Investigator-Initiated Trial

PROTOCOL INFORMATION

Study Title:

Phase 1/2 Study of Carfilzomib for the Prevention of Relapse and Graft-versus-host Disease in Allogeneic Hematopoietic Cell Transplantation for High-risk Hematologic Malignancies

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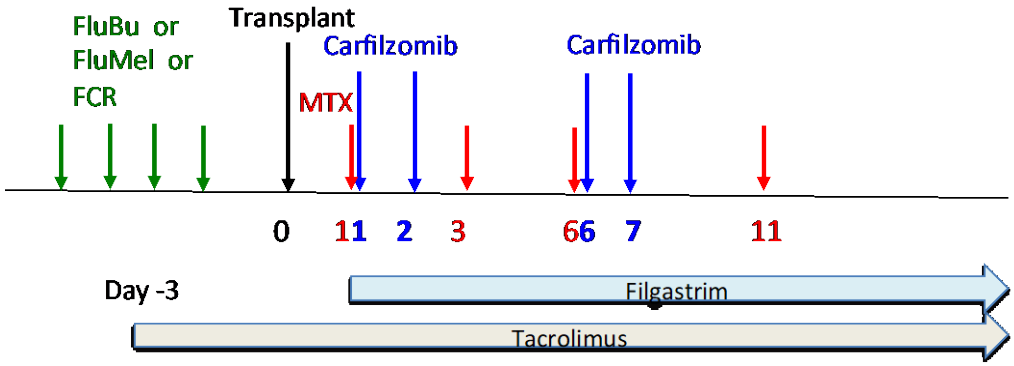
PROTOCOL SYNOPSIS

TITLE:	Phase 1/2 Study of Carfilzomib for the Prevention of Relapse and Graft-versus-host Disease in Allogeneic Hematopoietic Cell Transplantation for High-risk Hematologic Malignancies
OBJECTIVES:	**Primary Objective:** To determine whether the addition of carfilzomib to fludarabine-based conditioning chemotherapy, followed by allogeneic hematopoietic cell transplant for hematologic malignancies will decrease relapse/progression and severe graft-versus-host disease (GVHD). **Secondary Objectives:** To determine the efficacy of this regimen in the improvement of overall transplant outcomes.
STUDY DESIGN:	**Phase 1 Dose Finding**: 3+3 design, 4 dose levels [20, 27, 36, 45 mg/m^2] on day +1, +2, +6, +7 **Phase 2 Efficacy Testing:** expansion of the optimal dose level
STUDY POPULATION:	Adult patients with hematologic malignancy requiring allogeneic hematopoietic cell transplantation
INCLUSION CRITERIA:	1. Age: ≥18 and ≤70 years old at the time of transplant admission (<71 years) 2. A 8/8 or 7/8 HLA–matched donor is available 3. Hematologic malignancies requiring allogeneic hematopoietic cell transplantation 4. Adequate cardiac [LVEF≥0.4], pulmonary [FEV1, FVC, corrected DLCO ≥ 50% predicted], hepatic [DB ≤1.5xULN, AST/ALT ≤3xULN] and renal function [GFR≥60 mL/min/1.73 m^2] and Karnofsky PS ≥70%. 5. Prior autologous hematopoietic cell transplant (s) allowed
EXCLUSION CRITERIA:	1. Progressive disease 2. Active central nervous system involvement by malignancy 3. Active or uncontrolled infection 4. Life expectancy <6 months 5. Serious cardiac conditions: congestive heart failure NYHA class III and IV, uncontrolled or persistent atrial fibrillation/flutter, history of ventricular fibrillation, ventricular tachycardia/torsade de pointes or myocardial infarction within the last 6 months 6. HIV-1/HIV-2 or HTLV-1/HTLV-2 seropositivity 7. Active hepatitis A, B or C infection 8. History of pulmonary hypertension
PROCEDURES:	Allogeneic hematopoietic cell transplantation using standard fludarabine-based conditioning regimen and tacrolimus/methotrexate graft-versus-host disease [GVHD] prophylaxis
STUDY TREATMENT:	Adding Carfilzomib to the above regimen on day +1, +2, +6, +7.
PRIMARY ENDPOINT	Event-free survival at 1 year [Event is defined as relapse/progression or grade III-IV acute GVHD or chronic GVHD requiring systemic treatment]
SECONDARY ENDPOINTS:	Progression/Relapse-free survival [PFS/RFS], overall survival [OS], regimen-related toxicity (RRT), graft failure, treatment-related mortality (TRM), acute GVHD and chronic GVHD Molecular Correlates: PD [proteasome inhibition], GVHD,cytokines
STATISTICAL METHODS:	Dose finding: a 3+3 dose escalation method Chi-square test [categorical variables], t-test [continuous variables] Kaplan-Meier model [Survival], Cox-Regression, Competing-Risk Regression

TREATMENT SCHEMA

Subjects will be admitted to in-patient BMT unit and receive a standard fludarabine-based conditioning regimen,,followed by an allo-HCT, with the addition of carfilzomib per the schema:



Carfilzomib will be administered starting at dose level 1 (20 mg/m^2 IV) on Day +1, +2, +6 and +7, based on the phase 1/2 carfilzomib studies and the previous Dana Farber phase 1 safety experience on the addition of a proteasome inhibitor into a fludarabine-based conditioning regimen.

Dexamethasone 4 mg will be administered IV prior to each dose of 20 or 27 mg/m^2 carfilzomib.
Dexamethasone 8 mg will be administered IV prior to each dose of 36 or 45 mg/m^2 carfilzomib.

Dose escalation of the phase 1 part will follow the standard 3+3 model.

Dose Level	Carfilzomib (mg/m^2)			
	Day +1	Day +2	Day +6	Day +7
1	20	20	20	20
2	20	20	27	27
3	20	20	36	36
4	20	20	45	45

Standard BMT Procedure

Fludarabine and Busulfan [FluBu2 or FluBu4]

Fludarabine 40 mg/m^2/day IV x 4 on day -5 to day -2
Busulfan 3.2 mg/kg/day IV x 2 on day -5 to day -4 [FluBu2] or
Busulfan 3.2 mg/kg/day IV x 4 on day -5 to day -2 [FluBu4

Fludarabine and Melphalan (FluMel140 or FluMel180)

Fludarabine 30 mg/m^2/day IV x 4 on day -5 to day -2
Melphalan 140 mg/m^2 IV x 1 on day -1 [FluMel140] or
Melphalan 180 mg/m^2 IV x 1 on day -1 [FluMel180]

Fludarabine, Cyclophosphamide, Rituximab (FCR)

Rituximab 375 mg/m^2/day IV x 4 on days -13, -6, +1 and +8
Fludarabine 30 mg/m^2/day IV x 3 on day -5 to day -3
Cyclophosphamide 750 mg/m^2/day IV x 3 on day -5 to day -3

Low-dose total body irradiation (TBI) at 200 cGy x 1 or anti-thymocyte globulin/thymoglobulin may be used in transplants using a 7/8 HLA matched donor per institutional guidelines.
Ritumximab may be used in patients with CD20$^+$ B cell malignancies per institutional guidelines.

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1. INTRODUCTION

1.1 ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

1.1.1 Allogeneic Hematopoietic Cell Transplant for Hematologic Malignancies

Chemotherapy and novel targeted agents have a curative potential for patients with standard and low-risk hematologic malignancies. However, high-risk and advanced relapsed/refractory diseases remain incurable with these modalities. Few effective therapies exist for patients with high-risk disease. Since immune tolerance to cancer plays a major role in cancer pathogenesis, allogeneic hematopoietic cell transplantation (allo-HCT), which is considered the most potent immunotherapy via the graft-versus-tumor (GVT) effect, is the only treatment option with a curative potential or the one which may provide a prolonged progression-free survival.[1-6]

The major obstacles for the success of allo-HCT are graft-versus-host disease (GVHD) and relapse. Myeloablative HCT was first explored >30 years ago but its use resulted in a very high early transplant-related mortality (TRM) from direct regimen-related toxicities (RRT) and severe acute graft- versus-host disease (aGVHD).[7-11] The attempts to improve transplant outcomes and to expand this option to ineligible elderly population and to those with comorbidities with the development of reduced-intensity HCT resulted in an increase in relapse, despite a decrease in TRM and regimen- related toxicity, and thus there was no improvement in overall outcome.[12-16] Moreover, acute GVHD rates did not decrease but were only delayed in onset.[17]

1.1.2 Acute Graft-versus-Host Disease (aGVHD)

Acute GVHD is an allo-immune reaction of donor allo-reactive T-cells against normal host tissues and contributes significantly to post-transplant morbidity and mortality [18,19]. It remains a major obstacle of success for both myeloablative and reduced-intensity HCTs, with cumulative incidences [CI] of 40- 50% for grade II-IV and 10-20% for severe grade III-IV aGVHD in related donor HCTs. The frequency and severity of aGVHD is higher in unrelated donor HCTs, with the CIs of 50-60% for grade II-IV and 20% for grade III-IV aGVHD.[20-27] In addition to the increased risk of serious life-threatening infections from the use of systemic high-dose steroids and more potent immunosuppressive therapy, most aGVHD therapies do not have differential suppressive effects on GVHD and graft versus tumor (GVT) and thus obviously have a deleterious effect on the latter. Consequently, the risk of primary disease relapse increases. As a result, prevention of severe aGVHD is of critical importance for the success of allo-HCT.

Our University of Michigan experience on allo-HCT using a fludarabine and busulfan conditioning in patients with acute myeloid leukemia (AML) revealed the CIs of grade II-IV and grade III-IV aGVHD of 45% and 10% in the related donor HCT setting, and 50% and 10-15% in the unrelated HCT setting, respectively. [28,29]

1.1.3 Lymphoid Malignancies and Allogeneic Hematopoietic Cell Transplantation (Allo-HCT)

1.1.3.1 Non-Hodgkin's Lymphoma (NHL) and Allo-HCT

NHL is a heterogeneous group of malignancy of the lymphoid organs.[31] It is the seventh leading site of new cancer cases among men and women, accounting for 79,190 new cancer cases and 20,130 cancer-related deaths in 2012.[32] Effective treatments are very limited for primary refractory or advanced chemotherapy-resistant NHLs of any histologic types, and new treatment approaches are needed.[33-40]

In addition to anti-lymphoma effect, myeloablative allo-HCT provides an alloimmune donor T-cell reaction against lymphoma (GVL effect).[41-46] Several studies of myeloablative allo-HCT reported a significantly low relapse rate compared to that with HDT/ASCT.[31,36-57] Unfortunately, this observations occurred at the expense of unacceptably high TRM, particularly GVHD and regimen-

related toxicity, resulting in similar OS to that from HDT/ASCT.[36,58,59] The degree of tissue injury after conditioning regimen correlates the severity of GVHD,[60-62] which has high impact on TRM.[62-64] To decrease TRM and expand eligible candidates for allo-HSCT, reduced-intensity HSCT has been extensively explored during the past 10 years.[61,65-76] Fludarabine is a potent immunosuppressive agent with less toxicity, compared with high-dose cyclophosphamide in myeloablative conditioning, and has replaced the latter in fludarabine-based regimens e.g. fludarabine/Busulfan [22] and fludarabine/Melphalan.[77] However, the relapse rate increased due to the less intensity of the regimen and thus progression-free survival (PFS) and overall survival (OS) did not improve .[31,36-57,58,65-76] .

Allogeneic HSCT for NHLs at University of Michigan

During 1996-2012, we performed 120 (82 myeloablative and 38 fludarabine-based) allo-HCTs on patients with relapsed/refractory or advanced diffuse large B cell NHL, which constituted the majority of lymphoma patients undergoing allo-HCT at University of Michigan. The 3-yearOS and PFS) were 40% and 38 % for myeloablative transplant []Blue] and 18% and 15% only for fludarabine-based transplant [Green][Figure 1], indicating relapse was the major problem after allo-HCT, especially fludarabine-based transplant. These results were consistent with the literature.

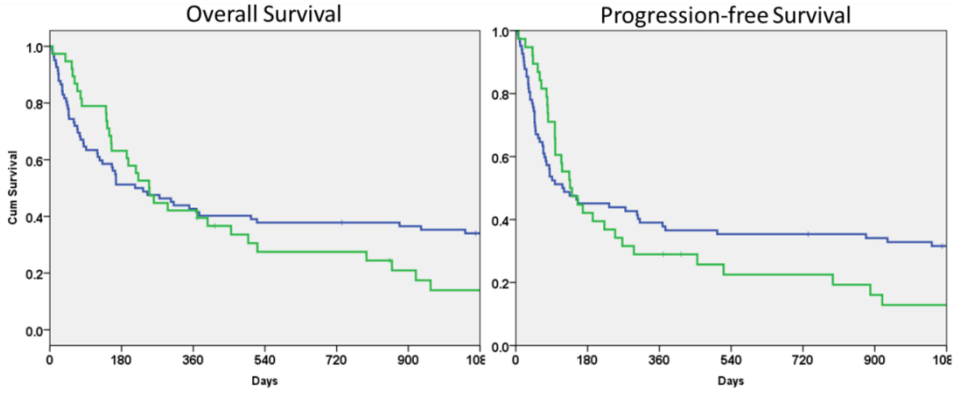


Figure 1: Kaplan-Meier estimates of overall survival and progression free survival for DLBCL patients undergoing myeloablative non-fluadarine-based (n=82; Blue) and fludarabine-based (n=38; Green) allogeneic HCTs at University of Michigan. [unpublished data]

1.1.3.2 Hodgkin's Lymphoma (HL) and Allo-HCT

Approximately 80% of HL patients are cured with standard chemotherapy with/without radiotherapy and those who relapse may still then be salvaged with HDT/ASCT, resulting in durable response in 40-50% of relapsed and 25-40% of primary refractory patients, respectively.[78-81] Unfortunately, very limited effective treatment options are available for patients who relapse after HDT/ASCT. Even though, several series reported the existence of graft-versus-HL effect, outcomes of myeloablative allo-HCT have remained disappointing due to the unacceptable TRM as high as 43-61%.[46,82-87]. Reduced-intensity allo-HCT has been used in patients with relapsed HL after autologous HSCT, but the outcomes are not promising.[76,88-101]. Most series demonstrated the existence of graft-vs HL effect, but still noted high relapse rate and TRM. Novel approach to decrease relapse after allo-HCT is needed to improve outcome of advanced refractory HL in this unfortunate young population.

1.1.3.3 Multiple Myeloma and Allo-HCT

The American Cancer Society has estimated 22,350 new cases of multiple myeloma (MM) in the United States in 2013.[32] MM is a clonal neoplastic proliferation of plasma cells and is considered chronic and incurable, with current novel chemo-biologic targeted agents. In the previous conventional chemotherapy era, the median overall survival was ~4-5 years for average-risk patients while this has been estimated to be much improved to >7 years in the current targeted therapy era.[102-108] However, outcomes of high-risk or advanced MM therapy remains poor, with a median survival only ~8-14 months after therapy.[109-113].

The current standard therapy for MM consists of 3 phases: 1) primary induction therapy 2) consolidative high-dose melphalan/ASCT and 3) post-transplant maintenance therapy.[114] Despite these measures, relapse or progression during maintenance therapy is inevitable. Few effective

treatment options are available for advanced relapsed or refractory MM. In addition, MM with certain cytogenetic abnormalities (t(4;14), t(14;16), (14:20), 17p-, 13- by conventional karyotyping, complex karyptype and hypodiploidy) and plasma cell leukemia are associated with an extremely poor prognosis, with a median survival of 8-14 months post HDT/ASCT.[109-113] Certain novel targeted agents e.g. bortezomib have been shown to overcome resistance of some types of high-risk MMs [115,116] but none is proven to be curative or to provide meaningful long-term MM control.

The use of myeloablative allo-HCT for advanced MM resulted in very high early TRM up to 50% in the first 6 months post transplant.[117] However, those who had survived subsequently enjoyed a sustained long-term MM control and likely a cure of MM. Attempts have been made to reduce TRM by the use of reduced-intensity allo-HCT; however, the success was at the expense of increasing MM relapse, thus resulting in no improvement of overall outcomes.[6,118-120]. To improve MM control, HDT/ASCT was incorporated prior to reduced-intensity allo-HCT (tandem auto-allo HCTs). As expected, auto-allo transplant patients experienced increased TRM but a trend towards a better MM control and no definite improvement in the overall survival.[5,121-123]

University of Michigan (UM) experience on allo-HCT for high-risk MMs

Between 2008-2011, UM BMT program enrolled 22 patients with high-risk or advanced MM on a phase 2 study using the fluadarabine and busulfan x 4 (FluBu4).[30] TRMs were very low (19% at 1 year), with similar rates of GVHD, compared with those reported in the literature.[6,118-120] However, relapse rates remained high. There was no improvement in OS [40% 3-year OS and 5% 3-year PFS;, Figure 2], similar to those reported in the literature.[6,118-120]

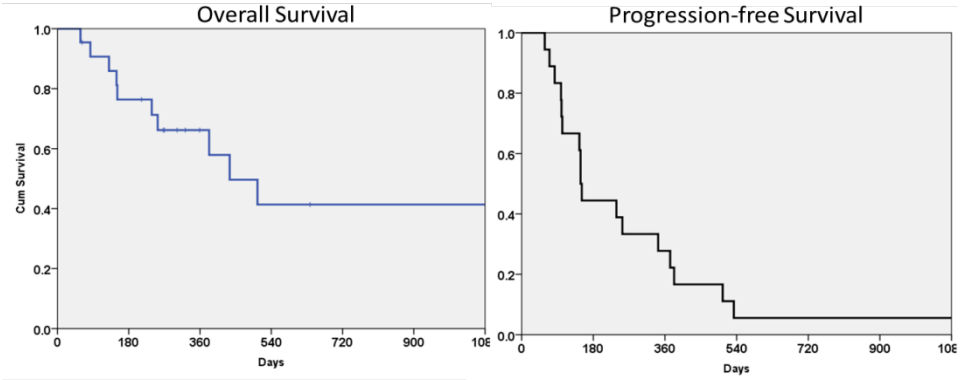


Figure 2: Kaplan-Meier estimates of overall survival and progression free survival for high-risk multiple myeloma patients undergoing fluadarbine-basd allo-HCTs at University of Michigan [30]

1.1.4 Myeloid Malignancies and Allo-HCT

Myeloid malignancies constitute the majority of hematologic diseases requiring HCT due to the strong evidence of potent graft-versus-tumor effect.[8] In addition, as in the case of lymphoid malignancies, allo-HCT is the only treatment option, which may offer a curative potential or long-term survival for patients with high-risk or advanced relapsed/refractory myeloid malignancies. [1,7-11] One-year relapse-free survival in elderly patients with very high-risk AML at UM was ~50% only.[28,29]

1.2 PROTEASOME

The proteasome-ubiquitin system is a multi-catalytic proteinase complex that is responsible for degradation of a wide variety of protein substrates within normal and transformed cells. Intracellular proteins targeted for degradation by the proteasome are first ubiquitinated via the ubiquitin conjugation system. Ubiquitinated proteins are cleaved within the proteasome by one or more of three separate threonine protease activities: a chymotrypsin-like activity, a trypsin-like activity, and a caspase-like activity.[124-128] Proteasome activity has an important a role in promoting constitutional activation of survival pathways in some cancer cells. In the NF-κB transcription factor pathway, this effect is mediated by 1) the degradation of the inhibitory chaperone IκB, thus releasing the active p50/p65 hetero-dimer, in the classic pathway or 2) the degradation of the inactive substrates precursor p100 and p105 into the active p50 and p52, respectively, in the alternative pathway. The resultant transcription homo- and hetero-dimers translocate into nucleus where they bind to NF-κB binding sites of the target genes.

Proteasome inhibition leads to the accumulation of inhibitory IκB within MM cells with relatively increased constitutive NF-κB transciption factor expression, resulting in the selective induction of apoptosis in MM cells, while sparing most normal cells. The down-regulation of NF-κB transcription factors inhibits interleukin-6 (IL-6) production and causes direct apoptosis of MM cells. In addition, this leads to an indirect anti-angiogenesis effect, contributing to anti-tumor activity.[126-128]

In addition to its important role in tumor survival, NF-κB transcription factor system is pivotal in T cell function.[129-132] NF-κB pathway expression is increased in activated T cells, compared with the resting counterparts. The activation through T-cell receptor/CD3/co-stmulating molecules results in translocation of NF-κB transcription factor complex into nucleus, leading to increased Th_1 and Th_{17} cytokine signaling and T-cell activation and proliferation.[131-132] Moreover, the activated NF-κB pathway promotes antigen-presenting dendritic cell function - antigen uptake through phagocytosis and the response to activating cytokines.[133-134] Lastly, proteasome activity is important in maintaining activated B cell survival. BIM, which induces apoptosis of activated B cells, is degraded by proteasome. Thus, proteasome inhibition results in increased level of BIM and shortened survival of activated B cells.[135]

1.3 PROTEASOME INHIBITORS

Bortzomib is a first-generation dipeptide boronic acid which reversibly inhibits the chymotrypsin-like (CT-L) activity of the 20s proteasomes of the ubiquitin-proteasome pathway. Bortezomib has anti-tumor activity in pre-clinical and clinical settings in various hematologic malignancies especially lymphoid cancers.[136-143] Bortezomib is currently used in the therapy for MM, with a potential superior activity to other targeted agents for high-risk refractory disease.

