HUNTSMAN CANCER INSTITUTE
UNIVERSITY OF UTAH

Allogeneic Stem Cell Transplantation for Multiple Myeloma and Myelofibrosis

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IND Number Exempt

Historical Protocol Versions

Version 1:26APR2017
Version 2:27OCT2017
Version 3: 02JUL2018
Version 4: 29JAN2019

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LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events

Abbreviation or Term[1]	Definition/Explanation
CV	Coefficient of variation
CYP	Cytochrome P450
D/C	Discontinue
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
Eg	Exempli gratia (for example)
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
INR	International normalized ratio
IRB	Institutional review board
IU	International unit

Abbreviation or Term[1]	Definition/Explanation
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LLQ	Lower limit of quantitation
MedRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
PD	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cell
QD	Once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Frederichia equation
SAE	Serious adverse event
SD	Standard deviation or stable disease
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine
T_{max}	Time of maximum observed concentration
TID	Three times daily

Abbreviation or Term[1]	Definition/Explanation
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
UV	Ultraviolet
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of nonchildbearing potential

All of these abbreviations may or may not be used in protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

Note: This document is signed electronically through submission and approval by the Principal Investigator at Huntsman Cancer Institute in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system. For this reason, the Principal Investigator at Huntsman Cancer Institute will not have a hand-written signature on this signature page.

STUDY SUMMARY

Title	A Phase II study of Allogeneic stem cell transplantation for multiple myeloma and myelofibrosis
Short Title	Allo SCT for MM and MF
Protocol Number	98381
IND	Exempt
Phase	II
Design	Single arm, open labeled study of allogenic stem cell transplantation for multiple myeloma and myelofibrosis with related and unrelated stem cell donors.
Study Duration	Patients will receive treatment for 2 weeks with 1 year follow up Accrual will take 3 years Total study duration will be 4 years
Study Center(s)	Single Center: HCI
Objectives	**Primary endpoints:** To evaluate Non-Relapse Mortality (NRM) up to day +100. **Secondary endpoints:** To evaluate Non-Relapse Mortality (NRM) up to day +365. To evaluate the incidence of acute GVHD and chronic GVHD up to day +365 post-transplant. To evaluate the Overall Survival and Disease Free Survival up to 1 year. To evaluate Clinical Response and Molecular Response up to 1 year.
Number of Subjects	24
Diagnosis and Main Eligibility Criteria	**Inclusion Criteria:** Age 18-75 years. ECOG status 0-1 **Patients must have histologically documented Multiple Myeloma (MM)** A) Patients in early relapse (less than 24 months from initiation of systemic anti-myeloma therapy which may include single or planned tandem autologous transplant) after primary therapy that included an autologous HSCT OR

	B) Later Stage OR C) High risk factors defined by the presence of any one of the following detected at any time prior to enrollment: deletion of chromosome 13 by conventional cytogenetics, hypodiploidy, abnormality in chromosome 1 (1q amplification or 1p deletion), t(4;14), t(14;16), t(14;20) or deletion of 17p by fluorescence in situ hybridization (FISH) or conventional karyotyping; high risk criteria based on commercially available gene expression profiling OR D) extramedullary disease, plasma cell leukemia or high LDH [19] **Patients must have histologically documented Myelofibrosis (MF)** 1) Patients with DIPSS plus intermediate stage 2 or higher risk MF OR 2) Subset of intermediate stage 1 patients. Defined by: a) Poor-risk molecular profile (triple negative: JAK2, CALR, MPL) OR b) Presence of any of the following mutations: (ASXL1, SRSF2, EZH2, IDH1/2) OR c) Severe thrombocytopenia, severe anemia, high peripheral blood blasts percentage OR d) Unfavorable cytogenetic abnormalities (rearrangements of chromosome 5 or 7 or ≥ 3 abnormalities [40]).

	Exclusion Criteria: a. Cardiac-left ventricular ejection fraction <40%, symptomatic coronary artery disease, or uncontrolled arrhythmias b. Pulmonary- FEV1 or DLCO < 40% or history of chronic use of supplemental oxygen. Temporary use of supplemental oxygen at the time of screening or registration is allowed if the investigator feels that the underlying cause of requiring oxygen is reversible by the time treatment begins c. Renal- calculated or measured GFR <30 ml/min, dialysis-dependent, or history of renal transplant d. Hepatic- bilirubin > 2 X ULN, ALT> 2.5 X ULN, cirrhosis e. Patients with active or uncontrolled bacterial, viral, or fungal infections requiring systemic therapy f. Pregnant women, nursing mothers or women of child-bearing potential who are unwilling to use medically accepted methods of contraception
Study Product, Dose, Route, Regimen	Allogenic transplant using a divided regimen of busulfan at Day-5 to Day-2 and post-transplant cyclophosphamide at Day +3 and Day +4.
Duration of administration	10 days
Reference therapy	Standard of care continuous conditioning regimen using busulfan and cyclophosphamide.
Statistical Methodology	Comparison of primary endpoint with historical benchmarks of patients treated with allogenic transplants. Analysis of secondary endpoints will be done descriptively.

OBJECTIVES

This study will investigate a variation on a proven conditioning program for allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for treatment of patients with Multiple Myeloma (MM) and primary Myelofibrosis (PMF). The current protocol allows stem cell transplant from matched related donors (MRD), matched unrelated donors (MUD), mismatched unrelated donor(s) (mMUD) and haploidentical donor(s) (Haplo).

1.1 Primary Objectives and Endpoint

1.1.1 To evaluate Non-Relapse Mortality (NRM) up to day +100.

1.2 Secondary Objectives and Endpoint

1.2.1 To evaluate Non-Relapse Mortality (NRM) up to day +365.

1.2.2 To evaluate the incidence of acute GVHD and chronic GVHD up to day +365 post-transplant.

1.2.3 To evaluate the Overall Survival and Disease Free Survival up to 1 year.

1.2.4 To evaluate Clinical Response and Molecular Response (complete response and partial response [section 9.4]) up to 1 year

BACKGROUND

The proposed conditioning regimen modifies the combination of busulfan-cyclophosphamide, one of the most successful in the treatment of Multiple Myeloma [(2)], from a continuous conditioning regimen to a divided regimen where busulfan is given before allogeneic HSCT and cyclophosphamide on day +3 and +4 post allogeneic HSCT. This is the accepted standard therapy for Graft Versus Host Disease (GVHD) prevention in haploidentical transplantation and has been explored in the other 3 types of transplant. To allow for engraftment in this combination, a moderate dose of fludarabine is given, since busulfan alone might not be immunosuppressive enough.

This variation regimen is designed to maximize the antitumor effect in myeloma and myelofibrosis and minimizes the toxicity by PK directed busulfan administration and may also minimize acute and chronic GVHD by administering cyclophosphamide at day +3 and day +4 post allogeneic HSCT.

2.1 Allogeneic in Stem Cell Transplantation in Multiple Myeloma

Allogeneic HSCT is the only potentially curative therapy for Multiple Myeloma (MM). The use of reduced-intensity conditioning (RIC) has broadened the use of allogeneic HSCT in MM especially in patients with refractory disease and relapsed after an autograft. [(1,2,3,4,5)] B. Andersson introduced the PK directed busulfan regimen to optimize dose-targeting and reduced transplant related mortality.[(6,15)]

Risk criteria for allogeneic HSCT in MM are early relapse after primary therapy and/or high risk factors (i.e. cytogenetics, extramedullary disease, plasma cell leukemia or high LDH).

2.2 Allogeneic Stem Cell Transplant in Myelofibrosis

Allogeneic HSCT is the only curative treatment for primary myelofibrosis (PMF), a clonal myeloproliferative neoplasm with a high risk for clonal evolution and mortality.

