Masonic Cancer Center
University of Minnesota
Cancer Experimental Therapeutics Initiative (CETI) and Bone Marrow Transplant Program

A Multi-Center Phase 2 Study of Combined Modality Treatment with Ruxolitinib, Decitabine, and Donor Lymphocyte Infusion for Post-Transplant Relapse of AML or MDS

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Confidential

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Revision History

Revision #	Version Date	Detail of Changes	Consent change
	12/03/2018	Original to CPRC	
	1/16/2019	Updated study committee Section 15: Statistical clarifications and minor edits (error corrections and clarifications) per UMN and University of Rochester CPRC stipulations Section 11.2: Added optional research bone marrow biopsy prior to cycle one Section 12.5: Clarified institutional SAE reporting table based on current MCC SOPs	
1	03/18/2019	Title Page: Added IND # Per FDA request – Section 5.2: Eligibility- Patients with Active GVHD will be excluded from the study Per FDA request - Section 15.4 Stopping Rules and section 12.3, Event Reporting – the FDA will be notified if stopping rule is triggered	No
2	03/27/2019	Clarifications to Section 11: after clinical care planning meeting and IRB initial review: • Updated timing of windows around clinical care evaluations and research samples • Added recipient type and screening to clinical care evaluations • Clarified bone marrow biopsy timing • Removed specification of sample tube color Section 12.3, Section 12.4, and Section 12.5 Updated sponsor reporting criteria Corrected typographical errors	Yes
3	05/01/2019	Administrative change: Section 11.1 and Section 11.2 Clarified standard of care and research bone marrow in order to synchronize timing.	No
3A	09/03/2019	Administrative change: Section 11.1 and Section 11.2 Reorganized calendars for clarity	No
4	11/25/2019	Administrative Changes: • Section 5.1: Clarified that minors will either assent or be given an information sheet, per institutional IRB requirements • Removed eligibility checklists – these documents will now be stored in Oncore • Correction of typographical errors	Yes
4A	01/03/2020	Section 8.5 removed karnofsky from re-screening procedures	No

Revision #	Version Date	Detail of Changes	Consent change
5	09/18/2020	Synopsis, Section 5.1 Clarifications to Inclusion criteria Section 6, Section 11.3 Clarified that related / unrelated donors will be screened and consented per individual institutional and/or NMDP SOPs Section 8.8 – Clarified that patients discontinuing DLI treatments, may continue to receive Ruxolitinib Section 11.1 Clarified timing of clinical screening labs Section 11.2 Removed screening research labs Section 12.3, Section 13.3 and Section 13.5 Minor clarification to institutional monitoring	Yes; also removed study specific donor consents
6	12/30/2020	Section 11.1 and Section 11.2 Clarifications to timing of procedures Section 12.2 and Section 15.4 Clarification to timing period of AE documentation and stopping rules	No
7	06/23/2021	Section 9.1 updated expected adverse events based on new Ruxolitinib IB Section 8.8 Minor edit to Duration of Study. Rationale clarification and consistency	Yes
8	02/25/2022	Updated study PI and biostatistician	Yes

Table of Contents

Abbreviations

Abbreviation	Definition
ABO	type A, type B, type O, or type AB
AE	adverse event
aGVHD	acute graft versus host disease
AHC	Academic Health Center
ALT	alanine aminotransferase
AML	Acute myeloid leukemia
AST	aspartate aminotransferase
BMP	basic metabolic panel
BMT	bone marrow transplant
CBC	Complete Blood Count
CETI	Cancer Experimental Therapeutics Initiative
CFR	Code of Federal Regulations
CMP	Comprehensive Metabolic Profile
CPRC	Cancer Protocol Review Committee
CMV	cytomegalovirus
CNS	central nervous system
CR	complete remission
CRCL	Creatinine clearance
CRF	case report form
CTCAE	Common Toxicity Criteria Adverse Event
CTEP	Cancer Therapy Evaluation Program
CTO	Clinical Trials Office
CTSI	Clinical and translational science institute
DLI	Donor lymphocyte infusion
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DSMP	Data and Safety Monitoring Plan
ECG	electrocardiogram
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
G-CSF	granulocyte-colony stimulating factor
GVHD	graft versus host disease
GVL	graft-versus-leukemia
HBV	Hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMA	hypomethylating agents
HTLV1/2	human T cell lymphotropic virus 1/2
IB	Investigator's Brochure
IGG	Immunoglobulin G
IRB	institutional review board
IV	Intravenous

Abbreviation	Definition
JAK	Janus kinase
MCC	Masonic Cancer Center
MCC-CISS	Masonic cancer center - Clinical Informatics Shares Services
MDS	Myelodysplastic syndrome
MPN	Myeloproliferative Neoplasms
MSD	matched sibling donor
MUD	Matched unrelated donor
NAT	nucleic acid testing
NCI	National Cancer Institute
NK	Natural killer cells
NRM	non-relapse mortality
ONCORE	Online Enterprise Research Management Environment
OS	Overall survival
PFS	Progression Free Survival
PHI	Protected Health Information
RFLP	Restriction Fragment Length Polymorphism
RH	Rhesus
SAE	serious adverse event
SOP	standard operating procedure
STAT	signal transducer and activator of transcription
T. Cruzi	Trypanosoma Cruzi
TTL	Translational Therapy Lab
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	women of childbearing potential

