

**Abbreviated Title:** *Lupron & 18F FLT in allo-HSCT*

**Version Date:** *December 28, 2017*

Abbreviated Title: Lupron & 18F FLT in allo-HSCT

CC Protocol #: 11-C-0136

NCT# NCT01338987

Version Date: December 28, 2017

Amendment: T

**Title of Study:** Multi-institutional Prospective Pilot Study of Lupron to Enhance Lymphocyte Immune Reconstitution following Allogeneic Bone Marrow Transplantation in Post-pubertal Children and Adults with Molecular Imaging Evaluation

**NIH Principal Investigator:** Christopher Kanakry, M.D. <sup>A-F</sup>  
Experimental Transplantation & Immunology Branch  
Center for Cancer Research,  
National Cancer Institute, National Institutes of Health  
10 Center Drive, Rm. 4-3142, MSC 1203  
Telephone: 240-760-6171  
Email: [christopher.kanakry@nih.gov](mailto:christopher.kanakry@nih.gov)

**Lead Associate Investigator:** Ronald Gress, M.D. <sup>A-F</sup>  
Branch Chief, ETIB, CCR, NCI, NIH

**Medical Advisory Investigator:** Peter Choyke, M.D. <sup>A-F</sup>  
Branch Chief, Molecular Imaging, NCI, CCR, NIH

**NIH Associate Investigators:**

Daniele Avila, CRNP, ETIB, CCR, NCI, NIH <sup>A-E</sup>	Meg Kenyon, CRNP, ETIB, CCR, NCI, NIH <sup>A-E</sup>
Stephanie Cotton, RN, OCD, CCR, NCI, NIH <sup>A-B</sup>	Jennifer Sadler, RN, OCD, CCR, NCI, NIH <sup>A-B</sup>
Bazetta Blacklock Schuver, RN, OCD, CCR, NCI, NIH <sup>A-B</sup>	Karen Kurdziel, MD, MIP, CCR, NCI, NIH <sup>A-F</sup>
Deborah Citrin, MD, ROB, CCR, NCI, NIH <sup>A-F</sup>	Seth M. Steinberg, PhD, BDMS, CCR, NCI, NIH <sup>B, E</sup>
Kristen Cole, RN, OCD, CCR, NCI, NIH <sup>A-B</sup>	Constance Yuan, MD, PhD, LP, CC, NIH <sup>E-F</sup>
Dennis Hickstein, MD, ETIB, CCR, NCI, NIH <sup>A-F</sup>	Bonnie Yates, RN, POB, CCR, NCI, NIH <sup>A-B</sup>
Fran Hakim, PhD, ETIB, CCR, NCI, NIH <sup>E-F</sup>	Cindy Delbrook, RN, OCD, CCR, NCI, NIH <sup>A-B</sup>
James Kochenderfer, MD, ETIB, CCR, NCI, NIH <sup>A-F</sup>	Terry Fry, MD, POB, CCR, NCI, NIH <sup>A-F</sup>
Nirali Shah, MD, POB, CCR, NCI, NIH <sup>A-F</sup>	Maya Lodish, MD, NICHD <sup>A-F</sup>
Steven Z. Pavletic, MD, ETIB, CCR, NCI, NIH <sup>A-F</sup>	Jennifer Kanakry, MD, ETIB, CCR, NCI, NIH <sup>A-F</sup>

**Abbreviated Title: Lupron & 18F FLT in allo-HSCT**

**Version Date: December 28, 2017**

Tracey Chinn RN, ETIB, CCR, NCI, NIH <sup>A-B</sup>	David Stroncek, MD, DTM, CC, NIH <sup>E-F</sup>
Ellen Carroll, RN, OCD, CCR, NCI, NIH <sup>A-B</sup>	Maria Liza Lindenberg, MD, MIP, CCR, NIH <sup>A-F</sup>
Brenna Hansen, RN, OCD, CCR, NCI, NIH <sup>A-B</sup>	Willy Flegel, MD, DTM, CC, NIH <sup>E-F</sup>
Jennifer Mann, CRNP, ETIB, CCR, NCI, NIH <sup>A-E</sup>	

**Site Principal Investigator:** Jennifer Holter, M.D., University of Oklahoma

**Site Principal Investigator** Kirsten Williams, MD., Children's National Medical Center, Washington

**Referral Contact:** Bazetta Blacklock Schuver, RN

**Study Coordinator:** Jennifer Sadler, RN  
240-760-6175  
Email: jennifer.sadler@nih.gov

**Non-NIH Associate Investigators:**

Jennifer Wilder, RN., Leidos Inc. <sup>A-B</sup>	
--	--

For each person listed above, roles are identified with the appropriate letter

- A. Obtain information by intervening or interacting with living individuals for research purposes
- B. Obtaining identifiable private information about living individuals
- C. Obtaining the voluntary informed consent of individuals to be subjects
- D. Makes decisions about subject eligibility
- E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes
- F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes
- G. Some/all research activities performed outside NIH

**IND Information:** IND Number: 111119  
IND Sponsor: Center for Cancer Research, NCI

**Commercial Agents:** Lupron Depot, Cyclophosphamide, Methotrexate, Tacrolimus, Fludarabine, Busulfan

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

Multi-institutional data:

**University of Oklahoma**

**Principal Investigator:** Jennifer Holter, M.D.  
Associate Professor of Hematology/Oncology and BMT

**Associate Investigator:** George Selby, MD

**Institution:** University of Oklahoma

**MPA or SPA Number:** Federal-Wide Assurance program FWA#00003191.

**Complete Address:** 920 Stanton L. Young, WP 2040  
Oklahoma City, OK 73104

**Phone Number:** 405-271-4022 Ext 48397 Contact Elizabeth Cambron

**E-mail:** jholter2@ouhsc.edu

**Name of IRB Contact:** Meg Ribaud, Director

**Complete Address:** 1000 Stanton L Young Blvd, Suite 176, Oklahoma City, OK 73117

**Phone Number:** 405-271-2045

**E-mail of Contact:** meg-ribaud@ouhsc.edu

**Name of Pharmacy Contact:** N/A

**Children's National Medical Center (CNMC)**

**Principal Investigator:** Kirsten Williams, M.D.  
Assistant Professor of Pediatrics/Hematology/Oncology and BMT

**Institution:** Children's National Medical Center

**MPA or SPA Number:** Federal-Wide Assurance program FWA# 00004487.

**Complete Address:** 111 Michigan Ave NW  
Washington DC, 20010

**Phone Number:** 202-476-2694

**E-mail:** kmwillia@cnmc.org

**Name of IRB Contact:** Fahmida Hoq, MD

**Complete Address:** 111 Michigan Ave NW

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

Washington DC, 20010

**Phone Number:** 202-476-5000

**E-mail of Contact:** FHoq@childrensnational.org

**Name of Pharmacy Contact:** N/A

**PRÉCIS****Background:**

- Impaired lymphocyte immune reconstitution is associated with morbidity and mortality following allogeneic hematopoietic stem cell transplantation (HSCT).
- Data suggest that one of the limitations of immunity after HSCT is the lack of thymus recovery and proper B cell development.
- Androgen withdrawal has been shown to enhance T and B lymphopoiesis.
- Lupron is an approved, safe, gonadotropin releasing hormone (GnRH) agonist/antagonist.
- Noninvasive imaging modalities to study immune reconstitution would be invaluable to predict optimal or impaired immune recovery permitting early institution of therapies.
- FLT is 3'-deoxy-3 18F-fluorothymidine, a radiolabeled thymidine analogue that illustrates dividing hematopoietic cells and may predict immune recovery after allogeneic HSCT.
- FLT has been used safely in patients who have received intensive chemotherapy.

**Objectives:**

- Primary: To determine if Lupron improves B lymphocyte reconstitution after HSCT.
- Primary: To assess whether 18F FLT PET/CT could predict early engraftment/immune reconstitution in marrow and thymus after allogeneic HSCT.
- Primary: To assess safety of Lupron after 2<sup>nd</sup> HSCT evaluated in a separate arm.

**Eligibility:**

- Patients > 9 years old and pubertal and/or >15 year and ≤ 55 years, with aggressive leukemia (Acute Myelogenous Leukemia (AML), myelodysplastic syndromes (MDS) with high risk cytogenetics, Acute Lymphocytic Leukemia (ALL), CMML, certain CML) requiring HSCT will be enrolled at NCI.
- At University of Oklahoma, Age > 17 years old and ≤55 years for recipient.
- Patients > 4 and < 24 years with the above diseases will be enrolled at Children's National Medical Center.

**Design:**

- This is a prospective pilot study, the primary aims of which are: 1) to assess whether Lupron enhances lymphocyte recovery after HSCT and 2) whether FLT imaging can be used to predict engraftment/immune reconstitution, and 3) whether Lupron and FLT are tolerable for second HSCT.
- At NCI and Univ of Oklahoma, post-pubertal pediatric male patients (<18 years) will be randomized to receive a 3 month (11.25 mg) injection and adult male patients will be randomized to receive 4-month preparation of Lupron (30 mg) or placebo two weeks before the preparative regimen for first BMT. Women and all individuals undergoing

2<sup>nd</sup> BMT will receive Lupron at these doses per age and be evaluated in the treated cohort. At Children's National Medical Center, the patients will not receive Lupron outside of the context of clinical care, and will receive myeloablative HSCT as per standard of care with FLT imaging for engraftment as the only primary endpoint.

- A target of 68 evaluable adult patients will be enrolled on this trial, which may necessitate up to 118 patients (118 donors) enrolled to reach this target at NCI and University of Oklahoma. A total of 10 pediatric patients will be enrolled at Children's National Medical Center for FLT imaging only. Sixteen of these patients will be enrolled to undergo second BMT.
- At NCI, adults greater than 18 years old both female and adult male patients undergoing 2<sup>nd</sup> BMT will receive 4-month preparation of Lupron (30 mg) two weeks before the preparative regimen. All patients will undergo FLT imaging to evaluate whether this may predict HSCT response or failure (relapse). This will be a pilot arm of 16 patients total.
- The planned length of this trial is 7 years with interim analyses at day 100 and day 365.
- Some of the patients are anticipated to be evaluated using FLT (to include only patients needed for the immunological primary endpoint, not increasing total patient numbers). 23 adult NCI patients in total will undergo FLT PET/CT imaging on day -1, at day +5 or day +9, at 4 weeks, and at a future point to include evidence of GVHD relapse, or immune recovery. An estimated 50 patients (including subset of the 23 patients undergoing serial scanning) will be imaged approximately at 1 year for evaluation of thymus reconstitution. The total possible numbers will include no more than 118 patients to achieve the 68 evaluable adults for the immunological primary endpoint. However, all NCI patients will undergo a single 1 year FLT for evaluation of thymus reconstitution. 10 pediatric patients at CNMC will undergo FLT PET/CT imaging on Day -1, day+9, and day +28 (if possible). Initial images will be correlated with engraftment and other secondary endpoints.
- Study endpoints to include: 1) safety of Lupron in the context of allogeneic BMT, 2) lymphocyte reconstitution after Lupron administration, 3) the incidence of acute and chronic GVHD and infectious complications, 4) remission rates after HSCT.

**TABLE OF CONTENTS**

PRÉCIS .....	5
TABLE OF CONTENTS.....	7
1 INTRODUCTION .....	14
1.1 Study Objectives .....	14
1.1.1 Primary Objectives.....	14
1.1.2 Secondary Objectives.....	14
1.2 Background and Rationale.....	15
1.2.1 Impaired Immune Reconstitution after Stem Cell Transplantation .....	15
1.2.2 Androgen Withdrawal Enhances T and B Lymphopoiesis.....	16
1.2.3 Lupron for Androgen Suppression.....	18
1.2.4 Lupron Safety Profile.....	18
1.2.5 Lupron Pharmacology.....	18
1.2.6 FLT imaging modality .....	19
1.2.7 <sup>18</sup> F FLT Safety Profile .....	21
1.2.8 <sup>18</sup> F FLT Pharmacology .....	21
1.2.9 FLT Availability .....	22
1.2.10 Trial Plan.....	22
2 ELIGIBILITY ASSESSMENT AND ENROLLMENT.....	23
2.1 Eligibility Criteria .....	23
2.1.1 Inclusion Criteria: Transplant Recipient.....	23
2.1.2 Exclusion Criteria: Transplant Recipient.....	25
2.1.3 Inclusion Criteria: Matched Related Transplant Donor.....	26
2.1.4 Exclusion Criteria: Matched Related Transplant Donor.....	26
2.1.5 Inclusion Criteria- Matched Unrelated Donor .....	27
2.1.6 Inclusion Criteria- <sup>18</sup> F FLT Candidate Transplant Recipient .....	27
2.1.7 Exclusion Criteria- <sup>18</sup> F FLT Candidate Transplant Recipient .....	27
2.2 Screening Evaluation and Criteria for HSCT .....	27
2.2.1 Recipient .....	27
2.2.2 Matched Related Donor .....	29
2.3 Registration Procedures .....	30
2.3.1 Protocol Entry Date.....	30

**Abbreviated Title: Lupron & 18F FLT in allo-HSCT**

**Version Date: December 28, 2017**

2.3.2	Registration .....	30
2.3.3	University of Oklahoma Donors and Recipients .....	30
2.3.4	Children's National Medical Center Donors and Recipients.....	31
2.4	Randomization Procedures .....	31
2.4.1	Female Recipients .....	31
2.4.2	Male Recipients .....	31
3	STUDY IMPLEMENTATION .....	32
3.1	Study Design .....	32
3.1.1	NCI and University of Oklahoma for 1 <sup>st</sup> BMT .....	32
3.1.2	Children's National Medical Center .....	33
3.2	Drug Administration .....	33
3.2.1	Lupron .....	33
3.2.2	<sup>18</sup> F-FLT .....	33
3.3	On Study Protocol Evaluation Pre-Transplant Work-up .....	34
3.3.1	Within 4 weeks of Transplant Date .....	34
3.3.2	FLT on Study Evaluations .....	34
3.4	Biologic Studies .....	35
3.4.1	Immune Reconstitution .....	35
3.4.2	Immunologic Studies .....	36
3.4.3	Objectives/Specific Aims.....	36
3.4.4	Methodology .....	36
3.5	Collaborative research Studies.....	37
3.6	Donor Collection.....	38
3.6.1	Matched Unrelated Donors .....	38
3.6.2	Matched Related Donors.....	38
3.7	Preparative Regimen for HSCT and GVHD Prophylaxis.....	39
3.7.1	Central Access .....	39
3.7.2	Remission Status.....	39
3.7.3	Conditioning Regimen .....	39
3.7.4	GVHD Prophylaxis.....	41
3.7.5	Growth Factors (GCSF).....	41
3.8	Transplant Procedure for 1 <sup>st</sup> and 2 <sup>nd</sup> BMT.....	42



**Abbreviated Title: Lupron & 18F FLT in allo-HSCT**

**Version Date: December 28, 2017**

3.8.1	Day 0 .....	42
3.8.2	Transplant Outcome Determinations .....	42
3.9	Post-transplant monitoring (1 <sup>st</sup> and 2 <sup>nd</sup> BMT) .....	42
3.9.1	Day 0 to day +100 .....	42
3.9.2	Specific evaluation time points (1 <sup>st</sup> and 2 <sup>nd</sup> BMT) .....	43
3.9.3	Long term follow-up guidelines (1 <sup>st</sup> and 2 <sup>nd</sup> BMT) .....	43
3.9.4	FLT on study evaluations.....	44
3.10	Criteria for Removal from Protocol Therapy and Off Study Criteria.....	44
3.10.1	Criteria for Removal from Protocol Therapy.....	44
3.10.2	Off-Study Criteria .....	45
3.10.3	Off Protocol Therapy and Off Study Procedure at NCI .....	45
3.10.4	Participating Site Off-Study Notification .....	45
4	SUPPORTIVE CARE.....	46
4.1	Infection Prophylaxis .....	46
4.1.1	Infectious Disease Surveillance: .....	47
4.2	Management of Engraftment Syndrome .....	47
4.3	Treatment of Graft-Versus-Host Disease.....	47
4.4	Menses Suppression and Contraception .....	48
4.5	Blood Product Support.....	48
4.6	Nutritional Support .....	49
4.7	Anti-Emetic Usage.....	49
4.8	Intravenous Immune Globulin (IVIG) .....	49
4.9	Hepatic Function Support .....	49
4.10	Central Nervous System Prophylaxis .....	50
4.11	Fluid Management During First 30 Days Following Transplantation.....	50
4.12	Ancillary Support.....	50
4.13	Supportive Care For Relapse .....	50
4.14	Additional cell infusions for graft failure, impending graft failure, or poor graft function. ....	50
5	DATA COLLECTION AND EVALUATION.....	50
5.1	Data Collection .....	50
5.1.1	Adverse event recording .....	52

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

5.2	Response Criteria .....	52
5.2.1	Primary Endpoints .....	52
5.2.2	Secondary Endpoints .....	52
5.3	Toxicity Criteria .....	53
6	STATISTICAL SECTION .....	53
6.1	Subject Accrual .....	53
6.1.1	Statistics and Feasibility .....	53
7	HUMAN SUBJECTS PROTECTIONS .....	56
7.1	Rationale For Subject Selection .....	56
7.2	Participation of Children .....	56
7.3	Participation of Subjects Unable to Give Consent .....	57
7.4	Evaluation of Benefits and Risks/Discomforts .....	57
7.4.1	Recipient .....	57
7.4.2	Risks in relation to benefit for Donor .....	58
7.4.3	Pediatric Patients .....	58
7.5	Consent and Assent Process and Documentation .....	58
7.5.1	Consent for minors when they reach the age of majority .....	59
7.5.2	Telephone consent and re-consent procedure .....	60
7.5.3	Informed consent of Spanish speaking subjects .....	60
7.5.4	Short form consent process for other non-English speaking patients .....	60
8	SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN	
	61	
8.1	Definitions .....	61
8.1.1	Adverse Event .....	61
8.1.2	Suspected adverse reaction .....	61
8.1.3	Unexpected adverse reaction .....	61
8.1.4	Serious .....	61
8.1.5	Serious Adverse Event .....	61
8.1.6	Disability .....	62
8.1.7	Life-threatening adverse drug experience .....	62
8.1.8	Protocol Deviation (NIH Definition) .....	62
8.1.9	Non-compliance (NIH Definition) .....	62

**Abbreviated Title: Lupron & 18F FLT in allo-HSCT**

**Version Date: December 28, 2017**

8.1.10	Unanticipated Problem.....	62
8.2	NCI-IRB and Clinical Director Reporting.....	62
8.2.1	NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths 62	
8.2.2	NCI-IRB Requirements for PI Reporting at Continuing Review .....	63
8.2.3	NCI-IRB Reporting of IND Safety Reports.....	63
8.3	NCI Guidance for Reporting Expedited Adverse Events for Multi-Center Trials .....	64
8.4	IND Sponsor Reporting Criteria .....	64
8.5	Data Recording of Unrelated Donors from NMDP .....	64
8.6	Data and Safety Monitoring Plan.....	64
8.6.1	Principal Investigator/Research Team .....	64
8.6.2	Sponsor Monitoring Plan .....	65
8.6.3	Safety Monitoring Committee (SMC) .....	65
9	Multi-Institutional Guidelines.....	66
9.1.1	IRB Approvals .....	66
9.1.2	Amendments and Consents.....	66
9.1.3	Data and Specimen Collection Procedures .....	66
9.1.4	Data Center Audits.....	66
9.1.5	Protocol Monitoring Committees .....	66
10	PHARMACEUTICAL INFORMATION.....	66
10.1	Lupron depot.....	66
10.1.1	Chemical name.....	66
10.1.2	Chemical structure .....	67
10.1.3	Commercial Formulation .....	67
10.1.4	Storage .....	67
10.1.5	Stability .....	67
10.1.6	Route of administration.....	67
10.1.7	Dose .....	67
10.1.8	Drug Interactions .....	67
10.1.9	Known toxicities for patients >18.....	67
10.1.10	Known toxicities for patients <18.....	68
10.2	Cyclophosphamide.....	69

**Abbreviated Title: Lupron & 18F FLT in allo-HSCT**

**Version Date: December 28, 2017**

10.2.1	Chemical name.....	69
10.2.2	Chemical structure .....	69
10.2.3	Commercial Formulation .....	70
10.2.4	Storage .....	70
10.2.5	Stability .....	70
10.2.6	Route of administration.....	70
10.2.7	Dose .....	70
10.2.8	Drug Interactions .....	70
10.2.9	Known toxicities .....	70
10.3	Total Body Irradiation.....	71
10.3.1	Chemical name.....	71
10.3.2	Known toxicities .....	71
10.4	FLT .....	71
10.4.1	Chemical Name.....	71
10.4.2	Commercial Formulation .....	71
10.4.3	Storage .....	71
10.4.4	Chemical Structure.....	71
10.4.5	Method of Administration.....	72
10.4.6	Availability .....	72
10.4.7	Known Toxicites.....	72
10.5	Fludarabine (Fludara, Berlex Laboratories).....	72
10.5.1	Chemical Name.....	72
10.5.2	Supply .....	72
10.5.3	Preparation .....	72
10.5.4	Storage and Stability .....	72
10.5.5	Administration .....	72
10.5.6	Toxicities.....	72
10.6	Busulfan (Busulfex).....	73
10.6.1	Source .....	73
10.6.2	Storage and Stability.....	73
10.6.3	Administration .....	73
10.6.4	Toxicities.....	73

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

10.6.5	Drug Interactions .....	73
11	REFERENCES .....	74
12	APPENDICES .....	78
12.1	Appendix 1: Performance Scales .....	78
12.2	Appendix 2A: Recipient (arm 1 and 2).....	80
12.3	Appendix 2B: Donor (arm 1 and 2) .....	82
12.4	Appendix 3a: FLT ( 1 <sup>st</sup> BMT).....	83
12.5	Appendix 4A: Adult (>22 years) BMT Roadmap .....	85
12.6	Appendix 4B: Pediatric (<22 years) BMT Roadmap .....	89
12.7	Appendix 5: Research Specimens.....	93
12.8	Appendix 6: Immunization Post-Transplant.....	94
12.9	Appendix 7: Management of Engraftment Syndrome .....	95
12.10	Appendix 8A: Grading and Management of Acute Graft-Versus-Host-Disease.....	97
12.11	Appendix 8B .....	99
12.12	Appendix 8C: Signs and Symptoms of cGVHD .....	102
12.13	Appendix 8D: cGVHD Score Sheet .....	104
12.14	Appendix 9: ETIB Policy for Sample Handling.....	107
12.14.1	Sample Processing .....	107
12.14.2	Labeling .....	107
12.14.3	Storage/Tracking in the Preclinical Development and Clinical Monitoring Facility (PDCMF) .....	107
12.14.4	Protocol Completion/Sample Destruction .....	108
12.14.5	Handling for subjects at other Participating Institutions.....	109
12.15	Appendix 10: Data Collection elements Required by Protocol .....	110
12.16	APPENDIX 11: Problem Report Form.....	113

## 1 INTRODUCTION

### 1.1 STUDY OBJECTIVES

#### 1.1.1 Primary Objectives

- To determine whether Lupron leads to accelerated B cell recovery after allogeneic hematopoietic stem cell transplantation (after 1<sup>st</sup> and 2<sup>nd</sup> BMT).
- To assess whether 18F FLT PET/CT could predict early engraftment/immune reconstitution in marrow and thymus after allogeneic HSCT (1<sup>st</sup> BMT only).
- To assess safety of Lupron after 2<sup>nd</sup> HSCT and evaluate whether FLT can predict relapse (evaluated after 2<sup>nd</sup> BMT)

#### 1.1.2 Secondary Objectives

- To investigate whether Lupron will accelerate thymic reconstitution after allogeneic HSCT using CT scan thymic index, flow cytometric measurements of naïve T cells, peripheral blood TREC on sorted CD4+ and CD8+ T cells, and Spectratype analysis of T cell receptor diversity on sorted CD4+ and CD8+ T cells (1<sup>st</sup> BMT)
- To assess the feasibility of 4 month Lupron in male patients after allogeneic HSCT in post-pubertal individuals (after 1<sup>st</sup> and 2<sup>nd</sup> BMT).
- To investigate whether Lupron will decrease the incidence of acute or chronic graft-versus-host disease (GVHD) after allogeneic HSCT, comparing the Lupron treated and untreated groups using NIH developed criterion for the definition of clinical and biopsy-proven acute and chronic GVHD (after 1<sup>st</sup> BMT).
- To evaluate if Lupron will decrease the incidence of infectious complications in recipients of allogeneic HSCT, comparing the number and clinical severity of infectious complications between patients who received Lupron as compared to those that did not (after 1<sup>st</sup> BMT).
- To evaluate if Lupron will enhance graft-versus-tumor (GVT) effects by comparing the remission rates of patients who did vs. did not receive Lupron (after 1<sup>st</sup> BMT). To compare the outcomes of the pilot patients after 2<sup>nd</sup> HSCT in terms of relapse as compared to historical controls.
- To evaluate if Lupron treatment results in other changes in immune reconstitution (e.g. dendritic cell reconstitution, monocyte reconstitution, and immunoglobulin recovery) (after 1<sup>st</sup> BMT).
- To demonstrate that 18F FLT imaging is safe in the peri-transplant period (after 1<sup>st</sup> BMT).

FLT endpoints include: 1) Ability of 18F FLT-PET to document preparative regimen ablation success 2) Evaluate the potential of 18F FLT/PET imaging to predict engraftment at week one 3) Assessment of GVHD using 18F FLT, 4) Assess relapse using FLT (after 1<sup>st</sup> and 2<sup>nd</sup> BMT).

## 1.2 BACKGROUND AND RATIONALE

### 1.2.1 Impaired Immune Reconstitution after Stem Cell Transplantation

Impaired immune reconstitution contributes to morbidity and mortality after allogeneic stem cell transplant. Data suggest that this is due to the delayed and often disturbed recovery of T and B cells post-transplant. Although the innate immune system regenerates functionally and quickly post-transplant, the recovery of T and B lymphocytes is delayed for many months to years. This delay in lymphocyte cell recovery compared to other leukocytes is more pronounced in adult patients as compared to children. As shown in Figure 1 and Figure 2 below, the two figures compare the percentage of normal leukocyte recovery in peripheral blood between adults and children. These show that B cell recovery in children approaches 50% by day 180 and 100% by day 270 and CD4+ numbers approach 100% at 2 years. In contrast, for adults, B cell recovery is 30% at day 180 and 80% at day 270 with CD4 recovery delayed indefinitely [1]

Figure 1

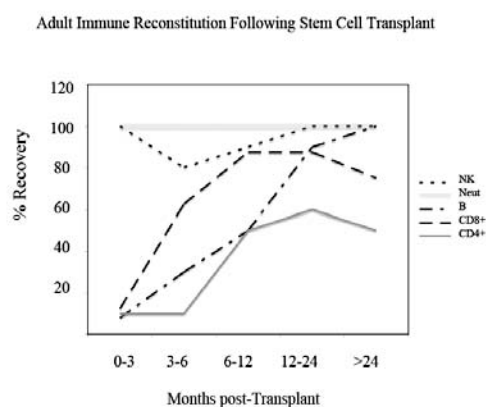
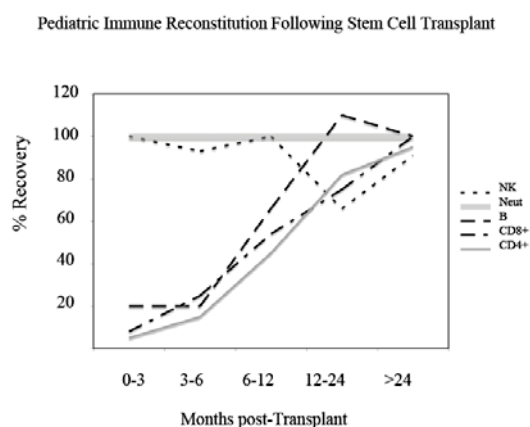


Figure 2



Not only are the absolute numbers of T and B lymphocytes decreased post-transplant, the function of these populations remains compromised even after normal numbers are achieved. In part, this is due to the mechanism of lymphoid reconstitution post-transplant. In contrast to normal ontogeny where the thymus provides the vast majority of T cells to the peripheral pool,

post-transplant T cell regeneration relies upon the mechanism of peripheral expansion for T cell recovery. In the thymus, T cells are produced de novo from marrow precursors. These T cells undergo T cell receptor (TCR) rearrangement, resulting in naïve T cells with diverse TCRs, capable of recognizing a wide array of infectious or tumor antigens. These developing T cells undergo positive and negative selection, permitting the deletion of autoreactive clones. In contrast, when thymic function is poor as is often the case after adult allo-HSCT, T cell reconstitution is accomplished through the rapid proliferation of mature T cell clones, leading to a skewed, oligoclonal population of T cells with the potential for alloimmunity.[\[1\]](#) Poor thymic function has significant clinical consequences in the setting of hematopoietic stem cell transplantation. Impaired thymopoiesis is associated with poor clearance of infections and diminished responses to vaccines (due to resulting B cell dysfunction). [\[2-6\]](#) Successful T cell reconstitution also confers significant protection from relapse of malignant disease as well. [\[7-9\]](#) Furthermore, impaired thymopoiesis is linked to the development and persistence of acute and chronic graft-versus-host disease. [\[6, 10-12\]](#) Thus, improving thymopoiesis and thus lymphopoiesis may partially abrogate GVHD, enhance immune surveillance, and improve HSCT outcomes.