In addition, a few series reported the safety of its use after allogeneic HCT as either maintenance or salvage therapy for relapse.[144-147] Unlike lenalidomide, which was found to increase GVHD, the use of bortezomib post-allo-HCT did not appear to do so. Interestingly, some patients with a baseline severe refractory chronic GVHD improved or resolved with bortezomib therapy. This indicated that bortezomib might have immunomodulatory property, in addition to anti-tumor effect.[147]

Bortezomib also has anti-tumor activity in other lymphoid malignancies, especially mantle cell lymphoma,[148-154] and myeloid malignancies.[155-161] It has been used in combination with other chemotherapeutic and/or immuno-biologic agents in phase 2 and 3 trials.[149-153, 156-158] More importantly, it has been also incorporated into high-dose melphalan conditioning chemotherapy in various fashions.[162-165] These were feasible, without excess toxicities or effects on engraftment or other transplant-related events. However, no clear clinical benefits were seen in this approach.

A phase 1 study by Massachusette General Hospital of the addition of bortezomib to a standard 3+7 induction regimen, idarubicin and cytarabine in 31 patients with very high-risk myeloid malignancies (22 patients older than 60 years, 8 had therapy-related or secondary AML/MDS). Bortezomib was dosed as standard full cycle scheduling on day1, 4, 8 and 11.[160] The MTD was 1.5 mg/m^2, which was higher than 1.3 mg /m^2 standard dose for lymphoid malignancies in chronic therapy. The CR and CRi rates were 61% and 10%, respectively in this high-risk population.

1.3.1 Proteasome Inhibitors and Their Immunomodulatory Effect

The NF-κB transcription factor system is pivotal in activated T cell function. Activation of membrane receptors leads to cytoplasmic proteasome degradation of the inhibiting chaperone, IκB [classical pathway] or the precursor NF-κB transcription factors into active NF-κB transcription dimmers [alternative pathway]. Activated NF-κB transcription dimers subsequently translocate into nucleus where they bind to NF-κB binding sites and initiate target gene transcription.[129-132] NF-κB pathway expression is increased in activated T cells, compared with the resting counterparts. The activation through T-cell receptor/CD3/co-stmulating molecules results in translocation of NF-κB transcription factor complex into nucleus, leading to increased Th1 cytokine signaling and T-cell activation and proliferation.[130-132] Moreover, the activated NF-κB pathway promotes antigen-presenting dendritic cell function- antigen uptake through phagocytosis and the response to activating cytokines. [133-134]

Bortezomib has been shown to inhibit T cell and dendritic cell functions via abrogating NF-κB mediating transcription pathway by inhibition of proteasome degredation. In addition, the inhibition of IL-6 production promotes TGF-β induced regulatory T cell (T_{reg}) differentiation.[131] Of note,T_{reg} plays a pivotal role in modulating GVHD.[60]

Based on the above, bortezomib appears to have immunomodulatory effect toward abrogation of activated alloreactive T-cell and dendritic function, which plays a pivotal role in pathogenesis of aGVHD. In addition, bortezomib has been shown to inhibit alloreactive B cells through the stimulation of Bim, which triggers B-cell apoptosis. Bim signaling is up-regulated in activated B lymphocytes and is degraded by proteasome. Moreover, Bim is down-regulated by BAFF, which, in turn, promotes B- cell survival and maturation. High BAFF level was detected in patients with chronic GVHD. [135]

1.3.2 Proteasome Inhibitor Use After Allo-HCT

Unlike lenalidomide, the use of bortezomib post-allo-HCT did not increase GVHD. Some cases with baseline severe refractory chronic GVHD improved with bortezomib therapy. This was likely due to its immunomodulatory effect through promoting Treg proliferation and differentiation and inhibition of allo-reactive antigen presenting dendritic cells and B-cells as stated above.[130-135]

1.3.3 Proteasome Inhibitor and GVHD Prophylaxis

Based on its immuno-modulatory property against alloreactive T cell and dendritic cells, bortezomib was tested in a mouse model for GVHD prevention.[166-167] Bortezomib was administered daily from day 0-3 and was able to protect severe acute GVHD in a fully-H2 mismatched HCTs, without impairing engraftment. For a less severe mismatched setting, it protected 100% of mice against GVHD while preserving graft-versus-tumor effect. However, when bortezomib was given in a later period (day 12-14), it increased mortality from severe gastrointestinal (GI) GVHD in mice.[167]

Based on this very promising pre-clinical data, Dana Faber Cancer Institute group conducted a phase 1/2 study of bortezomib GVHD prophylaxis in a very high-risk patient cohort for developing severe GVHD.[168] All the 45 patients with advanced hematologic malignancies received a 1 or 2 HLA-mismatched unrelated transplant with a standard reduced-intensity fludarabine/busualfan conditioning and tacrolimus/methotrexate GVHD prophylaxis. The phase 1 part identified the same standard dose of bortezomib for primary MM therapy, 1.3 mg/m^2, given at day 1, 4 and 7, as the optimal dose level. This was the dose used in the standard schedule [Day 1, 4, 8, 11 of a 3- or 4-week cycle) in chronic therapy. The day-11 dose was omitted due to the preclinical data showing increased GI GVHD mortality with delay administration in a mouse model. The tacrolimus, methotrexate and bortezomib GVHD prophylaxis was well-tolerated, with no grade 3/4 toxicities attributed to bortezomib. The median (range) neutrophil and platelet engraftment time were 13 (6-29) and 20 (13-27) days, respectively. The engraftment was robust, with day-30 and day-100 donor chimerism of 97% and 99%. With the median follow-up time of 36 months, cumulative grade II-III and grade III acute GVHD were 22% and 7% respectively. Of note, there were no grade IV GVHDs occurring and the 1-year cumulative incidence of chronic GVHD was 29% only, resulting in a TRM of 9% only in this cohort receiving a very high–risk mismatched unrelated transplant. The 1-year PFS and OS were impressive at 60% and 76% respectively. In summary, the addition of the proteasome inhibitor bortezomib to standard GVHD prophylaxis regimen was safe and feasible, with unexpectedly impressive low rates of GVHD and TRM.

1.4 CARFILZOMIB

Carfilzomib (PR-171) is a tetrapeptide ketoepoxide-based inhibitor specific for the chymotrypsin-like active site of the 20S proteasome. Carfilzomib is structurally and mechanistically distinct from the dipeptide boronic acid proteasome inhibitor bortezomib. When measured against a broad panel of proteases including metallo, aspartyl, and serine proteases, carfilzomib demonstrated less reactivity against non-targeted non-proteasomal proteases when compared to bortezomib.[169-174]

1.4.1 Carfilzomib Preclinical Antitumor Activity

Based upon the results of in vitro and in vivo studies, it is anticipated that the more intense and longer duration of proteasome inhibition that can be achieved with carfilzomib will result in enhanced anti- tumor activity relative to bortezomib. Continuous 72-hour exposure to carfilzomib is associated with potent cytotoxic and pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture.[169,170,175] Incubation of hematologic tumor cell lines with carfilzomib for as little as one hour leads to rapid inhibition of proteasome activity followed by accumulation of polyubiquitinated proteins and induction of apoptotic cell death. Carfilzomib has also been demonstrated to be cytotoxic in bortezomib-resistant tumor cell lines.[169,170,175]

The anti-tumor efficacy of carfilzomib has been tested in immunocompromised mice implanted with various tumor cell lines. In addition to MM,[175] carfilzomib has been shown to have anti-tumor activity against other hematologic malignancies.[176,177] It is synergistic with histone deacetylase inhibitors in tumor killings.[178,179]

1.4.2 Carfilzomib Toxicology Studies

In the initial Good Laboratory Practice (GLP)-compliant toxicity studies, carfilzomib was tested in rats and monkeys as two two-week cycles of QDx5 days.[180]. When administered to rats at 12 mg/m2, the severely toxic dose in 10% of animals (STD_{10}), caused > 90% proteasome inhibition in red blood cells one hour after dosing. Overall, stronger inhibition of the proteasome and longer duration of inhibition was tolerated with carfilzomib compared with bortezomibA dose-dependent decrease in proteasome activity was demonstrated in animals, and equivalent levels of proteasome inhibition were achieved with administration of carfilzomib as either an IV push or an IV infusion. The DLTs of carfilzomib in both the rat and monkey 28 day GLP toxicity studies included toxicity to the GI tract, bone marrow, pulmonary, and cardiovascular systems. No behavioral or histopathological signs of neurotoxicity were observed, and carfilzomib does not cross the blood-brain barrier.

In chronic toxicity studies, carfilzomib was administered on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle, mimicking the active anti-tumor regimen being used in ongoing Phase II studies in myeloma and solid tumors [3]. Tolerability was excellent, with no evidence of neurotoxicity, observed even at high doses. This is in stark contrast to that observed with bortezomib.[181,182] DLTs included effects on the GI, renal, pulmonary, and cardiovascular systems and appeared to related to Cmax effects. Of note, neutropenia was not observed; rather, transient neutrophilia was seen following acute dosing. Renal, cardiovascular and GI toxicities were similar to those observed with bortezomib. Finally, cyclical thrombocytopenia, likely due to inhibition of platelet budding from megakaryocytes, was similar to that seen with bortezomib. Proteasome inhibition in the blood in excess of 90% was achievable at well-tolerated doses, which contrasts with the ~70% proteasome inhibition achieveable with bortezomib at its maximum tolerated dose (MTD). In summary, these animal toxicity studies support the tolerability of carfilzomib in clinical studies, even on intensive dosing schedules and at doses achieving proteasome inhibition in excess of what can be achieve with bortezomib at its MTD on a less intensive schedule.

1.4.3 Phase 1 Experience with Carfilzomib As A Monotherapy

In the Phase 1 PX-171-002 study testing carfilzomib in subjects with relapsed/refractory hematologic malignancies,[183,184]36 subjects received carfilzomib on Days 1, 2, 8, 9, 15, and 16 of a 28-day

cycle. Subjects with advanced MM, NHL, Waldenström's macroglobulinemia, and Hodgkin's Lymphoma (HL) were enrolled on the study.

No dose limiting toxicities (DLTs) were observed in the initial 7 cohorts (1.2 to 15 mg/m2). At the 20 mg/m2 dose level, 1/8 patients had a Grade 3 renal failure at Cycle 1, Day 2 which was considered possibly related to study drug and lasted for six days. The patient continued on study for the remainder of Cycle 1 before having disease progression. At the 27 mg/m2 dose level, 1/6 subjects experienced a DLT during Cycle 1, consisting of severe hypoxia with pulmonary infiltrates following Day 2 of dosing. In subjects where the 27 mg/m2 dose was efficacious, a "first dose effect" was seen that included a constellation of findings that appeared to be the clinical sequelae of tumor lysis syndrome (TLS) and/or cytokine release. This effect was notable for fever, chills, and/or rigors occurring during the evening following the first day of infusion. On the second day, 3/5 subjectsexperienced an increase in serum creatinine to Grade 2 (including the subject with the DLT). This elevation was rapidly reversible and all 3 subjects were re-challenged with carfilzomib without recurrence of the events. Interestingly, all three subjects had a rapid decline in serum and/or urine M- protein levels; two subjects achieved a PR and the third subject achieved a minimal response (MR). There were no consistent changes in potassium, calcium, phosphorous, or uric acid levels although some increases in LDH and other markers of tumor lysis were noted. Because of the possible TLS and reversible creatinine elevations, hydration and very-low dose dexamethasone prophylaxis were instituted in subsequent studies and have essentially eliminated clinically significant TLS/creatinine elevations and the other "first-dose" effects. Hematologic toxicities were primarily mild or moderate. The thrombocytopenia reported with carfilzomib is cyclical and similar to that reported with bortezomib.

Of the 36 evaluable patients enrolled in PX-171-002, 20 subjects had MM.[183,184] Four MM patients achieved a partial response (PR), 1/2 at the 15 mg/m2 dose, 1/6 at the 20 mg/m2 dose, and 2/5 at the 27 mg/m2 dose. The responses have been rapid in onset, beginning in some subjects after 1-2 doses. The duration of response (DOR) ranged from 134 to 392 days. The minimal effective dose was 15 mg/m2 wherein >80% proteasome inhibition in peripheral blood mononuclear cells [PBMCs] was observed one hour after dosing. At 27 mg/m2, ~90% inhibition of proteasome activity was achieved in PBMCs.[184] The median number of prior therapies for subjects on this trial was 5, and responses were seen in subjects who had relapsed from (including some refractory to) bortezomib and/or immunomodulatory agents. Stable disease also occurred in four NHL and five MM subjects, with subjects on therapy for up to 409 days. Such prolonged therapy, at "full" twice-weekly doses, is not possible with bortezomib. These results led to the initiation of two Phase 2 studies.

Another phase 1 study of carfilzomib in 29 patients with advanced lymphoid malignancies [MM, WM, NHL and HD] who received a more intensive schedule of carfilzomib IV push at doses of 1.2, 2.4, 4, 6, 8.4, 11, 15 and 20 mg/m2 for 5 consecutive days of a 14-day cycle until unacceptable toxicities or progressive disease [median=4.8 cycles (range, <1-16)] determined that the 15 mg/m2 dose level was the MTD.[17] Despite intensive scheduling, severe AEs were infrequent. Common (>20%) grade 3/4 non-hematologic treatment-emergent AEs were essentially absent [grade 3/4 dyspnea=6% and grade 3/4 fatigue=3%]. Grade 3/4 hematologic AEs were also rare, including thrombocytopenia (7%), anemia, febrile neutropenia and neutropenia (3% each). Proteasome inhibition of >75% was detected in WB and PBMCs after a single dose of carfilzomib at dose levels of 15 mg/m2 or higher. The inhibition was increased to >90% after the fifth consecutive day dosing due to accumulative effect with repeating dosing. Anti-tumor activity was observed at doses >11 mg/m2.[17]

1.4.4 Phase 2 Experience With Carfilzomib As A Monotherapy

Two phase 2 clinical studies were conducted with carfilzomib in MM patients, PX-171-003-A0 [186,187](N=46) in relapsed/ refractory MM and PX-171-004 (N=39) in relapsed MM.[188-190] In both studies, patients were dosed with 20 mg/m2 on Days 1, 2, 8, 9, 15, and 16 on a 28 day schedule. In these studies there were four cases of suspected or documented TLS prior to institution of the

prophylaxis guidelines. Since these guidelines were implemented, no further cases of TLS have been reported including in >350 additional patients with relapsed or refractory MM treated in other phase II studies. In both studies, the most common adverse events were fatigue, anemia, thrombocytopenia (primarily cyclical), gastrointestinal, and dyspnea. Almost all were Grades 1 or 2. There were reported cases of increased in serum creatinine that were primarily < Grade 2 and were transient, rapidly reversible, and non-cumulative. A very low rate of severe treatment-emergent peripheral neuropathy, 1 case (2.2%) with pre-existing Grade 2 neuropathy progressing to Grade 3, was observed in PX-171-003-A0 despite the fact that 87% of patients had Grade 1/2 neuropathy upon study entry.[186,187]

The response rate in PX-171-003-A0 was 16.7% PR, 7% MR and 41% SD in these patients that entered the study with progressive disease and were refractory to their most recent therapy, often including bortezomib (100%), lenalidomide (91%) and thalidomide (91%). The best overall response rate was 16.7% (95% CI, 7.0-31.4) months, with the duration of response (DOR) of 7.2 (CI, 1.9-not estimated) months. The clinical benefit response rate was 23.8% (95% CI, 12.1-39.5) months, with the DOR of 13.8 (95% CI, 4.8-16.6) months. The median time to progression on the PX-171-003-A0 study was 3.5 (95% CI, 2.4-6.7) months (mean follow up of 7.6 months).[186,187]

A “stepped up” dosing schedule, referred to as 20/27 mg/m2, has subsequently been incorporated into the PX-171-003 study (referred to as PX-171-003-A1) in order to maximize the clinical benefit of carfilzomib. Patients receive 20 mg/m2 for the first cycle and 27 mg/m2 thereafter. The study completed enrollment of 266 patients by the end of 2009 and may form the basis for an accelerated approval NDA filing by the end of 2010. This dosing schedule has been well tolerated.[183,184] An independent Safety Oversight Group (SOG) evaluated the safety data from the 40 of 250 patients to be enrolled on the 20/27 schedule and agreed that the trial should proceed without modification. No cases of TLS were observed and rates of BUN and creatinine elevation dropped sharply, with Grade 3/4 renal impairment dropping to 3.4% in A1 (from 15% in A0), most likely due to hydration and very low dose dexamethasone. The other most common adverse events were similar to the A0 portion of the study. Treatment-emergent peripheral neuropathy remains low on this portion of the study with 12.4% new onset or worsening of pre-exisiting Grade 1/2 peripheral neuropathy (77% had pre- exisitng Grade 1/2 peripheral neuropathy) and 1.1% Grade 3 event reported on PX-171-003- A1.[186,187] In addition, anemia rates in the PX-171-003-A1 (higher dose) were lower than those reported in the PX-171-003–A0 portion of the study, possibly indicating that the higher dose of carfilzomib is achieving better clearing of neoplastic cells in the bone marrow allowing superior normal marrow reconstitution. Grade 3/4 thromobocytopenia rate was 29% and grade 3/4 neutropenia rate was 11%.[186,187]

In PX-171-004, a first cohort of patients received 20 mg/m2. The subset of patients (N=54) that had not seen bortezomib had an ORR of 46% (2% CR, 9% VGPR and 35% PR), while the bortezomib treated patients (N=33) had an ORR of 18% (3% CR, 3% VGPR and 12% PR). [188,189] The median TTP was 7.6 and 5.3 months in these two groups, respectively. Thus, carfilzomib can induce very high levels of response in patients who have not previously been treated with bortezomib[190] and, even in bortezomib-treated patients,[191] substantial anti-tumor activity is observed. Of note, disease control (PR + MR + SD) was achieved in ~65% of patients with progressive MM entering the study. Patients on these studies have been treated for >12 cycles with good tolerability and no cumulative toxicity (e.g., bone marrow, severe fatigue, or neuropathy) have not been observed.

In these phase 2 studies, prolonged carfilzomib exposure at higher doses was associated with low incidence of new onset severe peripheral neuropathy or worsening of pre-existing peripheral neuropathy.[192,193] Carfilzomib was found to be safe in MM patients with renal insufficiency, including those requiring hemodialysis.[194] In addtion, pooled safety data from phase 1/2 and phase 2 studies of single agent carfilzomib confirmed safety and low rates of grade 3/4 treatment-emergent AEs [195-197].

Lastly, unfavorable cytogenetic characteristics in MM patients had no impact on response to carfilzomib.[198-200]

1.4.5 Experience With Carfilzomib In Combination With Lenalidomide [201-203]

PX-171-006 is a phase 1b study in patients with relapsed MM in which carfilzomib is administered in combination with lenalidomide (Revlimid®) and dexamethasone.[201,202]

Patients with MM who relapsed after 1 to 3 prior regimens enrolled into dose-escalation cohorts. CRd was administered on 28-day dosing cycles: carfilzomib 15 to 27 mg/m2 on days 1, 2, 8, 9, 15, and 16; Lenalidomide 10 to 25 mg on days 1 to 21; and dexamethasone 40 mg weekly.[201,202]

The maximum per protocol doses of carfilzomib (27mg/m2) with lenalidomide 25 mg and low dose dexamethasone were used. After 8 patients tolerated these doses well, an additional 44 patients were enrolled in an "expansion" cohort at this level, and this regimen is being taken into Phase 3 study PX- 171-009.

Forty patients enrolled in 6 cohorts.[201,202] Prior treatment included bortezomib (75%) and lenalidomide (70%); 20% and 36% were refractory overall. The MTD was not identified, and the highest dose combination tested was recommended for the phase II study. The most common toxicities of any grade were fatigue (62.5%), neutropenia (55.5%), and diarrhea (52.5%). Grade 3/4 toxicities included neutropenia (42.5%), thrombocytopenia (32.5%), and lymphopenia (27.5%), with no grade 3/4 neuropathy reported. Proteasome inhibition 1-hour after dose was more than 80% in cycles 1 and 2. The overall response rate was 62.5%, the clinical benefit response rate was 75.0%, and the median duration of response and PFS were 11.8 and 10.2 months, respectively. Importantly, lenalidomide-associated neutropenia and thrombocytopenia did not appear to be exacerbated by concurrent treatment with carfilzomib, even up to 27mg/m^2.

The phase 2 dose expansion at the maximum planned dose (MPD), focusing on the 52 patients enrolled in the MPD cohort.[203] Median follow-up was 24.4 months. In the MPD cohort, overall response rate (ORR) was 76.9% with median time to response of 0.95 month (range 0.5-4.6) and duration of response (DOR) of 22.1 months. Median progression-free survival was 15.4 months. ORR was 69.2% in bortezomib-refractory patients and 69.6% in lenalidomide-refractory patients with median DOR of 22.1 and 10.8 months, respectively. A median of 9.5 (range 1-45) carfilzomib cycles were started with 7.7% of patients requiring carfilzomib dose reductions and 19.2% discontinuing CRd due to adverse events (AEs). Grade 3/4 AEs included lymphopenia (48.1%), neutropenia (32.7%), thrombocytopenia (19.2%), and anemia (19.2%). CRd at the MPD was well tolerated with robust, rapid, and durable responses.

