A PHASE I/II TRIAL OF ESCALATING DOSE OF YTTRIUM-90-LABELED ANTI-CD20 MONOCLONAL ANTIBODY IN COMBINATION WITH HIGH-DOSE ETOPOSIDE AND CYCLOPHOSPHAMIDE FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION FOR PATIENTS WITH POOR RISK/RELAPSED B-CELL NON-HODGKIN'S LYMPHOMA

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05/10/00

TITLE: ***A PHASE I/II TRIAL OF ESCALATING DOSE OF YTTRIUM-90-LABELED ANTI-CD20 MONOCLONAL ANTIBODY IN COMBINATION WITH HIGH-DOSE ETOPOSIDE AND CYCLOPHOSPHAMIDE FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION FOR PATIENTS WITH POOR RISK/RELAPSED B-CELL NON-HODGKIN'S LYMPHOMA***

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10/29/03

1.0 BACKGROUND RATIONALE

Non-Hodgkin's lymphomas (NHLs) are the sixth most common cause of cancer-related deaths in the United States. The incidence of NHL has increased by 50% over the past 15 years. The incidence of both indolent and aggressive lymphomas increases with age, making these the most commonly diagnosed lymphoid malignancies in patients over 60 years old.[1] Despite the use of aggressive combination chemotherapy regimens, approximately 30-40% of patients with intermediate- and high-grade NHL does not achieve complete remission (CR) or suffers relapse after attaining remission.[2] High-dose chemotherapy or chemo/radiotherapy followed by autologous bone marrow or stem cell transplantation (ASCT) has been shown to induce long-term disease control in about 10-50% of patients with relapsed and refractory intermediate- and high-grade lymphoma.[3] Recently, the benefit of high-dose therapy and ASCT proved to be superior to conventional salvage chemotherapy in a randomized Parma study of 215 patients with chemotherapy-sensitive NHL in relapse.[4] The 5-year event-free survival (EFS) was 46% for the ASCT group as compared to 12% for the salvage therapy without transplantation ($p = 0.001$). Thus, high-dose therapy and ASCT has become a potential curative modality for patients with recurrent aggressive lymphoma. However, not all patients derive long-term benefits from this treatment and recurrent disease remains the single most common cause of treatment failure post-high-dose therapy and ASCT. Therefore, new therapeutic approaches are needed.

Patients with low-grade NHL have indolent clinical courses and are not cured by current treatment approaches. Although most patients can achieve a complete remission with standard treatment, the median duration of first CR ranges from 12 to 36 months. Relapsed low-grade lymphoma may still respond to salvage therapy. But the duration of subsequent remissions progressively decreases. High-dose therapy and ASCT has been shown to improve survival and to increase the duration of remission in some patients with relapsed low-grade NHL.[5] However, because of the long natural history and the continued pattern of relapse post-ASCT in some studies, the role of high-dose therapy and ASCT as a potential curative treatment for patients with relapsed low-grade lymphoma has not been clearly established.

Recently, the role of radioimmunotherapy for treatment of NHL has emerged. Radioisotope-labeled monoclonal antibodies provide a mechanism by which radioactivity can be directly targeted to tumors sites while sparing normal tissues. B-cell lymphomas are attractive targets for radioimmunotherapy because of their radiosensitivity, their well-defined surface antigens and the availability of multiple monoclonal antibodies to those antigens.

1.1 Results of High-Dose Chemo/Radiotherapy and ASCT for NHL

Several high-dose therapy regimens have been used as preparative regimens for NHL. But so far, none of these regimens have emerged as the best regimen. However, since NHL is radio-sensitive and based on experience with acute leukemia, the combination of total body irradiation (TBI) and cyclophosphamide (Cy) has been widely used as a preparative regimen for some patients with lymphoid malignancies. In an attempt to reduce relapse rates, etoposide has been added to the TBI and Cy regimen because of its known activity in lymphoma. The results of phase I and II studies of TBI 12.0 Gy, etoposide 60 mg/kg and Cy 100 mg/kg conducted at City of Hope[6], Stanford University[7] and Fred Hutchinson Cancer Research Center (FHCRC)[8] demonstrate the activity of this regimen in patients with lymphoid malignancies. The transplant-related mortality within 100 days was 7-8%, with the common causes of death being venoocclusive disease (VOD), diffuse alveolar hemorrhage and infection. The major transplant-related morbidities were mucositis and skin toxicities, which were fully reversible. The 5-year EFS and overall survival (OS) were 52% [95% Confidence interval (CI) 42-62%] and 61% (95% CI 50-73%), respectively for 134 patients with NHL who underwent ASCT utilizing this regimen at Stanford. These results have been confirmed in the Southwestern Oncology Group cooperative trial. Despite its effectiveness, the relapse rate of 34-53 % remains considerably high. Thus, new preparative regimens need to be explored.

1.2 Radionuclides for Radioimmunotherapy

Iodine-131 (^{131}I) has been the gold standard for radioimmunotherapy due to its long track record in treating thyroid carcinomas, its well-defined radiochemistry, its clinical availability, and its potential for both radioimmunoscintigraphy and radioimmunotherapy. ^{131}I has been employed in the majority of reported clinical trials of radioimmunotherapy. However, there are disadvantages to ^{131}I, including its long 8-day half life, the risks of radiation exposure to health care providers and the non-specific irradiation to normal organs from gamma components of ^{131}I.

Yttrium-90 (^{90}Y) may be an ideal radionuclide for radioimmunotherapy since it emits beta particles that are more potent than those delivered by ^{131}I. It is a pure beta emitter, making it a safer reagent for medical personnel to administer. In addition, the short half-life of ^{90}Y facilitates its use in combination with other agents, i.e. chemotherapy or total body radiation, and allows for high dose rates at localized sites. Unfortunately, ^{90}Y cannot be used for radioimmunoscintigraphy due to its absence of gamma emissions. Indium-111 (^{111}In) has been substituted as an imaging reagent to show tumor localization in patients scheduled for ^{90}Y therapy, based on its biodistribution which is close to that of ^{90}Y. ^{111}In-labeled murine monoclonals have been used successfully in clinical imaging trials for cutaneous T-cell lymphoma, chronic lymphocytic leukemia, melanoma, and colon cancer.

1.3 Anti-CD 20

Anti-CD20 (anti-B1) is a murine monoclonal antibody of isotype IgG2a, raised against cryopreserved Burkitt's lymphoma cells. The antibody reacts against the B1 antigen, an epitope of the CD20 developmental cell surface protein. CD20 is a 35 kD cell surface phosphoprotein found on 95% of normal mature B-cells and more than 90% of B-cell non-Hodgkin's lymphomas and B-cell chronic lymphocytic leukemias tested, but not on T-cells, plasma cells, uncommitted

hematopoietic-precursors stem cells, dendritic cells, granulocytes, monocytes, or erythrocytes, or on tumors of T cell, myeloid or erythroid origin. CD20 is not shed and does not modulate from the surface after binding of antibody.

Anti-CD20 has been used extensively as a therapeutic agent for use in bone marrow purging. Clinical use of this antibody in marrow purging has shown it to be selective in eradicating B cell lymphomas as well as normal B-cells, while leaving other lymphocyte population intact. Some subpopulation of B cell precursors is left intact, as evidence by engraftment of the normal B cell compartment.

1.4 IDEC-C2B8

IDEC-C2B8 is a chimeric antibody with a murine variable portion and a human IgG1 kappa constant portion that recognizes the CD20 antigens expressed on normal B-cells and most malignant B-cell lymphomas. IDEC-C2B8 shows specificity for the CD 20 antigen and binds with an apparent affinity of 4.3×10^{-9}M. IDEC-C2B8 has also been reported to induce apoptosis and to sensitize drug-resistant human B-cell lymphoma cell lines to cytotoxic chemotherapy.

A phase I dose escalation pharmacokinetic trial of IDEC-C2B8 given as a single intravenous infusion using doses ranging from 10 mg/m^2 to 500 mg/m^2 in patients with relapsed or refractory low-grade lymphoma was reported by Maloney et al.[9] The median half-life of the free antibody at doses ranging from 100 mg/m^2 to 500 mg/m^2 was 4.4 days (range 1.6-10.5 days). In phase II clinical studies, anti-tumor activity has been observed in patients with relapsed or refractory low-grade or follicular B-cell NHL. The majority of adverse events was mild to moderate and included fever, fatigue, chills and nausea which were primarily associated with the initial infusions. No quantifiable human anti-mouse antibodies (HAMA) or human anti-chimeric antibodies (HACA) were observed. Depletion of peripheral B-cells occurred rapidly following the first infusion with recovery beginning 6 months post-treatment. Despite this depletion of B-cells, there was minimal change in serum IgG, IgM, and IgA levels and no increase in the frequency or severity of infectious complications. Anti-tumor activity was observed at various disease sites including peripheral blood, bone marrow, lymph nodes, spleen and abdomen.

A phase III trial to assess the safety and efficacy of IDEC-C2B8 375 mg/m^2 given once weekly for four doses in 166 patients with relapsed or refractory low-grade or follicular NHL was reported by McLaughlin et al.[10] The overall response rate in 151 evaluable patients was 50% (9CR; 67 PR)**.** The median duration of response has not been reached after a median follow-up of 9+ months. Conversion to negative bcl-2 status occurred in 57% of patients who were positive at baseline and subsequently reevaluated after the fourth infusion. No positive HAMA responses were observed in 67 patients evaluated and the incidence of HACA was less than 1%. Severe neutropenia and thrombocytopenia were observed in less than 2% of patients. IDEC-C2B8 has also been studied in 44 patients with relapsed diffuse large B-cell and mantle cell lymphoma. The overall response rate was 31%, with a 10% CR rate. Thus anti-CD20 monoclonal antibody has become a very effective salvage therapy for CD20+ B-cell low-and intermediate-grade NHL and this treatment has become an important addition to our armamentarium.

IDEC-C2B8 has also been studied in combination with chemotherapy. Czuczman et al[11]

conducted a phase II multi-center study evaluating the safety and anti-tumor activity of IDEC-C2B8 375 mg/m^2 for six doses in combination with six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy in 40 patients with low-grade NHL. Combination therapy appeared safe and toxicity profile observed was consistent with that seen with CHOP alone. No HAMA or HACA responses were observed. The overall response rate in 35 patients who completed treatment was 100% (21 CR; 14 PR). The median time to disease progression has not been reached with follow-up time of 9-27+ months. Seven of eight patients who were bcl-2 positive at baseline by polymerase chain reaction (PCR) became negative in both peripheral blood and bone marrow following treatment. This combined therapy is being investigated in previously untreated patients with intermediate- and high-grade NHL.

1.5 Results of Radiolabeled Antibodies in the Treatment of Non-Hodgkin's Lymphoma

Most recent radioimmunotherapy trials for lymphoma have utilized ^{131}I-labeled anti-B1 (anti-CD20) antibody. Kaminski et al[12] first reported on a trial utilizing multiple treatments with low dose ^{131}I-labeled anti-B1 antibody in ten patients who had a CD20 positive B-cell lymphoma in whom primary therapy had failed. Six of the nine treated patients had tumor responses, including patients with bulky or chemotherapy-resistant diseases. Four patients had complete remissions (CR), and two had partial responses. The follow-up time was relatively short, but no disease progression was observed in the four patients who achieved a CR at 8-11 months. Toxicity was minimal with mild or no myelosuppression.

Based on these results, a phase I/II study of ^{131}I-labeled anti-B1 was conducted in 58 heavily pre-treated patients with NHL (28 low-grade, 14 transformed low-grade, 15 intermediate-grade, and 2 high-grade).[13] The median number of prior therapy was 4, 88% had stage III or IV disease, 36% had bulky disease, 51% had an elevated LDH level and 14 had failed BMT. Patients received 1-3 dosimetric doses followed by a therapeutic dose. The dosimetric dose involved the IV administration of 5 mCi of ^{131}I anti-B1 antibody to determine the rate of whole body clearance so that a whole body radiation dose could be calculated. Each dosimetric dose was preceded by 0, 95, or 475 mg of unlabeled antibody. Therapeutic dose escalation was initiated at 25 cGy and adjusted in 10 cGy increment until the MTD. The MTD was 75 cGy for patients who had not undergone BMT. The overall response rate in these heavily pre-treated patients was 71% with a CR rate of 34%. The median duration of response was 271 days (95% CI; 40-394 days) and the median duration of CR was 566 days. Response was observed in both low-grade and transformed low-grade NHL as well as in patients with bulky disease and patients who had relapsed post-BMT.

Further trials of ^{131}I-labeled anti-B1 antibody at non-myeloablative doses has been studied in 4 separate clinical trials (phase I and II, single and multi-center) in 113 patients with low-grade NHL including 25 with transformed low-grade NHL.[14] Patients received a single dosimetric dose of 450 mg of unlabeled anti-B1 infusion over one hour followed by 35 mg radiolabeled with 5 mCi ^{131}I over ½ hour. The therapeutic dose was administered 7 to 14 days after the dosimetric dose and consisted of the same unlabeled and labeled antibody doses. The overall response rate was 77% with a CR rate of 45% and 67% of the complete responders were in continuous remission for > 4 years. Reversible hematologic toxicity was the dose- limiting toxicity. ANC < 100/mm^3 was observed in 2.6% of patients and platelets < 10,000/mm^3 in 5.3%. The nadir

typically occurred at week 5-6 with recovery by week 8-9. The most common non-hematologic toxicities were transient mild to moderate fever, nausea, asthenia, and chills. None of the patients developed HAMA. These results suggest that ^{131}I-labeled anti-B1 is safe and effective and may induce prolonged CR in heavily pre-treated low-grade and transformed low-grade NHL.

1.6 Results of ^{131}I anti-B1 Monoclonal Antibody with Autologous Bone Marrow Support

Although promising results have been reported with radiolabeled MAb for NHL, these results may be improved by using higher dose or myeloablative radiation dose. The use of radiolabeled MAb at myeloablative radiation dose followed by autologous stem cell rescue has been explored by investigators from The Fred Hutchinson Cancer Research Center. Press et al[15] conducted a trial utilizing higher dose of ^{131}I-labeled anti-CD20 antibody with autologous bone marrow rescue in 43 patients with B-cell lymphoma in relapse. In this study, sequential biodistribution studies were performed with escalating doses of antibody (0.5, 2.5, and 10 mg/kg) trace-labeled with 5 to 10 mCi of ^{131}I. Patients whose tumors were estimated to receive greater doses of radiation than liver, lungs, or kidneys (a favorable biodistribution) were eligible for the therapeutic infusion of ^{131}I-labeled antibody. Of the 43 patients, 24 had a favorable biodistribution, and 19 received therapeutic infusion of 234-777 mCi of ^{131}I-labeled antibodies (58-1168 mg) followed by autologous marrow infusion. Sixteen patients achieved a CR, two had a partial response and one had a minor response. Nine of the complete responders have remained in continuous CR for 3 to 53 months. Toxicities include myelosuppression, nausea, infection and two episodes of cardiopulmonary toxicity. In this study, cardiopulmonary toxicity was the dose limiting, non-hematopoietic toxicity of high-dose ^{131}I-labeled antibody.

In an attempt to reduce toxicity to normal tissues and to directly deliver higher dose of radiation to tumor sites, ^{131}I-labeled-anti-CD20 MAb has been incorporated into high-dose therapy regimen instead of TBI. Press et al[16] reported results of a phase I/II study to define the MTD of an ^{131}I-labeled anti-B1 monoclonal antibody which can be given with high-dose etoposide and cyclophosphamide in conjunction with ASCT in 38 (26 low-grade; 12 aggressive) NHL patients. Patients were treated in a cohorts of 4 patients each with doses of ^{131}I-anti-B1 antibody (2.5 mg/kg, 318-840 mCi) calculated to deliver 20-27 Gy of radiation to dose-limiting, critical normal organs, followed by etoposide (0 or 60 mg/kg), cyclophosphamide (100 mg/kg), and ABMT (15 patients) or ASCT (22 patients). Of the 37 evaluable patients, 33 (89%) were currently alive and 29 (78%) were progression-free after a median follow-up of 1.5 yr. Toxicities included grade 4 myelosuppression in all patients, grade 2-3 nausea in 26 (70%), pulmonary infiltrate in 4 and grade 3 VOD in 2 patients. There were four death; 3 from progressive NHL and 1 from disseminated Varicella. These results suggest that ^{131}I- anti-B1 antibody can be given at doses delivering $\geq$ 25 Gy to critical normal organs, with pulmonary and gastrointestinal toxicities being dose-limiting. Although additional studies are needed, ^{131}I-anti-B1 antibody can be safely given in combination with high-dose chemotherapy in an autologous stem cell transplant setting for NHL.

1.7 ^{90}Y -Anti-CD20 Radioimmunotherapy for Relapsed NHL

A phase I/II dose escalation study of ^{90}Y-murine anti-CD20 monoclonal antibody (MAb) in patients with recurrent B-cell lymphoma was performed by Knox et al.[17] The primary objectives

of the study were: (a) to determine the effect of the preinfusion of unlabeled anti-CD20 MAb on the biodistribution of ^{111}In-anti-CD20 MAb; (b) to determine the maximal tolerated dose of ^{90}Y-anti-CD20 MAb that does not require bone marrow transplantation; and (c) to evaluate the safety and antitumor effect of ^{90}Y-anti-CD20 MAb in patients with recurrent B-cell lymphoma. Eighteen patients with relapsed low- or intermediate-grade non-Hodgkin's lymphoma were treated. Biodistribution studies with ^{111}In- anti-CD20 MAb were performed prior to therapy. Groups of three or four patients were treated at dose levels of approx 13.5, 20, 30, 40, and 50 mCi ^{90}Y-anti-CD20 MAb. Three patients were retreated at the 40 mCi dose level. The use of unlabeled antibody affected the biodistribution favorably. Nonhematological toxicity was minimal. The only significant toxicity was myelosuppression. The overall response rate following a single dose of ^{90}Y-anti-CD20 MAb therapy was 72%, with six complete responses and seven partial responses and freedom from progression of 3-29+ mo following treatment. Radioimmunotherapy with less than or equal to 50 mCi ^{90}Y-anti-CD20 MAb resulted in minimal nonhematological toxicity and durable clinical responses in patients with recurrent B-cell lymphoma. Doses of less than or equal to 40 mCi ^{90}Y-anti-CD20 MAb were not myeloablative.

Results of a phase I/II study utilizing chimeric antibody Rituximab as the unlabeled clearing antibody and ^{90}Y conjugated anti-CD20 (IDEC-Y2B8, conjugated to the parent murine monoclonal 2B8) was recently reported. In the study reported by Witzig et al[18], the first portion of the study compared 100 mg/m^2 with 250 mg/m^2 of Rituximab as the clearing dose and compared dosimetry imaging capabilities. It was determined that 250 mg/m^2 of Rituximab was the optimal dose to be used. In the second portion of the phase I study, the dose of IDEC-Y2B8 was escalated from 0.2 mCi/kg to 0.4 mCi/kg. No bone marrow or stem cell harvest was required. None of the patients treated at 0.2, 0.3 and 0.4 mCi/kg whose baseline platelet count > 150,000/mm^3 developed grade 4 hematologic toxicity, whereas 3 of 6 patients treated at 0.2 or 0.3 mCi/kg with baseline platelet counts between 100,000 to 150,000/mm^3 developed transient grade 4 hematologic toxicity.

The dosimetry from this phase I/II trial of IDEC-Y2B8 was reported by Wiseman et al.[19] Forty-two patients with low- and intermediate-grade NHL received IDEC-Y2B8 following injection of unlabeled Rituximab (cold antibodies) followed by 2 mg of mouse anti-CD20 antibody labeled with 5 mCi ^{111}In (IDEC-In2B8). ^{90}Y 0.2, 0.3, or 0.4 mCi/kg was given 7 days following ^{111}I. The patients had ^{111}In dosimetry performed by serial whole body gamma camera imaging, urine collection and blood sampling at 0, 2, 6, 24, 48, 72, 96 and 144 hours. The highest mean calculated ^{90}Y radiation dose to a normal organ was spleen with 24.16 rads/mCi (0.6-67.0), followed by liver with 17.2 rad/mCi (9.4-39.2) and lungs with 12.9 rads/mCi (4.2-67.7). ^{90}Y dose of 0.4 mCi/kg was the MTD for bone marrow toxicity (thrombocytopenia and neutropenia). These results suggest that: 1) no organ irradiated beyond safety levels; 2) ^{111}I can serve as a predictor of ^{90}Y; 3) Rituximab dose of 250 mg/m^2 has been established as the “cold” antibody with added benefits of its therapeutic effect; and 4) bone marrow toxicity was the dose-limiting effect with full and predictable recovery.

Outcomes from this trial have been compiled in a submitted publication.[19] The overall response rate (ORR) for the intent-to-treat population (n = 51) was 67% (26% CR, 41% PR); for the low-grade group (n = 34) 82% (27% CR, 56% PR); 43% for intermediate grade (n = 4); and 0% for mantle cell (n = 3). Responses were seen in patients with bulky (> 7 cm) disease (41%) and

splenomegaly (50%). Kaplan-Meier estimate of time-to-progression in responders and duration of response is 12.9+ months and 11.7+ months, respectively. Adverse events were primarily hematologic and correlated with baseline extent of marrow involvement with NHL and baseline platelet count. Only one patient developed an anti-antibody response (HACA/HAMA).

1.8 Study Proposal

The high-dose therapy regimen of FTBI 1200 cGy, etoposide 60 mg/kg and Cy 100 mg/kg has been used extensively at City of Hope as a preparative regimen for patients with hematological malignancies. Given the relatively high relapse rate associated with this regimen, the effective anti-lymphoma therapy of IDEC-C2B8, and the safety and feasibility of IDEC-Y2B8 with the ability to directly deliver radiation to tumors sites, we propose to study a new preparative regimen in patients with relapsed NHL which will utilize ^{90}Y-labeled anti-CD20 antibody (IDEC-Y2B8) instead of TBI in combination with high-dose etoposide and cyclophosphamide. We plan to conduct a phase I/II trial to define the maximum tolerated dose (MTD) of IDEC-Y2B8 that can be given with high-dose etoposide and cyclophosphamide followed by ASCT, and to define the response rate and toxicities associated with this regimen. To avoid liver toxicity, etoposide dose will be started at 40 mg/kg and escalated to 60 mg/kg and the dose of Cy will be fixed at 100 mg/kg.

05/03/01, 06/16/04 The patient will undergo a dosimetry study with IDEC-In2B8 to confirm favorable localization of isotope one week prior to administration of therapeutic dose IDEC-Y2B8. Serial gamma camera images will be obtained at the end of the infusion, 24 hours, 48 hours, 72 - 96 hours, 120 hours and 144 hours post-infusion. At each time point, one whole body and 4 spot planar scans will be acquired with the Toshiba dual head camera. In addition, two SPECT images will be obtained at 48 and 72 -96 hour time points. Nuclear Medicine images will be used to estimate the distribution of activity in various organs, especially liver, lungs, kidney, heart and spleen. Blood samples will be drawn prior to IDEC-C2B8 and at approximately 0 hours (immediately prior to IDEC-In2B8), 2 hours, 4 - 6 hours, 24 hours, 48 hours, 72 - 96 hours, 120 hours and 144 hours following antibody infusion. These samples will be used to analyze antibody clearance and bone marrow dose estimates. Urine samples will be collected daily for six days to analyze radioisotope clearance.