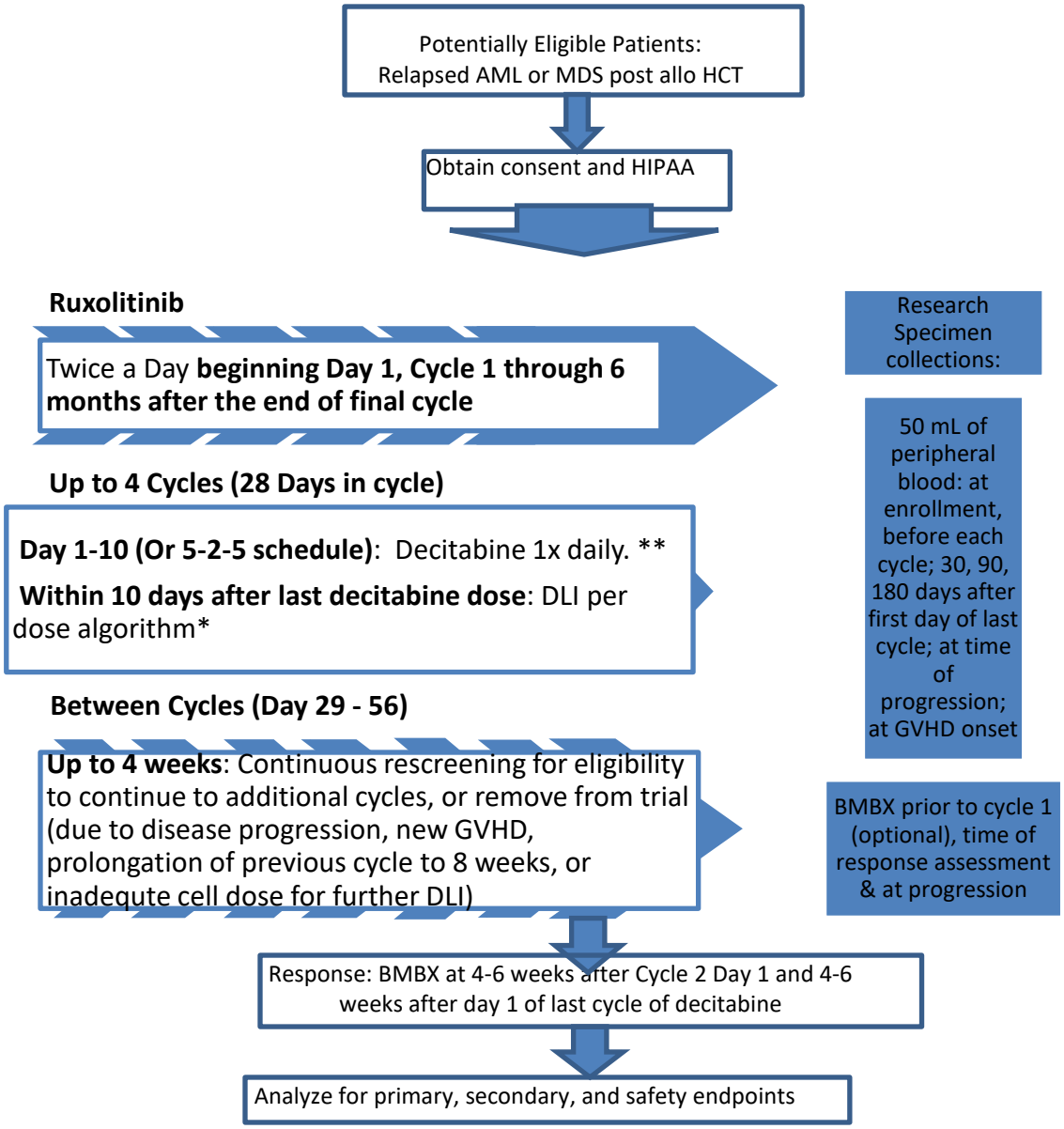
Synopsis

Study Design:	This is a multi-center, single-arm, open-label, phase II trial for the frontline treatment of relapsed AML or MDS following allo-HCT. Eligible subjects will receive up to 4 cycles of combined modality treatment. The number of cycles depends on response, toxicity, and the remaining cell dose. Cycles include: • 10 days of decitabine 20 mg/m^2 IV daily, or, alternatively on a 5-2-5 schedule with no weekend infusion. If a CR is achieved after 2 cycles using the 10-day schedule, subsequent cycles will change to a 5-day schedule. • Starting with day 1 of cycle 1 and continuing for up to 6 months after the end of the last cycle, patients will receive ruxolitinib 5 mg twice daily orally. Dose may be increased to 10 mg twice daily in cycles 2 through 4 if platelets improve to >100 x 10^9/L. • DLI from the original donor will be infused within 10 days after the last dose of decitabine in each cycle. Patients will be screened for ongoing eligibility before each subsequent cycle of therapy. Patients with disease progression, new GVHD (except grade I acute GVHD), prolongation of the most recent cycle to more than 8 weeks (for any reason), or inadequate cell dose for further DLI will not receive further treatment on study. The DLI dose in each cycle will be determined according to a donor-dependent dose-escalation algorithm (schema). The expected duration of treatment for each subject is 4 cycles of treatment, each lasting 4-8 weeks. Subjects will be followed on study for 12 months.
Primary Objectives:	Determine the efficacy of combined modality treatment (ruxolitinib, 10-day decitabine, and DLI) for relapsed AML or MDS post allo-HCT.
Secondary Objectives:	• Evaluate OS • Determine incidence of grade II-IV acute graft-versus-host disease (aGVHD II-IV) • Evaluate PFS • Determine incidence of relapse • Evaluate complete remission (CR) • Determine incidence of non-relapse mortality (NRM) • Best response
Correlative Objectives:	• Incidence and severity of adverse events (AEs) and serious AEs (SAEs) until 3 months after day 1 of the last received cycle • Correlative studies: T cell and NK cell subset analysis by flow cytometry, correlation between *TP53* mutation and response, clonal dynamics during and after the course of therapy
Key Inclusion Criteria:	• Age 12 years or older • Undergone first allo-HCT from a 6/6 matched sibling donor, 8/8 matched unrelated donor, or an HLA haploidentical donor.

	● AML or MDS ● Additional cells sufficient for the first DLI available from the same donor or the donor willing to donate ● Partial (or better) engraftment from the bone marrow showing relapse: Defined as >50% donor chimerism on non-split RFLP. Patients with chimerism of 25-50% may be enrolled with approval of the site PI and Sponsor/Investigator. ● Karnofsky Performance Status ≥ 50% ● Adequate organ function: Total bilirubin < 1.5 x ULN; AST/ALT < 2.5 x ULN; Creatinine clearance ≥40 mL/minute ● Peripheral white blood cell count <50 x 10^9/L ● Subjects and spouse/partner who are of childbearing potential must be using highly effective contraception consisting of 2 forms of birth control starting at Screening and continuing through the entire study ● Male subjects must not donate sperm during the Screening and Treatment Periods, and for at least 3 months after the last dose of ruxolitinib
Key Exclusion Criteria:	● Active uncontrolled infection. ● History of infection with human immunodeficiency virus (HIV), unresolved hepatitis B, or hepatitis C ● Untreated CNS leukemia ● Untreated or active GVHD (acute or chronic) ● History of grade III-IV acute GVHD ● Any form of iatrogenic immunosuppression except <0.5 mg/kg/day of prednisone or equivalent ● Unresolved veno-occlusive disease of the liver ● Subjects who are pregnant, breast feeding or sexually active and unwilling to use effective birth control for the duration of the study ● Radiation therapy within 14 days prior to consent ● Any prior therapy for relapse after allo-HCT ● Prior DLI. CD34-selected boost is allowed ● Exposure to any other investigational agent, device or procedure within 2 weeks prior to consent ● Patients or donors with any medical or psychological condition that, in the opinion of the Investigator, might interfere with the subject's participation in the trial, pose any additional risk for the patient/donor, or confounds the assessments of the subject ● Subjects with known allergies, hypersensitivity or intolerance to ruxolitinib or similar compounds
Key Rescreening Inclusion Criteria (before Cycle 2-4):	● Additional cells available from the same donor used for the first DLI or the donor willing to donate ● Karnofsky Performance Status ≥ 50% ● Adequate organ function: Total bilirubin < 1.5 x ULN; AST/ALT < 2.5 x ULN; Creatinine clearance ≥40 mL/minute within 3 days prior to day 1 ● Peripheral white blood cell count <50 x 10^9/L within 3 days prior to day 1
Key Rescreening	● Active uncontrolled infection ● Any new GVHD except grade I acute GVHD during the most recent cycle

Exclusion Criteria (before Cycle 2-4):	● Any form of iatrogenic immunosuppression except <0.5 mg/kg/day of prednisone or equivalent ● Unresolved veno-occlusive disease of the liver ● Subjects who are pregnant, breast feeding or sexually active and unwilling to use effective birth control for the remaining duration of the study ● Radiation therapy during the most recent cycle ● Disease progression during the most recent cycle. Screening bone marrow biopsy is required only before cycles 1 and 3. ● Exposure to any other investigational agent, device or procedure during the most recent cycle ● Patients or donor with any medical or psychological condition that, in the opinion of the Investigator, might interfere with the subject's continuation in the trial, pose any additional risk for the patient/donor, or confounds the assessments of the subject ● Any condition resulting in prolongation of the most recent cycle beyond 8 weeks. If in the view of the investigator, postponing the next cycle is justified for any reason, this is allowed as long as the current cycle does not exceed 8 weeks. If longer than 8 weeks, patients will not receive further therapy on study ● Consent withdrawal by patient
Enrollment:	Approximately 34 subjects will be enrolled (32 evaluable) over a period of 24 months, with an additional 12 months of follow up

Schema



***DLI dose escalation algorithm**

	MSD	MUD	Haploidentical
DLI #1, $x10^8$ CD3/kg	0.1-1	0.05-0.5	0.01-0.1
DLI #2, $x10^8$ CD3/kg	0.5-5	0.1-1	0.05-0.5
DLI #3, $x10^8$ CD3/kg	1-10	0.5-5	0.1-1
DLI #4, $x10^8$ CD3/kg	5-50	1-10	0.5-5

DLI: Donor lymphocyte infusion; MSD: Matched sibling donor; MUD: Matched unrelated donor

**If CR is achieved after cycle 2, patients will be switched to a 5 day schedule.

1 Objectives

1.1 Primary Objective

To determine the efficacy of combined modality treatment (ruxolitinib, decitabine, and DLI) for relapsed AML or MDS post allo-HCT as measured by overall survival (OS) at 6 months.

1.2 Secondary Objectives

- To evaluate OS
- To determine cumulative incidence of grade II-IV acute graft-versus-host disease (aGVHD II-IV)
- To evaluate PFS
- To determine incidence of relapse
- To determine complete remission (CR)
- To determine incidence of non-relapse mortality (NRM)
- To measure best response

1.3 Correlative Objectives

- To evaluate incidence and severity of adverse events (AEs) and serious AEs (SAEs) until 3 months after day 1 of the last received cycle
- Correlative studies: T cell and NK cell subset analysis by flow cytometry, correlation between *TP53* mutation and response, clonal dynamics during and after the course of therapy

2 Background

Although allo-HCT is a curative treatment approach for AML and MDS, relapse continues to be the primary cause of death after allo-HCT, with post-relapse 1-year overall survival of only about 20%[1,2]. Currently there is no standard treatment for post-HCT relapse. Commonly practiced approaches include withdrawal of immunosuppressive medications, hypomethylating agents, aggressive chemotherapy, second allo-HCT, targeted therapies, DLI, or a combination of these[3]. We will apply a combination approach as detailed in the following sections:

2.1 DLI

DLI is mechanistically based on the concept of restoration and augmentation of a graft-versus-leukemia (GvL) effect. However, the success of DLI is limited due to low efficacy and high toxicity. As a result, various strategies are implemented to increase DLI potency and decrease its toxicity. Examples for the former group of approaches include

the use of hypomethylating agents (HMA) or lymphodepleting chemotherapy prior to DLI. Lymphodepleting chemotherapy helps with cytoreduction and provides a favorable cytokine niche for the T cells of DLI to expand[4]. However, the use of lymphodepleting chemotherapy before DLI has been associated with high incidence of severe GVHD, the major toxicity of DLI[5].

2.2 HMAs

The use of HMAs before or after DLI is a popular and less toxic approach compared to lymphodepleting chemotherapy before DLI. HMAs increase antigen expression by leukemia cells and may make them more immunogenic, i.e. primed for a robust GvL effect from DLI[6,7]. A recent retrospective multicenter study by the German Cooperative Transplant Study Group using azacitidine prior to DLI in 154 patients with relapsed AML or MDS after allo-HCT showed that this therapy is well-tolerated and effective, particularly in patients with low disease burden. Overall response was achieved in a third of the patients and overall survival at 2 years was approximately 30%[8]. In another study using azacitidine prior to DLI in 65 patients with relapse after allo-HCT, there was temporary control of leukemia in ~45% of patients, but only 10% achieved a CR[9]. Furthermore, pioneer murine studies by Jaebok Choi have demonstrated that azacitidine mitigates GVHD while preserving GVL by peripheral conversion of alloreactive effector T cells into regulatory T cells, thus mitigating GVHD without sacrificing GVL effect[10]. Azacitidine after DLI was recently tested in a phase 1 study to prevent development of GVHD[11]. Azacitidine was administrated on days 4, 6, 8 and 10 after DLI with dose escalation schedule of 30–75 mg/m2 in 39 patients with relapsed AML after allo-HCT. None of the patients developed severe acute GVHD.

3 Study Rationale

In the proposed study, we add two novelties to the HMA-DLI platform with the goals of increasing efficacy and decreasing toxicity. First, while azacitidine is the more commonly used HMA in combination with DLI, we will replace azacitidine with 10-day courses of decitabine. This concept is based on two observations: (i) Unprecedented high response rates (100% in the recent report by Washington University investigators) to 10-day decitabine, particularly in *TP53*-mutated MDS/AML[12], and (ii) In a recent murine study, decitabine, but not azacitidine, potentiated the antileukemic activity of hematopoietic stem and progenitor cell-derived NK cells. Furthermore, the number of NK cells in the bone marrow was increased after decitabine treatment[13]. The second novelty in this protocol is adding JAK2 inhibitor ruxolitinib to the HMA/DLI combination. JAK inhibition has shown clinical activity in the treatment of acute GVHD[14,15,16]. Preliminary studies conducted by Jaebok Choi have shown

that JAK inhibition decreases PDL1 expression of neoplastic cells and augment GVL while preventing GVHD (Figure 1).