1.4.6 Experience With Carfilzomib In Combination with Chemotherapy

Carfilzomib has recently been shown to be safe and effective for the use in combination with conventional chemotherapy, including cyclophosphamide, melphalan and rituximab.[204-207]

Reeder *et al* [204] conducted a phase I/II trial of a combination of Cyclophosphamide, Carfilzomib, Thalidomide and Dexamethasone (CYCLONE) in patients with newly-diagnosed MM. [carfilzomib IV Days 1,2 8,9,15,16, cyclophosphamide 300 mg/m2 PO Days 1,8,15, thalidomide 100 mg PO Days 1-28 and dexamethasone 40 mg PO Days 1, 8, 15, 22. No DLTs were observed in the initial phase I/II regimen, with patients nearly fully accrued to the Phase 2 at 27mg/m2 and expansion MTD (36mg/m2). Ninety percent completed at least 4 cycles. Grade 3/4 toxicities occurring in >5% were uncommon (hypertension (8%), thromboembolic event (6%) and hyperglycemia (6%). There were no cardiac events seen in greater than 5% of patients. All patients advancing to ASCT successfully collected stem cells. The 1-year PFS was 90% and 1-year OS was 98%. Thus, the 4 drug CYCLONE regimen is highly efficacious at the dosing level of carfilzomib IV 20/27-36 mg/m^2 in newly diagnosed myeloma.

Toxicities are manageable, with minimal cardiac or pulmonary toxicity.

A Phase 2 Study with prolonged administration of Carfilzomib, Cyclophosphamide and Dexamethasone (CCd) for newly-diagnosed elderly MM (median age 71 years; 28% of patients >75 years).[205] The regimen included oral cyclophosphamide (300 mg/m2 on days 1,8,15), oral dexamethasone (40 mg on days 1, 8, 15, 22) and IV carfilzomib (20 mg/m2 on days 1, 2, and 36 mg/m2 on days 8, 9, 15, 16, cycle 1; 36 mg/m2 on days 1, 2, 8, 9, 15, 16, cycles 2-9) every 28 days for 9 cycles, followed by maintenance with IV carfilzomib (36 mg/m2 on days 1, 2, 15, 16) every 28 days until progression or intolerance. After 9 induction cycles, 96% of patients achieved at least PR, 76% VGPR, 64% CR/nCR, including 24% sCR. The 1-year PFS was 86% and the 1-year OS was 87%. G3/4 non-hematologic AEs were infections (7%), cardiac (5%), constitutional (4%), renal (4%) and GI complications (2%). Overall, the CCd regimen was well tolerated. After a median duration of maintenance of 6 months, the PR rate was 100%, including 68% CR/nCR. The most frequent toxicity (all grades) during maintenance was fever (G1/2 in 24%, G3 in 8%), not associated with chills, rigors, dyspnea and/or creatinine increase. There was only 1 (4%) G3 neutropenia. Thus, The CCd regimen is highly effective, (>nCR 64% and sCR24). It is well tolerated with limited grade 3-4 AEs.

A phase 1/2 study of a combination of Carfilzomib, Melphalan and Prednisone (CMP) in elderly patients (median age, 72 years) with newly diagnosed MM revealed the safety and efficacy of combined carfilzomib and chemotherapy in the elderly population.[206] Carfilzomib was started at 20mg/m^2, then escalated to 45mg/m^2, in 42-day cycles on D1,2,8,9,22,23,29,30 for 9 cycles. Melphalan 9mg/m^2 and prednisone 60mg/m^2 were given PO D1–4. The phase I part identified an MTD of 36mg/m2 in this combination. In Phase 2 expansion, 44 additional patients received CMP at 36mg/m^2 carfilzomib. CMP was well tolerated. Overall response rate was 89.5% including 56% ≥ very good partial response. The 2-year OS was 87%, and the median EFS was 22 months. Thus, carfilzomib 36mg/m2/melphalan/prednisone regimen is tolerable and effective in elderly patients.

Lastly, carfilzomib was reported to be safe in the use in combination with rituximab and dexamethasone (CaRD) in patients with Waldenstrom's macroglobulinemia.[207]

1.4.7. Experience With Carfilzomib In Combination with High-dose Chemotherapy And Hematopoietic Cell Transplant.

Costa *et al* has conducted a phase 1 study of combination of carfilzomib and standard high-dose melphalan conditioning, followed by autologous blood stem cell transplant in MM patients.[208] Treatment consisted of two doses of carfilzomib administered IV over 30 minutes on days -3 and -2.
The day -2 dose was administered one hour prior to administration of myeloabaltive high-dose melphalan 200 mg/m2. Carfilzomib dose consisted of 20 (day-3)/27 (day -2) mg/m2 (cohort 0), 27/27 mg/m2 (cohort 1), 27/36 mg/m2 (cohort 2), 27/45 mg/m2 (cohort 3) and 27/56 mg/m2 (cohort 4). All subjects received pegfilgrastim 6 mg subcutaneously on day +1. At the time of reporting, enrolment of cohort 4 (27/56 mg/m2) was ongoing. Twelve subjects were accrued in cohorts 0-3 with no DLT being identified. Median age was 56 (range 45-68) years. Median number of prior lines of therapy was 3 (range 2-6) and 5 subjects had previously received HDT/ASCT. There was no acute toxicity associated with carfilzomib infusion. Median CD34+ dose infused was 4.15 x 106/kg (range 2.21-9.34). Neutrophil engraftment occurred at a median of 11 days (range 8-15) and platelet engraftment at a median of 17.5 days (range 11-24). There were no non-hematologic grade 4 toxicities. The most frequent grade 3 toxicity was infection in 7/12 subjects consisting of 1 episode of pneumonia, 1 episode of bacteremia, 1 episode of urinary tract infection and 4 episodes of febrile neutropenia. Other grade 3 toxicities were rash (n=2), hypertension (n=1), hypophosphatemia (n=1) and hypocalcemia (n=1). At the time of reporting, nine subjects, from cohorts 0, 1 and 2 reached day +100 response assessment and the cumulative responses were PR in 3/9, VGPR in 3/9 and CR in 3/9 subjects. Pharmacodynamic studies in peripheral blood mononuclear cells revealed that carfilzomib. Thus, transplant conditioning with combined carfilzomib and standard high-dose melphalan is well tolerated, without impaired engraftment.

1.4.8 Dosing Rationale

Preliminary data suggest that carfilzomib as a single agent can produce substantial response rates in myeloma subjects across a variety of dosing cohorts. Responses were seen over a wide therapeutic window, from 15 to 27 mg/m^2. Maximum proteasome inhibition was seen at doses 11 mg/m^2 and higher in whole blood samples taken 1 hour after the first dose. The final analysis of the human pharmacokinetic (PK) data is ongoing but appears to be rapid and similar to the results from the animal studies. Carfilzomib is rapidly cleared from plasma with an elimination half-life of <60 minutes at the 20 mg/m2 dose. Large, single arm studies of the 27 mg/m^2 dose are ongoing and suggest that this dose is very well tolerated with patients being treated for >10 cycles without cumulative toxicities.

In multiple preclinical studies, the tolerability of carfilzomib in rats has been shown to be significantly higher when administered as a 30 min infusion as compared to a rapid IV bolus. Toxicities observed with IV bolus injection of carfilzomib above the MTD at a dose of 48 mg/m^2 include evidence of prerenal azotemia (transient increases in BUN > creatinine) as well as lethargy, piloerection, dyspnea, and gastrointestinal bleeding. Notably, death occurred in ~50% of animals at 48 mg/m^2 when carfilzomib was given as a bolus. Administration of the same dose (48 mg/m^2) as a 30 min continuous infusion was well tolerated, with no changes in BUN and creatinine and substantially reduced signs of lethargy, piloerection, or dyspnea. Moreover, all animals in the infusion treatment groups survived. The only toxicity observed following infusion of carfilzomib for 30 min was gastrointestinal bleeding. The reduced toxicity seen with dosing by infusion may reflect the reduced C_{max} of carfilzomib vs that with bolus dosing. Inhibition of the pharmacological target of carfilzomib (the chymotrypsin-like activity of the proteasome) was equivalent in the bolus and infusion treatment groups.

In the clinic, the MTD of carfilzomib has not been reached in the multiple myeloma (MM) setting, particularly when administered as a 30' infusion. 27mg/m2 of carfilzomib (bolus administration over 2- 10') is well tolerated in MM patients overall and can be tolerated for >12 cycles in late stage MM patients with substantial comorbidities.

A phase 1 dose escalation study (PX-171-007) of single agent carfilzomib administered is ongoing and as of 10 July 2009, over 65 patients with solid tumors had started treatment in the initial Phase 2 portion of the study at 36 mg/m2 (bolus administration over 2-10'). A review of the tolerability of 36 mg/m2 carfilzomib in these patients indicates that this regimen was very well tolerated with only one DLT (fatigue) and an overall adverse event profile similar to that seen with the 27mg/m^2 carfilzomib experience with bolus dosing (see IB for details). Three patients completed >12 cycles of therapy at 36 mg/m2 with no evidence of cumulative toxicity. There were no significant DLTs observed; the majority of discontinuations on the study were due to progressive disease. Because of the long-term tolerability carfilzomib, the Phase 1b portion of this study was reopened, and a separate arm for multiple myeloma was added.

In the PX-171-007 trial, more recently patients have been treated with carfilzomib given as a 30- minute infusion in order to potentially minimize Cmax-related infusion events. The protocol was amended and does of 20/36 (20 mg/m2 given on Days 1 and 2 of cycle 1 only; followed by 36 mg/m2 for all subsequent doses), 20/45, 20/56 mg/m2 and so forth are being investigated. Doses of 20/56 mg/m2 are currently being given in two separate cohorts of patients with advanced MM and advanced solid tumors; the lower doses were well tolerated. Preliminary tolerability information at this dose level (20/56 mg/m2) indicated that it is reasonably well tolerated, with minimal infusion reactions. In some cases at 20/56mg/m2, dexamethasone was increased from 4 mg/dose to 8mg with the 56mg/m2 doses in order to reduce fevers and hypotension. As of March 20, 2010, seven patients have received 20/56mg/m2 and are tolerating it. Patients with advanced, refractory MM being treated at 36mg/m2 and 45mg/m2 have shown very good tolerability (>6 months in some cases) with documented minimal and partial responses in these heavily pretreated patients. These data indicate that carfilzomib 30-minute infusion can be given at very high levels, with >95% inhibition of blood proteasome levels achievable and with (at least) acute tolerability. All protocols using ≥36mg/m2 carfilzomib are now administering the drug as a 30-minute infusion.

In addition to the above observations, a phase I study of carfilzomib in patients with relapsed and refractory multiple myeloma was reported in abstract form at the 2009 American Society of Hematology meeting which demonstrated that carfilzomib can be safely administered to patients with substantial renal impairment (CrCl<30, including patients on dialysis) without dose adjustment.[195].

1.5 STUDY RATIONALE

We are conducting a phase 1/2 study of fludarabine-based allo-HCT with the addition of carfilzomib in patients with hematologic malignancy.

The rationale for this strategy includes:

1. No effective therapies are available for high-risk or advanced relapsed/refractory hematologic malignancies. Current combination chemotherapy, chemo-immunotherapy or chemo-biologic targeted therapies can only provide short-term disease control, with inevitable subsequent relapse and refractoriness.

2. The use of conventional myeloablative allo-HCT resulted in poor outcomes due to high immediate treatment-related mortality (TRM) including regimen-related toxicities (RRT) and acute graft-versus- host disease (aGVHD). The attempts to decrease TRM by use of reduced-intensity conditioning, in turn, have resulted in higher relapse rates, despite decreased TRM, thus there was no improvement in overall outcome. In addition, despite a delay in onset, aGVHD incidence has remained high and has continued to be a major obstacle for transplant success. GVHD therapy with high-dose steroid and more aggressive immunosuppressive agents abrogate graft-versus-tumor effect and increase relapse. At UM, the incidence of grade II-IV aGVHD was ~45% while 1-year PFS was ~20-30% only for high-risk lymphoid malignancies and it was ~50% for high-risk myeloid malignancies, emphasizing the need of measure to decrease relapse and GVHD.

3. Proteasome-ubiquitin degradation system has a pivotal role in maintaining survival signaling in malignant cells. Inhibition of proteasome function results in down-regulation of the NF-κB signaling pathway and selective apoptosis of malignant cells with constitutive over-expression of this pathway. The NF-κB signaling pathway also mediates inflammatory and immune response by promoting activated T and dendritic cell function and survival. In addition, proteasome degradation system, independent of the NF-κB axis, promotes activated B cell survival.

4. Bortezomib, a reversible first-generation proteasome inhibitor, has anti-tumor activity in hematologic malignancies, especially lymphoid diseases. Moreover, it has been shown by Dana Farber group to decrease acute GVHD and relapse in a mouse model and in high-risk HLA- mismatched unrelated allo-HCTs for high-risk hematologic malignancies when incorporated into the conditioning regimen.

5. Carfilzomib, an irreversible and more potent second-generation proteozome inhibitor, has been shown to overcome bortezomib resistance, with significantly less off-target toxicities, especially myelosuppression and neuropathy, compared with bortezomib. Pooled safety data from phase 1 and 1/2 studies reported <20% incidences of grade 3/4 myelosuppression and GI toxicities. In addition, carfilzomib has been used safely when combined with other highly myelosuppressive agents in their full dosage. Lastly, carfilzomib, like bortezomib, may potentially prevent aGVHD through proteasome and non-proteasome mechanisms, while preserving GVL effect.

1.6 HYPOTHESIS

Based on the above rationale, we hypothesize that adding carfilzomib to standard fludarabine-based conditioning regimen for allo-HCT for advanced or high-risk hematologic malignancies will decrease post-transplant relapse and TRM by decreasing severe GVHD, leading to overall improvement in transplant outcomes.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

To determine whether the addition of carfilzomib to fludarabine-based conditioning, followed by allogeneic hematopoietic cell transplant for hematologic malignancies will decrease relapse/progression and severe GVHD.

2.2 SECONDARY OBJECTIVES

To determine the efficacy of this regimen in the improvement of overall transplant outcomes.

2.3 PRIMARY ENDPOINT

Event-free survival at 1 year after transplant.

Event is defined as relapse/progression or grade III-IV acute GVHD or chronic GVHD requiring systemic treatment.

2.4 SECONDARY ENDPOINTS

Progression/Relapse-free survival
Overall survival
Regimen related toxicity (RRT),
Graft failure, Treatment-related mortality (TRM)
Cumulative incidence of acute GVHD
Cumulative incidence of chronic GVHD
Molecular Correlates: Pharmacodymanics: Proteasome inhibition
GVHD cytokines

3. EXPERIMENTAL DESIGN

3.1 Study Design

This study is a phase 1/2 study. The phase 1 part consists of 4 dose levels [Table 2]. Subjects will be enrolled on the first dose level 1, following a standard 3+3 dose escalation rule until the optimal or maximal tolerated dose (MTD) [0/3 or 1/6 subject developing dose-limited toxicities (DLT)] is identified.

The phase 2 part is an extension of the optimal dose level which is identified from the phase 1 part.

3.2 NUMBER OF CENTERS

The University of Michigan only.

3.3 NUMBER OF SUBJECTS

A total of 55 subjects will be accrued.

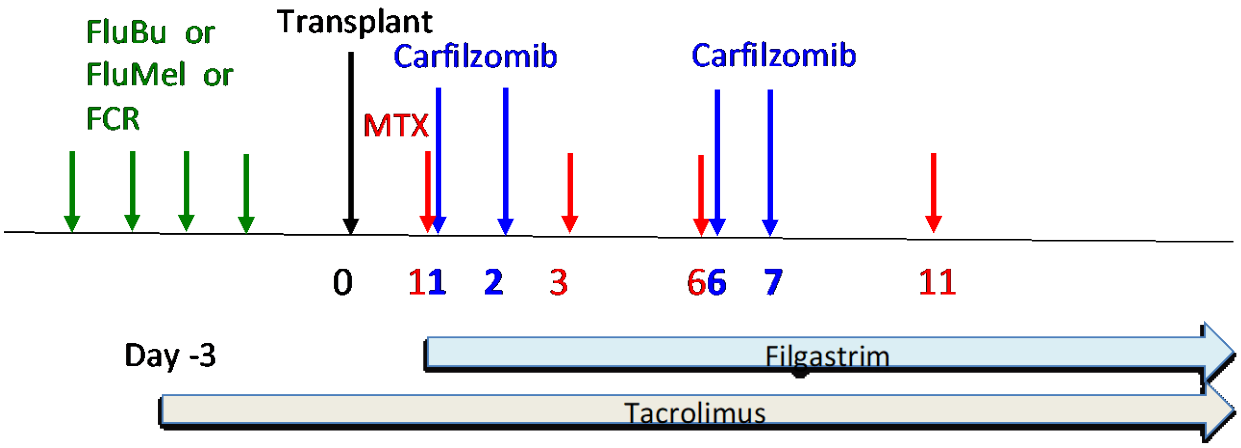
3.4 ESTIMATED STUDY DURATION

2 years of accrual

3.5 TREATMENT PROCEDURE

3.5.1 TRANSPLANT SCHEMA

Subjects will be admitted to in-patient BMT unit and receive a standard fludarabine-based conditioning chemotherapy regimen, followed by an allo-HCT, with the addition of carfilzomib per the schema:



3.5.2 STANDARD CONDITIONING REGIMENS

Either standard FluBu or FluMel regimen will be used, following Institutional Guidelines for blood and marrow transplant (BMT) Procedure.

3.5.2.1 Fludarabine and Busulfan (FluBu2 or FluBu4)

Fludarabine 40 mg/m^2/day IV x 4 on day -5 to day -2

Busulfan 3.2 mg/kg/day IV x 2 on day -5 to day -4 [FluBu2] or
Busulfan 3.2 mg/kg/day IV x 4 on day -5 to day -2 [FluBu4]

Standard anticonvulsant prophylaxis [e.g. Levetiracetam (Keppra®) 1,000 mg PO/IV bid] will be started on day -6 until 24 hours after the last dose of busulfan and busulfan pharmacokinetic study may be performed, following Institutional Guidelines for BMT Procedure for investigational conditioning regimens. Busulfan pharmacokinetic study is recommended for the FluBU4 regimen.

3.5.2.2 Fludarabine and Melphalan (FluMel140 or FluMel180)

Fludarabine 30 mg/m^2/day IV x 4 on day -5 to day -2
Melphalan 140 mg/m^2 IV x 1 on day -1 [FluMel140] or
Melphalan 180 mg/m^2 IV x 1 on day -1 [FluMel180]

3.5.2.3 Fludarabine, Cyclophosphamide and Rituximab (FCR)

Rituximab 375 mg/m^2/day IV x 4 on days -13, -6, +1 and +8
Fludarabine 30 mg/m^2/day IV x 3 on day -5 to day -3
Cyclophosphamide 750 mg/m^2/day IV x 3 on day -5 to day -3

Low-dose total body irradiation (TBI) at 200 cGy x 1 or anti-thymocyte globulin/thymoglobulin may be used for a transplant using a 7/8 HLA matched donor.

3.5.2.4 Other Chemo-immunologic Agent

Ritumximab [Monoclonal anti-CD20, Rituxan®] may be used for CD20+ B cell malignancies [R- FluBu4, R-FluMel180], following Institutional Guidelines for BMT Procedure for B-cell malignancies.

Commercially available fludarabine, busulfan, melphalan, cyclophosphamide and rituximab will be used following standard Institutional Guidelines for BMT Procedure.

3.5.3 HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic cell transplant will occur on day 0. If there are ≥2 days of transplant, day 0 will be adjusted accordingly e.g [day 0a and 0b] for a subject undergoing 2 days of transplant.

3.5.4 GVHD PROPHYLAXIS

A standard combination of tacrolimus (FK506) and low-dose (mini) methotrexate will be used following Institutional Guidelines for BMT Procedure.

- Tacrolimus will be administered by continuous IV infusion or by mouth, starting on day -3, with a targeted serum trough level following Institutional Guidelines for BMT procedure. Tacrolimus will be tapered off by day 180 if no clinically significant GVHD develops, following Institutional Guidelines for BMT Procedure. Cyclosporine may be used as a substitute for tacrolimus at the investigator's discretion.

- Methotrexate at 5 mg/m^2/day IV will be administered on day +1, +3, +6 and +11 following standard BMT protocol or Institutional Guidelines for BMT Procedure.

- Leucovorin may be administered after each dose of mini-methotrexate, following Institutional Guidelines for BMT Procedure for methotrexate GVHD prophylaxis.

- Commercially available tacrolimus, methotrexate and leucovorin (if any) will be used.

