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Protocol Title	Prospective Phase I/II Trial to Jointly Optimize the Administration Schedule(s) and Dose(s) of Melphalan for Injection (Evomela) as a Preparative Regimen for Autologous Hematopoietic Stem Cell Transplantation in Patients with Newly Diagnosed Multiple Myeloma
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Prospective Phase I/II Trial to Jointly Optimize the Administration Schedule(s) and Dose(s) of Melphalan for Injection (Evomela) as a Preparative Regimen for Autologous Hematopoietic Stem Cell Transplantation in Patients with Newly Diagnosed Multiple Myeloma

Institution Study Number: **2017-0399**

Sponsor: Acrotech Biopharma

IND Holder: The University of Texas MD Anderson Cancer Center

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Protocol Body

1.0 Objectives

1.1 Primary Objectives:

A. To determine the optimal dose and schedule of melphalan for injection (Evomela) prior to autologous hematopoietic stem cell transplantation (auto-HCT) for multiple myeloma (MM).

B. To collect the pharmacokinetic data and compare the exposure-response evaluations between the 2 infusion schedules.

1.2 Secondary Objectives:

A. To determine the incidence of treatment related mortality (TRM) at day 90 after auto-HCT in newly diagnosed myeloma patients treated on different schedules and doses of Evomela.

B. To determine the rate of minimal residual disease (MRD) negative complete response (CR) rate at day 90 after auto-HCT in newly diagnosed myeloma patients treated on different schedules and doses of Evomela. MRD negative is defined as absence of phenotypically aberrant clonal plasma cells by nerve growth factor (NGF) on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.

C. To determine the progression-free survival (PFS) after auto-HCT in newly diagnosed myeloma patients treated on different schedules and doses of Evomela.

2.0 Background and Rationale

2.1 Rationale and Hypothesis

The solubilizer used in alkeran (brand name melphalan) for injection is propylene glycol (PG), which is potentially associated with an array of side effects, such as renal failure, cardiac arrhythmias, hyperosmolality, increased anion gap metabolic acidosis, and sepsis like syndrome. In addition, melphalan has marginal solubility and limited chemical stability upon reconstitution and dilution that prevents the solution from being administered as a longer infusion. The commercial product; after reconstitution with sterile solution that contains PG; can develop an impurity (citrate derivative of melphalan) in <30 minutes and, when further diluted, melphalan loses its potency over time.

Melphalan for injection (Evomela) is a PG free reformulation of alkeran. Evomela incorporates Captisol brand of beta-cyclodextrin sulfobutyl ethers sodium salts. The substitution of Captisol for the excipients found in alkeran directly overcomes the formulation limitations of alkeran. Evomela can be dissolved directly using saline. Results show that based on the increase in total impurities in Evomela at 0.45 mg/mL, admixture solutions are about 5, 9, 15 and 29 times more stable at concentrations of 0.45, 1.0, 2.0 and 5.0 mg/mL, respectively. Results confirmed that reconstituted Evomela solution can be stored in the vial for up to 1 hour at room temperature or for up to 24 hours at refrigerated temperature (2 – 8 °C) with no significant degradation. After storage in the vial, it remains stable for an additional 3 to 29 hours after preparation of admixture solution in infusion bags at concentrations of 0.25 to 5.0 mg/mL,

respectively. In addition, Evomela solution in saline, at concentration of 5.0 mg/mL melphalan was bacteriostatic through 72 hours storage at 2 – 8 °C (Evomela Investigators Brochure, Appendix A).

Depending on the final concentration, it is stable at room temperature for up to 24-hours upon reconstitution followed by immediate dilution (Evomela Investigator Brochure, Appendix A). This results in less handling of this cytotoxic agent by pharmacy and nursing staff with a concomitant decrease in exposure risks and increase in convenience and administration flexibility.

Based on the above observations, we hypothesize that Evomela will be easier to handle and administer to the patients compared to alkeran. Furthermore, Evomela may actually be less toxic due to the absence of PG and this will allow for the escalation of dose and prolongation of infusion time, in order to increase the efficacy of melphalan in patients undergoing auto-HCT.

2.2 Introduction and Background

2.2.1 Autologous Hematopoietic Stem Cell Transplantation In Multiple Myeloma

A pivotal Intergroupe Francophone du Myelome (IFM) trial in 1996 showed that auto-HCT prolonged survival compared to the conventional chemotherapy[1]. Thereafter, several trials have shown that auto-HCT can prolong PFS[2, 3] or both PFS and OS[4, 5] compared to non-transplant based regimens (Table 1). Based on available data auto-HCT is recommended as consolidative therapy for patients with MM (grade A recommendation from American Society for Blood and Marrow Transplantation)[6].

Table 1. Summary of prospective randomized trials comparing conventional chemotherapy with auto-HCT that showed prolonged PFS and OS with auto-HCT.

Study	Patients	Regimen	Response	TRM	PFS	OS
Child et al.[4]	N=407 <65-years Untreated	*DBCM Vs. DVPC à M200 or M140+TBI (N=8)	CR rate 8% vs. 44% (p<0.001)	6 deaths within 100 days	**19.6 mo vs. 31.6 mo (p<0.001)	**42.3 mo vs. 54.1 mo (p=0.04)
Palumbo et al. [5]	N=194 50-70 years	MP x 6 Vs. M100 x 2	Near CR 6% vs. 25% (p=0.002)		At 3-year 37% vs. 16% (p<0.001)	At 3-year 77% vs. 62% (p<0.001)
Attal et al.[1]	N=200 <65-years Untreated	*VMCP alternating with BVAP Vs. VMCP alternating with BVAP à M140+TBI	CR+VGPR rate 14% vs. 38% (p<0.001)		18 mo vs. 41 mo (p=0.01)	37.4 mo vs. NR (p=0.03)

TRM, Treatment-related mortality; PFS, Progression-free survival; OS, overall survival; CR, Complete response; VGPR, Very good partial remission; NR, Not reached
D, Doxorubicin; B, (BCNU) Carmustine; C, Cyclophosphamide; M, Melphalan; V, Vincristine; P, Methylprednisolone/Prednisone; TBI, Total body irradiation;

*Both arms received maintenance therapy with interferon alfa-2a.
** Median.

