PennState Cancer Institute

TITLE: Clofarabine Pre-conditioning followed by Hematopoietic Stem Cell Transplant with Post-Transplant Cyclophosphamide for Non-remission Acute Myeloid Leukemia

PSCI Protocol Number # 18-011

National Clinical Trial (NCT) Identified Number: NCT04002115

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Statement of Compliance

This is an investigator-initiated study. The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and institutional requirements. The Sponsor-Investigator, Dr. Seema Naik, is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed. Dr. Naik will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

1.0 Protocol Synopsis

Study Title:	Clofarabine Pre-conditioning followed by Hematopoietic Stem Cell Transplant with Post-Transplant Cyclophosphamide for Non-remission Acute Myeloid Leukemia
Objectives:	Primary Objective: The primary objective is to determine the incidence of complete remission (CR) at day +30 post HSCT after Clofarabine followed by Hematopoietic Stem Cell Transplant (HSCT) with Post-Transplant Cyclophosphamide (PTCy). Secondary Objectives: • To determine disease-free survival (DFS) and overall survival (OS). • To determine the rate of non-relapse related mortality (NRM) at day 100. • To determine the incidence and severity of acute and chronic graft versus host disease (GVHD). • To determine the rate of engraftment.
Endpoints:	Primary Endpoint: The primary endpoint of the study will be the CR rate at day 30 post HSCT. The responses will be evaluated as complete remission (CR), Complete Remission with Incomplete Hematologic Recovery (CRi), and relapse. Secondary Endpoints • OS and DFS at one year after HSCT. • NRM by day 100 after HSCT. • The incidence and severity of acute and chronic GVHD. • Rate of engraftment.
Eligibility Criteria:	Inclusion Criteria: 1. Diagnostic criteria of AML, induction failure without having achieved remission after at least 2 attempts at induction chemotherapy, or relapsed after any complete remission (CR).

	2. 18 to 75 years of age. 3. Planned or scheduled to receive an allogeneic HSCT from haploidentical related donors or matched and mismatched unrelated donors. 4. Organ Function Criteria: All organ function testing should be done within 28 days of study registration. a. Performance status: Karnofsky ≥ 70% (Appendix A). b. Cardiac: Left Ventricle Ejection Fraction (LVEF) ≥ 50% by MUGA or echocardiogram. c. Pulmonary: Forced Expiratory Volume in One Second (FEV1) and Forced Vital Capacity (FVC) ≥ 50% predicted, Diffusing Capacity of Carbon Monoxide (DLCO) corrected for hemoglobin ≥ 50% of predicted. d. Renal: Creatinine clearance (CrCl) ≥60 mL/min/1.73 m^2 e. Hepatic: Serum bilirubin ≤1.5 × upper limit of normal (ULN); (AST)/(ALT) ≤2.5 × ULN; Alkaline phosphatase ≤ 2.5 × ULN. 5. Both men and women need to use an approved method of birth control and/or abstinence due to unknown risks to the fetus. <u>Exclusion Criteria</u> 1. Acute promyelocytic leukemia (APL) 2. Known history of non-compliance with medication regimens, scheduled clinic visits, or self-care. 3. In the opinion of the investigator, no appropriate caregivers identified. 4. HIV1 (Human Immunodeficiency Virus-1) or HIV2 positive 5. Active Hepatitis B and Hepatitis C or.hepatitis positive serology including HBsAg, hepatitis B core antibody, and hepatitis C antibody. Hepatitis B surface antibody positive due to vaccination or natural immunity are permitted. 6. In the opinion of the physician investigator, uncontrolled medical or psychiatric disorders. 7. Uncontrolled infections requiring treatment within 14 days of registration. 8. Active central nervous system (CNS) leukemia. 9. Cord blood transplant excluded. 10. Prior allogeneic HSCT within last 6 months. 11. Patients with >= grade 2 acute GVHD. 12. Patients with >=moderate chronic GVHD. 13. Pregnant or Breastfeeding. Women of child bearing potential (WCBP) are required to have a negative serum or urine pregnancy test prior to initiation of conditioning regimen. 14. Haploidentical related donors who are positive for DSA ≥ 5000 MFI by solid phase microarray method (Luminex).

	15. Any patient with steroid dose more than 10 mg/day within a week of registration. 16. Autoimmune disorder requiring any active immunosuppression therapy.
Phase:	2
Sample Size	20 evaluable subjects (25 subjects enrolled including 5 subjects with screen failures)
Sites/Facilities Enrolling:	Single site - Penn State Cancer Institute
Study Intervention:	Single arm Clofarabine pre-conditioning followed by HSCT with Post-Transplant Cyclophosphamide
Study Duration:	24 months from subject consenting
Participant Duration:	60 months from subject consenting

2.0 BACKGROUND

Approximately 30–40% of patients with acute myeloid leukemia (AML) experience induction failures. In these patients who do not achieve remission with two cycles of standard induction therapies, the probability of achieving remission with subsequent inductions is very limited. Hematopoietic stem cell transplantation (HSCT) is the only curative option for these patients, but high relapse rate and transplant-related mortality often preclude them to proceed to transplant. Thus, AML not in remission at time of HSCT remains a huge unmet need in current HSCT practice, particularly if the patient does not have a Human Leukocyte Antigen (HLA)-matched donor identified by the time of two induction failures.

Salvage chemotherapy with Clofarabine appears to be another promising option in relapsed and refractory AML. Clofarabine is a second-generation purine nucleoside analog with substantial single-agent activity in adult patients with AML. In addition, Clofarabine is an effective immunosuppressive agent and several trials have shown the feasibility of conditioning with Clofarabine-based regimen[1, 2]. In the past, a conditioning regimen of Clofarabine and Busulfan × 4 (Clo/Bu4) has been successfully used prior to allogeneic stem cell transplantation for non-remission AML with day +30 complete remission rates were 90–100%[1, 2]. However, these patients were transplanted with HLA matched donors.

It has been shown that Clo/Bu4 were utilized for refractory pediatric hematologic malignancies prior to haploidentical stem cell transplantation, with reported leukemia-free survival of 167, 49, and 31 weeks, respectively, in three cases[3]. However, there are also data that Clofarabine may not be as immunosuppressive as Fludarabine[4, 5].

In treatment of very aggressive leukemia, a new approach to start transplant conditioning at nadir during the previous chemotherapy defined as “preconditioning”, has been used in Europe since more than 10 years ago[6, 7]. In these studies, there were only 3 days of rest between induction chemotherapy and the beginning of transplant conditioning regimen. More recently, another European group[5] used Clofarabine (30 mg/m^2/day IV × 5 days) as a preconditioning, and (Flu/Cy/Mel+ total body irradiation (TBI)) for haploidentical transplant in high-risk AML patients. In this regimen, again, there were 3 days in between preconditioning (cytoreduction) and conditioning. The median duration of severe neutropenia following the initiation of Clofarabine was 31 days (range, 24–68 days). No patient died

during the very early phase of transplantation including cytoreduction, conditioning, and transplantation procedure. There was no case of Sinusoidal Obstructive Syndrome (SOS). Most commonly seen grade IIII–V toxicities were transient, as elevation of transaminases (44.4%), mucositis (38.9%), skin reactions including hand-foot syndrome (16.7%), creatinine elevation (16.7%), and nausea/vomiting (16.7%)[8].

Locke et al[9, 10] has reported prospective phase II study results of 29 patients given Clofarabine 30 mg/m^2/day IV × 5 days followed immediately by HCT conditioning while at the cytopenic nadir. Toxicities were acceptable, with transient hyperbilirubinemia (48%) and grade 3–4 infections (10%). Post HCT, 180 day non-relapse mortality (NRM) was 7% (95% confidence interval (CI): 1–21), relapse was 29% (95% CI: 13–46) and OS was 71% (95% CI: 51–85), comparing favorably to published data for high-risk patients. There were no cases of veno-occlusive disease. Therefore, Clofarabine used as a bridge to HCT reduces disease burden, is well tolerated, and permits high-risk patients to undergo HCT with acceptable NRM.

Moreover, Dr. Deborah Richardson and colleagues conducted 11 cases of Clofarabine preconditioning in patients with high-risk, refractory acute leukemia or advanced Myelodysplastic Syndrome (MDS). Six patients received even CyTBI conditioning, and five patients received various reduced intensity conditioning. The patients tolerated conditioning well and overall TRM (transplant related mortality) was 8% by one year. One-year overall survival was about 48% in this highly aggressive AML population.[11]

In addition, our group at Penn State Cancer Institute has recently used Clofarabine as preconditioning (cytoreduction), after 3 days followed by Flu/Bu3/total body irradiation (TBI) conditioning for haploidentical stem cell transplant with Post-Transplant Cyclophosphamide (PTCy) in two refractory AML patients. These patients had 45% and 60% bone marrow blasts at the time of transplant, respectively, which usually precludes patients as transplant candidates. Both patients achieved complete remission (CR) after transplant and now both are alive in CR for almost 2 years. Clofarabine was administered 30 mg/m^2/day IV × 5 days. Busulfan was 3-day infusion. Our proposed protocol will utilize a similar regimen except a reduced Busulfan dose.

These regimens are summarized in Appendix B. It has been shown that myeloablative transplant conditioning regimens can be tolerated during nadir after Clofarabine 30-40 mg/m^2 x 5 day treatment. Our proposed regimen in the current study is moderate in terms of intensity compared to published studies.

The lack of available donors, treatment toxicities, and poor responses to salvage chemotherapy results in very few non-remission AML patients proceeding to hematopoietic stem cell transplantation. As stated above, third or subsequent inductions are very unlikely to be successful. Thus, after two induction failures, moving towards transplantation may be desirable. To test this hypothesis, we would like to adopt scheme of stem cell transplantation after two induction failures for patients with haploidentical donors (related) as well as matched and mismatched unrelated donors using clofarabine preconditioning and post-transplant cyclophpsophamide (Fig. 1) to achieve a long-term remission as the goal of AML treatment. Even in the previous Clo/Bu4 studies, we observed a relapse rate of about 45% after achieving the first complete remission[1]. We would like to propose a protocol for non-remission AML and expand the patient population to older than 55 years of age as well as those who relapsed after initial allogeneic transplant to improve enrolling patients in the near future.[12-14] We have many patients achieving remission but for those without remission, clofarabine preconditioning may be a reliable protocol to bring these patients into the early complete remission.

3.0. OBJECTIVES

3.1. **Primary Objective**: The primary objective is to determine the incidence of complete remission (CR) at day +30 post HSCT after Clofarabine followed by HSCT using with post-transplant cyclophosphamide (PTCy).

3.2. Secondary Objectives:

- To determine disease-free survival (DFS) and overall survival (OS)
- To determine the rate of non-relapse related mortality (NRM) at day 100.
- To determine the incidence and severity of acute and chronic graft versus host disease (GVHD).
- To determine the rate of engraftment.

