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Phase II study of umbilical cord blood-derived natural killer cells in conjunction with elotuzumab, lenalidomide and high dose melphalan followed by autologous stem cell transplant for patients with multiple myeloma

Institution Study Number: **2011-0379**

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Principal Investigator: Samer Srour, MD
The University of Texas MD Anderson Cancer Center
Stem Cell Transplantation and Cellular Therapy Department
1515 Holcombe Blvd, Unit 0432
Houston, TX 77030
Telephone: 713-794-4354
Fax: 713-794-4902
ssour@mdanderson.org

Collaborators: Qaiser Bashir, MD[1]
Roland L. Bassett, Jr.[2]
Chitra M. Hosing, MD[1]
Partow Kebriaei, MD[1]
Yago Nieto, MD, PhD[1]
Uday R. Popat, MD[1]
Muzaffar H. Qazilbash, MD[1]
Katy Rezvani, MD, PhD[1]
Elizabeth Shpall, MD[1]

[1] The University of Texas MD Anderson Cancer Center, Stem Cell Transplantation and Cellular Therapy Department
[2] The University of Texas MD Anderson Cancer Center, Biostatistics Department

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Protocol Body

1.0 Objectives

Primary Objectives

This study has three primary objectives:

1. To find the maximum tolerated dose (MTD) of umbilical cord blood (UCB)-derived NK cells.
2. To determine efficacy by the percent of patients achieving VGPR + CR at 3 months post-transplant.
3. To assess the minimal residual disease rate 100 days post-transplant in high-risk patients. High risk will be defined as patients with any of the following:
   a. Fluorescence in situ hybridization showing t(4:14), t(14:16), t(14:20), gain (amp) 1q; deletion (Del) 17/17p [or tp53 gene mutation/deletion by next generation sequencing (NGS), or by conventional cytogenetics]
   b. Deletion 13 by conventional cytogenetic analysis
   c. High risk signatures as determined by the GEP-70 or EMC-92 gene expression profiles
   d. Relapsed disease within 18 months of prior ASCT

Secondary Objective

1. To quantify duration of infused allogeneic donor UCB-derived NK cells in the recipient.

2.0 Background

2.1 Umbilical cord blood-derived natural killer cells for multiple myeloma

2.1.1 *Natural killer cells*

Natural killer (NK) cells are cytotoxic lymphocytes that play a unique role in innate and anti-tumor immunity. They usually express the surface markers CD16 and CD56 and exert their cytotoxic effects via the release of cytoplasmic granules containing perforin and granzyme. NK cells can be activated by cytokines, antibodies (via Fc receptors) or a shift in the balance between their activating and inhibitory receptors, particularly in response to interaction with class I alleles.

Alloreactive NK cell-mediated cytotoxicity against leukemia cells has been demonstrated *in vitro* [1] and in murine models [2]. In addition, NK cells have the potential to inhibit host dendritic cell activity, thereby decreasing the risk of GvHD [3]. Of note, the cytotoxicity of NK cells can be augmented by administration of IL-2[4-6].

2.1.2 *Inducing NK cell reactivity*

NK cells recognize cells lacking MHC class I molecules and exert cytotoxic effects on these cells, the "missing self" hypothesis [7]. This is thought to occur via the inhibitory "killer cell Ig-like receptors" (KIRs), which inhibit cytotoxicity upon interacting with a self MHC class I molecule. In this way NK cells can be a valuable weapon against tumor cells, which often down-regulate MHC class I to avoid recognition by the immune system.

This interaction between the KIR and class I alleles is crucial for anti-tumor immunity. Normally, the (class I) HLA- C1, C2, Bw4 and Bw6 alleles interact only with specific KIR proteins. The NK repertoire therefore may vary from individual to individual and will depend on the HLA phenotype and on the KIR haplotype gene composition. It is generally accepted that, in order to avoid auto-reactivity, the NK repertoire is developed when both the inhibitory receptor and its specific HLA ligand are present and expressed in the same individual. Therefore, in an allogeneic transplantation setting in which the donor and recipient are mismatched in the alleles of HLA-B or in HLA-C, the NK cells from the donor may not be inhibited by the target cells of the recipient, which lack the appropriate HLA alleles that would normally interact with the KIR receptors. Some of the donor KIR's are therefore left without a corresponding ligand (the "missing ligand" hypothesis). This incompatibility (also known as alloreactivity) releases the NK cell from inhibitory KIR signaling and thus promotes cytotoxicity.

Clinically, NK cells have shown promise in exerting anti-tumor effects. In a study by Ruggeri et al of AML patients treated with haploidentical stem cell transplants, NK cell alloreactivity was associated with a lower risk of relapse and protection against GVHD [2]. In that study the probability of event-free survival at 5 years was 60 % in the patients who had received alloreactive NK cells versus 5% in the patients who had received non–alloreactive NK cells. In addition, a multivariate analysis showed that KIR ligand incompatibility was the only independent predictor of survival in the patients with AML. Finally, 0% of AML patients who received alloreactive NK cells demonstrated $\geq$ grade II GVHD, versus 14% of the patients who did not receive alloreactive NK cells. In another study, patients who underwent allogeneic stem cell transplant for AML, CML and ALL with an HLA-mismatched graft had a decreased hazard ration of relapse (HR, 0.61, $P < 0.004$) if there was a missing a KIR ligand versus no missing ligand[8].

There have been several prospective studies with NK cell therapy in hematologic malignancies. In one study, 19 poor-prognosis AML patients were treated with

cyclophosphamide and fludarabine and subsequently received haploidentical peripheral blood NK cells.[9] In this study 5 of the 19 patients achieved a CR and there was no significant GVHD. Here at MDACC there is an ongoing phase I study to explore the safety of peripheral blood-derived NK (PBNK) cells in patents with AML/MDS (IRB #2005-0508, IND #12,802). Thus far we have treated 13 patients with doses of 1e6 to 3 e7 total nucleated cells/kg (containing 0.014 to 8.24 e6 CD56+ cells/kg). These PBNK cells have been generated by collection from a sibling, culture with interleukin-2 (for 16 hours) and subsequent CD3-depletion in a manner similar to our culture conditions described in Section 5.2. To date, there have not been any infusional toxicities or other adverse effects.

Finally, the myeloma group at University of Arkansas has published a trial of haploidentical peripheral blood NK cells infused as part of an autologous transplant for relapsed multiple myeloma.[10] In this study, 10 patients were treated with fludarabine and melphalan and then received the haploidentical NK infusion. There was subsequently a delay of 14 days before the patients received their autologous stem cell graft for hematopoietic reconstitution. The NK cell dose ranged from 2.7 e6 cells/kg to 92.0 e6 cells/kg. Importantly, there were no episodes of GVHD or autograft rejection and none of the patients died within the first 100 days. This suggests that allogeneic NK cells can be infused safely without interfering with autologous hematopoetic reconstitution.

2.1.3 *NK cells are cytotoxic to multiple myeloma cells*

There is mounting evidence to support the cytotoxic potential of NK cells in multiple myeloma. In one study, IL-2 stimulated NK cells demonstrated significant *in vitro* cytotoxicity against multiple myeloma cell lines. These same NK cells, when adoptively transferred to a murine model of multiple myeloma were able to increase survival of the mice in a dose-dependent manner [11].

Interestingly, there is evidence to suggest that the newer, more effective pharmacotherapies in multiple myeloma may enhance the effect of NK cells. Thalidomide is thought to increase NK cell activity in multiple myeloma [12] and lenalidomide may also promote NK cell mediated apoptosis[13]. The proteosome inhibitor bortezomib may down-regulate expression of MHC class I on multiple myeloma cells, making them more susceptible to NK-induced lysis [14]. In addition, bortezomib has been shown to decrease DC activity in vitro [15]; thus bortezomib and NK cells could work synergistically to prevent GVHD in an allo-transplant setting.

