Single Autologous Transplant Followed by Consolidation and Maintenance for Participants ≥ 65 Years of Age Diagnosed with Multiple Myeloma or a Related Plasma Cell Malignancy

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Induction DPACE

Dexamethasone 20 mg oral days 1-4 and 8-11

Continuous Infusion on days 1-4:
Cisplatin 10mg/m^2/day, **Doxorubicin**10mg/m^2/day, **Etoposide** 40mg/m^2/day, **Cyclophosphamide** 400mg/m^2/day (**OR** 600mg/m^2 if high risk MM)

Peripheral Blood Stem Cell Collection [plus additional collection(s) if needed]

Dexamethasone 20mg daily on days 1-4 of a 14 day cycle

Transplant (VDT-Mel)

(4 weeks - 4 months from day 1 of induction)
*** may be up to 6 months after day 1 of DPACE if hard-to-mobilize PBSC**

Thalidomide 100mg oral on day -4 to +5, **Dexamethasone** 20mg oral days -4 to -1 and +2 to +5, **Bortezomib** 1mg/m2 IV Bolus on days -4, -1, +2 and +5 **Melphalan** 100mg/m2 (**OR** 70mg/m^2 if > age 70 or creatinine > 2.0 mg/dl) on days -4 and –1. **PBSC Infusion** 24 hrs post Melphalan on day 0.

Thal 100mg daily + Dex 20mg daily x 4 days every 21 days

Consolidation VDT-PACE*

(4 weeks - 4 months after transplant)
***Will only be given if all 4 criteria for treatment are met as described in the protocol.**

Bortezomib 1mg/m2 IV Bolus on days 1,4,8,11, **Dexamethasone** 20mg oral days 1-4 and 8-11, **Thalidomide** 100mg oral days 1-11.

Continuous Infusion on days 1-4:

Cisplatin 10mg/m^2/day, **Doxorubicin** 10mg/m^2/day, **Etoposide** 40mg/m^2/day, **Cyclophosphamide** 400mg/m^2/day

Maintenance Therapy

(4 weeks-6 months post- transplant or 6 weeks - 6 months from day 1 of consolidation if given)
Given per standard-of-care

COMMON ABBREVIATIONS

AE	Adverse Event
ANC	Absolute Neutrophil Count WBC x (Segs +Bands).
B2M	Beta-2 Microglobulin
CA	Cytogenetic Abnormalities
CBC	Complete Blood Count
CI	Continuous Infusion
CMP	Complete Metabolic Panel
CNS	Central Nervous System
CR	Complete Response
CTCAE	NCI Common Terminology for Adverse Events
DEX	Dexamethasone
DPACE	Dexamethasone, Cisplatin, Adriamycin®, Cytoxan®, Etoposide
DVT	Deep Vein Thrombosis
EFS	Event Free Survival
FDA	Food and Drug Administration
FDG PET	Fluorodeoxyglucose - Positron Emission Tomography
FISH	Fluorescence *in situ* hybridization
GCP	Good Clinical Practices
GEP	Gene Expression Profiling
HIPAA	Health Insurance Portability and Accountability Act
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
ME	Microenvironment
MEL	Melphalan
MGUS	Monoclonal Gammopathy of Undetermined Significance
MIRT	Myeloma Institute for Research and Therapy at the University of Arkansas
MM	Multiple Myeloma
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
n-CR	Near Complete Response
OS	Overall Survival
PBSC	Peripheral Blood Stem Cells
PCP	Pneumocystic pneumonia
PO	By mouth
PR	Partial Response
PS	Performance Status
QD	Every Day
SAE	Serious Adverse Event
SC/SQ	Subcutaneous
SRE	Skeletal Related Events
REV	Lenalidomide
THAL	Thalidomide
TIW	Three times per week
TT II	Total Therapy II
VDT	Velcade®, Dexamethasone, Thalidomide
WBC	White Blood Count

Modification #8
Modification version: 2.4
Modification version date: 5/18/15

Page	Change
Cover Page	Changed version number, version date, and prior version number.
5	Table of Contents updated to reflect revised pagination
3	Added CMP (Complete Metabolic Panel) as an abbreviation
6	Table of Contents updated.
66	Expedited Adverse and Serious Adverse Events will be reported to the Medical Monitor only. The assigned study monitor will not review these events in real time but will review them at the quarterly audits.
67	Background section further divided into 3 sub-sections for further clarification. Expanded upon rationale for adding bortezomib and thalidomide to high-dose melphalan. Added section 2.4 (rationale for allowing multiple modifications during maintenance therapy)

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1.0 Objectives

The hypothesis of this study is that participants ≥65 years of age diagnosed with MM or another plasma cell malignancy will have better outcomes with a transplant approach followed by maintenance, as primarily measured by PFS, but also by OS, versus non-transplant approaches.

Primary Objectives

1.1 To evaluate the progression-free survival (PFS) from the start of DPACE for all participants who have had at least one day of protocol treatment. It is hoped that the median progression-free survival will be 48 months versus 24 to 36 months for non-transplant regimens.

1.2 To evaluate how well such therapy is tolerated in patients mainly over the age of 65 years by assessing severe complications (ICU admission, death) and the percentage of participants able to complete the full course of therapy.

Secondary Objectives

1.3 To evaluate Quality-Of-Life post-transplant using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire QLQ-C30 and QLC-MY20.

Overall Survival (OS) is not an objective of this study because it is heavily influenced by the type and quality of therapy initiated after relapse, and therefore becomes a confounding variable. However, OS data will be collected and assessed.

2.0 Background and Rationale

2.1 Background

Although recent tandem autologous transplantation clinical trials for newly diagnosed patients have projected survivals of 10+ years and complete remission rates of approximately 80%, not every newly diagnosed (defined as <12 months of prior therapy) multiple myeloma patient will have the option of receiving tandem transplants, either because of a lack of insurance approval for two transplants, or because of clinical comorbidities that make the administration of two transplants unsafe. Most of these patients that fall into this category are ≥65 years of age, and in 2009, the median age of diagnosis for myeloma was 70 years.

There continues to be clear evidence in the literature that supports the superiority of a single autologous transplant over non-transplant chemotherapy, including chemotherapy combinations that employ the newer drugs (Lenalidomide, thalidomide, bortezomib, and Doxil). There is also convincing evidence that post-transplantation therapy with either thalidomide or Revlimid or the combination of bortezomib with thalidomide prolongs the progression-free survival. However, most of the literature

related to myeloma treatment in patients ≥65 years of age involves non-transplant chemotherapy regimens. The literature related to autologous transplantation for myeloma in the elderly (i.e. ≥ 65 years of age) is scarce.

Our group was the first to recognize that age is not a prognostic variable with autotransplants in myeloma (Siegel DS et al). While 83% of younger patients collected > 5 million CD34 cells/kg, 73% of patients 65 years or older attained this target (p= 0.2). The treatment-related mortality with the first transplant was 2% for younger patients, and 8% for patients 65 years or older. In multivariate analysis age was not a prognostic factor for either event-free (p=0.2) or overall survival (p=0.8). These observations were subsequently confirmed in another single institution study by El Cheikh et al (2011) comparing 82 elderly patients to 104 younger patient. The feasibility of transplantation in myeloma patients 70 years or older was also demonstrated by Bashir et al.

The table on the next page, taken from Gay and Palumbo's 2011 review in *Blood*[1], summarizes the results of various regimens used as frontline treatment in elderly patients diagnosed with multiple myeloma:

Table 2. Efficacy of regimens used as a front-line treatment in elderly patients with multiple myeloma.

		N	CR	≥PR	PFS/EFS/TTP	OS	Reference
Thalidomide-based							
TD	T: 200 mg D: 40 mg day 1–4, 15–18 for a 28-day cycle for 9 cycles	145	2%	68%	41% at 24 months	61% at 24 months	Ludwig et al.
MPT	M: 4 mg/m^2 day 1–7 P: 40 mg/m^2 day 1–7 T: 100 mg/day for six 4-week cycles *Maintenance*: T: 100 mg/day	129	16%	76%	50% at 22 months	50% at 45 months	Palumbo et al.
MPT	M: 0.25 mg/kg day1–4 P: 2 mg/kg day 1–4 T: 400 mg/day for twelve 6-week cycles	125	13%	76%	50% at 28 months	50% at 52 months	Facon et al.[1]
MPT	M: 0.25 mg/kg day 1–4 P: 2 mg/kg day 1–4 T: 100 mg/day for twelve 6-week cycles	113	7%	62%	50% at 24 months	50% at 44 months	Hulin et al.

		N	CR	≥PR	PFS/EFS/TTP	OS	Reference
MPT	M: 0.25 mg/kg day 1–4 P: 100 mg day 1–4 T: 200–400 mg/day for a 6-week cycle until plateau *Maintenance*: T: 200 mg/day	182	13%	57%	50% at 15 months	50% at 29 months	Waage et al.
MPT	M: 0.25 mg/kg P: 1 mg/day 1–5 T: 200 mg/day for eight 4-week cycles *Maintenance*: T: 50 mg/day	165	2%	66%	67% at 24 months	29% at 24 months	Wijermans et al.
CTD	C: 500 mg day 1, 8, 15 T: 100–200 mg/day D: 40 mg day 1–4, 12–15 for a 3 week cycle	450	21%	91%	ND	ND	Morgan et al.
Bortezomib-based							
VMP	M: 9 mg/m^2 day 1–4 P: 60 mg/m^2 day 1–4 V: 1.3 mg/m^2 day 1, 4, 8, 11, 22, 25, 29, 32 for the first four 6-week cycles; day 1, 8, 22, 29 for the subsequent five 6-week cycles	344	30%	71%	50% at 22 months	41% at 36 months	San Miguel et al. Mateos et al.
VMP	M: 9 mg/m^2 day 1–4 P: 60 mg/m^2 day 1–4 V: 1.3 mg/m^2 day 1, 8, 15, 22	257	24%	81%	41% at 36 months	87% at 36 months	Palumbo et al.
VMP	M: 9 mg/m^2 day 1–4 P: 60 mg/m^2 day 1–4 V: 1.3 mg/m^2 twice weekly (day 1, 4, 8, 11; 22, 25, 29, and 32) for one 6-week cycle, followed by once weekly (day 1, 8, 15, and 22) for five 5-week cycles *Maintenance*: V:1.3 mg/m^2 twice weekly on days 1, 4, 8, 11, every 3 months	130	20%	80%	50% at 34 months	74% at 36 months	Mateos et al.

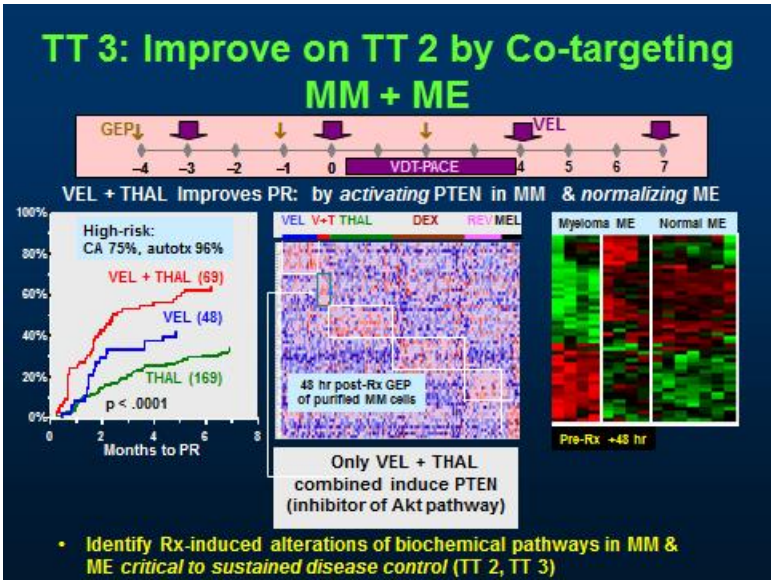
		N	CR	≥PR	PFS/EFS/TTP	OS	Reference
	T: 50 mg/day or V: 1.3 mg/m² twice weekly on days 1, 4, 8, 11, every 3 months P: 50 mg every other day						
Bortezomib- and thalidomide-based							
VTP	T: 100 mg/day P: 60 mg/m² day 1–4 V: 1.3 mg/m² twice weekly (day 1, 4, 8, 11; 22, 25, 29 and 32) for one 6-week cycle, followed by once weekly (day 1, 8, 15 and 22) for five 5-week cycles *Maintenance*: V: 1.3 mg/m² twice weekly on days 1, 4, 8, 11, every 3 months T: 50 mg/day or V:1.3 mg/m² twice weekly on days 1, 4, 8, 11, every 3 months P: 50 mg every other day	130	28%	81%	50% at 25 months	65% at 36 months	Mateos et al.
VMPT	M: 9 mg/m² day 1–4 P: 60 mg/m² day 1–4 V: 1.3 mg/m² day 1, 8, 15, 22 T: 50 mg day 1–42 for nine 5-week cycles *Maintenance*: V: 1.3 mg/m² every 15 days T: 50 mg/day	254	38%	89%	56% at 36 months	89% at 36 months	Palumbo et al.
Lenalidomide-based							
MPR	M: 0.18 mg/Kg day 1–4 P: 2 mg/Kg day 1-4 R: 10 mg day 1-21 for nine 4-week cycles *Maintenance*: R: 10 mg day 1-21	152	16%	77%	55% at 24 months	92% at 12 months	Palumbo et al.
Rd	R: 25 mg day 1–21 d: 40 mg day 1, 8, 15, 22 for a 4-week cycle	222	4%	68%	50% at 25 months	87% at 24 months	Rajkumar et al.

N indicates number of patients; CR, complete remission; PR partial response; PFS, progression-free survival; EFS, event-free survival; TTP, time to progression; OS, overall survival; M, melphalan; P, prednisone; T, thalidomide;V, bortezomib; R, lenalidomide; C, cyclophosphamide; D, high-dose dexamethasone; d, low-dose dexamethasone; MPT, melphalan–prednisone–thalidomide; VMP, bortezomib–melphalan–prednisone; VTP, bortezomib–thalidomide–prednisone; VMPT, bortezomib–melphalan–prednisone–thalidomide; CTD, cyclophosphamide–thalidomide–dexamethasone; MPR, melphalan–prednisone–lenalidomide; NA, not available. § Updated information was presented at the meeting (American Society of Clinical Oncology, European Haematology Association and American Society of Hematology congress).

The design of this protocol centers around a single autologous transplant followed by consolidation and maintenance therapy in patients ≥65 years of age with <12 months of prior therapy in order to compare event-free and overall survival rates to those in the literature cited above .