- For a subject who cannot continue to receive tacrolimus and cyclosporine due to a serious complication e.g. posterior reversible leukoencephalopthy syndrome (PRES) or thrombotic microangiopathy, an alternative GVHD prophylaxis regimen may be used at the investigator's discretion or per Institutional Guidelines for BMT Procedure.

3.5.5 CARFILZOMIB

- Only carfilzimib from the study supply will be used.

- Carfilzomib will be administered IV over 30 minutes, starting at dose level 1 (20 mg/m^2 IV) on Day +1, +2, +6 and +7 **(Table 1)**, based on the phase 1/2 carfilzomib studies and the previous Dana Farber phase 1 safety experience on the addition of a proteasome inhibitor into a fludarabine-based conditioning regimen.

- Carfilzomib will be admisnistered after methotrexate on day +1 and +6.

- Dexamethasone 4 mg IV will be administered 30-60 minutes prior to each dose of 20 and 27 mg/m^2 carfilzomib. Dexamethasone 8 mg IV will be administered prior to each dose of 36 and 45 mg/m^2 carfilzomib. In any case, subsequent doses of pre-medication dexamethasone may be increased as clinically indicated at the investigator's discretion.

- Subjects will be observed closely during carfilzomib treatment.

- Dose escalation of the phase 1 part will follow the standard 3+3 design as previously stated **(Table 1).**

Table 1: DOSE ESCALATION SCHEDULE

Dose Level	Carfilzomib (mg/m^2)			
	Day +1	Day +2	Day +6	Day +7
1	20	20	20	20
2	20	20	27	27
3	20	20	36	36
4	20	20	45	45

3.5.6 FILGRASTIM [Granulocyte-stimulating colony factor (G-CSF), NEUPOGEN®]

Filgrastim will be administered starting on day +1 at 5 µg/kg/day per the previous Dana Farber study, until ANC ≥2,500/µL for 2 consecutive days or ANC ≥5,000/µL x 1 or following Institutional Guidelines for BMT Procedure. After day +14, filgrastim dose may be increased up to 10 µg/kg/day and/or sargramostim [GM-CSF, Leukine®] may be added at investigator's discretion per Institional Guidelines for BMT Procedure.

3.5.7 INFECTION PROPHYLAXIS

Infection prophylaxis will follow Institutional Guidelines for BMT Procedure. The exception is that an "azole" anti-fungal prophylaxis other than fluconazole (e.g.voriconazole or posaconazole), if indicated, will be started after the last dose of carfilzomib or on/after day +8.

3.5.8 ALLOGENEIC HEMATOPOIETIC STEM CELL MOBILIZATION AND APHERESIS PROCEDURE FOR RELATED DONORS

3.5.8.1 STEM CELL SOURCE

Peripheral blood stem cells (PBSC) will be the preferred choice of stem cell source.

Bone marrow stem cells may be used; cord blood is not allowed.

3.5.8.2 STEM CELL MOBILIZATION AND COLLECTION

For related donors, PBSC mobilization and collection will follow the Institutional Guidelines for BMT Procedure. The apheresis procedure shall begin on day 0 of transplant, with a goal of collecting 3.0 to 8.0 x 106 CD34+ cells/kg, based on the recipient's body weight following Institutional Guidelines for BMT Procedure. For bone marrow stem cells, the recommended cell dose is ≥ 2.0 x 108 mononuclear cells/kg recipient weight.

For related donors, fresh PBSC and bone marrow stem cells should be infused into the patient on the same day of collection or following Institutional Guidelines for BMT Procedure.

For unrelated donors, fresh PBSC and bone marrow stem cells should be infused into the patient within 48 hours of collection. Further delay of stem cell infusion is at investigator's discretion but this must not beyond 72 hours of collection or following Institutional Guidelines for BMT Procedure.

3.5.8.3 Donor Lymphocyte Infusion (DLI)

The use of DLI is not mandated by this protocol, even in the setting of diminished T cell donor chimerism or relapse. In such circumstances, DLI may be considered at Investigator's discretion or following Institutional Guidelines for BMT Proceudure. Patients will be considered **"**off protocol therapy**"** at the time of DLI infusion. Patients who receive a DLI will still be followed for study endpoints.

3 SUBJECT SELECTION

4.1 INCLUSION CRITERIA

Subjects must meet all of the following inclusion criteria to be eligible to enroll in this study.

4.1.1 Disease-related: meeting one of the following diagnosis

1. Lymphoid malignancies requiring allogeneic hematopoietic cell transplantation

1.1 Multiple Myeloma including primary or secondary plasma cell leukemia and secondary amyloidosis

1.2 Lymphomas and related chronic lymphoid proliferative disorders: Hodgkin's lymphoma, Non-Hodgkin's lymphoma of any types (B-cell, T-cell, Null/NK-cell type), chronic lymphocytic leukemia (CLL), pro-lymphocytic leukemia (PLL), hairy-cell leukemia, large granular lymphocytic leukemia

1.3 Waldenstrom's macroglobulinemia / lymphoplasmacytic lymphoma

1.4 Acute lymphoblastic leukemia (ALL) of any types

2. Myeloid malignancies requiring allogeneic hematopoietic cell transplantation

2.1 Acute myeloid leukemia (AML) and acute leukemia of mixed or undetermined or ambiguous lineage

2.2 Myelodysplastic syndrome (MDS), myeloproliferative disorders (MPD) [chronic myeloid leukemia [CML], primary myelofibrosis, post-polycythemic/post-thrombocythemic myelofibrosis], chronic myelomonocytic leukemia [CMMoL] and acute blastic transformation of these conditions.

3. **Pathology review** by the study institution is required.
4. Prior high-dose chemotherapy and autologous HCT(s) is (are) allowed.
5. **Disease status**: Stable disease or better at the time of enrollement.

4.1.2 Demographic

1. Age: ≥18 and ≤70 years old at the time of transplant (<71 years at transplant admission)
2. Life expectancy ≥ 6 months after transplant
3. An 8/8 or 7/8 HLA–matched non-syngeneic **donor** is available and eligible to donate hematopoietic stem cells following Institutional Guidelines for BMT Procedure. High resolution HLA typing is required at HLA-A, -B, -C and –DR alleles.
4. Karnofsky Performance Stuatus ≥70% **[APPENDIX A]**

4.1.3 Laboratory

1. Cardiac: Left ventricular ejection fraction (LVEF) ≥0.4 by MUGA or echocardiogram
2. Pulmonary: FEV1, FVC and DLCO (corrected for hemoglobin) ≥ 50% predicted
3. Hepatic function: Serum AST/ALT ≤ 3 times the upper limit of normal (ULN) and serum direct bilirubin (DB) ≤ 1.5 times ULN within 14 days prior to admission

Renal: Serum creatinine ≤1.2 mg/dL or serum creatinine >1.2 mg/dL and an estimated glomerular filtration rate (GFR) >60 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease equation where Predicted GFR (ml/min/1.73 m^2) = 186 x (Serum Creatinine)$^{-1.154}$ x (age in years)$^{-0.023}$ x (0.742 if patient is female) x (1.212 if patient is black).

4.1.4 Ethical

1. Written informed consent in accordance with federal, local, and institutional guidelines.
2. Females of child-bearing potential must agree to ongoing pregnancy testing and to practice contraception as directed.
3. Male subjects must agree to practice contraception as directed.

4.2 EXCLUSION CRITERIA

4.2.1 Disease-related

1. Progressive disease **[APPENDIX B]** at the time of enrollement
2. Active central nervous system involvement by malignancy

4.2.2 Concurrent Conditions

1. Non compliance to medications or medical instructions
2. Lack of appropriate caregivers
3. Life expectancy <6 months
4. Pregnant or lactating females
5. Uncontrolled infection requiring active treatment (systemic antibiotics, anti-virals, or anti-fungals) within 14 days
6. HIV-1/HIV-2 or HTLV-1/HTLV-2 seropositivity
7. Active hepatitis A, B or C infection * Hepatitis A serology is not required for normal liver function.
8. Unstable angina or myocardial infarction within 6 months prior to randomization, NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, uncontrolled or persistent atrial fibrillation/flutter, history of ventricular fibrillation, ventricular tachycardia/torsade de pointes, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker
9. History of pulmonary hypertension
10. Uncontrolled hypertension or uncontrolled diabetes mellitus
11. Non-hematologic malignancy within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the cervix or breast; c) prostate cancer of Gleason Grade 6 or less with stable prostate- specific antigen (PSA) levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas
12. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib)
13. Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to all available anti-microbial drugs or intolerance to IV hydration due to pre-existing pulmonary or cardiac impairment
14. Subjects with pleural effusion requiring thoracentesis or ascites requiring paracentesis within 14 days prior to admission
15. Uncontrolled psychiatric condition
16. Any other clinically significant medical or psychiatric disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent

5. SUBJECT ENROLLMENT

5.1 REGISTRATION/ENROLLMENT PROCEDURES

This study will be conducted at the University of Michigan. Once a patient is deemed eligible for the protocol, a signed IRB-approved informed consent must be obtained form patients prior to the initiation of treatment with carfilzomib. Patient's data and eligibility criteria will be recorded at entry of the study. All screening evaluations will be completed as part of the standard workup for allogeneic transplant. Enrollment must be performed prior the initiation of treatment with carfilzomib.

This study is a phase 1/2 study. The phase 1 part consists of 4 dose levels [Table 1]. Subjects will be enrolled on the first dose level 1, following a standard 3+3 dose escalation rule until the optimal or maximal tolerated dose (MTD) [0/3 or 1/6 subject developing dose-limited toxicities (DLT)] is identified.

The phase 2 part is an extension of the optimal dose level which is identified from the phase 1 part and a total of 35 patients will be needed on this dose level [See 10.2].

5.2 STUDY DEFINITIONS

5.2.1 Screening: A subject will be considered to be in the "Screening" period from the time he/she signs consent until the date the subject is determined as either "eligible" or "ineligible" (screen failure) by PI or a Co-I. Patients may be consented to this study based on disease status and other criteria at the time of consent, but later removed from the study prior to admission and initiation of transplant conditioning regimen if the change of disease status makes the subject "ineligible". In the event that his occurs, the subject will be replaced.

5.2.2 Enrolled: A subject will be considered to be "Enrolled" onto the study once they have signed consent **AND** have successfully met all screening criteria, as documented by the inclusion/exclusion document, **AND** the eligibility criteria has been reviewed and accepted by the PI or a co-I. The date of enrollment will be documented as the date that the PI or a co-I has reviewed and approved the subject's eligibility. Enrollment must be performed prior the initiation of treatment with carfilzomib

5.2.3 Treatment Period: The **"Treatment Period"** is defined as the first day through the last day of treatment with carfilzomib [Day +1 to +7].

The assessment and reporting period for **adverse events (AE) related to the study drug (carfilzomib)** will start from day +1 at the time of carfilzomib administration through day +100.

5.2.4 Follow Up Period: The **"Follow Up period"** is defined as the first day a subject is no longer receiving carfilzomib (day +8) through at least 1-year post-transplant (primary efficacy endpoint)

However, subjects will be followed further for 3 years on secondary efficacy endpoints (relapse, GVHD, infections, late toxicities and survival). Data not concerning endpoints collected through other BMT clinical research studies may be used for analysis.

5.2.5 On Study: The **"On Study period"** starts from the day that a subject signs the protocol consent document and subsequently meets the protocol eligibility criteria ("Enrolled"), completes the study drug on day +1, +2, +6 and day +7 and ends on day +100 or prior to day 100 if one of the following event occurs earlier:

1. Death
2. Lost to follow-up
3. Withdrawal of consent
4. Entry on to a competing trial
5. Relapse and its treatment or development of new malignancy and its treatment
6. Grade III-IV acute GVHD and its treatment
7. Unacceptable or dose limiting toxicity or complication

After day +100, the patient will be considered "Off Study/Off Protocol." But they will be followed for the primary and secondary endpoints off study/off protocol until 3 year as mentioned in "Follow Up Peroid".

5.2.6 Off Treatment: The **"Off Treatment"** period starts after a patient has completed the study drug on day +7 or prior to day+7 if one of the listed event in 5.2.5 occurs earlier, and ends a day +100.

Subjects who take part in this study will be followed for adverse events (AEs) directly related to the study drug (carfilzomib) through day 100.

Adverse events occurring after the "Off Treatment" period (day+100) will not be reported unless related (probably or definitely) to the study drug (carfilzomib).

5.2.7 Evaluable: Subjects who have received all the 4 doses of carfilzomib will be considered "evaluable" for endpoint analysis. The number of subjects who are considered not "evaluble" for endpoint analysis will be monitored closely. Additional subjects will be replaced.

6. TREATMENT PROCEDURE

6.1 DRUG PREPARATION AND ADMINISTRATION

6.1.1 STUDY DRUG: CARLFILZOMIB

6.1.1.1 CARFILZOMIB DESCRIPTION

Carfilzomib is a modified tetrapeptidyl epoxide, isolated as the crystalline free base. The chemical name is (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. The molecular formula is $C_{40}H_{57}N_5O_7$ and the molecular weight is 719.91. It specifically functions as an inhibitor of the chymotrypsin-like activity of the 20S proteasome which leads to the accumulation of protein substrates within the cell and induction of apoptosis.

6.1.1.2 FORMULATION

Carfilzomib for Injection will be provided as a white to off-white lyophilized cake or powder which, when reconstituted, contains 2 mg/mL isotonic solution of carfilzomib free base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-b-cyclodextrin (SBE-b-CD, Captisol®).

6.1.1.3 STORAGE

Lyophilized Carfilzomib for Injection must be stored at 2–8ºC and in the original package to protect from light under the conditions outlined in the separate Pharmacy Manual, in a securely locked area to which access is limited to appropriate study personnel.

6.1.1.4 DOSING AND ADMINISTRATION

Carfilzomib for Injection is supplied as a lyophilized parenteral product in single-use vials. The lyophilized product is reconstituted with Water for Injection to a final carfilzomib concentration of 2.0 mg/mL prior to administration.

For a standard dosing of carfilzomib, the dose will be calculated using the subject's "**actual"** body surface area (BSA) at baseline. Subjects with a BSA >2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA.

Carfilzomib will be administered as an IV infusion over 30 minutes

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6.1.1.5 PRE-MEDICATION

Dexamethasone 4 mg IV will be administered 30-60 minutes prior to each dose of 20 and 27 mg/m^2 carfilzomib. Dexamethasone 8 mg IV will be administered prior to each dose of 36 and 45 mg/m^2 carfilzomib. In any case, subsequent doses of pre-medication dexamethasone may be increased as clinically indicated at the investigator's discretion.

6.1.1.6 HYDRATION

Per standard BMT procedure, subjects will receive adequate maintenance IV hydration, starting on the admission day, continuously through conditioning chemotherapy course, stem cell infusion (transplant), the first dose of carfilzomib on day +1 of transplant until the last dose of carfilzomib on day +6, following Institutional Guidelines for blood and marrow transplant procedure.

Pre and post dose IV hydration (between 250 mL and 500 mL normal saline or other appropriate IV fluid formulation) will be given for subjects, for any reasons, NOT receiving maintenance IV fluid hydration on days of IV carfilzomib administration.

6.1.2 STANDARD TRANSPLANTATION DRUGS

6.1.2.1 FLUDARABINE (FLUDARA®, FAMP)

Formulation: The chemical name for fludarabine phosphate is 9H-Purin-6-amine, 2-fluoro-9-(5-O-phosphono-D-arabinofuranosyl). The molecular formula of fludarabine phosphate is $C_{10}H_{13}FN_5O_7P$ (MW 365.2). A fluorinated nucleotide analog of the anti-viral agent vidarabine 9-D- arabinofuranosyladenine (ara-A) that is relatively resistant to deamination by adenosine deaminase.

Availability: FLUDARA® for injection contains fludarabine phosphate. Each vial of sterile lyophilized solid cake contains 50 mg of the active ingredient fludarabine phosphate, 50 mg of mannitol, and sodium hydroxide to adjust pH to 7.7. The pH range for the final product is 7.2-8.2. Reconstitution with 2 mL of Sterile Water for Injection USP results in a solution containing 25 mg/mL of fludarabine phosphate intended for intravenous administration.

Fludarabine is available as a 25mg/ml solution for injection and as powder for injection (Fludara). Both products are stored in the refrigerator (2° to 8° C / 36° to 46° F). Reconstituted Fludarabine IV is chemically and physically stable at room temperature or 48 hours if refrigerated. In addition, reconstituted fludarabine (IV) contains no antimicrobial preservative and thus care must be taken to ensure that there is sterility of the prepared solutions. Prepared solutions should be discarded 8 hours after initial use. Reconstituted powder vials are stable for 16 days at room temperature or refrigerated. Solutions diluted in 0.9%NaCl or Dextrose in Water are stable for 48 hours at room temperature or the refrigerator. However, as stated above, reconstituted and diluted solution do not contain antimicrobial preservative and should be used within 8 hours.

Administration: The recommended dose of fludarabine in a non-transplant setting is 25 mg/m^2 administered intravenously over a period of approximately 30 minutes daily for 5 consecutive days per cycle. Dosing for standard allogeneic stem cell transplant conditioning regimen is 120-160 mg/m^2 in a total course.

Potential and Expected Toxicities: Fludarabine can cause diarrhea, nausea, vomiting, and skin rash. Fludarabine can temporarily lower the number of white blood cells, which help defend the body against infection and other diseases in your blood. This can increase your chance of getting an infection. It can also lower the number of platelets, which are

necessary for proper blood clotting, resulting in easy bruising and excessive bleeding from wounds. Less common side effects are aching muscles, general feeling of discomfort or illness, headache and loss of appetite. Rare side effects include cough or hoarseness, fever or chills, loss of vision, lower back or side pain, painful or difficult urination. Rarely, fludarabine can cause a temporary loss of hair in some people.

6.1.2.2 BUSULFAN (BUSULFEX®)

Formulation: Busulfan is a bifunctional alkylating agent known chemically as 1,4-butanediol, dimethanesulfonate with a molecular formula of CH3SO2O(CH2)4OSO2CH3 and a molecular weight of 246 g/mole. The pharmacokinetics of IV busulfan was studied in 59 patients participating in a prospective trial of a busulfan-cyclophosphamide preparatory regimen prior to allogeneic hematopoietic progenitor stem cell transplantation. Patients received 0.8mg/kg busulfan IV every six hours, for a total of 16 doses over four days. Fifty-five of fifty-nine patients (93%) administered IV busulfan maintained AUC values below the target value (<1500 μM•min). Busulfan pharmacokinetics showed consistency between dose 9 and dose 13 as demonstrated by reproducibility of steady state Cmax and a low coefficient of variation for this parameter. In a pharmacokinetic study of IV busulfan in 24 pediatric patients, the population pharmacokinetic (PPK) estimates of busulfan for clearance (CL) and volume of distribution (V) were determined. For actual body weight, PPK estimates of CL and V were 4.04 L/hr/20 kg (3.37 ml/min/kg; interpatient variability 23%); and 12.8 L/20 kg (0.64 L/kg; interpatient variability 11%). IV busulfan daily infusion of 3.2 mg/kg has been tested in multiple studies and considered to be equal in terms of toxicity and efficacy. Thus most centers use every 24h dosing.

Availability: IV busulfan (Busulfex®) is supplied as a clear, colorless, sterile solution in 10-mL single-use glass vials each containing 60 mg of busulfan at a concentration of 6 mg/mL for intravenous use. IV busulfan is packaged in a tray pack of 8 vials. Unopened vials of Busulfex must be stored under refrigerated conditions between 2°-8°C (36°-46°F).

Administration: IV busulfan must be diluted prior to use with either NS or D5W. The diluent quantity should be 10 times the volume of Busulfex, so that the final concentration of busulfan is approximately 0.5 mg/mL. Infusion pumps should be used to administer the diluted busulfan solution. DO NOT infuse concomitantly with another intravenous solution of unknown compatibility. Warning: Rapid infusion of IV busulfan has not been tested and is not recommended. Follow the institutional guidelines for more detailed preparation and administration procedures of busulfan.

Potential and Expected Toxicities: For BMT setting, busulfan can cause nausea and vomiting, myelosuppression/ablation, seizures, diarrhea, impotence, sterility, generalized skin pigmentation, scarring of the heart muscle and lungs, testicular atrophy, cataracts and the development of a new cancer.

Toxicities reported in non-transplant setting as more than 10% incidence are: Tachycardia, hypertension, edema, thrombosis, chest pain, vasodilation, hypotension, insomnia, fever, anxiety, headache, chills, pain, dizziness, depression, confusion, rash, pruritus, alopecia, hypomagnesemia, hyperglycemia, hypokalemia, hypocalcemia, hypophosphatemia, nausea, mucositis/stomatitis, vomiting, anorexia, diarrhea, abdominal pain, dyspepsia, constipation, xerostomia, rectal disorder, abdominal fullness, myelosuppression, neutropenia, thrombocytopenia, lymphopenia, anemia, hyperbilirubinemia, ALT increase, veno-occlusive disease, jaundice, injection site inflammation, injection site pain, weakness, back pain, myalgia, arthralgia, creatinine increased, oliguria, rhinitis, lung disorder, cough, epistaxis, dyspnea, pneumonia, hiccup, pharyngitis, infection, allergic reaction. Toxicities with expected incidences of 1% to 10% are: Arrhythmia, cardiomegaly, atrial fibrillation, ECG abnormality, heart block, heart failure, pericardial effusion, tamponade, ventricular extrasystoles, hypervolemia, lethargy, hallucinations, agitation, delirium, encephalopathy, seizure, somnolence, cerebral hemorrhage, vesicular rash, vesiculobullous rash, skin discoloration, maculopapular rash, acne, exfoliative dermatitis, erythema nodosum, hyponatremia, ileus, weight gain, hematemesis, pancreatitis, prothrombin time increase, hepatomegaly, hematuria, dysuria, hemorrhagic cystitis, BUN increase, asthma, alveolar hemorrhage, hyperventilation, hemoptysis, pleural effusion, sinusitis, atelectasis, hypoxia.

