib therapy after receiving at least two cycles of treatment.
2. Patients with a complete response (CR) (including near CR and stringent CR) to conventional induction therapy and proceeding to transplantation.
3. Pregnant or nursing females or women of reproductive capability who are unwilling to use effective contraception. A woman of reproductive capability is one who has not undergone a hysterectomy (removal of the womb), has not had both ovaries removed, or has not been post-menopausal (stopped menstrual periods) for more than 24 months in a row].
4. Male subjects who refuse to practice effective barrier contraception during the entire study treatment period and through a minimum of 30 days after the last dose of study drug, or completely abstain from heterosexual intercourse. This must be done even if they are surgically sterilized (ie, post-vasectomy).
5. Patient with $\geq$ Grade 2 peripheral neuropathy
6. Inability to provide informed consent
7. Patient had myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (see Appendix C), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.[77] Prior to study entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant.
8. Known allergies to any of the components of the investigational treatment regimen or required ancillary treatments.
9. Serious medical or psychiatric illness likely to interfere with participation in this clinical study.
10. Diagnosed or treated for another malignancy within 3 years of enrollment (with the exception of non-melanoma skin cancer).
11. Participation in clinical trials with other investigational agents not included in this trial, within 14 days of the start of this trial and throughout the duration of this trial.
12. Prisoner

3.3. Prior concurrent therapy: Prior therapies are allowed provided that an adequate washout period is attained between therapies and the conditioning regimen for ASCT. The washout periods are as follows:

1. 3 weeks since prior chemotherapy with the exception of cyclophosphamide used for stem cell mobilization.
2. 4 weeks since prior biologic therapy.
3. 2 weeks since prior bisphosphonate therapy.

4. Pre-Transplant Study Activities: The patient will undergo pre-transplant work-up as follows:

4.1. Pre-Transplant

1. History and physical examination
2. Baseline assessment of myeloma burden, which includes disease assessment by SPEP, immunofixation, and FLCR
3. ABO and Rh type
4. CBC and CMP
5. PT INR and PTT
6. Infectious disease markers (IDM) including STS, CMV, Anti-HIV 1&2, HIV RNA, HBsAg, HBV RNA, Anti-HBc, Anti-HTLV I&II, Anti-HCV, HCV RNA, WNV, Chagas, EBV
7. β-HCG serum pregnancy test (females of reproductive capability only – refer to exclusion criteria)

8. Chest X ray (CXR) and ECG
9. Pulmonary function tests (PFT) with DLCO
10. ECHO to measure left ventricular ejection fraction (LVEF)
11. Urinalysis
12. Consults with dental, social work, infectious disease, physical therapy and nutrition prior to transplantation
13. Donor eligibility form

5. Conditioning Regimen (Appendix A):

5.1. Eligible patients will receive a cycle of carfilzomib 20 mg/m^2 on days -29, -28, -22, -21, -15, and -14. Upon admission to the hospital, the patient will continue conditioning with melphalan, bendamustine and carfilzomib. The carfilzomib dosing will be determined by cohort. The inpatient conditioning regimen is as follows:

1. Bendamustine 120 mg/m^2 on day -2 and 100 mg/m^2 day -1
2. Melphalan 140mg/m^2 daily on day -1
3. Carfilzomib on day -2, -1, and + 5
    - **i.** Cohort 1: Carfilzomib 15 mg/ m^2
    - **ii.** Cohort 2: Carfilzomib 20 mg/ m^2
    - **iii.** Cohort 2B: Carfilzomib 20 mg/ m^2
    - **iv.** Cohort 3B: Carfilzomib 27 mg/ m^2

5.2. Drug Preparation: The drug will be prepared under the supervision of a pharmacist, or appropriately qualified and trained personnel. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard nomogram or calculation. For patients with an actual body weight > 125% of the ideal body weight bendamustine, melphalan and carfilzomib will be calculated based on the adjusted body weight.

5.3. Drug Administration:

1. Bendamustine is administered in 500 mL NS (concentration 0.2-0.6 mg/mL), IV over 1 hour.
2. Melphalan is administered in NS for a concentration ≤ 0.45 mg/mL, IV over 30 minutes.
3. Carfilzomib is given in 50 D5W, IV over 10 minutes. Patients must receive 4 mg of dexamethasone PO or IV, 30 minutes before carfilzomib.

5.4. Supportive Care and Additional Therapies

1. All supportive care including anti-emetics, transfusion support, growth factors, and infection prophylaxis will be administered per established routine program practices. G-CSF injections will begin on day +7
2. Further post transplant therapy such as maintenance therapy or second transplant is allowed at the discretion of the treating physician starting after day + 100.

6. Study Required Activities

6.1 From admission to inpatient unit up to and including day +0

1. Daily CBC, CMP, BUN and creatinine, liver function tests (LFT)
2. Daily physical examination, including toxicity assessment
3. Collection and recording of conditioning regimen orders and SCT infusion records

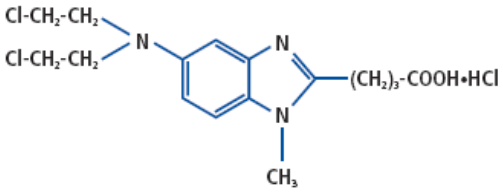
6.2. Post-Transplant

1. CBC, CMP, BUN, and creatinine daily until engraftment, then at least weekly until day +100.
2. LFT twice weekly until engraftment, then at least weekly until day +100.
3. Daily physical examination, including toxicity assessments until discharge and then weekly until day +100.
4. Disease assessment at day +100, +180, and +365 (+/- 7 days).

7. Drug Information

7.1. Treanda® (bendamustine) – Cephalon, Inc[78]

1. **Description:** TREANDA contains bendamustine hydrochloride, an alkylating drug, as the active ingredient. The chemical name of bendamustine hydrochloride is 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1 methyl-, monohydrochloride. Its empirical molecular formula is C16H21Cl2N3O2 · HCl, and the molecular weight is 394.7. Bendamustine hydrochloride contains a mechlorethamine group and a benzimidazole heterocyclic ring with a butyric acid substituent, and has the following structural formula:



TREANDA (bendamustine hydrochloride) for Injection is intended for intravenous infusion only after reconstitution with Sterile Water for Injection, USP, and after further dilution with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. It is supplied as a sterile non-pyrogenic white to off-white lyophilized powder in a single-use vial. Each 25-mg vial contains 25 mg of bendamustine hydrochloride and 42.5 mg of mannitol, USP. Each 100-mg vial contains 100 mg of bendamustine hydrochloride and 170 mg of mannitol, USP. The pH of the reconstituted solution is 2.5 - 3.5.

