

Abbreviated Title: ⁹⁰Y-daclizumab + ASCT in HL
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Phase I/II Trial of Yttrium-90-labeled Daclizumab (anti-CD25) Radioimmunotherapy with High-dose BEAM Chemotherapy and Autologous Hematopoietic Stem Cell Rescue in Recurrent and Refractory Hodgkin's Lymphoma

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Investigational Agents:

Drug Name:	⁹⁰ Y- daclizumab, ¹¹¹ In-daclizumab
IND Number:	5014
Sponsor:	Center for Cancer Research
Manufacturer:	Hoffmann-La Roche

Commercial Agents: filgrastim, plerixafor, Ca²⁺-DTPA, unlabeled daclizumab, basiliximab, carmustine, etoposide, cytarabine, melphalan

PRÉCIS

Background:

- Although Hodgkin's lymphoma (HL) is considered a highly treatable cancer, patients with relapsed and chemotherapy refractory disease represent a major therapeutic challenge.
- Only 30-65% of relapsed patients will achieve long-term disease-free survival with the current standard of care high-dose chemotherapy with autologous hematopoietic stem cell transplant (ASCT).
- The malignant Reed-Sternberg cells of HL and the surrounding "benign" T cell infiltrates often express CD25, the high affinity interleukin-2 receptor (IL-2R alpha).
- In study NCI-97-C-0110, we treated 30 patients with CD25-expressing relapsed or refractory HL with radioimmunotherapy (RIT) using ⁹⁰Y-labeled daclizumab (anti-CD25), and achieved a 63% response rate including 12 complete responses with few serious adverse events other than MDS in 4 patients.
- We propose integrating ⁹⁰Y-labeled daclizumab RIT into the induction regimen of ASCT in an effort to improve the response and disease-free survival in relapsed and refractory HL.

Objectives:

Phase I Primary Objectives:

- To assess the safety and adverse events associated with ⁹⁰Y-daclizumab (humanized anti-CD25) radioimmunotherapy (RIT) in combination with high-dose BEAM (carmustine, etoposide, cytarabine, [Ara-C, cytosine arabinoside] and melphalan) chemotherapy and autologous hematopoietic stem cell transplantation (ASCT) in patients with relapsed or refractory Hodgkin's lymphoma (HL) with adverse prognostic factors.
- To determine the maximum tolerated dose in mCi of ⁹⁰Y-daclizumab RIT in combination with high-dose BEAM chemotherapy and ASCT in patients with relapsed or refractory HL.

Phase II Primary Objectives:

- To assess the frequency of the failure to engraft, myelodysplastic syndrome (MDS), secondary leukemia for the development of abnormal bone-marrow cytogenetics in refractory or relapsed HL patients treated with ⁹⁰Y-daclizumab RIT in combination with high-dose BEAM chemotherapy and ASCT.
- To estimate the response rate [the number of complete and partial responses (CR and PR)] in patients with refractory or relapsed HD to ⁹⁰Y-daclizumab RIT administered in combination with high-dose BEAM chemotherapy and ASCT.

Eligibility:

- Patients must have a confirmed diagnosis of relapsed or refractory HL with at least 10% of malignant Reed-Sternberg cells or infiltrating T-cells expressing CD25 (IL-2R alpha).

A. Patients must have at least one of the following: (1) had an initial relapse less than 12 months after achieving a CR with primary chemotherapy for HL; (2) were Staged at III/IV at diagnosis; (3) exhibited chemotherapy resistant disease or (4) did not achieve a CR with cytoreductive chemotherapy prior to a planned transplant. B. Patient must have a lesion of at least 1.0 cm in its greatest diameter. C. Patients with lymphocyte predominant HL are excluded. D. Patients with pre-existing MDS or marrow cytogenetic abnormalities will not be eligible to participate.

- Omission of cytotoxic chemotherapy or other systemic therapy of HL for at least 4 weeks prior to entry into the trial.
- No prior ASCT or allogeneic stem cell transplant.

Design:

- A single institution non-randomized open-label phase I/II trial.
- Patients will undergo peripheral blood stem cell (PBSC) mobilization with granulocyte-colony stimulating factor (G-CSF, filgrastim) and Plerixafor followed by apheresis to collect a target dose of 4×10^6 CD34+ cells/kg (minimal dose of 2×10^6 CD34+ cells/kg) of actual body weight.
- Phase I study will be carried out using a standard 3 + 3 cohort dose-escalation design:
 - **Dose level 1:** Patients will receive a single dose of 15 mCi ⁹⁰Y-daclizumab RIT (day -15 ± 2 days) followed by high-dose BEAM chemotherapy (beginning Day -6) and ASCT (Day 0).
 - **Dose levels 2-7:** Patients will receive two doses of ⁹⁰Y-daclizumab RIT 6 weeks apart (Day -56 and -15 ± 2 days) followed by high-dose BEAM chemotherapy (beginning day -6) and ASCT (Day 0). The first dose of ⁹⁰Y-daclizumab will be fixed at 15 mCi. The second dose will be escalated in 15 mCi increments from 15 mCi until maximum tolerated dose, not to exceed 90 mCi.
- **Phase II:** All patients will receive two doses of ⁹⁰Y-daclizumab (Day -56 and -15 ± 2 days) followed by high-dose BEAM chemotherapy (beginning Day -6) and ASCT (Day 0). The first dose of RIT will be 15 mCi. The second dose will be the maximum tolerated dose as determined from phase I.
- ¹¹¹In-daclizumab (5 mCi) imaging may be performed concurrently with each ⁹⁰Y-daclizumab RIT and at day 100 after ASCT.

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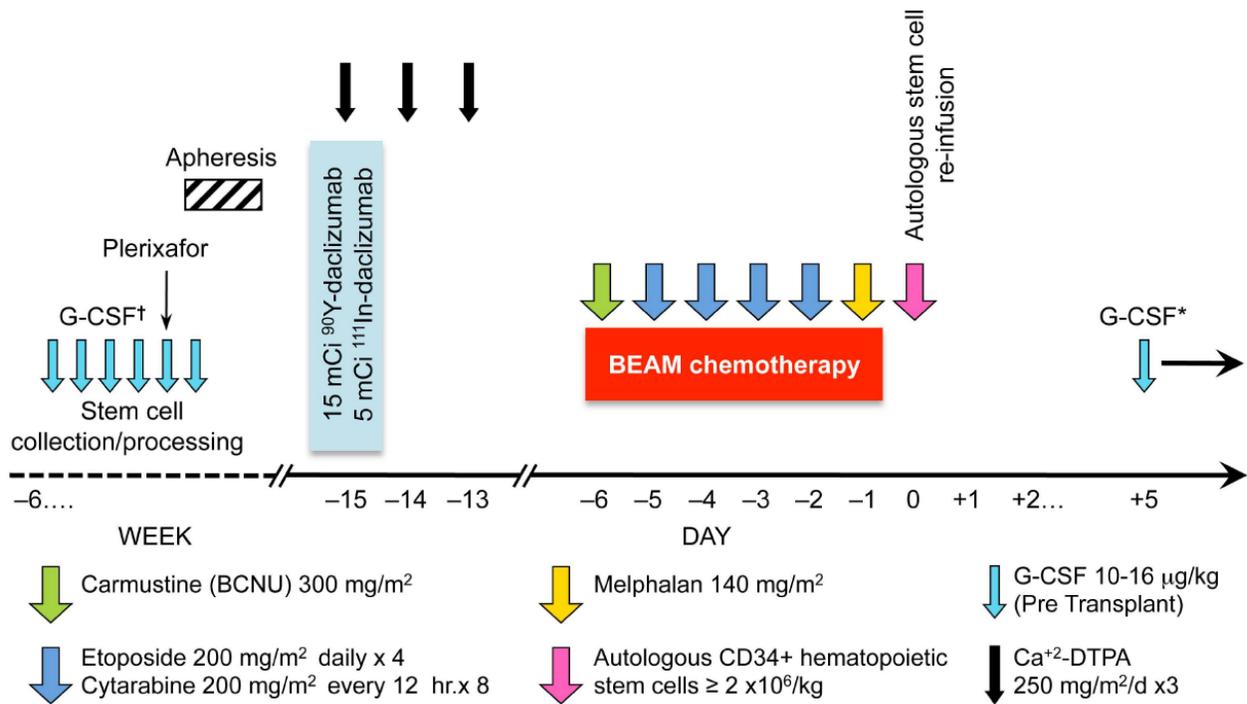
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Table 1. Phase I dose escalation of ⁹⁰Y-daclizumab.

Dose Level	⁹⁰ Y-daclizumab Dose (mCi)
1	Dose #1 15
2	Dose #1 15 Dose #2 15
3	Dose #1 15 Dose #2 30
4	Dose #1 15 Dose #2 45
5	Dose #1 15 Dose #2 60
6	Dose #1 15 Dose #2 75
7	Dose #1 15 Dose #2 90

Treatment Schema

Figure 1. Hodgkin lymphoma ⁹⁰Y-daclizumab/BEAM chemotherapy autotransplant schema dose level 1.



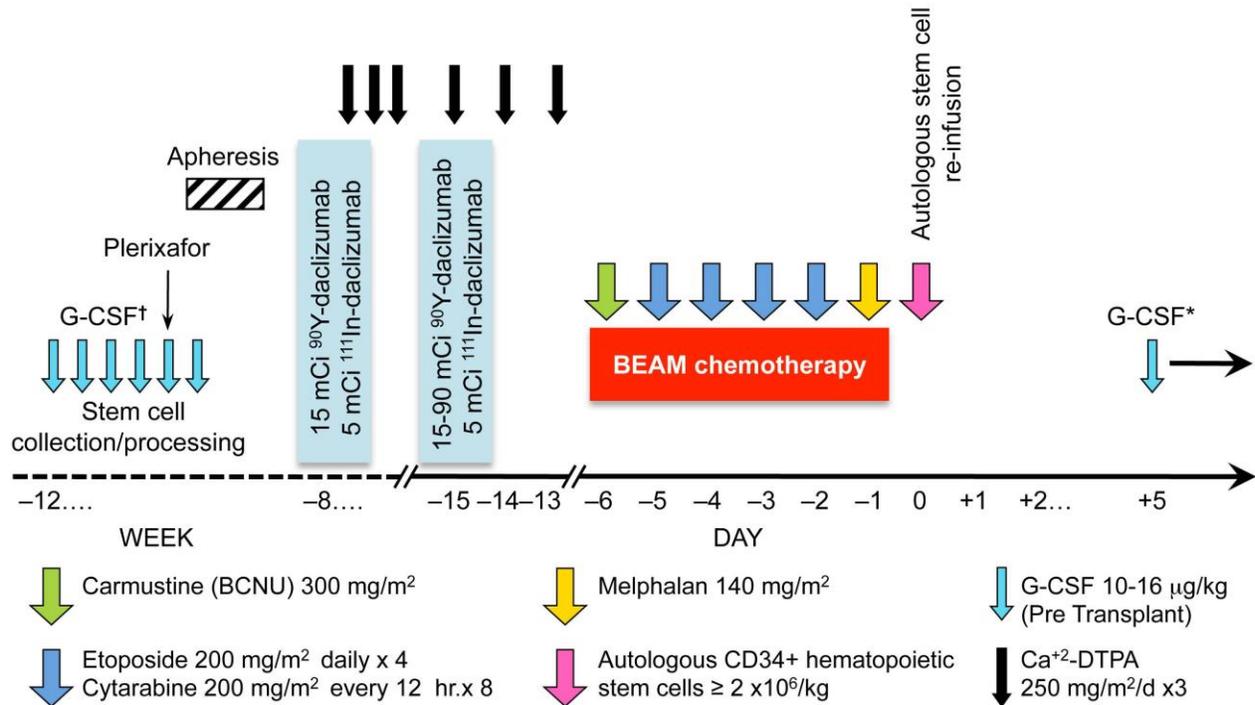
†G-CSF x 5-6 days with apheresis/CD34+ stem cell collection on days 5-7. May be repeated x1 after a >30 day rest period if first attempt yields inadequate numbers of stem cells. See appendix F for G-CSF dosing.

In addition Plerixafor on day 5.

*G-CSF 5 µg/kg post transplant to continue until AGC > 1,000/µL x3 consecutive days.

Treatment Schema

Figure 2. Hodgkin lymphoma ⁹⁰Y-daclizumab/BEAM chemotherapy autotransplant schema dose levels 2 thru 7.



[†]G-CSF x 5-6 days with apheresis/CD34+ stem cell collection on days 5-7. May be repeated x1 after a >30 day rest period if first attempt yields inadequate numbers of stem cells. See appendix F for G-CSF dosing. In addition Plerixafor on day 5.

*G-CSF 5 μg/kg post transplant to continue until AGC > 1,000/μL x3 consecutive days.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Phase I Primary Objectives:

- To assess the safety and adverse events associated with ⁹⁰Y-daclizumab (humanized anti-CD25) radioimmunotherapy (RIT) in combination with high-dose BEAM (carmustine, etoposide, cytarabine, [Ara-C, cytosine arabinoside] and melphalan) chemotherapy and autologous hematopoietic stem cell transplantation (ASCT) in patients with relapsed or refractory Hodgkin's lymphoma (HL) with adverse prognostic factors.
- To determine the maximum tolerated dose in mCi of ⁹⁰Y-daclizumab RIT in combination with high-dose BEAM chemotherapy and ASCT in patients with relapsed or refractory HL.

1.1.2 Phase I Secondary Objectives:

- Estimate ⁹⁰Y-daclizumab organ radiodosimetry in refractory or relapsed HL patients treated with ⁹⁰Y-daclizumab RIT in combination with high-dose BEAM chemotherapy and ASCT.
- To assess the time to hematopoietic recovery of refractory or relapsed HL patients treated with ⁹⁰Y-daclizumab RIT in combination with high-dose BEAM chemotherapy and ASCT.
- To assess treatment-related morbidity and mortality including failure to engraft of refractory or relapsed HL patients treated with ⁹⁰Y-daclizumab RIT in combination with high-dose BEAM chemotherapy and ASCT.

1.1.3 Phase II Primary Objective:

- To assess the frequency of the failure to engraft, myelodysplastic syndrome (MDS), secondary leukemia for the development of abnormal bone-marrow cytogenetics in refractory or relapsed HL patients treated with ⁹⁰Y-daclizumab RIT in combination with high-dose BEAM chemotherapy and ASCT.

1.1.4 Secondary Objectives:

- To estimate the response rate (the number of complete and partial responses) in patients with refractory or relapsed HL to ⁹⁰Y-daclizumab RIT administered in combination with high-dose BEAM chemotherapy and ASCT.
- To assess the progression of free survival (PFS) and overall survival (OS) of refractory or relapsed HL patients treated with ⁹⁰Y-daclizumab RIT in combination with high-dose BEAM chemotherapy and ASCT.

1.2 BACKGROUND AND RATIONALE

According to the American Cancer Society, there will be approximately 8500 new cases of Hodgkin lymphoma (HL) diagnosed this year and more than 1300 patients will die of their disease [1]. Although treatment with modern combination chemotherapy regimens such as doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) is associated with an 80% complete remission rate even in patients with advanced disease, 25-30% of patients will not respond to treatment or will relapse [2]. Failure to respond to therapy can be the result of primary refractory disease (HL that has not responded to primary and secondary therapy), progressive disease (disease that increases in size after an initial partial response), or relapsed disease (disease that reappears in original sites, new sites, or both after a complete remission). High-dose chemotherapy with autologous stem cell support (ASCT) has become the treatment of

choice for all three of these groups [3-6]. Between 30% and 65% of patients will achieve long-term disease-free survival with ASCT. However, despite this aggressive treatment a significant fraction of patients will not respond and a proportion of patients will develop recurrent disease. Newer approaches are needed to improve these numbers.

1.2.1 Prognostic Factors at Relapse

Prognostic models have been developed to help identify subgroups of relapsed patients likely to have a poor outcome with conventional ASCT [7-11]. Josting *et al* retrospectively analyzed 422 patients with early (≤ 12 months), or late (> 12 months) from completion of first-line chemotherapy relapsed HL registered in the database of the German Hodgkin's Lymphoma Study Group (GHSG) [7]. Fifty-seven percent of patients had received prior radiotherapy, 25% as a single modality for early stage disease and 32% (n = 133) as combined modality chemoradiation for intermediate stage disease. Forty-three percent (n = 182) of patients had advanced disease and received combination chemotherapy with radiotherapy only to sites of bulky disease. Patients who relapsed after radiotherapy for early stage disease had a higher 4-year freedom from second failure (FF2F) than patients who relapsed after salvage chemotherapy (81% vs. 33%, and 43% for patients with an early and late relapse, respectively). Time to recurrence, clinical stage and anemia were independent risk factors for relapse on multivariate analysis.

In a separate multivariate analysis of prognostic factors influencing time to progression (TTP) and overall survival (OS) in 357 patients with HL undergoing an ASCT at a first relapse, detectable disease at the time of ASCT was an adverse factor for both TTP and OS [11]. Chemosensitivity was in fact one of the most important prognostic factors for TTP with 68% of patients autografted in second complete remission (CR) being disease free at 5 years vs. 34% and 11% with chemosensitive and chemorefractory disease, respectively. Other prognostic factors for TTP included advanced stage at diagnosis, complementary radiation, and CR <12 months. Chemosensitivity was also an important prognostic factor for OS, with an OS of 75% at 5 years for patients autografted in second CR and of 43% and 19% at 5 years for those autografted with chemosensitive and chemorefractory disease, respectively.

1.2.2 Autologous Stem Cell Transplantation in Refractory HL

Autologous hematopoietic stem cell transplant has become the standard of care for relapsed HL. In addition to a number of single arm studies, two randomized clinical trials have demonstrated that ASCT improves freedom from treatment failure (FFTF) over conventional therapy for relapsed disease [5, 6, 12-14]. In a small study from the British National Lymphoma Investigation (BNLI) by Linch *et al*, 40 patients with active HL who failed conventional therapy, were randomized to receive BEAM (carmustine, etoposide, cytarabine, and melphalan) plus ASCT, or mini-BEAM (reduced doses of the same drugs) [5]. At three years, the actuarial event-free survival was 53% in the BEAM group and 10% in the mini-BEAM group (p = 0.025). There was no difference in overall survival between the two arms. Schmitz *et al* randomized 161 patients with relapsed HL to 2 cycles of dexamethasone-BEAM (Dexa-BEAM) and either two further courses of Dexa-BEAM, or high-dose BEAM with ASCT [6]. Only the 117 patients who achieved a CR or partial remission (PR) were able to continue treatment on the protocol such that 56 patients were treated with Dexa-BEAM and 61 patients were treated with BEAM and ASCT. FFTF at 3 years was significantly better for patients given BEAM-HSCT (55%) than for those on Dexa-BEAM (34%) (p = 0.019) regardless of the length of the initial remission. Again, overall

survival did not differ significantly between the two treatment groups.

1.2.3 Autologous Stem Cell Transplant in Primary Refractory HL

Patients who progress during first-line chemotherapy or within 3 months of the end of chemotherapy are defined as having “primary refractory disease.” Although these patients generally have an extremely poor prognosis, two retrospective registry-based analyses suggest that primary refractory patients may also benefit from high-dose therapy and ASCT. The European Group for Blood and Marrow Transplantation (EBMT) reported on 175 HL patients of whom 75 received ASCT after failure of an induction regimen [15]. Actuarial 5-year OS and PFS were 36% and 32%, respectively, for patients receiving ASCT. On multivariate analysis, only the interval between diagnosis and ASCT was prognostic for OS ($p = 0.02$). The Autologous Blood and Marrow Transplant Registry (ABMTR) reported on 122 HL patients who failed to achieve complete remission after one or more conventional therapy regimens and subsequently received an ASCT [16]. Probabilities of PFS and OS at 3 years were 38% and 50%, respectively. In multivariate analysis, “B” symptoms at diagnosis and poor performance score at transplantation were adverse prognostic factors for outcome.

1.2.4 Radioimmunotherapy in Lymphoma

Following the approval of the chimeric anti-CD20 monoclonal antibody rituximab for the treatment of relapsed and refractory follicular low-grade non-Hodgkin lymphoma (NHL) by the US Food and Drug Administration (FDA), therapeutic radioimmunoconjugates were developed given the frequent radiosensitivity of lymphoma [17]. Either yttrium-90 or iodine-131 was attached to the monoclonal antibody to enhance the cytotoxic potential of the antibody and target both the cell to which the antibody is bound and the surrounding tumor cells by the radiological bystander or “cross-fire effect.” The FDA ultimately approved two radioimmunoconjugates, I-131-tositumomab (Bexar®) and yttrium-90-ibritumomab tiuxetan (Zevalin®), for patients with refractory, relapsed, and transformed CD20-positive indolent lymphomas. Yttrium-90-ibritumomab tiuxetan is composed of a murine immunoglobulin G1-kappa monoclonal antibody ibritumomab linked to yttrium-90 by the chelator tiuxetan (MX-DTPA). I-131-tositumomab is composed of the murine immunoglobulin G2 monoclonal antibody tositumomab (B-1) antibody linked to I-131 by a chemical bond. Whereas iodine-131 delivers 0.81 MeV over a path length of 0.8 mm and a half-life of 8 days, yttrium-90 is a pure beta emitting isotope that delivers more energy (2.3 MeV) over a longer path length (5 mm) and a shorter half-life (2.5 days) [18].

In the initial multicenter phase I/II study of yttrium-90-ibritumomab administered at 0.4 mCi/kg in 51 patients with relapsed or refractory CD20+ NHL, the overall response rate (ORR) was 67% (26% CRs and 41% PRs) [19]. In 34 patients with low-grade NHL, an 82% response rate was achieved. All patients had received a median of two prior regimens, and 37% of treated patients had bulky disease. Estimated median time to progression (TTP) by Kaplan-Meier analysis was 12.9 months while the median duration of response was 11.7 months. The major hematologic toxicity, transient and reversible, was thrombocytopenia. The nadir count typically occurred at a median of 43 days after radioimmunotherapy, unlike chemotherapy after which nadir counts occur within 1-2 weeks following therapy. The mean nadir values were 50,000/ μ L for platelets and 1,100/ μ L for granulocytes. The most common non-hematological toxicities included asthenia, nausea, infection, chills, fever, and abdominal pain. Of note, when yttrium-90-ibritumomab was compared to rituximab alone in a randomized controlled trial of 143 patients with relapsed or refractory low-grade/follicular, or transformed B-cell NHL, the ORR was 80%

for the radioimmunoconjugate vs. 56% for the rituximab group alone (p = 0.002) [20].

