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DEPARTMENT OF RADIATION ONCOLOGY

TITLE: Phase I Study of Escalating Doses of 90Y-DOTA-anti-CD25 Monoclonal Antibody Added to the Conditioning Regimen of Fludarabine, Melphalan and Organ Sparing Total Marrow and Lymphoid Irradiation (TMLI) as Conditioning for Allogeneic Hematopoietic Cell Transplantation in Patients with High-Risk Acute Leukemia, Myelodysplastic Syndrome or Non-Hodgkin's Lymphoma

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Clinical Trial Protocol

Phase I Study of Escalating Doses of ^{90}y-DOTA-Anti-CD25 Basiliximab Monoclonal Antibody Added to the Conditioning Regimen of Fludarabine, Melphalan and Organ Sparing Total Marrow and Lymphoid Irradiation (TMLI) as Conditioning for Allogeneic Hematopoietic Cell Transplantation in Patients with High-Risk Acute Leukemia, Myelodysplastic Syndrome, or Non-Hodgkin's Lymphoma

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Short Title	^{90}Y-Basiliximab and TMLI added to Flu/Mel conditioning for allogeneic HCT for high-risk acute leukemias and MDS

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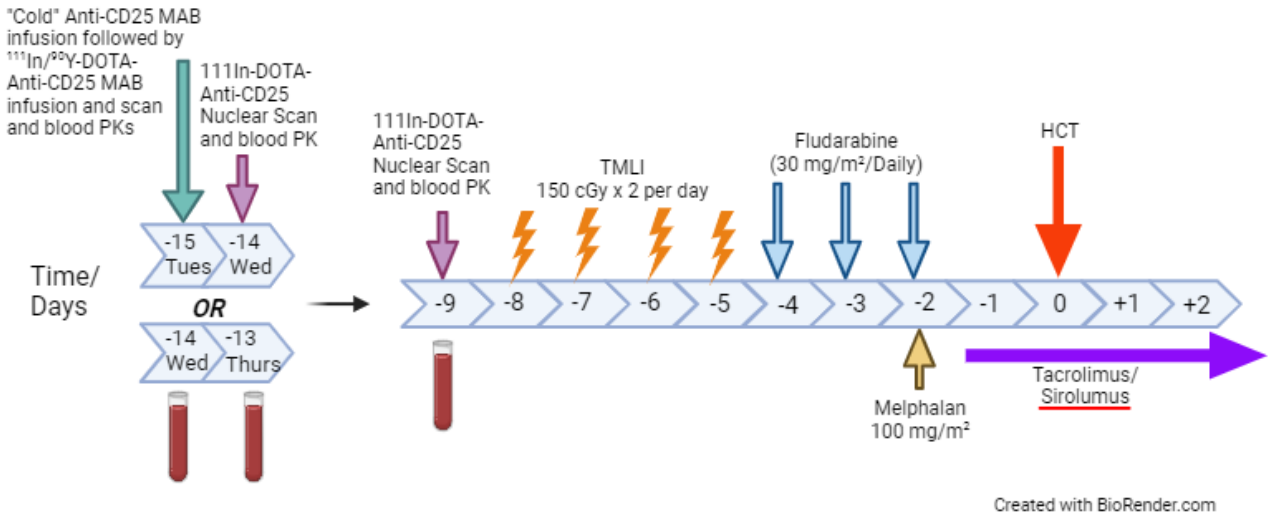
STUDY SCHEMA



Schema created with BioRender.com

HCT: Hematopoietic cell transplantation.
Note: A window of ±2 days is allowed for stem cell infusion.
The infusion of ^{90}Y-DOTA-anti-CD25 Basiliximab will be followed by serial blood (5 cc) samples at approximately time 1-2 hours, 3-4 hours, and at scan times of 1 day and 5/6 days after radiolabeled antibody infusion.
Planar serial nuclear scans will be performed on the day of infusion, 1 day post infusion and the day prior to TMLI start (day 5 or 6 post infusion). A SPECT scan will be performed at the 1 day post infusion timepoint.

PROTOCOL SYNOPSIS

Protocol Title	
Phase I Study of Escalating Doses of $^{90y\text{-}DOTA\text{-}Anti\text{-}CD25}$ Basiliximab Monoclonal Antibody Added to the Conditioning Regimen of Fludarabine, Melphalan and Organ Sparing Total Marrow and Lymphoid Irradiation (TMLI) as Conditioning for Allogeneic Hematopoietic	
Study Detail	
Population/Indication(s):	Acute leukemia/myelodysplastic syndrome, non-Hodgkin's lymphoma
Phase:	1
Sample Size:	12-15
Estimated Accrual Duration:	60 months
Estimated Study Duration	60 months
Participant Duration:	24 months
Study Agents:	^{90}y-DOTA-Anti-CD25 Basiliximab Monoclonal and TMLI.....
Study Design	
Myeloablative radiation and chemotherapy containing conditioning regimens followed by allogeneic HSCT rescue is an important treatment modality to improve long-term survival in patients with leukemia in first remission (1-3) as well as patient with more advanced acute myeloid leukemia (AML) and those with relapsed/refractory non-Hodgkin's lymphoma (NHL). The principal high-dose preparative or conditioning regimens administered before bone marrow transplantation include total-body irradiation (TBI) together with cyclophosphamide (CY) or other chemotherapy (4;5) (6;7). Various studies utilizing different myeloablative regimen have shown a long-term survival for AML patients in first remission between 50-80% (2;8-13). Three-year survival rates after HCT for patients with refractory or relapsed acute leukemia are significantly worse at 20% and new and novel conditioning regimens are needed for this population (14;15). TMLI is a form of targeted systemic radiotherapy that utilizes CT imaging to identify where to preferentially target radiotherapy. Radioimmunotherapy (RIT) is also a form of targeted systemic radiotherapy that utilizes monoclonal antibodies or related immunoconstructs linked to radionuclides to preferentially target cells that express a specific antigen. Studies to date demonstrate the promise of targeted systemic radiotherapy using either TMLI or RIT. Rather than being viewed as competing approaches, these two forms of targeted therapy should be viewed as complementary which when rationally combined can address the limitations of each modality. The addition of RIT to TMLI will likely add additional dose to marrow and leukemia cells without a significant increase in mucositis. Finally, the addition RIT helps to address the theoretical concern of sparing of leukemia cells in circulation and in areas of reduced dose with TMLI.	

Objectives

Primary Objective(s)

- Determine the maximum tolerated dose/recommended phase II dose (MTD/RP2D) of ^{90}Y-DOTA-anti-CD25 radioimmunotherapy with fixed doses of organ sparing TMLI, fludarabine and melphalan (FM 100) as conditioning regimen for allogeneic hematopoietic cell transplantation (HCT) for treatment of High-Risk Acute Leukemias or Myelodysplastic Syndrome (MDS) or non-Hodgkin's lymphoma (NHL), in patients who are not eligible for standard myeloablative regimens.
- Describe toxicities attributable to ^{90}Y-DOTA-anti-CD25 Basiliximab radioimmunotherapy containing regimen by dose level in patients treated under this regimen.

Secondary Objective(s)

Evaluate the safety of the regimen, at each dose level, by assessing the following:

- type, frequency, severity, attribution, time course and duration of adverse events, including acute/chronic GVHD, infection and delayed engraftment

Estimate overall survival (OS), event-free survival (EFS), GVHD Relapse Free Survival (GRFS), cumulative incidence (CI) of relapse/progression, and non-relapse mortality (NRM) at 100 days, 1 year and 2 years

- Describe biodistribution, pharmacokinetics and organ dosimetry of ^{90}Y-DOTA-anti-CD25 Basiliximab.

Endpoints

- The primary endpoint is: Toxicity
- Secondary Endpoints are Overall survival, event-free survival, cumulative incidence of relapse/progression, CR proportion at day +30, non-relapse infection, neutrophil recovery, acute GVHD of grades 2-4 and 3-4, chronic GVHD, and incidence, frequency and severity of CRS.

Intervention Description

This is a single-institution, non-randomized phase I trial to determine the maximum tolerated dose/ recommended phase II dose (MTD/RP2D) of ^{90}Y-DOTA-antoCD25 Basiliximab MAB when given in combination with fixed doses of fludarabine, melphalan, and 1200 cGy TMLI as conditioning regimen to patients with high-risk acute leukemia (lymphocytic or myelogenous), myelodysplastic syndrome or non-Hodgkin's lymphoma (NHL), who undergo alloHCT with matched related/unrelated donor.

Dose escalation will be based on a modified rolling 6 Phase I design, with dose level 1 starting at 0.3 mCi/Kg to a maximum dose level of 0.5 mCi/kg. There will also be a dose level -1 of 0.2 mCi/kg in the case that dose level 1 is too toxic

Main Eligibility Criteria

Main Inclusion Criteria

- Eligible patients will have a histopathological confirmed diagnosis of hematologic malignancy in acute myelogenous leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, or non-Hodgkin's lymphoma.
- Demonstration of CD25 expression by flow cytometry, immunohistochemistry or elevated CD25 serum levels
- Patients must be ≥ 18 years of age.
- Karnofsky performance status ≥70
- Eligible for allogeneic hematopoietic cell transplantation
- Patients should have discontinued all previous intensive therapy, chemotherapy or radiotherapy for 2 weeks prior to commencing therapy on this study.
- Adequate organ function.
- All candidates for this study must have an HLA (A, B, C, and DRB1) identical sibling who is willing to donate peripheral blood stem cells (preferred) or bone marrow, or have a 10/10 allele matched unrelated donor. A single allele mismatch at DQ will be allowed.

Main Exclusion Criteria

- Have any uncontrolled illness including ongoing or active bacterial, viral or fungal infection.
- Receiving any other investigational agents or concurrent biological, intensive chemotherapy or radiation therapy for the previous 2 weeks from conditioning*.

  *(NOTE: Low dose Chemotherapy or maintenance chemotherapy given within 7 days of planned study enrollment is permitted. These include: Hydroxyurea, 6-meraptopurine, oral methotrexate, vincristine, oral etoposide, and tyrosine kinase inhibitors (TKIs). FLT-3 inhibitors can also be given up to 3 days before conditioning regimen.)
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to any in the regimen.
- Patients with other active malignancies are ineligible for this study, other than non-melanoma skin cancers.
- The recipient has a medical problem or neurologic/psychiatric dysfunction which would impair his/her ability to be compliant with the medical regimen and to tolerate transplantation or would prolong hematologic recovery which in the opinion of the principal investigator would place the recipient at unacceptable risk.
- Patients may not have had a prior allogeneic transplant.
- No prior transplant BCNU conditioning
- For patients with leukemia or MDS: Patients may not have received more than 3 prior regimens, where the regimen intent was to induce remission.
- All patients with prior radiation treatment to the lung, liver, and kidney will be excluded.
- Patients who have recived prior total skin electron beam therapy for lymphoma are excluded
- Patients who have recived prior radiopharmaceutical therapy are excluded
- Inclusion of other patients with previous radiation exposure will be determined based on the radiation oncologist MD PI evaluation and judgement.

Special Assessments and Monitoring

- Correlative blood, bone marrow samples
- Special monitoring immune-related Aes, etc.

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Meaning
AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
Cy	Cyclophosphamide
DCC	Data Coordinating Center
DLT	Dose Limiting Toxicity
DSMC	Data & Safety Monitoring Committee
DSMP	Data & Safety Monitoring Plan
EOT	End of Treatment
FDA	Food and Drug Administration
FM	Fludarabine/Melphalan
GCP	Good Clinical Practice
GRFS	GVHD-free Relapse-free survival
GVHD	Graft-versus-Host Disease
HCT	Hematopoietic Cell Transplantation
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IDS	Investigational Drug Services
IND	Investigational New Drug
IRB	Institutional Review Board
MAC	Myeloablative Conditioning
MDS	Myelodysplastic Syndrome
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NIH	National Institutes of Health
NRM	Non-Relapse Mortality
OCTM	Office of Clinical Trials Monitoring
OIDRA	Office of IND Development and Regulatory Affairs
OS	Overall Survival
PD	Progressive Disease
PI	Principal Investigator
PMT	Protocol Management Team
PR	Partial Response
RIC	Reduced Intensity Conditioning
RIT	Radioimmunotherapy
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SD	Stable disease
TBI	Total Body Irradiation
TMI	Total Marrow Irradiation
TMLI	Total Marrow and Lymphoid Irradiation
UT	Unacceptable Toxicity

1.0 OBJECTIVES

1.1 Primary Objective(s)

- Describe toxicities attributable to ^{90}Y-DOTA-anti-CD25 Basiliximab radioimmunotherapy by dose level in patients treated under this regimen.
- Determine the maximum tolerated dose/recommended phase II dose (MTD/RP2D) of ^{90}Y-DOTA-anti-CD25 Basiliximab radioimmunotherapy with fixed doses of organ sparing TMLI (12 Gy), fludarabine and melphalan (FM100) as conditioning regimen for allogeneic hematopoietic cell transplantation (HCT) for treatment of High-Risk Acute Leukemias or Myelodysplastic Syndrome (MDS) or non-Hodgkin's lymphoma (NHL), in patients who are not eligible for standard myeloablative regimens.

1.2 Secondary Objective(s

- Evaluate the safety of the regimen, at each dose level, by assessing the following:
    - type, frequency, severity, attribution, time course and duration of adverse events, including acute/chronic GVHD, infection and delayed engraftment.
- Estimate overall survival (OS), event-free survival (EFS), GVHD relapse free survival (GRFS), cumulative incidence (CI) of relapse/progression, and non-relapse mortality (NRM) at 100 days, 1 year and 2 years
- Describe biodistribution, pharmacokinetics and organ dosimetry of ^{90}Y-DOTA-basiliximab

2.0 BACKGROUND

2.1 Myeloablative Conditioning Regimens for HCT in Acute Myelogenous Leukemia (AML)

Myeloablative radiation and chemotherapy containing conditioning regimens followed by allogeneic HSCT rescue is an important treatment modality to improve long-term survival in patients with AML in first remission (1-3) as well as patient with more advanced AML. The principal high-dose preparative or conditioning regimens administered before bone marrow transplantation include total-body irradiation (TBI) together with cyclophosphamide (CY) or other chemotherapy (4;5) (6;7). Various studies utilizing different myeloablative regimen have shown a long-term survival for AML patients in first remission between 50-80% (2;8-13). Three-year survival rates after HCT for patients with refractory or relapsed acute leukemia are significantly worse at 20% and new and novel conditioning regimens are needed for this population (14;15).

An alternative to CY/TBI treatment in pretransplant conditioning is the use of chemotherapy only, mostly busulfan and cyclophosphamide (BU/CY). Two Bu/CY regimens are commonly used: Bu/CY4, busulfan 16 mg/kg and cyclophosphamide 200 mg/kg each given over 4 days, and Bu/CY2, busulfan 16 mg/kg given over 4 days and cyclophosphamide 120 mg/kg given over 2 days (16;17). These regimens have been extensively studied in acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML). Several randomized trials have shown superior outcomes using fractionated total body irradiation (FTBI) compared with non-TBI containing regimens (11;18-21).

2.1.1 Allogeneic HCT for non-Hodgkin's Lymphomas

Although substantial therapeutic innovations in particular for B-cell lymphoma have entered the clinical stage recently, or are at the doorstep, Allogeneic HCT remains as a potential curative treatment for advanced non-Hodgkin's lymphoma (NHL), especially for patients with chemo-refractory disease, relapsed after prior autologous HCT and those with relapsed lymphoma who failed to collect adequate stem cells for autologous HCT. Unfortunately, cure rates with allogeneic HCT is only 55% and potent conditioning regimens including radiotherapy in conditioning are needed to improve outcomes in this patient population.

2.2 Total Body Irradiation: The Earliest Form of Systemic Radiotherapy

Since the initial pioneering efforts of Thomas and colleagues (22) radiation therapy continues to be an important part of conditioning regimens in patients undergoing hematopoietic cell transplantation (HCT). Radiation therapy is used primarily as a form of systemic therapy utilizing high energy photons and large fields to deliver total body irradiation (TBI). TBI is often part of the conditioning regimen in patients with leukemia undergoing allogeneic HCT. The primary indications for allogeneic HCT in acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL) are patients in first remission with intermediate to high risk features, induction failure, relapse, or in second remission or beyond. Patients with myelodysplastic syndrome (MDS) with high risk features or evolving to an acute state are also candidates for allogeneic HCT. The role of TBI in patients with multiple myeloma undergoing HCT is less well defined but has been used in patients undergoing autologous or allogenic HCT.

There are several advantages to using TBI as part of the conditioning regimen. TBI is effective at eradicating malignant cells, which for most hematologic malignancies are very radiosensitive. TBI also provides a powerful means of immunosuppression to prevent rejection of donor hematopoietic cells in patients undergoing allogeneic HCT. TBI offers distinct advantages compared to chemotherapy. Delivery of radiation therapy to the tumor site is not dependent on blood supply or influenced by inter-patient variability of drug absorption, metabolism, biodistribution, or clearance kinetics. Radiation therapy can reach potential sanctuary sites, such as testes and brain. Chemotherapy resistant clones that develop may still be sensitive to irradiation. Finally, non-TBI chemotherapy only conditioning regimens offer no obvious advantage in reducing toxicities or improving control rates compared to TBI containing regimens (23-28).

2.3 Limitations to TBI

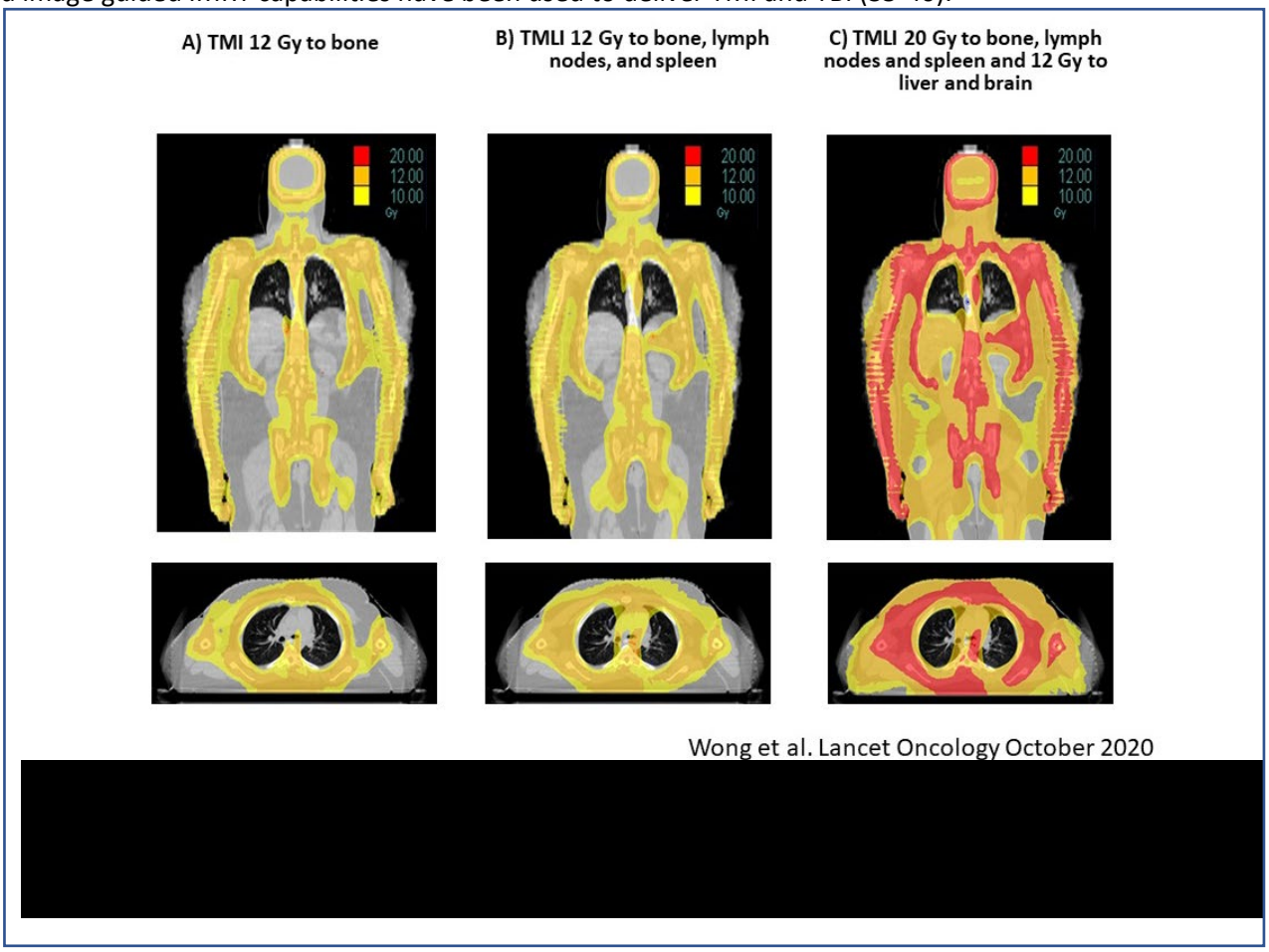
Understanding the limitations of TBI in the context of evolving strategies being used in HCT provide the basis for developing new more targeted radiotherapy approaches. A major limitation is that the recent technological advances in image guided organ sparing IMRT delivery have not been applied to the delivery of TBI. The traditional methods of delivering TBI developed over 30 years ago, utilize large opposed whole body fields, and are the least conformal in radiation oncology (29). This can result in dose heterogeneity of over 30% which would be unacceptable in any other clinical scenario (30). Although lung blocking has reduced the risks of pneumonitis and lethal pulmonary toxicity, recent studies have demonstrated that mean lung doses below 8 Gy, which are challenging to achieve using conventional TBI delivery methods, are needed to further reduce lung toxicity risks and improve overall survival.