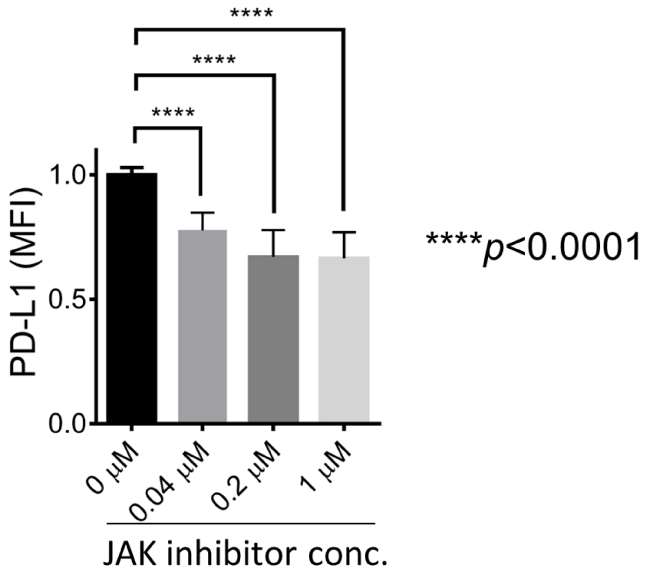


Figure 1: Effects of JAK inhibition on PD-L1 expression on a murine B-cell lymphoma cell line

4 Study Design

This is a multi-center, single-arm, open-label, phase II trial for the frontline treatment of relapsed AML or MDS following allo-HCT.

Eligible subjects will receive up to 4 cycles of combined modality treatment. The number of cycles depends on response, toxicity, and the remaining cell dose.

Cycles include:

- 10 days of decitabine 20 mg/m2 IV daily; or, alternatively, per institution, physician, or patient preference on a 5-2-5 schedule with no weekend infusion. If a CR is achieved after 2 cycles using the 10-day schedule, subsequent cycles will change to a 5-day schedule.
- Starting with decitabine and continuing for up to 6 months after the end of the last cycle, patients will receive ruxolitinib 5 mg twice daily orally.
- DLI from the original donor will be infused within 10 days after the last dose of decitabine in each cycle.

Patients will be screened for ongoing eligibility before each subsequent cycle of therapy. Patients with disease progression, new GVHD (except grade I acute GVHD), prolongation of the most recent cycle to more than 8 weeks (for any reason), or inadequate cell dose for further DLI will not receive further treatment on study. The DLI dose in each cycle will be

determined according to a donor-dependent dose-escalation algorithm (schema). If the collected cell dose in the DLI is less than the target dose, the patient will receive those collected cells and subsequently removed from further treatment cycles. These subjects will continue to be followed per protocol.

The expected duration of treatment for each subject is 4 cycles of treatment, each lasting 4-8 weeks.

Approximately 34 subjects will be enrolled (32 evaluable) over a period of 24 months, with an additional 12 months of follow up.

5 Patient Selection

Study entry is open to adult patients regardless of gender, race or ethnic background. While there will be every effort to seek out and include women and minority patients, the patient population is expected to be similar to that of other relapsed AML or MDS studies at the University Of Minnesota and other participating institutions.

5.1 Inclusion Criteria:

5.1.1 Age ≥12 years

5.1.2 Have undergone first allo-HCT from a 6/6 matched sibling donor, 8/8 matched unrelated donor, or an HLA haploidentical donor.

5.1.3 History of AML or MDS for which allo-HCT was performed. Overlap MPN/MDS is included.

5.1.4 Untreated relapse of the underlying malignancy as defined by >5% of malignant blasts (by morphology and/or flow cytometry) in the bone marrow, or myeloid sarcoma.

5.1.5 Additional cells sufficient for the first DLI available from the same donor, or the donor must be willing to donate. Both G-CSF mobilized and unmobilized products are allowed and the choice is at the discretion of the treating physician.

5.1.6 Partial (or better) engraftment from the bone marrow showing relapse, defined as >50% donor chimerism on non-split RFLP. Patients with chimerism of 25-50% may be enrolled with approval of the site PI and Sponsor/Investigator.

5.1.7 Karnofsky performance status ≥ 50% (appendix I)

5.1.8 Adequate organ function within 14 days of study registration defined as:

- Total bilirubin < 1.5 x upper limit of institutional normal, unless a diagnosis of Gilbert's disease
- AST/ALT ≤ 2.5 x upper limit of institutional normal
- Creatinine clearance ≥40 mL/minute as calculated by the Cockcroft-Gault formula. Cockcroft-Gault CrCl = (140-age) * (Wt in kg) * (0.85 if female) / (72 * Cr).

5.1.9 Peripheral white blood cell count <50 x 10^9/L. The use of hydroxyurea for cytoreduction is allowed and may continue until cycle 2 day 1

5.1.10 Subjects and spouse/partner who are of childbearing potential must be using highly effective contraception consisting of 2 forms of birth control (at least 1 of which must be a barrier method) starting at Screening and continuing through the entire study (for at least 3 months after the last dose of ruxolitinib if study treatment is stopped early or subject withdraws consent). Highly effective contraception is defined as:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device or intrauterine system.
- Double barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository (double barrier method will count as 2 forms of contraception).

5.1.11 Male subjects must not donate sperm during the Screening and Treatment Periods, and for at least 3 months after the last dose of ruxolitinib.

5.1.12 Subjects are willing and able to give written informed consent and to comply with all study visits and procedures. Parents or legal guardians will consent for minors and minors will be asked to assent, or be given a minor information sheet, per institutional IRB requirements.

5.2 Exclusion Criteria:

5.2.1 Active uncontrolled infection at the time of consent. An active uncontrolled infection is defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without signs or symptoms of infection will not be interpreted as an active uncontrolled infection. Subjects with a controlled infection receiving definitive therapy for 72 hours prior to enrollment are eligible.

5.2.2 History of infection with human immunodeficiency virus (HIV), unresolved hepatitis B, or hepatitis C.

5.2.3 Untreated CNS leukemia

5.2.4 Untreated or active GVHD (acute or chronic)

5.2.5 History of grade III-IV acute GVHD at any point in time

5.2.6 Any form of iatrogenic immunosuppression except <0.5 mg/kg/day of prednisone or equivalent at the time of consent.

5.2.7 Unresolved veno-occlusive disease of the liver, defined as persistent bilirubin abnormalities not attributable to GVHD and ongoing organ dysfunction (renal, ascites).

5.2.8 Subjects who are pregnant, breast feeding or sexually active and unwilling to use effective birth control for the duration of the study, as agents in this study are in pregnancy category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, and category D: there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans.

5.2.9 Radiation therapy within 14 days prior to consent.

5.2.10 Any prior therapy for relapse after allo-HCT.

5.2.11 Prior DLI. CD34-selected boost is allowed

5.2.12 Exposure to any other investigational agent, device or procedure within 14 days prior to consent

5.2.13 Patients or donors with any medical or psychological condition that, in the opinion of the Investigator, might interfere with the subject's participation in

the trial, pose any additional risk for the patient/donor, or confounds the assessments of the subject.

5.2.14 Subjects with known allergies, hypersensitivity or intolerance to ruxolitinib or similar compounds.

6 Donors

Additional cells sufficient for a DLI must be available, or the previous donor must be willing to donate again. The required total dose of CD3 cells ($x10^8$) per recipient's body weight in kg for 4 DLI procedures is 66, 16.6, and 1.66 for matched sibling, matched unrelated, haploidentical donors, respectively. Donor selection will be in compliance with 21 CFR Part 1271 and institutional guidelines. If requesting additional collections from the previous donor, donor assessment and consent process will occur per institutional SOPs for related donors or per National Marrow Donor Program (BeTheMatch.org) SOPs for matched unrelated donors, in the apheresis center or similar donor facility. No study-specific consent is needed from donors.

For affiliates: affiliate sites may use their institutional guidelines in evaluating related donor eligibility. Matched unrelated donors will be evaluated according to institutional and/or National Marrow Donor Program guidelines. The current study does not determine any donor-specific eligibility.

7 Study Registration

To be eligible for registration to this study, the patient must meet all of the inclusion criteria and none of the exclusion criteria listed on the eligibility checklist based on the eligibility assessment documented in the patient's medical record.

The eligibility checklist for both the patient and donor will be completed at the time of study registration.

7.1 Registration with the University of Minnesota Clinical Trials Office

Upon completion of the screening evaluation, eligibility checklist and obtaining consent, the Site Study Coordinator or designee will enroll the patient and donor in OnCore. Complete registration information is found in the study's Procedures Manual for Affiliate Sites.

Affiliate sites only: At the time of registration, the signed consents will be uploaded into OnCore as an attachment under the appropriate record (patient or donor).

Affiliates are responsible for fulfilling any local registration requirements.

7.2 Patients Who Do Not Begin Study Treatment

If a patient is registered to the study and is later found not able to begin study treatment (beginning with the ruxolitinib and decitabine); the patient will be removed from the study and treated at the physician's discretion. The study staff will update OnCore of the patient's non-treatment status (off study). The reason for removal from study prior to starting study treatment will be clearly indicated in OnCore. The patient will be replaced to complete enrollment.

8 Treatment Plan

In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care drug therapy (i.e. acetaminophen, diphenhydramine, G-CSF, antimicrobials, etc.).

