FRED HUTCHINSON CANCER RESEARCH CENTER

Title: Evaluation of Pretargeted anti-CD20 Radioimmunotherapy Combined with BEAM Chemotherapy and Autologous Stem Cell Transplantation for High-Risk B-cell Malignancies

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Investigational Agent: B9E9[scFv]$_4$SA Fusion Protein, Cluster Clearing Agent (CCA-16-Biotin), and Radiolabeled (^{111}In/^{90}Y) DOTA-biotin

Study Regimen: B9E9[scFv]$_4$SA Fusion Protein, Cluster Clearing Agent (CCA-16-Biotin), and Radiolabeled (^{111}In/^{90}Y) DOTA-biotin followed by BEAM chemotherapy and autologous stem cell transplantation

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I have carefully read Protocol 9189 entitled "Evaluation of Pretargeted anti-CD20 Radioimmunotherapy Combined with BEAM Chemotherapy and Autologous Stem Cell Transplantation for High-Risk B-cell Malignancies" ("Protocol") version date 04/21/2017.

I agree to carry out my responsibilities in accordance with the Protocol, applicable laws and regulations (including 21 CFR Part 312), Good Clinical Practice: Consolidated Guidance (ICH-E6), and applicable policies of Fred Hutch

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Acronyms

Ab	antibody
AE	Adverse Event
ASCT	autologous stem cell transplantation
B-NHL	B-cell non-Hodgkin's lymphoma
C-HDT	conventional high-dose therapy
CA	clearing agent
CFR	case report forms
CR	complete response
DLBCL	diffuse large B-cell
DLT	dose limiting toxicity
DOTA-biotin	radiobiotin
DSMC	Data Safety Monitoring Committee
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
Fred Hutch or FHCRC	Fred Hutchinson Cancer Research Center
FL	follicular
FLIPI	Follicular Lymphoma International Prognostic Index
HAMA	human anti-mouse antibody
HASA	human anti-streptavidin antibody
HCT	hematopoietic cell transplantation
HD-RIT	high-dose radioimmunotherapy
IND	investigational new drug
IPI	International Prognostic Index
IRB	Institutional Review Board
MCL	mantle cell
MoAb	monoclonal antibody
MTD	maximally tolerated dose
MZL	marginal zone lymphoma
NHL	non-Hodgkin's lymphoma
OS	overall survival
PBSC	peripheral blood stem cells
PFS	progression free survival
PK	Pharmacokinetic
PRIT	Pretargeted radioimmunotherapy
RIT	radioimmunotherapy
SA	streptavidin
SAE	Serious Adverse Event
SCCA	Seattle Cancer Care Alliance
SCT	stem cell transplant
SLL	small lymphocytic
SRC	Scientific Review Committee
UW	University of Washington
UWMC	University of Washington Medical Center

1.0 INTRODUCTION AND OVERVIEW

High dose chemoradiotherapy followed by autologous stem cell transplantation (ASCT) has become the standard of care for patients with relapsed or refractory intermediate or high grade non-Hodgkin's lymphoma (NHL) [1,2] and has also been shown to prolong survival in patients with relapsed indolent lymphomas or mantle cell lymphoma in first remission.[3,4] Despite the potential to improve outcomes, the majority of patients with aggressive B-NHL and nearly all patients with indolent or mantle cell lymphoma are likely to relapse as well as most with relapsed aggressive B-NHL that has failed rituximab-chemotherapy.[3,4,5] Based on the exquisite radiosensitivity of B-NHL, we have conducted phase I & II studies of directly radiolabeled anti-B-cell antibodies and have demonstrated improved outcomes when compared to non-randomized controls. [6,7] Though these results appear better than historical standards, many patients will still not be cured of their disease. Some of this may be due to the fact that the ratio of absorbed radiation dose to tumor sites vs normal organs with this approach is at best 2:1. Pretargeted radioimmunotherapy (PRIT) has been shown in preclinical and clinical non-transplant models to be able to improve this ratio up to 20:1.[8-15] This trial builds on our and other's extensive expertise and experience in this area to develop a myeloablative PRIT conditioning regimen to augment standard BEAM chemotherapy with the ultimate goal to improve remission durations and cure rates in patients with B-NHL.

2.0 BACKGROUND

2.1 Epidemiology and Pathologic Characteristics of Lymphomas

Each year in the United States over 75,000 individuals will be newly diagnosed with lymphoma, resulting in over 20,000 deaths annually. [16] The vast majority are B-NHL with the most common histologic entities including diffuse large B-cell (DLBCL), follicular (FL), mantle cell (MCL), small lymphocytic (SLL), and marginal zone lymphoma (MZL). These lymphomas express many similar surface antigens including CD19, CD20, and CD45.

2.2 Current Targeted Therapies for B-NHL

B-cell lymphomas are the first group of malignancies to have benefited from the development of targeted monoclonal antibody (MoAb) therapies. Rituximab, a MoAb that targets the pan-B-cell antigen CD20, has contributed to the first major improvement in the treatment of many B-cell malignancies in decades.[17-21] Despite its activity, most patients that receive rituximab alone achieve only partial responses and remission durations are limited. The addition of radionuclides such as Iodine-131 (^{131}I) or Yttrium-90 (^{90}Y) to anti-CD20 antibodies exploits the exquisite radiosensitivity of NHLs. This has resulted in improved rates of response and longer remission durations. [22,23] One approach to further improve outcomes, pioneered by our group and others, involves escalating the dose of CD20 targeted RIT combined with autologous stem cell rescue to support hematopoiesis. We have previously demonstrated that this approach delivers approximately twice the absorbed radiation dose to tumor sites as compared to the critical normal organ that received the highest radiation exposure, and ten times more radiation to tumors than is delivered to the whole body. Our data have confirmed that escalating the absorbed dose of RIT correlates with improved progression free survival (PFS).[6-8,23,24]

These phase II clinical trials demonstrated that high-dose anti-CD20 RIT yields response rates of >90% in heavily pre-treated B-NHL patients;[8] and, when compared to concurrent non-randomized controls treated with conventional conditioning regimens, RIT-based conditioning yielded improved overall survival (OS) and PFS (**Figure 1**).

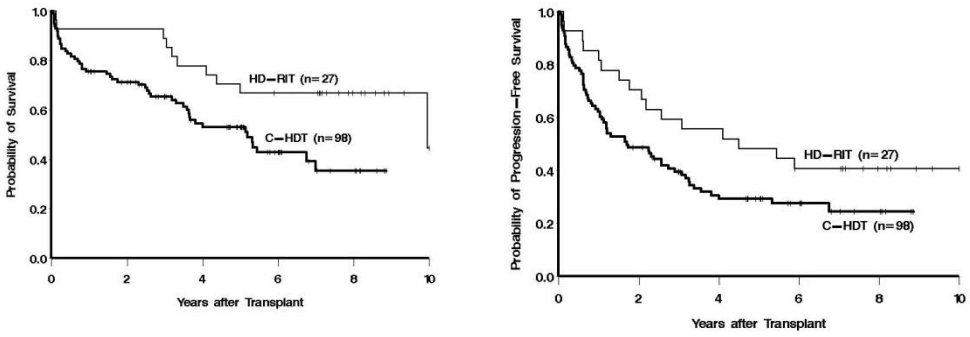

FIGURE 1. Overall survival (left) and progression-free survival (right) of patients treated either with high-dose radioimmunotherapy (HD-RIT) using ^{131}I-tositumomab and autologous hematopoietic stem cell transplantation (ASCT) or conventional high-dose therapy (C-HDT) and ASCT[6].

The efficacy and tolerability of high-dose anti-CD20 RIT and ASCT is further supported by our recent data suggesting that this approach can safely extend potentially curative therapies to adults into their mid-70s. Collectively, our studies have repeatedly demonstrated the feasibility, safety, and efficacy of delivering high-dose CD20-directed RIT and hematopoietic cell transplantation (HCT) for B-NHL. However, despite the promising outcomes using single step RIT, the absorbed radiation doses to tumor sites are at best twice that is delivered to non-target organs. [8,23,24] We hypothesize that improving this ratio and thereby increasing the absorbed dose to target sites we will be able to reduce relapse rates and improve long-term outcomes.

2.3 Addition of RIT to Standard BEAM Conditioning Regimens

In an effort to improve on one of the most commonly employed autologous transplant conditioning regimens for lymphoma, anti-CD20 RIT with ^{131}I-tositumomab or ^{90}Y-ibritumomab tiuxetan has been added to a variety of high-dose chemotherapy regimens prior to ASCT. [7,25-33] Generally, these reports demonstrate little additive toxicity attributable to RIT, considering the often-substantial toxicity seen from the myeloablative chemotherapy backbones to which it was added. However, there have been relatively few randomized controlled trials comparing myeloablative preparative regimens with or without RIT. In one study from Israel, the addition of ^{90}Y-ibritumomab tiuxetan to BEAM for relapsed DLBCL yielded superior 2-year overall survival compared to BEAM alone (91% vs 62%, respectively; P = 0.05).[7,31] However, a larger study comparing BEAM plus either rituximab or ^{131}I-tositumomab for relapsed DLBCL showed no difference in overall or progression-free survival between the two arms.[7,29]

These studies primarily used the standard low doses of ^{131}I-tositumomab or ^{90}Y-ibritumomab tiuxetan. Thus, it is possible that RIT was not sufficiently dose-intensified to achieve maximum efficacy. To

achieve this objective, Winter and colleagues escalated the dose of radiation delivered to critical organs by ^{90}Y-ibritumomab tiuxetan in combination with BEAM in patients with relapsed/refractory B-NHL.[7,27] They estimated the maximally tolerated dose (MTD) to be 15 gray (Gy), though they conceded that most of the toxicities observed were similar to those typically seen with BEAM alone (e.g., infections, pulmonary and hepatic toxicity, etc.). They also observed relatively promising clinical outcomes in this cohort of generally high-risk (i.e., heavily pre-treated, non-remission) patients.