A second challenge is the utilization of TBI is declining due to lack of new strategies to reduce TBI toxicities and the introduction of alternative non-TBI approaches. In a survey of the Center for International Blood and Transplant Research (CIBMTR) Database which surveyed 596 centers in 52 countries and included 219,341 patients from 1995-2010, TBI utilization decreased for both autologous (13% to 2% $p < 0.0001$) and allogeneic HCT (53% to 39%, $p < 0.0001$)(31). Reasons for this decline include the additional resources needed to perform TBI and concerns for TBI related acute and late effects, including second malignancies (32). Patients older than age 60, with co-morbidities or with poor performance status are not able to undergo TBI. As a result there has been increasing use of chemotherapy only myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC) regimens. In addition, the perspective of hematologists has evolved from viewing allogeneic HCT primarily as a cytotoxic tool to more of an immunologic tool which relies more on graft versus tumor effects for disease control. In an increasing number of clinical scenarios, TBI is no longer the primary modality but added when increased cytoreduction and immunosuppression are needed, and only if it can be added without significant additional toxicity.

2.4 Development of Organ Sparing Targeted TMI and TBI Using IG-IMRT

More targeted forms of TBI are needed to address these challenges and to redefine and expand the role of radiotherapy in HCT. Recent technological advances in radiotherapy systems now allow for the delivery of image

guided intensity modulated radiation therapy (IG-IMRT) to large regions of the body allowing for more targeted forms of TBI. These new forms of image guided targeted TBI are often referred to as total marrow irradiation (TMI) or total marrow and lymphoid irradiation (TMLI) and represent a spectrum of targeted TBI dose distributions now being performed at multiple institutions (**Figure 2.1**). The Tomotherapy HiArt System® was the first system used to deliver targeted TMI which integrated CT image-guided radiotherapy and helical delivery of IMRT in a single device (33). The first delivery of TMI was in 2005 (34) . More recently, linear accelerators with volumetric arc-based image guided IMRT capabilities have been used to deliver TMI and TBI (35-40).



This approach offers the radiation oncologist and transplant team unprecedented control of TBI radiation dose delivery to target regions and organs. The physician can simultaneously reduce dose to critical organs or any other user-defined avoidance structure, while simultaneously increasing dose to target regions depending on the tumor burden and clinical situation. **Figure 2.1** shows conformal dose distribution patterns that have been delivered to designated target structures, with simultaneous reduction of dose to critical organs. The term TMI (total marrow irradiation) has been used if the target structure is bone, although it has also been used if additional sites of disease (i.e. extramedullary leukemia) have been targeted. The term TMLI (total marrow and lymphoid irradiation) has been used to reflect the addition of the major lymph node chains as target regions. In some studies and clinical scenarios liver, brain and testes have been included as target regions. (41)

Table 2.1 compares the median (D50) doses for various normal organs at risk (OAR) delivered through standard TBI to 12 Gy with 50% transmission blocks for lung shielding and electron boost to the underlying chest wall versus TMI to 12 Gy to the skeletal bone in an initial test case (34). Significant reduction in dose and volume of organ receiving full dose is observed compared to standard TBI for all critical organs. Initial planning comparison studies

demonstrated that TMI could result in median organ doses that were approximately 15-65% of the prescribed dose to the target structure and predicted a reduction of acute and late toxicities compared to TBI. At TMI doses up to 20 Gy, median doses to all organs were still below that of TBI to 12 Gy. Comparison of lung DVH plots demonstrated that at 20 Gy TMI median (D50) lung doses remained below that of TBI 12 Gy with lung shielding and the D80 (minimum dose to at least 80% of the lung volume) was comparable, predicting for similar pneumonitis risks with TMI 20 Gy compared to TBI 12 Gy (34).

Table 2.1. Comparison of median doses TMI versus TBI

Organ at Risk	Median Dose (Gy) TMI	Median Dose (Gy) TBI	TMI/TBI Median Dose
Bladder	7.5	12.3	0.61
Brain	7.1	12.2	0.58
Breast	7.7	12.4	0.62
Esophagus	4.9	11.7	0.42
Orbits	6.0	12.0	0.50
Heart	6.1	11.5	0.53
Lens	2.3	10.5	0.22
Liver	6.9	11.7	0.59
Left Kidney	7.4	11.9	0.62
Right Kidney	6.9	11.9	0.58
Left Lung	6.3	9.0	0.70
Right Lung	6.4	9.7	0.66
Optic Nerve	6.4	12.3	0.52
Oral Cavity	2.5	12.5	0.20
Ovary	7.0	12.5	0.56
Parotids	4.6	13.1	0.35
Rectum	4.8	12.6	0.38
Small Intestine	5.0	12.5	0.40
Stomach	4.6	11.5	0.40
Thyroid	4.4	12.6	0.35

2.5 Dose escalation of TMI or TMLI to improve disease control in advanced refractory leukemia

The available clinical data indicate that there is a dose response for acute leukemia, particularly with AML. Chak et al. (42) demonstrated local control rates for chloromas treated at 2 Gy per day of approximately 20% at doses less than 10 Gy, 40% at doses of 10-20 Gy and over 80% at doses of > 20 Gy. A dose response relationship is also suggested from the TBI experience. Retrospective studies have observed a decrease in relapse rate with higher TBI doses (43-45). Two randomized phase II single institution trials have compared cyclophosphamide (Cy) combined with 12 Gy at 2 Gy/day or 15.75 Gy at 2.25 Gy/day. In a trial of 116 patients with CML in chronic phase, the higher dose resulted in a significantly lower relapse rate (0% versus 25% p = 0.008), but higher treatment related mortality (TRM) rate (24% 12 Gy and 34% 15.75 Gy, p = 0.13), and as a result no significant change in overall survival (46). In a separate report of 71 patients with AML in first remission, relapse rate was also decreased with the higher dose (14% versus 39% p = 0.06), but an increase in TRM rate was observed (38% versus 19%, p = 0.05), resulting in no difference in overall survival between the two arms (47). In summary escalation of TBI dose has been difficult. Gains in disease control are offset by an increase in regimen related toxicities, resulting in no improvement in overall survival(48). TMI offers the potential to escalate dose to reduce relapse rates without a significant increase in acute or late toxicities due to critical organ sparing.

In younger patients (< 60 years of age) with acute leukemia dose escalation of TMLI has been feasible with acceptable toxicities. TMLI dose escalation was also evaluated in combination with Cy and VP-16 (49). A phase I trial in 51 patients with relapsed or refractory AML and ALL underwent a conditioning regimen of escalating doses of TMLI (range 12-20 Gy, days -10 to -6) with Cy (100 mg/kg day -3) and VP-16 (60 mg/kg day -5). Fifty patients had detectable blasts in marrow (median 52%, range 5-98% involvement) and 27 patients had circulating blasts in the week prior to HCT conditioning. Dose-limiting toxicity was observed in only one patient at the 15 Gy dose level (grade 3 mucositis Bearman scale (48) and no further dose limiting toxicities were observed up to 20 Gy. All patients engrafted without delays. The maximum tolerated dose was declared at 20 Gy since, as noted earlier, TMI planning studies resulted in comparable lung D80 doses and predicted pneumonitis risks compared to standard 12 Gy TBI. Treatment related mortality (TRM) rates were 3.9% at day 100 and 8.1% at one year. With a median follow-up of 24.6 months in surviving patients, the overall one-year survival was 55.5% and progression free survival 40.0%. The authors concluded that the TMLI/CY/Etoposide conditioning regimen was feasible with acceptable toxicities at TMLI doses up to 20 Gy and with encouraging results in this very poor risk population. A phase II trial is currently ongoing with the primary endpoint of 2 year progression free survival. Recently reported interim results for the Phase II study are similar to those previously reported for the phase I study (50). All patients engrafted. The complete remission rate at day +30 was 92%. With a median follow-up of 16.1 months, the two-year estimates of overall survival (OS) and progression free survival (PFS) were 41% (95% CI:25-56) and 27% (95% CI: 13-42), respectively. Disease relapse/progression at 2 year was 64.6% (95% CI: 50-82). The estimates of TRM at 100 days and 1 year were 6% (95% CI: 1-21) and 8% (3-25).

2.6 TMI or TMLI added to reduced intensity conditioning (RIC) regimens

Older patients (older than age 55-60) or patients with co-morbidities are often not able to tolerate standard myeloablative TBI containing regimens. For this population reduced intensity conditioning (RIC) regimens have been developed which utilize lower chemotherapy or TBI doses (51). These regimens are better tolerated, less cytotoxic, and rely more on the graft versus tumor (GVT) effects to eradicate disease. RIC regimens being less myeloablative can be associated with increased relapse rates. In a recent multi-center phase III randomized trial in patients with AML in first remission or with MDS, the relapse rate was significantly higher (48.3% versus 13.5%, $p < 0.01$) and the relapse free survival (RFS) rate was significantly lower (47.3% versus 67.7%, $p < 0.01$), resulting in an 18 month overall survival difference of 67.7% versus 77.4% ($p = 0.07$) (52). Adding standard 9 Gy TBI to an RIC regimen has resulted in unacceptable toxicities in adults (53). Recently a regimen of low dose TBI (2 Gy x 2) combined with fludarabine and reduce dose melphalan was better tolerated with improved survival and disease control compared to standard RIC regimen of fludarabine and melphalan (54).

Table 2.2. Mean organ doses in 61 patients treated with TMLI

Organ	Mean (range)
Bladder	8.2 (4.6-11.8)
Brain	7.3 (4.1-14.7)
Breasts	9.5 (7.6-11.9)
Esophagus	4.5 (2.8-6.1)
Eyes	5.1 (1.4-7.2)
Heart	6.1 (4.7-8.1)
Kidneys	6.0 (2.5-8.1)
Lens	2.2 (1.2-3.1)
Liver	6.9 (4.8-8.2)
Lungs	5.8 (4.7-7.2)
Optic Nerve	6.6 (3.7-13.6)
Oral Cavity	3.0 (1.7-5.5)
Ovary	7.0 (3.9-9.7)
Parotids	5.5 (3.0-9.0)
Rectum	4.7 (3.1-7.7)
Small Intestine	5.0 (3.5-6.8)
Stomach	4.6 (3.3-6.8)
Testis	7.5 (3.3-13.0)
Thyroid	6.3 (3.5-13.2)

The addition of TMI to RIC regimens has the potential to improve outcomes with acceptable toxicities. In general trials have added myeloablative doses of TMI and TMLI to RIC. Rosenthal et al. (COH IRB 04199) evaluated the feasibility of combining TMLI (1.5 Gy BID, days -7 to -4) with the established RIC regimen of fludarabine (25 mg/m2/d Days -7 to -4) and melphalan (140 mg/m2 Day -2) in patients who were ineligible for standard TBI myeloablative regimens due to age greater than

50 years old or existing co-morbidities. (55;56). Study entry criteria required that marrow blasts be < 10% or reduced by over 50% after induction chemotherapy. The target structures for TMLI included bone, as well as major lymph node regions (TLI) and spleen to optimize the immunosuppression needed for allogeneic HCT and since these regions potentially harbored disease. Brain and testes were included as target regions in patients with ALL. Jensen et al. recently reported an update of this experience in 61 patients (56). The median patient age was 55 years (range, 9-70 years) and the median follow-up was 7.4 years. The 72% of patients had acute leukemia and 49% had high/very high-risk disease. The most common toxicity was mucositis. All patients engrafted without delays. Two-year OS, EFS, and TRM were 54%, 49%, and 30%, respectively. Five-year OS and EFS were 42% and 41%. The addition of TMLI to Flu/Mel conditioning was feasible, with favorable outcomes and with a TRM rate that was comparable that previously reported for fludarabine and melphalan alone. At COH this regimen has been utilized in the most patients to date and continues to be used as a standard regimen years after closure of this trial.

Table 2.2 shows median organ doses from the 61 patients treated with TMLI on IRB protocol 04199 titled "Allogeneic Stem Cell Transplantation with a Novel Conditioning Therapy Using Helical Tomotherapy, Melphalan, and Fludarabine in Hematological Malignancies" (56)

Dose escalation of TMLI/Flu/Mel was not possible on a successor trial (IRB 08076) which attempted to dose escalate TMLI using the same conditioning regimen as 04199 in the same patient population. DLT was observed at the first dose level of 12 Gy. A phase I trial (IRB 17505) has been initiated to determine whether dose escalation is feasible if TMLI is delivered prior to fludarabine and melphalan compared to IRB 04199 which administered the fludarabine and TMI on the same days. In addition, the fludarabine and melphalan doses are reduced. This trial is ongoing and it is not clear whether dose escalation will be possible beyond 14-16 Gy due to GI toxicities and mucositis.

2.7 Radioimmunotherapy, a Form of Biologically Targeted Systemic Radiotherapy

TMLI is a form of targeted systemic radiotherapy that utilizes CT imaging to identify where to preferentially target radiotherapy. Radioimmunotherapy (RIT) is also a form of targeted systemic radiotherapy that utilizes monoclonal antibodies or related immunoconstructs linked to radionuclides to preferentially target cells that express a specific antigen. Radiolabeled antibodies have been evaluated as a form of therapy in solid tumors and hematopoietic malignancies. Several detailed reviews on this topic have been published (57;58).

The following will focus on the use of RIT as a form of targeted TBI for leukemia. Table 2.3 lists just some of the antigens that radiolabeled antibodies have been developed against to target AML and ALL.

Table 2.3. Radioimmunotherapy Target Antigens in Acute Leukemia

Target	Disease	Expressed by
CD33	Myeloid leukemia	Promyelocytes to mature myeloid cells AML blasts (not ALL blasts) Not hematopoietic stem cells or ALL blasts
CD45	AML, ALL	Virtually all hematopoietic stem cells except plasma cells 90% of AML and ALL
CD66	AML, ALL	Mature myeloid and monocytic cells Not on AML blasts (relies on cross-fire effect)
CD22	ALL	B-cell acute lymphoblastic leukemia

RIT directed against CD33 has been evaluated as single modality therapy in pilot and phase I trials in acute myeloid leukemia. The CD33 antigen is a 67-kD glycoprotein expressed on most myeloid leukemias and leukemia

progenitors but not on normal stem cells. Anti-CD33 RIT has been developed and evaluated using the murine M195 and the HuM195 (linituzumab) humanized antibodies by the group at Memorial Sloan-Kettering Cancer Center (MSKCC). A phase I trial at MSKCC reported on the feasibility of administering 131I-CD33 antibodies (M195 and HuM195) in 31 patients and demonstrated that dose escalation to 135mCi/m2 achieved myelosuppression and allowed 8 patients to proceed to bone marrow transplant, with three patients remaining in complete remission at 59, 87, and 90 months (59). Rosenblat et al. (60) evaluated HuM195 anti-CD33 radiolabeled with the α-emitter 213Bi administered after cytarabine in a Phase I/II trial in patients with newly diagnosed, refractory or relapsed AML. The RIT agent was shown to be tolerable at all dose levels. Due to the short half-life of 213Bi, HuM195 has recently been evaluated in a phase I trial labeled with the α-emitter 225Ac by the same group with an overall response rate of 29% reported (61).

RIT has also been evaluated as part of conditioning regimens in patients with leukemia undergoing allogeneic HCT. RIT has been combined with established myeloablative or reduced intensity regimens. Table 2.4 lists select trials that have combined RIT with non-TBI conditioning regimens. Almost all trials have demonstrated the feasibility of combining RIT with established conditioning regimens and acceptable TRM rates. Results have been encouraging, although the experience to date has been limited to phase I and II trials, at a limited number of centers, and in a relatively small number of patients.

Table 2.4. Select HCT Trials Combining RIT with Myeloablative or Reduced Intensity Conditioning Regimens

First Author Year	Antibody (target)	No.	Disease	HCT	Toxicities
Burke 2003 (59) Phase I	131I-M195 or Hu195 (CD33)	31	AML relapsed AML refractory CML-AP MDS advanced	Bu/Cy	TRM 65%
Pagel 2006 (62) Phase I/II	131I-BC8 (CD45)	46	AML CR1	Bu/Cy	3 yr TRM 21%
Pagel 2009 (63) Phase I	131I-BC8 (CD45)	58	AML advanced MDS high risk Age > 50	RIC: Flu+TBI (2Gy)	1 yr TRM 22%
Mawad 2014 (64) Phase I	131I-BC8 (CD45)	58	AML advanced MDS high risk Age < 50	RIC: Flu+TBI (2Gy)	1 yr TRM 0%
Koenecke 2008 (65) Phase I/II	188Re-BW 250/183 (CD66)	21	AML high risk MDS advanced	Bu/Cy or RIC	1 yr TRM 28.6%
Ringhoffer 2005 (66) Phase I/II	188Re- or ^{90}Y-BW 250/183 (CD66)	20	AML, MDS Age 55-65	Flu + ATG or Mel	Cumulative TRM 25%
Lauter 2009 (67) Phase II	188Re-BW 250/183 (CD66)	22	AML advanced Age > 54	RIC: Flu/Bu/campath	2 yr TRM 23%

HCT = hematopoietic cell transplantation; RIT = radioimmunotherapy; AML = acute myelogenous leukemia; CML-AP = chronic myelogenous leukemia in acute phase; MDS = myelodysplastic syndrome; CR = complete remission; CR1 = first complete remission; Bu = busulfan; Cy = cyclophosphamide; RIC = reduced intensity conditioning regimen; Flu = fludarabine; TBI = total body irradiation; Gy = Gray; ATG = anti-thymocyte globulin; Mel = melphalan; DFS = disease free survival; RFS = relapse free survival; OS = overall survival; TRM = treatment related mortality.

2.8 Dose escalation of TBI with the Addition of RIT

As summarized earlier, attempts to dose escalate TBI by the Seattle group were not possible due to an increase in TRM related to an increase in toxicities (46;47), which were primarily mucositis, hepatic and renal (48). A number of groups have therefore evaluated radiation dose escalation by adding RIT to standard TBI (Table 5). Matthews et al. (68) combined 131I-BC8 anti-CD45 RIT with the myeloablative conditioning regimen of 12 Gy TBI and Cy is a phase I trial. RIT was escalated based on estimated dose to the bone marrow. One case of non-engraftment occurred with the combination of 12 Gy TBI and 31 Gy RIT. A RIT marrow dose of 24 Gy in combination with 12 Gy TBI was determined to be the MTD. Bunjes et al. (69) combined 188Re labeled anti-CD66 RIT with myeloablative conditioning regimen which included TBI to 12 Gy. This agent has greater biodistribution and dose to kidney than other agents. Late renal toxicity was seen in 14% and in 4 of 6 patients if the total renal dose exceeded 12 Gy. Renal toxicity was reduced in a subsequent study of the same agent when renal shielding was utilized with TBI (70).