05/03/01, 08/07/01, 06/16/04 Favorable biodistribution will be defined as tumor dose greater than any normal organ, except spleen and bone marrow, ie. liver, lung, kidney. For patients in CR at time of transplantation, no specific tumor localization is required as long as Ga 67 scan and/or FDG-PET scan is negative. Tumor dose will be calculated from multiple gamma camera images and blood/urine pharmacokinetics. If the patient shows favorable biodistribution, the therapeutic dose will be administered on day -14. Serial gamma camera images will be obtained at the end of the infusion, 24 hours, 48 hours, 72 - 96 hours, 120 hours and 144 hours post-infusion. At each time point, one whole body and 4 spot planar scans will be acquired with the Toshiba dual head camera. Nuclear Medicine images will be used to confirm estimates of the distribution of activity in various organs, especially liver, lungs, kidney, heart and spleen. Blood samples will be drawn prior to IDEC-C2B8 and at approximately 0 hours (immediately prior to IDEC-In2B8 / IDEC-Y2B8), 2 hours, 4 - 6 hours, 24 hours, 48 hours, 72 - 96 hours, 120 hours and 144 hours following antibody infusion. These samples will be used to analyze antibody clearance and bone

marrow dose estimation. Urine samples will be collected daily for six days to analyze radioisotope clearance. The therapeutic dose will be administered to deliver a target dose of 1000 cGy to the organ projected to receive the highest dose from the imaging study. After the first two dose levels the dose will be increased in increments of 250 cGy until a maximum of 2500 cGy is attained or dose limiting toxicity is encountered.

10/29/03

2.0 OBJECTIVES

05/10/00

2.1 To evaluate the safety and efficacy of a new preparative regimen of ^{90}Y-labeled anti-CD20 MAb (IDEC-Y2B8) in combination with high-dose etoposide and cyclophosphamide followed by ASCT for treatment of patients with relapsed/refractory and poor risk NHL.

2.2 To determine the MTD of ^{90}Y-anti-CD20 MAb which can be given with high-dose etoposide 60 mg/kg and high-dose cyclophosphamide 100 mg/kg followed by ASCT in patients with NHL.

2.3 To perform dosimetry study to estimate the radiation dose delivered to the tumor and normal organs.

2.4 To evaluate the short-term and long-term complication of this new preparative regimen.

3.0 STUDY DESIGN

This is an open-label phase I-II clinical and efficacy study of a new preparative regimen followed by autologous stem cell support in patients with relapsed and refractory NHL. Patients with low-, and intermediate-grade NHL who have relapsed followed conventional chemotherapy or have failed to achieve remission, and who are candidates for high-dose therapy and ASCT will be eligible for this study. All patients will receive IDEC-Y2B8 in combination with high-dose etoposide and cyclophosphamide followed by ASCT. The dose of Cy will be fixed at 100 mg/kg. There will be two doses escalating schema for etoposide and IDEC-Y2B8. Etoposide will be started at 40 mg/kg (cohort 1) and escalate to 60 mg/kg (cohort 2). The dose of Y2B8 will be the same for cohort 1 and 2, to deliver 1000 cGy to the normal organ receiving the greatest accumulation. If no dose limiting toxicity is observed, while the etoposide dose remains at 60 mg/kg, the dose of Y2B8 will be escalated to 1250 cGy, and then to a maximum of 2500 cGy, or until the MTD has been reached. Therefore, there will be cohorts with 3 patients per cohort as follows (an additional 2 patients per cohort will be accrued if there are eligible patients available prior to the determination of toxicity on the current dose level):

Cohort 1:	**Y2B8** to deliver **1000 cGy** to highest normal organ excluding spleen and bone marrow **etoposide 40 mg/kg** **cyclophosphamide 100 mg/kg**
Cohort 2:	Y2B8 to deliver 1000 cGy to highest normal organ excluding spleen and bone marrow **etoposide 60 mg/kg** cyclophosphamide 100 mg/kg

Cohort 3:	**Y2B8** to deliver **1250 cGy** to highest normal organ excluding spleen and bone marrow etoposide 60 mg/kg cyclophosphamide 100 mg/kg
Cohort 4:	**Y2B8** to deliver **1500 cGy** to highest normal organ excluding spleen and bone marrow etoposide 60 mg/kg cyclophosphamide 100 mg/kg
Cohort 5:	**Y2B8** to deliver **1750 cGy** to highest normal organ excluding spleen and bone marrow etoposide 60 mg/kg cyclophosphamide 100 mg/kg
Cohort 6 to 8:	**Y2B8** to deliver **2000-2500 cGy** to highest normal organ excluding spleen and bone marrow etoposide 60 mg/kg cyclophosphamide 100 mg/kg

05/03/01 All patients will have peripheral blood stem cell collected with the target CD34+ of $3.0x10^6$/kg. Patients will undergo dosimetry studies on day –21 and therapy on day -14. Etoposide will be given on day -4, followed by a day rest and cyclophosphamide on day -2. PBSC will be infused on day +1 when the radiation dose to the reinfused stem cells is estimated to be < 5 cGy.

4.0 DRUG FORMULATION

4.1 IDEC-Y2B8

a. Drug Formulation and Procurement

IDEC-2B8-MX-DTPA Two ml glass septum vial containing 2 ml (3.2 mg) IDEC-2B8-MX-DTPA in low metal normal saline at 1.6 mg/ml.

RITUXAN (IDEC-C2B8) Ten ml (100 mg) and/or 50 ml (500 mg) pharmaceutical grade glass vials at a concentration of 10 mg of protein per ml.
^{111}In-chloride 5 mCi of Indium-111 chloride supplied in .05M HCl.
^{90}Y-chloride 40-100 mCi Yttrium-90 chloride supplied in .05M HCl.

10/29/03 *b. Drug Toxicity*

Myelosuppression is the dose limiting toxicity in non marrow supported regimens. With marrow support liver, kidney, and lung are likely to be the dose limiting organs for toxicity. Infusional toxicity of chills and rigors are common with the first administration but rarely with subsequent doses. Decreasing the rate of infusion and the administration of antihistamines can control these toxicities.

c. Drug Storage, Reconstitution and Stability

All antibodies will be stored in the investigational pharmacy at 4ºC until the day of use.

Once diluted the unlabeled antibody is to be used within 24 hours if held at 4ºC and at room temperature for an additional 12 hours. The radiolabeled solutions should be used within 6 hrs and should be held at 2-8ºC until administered.

4.2 VP-16 (epipodophyllotoxin, etoposide, 4'-demethyl-9(4,6-o-ß) d-ethylideneglycopyranoside).

a. Drug Formulation and Procurement

VP-16 is supplied by Bristol Laboratories in a 100 mg ampule in 5 cc of a solution containing citric acid, 10 mg; benzyl alcohol, 150 mg; polysorbate 80, purified, 250 mg; polyethylene glycol 300, 3.75 gm; absolute alcohol q s., 5 cc.

b. Drug Toxicity

Myelosuppression, primarily granulocytopenia, is the dose-limiting toxicity. Gastrointestinal toxicity at high doses includes nausea, emesis and mucositis. Reversible hepatotoxicity may occur at very high doses. The acute side effects of occasional bronchospasm and hypotension are avoided by slow intravenous administration.

c. Drug Storage, Reconstitution and Stability

The contents of the ampoule are diluted with 50 volumes of NaCl solution for injection, USP, and administered by slow intravenous infusion. Patients will receive the drug through a central venous catheter at a rate of 60 mg/kg/4 hours.

4.3 Cyclophosphamide (Neosar, Cytoxan), NSC-26271

a. Drug Formulation and Procurement

Cyclophosphamide is an alkylating agent dispensed in 100, 200 and 500 mg vials containing a dry powder. Cyclophosphamide will be purchased from Adria Laboratories.

b. Drug Toxicity

Patients must be well hydrated before and for several hours following administration of cyclophosphamide to reduce the potential for hemorrhagic cystitis. The more common side effects include nausea and vomiting, and alopecia. Acute toxicity includes principally leukopenia, with the nadir occurring 7-14 days after a single IV dose. At high doses, occasional pulmonary toxicity has been reported. Rare cardiac toxicity (congestive heart failure) has occurred in patients previously treated with anthracyclines.

c. Drug Storage, Reconstitution and Stability

Cyclophosphamide is reconstituted with either sterile water for injection, USP or bacteriostatic water for injection, USP (Paraben preserved only), using 5 ml for the 100 mg vial, 10 ml for the 200 mg vial or 25 ml for the 500 mg vial. Each ml of reconstituted solution contains 20 mg cyclophosphamide per ml. The drug is diluted in 5% dextrose and water or physiological saline and given by IV infusion.

4.4 Mesna (Sodium 2-Mercaptoethane sulfonate)

a. Drug Formulation and Procurement

Mesna is provided by Bristol Laboratories as a 10% (100 mg/ml) solution in water with 0.25 mg EDTA as excipient in 4 ml ampules.

b. Drug Storage, Reconstitution and Stability

Mesna solutions have been shown to be stable on extended storage at room temperature in ampules. No change in composition of the ampules was noted at one year's storage in these conditions.

On exposure to air Mesna is known to undergo oxidation to disulfide. Since the Mesna concentration of opened ampules may decrease with time, the ampule should be opened just before use and the unused part discarded.

c. Administration

Each dose of Mesna will be diluted in 50 cc of 5% dextrose/water or 0.9% normal saline and infused intravenously over 15 minutes.

06/05/00

4.5 DTPA (Diethyltriaminepenatacetic acid)

a. Drug Formulation and Procurement

DTPA will be purchased from Heyl Pharmaceuticals, Berlin, Germany. It is supplied as a 1 gram ampule in 5 mls.

b. Drug toxicity

DTPA has been known to cause headaches, fever, chills, flu-like symptoms, nasal stuffiness, nausea, vomiting, abdominal cramping, and diarrhea. Other side effects that are less common include pain at the injection site, dehydration, decreased blood pressure, irregularities of heart rhythm, decreased blood counts, increased calcium, numbness and tingling, sneezing, excessive tearing, kidney damage, and zinc deficiency (which can result in a facial and perianal rash and tongue and mouth sores). In addition, there is always a risk of a very uncommon or previously unknown side effect occurring. Stopping the infusion normally reverses the side effects. Headaches and tingling have been observed at the City of Hope but were reversible. Trace metals will be administered at the end of infusion to replace any depleted heavy metals.

c. Drug Storage, Reconstitution and Stability

The DTPA solution will be diluted with 250 mls normal saline and administered over 24 hours. Additional IV fluids will be administered to maintain a minimum of 125 mls/hour of fluid. No other heavy metals should be administered during the 24 hour infusion. Potassium may be administered as needed. DTPA has a long aqueous stability but should

be used within 48 hours of being drawn up by the pharmacy. Patients will receive 250 mgs/m^2 to a maximum of a total dose of 500 mgs.

5.0 STAGING CRITERIA

Staging of disease must be evaluated at least 21 days after the end of the last chemotherapy and within 42 days prior to transplant.

5.1 The Ann Arbor staging criteria will be used. Stage is determined based on extent of disease at the time of diagnosis.

5.2 Ann Arbor Classification (AJCC Manual for Staging of Cancer, 4th ed. 1992)

STAGE I	Involvement of a single lymph node region (1) or a single extralymphatic organ or site (1_E).
STAGE II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and its associated regional lymph nodes (11_E).
STAGE III	Involvement of lymph node regions on both sides of the diaphragm (111) which may be accompanied by localized involvement of an associated extralymphatic organ or site (111_E) or spleen (111_S) or both (II(1_{SE}).
STAGE IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement.

A = Asymptomatic
B = Fever, sweats, weight loss > 10% of body weight

5.3 Definitions of Sensitivity of Disease:

Patients are grouped into one of three groups based on sensitivity of disease:

1. *Induction failure*: patients who did not achieve a CR or PR from induction chemotherapy;

2. *Resistant Relapse*: patients who did not achieve a CR or PR from the most recent standard salvage chemotherapy;

3. *Sensitive Relapse*: patients who did achieve a CR or PR from the most recent standard salvage chemotherapy.

05/10/00

5.4 Definitions of Poor Risk Disease

1. Age Adjusted International Prognostic Index (IPI) High- (3 risk factors) or High-Intermediate (2 risk factors) based on the following risk factors: stage III-IV, elevated serum lactate dehydrogenase level (LDH) and ECOG performance status 2-4.

2. Patients with aggressive NHL including mantle cell lymphoma who required 2 different induction chemotherapy regimens to achieve a partial/complete remission.

05/03/01 *3.* Patients with B-Cell NHL who fail to achieve a complete remission after adequate induction chemotherapy regimen(s).

05/10/00 **6.0 ELIGIBILITY CRITERIA**

05/10/00 ***6.1*** Favorable biodistribution on imaging dose

08/07/01 ***6.2*** age ≥ 18 and ≤ 60 years

10/29/03 ***6.3*** All patients must have biopsy proven diagnosis of low- and intermediate-grade NHL including follicular small cleaved, follicular mixed, follicular large cell, diffuse small cleaved, diffuse mixed, diffuse large cell, and immunoblastic lymphoma (working formulation B, C, D, E, F, G and H) including mantle cell lymphoma. Transformed low-grade lymphomas are eligible

6.4 Demonstrated monoclonal CD20 + B-cell population in lymph nodes and/or bone marrow

05/10/00 ***6.5*** Patients must have relapsed after achieving a complete or partial response to prior therapy, have never responded to prior therapy or have poor risk disease

05/10/00,05/30/02 10/29/03 ***6.6*** Patients must have bone marrow aspiration and biopsy within 42 days before salvage chemotherapy or stem cell collection which show ≤ 10% lymphomatous involvement of total cellularity

09/08/00, 05/30/02 ***6.7*** Platelet count should be normal before initiation of chemotherapy for salvage purposes or stem cell mobilization. If the patient collected his/her stem cells at an outside facility, then the platelet count must be normal before the imaging dose of antibody

6.8 Normal renal function test with serum creatinine of ≤ 1.5 mg/dl, or a creatinine clearance of ≥ 60 ml/min

6.9 Adequate pulmonary function as measured by FEV1 > 65% of predicted measured, or a DLCO ≥ 50% of predicted measured

04/06/04 ***6.10*** Cardiac Ejection fraction of > 50% by echocardiogram or multiple gated acquisition scan

6.11 Adequate liver function tests with a bilirubin of ≤ 1.5 x normal and SGOT or SGPT ≤ 2 x normal

6.12 Negative human immunodeficiency virus antibody

05/03/01 ***6.13*** ECOG performance status 0 or 1; or KPS ≥ 80

6.14 No active CNS disease or prior history of CNS disease

07/13/00 ***6.15*** Patients who have received involved field external beam therapy to area excluding lung, heart, liver and kidney are allowed, but will be evaluated on a case by case basis

6.16 Patients must have recovered from last therapy and should be at least four weeks from prior radiation or chemotherapy

08/07/01 ***6.17*** The patient should have a baseline CT scan and Ga 67 scan and/or FDG-PET scan after the last chemotherapy prior to initiation of treatment

10/29/03 ***6.18*** Normal cytogenetic study on bone marrow (prior to salvage chemotherapy or stem cell collection). However, cytogenetic study on peripheral blood is acceptable if bone marrow biopsy has already been done and shows no sign of MDS or lymphoma and a repeat bone marrow is deemed unnecessary by attending physician

7.0 EXCLUSION CRITERIA

7.1 Presence of human anti-mouse antibody (HAMA) or human anti-chimeric antibody

7.2 Prior radioimmunotherapy

7.3 Failure to collect adequate number of CD34 + cells $\geq 3x10^6$ /kg

7.4 Abnormal cytogenetic study on the bone marrow aspirate sample prior to stem cell collection

7.5 Prior bone marrow transplantation

07/13/00 ***7.6*** Prior malignancy except for adequately treated basal cell or squamous cell skin cancer, adequately treated noninvasive carcinomas, or other cancer from which the patient has been disease-free for at least five years

7.7 Active evidence of Hepatitis B and C infection; Hepatitis B surface antigen positive

02/08/01 ***7.8*** History of alcohol abuse

10/29/03 ***7.9*** Patient weighs more than 250 pounds

8.0 TREATMENT PLAN

8.1 Outline of the preparative regimen

	Day -21	Dosimetry with 5 mCi IDEC-In2B8 following 250 mg/M^2 Rituxan
	Day -14	IDEC-Y2B8 with 5 mCi IDEC-In2B8 following 250 mg/M^2 Rituxan
05/30/02	*Day -7*	Bone marrow biopsy and dose estimation
05/30/02, 10/29/03	*Day -4*	Etoposide 40 mg/kg adjusted ideal body weight (Cohort 1) or 60 mg/kg adjusted ideal body weight for other cohorts
10/29/03	*Day -2*	Cyclophosphamide 100 mg/kg ideal body weight
06/05/00	*Day 0*	DTPA infusion
	Day +1	Peripheral Stem Cell reinfusion
	Day +1	Start G-CSF 5 μg/kg/d IV

07/13/00 ***8.2 Pre-Transplant Therapy***

10/29/03 *a. Autologous Stem Cell Collection and Cryopreservation*

All patients should have bone marrow aspiration and biopsy which show no microscopic evidence of lymphomatous involvement, or ≤ 10% involvement at the time of stem cell collection. In addition, cytogenetic studies, immunophenotyping, gene rearrangement should be done. Peripheral blood stem cells (PBSCs) will be collected via leukapheresis procedures that have been previously described. Patients will receive PBSCs collected after mobilization by: 1) growth factors, ie. G-CSF 10 μg/kg/d or 2) chemotherapy with growth factors. A minimum of CD34+ cells, 3.0 x 10^6/kg should be collected.

b. Trimethoprim Sulfa

All patients should receive trimethoprim sulfa (one double-strength tablet PO bid) beginning day -8 through day -2 prior to PBSCT as prophylaxis against PCP. (The choice of trimethoprim sulfa as a prophylactic agent may be altered based on a history of sensitivity to this agent.) Dosing should be discontinued 48 hours prior to PBSC infusion because of potential myelosuppression.

10/29/03 *c. CNS Prophylaxis*

CNS prophylaxis is recommended for patients with mantle cell lymphoma or diffuse large cell lymphoma who had bone marrow involvement at diagnosis or at time of relapse. For patients with mantle cell lymphoma who have never received high-dose MTX, CNS prophylaxis with intrathecal chemotherapy should be given.

8.3 Radioimmunotherapy

08/07/01 *a.* Rituxan is to be administered by slow intravenous infusion having been diluted to 1-4 mg/ml in saline. Initial infusion should be through a dedicated line at a rate of 50 mg/hr. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes to a maximum rate of 400 mg/hr. If hypersensitivity or infusion-related events develop, the infusion should be temporarily slowed or interrupted. The infusion can be continued at one-half the previous rate when symptoms abate.

b. IDEC-In2B8 Administration - Two mg of IDEC-In2B8 (5.0 mCi of ^{111}In) will be administered for the dosimetry portion of the protocol. The imaging dose will be administered over 10 minutes by slow IV injection immediately following the infusion of Rituxan. A .22 micron filter must be on the line between the patient and the infusion port. Flush the line with at least 10 mls of normal saline after the IDEC-In2B8 has been infused.

c. IDEC-Y2B8 Administration – IDEC-Y2B8 (40-100 mCi of ^{90}Y with 3.2 – 6.4 mg of antibody) will be administered for the therapy portion of the protocol. The yttrium will be combined with a dose of IDEC-In2B8 (5.0 mCi of ^{111}In) identical to the dosimetry dose. The combined radiopharmaceuticals will be administered

by controlled infusion pump over 20 minutes. A .22 micron filter must be on the line between the patient and the infusion port. Flush the line with at least 10 mls of normal saline after the IDEC-In/Y2B8 has been infused.

d. Bone marrow biopsy.

8.4 Chemotherapy

10/25/00, 12/20/00

a. VP-16 is to be administered as a single infusion on day -4. The dose is 40 or 60 mg/kg and is calculated on adjusted ideal body weight to be consistent with standard VP-16 dosing for transplant protocols. The drug is infused undiluted directly into a port of a double or triple lumen indwelling intravenous catheter, with a total infusion time of 4 hours. The drug is to be drawn into one or more plastic syringes and infused with a syringe infusion pump, placed in an evacuated bottle and infused through a pediatric infusion pump, or infused by gravity without a pump. Thus the total dose for a 70 kg patient would be 4,200 mg. At 20 mg/ml, the volume of VP-16 would be 210 ml. The rate of infusion would thus be 210 ml/240 minutes or 0.875 ml/minute. Appropriate anti-emetics and sedatives should be given before the infusion begins. Before, and 2 hours into, the infusion the patient is to receive 25 mg of diphenhydramine, and 100 mg of hydrocortisone to prevent allergic reactions. If necessary, diuretics may be given. The intravenous hydration should be continued before, during and after the VP-16. Since in rare cases metabolic acidosis has been observed after high dose VP-16, additional NaHCO3 may be needed.

10/29/03

b. Cyclophosphamide is administered at a total dose of 100 mg/kg given in one dose on day -2 and is calculated on ideal body weight. Adjustments to the ideal body weight calculation for overweight patients are permitted. For patients who are weigh less than 95% of ideal body weight, cyclophosphamide will be dosed according to actual body weight. The drug should be dissolved in about 250 cc of D5W and infused IV over two hours. Appropriate anti-emetics and sedatives should be given. To prevent hemorrhagic cystitis, all patients should receive hydration with intravenous fluids, according to institutional standards, at the rate of 3.0 l/m2/day beginning four hours prior to cyclophosphamide and continuing until 24 hours after cyclophosphamide. In addition, mesna at 40 mg/kg (based on ideal body weight) will be given immediately before cyclophosphamide (hr 0) and at 3, 6, 9, 12, 15, 18 and 21 hrs later for a total of 8 doses. Each dose of mesna will be given IV over 15 minutes.

06/05/00, 10/29/03, 06/16/04

c. DTPA is to be administered by continuous intravenous infusion through a port of a double or triple lumen indwelling intravenous catheter. The dose should be $\geq$ 250 mgs/m^2, but $\leq$ 500 mgs. The DTPA should be made up in normal saline and infused over 24 hours by infusion pump. No magnesium or other heavy metal should be given during the same time period. Two hours after the end of the DTPA infusion 1 ml of trace metal solution should be infused every eight hours for five days. This should be given by slow intravenous delivery or else as part of standard hyperalimentation. Urine samples will be collected every 12 hours for

72 hours beginning 24 hours prior to DTPA infusion.

07/13/00, 05/03/01 ***8.5 Peripheral Stem Cell Reinfusion***

PBSCs will be thawed and infused according to standard guideline at approximately 72 hours after completion of cyclophosphamide.

8.6 Growth Factor Therapy

All patients will receive rh-G-CSF, 5 mcg/kg/day IV beginning on day +1, after PBSC infusion and continue daily until ANC >500 for 3 consecutive days.