Similar to the effects of peripheral expansion on T cells, mature memory B cells demonstrate a restricted repertoire post-HSCT. [\[13\]](#) In contrast, B cells produced in the marrow through de novo development (transitional B cells) display a diverse repertoire. [\[13, 14\]](#) These transitional B cells emerge gradually (within months) after HSCT and are not influenced by viral reactivations and GVHD, suggesting that this population would be best used to identify the influence of immunotherapy on lymphocyte reconstitution after HSCT. In addition, studies have suggested that transitional B cell development is delayed and diminished in older adults, those with reduced intensity conditioning for HSCT, findings similar to the influence of these factors on thymus derived T cell development. [\[15\]](#) Furthermore, there are data to suggest that transitional de novo B cell development would be associated with enhanced tolerance that could translate to diminished GVHD. [\[16\]](#) Thus, because thymus recovery could take years in young adults, is likely influenced by infections and GVHD, while transitional B cell reconstitution is faster, less modulated by other post-transplant factors, B cells will be used for the primary endpoint of lymphocyte engraftment in this study. Thymus recovery and restoration of T cell diversity will be included as important secondary endpoints though this will likely only be evaluable in the small subset of patients without relapse, GVHD, who survive greater than 2 years after HSCT.

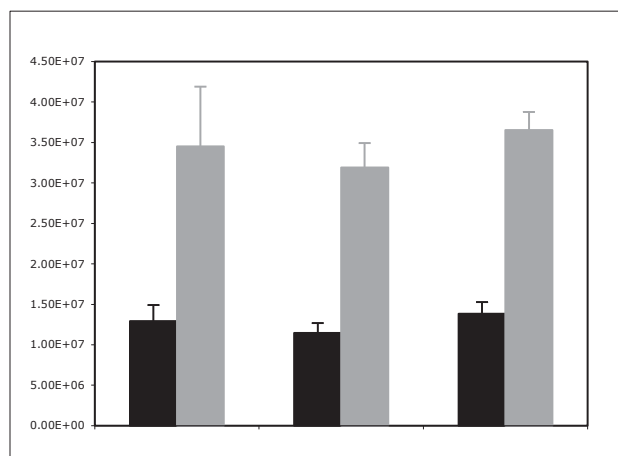
At this time, there are not data to determine the best source of HSCs between marrow and peripheral blood stem cells. Marrow is chosen as the stem cell source for this protocol due to: 1) this is the standard stem cell source in pediatrics, 2) there are evidence that marrow products lead to less GVHD without compromising graft-versus-leukemia effects [\[17, 18\]](#), and 3) all of the basic science work that models the lupron and FLT effects were performed with marrow grafts. In many adult oncology institutions, marrow remains the preferred source as well (including University of Oklahoma).

### 1.2.2 Androgen Withdrawal Enhances T and B Lymphopoiesis

Androgen inhibitors are excellent candidates for augmenting B lymphopoiesis and thymopoiesis. Many groups have demonstrated increase thymic size, weight, and thymocyte number following androgen withdrawal. [\[19-22\]](#) Murine and clinical data show that androgen withdrawal can

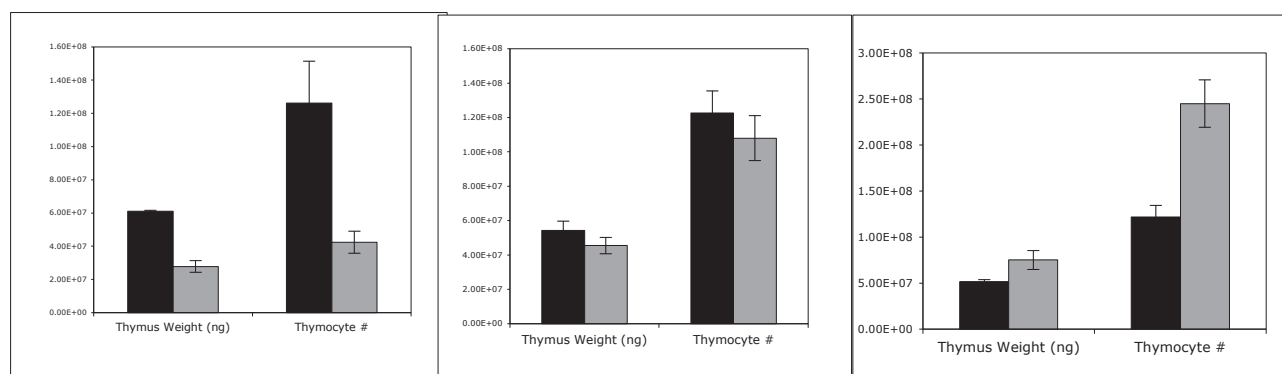


reverse age-related thymic atrophy and reconstitute normal, young thymocyte subsets with subsequent increased peripheral T cell numbers. [23] Similarly, B lymphopoiesis is also increased after androgen withdrawal. [24] Data suggest that these increases in B and T cell numbers following androgen suppression are due to increases in de novo production of B and T cells in the marrow and thymus respectively. [21, 25] As shown in Figure 3 below, following androgen withdrawal in male mice (light grey box), B cell total numbers are dramatically increased in the marrow as compared to control (black box) at 1, 3, and 4 weeks (see Figure 3 below, B subsets defined as B220+).



**Figure 3**

Similarly, the thymus of mice treated with lupron was increased in size and thymocytes were increased in number as compared to controls. Notably, because lupron initially leads to androgen release, followed by suppression, the thymus first involutes then expands with subsequent increase in thymocyte production. As shown in Figure 4 below, thymus weight (left) and thymocyte number (right) are initially decreased at 1 week after lupron (grey), then similar at 2 weeks, then increased after 4 weeks as compared to controls (black).



**Figure 4**

Additionally, recent data suggest that T and B cell reconstitution is accelerated after stem cell transplant in murine allogeneic transplant models after androgen withdrawal without decreasing graft-versus-tumor effect or worsening GVHD. [19] Our murine data demonstrate that the mechanism underlying the accelerated thymus recovery after androgen withdrawal involves: 1.

Increase in thymus epithelial cell (TEC) proliferation, 2. Increased production of CCL25 by these TEC, 3. Increased early thymic progenitor entry of marrow precursors by CCL25 interactions, 4. Accelerated development of thymocytes due to CCL25 signaling, and 5. Overall enhanced thymopoiesis with increased export of naïve selected diverse T cells [25]. Similarly, B cell increases after androgen withdrawal have also been attributed to marrow stromal influences, resulting in accelerated de novo B cell development (rather than expansion of peripheral clones). [21] Given this mechanism and these murine and clinical data, androgen withdrawal has the potential to enhance de novo lymphopoiesis in young adults following HSCT with possible benefits of: improved infection and tumor clearance and diminished GVHD. Because of the timing of the androgen release and thymic involution and the possibility that these effects occur in marrow stroma as well, male randomized subjects will receive the lupron injection approximately 1-2 weeks prior to HSCT to minimize the potential additive damage of thymus involution and radiotherapy.

### 1.2.3 Lupron for Androgen Suppression

Lupron is an FDA-approved gonadotropin-releasing hormone (GnRH) analog that has been used clinically for androgen suppression in prostate cancer patients for males [23, 26] and for menses suppression during HSCT for females [27]. In males with prostate cancer, there are data to suggest enhanced thymic function following this agent. [23] Notably, most of these subjects were older individuals in whom free testosterone is substantially lower than younger subjects (0.2 +/- 0.081 vs. 0.43 +/- 0.098). [28] Thus, while patients may have diminished circulating testosterone following chemotherapy, the levels were not lower than those of older men, and the subjects are likely to still exhibit immunologic changes after androgen withdrawal. [29] Because Lupron is an analog of GnRH, it leads to an initial burst of sex steroid release followed by suppression. A study of administration and efficacy of Lupron in females for the suppression of menses revealed that the greatest efficacy was achieved when Lupron was given greater than 2 weeks prior to thrombocytopenia. Similarly, our murine data has demonstrated that optimal administration for Lupron with regards to marrow transplantation is approximately 1-2 weeks pre-transplant. This is because the initial stimulation of GnRH leads to thymus involution and 1-2 weeks following this will be a period of relative stabilization for the thymus, and possibly marrow stroma. Thus, thymic epithelial cells will be at basal proliferation and less harmed by radiation damage. Taken together, Lupron (4 month preparation) will be administered at approved doses 1-2 weeks prior to the preparative regimen.

### 1.2.4 Lupron Safety Profile

Lupron has a very good safety profile with only 3 reported adverse events (testicular atrophy) in greater than 20% of 94 patients studied in two clinical trials for prostate cancer (see section 10 for details). There are data that HSCT alone leads to testicular atrophy in male patients, thus this particular AE is not likely to be unique in lupron-treated subjects after HSCT.

### 1.2.5 Lupron Pharmacology

Lupron (leuprolide acetate) is a synthetic nonapeptide analog of GnRH that binds more strongly than the endogenous hormone. The 4 month preparation is 30 mg is dispensed in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, upon mixing with diluent become a suspension that can be given as an intramuscular injection. Within several days, a marked increase in serum sex steroid (testosterone) occurs followed by equilibration to

baseline levels at 1 week and suppression by 2-4 weeks that is maintained until week 12 (data obtained from the prescription brochure). Although no specific drug interaction studies have been performed, drug interactions are unlikely to occur because the drug is only 46% plasma protein bound and degraded by peptidase not utilizing P-450 cytochromes. Furthermore, the drug has been used in HSCT for women for menses suppression without noted drug interactions. The effects are reversible as normal gonadal function is restored within 1-3 months upon discontinuation.

### 1.2.6 FLT imaging modality

Nuclear medicine imaging has been invaluable to assess tumor disease burden and response to therapy. PET/CT uses  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) to identify cells that rapidly uptake glucose including tumor cells. This modality has revealed: tumor metastases, responses to tumor after treatment cycle, tumor recurrence, and has been useful to accurately predict true complete response, correlating PET negativity with longterm survival [30-33]. Despite these data demonstrating the utility of this test for evaluation in lymphomas and cancer, FDG-PET is limited by lack of specificity. Because FDG-PET relies upon glucose incorporation into cells, the signal will be present not only in tumor cells, but also normal tissues such as brain and heart that require active glucose uptake and in inflammatory lesions (due to uptake by macrophages and granulation tissues).



**Figure 5 (from the investigator's brochure 1-03-05)**

A novel agent, FLT is 3'-deoxy-3  $^{18}\text{F}$ -fluorothymidine, a radiolabeled thymidine analogue that illustrates dividing hematopoietic cells. FLT is derived from the drug azidovudine (AZT) that uses thymidine kinase 1 for uptake into cells, part of the salvage pathway for DNA synthesis. This enzyme is tightly controlled in normal cells and increases during cell division, permitting increased FLT uptake in dividing cells. Furthermore, malignant cells have lost their regulation and thus have higher thymidine kinase 1 available, leading to even greater uptake of FLT than normal cells that divide at higher rates [34]. Thus, this imaging agent has the potential to distinguish rapidly dividing cells from static cells and both of these from malignant cells based on degree of uptake of FLT. FLT has been used to successfully stage and evaluate chemotherapy response in non-hodgkins lymphoma [35-38], breast cancer [39-41], and sarcoma [42]. In many of these studies, high background activity was noted within the marrow compartment, indicative of FLT uptake by hematopoietic cells. FLT was then used to evaluate acute myelogenous leukemia in a pilot study, revealing higher SUV in patients with disease compared to controls.[43, 44] Similarly, patients with aplastic anemia or myelofibrosis associated with lack of hematopoiesis had decreased uptake in the marrow compartment [44].

FLT has been used to document response following treatment of AML [43] and has been shown to be accurate and reproducible following chemotherapy in patients treated for testicular carcinoma [45]. It can further document changes in marrow following directed radiotherapy dosing, which may allow for more accurate assessment of response to therapy in marrow-borne malignancies [45]. These data suggest that FLT could be used to assess hematopoiesis in the marrow compartment, potentially illustrating empty vs. normal hematopoiesis vs. leukemia recurrence with greater sensitivity than single site marrow aspirates yield.



**Figure 6: Normal uptake in bone marrow[44]**



**Figure 7: Increased uptake in patient with MDS[44]**

Dr. Holter, our collaborator, has modeled FLT (3'-deoxy-3'  $^{18}\text{F}$ -fluorothymidine) in rat bone marrow transplantation and shown that by day 4, engraftment kinetics could be predicted and this time point preceded peripheral blood and full histologic evidence of marrow recovery. [46] As stated above, not only is immune reconstitution a major barrier to successful HSCT, but also our modalities for evaluating this are often invasive (bone marrow aspirate) or less informative (peripheral blood evaluation). In cord blood transplantation, this is a clinically significant problem as non-engraftment and late engraftment of the donor cells is common and there are currently no early predictive tests for whether a patient will engraft late or require a second conditioning regimen and new donor products. Furthermore, even in matched adult donor transplantation where graft failure rates are low, there are often periods post-transplant where the peripheral blood cellular counts decline and the differential includes graft loss, medication toxicities, infections, and relapse. Thus, a noninvasive imaging modality that could model engraftment kinetics would be invaluable to clinicians, potentially predicting graft failure early and narrowing the differential in the setting of cytopenias. These data prompted this clinical evaluation of FLT to determine if FLT could be used in conjunction with PET imaging at scheduled time points during HSCT for evaluation of engraftment. These data could: 1) predict the rate of marrow engraftment and the length of neutropenia, 2) demonstrate evidence of minimal residual disease at the time of transplant (the uptake should be null following myeloablative transplant preparative regimen), 3) predict thymus recovery. In this current

protocol, adults and children with aggressive leukemias and MDS will have both the greatest opportunity for: 1) evaluation of residual disease that should be positive by FLT at the time of transplant, 2) a differential in uptake over time as the myeloablative negative scan increases in uptake corresponding with increasing hematopoiesis, and 3) the greatest chance for thymus recovery in adults to evaluate by FLT.

### 1.2.7 <sup>18</sup>F FLT Safety Profile

<sup>18</sup>F FLT is currently in use in clinical trials and has currently been shown to be safe at the doses proposed in this study. Although <sup>18</sup>F FLT enters cells via an enzyme in the salvage pathway, it is not significantly incorporated into DNA due to the lack of a 3'-hydroxyl group, which is necessary for DNA propagation. Thus, although the agent remains within cells long enough for imaging, it will not persist long term nor should it be mutagenic. At the doses used in this study, several studies have been published and no adverse events reported in patients with leukemia and MDS [43, 44]. The planned dose is 0.07 mCi/kg with maximum dose of 3 mCi (maximum of 6.1 ug). At higher doses exceeding a 1000 fold increase in <sup>18</sup>F FLT from our planned dose, <sup>18</sup>F FLT has been associated with grade 3 hematologic toxicity (6/10 at 0.125 mg/kg q12 hours which equals area under the curve of 417 ng-h/mL and 5/15 patients at 200 ng-h/ml), hepatic failure (2/10 at dose of 200ng-h/mL and 10mg/day). At a dose 1000 fold higher than our planned dose, mild peripheral neuropathy occurred (2/10 at dose of 50 ng-h/mL) [47]. No AEs attributable to <sup>18</sup>F FLT administered at tracer levels have been reported in the published literature. While no related AEs are expected, patients will be monitored very closely with regards to hepatic, neurologic, and hematologic parameters following radiotracer injection.

Patients on this study who receive <sup>18</sup>F FLT/CT will be exposed to a maximum whole body dose (ED) of 6.2 rem whole body dose (ED), 1.2 rem from each <sup>18</sup>F FLT/CT scan and 0.73 from each FDG PET/CT. For comparison, the average person in the United States receives a radiation exposure of 0.3 rem per year from natural background sources, such as from the sun, outer space, and from radioactive materials that are found naturally in the earth's air and soil. The dose that a patient will receive from this research study is about the same amount that individual would normally receive in 20.5 years from these natural sources. A routine clinical <sup>18</sup>F FDG PET/CT is approximately 1.4 rem; for the purposes of this study, we have reduced the injected dose.

### 1.2.8 <sup>18</sup>F FLT Pharmacology

<sup>18</sup>F FLT has a half life of 108 minutes [48]. The administered dose will be 0.07 mCi/kg with a maximum dose of 3 mCi per scan. The drug is excreted in the liver and kidney. Transport of FLT across cell membranes occurs by active transport and passive diffusion [49]. The drug solution is stored at room temperature in a gray butyl septum sealed, sterile, pyrogen-free glass vial and has an expiration time of 8 hours. The injectable dose of <sup>18</sup>F FLT for most studies will be  $\leq 0.07$  mCi/kg of fluorine-18, not to exceed 3 mCi with a specific activity greater than 200 Ci/mmol at the time of injection. In the dose of FLT, only a small fraction of the <sup>18</sup>F FLT molecules are radioactive. The amount of injected drug is  $\leq 6.1$  ug ( $\leq 25$  nmol per dose) of <sup>18</sup>F FLT. <sup>18</sup>F FLT is administered to subjects by intravenous injection of  $\leq 10$  mL over 30 seconds. There is no evidence that nonradioactive and radioactive FLT molecules display different biochemical behavior.



### 1.2.9 FLT Availability

The Investigator-sponsored IND will be held by Karen Kurdziel, MD. <sup>18</sup>F FLT will be obtained from commercial sources, either from Cardinal Health, Beltsville, MD, or PETNET Solutions Inc., Philadelphia, PA according to the DMFs filed with the FDA respectively for both institutions.

### 1.2.10 Trial Plan

This study addresses 2 issues in transplantation: 1) the problem of delayed lymphoid engraftment after allogeneic transplantation in adults, and 2) the issue of evaluating engraftment of hematopoietic elements after allogeneic transplantation. Patients undergoing 1<sup>st</sup> BMT with aggressive leukemia and MDS who are Age  $\geq 15$  years old and/or  $\geq 9$  years old and pubertal and  $\leq 55$  years will be enrolled and evaluated for remission status. If the patient is not in remission upon study entry, the patient will progress to a chemotherapy regimen with the goal of obtaining complete remission. Once the patient meets criteria for complete remission, female patients and half of the male patients (randomized) will receive Lupron prior to initiation of a standard preparative regimen with standard GVHD prophylaxis. Immunologic assessment of transitional B cells and IgM levels will be used for the primary endpoint of the issue of delayed lymphoid engraftment. This randomization and Lupron arm of the trial will be open at University of Oklahoma as well as NCI.

A subset of these patients will undergo imaging analysis with <sup>18</sup>F FLT as part of their evaluations. <sup>18</sup>F FLT enrolled patients will be imaged at day -1, day 5 or 9, day 28 and a later time point to be determined by clinical events such as evidence of thymus recovery or GVHD. In addition, all newly enrolled NCI patients will be imaged at 1 year for evaluation of thymus reconstitution with the exception of those in the serial scanning subset that have been imaged at a 'later time' as discussed above. Ten FLT patients enrolled at Children's National Medical Center will be imaged at day -1, day +9, and if possible, day +28. Patients will not be imaged at University of Oklahoma.

The primary endpoint for this element of the protocol will be toxicity with a secondary endpoint of imaging analysis at day 5 and day 28 and correlation or prediction of engraftment as compared to a null baseline scan at day -1. Important secondary endpoints will also include other elements of engraftment (neutrophils, T cells, and dendritic cells), relapse/remission status, presence and severity of acute and chronic GVHD, severe infectious complications, and whether the later <sup>18</sup>F FLT nuclear imaging scan may assist in these clinical diagnoses.

Patients with aggressive leukemia and MDS who have relapsed after HSCT and are greater than or equal to 18 years and  $\leq 55$  will be enrolled and evaluated for remission status. Patients will undergo 2<sup>nd</sup> HSCT, after receiving Lupron and will all be evaluated with <sup>18</sup>F FLT imaging to explore the relapse rates and ability of FLT to predict relapse after 2<sup>nd</sup> HSCT. The primary endpoints are: To assess safety of Lupron after 2<sup>nd</sup> HSCT and evaluate whether <sup>18</sup>F FLT can predict relapse. Patients will undergo <sup>18</sup>F FLT imaging on day -1, and FLT and FDG imaging on day 28 and day 60 to predict relapse. Patients may also be imaged before and after therapy for relapse (to not exceed 5 scans total per patient). Note patients enrolled on this protocol who relapse may receive another HSCT product on this protocol but will not be eligible to undergo FLT imaging again.

## 2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

### 2.1 ELIGIBILITY CRITERIA

#### 2.1.1 Inclusion Criteria: Transplant Recipient

2.1.1.1 At NIH : Age  $\geq 15$  years old and/or  $\geq 9$  years old and pubertal and  $\leq 55$  years for recipient. Pubertal is defined by: prior menses at any time (females), documentation of clinical Tanner stage greater than 2 at some point pre-chemotherapy or at the current visit. (At this point, sex steroids have been produced for a few years which have driven initial pubertal development). Tanner 2 is defined as: breast buds for females with coarse pubic hair, and coarse pubic hair and testes  $> 2.5$ cm for males.

2.1.1.2 At Children's National Medical Center **only**: age  $> 4$  years old and  $< 24$ .

2.1.1.3 At University of Oklahoma: Age  $> 17$  years old and  $\leq 55$  years for recipient.

2.1.1.4 A diagnosis of a hematologic malignancy for which stem cell transplant is standard of care:

##### 2.1.1.4.1 Acute Lymphocytic Leukemia

- Adult: ( $\geq 22$  years)  $\geq$  CR2 *OR* CR1 with a high risk feature:
  - Matched sibling donor for recipient treated on adult leukemia regimen [50, 51]
  - t(9;22) or bcr-abl+; t(4;11), t(1;19), t(8;14), 11q23 (MLL rearrangements) complex cytogenetics (5 or more chromosomal abnormalities), hypodiploidy ( $< 44$  chromosomes). Note that patients with ALL blast crisis who emerge from CML are also eligible.
  - Primary induction failure, defined as failure to achieve CR with primary induction chemotherapy
  - High WBC ( $> 30,000$  for B-cell ALL and  $> 100,000$  for T-cell ALL) at diagnosis
  - Persistence of minimal residual disease despite induction chemotherapy
- Pediatric ( $< 22$  years):  $\geq$  CR2 *OR* CR1 with a high risk feature:
  - Matched sibling donor for recipient treated on adult leukemia regimen [50, 51]
  - Primary induction failure (M3 ( $> 25\%$  with greater 200 cells counted) marrow at day 29), M2 (5-25% blasts with greater than 200 cells counted) bone marrow or MRD  $> 1\%$  at day 29 who then fail at day 43 with either an M2 or M3 BM or MRD  $> 1\%$
  - Persistent leukemia and t(9;22) (MRD  $> 1\%$  day 29 or MRD  $> 0.01\%$  end-consolidation)
  - 11q23 (MLL) rearrangements detected by cytogenetic or PCR at initial diagnosis who are slow early responders (M2/M3 at day 14 or MRD  $> 0.01\%$  at day 29)
  - Extreme hypodiploidy ( $< 44$  chromosomes or DNA index of  $< 0.81$ ) detected by cytogenetic/ploidy analysis

## 2.1.1.4.2 Acute Myelogenous Leukemia

- Adult: ( $\geq 22$  years)  $\geq$  CR2 *OR* CR1 with one of the following high risk features:
  - Adverse or intermediate-risk cytogenetics including:
    - Normal cytogenetics [52]
    - complex karyotype ( $>2$  abnormalities) [53]
    - inv (3) or t(3;3); t(11;19)(q23;p13.1); +13; -17/17p-; -18; -20; t(6;9); t(6;11); -7, 7q-; -5, 5q-; trisomy 8; t(3;5); t(9;11)(p22q23) [52, 53]
    - monosomy karyotype (presence of an autosomal monosomy in conjunction with at least one other autosomal monosomy or structural abnormality. [52]
    - Any other karyotype **EXCEPT** t(8;21), t(9;11), inv(16), or t(16;16), and M3 (17; 17) [53] *unless ckit mutation present and then eligible.* [52]
    - AML emerging from CML (blast crisis) are eligible
  - Primary induction failure, defined as failure to achieve CR with primary induction chemotherapy
  - Secondary AML, defined as AML related to antecedent MDS, MPN, or cytotoxic chemotherapy
  - Hyperleukocytosis (WBC  $> 100,000$  at diagnosis)
  - Mutations in the FMS-like tyrosine kinase 3 (FLT3) gene (FLT3-LM; FLT-ITDs) [54-56]
  - Bilineage or biphenotypic leukemias are high risk features and eligible.
- Pediatric ( $< 22$  years):  $\geq$  CR2 *OR* CR1 with a high risk feature including:
  - Primary induction failure ( $\geq 5\%$  blasts in marrow after induction)
  - Persistent leukemia ( $>15\%$  after first course of chemotherapy)
  - Complex karyotype, monosomy 7, or -5/-5q, FLT3 ITD-AR ( $>0.4$ ) **EXCEPT** if also inv(16)/t(16;16), t(8,21)
  - Normal cytogenetics or abnormal cytogenetics **EXCEPT** if also inv(16)/t(16;16), t(8,21) are eligible for SIBLING transplant only
  - Bilineage or biphenotypic leukemias are high risk features and eligible.

2.1.1.4.3 Myelodysplastic Syndrome RAEB 1 or 2; cytogenetics showing complex karyotype (3 or more abnormalities), monosomy 7/del(7q), or inv(3)/t(3q)/del(3q); or transfusion dependent.

## 2.1.1.4.4 Chronic Myelomonocytic Leukemia

## 2.1.1.4.5 Chronic Myelogenous Leukemia who have failed 2G- tyrosine kinase inhibitors (TKI)



2.1.1.4.6 Standard pediatric indications for myeloablative transplantation for patients undergoing HSCT at Children's National Medical Center per institutional guidelines

#### 2.1.1.5 Disease status

If patients are found to not be in remission at screening, then the patient may be returned to their primary hematologist/oncologist or may receive chemotherapy as per standard of care for the malignant disease. Patients for whom this would be their first allogeneic transplant must be in remission (< 5% malignant blasts in marrow and peripheral blood and no evidence of extramedullary disease) for transplant. Patients enrolled on this protocol for their second transplant do not need to have attained remission prior to transplant.

2.1.1.6 Performance status: Karnofsky or Lansky performance status  $\geq 60\%$  AND life expectancy of greater than 3 months.

2.1.1.7 Ability to give informed consent. For recipients and donors < 18 years of age, their legal guardian must give informed consent. Pediatric patients will be included in an age appropriate discussion in accordance with institutional guidelines.

2.1.1.8 Hepatic function: Patients must have evidence of adequate liver function prior to enrollment defined by total bilirubin < 2.5 mg/dL (unless documented Gilbert's syndrome) AND transaminases  $\leq 5 \times$  the upper limit of normal for age appropriate indices.

2.1.1.9 Renal function: Patients must have evidence of adequate renal function to proceed with stem cell transplant, creatinine clearance > 60 ml/min/1.73 m<sup>2</sup>. GFR may also demonstrate adequate renal function.

2.1.1.10 Left ventricular ejection fraction  $\geq 50\%$  OR shortening fraction of  $\geq 27\%$  demonstrated on 2D echocardiogram or MUGA.

2.1.1.11 Pulmonary function of DLCO adj/VA and FEV1  $\geq 60\%$  of normal indices for age and height unless the patient has a likely acute reversible etiology of decline and then DLCO adj/VA  $\geq 30\%$  of normal. Pediatric patients unable to complete PFTs may be enrolled as per enrolling institution SOP for recipient guidelines.

2.1.1.12 Patients with prior autologous stem cell transplants will be included. Patients with prior allogeneic stem cell transplants will be eligible for 2nd BMT if not previously transplanted with FLT on 11-c-0136.

2.1.1.13 Prior experimental systemic therapies must have been completed greater than 2 weeks prior to study entry.

#### 2.1.2 Exclusion Criteria: Transplant Recipient

2.1.2.1 History of psychiatric disorder which may compromise compliance with transplant protocol, or which does not allow for appropriate informed consent.

2.1.2.2 Active infections not responding to therapy. All efforts should be made to clear the infection prior to enrollment.

- 2.1.2.3 Clinically significant systemic illness with manifestations of significant organ dysfunction which in the judgment PI or AI would render the patient unlikely to tolerate the protocol therapy or complete the study.
- 2.1.2.4 Presence of active malignancy from an organ system other than hematopoietic.
- 2.1.2.5 HIV infection.
- 2.1.2.6 Chronic active hepatitis B infection. Patients may be hepatitis B core antibody positive but must be surface antigen negative and without active evidence of disease.
- 2.1.2.7 Pregnant or lactating females will be excluded from this trial due to unknown risks to the developing fetus. Patients of child-bearing potential must use an effective form of contraception while on study.
- 2.1.2.8 Sexually active individuals capable of becoming pregnant who are unable or unwilling to use effective form(s) of contraception during time enrolled on study and for 1 year post-transplant (see section 4.4 for details).
- 2.1.2.9 History of prior Lupron intolerance. Note: patients ARE eligible if prior or current lupron exposure.
- 2.1.3 Inclusion Criteria: Matched Related Transplant Donor
  - 2.1.3.1 Age  $\geq 2$  and  $\leq 60$  years old and able to give consent or assent. For donors  $< 18$  years old, the legal guardian must be able to provide informed consent and an evaluation by a LSW or psychiatric personnel will be needed to determine willingness to participate. Pediatric patients will be included in an age appropriate discussion in accordance with institutional guidelines.
  - 2.1.3.2 HLA-matched related donor, excluding identical twins. Donors must be matched at least 7 loci out of 8 at the allele or antigen level excluding antigen DRB1 mismatch.
  - 2.1.3.3 Donor selection will be in accordance with NIH/CC Department of Transfusion Medicine criteria and must be able to medically endure stem cell collection or as per local institutional guidelines.
  - 2.1.3.4 Donors must be HIV negative, HTLV negative, HBsAg negative.
  - 2.1.3.5 Donors must be physically able to and willing to tolerate marrow harvest collection preferably, or in the absence of this option, able and willing to donate via peripheral blood pheresis.
- 2.1.4 Exclusion Criteria: Matched Related Transplant Donor
  - 2.1.4.1 History of medical illness that in the estimation of the PI or DTM physician precludes donation of marrow.
  - 2.1.4.2 Anemia (Hb  $< 10$  gm/dl) or thrombocytopenia ( $< 100,000$ /ul).
  - 2.1.4.3 Pregnant females (due to risk to fetus).
  - 2.1.4.4 Current psychiatric diagnosis that would compromise compliance with transplant protocol or precludes appropriate informed consent.