Kaminski *et al*, published early efficacy data using iodine-131-tositumomab in 9 patients with relapsed CD20-positive lymphomas in 1993 [21]. Six of 9 patients had tumor responses including 4 patients with complete remissions lasting from 8-11 months and 2 with PR. Most patients had reversible grade 1 myelosuppression 4-7 weeks after radioimmunotherapy. Long-term follow up of the University of Michigan database that included these 9 patients and 50 other patients with relapsed and refractory NHL was reported in 2000 [22]. Eighty-eight percent of patients had Ann Arbor stage III-IV disease at study entry and were heavily pretreated with a median of 4 prior regimens. Seventy-one percent of patients (n = 42) responded to treatment, including 20 patients who entered a CR. For all 42 responders, the median progression-free survival (PFS) was 12 months and reached 20.3 months for patients in a CR. As with yttrium-90-ibritumomab, the most common non-hematological toxicities were fever, asthenia, nausea, and chills. The major dose-limiting toxicity, albeit reversible, was hematological with the mean time to platelet and neutrophil nadir following treatment of 35 and 43 days, respectively. Of note, five heavily pretreated patients were diagnosed with myelodysplastic syndrome 1.2-7.5 years after treatment. Three patients also developed solid tumors, including 2 superficial transitional cell bladder cancers and one with squamous cell carcinoma of the rectum.

1.2.5 Radioimmunotherapy in Autologous Stem Cell Transplantation

The radiosensitivity of lymphomas is the basis for the inclusion of external beam total body irradiation (TBI) into transplant conditioning regimens [23, 24]. Among 96 patients with recurrent or refractory HL and poor-risk NHL treated with 12 Gy of total body irradiation (TBI), etoposide, and cyclophosphamide and autologous stem cell support following cytoreduction with conventional chemotherapy, the event-free survival (EFS) rate at 3 years was 47% and 53% for patients with HL and NHL, respectively [24]. In another series of 53 lymphoma patients treated with a similar approach using TBI, etoposide, and cyclophosphamide, the 2-year Kaplan-Meier estimates of survival, EFS, and relapse were 54%, 45%, and 43%, respectively [23]. The major morbidities seen in both studies were mucositis and skin toxicities. However, other potential toxicities of fractionated TBI include nausea, vomiting, diarrhea, interstitial pneumonitis, venoocclusive disease of the liver, renal insufficiency, cataracts, hypothyroidism, and the development of either myelodysplasia, or acute myeloid leukemia [25]. Integrating a radiolabeled monoclonal antibody into the induction regimen to achieve higher doses of radiation to tumor sites, while delivering lower doses to normal organs, maximizes the therapeutic benefit of radiation while minimizing toxicity.

Press *et al*, first documented the feasibility and efficacy of using radiolabeled monoclonal anti-B-cell-antibodies with high-dose therapy in patients with relapsed B cell lymphomas [26-28] Long term follow up in 29 patients treated with myeloablative iodine-131-anti-CD20 antibody and autologous stem cell rescue was reported by Liu *et al* [28]. All patients were previously treated with a median of three different regimens. Major tumor responses occurred in 25 of 29 patients with 23 patients achieving a CR. Kaplan-Meier estimates of overall survival (OS) and PFS at 4 years were 68% and 42%, respectively. With a median follow up of 42 months, the median time to treatment failure (TTF) after radioimmunotherapy was 37 months. Although severe myelosuppression occurred in all patients following treatment with iodine-131-anti-CD20 antibody, hematological reconstitution was achieved with autologous stem cells in all but one patient (one patient spontaneously recovered their blood counts without reinfusion of stem cells). Late toxicities were uncommon except for elevated thyroid-stimulating hormone levels in 60%

of patients. No patients developed MDS although 2 patients developed solid tumors (noninvasive transitional cell carcinoma of the bladder and metastatic colon cancer). When high-dose etoposide and cyclophosphamide were added to the same transplant regimen in 52 patients with relapsed B cell lymphomas, the 2-year OS and PFS were 83% and 68%, respectively [29].

Yttrium-90-ibritumomab tiuxetan has also been incorporated into transplantation regimens with high-dose chemotherapy [30-32]. Nademenee et al treated 31 poor-risk or relapsed patients with CD20+ NHL with high-dose yttrium-90-ibritumomab tiuxetan (71.6 mCi) in combination with high-dose etoposide and cyclophosphamide followed by ASCT [30]. Fifty-five percent of patients had bone-marrow involvement at diagnosis and the median number of prior chemotherapy regimens was 2. At a median follow up of 22 months, the 2-year estimated OS and relapse free survival were 92% and 78%, respectively. The therapy was relatively well tolerated with around 80% of patients developing mucositis, neutropenic sepsis and nausea. The only 2 deaths on the study were one patient who died at day +164 after transplantation from alcohol-induced liver failure and one patient who died from graft failure at day +44. Krishnan *et al* evaluated the safety and efficacy of combining yttrium-90-ibritumomab tiuxetan with high-dose carmustine, cytarabine, etoposide, and melphalan (BEAM) followed by ASCT in 41 patients with refractory, relapsed, or poor-risk NHL [32]. The median age of the patients was 60 years, and the median number of previous therapies was 2. Twenty out of 41 patients on the study had diffuse large B cell lymphoma. The median dose of yttrium-90-ibritumomab tiuxetan was 32.9 mCi. With a median follow-up of 18.4 months, the Kaplan-Meier estimated 2 year OS and PFS were 88.9% and 69.8%, respectively. There was only one incidence of grade 4 hepatic and pulmonary toxicity each, and they occurred in the same patient. Transplantation-related mortality at 100 days was 0%.

1.2.6 Clinical Experience with ⁹⁰Y-daclizumab

Our Branch developed daclizumab (Zenapax®), a humanized IgG1 monoclonal antibody that targets human CD25 (IL-2R alpha subunit) at the IL-2 binding site [33]. Unmodified daclizumab has been used in the treatment of HTLV-1-associated adult T-cell leukemia (ATL). To enhance the cytotoxicity of the antibody in the treatment of ATL and other CD25-expressing malignancies, daclizumab was conjugated to the pure beta-emitting isotope yttrium-90, i.e. ⁹⁰Y-daclizumab, as a means of delivering targeted radiation therapy to the tumor [34, 35].

In NCI protocol 96-C-0147, ⁹⁰Y-daclizumab was administered to 29 patients with HTLV-1-associated adult T-cell leukemia (ATL) (Waldmann *et al*, unpublished data). The starting dose in this trial was 15 mCi and was to be escalated in 5 mCi increments in patient cohorts. Bone-marrow suppression with repeated doses limited the ability to administer the same dose of radioimmunotherapy with each six-week cycle. The revised protocol dose escalated only the first dose and all subsequent treatments were given at a 5 mCi dose. Immediately following infusion of the radiolabeled antibody, Ca-DTPA, a decorporation agent, was infused over five hours and repeated on each of two subsequent days. The phase I portion of the trial accrued 20 patients and 52 cycles of therapy were administered. The first eight patients received initial 15 mCi doses under the original version of the protocol and the remaining patients were treated with the revised protocol treatment plan. Three patients were treated with initial doses of 20 mCi, 7 with 25 mCi, and 2 with 30 mCi. The hematologic toxicity was the major observed effect of treatment. The maximum tolerated dose (MTD) was 25 mCi with dose-limiting thrombocytopenia observed in both patients treated at the 30 mCi dose. One patient had grade 4 thrombocytopenia and the other failed to recover a platelet count of greater than 100,000/mm³ at

10 weeks after treatment. Of the 20 patients entered in the phase I study 11 patients (55%) developed grade 3 or 4 neutropenia, 3 patients (15%) had grade 3 anemia and 7 patients (35%) had grade 3 or 4 thrombocytopenia. Fourteen patients had grade 1 or greater granulocytopenia and all but two patients had grade 1 or greater thrombocytopenia. Only one patient developed grade 3 or 4 non-hematologic toxicity that occurred in conjunction with tumor lysis, and consisted of cardiac dysfunction with a drop in ejection fraction and hypoxia requiring intensive care support, but not intubation. There were two grade 2 infectious complications, herpetic and fungal, respectively. Mild nausea, vomiting, fever, and fatigue were reported in occasional patients. Nine patients entered the phase II study. Hematologic toxicity was similar to that observed in the phase I portion of the study with 6 patients (66%) with grade 3 or 4 granulocytopenia, and 3 patients (33%) with grade 3 or 4 thrombocytopenia. The only grade 3 non-hematologic toxicity was stomatitis and occurred in a patient with tumoral deposits in the oral mucosa. There were nine responses to treatment in the phase I portion of the study with 2 complete remissions (5 and 32 months) and 7 partial remissions (2, 2, 4, 5, 6, 8, 16 months).

In a separate protocol (97-C-0110), we treated 16 patients with CD25-positive malignancies other than ATL, including 8 CTCL, 3 PTCL, 1 ALCL, and 48 Hodgkin lymphoma patients with ⁹⁰Y-daclizumab doses of up to 20 mCi in association with Ca-DTPA in the phase I part (unpublished data). Repeat doses were administered as permitted by toxicity and lack of tumor progression. In contrast with the ATL study, the dose of ⁹⁰Y-daclizumab was maintained at the same level on subsequent treatment cycles. The maximum tolerated dose in this study was 15 mCi with dose-limiting thrombocytopenia seen in two of the three patients treated at the 20 mCi dose level. Both patients had thrombocytopenia that did not recover to a value of $\geq 100,000/\text{mm}^3$ by ten weeks after their initial treatment. Fifteen patients were treated with 26 cycles of therapy. Myelosuppression was the major treatment-related toxicity. Of the 16 patients entered in the study, 2 patients (13%) had grade 3 or 4 granulocytopenia, 5 patients (31%) grade 3 or 4 thrombocytopenia, and 4 patients (25%) grade 3 or 4 hemoglobin. There were two grade 3 or greater non-hematologic toxicities; one patient with a pre-existing hearing loss complained of a further decrement in hearing and one patient had hyperglycemia. As with the study in ATL, occasional patients experienced nausea, vomiting, fatigue, and low-grade fever. Response to treatment was not as frequent; 11 patients progressed, 3 had stable disease and 1 responded.

1.2.7 Rationale

Although an expanding number of monoclonal antibodies and RIT have been well studied in NHL, their successes in HL have been limited [36-38]. This is due to a number of factors including a limited number of unique surface antigens expressed in HL and their relatively low density. In HL, both the Reed-Sternberg cell and the T-cell infiltrate that surrounds the Reed-Sternberg cells may express CD25 (Figure 2) [36, 39].

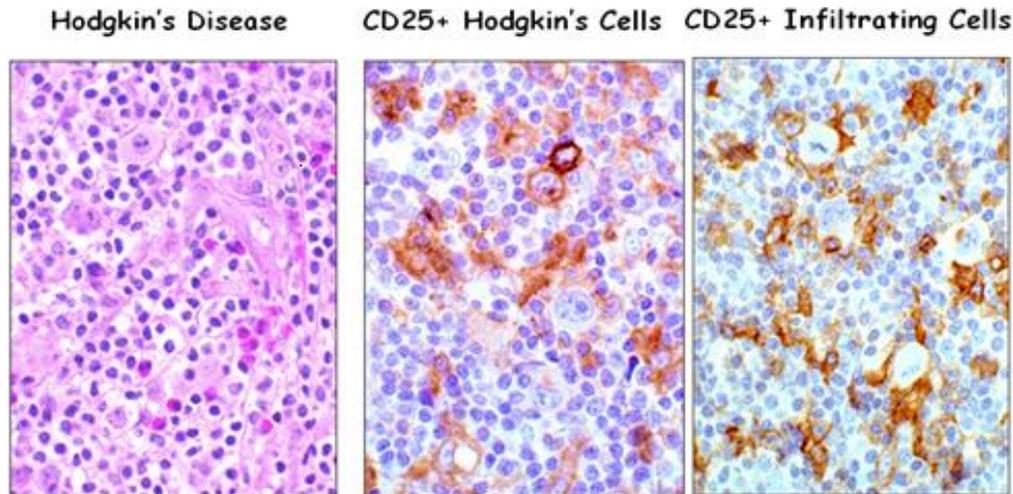


Figure 3. Lymph node biopsy showing classical HL (H&E stain; panel 1). Immunohistochemical stain demonstrating expression of CD25 by Reed-Sternberg cells (panel 2). In another patient's biopsy, an immunohistochemical stain demonstrating CD25-negative Reed-Sternberg cells, but strongly CD25-positive rosetting T-cells (panel 3).

While a significant fraction of Reed-Sternberg cells may lack expression of CD25, it is almost uniformly expressed on the associated rosetting polyclonal T-cells that increases the number of targets for the radiolabeled antibody and therefore the amount of radiation delivered to the tumor.

Hypothesizing that radioimmunoconjugate would enhance cytotoxicity to tumor cells while sparing normal tissues, in a single institution phase II study, 30 heavily pre-treated patients with recurrent or refractory HL were treated with up to 7 doses of ⁹⁰Y-daclizumab (Janik JE *et al*, manuscript submitted). These patients had received a median of 4 (range, 1-8) prior chemotherapy regimens with 20 having received a prior autologous stem cell transplant. Four patients had received both a prior autologous and allogeneic hematopoietic stem cell transplant. Even among this heavily pretreated group, 12 patients achieved a complete response while 7 achieved a partial response for an overall response rate of 63%. An example of a patient response is shown in Figures 4 and 5. Despite achieving this impressive response rate in a heavily pre-treated population, the median response duration was a somewhat disappointing 129 days (range, 28 to 720 days).

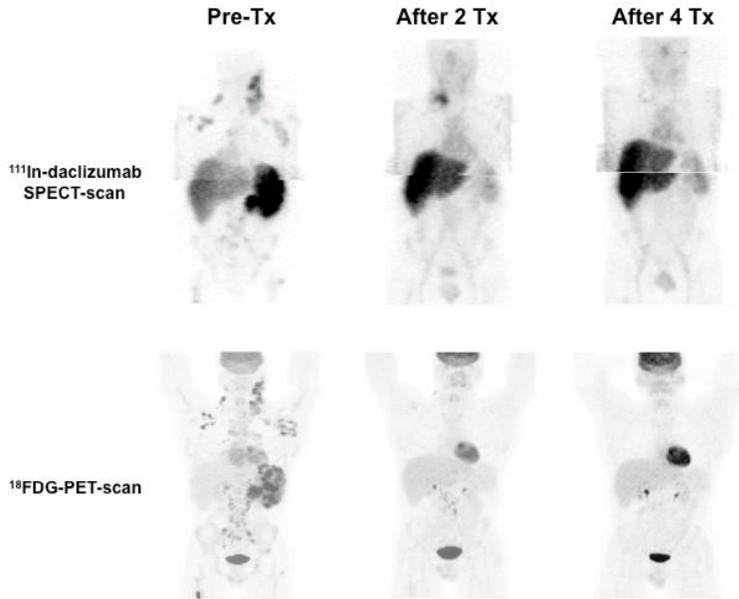


Figure 4. Indium-111-daclizumab (^{111}In) single photon-emission capture tomography (SPECT) imaging during ^{90}Y -daclizumab treatment in patient that achieved a complete response (upper panels). Imaging demonstrated binding of ^{111}In -daclizumab to HL in the spleen and lymph nodes. ^{18}F FDG-PET demonstrated serial decrease and resolution of tracer uptake consistent with the patient achieving a complete response.

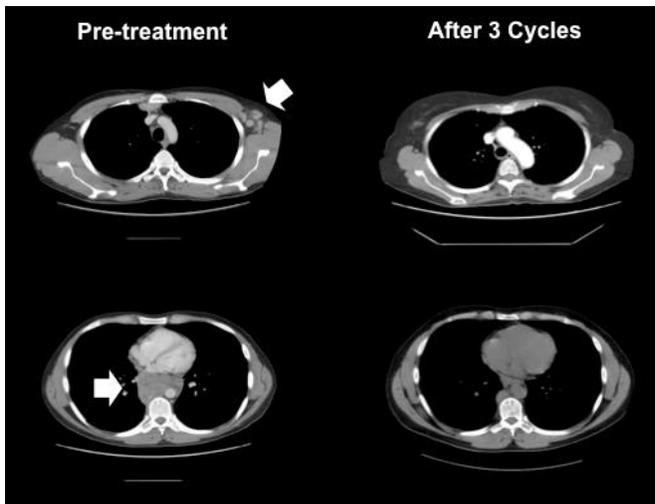


Figure 5. Computerized tomography (CT) demonstrated a complete response after 3 cycles of 15 mCi ^{90}Y -daclizumab in a patient with HL and multiple relapses. Arrows indicate enlarged left axillary lymph nodes and a posterior mediastinal mass that resolved with RIT.

The major toxicity, bone-marrow suppression, was transient in the majority of patients. However, ultimately six of forty eight HL patients treated on this protocol developed MDS/AML. Four of these patients started protocol treatment with normal bone marrow (BM) cytogenetics and two others had no pre-treatment assessment of their BM because they received the study therapy before the protocol required a pre-treatment cytogenetic assessment. With regards to the contribution of Yttrium Anti-Tac to their subsequent MDS, three of these patients

were heavily pretreated with known genotoxic regimens and received 3, 6, and 7 cycles of Yttrium daclizumab, respectively.

The preliminary analysis of response presented in the “waterfall” analysis shown in Figure 6 shows the number and quality of responses achieved in the initial 30 patients treated in this protocol; the remaining 18 patients are being analyzed.

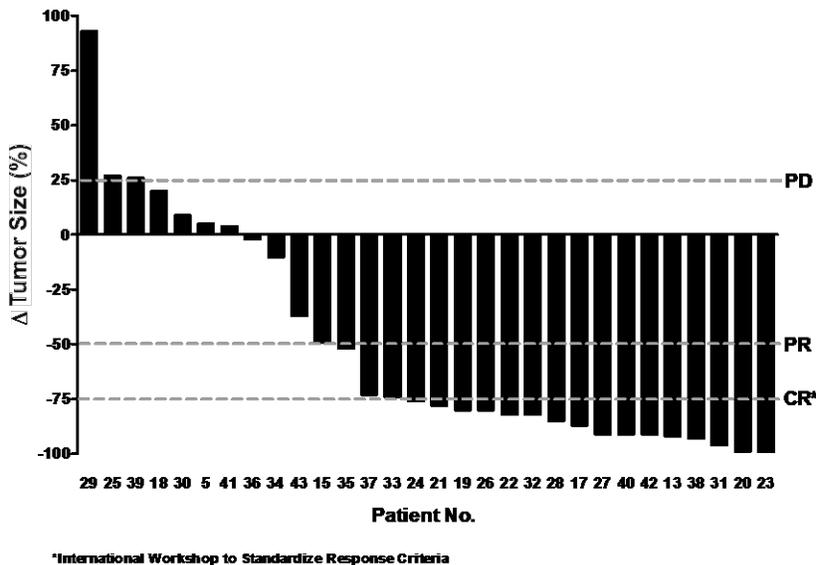


Figure 6. Waterfall analysis of 30 relapsed or refractory HL patients treated with ⁹⁰Y-daclizumab.

Given that recurrent disease remains the single most common cause of treatment failure after ASCT in patients with relapsed HL and given the 63% response rate achieved with ⁹⁰Y-daclizumab RIT in the heavily pretreated population reported above, we now seek to improve the long-term disease-free survival achievable with ASCT by incorporating ⁹⁰Y-daclizumab into the transplant pre-conditioning regimen. ⁹⁰Y-daclizumab provides a vehicle to target not only to the lymphoma cells that express CD25, but also rosetting CD25-expressing polyclonal T-cells that infiltrate the tumor. Furthermore, through a radiobiological “crossfire” or “bystander” effect, ⁹⁰Y-daclizumab provides radiation exposure to neighboring antigen negative tumor cells that are ordinarily inaccessible to the unmodified antibody. To maximize the crossfire effect ⁹⁰Y-daclizumab will be used as cytoreductive therapy. A maximal effect is obtained with macroscopic tumor volumes rather than minimal residual disease. We will administer 2 doses of ⁹⁰Y-radiolabeled daclizumab prior to BEAM conditioning therapy and autologous hematopoietic stem cell transplant. This is based on our observation that none of the 12 patients that achieved a complete remission did so following the first dose of radioimmunotherapy. It is expected that 2 cycles of radioimmunotherapy combined with ASCT will be well tolerated by patients while providing significant anti-tumor effects, thereby allowing a greater proportion of these patients to achieve a superior freedom from disease progression.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

- 2.1.1.1 All patients must have a pathologically confirmed diagnosis of classical Hodgkin's lymphoma (HL) as outlined in the WHO Classification System of Lymphoid Tumours [41]. Patients with nodular lymphocyte-predominant HL (NLPHL) are not eligible.
- 2.1.1.2 Refractory or relapsed HL patients that are also candidates for ASCT.
- 2.1.1.3 At least one adverse prognostic factor: (1) initial relapse \leq 12 months after primary chemotherapy, (2) staged as Ann Arbor Classification initial stage III or IV disease, (3) chemotherapy resistant disease, (4) Failure to achieve a complete response (CR) with cytoreductive chemotherapy or persistent positive ¹⁸F-DG-PET imaging.
- 2.1.1.4 At least 10% of the cells obtained from lymph node, or extranodal sites must react with anti-CD25 (anti-Tac) on immunofluorescent or immunoperoxidase staining. Because of the high frequency of CD25 positivity of the infiltrating T-cells in HL tumors, patients with CD25-positive infiltrating T cells will be eligible even if their Hodgkin's (Reed-Sternberg) cells are CD25-negative.
- 2.1.1.5 Measurable disease as defined by the Cheson Response Criteria for Malignant Lymphoma detailed in Section 6.2 with at least one lesion \geq 1.0 cm in longest diameter by CT scan.[40].
- 2.1.1.6 Omission of cytotoxic chemotherapy or other systemic therapy of the malignancy for \geq 4 weeks prior to entry into the trial. Patients must be \geq 4 weeks since major surgery, radiotherapy, or biotherapy/targeted therapies and recovered from the toxicity of prior treatment to \leq CTC grade 1, exclusive of grade 2 alopecia, fatigue, lymphopenia, CD4+ circulating T cells, WBC or bilirubin.
- 2.1.1.7 Patients must be \geq 18-years old.
- 2.1.1.8 Patients must have a life expectancy of greater than 3 months.
- 2.1.1.9 Patients must have an ECOG performance status of \leq 1.
- 2.1.1.10 The patient must have a granulocyte count of at least 1,500/ μ L and a platelet count of greater than 100,000/ μ L.
- 2.1.1.11 Patients must have a creatinine of less than 2.0 mg/dL, or if the patient has a serum creatinine \geq 2.0, a measured creatinine clearance (CrCl) must be $>$ 60 mL/min/1.73m².
- 2.1.1.12 Patients must have a serum alkaline phosphatase, ALT (SGOT), and AST (SGPT) $<$ 3 times the upper limit of normal (ULN), unless due to liver or bone involvement by HL. Under these circumstances, serum alkaline phosphatase, SGPT and SGOT must be $<$ 5x ULN.
- 2.1.1.13 Patients must have a total serum bilirubin $<$ 2.5 x ULN.
- 2.1.1.14 Patients must have a cardiac ejection fraction $>$ 45% on 2D echocardiography or MUGA obtained within 28 days of study enrollment.
- 2.1.1.15 Lung diffusion capacity for carbon monoxide (DL_{CO}) $>$ 50%, or forced expiratory volume at 1.0 seconds (FEV_{1.0}) $>$ 65% of predicted on pulmonary function testing

(PFT) obtained within 28 days of study enrollment.