6.1.2.3 MELPHALAN [ALKERAN®]

Formulation: Chemistry: Melphalan (L-phenylanine mustard) is a bifunctional alkylating agent. It forms covalent linkages with susceptible cellular proteins. IV administration of melphalan revealed rapid elimination from plasma with terminal half-life of 1.8 hours. 13% is excreted in the urine. It is rapidly distributed in total body water and eliminated in a biphasic manner. IP administration of 20-30 mg/M2 revealed a peak concentration in the peritoneal cavity of 6.4 ± 2.4 µg/ml and half-life of 85 ± 30 minutes. The peak plasma concentration was 1.22 µg/ml, and half-life was 86 ± 31 minutes. It induces formation of DNA interstrand and DNA protein cross-links.

Availability: The drug is available as an injectable kit. This kit contains an ampule of 100 mg (equivalent) melphalan, a 1 ml ampule of acid- alcohol diluent (containing 0.047 ml 37% HCl, q.s. to 1 ml with alcohol) and a 9 ml ampule of final duluent containing dipotassium phosphate, 108 mg propylene glycol 5.4 ml sterile water for injection q.s. 9.0 ml. This kit should be stored at room temperature and projected from light.

Adminstration: The 100 mg injectable formulation is put into solution initially with the addition of 1 m acid-alcohol diluent. When dissolution is complete, the 9 ml final diluent is added. This final solution has a pH of > 7 and should be used promptly. According to the manufacturer (8.5% hydrolysis 24 hours after mixing) a further dilution in D5W is also reportedly stable for 24 hours.

Potential and Expected Toxicities: Human Toxicology: Melphalan's major systemic toxicity is bone marrow depression with secondary anemia, leukopenia and thrombocytopenia, usually occurring within three to five weeks of the onset of therapy and lasting four to eight weeks. These effects are exacerbated by prior chemotherapy or radiotherapy. Other adverse reactins include nausea, vomiting, diarrhea, stomatitis, esophagitis, colitis, increases in liver function and kidney function tests, renal/bladder necrosis, pulmonary fibrosis, respiratory distress, peripheral neuropathy, paresthesia, alopecia, fever and hypersensitivity including edema, rash and anaphylaxis. At high doses, supraventricular arrhythmias, including atrial fibrillation, may occur. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

6.1.2.3 CYCLOPHOSPHAMIDE [CYTOXAN®]

Formulation: Cyclophosphamide is an alkylating agent related to nitrogen mustard. Cyclophosphamide is inactive until it is metabolized by P450 isoenzymes (CYP2B6, CYP2C9, and CYP3A4) in the liver to active compounds. The initial product is 4-hydroxycyclophosphamide (4- HC) which is in equilibrium with aldophosphamide which spontaneously releases acrolein to produce phosphoramide mustard. Phosphoramide mustard, which is an active bifunctional alkylating species, is 10 times more potent in vitro than is 4-HC and has been shown to produce interstrand DNA cross-link analogous to those produced by mechlorethamine. Approximately 70% of a dose of cyclophosphamide is excreted in the urine as the inactive carboxyphosphamide and 5-25% as unchanged drug. Cyclophosphamide is well absorbed orally with a bioavailability greater than 75%. The plasma half-life ranges from 4.1 to 16 hours after IV administration and 1.3 to 6.8 hours after oral administration.

Availability: Cyclophosphamide for injection is available as powder for injection or lyophilized powder for injection in 500 mg, 1 g, and 2 g vials. The powder for injection contains 82 mg sodium bicarbonate/100 mg cyclophosphamide and the lyophilized powder for injection contains 75 mg mannitol/100 mg cyclophosphamide. Storage at or below 25oC (77oF) is recommended. The product will withstand brief exposures to temperatures up to 30oC (86oF).

Administration: Cyclophosphamide for Injection: Reconstitute with Sterile Water or Bacteriostatic Water for Injection (paraben preserved only) to a concentration of 20 mg/mL. Solutions reconstituted with preservative should be used within 24 hours if stored at room temperature or within 6 days if stored under refrigeration. If administered as undiluted drug at the 20 mg/mL concentration, reconstitute with NS only to avoid a hypotonic solution. Cyclophosphamide may be further diluted in dextrose or saline containing solutions for IV use

Potential and Expected Toxicities: Common immediate toxicities related to the use in a conditioning chemotherapy include anorexia, nausea & vomiting (acute and delayed), bone marrow suppression (leukopenia, thrombocytopenia, anemia), hemorrhagic cystitis, alopecia, immune suppression, abdominal discomfort and diarrhea. Potential delayed toxicity is gonadal dysfunction.

6.1.2.5 RITUXIMAB (RITUXAN®)

Formulation: Rituximab is a genetically engineered chimeric murine/human monoclonal antibody, which binds specifically to the antigen CD20 (human B lymphocyte restricted differentiation antigen, Bp35) located on the surface of pre B and mature B lymphocytes of both normal and malignant cells. The antibody is an IgG kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids and has an approximate molecular weight of 145 kD. It is produced in mammalian cell (Chinese Hamster Ovary) culture. CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel. Rituximab binds to the CD20 antigen on B lymphocytes and recruits immune effector functions to mediate B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity and antibody-dependent cell mediated cytotoxicity. The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.

Availability: Rituximab is a sterile, clear, colorless, preservative free liquid concentrate for intravenous administration. Rituximab is supplied at a concentration of 10 mg/ml in either 100 mg (10 ml) or 500 mg (50 ml) single use vials. The product contains 9.0 mg/ml sodium chloride, 7.35 mg/ml sodium citrate dihydrate, 0.7 mg/ml polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5. Store refrigerated at temperatures of 2-8°C (36-46°F). Protect from direct sunlight.

Administration: Dilute to a final concentration of 1 to 4 mg/ml in saline or dextrose containing solutions. Rituximab solutions for infusion may be stored at 2-8°C (36-46°F) for 24 hours and have been shown to be stable for an additional 24 hours at room temperature. DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Premedication consisting of acetaminophen and diphenhydramine should be administered prior to each infusion. Since transient hypotension may occur during Rituximab infusions, consider withholding antihypertensive medications 12 hours prior to infusion.

For each course of Rituximab after premedication with acetaminophen and diphenhydramine, the first infusion should be started at 0.5 mg/kg/hr, maximum 50MG/HR for 30 minutes. The rate may be increased by 0.5 mg/kg/hr, maximum 50MG/HR increments every 30 minutes up to a maximum rate of 400MG/HR, as tolerated by the patient.

If infusion related events occur at any time during the infusion the rate should be slowed or the infusion stopped until resolution occurs. Additional diphenhydramine may need to be given or other medications to treat the events occurring. The patient may be re-challenged after resolution of the event with the rate at 50% of the rate at which the infusion was running when the event occurred.

Potential and Expected Toxicities: Single doses of up to 500 mg/m2 and weekly x 4 doses of 375 mg/m2 have been administered without dose limiting toxicity. Adverse events are most common during the initial antibody infusion and usually consist of grade 1 or 2 fever (73%), asthenia (16%) chills (38%) nausea (19%), vomiting (11%), rash (14%) and tumor site pain (3%). Hematologic toxicity is usually mild and reversible. Rituximab has caused severe infusion reactions including urticaria, hypotension, angioedema, hypoxia, or bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and anaphylactic and anaphylactoid events, transient decreases in the WBC or platelet count (patients with high levels of circulating tumor cells or bone marrow involvement), tumor lysis syndrome (patients with high numbers of circulating malignant lymphocytes or high tumor burden, bulky lesions), hepatitis B virus reactivation with fulminant hepatitis, hepatic failure, and death, other viral reactivations (JC virus, cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C virus), mucocutaneous reactions (paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis), bowel

obstruction and perforation, serious cardiovascular events e.g. cardiac arrhythmia (reported in rheumatoid arthritis patients), renal toxicity including acute renal failure requiring dialysis.

6.1.2.6 TACROLIMUS (FK506, PROGRAF®)

Formulation: Tacrolimus, previously known as FK506, is the active ingredient in Prograf®. Tacrolimus is a macrolide immunosuppressant produced by Stretocyces Tsukubaensis. Tacrolimus has an empirical formulation of C44H69NO12-H2O and a formula weight of 822.05. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform. Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression).

Availability: Prograf is available for oral administration as capsules (tacrolimus capsules) containing the equivalent of 1mg or 5mg of anhydrous tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. The 1 mg capsule shell contains gelatin and titanium dioxide, and the 5-mg capsule shell contains gelatine, titanium dioxide, and ferric oxide. Prograf® is also available as a sterile solution (tacrolimus injection) containing the equivalent of 5mg anhydrous tacrolimus in 1 ml for administration by IV infusion only. Each mL contains polyoxyl 60 hydrogenated castor oil (HCO-60), 200 mg, and dehydrated alcohol, USP, 80.0% v/v. Prograf injection must be diluted with 0.9% sodium chloride injection or 5% dextrose injection before use.

Administration: Tacrolimus is administered as a continuous infusion. Oral preparation will be administered on empty stomach every 12 hours.

Potential and Expected Toxicities: Possible side effects of tacrolimus include: depressed kidney function, high blood sugar, high blood potassium, skin rash, headache, nausea, vomiting. Less common side effects are loss of appetite, sleep disturbances, vivid dreams, hallucinations, high blood pressure, seizure, decreased level of consciousness, anemia, agitation, tremors, irritability, slurred speech, tingling in the hands and feet, pain in the palms and soles of the feet, weakness, and abnormal blood cell levels. All of these side effects are reversible by reducing the dose or discontinuing the drug. Rare fatal cases of severe allergic reactions have been reported in patients receiving cyclosporine and it is possible that similar reactions could also occur in patients receiving tacrolimus.

6.1.2.7 METHOTREXATE [TREXALL®]

Formulation: Methotrexate (formerly amethopterin) is an antimetabolite. Methotrexate inhibits dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates by this enzyme before they can be utilized as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular replication. Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are in general more sensitive to this effect of methotrexate. Refer to the FDA-approved package insert for more information. Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With intravenous administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. After intravenous administration, the initial volume of distribution is approximately 0.18l/kg (18% of body weight) and steady state volume of distribution is approximately 0.4 to 0.8 l/kg (40% to 80% of body weight). Methotrexate competes with reduced folates for active transport across

cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Availability: Each 20 mg and 1 g vial of lyophilized powder contains methotrexate sodium equivalent to 20 mg and 1 g methotrexate respectively. Store at controlled room temperature, 20°C-25°C (68°C- 77°C); excursions permitted to 15°C-30°C (59°F-86°F). Protect from light.

Potential Drug Interactions: Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored. Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad-spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria. Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

Potential and Expected Toxicities: The most frequently reported adverse reactions associated with methotrexate use as GVHD prophylaxis include ulcerative stomatitis, leucopenia and suppressed hematopoiesis, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills, and fever, dizziness and decreased resistance to infection. Methotrexate may be associated with increased rates of pulmonary complications after transplantation. The risk of infections is due to the suppression of hematopoiesis after transplantation.

6.1.2.8 LEVETIRACETAM (KEPPRA®)

Formulation: Levetiracetam, a single enantiomer, is (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide, its molecular formula is C8H14N2O2 and its molecular weight is 170.21. Levetiracetam is chemically unrelated to existing antiepileptic drugs (AEDs). Levetiracetam is a white to off-white crystalline powder with a faint odor and a bitter taste. It is very soluble in water (104.0 g/100 mL). It is freely soluble in chloroform (65.3 g/100 mL) and in methanol (53.6 g/100 mL), soluble in ethanol (16.5 g/100 mL), sparingly soluble in acetonitrile (5.7 g/100 mL) and practically insoluble in n-hexane. (Solubility limits are expressed as g/100 mL solvent.)

Availability: Keppra is an antiepileptic drug available as 250 mg (blue), 500 mg (yellow), 750 mg (orange), and 1000 mg (white) tablets and as a clear, colorless, grape-flavored liquid (100 mg/mL) for oral administration. Keppra (levetiracetam) 500 mg/5 mL injection is a clear, colorless, sterile solution. It is supplied in single-use 5 mL vials. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Administraion: Keppra injection is for intravenous use only and must be diluted prior to administration. Keppra injection (500 mg/5 mL) should be diluted in 100 mL of a compatible diluent (NS, Lactated Ringer's injection or D5W) and administered intravenously as a 15-minute IV infusion.

Potential and Expected Toxicities: Toxicities reported in more than 1% in adults are asthenia, headache, infection, pain, anorexia, somnolence, dizziness, nervousness, anorexia vertigo, amnesia, anxiety, hostility, paresthesia, emotional lability, pharingitis, rhinitis, increased cough, sinusitis, diplopia.

6.1.2.9 FILGRASTIM (r-metHuG-CSF, NEUPOGEN®)

Formulation: Filgrastim, (recombinant human granulocyte-colony stimulating factor, r-metHuG-CSF), is a protein produced by E. coli into which has been inserted the human granulocyte colony-stimulating factor gene. Filgrastim differs from the natural protein in that the N-terminal amino acid is a

methionine and it is not o- glycosylated. G-CSF functions as a hematopoietic growth hormone; it increases the proliferation, differentiation, maturation and release of precursor cells into mature blood cells of the neutrophil lineage. G-CSF has demonstrated in vitro effects on mature neutrophils, including an increased expression of chemotactic receptors, enhanced phagocytosis and intracellular killing of certain organisms, as well as enhanced killing of target cells that are bound by antibodies.

Approximately 6,400 patients in U.S. and international based trials have participated in clinical trials of filgrastim to date, and the worldwide commercial populations receiving filgrastim totaled approximately 190,000. The drug has been found to be well tolerated at dosages up to 69 µg/kg/day given IV or SC, with no toxic effects attributable to filgrastim. A maximum tolerated dose has not yet been determined.

Availability: Recombinant G-CSF, filgrastim, NEUPOGEN®, is supplied as a clear, colorless preservative-free liquid for parenteral administration. Single use vials contain filgrastim 300 µg/ml in a preservative-free solution with 0.59 mg/ml acetate, 50 mg/ml sorbitol, 0.004% Tween® 80, 0.035 mg/ml sodium, and water for injection, USP, pH 4.0 to make 1 ml filgrastim Neupogen® is commercially available in 2 vial sizes: 300 µcg/1 ml and 480 µg/1.6 ml. Dilution: If required, filgrastim may be diluted in 5% dextrose. Filgrastim diluted to concentrations between 5 and 15 µg/ml should be protected from adsorption to plastic materials by addition of albumin (Human) to a final concentration of 2 mg/ml. When diluted in 5% dextrose or 5% dextrose plus albumin (Human), filgrastim is compatible with glass bottles, PVC and polyolefin IV bags, and polypropylene syringes. Dilution of filgrastim to a final concentration of less than 5 µg/ml is not recommended at any time. Do not dilute with saline at any time; product may precipitate. Storage and Stability: Filgrastim should be stored in the refrigerator at 2 - 8°C (36 - 46°F). Avoidshaking. Prior to injection, filgrastim may be allowed to reach room temperature for a maximum of 24 ho urs. Any vial left at room temperature for greater than 24 hours should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit; if particulates or discoloration are observed, the container should not be used.

Administration: Filgrastim is administered as a single daily injection by SC bolus injection, by short IV infusion (15 - 30 minutes), or by continuous SC or continuous IV infusion.

Potential and Expected Toxicities: The most frequently reported adverse effect was medullary bone pain, occurring in 20 - 25% of patients in Phase II and III trials. When bone pain was reported it often preceded a rise in the circulating neutrophil count; it occurred more frequently in patients treated with 20 - 100 µg/kg/day of intravenously administered filgrastim and less often in lower subcutaneous doses. The pain was generally mild to moderate in severity, and usually controlled with non-narcotic analgesics such as acetaminophen. Other side effects include transient but reversible increases of alkaline phosphatase, lactate dehydrogenase and uric acid levels. These occurred in 27 - 58% of patients, without clinical sequelae observed. Elevations of leukocyte alkaline phosphatase levels have also been noted but the significance is not yet known. Less frequently reported adverse events related to filgrastim administration include subclinical splenomegaly, exacerbation of pre-existing skin rashes, alopecia, and thrombocytopenia, and cutaneous vasculitis. Rarely, allergic-type reactions have occurred. Since the commercial introduction of filgrastim there have been reports (<1 in 4,000 patients) of symptoms suggestive of an allergic-type reaction, but in which an immune component has not been demonstrated. These have generally been characterized by systemic symptoms involving at least two body systems, most often skin (rash, urticaria, edema), respiratory (wheezing, dypsnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first thirty minutes after administration and appeared to occur more frequently in those patients who received filgrastim intravenously. Rapid resolution of symptoms occurred in most cases after administration of standard supportive care, and symptoms recurred in more than half the patients when rechallenged.

6.2 DEFINITION OF DOSE-LIMITING TOXICITY

Subjects will be evaluated for toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) version 4.0 **[Appendix D]**

DLTs are defined as any of the below treatment emergent toxicities, **with attribution to carfilzomib**, which occur **within day +28**.

NON-HEMATOLOGIC

- ≥ Any Grade 3 toxicity (excluding nausea, vomiting, diarrhea)
- ≥ Grade 3 nausea, vomiting, or diarrhea, despite maximal antiemetic/antidiarrheal therapy
- ≥ Grade 4 fatigue lasting for ≥ 7 days
- ≥ Grade 2 neuropathy with pain

EXCEPTIONS

The following adverse events are NOT considered DLTs.

- Any grade hematologic adverse events which are fully expected after conditioning chemotherapy
- Fever ≤ 38.5 °C plus all the followings
    - No evidence of infection e.g. positive culture and
    - No unstable vital signs at the discretion of the investigator or the attending physician.
- Any grade alopecia
- Any grade hyperglycemia attributed to dexamethasone

6.3 DOSE WITHHOLD AND RESTART

If a DLT occurs before day +7, the remaining dose(s) of carfilzomib will NOT be administered. The remaining doses may be re-initiated at the investigator's discretion if the event is assessed not to be a true DLT. **However, carfilzomib will NOT be administered after day +7.**

6.4 SAFETY CONSIDERATIONS

Based upon the experience in the Phase 1 and 2 clinical studies with carfilzomib, the followings are recommended:

- Dexamethasone 4 or 8 mg IV (See 3.5.5) will be administered prior to each dose of carfilzomib. If treatment-related fever, rigors, chills, and/or dyspnea are observed with a 4 mg dexamethasone, an 8 mg dose IV may be administered prior to subsequent doses after resolution of the symptoms and no document infection is identified.

- In patients with high tumor burden, a "first dose effect", which is notable for fever, chills, rigors, and/or dyspnea occurring during the evening following the first day of infusion and an increase in creatinine on the next day, may be the clinical sequelae of rapid tumor lysis and/or cytokine release. Treatment with high-dose glucocorticoids (e.g. methylprednisolone 50–100 mg IV) is recommended. In addition, intravenous fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available for immediate use and instituted, as medically indicated. However, patients who are eligible for this study generally do not have high tumor burden at the time of carfilzomib administrations.
- Acyclovir or similar, which is used for standard infectious transplant prophylaxis, should be given per institutional prophylaxis guidelines.
- Renal function or creatinine clearance (CrCl) changes are mostly transient, reversible, and non-cumulative. All subjects should be well hydrated during carfilzomib administrations. Clinically significant electrolyte abnormalities should be promptly corrected prior to dosing with carfilzomib. Renal function must be monitored closely during treatment with carfilzomib. Serum chemistry values, including creatinine, must be obtained and reviewed prior to each dose of carfilzomib. **Carfilzomib must be held for subjects with a CrCl <15 mL/min at any time during study participation**.

- Subjects with documented infection should not be dosed with carfilzomib until the infection has been controlled with appropriate treatment. Low-grade fever alone (<38.5 C) without unstable vital signs or documented infection occurs frequently during transplant admission due to various non- infectious etiologies, and should not the sole reason to hold carfilzomib.

- Carfilzomib administration can cause nausea, vomiting, diarrhea, or constipation sometimes requiring the use of antiemetics or antidiarrheals. Fluid and electrolyte replacement should be administered to prevent dehydration.

6.4.1 CONTRAINDICATIONS

Besides allergy to carfilzomib, there are no known contraindications for carfilzomib.

6.4.2 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The warnings and precautions in this section are based on the analysis of safety data from Phase 1 and 2 clinical studies submitted as part of the initial FDA NDA submission for monotherapy treatment of multiple myeloma patients who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent.