- 2.1.4.5 Presence of any blood transmissible infectious disease that cannot be cleared prior to stem cell collection and poses an unacceptable risk for the recipient (excludes CMV).
- 2.1.4.6 Active malignancy will exclude the donor. Any malignancy less than five years post-remission will exclude the donor. Non-hematologic malignancies greater than 5 years ago will not exclude the donor. Any history of hematologic malignancy will be considered on a case by case basis.
- 2.1.4.7 Any medical contraindication to anesthesia or marrow donation will exclude the donor.
- 2.1.4.8 Donors receiving experimental therapy or investigational agents.
- 2.1.4.9 Active autoimmune disease that in the opinion of the PI or AI would compromise the success of the transplant.
- 2.1.5 Inclusion Criteria- Matched Unrelated Donor
  - 2.1.5.1 Unrelated donor matched at HLA-A, B, C, and DR loci by high resolution typing (at 8/8 or 7/8 antigen/allele match) are acceptable donors.
  - 2.1.5.2 The evaluation of donors shall be in accordance with existing National Marrow Donor Program (NMDP) Standard Policies and Procedures at all institutions.
- 2.1.6 Inclusion Criteria- <sup>18</sup>F FLT Candidate Transplant Recipient
  - 2.1.6.1 Meets criteria Sections [2.1.1](#) and [2.1.2](#)
  - 2.1.6.2 Age  $\geq$  18 years old at NCI, and age  $>$  4 years and  $<$  24 years at Children's National Medical Center
  - 2.1.6.3 Donor who is willing to undergo bone marrow or stem cell harvest.
- 2.1.7 Exclusion Criteria- <sup>18</sup>F FLT Candidate Transplant Recipient
  - 2.1.7.1 History of prior fluorothymidine allergy or intolerance.

## **2.2 SCREENING EVALUATION AND CRITERIA FOR HSCT**

### **2.2.1 Recipient**

The following clinical, laboratory, radiological assessments must be performed on the recipient within 45 days of initiating HSCT preparative regimen with the exception of Section [2.2.2.6](#) which may be performed within the preceding 3 months. These may be performed at outside institutions.

#### **2.2.1.1 Evaluations**

- Complete history and physical examination.
- CT scan of head, sinus, chest, abdomen, and pelvis.
- An echocardiogram (2D or MUGA) an electrocardiogram.
- Pulmonary function tests (PFTs) must be performed for eligibility and FEV1, FEV1/FEV ratio, DLC02 recorded for adult patients; Oxygenation  $>$  94% on RA may be used for pediatric patients unable to undergo PFTs at Children's National Medical Center.

- Laboratory studies:
  - CBC with differential, ABO blood type, PT/PTT, fibrinogen, thrombin time
  - Comprehensive chemistry
  - Lipid profile with triglycerides, TSH, free T4
  - Urine pregnancy test for women of childbearing potential
  - 24 hour creatinine clearance or GFR
  - Bone marrow biopsy and aspiration with studies appropriate to staging of malignant disease, a LP or other biopsy may be required depending upon the diagnosis (to include LP for all AML and ALL)
  - Infectious disease work-up at NCI only: antibody for Hepatitis A, B, C, HIV, T.Cruzi, HTLV-I/II, CMV, adenovirus, varicella, EBV, HSV, Toxoplasmosis, and syphilis. Work-up at other institutions may follow their policy.
- Immunology studies: Lymphocyte phenotype panel (T, B, NK), IgG, IgA, IgM for NCI patients only.
- Radiation Oncology Consult (within 28 days of initiating conditioning chemotherapy for HSCT at NCI). At Children's National Medical Center and University of Oklahoma, this is per institutional practice.
- Nutritional assessment (initial consult) and dental consult and social work consultation must be performed within 3 months of initiating preparative regimen and typing for HLA-A, -B, -C, and DR with PCR test of DNA mini-satellite regions for future determination of chimerism or as per local institutional practice. Note that when possible, the HLA and chimerism assays require 2 separate tubes of blood at NCI.

#### 2.2.1.2 Criteria to proceed to HSCT

- Disease status: Remission as defined by < 5% blasts in marrow and no evidence of extramedullary disease for patients undergoing their first allogeneic transplant. Patients undergoing their second transplant do not have to have obtained a complete remission.
- Performance status: Karnofsky or Lansky performance status > 60% AND life expectancy of greater than 3 months.
- Hepatic function: Patients must have evidence of adequate liver function prior to enrollment defined by total bilirubin < 2.5 mg/dL AND transaminases < 5 x the upper limit of normal for age appropriate indices.
- Renal function: Patients must have evidence of adequate renal function to proceed with stem cell transplant, creatinine clearance > 60 ml/min/1.73 m<sup>2</sup>.
- Left ventricular ejection fraction ≥ 50% demonstrated on 2D echocardiogram or MUGA.
- Pulmonary function of DLCO/Adj/VA and FEV1 > 60% of normal indices for height and weight for adults and >95% oxygenation on RA for pediatric patients.
- Patients who have received prior chemotherapy must have had resolution of significant toxicities to proceed to transplant.
- Negative pregnancy test (females)

- No evidence of an active infection (clinical assessment and review of CT) that is not currently being treated or responding to therapy.
- Either a HLA-matched related or unrelated donor, excluding identical twins. Donors must be matched at least 5 loci out of 6 by antigen matching or at least 8 of 10 using allele matching who met criteria for entry onto this protocol.

## 2.2.2 Matched Related Donor

(See Section [12.3](#))

The following clinical, laboratory, radiological assessments must be performed on the donor within 4 weeks of initiating HSCT preparative regimen with the exception of Section [2.2.2.6](#) at NCI. Note, where these differ from institutional practice at University of Oklahoma or Children's National Medical Center, the SOPs at those institutions may be followed.

### 2.2.2.1 Complete history and physical examination.

### 2.2.2.2 Laboratory studies:

- CBC with differential, ABO blood type, PT/PTT
- Comprehensive chemistry
- Urinalysis
- Urine pregnancy test for women of childbearing potential
- Screening for Hemoglobinopathy at NCI only if CBC suggests anemia due to hemoglobinopathy
- Infectious disease work-up: antibody for Hepatitis A, B, C, HIV, T.Cruzi, HTLV-I/II, CMV, adenovirus, EBV, HSV, varicella, Toxoplasmosis, and syphilis (RPR) at NIH or as per institutional practice at Children's National Medical Center or University of Oklahoma.

### 2.2.2.3 Immunology studies: Lymphocyte phenotype panel (TBNK) at NCI only.

### 2.2.2.4 Electrocardiogram

### 2.2.2.5 Chest radiograph

### 2.2.2.6 Typing for HLA-A, -B, -C, and DR with PCR test of DNA mini-satellite regions for future determination of chimerism (may be done at anytime prior to HSCT).

### 2.2.2.7 Donor Health History Screen through Dowling Apheresis Center for those undergoing peripheral blood stem cell collection at Dowling Apheresis Center at NCI, or as per institutional guidelines at: Univ of Oklahoma, or Children's National Medical Center.

### 2.2.2.8 DTM venous assessment and health history screen through Dowling Apheresis Center for those undergoing PBSC collection at NCI or as per institutional practice.

### 2.2.2.9 For donors undergoing bone marrow harvest, pre-anesthesia evaluation at NCI or as per local institutional practice.

## **2.3 REGISTRATION PROCEDURES**

### **2.3.1 Protocol Entry Date**

Protocol “entry date” is considered to be the day that the informed consent form has been signed by the recipient.

### **2.3.2 Registration**

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (<http://intranet.cancer.gov/ccr/welcome.htm>) must be completed and sent via encrypted email to: NCI Central Registration Office [ncicentralregistration-l@mail.nih.gov](mailto:ncicentralregistration-l@mail.nih.gov). After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.3.2.1 Donors at NIH will be registered on this study prior to stem cell collection. Donors at Children’s National Medical Center and University of Oklahoma need to be identified and eligible but may follow local institutional practice.

2.3.2.2 Unrelated donors from NMDP Centers will be consented on an approved NMDP consent prior to eligibility evaluation. NIH UID numbers will be generated on unrelated donors while maintaining the anonymity required by the NMDP. The recipient may not sign consent before the matched unrelated donor has been identified and cleared by NMDP and the patient has been determined to be eligible. At other institutions, this will be done as per institutional practice.

### **2.3.3 University of Oklahoma Donors and Recipients**

2.3.3.1 These patients will sign consent after meeting eligibility criteria at the University of Oklahoma (Site PI: Dr. Holter), may receive therapy at the National Cancer Institute or the University of Oklahoma.

2.3.3.2 Registration will be a two part process as patients are screened on this protocol. A protocol registration form will be supplied by the CCR study coordinator and updates will be provided as needed. Subject eligibility and demographic information is required for registration. To initially register a subject, after the participant has signed consent, complete the top portion of the form and send to CCR study coordinator. Once eligibility is confirmed, after completion of screening studies, complete the remainder of the form which is the eligibility checklist, indicating that the patient is being registered for treatment and send to CCR study coordinator. In addition, source documents supporting the eligibility criteria must be sent to the CCR study coordinator. The CCR study coordinator will notify you either by e-mail or fax that the protocol registration form has been received which will include the unique patient/subject ID number. Questions about eligibility should be directed to the CCR study coordinator or PI. Questions related to registration should be directed to the CCR study coordinator.



Subjects that do not meet screening criteria should be removed from the study following the procedure in section **3.10.4**.

#### 2.3.4 Children's National Medical Center Donors and Recipients

2.3.4.1 Patients will sign consent after meeting eligibility criteria at Children's National Medical Center (Site PI: Dr. Williams), and will receive therapy at Children's National Medical Center.

2.3.4.2 Registration will be a two part process as patients are screened on this protocol. A protocol registration form will be supplied by the CCR study coordinator and updates will be provided as needed. Subject eligibility and demographic information is required for registration. To initially register a subject, after the participant has signed consent, complete the top portion of the form and send to CCR study coordinator. Once eligibility is confirmed, after completion of screening studies, complete the remainder of the form which is the eligibility checklist, indicating that the patient is being registered for treatment and send to CCR study coordinator. In addition, source documents supporting the eligibility criteria must be sent to the CCR study coordinator. The CCR study coordinator will notify you either by e-mail or fax that the protocol registration form has been received which will include the unique patient/subject ID number. Questions about eligibility should be directed to the CCR study coordinator or PI. Questions related to registration should be directed to the CCR study coordinator.

Subjects that do not meet screening criteria should be removed from the study following the procedure in section **3.10.4**.

## 2.4 RANDOMIZATION PROCEDURES

### 2.4.1 Female Recipients

2.4.1.1 All female recipients will receive Lupron

### 2.4.2 Male Recipients

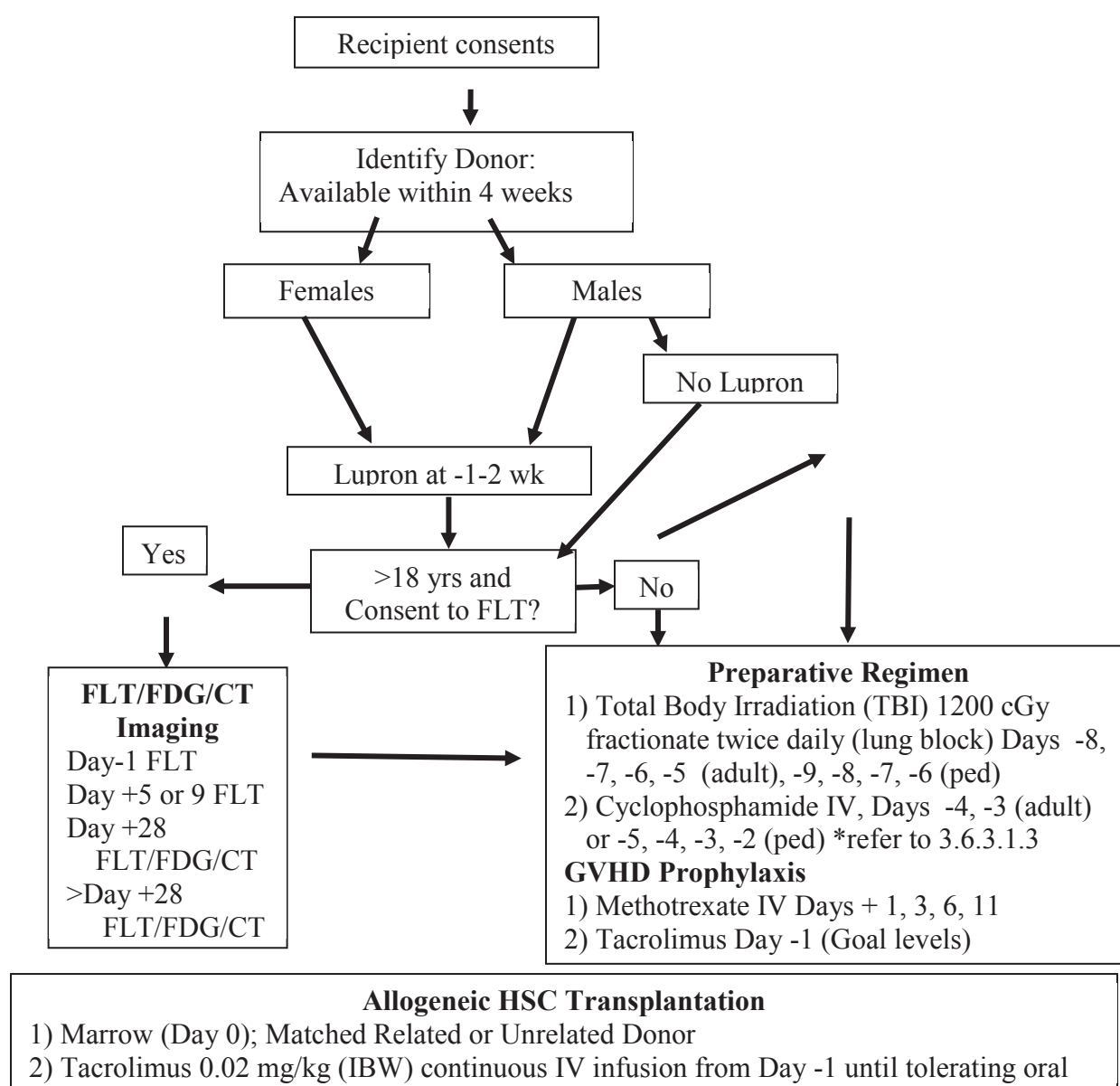
2.4.2.1 The CRO will provide the randomized treatment assignment to the PI based on random assignments determined by the study statistician for first BMT. For 2<sup>nd</sup> BMT, all patients will receive Lupron.

### 3 STUDY IMPLEMENTATION

#### 3.1 STUDY DESIGN

##### 3.1.1 NCI and University of Oklahoma for 1<sup>st</sup> BMT

(Note: FLT/FDG PET scans will not be performed at the University of Oklahoma)



Some of these patients are anticipated to be evaluated using FLT (to include only patients needed for the immunological primary endpoint, not increasing total patient numbers). 23 adult NCI patients in total will undergo FLT PET/CT imaging on day -1, at day +5 or day +9, at 4 weeks, and at a future point to include evidence of GVHD relapse, or immune recovery. An estimated 50 patients (including subset of the 23 patients undergoing serial scanning) will be imaged



approximately at 1 year for evaluation of thymus reconstitution. The total possible numbers will include no more than 118 patients to achieve the 64 evaluable adults for the immunological primary endpoint. However, as of amendment K, all NCI patients will undergo a single 1 year FLT for evaluation of thymus reconstitution.

For 2<sup>nd</sup> BMT, at NCI, all 16 patients will undergo FLT imaging at day -1, and FLT and FDG imaging on day 28, day 60 and at relapse and response to therapy (if this occurs).

### 3.1.2 Children's National Medical Center

Ten pediatric patients at CNMC will undergo FLT PET/CT imaging on Day -1, day +9, and day +28 (if possible). Initial images will be correlated with engraftment and other secondary endpoints. At Children's National Medical Center, the patients will not receive Lupron outside of the context of clinical care, and will receive myeloablative HSCT as per standard of care with FLT imaging for engraftment as the only primary endpoint.

## 3.2 DRUG ADMINISTRATION

### 3.2.1 Lupron

Lupron will be administered to all female patients and half of the male patients (randomized for first BMT) and to all patients for 2<sup>nd</sup> BMT, once optimally between day -13 and day -20 pre-HSCT but definitely prior to initiation of preparative regimen as a 4 month intramuscular injection for patients  $\geq 18$  years and as a 3 month injection (adult preparation) for patients  $< 18$  years. Subsequent injections may be given if clinically indicated to females. There will be no dose modifications. Females already on lupron therapy will receive the 4 month injection within 2 weeks prior to the next scheduled injection and prior to HSCT preparative regimen.

### 3.2.2 <sup>18</sup>F-FLT

All NCI patients will undergo PET imaging in the NCI Molecular Imaging Clinic (B3). Pediatric patients will undergo PET imaging in the Children's National Medical Center clinical imaging department. Patients at University of Oklahoma will not undergo PET imaging per protocol

A low dose transmission CT scan will be performed for the purpose of attenuation correction. <sup>18</sup>F FLT PET/CT will be performed per the described schedule to include 4 imaging sessions in the peri-transplant at NCI and a maximum of 3 at Children's National Medical Center. <sup>18</sup>F FLT PET/CT alone will be used to assess the marrow at a pre-HSCT baseline image and an image day +5 or +9 (to evaluate for early signs of engraftment). At both institutions, for first BMT, day +28 (+/- 5 days) image may be performed and at NIH only, a later time point (to be obtained when clinically indicated either with evidence of thymus recovery or GVHD), <sup>18</sup>F FLT and FDG imaging will be conducted within 48 hours. At NIH only, all newly accrued patients will undergo a <sup>18</sup>F FLT scan at 1 year post-HSCT with FDG. These will be used to distinguish dividing cells (<sup>18</sup>F FLT+) from cells high in glucose consumption (FDG+). A few patients in relapse who are consented to this protocol arm will undergo imaging analysis with <sup>18</sup>F FLT PET/CT alone for calculation of 'positive' control for leukemia relapse. For 2<sup>nd</sup> BMT, patients will undergo <sup>18</sup>F FLT imaging on day -1, day 28, and day 60 to predict relapse. Patients may also be imaged before and after therapy for relapse (to not exceed 5 scans total per patient).

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

The expected dose of [ $^{18}\text{F}$ ]FLT is 0.07 mCi/kg with a maximum of 3 mCi. Due to potential unpredictable delays, the total activity administered may be reduced at the discretion of the PI.

$^{18}\text{F}$  FLT will be provided by Cardinal Health or PETnet pharmacies. IND will be held by Dr. Karen Kurdziel, Molecular Imaging Program, CCR, NCI.

$^{18}\text{F}$  FLT and FDG uptake greater than surrounding background (T:B>1.2) will be considered positive. For hypermetabolic lesions, an estimated smoothed maximum SUV will be reported. Analysis of uptake will be performed using current practice guidelines within the Molecular Imaging Program, Children's National Medical Center and University of Oklahoma (on de-identified scans).

### **3.3 ON STUDY PROTOCOL EVALUATION PRE-TRANSPLANT WORK-UP**

See Sections [12.2](#) and [12.3](#)

#### **3.3.1 Within 4 weeks of Transplant Date**

- History and Physical Examination
- Laboratory studies must include the following:
  - Complete blood counts with differential.
  - Complete chemistry panel: sodium, potassium, chloride, CO<sub>2</sub>, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, ALT, AST, total and direct bilirubin.
  - Toxoplasma IGG, Varicella IGG, CMV IGG, HSV IGG.
  - Immunologic screening: Immunoglobulin levels (IgG with subclasses, IgA), CD4/CD8 total numbers and ratio at NCI only.
  - Flow cytometry of peripheral blood for T/B/NK and residual disease at NCI and Children's National Medical Center only
  - Chest and sinus CT
  - Pulmonary Function Tests for adult patients and oxygen saturation on room air for pediatric patients.
  - Echocardiogram or MUGA
  - Electrocardiogram
  - BM biopsy and aspirate with flow cytometry, and cytogenetics if previously positive
  - Lumbar puncture with flow cytometry for patients with ALL and AML
  - Testosterone and Estrogen levels, LH, FSH for all adult patients.

#### **3.3.2 FLT on Study Evaluations**

(For patients enrolled on 18F FLT arm, Section [12.4](#)):

- Imaging Study time points, 1<sup>st</sup> BMT:
  - Day -1: 18F FLT + low dose CT
  - Day +5 or +9: 18F FLT + low dose CT
  - Day +28, 29: 18F FLT + low dose CT, 18F FDG(not required at Children's National Medical Center) + CT
  - Day + (GVHD vs. thymus recovery): 18F FLT + low dose CT, 18F FDG + CT at NCI only
- Imaging Study time points 2<sup>nd</sup> BMT:
  - Day -1: 18F FLT + low dose CT
  - Day +28/29: 18F FLT + FDG (not required for Children's National Medical Center site) + low dose CT
  - Day +60/61: 18F FLT + FDG (not required for Children's National Medical Center site) + low dose CT
  - Day + of relapse and initial response to immunotherapy: 18F FLT + FDG + low dose CT at NCI only
- Laboratory studies for FLT within 24 hours prior:
  - Creatinine < 2, ALT and AST within 5 x ULN
  - TK1 serum measurement
- 18F FLT imaging protocol:
  - At NCI immediately following the IV infusion of 18F FLT, a dynamic PET emission will be performed for 45 minutes followed by a whole body static image. An additional PET emission imaging acquisition will be performed 120 minutes (+/- 15 minutes) post infusion. A corresponding low dose transmission CT will be acquired immediately before each emission scan. At Children's National Medical Center, the dynamic image will be omitted.

### 3.4 BIOLOGIC STUDIES

The total aliquot of phlebotomy will not exceed 3 mL/kg per draw and 7 ml/kg in a 4 week period for research studies. Should the research requests exceed these restrictions, research studies will be done in the order of Sections [12.5](#), [12.6](#) and [12.7](#).

#### 3.4.1 Immune Reconstitution

Studies to elucidate difference in immune reconstitution between Lupron treated and untreated groups to include multiparameter flow cytometry analysis of relevant cell populations (B and T) and serum analysis of relevant cytokines. If available, these will be compared with donor lymphocyte characteristics (whereby 5 million total donor nucleated cells of the donor product will be reserved for biologic studies and go to the clinical core of ETIB (Bldg 10, Room 12C-216, (301- 402-3627)). At Univ of Oklahoma, these may be stored within CETI lab or Holter lab respectively, or sent directly to the Pre-Clinical Core at NCI. At Children's National Medical

Center, these may be stored within CETI lab or Bollar lab respectively, or sent directly to the Pre-Clinical Core at NCI.

### 3.4.2 Immunologic Studies

Impaired lymphocyte reconstitution is believed to contribute to the morbidity and mortality of allogeneic stem cell transplantation as evidenced by poor clearance of infections, and allo-immunity (GVHD).<sup>[57]</sup> In adult HSCT recipients, T and B cell functions can be compromised indefinitely due to lack of thymus function and poor B cell education. This study will use immunologic studies to determine if Lupron may enhance thymus reconstitution and B cell development. Exploratory studies will include immunologic evaluations of HSCT complications to include: relapse, GVHD, infections, and the influence of thymus reconstitution on these complications. For these studies, prospective collection of infections to include: HHV6, adenovirus, EBV, CMV.

### 3.4.3 Objectives/Specific Aims

- 3.4.3.1 Determine the effect of Lupron on engraftment and the recovery of T and B cell subsets following allogeneic HSCT by enumeration of cellular subsets in patients with and without Lupron. Should thymus recovery be evident in subsets, secondary analysis of thymus function using T cell receptor excision circle analysis on peripheral T cells and using spectratype techniques.
- 3.4.3.2 Determine whether FLT uptake demonstrates engraftment, leukemia relapse or residual disease, and/or GVHD, and/or thymus recovery. FLT images will be compared as follows: pre-transplant image will be used for assessment of MRD (to be correlated with disease recurrence and histology at day 28), post infusion image will be used to assess homing and cellular growth at day +5 or +9 image to correlate to time to engraftment, and correlate with marrow stability at histological assessment day +28, day +28 image to be quantitatively evaluated to correlate with blast % and marrow repopulation with histology, and the final image to be performed at a time of new-onset GVHD, potential relapse, or thymus recovery. Exploratory studies to include the biology of HSCT.
- 3.4.3.3 For arm 2, exploratory analyses will include: whether FLT uptake can predict relapse or response to immunotherapy and whether there is an improvement in this small number of patients in relapse rates (from 80% as designated in historical controls). Immune studies will be undertaken to explore whether there is alterations in lymphocyte subsets similar to patients who remain in remission on the primary arm of the protocol.

### 3.4.4 Methodology

The following studies will be performed on peripheral blood (if available) samples. Blood samples (20 cc in red/green CPT heparin and 16 cc in EDTA tubes, age adjusted for weight in pediatric patients) will be drawn for evaluations. Time points are listed in section 3.8. Complete blood counts and TBNK will be collected on the same day. Samples should be delivered to the lab of Dr. Fran Hakim in Building 10, Room 3E-3288 (301-402-3627) at NCI and may be processed and frozen and shipped in batch from Children's National Medical Center and University of Oklahoma.

- 3.4.4.1 Peripheral blood: quantity (20mL). Flow cytometry will be performed on peripheral blood samples. Commercially available antibodies will be used to characterize T cell, B cell, dendritic cell and monocyte recovery after HSCT. Samples will be frozen and thawed in batches.
  - 3.4.4.1.1 Research blood sample aliquot size will be minimized for patients < 18 years of age and the total amount restricted to a maximum of 3 ml/kg per draw and 7 ml/kg per 6-week period (maximum 450 ml). In the event that blood draws are limited due to patient size, research studies will be performed in order of priority as listed in Section [12.7](#). Small volume apheresis collections will not be included in this calculation since such is performed isovolumetrically with minimal red cell loss.
- 3.4.4.2 Plasma (>20 mL). Plasma (EDTA and heparin) will be spun in refrigerated centrifuge and frozen immediately and subsequently utilized for cytokine studies using immunofluorescent technique.
- 3.4.4.3 Tissue, urine, and other fluid specimens (optional): Any pathology or biopsy specimen or fluid that is obtained for clinical indications from the recipient and has remaining (or extra specimen) following the clinically indicated test may be stored and used for immunological characterization. This includes any biopsies of bones obtained because of new onset pain, uptake of nuclear imaging scanning concerning for relapse or infection from the recipient. Patients will have the opportunity to opt out in writing to determine if extra fluids and tissues may be used for these studies.

### **3.5 COLLABORATIVE RESEARCH STUDIES**

Under Amendment P, coded serum samples and human peripheral blood will be sent to the Children's National Medical Center to evaluate comparisons of T and B cells between patients who received lupron and those who did not in terms of relapse, GVHD, and infections

Rationale: Dr. Williams is a recognized expert in multicolor flow cytometry for the analysis of human peripheral blood from post-allogeneic-transplant patients.

Specific Aims: To determine the effect of Lupron on engraftment and the recovery of T and B cell subsets following allogeneic HSCT by enumeration of cellular subsets in patients with and without Lupron.

#### **Design/Procedures:**

The samples will be sent to laboratories at the Children's National Medical Center to perform multicolor flow cytometry as per section [3.4.4.1](#) as well as cytokine studies as per section [3.4.4.2](#) after an MTA is executed between the NCI and the Children's National Medical Center. All excess samples will be destroyed at the conclusion of the planned studies. The serum and human peripheral blood samples will be sent to the following address:

Kirsten Williams MD  
Center for Cancer and Immunology Research

Program for Cell Enhancement and Technologies for Immunotherapy  
Children's National Medical Center  
5th Flr, Suite 5220  
111 Michigan Ave NW  
Washington, DC 20010

Coded serum samples will be sent to Dr. Williams from patients participating in the 11-C-0136 clinical protocol led by primary investigator, Dr. Christopher Kanakry at NCI. Cryopreserved heparinized serum from up to 25 patients will be transferred through this collaboration.

Laboratory results will be sent back to Dr. Kanakry for data compilation and analysis. Dr. Williams will not have access to patient identifiers or patient information.

Only the subject's unique identifier will be used and information about the enrolling site will be removed. Authorized investigators at NCI and Dr. Williams will maintain codes linking the laboratory specimens received to clinical information; however, Dr. Williams will not have access to any other patient identifiers or patient information. Sample identifiers are not derived from actual identifiers and Dr. Williams's research team will not have access to the re-identification key.

### **3.6 DONOR COLLECTION**

#### **3.6.1 Matched Unrelated Donors**

Matched unrelated donors will be collected as per NMDP policies and procedures. The concentration of CD34+ cells will be determined by flow cytometry. The product may be infused fresh or stored frozen prior to infusion. Every attempt will be made to obtain a marrow product for first BMT. Should PBSC be the only alternative, these patients will be analyzed separately and replaced. The target dose is  $\geq 350$  million total nucleated cells per kilogram. Of this product, 5 million total donor nucleated cells will be reserved for biologic studies and go to the clinical core of ETIB (Bldg 10, Room 12C-216, 301 402 3627) at NCI. Cell selection will not be performed on the HSC grafts. If samples are obtained at Children's National Medical Center and University of Oklahoma, these may be processed, frozen, and shipped in batch, or fresh to Dr. Hakim (above). MUD policies at Univ of Oklahoma and Children's National Medical Center will be followed as per SOPs of institutional practice. Please refer to Section 3.4 for research study details. For 2<sup>nd</sup> BMT, PBSC will be preferred over marrow.

