THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

Dose-Intense Yttrium-90 Ibritumumab Tiuxetan (Zevalin)-Containing Non-Myeloablative Conditioning for Allogeneic Stem Cell Transplantation in B-cell Malignancies
2011-0393

Core Protocol Information

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Full Title:	Dose-Intense Yttrium-90 Ibritumumab Tiuxetan (Zevalin)-Containing Non-Myeloablative Conditioning for Allogeneic Stem Cell Transplantation in B-cell Malignancies
Protocol Phase:	Phase II
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Abstract

Objectives:

Primary Objectives:
1) To characterize the safety of yttrium-90 ibritumumab tiuxetan calculated to deliver up to 10 Gy to critical organs, when administered in conjunction with fludarabine and bendamustine as non-myeloablative preparative regimen for allogeneic stem cell transplantation

Secondary Objectives:
1) To estimate the efficacy of this strategy (overall survival and event-free survival) in patients with b-cell lymphoid malignancies
2) To determine survival rates by histology subtype
3) To correlate blood radioactivity level and time to neutrophil and platelet recovery

Rationale: (Be as concise as possible)

Allogeneic non-myleoblative stem cell transplantation (NST) with fludarabine bendamustine and rituximab has been a successful strategy for patients with lymphomas and CLL who had a chemosensitive relapse (Protocol 2008-0246). Results, however, need to be improved upon in patients who had refractory disease or are in

kinetic failure at the time of transplantation. Intensification of the preparative regimen has been associated with increased toxicity with no improvement in outcomes. Immunomanipulation with donor lymphocytes or rapid immune suppression withdrawal has been associated with an increased risk of graft-versus-host disease without documented improvement in survival.

The anti-CD20 radioimmunoconjugates (RIC) (^{90}Y) ibritumomab tiuxetan and iodine-131 (^{131}I) tositumomab produce durable remissions in previously treated patients who have relapsed or refractory, low-grade, follicular or transformed lymphoma. The standard dose of (^{90}Y) ibritumomab tiuxetan is based on weight and is equal to 0.4 mCi/kg. Protocol (ID01-233), involving the use of this radiolabeled antibody together with fludarabine and cyclophosphamide as NST conditioning, has shown adequate engraftment and time to recovery of counts. Results also suggest that the addition of RIC can overcome the negative prognostic impact of PET+ in NST transplantation, and that it can be curative for patients with refractory, relapsed follicular lymphoma. Results remained suboptimal, however for patients with other histologies, such as mantle cell and diffuse large cell lymphoma. Optimizing drug delivery may improve outcomes.

Because myelosuppression is the major toxicity of anti-CD20 RICs, they are ideal candidates for dose-escalation with stem cell support. Phase I/II studies have demonstrated that anti-CD20 RICs may be dose escalated with limited toxicity and that higher radiation doses are associated with improved clinical outcomes.

Conventional, therapeutic-dose ^{131} tositumomab or (^{90}Y) ibritumomab tiuxetan has been added to the most commonly used high-dose chemotherapy program (i.e., carmustine, etoposide, cytarbine, melphalan [BEAM]) to intensify the regimen for NHL, but the combination has not been shown to be superior to high dose BEAM alone. More recently, the RIC was combined with BEAM with the goal of administering the highest possible dose of RIC without increasing toxicity.

The dose of RIC was patient-specific, was based on dosimetry rather than weight, and was calculated to deliver cohort-defined radiation-absorbed doses (RADs) to critical organs, excluding bone marrow and spleen. Fifteen Gy proved to be the maximum-tolerated RAD to critical organs. When doses were calculated according to weight, there was considerable variability among patients, which justified the dosimetry-based approach. Patient specific activity doses calculated to deliver a cohort-defined RAD to the critical organ varied widely. For example, the (90Y) ibritumomab tiuxetan doses administered to deliver an estimated 15 Gy to the liver in six patients ranged from 0.50 to 1.39 mCi/kg. Although eight patients safely received doses of 0.8 mCi/kg or greater, a weight-based strategy at twice the conventional 0.4 mCi/kg dose would have resulted in a wide range of RAD (median, 13 Gy; range, 4 to 31). Forty-four patients were treated.