2.1.4 *Endogenous NK cells are ineffective against multiple myeloma*

Unfortunately, the cytotoxic activity of NK cells in patients with advanced MM may actually be reduced [16]. Down-regulation of several key cell-surface proteins,

including CD16 and 2B4/CD244 have been implicated in this process [17]. These patients may thus be prone to disease progression and are possible candidates for an alternative NK cell source. Moreover, the data from the leukemia experience suggests that allogeneic source of NK cells would be the best weapon against MM.

2.1.5 *Umbilical cord blood as a source of NK cells*

Umbilical cord blood (UCB) is known to be a valuable reservoir for stem cells. UCB grafts have been used with marked success in the pediatric setting and are now increasingly being used for adult stem cell transplant (SCT). The UCB provides a unique source of stem cells: the cells have the potential to repopulate the hematopoetic system but have proportionately more naïve T cells, reducing the risk for GVHD. This allows for more flexibility in graft selection, as there can be a greater degree of mismatch between the donor and recipient. However, the advantages in GVHD are countered by the limitations of lower cell dose and delayed time to engraftment. These challenges have been addressed by using double (versus single) cord grafts and more diligent peri-transplant evaluation and prophylaxis against known common pathogens.

Multicenter clinical trials with UCB transplant have shown it to be as effective as transplant with unrelated or HLA-mismatched marrow for hematologic malignancies. [18,19] The rates of acute GVHD appear to be lower with UCB in these trials. Single-institution trials have demonstrated and advantage of UCB over marrow transplants [20]. In addition the use of double cords appears to confer a significantly decreased risk of relapse compared with single cord transplants, suggesting that double cord transplants may be comparable, if not superior, to marrow transplants [21].

As a source for NK cells UCB also has great promise. Purification, expansion and stimulation of NK cells from an UCB graft can yield a potent anti-tumor therapeutic. In addition, this fraction of the UCB unit will have lesser potential for GVHD (versus NK cells derived from donor peripheral blood) since any contaminating T cells would more likely have a naïve phenotype. Though the baseline percentage of CD16+/CD56+ NK cells is lower than that in peripheral blood grafts, this phenotype can be induced by stimulation with cytokines such as IL-2 [22].

In our lab, culturing cord blood mononuclear cells (CBMC's) with artificial antigen presenting feeder cells (APC's) and IL-2 has yielded a >600 fold expansion of NK cells from frozen UCB units and a >2000-fold expansion of NK cells from fresh

UCB units (Figure 1).

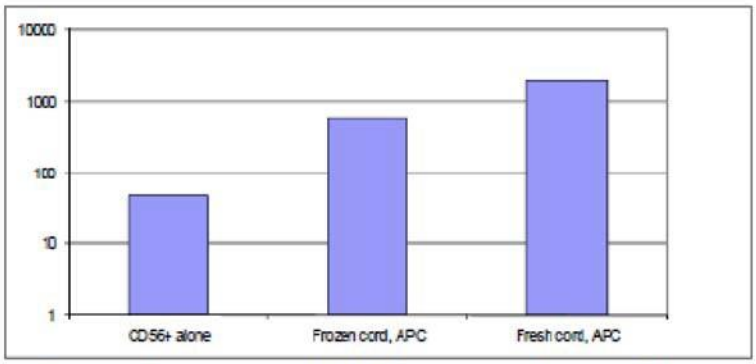


Fig. 1: UCB-NK cell fold expansion with IL-2 alone or with artificial APC feeder cells

In addition, expanded NK cells demonstrate a functional phenotype. The cytotoxicity of the UCB-derived NK cells against K562 (a classic NK cell target) is comparable to that of peripheral blood-derived NK cells (Figure 2). Furthermore, these UCB-derived NK cells also secrete IFN-ã and express the normal repertoire of killer cell Ig-like receptors (KIR's) and activating NK cytotoxic receptors (NCR's) (data not shown).

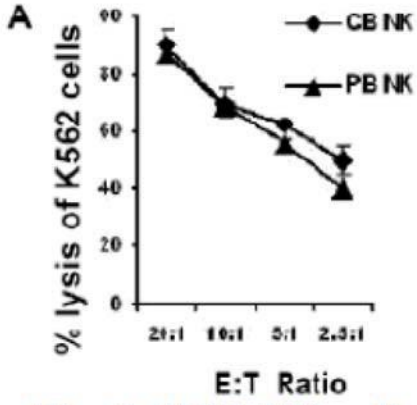


Fig. 2: UCB-NK cell activity is similar to that of PBNK cells

In addition, we have preliminary data to show that *ex vivo* expanded UCB NK cells are cytotoxic to and synapse with multiple myeloma cells lines (Figures 3 and 4). In addition, these UCB-NK cells were also active against primary, bone marrow-derived CD138+ plasma cells from myeloma patients, an effect which

was augmented by pre-incubation of UCB-NK cells with lenalidomide (Figure 5)

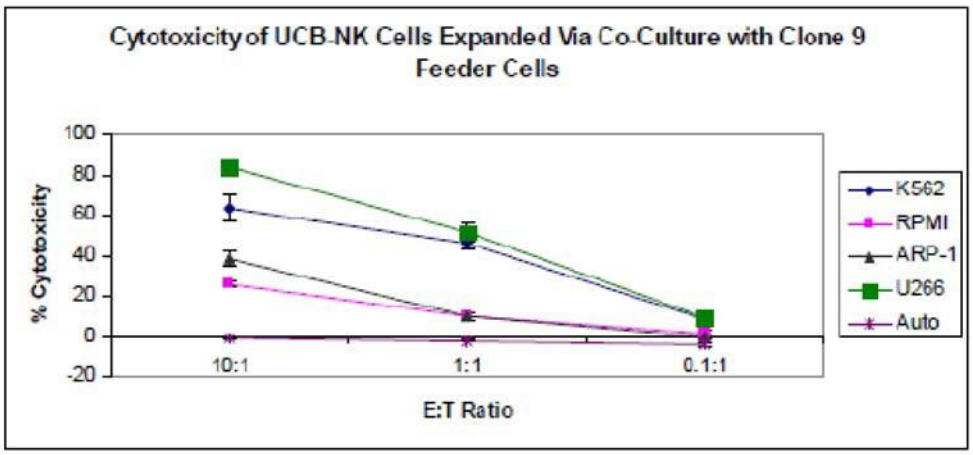


Fig. 3: Expanded UCB-NK cells exhibit dose-dependent cytotoxicity towards MM cell lines RPMI 8226 , ARP-1 and U266 versus negative control autologous UCB cells.

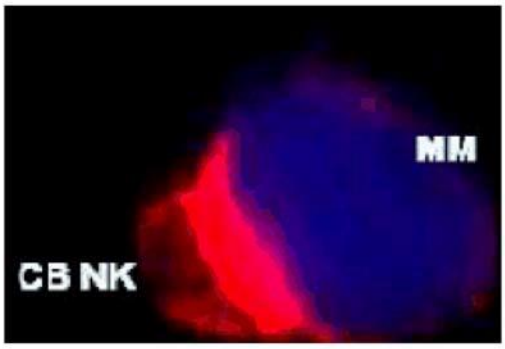


Fig. 4: Immunologic synapse between UCB-NK cell (red) and MM cell line RPMI 8226 (blue).