6.4.3 CARDIAC ARREST, CONGESTIVE HEART FAILURE, MYOCARDIALISCHEMIA

Death due to cardiac arrest has occurred within a day of carfilzomib administration. New onset or worsening of pre-existing congestive heart failure with decreased left ventricular function or myocardial ischemia has occurred following administration of carfilzomib. Cardiac failure events (eg, cardiac failure congestive, pulmonary edema, ejection fraction decreased) were reported in 7% of patients. Monitor for cardiac complications and manage promptly. Unless otherwise specified in the individual protocol, withhold carfilzomib for Grade 3 or 4 cardiac events until recovery and consider whether to restart carfilzomib based on a benefit/risk assessment. Patients with NYHAClass 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.

6.4.4 PULMONARY COMPLICATIONS

Pulmonary arterial hypertension (PAH) was reported in 2% of patients treated with carfilzomib and was Grade 3 or greater in less than 1% of patients. Evaluate with cardiac imaging and/or other tests as indicated. Unless otherwise specified in the individual protocol, withhold carfilzomib for pulmonary hypertension until resolved or returned to baseline and consider whether to restart carfilzomib based on a benefit/risk assessment. Dyspnea was reported in 35% of patients enrolled in clinical trials. Grade 3 dyspnea occurred in 5% of patients; no Grade4 eventsoccurred, and 1death (Grade 5) was reported. Monitor and manage dyspnea immediately. Unless otherwise specified in the individual protocol, interrupt carfilzomib until symptoms have resolved or returned to baseline.

6.4.5 INFUSION REACTIONS

Infusion reactions in clinical trials 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 carfilzomib. Administer dexamethasone prior to carfilzomib to reduce the incidence and severity of infusion reactions. Inform patients of the risk and symptoms and to contact physician if symptoms of an infusion reaction occur.

6.4.6 TUMOR LYSIS SYNDROME [TLS]

Tumor lysis syndrome occurred following carfilzomib administration in <1% of patients. Patients with multiple myeloma and a high tumor burden are at greater risk for TLS. Prior to receiving carfilzomib, patients must be well hydrated. Patients should be monitored for evidence of TLS during carfilzomib treatment, and manage promptly. Carfilzomib is to be on hold until TLS is resolved.

6.4.6.1 GUIDELINES FOR MONITORING, PROPHYLAXIS, AND TREATMENT OF TUMOR LYSIS SYNDROME (TLS)

TLS, which may be associated with multi-organ failure, has been observed in some patients with high tumor burden who have been treated with carfilzomib. This is not expected in typical patients undergoing allogeneic HCT. In addition, transplant subjects routinely receive IV hydration during conditioning chemotherapy and stem cell infusion.

For few subjects who are at high risk of developing TLS, standard TLS prevention measures must be followed including adequate hydration and initiation of allopurinol or alternative, per the institutional guidelines.

6.4.6.2 Hydration and Fluid Monitoring

Subjects should receive adequate IV hydration during conditioning chemotherapy until at least 24 hours after the last dose of carfilzomib per standard institutional guidelines for TLS. For few exceptional subjects who achieve adequate oral fluid intake and do not receive maintenance IV hydration during carfilzomib administrations [day +1 to +7], a bolus of 250–500 mL of IV normal saline (or other appropriate IV fluid formulation) must be given before AND after each dose.

6.4.6.3 Clinical and Laboratory Monitoring

Symptoms and signs that may be indicative of TLS, such as fevers, chills/rigors, dyspnea, nausea, vomiting, muscle tetany, weakness, or cramping, seizures, and decreased urine output. Appropriate chemistries, including creatinine, and complete blood counts (CBC) with platelet count are routinely performed and reviewed daily in transplant setting. Results of laboratory studies must be reviewed and deemed acceptable prior to administering the carfilzomib dose. Subjects with laboratory abnormalities consistent with lysis of tumor cells (e.g., serum creatinine ≥ 50% increase, LDH ≥ 2-fold increase, uric acid ≥ 50% increase, phosphate ≥ 50% increase, potassium ≥ 30% increase, calcium ≥ 20% decrease) prior to dosing should not receive the scheduled dose and appropriate management for TLS must be initiated per institutional guidelines.

6.4.6.4 Management of Tumor Lysis Syndrome

Management of TLS should be performed appropriately or per the institutional guidelines. All cases of TLS must be reported to Amgen as a Serious Adverse Event (SAE) through the normal process within 24 hours of the clinical site becoming aware of the event.

6.4.7 HEPATIC TOXICITY AND HEPATIC FAILURE

Cases of hepatic failure, including fatal cases, have been reported (<1%). Carfilzomib can cause elevations of serum transaminases and bilirubin. Unless otherwise specified in the individual protocol, withhold carfilzomib 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 carfilzomib is appropriate. However, carfilzomib will NOT be administered after day +7.

6.4.8 EMBRYO-FETAL TOXICITY

Carfilzomib 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 carfilzomib. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose.

In general, it is extremely rare for female subjects receiving conditioning chemotherapy to conceive in the first 2-4 weeks after transplant. However, all male and female subjects and their partners must use dual barrier methods of contraception in the first 8 weeks after transplant when having sexual intercourse.

6.5 CONCOMITANT MEDICATIONS

Concomitant medication is defined as any prescription or over-the-counter preparation including vitamins and supplements. Concomitant medications should be recorded from 14 days before transplant (day 0) through the end of the subject's study participation.

6.5.1 REQUIRED CONCOMITANT MEDICATIONS

Dexamethasone 4 or 8 mg IV (See 3.5.5) will be administered prior to each dose of carfilzomib. If treatment-related fever, rigors, chills, and/or dyspnea are observed with a 4 mg dexamethasone, an 8 mg dose IV may be administered prior to subsequent doses after resolution of the symptoms and no document infection is identified.

Subjects should receive antibiotic prophylaxis, which are already part of routine standard infectious prophylaxis in an allogeneic stem cell transplant setting. The carfilzomib-specific infectious prophylaxis includes ciprofloxacin or levofloxacin or similar and acyclovir or similar (famiciclovir, valacyclovir). Other transplant-specific fungal, PCP and encapsulated bacteria prophylaxis follows institutional guidelines.

6.5.2. OPTIONAL AND ALLOWED CONCOMITANT MEDICATIONS

Allogeneic transplantation procedure will follow standard allogeneic transplant protocol per institutional BMT guidelines including the use of

1. Granulocyte- and Granulocyte-Macrophage Colony-Stimulating Factors [G-CSF, GM-CSF]
2. Blood products
3. Concomitant supportive medications e.g. anti-emetics, anti-diarrheal, ursodiol (Actigall), narcotic pain medication, parenteral nutrition
4. Allopurinol or rasburicase is allowed.
5. Vitamins and supplements are allowed and at the Investigator's discretion.
6 Other supportive medications e.g. bisphosphonates and erythropoietic agents are generally not used during transplant admission but are allowed if indicated subsequently.

6.5.3 EXCLUDED CONCOMITANT MEDICATIONS

Concurrent therapy with other approved or investigative anticancer agents in the first 28 days is NOT allowed. Disease-specific maintenance therapy with targeted agents e.g. tyrosine kinase inhibitors may be used after day 28 at Investigator's discretion

7. STUDY TESTS AND OBSERVATIONS

7.1 REQUIRED OBSERVATIONS (TABLE 2)

Per standard BMT practice, subjects will be followed closely during a transplant admission, which typically lasts for 3-4 weeks and will be followed in outpatient BMT clinic after discharge per institutional guidelines and as clinically indicated. The required BMT Clinic visits for history and physical examination and tests are shown in **Table 2**.

After 1 year, subjects will be followed in clinic for history and physical examination, with appropriate tests and investigations per institutional guidelines or at Investigator's discretion for relapse and GVHD until 3 years post transplant.

First clinical GVHD or relapse (before or after 1 year) requires a complete workup per **Table 2**.

Table 2: REQUIRED OBSERVATIONS

	Baseline	Days Post-Transplant							
		3, 8, 14	30	60	100	180	270	365	First Clinical GVHD or Relapse
			+/- 7 days	+/-14 days	+/- 30 days	+/- 30 days	+/- 30 days	+/- 30 days	Within 7 days
Blood for PD study	day **-6, 0**	day **3**							
Blood for GVHD markers	day **-6, 0**	day **3,8,14**							
History and physical exam, Karnofsky	1 week prior to admission		X	X	X	X	X	X	X
CBC, chemistry, LFTs, * Direct Bilirubin			X	X	X	X	X	X	X
Blood for Chimerism			X		X	X		X	X
**** BM examination**	Per Institutional Guidelines				X				
**** Disease Staging**			X		X	X	X	X	X

* Direct Bilirubin is required at Basline. For subsequent timepoints, Direct Bilirubin is required only if Total Bilirubin (part of LFTs) is abnormal at that timepoint.

** Bone marrow specimens will be submitted for investigations following standard procedure or institutional guidelines for BMT procedure. Other special disease specific testings e.g. cytogeneitcs, FISH and molecular investigations are sent as indicated.

*** Disease restaging tests follow disease-specific institutional guidelines or at the Investigator's discretion. If disease restaging is not indicated at any time point per institutional guidelines, disease status is recorded at the investigator's discretion.

Correlative pharmacodynamic study on peripheral blood mononuclear cells (PBMC) on day -6, 0 and +3 and GVHD markers on day -6, 0, +3, +8, +14 and +30 are secondary endpoints, thus failure to acquire specimens will not be considered a protocol violation.

Required observations performed outside of the recommended window for emerging clinical indications may be accepted at the PI's discretion for the closest associated follow up and not considered a deviation.

7.2 DEFINITIONS OF END POINTS

7.2.1 SAFTY END POINTS

7.2.1.1 DOSE-LIMITED TOXICITIES [DLTs]

See Section 6.2.

7.2.1.2 GRAFT FAILURE

Primary graft failure will be defined as the inability to achieve an ANC ≥500/uL AND a platelet count ≥20,000/uL, without transfusion support and without other causes, e.g. viral infection or medication, within 35 days post transplant.

Secondary graft failure will be defined as the inability to maintain an ANC ≥500/uL and a platelet count ≥20,000/uL, without transfusion support and without other causes, e.g. viral infection or medication, after initial neutrophil AND platelet engraftments.

Neutrophil engraftment day will be defined as the first day of the 3 consecutive days of achieving ANC ≥500/uL

Platelet engraftment day will be defined as the first day of the 2 consecutive days of achieving platelet count ≥20,000/uL, without transfusion support

7.2.1.3 REGIMEN-RELATED TOXICITY [RRT]

An RTT is defined as an adverse event (AE) that occurs within 37 days after transplant or 30 days after the last dose of carfilzomib (day +7), and is considered to be a direct consequence and a related event as a result of the combination of conditioning chemotherapy, GVHD prophylaxis regimen and carfilzomib.

7.2.1.4 TREATMENT-RELATED MORTALITY [TRM]

TRM is defined as any death due to the transplant procedure, including death attributable directly to carfilzomib therapy. Death due to, but not limited to, the following events are considered a TRM: RRT, GVHD, infection and other transplant specific complications

7.2.2 EFFICACY END POINTS

7.2.2.1 EVENT

"Event" is defined as the occurrence of **"Relapse/Progression"** or **"Grade III-IV acute GVHD"** or "**Chronic GVHD requiring systemic treatment**".

7.2.2.2 RELAPSE / PROGRESSION

See **Appendix B** for disease-specific definitions of Response Criteria, including relapse/progression.

Patholigical confirmation of relapse is preferred. However, clinical diagnosis alone is allowed at the investigator's discretion if the manifestation is deemed unlikely to be an alternative diagnosis.

Progression is applied for disease not in complete remission or complete response at transplant.

7.2.2.3 GVHD

7.2.2.3.1 Acute GVHD

Pathological diagnosis of acute GVHD is preferred. Clinical diagnosis alone is allowed at the investigator's clinical judgment or following Institutional Guidelines for diagnosis of acute GVHD.

See **Appendix C** for Acute GVHD Assessment Guidelines. Acute GVHD onset may be beyond day +100. Grading of acute GVHD severity is mandatory and is the maximal grade that eventually occurs.

Only **grade III-IV acute GVHD** is defined as part of the "Event" in this study. However, the onset of Grade III-IV aGVHD is defined as the first day of acute GVHD onset of any grade.

7.2.2.3.2 Chronic GVHD

Diagnosis of chronic GVHD is mainly based on clinical evaluation. A biopsy is at the investigator's discretion. See **Appendix C** for Chronic GVHD Assessment Guidelines.

7.2.2.4 EVENT-FREE SURVIVAL [EFS]

7.2.2.4.1 EFS is defined as the period from day 0 to the "onset" day of the first **"Event"**.

7.2.24.2 Day 0 is the day of stem cell infusion (transplant) or the "LAST" day of stem cell infusion [Day 0B, Day 0C etc; in this case, Day 0A is the first day] if there are ≥2 days of stem cell infusion (transplant).

7.2.2.4.3 Event is defined as relapse/progression or clinical grade III-IV acute GVHD or chronic GVHD requiring systemic treatment.

7.2.2.4.4 The onset of "clinical Grade III-IV acute GVHD" is defined as the first day of any grade acute GVHD manifestation leading to the maximal clinical Grade III-IV aGVHD. Pathological dianosis of acute GVHD is preferred but not mandatory. Clinical diagnosis of acute GVHD at the investigator's discretion, after appropriate exclusion of other causes, is sufficient.

7.2.2.4.5 The onset of "chronic GVHD" is defined as the first day of initial chronic GVHD manifestation leading to subsequent systemic therapy.

Non-systemic or non-absorbable topical immunosuppressive medications, which are not considered systemic therapy, include

1. Topical preparation of immunosuppressive agents for skin, ocular and oral mucosa
2. Oral beclomethasone and oral budesonide for GI GVHD
3. Other immunosuppsive topical preparation which is not absorbed systemically.

Clinical diagnosis of chronic GVHD at investigator's discretion, after appropriate exclusion of other causes, is sufficient **[Appendix C].** Pathological diagnosis may be required as indicated.

7.2.4.4.6 The onset of Relapse/Progression is defined as the day of pathological diagnosis or, in case of no pathology confirmation, the day of first clinical manifestation of relapse/progression.

7.2.2.5 PROGRESSION-FREE SURVIVAL [PFS]

PFS is defined as the period from day 0 to the day of the first Progression /Relapse [see 7.2.2.2].

7.2.2.6 OVERALL SURVIVAL [OS]

OS is defined as the period from day 0 to the day of death from any cause.

7.3 CORRELATIVE STUDIES

We will obtain 6 heparinized (green top) blood samples (approximately 42 mL total) from each patient during the course of the study for pharmacodynamic and GVHD marker studies. [Table 3] Samples [a 7 mL extra draw each] will be collected coincidently with routine daily blood draws on the patients during transplant admission. All samples will be processed, frozen, and banked.

Correlative pharmacodynamic and GVHD markers study on day -6, 0, +3, +8, +14 and +30 are secondary endpoints, thus failure to acquire specimens will not be considered a protocol violation.

7.3.1 Pharmacodynamic (PD) Assay

A PD assay measuring the inhibition of proteasome chymotrypsin-like activity in peripheral blood mononuclear cells [PBMNs] will be used.

Peripheral blood will be collected in heparinized green top tubes prior to conditioning chemotherapy (day-6), prior to transplant (day 0) and after the first two doses of carfilzomib (day +3) when there remain an adequate number of PBMCs.

PBMCs will be isolated and frozen for PD assay of proteazome inhibition according to the manufacturer's protocol and samples and standards will be run in duplicate.

Samples will be batched and run simultaneously in order to maximize efficiency and enhance comparison of samples

7.3.2 Plasma GVHD Cytokine Assay

Peripheral blood will be collected in heparinized green top tubes prior to conditioning chemotherapy (day-6), prior to transplant (day 0) and after two and four doses of carfilzomib (day +3, +8, +14 and +30).

We will use commercially available ELISA kits to measure GVHD cytokine levels.

In each case, assays will be performed according to the manufacturer's protocol and samples and standards will be run in duplicate.

Samples will be batched and run simultaneously in order to maximize efficiency and enhance comparison of samples.

8. STUDY DISCONTINUATION

8.1 STOPPING RULE FOR EXCESSIVE GRAFT FAILURE

Stopping rules for excessive graft failure will apply to all subjects entered on study. Engraftment failure will be defined as the inability to achieve an ANC ≥500/uL and a platelet count ≥20,000/uL, without transfusion support, within 35 days post transplant. We consider engraftment failure in more than 10% of subjects to be unacceptable. Once 10 subjects have been enrolled and followed for 35 days, we will continually monitor the rate of EF35 and stop if we have strong evidence that the actual rate of EF35 is above 10%. Subjects who have not engrafted and die within 35 days of transplant will be considered to have graft failure and contribute to the number of events of EF35. The official stopping rules are displayed in **Table 3** and are the number of events that would produce a 95% confidence interval of which lower bound exceeds our upper limit of 10%. If AE35 equals or exceeds the numbers in **Table 3**, enrollment will be halted and the protocol will be re-evaluated and either closed or modified and re-approved before re-opening.

8.2 STOPPING RULE FOR EXCESSIVE MORTALITY

Stopping rules for excessive mortality will apply to all subjects entered on study. We consider all- cause mortality in more than 30% of all subjects within 100 days of transplant (ACM100) to be unacceptable. Once 10 subjects have been enrolled and followed for 100 days, we will continually monitor the rate of ACM100 and stop if we have strong evidence that the actual rate of ACM100 is above 30%. The official stopping rules are displayed in **Table 3** and are the number of events that would produce a 95% confidence interval of which lower bound exceeds our upper limit of 30%. If ACM100 equals or exceeds the numbers below, enrollment will be halted and the protocol will be re- evaluated and either closed or modified and re-approved before re-opening.

Although this stopping rule requires 100 days of follow-up for each subject, we will not halt accrual to wait for full follow-up of previously-enrolled subjects. For example, we will enroll the 11th subject as soon as they are eligible, regardless of whether the first 10 subjects have all been followed for 100 days. With a projected enrollment of just over 1 subject per month, we would expect to enroll the 11th and 12th subjects before the 10th subject is fully followed for ACM100. As a result, there is a possibility of enrolling one or two additional subjects on this study before we discover the stopping rule has been met.

Table 3: STOPPING RULES FOR EXCESS GRAFT FAILURE AND MORTALITY

Number of Enrolled Subjects	Number of Subjects with EF Within 35 Days	Number of Subjects with ACM Within 100 Days
10	4	7
15	5	9
20	6	11
25	7	13
30	8	15

9. ADVERSE EVENTS

9.1 ADVERSE EVENT REPORTING

Adverse events occurring following study registration, during standard conditioning chemotherapy, stem cell infusion until prior to carfilzomib administration, will not be reported. Study-related therapy does not begin until initiation of cafilzomib administration. Adverse events will be reported through day 100, directly related to the study drug (carfilzomib) as mentioned in section 5.2.6 previously. Following day 100, patients will still be followed for relapse, GVHD and survival data only.

9.2 DEFINITIONS OF ADVERSE EVENTS WITH COMMERCIALLY AVAILABLE AGENTS

This trial utilizes commercially available agents for transplant therapy for patients with hematological malignancies. Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases, an agent obtained commercially may be used for indications not included in the package label. In this case, the agent is still considered to be a commercial agent and the procedures described below should be followed.

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject whether or not it may have a causal relationship with this treatment. An AE includes significant exacerbation of any baseline medical condition including, but not limited to, the disease under study. Reporting requirements may include the following considerations: 1) the characteristics of the adverse event including the grade (severity); 2) the relationship to the study therapy (attribution); and 3) the prior experience (expectedness) of the adverse event.

Expected events are those that have been previously identified as resulting from administration of the agent. For commercially available agents, an adverse event is considered unexpected, for reporting purposes only, when either the type of event or the severity of the event is not listed in:

The current NCI Agent-Specific Adverse Event List (provided in the Drug Information Section of this protocol); or the drug package insert (for treatments with commercially available agents).

Except where otherwise specified, Common Terminology Criteria for Adverse Events (CTCAE) v.4.0 will be used to grade adverse events in this study.

9.3 DEFINITIONS OF ADVERSE EVENTS WITH INVESTIGATIONAL AGENTS

As previously stated, an AE is any untoward medical occurrence in a study subject administered an investigational product and that does not necessarily have a causal relationship with this treatment. An AE with investigational agents, therefore, can be any unfavorable and unintended sign (including laboratory finding), symptom or disease temporally associated with participation in an investigational study, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the subject signs a consent form for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current investigator's brochure (IB) or prescribing information for a marketed compound. Also, reports which add significant information on specificity or severity of a known, already documented AE, constitute unexpected AEs. For example, an event more specific or more severe than described in the IB would be considered "unexpected".