Table 1: Ten Day Dosing Schedule

Treatment	Cycle 1			Between Cycles	Cycles 2 -4			Month 1 – 6 after end of final cycle
	Day 1-10	Between Day 11-21	Day 22-28	Day 29 - 56	Day 1-10	Between Day 11-21	Day 22-28	
Decitabine	1X daily				1X daily			
DLI		Once per dose algorithm*				Once per dose algorithm*		
Ruxolitinib	2x daily →							
Rescreen for eligibility				Continuous rescreening per section 8.5				

***See section 8.2, Table 4: DLI dose escalation algorithm**

The expected duration of treatment for each subject is 4 cycles of treatment, each lasting 4-8 weeks. As soon as continued eligibility for a subsequent cycle is confirmed after a given cycle, the subsequent cycle will start. Days 29-56 provide a window to start the next cycle and can be used to allow for resolution of toxicities. Refer to Sections 11.1 and 11.2 for the schedule of clinical and research related evaluations and procedures, and section 11.3 for the schedule of donor evaluations. Decitabine schedule: 10 days (Table 1) or 5-2-5 (Table 2) will be per institution, physician, or patient preference. If a CR is achieved after 2 cycles using the 10-day schedule, subsequent cycles will change to a 5 day schedule (see Table 3).

Table 2: Alternative Ten Day Dosing Schedule

Treatment	Cycle 1			Between Cycles	Cycles 2 -4			Month 1 – 6 after end of final cycle
	Day 1-5 and 8-12	Between Day 13-22	Day 23-28	Day 29 - 56	Day 1-5 and 8-12	Between Day 13-22	Day 23-28	
Decitabine	1X daily				1X daily			
DLI		Once per dose algorithm*				Once per dose algorithm*		
Ruxolitinib	2x daily →							
Rescreen for eligibility				Continuous rescreening per section 8.5				

*** See section 8.2, Table 4: DLI dose escalation algorithm**

Table 3: Five Day schedule for Cycles 3 and 4 if CR is achieved after Cycle 2

Treatment	Cycle 3		Between Cycles	Cycle 4		Month 1 – 6 after end of final cycle
	Day 1-5	Between Day 6 - 16	Day 17 - 56	Day 1-5	Between Day 6-16	
Decitabine	1X daily			1X daily		
DLI		Once per dose algorithm*			Once per dose algorithm*	
Ruxolitinib	2x daily →					
Rescreen for eligibility			Continuous rescreening per section 8.5			

*** See section 8.2, Table 4: DLI dose escalation algorithm**

8.1 Chemotherapy Regimen

The administration of the preparative regimen will follow institutional drug and supportive care guidelines. Dose and/or schedule adjustments consistent with the standard of care may be made on an individual patient basis as needed for safety.

Ruxolitinib 5 mg twice daily orally beginning Day 1 and through Cycle 1. Consider dose increase to 10 mg twice daily in cycles 2 through 4 if platelets recover to over >100 x 10^9/L. Ruxolitinib will continue through six months after the completion of the final cycle. See section 8.4 for toxicity dose modification.

Decitabine: 20 mg/m2 IV daily, on the following possible schedules: day 1-10 for cycles 1-2 (alternative: day 1-5 and day 8-12 with no weekend infusion); day 1-5 for cycles 3-4 (if CR achieved after Cycle 2). There are no dose modifications.

8.2 DLI

Within 10 days after the last dose of decitabine in each cycle, a DLI product from the previous donor (either remaining from the original transplant unit, or a new unit) will be infused. Donor lymphocytes will be obtained by lymphapheresis from the same allogeneic donor used for transplantation. For local related donors, lymphocyte collections will be performed using standard automated mononuclear cell collection techniques by the University of Minnesota Blood Bank or study affiliate site's institutional guidelines. For unrelated donors or non-local related donors, the lymphocyte collection will be performed at an outside facility according to procedures set by the National Marrow Donor Program. If the collection is non-local, coordination for the timing of the cell collection and the ability to transport the cells to the study site is required. Similarly, for local related donors, the timing of collection (same day as infusion vs. cryopreserved) is according to the collaborating centers' institutional guidelines.

The duration of DLI will be determined according to the collaborating centers' institutional guidelines. DLI will be administered according to a donor-dependent dose-escalation algorithm (Table 4). In the absence of new GVHD (any grade), the dose of DLI for the next cycle will be higher than the previous cycle. Otherwise, the dose will remain the same. DLI will be given without adding immunosuppressive medications and without conditioning. Addition of immunosuppressive medications as indicated to treat grade I acute GVHD or other non-GVHD steroid-responsive conditions is allowed.

Table 4: DLI dose escalation algorithm

	MSD	MUD	Haploidentical
DLI #1, $x10^8$ CD3/kg	0.1-1	0.05-0.5	0.01-0.1
DLI #2, $x10^8$ CD3/kg	0.5-5	0.1-1	0.05-0.5
DLI #3, $x10^8$ CD3/kg	1-10	0.5-5	0.1-1
DLI #4, $x10^8$ CD3/kg	5-50	1-10	0.5-5

DLI: Donor lymphocyte infusion; MSD: Matched sibling donor; MUD: Matched unrelated donor

8.3 Monitoring

During infusions, patients will be monitored for occurrence of untoward effects of the infusion of allogeneic lymphocytes such as rash, acute allergic reaction, bronchospasm, respiratory distress, acute vascular leak syndrome, localized or systemic infections.

8.4 Ruxolitinib Dose modification

Dose adjustment for ruxolitinib is recommended (Table 5).

Table 5: Ruxolitinib dose adjustment

CTCAE grade 3 or greater bleeding related to low platelets	**Non-transfused platelets**		
	<10 x 10^9/L	10-50 x 10^9/L	>50 x 10^9/L
Hold. Reassess 2 weeks after resolution of bleeding	Hold	5 mg daily	5 mg twice daily[1]

[1]For cycles 2, 3, and 4, if platelets improve to >100 x 10^9/L, a dose increase to 10 mg twice daily may be considered.

8.5 Re-screening Eligibility for Cycles 2- 4

Patients will be screened for eligibility to continue onto each subsequent cycle of therapy. Patients with disease progression, new GVHD (except grade I acute GVHD), prolongation of the most recent cycle to more than 8 weeks (for any reason), or inadequate cell dose for further DLI will not receive further treatment on study. Rescreening will be an ongoing process. When patients meet the eligibility criteria outlined below, they may begin subsequent cycles.

Inclusion Criteria (on or before Day 1 of Cycles 2-4)

Patients must meet the following criteria within 7 days prior to day 1 of cycles 2-4 unless otherwise noted.

8.5.1 Stable disease or better on bone marrow biopsy within 7 days before cycle 3 (required) and cycles 2 and 4 (if performed). A bone marrow biopsy before cycles 2 and 4 is not required.

8.5.2 Additional cells available from the same donor used for the first DLI or the donor willing to donate (Table 4). This dose will allow for at least one more DLI. Both G-CSF mobilized and unmobilized products are allowed. If a sufficient number of cells for the next DLI is not available, patients will not receive further treatment on study.

8.5.3 Adequate organ function:

- Total bilirubin < 1.5 x upper limit of institutional normal, unless a diagnosis of Gilbert's disease
- AST/ALT < 2.5 x upper limit of institutional normal
- Creatinine clearance ≥40 mL/minute within 3 days prior to day 1, as calculated by the Cockcroft-Gault formula. Cockcroft-Gault CrCl = (140-age) * (Wt in kg) * (0.85 if female) / (72 * Cr).

8.5.4 Peripheral white blood cell count <50 x 10^9/L within 3 days prior to day 1. The use of hydroxyurea is allowed and may continue until day 1 of cycle 2.

Exclusion Criteria (on or before Day 1 of Cycles 2-4)

Patients must meet the following criteria at the time of screening for the next cycle unless otherwise noted.

8.5.5 Active uncontrolled infection. An active uncontrolled infection is defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without signs or symptoms will not be interpreted as an active uncontrolled infection. Subjects with a controlled infection receiving definitive therapy for 72 hours prior to screening are eligible.

8.5.6 Any new GVHD except grade I acute GVHD during the most recent cycle.

8.5.7 Any form of iatrogenic immunosuppression except <0.5 mg/kg/day of prednisone or equivalent.

8.5.8 Unresolved veno-occlusive disease of the liver, defined as persistent bilirubin abnormalities not attributable to GVHD and ongoing organ dysfunction (renal, ascites).

8.5.9 Subjects who are pregnant, breast feeding or sexually active and unwilling to use effective birth control for the remaining duration of the study.

8.5.10 Radiation therapy during the most recent cycle.

8.5.11 Disease progression during the most recent cycle.

8.5.12 Exposure to any other investigational agent, device or procedure during the most recent cycle.

8.5.13 Patients or donors with any medical or psychological condition that, in the opinion of the Investigator, might interfere with the subject's continuation in the trial, pose any additional risk for the patient/donor, or confounds the assessments of the subject.

8.5.14 Any condition resulting in prolongation of the most recent cycle beyond 8 weeks. If in the view of the investigator, postponing the next cycle is justified for any reason, this is allowed as long as the current cycle does not exceed 8 weeks. If longer than 8 weeks, patients will not receive further therapy on study.

8.5.15 Consent withdrawal by patient

8.6 Supportive Care

Supportive care will be provided per institutional guidelines and standard of care. The investigator may prescribe any concomitant medications or treatment deemed necessary to provide adequate supportive care. Supportive care may include antibiotics, anti-fungals, analgesics, transfusions, growth factors.

Patients with recent CNS involvement should continue on CNS therapy (chemotherapy or radiation) as medically indicated during the protocol.