One current approach (protocol 2728) utilizing ^{90}Y-anti-CD45 RIT in addition to BEAM chemotherapy and auto transplant and has shown that absorbed doses to non-target sites (primarily liver) up to 16 Gy can be delivered without evidence of dose limiting toxicities. There has also been no indication that engraftment has been impacted despite the use of standard single-step radioimmunotherapy. Though dose escalation continues with this approach, and combination of high-dose RIT with BEAM chemotherapy is clearly feasible, we recognize that with single-step RIT, at best the tumor to normal organ ratios of absorbed radiation dose will be 2:1 likely limiting our ability to maximally escalate the exposure of target sites to ionizing radiation. We plan to build on this experience with a PRIT-BEAM combination as described below.

2.4 Pretargeted RIT Approach

Another strategy to further improve the ability to selectively deliver targeted radiation to desired sites and limit exposure to normal organs is PRIT.

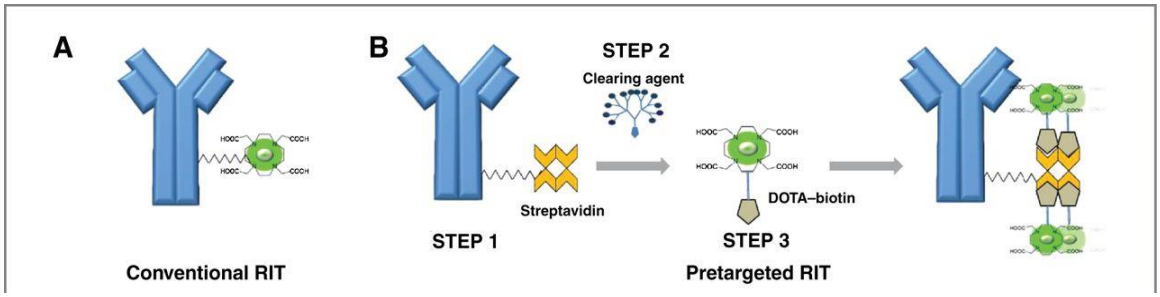

FIGURE 2: Components for PRIT. Schema depicting one-step conventional RIT (A) and multistep PRIT (B). PRIT involves infusion of the Ab-SA construct (step 1), followed by injection of a synthetic N-acetylgalactosamine–containing clearing agent (step 2) designed to facilitate hepatic clearance of excess Ab-SA from the bloodstream, and then infusion of the radiolabeled small molecule DOTA–biotin (Step 3)[34].

With traditional RIT, the slow clearance of unbound radiolabeled antibody (Ab) from the circulation and the resultant high levels of background radioactivity are major obstacles to the optimal implementation since these pharmacokinetic features limit the tumor-to-normal organ ratios of absorbed radiation that can be achieved.[7,35-37] PRIT approaches offer a potential to further reduce the toxicity and improve the sub-optimal therapeutic index (target to non-target ratio) currently achievable with conventional RIT methodologies. We have investigated a PRIT strategy that utilizes the high affinity streptavidin (SA)-biotin system in which the Ab-SA conjugate and the radioactive biotin are administered separately

(**Figure 2**).[7,35,36,38-42] The localization of the Ab-SA component to tumor is relatively slow and an unbound portion of the conjugate remains in circulation. However, because no radionuclide is attached, there are no toxic consequences due to the non-tumor bound unlabeled Ab-SA conjugate. The radiolabeled small molecule is delivered after maximal accumulation of Ab-SA conjugate in targeted tissues (*e.g.*, after 24-48 hours) and after clearance of unbound Ab-SA from the blood. The natural clearance of the unbound Ab-SA conjugate prevents it from complexing with the radiolabeled small molecule in the circulation.[7,15,43-49] The clearance of unbound Ab-SA in the blood can be further enhanced by the use of a synthetic N-acetylgalactosamine–containing clearing agent that removes excess antibody from the bloodstream.[11] Therapeutic radiobiotin, due to its small size, is able to penetrate tumor sites rapidly and attach to the pretargeted Ab-SA conjugate bound specifically to tumor cells. If the tumor-bound Ab-SA does not capture this small radioactive molecule, the kidney rapidly excretes it. This PRIT approach has been shown to improve the ratios of radiation delivered to tumors compared to normal organs in both preclinical and clinical models.[7,15,43-47,50-58] Our group has recently demonstrated reduced toxicity and markedly enhanced efficacy using a pretargeted anti-CD20 Ab-SA conjugate compared to the directly labeled anti-CD20 Ab in mouse xenograft studies.[7,15] We have further shown that results using either pretargeted anti-CD45 or anti-CD20 Ab-SA conjugates are comparable in murine preclinical NHL models.[7,51]

2.5 Clinical PRIT Data

Two pilot non-ablative PRIT Phase I clinical trials using anti-CD20 Ab-SA have been reported and preliminary results suggest that the use of this reagent is safe and that the pretargeted RIT approach is feasible.[7,57,58] These studies demonstrated rapid tumor localization and urinary excretion of Yttrium-90 (^{90}Y)-labeled biotin with resulting tumor-to-blood ratios of 65:1 and minimal toxicity.[7,57] The second phase I trial evaluated 2 doses of anti-CD20 antibody-streptavidin B9E9[scFv]$_4$SA fusion protein (B9E9-FP) (160 mg/m^2 and 320 mg/m^2) finding them both to be pharmacokinetically similar. The same trial also demonstrated that a molar excess of clearing agent (CA) (45 mg/m^2) administered at either 48 or 72 hours later highly effectively removed >95% of unbound B9E9-FP from the circulation (**Figure 3**). This was then followed by radiobiotin (DOTA-biotin) labeled with both ^{90}Y for therapeutic purposes and Indium-111 (^{111}In) for concurrent imaging/dosimetry. Importantly, this group was able to clearly demonstrate targeting to tumor sites (**Figure 4**) and resultant objective responses despite the phase I nature of this trial. The only clinically significant but expected adverse events observed in this trial were transient hematologic toxicity of ≥ grade 3 in 2 of 14 patients, all of whom were treated at the 15 mCi/m^2 dose. With this approach in mind, we have repeatedly been able to administer much higher myeloablative doses of radioisotopes followed by hematopoietic stem cell transplantation to abrogate the expected hematologic toxicity of high-dose radioimmunotherapy in published[6,59,60] or ongoing clinical trials (protocols 2238, 2361, 2728, 2398) with no impairment of engraftment or long-term cytopenias.

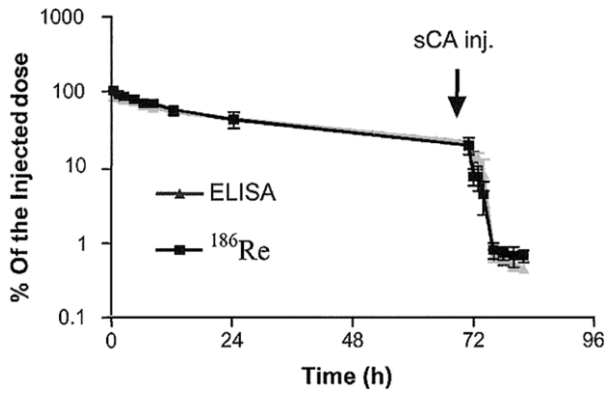

FIGURE 3: B9E9-FP serum clearance. Serum B9E9-FP concentration data from patients in cohort A (n = 3) generated from 186Re counting or ELISA shown as percent of injected dose (mean ± SD).

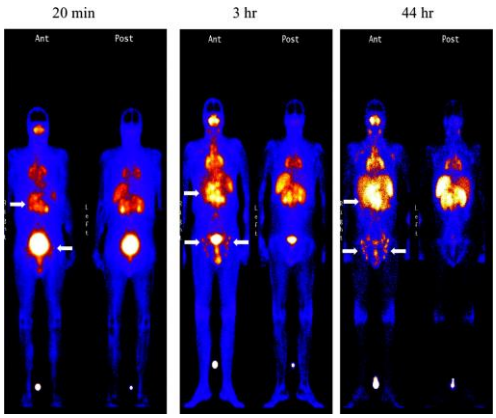

FIGURE 4: Tumor targeting of known sites of disease. Images obtained 20 minutes, 3 hours, and 44 hours after the administration of ^{111}In(5 mCi)/^{90}Y(15 mCi/m^2)-DOTA-biotin. Gamma camera whole-body scans of patient no. 1 (anterior views) obtained at 20 minutes, 3 hours, and 44 hours after infusion of ^{111}In/^{90}Y-DOTA-biotin. Arrows show radionuclide localization to known sites of tumor involvement.

2.6 Summary

We and others have demonstrated the feasibility and potential improved efficacy of high-dose RIT-based conditioning as a single agent or in combination with high-dose chemotherapy, but recognize the hypothetical limitations with this approach. Extensive preclinical data indicate that PRIT can further intensify the absorbed radiation dose to target sites while limiting dose to non-target normal organs. We have successfully piloted the high-dose PRIT strategy using CD45 targeting in the setting of AML. Prior clinical data indicate that the B9E9 anti-CD20 PRIT strategy is feasible, safe and has anti-tumor activity at low doses without the use of stem cell support. In this protocol, we will perform a phase I trial escalating the ^{90}Y activity delivered using a PRIT strategy to myeloablative doses along with BEAM chemotherapy prior to ASCT for patients with high-risk B-NHL. The B9E9-FP will be generated in the Fred Hutchinson Cancer Research Center ("Fred Hutch") Biological Production Facility, the Cluster Clearing Agent-16-Biotin (CA) will be produced in the Memorial Sloan Kettering Cancer Center Organic Synthesis Core Facility, and the radiolabeling and final product release testing of the radiolabeled DOTA-biotin will occur in a controlled environment at the University of Washington (UW) Nuclear Medicine Radiolabeling Laboratory, room BB030.