2.1.1.16 Women of childbearing potential must have a negative serum β -HCG pregnancy test at initial screening and within 3 days prior to registration.

2.1.1.17 The effects of ⁹⁰Y-daclizumab on the developing human fetus are unknown. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, while receiving treatment and for 4 months after undergoing ASCT. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

2.1.1.18 Patients receiving a stable dose (> 4 weeks) of corticosteroid therapy equivalent to 20 mg of prednisone per day or less are eligible.

2.1.1.19 Patients must be able to understand and sign informed consent.

2.1.2 Exclusion Criteria

2.1.2.1 Patients who have relapsed from their initial ABVD or similar standard treatment regimen and have not received any other chemotherapy or salvage systemic treatment.

2.1.2.2 Patients enrolled on another therapeutic study.

2.1.2.3 Patients that have received prior radioimmunotherapy.

2.1.2.4 Patients that have received a prior autologous or allogeneic stem cell transplant

2.1.2.5 Patients that have received prior radiation to the lung, excluding prior mediastinal radiation.

2.1.2.6 Patients with greater than 25% involvement of the bone marrow with HL.

2.1.2.7 Patients with evidence of myelodysplasia, leukemia by morphology, immunostains flow cytometry or abnormal cytogenetics on a bone- marrow aspirate or biopsy. The diagnosis of myelodysplasia will be made by an independent investigator of the Laboratory of Pathology, NCI taking into consideration the totality of the clinical, pathological, flow cytometric and cytogenetic information described in Section 12.4 Appendix D and present in a particular individual's evaluation.

2.1.2.8 Patients with history of CNS involvement or active CNS involvement by malignancy.

2.1.2.9 Patients with an active second primary cancer will not be eligible. Patients curatively treated for a second cancer > 5 years prior to enrollment without a recurrence are eligible. Patients curatively treated for a second primary cancer within the last 5 years with a \leq 5% risk of recurrence are eligible. Patients with a history of curatively treated basal cell carcinoma or intraepithelial neoplasia of the uterine cervix will be allowed on study.

2.1.2.10 Patients with serum human anti-human antibody (HAHA) against daclizumab.

2.1.2.11 Patients with HIV infection (antibody positive with positive confirmatory molecular test).

2.1.2.12 Patients who have chronic hepatitis B or hepatitis C.

2.1.2.13 Patients with an uncontrolled serious infection.

2.1.2.14 Pregnant or breastfeeding women.

- 2.1.2.15 Patients with significant medical comorbidities, including uncontrolled hypertension (diastolic BP > 115 mmHg), unstable angina, congestive heart failure (> NYHA class II), poorly controlled diabetes, severe chronic pulmonary disease, coronary angioplasty or myocardial infarction within the last 6 months, or uncontrolled atrial or ventricular cardiac arrhythmias.
- 2.1.2.16 Patients with a history of a psychiatric disorder that may interfere with the understanding and compliance with this protocol and the required follow up.
- 2.1.2.17 Exclusion at the discretion of the PI or delegate if participation to the study is deemed too risky (e.g. clinically significant pleural or pericardial effusion or ascites with possibly increased radio-toxicity)

2.2 SCREENING EVALUATION

- 2.2.1 Complete medical history and physical examination with vital signs and performance status with documentation of all measurable or evaluable abnormalities. Measurable disease will be documented in two dimensions.
- 2.2.2 Studies must be completed within 28 days prior to study entry with the exception of the bone- marrow aspirate and biopsy with cytogenetics that must be completed within 60 days prior to study entry.
- 2.2.3 Complete blood count (CBC) including differential leukocyte and platelet count, Acute Care, Mineral and Hepatic Panels, creatinine clearance if serum creatinine is > 2 mg/dL.
- 2.2.4 Blood will be tested for antibodies to HIV. Positive serologic tests will be confirmed by molecular assays.
- 2.2.5 Hepatitis B and hepatitis C serologies will be obtained. Positive serologic tests will be confirmed by molecular assays.
- 2.2.6 Assessment of serum [**two 4 mL or one 8 mL serum separator tube (SST tube)**] human anti-human antibody (HAHA) against daclizumab will be performed on the patients' serum by ELISA to detect immune responses against Yttrium- daclizumab. Samples are to be sent to Dr. William Kopp/Ms. Helen Rager at NCI/OD, Clinical Support Laboratory 560/11-27, Building 1050, Boyles Street, Frederick, Maryland 21702, telephone number: 301-846-1707 or 301-846-1917.
- 2.2.7 Serum pregnancy test (serum β -HCG) in women of child-bearing potential.
- 2.2.8 Computerized tomography (CT) scan of the neck, chest, abdomen, and pelvis
- 2.2.9 Echocardiogram or MUGA to determine cardiac ejection fraction
- 2.2.10 Pulmonary function testing (PFT) with diffusing capacity DL_{CO}.
- 2.2.11 Bone-marrow aspirate and biopsy with cytogenetics within 60 days prior to study entry. Results must be available before registration. Bone-marrow specimens will be reviewed by the Hematology Laboratory of the Clinical Center. HL will be classified according to the WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues [41].
- 2.2.12 Lumbar puncture, MRI and CSF analysis will be performed in patients with neurological signs or symptoms (e.g., cranial nerve palsies, leg weakness, bowel or bladder dysfunction, etc.) that are not known to be due to some other diagnosis and that could be

indicative of CNS involvement by lymphoma.

- 2.2.13 A pre-therapy lymph node biopsy may be obtained if required for diagnostic purposes, and to determine the expression of the CD25 antigen. All lymph node biopsies should be submitted fresh in saline to the Hematopathology Section, Laboratory of Pathology, NCI, (Bldg. 10/2N110–112, Ms. Theresa Davies-Hill at 301-496-1567, or 301-435-2628). Biopsy specimens will be processed for routine histopathology as well as immunohistochemistry in frozen sections and/or flow cytometry for expression of CD25 and other surface antigens as appropriate.

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (<http://home.ccr.cancer.gov/intra/eligibility/welcome.htm>) must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) ncicentralregistration@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.4 BASELINE EVALUATION

Blood drawing for research purposes will not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period.

The following test/procedures are to be performed within 28 days of starting treatment except as listed below.

- 2.4.1 CBC including differential leukocyte and platelet count, Acute Care, Mineral and Hepatic Panels and serum pregnancy test (β -HCG) will be repeated within three days before study entry.
- 2.4.2 LDH, uric acid, total protein, reticulocytes, PT, PTT, fibrinogen, creatine kinase (CK) zinc, cholesterol, triglycerides, quantitative immunoglobulins.
- 2.4.3 Baseline CMV serology and antigenemia.
- 2.4.4 Serum soluble IL-2R alpha (sCD25) will be measured by ELISA.
- 2.4.5 Urinalysis.
- 2.4.6 Whole body ¹⁸fluorodeoxyglucose (¹⁸FDG) positron emission tomography (PET) imaging.
- 2.4.7 Magnetic resonance imaging and/or ultrasonography may be performed if clinically indicated.
- 2.4.8 Baseline 12-lead electrocardiogram.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

The study will be conducted in accordance with the procedures established by the NCI, NIH Radiation Safety Branch, NIH Clinical Center Department of Nuclear Medicine, the Nuclear

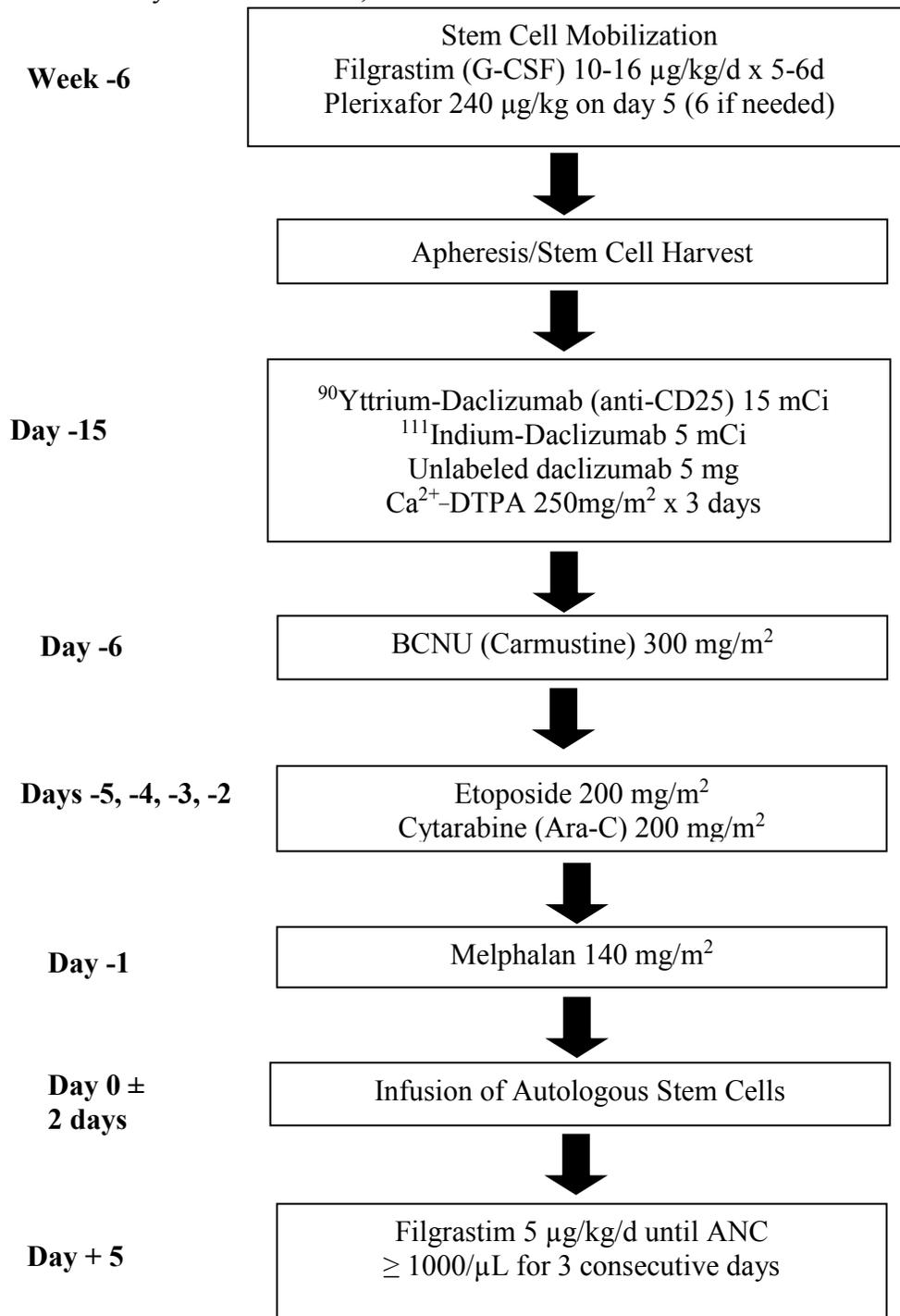
Abbreviated Title: ⁹⁰Y-daclizumab + ASCT in HL

Version Date: 02/05/2018

Regulatory Commission (NRC) and the U.S. Food and Drug Administration (FDA).

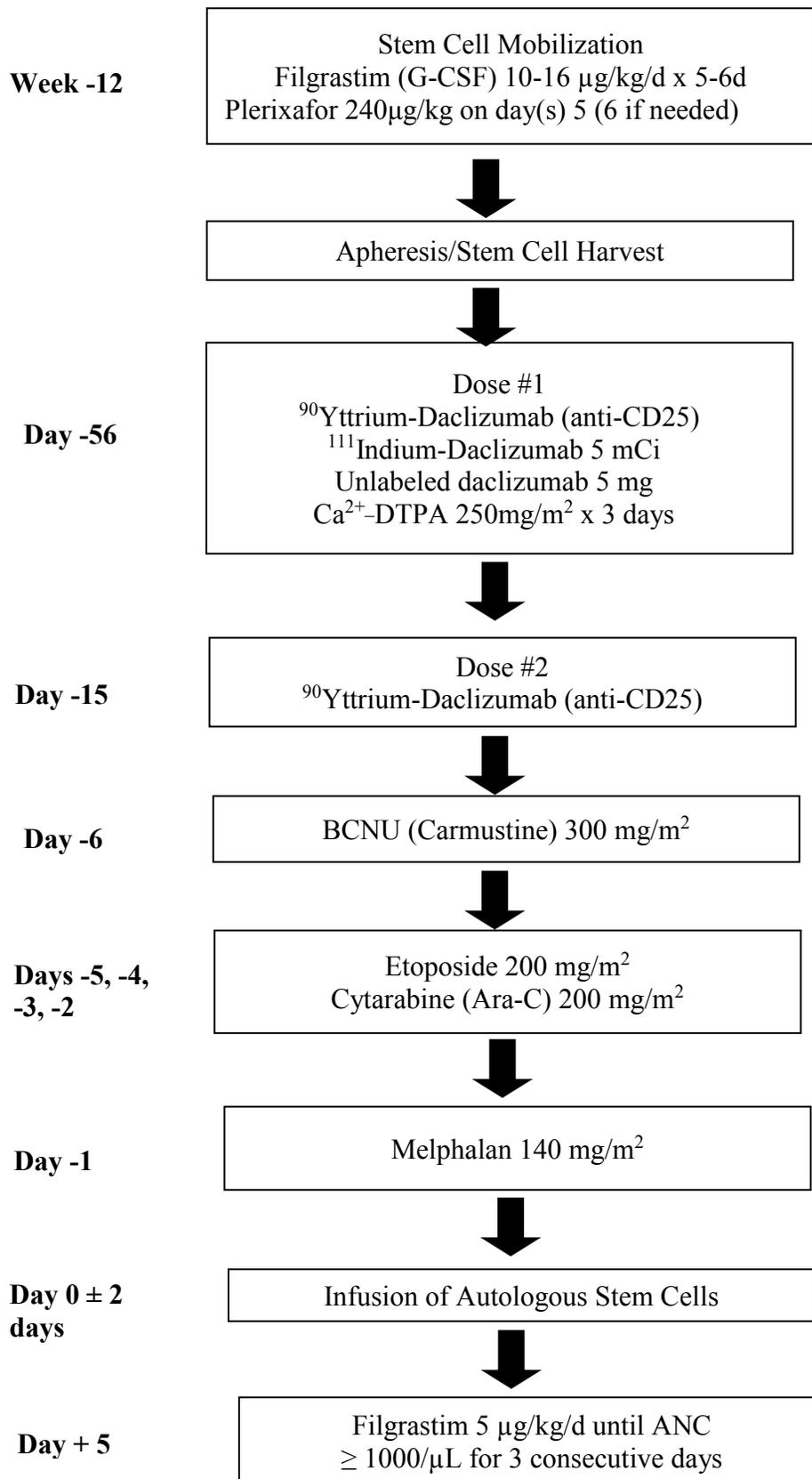
The study and Consent Document will be fully discussed with each patient and written Informed Consent obtained. It is the objective of this study to determine the dose of ⁹⁰Y-daclizumab in mCi that can be safely administered in combination with high-dose BEAM (carmustine, etoposide, cytarabine and melphalan) chemotherapy and autologous stem cell transplant (ASCT) in patients with refractory or relapsed HL, and to estimate the tumor response and duration of response to this treatment. Treatment will be administered on an inpatient basis.

3.1.1.1 Study Schema Phase I, Dose Level 1^f.



^f Dates between Week -6 and Day -15 are approximate and may be adjusted based on scheduling, stem cell harvest and other considerations. Patients that have evidence of rapidly progressive symptomatic disease requiring urgent salvage treatment after their stem cell mobilization and harvest will have their stem cells stored and receive the appropriate therapy to achieve disease control. These patients will be reconsented and allowed to re-enter the protocol treatment without having to undergo another stem cell mobilization/harvest.

3.1.2 Study Schema, Phase I, Dose Levels 2-7 and Phase II*.



* Dates between Week -12 and Day -15 are approximate and may be adjusted based on scheduling, stem cell harvest and other considerations.

* Patients that have evidence of rapidly progressive symptomatic disease requiring urgent salvage treatment after their stem cell mobilization and harvest will have their stem cells stored and receive the appropriate therapy to achieve disease control. These patients will be reconstented and allowed to re-enter the protocol treatment without having to undergo another stem cell mobilization/harvest.

3.1.3 Phase I dose-escalation of ⁹⁰Y-daclizumab

The first part of the study will be a phase I dose-escalation of ⁹⁰Y-daclizumab administered with a fixed dose of Ca-DTPA (trisodium calcium diethylenetriaminepentaacetate), a chelating agent that scavenges and binds free radioactive ⁹⁰Y and enhances its excretion [43]. Three patients will be entered at each sequential dose level of ⁹⁰Y-daclizumab. Based on dosimetric estimates for ⁹⁰Y-daclizumab in monkeys and humans and on our experience with ⁹⁰Y-murine-anti-CD25 and ⁹⁰Y-daclizumab in clinical trials, the initial intravenous dose of ⁹⁰Y-daclizumab will be 15 mCi. Assuming no dose-limiting toxicity (see Section 3.1.4), subsequent cohorts will receive 2 sequential doses of ⁹⁰Y-daclizumab each separated by 6 weeks. The second dose of ⁹⁰Y-daclizumab will be escalated by 15 mCi increments from 15 mCi to a maximum dose of 90 mCi until the maximum tolerated dose is reached (the dose level below the dose at which 2 of 6 patients develop dose-limiting toxicity, as defined in Section 3.1.4). We have already confirmed multiply relapsed heavily pretreated Hodgkin’s disease patients including patients who in some cases have already undergone stem cell transplants that ⁹⁰Y-daclizumab at a dose of 15 mCi can be given for up to 7 cycles. Never-the less, all treatments for dose levels 1 and 2 for this protocol will be the 15 mCi dose to reconfirm the tolerability in this patient population. For dose levels 2 through 7, at least three patients must have received both of their radiolabeled antibody infusions and undergone a 4-week post-transplant evaluation before patients can be started at the next dose level.

If 1/3 of patients treated at dose level 2 develop a DLT, the cohort will be expanded to 6 patients. If a second patient (2 of 6) experiences a DLT, the study will be terminated as not being feasible.

All patients enrolled on dose levels 2-7 will receive 2 sequential doses of ⁹⁰Y-daclizumab. The second dose of ⁹⁰Y-daclizumab will be escalated in increments of 15 mCi from 15 mCi to a maximum dose of 90 mCi as shown in Table 1. The highest dose that allows 0/6 or 1/6 DLT will be used in the Phase II portion of the trial.

We anticipate treating a maximum of 42 patients in the initial dose escalation phase of the study and up to 48 evaluable patients in the Phase II segment of the study, who will receive a dose defined during the dose escalation study.

Table 1. Phase I dose escalation of ⁹⁰Y-daclizumab.

Dose Level	⁹⁰ Y-daclizumab Dose (mCi)	
1	Dose #1: 15	
2	Dose #1: 15	Dose #2: 15
3	Dose #1: 15	Dose #2: 30
4	Dose #1: 15	Dose #2: 45
5	Dose #1: 15	Dose #2: 60
6	Dose #1: 15	Dose #2: 75
7	Dose #1: 15	Dose #2: 90

If a dose limiting toxicity (DLT) is observed in 2 patients at any time in a given dose level, accrual to that dose level will be halted. The event must be considered to be either possibly, probably or definitely related to the study therapy. The immediate previous dose level will then be increased as follows: the second dose of ⁹⁰Y-daclizumab will then be increased in groups of 3

to 6 patients by 5 mCi (e.g., 25, 30, 35 mCi) etc., rather than the 15 mCi increments until there have either been 2 incremental dose increases or 2 out of 2 to 6 patients at a given dose level develop DLT. There can be no more than 1 out of 6 patients with DLT at the MTD. The true MTD level must be confirmed in a cohort of 6 patients. ¹¹¹In-daclizumab 5 mCi will be administered with both ⁹⁰Y-daclizumab doses. In the Phase II portion of the study 48 patients will receive two doses of ⁹⁰Y-daclizumab (if demonstrated to be safe) followed by BEAM high-dose chemotherapy and ASCT. The first dose will be fixed at 15 mCi. The second dose of ⁹⁰Y-daclizumab will be the maximum tolerated dose determined from Phase I. ¹¹¹In-daclizumab 5 mCi will be administered with both ⁹⁰Y-daclizumab doses and at day 100 ±7 days for imaging purposes.

3.1.4 Dose-limiting Toxicity

Patients who develop either a CTCAE v4.0 grade 3 or greater non-hematological toxicity, with the exception of fatigue, of more than 5 days' duration possibly, probably or definitely related to the infusion of ⁹⁰Y-daclizumab prior to the start of BEAM chemotherapy (Day-6) will have developed by definition a dose-limiting toxicity (DLT) and may only continue on the study if the dose modifications described in Section 3.3.1 are made. Patients will receive a 2nd dose of ⁹⁰Y-daclizumab regardless of the level of hematologic toxicity at day -15. Patients who sustained CTCAE v4.0 grade 3 or greater non-hematological toxicity will not be eligible to receive further ⁹⁰Y-daclizumab. Once toxicity has recovered to grade 1 or less, the patient would proceed with BEAM chemotherapy and ASCT for medical and ethical reasons.

Hematologic toxicity following the 2nd dose of ⁹⁰Y-daclizumab will not be considered in determining DLT.

3.1.5 Maximum Tolerated Dose

A dose-limiting event in 2 patients at a given dose level will result in a halt to accrual at that dose level. These events must be considered to be either possibly, probably or definitely related to the study therapy. The second dose of ⁹⁰Y-daclizumab will then be increased from the previous dose level in increments of 5 mCi as described in Section 3.1.3. The maximum tolerated dose (MTD) will be defined as the dose level below the dose at which 2 out of 2 to 6 patients at a given dose level develop DLT. There can be no more than 1 out of 6 patients with DLT at the MTD.

On completion of the Phase I study, a Phase II study will be initiated using the same schema outlined in Section 3.1.2. The initial dose of ⁹⁰Y-daclizumab at day -56 would be 15 mCi whereas the second dose at day -15 would be the maximum tolerated dose determined from Phase I. Early termination would occur based on a 100-day post-transplant mortality of 15% or greater.