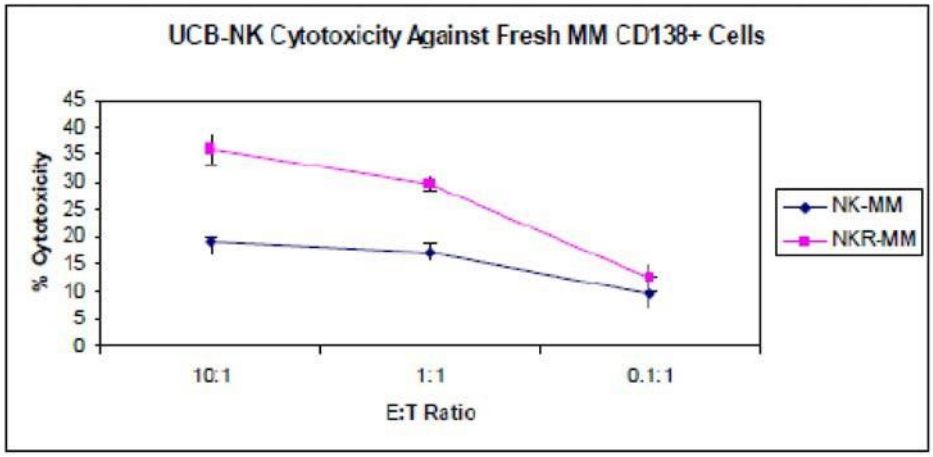


Figure 5. UCB-NK cells expanded with APC feeder stimulation are cytotoxic to primary, patient-derived CD138+ cells (NK-MM). This cytotoxicity appears to be augmented by pre-incubation of UCB-NK cells with lenalidomide (NKR-MM).

Peripheral blood-derived allogeneic NK cells are eliminated by the normal physiological process of cell death. Based on preliminary data from our institution and others[9,10] we know that peripheral blood-derived NK cells are well-tolerated between doses of greater than 1 e6 cells/kg up to 92 e6 cells/kg. Thus our dose levels are between 5 e6 cells/kg and 1 e8 cells/kg, intravenously, as outlined in the schema above.

2.2 Multiple Myeloma

Multiple myeloma (MM) is a malignancy characterized by the clonal expansion of plasma cells. It accounts for 10% of all hematologic malignancies and has a 5 year survival rate of 34% [23]. The disease has numerous systemic consequences, including hypercalcemia, renal failure, cytopenias and skeletal lesions. Though there are numerous treatment modalities, including several novel agents as well as stem cell transplant, the disease is still considered incurable.

Based on a large, phase III study, high dose chemotherapy with autologous stem cell rescue is now part of the standard of care for patients under 65 with multiple myeloma. This method of consolidation has yielded a 1year overall survival benefit for patients. However there is still a significant recurrence rate after transplant, with a median PFS of only 31.6 months [24]. Efforts to decrease recurrence have focused on newer induction and pre-transplant therapies,

post-transplant maintenance and the possibility of a second transplants with an allograft.

The idea of allogeneic stem cell transplant is appealing because it provides the opportunity for a graft versus myeloma (GVM) effect. However this benefit may be countered by the deleterious effects of graft versus host disease (GVHD). One way to avoid this adverse effect may be to use donor lymphocytes which are tumor-reactive but with lower GVHD potential, such as NK cells. Therefore we are proposing the use of UCB-NK cells as part of the preparative regimen for patients undergoing an AUTOlogous stem cell transplant to treat relapsed or refractory disease. This strategy may provide the critical cellular alloreactivity necessary to eradicate the primary disease while limiting the potential for GVHD.

2.3 Lenalidomide and Multiple Myeloma

Lenalidomide has been established as a potent anti-myeloma agent for either up-front or salvage therapy.[25-27] Our department has recently completed the phase I portion of a study of high dose lenalidomide in combination with high dose melphalan and autologous SCT (protocol 2008-0661, PI: Qazilbash). Thus far, in this trial, there have been no dose-limiting toxicities at the highest planned dose level (100 mg PO x 7 days). In 11 evaluable patients, there have been no delays in engraftment or additional thromboembolic events. Therefore, lenalidomide appears to be safe in the setting of myeloablative chemotherapy and autologous stem cell transplant.

2.4 Rationale

In summary, NK cells appear to be active against hematologic malignancies, including multiple myeloma, and this activity is dependent on alloreactivity between the NK cell and the target tumor cell. Umbilical cord blood can now be expanded and enriched for the population of NK cells which still demonstrate cytotoxicity and theoretically carry lesser risk of GVHD. These NK cells are cytotoxic to primary myeloma cells and their activity may be further enhanced with lenalidomide. Finally, lenalidomide appears to be safe and well-tolerated in the setting of high dose chemotherapy and autologous stem cell rescue. Therefore we are proposing the use of UCB-derived NK cells as a potent anti-myeloma therapeutic in the setting of lenalidomide and melphalan chemotherapy and autologous transplant for multiple myeloma.

2.5 Correlative Studies Background- Quantification of donor NK cells in recipient

In an allogeneic NK cell study from another institution patients' (recipients') blood was analyzed for the presence these donor NK cells[9]. Polymerase chain reaction (PCR) technology was employed, using known primers against donor Class I HLA genes. This method can be used to determine the duration of

persistence of the donor NK cells in the patient. A similar analysis has been performed in our department in the setting of double UCB SCT to identify per cent contributions of each cord to recipient hematopoiesis. [28]

3.0 Background Drug Information

3.1 Melphalan

THERAPEUTIC CLASSIFICATION: Antineoplastic alkylating agent

MECHANISM OF ACTION: Interferes with DNA replication and transcription of RNA and ultimately results in the disruption of nucleic acid function.

STORAGE AND STABILITY: Reconstituted solution retains 90% potency for about 3 hours at 30°C. Storage at 5°C results in precipitation. Intact packages can be stored at room temperature.

ADMINISTRATION: Supplied as 50 mg vials and should be reconstituted in 10 ml of diluent. Infuse over 30 minutes (complete administration within 60 minutes of reconstitution). Dilute with NS to a maximum concentration of 1.5 mg/ml.

KNOWN ADVERSE EFFECTS :
High-dose melphalan is well tolerated by patients when they are supported with blood component transfusions, PBSC transplantation and broad-spectrum antibiotics. The duration of profound bone marrow suppression decreases with the use of PBSC transplantation and colony stimulating factors. Gastrointestinal toxicity, which includes potentially severe stomatitis, esophagitis and severe diarrhea, can become the dose-limiting toxicity in these patients. The majority of patients receiving high-dose melphalan will require parenteral narcotics for mucositis related pain, IV hydration and potentially IV alimentation and broad spectrum IV antibiotics. Despite moderate to severe symptoms in many patients, recovery is the norm, coincident with recovery of granulocytes. Other toxicities reported include pulmonary fibrosis and interstitial pneumonitis, skin hypersensitivity, vasculitis, alopecia, hemolytic anemia, and allergic reaction. Melphalan may cause sterility, and/or disruption of menstruation in females. Melphalan may cause mouth sores, skin rash, and/or hair loss. It may cause injury to the kidneys, lungs, heart, and/or liver. It may cause allergic reactions, including itching, hives, flushing, wheezing, chest tightness, fever, chills, muscle stiffening, breathing problems, and/or loss of appetite. It may cause heart failure, bleeding from the bladder, and/or seizures. It may increase risk of developing a second cancer.

SUPPLY: Commercially available.

3.2 Filgrastim-sndz (G-CSF, Zarxio)

THERAPEUTIC CLASSIFICATION: Recombinant growth factor
MECHANISM OF ACTION: Filgrastim, filgrastim-sndz, and tbo-filgrastim are granulocyte colony stimulating factors (G-CSF) produced by recombinant DNA technology. G-CSFs stimulate the production, maturation, and activation of neutrophils to increase both their migration and cytotoxicity.