07/13/00 ***8.7 Supportive Care:***

All patients will be housed in private rooms during the period of granulocytopenia. Nonabsorbable antibiotics for gastrointestinal decontamination should be used according to institutional guideline. Trimethoprim-sulfamethoxazole will be administered from day -8 to day -2 and prophylaxis should be re-instituted when white blood cells are > 3000 and continued until 6 months post-transplant. Empiric broad spectrum antibiotics and parenteral nutrition should be used as clinically indicated. Low-dose amphotericin-B (0.1 to 0.2 mg/kg) should be administered on day +1 and continued daily until granulocytopenia resolves. All blood components should be irradiated to 1,500 cGy.

a. Access to Vessels

Prior to admission, during pre-transplant evaluation, all patients should have a permanent central catheter placed.

b. Hyperalimentation

All patients will receive appropriate Hyperalimentation as soon as necessary after admission. The goal will be to prevent even a short duration of negative nitrogen balance.

c. Platelet Transfusion

1. Indication. Platelets are transfused to prevent bleeding and an attempt is made to keep the circulating level greater than 20,000/mm3 at all times. This goal may be changed by the attending physician as clinically indicated.

2. Irradiation. All blood products (except the autologous stem cells) are irradiated with 1,500 cGy prior to infusion.

d. Management of Fever/Infections

Treatment of patients on this protocol is not intended to restrict the freedom of the managing physician to treat suspected or documented infections. In neutropenic patients, however, the following guidelines should be followed.

1. All febrile, neutropenic patients should be treated with IV antibiotic(s), the choice

of which should be guided by the patient's clinical history, institutional practices and subsequent culture results.

2. Patients with documented, invasive fungal infection or with persistent, unexplained fevers while neutropenic and on broad-spectrum antibiotic therapy should receive antifungal therapy with Amphotericin-B.

8.8 Criteria for Removal from Protocol Treatment

a. Progression of disease.

b. Patients may withdraw from study at any time for any reason.

8.9 All reasons for discontinuation of treatment must be documented in the Flow Sheets.

8.10 All patients will be followed for survival until death. Secondary malignancy monitoring on this protocol will be done through 5 years post HCT. After such time, secondary malignancy monitoring will be done by the Long Term Follow Up office.

9.0 STUDY DESIGN AND RULES FOR DOSE ESCALATION

This is a phase I/II trial. For the phase I portion of the study, the rules for dose escalation, dose expansion, and termination of escalation are given in section 9.2. Prior to treatment with Y2B8, patients are required to undergo an imaging scan to verify that they have a favorable biodistribution. While waiting to assess toxicities in the initial cohort of 3 to 6 patients, additional patients who are determined to be eligible may be accrued at the unescalated dose level. The rationale for this is twofold. First, patients must be evaluated for distribution as soon as possible in order to have patients ready for timely accrual to the next dose level. If the dose escalation decision is delayed, the investigators want to treat the patients at the unescalated dose level so that their disease does not progress. Second, patients will be accrued to unescalated dose levels to avoid a loss of momentum in patient accrual. Modifications to the standard phase I design involving accrual of cohorts of 3-6 patients per dose level have been incorporated to appropriately handle the varying number of patients accrued to each dose level (see section 9.2). Study design considerations and targeted response rates for the phase II portion of the trial are given in section 9.3. Because the eligibility criteria are the same for both the phase I and the phase II portions of the trial, the patients treated at the dose level defined as the MTD from the phase I portion of the trial will count towards the accrual for the phase II portion of the trial.

9.1 Dose Limiting Toxicity (DLT)

05/03/01

Dose limiting toxicity (DLT) in a given patient is defined as any grade III non-hematologic toxicity not reversible to grade II or less within 96 hours, or any grade IV non-hematologic toxicity. Toxicity will be graded according to the NCI Common Toxicity Criteria (CTC) version 2.0 and toxicity Module (Appendices I and II, http://ctep.info.nih.gov/ctc3/ctc.htm) with the addition of BMT Complex/Multi-Component Events (Appendix VI, http://ctep.info.nih.gov/ctc3/ctc.htm). To be evaluable for toxicity, a patient must receive a complete course of treatment and be observed for 6 weeks after the administration of Y2B8 or have experienced a DLT. All patients who are not evaluable for toxicity will be replaced.

9.2 Definition of Maximum Tolerated Dose (MTD) and DLT-Level and Rules for Dose Escalation

This trial differs from the standard phase I design in that additional patients beyond the standard 3 or 6 patients per dose level may be accrued to the current dose level while waiting to assess toxicities in the initial 3 or 6 patients. To this end, a decision rule has been added that incorporates toxicity information from the additional patients accrued to a dose level. As toxicity information on each additional patient accrued to the trial becomes available, the decision to escalate, de-escalate and expand the previous dose level, expand the current cohort or stop the trial will be evaluated. The decision rule (R) will be as follows: Let x = number of DLTs in n patients. Escalate to the next dose level if $R = (x + 0.5) / (n + 2)$ is ≤ 0.20. Stop accrual to a dose level if $R > 0.30$. Continue accrual to a dose level if $0.20 < R \leq 0.30$. A minimum of three patients must be accrued to a dose level. As soon as 3 patients have been accrued to a dose level and toxicity has been assessed, escalation to the next level is allowed, provided that acceptable toxicity has been observed. If accrual to a dose level must be expanded due to toxicity, a minimum of 6 patients must be accrued to the expanded dose level.

Operationally, the rule is to close a dose level and de-escalate if 2 DLTs are observed among 6 or fewer patients, or if 3 DLTs are observed among any number of patients. The dose will be escalated if 0 DLTs are observed in 3 or more evaluated patients, if 1 DLT is observed in 6 or more evaluated patients, or if 2 DLTs are observed in 11 patients. At most, 11 patients will be accrued to a dose level. However, if a dose is escalated while toxicity follow-up is still outstanding for some patients, the accumulating results from the two dose levels may be pooled for the purpose of justifying the continued accrual to the higher dose.

Table 1 shows values for R based on different combinations of DLTs and numbers of patients. Values indicating continued accrual to the current dose are shown in bold.

Table 1

	Number of DLTs (x)		
Number of Patients (n)	**0**	**1**	**2**
3	0.10	**0.30**	0.50
4	0.08	**0.25**	0.42
5	0.07	**0.21**	0.36
6	0.06	0.19	0.31
7	0.06	0.17	**0.28**
8	0.05	0.15	**0.25**
9	0.05	0.14	**0.23**
10	0.04	0.13	**0.21**
11	0.04	0.12	0.19

This criterion is the posterior mean with a beta (0.5, 1.5) prior, which has a smaller mean, but is no more informative than a flat prior. The criterion is consistent with the conventional rule of expanding a dose level to six patients if 1 out of 3 patients experience DLT and stopping if 2 or

more patients out of 6 treated at the same dose level experience DLT. The proposed criterion rationalizes the conventional design in order to rationally extend if to larger numbers of patients per dose level. The rationalization is that a dose level is opened with a weak prior expectation of a 25% DLT rate, and the dose is escalated or de-escalated as the accumulating data indicate a rate below 20% or above 30%.

The phase I portion of the trial will be closed when 6 patients have been accrued to the highest dose level below the DLT level with at most 1 patient experiencing DLT or when 11 patients have been accrued with at most 2 patients experiencing DLT. This dose level will be defined as the MTD.

To demonstrate an application of the escalation rule, consider the following examples:

Example 1: Three patients are accrued to dose level 1. A fourth patient is accrued to the trial prior to assessment of toxicity for the third patient and is therefore also treated at dose level 1. No DLTs are observed in the first 3 patients such that the fifth patient is accrued to dose level 2 and subsequent to this the fourth patient accrued to dose level 1 experiences a DLT. With 1 DLT in four patients, from Table 1 the value for R is 0.25 therefore accrual to dose level 2 must be halted such that accrual to dose level 1 can be expanded. Six patients will need to be accrued with at most 1 out of 6 patients experiencing DLT in order for accrual to dose level 2 to resume. The patient treated at dose level 2 may be counted among the required 6 patients if no DLT is encountered.

Example 2: Dose level 3 is expanded such that 6 patients are accrued. A seventh patient is accrued to the trial prior to assessment of toxicity for the sixth patient and is therefore also treated at dose level 3. Only one DLT is observed in the first 6 patients such that the eighth patient is accrued to dose level 4 and subsequent to this the seventh patient accrued to dose level 3 experiences a DLT. With 2 DLTs in seven patients, from Table 1 the value for R is 0.28 therefore accrual to dose level 4 must be halted so that accrual to dose level 3 can be expanded. Eleven patients (including the patient treated at dose level 4) will need to be accrued to dose level 3 (or above) with at most 2 patients experiencing DLTs in order for accrual to dose level 4 to resume. Two DLTs among 11 patients corresponds to R = 0.19 which is consistent with 1 DLT among 6 patients. A maximum of 11 patients can be accrued to a single dose level.

9.3 Design Considerations for the Phase II Trial

All patients accrued to the dose level established to be the MTD will be included in the assessment of response for the phase II portion of the trial. The primary goal of this portion of the trial is to obtain estimates of the efficacy of IDEC-Y2B8 in combination with high-dose etoposide and cyclophosphamide followed by ASCT for treatment of patients with relapsed and refractory NHL. A minimum of 17 and a maximum of 37 patients will be accrued to this portion of the trial. Justification for the sample size as well as a description of the study design for the phase II portion of the trial is provided in section 12.0.

10.0 STUDY CALENDAR - PREPARATIVE REGIMEN AND PBSCT

	REQUIRED STUDIES	Pre Study	DAY -21	DAY -14	DAY -7	DAY -4	DAY -2	DAY 0	DAY 7	DAY 14	DAY 30	DAY 60	DAY 100	DAY 180	YR 1	YR 2
	PHYSICAL															
	H & PE	X		X	X	X	X	X	X	X	X	X	X	X	X	X[$]
10/29/03	Weight and KPS	X			X			X			X	X	X	X	X	X[$]
	Tumor Assessment	X									X			X	X	X[$]
	Toxicity Notation				X	X	X	X	X	X	X	X	X	X	X[$]	X[$]
	LABORATORY															
10/29/03	CBC/Platelets	X			X	X	X	X	X	X	X	X	X	X	X	X[$]
10/29/03	Differential[¥]	X			X				X	X	X	X	X	X	X	X[$]
08/07/01, 10/29/03	HAMA/HACA	X										X	X	X[«]	X	
10/29/03	Comp Metabolic Panel + LDH	X		X	X	X	X	X	X	X	X	X	X	X	X	X[$]
10/29/03	Magnesium	X		X	X	X	X	X	X	X	X					
	PT/PTT	X														
	Immunoglobulin Levels	X									X		X	X	X	
08/07/01	Peripheral Blood Mononuclear Immunophenotyping	X									X		X	X	X	
	CMV Titer	X														
	Hepatitis Profile	X														
10/29/03	Herpes Simplex	X														
	HIV Antibody	X														
08/07/01, 05/30/02	BM[%, #]	X			X^								X		X	X
05/03/01	Creatinine Clearance													X	X	
	X-RAYS AND SCANS															
05/30/02	Chest X-ray or CT Chest	X			X			X		X	X		X	X	X	X[&]
05/30/02	CT scans*, [+]	X									X		X	X	X	X[&]
	EKG	X													X	
	MUGA or ECHO	X												X	X	
	DLCO/FEV1	X												X	X	
08/07/01, 10/29/03, 04/06/04	Ga 67 Scan and/or FDG-PET Scan	X[¢]									X[◊]			X	X	
	TREATMENT															
	Stem Collections	X														
	IDEC-In2B8		X	X												
	IDEC-Y2B8			X												
	Rituxan		X	X												
	VP-16					X										
	Cyclophosphamide						X									
06/16/04	PBSCT							X[§]								
06/16/04	G-CSF							X[§]								
06/05/00	DTPA							X								

10/29/03 (delete @,06/20/07) & restaging at Day 100, at 6 months then follow-up evaluation every six months for three years, and then yearly up to 5 yrs post BMT

$ All late complications such as cataracts formation and occurrence of second malignancies must be documented and reported.

***** CT scans of chest, abdomen and pelvis as indicated

08/07/01 (delete #, add^) ^ biopsy core for determination of radioactivity

05/03/01 % bone marrow aspiration and biopsy, cytogenetic study, immunophenotyping and gene rearrangement

05/30/02, 06/20/07 # Follow-up bone marrow is required at day 180, yr 1 up to 5 yrs post BMT.

05/30/02, 10/29/03 + For pts in CR at time of transplant, CT scans to be done between days 30 and 100.

10/29/03 « Day 180 HAMA/HACA acceptable between days 150 and 210

10/29/03 ¢ Pre-study PET scan should be done 14 days after stem cell collection to avoid GCSF enhancement effect

10/29/03 ¥ ANC is acceptable in lieu of differential

04/06/04 ◊ If PET scan positive at baseline, day +30 PET scan required

06/16/04 § Day +1

11.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Definitions

a. *Measurable Disease*: Bidimensionally measurable lesions with clearly defined margins by: 1) medical photograph (skin or oral lesion), or plain x-ray with at least one diameter .5 cm or greater (bone lesions are not included) or, 2) CT, MRI or other imaging scan with both diameters greater than the distance between cuts of the imaging study, or 3) palpation with both diameters 2 cm or greater.

05/30/02

b. *Evaluable Disease*: Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with both diameters less than 0.5 cm, lesions on scan with either diameter smaller than the distance between cuts, palpable lesions with either diameter less than 2 cm, bone disease.

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

d. *Objective Status, To Be Recorded at Each Evaluation*: If an organ has too many measurable lesions to measure at each evaluation, choose three to be followed before the patient is entered on study. The remaining measurable lesions in that organ will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when ALL is measurable and evaluable sites and lesions are assessed.

11.1 Complete Response (CR)

Complete disappearance of all measurable evidence of non-evaluable disease. No new lesions. No disease related symptoms. No evidence of non-evaluable disease, including normalization of markers and other abnormal lab values. All measurable, evaluable and non-evaluable lesions and sites must be assessed using the same techniques as baseline. Refers to clinical CR-when restaging surgery is required, a separate pathologic response variable is defined.

11.2 Partial Response (PR)

Applies only to patients with at least one measurable lesion. Greater than or equal to 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. All measurable and evaluable lesions and sites must be assessed using the same techniques as baseline.

11.3 Stable Disease (SD)

Does not qualify for CR, PR or Progression. All measurable and evaluable sites and lesions must be assessed using the same techniques as baseline.

11.4 Progressive Disease (PD)

50% increase or an increase of 10 cm^2 (whichever is smaller) in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same

techniques as baseline, OR clear worsening of any evaluable disease, OR reappearance of any lesion which had disappeared, OR appearance of any new lesion/site, OR failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer). For "scan only" bone disease, increased uptake does not constitute clear worsening. Worsening of existing non-evaluable disease not constitute progression.

11.5 Relapse

08/07/01 Relapse is defined as the re-appearance of any clinical evidence of lymphoma in a patient who has had a CR. Relapse for partial responders are defined as progressive disease relative to disease status during the partial remission.

11.6 Duration of Response

This is measured from the documented beginning of response (CR or PR)

11.7 Performance Status

Patients will be graded according to the current Performance Status Scales/Scores (Appendix IV).

11.8 Time to Progression

From date of registration to date of first observation of progressive disease or death due to any cause.

11.9 Time to Death

From date of registration to date of death due to any cause.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design and Justification of Sample Size

The definition of dose limiting toxicity is given in section 6.1. The maximum tolerated dose is defined in section 6.2. The number of patients to be treated at each dose level examined in the phase I trial as well as the rules for dose escalation is given in section 6.2.

The phase II portion of the study will follow a two-stage minimax design suggested by Simon (1). It is assumed that a true response rate less than 20% would not warrant further study of this agent. It is also assumed that a response rate of 40% would be considered promising for further studies in these patients. In the first stage, seventeen evaluable patients will be entered. If less than four responses are observed, the accrual will stop with the conclusion that the regimen is not promising for further study. If four or more responses are observed in the first 17 patients, additional 20 patients will be accrued during the second stage of the study. Eleven or more responses out of 37 patients will be considered as evidence warranting further study of the regimen providing other factors, such as toxicity and survival, also appear favorable. If less than 11 responses out of 37 patients are observed, further study of the regimen would not be warranted.

The probability of falsely declaring an agent with a 20% response probability as warranting further

study is 0.10 (alpha) and the probability of correctly declaring an agent with a 40% response probability as warranting further study is 0.90 (power). With 37 patients the true probability of response can be estimated with a maximum standard error equal to 0.08.

The phase I portion study is expected to accrue a minimum of 15-18 evaluable patients and a maximum of 30. The phase II portion of the study will accrue a minimum of 17 patients and a maximum of 37 patients, of which at least six of these patients will have been included in the phase I portion of the study. It should take approximately 24-36 months to complete both the phase I and phase II portions of this trial.

12.2 Analysis of Clinical Endpoints

Patients will be considered evaluable for response and evaluable for toxicity as outlined in section 11.0. The toxicities observed at each dose level will be summarized in terms of type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI Common Toxicity Criteria and nadir or maximum values for the laboratory measures), time of onset (i.e. course number), duration, and reversibility or outcome. Tables will be created to summarize these toxicities and side effects by dose and by course. Baseline information (e.g. the extent of prior therapy) and demographic information will be presented, as well, to describe the patients treated in the phase I portion of the study. All responses will be reported from the phase I portion of the study

Response rates and duration of response will be estimated for the phase II portion of survival. Confidence intervals for the response rate will be established by calculating exact 95% confidence limits for a binomial parameter. The duration of overall and disease-free survival of the patient will be estimated using the product-limit method of Kaplan and Meier.

13.0 REGISTRATION GUIDELINES

08/07/01 Once a signed, written informed consent has been obtained and all pretreatment evaluations have been performed, patients will be entered on study, after review of patient eligibility criteria by the assigned Data Manager from the City of Hope Department of Biostatistics. Patients may be screened for registration by calling the Department of Biostatistics, ext. 62468.

14.0 RECORDS TO BE KEPT AND DATA SUBMISSION SCHEDULE

14.1 Confidentiality of Records

The original data collection forms will be stored in secure cabinets in the Department of Biostatistics. All radioimmunotherapy associated data will be kept in the Department of Radioimmunotherapy.

14.2 Patient Consent Form

At the time of registration, signed and dated copies of the patient Informed Consent form with the Human Rights must be available (for patient, chart, and Biostatistics Office).

15.0 GENDER AND MINORITIES

15.1 Planned Gender and Minority Inclusion for Transplant Patients with Intermediate Grade Lymphoma at City of Hope

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	White, Hispanic or not-Hispanic Unknown	Other or Unknown	Total
Female	0%	9%	4%	16%	54%	17%	0%	100%
Male	0%	5%	2%	20%	60%	12%	1%	100%
Unknown	0%	0%	0%	0%	0%	0%	0%	0%

15.2 Actual Gender and Minority Inclusion for Transplant Patients with Intermediate Grade Lymphoma at City of Hope

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	White, Hispanic or not-Hispanic Unknown	Other or Unknown	Total
Female	0%	0%	0%	0%	0%	0%	0%	0%
Male	0%	0%	0%	0%	0%	0%	0%	0%
Unknown	0%	0%	0%	0%	0%	0%	0%	0%

16.0 DATA MANAGEMENT

Clinical Statistics maintains a patient database at City of Hope Medical Center, Department of Biostatistics to allow storage and retrieval of patient data collected from a wide variety of sources. The investigator will ensure that data collected conform to all established guidelines for coding, collection, key-entry, and verification. All patients are assigned a unique patient number to assure patient confidentiality. Any publications or presentations refer to patient by unique patient number, not name. The licensed medical records department, affiliated with the institution where the patient receives medical care, maintains all original inpatient and outpatient chart documents. Patient research files are kept in a locked room. They are maintained by the COHMC data collection staff. Access is restricted to personnel authorized by the Division of Clinical Research.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

This study is to be approved by the Institutional Review Board according to City of Hope ethical and regulatory guidelines. All patients will have signed an informed consent for participation in research activities, and will have been given a copy of the Experimental Subject's Bill of Rights.

When results of this study are reported in medical journals or at meetings, identification of those taking part will be withheld. Medical records of patients will be maintained in strictest confidence,

according to current legal requirements. However, they will be made available for review, as required by the Food and Drug Administration (FDA) or other authorized users such as the National Cancer Institute (NCI), under the guidelines established by the Federal Privacy Act, or IDEC Pharmaceuticals Corporation.

18.0 REFERENCES

1. Parker SL, Tong T, Bolden S, Wingo PA: Cancer Statistics, 1997 [published erratum appears in CA Cancer J Clin 1997 Mar-Apr;47(2):68]. CA.Cancer J.Clin. 47:5, 1997
2. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, Glick JH, Coltman CAJ, Miller TP: Comparison of a Standard Regimen (CHOP) with Three Intensive Chemotherapy Regimens for Advanced Non-Hodgkin's Lymphoma [see comments]. N.Engl.J.Med. 328:1002, 1993
3. Vose JM, Anderson JR, Kessinger A, Bierman PJ, Coccia P, Reed EC, Gordon B, Armitage JO: High-Dose Chemotherapy and Autologous Hematopoietic Stem-Cell Transplantation for Aggressive Non-Hodgkin's Lymphoma [see comments]. J.Clin.Oncol. 11:1846, 1993
4. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, Sonneveld P, Gisselbrecht C, Cahn JY, Harousseau JL: Autologous Bone Marrow Transplantation as Compared with Salvage Chemotherapy in Relapses of Chemotherapy-Sensitive Non-Hodgkin's Lymphoma [see comments]. N.Engl.J.Med. 333:1540, 1995
5. Bierman PJ, Vose JM, Anderson JR, Bishop MR, Kessinger A, Armitage JO: High-Dose Therapy with Autologous Hematopoietic Rescue for Follicular Low-Grade Non-Hodgkin's Lymphoma. J.Clin.Oncol. 15:445, 1997
6. Nademanee A, Schmidt GM, O'Donnell MR, Snyder DS, Parker PM, Stein A, Smith E, Molina A, Wong KK, Stepan DE, Margolin KA, Somlo G, Raschko J, Sniecinski I, Lipsett JA, Dagis A, Niland JC, Forman SJ: Fractionated Total Body Irradiation (FTBI), High-Dose Etoposide (VP-16) and Cyclophosphamide (CY) Followed by Autologous Bone Marrow Transplantation (ABMT): The Results in 110 Patients with Non-Hodgkin's Lymphoma (NHL). Blood 82:143a (559), 1993 (abstr.)
7. Horning SJ, Negrin RS, Chao JC, Long GD, Hoppe RT, Blume KG: Fractionated Total-Body Irradiation, Etoposide, and Cyclophosphamide Plus Autografting in Hodgkin's Disease and Non-Hodgkin's Lymphoma. J.Clin.Oncol. 12:2552, 1994
8. Weaver CH, Petersen FB, Appelbaum FR, Bensinger WI, Press O, Martin P, Sandmaier B, Deeg HJ, Hansen JA, Brunvand M: High-Dose Fractionated Total-Body Irradiation, Etoposide, and Cyclophosphamide Followed by Autologous Stem-Cell Support in Patients with Malignant Lymphoma. J.Clin.Oncol. 12:2559, 1994
9. Maloney DG, Grillo-Lopez AJ, White CA, Bodkin D, Schilder RJ, Neidhart JA, Janakiraman N, Foon KA, Liles TM, Dallaire BK, Wey K, Royston I, Davis T, Levy R: IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients With Relapsed Low-Grade Non-Hodgkin's Lymphoma. Blood 90:2188, 1997
10. McLaughlin P, Grillo-López AJ, Link BK, Levy R, Czuczman MS, Williams ME, Heyman MR, Bence-Bruckler I, White CA, Cabanillas F, Jain V, Ho AD, Lister J, Wey K, Shen D, Dallaire BK: Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program. Journal of Clinical Oncology 16:2825, 1998
11. Czuczman M, Grillo-López AJ, White CA, Saleh M, Gordon L, LoBuglio AF, Jonas C, Dallaire B, Varns C: IDEC-C2B8/CHOP Chemoimmunotherapy in Patients With Low-

Grade Lymphoma: Clinical and BCL-2 (PCR) Final Results. Blood 88:453a (1799), 1996 (abstr.)