2.2 The Rationale for Adding Bortezomib and Thalidomide to High-Dose Melphalan

In addition to traditional mechanisms of drug resistance such as overexpression of efflux pumps, up-regulation of anti-apoptotic factors, down-regulation of proapoptotic factors, up-regulation of detoxifying enzymes and subcellular redistribution of drug targets, drug resistance is also mediated by binding of tumor cells to extracellular matrix proteins. This type of drug resistance is called cell adhesion-mediated drug resistance (CAM-DR) and is particularly relevant in hematologic malignancies such as multiple myeloma, where the myeloma cells interact with the bone marrow stroma, initiating the production of proteins that stimulate and support tumor cell survival. Myeloma cells bind to fibronectin in the micro-environment, which up-regulates drug resistance mainly through increased NF-κB activity. Bortezomib blocks the paracrine growth of myeloma cells by decreasing their adherence to the bone marrow stroma and by blocking NF-κB activity (Hideshima). In addition, bortezomib prevents DNA repair, which is the major mechanism of drug resistance to high dose melphalan. The Fanconi anemia (FA)/BRCA genes are overexpressed and cause drug resistance in melphalan-resistant cell lines. This pathway is activated by NF-κB. Bortezomib drastically reduces FA/BRCA gene expression and FANCD2 protein expression in myeloma cells, resulting in diminished DNA repair and enhanced melphalan sensitivity (Yarde et al). Thalidomide directly induces apoptosis or G1 growth arrest in myeloma cells, which are resistant to melphalan. Although thalidomide does not alter adhesion of myeloma cells to the bone marrow stroma, it inhibits the up-regulation of IL-6 and VEGF secretion triggered by the binding of myeloma cells to the bone marrow stroma. It also inhibits TNFα-induced NF- κB. TNFα increases myeloma cell adhesion to the bone marrow stroma (Hideshima). Our own studies have demonstrated that the combination of bortezomib with thalidomide induces higher response rates than each drug separately. When analyzing the bone marrow stroma signature by gene expression profiling, multiple genes were different between a normal bone marrow stroma signature and that of a myeloma bone marrow stroma. However, after treatment for 48 hours with bortezomib and thalidomide, the bone marrow stroma signature of myeloma patients almost completely normalized and the stimulatory effects of the stroma on the myeloma cells was abrogated.



These observations formed the basis of our Total Therapy 3 trial, which included bortezomib and thalidomide in the maintenance phase, but not with the transplant.

Several investigators have combined high-dose melphalan with bortezomib. They concluded that this combination is safe and that there was a suggestion of improved efficacy (Lonial et al; Roussel et al; Thompson et al).

Palumbo et al combined intermediate dose melphalan (100mg/m^2) with bortezomib, thalidomide, and dexamethasone in 26 relapsed/refractory patients who had all received at least one prior transplant [13 (50%) received a second transplant as salvage prior to study enrollment]. Responses occurred in 17/26 patients, including 1 CR, 3 nCR(12%), and 2 VGPR (8%). Response rate was higher than that induced by the previous line of treatment in 12 patients (46%). The authors concluded that the regimen had encouraging anti-myeloma activity in heavily pre-treated patients, and that the addition of thalidomide and bortezomib only slightly increased overall toxicity caused by IV melphalan 100mg/m^2 as a single agent. Infections requiring IV antibiotics occurred in 50% of patients, but it was not clear whether this was due to the immunomodulatory effect of the added agents or the infection susceptibility in heavily pre-treated patients.

Barlogie et al reported in 2009 on the incorporation of bortezomib, thalidomide, dexamethasone with the addition of cisplatin, and rapamycin into the BEAM regimen as a salvage regimen in myeloma. Ninety-five patients were enrolled in their study. Patient characteristics included age >=65, 19%; LDH>ULN, 43%; CA, 67%; GEP high-risk, 44%; GEP MF, 15%; GEP delTP53, 22%; prior AT, 75% including 46% with 2 AT and 12% with 3 AT. CR and near-CR status was documented in 50%; TRM occurred within 100 days in 6%. Three-year estimates of overall survival (OS) and event-free survival (EFS) were 34% and 18%; OS/EFS were superior: (a) without CA – 60%/50% versus 15%/5% with CA (p=0.003/0.0005); (b) with GEP low-risk – 55%/20% versus 10%/15% with high-risk MM (p=0.009/0.01); (c) with GEP hyperdiploidy and low bone disease molecular subgroups – 70%/35% versus 20%/10% in the remainder (p=0,001/0.002); and (d) absence of progression prior to SB – 52%/35% versus 16%/5% for the remainder (p=0.002/0.0006). They concluded that Super-BEAM (SB) was safe as a salvage regimen and well-tolerated by the majority of patients in the outpatient

setting. Although SB was very beneficial for a subset of the study patients, pre-SB relapse (relapse just prior to SB) was one of the significantly adverse variables for OS and EFS, which is why we would like to incorporate VTD-Mel upfront in newly diagnosed patients.

2.3 The Rationale for Post-Transplant Maintenance

Although the role of maintenance therapy post-transplantation has been controversial for a long time, recent evidence clearly shows the superiority of such maintenance therapy. In a study by Attal et al, including 614 patients, lenalidomide given after transplantation significantly prolonged progression-free survival in a randomized study comparing lenalidomide post-transplantation versus placebo ($p< 0.001$). Median follow up was only 30 months, which is too short to see a difference in overall survival (Attal et al, 2012). A second study by McCarthy et al included 460 patients and had a median follow-up of 34 months also showed a significant benefit in progression-free survival with lenalidomide maintenance compared to placebo ($p<0.001$). In spite of the short follow-up, this study also showed an overall benefit for lenalidomide maintenance ($p=0.03$). It should be mentioned that both studies noted increased toxicities related to maintenance therapy and more specifically showed a significant increase in secondary malignancies in the lenalidomide arms, which was 3.1 versus 1.2 per 100 patient years in the Attal study, and 8% versus 3% in the McCarthy study. A recent consensus on maintenance therapy in multiple myeloma was reported by Ludwig et al. Thalidomide maintenance showed a benefit in progression-free survival in all 6 studies performed and an overall survival benefit in 3 of these studies. In a randomized Phase III study, superior complete (CR)/near complete response (nCR) and extended progression-free survival were demonstrated with bortezomib-thalidomide-dexamethasone (VTD) versus thalidomide-dexamethasone (TD) when give as induction and maintenance therapy after transplantation in newly diagnosed myeloma patients by Cavo and colleagues. The study included 321 patients. VTD maintenance significantly increased CR/nCR rates while TD did not. With a median follow-up of 30 months from the start of maintenance, progression-free survival at 3 years was 60% versus 48% ($p= 0.04$). The benefit of VTD maintenance was seen irrespective of poor prognostic variables. In newly diagnosed myeloma patients, lenalidomide/ dexamethasone (RD) was compared to cyclophosphamide/lenalidomide/dexamethasone (CRD) and bortezomib/cyclophosphamide/ dexamethasone (VCD). VCD resulted in superior responses and less frequent serious toxicities compared to RD and CRD. With a median follow-up of 35 months no difference in progression-free survival was seen yet. Bensinger and colleagues reported sequential VCD and VTD as frontline therapy in myeloma in a Phase II study including 44 patients. They concluded that this novel sequential three-drug combination therapy is effective and well tolerated in previously untreated myeloma patients.

2.4 The Rationale for Allowing Multiple Modifications During Maintenance Therapy

In this protocol, we will administer two years of maintenance therapy. Years one and two will consist of 12 cycles of 28 days each. During year 1, we will administer VTD, while in year 2 we will administer VCD. We consider it of vital importance that patients are able to complete two years of maintenance. However, because of anticipated toxicity during maintenance, we allow alternate dosing schedules, dose reductions, or replacement with a similar categorical agent (i.e. proteasome inhibitor with a proteasome inhibitor, IMID with an IMID, corticosteroid with a corticosteroid) so that as many patients as possible will complete the two years of maintenance therapy, and with 3-drug maintenance

regimens whenever possible, as many studies have shown a direct correlation to the length and type of maintenance therapy and its efficacy in increasing PFS. Although the replacement drugs may have different and better toxicity profiles, the experience with these drugs is still limited.

Several myeloma physicians now advocate continuing therapy until relapse. We prefer to stop all treatment after two years of maintenance because: 1) Patients value the amount of time without symptoms, therapy, and toxicity 2) If therapy is continued until relapse, these drugs will by definition no longer be active at that time, while it is our experience that in patients relapsing more than 2 years after stopping all treatment, the drugs given during maintenance remain effective 3) There is a clear association between prolonged use of IMIDS and secondary malignancies, including MDS and AML.

3.0 Drug Information

3.1 **Bortezomib** (Velcade)

Bortezomib for injection is a sterile lyophilized powder for reconstitution and is supplied in vials containing bortezomib and mannitol at a 1:10 ratio. For example, vials containing 3.5 mg of bortezomib contain 35 mg of mannitol.

Vials containing lyophilized bortezomib for injection should be stored refrigerated at 2° to 8°C. To date, stability data indicate that the lyophilized drug product is stable for at least 12 months when stored under the recommended conditions. Stability studies are ongoing, and Millennium will notify the Investigator should this information be revised during the conduct of the study.

Bortezomib is cytotoxic. As with all cytotoxic drugs, caution is required when preparing and handling bortezomib solutions. Cytotoxic drugs should only be handled by staff specially trained in the safe handling of such preparations. The use of gloves and other appropriate protective clothing is recommended.

Study drug will be supplied in sterile, single use vials containing 3.5 mg of bortezomib. Each vial of bortezomib for Injection should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with 3.5 mL of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains bortezomib at a concentration of 1 mg/mL. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. Reconstituted bortezomib should be administered promptly and in no case more than eight hours after reconstitution. In case of skin contact, wash the affected area immediately and thoroughly with soap and water and diluted hydrogen peroxide. Remove contaminated clothing and dispose of according to standard procedures. In case of contact with mucous membranes, flush thoroughly with water. Always contact a physician after any form of body contact. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

Clinical Experience

It is estimated that as of June 2005, more than 24,000 participants have been treated with bortezomib, including participants treated through Millennium-sponsored clinical trials, Investigator-

Initiated Studies, the US NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. Bortezomib has been commercially available since 13 May 2003.

The overall goal of the Millennium phase 1 program was to determine the MTD and dose-limiting toxicity (DLT) of VELCADE in a number of therapeutic settings involving subjects with various advanced malignancies. In a Phase I trial in participants with refractory hematologic malignancies, the MTD for a twice weekly for 4 weeks of a 42 day cycle was 1.04 mg/m^2/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise (Orlowski et al., 2002). The toxicity was greatest during the third and fourth weeks of therapy. In the 3-week schedule of bortezomib monotherapy (4 doses, given on Days 1, 4, 8, and 11 of a 21-day treatment cycle), the DLT occurred at 1.56 mg/m^2/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m^2/dose. In a 35-day treatment cycle with 4 weekly doses of VELCADE monotherapy, the MTD was 1.6 mg/m^2/dose and DLT included hypotension, tachycardia, diarrhea, and syncope.

In phase 1 clinical studies, anti-tumor activity was reported in subjects with NHL, multiple myeloma, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer.

The safety and efficacy of bortezomib in subjects with multiple myeloma were investigated in two phase 2 clinical studies, studies M34100-024 (subjects with first relapse) and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy). In M34100-025, 202 heavily pre-treated subjects with refractory multiple myeloma after at least 2 previous treatments received bortezomib, 1.3 mg/m^2 on Days 1, 4, 8, and 11 of a 21-day treatment cycle. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade (Blade et al., 1998) were utilized to determine disease response. CRs were observed in 4% of subjects, with an additional 6% of participants meeting all criteria for CR but having a positive immunofixation test. PR or better was observed in 27% of subjects, and the overall response rate (CR, PR and minor response [MR] combined) was 35%. Seventy percent of subjects experienced stable disease or better.

The phase 3 study (M34101-039), also referred to as the APEX study, was designed to determine whether bortezomib provided benefit (time to progression [TTP], response rate, and survival) to participants with relapsed or refractory MM relative to treatment with high-dose dexamethasone. The study was also designed to determine the safety and tolerability of bortezomib relative to high-dose dexamethasone, and whether treatment with bortezomib was associated with superior clinical benefit and quality of life relative to high-dose dexamethasone. A total of 669 participants were enrolled and 663 participants received study drug (VELCADE: 331; dexamethasone: 332). Participants randomized to bortezomib received 1.3 mg/m^2 I.V. push twice weekly on days 1, 4, 8, and 11 of a 3-week cycle for up to eight treatment cycles as induction therapy, followed by 1.3 mg/m^2 bortezomib weekly on days 1, 8, 15, and 22 of a 5-week cycle for three cycles as maintenance therapy. Participants randomized to dexamethasone received oral dexamethasone 40 mg once daily on days 1 to 4, 9 to 12, and 17 to 20 of a 5-week cycle for up to four treatment cycles as induction therapy, followed by dexamethasone 40 mg once daily on days 1 to 4 followed of a 4-week cycle for five cycles as maintenance therapy. The European Group for Blood and Marrow Transplant (EBMT)

response criteria, as described by Blade (Blade et al., 1998) were utilized to determine disease response. There was a 78% increase in TTP for the bortezomib arm. Median TTP was 6.2 months for the bortezomib arm and 3.5 months for the dexamethasone arm (*P*<.0001). CR (complete response) + PR (partial response) was 38% with VELCADE vs. 18% with dexamethasone (*P*<.0001). CR was 6% with VELCADE vs. <1% with dexamethasone (*P*<.0001). The CR + nCR rate was13% with bortezomib vs. 2% with dexamethasone. In participants who had received only one prior line of treatment (VELCADE: 132; dexamethasone: 119), CR + PR was 45% with bortezomib vs. 26% with dexamethasone (*P*=.0035). With a median 8.3 months of follow-up, overall survival was significantly longer (*P*=.0013) for participants on the VELCADE arm vs. participants on the dexamethasone arm. The probability of survival at one year was 80% for the bortezomib arm vs. 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with bortezomib (*P*=.0005). In participants who had received only one prior line of treatment, the probability of survival at one year was 89% for the bortezomib arm vs. 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with VELCADE (*P*=.0098). (Richardson et al., 2005)

Studies using bortezomib as monotherapy and in combination with other chemotherapy agents are continuing.

Potential Risks of Bortezomib

Most common side effects of bortezomib (i.e., incidence ≥30%) observed in participants are weakness, fatigue, and general discomfort; gastrointestinal (GI) effects such as constipation, diarrhea, nausea, vomiting and anorexia, which may result in dehydration and/or weight loss; fever; peripheral neuropathy (including painful sensations or numbness and tingling in hands and feet that may not get better after discontinuation of VELCADE); thrombocytopenia that may increase the risk of bleeding, and anemia.

Very common side effects of bortezomib (i.e., incidence 10–29%) observed in participants are neutropenia that may increase the risk of infection; abdominal pain; dyspepsia; nasopharyngitis; arthralgias; myalgias; skin rash that can be erythematous, pruritic and display leukocytoclastic vasculitis at biopsy; rigors; hypotension; dizziness; fluid retention; pain in limbs and bones; paresthesia; dysesthesia; dyspnea; cough; epistaxis; headache; blurred vision; changed sense of taste; insomnia; anxiety; herpes zoster, and lower respiratory/lung infections including pneumonia.

Common side effects of bortezomib (i.e., incidence 1–9%) observed in participants are lymphopenia; pancytopenia; palpitations; tachycardia; bradycardia; atrial fibrillation; angina pectoris; acute onset of congestive heart failure including pulmonary edema (participants with risk factors for, or existing, heart disease should be closely monitored); pleural effusion; tinnitus; conjunctivitis; ; abdominal distension; oral and esophageal mucositis; oral candidiasis; upper and lower GI bleeding; bronchitis; sinusitis; urinary tract infection; gastroenteritis; sepsis; hyponatremia; hyperglycemia; hypoglycemia (Participants on oral antidiabetic agents may require close monitoring of their blood sugar levels.); dehydration; orthostatic hypotension; syncope; convulsions; renal failure; hematuria; depression; confusion; increases in serum AST, ALT, GGT and alkaline phosphatase.

