

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.

19.0 STATISTICAL CONSIDERATIONS

19.1 ⁹⁰Y dose escalation

One primary objective of this study is to estimate the MTD of ⁹⁰Y-BC8-DOTA that can be delivered 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 DLT rate of 25%, where a DLT is defined as a therapy-related grade III or IV Bearman (transplant) toxicity within 30 days of transplant^[80]. Dose escalation/de-escalation will be conducted by the “two-stage” approach introduced by Storer^[81]. The starting dose level will be level 1 (10 Gy). In the first stage, single patients will be treated at escalating doses in 2-Gy increments (**Table 4**) 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 according to the following rules. If no DLT is observed in a cohort of 4 the next cohort will be treated at a dose that is 2 Gy higher; if 1 of 4 experiences a DLT the next group will be treated at the same dose; if 2 DLT’s are seen among 4 (or fewer) in a cohort, the next group of 4 will be treated at a dose that is 2 Gy lower. 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 all 4 patients in a cohort 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.

19.2 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). The second primary endpoint of this study will be to estimate the rate of PFS at 1 year from ASCT when conditioned with ⁹⁰Y-BC8-DOTA + 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, HL with positive

functional imaging prior to ASCT) [62, 82]. Furthermore, this study will enroll a variety of histologies: B-NHL, T-NHL, and HL; indolent and aggressive. 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, 40% for HL with a positive PET scan following salvage therapy, and 40% for relapsed/refractory T-NHL [62, 63, 83-85]. 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.

19.3 Antibody dose adjustment

A secondary objective of this protocol is to identify the lowest antibody (BC8) dose (mg/kg) that is consistent with a favorable biodistribution rate $\geq 80\%$ in lymphoma patients. A favorable biodistribution in a given patient will be defined by the target tissue receiving higher radiation dose per unit-administered activity (cGy/mCi) relative to all critical normal organs (lung, liver, kidney, etc.). To accomplish this goal, the dose to tumor sites (lymph nodes, marrow, spleen) and critical normal organs (lung, liver, kidney) will be calculated from the measurement data which includes the tumor biopsy data, conjugate views and SPECT/CT images for each patient and whole-body counts using methods previously published and described above [8, 57, 61, 86-89]. Towards this end, we will implement a "stopping rule" that will lead to escalation of the protein dose of BC8 used for the initial biodistribution study in each patient (see **Table 2**) if there is ever sufficient evidence to suggest that the true proportion of patients who have a favorable biodistribution following the infusion of $^{111}\text{In-BC8-DOTA}$ is less than 80%. Equivalently, if we have sufficient evidence to suggest that the proportion of patients who fail to achieve favorable biodistribution exceeds 20%, we will escalate the dose of BC8. Sufficient evidence will be taken to be any proportion of patients who fail for which the lower limit of the associated one-sided 80% confidence interval exceeds 20%. Operationally, this rule would activate if any of the following number-of-failures-among-patients-treated is seen: 2 of 4 or fewer, 3 of 7 or fewer, 4 of 11 or fewer, 5 of 15 or fewer, 6 of 20 or fewer, 7 of 24 or fewer, 8 of 27 or fewer, 8 of 28 or fewer, 9 of 32 or fewer, 10 of 37 or fewer, 11 of 41 or fewer, 12 of 46 or fewer, 13 of 50 or fewer, 14 of 52 or fewer. These rules have been listed out to the maximum possible number to be enrolled as the total sample size will depend on the number of patients treated on the dose-finding portion described above. If the true probability of "failure" is 10%, then the probability of escalation of BC8 is approximately .08; if the true probability of failure is 30% or 40%, then the probability of escalation is approximately .90 and .99, respectively (probabilities estimated from 5,000 simulations).