Prognostic tools have been developed that assist in therapeutic decision making. The International Prognostic Symptom Score (IPSS) is a clinical based model to assess prognosis at the time of primary myelofibrosis diagnosis. The IPSS score was upgraded to the dynamic IPSS plus (DIPPS plus) score, which further clarified risk variables and risk categories (Appendix A) Four risk categories are included in DIPSS plus: low, intermediate 1, intermediate 2, and high. These categories are assessed by: age,

constitutional symptoms, hemoglobin, the basis of WBC, circulating blasts, platelet count, RBC transfusions needed, and unfavorable karyotype.

Only MF patients with intermediate 2 and intermediate 1 with high risk designations according to DIPPS plus should be transplanted.[8]

2.3 Post allograft Cyclophosphamide

Post allograft cyclophosphamide (Cytoxan) has been introduced as measure for GVHD prevention in recipients of haploidentical, mismatched unrelated, and matched unrelated transplants. The results of post allograft cyclophosphamide are comparable to or better than other ways of immunosuppression, like ATG in mismatched and matched recipients of stem cell transplants. Post allograft cyclophosphamide is believed to work by destroying early activated donor T-cells and by sparing regulatory T-cells via increased expression of ALDH, one of the enzymes which metabolizes cyclophosphamide. [9,10,11,12,13] Post allograft cyclophosphamide as sole means of GVHD prophylaxis is not sufficient and should therefore be combined with other immunosuppressant like tacrolimus and mycophenolic acid (MMF) as standard of care.

2.4 Detection of minimal residual disease (MRD) following transplantation in MM and MF

Relapse represents the main cause of treatment failure after hematopoietic stem cell transplantation (HSCT). Monitoring of Minimal Residual Disease (MRD) allows for early detection and subsequent intervention prior to clinically detectable relapse.

MRD-determination will be done as a standard procedure approximately every 3-6 months in patients that achieve a complete response only.

MRD monitoring in MM is done by Flow Cytometry (preferred), ASO-PCR, by determining the VDOH rearrangements or NGS.[14,15,16]

MRD-Monitoring in MF is done by JAK2 PCR, cMPL, Calreticulin mutation PCR and donor-recipient chimerism determination.

Molecular relapse will be treated by DLI infusion ($1X10^6$/kg BW for matched related donors as defined by the HCI BMT SOP (https://pulse.utah.edu/policies/FilteredFor/Blood%20and%20Marrow%20Transplant.aspx – or consult with BMT pharmacist). Infusion of donor lymphocytes (DLI) leads to molecular responses in 30-50% of cases with MM and MF.[17,18]

DRUG INFORMATION

3.1 Busulfan

For HSCT conditioning, intravenous busulfan is more often utilized due to less pharmacokinetic variability. With conditioning doses of busulfan, antiepileptic medication must be given. Seizure prophylaxis with levetiracetam should start prior to receiving busulfan and continue until at least 24 hours after the infusions are complete. Newer second-generation antiepileptics such as levetiracetam have become a favorable option due to decreased adverse effects and minimal drug interactions. Side effects of busulfan include nausea, diarrhea, myelosuppression, transient increase in liver enzymes, and rarely more serious liver and lung toxicity.[20] The pharmacokinetic levels

of busulfan are determined by measuring levels in the blood following the first IV infusion according to HCI BMT SOPs: (https://pulse.utah.edu/policies/FilteredFor/Blood%20and%20Marrow%20Transplant.aspx – or consult with BMT pharmacist).

3.2 **Fludarabine**

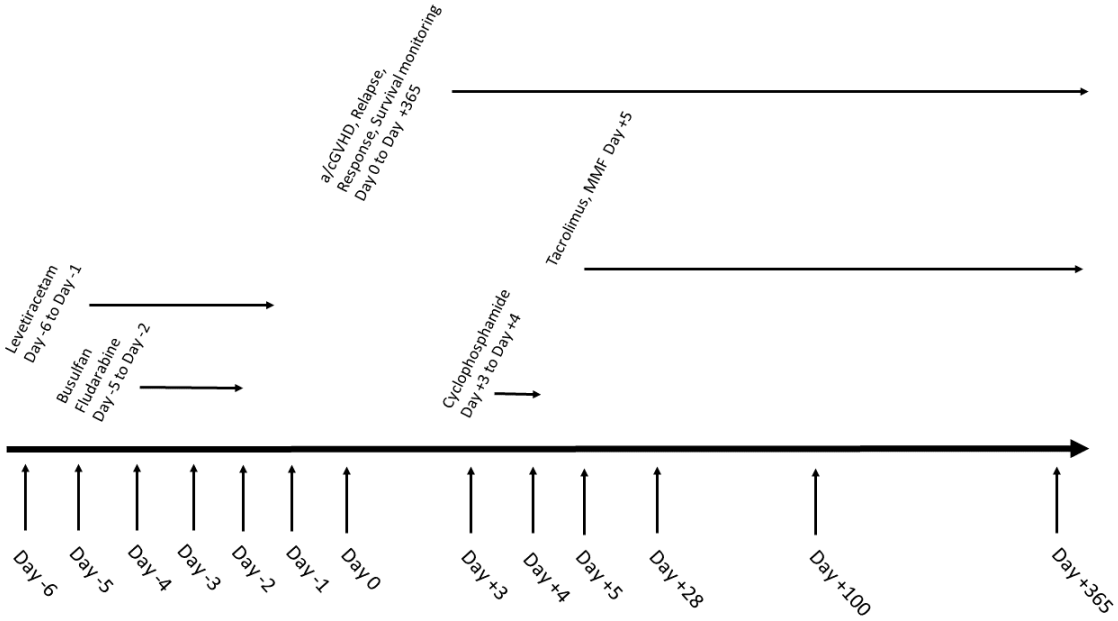
Fludarabine or fludarabine phosphate (Fludara) is a chemotherapy drug used in the treatment of hematological malignancies (cancers of blood cells such as leukemias and lymphomas). It is a purine analog, which interferes with DNA synthesis. Fludarabine is highly effective in the treatment of chronic lymphocytic leukemia, producing higher response rates than alkylating agents, such as chlorambucil, alone. Fludarabine is used in various combinations with cyclophosphamaide, mitoxantrone, dexamethasone and rituximab in the treatment of indolent non-Hodgkins lymphomas. As part of the FLAG regiment, fludarabine is used together with cytarabine and granulocyte colony stimulating factor in the treatment of acute myeloid leukemia. Because of its immunosuppressive effects, fludarabine is also used in some conditioning regimens prior to allogeneic stem cell transplant.

3.3 **Cyclophosphamide**

Cyclophosphamide is an alkylating agent of the nitrogen mustard type (specifically, the oxazaphosphorine group). An alkylating agent adds an alkyl group to DNA. It attaches the alkyl group to the guanine base of DNA, at the number 7 nitrogen atom of the imidazole ring. This interferes with DNA replication by forming intrastrand and interstrand DNA crosslinks. Cyclophosphamide is used to treat cancers, autoimmune disorder and AL amyloidosis. As a prodrug, it is converted by liver cytochrome P450 (CYP) enzymes to form the metabolite 4-hydroxycyclophosphamide that has chemotherapeutic activity. Cyclosphosphamide has severe and life-threatening adverse effects, including acute myeloid leukemia, bladder cancer, hemorrhagic cystitis and permanent infertility, especially at higher doses. The addition of cyclophosphamide at day +3 and day +4 has two purposes: a) optimizing the antineoplastic effect against MM and MF and b) to prevent serious life-threatening GVHD.

STUDY DESIGN

STUDY SCHEMA



Description

Patients will receive pre-transplant conditioning with busulfan (PK directed) and Fludarabine, followed by post-transplant cyclophosphamide on day +3 and day +4 as GVHD prophylaxis.