Uncommon side effects of bortezomib (i.e., incidence <1%) observed in participants are febrile neutropenia; atrial flutter; bradycardia; new onset of decreased left ventricular ejection fraction; cardiogenic shock; hearing impairment; ileus paralytic/small bowel obstruction; upper gastrointestinal hemorrhage; oral mucosal petechiae; liver injury including abnormal liver function tests, hyperbilirubinemia, hepatitis, and liver failure (reported in participants receiving multiple concomitant medications and with serious underlying medical conditions); drug hypersensitivity; injection site reaction; aspergillosis; pulmonary embolism; hemoptysis; cerebral hemorrhage; and tumor lysis syndrome. Isolated cases of QT-interval prolongation have been reported, but are not thought to be related to bortezomib treatment. Complications arising from these bortezomib toxicities may result in death.

The effect of bortezomib on reproduction and its safety in pregnancy are unknown. Laboratory tests show that bortezomib may damage DNA therefore it is possible that bortezomib may cause infertility in men and women.

3.2 **Thalidomide** (Thalomid)

Description

Thalidomide is an N-phthaloyl-glutamic acid imide. Its chemical name is α-(N- phthalimido) glutarimide. The empirical formula is $C_{13}H_{10}N_2O_4$ and the gram molecular weight is 258.2. The CAS number of thalidomide is 50-35-1. Thalidomide is an off-white to white, nearly odorless, crystalline powder that is soluble at 25°C in dimethyl sulfate (50 mg/ml) and ethanol (1 mg/ml). The glutarimide part of the molecule contains a single asymmetric center and, therefore, may exist in either of two optically active forms designated S(-) or R(+). Thalidomide is an equal mixture of the S(-) and R(+) forms and therefore has a net optical rotation of zero. The enantiomers, both the S(-) and R(+) forms differ from the racemic thalidomide in having higher solubility in water (Hague and Smith, 1988, Williams 1968, Williams et al. 1965) and undergoing faster hydrolytic cleavage (Hague and Smith, 1988).

Contraindications and Precautions

Thalidomide causes severe birth defects. It must not be taken during pregnancy or within one month of having sexual intercourse that could result in pregnancy. Females of childbearing potential should be instructed that they must not be pregnant when thalidomide therapy is initiated. A blood test or professionally conducted urine test to rule out pregnancy prior to initiating thalidomide therapy is required. While taking thalidomide, all female participants of childbearing potential must use two methods of birth control, one barrier and one hormonal or should abstain from sexual intercourse that could result in pregnancy. It is not known if thalidomide is present in semen; therefore, it is recommended that male participants use barrier contraception while on thalidomide. Both males and females of childbearing potential should continue with the contraceptive measures described above for one month after dosing has been discontinued.

Toxicology

The most important of the adverse events reported during the administration of thalidomide are peripheral neuropathy, rash, drowsiness, and teratogenicity. Other frequent adverse events that have been reported include constipation and xerostomia. Increased appetite, loss of libido, dryness of the skin, edema of the face and limbs, nausea, pruritis, headache, gastric pain, and menstrual abnormalities have occasionally been observed. In addition, hangover feeling, giddiness, or nervousness at higher doses, shivering, aural buzzing, and addiction after several months have been reported. Some participants have had a decrease in their white blood cell count and in some HIV-positive participants an increase in the HIV RNA load has been reported. There have been reports of changes of the heart rate and rhythm. Allergic reactions include low blood pressure, rash, fever and rapid heartbeat associated with thalidomide use.

Serious dermatologic (skin) reactions including a disease called Stevens-Johnson syndrome (which could be fatal) have been reported with thalidomide. Symptoms of Stevens-Johnson Syndrome include flu-like symptoms (fever, achiness), and a crusty rash may form on mouth, lips, nose and genitals. The eyes may also become red and itchy and the disease may eventually result in blindness. The disease can also affect the lungs, stomach and bowel, kidneys and heart if not treated. If any of the above-mentioned symptoms or a skin rash of any type develop, thalidomide should be discontinued until thorough evaluation of the rash can be evaluated.

Seizures, including generalized tonic-clonic convulsions, have been reported after thalidomide was approved by the FDA in clinical practice, but it has not been determined that thalidomide caused these seizures. During therapy with thalidomide, participants with a history of seizures or with other risk factors for the development of seizures should be closely monitored for changes that could cause acute seizure activity.

DRUG INTERACTIONS

Drug-drug interactions do not appear to have been systematically studied but it has been reported that thalidomide enhances the sedative effects of barbiturates, alcohol, chlorpromazine, and reserpine. Its sedative action is antagonized by methylphenidate and methylamphetamine (Somers 1960).

Females who require treatment with rifampin, rifabutin, barbiturates, glucocorticoids, phenytoin, or carbamazepine should not rely upon hormonal contraception since these agents have been shown to reduce the efficacy of the contraceptives.

PHARMACOLOGY

Thalidomide is available as 50 mg strength, hard gelatin capsules.

Stability and Storage: The drug product has been shown to be stable for at least one year when stored under ambient conditions. Over this time period, the capsules show no significant loss in potency and no significant increase in degradation products. Furthermore, the drug product has been shown to be stable when stored under conditions of stress (40°C/75% relative humidity, 6 months).

Based upon these results, the drug product has been assigned a tentative expiration dating period of 2 years.

Clinical supplies should be retained in a secure, cool, dry place.

Label Information: The immediate container dispensed to the participant must contain the following warnings:

WARNING: This drug causes severe birth defects. It must not be taken during pregnancy or within one month of having sexual intercourse that could result in pregnancy.

CAUTION: This drug must only be used by the person for whom it is prescribed. Do not share this drug.

3.3 **Dexamethasone** (Decadron)

DESCRIPTION

Dexamethasone is a synthetic adrenocortical steroid and is readily absorbed from the gastrointestinal tract. Chemically, dexamethasone is 9-fluoro-11ß, 17, 21-thrihydroxy-16α-methyl-pregna-1, 4-diene-3, 20-dione.

TOXICOLOGY

Human Toxicology: Possible adverse effects associated with the use of dexamethasone are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection (e.g., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some participants have experienced itching and other allergic, anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia. Phenytoin, phenobarbital and ephedrine enhance metabolic clearance of corticosteroids.

Corticosteroids should be used cautiously in participants with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Immunization procedures (especially smallpox vaccination) should not be undertaken in participants on corticosteroids.

PHARMACOLOGY

Kinetics: Natural and synthetic glucocorticoids are readily and completely absorbed from the GI tract. Dexamethasone is insoluble in water. Glucocorticoids have salt-retaining properties, although dexamethasone nearly completely lacks this property. The anti-inflammatory property of this drug is its ability to modify the body's immune system. On the other hand, glucocorticoids suppress the body's response to viral and bacterial infections.

Formulation: Dexamethasone is available in six potencies (0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg, 4 mg, and 6 mg) in capsule or tablet form.

Storage and Stability: Dexamethasone is to be stored at room temperature.

Administration: The drug is administered orally.

3.4 **Melphalan** (Alkeran)

DESCRIPTION

Chemistry: Melphalan (L-phenylamine mustard, L-PAM, L-Sarcolysin) is an alkylating agent coupled to an amino acid.

Molecular Formula: $C_{13}H_{18}C_{12}N_2O_2$ M.W.: 305

TOXICOLOGY

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. Prior chemotherapy or radiotherapy exacerbates these effects. Other side-effects 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. The occurrence of acute leukemia has been rarely reported in participants treated with anthracycline/alkylator combination chemotherapy.

PHARMACOLOGY

Formulation: The intravenous preparation is available in a sterile, 50 mg vial. The product is prepared as a lyophilized powder with 20 mg of povidone per vial. Also provided is 10 ml of special diluent for use in constituting the product.

Solution preparation: Vial/50 mg: Constitute with 10 ml of the special diluent to yield a 5 mg/ml melphalan concentration. Prior to administration, dilute the constituted solution with 0.9% Sodium Chloride Injection, USP, to a concentration no greater than 2 mg/ml.

Storage and Stability: The intact packages of melphalan for intravenous administration should be stored at room temperature (15-30°C) protected from light. Shelf surveillance of the intact dosage form is ongoing.

Constitution with the special diluent as directed results in a solution that retains at least 90% melphalan potency for about 3 hours at 30°C. Storage at 5°C results in precipitation.

When the constituted solution is diluted to concentrations of 0.45 or 0.1 mg/ml in 0.9% Sodium Chloride Injection USP, 90% melphalan potency is retained for 45 minutes at 30°C. At 20°C, the 0.1 mg/ml concentration retained 90% potency for 3 hours. **The manufacturer recommends administration of melphalan within one hour of constitution.**

In dilute solutions of approximately 40 μg/ml, increasing amounts of chloride ion appear to enhance stability. For example, increasing the chloride content of such a solution from 0.2% to 0.9% increases the half-life from 8 to 16 hours.

Increased temperature as well as decreased chloride ion is associated with much higher degradation rates. An increase of temperature from 20°C to 25°C decreased the time to 10% decomposition by about one-half in each case.

Administration: melphalan will be administered intravenously.

3.5 **Cisplatin** (Cis-diamminedichloroplatinum [CDDP], Platinol)

DESCRIPTION

Cisplatin is a heavy metal complex and is water-soluble. It is a white lyophilized powder with a molecular weight of 300.1. Mechanism of action: It acts as a bifunctional alkylating agent.

TOXICOLOGY

Human Toxicology: Human toxicity includes anorexia, nausea, vomiting, renal toxicity (with an elevation of BUN, creatinine, serum uric acid and impairment of endogenous creatinine clearance, as well as renal tubular damage), ototoxicity (with hearing loss which is initially in the high frequency range, as well as tinnitus), and hyperuricemia. Much more severe and prolonged toxicity has been observed in participants with abnormal or obstructed urinary excretory tracts. Raynaud's phenomena and digital ischemia has been described. Anaphylactic-like reactions including facial edema, bronchoconstriction, tachycardia and hypotension may occur within minutes of administration. Myelosuppression, often delayed erythrosuppression, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white cells and platelets occurred regularly at about two weeks with recovery generally at about three weeks after the initiation of therapy. Rare complications are alopecia, seizures, loss of taste, allergic reactions, and loss of muscle or nerve function. Tetany may occur due to hypomagnesemia and/or hypercalcemia. Other electrolyte disturbances may occur. At high doses, participants have experienced optic neuritis, papilledema, cerebral blindness, blurred vision, and altered color perception. Participants have also experienced cardiac abnormalities, elevated SGOT and rash. Subsequent courses should not be given until serum creatinine returns to normal, if elevated. Audiometric analyses should be monitored and courses withheld until auditory acuity is within normal limits. The occurrence of acute leukemia has been reported rarely in participants treated with anthracycline/alkylator combination chemotherapy.

PHARMACOLOGY

Kinetics: After a single IV dose, increased concentration is found in the liver, kidneys, and small and large intestines. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25 to 49 minutes, and a secondary phase ranging from 58 to 73 hours. This prolonged phase is due to protein binding, which exceeds 90% of the radioactivity, excreted in the first five days. The initial fractions of radioactivity are largely unchanged drugs. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents. Cisplatin penetrates poorly into CNS.

Formulation: Cisplatin is available in 50 mg and 100 mg reconstituted vials.

Storage and Stability: The intact vials may be stored at room temperature (15-25°C) for the lot life indicated on the package. Do not refrigerate. The solution may be further diluted in a chloride-containing vehicle such as D5NS, NS, or D5½NS (precipitate occurs in D5W).

Administration: Cisplatin should be given as a slow intravenous infusion. Needles or intravenous sets containing aluminum parts that may come in contact with cisplatinum (Platinol) should not be used for preparation or administration, as a black precipitate is formed within 30 minutes.

3.6 **Doxorubicin** (Adriamycin)

DESCRIPTION

Mechanism of action: Doxorubicin is a cytotoxic anthracycline antibiotic different from daunorubicin by the presence of a hydroxyl group in the C-14 position. Doxorubicin is produced by fermentation from S. *peucetius* var. *caesius.* Its mechanism of action is thought to be the binding of nucleic acids, preventing DNA and possibly RNA synthesis.

TOXICOLOGY

Human Toxicology: Studies with doxorubicin have shown that the major toxic effects of this drug are alopecia, which is often total but always reversible; nausea and vomiting, which develops shortly after drug administration, occasionally persisting for 2-3 days; fever on the day of administration; and phlebitis at the site of the drug's injection. Extravasation of the drug will lead to soft tissue necrosis. Phleboscleriosis, cellulitis, vesication and erythematous streaking have also been seen. Mucositis may be seen 5-10 days after administration. Ulceration and necrosis of the colon, particularly the cecum, with bleeding and severe infection have been reported with concomitant administration of cytarabine. Anorexia and diarrhea have also been observed. Hyperpigmentation of nail beds and dermal creases, onycholysis and recall of skin reaction from prior radiotherapy may occur. Cardiac toxicity manifested as acute left ventricular failure, congestive heart failure, arrhythmia or severe cardiomyopathy has been reported, but appears to occur predominantly in participants who receive total doses in excess of 550 mg/m^2.

Myelosuppression, predominantly neutropenia, is common with nadir occurring approximately two weeks after a single injection; lesser degrees of anemia and thrombocytopenia have been reported. Rapid recovery of blood counts approximately two and a half weeks after a single injection generally permits an every three-week dosing schedule.

Participants with obstructive liver disease have more severe myelosuppression due to impaired drug excretion. Thus, participants with hepatic dysfunction may need to have reduced dosage or be excluded from therapy. Renal excretion of doxorubicin is minimal, but enough to color the urine red; thus impaired renal function does no appear to increase the toxicity of doxorubicin. Other side effects include fever, chills, facial flushing, itching, anaphylaxis, conjunctivitis and lacrimation. The occurrence of acute leukemia has been reported rarely in participants treated with anthracycline/alkylator combination chemotherapy.

Safe use of doxorubicin in pregnancy has not been established. It is embryotoxic and teratogenic in rats and embryotoxic and aborticacient in rabbits. The possible effects on fertility have not been adequately evaluated. Safety in nursing women has not been proven.

PHARMACOLOGY

Kinetics: Intravenous administration is followed by a rapid plasma clearance with significant tissue binding. Urinary excretion is negligible; biliary excretion accounts for 40 to 50% of the administered dose being recovered in the bile or the feces in 7 days. The drug does not cross the blood-brain barrier.

Formulation: Doxorubicin is supplied in 10, 20, and 50 mg single use vials, and 150 and 200 mg multidose vials.

Storage and Stability: Doxorubicin is stable for 24 hours at room temperature and 15 days under refrigeration (2°-8°C). It should be protected from exposure to sunlight. Discard any unused solution from the vials. Bacteriostatic diluents with preservatives are NOT recommended as they might possibly worsen the reaction to extravasated drug.

Administration: Doxorubicin may be further diluted in 5% dextrose or sodium chloride injection and should be administered slowly into tubing of a freely flowing intravenous infusion with great care taken to avoid extravasation.