Table 2.5. Select HCT Trials Combining RIT and TBI (12 Gy)

First Author year	Antibody (target)	No.	Disease	HCT	Toxicities
Appelbaum 1992 (71) Phase I	131I-p67 (CD33)	4	AML Relapse, second CR	Cy/TBI (12 Gy)	
Matthews 1999 (68) Phase I	131I-BC8 (CD45)	44	AML, ALL beyond first remission	Cy/TBI (12 Gy)	One engraftment failure at 31 Gy RIT + 12 Gy TBI
Bunjes 2002 (69) Phase I/II	188Re-BW 250/183 (CD66)	57	High risk AML and MDS < 25% marrow blasts	Cy/TBI (12 Gy) TBI/Cy/TT Bu/Cy	14% late renal toxicity Radiation nephropathy in 6 patients (4/6 if > 12 Gy) 26 month TRM 30%
Zenz 2006 (70) Phase I	188Re-BW 250/183 (CD66)	20	Ph+ ALL Advanced CML	Bu/Cy or Cy/TBI (12 Gy) Kidney shielded to 6 Gy	1 yr TRM 20%

HCT = hematopoietic cell transplantation; RIT = radioimmunotherapy; AML = acute myelogenous leukemia; ALL = acute lymphoblastic leukemia; CML = chronic myelogenous leukemia; MDS = myelodysplastic syndrome; CR = complete remission; CR1 = first complete remission; NED = no evidence of disease; Bu = busulfan; Cy = cyclophosphamide; TT = thiotepa; TBI = total body irradiation; Gy = Gray; DFS = disease free survival; OS = overall survival; TRM = treatment related mortality

2.9 The Rationale for Combining TMLI and RIT

Studies to date demonstrate the promise of targeted systemic radiotherapy using either TMLI or RIT. Rather than being viewed as competing approaches, these two forms of targeted therapy should be viewed as complementary which when rationally combined can address the limitations of each modality. With RIT there is unintended

normal organ uptake, depending on the agent, to liver or kidney which limits dose escalation alone or when added to TBI. TMLI can significantly reduce doses to these organs without compromising dose to marrow and is better positioned to be combined with RIT than standard TBI. With RIT, doses to target areas such a bone marrow are subject to inter-patient variability and in general are lower than can be achieved with TMLI which is able to deliver higher doses to bone, bone marrow and lymph nodes with minimal variability between patients. TMLI dose escalation has proven to be challenging especially in the older population with mucositis and GI toxicities being the most common toxicity. The addition of RIT to TMLI will likely add additional dose to marrow and leukemia cells without a significant increase in mucositis. Finally, the addition RIT helps to address the theoretical concern of sparing of leukemia cells in circulation and in areas of reduced dose with TMLI.

2.10 RIT Directed Against CD25 in Hematopoietic Malignancies

CD25 is the interleukin-2 receptor α-subunit (IL-2αR) and is a 55 kD transmembrane glycoprotein. CD25 is expressed at high frequency by abnormal T and B cells in patients with lymphoid malignancies, and on Reed-Sternberg cells and the surrounding lymphoid tissue in Hodgkin's lymphoma. There have been several RIT trials evaluating antibodies directed against CD25. ^{90}Y is a radiometal commonly used in RIT and is a pure β emitter. The mean β emission range is approximately 2.7 mm compared to 0.8 mm for 131I. ^{90}Y β emissions travel only a few mm and thus mainly affect the cells which are targeted or adjacent malignant cells through what is termed a cross-fire effect.

Waldmann and colleagues administered ^{90}Y-murine anti-CD25 anti-Tac to 18 patients with adult T-cell leukemia lymphoma. The first 9 were treated in a dose escalation phase I trial and the remaining 9 patients in a subsequent phase II trial at 10 mCi per cycle. Administered doses ranged from 185 to 555 Mbq (5-15 mCi) per cycle with patients receiving up to 9 total cycles. For the phase I trial a total of 10 mg antibody protein and for the phase II trial 2-10 mg antibody protein was administered. Estimated organ doses for a patient receiving a 10 mCi administered dose was 105 cGy to the marrow, 228 cGy to the liver, and 336 cGy to the spleen. Tumor doses ranged from 140-243 cGy. The predominant toxicity was hematologic, with transient hepatotoxicity and proteinuria seen in 3 and 4 patients, respectively. They reported 2/16 complete responses (one for more than 3 years duration) and 7/16 partial responses of 1.6 to 22.4 months duration (72).

Dancey and colleagues reported results of a Phase I trial of 131I-basiliximab, a chimeric anti-CD25 monoclonal antibody, in 15 patients with Hodgkin's and non-Hodgkin's lymphoma (73). Dose levels were 370, 740, 1,480, 2,220, and 2,960 MBq/m2 (10, 20, 40, 60, and 80 mCi/m2) Three complete response and 3 partial response were observed in 9 patients that received > 1.2 GBq/m2..

A phase I trial also evaluated the humanized anti-CD25 daclizumab radiolabeled with ^{90}Y in 46 patients with Hodgkin's lymphoma. Fifteen mCi per cycle was given up to 7 cycles. Total cumulative activity ranged from 10-90 mCi. Complete responses were observed in 14 patients and partial responses in 9 (74). The estimated tissue radiation dose per 15 mCi of ^{90}Y-daclizumab was 173 cGy to bone marrow, 263 cGy to liver, 1,062 cGy to spleen, and 33 cGy to the whole body. The estimated tumor dose with 15 mCi ranged from 210 to 365 cGy.

Anti-CD25 Basiliximab RIT has also been evaluated as part of the conditioning regimen in patients undergoing autologous HCT. AT COH IRB 08179 (PI Eileen Smith) is a Phase I trial recently completed which added ^{90}Y-anti-CD25 basiliximab radioimmuno-conjugate combined with BEAM conditioning prior to AHCT in patients with relapsed/refractory HL (aTac-BEAM). With 27 patients imaged with ^{111}In-basiliximab pre-therapy, the biodistribution of the imaging agent was evaluated over the course of a week for the four cohorts treated at 0.3, 0.4, 0.5 and 0.6 mCi/kg doses of ^{90}Y-basiliximab. 25 patients received a therapeutic dose of ^{90}Y-basiliximab-DOTA and proceeded to aTac-BEAM HCT. Administered activity ranged from 20.2 to 60 mCi. Of the 22 patients who received a therapeutic dose of ^{90}Y-basiliximab-DOTA, 3 patients were treated at a dose of 0.3mCi/kg, 10 patients were treated at 0.4mCi/kg, 3 patients were treated at 0.5mCi/kg, and 6 were treated at 0.6mCi/kg (Table 2). No DLTs were observed at any dose level and 0.6mCi/kg was determined to be the recommended phase II dose. No

patients experienced graft failure after aTac-BEAM autoHCT. The median time to neutrophil engraftment was 10 days (range, 9-14 days) and the median time to platelet engraftment was 12 days (range, 9-21 days). Following aTac-BEAM autoHCT, the best overall response and CR rate were 95% (21/22) and 91% (20/22), respectively. Seven (32%) patients relapsed. The median follow-up time in surviving patients is 59 months (range, 18.3-65.7 months).

Dosimetry was performed to evaluate the radiation doses for 3 patients on each dose level, and two patients with altered biodistribution with potential lung uptake or elevated blood pool activity (one each on 0.4 and 06 mCi/kg dose). Whole body planar scans were acquired at 2, 24, 48, 120 and 144-168 hours post- ^{111}In-anti-CD25 basiliximab injection. Blood activity and urine clearance were used to calculate the red marrow dose and the residual activity in the body. Heart, liver, lungs, kidney and spleen were segmented on the images and were used to quantify the time activity curves (TACs) for the organs. Background-corrected organ activity measurements were further corrected for attenuation and overlying tissue activity. ^{111}In-basiliximab time activity curves (TACs) were used to calculate ^{90}Y-basiliximab TACs and the corresponding residence times which were then used to calculate (in OLINDA) the radiation doses to the different organs. Absorbed dose estimates were calculated using the standard adult human model in OLINDA/EXM (Table 1). A phase II trial is planned at a dose level of 0.6 mCi/kg.

Table 2.6. Organ doses calculated in mGy/MBq and Gy/mCi (14 patients)

Organ	Average dose (mGy/MBq)	Average dose (Gy/mCi)	total dose (Gy) assuming administered activity of 45 mCi
Heart wall	10.30	0.38	17.17
Kidneys	5.20	0.19	8.67
Liver	6.30	0.23	10.50
Lungs	6.30	0.23	10.50
Spleen	13.10	0.49	21.83

IRB 14349 (PI Jasmine Zain) also evaluated the same conditioning regimen in patients with peripheral T cell lymphomas (PTCL). CD25 is a targetable protein expressed differentially in PTCL. From 07/29/2015 to 05/29/2018, 14 PTCL patients underwent ASCT on this trial; n=4 at the 0.4mCi/kg dose, n=4 at the 0.5mCi/kg dose and n=6 at the 0.6mCi/kg dose. Patient characteristics are as follows: Median age at ASCT (years): 51(range: 18 – 76); Mature T-cell lymphoma, NOS n=7; alk-ve ALCL n=3; Angioimmunoblastic T-cell lymphoma n=2; and Intestinal T-cell lymphoma n=2; Disease status at HCT: 1CR n=12, 2CR n=2; Median number of prior therapies: 1 (1-2). No dose limiting toxicities were experienced. The 0.6mCi/kg dose level was declared as the recommended phase II dose. The most common/highest grade toxicity experienced (per Bearman Scale) was grade 2 stomatitis. 0.4mCi/kg n=3; 0.5 mCi/kg n=4; 0.6mCi/kg n=3. The only other grade 2 toxicities seen were: at 0.4mCi/kg dose n=2 grade 2 GI and at 0.6mCi/kg dose n=1 grade 2 bladder. Toxicities >grade 2 were not seen. Issues with engraftment were not seen, Median FU (months) was 14.4 (range: 0.9-26.2). There were complete responses in 8 and relapses in 4. Overall Survival at 100-days was 100% (95% CI: N/A) and at 1-year 89% (95% CI: 43-98). Non-relapse mortality at 100-days and 1-year, 0% (95%CI: N/A). The combination of ^{90}Y- basliximab plus BEAM was safe as a conditioning regimen for PTCL with no added toxicities seen undergoing transplants.

Recently, Conlon et al. reported on 4 patients with refractory and relapsed Hodgkin's disease with 3 patients who received a single dose of ^{90}Y-anti CD25 daclizumab (564.6 - 574.6 MBq or 15.26 – 15.53 mCi) and the fourth patient two doses of 580.9 to 566.1 MBq (15.7 – 15.3 mCi) and BEAM conditioning followed by AHCT. Four of 6 patients achieved CR and remain in CR 4.5-7 years out from transplant (75).

2.11 Rationale for Anti-CD25 in Leukemia

Saito et al. (76) examined CD25 expression on the surface of leukemia stem cells from 61 patient samples. CD25 was expressed on the cell surface in 24.6% of the cases. CD25 positive cells from AML patients initiated AML when transplanted into mice. CD25 expression was seen on the cell cycle quiescent AML-initiating cells residing within the endosteal niche that may be responsible for AML relapse, indicating that CD25 is expressed by leukemia stem cells. Elimination of normal human CD25 expressing hematopoietic stem cells did not compromise normal hematopoietic development. For these reasons the authors concluded that CD25 directed therapies to AML leukemia stem cells in the consolidation or pre-transplant conditioning period should be explored and have therapeutic promise since CD25 was frequently expressed in AML patients in which 85% were poor risk and in need of more effective therapies.

These findings are consistent with the findings of Terwijn et al (77), who analysed by flow cytometry CD25 expression of AML blasts in 72 newly diagnosed patients with AML. Patients with CD25 expression of >10% had a significantly shorter overall survival (p=0.0005) and relapse free survival (p=0.005). In multi-variate analysis, CD25 expression was an independent prognostic factor. In addition, after the first cycle of chemotherapy there was significantly higher rate of minimal residual disease (MRD) in patients with higher CD25 expression.

In B lymphoblastic leukemia/lymphoma CD25 expression was greater in Ph+ patients (80%) than Ph – patients (17%). In addition in Ph- patients CD25 expression was associated with an increased incidence of residual disease (78).

Finally, Waldmann and colleagues administered ^{90}Y-murine anti-CD25 anti-Tac to 18 patients with adult T-cell leukemia lymphoma. The first 9 were treated in a dose escalation phase I trial and the remaining 9 patients in a subsequent phase II trial at 10 mCi per cycle. Administered doses ranged from 185 to 555 Mbq (5-15 mCi) per cycle with patients receiving up to 9 total cycles. For the phase I trial a total of 10 mg antibody protein and for the phase II trial 2-10 mg antibody protein was administered. Estimated organ doses for a patient receiving a 10 mCi administered dose was 105 cGy to the marrow, 228 cGy to the liver, and 336 cGy to the spleen. Tumor doses ranged from 140-243 cGy. The predominant toxicity was hematologic, with transient hepatotoxicity and proteinuria seen in 3 and 4 patients, respectively. They reported 2/16 complete responses (one for more than 3 years duration) and 7/16 partial responses of 1.6 to 22.4 months duration (72).

Both Hodgkin's Lymphoma and NHL malignant cells have demonstrated expression of CD25 [2, 3]. NHL tumors with high levels of surface CD25 expression include DLBCL, follicular lymphoma, peripheral T cell lymphoma including angioimmunoblastic T cell lymphoma and anaplastic large cell lymphoma[4], and anti-CD25 drugs including ^{131}I-basiliximab. LMB-2, and ADCT-301 have been used in treatment of NHL in phase 1 and 2 trials[4].

2.12 Study Rationale

This is a single-institution, non-randomized phase I trial to determine the maximum tolerated dose/recommended phase II dose (MTD/RP2D) of ^{90}Y-DOTA-anti-CD25 Basiliximab MAB in combination with fixed doses of fludarabine, melphalan and 1200 cGy TMLI as part of the conditioning regimen to patients with high-risk acute leukemia (lymphocytic or myelogenous), myelodysplastic syndrome, or non-Hodgkin's Lymphoma (NHL) who undergo alloHCT with matched related/unrelated. The rationale for combining TMLI and RIT is detailed in **Section 2.9** and the rationale for administration of anti-CD25 in leukemias and NHL could be found in **Section 2.11**.

3.0 ELIGIBILITY CRITERIA

Participants must meet all of the following criteria on screening examination to be eligible to participate in the study:

3.1 Patient Inclusion Criteria

Informed Consent

Documented informed consent of the participant and/or legally authorized representative.

- Assent, when appropriate, will be obtained per institutional guidelines

Age Criteria, Performance status, Language

__1. Age ≥ 18 years old

__2. Karnofsky performance status ≥70 (see Appendix A)

Nature of Illness and Illness Related Criteria

__3. Eligible patients will have a histopathological confirmed diagnosis of hematologic malignancy in one of the following categories :

- Acute myelogenous leukemia:

  __Patients with de novo or secondary disease in unfavorable risk group including poor risk cytogenetics according to NCCN guidelines for AML[5] i.e., monosomal karyotype, -5,5q-,-7,7q-,11q23-non t(9;11), inv (3), t(3;3), t(6;9), t(9;22) and complex karyotypes (≥ 3 unrelated abnormalities), or all patient in intermediate risk groups accept patients with FLT3-NPM1+ disease, OR

  __Patients with a complete morphological remission (CR) with MRD-positive status by flow cytometry (≥ 0.1% by flow cytometry) or cytogenetic after at least 2 prior induction therapies, OR

  __Patients with chemosensitive active disease defined as at least 50% reduction in their blast count after last treatment.

- Acute lymphocytic leukemia:

  __Patients with de novo or secondary disease according to NCCN guidelines for ALL[6] hypoploidy (<44 chromosomes); t(v;11q23): MLL rearranged; t(9;22) (q34;q11.2); complex cytogenetics (5 or more chromosomal abnormalities); high WBC at diagnosis (≥ 30,000 for B lineage or ≥50,000 for T lineage); iAMP21loss of 13q, and abnormal 17p [7], OR

  __Patients with a CR with MRD-positive status by flow cytometry (≥ 0.1% by flow cytometry) or cytogenetics after at least 2 prior induction therapies, OR

  __Patients with chemosensitive active disease defined as at least 50% reduction in their blast count after last treatment.

- Myelodysplastic syndrome in high-intermediate (int-2) and high-risk categories per IPSS-R [8]
- T cell Non-Hodgkin's Lymphoma with a confirmed diagnosis as defined by WHO 2022 criteria[9] including but not limited to PTCI-nos, TFH- T cell lymphoma, ALCL, HSCTCL, Intestinal T cell lymphoma, cutaneous T cell lymphoma including TMF, and ATLL. Diagnosis should be confirmed at COH.

__4. Demonstration of CD25 expression by flow cytometry for patients with leukemia or MDS.

__5. Demonstration of CD25 tumor cell expression by flow cytometry or immunohistochemistry for patients with NHL

*Clinical Laboratory and Organ Function Criteria (To be performed within 30 days prior to Day 1 of protocol therapy unless otherwise stated) or (acceptable windows for tests are indicated in the **Study Calendar Section 10.0**).*

__6. A pretreatment measured creatinine clearance (absolute value) of ≥60 ml/minute.

__7. Patients must have a serum bilirubin ≤2.0 mg/dl (unless has Gilbert's disease), SGOT and SGPT ≤2.5 times the institutional upper limits of normal.

__8. Ejection fraction measured by echocardiogram or MUGA ≥50%

__9. DLCO and FEV1 > 50% predicted.

Contraception

__10. Agreement by females **and** males of childbearing potential* to use an effective method of birth control or abstain from heterosexual activity for the course of the study through at least 6 months after the last dose of protocol therapy. …

* Childbearing potential defined as not being surgically sterilized (men and women) or have not been free from menses for > 1 year (women only).

3.2 Patient Exclusion Criteria

Prior and concomitant therapies

__1. Patients who had a prior allogeneic transplant.

__2. No prior transplant BCNU conditioning

__3. All patients with prior radiation treatment to the lung, liver, and kidney.

__4. Patients who have received prior total skin electron beam therapy for lymphoma.

__5. Patients who have received prior radiopharmaceutical therapy.

__6. Inclusion of other patients with previous radiation exposure will be determined based on the radiation oncologist MD PI evaluation and judgement.

__7. Receiving any other investigational agents or concurrent biological, intensive chemotherapy or radiation therapy for the previous 2 weeks from conditioning.

__8. Patients should have discontinued all previous intensive therapy, chemotherapy, or radiotherapy for 2 weeks prior to commencing therapy on this study. **Note**: Low dose chemotherapy or maintenance chemotherapy given within 7 days of planned study enrollment is permitted. These include hydroxyurea, 6-meraptopurine, oral methotrexate, vincristine, oral etoposide, and tyrosine kinase inhibitors (TKIs). FLT-3 inhibitors can also be given up to 3 days before conditioning regimen.

Other illnesses or conditions

__9. History of allergic reactions attributed to compounds of similar chemical or biologic composition to study agent

__10. Patients with other active malignancies are ineligible for this study, other than non-melanoma skin cancers.

__11. Patients should not have any uncontrolled illness including ongoing or active bacterial, viral or fungal infection.

__12. The recipient has a medical problem or neurologic/psychiatric dysfunction which would impair his/her ability to be compliant with the medical regimen and to tolerate transplantation or would prolong hematologic recovery which in the opinion of the investigator (treating physician) would place the recipient at unacceptable risk.

__13. *Females only*: Pregnant or breastfeeding

__14. Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns with clinical study procedures.

Noncompliance

__15. Prospective participants who, in the opinion of the investigator, may not be able to comply with all study procedures (including compliance issues related to feasibility/logistics).

Eligibility Confirmed* by (Choose as applicable):	**Print Name**	**Signature**	**Date**
☐ Site PI			
☐ Authorized study MD			
☐ Study Nurse			
☐ Study CRA/ CRC			
☐ Other:_____			
*Eligibility should be confirmed per institutional policies.			

3.3 Donor Specific Criteria

All candidates for this study must have an HLA (A, B, C, and DR) identical sibling who is willing to donate mobilized peripheral blood stem cells (preferred) or bone marrow, or have a 10/10 (A, B, C, DR and DQ) allele matched unrelated donor. DQ or DP mismatch is allowed per discretion of the Principal Investigator. COH SOP (B.001.11) will be used for allogeneic donor evaluation, selection, and consent. Donor screening will be in compliance with all requirements of FDA regulation 21 CFR Part 1271 including donor screening for COVID-19 exposure or infection.

4.0 PARTICIPANT ENROLLMENT, ASSIGNMENT

4.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained.

The informed consent process is to be fully documented (see Section 17.4), and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in Section 10.0 (Study Calendar).

4.2 Participant Enrollment

Registration of participants will be according to the following steps:

Prospective participants must complete the informed consent process, including a signed informed consent, prior to proceeding to study screening.

Once all the pre-study requirements have been fulfilled, including a completed eligibility checklist (**Section 3.0**) the study coordinator will register the eligible patient into the OnCore Clinical Trials Management System.

