THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

Zevalin/BEAM/Rituximab vs BEAM/Rituximab with or without Rituximab Maintenance in Autologous Stem Cell Transplantation for Diffuse Large B-Cell Lymphomas
2006-1018

Core Protocol Information

Short Title:	Zevalin/BEAM/Rituximab vs BEAM/Rituximab with or without Rituximab in Autologous Stem Cell Transplantation
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Unit:	423
Full Title:	Zevalin/BEAM/Rituximab vs BEAM/Rituximab with or without Rituximab Maintenance in Autologous Stem Cell Transplantation for Diffuse Large B-Cell Lymphomas
Protocol Phase:	Phase II
Version Status:	Activated -- Closed to new patient entry as of 10/27/2017
Version:	18
Document Status:	Final

Abstract

Objectives:

Primary Objective:

1. To compare the efficacy [2-year progression-free survival (PFS) rates] of Zevalin-BEAM (BCNU, etoposide, cytarabine, melphalan)-R (Rituximab) and BEAM-R in patients with diffuse large B-cell Lymphoma (DLBCL) undergoing autologous stem-cell transplantation.

Secondary Objectives:

1. To assess the association between maintenance Rituximab after transplantation and PFS.
2. To assess the association between PET status, International Prognostic Index (IPI), Rituximab levels after transplantation, and PFS.

Rationale: (Be as concise as possible)

High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) has the potential to cure about 30 - 40% of patients with DLBCL who relapse or progress after initial therapy. The worst outcome was seen among patients with positive PET (+) scans, high International Prognostic Index (IPI), who did not receive rituximab with their transplant. (PFS, 17%; $P < 0.001$). Innovative studies are needed to improve outcome in these patients.

Emerging data from our institution demonstrate that the addition of the anti-CD20, Zevalin, given at the fixed dose of 0.4 mCi/Kg to the standard conditioning of BEAM can induce a 2-year overall and disease-free survival rates of 92% and 83%, respectively. There was no difference in outcome between PET(+) or PET(-) patients. Similarly, non-myeloablative stem cell transplantation has been shown to have equally successful results in both categories of patients. Overall survival for all patients was 88%.The risk of relapse in PET(+) or (-) disease was not significant (P=0.15). In addition, recent studies are suggesting that maintenance treatment with rituximab may improve the outcome in b-cell lymphoma.

In this study, we propose to stratify patients with DLBCL in chemosensitive relapse according to their IPI, and their PET status at transplant (see Appendix H). Patients who are PET (+) at transplant and have high IPI of $\geq$ 2 would receive an allogeneic non-myeloablative SCT if they have a matched sibling donor. All others will be randomized to receive one of 2 conditioning regimens in preparation for ASCT regimens: BEAM-Rituximab vs. Zevalin-BEAM-Rituximab. Patients who are not progressing at approximately one month, after ASCT, will have a second randomization to receive or not, maintenance rituximab for 18 months.

Eligibility: (List All Criteria)

Inclusion:

1) Relapsed CD20-positive B-cell diffuse large cell lymphoma (demonstrated in lymph nodes or bone marrow), chemosensitive (at least PR).
2) Age: up to 18-70 years of age.
3) Prestudy performance status of 0, 1, or 2 according to the WHO.
4) No anti-cancer therapy started within three weeks, prior to study initiation, and fully recovered from all toxicities associated with prior surgery, radiation treatments, chemotherapy, or immunotherapy. No prior rituximab within three weeks of starting therapy.
5) If patients had prior radiation, this should have not involved more than 25% of the bone marrow.
6) Acceptable hematologic status within two weeks prior to patient registration, including: Absolute neutrophil count ({segmented neutrophils + bands} x total WBC) > 1,500/mm³ and platelet counts > 80,000/mm³
7) IRB -approved signed informed consent.
8) Patients determined to have <10% bone marrow involvement with lymphoma within 60 days before study entry as defined by bone marrow aspirates and biopsies.
9) Female patients included must not be pregnant or lactating.
10) Patients should have at least 4-6 x 10^6 CD34+/kg peripheral stem cells collected. Around 1-2 million cells will beheld as back up.
11) Voluntary signed, written IRB-approved informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.
12) Men and women of reproductive potential must agree to follow accepted birth control methods for the duration of the study. Female subject is either post-menopausal or surgically sterilized or willing to use an acceptable method of birth control (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study. Male subject agrees to use an acceptable method for contraception for the duration of the study.