3.3. Primary Endpoint: The primary endpoint of the study will be the CR rate at day 30 post HSCT. The responses will be evaluated as complete remission (CR), Complete Remission with Incomplete Hematologic Recovery (CRi), and relapse (referenced in section 4.5. Disease Criteria).

3.4. Secondary Endpoints

- OS and DFS at one year after HSCT.
- NRM by day 100 after HSCT.
- The incidence and severity of acute and chronic GVHD.
- Rate of engraftment.

4.0. PATIENT SELECTION

4.1. Inclusion Criteria:

1. Diagnostic criteria of AML, induction failure without having achieved remission after at least 2 attempts at induction chemotherapy, or relapsed after any complete remission (CR).
2. 18 to 75 years of age.
3. Planned or scheduled to receive an allogeneic HSCT from haploidentical related donors, matched and mismatched unrelated donors.
4. All organ function testing should be done within 28 days of study registration.
    - *Performance* status: Karnofsky ≥ 70% (Appendix A).
    - Cardiac: LVEF ≥ 50% by MUGA or echocardiogram.
    - Pulmonary: FEV1 and FVC ≥ 50% predicted, DLCO (corrected for hemoglobin) ≥ 50% of predicted.
    - Renal: Creatinine clearance (CrCl) ≥60 mL/min/1.73 m^2
    - Hepatic: *Serum bilirubin ≤1.5 × upper limit of normal (ULN); (AST)/(ALT) ≤2.5 × ULN; Alkaline phosphatase ≤ 2.5 × ULN.*
5. Both men and women need to use an approved method of birth control and/or abstinence due to unknown risks to the fetus.

4.2. Exclusion Criteria

1. Acute promyelocytic leukemia (APL)
2. Known history of non-compliance with medication regimens, scheduled clinic visits, or self-care.
3. In the opinion of the investigator, no appropriate caregivers identified.
4. HIV1 (Human Immunodeficiency Virus-1) or HIV2 positive
5. Active Hepatitis B and Hepatitis C orepatitis positive serology including HBsAg, hepatitis B core antibody, and hepatitis C antibody. Hepatitis B surface antibody positive due to vaccination or natural immunity are permitted.
6. In the opinion of the physician investigator, uncontrolled medical or psychiatric disorders.
7. In the opinion of the physician investigator, uncontrolled infections requiring treatment within 14 days of registration.
8. Active central nervous system (CNS) leukemia.
9. Cord blood transplant excluded.
10. Prior allogeneic transplant within last 6 months.
11. Patients with >= grade 2 acute GVHD.
12. Patients with >= moderate chronic GVHD.
13. Pregnant or breastfeeding. Women of child bearing potential (WOCBP) are required to have a negative serum or urine pregnancy test prior to conditioning regimen.
14. Haploidentical related donors who are positive for DSA ≥ 5000 MFI by solid phase microarray method (Luminex).
15. Any patient with steroid dose more than 10 mg/day within a week of registration.
16. Autoimmune disorder requiring any active immunosuppression therapy.

4.3. Inclusion of Women and Minorities: Adult men and women and members of all races and ethnic groups are eligible for this trial. Pregnant females are excluded as the effect of the HSCT related medications and infusion on a fetus is unknown.

4.4 Consent: The patients must be informed of the investigational nature of this study in accordance with institutional and federal guidelines. Additionally, patients must have the ability to provide written informed consent prior to initiation of any study-related procedures, and ability, in the opinion of the physician investigator, to comply with all the requirements of the study.

4.5. Definitions:

4.5.1. Primary Induction failure: AML without having achieved remission after at least 2 attempts at induction chemotherapy.

4.5.2. Relapsed AML: AML having achieved remission but relapsed within 6 months of induction (early relapse) or relapsed after 6 months post induction therapy (late relapse). Relapse is defined as the recurrence of disease after CR, meeting one or more of the following criteria:

- ≥ 5% blasts in the marrow or peripheral blood
- Extramedullary relapsed disease
- Disease presence determined by a physician upon clinical assessment

4.5.3. AML Not in Remission:

- AML not in remission at the time of transplant ("not in remission" is defined as "more than 5% of bone marrow blasts by smear within 4 weeks prior to starting the first dose of clofarabine.
- If the bone marrow biopsy right before transplant is hypoplastic and cannot determine the blast percentages, the patient is eligible if the preceding bone marrow meets the above criteria.
- Patients with peripheral circulating blasts or patients with extramedullary leukemia are eligible if bone marrow meets above criteria.

4.5.4. Definitions of Response Criteria

4.5.4.1. Hematologic complete remission (CR): defined as meeting all of the following response criteria for at least four weeks from transplant day 0.

- < 5% blasts in the bone marrow
- No blasts with Auer rods
- Normal maturation of all cellular components in the bone marrow
- No extramedullary disease (e.g., CNS, soft tissue disease)
- Neutrophils ≥ 1,000/µL
- Platelets ≥ 100,000/µL
- Transfusion independent

4.5.4.2. Hematologic complete remission with incomplete hematologic recovery (CRi): defined as meeting all of the following response criteria for at least four weeks from transplant day 0.

- < 5% blasts in the bone marrow
- No blasts with Auer rods
- Normal maturation of all cellular components in the bone marrow
- No extramedullary disease (e.g., CNS, soft tissue disease)
- Transfusion independent (Please note, if the physician documents transfusion dependence related to treatment and not the patient's underlying AML, CRi can be reported)

4.6. Donor Selection Criteria:

1. Haploidentical related donors.
2. Matched unrelated donors.
3. Mismatched unrelated donors.
4. Cord blood donor cells are excluded.

5.0. REGISTRATION PROCEDURES

5.1. General Guidelines: Eligible patients will be registered on study by the assigned Study Coordinator within the Penn State Cancer Institute Clinical Trials Office (PSCI-CTO).

6.0. TREATMENT PLAN

6.1. Preparative Regimen

Regimen A: for reduced intensity conditioning is as follows:

Day -14	Clofarabine 30 mg/m^2 IV
Day -13	Clofarabine 30 mg/m^2 IV
Day -12	Clofarabine 30 mg/m^2 IV
Day -11	Clofarabine 30 mg/m^2 IV
Day -10	Clofarabine 30 mg/m^2 IV
Day -9	Rest
Day -8	Rest
Day -7	Rest
Day -6	Fludarabine 40 mg/m^2 IV, Busulfan 3.2 mg/kg IV
Day -5	Fludarabine 40 mg/m^2 IV, Busulfan 3.2 mg/kg IV
Day -4	Fludarabine 40 mg/m^2 IV
Day -3	Fludarabine 40 mg/m^2 IV
Day -2	Rest
Day -1	TBI 200 cGy
Day 0	HSCT
Day 1	Rest
Day 2	Rest
Day 3	Cyclophosphamide 50 mg/kg IV
Day 4	Cyclophosphamide 50 mg/kg IV
Day 5	G-CSF, Tacrolimus, and Mycophenolate Mofetil (MMF) will be started.

Regimen B (Hopkins Regimen based on haploidentical donor protocol): for patients of age 56 to 75 years old, or those who had prior allogenic transplant, or who are not candidate for intense regimen.

Day -14	Clofarabine 30 mg/m^2 IV
Day -13	Clofarabine 30 mg/m^2 IV
Day -12	Clofarabine 30 mg/m^2 IV
Day -11	Clofarabine 30 mg/m^2 IV
Day -10	Clofarabine 30 mg/m^2 IV

Day -9	Rest
Day -8	Rest
Day -7	Rest
Day -6	Fludarabine 24mg/m^2 IV; Cyclophosphamide 14.5 mg/kg IV
Day -5	Fludarabine 24mg/m^2 IV; Cyclophosphamide 14.5 mg/kg IV
Day -4	Fludarabine 24mg/m^2 IV
Day -3	Fludarabine 24 mg/m^2 IV
Day -2	Fludarabine 24mg/m^2 IV
Day -1	TBI 200 cGy
Day 0	HSCT
Day 1	Rest
Day 2	Rest
Day 3	Cyclophosphamide 50 mg/kg IV
Day 4	Cyclophosphamide 50 mg/kg IV
Day 5	G-CSF, Tacrolimus, and Mycophenolate Mofetil (MMF) will be started.

Clofarabine Administration

Prior to administration of clofarabine, the following must occur:

• Drugs with known renal toxicity should be avoided during the 5 days of clofarabine treatment.
• Concomitant use of medications known to induce hepatic toxicity should be avoided.
• Hepatic and renal function should be assessed prior to and during treatment.
• Patients should receive hydration each day of clofarabine treatment.
• To the extent possible, use of nephrotoxic (e.g., vancomycin, amphotericin B, etc.) and hepatotoxic (e.g., voriconazole, cyclosporine, etc.) agents is to be avoided during clofarabine administration.

Pre Medication

Prophylactic steroid administration for this study is Dexamethasone 10 mg IV daily during the 5 days of Clofarabine. The Dexamethasone should be given at least 30 minutes prior to clofarabine initiation.

Assessments for Capillary Leak Syndrome:

The following should be assessed daily during clofarabine administration:

- ≥ grade 2 tachypnea or other evidence of respiratory distress;
- unexplained hypotension;
- unexplained tachycardia

If one or more of the above occur during study drug infusion, clofarabine administration is to be interrupted until the resolution of the symptoms. Thus, if the patient's condition stabilizes or improves, clofarabine administration may resume. Standard infusion time for this dose of clofarabine is planned for 1 hour, however a slower infusion rate over at least 2 hours may be considered with the development of Capillary Leak Syndrome. If prophylactic dexamethasone is given and grade 2 or greater signs or symptoms of Capillary Leak Syndrome develop, it is suggested to increase the dexamethasone dose to 20 mg prior to each subsequent dose upon recovery to grade 1 or lower toxicity. If Capillary Leak Syndrome (grade 2 or greater) recurs despite reducing infusion rate by over 2 hours and increasing Dexamethasone, a 25% dose reduction of the clofarabine should be employed after recovery to grade 1 or lower toxicity.

Anti-Emetics

Clofarabine is moderately emetogenic; therefore, standard anti-emetic therapy such as ondansetron and dexamethasone should be administered prior to use of clofarabine.

Clofarabine Dose Modifications

The trial will start the clofarabine dose of 30 mg/m^2 and use the following stopping rule: if any grade 4 or 5 non-hematological toxicities which are unexpected and related occur in 2 of the first 3 subjects, or 3 of 6, 4 of 9, 5 of 12, 6 of 16 or 7 of 19, then clofarabine will be reduced to 20 mg/m^2 with the next subject enrolled.

Once the dose modification has occurred, re-escalation of clofarabine to 30mg/m^2 is not permitted.

If the dose de-escalates to 20 mg/m^2, the following same stopping rule will be used to ensure subject safety. If any grade 4 or 5 non-hematological toxicities which are unexpected and related occur in the 2 of the first 3, or 3 of 6, 4 of 9, 5 of 12, 6 of 16 or 7 of 19, subjects at the 20 mg/m^2 dose level, the trial will be stopped.