Patients failing to meet all protocol eligibility criteria, including informed consent, may not be registered for the trial.

Eligible participants will be registered on the study centrally by the Data Coordinating Center (DCC) at City of Hope.

DCC staff are available **between the hours of 8.00 am and 5.00 pm PST, Monday through Friday (except holidays)**.

E-mail: DCC@coh.org

4.2.1 Slot verification and reservation

A designated study team member should email the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject (provide DCC with subject initials), including a tentative treatment date. Slots can only be held for a limited time, at the discretion of the study PI.

The DCC should be notified of cancellations of prospective participants holding slots as soon as possible.

4.2.2 Registration Process

Allow up to 24 hours for the DCC to review. To register a participant the following procedure must be followed:

1. The study team should contact the DCC via email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.
2. The study team will email a **Complete Registration Packet** to the DCC, which consists of a copy of the following documents:

   Completed eligibility checklist (printed from Section 3.0 of the protocol) with required signature(s)

   Signed Informed Consent

   Signed HIPAA authorization form (if separate from informed consent)

   Signed subject's bill of Rights (California only)

3. When all documents are received, the DCC will review and work with the study team to resolve any missing elements. Any missing documents may delay registration. A participant failing to meet all requirements will not be registered and the study team will be immediately notified.
4. The DCC will send a Confirmation of Registration Form, including the Subject Study Number and cohort assignment to:

   The COH Study PI and COH study team designees (including but not limited to study monitor(s) and statistician(s)).
5. Upon receipt of the Confirmation of Registration Form, COH study team will register the patient in OnCore.

4.3 Screen Failures and Registered Participants Who Do Not begin Study Treatment

Notify the DCC immediately if the participant screen fails after registration or if the participant does not start treatment.

Issues that would cause treatment delays should be discussed with the Study Principal Investigator.

4.4 Dose Level Assignment

During the dose escalation stage, eligible Phase 1 participants will be assigned a dose level (**Section 5.3**) based on the study design rules (**Section 12.1**). Escalation/de-escalation to the next dose level, patient replacement, or expansion of a dose level must be approved by the study PI and biostatistician, who will inform the DCC prior to enrollment of the next patient.

5.0 TREATMENT PROGRAM

5.1 Treatment Program Overview

This is a single-institution, non-randomized phase I trial to determine the maximum tolerated dose/recommended phase II dose (MTD/RP2D) of ^{90}Y-DOTA-anti-CD25 Basiliximab MAB in combination with fixed doses of fludarabine, melphalan and 1200 cGy TMLI as part of the conditioning regimen to patients with high-risk acute leukemia (lymphocytic or myelogenous), myelodysplastic syndrome (MDS), or Non-Hodgkin's Lymphoma (NHL) who undergo alloHCT from a matched related/unrelated donor.

Dose escalation will be based on a modified rolling 6 Phase I design with dose level 1 starting at 0.3 mCi/kg and escalating in increments of 0.2 to a maximum of 0.5 mCi/Kg (dose level 3). There will also be a dose level -1 of o.2 mCi/Kg in the case that dose level 1 is too toxic.

5.2 Cycle Definition

There will be only one cycle of treatment for this study.

5.3 Treatment Plan

The conditioning regimen will start on day -15 or day -14 consisting of an infusion of 5 mg cold basiliximab followed by the radiolabeled dose of 5 mg of antibody protein ^{111}In-DOTA-anti CD25 Basiliximab Mab (5 mCi) and ^{90}Y-DOTA-anti-CD25 Basiliximab (therapy mCi activity).

This will be followed by serial blood (5 cc) samples at approximately time 1-2 hours, 3-4 hours, and at scan times of 1 day and 5/6 days after radiolabeled antibody infusion. Blood samples will be analyzed for total activity and

by radiometric HPLC. These studies will acquire data on antibody metabolism and pharmacokinetics. Planar serial nuclear scans will be performed at Day 0, Day 1 and Day 5/6. A SPECT scan will be performed at Day 1.

A maximum administered activity will be capped at 45 mCi regardless of dose level.

(**Note:** The dose of In-111 or Y-90 administered may be +/- 20% of prescribed dose in accord with Nuclear Regulatory Commission Guidelines.)

Dose Level	Administered activity (mCi/kg)
-1	0.2
1	0.3
2	0.4
3	0.5

5.3.1 Pre-dosing with unlabeled anti-CD25 antibody (basiliximab)

Prior to the infusion of radiolabeled antibody (combined ^{111}In-/^{90}Y- basiliximab/DOTA on day -15), 5 mg unlabeled "cold" anti-CD25 antibody (basiliximab) will be administered intravenously to block the circulating soluble antigen (sCD25) and to improve the radioimmunoconjugate biodistribution and tumor targeting of the radiolabeled basiliximab. Pre-medication with acetaminophen and diphenhydramine will be given 30-60 minutes prior to the cold antibody infusion (alternative pre-medication for patients who are allergic to acetaminophen and/or diphenhydramine to be discussed with the study P.I.). Basiliximab should be administered as an intravenous infusion over 20-30 minutes. The infusion of cold basiliximab should be completed within 1-2 hours prior to the administration of the radiolabeled antibody.

5.3.2 Administration of ^{111}In- and ^{90}Y- basiliximab/DOTA

^{111}In- and ^{90}Y- basiliximab/DOTA will be administrated intravenously. The radioimmunoconjugate for the day -15/-14 therapeutic infusion will be prepared in a single syringe containing 5 mg of basiliximab conjugated to the non-myeloablative, therapeutic dose of either 0.3, 0.4, or 0.5 mCi/kg ^{90}Y, plus 1 mg of basiliximab conjugated to 5 mCi ^{111}In for imaging.

Within 1-2 hours following the completion of the "cold" basiliximab infusion, the patient will be given the therapeutic dose of ^{90}Y-basiliximab/DOTA (along with 5 mCi ^{111} In-basiliximab/DOTA in the same syringe). Maximum dose = 45 mCi ^{90}Y-basiliximab/DOTA. The combined ^{111}In/^{90}Y-basiliximab/DOTA dose will be administered IV using a syringe pump over approximately 20-40 min. Line will then be flushed with at least 10ml of normal saline.

Nursing and physician personnel will be present at all times during the administration of the radiolabeled antibody. Nursing personnel will be present for 2 hours following administration of the radiolabeled antibody. An "Emergency Drug Reaction Kit" will be at the bedside. VS will be monitored prior to administration and every 5–15min during administration and the immediate post administration period x 1hr, then at 3-4 hr time point when pharmacokinetic blood samples are drawn. After study drug administration, the IV will be flushed with normal saline, then set at TKO during the immediate post, and up to 2 hours post administration period, for use if necessary, during an adverse event. If pt is stable after 2 hours, may DC IV and discharge patient. Pt to return for blood draw at the 3-4 hour time point post end of infusion of study drug.

After ^{111}In/^{90}Y-basiliximab/DOTA administration on day -15/-14, serial gamma camera images will be obtained as defined above. Nuclear scan images will be used to estimate the distribution of activity and absorbed radiation doses in various normal organs, especially liver, lungs, kidney, heart and spleen. After ^{111}In/^{90}Y-basiliximab/DOTA administration on day -15/-14, blood samples will be collected as defined above. Blood samples will be used for analysis of antibody clearance, metabolism and pharmacokinetics.

5.3.3 TMLI, and Flu/Mel

One week after the infusion of the $^{111}In/^{90}Y$-DOTA-anti-CD25 Basiliximab, the patient will receive 1200 cGy of TMLI delivered over 4 days (days -8 to -5), fludarabine 30 mg/m² based on adjusted body weight (days -4 to -2) and melphalan 100 mg/m2 (day -2).
Each fraction of TMLI is 150 cGy, with two fractions delivered each day for 4 days. There will be a minimum of 6 hours between each fraction. Treatment will utilize helical tomotherapy (6MV) or rapid arc IMRT as a means of conformal avoidance or minimization of radiation dose to normal organs.

- The target region will include bone marrow compartments and major lymph node regions (mediastinal, para-aortic, pelvic)
- Brain and testes will be treated to 1200 cGy for patients with ALL.
- Avoidance organs with dose sparing include brain (except ALL), liver, spleen, eyes, lens, parotids, thyroid, esophagus, oral cavity, lungs, heart, kidneys, stomach, upper GI and lower GI tract, rectum, bladder, and in women breast, uterus and ovaries.
- Mean organ dose constraints for right and left lung 4 Gy, right and left kidney 4 Gy, liver 4 Gy and heart 6 Gy.

5.3.4 GVHD prophylaxis

Patients will receive a loading dose of and Sirolimus (12mg) once on day -1 then 4 mg daily starting on day 0 and tacrolimus 1mg CIV/daily starting on day -1.

5.4 Agent Administration and Pre-medications

Fludarabine, melphalan, tacrolimus, and sirolimus will be administered per City of Hope HCT Standard Operating Procedures (COH intranet SOPs)

See Sections 5.3.1.1 and 5.3.1.2 for Pre-dosing with unlabeled anti-CD25 antibody (basiliximab) and Administration of ^{111}In- and ^{90}Y- basiliximab/DOTA, respectively.

5.5 Special Assessments and Monitoring

For a detailed list of all study procedures including timing and windows, see Section 10.0.

5.6 Duration of Protocol Therapy and Criteria for Removal

Initial therapy will require ~4 weeks of inpatient treatment during transplantation

Participants will receive protocol therapy until one of the below criteria are met:

- (Confirmed) Disease progression
- Completed full prescribed protocol therapy
- Participant is deemed intolerant to protocol therapy because of toxicity, despite dose modification/ delay
  - **Note:** If one agent is discontinued due to toxicity, then the participant may continue to receive the other study agents

General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator

Withdrawal of consent for further protocol therapy (See Section 17.5)

Once participants meet criteria for removal from protocol therapy, the participant should then proceed to End of Treatment assessments, and then to follow-up (Refer to the Follow-Up section below).

Documentation of the reason for discontinuing protocol therapy and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF.

5.7 Follow-Up

Outpatient follow-up will be twice weekly for the first 100 days post-transplant, twice monthly until 6 months post-transplant, and monthly until the patient discontinues immunosuppressive therapy without evidence of GVHD (see **Study Calendar Section 10.0**), with at least yearly study follow-up extending 2 years beyond the date of stem cell infusion. Patients will be encouraged to be co-enrolled in the COH long-term follow-up protocol for allogeneic transplantation (Protocol #00029) and Protocol #07173 Correlating Organ Dose and Dose-Volume with Toxicities after Total Marrow Irradiation (TMI) Using Helical Tomotherapy in Patients Undergoing Hematopoietic Cell Transplantation (HCT). Once a patient has relapsed after transplant, the subject will be taken off trial and followed only for survival, and the study calendar requirements are no longer required.

5.8 Duration of Study Participation

Study participation may conclude when any of the following occur:

- Completion of study activities (treatment and 2 years of follow-up after protocol treatment)
- Withdrawal of consent (Refer to Withdrawal Section for Ethical Considerations)
- Participant is lost to follow-up. All attempts to contact the participant must be documented.
- At the discretion of the investigator for safety, behavioral, study termination or administrative reasons.

Documentation of the reason for discontinuing study participation and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF.

5.9 Concomitant Therapies/Medications

Participant should receive prophylactic or supportive care as indicated in instructional policies.

5.10 Supportive care

Participants should receive prophylactic or supportive as clinically indicated per institutional policies.

6.0 ANTICIPATED ADVERSE EVENTS

6.1 Basiliximab

Severe, acute (onset within 24 hours) hypersensitivity reactions including anaphylaxis have been reported for both on initial exposure to basiliximab and following re-exposure. These reactions include hypotension, tachycardia, cardiac failure, dyspnea, wheezing, bronchospasm, pulmonary edema, respiratory failure, urticaria, rash, pruritus, and/or sneezing, as well as capillary leak syndrome and cytokine release syndrome. If a severe hypersensitivity reaction occurs, therapy with basiliximab should be permanently discontinued. Medications for the treatment of severe hypersensitivity reactions including anaphylaxis should be available for immediate use.

Per the basiliximab package insert, of renal transplantation patients treated with basiliximab (Simulect®) and tested for anti-idiotype antibodies, 4/339 developed an anti-idiotype antibody response, with no deleterious clinical effect upon the patient. In none of these cases was there evidence that the presence of anti-idiotype antibody accelerated Simulect® clearance or decreased the period of receptor saturation. In Study 2, the

incidence of human anti-murine antibody (HAMA) in renal transplantation patients treated with Simulect® was 2/138 in patients not exposed to muromonab-CD3 and 4/34 in patients who subsequently received muromonab-CD3. The available clinical data on the use of muromonab-CD3 in patients previously treated with Simulect® suggest that subsequent use of muromonab-CD3 or other murine anti-lymphocytic antibody preparations is not precluded.

6.2 ^{111}In-Basiliximab/DOTA

There are no additional acute drug toxicities associated with the In-111 labeled basiliximab above that associated with the basiliximab alone. There is a small risk from the radiation exposure of the In-111 considered appropriate for the patient population under study.

6.3 ^{90}Y-Basiliximab/DOTA

There are no additional acute drug toxicities associated with the Y-90 labeled basiliximab above that associated the basiliximab alone except for occasional nausea and diarrhea. The radiation exposure of the Y-90 in combination with the high-dose chemotherapy conditioning regimen will cause severe myelosuppression requiring hematopoietic stem cell support. There is potential for radiation damage to heart, lung, kidney, and liver. There is a risk for developing secondary malignancies.

6.4 Fludarabine

Human Toxicity: The major human toxicity has been myelosuppression. At higher dose levels or in patients with renal impairment, central nervous system toxicity has been seen and is characterized by numbness, paraparesis and cortical blindness.

6.5 Melphalan

Human Toxicity: The dose-limiting toxicity of melphalan is myelosuppression. Other toxicities after IV melphalan include mucositis, nausea, vomiting, and diarrhea. Alopecia is generally seen only with high doses associated with bone marrow transplant settings. Rarely reported reactions include pulmonary fibrosis, skin rash, vasculitis, and allergic reactions. With high dose chemotherapy, gastrointestinal toxicity becomes dose limiting. At such high doses, elevated transaminases, syndrome of inappropriate antidiuretic hormone secretion, depression, interstitial pneumonitis, and hepatic veno-occlusive disease have been reported. Acute non-lymphocytic leukemia and myeloproliferative syndromes may occur as secondary cancers from any alkylating agent such as melphalan. Amenorrhea, permanent in many cases, have been noted when melphalan was used in premenopausal women undergoing adjuvant therapy for breast cancer. Azoospermia would be expected, but is not well documented in the literature.

6.6 TMLI

Acute toxicities: Toxicities from TMLI may include bone marrow suppression, alopecia, fatigue, and skin erythema. Other acute toxicities, which occur with traditional total body irradiation and may also occur with TMI, include mucositis, esophagitis, enteritis, cystitis, proctitis, pneumonitis, nausea and vomiting, and sterility.

Potential Late Toxicities: Because of conformal avoidance of dose to normal organs, late toxicities from TMI are anticipated to be less frequent and/or severe compared with total body irradiation. Potential late toxicities may include sterility, endocrinopathies (i.e., hypothyroidism), cataract formation, pneumonitis, veno-occlusive disease, and second malignancy induction.

6.7 Tacrolimus

Human Toxicity: Common toxicities: anorexia, constipation, nausea, vomiting, myelosuppression. Less common: Convulsions, anaphylaxis, hemiparesis, dizziness, ataxia, confusion, dysphagia, anxiety, thrombo-embolism; prolonged lymphopenia with increased risk of infection or death, amnesia, insomnia, depression, myalgia, diplopia, visual changes; Secondary tumors or cancer.

6.8 Sirolimus

Human Toxicity: The most common (> 30%) adverse reactions are: peripheral edema, hypertriglyceridemia, hypertension, hypercholesterolemia, creatinine increased, abdominal pain, diarrhea, headache, fever, urinary tract infection, anemia, nausea, arthralgia, pain, and thrombocytopenia.

7.0 DOSE DELAY / MODIFICATION GUIDELINES

The treatment involves a single cycle of the planned regimen; there are no planned dose delays. One dose reduction (dose level -1) to 0.2 mCi/kg will be considered if dose limiting toxicity is seen at 0.3 mCi/kg (dose level 1). Dose levels above 0.5 mCi/kg will not be considered, as radiation exposure to non-targeted organs would approach levels received during standard myeloablative TBI.

8.0 AGENT INFORMATION

8.1 Basiliximab

Simulect® (basiliximab) is a chimeric (murine/human) monoclonal antibody (IgG1k), produced by recombinant DNA technology, that functions as an immunosuppressive agent, specifically binding to and blocking the interleukin-2 receptor a-chain (IL-2Ra, also known as CD25 antigen) on the surface of activated T-lymphocytes. Based on the amino acid sequence, the calculated molecular weight of the protein is 144 kilodaltons. It is a glycoprotein obtained from fermentation of an established mouse myeloma cell line genetically engineered to express plasmids containing the human heavy and light chain constant region genes and mouse heavy and light chain variable region genes encoding the RFT5 antibody that binds selectively to the IL-2Ra. Simulect® is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplantation when used as part of an immunosuppressive regimen that includes cyclo-sporine, USP (MODIFIED) and corticosteroids. The efficacy of Simulect® for the prophylaxis of acute rejection in recipients of other solid organ allografts has not been demonstrated.

A. Drug formulation and Procurement

The active ingredient, basiliximab, is water soluble. The drug product, Simulect®, is a sterile lyophilisate which is available in 6 mL colorless glass vials and is available in 10 mg and 20 mg strengths. Each 10 mg vial contains 10 mg basiliximab, 3.61 mg monobasic potassium phosphate, 0.50 mg disodium hydrogen phosphate (anhydrous), 0.80 mg sodium chloride, 10 mg sucrose, 40 mg mannitol and 20 mg glycine, to be reconstituted in 2.5 mL of Sterile Water for Injection, USP. No preservatives are added. Each 20 mg vial contains 20 mg basiliximab, 7.21 mg monobasic potassium phosphate, 0.99 mg disodium hydrogen phosphate (anhydrous), 1.61 mg sodium chloride, 20 mg sucrose, 80 mg mannitol and 40 mg glycine, to be reconstituted in 5 mL of Sterile Water for Injection, USP. No preservatives are added. Basiliximab will be purchased from Novartis Pharmaceutical Corp. in 20 mg glass vials.

b. Drug storage, Reconstitution and Stability

The active ingredient, basiliximab, is water soluble. The drug product, Simulect®, is a sterile lyophilisate which is available in 6 mL colorless glass vials and is available in 10 mg and 20 mg strengths. Each 10 mg vial contains 10

mg basiliximab, 3.61 mg monobasic potassium phosphate, 0.50 mg disodium hydrogen phosphate (anhydrous), 0.80 mg sodium chloride, 10 mg sucrose, 40 mg mannitol and 20 mg glycine, to be reconstituted in 2.5 mL of Sterile Water for Injection, USP. No preservatives are added. Each 20 mg vial contains 20 mg basiliximab, 7.21 mg monobasic potassium phosphate, 0.99 mg disodium hydrogen phosphate (anhydrous), 1.61 mg sodium chloride, 20 mg sucrose, 80 mg mannitol and 40 mg glycine, to be reconstituted in 5 mL of Sterile Water for Injection, USP. No preservatives are added.

Simulect® is for central or peripheral intravenous administration only. Reconstituted Simulect® should be given either as a bolus injection or diluted to a volume of 25 mL (10 mg vial) or 50 mL (20 mg vial) with normal saline or dextrose 5% and administered as an intravenous infusion over 20 to 30 minutes. Bolus administration may be associated with nausea, vomiting and local reactions, including pain.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration. After reconstitution, Simulect® should be a clear to opalescent, colorless solution. If particulate matter is present or the solution is colored, do not use.

Care must be taken to assure sterility of the prepared solution because the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

It is recommended that after reconstitution, the solution should be used immediately. If not used immediately, it can be stored at 2ºC to 8ºC for 24 hours or at room temperature for 4 hours. Discard the reconstituted solution if not used within 24 hours.