STORAGE AND STABILITY: Filgrastim should be stored at 2° to 8°C. Prior to injection, Filgrastim may be allowed to reach room temperature; however, any vials left at room temperature for greater than 24 hours should be discarded. Vials should not be shaken. Vials should be inspected for sedimentation or discoloration prior to administration. If sedimentation or discoloration is observed, the vials should not be used. Commercially available in single-dose, preservative-free vials containing 300
mcg (1 mL) and 480 mcg (1.6 mL) and prefilled syringes containing 300 mcg (0.5 ml) and 480 mcg (0.8 ml) of Filgrastim.

KNOWN ADVERSE EFFECTS: Mild to moderate bone pain, general skin rash, alopecia, fevers, thrombocytopenia, osteoporosis, nausea, vomiting, diarrhea, mucositis, anorexia, inflammation of the blood vessels, and/or cardiac dysrhythmia can occur. Splenomegaly may result at high doses of Filgrastim. Filgrastim may cause irritation, bruising, and/or bleeding at the site of injection. It may cause chest pain. It may cause constipation, swelling of the mucous membranes, and/or irregular heartbeat. It may also cause joint pain in the hips and/or lower back. Filgrastim may cause bone pain, headache, fever, and/or leg cramps. It may also cause a flare-up of previous skin conditions such as psoriasis. It may cause rash, itching, swelling in the face and/or ankles, wheezing, shortness of breath, low blood pressure, and/or irregular heartbeat. Enlargement and rupture of the spleen and/or loss of hair may occur. Filgrastim may decrease the number of blood platelets, which can result in easy bruising or bleeding for a longer time and may also cause an increase in white blood cells. Filgrastim may also cause inflammation, swelling, redness, and irritation of the liver and/or low blood flow to the colon, stomach, and/or intestine. Filgrastim may cause the white blood cell count to be very high, which will be monitored Filgrastim may also speed up the growth of tumors or cancers.

SUPPLY: Commercially available.

3.3 Lenalidomide

Common trade named
Revlimid®

Class
Angiogenesis inhibitor
immunomodulating agents (IMiDs).
Antineoplastic agent

Tumor Necrosis factor (TNF) blocking agent

Dosage, adult (usual)
Myelodysplastic Syndromes: The recommended starting dose is 10 mg daily orally. Dosing is continued or modified based upon clinical and laboratory findings.
Myeloma: 25 mg once daily orally for 21 out of 28 days

Administration
Lenalidomide capsule are administrated orally with water. Patients should not break, chew or open the capsules

Monitoring
Platelet count, hemoglobin, WBC, and differential at start of therapy and prior to each subsequent course of therapy; serum creatinine, liver function tests, thyroid function tests; monitor for signs and symptoms of thromboembolism
Women of childbearing age must have a pregnancy test within 10-14 days and 24 hours before lenalidomide, then 4 weeks after therapy discontinued.

Pregnancy Testing
Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

For FCBP, pregnancy tests must occur within 10 - 14 days and again within 24 hours prior to prescribing lenalidomide. (prescriptions must be filled within 7 days) and at Day +30 (+/- 2days) post the last dose (D-2) of lenalidomide. (see Appendix C.: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

Indications
- FDA labeled indications
- Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.
-Multiple myeloma in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy.
- Non FDA labeled indications
- Metastatic malignant melanoma (investigational use): 10-25 mg once daily
- Myelofibrosis (investigational use): 5-10 mg once daily

Contraindications
- Hypersensitivity of lenalidomide products
- Previous resistance to the drug

- Pregnancy

Precautions

- No formal studies have been conducted in patients with renal impairment. this drug is known to be excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function.
- Patients with Hepatic Disease: The pharmacokinetics of lenalidomide in patients

with hepatic impairment have not been studied.
- Age: lenalidomide has been used in multiple myeloma (MM) clinical trials in patients up to 86 years of age.
- Check pregnancy test before administering lenalidomide
- Check CBC before administering lenalidomide
- Hypersensitivity reaction; do not re challenge
- Impairment of fertility
- Mutagenic, potentially
- Severe bone marrow depression
- Women of childbearing age should avoid becoming pregnant
- monitor for signs and symptoms of thromboembolism: prophylaxis

Adverse effects

>10%:

- Cardiovascular: Peripheral edema (8% to 21%) - Central nervous system: Fatigue (31% to 38%), pyrexia (21% to 23%), dizziness (20% to 21%), headache (20%)
- Dermatologic: Pruritus (42%), rash (16% to 36%), dry skin (14%)
- Endocrine & metabolic: Hyperglycemia (15%), hypokalemia (11%)
- Gastrointestinal: Diarrhea
(29% to 49%), constipation (24% to 39%), nausea (22% to 24%), weight loss (18%), dyspepsia (14%), anorexia (10% to 14%), taste perversion (6% to 13%), abdominal pain (8% to 12%)
- Genitourinary: Urinary tract infection (11%)
- Hematologic: Thrombocytopenia (17% to 62%; grades 3/4:10% to 50%), neutropenia (28% to 59%; grades 3/4: 21% to 53%), anemia (12% to 24%: grades 3/4: 6% to 9%); myelosuppression is dose-dependent and reversible with treatment interruption and/or dose reduction
- Neuromuscular & skeletal: Muscle cramp (18% to 30%), arthralgia (10% to 22%), back pain (15% to 21%), tremor (20%), weakness (15%), paresthesia (12%), limb pain (11%)
- Ocular: Blurred vision (15%)
- Respiratory: Nasopharyngitis (23%), cough (20%), dyspnea (7% to 20%), pharyngitis (16%), epistaxis (15%), upper respiratory infection (14% to 15%), pneumonia (11% to 12%)

Pregnancy category - X

- Breast feeding
    - Infant risk cannot be ruled out

- How supplied
    - 5 mg, 10 mg, 15 mg and 25 mg capsules

SUPPLY: Celgene Corporation/Bristol-Myers Squibb.

3.4 Elotuzumab

INDICATION

Elotuzumab is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

DOSAGE AND ADMINISTRATION

10 mg/kg administered intravenously (IV).

Premedicate with dexamethasone, diphenhydramine, ranitidine and acetaminophen.

DOSAGE FORMS AND STRENGTHS

For Injection: 300 mg or 400 mg lyophilized powder in a single-dose vial for reconstitution

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Infusion reactions: Premedication is required. Interrupt EMPLICITI (elotuzumab) for Grade 2 or higher and permanently discontinue for severe infusion reaction.

Infections: Monitor for fever and other signs of infection and treat promptly.

Second Primary Malignancies (SPM): Higher incidences of SPM were observed in a controlled clinical trial of patients with multiple myeloma receiving Elotuzumab.

Hepatotoxicity: Monitor liver function and stop Elotuzumab if hepatotoxicity is suspected.

Interference with determination of complete response: Elotuzumab can interfere with assays used to monitor M-protein. This interference can impact the determination of complete response.

ADVERSE REACTIONS

Most common adverse reactions include fatigue, diarrhea, pyrexia, constipation, cough, peripheral neuropathy, nasopharyngitis, upper respiratory tract infection, decreased appetite, pneumonia, low red and white blood cell counts.

> 20%

- General disorders: Tiredness; fever; swelling.

- Gastrointestinal: Diarrhea; constipation; nausea.

- Blood disorders: Low red and white blood cells counts.