12. Kaminski MS, Zasadny KR, Francis IR, Milik AW, Ross CW, Moon SD, Crawford SM, Burgess JM, Petry NA, Butchko GM: Radioimmunotherapy of B-Cell Lymphoma with [^{131}I]Anti-B1 (Anti-CD20) Antibody. N.Engl.J.Med. 329:459, 1993
13. Stagg R, Wahl RL, Estes J, Tidmarsh G, Kroll S, Shochat D, Zasadny K, Kaminski MS: Phase I/II Study of Iodine-131 Anti-B1 Antibody for Non-Hodgkin's Lymphoma (NHL): Final Results. Proceedings of ASCO 17:39a (150), 1998 (abstr.)
14. Vose J, Saleh M, Lister A, Rohatiner A, Knox S, Radford J, Zelenetz AD, Stagg R, Tidmarsh G, Wahl R, Kaminski MS: Iodine-131 Anti-B1 Antibody for Non-Hodgkin's Lymphoma (NHL): Overall Clinical Trial Experience. Proceedings of ASCO 17:10a (38), 1998 (abstr.)
15. Press OW, Eary JF, Appelbaum FR, Martin PJ, Badger CC, Nelp WB, Glenn S, Butchko G, Fisher D, Porter B: Radiolabeled-Antibody Therapy of B-Cell Lymphoma With Autologous Bone Marrow Support [see comments]. N.Engl.J.Med. 329:1219, 1993
16. Press O, Eary J, Liu S, Petersdorf S, Bush S, Durack L, Martin P, Maloney D, Matthews D, Fisher D, Gooley T, Appelbaum F, Bernstein I: A Phase I/II Trial of High Dose Iodine-131-Anti-B1 (Anti-CD20) Monoclonal Antibody, Etoposide, Cyclophosphamide, and Autologous Stem Cell Transplantation for Patients With Relapsed B Cell Lymphomas. Proceedings of ASCO 17:3a (9), 1998 (abstr.)
17. Knox SJ, Goris ML, Trisler K, Negrin R, Davis T, Liles TM, Grillo-Lopez A, Chinn P, Varns C, Ning S, Fowler S, Deb N, Becker M, Marquez C, Levy R: Yttrium-90-Labeled Anti-CD20 Monoclonal Antibody Therapy of Recurrent B-Cell Lymphoma. Clin.Cancer Res. 2:457, 1996
18. Witzig T, Wiseman G, White CA, Solinger A, Gordon L, Raubitschek A, Emmanoulides C, Royston I, Parker E, Chinn P, Grillo-López A: IDEC-Y2B8 ^{90}Yttrium Anti-CD20 Radioimmunotherapy of Relapsed Non-Hodgkin's Lymphoma (NHL): Interim Results of a Phase I/II Trial. Blood 90:586a (2606), 1997 (abstr.)
19. Wiseman GA, Solinger AM, Grillo-López A, Stabin M, Dunn WL, Witzig TE, Spies S, Gordon L, Raubitschek A, Margolin K, Karvelis K, Janakiraman N, Silverman DH, Emmanoulides C, Royston I, Chinn P, Parker E, Carter W, White CA: IDEC-Y2B8 (^{90}Y Conjugated Anti-CD20) Dosimetry Calculated From ^{111}In Anti-CD20 in Patients With Low and Intermediate Grade B-Cell Non-Hodgkin's Lymphoma (NHL) Emphasis on Bone Marrow (BM). Blood 90:510a (2273), 1997 (abstr.)
20. Witzig TE, White CA, Wiseman GA, Gordon LI, Emmanoulides C, Raubitschek A, Janakiraman N, Gutheil J, Schilder RJ, Spies S, Silverman DH, Parker E, and Grillo-López A: Phase I/II Trial of Yttrium 90 Ibritumomab Tiuxetan (IDEC-Y2B8) Radioimmunotherapy for Treatment of Relapsed or Refractory CD20 Positive B-Cell Mon-Hodgkin's Lymphoma. Submitted 1999.

Appendix I
Common Toxicity Criteria (CTC)

FINAL 1/30/98

CTC Version 2.0

Toxicity	Grade 0	1	2	3	4
ALLERGY/IMMUNOLOGY					
Allergic reaction/ hypersensitivity (including drug fever)	none	transient rash, drug fever < 38°C (<100.4°F)	urticaria, drug fever ≥ 38°C (≥100.4°F), and/or asymptomatic bronchospasm	symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema	anaphylaxis
Note: Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN category.					
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	none	mild, not requiring treatment	moderate, requiring treatment	-	-
Autoimmune reaction	none	serologic or other evidence of autoimmune reaction but patient is asymptomatic (e.g., vitiligo), all organ function is normal and no treatment is required	evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism), requiring treatment other than immunosuppressive drugs	reversible autoimmune reaction involving function of a major organ or other toxicity (e.g., transient colitis or anemia), requiring short-term immunosuppressive treatment	autoimmune reaction causing major grade 4 organ dysfunction; progressive and irreversible reaction; long-term administration of high-dose immuno-suppressive therapy required
Also consider Hypothyroidism, Colitis, Hemoglobin, Hemolysis.					
Serum sickness	none	-	-	present	-
Urticaria is graded in the DERMATOLOGY/SKIN category if it occurs as an isolated symptom. If it occurs with other manifestations of allergic or hypersensitivity reaction, grade as Allergic reaction/hypersensitivity above.					
Vasculitis	none	mild, not requiring treatment	symptomatic, requiring medication	requiring steroids	ischemic changes or requiring amputation
Allergy/Immunology -Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling

Toxicity	Grade 0	1	2	3	4
AUDITORY/HEARING					
Conductive hearing loss is graded as Middle ear/hearing in the AUDITORY/HEARING category.					
Earache is graded in the PAIN category.					
External auditory canal	normal	external otitis with erythema or dry desquamation	external otitis with moist desquamation	external otitis with discharge, mastoiditis	necrosis of the canal soft tissue or bone
Note: Changes associated with radiation to external ear (pinnae) are graded under Radiation dermatitis in the DERMATOLOGY/SKIN category.					
Inner ear/hearing	normal	hearing loss on audiometry only	tinnitus or hearing loss, not requiring hearing aid or treatment	tinnitus or hearing loss, correctable with hearing aid or treatment	severe unilateral or bilateral hearing loss (deafness), not correctable
Middle ear/hearing	normal	serous otitis without subjective decrease in hearing	serous otitis or infection requiring medical intervention; subjective decrease in hearing; rupture of tympanic membrane with discharge	otitis with discharge, mastoiditis or conductive hearing loss	necrosis of the canal soft tissue or bone
Auditory/Hearing-Other (Specify,)	normal	mild	moderate	severe	life-threatening or disabling
BLOOD/BONE MARROW					
Bone marrow cellularity	normal for age	mildly hypocellular or 25% reduction from normal cellularity for age	moderately hypocellular or >25 - ≤ 50% reduction from normal cellularity for age or >2 but <4 weeks to recovery of normal bone marrow cellularity	severely hypocellular or >50 - ≤ 75% reduction in cellularity for age or 4 - 6 weeks to recovery of normal bone marrow cellularity	aplasia or >6 weeks to recovery of normal bone marrow cellularity
Normal ranges: children (≤ 18 years) younger adults (19-59) older adults (≥ 60 years)	90% cellularity average 60-70% cellularity average 50% cellularity average				
Note: Grade Bone marrow cellularity only for changes related to treatment not disease.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
CD4 count	WNL	< LLN - 500/mm^3	200 - < 500/mm^3	50 - < 200/mm^3	< 50/mm^3
Haptoglobin	normal	decreased	-	absent	-
Hemoglobin (Hgb)	WNL	< LLN - 10.0 g/dl < LLN - 100 g/L < LLN - 6.2 mmol/L	8.0 - < 10.0 g/dl 80 - < 100 g/L 4.9 - < 6.2 mmol/L	6.5 - < 8.0 g/dl 65 - 80 g/L 4.0 - < 4.9 mmol/L	< 6.5 g/dl < 65 g/L < 4.0 mmol/L
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic processes	WNL	10 - <25% decrease from pretreatment	25 - <50% decrease from pretreatment	50 - <75% decrease from pretreatment	≥75% decrease from pretreatment
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other) Also consider Haptoglobin, Hgb.	none	only laboratory evidence of hemolysis [e.g., direct antiglobulin test (DAT, Coombs') schistocytes]	evidence of red cell destruction and ≥ 2gm decrease in hemoglobin, no transfusion	requiring transfusion and/or medical intervention (e.g., steroids)	catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
Leukocytes (total WBC)	WNL	< LLN - 3.0 x 10^9 /L < LLN - 3000/mm^3	≥2.0 - < 3.0 x 10^9 /L ≥2000 - < 3000/mm^3	≥1.0 - < 2.0 x 10^9 /L ≥1000 - < 2000/mm^3	< 1.0 x 10^9 /L < 1000/mm^3
For BMT studies:	WNL	≥2.0 - <3.0 X 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9 /L ≥1000 - <2000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3
Note: The following criteria using age, race and sex normal values may be used for pediatric studies if the protocol so specifies.					
		≥75 - <100% LLN	*≥50 - <75% LLN*	*≥25 - 50% LLN*	*<25% LLN*
Lymphopenia	WNL	<LLN - 1.0 x 10^9 /L <LLN - 1000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3	-
Note: The following criteria using age, race, and sex normal values may be used for pediatric studies if the protocol so specifies.					
		≥75-<100%LLN	*≥50-<75%LLN*	*≥25-<50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC)	WNL	≥1.5 - <2.0 x 10^9 /L ≥1500 - <2000/mm^3	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	< 0.5 x 10^9 /L < 500/mm^3
For BMT:	WNL	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	≥0.1 - <0.5 x 10^9 /L ≥100 - <500/mm^3	<0.1 x 10^9 /L <100/mm^3

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Platelets	WNL	< LLN - <75.0 x 10^9 /L < LLN - 75000/mm^3	≥50.0 - < 75.0 x 10^9 /L ≥50000 - < 75000/mm^3	≥10.0 - < 50.0 x 10^9 /L ≥10000 - < 50000/mm^3	< 10.0 x 10^9 /L < 10000/mm^3
For BMT:	WNL	≥50.0 - <75.0 x 10^9 /L ≥50000 - <75000/mm^3	≥20.0 - <50.0 x 10^9 /L ≥20000 - <50000/mm^3	≥10.0 - <20.0 x 10^9 /L ≥10000 - <20000/mm^3	<10.0 x 10^9 /L <10000/mm^3
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Transfusion: Platelets	none	-	-	yes	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
For BMT:	none	1 platelet transfusion in 24 hours	2 platelet transfusions in 24 hours	≥3 platelet transfusions in 24 hours	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Also consider Platelets.					
Transfusion: pRBCs	none	-	-	Yes	-
For BMT:	none	≤2 u pRBC (≤*15cc/kg*) in 24 hours elective or planned	3 u pRBC (*>15* ≤*30cc/kg*) in 24 hours elective or planned	≥4 u pRBC (*>30cc/kg*) in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
Also consider Hemoglobin.					
Blood/Bone Marrow-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
CARDIOVASCULAR (ARRHYTHMIA)					
Conduction abnormality/ Atrioventricular heart block	none	asymptomatic, not requiring treatment (e.g., Mobitz type I second-degree AV block, Wenckebach)	symptomatic, but not requiring treatment	symptomatic and requiring treatment (e.g., Mobitz type II second-degree AV block, third-degree AV block)	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Nodal/junctional arrhythmia/dysrhythmia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Palpitations	none	present	-	-	-
Note: Grade palpitations only in the absence of a documented arrhythmia.					

Toxicity	Grade 0	1	2	3	4
Prolonged QTc interval (QTc > 0.48 seconds)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus bradycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus tachycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment of underlying cause	-
Supraventricular arrhythmias (SVT/atrial fibrillation/ flutter)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Syncope (fainting) is graded in the NEUROLOGY category.					
Vasovagal episode	none	-	present without loss of consciousness	present with loss of consciousness	-
Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ ventricular tachycardia)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Cardiovascular/ Arrhythmia-Other (Specify, _____)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic, and requiring treatment of underlying cause	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
		CARDIOVASCULAR (GENERAL)			
Acute vascular leak syndrome	absent	-	symptomatic, but not requiring fluid support	respiratory compromise or requiring fluids	life-threatening; requiring pressor support and/or ventilatory support
Cardiac-ischemia/infarction	none	non-specific T-wave flattening or changes	asymptomatic, ST- and T- wave changes suggesting ischemia	angina without evidence of infarction	acute myocardial infarction

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Cardiac left ventricular function	normal	asymptomatic decline of resting ejection fraction of ≥ 10% but < 20% of baseline value; shortening fraction ≥ 24% but < 30%	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction ≥ 20% of baseline value; < 24% shortening fraction	CHF responsive to treatment	severe or refractory CHF or requiring intubation
CNS cerebrovascular ischemia is graded in the NEUROLOGY category.					
Cardiac troponin I (cTnI)	normal	-	-	levels consistent with unstable angina as defined by the manufacturer	levels consistent with myocardial infarction as defined by the manufacturer
Cardiac troponin T (cTnT)	normal	≥ 0.03 - < 0.05 ng/ml	≥ 0.05 - < 0.1 ng/ml	≥ 0.1 - < 0.2 ng/ml	≥ 0.2 ng/ml
Edema	none	asymptomatic, not requiring therapy	symptomatic, requiring therapy	symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation	anasarca (severe generalized edema)
Hypertension	none	asymptomatic, transient increase by >20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	recurrent or persistent or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	requiring therapy or more intensive therapy than previously	hypertensive crisis
**Note: For pediatric patients, use age and sex appropriate normal values > 95th percentile ULN.*					
Hypotension	none	changes, but not requiring therapy (including transient orthostatic hypotension)	requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Also consider Syncope (fainting). Note: Angina or MI is graded as Cardiac- ischemia/infarction in the CARDIOVASCULAR (GENERAL) category. *For pediatric patients, systolic BP 65 mmHg or less in infants up to 1 year old and 70 mmHg or less in children older than 1 year of age, use two successive or three measurements in 24 hours.*					
Myocarditis	none	-	-	CHF responsive to treatment	severe or refractory CHF

Toxicity	Grade 0	1	2	3	4
Operative injury of vein/artery	none	primary suture repair for injury, but not requiring transfusion	primary suture repair for injury, requiring transfusion	vascular occlusion requiring surgery or bypass for injury	myocardial infarction; resection of organ (e.g., bowel, limb)
Pericardial effusion/ pericarditis	none	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and/or chest pain)	physiologic consequences resulting from symptoms	tamponade (drainage or pericardial window required)
Peripheral arterial ischemia	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., amputation)
Phlebitis (superficial)	none	-	present	-	-
Note: Injection site reaction is graded in the DERMATOLOGY/SKIN category. Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Syncope (fainting) is graded in the NEUROLOGY category.					
Thrombosis/embolism	none	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the CARDIOVASCULAR (GENERAL) category.					
Visceral arterial ischemia (non-myocardial)	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., resection of ileum)
Cardiovascular/ General-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
COAGULATION					
Note: See the HEMORRHAGE category for grading the severity of bleeding events.					
DIC (disseminated intravascular coagulation) Also grade Platelets. Note: Must have increased fibrin split products or D-dimer in order to grade as DIC.	absent	-	-	laboratory findings present with no bleeding	laboratory findings and bleeding
Fibrinogen	WNL	≥0.75 - <1.0 x LLN	≥0.5 - <0.75 x LLN	≥0.25 - <0.5 x LLN	<0.25 x LLN
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					

Toxicity	Grade 0	1	2	3	4
For leukemia studies:	WNL	<20% decrease from pretreatment value or LLN	≥20 - <40% decrease from pretreatment value or LLN	≥40 - <70% decrease from pretreatment value or LLN	<50 mg%
Partial thromboplastin time (PTT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Phelbitis is graded in the CARDIOVASCULAR (GENERAL) category.					
Prothrombin time (PT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS)	absent	-	-	laboratory findings present without clinical consequences	laboratory findings and clinical consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure) requiring therapeutic intervention
For BMT:	-	evidence of RBC destruction (schistocytosis) without clinical consequences	evidence of RBC destruction with elevated creatinine (≤3 x ULN)	evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy
Also consider Hemoglobin (Hgb), Platelets, Creatinine. Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).					
Coagulation-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia)	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities	bedridden or disabling
Note: See Appendix IV (http://ctep.info.nih.gov/ctc3/ctc.htm) for performance status scales.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x 10^9/L)	none	38.0 - 39.0°C (100.4 - 102.2°F)	39.1 - 40.0°C (102.3 - 104.0°F)	> 40.0°C (>104.0°F) for < 24hrs	> 40.0°C (>104.0°F) for > 24hrs
Also consider Allergic reaction/hypersensitivity. Note: The temperature measurements listed above are oral or tympanic.					
Hot flashes/flushes are graded in the ENDOCRINE category.					
Rigors, chills	none	mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication	severe and/or prolonged, requiring narcotic medication	not responsive to narcotic medication	-
Sweating (diaphoresis)	normal	mild and occasional	frequent or drenching	-	-
Weight gain	< 5%	5 - <10%	10 - <20%	≥ 20%	-
Also consider Ascites, Edema, Pleural effusion.					
Weight gain - veno-occlusive disease (VOD) Note: The following criteria is to be used ONLY for weight gain associated with Veno-Occlusive Disease.					
	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascities	≥10% or fluid retention resulting in pulmonary failure
Weight loss	< 5%	5 - <10%	10 - <20%	≥20%	-
Also consider Vomiting, Dehydration, Diarrhea.					
Constitutional Symptoms-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
DERMATOLOGY/SKIN					
Alopecia	normal	mild hair loss	pronounced hair loss	-	-
Bruising (in absence of grade 3 or 4 thrombocytopenia)	none	localized or in dependent area	generalized	-	-
Note: Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura and Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, not in the DERMATOLOGY/SKIN category.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Dermatitis, focal (associated with high-dose chemotherapy and bone marrow transplant)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding not induced by minor trauma or abrasion
Dry skin	normal	controlled with emollients	not controlled with emollients	-	-
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	absent	-	scattered, but not generalized eruption	severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Flushing	absent	present	-	-	-
Hand-foot skin reaction	none	skin changes or dermatitis without pain (e.g., erythema, peeling)	skin changes with pain, not interfering with function	skin changes with pain, interfering with function	-
Injection site reaction	none	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-
Nail changes	normal	discoloration or ridging (koilonychia) or pitting	partial or complete loss of nail(s) or pain in nailbeds	-	-
Petechiae is graded in the HEMORRHAGE category.					
Photosensitivity	none	painless erythema	painful erythema	erythema with desquamation	-
Pigmentation changes (e.g., vitiligo)	none	localized pigmentation changes	generalized pigmentation changes	-	-
Pruritus	none	mild or localized, relieved spontaneously or by local measures	intense or widespread, relieved spontaneously or by systemic measures	intense or widespread and poorly controlled despite treatment	-
Purpura is graded in the HEMORRHAGE category.					

Toxicity	Grade 0	1	2	3	4
Radiation dermatitis	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Note: Pain associated with radiation dermatitis is graded separately in the PAIN category as Pain due to radiation.					
Radiation recall reaction (reaction following chemotherapy in the absence of additional radiation therapy that occurs in a previous radiation port)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Rash/desquamation	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritis or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis
For BMT:	none	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms	macular or papular eruption or erythema with pruritis or other associated symptoms covering ≥25 - <50% of body surface or localized desquamation or other lesions covering ≥25 - <50% of body surface area	symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation
Also consider Allergic reaction/hypersensitivity.					
Note: Erythema multiforme (Stevens-Johnson syndrome) is graded separately as Erythema multiforme.					

Toxicity	Grade 0	1	2	3	4
Urticaria (hives, welts, wheals)	none	requiring no medication	requiring PO or topical treatment or IV medication or steroids for <24 hours	requiring IV medication or steroids for ≥24 hours	-
Wound- infectious	none	cellulitis	superficial infection	infection requiring IV antibiotics	necrotizing fascitis
Wound- non-infectious	none	incisional separation	incisional hernia	fascial disruption without evisceration	fascial disruption with evisceration
Dermatology/Skin-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
ENDOCRINE					
Cushingoid appearance (e.g., moon face with or without buffalo hump, centripetal obesity, cutaneous striae) Also consider Hyperglycemia, Hypokalemia.	absent	-	present	-	-
Feminization of male	absent	-	-	present	-
Gynecomastia	none	mild	pronounced or painful	pronounced or painful and requiring surgery	-
Hot flashes/flushes	none	mild or no more than 1 per day	moderate and greater than 1 per day	-	-
Hypothyroidism	absent	asymptomatic,TSH elevated, no therapy given	symptomatic or thyroid replacement treatment given	patient hospitalized for manifestations of hypothyroidism	myxedema coma
Masculinization of female	absent	-	-	present	-
SIADH (syndrome of inappropriate antidiuretic hormone)	absent	-	-	present	-
Endocrine-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
GASTROINTESTINAL					
Amylase is graded in the METABOLIC/LABORATORY category.					
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition

Toxicity	Grade 0	1	2	3	4
Ascites (non-malignant)	none	asymptomatic	symptomatic, requiring diuretics	symptomatic, requiring therapeutic paracentesis	life-threatening physiologic consequences
Colitis	none	-	abdominal pain with mucus and/or blood in stool	abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	perforation or requiring surgery or toxic megacolon
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension.					
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Dehydration	none	dry mucous membranes and/or diminished skin turgor	requiring IV fluid replacement (brief)	requiring IV fluid replacement (sustained)	physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Hypotension, Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Diarrhea Patients without colostomy:	none	increase of < 4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
Patients with a colostomy:	none	mild increase in loose, watery colostomy output compared with pretreatment	moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	physiologic consequences, requiring intensive care; or hemodynamic collapse
For BMT	none	>500 - ≤1000ml of diarrhea/day	>1000 - ≤1500ml of diarrhea/day	>1500ml of diarrhea/day	severe abdominal pain with or without ileus
For Pediatric BMT:		*>5 - ≤10 ml/kg of diarrhea/day*	*>10 - ≤15 ml/kg of diarrhea/day*	*>15 ml/kg of diarrhea/day*	-
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain, Dehydration, Hypotension.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Duodenal ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	uncontrolled by outpatient medical management; requiring hospitalization	perforation or bleeding, requiring emergency surgery
Dyspepsia/heartburn	none	mild	moderate	severe	-
Dysphagia, esophagitis, odynophagia (painful swallowing) Note: If toxicity is radiation-related, grade either under Dysphagia- esophageal related to radiation or Dysphagia-pharyngeal related to radiation.	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring IV hydration	complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support, or perforation
Dysphagia- esophageal related to radiation Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula- esophageal.	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly liquid, pureed or soft diet	dysphagia requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Dysphagia - pharyngeal related to radiation Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula- pharyngeal.	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Fistula- esophageal	none	-	-	present	requiring surgery
Fistula- intestinal	none	-	-	present	requiring surgery
Fistula- pharyngeal	none	-	-	present	requiring surgery
Fistula- rectal/anal	none	-	-	present	requiring surgery
Flatulence	none	mild	moderate	-	-

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
Gastric ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery	perforation or bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Gastritis	none	-	requiring medical management or non-surgical treatment	uncontrolled by out-patient medical management; requiring hospitalization or surgery	life-threatening bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Hematemesis is graded in the HEMORRHAGE category.					
Hematochezia is graded in the HEMORRHAGE category as Rectal bleeding/hematochezia.					
Ileus (or neuroconstipation)	none	-	intermittent, not requiring intervention	requiring non-surgical intervention	requiring surgery
Mouth dryness	normal	mild	moderate	-	-
Mucositis Note: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginititis. Radiation-related mucositis is graded as Mucositis due to radiation.					
Mucositis due to radiation	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally ≤ 1.5 cm in diameter and non-contiguous)	confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
Also consider Pain due to radiation. Note: Grade radiation mucositis of the larynx here. Dysphagia related to radiation is also graded as either Dysphagia- esophageal related to radiation or Dysphagia-pharyngeal related to radiation, depending on the site of treatment.					
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Pancreatitis	none	-	-	abdominal pain with pancreatic enzyme elevation	complicated by shock (acute circulatory failure)
Also consider Hypotension.					