8.2 ^{111}In-Basiliximab/DOTA

a. Drug formulation and Procurement

Basiliximab will be conjugated with DOTA-NHS in the CBG facility at the City of Hope under cGMP conditions and vialed at 5mgs and stored at 2-8°C. The material will be transferred to the investigational pharmacy once it has passed all required quality control testing.

b. Drug storage, Reconstitution, and Stability

The Indium-111 basiliximab/DOTA will be prepared in the RIT Radiopharmacy under SOPs. The conjugated material will be obtained from the investigational pharmacy with 24 hours of planned labeling and stored in a monitored refrigerator at 2-8°C. The antibody will be incubated with clinical grade ^{111}InCl after neutralization with acetate buffer. The radioimmunoconjugate will then undergo quality control testing before released to the radioimmunotherapist for administration to the patient. The material will be held at 2-8°C prior to administration, which is to be performed within 6 hrs of radiolabeling.

8.3 ^{90}Y-Basiliximab/DOTA

a. Drug formulation and Procurement

Basiliximab will be conjugated with DOTA-NHS in the CBG facility at the City of Hope under CGMP conditions and vialed at 5mgs and stored at 2-8°C. The material will be transferred to the investigational pharmacy once it has passed all required quality control testing.

b. Drug storage, Reconstitution, and Stability

The ^{90}Y–basiliximab/DOTA will be prepared in the RIT Radiopharmacy under SOPs. The conjugated material will be obtained from the investigational pharmacy within 24 hours of planned labeling and stored in a monitored refrigerator at 2-8°C. The antibody will be incubated with clinical grade ^{90}Ycl after neutralization with acetate buffer. The radioimmunoconjugate will then undergo quality control testing before release to the physician for administration to the patient. The material will be held at 2-8°C prior to administration, which is to be performed within 6 hrs of radiolabeling.

8.4 Fludarabine phosphate (2-fluoro-ara-AMP)

8.4.1 Description

Mechanism of Action: The mechanism of action of fludarabine phosphate is analogous to that of ara-C and ara-A. The active metabolite appears to be the triphosphate, F-ara-ATP. Like ara-CTP and ara-ATP, 2-F-ara-ATP is a substrate for DNA polymerase and is incorporated into DNA, causing strand breaks and inhibition of DNA synthesis.

8.4.2 Toxicology

Human Toxicity: The major human toxicity has been myelosuppression. At higher dose levels or in patients with renal impairment, central nervous system toxicity has been seen and is characterized by numbness, paraparesis and cortical blindness

8.4.3 Pharmacology – Handling, Storage, Dispensing and Disposal

Sterile 50 mg/vial. When reconstituted with 2 mL sterile water, each mL will contain 25 mg of fludarabine phosphate. Administered intravenously (IV). Commercially available.

8.5 Melphalan (L-phenylalanine mustard, L-PAM, Alkeran)

8.5.1 Description

Mechanism of Action: The mechanism of action of fludarabine phosphate is analogous to that of ara-C and ara-A. The active metabolite appears to be the triphosphate, F-ara-ATP. Like ara-CTP and ara-ATP, 2-F-ara-ATP is a substrate for DNA polymerase and is incorporated into DNA, causing strand breaks and inhibition of DNA synthesis.

8.5.2 Toxicology

Human Toxicity: The dose-limiting toxicity of melphalan is myelosuppression. Other toxicities after IV melphalan include mucositis, nausea, vomiting, and diarrhea. Alopecia is generally seen only with high doses associated with bone marrow transplant settings. Rarely reported reactions include pulmonary fibrosis, skin rash, vasculitis, and allergic reactions. With high dose chemotherapy, gastrointestinal toxicity becomes dose limiting. At such high doses, elevated transaminases, syndrome of inappropriate antidiuretic hormone secretion, depression, interstitial pneumonitis, and hepatic veno-occlusive disease have been reported. Acute non-lymphocytic leukemia and myeloproliferative syndromes may occur as secondary cancers from any alkylating agent such as melphalan. Amenorrhea, permanent in many cases, have been noted when melphalan was used in premenopausal women undergoing adjuvant therapy for breast cancer. Azoospermia would be expected, but is not well documented in the literature.

8.5.3 Pharmacology – Handling, Storage, Dispensing and Disposal

Sterile 50 mg/vial. When reconstituted with 2 mL sterile water, each mL will contain 25 mg of fludarabine phosphate. Administered intravenously (IV). Commercially available.

8.6 Tacrolimus

8.6.1 Description

Mode of Action: Tacrolimus is a macrolide immunosuppressant produced by Streptomyces tsukubaensis. It prolongs the survival of the host and transplanted grafts in animal transplant models of liver, kidney, heart, bone

marrow, small bowel and pancreas, lung and trachea, skin, cornea, and limb. Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed, and the phosphatase activity of calcineurin is inhibited.

Drug Interactions: Frequent monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when concomitant use of the following drugs with tacrolimus is initiated or discontinued. This process will be done according to COH standard of care.

- Telaprevir: In a single dose study in 9 healthy volunteers, co-administration of tacrolimus (0.5 mg single dose) with telaprevir (750 mg three times daily for 13 days) increased the tacrolimus dose-normalized Cmax by 9.3-fold and AUC by 70-fold compared to tacrolimus alone.
- Boceprevir: In a single dose study in 12 subjects, coadministration of tacrolimus (0.5 mg single dose) with boceprevir (800 mg three times daily for 11 days) increased tacrolimus Cmax by 9.9-fold and AUC by 17-fold compared to tacrolimus alone.
- Nelfinavir: Based on a clinical study of 5 liver transplant recipients, co-administration of tacrolimus with nelfinavir increased blood concentrations of tacrolimus significantly and, as a result, a reduction in the tacrolimus dose by an average of 16-fold was needed to maintain mean trough tacrolimus blood concentrations of 9.7 ng/mL. It is recommended to avoid concomitant use of tacrolimus and nelfinavir unless the benefits outweigh the risks.
- Grapefruit juice: increased tacrolimus concentrations via CY3A inhibition; avoid concomitant use.
- Rifampin: In a study of 6 normal volunteers, a significant decrease in tacrolimus oral bioavailability (14±6% vs. 7±3%) was observed with concomitant rifampin administration (600 mg). In addition, there was a significant increase in tacrolimus clearance (0.036±0.008 L/hr/kg vs. 0.053±0.010 L/hr/kg) with concomitant rifampin administration.
- Magnesium-aluminum-hydroxide: In a single-dose crossover study in healthy volunteers, co-administration of tacrolimus and magnesium-aluminum-hydroxide resulted in a 21% increase in the mean tacrolimus AUC and a 10% decrease in the mean tacrolimus Cmax relative to tacrolimus administration alone.
- Ketoconazole: In a study of 6 normal volunteers, a significant increase in tacrolimus oral bioavailability (14±5% vs. 30±8%) was observed with concomitant ketoconazole administration (200 mg). The apparent oral clearance of tacrolimus during ketoconazole administration was significantly decreased compared to tacrolimus alone (0.430±0.129 L/hr/kg vs. 0.148±0.043 L/hr/kg). Overall, IV clearance of tacrolimus was not significantly changed by ketoconazole coadministration, although it was highly variable between patients.
- Voriconazole (see complete prescribing information for VFEND®): Repeat oral dose administration of voriconazole (400 mg every 12 hours for one day, then 200 mg every 12 hours for 6 days) increased tacrolimus (0.1 mg/kg single dose) Cmax and AUCτ in healthy subjects by an average of 2-fold (90% CI: 1.9, 2.5) and 3-fold (90% CI: 2.7, 3.8), respectively.
- Posaconazole (see complete prescribing information for Noxafil®): Repeat oral administration of posaconazole (400 mg twice daily for 7 days) increased tacrolimus (0.05 mg/kg single dose) Cmax and AUC in healthy subjects by an average of 2-fold (90% CI: 2.01, 2.42) and 4.5-fold (90% CI 4.03, 5.19), respectively.
- Caspofungin (see complete prescribing information for CANCIDAS®): Caspofungin reduced the blood AUC0-12 of tacrolimus by approximately 20%, peak blood concentration (Cmax) by 16%, and 12-hour blood concentration (C12hr) by 26% in healthy adult subjects when tacrolimus (2 doses of 0.1 mg/kg 12 hours apart) was administered on the 10th day of caspofungin 100 mg daily, as compared to results from a control period in which tacrolimus was administered alone.
- Vaccination: Immunosuppressants may affect response to vaccination. The use of live vaccines should be avoided; live vaccines may include, but are not limited to, the following: measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid.

8.6.2 Toxicology

Human Toxicity: Common toxicities: anorexia, constipation, nausea, vomiting, myelosuppression. Less common: Convulsions, anaphylaxis, hemiparesis, dizziness, ataxia, confusion, dysphagia, anxiety, thrombo-embolism; prolonged lymphopenia with increased risk of infection or death, amnesia, insomnia, depression, myalgia, diplopia, visual changes; Secondary tumors or cancer.

8.6.3 Pharmacology – Handling, Storage, Dispensing and Disposal

Pharmaceutical Data: Injection: Tacrolimus is available as a sterile solution (tacrolimus injection) containing the equivalent of 5 mg anhydrous tacrolimus per 1 mL. Oral: It is also available for oral administration as capsules containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus.

Storage and Administration: Injection: Diluted infusion solution should be stored in glass or polyethylene containers and should be discarded after 24 hours. The polyoxyethylated castor oil contained in the concentrate for intravenous infusion can cause phthalate stripping from PVC. It is strongly recommended that glass bottles and non-PVC tubing be used to minimize patient exposure to DEHP. Because of the chemical instability of tacrolimus in alkaline media, tacrolimus injection should not be mixed or co-infused with solutions of pH 9 or greater (e.g., ganciclovir or acyclovir). Tacrolimus Injection must be diluted with NS or D5W before use to a concentration between 0.004 mg/mL and 0.02 mg/mL. Monitor closely for an acute allergic reaction for the first 30 minutes and at frequent intervals thereafter. Oral: Store at 25°C (77°F); excursions are permitted (to 15-30ºC). Administer at a consistent time of day and at consistent intervals with regard to meals. Tacrolimus may be given with food as long as it is given the same way each time; however; administration with food significantly decreases the rate and extent of absorption. Grapefruit juice should be avoided during the entire course of tacrolimus administration.

8.7 Sirolimus

8.7.1 Description

Mode of Action: Rapamune (sirolimus) is a macrocyclic lactone produced by Streptomyces hygroscopic/I. Sirolimus inhibits T -lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. The sirolimus:FKBP-12 complex has no effect on calcineurin activity. This complex binds to and inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G I to the S phase of the cell cycle.

8.7.2 Toxicology

Human Toxicity: The most common (> 30%) adverse reactions are: peripheral edema, hypertriglyceridemia, hypertension, hypercholesterolemia, creatinine increased, abdominal pain, diarrhea, headache, fever, urinary tract infection, anemia, nausea, arthralgia, pain, and thrombocytopenia.

8.7.3 Pharmacology – Handling, Storage, Dispensing and Disposal

Drug Interactions: Sirolimus is known to be a substrate for both cytochrome P-450 3A4 (CYP3A4) and p-glycoprotein (Pgp). Inducers of CYP3A4 and P-gp may decrease sirolimus concentrations, whereas inhibitors of CYP3A4 and P-gp may increase sirolimus concentrations.

- Strong inducers and strong inhibitors of CYP3A4 and P-gp: avoid concomitant use of sirolimus with a strong inducer (e.g., rifampin, rifabutin) or strong inhibitor (e.g., ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, clarithromycin) of CYP3A4 and P-gp.
- Grapefruit juice: Because grapefruit juice inhibits the CYP3A4-mediated metabolism of sirolimus, it must not be taken with or be used for dilution of sirolimus.

Vaccination: Immunosuppressants may affect response to vaccination. The use of live vaccines should be avoided; live vaccines may include, but are not limited to, the following: measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid.

8.8 Total Marrow and Lymphoid Irradiation (TMLI)

Administration: Total marrow irradiation will be delivered using an Arc based IG-IMRT using a Helical Tomotherapy HiArt System (Tomotherapy, Inc) or Varian True Beam Rapid Arc (Varian, Inc.). The administration schedule and dose escalation scheme are described below.

8.8.1 Methodology:

CT simulation and immobilization: All patients undergo CT simulation for treatment planning purposes. The patient is scanned supine with arms at side on a CT simulator. Two planning CT scans are performed, one to plan body regions from head to pelvis and the other to plan for lower extremities. The body CT scan is obtained with normal shallow breathing. 4D CT scan data are acquired for chest and abdomen. If 4D CT is not available, shallow inspiration and expiration breath hold CT scans can be acquired instead. The normal shallow breathing CT data set is used for dose calculation and planning. The 4D CT datasets are registered to the planning CT to account for any organ motion during respiration. AccuFormTM (CIVCO Medical Systems, Kalona, IA) cushion is used in combination with Silverman headrest to support and stabilize the head and neck. A body vac-lokTM bag (CIVCO Medical Systems, Kalona, IA) and a thermoplastic head and shoulder mask are used as additional immobilization devices. The patient's arms, legs and feet are positioned using a vac-lok bag to enhance comfort and repositioning accuracy. Oral contrast is used to help visualize the esophagus. Couch height is approximately 10 cm below the isocenter of the gantry, and the patient is positioned on the couch so that the top of the head is approximately 5 cm from the end of the couch. Those settings are used to maximize the available length for the CT scanning and treatment delivery.

Target delineation: Target and avoidance structures and normal organs are contoured on an EclipseTM treatment planning system (Varian Medical Systems, Palo Alto, CA) or similar planning system. Avoidance structures contoured are user-defined and include lungs, heart, kidneys, liver, esophagus, oral cavity, parotid glands, thyroid gland, eyes, lens, optic chiasm and nerves, stomach, small and large intestine, breasts, rectum, ovary, and bladder. The 4D CT datasets are registered to the planning CT so that the contours of ribs, esophagus, kidneys, spleen and liver are enlarged to account for the organ movements during respiration. An additional 3 to 5 cm margin is usually added to the CTV to define the PTV target. Our center has added up to 10 cm margins in areas where larger setup uncertainty is observed, such as in the regions of the shoulder, arms, thighs, and posterior spinous processes. Spinal cord (part of the target) is outlined separately so to avoid hot spots in the spinal canal during planning. The mandible and maxillary bones are excluded from the target in an effort to minimize oral cavity dose and mucositis.

Treatment planning with a helical tomographic delivery system (Tomotherapy): DICOM-RT images are transferred to the Hi-ArtTM Tomotherapy treatment planning system (Accuray Inc. Palo Alto, CA). Helical Tomotherapy plan is designed such that a minimum of 85% of the target receives the prescribed dose. For the body treatment plan, jaw size of 5 cm, pitch of 0.287 and modulation factor of 2.5 are used for most patients as a balance of treatment time and plan quality. Plan quality index comprises target dose uniformity and critical organ doses. Since the first TMI patient treated in 2005, TMI treatment planning efforts at City of Hope have continued to evolve. Our current approach is to perform plan optimization in two stages. Critical organ sparing is optimized before target dose

uniformity optimization is done resulting in being able to escalate target doses without a proportionate increase in normal organ dose. Legs and feet are planned in Tomo-Direct mode. A 5 cm jaw size is used. Gantry angles of 0 and 180 degrees are selected. A composite dose of body plan and leg plan is generated to double check there is no dose gap or overlap at the junction.

Treatment planning with a VMAT conventional linear accelerator system: TMLI can be planned and treated using a conventional linear accelerator with VMAT capability as well. Multiple dynamic IMRT arcs with usually 3 to 4 isocenters are used to cover target regions. Collimator angles are varied for each arc to increase the planning degree of freedom and plan quality. After the plan of the body is finalized, the lower extremities are planned with two or three additional AP-PA fields given the lack of sensitive organs in this area. AP-PA fields are opened at 40 cm x 40 cm and gapped at 50% isodose line at midplane.

Treatment delivery: Our current procedure involves initial laser alignment of the patient in the vac-lok bag and thermoplastic mask. Verification CT positioning scans are performed prior to each treatment session using multiple cone beam CT scans (CBCTs) or one megavoltage CT (MVCT) scan from orbit to ischial tuberosities and is fused to the planning CT. Registration and couch shifts are reviewed and approved by attending physician before treatment is delivered. The Tomotherapy has a maximum treatment length of approximately 150 cm. A jaw size of 5 cm and pitch of 0.287 usually result a beam-on time of approximately 25 minutes to treat the upper body. On the Tomotherapy system, the patient translates through the unit head first to treat from the head to proximal thighs and is then re-setup and translates through the unit feet first to treat the lower extremities. Treatment of legs has a beam-on of time of approximately 10 minutes. With a conventional linear accelerator with VMAT capability, the verification CBCT will be performed for each isocenter before treatment delivery. The total treatment time is similar to TMI delivery using a helical topographic approach.
Each fraction of TMLI is 150 cGy, with two fractions delivered each day for 4 days. There will be a minimum of 6 hours between each fraction. Treatment will utilize helical tomotherapy or rapid arc IMRT as a means of conformal avoidance or minimization of radiation dose to normal organs.

- The target region will include bone marrow compartments and major lymph node regions (mediastinal, para-aortic, pelvic)
- Brain and testes will be treated to 1200 cGy for patients with ALL.
- Avoidance organs with dose sparing include brain (except ALL), liver, spleen, eyes, lens, parotids, thyroid, esophagus, oral cavity, lungs, heart, kidneys, stomach, upper GI and lower GI tract, rectum, bladder, and in women breast, uterus and ovaries.

Mean organ dose constraints for right and left lung 4 Gy, right and left kidney 4 Gy, liver 4 Gy and heart 8 Gy.

9.0 CORRELATIVE/ SPECIAL STUDIES

9.1 Laboratory Studies Performed

9.1.1 Pharmacokinetic Studies

9.1.1.1 Specimen Collection

All patients enrolled will be asked to undergo serial blood sampling to evaluate the systemic pharmacokinetics of ^{111}In- and ^{90}Y- basiliximab/DOTA. Prior to drug administration an indwelling heparin lock should be placed so that serial specimens can be collected. At each sampling time, 1 mL of blood will be withdrawn and discarded to assure that the solution used to maintain catheter patency does not dilute the sample. Alternatively, if the patient has a central venous catheter, it may be used for sample collection. In the event that the central venous catheter is used, sufficient blood should be withdrawn before each PK sample to assure that the solution used to maintain catheter patency does not dilute the PK sample.

9.1.1.2 PK Collection Time Points

Serial blood (5 cc) samples will be done at approximately time 1-2 hours, 3-4 hours, and at scan times of 1 day and 5/6 days after end of radiolabeled antibody infusion. Blood samples will be analyzed for total activity and by radiometric HPLC. These studies will acquire data on antibody metabolism and pharmacokinetics.

9.1.2 Bone marrow and blood samples - CD25 expression and histopathologic changes pre and post ^{90}Y-CD25 and TMLI conditioning.

The ***primary objective*** of the correlative studies is to evaluate CD25 expression of leukemia cells by flow cytometry, immunohistochemistry and serum CD25 levels pre-HCT, at 1 year and at time of first relapse, as was performed in prior COH studies evaluating ^{90}Y-CD25 in HL (IRB 08179). Serum levels of CD25 will be done at additional time-points, specified in the study calendar. In addition, histopathologic changes in bone marrow and estimated changes in bone marrow cellularity will be evaluated in patients with high-risk acute leukemia and myelodysplastic syndrome treated with the ^{90}Y-anti-CD25 basiliximab and total marrow and lymphoid irradiation (TMLI)/FLU/MEL hematopoietic cell transplantation (HCT) conditioning regimen.

9.1.2.1 Bone Marrow Aspirate Collection and Delivery

Schedule of sample collection will occur as stated in the Study Calendar (see Section 10.0).

1. Each bone marrow aspirate tube should be labeled with the study IRB number, research participant number (RPN), and sample collection time point.
2. After material for diagnostic tests has been removed, approximately **10 ml of bone marrow aspirate in EDTA (lavender top) tube(s)** will be collected.
3. Gently invert tube several times after collection.
4. Sample should be transferred to the Hematopoietic Tumor Bank (HTB) for registration. Once registration is complete, the HTB will inform the Hui laboratory that the de-identified specimen is ready to be picked up. A representative of the Wong/Hui laboratory will pick up the specimen and process it within 2-4 hours of harvest.
5. Note: for cases in which the baseline bone marrow aspirate was collected per standard-of-care at City of Hope prior to the patient's consent on trial, we will use the banked sample from the HTB (if available) to perform these tests. This may not be possible if the baseline marrow was performed at an outside institution.

9.1.2.2 Bone Marrow Trephine Sample Collection, Processing and Delivery

Schedule of sample collection will occur as stated in the Study Calendar (see Section 10.0).