3.7 **Cyclophosphamide** (Cytoxan)

DESCRIPTION

2[bis (2chloroethyl)amino]tetrahydro-2H-1,3,2-oxazophosphorine 2-oxide mono-hydrate. Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites that cross-link to DNA.

TOXICOLOGY

Human Toxicology: Toxicity from cyclophosphamide includes bone marrow suppression which usually occurs 10 to 12 days after administration; nausea, vomiting, anorexia, abdominal discomfort, diarrhea and stomatitis; reversible alopecia; hemorrhagic cystitis, which can frequently be prevented with increased hydration; fibrosis of the bladder; cardiac toxicity, which may potentiate doxorubicin-induced cardiotoxicity; rare anaphylactic reaction, skin rash, hyperpigmentation, interstitial pulmonary fibrosis, and cross sensitivity with other alkylating agents. Treatment with cyclophosphamide may cause significant suppression of the immune system.

Secondary malignancies, most frequently of the urinary bladder and hematologic systems, have been reported when Cytoxan® is used alone or with other anti-neoplastic drugs. Malignancies may occur several years after treatment has been discontinued. Cyclophosphamide interferes with oogenesis and spermatogenesis and may cause sterility in both sexes, which is dose and duration related. Cyclophosphamide has been found to be teratogenic, and women of childbearing potential should be advised to avoid becoming pregnant. Increased myelosuppression may be seen with chronic

administration of high doses of phenobarbital. Cyclophosphamide inhibits cholinesterase activity and potentiates the effect of succinylcholine chloride. If a participant requires general anesthesia within 10 days after cyclophosphamide administration, the anesthesiologist should be alerted. Adrenal insufficiency may be worsened with cyclophosphamide. Cyclophosphamide is excreted in breast milk, and it is advised that mothers discontinue nursing during cyclophosphamide administration. The occurrence of acute leukemia has been reported rarely in participants treated with anthracycline/alkylator combination chemotherapy.

PHARMACOLOGY

Kinetics: Cyclophosphamide is activated principally in the liver by a mixed function microsomal oxidase system. PO administration is well absorbed, with bioavailability greater than 75%. 5-25% of unchanged drug is excreted in the urine. Several active and inactive metabolites have been identified with variable plasma protein binding. There appears to be no evidence of clinical toxicity in participants with renal failure, although elevated levels of metabolites have been observed.

Formulation: Cyclophosphamide is supplied in 100 mg, 200 mg, 500 mg, 1 gm and 2 gm vials as a white powder. The drug should be reconstituted with sterile water for injection and may be diluted in normal saline or D5W. Cyclophosphamide is also available as a reconstituted solution available in the same size vial as the lyophilized form.

Storage and Stability: The reconstituted vial is stable for 24 hours at room temperature and 6 days when refrigerated.

Administration: The drug should be further diluted in saline or D5W and administered by slow IV infusion.

3.8 **Etoposide** (VP-16), (Vepesid) (Ethylidene-Lignan P)

DESCRIPTION

Chemistry: Etoposide is a semi-synthetic podophyllotoxin derivative from the plant podophyllum pletatum, and has antineoplastic properties in experimental animals and in humans. The empiric formula $C_{29}H_{32}O$ has a molecular weight of 588.

Mechanism of Action: The epipodophyllotoxins exert phase specific spindle poison activity with metaphase arrest, but in contrast to the vinca-alkaloids, have an additional activity of inhibiting cells from entering mitosis. Suppression of tritiated thymidine, uridine, and leucine incorporation in human cells in tissue culture suggests effects against DNA, RNA and protein synthesis.

Animal Tumor Data: Significant antitumor effect has been demonstrated in L1210, mouse sarcoma 37 and 180, Walker carcinosarcoma and Erlich ascites tumor. With the L1210 system, activity was schedule-dependent, having greater effect with a twice-weekly administration than with daily dosing or the administration of single large doses. The drug is active given intraperitoneally or orally in L1210. No effect was demonstrated against intracerebrally inoculated L1210.

TOXICOLOGY

Animal Toxicology: The predominant toxicities of etoposide in animal studies involve the hematopoietic system, with toxicity to the liver and GI tract occurring only at doses producing profound myelosuppression. Anemia, leukopenia, and lymphoid involution occur in mice, rats and monkeys. Acute toxicity investigations have been complicated by the toxicity of the solvent system. The LD-50 of the solvent plus drug approached that of the solvent alone. Immunosuppressive effects occur with an inhibition of antibody production in mice and monkeys, and prevention of experimental allergic encephalomyelitis in rats (cell-mediated immunity).

Human Toxicology: Reversible myelotoxicity has been uniformly observed to be the major toxicity of etoposide and to represent the only clinically significant side effect. Following a single IV injection, peak myelotoxicity occurs at seven to nine days. Following daily IV injections for five to seven days, myelotoxicity is maximal between 12 - 16 days from the initiation of therapy. Bone marrow suppression is mainly manifested as granulocytopenia, with thrombocytopenia and anemia occurring to a lesser extent. Gastrointestinal toxicities including transient modest nausea, vomiting and diarrhea, are common. Other reactions could include aftertaste, rash, pigmentation, pruritis, abdominal pain, constipation and dysphagia. Occasional alopecia is reported. Etoposide does not produce phlebitis or nephrotoxicity. Rarely, anaphylactic-like reactions have been reported, as well as hypotension. Hypotension can be managed by infusing the drug over at least a 30-minute period. Occasionally, chills, fever, peripheral neurotoxicity, stomatitis, hepatotoxicity, transient cortical blindness and radiation recall dermatitis may be a result of etoposide administration. The occurrence of acute leukemia has been rarely reported in participants treated with etoposide in association with other antineoplastic agents.

Pregnancy and Lactation: Etoposide can cause fetal harm when administered to a pregnant woman. Etoposide has been shown to be teratogenic in mice and rats. In these studies, etoposide caused dose-related maternal toxicity, embryotoxicity, and teratogenicity. Fetal abnormalities included decreased weight, major skeletal abnormalities, exencephaly, encephalocele, anophthalmia, and retarded ossification. No information is available on excretion of this drug in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued.

PHARMACOLOGY

Kinetics: After IV administration, disposition is biphasic with initial half-life of 1.5 hours and terminal half-life of 4 - 11 hours. Drug does not accumulate in plasma following daily administration of 100 mg/M^2 for 4 - 5 days. Drug poorly crosses blood-brain barrier. Recovery after IV administration of radiolabeled etoposide in the urine ranges from 42 - 67% and feces from 0 - 16%. The mutagenic and genotoxic potential has been established in mammalian cells.

Formulation: 100 mg of etoposide is supplied as 5 ml of solution in Sterile Multiple Dose Vials for injection. The pH of the yellow clear solution is 3 - 4. Each ml contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5% (v/v) alcohol. Etoposide must be diluted prior to use with either 5% Dextrose Injection, USP, or 0.9% sodium Chloride Injection, USP. The time before precipitation occurs depends on

concentration; however, when at a concentration of 0.2 mg/ml it is stable for 96 hours at room temperature and at 0.4 mg/ml it is stable for 48 hours.

Storage and Stability: The drug is available as a box of 10 vials that are stored at room temperature. Each vial should be kept in the box to protect it from light. Etoposide is less stable in 5% Dextrose injection and precipitation is reported.

Administration: Etoposide is administered by slow IV infusion to reduce hypotension.

3.9 **Lenalidomide** (Revlimid)

WARNING: FETAL RISK, HEMATOLOGIC TOXICITY, and DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

FETAL RISK

Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or death to a developing baby.

Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

HEMATOLOGICAL TOXICITY

Can cause significant neutropenia and thrombocytopenia.

DVT AND PE

Significantly increased risk of DVT and PE in participants with multiple myeloma receiving lenalidomide with dexamethasone. Participants and physicians are advised to be observant for the signs and symptoms of thrombo-embolism. Participants should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with lenalidomide may lessen the potential for venous thromboembolic events. The decision to take prophylactic measures should be done carefully after an assessment of an individual participant's underlying risk.

INDICATIONS AND USAGE

Lenalidomide is a thalidomide analogue indicated for the treatment of multiple myeloma (MM), in combination with dexamethasone, in participants who have received at least one prior therapy.

DOSING AND ADMINISTRATION

MM: 25 mg once daily orally on Days 1-21 of repeated 28-day cycles. Recommended dose of dexamethasone is 40 mg once daily on Days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg/day orally on Days 1-4 every 28 days. Treatment is continued or modified based upon clinical and laboratory findings.

DOSE ADJUSTMENTS FOR HEMATOLOGIC TOXICITIES DURING MULTIPLE MYELOMA TREATMENT

Dose modification guidelines are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicity judged to be related to lenalidomide.

DOSE ADJUSTMENTS FOR RENAL IMPAIRMENT IN MM

Since lenalidomide is primarily excreted unchanged by the kidney, adjustments to the starting dose of lenalidomide are recommended to provide appropriate drug exposure in participants with moderate or severe renal impairment and in participants on dialysis. Based on a pharmacokinetic study in participants with renal impairment due to non-malignant conditions, LENALIDOMIDE starting dose adjustment is recommended for participants with CLcr <60 mL/min. Non-dialysis participants with creatinine clearances less than 11 mL/min and dialysis participants with creatinine clearances less than 7 mL/min have not been studied. After initiation of LENALIDOMIDE therapy, subsequent LENALIDOMIDE dose modification should be based on individual participant treatment tolerance.

DOSAGE FORMS AND STRENGTHS

Lenalidomide 5 mg, 10 mg, 15 mg and 25 mg capsules will be supplied through RevAssist.

CONTRAINDICATIONS

Lenalidomide may cause fetal harm when administered to a pregnant woman. Limb abnormalities were seen in the offspring of monkeys that were dosed with lenalidomide during organogenesis. This effect was seen at all doses tested. Due to the results of this developmental monkey study, and lenalidomide's structural similarities to thalidomide, a known human teratogen, lenalidomide is contraindicated in pregnant women and women capable of becoming pregnant. Females of childbearing potential may be treated with lenalidomide provided adequate precautions are taken to avoid pregnancy. Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, including at least one highly effective method (e.g., hormonal contraception, tubal ligation, IUD or partner's vasectomy) and one additional effective method (e.g., latex condom, diaphragm, or cervical cap), beginning 4 weeks prior to initiating treatment with lenalidomide, during therapy, during therapy delay, and continuing for 4 weeks following discontinuation of lenalidomide therapy. If hormonal or IUD contraception is medically contraindicated, two other effective or highly effective methods may be used.

Females of childbearing potential being treated with lenalidomide must have pregnancy testing (sensitivity of at least 50 mIU/mL). Pregnancy testing and counseling must be performed if a participant misses her period or if there is any abnormality in menstrual bleeding. If pregnancy occurs, lenalidomide must be immediately discontinued. Under these conditions, the participant should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Lenalidomide is also contraindicated in participants who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide.

WARNINGS AND PRECAUTIONS

Fetal Risk

Lenalidomide is a thalidomide analogue. Thalidomide is a known human teratogen that causes life-threatening human birth defects. An embryo-fetal development study in non-human primates indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy. If lenalidomide is used during pregnancy, it may cause birth defects or death to a developing baby. Females of childbearing potential must be advised to avoid pregnancy while on lenalidomide. Two effective contraceptive methods should be used during therapy, during therapy interruptions and for at least 4 weeks after completing therapy. There are no adequate and well-controlled studies in pregnant females.

Hematologic Toxicity

Lenalidomide can cause significant neutropenia and thrombocytopenia. In the pooled multiple myeloma studies Grade 3 and 4 hematologic toxicities were more frequent in participants treated with the combination of lenalidomide and dexamethasone than in participants treated with dexamethasone alone.

Deep Vein Thrombosis and Pulmonary Embolism

Venous thromboembolic events (predominantly deep venous thrombosis and pulmonary embolism) have occurred in participants with multiple myeloma treated with lenalidomide combination therapy or treated with lenalidomide monotherapy. A significantly increased risk of DVT and PE was observed in participants with multiple myeloma who were treated with lenalidomide and dexamethasone therapy in a clinical trial. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with lenalidomide may lessen the potential for venous thromboembolic events. The decision to take prophylactic measures should be done carefully after an assessment of an individual participant’s underlying risk factors.

Allergic Reactions

Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal. Participants with a prior history of Grade 4 rash associated with thalidomide treatment should not receive lenalidomide. Lenalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Lenalidomide must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected and should not be resumed following discontinuation for these reactions.

Tumor Lysis Syndrome

Fatal instances of tumor lysis syndrome have been reported during treatment with lenalidomide. The participants at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These participants should be monitored closely and appropriate precautions taken.

Tumor Flare Reaction

Tumor flare reaction has occurred during investigational use of lenalidomide for CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. Treatment of CLL or lymphoma with lenalidomide outside of a well-monitored clinical trial is discouraged.

ADVERSE REACTIONS

Clinical Trials Experience in Multiple Myeloma

Data were evaluated from 703 participants in two studies who received at least one dose of lenalidomide/dexamethasone (353 participants) or placebo/dexamethasone (350 participants). In the lenalidomide/dexamethasone treatment group, 269 participants (76%) underwent at least one dose interruption with or without a dose reduction of lenalidomide compared to 199 participants (57%) in the placebo/dexamethasone treatment group. Of these participants who had one dose interruption with or without a dose reduction, 50% in the lenalidomide/dexamethasone treatment group underwent at least one additional dose interruption with or without a dose reduction compared to 21% in the placebo/dexamethasone treatment group. Most adverse events and Grade 3/4 adverse events were more frequent in participants who received the combination of lenalidomide/dexamethasone compared to placebo/dexamethasone.

Median duration of exposure among participants treated with lenalidomide/dexamethasone was 44 weeks while median duration of exposure among participants treated with placebo/dexamethasone was 23 weeks. This should be taken into consideration when comparing frequency of adverse events between two treatment groups lenalidomide/dexamethasone vs. placebo/dexamethasone.

Deep Vein Thrombosis and Pulmonary Embolism

Deep vein thrombosis (DVT) was reported as a serious adverse drug reaction (7.4%) or Grade 3/4 (8.2%) at a higher rate in the lenalidomide/dexamethasone group compared to 3.1% and 3.4% in the placebo/dexamethasone group, respectively. Discontinuations due to DVT adverse reactions were reported at comparable rates between groups.

Pulmonary embolism (PE) was reported as a serious adverse drug reaction including Grade 3/4 (3.7%) at a higher rate in the lenalidomide/dexamethasone group compared to 0.9% in the placebo/dexamethasone group. Discontinuations due to PE adverse reactions were reported at comparable rates between groups.

Other Adverse Events

In these clinical studies of lenalidomide in participants with multiple myeloma, the following adverse drug reactions (ADRs) not described above that occurred at ≥1% rate and of at least twice of the placebo percentage rate were reported:

Blood and lymphatic system disorders: pancytopenia, autoimmune hemolytic anemia

Cardiac disorders: bradycardia, myocardial infarction, angina pectoris

Endocrine disorders: hirsutism

Eye disorders: blindness, ocular hypertension

Gastrointestinal disorders: gastrointestinal hemorrhage, glossodynia

General disorders and administration site conditions: malaise

Investigations: liver function tests abnormal, alanine aminotransferase increased,

Nervous system disorders: cerebral ischemia

Psychiatric disorders: mood swings, hallucination loss of libido

Reproductive system and breast disorders: erectile dysfunction,

Respiratory, thoracic and mediastinal disorders: cough, hoarseness

Skin and subcutaneous tissue disorders: exanthem, skin hyperpigmentation

DRUG INTERACTIONS

Results from human in vitro metabolism studies and nonclinical studies show that lenalidomide is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be subject to P450-based metabolic drug interactions in man.