Exclusion:

1) Failed stem cell collection of >/= 4x10^6CD34+/kg.
2) Prior radioimmunotherapy.
3) Presence of active CNS lymphoma.
4) Patients with abnormal liver function: total bilirubin > 1.5 mg/dl.
5) Patients with abnormal renal function: serum creatinine > 1.6 mg/dl.
6) Serious nonmalignant disease or infection which, in the opinion of the investigator and/or the sponsor, would compromise other protocol objectives.
7) Corrected DLCO < 50% and FEV subscript 1 or FVC < 50% predicted.
8) Cardiac EF < 50% by 2-D Echogram.
9) Prior radiation to lungs.
10) Abnormal cytogenetics predictive of secondary cancers, such as -5,-7.
11) Pregnant (Positive Beta HCG test in a woman with child bearing potential defined as not post-menopausal for 12 months or no previous surgical sterilization) or currently breast-feeding. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
12) Patients with other malignancies diagnosed within 2 years prior to Study entry (except skin squamous or basal cell carcinoma).
13) Active uncontrolled bacterial, viral fungal infections.
14) Major surgical procedure or significant traumatic injury within 4 weeks prior to Study entry.
15) Serious, non-healing wound, ulcer, or bone fracture.
16) History of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 3 months prior to Study entry.
17) History of Stroke within 6 months.
18) Myocardial infarction within the past 6 months prior to Study Day 1, or has New York Heart Association (NYHA) Class III or IV heart failure or arrythmias, unstable angina, uncontrolled congestive heart failure or arrythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening must be documented by investigator as not medically relevant.
19) Uncontrolled chronic diarrhea.
20) Serious medical or psychiatric illness likely to interfere with participation in this clinical study.

Is there an age limit? Yes

Why? Provide scientific justification:
There is little experience with the use of Zevalin in patients <18 years of age.
The risk of autologous transplantation in patients older than age 65 is unknown. A separate study is addressing this issue.

Disease Group:

Lymphoma

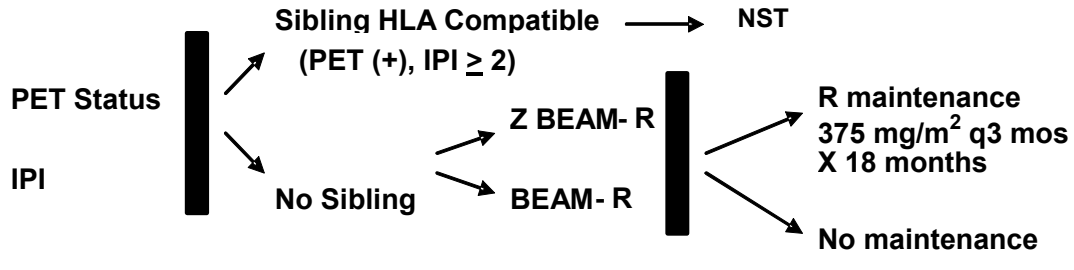
Treatment Agents/Devices/Interventions:

Carmustine, Cytarabine, Etoposide, Melphalan, Rituximab, Zevalin

Proposed Treatment/Study Plan:

Treatment Plan

Study Schema



(NST = Non-myeloblative allogeneic transplant)

This is a randomized Phase II study comparing the standard treatment, BEAM + rituximab to Zevalin (0.4 mCI/Kg)+ BEAM + rituximab as preparative regimen for autologous stem cell transplantation in patients with advanced DLBCL expressing CD20. Patients will be stratified by their PET status at the initiation of stem cell collection {PET(+) vs PET(-)}, as well as by their IPI (0 vs $\geq$1)**.**

If the PET(+) and IPI $\geq$2 patients have a sibling donor, those patients will receive an allogeneic transplant and will not be included in the study. All other patients will be receiving ASCT and will be randomized to receive either Zevalin-BEAM-rituximab or BEAM-rituximab alone. Patients will then be assessed at 25-35 days post transplant. Those who are in CR, PR or have stable disease will then be randomized to receive maintenance rituximab, one dose (375 mg/m²) at 3, 6, 9, 12, 15 and 18 months post ASCT vs observation. Rituximab levels will be measured at these time intervals in all patients.

Statistical Considerations:

Patients will be randomized equally to receive either the standard treatment, BEAM + rituximab or the experimental treatment Zevalin + BEAM+ rituximab. The randomization will be stratified by the prognostic factor PET status and IPI. At day 30 after the beginning of treatment, response status will be assessed. Patients who achieve a complete or partial response or have stable disease will then be randomized to either receive maintenance rituximab or the standard of care, observation.

