MDACC ID: 2012-0265
NCT ID: NCT01664910

Anti-CD22 Immunoconjugate Inotuzumab Ozogamicin (CMC-544) Added to Fludarabine, Bendamustine and Rituximab and Allogeneic Transplantation for CD22 Positive-Lymphoid Malignancies

Institution Study Number: **2012-0265**

IND Holder: MD Anderson Cancer Center

IND Number: 116121

Financial Supporter: Pfizer, Inc.

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Protocol Body

1.0 Objectives

1.1 Primary Objectives:

1.1.1 To characterize the safety of anti-CD22 immunoconjugate inotuzumab ozogamicin (CMC-544), when administered in conjunction with fludarabine, bendamustine, and rituximab as non-myeloablative preparative regimen for allogeneic stem cell transplantation for CD22-positive lymphoid malignancies.

1.2 Secondary Objectives:

1.2.1 To estimate tumor response.

1.2.2 To determine overall and event-free survival rates by histology subtype.

2.0 Background

2.1 Non-myeloablative Allogeneic Stem Cell Transplantation for Lymphoid Malignancies.

In conventional transplants, high-dose chemotherapy plus radiation, is used to destroy as many lymphoma cells as possible. However, these high dose associated with conventional stem cell transplantation. This has restricted the use of conventional transplantation to younger patients who may be more able to undergo this treatment.

In a European Bone Marrow Transplantation Group study in which the majority of patients received total body irradiation-based preparative (pre-transplant) regimens, the treatment-related mortality for the allogeneic group was 25% compared with 11% for the autologous group.[1] Another multicenter analysis of allogeneic transplantation in 113 patients with advanced low-grade lymphoma reported a treatment-related mortality of 40%.[2] A similar high mortality has been seen using the chemotherapy conditioning regimen of cyclophosphamide, carmustine and etoposide.[3]

Non-myeloablative allogeneic stem cell transplantation (NST) was developed following the observation that leukemia/lymphoma patients, who had received allogeneic transplantation and then subsequently relapsed, went back into remission following infusions of donor lymphocytes.[4] This and other findings confirmed that a graft-versus-tumor effect, where donor lymphocytes recognize cancer cells as foreign and then destroy them, is responsible for at least part of the efficacy of allogeneic bone marrow transplantation. If donor lymphocytes can control, or even eradicate malignant cells that have proved resistant to high-dose chemotherapy and irradiation, then these highly toxic therapies may not be necessary for the success of allogeneic stem cell transplantation strategies.

Evidence for a graft-versus-lymphoma (GVL) effect includes the observation that patients who develop chronic graft-versus-host-disease (cGVHD) following allogeneic transplantation, where the donor's immune cells

attack the patient's normal tissue, have a lower probability of relapsing than patients who do not develop cGVHD. Chopra, et. al. demonstrated a lower incidence of relapse in patients who acquired cGVHD (0% relapse with cGVHD versus 35% relapse with no cGVHD).[1] Perhaps the most direct data supporting the evidence and clinical significance of GVL comes from small studies and case reports whereby patients with progressive disease after allogeneic transplantation undergo withdrawal of drugs to suppress their immune system and induce cGVHD, which is often accompanied by a simultaneous decrease in the size of their lymphomas. Van-Besien demonstrated that of 9 patients who relapsed after allogeneic transplantation, 4 (44%) responded to withdrawal of immunosuppression drugs (2 complete remissions, 2 partial remissions), with responses that lasted nearly 2 years.[5]

The aim of NST is to establish immunological tolerance between the patient's immune system and the new stem cells from the donor, and to use this as a platform for immunotherapy involving the activation of immune cells, with donor lymphocytes as the active agent.[6] In NST, the patient receives low doses of chemotherapy and radiation, as well as drugs to suppress the immune system in order to prevent rejection of the donor stem cells. The donor stem cells are then infused into the patient. The patient's suppressed immune system allows the donor cells to travel to the bone marrow where they produce replacement blood cells. This process is known as engraftment. Once engraftment occurs, the patient's new blood and immune systems, resulting from the donor cells, have the ability to recognize and eradicate both the patient's remaining stem cells and the lymphoma cells.

Therefore, although NST was initially designed to decrease transplant related morbidity so that elderly patients, patients with other serious conditions, and patients relapsing from prior autologous transplants could be more safely treated, it is now seen as an effective form of immunotherapy for possibly all lymphomas.

2.2 Preparative Regimens for Non-myeloablative Transplantation for Lymphoid Malignancies.

The low-dose transplant regimen must (a) produce suppression of the patient's immune system to prevent rejection of the donor cells and (b) suppress the lymphoma sufficiently to prevent marked progression of the tumor and allow time for the GVL effect to occur.