Toxicity	Grade 0	1	2	3	4
Note: Asymptomatic amylase and Amylase are graded in the METABOLIC/LABORATORY category.					
Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Proctitis	none	increased stool frequency, occasional blood-streaked stools, or rectal discomfort (including hemorrhoids), not requiring medication	increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	increased stool frequency/diarrhea, requiring parenteral support; rectal bleeding, requiring transfusion; or persistent mucus discharge, necessitating pads	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, and Pain due to radiation. Note: Fistula is graded separately as Fistula- rectal/anal. Proctitis occurring more than 90 days after the start of radiation therapy is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. (See Appendix V, http://ctep.info.nih.gov/ctc3/ctc.htm)					
Salivary gland changes	none	slightly thickened saliva/may have slightly altered taste (e.g., metallic); additional fluids may be required	thick, ropy, sticky saliva; markedly altered taste; alteration in diet required	-	acute salivary gland necrosis
Sense of smell	normal	slightly altered	markedly altered	-	-
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylatic intubation
For BMT:	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
Note: Radiation-related mucositis is graded as Mucositis due to radiation.					
Taste disturbance (dysgeusia)	normal	slightly altered	markedly altered	-	-

Toxicity	Grade 0	1	2	3	4
Typhlitis (inflammation of the cecum)	none	-	-	abdominal pain, diarrhea, fever, or radiographic documentation	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile/neutropenia.					
Vomiting	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Dehydration.					
Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category.					
Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category.					
Gastrointestinal-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
HEMORRHAGE					
Note: Transfusion in this section refers to pRBC infusion. For any bleeding with grade 3 or 4 platelets (< 50,000), always grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider platelets, transfusion- pRBCS, and transfusion-platelets in addition to the grade that incorporates the site or type of bleeding. If the site or type of hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: CNS hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/hematochezia, Vaginal bleeding. If the platelet count is ≥50,000 and the site or type of bleeding is listed, grade the specific site. If the site or type is not listed and the platelet count is ≥50,000, grade Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia and specify the site or type in the OTHER category.					
Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs.					
Note: This toxicity must be graded for any bleeding with grade 3 or 4 thrombocytopenia. Also grade the site or type of hemorrhage/bleeding. If the site is not listed, grade as Other in the HEMORRHAGE category.					

Toxicity	Grade 0	1	2	3	4
Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs. Note: Bleeding in the absence of grade 3 or 4 thrombocytopenia is graded here only if the specific site or type of bleeding is not listed elsewhere in the HEMORRHAGE category. Also grade as Other in the HEMORRHAGE category.					
CNS hemorrhage/bleeding	none	-	-	bleeding noted on CT or other scan with no clinical consequences	hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms
Epistaxis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematemesis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematuria (in the absence of vaginal bleeding)	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Hemoptysis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention

Toxicity	0	1	2	3	4
			Grade		
Hemorrhage/bleeding associated with surgery Note: Expected blood loss at the time of surgery is not graded as a toxicity.	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Melena/GI bleeding	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	none	rare petechiae of skin	petechiae or purpura in dependent areas of skin	generalized petechiae or purpura of skin or petechiae of any mucosal site	-
Rectal bleeding/ hematochezia	none	mild without transfusion or medication	persistent, requiring medication (e.g., steroid suppositories) and/or break from radiation treatment	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Vaginal bleeding	none	spotting, requiring < 2 pads per day	requiring ≥ 2 pads per day, but not requiring transfusion	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage-Other (Specify site, _____)	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
			HEPATIC		
Alkaline phosphatase	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Bilirubin	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Bilirubin- graft versus host disease (GVHD) Note: The following criteria are used only for bilirubin associated with graft versus host disease.	normal	≥2 - <3 mg/100 ml	≥3 - <6 mg/100 ml	≥6 - <15 mg/100 ml	≥15 mg/100 ml

Toxicity	0	1	2	3	4
			Grade		
GGT (γ - Glutamyl transpeptidase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic enlargement	absent	-	-	present	-
Note: Grade Hepatic enlargement only for changes related to VOD or other treatment related toxicity.					
Hypoalbuminemia	WNL	<LLN - 3 g/dl	≥2 - <3 g/dl	<2 g/dl	-
Liver dysfunction/failure (clinical)	normal	-	-	asterixis	encephalopathy or coma
Note: Documented viral hepatitis is graded in the INFECTION category.					
Portal vein flow	normal	-	decreased portal vein flow	reversal/retrograde portal vein flow	-
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
SGPT (ALT) (serum glutamic pyruvic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
INFECTION/FEBRILE NEUTROPENIA					
Catheter-related infection	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment or hospitalization	life-threatening sepsis (e.g., septic shock)
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC < 1.0 x 10^9/L, fever ≥38.5°C)	none	-	-	Present	Life-threatening sepsis (e.g., septic shock)
Note: Hypothermia instead of fever may be associated with neutropenia and is graded here.					

Toxicity	Grade 0	1	2	3	4
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC < 1.0 x 10^9/L)	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Note: Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection with grade 3 or 4 neutropenia, grade as Febrile neutropenia.					
Infection with unknown ANC Note: This toxicity criterion is used in the rare case when ANC is unknown.	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection without neutropenia	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)
Infection/Febrile Neutropenia-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
Wound-infectious is graded in the DERMATOLOGY/SKIN category.					
LYMPHATICS					
Lymphatics	normal	mild lymphedema	moderate lymphedema requiring compression; lymphocyst	severe lymphedema limiting function; lymphocyst requiring surgery	severe lymphedema limiting function with ulceration
Lymphatics-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
METABOLIC/LABORATORY					

Toxicity	Grade 0	1	2	3	4
Acidosis (metabolic or respiratory)	normal	pH < normal, but ≥7.3	-	pH < 7.3	pH < 7.3 with life-threatening physiologic consequences
Alkalosis (metabolic or respiratory)	normal	pH > normal, but ≤7.5	-	pH > 7.5	pH > 7.5 with life-threatening physiologic consequences
Amylase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	>5.0 x ULN
Bicarbonate	WNL	< LLN - 16 mEq/dl	11 - 15 mEq/dl	8 - 10 mEq/dl	< 8 mEq/dl
CPK (creatine phosphokinase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5 x ULN	> 5 - 10 x ULN	> 10 x ULN
Hypercalcemia	WNL	> ULN - 11.5 mg/dl > ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dl > 2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dl > 3.1 - 3.4 mmol/L	> 13.5 mg/dl > 3.4 mmol/L
Hypercholesterolemia	WNL	> ULN - 300 mg/dl > ULN - 7.75 mmol/L	> 300 - 400 mg/dl > 7.75 - 10.34 mmol/L	> 400 - 500 mg/dl >10.34 - 12.92 mmol/L	> 500 mg/dl > 12.92 mmol/L
Hyperglycemia	WNL	> ULN - 160 mg/dl > ULN - 8.9 mmol/L	> 160 - 250 mg/dl > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dl > 13.9 - 27.8 mmol/L	> 500 mg/dl > 27.8 mmol/L or ketoacidosis
Hyperkalemia	WNL	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Hypermagnesemia	WNL	> ULN - 3.0 mg/dl > ULN - 1.23 mmol/L	-	> 3.0 - 8.0 mg/dl > 1.23 - 3.30 mmol/L	> 8.0 mg/dl > 3.30 mmol/L
Hypernatremia	WNL	> ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hypertriglyceridemia	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10 x ULN	> 10 x ULN

Toxicity	Grade 0	1	2	3	4
Hyperuricemia	WNL	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L without physiologic consequences	-	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dl > 0.59 mmol/L
Also consider Tumor lysis syndrome, Renal failure, Creatinine, Potassium.					
Hypocalcemia	WNL	<LLN - 8.0 mg/dl <LLN - 2.0 mmol/L	7.0 - < 8.0 mg/dl 1.75 - < 2.0 mmol/L	6.0 - < 7.0 mg/dl 1.5 - < 1.75 mmol/L	<6.0 mg/dl < 1.5 mmol/L
Hypoglycemia	WNL	<LLN - 55 mg/dl <LLN - 3.0 mmol/L	40 - < 55 mg/dl 2.2 - < 3.0 mmol/L	30 - < 40 mg/dl 1.7 - < 2.2 mmol/L	< 30 mg/dl < 1.7 mmol/L
Hypokalemia	WNL	<LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L
Hypomagnesemia	WNL	<LLN - 1.2 mg/dl <LLN - 0.5 mmol/L	0.9 - <1.2 mg/dl 0.4 - < 0.5 mmol/L	0.7 - < 0.9 mg/dl 0.3 - < 0.4 mmol/L	< 0.7 mg/dl < 0.3 mmol/L
Hyponatremia	WNL	<LLN - 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
Hypophosphatemia	WNL	<LLN -2.5 mg/dl <LLN - 0.8 mmol/L	≥2.0 - <2.5 mg/dl ≥0.6 - <0.8 mmol/L	≥1.0 - <2.0 mg/dl ≥0.3 - <0.6 mmol/L	< 1.0 mg/dl <0.3 mmol/L
Hypothyroidism is graded in the ENDOCRINE category.					
Lipase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Metabolic/Laboratory-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
MUSCULOSKELETAL					
Arthralgia is graded in the PAIN category.					
Arthritis	none	mild pain with inflammation, erythema or joint swelling but not interfering with function	moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living	severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living	disabling

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Muscle weakness (not due to neuropathy)	normal	asymptomatic with weakness on physical exam	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	bedridden or disabling
Myalgia is graded in the PAIN category.					
Myositis (inflammation/damage of muscle) Also consider CPK. Note: Myositis implies muscle damage (i.e., elevated CPK).	none	mild pain, not interfering with function	pain interfering with function, but not interfering with activities of daily living	pain interfering with function and interfering with activities of daily living	bedridden or disabling
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic; or disabling
Musculoskeletal-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
NEUROLOGY					
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Arachnoiditis/meningismus/ radiculitis Also consider Headache, Vomiting, Fever.	absent	mild pain not interfering with function	moderate pain interfering with function, but not interfering with activities of daily living	severe pain interfering with activities of daily living	unable to function or perform activities of daily living; bedridden; paraplegia
Ataxia (incoordination)	normal	asymptomatic but abnormal on physical exam, and not interfering with function	mild symptoms interfering with function, but not interfering with activities of daily living	moderate symptoms interfering with activities of daily living	bedridden or disabling
CNS cerebrovascular ischemia	none	-	-	transient ischemic event or attack (TIA)	permanent event (e.g., cerebral vascular accident)
CNS hemorrhage/bleeding is graded in the HEMORRHAGE category.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Cognitive disturbance/ learning problems	*none*	*cognitive disability; not interfering with work/school performance; preservation of intelligence*	*cognitive disability; interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones*	*cognitive disability; resulting in significant impairment of work/school performance; cognitive decline > 2 SD*	*inability to work/frank mental retardation*
Confusion	normal	confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living	confusion or delirium interfering with activities of daily living	harmful to others or self; requiring hospitalization
Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.					
Delusions	normal	-	-	present	toxic psychosis
Depressed level of consciousness Note: Syncope (fainting) is graded in the NEUROLOGY category.	normal	somnolence or sedation not interfering with function	somnolence or sedation interfering with function, but not interfering with activities of daily living	obtundation or stupor; difficult to arouse; interfering with activities of daily living	coma
Dizziness/lightheadedness	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Dysphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Extrapyramidal/ involuntary movement/ restlessness	none	mild involuntary movements not interfering with function	moderate involuntary movements interfering with function, but not interfering with activities of daily living	severe involuntary movements or torticollis interfering with activities of daily living	bedridden or disabling
Hallucinations	normal	-	-	present	toxic psychosis
Headache is graded in the PAIN category.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Insomnia	normal	occasional difficulty sleeping not interfering with function	difficulty sleeping interfering with function, but not interfering with activities of daily living	frequent difficulty sleeping, interfering with activities of daily living	-
Note: This toxicity is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia.					
Irritability *(children <3 years of age)*	*normal*	*mild; easily consolable*	*moderate; requiring increased attention*	*severe; inconsolable*	-
Leukoencephalopathy associated radiological findings	*none*	*mild increase in SAS (subarachnoid space) and/or mild ventriculomegaly ; and/or small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or < 1/3 of susceptible areas of cerebrum*	*moderate increase in SAS; and/or moderate ventriculomegaly ; and/or focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum*	*severe increase in SAS; severe ventriculomegaly ; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)*	*severe increase in SAS; severe ventriculomegaly ; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)*
Memory loss	normal	memory loss not interfering with function	memory loss interfering with function, but not interfering with activities of daily living	memory loss interfering with activities of daily living	amnesia
Mood alteration-anxiety agitation	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-depression	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Mood alteration-euphoria	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	danger to self
Neuropathic pain is graded in the PAIN category.					
Neuropathy- cranial	absent	-	present, not interfering with activities of daily living	present, interfering with activities of daily living	life-threatening, disabling
Neuropathy- motor	normal	subjective weakness but no objective findings	mild objective weakness interfering with function, but not interfering with activities of daily living	objective weakness interfering with activities of daily living	paralysis
Neuropathy-sensory	normal	loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paresthesia interfering with activities of daily living	permanent sensory loss that interferes with function
Nystagmus Also consider Vision-double vision.	absent	present	-	-	-
Personality/behavioral	normal	change, but not disruptive to patient or family	disruptive to patient or family	disruptive to patient and family; requiring mental health intervention	harmful to others or self; requiring hospitalization
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	normal	asymptomatic with abnormality on physical examination	symptomatic or interfering with function but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling; paralysis
Seizure(s)	none	-	seizure(s) self-limited and consciousness is preserved	seizure(s) in which consciousness is altered	seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)

Toxicity	Grade 0	1	2	3	4
Speech impairment (e.g., dysphasia or aphasia)	normal	-	awareness of receptive or expressive dysphasia, not impairing ability to communicate	receptive or expressive dysphasia, impairing ability to communicate	inability to communicate
Syncope (fainting)	absent	-	-	present	-
Also consider CARDIOVASCULAR (ARRHYTHMIA), Vasovagal episode, CNS cerebrovascular ischemia.					
Tremor	none	mild and brief or intermittent but not interfering with function	moderate tremor interfering with function, but not interfering with activities of daily living	severe tremor interfering with activities of daily living	-
Vertigo	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Neurology-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
OCULAR/VISUAL					
Cataract	none	asymptomatic	symptomatic, partial visual loss	symptomatic, visual loss requiring treatment or interfering with function	-
Conjunctivitis	none	abnormal ophthalmologic changes, but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Dry eye	normal	mild, not requiring treatment	moderate or requiring artificial tears	-	-
Glaucoma	none	increase in intraocular pressure but no visual loss	increase in intraocular pressure with retinal changes	visual impairment	unilateral or bilateral loss of vision (blindness)

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Keratitis (corneal inflammation/ corneal ulceration)	none	abnormal ophthalmologic changes but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	unilateral or bilateral loss of vision (blindness)
Tearing (watery eyes)	none	mild: not interfering with function	moderate: interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	-
Vision- blurred vision	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- double vision (diplopia)	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- flashing lights/floaters	normal	mild, not interfering with function	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- night blindness (nyctalopia)	normal	abnormal electro-retinography but asymptomatic	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- photophobia	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Ocular/Visual-Other (Specify,)	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)
PAIN					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Abdominal pain or cramping	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthralgia (joint pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthritis (joint pain with clinical signs of inflammation) is graded in the MUSCULOSKELETAL category.					
Bone pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Chest pain (non-cardiac and non-pleuritic)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dysmenorrhea	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dyspareunia	none	mild pain not interfering with function	moderate pain interfering with sexual activity	severe pain preventing sexual activity	-
Dysuria is graded in the RENAL/GENITOURINARY category.					
Earache (otalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Hepatic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pain due to radiation	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pelvic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pleuritic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

Toxicity	Grade 0	1	2	3	4
Rectal or perirectal pain (proctalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor pain (onset or exacerbation of tumor pain due to treatment)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor flair is graded in the SYNDROME category.					
Pain-Other (Specify,)	none	mild	moderate	severe	disabling
PULMONARY					
Adult Respiratory Distress Syndrome (ARDS)	absent	-	-	-	present
Apnea	none	-	-	present	requiring intubation
Carbon monoxide diffusion capacity (DL_{CO})	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	-
Dyspnea (shortness of breath)	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support
FEV_1	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Hiccoughs (hiccups, singultus)	none	mild, not requiring treatment	moderate, requiring treatment	severe, prolonged, and refractory to treatment	-

Toxicity	Grade 0	1	2	3	4
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest, requiring supplemental oxygen	decreased O_2 saturation, requiring pressure support (CPAP) or assisted ventilation
Pleural effusion (non-malignant)	none	asymptomatic and not requiring treatment	symptomatic, requiring diuretics	symptomatic, requiring O_2 or therapeutic thoracentesis	life-threatening (e.g., requiring intubation)
Pleuritic pain is graded in the PAIN category.					
Pneumonitis/pulmonary infiltrates	none	radiographic changes but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation
Pneumothorax	none	no intervention required	chest tube required	sclerosis or surgery required	life-threatening
Pulmonary embolism is graded as Thrombosis/embolism in the CARDIOVASCULAR (GENERAL) category.					
Pulmonary fibrosis	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	requiring steroids or diuretics	requiring oxygen	requiring assisted ventilation
Note: Radiation-related pulmonary fibrosis is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme-Lung. (See Appendix V, http://ctep.info.nih.gov/ctc3/ctc.htm)					
Voice changes/stridor/larynx (e.g., hoarseness, loss of voice, laryngitis)	normal	mild or intermittent hoarseness	persistent hoarseness, but able to vocalize; may have mild to moderate edema	whispered speech, not able to vocalize; may have marked edema	marked dyspnea/stridor requiring tracheostomy or intubation
Note: Cough from radiation is graded as cough in the PULMONARY category. Radiation-related hemoptysis from larynx/pharynx is graded as Grade 4 Mucositis due to radiation in the GASTROINTESTINAL category. Radiation-related hemoptysis from the thoracic cavity is graded as Grade 4 Hemoptysis in the HEMORRHAGE category.					
Pulmonary-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
RENAL/GENITOURINARY					
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmotic	severe symptoms requiring narcotic	-
Creatinine	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Note: Adjust to age-appropriate levels for pediatric patients.					
Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	-

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Fistula or GU fistula (e.g., vaginal, vesicovaginal)	none	-	-	requiring intervention	requiring surgery
Hemoglobinuria	-	present	-	-	-
Hematuria (in the absence of vaginal bleeding) is graded in the HEMORRHAGE category.					
Incontinence	none	with coughing, sneezing, etc.	spontaneous, some control	no control (in the absence of fistula)	-
Operative injury to bladder and/or ureter	none	-	injury of bladder with primary repair	sepsis, fistula, or obstruction requiring secondary surgery; loss of one kidney; injury requiring anastomosis or re-implantation	septic obstruction of both kidneys or vesicovaginal fistula requiring diversion
Proteinuria	normal or < 0.15 g/24 hours	1+ or 0.15 - 1.0 g/24 hours	2+ to 3+ or 1.0 - 3.5 g/24 hours	4+ or > 3.5 g/24 hours	nephrotic syndrome
Note: If there is an inconsistency between absolute value and uristix reading, use the absolute value for grading.					
Renal failure	none	-	-	requiring dialysis, but reversible	requiring dialysis and irreversible
Ureteral obstruction	none	unilateral, not requiring surgery	-	bilateral, not requiring surgery	stent, nephrostomy tube, or surgery
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	none	asymptomatic, not requiring treatment	mild, reversible and manageable with oral replacement	reversible but requiring IV replacement	irreversible, requiring continued replacement
Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia.					
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x normal	increase > 2 x normal but < hourly	hourly or more with urgency, or requiring catheter	-
Urinary retention	normal	hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period	hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for < 6 weeks	requiring frequent in/out catheterization (≥ 4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy)	bladder rupture

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria)	normal	asymptomatic, change in urine color	-	-	-
Vaginal bleeding is graded in the HEMORRHAGE category.					
Vaginitis (not due to infection)	none	mild, not requiring treatment	moderate, relieved with treatment	severe, not relieved with treatment, or ulceration not requiring surgery	ulceration requiring surgery
Renal/Genitourinary-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
SECONDARY MALIGNANCY					
Secondary Malignancy-Other (Specify type, _____) excludes metastatic tumors	none	-	-	-	present
SEXUAL/REPRODUCTIVE FUNCTION					
Dyspareunia is graded in the PAIN category.					
Dysmenorrhea is graded in the PAIN category.					
Erectile impotence	normal	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for intercourse)	no erections	-
Female sterility	normal	-	-	sterile	-
Femininization of male is graded in the ENDOCRINE category.					
Irregular menses (change from baseline)	normal	occasionally irregular or lengthened interval, but continuing menstrual cycles	very irregular, but continuing menstrual cycles	persistent amenorrhea	-
Libido	normal	decrease in interest	severe loss of interest	-	-
Male infertility	-	-	Oligospermia (low sperm count)	Azoospermia (no sperm)	-
Masculinization of female is graded in the ENDOCRINE category.					