1. As part of diagnostic tests, the BM biopsy core will be sent to and processed by COH Histopathology Core.
2. Histopathology Core will prepare 1 H&E and 10 unstained slides from the core block and label each slide with the study IRB number, research participant number (RPN), and sample collection time point.
3. Slides should be transferred to the Wong/Hui lab, Kaplan-Black, Room 109a (Susanta Hui x80556).
4. Note: for cases in which the baseline bone marrow biopsy was collected prior to the patient's consent on trial, we will obtain slides from the archived specimen, if available.

9.2 Research Sample Collection and Dispensation

Study Analysis	Sample Type	Tube Type	Volume (mls/tube) / # of tubes	Collection	Processing / Storage	Deliver to Lab (time limit)
CD25 serum levels	Blood	Red top tube	5-7 ml 1 tube	N/A	No processing	Clinical Laboratory per COH SOPs
Pharmacokinetics	Blood	Purple top (EDTA) and Red top	2.5 ml per tube per time-point	Invert 8 times/ambient	No processing	Radiopharmacy lab
CD25 expression and BM damage	Bone Marrow Aspirate And Biopsy	Purple top (EDTA) (aspirate)	(1)10 ml tube	Invert 8 times	No processing	HTB, then Joo Song MD in Pathology and Wong/Hui Lab
		1 H&E and 10 unstained slides from the core block		N/A	No processing	Histopathology Core then Joo Song MD in Pathology and Wong/Hui Lab

Note: The order of tube collection should be per Clinical and Laboratory Standards Institute (ex. Order of draw: sodium citrate tube, serum tube, heparin tube, EDTA tube). It is acceptable to use other available tube sizes to ensure collection of the required volume of blood.

10.0 STUDY CALENDAR

All assessments may increase in frequency as clinically indicated.

10.1 Pre-transplant Study Calendar

Procedure	Pre-Study Screening	Day -15 or -14	Day -14 or -13	Day -9	Day-8	Day -7	Day -6	Day-5	Day-4	Day-3	Day -2	Day -1
Medical History[2]	X											
Physical exam/vital signs[3]	X[1]											
Height	X											
Weight	X[1]											
KPS score	X[1]											
Pulmonary function test[4]	X[14]											
Echocardiogram/MUGA Scan	X[14]											
CT Chest	X[14]											
FDG-PET/CT[5]	X											
Laboratory Tests												
CBC with diff	X[1]	X[15]		X								
CMP[6]	X[1]											
Coagulation panel + PT/PTT	X[1]											
Ferritin	X[1]											
Immunoglobulin/IgG level	X[1]											
Serum thyroid panel[7]	X[1]											
ABO/Rh type and antibody	X[14]											
Serum HCG/urine pregnancy[8]	X[1]											
Urinalysis	X[1]											
24 hr. urine creatinine clearance[9]	X[14]											
BM biopsy/Cytogenetics[10]	X[14]											
CMV qPCR	X[14]											
SOC HIV ag/ab combo	X[14]											
Hepatitis (B and C)	X[14]											
Syphilis panel by RPR	X[14]											
High resolution HLA typing	X											
Consultation												
Surgery or IR[11]	X											
Ancillary[12]	X											
Treatment												
"Cold" Basiliximab		X										
^{111}In/^{90}Y-antiCD25 Basiliximab		X										
^{111}In-antiCD25 Basiliximab nuclear scans		X	X	X								
TMLI (1200 cGy)					X	X	X	X				
Fludarabine									X	X	X	
Melphalan											X	
Sirolimus and tacrolimus												X
Study evaluations												
Toxicity and/or GvHD grading												
Blood draw for sCD25	X	X										
Research BM sample collection[13]	X											
Blood sample for Pharmacokinetics		X	X	X								

1. To occur within 30 days prior to start of protocol therapy, or at the discretion of the physician.
2. To include a review of treatment history, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study
3. Vital signs: heart rate, blood pressure, respiration rate, and temperature
4. Pulmonary function test with DLCO and FEV1
5. For patients with NHL, only
6. CMP with lactate dehydrogenase (LDH), uric acid, magnesium, phosphorus, triglycerides
7. Serum thyroid panel including Thyroid Stimulating Hormone (TSH), T3 and free Thyroxine
8. For women of childbearing potential only
9. Should the creatinine clearance be reported as below the level required for eligibility, a renal GFR scan may be performed to determine the renal status for eligibility
10. Unilateral
11. All patients must have a double lumen central venous catheter, Hickman catheter or PICC line in place to allow proper therapy and supportive care
12. Dietitian, psycho-social team when indicated
13. Correlative studies are to evaluate CD25 expression of leukemia cells by flow cytometry, immunohistochemistry and serum CD25 levels pre-HCT, at 1 year and at time of first relapse, as was performed in prior COH studies evaluating 90Y-CD25 in HL (IRB 08179). In addition, histopathologic changes in bone marrow and estimated changes in bone marrow cellularity will be evaluated in patients with high-risk acute leukemia and myelodysplastic syndrome treated with the 90Y-anti-CD25 basiliximab and total marrow and lymphoid irradiation (TMLI)/FLU/MEL hematopoietic cell transplantation (HCT) conditioning regimen.
14. To occur within 8 weeks prior to start of protocol therapy, or at the discretion of the physician.
15. CBC with differential should be done prior to infusion of study drug.

10.2 Post-Transplant Study Calendar

Procedure	Day 0[9]	Day +3	Day +4	Day +5	Day +30[10]	Day +60[10]	Day +100[10]	Day +180[11]	Year 1[12]	Year 2[12]	At First relapse[14]
Standard of care											
Physical exam/vital signs[1]	X	X	X	X	X	X	X	X	X	X	
Weight[1]	X	X	X	X	X		X	X	X	X	
FDG-PET/CT[2]					X		X	X	X	X	
CBC with diff + platelet count[1]	X	X	X	X	X	X	X	X	X	X	
CMP[3]					X			X	X	X	
IgG level					X						
Serum thyroid panel[4]								X	X	X	
Pulmonary function test									X	X	
Echocardiogram/MUGA scan									X	X	
EKG									X	X	
CMV qPCR[5]	X				X	X	X				
Coagulation panel + PT/PTT[6]	X										
Engraftment status[7]					X	X	X	X	X	X	
Bone marrow biopsy/aspirate[8]					X		(X)	X	X	X	
GVHD assessment and grading[6]	X				X	X	X	X	X	X	
Treatment											
Stem cell infusion	X										
Tacrolimus/Sirolimus (Per Section 5.4)				X							
Study intervention											
Toxicity and/or GvHD grading	X				X	X	X	X	X	X	
Blood draw for sCD25	X				X	X	X		X		X
Research BM sample collection and serum CD25 levels [13]									X		X

1. Daily during admission until discharge, then in every clinic visit (diff to be done when valid differential can be run per lab rules)
2. Only for patients with NHL. The day 30 PET/CT will be done only if clinically indicated. CT NCAP can be done for restaging in cases in which PET/CT scan may not be feasible (example: insurance issues).
3. CMP with lactate dehydrogenase (LDH), uric acid, magnesium, phosphorus, triglycerides
4. Serum thyroid panel including Thyroid Stimulating Hormone (TSH), T3 and free Thyroxine
5. Weekly from transplant through day 99 then monthly until off all immunosuppression
6. Weekly from transplant until discharge then per COH SOPs
7. Chimerism studies on peripheral blood for total CD3+, and CD15+ subsets
8. For leukemia and MDS patients: with cytogenetics, FISH, chimerism and MRD. BMBx not required at day 100.
   For patients with NHL: BMBx only required at day 100 and should include chimerism as well as testing per standard of care.
9. A window of ±2 days is allowed for stem cell infusion
10. A window of ±7 days is allowed
11. A window of ±14 days is allowed
12. A window of ± 1 month is allowed
13. Correlative studies are to evaluate CD25 expression of leukemia cells by flow cytometry, immunohistochemistry and serum CD25 levels pre-HCT, at 1 year and at time of first relapse, as was performed in prior COH studies evaluating ^{90}Y-CD25 in HL (IRB 08179). In addition, histopathologic changes in bone marrow and estimated changes in bone marrow cellularity will be evaluated in patients with high-risk acute leukemia and myelodysplastic syndrome treated with the ^{90}Y-anti-CD25 basiliximab and total marrow and lymphoid irradiation (TMLI)/FLU/MEL hematopoietic cell transplantation (HCT) conditioning regimen. Note: When feasible, flow cytometry for CD25 may be done anytime a bone marrow examination is taken after transplant up until year 2 or 1st relapse, whichever comes first.
14. Once a patient has relapsed after transplant, the subject will be followed only for survival, and the study calendar requirements are no longer required.

11.0 ENDPOINT DEFINITIONS/MEASUREMENT OF EFFECT

11.1 Primary Endpoint(s)

- Maximum tolerated dose/recommended phase II dose (MTD/RP2D) of ^{90}Y-DOTA-anti-radioimmunotherapy.
- Toxicity: Toxicity will be scored on both the Bearman Scale (**Appendix A**) and NCI CTCAE v5 Scale (**Appendix A**).

11.2 DLT Definition

For the purposes of this study, Dose limiting toxicity (DLT) will be defined as any of the following that are assigned an attribution level of at least possibly related to the conditioning regimen (^{90}Y-basiliximab-DOTA, TMLI, fludarabine and melphalan) and other treatment related AE's (non-related to the conditioning regimen):

- For non-hematologic toxicities, any grade III/IV toxicity per Bearman Toxicity Grading Scale or
- For non-hematologic toxicities (not part of the Bearman toxicity grading scale), any ≥grade 4 toxicity per NCI CTCAE v5.
- For hematologic toxicities, per NCI CTCAE v5 toxicity criteria, any grade 4 neutropenia associated with fever or infection and lasting for more than 21 days, or grade 4 neutropenia lasting for more than 28 days (engraftment failure).
- Any other conditioning regimen-related cause of death.
- In addition, septic DLT is defined as: any grade 5 sepsis-related toxicity that is assigned an attribution level of at least possibly related to the conditioning regimen.

Note: The NCI CTCAE v5 scale will also be used for adverse event reporting.

11.3 Secondary Endpoint(s)

- Overall survival (OS): Patients are considered a failure for this endpoint if they die, regardless of cause. Time to this event is the time from start of protocol therapy to death, or last follow-up, whichever comes first.
- Event-free survival (EFS): Patients are considered a failure for this endpoint if they relapse/progress or die, regardless of cause. Time to this event is the time from start of protocol therapy to death, relapse/progression, or last follow-up, whichever comes first.
- Relapse/Progression (CIR): The event is relapse/progression. Time to this event is measured from start of therapy. Death without relapse/progression is considered a competing risk. Surviving patients with no history of relapse/progression are censored at time of last follow-up.
- Graft versus host disease and relapse free survival (GRFS): The event is relapse/progression, acute grade 3 or 4 GVHD, or chronic GVHD requiring systemic therapy. Time to this event is measured from start of therapy. Death without relapse/progression, acute grade 3 or 4 GVHD or chronic GVHD requiring systemic therapy is considered a competing risk. Surviving patients with no history of relapse/progression or GVHD are censored at time of last follow-up
- CR Proportion at Day +30: The event is documented complete remission (CR) at Day +30. Time to event is measured from the start of therapy to the time of biopsy proven CR.
- Non-relapse Mortality (NRM): Patients are considered a failure for this endpoint if they die from causes other than disease relapse or progression. NRM is measured from start of therapy until non-disease related death, or last follow-up, whichever comes first.

- Incidence of Infection: Microbiologically documented infections will be reported by site of disease, date of onset, severity and resolution, if any. These data will be captured via case report form and will be collected from Day 0 until 100 days post-transplant.
- Neutrophil Recovery: Measured from stem cell infusion to the first to three consecutive days with neutrophil count greater than 0.5x109/l.
- Acute Graft versus Host Disease (aGVHD) of grades 2-4 and 3-4: Documented/biopsy proven acute graft versus host disease is graded according to the Consensus Grading (**Appendix B**). Time to event is measured from date of stem cell infusion to document/biopsy proven acute GVHD onset date (within the first 100 days post-transplant) and will be used to estimate the cumulative incidence.
- Chronic Graft versus Host Disease (cGVHD): Documented/biopsy proven chronic graft versus host disease is scored according to NIH Consensus Staging (**Appendix B**). Time to event is measured from approximately 80-100 days post-transplant to the documented/biopsy proven chronic GVHD onset date and will be used to estimate the cumulative incidence.

11.4 Response Criteria Definition

Response criteria will be specific to each disease with only the following categories being relevant post-transplant:

a. Complete remission

b. Relapse

c. Disease persistence/progression

d. Minimal residual disease

For detailed description of the corresponding categories within the response criteria for each disease check the references:

11.4.1 AML: Per Dohner et al.[10]

a. Complete Remission: Remission is defined as <5% blasts with no morphological characteristics of acute leukemia (e.g., Auer rods) or myelodysplasia in a bone marrow with >20% cellularity, and peripheral blood counts showing ANC >1000/µL (including patients in CR with incomplete platelet recovery). In addition, normalization of cytogenetics must be demonstrated by the absence of previous cytogenetic abnormalities identified prior to transplantation in the bone marrow aspirate, without appearance of new abnormalities.

b. Relapse

Any of the following indicates relapse:

- The reappearance of blast cells in the peripheral blood
- >5% blasts in the marrow, not attributable to another cause (e.g., bone marrow regeneration)
- The appearance of new dysplastic changes within the bone marrow
- Development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid
- Reappearance of cytogenetic abnormalities present prior to transplantation

c. Disease persistence/progression

Patient does not achieve CR upon repeat bone marrow examination after therapy and displays persistent evidence of disease by cytogenetics in blood or bone marrow consistent with pre-transplant features, or consistent with progression of MDS to AML.

d. Minimal residual disease (MRD)

MRD will be assessed from bone marrow aspirates on days 30, 100, and 180 post-transplant.

11.4.2 ALL: NCCN guidelines for ALL Version 3.2017

a. Complete remission:
   - No circulating blasts or extramedullary disease
   - No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement
   - Trilineage hematopoiesis (TLH) and 5% blast
   - Absolute neutrophil count (ANC)>1000/microL
   - Platelets>100,000/microL
   - No recurrence for 4 weeks

b. Relapse
   - Reappearance of blasts in the blood or BM (>5%) or in any extramedullary site after CR

c. Disease persistence/progression
   - Failure to achieve CR at the end of induction
   - Increase of at least 25% in the absolute number of circulating or BM blasts or development of extramedullary disease

11.4.3 MDS: Savona, Malcovati et al. 2015[11]

a. Complete Remission (presence of all of the following improvements)
   - Bone marrow:
     - ≤5% myeloblasts (including monocytic blast equivalent in case of CMML) with normal maturation of all cell lines and return to normal cellularity
     - Osteomyelofibrosis absent or equal to “mild reticulin fibrosis” (≤grade 1 fibrosis)
   - Peripheral blood
     - WBC ≤10 × 109 cells/L
     - Hgb ≥11 g/dL
     - Platelets ≥100 × 109/L; ≤450 × 109/L
     - Neutrophils ≥1.0 × 109/L
     - Blasts 0%
     - Neutrophil precursors reduced to ≤ 2%
     - Monocytes ≤1 × 109/L
   - Extramedullary disease: Complete resolution of extramedullary disease present before therapy (eg, cutaneous disease, disease-related serous effusions), including palpable hepatosplenomegaly

- Provisional category of CR with resolution of symptoms: CR as described above, and complete resolution of disease-related symptoms as noted by the MPN-SAF TSS
- Persistent low-level dysplasia is permitted given subjectivity of assignment of dysplasia

b. Relapse (Partial Remission)

- Normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity *except* in cases of MDS/MPN with ≤5% bone marrow blasts at baseline.
- **Marrow response**
    - Optimal marrow response: Presence of all marrow criteria necessary for CR without normalization of peripheral blood indices as presented above.
    - Partial marrow response: Bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity, *or* reduction in grading of reticulin fibrosis from baseline on at least 2 bone marrow evaluations spaced at least 2 mo apart

c. Disease persistence/progression: (Combination of 2 major criteria, 1 major and 2 minor criteria, or 3 minor criteria from list)

- Major criteria
    - Increase in blast count*
        - <5% blasts: ≥50% increase and to >5% blasts
        - 5-10% blasts: ≥50% increase and to >10% blasts
        - 10-20% blasts: ≥50% increase and to >20% blasts
        - 20-30% blasts: ≥50% increase and to >30% blasts
    - Evidence of cytogenetic evolution
        - Appearance of a previously present or new cytogenetic abnormality in complete cytogenetic remission via FISH or classic karyotyping
        - Increase in cytogenetic burden of disease by ≥50% in partial cytogenetic remission via FISH or classic karyotyping
    - New extramedullary disease
        - Worsening splenomegaly
        - Progressive splenomegaly that is defined by IWG-MRT: the appearance of a previously absent splenomegaly that is palpable at >5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of >10 cm
        - Extramedullary disease outside of the spleen
        - To include new/worsening hepatomegaly, granulocytic sarcoma, skin lesions, etc.
- Minor criteria
    - Transfusion dependence§

- Significant loss of maximal response on cytopenias ≥50% decrement from maximum remission/response in granulocytes or platelets
- Reduction in Hgb by ≥1.5g/dL from best response or from baseline as noted on complete blood count
- Increasing symptoms as noted by increase in ≥50% as per the MPN-SAF TSS||
- Evidence of clonal evolution (molecular)

11.4.4. Response Criteria for NHL

This will be done using the Lugano Response Criteria (cheson 2016)

Revised Criteria for Response Assessment[12]		
Response and Site	**PET-CT–Based Response**	**CT-Based Response**
Complete Response	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 a with or without a residual mass on 5PS[b]. It is recognized that in Waldeyer's ring or extra-nodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake. No evidence of FDG-avid disease in marrow.	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi. No extra-lymphatic sites of disease.
Bone Marrow	No evidence of FDG-avid disease in marrow.	Normal by morphology; if indeterminate, IHC negative.
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease. At end of treatment, these findings indicate residual disease.	Or ≥ 50% decrease in SPD of up to 6 target measurable nodes and extra-nodal sites. When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value, when no longer visible, 0 × 0 mm. For a node >5 mm× 5 mm, but smaller than normal, use actual measurement for calculation. Spleen must have regressed by > 50% in length beyond normal
Bone Marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	N/A

No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extra-nodal lesions	Score 4 or 5[b] with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Bone Marrow	No change from baseline	N/A
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal Masses.	Score 4 or 5[b] with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment. New lesions New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation); if uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	PPD progression: An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase in by ≥ 50% from PPD nadir and An increase in LD or SD from nadir: 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline. If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly New or clear progression of preexisting non-measured lesions Regrowth of previously resolved lesions A new node > 1.5 cm in any axis. A new extra-nodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. Assessable disease of any size unequivocally attributable to lymphoma
Bone Marrow	New or recurrent FDG-avid foci	New or recurrent involvement

5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; IHC = immunohistochemistry; LD = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LD and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

[a]A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extra-nodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured; dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extra-nodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extra-nodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

[b]PET 5PS: 1 = no uptake above background; 2 = uptake ≤ mediastinum; 3 = uptake > mediastinum but ≤ liver; 4 = uptake moderately > liver; 5 = uptake markedly higher than liver and/or new lesions: X = new areas of uptake unlikely to be related to lymphoma.

Cheson, B.D., et al., Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood, 2016. 128(21): p. 2489-2496.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design

This is a single-institution, non-randomized phase I trial to determine the maximum tolerated dose/ recommended phase II dose (MTD/RP2D) of ^{90}Y-DOTA-anti-CD25 Basiliximab MAB when given in combination with fixed doses of fludarabine, melphalan, and 1200 cGy TMLI as conditioning regimen to patients with high-risk acute leukemia (lymphocytic or myelogenous) or myelodysplastic syndrome who undergo alloHCT with matched related/unrelated or haploidentical donor. Dose escalation will be based on a modified rolling 6 Phase I design. There will also be a dose level -1 of 0.2 mCi/kg in the case that dose level 1 is too toxic (Table 12.1).