2.2.1 FCR regimen.

Our initial studies at MD Anderson involved a combination of fludarabine, cyclophosphamide and rituximab (FCR) as a conditioning regimen for patients who had chemosensitive disease (Protocol ID99-035) and who were to receive a transplant from a compatible sibling donor.[7] A recent update reported an overall survival (OS) rate of 85% and progression-free survival (PFS) rates of 83% in patients with follicular lymphoma patients. Median follow-up time was 5 years. While NST with FCR has been a successful strategy for patients with indolent lymphomas who had a chemosensitive relapse, results in patients who aggressive histologies or had refractory disease or were in kinetic failure at the time of transplantation need to be improved upon. The 5-year OS and PFS rates

in mantle cell lymphoma were 53% and 46%, respectively.[8] Results were poorer in diffuse large cell lymphoma. Intensification of the preparative regimen has been associated with increased toxicity with no improvement in outcomes. Immunomanipulation with donor lymphocytes or rapid immune suppression withdrawal has been associated with an increased risk of GVHD without documented improvement in survivals.

2.2.2 Bendamustine-based regimen (FBR).

Bendamustine is an alkylating agent with a unique structure containing both a nitrogen mustard group and a benzimidazole ring. It has been shown to be active against cell lines that are resistant to other alkylating agents in pre-clinical experiments in vitro. Its activity profile, when compared with other commercially available chemotherapeutics in the NCI human 60 cell line assay, appears unique. Studies are underway to further elucidate the possible existence of a unique mechanism of action, including potential contribution of the purine-like structure of the agent. There were 13 published reports of combination therapy with bendamustine for the treatment of low-grade NHL. In the publications that included only patients with NHL, overall response rates ranged from 66% to 96%, CR rates ranged from 20% to 60%, and PR rates ranged from 30% to 53%.There were 8 published reports of combination therapy with bendamustine for the treatment of high-grade NHL (N=72); overall response rates in these studies were 50%.[10,11]

Patients with lymphoid malignancies who are considered for allogeneic transplantation usually have had multiple relapses and have been thus rendered resistant to cyclophosphamide, the backbone of most conventional treatment regimens for NHL. In vitro studies suggest that there is no cross-resistance between cyclophosphamide and bendamustine, and that the latter may overcome the resistance to cyclophosphamide with lesser toxicities. Some other studies have also suggested recently a synergy between bendamustine and purine analogs.

We have recently initiated a phase I/II trial of NST with bendamustine (maximum dose of 130 mg/m2/day x3) together with fludarabine and rituximab for patients with relapsed lymphoid malignancies (Protocol 2008-0246). Twenty-four patients have been treated. No DLT was observed. Myelosuppression was minimal (80% of patients did not require platelet transfusions, and 61% did not have a neutrophil nadir of below 500) and only one death occurred (ASH 2011, abstract # 894, oral presentation) This regimen is now replacing the FCR as a backbone for our NST regimens, and can be used as a platform for combination with additional agents to increase efficacy especially in patients with aggressive histologies and/or refractory disease.

2.3 Anti-CD22 Immunoconjugate Inotuzumab Ozogamicin (CMC-544).

CMC-544 is a humanized antibody conjugated to calicheamicin, a cytotoxic agent. CMC-544 targets CD22, which is expressed in the majority of B-cell NHL and in more than 80% of acute lymphocytic leukemia (ALL). CMC-544 alone and in combination with rituximab has demonstrated efficacy and tolerability in indolent and aggressive NHL patients including diffuse large B-cell lymphoma[12,13] , and more recently a 57% response rate was seen in relapsed

ALL.[14] The recommended dose in the phase 2 studies was 1.8 mg/m2 every 3-4 weeks. Most common side effects were hematologic, and thrombocytopenia was a dose-limiting toxic effect, which can be minimized after an allogeneic NST.

2.4 Proposed Study.

Because of the above properties, CMC-544 would be an ideal candidate for dose-escalation, as part of a non-myeloablative nontoxic conditioning (such as FBR) and allogeneic NST. We propose to treat cohorts of patients in an escalating dose of 0.6, 1.2 and 1.8 mg/m2. CMC-544 would be given on D-13 in order to decrease the risk of veno-occlusive disease or unforeseen additive toxicity to the conditioning. We propose the FBR as conditioning due to its well known favorable safety profile. We hope that this unique strategy will further decrease the relapse rate, especially in patients with aggressive histologies.