Thirty percent of patients had achieved less than a partial remission to their most recent therapy and would not have been eligible for autologous transplantation at most centers. Results were encouraging with an estimated 3-year PFS and Os rates of 43%

and 60%, respectively.

Proposed Study:
The weight-based activity doses (mCi/kg) varies considerably, which justifies the dosimetry-based, rather than weight-based, strategy for dose escalation of radioimmunotherapy (RIT). We are proposing to combine RIT with (^{90}Y) ibritumomab tiuxetan (Zevalin), at a dosimetric-determined RAD of 10 Gy to the critical organs (i.e., liver, lungs, kidneys), excluding bone marrow and spleen, with the bendamustine-fludarabine as non-myeloablative conditioning for allogeneic stem cell transplantation in patients with b-cell non-Hodgkin's lymphoma. Rationale for the RAD of 10Gy:

1) Based on the Winter's trial described above, all patients treated at this level received a median of 0.57mCi/kg (range, 0.5-0.75), which is at least equal to or better than the targeted standard dose of 0.4 mCi/kg;
2) the total RAD to marrow from the time of transplantation onward at this level appears to be <5cGy;
3) would allow a more lenient eligibility criteria regarding the platelets counts at study entry; and,
4) there is no strong evidence that a higher dose could be more beneficial. We hope that this unique strategy will further improve the outcomes without adding toxicity, especially in patients with aggressive histologies.

While each patient will be receiving a mCi/kg Zevalin dosage based on patient-specific radiation dosimetry, an attempt to homogenize the dosage will be undertaken. For this purpose, the dosage will be rounded to one of the following values: 0.5 mCi/kg, 0.75 mCi/kg, 1.0 mCi/kg, 1.25 mCi/kg, 1.5mCi/kg.

Each patient's dosage will be rounded to the highest mCi/kg level that maintains the absorbed dose estimated from the dosimetry nearest, but not below 10 Gy to the critical organs (liver, lungs and kidneys). Dose will not be allowed to exceed 12 Gy to critical organs, as this has been shown in a previous published study to be well tolerated by those organs without additional toxicity. If the dose nearest to but not below 10 Gy exceeds 12 Gy, the patient will be treated at the mCi/kg one level below. Patients who would be estimated to receive > 12 Gy to any of the critical organs at the 0.5 mCi/kg level will be treated at standard dosage (0.4 mCi/kg up to 32 mCi).

Eligibility: (List All Criteria)

Inclusion:

1) 18 to 70 years of age.

2) Patients with the following CD20+ lymphoid malignancies who are eligible for allogeneic transplantation: a. Relapsed or refractory follicular lymphoma; b. Relapsed or refractory or high risk mantle cell lymphoma (hi ki67; blastic); c. Recurrent or refractory marginal zone; d. Recurrent or refractory CLL/small lymphocytic lymphoma; e. Double-hit lymphoma; f. Diffuse large B cell lymphoma; g. Richter's patients; or h. Refractory or recurrent Burkitts.

3) Patients who meet criterion #2 or have any of the following are eligible: a. Less than PR to salvage chemotherapy; b. Kinetic failure; c. Having received more than 3 lines of therapy; d. Failure to mobilize autologous stem cell; e. 10% or more marrow involvement; f. 6 months post autologous stem cell transplant.

4) Patients must have a fully-matched related donor or a matched unrelated donor identified. Double cord (at least 4/6 matched) can be used if no adult matched donor is available.

5) Performance score of at least 80% by Karnofsky or 0 to 2 ECOG.

6) Left ventricular EF >/= 45% with no uncontrolled arrythmias or symptomatic heart disease.

7) FEV1, FVC >/= 60% and corrected DLCO >/= 60%.