DIGOXIN

When digoxin was co-administered with lenalidomide, the digoxin AUC was not significantly different; however, the digoxin Cmax was increased by 14%. Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in participants receiving this medication, is recommended during administration of lenalidomide.

WARFARIN

Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S-warfarin. Co-administration of single 25-mg dose warfarin had no effect on the pharmacokinetics of total lenalidomide. Expected changes in laboratory assessments of PT and INR were observed after warfarin administration, but these changes were not affected by concomitant lenalidomide administration.

Concomitant Therapies That May Increase the Risk of Thrombosis

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution in multiple myeloma participants receiving lenalidomide with dexamethasone.

GERIATRIC USE

Lenalidomide has been used in multiple myeloma (MM) clinical trials in participants up to 86 years of age. Of the 703 MM participants who received study treatment in Studies 1 and 2, 45% were age 65 or over while 12% of participants were age 75 and over. The percentage of participants age 65 or over was not significantly different between the lenalidomide/ dexamethasone and placebo/dexamethasone groups. Of the 353 participants who received lenalidomide/dexamethasone, 46% were age 65 and over. In both studies, participants >65 years of age were more likely than participants ≤65 years of age to experience DVT, pulmonary embolism, atrial fibrillation, and renal failure following use of lenalidomide. No differences in efficacy were observed between participants over 65 years of age and younger participants.

DESCRIPTION

Lenalidomide, a thalidomide analogue, is an immunomodulatory agent with antiangiogenic and antineoplastic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro-2H -isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure: 3-(4-amino-1-oxo 1,3-dihydro-2H -isoindol-2-yl) piperidine-2,6-dione The empirical formula for lenalidomide is C13H13N3O3, and the gram molecular weight is 259.3. Lenalidomide is available in 5 mg, 10 mg, 15 mg and 25 mg capsules for oral administration.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory, antiangiogenic, and antineoplastic properties. Experiments have demonstrated that lenalidomide inhibits the growth of cells derived from participants with multiple myeloma and del (5q) myelodysplastic syndromes in vitro. Lenalidomide causes a delay in tumor growth in some in vivo nonclinical hematopoietic tumor models, including multiple myeloma. Lenalidomide inhibits the secretion of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), from peripheral blood mononuclear cells. Lenalidomide also inhibited the expression of cycoloxygenase-2 (COX-2) but not COX-1 in vitro.

Pharmacokinetics

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmaco -kinetic disposition of lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic sampling in myelodysplastic syndromes participants was not performed. In multiple myeloma participants maximum plasma concentrations occurred between 0.5 and 4.0 hours post-dose both on Days 1 and 28. AUC and Cmax values increase proportionally with dose following

single and multiple doses. Exposure (AUC) in multiple myeloma participants is 57% higher than in healthy male volunteers.

Distribution

In vitro (14C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and Excretion

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

SPECIAL POPULATIONS

Participants with Renal Impairment

In multiple myeloma participants, those participants with mild renal impairment had an AUC 56% greater than those with normal renal function. Adjustment of the starting dose of lenalidomide is recommended in participants with moderate or severe (CLcr <60 mL/min) renal impairment and in participants on dialysis.

3.10 **Carfilzomib** (Kyprolis)

For Injection, for intravenous use. Initial U.S. Approval: 2012

DOSAGE AND ADMINISTRATION

Administer intravenously over 2 to 10 minutes, on two consecutive days each week for three weeks followed by a 12-day rest period. Recommended Cycle 1 dose is 20 mg/m^2/day, and if tolerated, increase Cycle 2 dose and subsequent cycles doses to 27 mg/m2/day. Carfilzomib may also be given 56 mg/m^2 on days 1, 8, 15 and 22, if deemed beneficial for patient by the treating physician.

The safety of carfilzomib was evaluated in clinical studies of 526 patients with relapsed and/or refractory multiple myeloma.

Cardiac Arrest, Congestive Heart Failure, Myocardial Ischemia

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 have occurred following administration of carfilzomib. Cardiac failure events (e.g., cardiac failure congestive, pulmonary edema, ejection fraction decreased) were reported in 7% of patients. Monitor for cardiac complications and manage promptly. Withhold carfilzomib for Grade 3 or 4 cardiac events until recovery and consider whether to restart carfilzomib based on a benefit/risk assessment. Patients with New York Heart Association Class III and IV heart failure, myocardial infarction in the preceding 6 months, and conduction abnormalities uncontrolled by medications may be at greater risk for cardiac complications.

Pulmonary Hypertension

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. Withhold carfilzomib for pulmonary hypertension until resolved or returned to baseline and consider whether to restart based on a benefit/risk assessment.

Pulmonary Complications

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

Infusion Reactions

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

Tumor Lysis Syndrome

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

Thrombocytopenia

Carfilzomib causes thrombocytopenia with platelet nadirs occurring around Day 8 of each 28-day cycle and recovery to baseline by the start of the next 28-day cycle. In patients with multiple myeloma, 36% of patients experienced thrombocytopenia, including Grade 4 in 10%. Thrombocytopenia following carfilzomib administration resulted in a dose reduction in 1% of patients and discontinuation of treatment with cariflzomib in < 1% of patients. Monitor platelet counts frequently during treatment with carfilzomib. Reduce or interrupt dose as clinically indicated.

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. Withhold carfilzomib in patients experiencing Grade 3 or greater elevations of transaminases, bilirubin, or other liver enzyme abnormalities until resolved or returned to baseline. After resolution, consider if restarting carfilzomib is appropriate. Monitor liver enzymes frequently.

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. Females of reproductive potential should be advised to avoid becoming pregnant while being treated with carfilzomib.

ADVERSE REACTIONS

Serious adverse reactions were reported in 45% of patients. The most common serious adverse reactions were pneumonia (10%), acute renal failure (4%), pyrexia (3%), and congestive heart failure (3%). Adverse reactions leading to discontinuation of carfilzomib occurred in 15% of patients and included congestive heart failure (2%), cardiac arrest, dyspnea, increased blood creatinine, and acute renal failure (1% each).

The most common adverse reactions (incidence ≥ 30%) were fatigue (56%), anemia (47%), nausea (45%), thrombocytopenia (36%), dyspnea (35%), diarrhea (33%), and pyrexia (30%).

USE IN SPECIFIC POPULATIONS

Since dialysis clearance of carfilzomib concentrations has not been studied, the drug should be administered after the dialysis procedure.

3.11 **Pomalidomide** (Pomalyst)

INDICATION

Patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.

CONTRAINDICATIONS

Pomalidomide can cause fetal harm and is contraindicated in females who are pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Pomalidomide is a thalidomide analogue and is teratogenic in both rats and rabbits when administered during the period of organogenesis.

WARNINGS AND PRECAUTIONS

Females of Reproductive Potential

Must avoid pregnancy while taking pomalidomide and for at least 4 weeks after completing therapy. Must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control, beginning 4 weeks prior to initiating treatment with pomalidomide, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of pomalidomide therapy. Must obtain 2 negative pregnancy tests prior to initiating therapy.

Males

Pomalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking pomalidomide and for up to 28 days after discontinuing pomalidomide, even if they have undergone a successful vasectomy. Males must not donate sperm.

Blood Donation

Patients must not donate blood during treatment with pomalidomide and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to pomalidomide.

ADVERSE REACTIONS

In the clinical trial of 219 patients who received pomalidomide alone (n=107) or pomalidomide+ low-dose dexamethasone (low-dose dex) (n=112), all patients had at least one treatment-emergent adverse reaction.

In the pomalidomide alone versus pomalidomide + low dose dexamethasone arms, respectively, most common adverse reactions (≥30%) included fatigue and asthenia (55%, 63%), neutropenia (52%, 47%), anemia (38%, 39%), constipation (36%, 35%), nausea (36%, 22%), diarrhea (34%, 33%), dyspnea (34%, 45%), upper respiratory tract infection (32%, 25%), back pain (32%, 30%), and pyrexia (19%, 30%)

90% of patients treated with pomalidomide alone and 88% of patients treated with pomalidomide + low-dose dex had at least one treatment-emergent NCI CTC Grade 3 or 4 adverse reaction.

In the pomalidomide alone versus pomalidomide+ low dose dexamethasone arms, respectively, most common Grade 3/4 adverse reactions (≥15%) included neutropenia (47%, 38%), anemia (22%, 21%), thrombocytopenia (22%, 19%), and pneumonia (16%, 23%). For other Grade 3 or 4 toxicities besides neutropenia and thrombocytopenia, hold treatment and restart treatment at 1 mg less than the previous dose when toxicity has resolved to less than or equal to Grade 2 at the physician's discretion.

67% of patients treated with pomalidomide and 62% of patients treated with pomalidomide + low-dose dex had at least one treatment-emergent serious adverse reaction.

In the pomalidomide alone versus pomalidomide + low dose dexamethasone arms, respectively, most common serious adverse reactions (≥5%) were pneumonia (14%, 19%), renal failure (8%, 6%), dyspnea (5%, 6%), sepsis (6%, 3%), pyrexia (3%, 5%), dehydration (5%, 3%), hypercalcemia (5%, 2%), urinary tract infection (0%, 5%), and febrile neutropenia (5%, 1%).

Venous Thromboembolism

Patients receiving pomalidomide have developed venous thromboembolic events reported as serious adverse reactions. In the trial, all patients were required to receive prophylaxis or antithrombotic treatment. The rate of DVT or PE was 3%. Consider anticoagulation prophylaxis after an assessment of each patient's underlying risk factors.

Hematologic Toxicity

Neutropenia of any grade was reported in 50% of patients and was the most frequently reported Grade 3/4 adverse event, followed by anemia and thrombocytopenia. Monitor patients for hematologic toxicities, especially neutropenia, with complete blood counts weekly for the first 8 weeks and monthly thereafter. Treatment is continued or modified for Grade 3 or 4 hematologic toxicities based upon clinical and laboratory findings. Dosing interruptions and/or modifications are recommended to manage neutropenia and thrombocytopenia.

Hypersensitivity Reactions

Patients with a prior history of serious hypersensitivity associated with thalidomide or lenalidomide were excluded from studies and may be at higher risk of hypersensitivity.

Dizziness and Confusional State

18% of patients experienced dizziness and 12% of patients experienced a confusional state; 1% of patients experienced grade 3/4 dizziness, and 3% of patients experienced grade 3/4 confusional state. Instruct patients to avoid situations where dizziness or confusion may be a problem and not to take other medications that may cause dizziness or confusion without adequate medical advice.

Neuropathy

18% of patients experienced neuropathy (approximately 9% peripheral neuropathy). There were no cases of grade 3 or higher neuropathy adverse reactions reported.

Risk of Second Primary Malignancies

Cases of acute myelogenous leukemia have been reported in patients receiving POMALYST as an investigational therapy outside of multiple myeloma.

3.12 **Methylprednisolone** (Medrol)

DESCRIPTION

Methylprednisolone tablets contain methylprednisolone which is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Methylprednisolone occurs as a white to practically white, odorless, crystalline powder. It is sparingly soluble in alcohol, in dioxane, and in methanol, slightly soluble in acetone, and in chloroform, and very slightly soluble in ether. It is practically insoluble in water. The chemical name for methylprednisolone is pregna-1,4-diene-3,20-dione, 11,17,21-trihydroxy-6-methyl-, (6α,11β)-and the molecular weight is 374.48. Each tablet for oral administration contains 2 mg, 4 mg, 8 mg, 16 mg or 32 mg of methylprednisolone.

ACTIONS

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have saltretaining properties, are used as replacement therapy in adrenocortical deficiency states.
Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify

the body’s immune responses to diverse stimuli.

INDICATIONS AND USAGE

Methylprednisolone tablets are indicated in the following conditions:

1. Endocrine Disorders

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance).

Congenital adrenal hyperplasia

Nonsuppurative thyroiditis

Hypercalcemia associated with cancer

2. Rheumatic Disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)

Ankylosing spondylitis

Acute and subacute bursitis

Synovitis of osteoarthritis

Acute nonspecific tenosynovitis

Post-traumatic osteoarthritis

Psoriatic arthritis

Epicondylitis

Acute gouty arthritis

3. Collagen Diseases

During an exacerbation or as maintenance therapy in selected cases of:

Systemic lupus erythematosus

Systemic dermatomyositis (polymyositis)

Acute rheumatic carditis

4. Dermatologic Diseases

Bullous dermatitis herpetiformis

Severe erythema multiforme

(Stevens-Johnson syndrome)

Severe seborrheic dermatitis

Exfoliative dermatitis

Mycosis fungoides

Pemphigus

Severe psoriasis

5. Allergic States

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:

Seasonal or perennial allergic rhinitis

Drug hypersensitivity reactions

Serum sickness

Contact dermatitis

Bronchial asthma

Atopic dermatitis

6. Ophthalmic Diseases

Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:

Allergic corneal marginal ulcers

Herpes zoster ophthalmicus

Anterior segment inflammation

Diffuse posterior uveitis and choroiditis

Sympathetic ophthalmia

Keratitis

Optic neuritis

Allergic conjunctivitis

Chorioretinitis

Iritis and iridocyclitis

7. Respiratory Diseases

Symptomatic sarcoidosis

Berylliosis

Loeffler's syndrome not manageable by other means

Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy

Aspiration pneumonitis

8. Hematologic Disorders

Idiopathic thrombocytopenic purpura in adults

Secondary thrombocytopenia in adults

Acquired (autoimmune) hemolytic anemia

Erythroblastopenia (RBC anemia)

Congenital (erythroid) hypoplastic anemia

9. Neoplastic Diseases

For palliative management of: Leukemias and lymphomas in adults; Acute leukemia of childhood

10. Edematous States

To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

11. Gastrointestinal Diseases

To tide the patient over a critical period of the disease in:

Ulcerative colitis

Regional enteritis

12. Nervous System

Acute exacerbations of multiple sclerosis

13. Miscellaneous

Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.

Trichinosis with neurologic or myocardial involvement.

CONTRAINDICATIONS

Systemic fungal infections and known hypersensitivity to components.

WARNINGS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated. Corticosteroids may mask some signs of infection, and new infections may appear during their use. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic infections, in any location of the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function.

These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses

Usage in pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of child-bearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy, should be carefully observed for signs of hypoadrenalism.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving nonimmunosuppressive doses of corticosteroids.

The use of methylprednisolone tablets in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. If chicken pox develops, treatment with antiviral agents may be considered. Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

PRECAUTIONS

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy.

Discontinuation of corticosteroids may result in clinical remission.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

DRUG INTERACTIONS

The pharmacokinetic interactions listed below are potentially clinically important. Mutual inhibition of metabolism occurs with concurrent use of cyclosporin and methylprednisolone; therefore, it is possible that adverse events associated with the individual use of either drug may be more apt to occur. Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Drugs that induce hepatic enzymes such as phenobarbital, phenytoin and rifampin may increase the clearance of methylprednisolone and may require increases in methylprednisolone dose to achieve the desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of methylprednisolone and thus decrease its clearance. Therefore, the dose of methylprednisolone should be titrated to avoid steroid toxicity.