Less likely (occurring in between 3% and 20% of patients)

- General Disorders: Allergic type infusion reactions that may occur during or after elotuzumab administration and include symptoms such as chills, fever, nausea, rash, flushing, chest discomfort, increased sweating, high blood pressure, abdominal pain, swelling around the eyes or muscle spasms.

- Gastrointestinal disorders: Vomiting; mouth sores or pain; upset stomach or heartburn.

- Musculoskeletal disorders: General weakness; back pain, bone, joint, or muscle pain; muscle aches or weakness; chest pain.

- Nervous system disorder: Pain, numbness or tingling in the hand, legs, or feet; headache; dizziness; difficulty sleeping; tremor; taste changes.

- Respiratory disorders: Cough; shortness of breath; voice changes; nose bleeds; hiccups.

- Metabolism and nutrition disorders: Poor appetite; increased blood sugar; change in blood electrolytes (salts or minerals).

- Investigations: Decreased weight; change in liver or kidney function blood tests.

- Infections: Infection of the throat, mouth, lung, sinus, blood, kidney, bladder, skin, stomach, or intestine.

- Blood disorders: Low platelets.

- Skin disorders: Itching or hives.

- Psychiatric disorders: Anxiety; depression.

- Vascular disorders: Low blood pressure.

- Eye disorders: Blurred or reduced vision.

- Infrequent (occurring in 1- 3% of patients or serious side effects in at least 1 patient)

- General disorders: Abnormal walking or falling; irritability or agitation; deterioration of health; sudden death.

- Psychiatric disorders: Mood changes; confusion.

- Eye disorders: Dry eyes; cataract; pink eye.

Infrequent (occurring in 1- 3% of patients or serious side effects in at least 1 patient)

- General disorders: Abnormal walking or falling; irritability or agitation;

deterioration of health; sudden death.
- Psychiatric disorders: Mood changes; confusion.
- Eye disorders: Cataract; pink eye.
- Skin disorders: Dry mouth or skin; skin inflammation; hair loss.
- Gastrointestinal disorders: Toothache; gas or bloating; difficulty swallowing; hemorrhoids; inflammation of the liver or colon.
- Musculoskeletal disorders: Neck or jaw pain; joint or muscle stiffness.
- Nervous system disorders: Sleepiness; difficulty remembering; fainting.
- Respiratory tract disorders: Runny or stuffy nose; sinus congestion; wheezing; fluid in the lungs; inflammation of the lung.
- Infejctions: Viral infections such as herpes virus or the flu; fever with low white blood cell counts; life threatening infections/infections leading to death.
- Metabolism and nutrition disorders: Dehydration; gout.
- Vascular disorders: Blood clots in the leg or lung; localized collection of blood outside the blood vessel; inflammation of the vein(s).
- Kidney or urinary disorders: Kidney damage or failure; problems with urination or bladder control; pain while urinating.
- Ear disorders: Ringing in the ears.
- Heart disorders: Rapid or slow heart rate; abnormal heart rhythm; palpitations; heart failure; complete block of the electrical system in the heart; heart attack; inflammation of the heart muscle.
- Investigations: Weight gain.
- Blood disorders: Breakage of red blood cells.

SUPPLY: Bristol-Myers Squibb.

4.0 Patient Eligibility

Inclusion Criteria

1. Patients with high risk multiple myeloma who are transplant candidates, in partial response (PR) or better.
   High risk will be defined as patients with any of the following:
   a. Fluorescence in situ hybridization showing t(4:14), t(14:16), t(14:20), gain (amp) 1q; deletion (Del) 17/17p [or tp53 gene mutation/deletion by next generation sequencing (NGS), or by conventional cytogenetics]
   b. Deletion 13 by conventional cytogenetic analysis
   c. High risk signatures as determined by the GEP-70 or EMC-92 gene expression profiles
   d. Relapsed disease within 18 months of prior ASCT

2. Patients with plasma cell leukemia.

3. 18 to 75 years old.

4. Performance score of at least 70% by Karnofsky or 0 to 2 ECOG.

5. Adequate major organ system function as demonstrated by:
   a. Left ventricular ejection fraction greater than 40%.
   b. Pulmonary function test (PFT) demonstrating a diffusion capacity of least 40% predicted.
   c. Estimated serum creatinine clearance >/=60 ml/min (using the Cockroft-Gault formula: creatinine clearance = [(140-age)*kg/(72*serum creatinine)] * 0.85 if female) and/or serum creatinine </=1.6 mg/dL.
   d. SGPT less than 3 x upper limit of normal.
   e. Total bilirubin less than 2 x upper limit of normal.

6. All study participants must be registered into the mandatory Revlimid REMS™ program, and be willing and able to comply with the requirements of the Revlimid REMS™ program.

7. Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS™ program (see Appendix C).

8. Men must agree to use a latex condom during sexual contact with females of child bearing potential even if they have had a successful vasectomy.

9. Patients must have a CB unit available which is matched with the patient at 4, 5, or 6/6 HLA class I (serological) and II (molecular) antigens.

10. Patient or legally authorized representative able to sign informed consent.

Exclusion Criteria

1. Patients receiving any other investigational agents.

2. History of allergic reactions attributed to compounds of similar chemical or biologic composition to melphalan.

3. Known hypersensitivity or desquamating rash to either thalidomide or lenalidomide.

4. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, uncontrolled hypertension (systolic >160, diastolic >100 despite antihypertensive therapy, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

5. HIV-positive patients are excluded due to increased risk of lethal infections when treated with myeloablative chemotherapy.

5.0 Treatment Plan

The investigational component of the proposed treatment plan is the infusion of ex-vivo expanded CB NK cells with elotuzumab and lenalidomide in the setting of autologous stem cell transplantation.

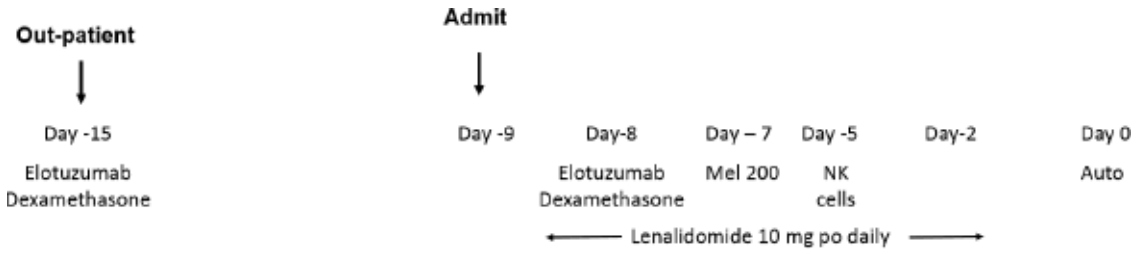
The transplant day is referred as day zero (D0), treatment plan activities prior or after D0 are denominated as day minus (D-) or day plus (D+).

The production of the NK cells will be carried out by the Good Manufacturing Process (GMP) Laboratory at M.D. Anderson Cancer Center. This process will start no less than 14 days (D-19) prior to its infusion which is D-5.

The targeted CD34+ cell dose for the autologous peripheral blood stem cell graft is at least 4.0 x 10^6 CD34+ cells/kg, except those with relapsed disease within 18 months of prior ASCT, who should have at least 2.5 x 10^6 CD34+ cells/kg available.

Up to 60 patients will be enrolled.

The study schema is depicted below:



Chemotherapy agents, doses, and administration.