8) Serum creatinine </=1.6 mg/dL. Serum bilirubin < 2 mg/dL (unless due to Gilbert's Syndrome).

9) SGPT < 2 X upper limit of normal.

10) Men and women of reproductive potential must agree to follow accepted birth control methods (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study.

11) Negative Beta HCG test within 30 days in a woman with child bearing potential defined as not post-menopausal for 12 months or no previous surgical sterilization). Pregnancy testing is not required for post-menopausal or surgically sterilized women.

Exclusion:

1) Patient with active CNS involvement with lymphoid malignancy.

2) Known infection with HIV, HTLV-I, Hepatitis B, or Hepatitis C.

3) Patients with other malignancies diagnosed within 2 years prior to study registration. Skin squamous or basal cell carcinoma are exceptions.

4) Active bacterial, viral or fungal infections.

5) History of stroke within 6 months prior to study registration.

6) A prior allogeneic stem cell transplant.

7) Patient has received other investigational drugs within 3 weeks before study registration.

8) Presence of circulating malignant lymphoid cells or bone marrow with lymphoma that constituted more than 25% of the cellular elements.

9) Serious nonmalignant or malignant disease or psychiatric illness, which, in the opinion of the investigator would compromise protocol objectives or interfere with participation.

10) Patients who are breast-feeding.

Are patients <18 years of age eligible to participate in this study? ○ **Yes** ● **No**

Studies that include children must meet the criteria for inclusion.
http://www.fda.gov/ohrms/dockets/AC/04/briefing/4028B1_05_NIH-Inclusion%20of%20Children.doc

http://www.hhs.gov/ohrp/policy/populations/children.html

Studies that exclude children must have appropriate justification. Please select all that apply:

Other:

Please Specify:
There is limited safety profile of radioimmunotherapy or bendamustine in patients who are younger than age 18 or older than 70 years of age.

Are participants >65 years of age eligible to participate in this study? ● **Yes** ○ **No**

Are pregnant women eligible to participate in this study? ○ **Yes** ● **No**

Will the recruitment population at M. D. Anderson include persons who are incarcerated at time of enrollment (e.g., prisoners) or likely to become incarcerated during the study?
○ **Yes** ● **No**

Disease Group:

Leukemia, Lymphoma

Treatment Agents/Devices/Interventions:

111In-ibritumomab tiuxetan, 90Y-ibritumomab tiuxetan, Allogeneic Stem Cell Transplant, Antithymocyte Globulin, Bendamustine HCl, Fludarabine, Rituximab

Proposed Treatment/Study Plan:

Is treatment assignment randomized? ○ **Yes** ● **No**

Is this a blinded or double-blinded study? ○ **Yes** ● **No**

The transplant day is referred as day zero (D0), treatment plan activities prior or after D0 are denominated as day minus (D-) or day plus (D+).

Within 3 weeks prior to start treatment, D-22, patients must be off any prior biological therapy, chemotherapy, radiotherapy, or other investigational therapy.

Chemotherapy agent doses and administration

D-22 and -14, Rituximab will be given at 250 mg/m^2 (based on actual body weight) preceding ^{111}In Ibritumumab and (^{90}Y) ibritumumab tiuxetan administration, respectively. Rituximab infusion will follow SCT&CT department standard practice.

D-22, ^{111}In Ibritumumab Administration. ^{111}In Ibritumumab (5.0 mCi +/- 10% of ^{111}In) will be used for quantitative radionuclide imaging. The imaging dose of ^{111}In Ibritumumab will be administered by a slow IV push infusion immediately following the infusion of

rituximab. ^{111}In Ibritumumab may be directly infused by stopping the flow from the IV bag and injecting the radiolabeled antibody directly into the line. A 0.22 micron filter must be on line between the patient and the infusion port. The line will be flushed with at least 10 mL normal saline after ^{111}In Ibritumumab has been infused.