3.1.6 Phase II Study Design

For the Phase II Study the following considerations apply.

Two main goals of the Phase II portion of the trial are to assess the rate of engraftment and to assess if an adequate fraction of patients can avoid MDS or cytogenetic abnormalities.

Since the purpose of high-dose chemotherapy and ASCT is to achieve a steep-dose response in the tumor, the absolute hematological values achieved except for a CTCAE v4.0 grade 5 events (death) are of little value in assessing dose-limiting toxicity. Rather failure of the autologous hematopoietic stem cells to achieve engraftment as defined below will be DLT:

Failure to achieve neutrophil engraftment by day 21, defined from day 0 (the day when autologous stem cells are infused) as the first of three consecutive days on which the patient's absolute neutrophil count is greater than $0.5 \times 10^9/L$ following the nadir.

Failure to achieve platelet engraftment by day 28, defined from day 0 (the day when autologous stem cells are infused) as the first of seven consecutive days on which the patient's unsupported platelet count is greater than $20 \times 10^9/L$ following the nadir.

The first 20 patients in the Phase II portion of the trial will be evaluated with respect to the number that fails to engraft as explained in detail in Section 8. If there are 2 or more patients who fail to engraft in the initial 20 patients, this is more likely to be consistent with an unacceptably high rate of engraftment failure such as 15% than a potentially reasonable rate of engraftment failure, and the trial would stop under these circumstances. If it does not stop accrual prior to 20 patients, future patients will continue to be monitored for engraftment failure, and if at any point beyond the first 20 patients, greater than 10% are cumulatively noted to fail to engraft, the study will no longer accrue further patients unless a revision to the design is approved.

At all times during the trial patients will be monitored for the occurrence of an unacceptably high day-100 Transplant Related Mortality (TRM) as detailed in Section 8.

We will perform bone-marrow aspirates/biopsies for morphology and cytogenetics prior to study entry, at day 100 (± 7 days) post-transplant, then yearly for 5 years, and as medically indicated following treatment for early detection of MDS/secondary leukemia. Patients with pre-existing MDS or cytogenetic abnormalities will not be eligible to participate in this trial. The study will be conducted in order to rule out an unacceptably low 75% proportion avoiding MDS ($p_0 = 0.75$) in favor of a higher MDS avoidance rate of 90% ($p_1 = 0.90$). As detailed in Section 8, if 11 or more of the first 13 avoid engraftment failure and/or MDS and/or cytogenetic abnormality initially, then accrual would continue until a total of 48 evaluable patients have been enrolled. If there are 11-40 of 48 patients who avoid MDS or its corresponding cytogenetic abnormality, this would be an unacceptably low rate of avoiding MDS while if there were 41 or more of 48 patients who do not develop MDS then this would be sufficiently interesting to warrant further study.

3.2 STUDY PROCEDURES/DRUG ADMINISTRATION

3.2.1 Peripheral blood stem cell (PBSC) mobilization

Approximately one month prior to the first planned dose of ⁹⁰Y-daclizumab, patients will undergo apheresis to collect a minimum CD34+ cell dose of 2.0×10^6 CD34+ cells/kg following mobilization with filgrastim (granulocyte-colony stimulating factor, G-CSF) and plerixafor (AMD3100, Mozobil). Patients are required to have adequate hematological recovery (platelet count $>100,000/\mu L$ and ANC $>2500/\mu L$) prior to starting stem cell mobilization.

3.2.1.1 Granulocyte-colony stimulating factor (G-CSF, filgrastim)

G-CSF will be administered subcutaneously at 10-16 $\mu g/kg/day$ (See Section 12.5 Appendix E for G-CSF dosing algorithm) for five to six days (dependent on achieving an adequate collection of stem cells), beginning at least one month prior to the first planned dose of ⁹⁰Y-daclizumab. The G-CSF will be given between 8:00 A.M. to 5:00 P.M. on days 1-4, and 6 hours prior to starting apheresis on days 5-6. Cells will be processed, cryopreserved in DMSO, and frozen according to DTM Cell Processing Section SOP. If mobilization of

CD34+ cells does not yield sufficient numbers (minimum of 2×10^6 CD34+ cells/kg of actual body weight), G-CSF will be discontinued for a minimum of three weeks, after which mobilization and collection will be attempted again. Patients from whom adequate numbers of CD34+ cells cannot be collected in two mobilization cycles will be removed from the study. If the initial week -6 mobilization and harvest has a poor CD34+ cell yield (i.e. $< 1 \times 10^6$ CD34+ cells/kg), consideration will be given to withdrawing the patient from the protocol at that time rather than proceeding with a futile second round of stem cell mobilization.

Patients enrolled in this study will have undergone many prior cycles of alkylator-based chemotherapy, often in combination with radiation therapy, and are expected to have poor marrow reserve. To optimize the likelihood of robust mobilization of CD34+ cells into the circulation and thus collection of the targeted CD34+ cell dose during the first mobilization cycle, G-CSF will be administered according to a weight- and vial-based algorithm, as described in Section 12.5 Appendix E. This algorithm is in widespread use in NIH protocols for patients predicted to have poor marrow reserve.

3.2.1.2 Plerixafor administration

A single dose of plerixafor (Mozobil™, Genzyme), 240 mcg/kg subcutaneous injection, will be given on the fifth day of mobilization 6 hours prior to apheresis along with G-CSF.

3.2.2 Peripheral blood stem cell (PBSC) collection by apheresis and cryopreservation

On the fifth day of mobilization, patients will undergo PBSC collection by apheresis in the Dowling Clinic of the Clinical Center Department of Transfusion Medicine (DTM), see Section 12.5 Appendix E for detail. They will receive intravenous calcium prophylaxis to prevent citrate toxicity during apheresis, in accordance with DTM standard operating procedures (SOP). Targeted cell dose is 4×10^6 CD34+ cells/kg of actual body weight, with a minimum cell dose of 2×10^6 CD34+ cells/kg necessary for continued participation in protocol. Apheresis and G-CSF / Plerixafor administration will continue daily for up to two consecutive days (maximum number of apheresis procedures is two) until the minimum cell dose of 2×10^6 CD34+ cells/kg of actual body weight is obtained. Fifteen to 25 ml of blood may be processed daily, with the exact volume processed per procedure determined by DTM medical staff on the day of apheresis, based on stat peak CD34 cell count drawn immediately prior to starting apheresis. Cells will be processed, cryopreserved in DMSO, and frozen according to DTM Cell Processing Section SOP. The total hematopoietic stem cell product yield will be aliquoted and cryopreserved in multiple bags such that separate infusions of cryopreserved hematopoietic stem cells, each with a CD34+ cell dose of at least 2×10^6 /kg actual body weight can occur.

If collection of CD34+ cells does not yield at least 2×10^6 CD34+ cells/kg of actual body weight during the first mobilization and apheresis cycle, G-CSF / Plerixafor will be discontinued for a minimum of three weeks, after which the mobilization and collection will be attempted again using the schedule and procedures described above. Patients from whom adequate numbers of CD34+ cells cannot be collected will be excluded and removed from the study.

3.2.3 Administration of ⁹⁰Y-daclizumab and ¹¹¹In-daclizumab: Dose level 1, Day -15; dose levels 2 – 7, and phase II days -56 & -15

Five mCi of ¹¹¹In-daclizumab will be administered to patients with each therapeutic infusion of ⁹⁰Y-daclizumab in order to follow the kinetics of disappearance of CD25 from the plasma, to define the distribution of radiolabeled daclizumab, and to allow visualization by scans.

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Radiolabeled antibody will be administered by the Radiolabeled Biologics Section of the Nuclear Medicine Department, Clinical Center, in the Nuclear Medicine Department suites. ^{90}Y -daclizumab and ^{111}In -daclizumab will be intravenously administered simultaneously over 2 hours. The radiolabeled antibodies will be diluted in normal saline 5% human serum albumin solution and administered intravenously with a slow infusion over 2 hours. Vital signs will be monitored during administration (hourly for the first 4 hrs. and then per routine), and emergency support for anaphylactic reactions will be available. All patients will receive their infusions as inpatients. A physician or trained research nurse will be present to handle problems arising from the infusion. For dose levels beyond dose level 1, 2 doses of ^{90}Y -daclizumab will be administered 6 weeks apart such that the second dose of ^{90}Y -daclizumab is administered 15 days prior to the administration of the autologous stem cells. ^{111}In -daclizumab will be administered with each dose of ^{90}Y -daclizumab and the patient will undergo CT-SPECT imaging to assess antibody binding to tumor.

3.2.4 Estimate ^{90}Y -daclizumab organ radiodosimetry in refractory or relapsed HL patients treated with ^{90}Y -daclizumab RIT in combination with high-dose BEAM chemotherapy and ASCT.

As ^{90}Y is difficult to image, with each ^{90}Y -daclizumab injection, ^{111}In daclizumab will also be injected to permit estimation of ^{90}Y -daclizumab radiation dose to the tumor and organs. ^{90}Y -daclizumab and ^{111}In daclizumab are expected to have near identical biodistributions and the biodistribution will be driven by the larger daclizumab components (not the small amount of radionuclide (^{90}Y or ^{111}In)). In a similar situation, ^{111}In rituximab is used clinically to estimate ^{90}Y rituximab biodistribution.

A series of three images will be obtained following the administration of ^{111}In daclizumab:

The day of injection [2-8 hours post-injection]

24-72 (+/-12) hours after injection

96-168 (+/-12) hours after injection

The images will consist of SPECT CT of the torso (2-3 fields of view) which will result in a volume image. As no significant uptake has been noted in the brain, only the torso will be imaged. The expected imaging time is 45-75 mins. A scatter window will be set to improve quantification. A small amount of a known activity of ^{111}In will be included in each field of view to permit calibration of imaging counts to activity.

Volumetric regions of interest (VOIs) will be drawn on images at each time point to create time-activity curves. For the solid organs, the VOI will be in a homogenous area of the organ and an activity concentration will be calculated. For the hollow organs (i.e. gut, gallbladder, urinary bladder) and the whole body, generous VOIs will be drawn to include all of the organ activity (including spillover) and the total organ activity at each time point will be calculated.

The resultant time activity curves will be used to calculate the organ residence times from which dosimetry estimates will be obtained using OLINDA/EXM software.

The total activity in the tumor will also be measured and an integrated tumor dose will be estimated.

3.2.5 Administration of unlabeled daclizumab

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Simultaneous with each dose of radiolabeled ⁹⁰Y-daclizumab administered in the phase I and phase II studies, patients will receive a fixed dose of 5 mg of unlabeled daclizumab (Zenapax™, humanized anti-CD25, anti-IL-2R alpha, anti-Tac). The quantity of unlabeled daclizumab administered is based on studies of ATL patients with circulating malignant cells and elevated soluble CD25 levels. The rationale for administering an unlabeled antibody directed to CD25 (e.g., daclizumab) is that there is an increase in the serum concentration of the released IL-2R alpha (Tac peptide, CD25) in patients with IL-2R alpha expressing malignancies such as HL. The administered unlabeled daclizumab binds to this circulating IL-2R alpha and increases the proportion of the radiolabeled ⁹⁰Y-daclizumab that binds to the CD25 expressing target cell. In those patients it is estimated to yield binding of radiolabeled daclizumab to all circulating CD25-expressing tumor cells and to produce approximately 25 to 75% saturation of the IL-2 receptors in patients with soluble CD25 levels of 2,000 to 10,000 units/mL. These estimates are made on the basis of the observations during the Phase I trial of ⁹⁰Y-murine anti-CD25 (anti-Tac) antibody, where binding was assessed by FACS analysis and by binding to the circulating cells of

¹¹¹In-murine anti-CD25 antibody co-administered with ⁹⁰Y-murine anti-CD25 antibody. The soluble CD25 levels of the majority of patients on this study are expected to be in the above range.

3.2.6 Administration of unlabeled basiliximab

If unlabeled daclizumab is unavailable, 5 mg basiliximab that defines the same epitope of IL-2R alpha can be used in lieu of unlabeled daclizumab.

3.2.7 Days -15, -14, -13 Calcium diethylenetriaminepentaacetate (Ca-DTPA).

Ca-DTPA in normal saline will be administered as a 5 hr intravenous infusion daily for 3 days, starting immediately after ⁹⁰Y-daclizumab is administered. The dose of Ca-DTPA will be 250 mg/m²/day x3. The Ca-DTPA will be supplied by the NIH Pharmacy using commercially available FDA-approved Ca-DTPA.

3.2.8 Mucositis prophylaxis

Keratinocyte Growth Factor (Palifermin/Kepivance™) will be used at the dose of 60 µg/kg starting at day -9 of ASCT (see Sections 4.5 and 10.13 for dose and schedule).

3.2.9 Day -6: Initiation of the BEAM conditioning chemotherapy.

Day -6: BCNU (Carmustine).

Intravenous BCNU will be administered at a dose of 300 mg/m² on day -6 based on adjusted ideal body weight. BCNU will be diluted in 500 mL 5% dextrose and administered IV over 2 hours. Patients will be premedicated with a sedative and anti-emetics according to the BMT Consortium Guidelines (<http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml>).

Days -5, -4, -3, and -2: Cytarabine (cytosine arabinoside, Ara-C).

Cytarabine 200 mg/m² calculated based on adjusted ideal body weight is to be administered every 12 hours on Days -5, -4, -3 and -2 for a total of 8 doses. Cytarabine will be infused in 100 mL 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP, IV over 30 minutes every 12 hours. Anti-emetics should be given according to NIH BMT Consortium guidelines

<http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml>). Daily dose = 400 mg/m² for 4 consecutive days for a total dose = 1600 mg/m².

Days -5, -4, -3, and -2: Etoposide (VP-16).

Intravenous hydration should be continued before, during and after the etoposide. Etoposide 200 mg/m² calculated on adjusted ideal body weight is to be administered daily on Days -5, -4, -3, and -2 for a total of 4 doses. Etoposide injection must be diluted prior to use with either 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP to give a final concentration of 0.2 to 0.4 mg/mL and administered over 2 to 4 hours. A longer duration of administration may be used if the volume of fluid to be infused is a concern.

Appropriate antiemetics should be given according to Consortium guidelines (<http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml>). Two hours before infusion, 25 mg of diphenhydramine HCl and 50 mg of hydrocortisone will be given to prevent allergic reactions. If necessary, diuretics may be given.

Day -1: Melphalan.

Melphalan 140 mg/m² calculated according to adjusted ideal body weight will be administered Day -1. The drug will be diluted in 0.9% NS at a concentration of 0.4 mg/mL and administered at a rate of 5 mg/min will be infused over 30 min.

Hydration during the conditioning regimen (BEAM):

- a) Hydration will be initiated 12 hours prior to BCNU infusion (on Day -7 of the transplant), consisting of 0.9% sodium chloride supplemented with 10 mEq/L potassium chloride (KCl) at an initial rate of 100 mL/hour. For patients with poor oral intake, the rate of hydration may be increased as clinically indicated to meet fluid requirements. Hydration will continue until 24 hours after the last chemotherapy dose has been completed.
- b) During hydration, serum potassium level will be monitored every 12 hours and adjusted accordingly.
- c) During hydration, if urine output is < 1.5 mL/kg/hour or if fluid intake exceeds urine output by greater than 500 mL during an 8-hour period, an additional furosemide 20 mg will be administered.

3.2.10 Day 0: Peripheral Blood Stem Cell Infusion

Hematopoietic progenitor cells obtained from DTM will be thawed and infused according to NIH standard operating guidelines on Day 0 (7 days after initiation of high-dose chemotherapy, i.e., BEAM). They are rapidly brought to physiologic temperature in a 37°C water bath. They are then infused at a rate of 100 mL/hr. Patients should be pre-medicated with diphenhydramine 50 mg PO or IV and acetaminophen 500 mg PO 30 minutes prior to the infusion. Toxicities that can be associated with the reinfusion of autologous progenitor cells include “garlic”-like taste and odor due to dimethylsulfoxide (DMSO), nausea and vomiting, hypotension, fever and hemoglobinuria.

3.2.11 Day +5: filgrastim (G-CSF)

All patients will receive G-CSF 5 µg/kg/day subcutaneously beginning on Day +5 after PBSC are infused and continued daily until ANC > 1000/µL for 3 consecutive days.

3.3 DOSE MODIFICATION FOR TOXICITIES

3.3.1 Phase I management of ⁹⁰Y-daclizumab for non-hematological toxicity

Grade	Occurrence	Immediate Action	Resumption of Therapy
1	Any	None	No interruption
2	Any	Hold therapy until grade \leq 1	<p>1) Continue BEAM chemotherapy and ASCT if toxicity occurred after the second dose of ⁹⁰Y-daclizumab was administered.</p> <p>2) Resume ⁹⁰Y-daclizumab if toxicity occurred after the first dose of ⁹⁰Y-daclizumab was administered.</p>
3 or 4	Any	Discontinue ⁹⁰ Y-daclizumab and hold BEAM chemotherapy/ASCT until grade \leq 1	<p>1) May proceed with BEAM chemotherapy and ASCT if toxicity occurred after the second dose of ⁹⁰Y-daclizumab was administered.</p> <p>2) Do not proceed with second dose of ⁹⁰Y-daclizumab if toxicity occurred after the first dose of ⁹⁰Y-daclizumab was administered but may proceed with BEAM chemotherapy and ASCT once recovered to \leq grade 1</p>

3.3.2 Phase II Dose Modification ⁹⁰Y-daclizumab for non-hematological toxicity

Table 2. Dose modification ⁹⁰Y-daclizumab dose for non-hematological toxicity.

Grade	Occurrence	Immediate Action	Resumption of Therapy
1	Any	None	No interruption
2	Any	Hold therapy until grade ≤ 1	1) Continue BEAM chemotherapy and ASCT if toxicity occurred after the second dose of ⁹⁰ Y-daclizumab was administered. 2) Resume ⁹⁰ Y-daclizumab if toxicity occurred after the first dose of ⁹⁰ Y-daclizumab was administered.
3	Any	Discontinue ⁹⁰ Y-daclizumab and hold BEAM chemotherapy/ ASCT until grade ≤ 1	1) May proceed with BEAM chemotherapy and ASCT if toxicity occurred after the second dose of ⁹⁰ Y-daclizumab was administered. 2) Do not proceed with second dose of ⁹⁰ Y-daclizumab if toxicity occurred after the first dose of ⁹⁰ Y-daclizumab was administered. May proceed with BEAM chemotherapy and ASCT once recovered to \leq grade 1
4	Any	Discontinue ⁹⁰ Y-daclizumab therapy and hold BEAM chemotherapy/ ASCT until grade ≤ 1	1) May continue with BEAM chemotherapy and ASCT once recovered to \leq grade 1

3.3.3 Phase I and Phase II Dose Modification ⁹⁰Y-daclizumab for hematological toxicity:

Table 3. Dose modification ⁹⁰Y-daclizumab for hematological toxicity.

Grade	Occurrence	Immediate Action	Resumption of Therapy
1	Any	None	No interruption
2	1 st Cycle	None	Continue ⁹⁰ Y-daclizumab at protocol specified dose for the second dose of ⁹⁰ Y-daclizumab and may proceed with BEAM chemotherapy/ ASCT as per protocol
	2 nd Cycle	None	Proceed with BEAM chemotherapy/ ASCT as per protocol
3	1 st Cycle	Hold therapy until grade ≤ 1	Then resume 2nd dose of ⁹⁰ Y –daclizumab at protocol specified dose.
	2 nd Cycle	None	Proceed with BEAM chemotherapy/ ASCT as per protocol.
4	1 st Cycle	Hold therapy until grade ≤ 1	Then resume ⁹⁰ Y-daclizumab with 5 mCi decrease in the second dose of ⁹⁰ Y-daclizumab.
	2 nd Cycle	None	Proceed with BEAM chemotherapy/ ASCT

3.3.4 Additional Dose Modifications of ⁹⁰Y-daclizumab:

If grade 3 or greater allergic toxicity occurs, the patient is to discontinue ⁹⁰Y-daclizumab, but may proceed with BEAM chemotherapy and ASCT.

3.4 STOPPING RULES FOR UNACCEPTABLE TOXICITY

3.4.1 Unacceptable toxicity from this treatment will be defined as two or more events of the following occurring in the first 20 patients during the phase II part of the study:

- Failure to achieve neutrophil engraftment by day 21, defined from day 0 (the day when autologous stem cells are infused) as the first of three consecutive days on which the patient’s absolute neutrophil count is greater than $0.5 \times 10^9/L$ following the nadir.
- Failure to achieve platelet engraftment by day 28, defined from day 0 (the day when autologous stem cells are infused) as the first of seven consecutive days on which the patient’s unsupported platelet count is greater than $20 \times 10^9/L$ following the nadir.
- Development of MDS in over 3 of the first 13 patients in phase II of the study.

3.4.2 Unacceptably high transplant related mortality (TRM) will be defined as:

- TRM in 2 or more of the first 20 patients during the first one hundred days following transplant;
- TRM during the first one hundred days following transplant is greater than 15%, at any point beyond the first 20 patients

3.5 MONITORING DURING THERAPY

- 3.5.1 Weekly evaluation starting 1 week prior to administration of ⁹⁰Y-daclizumab and continuing until administration of either second dose of ⁹⁰Y-daclizumab, or administration of BEAM preparative regimen to include:
- History, physical examination, vital signs, and performance status
 - CBC with differential, platelet count, reticulocyte count
 - Coagulation studies: PT, PTT, fibrinogen
 - Acute Care, Mineral and Hepatic panels, LDH, uric acid, total protein, CK and zinc.
- 3.5.2 Evaluation starting with administration of BEAM preparative regimen and continuing until ANC > 1000/μL for 3 consecutive days following infusion of autologous stem cells:
- Once daily: History, physical examination, vital signs and performance status
 - Twice daily: CBC with differential and platelet count
 - Twice daily: Acute Care, Mineral and Hepatic panels, LDH, uric acid, total protein and CK
- 3.5.3 When ANC > 1000/μL for 3 days: At a minimum of every week for 4 weeks, then at a minimum of every 2 weeks x 2.
- History, physical examination, vital signs and performance status
 - CBC with differential and platelet count
 - Acute Care, Mineral and Hepatic panels, LDH, uric acid, total protein, CK and zinc
 - Weekly CMV antigenemia, if CMV serology positive at baseline
- 3.5.4 Serum soluble IL-2R alpha days -56 and -15 and every 4 weeks after -15 till day 100
- 3.5.5 Collection of blood for radioimmunotherapy (i.e., ⁹⁰Y-daclizumab):
- 3.5.5.1 7 mL of blood in a green-top tube and 4 mL of blood in an SST tube will be drawn prior to administration of ⁹⁰Y-daclizumab. Similar volumes will be drawn at midpoint of infusions if deemed necessary by principal investigator.
- 3.5.5.2 Furthermore 8 mL of blood will be divided into a green-top tube and a tiger-top tube at the following time points after the infusion of ⁹⁰Y-daclizumab:
- ½ hour,
 - 1 hour,
 - 2 hours,
 - 6 hours,
 - 12 hours,
 - 24 hours and
 - daily up to 7 days following infusion of ⁹⁰Y-daclizumab.
- 3.5.6 Collection of blood to assess for antibodies to daclizumab:
- 3.5.6.1 Human antibody to daclizumab (HAHA) must be assessed prior to the first and second infusion of ⁹⁰Y-daclizumab and must be deemed negative for infusion and day -15.
- 3.5.6.2 Between days -35 and -21, **Collect two 4 ml or one 8 mL SST** and send sample to Dr. William Kopp/Ms. Helen Rager at NCI/OD, Clinical Support Laboratory 560/11-

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27, Building 1050, Boyles Street, Frederick, Maryland 21702, telephone number: 301-846-1707 or 301-846-1917.