8.7 General Concomitant Medication Guidelines

- Coadministration with potent CYP3A inhibitors; consider alternative agents with less CYP3A inhibition
- Coadministration with potent CYP3A4 inducers.
- If concomitant administration of an anticoagulant/antiplatelet medication is indicated, then caution and enhanced monitoring is required. History of thrombocytopenia should be a factor in the choice of anticoagulant and dose.

8.8 Duration of Study Treatment

The expected duration of treatment for each subject is 4 cycles of treatment, each cycle lasting 4 weeks; with up to 4 weeks of rescreening for eligibility to continue on to subsequent cycles; followed by six additional months of ruxolitinib. The following may be reasons for removal from additional study treatment:

- unacceptable toxicity
- disease progression

- new GVHD (except grade I acute GVHD)
- prolongation of the most recent cycle to more than 8 weeks (for any reason)
- inadequate cell dose for further DLI
- consent is withdrawn or patient is not compliant

Patients who are unable to receive further DLIs after initial cycle(s), may continue to receive ruxolitinib as long as the physician believes they are benefiting from the treatment, the patient has not withdrawn consent, and they have not developed unacceptable toxicity.

All patients receiving at least one cycle of treatment will be followed per Sections 11.1 and 11.2 and be evaluable per Section 15.

Patients unable to continue DLI may be treated per physician's choice. These patients will still be followed per Sections 11.1 and 11.2.

8.9 Duration of Study Participation

All patients must be followed for 12 months after the last dose of ruxolitinib for disease response and survival unless one of the following occurs earlier:

- consent is withdrawn
- new anti-cancer treatment is started (follow for survival only),
- patient is discharged to hospice (terminal) care (follow for survival only)

9 Expected Adverse Events and Potential Risks

9.1 Ruxolitinib

Refer to the most current IB for the comprehensive list of adverse events.

The followings severe events have been seen in patients being treated for myelfibrosis or polycythemia vera and are considered expected:

Very Common (greater than or equal to 10%, or 10 or more out of 100 people)	Common (between 1 to 10%, or between 1 and 10 out of 100 people)	Rare (less than 1 out of 100 people)
• Ruxolitinib may cause low platelet counts (thrombocytopenia), low red blood cell counts	• Infection • chills • aches • fever	• Progressive multifocal leukoencephalopathy • Non-Melanoma Skin Cancer

Very Common (greater than or equal to 10%, or 10 or more out of 100 people)	Common (between 1 to 10%, or between 1 and 10 out of 100 people)	Rare (less than 1 out of 100 people)
(anemia), and low white blood cell counts (neutropenia) • unusual bleeding • bruising • tiredness • shortness of breath • fever • Cholesterol increases	• nausea • vomiting • weakness • painful skin rash or blisters	

The following severe events have been seen in patients being treated for acute or chronic GVHD and are considered expected.

Common for acute GVHD (1 - 10%)	Uncommon for acute GVHD (<1%)	Common for chronic GVHD (1-10%)	Uncommon for chronic GVHD (<1%)
• low platelet counts (thrombocytopenia), and low white blood cell counts (neutropenia): or low red cell, white cell, and platelet counts (pancytopenia) • CMV infection • Sepsis	• Septic shock	• low red blood cell counts (anemia)	• low platelet counts (thrombocytopenia) • Urinary tract infection • Sepsis • Septic shock

9.2 Decitabine

Refer to the most current IB or package insert(s) for the comprehensive list of adverse events.

Very Common (greater than or equal to 10%, or 10 or more out of 100 people)	Common (between 1 to 10%, or between 1 and 10 out of 100 people)	Rare (less than 1 out of 100 people)
• low platelet count with increased risk of bruising/bleeding	• blurred vision • pain • high blood sugar • headache	• confusion • trouble sleeping • fluid in the lungs

Very Common (greater than or equal to 10%, or 10 or more out of 100 people)	Common (between 1 to 10%, or between 1 and 10 out of 100 people)	Rare (less than 1 out of 100 people)
• low white blood cell count with increased risk of infection • low red blood cell count (anemia) with symptoms like tiredness, low energy, or shortness of breath • nausea • vomiting • diarrhea • constipation • tiredness • fever • pain or swelling in the arms or legs	• bruises or bleeding • swollen lymph nodes ("glands") • sores in mouth, on tongue, or on lips • infection • indigestion or sour stomach • abnormal blood tests which suggest that the drug is affecting the liver	• severe allergic reaction, with symptoms like flushing, hives, trouble breathing or swallowing, dizziness, swelling of mouth or throat (while drug is being infused) • serious infections • death from infection, bleeding, or other cause

9.3 Risks Due to DLI

Acute Infusion Reaction Following Donor Lymphocytes

Although infusion of donor lymphocytes has reportedly not been associated with serious acute hypersensitivity reactions, patients will be closely watched for the occurrence of hypotension, dyspnea and angiodema during the infusion and immediately thereafter. Corticosteroids should be avoided and acetaminophen and Benadryl may be administered as needed.

Acute Graft-Versus-Host Disease

Infusion of donor lymphocytes into patients who relapse post allogeneic bone marrow transplantation has frequently resulted in development of acute graft-versus-host disease with involvement of the skin and liver, often requiring treatment. Despite treatment, some cases of GVHD have been of high grade and deaths from GVHD have been reported. GVHD may occur between 1 and 24 weeks post-infusion of the donor lymphocytes. Patients will have regular assessment for development of new or worsening of existing GVHD during the entire study period.

Bone Marrow Aplasia

After donor lymphocyte infusions, patients may develop aplasia requiring blood product transfusions and/or growth factor support. This has been reported in 10-15% of reported

cases and some patients have developed severe marrow aplasia requiring a boost or second marrow infusion. Marrow aplasia and pancytopenia may be delayed and develop between 1 and 6 months after donor lymphocyte infusions. Deaths from infection or bleeding complicating pancytopenia have been reported.

10 Study Agent Information

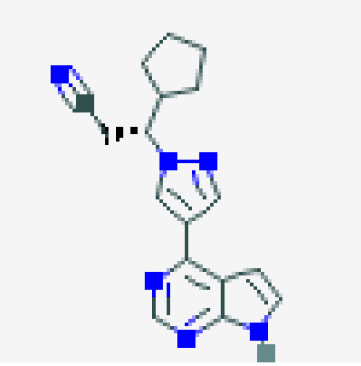
10.1 Ruxolitinib

10.1.1 Other Names

Jakafi®
INCB018424

10.1.2 Product Description

Ruxolitinib phosphate is a kinase inhibitor with the chemical name (R)-3-(4-(7H-pyrrolo[2,3-d] pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate and a molecular weight of 404.36. Ruxolitinib phosphate has the following structural formula:



Ruxolitinib phosphate is a white to off-white to light pink powder and is soluble in aqueous buffers across a pH range of 1 to 8.

Jakafi (ruxolitinib) Tablets are for oral administration. Each tablet contains ruxolitinib phosphate equivalent to 5 mg of ruxolitinib free base together with microcrystalline cellulose, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxypropyl cellulose.

10.1.3 Procurement

Incyte Corporation will supply Ruxolitinib at no charge to patients participating in this clinical trial.

Ruxolitinib will be supplied as 5 mg tablets packaged in 60-count high-density polyethylene bottles. All tablet excipients comply with the requirements of the applicable compendial monographs.

All Incyte product labels will state "Caution: New Drug--Limited by Federal (or United States) law to investigational use."

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.1.4 Storage Requirements

Bottles of tablets should be stored at room temperature, 15°C to 30°C (59°F to 86°F).

10.1.5 Preparation and Administration

Tablets can be taken with or without food. Grapefruit juice should not be consumed while on Ruxolitinib.

10.1.6 Drug Accountability and Destruction

Ruxolitinib must be dispensed only from official study sites and to eligible patients under the supervision of the site investigator. Ruxolitinib should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to patients. After final drug reconciliation, unused ruxolitinib will be disposed at the site following procedures for the disposal of anticancer drugs.

10.2 Decitabine

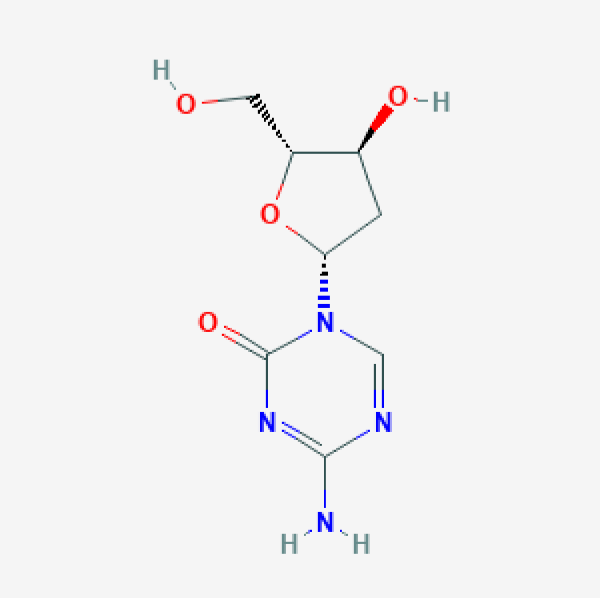
10.2.1 Other Names

Dacogen

10.2.2 Product Description

Dacogen™ (decitabine) for Injection contains decitabine (5-aza-2'-deoxycytydine), an analogue of the natural nucleoside 2'-deoxycytidine. Decitabine is a fine, white to almost white powder with the molecular formula

of C8H12N4O4 and a molecular weight of 228.21. Its chemical name is 4-amino-1-(2- deoxy-β-D-erythro-pentofuranosyl)-1,3,5-triazin-2(1H)-one and it has the following structural formula:



Decitabine is slightly soluble in ethanol/water (50/50), methanol/water (50/50) and methanol; sparingly soluble in water and soluble in dimethylsulfoxide (DMSO). Dacogen™ (decitabine) for Injection is a white to almost white sterile lyophilized powder supplied in a clear colorless glass vial. Each 20 mL, single dose, glass vial contains 50 mg decitabine, 68 mg monobasic potassium phosphate (potassium dihydrogen phosphate) and 11.6 mg sodium hydroxide.