All patients will receive additional GVHD prophylaxis with post allogeneic HSCT Cyclophosphamide, Tacrolimus and MMF per standard of care (HCI BMT SOPs: [https://pulse.utah.edu/policies/FilteredFor/Blood%20and%20Marrow%20Transplant.aspx – or consult with BMT pharmacist]). Residual or relapse disease will be treated with DLI infusions.

4.1 Number of Patients

24 patients will be enrolled. There is no limit to the ratio of MM and MF patients that enroll. (4, 8, 12 in 1st, 2nd and 3rd year)

4.2 Number of Study Centers

Huntsman Cancer Institute will be the sole enrolling site.

4.3 Study Duration

Total Study duration will be four years.

ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with investigators signature in the patient research chart.

Patient No. _____
Patient's Initials: (L,F,M) _____

5.1 **Inclusion Criteria**
Yes/No (Response of "no" = patient ineligible)

5.1.1 _____ Age 18-75 years

5.1.2 _____ ECOG Performance status 0-1

5.1.3 _____ Patients must have one of the following diagnoses of Multiple Myeloma (MM) or primary/secondary Myelofibrosis (MF):

_____ Patients must have histologically documented Multiple Myeloma (MM) Appendix A.

A) Patients in early relapse (less than 24 months from initiation of systemic anti-myeloma therapy which may include single or planned tandem autologous transplant) after primary therapy that included and autologous HSCT.

OR

B) Later Stage.

OR

C) High risk factors defined by the presence of any one of the following detected at any time prior to enrollment: deletion of chromosome 13 by conventional cytogenetics, hypodiploidy, abnormality in chromosome 1 (1q amplification or 1p deletion), t(4;14), t(14;16), t(14;20) or deletion of 17p by fluorescence in situ hybridization (FISH) or conventional karyotyping; high risk criteria based on commercially available gene expression profiling.

OR

D) Extramedullary disease, plasma cell leukemia or high LDH [19].

_____ Patients must have histologically documented Myelofibrosis (MF) Appendix A.

A) Patients with DIPSS plus intermediate stage 2 or higher risk MF.

OR

B) Subset of intermediate stage 1 patients. Defined by:

i) Poor-risk molecular profile (triple negative: JAK2, CALR, MPL).

OR

ii) Presence of any of the following mutations: ASXL1, SRSF2, EZH2, IDH1/2.

OR

C) Severe thrombocytopenia, severe anemia, high peripheral blood blasts percentage.

OR

D) Unfavorable cytogenetic abnormalities (rearrangements of chromosome 5 or 7 or ≥ 3 abnormalities [40].

5.1.4 _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.2 Exclusion Criteria

Yes/No (Response of "yes" = patient ineligible)

5.2.1 _____ Cardiac- left ventricular ejection fraction <40%, symptomatic coronary artery disease, or uncontrolled arrhythmias.

5.2.2 _____ Pulmonary- FEV1 or DLCO < 40% or history of chronic use of supplemental oxygen. Temporary use of supplemental oxygen at the time of screening or registration is allowed if the investigator feels that the underlying cause of requiring oxygen is reversible by the time treatment begins.

5.2.3 _____ Renal- calculated or measured GFR <30 ml/min, dialysis-dependent, or history of renal transplant.

5.2.4 _____ Hepatic- bilirubin > 2 X ULN, ALT> 2.5 X ULN or cirrhosis.

5.2.5 _____ Patients with active or uncontrolled bacterial, viral, or fungal infections requiring systemic therapy.

5.2.6 _____ Pregnant women, nursing mothers or women of child-bearing potential who are unwilling to use medically accepted methods of contraception

5.2.7 _____Male and female subjects not willing to agree to medically accepted methods of contraception.

5.3 Donor Inclusion Criteria

The evaluation of donors shall be in accordance with existing Foundation for the Accreditation of Cellular Therapy standards. The University of Utah Blood and Marrow Transplant and Myeloma Program are a FACT accredited Cellular Therapy programs.

5.3.1 _____ A related donor –fully matched.

5.3.2 _____ A related donor – haploidentical.

5.3.3 _____ An unrelated donor – fully matched.

5.3.4 _____ An unrelated donor – 9/10 matched.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

Investigator Signature	**Date**	**Time**

TREATMENT PLAN

HCI BMT SOPs found:

https://pulse.utah.edu/policies/FilteredFor/Blood%20and%20Marrow%20Transplant.aspx – or consult with BMT pharmacist).

6.1 Administration Schedule

Day	Therapy
Day - 6	Start Levetiracetam[1] (per standard of care dosing)
Day - 5	Busulfan daily dose of 3.2 mg/kg/day IV
	Busulfan goal Css = 800 to 900 ng/mL as determined by the PI (PK Blood Draw required per HCI MBT SOPs)
	Fludarabine 30 mg/m^2 IV
	Levetiracetam
Day - 4	Busulfan
	Fludarabine 30 mg/m^2
	Levetiracetam
Day - 3	Busulfan
	Fludarabine 30 mg/m^2
	Levetiracetam
Day - 2	Busulfan
	Fludarabine 30 mg/m^2
	Levetiracetam
Day -1	Rest
	Levetiracetam
Day 0	HPC infusion per HCI BMT Standard of Care SOP
Day+3	Cyclophosphamide 50mg/kg IV over 60 minutes per HCI BMT standard of Care SOP
Day+4	Cyclophosphamide 50mg/kg IV over 60 minutes
Day +5	Tacrolimus per standard dosing guidelines with Mycophenolate mofetil (MMF) 15 mg/kg IV or PO q8 hrs (max dose 3g/day) and continued until day +35

[1]With conditioning doses of busulfan, antiepileptic medication (levetiracetam) must be given. Seizure prophylaxis should start prior to receiving busulfan and continue at least 24 hours after the infusions are complete.

[2]Tacrolimus and Mycophenolate mofetil (MMF) can also be used post-transplant as GVHD prophylaxis per PI discretion as HCI BMT standard of care SOP.

*Residual or relapsing disease will be treated with DLI infusions per HCI BMT SOP.

MF patients who take Ruxolitinib prior to transplant will continue to do so. The dose of Ruxolitinib is reduced to 2 x 5 mg and continued until stable engraftment, then tapered and stopped around day +28. In case of early CMV reactivation, the drug will be tapered earlier[41].

6.2 Treatment Administration

All treatments associated with protocol are commercially available agents and will be administered per institutional guidelines only to eligible patients under the supervision of the investigator or sub-investigator(s). The treatments will be prepared under the supervision of a pharmacist at Huntsman Cancer Institute. The amount of drug to be administered will be determined based on targeted PK, body surface area, ideal body weight, actual or adjusted body weight and calculated based on institutional standards.

6.2.1 Busulfan:

See HCI BMT SOP for details of busulfan administration, toxicities, PK sample collection and targeted level and levetiracetam prophylaxis.

a. Dosage: the initial dose for intravenous busulfan is 3.2 mg/kg/dose IV daily. Busulfan Css goal is 800 ng/mL to 900 ng/mL, as per the investigator's clinical judgement. Busulfan dose may need to be adjusted based on busulfan levels drawn after the first dose. Therefore, without dose adjustment, the total dose is 12.8 mg/kg. Busulfan will only be given intravenously over 3 hours from Days –5 through –2. Doses should be rounded to the nearest 1 mg.

b. Dosage calculation is based on actual or adjusted body weight see HCI BMT SOP for calculation of chemotherapy.

6.2.2 Fludarabine:

See HCI BMT SOP for details of Fludarabine administration and toxicities.

a. Dosage: 30 mg/m^2/day IV on Days -5 through Day –2, for a total dose of 120 mg/m^2. The dose is rounded to the nearest 5 mg and given intravenously over 30 minutes.

b. Dosage calculation is based on actual body weight. HCI BMT SOP for calculation of chemotherapy.