3.0 OBJECTIVES

3.1 Primary Objective

To estimate the MTD of ^{90}Y activity that can be delivered *via* PRIT using B9E9-FP, CA, and radiolabeled DOTA-biotin when followed by BEAM chemotherapy and autologous stem cell transplantation.

3.2 Secondary Objectives

3.2.1 Clinical

a. To assess the overall and progression-free survival of the above regimen in such patients.
b. To evaluate the response rates of the above therapy.
c. To evaluate the toxicity and tolerability of the above therapy.
d. To evaluate the feasibility of delivering sequential high-dose PRIT and chemotherapy.

3.2.2 Correlative

a. Assess biodistribution and pharmacokinetics of B9E9-FP and radiolabeled DOTA-Biotin.
b. Assess ability of the CA to remove excess B9E9-FP from the serum.
c. Evaluate the impact, if any, of circulating rituximab on biodistributions.

4.0 PATIENT SELECTION

Evaluations done as part of the standard clinical work-up for patients undergoing autologous transplantation may be used for determination of eligibility if performed within 30 days of enrollment (PET-CT may be used if performed within 56 days prior to treatment).

4.1 Inclusions

1) Patients must have a histologically confirmed diagnosis of lymphoma expressing the CD20 antigen and generally must have failed at least one prior standard systemic therapy. The exception will be MCL patients, who may be enrolled while in first CR as well as other select high-risk lymphomas (e.g., Burkitt's, double hit DLBCL, transformed indolent B-NHL, etc.) in accordance with current transplant standard of care for these patients.

2) Patients must have normal renal function (Cr <2.0) and normal hepatic function (bilirubin <1.5 mg/dL), with the exception of patients thought to have Gilbert's syndrome, who may have a total bilirubin above 1.5 mg/dL.

3) All patients eligible for therapeutic study must have (≥2x10^6 CD34/kg) autologous hematopoietic stem cells harvested and cryopreserved.

4) Patients must have an expected survival of >60 days and must be free of major infection.

5) Patients of childbearing potential must agree to abstinence or the use of effective contraception.

4.2 Exclusions

1) Systemic anti-lymphoma therapy given in the previous 30 days before the scheduled ^{90}Y therapy dose

2) Inability to understand or give an informed consent

3) Prior radiation >20 Gy to any critical normal organ (e.g., lung, liver, spinal cord, both kidneys) within 1 year of the treatment date

4) Active central nervous system lymphoma
5) Other serious medical conditions considered to represent contraindications to BMT (e.g., abnormally decreased cardiac ejection fraction, DLCO<50% predicted, patient on supplemental oxygen, AIDS, etc.)
6) Age < 18 years
7) Pregnancy or breast feeding
8) Prior bone marrow or stem cell transplant
9) SWOG performance status ≥ 2.0 (**Appendix 4**)
10) Known sensitivity to kanamycin and other aminoglycosides. Patients with known hypersensitivity to kanamycin or any other aminoglycoside antibiotic will be excluded.

5.0 DONOR SELECTION

Not Applicable. This protocol employs autologous transplantation, utilizing the patient's own hematopoietic stem cells obtained from either the peripheral blood or bone marrow.

6.0 EVALUATION AND COUNSELING OF PATIENT

This protocol should be discussed thoroughly with the patient and family (if appropriate), and all known risks and hazards to the patient should be described. The stem cell transplant procedure of this protocol as well as possible and alternative forms of therapy should be reviewed as objectively as possible. Consent will be obtained using forms approved by the Fred Hutch Institutional Review Board (IRB). A summary of the conference should be dictated for the medical record detailing what was covered.

7.0 PROTOCOL REGISTRATION

Patients will be assigned and registered utilizing the institution's standard procedures.

8.0 PLAN OF TREATMENT

8.1 Overview

Each patient will undergo concurrent therapy based on mCi/m^2 dosing of ^{90}Y and flat (5-10 mCi) dosing of ^{111}In along with concurrent imaging and dosimetry for correlative and safety purposes. The sequence of events is summarized in **Table 1** and **Figure 5**. The therapy/biodistribution dose will be given approximately 7 days prior to initiation of BEAM chemotherapy and approximately 2 weeks prior to ASCT. The ^{90}Y activity will be escalated to estimate a maximally tolerated dose when combined with BEAM chemotherapy.

TABLE 1: General Treatment Schema*

Day	Event
-17	B9E9-FP administration
-15**	Clearing Agent (CA) administration
-14	^{111}In-DOTA-biotin (~5-10 mCi) trace-labeled infusion

Day	Event
	^{90}Y-DOTA-biotin therapeutic infusion Gamma Camera Imaging
-14 -7	Gamma Camera Imaging
-7	BEAM Chemotherapy
0	PBSC infusion

* Following the infusion of radiobiotin, the remainder of the treatment will be considered standard of care and can be adjusted as per standard of care at the discretion of the treating provider. The exact dates of the gamma scans can be adjusted +/- 3 days based on the patient schedule and the guidance of the nuclear medicine team for that given patient.

** CA may be given up to 3 days after B9E9-FP if needed due to scheduling or clinical reasons and all other days will need to be shifted accordingly.

FIGURE 5: Study Schema

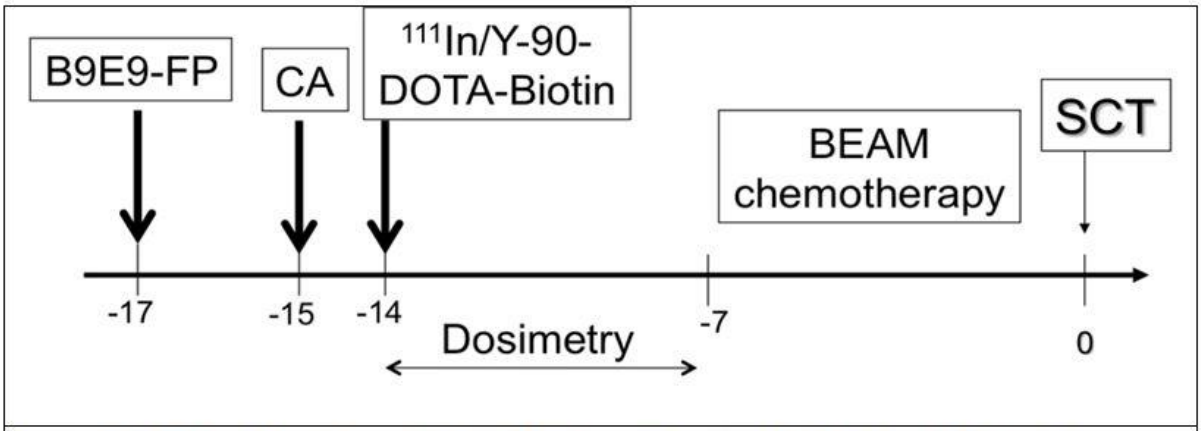

Figure 5: Note these days are approximate. Please see the protocol text for detailed times of administration. In addition, BEAM chemotherapy and SCT is standard of care. B9E9-FP=B9E9fusion protein, CA=clearing agent, SCT= autologous stem cell transplant. Note that clinical adjustment of the treatment dates after the radiobiotin infusion is allowed up to +/- 3 days as per standard of care.

8.2 Investigational Product Dosing

Doses of the investigational reagents should be as follows:

- B9E9-FP: 160 mg/m^2
- CA: 100 mg
- DOTA-biotin: 1.3 mg/m^2
- In-111: 10+/-5 mCi
- Y-90: (see dose escalation schema in **Table 2**)

TABLE 2: Dose Levels to be Used (See 15.2 for further explanation of dose escalation):

Dose level	B9E9-FP (mg/m^2)	Clearing Agent (mg)	DOTA-biotin (mg/m^2)	In-111 (mCi)	Y-90 (mCi/m^2)
1	160	100	1.3	~10	30
2	160	100	1.3	~10	40
3	160	100	1.3	~10	50
4	160	100	1.3	~10	60
5	160	100	1.3	~10	70
6	160	100	1.3	~10	80
7	160	100	1.3	~10	90
8	160	100	1.3	~10	100
9	160	100	1.3	~10	110
10	160	100	1.3	~10	120
11	160	100	1.3	~10	130
12	160	100	1.3	~10	140

8.3 Peripheral Blood Stem Cell Collection

Peripheral blood stem cell collection is not part of this protocol, however, prior to the B9E9-FP infusion, peripheral blood stem cells (PBSC) will need to be collected by serial leukaphereses per standard of care.

8.4 Investigation Product Administration

8.4.1 B9E9-FP infusion

- **Premedications:** Premedications are not required for B9E9-FP infusion based on prior experience utilizing this agent without premedications. However, standard premeds may be used at the discretion of the treating team.
- **Vital signs:** Vital signs should be obtained prior to infusion, at the completion of the infusion, and as clinically needed during the infusion.
- **Infusion rate:** B9E9-FP will be infused at a dose of 160 mg/m^2 IV over a **minimum** of 2 hours.

8.4.2 Clearing Agent Infusion

- **Premedications:** Premedications are not required for the CA infusion based on prior experience utilizing this agent without premedications. However, standard premeds may be used at the discretion of the treating team.
- **Vital signs:** Vital signs should be obtained prior to infusion, at the completion of the infusion, and as clinically needed during the infusion.
- **Infusion rate:** The clearing agent will be administered at a dose of 100 mg over a **minimum** of 30 minutes.

8.4.3 Radiolabeled DOTA-biotin infusion

- **IV Fluids, pre and post radiolabeled DOTA-biotin infusion:** IV hydration of physician/provider's choice at ≥ 200 ml/hr starting prior to the infusion, continuing throughout the radiolabeled DOTA-biotin infusion, and post infusion for a total volume as clinically indicated.