Table 12.1. ^{90}Y-DOTA-antiCD25 Basiliximab Mab dose escalation

Dose Level	Administration Dose
-1	0.2 mCi/kg
1	0.3 mCi/kg
2	0.4 mCi/kg
3	0.5 mCi/kg

12.2 Dose Escalation Schedule: Adapted Rolling 6 Design

This study will employ a modified, more conservative version of the rolling 6 design of Skolnik, J.M., et al, 2008. In this design, at most 3 patients will be under observation for DLT on the current test dose level at any time. Patients who are not evaluable for DLT will be replaced. Once each patient is evaluable for toxicity and passes without a DLT, an additional patient may be accrued on that dose level, with up to 6

total patients treated per dose level. Once 3 patients are evaluable with no patient at that dose level experiencing a DLT, the dose can be escalated, or up to 3 additional patients may be treated at the current dose level at discretion of PI. Although this design does not require that 6 patients be treated at a given dose level, no more than 6 evaluable patients will be accrued to any dose level during the dose finding portion of this study. If at any time, the dose level has 1 documented DLT with fewer than 6 evaluable patients, accrual will continue until 6 patients are evaluable or a second DLT occurs. Escalation will terminate as soon as two or more patients experience any DLT attributable to the study treatment, at a given dose level, and the next lower dose will be expanded. MTD/RP2D will be declared as the highest dose where 6 patients have been treated and at most one patient experiences DLT. There will be no dose escalation within a patient. Dose escalation rules are outlined in **Table 12.2**.

Note: no more than 3 patients can be <30 days post stem cell infusion at any time. If at the starting dose, level 1, >1/6 patients experiences unacceptable toxicity within 30 days after stem cell infusion, subsequent patients will receive a de-escalated dose to dose level -1. Note: the fludarabine dose, melphalan dose and TMLI dose will remain fixed (see section 5.1) for all defined dose levels and will not be reduced at any point.

At the MTD/RP2D, or if ≤ 1/6 patients treated at the highest dose experiences DLT, the trial will enroll up to an additional 6 patients at the that dose.

Table 12.2. Dose escalation rules

# Patients on Current Level			**Action**
DLT	**EVAL**	**EVAL+At Risk**	
0	0	1-2	Accrue next patient at this level*
0	0	3	Hold accrual
0	1	1-3	Accrue next patient at this level
0	1	4	Hold accrual
0	2	2-4	Accrue next patient at this level
0	2	5	Hold accrual
0	3-6	3-6	Accrue next patient at the next higher level*,+
1	1	1-2	Accrue next patient at this level
1	1	3	Hold Accrual
1	2	2	Accrue next patient at this level
1	2	3-4	Hold accrual
1	3-5	3-5	Accrue next patient at this level
1	3-5	6	Hold accrual
1	6	6	Accrue next patient at the next higher level*
2**	Any	any	Accrue next patient at the next lower level to a maximum of 6

*During the dose-escalation portion, if higher dose level is already closed, the next lower dose will accrue to a total of 6 patients, with 2 or higher DLTs requiring further dose de-escalation.
+Although under this scenario escalating to the next higher dose level is suggested, additional patients can be accrued to the current level -up to n=6 patients.
**Patients treated on a higher dose will have their treatment modified to the dose below the dose level with 2 DLTs, if pending patients have DLT.
DLT: a patient with a documented DLT; PASS: a patient without a DLT fully evaluable for toxicity for the purpose of dose escalations (see section 10.1 for detail); EVAL: a patient who is either DLT or PASS; Inevaluable: a patient who is off treatment without being DLT or PASS; At Risk: a patient who is on study and not yet DLT, PASS, or Inevaluable

12.3 DLT Window

The DLT window is from the start of conditioning through 30 days post stem cell infusion. Based on our TMLI experience late breaking DLTs have not been seen and patients are continue to be followed on our Long-Term toxicity protocols. While not expected, patients with DLTs (beyond day +30) will be followed until resolution or stability.

Note: all transplant patients are followed for longer-term follow-up as part of the Survivorship Program and all TMLI patients as part of IRB#07173. The first TMLI patient was treated in 2005.

12.4 Participant Evaluability and Replacement

To be evaluable for toxicity, a patient must start conditioning. Patients are evaluable for DLTs if they receive the ^{90}Y-basiliximab-DOTA and be followed for 30 days post-transplant or experience a DLT. Patients who are not evaluable for DLTs within the context of dose escalation will be replaced.

(**Note**: A planned dose might not be received by a patient due to patient choice or treating physician's judgment.)

12.5 Sample Size, Accrual Rate and Study Duration

Assuming the highest dose level is well tolerated, dose levels 1-2 will accrue 3 patients at each dose level, 6 patients will be enrolled at the top dose level (3), for a total of 12 patients.

12.6 Additional Toxicity Monitoring

To ensure patient safety, if >1 subject experiences any grade 3 or 4 toxicity per the Bearman Scale -among the first six subjects enrolled/treated, or at a rate ≥ 25% anytime thereafter, the study will halt the accrual of BM patients, the DSMC will then be notified, and an amendment will be submitted for approval by the CPRMC and IRB.

Out of an abundance of caution, non-relapse mortality (NRM) by day 180 as a safety endpoint will also be monitored in all patients. NRM is defined as death occurring in a patient from causes other than relapse or progression. NRM is measured from date of stem cell infusion until non-disease related death. Deaths from relapse/progression are considered a competing risk. NRM will be censored at last follow-up if patients are alive and remain disease free.

We will suspend accrual and perform safety review whenever the stopping boundary is crossed and submit reports to COH DSMC. DSMC approval is required before reopening the study for accrual. The stopping boundaries due to safety concerns are as follows and are based on a previously published TMLI/Flu/Mel trial in a similar population which reported an NRM rate of 30% (Jensen LG, Stiller T, Wong JYC, Palmer J, Stein A, Rosenthal J. Total Marrow Lymphoid Irradiation/Fludarabine/Melphalan Conditioning for Allogeneic Hematopoietic Cell Transplantation. Biology of Blood and Marrow Transplantation. 2018;24(2):301-7.

	Stopping Boundary	
	N=10	N=20
D180 NRM	>=5	>=6

12.7 Statistical Analysis Plan

Toxicity information recorded in each patient will include the type, severity, and the probable association with the study regimen. Tables will be constructed to summarize the observed incidence by severity and type of toxicity, and dose levels. Baseline disease information (e.g. the extent of prior therapy) and demographic information will be presented, to describe the patients treated in this study. All patients who begin/receive treatment will be included as part of an 'as treated' analysis, in terms of survival, relapse/progression, non-relapse mortality and toxicities/complications. Survival estimates will be calculated using the Kaplan-Meier method. The cumulative incidence of relapse/progression, non-relapse mortality and acute/chronic GVHD will be calculated as competing risks.

13.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

13.2 Data Capture Methods and Management

Data for this trial will be collected using City of Hope's electronic capture system (EDC) that is compliant with 21 CFR Part 11.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

13.3 Case Report Forms

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Investigator or designee in a timely fashion.

13.4 All data will be collected using electronic data collection.Regulatory Records

The Investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

14.0 REPORTING OF ADVERSE EVENTS, UNANTICIPATED PROBLEMS & OTHER EVENTS OF INTEREST

The research team is responsible for classifying adverse events (AEs) and unanticipated problems (UPs) as defined in the relevant regulations and reporting to all applicable parties, including but not limited to the COH IRB, DSMC, Food and Drug Administration (FDA), National Institutes of Health (NIH) and other collaborators, e.g., pharmaceutical companies. The research team is responsible for the continued monitoring and tracking of all AEs in order to ensure non-reportable events are reviewed and monitored and do not rise to a reporting level.

14.1 Assessment of Adverse Events

The site Investigator will be responsible for determining the event name, and assessing the severity (i.e., grade), expectedness, and attribution of all adverse events as applicable per the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. Adverse events will be characterized using the descriptions and grading scales found in NCI CTCAE v5.0. A copy of the scale can be found at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated –** The event is clearly NOT related to study treatment, and is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.
- **Unlikely –** The event is unlikely related to the study treatment, and is most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event may be related to study treatment, as it follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable –** The event is most likely related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is unlikely related to the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Definite –** The event is clearly related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is not reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs.

14.2 Adverse Events of Special Interest (AESI)

14.2.1 Overdose

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of the investigational drug of ^{111}In/^{90}Y-DOTA-basiliximab assigned to a given patient, regardless of any associated adverse events or sequelae.

PO	any amount over the protocol-specified dose
IV	10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported.

14.3 Pregnancies

14.3.1 Female participants:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female participant occurring after the participant receives the first dose of protocol therapy up to 6 months following duration of study participation are considered immediately reportable events. **Protocol therapy is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Study PI immediately within 24 hours of awareness (Sections 14.5.1 and 14.5.2)**. The female subject may be referred to an obstetrician-gynecologist (preferably one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator should make every effort to follow the female participant until completion of the pregnancy per institutional policies.

Abnormal pregnancy outcomes and neonatal deaths that occur within 28 days of birth should be reported as an SAE per expedited reporting guidelines.

Any infant death after 28 days that the Investigator suspects is related to the *in utero* exposure to protocol therapy should also be reported as an SAE per expedited reporting guidelines.

14.3.2 Male participants:

If a female partner of a male participant becomes pregnant, the male participant should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

The Investigator should make every effort to follow the outcome of the pregnancy per institutional policies.

14.4 Routine AE Collection and Reporting Guidelines

AEs will be collected from the signing of informed consent until ending study participation. Routine AE reporting will occur via data entry into the study eCRF. AEs will be monitored by the Protocol Management Team (PMT). AEs reported through expedited processes (e.g., reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

Routine recording of adverse events will occur via data entry into the study eCRF. Collect the start date and highest grade of toxicity using the Bearman Scale and CTCAE v5 for these time points:

- Day -15 to Day -1,
- Day 0 to Day +30, and
- Day +31 to +100 post-transplant.

After day 100, collect only AEs that are grade 3 or above(or any event that is considered an SAE) that are considered possibly, probably or definitely related to treatment (per table below), until the patient is off study. **Note**: for any grade 4 neutropenia, stop dates will also be collected. If a patient relapses and begins other anti-cancer therapy, only SAEs related to study therapy will be recorded (as per table below).

Adverse events will be monitored by the Protocol Management Team (PMT). Adverse events that do not meet the criteria of serious OR are not unanticipated problems do not require expedited reporting. AEs reported through expedited processes (i.e. reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

14.5 Expedited Reporting

Table 14.5 indicates what events must be reported expeditiously.

Serious Adverse Events that require expedited reporting and unanticipated problems will be reported according to the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy.

Reporting of SAEs will begin once the patient receives the ^{90}Y-basiliximab-DOTA dose, and must be followed until the event is resolved, stabilized, or determined to be irreversible by the investigator. Follow-up SAE reports must be submitted for all events that require expedited reporting when the status of the event changes and until the resolution or stabilization of the event.

Table 14.5 Criteria for Expedited Reporting

Time point	What to report
From signing of the consent to study completion	• All UPs
For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier	• All SAEs regardless of relationship to protocol therapy • All UPs and AEs that meet the definition of a UP
From Day 1 of protocol therapy up to 6 months following duration of study participation	• Pregnancies and lactation
Post Safety Follow-Up to removal from study	• All SAEs that are considered possibly, probably or definitely related to treatment
NOTE: All events reported expeditiously require follow-up reporting until the event is resolved, stabilized, or determined to be irreversible by the investigator.	

14.6 Reporting to the FDA

The study PI (or designee) will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy.

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the MedWatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA **no later than 7 calendar days** after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted **no later than 15 calendar days** after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported **as soon as** the relevant information becomes available. [21 CFR 312.32(d)(3)]

In addition, on behalf of the study PI, OIDRA will submit annually within 60 days of the anniversary of the date the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report of adverse drug experiences, and history of actions taken since the last report because of adverse drug experiences.

15.0 ADHERENCE TO THE PROTOCOL & REPORTING OF PROTOCOL DEVIATIONS

Deviations from the protocol should be avoided, except when necessary to eliminate immediate hazard(s) for the protection, safety, and well-being of a research participant. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly. All protocol deviations and planned protocol deviations will be reported in accordance with the City of Hope Clinical Research Protocol Deviation policy.

16.0 STUDY OVERSIGHT, QUALITY ASSURANCE, & DATA AND SAFETY MONITORING

16.1 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

16.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities are executed in accordance with federal regulations.

16.3 Protocol Management Team (PMT)

The Protocol Management Team (PMT), minimally consisting of the study PI, collaborating investigators, research nurse, clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) to review study status. The meeting is a forum to discuss study related issues including accrual, SAE/AE/UPs experienced, study response, deviations/violations, and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed.

16.4 Quality Assurance

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the City of Hope Office of Clinical Trials Monitoring (OCTM), within City of Hope's Office for Safety and Data Quality.

Details of clinical site monitoring are documented in the OCTM SOP and the Risk Based Monitoring (RBM) plan. These documents specify the frequency of monitoring, monitoring procedures, the amount of subject data to be reviewed, and the distribution of monitoring reports to the study team and the COH DSMC.

16.5 Risk Determination

This is a high risk study, as defined in the City of Hope Institutional DSMP. This determination was made because the study involves a COH IND.

16.6 City of Hope Data and Safety Monitoring Committee

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor study progress, compliance, toxicity, safety, and accrual data from this trial via the PMT Progress Report (submitted by the Study Principal Investigator according to the frequency outlined in the City of Hope Institutional DSMP). The DSMC is composed of clinical specialists who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Protocol Management Team.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

17.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
  - Title 21 Part 312 – Investigational New Drug Application
  - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
- Applicable NIH policies and procedures
- Applicable institutional research policies and procedures

17.3 Institutional Review Board

An Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol, informed consent form and any additional documents that the IRB may need to fulfill its responsibilities (Investigator's Brochure, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) prior to initiation of the study. Revisions to approved documents will require review and approval by the IRB before the changes are implemented in the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator before the study is initiated.

The IRB will be informed of serious unexpected, unanticipated adverse experiences, and unanticipated problems occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

All participating sites must follow the lead institution's IRB-approved protocol.

17.4 Informed Consent

The Principal Investigator or IRB approved named designee will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights if applicable, and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

Children will provide assent when appropriate and indicated per institutional policy. Participants who are minors, who attain the age of majority while the study is still underway, must consent to continue taking part in the research.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection by sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

17.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies. The COH DCC should be promptly notified of the change in participant status.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures and chart review and survival follow-up.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and survival follow-up.
- Withdrawal from study treatment, all active procedures, and any future data collection.

Participants who agreed to the collection of research blood samples may withdraw consent to use their specimens, if they are not yet processed as detailed in the consent form. Once the PI and site PI is notified

of this withdrawal of informed consent, the research specimens will not be used in any research. At that time, any of the existing specimens will be destroyed.

17.6 Special and Vulnerable Populations

17.6.1 Women and Minorities

The study is open to anyone regardless of gender, race or ethnicity. Efforts will be made to extend the accrual to a representative population. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Pregnant women are excluded because ^{90}Y-DOTA-anti-CD25 is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Name of Agent, breastfeeding should be discontinued if the mother is treated with ^{90}Y-DOTA-anti-CD25.

17.6.2 Pediatric Population

Pediatric participants (< 18 years of age) are excluded from this study because safety and effectiveness of protocol therapy has not yet been defined for the study population. Additional studies may be performed in the pediatric population once safety and effectiveness of protocol therapy is defined in the adult study population.

17.6.3 HIV Positive Individuals

Participants with HIV are excluded due to concerns about inadvertent augmentation of infectious and/or inflammatory activity.

Participants with HIV are included based on specifications outlined in inclusion criteria.

17.6.4 Vulnerable Populations

Per 45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, and economically or educationally disadvantaged persons as vulnerable populations.

17.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed subject authorization informing the subject of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, and the rights of a research participant to revoke their authorization for use of their PHI. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number.

The Investigator/Institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB reviews, and FDA/regulatory authority inspections. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participant specimens will be de-identified (coded) prior to submission to research laboratories. The specimens will be labeled with the study number, subject (accession) ID, date and time point of collection. The key to the code will be maintained in the COH clinical trials management system which is a secure environment.

17.8 Use of Unused (Leftover) Specimens Collected for this Trial

Unused samples in existence at study completion (i.e. completion of all research activities under this study) will either be: (a) placed in a COH IRB approved biorepository with some clinical information and potentially PHI attached or (b) discarded.

17.9 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

17.10 Financial Obligations, Compensation, and Reimbursement of Participants

Drug ^{111} In /^{90} Y-DOTA-Anti-CD25 MAB and scans will be provided free of charge to participants.

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

Standard of care drugs or procedures provided during the course of study participation will be the responsibility of the research participant and/or the insurance carrier. The participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the participant were not in a research study.

In the event of physical injury to a participant resulting from research procedures, appropriate medical treatment will be available at City of Hope to the injured participant. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a participant.

The research participant will not receive reimbursement or payment for taking part in this study.

17.11 Publication/ Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the City of Hope PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov; it is City of Hope policy to register the trial prior to enrollment of the first patient. Results will be reported on ClinicalTrials.gov generally within 12 months after the primary completion date unless criteria to delay submission are met per the final rule.

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

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APPENDIX A: PERFORMANCE STATUS SCALES

ECOG Performance Scale [13]	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Karnofsky Scale %	Karnofsky Description	ECOG Scale*	ECOG Description
100	Normal, no complaints, no evidence of disease.	**0**	Fully active, able to carry on all pre-disease activities without restriction
90	Able to carry on normal activity, minor symptoms or signs of disease.	**1**	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.
80	Normal activity with effort, some signs or symptoms of disease.		
70	Cares for self, unable to carry on normal activity or to do active work.	**2**	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
60	Requires occasional assistance, but is able to care for most of own needs.		
50	Requires considerable assistance and frequent medical care.	**3**	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
40	Disabled, requires special care and assistance.		
30	Severely disabled, hospitalization is indicated although death is not imminent.	**4**	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
20	Hospitalization necessary, very sick, active supportive treatment necessary.		
10	Moribund, fatal processes		
Dead		**5**	**Dead**

*also known as Zubrod, SWOG or WHO scale

APPENDIX B: TOXICITY SCALES

Modified Bearman Scale [14]

HCT Regimen-related toxicity by organ system

Organ	Grade I	Grade II	Grade III
Cardiac toxicity	Mild EKG abnormality, not requiring medical intervention; or noted heart enlargement on chest x-ray with no clinical symptoms	Moderate EKG abnormalities requiring and responding to medical intervention; or requiring continuous monitoring without treatment; or congestive heart failure responsive to digitalis or diuretics	Severe EKG abnormalities with no or only partial response to medical intervention; or heart failure with no or only minor response to medical intervention; or decrease in voltage by more than 50%
Bladder toxicity	Macroscopic hematuria after 2 days from last chemotherapy dose with no subjective symptoms of cystitis and not caused by infection	Macroscopic hematuria after 7 days from last chemotherapy dose not caused by infection; or hematuria after 2 days with subjective symptoms of cystitis not caused by infection	Hemorrhagic cystitis with frank blood, necessitating invasive local intervention with installation of sclerosing agents, nephrostomy or other surgical procedure
Renal toxicity	Increase in creatinine up to twice the baseline value (usually the last recorded before start of conditioning)	Increase in creatinine above twice baseline but not requiring dialysis	Requirement of dialysis
Pulmonary toxicity	Dyspnea without chest x-ray changes not caused by infection or congestive heart failure; or chest x-ray showing isolated infiltrate or mild interstitial changes without symptoms not caused by infection or congestive heart failure	Chest x-ray with extensive localized infiltrate or moderate interstitial changes combined with dyspnea and not caused by infection or CHF; or decrease of PO2 (> 10% from baseline) but not requiring mechanical ventilation or > 50% O2 on mask and not caused by infection or CHF	Interstitial changes requiring mechanical ventilatory support or > 50% oxygen on mask and not caused by infection or CHF
Hepatic toxicity	Mild hepatic dysfunction with bilirubin ≥ 2.0 mg/dL and ≤ 6.0 mg/dL or weight gain > 2.5% and < 5% from baseline, of non-cardiac origin; or SGOT increase more than 2-fold but less than 5-fold from lowest preconditioning	Moderate hepatic dysfunction with bilirubin > 6.0 mg/dL and < 20 mg/dL; or SGOT increase > 5-fold from preconditioning; or clinical ascites or image documented ascites > 100 mL; or weight gain > 5% from baseline of non-cardiac origin	Severe hepatic dysfunction with bilirubin > 20 mg/dL; or hepatic encephalopathy; or ascites compromising respiratory function
CNS toxicity	Somnolence but the patient is easily arousable and oriented after arousal	Somnolence with confusion after arousal; or other new objective CNS symptoms with no loss of consciousness not more easily explained by other medication, bleeding or CNS infection	Seizures or coma not explained (documented) by other medication, CNS infection, or bleeding
Stomatitis	Pain and/or ulceration not requiring a continuous IV narcotic drug	Pain and/or ulceration requiring a continuous IV narcotic drug (morphine drip)	Severe ulceration and/or mucositis requiring preventive intubation; or resulting in documented aspiration pneumonia with or without intubation
GI toxicity	Watery stools > 500 mL but < 2,000 mL every day not related to infection	Watery stools > 2,000 mL every day not related to infection; or macroscopic hemorrhagic stools with no effect on cardiovascular status not caused by infection; or subileus not related to infection	Ileus requiring nasogastric suction and/or surgery and not related to infection; or hemorrhagic enterocolitis affecting cardiovascular status and requiring transfusion

Note: Grade IV regimen-related toxicity is defined as fatal toxicity

Common Terminology Criteria for Adverse Events (Version 5):
A copy of the CTCAE version 5 can be downloaded from the CTEP web site:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

APPENDIX C: RESPONSE CRITERIA/GRADING/STAGING CRITERIA

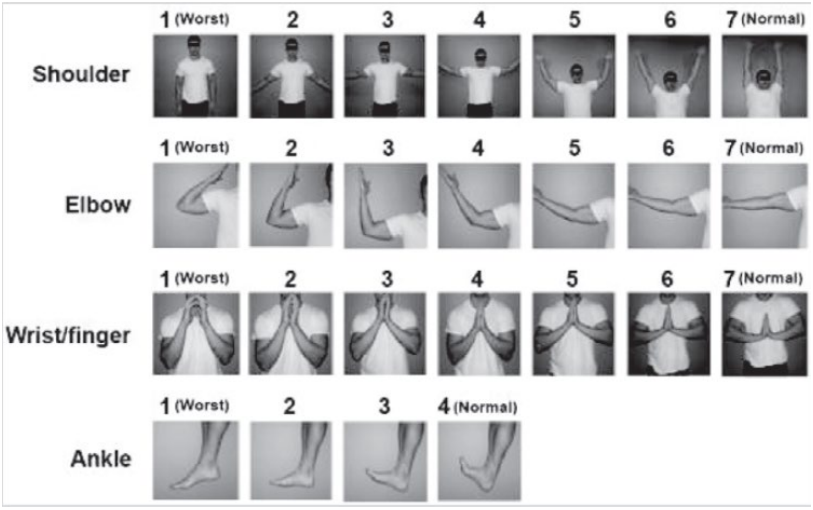
1. GvHD scoring criteria per Jagasia et.al., 2015[15]

	Score 0	Score 1	Score 2	Score 3
Performance score:_____ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **Score % BSA:_____** *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail Involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify)*:_____				
† Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.				