Methylprednisolone may increase the clearance of chronic high dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when methylprednisolone is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia.

The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulant when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effect.

Information for the Patient

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances

- Sodium retention
- Congestive heart failure in susceptible patients
- Hypertension
- Fluid retention
- Potassium loss
- Hypokalemic alkalosis

Musculoskeletal

- Muscle weakness
- Loss of muscle mass
- Steroid myopathy
- Osteoporosis
- Tendon rupture, particularly of the Achilles tendon
- Vertebral compression fractures
- Aseptic necrosis of femoral and humeral heads
- Pathologic fracture of long bones

Gastrointestinal

- Peptic ulcer with possible perforation and hemorrhage
- Pancreatitis
- Abdominal distention
- Ulcerative esophagitis
- Increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT), and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.

Dermatologic

- Impaired wound healing
- Petechiae and ecchymoses
- May suppress reactions to skin tests
- Thin fragile skin
- Facial erythema
- Increased sweating

Neurological

- Increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment
- Convulsions
- Vertigo
- Headache

Endocrine

- Development of Cushingoid state
- Suppression of growth in children
- Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness
- Menstrual irregularities
- Decreased carbohydrate tolerance
- Manifestations of latent diabetes mellitus
- Increased requirements of insulin or oral hypoglycemic agents in diabetics

Ophthalmic

- Posterior subcapsular cataracts
- Increased intraocular pressure
- Glaucoma
- Exophthalmos

Metabolic

- Negative nitrogen balance due to protein catabolism

The following additional reactions have been reported following oral as well as parenteral therapy: Urticaria and other allergic, anaphylactic or hypersensitivity reactions.

DOSAGE AND ADMINISTRATION

The initial dosage of methylprednisolone tablets may vary from 4 mg to 48 mg of methylprednisolone per day depending on the specific disease entity being treated. In situations of less severity lower doses will generally suffice while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, methylprednisolone should be discontinued and the patient transferred to other appropriate therapy.

4.0 Staging Criteria

4.1 Multiple Myeloma Durie-Salmon Staging Criteria

<u>High Tumor Mass (Stage III</u>)

<u>One</u> of the following abnormalities must be present:

a. Hemoglobin <8.5 gm%, hematocrit < 25 vol. %, or

b. Serum calcium > 12 mg% or

c. Very high serum or urine myeloma protein production rates:

1. IgG peak > 7 gm%

2. IgA peak > 5 gm%

3. Bence-Jones protein > 12 gm/day (24 hours), or

d. > 3 lytic lesions on bone survey (bone scan not acceptable)

Low Tumor Mass (Stage I)

All of the following must be present:

a. Hemoglobin > 10.5 gm% or hematocrit > 32 vol%

b. Serum calcium normal

c. Low serum myeloma protein production rates:

1. IgG peak < 5 gm%

2. IgA peak < 3 gm%

3. Bence-Jones protein < 4 gm/day (24 hours)

d. Bone lesions scaled (none) or 1 normal bone structure or osteoporosis only, or solitary bone plasmacytoma.

Intermediate Tumor Mass (Stage II)

All other participants who do not qualify specifically for high or low tumor mass categories are considered to have intermediate tumor mass.

4.2.1 Assessment of Renal Status (Renal Substage):

A = Good renal function (creatinine ≤ 2.0 mg %)

B = Poor renal function (creatinine > 2.0 mg %)

4.2 International Staging Criteria

In 2005, a new, international classification method was utilized for myeloma prognosis, based on the clinical and laboratory data gathered from 10,750 previously untreated symptomatic myeloma patients from 17 institutions in Asia, Europe, and North America. The International Staging System utilizes a combination of serum β^2 microglobulin and serum albumin to provide a simple, powerful, and reproducible three-stage classification. It was validated in patients younger and older than 65 years; with standard therapies or autotransplant; and in comparison with the Durie/Salmon staging system.

I Serum β2 microglobulin <3.5 mg/L
Serum albumin ≥ 3.5 g/dL

II Not I or III*

III Serum β2 microglobulin >5.5 mg/L

*There are two possibilities for stage II:

- Serum β2 microglobulin <3.5 mg/L, but serum albumin <3.5 g/dL

OR

- Serum β2 microglobulin 3.5 – 5.5 mg/L irrespective of the serum albumin

5.0 Study Eligibility Criteria

5.1 Inclusion Criteria

1. Participants must have had a diagnosis of symptomatic MM, MM + amyloidosis, or POEMS (osteosclerotic myeloma: Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) requiring treatment. Participants with a previous history of smoldering myeloma will be eligible if there is evidence of progressive disease requiring chemotherapy. **Note that study participants do not need to have active disease at the time of study entry, as participants may have received up to 12 months of prior chemotherapy, which might have induced a response.**

2. Protein criteria must be present at diagnosis (quantifiable M-component of IgG, IgA, IgD, or IgE and/or urinary kappa or lambda light chain, Bence-Jones protein, or Free Kappa Light Chain or Free Lambda Light Chain) in order to evaluate response. Non-secretory participants are eligible provided the participant has $\geq$ 20% plasmacytosis OR multiple (≥3) plasmacytomas or lesions on MRI at the time of diagnosis or study enrollment , OR the presence of lesions on PET/CT scan or skeletal survey at diagnosis or study enrollment.

3. Participants must have received ≤12 months of prior chemotherapy for this disease without evidence of progressive disease with treatment. **Participants may have received prior radiotherapy provided approval has been obtained from the PI. Participants with a history of radiation who have a platelet count <150,000 due to radiation (disease, chemo, and other factors have been ruled out) will be excluded from this study.**

4. Participants must not have had a prior transplant.

5. Participants must be 65-85 years of age at the time of study entry.

6. Ejection fraction by ECHO or MUGA of ≥ 40% performed.

7. Participants must have adequate pulmonary function studies (PFTs), $\geq$ 50% of predicted on mechanical aspects (FEV^1, FVC) and diffusion capacity (DLCO) $\geq$ 50% of predicted (adjusted for hemoglobin). **If the participant is unable to complete PFTs due to disease-related pain or other circumstances that make it difficult to reliably perform PFTs, documentation of pulmonary function adequate for transplant will**

occur via a CT scan without evidence of major pulmonary disease, and arterial blood gas results.

8. Participants must have a creatinine < 3 mg/dl and a GFR >30mL/min/1.73m^2.

9. Participants must have a performance status of 0-2 based on ECOG criteria. Participants with a poor performance status (3-4) based solely on bone pain will be eligible, provided there is documentation to verify this.

10. Participants must sign the most current IRB-approved study ICF (Informed Consent Form).

5.2 Exclusion Criteria

1. Prior autologous or allogeneic transplant.

2. Progressive disease on prior treatment.

3. Platelet count < 30 x 10^9/L, unless myeloma-related. If MM-related (hypercellular marrow biopsy of >80% and packed with at least 80% plasma cells) the enrolling investigator must document this.

4. > grade 3 neuropathy.

5. Known hypersensitivity to bortezomib, boron, or mannitol.

6. Uncontrolled diabetes on appropriate therapy.

7. Recent (≤ 6 months) myocardial infarction, unstable angina, difficult to control congestive heart failure, uncontrolled hypertension on appropriate therapy, or difficult – to-control cardiac arrhythmias.

8. Participants must not have a creatinine >3 mg/dl or a GFR <30mL/min/1.73m^2.

9. Participants must not have a concurrent malignancy **unless** it can be adequately treated by non-chemotherapeutic intervention. Participants may have a history of prior malignancy, provided that he/she has not had any chemotherapy within 365 days of study entry **AND** that life expectancy exceeds 5 years at the time of study entry.

10. Participants must not have life-threatening co-morbidities.

An inclusion/exclusion checklist signed by the enrolling research coordinator/nurse and the enrolling investigator verifying participant eligibility will be kept in each participant's research chart.

6.0 Treatment Plan

Throughout treatment, antibiotic/antifungal/antiviral/anticoagulant prophylaxis will be administered as per institutional guidelines and SOPs.

Infectious prophylaxis will include:

1. Antibiotics (e.g. ciprofloxacin, levofloxacin, or doxycycline)

2. Antifungals (e.g. clotrimazole, fluconazole, voriconazole or caspofungin)

3. Antivirals (e.g. acyclovir, famciclovir, or valacyclovir)

The drugs listed above represent current commonly used prophylactic agents within each category, but these may be substituted by similar drugs as appropriate since institutional standard-of-care prophylaxis may change over time. All agents used for infection prophylaxis during the course of this study will be captured in the concomitant medication section of the Case Report forms (CRFs).

Throughout study treatment, supportive care will be administered as per institutional guidelines and SOPs.

6.1 Induction and PBSC Collection

Initial chemotherapy will consist of 1 cycle of combination D-PACE chemotherapy and peripheral blood stem cell collection. It is mandated that chemotherapy be given through a central venous access catheter to avoid potential complications of extravasation.

D-PACE

Dexamethasone 20 mg oral on days 1-4 and 8-11.

Cisplatin 10 mg/m2/day on days 1-4 CI (**Continuous Infusion**).

Doxorubicin 10 mg/m2/day on days 1-4 CI.

Cyclophosphamide 400 mg/m2/day or 600 mg/m2 on days 1-4 CI*

Etoposide 40 mg/m2/day on days 1-4 CI

See Appendix I for appropriate algorithms when computing chemotherapy doses. The daily dose of cyclophosphamide, etoposide, and cisplatin will be infused over approximately 24 hours, for a total infusion time of approximately 96 hours.

*Cyclophosphamide may be dose escalated from 400mg/m2 to 600 mg/m2 in cases of high-risk myeloma, based on an LDH ≥ 400 u/L or high-risk cytogenetics [t(4,14), t(14,16) and t(14,20) and del17p13 on FISH; del13 or del13q on metaphase cytogenetics, as per Mayo clinic criteria].

PBSC (Peripheral Blood Stem Cell) Collection Guidelines

Pegfilgrastim will be administered at a dose of 6 mg on days +6 and +13 after D-PACE chemotherapy. If peripheral CD34 cell count is <20 µL, once WBC count is >1,000/µL, G-CSF may be given at a dose of 10 mcg/kg/day(rounded to the nearest vial size) and divided into a morning and evening dose, with the larger dose given in the morning. G-CSF will be discontinued upon completion of apheresis. If patient is unable to collect by day 17 post-D-PACE, plerixafor should be given as per SOP until the stem cell collection is completed.

PBSC will be collected and processed according to institutional standards. These cells will be assessed by flow cytometry for the presence of CD34 for a target of > 15 x 10^6 CD34+ cells/kg. (5 x 10^6 CD34+ cells/kg minimum necessary).

Participants unable to collect at least 5 x 10^6 CD34/kg may undergo other collection(s) as per program practice. Participants unable to collect at least 5 x 10^6 CD34/kg after two attempts will be removed from the protocol, since it is unlikely that they will complete 2 years of maintenance. If the interval between the cycle of D-PACE and transplant is > 4 months (or >6 months in a participant that requires > 1 PBSC collection), that participant will be removed from the study.

In the unlikely event that the PBSC product becomes contaminated with excessive myeloma cells (≥ 5%), participants will undergo a second round of chemotherapy with VDT-PACE (see section 6.3 of this protocol for chemotherapy schedule) prior to an additional collection attempt in order to decrease the possibility of another myeloma-contaminated stem cell collection. The same collection guidelines as above apply to this second round of chemo mobilization.

Pre-Maintenance Therapy Modifications

Cisplatin doses will be modified for renal insufficiency as follows:

Cisplatin dose	Creatinine
10 mg/m2 (full dose)	≤1.5 mg/dl
5 mg/m2	1.6 – 2.0 mg/dl
0 mg/m2 (hold Cisplatin)	>2.0 mg/dl

Dexamethasone: If study participants are sensitive to steroids and experience a steroid “crash” when stopping the drug, dexamethasone doses may be tapered after each dosing increment. Depending on the severity of the symptoms, 4-8mg of dexamethasone may be given for two additional days before stopping the drug completely.

For suspected dexamethasone-related toxicity (non-infectious) ≥ grade 2 that does not abate or resolve with supportive care measures or a 7-14 day drug hold, **methylprednisolone** 16mg every other day may be prescribed as substitution.

Doxorubicin: For participants with hepatic dysfunction (transaminases > 2 x ULN or direct bilirubin > 2.0 mg/dl if performed) before the start of induction or consolidation, the doxorubicin dose should be reduced by 50%. It may be raised if hepatic function improves. For participants developing evidence of significant cardiac toxicity or cardiac failure, doxorubicin should be discontinued.

Thalidomide: For grade 2 toxicity non-infectious or non-hematologic toxicity, thalidomide may be dose reduced to 50mg daily, depending on the toxicity and possibility of recurrence/worsening with the re-introduction of therapy at full dose. For ≥grade 3 non-hematologic toxicity, thalidomide will be held until toxicity resolves to a grade 2 or better. Thalidomide may be resumed at full dose (100mg/day) or dose-reduced to 50mg per day, depending on the toxicity and possibility of recurrence/worsening with the re-introduction of therapy at full dose. The rationale for the dose reduction must be recorded in source notes. Dose reductions below 50mg daily are not allowed.

Interim between Induction D-PACE and Transplant

Following D-PACE and PBSC collection, participants may receive interim dexamethasone at 20mg days 1-4 every 14 days, but this may be omitted by the treating physician. Any planned omission of the dexamethasone must be documented by the treating physician.

6.2 Transplant Phase

Transplant (VDT-MEL)

Transplant should preferably occur 6 weeks after the induction PACE continuous infusion has been completed, but can occur as early as 4 weeks and as late as 3 months if the participant fails to mobilize stem cells after the PACE administration. Transplant may be given on an inpatient or outpatient basis.

Dexamethasone 20 mg oral on days -4 to -1 and +2 to +5.

Bortezomib 1mg/m2 IV Bolus on days -4, -1, +2, and +5.

Thalidomide 100mg/day oral on days -4 to +5.

Melphalan will be given at a dose of 100 mg/m2 on days -4 and -1 (Participants > 70 years of age or with a creatinine > 2.0 mg/dl will receive Melphalan 70 mg/m2 on days -4 and -1). See Appendix I for appropriate algorithms when computing chemotherapy doses.

Peripheral blood stem cell infusion will be given intravenously on day 0, i.e., at least 18 hours after the second dose of melphalan. The participant will be pre-medicated according to institutional practice. No less than approximately 5 x 10^6 /kg CD34cells will be infused with the transplant.

If deemed medically necessary (graft failure, graft delay, inadequate platelet recovery, etc), and if a participant has sufficient stem cells in storage, a boost of stem cells may be given at any point after transplant, including subsequent treatment phases.

Interim between Transplant and Consolidation/Maintenance Therapy

Participants will receive dexamethasone 20 mg oral days 1-4 every 21 days and thalidomide 100 mg oral and daily in the interim between transplant and consolidation.

Interim therapy between transplant and consolidation may be held or dose-modified, but the reasons for this must be documented in source notes.