3.0 Patient Eligibility

3.1 Inclusion Criteria:

1. Age 18 to 70 years of age.
2. Patients with B-cell hematological malignancies who are eligible for allogeneic transplantation.
3. Patients must have a fully-matched sibling donor or a matched unrelated donor identified.
4. Performance score of at least 80% by Karnofsky or 0 to 2 ECOG.
5. Left ventricular EF $\geq$ 45% with no uncontrolled arrhythmias or symptomatic heart disease.
6. FEV1, FVC $\geq$ 50% and corrected DLCO $\geq$ 50%.
7. Serum creatinine $\leq$1.6 mg/dL. Serum bilirubin < 2 mg/dL upper limit of normal (unless due to Gilbert's Disease; patient with this disease should have a right upper quadrant ultrasound evaluation before treatment).
8. SGPT < 2 X upper limit of normal.
9. Men and women of reproductive potential must agree to follow accepted birth control methods (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study.
10. Negative Beta HCG test in a woman with child bearing potential defined as not post-menopausal for 12 months or no previous surgical sterilization) or currently breast-feeding. Pregnancy testing is not required for post-menopausal or surgically sterilized women.

3.2 Exclusion Criteria:

1. Patient with active CNS involvement.
2. Known infection with HIV, HTLV-I, Hepatitis B, or Hepatitis C.
3. Patients with other malignancies diagnosed within 2 years prior to study registration. Skin squamous or basal cell carcinoma are exceptions.
4. Active bacterial, viral or fungal infections.
5. History of stroke within 6 months.
6. History of biliary colic attack.
7. A prior autologous transplant within 3 months of study entry or allogeneic stem cell transplant.
8. Serious medical or psychiatric illness likely to interfere with participation in this clinical study.
9. Patient has received other investigational drugs within 3 weeks before study registration.
10. Serious nonmalignant disease which, in the opinion of the investigator would compromise protocol objectives.
11. Prior exposure to CMC-544 within past 6 months.
12. Established refractoriness to CMC-544.

4.0 Treatment Plan

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+).

Within 3 weeks prior to start treatment, D-13, patients must be off any prior biological therapy, chemotherapy, radiotherapy, or other investigational therapy.

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

4.1 Chemotherapy agent doses and administration.

D-13, CMC-544 will be infused intravenously (IV) as outpatient. Dose per cohort: 0.6,1.2 or 1.8 mg/m^2. Dose is based on actual body weight. Patients receive 650 mg Tylenol orally, 25 mg diphenhydramine, and 25 mg hydrocortisone IV, before inotuzumab ozogamicin.

D-5, -4 and -3, Fludarabine and Bendamustine will be administered IV following

SCT&CT department standard practice. These will be dosed per adjusted body weight for patients weighing > 20% above their ideal body weight. For patients less than or equal to 20% above their ideal body weight, the actual body weight is used.

Fludarabine will be administrated at a dose of 30 mg/m2 IV followed by Bendamustine at a dose of 130 mg/m^2 IV.

Patients with CD20+ disease will also receive rituximab IV at 375 mg/m^2 (based on actual body weight) on D-6, D+1 and D+8. Rituximab infusion will follow SCT&CT department standard practice.

D0, Transplant. Fresh or cryopreserved bone marrow or peripheral blood progenitor cells will be infused on day 0. Depending on arrival time, patients who receive a graft from an unrelated donor might have one day delayed from D0.

Supportive Treatment. All patients will receive Graft Versus Host Disease (GvHD) prophylaxis, infections disease prophylaxis, growth factors, blood and platelet transfusion and other supportive treatment as per departmental standard practice in patients receiving allogeneic transplant.

D-2 and D-1, Thymoglobulin 1 mg/kg (based on actual body weight) will be administrated IV to patients receiving a matched unrelated donor (MUD). Premedicate each dose with methylprednisolone and diphenhydramine per standard practice.

D-2, Tacrolimus will start on D-2 administered at starting dose of 0.015 mg/kg (ideal body weight) as a 24 hour continuous infusion daily adjusted to achieve a therapeutic level of 5-15 ng/ml. Tacrolimus is changed to oral dosing when tolerated and can be tapered off after 6 months if no GVHD is present.

D+1, +3 and +6, Methotrexate 5 mg/m2 will be administered IV for all patients. Patients receiving an unrelated graft will also be given methotrexate on D+11 after the transplant.

G-CSF (filgrastim-sndz, Zarxio) will be administered at a dose of 5 mcg/kg/day (rounded up the nearest vial size) subcutaneously beginning on D+7 for patients receiving related and MUD. G-CSF will continue until the absolute neutrophil count (ANC) is > 500 x 10/L for 3 consecutive days.

In order to avoid liver toxicity related to antifungal agents, patients should receive caspofungin up until day +30 after which time therapy could be changed to an azole per SCT standard of care if LFTs are within normal limits.