Consider a 25% dose reduction of fludarabine in patients with creatinine clearance <50 mL/min. Fludarabine should be avoided in patients with creatinine clearance <30 mL/min.

6.2.3 HPC infusion

Source of hematopoietic progenitor cells (HPC) to be determined by BMT attending physician. Infusion to be given per HCI BMT SOP.

Graft versus Host Disease prophylaxis

6.2.4 Cyclophosphamide

Cyclophosphamide 50mg/kg IV over 60 minutes on Day +3 and Day +4. Post-transplant cyclophosphamide should be started between 60-72 hours after HPC

infusion. Dosage calculation is always based on ideal body weight, unless the patient weighs less than ideal body weight, then use actual body weight.

Hydration prior to cyclophosphamide may be given according to institutional standards. Mesna should be started prior to cyclophosphamide at a dose of 100% of cyclophosphamide dose in 1 liter of 0.9% sodium chloride, given as a continuous infusion. Discontinue mesna approximately 24 hours after the last dose of cyclophosphamide.

It is crucial that no immunosuppressive agents are given until 24 hours after the completion of the post-transplant cyclophosphamide. This includes corticosteroids as anti-emetics.

6.2.5 Tacrolimus

Tacrolimus will be initiated at Day +5 per standard dosing guidelines with a goal of being tapered to off by Day +180, in the absence of GVHD.

- 0.01-0.03 mg/kg/day IV continuous infusion depending on age and prophylactic antifungal choice. In some patients, tacrolimus may be started as an oral formulation at a dose of 0.045-0.06 mg/kg/dose PO BID and titrated as needed. The conversion from IV to PO tacrolimus is approximately 1:3.

6.2.6 Mycophenolate mofetil (MMF) WITH Tacrolimus

MMF will be initiated at Day +5 at a dose of 15mg/kg IV or PO q8 hrs (max dose 3 gm/day) and discontinued on Day +35 in the absence of GVHD.

See HCI BMT SOP for details of tacrolimus plus MMF administration:

6.3 **Accountability and Compliance**

Accountability for the treatment is the responsibility of the principal investigator. The investigator will ensure that treatment is used only in accordance with this protocol. Drug accountability records will be maintained per institutional practice.

6.4 **Prohibited Concomitant Medications**

Medications will be managed at PI discretion.

6.5 **Duration of Therapy**

Patients will receive a conditioning regimen, transplant, GVHD prevention and one year of assessment on study.

TOXICITIES AND DOSEAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for adverse event and serious adverse event reporting. A copy of the CTCAE Version 5.0 can be downloaded: (**http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx**).

7.1 Supportive Care

7.1.1 Prophylactic Care

All supportive measures consistent with optimal patient care will be given throughout the study. Institutional guidelines will be followed and include the following:

- Prophylactic antibiotics consisting of a quinolone or equivalent depending upon patient tolerance as per institutional standards.
- Prophylactic antifungals consisting of caspofungin, fluconazole, voriconazole, or posaconazole as per institutional standards. The use of azole antifungals should be avoided until Day +5 due to potential drug-drug interaction between azoles and cyclophosphamide.
- Prophylactic acyclovir or valacyclovir starting by day 0 and continuing until one year post transplant.
- Patients receiving haploidentical transplant, will receive filgrastim or filgrastim-sndz 5 mcg/kg/day starting on Day +5 and continued until engraftment.
- Patients should be started on ursodiol prior to transplant per institutional standards. We will provide viral weekly screening for CMV and EBV as needed (see study calendar). Screening and infection treatment will be instituted per HCI BMT SOP.

7.2 Diagnosis and Treatment of Acute GVHD

GVHD assessment should be conducted standard of care once weekly for the first 100 days and then monthly until one year following BMT by the treating transplant physician or GVHD experienced members of the BMT team including midlevel providers using the forms provided in appendix B. Additional time points of assessment depend on clinical necessity and or when symptoms of GVHD arise.

Acute GVHD can affect various target organs, predominantly the GI tract, liver and skin. It is not defined by time of onset but by clinical symptoms. The recommended staging and grading of acute GVHD, and the functional grading of acute GVHD is presented in HCI BMT SOP (appendix B). Whenever possible, the clinical diagnosis of GVHD should be confirmed by biopsy of an affected end organ, but should not delay management. Other complications affecting the skin, liver, and gastrointestinal (GI) tract should be ruled out.

GVHD grade I:

- topical treatment (steroid cream, tacrolimus 0.01 – 0.03%, antihistamine containing lotion against pruritus)

GVHD grade II:

- systemic treatment with corticosteroids (1mg/kg prednisolone)

GVHD grade III and IV:

- systemic treatment with corticosteroids (2mg/kg methylprednisolone; equivalent to prednisone 2.5mg/kg) plus calcineurin inhibitor.

For skin involvement: additional topical agents allowed. For GI tract involvement: additional nonabsorbable agents (budesonide, beclomethasone) allowed.

See HCI BMT SOP for additional treatment of acute GVHD: (https://pulse.utah.edu/policies/FilteredFor/Blood%20and%20Marrow%20Transplant.aspx – or consult with BMT pharmacist).

7.3 **Diagnosis and Treatment of Chronic GVHD**

GVHD assessments should be conducted standard of care once weekly for the first 100 days and then monthly until one year following BMT by the treating transplant physician or GVHD experienced members of the BMT team including midlevel providers.

Additional time points of assessment depend on clinical necessity and or when symptoms of GVHD arise. See HCI BMT SOP for details of chronic GVHD assessments and treatments.

STUDY CALENDAR

Examination	Screening[1]	**Day -6**	**Day -5**	**Day -4**	**Day -3**	**Day -2**	**Day -1**	**Day 0**	**Day +3**	**Day +4**	**Day +28 M1 (±7 Days)**	**Day +100 M4 (±7 Days)**	**Day +180 M6 (±7 Days)**	**Day +365 M12 (±7 Days)**
Informed Consent	**X**													
Medical History	**X**													
Demographics	**X**													
Eligibility Criteria	**X**													
Disease Staging	**X**													
Pregnancy Test[4]	**X**													
Adverse Events[7]		**X**												
Vital signs	**X**	**X**						**X**	**X**		**X**	**X**		**X**
Physical examination	**X**	**X**						**X**	**X**		**X**	**X**		**X**
ECOG performance status	**X**	**X**						**X**	**X**		**X**	**X**		**X**
CMV, EBV test	**X**[10]							**X**[10]			**X**	**X**		**X**
Hematology[2]	**X**	**X**						**X**	**X**		**X**	**X**		**X**
Serum Chemistries[3]	**X**	**X**						**X**	**X**		**X**	**X**		**X**
LDH	**X**										**X**	**X**		**X**
ECHO	**X**													**X**
Pulmonary Function Tests	**X**													**X**
Multiple Myeloma Disease Assessments[8]	**X**											**X**	**X**	**X**
Myelofibrosis Disease Assessment[9]	**X**											**X**	**X**	**X**
Busulfan			**X**	**X**	**X**	**X**								
Busulfan PK			**X**											
Fludarabine			**X**	**X**	**X**	**X**								
Cyclophosphamide									**X**	**X**				

Transplant HSCT								**X**						
Minimal Residual Disease[5]	**X**											**X**	**X**	**X**
Acute and Chronic GVHD Assessment[6]									**X**	**X**	**X**	**X**		**X**
Clinical CR up through 1 year[8,9]												**X**		
Molecular CR up through 1 year[8,9]												**X**		

1 ALL Pre-study/Screening procedures should be completed within 4 weeks of study enrollment - with the exception of laboratory tests which need to be completed within 2 weeks prior to study enrollment and bone marrow aspirate and biopsy which could be completed within 60 days of study enrollment. Prior medical history will be assessed at screening, including assessment of comorbidities.

2 Hematology includes CBC with differential and platelets. Assessments should be done weekly at the discretion of the investigator.