6.3 Consolidation Therapy

If administered, post-transplant consolidation therapy should begin 4-6 weeks after transplant, but should occur no later than 4 months after transplant. Consolidation will consist of one cycle of VDT-PACE.

Consolidation VDT-PACE should only be given if all of the following criteria are met:

1. Participant has high-risk disease as per Mayo clinic criteria (see induction DPACE section)
2. Platelet count should be > 80,000/ mcl.
3. Participant does not have a medical complication that will make it unsafe to administer consolidation.
4. Participant must have achieved a PR or better (as defined in this protocol in the Response Categories section) after induction DPACE.

Consolidation VDT-PACE

Dexamethasone 20 mg oral on days 1-4 and days 8-11

Thalidomide 100mg oral on days 1-11

Bortezomib 1mg/m2 IV Bolus on days 1, 4, 8, 11

Cisplatin 10 mg/m2 on days 1-4 CI

Doxorubicin 10mg/m2 on days 1-4 CI

Cyclophosphamide 400 mg/m2 on days 1-4 CI

Etoposide 40 mg/m2 on days 1-4 CI

See Appendix I for appropriate algorithms when computing chemotherapy doses. The daily dose of cyclophosphamide, etoposide, and cisplatin will be infused over approximately 24 hours, for a total infusion time of approximately 96 hours.

6.4 Maintenance Therapy

Maintenance will begin 4 weeks to 6 months after transplant, or between 6 weeks to 6 months after consolidation if administered. This is considered standard of care. Platelets must have recovered to ≥ 70,000µl, although a variance of 5,000 µl is acceptable if it is otherwise clinically appropriate to proceed to maintenance therapy.

Participants will be evaluated at least 3 times per year (after completion of 4 cycles ± 21 days) by the treating investigator during maintenance therapy. Local oncologists will be encouraged to call the treating investigator with any questions regarding toxicities**.**

An order for a blood draw to check MM markers will be sent to the participant's local physician's office every three months during long term follow up. If 3 consecutive serum MM markers are missed, the study team will follow up with the participant and/or local oncologist to reinforce the necessity of close disease marker tracking while on study treatment. Subjects may be removed from study if non-compliance with this request continues.

Participants will be evaluated for adverse events according to the National Cancer Institute Common Terminology for Adverse Events (CTCAE), version 4.0.

Any protocol treatment(s) may be delayed or held by the treating investigator if the participant's safety is considered to be at risk. This must be adequately documented in source notes. For serious adverse events, treatment will be held until it is clinically appropriate to continue.

If excessive toxicity occurs, a participant may stop maintenance treatment but will still be followed for event-free and overall survival.

8.0 Study Calendar

All pre-study testing necessary to determine eligibility must be performed within 60 days of study enrollment. All other pre-phase testing must be done within 45 days of the start of the phase.

	Pre-study	**Pre-Induction**[2]	**Pre-Transplant** **4wks-4mos from day 1 of induction**	**Pre- Consolidation** **4wks-4 mos post-transplant** **OR** **Pre-Maintenance**	**Maintenance Therapy**[5]	**Long-term follow-up**[6] **(+/-2 weeks)**

				4 wks-6 mos post-transplant if no consolidation		
H&P[1]	X	X	X	X	3 times per year	Once per year
Toxicity Evaluation	X	X	X	X	3 times per year	Once per year
ECG	X					
CBC with diff	X	X	X	X	3 times per year	Once per year
CMP[3], Mg, Phos, CRP, LDH	X	X	X	X	3 times per year	Once per year
PT, INR	X	X	X	X	3 times per year	Once per year
Serum Electrophoresis	X	X	X	X	3 times per year	Once per year
Quantitative Immunoglobulins	X	X	X	X	3 times per year	Once per year
Serum Free Light Chains	X	X	X	X	3 times per year	Once per year
Serum IFE	X	X	X	X	3 times per year	Once per year
Beta-2-Microglobulin	X	X	X	X	3 times per year	Once per year
24 hr urine for total protein, electrophoresis, and IFE (if indicated).	X					
TSH	X	X	X	X	3 times per year	Once per year
Bone Marrow Aspirate & Biopsy[4]	X	X	X	X	3 times per year	once per year
PFTs with DLCO	X					

1. H&P to include detailed medical and treatment history and performance status.
2. If Induction DPACE is started within 2 weeks from study enrollment, the pre-study testing can be used to satisfy the pre-Induction requisite testing as well.
3. CMP includes: ALT, AST, Albumin, total bilirubin, Ca, CO2, Cl, Creatinine, Glucose, Alk Phos, K, Na, BUN, total protein
4. In the event that a subject had a normal bone marrow core biopsy at baseline (i.e. <5% plasma cells), bone marrow biopsies will be performed at intervals deemed appropriate by the treating physician.
5. Maintenance therapy consists of 24 cycles of standard-of-care chemotherapy. Maintenance evaluations will be done 3 times per year (after 4 cycles ± 21 days) at the study center. Participants will be asked to send in blood for MM marker analysis on a monthly basis, preferably drawn on day 1 of each cycle. If 3 consecutive monthly serum MM markers are missed, the study team will follow up

with the participant and/or local oncologist to reinforce the necessity of close disease marker tracking while on study treatment. Subjects may be removed from study if non-compliance with this request continues.
6. During long-term follow-up, study participants will be evaluated at the study center at least once per year.
At the first sign of progression, every attempt will be made to bring the participant back to the study center as soon as possible for evaluation of progressive disease.

Radio-imaging studies to be performed while on study

	Pre-study	**Pre-Induction**	**Pre-Transplant**	**Pre-Consolidation/Pre-Maintenance**	**Maintenance**	**Long-term follow-up**
MRI or PET[1]	X	X	X	X	As clinically indicated	As clinically indicated
Echo or MUGA	X					

1. Ideally, study participants will have both a PET and MRI pre-study, and then alternate between MRI and PET thereafter at the time points on this calendar. However, if a participant cannot receive either an MRI or PET for any reason, the participant will receive only the applicable radiographic test.

Optional Quality-of-Life Questionnaires

See section 11.0 of this protocol for further discussion.

	Pre-study	**Pre-Consolidation/Pre-Maintenance**	**Maintenance Phase**	**Follow-up**
EORTC QLQ-C30	X	X	2 times per year	Once per year for 3 years
EORTC QLQ-MY20	X	X	2 times per year	Once per year for 3 years

9.0 Criteria for Evaluation and Endpoint Definitions

Response Categories

International Myeloma Working Group uniform response criteria

Response	***IMWG criteria***
sCR	CR as defined below plus normal FLC ratio, if it can be calculated, and absence of clonal cells in bone marrow[3] by immunohistochemistry or immunofluorescence[4] If the FLC ratio is abnormal due to the non-involved light chain, it does not exclude a sCR.

CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow[3]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
PR	≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h If the serum and urine M-protein are unmeasurable,[5] 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 not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
MR	NA
No change/Stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease
Plateau	NA
Progressive disease[5]	Increase of ≥ 25% from lowest response value in any one or more of the following: • Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)[6] • Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h) • Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL • Bone marrow plasma cell percentage; the absolute percentage must be ≥ 10%[7] • 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 hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).[6] It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice • Development of new soft tissue plasmacytomas or bone lesions • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the product of the cross-diameters of the measurable lesion • Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] • Decrease in haemoglobin of ≥ 2 g/dL [1.25 mmol/L] • Rise in serum creatinine by 2 mg/dL or more [177 mmol/L or more]
Relapse from CR[5] (To be used only if the	Any one or more of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis

end point studied is DFS)[8]	• Development of ≥ 5% plasma cells in the bone marrow[7] • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia)

[1] BGM Durie *et al.* International uniform response criteria for multiple myeloma. *Leukemia* (2006) 1-7.
Adapted from Durie BGM, et al. Leukemia 2006; 20: 1467-1473; and Kyle RA, Rajkumar SV. Leukemia 2008;23:3-9.
Note: A 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. (If one of the serum free light chains is not measurable, the involved free light chain should be within or below the normal range. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.
[3] Confirmation with repeat bone marrow biopsy not needed.
[4] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.
[5] All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression-free survival.
[6] For progressive disease, serum M-component increases of ≥1 gm/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.
[7] Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.
[8] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

Note: In ≥90% of MM patients, PD will be documented according to the above criteria. However, in some cases, an investigator may document PD prior to reaching the thresholds outlined in this table if holding salvage treatment until these thresholds are reached is not clinically sound. In such cases, PD may be documented earlier but must be cleared with the PI.

MDS/AML

All persistent cytopenias will be investigated by BM aspirate and biopsy for cytogenetics/FISH. Participants who develop MDS not requiring treatment will remain on study, but participants who develop MDS requiring treatment or AML will be taken off study.

Survival Outcomes

Progression-Free Survival: measured from day 1 of DPACE for all participants who have had at least one day of treatment on study.

Overall Survival: measured as the time from initial study enrollment to death from any cause.

Event-Free Survival: measured as the time from initial study enrollment to progression/relapse of disease or death from any cause.

Performance Status

Participants will be graded according to the following ECOG grading scale. If a Karnofsky score is provided instead of an ECOG, performance status may be converted to the equivalent score.

Grade	Scale
0	Fully active; able to carry on all pre-disease activities without restriction. (Karnofsky 90-100).

1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. (Karnofsky 70-80).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60).
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

Off Study Criteria

Participants will be informed during the informed consent process that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw participants from study treatment or from the study for any of the following reasons:

Off Treatment Criteria

- Initiation of ongoing medical treatment that makes it difficult to evaluate the safety or efficacy of study treatment
- Occurrence of an adverse event that makes it unsafe to administer further study treatment
- Major or recurrent non-compliance
- Participant request
- Failure to return for follow-up as required per study calendar
- Deterioration in the patient's condition, which may not be study treatment-related, but which makes it unsafe to administer further treatment
- Other

Off Study Criteria

- Participant request
-
- Inability to return for any further study visits, including follow-up visits.
- Lost-to-Follow-Up
-
- Early termination of the study

Unless the study terminates early, HIPAA consent is withdrawn, or a participant is lost to follow-up, all study participants will be monitored for progression-free and overall survival.

10.0 Statistical Considerations

Power and Sample Size

The primary objective of this study is to evaluate progression-free survival for the proposed treatment regimen. The study is powered to test the null hypothesis that median survival is no greater than 30 months versus the alternative that it is at least 48 months. Study power and sample size are based on the assumption of exponentially distributed progression times and use of maximum-likelihood methods (Lawless, 1982) to test the one-sided alternative hypothesis at the 5% level of significance. Accordingly, the planned enrollment of 41 patients accrued uniformly over 3 years and followed for 4 additional years will ensure 80% study power.

Reference

Lawless, J. *Statistical Models and Methods for Lifetime Data*, John Wiley and Sons, 1982.

Suspension of Study

Stopping rule with respect to mortality:

For subjects enrolled on Total Therapy II, the mortality rate was found to be 6% for participants under 65, and 12% for those over 65, with an overall mortality rate of 8%. Since we will be enrolling more heavily-pretreated participants (up to 12 months of prior therapy versus up to 1 month in Total Therapy II and III), and participants over 65, a treatment-related mortality rate of up to 15% is considered acceptable in this participant population.

Treatment-Related Mortality calculations will include all deaths that are deemed by the Principal Investigator to be possibly, probably, or definitely related to treatment, that cannot be explained by any other event, and are not related to relapse or progressive disease.

Mortality Suspension Rules

The study will be suspending and a DSMB review triggered if X deaths occur within the first N patients, for X/N = 2/4, 3/8, 4/12, 5/16, 6/20, 7/25, 8/29, 9/34, 10/39, and 11/41. The probability of study suspension and the expected enrollment (if terminated) are summarized in the table below over a range of hypothetical true mortality rates. In it, the suspension probability can be seen to be 7.6% for the mortality rate of 15% deemed to be acceptable, and 73.8% for a rate of 30%. The aforementioned sequential suspension rules were based on Pocock boundaries (1977) and computed with the 'clinfun' software (Ivanova et al., 2005; Seshan, 2013).

True Mortality Rate	Suspension Probability	Expected Enrollment
15%	7.6%	39.1
20%	24.1%	35.5
25%	49.4%	30.0

30%	73.8%	23.6

References

Ivanova A, Qaqish BF, Schell MJ. (2005) Continuous Toxicity Monitoring in Phase II Trials in Oncology, Biometrics, 61, 540-545.

Pocock SJ. (1977) Group Sequential Methods in the Design and Analysis of Clinical Trials. Biometrika, 64, 191-199.

Seshan VE. (2013) clinfun: Clinical Trial Design and Data Analysis Functions. R package version 1.0.5. http://CRAN.R-project.org/package=clinfun

Statistical Analyses

Overall analyses

CR rate, EFS, TTP, and OS will be calculated for all participants who have signed an informed consent form. All analyses will be performed on an intent-to-treat basis. The TTP is defined as the time that patient will need either to start treatment if he/she is off treatment or will need a change in treatment if he/she was still on treatment. The TTP study hypothesis that the median TTP is 4 years will be tested with an exponential survival model. TTP probabilities will be estimated with the method of Kaplan-Meier and modeled as functions of clinicopathological factors with Cox regression. CR will be summarized with binomial proportions.

Frequencies of toxicities will be tabulated on all participants who have completed at least one day of induction treatment. Toxicities will be compared descriptively to historical controls.

Interim analysis for efficacy

The typical use of interim analysis for efficacy is in randomized clinical trials to assess accumulating evidence that one treatment is more efficacious that the other(s). The proposed single-arm registry trial for multiple myeloma participants proposes a treatment regimen that is more intensive than any other available therapy. Therefore, with only one treatment regimen being considered that is more intensive than applied in any other study, this study does not fit the multi-arm comparison setting, and it is unclear that an interim analysis for efficacy is beneficial. Toxicity assessment, and not efficacy, will be the main reason for prematurely stopping this study.

A second complication to an interim efficacy analysis is the short time period that would be available for participant follow-up. The study proposes to enroll 41 participants in 3 years. If an interim analysis is performed, it would be done so during the enrollment period and at a time when most participants have less than two years of follow-up. Conversely, the design for statistical analysis is based on median TTP of 4 years. By the time the interim enrollment is reached, few of the participants will have been followed long enough to experience a relapse. Thus, it is unlikely that we would be able to draw any meaningful conclusions regarding TTP with an interim analysis. For these reasons, an interim analysis to evaluate treatment efficacy is not warranted for this single-arm trial.

11.0 Ancillary Studies

Study subjects may refuse to participate in the optional quality-of-life sub-study and still participate in the study treatment.

The EORTC quality of life questionnaire (QLQ) is an integrated system for assessing the health-related quality of life (QoL) of cancer patients participating in international clinical trials. The core questionnaire, the QLQ-C30, is the product of more than a decade of collaborative research. It is a copyrighted instrument, which has been translated and validated into 81 languages and is used in more than 3,000 studies worldwide. Presently QLQ-C30 Version 3.0 is the most recent version and should be used for all new studies.

It is supplemented by disease specific modules. Those for Breast, Lung, Head & Neck, Oesophageal, Ovarian, Gastric, Cervical cancer, Multiple Myeloma, Oesophago-Gastric, Prostate, Colorectal Liver Metastases, Colorectal and Brain cancer have been validated and are distributed from the EORTC Quality of Life Department.