5.0 Evaluation During Study

5.1 Assessment and documentation of adverse events present at time of treatment initiation.

5.2 Disease assessment prior to start treatment (baseline):

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

1. Unilateral bone marrow biopsy and aspiration.
2. Disease specific PCR only if previously detected (mbr, mcr, and/or JH for follicular), BCL-1, and/or JH for Mantle cell Lymphoma-MCL), (JH for others).
3. Cytogenetics and flow cytometry.
4. Disease specific fluorescence in situ hybridization (FISH) only if previously detected (14, 18 for follicular) (11, 14 for MCL).
5. Immunophenotyping.
6. PET only if previously positive.
7. Chest x-ray.
8. CT neck, chest, abdomen and pelvis.
9. Laboratory studies: CBC with differential, platelet count, PT, PTT, creatinine, ALT, bilirubin, LDH, alkaline phosphatase Beta 2 microglobulin level, Hepatitis serology, HIV, HTLV-1, quantitative serum immunoglobulins, baseline peripheral CD4/CD8 counts and immunodeficiency panel.
10. Patients with history of Gilbert's Disease: Right upper quadrant abdominal ultrasound.

5.3 Evaluation During Study:

Evaluations during this study follow our standard practice, if clinically indicated these studies may be done at other time points which can replace the nearest planned timepoint. After 12 months, follow-up testing to determine disease status will be done annually around years 2 and 3 as clinically indicated.

1. To be performed around engraftment time:
   a) Chimerism studies from peripheral blood performed on separated T-cells and myeloid cells. After engraftment patients that have 100% donor cells, chimerism studies will be done every 3 months during the first year and then every 6 months while the patient is on study.

2. To be performed as clinically indicated:
   a) Physical examination and adverse event assessment including GvHD assessment.
   b) Laboratory:
      1) Complete blood count with differential
      2) Standard Chemistries including LFT, BUN, Cr, albumin.

3. Disease assessment to be performed around 1, 3, 6 and 12 months post transplant:
   a) Unilateral bone marrow aspiration and biopsy. As clinically indicated if this was negative pre-transplant.

b) PCR (mbr, mcr, and/or JH for follicular), (BCL-1, and/or JH for CL), (JH if previously + for others) (repeat these only if a positive history)
c) Cytogenetics, flow cytometry.
d) FISH (14,18 for foll), (11,14 for MCL), XX/XY for sex mismatched donors only
e) CT scans of neck. chest, abdomen and pelvis.
f) PET if it was positive any time in the past. PET would not be repeated once CR is documented after transplant unless there are suspicious lymph nodes by CT.
g) Quantitative serum immunoglobulins levels.
h) PB CD4/CD8, immunodeficiency panel (only repeat in pts with recurrent infections).

Patients who do not achieve CR or who progress will receive immunomodulation with rituximab and donor lymphocyte infusion (DLI) as per SCT&CT department standard practice. Those who progress after DLI will be taken off study.

6.0 Background Drug Information

6.1 Bendamustine

Description: Bendamustine is a bifunctional alkylating agent containing a purine-like benzimidazole ring. Bendamustine forms covalent bonds with DNA causing both single and double-strand DNA breaks leading to cell death.

Preparation and stability: BENDEKA™ (Bendamustine) is supplied as 100mg/4mL (25 mg/mL) as a clear and colorless to yellow ready-to-dilute solution in a multiple-dose vial. Bendamustine hydrochloride injection contains no antimicrobial preservative. The admixture should be prepared as close as possible to the time of patient administration. If diluted with 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36-46°F) or for 6 hours when stored at room temperature (15-30°C or 59-86°F) and room light. **Administration of diluted bendamustine hydrochloride (BENDEKATM) injection must be completed within this period of time.**

In the event that 5% Dextrose Injection, USP is utilized, the final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36-46°F) or for only 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light. **Administration of diluted BENDEKA™ must be completed within this period of time.** Retain the partially used vial in original package to protect from light and store refrigerated (2-8°C or 36-46°F) if additional dose withdraw from the same vial is intended.

Stability of Partially Used Vials (Needle Punched Vials):
Bendamustine hydrochloride (BENDEKA™) is supplied in a multiple-dose vial. Although it does not contain any antimicrobial preservative, it is bacteriostatic. The partially used vials are stable for up to 28 days when stored in its original carton under refrigeration (2-8°C or 36-46°F). Each vial is not recommended for more than a total of six (6) dose withdrawals. After first use, the partially used vial

should be stored in the refrigerator in the original carton at 2°C to 8°C or 36-46°F and then discarded after 28 days.