The primary objective of the trial is to examine the effect of treatment on the 2-year progression- free survival (PFS) rates. For that purpose, we will use a Cox proportional hazards model.

Interim Monitoring

This study will be monitored for both efficacy and safety during the first 30 days of treatment. However, we will not monitor for our primary efficacy outcome measure of 2-year PFS because nearly the entire patient population will have been enrolled by the time the first patients reach 2 years of follow-up. Instead we will include interim monitoring for the response rate at day 30 where response is defined as above (i.e. complete or partial response, or stable disease). Each arm will be monitored separately according to the following rules; the arms will not be compared to each other while the study is ongoing. For this trial we desire the response rate to be at least 75% and if this level of response is not seen, we will terminate the trial early.

The safety monitoring rule will monitor for treatment related mortality (TRM) during the 1st 30 days. If there is a high probability that the TRM rate is greater than 10% in either arm we will terminate the trial early. The method of Thall, Simon, and Estey Thall PF, Simon R, and Estey EH. "New statistical strategy for monitoring safety and efficacy in single-arm clinical trials", Journal of Clinical Oncology*,* 14(1):296-303 (1996). will be employed to perform the interim monitoring.

We will not include a safety monitoring rule for the rituximab randomization, as the regimen being used is lower than a standard safe regimen and numerous trials and publications have confirmed the safe use of rituximab.

When monitoring both the 30-day response rate and the 30-day TRM rate, each a binary outcome, there are four possible elementary outcomes. These are 1 = [response, TRM], 2 = [no response, TRM], 3 = [response, no TRM], 4 = [no response, no TRM]. We denote the corresponding standard outcome probability vector by qS, and the probability vector with the experimental treatment by qE. For the response rate distribution, we assume a marginal Beta (75, 25) prior on qS, which in particular has mean 30-day response rate of 75%. We assume a marginal Beta (1.5, 0.5) prior on qE for response, which has the same prior rates but carries little prior information.

For the TRM rate distribution, we assume a marginal Beta (10, 90) prior on qS, which in particular has mean TRM rate of 10%. Hence, we assume a marginal Beta (0.2, 1.8) prior on qE for the TRM rate, which has the same prior rates but carries little prior information.

The maximum sample size for each arm will be 25, which will ensure that if, for example 20/25 (80%) patients are observed to have a response, then the posterior 95% credible interval for the probability of the 30-day response rate, based on the marginal beta (1.5, 0.5) prior assumed, will run from 68% to 89%. The minimal sample size will be 10 in each arm.

The following decision criteria will be applied to each arm after each cohort of 5 patients has been evaluated, up to the 25th patient accrued. Targeting a 75% response rate at day 30 and allowing a 10% TRM rate by day 30, the trial will be stopped early according to the following two monitoring rules:

1) 30-day response rate

$$Pr[qS(\text{Response rate}) > qE(\text{Response rate}) \mid \text{data}] > 0.95$$

That is, if at any time during the trial we determine that we have greater than a 95% chance of showing that the average 30-day response rate in the experimental treatment group is lower than what would be desired on the standard of care (i.e. 75%) we will stop the study. Stopping boundaries corresponding to this probability criterion are to terminate the trial if

(# of responses at day 30) / (# patients evaluated) $\leq$
4/10, 7/15, 11/20, or 14/25.

Or 2) TRM rate

$$Pr[qS(\text{TRM}) < qE(\text{TRM}) \mid \text{data}] > 0.925$$

That is, if at any time during the study we determine that there is more than a 92.5% chance that the average TRM rate at day 30 in the experimental treatment group is more than would be expected on the standard of care (i.e. 10%) we will stop the study. Stopping boundaries corresponding to this probability criterion are to terminate the trial if

(# of patients with TRM by day 30) / (# patients evaluated) ≥
4/10, 4/15, 5/20, or 6/25.

If we see 3 TRMs in the first 10 patients, we will suspend accrual and wait for patient number 10 to be evaluated for TRM in the 30-day window.