- **Premedications:** Premedications are not required for the radiolabeled DOTA-biotin infusion based on prior experience utilizing this agent without premedications. However, standard premeds may be used at the discretion of the treating team.

- **Vital signs:** Vital signs will be obtained prior to administration and afterwards and as clinically needed thereafter.

- **Infusion rate:** DOTA-biotin will be administered at a total dose of approximately 1.3 mg/m^2. The radiolabeled (^{111}In/^{90}Y)-DOTA-biotin infusions may be administered concurrently over 2 to 5 minutes or serially over 2 to 5 minutes each. All appropriate shielding and radiation safety precautions will be followed during the administration.

- **Inpatient hospital admission:** Patients may be admitted for up to 3 days (more typically 1 day) as inpatients at University of Washington Medical Center (UWMC) for monitoring or longer if clinically required.

8.4.4 Management of Toxicities

Management of infusion reactions following any of the investigational agents are outlined in **Table 3**

TABLE 3: Management of Infusion Related Reactions/ Infusion Related Adverse Events

Infusion Reaction	Suggested Medication
Fever	Acetaminophen 650 mg PO every 4 hours PRN
Rigors	Meperidine ≤ 25-50 mg IV every 2-4 hours PRN
Pruritus	Diphenhydramine ≤ 25 mg every 2 hours or ≤50 mg every 4 hours PO or IV PRN
Nausea	Lorazepam 0.5-2 mg IV every 4 hours PRN
	Diphenhydramine ≤ 25 mg every 2 hours or ≤ 50 mg every 4 hours IV PRN
	Prochlorperazine ≤ 5-10 mg IV/PO every 4 hours PRN
	Ondansetron 8 mg IV every 8 hours PRN
Cough, chest, or throat tightness or wheezing	Diphenhydramine ≤ 25 mg every 2 hours or ≤ 50 mg every 4 hours IV or PO PRN
	Hydrocortisone 100 mg IV every 2 hours PRN
	Albuterol by nebulizer 2.5–5 mg up to every 1 hours PRN
Low blood pressure	Up to 500 ml Normal Saline Bolus given IV over 30 min. May repeat x 1 PRN
Hypoxemia	Supplemental oxygen PRN to keep Oxygen saturation within normal limits
Anaphylaxis	Cessation of investigational product and alert the Code Team or Rapid Response Team or patient's inpatient team for additional orders

8.5 Assessment of B9E9-FP Levels

Blood levels of B9E9-FP will be assessed at specified time points (see Section 8.7.1) post infusion to confirm a decrease of at least 50% concentration from completion of infusion before administration of

radiolabeled DOTA-biotin. This demonstration of clearance from the circulation will provide assurance that the majority of the radiolabeled DOTA-biotin will clear the bloodstream rapidly as it homes to the B9E9-FP, thereby supporting the goal of limiting radiation exposure throughout the circulation.

8.6 Quantitative Biodosimetry

In order to estimate the localization of radioisotopes to normal organs and tumor sites to potentially correlate with antitumor response and toxicity planar gamma camera imaging and optional SPECT/CT and PET/CT imaging as previously published. OLINDA dosimetry software will be utilized for internal dosimetry estimation.[61] Gamma scans will be done at the following time points: prior to infusion (attenuation), immediately following infusion, and up to 4 additional time points over the following 7 days. Optional core bone marrow (at 24-48 hours) and lymph node biopsies (at 48-96 hours) can occur over this time frame to further refine absorbed dose estimates to these sites.

8.7 Pharmacokinetic (PK) Sample Collection

The following PK samples will be obtained from a minimum of three patients:

8.7.1 B9E9-FP PK samples

Blood: 2-5 cc in purple top tubes taken immediately post B9E9-FP infusion, immediately prior to CA infusion, immediately post CA infusion, and immediately prior to radiolabeled DOTA-biotin infusion.

8.7.2 Radiolabeled DOTA-biotin PK samples

Blood: 2-5 cc in purple top tubes taken prior to treatment, and then after treatment at approximately 15 and 30 minutes, and approximately 2, 4, 8, 24, 48 and 72 hours (some variation in time points is allowable due to logistics of patient visits and sample collection in the collection of up to 8 PK blood sample post infusion).

Urine: may be collected as 24-hour samples by taking aliquots from total volume of first void after treatment, next void-24 hours, 24-48 hours, and 48-72 hours; or may be collected as aliquots from individual voids during the first 3 days following infusion.

8.8 BEAM Chemotherapy

Approximately 7 days after the radiobiotin infusion, BEAM chemotherapy will be initiated according to Seattle Cancer Care Alliance (SCCA)'s standard pharmacy guidelines. In general, BEAM will be given as per **Table 4**, but doses of individual agents may be adjusted at the discretion of the attending physician as per standard of care. *If at any time the SCCA develops Standard Practice Guidelines for BEAM, then this protocol's administration schedule and dosage will change to concur with the SCCA Guidelines.

- BCNU (Carmustine): administered on day -7. Dose: 300 mg/m^2 IV in D5W 250 ml over 3 hours (one day only)
- Etoposide (VP-16, Vepesid): administered on days -6, -5, -4 & -3. Dose: 100 mg/m^2 IV in D5W per Pharmacy standard over 2 hours BID x 4 days (or 200 mg/m^2 total daily dose x 4 days)
- Ara-C (Cytarabine): administered on days -6, -5, -4 & -3. Dose: 100 mg/m^2 IV in D5W 250 ml over 4 hours BID x 4 days (or 200 mg/m^2 total daily dose x 4 days)
- Melphalan: administered on day -2. Dose: 140 mg/m2 IV in NS 250 ml over 30 minutes (one day only)

TABLE 4: BEAM Treatment Schedule

Medication	Day							
	-7	-6	-5	-4	-3	-2	-1	0
BCNU (300 mg/m^2 IV x 1 d)	X							
Etoposide (100 mg/m^2 IV BID x 4 days or 200 mg/m^2 total daily dose x 4 days)		X	X	X	X			
Ara-C (100 mg/m^2 IV BID x 4 days or 200 mg/m^2 total daily dose x 4 days)		X	X	X	X			
Melphalan (140 mg/m^2 IV x 1 day)						X		
Day of REST (optional- see Section 8.9)							X	
Autologous Stem Cell Infusion								X

NOTE: The above dates are to be used as a general timeframe. The precise days of initiation for BEAM relative to the date of stem cell infusion can be adjusted +/- 1 day if necessary to accommodate clinic/hospital scheduling.

8.9 Stem Cell Infusion

PBSC will be thawed and infused per standard practice approximately 14 days after the ^{90}Y therapy dose. *Stem cells should not be infused within 24 hours of melphalan infusion if a day of rest is not taken (**Table 4**).

8.10 Adjunctive Therapy

Adjunctive therapy will follow standard practice guidelines.

8.11 Criteria for Removal from Protocol Treatment

Patients will be removed from protocol treatment for the following reasons:

- Patient request
- Unacceptable toxicity
- Treating physician or investigator request to prevent unacceptable risk to the patient.

9.0 EVALUATIONS

9.1 Pre-transplant Evaluations

Patients will undergo a pre-transplant work-up as per standard practice for patients undergoing autologous transplantation, including standard clinical staging assessments for lymphoma (e.g., CT scans of chest, abdomen, and pelvis, and neck at the discretion of treating MD or investigator; PET-CT within 56 days prior to treatment is strongly recommended for patients with aggressive B-NHL; bone marrow biopsy if indicated; etc.), and standard clinical workup for transplant including pulmonary function testing and assessment of cardiac ejection fraction (usually by echocardiogram or MUGA scan, performed commonly per standard practice but not required in all instances). In addition, the following assessments will be performed:

- Testing for presence of HAMA and HASA
- Serum rituximab level will be measured at baseline (prior to any study-related treatment) to evaluate the potential impact of the presence of rituximab on CD20 targeting.
- Measurement of organ volumes (obtained from imaging studies used for pre-transplant staging) for purposes of dosimetry when possible.
- Tumor volumes may be measured when possible from pre-transplant imaging.

9.2 Post-transplant Evaluations

Patients will routinely be followed within the general institutional guidelines and based on the patient's clinical condition. Common follow-up guidelines used when patients are followed on an outpatient basis until engraftment are summarized in **Table 5** below. All hospitalized patients have daily clinical assessments. Initial response assessments will be conducted approximately 1 month post-transplant as described below.

TABLE 5: General Post-transplant Outpatient Monitoring Guidelines

Assessment	Interval	
	When ANC<500 or PLT<20	When ANC≥500 and PLT≥20K
CBC	Daily	Weekly
Electrolytes	Weekly	Weekly
Liver Function Tests	Weekly	Weekly
Clinical assessment	Weekly	Weekly

9.3 Definitions

- Measurable Disease: Bidimensionally measurable lesions with clearly defined margins by physical examination (e.g., adenopathy), plain x-ray with one diameter 0.5 cm or greater, or CT/MRI (both diameters must be greater that the distance between the cuts of the imaging study).

- Evaluable Disease: Unidimensional measurable lesions, masses with margins not clearly defined, lesion with both diameters less than 0.5 cm, or lesions on scans with both diameters smaller than the distance between cuts.

- Non-Evaluable Disease: Pleural effusions, ascites, or disease documented only by indirect evidence (e.g., by lab values).

9.4 Measurement of Response

Response will be interpreted by investigator review of radiographic findings along with MD assessed physical findings and bone marrow or blood reports and will follow the revised lymphoma response criteria established by an international working group.[62] Disease response is not a primary endpoint in this dose-finding study; however, response will be assessed using standard criteria.