Toxicity	Grade 0	1	2	3	4
Vaginal dryness	normal	mild	requiring treatment and/or interfering with sexual function, dyspareunia	-	-
Sexual/Reproductive Function-Other (Specify,)	none	mild	moderate	severe	disabling
SYNDROMES (not included in previous categories)					
Acute vascular leak syndrome is graded in the CARDIOVASCULAR (GENERAL) category.					
ARDS (Adult Respiratory Distress Syndrome) is graded in the PULMONARY category.					
Autoimmune reactions are graded in the ALLERGY/IMMUNOLOGY category.					
DIC (disseminated intravascular coagulation) is graded in the COAGULATION category.					
Fanconi's syndrome is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Renal tubular acidosis is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Stevens-Johnson syndrome (erythema multiforme) is graded in the DERMATOLOGY/SKIN category.					
SIADH (syndrome of inappropriate antidiuretic hormone) is graded in the ENDOCRINE category.					
Thrombotic microangiopathy (e.g., thromboitic thrombocytopenic purpura/TTP or hemolytic uremic syndrom/HUS) is graded in the COAGULATION category.					
Tumor flare Also consider Hypercalcemia. Note: Tumor flare is characterized by a constellation of symptoms and signs in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances.	none	mild pain not interfering with function	moderate pain; pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain; pain or analgesics interfering with function and interfering with activities of daily living	Disabling
Tumor lysis syndrome Also consider Hyperkalemia, Creatinine.	absent	-	-	present	-
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) is graded under the RENAL/GENITOURINARY category.					
Syndromes-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling

Appendix II
Toxicity Module

To be implemented at the request of the study sponsor or principal investigator in the protocol or by protocol amendment when more detailed information is considered pertinent.

Toxicity:	Date of Treatment:		Course Number:
Date of onset:			Grade at onset:
Date of first change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Did toxicity resolve? If so, date of resolution of toxicity:	Yes_____	No_____	
Date of last observation (if prior to recovery):			
Reason(s) observations stopped (if prior to recovery):			
Was patient retreated?	Yes_____	No_____	
If yes, was treatment delayed for recovery?	Yes_____	No_____	
Date of next treatment?			
Dose reduced for next treatment?	Yes_____	No_____	

Additional Comments:

_____

_____

If module is being activated for new toxicity, not currently in CTC, please provide definitions for toxicity grading:

Grade 0 =

_____

Grade 1 =

_____

Grade 2 =

_____

Grade 3 =

_____

Grade 4 =

_____

Appendix III
Infection Module

To be implemented at the request of the study sponsor or principal investigator in the protocol or by protocol amendment when more detailed information is considered pertinent.

1. Use the Common Toxicity Criteria definitions to grade the severity of the infection.
2. Specify type of infection from the following (CHOOSE ONE):
   BACTERIAL FUNGAL PROTOZOAL VIRAL UNKNOWN
3. Specify site of infection from the following (CHOOSE ALL THAT APPLY):
   BLOOD CULTURE POSITIVE
   BONE INFECTION
   CATHETER (intravenous)
   CATHETER (intravenous), tunnel infection
   CENTRAL NERVOUS SYSTEM INFECTION
   EAR INFECTION
   EYE INFECTION
   GASTROINTESTINAL INFECTION
   ORAL INFECTION
   PNEUMONIA
   SKIN INFECTION
   UPPER RESPIRATORY INFECTION
   URINARY TRACT INFECTION
   VAGINAL INFECTION
   INFECTION, not otherwise specified (Specify site, _____)
4. Specify organism, if known: _____.
5. Prophylactic antibiotic, antifungal, or antiviral therapy administration
   Yes_____ No_____
   If prophylaxis was given prior to infection, please specify below:
   Antibiotic prophylaxis _____
   Antifungal prophylaxis _____
   Antiviral prophylaxis _____
   Other prophylaxis _____

Appendix IV
Performance Status Scales/Scores

ECOG or Zubrod Scale		Karnofsky Score
0	Asymptomatic and fully active	100%
1	Symptomatic; fully ambulatory; restricted in physically strenuous activity	80-90%
2	Symptomatic; ambulatory; capable of self-care; more than 50% of waking hours are spent out of bed	60-70%
3	Symptomatic; limited self-care; spends more than 50% of time in bed, but not bedridden	40-50%
4	Completely disabled; no self-care; bedridden	20-30%

Appendix V

RTOG/EORTC Late Radiation Morbidity Scoring Scheme
Use for toxicities occurring greater than 90 days after radiation therapy.

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Bladder- Late RT Morbidity Scoring	No change from baseline	Slight epithelial atrophy/minor telangiectasia (microscopic hematuria)	Moderate frequency/ generalized telangiectasia/ intermittent macroscopic hematuria	Severe frequency and dysuria/severe generalized telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (< 150 cc)	Necrosis/contracted bladder (capacity < 100 cc)/severe hemorrhagic cystitis
Bone- Late RT Morbidity Scoring	No change from baseline	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis/ spontaneous fracture
Brain- Late RT Morbidity Scoring	No change from baseline	Mild headache; slight lethargy	Moderate headache; great lethargy	Severe headaches; severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; coma
Esophagus- Late RT Morbidity Scoring	No change from baseline	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semi-solid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilation required	Necrosis/ perforation; fistula
Heart- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms; transient T wave inversion and ST changes; sinus tachycardia > 110 (at rest)	Moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low QRS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities	Tamponade/severe heart failure/severe constrictive pericarditis
Joint- Late RT Morbidity Scoring	No change from baseline	Mild joint stiffness; slight limitation of movement	Moderate stiffness; intermittent or moderate joint pain; moderate	Severe joint stiffness; pain with severe limitation of movement	Necrosis/complete fixation

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
			limitation of movement		
Kidney- Late RT Morbidity Scoring	No change from baseline	Transient albuminuria; no hypertension; mild impairment of renal function; urea 25 - 35 mg%; creatinine 1.5 - 2.0 mg%; creatinine clearance > 75%	Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function; urea > 36 - 60 mg%; creatinine clearance > 50 - 74%	Severe albuminuria; severe hypertension; persistent anemia (< 10 g%); severe renal failure; urea > 60 mg%; creatinine > 4 mg%; creatinine clearance < 50%	Malignant hypertension; uremic coma/urea > 100%
Larynx- Late RT Morbidity Scoring	No change from baseline	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis
Liver- Late RT Morbidity Scoring	No change from baseline	Mild lassitude; nausea; dyspepsia; slightly abnormal liver function	Moderate symptoms; some abnormal liver function tests; serum albumin normal	Disabling hepatic insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites	Necrosis/hepatic coma or encephalopathy
Lung- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms (dry cough); slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); low grade fever; patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; dense radiographic changes	Severe respiratory insufficiency/ continuous O2/assisted ventilation
Mucous membrane- Late RT Morbidity Scoring	No change from baseline	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucus	Marked atrophy with complete dryness; severe telangiectasia	Ulceration
Salivary glands- Late RT Morbidity Scoring	No change from baseline	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
Skin- Late RT Morbidity Scoring	No change from baseline	Slight atrophy; pigmentation change; some hair loss	Patchy atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Small/Large intestine- Late RT Morbidity Scoring	No change from baseline	Mild diarrhea; mild cramping; bowel movement 5 x daily slight rectal discharge	Moderate diarrhea and colic; bowel movement > 5 x daily; excessive	Obstruction or bleeding, requiring surgery	Necrosis/ perforation fistula

Toxicity	Grade 0	1	2	3	4
		or bleeding	rectal mucus or intermittent bleeding		
Spinal cord- Late RT Morbidity Scoring	No change from baseline	Mild Lhermitte's syndrome	Severe Lhermitte's syndrome	Objective neurological findings at or below cord level treatment	Mono-, para-, quadriplegia
Subcutaneous tissue- Late RT Morbidity Scoring	No change from baseline	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; < 10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture > 10% linear measurement	Necrosis
Eye- Late RT Morbidity Scoring	No change from baseline	Asymptomatic cataract; minor corneal ulceration or keratitis	Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment; severe glaucoma	Panophthalmitis; blindness
Radiation-Other (Specify,)	None	Mild	Moderate	Severe	Life-threatening or disabling

Appendix VI
BMT Complex/Multi-Component Events

Toxicity	Grade 0	1	2	3	4
Note: The grading of Complex/Multi-Component Events in bone marrow transplant will be defined in the protocol. The grading scale must use the CTC criteria for grading the specific component events (toxicities).					
Failure to engraft Also consider Hemoglobin (Hgb), Neutrophils/granulocytes (ANC/AGC), Platelets	absent	mild	moderate	severe	life-threatening
Graft versus host disease Also consider Fatigue, Rash/desquamation, Diarrhea, Bilirubin-GVHD	absent	mild	moderate	severe	life-threatening
Stem cell infusion complications Also consider Allergic reaction/hypersensitivity, Arrhythmia, Hypertension, Hypotension, Fever, Rigors/chills, Sweating, Rash/desquamation, Urticaria, Diarrhea, Nausea, Vomiting, Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hemoptysis, Alkaline phosphatase, Bilirubin, GGT, SGOT, SGPT, Infection, Hyperkalemia, Hypernatremia, Hypokalemia, Depressed level of consciousness, Seizures, Abdominal pain, Headache, Creatinine, Hemoglobinuria	absent	mild	moderate	severe	life-threatening
Veno-Occlusive Disease (VOD) Also consider Weight gain-VOD, Bilirubin, Depressed level of consciousness, Hepatic pain, Renal failure, Hepatic enlargement.	absent	mild	moderate	severe	life-threatening

06/20/07

CITY OF HOPE NATIONAL MEDICAL CENTER
1500 EAST DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF HEMATOLOGY / BONE MARROW TRANSPLANTATION

05/10/00

TITLE: ***A PHASE I/II TRIAL OF ESCALATING DOSE OF YTTRIUM-90-LABELED ANTI-CD20 MONOCLONAL ANTIBODY IN COMBINATION WITH HIGH-DOSE ETOPOSIDE AND CYCLOPHOSPHAMIDE FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION FOR PATIENTS WITH POOR RISK/RELAPSED B-CELL NON-HODGKIN'S LYMPHOMA***

CITY OF HOPE PROTOCOL NUMBER/VERSION NUMBER: **IRB#** ***98153*** **VERSION** ***17***

10/29/03, 04/06/04, 06/16/04

DATE(S) OF AMENDMENT(S)/REVISION(S):

Amendment 1 – 01/31/00 – Version 01
Amendment 2 – 05/10/00 – Version 02
Amendment 3 – 06/05/00 – Version 03
Amendment 4 – 07/13/00 – Version 04
Amendment 5 – 09/08/00 – Version 05
Amendment 6 – 10/25/00 – Version 06
Amendment 7 – 12/20/00 – Version 07
Amendment 15 – 06/20/07 – Version 15

Amendment 8 – 02/08/01 – Version 08
Amendment 9 – 05/03/01 – Version 09
Amendment 10 – 08/07/01 – Version 10
Amendment 11 – 05/30/02 – Version 11
Amendment 12 – 10/29/03 – Version 12
Amendment 13 – 04/06/04 – Version 13
Amendment 14 – 06/16/04 – Version 14
Amendment 16 – 04/18/12 – Version 16 (title page only change)
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SITE: Lymphoma
HISTOLOGY: Low and Intermediate Grade CD20 (+)
STAGE (IF APPLICABLE): II, III, IV
MODALITY: Chemotherapy/Radioimmunotherapy
TYPE: Phase I/II

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INVESTIGATIONAL NEW DRUG (IND) NUMBER: BB-IND 8836

05/10/00, 06/05/00, 09/08/00, 10/29/03, 06/16/04

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10/29/03

1.0 BACKGROUND RATIONALE

Non-Hodgkin's lymphomas (NHLs) are the sixth most common cause of cancer-related deaths in the United States. The incidence of NHL has increased by 50% over the past 15 years. The incidence of both indolent and aggressive lymphomas increases with age, making these the most commonly diagnosed lymphoid malignancies in patients over 60 years old.[1] Despite the use of aggressive combination chemotherapy regimens, approximately 30-40% of patients with intermediate- and high-grade NHL does not achieve complete remission (CR) or suffers relapse after attaining remission.[2] High-dose chemotherapy or chemo/radiotherapy followed by autologous bone marrow or stem cell transplantation (ASCT) has been shown to induce long-term disease control in about 10-50% of patients with relapsed and refractory intermediate- and high-grade lymphoma.[3] Recently, the benefit of high-dose therapy and ASCT proved to be superior to conventional salvage chemotherapy in a randomized Parma study of 215 patients with chemotherapy-sensitive NHL in relapse.[4] The 5-year event-free survival (EFS) was 46% for the ASCT group as compared to 12% for the salvage therapy without transplantation ($p = 0.001$). Thus, high-dose therapy and ASCT has become a potential curative modality for patients with recurrent aggressive lymphoma. However, not all patients derive long-term benefits from this treatment and recurrent disease remains the single most common cause of treatment failure post-high-dose therapy and ASCT. Therefore, new therapeutic approaches are needed.

Patients with low-grade NHL have indolent clinical courses and are not cured by current treatment approaches. Although most patients can achieve a complete remission with standard treatment, the median duration of first CR ranges from 12 to 36 months. Relapsed low-grade lymphoma may still respond to salvage therapy. But the duration of subsequent remissions progressively decreases. High-dose therapy and ASCT has been shown to improve survival and to increase the duration of remission in some patients with relapsed low-grade NHL.[5] However, because of the long natural history and the continued pattern of relapse post-ASCT in some studies, the role of high-dose therapy and ASCT as a potential curative treatment for patients with relapsed low-grade lymphoma has not been clearly established.

Recently, the role of radioimmunotherapy for treatment of NHL has emerged. Radioisotope-labeled monoclonal antibodies provide a mechanism by which radioactivity can be directly targeted to tumors sites while sparing normal tissues. B-cell lymphomas are attractive targets for radioimmunotherapy because of their radiosensitivity, their well-defined surface antigens and the availability of multiple monoclonal antibodies to those antigens.

1.1 Results of High-Dose Chemo/Radiotherapy and ASCT for NHL

Several high-dose therapy regimens have been used as preparative regimens for NHL. But so far, none of these regimens have emerged as the best regimen. However, since NHL is radio-sensitive and based on experience with acute leukemia, the combination of total body irradiation (TBI) and cyclophosphamide (Cy) has been widely used as a preparative regimen for some patients with lymphoid malignancies. In an attempt to reduce relapse rates, etoposide has been added to the TBI and Cy regimen because of its known activity in lymphoma. The results of phase I and II studies of TBI 12.0 Gy, etoposide 60 mg/kg and Cy 100 mg/kg conducted at City of Hope[6], Stanford University[7] and Fred Hutchinson Cancer Research Center (FHCRC)[8] demonstrate the activity of this regimen in patients with lymphoid malignancies. The transplant-related mortality within 100 days was 7-8%, with the common causes of death being venoocclusive disease (VOD), diffuse alveolar hemorrhage and infection. The major transplant-related morbidities were mucositis and skin toxicities, which were fully reversible. The 5-year EFS and overall survival (OS) were 52% [95% Confidence interval (CI) 42-62%] and 61% (95% CI 50-73%), respectively for 134 patients with NHL who underwent ASCT utilizing this regimen at Stanford. These results have been confirmed in the Southwestern Oncology Group cooperative trial. Despite its effectiveness, the relapse rate of 34-53 % remains considerably high. Thus, new preparative regimens need to be explored.

1.2 Radionuclides for Radioimmunotherapy

Iodine-131 (^{131}I) has been the gold standard for radioimmunotherapy due to its long track record in treating thyroid carcinomas, its well-defined radiochemistry, its clinical availability, and its potential for both radioimmunoscintigraphy and radioimmunotherapy. ^{131}I has been employed in the majority of reported clinical trials of radioimmunotherapy. However, there are disadvantages to ^{131}I, including its long 8-day half life, the risks of radiation exposure to health care providers and the non-specific irradiation to normal organs from gamma components of ^{131}I.

Yttrium-90 (^{90}Y) may be an ideal radionuclide for radioimmunotherapy since it emits beta particles that are more potent than those delivered by ^{131}I. It is a pure beta emitter, making it a safer reagent for medical personnel to administer. In addition, the short half-life of ^{90}Y facilitates its use in combination with other agents, i.e. chemotherapy or total body radiation, and allows for high dose rates at localized sites. Unfortunately, ^{90}Y cannot be used for radioimmunoscintigraphy due to its absence of gamma emissions. Indium-111 (^{111}In) has been substituted as an imaging reagent to show tumor localization in patients scheduled for ^{90}Y therapy, based on its biodistribution which is close to that of ^{90}Y. ^{111}In-labeled murine monoclonals have been used successfully in clinical imaging trials for cutaneous T-cell lymphoma, chronic lymphocytic leukemia, melanoma, and colon cancer.

1.3 Anti-CD 20

Anti-CD20 (anti-B1) is a murine monoclonal antibody of isotype IgG2a, raised against cryopreserved Burkitt's lymphoma cells. The antibody reacts against the B1 antigen, an epitope of the CD20 developmental cell surface protein. CD20 is a 35 kD cell surface phosphoprotein found on 95% of normal mature B-cells and more than 90% of B-cell non-Hodgkin's lymphomas and B-cell chronic lymphocytic leukemias tested, but not on T-cells, plasma cells, uncommitted

hematopoietic-precursors stem cells, dendritic cells, granulocytes, monocytes, or erythrocytes, or on tumors of T cell, myeloid or erythroid origin. CD20 is not shed and does not modulate from the surface after binding of antibody.

Anti-CD20 has been used extensively as a therapeutic agent for use in bone marrow purging. Clinical use of this antibody in marrow purging has shown it to be selective in eradicating B cell lymphomas as well as normal B-cells, while leaving other lymphocyte population intact. Some subpopulation of B cell precursors is left intact, as evidence by engraftment of the normal B cell compartment.

1.4 IDEC-C2B8

IDEC-C2B8 is a chimeric antibody with a murine variable portion and a human IgG1 kappa constant portion that recognizes the CD20 antigens expressed on normal B-cells and most malignant B-cell lymphomas. IDEC-C2B8 shows specificity for the CD 20 antigen and binds with an apparent affinity of 4.3×10^{-9}M. IDEC-C2B8 has also been reported to induce apoptosis and to sensitize drug-resistant human B-cell lymphoma cell lines to cytotoxic chemotherapy.

A phase I dose escalation pharmacokinetic trial of IDEC-C2B8 given as a single intravenous infusion using doses ranging from 10 mg/m^2 to 500 mg/m^2 in patients with relapsed or refractory low-grade lymphoma was reported by Maloney et al.[9] The median half-life of the free antibody at doses ranging from 100 mg/m^2 to 500 mg/m^2 was 4.4 days (range 1.6-10.5 days). In phase II clinical studies, anti-tumor activity has been observed in patients with relapsed or refractory low-grade or follicular B-cell NHL. The majority of adverse events was mild to moderate and included fever, fatigue, chills and nausea which were primarily associated with the initial infusions. No quantifiable human anti-mouse antibodies (HAMA) or human anti-chimeric antibodies (HACA) were observed. Depletion of peripheral B-cells occurred rapidly following the first infusion with recovery beginning 6 months post-treatment. Despite this depletion of B-cells, there was minimal change in serum IgG, IgM, and IgA levels and no increase in the frequency or severity of infectious complications. Anti-tumor activity was observed at various disease sites including peripheral blood, bone marrow, lymph nodes, spleen and abdomen.

A phase III trial to assess the safety and efficacy of IDEC-C2B8 375 mg/m^2 given once weekly for four doses in 166 patients with relapsed or refractory low-grade or follicular NHL was reported by McLaughlin et al.[10] The overall response rate in 151 evaluable patients was 50% (9CR; 67 PR)**.** The median duration of response has not been reached after a median follow-up of 9+ months. Conversion to negative bcl-2 status occurred in 57% of patients who were positive at baseline and subsequently reevaluated after the fourth infusion. No positive HAMA responses were observed in 67 patients evaluated and the incidence of HACA was less than 1%. Severe neutropenia and thrombocytopenia were observed in less than 2% of patients. IDEC-C2B8 has also been studied in 44 patients with relapsed diffuse large B-cell and mantle cell lymphoma. The overall response rate was 31%, with a 10% CR rate. Thus anti-CD20 monoclonal antibody has become a very effective salvage therapy for CD20+ B-cell low-and intermediate-grade NHL and this treatment has become an important addition to our armamentarium.

IDEC-C2B8 has also been studied in combination with chemotherapy. Czuczman et al[11]

conducted a phase II multi-center study evaluating the safety and anti-tumor activity of IDEC-C2B8 375 mg/m^2 for six doses in combination with six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy in 40 patients with low-grade NHL. Combination therapy appeared safe and toxicity profile observed was consistent with that seen with CHOP alone. No HAMA or HACA responses were observed. The overall response rate in 35 patients who completed treatment was 100% (21 CR; 14 PR). The median time to disease progression has not been reached with follow-up time of 9-27+ months. Seven of eight patients who were bcl-2 positive at baseline by polymerase chain reaction (PCR) became negative in both peripheral blood and bone marrow following treatment. This combined therapy is being investigated in previously untreated patients with intermediate- and high-grade NHL.

1.5 Results of Radiolabeled Antibodies in the Treatment of Non-Hodgkin's Lymphoma

Most recent radioimmunotherapy trials for lymphoma have utilized ^{131}I-labeled anti-B1 (anti-CD20) antibody. Kaminski et al[12] first reported on a trial utilizing multiple treatments with low dose ^{131}I-labeled anti-B1 antibody in ten patients who had a CD20 positive B-cell lymphoma in whom primary therapy had failed. Six of the nine treated patients had tumor responses, including patients with bulky or chemotherapy-resistant diseases. Four patients had complete remissions (CR), and two had partial responses. The follow-up time was relatively short, but no disease progression was observed in the four patients who achieved a CR at 8-11 months. Toxicity was minimal with mild or no myelosuppression.

Based on these results, a phase I/II study of ^{131}I-labeled anti-B1 was conducted in 58 heavily pre-treated patients with NHL (28 low-grade, 14 transformed low-grade, 15 intermediate-grade, and 2 high-grade).[13] The median number of prior therapy was 4, 88% had stage III or IV disease, 36% had bulky disease, 51% had an elevated LDH level and 14 had failed BMT. Patients received 1-3 dosimetric doses followed by a therapeutic dose. The dosimetric dose involved the IV administration of 5 mCi of ^{131}I anti-B1 antibody to determine the rate of whole body clearance so that a whole body radiation dose could be calculated. Each dosimetric dose was preceded by 0, 95, or 475 mg of unlabeled antibody. Therapeutic dose escalation was initiated at 25 cGy and adjusted in 10 cGy increment until the MTD. The MTD was 75 cGy for patients who had not undergone BMT. The overall response rate in these heavily pre-treated patients was 71% with a CR rate of 34%. The median duration of response was 271 days (95% CI; 40-394 days) and the median duration of CR was 566 days. Response was observed in both low-grade and transformed low-grade NHL as well as in patients with bulky disease and patients who had relapsed post-BMT.