2. **Therapeutic Class:** alkylating agent
3. **Indication:** for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established. TREANDA for Injection is indicated for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. TREANDA is contraindicated in patients with a known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine or mannitol.
4. **Mechanism of Action:** Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. The bifunctional covalent linkage can lead to cell death via several pathways. Bendamustine is active against both quiescent and dividing cells. The exact mechanism of action of bendamustine remains unknown.
5. **Pharmacokinetics: Absorption:** Following a single IV dose of bendamustine hydrochloride Cmax typically occurred at the end of infusion. The dose proportionality of bendamustine has not been studied. **Distribution:** In vitro, the binding of bendamustine to human serum plasma proteins ranged from 94-96% and was concentration independent from 1-50 µg/mL. Data suggest that bendamustine is not likely to displace or to be displaced by highly protein-bound drugs. The blood to plasma concentration ratios in human blood ranged from 0.84 to 0.86 over a concentration range of 10 to 100 µg/mL indicating that bendamustine distributes freely in human red blood cells. In humans, the mean steady state volume of distribution (Vs.) was approximately 25 L. **Metabolism:** In vitro data indicate that bendamustine is primarily metabolized via hydrolysis to metabolites with low cytotoxic activity. In vitro, studies indicate that two active minor metabolites, M3 and M4, are primarily formed via CYP1A2. However, concentrations of these metabolites in plasma are 1/10 and 1/100 that of the parent compound, respectively, suggesting that the cytotoxic activity is primarily due to bendamustine. In vitro studies using human liver microsomes indicate that bendamustine does not inhibit CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5. Bendamustine did not induce metabolism of CYP1A2, CYP2A6, CYP2B6, CYP2C8,

CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5 enzymes in primary cultures of human hepatocytes. **Elimination:** No mass balance study has been undertaken in humans. Preclinical radiolabeled bendamustine studies showed that approximately 90% of drug administered was recovered in excreta primarily in the feces. Bendamustine clearance in humans is approximately 700 mL/minute. After a single dose of 120 mg/m2 bendamustine IV over 1-hour the intermediate t1⁄2 of the parent compound is approximately 40 minutes. The mean apparent terminal elimination t1⁄2 of M3 and M4 are approximately 3 hours and 30 minutes respectively. Little or no accumulation in plasma is expected for bendamustine administered on Days 1 and 2 of a 28-day cycle. **Renal Impairment:** In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m2 there was no meaningful effect of renal impairment (CrCL 40 - 80 mL/min, N=31) on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with CrCL < 40 mL/min. These results are however limited, and therefore bendamustine should be used with caution in patients with mild or moderate renal impairment. Bendamustine should not be used in patients with CrCL < 40 mL/min. **Hepatic Impairment:** In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m2 there was no meaningful effect of mild (total bilirubin ≤ ULN, AST ≥ ULN to 2.5 x ULN, and/or ALP ≥ ULN to 5.0 x ULN, N=26) hepatic impairment on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with moderate or severe hepatic impairment. These results are however limited, and therefore bendamustine should be used with caution in patients with mild hepatic impairment. Bendamustine should not be used in patients with moderate (AST or ALT 2.5 - 10 x ULN and total bilirubin 1.5 - 3 x ULN) or severe (total bilirubin > 3 x ULN) hepatic impairment. **Effect of Age:** Bendamustine exposure (as measured by AUC and Cmax) has been studied in patients ages 31 through 84 years. The pharmacokinetics of bendamustine (AUC and Cmax) were not significantly different between patients less than or greater than/equal to 65 years of age. **Effect of Gender:** The pharmacokinetics of bendamustine were similar in male and female patients. **Effect of Race:** The effect of race on the safety, and/or efficacy of bendamustine has not been established. Based on a cross-study comparison, Japanese subjects (n = 6) had on average exposures that were 40% higher than non-Japanese subjects receiving the same dose. The significance of this difference on the safety and efficacy of TREANDA in Japanese subjects has not been established.

6. **Supply:** bendamustine hydrochloride for Injection is supplied in individual cartons as follows: TREANDA (bendamustine hydrochloride) for Injection, 25 mg in 8 mL amber single-use vial. TREANDA (bendamustine hydrochloride) for Injection, 100 mg in 20 mL amber single-use vial.
7. **Storage, Administration and Stability:** may be stored up to 25°C (77°F) with excursions permitted up to 30°C (86°F). Retain in original package until time of use to protect from light. Aseptically reconstitute each TREANDA vial as follows: 25 mg TREANDA vial: Add 5 mL of only Sterile Water for Injection, USP, 100 mg TREANDA vial: Add 20 mL of only Sterile Water for Injection, USP. Refer to Prescribing Information for reconstitution procedures. TREANDA contains no antimicrobial preservative. The admixture should be prepared as close as possible to the time of patient administration. Once diluted with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36-47°F) or for 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of TREANDA must be completed within this period.
8. **Toxicity**
    a. **Myelosuppression:** Patients treated with TREANDA are likely to experience myelosuppression. In the two NHL studies, 98% of patients had Grade 3-4 myelosuppression. Three patients (2%) died from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with Grade 3 thrombocytopenia, and pneumonia from an opportunistic

infection (CMV). In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb), and neutrophils closely. In the clinical trials, blood counts were monitored every week initially. Hematologic nadirs were observed predominantly in the third week of therapy. Hematologic nadirs may require dose delays if recovery to the recommended values have not occurred by the first day of the next scheduled cycle. Prior to the initiation of the next cycle of therapy, the ANC should be ≥ 1 x 10^9/L and the platelet count should be ≥ 75 x 10^9/L.

b. **Infections:** Infection, including pneumonia and sepsis, has been reported in patients in clinical trials and in post-marketing reports. Infection has been associated with hospitalization, septic shock and death. Patients with myelosuppression following treatment with TREANDA are more susceptible to infections. Patients with myelosuppression following TREANDA treatment should be advised to contact a physician if they have symptoms or signs of infection.

c. **Infusion Reactions and Anaphylaxis:** Infusion reactions to TREANDA have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Monitor clinically and discontinue drug for severe reactions. Patients should be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Patients who experienced Grade 3 or worse allergic-type reactions were not typically re-challenged. Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids should be considered in subsequent cycles in patients who have previously experienced Grade 1 or 2 infusion reactions. Discontinuation should be considered in patients with Grade 3 or 4 infusion reactions.

d. **Tumor Lysis Syndrome:** Tumor lysis syndrome associated with TREANDA treatment has been reported in patients in clinical trials and in post-marketing reports. The onset tends to be within the first treatment cycle of TREANDA and, without intervention, may lead to acute renal failure and death. Preventive measures include maintaining adequate volume status, and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of TREANDA therapy. However, there may be an increased risk of severe skin toxicity when TREANDA and allopurinol are administered concomitantly.

e. **Skin Reactions:** A number of skin reactions have been reported in clinical trials and post-marketing safety reports. These events have included rash, toxic skin reactions and bullous exanthema. Some events occurred when TREANDA was given in combination with other anticancer agents, so the precise relationship to TREANDA is uncertain. In a study of TREANDA (90 mg/m2) in combination with rituximab, one case of toxic epidermal necrolysis (TEN) occurred. TEN has been reported for rituximab (see rituximab package insert). Cases of Stevens-Johnson syndrome (SJS) and TEN, some fatal, have been reported when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes. The relationship to TREANDA cannot be determined. Where skin reactions occur, they may be progressive and increase in severity with further treatment. Therefore, patients with skin reactions should be monitored closely. If skin reactions are severe or progressive, TREANDA should be withheld or discontinued.

f. **Other Malignancies:** There are reports of pre-malignant and malignant diseases that have developed in patients who have been treated with TREANDA, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma. The association with TREANDA therapy has not been determined.

g. **Extravasation:** There are postmarketing reports of bendamustine extravasations resulting in hospitalizations from erythema, marked swelling, and pain. Precautions should be taken to avoid

extravasation, including monitoring of the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of TREANDA.

h. **Use in Pregnancy:** TREANDA can cause fetal harm when administered to a pregnant woman. Single intraperitoneal doses of bendamustine in mice and rats administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations, and decreased fetal body weights.