Melphalan Dose Escalation Studies

Melphalan remains the mainstay of pre-transplant conditioning therapy for myeloma and no other drug combination has convincingly shown superiority over melphalan alone. The data suggests that more intense chemotherapy may be useful in prolonging survival. For instance, the IFM 9502 randomized study comparing total body irradiation (TBI) + melphalan 140 mg/m2 (MEL 140) to melphalan 200 mg/m2 (MEL 200) in newly diagnosed symptomatic myeloma patients younger then 65-year old showed that higher dose melphalan lead to superior overall survival (OS), 45.6% vs. 65% at 45 months, despite equivalent treatment related mortality (TRM)[7]. The incidence of grade 3-4 mucositis was 30%

In another study by Palumbo et al.[8], MEL 200 and MEL 100 were compared in a randomized manner in newly diagnosed myeloma patients assigned to receive 2 auto-HCTs. OS did not differ (*P* = .13); median PFS (31.4 vs 26.2 months, *P* = .01), median time to progression (34.4 vs 27.0 months, *P* = .014) were longer in the MEL200. Treatment-related mortality was 3.1% in the MEL 200 and 2.9% in the MEL 100 group. Severe neutropenia and infections were marginally superior, whereas severe thrombocytopenia, mucositis, gastrointestinal adverse events, and the overall occurrence of at least 1 non-hematologic grade 3 or 4 adverse event were significantly higher in the MEL200 cohort.

Moreau et al.[9] treated 27 patients with advanced myeloma with high-dose therapy with MEL 220 followed by auto-HCT. No toxic deaths were observed. The major adverse side effect was grade 4 mucositis (WHO scale) in 63% of patients. Two patients experienced reversible paroxysmal atrial fibrillation after MEL 220. No liver, renal, or pulmonary toxicity was observed.

Phillips et al.[10] conducted a study to define a new maximum tolerated dose (MTD) and the dose-limiting toxicity (DLT) of melphalan and auto-HCT when used with the cytoprotective agent amifostine. Escalating doses of melphalan beginning at 220 mg/m2 and advancing by 20 mg/m2 increments were used until severe regimen-related toxicity (RRT) was encountered. Melphalan was given in doses up to and including 300 mg/m2. Although mucosal RRT was substantial, it was not the DLT, and some patients given the highest melphalan doses (ie, 300 mg/m2) did not develop mucosal RRT. There was no obvious increased incidence of grade I versus grade II mucosal toxicity at any dose level beyond melphalan 220 mg/m2. No patient developed grade ·III mucosal or gastrointestinal RRT. The DLT was not clearly defined. Cardiac toxicity in the form of atrial fibrillation occurred in 3 of 36 patients treated with melphalan doses ·280 mg/m2 and was deemed fatal in 1 patient given melphalan 300 mg/m2 (Table 2). Another patient given melphalan 300 mg/m2 died of hepatic necrosis. The MTD of melphalan in this setting was thus considered to be 280 mg/m2, and 27 patients were given this dose without severe RRT. There was no delayed toxicity.

Table 2[10].
Nonmucosal RRT, Graded According to the Seattle (Bearman) Criteria

Melphalan Dose (mg/m2)	Total No. Patients	Affected Patients	Organ System	Grade
220	11	1	Cardiac	IV
240	5	0	—	—
260	6	0	—	—
280	27	1	Hepatic	I
		1	Cardiac	II
300	9	2	Cardiac	II, IV
		1	Hepatic	IV
All doses	58	6	—	—

In a more recent trial of 19 patients, dose-escalation of melphalan administered on day -2 began at 200 mg/m2 with palifermin administered at a fixed dose of 60 mcg/kg/day. Subsequent dose escalations of melphalan were done at 20 mg/m2 increments up to a maximum dose of 280 mg/m2. There were no treatment-related deaths by day 100. The overall incidence of oral mucositis grade 3 was 44% (8/18) with a median duration of severe mucositis of 5 days. Grade 4 mucositis was seen in only 1 patient who was given MEL 200 (Table 3). Two of 6 patients who were given MEL 280 did not develop oral mucositis. Cardiac DLT in the form of atrial fibrillation did occur in 1 of 6 patients treated with MEL 280. Further dose escalation was not allowed due previous report of cardiac toxicity with MEL 300[11].

Table 3 [11]
Melphalan Dose and Severity of Oral mucositis (OM).

Patients	WHO-OM Score Range	Duration of Severe OM (Grade 3)*	Days to Resolution of OM
Level 1 = melphalan 200			
1*	2-4	5	9
2	1-2	-	8
3	1-3	6	10
Level 2 = melphalan 220			
4	0	-	-
5	1-3	5	10
6	2-3	6	11
Level 3 = melphalan 240			
7	0	-	-
8	1-3	5	12
9	1-2	-	12
Level 4 = melphalan 260			
10	0	-	-
11	1-3	6	20
12	2-3	5	16
Level 5 = melphalan 280			
13	0	-	-
14	0-1	-	4
15	0-1	-	8
16	1-2	-	10
17	1-3	3	17
18	0	-	-

Only 1 patient in the whole group receiving melphalan 200 mg/m2 developed grade 4 OM for 3 days.

In another phase II trial, myeloma patients with a median of 1 prior regimen received MEL 280 prior to auto-HCT[12]. Two doses of amifostine 740 mg/m2 IV over 5-15 minutes were administered 24 hour and 15 min before MEL 280 to ameliorate mucosal toxicity. Between 5/1999 and 10/2003, 58 MM patients received this high dose regimen after dexamethasone-based induction regimens. Bearman critieria were utilized for grading RRT: grade 1 mucositis was seen in 41%, grade 2 in 14% and grade 3 in 1.7%. Other grade 3 toxicities included: lung (1.7%) and renal (1.7%); 1 patient died from melphalan-induced interstitial pneumonitis; 7% experienced atrial fibrillation or flutter. Of the 57 evaluable patients, CR was achieved in 28 (49%), VGPR in 6 (11%), PR in 17 (30%), SD in 4 (7%) unknown in 1 (1.5%) and progression in 1 (1.5%). PFS and OS at 7 years was 10% and 39% respectively. The authors concluded that MEL 280 dose escalation increased response depth, however, sustainability of response was not impacted.