- 3.5.7 To evaluate effect of ⁹⁰Y-daclizuamb administered on day -56, perform CT scan of C/A/P/neck and FDG- PET (torso) scan at the following time points:
- baseline and
 - post therapy at day 100 ± 7 days post-transplant
- 3.5.8 SPECT/CT scans will be performed using SPECT/CT on days -56 and -15 to assess RIT organ distribution, uptake and clearance.
- 3.5.9 Response evaluations will be performed on the patients at day 100 ± 7 days following infusion of autologous stem cells:
- History, physical examination, vitals and performance status
 - CBC with differential, platelet count and reticulocyte count
 - Acute Care, Mineral and Hepatic panels, LDH, uric acid, total protein and CK
 - Serum soluble IL-2R alpha
 - Urinalysis
 - Tumor Assessment with CT of chest/abdomen/pelvis (C/A/P) and ¹⁸F¹⁸FDG-PET-scan
 - Bone marrow biopsy to assess for abnormal cytogenetics
 - Pulmonary function tests
 - EKG
 - Echocardiogram or MUGA

3.6 FOLLOW-UP AFTER THE COMPLETION OF THERAPY

After Day 100, patients will be followed at 4, 6, 9, 12, 16, 20, 24 (± 14 days) months after the end of treatment. During the 3rd, 4th and 5th year, patients will be followed every 6 months (± 28 days) and yearly thereafter for regular physical and laboratory examinations. :

- 3.6.1.1 History, physical examination, vital signs and performance status
- 3.6.1.2 CBC with differential
- 3.6.1.3 Acute Care, Mineral and Hepatic panels, LDH, uric acid, total protein and CK
- 3.6.1.4 Serum soluble IL-2R alpha
- 3.6.1.5 Urinalysis
- 3.6.1.6 Tumor assessment with CT chest/abdomen/pelvis/neck and FDG-PET will be performed at the follow-up visits that occur 6, 12, 16 and 24 months after the end of treatment, then as clinically indicated
- 3.6.1.7 Pulmonary function tests should be repeated at the follow-up visit that occurs 12 months after the end of treatment

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3.7 STUDY CALENDAR

Except for chemotherapy and stem cell reinfusion, all time points can be obtained within ±5 days (unless otherwise indicated) of scheduled measurement to allow for holidays, travel and other events.

Table 4 Study Calendar

Procedure	Screening Eligibility	Baseline	Week -12,		Week -9	D -56 ¹	Week -6		D-15	D -6 to D-1	Day 0 ³	D +5 until ANC > 1000 ⁴	Day 100 ± 7 days	Post Therapy ⁵ Follow up
			D-84 to -80	D -79 (-78)			Days -42 to -38	Day -37 (-36)						
Study Drug Administration/Procedures														
G-CSF.			X	X			X	X						
Plerixafor, Apheresis				X				X						
Administration of unlabeled, ⁹⁰ Y and ¹¹¹ In daclizumab ²						X			X					
Ca ²⁺ DTPA						X ^a			X ^a					
BEAM										X ^b				
ASCT											X			
Clinical Assessments														
History and PE ^d	X					X	X ^f	-----					X	X ^f
Vitals	X					X		X	X	X	X	X	X	X
Performance Status	X					X		X	X	X	X	X	X	X
EKG		X											X	
Echocardiogram or MUGA	X												X	
Pulmonary Function Tests	X												X	
Laboratory Assessments														
CBC with differential	X	X				X ^e	-----					X	X ^e	
Reticulocyte Count		X				X			X			X	X	
PT, PTT, Fibrinogen		X				X ^e	-----					X		
Acute Care, Mineral and Hepatic panels	X ^c	X				X ^e	-----					X	X ^e	
LDH, uric acid, total protein, CK		X				X ^e	-----					X	X ^e	
Total cholesterol and triglycerides		X					-----							
Zinc		X				X ^g			X ^g					
Quantitative Immunoglobulins		X					-----							
HBV & HCV serologies	X						-----							
HIV ELISA	X						-----							
CMV Serology, Antigenemia ^h		X ^h					-----							

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Procedure	Screening Eligibility	Baseline	Week -12,		Week -9	D -56 ^l	Week -6		D-15	D -6 to D-1	Day 0 ³	D +5 until ANC > 1000 ⁴	Day 100 ± 7 days	Post Therapy ⁵ Follow up	
			D-84 to -80	D -79 (-78)			Days -42 to -38	Day -37 (-36)							
Green Top Tube for RIT ⁱ						X			X						
Serum Soluble IL2R ^{j,1}	X					X	-----							X	X
Ab to daclizumab ^{k,1}	X					X			X						
UA ^m		X				X ⁿ			X ^m				X	X	
Serum β-HCG	X	X													
Bone Marrow Biopsy ⁿ	X ⁿ												X ⁿ		
Lymph Node Biopsy ^o	X														
Radiologic Procedures^{p,q}															
CT scan C/A/P and neck	X												X	X	
FDG-PET Scan		X											X	X	
SPECT/CT						X			X						
Response Assessments													X	X	
Concomitant Medications						X	-----							X	

Footnotes:

1 - D-56: Week 1, Day 1.

2 - RIT: radioimmunotherapy (i.e., ⁹⁰Y-daclizumab.)

3- Day -4: 4 days prior to infusion of stem cells; day 0 is the day of infusion of stem cells.

4- ANC must be > 1000/μl on 3 consecutive days.

5- Post Therapy: After Day 100± 7 days, patients will be followed at 4, 6, 9, 12, 16, 20, 24 (± 14 days) months after the end of treatment. During the 3rd, 4th and 5th year, patients will be followed every 6 months (± 28 days) and yearly thereafter for regular physical and laboratory examinations.

a. CaDTPA is to be administered for three consecutive days starting on the day of radiolabeled antibody infusion.

b. The components of BEAM will be administered as follows: carmustine on day -6; etoposide and cytarabine on days -5 to -2; melphalan on day -1.

c. Creatinine clearance to be performed if serum creatinine ≥2.0 mg/dL.

d. History, physical exam, vital signs and performance status assessed weekly from day -63+/-3days until second dose of daclizumab or administration of BEAM regimen. Daily following BEAM until ANC >1000/μl.

e. To be assessed weekly from week -9 to day -6; assessed BID day -6 through ANC recovery and as indicated in post-therapy follow-up.

f. To be assessed daily from day -6 through ANC recovery and as indicated post-therapy follow up.

g. Serum zinc levels: For three days following infusion of CaDTPA.h. If CMV serology positive, CMV antigenemia will be obtained weekly until Day 100; then as clinically indicated.

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- i. *Green-top tube for RIT: For analysis in nuclear medicine, 7 mL of blood in a green-top tube and 4 mL of blood in an SST tube will be drawn prior to administration of ⁹⁰Y-daclizumab. Similar volumes will be drawn at the midpoint of the infusion and at the completion of the infusion if deemed necessary by the PI. Furthermore, 8 mL of blood will be divided into a green-top tube and a tiger-top tube at ½ hour, 1 hr, 2 hr, 6 hr, 12 hr, 1 day, and daily up to 7 days following infusion of ⁹⁰Y-daclizumab.*
- j. *Serum soluble IL-2R alpha to be tested on days -56 and -15, and then every 4 weeks till day 100 and at every follow-up visit. **Collect two 4 ml SST and send sample to Dr. William Kopp/Ms. Helen Rager at NCI/OD, Clinical Support Laboratory.***
- k. *Antibodies to daclizumab: Human anti-human antibody (HAHA) responses must be assessed prior to the first and second infusion of ⁹⁰Y-daclizumab and must be deemed negative for infusion on day -15; draw between days -35 to -21. **Collect two 4 ml or one 8 ml SST and send sample to Dr. William Kopp/Ms. Helen Rager at NCI/OD, Clinical Support Laboratory.***
- l. *When Serum soluble IL-2R alpha and Antibodies to daclizumab samples are drawn at same time, they may be drawn in the same tube.*
- m. *UA: Collected into separate bottles labeled with date and time for radioactivity counting in the Nuclear Medicine Department, Clinical Center, at 0-2 hr, 2-24 hr, 24-48 hr, 48-72 hr, and 72-96 hr.*
- n. *Bone- marrow biopsy and aspirate with cytogenetics: Unilateral aspirate and biopsy will be performed pretreatment to rule out abnormal cytogenetics and post-treatment at day 100.*
- o. *Lymph node biopsy: Lymph node biopsy will be performed pre-treatment to establish CD25 positivity if necessary.*
- p. *SPECT/CT: Scans will be performed using SPECT-CT to assess RIT organ distribution, uptake, and clearance.*
- q. *Tumor assessment with CT chest/abdomen/pelvis/neck and FDG-PET will be performed at the follow-up visits that occur 6, 12, 16 and 24 months after the end of treatment.*

3.8 CONCURRENT THERAPIES

With the exception of drugs that would exclude the patient from the protocol (e.g., other investigational antineoplastic drugs, or chemotherapy), patients can take other medications as indicated. All medications, their dose and frequency, as well as the start and stop dates are to be recorded.

3.9 SURGICAL GUIDELINES

3.9.1 Bone-Marrow Aspirate and Biopsy.

Bone-marrow examination is required prior to study enrollment to assess for the presence of HL and its extent CD25 expression, myelodysplastic changes or cytogenetic abnormalities. A second bone-marrow biopsy will be performed at day 100 ± 7 days following the infusion of autologous stem cells. In addition, bone-marrow aspirate and biopsy will be performed yearly for 5 years. Any other bone-marrow aspirate and biopsy will be obtained as clinically indicated during the course of the patient's treatment.

3.9.2 Lymph Node and Tumor Biopsies:

A lymph node or tumor biopsy will be obtained for diagnostic purposes and to determine the expression of CD25 antigen. A separate consent will be obtained for this procedure.

3.10 RADIATION THERAPY GUIDELINES:

No external radiation therapy is planned as part of this protocol.

3.11 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF-STUDY CRITERIA:

3.11.1 Patients will be removed from protocol therapy for any of the following:

- Progression of disease
- Unacceptable toxicity as defined in Section 3.4
- If chelated daclizumab becomes unavailable
- If judged by the Principal Investigator to be in the best interest of the patient
- See 3.1.4 Dose-Limiting Toxicity
- Patient requests to be withdrawn from active therapy
- Patients that have evidence of rapidly progressive symptomatic disease requiring urgent salvage treatment after their stem cell mobilization and harvest will have their stem cells stored and receive the appropriate therapy to achieve disease control. These patients may be re-consented and allowed to re-enter the protocol treatment without having to undergo another stem cell mobilization/harvest.

3.11.2 Off Study Criteria

- Patient noncompliance or refusal to continue with the study
- Patient withdraws consent to continue participation in study
- Inadequate harvest of stem cells- less than 2 x 10⁶ CD34+ stem cells/kg obtained after 2 attempts 3 weeks apart to mobilize stem cells
- Unrelated medical illness or complications that unacceptably increase the risks of participation in this trial
- Death

3.11.3 Off Protocol Therapy and Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the website (<http://home.ccr.cancer.gov/intra/eligibility/welcome.htm>) main page must be completed and sent via encrypted email to: NCI Central Registration Office at ncicentralregistration-1@mail.nih.gov.

4 SUPPORTIVE CARE

4.1 BLOOD COMPONENT SUPPORT

Platelets and red blood cell (RBC) support will be given as medically indicated with the general guideline to maintain a hemoglobin > 8.0 g/dl and to maintain the platelet count at a level of at least 10,000/ μ l (unless there is evidence of significant bleeding in which case a platelet count of 50,000/ μ l will be maintained). Final decision of the necessity of transfusion will remain in the hands of the treating team. All administered blood products will be irradiated and depleted of leukocytes.

4.2 G-CSF (FILGRASTIM) SUPPORT

G-CSF, in the commercially available form, will be administered subcutaneously at a dose of 5 μ g/kg daily to patients whose neutrophil count falls below 500/ μ l following treatment with ⁹⁰Y-daclizumab and continued until the neutrophil count exceeds 5,000/ μ L. G-CSF may be continued until the neutrophil count exceeds 1,000/ μ L for 3 consecutive days after ASCT. Patients will be instructed regarding the self-administration of G-CSF if being discharged from the hospital. G-CSF will be obtained from the Clinical Center Pharmacy.

4.3 ANTIBIOTIC THERAPY

Antibiotic therapy for neutropenic patients will be managed in accordance with NIH BMT Consortium guidelines. <http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml>)

4.4 ANTIEMETICS

Adequate antiemetics should be given as outlined in the NIH BMT Consortium guidelines. <http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml>)

4.5 MANAGEMENT OF MUCOSITIS

All patients with severe mucositis should receive adequate hydration and pain control using continuous intravenous narcotics or patient controlled analgesia (PCA). Additional nutritional support should be considered in the event of prolonged inability to acquire adequate nutrition by the oral route. Mouth care consistent with established NCI guidelines should be instituted in all patients 24 hours prior to high-dose chemotherapy. The suggested regimen is described below:

Sodium bicarbonate mouth rinse: (1 teaspoonful powder per 500 mL) 15 mL swish for 30-60 seconds and spit, daily at 8 am, noon, 4 pm, 8 pm, and midnight. The solution is to be prepared on the unit every other day. Patients may rinse their mouths at night if they awaken. Patients should rinse their mouth after the bicarbonate rinse with water to avoid inactivating chlorhexidine.

Biotene mouthwash: 15 mL swishes for 30-60 second swish and spit q 2 hrs while awake. This medication, when used as directed, binds to mucosal tissues to provide a prolonged effect. Do not leave at the bedside to be used as a "prn" medication.

Sucralfate suspension: Use only AFTER establishment of mucositis. Sucralfate suspension MUST be used last as it will block the effect of the other medications above. 15-30 mL are swished in mouth for 15-30 seconds and then remainder swallowed three times a day. Additional doses may be given; up to six total doses in a 24 hr. period.

4.6 MUCOSITIS PROPHYLAXIS

Keratinocyte Growth Factor (Palifermin/Kepivance™) will be used at the dose of 60 µg/kg iv push as follows:

- 4.6.1 daily for three days starting day -9 pre-ASCT (i.e., days -9, -8 and -7)
- 4.6.2 then for three additional daily doses on days +1, +2 and +3 of ASCT
- 4.6.3 Palifermin should not be used during or within 24 hours preceding or following myelotoxic therapy administration

4.7 PCP PROPHYLAXIS

All patients will receive prophylaxis against *Pneumocystis jiroveci (carinii)* pneumonia, beginning with the first dose of ⁹⁰Y-daclizumab, continuing until the preparative regimen is to be administered prior to transplantation (Day -6), and resuming at the time of platelet recovery (> 50,000) following the infusion of autologous stem cells. All patients will receive empiric treatment with one trimethoprim/sulfamethoxazole (TMP/SMX) DS tablet twice daily, three times per week unless they are allergic to this medication. If the patient is allergic to trimethoprim or sulfamethoxazole, alternatives include dapsone (100 mg daily), atovaquone (750 mg twice daily) or inhaled pentamidine through day 100 and/or until CD4 count is confirmed to be > 200/mL.

4.8 FUNGAL PROPHYLAXIS

All patients will receive fluconazole (100 mg) prophylaxis against *Candida* infections, beginning with the first dose of ⁹⁰Y-daclizumab, continuing until the preparative regimen is to be administered prior to transplantation (Day -6), and then resuming after transplantation for a minimum of 3 months unless clinical contraindication develops.

4.9 HERPES SIMPLEX AND VZV PROPHYLAXIS

All patients will receive acyclovir or valacyclovir for prophylaxis against herpes simplex virus and varicella zoster virus infection/reactivation. This therapy will start with the first dose of ⁹⁰Y-daclizumab, and continue through transplantation, for a minimum of 3 months unless clinical contraindication develops.

4.10 CMV PROPHYLAXIS

Patients with positive pre-transplant serology for cytomegalovirus (CMV) will be monitored for CMV reactivation by weekly testing for CMV PCR. CMV reactivation will be managed according to NIH BMT Consortium guidelines. <http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml>

5 BIOSPECIMEN COLLECTION

5.1 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples

will not be sent outside NIH without IRB notification and an executed MTA.

The Clinical Support Laboratory, Leidos Biomedical Research, Inc -Frederick, processes and cryopreserves samples in support of IRB-approved, NCI clinical trials. The laboratory is located in a controlled access building and laboratory doors are kept locked at all times. Upon specimen receipt each sample is assigned a unique, sequential laboratory accession ID number. All products generated by the laboratory that will be stored either in the laboratory freezers or at a central repository facility are identified by this accession ID. An electronic database is used to store information related to patient samples processed by the laboratory. Vial labels do not contain any personal identifier information. Samples are stored inventoried in locked laboratory freezers and are routinely transferred to the NCI-Frederick repository facilities for long-term storage. These facilities are operated under subcontract to Leidos Biomedical Research, Inc.-Frederick. Access to stored clinical samples is restricted. Investigators establish sample collections under “Source Codes” and the investigator responsible for the collections, typically the protocol Principal Investigator, specifies who has access to the collection.

When requests are submitted by the NCI investigator for shipment of samples outside of the NIH it is the policy of the laboratory to request documentation that a Material Transfer Agreement is in place that covers the specimen transfer. The laboratory does not provide patient identifier information as part of the transfer process but may, at the discretion of the NCI investigator, group samples from individual patients when that is critical to the testing process. The NCI investigator responsible for the sample collection is responsible for ensuring appropriate IRB approvals are in place and that a Material Transfer Agreement has been executed prior to requesting the laboratory to ship samples outside of the NIH.

Blood and tissue specimens collected in the course of this research project may be banked and used in the future to investigate new scientific questions related to this study. However, this research may only be done if the risks of the new questions were covered in the consent document and the proposed research has undergone prospective IRB review and approval. If new risks are associated with the research (e.g. analysis of germ line genetic mutations...) the principal investigator must amend the protocol and obtain informed consent from all research subjects.

Once primary research objectives for the protocol are achieved, intramural researchers can request access to remaining samples providing they have an IRB approved protocol and patient consent. Any loss or unintentional destruction of samples or data will be reported to the NCI IRB.

The P.I. will report any loss or destruction of samples to the IRB.

Serum samples for IL-2R alpha and for detection of antibodies to daclizumab will be sent to Dr. William Kopp/Ms. Helen Rager at NCI/OD, Clinical Support Laboratory 560/11-27, Building 1050, Boyles Street, Frederick, MD 21702, TEL: +1-301-846-1707 or +1-301-846-1917. The primary contact for courier scheduling is Ms. Jennifer Bangh, telephone number +1-301-846-5893 or at E-mail address banghj@mail.nih.gov.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist

with the data management efforts. All human subjects personally identifiable information (PII) as defined in accordance to the Health Insurance Portability and Accountability Act, eligibility and consent verification will be recorded. Primary data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for at least 30 days after removal from study treatment or until off-study, whichever comes first.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

End of study procedures: Data will be stored according to HHS and FDA regulations as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

6.1.1 Recording of Grade 3 and 4 BEAM Related Toxicity

Toxicity such as profound pancytopenia is expected to occur in every instance the BEAM preparative regimen is administered and this toxicity is well accepted as part of the standard of care during ASCT.

- Grade 3 and 4 toxicity that will not be reported:
 - Toxicity occurring within 24 hours of the stem cell infusion deemed attributable to the infusion.
 - Hematologic toxicity, unless it constitutes a dose limiting toxicity as defined in Section **3.1.4**:
 - Failure to achieve neutrophil engraftment by day 21 post ASCT
 - Failure to achieve platelet engraftment by day 28 post ASCT
 - Grade 3 and 4 toxicity which is a direct consequence of an expected toxicity of the BEAM preparative regimen:
 - Pancytopenia (e.g. fever, infections),
 - Nausea, vomiting, diarrhea (e.g. dehydration or electrolytes imbalance)
 - Mucositis (pain requiring narcotics and / or parenteral nutrition).
 - Transient altered mental status at the time of BCNU administration

- Signs and symptoms consistent with Cytarabine (Ara-C) Syndrome as described in Section **10.9.3.3**.
- The decision of relatedness to expected toxicity during ASCT will be made PI or delegate based on their clinical judgment and expertise in the field of transplantation. As examples, the following events would not be reported as they represent complications of a well-known and expected toxicity during ASCT:
 - Systemic infection with septic shock during the initial period of pancytopenia
 - Acute respiratory distress syndrome (possibly requiring mechanical ventilation) and renal failure (possibly requiring hemodialysis) secondary to septic shock during the initial period of neutropenia. Nausea, vomiting, diarrhea and mucositis of any grade as well as electrolyte and secondary other biochemical abnormalities.
- Grade 3 or 4 toxicity that will be reported
 - Grade 3 or 4 infections with septic shock occurring several weeks after initial marrow engraftment will be reported.
 - Any grade 3 or 4 acute liver toxicity (although possibly related to the preparative regimen) will be reported.
 - Any grade 3 or 4 toxicity occurring after recovery from and not the consequence of the initial preparative regimen toxicity.

6.1.2 ⁹⁰Y-daclizumab Related Toxicity That Will Not Be Reported:

- Grade 3 and 4 hematologic toxicity including thrombocytopenia, lymphocytopenia, neutropenia and anemia is expected in the 4 to 7-week period following Y⁹⁰-daclizumab therapy and will not be reported.

6.2 RESPONSE ASSESSMENTS

Response assessments will be performed at day -15 and 100 days (\pm 7 days) post-ASCT and subsequent post ASCT follow up visits. Response assessment will be based on the definitions recently published by Cheson BD et al, in the Revised Response Criteria for Malignant Lymphoma [40]. Cervical, thoracic, abdominal, and pelvic CT-scans are recommended if those nodal areas are involved. A bone-marrow aspirate and biopsy should only be performed to confirm CR if initially positive or if clinically indicated by new abnormalities in the peripheral blood count or blood smear. ¹⁸FDG-PET will also be used for assessment of response.