#### **3.6.2 Matched Related Donors**

Matched related donors will undergo marrow harvest with general anesthesia. Subjects will undergo anesthesia consultation, and meet criteria for eligibility/enrollment. CD34+ fraction will be determined. Subjects will also undergo the Donor Health History Screen to determine donor eligibility using standard DTM criteria in the Dowling Apheresis Clinic by skilled staff in the Blood Services Section for adult patients and age-appropriate questioning when indicated for pediatric subjects at NCI, the Oklahoma Blood Institute, and will be evaluated and exam performed by a member of the Oklahoma Transplant team for both PBSC collection and marrow donation, and by BMT staff at Children's National Medical Center as per institutional protocol. Subjects will undergo follow-up history and physical examination within 1 week of donation, at



NCI or as per local institutional guidelines. Donor recipient weight discrepancy with smaller donors placing the recipient at risk for non-engraftment will necessitate PBSC collection. Calculations will be performed by weight; for obese patients, an average between ideal and actual body weight. PBSC collection will be done as per standard of care and local institutional practice; at NCI, with donors receiving 10 ug/kg of GCSF for 5 days, with first collection through large bore venous catheter on the 5<sup>th</sup> day and potential second collection on day 6 (for insufficient sample) with a 6<sup>th</sup> dose of GCSF. Should PBSC be the only alternative, these patients will be analyzed separately and may be replaced. The target dose is  $\geq 350$  million total nucleated cells per kilogram; however  $> 100$  million total nucleated cells per kilogram will be sufficient for marrow collections and between 3-4 million CD34/kg for PBSC products. Of this product, 5 million total donor nucleated cells will be reserved for biologic studies and go to the clinical core of ETIB (Bldg 10, Room 12C-216, 301 402 3627) at NCI, and may be processed and stored and shipped frozen from outside institutions. Cell selection will not be performed on the HSC grafts. Note that TTV testing sample will be drawn as per institutional practice (e.g. on the day of marrow collection at NCI). Harvested cells will be processed in DTM at NCI, within the Stem Cell laboratory at Children's National Medical Center and in the Oklahoma Stem cell processing center at Univ. of Oklahoma. For all frozen samples and all fresh samples with ABO mismatch, the product will be depleted of red cells until less than 0.5 cc/kg or 50 cc total remain (whichever is smallest) when possible. For fresh harvest products, plasma pheresis may also be required if indicated by ABO mismatch. DTM at NCI, the Stem Cell laboratory at Children's National Medical Center, and the Oklahoma Stem Cell processing unit at Univ. of OK will notify the Adjunct PI and/or NIH PI and /or site PI and research RN of any problems in regard to cell number or red cell volume prior to freezing product. Note: for 2<sup>nd</sup> BMT, PBSC products will be preferred.

### **3.7 PREPARATIVE REGIMEN FOR HSCT AND GVHD PROPHYLAXIS**

(Refer to Sections [12.5](#) and [12.6](#))

#### **3.7.1 Central Access**

An appropriate form of central access will be obtained prior to HSCT procedure. Tunneled triple lumen catheter is preferred in thorax at NCI. Other institutions will follow institutional standards.

#### **3.7.2 Remission Status**

Patients undergoing first HSCT must be in remission prior to HSCT; this may include patients without evidence of disease in aplasia.

#### **3.7.3 Conditioning Regimen**

##### **3.7.3.1 Adults (>22 years and on ETIB service at NCI, on adult BMT at Univ of Oklahoma):**

##### **3.7.3.1.1 TBI will be delivered to a total midplane dose of 12Gy and median lung dose of 6Gy. Radiation will be fractionated twice daily over 4 days (days -8, -7, -6, -5). Opposed lateral fields with lung compensation will be treated to 1.5 Gy for each fraction to a total cumulative dose of 12Gy. Mediastinal fields will be treated AP-PA concurrently with the opposed lateral fields at a dose of 75cGy twice daily to bring the mediastinal dose to 12Gy with a median lung dose of 6 Gy. Fractions will be delivered with at**

least a 6 hour interfraction interval. Gonadal shielding will not be used. Head and neck compensation and other technical modifications may be made at the discretion of the treating radiation oncologist. For patients with CNS positive disease at any time after diagnosis, **CNS boost may be delivered unless contraindicated by PI or AI.** The CNS boost will be delivered as a 6 Gy boost in once daily 2 Gy fractions. The boost will be delivered prior to TBI. Patients with sites identified by nuclear imaging or other clinically accepted diagnostic tests may receive a boost to these areas as clinically indicated at any time point pre- or post transplantation.

3.7.3.1.2 Cyclophosphamide: cyclophosphamide 60 mg/kg IV, Days -4, -3 with forced diureses with IV hydration to maintain urine output at 2-3ml/kg/hr and mesna 60mg/kg/dose IV at continuous intravenous infusion equal to the dose of cyclophosphamide. For patients with BMI > 35, the cyclophosphamide and mesna dosing will be based on a modified weight half way between the ideal and actual body weights.

3.7.3.1.3 **Modifications:** For adult patients with MDS who are aplastic after induction therapy, a modified regimen may be used as the preparative regimen including: Fludarabine 30 mg/m<sup>2</sup> for 3 days (day -4, -3, -2) and TBI 200cGy day -1.

For patients who have already received TBI, or exceeded the radiation maximum tolerated dose to preclude TBI for first or second BMT, preferred second choice is busulfan (with goal steady state of 800-1000) with fludarabine or cyclophosphamide at myeloablative dosing or non-myeloablative dosing if recommended for 2<sup>nd</sup> BMT.

3.7.3.2 Pediatric ( $\leq 22$  years and on POB service at NCI or at Children's National Medical Center):

3.7.3.2.1 At NCI: TBI will be delivered to a total midplane dose of 12Gy and median lung dose of 6Gy. Radiation will be fractionated twice daily over 4 days (days -9, -8, -7, -6). Opposed lateral fields with lung compensation will be treated to 1.5 Gy for each fraction to a total cumulative dose of 12Gy. Mediastinal fields will be treated AP-PA concurrently with the opposed lateral fields at a dose of 75cGy twice daily to bring the mediastinal dose to 12Gy with a median lung dose of 6Gy. Fractions will be delivered with at least a 6 hour interfraction interval. Gonadal shielding will not be used. Head and neck compensation and other technical modifications may be made at the discretion of the treating radiation oncologist. For patients with CNS positive disease at any time after diagnosis without definitive prior cranial radiation, **CNS boost may be delivered unless contraindicated by PI or AI.** Adjustments to the boost dose in pediatric patients may be made if contraindicated at the discretion of the PI or AI. The CNS boost will be delivered as a 6 Gy boost in once daily 2 Gy fractions. The boost will be delivered prior to TBI. Patients with sites identified by nuclear imaging may receive a boost to these areas as clinically indicated at any time point pre- or post transplantation.

3.7.3.2.2 At NCI: Cyclophosphamide: cyclophosphamide 50 mg/kg IV, Days -5, -4, -3, -2 with forced diureses with IV hydration to maintain urine output at 2-3ml/kg/hr and mesna



as 24 hour continuous intravenous infusion equal to the dose of cyclophosphamide. For patients with BMI > 35, the cyclophosphamide and mesna dosing will be based on a modified weight half way between the ideal and actual body weights.

3.6.3.2.3 For patients who have already received TBI, or exceeded the radiation maximum tolerated dose to preclude TBI for first or second BMT, preferred second choice is busulfan (with goal steady state of 800-1000) with fludarabine or cyclophosphamide at myeloablative dosing or non-myeloablative dosing if 2<sup>nd</sup> BMT.

3.6.3.2.4 At Children's National Medical Center, myeloablative transplantation for FLT imaging may be according to current standard practice including the regimens of: TBI

### 3.7.4 GVHD Prophylaxis

GVHD prophylaxis at NCI and Univ of Oklahoma will include: methotrexate 10 mg/m<sup>2</sup> IV on day +1, and 5 mg/m<sup>2</sup> IV Days + 3, 6, 11 and tacrolimus starting Day -1 at dose of 0.02 mg/kg/day continuous infusion (with target level between 5 and 10 ng/ml though up to 15 acceptable). Note, methotrexate dose should be discussed with pharmacy and adjusted for renal or liver dysfunction. Should either agent not be tolerated (for example, posterior reversible encephalopathy from tacrolimus) or other risks put patients at added risk, these may be substituted with standard alternatives (e.g. cyclosporine, sirolimus, cellcept). When the patient is tolerating orals, tacrolimus may be converted to oral administration. Taper of tacrolimus may be initiated on day +100 if there is no evidence of GVHD. Patients should be evaluated weekly after the initiation of tacrolimus taper and tacrolimus taper held or increased for evidence of GVHD (to include diarrhea, mouth sores, unexplained elevation of liver enzymes). If taper is not able to be initiated at day +100, by day +180, a new evaluation should occur to attempt taper. Patients are at high risk of relapse and every attempt should be made in this protocol to permit graft-versus-leukemia effects. For patients after 2<sup>nd</sup> BMT, taper may be initiated as early as day 45 and the plan will be to taper as rapidly as possible.

### 3.7.5 Growth Factors (GCSF)

GCSF will not be administered unless clinically indicated such as life threatening infection and neutropenia or significantly delayed engraftment (greater than day 18) during the initial transplant phase (less than day 30). A PI or AI must be involved in this clinical decision. While there are data that GCSF accelerates neutrophil engraftment by several days without effects on GVHD and relapse in two randomized, placebo controlled studies [58, 59], there are also data from larger historical cohorts that suggest higher rates of GVHD and relapse without significant differences in neutrophil recovery times. [17, 60] In addition, GCSF has the potential to induce leukemic expansion in AML patients [60] and to alter the imaging evaluation by FLT studies. Notably, GCSF is not standard practice for pediatric patients receiving marrow grafts which are the primary source for pediatric transplantations currently. Given the lack of clear benefit from these studies and the likelihood that patients will recover neutrophils prior to life-threatening infections with matched marrow products, GCSF will not be part of the planned BMT support but rather an option for the few patients who may benefit from its administration (due to delayed engraftment or infections). GCSF may be used after engraftment in the setting of secondary

neutropenia (often associated with medications administered post-transplant (e.g. antimicrobials).

### 3.8 TRANSPLANT PROCEDURE FOR 1<sup>ST</sup> AND 2<sup>ND</sup> BMT

#### 3.8.1 Day 0

On day 0, the patient will receive the donor product from the selected donor intravenously per DTM standard operating procedures or local institutional guidelines.

#### 3.8.2 Transplant Outcome Determinations

- **Neutrophil Recovery:** Designated by the first of 3 consecutive days with an ANC above 500/mm<sup>3</sup>.
- **Platelet Recovery:** Designated by the first of 7 days where the platelet count remains above 20,000/mm<sup>3</sup> without transfusion support.
- **Sustained Donor Engraftment:** Neutrophil recovery associated with complete donor chimerism at day 100. Any patient who dies before day 28 will not be evaluated for engraftment but will be evaluable by FLT.
- **Primary Graft Failure:** Failure to achieve sustained donor engraftment
- **Secondary Graft Failure:** Documented sustained donor engraftment as defined above followed by: 1) severe neutropenia (ANC < 500/mm<sup>3</sup>) and bone marrow biopsy revealing a cellularity of less than 25% or 2) absence of donor cells in the marrow or blood as demonstrated by a chimerism assay without subsequent improvement occurring either spontaneously or after growth factor treatment. Improvement is defined as ANC > 500/mm<sup>3</sup> consistently. Severe neutropenia with marrow cellularity > 25% is not secondary graft failure.
- **Aplasia:** Less than 5% marrow cellularity as measured on bone marrow biopsy.

### 3.9 POST-TRANSPLANT MONITORING (1<sup>ST</sup> AND 2<sup>ND</sup> BMT)

(See Sections 12.5 and 12.6)

At NCI, patients will be admitted during the preparative regimen and throughout the peri-transplant period until engraftment has occurred and the patient is deemed stable for discharge. After discharge, the patient will be monitored as clinically indicated until day +100.

#### 3.9.1 Day 0 to day +100

- History and physical evaluation
- CMV, Adenovirus, EBV PCR
- CBC with differential
- Acute, Hepatic and Mineral Panels, CK, Uric acid and LDH
- Lipid panel (**days +28, +60, and +100 (+/- 10 days)**)
- Tacrolimus level as long as on tacrolimus
- Monitoring for aGVHD (documented day **+28, +60, +100**) (see Section 12.10)

- Monitoring for HHV6 in peripheral blood (all patients) and CSF (for those with leukemia diagnosis) at day +28, +60, +100 +/- 10 days for patients **at NCI only**
- Research blood (day **+5, +7, +14, +21, +28, +60, +100**)
  - +/- Allowances for the drawing of research blood is +/-1 day for day +5 and +7, +/- 2 days for day +14, +/- 3 days for day +28, +/- 7 days for day +60, +/- 14 days for day +100, and +/- 30 days for later time points.

### 3.9.2 Specific evaluation time points (1<sup>st</sup> and 2<sup>nd</sup> BMT)

Patients will be followed as clinically indicated. These evaluations should occur within 10 days of anticipated date for time points less than day 100 and within 1 month for time points after day 100.

- History and physical evaluation on day **+180, +270, +365**
- Bone marrow aspirate with studies appropriate to staging of malignant disease, a LP or other biopsy may be required depending upon the diagnosis (to include LP for all AML and ALL) with chimerism on day **+28, +60, +100, +365**
- Bone marrow biopsy on day **+28, +60, +100, +365**
- Lymphocyte phenotyping (T,B,NK) on day **+28, +60, +100, +180, +270, +365** (to be performed at NCI including those from outside institutions)
- Pulmonary function tests on day **+ 100, +180, +270, +365**
- Chimerism of peripheral blood on day **+28, +100, +180, +270, +365 for all adult patients**
- Immunoglobulins (IgG, IgM, IgA) on day **+28, +100, +180, +270, +365**
- Acute, Hepatic and Mineral Panels, CK , Uric acid and LDH and lipid on day **+28, +100, +180, +270, +365**
- cGVHD evaluations on day **+100, +180, +270, +365** (see Sections [12.11](#), [12.12](#) and [12.13](#))
- Research blood on day **+180, +270, +365**, and when clinically significant events such as cGVHD, laboratory suspicion of relapse, or thymus recovery occur.
- Chest CT **+100, +365**

### 3.9.3 Long term follow-up guidelines (1<sup>st</sup> and 2<sup>nd</sup> BMT)

Ref: recommendations [[61](#)]

These guidelines are for all NIH patients. All patients may obtain these studies within 1 month of desired date and these may be done in other institutions than NIH with documentation. Please note that these should be performed yearly for 5 years after transplantation either as part of this protocol or in another setting for abnormal results. Pediatric follow-up for CNMC patients will be done as per Children's National Medical Center guidelines.

- Dental evaluations day **+180, +365**
- Ferritin and iron studies on day **+180, +270, +365**

- Thyroid studies on day +180, +270, +365
- FSH, LH on day +180, +270, +365
- Ophthalmological evaluation on day +180, +365
- DEXA scan on day +365
- Echocardiogram on day +365
- **Pulmonary Function Test yearly for 5 years**
- GYN examination (female patients) day +365
- Urinalysis/protein screening day +180, +365

### 3.9.4 FLT on study evaluations

(For patients enrolled on FLT arm at NCI or Children's National Medical Center)

- Imaging Study time points 1<sup>st</sup> BMT:
  - Day -1: <sup>18</sup>F FLT + low dose CT
  - Day +5 or +9: <sup>18</sup>F FLT + low dose CT
  - Day +28/29: <sup>18</sup>F FLT + FDG (not required for Children's National Medical Center site) + low dose CT
  - Day + (GVHD vs. thymus recovery): <sup>18</sup>F FLT + FDG + low dose CT at NCI only
- Imaging Study time points 2<sup>nd</sup> BMT:
  - Day -1: <sup>18</sup>F FLT + low dose CT
  - Day +28/29: <sup>18</sup>F FLT + FDG (not required for Children's National Medical Center site) + low dose CT
  - Day +60/61: <sup>18</sup>F FLT + FDG (not required for Children's National Medical Center site) + low dose CT
  - Day + of relapse and initial response to immunotherapy: <sup>18</sup>F FLT + FDG + low dose CT at NCI only
- Laboratory studies for FLT within 24 hours prior :
  - Creatinine < 2, ALT and AST within 5 x ULN
  - TK1 serum measurement
- <sup>18</sup>F FLT imaging protocol:
  - At NCI, Immediately following the IV infusion of <sup>18</sup>F FLT, a dynamic PET emission imaging will be performed for 60 minutes, immediately followed by a whole body static image. An additional PET emission imaging acquisition will be performed 120 minutes (+/- 15 minutes) post infusion. A corresponding transmission CT will be acquired immediately before each emission scan. Children's National Medical Center will omit the dynamic protocol.

## 3.10 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

### 3.10.1 Criteria for Removal from Protocol Therapy

- Completion of 1 year protocol therapy
- Participant requests to be withdrawn from active therapy
- The option to treat the patient after protocol therapy with alternative therapies.
- Investigator discretion

Please note: The AEs as outlined in the treatment protocol will not be collected from that point forward.

### 3.10.2 Off-Study Criteria

- Failure to meet pre-transplant eligibility criteria as defined in section **3.3.1** and **3.7.2**.
- Patients who do not have a suitable donor or patients for whom the collection product is deemed insufficient without opportunity for further collection of the donor (via PBSC). Patients may proceed on standard of care if this is deemed to be the best medical management by the PI or AI.
- The donor or recipient refuses to continue therapy
- Patients for whom a suitable donor cannot be found
- Donor subjects who become decisionally impaired
- Lost to follow-up
- PI decision to end this study
- Death
- Completed post-transplant follow up period (5 years)

In all cases, the reason(s) for withdrawal will be documented.

In addition, a patient may at anytime be removed from protocol at the principal investigator's discretion, if the P.I. deems the subject to be at unacceptable risk to remain on study. Reasons for this action may include (but are not limited to) disease progression with declining organ function/performance status before transplantation; inadequate family/caregiver support; noncompliance.

Note: Minors should remain on study until they reach the age of 18 and have an opportunity to be consented for the future use of their data and specimens.

### 3.10.3 Off Protocol Therapy and Off Study Procedure at NCI

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-protocol therapy and when a subject is taken off-study. A Participant Status Update Form from the web site (<http://camp.nci.nih.gov/ccr/welcome.htm>) main page must be completed and sent via encrypted email to: NCI Central Registration Office<[ncicentralregistration-l@mail.nih.gov](mailto:ncicentralregistration-l@mail.nih.gov).

### 3.10.4 Participating Site Off-Study Notification

The Participant Status Update Form will be supplied by the CCR study coordinator. Send the completed form to the CCR study coordinator.

## 4 SUPPORTIVE CARE

### 4.1 INFECTION PROPHYLAXIS

For a full description of infection prophylaxis for NCI patients please refer to the NIH BMT Consortium Supportive Care Guidelines at <http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml>) which are recommended. Infection prophylaxis for pediatric patients at NCI should follow the NIH BMT Consortium Supportive Care Guidelines found at <http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml> or as per local institutional practice.

Below is a table summarizing adult recommendations at NCI. Please note that the numbers correspond to the order in which the agents should be attempted (i.e. first choice for PJP is trimethoprim/sulfamethoxazole and the second choice is atovaquone). Whenever possible, these should be followed at University of Oklahoma. Children's National Medical Center pediatric patients should follow Children's National Medical Center guidelines (SOP). Also, please note that these should be followed for patients receiving chemotherapy on this protocol as well.

Table 1

Organism	Prophylaxis Recommendations	Timing
Pneumocystis jiroveci pneumonia	1) Trimethoprim/sulfamethoxazole DS (or pediatric dose equivalent) once a day three times weekly 2) Atovaquone 1500 mg daily 3) Inhaled Pentamidine monthly	Start after immune reconstitution or by day 28. Stop > 6 months after immunosuppression withdrawal without evidence of GVHD and greater than 1 year after HSCT.
Fungus	1) Caspofungin 2) Voriconazole or Posaconazole (Check levels and target dose to Vori > 2 for prophylaxis, >4 for treatment; posa > 1000) 3) Liposomal amphotericin B	Start caspofungin with preparative regimen for mold prophylaxis and continued until neutrophil recovery and not on prednisone equivalent exceeding 0.8mg/kg/qod. Plan to switch to or add azole for evidence of invasive mold. Note: azoles will need to modify tacrolimus dosing. History of presumed or proven invasive fungal infection necessitates continuous antifungal coverage throughout HSCT until off immunosuppression unless there is a significant complication of therapy.



Organism	Prophylaxis Recommendations	Timing
Virus	1) Acyclovir 800 mg po BID or 250mg/m <sup>2</sup> IV q12.	Positive HSVI/II serology, history of Herpes Simplex or varicella infection, or CMV infection. Starting on day -4.
Bacteria	1) Cefazidime 2 gm IV q 8 hrs 2) Levofloxacin 500 mg PO or IV	Start at neutropenia, discontinue after resolution of neutropenia. Note: patients should remain on PCN (encapsulated organism prophylaxis) until off immunosuppression > 6 months and without ongoing or cGVHD.

This study will also monitor for viral infections to include adenovirus, EBV, CMV, and HHV6.

If the patient develops chronic GVHD, he/she will receive penicillin V for prophylaxis against bacterial infections. He/she will undergo vaccination against *S. pneumoniae* and *H. influenzae*, beginning 12 months after transplantation as per the NIH BMT Consortium Supportive Care Guidelines.

Administration of live vaccines will be avoided during the first 2 years after transplantation or in patients with ongoing chronic GVHD or immunosuppression. Immunizations with inactive vaccines will be administered starting 6 months after withdrawal of immunosuppression or one year whichever comes first with the exception of influenza vaccine and prevnar. Response to vaccines is an exploratory endpoint on this trial. Vaccine response is one of the best markers of T and B cell function (requiring CD4+ T cells to convert B cells to IgG).

#### 4.1.1 Infectious Disease Surveillance:

Adenovirus PCR will be sent weekly during engraftment. For patients who have Toxoplasmosis titer positive (at any point prior to HSCT), toxoplasmosis will be monitored weekly during engraftment at NCI only. HHV6 will be monitored in blood and CSF at day +28, +60, +100 +/- 10 days (for those undergoing CSF evaluation at these time points at NCI only).

## 4.2 MANAGEMENT OF ENGRAFTMENT SYNDROME

Engraftment syndrome is characterized by noninfectious fever, rash, and vascular leak causing non-cardiogenic pulmonary edema, weight gain, and renal. Diagnostic criteria and a treatment schema for engraftment syndrome are included in Section [12.9](#).

## 4.3 TREATMENT OF GRAFT-VERSUS-HOST DISEASE

In patients in whom GVHD is suspected, standard clinical criteria and biopsy findings (when clinically indicated) will be used to establish the diagnosis. Acute GVHD will be assessed according to 1994 Consensus Conference on Acute GVHD Grading criteria [62]. Chronic GVHD will be assessed according to 2005 Chronic GVHD Consensus Project [62]. See Section [12.12](#) for details concerning the assessment of acute and chronic GVHD.



Patients with clinical Stage 1 or 2 (Grade I) GVHD of the skin without any other organ involvement will be treated with a topical corticosteroid cream.

In general, patients with  $\geq$  Grade II acute GVHD will be treated with high-dose, systemic corticosteroids.

Patients who fail to respond to corticosteroids within 3 days will be considered for second-line immunosuppressive therapy. Given that the patients in this protocol are young adults with the potential for rapid response to immunosuppressive agents, every effort will be made for rapid taper of high dose steroids and rescue with other, less immunosuppressive agents.

As standard treatment of steroid-refractory acute GVHD and of chronic GVHD is often unsuccessful, treatment of either can include standard systemic or local therapies. This can specifically include autologous serum eye drops when recommended by ophthalmology for ocular GVHD per NIH Consensus Guidelines.

#### 4.4 MENSES SUPPRESSION AND CONTRACEPTION

For a full description of menses suppression and contraception guidelines for NCI please refer to the NIH BMT Consortium Supportive Care Guidelines at:

<http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml>

Pre-menopausal women who have not undergone hysterectomy will receive Lupron within 2 weeks of preparative regimen. Adult women will receive the 4 month (30 mg) preparation and females < 18 years old will receive the 3 month (11.25 mg) preparation. Subsequent therapy will continue until platelet recovery after transplantation ( $> 50,000/\mu\text{l}$  without transfusion) and may include repeat Lupron dosing or Lo-Ovral (300 $\mu\text{g}$  norgestrol and 30  $\mu\text{g}$  ethinyl estradiol) 1 tablet daily without placebo tablets. If Lo-Ovral is started when the patient is bleeding and bleeding persists for more than 2-3 days, increase the dose to 1 tablet twice daily. If bleeding persists for more than an additional 2-3 days (total 5 to 6 days after starting hormones), consult the NIH Gynecology Consult Service. However, Lo-Ovral will be stopped as soon as possible and patients who receive it may be analyzed separately from the lupron-treated female cohort. Female transplant recipients will be advised to use an effective form of contraception for at least 1 year after transplantation, and to have their male partners use condoms.

Male transplant recipients will be advised to use contraception, preferably condoms, for 1 year after transplantation.

#### 4.5 BLOOD PRODUCT SUPPORT

Patient's blood counts will be monitored daily during the transplant hospitalization. Patients will receive packed red blood cells and platelets as needed to maintain **Hb > 8.0 gm/dl** at NCI and CNMC and **Hb > 7.0 gm/dl** at Univ. of OK as per institutional practice, and **plts > 10,000/mm<sup>3</sup>** (or higher, if clinically indicated) unless the **patient is not group 0 blood type and the donor is, then Hb > 9.4 until after day 15 at NCI and per institutional practice**. All blood products, with the exception of the stem cell product and Donor Cell Infusion (DCI), will be irradiated and leukoreduced as per DTM protocol at NIH, and per the Blood Bank at Children's National Medical Center or the University of Oklahoma. The patient, who is seronegative for CMV and whose donor is seronegative, should receive CMV-negative blood products whenever possible.

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

Notably, all future transplant recipients should receive transfusion only of irradiated blood and cellular blood products. Transfusion of irradiated blood and cellular blood products will continue to at least one year after transplantation. Patients receiving immunosuppressive medication will continue to have all blood and cellular blood products irradiated until discontinuation of immunosuppressive treatment.

Patients sensitized to HLA or platelet specific antigens should receive HLA matched apheresis platelet collections.

#### **4.6 NUTRITIONAL SUPPORT**

If mucositis or GVHD prevent adequate PO intake, nasogastric tube feeds or parenteral hyperalimentation will be instituted and discontinued with input from the Pharmacy and Nutrition Departments at NCI. Oral intake will resume when clinically appropriate under the supervision of the dietary service of the Clinical Center. At Children's National Medical Center and University of Oklahoma, this should be done as per institutional practice.

#### **4.7 ANTI-EMETIC USAGE**

Anti-emetic usage will follow recommendations from the NIH CC Pharmacy or as per institutional practice.

#### **4.8 INTRAVENOUS IMMUNE GLOBULIN (IVIG)**

IVIG administration will follow Guidelines for Infection Management in pediatric standard practices due to the difficulties of avoidance of viral exposures in pediatric patients. For an IgG values less than 400 mg/dl, 500 mg/kg IVIG will be administered intravenously as per institutional guidelines. Administration of IVIG may also occur if clinically indicated (e.g. setting of severe viral infection and vascular leak).

#### **4.9 HEPATIC FUNCTION SUPPORT**

All patients will receive ursodeoxycholic acid (Ursodiol) for the prevention of hepatic complications after allogeneic stem cell transplantation. Ursodiol will start by day -4 prior to the transplant and will continue until day +100 post-transplant (or longer if clinically indicated). Patients weighing less than 90 kg will receive 300mg orally twice daily (600mg total dose each day). Those patients weighing more than 90 kg will receive 300 mg orally each morning and 600 mg orally each evening (900 mg total dose each day). CNMC pediatric patients will be dosed as per Children's National Medical Center guidelines.

The primary hepatic complication after transplantation is sinusoidal obstructive syndrome (also known as veno-occlusive disease or VOD). This has been defined using Seattle criteria as: unexplained weight gain, hepatic tenderness, and jaundice; these criteria have been refined by Baltimore to include: total bilirubin > 2, and 2 of the following: hepatomegaly, weight gain 5%, and ascites. Because no drugs are approved to treat VOD, and access to defibrotide, the only drug that has demonstrated promise, is limited, every effort will be made to optimize management to minimize the severity of VOD. Throughout the first 30 days of transplantation, management should include equal ins and outs without weight gain. Salt loads should not occur in the absence of clear benefit to the patient (e.g. sepsis). Close monitoring for this condition and immediate fluid restriction, use of oncotics and lasix (see Section 4.11), and salt removal from infusions should be instituted.

**4.10 CENTRAL NERVOUS SYSTEM PROPHYLAXIS**

Patients with history of CNS positive disease will receive CNS boost.

**4.11 FLUID MANAGEMENT DURING FIRST 30 DAYS FOLLOWING TRANSPLANTATION**

Patients should be well-hydrated prior to stem cell infusion (within 12 hours prior). Following stem cell infusion, weights and abdominal girths should be followed closely. Patients should be kept EVEN in fluid status with every attempt to minimize salt and fluid loading. High salt and fluid loads have been implicated in the physiology that leads to severe engraftment syndrome and VOD. Lasix may be used to maintain this. In addition, an oncotic (e.g. blood, IVIG, platelets, albumin) may be used followed by lasix to preserve renal function while optimizing fluid management.

**4.12 ANCILLARY SUPPORT**

Other supportive care to include: physical therapy, occupational therapy, psychosocial therapy as deemed clinically appropriate.

**4.13 SUPPORTIVE CARE FOR RELAPSE**

Patients who experience relapse on this protocol may receive therapy for relapse to include intrathecal or systemic chemotherapy, donor lymphocyte infusions or other treatments.

**4.14 ADDITIONAL CELL INFUSIONS FOR GRAFT FAILURE, IMPENDING GRAFT FAILURE, OR POOR GRAFT FUNCTION.**

Patients who experience graft failure (primary or secondary), impending graft failure (falling counts and/or donor chimerism after initial engraftment in the absence of relapse), or poor graft function posttransplant (hypoplastic bone marrow, complete or near-complete donor chimerism, absence of relapse or cytopenias clinically thought to be caused by medication or infection, severe cytopenias in at least two lines [Hb < 10 g/dL, platelet count < 30 x 10<sup>9</sup>/L, neutrophil count < 1.0 x 10<sup>9</sup>/L] lasting at least 2 weeks beyond day +14 and with transfusion requirement) will be eligible to receive a CD34<sup>+</sup>-selected cell boost. The same donor for the most recent BMT must be used. The donor will have a GCSF-mobilized peripheral blood stem cell product collected and CD34<sup>+</sup>-selected using the Miltenyi CliniMACS® system prior to infusion into the patient. A fresh product will be preferred although a cryopreserved product will be acceptable.