6.2. Anti-Seizure Prophylaxis: Anti-seizure prophylaxis will be administered as per standard practice.

6.3. Infection Prophylaxis and Testing: Antibacterial, antiviral, and antifungal prophylaxis and related blood testing during neutropenia until engraftment will be according to standard practice.

6.4. GVHD Prophylaxis: GVHD prophylaxis consists of post-HSCT Cyclophosphamide, Mycophenolate Mofetil (MMF), and Tacrolimus per standard practice.

6.4.1. Post-Transplant Cyclophosphamide*: Cyclophosphamide* (Cytoxan) will be administered on Day +3 and +4 at 50 mg/kg IV per standard practice.

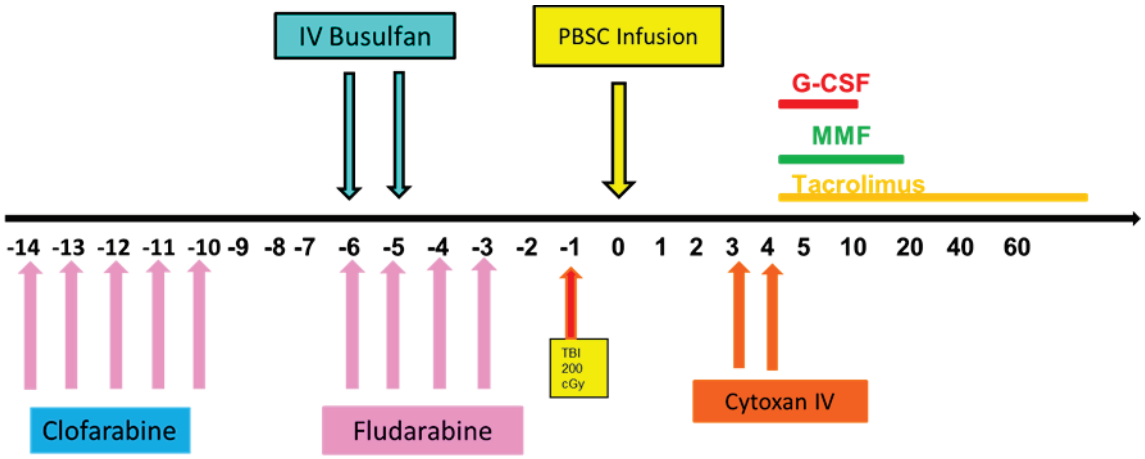
6.4.2. Mycophenolate Mofetil (MMF): MMF will be administered starting day +5 to patients who received transplants from matched related haploidentical donors. Dosing will follow therapeutic standards for this medication. Dosing will initially be intravenous and then change to oral when patient can tolerate oral intake. MMF will be continued until approximately day +35 unless there is active GVHD.

6.4.3. Tacrolimus*:* Tacrolimus will be administered starting on day +5. Dosing will follow therapeutic standards for GVHD prophylaxis. Tacrolimus will be continued until approximately day +180 with taper starting on approximately day +100 unless there is active GVHD.

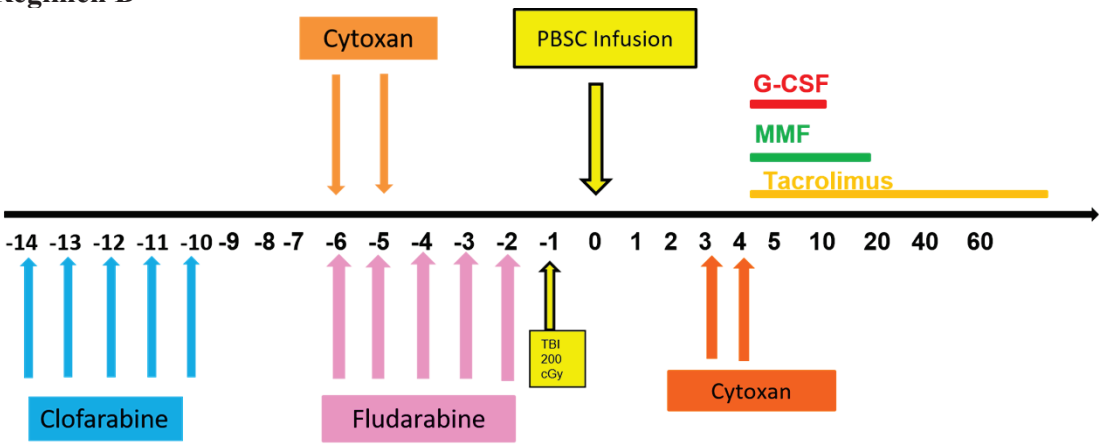
7.0. TREATMENT SCHEMAS:

Figure 1.

Regimen A



Regimen B



8.0. ALLOGENEIC STEM CELL INFUSION: The day of the stem cell/marrow infusion will be defined as day 0. If more than one day of infusion is required, then these days are defined as day 0a and day 0b accordingly. The first day after the last stem cell infusion will be defined as day +1.

Patients will not receive any immunosuppression (unless definitely indicated per the treating physician) between day 0 and day 5 due to concern for mitigating the immuno-suppressive effect of post-transplant Cyclophosphamide (given on days +3 and +4).

8.1. Stem Cell Source: The source of Haploidentical donor stem cells will be peripheral blood stem cells (PBSC) or bone marrow (BM). PBSC will be preferred. Cord blood will not be allowed.

8.2. PBSC Mobilization and Collection: PBSC mobilization and collection procedures and BM collection procedures will follow standard practice.

8.3. Stem Cell Dosing for PBSC Infusions: The recommended stem cell dose is 4-5 x10^6 CD34 cells/kg recipient weight. The minimum accepted stem cell dose is 2 x10^6 CD34 cells/kg recipient weight.

8.4. Stem Cell Dosing for Marrow Infusions: The recommended stem cell dose is 4-5 x10^8 mononuclear cells/kg recipient weight. The minimum accepted stem cell dose is 2 x10^8

mononuclear cells/kg recipient weight.

8.5. Protection of Recipients From Transmission of Infections: Recovery, processing, storage, labelling, packaging and distribution of PBSC and BM, as well as, screening and testing cell and tissue donors for relevant communicable diseases (HIV1, HIV2, hepatitis B, and hepatitis C) will be carried out in a way that prevents the introduction, transmission, or spread of communicable diseases in accordance with 21 CFR 1271 Subpart C (Donor Eligibility) and Subpart D (Current Good Tissue Practice/Section 1271.145: Prevention of the introduction, transmission, or spread of communicable diseases), as per institutional guidelines.

9.0. DRUG INFORMATION

9.1. Clofarabine

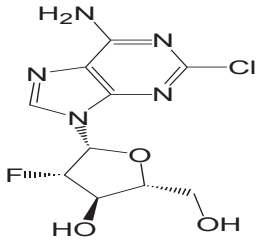
9.1.1. Nomenclature

Chemical Name: 2-chloro-9-(2′-deoxy-2′-fluoro-ß-D-arabinofuranosyl)-9H-purine-6-amine

Other names: CLOLAR; CAFdA; Cl-F-ara-A;
2-chloro-2′-fluoro-deoxy-9-ß arabinofuranosyladenine
2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl) adenine (Cl-F-ara-A)
2-chloro-2′-arabino-fluoro-2′-deoxyadenosine
2-chloro-2′-ara-fluorodeoxyadenosine (CAFdA)
2-chloro-2′-fluorodeoxyadenosine (CAFdA)

9.1.2. Molecular Structure

$C_{10}H_{11}ClFN_5O_3$



9.1.3. Physical and Chemical Characteristics: Clofarabine is a white to off-white solid with a melting point of 228°C to 230°C and a molecular weight of 303.5 g/mol. The drug substance is very stable in the dry state, and aqueous solutions are stable to heat treatment. Clofarabine is freely soluble in water (1.5 mg/mL) or buffered solutions at room temperature. Clofarabine is not less than 97% pure on a dried basis by high performance liquid chromatography (HPLC) analysis.

Clofarabine is formulated at a concentration of 1 mg/mL. Clofarabine is supplied in 1 vial size: a 20 mL clear, glass vial with gray stopper and blue flip off seal. The 20-mL vials contain 20 mL (20 mg) of sterile solution. The pH range of the solution is 4.5 to 7.5. The solution is clear and practically colorless, preservative free, and free from foreign matter.

9.1.4. Storage and Handling: Vials containing undiluted Clofarabine for injection should be stored at controlled room temperature. The commercial expiry period for Clolar (Clofarabine)

is 24 months at room temperature. Ongoing stability studies will continue to confirm the appropriate quality of drug product used for clinical trials beyond 24 months.

Clofarabine for injection should be diluted with 0.9% sodium chloride injection USP or European Pharmacopeia (EP) normal saline (NS) or 5% dextrose injection (D5W) USP or EP prior to IV infusion. The resulting admixture may be stored at room temperature, but must be used within 24 hours of preparation.

9.1.5. Toxicity: Adult Patients: Drug-related adverse effects observed in at least 10% of adult patients treated with Clofarabine in previous clinical trials include myelosuppression, nausea, vomiting, infections, fatigue, headache, diarrhea, rigors, dermatitis, anorexia, febrile neutropenia, myalgia, asthenia, petechiae, transient elevated liver enzymes, stomatitis, mucositis, pyrexia, flushing, constipation, edema, dehydration, nervousness, stomach pain, insomnia, depression, dry skin, back pain, and decreased weight.[8]

Adverse effects reported in <10% of adult patients include tumor lysis syndrome, capillary leak syndrome, palmar plantar erythrodysesthesia, pancreatitis, seizures, irregular heartbeat, edema, pericardial effusion, multi-organ failure, Stevens Johnson syndrome, and death. [B]

9.1.6. Guidelines for Clofarabine Administration*:* Clofarabine should be diluted with NS or D5W prior to administering by IV infusion. The dosage is based on the patient's body surface area (BSA), calculated using the actual height and weight before the start of each cycle. The timing for the infusion will be as per standard practices for this medication. To prevent drug incompatibilities, no other medications should be administered through the same IV line. Drug dosages can be rounded to the nearest integer per standard practice.

Clofarabine Administration

Prior to administration of clofarabine, the following must occur:

- Drugs with known renal toxicity should be avoided during the 5 days of clofarabine treatment.
- Concomitant use of medications known to induce hepatic toxicity should be avoided.
- Hepatic and renal function should be assessed prior to and during treatment.
- Patients should receive hydration each day of clofarabine treatment.
- To the extent possible, use of nephrotoxic (e.g., vancomycin, amphotericin B, etc.) and hepatotoxic (e.g., voriconazole, cyclosporine, etc.) agents is to be avoided during clofarabine administration.