9. Clinical Experience

a. **Chronic Lymphocytic Leukemia (CLL):** The safety and efficacy of TREANDA were evaluated in an open-label, randomized, controlled multicenter trial comparing TREANDA to chlorambucil. The trial was conducted in 301 previously-untreated patients with Binet Stage B or C (Rai Stages I - IV) CLL requiring treatment. Need-to-treat criteria included hematopoietic insufficiency, B-symptoms, rapidly progressive disease or risk of complications from bulky lymphadenopathy. Patients with autoimmune hemolytic anemia or autoimmune thrombocytopenia, Richter's syndrome, or transformation to prolymphocytic leukemia were excluded from the study. The patient populations in the TREANDA and chlorambucil treatment groups were balanced with regard to the following baseline characteristics: age (median 63 vs. 66 years), gender (63% vs. 61% male), Binet stage (71% vs. 69% Binet B), lymphadenopathy (79% vs. 82%), enlarged spleen (76% vs. 80%), enlarged liver (48% vs. 46%), hypercellular bone marrow (79% vs. 73%), "B" symptoms (51% vs. 53%), lymphocyte count (mean 65.7x109/L vs. 65.1x109/L), and serum lactate dehydrogenase concentration (mean 370.2 vs. 388.4 U/L). Ninety percent of patients in both treatment groups had immuno-phenotypic confirmation of CLL (CD5, CD23 and either CD19 or CD20 or both). Patients were randomly assigned to receive either TREANDA at 100 mg/m2, administered intravenously over a period of 30 minutes on Days 1 and 2 or chlorambucil at 0.8 mg/kg (Broca's normal weight) administered orally on Days 1 and 15 of each 28-day cycle. Efficacy endpoints of objective response rate and progression-free survival were calculated using a pre-specified algorithm based on NCI working group criteria for CLL1.The results of this open-label randomized study demonstrated a higher rate of overall response and a longer progression-free survival for TREANDA compared to chlorambucil (see table: Efficacy Data for CLL). Survival data are not mature.

Table: Efficacy Data for CLL

	TREANDA (N=153)	Chlorambucil (N=148)	p-value
Response Rate n(%)			
Overall response rate	90 (59)	38 (26)	<0.0001
(95% CI)	(51.0, 66.6)	(18.6, 32.7)	
Complete response (CR)*	13 (8)	1 (<1)	
Nodular partial response (nPR)**	4 (3)	0	
Partial response (PR)†	73 (48)	37 (25)	
Progression-Free Survival††			
Median, months (95% CI)	18 (11.7, 23.5)	6 (5.6, 8.6)	
Hazard ratio (95% CI)	0.27 (0.17, 0.43)		<0.0001

CI = confidence interval

* CR was defined as peripheral lymphocyte count ≤ 4.0 x 10^9/L, neutrophils ≥ 1.5 x 10^9/L, platelets >100 x 10^9/L, hemoglobin > 110g/L, without transfusions, absence of palpable hepatosplenomegaly, lymph nodes ≤ 1.5 cm, < 30% lymphocytes without nodularity in at least a normocellular bone marrow and absence of "B" symptoms. The clinical and laboratory criteria were required to be maintained for a period of at least 56 days.

** nPR was defined as described for CR with the exception that the bone marrow biopsy shows persistent nodules.

† PR was defined as ≥ 50% decrease in peripheral lymphocyte count from the pretreatment baseline value, and either ≥50% reduction in lymphadenopathy, or ≥50% reduction in the size of spleen or liver, as well as one of the following hematologic improvements: neutrophils ≥ 1.5 x 10^9/L or 50% improvement over baseline, platelets >100 x 10^9/L or 50% improvement over baseline, hemoglobin >110g/L or 50% improvement over baseline without transfusions, for a period of at least 56 days.

†† PFS was defined as time from randomization to progression or death from any cause.

Figure: Progression-Free Survival: Kaplan-Meier estimates of progression-free survival comparing TREANDA with chlorambucil.

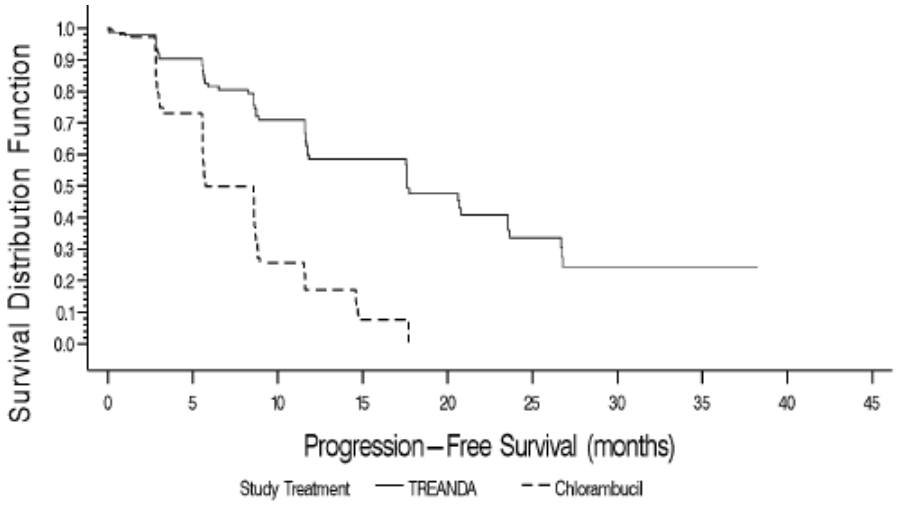


Table: Non-Hematologic Adverse Reactions Occurring in Randomized CLL Clinical Study in at Least 5% of Patients: the treatment emergent adverse reactions, regardless of attribution, that were reported in ≥ 5% of patients in either treatment group in the randomized CLL clinical study.

	Number (%) of patients			
	TREANDA (N=153)		Chlorambucil (N=143)	
System organ class Preferred term	All Grades	Grade 3/4	All Grades	Grade 3/4
Total number of patients with at least 1 adverse reaction	**121 (79)**	**52 (34)**	**96 (67)**	**25 (17)**
Gastrointestinal disorders				
Nausea	31 (20)	1 (<1)	21 (15)	1 (<1)
Vomiting	24 (16)	1 (<1)	9 (6)	0
Diarrhea	14 (9)	2 (1)	5 (3)	0
General disorders and administration site conditions				
Pyrexia	36 (24)	6 (4)	8 (6)	2 (1)
Fatigue	14 (9)	2 (1)	8 (6)	0
Asthenia	13 (8)	0	6 (4)	0
Chills	9 (6)	0	1 (<1)	0
Immune system disorders				
Hypersensitivity	7 (5)	2 (1)	3 (2)	0
Infections and infestations				
Nasopharyngitis	10 (7)	0	12 (8)	0
Infection	9 (6)	3 (2)	1 (<1)	1 (<1)
Herpes simplex	5 (3)	0	7 (5)	0
Investigations				
Weight decreased	11 (7)	0	5 (3)	0
Metabolism and nutrition disorders				
Hyperuricemia	11 (7)	3 (2)	2 (1)	0
Respiratory, thoracic and mediastinal disorders				
Cough	6 (4)	1 (<1)	7 (5)	1 (<1)
Skin and subcutaneous tissue disorders				
Rash	12 (8)	4 (3)	7 (5)	3 (2)
Pruritus	8 (5)	0	2 (1)	0

Incidence of Hematology Laboratory Abnormalities in Patients Who Received TREANDA or Chlorambucil in the Randomized CLL Clinical Study: The Grade 3 and 4 hematology laboratory test values by treatment group in the randomized CLL clinical study. These findings confirm the myelosuppressive effects seen in patients treated with TREANDA. Red blood cell transfusions were administered to 20% of patients receiving TREANDA compared with 6% of patients receiving chlorambucil.