9.5 Long-term Evaluations

After the primary endpoint is reached for each patient (Day 30 toxicity) patients will be followed primarily for serious adverse events/toxicity, disease progression and survival. Patients with progressive disease will only be followed for survival and development of myelodysplasia or secondary malignancies. Follow-up evaluations (outlined in **Appendix 2**) will be within the standard of care for lymphoma patients following transplant. Data and samples provided by outside locations will be accepted for study evaluation purposes, and the Principal Investigator will continue to assess disease response objectively based on the data received. In addition we will specifically request renal function (BUN, creatinine) and hepatic function (transaminases, bilirubin, alkaline phosphatase) for all patients until 5 years after transplant or until the initiation of additional anti-neoplastic therapy. We will request these laboratory data approximately every three months for the first year, then every 6 months through the second year then annually through 5 years.

10.0 TOXICITIES AND COMPLICATIONS

1) Toxicity attributable to foreign mouse proteins

Allergic reactions to administration of foreign mouse proteins may include fever, urticaria, bronchospasm, anaphylaxis, Arthus reaction, vasculitis and serum sickness. In addition, infusion of foreign mouse proteins may produce pulmonary, renal or hepatic toxicity as a result of lysis or agglutination of circulating cells. Management of infusion toxicities are described in **Table 3**.

2) Radiation Toxicity:

Severe bone marrow suppression was expected during the course of ^{90}Y dose escalation. It is anticipated that bone marrow suppression will occur 7-14 days after radiobiotin infusion, but will be rescued by the planned stem cell transplantation. Other organs that may receive significant radiation

doses and thus experience toxicity include liver, lung, gastrointestinal tract, kidney and thyroid. Late effects of radiation may include hypothyroidism, pulmonary fibrosis, cataracts, renal insufficiency, growth retardation, sterility and carcinogenesis.

3) BEAM Toxicity:

BCNU (Carmustine) – a nitrosourea derivative/alkylating agent:

Adverse Effects: The most serious and frequent adverse effect is delayed hematologic toxicity, which is cumulative and usually occurs weeks after administration. Nausea and vomiting occur frequently after IV administration. Pulmonary toxicity, which can be rapidly progressive and fatal, is characterized by pulmonary infiltrates and hypoxia. Most of the cases have occurred in patients receiving total doses exceeding 1400 mg/m^2, although pulmonary fibrosis has occurred with lower total doses. Hepatotoxicity (reported in up to 26% of patients) is generally mild and reversible. Progressive azotemia and renal failure have occurred in patients who have received large cumulative doses, and occasionally in patients after lower doses.

Etoposide (VP-16, Vepesid) – a semi-synthetic podophyllotoxin:

Adverse Effects: Reversible myelotoxicity has been uniformly observed to be the major toxicity of Etoposide and represents the only clinically significant side effect. Transient, modest nausea, usually without vomiting, is common. Occasional alopecia is reported, as well as occasional hypotension, anaphylaxis or fever.

Ara-C (Cytarabine) – a synthetic pyrimidine nucleoside and pyrimidine antagonist antimetabolite:

Adverse Effects: The major adverse event is myelosuppression. Nausea and vomiting may occur more frequently in patients receiving rapid IV infusion of the drug. Other reported adverse effects include fever, rash, alopecia, skin ulceration, conjunctivitis, chest pain, urinary retention, renal dysfunction, dizziness, somnolence, neuritis or neurotoxicity, and reactions at the injection site including pain, inflammation, thrombophlebitis, or cellulitis. A cytarabine syndrome manifested as fever, myalgia, bone pain, maculopapular rash, conjunctivitis, malaise and occasionally chest pain has been reported. If symptoms of the syndrome require treatment, administration of corticosteroids should be considered.

Melphalan (L-phenylalanine mustard) – an alkylating agent:

Adverse Effects: The most common side effect is bone marrow suppression. Gastrointestinal disturbances such as nausea, vomiting, diarrhea and oral ulceration occur infrequently. Other reported adverse reactions include pulmonary fibrosis and interstitial pneumonitis, skin hypersensitivity, vasculitis, alopecia, hemolytic anemia and allergic reaction.

4) Transplant related toxicities:
It is expected that patients will frequently require admission during the first 30 days post-transplant for transplant-related toxicities, often due to neutropenic fever, infections, or mucositis causing severe pain and/or interfering with food and fluid intake.

11.0 PROTOCOL ENROLLMENT AND SPECIAL CONSIDERATIONS

- All patients will require placement of a double lumen central venous catheter prior to the therapeutic infusion; for the biodistribution infusion, alternative devices (e.g., peripherally-inserted central catheter [PICC] or port) are permitted.

- All blood and tissue samples containing radioisotopes should be clearly identified as such. Samples containing high levels of activity (>50 μCi) should be transported in appropriate containers. All samples should be processed by personnel trained in the use of radioisotopes and sample volumes submitted to clinical laboratories will be as small as possible.

- Potential alternative therapies will be discussed with all patients including observation alone, conventional chemotherapy and radiation therapy, and marrow transplantation with conventional conditioning regimens for which the patients are eligible.

- Neither gender nor ethnicity is criteria for enrollment on this study. Based on previous enrollment experience at FHCRC/UW the expected gender and ethnicity distribution is shown in **Table 6**.

TABLE 6: Projected Target Accrual/Ethnic and Gender Distribution Chart

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	1	2	3
Not Hispanic or Latino	17	24	41
Ethnic Category: Total of All Subjects *	18	26	44
Racial Categories			
American Indian/Alaska Native	0	1	1
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	1	1	2
White	15	22	37
Racial Categories: Total of All Subjects *	18	26	44

12.0 ADVERSE EVENT REPORTING

12.1 Adverse Event Definitions

- **Adverse Event**
  An Adverse Event (AE) is any untoward medical occurrence in a clinical investigation subject administered a medicinal product; the event does not necessarily have a causal relationship with

study drug administration or usage. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

- **Serious Adverse Event**
  A serious adverse event (SAE) is defined as an untoward medical occurrence that results in any of the following outcomes:
  - Death.
  - Life-threatening situation (i.e., with an immediate risk of death from the event as it occurred but not including an event that, had it occurred in a more serious form, might have caused death).
  - In-patient hospitalization or prolongation of existing hospitalization. Inpatient hospitalization comprises formal admission to a hospital for medical reasons, for any length of time, whether or not hospitalization extends overnight. However, hospital admissions for administration of the study drug, procedures required by the study protocol, or tumor-related diagnostic procedures are not considered serious.
  - Persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
  - Congenital anomaly/birth defect.
  - An important medical event that requires intervention to prevent one of the above outcomes.
- **Unexpected Adverse Event**
  An unexpected adverse event is defined as an event that has a nature or severity, or frequency that is not consistent with the applicable investigator brochure. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed and reported rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

12.2 Monitoring and Recordings AEs

All adverse events will be assessed by the investigator or qualified designee and recorded in the CRFs. The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the adverse event and/or serious adverse event and not described as the individual signs or symptoms. The following information should be recorded:

- Description of the adverse event using concise medical terminology
- Description as to whether or not the adverse event is serious
- The start date (date of adverse event onset)
- The stop date (date of adverse event resolution)
- The severity (grade) of the adverse event
- A description of the potential relatedness of the adverse event to study drug or a study procedure
- The action taken due to the adverse event
- The outcome of the adverse event.

12.3 Grading of the Severity of an Adverse Event

All AEs will be graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/About.html). If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event. However, the Bearman Scale of Regimen-Related Toxicity will be used for decisions regarding dose escalation/ de-escalation and invocation of stopping rules.

12.4 Attribution of Adverse Event

Association or relatedness to the study agent will be assessed by the investigator as follows:

- Definite: The event follows a reasonable temporal sequence from exposure to the investigational agent, has been previously described in association with the investigational agent, and cannot reasonably be attributed to other factors such as the patient's clinical state, other therapeutic interventions or concomitant medications; AND the event disappears or improves with withdrawal of the investigational agent and/or re-appears on re-exposure (e.g., in the event of an infusion reaction).
- Probable: The event follows a reasonable temporal sequence from exposure to the investigational agent and has been previously been described in association with the investigational agent OR cannot reasonably be attributed to other factors such as the patient's clinical state, other therapeutic interventions or concomitant medications.
- Possible: The event follows a reasonable temporal sequence from exposure to the investigational agent, but could be attributable to other factors such as the patient's clinical state, other therapeutic interventions or concomitant medications.
- Unlikely: Toxicity is doubtfully related to the investigational agent(s). The event may be attributable to other factors such as the patient's clinical state, other therapeutic interventions or concomitant medications.
- Unrelated: The event is clearly related to other factors such as the patient's clinical state, other therapeutic interventions or concomitant medications.

For general AE assessment, an AE is considered related if it is assessed as definitely, probably, or possibly related; unrelated if it is assessed as unlikely related or unrelated. For determination of IND safety reporting, AE attribution will be assessed according to the suspected adverse reaction definition described in 21 CFR 312.32 as an AE for which there is a reasonable possibility that the drug caused the adverse event where "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reactions that are both serious and unexpected will be reported to the FDA as an IND safety report, in accordance with regulations under 21 CFR 312.32.

12.5 Adverse Event Reporting Period

AEs will be monitored and recorded in study-specific case report forms (CRFs). From the time of first exposure to an investigational agent (i.e., the start of the B9E9-FP infusion) through the start of BEAM

chemotherapy treatment all SAEs and all grades of adverse events will be captured. From the start of BEAM chemotherapy through day +30 post-transplant non-hematologic adverse events of ≥ grade 3, and all serious adverse events will be captured. Beyond day +30 after transplant/discharge from the transplant service until day +100, only SAEs and grade 4 and 5 toxicities will be collected. Beyond day +100, disease progression, development of myelodysplasia or secondary malignancies, and survival only will be collected. AEs with an onset date prior to the first exposure to an investigational product will not be recorded, except in the case of clinically significant worsening of the AE during the specified monitoring time frame. A subject withdrawn from the study because of an adverse event must be followed until the clinical outcome from the adverse event is determined.