Pre Medication

Prophylactic steroid administration for this study is Dexamethasone 10 mg IV during the 5 days of Clofarabine. The Dexamethasone should be given at least 30 minutes prior to clofarabine initiation.

Assessments for Capillary Leak Syndrome:

The following should be assessed daily during clofarabine administration:

- ≥ grade 2 tachypnea or other evidence of respiratory distress;
- unexplained hypotension;
- unexplained tachycardia

If one or more of the above occur during study drug infusion, clofarabine administration is to be interrupted until the resolution of the symptoms. Thus, if the patient's condition stabilizes or improves, clofarabine administration may resume. Standard infusion time for this dose of clofarabine is planned for 1 hour, however a slower infusion rate over at least 2 hours may be considered with the development of Capillary Leak Syndrome. If prophylactic dexamethasone is given and grade 2 or greater signs or symptoms of Capillary Leak Syndrome develop, it is suggested to increase the dexamethasone dose to 20 mg prior to each subsequent dose upon recovery to grade 1 or lower toxicity. If Capillary Leak

Syndrome (grade 2 or greater) recurs despite reducing infusion rate by over 2 hours and increasing Dexamethasone, a 25% dose reduction of the clofarabine should be employed after recovery to grade 1 or lower toxicity.

Anti-Emetics
Clofarabine is moderately emetogenic; therefore, standard anti-emetic therapy such as ondansetron and dexamethasone should be administered prior to use of clofarabine.

Clofarabine Dose Modifications

The trial will start the clofarabine dose of 30 mg/m^2 and use the following stopping rule: if any grade 4 or 5 non-hematological toxicities which are unexpected and related occur in 2 of the first 3 subjects, or 3 of 6, 4 of 9, 5 of 12, 6 of 16 or 7 of 19, then clofarabine will be reduced to 20 mg/m^2 with the next subject enrolled.

Once the dose modification has occurred, re-escalation of clofarabine to 30mg/m^2 is not permitted.

If the dose de-escalates to 20 mg/m^2, the following same stopping rule will be used to ensure subject safety. If any grade 4 or 5 non-hematological toxicities which are unexpected and related occur in the 2 of the first 3, or 3 of 6, 4 of 9, 5 of 12, 6 of 16 or 7 of 19, subjects at the 20 mg/m^2 dose level, the trial will be stopped.

9.2. Fludarabine (Fludara®)

General: Fludarabine phosphate (Fludarabine) is an antimetabolite with chemical name 9H-Purin-6-amine, 2-fluoro-9-(5-0-phosphono- 0-D-arabino-furanosyl) (2-fluoro-ara-AMP). The molecular formula is C10H13FN5O7P with molecular weight of 365.2.

Toxicity:

Toxicities reported as more than 10% incidence include: Myelosuppression (neutropenia, thrombocytopenia, and anemia), fever and chills, infections, nausea and vomiting, pain, weakness, cough, pneumonia, dyspnea, diarrhea, anorexia, rash, edema.

Toxicities with expected incidences between 1% and 10% include: Malaise, stomatitis, myalgia, paresthesia, visual disturbance, gastrointestinal bleeding, upper respiratory infection, diaphoresis, dysuria, urinary infection, sinusitis, hearing loss, hyperglycemia, headache, pharyngitis, hemoptysis, esophagitis, mucositis, hematuria, osteoporosis, alopecia, anaphylaxis, hemorrhage, dehydration, sleep disorder, depression, cerebellar syndrome, impaired mentation, allergic pneumonitis, epistaxis, bronchitis, hypoxia, liver failure, abnormal liver function, cholelithiasis, ARDS, respiratory distress, pulmonary hemorrhage, pulmonary fibrosis, respiratory failure, constipation, dysphagia, pruritus, seborrhea, renal failure, abnormal, renal function test, proteinuria, hesitancy, angina, congestive, heart failure, arrhythmia, supraventricular tachycardia, myocardial infarction, deep venous thrombosis, phlebitis, transient ischemic attack, aneurysm, cerebrovascular accident, arthralgia, tumor lysis syndrome.

Available Forms: IV Fludarabine is packaged as a white lyophilized solid cake in a vial. Each vial has 50 mg Fludarabine phosphate and only one vial is enclosed per carton. Unopened vials of fludarabine should be stored at 20° to 25°C (68° TO 77°F); excursions permitted between 15° to 30°C (59° TO 86°F).

Reconstitution and Administration: IV Fludarabine is prepared by adding sterile water to

the white solid cake. Reconstituted in 2mL of sterile water, the solid cake produces a solution with approximate concentration of 25mg/mL Fludarabine phosphate. Standard practice for preparation and administration procedures of Fludarabine will be followed. Reconstituted drug contains no antimicrobial preservative hence should be utilized within 8 hours of reconstitution. DO NOT infuse concomitantly with another intravenous solution of unknown compatibility.

9.3 Cyclophosphamide (Cytoxan®)

General: Cyclophosphamide monohydrate (cyclophosphamide) is a synthetic antineoplastic drug chemically recognized as 2-[bis(2-cholorethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate. The molecular formula of cyclophosphamide is C7H15Cl2N2O2P·H2O with a molecular weight of 279.1 g/mol. Unopened vials should be stored at or below 25°C (77°F).

Mechanisms of Action: A multistep process activates it by conversion to 4 hydroxycyclophosphamide by the liver microsomal oxidase system and to aldophosphamide by tautomerization in the peripheral tissues. Aldophosphamide spontaneously degrades into acrolein and phosphoramide mustard, which cause cellular glutathione depletion and DNA alkylation. This results in inhibition of DNA replication and transcription. Cells expressing high levels of aldehyde dehydrogenase (e.g. stem cells, L1210 leukemia cells) resist cyclophosphamide-mediated cytotoxicity as aldophosphamide is inactivated by this enzyme. The drug also does not affect quiescent cells and therefore stem cells are generally protected, an important factor if autologous hematopoietic recovery is relied on in the event of graft failure.

Metabolism: Cyclophosphamide is broken down as described above and the breakdown products are excreted by the kidneys. It is a substrate of CYP2A6 (minor), CYP2B6 (major), CYP2C19 (minor), CYP2C9 (minor), CYP3A4 (minor); Note: Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; Inhibits CYP3A4 (weak); Induces CYP2B6 (weak/moderate), CYP2C9 (weak/moderate).

Incompatibilities: Phenobarbital or rifampin may increase the toxicity of cyclophosphamide. Concurrent allopurinol or thiazide diuretics may exaggerate bone marrow depression, may prolong neuromuscular blockade from succinylcholine cardiotoxicity, may be additive with other cardio toxic agents (cytarabine, daunorubicin, doxorubicin) and may decrease serum digoxin levels. Additive bone marrow depression with other antineoplastics, or radiation therapy, may potentiate the effects of warfarin. Other incompatibilities include possible decreased antibody response to live-virus vaccines and increased risk of adverse reactions, as well as, prolongation of the effects of cocaine.

Toxicity:

Common side effects of cyclophosphamide include: nausea, vomiting, alopecia, leucopenia, interstitial pneumonitis, interstitial pulmonary fibrosis, anaphylactic reactions, amenorrhea, hemorrhagic cystitis, oligospermia or azoospermia and suppression of immune responses. Less common side effects include: secondary malignancies in patients diagnosed with a primary malignancy, fetal harm when administered to pregnant women, acute cardiac toxicity, congestive heart failure, hemorrhagic myocarditis, hemopericardium, and possible cross sensitivity with other alkylating agents. Additional less common side effects include: water retention due to inappropriate secretion of anti-diuretic hormone (SIADH), cardiomyopathy with myocardial necrosis, congestive heart failure, hemorrhagic cystitis, alopecia, skin rash, pulmonary fibrosis, and sterility.

Available Forms: IV Cyclophosphamide is available as a sterile white crystalline powder.

Cyclophosphamide is stored in a single dose vial with 500mg of the powder.

Reconstitution and Administration: Cyclophosphamide for parenteral use must be prepared by either adding 0.9% sodium chloride solution, if injected directly, or sterile water, if infused. Constituted in water, Cyclophosphamide is hypotonic, hence should not be injected directly. Solutions of Cyclophosphamide with sodium chloride solution may be injected, intravenously, intramuscularly, intraperitoneally, or intrapleurally. Constituted Cyclophosphamide is physically and chemically stable for 24 hours at room temperature or six days refrigerated. Prepared solutions do not contain any microbial preservative; hence sterility of the solutions should be monitored.

9.4 Busulfan (Busulfex®):

General: Busulfan is a bifunctional alkylating agent known chemically as 1,4-butanediol, dimethanesulfonate with a molecular formula of CH3SO2O(CH2)4OSO2CH3 and a molecular weight of 246 g/mol.

Toxicity:

Toxicities reported as more than 10% incidence include: Tachycardia, hypertension, edema, thrombosis, chest pain, vasodilation, hypotension, insomnia, fever, anxiety, headache, chills, pain, dizziness, depression, confusion, rash, pruritus, alopecia, hypomagnesemia, hyperglycemia, hypokalemia, hypocalcemia, hypophosphatemia, nausea, mucositis/stomatitis, vomiting, anorexia, diarrhea, abdominal pain, dyspepsia, constipation, xerostomia, rectal disorder, abdominal fullness, myelosuppression, neutropenia, thrombocytopenia, lymphopenia, anemia, hyperbilirubinemia, ALT increase, veno-occlusive disease, jaundice, injection site inflammation, injection site pain, weakness, back pain, myalgia, arthralgia, creatinine increased, oliguria, rhinitis, lung disorder, cough, epistaxis, dyspnea, pneumonia, hiccup, pharyngitis, infection, allergic reaction.

Toxicities with expected incidences are 1% to 10% include: Arrhythmia, cardiomegaly, atrial fibrillation, ECG abnormality, heart block, heart failure, pericardial effusion, tamponade, ventricular extrasystoles, hypervolemia, lethargy, hallucinations, agitation, delirium, encephalopathy, seizure, somnolence, cerebral hemorrhage, vesicular rash, vesiculobullous rash, skin discoloration, maculopapular rash, acne, exfoliative dermatitis, erythema nodosum, hyponatremia, ileus, weight gain, hematemesis, pancreatitis, prothrombin time increase, hepatomegaly, hematuria, dysuria, hemorrhagic cystitis, BUN increase, asthma, alveolar hemorrhage, hyperventilation, hemoptysis, pleural effusion, sinusitis, atelectasis, hypoxia.

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

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

9.5 Tacrolimus (Prograf®):

General: Tacrolimus is a macrolide immunosuppressant produced by Streptomyces Tsukubaensis. Tacrolimus has an empirical formulation of C44H69NO12-H2O and a formula

weight of 822.05 g/mol. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

Mechanisms of Action: Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin is inhibited. This effect may prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression).

Toxicity:

Possible side effects of Tacrolimus include: Depressed kidney function, high blood sugar, high blood potassium, skin rash, headache, nausea, vomiting.