	TREANDA N=150		Chlorambucil N=141	
Laboratory Abnormality	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**
Hemoglobin Decreased	134 (89)	20 (13)	115 (82)	12 (9)
Platelets Decreased	116 (77)	16 (11)	110 (78)	14 (10)
Leukocytes Decreased	92 (61)	42 (28)	26 (18)	4 (3)
Lymphocytes Decreased	102 (68)	70 (47)	27 (19)	6 (4)
Neutrophils Decreased	113 (75)	65 (43)	86 (61)	30 (21)

b. **Non-Hodgkin's Lymphoma (NHL):** The efficacy of TREANDA was evaluated in a single arm study of 100 patients with indolent B-cell NHL that had progressed during of within six months of treatment with rituximab or a rituximab-containing regimen. Patients were included if they relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab. All patients received TREANDA intravenously at a dose of 120

mg/m2, on Days 1 and 2 of a 21-day treatment cycle. Patients were treated for up to 8 cycles. The median age was 60 years, 65% were male, and 95% had a baseline WHO performance status of 0 or 1. Major tumor subtypes were follicular lymphoma (62%), diffuse small lymphocytic lymphoma (21%), and marginal zone lymphoma (16%). Ninety-nine percent of patients had received previous chemotherapy, 91% of patients had received previous alkylator therapy, and 97% of patients had relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab. Efficacy was based on the assessments by a blinded independent review committee (IRC) and included overall response rate (complete response + complete response unconfirmed + partial response) and duration of response (DR) as summarized in Table: Efficacy Data for NHL.

Table: Efficacy Data for NHL

	TREANDA (N=100)
Response Rate (%)	
Overall response rate (CR+CRu+PR)	74
(95% CI)	(64.3, 82.3)
Complete response (CR)	13
Complete response unconfirmed (CRu)	4
Partial response (PR)	57
Duration of Response (DR)	
Median, months (95% CI)	9.2 months (7.1, 10.8)

CI = confidence interval
*IRC assessment was based on modified International Working Group response criteria (IWG-RC)[2]. Modifications to IWG-RC specified that a persistently positive bone marrow in patients who met all other criteria for CR would be scored as PR. Bone marrow sample lengths were not required to be ≥20 mm.

Non-Hematologic Adverse Reactions Occurring in at Least 5% of NHL Patients Treated with TREANDA by System Organ Class and Preferred Term (N=176)

System organ class Preferred term	Number (%) of patients*	
	All Grades	Grade 3/4
Total number of patients with at least 1 adverse reaction	176 (100)	94 (53)
Cardiac disorders		
Tachycardia	13 (7)	0
Gastrointestinal disorders		
Nausea	132 (75)	7 (4)
Vomiting	71 (40)	5 (3)
Diarrhea	65 (37)	6 (3)
Constipation	51 (29)	1 (<1)
Stomatitis	27 (15)	1 (<1)
Abdominal pain	22 (13)	2 (1)
Dyspepsia	20 (11)	0
Gastroesophageal reflux disease	18 (10)	0
Dry mouth	15 (9)	1 (<1)
Abdominal pain upper	8 (5)	0
Abdominal distension	8 (5)	0
General disorders and administration site conditions		
Fatigue	101 (57)	19 (11)
Pyrexia	59 (34)	3 (2)
Chills	24 (14)	0
Edema peripheral	23 (13)	1 (<1)
Asthenia	19 (11)	4 (2)
Chest pain	11 (6)	1 (<1)
Infusion site pain	11 (6)	0

Pain	10 (6)	0
Catheter site pain	8 (5)	0
Infections and infestations		
Herpes zoster	18 (10)	5 (3)
Upper respiratory tract infection	18 (10)	0
Urinary tract infection	17 (10)	4 (2)
Sinusitis	15 (9)	0
Pneumonia	14 (8)	9 (5)
Febrile Neutropenia	11 (6)	11 (6)
Oral Candidiasis	11 (6)	2 (1)
Nasopharyngitis	11 (6)	0
Investigations		
Weight decreased	31 (18)	3 (2)
Metabolism and nutrition disorders		
Anorexia	40 (23)	3 (2)
Dehydration	24 (14)	8 (5)
Decreased appetite	22 (13)	1 (<1)
Hypokalemia	15 (9)	9 (5)
Musculoskeletal and connective tissue disorders		
Back pain	25 (14)	5 (3)
Arthralgia	11 (6)	0
Pain in extremity	8 (5)	2 (1)
Bone pain	8 (5)	0
Nervous system disorders		
Headache	36 (21)	0
Dizziness	25 (14)	0
Dysgeusia	13 (7)	0
Psychiatric disorders		
Insomnia	23 (13)	0
Anxiety	14 (8)	1 (<1)
Depression	10 (6)	0
Respiratory, thoracic and mediastinal disorders		
Cough	38 (22)	1 (<1)
Dyspnea	28 (16)	3 (2)
Pharyngolaryngeal pain	14 (8)	1 (<1)
Wheezing	8 (5)	0
Nasal congestion	8 (5)	0
Skin and subcutaneous tissue disorders		
Rash	28 (16)	1 (<1)
Pruritus	11 (6)	0
Dry skin	9 (5)	0
Night sweats	9 (5)	0
Hyperhidrosis	8 (5)	0
Vascular disorders		
Hypotension	10 (6)	2 (1)

*Patients may have reported more than 1 adverse reaction.

NOTE: Patients counted only once in each preferred term category and once in each system organ class category.

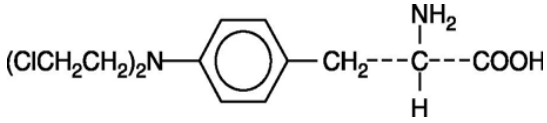
Incidence of Hematology Laboratory Abnormalities in Patients Who Received TREANDA in the NHL Studies

Hematology variable	Percent of patients	
	All Grades	Grades 3/4
Lymphocytes Decreased	99	94
Leukocytes Decreased	94	56
Hemoglobin Decreased	88	11
Neutrophils Decreased	86	60
Platelets Decreased	86	25

7.2. Alkeran® (melphalan hydrochloride) – Celgene Corporation[83]

1. **Description:** also known as L-phenylalanine mustard, phenylalanine mustard, L-PAM, or L-sarcolysin, is a phenylalanine derivative of nitrogen mustard. Melphalan is a bifunctional alkylating agent that is active against selected human neoplastic diseases. It is known chemically as 4-[bis(2-chloroethyl)amino]-L-

phenylalanine. The molecular formula is C13H18Cl2N2O2 and the molecular weight is 305.20. The structural formula is:



Melphalan is the active L-isomer of the compound and was first synthesized in 1953 by Bergel and Stock; the D-isomer, known as medphalan, is less active against certain animal tumors, and the dose needed to produce effects on chromosomes is larger than that required with the L-isomer. The racemic (DL-) form is known as merphalan or sarcolysin. Melphalan is practically insoluble in water and has a pKa1 of 2.5.