10.2.3 Procurement

Commercially available.

10.2.4 Storage Requirements

Store vials at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F).

10.2.5 Preparations and Administration

Decitabine is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing decitabine.

Decitabine should be aseptically reconstituted with 10 mL of Sterile Water for Injection (USP); upon reconstitution, each mL contains approximately 5.0 mg of decitabine at pH 6.7-7.3. Immediately after reconstitution, the solution

should be further diluted with 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer's Injection to a final drug concentration of 0.1 - 1.0 mg/mL.

Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2°C - 8°C) infusion fluids and stored at 2°C - 8°C (36°F - 46°F) for up to a maximum of 7 hours until administration.

10.2.6 Stability

Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2°C - 8°C) infusion fluids and stored at 2°C - 8°C (36°F - 46°F) for up to a maximum of 7 hours until administration.

10.2.7 Drug Accountability

Decitabine is commercially available and will be procured by the inpatient pharmacy per institutional guidelines.

11 Clinical Evaluations and Procedures

Scheduled evaluations up to Day +28 in each cycle may be performed +/-3 days from the targeted date; evaluations and procedures (including research related) performed after Day +28 through end of final cycle may be done +/-7 days of the targeted date. Follow-up beginning at 6 months may be done +/- 2 weeks of the targeted date. In addition, targeted days may be altered as clinically appropriate.

11.1 Required Clinical Care Evaluations

	Screening within 28 days of study enrollment (within 14 days of C1D1 for eligibility labs)	**Every Treatment Cycle**		**Between study cycles (day 29-56)[3]**	**Post DLI Visit** (4-6 weeks after last DLI)	**Follow-Up** Q 3 months from the end of last cycle through 12 months
		During Decitabine admin	Day of DLI			
Written Consent	X					
Medical history	X					
Histological confirmation of diagnosis and staging	X					
Prior treatment	X					
Physical exam	X	X[8]	X		X	X
Provider assessment	X	X[8]	X			
Weight (Height also during screen)	X	X[8]				
Concomitant medications	X	X (day 1 each cycle)				
Karnofsky performance status	X			X		
ECG	X			X		
Type and Screen (ABO/RH/ Indirect Antiglobulin)	X					
Assessment of AEs	X	X	X		X	
Complete Blood Count with diff (CBC)	X	X[8]	X	X	X	X
Comprehensive Metabolic Profile (CMP)[1]	X	X[8]	X	X	X	X
HIV test	X					
Hepatitis B and C	X					
Pregnancy test (urine or serum) for WOCBP	X[2]			X		
Bone Marrow biopsy	X[4]			X[5]	X	
Relapse/progression status	X			X		
Survival status						X

	Screening within 28 days of study enrollment (within 14 days of C1D1 for eligibility labs)	**Every Treatment Cycle**		**Between study cycles (day 29-56)[3]**	**Post DLI Visit** (4-6 weeks after last DLI)	**Follow-Up** Q 3 months from the end of last cycle through 12 months
		During Decitabine admin	Day of DLI			
Study treatment						
Decitabine		X (day 1-10 or day 1-5 & 8-12)[6]				
DLI			X (between 11-21 or 13 -22)[7]			
Ruxolitinib		2 times a day →				Through 6 months post end of last cycle
Research Nurse visit		Every two weeks			X	X

[1]CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen, and liver function tests including AST, ALT, total bilirubin, and alkaline phosphatase

[2]For women of childbearing potential (WOCBP): urine or serum pregnancy test within 14 days prior to study registration. If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[3]Continuous reassessment for eligibility to proceed to subsequent cycles

[4]Results taken out of window may used as enrollment verification and will not be considered a deviation.

[5]Required prior to cycle 3. This sample will not be taken if not moving on to cycle 3.

[6]Day 1-5 in cycle 3 and 4 if CR achieved;

[7]Between day 6 and 16 in cycle 3 and 4 if CR achieved

[8] Day 1 of cycle and additional frequency per site institutional guidelines for clinical care. If screening (baseline) labs were performed within 7 days of Day 1 of treatment, these do not need to be repeated. For cycle 2 and later, lab work may be performed up to 3 days prior to the day 1 treatment day.

11.2 Patient – Research Related

Note: if a patient is not abiding by the required clinical care calendar (Section 11.1), the collection schedule of the toxicity data and research related samples may be altered or discontinued on an individual patient basis, as appropriate.

It is recognized that with novel therapies as used in this study, the timing of protocol directed research samples may miss important patient specific events. For this reason, up to 3 extra samples for a total of 180 ml of blood may be drawn at additional time points that are not specified above.

	Prior to Cycle 1	Every Treatment Cycle	Prior to Cycle 3	Post DLI (4-6 weeks after last DLI)	90 days (+/- 7 days) after the last day of last cycle	180 days (+/- 14 days) after the last day of last cycle	Event Driven	Event Driven
		Day 1					At disease progression	At GVHD diagnosis (+7 days)
Peripheral blood: Four 10 mL heparin tubes and one 10 ml clot tube		X[1]		X[4]	X	X	X[4]	X
Research bone marrow aspirate samples (max 10 ml, transferred to a heparin tube)	X[2]		X[3]	X[4]			X[4]	

[1] Prior to decitabine and ruxolitinib administration
[2] Optional, Adult patients only
3 This sample will not be taken if not moving on to cycle 3
4 At the time of clinical biopsy. If disease progression research samples are taken prior to the post-DLI samples, additional samples are not needed

11.2.1 Correlative Studies

Blood and Bone Marrow samples should be shipped the day of collection (Monday-Thursday) for next day delivery to the Masonic Cancer Center's Translational Therapy Lab (TTL). Refer to the Laboratory Manual for additional details. Pre-cycle 1 bone marrow sample is optional as it requires patient to undergo additional biopsy, while subsequent research bone marrow samples will be collected when the patient is having a bone marrow biopsy as part of clinical care.

TTTL will process the samples to obtain mononuclear cells (MNC) and serum/plasma. TTL will analyze MNC by flow cytometry to evaluate NK cells for possible effects of therapy on phenotype and functional characteristics. Remaining MNC will be cryopreserved for batch analysis of effects on T cells and for other future testing.

Potential mechanisms of action for JAK/STAT inhibition in the prevention of GVHD and augmentation of GVL include alterations in cytokine signaling, alterations in T-cell trafficking through CXCR3 expression,

effects on cellular differentiation, and effects on antigen presenting cell function. An exploratory objective of this study will be to evaluate the effects of the combination on immune effectors and to measure changes in biomarkers of GVHD and GVL. To address this objective, correlative studies may include: cellular phenotyping; leukemia antigen expression; cytokine and other soluble biomarker expression; chemokine receptor expression and RNA transcript analysis. DNA samples may be used to test for genetic associations of response to therapy or GVHD. These studies will be performed at Washington University at the end of study using batch analysis of banked samples. Remaining cryopreserved samples may be used for future research studies at the discretion of the principle investigator.

11.3 Donor – Recommended Standard of Care

Individual institutions may use local SOPs and clinical care guidelines, and unrelated donors will be screened through the NMDP.

12 Adverse Event Monitoring, Documentation, and Reporting

Toxicity and adverse events will be classified and graded according to NCI's Common Terminology Criteria for Adverse Events V 5.0 (CTCAE) and reported on the schedule below. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

The following definitions of adverse events (AEs) and serious adverse events (SAEs) will determine whether the event requires expedited reporting via the OnCore SAE Report Form in addition to routine documentation in the OnCore AE case report form (CRF).

The reporting timeframes for SAEs, product related issues, and other reportable events are located in Section 12.3.

Note: throughout this section the generic term “study drug” refers to the study related treatment (the ruxolitinib, decitabine, and DLI).

12.1 Adverse Event Terminology

The following definitions are based on the Code of Federal Regulations Title 21 Part 312.32 (21CFR312.32(a)).

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there

is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Life-Threatening Adverse Event Or Life-Threatening Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Unexpected adverse event or unexpected suspected adverse reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Expedited (Rapid) Reporting: Certain events may require rapid notification to entities providing patient safety oversight (e.g. IRB) as detailed in Section 12.3. For the IRB this is 5 business days from discovery.
The categories for AE attribution to study treatment are as follows:

- Definite – clearly related
- Probable – likely related
- Possible – may be related
- Unlikely – doubtfully related

- Unrelated – clearly not related

The following definitions are from the Masonic Cancer Center's Standard Operating Procedure (SOP) Deviation Reporting:
Major Deviation: A deviation or violation that impacts the risks and benefits of the research; may impact subject safety, affect the integrity of research data and/or affect a subject's willingness to participate in the research. Deviations that place a subject at risk, but do not result in harm are considered to be major deviations.

Minor Deviation: A deviation or violation that does not impact subject safety, compromise the integrity of research data and/or affect a subject's willingness to participate in the research.

12.2 AE Documentation

AE reporting will occur via data entry into the study eCRF. AEs reported through expedited processes (e.g., reported to Incyte, IRB, FDA, etc.) must also be reported in routine study data submissions. Patients will be monitored for adverse events after the subject has signed the ICF through 30 days after the last dose of study drug. Adverse events recorded in the eCRFs include the following:

- CTCAE grade 3 and greater allergic reactions related to ruxolitinib or decitabine occurring until 30 days after the last treatment on study
- CTCAE grades 3 and greater organ toxicity (cardiac, dermatologic, gastrointestinal, hepatic, pulmonary, renal/genitourinary, or neurologic) occurring until 30 days after the last treatment on study
- aGVHD III-IV occurring until 3 months after the last cycle of treatment
- CTCAE grade 4 neutropenia lasting more than 14 days, occurring until 30 days after the last treatment on study
- CTCAE grades 3 and greater febrile neutropenia, or grade ≥ 3 neutropenia with documented infection, occurring until 30 days after the last treatment on study
- CTCEA grade 4 thrombocytopenia lasting more than 14 days if pre-treatment platelet count > 100 x 10^9/L, occurring until 30 days after the last treatment on study

In addition any event meeting the definition of a serious adverse event (SAE) regardless of attribution that occurs during this period will be documented in the source document and recorded in OnCore.