Further trials of ^{131}I-labeled anti-B1 antibody at non-myeloablative doses has been studied in 4 separate clinical trials (phase I and II, single and multi-center) in 113 patients with low-grade NHL including 25 with transformed low-grade NHL.[14] Patients received a single dosimetric dose of 450 mg of unlabeled anti-B1 infusion over one hour followed by 35 mg radiolabeled with 5 mCi ^{131}I over ½ hour. The therapeutic dose was administered 7 to 14 days after the dosimetric dose and consisted of the same unlabeled and labeled antibody doses. The overall response rate was 77% with a CR rate of 45% and 67% of the complete responders were in continuous remission for > 4 years. Reversible hematologic toxicity was the dose- limiting toxicity. ANC < 100/mm^3 was observed in 2.6% of patients and platelets < 10,000/mm^3 in 5.3%. The nadir

typically occurred at week 5-6 with recovery by week 8-9. The most common non-hematologic toxicities were transient mild to moderate fever, nausea, asthenia, and chills. None of the patients developed HAMA. These results suggest that ^{131}I-labeled anti-B1 is safe and effective and may induce prolonged CR in heavily pre-treated low-grade and transformed low-grade NHL.

1.6 Results of ^{131}I anti-B1 Monoclonal Antibody with Autologous Bone Marrow Support

Although promising results have been reported with radiolabeled MAb for NHL, these results may be improved by using higher dose or myeloablative radiation dose. The use of radiolabeled MAb at myeloablative radiation dose followed by autologous stem cell rescue has been explored by investigators from The Fred Hutchinson Cancer Research Center. Press et al[15] conducted a trial utilizing higher dose of ^{131}I-labeled anti-CD20 antibody with autologous bone marrow rescue in 43 patients with B-cell lymphoma in relapse. In this study, sequential biodistribution studies were performed with escalating doses of antibody (0.5, 2.5, and 10 mg/kg) trace-labeled with 5 to 10 mCi of ^{131}I. Patients whose tumors were estimated to receive greater doses of radiation than liver, lungs, or kidneys (a favorable biodistribution) were eligible for the therapeutic infusion of ^{131}I-labeled antibody. Of the 43 patients, 24 had a favorable biodistribution, and 19 received therapeutic infusion of 234-777 mCi of ^{131}I-labeled antibodies (58-1168 mg) followed by autologous marrow infusion. Sixteen patients achieved a CR, two had a partial response and one had a minor response. Nine of the complete responders have remained in continuous CR for 3 to 53 months. Toxicities include myelosuppression, nausea, infection and two episodes of cardiopulmonary toxicity. In this study, cardiopulmonary toxicity was the dose limiting, non-hematopoietic toxicity of high-dose ^{131}I-labeled antibody.

In an attempt to reduce toxicity to normal tissues and to directly deliver higher dose of radiation to tumor sites, ^{131}I-labeled-anti-CD20 MAb has been incorporated into high-dose therapy regimen instead of TBI. Press et al[16] reported results of a phase I/II study to define the MTD of an ^{131}I-labeled anti-B1 monoclonal antibody which can be given with high-dose etoposide and cyclophosphamide in conjunction with ASCT in 38 (26 low-grade; 12 aggressive) NHL patients. Patients were treated in a cohorts of 4 patients each with doses of ^{131}I-anti-B1 antibody (2.5 mg/kg, 318-840 mCi) calculated to deliver 20-27 Gy of radiation to dose-limiting, critical normal organs, followed by etoposide (0 or 60 mg/kg), cyclophosphamide (100 mg/kg), and ABMT (15 patients) or ASCT (22 patients). Of the 37 evaluable patients, 33 (89%) were currently alive and 29 (78%) were progression-free after a median follow-up of 1.5 yr. Toxicities included grade 4 myelosuppression in all patients, grade 2-3 nausea in 26 (70%), pulmonary infiltrate in 4 and grade 3 VOD in 2 patients. There were four death; 3 from progressive NHL and 1 from disseminated Varicella. These results suggest that ^{131}I- anti-B1 antibody can be given at doses delivering $\geq$ 25 Gy to critical normal organs, with pulmonary and gastrointestinal toxicities being dose-limiting. Although additional studies are needed, ^{131}I-anti-B1 antibody can be safely given in combination with high-dose chemotherapy in an autologous stem cell transplant setting for NHL.

1.7 ^{90}Y -Anti-CD20 Radioimmunotherapy for Relapsed NHL

A phase I/II dose escalation study of ^{90}Y-murine anti-CD20 monoclonal antibody (MAb) in patients with recurrent B-cell lymphoma was performed by Knox et al.[17] The primary objectives

of the study were: (a) to determine the effect of the preinfusion of unlabeled anti-CD20 MAb on the biodistribution of ^{111}In-anti-CD20 MAb; (b) to determine the maximal tolerated dose of ^{90}Y-anti-CD20 MAb that does not require bone marrow transplantation; and (c) to evaluate the safety and antitumor effect of ^{90}Y-anti-CD20 MAb in patients with recurrent B-cell lymphoma. Eighteen patients with relapsed low- or intermediate-grade non-Hodgkin's lymphoma were treated. Biodistribution studies with ^{111}In- anti-CD20 MAb were performed prior to therapy. Groups of three or four patients were treated at dose levels of approx 13.5, 20, 30, 40, and 50 mCi ^{90}Y-anti-CD20 MAb. Three patients were retreated at the 40 mCi dose level. The use of unlabeled antibody affected the biodistribution favorably. Nonhematological toxicity was minimal. The only significant toxicity was myelosuppression. The overall response rate following a single dose of ^{90}Y-anti-CD20 MAb therapy was 72%, with six complete responses and seven partial responses and freedom from progression of 3-29+ mo following treatment. Radioimmunotherapy with less than or equal to 50 mCi ^{90}Y-anti-CD20 MAb resulted in minimal nonhematological toxicity and durable clinical responses in patients with recurrent B-cell lymphoma. Doses of less than or equal to 40 mCi ^{90}Y-anti-CD20 MAb were not myeloablative.

Results of a phase I/II study utilizing chimeric antibody Rituximab as the unlabeled clearing antibody and ^{90}Y conjugated anti-CD20 (IDEC-Y2B8, conjugated to the parent murine monoclonal 2B8) was recently reported. In the study reported by Witzig et al[18], the first portion of the study compared 100 mg/m^2 with 250 mg/m^2 of Rituximab as the clearing dose and compared dosimetry imaging capabilities. It was determined that 250 mg/m^2 of Rituximab was the optimal dose to be used. In the second portion of the phase I study, the dose of IDEC-Y2B8 was escalated from 0.2 mCi/kg to 0.4 mCi/kg. No bone marrow or stem cell harvest was required. None of the patients treated at 0.2, 0.3 and 0.4 mCi/kg whose baseline platelet count > 150,000/mm^3 developed grade 4 hematologic toxicity, whereas 3 of 6 patients treated at 0.2 or 0.3 mCi/kg with baseline platelet counts between 100,000 to 150,000/mm^3 developed transient grade 4 hematologic toxicity.

The dosimetry from this phase I/II trial of IDEC-Y2B8 was reported by Wiseman et al.[19] Forty-two patients with low- and intermediate-grade NHL received IDEC-Y2B8 following injection of unlabeled Rituximab (cold antibodies) followed by 2 mg of mouse anti-CD20 antibody labeled with 5 mCi ^{111}In (IDEC-In2B8). ^{90}Y 0.2, 0.3, or 0.4 mCi/kg was given 7 days following ^{111}I. The patients had ^{111}In dosimetry performed by serial whole body gamma camera imaging, urine collection and blood sampling at 0, 2, 6, 24, 48, 72, 96 and 144 hours. The highest mean calculated ^{90}Y radiation dose to a normal organ was spleen with 24.16 rads/mCi (0.6-67.0), followed by liver with 17.2 rad/mCi (9.4-39.2) and lungs with 12.9 rads/mCi (4.2-67.7). ^{90}Y dose of 0.4 mCi/kg was the MTD for bone marrow toxicity (thrombocytopenia and neutropenia). These results suggest that: 1) no organ irradiated beyond safety levels; 2) ^{111}I can serve as a predictor of ^{90}Y; 3) Rituximab dose of 250 mg/m^2 has been established as the “cold” antibody with added benefits of its therapeutic effect; and 4) bone marrow toxicity was the dose-limiting effect with full and predictable recovery.

Outcomes from this trial have been compiled in a submitted publication.[19] The overall response rate (ORR) for the intent-to-treat population (n = 51) was 67% (26% CR, 41% PR); for the low-grade group (n = 34) 82% (27% CR, 56% PR); 43% for intermediate grade (n = 4); and 0% for mantle cell (n = 3). Responses were seen in patients with bulky (> 7 cm) disease (41%) and

splenomegaly (50%). Kaplan-Meier estimate of time-to-progression in responders and duration of response is 12.9+ months and 11.7+ months, respectively. Adverse events were primarily hematologic and correlated with baseline extent of marrow involvement with NHL and baseline platelet count. Only one patient developed an anti-antibody response (HACA/HAMA).

1.8 Study Proposal

The high-dose therapy regimen of FTBI 1200 cGy, etoposide 60 mg/kg and Cy 100 mg/kg has been used extensively at City of Hope as a preparative regimen for patients with hematological malignancies. Given the relatively high relapse rate associated with this regimen, the effective anti-lymphoma therapy of IDEC-C2B8, and the safety and feasibility of IDEC-Y2B8 with the ability to directly deliver radiation to tumors sites, we propose to study a new preparative regimen in patients with relapsed NHL which will utilize ^{90}Y-labeled anti-CD20 antibody (IDEC-Y2B8) instead of TBI in combination with high-dose etoposide and cyclophosphamide. We plan to conduct a phase I/II trial to define the maximum tolerated dose (MTD) of IDEC-Y2B8 that can be given with high-dose etoposide and cyclophosphamide followed by ASCT, and to define the response rate and toxicities associated with this regimen. To avoid liver toxicity, etoposide dose will be started at 40 mg/kg and escalated to 60 mg/kg and the dose of Cy will be fixed at 100 mg/kg.

05/03/01, 06/16/04 The patient will undergo a dosimetry study with IDEC-In2B8 to confirm favorable localization of isotope one week prior to administration of therapeutic dose IDEC-Y2B8. Serial gamma camera images will be obtained at the end of the infusion, 24 hours, 48 hours, 72 - 96 hours, 120 hours and 144 hours post-infusion. At each time point, one whole body and 4 spot planar scans will be acquired with the Toshiba dual head camera. In addition, two SPECT images will be obtained at 48 and 72 -96 hour time points. Nuclear Medicine images will be used to estimate the distribution of activity in various organs, especially liver, lungs, kidney, heart and spleen. Blood samples will be drawn prior to IDEC-C2B8 and at approximately 0 hours (immediately prior to IDEC-In2B8), 2 hours, 4 - 6 hours, 24 hours, 48 hours, 72 - 96 hours, 120 hours and 144 hours following antibody infusion. These samples will be used to analyze antibody clearance and bone marrow dose estimates. Urine samples will be collected daily for six days to analyze radioisotope clearance.

05/03/01, 08/07/01, 06/16/04 Favorable biodistribution will be defined as tumor dose greater than any normal organ, except spleen and bone marrow, ie. liver, lung, kidney. For patients in CR at time of transplantation, no specific tumor localization is required as long as Ga 67 scan and/or FDG-PET scan is negative. Tumor dose will be calculated from multiple gamma camera images and blood/urine pharmacokinetics. If the patient shows favorable biodistribution, the therapeutic dose will be administered on day -14. Serial gamma camera images will be obtained at the end of the infusion, 24 hours, 48 hours, 72 - 96 hours, 120 hours and 144 hours post-infusion. At each time point, one whole body and 4 spot planar scans will be acquired with the Toshiba dual head camera. Nuclear Medicine images will be used to confirm estimates of the distribution of activity in various organs, especially liver, lungs, kidney, heart and spleen. Blood samples will be drawn prior to IDEC-C2B8 and at approximately 0 hours (immediately prior to IDEC-In2B8 / IDEC-Y2B8), 2 hours, 4 - 6 hours, 24 hours, 48 hours, 72 - 96 hours, 120 hours and 144 hours following antibody infusion. These samples will be used to analyze antibody clearance and bone

marrow dose estimation. Urine samples will be collected daily for six days to analyze radioisotope clearance. The therapeutic dose will be administered to deliver a target dose of 1000 cGy to the organ projected to receive the highest dose from the imaging study. After the first two dose levels the dose will be increased in increments of 250 cGy until a maximum of 2500 cGy is attained or dose limiting toxicity is encountered.

10/29/03

2.0 OBJECTIVES

05/10/00

2.1 To evaluate the safety and efficacy of a new preparative regimen of ^{90}Y-labeled anti-CD20 MAb (IDEC-Y2B8) in combination with high-dose etoposide and cyclophosphamide followed by ASCT for treatment of patients with relapsed/refractory and poor risk NHL.

2.2 To determine the MTD of ^{90}Y-anti-CD20 MAb which can be given with high-dose etoposide 60 mg/kg and high-dose cyclophosphamide 100 mg/kg followed by ASCT in patients with NHL.

2.3 To perform dosimetry study to estimate the radiation dose delivered to the tumor and normal organs.

2.4 To evaluate the short-term and long-term complication of this new preparative regimen.

3.0 STUDY DESIGN

This is an open-label phase I-II clinical and efficacy study of a new preparative regimen followed by autologous stem cell support in patients with relapsed and refractory NHL. Patients with low-, and intermediate-grade NHL who have relapsed followed conventional chemotherapy or have failed to achieve remission, and who are candidates for high-dose therapy and ASCT will be eligible for this study. All patients will receive IDEC-Y2B8 in combination with high-dose etoposide and cyclophosphamide followed by ASCT. The dose of Cy will be fixed at 100 mg/kg. There will be two doses escalating schema for etoposide and IDEC-Y2B8. Etoposide will be started at 40 mg/kg (cohort 1) and escalate to 60 mg/kg (cohort 2). The dose of Y2B8 will be the same for cohort 1 and 2, to deliver 1000 cGy to the normal organ receiving the greatest accumulation. If no dose limiting toxicity is observed, while the etoposide dose remains at 60 mg/kg, the dose of Y2B8 will be escalated to 1250 cGy, and then to a maximum of 2500 cGy, or until the MTD has been reached. Therefore, there will be cohorts with 3 patients per cohort as follows (an additional 2 patients per cohort will be accrued if there are eligible patients available prior to the determination of toxicity on the current dose level):

Cohort 1:	**Y2B8** to deliver **1000 cGy** to highest normal organ excluding spleen and bone marrow **etoposide 40 mg/kg** **cyclophosphamide 100 mg/kg**
Cohort 2:	Y2B8 to deliver 1000 cGy to highest normal organ excluding spleen and bone marrow **etoposide 60 mg/kg** cyclophosphamide 100 mg/kg

Cohort 3:	**Y2B8** to deliver **1250 cGy** to highest normal organ excluding spleen and bone marrow etoposide 60 mg/kg cyclophosphamide 100 mg/kg
Cohort 4:	**Y2B8** to deliver **1500 cGy** to highest normal organ excluding spleen and bone marrow etoposide 60 mg/kg cyclophosphamide 100 mg/kg
Cohort 5:	**Y2B8** to deliver **1750 cGy** to highest normal organ excluding spleen and bone marrow etoposide 60 mg/kg cyclophosphamide 100 mg/kg
Cohort 6 to 8:	**Y2B8** to deliver **2000-2500 cGy** to highest normal organ excluding spleen and bone marrow etoposide 60 mg/kg cyclophosphamide 100 mg/kg

05/03/01 All patients will have peripheral blood stem cell collected with the target CD34+ of $3.0x10^6$/kg. Patients will undergo dosimetry studies on day –21 and therapy on day -14. Etoposide will be given on day -4, followed by a day rest and cyclophosphamide on day -2. PBSC will be infused on day +1 when the radiation dose to the reinfused stem cells is estimated to be < 5 cGy.

4.0 DRUG FORMULATION

4.1 IDEC-Y2B8

a. Drug Formulation and Procurement

IDEC-2B8-MX-DTPA Two ml glass septum vial containing 2 ml (3.2 mg) IDEC-2B8-MX-DTPA in low metal normal saline at 1.6 mg/ml.

RITUXAN (IDEC-C2B8) Ten ml (100 mg) and/or 50 ml (500 mg) pharmaceutical grade glass vials at a concentration of 10 mg of protein per ml.
^{111}In-chloride 5 mCi of Indium-111 chloride supplied in .05M HCl.
^{90}Y-chloride 40-100 mCi Yttrium-90 chloride supplied in .05M HCl.

10/29/03 *b. Drug Toxicity*

Myelosuppression is the dose limiting toxicity in non marrow supported regimens. With marrow support liver, kidney, and lung are likely to be the dose limiting organs for toxicity. Infusional toxicity of chills and rigors are common with the first administration but rarely with subsequent doses. Decreasing the rate of infusion and the administration of antihistamines can control these toxicities.

c. Drug Storage, Reconstitution and Stability

All antibodies will be stored in the investigational pharmacy at 4ºC until the day of use.

Once diluted the unlabeled antibody is to be used within 24 hours if held at 4ºC and at room temperature for an additional 12 hours. The radiolabeled solutions should be used within 6 hrs and should be held at 2-8ºC until administered.

4.2 VP-16 (epipodophyllotoxin, etoposide, 4'-demethyl-9(4,6-o-ß) d-ethylideneglycopyranoside).

a. Drug Formulation and Procurement

VP-16 is supplied by Bristol Laboratories in a 100 mg ampule in 5 cc of a solution containing citric acid, 10 mg; benzyl alcohol, 150 mg; polysorbate 80, purified, 250 mg; polyethylene glycol 300, 3.75 gm; absolute alcohol q s., 5 cc.

b. Drug Toxicity

Myelosuppression, primarily granulocytopenia, is the dose-limiting toxicity. Gastrointestinal toxicity at high doses includes nausea, emesis and mucositis. Reversible hepatotoxicity may occur at very high doses. The acute side effects of occasional bronchospasm and hypotension are avoided by slow intravenous administration.

c. Drug Storage, Reconstitution and Stability

The contents of the ampoule are diluted with 50 volumes of NaCl solution for injection, USP, and administered by slow intravenous infusion. Patients will receive the drug through a central venous catheter at a rate of 60 mg/kg/4 hours.

4.3 Cyclophosphamide (Neosar, Cytoxan), NSC-26271

a. Drug Formulation and Procurement

Cyclophosphamide is an alkylating agent dispensed in 100, 200 and 500 mg vials containing a dry powder. Cyclophosphamide will be purchased from Adria Laboratories.

b. Drug Toxicity

Patients must be well hydrated before and for several hours following administration of cyclophosphamide to reduce the potential for hemorrhagic cystitis. The more common side effects include nausea and vomiting, and alopecia. Acute toxicity includes principally leukopenia, with the nadir occurring 7-14 days after a single IV dose. At high doses, occasional pulmonary toxicity has been reported. Rare cardiac toxicity (congestive heart failure) has occurred in patients previously treated with anthracyclines.

c. Drug Storage, Reconstitution and Stability

Cyclophosphamide is reconstituted with either sterile water for injection, USP or bacteriostatic water for injection, USP (Paraben preserved only), using 5 ml for the 100 mg vial, 10 ml for the 200 mg vial or 25 ml for the 500 mg vial. Each ml of reconstituted solution contains 20 mg cyclophosphamide per ml. The drug is diluted in 5% dextrose and water or physiological saline and given by IV infusion.

4.4 Mesna (Sodium 2-Mercaptoethane sulfonate)

a. Drug Formulation and Procurement

Mesna is provided by Bristol Laboratories as a 10% (100 mg/ml) solution in water with 0.25 mg EDTA as excipient in 4 ml ampules.

b. Drug Storage, Reconstitution and Stability

Mesna solutions have been shown to be stable on extended storage at room temperature in ampules. No change in composition of the ampules was noted at one year's storage in these conditions.

On exposure to air Mesna is known to undergo oxidation to disulfide. Since the Mesna concentration of opened ampules may decrease with time, the ampule should be opened just before use and the unused part discarded.

c. Administration

Each dose of Mesna will be diluted in 50 cc of 5% dextrose/water or 0.9% normal saline and infused intravenously over 15 minutes.

06/05/00

4.5 DTPA (Diethyltriaminepenatacetic acid)

a. Drug Formulation and Procurement

DTPA will be purchased from Heyl Pharmaceuticals, Berlin, Germany. It is supplied as a 1 gram ampule in 5 mls.

b. Drug toxicity

DTPA has been known to cause headaches, fever, chills, flu-like symptoms, nasal stuffiness, nausea, vomiting, abdominal cramping, and diarrhea. Other side effects that are less common include pain at the injection site, dehydration, decreased blood pressure, irregularities of heart rhythm, decreased blood counts, increased calcium, numbness and tingling, sneezing, excessive tearing, kidney damage, and zinc deficiency (which can result in a facial and perianal rash and tongue and mouth sores). In addition, there is always a risk of a very uncommon or previously unknown side effect occurring. Stopping the infusion normally reverses the side effects. Headaches and tingling have been observed at the City of Hope but were reversible. Trace metals will be administered at the end of infusion to replace any depleted heavy metals.

c. Drug Storage, Reconstitution and Stability

The DTPA solution will be diluted with 250 mls normal saline and administered over 24 hours. Additional IV fluids will be administered to maintain a minimum of 125 mls/hour of fluid. No other heavy metals should be administered during the 24 hour infusion. Potassium may be administered as needed. DTPA has a long aqueous stability but should

be used within 48 hours of being drawn up by the pharmacy. Patients will receive 250 mgs/m^2 to a maximum of a total dose of 500 mgs.

5.0 STAGING CRITERIA

Staging of disease must be evaluated at least 21 days after the end of the last chemotherapy and within 42 days prior to transplant.

5.1 The Ann Arbor staging criteria will be used. Stage is determined based on extent of disease at the time of diagnosis.

5.2 Ann Arbor Classification (AJCC Manual for Staging of Cancer, 4th ed. 1992)

STAGE I	Involvement of a single lymph node region (1) or a single extralymphatic organ or site (1_E).
STAGE II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and its associated regional lymph nodes (11_E).
STAGE III	Involvement of lymph node regions on both sides of the diaphragm (111) which may be accompanied by localized involvement of an associated extralymphatic organ or site (111_E) or spleen (111_S) or both (II(1_{SE}).
STAGE IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement.

A = Asymptomatic
B = Fever, sweats, weight loss > 10% of body weight

5.3 Definitions of Sensitivity of Disease:

Patients are grouped into one of three groups based on sensitivity of disease:

1. *Induction failure*: patients who did not achieve a CR or PR from induction chemotherapy;

2. *Resistant Relapse*: patients who did not achieve a CR or PR from the most recent standard salvage chemotherapy;

3. *Sensitive Relapse*: patients who did achieve a CR or PR from the most recent standard salvage chemotherapy.

05/10/00

5.4 Definitions of Poor Risk Disease

1. Age Adjusted International Prognostic Index (IPI) High- (3 risk factors) or High-Intermediate (2 risk factors) based on the following risk factors: stage III-IV, elevated serum lactate dehydrogenase level (LDH) and ECOG performance status 2-4.

2. Patients with aggressive NHL including mantle cell lymphoma who required 2 different induction chemotherapy regimens to achieve a partial/complete remission.

05/03/01 *3.* Patients with B-Cell NHL who fail to achieve a complete remission after adequate induction chemotherapy regimen(s).