- Elotuzumab will be dosed at **10 mg/kg** to be given on day -15 (out-patient) and day -8 (in-patient). Elotuzumab will be provided by Bristol-Myers Squibb.
- Pre-medication with dexamethasone, acetaminophen, diphenhydramine and ranitidine (see dosing below):
  a) Dexamethasone: Give dexamethasone 28 mg **PO** 3 to 24 hours before elotuzumab infusion **plus** dexamethasone 8 mg **IV** 45 to 90 minutes prior to infusion.
  b) Acetaminophen 650 to 1000 mg PO X 1
  c) Diphenhydramine 25 to 50 mg PO or IV X 1
  d) Ranitidine: 50 mg IV or 150 mg PO X 1

Monitor for infusion reaction. Interrupt infusion for grade 2 or higher infusion reactions; if the reaction resolves or improves to ≤ grade 1, may resume infusion (see Dosage Adjustment for Toxicity). Monitor vital signs every 30 minutes during and for 2 hours after the end of the infusion in patients who experience an infusion reaction.

Infusion rate: *First infusion:* Infuse at 0.5 mL/minute for the first 30 minutes; increase to 1 mL/minute for the next 30 minutes if no infusion reactions occur. If this rate is tolerated, then increase to 2 mL/minute max rate until infusion is complete.

Melphalan is commercially available, and patients will be using the commercial supply.

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Celgene Corporation's/Bristol-Myers Squibb's Revlimid REMS™ program. Per standard Revlimid REMS™ program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS™ program.

Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

Must follow pregnancy testing requirements as outlined in the Revlimid REMS™ program material (see Appendix C).

From D-8 to D-2, lenalidomide will be administered at a dose of 10 mg PO daily.

Females of childbearing potential must have a negative serum pregnancy test with a sensitivity of at least 50 mIU/mL within 10-14 days prior to and again 24 hours of prescribing lenalidomide (prescriptions must be filled within 7 days).

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

On D-15, elotuzumab will be administered at **10** mg/kg IV as an outpatient.

Day -9, admission and IV hydration.

On D-8, patient will be admitted to start hydration. Elotuzumab will be administered at **10** mg/kg IV.

On D-7, high-dose melphalan will be administered at a dose of 200 mg/m^2 IV.

Melphalan will be dosed as follows: for patients whose actual body weight is ≤ 40% above ideal body weight, the actual body weight is used to calculate the body surface area (BSA). For patients whose actual body weight is >40% above ideal body weight, an "adjusted body weight" is used to calculate the BSA.

Formula to calculate adjusted body weight: Adjusted BW (Kg) = IBW + 0.5 (Actual body weight - IBW).

On D-5, the NK cell infusion of 1 x 10^8 cells/kg will be administered intravenously. This may occur on Day -6 or Day -4 if necessary per the Cell Therapy Laboratory. Premedicate with Benadryl 25 mg IV and Tylenol 650 mg po. The use of steroids is contraindicated.

If target NK cell dose is not reached, we will give the dose that has been generated.

NK cells will be obtained by the following method:
Frozen cord blood units will be thawed and mononuclear cells will be isolated by Ficoll density gradient centrifugation. NK cells will be generated over 14 days in liquid cultures using APC feeder cells as described in detail in the Chemistry, Manufacturing and Controls (CMC).

NK Product Release Criteria
The following minimum criteria will be required for release of the expanded NK cells for reinfusion:

Stat Gram stain is reported as "No Organisms Seen".
CD3+ number is < 2 e5 CD3+ cells/kg.
Visual inspection reveals "No Evidence of Contamination" (turbidity; change in media color).
Endotoxin Assay- < 5EU/Kg.
Viability is greater than 70%.
Other parameters which will be monitored include sterility culture for bacteria and fungi.

If more than 2 e5 CD3+ cells/kg are present, a second cycle of CD3 depletion may be performed. The cell dose for infusion may be reduced so that the infused CD3+ cells are 2 e5/ kg.

On D0, autologous stem cell infusion minimum cell dose of 2 e6 cells/kg.

Filgrastim-sndz (Zarxio, G-CSF) at a dose of 5 mcg/kg/day (round up to the nearest vial) subcutaneously beginning on D0, and continuing until evidence of an absolute neutrophil count (ANC) of 0.5 x 10^9/L per 3 consecutive days.

Supportive treatment

All patients will receive supportive care as clinically indicated following standard practice.

6.0 Pretreatment Evaluation

Disease assessment prior to start treatment (baseline).
Studies listed below will be done prior to start of 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
2. Bone survey with long bones
3. SPEP and serum IFE,
4. UPEP and urine IFE,
5. Serum free light chain assay, immunoglobulins IgG, IgA, IgM
6. Beta 2 microglobulin
7. Assessment of baseline toxicity

Prior to start Preparative Regimen:
Women of childbearing age must have a pregnancy test within 10-14 days and again 24 hours before prescribing lenalidomide, then 4 weeks after therapy discontinued.

7.0 Evaluation During Study

1. Peripheral blood for NK chimerism studies:
The first 12 patients will have chimerism analysis up to twice a week (as permitted by laboratory availability) from D-4 to D+7, then only if positive for donor NK cells, weekly up to around D+30 (+/- 3 days). After D+30 and until D+100 is not mandatory, only if possible while the patient comes for routine follow up as below. The next six patients may have NK chimerisms if additional funding is obtained.

2. GvHD assessment:
After the NK infusion (D-5) at each visit or as clinically indicated. When symptoms of GvHD are suspected a biopsy must be done prior to initiating treatment.

3. Disease assessment around D+30 and D+100, and then around 6 months and 12 months post-transplant (can replace the nearest timepoint):

1. Bone marrow aspirate and biopsy for morphology and flow, and may add cytogenetics/FISH studies if cytogenetic abnormalities were diagnosed at baseline.
2. SPEP +/- serum IFE.
3. UPEP +/- urine IFE.
4. Serum free light chain assay, immunoglobulins IgG, IgA, IgM.
5. B-type natriuretic peptide (BNP) or NT-Pro-BNP, only if history or new concerns for amyloidosis.

4. The following lab tests are to be performed as frequently as clinically indicated:

CBC, differential, platelets, SGPT, calcium, glucose, uric acid, magnesium, serum bilirubin, BUN and creatinine, serum protein, albumin, alkaline phosphatase, electrolytes, urinalysis.

5. Pregnancy Testing:
Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

For FCBP, pregnancy tests must occur within 10 - 14 days and again within 24 hours prior to prescribing lenalidomide. (prescriptions must be filled within 7 days) and at Day +30 (+/- 2 days) post the last dose (D-2) of lenalidomide (see Appendix C.: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

8.0 Study Definitions

8.1 Disease Response

International Myeloma Working Group uniform response criteria.

All response categories require two consecutive assessments made at any time.
All response categories require no known evidence of progressive or new bone lesions.

Stringent complete response (sCR) (all of the following)**:**
1. CR as defined.
2. Normal free light chain ratio
3. Absence of clonal cells in bone marrow by inmmunohistochemistry or immunofluorescence (defined by absence of abnormal κ/λ ratio of $\geq$ 4:1 or $\leq$1:2)

Complete response (CR) (all of the following):
1. Negative immunofixation in serum and urine.
2. < 5% plasma cells in the bone marrow.
3. Disappearance of any soft tissue plasmacytomas.

Note: While healing of preexisting bone lesions is not required, no new lytic lesions should appear. Further compression fracture of previously known spine lesion will not be considered as progressive disease.

Very good partial response (VGPR) (one of the following):
1. Serum and urine M protein detectable by immunofixation but not by electrophoresis.
2. 90% or greater reduction in serum M protein plus urine M protein level <100 mg per 4h.

Partial response (PR) (all of the following):
1. Reduction by > 50% in serum monoclonal protein.
2. Reduction of urinary monoclonal protein to < 200 mg/24h or >90%.