2.3 Rationale For Melphalan Dose Escalation

Increasing the dose of melphalan can result in improvement in response rates[12]. In order to investigate the pharmacokinetics of total and unbound plasma melphalan using a population approach, population pharmacokinetic modelling was performed with total and unbound concentration–time data from 100 myeloma patients (36–73 years) who had received a median 192 mg m2 melphalan dose[13]. Total area under the curve (AUC; range 4.9–24.4 mg l-1 h) and unbound AUC (range 1.0–6.5 mg l-1 h) were significantly higher in patients who had oral mucositis (·grade 3) and long hospital admissions ($P < 0.01$). Patients who responded well had significantly higher unbound AUC (median 3.2 *vs.* 2.8 mg l-1 h, $P < 0.05$) when assessed from diagnosis to post-melphalan and higher total AUC (median 21.3 *vs.* 13.4 mg l-1 h, $P= 0.06$), when assessed from pre- to post-melphalan.

Despite the hints at better efficacy of melphalan with the higher dose, the most widely used dose is 200 mg/m2, primarily due to concerns of toxicity and lack of prospective data. With the availability of a more stable and potentially less toxic Evomela, it seems reasonable to study the dose escalation in order to improve the outcomes.

2.4 Rationale For Prolonging Infusion Time

The use of continuous infusion or frequent fractionated-dose delivery in clinical trials have been demonstrated to increase the antitumour activity of several drugs (for example, cytarabine in the treatment of acute leukemia, bleomycin in cervical carcinoma, 5-fluorouracil in colon carcinoma, methotrexate in acute lymphocytic leukemia)[14].

For several reasons melphalan maybe a good candidate for continuous infusion: 1) a short half-life, 2) a small volume of distribution, 3) a mechanism of action that is not cycle specific and is time-dependent, and 4) its uptake is a saturable process[14]. Indeed, pre-clinical data suggests that sequential exposure of melphalan was more effective than solid exposure at the same dose in myeloma cell lines[14]. However, due to the instability of the currently available alkeran at the room temperature, the infusional studies have not been possible. This limitation will be overcome by Evomela as the compound is stable for several hours at the room temperature thus allowing us to study the infusional schedules in addition to the traditional 30-60 minute bolus doses.

2.5 Clinical Experience and Potential Benefits of Using Evomela

In a phase IIa, open-label, randomized, cross-over design bioequivalence study, the pharmacokinetics of Evomela were compared with the marketed formulation of melphalan (Alkeran)[15]. Patients received half of the total dose of melphalan in the form of Alkeran and the other half in the form of Evomela in an alternating manner. Twenty-four patients were enrolled between 4 February 2010 and 16 May 2011. The median age of enrolled subjects was 58 years (range: 48–65). All patients achieved myeloablation 3 days post auto-HCT followed by successful neutrophil engraftment with a median of 11 days after transplant. Pharmacokinetic analysis showed that Evomela was bioequivalent with Alkeran and also revealed that maximum plasma concentration (Cmax) and area under the plasma concentration-time curve were higher (~10%) after Evomela administration. The authors concluded that Evomela is bioequivalent to Alkeran while also demonstrating a marginally higher systemic drug exposure.

In another clinical trial Evomela (200 mg/m2) was administered as 2 doses of 100 mg/m2 each

in a phase IIb, open-label, multicenter study to confirm its safety and efficacy as a high-dose conditioning regimen for patients with MM undergoing auto-HCT. Sixty-one patients were enrolled[16]. All achieved myeloablation. Median time to neutrophil and platelet engraftment was 12 days and 13 days, respectively. Day-100 TRM was 0%. Overall response rate (ORR) was 100% with a CR rate of 21%. The incidence of grade 3 mucositis and stomatitis was low (10% and 5%, respectively) with no grade 4 mucositis or stomatitis reported (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events).

Evomela appears to be a safe alternative to Alkeran and has demonstrated that when used as conditioning regimen, it is able to meet the pertinent transplant related outcomes such as myeloablation and engraftment.

In summary Evomela can potentially be associated with the following benefits:

- Evomela results in marginally, but statistically significant, higher systemic drug levels than Alkeran (~110%) (P<0.05).
- Evomela is more stable following reconstitution, which eliminates the time constraints that are imposed on pharmacists and nursing staff when preparing high-dose Alkeran for infusion. These timing issues might result in delivery of a less than intended dose of high-dose melphalan at time of transplant, which results in effective-dose variability between patients.
- Evomela can potentially enable safe administration of higher doses of melphalan, which may lead to better myeloma responses. This is expected because response to high-dose therapy is dose dependent and has a linear, steep dose-response curve[17].
- Evomela might also be considered in situations where Alkeran is associated with suspected infusion reactions[18].
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3.0 Background Drug Information

3.1 Melphalan HCL for Injection (Evomela)

Pharmacologic Category: Alkylating Agent
Mechanism of Action: Alkylating agent which is a derivative of mechlorethamine that inhibits DNA and RNA synthesis via formation of carbonium ions; cross-links strands of DNA; acts on both resting and rapidly dividing tumor cells.
Major Excipient:
Captisol is a substituted ß-cyclodextrin that serves as the major functional excipient in Evomela. Captisol performs as a solubilizing and stabilizing agent by forming reversible complexes with melphalan in the formulation. When the formulation is administered intravenously, the equilibrium between melphalan and melphalan-Captisol complex rapidly shifts in favor of melphalan due to its dilution by blood and the distribution and binding of melphalan to body tissues and blood components
Dosage Forms: IV
Compatibility:
The presence of Captisol facilitates the use of an aqueous initial diluent (Sodium Chloride for Injection) for the resultant freeze-dried product instead of the co-solvent diluent necessary for the reconstitution of Alkeran. The Ligand formulation does not need a second vial of solvent for reconstitution and can be dissolved directly using saline.