D-22, -21 to -16, Imaging. Planar scintigraphy whole-body imaging will be started on D-22 post ^{111}In Ibritumumab infusion prior to voiding. Imaging will be repeated 3-6 hours later. Whole-body planar scintigraphy imaging will be repeated between 22-26 hours, then between 70-74 hours, and later between 142-146 hours post ^{111}In Ibritumumab injection.

D-15, Dosimetry. This trial requires patient-specific activities of (^{90}Y) ibritumumab tiuxetan to deliver a maximum radiation-absorbed dose (RAD) of 10 Gy to vital organs, including liver, lungs, and kidneys. The methodology for estimating the RAD will be based on quantitative whole-body planar (2D) radionuclide imaging of (^{111}In) ibritumumab tiuxetan pretreatment diagnostic tracer at multiple time points (5 in this proposal). The time-activity curves (TAC) of radiopharmaceutical uptake for different organs will be calculated and used as input to the FDA-approved OLINDA/EXM 1.1 model-based internal radionuclide dosimetry software for calculation of radiation-absorbed dose to critical organs. The RAD estimates will be corrected for critical organ mass that will be calculated from CT-based volume measurements.

D-14, (^{90}Y) ibritumumab tiuxetan Administration. (^{90}Y) ibritumumab tiuxetan will be given post rituximab, as described above. While each patient will be receiving a mCi/kg Zevalin dosage based on patient-specific radiation dosimetry, an attempt to homogenize the dosage will be undertaken. For this purpose, the dosage will be rounded to one of the following values: 0.5 mCi/kg, 0.75 mCi/kg, 1.0 mCi/kg, 1.25 mCi/kg, 1.5mCi/kg.

Each patient's dosage will be rounded to the highest mCi/kg level that maintains the absorbed dose estimated from the dosimetry nearest, but not below 10 Gy to the critical organs (liver, lungs and kidneys). Dose will not be allowed to exceed 12 Gy to critical organs, as this has been shown in a previous published study to be well tolerated by those organs without additional toxicity. If the dose nearest to but not below 10 Gy exceeds 12 Gy, the patient will be treated at the mCi/kg one level below. Patients who would be estimated to receive > 12 Gy to any of the critical organs at the 0.5 mCi/kg level will be treated at standard dosage (0.4 mCi/kg up to 32 mCi).

D-5, -4 and -3, Fludarabine and Bendamustine will be administered following SCT&CT department standard practice. These will be dosed per adjusted body weight for patients weighing > 20% above their ideal body weight. For patients less than or equal to 20% above their ideal body weight, the actual body weight is used.

Fludarabine will be administrated at a dose of 30 mg/m2 intravenously followed by Bendamustine at a dose of 130 mg/m^2 intravenously.

Optional Research Blood Samples:
D0, Measurement of Peripheral-Blood Radioactivity. A peripheral blood sample will be obtained prior to stem cell transplantation on D0 for measurement of residual (^{90}Y) radioactivity level in the blood.

Duplicate, 1.0-mL whole-blood aliquots will be drawn on day 0. A 1.0 mL (^{90}Y) standard will be prepared from a decayed, known, (^{90}Y) activity sample prepared on day -14. Blood, standard, and background samples will each be counted for 1 minute with a wide energy window in a thallium-doped sodium iodide crystal gamma scintillation well counter interfaced to a multichannel analyzer. After background correction, patient blood sample results will be expressed as mean microCi (^{90}Y)/mL in whole blood.

Supportive Treatment. All patients will receive Graft Versus Host Disease (GvHD) prophylaxis, infections disease prophylaxis, growth factors, blood and platelet transfusion and other supportive treatment as per standard practice in patients receiving allogeneic transplant.