2. **Therapeutic Class:** alkylating agent
3. **Indication:** for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate. Melphalan should not be used in patients whose disease has demonstrated prior resistance to this agent. Patients who have demonstrated hypersensitivity to melphalan should not be given the drug.
4. **Mechanism of Action:** Melphalan is an alkylating agent of the bischloroethylamine type. As a result, its cytotoxicity appears to be related to the extent of its interstrand cross-linking with DNA, probably by binding at the N7 position of guanine. Like other bifunctional alkylating agents, it is active against both resting and rapidly dividing tumor cells.
5. **Pharmacokinetics:** The pharmacokinetics of melphalan after IV administration has been extensively studied in adult patients. Following injection, drug plasma concentrations declined rapidly in a biexponential manner with distribution phase and terminal elimination phase half-lives of approximately 10 and 75 minutes, respectively. Estimates of average total body clearance varied among studies, but typical values of approximately 7 to 9 mL/min/kg (250 to 325 mL/min/m2) were observed. One study has reported that on repeat dosing of 0.5 mg/kg every 6 weeks, the clearance of melphalan decreased from 8.1 mL/min/kg after the first course, to 5.5 mL/min/kg after the third course, but did not decrease appreciably after the third course. Mean (±SD) peak melphalan plasma concentrations in myeloma patients given IV melphalan at doses of 10 or 20 mg/m2 were 1.2 ± 0.4 and 2.8 ± 1.9 mcg/mL, respectively. The steady-state volume of distribution of melphalan is 0.5 L/kg. Penetration into cerebrospinal fluid (CSF) is low. The extent of melphalan binding to plasma proteins ranges from 60% to 90%. Serum albumin is the major binding protein, while α1-acid glycoprotein appears to account for about 20% of the plasma protein binding. Approximately 30% of the drug is (covalently) irreversibly bound to plasma proteins. Interactions with immunoglobulins have been found to be negligible. Melphalan is eliminated from plasma primarily by chemical hydrolysis to monohydroxymelphalan and dihydroxymelphalan. Aside from these hydrolysis products, no other melphalan metabolites have been observed in humans. Although the contribution of renal elimination to melphalan clearance appears to be low, one study noted an increase in the occurrence of severe leukopenia in patients with elevated BUN after 10 weeks of therapy.
6. **Supply:** Alkeran for Injection is supplied in a carton containing one single-use clear glass vial of freeze-dried melphalan hydrochloride equivalent to 50 mg melphalan and one 10-mL clear glass vial of sterile diluent (NDC 59572-301-01).
7. **Storage, Administration and Stability:** Store at controlled room temperature 15° to 30°C (59° to 86°F) and protect from light. Refer to Prescribing Information for reconstitution procedures. Administer the diluted product over a minimum of 15 minutes. Complete administration within 60 minutes of reconstitution. The time between reconstitution/dilution and administration of ALKERAN should be kept to a minimum because reconstituted and diluted solutions of ALKERAN are unstable. Over as short a time as 30 minutes, a citrate derivative of melphalan has been detected in reconstituted material from the reaction of ALKERAN with Sterile Diluent for ALKERAN. Upon further dilution with saline, nearly 1%

label strength of melphalan hydrolyzes every 10 minutes. A precipitate forms if the reconstituted solution is stored at 5°C. DO NOT REFRIGERATE THE RECONSTITUTED PRODUCT.

8. **Toxicity:**
   a. **Hematologic:** The most common side effect is bone marrow suppression leading to leukopenia, thrombocytopenia, and anemia. White blood cell count and platelet count nadirs usually occur 2 to 3 weeks after treatment, with recovery in 4 to 5 weeks after treatment. Irreversible bone marrow failure has been reported.
   b. **Gastrointestinal:** Gastrointestinal disturbances such as nausea and vomiting, diarrhea, and oral ulceration occur infrequently. Hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice have been reported. Hepatic veno-occlusive disease has been reported.
   c. **Hypersensitivity:** Acute hypersensitivity reactions including anaphylaxis were reported in 2.4% of 425 patients receiving ALKERAN for Injection for myeloma. These reactions were characterized by urticaria, pruritus, edema, skin rashes, and in some patients, tachycardia, bronchospasm, dyspnea, and hypotension. These patients appeared to respond to antihistamine and corticosteroid therapy. If a hypersensitivity reaction occurs, IV or oral melphalan should not be readministered since hypersensitivity reactions have also been reported with oral melphalan. Cardiac arrest has also been reported rarely in association with such reports.
   d. **Miscellaneous:** Other reported adverse reactions include skin hypersensitivity, skin ulceration at injection site, skin necrosis rarely requiring skin grafting, maculopapular rashes, vasculitis, alopecia, hemolytic anemia, allergic reaction, pulmonary fibrosis (including fatal outcomes), and interstitial pneumonitis. Temporary significant elevation of the blood urea has been seen in the early stages of therapy in patients with renal damage. Subjective and transient sensation of warmth and/or tingling.
9. **Clinical Experience:** A randomized trial compared prednisone plus IV melphalan to prednisone plus oral melphalan in the treatment of myeloma. As discussed below, overall response rates at week 22 were comparable; however, because of changes in trial design, conclusions as to the relative activity of the 2 formulations after week 22 are impossible to make. Both arms received oral prednisone starting at 0.8 mg/kg/day with doses tapered over 6 weeks. Melphalan doses in each arm were: Arm 1 Oral melphalan 0.15 mg/kg/day x 7 followed by 0.05 mg/kg/day when

WBC began to rise. Arm 2 IV melphalan 16 mg/m^2 q 2 weeks x 4 (over 6 weeks) followed by the same dose every 4 weeks. Doses of melphalan were adjusted according to the following criteria.

Table: Criteria for Dosage Adjustment in a Randomized Clinical Trial

WBC/mm3	Platelets	Percent of Full Dose
≥4,000	≥100,000	100
≥3,000	≥75,000	75
≥2,000	≥50,000	50
<2,000	<50,000	0

One hundred seven patients were randomized to the oral melphalan arm and 203 patients to the IV melphalan arm. More patients had a poor-risk classification (58% versus 44%) and high tumor load (51% versus 34%) on the oral compared to the IV arm (P<0.04). Response rates at week 22 are shown in the following table (Response Rates at Week 22).

Table: Response Rates at Week 22

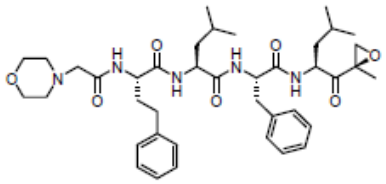
Initial Arm	Evaluable Patients	Responders n (%)	*P*
Oral melphalan	100	44 (44%)	*P*>0.2
IV melphalan	195	74 (38%)	

Because of changes in protocol design after week 22, other efficacy parameters such as response duration and survival cannot be compared. Severe myelotoxicity (WBC ≤1,000 and/or platelets ≤25,000) was more common in the IV melphalan arm (28%) than in the oral melphalan arm (11%). An association was noted between poor renal function and myelosuppression; consequently, an amendment to the protocol required a 50% reduction in IV melphalan dose if the BUN was ≥30 mg/dL. The rate of severe leukopenia in the IV arm in the patients with BUN over 30 mg/dL decreased from 50% (8/16) before protocol amendment to 11% (3/28) (*P* = 0.01) after the amendment. Before the dosing amendment, there was a 10% (8/77) incidence of drug-related death in the IV arm. After the dosing amendment, this incidence was 3% (3/108). This compares to an overall 1% (1/100) incidence of drug-related death in the oral arm.