Solvent	Solubility (mg/mL)	Classification
Water	<0.1	Practically insoluble
1 N HCl	>100 <1000	Freely soluble
Ethanol	~40	Soluble
Methanol	>100 <1000	Freely soluble
Diethyl Ether	<0.1	Practically insoluble

Administration: Hazardous agent and vascular irritant; use appropriate precautions for handling and disposal.

For the purpose of this study, Evomela (2 mg/ml) will be infused using two different infusion schedules. Patients will be randomized to different schedule cohorts as explained in section 11.2.1 and given either a 30-60 minute infusion or 8-9 hour infusion. Because 2 mg/ml Evomela is stable for 10 hours, patients receiving the 8-9 hour infusion will receive the total dose in one single bag to complete the infusions.

Note: Melphalan is a vascular irritant; local reactions may occur. Extravasation may cause local tissue damage; administration via a central line is recommended; do not administer by direct injection into a peripheral vein.

Pregnancy Risk: May cause fetal harm if administered during pregnancy. Women of childbearing potential should be advised to avoid pregnancy while on melphalan therapy.

Lactation: Use not recommended.
Storage and Handling: Melphalan for injection (Evomela) is a PG free reformulation of alkeran. Evomela incorporates Captisol brand of beta-cyclodextrin sulfobutyl ethers sodium salts. The substitution of Captisol for the excipients found in alkeran directly overcomes the formulation limitations of alkeran. Evomela can be dissolved directly using saline. Results show that based on the increase in total impurities in Evomela injection at 0.45 mg/mL, admixture solutions are about 5, 9, 15 and 29 times more stable at concentrations of 0.45, 1.0, 2.0 and 5.0 mg/mL, respectively. Results confirmed that reconstituted Evomela solution can be stored in the vial for up to 1 hour at room temperature or for up to 24 hours at refrigerated temperature (2 – 8 °C) with no significant degradation. After storage in the vial, it remains stable for an additional 3 to 29 hours after preparation of admixture solution in infusion bags at concentrations of 0.25 to 5.0 mg/mL, respectively. In addition, Evomela solution in saline, at concentration of 5.0 mg/mL melphalan was bacteriostatic through 72 hours storage at 2 – 8 °C Evomela Investigators Brochure, Appendix A).

Adverse reactions:
> 10%:
Cardiovascular: Peripheral edema (conditioning: 33%)
Central nervous system: Fatigue (³50%; conditioning: 77%), dizziness (conditioning: 38%)
Endocrine & metabolic: Hypokalemia (³50% conditioning: 74%), hypophosphatemia (conditioning: 49%)
Gastrointestinal: Diarrhea (≥50%; conditioning: 93%), nausea (≥50%; conditioning: 90%), vomiting (≥50%; conditioning: 64%), decreased appetite (conditioning: 49%), constipation (conditioning: 48%), mucositis (conditioning: 38%), abdominal pain (conditioning: 28%),

dysgeusia (conditioning: 28%), stomatitis (conditioning: 28%), dyspepsia (conditioning: 26%)
Hematologic & oncologic: Anemia (≥50%), decreased absolute lymphocyte count (≥50%), decreased neutrophils (≥50%), decreased platelet count (≥50%; nadir: 14 to 21 days; recovery: 28 to 35 days), decreased white blood cell count (·50%; nadir: 14 to 21 days; recovery: 28 to 35 days), febrile neutropenia (conditioning: 41%; grades 3/4: 28%)
Miscellaneous: Fever (conditioning: 48%)

1% to 10%:
Gastrointestinal: Hematochezia
Genitourinary: Amenorrhea (9%)
Hypersensitivity: Hypersensitivity reaction (IV: 2%; less common in oral formula; includes bronchospasm, dyspnea, edema, hypotension, pruritus, skin rash, tachycardia, urticaria), anaphylaxis (£2%)
Renal: Renal failure

Frequency not defined:
Cardiovascular: Hepatic veno-occlusive disease (hepatic sinusoidal obstruction syndrome; SOS), vasculitis
Central nervous system: Flushing sensation, tingling sensation
Endocrine & metabolic: SIADH (dose related; Greenbaum-Lefkoe 1985)
Genitourinary: Infertility, inhibition of testicular function
Hematologic & oncologic: Bone marrow depression
Hepatic: Hepatitis, increased serum transaminases, jaundice
Renal: Increased blood urea nitrogen
Miscellaneous: Chromosomal abnormality

<1%, postmarketing, and/or case reports: Alopecia, bone marrow failure (irreversible), hemolytic anemia, interstitial pneumonitis, maculopapular rash, pulmonary fibrosis, skin ulceration at injection site, tissue necrosis at injection site (rarely requiring skin grafting)

Supply:
Acrotech Biopharma will supply Evomela for this study.

4.0 Patient Eligibility

4.1 Inclusion Criteria

1. Patients with non-relapsed multiple myeloma in complete response (CR), partial remission (PR), very good partial remission (VGPR), or symptomatic stable disease (no evidence of progression) including patients with light chain MM detected in the serum by free light chain assay **OR** patients with non-secretory multiple myeloma [absence of a monoclonal protein (M protein) in serum as measured by electrophoresis (SPEP) and immunofixation (SIFE) and the absence of Bence Jones protein in the urine (UPEP) defined by use of conventional electrophoresis and immunofixation (UIFE) techniques] but with measurable disease on imaging studies like MRI, CT scan or PET scan.
2. Patients who have received at least two cycles of initial systemic therapy and are within 2 to 12 months of the first dose. Mobilization therapy is not considered initial therapy.
3. Age 18 - 70 years.
4. Karnofsky performance score 70% or higher.
5. Cardiac function: left ventricular ejection fraction at rest > 40% within 3 months of registration.
6. Hepatic function: bilirubin < 2x the upper limit of normal (except patients with Gilbert Syndrome in whom bilirubin level of > 2x upper normal limit will be allowed) and ALT and AST < 2.5x the upper limit of normal.
7. Renal function: creatinine clearance of >/= 40 mL/min, estimated or calculated using the Cockcroft-Gault equation.
8. Pulmonary function: DLCO, FEV1, FVC > 50% of predicted value (corrected for hemoglobin) within 3 months of registration.
9. All female and male subjects of reproductive potential must consent to the use of effective contraceptive methods as advised by the study doctor during treatment.
10. Signed informed consent form.