The following events are *not* identified as AEs in this study:

- Disease progression or relapse. However, clinical events associated with progression/relapse may be reportable as AEs.
- Hospitalization for the purpose of facilitating stem cell transplant is not considered an AE. Any AE requiring prolongation of this hospitalization will be recorded and subject to applicable SAE reporting.
- Medical or surgical procedures in and of themselves, including those that require hospitalization (e.g., surgery, endoscopy, biopsy procedures) are not considered AEs. However, an event or condition requiring such procedures may be an AE.

12.6 Adverse Event Reporting Requirements

12.6.1 Research Site Reporting Requirements

Classification of an event as serious or non-serious (see Section 12.1) determines the reporting procedures to be followed by the site for reporting the event to the Sponsor which are outlined in **Table 7**. The investigator must report events to the Fred Hutch IRB in accordance with the policies of the IRB.

TABLE 7: Site to Sponsor Reporting Requirements for Adverse Events

Classification		Reporting Time	Reporting Action	Contact Information
Serious Adverse Event (SAE)	Fatal or life-threatening	Within 24 hours of research team awareness	Email notification to Sponsor's Medical Monitor & ISIOC Administrator	Medical Monitor email: tillb@fredhutch.org ISIOC email: ISIOC@fredhutch.org
	All SAEs	Within 2 business days of research team awareness	Submit completed Institution-Sponsored IND SAE Reporting Form signed by PI or designated sub-Investigator	ISIOC Fax: 206-667-6068 ISIOC email: ISIOC@fredhutch.org
Non-serious Adverse Event		Per CRF completion guidelines	Record information on appropriate CRFs	N/A

*Research team is defined as the individuals listed on the delegation of authority log. Physicians listed on the study's delegation of authority log as transplant service attending physicians delegated authority to administer informed consent will not be considered part of the research team unless additional responsibilities related to the conduct of the study have been delegated to them by the Principal Investigator.

The information in the Institution-Sponsored IND SAE Reporting Form must match or be reconciled with the information recorded in the adverse events section of the CRF and study database. For example, the same adverse event term should be used on both forms.

The investigator must report events to the Fred Hutch IRB in accordance with the policies of the IRB. The sponsor assumes responsibility for IND safety reporting to the FDA and participating investigators, in accordance with regulations under 21 CFR 312.32.

12.6.2 Fred Hutch Sponsor Reporting Requirements

The sponsor assumes responsibility for IND safety reporting to the FDA and participating investigators, in accordance with regulations under 21 CFR 312.32.

Each serious adverse event report received from the investigator will be evaluated by the Medical Monitor who will assess the seriousness of the event (see Section 12.1), the expectedness of the event (see Section 12.1), and the relationship to participation in the study (see Section 12.4). For regulatory reporting purposes, the Sponsor will determine expectedness relating to the investigational product using safety information specified in the Investigator Brochure. An event will be classified as related if either the investigator or the Sponsor determines that the event may be related to the study drug.

The Sponsor or its designee will provide all investigators with a safety letter notifying them of an event that meets FDA IND Safety Reporting criteria. Investigators will be requested to provide written notification of safety report to the Fred Hutch IRB as soon as is practical, consistent with IRB requirements.

12.7 SAEs Commonly Associated with ASCT

Certain events that are commonly observed as SAEs following ASCT are outlined in **Table 8**. SAEs that are identified as routinely experienced in the autologous transplant setting will be assessed as unrelated to the radioimmunotherapy regimen used in this protocol. All of the SAEs listed in Table 8 will nevertheless be collected and graded.

TABLE 8: SAEs Commonly Observed Following Autologous Stem Cell Transplant

CTCAE Category	Toxicity
Blood and lymphatic system disorders	*As noted above, all patients undergoing HCT are expected to have ≤ Grade 4 pancytopenia as an intended therapeutic effect. These hematologic adverse events will be tracked and recorded only as time to recovery of blood counts/engraftment.* Febrile neutropenia
General disorders and administration site conditions	Fatigue Fever Rigors, chills
Gastrointestinal	Diarrhea Dysphagia Esophagitis Mucositis/Stomatitis Nausea Vomiting
Hemorrhage/Bleeding	Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia

CTCAE Category	Toxicity
Infections and infestations	*Infections may be associated with neutropenia following HCT*
Metabolism and nutrition disorders	Anorexia Dehydration Hypokalemia (e.g., potassium < 2.5 can result from wasting induced by HCT related medications)
Reproductive system and breast disorders	Reproductive system and breast disorders – Other: Sterility/infertility

13.0 DATA AND SAFETY MONITORING

This is a single institution trial where all patients are followed closely by the investigators. Additionally, the trial design provides rules for dose escalation depending upon the rate of development of Grade III/IV RRT (Bearman Scale). This design mandates ongoing review of the outcome of previous patients treated on study so that the appropriate Dose Level for the current patient can be assigned. The principal investigator, primary research nurse, and study data communicate routinely (typically weekly) to review recently acquired data, stopping rules, and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. Data detailed in the research case report forms includes the nature and severity of all significant toxicities, which are also reported as described above. All investigators on the protocol have received formal training in the ethical conduct of human research.

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan (DSMP). Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

14.0 DATA MANAGEMENT/CONFIDENTIALITY

The investigator will ensure that data collected conform to all established guidelines. Each subject is assigned a unique subject number to assure subject confidentiality. Subjects will not be referred to by

this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the institution where the subject receives medical care, maintains all original inpatient and outpatient chart documents. Additional clinical data may be made available from the Fred Hutch core database (Gateway), which is managed and verified independent of the research group.

The research team will maintain Case Report Forms (CRF) and associated research documentation for each patient treated under the protocol. This documentation includes both clinical data and study-specific documents for each patient. Additional study-specific documents and radiologic data are maintained by the UW Division of Nuclear Medicine. The Principal Investigator or a designee will verify completed CRFs against source documentation on an ongoing basis as they are completed for individual patients. CRFs should be complete and data entered into the study database within 120 days of transplant. Data required for analysis of patients treated on this protocol will be maintained in a password-protected study-specific database. Data from the CRFs are keyed directly into the database by authorized research staff and verified on an ongoing basis.

15.0 STATISTICAL CONSIDERATIONS

15.1 Randomization/Stratification/Descriptive Factors

1) Randomization-none

2) Stratification-none

3) Descriptive factors- Histological subtype by WHO classification should be supplied. Patients will be classified as *chemo-responsive* if they achieve at least a partial response with their most recent chemotherapy (e.g., cytoreductive or mobilization chemotherapy). Patients that have never achieved at least a PR will be categorized as *primary refractory*. Other patients will be categorized as *chemo-resistant* (i.e., patients that have previously achieved at least a PR, but have not responded to their most recent chemotherapy*)* .Patients' disease stage should be recorded both at the time of diagnosis and the time of treatment. International Prognostic Index (IPI) or Follicular Lymphoma International Prognostic Index (FLIPI) score, as appropriate, will be calculated and recorded directly on case report forms.[63, 64]

15.2 ^{90}Y-DOTA-biotin dose escalation

The primary objective of this study is to estimate the MTD of ^{90}Y-biotin that can be delivered in a pre-targeted fashion prior to BEAM chemotherapy and ASCT in patients with relapsed/refractory lymphoma. The MTD is defined as the dose that is associated with a true dose-limiting toxicity (DLT) rate of 25%, where a DLT is defined as a grade III or IV Bearman (transplant) toxicity within 30 days of transplant [65]. Dose escalation/de-escalation will be conducted by a modification of the "two-stage" approach introduced by Storer [66]. The starting dose level will be level 1 (30 mCi/m^2). In the first stage, up to two patients will be treated at escalating doses in 20 mCi/m^2 increments (**Table 2**) until a DLT is observed**.** Once a DLT is observed, the second stage will begin at the next lower dose level and patients will be treated in cohorts of

4 with 10 mCi/m^2 increments according to the following rules (if the first of the two patients has a DLT, the second patient will not be treated at this dose and the second stage will commence at the next lower dose level). If no DLT is observed in a cohort of 4 the next cohort will be treated at a dose that is one dose level higher; if 1 of 4 experiences a DLT the next group will be treated at the same dose; if 2 DLTs are seen among 4 (or fewer) in a cohort, the next group of 4 will be treated at a dose that is one dose level lower, and no further testing will be done with the dose at which 2 DLTs were observed. This algorithm will continue until 24 patients are treated in the second stage. Following the completed observation of the final patient, a two-parameter logistic model will be fit to the data, thereby generating a dose-toxicity curve based on the observed DLT rate at the various dose levels visited. Based on this fitted model, the MTD is estimated to be the dose that is associated with a DLT rate of 25%.

It is possible that a patient will be entered on the protocol before the prior patient (in the first stage) or all patients in a cohort (in the second stage) have been followed sufficiently long to evaluate toxicity. Such patients will be treated at the current dose level and will be used for purposes of fitting the dose-toxicity curve. These patients will not be used for purposes of dose-modification, however, nor will they be counted towards the total of 24 patients on the second stage for completion of the dose-adjustment phase of the trial. A maximum of 2 additional patients may be added to a given dose level while the initial patients are completing the DLT period. It is important to note that the overall sample size of this trial cannot be completely predicted as this will be determined by observed DLTs and timing of accruals.