Stable disease:
1. Not meeting criteria for CR, VGPR, PR or PD.

Progressive disease (PD) (any one or more of the following): Increase of >/= 25% from baseline in:

Serum M protein (absolute increase must be >/= 0.5 g/dL).
Urine M component (absolute increase must be >/= 200 mg/24h).Only in patients without measurable serum and urine M protein levels.
Difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL).
Bone marrow plasma percentage (absolute % must be >/=10%).

1. Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
2. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.65 mol/L) that can be solely attributed to the myeloma.

Relapse from CR (any one or more of the following):
1. Reappearance of serum or urine M protein by immunofixation or electrophoresis.
2. Development >/=5% plasma cells in the bone marrow.
3. Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion or hypercalcemia).

8.2 Active treatment administration is defined from the first day of treatment administration as outlined in the treatment plan through D0.

8.3 Active treatment period is defined from Day -5 (the start of NK cell infusion) through Day +30.

8.4 Follow-up period is defined from BMT Day +31 until 12 months post-transplant.

8.5 Engraftment

Engraftment is defined as a sustained ANC >/= 0.5 x 10^9/L for 3 consecutive days.

Primary Graft Failure is defined as failure to achieve an ANC >/= 0.5 x 10^9/L for 3 consecutive days by day +28.

9.0 Evaluation of Adverse Events

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

Adverse events and protocol specific data will be entered into PDMS/CORe. PDMS/CORe will be used as the electronic case report form for this protocol.

Severity of the adverse events (AEs)

The severity of the adverse events (AEs) will be graded according to the Common Terminology Criteria v4.03 (CTCAE) from Day -5 (the start of NK cell infusion) up to D+30 (+3 days if necessary). Events not included in the CTCAE chart will be scored as follows:

General grading:

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

Causality Assessment

The investigational component of the treatment plan of this study is the is the infusion of

ex-vivo expanded CB NK cells when administrated with elotuzumab, lenalidomide, high-dose melphalan and autologous stem cell transplantation.

Therefore, events known to be caused by the NK cell infusion and its direct consequences will be assessed as definitely related when assessing the casuality. When the relationship of the adverse event cannot be rule out between the NK cell infusion and the treatment plan, the event will be scored as probably or possible related.

Events known to be related to drugs used as part of the treatment plan as well as to drugs used as supportive treatment will be scored as unrelated to the NK cells infusion.

Causality will be determined as per the guidelines above and based on the expected toxicities listed below.

The principal investigator will be the final arbiter in determining the causality assessment.

AEs related to the NK cells infusion:

1. These expected events will be monitored during the first 24 hours post infusion:
   - fever,
   - chills,
   - decrease in blood pressure,
   - rash,
   - shortness of breath.

2. Dose limiting, (also considered unexpected):
   - grade 4 NK infusion related toxicity,

- failure to engraft by D+28 or delayed engraftment,
- grades 3-5 allergic reactions related to study cell infusion,
- grade 3-5 organ toxicity (cardiac, dermatologic, gastrointestinal, hepatic, pulmonary, renal/genitourinary, or neurologic) not pre-existing or due to the underlying malignancy or due to preparative chemotherapy and occurring within 30 days (+3 days if necessary)post-transplant,
- grades 3-4 acute GVHD occurring within 45 dayspost-transplant,[10]
- treatment-related death within 8 weeks of the study cell infusion.[32]

Expected AEs related to high dose chemotherapy followed by autologous stem cell infusion are:

- Related to myelosuppression: thrombocytopenia, bleeding, platelets and RBCs transfusions.
- Fever: Non Neutropenic or Neutropenic without infection.
- Infections in the presence or absence of neutropenia.
- Readmissions (lasting <10 days).
- Cytopenias post transplant including secondary graft failure.
- Low blood pressure due to dehydration requiring fluid replacement.
- Fluid overload leading to cardiac dysfunction.
- GI related: nausea, vomiting, diarrhea, mucositis.
- Organ dysfunction: cardiac, pulmonary, hepatic, CNS and/ or renal.
- Stem Cell Transplant Syndromes: Cytokine Storm, TTP, hemorrhagic cystitis, interstitial pneumonitis (including pulmonary hemorrhage).

Adverse Events Considered Serious:

- Grade 4 NK infusion related toxicity.
- Failure to engraft or delayed engraftment.
- GvHD.
- Prolonged hospitalization due to infections and/or organ failure requiring extensive supportive care (i.e. dialysis, mechanical ventilation).
- Any expected or unexpected event resulting in an irreversible condition and/ or leading to death.

For the purpose of this study, abnormal laboratory findings considered associated to the original disease as well as isolated changes in laboratory parameters such as electrolyte magnesium and metabolic imbalances, uric acid changes, elevations of GPT,

GOT, LDH and alkaline phosphatase would not be considered adverse events and will not be collected in the database.

Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on Lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene/Bristol-Myers Squibb Drug Safety immediately by facsimile or email, using the Pregnancy Initial Report Form. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene/Bristol-Myers Squibb Drug Safety and Bristol-Myers Squibb immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene/Bristol-Myers Squibb Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the lenalidomide should also be reported to Celgene/Bristol-Myers Squibb Drug Safety and Bristol-Myers Squibb immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking Lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Celgene/Bristol-Myers Squibb Drug Safety Contact Information:

Celgene Corporation/Bristol-Myers Squibb
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

Bristol-Myers Squibb Contact Information:
All SAEs must be reported by confirmed facsimile (fax) transmission or reported via electronic mail to:

BMS Worldwide Safety

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1-609-818-3804

If only limited information is initially available, follow-up reports may be required.

Data Collection
From Day -5 (start of NK cell infusion) up to D+30 (+3 days if necessary), only adverse events considered unexpected and related will be collected. The data 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 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. Medical events not considered adverse events will not be collected. Co-morbid events will not be scored separately. All adverse events will be documented in the medical record and entered into the CRF.

Concurrent medication
As stated in the treatment plan, patients treated on this protocol will require supportive care treatment (concurrent medication). These medications are considered standard of care and have no scientific contributions to the protocol, therefore no data will be captured on the various medications needed or their side effects.

10.0 Statistical Design

10.1 Study Design

This study has three primary objectives:

1. To find the maximum tolerated dose (MTD) of UCB-derived NK cells.
2. To determine efficacy by the percent of patients achieving VGPR + CR at 3 months post-transplant.
3. To assess the minimal residual disease rate 100 days post-transplant in high-risk patients.

The study has two parts. In Part I, we will employ the phase I study design developed by Ji et al.[30] to find the MTD of NK cells. We will consider four dose levels of NK:

1) 5×10^6 cells/kg

2) 1 x 10^7 cells/kg
3) 5 x 10^7 cells/kg
4) 1 x 10^8 cells/kg

Prior to advancing/changing dose levels a cohort summary must be completed and submitted to the Clinical Research Monitor (IND Office).

DLT is defined as grade 4 NK infusion related toxicity; failure to engraft by D+28 or delayed engraftment; grades 3-5 allergic reactions related to study cell infusion; grade 3-5 organ toxicity (cardiac, dermatologic, gastrointestinal, hepatic, pulmonary, renal/genitourinary, or neurologic) not pre-existing or due to the underlying malignancy or due to preparative chemotherapy and occurring within 30 days (+3 if necessary) post-transplant; grades 3-4 acute GVHD occurring within 45 days post-transplant;[10] treatment-related death within 8 weeks of the study cell infusion.[32] The dose escalation scheme is outlined in Table 1 below.

DLT will be assessed within 30 days (+3 days if necessary) post-transplant. The maximum acceptable toxicity rate is 20%. We assume the prior distribution of the toxicity rate is beta (1, 1) and an equivalence interval of (0.175, 0.225).