Less common side effects include: Loss of appetite, sleep disturbances, vivid dreams, hallucinations, high blood pressure, seizure, decreased level of consciousness, anemia, agitation, tremors, irritability, slurred speech, tingling in the hands and feet, pain in the palms and soles of the feet, weakness, and abnormal blood cell levels. All of these side effects are reversible by reducing the dose or discontinuing the drug. Rare fatal cases of severe allergic reactions have been reported in patients receiving Cyclosporine and it is possible that similar reactions could also occur in patients receiving tacrolimus.

Available Forms: Tacrolimus is available for oral administration as capsules (Tacrolimus capsules) containing the equivalent of 0.5 mg, 1 mg and 5 mg of anhydrous Tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. The 0.5 mg and 1 mg capsule shell contains gelatin and titanium dioxide, and the 5 mg capsule contains gelatine, titanium dioxide, and ferric oxide. Tacrolimus is also available as a sterile solution (tacrolimus injection) containing the equivalent of 5 mg anhydrous Tacrolimus in 1 mL for administration by IV infusion only. Each mL contains polyoxyl 60 hydrogenated castor oil (HCO-60), 200 mg, and dehydrated alcohol, USP, 80.0% v/v.

Tacrolimus capsules should be stored at room temperature between 15° and 30°C (59° and 86°F). Tacrolimus injection should be stored between 5° and 25°C (41° and 77°F).

Reconstitution and Administration: Tacrolimus (Prograf injection) must be diluted with NS or D5W before use. Tacrolimus is administered as a continuous infusion. Oral preparation will be administered on empty stomach every 12 hours.

9.6 Mycophenolate Mofetil (MMF, CellCept):

General: CellCept (Mycophenolate Mofetil) is the 2-morpholinoethyl ester of mycophenolic acid (MPA); an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor. The chemical name for mycophenolate mofetil (MMF) is 2-morpholinoethyl (E)-6-(l,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate. It has an empirical formula of C23H31NO7 a molecular weight of 433.50 g/mol. Mycophenolate Mofetil is a white to off-white crystalline powder. It is slightly soluble in water (43 µg/mL at pH 7.4); the solubility increases in acidic medium (4.27 mg/mL at pH 3.6). It is freely soluble in acetone, soluble in methanol, and sparingly soluble in ethanol. The apparent partition coefficient in 1-octanol/water (pH 7.4) buffer solution is 238. The pKa values for mycophenolate mofetil are 5.6 for the morpholino group and 8.5 for the phenolic group.

Mycophenolate mofetil hydrochloride has a solubility of 65.8 mg/mL in D5W. The pH of the reconstituted solution is 2.4 to 4.1.

Mechanisms of Action: Inhibits the enzyme inosine monophosphate dehydrogenase, which is involved in purine synthesis. This inhibition results in suppression of T- and B-lymphocyte proliferation.

Metabolism: Following oral and IV administration, mycophenolate is rapidly hydrolyzed to mycophenolic acid (MPA), its active metabolite. Distribution is unknown. MPA is extensively metabolized; <1% excreted unchanged in urine. Some enterohepatic recirculation of MPA occurs. Half Life: MPA¾17.9 hr.

Incompatibilities: Combined use with Azathioprine is not recommended as, the effects are unknown. Acyclovir and Ganciclovir compete with MPA for renal excretion and, in patients with renal failure, may increase each other's toxicity. Magnesium and aluminum hydroxide antacids decrease the absorption of MPA; therefore, subjects should avoid simultaneous administration. Cholestyramine and colestipol decrease the absorption of MPA; therefore, subjects should avoid concurrent use. Toxicity may be increased by salicylates. Use of MMF may interfere with the action of oral contraceptives. As a result of this interference, additional contraceptive method should be used. Use of MMF may also decrease the antibody response to and increase risk of adverse reactions from live-virus vaccines, although influenza vaccine may be useful. When administered with food, peak blood levels of MPA are significantly decreased.

Toxicity:

Toxicities reported as more than 20% incidence include: Hypertension, hypotension, peripheral edema, chest pain, tachycardia, pain, headache, insomnia, fever, dizziness, anxiety, rash, hyperglycemia, hypercholesterolemia, hypomagnesemia, hypokalemia, hypocalcemia, hyperkalemia, abdominal pain, nausea, diarrhea, constipation, vomiting, anorexia, dyspepsia, urinary tract infection, leukopenia, anemia, leukocytosis, thrombocytopenia, liver function tests abnormality, ascites , back pain, weakness, tremor, paresthesia, abnormal kidney function, dyspnea, respiratory tract infection, pleural effusion, cough, lung disorder, sinusitis, infection, sepsis, lactate dehydrogenase increase.

Toxicities with expected incidences are 3% to 20% include:

Angina, arrhythmia, arterial thrombosis, atrial fibrillation, atrial flutter, bradycardia, cardiac arrest, cardiac failure, CHF, extrasystole, facial edema, hyper-/hypovolemia, pallor, palpitation, pericardial effusion, peripheral vascular disorder, postural hypotension, supraventricular extrasystoles, supraventricular tachycardia, syncope, thrombosis, vasodilation, vasospasm, venous pressure increased, ventricular extrasystole, ventricular tachycardia, chills with fever, confusion, delirium, depression, emotional lability, hallucinations, hypoesthesia, malaise, nervousness, psychosis, seizure, somnolence, thinking abnormal, vertigo , acne, alopecia, bruising, cellulitis, fungal dermatitis, hirsutism, petechiae, pruritus, skin carcinoma, skin hypertrophy, skin ulcer, vesiculobullous rash, acidosis, alkalosis, Cushing's syndrome, dehydration, diabetes mellitus, gout, hypercalcemia, hyper-hypophosphatemia, hyperlipidemia, hyperuricemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, hypothyroidism, parathyroid disorder, abdomen enlarged, dysphagia, esophagitis, flatulence, gastritis, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, gum hyperplasia, ileus, melena, mouth ulceration, oral moniliasis, stomach disorder, stomach ulcer, stomatitis, xerostomia, weight gain/loss, impotence, nocturia, pelvic pain, prostatic disorder, scrotal edema, urinary frequency, urinary incontinence, urinary retention, urinary tract disorder, coagulation disorder, hemorrhage, neutropenia, pancytopenia, polycythemia, prothrombin time

increased, thromboplastin time increase, alkaline phosphatase increased, bilirubinemia, cholangitis, cholestatic jaundice, GGT increased, hepatitis, jaundice, liver damage, transaminases increase, abscess, arthralgia, hypertonia, joint disorder, leg cramps, myalgia, myasthenia, neck pain, neuropathy, osteoporosis, amblyopia, cataract, conjunctivitis, eye hemorrhage, lacrimation disorder, vision abnormality, deafness, ear disorder, ear pain, tinnitus, albuminuria, creatinine increased, dysuria, hematuria, hydronephrosis, oliguria, pyelonephritis, renal failure, renal tubular necrosis, apnea, asthma, atelectasis, bronchitis, epistaxis, hemoptysis, hiccup, hyperventilation, hypoxia, respiratory acidosis, pharyngitis, pneumonia, pneumothorax, pulmonary edema, pulmonary hypertension, respiratory moniliasis, rhinitis, sputum increased, voice alteration, thirst. Women of child bearing potential will be evaluated and consented per REMS guidelines.

Available Forms: CellCept is available for oral administration as capsules containing 250 mg of Mycophenolate Mofetil, tablets containing 500 mg of Mycophenolate Mofetil, and as a powder for oral suspension, which when constituted contains 200 mg/mL MMF.

Reconstitution and Administration: Oral dosage formulations (tablet, capsule, suspension) should be administered on an empty stomach to avoid variability in MPA absorption. The oral solution may be administered via a nasogastric tube (minimum 8 French, 1.7 mm interior diameter); oral suspension should not be mixed with other medications. Delayed release tablets should not be crushed, cut, or chewed.

Intravenous solutions should be administered over at least 2 hours through either peripheral or central vein. Administration of intravenous solution should not occur by rapid or bolus injection.

9.7 Filgrastim (Neupogen®)/Biosimilar Filgrastim:

General: Neupogen is the trademark name for Filgrastim, representing recombinant methionyl human granulocyte colony-stimulating factor (r-methHuG-CSF). Neupogen is a 175 amino acid protein produced by recombinant DNA technology utilizing Escherichia coli (E. coli). Neupogen has molecular weight 18,800 daltons and an amino acid sequence similar to that of natural human DNA except for the additional methionine at the N-terminal, necessary for expression in E. coli. Use of either Filgrastim (Neupogen®)or Biosimilar Filgrastim as a growth factor support until engraftment is appropriate in this study.

Toxicity:

Common side effects include: nausea, vomiting, skeletal pain, spontaneous reversible elevations in uric acid, lactate dehydrogenase and alkaline phosphatase, alopecia, palpable splenomegaly and petechiae.

Other side effects include: diarrhea, neutropenic fever, mucositis, fever, fatigue, thrombocytopenia, anorexia, dyspnea, headache, epistaxis, transfusion reaction, cough, skin rash, chest pain, generalized weakness, sore throat, stomatitis, pain, myocardial infarctions, constipation, arrhythmias, hypotension, hemorrhagic events, renal insufficiency, capillary leak syndrome, hepatomegaly, arthralgia, osteoporosis, cutaneous vasculitis, hematuria/proteinuria, exacerbation of some pre-existing skin disorders, splenic rapture, sickle cell crisis, Sweet's syndrome and decreased bone density.

Available Forms: Neupogen is marketed as a sterile, clear, colorless preservative-free liquid. It is packaged in vials and prefilled syringes. The vials are single-dose, preservative-free and contain 300 mcg/mL of Filgrastim. The prefilled syringes are single-dose, preservative free and hold 600 mcg/mL of Filgrastim. Neupogen must be stored refrigerated at 2° to 8°C (36° TO

46°F). Avoid shaking. Preceding injection, Neupogen must reach room temperature for at most 24 hours. Discard any vials or prefilled syringes left at room temperature for more than 24 hours. Avoid use if particulate matter or discoloration is observed prior to administration

Reconstitution and Administration: Neupogen may be administered as an IV or a subcutaneous infusion. It is recommended that Neupogen be administered at least 24 hours after bone marrow infusion, with dosage modifications determined by neutrophil response. If necessary, Neupogen maybe diluted in 5% dextrose with addition of albumin (human) to prevent absorption to plastic materials. Dilution to final concentration less than 5 mcg/mL is not recommended at any time. Do not dilute with saline as product may precipitate. When using either vials or prefilled syringes, do not save unused drugs for later administration. Dispose of all unused portions.

Filgrastim (G-CSF) will be administered per therapeutic standard of care beginning Day +5 at approximately 5 mcg/kg with rounding to the nearest vial size permitted. Treatment will continue until engraftment. Additional doses may be given at the discretion of the treating physician.