3 Chemistry includes Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, Urea Nitrogen.

4 Pregnancy test must be done at screening for all women of childbearing potential and repeated as clinically indicated.

5 MRD monitoring in Multiple Myeloma done by Flow Cytometry (preferred), ASO-PCR, by determining the VDOH rearrangements or NGS. MRD-Monitoring in Myelofibrosis to be done by JAK2 PCR or cMPL or Calreticulin mutation PCR and donor-recipient chimerism determination. This testing should be done at screening to determine the molecular markers that will determine MRD after transplant. MRD-determination should be done as a standard procedure every 3-6 months ONLY if the patient has demonstrated complete response. Previous MRD testing results may be used for screening requirement, if performed within 60 days of study enrollment.

6 GVHD assessments for acute and chronic GVHD should be conducted as per standard of care once weekly from Day 0 to day +100. Assessments should continue monthly after day +100 until day +365.

7 Adverse Events will start at Day-6 and continue to Day+365.

8 Multiple Myeloma disease assessments should include evaluation of quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE), 24-hour urine for total urine protein, urine immunofixation electrophoresis (UIFE), serum free light chains. Bone marrow aspirate and biopsy including cytogenetics, plasma cell FISH and other molecular testing for MM associated mutations and/or other chromosomal abnormalities, bone scans and/or PET/CT should be performed as clinically indicated (if supported by increased signs and symptoms). Response should be monitored every 3 – 6 months until disease progression.

9 Myelofibrosis disease assessments should include evaluation of symptoms, evaluation of the spleen by physical exam, and/or CT or MRI. Bone marrow aspirate and biopsy including cytogenetics, flow cytometry and molecular testing for MF associated mutations and/or other chromosomal abnormalities should be performed as clinically indicated (if supported by increased signs and symptoms). Response should be monitored every 3 – 6 months until disease progression.

10 As Needed

CRITERIA FOR EVALUATION AND ENDPOINT

9.1 Non-relapse mortality (NRM) up to day +365

NRM is defined as death due to GVHD, infections, sepsis, organ (lung, liver, kidney) toxicity. Death from underlying disease (i.e. progression or relapse) is not considered NRM.

9.2 Rate of acute GVHD grade II-IV at Day +100 post-transplant

GVHD should be assessed according to the standard of care by the treating physician or other member of the BMT clinical team including mid-level providers once weekly through day +100 post transplant and monthly for 1 year. Acute GVHD may affect the skin, the gastrointestinal tract, and the liver. Diagnosis of acute GVHD is based on criteria established according to the criteria as described by the 1994 Consensus conference on acute GVHD grading. The recommended staging and grading of acute GVHD and the functional grading of acute GVHD is presented in HCI BMT SOP (see worksheet in appendix B).

9.3 Cumulative chronic GVHD rates

Diagnosis of chronic GVHD is based on criteria established by the National Institutes of Health Consensus Development Project in 2005 (Filipovich et al. 2005), and recently updated in 2014. Diagnostic and distinctive manifestations of chronic GVHD are present in the skin and appendages, mouth, eyes, female genitalia, esophagus, lungs and connective tissues. Diagnosis of chronic GVHD requires the presence of at least 1 diagnostic clinical sign (e.g. poikiloderma or esophageal web) or the presence of at least 1 distinctive manifestation (e.g. keratoconjunctivitis sicca) confirmed by pertinent biopsy or other relevant tests (e.g. Schirmer test) in the same or another organs. Biopsy or other testing is not always feasible to confirm the presence of chronic GVHD and is not mandatory if the patient has at least 1 of the diagnostic findings of chronic GVHD. Other possible diagnoses for clinical symptoms must be excluded.

The National Institutes of Health Consensus Development Project recognizes 2 main categories of GVHD each of which having 2 subcategories as shown in Table 4. The broad category of chronic GVHD includes (a) classic chronic GVHD without features characteristic of acute GVHD, and (b) an overlap syndrome in which features of chronic and acute GVHD appear together.

Table 4: Categories of GVHD

Category	**Time of Symptoms after HSCT**	**Presence of Acute GVHD Features***	**Presence of Chronic GVDH Features***
Acute GVHD			
Classic acute	≤ 100 days	Yes	No
Persistent, recurrent or late onset	>100 days	Yes	No
Chronic GVHD			

Classic chronic	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

No time limit is set for the diagnosis of chronic GVHD. In the absence of histological or clinical signs or symptoms of chronic GVHD, the persistence, recurrence or new onset of characteristic skin, GI tract or liver abnormalities should be classified as acute GVHD regardless of the time of onset after transplantation.

Scoring of chronic GVHD (mild, moderate or severe) is similarly based upon criteria established by the National Institutes of Health Consensus Development Project, updated in 2014 (see worksheets appendix C). The following scoring system determines severity:

Mild Chronic GVHD

1 or 2 organs involved with no more than score 1

AND

Lung score of 0

Moderate Chronic GVHD

3 or more organs involved with no more than score 1

OR

At least 1 organ (not lung) with a score of 2

OR

Lung score 1

Severe Chronic GVHD

At least 1 organ with a score of 3

OR

Lung score of 2 or 3

9.4 Response (clinical and molecular, disease free survival)

A clinical and molecular response will be assessed up to Day +365.

For Multiple Myeloma, the IMWG criteria will be used to assess clinical/molecular response:

Complete Response (CR)

- Negative immunofixation on the serum and urine

AND

- Disappearance of any soft tissue plasmacytomas

AND

- <5% plasma cells in bone marrow aspirates

Stringent complete response (sCR)

- Complete response as defined above plus normal FLC ratio[1]

AND

- Absence of clonal cells in bone marrow biopsy by immunohistochemistry (k/λ ration ≤ 4:1 or ≥ 1:2 for k and λ patients respectively after counting ≥ 100 plasma cells[2]

Partial Response (PR):

- ≥ 50% reduction of serum M-protein plus reduction in 24hr urinary M-proteins by a ≥90% or to < 200mg per 24hr
  - If the serum and urine M-protein are unmeasurable,
    - a ≥50% decrease in the difference between involved and uninvolved FLC levels are is required in place of the M-protein criteria
  - If serum and urine M-proteins are unmeasurable, and serum-free light assay is also unmeasurable
    - ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%.

AND

If present at baseline, a ≥50% reduction in the size (SPD)[3] of soft tissue plasmacytomas is also required

1. All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).
2. Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.
3. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

For Myelofibrosis:

Complete Response (CR)

Bone marrow:[1] Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF[2]

AND

Peripheral blood: Hemoglobin ≥100 g/L and <UNL; Neutrophil count ≥ 1 x 10^9/L and ≥UNL; Platelet count ≥100 x 10^9/L and <UNL; <2% immature myeloid cells[3]

AND

Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH

Partial Response (PR)

Peripheral blood: Hemoglobin ≥100 g/L and <UNL; Neutrophil count ≥1 x 10^9/L and <UNL; Platelet count ≥100 x 10^9/L and <UNL; <2% immature myeloid cells[3]

AND

Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH

OR

Bone marrow:[1] Age-adjusted normocellularity; < 5% blasts; ≤ grade 1 MF[2]

AND

peripheral blood: Hemoglobin ≥ 85 but ≤ 100 g/L and <UNL; neutrophil count ≥ 1 x 10^9/L and < UNL; platelet count ≥50, but≤ ,100 x 10^9/L and <UNL; <2% immature myeloid cells[3]

AND

Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH

EMH, extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven non-hepatosplenic EMH); LCM, left costal margin; UNL, upper normal limit.

1. Baseline and post-treatment bone marrow slides are to be interpreted at one sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.
2. Grading of MF is according to the European classification (Thiele et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica. 2005;90:1128).
It is underscored that the consensus definition of a CR bone marrow is to be used only in those patients in which all other criteria are met, including resolution of leukoerythroblastosis.
It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histologic remission.
3. Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, <5% immature myeloid cells is allowed.