As in the case of commercially available agents, whenever possible, the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 should be used to describe the event and for assessing the severity of AEs. Any events representing a change in the CTCAE Grade need to be reported on the AE case report form. This includes any change in laboratory values.
For AEs not adequately addressed in the CTCAE, the severity **Table 4** below may be used:

Table 4

Severity	Description
GRADE 1 – Mild	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
GRADE 2 – Moderate	Mild to moderate limitation in activity—some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3 – Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4 – Life-threatening	Extreme limitation in activity, significant assistance required; life-threatening (immediate risk of death); significant medical intervention/therapy required, hospitalization or hospice care probable.
GRADE 5 – Fatal	Death

Any condition, laboratory abnormality, or physical finding with an onset date prior to the subject signing consent for study participation is considered to be pre-existing in nature and part of the subject's medical history.

9.4 CAUSALITY

Using the following criteria, the relationship of the AE to the study drug should be assessed as follows:

- **Yes**: The event is suspected to be related if:
  - there is a clinically plausible time sequence between onset of the AE and administration of study treatment; and/or
  - there is a biologically plausible mechanism for the study treatment to cause or contribute to the AE; and/or
  - the event responds to withdrawal of the study medication (dechallenge) and/or recurs with rechallenge (when clinically feasible); and/or
  - the AE cannot be reasonably attributed to concurrent/underlying illness, other drugs, or procedures
- **No**: The event is suspected to be not related if:
  - the AE is more likely to be explained by the subject's clinical state, underlying disease, concomitant medication, study or non-study procedure; and/or
  - the time of occurrence of the AE is not reasonably related to administration of study treatment; and/or
  - the event is unlikely to be related to the investigational product(s).

9.5 REQUIRED ADVERSE EVENT REPORTING

Therapy for hematological malignancies, with or without stem cell transplantation, is associated with significant toxicity. These toxicities are generally viewed as an anticipated consequence of therapy rather than an adverse event. To summarize, any grades 1 or 2 toxicities and any "expected" hematologic grade 3 or 4 toxicities will not be reported to the IRB nor to the FDA, as these are expected in patients undergoing stem cell transplantation for hematological malignancies.

DLTs and grade 3, 4 and 5 non-hematologic toxicity events with a possible, probable or definite relation to the commercial agent will be reported to the IRB and the FDA. In addition, high rate of engraftment failure or excessive mortality will trigger a stopping rule (section 8). Only adverse events, directly related to the study drug (carfilzomib) will be reported through day 100, as mentioned in section 5.2.6 previously.

9.6 HEMATOLOGIC TOXICITY AND DEFINITION OF PRIMARY ENGRAFTMENT FAILURE

For hematologic toxicity purposes, neutrophil recovery will be evaluated in all study subjects. Neutrophil toxicity will be graded by a modification of the Autologous Bone Marrow Transplant Studies Supplementary Toxicity Criteria. The occurrence of any grade 3-5 neutrophil toxicity will be reported as an adverse event within 7 days of its occurrence. Neutrophil toxicity will be evaluated post transplant using the following criteria:

Grade 3: Neutrophils< 500/uL for 35 – 56 days post therapy.
Grade 4: Neutrophils< 500/uL for > 56 days post therapy.
Grade 5: Death due to infection associated with neutrophil count < 500/uL.

The failure to achieve a neutrophil count >500/uL within 35 days of the stem cell infusion will be defined as primary engraftment failure, and reported as an adverse event and counted in the stopping rules for Engraftment Failure (section 8).

9.7 SERIOUS ADVERSE EVENT REPORTING PROCEDURES

All serious adverse events (SAE) which require reporting must be reported immediately (i.e. within 24 hours) to the Principal Investigator or a designee, followed by written documentation to the IRB from the Principal Investigator (including the PI's or designee's medical summary of the SAE) within 7 days of the Investigator's knowledge of occurrence. The Clinical Trials Office (CTO) staff will coordinate the reporting process between the investigator and the IRBMED and between the investigator and the FDA within the applicable regulatory reporting regulations. Copies of all correspondence and reporting documents will be maintained in a regulatory file held by the CTO.

Patients removed from study due to graft failure or other reasons will continue to be observed for adverse events for an additional 30 days. Deaths due to primary graft failure will be reported as a SAE regardless of when the patient was removed from study. Other significant events or deaths related to causes other than graft failure occurring after the 30-day observation period will be considered not related to the study drug and will therefore not be reported.

In addition to complying with all applicable regulatory reporting laws and regulations, Sponsors and Investigators are requested to immediately (within 24 hours) notify Amgen GlobalSafety of all serious adverse events/experiences (SAEs) prior to or at the same time they are reported to either an IRB or a regulatory authority.

Amgen Global Saftey:

- Hotline: Amgen Safety 800-77-AMGEN (800-772-6436)
- Safety Fax: 1-888-814-8653
- Secure connection email: svc-ags-in-us@amgen.com

See **Appendix E** for Amgen specific Policy on Adverse Reaction Reporting Procedure.

9.8 DATA SAFETY MONITORING BOARD (DSMB)

A Data and Safety Monitoring Committee (DSMC) consisting of protocol investigators and the data managers involved in the conduct of the trial will meet monthly to review the conduct and activity of the trial. A written summary will be made at each meeting and signed by the Principal Investigator (or a co-investigator designated by the principal investigator, if necessary) and the data manager responsible for the study.

During the course of these meetings, the investigators will discuss issues relating to (a) enrollment activity, (b) safety and adverse event reporting, (c) protocol violations or deviations by individual

subjects, (d) data entry and completeness. A determination will be made at each meeting to continue the trial without modification, modify the trial, or terminate the trial based the attainment of stopping rule criteria.

Reports of these DSMC meetings will be kept on file in the Cancer Center Clinical Trials office (CTO). The data manager assigned to the trial will be responsible for maintenance of these records. These Data and Safety Monitoring Reports and any other pertinent documents will be submitted to the University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Board (DSMB) for review on a monthly basis unless specified more frequently by a DSMB ruling.

10. STATISTICAL ANALYSIS

10.1 STUDY DESIGN

Subjects will be enrolled on the first dose level 1 of phase 1 part (Table 2), following a standard 3+3 dose escalation. For any given dose level, if none of the 3 subjects has developed a DLT, dose escalation will follow. If a DLT occurs in any dose level, the cohort will be expanded to 6. Further dose escalation will be made only if DLTs occur in <2 out of 6 subjects. If $\geq$2 of 6 develop DLTs, dose de-escalation will be made to the previous level. The optimal or maximal tolerated dose (MTD) is the dose level in which 0 of 3 or 1 of 6 subjects develops DLTs.

Table 1: DOSE ESCALATION SCHEDULE

Dose Level	Carfilzomib (mg/m^2)			
	Day +1	Day +2	Day +6	Day +7
1	20	20	20	20
2	20	20	27	27
3	20	20	36	36
4	20	20	45	45

After MTD or the optimal dose level is identified, a total of 35 subjects are needed on this dose level. [See 10.2].

10.2 SAMPLE SIZE CONSIDERATIONS

Based on the University of Michigan experience on fludarabine-based related donor allo-HCT, the event-free survival at 1 year was 15% [unpublished data]. Event is defined as relapse/progression, grade III-IV acute GVHD or chronic GVHD requiring systemic therapy.

We expect that adding carfilzomib to a standard regimen will increase EFS at 1 year from 15% to 35% and 35 subjects need to be evaluated for primary efficacy endpoint, with α error of 0.05 and statistical power of 80%. Thus, we will enroll 37 patients in the optimal dose used in the phase II part, assuming 2 patients will not be evaluable for endpoint analysis.

$$N = \frac{\left(Z_\alpha \sqrt{p_0(1-p_0)} + Z_\beta \sqrt{p_1(1-p_1)}\right)^2}{(p_0 - p_1)^2}$$

N = Number required
p_0 = Historical probability of event within 1 year = (1-0.15) = 0.85
p_1 = Desired probability of event within 1 year = (1-0.35) = 0.65
Z_α = 1.96 for 5% significance level
Z_β = 0.84 for 80% power

For phase 1 part, up to 18 additional subjects may be needed for possibility of 6 subjects per cohort. Thus, we plan to enroll a maximum 55 patients (18 max Phase I, 37 Phase II).

10.3 PLANNED METHODS OF ANALYSIS

10.3.1 PRIMARY AND SECONDARY OUTCOMES

OS and PFS will be modeled using the Kaplan-Meier method. TRM, relapse and GVHD will be estimated with the cumulative incidence.

10.3.2 LABORATORY CORRELATES

The association of the values and percentage change of each NFκB and GVHD biomarker with the primary and secondary outcomes will be estimated with Cox regression (for OS and PFS) and competing risks regression (TRM, relapse, and GVHD).

10.4 SAFETY ANALYSIS

Subjects will be followed closely for AEs and SAEs, the details of which including incidences, relationship, severity, etc, will be reported to IRB and Amgen Global Saftey within required intervals. Once 10 patients have been followed for 35 days, graft failure rate will be determined for excess graft failure [section 8.1]. Once they have been followed for 100 days, all- cause-mortality will be determined for excess all-cause-mortality [section 8.2].

11. INVESTIGATIONAL PRODUCT

11.1 CARFILZOMIB DESCRIPTION

Carfilzomib is a synthetic small molecule peptide bearing the chemical name (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide.The molecular formula is $C_{40}H_{57}N_5O_7$ and the molecular weight is 719.91. It specifically functions as an inhibiton of the chymotrypsin-like activity of the 20S proteasome which leads to the accumulation of protein substrates within the cell and induction of apoptosis.

11.2 FORMULATION

Carfilzomib for Injection will be provided as a lyophilized powder which, when reconstituted, contains 2 mg/mL isotonic solution of carfilzomib Free Base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-b-cyclodextrin (SBE-b-CD, Captisol®).

11.3 STORAGE

Lyophilized Carfilzomib for Injection must be stored at 2–8ºC under the conditions outlined in the separate Pharmacy Manual, in a securely locked area to which access is limited to appropriate study personnel. See **INSTRUCTIONS FOR STORAGE AND USE OF LYOPHILIZED CARFILZOMIB FOR INJECTION,** for Investigator Sponsored Trials (IST's), 19 February 2013, Version 3.0.

11.4 ACCOUNTABILITY

Amgen Inc. and the Investigator will maintain records of each shipment of investigational product. The records will document shipment dates, method of shipment, batch numbers, and quantity of vials contained in the shipment. Upon receipt of the investigational product, the designated recipient at the study site will inspect the shipment, verify the number and condition of the vials, and prepare an inventory or drug accountability record.

Drug accountability records must be readily available for inspection by representatives of Amgen Inc. and by regulatory authorities.

Empty and partially used vials should be accounted for and destroyed at the study site in accordance with the internal standard operating procedures. Drug destruction records must be readily available for inspection by representatives of Amgen Inc. and by regulatory authorities.

Only sites that cannot destroy unused drug on-site will be required to return their unused supply of investigational product.

12. REGULATORY OBLIGATIONS

12.1 INFORMED CONSENT

Informed consent shall be obtained prior to an enrollment of a subject into the study.

12.2 COMPLIANCE WITH LAWS AND REGULATIONS

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, Health Canada, any applicable local health authority, and Institutional Review Board (IRB) or Ethics Committee requirements.

This study must have the approval of a properly constituted IRB or Ethics Committee. Before the investigational drug is shipped to the Investigator, the Investigator or designee will provide Amgen Inc. with a copy of the IRB or Ethics Committee approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

The Investigator or designee will be responsible for obtaining annual IRB or Ethics Committee re-approval throughout the duration of the study. Copies of the Investigator's annual report to the IRB or Ethics Committee and copies of the IRB or Ethics Committee continuance of approval must be provided to Amgen Inc. as follows:

Amgen Inc..
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

The Investigator is also responsible for notifying their IRB or Ethics Committee of any significant adverse events that are serious and/or unexpected. The Sponsor-Investigator is also required to notify the FDA in writing of any SAE that is both unexpected and related to the study drug, within 15 days of knowledge of the event, and within 7 days of a death related to the study drug.

All safety information will be provided to investigator initiated study PI/institution **in the Investigator Brochure (IB)**. Updates to the IB will be sent to the PI/institution in a timely manner to allow him/her to fulfill his/her obligation for timely reporting to the IRB/ECs and other Investigators participating in the study.
Upon completion of the trial, the Investigator must provide the IRB or Ethics Committee and Amgen Inc. with a summary of the trial's outcome.

12.3 PRE-STUDY DOCUMENTATION REQUIREMENTS

Informed consent, eligibility checklist and registration forms shall be obtained before subjects can receive any study treatments, including conditioning chemotherapy.

12.4 SUBJECT CONFIDENTIALITY

Subject medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician.

The Investigator/Institution will permit direct access to source data and documents by Amgen Inc., its designee, the FDA and/or other applicable regulatory authority. The access may consist of trial-related monitoring, audits, IRB or Ethics Committee reviews, and FDA inspections.
Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually

Identifiable Health Information, 45 CFR 164.508.

13. ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

Shall any evidence of safety concerns or lack of efficacy arises, study enrollment will be on hold Investigation and assessment will be performed for a determination to amend or terminate the study.

13.2 STUDY DOCUMENTATION AND ARCHIVE

Required study documentation and archive will be maintained by institutional Clinical Trial Office and Amgen Inc.

13.3 STUDY MONITORING AND DATA COLLECTION

13.3.1 Subject Safety

A Data and Safety Monitoring Committee (DSMC) consisting of protocol investigators and the data managers involved in the conduct of the trial will meet monthly to review the conduct and activity of the trial. A written summary will be made at each meeting and signed by the Principal Investigator (or a co-investigator designated by the principal investigator, if necessary) and the data manager responsible for the study.

During the course of these meetings, the investigators will discuss issues relating to (a) enrollment activity, (b) safety and adverse event reporting, (c) protocol violations or deviations by individual subjects, (d) data entry and completeness. A determination will be made at each meeting to continue the trial without modification, modify the trial, or terminate the trial based on the attainment of stopping rule criteria.

Reports of these DSMC meetings will be kept on file in the Cancer Center Clinical Trials office (CTO). The data manager assigned to the trial will be responsible for maintenance of these records. These Data and Safety Monitoring Reports and any other pertinent documents will be submitted to the University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Board (DSMB) for review on a monthly basis unless specified more frequently by a DSMB ruling.

13.3.2 Lack of Efficacy

Subjects will be followed closely for AEs and SAEs, which will be reported to IRB and Amgen Inc. and required interval. Once 20-25 subjects have been followed for 100 days, we will perform an interim analysis to evaluate whether the projected primary endpoint will be potentially achieved or, in contrast, relapse and/or GVHD increase(s).

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15. APPENDICES

APPENDIX A

KARNOFSKY PERFORMANCE SCALE

Scale %	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor symptoms of disease
80	Normal activity with effort, some signs of symptoms of disease
70	Cares for self (consistent with age), unable to carry on normal activity or do active work/school/play
60	Requires occasional assistance (beyond age-appropriate care), but is able to care for most of their needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special caer and assistance
30	Severely disabled, hospitalization is indicated although death is not imminent
20	Hospitalization is necessary, very sick, active support treatment is necessary
10	Moribund, fatal processes progressing rapidly

APPENDIX B

TABLE A. RECOMMENDED RESPONSE DEFINITIONAFTER TREATMENT FOR CLL

Parameter	Complete Response	Partial Response	Progressive Disease	Stable Disease
***Lymphadenopathy**	None above1.0 cm	Decrease ≥ 50% from baseline	Increase ≥50% over baseline	Change -49% to +49% from baseline
Liver and/or spleen size	Normal size	Decrease ≥ 50% from baseline	Increase ≥50% over baseline	Change -49% to +49% from baseline
Constitutional symptoms	None	Any	Any	Any
Leukocyte Count	≥ 1500/mm^3	<1500/mm^3 AND ≥ 50% improvement from pre-CloBu2 baseline	Any	Any
Circulating B lymphocytes	Normal	Decrease of ≥ 50% from pre-CloBu2 baseline	Increase ≥ 50% overpre-CloBu2 baseline	Change -49% to +49%from pre-CloBu2 baseline
Platelet count	≥ 100,000/mm^3 (untransfused)	<100,000/mm^3 AND Increase ≥50% from pre-CloBu2 baseline	Decrease ≥50% from pre-CloBu2 baseline	<100,000/mm^3 AND Change -49% to +49%from pre-CloBu2 baseline
Hemoglobin	≥ 11.0 g/dL (untransfused)	<11.0 g/dL AND Increase of ≥ 2 g/dL over pre-CloBu2baseline	Decrease of ≥2 g/dL from pre-CloBu2 baseline	<11.0 g/dL AND Change -1.9 g/dL to -1.9 g/dLfrom pre-CloBu2 baseline
Marrow	Normocellular, AND < 30% lymphocytes, AND no B-lymphoid nodules	Hypocellular, OR B-lymphoid nodules, OR Decrease of lymphocytes ≥ 50% from baseline BUT remaining ≥ 30% involvement , Or not done	Increase of lymphcytes >30% from baseline	No change of marrow infiltratefrom baseline

Modified from Eichhorst B and Hallek M. Revision of the guidelines for diagnosis and therapy of chronic lymphocytic leukemia (CLL). Best Practice & Research Clinical Haematology 2007;20:469-477.

* Sum of the product of the diameters of multiple lymph nodes

TABLE B. RECOMMENDED RESPONSE CRITERIA FOR LYMPHOMA (including PET CT)

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
Complete Response	Disappearance of all evidenceof disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PETnegative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy indeterminate by morphology,immunohistochemistr should be negative
Partial Response	Regression of measurable disease AND no new sites	≥50% decrease in SPD of up to 6largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PETpositive at previously involved site (b) Variably FDG-avid or PETnegative; regression on CT	≥50% decrease in SPD of nodules (for single nodule ingreatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to thera p cell type should be specified
Stable Disease	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease AND no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or Progressive disease	Any new lesion or increase by 50% of previously involved sites from nadir	(a) Appearance of a new lesion(s) ≥1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis (b) Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	≥50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma.J of Clin Oncol 2007;25(5):579-586.
Recommended for use with Diffuse Large B-CellLymphoma and Hodgkin Disease/Lymphoma.
SPD denotes sum of the product of the diameters.

TABLE C. RECOMMENDED RESPONSE CRITERIA FOR LYMPHOMA (not including PET CT)

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
Complete Response	Normal	Normal	Normal	Normal
Complete Response (unconfirmed)	Normal	Normal	Normal	indeterminate
	Normal	Normal	≥75% decrease	Normal or indeterminate
Partial Response	Normal	Normal	Normal	Positive
	Normal	≥ 50% decrease	≥ 50% decrease	Irrelevant
	Decrease in liver/spleen	≥ 50% decrease	≥ 50% decrease	Irrelevant
Relapse/Progression	Enlarging liver/spleen, new sites	New or increased	New or increased	Reappearance

Cheson BD, Horning SJ, Coiffier B et al. Report of an International Workshop to Standardize Response Criteria forNon-Hodgkin's Lymphoma. J of Clin Oncol 17(4); 1999: 1244.

TABLE D.

Cheson B, Fisher R, Barrington S, et al. Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma – the Lugano Classification. J Clin Oncol 2014;32:3059-3067.

TABLE D. (CONT'ED)

Cheson B, Fisher R, Barrington S, et al. Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma – the Lugano Classification. J Clin Oncol 2014;32:3059-3067.

TABLE D. (CONT'ED)

Cheson B, Fisher R, Barrington S, et al. Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma – the Lugano Classification. J Clin Oncol 2014;32:3059-3067.

TABLE E. RECOMMENDED RESPONSE CRITERIA FOR MULTIPLE MYELOMA [MM]

Response subcategory	*Response criteria*
Complete response[a] (CR)	Negative immunofixation of serum and urine and Disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow
Stringent complete response (sCR)	CR as defined above plus Normal FLC ratio and Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Very good partial response (VGPR)[a]	Serum and urine M-component detectable by immunofixation but not on electrophoresis or ⩾90% or greater reduction in serum M-component plus urine M-component <100 mg per 24 h
Partial response (PR)	⩾50% reduction of serum M protein and reduction in 24-h urinary M protein by ⩾90% or to <200 mg per 24 h If the serum and urine M protein are unmeasurable, a ⩾50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M protein criteria If serum and urine M protein are unmeasurable, and serum free light assay is also unmeasurable, ⩾50% reduction in bone marrow plasma cells is required in place of M protein, provided baseline percentage was ⩾30% In addition to the above criteria, if present at baseline, ⩾50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR or progressive disease
Progressive disease (PD)[a]	Increase of 25% from lowest response value in any one or more of the following: Serum M-component (absolute increase must be ⩾0.5 g/100 ml)[c] and/or Urine M-component (absolute increase must be ⩾200 mg per 24 h) and/or Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >100 mg/l) Bone marrow plasma cell percentage (absolute % must be ⩾10%) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/100 ml) that can be attributed solely to the plasma cell proliferative disorder

[a]Note clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.
All response categories (CR, sCR, VGPR and PR) require two consecutive assessments made at any time before the institution of any new therapy; complete, PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.
Adapted with permission from Durie *et al.* [29]
c for progressive disease, serum M-component increases of ⩾1 gm/100 ml are sufficient to define relapse if starting M-component is ⩾5 gm/100 ml.