7.3. Kyprolis® (carfilzomib): Onyx Pharmaceuticals, Inc.[79]

1. **Description:** KYPROLIS (carfilzomib) for Injection is an antineoplastic agent available for intravenous use only. KYPROLIS is a sterile, white to off-white lyophilized powder and is available as a single-use vial. Each vial of KYPROLIS contains 60 mg of carfilzomib, 3000 mg sulfobutylether beta-cyclodextrin, 57.7 mg citric acid, and sodium hydroxide for pH adjustment (target pH 3.5). Carfilzomib is a modified tetrapeptidyl epoxide, isolated as the crystalline free base. The chemical name for carfilzomib is (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)4-phenylbutanamido)-4-methylpentanamide.

   Carfilzomib has the following structure:



   Carfilzomib is a crystalline substance with a molecular weight of 719.9. The molecular formula is C40H57N5O7. Carfilzomib is practically insoluble in water, and very slightly soluble in acidic conditions.
2. **Therapeutic Class:** proteasome inhibitor.
3. **Indication:** KYPROLIS is indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.
4. **Mechanism of Action:** Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. Carfilzomib had antiproliferative and proapoptotic activities *in vitro* in solid and hematologic tumor cells. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumor growth in models of multiple myeloma, hematologic, and solid tumors.
5. **Pharmacokinetics: Absorption:** The Cmax and AUC following a single intravenous dose of 27 mg/m^2 were 4232 ng/mL and 379 ng▪hr/mL, respectively. Following repeated doses of carfilzomib at 15 and 20 mg/m^2, systemic exposure (AUC) and half-life were similar on Days 1 and 15 or 16 of Cycle 1, suggesting there was no systemic carfilzomib accumulation. At doses between 20 and 36 mg/m^2, there

was a dose-dependent increase in exposure. **Distribution:** The mean steady-state volume of distribution of a 20 mg/m^2 dose of carfilzomib was 28 L. When tested in vitro, the binding of carfilzomib to human plasma proteins averaged 97% over the concentration range of 0.4 to 4 micromolar. **Metabolism:** Carfilzomib was rapidly and extensively metabolized. The predominant metabolites measured in human plasma and urine, and generated *in vitro* by human hepatocytes, were peptide fragments and the diol of carfilzomib, suggesting that peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism. Cytochrome P450-mediated mechanisms played a minor role in overall carfilzomib metabolism. The metabolites have no known biologic activity. **Elimination:** Following intravenous administration of doses ≥ 15 mg/m^2, carfilzomib was rapidly cleared from the systemic circulation with a half-life of ≤ 1 hour on Day 1 of Cycle 1. The systemic clearance ranged from 151 to 263 L/hour, and exceeded hepatic blood flow, suggesting that carfilzomib was largely cleared extrahepatically. The pathways of carfilzomib elimination have not been characterized in humans. **Age:** Analysis of population pharmacokinetics data after the first dose of Cycle 1 (Day 1) in 154 patients who had received an IV dose of 20 mg/m^2 showed no clinically significant difference in exposure between patients < 65 years and ≥ 65 years of age. **Gender:** Mean dose-normalized AUC and Cmax values were comparable between male and female patients in the population pharmacokinetics study. **Hepatic Impairment:** No pharmacokinetic studies were performed with KYPROLIS in patients with hepatic impairment. **Renal Impairment:** A pharmacokinetic study was conducted in which 43 multiple myeloma patients who had various degrees of renal impairment and who were classified according to their creatinine clearances (CLcr) into the following groups: normal function (CLcr > 80 mL/min, n = 8), mild impairment (CLcr 50–80 mL/min, n = 12), moderate impairment (CLcr 30–49 mL/min, n =8), severe impairment (CLcr < 30 mL/min, n = 7), and chronic dialysis (n = 8). KYPROLIS was administered intravenously over 2 to 10 minutes, on two consecutive days, weekly for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period every 28 days. Patients received an initial dose of 15 mg/m^2, which could be escalated to 20 mg/m^2 starting in Cycle 2 if 15 mg/m^2 was well tolerated in Cycle 1. In this study, renal function status had no effect on the clearance or exposure of carfilzomib following a single or repeat-dose administration. **Cytochrome P450:** In an in vitro study using human liver microsomes, carfilzomib showed modest direct and time-dependent inhibitory effect on human cytochrome CYP3A4/5. In vitro studies indicated that carfilzomib did not induce human CYP1A2 and CYP3A4 in cultured fresh human hepatocytes. Cytochrome P450-mediated mechanisms play a minor role in the overall metabolism of carfilzomib. A clinical trial of 17 patients using oral midazolam as a CYP3A probe demonstrated that the pharmacokinetics of midazolam were unaffected by concomitant carfilzomib administration. KYPROLIS is not expected to inhibit CYP3A4/5 activities and/or affect the exposure to CYP3A4/5 substrates. **P-gp:** Carfilzomib is a P-glycoprotein (P-gp) substrate and showed marginal inhibitory effects on P-gp in a Caco-2 monolayer system. Given that KYPROLIS is administrated intravenously and is extensively metabolized, the pharmacokinetic profile of KYPROLIS is unlikely to be affected by P-gp inhibitors or inducers.

6. **Supply:** KYPROLIS (carfilzomib) for Injection is supplied as an individually cartoned single-use vial containing a dose of 60 mg of carfilzomib as a white to off-white lyophilized cake or powder. NDC 76075-101-01, 60 mg carfilzomib per vial. KYPROLIS single-use vial contains 60 mg of carfilzomib as a sterile, white to off-white lyophilized cake or powder.
7. **Storage, Administration and Stability:** Unopened vials should be stored refrigerated (2°C to 8°C; 36°F to 46°F). Retain in original package to protect from light. KYPROLIS vials contain no antimicrobial preservatives and are intended only for single use. Unopened vials of KYPROLIS are stable until the date indicated on the package when stored in the original package at 2°C to 8°C (36°F to 46°F). The reconstituted solution contains carfilzomib at a concentration of 2 mg/mL. Read the complete

preparation instructions prior to reconstitution. The stabilities of reconstituted KYPROLIS under various temperature and container conditions are shown in Table 3.

Table: Stability of Reconstituted KYPROLIS

Storage Conditions of Reconstituted KYPROLIS	Stability[a] per Container		
	Vial	Syringe	IV Bag (D5W[b])
Refrigerated (2°C to 8°C; 36°F to 46°F)	24 hours	24 hours	24 hours
Room Temperature (15°C to 30°C; 59°F to 86°F)	4 hours	4 hours	4 hours

[a] Total time from reconstitution to administration should not exceed 24 hours.
[b] 5% Dextrose Injection, USP.