6.2.1 Complete Response

The designation of a complete response (CR) requires all of the following: **(1)** Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy; **(2)** A post-treatment residual mass is permitted as long as it is PET negative. If a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size ($<$ 1.5 cm in their greatest transverse diameter for nodes $>$ 1.5 cm before therapy); **(3)** Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to $<$ 1.0 cm in their short axis after treatment; **(4)** The spleen and/or liver if considered enlarged before therapy based on a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and **(5)** If the bone marrow was involved by lymphoma before treatment the infiltrate must have cleared on repeat bone-marrow biopsy.

6.2.2 Partial Response

The designation of a partial response (PR) requires all of the following: **(1)** At least a 50% reduction in the sum of the product of the diameters of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least two perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved; **(2)** No increase in the size of other nodes, liver, or spleen; **(3)** Splenic and hepatic nodules must regress by >50% in their SPD or for single nodules in the greatest transverse diameter; **(4)** With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present. Bone-marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. Patients who achieve a CR by the above criteria but who have persistent morphologic bone-marrow involvement will be considered partial responders; **(5)** No new sites of disease; **(6)** If the pretreatment PET scan was positive, the post-treatment PET should be positive in at least one previously involved site; and **(7)** If a pretreatment PET was negative, CT criteria should be used.

6.2.3 Stable Disease

A patient is considered to have stable disease (SD) when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease. The PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET. If the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

6.2.4 Progressive Disease

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0 cm. Lymph nodes < 1.0 X < 1.0 cm will not be considered as abnormal for relapse or progressive disease. Other criteria for progressive disease include the following: **(1)** Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. **(2)** At least a 50% increase from nadir in the sum of the products of the diameters of any previously involved nodes, or in a single involved node, or the size of other lesions. A lymph node with a diameter of the short axis of less than 1.0 cm must increase by >50% and to a size of 1.5 X 1.5 cm or more than 1.5 cm in the long axis. **(3)** At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis; **(4)** Lesions should be PET positive if the lesion was PET positive before therapy unless the lesion is too small to be detected by PET; **(5)** Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical exam, it is found to be histologically negative.

6.2.5 Progression Free Survival

PFS is defined as the time from the date of registration to the date of first observation of progressive disease or death due to any cause. If none of these occur the patient will be censored at the last documented information.

6.2.6 Overall Survival

This is defined as the time from the date of registration to the date of death due to any cause or if no death occurs to the last documented information on the patient.

6.3 TOXICITY CRITERIA

Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Event version 4.0. A copy of CTC version 4.0 can be downloaded from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 ADVERSE EVENT DEFINITIONS

7.1.1 Adverse Event

An adverse event is defined as any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom or disease, temporarily associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

7.1.2 Suspected Adverse Reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected Adverse Reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.8 Protocol Deviation (NIH definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
 - (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
 - (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NCI-IRB AND CLINICAL DIRECTOR REPORTING

7.2.1 NCI-IRB Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
 - All Grade 2 unexpected events that are possibly, probably or definitely related to the research;
 - All Grade 3 and 4 events that are possibly, probably or definitely related to the research except as excluded in Section **6.1.2**
 - All Grade 5 events regardless of attribution;
 - All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

7.3 IND SPONSOR REPORTING CRITERIA

During the first 30 days after the subject receives investigational agent/intervention, the investigator must **immediately** report to the sponsor, using the mandatory MedWatch form 3500a, any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. For serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention, only report those that have an attribution of at least possibly related to the agent/intervention.

Required timing for reporting per the above guideline:

- Deaths (except death due to progressive disease) must be reported via email within 24 hours. A complete report must be submitted within one business day.
- Other serious adverse events as well as deaths due to progressive disease must be reported within one business day

Events will be submitted to the Center for Cancer Research (CCR) at: CCRsafety@mail.nih.gov and to the CCR PI and study coordinator.

7.4 DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure

safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

As information is gathered from this trial, clinical results will be shared with the patients.

7.4.2 Sponsor Monitoring Plan

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary study endpoints; adherence to the protocol, regulations, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

8 STATISTICAL CONSIDERATIONS

The primary objectives of this study are to determine the maximum tolerated dose of ⁹⁰Y-daclizumab in combination with BEAM chemotherapy and autologous transplant in patients with refractory/relapsed Hodgkin's lymphoma, and to determine the safety of this combination in a moderately large group of patients. Safety will primarily be evaluated in terms of determining if the combination of treatments at the MTD is associated with a sufficiently high fraction of patients who are able to avoid MDS. Obtaining an acceptably low rate of engraftment failure as well as of Transplant Related Mortality at day 100 are also of great importance. Evaluation of clinical outcomes, such as overall response rate, complete response rate, DFS and OS are also of interest as secondary endpoints.

The study will initially have a Phase I dose escalation portion that uses a standard 3 + 3 design. Thus, with a maximum of 7 dose levels of ⁹⁰Y-daclizumab to be explored, the maximum number of patients to be evaluated in the Phase I portion of the trial is 42. Once the MTD has been determined, the trial will plan to enroll subsequent patients using an optimal two-stage phase II trial design, which will be focused on estimating the ability to avoid MDS development and cytogenetic abnormalities. Currently, the fraction of patients with MDS on other studies is approximately 10%. It would be desirable if the rate of developing MDS on this trial were approximately the same or not much worse than 10%. Since it can take years for MDS to materialize, development of MDS (which may include the development of isolated cytogenetic abnormality associated with it, based on the expert judgment of the NCI Laboratory of Pathology pathologists) must be considered a negative outcome and all events pertaining to a putative diagnosis of MDS will be considered in determining whether the trial may continue past the first

stage of accrual. The study will be conducted in order to rule out an unacceptably low 75% proportion avoiding MDS ($p_0=0.75$) in favor of a higher MDS avoidance rate of 90% ($p_1=0.90$). With $\alpha=0.05$ (probability of accepting a poor treatment=0.05) and $\beta=0.20$ (probability of rejecting a good treatment=0.20), the first stage of the phase II trial will initially enroll 13 evaluable patients and if 0 to 10 of the 13 avoid MDS then no further patients will be accrued. If 11 or more of the first 13 avoid both issues initially, then accrual would continue until a total of 48 patients have been enrolled. As it may take several weeks to determine if a patient has a cytogenetic abnormality that would be a precursor to MDS, and much longer for actual MDS to develop, a temporary pause of 3 months time for the 13 patients in the accrual to the trial may be necessary to ensure that enrollment to the second stage is warranted. If there are 11-40 of the 48 patients who avoid MDS this would be an unacceptably low rate of avoiding MDS while if there were 41 or more of 48 patients who do not have either problem, then this would be sufficiently interesting to warrant further study. Under the null hypothesis (75% avoidance of MDS rate), the probability of early termination is 67%.

In addition, the rate of engraftment will be evaluated, and an early stopping rule on the basis of this endpoint will also be incorporated in the trial. The first 20 patients in the phase II portion of the trial will be evaluated with respect to the number which fails to engraft. If there are 2 or more patients who fail to engraft in the initial 20 patients, the probability of this occurring would be 12.0% if the true rate of engraftment failure were 3% and it would be 82.4% if the true rate of engraftment failure were 15%. Thus, if there are 2 or more patients who fail to engraft in the first 20 patients, this is more likely to be consistent with an unacceptably high rate of engraftment failure such as 15% than a potentially reasonable rate of engraftment failure, and the trial would stop under these circumstances. If engraftment failure does not stop accrual prior to 20 patients, future patients will continue to be monitored for engraftment failure, and if at any point beyond the first 20 patients, greater than 10% are cumulatively noted to fail to engraft, the study will no longer accrue further patients unless a revision to the design is approved.

The one-hundred day Transplant Related Mortality (TRM) will be evaluated as well in an early stopping rule. The first 20 patients in the phase II portion of the trial will be evaluated with respect to TRM. If there are 2 or more patients who die during the first one hundred days following transplant in the initial 20 patients, the probability of this occurring would be 12.0% if the true rate of TRM were 3% and it would be 82.4% if the true rate of TRM were 15%. Thus, if there are 2 or more patients who die during the first one hundred days following transplant in the first 20 patients, this is more likely to be consistent with an unacceptably high TRM such as 15% than a potentially reasonable TRM, and the trial would stop under these circumstances. If TRM does not stop accrual prior to 20 patients, future patients will continue to be monitored for TRM, and if at any point beyond the first 20 patients, TRM is greater than 15%, the study will no longer accrue further patients unless a revision to the design is approved.

Clinical outcomes such as overall response rate, complete response rate, DFS and OS will also be evaluated and reported as secondary outcomes. Because the study may enroll a heterogeneous population with respect to risk categories, following completion of the trials, patients will be evaluated on the basis of their underlying risk category as well as overall, and results will be reported accordingly. Since the historical comparison for response rates is not clearly determined for this population, there will not be any formal two-stage stopping rule on the basis of clinical response.

In order to complete the initial single arm phase I portion of this trial, up to 42 evaluable patients

may be required and up to 48 in the phase II portion based on safety. Up to 6 patients who are enrolled at the MTD may be included in the first stage of the phase II portion of the trial if they are fully eligible for this portion of the trial. Thus, up to 84-90 patients may be required. It is anticipated that up to 1-2 patients per month may be enrolled onto this trial, and thus approximately 4-6 years may be required to enroll up to 90 evaluable patients. To allow for the possibility of a small number of inevaluable patients, the accrual ceiling for the trial will be set at 95.

9 HUMAN SUBJECTS PROTECTIONS

9.1 RATIONALE FOR SUBJECT SELECTION

CD25 is expressed on the malignant cells of patients with Hodgkin's lymphoma and the non-malignant infiltrating lymphocytes found in Hodgkin's tumors. Antibodies to CD25 can be used to target radioimmunotherapy to the sites of tumor and have demonstrated antitumor activity in animal models and in patients with cancer. In a Phase II trial, we treated 30 patients with CD25-expressing recurrent or refractory HL with single agent ⁹⁰Y-labeled daclizumab. Twelve of these patients achieved a complete response and 7 a partial response for an overall response rate of 63.3%; however, despite this high response rate in a group of refractory and heavily pretreated HL patients including ones that had failed to respond or relapsed after autologous and allogeneic stem cell transplants, the median response duration was a disappointing 129 days (range, 28 to 720 days).

The current standard of care for patients with relapsed or refractory Hodgkin lymphoma is, however, autologous stem cell transplant. Although between 30% and 65% of patients will achieve long-term disease free survival with high-dose chemotherapy followed by ASCT, a significant proportion of these patients will develop recurrent disease after transplantation. We are, therefore, attempting to improve long-term disease free survival by using the combination of radioimmunotherapy and ASCT. Patients with refractory and relapsed HL except nodular lymphocyte predominant HL that have at least 10% of the cells from the lymph node or extranodal site reactive with anti-CD25 will be eligible in the study. Patients will be recruited from those referred to the NCI.

9.2 RESEARCH ETHICS

The investigational nature and objectives of this trial, the procedures and treatments involved and their attendant risks and discomforts, potential benefits, and potential alternative therapies will be carefully explained to the patient and a signed informed consent document will be obtained. No imbalance of ethnic, racial or sex ratios are expected in the accrual to this trial other than that which may naturally be observed in patients diagnosed with Hodgkin's lymphoma.

9.3 PARTICIPATION OF CHILDREN

Children will not be permitted to participate in this study due to the increased risk from radiation exposure in children and until the safety and efficacy of this treatment has been demonstrated in adults.

9.4 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary as well as ongoing follow-up after the completion of treatment, and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation, including long-term follow-up for disease status and outcomes (Section 9.6), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the “NIH Advance Directive for Health Care and Medical Research Participation” form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MAS Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

9.5 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The potential benefits to the subject are that the patient may undergo a partial or complete remission. Radioimmunoconjugates directed against CD25 have antitumor activity against CD25 positive malignancies in animal models, and specifically, remissions have been observed in patients with Hodgkin’s lymphoma. Patients entered on the study will need to be hospitalized in order to receive both the antibody treatment and the autologous stem cells. They will remain in the hospital until they recover their blood counts. They will have to undergo bone-marrow biopsy after therapy to determine to assure engraftment of the infused autologous stem cells.

Patients treated with ⁹⁰Y-labeled daclizumab may experience side effects associated with infusions of monoclonal antibodies, but the major side effect of treatment is bone-marrow suppression, especially thrombocytopenia and neutropenia. There is the possibility of life-long transfusion dependence, life-threatening infections when the blood counts are low, the development of myelodysplasia, secondary leukemias, and even death due to treatment. We hope to minimize the possibility of life-long transfusion dependence by reinfusing the patient’s autologous stem cells following treatment with the ⁹⁰Y-labeled daclizumab and high-dose chemotherapy with BCNU, etoposide, cytarabine and melphalan. We hope to minimize hospitalizations associated with life-threatening infections and low blood counts by using granulocyte-colony stimulating growth factor (G-CSF, filgrastim) to raise the white blood cell count.

The amount of whole body radiation received in this study is 200 rad, with the most exposed organs, the liver, red bone marrow and bone surfaces receiving 1600 rad, 1000 rad and 710 rad respectively. The amount of radiation received in this study exceeds the dose guideline established by the NIH Radiation Safety Committee for research subjects (this radiation is therapeutic so it is deemed reasonable). The guideline is an effective dose of 5 rad (or 5,000 mrad) received per year.

9.6 RISKS/BENEFIT ANALYSIS

Patients entered on this study will have relapsed after standard chemotherapy or have disease that is refractory to standard chemotherapy. Although autologous stem cell transplant would be the next step in many of these patients, only 30-65% of patients will achieve long-term disease free survival with this therapy. The combination of an autologous stem cell transplant and radioimmunotherapy has the potential to increase the number of patients achieving long-term

disease free survival. No cognitively impaired patients requiring durable power of attorney will be included in the study.

9.7 CONSENT AND ASSENT PROCESSES AND DOCUMENTS

Informed consent will be obtained in all patients on this trial. There will be no minors enrolled < 18 years of age; therefore, assent is unnecessary. The attached informed consent contains all elements required for consent. In addition, the Principal Investigator and/or associate investigators will discuss the protocol in detail with the patient and will be available to answer all patient questions to allow the patient to give informed consent.

9.7.1 Telephone re-consent

Re-consent on this study may be obtained via telephone according to the following procedure: the informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent document. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator.

9.7.2 Informed consent of non-English speaking subjects

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, 45 CFR 46.117 (b) (2) and 21 CFR 50.27 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation. Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

10 PHARMACEUTICAL INFORMATION

10.1 Daclizumab

10.1.1 Source

Unlabeled daclizumab will be provided from the existing supply held by the NIH Clinical Center Pharmacy.

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10.1.2 Toxicity

Toxicities that may follow the administration of monoclonal antibodies include all of the well-recognized allergic reactions to foreign protein: fever, urticaria, bronchospasm, anaphylaxis, Arthus reaction, vasculitis, and serum sickness. The most frequently reported adverse events of daclizumab administration were gastrointestinal disorders, which were reported at 67% frequency. Placebo treated patients experienced GI toxicity at 68%.

Please see package insert for complete toxicity information.

10.1.3 Formulation and Preparation:

Daclizumab is supplied as a clear, sterile, colorless concentrate (25 mg/5mL) for further dilution and intravenous administration. Each mL of Zenapax contains 5 mg of daclizumab and 3.6 mg sodium phosphate monobasic monohydrate, 11 mg sodium phosphate dibasic heptahydrate, 4.6 mg sodium chloride, 0.2 mg polysorbate 80 and may contain hydrochloric acid or sodium hydroxide to adjust the pH to 6.9. No preservatives are added.

10.1.4 Stability and Storage:

Daclizumab storage and stability, based on a 1 mg/kg dose, diluted in 50 mL of 0.9% Sodium Chloride Injection, USP. See package insert for more information.

- **Storage:**

Store the intact vials in the refrigerator (2°C – 8°C) (36°F - 46°F). Protect from light and freezing. If the infusion solution is not administered immediately, it should be stored in the refrigerator.

- **Stability:**

Daclizumab does not contain preservatives. Prepared solutions of daclizumab should be administered within 4 hours. If not administered immediately following preparation, the infusion solution should be refrigerated (2°C – 8°C) (36°F - 46°F) and administered within 24 hours of preparation. After 24 hours, the solution should not be administered. The prepared solution should be inspected for particulate matter and clarity before administration to the patient, and should be discarded if particulate matter is present.

10.1.5 Administration Procedures:

Simultaneous with each dose of radiolabeled ⁹⁰Y-daclizumab administered in the phase I and phase II studies, patients will receive a fixed dose of 5 mg of unlabeled daclizumab (Zenapax™, humanized anti-CD25, anti-IL-2R alpha, anti-Tac). The quantity of unlabeled daclizumab administered is based on studies of ATL patients with circulating malignant cells and elevated soluble CD25 levels. The rationale for administering an unlabeled antibody directed to CD25 (e.g., daclizumab) is that there is an increase in the serum concentration of the released IL-2R alpha (Tac peptide, CD25) in patients with IL-2R alpha expressing malignancies such as HL. The administered unlabeled daclizumab binds to this circulating IL-2R alpha and increases the proportion of the radiolabeled ⁹⁰Y-daclizumab that binds to the CD25 expressing target cell [42]. In those patients it is estimated to yield binding of radiolabeled daclizumab to all circulating CD25-expressing tumor cells and to produce approximately 25 to 75% saturation of the IL-2 receptors in patients with soluble CD25 levels of 2,000 to 10,000 units/mL. These estimates are made on the basis of the observations during the Phase I trial of ⁹⁰Y-murine anti-CD25 (anti-Tac) antibody, where binding was assessed by FACS analysis and by binding to the circulating cells of

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¹¹¹In-murine anti-CD25 antibody co-administered with ⁹⁰Y-murine anti-CD25 antibody. The soluble CD25 levels of the majority of patients on this study are expected to be in the above range.

10.1.6 Incompatibilities:

Please refer to daclizumab package insert for drug interactions.

10.2 BASILIXIMAB

Basiliximab (trade name Simulect) is a chimeric mouse-human monoclonal antibody to the alpha chain (CD25) of the IL-2 receptor of T cells. It is a Novartis Pharmaceuticals product that was approved by the Food and Drug Administration (FDA) in 1998. It is a chimeric CD25 directed antibody of the IgG1 isotope. It acts as an antagonist at the interleukin-2 (IL-2) binding site of the p55 subunit (Tac antigen) of the high-affinity IL-2 receptor (CD25) on the surface of activated T lymphocytes and of ATL cells.

10.2.1 Source

Basiliximab will be obtained from the commercial supply by the Clinical Center Pharmacy.

10.2.2 Mechanism of Action:

Basiliximab functions as an IL-2 receptor antagonistic by binding with high-affinity ($K_{\text{alpha}} = 1 \times 10^{10} \text{m}^{-1}$) to the alpha chain of the high-affinity IL-2 receptor complex thereby inhibiting IL-2 binding. Basiliximab is specifically targeted against IL-2R alpha which is both selectively expressed on the surface of activated T lymphocytes and ATL cells but also circulates as the soluble released sIL-2R alpha peptide. Basiliximab blocks the binding of ⁹⁰Y-CHX-A” daclizumab to the circulating IL-2R alpha peptide.

10.2.3 Toxicity

The incidence of adverse events for basiliximab was determined in four randomized double-blind placebo controlled clinical trials for the prevention of renal allograft rejection. Basiliximab did not appear to add to the background of adverse events seen in organ transplantation patients as a consequence of their underlying disease and in concurrent administration of immunosuppressants and other medications. Adverse events were reported by 96% of the patients in the placebo-treated group and 96% in the basiliximab-treated groups. The pattern of adverse events with the recommended dose of basiliximab was similar to that of patients receiving a placebo. Basiliximab did not increase the incidence of serious adverse events observed compared to the placebo. Reported adverse events were gastrointestinal disorders reported by 69% of basiliximab-treated patients and 67% of placebo-treated patients. Basiliximab like daclizumab has the toxicities that may follow the administration of monoclonal antibodies including all the well-known recognized allergic reactions to foreign protein: fever, urticaria, bronchospasm, anaphylactic reactions, vasculitis, and serum sickness.

Please see package insert for complete toxicity information.

Basiliximab should not be administered to patients with a known allergy to basiliximab.

10.2.4 Formulation and Preparation:

Basiliximab (Simulect) is a sterile lyophilisate which is available in 6 mL colorless glass vials and it is available in 10 mg and 20 mg strengths (use the 10 mg strength). Each 10 mg vial contains 10 mg basiliximab, 3.61 mg monobasic potassium phosphate, 0.5 mg disodium hydrogen phosphate

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(anhydrous), 0.8 mg sodium chloride, 10 mg sucrose, 40 mg mannitol, and 20 mg glycine to be reconstituted in 2.5 mL of Sterile Water for Injection (USP). No preservatives are added.

10.2.5 Stability and Storage:

- **Storage:**

Store the basiliximab in a refrigerator at between 36 and 46 degrees F. (2 and 8C.) protected from light and moisture. **Do not freeze.**

- **Stability:**

Basiliximab does not contain preservatives. Prepared solutions of basiliximab should be administered within 4 hours. If not administered immediately following preparation the solution should be refrigerated (2°C - 8°C) (36°F - 46°F) and administered within 24 hours of preparation. After 24 hours the solution should not be administered. The prepared solution should be inspected for particulate matter and clarity before administration to the patient and should be discarded if particulate matter is present.

10.2.6 Administration Procedures:

To prepare the reconstituted solution add 2.5 mL of Sterile Water for Injection, USP using aseptic techniques to the vial containing the basiliximab (Simulect) powder, shake the vial gently to dissolve the powder.

The reconstituted solution is isotonic and may be given either as a bolus injection or diluted in a volume of 25 mL with normal saline or dextrose 5% for infusion. When mixing this solution, gently invert the bag in order to avoid foaming, do not shake.

10.2.7 Incompatibilities:

None are listed. Please refer to the basiliximab (Simulect) package insert for drug interactions.

10.3 CHX-A DACLIZUMAB

⁹⁰Y-daclizumab (humanized anti-CD25, humanized anti-Tac, Zenapax®) monoclonal antibody is a radioimmunoconjugate linking daclizumab, a humanized IgG1 monoclonal antibody directed against the IL-2 binding site of the human IL-2R alpha subunit (CD25), to the radioisotope, yttrium-90.