Aseptically withdraw the volume needed for the required dose from the 25 mg/mL solution as per Table (available in the package insert) and immediately transfer the solution to a 50 mL infusion bag of one of the following diluents:
- 0.9% Sodium Chloride Injection, USP; or
- 2.5% Dextrose/0.45% Sodium Chloride Injection, USP; or
- 5% Dextrose Injection, USP

The resulting final concentration of bendamustine hydrochloride in the infusion bag should be within 1.85 mg/mL – 5.6 mg/mL. After transferring, thoroughly mix the contents of the infusion bag.

Administration: Administer each bendamustine dose intravenously over 30 to 60 minutes.

Adverse reactions: myelosuppression, infection, infusion reactions (rarely anaphylaxis), extravasation, skin reactions such as mild rash/itching or rarely toxic epidermal necrolysis, tumor lysis syndrome, diarrhea, nausea/vomiting, fatigue, and rarely secondary malignancies such as myelodysplastic syndrome or acute leukemia.

Storage: BENDEKA™ (bendamustine hydrochloride) Injection should be stored in refrigerator, 2° to 8°C (36° to 46°F). Retain in original carton until time of use to protect from light.

See the current package insert for additional information.

6.2 Rituximab

Description: Rituximab is a monoclonal antibody targeted against CD20 primarily found on B lymphocytes. Rituximab causes cell lysis through complement mediated cytotoxicity and antibody-dependent cytotoxicity.

Preparation and stability: Dilute with NS or D5W to a final concentration of 1-4mg/mL. Solution is stable at 2-8 degrees C for 24 hours and additional 24 hours at room temperature. Rituximab is supplied as 100mg and 500mg vials.

Administration: Administer according to institutional standards.

Adverse reactions: infusion reactions (fever, chills, hypotension), rarely anaphylaxis, acute respiratory distress syndrome, arrhythmias, lymphopenia, infection, hepatitis B reactivation, rarely progressive multifocal leukoencephalopathy, skin rash, tumor lysis syndrome, nausea/vomiting, arthralgias, myalgias, and severe mucocutaneous reactions (including Stevens-Johnson Syndrome and toxic epidermal necrolysis).

Storage: Diluted solutions of Rituximab should be stored refrigerated at 2-8 degrees C. Rituximab vials should be stored at 2-8 degrees C. and protected

from direct sunlight. Do not freeze or shake.

See package insert for additional information.

6.3 Fludarabine

Therapeutic classification: Fluorinated nucleoside analog

Pharmaceutical data: Each vial contains 50 mg lyophilized drug, to be reconstituted prior to its use. Reconstitute each vial with 2 ml sterile water, each ml of solution will contain 25 mg of fludarabine phosphate. Vials should be stored refrigerated at 2-8 degrees C.

Solution Preparation: mix each vial with 100mL NS and infuse over 30 minutes. Reconstituted solution should be used within 8 hours.

Side effects: Pancytopenia, immunosuppression, autoimmune hemolytic anemia has (rarely) been reported, and recurred when patients were retreated with the drug.

Nausea, vomiting, anorexia, weakness.

From the CNS: Agitation, visual disturbances, confusion, coma, peripheral neuropathies have been reported. With high dose use confusion, blindness, coma and death have been reported.

Special Precautions: As for other antineoplastic agents Fludarabine should be handled by trained personnel using procedures for proper handling. The use of gloves and protective glasses is recommended to avoid exposure upon accidental spillage.

Mechanism of action: After phosphorylation to fluoro-ara-ATP the drug appears to incorporate into DNA and inhibit DNA polymerase alpha, ribonucleotide reductase and DNA primase, thus inhibiting DNA synthesis.

Human safety and pharmacology: The half-life of the activated compound is approximately 10 hours, but the pharmacology is incompletely understood. Excretion is impaired in patients with impaired renal function.

See package insert for additional information.

6.4 CMC-544 (inotuzumab ozogamicin)

Description: CMC544 is a humanized monoclonal antibody target to CD22 and conjugated to calicheamicin. It is supplied as amber vials with white, unpreserved, lyophilized cake. Each vial contains 4mg.

Preparation and stability: Allow vials to reach room temperature prior to reconstitution. Reconstitute each vial with 4mL sterile water for injection for a concentration of 1mg/mL. Gently swirl each vial to dissolve. Do not shake vigorously. Dilute reconstituted solution (entire dose) with 0.9% sodium chloride

to a final volume of 50mL. Infusion must be completed within 8 hours of reconstitution. Bags made of PVC or polyolefin are recommended. Unused or expired drug will be destroyed per institutional policy.

Administration: Each dose should be administered at 50mL/hr. Flush line with 22mL 0.9% sodium chloride after infusion is complete. Protect from light during preparation and administration.

Adverse events: common and expected are thrombocytopenia and neutropenia, low grade liver function tests, increased risk of infections due to neutropenia and depletion of B-cells, nausea, vomiting, abdominal pain, constipation, diarrhea, and decreased appetite.