**5 DATA COLLECTION AND EVALUATION****5.1 DATA COLLECTION**

Data will be prospectively and entered into an NCI, CCR C3D Database from each institution. After obtaining Informed Consent, a file will be created in the database with standardized forms. The database will maintain complete records on each patient including any pertinent supplementary information obtained from outside laboratories, outside hospitals, radiology reports, laboratory reports, or other patient records. Patient records will be summarized at key time points in protocol visit notes at: pre-transplant, day 28, 60, 100, 6 month, 9 month, 12 months, and yearly post-transplant. These protocol notes will serve as the primary source material from which data will be collected and research

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

analyses will be performed. These will be reviewed by the Adjunct PI or site PI and research nurse/coordinator for accuracy and include interpretation of the events prior to this note. This is done to minimize the day to day confusion that may occur (e.g. patient has diarrhea, thought initially to be GVHD but later determined to be CMV). The following will be used for source data and wherever possible will use the interpretations from the protocol visit notes as detailed below:

- Eligibility Checklist: To be completed at study entry and forwarded to the protocol research nurse.
- Patient history and physical examinations while on study (protocol visit notes)
- Patient flow sheets (protocol visit notes)
- Patient pathology, radiology, chimerism data, laboratory evaluations. (interpreted in protocol visit notes)
- Relevant data will also be sent to the Center for International Bone Marrow Transplant Registry (CIBMTR). This will include outcome data and patient characteristics, but do not include adverse events.
- Protocol Deviations/Unanticipated problems (UPs): Any protocol deviations or UPs should be directly reported to the PI, PC, or AI. These will be submitted to each site's respective IRB. Outside institutions are required to send all protocol deviations and UPs to the Adjunct PI to be submitted to NCI IRB.
- Confidentiality Protection: Prior to analysis, all identifiers will be removed and a random number ascribed to protect patient confidentiality.

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for at least 30 days after removal from study treatment or until off-study, whichever comes first.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

**End of study procedures:** Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

**Loss or destruction of data:** Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

#### 5.1.1 Adverse event recording

- Grade 1 adverse events will not be recorded
- All serious adverse events regardless of the attribution will be recorded
- If adverse events are not serious and possibly, probably, or definitely attributable to either Lupron or FLT imaging then they will be recorded.

## 5.2 RESPONSE CRITERIA

### 5.2.1 Primary Endpoints

5.2.1.1 To determine whether Lupron leads to accelerated B cell recovery after allogeneic hematopoietic stem cell transplantation.

5.2.1.2 To determine if FLT imaging can be used safely to evaluate for engraftment of transplanted cells.

5.2.1.3 B cell recovery will be assessed on day 180 for comparison between two groups: those who have received Lupron and those who have not.

5.2.1.4 Patients will be evaluated for complete clinical response to primary malignancy at day +28, day +100, and day +365; those with and without Lupron will be compared. Complete response will include M1 marrow and no evidence of disease by flow cytometry, cytogenetics or FISH testing in all sites evaluated (lumbar puncture, bone marrow). Minimal residual disease will be used to denote < 5 % blasts in marrow but detection of disease by one of these measures.

### 5.2.2 Secondary Endpoints

5.2.2.1 Thymus studies with CT scan thymic index, flow cytometry measurements of naïve T cells.

5.2.2.2 Assess feasibility and tolerability of Lupron in male HSCT recipients. Assess recovery of testicular and ovarian function after HSCT.

5.2.2.3 Rates and details of acute and chronic GVHD in Lupron vs. no-Lupron HSCT recipients.

5.2.2.4 Rates and details of infectious episodes in Lupron vs. no-Lupron HSCT recipients.

5.2.2.5 Recovery of other populations to include: neutrophils, red blood cells, platelets, and other cell subsets (e.g. monocytes) will be assessed and compared between groups.

- 5.2.2.6** Transplant related mortality, incidence of graft rejection, disease-free and overall survival will also be collected.
- 5.2.2.7** The FLT images will be used in exploratory fashion to determine if the day +5 or day +9 image can be used to predict engraftment of donor cells by comparing the uptake of FLT at day -1 with day +5 or day +9 and day +28 (post-engraftment) and correlating this will leukocyte recovery for first BMT. Difference between patients who receive bone marrow or peripheral blood stem cell products will also be explored. For 2<sup>nd</sup> BMT, exploratory analyses will compare day -1 FLT image with relapse rates, and day +28 and +60 image abnormalities suggestive of relapse with relapse rates.
- 5.2.2.8** Evaluate thymic reconstitution by FLT (1<sup>st</sup> BMT).
- 5.2.2.9** Evaluate whether FLT vs. FDG could distinguish GVHD vs. infection and relapse vs. healthy donor engraftment (1<sup>st</sup> and 2<sup>nd</sup> BMT).
- 5.2.2.10** Evaluate the safety of FLT imaging in the peritransplant period (1<sup>st</sup> and 2<sup>nd</sup> BMT).

### **5.3 TOXICITY CRITERIA**

Adverse events on this study will be reported using the NIH mechanism of NCI Common Terminology Criteria for Adverse Events. This study will utilize the CTCAE version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>) under reporting guidelines. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

An adverse event will be defined as any novel, concerning medical condition or worsening of a previously existing medical condition. Please refer to section 8 for details on adverse event collection.

## **6 STATISTICAL SECTION**

### **6.1 SUBJECT ACCRUAL**

Non-pregnant female and male subjects from all racial and ethnic groups are eligible for this trial if they meet entry criteria. Although every effort will be made to incorporate individuals representative of the national population with the eligible malignant diseases, issues of limited accrual may not permit this study to explore the impact of race or gender. Should the analysis suggest that there is a difference observed across race or gender, accrual may be expanded or additional studies will be designed to address these questions.

#### **6.1.1 Statistics and Feasibility**

The primary objectives of this study are:

- 1) To determine if there is a difference in the percentage of B cells which recover at 12 months between males who are randomized to receive Lupron or not, and to estimate the fraction of females, all of whom will receive Lupron, who have B cells which recover at 12 months.
- 2) To evaluate engraftment kinetics to estimate the relationship between level of uptake of FLT at a day +5 scan and the day at which neutrophils recover to >500, statistical analyses were performed for this secondary endpoint.

##### **6.1.1.1 Statistics on FLT**



This subset of the total male and female patients receiving marrow transplants will undergo pre-transplant conditioning and FLT imaging agent. The patients will have their level of FLT uptake evaluated at a day +5 scan, and will be followed until they recover their neutrophils to >500. A Spearman correlation coefficient will be used to estimate the degree of association between these two parameters. With 13 evaluable patients, who have both a day +5 scan level of uptake and a known number of days to recovery of neutrophils, a correlation coefficient will be estimated in a pilot fashion; a 0.10 one-sided Fisher's test of whether the correlation coefficient has a value of 0.85 rather than a null value of 0.50 can be performed with 80% power if 13 patients are included in the evaluation. Fifteen patients will be studied in this cohort to obtain 13 fully evaluable images given that 2 may have early events that preclude day 28 evaluation. Patients enrolled on this arm of the protocol who do not complete a day 28 evaluation may be substituted to achieve 13 evaluable patients unless the patients are not evaluable due to toxicities attributed to FLT. Interim safety analysis of AEs attributed to FLT imaging will be performed on the first 7 patients. Should greater than 1 of these 7 patients not engraft and require a back-up product, the FLT arm of this protocol will be halted. Notably, patients who experience early relapse may be analyzed separately for some statistical evaluations as leukemia cells upregulate TK1 and may alter images obtained around the time of relapse. An additional eight evaluable patients will permit us to evaluate the day +9 scan rather than a day +5 scan and correlate this with engraftment and explore differences between peripheral blood stem cell source and bone marrow stem cell source. These demonstrate different kinetics of marrow recovery (with engraftment of neutrophils typically 14 days earlier with peripheral blood stem cells). Finally, not only will these kinetics help us to understand the biology of stem cell transplantation, they will also serve as a critical piece of information for a future study with cord blood as the stem cell source (which has even greater delay in neutrophil recovery, typically engrafting 2 weeks later than a marrow product).

Because the interim analysis confirmed safety in adults, up to 10 pediatric patients will now be enrolled at Children's National Medical Center. These patients will be imaged on day -1, day +9, and if possible, day +28. Analyses will mirror the adult statistics and also permit exploratory comparisons between pediatric and adult patients. The same safety stopping rules will apply: should greater than 1 of these 7 patients not engraft and require a back-up product, the FLT arm of this protocol will be halted.

In addition, because there is a suggestion that FLT may predict relapse (showing relapse in 4/4 imaged patients to date, and predicting relapse in  $\frac{3}{4}$ ), FLT will be incorporated into the evaluation of all patients in arm 2 (who are undergoing 2<sup>nd</sup> HSCT for relapse after 1<sup>st</sup> HSCT). This will be exploratory analyses to use FLT to try to predict response of therapy (in the day -1 image) and relapse in subsequent images in this population at high risk for relapse (80% historically). For patients who do relapse after this 2<sup>nd</sup> HSCT, a scan may be performed pre- and after therapies to treat this relapse to explore the effect of immunotherapy on FLT uptake.

#### 6.1.1.2 Statistics on Lupron

For 1<sup>st</sup> BMT the larger cohort of patients (of which some of these patients may undergo FLT imaging as well) will be eligible male subjects who will be randomized in a 1:1 ratio to receive



Lupron vs. no Lupron prior to receiving their pre-transplant preparative regimen. The objective will be to determine if there is a difference in the percentage of these subjects who recover their B cells by 12 months according to whether they receive Lupron or not. With 17 evaluable patients per arm (34 total evaluable patients), there is 80% power to detect a difference equal to one standard deviation (one SD effect size) between the two arms using a 0.05 two-sided two-sample t-test (that is, that the difference in the means of the two groups differs by one SD, assumed to be the same in both groups). In practice, if the data from the two groups are not normally distributed ( $p < 0.05$  by a Shapiro-Wilks test in either group), then a Wilcoxon rank sum test will be used. Since only patients who have not relapsed by 12 months would be eligible for this definitive evaluation, up to 68 patients may need to be enrolled in order to obtain this definitive evaluation.

For 1<sup>st</sup> BMT, a second cohort of patients (which may include FLT exposed patients) will be eligible female subjects who will each receive Lupron prior to receiving their pre-transplant preparative regimen. The objective in this cohort will be to estimate the fraction of patients who recover their B cells by 12 months. If there are 30 eligible female patients who have this value determined at 12 months, then a two-sided 95% confidence interval could have width of approximately  $\pm 4$  if the standard deviation was equal to 10. Since the female patients may also relapse prior to 12 months and not provide a definitive value for evaluation, up to 50 females will be enrolled into this cohort to try to ensure that at least 30 are evaluable.

For 1<sup>st</sup> BMT, for the female and male cohorts, all enrolled patients will be evaluated at the latest time point possible for a variety of immune reconstitution parameters. Thus, even if they are unable to ultimately contribute information to the definitive evaluation at 12 months, the values that are obtained at any time point will be used to estimate the recovery at various time points prior to 12 months.

In order to complete accrual to these cohorts, up to  $68+50=118$  patients may need to be enrolled. If 2-3 patients per month are able to be accrued onto this trial, accrual should be completed within 3 to 5 years. Patients who do not undergo allogeneic transplantation may be substituted.

Toxicity of FLT and Lupron in this population will be evaluated in all exposed patients.

For 1<sup>st</sup> BMT, exploratory analyses will evaluate other leukocyte subsets of immune reconstitution with and without Lupron (including transitional B cells, dendritic cells, recent thymus emigrants, naïve and memory T cells), disease control by treatments pre- and peri-transplant, whether FLT can identify relapse disease, or GVHD. The effect of cell dose and age on lymphoid engraftment will also be explored. In addition, evidence of functional immune recovery as per vaccine response will also be explored. For patients to receive benefit from vaccines after myeloablative HSCT, the immune system must mount a durable response. If the patient receives a vaccine without evidence of a rise in antibody titers, it is possible or even likely that the patient does not receive benefit from this vaccine. In pediatric HSCT recipients in many institutions, it is standard practice to test for a vaccine response and repeat vaccinations when one is achieved to maximize the potential for long-lasting immunity to this pathogen. In adult HSCT recipients, this is not standard of care because both there is less likelihood that older adults can achieve this after myeloablative transplantation and high likelihood that residual plasma cells (of host origin) will respond after non-myeloablative transplantation which may not be meaningful for long-lasting immunity. Because the immune modulation of lupron may improve the immune system of these young adults similar to those often achieved in pediatric patients, the optimal approach for long

lasting immunity is to attempt to determine a functional benefit to the vaccines, to give the vaccine to the patient when they can respond and develop durable benefit (prophylaxis from infections).

Interim analyses will be conducted on FLT treated patients after 7 patients have completed day 28 imaging and on the lupron treated vs. untreated male subjects after 15 have been enrolled to each arm to evaluate for safety (lupron and FLT) and efficacy (lupron).

Using the CIBMTR (international registry data), the expected survival is <30% for acute myelogenous leukemia and 30% for acute lymphoid leukemia at 2 years. Because 10% of these patients die of non-relapse causes, this means that the expected relapse rate is 60% for similar patients, suggesting that our relapse rate of less than half this is considerably better. The relapse rate for patients after 2<sup>nd</sup> BMT is even higher, so these patients will need to be analyzed separately from patients who have only undergone 1 BMT. These patients will be added via amendment L, which will have the following characteristics: males and females who have previously failed a transplant will be enrolled onto the trial and receive Lupron. The patients will be followed for progression and for survival. With 16 patients, there would be 82% power to detect an improvement from 60% who relapse by one year to 30% who relapse by one year (using data for 2<sup>nd</sup> BMT where the relapse rates exceed 60%), using an exact binomial test with a 0.10 one-sided significance level. In practice, the fraction of the 16 evaluable patients who survive without relapse to one year will be estimated; this fraction will be reported along with appropriate confidence intervals, such as a one-sided 90% interval to show if the fraction is below 60%, as well as a two-sided 95% confidence interval to help describe the observed fraction of patients who are relapse free at one year. In addition, a Kaplan-Meier curve of relapse free survival will be constructed to estimate the relapse free probabilities at various time points.

To ensure that patients are not continued to enroll onto this arm in the event that results are not adequate, the following early stopping rule will apply: if among the first 8 patients enrolled, 0 of 8 are able to survive to one year, then no further patients will be enrolled onto this trial as soon as this can be determined, as this will indicate worse than expected results: the upper one sided 90% Confidence interval on 0/8 is 0.25, which would indicate that this result would not be consistent with tolerable results.

## **7 HUMAN SUBJECTS PROTECTIONS**

### **7.1 RATIONALE FOR SUBJECT SELECTION**

All patients with eligible malignant diseases who may benefit from allogeneic stem cell transplantation are eligible for this trial. All ethnic groups and both sexes may be enrolled. Ethnic enrollment may vary as ethnic groups afflicted by these diseases may vary. Pregnant females will be excluded from this trial. It is unlikely that our patient numbers will permit statistics of individual ethnic or age groups, however this will be attempted should numbers permit.

### **7.2 PARTICIPATION OF CHILDREN**

In addition, this trial is open to pediatric as well as adult patients; however, at Univ of Oklahoma only adult patients will be enrolled and at Children's National Medical Center only pediatric patients will be enrolled. Patients  $\geq 15$  years old and/or  $> 9$  years and after Tanner stage 2 are

eligible at NCI, because these; patients who are pre-pubertal are unlikely to receive benefit (and may be harmed) by exposure to Lupron. At Children's National Medical Center pediatric patients > 4 years of age will be eligible. Donors less than 2 years of age will not be included on this protocol. Physicians, nurses, and multidisciplinary support teams of the POB, NCI, and CC at NIH, and Oklahoma Transplant Team, Children's Hospital, Stephenson Cancer Center, and HCA at Univ of Oklahoma, and the BMT team, Blood Bank at Children's National Medical Center will provide patient care. The staff of the POB has expertise in the management of children with complex oncologic disorders and complications of therapy. Full pediatric support and subspecialty services are available at the NIH CC. Note: arm 2 is for adults only at NIH.

### **7.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT**

.Re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section 7.4), all recipients subjects  $\geq$  age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MAS Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

Donor subjects who become incapacitated or cognitively impaired during the course of the study will come off study since there are no direct benefit to the donor subjects.

### **7.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS**

#### **7.4.1 Recipient**

Patients are likely to obtain direct benefit from the HSCT as the eligible diseases for this protocol are aggressive and likely to lead to death without HSCT. The transplantation preparative regimen and GVHD prophylaxis are standard of care for patients of these ages with these diseases. These regimens carry an acceptable risk of direct toxicities including: organ toxicity (lung, heart, kidney, endocrinological, neurological, and liver), immunosuppression with increased risk of infections, potential for graft versus host disease. The patients will be monitored for toxicities using the current best practice guidelines and will receive prophylaxis for those complications that we can prevent (e.g. infectious, mesna for cyclophosphamide to minimize kidney toxicity). See section 10 for details. The greatest risk to mortality remains relapse in this population. Thus, a myeloablative regimen has been chosen that confers the greatest potential for disease control. Lupron may not impact on disease control, or it may improve disease control by decreasing androgen levels (leukemias often have androgen receptor and may respond to this substrate) and through enhanced post-transplant lymphocyte reconstitution (with potential to improve GVL).

##### **7.4.1.1 FLT risks to exposed recipient**

The greatest risks of clinical FLT scans to patients enrolled on imaging studies to date have included bruising at the injection site; no significant adverse events were reported in the literature. Please see section 1.2.7 for details and toxicities at much higher doses of FLT than patients on this protocol will receive, none of which are expected. The one theoretical risk to patients undergoing HSCT is that the newly dividing hematopoietic stem cells could be affected by FLT delaying engraftment or contributing to failure to engraft. However, the actual radiation dose to which the bone marrow is exposed is equivalent to the dose received in an abdominal CT with contrast, a test routinely performed for clinical indications without adverse effects on engraftment. Stopping rules are in place for nonengraftment.

#### 7.4.2 Risks in relation to benefit for Donor

Healthy HLA-matched donors will be co-enrolled onto this study. The collection aspect of this protocol is not investigational. There is potential benefit for donors, as they may derive psychological benefit from participating in a clinical trial designed to improve the health of the recipient of the prior transplant donation. Other potential benefits include the diagnosis of previously unknown illnesses (such as viral hepatitis) at the time of donor screening.

#### 7.4.3 Pediatric Patients

Pediatric patients are eligible to participate in this trial if they meet criteria including a disease for which BMT is the recommended therapy. The diseases addressed in this protocol are the current diseases recommended for transplantation by the national cooperative groups (Children's Oncology Group). The preparative regimen is one of the standard recommended regimens. Pediatric patients at Children's National Medical Center are now eligible for FLT, because this testing did not increase the risk to recipients in the adult study (14 adult patients have undergone FLT without attributable toxicities at NCI). Female patients who have begun puberty will receive the standard of care for menses prophylaxis, lupron at the dose of 11.25 mg for patients < 18 years. Thus, the only additive risk to pediatric patients beyond standard of care is the exposure of male patients to lupron. Given that female children have tolerated this agent well, the risks of lupron in male subjects are expected to be mild and reversible (the drug will clear in 3 months and not redosed in this study in male subjects). The potential benefits include: 1) improved immune reconstitution, 2) potential anti-tumor effects, and 3) possible benefit for preservation of fertility.

### 7.5 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

Informed consent will be obtained from all patients, and/or the patient's parents or legal guardian (if he/she is < 18 years of age) and matched related donors prior to entry.. The procedures and treatments involved in this protocol, with their attendant risks and discomforts, potential benefits, and potential alternative therapies will be carefully explained to the recipient and/or parent/guardian. Where deemed appropriate by the clinician and the child's parent(s) or guardian, the child will also be included in all discussions about the trial and age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts and benefits of participation. Verbal assent will be obtained as appropriate for children ages (12 years and older) and the parent or guardian will sign the designated line on the informed consent attesting to the fact that the child has given assent. Children under the age of 12 years will not be required to provide assent as they typically do not have the cognitive ability to fully understand the nature of research. The consent/assent process will be documented in the

child's medical record, including the assessment of the child's ability to provide verbal assent. All children will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time. Note that NMDP consents will be used for unrelated donor patients.

The investigators are requesting a waiver from the IRB to allow only one parent to sign the informed consent to enter a child on the protocol. Because many patients must travel to the NIH from long distances at substantial expense, requiring both parents to be present for the consent process could be a financial hardship for many families. When guardianship status of the child is uncertain, a social worker will be asked to investigate and, if necessary, seek documentation of custody status. In situations where there is joint custody of a child, both parents must sign consent. If only one parent can be present at NIH, the other parent's consent can be obtained by telephone via the procedure described in section 7.5.1. Similarly, the procedures and treatments involved in this protocol, with their attendant risks and discomforts, will be carefully explained to the matched unrelated donors at the respective donor center as required by NMDP. The original signed informed consent goes to Medical Records; a copy will be kept for the research record. The Central Registration Office (CRO), Data Management Section will also retain a copy of the informed consent document. A copy of the signed informed consent document will also be given to the recipient (and matched related donor, when applicable). b) The Central Registration Office (CRO) will ascertain the date of IRB approval before registering the first patient.

The Principal Investigator and/or an authorized designee will consent the patient and matched related donor (when applicable) and will be available to answer all patient questions.

If any new information becomes available relating to risks, adverse events, or toxicities, while patients are participating in this protocol, this information will be provided orally and/or in writing to all enrolled and prospective patient participants. Documentation will be provided to the IRB and if necessary the informed consent amended to reflect relevant information.

The possible risks and benefits of this trial will be explained in layman's terms for patients and guardians. For patients who elect to enroll, consent will be obtained. A signed consent must be obtained by patient or legal guardian prior to study entry. The PI, an Associate investigator, or an appropriate designee will answer all questions regarding this medication and the purpose of the trial prior to obtaining consent.

#### 7.5.1 Consent for minors when they reach the age of majority

When a pediatric subject reaches age 18, continued participation (including ongoing interactions with the subject or continued analysis of identifiable data) will require consenting of the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained. We request waiver of informed consent for those individuals who have completed their participation in the research study and subjects who have been lost to follow-up. Requirements for Waiver of Consent consistent with 45 CFR 46.116 (d):

- 1) The research involves no more than minimal risk to the subjects. a. Analysis of samples and data from this study involves no additional risks to subjects.
- 2) The waiver or alteration will not adversely affect the rights and welfare of the subjects. a. Retention of these samples or data does not affect the welfare of subjects.



- 3) The research could not practicably be carried out without the waiver or alteration. a. Considering the length of time between the minor's last contact with the research team and their age of majority, it will likely be very difficult to locate them again. A significant reduction in the number of samples analyzed is likely to impact the quality of the research.
- 4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation. a. We only plan to request a waiver of reconsent for those subjects who have been lost to follow-up or prior to amendment T, have been taken off study prior to reaching the age of majority.

#### 7.5.2 Telephone consent and re-consent procedure

The following procedure may be used in cases of re-consent or for initial consent in cases where the consent of both parents of a minor participant is required as discussed in section 7.5. the informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent. The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone. A fully executed copy will be returned via mail for the subject's records. The informed consent process will be documented on a progress note by the consenting investigator.

#### 7.5.3 Informed consent of Spanish speaking subjects

We anticipate the enrollment of Spanish speaking research participants into our study. The IRB approved full consent document will be translated into that language in accordance with the Clinical MAS Policy M77-2.

#### 7.5.4 Short form consent process for other non-English speaking patients

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, 45 CFR 46.117 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation. Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

## **8 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN**

### **8.1 DEFINITIONS**

#### **8.1.1 Adverse Event**

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

8.1.2 This study incorporates a standard myeloablative bone marrow transplantation platform that has been in use for ~50 years and has many expected adverse events. As the purpose of this study is to assess the integration of lupron and FLT imaging with this transplantation platform, only 1) serious adverse events and 2) adverse events not attributable to the standard BMT platform and either possibly, probably, or definitely attributable to either lupron or FLT imaging will be reported.

Suspected adverse reaction means 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. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

#### **8.1.3 Unexpected 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.

"Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **8.1.4 Serious**

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

#### **8.1.5 Serious Adverse Event**

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A significant disability/incapacity



*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

- A congenital anomaly/birth defect.

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

#### 8.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

#### 8.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

#### 8.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB approved research protocol

#### 8.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subject.

#### 8.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
  - (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
  - (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

## 8.2 NCI-IRB AND CLINICAL DIRECTOR REPORTING

### 8.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

### 8.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
  - All Grade 2 **unexpected** events that are possibly, probably, or definitely related to lupron or the IND;
  - All Grade 3 and 4 events that are possibly, probably, or definitely related to the lupron or the IND;
  - All Grade 5 events regardless of attribution;
  - All Serious Events regardless of attribution.

**NOTE:** Grade 1 events are not required to be collected or reported.

**Note:** With the exception of severe adverse events, AE that occur prior to the initiation of protocol directed therapy (to include standard of care chemotherapy that could be given due to delay in donor availability or for other reasons) will not be collected or reported.

**NOTE:** Expected AE of transplantation that will be exempt from reporting (because they will not be related to research) include:

- Leukopenia, anemia, and thrombocytopenia until engraftment of these cellular populations. Should a patient not engraft, this will be captured as an AE.
- Coagulation abnormalities
- Electrolyte abnormalities including sodium, potassium, chloride, magnesium, calcium, phosphorus, bicarb, blood urea nitrogen, lactate dehydrogenase, creatinine kinase.
- Endocrine abnormalities, bone mineralization abnormalities, avascular necrosis, delay in growth/development, and nutritional data (to include lipid levels, prealbumin, albumin).
- Dermatology abnormalities (to include changes in nails, pigmentation)
- Mucositis

### 8.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

### **8.3 NCI GUIDANCE FOR REPORTING EXPEDITED ADVERSE EVENTS FOR MULTI-CENTER TRIALS**

The site PI must immediately report to the coordinating center PI any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event within 24 hours of PI awareness of the event. The Site PI must also report any protocol deviations to the coordinating center PI within 7 days of PI awareness. Participating centers must also submit the report to their IRB in accordance with their institutional policies.

A participating site problem form (available in section [12.16](#)) is to be filled out and sent to the Coordinating Center's PI.

### **8.4 IND SPONSOR REPORTING CRITERIA**

During the first 30 days after the subject receives investigational agent/intervention, the investigator must immediately report to the sponsor using the mandatory MedWatch form 3500a, or equivalent any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. For serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention, only report those that have an attribution of at least possibly related to the agent/intervention.

Required timing for reporting per the above guideline:

- Deaths (except death due to progressive disease) must be reported via email within 24 hours. A complete report must be submitted within one business day.
- Other serious adverse events as well as deaths due to progressive disease must be reported within one business day

Events will be submitted to the Center for Cancer Research (CCR) at: [CCRsafety@mail.nih.gov](mailto:CCRsafety@mail.nih.gov) and to the CCR PI and study coordinator.

### **8.5 DATA RECORDING OF UNRELATED DONORS FROM NMDP**

Per NMDP regulations, and to maintain donor confidentiality, unrelated donor source documents will *not* be sent to the NIH. The NMDP will maintain all required source documents in accordance with NMDP policies and procedures. The NMDP will confirm donor eligibility and will notify the NIH of any deviations in regard to protocol requirements.

The National Marrow Donor Program (NMDP) IRB will be responsible for the review and continuing oversight of protocol procedures that relate only to NMDP unrelated donors.

### **8.6 DATA AND SAFETY MONITORING PLAN**

#### **8.6.1 Principal Investigator/Research Team**

The clinical research team will meet on a regular basis weekly when patients are being actively treated on the trial to discuss each patient.

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Pertinent data includes: GVHD acute or chronic and characterization as per appendices and medications to treat this documented at day 30, 60, 100, 180, 270, 365, and yearly after this, infections and medications and disease response and therapies for recurrent disease also collected at these key time points. Ancillary medications taken at the time of these time points needs to be collected, however, ancillary medications not associated with the aforementioned that are started and stopped between key time points need not to be collected/recorded unless associated with adverse events. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The site principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The site principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

#### 8.6.2 Sponsor Monitoring Plan

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary study endpoints; adherence to the protocol, regulations, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

8.6.3 This trial will be monitored by personnel employed by an NCI contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conductSafety Monitoring Committee (SMC)

This protocol will require oversight from the Safety Monitoring Committee (SMC). Initial review will occur as soon as possible after the annual NCI-IRB continuing review date. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period. Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

## **9 MULTI-INSTITUTIONAL GUIDELINES**

This is a multi-institutional trial with University of Oklahoma and National Institutes of Health, National Cancer Institute, and Children's National Medical Center.

Children's National Medical Center will enroll only children and open only the FLT arm of the study. Univ. of Oklahoma will enroll only adults and open only the Lupron arm.

### **9.1.1 IRB Approvals**

The PI will provide the NCI IRB and Central Registration Office with a copy of the participating institution's approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NCI IRB.

### **9.1.2 Amendments and Consents**

The PI will provide NIH IRB with any and all documentation of amendments, consents, and approvals from IRB reviews at all participating institutions. All amendments to the protocol or the NCI consent are to be approved by the NCI PI and the NCI IRB and then submitted to the participating institution's IRB for approval.

### **9.1.3 Data and Specimen Collection Procedures**

The NCI C3D data base will be utilized; data will only be collected at the time points specified in this trial. Participating sites will be trained in the use of C3D and directly enter data at these sites into C3D. Any questions or concerns should elicit immediate contact of the NCI PI or AI.