9.5 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

Physical Examination

Complete and symptom-directed physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner)

Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate and temperature) will be obtained in the sitting position.

Safety Laboratory Determinations

Laboratory evaluations will be performed as noted in the flow chart.

9.6 Stopping Rules

Stopping rules will be met when 4 out of 12 patients experience Non-relapse mortality (NRM) by Day+100. If the true probability of NRM is 50% there is an 81% chance that the trial will be stopped early for NRM. If the true probability NRM is 15% there is a 2.4% chance that the trial will be stopped early for NRM.

STATISTICAL CONSIDERATIONS

The protocol proposes to study 24 patients with Myelofibrosis (MF) and Multiple Myeloma (MM).

The primary outcome is non relapse related mortality (NRM) for the entire cohort. The outcome will be reported along with exact binomial confidence intervals for informal comparison to the literature. A review of the literature yielded similar results for NRM in 19 studies for MM and 8 studies for MF. In MM we collected 19 studies with 1686 allogenic transplant patients and selected the 3 largest studies with 880 patients. These three studies reported NRM of 18%, 21.5%, and 22% for a weighted average of 21%. Weighted averaging revealed a benchmark of 25% for NRM. We hope to achieve a modest improvement over these results from the literature. We have 83% power to reject the null hypothesis that NRM = 25% at the one sided 0.05 significance level using an exact binomial test provided the true NRM = 6%. The null hypothesis will be rejected if ≤ 3/24 patients have NRM. If NRM is observed 3 or fewer out of 24 patients an exact 80% upper confidence bound will exclude 22%.

Analysis of acute and chronic GVHD and response (clinical and molecular response up to 1 year and disease free survival) is secondary and will be done descriptively. Proportions and exact binomial confidence intervals will be reported for secondary binary outcomes and Kaplan-Meier techniques will be used to report secondary time to event outcomes. Response outcomes will be reported for the entire cohort and also stratified by response to therapy prior to transplant, number of preceding treatment regimens and staging of disease at diagnosis.[21-39]

REGISTRATION GUIDELINES

Patients must meet all of the eligibility requirements listed in Section 5 prior to registration.

Study related screening procedures can only begin once the patient has signed a consent form. Patients must not begin protocol treatment prior to registration.

Treatment should start within five working days after registration.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to: CTORegistrations@hci.utah.edu.

DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRF's should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts. These forms will be

completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB approved version.

13.2 Institutional Review

Study will be approved by the Institutional Review Board of University of Utah.

13.3 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) and approved by the NCI to assure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. Roles and responsibilities of the DSMC are set forth in the NCI approved plan. The activities of this committee include a quarterly review of adverse events including SAEs, important medical events, significant revisions or amendments to the protocol, and approval of cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

All phase II studies are reviewed by the full committee at each quarterly DSMC meeting. This includes a review of all serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates as well as all grade 3 or greater toxicities for patients on treatment and within 30 day follow-up window (only if possibly, probably or definitely related).

13.4 Adverse Events / Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for AE and SAE reporting. An electronic copy of the CTCAE Version 5.0 can be downloaded from:

http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx

This is a protocol for allogeneic stem cell transplantation with the expected spectrum of transplant related SAEs like acute and chronic GVHD, life threatening infections, bleeding and graft rejection. A transplant related mortality of 10-20% is expected (2-5 patients).

Anticipated frequent AEs during the acute transplant period (admission to day 28) are nausea, vomiting, diarrhea, fever, infections, mucositis. These will only be considered and documented as AE post engraftment

Grade 3 and 4 cytopenias will not be considered AE or SAE (as applicable) until after engraftment.

13.4.1 Adverse Events (AE)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Adverse event monitoring and collection will begin on Day -6 and end 365 days post-transplant. Any signs, symptoms or medical conditions occurring prior to Day -6 will be captured as medical history/baseline events. All adverse events will be captured in source documentation (with severity grading and causality noted) as defined in section 13.4; however, only events meeting the following criteria will be captured in OnCore (electronic CRFs):

- CTCAE ≥ grade 3-4 non-hematologic toxicities related to study treatment
- Relapse of the underlying hematological malignancy and acute/chronic GVHD will be documented on specific CRFs pages; this information should not be recorded on the CRF “Adverse Event” page and should not be treated as an adverse event (AE) unless leading to fatal outcome, which will trigger a SAE report (see Section 13.4.2).
- Engraftment failure needs to be documented as an AE. In case it meets SAE criteria, 13.4.2, an SAE report must be sent.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade based on CTCAE v.5 (grade 1-5)
2. its relationship to the study treatment (definite, probable, possible, unlikely, not related)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant

medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)

5. whether it constitutes an SAE

All adverse events will be treated appropriately. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Information about common side effects already known about the study treatment is described in the Drug Information (section 3) and the FDA-approved product labels. This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be immediately recorded in the patient research chart.

13.4.2 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- causes congenital anomaly or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition

The collection of SAEs will begin on Day -6 and end at Day +365.

Any death from any cause while a patient is receiving treatment on this protocol or up to 365 days post-transplant, or any death which occurs more than 365 days post-transplant but which is felt to be treatment related, must be reported.

Grade 3 and 4 cytopenias will not be considered SAE until after engraftment.

Anticipated, but less frequent SAEs beyond day +28 are acute GVHD (liver, gut, skin), VOD, CMV activation, interstitial and fungal pneumonia, and cystitis which may require hospitalization

Anticipated, but less frequent SAEs after day +100 are, chronic GVHD, relapse of MM or MF.

If subjects fail to engraft by Day+28, this must be reported as an SAE.

Graft failure after allogenic hemaopoietic cell transplantation (AHCT) may manifest as either a lack of initial engraftment of donor cells, or loss of donor cells after minimal engraftment; this may occur for a variety of reasons, including recipient T-cells, natural killer cells, or antibodies. Risk of graft failure can be decreased by more intense conditioning, increased cell dose, or more effective immunosuppression. Occurrence of graft failure will be confirmed by the treating transplant physician.

Fatal relapses, fatal acute GVHD and fatal chronic GVHD are to be reported as SAEs.

This study should be handled like a phase II study. All phase II studies are reviewed by the full committee at each quarterly DSMC meeting. This includes a review of all serious adverse events (SAEs) occurring in patients treated at HCI as well as all grade 3 or greater toxicities for patients on treatment up to day +365 (only if possibly, probably or definitely related).

Toxicities which fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be documented as AEs in the patient research chart.

13.5 **SAE Reporting Requirements**

SAEs must be reported to the DSMC, the FDA, the IRB, according to the requirements described below:

A MedWatch 3500A form must be completed and submitted to compliance@hci.utah.edu within 1 business day of first knowledge or notification of event.

DSMC Notifications:

- An HCI Research Compliance Officer (RCO) will process and submit the MedWatch form to the proper DSMC member as necessary for each individual study.
- The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the quarterly DSMC meeting.

  Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

  - is fatal or life-threatening
  - results in persistent or significant disability/incapacity

- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- causes congenital anomaly or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study treatment
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition

Toxicities which fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be documented as AEs in the patient research chart.

FDA Notifications:

- Adverse events occurring during the course of a clinical study that meet the following criteria will be promptly reported to the FDA:
- Serious
- Unexpected
- Definitely, Probably or Possibly Related to the investigational drug
- Fatal or life-threatening events that meet the criteria above will be reported within 7 calendar days after first knowledge of the event by the investigator; followed by as complete a report as possible within 8 additional calendar days.
- All other events that meet the criteria above will be reported within 15 calendar days after first knowledge of the event by the investigator.
- The RCO will review the MedWatch report for completeness, accuracy and applicability to the regulatory reporting requirements.
- The RCO will ensure the complete, accurate and timely reporting of the event to the FDA.
- The MedWatch report will be submitted to the FDA through the voluntary

reporting method by the Regulatory Coordinator.