Less common but serious and sometimes fatal are venoocclusive liver disease/sinusoidal obstructive syndrome (VOD/SOS), nodular regenerative hyperplasia, hepatic fibrosis / biliary cirrhosis, hepatic failure, ascites, hyperbilirubinemia, cytolytic hepatitis, hepatitis/hepatitis acute, and abnormal hepatic function.

Fatigue and asthenia are common and sometimes severe. Chills, headache, pyrexia, and epistaxis have also been reported.

No serious prolongation of QTc although no well characterized have been observed.

Storage: Vials should be refrigerated (2-8°C) and protected from light.
For additional information, please see the current investigator's brochure .

6.5 Antithymocyte globulin (ATG) (Rabbit) (Thymoglobulin®)

Description: Antithymocyte globulin is a polyclonal IgG against human T-lymphocytes causing profound immunosuppression

Preparation and stability: Reconstitute each vial of antithymocyte globulin with 5mL of sterile water. The final concentration will be 5mg/ml of Thymoglobulin. May further dilute with either D5W or NS. The recommended final concentration is 0.5mg/mL. Diluted solutions should be used immediately as there are no preservatives in the vials. The solution is stable at room temperature for 24 hours; however, this is not recommended. Antithymocyte globulin is supplied as 25mg vials.

Administration: Administer each dose over 4-6 hours. Administer via in-line 0.22 micron filter. Premedication with corticosteroids, acetaminophen, and antihistamines are recommended to reduce infusion related reactions.

Adverse reactions: infusion reactions (fever, chills, hypotension), serum sickness, rash, infection, myelosuppression, allergic reactions including anaphylaxis, post-transplant lymphoproliferative disorders, and acute respiratory distress syndrome.

Storage: Antithymocyte globulin (Thymoglobulin) is supplied as 25 mg vials which should be stored refrigerated 2-8 degrees C. Protect from freezing. Protect from light.

See package insert for additional information.

7.0 Statistical Considerations

Statistical section - patient sample size and analysis plan:

7.1 The study design developed by Ji, Li, and Bekele (2007) will be used to determine the MTD of CMC-544 targeting a toxicity rate not greater than 30% using a prior beta(0.5, 0.5). Three doses of CMC-544 will be studied (0.6, 1.2, 1.8 mg/m2). The dose-limiting toxicity (DLT) is defined as grade III or IV renal, hepatic, intestinal, neurologic, pulmonary or cardiac adverse events, as well as any graft failure or treatment-related death at any time from first CMC-544 administration (D-13) through 30 days post transplant (D30).

Patients will be enrolled in cohorts of two, beginning at 0.6 mg/m2. Each cohort of two must be fully evaluated for toxicity through D30 before enrolling the next cohort. The trial monitoring chart is displayed in Table 1. This table describes when a dose is declared too toxic and should be de-escalated or is safe and can be escalated or chosen as the MTD. The MTD is defined as the highest dose for which the probability of toxicity is closest to 30%. A legend is displayed below the table. Prior to advancing dose levels a cohort summary must be completed and submitted to the Clinical Research Medical Monitor (IND Office).

Table 1. Phase I Dose-finding Trial Monitoring Chart

Number of toxicities	Number of patients treated at current dose														
	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
0	E	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	E
2	DU	S	S	S	S	E	E	E	E	E	E	E	E	E	E
3		DU	S	S	S	S	S	E	E	E	E	E	E	E	E
4		DU	DU	D	S	S	S	S	S	S	E	E	E	E	E
5			DU	DU	D	S	S	S	S	S	S	S	E	E	E
6			DU	DU	DU	D	S	S	S	S	S	S	S	S	E
7				DU	DU	DU	D	S	S	S	S	S	S	S	S
8				DU	DU	DU	DU	DU	S	S	S	S	S	S	S
9					DU	DU	DU	DU	DU	S	S	S	S	S	S
10					DU	DU	DU	DU	DU	DU	D	S	S	S	S
11						DU	DU	DU	DU	DU	DU	DU	S	S	S
12						DU	DU	DU	DU	DU	DU	DU	DU	S	S
13							DU	DU	DU	DU	DU	DU	DU	DU	S
14							DU	DU	DU	DU	DU	DU	DU	DU	DU
15								DU	DU	DU	DU	DU	DU	DU	DU
16								DU	DU	DU	DU	DU	DU	DU	DU
17									DU	DU	DU	DU	DU	DU	DU
18									DU	DU	DU	DU	DU	DU	DU
19										DU	DU	DU	DU	DU	DU
20										DU	DU	DU	DU	DU	DU
21											DU	DU	DU	DU	DU
22											DU	DU	DU	DU	DU
23												DU	DU	DU	DU
24												DU	DU	DU	DU
25													DU	DU	DU
26													DU	DU	DU
27														DU	DU
28														DU	DU
29															DU
30															DU

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
U = The current dose is unacceptably toxic
MTD = 30%
Sample Size = 30

If the current dose is 1.8 mg/m^2 and the decision rule from Table 1 is E (escalate), then future patients will be treated at 1.8 mg/m^2. We will terminate the trial when the maximum sample size (n=30) is reached.