Study Enrollment:
The study population for this research will consist of participants from:

Only at MDACC

Estimated Accrual:

Total Accrual at MDACC:	20
Estimated monthly accrual at MDACC:	1

Accrual Comments:
None

Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)? No

Is this an NCI-Division of Cancer Prevention Protocol (DCP)? Yes

Please send the Approval Letter in a PDOL generic memo to: "CRC PBHSRC Help Desk"

Statistical Considerations:

Statistical section - patient sample size and analysis plan:

This is a Phase II study of high-dose (^{90}Y) ibritumumab tiuxetan added to fludarabine and bendamustine in patients undergoing stem cell transplantation. The study will enroll a maximum of 20 patients. Patients will be enrolled in one of three histologies: follicular + other indolent histologies, mantle-cell lymphoma, and diffuse large B-cell lymphoma. We wish to ensure that at least 10 patients are enrolled in each histology. With a true incidence rate of 25%, the probability that we enroll at least 10 out of 20 patients in a

particular histology is greater than 95%.

The primary endpoint of the protocol is safety and feasibility. Several studies, including protocol ID01-233 (ASH 2011, abstract 662) are showing a similar safety profile between matched sibling and matched unrelated donor transplants. We believe that the safety profile will be similar in this study as well. However, we will report the results within each category, and we have added as a secondary analysis that we will repeat the primary analyses of event-free and overall survival stratified by transplant graft source.

Monitoring:
Two statistical monitoring rules are used to monitor the rate of TRM in all patients and the rate of engraftment failure/acute grade 4 GVHD in patients who receive a cord blood transplant.

TRM (All Patients):
We will use the method of Thall, Simon, and Estey to monitor the TRM rate in all patients within the first 100 days during the course of the trial. We will assume a Beta(0.40, 1.60) prior distribution for the 100-day TRM rate, which has a mean of 20%.

The following decision rule will be used: stop accrual if at any time during the course of the trial

Pr{100-day TRM rate > 20% | data from patients evaluated} > 0.975

In other words, if at any time during the study we determine that there is at least a 97.5% chance that the 100-day TRM rate is at greater than 20%, we will stop enrollment into the study. For logistical reasons, patients will be monitored in cohorts of 5. Stopping boundaries corresponding to this probability criterion are as follows: stop if:

[# of patients with TRM at day 100/ # of patients evaluated at day 100]
>/= 4/5, 6/10, 7/15, or 9/20

The operating characteristics for this rule are found in the table below. If the true 100-day TRM rate is less than the maximum targeted rate of 20%, the trial will stop early less than 6% of the time.

True 100-Day TRM Rate	Probability of Stopping Early
20%	5.9%
10%	<0.1%
30%	48.8%
40%	92.4%

Engraftment Failure/Acute Grade 4 GVHD (Cord Blood Patients):

Because patients who receive a transplant from umbilical cord blood are at higher risk of engraftment failure and GVHD, we will also monitor the rate of engraftment failure or acute grade 4 GVHD in these patients. We expect no more than 10 patients will receive a cord blood transplant.

We will use the method of Thall, Simon, and Estey to monitor the combined engraftment failure/grade 4 acute GVHD rate in cord blood patients within the first 100 days during the course of the trial. We will assume a Beta(0.60, 1.40) prior distribution for the 100-day rate, which has a mean of 30%.

The following decision rule will be used: stop accrual in cord blood patients if at any time during the course of the trial

Pr{100-day engraftment failure/grade 4 acute GVHD rate > 20% |
data from cord blood patients evaluated} > 0.975

In other words, if at any time during the study we determine that there is at least a 97.5% chance that the 100-day engraft failure/grade 4 acute GVHD rate is greater than 20%, we will stop enrollment into cord blood patients. Stopping boundaries corresponding to this probability criterion are as follows: stop if:

[# of cord blood patients with engraft failure or grade 4 acute GVHD at day 100/
# of cord blood patients evaluated at day 100]
>/= 3/3, 5/6, 6/8, 7/10, 8/12, 9/14, 10/17, or 11/19

The table below presents the operating characteristics for this rule.

True Failure Rate	Probability of Stopping Early	P25	Median	P75
10%	0.1 %	20	20	20
20%	1.8 %	20	20	20
30%	7.8 %	20	20	20
40%	25.6 %	18	20	20
50%	54.5 %	7	16	20
60%	81.5 %	5	9	16
70%	96.2 %	3	5	9

Analyses:

At the end of the trial, the 100-day TRM rate will be reported with a 95% credible interval. The 100-day engraft failure/grade 4 acute GVHD rate in cord blood patients will also be reported with a 95% credible interval.