IRB Notification:

- Events meeting the University of Utah IRB reporting requirements (http://www.research.utah.edu/irb/) will be submitted through the IRB's electronic reporting system within 10 working days.

*Medwatch 3500A form can be found online

13.6 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject, including the pregnancy of a male subjects' female partner as an SAE. Pregnancies or lactation that occurs during the course of the trial or with 30 days of completing the trial or starting another new anticancer therapy, whichever is earlier, must be reported to the DSMC, IRB, FDA, and the sponsor as applicable. All subjects and female partners who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events.

13.7 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

13.8 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

13.9 FDA Annual Reporting

This study is IND exempt therefore there are no annual reporting requirements to the FDA.

13.10 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

13.11 Record Keeping

Per 21 CFR 312.57, Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

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APPENDICES

Appendix A (staging criteria)

MULTIPLE MYELOMA
Clinical Presentation, Diagnosis and Staging

High risk disease — Approximately 15 percent of people with multiple myeloma have high risk disease based on cytogenetic testing (patients with translocation t (14;16)), translocation t (14;20) and deletion chromosome 17p). This is the aggressive form of multiple myeloma and may shorten survival; patients at high risk disease are treated with more aggressive therapy.

Intermediate risk disease — Approximately 10 percent of people with multiple myeloma have intermediate risk disease based on cytogenetic testing (patients with translocation t (4;14)). With appropriate therapy, patients with this form of multiple myeloma can have outcomes similar to those of standard risk multiple myeloma.

Standard risk disease — All patients with multiple myeloma who lack high or intermediate risk genetic abnormalities are considered to have standard risk multiple myeloma, and with appropriate therapy have an estimated median survival of 8 to 10 years.

Stage I - All of the following:
- Hemoglobin value > 10 g/dL
- Serum calcium value normal or ≤ 12 mg/dL
- Bone x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only
- Low M-component production rate (IgG value < 5 g/dL; IgA value < 3 g/dL)
- Bence Jones protein < 4 g/24 hr

Stage II - Neither Stage I nor Stage III
Stage III - One or more of the following:
- Hemoglobin value < 8.5 g/dL
- Serum calcium value > 12 mg/dL
- Advanced lytic bone lesions (scale 3)
- High M-component production rate - (IgG value > 7 g/dL; IgA value > 5 g/dL)
- Bence Jones protein > 12 g/24 h

Sub-classifications (either A or B)
A: Relatively normal renal function (serum creatinine value < 2.0 mg/dL)
B: Abnormal renal function (serum creatinine value = 2.0 mg/dL)

The International Staging System, which is the most recent, most reliantly used risk assessment system and identifies three risk groups on the basis of serum β2-microglobulin and albumin levels (Greipp et al., 2005):

Stage I - Serum beta-2 microglobulin is less than 3.5 (mg/L) and the albumin level is 3.5 (g/dL) or greater
Stage II - Neither stage I or III, meaning that either: The beta-2 microglobulin level is between 3.5 and 5.5 (with any albumin level), OR the albumin is below 3.5 while the beta-2 microglobulin is less than 3.5
Stage III - Serum beta-2 microglobulin is 5.5 or greater.

MYELOFIBROSIS

The prognosis of MF was initially guided by the Lille score (a.k.a., the Dupriez score), which used hemoglobin and white blood cell counts to classify patients as "long-lived" (median survival of ten years) or "short-lived" (median survival of two years) (Dupriez, 1996). Patients were further grouped by risk, as shown in the table below:

Lille risk group	**Number of risk factors**	**Median survival (years)**
Low	None	7 - 8
Intermediate	1	2.2
High	2	1

In the past decade the International Prognostic Scoring System (IPSS), which has been progressively updated to first the dynamic IPSS (DIPSS) and now the DIPSSplus as the understanding of the natural history and especially the impact of cytogenetics on the pathogenesis of MF has increased (Alchalby & Kroger, 2014) has gained prominence. The DIPSSplus prognostic score is based on eight risk factors (need for red blood cell transfusion, hemoglobin level, platelet count, leukocyte count, circulating blasts in the blood, constitutional symptoms, unfavorable cytogenetic profile and age). There are four risk categories based on the DIPSSplus score as show in the following table (Gangat et al., 2011):

Variable	IPSS	DIPSS	DIPSS plus[a]
Age >65 years	1	1	—
Constitutional symptoms	1	1	—
Hb <10 g/dL	1	2	—
Leukocyte count >25×10⁹/L	1	1	—
Circulating blasts ≥1%	1	1	—
Platelet count <100×10⁹/L	—	—	1
RBC transfusion need	—	—	1
Unfavorable karyotype	—	—	1
Risk groups	**IPSS risk score**	**DIPSS risk score**	**DIPSS plus risk score[b]**
Low-risk	0	0	0
Intermediate-1 risk	1	1 or 2	1
Intermediate-2 risk	2	3 or 4	2 or 3
High-risk	≥3	5 or 6	≥4

MF – Myelofibrosis; RBC – Red blood cell; Hb – Hemoglobin; IPSS – International Prognostic Scoring System; DIPSS – Dynamic IPSS. [a]For DIPSS plus, the score is derived from the DIPSS score, and additional points added as per the table; [b]1 adverse point was assigned to DIPSS intermediate-1 risk. DIPSS intermediate-2 and high-risk were assigned 2 and 3 adverse points, respectively

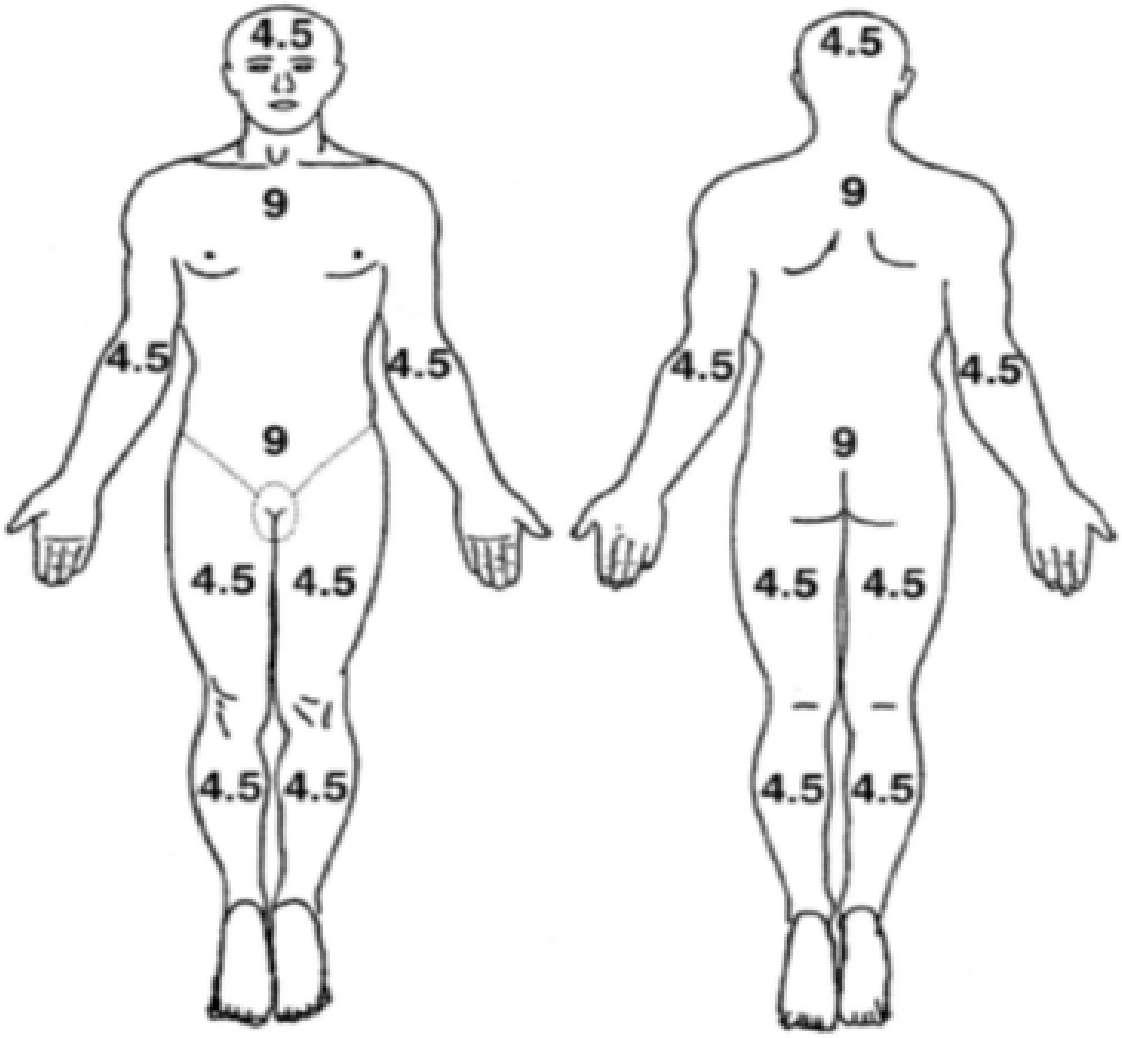
Unfavorable karyotype: complex karyotype or sole or two abnormalities that include trisomy 8, 7/7q-, i(17q), 5/5q-, 12p-, inv(3), or 11q23