	Score 0	Score 1	Score 2	Score 3
MOUTH *Lichen planus-like features present:* ☐ Yes ☐ No	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms **with** disease signs with partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist*: ☐ **Yes** ☐ **No** ☐ **Not Examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye Symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify)*:_____				
GI Tract ***Check all that apply*:** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5% within 3 months ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss within 3 months (<5%)	☐ Symptoms associated with mild to moderate weight loss within 3 months (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss within 3 months >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify)*:_____				
LIVER	☐ Normal total bilirubin and ALT or AP <3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT >5x ULN	☐ Elevated total bilirubin >3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

	Score 0	Score 1	Score 2	Score 3
LUNGS** **Symptom score:**	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath at after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring O_2)
Lung score: % FEV1 _____ *Pulmonary function tests* ☐ Not performed	☐ FEV1≥80%	☐ FEV1 60-79%	☐ EFV1 40-59%	☐ FEV1 ≤39%
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
**Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.				
JOINTS AND FASCIA P-ROM score (*see below*) Shoulder (1-7):___ Elbow (1-7):___ Wrist/finger (1-7):___ Ankle (1-4)___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms **OR** legs or joint contractures, erythema thought due to fasciitis, moderate decreased ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM **AND** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify)*:_____				

Photographic Range of Motion (P-ROM)



	Score 0	Score 1	Score 2	Score 3
GENITAL TRACT (see Appendix-XXD‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms

☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify)*:_____

‡ To be completed by specialist or trained medical providers (see Appendix-XXD: GENITAL GVHD AND SCORING FORM)

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

☐ Ascites (serositis) _____	☐ Myasthenia Gravis_____	☐ Eosinophilia > 500/µl_____
☐ Pericardial Effusion_____	☐ Peripheral Neuropathy_____	☐ Platelets <100,000/ µl_____
☐ Pleural Effusion(s) _____	☐ Polymyositis_____	☐ Others (specify): _____
☐ Nephrotic syndrome	☐ Weight loss > 5% within 3 months without GI symptoms___	

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

2. Physician-Reported Global cGVHD Activity Assessment Form A

FORM A

Current Patient Weight: _____ Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

Health Care Provider Global Ratings:

0=none
1= mild
2=moderate
3=severe

Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:

0 1 2 3 4 5 6 7 8 9 10

cGvHD symptoms not at all severe — **Most severe cGvHD symptoms possible**

Over the <<time>> would you say that this patient's cGvHD is
+3= Very much better
+2= Moderately better
+1= A little better
0= About the same
-1=A little worse
-2=Moderately worse
-3=Very much worse

Mouth

Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
			Total score for all mucosal changes					

Gastrointestinal-Esophageal
- Dysphagia OR Odynophagia

0= no esophageal symptoms
1=Occasional dysphagia or odynophagia with solid food or pills during the past week
2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week
3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week

Gastrointestinal-Upper GI
- Early satiety OR
- Anorexia OR
- Nausea & Vomiting

0= no symptoms
1=mild, occasional symptoms, with little reduction in oral intake during the past week
2=moderate, intermittent symptoms, with some reduction in oral intake during the past week
3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week

Gastrointestinal-Lower GI
- Diarrhea

0= no loose or liquid stools during the past week
1= occasional loose or liquid stools, on some days during the past week
*2=intermittent loose or liquid stools throughout the day, on almost every day of the past week, **without requiring** intervention to prevent or correct volume depletion*
*3=voluminous diarrhea on almost every day of the past week, **requiring** intervention to prevent or correct volume depletion*

Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1	FVC	Single Breath DLCO (adjusted for hemoglobin)	TLC	RV
Liver Values	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L / ULN U/L	Alkaline Phosphatase U/L	ULN U/L
Baseline Values	Total Distance Walked in 2 or 6 Mins: ❑ 2 min ❑ 6 min	Karnofsky or Lansky	Platelet Count K/uL	Total WBC K/uL	Eosinophils %

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____

Figure 1. Chronic GVHD Activity Assessment- Clinician Report.

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3. Chronic GVHD Activity Assessment-Patient Self Report

FORM B

Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

Symptoms **Please rate how severe the following symptoms have been in the last seven days. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.**	**Not Present** 0	1	2	3	4	5	6	7	8	9	**As Bad As You Can Imagine** 10
Your **skin itching** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth dryness** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth pain** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth sensitivity** at its WORST?	O	O	O	O	O	O	O	O	O	O	O

Eyes	What is your main complaint with regard to your eyes?	
	Please rate how severe is this eye symptom, between 0 (not at all severe) and 10 (most severe):	0 1 2 3 4 5 6 7 8 9 10
Vulvovaginal Symptoms (females only)	Do you have any burning, pain or discomfort in the area of your vagina, vulva or labia? **OR** Do you have any discomfort or pain with sexual intercourse?	o Yes o No o Not applicable

Patient Global Ratings:

1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe?
0= none
1= mild
2=moderate
3=severe

2. Please circle the number indicating how severe your chronic graft versus host disease symptoms are, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe chronic GVHD symptoms possible.

0 1 2 3 4 5 6 7 8 9 10

cGVHD symptoms not at all severe — Most severe cGVHD symptoms possible

3. Compared to a month ago, overall would you say that your cGVHD symptoms are:

+3= Very much better
+2= Moderately better
+1=A little better
0= About the same
-1=A little worse
-2=Moderately worse
-3=Very much worse

Attach copies of:

Adults (persons 18 years or older):
-Lee cGvHD Symptom Scale
-Human Activity Profile
-SF-36 v.2
-FACT-BMT

Children/Adolescents (persons 17 years or younger):
-Lee cGVHD Symptom Scale (persons 8-12 years old may complete with help of the health care professional)
-ASK - Activities Scale for Kids
-CHRIs-Generic and Disease Specific Inventory

Abstracted from: Lee SJ, Wolff D, Kitko C, et al. Measuring Therapeutic Response in Chronic Graft-versus-Host Disease. National Institutes of Health Consensus Development Project on Criteria for ClinicalTrials in Chronic Graft-versus-Host Disease: IV. The 2014 Response Criteria Working Group Report. *Biol Blood Marrow Transplant* 2015; 21:984 – 999

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	Not at all	Slightly	Moderately	Quite a bit	Extremely
SKIN:					
a. Abnormal skin color	0	1	2	3	4
b. Rashes	0	1	2	3	4
c. Thickened skin	0	1	2	3	4
d. Sores on skin	0	1	2	3	4
e. Itchy skin	0	1	2	3	4
EYES AND MOUTH:					
f. Dry eyes	0	1	2	3	4
g. Need to use eyedrops frequently	0	1	2	3	4
h. Difficulty seeing clearly	0	1	2	3	4
i. Need to avoid certain foods due to mouth pain	0	1	2	3	4
j. Ulcers in mouth	0	1	2	3	4
k. Receiving nutrition from an intravenous line or feeding tube	0	1	2	3	4
BREATHING:					
l. Frequent cough	0	1	2	3	4
m. Colored sputum	0	1	2	3	4
n. Shortness of breath with exercise	0	1	2	3	4
o. Shortness of breath at rest	0	1	2	3	4
p. Need to use oxygen	0	1	2	3	4
EATING AND DIGESTION:					
q. Difficulty swallowing solid foods	0	1	2	3	4
r. Difficulty swallowing liquids	0	1	2	3	4
s. Vomiting	0	1	2	3	4
t. Weight loss	0	1	2	3	4
MUSCLES AND JOINTS:					
u. Joint and muscle aches	0	1	2	3	4
v. Limited joint movement	0	1	2	3	4
w. Muscle cramps	0	1	2	3	4
x. Weak muscles	0	1	2	3	4
ENERGY:					
y. Loss of energy	0	1	2	3	4
z. Need to sleep more/take naps	0	1	2	3	4
aa. Fevers	0	1	2	3	4
MENTAL AND EMOTIONAL:					
bb. Depression	0	1	2	3	4
cc. Anxiety	0	1	2	3	4
dd. Difficulty sleeping	0	1	2	3	4

4. **Lee cGVHD Symptom Scale**

Abstracted from: Lee S, Cook EF, Soiffer R, et al. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2002; 8:444-452.

APPENDIX D: ANTIBODY PREPERATION, RADIOLABELING, AND QUALITY CONTROL

Simulect (basiliximab) is a chimeric IgGl monoclonal antibody produced by recombinant DNA technology that binds specifically to the alpha subunit (p55 alpha, CD25, or Tac subunit) of the human high-affinity interleukin-2 (IL-2) receptor that is expressed on the surface of activated lymphocytes. Basiliximab is a composite of human and murine antibody sequences. The human sequences were derived from the constant domains of human IgGl and the variable framework regions of the Eu myeloma antibody. The murine sequences were derived from the complementarity-determining regions of a murine anti-Tac antibody. The molecular weight predicted from the DNA sequence is 144 kilodaltons.

The anti-CD25 MAb is supplied by Novartis as a clear, sterile, colorless concentrate for further dilution and intravenous administration. Each 20-mg vial contains 20 mg basiliximab, 7.21 mg monobasic potassium phosphate, 0.99 mg disodium hydrogen phosphate (anhydrous), 1.61 mg sodium chloride, 20 mg sucrose, 80 mg mannitol and 40 mg glycine, to be reconstituted in 5 mL of Sterile Water for Injection, USP. No preservatives are added. The anti-CD25 MAb was obtained from the City of Hope Pharmacy and then concentrated, dialyzed and conjugated with a macrocyclic chelate, DOTA, and then vialed in The City of Hope (COH) Center for Biomedicine and Genetics (CBG) Pilot Manufacturing Facility under cGMP. The purified conjugated product was tested according to Quality Assurance Safety Guidelines of the US Code of Federal Regulations for Biologicals, CFR Section 21 Part 610, FDA Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1997) and Points to Consider in the Characterization of Cells Lines used to Produce Biologicals (1993). Each lot of anti-CD25-DOTA undergoes testing for sterility, identity, purity, lack of pyrogenicity, immunologic specificity, potency, and protein concentration.

This study will use ^{111}In– and ^{90}Y–DOTA–anti-CD25 monoclonal antibody (MAb) radiolabeled in the Research Radiopharmacy and then purified by size exclusion chromatography immediately prior to patient infusion, assuring that the radiopharmaceutical is of highest purity, having eliminated any free radionuclide or radiolytically damaged protein. In addition, the product will be tested for the presence of endotoxin prior to administration and will then be tested for sterility, purity and immunoreactivity.

APPENDIX E: IMAGING PROTOCOLS

IMAGING PROTOCOL FOR ^{111}In-basiliximab/DOTA

BACKGROUND

Scans are acquired with an in-line SPECT-CT scanner comprising a dual-headed gamma camera and single-slice x-ray CT scanner. Internal standards, i.e., one or more known In-111 sources, are placed within the field of view in order to calibrate the scanner sensitivity. A total of three planar conjugate-view whole-body scans are performed beginning at the approximately 0-2 hours post start of ^{111}In-basiliximab/DOTA infusion and again at approximately 1 day, and 5/6 days post infusion. Following the planar scans at 1 day, SPECT scans will also be obtained at Day 1. Blood samples (1 EDTA purple top tube and 1 red top tube) will be obtained at 1-2 hours and 3-4 hours post start of infusion of ^{111}In-/^{90}Y-basiliximab/DOTA, and scan times of 1 day, and 5/6 days post infusion of the radiolabeled antibody.

The method for image processing, extraction of pharmacokinetic data and dose estimation is as follows. Conjugate-view, geometric mean images and a standard program for calculating radionuclide radiation absorbed dose (Stabin et al., 2005) are used for estimating tissue activity concentrations and absorbed doses. Attenuation corrections are based on body thickness and organ depth measurements made from CT scans. Regions of interest are defined on the radionuclear images. Tissue time-activity curves derived from the image sets are corrected for the difference in half life between ^{111}In and ^{90}Y. Time extrapolation is achieved for blood and liver by fitting a 5-compartment systemic model to the time-activity data obtained for those regions plus residual body, urine and feces. The time-activity curve for red marrow is assumed proportional to that for blood. Time-activity curves for other normal tissue regions (heart, kidneys, spleen, residual body), and for tumor if available, are assumed to follow the physical decay of ^{90}Y after the final time of observation. The extrapolated time-activity curves are numerically integrated to estimate cumulated activities, which are used in conjunction with OLINDA to calculate absorbed doses to various organs, tissues and whole body. Results are adjusted to better reflect the actual anatomy of the individual patient based on organ size measurements made from CT images.

The current image processing software for SPECT scans obtained with the camera includes CT-based attenuation correction. We also have access to advanced software for quantitative SPECT developed by Frey et al., at Johns Hopkins. This includes iterative reconstruction-based corrections for scatter and collimator-detector response. We expect the fully-corrected SPECT images to provide estimates of In-111 concentration in normal organs that are accurate to within 20%. (He et al., 2005). Furthermore, the availability of coregistered CT will greatly facilitate region-of-interest definitions for SPECT quantitation for organs.

REFERENCES

He B, Du Y, Song X, Segars WP, Frey EC. A Monte Carlo and Physical Phantom Evaluation of Quantitative In-111 SPECT. Phys Med Biol 2005; 50(17):4169-4185.

Stabin MG, Sparks RB, Crowe E. OLINDA/EXM: The Second-Generation Personal Computer Software for Internal Dose Assessment in Nuclear Medicine. J Nucl Med 2005; 46(6):1023-1027.

PROTOCOL: Indium–111 (^{111}In)–basiliximab Data Acquisition

I. Equipment and Materials

1. SPECT-CT: camera using medium energy collimators

2. ^{111}In standards are to be included in the whole body γ–camera scans.

II. Patient ^{111}In–basiliximab Injection, Post–Injection Imaging and Fluid Collection

A. Injected Activity

1. Intended radioactive dose is 5 mCi.
2. Just prior to infusion, verify and record the dose using a dose calibrator. Record the time and date.
3. Count the empty syringe after injection using the dose calibrator to determine residual activity to calculate and record the total activity injected.

B. Image Acquisition and Fluid Sampling

1. Beginning immediately after infusion of the ^{111}In–basiliximab and prior to urination, perform a whole body scan acquiring both anterior and posterior images (160 s/pixel) using a medium energy collimator(MEGP-M2), a 256 x 1024 computer acquisition matrix and acquisition photo peak settings of 172 and 247 keV with 20% windows.
2. Repeat whole body images at 1 day and 5/6 days post–^{111}In– basiliximab injection.
3. After the ^{111}-In/^{90}-Y-basiliximab administration, blood samples (1 EDTA purple top tube and 1 red top tube) will be obtained at 1-2 hours, 3-4 hours, 1 day, and 5/6 days post start of infusion of the radiolabeled antibody.
4. For the Day 1 time point, acquire SPECT-CT scans (2 bed positions beginning at top of head) following the whole-body scans. Collimators and energy windows are the same as for the whole-body scans. The SPECT acquisition technique is 60 steps (120 views), 3o and 30 s/step, planar image matrix 128x128.
5. Record the start times of the whole-body and SPECT acquisitions as well as the times of blood sampling.

Each set of whole-body images should include a standard of ^{111}In in a small plastic vial (such as a γ–counting vial). A standard of ~ 50 μCi in 10 ml water should be made up prior to the 0 hr image and the same standard used with each planar image acquisition beginning after the dose is infused. Measure the exact standard activity in a dose calibrator and record the time and activity. This should correspond to the time of the start of the first scan. Place the standard on the imaging table ~ 10 cm from the body, lateral to the feet. Place standard on the same side of the body for each scan.

B. SPECT Image Reconstruction

1. Perform standard OSEM reconstructions (image matrix 64x64x64) without and with CT-based attenuation correction.
2. Imaging Physicists will also perform image reconstruction that includes scatter and collimator-detector response corrections.

APPENDIX F. IMMUNOHISTOCHEMISTRY

CD25 (IL2RA) is expressed in activated B-cells, T-cells, as well as myeloid precursors. It is also expressed in cases of acute myeloid leukemia (AML) and in some instances associated with poor survival1. CD25 expression will be determined by immunohistochemistry at the City of Hope Laboratories and evaluated for positivity in the myeloid blasts in formalin-fixed paraffin-embedded tissue sections by a pathologist. Cases will be deemed positive if there is greater than 20% positivity in the blasts.

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APPENDIX G: HCT-CI INDEX

IRB 21016

City of Hope

Patient Name _____ MR#_____

HCT-SPECIFIC COMORBIDITY INDEX SCORE

Comorbidities	Definition	Score
Migraine/headache		0
Osteoporosis		0
Osteoarthritis		0
Hypertension		0
Gastrointestinal	Including inflammatory bowel disease	0
Mild pulmonary	DLCo and/or FEV_1 >80% or Dyspnea on moderate activity	0
Mild renal	Serum creatinine 1.2-2 mg/dl	0
Endocrine		0
Bleeding		0
Coagulopathy	Deep venous thrombosis or pulmonary embolism	0
Asthma		0
Arrhythmia		1
Myocardial	Coronary artery disease, congestive HF, history of medically documented MI, EF≤50%	1
Mild hepatic	Chronic hepatitis, Bilirubin >ULN- 1.5 X ULN, or AST/ALT >ULN-2.5XULN	1
Cerebro-vascular accident	History of transient ischemic attack or cerebro-vascular accident	1
Morbid obesity		1
Diabetes	Requiring treatment	1
Depression/anxiety		1
Infection	Requiring continuation of treatment after Day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica	2
Moderate pulmonary	DLCo and/or FEV_1 66-80% or Dyspnea on slight activity	2
Peptic ulcer	Patients who have required treatment	2
Moderate-severe renal	Serum creatinine >2 mg/dl, on dialysis, or prior renal transplantation	2
Valvular heart disease	Except mitral valve prolapse	3
Prior solid tumor	Requiring treatment with chemotherapy	3
Moderate-severe hepatic	Liver cirrhosis, Bilirubin >1.5 X ULN, or AST/ALT >2.5XULN	3
Severe pulmonary	DLCo and/or FEV_1 ≤65% or Dyspnea at rest or requiring oxygen	3

Total score is the sum of all comorbidities present pre-transplant. Score_____

Physician Signature_____ Date_____