After the final treatment visit, monitoring for adverse event will become less frequent based on the schedule in Section 11 and only events at least possibly related to study treatment (based on the table above) will be documented upon knowledge.

12.3 SAE Documentation and MCC Reporting Requirements

Individual institution reporting requirements are listed in section 12.5.

All SAEs are documented using the MCC OnCore SAE Report Form and reported within the timeframes indicated below:

Agency	Criteria for reporting	Timeframe	Form to Use	Submission address/ fax numbers
U of MN IRB	Events requiring prompt reporting including, but not limited to unanticipated death of a locally enrolled subject(s); new or increased risk; any adverse event that require a change to the protocol or consent form or any protocol deviation that resulting in harm For a complete list refer to http://www.research.umn.edu/irb/guidance/ae.html#.VC7xraI0-sh	Within 5 business days of event discovery	MCC SAE Report Form	ETHOS copy SAEs to Incyte at SafetyReporting @incyte.com (note: Incyte does not need copies of deviations)
	Deviations from the protocol, per current IRB reporting requirements		Deviation Report	
FDA	Unexpected and fatal or unexpected and life threatening suspected adverse reaction	no later than 7 Calendar Days	MCC SAE Report Form	Submit to FDA as an amendment to IND
	1) Serious and unexpected suspected adverse reaction or 2) increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure or 3) findings from other sources (other studies, animal or in vitro testing)	no later than 15 Calendar-Days		
	Events that trigger an early study stopping rule.	no later than 7 Calendar Days	Event Form	
Incyte Corporation	Every SAE, regardless of suspected causality (eg, relationship to study drug(s) or study procedure or disease progression), occurring after the subject has signed the ICF through the last study visit (or 30 days) after the last dose of study drug, whichever is later) must be reported to the Incyte within 24 hours of learning of its occurrence, Incyte may request follow-up and other additional information from the Sponsor Investigator.	Within 24 hours of event discovery	MCC SAE Report Form	SafetyReporting@ incyte.com
Masonic Cancer Center SAE Coordinator	Events that count toward early study stopping rule.	At time of reporting	Event Form	SAE Coordinator mcc-saes@umn.edu with copy to Incyte

Expedited SAE Reporting Requirements:

Report Within 24 Hours: SAEs must be reported expeditiously to the Masonic Cancer Center Affiliate Sites Manager within 24 hours of knowledge.

12.4 Early Stopping Rule Events Documentation and Reporting Requirements

The following events count toward an early study stopping rule per Section 15.4 and must be reported to the MCC Affiliate Sites Manager and to Incyte Pharmaceuticals using the Event Form found OnCore under the reports tab: grade III-IV aGVHD until 3 months after the last cycle of treatment.

An event that counts toward an early stopping rule does not necessarily constitute a SAE and should be reported as such only if they meet the criteria for reporting as defined in Section 12.3.

12.5 Institutional Event Reporting Table

Individual institutional sites will be responsible for reporting any event meeting local reporting requirements to their institutional IRB and/or other research oversight committees.

Institutional sites will be responsible for reporting events as defined in sections 12.1, 12.2, 12.3 and 12.4 within the following time frames to the MCC Affiliate Sites Manager

Event Type	Reporting Timeframe	OnCore Form to Use	Report to**
Any event meeting the definition of a SAE occurring after the subject has signed the ICF through the last study visit (or 30 days after the last dose of study drug, whichever is later)	Within 24 hours of knowledge	SAE Report Form	Masonic Cancer Center (MCC) Affiliate Sites Manager affiliates@umn.edu The affiliate manager will submit SAEs to Incyte (SafetyReporting@incyte.com) Local institutional IRB or other entities per institutional policies and guidelines
Stopping Rule Events as defined in section 12.4	Within 24 hours of knowledge	Stopping Rule Event Form	
Major and Critical Clinical Deviations, as defined in Section 12.1.	Within 5 working days of knowledge	Deviation Report Form	

Event Type	Reporting Timeframe	OnCore Form to Use	Report to**
Minor Deviations, as defined in Section 12.1.	Per Institutional Policy	n/a (record in Deviations Tab) but it is not necessary to report the event to MCC	For UMN MCC only: minor deviations are reported to the UMN IRB by the study's regulatory specialist per IRB reporting requirements. For Affiliate Sites: minor deviations are not reportable to the Masonic Cancer Center. Report to local institutional IRB or other entities per institutional policies and guidelines.

**events occurring at the University of Minnesota are reported to the study's Regulatory Specialist who will submit Incyte and other entities as usual

13 Study Data Collection and Monitoring

13.1 Data Management

This study will collect regulatory and clinical data using University of Minnesota CTSI's instance of OnCore® (Online Enterprise Research Management Environment).

The Oncore database resides on dedicated secure and PHI compliant hardware consisting of 3 physical servers: dev, DR, and production. The dev server is located in the University of Minnesota (UMN) datacenter (WBOB) and houses six database instances (test, train, sandbox, mcc reports, oncdm, and vendor) that are backed up locally because the data is refreshed from Oncore production data. The production server is located in the UMN datacenter (WBOB). All the data servers are managed by the Academic Health Center – Information Systems (AHC-IS) virtual servers which utilize clustered infrastructure to provide real-time failover of virtual servers. This real-time clustering is physically limited to the UMN data center. All relevant AHC IS procedures related for PHI compliant servers (as required by the Center of Excellence for HIPAA Data) apply to Oncore databases.

The integrated data will be stored in PHI compliant servers managed by AHC IS with access given to those authorized users in the Clinical and Translation Science Institute Informatics team (CTSI BPIC and MCC CISS). The data will be integrated and extracted to researchers through the CTSI Informatics team and will be delivered through secure and compliant mechanisms (e.g. AHC IE data shelter, BOX, sftp, etc). If data de-identification is needed, then compliant AHC IE data de-identification tools will be used. The informatics team will grant the IRB approved study team members access to data.

Additional data about correlative laboratory samples generated by the Masonic Cancer Center Translational Therapy Laboratory (TTL) from the protocol-directed correlative research samples is stored in their Laboratory Information Management System (LIMS).The LIMS database application is also stored on a production server located in the UMN datacenter (WBOB) and is managed by the Academic Health Center

Key study personnel are trained on the use of OnCore and will comply with protocol specific instructions embedded within the OnCore.

13.2 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRFs) developed within OnCore based on its library of standardized forms. The e-CRF will be approved by the study's Principal Investigator and the Biostatistician prior to release for use. The Study Coordinator or designee will be responsible for registering the patient into OnCore at time of study entry, completing e-CRFs based on the patient specific calendar, and updating the patient record until patient death or end of required study participation.

13.3 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at https://z.umn.edu/dsmp.

For the purposes of data and safety monitoring, this study is classified as high risk. Therefore the following requirements will be fulfilled:

- At least bi-annual review of the study's progress by the Masonic Cancer Center Data and Safety Monitoring Council (DSMC).
- The PI will comply with at least twice yearly monitoring of the project by the institution's monitoring services.
- The PI will oversee the submission of all reportable adverse events per Section 12.3 to the Masonic Cancer Center's SAE Coordinator, the University of Minnesota IRB, and the FDA.
- The PI with the CTO has oversight responsibility for trial monitoring at affiliate sites.

In addition, at the time of the continuing review with the University of Minnesota IRB, a copy of the report with any attachments will be submitted to the Cancer Protocol Review Committee (CPRC).

IND Annual Reports

In accordance with regulation 21 CFR § 312.33, the Sponsor-Investigator will submit a progress report annually. The report will be submitted within 60 days of the anniversary date that the IND went into effect.

13.4 Teleconferences – Lead Site and Affiliate Site

Regular teleconferences to facilitate communication between participating sites regarding the study's progress, patient updates, summary of safety reports, case report form completion, and other issues for discussion. The University of Minnesota Affiliate Manager will be responsible for arranging these teleconferences and preparing the agenda. Meetings will occur at least every 3 weeks; however, these may be scheduled more or less frequently at the discretion of the lead institution. Participation of a minimum of one representative from each affiliate site will be required. These teleconferences are in addition to other previously described site interactions including centralized patient registration, institutional and MCC required reporting of safety related issues, case report form completion in the study's central database (OnCore) and affiliate oversight through self-monitoring in compliance with the Masonic Cancer Center's Data and Safety Monitoring plan.

13.5 Affiliate Site Monitoring

The PI (Dr. Juckett) with the CTO has oversight responsibility for trial monitoring at affiliate sites. Affiliate sites must self-monitor following the University of Minnesota Masonic Cancer Center Data and Safety Monitoring Plan (DSMP - http://z.umn.edu/dmsp).

The investigator will permit study-related monitoring, audits, and inspections by the study's Principal Investigator or any designees, the local IRB, government regulatory bodies, and University of Minnesota compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

13.6 Record Retention

The investigator will retain study records including source data, copies of case report form, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at least 6 years after the study file is closed with the IRB.

Please contact the CTO before destroying any study related records.

14 Study Endpoints

14.1 Primary Endpoint

Efficacy is measured by overall survival (OS) at 6 months.

14.2 Secondary Endpoints

Secondary endpoints of safety and efficacy are measured as below.