Appendix B: ACUTE GVHD GRADING SCALE

Acute GVHD Grading

NAME:					**TX Date:**		
MRN:					**Day 100:**		
Week							**Max**
Day							
Date							
Skin	**Type**						
	%BSA						
	Date						
LGI	**Stool**						
	Date						
UGI	**Emesis**						
	Date						
Liver	**Tbili**						
	Date						
Biopsy Date							
Biopsy Results							
GVHD Treatment, Drug changes, dose changes, start and end dates							
Other							
Prepared By: _____					Reviewed By: _____		
					Date/Time:_____		

Patient Name: MRN: Current GVHD Stage: Skin: 1 2 3 4 Liver: 1 2 3 4 GI: 1 2 3 4 Current Overall GVHD Grade: Physician Signature: _____	Transplant Date: Progressed to acute GVHD?: Yes / No Date Progressed to aGVHD: N/A Progressed to chronic GVHD?: Yes/No Date Progressed to cGVHD: N/A *If primary graft failure occurs, notify RCO. If acute GVHD occurs before Day +60, notify RCO: Compliance@hci.utah.edu



Clinical grading of severity of acute graft-versus-host disease

Grade	Degree of Organ Involvement
I	+ to ++ skin rash; [and] no gut involvement; [and] no liver involvement; [and] no decrease in clinical performance
II	+ to +++ skin rash; [or] + gut involvement [and/or] + liver involvement); [and] mild decrease in clinical performance
III	++ to +++ skin rash; [and/or] ++ to +++ gut involvement [and/or] ++ to ++++ liver involvement); [and] marked decrease in clinical performance
IV	Similar to Grade III with ++ to ++++ organ involvement and extreme decrease in clinical performance

APPENDIX I

Criteria for Acute Graft-vs-Host Disease

Clinical staging of acute graft-versus-host disease according to organ involvement.

Stage	Skin	Liver	Intestinal Tract
0	No rash	Bilirubin < 2.0 mg/dL < 34 µmol/L	Diarrhea ≤500 ml/day or <280 ml/m^2/day
+	Maculopapular rash <25% of body surface	Bilirubin 2.0 - 3.0 mg/dL 34 - 52 µmol/L	Diarrhea >500 but ≤1000 ml/day or 280-555 ml/m^2/day
++	Maculopapular rash 25-50% of body surface	Bilirubin 3.1 - 6.0 mg/dL 53 - 103 µmol/L	Diarrhea >1000 but ≤1500 ml/day or 556-833 ml/m^2/day
+++	Generalized erythroderma	Bilirubin 6.1 - 15.0 mg/dL 104 - 256 µmol/L	Diarrhea >1500 ml/day or >833 ml/m^2/day
++++	Generalized erythroderma with bullous formation and desquamation	Bilirubin > 15.0 mg/dL > 256 µmol/L	Severe abdominal pain with or without ileus

Appendix C: CHRONIC GVHD GRADING SCALE

	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, capabl of self-care, >50% of waking hours ou 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† ☐ **SCORE % BSA** *GVHD features to be scored by BSA:* **Check all that apply:** Maculopapular rash/erythema; Lichen planus-like features; Sclerotic features; Papulosquamous lesions or ichthyosis; Keratosis pilaris-like GVHD	No BSA involved	1-18% BSA	19-50% BSA	>50% BSA
SKIN FEATURES SCORE:	No sclerotic features		**S**uperficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** Deep sclerotic features; "Hidebound" (unable to pinch); Impaired mobility; Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** Hyperpigmentation; Hypopigmentation; Poikiloderma; Severe or generalized pruritus; Hair involvement; Nail involvement; *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
MOUTH *Lichen planus-like features present:* **Yes** **No**	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
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* **Yes** **No** **Not examined**	No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GI Tract ***Check all that apply:*** Esophageal web/ proximal stricture or ring Dysphagia Anorexia Nausea Vomiting Diarrhea Weight loss ≥5%* Failure to thrive	No symptoms	Symptoms without significant weight loss* (<5%)	Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
LIVER	Normal total bilirubin and ALT or AP < 3 x ULN	Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	Elevated total bilirubin > 3 mg/dL
Abnormality present but explained entirely by non-GVHD documented cause (specify):				
LUNGS**				
Symptom score:	No symptoms	Mild symptoms (shortness of breath after climbing one flight of steps)	Moderate symptoms (shortness of breath after walking on flat ground)	Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **%** FEV1 ☐	FEV1≥80%	FEV1 60-79%	FEV1 40-59%	FEV1 ≤39%
Pulmonary function tests Not performed				
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

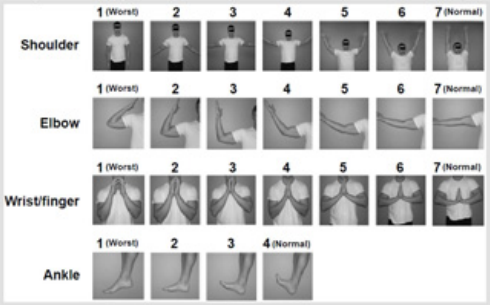
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	Tightness of arms or legs **OR** 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.)
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*‡) Not examined *Currently sexually active* Yes No	No signs	Mild signs‡ and females with or without discomfort on exam	Moderate signs‡ and may have symptoms with discomfort on exam	Severe signs‡ with or without symptoms
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

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

Ascites (serositis)___	Myasthenia Gravis___	
Pericardial Effusion___	Peripheral Neuropathy___	Eosinophilia > 500/µl___
Pleural Effusion(s)___	Polymyositis___	Platelets <100,000/µl ___
Nephrotic syndrome___	Weight loss>5%* without GI symptoms ___	Others (specify):_____

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

Photographic Range of Motion (P-ROM)



† Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.

* Weight loss within 3 months.

**Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

Abbreviations: ECOG (Eastern Cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status); BSA (body surface area); ADL (activities of daily living); LFTs (liver function tests); AP (alkaline phosphatase); ALT (alanine aminotransferase); ULN (normal upper limit).

‡ To be completed by specialist or trained medical providers (see Supplemental Figure).