The QLQ-C30, the core questionnaire, and the QLQ-MY20, the myeloma module, will be administered at the timepoints indicated on the study calendar if participants consent to this optional sub-study.

Appendix III contains a copy of the QLQ-30 and QLQ-MY20.

12.0 Ethical and Regulatory Considerations

Definitions

Unanticipated Problem Involving Risks to Participants or Others: Any event that is a) unanticipated b) caused harm or placed a person at increased risk of harm and c) is related to the research procedures.

Serious Adverse Event: An event is “serious” if it involves considerable detriment or harm to one or more persons (who may or may not be participants), or required intervention to prevent one or more persons from experiencing considerable detriment or harm. Serious adverse events include:

- Death
- Life-threatening experience – Disease or condition where the likelihood of death is high unless the course of the disease/condition is interrupted or diseases/conditions with potentially fatal outcomes where the end point of the clinical trial analysis is survival
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in participant’s offspring
- Any other important medical event that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of

the outcomes listed above. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in participant hospitalization, the development of drug dependency or drug abuse, suicidal ideation or attempts, or the unintentional revealing of some genetic information to insurers.

Related: An event is "related" if more likely than not it was caused by the research activity.

Unexpected: An event is "unexpected" when its specificity, nature, severity or incidence are not accurately reflected in the consent form previously reviewed and approved by the IRB. Examples include a lower rate of response to treatment or a side effect that is more severe than initially expected.

NCI Common Terminology Criteria for Adverse Events

The toxicity criteria to be used in this study are the Common Terminology Criteria for Adverse Events (CTCAE Version 4.0).

Investigator Reporting Responsibilities

To the IRB:

The following must be reported to the IRB by the Principal Investigator, and, except where noted, such reporting is due **no later than 10 business days** after the investigator's first knowledge of the event:

Deaths that are probably or definitely related to the study.

Any event, other than death, that in the PI's opinion is **Serious or Unexpected,** and **Possibly, Probably or Definitely Related** to the study, regardless of whether the participant is on or off study. The PI is responsible for determining the relationship between the administration of study drug and the occurrence of the AE.

An accidental or unintentional change (**Protocol Violation**) to the IRB-approved protocol that increases risk or decreases benefit, affects the participant's rights, safety, welfare, affects the integrity of the data, or has the potential to occur again. (NOTE: Any protocol violation that does not meet this definition should be reported with the next continuing review.)

Pregnancies occurring while the participant is on are considered immediate reportable events. The study regimen should be discontinued immediately.

The treating investigator will follow the participant until completion of the pregnancy, and must notify the IRB of the outcome within 10 business days. The Principal Investigator will provide this information as a follow-up to the initial SAE.

Any neonatal death that occurs within thirty (30) days of birth should be reported to the IRB, without regard to causality. In addition, any infant death after thirty (30) days that the PI suspects is related to in utero exposure to the study regimen should also be reported to the IRB.

If an **Emergency** requiring a protocol occurs for a participant, a deviation will be made only for that participant. The Principal Investigator or other designee in such an emergency will, if circumstances and time permit, contact the IRB immediately by telephone. If time does not allow for this, the Investigator will notify the IRB of the deviation as soon as possible in writing or by phone.

Such contacts will be made as soon as possible to determine whether or not the participant (for whom the deviation from protocol was effected) is to continue in the study. The participant's research chart will contain a description of the deviation from the protocol and state the reasons for such deviation.

The following must be reported to the IRB by the Principal Investigator within 30 days of the PI's first knowledge of the event:

The PI must notify the IRB of pending **audits or inquiries** by external bodies (e.g. FDA, NCI or NIH). This includes any communication that questions the conduct of the research or suggests an impending inquiry, audit or investigation.

Any publication in the literature, interim result, or other finding that indicates an **unexpected change to the risk/benefit ratio** of the research must be reported to the IRB.

Any **breach in confidentiality** that may involve risk to a participant or others (Examples include the loss of a laptop computer on which subject identifies are stored or inadvertent loss study records) must be reported by the IRB.

Any **participant complaint that indicates unanticipated risk** must be reported to the IRB.

Any **incarceration of a participant** if study was not previously reviewed with the anticipation of enrolling prisoners (NOTE: No further interactions may occur with the participant until reviewed by IRB Prisoner Representative.) must be reported to the IRB.

Any **change in FDA labeling or withdrawal from marketing of a drug** used in this research protocol must be reported to the IRB.

To the Medical Monitor:

Expedited reports shall be completed using the SAE form in OnCore, within the timeframe noted, following the investigator having knowledge of the event.

Expedited reporting requirements for Adverse Events and Serious Adverse Events that occur during treatment and within 30 days of last dose of commercial agent:

Attribution	Grade 1	Grade 2	Grade 3 Unexpected With Hosp**	Grade 3 Unexpected W/O Hosp	Grade 3 Expected With Hosp**	Grade 3 Expected w/o Hosp	Grade 4 & 5 Unexpected	Grade 4 & 5 Expected	Prolonged * Hospital stay
Unrelated Unlikely	Not required	Not required	10 calendar days	Not required	10 calendar days	Not required	10 calendar days	10 calendar days	Not required
Possible Probable Definite	Not required	Not required	10 calendar days	10 calendar days	10 calendar days	Not required	24 hours	10 calendar Days***	24 hours

*Prolonged hospital stay: Hospitalization exceeding 12 days for induction or consolidation. Hospitalization exceeding 28 days post-transplant for planned transplant hospitalization.
**Hospitalization refers to any un-planned hospitalization
***Excluding grade 4 hematology and chemistry labs results

Adverse events (AEs ≥ grade 3), for which expedited reporting is not required, will be monitored and recorded on the AE eCRF .AEs will not be recorded by start and stop date but by phase of treatment in which the AE occurred. AEs will be recorded as the worst grade achieved during that phase of treatment. AEs will be categorized by an AE term in the CTCAE, and "other" will not be used as a term within a system organ class unless there is no satisfactory alternative.

Expedited reports will consist of an initial report and follow-up report when applicable (i.e. the initial report does not contain discharge/resolution information). Follow up reports will be completed as data becomes available and within 5 days of the initial report whenever possible. Every attempt will be made to have a complete report submitted if reporting is required within 10 days of knowledge of the event. These events will be reported as a single term (superordinate event) or syndrome. These events will also be assessed for grade and causality by the treating physician or BMT attending and subsequently reviewed by the PI. PI comments on the expedited reports will only be recorded in Oncore in those cases where a disagreement between the co-investigator and the PI exists with respect to the grading or causality assessment of the event.

Monitoring of Adverse Events

All participants will be monitored for AEs during the study. Assessments may include monitoring the participant's clinical symptoms; laboratory, pathological, radiological, or surgical findings; physical examination; or other appropriate tests and procedures.

For this study's purposes, ≥grade 3 toxicities that are possibly, probably, or definitely related to the protocol treatment will be captured in participant case report forms (CRFs) from the time of the start of the study regimen through 30 days after the last protocol treatment administered.

Any toxicities that meet the above criteria, but develop >30 days after the last protocol treatment **and** are probably or definitely still related to treatment, will also be captured in the CRFs.

Data and Safety Monitoring

Type of Clinical Trial:

- ☑ Investigator-initiated (UI/HCCC)
- ❑ Investigator-initiated, participating site
- ❑ Pilot study
- ❑ Phase I
- ❑ Phase I/II
- ☑ Phase II

❑ Phase III

❑ Compassionate-use/Expanded Access

☑ Interventional Treatment

❑ Interventional Non-Treatment

❑ Non-Interventional

Study risk-level:

❑ Level 1—low risk of morbidity or death, * <1% of death or any adverse event

❑ Level 2—risk of death* <1% or any adverse event 1% – 5%

❑ Level 3—risk of death* 1% – 5% or grade 4 – 5 SAE 1% – 5%

☑ Level 4—risk of death* >5% or grade 4 – 5 SAE >5%

❑ Drugs being used on a "compassionate" basis

***** *Risk of death" refers specifically to 100-day treatment-related mortality*

Reporting and Monitoring Requirements:

All institutional investigator initiated trials (IITs), regardless of assigned risk level are subject to routine DSMC monitoring activities which may include but are not limited to review of signed consent documents, eligibility and adverse event reporting.

All institutional IITs have the following **reporting requirements** as part of their DSMP:

- Provide an annual progress report to the DSMC and PRMC
- Register subjects in HCCC's Clinical Trial Management System, OnCore
- Document Adverse Events
- Document protocol deviations

Risk Level 4

Interventional treatment trials involving investigational agents or devices with a risk of death* (>5% or grade 4 – 5 SAE >5%), e.g. all investigator initiated INDs, most Phase I/II trials, gene therapy, gene manipulation or viral vector systems high-risk clinical procedures if performed solely for research purposes. The use of a new chemical or drug for which there is limited or no available safety data in humans.

Study Safety Review

An independent study monitor and/or the DSMC Chair (or designee), will review study data (provided by the PI/available in OnCore) and communicate with the PI at least biannually. A copy of this communication will be forwarded to the DSMC and PRMC Chairs.

Additional Reporting Requirements:

- A scanned copy of the completed eligibility checklist, with screening information and PI signature, will be attached in OnCore for ongoing review by DSMC staff.
- Serious adverse events will be entered directly into an OnCore SAE report by the research team. OnCore will send an automatic notification to the DSMC Chair/acting Chair and staff for review.
- The DSMC utilizes a risk-based monitoring approach. The trial's research records will be monitored at minimum twice per year. Monitoring may be done more frequently depending on the protocol, risks to subjects, reported serious/adverse events, patient population and accrual rate. Records for a minimum of 25% of subjects will be monitored for the entire study.

  Monitoring will involve the following:

  - review eligibility of patients accrued to the study,
  - check for the presence of a signed informed consent,
  - determine compliance with protocol's study plan,
  - determine whether SAEs are being appropriately reported to internal and external regulatory agencies,
  - compare accuracy of data in the research record with the primary source documents,
  - review investigational drug processing and documentation,
  - assess cumulative AE/SAE reports for trends and compare to study stopping rules.

Routine Adverse Event Reporting

For non-serious Adverse Events (AEs ≥ grade 3), documentation must begin from the first day of study treatment and typically continue through the 30 day follow-up period after treatment is discontinued.

Collected information should be recorded in the electronic/Case Report Forms (eCRF/CRF) for that subject. A description of the event, its severity or toxicity grade (according to NCI's Common Toxicity Criteria (CTCAE)), onset and resolved dates (if applicable), and the relationship to the study drug should be included. Documentation should occur in real time. The principal investigator has final responsibility for determining the attribution of the event as it is related to the study drug.

Serious Adverse Event Reporting

For any experience or condition that meets the definition of a serious adverse event (SAE), recording of the event must begin after signing of the informed consent and continue through the 30 day follow-up period after treatment is discontinued.

Reporting requirements are outlined on page 67. An adverse event is considered **serious** if it results in ANY of the following outcomes:

1. Death
2. A life-threatening adverse event

3. An adverse event that results in inpatient hospitalization OR prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

Data Monitoring and Management

All studies that undergo PRMC review and/or utilize HCCC Clinical Research Services (CRS) resources are required to register subjects in OnCore. Subject registration includes the following:

- Consent date and the IRB approved consent used
- Date of eligibility and eligibility status (eligible, not eligible)
- On study date and subject's disease site (and histology if applicable)
- On treatment date (if applicable)

Subject Data

In addition to the subject registration and subject status data entered in OnCore for all HCCC trials, research staff also enters the subject study data into electronic case report forms (eCRFs) for HCCC investigator initiated studies. eCRFs are approved by the PI and statistician prior to study activation to ensure the most effective data acquisition. All information on eCRFs will be traceable to the source documents which are generally maintained in the subject's file. eCRF data are expected to be entered into OnCore within 30 calendar days after a subject's study visit.

Forms Monitoring

OnCore eCRF data are monitored on a routine basis (dependent on accrual) to ensure all mandatory fields are entered completely, accurately and within time requirements. The assigned DSMC monitor manages the logistics associated with the data monitoring review. Once the clinical trial is identified for monitoring, the monitor arranges for a selection of cases to review from among the subjects registered in OnCore. As part of the forms monitoring process, the assigned monitor will issue queries within the eCRF to resolve missing, incomplete and/or incorrect information. A member of the research team is expected to respond to monitoring queries within 14 business days.

This process can often identify a misunderstanding or deficiency in protocol requirements early in the study and can improve data quality.

Final Reports

A summary of each subject's data record is continually available to the PI, research staff, and DSMC from OnCore's Biostat Console. The availability of this information is a valuable tool for the preparation of final reports and manuscripts as well as ongoing deficiency reports.

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed in order to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by the Institutional Review Board, as defined by Federal Regulatory Guidelines (Ref Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

The PI will be responsible for protocol submissions (initial application, amendments, continuing reviews, SAEs, protocol violations, reports of information, etc) to the pertinent IRB and for obtaining and maintaining written IRB approval for this study. IRB approval must be obtained prior to the initiation of the study. Amendments to the protocol may not be instituted without written IRB approval.

Drug Accountability

Because all of the study drugs employed in this schema are commercially approved and have been used extensively in the treatment of multiple myeloma, investigational drug accountability logs will not be kept.

Participant medication diaries will be issued to each study participant in order to track compliance with taking the study protocol's oral, therapeutic medications and will be collected at clinic visits. Participants will have the option of faxing or e-mailing their medication diaries as well. If a participant fails to return his/her medication diaries more than three times consecutively, he/she will be considered for removal from the study for participant non-compliance.

Concomitant Medications

Recording of concomitant medications will be limited to infection prophylaxis, infection treatment, and any newly ordered medications used to treat an event requiring expedited reporting.

Study Records Requirements

The Principal Investigator must ensure that records and documents pertaining to the conduct of the study be retained for a minimum of 10 years after the completion of the study.

At any time the Principal Investigator may be subject to a field audit by regulatory authorities in order to validate the participation of participants in the study. Therefore, careful attention should be paid to ensuring that all study records are complete, accurate, filed and retained by the Investigator.

The Principal Investigator, or a designated member of the Investigator's staff, must be available at some time during auditing visits to review data and resolve any queries and to allow direct access to the participant's records (e.g. medical records, office charts, hospital charts, and study related charts) for source data verification. All study documents must be made available to the auditing representative so that the accuracy and completeness may be confirmed.

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14. Appendices

Appendix I

Instructions for Determining Body Weight

For participants with weight <60kg, or who are under 5 ft tall, all doses will be based on actual body weight.

For participants with weight >60kg and who are at least 5 ft tall, doses will be based on adjusted body weight, not to exceed a BSA of 2.0m^2 during the D-PACE, transplant and consolidation phases. However, during the maintenance phase, adjusted body weight is preferred, but not required for participants with weight >60 kg and who are at least 5 ft tall.

1. Actual Body Weight (ABW) is the weight in Kg.

2. Adjusted body weight (ABW): ABW = IBW + 0.4(actual weight - IBW).

Ideal Body Weight (IBW):

Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet or 60 inches

Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet or 60 inches

Appendix II

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): _____

	Not at All	A Little Bit	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little Bit	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4

10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

EORTC QLQ – MY20

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4

37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4

Please turn to next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you been thinking about your illness?	1	2	3	4
49. Have you been worried about dying?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4