4.2 Exclusion Criteria

1. Patients with uncontrolled bacterial, viral or fungal infections (currently taking medication and progression of clinical symptoms).
2. Patients seropositive for the human immunodeficiency virus (HIV).
3. Patients with history of myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.
4. Patients receiving an investigational new drug within 14 days before enrollment.
5. Female patients who are pregnant (positive b-HCG) or breast feeding.
6. Prior hematopoietic cell transplantation allogeneic or autologous (a prior autologous HCT will be allowed as long as it was part of tandem transplantation).
7. Prior organ transplant requiring immunosuppressive therapy.

5.0 Pretreatment evaluation

5.1 Disease Assessment Prior to Starting Treatment (within 30 days)

Studies listed below will be done prior to starting treatment only if these were not done before study entry either as part of diagnostic or routine pre-transplant workup.

1. Bone marrow aspirate and biopsies with cytogenetics, FISH* analysis, and multiparameter flow cytometry for MRD** monitoring.
2. Bone survey with long bones within 6 months of registration unless MRI skeletal survey or PET/CT have been completed within 60 days of study treatment
3. SPEP and serum IFE.
4. UPEP and urine IFE.
5. Serum free light chain assay, immunoglobulins IgG, IgA, IgM, IgD (if patient has IgD MM).
6. Beta 2 microglobulin.

5.2 To be done within 14 days of study entry

CBC with differential, electrolytes, BUN, creatinine, glucose, total protein, albumin, calcium, phosphorus, uric acid, total bilirubin, alkaline phosphatase, LDH, AST, ALT, and magnesium

* The following FISH probes are recommended: TP53 gene deletion; monosomy 13; CDKN2C deletion; CKS1B gain/amplification; IgH/CCND1/MYEOV gene rearrangement.

** MRD will be monitored on the bone marrow samples using multiparameter flow cytometry. We plan to collect 500,000 – 2 Million events for MRD panels. The antibodies we will use in flow are:
CD138, CD38, CD19, CD20, CD45, CD56, CD81, CD117
Gating strategy: CD138 (bright), CD38 (bright) [the MRD probes may be changed/updated to reflect the current practices of flowcytometry at MD Anderson].

6.0 Treatment Plan

6.1 Mobilization and Collection of Peripheral Blood Progenitor Cells (PBPCs)

The mobilization and collection of the PBPCs is a standard procedure for which patients sign a separate informed consent. This procedure does not constitute part of the proposed research therefore can occur prior or after protocol registration.

6.2 Treatment Plan

Day -3 Admission / IV Hydration

Day -2 Melphalan for injection (Evomela) IV (based on cohort/dose level)
Pharmacokinetic samples collected

Day -1 Rest

Day 0 Autologous Stem Cell Infusion

Day +5 G-CSF (filgrastim-sndz, Zarxio) administered per SCTCT departmental Guidelines of Care

6.3 Chemotherapy Agents Administration and Dosing

All chemotherapy will be administered inpatient.

Evomela:

1. The patients will be admitted on day -3 to start hydration.
2. Evomela will be administered on day -2 (dose and schedule based on the cohort/dose level).
3. Unused/expired study drug will be disposed of following Investigational Pharmacy SOC guidelines.

Schedules	Evomela Dose* Day -2
Group 1 (30-60 minute infusion)	200 mg/m2
	225 mg/m2
Group 2 (8-9 hour infusion)	200 mg/m2
	225 mg/m2

Evomela doses and schedules to be studied:

Please see Section 11.0 (Statistical Considerations) for details of trial progression and dose assignment in each schedule. First cohort in each schedule will be treated at 200 mg/m2.

For Group 1, the 2 mg/ml concentration of Evomela will be infused over approximately 30-60 minutes, as this is stable for 10 hours.

For Group 2, the 2 mg/ml concentration of Evomela will be infused over approximately 8-9 hours.

* For patients who weigh more than 130% of their ideal body weight, body surface area should be calculated based on adjusted ideal body weight (per package insert). Weight will be obtained within 7 days prior to admission for dose calculation. Adjusted ideal body weight is calculated as follows:

Adjusted ideal body weight = (Ideal body weight + actual body weight)/2

6.4 Supportive Care

Supportive treatment including antibiotic prophylaxis, treatment, and blood product support will follow current departmental guidelines.

Cryotherapy: Patients will be instructed to place approximately 1 ounce of crushed ice in the mouth. The ice will be allowed to melt and replenished as soon as it has completely melted. Patients will be instructed to begin placing the ice chips in their mouth 30 minutes before the start of Evomela infusion and continue this procedure as follows:

- 30 minutes prior to the infusion, during the infusion, and for at least 2 hours after the end of infusion (in 30-60 minute infusion group).
- 30 minutes prior to the infusion, during the infusion (intermittently, as tolerated), and for 2 hours after the end of infusion (in 8-9 hour infusion group).

7.0 Evaluation During Study

Every effort will be made to adhere to the schedule of events and all protocol requirements. Variations in schedule of events and other protocol requirements that do not affect the rights and safety of the patient will not be considered as deviations. Such variations may include laboratory assessments completed outside of schedule and occasional missed required research samples.

The active study follow-up period will be up to one year post-transplant. Subsequent follow up will be according to departmental practices.

7.1 Assessment schedule during the active study period

All patients on the study will be admitted for auto-HCT.

The patients will be admitted on Day -3 of transplant (day of stem cells infusion is considered Day 0).

Evaluations during the hospital stay and until Day +30:

Starting Day -2 until the day of discharge, evaluations will follow our SOC guidelines. If clinically indicated these studies may be done at other time points which can replace the nearest planned time point. During the treatment administration and until 30 days after Evomela administration, all patients will be monitored for toxicity, which will be evaluated according to CTCAE v5.0. While

admitted in the hospital, patients will be monitored daily. Once discharged, they will be followed per standard of care.