¹¹¹In-Daclizumab (humanized anti-CD25, humanized anti-Tac, Zenapax®) monoclonal antibody)

¹¹¹In-daclizumab is a radioimmunoconjugate linking daclizumab, a humanized IgG1 monoclonal antibody directed against the IL-2 binding site of the human IL-2R alpha subunit (CD25), to the radioisotope, indium-111.

10.3.1 Preparation

Daclizumab was obtained from Roche Pharmaceuticals (Nutley, NJ). Daclizumab (Zenapax®) 25 mg/5mL is supplied as a clear, sterile, colorless concentrate for further dilution and intravenous administration. Each mL of Zenapax contains 5 mg of daclizumab and 3.6 mg sodium phosphate monobasic monohydrate, 11 mg sodium phosphate dibasic heptahydrate, 4.6 mg sodium chloride, 0.2 mg polysorbate 80 and may contain hydrochloric acid or sodium hydroxide to adjust the pH to 6.9. No preservatives are added.

NIH was responsible for the manufacture and testing of the chelator, CHX-A” DTPA (N-[(R)-2-

amino-3-(p-isothiocyanato-phenyl)propyl]-trans-(S,S)-cyclohexane-1,2-diamine N, N, N', N'', N'''-pentaacetic acid) as well as Drug Substance and Drug Product testing. CHX-A''DTPA, was manufactured under controlled conditions, tested for purity, and vialled and stored by Dr. Thomas A. Waldmann, Bldg 10, Room 4N115, 10 Center Drive, 9000 Rockville Pike, Bethesda, MD 20892. The chelate modification of daclizumab was performed using good manufacturing practices by Goodwin Biotechnology Incorporated (Plantation, FL).

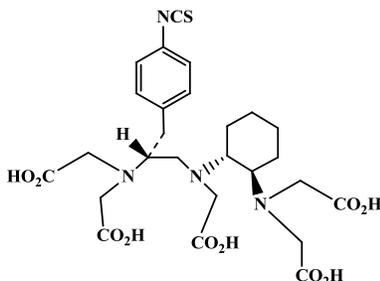


Figure 6. Structural formula of CHX-A'' chelating agent (N-[(R)-2-amino-3-(p-isothiocyanato-phenyl)propyl]-trans-(S, S)-cyclohexane-1,2-diamine N, N, N', N'', N'''-pentaacetic acid).

10.3.2 Toxicity

Toxicities that may follow the administration of monoclonal antibodies include all of the well-recognized allergic reactions to foreign protein: fever, urticaria, bronchospasm, anaphylaxis, Arthus reaction, vasculitis, and serum sickness. The major expected toxicity from the radioisotopes, is bone-marrow suppression, although the potential exists for additional toxicities including renal, lung, or hepatic dysfunction.

Yttrium in its elemental form is considered mildly toxic with its primary effects on the liver (elevated serum transaminases) and it can cause a mild perturbation of calcium homeostasis. We are able to report on our own experience giving ⁹⁰Y-labeled daclizumab to 30 patients with relapsed or refractory Hodgkin's lymphoma enrolled on a Phase II trial (Janik *et al*, manuscript submitted). Patients on this study actually received multiple doses of the drug (up to 7) every 6-10 weeks. The median aggregate radiation dose administered was 40 mCi. No infusion reactions were observed. Thrombocytopenia and granulocytopenia were the predominant toxicities occurring at weeks 4-5 after the ⁹⁰Y-labeled daclizumab infusion with the nadirs usually occurring during weeks 5-7 after treatment. Seven patients experienced cytopenias that persisted for more than 10 weeks although no blood component support was required and all patients recovered hematologic values to baseline. Three patients developed myelodysplastic syndrome at 5, 9.5, and 35 months after the first dose of ⁹⁰Y-labeled daclizumab, respectively.

Pure indium in metal form is considered non-toxic. At the doses used in the present study there are no reports of toxicity from Indium-111.

10.3.3 Storage of CHX-A'' daclizumab chelate

The CHX-A''-daclizumab chelate is stored at -70°C in 0.15 M NaCl, 10 mM KPO₄, 1 mM EGTA, pH 7.2. The material is stable in this form. Over several months, no detectable decrease in binding to CD25-positive cells has been noted. The chelator currently used is CHX-A'' DTPA (N-[(R)-2-Amino-3-(p-isothiocyanato-phenyl)propyl]-trans-(S,S)-cyclohexane-1,2-diamine N, N, N', N'', N'''-pentaacetic acid. Prior to storage, the material is filtered through a MILLEX-GV 0.22 µm filter that is "pre-wet" with human serum albumin. Each chelate preparation will be assayed for

ability to bind to CD25-expressing HUT102 and for sterility, pyrogenicity and general safety.

10.4 CALCIUM DIETHYLENTRIAMINEPENTAACETATE (CA-DTPA).

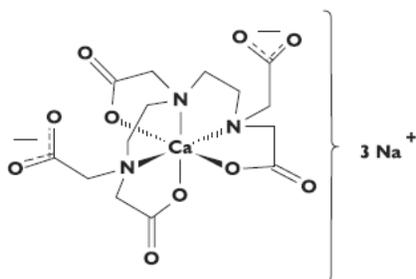


Figure 7. Structural formula of calcium-DTPA (sodium calcium diethylenetriaminepentaacetic acid).

10.4.1 Formulation and Preparation

Ca-DTPA (diethylenetriaminepenta-acetic acid) with an empirical formula $C_{14}H_{23}N_3O_{10}$ belongs to the group of synthetic polyamino-polycarboxylic acids that form stable complexes (metal chelates) with a large number of metal ions [45, 46]. When releasing a metal such as calcium it binds to another metal of greater affinity and carries it to the kidney where it is excreted in the urine. The plasma half-life of DTPA is 20–60 minutes. Almost the entire administered dose is excreted in 12 hours with only a small amount bound to plasma proteins. This bound form has a half-life of > 20 hours. DTPA undergoes only a minimal amount of metabolic change in the body. Only a very minor release of acetate groups has been demonstrated and splitting of ethylene groups has not been detected. Following intravenous administration Ca-DTPA is rapidly distributed throughout the extracellular fluid space. No significant amount of DTPA penetrates into erythrocytes or other tissues. No accumulation of DTPA in specific organs has been observed. There is little or no binding of the chelate by the renal parenchyma and it is promptly cleared from the body by glomerular filtration. Ca-DTPA can deplete the body of zinc and to a lesser extent, manganese with repeated dosing.

Ca-DTPA is commercially available as an FDA-approved agent for the treatment of radiation exposure emergencies. It is available through Hameln Pharmaceuticals through Akorn, Inc. (Buffalo Grove, IL). It is available as single use ampoules containing 5 mL of solution containing Ca DTPA at a concentration of 200 mg/mL.

10.4.2 Toxicity

When given with repeated doses at short intervals, Ca-DTPA treatment may cause nausea, vomiting, diarrhea, chills, fever, pruritus, and muscle cramps in the first 24 hours. Anosmia (loss of sense of smell) was observed in one individual after 123 grams of Ca-DTPA over 27 months of therapy, possibly related to zinc depletion. After 100 days of no further Ca-DTPA administration the patient's sense of smell began to return. At higher doses Ca-DTPA has caused renal tubular damage and, in two cases, death.

Studies in animals indicate that the toxicity of Ca-DTPA depends on total dose and the dose schedule [45,46]. When administered to animals in high doses (>2000 mmol/kg- the clinical dose range is 10–30 mmol/kg), it can produce lesions of the kidney, intestinal mucosa, and liver and can even be lethal [44-47]. When fractionated doses are used, toxicity may result from depletion of Zn

and Mn ions needed in enzymatic steps leading to DNA synthesis that renews epithelial cells in the intestinal epithelium. Zn concentrations will be determined prior to therapy and 24 and 48 hours following Ca-DTPA treatment. Normal serum Zn levels are 70–130 mcg/L. The infusions of Ca-DTPA will be terminated and oral Zn sulfate 220 mg/day will be administered if the concentration of Zn falls below 35 mcg/L and I.V. zinc sulfate 220 mg diluted with 0.9N saline if the serum Zn level falls below 25 mcg/L.

10.5 FILGRASTIM (NEUPOGEN® G-CSF)

NEUPOGEN® (filgrastim, G-CSF) is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology. NEUPOGEN® is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever. NEUPOGEN® will be obtained from the commercial supply in the Clinical Center Pharmacy.

10.5.1 Formulation, Storage, and Stability

Recombinant granulocyte-colony stimulating factor (G-CSF) manufactured by Amgen (Thousand Oaks, CA) is supplied as a clear sterile solution of 300 mcg/mL packaged into either 1-mL (300 mcg) or 1.6-mL (480 mcg) vials. NEUPOGEN® should be stored in the refrigerator at 2° to 8°C (36° to 46°F). Avoid shaking. Prior to injection, NEUPOGEN® may be allowed to reach room temperature for a maximum of 24 hours. Any vial or prefilled syringe left at room temperature for greater than 24 hours should be discarded. Do not freeze. G-CSF is stable for at least 1 year when refrigerated.

10.5.2 Administration

G-CSF 10-16 µg/kg will be administered for five to six consecutive days as a subcutaneous injection to mobilize peripheral blood stem cells for collection by apheresis. See Section 12.5 Appendix E for sliding scale G-CSF dosing algorithm.

Patients may be instructed on the self-administration of G-CSF.

10.5.3 Toxicity

Bone pain, which can sometimes be severe. Other adverse reactions include fatigue, muscle cramps, back/leg pain, splenomegaly and thinning hair.

10.6 PLERIXAFOR (MOZOBIL®)

Plerixafor is a CXCR4 chemokine receptor antagonist that blocks the binding of stromal cell-derived factor 1α (SDF-1α). It inhibits the retention of hematopoietic stem cells in bone marrow, and increases their number in peripheral blood. It is used, with granulocyte colony-stimulating factor (G-CSF), to mobilize stem cells for collection and subsequent autologous transplantation. Mozobil® will be obtained from the commercial supply in the Clinical Center Pharmacy.

10.6.1 Formulation, Storage, and Stability

Subcutaneous Solution: 20 mg/mL

Inspect vial for particulate matter and discoloration prior to administration; do not use if particulate matter present or solution is discolored. (Prod Info MOZOBIL(R) subcutaneous injection, 2008).

Store at controlled room temperature, 25 degrees C (77 degrees F), with excursions permitted

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between 15 and 30 degrees C (59 and 86 degrees F)

10.6.2 Administration

Plerixafor 240µg/kg will be administered for one to two consecutive days as a subcutaneous injection to mobilize peripheral blood stem cells for collection by apheresis. See Section 12.5 Appendix E for dosing algorithm.

Plerixafor will be administered on the 5th day of filgrastim administration, 6 to 8 hours before the apheresis. In case stem cell collection is insufficient with one apheresis, an additional dose of Plerixafor may be administered the next day at the same dose, 6 to 8 hours before the apheresis procedures.

10.6.3 Pharmacokinetics

Peak plasma concentrations of plerixafor occur about 30 to 60 minutes after a subcutaneous dose. It is about 58% bound to plasma proteins and largely confined to the extravascular fluid space. About 70% of a dose is eliminated in the urine within 24 hours after a dose, and the terminal half-life is about 3 to 5 hours.

Plerixafor is not metabolized using human liver microsomes or human primary hepatocytes. Additionally, plerixafor does not exhibit inhibitory activity towards the major drug metabolizing cytochrome P450 enzymes nor did it induce CYP1A2, CYP2B6, or CYP3A4 enzymes.

10.6.4 Adverse effects

Common adverse effects include diarrhea, nausea, vomiting, flatulence, fatigue, arthralgia, headache and dizziness, mild injection site reactions.

Less commonly, insomnia or systemic reactions occurring about 30 minutes after injection (urticaria, periorbital swelling, dyspnea, and hypoxia).

Some cases of vasovagal reactions, orthostatic hypotension, and syncope, within 1 hour of injection, have also been reported.

10.7 BCNU (BiCNU®, CARMUSTINE)

BiCNU® (carmustine for injection) is a nitrosourea that alkylates DNA and RNA. It is not cross-resistant with other alkylators. It may also inhibit several key enzymatic processes by carbamylation of amino acids in proteins.

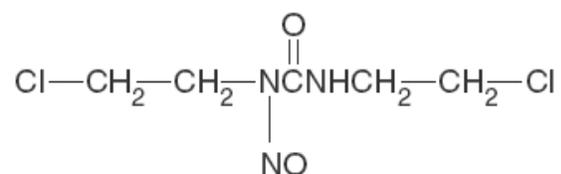


Figure 8. Structural formula of carmustine.

10.7.1 Formulation and Preparation

It is lyophilized pale yellow flakes or congealed mass with a molecular weight of 214.06. It is highly soluble in alcohol and lipids, and poorly soluble in water. First, dissolve BCNU with 3 mL of the supplied sterile diluent (Dehydrated Alcohol Injection, USP). Second, aseptically add 27 mL Sterile Water for Injection, USP. Each mL of resulting solution contains 3.3 mg of BCNU in 10%

ethanol. Such solutions should be protected from light. Reconstitution as recommended results in a clear, colorless to yellowish solution which may be further diluted with 5% Dextrose Injection, USP. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. BCNU is administered by intravenous infusion after reconstitution as recommended. Accidental contact of reconstituted BCNU with the skin has caused transient hyperpigmentation of the affected areas. The use of gloves is recommended. If BCNU lyophilized material or solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

10.7.2 Clinical Pharmacology

Intravenously administered carmustine is rapidly degraded, with no intact drug detectable after 15 minutes. However, in studies with ¹⁴C-labeled drug, prolonged levels of the isotope were detected in the plasma and tissue, probably representing radioactive fragments of the parent compound. It is thought that the antineoplastic and toxic activities of carmustine may be due to metabolites. Approximately 60% to 70% of a total dose is excreted in the urine in 96 hours and about 10% as respiratory CO₂. The fate of the remainder is undetermined. Because of the high lipid solubility and the relative lack of ionization at physiological pH, carmustine crosses the blood-brain barrier quite effectively. Levels of radioactivity in the CSF are ≥50% of those measured concurrently in plasma.

10.7.3 Toxicity

10.7.3.1 Pulmonary Toxicity

Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported to occur from 9 days to 43 months after treatment with BiCNU and related nitrosoureas. Most of these patients were receiving prolonged therapy with total doses of BiCNU greater than 1400 mg/m². However, there have been reports of pulmonary fibrosis in patients receiving lower total doses. Other risk factors include past history of lung disease and duration of treatment. Cases of fatal pulmonary toxicity with BiCNU have been reported.

10.7.3.2 Hematologic Toxicity

A frequent and serious toxicity of BiCNU is delayed myelosuppression. It usually occurs 4 to 6 weeks after drug administration and is dose related. Thrombocytopenia occurs at about 4 weeks post-administration and persists for 1 to 2 weeks. Leukopenia occurs at 5 to 6 weeks after a dose of BiCNU and persists for 1 to 2 weeks. Thrombocytopenia is generally more severe than leukopenia. However, both may be dose-limiting toxicities. BiCNU may produce cumulative myelosuppression, manifested by more depressed indices or longer duration of suppression after repeated doses. The occurrence of acute leukemia and bone-marrow dysplasias have been reported in patients following long-term nitrosourea therapy. Anemia also occurs, but is less frequent and less severe than thrombocytopenia or leukopenia.

10.7.3.3 Gastrointestinal Toxicity

Nausea and vomiting after I.V. administration of BiCNU are noted frequently. This toxicity appears within 2 hours of dosing, usually lasting 4 to 6 hours, and is dose related. Prior administration of antiemetics is effective in diminishing and sometimes preventing this side effect.

10.7.3.4 Hepatotoxicity

A reversible type of hepatic toxicity, manifested by increased transaminase, alkaline phosphatase, and bilirubin levels, has been reported in a small percentage of patients receiving BiCNU.

10.7.3.5 Nephrotoxicity

Renal abnormalities consisting of progressive azotemia, decrease in kidney size and renal failure have been reported in patients who received large cumulative doses after prolonged therapy with BiCNU and related nitrosoureas. Kidney damage has also been reported occasionally in patients receiving lower total doses.

10.7.3.6 Other Toxicities

Accidental contact of reconstituted BiCNU with skin has caused burning and hyperpigmentation of the affected areas. Rapid I.V. infusion of BiCNU may produce intensive flushing of the skin and suffusion of the conjunctiva within 2 hours, lasting about 4 hours. It is also associated with burning at the site of injection although true thrombosis is rare. Neuroretinitis, chest pain, headache, allergic reaction, hypotension and tachycardia have been reported as part of ongoing surveillance.

10.7.4 Storage and Stability

Unopened vials of the dry drug must be stored in a refrigerator (2°C to 8°C; 36°F to 46°F). The recommended storage of unopened vials provides a stable product for 2 years. After reconstitution as recommended, BiCNU is stable for 8 hours at room temperature (25°C; 77°F), protected from light.

10.8 ETOPOSIDE

Etoposide (also known as VP-16) is a semisynthetic derivative of podophyllotoxin whose predominant macromolecular effect is DNA synthesis inhibition.

The structural formula is:

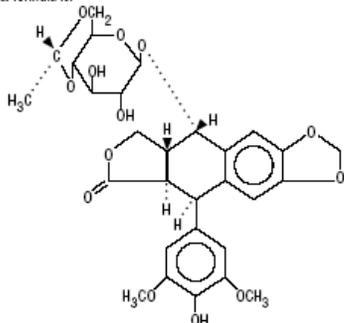


Figure 9. Structural formula of etoposide (VP-16).

10.8.1 Formulation and Preparation

Etoposide Injection is available for intravenous use as a sterile 20 mg/mL solution in 5 mL, 25 mL, or 50 mL sterile multiple dose vials. The solution is clear yellow. It has a molecular weight of 588.56 and a molecular formula of C₂₉H₃₂O₁₃.

Etoposide injection must be diluted prior to use with either 5% Dextrose Injection, USP or 0.9%

Sodium Chloride Injection, USP to give a final concentration of 0.2 to 0.4 mg/mL. If solutions are prepared at concentrations above 0.4 mg/mL, precipitation may occur. Hypotension following rapid intravenous administration has been reported, hence, it is recommended that the etoposide solution be administered over a 2 to 4 hour period. A longer duration of administration may be used if the volume of fluid to be infused is a concern. **Etoposide should not be given by rapid intravenous injection.** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

As with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of etoposide. Skin reactions associated with accidental exposure to etoposide may occur. The use of gloves is recommended. If etoposide solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

10.8.2 Clinical Pharmacology

On intravenous administration, the disposition of etoposide is best described as a biphasic process with a distribution half-life of about 1.5 hours and terminal elimination half-life ranging from 4 to 11 hours. *In vitro*, etoposide is highly protein bound (97%) to human plasma proteins.

After intravenous administration of ³H-etoposide (70-290 mg/m²), mean recoveries of radioactivity in the urine range from 42 to 67%, and fecal recoveries range from 0 to 16% of the dose. Less than 50% of an intravenous dose is excreted in the urine as etoposide with mean recoveries of 8 to 35% within 24 hours.

Biliary excretion appears to be a minor route of etoposide elimination. Only 6% or less of an intravenous dose is recovered in the bile as etoposide. Metabolism accounts for most of the nonrenal clearance of etoposide. The major urinary metabolite of etoposide in adults is the hydroxy acid [4'-demethylepipodophyllic acid-9-(4,6-O-(*R*)-ethylideneβ-D-glucopyranoside)], formed by opening of the lactone ring. It is also present in human plasma, presumably as the *trans* isomer. Glucuronide and/or sulfate conjugates of etoposide are excreted in human urine and represent 5 to 22% of the dose.

10.8.3 Toxicity

10.8.3.1 Hematologic Toxicity

Myelosuppression is dose related and dose limiting, with granulocyte nadirs occurring 7 to 14 days after drug administration and platelet nadirs occurring 9 to 16 days after drug administration. Bone-marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported. The occurrence of acute leukemia with or without a preleukemic phase has been reported rarely in patients treated with etoposide in association with other antineoplastic agents.

10.8.3.2 Gastrointestinal Toxicity

Nausea and vomiting are the major gastrointestinal toxicities. The severity of such nausea and vomiting is generally mild to moderate with treatment discontinuation required in 1% of patients. Nausea and vomiting can usually be controlled with standard antiemetic therapy. Gastrointestinal toxicities are slightly more frequent after oral administration than after intravenous infusion.

10.8.3.3 Hypotension

Transient hypotension following rapid intravenous administration has been reported in 1% to

2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted. To prevent this rare occurrence, it is recommended that Etoposide Injection be administered by slow intravenous infusion over a 30 to 60 minute period. If hypotension occurs, it usually responds to cessation of the infusion and administration of fluids or other supportive therapy as appropriate. When restarting the infusion, a slower administration rate should be used.

10.8.3.4 Allergic Reactions

Anaphylactic-like reactions characterized by chills, fever, tachycardia, bronchospasm, dyspnea, and/or hypotension have been reported to occur in 0.7% to 2% of patients receiving intravenous etoposide and in less than 1% of the patients treated with the oral capsules. These reactions have usually responded promptly to the cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines, or volume expanders as appropriate; however, the reactions can be fatal. Hypertension and/or flushing have also been reported. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-like reactions have occurred during the initial infusion of etoposide. Facial/tongue swelling, coughing, diaphoresis, cyanosis, tightness in throat, laryngospasm, back pain, and/or loss of consciousness have sometimes occurred in association with the above reactions. In addition, an apparent hypersensitivity-associated apnea has been reported rarely. Rash, urticaria, and/or pruritus have infrequently been reported at recommended doses. At investigational doses, a generalized pruritic erythematous, maculopapular rash, consistent with perivasculitis, has been reported.

10.8.3.5 Alopecia

Reversible alopecia, sometimes progressing to total baldness was observed in up to 66% of patients.

10.8.3.6 Other Toxicities

The following adverse reactions have been infrequently reported: aftertaste, fever, pigmentation, abdominal pain, constipation, dysphagia, transient cortical blindness, optic neuritis, and a single report of radiation recall dermatitis. Hepatic toxicity, generally in patients receiving higher doses of the drug than those recommended, has been reported with etoposide. Metabolic acidosis also has been reported in patients receiving higher doses.

10.8.4 Storage and Stability

Unopened vials of Etoposide Injection are stable for 24 months at room temperature (25°C). Vials diluted as recommended to a concentration of 0.2 to 0.4 mg/mL are stable for 96 and 24 hours, respectively, at room temperature (25°C) under normal room fluorescent light in both glass and plastic containers.

10.9 CYTARABINE (ARA-C, CYTOSINE ARABINOSIDE)

Cytarabine is an antineoplastic that acts through the inhibition of DNA polymerase.