Table of operating characteristics:

True Pr(30-day response rate), Pr(TRM)	Early Stopping Probability	Mean number of patients
0.75, 0.1 (acceptable target rates)	0.12	23.8
0.65, 0.1 (poor response rate)	0.31	21.9
0.55, 0.1 (very poor response rate)	0.64	18.3
0.75, 0.2 (acceptable response rate but poor TRM rate)	0.46	20.2
0.75, 0.3 (acceptable response rate but very poor TRM rate	0.80	15.6
0.65, 0.2 (poor response rate and poor TRM rate)	0.58	18.8
0.55, 0.3 (very poor response rate and very poor TRM rate)	0.92	13.7
0.85, 0.1 (good response rate and acceptable TRM)	0.08	24.3
0.85, 0.05 (good response rate and good TRM rate)	0.01	24.9

Where Will Participants Be Enrolled:

Only at MDACC

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

Is this an NCI-Division of Cancer Prevention Protocol (DCP)? No

Estimated Accrual:

Total Accrual at MDACC: 50
Estimated monthly accrual at MDACC: 1

Accrual Comments:
Estimated accrual time to be completed in 3½ - 4 years.

Do you expect your target population to include non-english speaking participants? Yes

Please select expected languages of non-English speaking participants. (Select all that apply)
Expected languages of non-English speaking participants:

Spanish

Location of Treatment:

This protocol is performed on an Inpatient AND Outpatient basis.

Length of Stay: What is the length & frequency of hospitalization?

Stay in hospital 3-4 weeks.

Return Visits: How often must participants come to MDACC?

Every 3 months for the first year, then every 6 months.

Home Care: Specify what, if any, treatment may be given at home.

Maintenance Rituximab (dose #5)

Name of Person at MDACC Responsible for Data Management: Celina Ledesma

Prior protocol at M. D. Anderson:
Has the Principal Investigator ever had a clinical or behavioral protocol at MDACC that accrued patients?
Yes

Data Monitoring Committee:

Is treatment assignment randomized? Yes

Is this a blinded or double-blinded study? No

Does this Protocol need data safety monitoring? Yes

Provide the name of the data safety monitoring board (DSMB) monitoring this protocol:
MDACC DMC

Does this protocol have a schedule for interim and final analysis? Yes

Please describe:
The safety monitoring rule will monitor for treatment related mortality (TRM) during the 1st 30 days. If there is a high probability that the TRM rate is greater than 10% in either arm we will terminate the trial early. The method of Thall, Simon, and Estey Thall PF, Simon R, and Estey EH. "New statistical strategy for monitoring safety and efficacy in single-arm clinical trials", Journal of Clinical Oncology, 14(1):296-303 (1996). will be employed to perform the interim monitoring.

We will not include a safety monitoring rule for the Rituximab randomization, as the regimen being used is lower than a standard safe regimen and numerous trials and publications have confirmed the safe use of Rituximab.

Radiation Safety:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent?	Yes
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 trial)?	No
Is the radioactive compound (or drug) FDA approved and/or commercially available?	Yes

Investigational New Drugs:

Does this protocol require an IND? No

☒Please confirm **that the protocol meets all criteria for exemption according to 21CFR 312.2(b), noted below:**

(b) Exemptions. (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of 312.7.

Rationale for Exemption:
Please include a detailed rationale as to why this drug should be considered exempt from FDA IND regulations, including any available references to the prior use of the regimen or drug combination in human subjects.

Zevalin has been approved by the FDA for treatment of relapsed lymphoma. The drug and the other chemotherapy agents are commercially available. We have conducted a prior Phase II trial with Zevalin for autologous transplants. Results have been published.

If this protocol includes an FDA Approved Therapy, please list the disease, dose and route of administration:

	Approved Use	Proposed in this Protocol
Disease:	Lymphoma	Lymphoma
Dose:	.4 mCI/kg	.4 mCI/kg
Route of Administration:	IV	IV

Investigational Device:

Is the Investigational Device approved by the FDA? N/A

Is the Investigational Device being used in the manner approved by the FDA?	N/A
Has the Investigational Device been modified in a manner not approved by the FDA?	N/A

Name of Device:

Manufacturer:

What is the FDA Status of the Investigational Device?	Not Marketed.
Is the study being conducted under an Investigational Device Exemption (IDE)?	No

IDE Holder:

IDE Number:

Risk Assessment:
Please answer the following questions regarding the Investigational Device.

Intended as an implant?	No
Purported or represented to be for use supporting or sustaining human life?	No
For use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health?	No

You may attach sponsor documentation of the risk assessment:

Will participant be charged for the Investigational Device?	No

Sponsorship and Support Information:

Does the Study have a Sponsor or Supporter?	No
Is this Protocol listed on any Federal Grant or Foundation Funding Application?	No

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 stem cells?	No

Technology Commercialization:

Does this study include any agents or devices manufactured or produced at MD Anderson Cancer Center?	No

Laboratory Tests:

Where will laboratory tests be performed on patient materials? (Please select all that apply)
Division of Pathology & Laboratory Medicine CLIA Certified Laboratory

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