9.8 Total Body Irradiation (TBI):

General: TBI shall be administered in accordance with the American College of Radiology-American Society for Radiation Oncology (ACR-ASTRO) Practice Guideline for the Performance of Total Body Irradiation. The subject will be evaluated by a qualified radiation oncologist prior to initiation of TBI, and the plan of care communicated with the referring physician and other physicians involved in the subject's care. The recipient's diagnosis, relevant medical history including pre-existing comorbid conditions, and proposed preparative regimen will be made available to the radiation oncologist in writing. The radiation oncologist's clinical evaluation will be documented in the electronic medical record and will address any prior radiation treatment the recipient may have received, any other factors that may increase the toxicity of radiation, and will describe a plan for delivery of radiation treatment.

After obtaining informed consent for TBI, a planning simulation in the anticipated treatment position will be performed for the subject. The treatment position will be determined by the radiation oncologist in collaboration with the medical physicist and radiation therapist. Physical measurements of the subject at multiple locations for both anterior-posterior and lateral separations will be taken by the medical physicist and radiation therapist. The radiation prescription will be 200 cGy in 1 fraction prescribed to the midline at the level of the umbilicus. For low-dose TBI used on this protocol, organ shielding such as lung blocks will not be routinely utilized. Individual subject specific considerations such as prior radiotherapy or clinically significant pulmonary comorbidities may warrant organ shielding at the discretion of the radiation oncologist.

Calculations will be performed by a qualified medical dosimetrist or medical physicist to determine the beam-on time necessary to achieve the prescribed dose. Consideration will be given to differences in the subject's separation in different body regions with the resulting dose heterogeneities. The dose rate will be kept to <0.2 Gy per minute to reduce risk of interstitial pneumonitis.

TBI will be delivered on Day –1 per protocol. Verification simulation will be performed in the treatment position prior to treatment. A treatment margin of at least 5 cm around the subject will be verified. A beam spoiler will be used to prevent skin sparing. The subject setup will be reviewed by the radiation oncologist including any organ block placement verification imaging if applicable. The subject will be treated according to the approved simulation and treatment plan

instructions by at least two licensed radiation therapists under the direct supervision of the radiation oncologist. The radiation treatment team will follow neutropenic precautions including proper hand hygiene and the use of facial masks throughout the pre-treatment setup and TBI treatment delivery.

All treatment planning and delivery documents will be maintained the radiation oncology electronic medical record.

Toxicity: TBI will be administered per standard practice as implemented by radiation oncologists. TBI alone for post-pubescent subjects with dose/fractionation not exceeding 2 Gy x 6 is well within the tolerance of most normal organs for <5% risk of severe late toxicity (organ failure or major dysfunction) by 5 years. Notable exceptions are risk of cataract development, bone marrow suppression, ovarian and testicular dysfunction. Also, there is a small risk of second malignancy. The most common acute effects include nausea, vomiting, diarrhea, and painful swelling of the parotid glands.

When TBI is given in conjunction with other therapies in the transplant setting, there is additional risk of side effects including loss of appetite, dry mouth, difficult or painful swallowing, headache, stomatitis (sore throat/mouth), altered skin integrity, hair loss, swelling, increased risk for infection and/or bleeding, possible lung failure, dry cough, fatigue, anxiety, fever, possible liver failure, lung scarring, loss of vision, shortness of breath, sterility, heartburn, cystitis, sleep disturbances altered gastrointestinal, genitourinary, and endocrine function, neuropathy, fistulas, pericarditis and increased risk of a second cancer.

Overall, the incidence of most major toxicities when radiation is given in conjunction with other therapy as outlined above is still low, but rare, serious side effects are possible.

10.0 LABORATORY EVALUATIONS, CORRELATIVE AND SPECIAL STUDIES

10.1. Laboratory Correlative Studies

10.1.1. Chimerism Study After Stem Cell Transplant

After HSCT, donor cells and recipient cells co-exist for a while in a condition called mixed chimera. As time goes by, the donor cells become dominant if engraftment is successful. Once recipient cells are no longer detected (>95% donor), it is called complete donor-type chimera. At PSCI's Bone Marrow Transplant (BMT) program, whole blood and T-cell chimerism are tested as a part of standard practice. T-cell chimerism may be more predictive of the fate of graft (complete chimerism, rejection, and possibly relapse of underlying diseases).

Results of routine chimerism studies will be entered into the study database. Laboratory testing for chimerism evaluation will be obtained by the inpatient or outpatient clinical team and submitted to the Penn State HLA Laboratory for standard processing. Guidelines for chimerism processing is noted below.

- DNA extraction is performed by automated DNA extractor, EZ1 Advanced XL (Qiagen), using EZ1 DNA Blood kit for whole blood DNA and EZ1 DNA tissue kit for T-cell DNA.
- Donor/recipient pre-and post-HSCT chimerism are evaluated for 22 short-tandem repeat (STR) markers of by PowerPlex Fusion System (200) (Promega). PCR products are analyzed by 3130XL genetic analyzer (Applied Biosystems). Post-HSCT % donor is evaluated using Gene Mapper Software

(Thermo Fisher) and determined as an average of the % donor from the 5 informative markers (loci where genotype is distinctive between donor/recipient).

11.0. REQUIRED EVALUATIONS AND INTERVENTIONS (Appendix C):

11.1. Screening (within 28 days of Registration)

- Informed Consent
- Assessment of eligibility
- Medical history
- Full physical examination
- Height (collected at Screening only)
- Weight
- Vital signs (including blood pressure, heart rate, temperature, respiratory rate and oxygen saturation)
- ECG
- PFTs and Echocardiogram or MUGA within 2 months of registration
- HIV1, HIV2, hepatitis B, hepatitis C
- Serum pregnancy test (within 7 days of initiation of Clofarabine (Day -14))
- Coagulation test (PT/INR)
- Karnofsky status (Appendix A; within 14 days of Registration)
- Bone marrow biopsy and aspirate to assess morphology and cytogenetics
- Complete Blood Count (CBC) with differential
- Complete Metabolic Profile (CMP) includes Albumin, Alkaline Phosphatase, ALT, AST, Bicarbonate, Calcium, Chloride, Glucose, Magnesium, Potassium, Sodium, Total Bilirubin and Total Protein
- LDH and uric acid
- Concomitant medications

11.2 Pre-Transplant (Day -14 to Day -1)

The following pre-HSCT evaluations and assessments are standard for evaluation of candidacy for HSCT at Penn State Health.

Day -14

- Physical examination (modified or limited exams may be completed)
- Weight
- Vital signs (including blood pressure, heart rate, temperature, respiratory rate and oxygen saturation)
- Assessment of AEs
- Karnofsky status
- CBC with differential (to be added if WBC > 500/ul)
- CMP
- LDH and uric acid
- Concomitant medications

Day -13 to Day -1

- Physical examination (modified or limited exams may be completed; daily)
- Assessment of AEs (daily)
- CBC with differential (daily) (to be added if WBC > 500/ul)
- CMP (daily)
- LDH and uric acid (daily)
- Clofarabine: 5 days (Day -14 to Day -10)
- Fludarabine: 4 days (Day -6 to Day -3) for Regimen A, 5 days (Day -6 to Day -2) for Regimen B
- Busulfan: 2 days (Day -6 and Day -5) only for Regimen A
- Cyclophosphamide: 2 days (Day -6 and Day -5) only for Regimen B
- TBI 200 cGy: 1 day (Day -1)
- Concomitant medications (daily)

11.3 HSCT (Day 0)

- Physical examination (modified or limited exam may be completed)
- Weight
- Vital signs (including blood pressure, heart rate, temperature, respiratory rate and oxygen saturation)
- Assessment of AEs
- Karnofsky status
- CBC with differential (to be added if WBC > 500/ul)
- CMP
- LDH and uric acid
- Hematopoietic Stem Cell Transplant
- Concomitant medications

11.4 Post-Transplant

Post-Transplant (Day +3, Day +4, Day +5)

- Assessment of AEs (daily)
- ECG (Day +3 and Day +4 only)
- CBC with differential (three times a week) (to be added if WBC > 500/ul)
- CMP (three times a week)
- LDH and uric acid (three times a week)
- Cyclophosphamide (50mg/kg): 2 days (Day +3 and Day +4 only)
- Tacrolimus and Mycophenolate Mofetil: Start on Day +5
- Filgrastrim (G-CSF): Start on Day +5
- Concomitant medications (daily)

Post-Transplant (Day +6 to Day +29)

- Assessment of AEs
- CBC with differential -three times a week until neutrophil engraftment or day +30 whichever occurs first (to be added if WBC > 500/ul)
- CMP - three times a week until neutrophil engraftment or day +30 whichever occurs first
- LDH and uric acid - three times a week until neutrophil engraftment or day +30 whichever occurs first
- GVHD assessments: GVHD will be assessed weekly (±3 days) to 100 days post-HSCT. then will be assessed monthly (±14 days) to Year +1
- Concomitant medications (three times a week)

Post-Transplant (Day +30 (± 7 days))

- Physical examination (modified or limited exams may be completed)
- Weight
- Vital signs (including blood pressure, heart rate, temperature, respiratory rate and oxygen saturation)
- Assessment of AEs
- Karnofsky status (Appendix A)
- Concomitant medications
- Disease assessment
- CBC with differential – until neutrophil engraftment or day +30 whichever occurs first
- CMP-until neutrophil engraftment or day +30 whichever occurs first
- LDH and uric acid-until neutrophil engraftment or day +30 whichever occurs first
- GVHD assessments
- Bone marrow biopsy and aspirate to assess morphology and cytogenetics
- Chimerism studies

11.5 Follow-Up (Day +100 (±14 days), Day +180 (±21 days), Year +1 (±30 days))

- Participants who relapse after transplant will be followed for survival only
- Physical examination (modified or limited exams may be completed)
- Weight
- Vital signs (including blood pressure, heart rate, temperature, respiratory rate and oxygen saturation)
- Karnofsky status (Appendix A)
- Disease assessment
- Bone marrow biopsy and aspirate to assess morphology and cytogenetics
- Chimerism studies
- CBC with differential
- CMP

- GVHD assessments

11.6 Follow-Up (Yearly for 5 years (±30 days))

- Survival and disease status for all subjects

11.7 Relapse

- Bone marrow biopsy and aspirate to assess morphology and cytogenetics
- Subjects that relapse will be followed for survival only

11.8 EOS (End of Study)

Subjects who relapse or start maintenance any time after Day +30 will be taken off study. Progression and survival should only be performed once the subject off study, either from progression or the subjects have completed the trial. For those that have progressed, it should be every six months for the first year then annually for five years. For those that have completed the trial, it should be every six months from end of study for the first year then annually for five years.

11.9 Assessment of GVHD

Acute GVHD typically occurs after engraftment of the stem cells. Clinical assessment for acute GVHD will start after infusion of the stem cells on Day 0. There are 2 grading systems used for acute GVHD: the modified Keystone (Glucksberg) and consensus criteria (grades I-IV). Both systems were shown to equally predict survival[15]. The National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) will not be used for capturing or grading GVHD.