Around 3 months post transplant.
1. Bone marrow aspirate and biopsy for morphology with cytogenetics, FISH* analysis, and multiparameter flow cytometry for MRD** monitoring.
2. PET scan (only in patients who had a PET scan prior to auto-HCT and had disease detectable on PET scan).

Approximately every three months during the first year post transplant
1. SPEP and serum IFE only if SPEP is negative.
2. UPEP and urine IFE only if UPEP is negative.
3. Serum free light chain assay, immunoglobulins IgG, IgA, IgM, IgD (if patient has IgDMM).
4. LDH.

Around one year post transplant
1. Bone survey with long bones only if abnormal at baseline.
2. Bone marrow aspirate and biopsy for morphology with cytogenetics, FISH* analysis, and multiparameter flow cytometry for MRD**monitoring.

Labs at each visit or as clinically indicated
CBC with differential, electrolytes, BUN, creatinine, glucose, total protein, albumin, calcium, phosphorus, uric acid, total bilirubin, alkaline phosphatase, LDH, AST, ALT, and magnesium

* The following FISH probes are recommended: TP53 gene deletion; monosomy 13; CDKN2C deletion; CKS1B gain/amplification; IgH/CCND1/MYEOV gene rearrangement.

** MRD will be monitored on the bone marrow samples using multiparameter flow cytometry. We plan to collect 500,000 – 2 Million events for MRD panels. The antibodies we will use in flow are for:

CD138, CD38, CD19, CD20, CD45, CD56, CD81, CD117
Gating strategy: CD138 (bright), CD38 (bright) [the MRD probes may be changed/updated to reflect the current practices of flow cytometry at MD Anderson].

7.2 Pharmacokinetics of Evomela in different infusion schedules and their effect on safety and efficacy.

Intense pharmacokinetic sampling will be done for the first 30 patients. Sparse sampling will be done for the remaining 30 patients as described below.

INTENSE Sampling
Sample collection for 30-60 minute infusion – Blood samples (10 ml) will be collected at the following time points:
A) Pre-dose.
B) After the end of infusion: At 10 min (± 5 minutes) , 30 min (± 5 minutes) , 60 min (± 5 minutes), 90 min (± 15 minutes),120 min (± 15 minutes), 240 min (± 15 minutes), 360 min (± 15 minutes), and 480 min (± 60 minutes).

Sample collection for 8-9 hour infusion – Blood samples (10 ml) will be collected at the following time points:

A) Pre-dose.
B) During the infusion: At 3 hr (± 15 minutes), 5 hr (± 15 minutes), and 8 hr (± 15 minutes) after the start of infusion (before completing the infusion).
C) After the end of infusion: At 60 min (± 5 minutes), 120 min (± 15 minutes), 240 min (± 15 minutes), 360 min (± 15 minutes) and 480 min (± 60 minutes) after the end of infusion.

SPARSE Sampling

Sample collection for 30-60 minute infusion – Blood samples (10 ml) will be collected at the following time points:

A) Pre-dose.
B) After the end of infusion: At 10 min (± 5 minutes), 30 min (± 5 minutes), 90 min (± 15 minutes), 240 min (± 15 minutes), and 480 min (± 60 minutes) after the end of infusion.

Sample collection for 8-9 hour infusion – Blood samples (10 ml) will be collected at the following time points:

A) Pre-dose.
B) During the infusion: At 5 hr (± 15 minutes), and 8 hr (± 15 minutes) after the start of infusion (before completing the infusion).
C) After the end of infusion: At 240 min (± 15 minutes) and 480 min (± 60 minutes) after the end of infusion.

Plasma will be separated and stored in -80°C until further analysis. Evomela concentration will be determined using high performance liquid chromatography assay and ultraviolet detection as described previously.

Melphalan concentrations over time will be modeled using non-compartmental analysis (via Phoenix WinOnlin) to estimate PK parameters such as melphalan exposure (AUC), Cmax, and clearance.

7.3 Maintenance Therapy

Study participants may be concurrently enrolled in other IND studies for consolidation or maintenance therapy, with consolidation or maintenance treatment to begin after 3 month post-transplant evaluations are completed.

8.0 Adverse Events and Reporting Requirements

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

8.1 Definitions

Active Treatment

For the purpose of this study, the investigational component of the treatment plan is Evomela used for transplant conditioning.

Active treatment period
The time of administration of this drug as per treatment plan outlined above, up to 30 days after the Evomela infusion.

Follow-up period
Is defined as 31 days after Evomela infusion until off study criteria is met. Thereafter patients will be followed per standard procedure for hematopoietic transplant recipients including monitoring for relapse, survival and late events.

8.2 Causality Assessment

Evomela used for transplant conditioning is the investigational component therefore adverse events known to be caused by Evomela and its direct consequences will be scored as definitive related.

When the relationship of the adverse event cannot be ruled out with certainty the AE may be considered probable or possible related.

Adverse events known to be related to drugs used for supportive treatment will be scored as unrelated.

8.3 Concomitant medications

Patients treated on this protocol will require supportive care treatment (concomitant medications). These medications are considered standard of care and have no scientific contribution to the protocol; therefore no data will be captured on various medications needed or their side effects. All concomitant meds will be captured in the medical record only.

8.4 Data collection

Collection of adverse events will reflect the onset and resolution date and maximum grade. Intermittent events should be labeled as such and followed until resolution. If a patient is taken off study while an event is still ongoing, this will be followed until resolution unless another therapy is initiated. Pre-existing medical conditions will be recorded only if an exacerbation occurs during the active treatment period. Adverse events will be collected starting on the day of Evomela administration until 30 days after infusion. Adverse Events known to be definitely related to G-CSF and autologous stem cell transplant will not be captured.

Minor electrolyte abnormalities will be captured in the medical record and corrected as per standard guidelines of the Stem Cell Transplantation & Cellular Therapy department. Electrolyte and metabolic imbalances, which are considered clinically significant and unexpected in routine stem cell transplant setting and are considered related to Evomela will be recorded.