### **9.1.4 Data Center Audits**

All participating sites will be monitored as per section **8.7.2**. Scans and data may also be reviewed of primary NIH or Children's National Medical Center patients at Univ of Oklahoma after de-identification for exploratory analyses. The NCI PI or AI will oversee the implementation of any necessary quality improvement measures that may be indicated as a result of these quality assurance activities.

### **9.1.5 Protocol Monitoring Committees**

The NCI PI or AI will have either a meeting or phone conversation with all IRB-approved participating institution PIs to discuss protocol progress at least monthly after the outside site as begun accrual.

## **10 PHARMACEUTICAL INFORMATION**

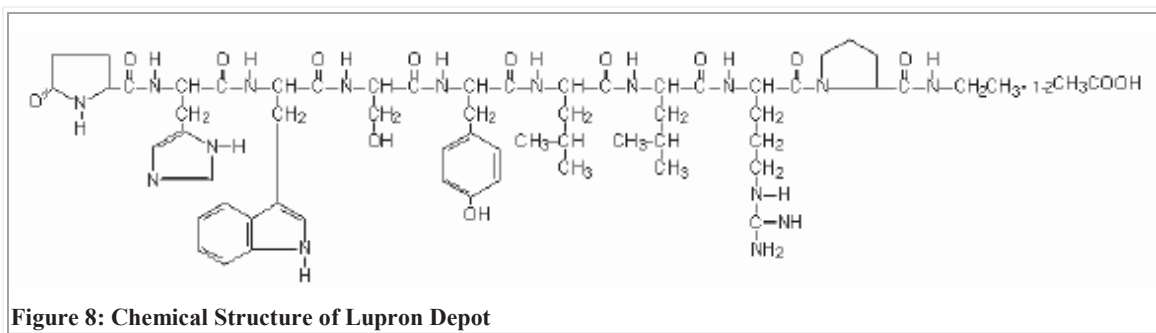
### **10.1 LUPRON DEPOT**

#### **10.1.1 Chemical name**

5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate

Lupron is a synthetic nonapeptide analog of naturally produced gonadotropin-releasing hormone (GnRH).

### 10.1.2 Chemical structure



### 10.1.3 Commercial Formulation

Supplied either daily or extended release injections. Daily formulation is a 2.8 mL multi-dose vial with 5 mg/mL Lupron, administered as 1 mg (0.2 mL) subcutaneously per day. Lupron also is supplied as Lupron Depot in either a 1, 3, or 4 month preparation with 3.75, 22.5 mg, or 30 mg leuprolide acetate respectively for adults and as 11.25 mg 3 month preparation for children. Lupron Depot is given as an intramuscular injection in a dual chamber syringe system that contains sterile lyophilized microspheres which become suspended in the carrier solution upon injection and continue drug release for the recommended timeframe.

#### 10.1.4 Storage

Room temperature

### 10.1.5 Stability

Lupron remains stable when stored at 15-30 deg. Celsius. The product should be stored in the original container and away from light sources.

### 10.1.6 Route of administration

Intramuscular injection. Emla may be given prior to injection to minimize discomfort at injection site.

### 10.1.7 Dose

Lupron will be administered as 30 mg intramuscular injection once prior to stem cell transplant for adult patients and as an adult preparation 3 month extended release 11.25 mg intramuscular injection once prior to stem cell transplant for patients <18 years.

### 10.1.8 Drug Interactions

There are no reported drug interactions with Lupron. It is metabolized by peptidases and does not involve the P450 enzyme system. However, given the mechanism of action of sex hormone suppression, all sex hormones are contraindicated (including: testosterone, progesterone, and estrogen) in all preparations.

### 10.1.9 Known toxicities for patients >18

(see table below)

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

Please utilize the table for the most accurate assessment of Lupron toxicities. The most common side effects in large trials include headache and fatigue. A toxicity table from the Lupron insert is included here:

Table 2: Adverse Events in  $\geq 5\%$  of Patients Regardless of Causality

<b>Adverse Events Reported in <math>\geq 5\%</math> of Patients Regardless of Causality</b>				
<b>LUPRON DEPOT-4 Month 30 mg</b>				
	<b>Nonorchietomized, N=49</b>		<b>Orchiectomized, N=24</b>	
	<b>Study 013</b>		<b>Study 012</b>	
	<b>N</b>	<b>(%)</b>	<b>N</b>	<b>(%)</b>
<b>Body As a Whole</b>				
Asthenia	6	(12.2)	1	(4.2)
Flu Syndrome	6	(12.2)	0	(0.0)
General Pain	16	(32.7)	1	(4.2)
Headache	5	(10.2)	1	(4.2)
Injection Site Reaction	4	(8.2)	9	(37.5)
<b>Cardiovascular System</b>				
Hot flashes/Sweats*	23	(46.9)	2	(8.3)
<b>Digestive System</b>				
GI Disorders	5	(10.2)	3	(12.5)
<b>Metabolic and Nutritional Disorders</b>				
Dehydration	4	(8.2)	0	(0.0)
Edema	4	(8.2)	5	(20.8)
<b>Musculoskeletal System</b>				
Joint Disorder	8	(16.3)	1	(4.2)
Myalgia	4	(8.2)	0	(0.0)
<b>Nervous System</b>				
Dizziness/Vertigo	3	(6.1)	2	(8.3)
Neuromuscular Disorders	3	(6.1)	1	(4.2)
Paresthesia	4	(8.2)	1	(4.2)
<b>Respiratory System</b>				
Respiratory Disorder	4	(8.2)	1	(4.2)
<b>Skin and Appendages</b>				
Skin Reaction	6	(12.2)	0	(0.0)
<b>Urogenital System</b>				
Urinary Disorders	5	(10.2)	4	(16.7)

10.1.10 Known toxicities for patients  $<18$

(see table below)

In two studies of children with central precocious puberty, in 2% or more of the patients receiving the drug, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician. Reactions which are not considered drug related are excluded.



Table 3

	Number of Patients	
	N = 421	(%)
Body as a Whole		
General Pain	12	(3)
Headache	11	(3)
Injection Site Reactions Including Abscess*	37	(9)
Cardiovascular System		
Vasodilation	9	(2)
Integumentary System (Skin and Appendages)		
Acne/Seborrhea	13	(3)
Rash Including Erythema Multiforme	12	(3)
Nervous System		
Emotional Lability	19	(5)
Urogenital System		
Vaginitis/Vaginal Bleeding/Vaginal Discharge	13	(3)
*Most events were mild or moderate in severity.		

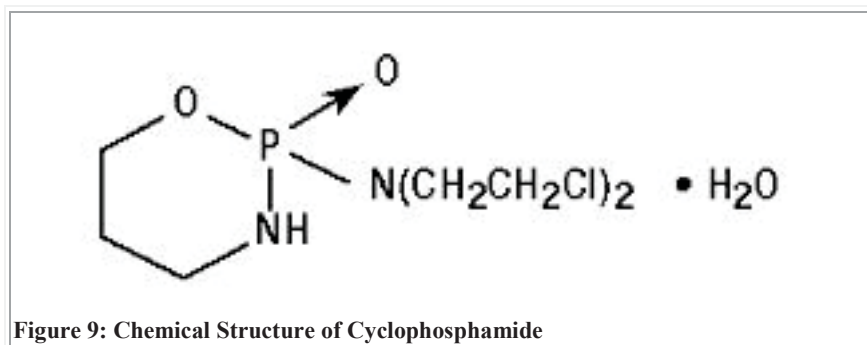
## 10.2 CYCLOPHOSPHAMIDE

### 10.2.1 Chemical name

2-[bis(2-chloroethyl)amino] tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate.

Cyclophosphamide is a chemotherapy metabolized in the liver to an active alkylator that interferes with cell division through cross-linking of DNA.

### 10.2.2 Chemical structure



**Abbreviated Title: Lupron & 18F FLT in allo-HSCT**

**Version Date: December 28, 2017**

### 10.2.3 Commercial Formulation

Supplied as lyophilized powder that will be reconstituted with normal saline prior to intravenous administration. Oral tablets are available but not relevant to this trial.

### 10.2.4 Storage

Room temperature

### 10.2.5 Stability

Cyclophosphamide reconstituted is stable for 24 hours at room temperature or for 6 days in the refrigerator.

### 10.2.6 Route of administration

Intravenous injection

### 10.2.7 Dose

Cyclophosphamide will be administered as per Section [12.4](#).

### 10.2.8 Drug Interactions

The rate of metabolism and the activity of cyclophosphamide are increased with concomitant administration of Phenobarbital. Cyclophosphamide also increases the activity of succinylcholine chloride. If the patient has been treated with cyclophosphamide within 10 days of general anesthesia, the anesthesiologist should be alerted.

### 10.2.9 Known toxicities

(see table below)

**Table 4: Toxicity**

	<b>Common</b>	<b>Occasional</b>	<b>Rare</b>
<b>Immediate:</b> Within 1-2 days of receiving drug	Anorexia (L), nausea (L), vomiting(L)	Metallic taste (L), Inappropriate ADH <sup>1</sup>	Transient blurred vision <sup>1</sup> cardiac toxicity with arrhythmias <sup>1</sup> myocardial necrosis <sup>2</sup> (L)
<b>Prompt:</b> Within 2-3 weeks, prior to the next course	Myelosuppression (L), alopecia (L)	Hemorrhagic cystitis (L)	
<b>Delayed:</b> Any time later during therapy, excluding the above conditions	Immunosuppression, gonadal dysfunction /sterility (L)		Pulmonary fibrosis <sup>3</sup> (L)
<b>Late:</b> Any time after completion of treatment			Secondary malignancy, bladder fibrosis

**Unknown Frequency and Timing:** \*\*Fetal and teratogenic toxicities and toxicities in breast-fed children

<sup>1</sup> Less common with lower doses.

<sup>2</sup>Only with very high doses.

<sup>3</sup> Risk increased with chest radiation.

*(L) Toxicity may also occur later.*

**Abbreviated Title:** *Lupron & 18F FLT in allo-HSCT*

**Version Date:** *December 28, 2017*

**\*\*Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosome abnormalities, multiple anomalies, pancytopenia, and low birth weight.**

**\*\*Cyclophosphamide is excreted into breast milk. Neutropenia has been reported in breast-fed infants. Cyclophosphamide is considered to be contraindicated during breast feeding because of the reported cases of neutropenia and because of the potential adverse effects relating to immune suppression, growth, and carcinogenesis.**

### 10.3 TOTAL BODY IRRADIATION

#### 10.3.1 Chemical name

Not applicable

#### 10.3.2 Known toxicities

The side effects of radiation have been well described. The most common include nausea and mucositis. There also exists a risk of hypothyroidism, cataracts, interstitial pneumonitis, nephropathy, and an unspecified long-term risk of developing secondary malignancies [63]. Importantly, the majority of the non-neoplastic effects were subclinical and/or reversible [64]. Studies attempting to evaluate the risk attributed to radiation within a preparative regimen have implicated secondary malignancies, however this is difficult to ascribe since secondary malignancies are also increased with cGVHD and other post-transplant complications [65] [66]. Pediatric patients who require sedation in order to undergo TBI will be asked to sign a separate consent outlining the risk of the selected anesthesia.

### 10.4 FLT

#### 10.4.1 Chemical Name

3'-deoxy-3 <sup>18</sup>F-fluorothymidine

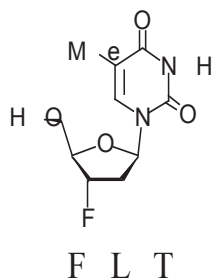
#### 10.4.2 Commercial Formulation

FLT is supplied as a unit dose by intravenous injection.

#### 10.4.3 Storage

Room Temperature

#### 10.4.4 Chemical Structure



**Figure 10: Chemical Structure of FLT**

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

#### 10.4.5 Method of Administration

[<sup>18</sup>F] FLT is administered by intravenous injection over 15 seconds with a saline flush. Appropriate shielding will meet the Radiation Safety Guidelines of NIH.

#### 10.4.6 Availability

[<sup>18</sup>F] FLT will be synthesized and delivered to Building 21 by Cardinal Health, or PETnet Pharmacies. [<sup>18</sup>F] FLT will be synthesized and delivered Radiology Department located on 2<sup>nd</sup> floor of hospital at Children's National Medical Center by Cardinal Health or PETnet Pharmacies.

#### 10.4.7 Known Toxicities

No AEs attributable to <sup>18</sup>F FLT administered at tracer levels have been reported in the published literature. While no related AEs are expected, patients will be monitored very closely with regards to hepatic, neurologic, and hematologic parameters following radiotracer injection.

### 10.5 FLUDARABINE (FLUDARA, BERLEX LABORATORIES)

#### 10.5.1 Chemical Name

Fludarabine monophosphate

#### 10.5.2 Supply

Fludarabine monophosphate will be purchased by the NIH Clinical Center Pharmacy Department from commercial sources and is supplied as a white, lyophilized powder. Each vial contains 50 mg of fludarabine phosphate, 50 mg of mannitol, and sodium hydroxide to adjust pH. Fludara is stored at room temperature.

#### 10.5.3 Preparation

FLUDARA IV should be prepared for parenteral use by aseptically adding Sterile Water for Injection, USP. When reconstituted with 2 ml of Sterile Water for Injection, each ml of the resulting solution will contain 25 mg of Fludarabine Phosphate, 25 mg of mannitol, and sodium hydroxide to adjust the pH to 7–8.5. Fludarabine will be diluted in 100 to 125ml of either 5% dextrose in water or 0.9% sodium chloride, and infused IV over 30 minutes.

#### 10.5.4 Storage and Stability

Reconstituted FLUDARA IV is chemically and physically stable for 24 hours at room temperature or for 48 hours if refrigerated. Because reconstituted FLUDARA IV contains no antimicrobial preservative, care must be taken to assure the sterility of the prepared solution; for this reason, reconstituted FLUDARA IV should be used or discarded within 8 hours.

#### 10.5.5 Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

#### 10.5.6 Toxicities

Fludarabine toxicities include myelosuppression (dose limiting toxicity), fever, nausea, vomiting, stomatitis, diarrhea, gastrointestinal bleeding, anorexia, edema, skin rashes, myalgia, headache,

agitation, hearing loss, transient episodes of somnolence and fatigue, auto-immune hemolytic anemia, auto-immune thrombocytopenia, paresthesias, peripheral neuropathy, renal, and pulmonary toxicity (interstitial pneumonitis). Severe fatal CNS toxicity presenting with loss of vision and progressive deterioration of mental status were encountered almost exclusively after very high doses of fludarabine monophosphate. Such toxicity has only rarely been demonstrated at the 25-30 mg/m<sup>2</sup>/day dosage of fludarabine. Very rarely described complications include transfusion-associated graft-versus-host disease, thrombotic thrombocytopenic purpura, and liver failure. Tumor lysis syndrome following fludarabine administration has been observed, especially in patients with advanced bulky disease. Opportunistic infections (protozoan, viral, fungal, and bacterial) have been observed post-fludarabine, especially in heavily pre-treated individuals, and in individuals receiving fludarabine combined with other agents.

## **10.6 BUSULFAN (BUSULFEX)**

Busulfan is a bifunctional alkylating agent approved for use as a conditioning agent prior to allogeneic hematopoietic stem cell transplantation at NCI on protocol 10-c-0174 amendment M. The IV formulation is administered as Busulfan (Busulfex, Otsuka America Pharmaceutical, Inc.)

### **10.6.1 Source**

For patient administration, IV Busulfan is purchased by the NIH Clinical Center Pharmacy Department from commercial sources. The drug is supplied as a clear, colorless sterile solution in 10ml single use vials. Each vial of Busulfan contains 60 mg (6mg/ml) of busulfan.

### **10.6.2 Storage and Stability**

Unopened vials of Busulfan are stable until the date indicated on the package when stored under refrigeration at 2-6 degrees C (36-46 degrees F).

### **10.6.3 Administration**

Busulfan must be diluted prior to use with either 0.9% Sodium chloride or 5% Dextrose Injection. The diluent quantity should be 10 times the volume of Busulfan so that the final concentration of busulfan is approximately 0.5 mg/ml. Busulfan should be administered intravenously via a central venous catheter as a two-hour infusion every 24 hours for a total of 4 doses over four days.

### **10.6.4 Toxicities**

At the indicated dose and schedule Busulfan induces profound myelosuppression; 2) All patients should be given a seizure prophylaxis regimen (e.g. Clonazepam plus levetiracetam) since busulfan is known to cross the blood brain barrier and induce seizures; 3) Nausea, vomiting, and stomatitis are common side effects of busulfan.

### **10.6.5 Drug Interactions**

Itraconazole increases the clearance of busulfan by up to 25%. Phenytoin increases the clearance of busulfan by 15%.

**11 REFERENCES**

1. Hakim, F.T., et al., *Constraints on CD4 recovery postchemotherapy in adults: thymic insufficiency and apoptotic decline of expanded peripheral CD4 cells*. Blood, 1997. **90**(9): p. 3789-98.
2. Hazenberg, M.D., et al., *T-cell receptor excision circle and T-cell dynamics after allogeneic stem cell transplantation are related to clinical events*. Blood, 2002. **99**(9): p. 3449-53.
3. Storek, J., et al., *Infectious morbidity in long-term survivors of allogeneic marrow transplantation is associated with low CD4 T cell counts*. Am J Hematol, 1997. **54**(2): p. 131-8.
4. Roux, E., et al., *Recovery of immune reactivity after T-cell-depleted bone marrow transplantation depends on thymic activity*. Blood, 2000. **96**(6): p. 2299-303.
5. Dumont-Girard, F., et al., *Reconstitution of the T-cell compartment after bone marrow transplantation: restoration of the repertoire by thymic emigrants*. Blood, 1998. **92**(11): p. 4464-71.
6. Lewin, S.R., et al., *Direct evidence for new T-cell generation by patients after either T-cell-depleted or unmodified allogeneic hematopoietic stem cell transplantations*. Blood, 2002. **100**(6): p. 2235-42.
7. Novitzky, N., et al., *Immune reconstitution at 6 months following T-cell depleted hematopoietic stem cell transplantation is predictive for treatment outcome*. Transplantation, 2002. **74**(11): p. 1551-9.
8. Koehl, U., et al., *Immune recovery in children undergoing allogeneic stem cell transplantation: absolute CD8+ CD3+ count reconstitution is associated with survival*. Bone Marrow Transplant, 2007. **39**(5): p. 269-78.
9. Parkman, R., et al., *Successful immune reconstitution decreases leukemic relapse and improves survival in recipients of unrelated cord blood transplantation*. Biol Blood Marrow Transplant, 2006. **12**(9): p. 919-27.
10. Weinberg, K., et al., *Factors affecting thymic function after allogeneic hematopoietic stem cell transplantation*. Blood, 2001. **97**(5): p. 1458-66.
11. Fallen, P.R., et al., *Factors affecting reconstitution of the T cell compartment in allogeneic haematopoietic cell transplant recipients*. Bone Marrow Transplant, 2003. **32**(10): p. 1001-14.
12. Jimenez, M., et al., *Clinical factors influencing T-cell receptor excision circle (TRECs) counts following allogeneic stem cell transplantation in adults*. Transpl Immunol, 2006. **16**(1): p. 52-9.
13. Omazic, B., et al., *Memory B lymphocytes determine repertoire oligoclonality early after haematopoietic stem cell transplantation*. Clin Exp Immunol, 2003. **134**(1): p. 159-66.

14. Marie-Cardine, A., et al., *Transitional B cells in humans: characterization and insight from B lymphocyte reconstitution after hematopoietic stem cell transplantation*. Clin Immunol, 2008. **127**(1): p. 14-25.
15. Omazic, B., et al., *Reconstitution of the Ig heavy chain CDR3 repertoire after allogeneic haematopoietic stem cell transplantation with myeloablative or reduced-intensity conditioning regimens*. Scand J Immunol, 2005. **61**(1): p. 72-81.
16. Parsons, R.F., et al., *Acquisition of Humoral Transplantation Tolerance upon De Novo Emergence of B Lymphocytes*. J Immunol, 2010.
17. Chu, R., et al., *Comparison of Outcomes after Transplantation of G-CSF Stimulated Bone Marrow Grafts versus Bone Marrow or Peripheral Blood Grafts from HLA-Matched Sibling Donors for Patients with Severe Aplastic Anemia*. Biol Blood Marrow Transplant, 2010.
18. Anderson, D., et al., *A comparison of related donor peripheral blood and bone marrow transplants: importance of late-onset chronic graft-versus-host disease and infections*. Biol Blood Marrow Transplant, 2003. **9**(1): p. 52-9.
19. Goldberg, G.L., et al., *Enhanced Immune Reconstitution by Sex Steroid Ablation following Allogeneic Hemopoietic Stem Cell Transplantation*. J Immunol, 2007. **178**(11): p. 7473-84.
20. Leposavic, G., et al., *Differential effects of gonadectomy on the thymocyte phenotypic profile in male and female rats*. Pharmacol Biochem Behav, 1996. **54**(1): p. 269-76.
21. Olsen, N.J. and W.J. Kovacs, *Effects of androgens on T and B lymphocyte development*. Immunol Res, 2001. **23**(2-3): p. 281-8.
22. Olsen, N.J., et al., *Induction of immature thymocyte proliferation after castration of normal male mice*. Endocrinology, 1994. **134**(1): p. 107-13.
23. Sutherland, J.S., et al., *Activation of thymic regeneration in mice and humans following androgen blockade*. J Immunol, 2005. **175**(4): p. 2741-53.
24. Ellis, T.M., et al., *Alterations in peripheral B cells and B cell progenitors following androgen ablation in mice*. Int Immunol, 2001. **13**(4): p. 553-8.
25. Williams, K.M., et al., *CCL25 increases thymopoiesis after androgen withdrawal*. Blood, 2008. **112**(8): p. 3255-63.
26. Aragon-Ching, J.B., K.M. Williams, and J.L. Gulley, *Impact of androgen-deprivation therapy on the immune system: implications for combination therapy of prostate cancer*. Front Biosci, 2007. **12**: p. 4957-71.
27. Ghalie, R., et al., *Prevention of hypermenorrhea with leuprolide in premenopausal women undergoing bone marrow transplantation*. Am J Hematol, 1993. **42**(4): p. 350-3.
28. Vermeulen, A. and Oddens, *Androgens and the Aging Male*, in *Declining Androgens with age: an overview*, A. Vermeulen, Editor. 1996, Parthenon Publishing: New York. p. 3-14.
29. Huang, C.X., L.Z. Chen, and J.G. Zhao, *[Influence of chemotherapy with FOLFOX protocol on sex hormones of male patients and the protective effect of herbal medicines*



- for reinforcing Shen and supplementing qi on it]. *Zhongguo Zhong Xi Yi Jie He Za Zhi*, 2008. **28**(11): p. 986-9.
30. Isasi, C.R., P. Lu, and M.D. Blaufox, *A metaanalysis of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma*. Cancer, 2005. **104**(5): p. 1066-74.
  31. Spaepen, K., et al., *Prognostic value of pretransplantation positron emission tomography using fluorine 18-fluorodeoxyglucose in patients with aggressive lymphoma treated with high-dose chemotherapy and stem cell transplantation*. Blood, 2003. **102**(1): p. 53-9.
  32. Spaepen, K., et al., *Can positron emission tomography with [(18)F]-fluorodeoxyglucose after first-line treatment distinguish Hodgkin's disease patients who need additional therapy from others in whom additional therapy would mean avoidable toxicity?* Br J Haematol, 2001. **115**(2): p. 272-8.
  33. Spaepen, K., et al., *[(18)F]FDG PET monitoring of tumour response to chemotherapy: does [(18)F]FDG uptake correlate with the viable tumour cell fraction?* Eur J Nucl Med Mol Imaging, 2003. **30**(5): p. 682-8.
  34. Schwartz, J.L., et al., *Monitoring tumor cell proliferation by targeting DNA synthetic processes with thymidine and thymidine analogs*. J Nucl Med, 2003. **44**(12): p. 2027-32.
  35. Kasper, B., et al., *Functional diagnosis of residual lymphomas after radiochemotherapy with positron emission tomography comparing FDG- and FLT-PET*. Leuk Lymphoma, 2007. **48**(4): p. 746-53.
  36. Buchmann, I., et al., *[18F]3'-deoxy-3'-fluorothymidine-PET in NHL patients: whole-body biodistribution and imaging of lymphoma manifestations--a pilot study*. Cancer Biother Radiopharm, 2004. **19**(4): p. 436-42.
  37. Herrmann, K., et al., *Early response assessment using 3'-deoxy-3'-[18F]fluorothymidine-positron emission tomography in high-grade non-Hodgkin's lymphoma*. Clin Cancer Res, 2007. **13**(12): p. 3552-8.
  38. Buck, A.K., et al., *Molecular imaging of proliferation in malignant lymphoma*. Cancer Res, 2006. **66**(22): p. 11055-61.
  39. Been, L.B., et al., *Positron emission tomography in patients with breast cancer using (18)F-3'-deoxy-3'-fluoro-L-thymidine ((18)F-FLT)-a pilot study*. Eur J Surg Oncol, 2006. **32**(1): p. 39-43.
  40. Kenny, L., et al., *Imaging early changes in proliferation at 1 week post chemotherapy: a pilot study in breast cancer patients with 3'-deoxy-3'-[18F]fluorothymidine positron emission tomography*. Eur J Nucl Med Mol Imaging, 2007. **34**(9): p. 1339-47.
  41. Pio, B.S., et al., *Usefulness of 3'-[F-18]fluoro-3'-deoxythymidine with positron emission tomography in predicting breast cancer response to therapy*. Mol Imaging Biol, 2006. **8**(1): p. 36-42.
  42. Cobben, D.C., et al., *Detection and grading of soft tissue sarcomas of the extremities with (18)F-3'-fluoro-3'-deoxy-L-thymidine*. Clin Cancer Res, 2004. **10**(5): p. 1685-90.

43. Buck, A.K., et al., *First demonstration of leukemia imaging with the proliferation marker 18F-fluorodeoxythymidine*. J Nucl Med, 2008. **49**(11): p. 1756-62.
44. Agool, A., et al., *18F-FLT PET in hematologic disorders: a novel technique to analyze the bone marrow compartment*. J Nucl Med, 2006. **47**(10): p. 1592-8.
45. Agool, A., et al., *Effect of radiotherapy and chemotherapy on bone marrow activity: a 18F-FLT-PET study*. Nucl Med Commun, 2011. **32**(1): p. 17-22.
46. Awasthi, V., et al., *F-18-fluorothymidine-PET evaluation of bone marrow transplant in a rat model*. Nucl Med Commun. **31**(2): p. 152-8.
47. Flexner, C., et al., *Relationship between plasma concentrations of 3'-deoxy-3'-fluorothymidine (alovudine) and antiretroviral activity in two concentration-controlled trials*. J Infect Dis, 1994. **170**(6): p. 1394-403.
48. Shields, A.F., et al., *Imaging proliferation in vivo with [F-18]FLT and positron emission tomography*. Nat Med, 1998. **4**(11): p. 1334-6.
49. Kong, X.B., et al., *Comparisons of anti-human immunodeficiency virus activities, cellular transport, and plasma and intracellular pharmacokinetics of 3'-fluoro-3'-deoxythymidine and 3'-azido-3'-deoxythymidine*. Antimicrob Agents Chemother, 1992. **36**(4): p. 808-18.
50. Goldstone, A.H., et al., *In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993)*. Blood, 2008. **111**(4): p. 1827-33.
51. Stock, W., *Adolescents and young adults with acute lymphoblastic leukemia*. Hematology Am Soc Hematol Educ Program, 2010. **2010**: p. 21-9.
52. Foran, J.M., *New prognostic markers in acute myeloid leukemia: perspective from the clinic*. Hematology Am Soc Hematol Educ Program, 2010. **2010**: p. 47-55.
53. Byrd, J.C., et al., *Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461)*. Blood, 2002. **100**(13): p. 4325-36.
54. Bornhauser, M., et al., *Improved outcome after stem-cell transplantation in FLT3/ITD-positive AML*. Blood, 2007. **109**(5): p. 2264-5; author reply 2265.
55. Scholl, S., et al., *Clinical impact of nucleophosmin mutations and Flt3 internal tandem duplications in patients older than 60 yr with acute myeloid leukaemia*. Eur J Haematol, 2008. **80**(3): p. 208-15.
56. Thiede, C., et al., *Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis*. Blood, 2002. **99**(12): p. 4326-35.

57. Williams, K.M. and R.E. Gress, *Immune reconstitution and implications for immunotherapy following haematopoietic stem cell transplantation*. Best Pract Res Clin Haematol, 2008. **21**(3): p. 579-96.
58. Bishop, M.R., et al., *A randomized, double-blind trial of filgrastim (granulocyte colony-stimulating factor) versus placebo following allogeneic blood stem cell transplantation*. Blood, 2000. **96**(1): p. 80-5.
59. Ernst, P., et al., *A Phase 3, Randomized, Placebo-controlled Trial of Filgrastim in Patients with Haematological Malignancies Undergoing Matched-related Allogeneic Bone Marrow Transplantation*. Arch Drug Inf, 2008. **1**(3): p. 89-96.
60. Battiwalla, M. and P.L. McCarthy, *Filgrastim support in allogeneic HSCT for myeloid malignancies: a review of the role of G-CSF and the implications for current practice*. Bone Marrow Transplant, 2009. **43**(5): p. 351-6.
61. Rizzo, J.D., et al., *Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, and the American Society of Blood and Marrow Transplantation*. Biol Blood Marrow Transplant, 2006. **12**(2): p. 138-51.
62. Filipovich, A.H., et al., *National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report*. Biol Blood Marrow Transplant, 2005. **11**(12): p. 945-56.
63. Buchali, A., et al., *Immediate toxicity during fractionated total body irradiation as conditioning for bone marrow transplantation*. Radiother Oncol, 2000. **54**(2): p. 157-62.
64. Thomas, O., et al., *Long-term complications of total body irradiation in adults*. Int J Radiat Oncol Biol Phys, 2001. **49**(1): p. 125-31.
65. Curtis, R.E., et al., *Solid cancers after bone marrow transplantation*. N Engl J Med, 1997. **336**(13): p. 897-904.
66. Kolb, H.J., et al., *Malignant neoplasms in long-term survivors of bone marrow transplantation. Late Effects Working Party of the European Cooperative Group for Blood and Marrow Transplantation and the European Late Effect Project Group*. Ann Intern Med, 1999. **131**(10): p. 738-44.