15.3 Evaluation of Efficacy

After completing sufficient enrollment to estimate the MTD of this approach, patients will be enrolled into a second cohort to evaluate its efficacy in terms of overall response rate, overall survival, and progression-free survival (PFS). A secondary endpoint of this study will be to estimate the rate of PFS at 1 year from ASCT when conditioned with pretargeted ^{90}Y-biotin + BEAM, which we will compare to a historical control. This study will not necessarily exclude patients that are traditionally felt to have poor outcomes from standard myeloablative conditioning (e.g., DLBCL failing to achieve remission after first salvage) .[5,67] Furthermore, this study will enroll a variety of B-NHL histologies. Thus, finding an accurate comparison to use as a historical control is challenging. Based on other reports, we will use the following benchmarks for 1-year PFS for each of these unfavorable-risk subgroups: for example, 10% for DLBCL that relapsed within 1 year of diagnosis (following a rituximab-based induction regimen); 30% for relapsed/refractory MYC+ DLBCL; 60% for rituximab-refractory FL. We'll assume that our proposed treatment will have roughly the same impact across these various histologies, and the ultimate benchmark that we'll use to assess potential efficacy will be a weighted average of these individual benchmarks, with the weights derived from the proportion of patients with each histology enrolled on the trial. For the current purposes, we'll assume that the overall benchmark to be used will be 30%. If the true 1-year PFS rate using the proposed approach is 54%, then 24 patients will provide 80% power to detect a statistically significant increased rate of PFS from the fixed rate of 30%, based on a one-sample chi-square test with one-sided significance level of 5%. We will include patients who were treated at the MTD in the dose-adjustment phase of the trial in this efficacy sample. Thus, the number of patients to be enrolled in this phase of the trial will be 24-n, where n is the number treated at the MTD in the Phase 1 portion of the trial.

Based on current referral patterns, dose escalation/de-escalation rules, and competing protocols, we anticipate entering 1 patient per month to this phase I protocol which we project will take up to 4 years to complete. Secondary endpoints will include descriptive statistics on the number and percent toxicities and responses will be calculated.

15.4 Estimation of Dosimetry

We will also describe the estimated dose to normal organs and tumor sites based on the tumor to normal organ ratios derived from dosimetry estimates coupled with the absorbed dose to normal organs based on the administered activity of ^{90}Y. This evaluation will be made among all patients and among those treated at the estimated MTD.

15.5 Stopping Rules

Since the patients enrolled on this trial would be expected to have a poor outcome from a standard autologous transplant, we will accept a progression rate of up to 80% of patients experiencing progression at day 30 following transplantation. If the observed progression rate exceeds 80% by day 30 after transplant, the study will be suspended for lack of efficacy, pending a detailed review by an ad hoc safety committee comprised of individuals with appropriate clinical and research expertise who are independent of this research program, and/or by the Fred Hutch/UW Cancer Consortium Data and Safety Monitoring Committee (DSMC). In addition, rules will be in place for suspending the study due to an excess of late toxicities, as defined by grade III/IV Bearman toxicity that occurs prior to progressive disease or additional antineoplastic therapy. If there is ever sufficient evidence to suggest that the true probability of late toxicity exceeds 25%, then the study will be suspended pending review by an ad hoc safety committee or DSMC as described above. Sufficient evidence will be taken to be any proportion of late toxicities to patients treated whose lower one-sided 80% confidence limit exceeds 0.25. Any of the following ratios would satisfy this: 2/2-3, 3/4-6, 4/7-9, 5/10-12, 6/13-16, 7/17-19, 8/20-23, 9/24-26, 10/27-30, 11/31-33, 12/34-35. If the true probability of late toxicity is 0.15, then the probability of suspending the trial after 20 or 30 patients is approximately 0.10 and 0.11, respectively. If the true probability of late toxicity is 0.40, these probabilities are approximately 0.80 and 0.90, respectively (estimated from 5,000 simulated trials). Each of these rules will be evaluated among all patients, regardless of the dose delivered.

16.0 TERMINATION OF THE STUDY

The study will be terminated upon complete accrual of patients, when toxicity criteria noted above are met, or at the discretion of the PI or sponsor.

17.0 REFERENCES

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APPENDIX 1: GRADING OF TOXICITY (BEARMAN SCALE)

Parameter	I (mild)	II (moderate)	III (severe)	IV (life threatening)
Allergic	Pruritus, rash	Generalized Urticaria	Anaphylaxis	Fatal
Renal				
Creatinine	1.5-2x increase	>2x increase No dialysis	Dialysis	Fatal
Pulmonary	Dyspnea	Interstitial pneumonia	Ventilatory support or $F10_2$ >50%	Fatal
Cardiac	Mild CHF No therapy needed	Moderate CHF Diuretics needed	Severe CHF Ejection Fraction <30%	Fatal
Hepatic				
Bilirubin	2-6 mg/L	6-2 mg/L	>20 mg/dL	Fatal
SGOT 2-	5 x increase	>5 x increase	Encephalopathy	
Ascites	Ascites <100 ml	Ascites >100 ml		
CNS	Transient somnolence	Somnolence >36 hr	Seizure or coma	Fatal
Stomatitis	Ulcerations	IV opiates	Intubation or aspiration pneumonia	Fatal
GI	Watery stools 0.5-2 L/d	Stools>2L/day Subileus	Hemorrhagic enterocolitis NG suction	Fatal
Bladder	Macroscopic Hematuria <7 days	Macroscopic hematuria >7 days	Sclerosing agents or surgery needed	Fatal

APPENDIX 2: SUGGESTED POST TREATMENT EVALUATIONS*

EVALUATION	TIME (MONTHS)[1]					
	1	3	6	12	18	24* (annually until relapse/progression or initiation of additional anti-neoplastic therapy.)
CBC	X	X	X	X		X
Chemistries[2]	X	X	X	X	X	X
Bone Marrow Biopsy[3]	X			X		X
Bone Marrow Aspirate[3]	X			X		X
SPEP[4]				X		X
CT/MRI[5]	X	X	X	X		X
PET-CT[6]	X	X	X	X		X
Pulmonary Function Testing				X		

[1] Timepoints for these assessments are relative to the date of stem cell infusion.

[2] Chemistries = BUN, creatinine, LDH, transaminases, bilirubin, and alkaline phosphatase.

[3] Only when clinically indicated, BM biopsy/aspirate PCR (only patients that had prior positive PCR studies), flow cytometry, cytogenetics as performed at baseline per standard practice.

[4] Only patients with a prior documented monoclonal protein are required to undergo follow up SPEP testing

[5] CT/MRI = chest, abdomen and pelvis.

[6] Post-treatment PET-CT scan at 1 month is strongly recommended (but is not required by the study) if baseline scan was positive. Subsequent PET-CT scans are to be considered (but are not required by the study) until complete treatment response has been documented by a negative PET-CT.

**Following relapse or disease progression, patients will be followed annually for survival and development of secondary malignancies. Following other significant diagnoses and/or therapies that would confound assessment of the relationship between the study treatment and adverse events (e.g., further therapy intended to maintain disease remission), patients will be followed annually for disease status, survival, and development of secondary malignancies. Follow up will in general mirror the current standard of care.*

Appendix 3: Methods Used to Estimate Radiation Absorbed Doses

The calculation of radiation absorbed dose to internal organs, tissues, the whole-body, and tumor tissues is a fundamentally important aspect of successfully achieving the desired clinical objectives of radiopharmaceutical therapy. The use of radiopharmaceuticals for cancer treatment requires detailed, patient-specific dosimetry and dose planning for assessments of absorbed dose to both normal tissues and tumors. Dosimetry serves two primary goals: (a) to ascertain the maximally achievable radiation doses to cancerous tumors and lesions for complete disease eradication, and (b) at the same time and under the same circumstances, to ensure that radiation doses to critical normal organs and tissues do not exceed maximally tolerated levels.

a. Scientific Basis for Internal Dosimetry Calculations

Direct measurements of organ or tissue radioactivity must account for the geometry and density of the source organ or tissue, organ size and mass, potential overlap, thickness of tissue between the organ and the detector, and the spatial distribution of activity with a tissue. Measurements are corrected for background, photon attenuation, and photon scatter that may influence the accuracy of direct counting. For any radionuclide, the Information needed to calculate absorbed dose includes: the total activity administered to the patient and time of infusion, the fraction of the administered activity that is taken up by each major source organ or tissue, and the time-dependent retention and clearance of activity in each major source organ through complete radiological decay.

Radiation absorbed doses will be calculated for each patient's normal organs and tissues, the whole body, and for imageable tumors using methods recommended by the Medical Internal Radiation Dose (MIRD) Committee of The Society of Nuclear Medicine (Loevinger et al., 1991). The MIRD methods account for both the penetrating gamma and the non-penetrating beta radiation (electrons) emitted by radioactivity distributed throughout the body. In the MIRD schema, dosimetry calculations are based on a series of direct measurements of the organ biodistribution of radiolabeled antibody in individual patients. These include gamma-camera images and quantitative activity measurements of the radionuclide used (^{111}In as a tracer for yttrium-90-labeled-biotin) in the major imageable source organs, tumor tissue, red marrow, and the total body at various time-points post-infusion. Radiation doses to red marrow may be determined by direct measurement of radioactivity in distinct spaces such as acetabulum and sacrum, or by a combination of direct imaging and marrow tissue biopsy. When available, the patient-specific organ masses are used for internal dose calculations rather than generic model values. The mathematical foundations for application of these methods to critical organs in high-dose radioimmunotherapy are well-established (Fisher 1994, 2000; Fisher et al. 2009). Fully implemented, the MIRD formalism accounts for all source regions and all target organs, all source-target geometries, and all radioactive emissions contributing to absorbed dose.

b. Rationale for the Use of Indium-111 to Predict Yttrium-90 Biodistribution.