8. **Toxicity:**

   a. **Cardiac Arrest, Congestive Heart Failure, Myocardial Ischemia:** Death due to cardiac arrest has occurred within a day of KYPROLIS administration. New onset or worsening of pre-existing congestive heart failure with decreased left ventricular function or myocardial ischemia have occurred following administration of KYPROLIS. Cardiac failure events (e.g., cardiac failure congestive, pulmonary edema, ejection fraction decreased) were reported in 7% of patients. Monitor for cardiac complications and manage promptly. Withhold KYPROLIS for Grade 3 or 4 cardiac events until recovery and consider whether to restart KYPROLIS based on a benefit/risk assessment. Patients with New York Heart Association Class III and IV heart failure, myocardial infarction in the preceding 6 months, and conduction abnormalities uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications.

   b. **Pulmonary Hypertension:** Pulmonary arterial hypertension (PAH) was reported in 2% of patients treated with KYPROLIS and was Grade 3 or greater in less than 1% of patients. Evaluate with cardiac imaging and/or other tests as indicated. Withhold KYPROLIS for pulmonary hypertension until resolved or returned to baseline and consider whether to restart KYPROLIS based on a benefit/risk assessment.

   c. **Pulmonary Complications:** Dyspnea was reported in 35% of patients enrolled in clinical trials. Grade 3 dyspnea occurred in 5%; no Grade 4 events, and 1 death (Grade 5) was reported. Monitor and manage dyspnea immediately; interrupt KYPROLIS until symptoms have resolved or returned to baseline.

   d. **Infusion Reactions:** Infusion reactions were characterized by a spectrum of systemic symptoms including fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of KYPROLIS. Administer dexamethasone prior to KYPROLIS to reduce the incidence and severity of reactions. Inform patients of the risk and symptoms and to contact physician if symptoms of an infusion reaction occur.

   e. **Tumor Lysis Syndrome:** Tumor lysis syndrome (TLS) occurred following KYPROLIS administration in < 1% of patients. Patients with multiple myeloma and a high tumor burden should be considered to be at greater risk for TLS. Prior to receiving KYPROLIS, ensure that patients are well hydrated. Monitor for evidence of TLS during treatment, and manage promptly. Interrupt KYPROLIS until TLS is resolved.

   f. **Thrombocytopenia:** KYPROLIS causes thrombocytopenia with platelet nadirs occurring around Day 8 of each 28-day cycle and recovery to baseline by the start of the next 28-day cycle. In patients with multiple myeloma, 36% of patients experienced thrombocytopenia, including Grade 4

in 10%. Thrombocytopenia following KYPROLIS administration resulted in a dose reduction in 1% of patients and discontinuation of treatment with KYPROLIS in < 1% of patients. Monitor platelet counts frequently during treatment with KYPROLIS. Reduce or interrupt dose as clinically indicated.

g. **Hepatic Toxicity and Hepatic Failure:** Cases of hepatic failure, including fatal cases, have been reported (< 1%). KYPROLIS can cause elevations of serum transaminases and bilirubin. Withhold KYPROLIS in patients experiencing Grade 3 or greater elevations of transaminases, bilirubin, or other liver abnormalities until resolved or returned to baseline. After resolution, consider if restarting KYPROLIS is appropriate. Monitor liver enzymes frequently.

h. **Embryo-fetal Toxicity:** KYPROLIS can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using KYPROLIS. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose. Females of reproductive potential should be advised to avoid becoming pregnant while being treated with KYPROLIS. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

9. **Clinical Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug, and may not reflect the rates observed in medical practice. A total of 526 patients with relapsed and/or refractory multiple myeloma received KYPROLIS as monotherapy or with pre-dose dexamethasone. Patients received a median of four treatment cycles with a median cumulative KYPROLIS dose of 993.4 mg. Deaths due to all causes within 30 days of the last dose of KYPROLIS occurred in 37/526 (7%) of patients. Deaths not attributed to disease progression were cardiac in 5 patients (acute coronary syndrome, cardiac arrest, cardiac disorder), end-organ failure in 4 patients (multi-organ failure, hepatic failure, renal failure), infection in 4 patients (sepsis, pneumonia, respiratory tract bacterial infection), dyspnea and intracranial hemorrhage in 1 patient each, and 1 patient found dead of unknown causes. Serious adverse reactions were reported in 45% patients. The most common serious adverse reactions were pneumonia (10%), acute renal failure (4%), pyrexia (3%), and congestive heart failure (3%). Adverse reactions leading to discontinuation of KYPROLIS occurred in 15% of patients and included congestive heart failure (2%), cardiac arrest, dyspnea, increased blood creatinine, and acute renal failure (1% each). Adverse reactions occurring at a rate of 10% or greater are presented in **Table 6.3.9.**

Table 6.3.9: Incidence of Adverse Reactions Occurring in ≥ 10% of Multiple Myeloma Patients Treated with KYPROLIS.

Event	Patients (N = 526) [n (%)]		
	All Grades[a]	Grade 3 Events	Grade 4 Events
Fatigue	292 (55.5)	38 (7.2)	2 (0.4)
Anemia	246 (46.8)	111 (21.1)	7 (1.3)
Nausea	236 (44.9)	7 (1.3)	0
Thrombocytopenia	191 (36.3)	69 (13.1)	54 (10.3)
Dyspnea	182 (34.6)	25 (4.8)	1 (0.2)[b]
Diarrhea	172 (32.7)	4 (0.8)	1 (0.2)
Pyrexia	160 (30.4)	7 (1.3)	2 (0.4)
Upper respiratory tract infection	149 (28.3)	17 (3.2)	0
Headache	145 (27.6)	7 (1.3)	0
Cough	137 (26.0)	1 (0.2)	0
Blood creatinine increased	127 (24.1)	13 (2.5)	1 (0.2)
Lymphopenia	126 (24.0)	84 (16.0)	11 (2.1)
Edema peripheral	126 (24.0)	3 (0.6)	0
Vomiting	117 (22.2)	5 (1.0)	0
Constipation	110 (20.9)	1 (0.2)	0
Neutropenia	109 (20.7)	50 (9.5)	4 (0.8)
Back pain	106 (20.2)	15 (2.9)	0
Insomnia	94 (17.9)	0	0
Chills	84 (16.0)	1 (0.2)	0
Arthralgia	83 (15.8)	7 (1.3)	0
Muscle spasms	76 (14.4)	2 (0.4)	0
Hypertension	75 (14.3)	15 (2.9)	2 (0.4)
Asthenia	73 (13.9)	12 (2.3)	1 (0.2)
Hypokalemia	72 (13.7)	14 (2.7)	3 (0.6)
Hypomagnesemia	71 (13.5)	2 (0.4)	0
Leukopenia	71 (13.5)	27 (5.1)	1 (0.2)
Pain in extremity	70 (13.3)	7 (1.3)	0
Pneumonia	67 (12.7)	52 (9.9)	3 (0.6)[b]
Aspartate aminotransferase increased	66 (12.5)	15 (2.9)	1 (0.2)
Dizziness	66 (12.5)	5 (1.0)	1 (0.2)
Hypoesthesia	64 (12.2)	3 (0.6)	0
Anorexia	63 (12.0)	1 (0.2)	0
Pain	63 (12.0)	12 (2.3)	1 (0.2)
Hyperglycemia	62 (11.8)	16 (3.0)	3 (0.6)
Chest wall pain	60 (11.4)	3 (0.6)	0
Hypercalcemia	58 (11.0)	13 (2.5)	8 (1.5)
Hypophosphatemia	55 (10.5)	24 (4.6)	3 (0.6)
Hyponatremia	54 (10.3)	31 (5.9)	3 (0.6)

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0

[b] One event was Grade 5 severity.

a. Description of Selected Adverse Drug Reactions

7.3.9.a.1. ***Renal Events:*** The most common renal adverse reactions were increase in blood creatinine (24%) and renal failure (9%), which were mostly Grade 1 or Grade 2 in severity. Grade 3 renal adverse reactions occurred in 6% of patients and Grade 4 events occurred in

1%. Discontinuations due to increased blood creatinine and acute renal failure were 1% each. In one patient, death occurred with concurrent sepsis and worsening renal function.