The Glucksberg criteria will be followed in assessment of acute GVHD and the highest grade will be recorded (Appendix D). Chronic GVHD is graded based on clinical manifestations of organ systems based on the National Institutes of Health (NIH) consensus criteria (8) and Center for International Blood and Marrow Transplant Research (CIBMTR) grading guidelines (Appendix E). GVHD will be assessed weekly until Day +100 while inpatient and at specific time point per section 11.4 and 11.5.

12.0 ADVERSE EVENTS

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

AE collection will begin on Day -14 through Day +30 post-transplant.

12.1 Criteria for Defining AE

The CTCAE, version 5.0, will be used to determine AE terms, definitions and grades for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE, version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

12.1.1 'Expectedness': AEs must be documented as 'Unexpected' or 'Expected' for expedited reporting purposes.

12.1.2 An Unanticipated AE is defined as one that is serious, unexpected, related (definitely, probably) to the study drug, and suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

12.1.3 Attribution of the AE:

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

12.2 Required AEs Collection and Entry to Study Database

All AEs from day-14 to day +30 post-transplant will be collected and documented in the source document regardless of grade, attribution or expectancy.

Therapy for hematologic malignancies, with or without stem cell transplantation, is associated with significant hematologic and non-hematologic toxicities. These toxicities are generally viewed as anticipated events of therapy. Grades 1 and 2 AEs **that are expected** will not be entered into the study database.

Grade 3, 4 and 5 adverse events regardless of relationship, expectancy or attribution, will be collected and entered into the study database.

12.3 Definition of Primary Engraftment Failure

Failure to achieve a neutrophil count >500/μL within 35 days of the stem cell infusion will be defined as primary engraftment failure. If primary engraftment failure occurs, an action to obtain neutrophil recovery (such as the use of growth factors or stem cell boost) will be allowed. Neutrophil count recovery will continue to be monitored in these subjects until they reach statistical endpoint. Hospitalization (prolonged) due to engraftment failure would be SAE.

12.4 Serious Adverse Event and Unanticipated Adverse Events

An SAE is an AE that occurs and results in ANY of the following:

1. Death.

2. A life-threatening adverse drug experience. The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

3. Inpatient hospitalization or prolongation of existing hospitalization. Emergency room visits that do not result in admission to the hospital are not SAEs unless they meet one of the other criteria noted. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., initiation of conditioning, surgical insertion or revision of central line) should not be recorded as an AE or SAE. Hospitalization (prolonged) due to engraftment failure would be SAE.

4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

5. Important Medical Events (IMEs) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

12.5 Required Reporting of AEs and SAEs

12.5.1 Reporting Adverse Reactions and Unanticipated Problems to the IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the PI will report to the IRB any harm experienced by a subject or other individual, which in the opinion of the investigator are unexpected and probably related to the research procedure. AEs of this nature as well as SAEs will be reported to the IRB within 5 business days in accordance with the IRB policies and procedures.

12.5.2 Reporting Adverse Reactions and Unanticipated Problems to the FDA

The sponsor investigator will be responsible for notifying the FDA of certain unanticipated events. Unexpected and related (possibly, probably or definitely) fatal or life-threatening events require reporting to the FDA as soon as possible but no later than 7 calendar days after study team’s notification of the event. A written follow up must be provided when necessary by 15 calendar days after becoming aware of the event. Those SAEs that are not life threatening or fatal must be reported within 15 calendar days of becoming aware of the event.

Safety reports to the FDA must be submitted on a Medwatch Form FDA 3500A and be accompanied by Form FDA 1571, Investigational New Drug Application (IND). The type of report (initial or follow-up) should be checked in the respective boxes on both forms. The submission must be identified as:

- "IND safety report" for 15-day reports, or
- "7-day IND safety report" for unexpected fatal or life-threatening suspected adverse reaction reports, or
- "Follow-up IND safety report" for follow-up information.

The report must be submitted to an appropriate FDA Review Division that has the responsibility to review the IND application under which the safety report is submitted. FDA recommends that all sponsors submit safety reports electronically. Other means of rapid communication to the respective review division's Regulatory Project Manager (e.g., telephone, facsimile transmission, email) may also be used.

SAEs and reportable events will be reported to the sponsor via MedWatch form 3500A within 24 hours of knowledge. Updates to the SAE should be made as events change. SAEs will be collected until Day +30 for all subjects.

13.0 DATA REQUIREMENTS, COMPLIANCE AND QUALITY ASSURANCE

13.1 Confidentiality of Records:

Research related documents will be stored in the limited access, locked PSCI CTO. Institutional policy and guidance on requirements for managing clinical research data will be followed, including the appropriate levels of safeguard to ensure the confidentiality, integrity and availability of clinical research data.

13.2 Participant Consent Form:

Prior to commencement of any research related activities, written, signed and dated participant consent for the study protocol must be obtained. A copy of the signed and dated informed consent form must be provided to the research participant. The original signed consent form and additional consents will be maintained in the PSCI CTO. Copies will also be uploaded in the participant's Electronic Medical Record (EMR). The original signed consent form for institutional Hematopoietic Stem Cell Transplant as part of standard of care will sent to PSH EMR while the copy will be obtained and kept in the subject's research binder in PSCI CTO.

13.3 Data Collection and Maintenance:

Electronic data capture will occur via electronic case report forms in On-line Clinical Oncology Research Environment (OnCore®). OnCore® is the primary data management system for clinical trials activity at PSHCI. OnCore® was developed by Forte, Inc., and is a highly secure, web-based, customizable system that provides fully integrated clinical data management and protocol management capabilities. OnCore® houses regulatory tracking information, study management activity and clinical data.

13.4 Study Monitoring:

To ensure compliance with current federal regulations and the ICH guidelines, data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, the Sponsor-Investigator and duly authorized representative of any entity providing support for this trial. The study will be monitored by Penn State Cancer Institute Compliance

Program. The monitors will provide an independent review of the regulatory and subject records and the data collected to assure compliance with the protocol, GCP, and applicable federal regulations. The comprehensive monitoring will occur within 2 weeks after the first subject's receives protocol therapy; After the 1st monitoring visit, Interim Monitoring Visits will occur every 8 weeks for the first 3 subjects enrolled then every 4 months thereafter; follow-up visit will be annually until study closure; If there has been no treatment activity, monitoring visits must occur at a minimum of every 3 months. and ad-hoc for any study based on findings. A Close-out Visit (COV) will be conducted no later than 3 months after the final subject has completed the study, all data has been collected and all queries have been resolved; or at the request of the Sponsor or designees.

13.5 Audit and Inspection

Applicable federal, state and local entities may request an audit or inspection at any time. The PI will ensure all requested documentation is provided to auditors and inspectors, including appropriate access to the study database, source documentation and Case Report Forms (CRFs).

13.6. Protocol Non-Compliance and Departures

A protocol departure is any non-compliance with the clinical trial protocol, ICH GCP, or Federal and local regulations. The non-compliance may be either on the part of the subject, the PI or Sub-Is, or the study site staff. As a result of departures, corrective actions must be developed by the site and implemented. Reporting of protocol non-compliance to the IRB will be completed as directed in the Penn State IRB Investigator Manual. Study subjects will be notified of any significant departures. Documentation of the departure and the notification discussion with the subject must be included in the research record.

For the purpose of this protocol, any deviation in the administration of the study drug will be deemed non-compliance. Any modification to the conditioning regimen, post-transplant medication, general assessments (laboratory assessments, physical exams, biopsy timelines, etc), and timelines will be done for the purpose of standard medical management and will not be reported as protocol non-compliance.

13.7 Data Safety Monitoring Plan

The PSHCI Data and Safety Monitoring Committee (DSMC) will serve as the internal DSMB for data and safety review for this protocol. The PI will continuously monitor study progress for safety and will hold routine meetings with the study team and disease center personnel to review overall conduct and progress of this study. The frequency of such discussions will be dependent upon accrual to the trial and issues that arise. Study team and disease team meetings will cover accrual, AEs and safety issues, response and overall progress of the trial.

Every three months, the PI will provide the PSHCI DSMC with reports showing the number of subjects enrolled, SAE assessments, information on any protocol deviations or breaches of confidentiality, response, if appropriate, and overall status of the trial. The PSHCI DSMC meets regularly (currently every three months), as well as, on an ad hoc basis. Also, at the completion of each dosing cohort, the cohort results must be presented to the committee before proceeding to the next planned cohort. The PI will be asked for a report for the DSMC sufficiently in advance of annual IRB renewal in order to include DSMC findings with annual IRB submission. AE reporting to the IRB will occur in compliance with IRB guidelines. Unanticipated AEs, as well as, any significant literature reporting developments that may affect the safety of subjects in this study will be reported to the IRB as they arise. Unanticipated AEs will be reported to PSHCI DMSC simultaneously with the IRB reporting.

Reportable AEs, UAP, SAEs and Protocol Deviation reporting to DSMC.

Type of Event	To whom will it be reported	Time Frame for Reporting	How to report?
Death of a research participant unless the death is expected (e.g., due to disease progression).	PSCI DSMC and designated IRB, if applicable per IRB policy.	DSMC: Within 24 hours	DSMC: Email to PSCI-DSMC@pennstatehealth.psu.edu
Serious Adverse Event, *regardless of relatedness of expectedness*	PSCI DSMC and designated IRB, if applicable per IRB policy.	DSMC: Within 10 working days from the time the study team received knowledge of the event.	DSMC: Email to PSCI-DSMC@pennstatehealth.psu.edu
Unanticipated Problems that are not adverse events or protocol deviations	PSCI DSMC and designated IRB, if applicable per IRB policy.	DSMC: Within 10 working days from the time the study team received knowledge of the event.	DSMC: Email to PSCI-DSMC@pennstatehealth.psu.edu

13.8 Institutional Review Board Review and Approval:

This protocol, the informed consent document, relevant supporting information and all types of patient recruitment and advertisement information must be submitted to the local IRB for review and must be approved before the study is initiated. An amendment to remove a life-threatening situation can by implemented by the PI prior to obtaining IRB approval by the site. In such situations, the IRB must be notified immediately and the amendment forwarded to the IRB for their consideration.

The PI is responsible for keeping their local IRB informed on the progress with study renewal at least once a year. The PI must also keep the local IRB informed of any significant AEs, per local institutional guidelines.

13.9 Record Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all study-related documentation, including source document and CRFs, long enough to allow the sponsor to use the data to support marketing applications. If this study is conducted under an IND, all records must be maintained for:

- Two years after the FDA approved the marketing application, or

- Two years after the FDA disapproves the application for the indicating being studied, or
- Two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

The Sponsor Investigator will take measures to prevent accidental or premature destruction of study documents. For such studies, records will be retained for a minimum of seven (7) years past official study termination.