Table 2 presents the operating characteristics of the proposed design for this trial based on 2000 simulations using 5 scenarios with varying toxicity rates for each of the three doses. The first two scenarios contain safe toxicity rates for all doses (<30%) and the

last scenario contains unsafe toxicity rates for all doses (>30%).

Table 2. Operating Characteristics of the Phase I Study Design

Scenario		Doses 0.6 mg/m2	1.2 mg/m2	1.8 mg/m2	P(No Dose Selected)	Total Number of Pts	Number with DLT
1	P(Tox)	0.05	0.10	0.15			
	P(MTD)	0.01	0.04	0.95	<0.01	29.9	4.1
	Avg. # pts	2.8	3.9	23.2			
2	P(Tox)	0.10	0.15	0.25			
	P(MTD)	0.05	0.18	0.77	<0.01	29.7	6.2
	Avg. # pts	4.5	6.9	18.3			
3	P(Tox)	0.15	0.25	0.35			
	P(MTD)	0.14	0.39	0.44	0.03	29.2	7.8
	Avg. # pts	7.1	10.5	11.6			
4	P(Tox)	0.25	0.35	0.45			
	P(MTD)	0.40	0.35	0.13	0.12	27.1	8.7
	Avg. # pts	12.7	9.6	4.8			
5	P(Tox)	0.35	0.45	0.55			
	P(MTD)	0.48	0.17	0.02	0.33	22.8	8.9
	Avg. # pts	14.9	6.4	1.6			

Secondary Outcomes

We will estimate the objective overall response (CR+PR) with a 95% confidence interval in the dose that is declared the MTD. We will use logistic regression to assess the association between response and disease and clinical characteristics of interest.

Kaplan-Meier[16] survival curves will be used to estimate overall survival and recurrence-free survival. We will use Cox proportional hazards regression methodology to assess the association between disease and clinical characteristics and the survival outcomes. We will use the method of Gooley et al[17] to estimate the cumulative incidence of acute and chronic GVHD.

8.0 Study Definitions

8.1 Treatment periods:

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

Active treatment period is defined from the first day of treatment administration through Day +30.

Follow-up period is defined from BMT Day +31 until one year of treatment completion.

8.2 Disease Response is defined according to disease specific criteria as per the CIBMTR.

Complete Response (CR):
1. No clinical or radiological evidence of disease.
a) Negative bone marrow biopsy
b) No palpable liver or spleen
c) Negative scans

Partial Remission (PR):
1. Equal or more than 50% reduction in lymphadenopathy, liver and or spleen if abnormal at pre-treatment.
2. No new site of disease.

Stable Disease (SD):
No change in disease status from baseline, no evidence of new sites of disease.

Disease Progression:
1. More than 50% increase in lymph nodes size.
2. Evidence of new sites of disease (lymph nodes, bone marrow or other sites).
3. If previously positive increased in PET uptake.

8.3 Engraftment is defined as the evidence of donor derived cells (more than 95%) by chimerism studies in the presence of neutrophil recovery by D+ 28 post stem cell infusion.

8.3.1 Other definitions used to assess engraftment:
Neutrophil recovery is defined as a sustained absolute neutrophil count (ANC) > 0.5 x 10^9/L for 3 consecutive days.
Engraftment date is the first day of three (3) consecutive days that the ANC exceeds 0.5 x10^9/L.
Delayed engraftment is defined as the evidence of engraftment beyond D+28, as above, achieved after the administration of therapeutic (high dose) hematopoietic growth factors.
Primary Graft failure is defined as failure to achieve an ANC > 0.5 x 10^9/L for 3 consecutive days by D+ 28, as above, with no evidence of donor derived cells by bone marrow chimerism studies and no evidence of persistent or relapsing disease.
Secondary graft failure is defined as a sustained declined of ANC <0.5 x 10^9/L for 3 consecutive days after initial documented engraftment with no evidence of disease progression.
Autologous reconstitution is defined by the presence of ANC > 0.5 x 10^9/L without evidence of donor-derive cells by bone marrow chimerism studies. This can occur at initial engraftment or later after initial engraftment has been documented.