7.3.9.a.2. ***Peripheral Neuropathy:*** Peripheral neuropathy (including all events of peripheral sensory neuropathy and peripheral motor neuropathy) occurred in 14% of patients enrolled in clinical trials. Grade 3 peripheral neuropathy occurred in 1% of patients. Serious peripheral neuropathy events occurred in < 1% of patients, which resulted in dose reduction in < 1% and treatment discontinuation in < 1%. Withhold or discontinue treatment as recommended.

7.3.9.a.3. ***Herpes Virus Infection:*** Herpes zoster reactivation was reported in 2% of patients. Consider antiviral prophylaxis for patients who have a history of herpes zoster infection.

8. Post-transplant Criteria for Response, Progression and Relapse

8.1. Patients' disease status at each data collection period will be evaluated based on the International Uniform Response Criteria: Appendix D[82]

9. Removal of Subjects from Study:

9.1. The investigator will make every reasonable effort to keep each patient in the study until all planned treatments and assessments have been performed. Unplanned discontinuation may occur for any of the following reasons:

1. Patient develops allergy to either study drug
2. Treating physician feels that continuation in study is not appropriate. Such a determination may be made if the patient experiences adverse events related to carfilzomib of ≥ grade 3 other than hematologic toxicity that the physician or PI determines the study is no longer in the subject's best interest. This will also include allergic reaction to carfilzomib.
3. Patient withdraws informed consent
4. Patient is not meeting the follow up requirements

9.2. The principal investigator can decide to replace patients withdrawn from the study at his discretion. All patients who receive the three study drugs will be evaluated. No more than 26 patients will be enrolled.

10. Statistical Consideration

10.1. Sample size: The study will enroll 3-6 patients in each of the cohorts. Allowing for 2 withdrawals from the study and including the 6 patient planned expansions at the highest dose level associated with < 33% incidence of DLT, the maximum number of patients allowed on the study will be 26 patients.

11. Adverse Events: The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. AEs and SAEs will be followed from the first administration of carfilzomib up until 30 days after the last study drug administration and/or until treatment-related adverse events resolve or stabilize, whichever occurs first.

1. **Definition of Adverse Event:** An adverse event (AE) is untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. **Note:** An AE can therefore be any unfavorable and unintended sign, symptom, abnormal laboratory finding, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse. The Common Terminology Criteria for Adverse Events, Version 4.0, will be used for assessing the severity of adverse events. See http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

2. **Reporting an Adverse Event:** All adverse events, whether observed by the investigator or reported by the patient, must be recorded with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse event for its relationship to the test drug and for its seriousness.

11.2. Definition of Serious Adverse Event (SAE): A SAE is any untoward medical occurrence that, at any dose:

- Results in death (NOTE: death is an outcome, not an event)
- Is life-threatening: (NOTE: the term 'life-threatening' refers to an event in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.)
- Requires hospitalization or prolongation of existing hospitalization
- Results in disability/incapacity
- Is a congenital anomaly/birth defect

1. **Reporting a Serious Adverse Event:** The Principal Investigator (PI), Dr. Muneer Abidi, (who may also sometimes be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

   11.2.1.a.1. All SAEs, regardless of expectedness or relationship with any study drug, must be reported to the sponsor-investigator, as soon as possible, but no later than 24 hours of the investigator's observation or awareness of the event.

   11.2.1.a.2. Intensity for each SAE, including any lab abnormality, will be determined by using the NCI CTCAE v4, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

   11.2.1.a.3. The investigator must also provide the sponsor or designee with a copy of all communications with applicable regulatory authorities related to the study or study drug(s), including, but not limited to, telephone conversation logs, as soon as possible but no later than 5 calendar days of such communication.

2. Procedures for **Reporting Drug Exposure during Pregnancy and Birth Events:** If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug(s). The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and PI will request this information from the investigator. If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to PI immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

12. Administrative Requirements

12.1. Good Clinical Practice: The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s).[85] The investigator will be thoroughly familiar with the appropriate use of the study drugs as described in the protocol and Investigator's Brochures. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

1. **Ethical Considerations:** The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, informed consent,

advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

12.2. Patient Information and Informed Consent: After the study has been fully explained, written informed consent will be obtained from the patient. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

1. **Patient Confidentiality:** In order to maintain patient privacy, all information obtained in connection with this study which identifies the patient will remain confidential in accordance with state and federal law.
2. **Protocol Compliance:** The investigator will conduct the study in compliance with the protocol, and given approval/favorable opinion by the IRB, sponsor, and the appropriate regulatory authority(ies). Any departures from the protocol must be fully documented in the source documents.

12.3. On-Site Audits: Regulatory authorities and IRB may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

1. **Drug Accountability:** Drug will be purchased per standard of practice from a commercial source and compounded according to the package insert by the main hospital pharmacy. Accountability for the drug at all study sites (including all subsites, if applicable) is the responsibility of the sponsor-investigator. The sponsor-investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's use by each patient and the return or disposal of the drug will be maintained by the site and/or subsites. All material containing carfilzomib will be treated and disposed of as hazardous waste in accordance with governing regulations.
2. **Product Complaints:** A product complaint is a verbal, written, or electronic expression which implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact the PI at 616-486-5933 and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions.
3. **Premature Closure of Study:** This study may be prematurely terminated, if in the opinion of the sponsor-investigator there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the sponsor-investigator by the terminating party. Circumstances that may warrant termination include, but are not limited to:
   - **a.** Determination of unexpected, significant, or unacceptable risk to patients,
   - **b.** Failure to enter patients at an acceptable rate,
   - **c.** Insufficient adherence to protocol requirements,
   - **d.** Insufficient complete and/or evaluable data,
   - **e.** Plans to modify, suspend, or discontinue the development of the drug
4. **Record Retention:** The sponsor-investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

12.4. Medical care and Compensation for Injury: Any medical complications experienced relative to this research will be treated in accordance with current standards of care. No study funds have been set aside to compensate subjects for injury.

12.5. Cost to Subjects: Study drug and its preparation/administration will be billed to the subjects. All other aspects of the subject's care are considered standard of care, and will be billed to the patient and/or their insurance company.

12.6. Sharing of Results with Subjects: Study results may be published, and patients may access the results of this study via clinicaltrails.gov or any published media. However, no results will be sent directly to subjects.

13. **Data Reporting to the Center for International Blood and Transplant Research (CIBMTR):** All transplant centers are required to pre-register patients with the Center for International Blood and Marrow Transplant Research (CIBMTR) and complete pre-transplant essential data forms, day 100 report forms and follow-up forms.

14. Attachments

14.1. Appendix A: Required Study Activities

14.2. Appendix B: Karnofsky Scale

14.3. Appendix C: New York Heart Association (NYHA) Classification of Cardiac Disease

14.4. Appendix D: International Myeloma Working Group Uniform Response Criteria

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