- OS at 12 months
- Cumulative incidence of grade II-IV acute graft-versus-host disease (aGVHD II-IV) at 3 months
- PFS at 6 and 12 months in patients
- Cumulative incidence of relapse at 6 and 12 months
- Complete remission (CR) at 6 and 12 months
- Cumulative incidence of non-relapse mortality (NRM) at 6 and 12 months
- Best response until next line of treatment, death, or last follow up, whichever occurs sooner

14.3 Correlative Endpoints

- Incidence and severity of adverse events (AEs) and serious AEs (SAEs) until 3 months after day 1 of the last received cycle
- Correlative studies: T cell and NK cell subset analysis by flow cytometry, correlation between *TP53* mutation and response, clonal dynamics during and after the course of therapy

15 Statistical Considerations

15.1 Objectives and Study Design

This is a single-arm, open-label, multi-center modified Simon's two-stage phase II trial of a combined modality treatment for relapsed AML and MDS after allo-HCT. The primary endpoint is 6 month OS measured from day 1, cycle 1. We expect a total of 34 enrolled subjects will allow us to obtain 32 evaluable patients.

Patients are considered evaluable if they receive the first dose of decitabine and ruxolitinib. All other patients will be replaced.

15.2 Statistical Analysis

Analysis of the Primary Endpoint

Overall survival will be estimated by Kaplan-Meier curves along with 95% confidence bands to provide precision.

Secondary and exploratory analysis

Analysis of secondary endpoints will be primarily descriptive. Progression-free survival will be estimated by Kaplan-Meier curves. Cumulative Incidence will be used to estimate the probability of relapse and acute GVHD, treating non-event death as a competing risk. Likewise, relapse will be treated as a competing risk when estimating the probability of non-relapse mortality. Response and the number of patient in complete remission will be estimated with simple proportions. Summary statistics using frequencies and proportions of patients will be used to assess adverse and severe adverse events and medians, ranges and descriptive plots for immune therapy. The correlation between *TP53* mutation and response will be assessed with a chi-square test or Fisher's exact test depending on expected cell frequencies. Similar statistics will be used for the correlation against clonal dynamics curing and after the course of therapy.

Subgroup Analysis

We will assess subgroup analysis of endpoints by donor type. Overall survival is not assumed to differ by donor type and this trial is not powered to determine differences within subgroups and will therefore be considered exploratory.

15.3 Sample Size

This study is designed as a two-stage phase II trial to estimate OS. Since the goal is to estimate the OS at a long-term time-point (6 months), our design is a generalization of the Simon design. Rather than suspension of the trial for evaluation after stage 1, this design uses an optimal interim analysis for futility without suspension of accrual as proposed by Huang et al[17]. The goal of this design minimizes the expected sample size under the assumed parameters. Our trial assumes that a 6-month OS of 25% is unacceptably low and a 6-month OS of 50% is a rate worthy of further study. Both the null and alternative hypotheses assume that the OS follow an exponential distribution. Given an overall one-sided type I error of 5%, 32 evaluable patients will provide 80% statistical power.

When 14 patients have been enrolled (stage 1), it is expected that the accrual will stop if the 6 month Kaplan-Meier estimate of OS is less than 30.0%. It is not required that the 14th patient be followed for 6 months prior to making a decision of whether to continue the trial. Once the 14th patient has been enrolled, the statistician can calculate survival to determine if it falls below the cut-point. If the trial reaches the end of stage II after 32 evaluable patients, significant clinical activity would require at least a 6 month Kaplan-Meier estimate of OS of 39.2%. The probability of stopping at the interim analysis under the null hypothesis is 63.5% and 10.9% under the alternative hypothesis. The R package 'Optinterm' with functions 'OptimDes' and 'SimDes' were used to create design parameters. Assuming that 5% of enrolled patients are not evaluable, we expect recruitment of 34 patients.

Accrual

We perform approximately 30 DLIs per year at the collaborating institutions combined. Considering ~50% screen failures and enrollment on competing trials, we expect to complete enrollment in approximately 2 years with an additional year of follow up after the last patient has been enrolled.

15.4 Stopping Rules

Toxicity Monitoring and stopping rules

Monitoring guidelines are developed to monitor excess toxicity using a continuous monitoring strategy based on an adaptation of Pocock stopping boundaries[20]. In the event that a stopping rule is triggered, enrollment will be halted and reviewed by the full study committee and if appropriate by the IRB, prior to initiation of re-enrollment. Additionally, the FDA will be informed if a stopping rule is triggered. The stopping rule was calculated using the following website: http://cancer.unc.edu/biostatistics/program/ivanova/ContinuosMonitoringForToxicity.aspx

Grade III-IV aGVHD until 3 months after the last cycle of treatment

Stopping rules were developed for excessive grade III-IV aGVHD. Previous results from trials of HMA plus DLI have reported an incidence of ~10% for aGVHD III-IV[8,9,18,19]. The goal is to construct a boundary based on aGVHD grade III-IV such that the probability of early stopping is at most 5% if the true rate is equal to 10% and our sample size is 34. Given these parameters, the upper stopping boundary for aGVHD grade III-IV is 2 events out of 2 patients, 3 out of 6, 4 out of 10, 5 out of 15, 6 out of 21, 7 out of 27 or 8 out of 33. The probability of early stopping from excessive aGVHD grade III-IV if the true probability is 30% is 86%.

16 Ethical and Regulatory Considerations

16.1 Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

16.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, informed consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

16.3 Informed Consent

All potential study participants will be given a copy of the IRB-approved consent to review. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the consent document. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

17 References

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Appendix I – Karnofsky Performance Status Scale

Percentage	
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 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 necessary, active supportive treatment necessary
10	Moribund, fatal processes, progressing rapidly
0	Dead

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Appendix II — GVHD Grading Scales

Acute GVHD:

Consensus Clinical Stage and Grade of Acute GVHD (Glucksberg *et al*, 1974; Thomas *et al*, 1975, Przepiorka *et al*, 1995)

Stage	Skin	Liver	Lower Gastrointestinal Tract	Upper Gastrointestinal Tract
1	Maculopapular rash <25% of body surface	Bilirubin 2.0 – 3.0 mg/dl	Diarrhea 500 – 1000 mL/day or 280 – 555 mL/m^2	No protracted nausea and vomiting
2	Maculopapular rash 25-50% body surface	Bilirubin 3.1 – 6.0 mg/dl	Diarrhea 1000 – 1500 mL/day or 556 – 833 mL/m^2	Persistent nausea, vomiting or anorexia
3	Generalized erythroderma	Bilirubin 6.1 – 15.0 mg/dl	Diarrhea >1500 mL/day or >833 mL/m^2	
4	Generalized erythroderma with bullous formation and desquamation	Bilirubin > 15 mg/dl	Severe abdominal pain, with or without ileus, or stool with frank blood or melena	

University Of Minnesota Acute GVHD Grading

Acute GVHD Grade	Skin Stage	Liver Stage	Lower GI Stage	Upper GI Stage
I	1-2	0	0	0
II	3	1	1	1
III	-	2-4	2-3	
IV	4	-	4	

- Each column identifies minimum criteria for organ grade.
- Each grade is based on maximum stage for each individual organ involved

e.g. Grade II = skin stage 3 and/or liver stage 1 and/or gut stage 1 and/or UGI stage 1

Late Acute and Chronic GVHD:

Late acute and chronic GVHD will be assessed using the National Institutes of Health (NIH) Consensus Criteria.

Patient ID: _____

Date of late acute or chronic GVHD diagnosis (mm/dd/yyyy) ☐☐/☐☐/☐☐☐☐

Onset of chronic GVHD was:

- ○ Progressive (acute GVHD progressed directly to chronic GVHD)
- ○ Interrupted (acute GVHD resolved, then chronic GVHD developed)
- ○ De novo (acute GVHD never developed)
- ○ Chronic GVHD flare (symptoms reactivated within 30 days of drug tapering or discontinuation)

Karnofsky Performance status:

- ○ 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 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 is indicated. Death not imminent
- ○ 20 Very Sick, hospitalization necessary, active supportive treatment necessary
- ○ 10 Moribund, fatal processes, progressing rapidly
- ○ 0 Dead

Diagnosis was based on:

- ○ Histologic evidence / biopsy proven
- ○ Clinical evidence
- ○ Both
- ○ Unknown

Overall severity of chronic GVHD

- ○ Mild
- ○ Moderate
- ○ Severe

Organ/System Involvement (check if yes)

- ○ Sclerosis of skin
- ○ Other skin or hair involvement (rash, ulcers, pruritus or itching, dyspigmentation, alopecia, lichenoid skin changes, etc)
- ○ Eyes (xerophthalmia (dry eyes), abnormal Schirmer's test, abnormal slit lamp, corneal erosion / conjunctivitis, etc)
- ○ Mouth (lichenoid changes, mucositis / ulcers, erythema, etc)
- ○ Bronchiolitis obliterans
- ○ Other lung involvement

Organ/System Involvement (check if yes)

- ○ Gastrointestinal tract (esophageal involvement, chronic nausea / vomiting, chronic diarrhea, malabsorption, abdominal pain / cramps, etc)

- ○ Liver
- ○ Genitourinary tract (vaginitis / stricture, etc)
- ○ Musculoskeletal (arthritis, contractures, myositis, myasthenia, etc)
- ○ Thrombocytopenia (< 100 x 10^9/L)
- ○ Eosinophilia
- ○ Autoantibodies
- ○ Other hematologic involvement
- ○ Serositis
- ○ Weight loss
- ○ Other organ involvement from chronic GVHD

Specify other organ:

Ref: Jagasia MH, Greinix HT, Arora M. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant. 2015 March; 21(3): 389–401.e1. doi:10.1016/j.bbmt.2014.12.001.