14.0 **STATISTICAL CONSIDERATIONS**

14.1. Summary of Design: This is a single-arm phase II trial to study the effectiveness of the proposed treatment (Clofarabine followed by HSCT with Post-Transplant Cyclophosphamide for non-remission AML). The primary endpoints will be CR rate at day +30 post HSCT, as well as, feasibility, safety and toxicity of the regimen. The secondary endpoints will be OS and DFS at year +1 after HSCT, NRM by day +100 after HSCT, incidence and severity of acute and chronic GVHD and rate of engraftment.

14.2. Sample Size Justification and continuous monitoring for serious adverse effects: Based on published papers on CloBu4 regimen in non-remission AML, it is estimated that the remission rate for this new treatment is >90%. The remission rate for the standard treatment is <56%[16]. This study intends to show the superiority of the proposed treatment and to reject the null hypothesis that the remission rate for the proposed treatment is 56% or lower. The proposed sample size of 20 subjects achieves this with 80% power at 5% type one error.

Enrollment will begin at 30 mg/m^2 to analyze any unexpected and related grade 4-5 organ toxicities as defined in Section 12.2. If the trial is stopped due to excessive toxicities, then dose de-escalation to 20 mg/m^2 will occur for the next cohort of participants. For each subject, the observation period is from day -14 through post-transplant day 30. For this trial, the adverse effects will be continuously monitored as patients are enrolled. We shall use a Bayes procedure developed by Chen, C., and Chaloner, K.[17] We will stop the trial when the toxicity rate exceeds 20% with a posterior probability of 80% and a margin of no more than 5%. The trial will start the clofarabine dose of 30 mg/m2 and use the following stopping rule: if any grade 4 or 5 non-hematological toxicities which are unexpected and related occur in 2 of the first 3 subjects, or 3 of 6, 4 of 9, 5 of 12, 6 of 16 or 7 of 19, then clofarabine will be reduced to 20 mg/m2 with the next subject enrolled. Once the dose modification has occurred, re-escalation of clofarabine to 30mg/m2 is not permitted. If the dose de-escalates to 20 mg/m2, the following same stopping rule will be used to ensure subject safety. If any grade 4 or 5 non-hematological toxicities which are unexpected and related occur in the 2 of the first 3, or 3 of 6, 4 of 9, 5 of 12, 6 of 16 or 7 of 19, subjects at the 20 mg/m2 dose level, the trial will be stopped.

The non relapse mortality (NRM) will be observed from start of treatment through post-transplant day 100. We will stop the trial when the day-100 NRM rate exceeds 25% with a posterior probability of 80%. This leads to the stopping rule that the trial will be stopped when NRM occurs in greater than or equal to 3 of 6, 4 of 9, 5 of 12, 6 of 16 or 7 of 19 patients.

14.3. Statistical Analysis Plan: The remission of each patient on the trial will be carefully documented and the 30-day remission rate calculated, which will be compared to the 56% remission rate of standard treatment using exact binomial test. For the secondary endpoints of progression free survival and overall survival, Kaplan-Meier Methods will be used to estimate the survival curves. The one-year relapse rate, one-year overall survival probability and one-year disease free survival will be provided with 95% confidence interval. Key regimen related toxicities will be described as reported. Time to engraftment will be captured by retrieving the cell counts data after transplant and will be recorded as a standard method. Relapse rate at 2 years will be calculated as the cumulative incidence

of relapse, as death a competing event.

14.4 ***Sample Size and Accrual Rate:*** *Anticipated enrollment rate is 1-2 participants per month. Total sample size is 20. Given this accrual rate, expected duration of enrollment for this study is 24 months.*

14.5 Reporting and Exclusions

Evaluation of toxicity: All patients will be evaluable for toxicity as defined in Section 11.0 from day -14 pre-transplant to day +30 post HSCT.

Evaluation of response: CR rate at day +30 post HSCT will be calculated and toxicity and engraftment will be assessed in order to evaluate response.

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APPENDIX A: KARNOFSKY PERFORMANCE SCALE

Karnofsky Performance Scale	
Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

This assessment may be performed by a Registered Nurse or Physician/designee.

			Transplant Conditioning							GVHD Prophylaxis			Intensity				
Investigator	Clofarabine	Days Clo to Conditioning	Flu	Cy	Etopo	Bu	Treo	Mel	TBI	Alem	rATG	PTCy	Myelo-ablative	RIC	Patient #	TRM	OS
Tische	30 mg/m2 x 5	3 Days	30 mg/m2 x 5	14.5 mg/kg x 2				110 mg/m2				Yes		X	10	23%	55%
			30 mg/m2 x 5	14.5 mg/kg x 2			10 g/m2 X3					Yes		X	1		
			30 mg/m2 x 5	14.5 mg/kg x 2	40 mg/kg x 1		10 g/m2 X3					Yes		X	1		
			30 mg/m2 x 5	14.5 mg/kg x 2					2Gy			Yes		X	1		
			30 mg/m2 x 5	14.5 mg/kg x 2					4 Gy			Yes		X	4		
			30 mg/m2 x 5	14.5 mg/kg x 2					12 Gy			Yes	X		1		
Locke	30 mg/m2 x 5	9 Days	30 mg/m2 x 5					140 mg/m2		100 mg total				X	17	7%	31%
								140 mg/m2		100 mg total				X	1		
			30 mg/m2 x 5			3.2 mg/kg IV x 4				100 mg total			X		2		
			30 mg/m2 x 5					140 mg/m2			6 mg/kg total			X	5		
					60 mg/kg				12 Gy	100 mg total			X		1		
					60 mg/kg				12 Gy				X		1		
Richardson	40 mg/m2 x 5	3 Days		60 mg/kg x 2					12 Gy				X		6	8%	48%
			30 mg/m2 x 5					140 mg/m2						X	2		
			30 mg/m2 x 5			3.2 mg/kg IV x 2								X	2		
			30 mg/m2 x 5			3.2 mg/kg IV x 3							X		1		
Rakszawski	30 mg/m2 x 5	3 Days	40 mg/m2 x 4			3.2 mg/kg IV x 3			2 -4 Gy			Yes	X		2	0	100%
Current Proposal	30 mg/m2 x 5	3 Days	40 mg/m2 x 4			3.2 mg/kg IV x 2			2 Gy			Yes		X			

APPENDIX B (Above): TABLE OF CLOFARABINE REGIMEN IN PREVIOUS STUDIES

APPENDIX C: TABLE OF EVALUATIONS AND INTERVENTIONS

	Within 28 D of Registration	Day -14	During time period of D-13 to D-1	DAY 0	Day +3	Day +4	Day +5	Day +6 to Day +29	Day +30 (±7)	Day +100 (±14)	Day +180 (±21)	Relapse	Year +1 (±30)
Informed Consent	X												
Assessment of Eligibility	X												
Medical History	X												
Physical Exam[1]	X	X	X	X					X	X	X		X
Height[2]	X												
Weight and Vital Signs and Pulse Oximetry	X	X		X					X	X	X		X
Assessment of AEs		X	X	X	X	X	X	X	X				
ECG	X				X	X							
PFTs and Echocardiogram or MUGA [3]	X												
HIV1, HIV2, Hepatitis B (HBsAg, HBcAb, HBsAb), Hepatitis C (HCV Ab) and Serum Pregnancy Test [4]	X												
Coagulation Test (PT/INR)	X												
Karnofsky Status	X	X		X					X	X	X		X
Concomitant medications	X	X	X	X	X	X	X	X	X				
Disease Assessment									X	X	X		X
Bone Marrow biopsy and aspirate to assess Morphology and Cytogenetics [5,6]	X								X	X	X	X	X
Chimerism Studies									X	X	X		X
CBC with differential and CMP [7]	X	X	X	X	X	X	X	X	X	X	X		X
Hematopoietic Stem Cell Transplant				X									
LDH, uric acid [7]	X	X	X	X	X	X	X	X	X				
Clofarabine		X	X										
Post-transplant Cyclophosphamide					X	X							
Total Body Irradiation			X										

GVHD Assessments [8]								X	X	X	X		X
Tacrolimus and Mycophenolate Mofetil							X						
Filgrastim (G-CSF)							X						

Notes:

1. Full physical examination must be completed at registration. Modified or limited exams may be completed at other time points.
2. Height will be collected at registration only.
3. PFTs and Echocardiogram or MUGA will be collected within 2 months of registration.
4. Serum pregnancy test for WOCP must be collected within 7 days of initiation of pre-conditioning regimen (prior to usage of Clofarabine).
5. A bone marrow aspirate and biopsy will be performed within 28 days of registration to assess morphology and cytogenetics.
6. A bone marrow aspirate will be collected whenever relapse is suspected. Participants that relapse will be followed for survival only.
7. Complete Metabolic Profile (CMP) chemistry testing includes: Albumin, Alkaline Phosphatase, ALT, AST, Bicarbonate, Calcium, Chloride, Glucose, Magnesium, Potassium, Sodium, Total Bilirubin, and Total Protein. Complete Blood Count (CBC) with differential, CMP, LDH and uric acid will be collected daily from Day -14 to Day -1, then three times per week through neutrophil engraftment or day +30 whichever occurs first.
8. GVHD will be assessed weekly (±3 days) through day +100. then monthly (±14 days) to Year +1
9. Survival only for the relapsed subjects.

APPENDIX D: Grading of Acute Graft versus Host Disease

Acute GVHD will be graded using the below criteria and not NCI CTC.

(Per modified Glucksberg criteria = Keystone criteria)[15]

STAGES OF ORGAN INVOLVEMENT		
Skin	1	Maculopapular eruption involving less than 25% of the body surface
	2	Maculopapular eruption involving 25-50% of the body surface
	3	Generalized erythroderma
	4	Generalized erythroderma with bullous formation.
GI	1	> 500 ml of liquid stool/day or biopsy-proven upper GI involvement
	2	> 1,000 ml of stool/day
	3	> 1,500 ml of stool/day
	4	Severe abdominal pain with or without ileus
Liver	1	Bilirubin is 2 -2.9 mg/dl
	2	Bilirubin is 3 - 5.9 mg/d1
	3	Bilirubin is 6 - 14.9 mg/dl
	4	Bilirubin is > 15 mg/dl

OVERALL GRADING OF ACUTE GVHD BY ORGAN STAGING			
	Skin	GI	Liver
I	1-2	None	None
II	3 or	1 or	1
III	---	2-4	2-3
IV*	4	---	4

*If Karnofsky performance status < 30%, then grade IV.

APPENDIX E: Grading of Chronic Graft versus Host Disease

Chronic GVHD will be graded using the below criteria and not NCI CTC.

1.1. Clinical scoring of organ systems

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

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

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

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

OTHERS: Specify:_____

Overall GVHD Severity *(Opinion of the evaluator)*	❑ **No GVHD**	❑ **Mild**	❑ **Moderate**	❑ **Severe**