9.0 Criteria for Removal from the Study

1. Patient withdrawal of the informed consent.
2. Patient not being compliant or fails to return for follow-up.
3. An increasing or unexpected pattern of toxicity observed deemed unacceptable by the Study Chairman.
4. Disease progression after donor lymphocyte infusion.
5. Investigator judgment when the well being and best interest of the patient is compromised.
6. After 3 years of study completion.

10.0 Reporting Requirements

PDMs/CORe will be used as the electronic case report form (eCRF) for this protocol and protocol specific data including adverse events will be entered into PDMs/CORe.

Severity of the adverse events (AEs).
The severity of the adverse events (AEs) will be graded according to the Common Terminology Criteria v4.0 (CTCAE). 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

Grading for specific syndromes:
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

Causality Assessment.

For the purpose of this study common adverse events of Fludarabine, Bendamustine and Rituximab as preparative regimen for allogeneic stem cell transplantation are known and well described. Therefore an increased pattern of frequency and or severity of these events will be assessed and reported as definitive related to the preparative regimen in combination of CMC-544.

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.

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

List of most common expected AEs related to high dose chemotherapy followed by allogeneic stem cell transplantation:

1. Infections in the presence or absence of neutropenia: fungal, bacterial and or viral infections.
2. Fever: Non-neutropenic or neutropenic without infection
3. Acute graft versus host disease (aGVHD): most commonly manifested by skin rash, diarrhea and abnormal liver function tests could also present with some degree of fever, upper gastrointestinal symptoms (nausea and vomiting) mucositis and eye dryness.
4. Gastrointestinal (GI tract): the GI tract manifestations could be not only due to direct damage from the preparative regiment but also be a manifestation of GVHD or infections. Therefore, the time, course, and its presentation are crucial when assessing these as adverse events. Nausea/vomiting, mucositis, and diarrhea when presented within first 7 to 10 days most likely will be related to the preparative regimen.
5. Skin rash: not related to GVHD could be caused by chemotherapy used for the preparative regimen or antibiotics used as supportive treatment.
6. Transaminitis: liver function test elevation.
7. Pulmonary events: not related to CHF most likely caused by drug injury or infection. These could present with a pneumonitis pattern manifested with shortness of breath, pulmonary infiltrates on chest radiograph, sometimes accompanied by fever and cough and progress to acute respiratory insufficiency and a diffuse bilateral alveolar pattern.
8. Cytokine Storm/ engraftment syndrome: most likely caused by released cytokines.
9. Hemorrhagic cystitis: not related to chemotherapy agents used in the proposed preparative regimen is most likely caused by viral infection.

10. Thrombotic thrombocytopenic purpura (TTP).
11. Veno-occlusive Disease of the Liver (VOD): known to have a higher incidence in patients undergoing high dose chemotherapy. Some antimicrobial agents have been also incriminated in its development.
12. Fluid overload due to hydration required for conditioning regimen, blood product transfusions and or IV alimentation
13. Graft failure.
14. Chronic GVHD.
15. For the purpose of this study the following events would not be considered adverse events and would not be recorded in the database:
    1. Flu-like symptoms not associated with infection
    3. Abnormal laboratory findings considered associated to the original disease
    4. Isolated changes in laboratory parameters such as electrolyte, magnesium and metabolic imbalances, uric acid changes, elevations of ALT, AST, LDH and alkaline phosphatase.

Dose-limiting toxicity (DLT) is defined as grade III or IV occurring during the first 30 days:

Renal
Hepatic
Intestinal
Neurologic
Pulmonary
Cardiac
Graft failure
Treatment related death

Adverse events considered serious

1. Prolonged hospitalization due to infections and/or organ failure requiring extensive supportive care (i.e. dialysis, mechanical ventilation).
2. Readmissions from any cause resulting in a prolonged hospitalization (>10 days).
3. Graft Failure/ rejection.
4. Any expected or unexpected event resulting in an irreversible condition and/or leading to death.

Adverse events data collection

From the start of preparative regimen up to D+100 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.

Adverse events will be documented based on progress notes, including the flowsheet, in the electronic (Clinic Station) patient medical record.

Concurrent medication

As stated in the treatment plan, patients treated on this protocol will require supportive care treatment (concurrent medications). 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.

Serious Adverse Events 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 CFR312.32).

- **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 ofthe event to the Safety Project Manager in the IND Office.

- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilizedfor 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.

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.

Investigator Communication with Pfizer:

For the purposes of SAE reporting on this protocol, SAE's should also be reported to Pfizer only if the patient has received at least one dose of CMC-544 and up to 28 days after the last dose of study drug. SAE's which occur prior to a patient receiving CMC-544 shall not be reported to Pfizer.

11.0 References

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