## 12 APPENDICES

### 12.1 APPENDIX 1: PERFORMANCE SCALES

<b>%</b>	<b><u>Karnofsky</u><sup>†</sup></b>	<b><u>Status</u></b>	<b><u>Lansky Scale</u><sup>#</sup></b>
<b>100</b>	Normal; no complaints/ no evidence of disease	<b>100</b>	Fully Active
<b>90</b>	Able to carry on normal activity; minor signs or symptoms of disease	<b>90</b>	Minor restrictions in physically strenuous play

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

<b>80</b>	Normal activity with effort; some signs or symptoms of disease	<b>80</b>	Restricted in strenuous play, tires more easily, otherwise active
<b>70</b>	Cares for self; unable to carry on normal activity or do active work	<b>70</b>	Both greater restrictions of and less time spent in active play
<b>60</b>	Requires occasional assistance but is able to care for most of his needs	<b>60</b>	Ambulatory up to 50% of time, limited active play with assistance / supervision
<b>50</b>	Requires considerable assistance and frequent medical care	<b>50</b>	Considerable assistance required for any active play; fully able to engage in quiet play
<b>40</b>	Disabled, requires special care and assistance	<b>40</b>	Able to initiate quiet activities
<b>30</b>	Severely disabled; hospitalization is indicated though death not imminent	<b>30</b>	Needs considerable assistance for quiet activity
<b>20</b>	Very sick; hospitalization is necessary	<b>20</b>	Limited to very passive activity initiated by others e.g. TV
<b>10</b>	Moribund; fatal process progressing rapidly	<b>10</b>	Completely disabled, not even passive play
		<b>0</b>	Unresponsive, coma

† Karnofsky = D.A., et al., Cancer 1: 634-656, 1948

# Lansky Scale = Lansky, et. al., Cancer Oct 1; 60(7): 1651-1656, 1987

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

Should be completed within 45 days of BMT.

May need to repeated if chemo required.

## 12.2 APPENDIX 2A: RECIPIENT (ARM 1 AND 2)

Name: \_\_\_\_\_

Donor: \_\_\_\_\_

DOB: \_\_\_\_/\_\_\_\_/\_\_\_\_

MR# \_\_\_\_\_

Tentative Transplant Date \_\_\_\_/\_\_\_\_/\_\_\_\_

**Pre-Tx W/u: Scheduled Date Done Comments**

H/P: ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_

CT Scans:

Head ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_

Sinus ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_

Chest ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_

Abd/Pel ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_

Echo ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_

EKG ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_

PFT

DLCO ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_

FEV1 ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_

Dental Ex ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_

Broviac p. ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_

Radiation ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_

BM/LP ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_

Nutrition ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_

**Date Done Result**

CBC \_\_\_\_/\_\_\_\_/\_\_\_\_

ABO Type \_\_\_\_/\_\_\_\_/\_\_\_\_

PT/PTT \_\_\_\_/\_\_\_\_/\_\_\_\_

Acute care panel \_\_\_\_/\_\_\_\_/\_\_\_\_

Hepatic panel \_\_\_\_/\_\_\_\_/\_\_\_\_

Mineral Panel \_\_\_\_/\_\_\_\_/\_\_\_\_

CK and LDH \_\_\_\_/\_\_\_\_/\_\_\_\_

Uric Acid \_\_\_\_/\_\_\_\_/\_\_\_\_

Lipid/TRI \_\_\_\_/\_\_\_\_/\_\_\_\_

U Preg (F) \_\_\_\_/\_\_\_\_/\_\_\_\_

Hep A Ab \_\_\_\_/\_\_\_\_/\_\_\_\_

Hep B Ab \_\_\_\_/\_\_\_\_/\_\_\_\_

Hep C Ab \_\_\_\_/\_\_\_\_/\_\_\_\_

HIV Ab \_\_\_\_/\_\_\_\_/\_\_\_\_

Toxo IgG/IgM \_\_\_\_/\_\_\_\_/\_\_\_\_

CMV IgG/IgM \_\_\_\_/\_\_\_\_/\_\_\_\_

HTLV I/II IgG \_\_\_\_/\_\_\_\_/\_\_\_\_

HSV1,2 IgG/IgM \_\_\_\_/\_\_\_\_/\_\_\_\_

Adenovirus IgG \_\_\_\_/\_\_\_\_/\_\_\_\_

EBV IgM/IgG \_\_\_\_/\_\_\_\_/\_\_\_\_

Syphilis \_\_\_\_/\_\_\_\_/\_\_\_\_

Varicella IgG \_\_\_\_/\_\_\_\_/\_\_\_\_

T/B/NK \_\_\_\_/\_\_\_\_/\_\_\_\_

Disease diagnosis:

CNS+ ever? \_\_\_\_\_

Cytogenetics:

Flow:

Extra evaluations based on hx:

Social work?

Ophtho?

ID?

**Testosterone and Estrogen level**

Pre-Lupron for females and males.

Radiation records (prior)?

***Abbreviated Title: Lupron & 18F FLT in allo-HSCT***

***Version Date: December 28, 2017***

24 hr CCL/GFR	__/_/_	_____
NMDP sample	__/_/_	
IgG, IgA, IgM	__/_/_	
RFLP	__/_/_	
TSH/FreeT4	__/_/_	_____
Urinalysis	__/_/_	_____

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*  
*Version Date: December 28, 2017*

Should be completed within 30 days of BMT.  
 May need to repeated if chemo required.

### 12.3 APPENDIX 2B: DONOR (ARM 1 AND 2)

Name: \_\_\_\_\_

Recipient: \_\_\_\_\_

DOB: \_\_\_\_/\_\_\_\_/\_\_\_\_

MR# \_\_\_\_\_

Diagnosis: \_\_\_\_\_

Tentative Transplant Date \_\_\_\_/\_\_\_\_/\_\_\_\_

#### Pre-Tx W/u: Scheduled Date Done Comments

H/P: ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_ \_\_\_\_/\_\_\_\_/\_\_\_\_

EKG ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_ \_\_\_\_/\_\_\_\_/\_\_\_\_

CXR ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_ \_\_\_\_/\_\_\_\_/\_\_\_\_

Anesthesia ☐ \_\_\_\_/\_\_\_\_/\_\_\_\_ \_\_\_\_/\_\_\_\_/\_\_\_\_

	Date Done	Result
CBC	____/____/____	_____
ABO Type	____/____/____	_____
PT/PTT	____/____/____	_____
Acute care, hepatic, and mineral panel plus LDH	____/____/____	_____
Lipid/TRI	____/____/____	_____
U Preg (F)	____/____/____	_____
Hep A Ab	____/____/____	_____
Hep B Ab	____/____/____	_____
Hep C Ab	____/____/____	_____
HIV Ab	____/____/____	_____
Toxo IgG/IgM	____/____/____	_____
CMV IgG/IgM	____/____/____	_____
HTLV I/II IgG	____/____/____	_____
HSV1,2 IgG/IgM	____/____/____	_____
Adenovirus IgG	____/____/____	_____
EBV IgM/IgG	____/____/____	_____
Syphilis	____/____/____	_____
Varicella IgG	____/____/____	_____
T/B/NK	____/____/____	_____
NMDP sample	____/____/____	_____
RFLP	____/____/____	_____
Urinalysis	____/____/____	_____



Abbreviated Title: *Lupron & 18F FLT in allo-HSCT*  
Version Date: *December 28, 2017*

12.4 APPENDIX 3A: FLT (1<sup>ST</sup> BMT)

PATIENT Name \_\_\_\_\_ MR# \_\_\_\_\_ DOB \_\_\_\_\_

Date Due	Date Given	Week	Day	18F FLT	18F FDG	Pre-Eval	Post-Eval	Comments
_____	_____		-1	_____		Cr, ALT, AST, TK	F18 1,2hr	
_____	_____	1	0					
_____	_____		1					
_____	_____		2					
_____	_____		3					
_____	_____		4					
_____	_____		5/9			CR, ALT, AST, TK	F18 1,2hr	
_____	_____		6					
_____	_____		7					
_____	_____	2	8					
_____	_____	3	15					
_____	_____	4	28			CR, ALT, AST, TK	F18 1,2hr	
_____	_____		29					
_____	_____	+				CR, ALT, AST, TK	F18 1,2hr	To occur with GVHD, or thymus recovery
_____	_____							

Appendix 3B: FLT (2<sup>nd</sup> BMT)

Patient Name _____			MR# _____		DOB _____			
Date Due	Date Given	Week	Day	18F FLT	18F FDG	Pre-Eval	Post-Eval	Comments
_____	_____		-1	_____		Cr, ALT, AST, TK	F18 1,2hr	
_____	_____	1	0					
_____	_____		1					
_____	_____		2					
_____	_____		3					
_____	_____	4	28	_____		CR, ALT, AST, TK	F18 1,2hr	
_____	_____		29					
_____	_____	5-7			_____			
_____	_____							
_____	_____	8	60	_____		CR, ALT, AST, TK	F18 1,2hr	
_____	_____		61			_____		
_____	_____	+	PD	_____		CR, ALT, AST, TK	F18 1,2hr	
_____	_____		P+1					
_____	_____	+	TX	_____	_____	CR, ALT, AST, TK	F18 1,2hr	To occur with progressive disease
_____	_____		T+1		_____	_____		

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

## 12.5 APPENDIX 4A: ADULT (>22 YEARS) BMT ROADMAP

### Bone Marrow Transplant with Total Body Irradiation and Cyclophosphamide

This roadmap represents the general plan of care for this patient during the bone marrow transplant process. This is not an order sheet. Transplant Date: \_\_\_\_\_

Patient/Diagnosis		Basis for Dose Calculations		Transplant		Donor	
Name:		Ht (cm):		Type of Match:		Name:	
MR#:		Wt (kg):		Prep Regimen:	TBI, Cytosan	NMDP/MR#:	
Sex:		BSA(m2):		Product:	Marrow	Sex:	
DOB:	/ /	IBW (kg):		GVH Regimen:	Methotrexate , Tacrolimus	Age:	
Age:	y/o	Allergies:		Day 0:	/ /	Relationship:	
ABO/Rh:						Wt (kg):	
CMV IgG:						ABO/Rh:	
HSV (I/II):						CMV IgG:	
Toxo IgG:						HLA: A ( , ), Cw ( , ), B ( , ), Bw ( , ), DRB1 ( , ), DRB3 ( , ), DQB1 ( , )	
HLA:							
Diagnosis:							
Status:							
Cytogenetics:							
Risk Factors:							
Performance Score:							

Chemotherapy started on: (write in date) \_\_\_\_\_ Was dose of prep regimen modified? If yes, explain:

\_\_\_\_\_

**Abbreviated Title: Lupron & 18F FLT in allo-HSCT****Version Date: December 28, 2017**

Ht (cm):	Dx:	Prep Regimen: TBI/Cytosan	Type of Match:
Wt (kg):	Status:	Product: Marrow	Donor CMV:
IBW (kg):	Risk Factors:	GVH Regimen: MTX/tacro	Donor ABO/Rh:
BSA (m2):		Day 0: / /	
Age:	ABO/Rh:		

Day#:	Date:	Regimen:	Medications/Interventions:	Notes:
-14 to day -7	/ /		+/- male LUPRON (+females)	One injection of 4 month preparation.
-8		<b>TBI</b>	Start Pneumocystis carinii (PCP) and Caspofungin prophylaxis	Weekly Fungitall, Asp ag, Adeno +/- Toxo (for positive patients).
-7		<b>TBI</b>		
-6		<b>TBI</b>		
-5		<b>TBI</b>		
-4		<b>CY Mesna</b>		Forced diuresis with IV hydration to maintain UOP volume of 2-3ml/kg/hr
-3		<b>CY Mesna</b>	Discontinue PCP prophylaxis	Forced diuresis with IV hydration to maintain UOP volume of 2-3ml/kg/hr
-1		<b>+/- FLT (1<sup>st</sup> or 2<sup>nd</sup> BMT)</b>	Tacro 0.02mg/kg/day IBW continuous infusion	TAC trough at least weekly, adjust to goal of 5-10ng/ml.
0		<b>TX</b>	Start prophylactic antibiotics	TAC trough at least weekly, adjust to goal of 5-10ng/ml.
+1		<b>Methotrexate 10mg/m2 IV</b>		
+3		<b>Methotrexate 5mg/m2 IV</b>		TAC trough at least weekly, adjust to goal of 5-10ng/ml.
+5		<b>+/- FLT (1<sup>st</sup> BMT)</b>		FLT can be on either day 5 or day 9 (BMT# 1 only)
+6		<b>Methotrexate 5mg/m2 IV</b>		
+11		<b>Methotrexate 5mg/m2 IV</b>		TAC trough at least weekly, adjust to goal of 5-10ng/ml.
+14				- Research Blood

**Abbreviated Title: Lupron & 18F FLT in allo-HSCT****Version Date: December 28, 2017**

+28		<b>+/- FLT (1<sup>st</sup> or 2<sup>nd</sup> BMT)</b>	Restart PCP prophylaxis	-BMB, BMA morphology, RFLP, -BMA FISH, flow -diagnostic LP, Research Pl/BM -Chimerism Bl/BM, -H/P aGVHD, IgGs, TBNK
+29		<b>+/- FDG (1<sup>st</sup> or 2<sup>nd</sup> BMT)</b>		
+30		+/- FLT When GVHD or thymus		
+60		<b>+/- FLT &amp; FDG (2<sup>nd</sup> BMT only)</b>		-BMB, BMA morphology, RFLP, -BMA cytogenetics, FISH, flow -diagnostic LP -Chimerism Bl/BM, - Research blood/BM -TBNK, H/p w/ AGVHD eval.
+100			Taper Tacrolimus if no signs of GVHD	-H/P w/a or cGVHD, -BMB, BMA morphology, RFLP -BMA cytogenetics, FISH, flow - diagnostic LP - Chimerism Bl/BM, - Research blood/BM, TBNK - LDH, IGs, - PFTs, CHEST CT.
+180			Taper Tacrolimus if no signs of GVHD	-H/P w/ cGVHD, - Chimerism Bl, - Research blood, TBNK - Ferritin, Fe, LDH, IGs, - PFTs. - Ophthalmology - Dental - LH/FSH, TSH/T4, U/A, Chem20
+270				-H/P w/ cGVHD, - Chimerism Bl, - Research blood, TBNK - Ferritin, Fe, LDH, IGs, - PFTs. - LH/FSH, TSH/T4, Chem20
+365			Consider Immunizations 6 months after withdrawal of immunosuppression.	-H/P w/a or cGVHD, -BMB, BMA morphology, RFLP -BMA cytogenetics, FISH, flow - diagnostic LP

**Abbreviated Title: Lupron & 18F FLT in allo-HSCT**

**Version Date: December 28, 2017**

				<ul style="list-style-type: none"> <li>- Chimerism BI/BM,</li> <li>- Research blood/BM, TBNK</li> <li>- Ferritin, LDH, IGs,</li> <li>- PFTs, CHEST CT.</li> <li>- Ophthalmology</li> <li>- Dental</li> <li>- LH/FSH, TSH/T4, U/A, Chem20</li> <li>- Echo</li> <li>- Dexa</li> <li>- GYN (female)</li> </ul>
--	--	--	--	---

TBI twice daily fractionated with lung block on days -7, -6, -5, and -4. Cumulative dose = 1200 cGy/course. CNS boost if CNS positive at any time prior to HSCT.

Cyclophosphamide 60mg/kg IV over 1 hour on days -3, -2. Cumulative dose = 120mg/kg.

*\*\*\*Note: Use a modified dose in obese patients that is defined as BMI > 35 and modified weight is half way between actual and ideal body weight for Cyclophosphamide and Mesna dosing*

Mesna IV 24 hour infusion = to total Cyclophosphamide dose on days -3, -2.

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

## 12.6 APPENDIX 4B: PEDIATRIC ( $\leq 22$ YEARS) BMT ROADMAP

### Bone Marrow Transplant with Total Body Irradiation and Cyclophosphamide

This roadmap represents the general plan of care for this patient during the bone marrow transplant process. This is not an order sheet.

Transplant Date: \_\_\_\_\_

Patient/Diagnosis		Basis for Dose Calculations		Transplant		Donor	
Name:		Ht (cm):		Type of Match:		Name:	
MR#:		Wt (kg):		Prep Regimen:	TBI, Cytosan	NMDP/MR#:	
Sex:		BSA(m2):		Product:	Marrow	Sex:	
DOB:	/ /	IBW (kg):		GVH Regimen:	Methotrexate, Tacrolimus	Age:	
Age:	y/o	Allergies:		Day 0:	/ /	Relationship:	
ABO/Rh:						Wt (kg):	
CMV IgG:						ABO/Rh:	
HSV (I/II):						CMV IgG:	
Toxo IgG:						HLA:	A ( , ), Cw ( , ), B ( , ), Bw ( , ), DRB1 ( , ), DRB3 ( , ), DQB1 ( , )
HLA:	A ( , ), Cw ( , ), , B ( , ), , Bw ( , ), DRB1 ( , ), , DRB3 ( , ), DQB1 ( , )						
Diagnosis:							
Status:							
Cytogenetics:							
Risk Factors:							
Performance Score:							

Chemotherapy started on: (write in date) \_\_\_\_\_

Was dose of prep regimen modified? If yes, explain:

\_\_\_\_\_



**Abbreviated Title: Lupron & 18F FLT in allo-HSCT**

**Version Date: December 28, 2017**

Ht (cm):	Dx:	Prep Regimen: TBI/Cytosan	Type of Match:
Wt (kg):	Status:	Product: Marrow	Donor CMV:
IBW (kg):	Risk Factors:	GVH Regimen: MTX/tacro	Donor ABO/Rh:
BSA (m2):		Day 0: / /	
Age:	ABO/Rh:		

**Abbreviated Title: Lupron & 18F FLT in allo-HSCT****Version Date: December 28, 2017**

<b>Day#:</b>	<b>Date:</b>	<b>Regimen:</b>	<b>Medications/Interventions:</b>	<b>Notes:</b>
-14 to day -7	/ /		+/- male <b>LUPRON</b> (+females)	One injection of 4 month preparation.
-9		<b>TBI</b>	Start Pneumocystis carinii (PCP) and Caspofungin prophylaxis	Weekly Fungitall, Asp ag, Adeno +/- Toxo (for positive patients).
-8		<b>TBI</b>		
-7		<b>TBI</b>		
-6		<b>TBI</b>		
-5		<b>CY Mesna</b>		Forced diuresis with IV hydration to maintain UOP volume of 2-3ml/kg/hr
-4		<b>CY Mesna</b>		Forced diuresis with IV hydration to maintain UOP volume of 2-3ml/kg/hr
-3		<b>CY Mesna</b>		Forced diuresis with IV hydration to maintain UOP volume of 2-3ml/kg/hr
-2		<b>CY Mesna</b>	Discontinue PCP prophylaxis	Forced diuresis with IV hydration to maintain UOP volume of 2-3ml/kg/hr
-1		+/- <b>FLT*</b>	Tacro 0.02mg/kg/day IBW continuous infusion	TAC trough at least weekly, adjust to goal of 5-10ng/ml.
0		<b>TX</b>	Start prophylactic antibiotics	TAC trough at least weekly, adjust to goal of 5-10ng/ml.
+1		<b>Methotrexate 10mg/m2 IV</b>		
+3		<b>Methotrexate 5mg/m2 IV</b>		TAC trough at least weekly, adjust to goal of 5-10ng/ml.
+5		+/- <b>FLT</b>		
+6		<b>Methotrexate 5mg/m2 IV</b>		
+11		<b>Methotrexate 5mg/m2 IV</b>		TAC trough at least weekly, adjust to goal of 5-10ng/ml.
+14				- Research Blood
+28		+/- <b>FLT</b>	Restart PCP prophylaxis	-BMB, BMA morphology, RFLP, -BMA cytogenetics, FISH, flow -diagnostic LP, Research PI/BM -Chimerism BI/BM, -H/P aGVHD, IgGs, TBNK
+29		+/- <b>FDG</b>		
+30		+/- <b>FLT</b> When GVHD or thymus		
+60				-BMB, BMA morphology, RFLP, -BMA cytogenetics, FISH, flow -diagnostic LP -Chimerism BI/BM, - Research blood/BM -TBNK, H/p w/ AGVHD eval.
+100			Taper Tacrolimus if no signs of GVHD	-H/P w/a or cGVHD, -BMB, BMA morphology, RFLP -BMA cytogenetics, FISH, flow - diagnostic LP - Chimerism BI/BM, - Research blood/BM, TBNK

**Abbreviated Title: Lupron & 18F FLT in allo-HSCT****Version Date: December 28, 2017**

				<ul style="list-style-type: none"> <li>- Ferritin, LDH, IGs,</li> <li>- PFTs, CHEST CT.</li> </ul>
+180			Taper Tacrolimus if no signs of GVHD	<ul style="list-style-type: none"> <li>-H/P w/ cGVHD,</li> <li>- Chimerism BI,</li> <li>- Research blood, TBNK</li> <li>- Ferritin, Fe, LDH, IGs,</li> <li>- PFTs.</li> <li>- Ophthalmology</li> <li>- Dental</li> <li>- LH/FSH, TSH/T4, U/A, Chem20</li> </ul>
+270				<ul style="list-style-type: none"> <li>-H/P w/ cGVHD,</li> <li>- Chimerism BI,</li> <li>- Research blood, TBNK</li> <li>- Ferritin, Fe, LDH, IGs,</li> <li>- PFTs.</li> <li>- LH/FSH, TSH/T4, Chem20</li> </ul>
+365			Consider Immunizations 6 months after withdrawal of immunosuppression.	<ul style="list-style-type: none"> <li>-H/P w/a or cGVHD,</li> <li>-BMB, BMA morphology, RFLP</li> <li>-BMA cytogenetics, FISH, flow</li> <li>- diagnostic LP</li> <li>- Chimerism BI/BM,</li> <li>- Research blood/BM, TBNK</li> <li>- Ferritin, LDH, IGs,</li> <li>- PFTs, CHEST CT.</li> <li>- Ophthalmology</li> <li>- Dental</li> <li>- LH/FSH, TSH/T4, U/A, Chem20</li> <li>- Echo</li> <li>- DEXA</li> <li>- GYN (female)</li> </ul>

TBI twice daily fractionated with lung block on days -8, -7, -6, -5. Cumulative dose = 1200 cGy/course. CNS boost if CNS positive at any time prior to HSCT.

Cyclophosphamide 50mg/kg IV over 1 hour on days -5, -4, -3, -2. Cumulative dose = 200mg/kg.

*\*\*\*Note: Use a modified dose in obese patients that is defined as BMI > 35 and modified weight is half way between actual and ideal body weight for Cyclophosphamide and Mesna dosing*

Mesna IV 24 hour infusion = to total Cyclophosphamide dose on days -5, -4, -3, -2.

**Abbreviated Title: Lupron & 18F FLT in allo-HSCT**

**Version Date: December 28, 2017**

## 12.7 APPENDIX 5: RESEARCH SPECIMENS

Please note that any extra clinical specimen taken from the patient on protocol may become a research specimen if the patient has agreed to this, to include: BAL, biopsies of lung, bone, or liver etc.

Note total aliquot will not exceed 3 ml/kg/draw nor 7 ml/kg in 4 week period for research.

<b>Day#:</b>	<b>From:</b>	<b>Source:</b>	<b>Notes:</b>
-	DONOR	Donor marrow product	5 million total nucleated donor cells (of marrow product)
-1	HOST	Peripheral Blood – FLT patients	TK for FLT 1 <sup>st</sup> or 2 <sup>nd</sup> BMT patients. 3 cc EDTA PB
+5	HOST	Peripheral Blood – FLT patients Peripheral Blood – cells, EDTA, HEP pl, TBNK	TK 3 cc EDTA PB for FLT 1 <sup>st</sup> BMT only patients. 20cc in red/green CPT PB 16 cc in EDTA PB
+7, 14, 21	HOST	Peripheral Blood – cells, EDTA, HEP pl, TBNK	20cc in red/green CPT PB 16 cc in EDTA PB
+28	HOST	Peripheral Blood – cells, EDTA, HEP pl Bone marrow aspirate Bone marrow biopsy Peripheral Blood – FLT patients	20cc in red/green CPT PB 16 cc in EDTA PB + TK 3 cc EDTA PB for FLT 1 <sup>st</sup> or 2 <sup>nd</sup> BMT patients
+45	HOST	Peripheral Blood – cells, EDTA, HEP pl, TBNK	
+ 60	HOST	Peripheral Blood – cells, EDTA, HEP pl Bone marrow aspirate Bone marrow biopsy	20cc in red/green CPT PB 16 cc in EDTA PB + TK 3 cc EDTA PB for FLT 2 <sup>nd</sup> BMT patients
<b>+ONSET AGVHD</b>	HOST	Peripheral Blood – cells, EDTA, HEP pl	20cc in red/green CPT PB 16 cc in EDTA PB
+100	HOST	Peripheral Blood – cells, EDTA, HEP pl Bone marrow aspirate Bone marrow biopsy	20cc in red/green CPT PB 16 cc in EDTA PB
<b>+ONSET cGVHD</b>	HOST	Peripheral Blood – cells, EDTA, HEP pl	20cc in red/green CPT PB 16 cc in EDTA PB
+180	HOST	Peripheral Blood – cells, EDTA, HEP pl	20cc in red/green CPT PB 16 cc in EDTA PB
+270	HOST	Peripheral Blood – cells, EDTA, HEP pl	
+365	HOST	Peripheral Blood – cells, EDTA, HEP pl Bone marrow aspirate Bone marrow biopsy	
+yearly on study until 5 years	HOST	Peripheral Blood – cells, EDTA, HEP pl	

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*  
*Version Date: December 28, 2017*

## **12.8 APPENDIX 6: IMMUNIZATION POST-TRANSPLANT**

Immunizations: All recipients will receive immunizations after transplant, according to the BMT consortium guidelines

([https://cccasper.cc.nih.gov/cvnp/aHR0cDovL2ludHJhbmV0LmNjLm5paC5nb3Y/bmt/clinicalcare/pdf/Table\\_II.pdf](https://cccasper.cc.nih.gov/cvnp/aHR0cDovL2ludHJhbmV0LmNjLm5paC5nb3Y/bmt/clinicalcare/pdf/Table_II.pdf))

**12.9 APPENDIX 7: MANAGEMENT OF ENGRAFTMENT SYNDROME****Clinical Definition of Engraftment Syndrome**

*A constellation of clinical symptoms and signs has been observed during neutrophil recovery following HSCT, most commonly termed “engraftment syndrome” (ES), sometimes “hyperacute” graft-versus-host reaction. Below are guidelines for diagnosis and treatment.*

<i>Major criteria:</i>	<ul style="list-style-type: none"> <li>• Fever &gt; 38.3° with no identifiable infectious etiology</li> <li>• Erythrodermatous rash involving more than 25% of body surface area and not attributable to a medication</li> <li>• Noncardiogenic pulmonary edema, manifested by diffuse pulmonary infiltrates and hypoxia</li> </ul>
<i>Minor criteria</i>	<ul style="list-style-type: none"> <li>• Hepatic dysfunction with either total bilirubin &gt; 2 mg/dl or transaminases levels &gt; two times normal</li> <li>• Renal insufficiency (serum creatinine &gt; two times baseline)</li> <li>• Weight gain &gt; 2.5% of baseline body weight</li> <li>• Transient encephalopathy unexplainable by other causes</li> </ul>

*A diagnosis of ES is established by the presence of all three major criteria, or two major criteria and one or more minor criteria; the clinical signs and symptoms should appear within 96 hours of neutrophil recovery, according to the above proposed definition.*

- ❑ Neutrophil recovery after transplantation may result in “engraftment syndrome” (which may include fever, rash, edema, hypoxia)
- ❑ The following criteria will be utilized to diagnose engraftment syndrome (must have 3 major criteria or 2 major + 1 minor criteria):
- ❑ To promote consistency of our clinical practice, the following will be the recommended therapy for engraftment syndrome. However, this schedule may be modified (taper either accelerated or delayed) for individual patients as clinical circumstances warrant. In particular, every attempt should be made to rapidly wean steroids due to infection and disease control issues in our patient population.

**Treatment of Engraftment Syndrome without pulmonary edema:**

- attempt to use diuretics first.
- If progression of edema, consider methylprednisolone at 0.5mg/kg/day x 3 days.

**Treatment of Engraftment Syndrome if pulmonary edema is present**

Day 1: Methylprednisolone 250 mg IV Q6 hours x 4 doses  
 Day 2: Methylprednisolone 250 mg IV Q8 hours x 3 doses  
 Day 3: Methylprednisolone 250 mg IV Q12 hours x 2 doses  
 Day 4: Methylprednisolone 125 mg IV Q12 hours x 2 doses  
 Day 5: Methylprednisolone 60 mg IV Q12 hours x 2 doses  
 Day 6: Methylprednisolone 30 mg IV Q12 hours x 2 doses  
 Days 7-8: Prednisone 60 mg PO QD x 2 days  
 Days 9-10: Prednisone 50 mg PO QD x 2 days

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

Days 11-12: Prednisone 40 mg PO QD x 2 days  
Days 13-14: Prednisone 30 mg PO QD x 2 days  
Days 15-16: Prednisone 20 mg PO QD x 2 days  
Days 17-18: Prednisone 10 mg PO QD x 2 days  
Day 19: Discontinue prednisone

*In the event that symptoms or clinical signs of ES recur during the steroid taper, patients should be retreated with methylprednisolone at a minimum dose of 60 mg IV QD. This schema is intended to serve as a guideline and to promote consistency in our clinical practice; it may be modified for individual patients as clinical circumstances warrant. **In particular, steroid dosing for pediatric patients (< 18) will be determined on a case-by-case basis.***



*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

## 12.10 APPENDIX 8A: GRADING AND MANAGEMENT OF ACUTE GRAFT-VERSUS-HOST-DISEASE

Clinical Staging of Acute GVHD to be done/documented day +28, +60, +100 at minimum

<u>Stage</u>	<u>Skin</u>	<u>Liver</u>	<u>Gut</u>
1	Rash < 25% BSA	Total bilirubin 2-3 mg/dl	Diarrhea 500-999ml/d
2	Rash 25-50% BSA	Total bilirubin 3-6 mg/dl	Diarrhea 1000-1499ml/d
3	Rash > 50% BSA	Total bilirubin 6-15 mg/dl	Diarrhea $\geq$ 1500ml/d
4	Generalized erythoderma with desquamation and bullae	Total bilirubin > 15 mg/dl	Severe abdominal pain +/- ileus

BSA = body surface area; use “rule of nines” or burn chart to determine extent of rash.