We will enroll a maximum of 42 patients in this part of the study*. We will begin by enrolling 3 patients at the dose 5 x 10^6 cells/kg, and we will enroll patients in cohorts of size 3. Table 1 illustrates the trial monitoring chart to determine whether one should:

1) Escalate to the next higher dose (E),
2) Continue to enroll patients at the current dose (S),
3) De-escalate to the next lower dose (D), or
4) Determine that the current dose is unacceptable (DU).

* Note that the protocol originally planned to enroll 30 patients in the dose-escalation phase, after which the MTD would be determined, and an additional 12 patients would have been treated at this dose with the addition of IL-2. Based upon current clinical knowledge, we will not add IL-2, and the additional 12 patients will be used instead to provide additional information to better estimate the MTD.

Table 1. Phase I Dose-Finding Trial Monitoring Chart

Number of DLTs	Number of Patients at Current Dose													
	3	6	9	12	15	18	21	24	27	30	33	36	39	42
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	E	E	E	E	E	E	E	E	E	E	E	E
2	DU	S	S	S	S	E	E	E	E	E	E	E	E	E
3	DU	DU	S	S	S	S	S	E	E	E	E	E	E	E
4		DU	DU	S	S	S	S	S	S	S	E	E	E	E
5		DU	DU	DU	S	S	S	S	S	S	S	S	S	E
6		DU	DU	DU	DU	S	S	S	S	S	S	S	S	S
7			DU	DU	DU	DU	S	S	S	S	S	S	S	S
8			DU	DU	DU	DU	DU	DU	S	S	S	S	S	S
9			DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S
10				DU	DU	DU	DU	DU	DU	DU	S	S	S	S
11				DU	DU	DU	DU	DU	DU	DU	DU	S	S	S
12				DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S
13					DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
14					DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
15					DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

E = Escalate to the next higher dose
S = Stay at the current dose
DU = The current dose is unacceptably toxic. De-escalate to the next lower dose.
Target = 20%
Sample Size = 42
Epsilon1 = 0.025
Epsilon2 = 0.025

There are 2 exceptions to the above decisions. These are:

1) If the current dose level is 5 x 10^6 cells/kg and the action is D, then treat future patients at 5 x 10^6 cells/kg.

2) If the current dose level is 1 x 10^8 cells/kg and the action is E, then treat future patients at 1 x 10^8 cells/kg.

Otherwise Part 1 of the trial will be stopped when the maximum sample size of 42 patients is reached. The MTD is defined as the highest dose for which the probability of toxicity is closest to 20%. Table 2 presents the operating characteristics of the proposed design of this trial for 5 scenarios defined by different toxicity rates for the 4 doses. These operating characteristics are based on 2000 simulations of the trial.

Table 2. Operating Characteristics of Study Design

Dose	1 (5×10^6)	2 (1×10^7)	3 (5×10^7)	4 (1×10^8)	No Dose
Scenario 1					
True Toxicity Rate	0.01	0.05	0.10	0.20	
Selection Probability	0.009	0.046	0.240	0.706	0
Avg. # of Patients Treated	3.5	5.5	10.2	22.7	
Total Patients	42.0				
Overall Toxicity	0.139				
Scenario 2					
True Toxicity Rate	0.05	0.10	0.15	0.25	
Selection Probability	0.037	0.144	0.385	0.431	0.004
Avg. # of Patients Treated	5.3	9.1	12.8	14.6	
Total Patients	41.8				
Overall Toxicity	0.163				
Scenario 3					
True Toxicity Rate	0.05	0.20	0.35	0.45	
Selection Probability	0.223	0.597	0.160	0.013	0.009
Avg. # of Patients Treated	10.7	20.3	8.9	1.8	
Total Patients	41.6				
Overall Toxicity	0.203				
Scenario 4					
True Toxicity Rate	0.25	0.35	0.45	0.55	
Selection Probability	0.443	0.119	0.007	0	0.432
Avg. # of Patients Treated	20.7	7.3	1.4	0.2	
Total Patients	29.6				
Overall Toxicity	0.288				
Scenario 5					
True Toxicity Rate	0.35	0.45	0.55	0.65	
Selection Probability	0.165	0.015	0	0	0.821
Avg. # of Patients Treated	14.8	2.8	0.3	0	
Total Patients	18.0				
Overall Toxicity	0.369				

After Part I is complete, we will treat an additional 30 **high-risk** patients in Part II, Dose Expansion. The primary endpoint for the expansion cohort is the minimal residual disease (MRD) negative rate 100 days post-transplant ($MRD\text{-}NR_{100days}$). We expect that 12-15 of the patients treated at the MTD in Part I will be in the high-risk group, yielding a total of up to 45 high-risk patients treated at this dose.

10.2 Efficacy

We will estimate the VGPR + CR rate for patients treated at the MTD with a 95% credible interval. We expect the VGPR + CR rate to be about 20% with standard transplant, and we assume a beta (0.40, 1.60) prior distribution for the VGPR + CR rate. This prior distribution has a mean of 0.20 and a standard deviation of 0.23. For example, if we complete the study with 66 patients treated at the MTD and 13 of these patients have a VGPR or CR, then the 95% credible interval will be 11.2% to 29.9%. We will also estimate the MRD rate at day 100 in high-risk patients treated at the MTD with a 95% credible interval. We will assume a Beta (1.2, 0.8) distribution for the MRD rate. With 45 high-risk patients at the MTD, if 27 have MRD at day 100, a 95% credible interval will be (45.8%, 73.4%).

10.3 Analysis Plan

We will use descriptive statistics to summarize patient demographic and clinical information. We will tabulate response by dose. We will use logistic regression methods to model the rate of VGPR + CR as a function of potential prognostic factors (such as demographics, International Staging System stage, and cytogenetic abnormalities.). We will similarly model the DLT rate. We will also model the MRD rate in high-risk patients using logistic regression. We will estimate overall survival (OS) and progression-free survival (PFS) using the Kaplan-Meier product limit estimator, and we will use Cox proportional hazards regression to model OS and PFS as functions of the potential prognostic factors noted above.

10.4 Sample Size/Accrual Rate

Up to 72 patients will be enrolled. Based on the data from our institution we expect to finish accrual in approximately 6 years.

10.5 Analysis of Secondary Endpoints

For duration of infused UCB-NK cells in new host the statistics will be reported as an average time value with standard deviation. These data may also be used as covariates in the regression models described above.

11.0 Reporting Requirements

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.
- Grades 3-5 reactions related to study cell infusion.
- 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.

- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**

- **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. 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. This may include the development of a secondary malignancy.**

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.

Grade 3-5 product infusion reactions will be reported in an expedited fashion in addition to all Serious Unexpected Adverse Reactions.

It is the responsibility of the PI and the research team to ensure 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.

Expedited Reporting by Investigator to Celgene/Bristol-Myers Squibb
Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene/Bristol-Myers Squibb SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene/Bristol-Myers Squibb tracking number (RV-MM-PI-0691) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene/Bristol-Myers Squibb. A copy of the fax transmission confirmation of the SAE report to Celgene/Bristol-Myers Squibb should be attached to the SAE and retained with the patient records.

12.0 Criteria for Removal from the Study

1. Patient withdrawal of consent.

2. Inability to produce the NK product.
3. Patient's lack of compliance with the requirements of the study.
4. Patient's intercurrent illness that, in the opinion of the Investigator, will affect their ability to conform to the study protocol.
5. Disease progression requiring salvage treatment.
6. At study completion around 12 months post-transplant.
7. Graft failure requiring further treatment.

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