Expected adverse events in post auto transplant period:

A. Related to myelosuppression: thrombocytopenia, bleeding, platelets and RBC transfusions.
B. Fever: Non-neutropenic or neutropenic without infection.
C. Infections in the presence or absence of neutropenia.
D. Readmissions (lasting <10 days).
E. Cytopenias post-transplant including secondary graft failure.
F. Low blood pressure due to dehydration requiring fluid replacement.
G. Fluid overload leading to cardiac dysfunction.

H. GI related: nausea, vomiting, diarrhea, mucositis.
I. Organ dysfunction: cardiac, pulmonary, hepatic, CNS and/or renal.
J. Fatigue.
K. Neurologic: seizures, neuropathies.
L. Stem Cell Transplant Syndromes: Cytokine Storm, TTP, hemorrhagic cystitis, interstitial pneumonitis (including pulmonary hemorrhage).

Adverse Events Considered Serious:
A. Graft failure/ rejection.
B. Prolonged hospitalization due to infections and/or organ failure requiring extensive supportive care (i.e., dialysis, mechanical ventilation).
C. Readmissions from any cause resulting in a prolonged hospitalization (>10 days).
D. Any expected or unexpected event resulting in an irreversible condition and/ or leading to death.

Adverse events will be documented in the medical record and entered into the electronic case report form in MD Anderson Cancer Center's Clinical Oncology Research system (CORe)/BMTWeb. All other protocol specific data will be entered into BMTWeb/CORe.

8.5 Dose Limiting Toxicity (For dose finding in Stage I)

Toxicity will be defined as grade 4 mucositis or any grade 4 or 5 non-hematologic or non-infectious toxicity occurring within 30 days from the start of the infusion.

8.6 Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

All events occurring during the conduct of a protocol and meeting the definition of a SAE, must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office. If a death is possibly related to study agent administration, we will hold study enrollment and agent administration pending assessment of the event.
- The electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office, IRB, and Acrotech Biopharma.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent/assent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office.

8.7 Assessment of the Adverse Events Severity

The severity of the adverse events (AEs) will be graded according to the Common Terminology Criteria v5.0 (CTCAE) from the day of Evomela infusion up to 30 days after the Evomela infusion. Events not included in the CTCAE chart will be scored as follows:

<u>General grading:</u>
Grade 1: Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.
Grade 2: Moderate: discomfort present with some disruption of daily activity, require treatment.
Grade 3: Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
Grade 4: Life Threatening: discomfort that represents immediate risk of death

<u>Grading for specific syndromes:</u>
Veno-occlusive disease (VOD):
Grade 3: Bili >2mg/dl with at least two of the following: increased weight >4% from baseline, ascites or hepatomegaly
Grade 4: pulmonary and or renal failure

Pulmonary events not caused by CHF (interstitial pneumonitis (IP), pulmonary hemorrhage (DAH):
Grade 1: CXR showing mild infiltrates or interstitial changes
Grade 2: mild SOB
Grade 3: requires supplemental oxygen, or is a documented infection
Grade 4: requires intubation

Thrombotic thrombocytopenic purpura (TTP):

Grade 1: No treatment required
Grade 2: Requires steroids and/or plasma transfusions
Grade 3: Requires plasma exchange

Cytokine storm or engraftment syndrome:

Grade 1: No treatment required
Grade 2: Treatment required
Grade 3: Organ dysfunction
Grade 4: Total Bilirubin >5

Hemorrhagic Cystitis:

Grade 1: minimal or microscopic bleeding/pain
Grade 2: gross bleeding/pain and spasms
Grade 3: transfusion/irrigation required
Grade 4: dialysis required

8.8 Reporting to FDA

Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

8.9 Sponsor Reporting Requirements

Acrotech will be notified of all life-threatening or fatal Serious Adverse Events within 24 hours after learning of the Event. All other Serious Adverse Events will be reported within 5 working days of knowledge. A copy of the MDACC eSAE will be submitted to:

Acrotech Pharmacovigilance via e-mail to pvg@aurobindousa.com or via fax to +(732) 289-6189.

9.0 Criteria for Response and Progression

Disease response, progression, and relapse will be defined according to International Myeloma Working Group uniform response criteria (Appendix B).

10.0 Criteria for Removal from the Study

1. Patient withdrawal of the informed consent.
2. Patient's inability or unwillingness to have follow-up visits and/or laboratory tests required by this protocol.
3. An unexpected toxicity that is deemed unacceptable by the study chairman.
4. Disease progression.
5. After one year post stem cell transplant.

Patients who experience an unexpected toxicity that is deemed unacceptable by the Principal Investigator will not be replaced.

11.0 Statistical Considerations

11.1 Preliminaries

This is a two-stage phase I-II trial to optimize the dose and schedule of PGF Melphalan given as a single agent preparative regimen for auto-HCT. Two doses will be studied, 200 and 225 mg/m2. Two infusion schedules will be studied, 30-60 minutes and 8-9 hours, which we will refer to below as schedules 1 and 2, respectively. For dose-finding in stage 1, toxicity will be defined as grade 4 mucositis, or any grade 4 or 5 non-hematologic or non-infectious toxicity occurring within 30 days from the start of infusion. Complete response will be defined as negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow aspirates. Schedule selection in stage 2 is based on complete remission at day 90 (CR90). Secondary outcomes will include overall survival (OS) time and progression free survival (PFS) time.

Stringent complete response (sCR) will be defined as complete response as defined above plus normal FLA ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry.

11.2. Stage I Dose-Finding Design

11.2.1 Schedule Randomization Scheme

Patients will be randomized between the 2 schedules, as they are accrued, until a total of 60 patients have been accrued. The randomization will be restricted so that the sample size is perfectly balanced between the 2 schedules, with 15 patients in each schedule at n=30, and 30 patients in each schedule at n=60 patients. Within each schedule, the adaptive BMA-CRM[19] decision rules (either choose a dose or stop accrual in that schedule due to excessive toxicity at

the lowest dose d=200) will be applied for each new cohort of 3 patients, subject to the constraints given below, in section 11.2.2. If a schedule is terminated early, then, up to the total overall maximum of 60, thereafter patients will be treated with the remaining schedule. If both schedules are terminated early, then the trial will be stopped.