Event-free survival (EFS) and overall survival (OS) will be estimated using the method of Kaplan and Meier for all patients overall and separately by histology. Overall survival will be calculated from the date of transplant to the date of death. Patients who survive will be censored at their last contact date. Event-free survival will be calculated from the date of transplant to the date of relapse or death. Patients who survive relapse-free will be censored at the time of last contact. The method of Brookmeyer and Crowley will be used to estimate 95% confidence intervals for median EFS. Cox proportional hazards regression analysis will be used to assess the association between EFS and OS and demographic and disease-related covariates of interest.

The association between time to neutrophil and platelet recovery and blood radioactivity level and other disease characteristics will be assessed using Cox proportional hazards regression analysis.

Because a variety of graft transplant sources will be used in this study, to account for potential heterogeneity, the above analyses will be repeated, stratifying by graft transplant source.

Exploratory analyses will be conducted to compare the 2.5D dosimetry and 2D dosimetry methods.

For safety, descriptive statistics will be used to report the number and proportion of patients with adverse events by grade.

Data Safety Monitoring Board / DSMB at MDACC:

Select the name of the data safety monitoring board (DSMB) monitoring this protocol:
Not Applicable

Please explain:
This study is not randomized nor blinded.

Protocol Monitoring:

Does this protocol have a schedule for interim and final analysis? No

Provide a rationale for no interim analysis.

This is a non-randomized trial. Will follow the operating characteristics described within the statistical considerations section.

Protocol Monitoring Plan:

See Statistical Considerations section.

Intellectual Property:

1. Does this study include any agents, devices, or radioactive compound (or drug) manufactured at MD Anderson Cancer Center or by a contract manufacturer? No

Investigational New Drugs (IND):

Does this protocol require an IND? Yes

Who is the IND Holder/Regulatory Sponsor?
MDACC
IND Number: 113934

Please "Compose" an Investigator's Brochure Cover Letter. For technical assistance, contact the PDOL Help Desk, 713-745-7365.

Investigational Device (IDE):

Does this study utilize an Investigational Device? No

Sponsorship and Support Information:

Does the Study have a Sponsor, Supporter or Granting Agency? Yes

Sponsor Name: Spectrum Pharmaceuticals
Support Type: Industry Funding
Agent Name(s): Ibritumumab Tiuxetan

This Sponsor/Supporter/Granting Agency will receive data.

Radioactive Material:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent? Yes
Click here for help

M.D. Anderson's Radioactive Material Authorization:

Authorized User: Aaron Jessop, M.D.

Authorization Number (or state that Authorization Application is under Radiation Safety Committee review): 1412

Does this protocol include the administration of a radioactive compound (or drug) to a patient intended to obtain basic information regarding metabolism (including kinetics, distribution, and localization) of the drug or regarding human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e. to carry out a clinical study)?	No

Is the radioactive compound (or drug) FDA approved and/or commercially available?	No

Name the facility where the investigational agent is labeled or bound to the radioisotope (include the name of the laboratory at MDACC or the name of the company if outside MDACC):
N/A

Biosafety:

Does this study involve the use of Recombinant DNA Technology?	No
Does this study involve the use of organisms that are infectious to humans?	No
Does this study involve human/animal tissue other than blood derived hematopoietic stem cells?	No

Questions should be addressed to the Transfusion Medicine Tissue Coordinator at 713-792-8630.

Laboratory Tests:

Is there any biomarker testing in this study being used to determine patient/participant eligibility, treatment assignment, or management of patient/participant care?

- ○ Yes
- ● No
- ○ Not Applicable For This Protocol

Manufacturing:

Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study?	No

Student/Trainee Information:

Is this research being conducted as a partial fulfillment for completion of a degree?	No