TABLE E. RECOMMENDED RESPONSE CRITERIA FOR MULTIPLE MYELOMA [CONT'ED]

Category	*Criteria*
Definition of relapsed myeloma and relapsed and refractory myeloma	Relapsed myeloma: at least one prior regimen, and not meeting criteria for relapsed and refractory myeloma Relapsed and refractory myeloma: relapse of disease while on salvage therapy, or progression within 60 days of most recent therapy
Minor response (MR) in patients with relapsed refractory myeloma	⩾25% but <49% reduction of serum M protein *and* reduction in 24 h urine M protein by 50–89%, which still exceeds 200 mg per 24 h In addition to the above criteria, if present at baseline, 25–49% reduction in the size of soft tissue plasmacytomas is also required No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Progression to active myeloma in patients with smoldering myeloma	Evidence of progression based on the IMWG criteria for progressive disease in myeloma (Table 5) *and* Any one or more of the following felt related to the underlying clonal plasma cell proliferative disorder Development of new soft tissue plasmacytomas or bone lesions Hypercalcemia (>11 mg/100 ml) Decrease in hemoglobin of ⩾2 g/100 ml Serum creatinine level ⩾2 mg/100 ml

Abbreviation: IMWG, International Myeloma Working Group.
Adapted with permission from Anderson *et al*.[30]

TABLE F. RECOMMENDED RESPONSE CRITERIA FOR WALDENSTROM'S MACROGLOBULINEMIA [WM]

Complete Response	CR	IgM in normal range, and disappearance of monoclonal protein by immunofixation; no histological evidence of bone marrow involvement, and resolution of any adenopathy /organomegaly (ifpresent at baseline), along with no signs or symptoms attributable to WM. Reconfirmation of the CR status is required by repeat immunofixationstudies.
VeryGoodPartial Response	VGPR	A 90% reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on Physical examination or on CT scan. No new symptoms or signs of active disease.
Partial Response	PR	A 50% reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CTscan.No new symptoms or signs of active disease.
MinorResponse	MR	A 25% but <50% reduction of serum IgM. No new symptoms or signs of active disease.
StableDisease	SD	A <25% reduction and <25%increase of serum IgM without progression of adenopathy/organomegaly, cytopenias or clinically significant symptoms due to disease and/or signs of WM.
Progressive Disease	PD	A ≥25% increase in serum IgM by protein electrophoresis confirmed by a second measurement or progression of clinically significant findings due to disease (i.e. anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever 38.4°C, drenching nightsweats, 10% body weight loss, or hyperviscosity, neuropathy, symptomatic cryoglobulinemia or amyloidosis) attributable to WM.

Treon SP, Merlini G, Morra E, et al. Report from the Sixth International Workshop on Waldenstrom's Macroglobulinemia. Clin Lymph Myeloma Leukemia 2011; 11:69-73.
VargheseAM, RawstronAC,AshcroftAJ, et al.Assessment of bone marrow response in Waldenström's macroglobulinemia. Clin Lymph Myeloma 2009; 9:53-5. Table 1. Summary of Updated Response Criteria adopted at the 6th International Workshop on Waldenstrom's Macroglobulinemia.

TABLE G. RECOMMENDED RESPONSE CRITERIA FOR ACUTE LYMPHOBLASTIC LEUKEMIA [ALL]

Response Criteria for Blood and Bone Marrow

CR
No circulating blasts or extramedullary disease
No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement
Trilineage hematopoiesis (TLH) and <5% blasts
Absolute neutrophil count (ANC) >1000/microL
Platelets >100,000/microL
No recurrence for 4 weeks
CR with incomplete blood count recovery (CRi)
Recovery of platelets but <100,000 orANC is <1000/microL
Overall response rate (ORR=CR + CRi)
Refractory disease
Failure to achieve CR at the end of induction
Progressive disease (PD)
Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease
Relapsed disease
Reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after a CR

Response Criteria for CNS Disease

CNS remission:Achievement of CNS-1 status ( ) in a patient with CNS-2 or CNS-3 status at diagnosis.
CNS relapse: New development of CNS-3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome.

Response Criteria for Mediastinal Disease

CR: Complete resolution of mediastinal enlargement by CT.
CR Unconfirmed (CRu): Residual mediastinal enlargement that has regressed by >75% in the sum of the product of the greatest perpendicular diameters (SPD).
PR: >50% decrease in the SPD of the mediastinal enlargement.
PD: >25% increase in the SPD of the mediastinal enlargement.
No Response (NR): Failure to qualify for PR or PD.
Relapse: Recurrence of mediastinal enlargement after achieving CR or CRu.

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TABLE H. RECOMMENDED RESPONSE CRITERIA FOR ACUTE MYELOID LEUKEMIA [AML]

Category	Definition
Complete remission (CR)*	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0×10^9/L (1000/μL); platelet count > 100×10^9/L (100 000/μL); independence of red cell transfusions
CR with incomplete recovery (CRi)†	All CR criteria except for residual neutropenia (< 1.0×10^9/L [1000/μL]) or thrombocytopenia (< 100×10^9/L [100 000/μL])
Morphologic leukemia-free state‡	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	Relevant in the setting of phase 1 and 2 clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Cytogenetic CR (CRc)§	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular CR (CRm)‖	No standard definition; depends on molecular target
Treatment failure	
Resistant disease (RD)	Failure to achieve CR or CRi (general practice; phase 2/3 trials), or failure to achieve CR, CRi, or PR (phase 1 trials); only includes patients surviving ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
Relapse¶	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease

TABLE I. RECOMMENDED RESPONSE CRITERIA FOR CHRONIC MYELOID LEUKEMIA [CML]

CRITERIA FOR HEMATOLOGIC, CYTOGENETIC AND MOLECULAR RESPONSE

Complete Hematologic Response [1]

Complete normalization of peripheral blood counts with leukocyte count <10 x 10^9/L
Platelet count < 450 x 10^9/L
No immature cells, such as myelocytes, promyelocytes, or blasts in peripheral blood
No signs and symptoms of disease with disappearance of palpable splenomegaly

Cytogenetic Response [2]

Complete- No Ph-positive metaphases
Partial- 1%-35% Ph-positive metaphases
Major- 0%-35% Ph-positive metaphases (complete + partial)
Minor- >35% Ph-positive metaphases

Molecular Response [3,4]

Complete molecular response - no detectable BCR-ABL by QPCR (International scale) using an assay with a sensitivity of at least 4.5 logs below the standardized baseline.
Major molecular response - 3-log reduction in International Scale of BCR-ABL mRNA

Relapse

Any sign of loss of response (defined as hematologic or cytogenetic relapse)
1 log increase in BCR-ABLtranscript levels with loss of MMR should prompt marrow evaluation for loss of CCyR but is not itself defined as relapse.

1. Faderl S et al: Chronic myelogenous leukemia: Biology and therapy.Ann Intern Med 1999;131:207 219.
2. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
3. HughesTP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med 2003;349:1423-1432.
4. HughesT, Deininger M, HochhausA, et al. Monitoring CMLpatients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABLtranscripts and kinase domain mutations and for expressing results. Blood 2006;108:28-37.

TABLE J.

MODIFIED INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR ALTERING NATURAL HISTORY OF MYELODYSPLASTIC SYNDROME

Category	Response criteria (responses must last at least 4 wk)
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines*
	Persistent dysplasia will be noted*†
	Peripheral blood‡
	Hgb ≥ 11 g/dL
	Platelets ≥ 100 × 10^9/L
	Neutrophils ≥ 1.0 × 10^9/L†
	Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except:
	Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5%
	Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment†
	Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following:
	Return to pretreatment bone marrow blast percentage
	Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets
	Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete
	Disappearance of the chromosomal abnormality without appearance of new ones
	Partial
	At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with:
	Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts
	5%-10% blasts: ≥ 50% increase to > 10% blasts
	10%-20% blasts: ≥ 50% increase to > 20% blasts
	20%-30% blasts: ≥ 50% increase to > 30% blasts
	Any of the following:
	At least 50% decrement from maximum remission/response in granulocytes or platelets
	Reduction in Hgb by ≥ 2 g/dL
	Transfusion dependence
Survival	Endpoints:
	Overall: death from any cause
	Event free: failure or death from any cause
	PFS: disease progression or death from MDS
	DFS: time to relapse
	Cause-specific death: death related to MDS

Deletions to IWG response criteria are not shown.

To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.

*Dysplastic changes should consider the normal range of dysplastic changes (modification).[41]

†Modification to IWG response criteria.

‡In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419-425.

TABLE J. (CONT'ED)

MODIFIED INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR HEMATOLOGIC IMPROVEMENT FOR MYELODYSPLASIA

Hematologic improvement*	Response criteria (responses must last at least 8 wk)†
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL
	Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation†
Platelet response (pretreatment, $< 100 \times 10^9$/L)	Absolute increase of $\geq 30 \times 10^9$/L for patients starting with $> 20 \times 10^9$/L platelets
	Increase from $< 20 \times 10^9$/L to $> 20 \times 10^9$/L and by at least 100%†
Neutrophil response (pretreatment, $< 1.0 \times 10^9$/L)	At least 100% increase and an absolute increase $> 0.5 \times 10^9$/L†
Progression or relapse after HI‡	At least 1 of the following:
	At least 50% decrement from maximum response levels in granulocytes or platelets
	Reduction in Hgb by ≥ 1.5 g/dL
	Transfusion dependence

Deletions to the IWG response criteria are not shown.
To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
Hgb indicates hemoglobin; RBC: red blood cell; HI: hematologic improvement.
*Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) $\geq$ 1 week apart (modification).
†Modification to IWG response criteria.
‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419-425.

APPENDIX C

TABLE A. RECOMMENDED GRADING AND STAGING OF ACUTE GVHD

Organ	Skin	Liver	Gut
Individual Organ Staging			
Stage	BSA (%)*	Bilirubin (mg/dL)	Diarrhea (mL/day)
1	Rash <25	2-2.9	500-1000 or biopsy-proven upper GI involvement
2	Rash 25-50	3-6	1000-1500
3	Rash >50	6.1 to >15	1500-2000
4	Generalized erythro-derma with bullae	>15	>2000 or severe abdominal pain with or without ileus
Consensus Grading			
I	Stage 1-2	None	None
II	Stage 3	Stage 1	Stage 1
III	–	Stage 2-3	Stage 2-4
IV	Stage 4	Stage 4	–
IBMTR Grading			
A	Stage 1	None	None
B	Stage 2	Stage 1 or 2	Stage 1 or 2
C	Stage 3	Stage 3	Stage 3
D	Stage 4	Stage 4	Stage 4

*Use "rule-of-nines" to determine BSA.
BSA = body surface area; GI = gastrointestinal; IBMTR = International Bone Marrow Transplant Registry.

TABLE B. RECOMMENDED CATEGORIES OF ACUTE AND CHRONIC GVHD

Category	Time of Symptoms after HCT or DLI	Presence of Acute GVHD Features*	Presence of Chron GVHD Features*
Acute GVHD			
Classic acute GVHD	**≤100 d**	**Yes**	**No**
Persistent, recurrent, or late-onset acute GVHD	**>100 d**	**Yes**	**No**
Chronic GVHD			
Classic chronic GVHD	**No time limit**	**No**	**Yes**
Overlap syndrome	**No time limit**	**Yes**	**Yes**

GVHD indicates graft-versus-host disease; HCT, hematopoietic cell transplantation; DLI, donor lymphocyte infusion.
*See Table 1 for features.

TABLE C. CLINCIAL FEATURES OF CHRONIC GVHD

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)	Other Features*	Common (Seen with Both Acute and Chronic GVHD)
Skin	Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosus-like features	Depigmentation	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric; affects most nails)†		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Scaling, papulosquamous lesions	Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes) Premature gray hair	
Mouth	Lichen-type features Hyperkeratotic plaques Restriction of mouth opening from sclerosis	Xerostomia Mucocele Mucosal atrophy Pseudomembranes† Ulcers†		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes‡ Cicatricial conjunctivitis Keratoconjunctivitis sicca‡ Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	
Genitalia	Lichen planus-like features Vaginal scarring or stenosis	Erosions† Fissures† Ulcers†		
GI tract	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus†		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children)
Liver				Total bilirubin, alkaline phosphatase >2 × upper limit of normal† ALT or AST >2 × upper limit of normal†
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs and radiology‡		BOOP
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis‡	Edema Muscle cramps Arthralgia or arthritis	

TABLE C. CLINCIAL FEATURES OF CHRONIC GVHD [Cont'ed]

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)	Other Features*	Common (Seen with Both Acute and Chronic GVHD)
Hematopoietic and immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hypergammaglobulinemia Autoantibodies (AIHA and ITP)	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

GVHD indicates graft-versus-host disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BOOP, bronchiolitis obliterans-organizing pneumonia; PFTs, pulmonary function tests; AIHA, autoimmune hemolytic anemia; ITP, idiopathic thrombocytopenic purpura.

*Can be acknowledged as part of the chronic GVHD symptomatology if the diagnosis is confirmed.

†In all cases, infection, drug effects, malignancy, or other causes must be excluded.

‡Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Schirmer test for eyes).

TABLE D. RECOMMENDED ORGAN SCORING OF CHRONIC GVHD

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐	☐ No Symptoms	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
MOUTH	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI TRACT	☐ No symptoms	☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation
LIVER	☐ Normal LFT	☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	☐ Bilirubin or enzymes > 5 x ULN

TABLE D. RECOMMENDED ORGAN SCORING OF CHRONIC GVHD [Cont'ed]

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LUNGS† FEV1 ☐ DLCO ☐	☐ No symptoms ☐ FEV1 > 80% **OR** LFS=2	☐ Mild symptoms (shortness of breath after climbing one flight of steps) ☐ FEV1 60-79% **OR** LFS 3-5	☐ Moderate symptoms (shortness of breath after walking on flat ground) ☐ FEV1 40-59% **OR** LFS 6-9	☐ Severe symptoms (shortness of breath at rest; requiring 0_2) ☐ FEV1 ≤39% **OR** LFS 10-12
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
GENITAL TRACT	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

Other indicators, clinical manifestations or complications related to chronic GVHD (check all that apply and assign a score to its severity (0-3) based on its functional impact where applicable (none – 0,mild -1, moderate -2, severe – 3)

Esophageal stricture or web___	Pericardial Effusion___	Pleural Effusion(s)___
Ascites (serositis)___	Nephrotic syndrome___	Peripheral Neuropathy___
M yasthenia Gravis___	Cardiomyopathy___	Eosinophilia > 500µl___
Polymyositis___	Cardiac conduction defects___	Coronary artery involvement___
Platelets <100,000/µl ___	Progressive onset___	

OTHERS: Specify:_____

APPENDIX D: NCI-CTCAE VERSION 4.0

Common Terminology Criteria for Adverse Events (CTCAE) of the
National Cancer Institute (NCI) v4.0

Publish Date: September 15, 2009
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

APPENDIX E:
AMGEN INC. DRUG SAFETY

ADVERSE EVENTS REPORTING PROCEDURES

All AEs (e.g., any new event or worsening in severity or frequency of a pre-existing condition or laboratory finding) with an onset date after the subject signs consent for study participation must be promptly documented on the appropriate summary. Details of the event must include severity, relationship to study drug, duration, action taken, and outcome. Serious adverse events (SAEs) will be recorded on the appropriate form.

All AEs that are considered related to study drug must be followed to resolution or stabilization if improvement is not expected.
AEs should be reported from the time the subject signs consent through 30 days post-last dose of study drug or initiation of a new anti-cancer therapy, whichever occurs first. In addition, the Investigator should report any AE that may occur after this time period that is believed to have a reasonable possibility of being associated with study drug. If a subject is randomized but discontinues study prior to receiving any study drug, AEs must be reported through the end-of-study visit. AEs which completely resolve and then recur should be recorded as a new AE. For subjects who complete the end of study visit less than 30 days following their last dose of study drug, a follow up of ongoing AEs should be attempted by telephone, and documented in the subject's source. AEs continuing at 30 days post-last dose should have a comment in the source by the Investigator that the event has stabilized or is not expected to improve.

The Principal Investigator is responsible for evaluating all AEs, obtaining supporting documents, and determining that documentation of the event is adequate. Adverse events will be assigned a severity grade using the NCI-CTCAE grading scale v4.0.
All Grade 3 and 4 laboratory abnormalities must be recorded as AEs on the CRF. Grade 1 and 2 abnormalities should only be recorded if they require treatment or are otherwise considered clinically significant by the Investigator.

The Principal Investigator may delegate these duties to Sub-investigators and must ensure that these Subinvestigators are qualified to perform these duties under the supervision of the Principal Investigator and that they are listed on the FDA Form 1572.

A. SERIOUS ADVERSE EVENTS DEFINITIONS

An SAE is one that meets the following criteria:

- Death
- Life threatening experience defined as any adverse experience that places the subject, in the view of the Investigator, at immediate risk of death at the time of occurrence; i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of an existing hospitalization (except scheduled hospitalizations for non-acute, unrelated cause such as an elective surgery)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in the offspring of an exposed subject
- Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE, when, based upon appropriate medical judgment, it jeopardizes the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Any death occurring within 30 days of the subject receiving study drug, regardless of the subject having discontinued from the study must be reported to the Sponsor as an SAE.

B. SERIOUS ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS

All SAEs occurring from the time that the subject signs consent for study participation through 30 days after the last administered dose of study drug will be reported. All SAEs regardless of relationship to study drug must be followed to resolution or to stabilization if improvement or resolution is not expected.
If a subject is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report as well as the appropriate form for Study Discontinuation.

The sponsor is responsible for notifying the appropriate Regulatory Agencies, when required, and in accordance with applicable laws and regulations of any Expedited Safety Reports. Generally, these are all SAEs that are judged to be unexpected and related to study drug(s), as specified in ICH E2B guidelines: Clinical Safety Data Management Data Elements for Transmission of Individual Case Safety Reports. However, certain Regulatoru Agencies may have additional requirements for expedited safety report submissions.
This submission of IND Safety Reports (North America) or Suspected Unexpected Serious Adverse Reactions (SUSARS [Europe]) will be cross referenced according to local regulations to Amgen Inc. Saftey at the time of submission.

The Investigator is also responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with local regulations, of all SAEs.
[ONLY FOR EUROPE: The Investigator is responsible to create an Annual Safety Report of the overall conduct of the specific study for distribution to the EC(s) and Regulatory Agencies. Amgen Inc. in addition creates an Annual Safety Report including listings of all Serious Adverse Drug Reactions from both Amgen Inc. sponsored research and Investigator Sponsored Trials, and Amgen Inc. submits this report to the Regulatory Agencies in any country where there is clinical development or where the product is marketed. Amgen Inc. will provide the Sponsor with the summary sections and overall conclusions of this Annual Safety Report.]Additionally, the Investigator is responsible for reporting adverse events to Amgen Inc. as described below:

Expedited Reporting by Investigator to Amgen Inc.
The Investigator must inform Amgen Inc. in writing by Fax at the contact information listed below of all Expedited Safety Reports submitted to the relevant Regulatory Agencies. These notifications should be performed in parallel to the Regulatory Agency submissions [e.g., within 7 calendar days for any Fatal or Life-threatening SUSARs and within 15 calendar days for all other

SUSARs}, but in no case any later than 1 business day from the submission date. This must be documented on a FDA 3500A MEDWATCH or CIOMS I (for EU studies) form. This form must be completed and supplied to Amgen Inc. in English.

The initial report must be as complete as possible, at a minimum including the serious adverse event term (s), patient identifier, date of awareness of the event, an assessment of the causal relationship between the event and the investigational product(s), and name of the reporter (investigator). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow- up MEDWATCH or CIOMS I form, and submitted to Amgen Inc. in the same timelines as outlined above. The Amgen Inc. protocol and the institutional protocol number should be included on all reports to Amgen Inc..

All other SAE's will be sent to Amgen Inc. on a biannual basis in the form of a line listing in English. The line listing must include the following information; patient initials, date of birth, sex, SAE onset date, SAE stop date, event name (term), outcome, date of first dose of study drug(s), date of last dose of study drug(s) prior to the event, action taken with study drug(s) the Investigator's assessment of causality (relationship to carfilzomib), and the Investigator's assessment of expectedness to carfilzomib. The sponsor reserves the right to review the CRFs or source documents in response to any inquires by regulatory agencies that the sponsor may receive.

Amgen Global Safety
Safety contact information:

- Hotline: Amgen Safety 800-77-AMGEN (800-772-6436)
- Safety Fax: 1-888-814-8653
- Secure connection email: svc-ags-in-us@amgen.com

C. PREGNANCY

If a subject or spouse or partner of a subject becomes pregnant while enrolled in this clinical trial or up to three months following administration of carfilzomib, Amgen Global Safety must be notified within 24 hours of the Investigator, designee, or site personnel learning of the pregnancy (See Amgen Global Safety and Pharmacovigilance Contact information above). If the subject is pregnant, carfilzomib must be withheld.

Subjects, spouses, or partners will be followed through the outcome of the pregnancy. The Investigator will be required to report the results to Amgen Global Safety.

If the outcome of the pregnancy meets a criterion for immediate classification as an SAE—spontaneous abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly—the Investigator should repeat the procedures for expedited reporting of SAEs as outlined above.