Because ^{90}Y is a pure beta-emitter, it cannot be imaged accurately or conveniently in the patient. Based on prior studies, we assume that the biodistribution of the trace-labeled ^{111}In-biotin faithfully represents the biodistribution of the ^{90}Y-labeled-therapeutic conjugate in the cancer patient. Preclinical studies

show that the biodistribution of ^{111}In-labeled-biotin usually correlates well with ^{90}Y-labeled-biotin biodistribution (Fisher et al. 2009). Therefore, it is common practice in nuclear medicine to use ^{111}In-conjugates measurement data to predict the biodistribution of ^{90}Y-conjugate. We have found two exceptions: If the indium-111 or yttrium-90 disassociates from the protein, (1) free (unbound) ^{90}Y may deposit on bone surfaces, and (2) free ^{111}In may preferentially deposit in the testes due to natural uptake of indium by germ cells. During radiolabeling, quality control usually allows less than 2% unbound ^{111}In. We will not measure the unbound fraction in serum after injection. For dosimetry calculations, however, we will assume that the biodistributions of ^{111}In and ^{90}Y labeled antibody are equivalent, recognizing the exceptions that without further correction this assumption may lead to underestimates of ^{90}Y dose to bone surfaces and red marrow, and to overestimates of ^{90}Y dose to the testes.

c. Direct Measurements in Patients

In planar imaging, the geometric mean of counts obtained from anterior and posterior views is determined. The counts obtained in an organ or tissue region of interest must be converted to units of radioactivity using appropriate measurement methods and calibration standards, including: daily quality assurance, patient positioning, patient-thickness measurements, background subtraction, attenuation correction, and scatter correction.

(i) Conjugate Views

Conjugate-view quantitative planar imaging with anterior and posterior measurements is the most widely used method for assessing source-organ activity in patients. The conjugate view method does not require knowing the depth of the source region and does not depend on assumptions inherent in single-view phantom simulations, but does incorporate correction for background, scatter, and photon attenuation.

(ii) Biodistribution Imaging

After a tracer quantity of ^{111}In (usually 111 to 222 MBq or 3 to 6 mCi) labeled to DOTA-biotin is administered, the patient is imaged using collimated anterior and posterior planar gamma-camera imaging. Biodistribution imaging begins immediately after infusion of ^{111}In trace-labeled DOTA-biotin on day 0. A nuclear medicine camera with a medium energy collimator, with photopeak settings at 171 and 245 keV, and a symmetric 15% window around each photopeak, is used for imaging. Images include chest with upper humeri and thyroid, abdomen, and pelvis with upper femurs. Regions of interest are typically selected for the major source organs that visualize above background, which may include, but are not limited to, the liver, spleen, heart volume, red marrow space, lungs, kidneys, thyroid, and testes.

Normal organs and tumors are visualized when concentrations of ^{111}In antibody in the organ or tumor are greater than in the surrounding tissue. Background regions are drawn for each organ/region similar to the methods described above. In addition, attenuation correction factors are determined for the chest and abdomen using the methods described below. We image tumor sites that have well-defined uptakes and retention of ^{111}In-radiopharmaceuticals, allowing us to determine the percent of administered activity per gram of tumor tissue for all tumors selected for dose assessment. Imaging of

selected tumors may be conducted for various time points, and time-activity curves can be constructed and integrated for tumor dose assessments.

Measurements are also made of representative background tissue and of an imaging standard without the patient in the camera field-of-view. The outlines for the regions of interest are drawn by a technologist from the acquired images, and counts are obtained from the selected regions. The counts are decay-corrected to the ^{111}In imaging standard. The geometric mean of the anterior and posterior counts is obtained for each region of interest. Counts are then corrected for attenuation, decay, and background. Total-body measurements are obtained using whole-body gamma camera images in both anterior and posterior projections, to quantify the total ^{111}In activity remaining in the patient, over time, as a fraction of the total administered activity.

(iii) Attenuation

Prior to antibody infusion, all patients will have measurement made of their abdomen attenuation by transmission scans. A fluid filled sheet source, large enough to cover the entire useful field of view of the camera, is loaded with approximately 0.7 mCi of ^{111}In. Uniform distribution of the isotope throughout the sheet source is ensured. The source is placed on the lower detector, and with the patient on the scanning table and their abdomen in the field of view, the upper detector is lowered into place. A five-minute transmission image is acquired. Without moving the detectors and with the scanning table alone between them, another five minute image (flood) is acquired. The observed ratio of counts in the flood source activity counted with and without the patient overlying is the attenuation correction factor for the various organs of interest.

(iv) Sampling Times

Selecting an appropriate number of counting times requires trade-offs between obtaining sufficient data, economizing the imaging costs, and minimizing patient inconvenience. The objective is to select the fewest time points that will provide a reasonable description of the activity-time curve. Three to five data measurement points will typically be required for ^{111}In-DOTA-biotin imaging. Imaging includes one measurement at or as close as possible to time zero (time of radiopharmaceutical infusion), plus additional measurements on the day of infusion and on subsequent days post-infusion. On Days 1 and 2 post infusion, patients will have a total of at ideally two sessions of gamma camera images (for example, in the morning of Day 1 and the afternoon of Day 2 post infusion). The final imaging time point should ideally be on Days 4 to 6 post-infusion. Analyses of time-activity functions provide an estimate of the fraction of the administered activity that resides in each source organ and in the total body at each measurement time point.

d. Time-Activity Curves

The sequential measurement data are plotted to determine the cumulated activity and residence times for each source organ. Separately for each organ or tissue, we plot the fraction of the total administered activity observed at each measurement time point in the organ. We then identify an appropriate mathematical function to represent the data by curve-fitting and least-squares regression analysis. These functions may be single-exponentials, bi-exponentials, or mathematical equations of other forms. Time-activity curves are constructed from the measurement data and are integrated to

infinite time to determine the time-integrated activity coefficient (τ, hours), or area-under-curve for each source organ, tumor, the red marrow, and the whole body. An estimate of the long-term tail of the time-activity curve may be made by fitting an exponential function to the last two points. We plot the *effective* fractions present (as measured), rather than the values that were decay-corrected from a radionuclide standard, because internal doses are calculated from the integral areas under the effective time-activity curves. Standard mathematical software packages are used to fit the measurement points to representative equations.

e. Time-integrated Activity Coefficients

The time-integrated activity coefficient (previously known as "residence time" (Bq-sec/Bq or μCi-hr/μCi administered) for a source organ is the fraction of the administered activity in an organ or tissue over time to complete decay, obtained by integrating the time-activity curve. The coefficient is the basic input value to dosimetry software packages (such as OLINDA-EXM, Vanderbilt University, Nashville, Tennessee) that implement the MIRD dosimetry schema. We will use OLINDA-EXM for this project.

The cumulated activity, $\tilde{A}_h$, and time-integrated activity coefficient, τ_h, are determined by integrating the area under the activity-time curves for the clinical measurement data for each source organ and the remainder tissues. The integrations are carried to infinity for accuracy and simplicity.

f. Patient-specific Dosimetry

Since organ dose is approximately proportional to the inverse of target mass, a correction should be made for patient weight and organ mass when actual organ weights are known from CT-imaging. Actual patient weights and organ sizes vary, but OLINDA corrects for those differences when actual masses are known. The correction involves recalculating the S values for each of the source-target combinations where patient-specific organ volumes are used. The recalculated S values account for both the gamma component specific absorbed fraction of energy and the mass over which the beta component is averaged. For most radionuclides, the beta self-irradiation dose in a source organ is the greater contributor to total organ dose (usually more than 90 percent of the total). For yttrium-90, which emits no gamma rays, this self-irradiation component is essentially 100%.

g. Estimate of Dose to Testes

In male patients with significant testicular uptake of ^{111}In, we estimate the ^{90}Y dose to testes with corrections for ^{111}In disassociation and thickness of tissue due to their superficial position in anterior scans. Regions may be drawn around the testicular uptake on serial anterior gamma camera images. Care is taken to separate the penile activity by instructing the patient to physically move the penis away from the testes during each scanning session. A suitable background is used to correct the counts, but no attenuation correction factor are used because the testes are positioned to the anterior view without any significant attenuating tissues.

h. Estimate of Dose to the Bone Marrow:

Red marrow dosimetry is challenging because it is difficult to assess 1) the highly variable concentration of radioactivity in marrow by anatomical location, and 2) the mass of red marrow in the patient. Common approaches to marrow dosimetry often rely on unreliable estimates of radiolabeled antibody

concentration in red marrow or in red marrow relative to the concentration in circulating blood or blood plasma. Rather than measure blood plasma activity and make uncertain assumptions, we employ quantitative imaging of defined marrow spaces (acetabulum, sacrum, femoral head, or lumbar vertebrae) by repetitive direct counting. These measurements provide data for evaluating the red marrow time-activity curve. The sacrum is assumed to contain exactly 9.9 percent of total body marrow (Siegel et al., 1989). One may then assume that total-body marrow activity is directly proportional to the concentration measured in the sacrum to obtain the time-integrated activity coefficient for red marrow (Siegel et al., 1989). Alternatively, a marrow time-activity function may be normalized through a marrow biopsy measurement (radioactivity per gram), if a biopsy measurement is available.

i. Dosimetry Results. Results of radiation dose calculations for individual patients are summarized and reported back to the University of Washington, Division of Nuclear Medicine. The report includes the gamma camera measurement data (percent administered activity in each major source organ and the whole body), the calculated time-integrated activity coefficients, values of Ao (an estimate of initial organ uptake immediately following radiolabeled antibody infusion, the effective and biological retention half-times, and the correlation coefficients applicable to the mathematical retention equations used. The report also includes the calculated radiation absorbed doses (cGy) to each of the listed organs and tissues of the body, plus the whole-body, per unit administered activity (milliCuries).

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APPENDIX 4: SWOG PERFORMANCE STATUS

Grade	Scale
0	Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100)
1	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 (Karnofsky 70-80)
2	Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60%)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40%)
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair (Karnofsky 10-20 %)
5	Dead