10.9.1 Formulation and Preparation

Cytarabine is an odorless, white to off-white, crystalline powder that is freely soluble in water and slightly soluble in alcohol and in chloroform. Molecular weight: 243.22. Molecular formula: C₉H₁₃N₃O₅.

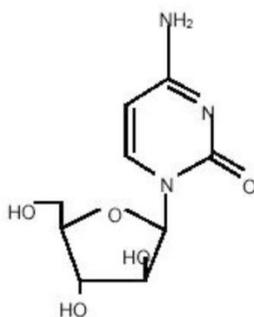


Figure 10. Structural formula of cytarabine.

10.9.2 Human Pharmacology

Cytarabine is rapidly metabolized. Following rapid intravenous injection of cytarabine labeled with tritium, the disappearance from plasma is biphasic. There is an initial distributive phase with a half-life of about 10 minutes, followed by a second elimination phase with a half-life of about 1 to 3 hours. After the distributive phase, more than 80% of plasma radioactivity can be accounted for by the inactive metabolite 1-β-D-arabinofuranosyluracil (Ara-U). Within 24 hours about 80% of the administered radioactivity can be recovered in the urine, approximately 90% of which is excreted as Ara-U. Relatively constant plasma levels can be achieved by continuous intravenous infusion.

10.9.3 Toxicity

10.9.3.1 Expected Reactions

Because cytarabine is a bone-marrow suppressant, anemia, leukopenia, thrombocytopenia, megaloblastosis and reduced reticulocytes can be expected as a result of administration with Cytarabine. Cellular changes in the morphology of bone marrow and peripheral smears can be expected. Following 5-day constant infusions or acute injections of 50 mg/m² to 600 mg/m², white cell depression follows a biphasic course. Regardless of initial count, dosage level, or schedule, there is an initial fall starting the first 24 hours with a nadir at days 7-9. This is followed by a brief rise that peaks around the twelfth day. A second and deeper fall reaches nadir at days 15-24. Then there is rapid rise to above baseline in the next 10 days. Platelet depression is noticeable at 5 days with a peak depression occurring between days 12-15. Thereupon, a rapid rise to above baseline occurs in the next 10 days.

10.9.3.2 Infectious Complications

Viral, bacterial, fungal, parasitic, or saprophytic infections, in any location in the body may be associated with the use of Cytarabine for Injection, USP alone or in combination with other immunosuppressive agents following immunosuppressant doses that affect cellular or humoral immunity. These infections may be mild, but can be severe and at times fatal.

10.9.3.3 Cytarabine (Ara-C) Syndrome

A cytarabine syndrome has been described. It is characterized by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs 6 to 12 hours following drug administration. Corticosteroids have been shown to be beneficial in

treating or preventing this syndrome. If the symptoms of the syndrome are deemed treatable, corticosteroids should be contemplated as well as continuation of therapy with cytarabine.

10.9.3.4 Most Frequent Adverse Reactions

Most frequent adverse reactions include anorexia, oral and anal inflammation or ulceration, rash, nausea, thrombophlebitis, vomiting, hepatic dysfunction, bleeding (all sites), diarrhea, and fever. Nausea and vomiting are most frequent following rapid intravenous injection.

10.9.3.5 Less Frequent Adverse Reactions

Less frequent adverse reactions include sepsis, esophageal ulceration, conjunctivitis (may occur with rash), pneumonia, esophagitis, dizziness, cellulitis at injection site, chest pain, alopecia, skin ulceration, pericarditis, anaphylaxis, urinary retention, bowel necrosis, allergic edema, renal dysfunction, abdominal pain, pruritus, neuritis, pancreatitis, shortness of breath, neural toxicity, freckling, urticaria, sore throat, jaundice, and headache.

10.9.4 Storage and Stability

Store the product at controlled room temperature 15° to 30° C (59° to 86° F).

When reconstituted Cytarabine was added to Sterile Water for Injection, 5% Dextrose Injection or Sodium Chloride Injection, 94 to 96 percent of the cytarabine was present after 192 hours storage at room temperature. Parenteral drugs should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution and container permit.

10.10 MELPHALAN

Melphalan, also known as L-phenylalanine mustard, phenylalanine mustard, L-PAM, or L-sarcosylsin, is a phenylalanine derivative of nitrogen mustard and is a bifunctional alkylating agent whose cytotoxicity appears to be related to the extent of its interstrand cross-linking with DNA.

10.10.1 Formulation and Preparation

Melphalan for Injection is supplied as a sterile, nonpyrogenic, freeze-dried powder. Each single-use vial contains melphalan hydrochloride equivalent to 50 mg melphalan and 20 mg povidone. It is reconstituted using the sterile diluent provided and administered intravenously. The molecular formula is C₁₃H₁₈Cl₂N₂O₂, and the molecular weight is 305.20.

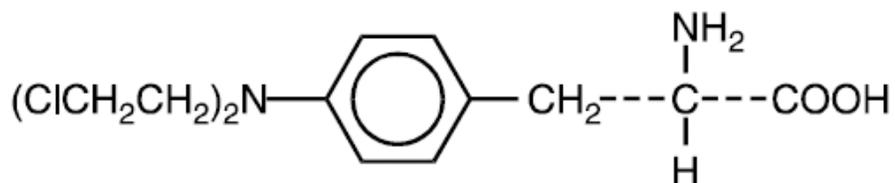


Figure 11. Structural formula of melphalan (L-phenylalanine mustard).

10.10.2 Pharmacokinetics

Drug plasma concentrations of melphalan decline rapidly in a biexponential manner with distribution phase and terminal elimination phase half-lives of approximately 10 and 75 minutes, respectively. The extent of melphalan binding to plasma proteins ranges from 60% to 90%. Melphalan is eliminated from plasma primarily by chemical hydrolysis to monohydroxy-

melphalan and dihydroxymelphalan. Aside from these hydrolysis products, no other melphalan metabolites have been observed in humans.

10.10.3 Toxicity

The following information on adverse reactions is based on data from both oral and I.V. administration of melphalan as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

10.10.3.1 Hematological

The most common side effect is bone-marrow suppression. White blood cell count and platelet count nadirs usually occur 2 to 3 weeks after treatment, with recovery in 4 to 5 weeks after treatment. Irreversible bone-marrow failure has been reported.

10.10.3.2 Gastrointestinal

Gastrointestinal disturbances such as nausea and vomiting, diarrhea, and oral ulceration occur infrequently. Hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice have been reported. Hepatic veno-occlusive disease has been reported.

10.10.3.3 Hypersensitivity

Acute hypersensitivity reactions including anaphylaxis were reported in 2.4% of 425 patients receiving melphalan for Injection for myeloma. These reactions were characterized by urticaria, pruritus, edema, and in some patients, tachycardia, bronchospasm, dyspnea, and hypotension. These patients appeared to respond to antihistamine and corticosteroid therapy. If a hypersensitivity reaction occurs, IV or oral melphalan should not be re-administered since hypersensitivity reactions have also been reported with oral melphalan.

10.10.3.4 Miscellaneous

Other reported adverse reactions include skin hypersensitivity, skin ulceration at injection site, skin necrosis rarely requiring skin grafting, vasculitis, alopecia, hemolytic anemia, allergic reaction, pulmonary fibrosis, and interstitial pneumonitis.

10.10.3.5 Secondary malignancies

Secondary malignancies including acute nonlymphocytic leukemia, myeloproliferative syndrome, and carcinoma, have been reported in patients with cancer treated with alkylating agents (including melphalan). Some patients also received other chemotherapeutic agents or radiation therapy. Precise quantitation of the risk of acute leukemia, myeloproliferative syndrome, or carcinoma is not possible. Published reports of leukemia in patients who have received melphalan (and other alkylating agents) suggest that the risk of leukemogenesis increases with chronicity of treatment and with cumulative dose.

10.11 ADMINISTRATION

Melphalan for Injection must be reconstituted by rapidly injecting 10 mL of the supplied diluent directly into the vial of lyophilized powder using a sterile needle (20-gauge or larger needle diameter) and syringe. Immediately shake vial vigorously until a clear solution is obtained. This provides a 5-mg/mL solution of melphalan. Rapid addition of the diluent followed by immediate vigorous shaking is important for proper dissolution. Immediately dilute the dose to be administered in 0.9% Sodium Chloride Injection, USP, to a concentration not greater than 0.45

Abbreviated Title: ⁹⁰Y-daclizumab + ASCT in HL
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mg/mL. Administer the diluted product over a minimum of 15 minutes. Complete administration should be accomplished within 60 minutes of reconstitution. The time between reconstitution/dilution and administration of melphalan should be kept to a minimum because reconstituted and diluted solutions of melphalan are unstable.

10.12 STORAGE AND STABILITY

Store at controlled room temperature 15° to 30°C (59° to 86°F) and protect from light

10.13 PALIFERMIN (KEPIVANCE™)

Palifermin is a human recombinant keratinocyte growth factor (KGF) used to reduce the incidence and duration of severe oral mucositis.

Palifermin is commercially available and will be purchased by the Clinical Center Pharmacy.

10.13.1 Formulation storage

intravenous powder for solution: 6.25 mg

add sterile water for injection to vial for a final concentration of 5 mg/mL, gently swirl,

do not shake or vigorously agitate vial

destroy reconstituted solution after 1 hour if left at room temperature or 24 hours if refrigerated

10.13.2 Administration

add sterile water for injection to vial for a final concentration of 5 mg/mL, gently swirl, do not shake or vigorously agitate vial

give reconstituted solution immediately or destroy after 1 hour if left at room temperature or 24 hours if refrigerated

do not filter reconstituted solution during preparation or administration

if heparin is used to maintain the i.v. line, flush with saline prior to and after the dose to prevent binding to heparin

palifermin should not be used during or within 24 hours preceding or following myelotoxic therapy administration

10.13.3 Dose and schedule

- 60 µg/kg intravenously push
- daily for three days starting day -9 pre-ASCT (i.e. days -9, -8 and -7)
- then for three additional daily doses on days +1, +2 and +3 of ASCT

10.13.4 Drug interaction

In vitro and *in vivo* data suggest that palifermin binds to unfractionated as well as low-molecular-weight heparins, and licensed product information therefore recommends that such combinations should be used with care, although the clinical relevance is unclear.

10.13.5 Toxicity

Abbreviated Title: ⁹⁰Y-daclizumab + ASCT in HL

Version Date: 02/05/2018

The following adverse events were found in excess in the palifermin group over the control group in randomized studies and may be related to palifermin administration:

Rash, pruritus, erythema, cough, edema, taste changes or taste loss, coating of the tongue, sensation of increased tongue thickness, rhinitis, arthralgia, perianal pain, numbness, paresthesia

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Abbreviated Title: ⁹⁰Y-daclizumab + ASCT in HL

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12 APPENDICES

12.1 APPENDIX A: WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION OF LYMPHOID TUMORS.

TABLE 3: WHO classification of lymphoid neoplasms

B-cell neoplasms

Precursor B-cell neoplasm

Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)

Mature (peripheral) B-cell neoplasms

B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma

B-cell prolymphocytic leukemia

Lymphoplasmacytic lymphoma

Splenic marginal zone B-cell lymphoma (± villous lymphocytes)

Hairy cell leukemia

Plasma cell myeloma/plasmacytoma

Extranodal marginal zone B-cell lymphoma of MALT type

Nodal marginal zone B-cell lymphoma (± monocytoid B cells)

Follicular lymphoma

Mantle cell lymphoma

Diffuse large B-cell lymphoma

Mediastinal large B-cell lymphoma

Primary effusion lymphoma

Burkitt lymphoma/Burkitt-like lymphoma

T-cell and NK-cell neoplasms

Precursor T-cell neoplasm

Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)

Mature (peripheral) T-cell neoplasms

T-cell prolymphocytic leukemia

T-cell granular lymphocytic leukemia

Aggressive NK-cell leukemia

Adult T-cell lymphoma/leukemia (HTLV-1+)

Extranodal NK/T-cell lymphoma, nasal type

Enteropathy-type T-cell lymphoma

Hepatosplenic γ/δ T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma

Mycosis fungoides/Sézary syndrome

Anaplastic large cell lymphoma, T-/null-cell, primary cutaneous type

Peripheral T-cell lymphoma, unspecified

Angioimmunoblastic T-cell lymphoma

Anaplastic large cell lymphoma, T-/null-cell, primary systemic type

Hodgkin lymphoma (Hodgkin disease)

Nodular lymphocyte-predominant Hodgkin lymphoma

Classic Hodgkin lymphoma

Nodular sclerosis Hodgkin lymphoma (grades 1 and 2)

Lymphocyte-rich classic Hodgkin lymphoma

Mixed cellularity Hodgkin lymphoma

Lymphocyte-depletion Hodgkin lymphoma

Italic type denotes more common clinical entities. WHO = World Health Organization; MALT = mucosa-associated lymphoid tissue; NK = natural killer; HTLV-1 = human T-cell lymphotropic virus-1

12.2 APPENDIX B: REVISED RESPONSE CRITERIA FOR MALIGNANT LYMPHOMA⁴⁰

Table 2. Response Definitions for Clinical Trials				
Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [¹⁸F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

12.3 APPENDIX C: ECOG PERFORMANCE STATUS SCALE

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

12.4 APPENDIX D: ABNORMALITIES ENCOUNTERED IN MDS THAT CAN CONTRIBUTE TO THE DIAGNOSIS

The diagnosis of Myelodysplasia will be made by an independent investigator of the Laboratory of Pathology, NCI taking into consideration the totality of the clinical, pathological, flow cytometric and cytogenetic information described below and present in a particular individual's evaluation

The following is derived from the "WHO Classification of tumours of Haematopoietic and lymphoid tissues" 4th Edition. International Agency for Research on cancer

Disease	Blood findings	Bone marrow findings
Refractory cytopenias with unilineage dysplasia (RCUD) Refractory anaemia (RA); Refractory neutropenia (RN); Refractory thrombocytopenia (RT)	Unicytopenia or bicytopenia ¹ No or rare blasts (<1%) ²	Unilineage dysplasia: ≥10% of the cells in one myeloid lineage <5% blasts <15% of erythroid precursors are ring sideroblasts
Refractory anaemia with ring sideroblasts (RARS)	Anaemia No blasts	≥15% of erythroid precursors are ring sideroblasts Erythroid dysplasia only <5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s) No or rare blasts (<1%) ² No Auer rods <1x10 ⁹ /L monocytes	Dysplasia in ≥10% of the cells in ≥ two myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) <5% blasts in marrow No Auer rods ±15% ring sideroblasts
Refractory anaemia with excess blasts-1 (RAEB-1)	Cytopenia(s) <5% blasts ² No Auer rods <1x10 ⁹ /L monocytes	Unilineage or multilineage dysplasia 5-9% blasts ² No Auer rods
Refractory anaemia with excess blasts-2 (RAEB-2)	Cytopenia(s) 5–19% blasts Auer rods ± ³ <1x10 ⁹ /L monocytes	Unilineage or multilineage dysplasia 10–19% blasts Auer rods ± ³
Myelodysplastic syndrome – unclassified (MDS-U)	Cytopenias ≤1% blasts ²	Unequivocal dysplasia in less than 10% of cells in one or more myeloid cell lines when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS (See Table 5.04) <5% blasts
MDS associated with isolated del(5q)	Anaemia Usually normal or increased platelet count No or rare blasts (<1%)	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

¹ Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U.

² If the marrow myeloblast percentage is <5% but there are 2-4% myeloblasts in the blood, the diagnostic classification is RAEB 1. Cases of RCUD and RCMD with 1% myeloblasts in the blood should be classified as MDS, U.

³ Cases with Auer rods and <5% myeloblasts in the blood and <10% in the marrow should be classified as RAEB 2.

Dyserythropoiesis

Nuclear

- Nuclear budding
- Internuclear bridging
- Karyorrhexis
- Multinuclearity
- Nuclear hyperlobation
- Megaloblastic changes

Cytoplasmic

- Ring sideroblasts
- Vacuolization
- Periodic acid-Schiff positivity

Dysgranulopoiesis

- Small or unusually large size
- Nuclear hypolobation
(pseudo Pelger-Huët; pelgeroid)
- Irregular hypersegmentation
- Decreased granules; agranularity
- Pseudo Chediak-Higashi granules
- Auer rods

Dysmegakaryocytopoiesis

- Micromegakaryocytes
- Nuclear hypolobation
- Multinucleation (normal megakaryocytes are uninucleate with lobulated nuclei)

Table 5.04 Recurring chromosomal abnormalities and their frequency in the myelodysplastic syndromes at diagnosis.

Abnormality	MDS	t-MDS
<i>Unbalanced</i>		
+8*	10%	
-7 or del(7q)	10%	50%
-5 or del(5q)	10%	40%
del(20q)*	5-8%	
-Y*	5%	
i(17q) or t(17p)	3-5%	
-13 or del(13q)	3%	
del(11q)	3%	
del(12p) or t(12p)	3%	
del(9q)	1-2%	
idic(X)(q13)	1-2%	
<i>Balanced</i>		
t(11;16)(q23;p13.3)		3%
t(3;21)(q26.2;q22.1)		2%
t(1;3)(p36.3;q21.2)	1%	
t(2;11)(p21;q23)	1%	
inv(3)(q21q26.2)	1%	
t(6;9)(p23;q34)	1%	

* The presence of these abnormalities as the sole cytogenetic abnormality in the absence of morphologic criteria is not considered definitive evidence for MDS. In the setting of persistent cytopenias of undetermined origin, the other abnormalities shown are considered presumptive evidence of MDS in the absence of definitive morphologic features.

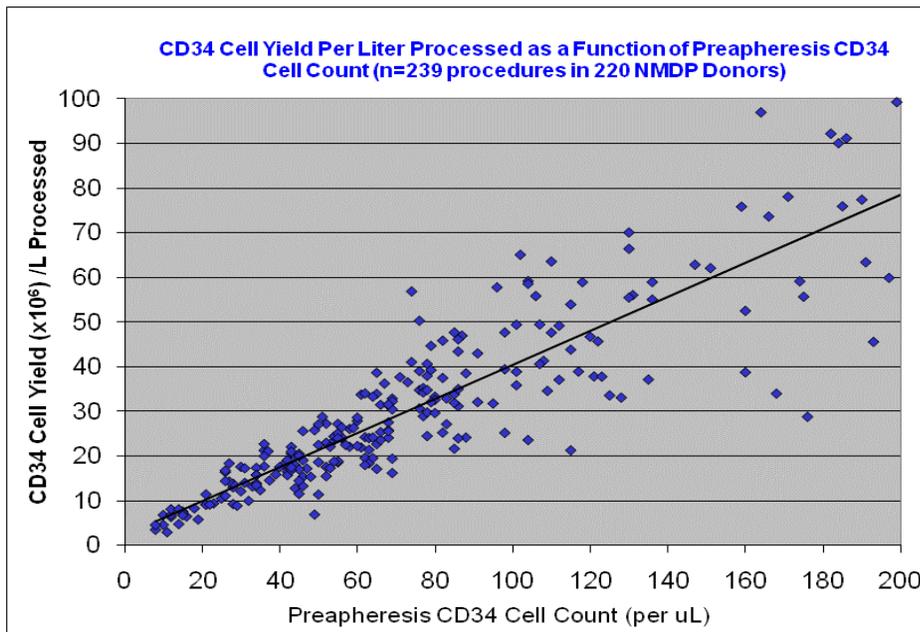
12.5 APPENDIX E: PROTOCOL FOR AUTOLOGOUS PBSC COLLECTION BY APHERESIS FOLLOWING MOBILIZATION WITH FILGRASTIM AND PLERIXAFOR

Mobilization of CD34 cells with G-CSF and Plerixafor

Patients will undergo mobilization with filgrastim (Neupogen, Amgen) and plerixafor (Mozobil, Genzyme). The filgrastim will be administered as a single daily dose in a dose range of 10-15.9 ug/kg/day subcutaneously for 5-6 days (see Table below for sliding-scale filgrastim dose schedule). The filgrastim doses for days 1-4 may be given between 8:00A.M. to 5:00 P.M. The filgrastim that is administered on day 5, and if necessary day 6, will be combined with a concurrent dose of plerixafor 240 mcg/kg subcutaneously. On days 5 and 6, both drugs must be given approximately six hours prior to starting apheresis. Predictable side effects of filgrastim, including headache, bone pain, and myalgia, will be treated as appropriate.

Filgrastim administration

Filgrastim will be administered according to a vial-based algorithm to reduce wastage and increase the total filgrastim dose given to lighter weight donors in order to improve CD34 yields.¹



CD34 cell yield per liter processed as a function of pre-apheresis CD34 cell count in 220 NMDP donors.

¹Vasu S, Leitman SF, Tisdale JF, et al. Donor demographic and laboratory predictors of allogeneic peripheral blood stem cell mobilization in an ethnically diverse population. Blood 2008; 112:2092-100

<u>Subject Weight</u>	<u>Total Filgrastim Dose</u>	<u>Dose /kg (range)</u>
38 - 48 kg	600 mcg	(12.5 to 15.8 mcg/kg)
49 - 56 kg	780 mcg	(13.9 to 15.9 mcg/kg)
57 - 60 kg	900 mcg	(15.0 to 15.8 mcg/kg)
61 - 67 kg	960 mcg	(14.3 to 15.7 mcg/kg)
68 - 108 kg	1080 mcg	(10.0 to 15.9 mcg/kg)
≥ 109 kg	1200 mcg	(11.0 or less)

Plerixafor Administration

<u>Subject Weight</u>	<u>Total Plerixafor Dose</u>
≤ 90 kg	calculate dose at 240 mcg/kg
> 90 kg	24,000 mcg (flat dose, equal to one full 1.2-mL vial)

Stem cell collection by apheresis

Peripheral blood stem cell (PBSC) collection will be performed in the Dowling Apheresis Clinic of the Department of Transfusion Medicine (DTM). A DTM physician is within the immediate vicinity of the procedure or available within one minute by pager. The minimum CD34 dose that must be collected in order to proceed with a single autologous transplantation is 2×10^6 /kg. When feasible, based on the mobilization response of the donor, a higher dose of $>4 \times 10^6$ CD34 cells/kg will be targeted, to permit more than one cycle of high dose chemotherapy with autologous stem cell rescue.

The volume processed per apheresis procedure will be determined by DTM medical staff on the day of apheresis, based on peak CD34 cell mobilization response to filgrastim and optimum and minimum CD34 cell dose needed (see graph below). Volume processed will range from 12 to 25 liters per procedure for 1 to 3 consecutive daily procedures, not to exceed a total of 75 liters over 3 days.

Collections will be performed with use of a dual-access continuous-flow apheresis device (Spectra Apheresis System, Caridian). Most donors will require a central double lumen apheresis catheter. Donors will receive continuous intravenous calcium prophylaxis to prevent citrate toxicity during apheresis, in accordance with standard DTM policies.