11.2.2 Phase I BMA-CRM Adaptive Decision Rules

The same phase I dose-finding design will be used for each schedule. This will be an application of the Bayesian Model Averaging continual reassessment method (BMA-CRM)[19], with target toxicity probability .20, cohort size 3, the three CRM model probability skeletons (.10, .21), (.05, .08), and (.07, .15), maximum sample size 30 (10 cohorts of 3 patients each), and the first cohort treated at 200 mg/m2. Denoting the probability of toxicity at dose 200 by p(200), accrual will be stopped early due to excessive toxicity for a schedule, with no dose selected for that schedule, if Pr[p(200) > .20 | data] > .90, that is, if the lowest dose is too toxic. The operating characteristics (OCs) were computed using the BMA-CRM application (version 2.2.3) from the MDACC Biostatistics department. Based on a simulation with 1000 replications per scenario, assuming maximum sample size 30, accrual rate 3 per month, 50% toxicities observed in the second half of the assessment period, the within-schedule operating characteristics of this design are as follows. If a schedule receives > 30 patients due to early termination of the other schedule, then the OCs for the remaining schedule will be improved over the tabulated values.

Table 4. Within-schedule operating characteristics of the BMA-CRM design, with maximum sample size 30, cohort size 3, and target ptox = .20, based on 1000 replications per scenario.

Scenario 1

Dose Level	True Prob(tox)	Selection Probability	# of Subjects Treated	# of Toxicities
1	0.050	0.10	8.0	0.4
2	0.200	0.88	21.6	4.2
Probability of Early Termination: 0.02				
Toxicities per Trial: 4.6				

Scenario 2

Dose Level	True Prob(tox)	Selection Probability	# of Subjects Treated	# of Toxicities
1	0.100	0.20	10.5	1.0
2	0.200	0.77	18.7	3.7
Probability of Early Termination: 0.04				
Toxicities per Trial: 4.8				

Scenario 3

Dose Level	True Prob(tox)	Selection Probability	# of Subjects Treated	# of Toxicities
1	0.020	0.03	5.3	0.1
2	0.150	0.97	24.7	3.7
Probability of Early Termination: 0.00				
Toxicities per Trial: 3.8				

Scenario 4

Dose Level	True Prob(tox)	Selection Probability	# of Subjects Treated	# of Toxicities
1	0.020	0.00	3.8	0.1
2	0.080	1.00	26.2	2.1
Probability of Early Termination: 0.00				
Toxicities per Trial: 2.1				

Scenario 5

Dose Level	True Prob(tox)	Selection Probability	# of Subjects Treated	# of Toxicities
1	0.300	0.33	13.5	4.0
2	0.390	0.04	3.6	1.4
Probability of Early Termination: 0.63				
Toxicities per Trial: 5.4				

Scenario 6

Dose Level	True Prob(tox)	Selection Probability	# of Subjects Treated	# of Toxicities
1	0.460	0.04	7.8	3.5
2	0.550	0.00	0.9	0.5
Probability of Early Termination: 0.96				
Toxicities per Trial: 4.0				

11.2.3 Pharmacokinetics analysis

Pharmacokinetic data such as Evomela exposure between the 2 infusion schedules will be compared in first 30 patients enrolled and exposure-response will be evaluated to determine if there is difference in safety and efficacy between the 2 infusion schedules. Dose-escalation in each treatment schedule will be initiated only after the PK and safety data at each dose is analyzed and it is determined that there is no safety concern as per DLT guidelines specified in the statistical section.

11.3 Stage 2 Selection

At the end of the phase I portion of the trial, for each schedule, the last patient treated at the optimal dose will be followed for 90 days to evaluate response. For each schedule that is not terminated early due to excessive toxicity, the empirical response rate will be computed for the subsample of patients treated at the optimal dose chosen by the BMA-CRM for that schedule. Among these, the (dose, schedule) combination having maximum empirical Pr(CR90) will be selected for future evaluation.

11.4 Implementation

The BMA-CRM design will be implemented using the Clinical Trials Conduct Website in the MDACC Department of Biostatistics. A block randomization scheme for schedule assignments to achieve balance between schedules as described above will be provided to the Website personnel prior to trial initiation. The randomization will be conducted using the Clinical Trials Conduct Website.

11.5 Statistical Data Analysis Plan

Toxicity will be tabulated by dose, type, and grade. The probability of toxicity over 30 days as a function of dose will be estimated by fitting a Bayesian binary outcome regression model (Gelman, et al.)[20]. The times for overall survival (OS) and progress-free survival (PFS) will be computed from the date of Evomela injection to the last time of follow-up or the event of interest (progression or death). Unadjusted OS and PFS distributions will be estimated by the Kaplan and Meier method [21]. The posterior probabilities of transplant related mortality (TRM), minimal residual disease (MRD), and CR90 will be estimated along with 95% posterior credible intervals, assuming beta (.50, .50) priors. The probabilities of TRM, MRD, and CR90 from the two infusion schedules will also be compared using posterior probabilities of the form Pr(p1 < p2 | data), where pj denotes the probability of the event with schedule j=1,2, based on the data for patients treated at the optimal within-schedule dose chosen by the BMA-CRM.

11.6 Toxicity/Efficacy Summary Reports

The Investigator is responsible for completing toxicity/efficacy summary reports and submitting them to the IND office Medical Affairs and Safety Group for review. These should be submitted as follows:

Phase I (Dose Finding)/Phase II (Efficacy Assessment)

Toxicity Summary, after the first cohort of 3 evaluable patients per schedule, complete 30 days after Melphalan infusion, and every 3 evaluable patients thereafter, IND Office approval must be obtained prior to advancing/changing dose levels.
During every submission update the response data of previously submitted patients once they complete 90 days of treatment.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

12.0 References

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