### Clinical Grading of Acute GVHD

	<u>Stage</u>			
<u>Grade</u>	<u>Skin</u>	<u>Liver</u>	<u>Gut</u>	
0 (none)	0	0	0	
I	1-2	0	0	
II	3 or	1 or	1	
III		2-3 or	2-4	
IV	4 or	4		

**Grade IV may also include lesser organ involvement but with an extreme decrease in performance status.**

### Treatment of Acute GVHD

This schema is intended to serve as a guideline and to promote consistency in our clinical practice; it may be modified for individual patients as clinical circumstances warrant.

#### Grade I GVHD:

- 1) Supportive care or topical corticosteroids (usually 0.1% triamcinolone; 1% hydrocortisone to face) applied to rash BID.

#### Grade II GVHD

- 1) Supportive care or topical corticosteroids or oral/IV corticosteroids as deemed necessary by the clinical providers.

#### Grade III-IV GVHD:

- 1) Methylprednisolone (MP) 1 mg/kg per dose IV, BID for 3 consecutive days.
- 2) If no response after 4 days, continue until response (7-day maximum trial) add second line therapy which could include: MMF, ECP, rituximab, sirolimus, and will be directed based on

organ and severity and patient co-morbidities. 3) Regardless of response within 7 days, taper as follows (note add other agents prior to taper for non-responders):

- a) 0.75 mg/kg per dose IV BID for 7 days.
- b) 0.5 mg/kg per dose IV BID for 7 days.
- c) 0.375 mg/kg per dose IV BID for 7 days.
- d) If clinically appropriate, change MP to oral prednisone to equivalent of IV dose) daily for 2 days. MP may be converted to prednisone later in the taper at the investigators' discretion.
- e) After this, steroids will be reduced by 10% of starting oral dose each week until a dose of 10 mg/day is reached. Subsequent reductions will be made at the investigators' discretion.
- f) If GVHD worsens during taper, steroids should be increased to previous dose.
- g) During steroid taper, maintain tacrolimus at therapeutic levels.

5) *Antifungal prophylaxis with agents effective against mold will be started when it is anticipated that the patient will be receiving steroids at  $\geq 1$  mg/kg/day of methylprednisolone (or equivalent) for  $\geq 2$  weeks. Voriconazole, caspofungin, liposomal amphotericin B (Ambisome), posaconazole, or amphotericin B lipid complex (Abelcet) are valid alternatives. During prophylaxis with any of the above agents, fluconazole should be discontinued. In patients with therapeutic cyclosporine levels at the initiation of voriconazole therapy, the cyclosporine or tacrolimus dose should be decreased by approximately 50%. In patients with therapeutic sirolimus levels at the initiation of voriconazole therapy, the sirolimus dose should be decreased by approximately 90%.*

6) Determination of GVHD treatment response should be made within 96 hours of starting the treatment. The following are criteria to determine definitions of response to GVHD treatment:

- a) Complete response: Complete resolution of all clinical signs and symptoms of acute GVHD.
- b) Partial Response: 50% reduction in skin rash, stool volume or frequency, and/or total bilirubin. Maintenance of adequate performance status (Karnofsky Score  $\geq 70\%$ ).
- c) Non-responder:  $< 50\%$  reduction in skin rash, stool volume or frequency, and/or total bilirubin. Failure to maintain adequate performance status (Karnofsky Score  $\leq 70\%$ ).
- d) Progressive disease: Further progression of signs and symptoms of acute GVHD, and/or decline in performance status after the initiation of therapy.

#### Treatment

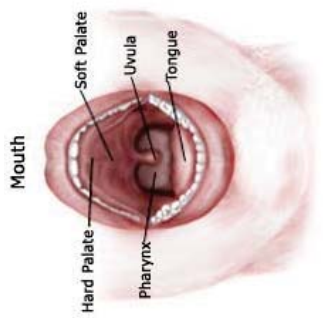
This schema is intended to serve as a guideline and to promote consistency in our clinical practice; it may be modified for individual patients as clinical circumstances warrant.

## 12.11 APPENDIX 8B

Please complete for new diagnosis and follow-up with cGVHD (and/or day +100, 180, 270, 365)

**Current Patient Weight:** \_\_\_\_\_ Today's Date: \_\_\_\_\_ MR#/Name: \_\_\_\_\_

### CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

Component	Findings	Scoring (see skin score worksheet)		
<b>Skin</b>	Erythematous rash of any sort	% BSA (max 100%)		
	Moveable sclerosis	% BSA (max 100%)		
	Non-moveable sclerosis (hidebound/non-pinchable) or subcutaneous sclerosis/fasciitis	% BSA (max 100%)		
	Ulcer(s): select the largest ulcerative lesion, and measure its largest dimension in cm and mark location of ulcer	Location: _____ Largest dimension: _____ cm		
<b>Eyes</b> Bilateral Schirmer's Tear Test (without anesthesia) in persons 9 years or older	Right Eye: _____ mm of wetting Left Eye: _____ mm of wetting			
<b>Mouth</b>				
<b>Mucosal change</b>	<b>No evidence of cGVHD</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
<b>Erythema</b>	None	Mild erythema or moderate erythema (<25%)	Severe erythema (>25%) or Severe erythema (<25%)	Severe erythema (>25%)
<b>Lichenoid</b>	None	Hyperkeratotic changes (<25%)	Hyperkeratotic changes (>25%)	Hyperkeratotic changes (>50%)
<b>Ulcers</b>	None	Non	Ulcers involving (<20%)	Severe ulcerations (>20)
<b>Mucocoeles*</b>	None	1-5 mucocoeles	6-10 scattered mucocoeles	Over 10 mucocoeles
		*Mucocoeles score for lower labial and soft palate only	<b>Total score for all mucosal changes</b>	



70	Both greater restriction of and less time spent in play activity	Cares for self; unable to carry on normal activity or to do active work
60	Up and around, but minimal active play; keeps busy with quieter activities	Requires occasional assistance but is able to care for most personal needs
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities	Requires considerable assistance and frequent medical care
40	Mostly in bed; participates in quiet activities	Disabled; requires special care and assistance
30	In bed; needs assistance even for quiet play	Severely disabled; hospital admission is indicated although death not imminent
20	Often sleeping; play entirely limited to very passive activities	Very sick; hospital admission necessary; active supportive treatment necessary
10	No play; does not get out of bed	Moribund; fatal processes progressing rapidly
0	Unresponsive	Dead

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

## 12.12 APPENDIX 8C: SIGNS AND SYMPTOMS OF CGVHD

<b>ORGAN OR SITE</b>	<b>DIAGNOSTIC</b> (Sufficient to establish the diagnosis of chronic GVHD)	<b>DISTINCTIVE</b> (Seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)	<b>OTHER FEATURES*</b>	<b>COMMON</b> (Seen with both acute and chronic GVHD)
Skin	<ul style="list-style-type: none"> <li>• Poikiloderma</li> <li>• Lichen planus-like features</li> <li>• Sclerotic features</li> <li>• Morphea-like features</li> <li>• Lichen sclerosus-like features</li> </ul>	<ul style="list-style-type: none"> <li>• Depigmentation</li> </ul>	<ul style="list-style-type: none"> <li>• Sweat impairment</li> <li>• Ichthyosis</li> <li>• Keratosis pilaris</li> <li>• Hypopigmentation</li> <li>• Hyperpigmentation</li> </ul>	<ul style="list-style-type: none"> <li>• Erythema</li> <li>• Maculopapular rash</li> <li>• Pruritus</li> </ul>
Nails		<ul style="list-style-type: none"> <li>• Dystrophy</li> <li>• Longitudinal ridging, splitting or brittle features</li> <li>• Onycholysis</li> <li>• Pterygium unguis</li> <li>• Nail loss** (usually symmetric, affects most nails)</li> </ul>		
Scalp and Body Hair		<ul style="list-style-type: none"> <li>• New onset of scarring or non-scarring scalp alopecia, (after recovery from chemoradiotherapy)</li> <li>• Scaling, papulosquamous lesions</li> </ul>	<ul style="list-style-type: none"> <li>• Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes),</li> <li>• Premature gray hair</li> </ul>	
Mouth	<ul style="list-style-type: none"> <li>• Lichen-type features</li> <li>• Hyperkeratotic plaques</li> <li>• Restriction of mouth opening from sclerosis</li> </ul>	<ul style="list-style-type: none"> <li>• Xerostomia</li> <li>• Mucocele</li> <li>• Mucosal Atrophy</li> <li>• Pseudomembranes**</li> <li>• Ulcers**</li> </ul>		<ul style="list-style-type: none"> <li>• Gingivitis</li> <li>• Mucositis</li> <li>• Erythema</li> <li>• Pain</li> </ul>
Eyes		<ul style="list-style-type: none"> <li>• New onset dry, gritty, or painful eyes<sup>†</sup></li> <li>• Cicatricial conjunctivitis</li> <li>• Keratoconjunctivitis sicca<sup>†</sup></li> <li>• Confluent areas of punctate keratopathy</li> </ul>	<ul style="list-style-type: none"> <li>• Photophobia</li> <li>• Periorbital hyperpigmentation</li> <li>• Blepharitis (erythema of the eye lids with edema)</li> </ul>	
Genitalia	<ul style="list-style-type: none"> <li>• Lichen planus-like features</li> <li>• Vaginal scarring or stenosis</li> </ul>	<ul style="list-style-type: none"> <li>• Erosions**</li> <li>• Fissures**</li> <li>• Ulcers**</li> </ul>		
GI Tract	<ul style="list-style-type: none"> <li>• Esophageal web</li> <li>• Strictures or stenosis in the upper to mid third of the esophagus**</li> </ul>		<ul style="list-style-type: none"> <li>• Exocrine pancreatic insufficiency</li> </ul>	<ul style="list-style-type: none"> <li>• Anorexia</li> <li>• Nausea</li> <li>• Vomiting</li> <li>• Diarrhea</li> <li>• Weight loss</li> </ul>

**Abbreviated Title: Lupron & 18F FLT in allo-HSCT****Version Date: December 28, 2017**

<b>ORGAN OR SITE</b>	<b>DIAGNOSTIC</b> (Sufficient to establish the diagnosis of chronic GVHD)	<b>DISTINCTIVE</b> (Seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)	<b>OTHER FEATURES*</b>	<b>COMMON</b> (Seen with both acute and chronic GVHD)
Liver				<ul style="list-style-type: none"> <li>• Failure to thrive (infants and children)</li> <li>• Total bilirubin, alkaline phosphatase &gt; 2 x upper limit of normal<sup>†</sup></li> <li>• ALT or AST &gt; 2x upper limit of normal<sup>†</sup></li> </ul>
Lung	<ul style="list-style-type: none"> <li>• Bronchiolitis obliterans diagnosed with lung biopsy</li> </ul>	<ul style="list-style-type: none"> <li>• Bronchiolitis obliterans diagnosed with PFTs and radiology<sup>†</sup></li> </ul>		<ul style="list-style-type: none"> <li>• BOOP</li> </ul>
Muscles, Fascia, Joints	<ul style="list-style-type: none"> <li>• Fasciitis</li> <li>• Joint stiffness or contractures secondary to sclerosis</li> </ul>	<ul style="list-style-type: none"> <li>• Myositis or polymyositis <sup>†</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Edema</li> <li>• Muscle cramps</li> <li>• Arthralgia or arthritis</li> </ul>	
Hematopoietic and Immune			<ul style="list-style-type: none"> <li>• Thrombocytopenia</li> <li>• Eosinophilia</li> <li>• Lymphopenia</li> <li>• Hypo- or hyper-gammaglobulinemia</li> <li>• Autoantibodies (AIHA, ITP)</li> </ul>	
Other			<ul style="list-style-type: none"> <li>• Pericardial or pleural effusions</li> <li>• Ascites</li> <li>• Peripheral neuropathy</li> <li>• Nephrotic syndrome</li> <li>• Myasthenia gravis</li> <li>• Cardiac conduction abnormality or cardiomyopathy</li> </ul>	

\*Can be acknowledged as part of the chronic GVHD symptomatology if diagnosis is confirmed

\*\*In all cases, infection, drug effect, malignancy or other causes must be excluded.

<sup>†</sup>**Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Schirmer's test foreyes). GVHD (graft versus host disease); ALT (alanine aminotransferase); AST (aspartate aminotransferase); BOOP (bronchiolitis obliterans organizing pneumonia); PFTs (pulmonary function tests); AIHA (autoimmune hemolytic anemia)**



## 12.13 APPENDIX 8D: cGVHD SCORE SHEET

Please complete for new diagnosis and follow-up with cGVHD (and/or day +100, 180, 270, 365)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
<b>PERFORMANCE SCORE:</b> <div style="border: 1px solid black; width: 50px; height: 20px; display: inline-block;"></div> <b>KPS ECOG LPS</b>	<input type="checkbox"/> Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	<input type="checkbox"/> Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	<input type="checkbox"/> Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	<input type="checkbox"/> Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
<b>SKIN</b> <u>Clinical features:</u> <input type="checkbox"/> Maculopapular rash <input type="checkbox"/> Lichen planus-like features <input type="checkbox"/> Papulosquamous lesions or ichthyosis <input type="checkbox"/> Hyperpigmentation <input type="checkbox"/> Hypopigmentation <input type="checkbox"/> Keratosis pilaris <input type="checkbox"/> Erythema <input type="checkbox"/> Erythroderma <input type="checkbox"/> Poikiloderma <input type="checkbox"/> Sclerotic features <input type="checkbox"/> Pruritus <input type="checkbox"/> Hair involvement <input type="checkbox"/> Nail involvement <b>% BSA involved</b> <div style="border: 1px solid black; width: 50px; height: 20px; display: inline-block;"></div>	<input type="checkbox"/> No Symptoms	<input type="checkbox"/> <18% BSA with disease signs but <b>NO</b> sclerotic features	<input type="checkbox"/> 19-50% BSA <b>OR</b> involvement with superficial sclerotic features "not hidebound" (able to pinch)	<input type="checkbox"/> >50% BSA <b>OR</b> deep sclerotic features "hidebound" (unable to pinch) <b>OR</b> impaired mobility, ulceration or severe pruritus
<b>MOUTH</b>	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild symptoms with disease signs but not limiting oral intake significantly	<input type="checkbox"/> Moderate symptoms with disease signs <b>with</b> partial limitation of oral intake	<input type="checkbox"/> Severe symptoms with disease signs on examination <b>with</b> major limitation of oral intake
<b>EYES</b>  Mean tear test (mm): <input type="checkbox"/> >10 <input type="checkbox"/> 6-10 <input type="checkbox"/> ≤5 <input type="checkbox"/> Not done	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) <b>OR</b> asymptomatic signs of keratoconjunctivitis sicca	<input type="checkbox"/> Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), <b>WITHOUT</b> vision impairment	<input type="checkbox"/> Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) <b>OR</b> unable to work because of ocular symptoms <b>OR</b> loss of vision caused by keratoconjunctivitis sicca

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT**Version Date: December 28, 2017*

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
<b>GI TRACT</b>	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	<input type="checkbox"/> Symptoms associated with mild to moderate weight loss (5-15%)	<input type="checkbox"/> Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs <b>OR</b> esophageal dilation
<b>LIVER</b>	<input type="checkbox"/> Normal LFT	<input type="checkbox"/> Elevated Bilirubin, AP*, AST or ALT <2 x ULN	<input type="checkbox"/> Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	<input type="checkbox"/> Bilirubin or enzymes > 5 x ULN
<b>LUNGS*</b>	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild symptoms (shortness of breath after climbing one flight of steps)	<input type="checkbox"/> Moderate symptoms (shortness of breath after walking on flat ground)	<input type="checkbox"/> Severe symptoms (shortness of breath at rest; requiring O <sub>2</sub> )
<b>FEV1</b> <input type="text"/>				
<b>DLCO</b> <input type="text"/>	<input type="checkbox"/> FEV1 > 80% <b>OR</b> LFS=2	<input type="checkbox"/> FEV1 60-79% <b>OR</b> LFS 3-5	<input type="checkbox"/> FEV1 40-59% <b>OR</b> LFS 6-9	<input type="checkbox"/> FEV1 ≤39% <b>OR</b> LFS 10-12
<b>JOINTS AND FASCIA</b>	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) <b>AND</b> not affecting ADL	<input type="checkbox"/> Tightness of arms or legs <b>OR</b> joint contractures, erythema due to fasciitis, moderate decrease ROM <b>AND</b> mild to moderate limitation of ADL	<input type="checkbox"/> Contractures <b>WITH</b> significant decrease of ROM <b>AND</b> significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
<b>GENITAL TRACT</b>	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Symptomatic with mild signs on exam <b>AND</b> no effect on coitus and minimal discomfort with gynecologic exam	<input type="checkbox"/> Symptomatic with moderate signs on exam <b>AND</b> with mild dyspareunia or discomfort with gynecologic exam	<input type="checkbox"/> Symptomatic <b>WITH</b> advanced signs (stricture, labial agglutination or severe ulceration) <b>AND</b> severe pain with coitus or inability to insert vaginal speculum

\* AP may be elevated in growing children, and not reflective of liver dysfunction

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

↑ Esophageal stricture or web ____	↑ Pericardial Effusion ____	↑ Pleural Effusion(s) ____
↑ Ascites (serositis) ____	↑ Nephrotic syndrome ____	↑ Peripheral Neuropathy ____
↑ Myasthenia Gravis ____	↑ Cardiomyopathy ____	↑ Eosinophilia > 500/μl ____
↑ Polymyositis ____	↑ Cardiac conduction defects ____	↑ Coronary artery involvement ____
↑ Platelets <100,000/μl ____	↑ Progressive onset	

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

<sup>†</sup>OTHERS: \_\_\_\_\_

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

## **12.14 APPENDIX 9: ETIB POLICY FOR SAMPLE HANDLING**

Experimental Transplantation and Immunology Branch

Preclinical Service Policy for Sample Handling

### **12.14.1 Sample Processing**

#### **EDTA plasma:**

Spin down cells at 1500 rpm, 10 min, 10°C. Draw off plasma. Store >6 ml of plasma in 1ml conical tubes, labeled as EDTA plasma. Store at -80°C. Heparinized Blood:

Heparinized whole blood is collected for analysis of relevant cytokine/chemokines content. Separate plasma by centrifugation and freeze > 6ml samples in 1ml conical tubes, labeled as heparinized plasma. Store at -80°C.

*If whole blood is being processed for flow cytometry:*

Place 1 ml of well mixed whole blood in a 15ml tube. Add 10ml ACK. Mix well by repeatedly inverting tube. Hold 5 min RT. Spin down (1500 rpm, 10 min, 10°C), Resuspend in 0.5ml FACS buffer. Distribute to staining tubes.

*If whole blood is cryopreserved*

Ficoll blood and cryopreserve cells, divided into two 1ml aliquots. Store in LN2.

Our freezing protocol is attached, but any commercial cryopreserve media will suffice.

### **12.14.2 Labeling**

All samples are to be labeled with an anonymized Patient identifier such as the patient # in the protocol#, date, content (EDTA or heparinized plasma, PBMC with cell number,) and preferably stage (pre, 3m, 6m). We need to be able to link all timepoints collected on a single patient but not an identity.

### **12.14.3 Storage/Tracking in the Preclinical Development and Clinical Monitoring Facility (PDCMF)**

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without IRB notification and an executed MTA. Normal donor and patient blood and tissue samples, collected for the purpose of research under IRB approved protocols of the Experimental Transplantation and Immunology Branch, may be archived by the ETIB Preclinical Service. All data associated with archived clinical research samples is entered into the ETIB Preclinical Services's Microsoft Excel databases on frozen cells and plasma. These databases are stored on the NCI group drive in the ETIB Preclinical Service folder. Access to this folder is limited to ETIB clinical staff, requiring individual login and password. All staff in the Preclinical Service laboratory have received annually updated

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

NIH/CIT training and maintain standards of computer security. Only NIH PI and Adjunct PI may appropriate samples for use and interpret data in the context of the endpoints of this trial.

The data recorded for each sample includes the patient ID, name, trial name/protocol number, date drawn, treatment cycle/post transplant time point, cell source (e. g. peripheral blood, lymphapheresis, mobilized peripheral blood stem cells, marrow, pleural fluid) as well as box and freezer location. Patient demographics that correlate treatment outcomes and therapies with the samples can be obtained only through the NCI/ETIB clinical records or NCI C3D. As of January 2007, all newly received samples will receive a unique bar code number, which will be added to the sample Preclinical Service database. Only this bar code will be recorded on the sample vial and the vials will not be traceable back to patients without authorized access to the Preclinical Service database. All non-coded samples previously archived will be stripped of identifiers prior to distribution for any use other than as a primary objective of the protocol under which they were collected.

Samples are stored in locked freezers. All samples will be labeled solely with a bar code (which includes the date, and serially determined individual sample identifier). The key will be available to a restricted number of ETIB investigators and associate investigators on the protocol. Coded samples will be stored frozen at -20°, -80° or liquid nitrogen vapor phase according to the stability requirements under the restricted control of the PDCM Facility of ETIB..

Access to samples from a protocol for research purposes will be by permission of the Principal Investigator of that protocol in order to be used (1) for research purposes associated with protocol objectives for which the samples were collected, or (2) for a new research activity following submission and IRB approval of a new protocol and consent, or (3) for use only as unlinked or coded samples under the OHSRP Exemption Form guidelines stipulating that the activity is exempt from IRB review. Unused samples must be returned to the PDCMF laboratory.

Samples, and associated data, will be stored permanently unless the patient withdraws consent. If researchers have samples remaining once they have completed all studies associated with the protocol, they must be returned to the PDCMF laboratory.

These freezers are located onsite at the PDCMF laboratory (12C216) or in ETIB common equipment space (CRC/3-3273).

#### 12.14.4 Protocol Completion/Sample Destruction

Once primary research objectives for the protocol are achieved, researchers can request access to remaining samples, providing they have both approval of the Principal Investigator of the original protocol under which the samples or data were collected and either an IRB approved protocol and patient consent or the OHSRP Exemption Form stipulating that the activity is exempt from IRB review..

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

The PDCMF staff will report to the Principal Investigators any destroyed samples, if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container), lost in transit between facilities or misplaced by a researcher.

The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

#### 12.14.5 Handling for subjects at other Participating Institutions

- Blood specimen obtained from University of Oklahoma and Children's National Medical Center may be frozen as above, stored, and shipped in batch to NCI. The specimens should be shipped to arrive Monday-Friday, to Dr. Fran Hakim's ETIB Core lab (Bldg 10, room 12C216. Attention Jeremy Rose phone: 301-594 5339, 10 Center Drive, CRC 3-3330, Bethesda, MD 20892.

**12.15 APPENDIX 10: DATA COLLECTION ELEMENTS REQUIRED BY PROTOCOL**

All of the following elements will be recorded in the C3D database.

**A. Patient Enrollment****Recipient**

- Date of birth, age, gender, race, ethnicity
- Height
- Weight
- Performance Status
- Date of original diagnosis
- Stage at diagnosis
- Stage at study entry
- Sites of disease at diagnosis and study entry
- Tumor Histology and date of confirmation
- Date of Informed Consent signature, consent version and date of registration
- Baseline History/Physical
- Baseline Symptoms
- Prior therapy
- Prior surgery
- Findings of consultations done at screening
- ABO

**Donor**

- Date of birth, age, gender, race, ethnicity
- Height
- Weight
- Baseline History/Physical (Y/N)
- Serology (CMV)
- ABO

**B. Study Drug administration and response for each course of therapy given**

- Dates study drugs given
- Dose level, actual dose, schedule and route given
- Height, weight, and body surface area at start of each course
- Response assessment for each restaging performed
- For women, the administration of estrogen supplementation will be captured.

**C. Laboratory and Diagnostic Test Data**

- All Clinical laboratory and diagnostic test results done at screening (recipient and donor) and until day 365 post transplant with the following exceptions:



- Diagnostic tests which are not specified in the protocol, and if the results are not needed to document the start or end of an adverse event that requires reporting.
- All clinical laboratory and diagnostic tests done after day 100 that support a possible, probable or definite diagnosis of GVHD, infection or secondary malignancy and those done to document a change in grade and the end of these adverse events.
- All tests done to document resolution of adverse events that occurred in the first 100 days post transplant
- HLA data (patient and donor).
- Serologies-CMV, HSV, EBV, toxoplasmosis, adenovirus (patient and donor)
- TTV data (patient and donor)
- Blood, bone marrow, and tumor chimerism data
- FEV1, DLCO (adjusted but not /VA) pre-transplant
- EF pre-transplant
- Acute care, hepatic, and mineral panel plus LDH at transplant
- GFR or CrCL pre-transplant
- Complete blood count pre-transplant
- Lymphocyte total number, % CBC, and TBNK at research time points for primary endpoint
- IgA, IgM, IGG at research primary endpoints
- Engraftment endpoints: neutrophil, plt, hbg
- LH/FSH/sex hormone levels
- Vaccine serologies.

#### D. Adverse Events

- All grade 2, 3, or 4 adverse events possibly, probably, or definitely attributable to lupron or the IND and all serious adverse events will be recorded.
- Data will also be reported to the Center for International Bone Marrow Transplant Registry

#### E. Concomitant Measures

- Baseline medications
- Antibiotics
- GVHD prophylaxis and treatment
- Other therapy for recorded adverse events

#### F. Treatment of Persistent/Progressive Disease with Standard Therapy

- Chemotherapy
- Immunotherapy
- Radiation therapy

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

- Donor Lymphocyte Infusion

G. Tumor response and measurements

- Restaging studies performed at protocol specified time points and as clinically indicated.

H. Off study

- Date and reason for off study
- Date and cause of death
- Autopsy findings
- PI decision to end this study

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

## 12.16 APPENDIX 11: PROBLEM REPORT FORM

<b>NCI Protocol #:</b>	<b>Protocol Title:</b>
	<b>Report version: (select one)</b> ____ Initial Report ____ Revised Report ____ Follow-up
<b>Site Principal Investigator:</b>	
<b>Date of problem:</b>	<b>Location of problem: (e.g., patient's home, doctor's office )</b>
<b>Who identified the problem? (provide role (not name of person): nurse, investigator, monitor, etc...)</b>	
<b>Brief Description of Subject (if applicable)</b> (Do NOT include personal identifiers)	Sex: ____ Male ____ Female      Age: ____ ____ Not applicable (more than subject is involved)
<b>Diagnosis under study:</b>	
<b>Name the problem: (select all that apply)</b> <input type="checkbox"/> Adverse drug reaction <input type="checkbox"/> Abnormal lab value <input type="checkbox"/> Death <input type="checkbox"/> Cardiac Arrest/ code <input type="checkbox"/> Anaphylaxis <input type="checkbox"/> Sepsis/Infection <input type="checkbox"/> Blood product reaction <input type="checkbox"/> Unanticipated surgery/procedure <input type="checkbox"/> Change in status (e.g. increased level of care required) <input type="checkbox"/> Allergy (non-medication) <input type="checkbox"/> Fall <input type="checkbox"/> Injury/Accident (not fall) <input type="checkbox"/> Specimen collection issue <input type="checkbox"/> Informed consent issue <input type="checkbox"/> Ineligible for enrollment <input type="checkbox"/> Breach of PII	

<input type="checkbox"/> Tests/procedures not performed on schedule <input type="checkbox"/> Other, brief 1-2 word description: _____
<b>Detailed Description of the problem:</b> <i>(Include any relevant treatment, outcomes or pertinent history):</i>  
<b>*Is this problem unexpected?</b> <i>(see the definition of unexpected in the protocol)</i> __YES __NO Please explain:
<b>*Is this problem related or possibly related to participation in the research?</b> __YES __NO Please explain:
<b>*Does the problem <u>suggest</u> the research places subjects or others at a greater risk of harm than was previously known or recognized?</b> __YES __NO Please explain:
<b>Is this problem?</b> <i>(select all that apply)</i> <input type="checkbox"/> An Unanticipated Problem* that is: <input type="checkbox"/> Serious <input type="checkbox"/> Not Serious <input type="checkbox"/> A Protocol Deviation that is: <input type="checkbox"/> Serious <input type="checkbox"/> Not Serious <input type="checkbox"/> Non-compliance <i>*Note if the 3 criteria starred above are answered, "YES", then this event is also a UP.</i>
<b>Is the problem also</b> <i>(select one)</i> <input type="checkbox"/> AE <input type="checkbox"/> Non-AE
<b>Have similar problems occurred on this protocol at your site?</b> __YES __NO <b>If "Yes", how many?</b> _____ <b>Please describe:</b>
<b>Describe what steps you have already taken as a result of this problem:</b>  
<b>In addition to the NCI IRB, this problem is also being reported to:</b> <i>(select all that apply)</i> <input type="checkbox"/> Local IRB <input type="checkbox"/> Study Sponsor <input type="checkbox"/> Manufacturer : _____ <input type="checkbox"/> Institutional Biosafety Committee <input type="checkbox"/> Data Safety Monitoring Board <input type="checkbox"/> Other: _____ <input type="checkbox"/> None of the above, not applicable

*Abbreviated Title: Lupron & 18F FLT in allo-HSCT*

*Version Date: December 28, 2017*

<b>INVESTIGATOR'S SIGNATURE:</b>	<b>DATE:</b>
----------------------------------	--------------