05/10/00 **6.0 ELIGIBILITY CRITERIA**

05/10/00 ***6.1*** Favorable biodistribution on imaging dose

08/07/01 ***6.2*** age ≥ 18 and ≤ 60 years

10/29/03 ***6.3*** All patients must have biopsy proven diagnosis of low- and intermediate-grade NHL including follicular small cleaved, follicular mixed, follicular large cell, diffuse small cleaved, diffuse mixed, diffuse large cell, and immunoblastic lymphoma (working formulation B, C, D, E, F, G and H) including mantle cell lymphoma. Transformed low-grade lymphomas are eligible

6.4 Demonstrated monoclonal CD20 + B-cell population in lymph nodes and/or bone marrow

05/10/00 ***6.5*** Patients must have relapsed after achieving a complete or partial response to prior therapy, have never responded to prior therapy or have poor risk disease

05/10/00,05/30/02 10/29/03 ***6.6*** Patients must have bone marrow aspiration and biopsy within 42 days before salvage chemotherapy or stem cell collection which show ≤ 10% lymphomatous involvement of total cellularity

09/08/00, 05/30/02 ***6.7*** Platelet count should be normal before initiation of chemotherapy for salvage purposes or stem cell mobilization. If the patient collected his/her stem cells at an outside facility, then the platelet count must be normal before the imaging dose of antibody

6.8 Normal renal function test with serum creatinine of ≤ 1.5 mg/dl, or a creatinine clearance of ≥ 60 ml/min

6.9 Adequate pulmonary function as measured by FEV1 > 65% of predicted measured, or a DLCO ≥ 50% of predicted measured

04/06/04 ***6.10*** Cardiac Ejection fraction of > 50% by echocardiogram or multiple gated acquisition scan

6.11 Adequate liver function tests with a bilirubin of ≤ 1.5 x normal and SGOT or SGPT ≤ 2 x normal

6.12 Negative human immunodeficiency virus antibody

05/03/01 ***6.13*** ECOG performance status 0 or 1; or KPS ≥ 80

6.14 No active CNS disease or prior history of CNS disease

07/13/00 ***6.15*** Patients who have received involved field external beam therapy to area excluding lung, heart, liver and kidney are allowed, but will be evaluated on a case by case basis

6.16 Patients must have recovered from last therapy and should be at least four weeks from prior radiation or chemotherapy

08/07/01 ***6.17*** The patient should have a baseline CT scan and Ga 67 scan and/or FDG-PET scan after the last chemotherapy prior to initiation of treatment

10/29/03 ***6.18*** Normal cytogenetic study on bone marrow (prior to salvage chemotherapy or stem cell collection). However, cytogenetic study on peripheral blood is acceptable if bone marrow biopsy has already been done and shows no sign of MDS or lymphoma and a repeat bone marrow is deemed unnecessary by attending physician

7.0 EXCLUSION CRITERIA

7.1 Presence of human anti-mouse antibody (HAMA) or human anti-chimeric antibody

7.2 Prior radioimmunotherapy

7.3 Failure to collect adequate number of CD34 + cells $\geq 3x10^6$ /kg

7.4 Abnormal cytogenetic study on the bone marrow aspirate sample prior to stem cell collection

7.5 Prior bone marrow transplantation

07/13/00 ***7.6*** Prior malignancy except for adequately treated basal cell or squamous cell skin cancer, adequately treated noninvasive carcinomas, or other cancer from which the patient has been disease-free for at least five years

7.7 Active evidence of Hepatitis B and C infection; Hepatitis B surface antigen positive

02/08/01 ***7.8*** History of alcohol abuse

10/29/03 ***7.9*** Patient weighs more than 250 pounds

8.0 TREATMENT PLAN

8.1 Outline of the preparative regimen

	Day -21	Dosimetry with 5 mCi IDEC-In2B8 following 250 mg/M^2 Rituxan
	Day -14	IDEC-Y2B8 with 5 mCi IDEC-In2B8 following 250 mg/M^2 Rituxan
05/30/02	*Day -7*	Bone marrow biopsy and dose estimation
05/30/02, 10/29/03	*Day -4*	Etoposide 40 mg/kg adjusted ideal body weight (Cohort 1) or 60 mg/kg adjusted ideal body weight for other cohorts
10/29/03	*Day -2*	Cyclophosphamide 100 mg/kg ideal body weight
06/05/00	*Day 0*	DTPA infusion
	Day +1	Peripheral Stem Cell reinfusion
	Day +1	Start G-CSF 5 μg/kg/d IV

07/13/00 ***8.2 Pre-Transplant Therapy***

10/29/03 *a. Autologous Stem Cell Collection and Cryopreservation*

All patients should have bone marrow aspiration and biopsy which show no microscopic evidence of lymphomatous involvement, or ≤ 10% involvement at the time of stem cell collection. In addition, cytogenetic studies, immunophenotyping, gene rearrangement should be done. Peripheral blood stem cells (PBSCs) will be collected via leukapheresis procedures that have been previously described. Patients will receive PBSCs collected after mobilization by: 1) growth factors, ie. G-CSF 10 μg/kg/d or 2) chemotherapy with growth factors. A minimum of CD34+ cells, 3.0 x 10^6/kg should be collected.

b. Trimethoprim Sulfa

All patients should receive trimethoprim sulfa (one double-strength tablet PO bid) beginning day -8 through day -2 prior to PBSCT as prophylaxis against PCP. (The choice of trimethoprim sulfa as a prophylactic agent may be altered based on a history of sensitivity to this agent.) Dosing should be discontinued 48 hours prior to PBSC infusion because of potential myelosuppression.

10/29/03 *c. CNS Prophylaxis*

CNS prophylaxis is recommended for patients with mantle cell lymphoma or diffuse large cell lymphoma who had bone marrow involvement at diagnosis or at time of relapse. For patients with mantle cell lymphoma who have never received high-dose MTX, CNS prophylaxis with intrathecal chemotherapy should be given.

8.3 Radioimmunotherapy

08/07/01 *a.* Rituxan is to be administered by slow intravenous infusion having been diluted to 1-4 mg/ml in saline. Initial infusion should be through a dedicated line at a rate of 50 mg/hr. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes to a maximum rate of 400 mg/hr. If hypersensitivity or infusion-related events develop, the infusion should be temporarily slowed or interrupted. The infusion can be continued at one-half the previous rate when symptoms abate.

b. IDEC-In2B8 Administration - Two mg of IDEC-In2B8 (5.0 mCi of ^{111}In) will be administered for the dosimetry portion of the protocol. The imaging dose will be administered over 10 minutes by slow IV injection immediately following the infusion of Rituxan. A .22 micron filter must be on the line between the patient and the infusion port. Flush the line with at least 10 mls of normal saline after the IDEC-In2B8 has been infused.

c. IDEC-Y2B8 Administration – IDEC-Y2B8 (40-100 mCi of ^{90}Y with 3.2 – 6.4 mg of antibody) will be administered for the therapy portion of the protocol. The yttrium will be combined with a dose of IDEC-In2B8 (5.0 mCi of ^{111}In) identical to the dosimetry dose. The combined radiopharmaceuticals will be administered

by controlled infusion pump over 20 minutes. A .22 micron filter must be on the line between the patient and the infusion port. Flush the line with at least 10 mls of normal saline after the IDEC-In/Y2B8 has been infused.

d. Bone marrow biopsy.

8.4 Chemotherapy

10/25/00, 12/20/00

a. VP-16 is to be administered as a single infusion on day -4. The dose is 40 or 60 mg/kg and is calculated on adjusted ideal body weight to be consistent with standard VP-16 dosing for transplant protocols. The drug is infused undiluted directly into a port of a double or triple lumen indwelling intravenous catheter, with a total infusion time of 4 hours. The drug is to be drawn into one or more plastic syringes and infused with a syringe infusion pump, placed in an evacuated bottle and infused through a pediatric infusion pump, or infused by gravity without a pump. Thus the total dose for a 70 kg patient would be 4,200 mg. At 20 mg/ml, the volume of VP-16 would be 210 ml. The rate of infusion would thus be 210 ml/240 minutes or 0.875 ml/minute. Appropriate anti-emetics and sedatives should be given before the infusion begins. Before, and 2 hours into, the infusion the patient is to receive 25 mg of diphenhydramine, and 100 mg of hydrocortisone to prevent allergic reactions. If necessary, diuretics may be given. The intravenous hydration should be continued before, during and after the VP-16. Since in rare cases metabolic acidosis has been observed after high dose VP-16, additional NaHCO3 may be needed.

10/29/03

b. Cyclophosphamide is administered at a total dose of 100 mg/kg given in one dose on day -2 and is calculated on ideal body weight. Adjustments to the ideal body weight calculation for overweight patients are permitted. For patients who are weigh less than 95% of ideal body weight, cyclophosphamide will be dosed according to actual body weight. The drug should be dissolved in about 250 cc of D5W and infused IV over two hours. Appropriate anti-emetics and sedatives should be given. To prevent hemorrhagic cystitis, all patients should receive hydration with intravenous fluids, according to institutional standards, at the rate of 3.0 l/m2/day beginning four hours prior to cyclophosphamide and continuing until 24 hours after cyclophosphamide. In addition, mesna at 40 mg/kg (based on ideal body weight) will be given immediately before cyclophosphamide (hr 0) and at 3, 6, 9, 12, 15, 18 and 21 hrs later for a total of 8 doses. Each dose of mesna will be given IV over 15 minutes.

06/05/00, 10/29/03, 06/16/04

c. DTPA is to be administered by continuous intravenous infusion through a port of a double or triple lumen indwelling intravenous catheter. The dose should be $\geq$ 250 mgs/m^2, but $\leq$ 500 mgs. The DTPA should be made up in normal saline and infused over 24 hours by infusion pump. No magnesium or other heavy metal should be given during the same time period. Two hours after the end of the DTPA infusion 1 ml of trace metal solution should be infused every eight hours for five days. This should be given by slow intravenous delivery or else as part of standard hyperalimentation. Urine samples will be collected every 12 hours for

72 hours beginning 24 hours prior to DTPA infusion.

07/13/00, 05/03/01 ***8.5 Peripheral Stem Cell Reinfusion***

PBSCs will be thawed and infused according to standard guideline at approximately 72 hours after completion of cyclophosphamide.

8.6 Growth Factor Therapy

All patients will receive rh-G-CSF, 5 mcg/kg/day IV beginning on day +1, after PBSC infusion and continue daily until ANC >500 for 3 consecutive days.

07/13/00 ***8.7 Supportive Care:***

All patients will be housed in private rooms during the period of granulocytopenia. Nonabsorbable antibiotics for gastrointestinal decontamination should be used according to institutional guideline. Trimethoprim-sulfamethoxazole will be administered from day -8 to day -2 and prophylaxis should be re-instituted when white blood cells are > 3000 and continued until 6 months post-transplant. Empiric broad spectrum antibiotics and parenteral nutrition should be used as clinically indicated. Low-dose amphotericin-B (0.1 to 0.2 mg/kg) should be administered on day +1 and continued daily until granulocytopenia resolves. All blood components should be irradiated to 1,500 cGy.

a. Access to Vessels

Prior to admission, during pre-transplant evaluation, all patients should have a permanent central catheter placed.

b. Hyperalimentation

All patients will receive appropriate Hyperalimentation as soon as necessary after admission. The goal will be to prevent even a short duration of negative nitrogen balance.

c. Platelet Transfusion

1. Indication. Platelets are transfused to prevent bleeding and an attempt is made to keep the circulating level greater than 20,000/mm3 at all times. This goal may be changed by the attending physician as clinically indicated.

2. Irradiation. All blood products (except the autologous stem cells) are irradiated with 1,500 cGy prior to infusion.

d. Management of Fever/Infections

Treatment of patients on this protocol is not intended to restrict the freedom of the managing physician to treat suspected or documented infections. In neutropenic patients, however, the following guidelines should be followed.

1. All febrile, neutropenic patients should be treated with IV antibiotic(s), the choice

of which should be guided by the patient's clinical history, institutional practices and subsequent culture results.

2. Patients with documented, invasive fungal infection or with persistent, unexplained fevers while neutropenic and on broad-spectrum antibiotic therapy should receive antifungal therapy with Amphotericin-B.

8.8 Criteria for Removal from Protocol Treatment

a. Progression of disease.

b. Patients may withdraw from study at any time for any reason.

8.9 All reasons for discontinuation of treatment must be documented in the Flow Sheets.

8.10 All patients will be followed for survival until death. Secondary malignancy monitoring on this protocol will be done through 5 years post HCT. After such time, secondary malignancy monitoring will be done by the Long Term Follow Up office.

9.0 STUDY DESIGN AND RULES FOR DOSE ESCALATION

This is a phase I/II trial. For the phase I portion of the study, the rules for dose escalation, dose expansion, and termination of escalation are given in section 9.2. Prior to treatment with Y2B8, patients are required to undergo an imaging scan to verify that they have a favorable biodistribution. While waiting to assess toxicities in the initial cohort of 3 to 6 patients, additional patients who are determined to be eligible may be accrued at the unescalated dose level. The rationale for this is twofold. First, patients must be evaluated for distribution as soon as possible in order to have patients ready for timely accrual to the next dose level. If the dose escalation decision is delayed, the investigators want to treat the patients at the unescalated dose level so that their disease does not progress. Second, patients will be accrued to unescalated dose levels to avoid a loss of momentum in patient accrual. Modifications to the standard phase I design involving accrual of cohorts of 3-6 patients per dose level have been incorporated to appropriately handle the varying number of patients accrued to each dose level (see section 9.2). Study design considerations and targeted response rates for the phase II portion of the trial are given in section 9.3. Because the eligibility criteria are the same for both the phase I and the phase II portions of the trial, the patients treated at the dose level defined as the MTD from the phase I portion of the trial will count towards the accrual for the phase II portion of the trial.

9.1 Dose Limiting Toxicity (DLT)

05/03/01

Dose limiting toxicity (DLT) in a given patient is defined as any grade III non-hematologic toxicity not reversible to grade II or less within 96 hours, or any grade IV non-hematologic toxicity. Toxicity will be graded according to the NCI Common Toxicity Criteria (CTC) version 2.0 and toxicity Module (Appendices I and II, http://ctep.info.nih.gov/ctc3/ctc.htm) with the addition of BMT Complex/Multi-Component Events (Appendix VI, http://ctep.info.nih.gov/ctc3/ctc.htm). To be evaluable for toxicity, a patient must receive a complete course of treatment and be observed for 6 weeks after the administration of Y2B8 or have experienced a DLT. All patients who are not evaluable for toxicity will be replaced.

9.2 Definition of Maximum Tolerated Dose (MTD) and DLT-Level and Rules for Dose Escalation

This trial differs from the standard phase I design in that additional patients beyond the standard 3 or 6 patients per dose level may be accrued to the current dose level while waiting to assess toxicities in the initial 3 or 6 patients. To this end, a decision rule has been added that incorporates toxicity information from the additional patients accrued to a dose level. As toxicity information on each additional patient accrued to the trial becomes available, the decision to escalate, de-escalate and expand the previous dose level, expand the current cohort or stop the trial will be evaluated. The decision rule (R) will be as follows: Let x = number of DLTs in n patients. Escalate to the next dose level if $R = (x + 0.5) / (n + 2)$ is ≤ 0.20. Stop accrual to a dose level if $R > 0.30$. Continue accrual to a dose level if $0.20 < R \leq 0.30$. A minimum of three patients must be accrued to a dose level. As soon as 3 patients have been accrued to a dose level and toxicity has been assessed, escalation to the next level is allowed, provided that acceptable toxicity has been observed. If accrual to a dose level must be expanded due to toxicity, a minimum of 6 patients must be accrued to the expanded dose level.

Operationally, the rule is to close a dose level and de-escalate if 2 DLTs are observed among 6 or fewer patients, or if 3 DLTs are observed among any number of patients. The dose will be escalated if 0 DLTs are observed in 3 or more evaluated patients, if 1 DLT is observed in 6 or more evaluated patients, or if 2 DLTs are observed in 11 patients. At most, 11 patients will be accrued to a dose level. However, if a dose is escalated while toxicity follow-up is still outstanding for some patients, the accumulating results from the two dose levels may be pooled for the purpose of justifying the continued accrual to the higher dose.

Table 1 shows values for R based on different combinations of DLTs and numbers of patients. Values indicating continued accrual to the current dose are shown in bold.

Table 1

	Number of DLTs (x)		
Number of Patients (n)	**0**	**1**	**2**
3	0.10	**0.30**	0.50
4	0.08	**0.25**	0.42
5	0.07	**0.21**	0.36
6	0.06	0.19	0.31
7	0.06	0.17	**0.28**
8	0.05	0.15	**0.25**
9	0.05	0.14	**0.23**
10	0.04	0.13	**0.21**
11	0.04	0.12	0.19

This criterion is the posterior mean with a beta (0.5, 1.5) prior, which has a smaller mean, but is no more informative than a flat prior. The criterion is consistent with the conventional rule of expanding a dose level to six patients if 1 out of 3 patients experience DLT and stopping if 2 or

more patients out of 6 treated at the same dose level experience DLT. The proposed criterion rationalizes the conventional design in order to rationally extend if to larger numbers of patients per dose level. The rationalization is that a dose level is opened with a weak prior expectation of a 25% DLT rate, and the dose is escalated or de-escalated as the accumulating data indicate a rate below 20% or above 30%.

The phase I portion of the trial will be closed when 6 patients have been accrued to the highest dose level below the DLT level with at most 1 patient experiencing DLT or when 11 patients have been accrued with at most 2 patients experiencing DLT. This dose level will be defined as the MTD.

To demonstrate an application of the escalation rule, consider the following examples:

Example 1: Three patients are accrued to dose level 1. A fourth patient is accrued to the trial prior to assessment of toxicity for the third patient and is therefore also treated at dose level 1. No DLTs are observed in the first 3 patients such that the fifth patient is accrued to dose level 2 and subsequent to this the fourth patient accrued to dose level 1 experiences a DLT. With 1 DLT in four patients, from Table 1 the value for R is 0.25 therefore accrual to dose level 2 must be halted such that accrual to dose level 1 can be expanded. Six patients will need to be accrued with at most 1 out of 6 patients experiencing DLT in order for accrual to dose level 2 to resume. The patient treated at dose level 2 may be counted among the required 6 patients if no DLT is encountered.

Example 2: Dose level 3 is expanded such that 6 patients are accrued. A seventh patient is accrued to the trial prior to assessment of toxicity for the sixth patient and is therefore also treated at dose level 3. Only one DLT is observed in the first 6 patients such that the eighth patient is accrued to dose level 4 and subsequent to this the seventh patient accrued to dose level 3 experiences a DLT. With 2 DLTs in seven patients, from Table 1 the value for R is 0.28 therefore accrual to dose level 4 must be halted so that accrual to dose level 3 can be expanded. Eleven patients (including the patient treated at dose level 4) will need to be accrued to dose level 3 (or above) with at most 2 patients experiencing DLTs in order for accrual to dose level 4 to resume. Two DLTs among 11 patients corresponds to R = 0.19 which is consistent with 1 DLT among 6 patients. A maximum of 11 patients can be accrued to a single dose level.

9.3 Design Considerations for the Phase II Trial

All patients accrued to the dose level established to be the MTD will be included in the assessment of response for the phase II portion of the trial. The primary goal of this portion of the trial is to obtain estimates of the efficacy of IDEC-Y2B8 in combination with high-dose etoposide and cyclophosphamide followed by ASCT for treatment of patients with relapsed and refractory NHL. A minimum of 17 and a maximum of 37 patients will be accrued to this portion of the trial. Justification for the sample size as well as a description of the study design for the phase II portion of the trial is provided in section 12.0.

10.0 STUDY CALENDAR - PREPARATIVE REGIMEN AND PBSCT

	REQUIRED STUDIES	Pre Study	DAY -21	DAY -14	DAY -7	DAY -4	DAY -2	DAY 0	DAY 7	DAY 14	DAY 30	DAY 60	DAY 100	DAY 180	YR 1	YR 2
	PHYSICAL															
	H & PE	X		X	X	X	X	X	X	X	X	X	X	X	X	X[$]
10/29/03	Weight and KPS	X			X			X			X	X	X	X	X	X[$]
	Tumor Assessment	X									X			X	X	X[$]
	Toxicity Notation				X	X	X	X	X	X	X	X	X	X	X[$]	X[$]
	LABORATORY															
10/29/03	CBC/Platelets	X			X	X	X	X	X	X	X	X	X	X	X	X[$]
10/29/03	Differential[¥]	X			X				X	X	X	X	X	X	X	X[$]
08/07/01, 10/29/03	HAMA/HACA	X										X	X	X[«]	X	
10/29/03	Comp Metabolic Panel + LDH	X		X	X	X	X	X	X	X	X	X	X	X	X	X[$]
10/29/03	Magnesium	X		X	X	X	X	X	X	X	X					
	PT/PTT	X														
	Immunoglobulin Levels	X									X		X	X	X	
08/07/01	Peripheral Blood Mononuclear Immunophenotyping	X									X		X	X	X	
	CMV Titer	X														
	Hepatitis Profile	X														
10/29/03	Herpes Simplex	X														
	HIV Antibody	X														
08/07/01, 05/30/02	BM[%, #]	X			X^								X		X	X
05/03/01	Creatinine Clearance													X	X	
	X-RAYS AND SCANS															
05/30/02	Chest X-ray or CT Chest	X			X			X		X	X		X	X	X	X[&]
05/30/02	CT scans*, [+]	X									X		X	X	X	X[&]
	EKG	X													X	
	MUGA or ECHO	X												X	X	
	DLCO/FEV1	X												X	X	
08/07/01, 10/29/03, 04/06/04	Ga 67 Scan and/or FDG-PET Scan	X[¢]									X[◊]			X	X	
	TREATMENT															
	Stem Collections	X														
	IDEC-In2B8		X	X												
	IDEC-Y2B8			X												
	Rituxan		X	X												
	VP-16					X										
	Cyclophosphamide						X									
06/16/04	PBSCT							X[§]								
06/16/04	G-CSF							X[§]								
06/05/00	DTPA							X								

10/29/03 (delete @,06/20/07) & restaging at Day 100, at 6 months then follow-up evaluation every six months for three years, and then yearly up to 5 yrs post BMT

$ All late complications such as cataracts formation and occurrence of second malignancies must be documented and reported.

***** CT scans of chest, abdomen and pelvis as indicated

08/07/01 (delete #, add^) ^ biopsy core for determination of radioactivity

05/03/01 % bone marrow aspiration and biopsy, cytogenetic study, immunophenotyping and gene rearrangement

05/30/02, 06/20/07 # Follow-up bone marrow is required at day 180, yr 1 up to 5 yrs post BMT.

05/30/02, 10/29/03 + For pts in CR at time of transplant, CT scans to be done between days 30 and 100.

10/29/03 « Day 180 HAMA/HACA acceptable between days 150 and 210

10/29/03 ¢ Pre-study PET scan should be done 14 days after stem cell collection to avoid GCSF enhancement effect

10/29/03 ¥ ANC is acceptable in lieu of differential

04/06/04 ◊ If PET scan positive at baseline, day +30 PET scan required

06/16/04 § Day +1

11.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Definitions

a. *Measurable Disease*: Bidimensionally measurable lesions with clearly defined margins by: 1) medical photograph (skin or oral lesion), or plain x-ray with at least one diameter .5 cm or greater (bone lesions are not included) or, 2) CT, MRI or other imaging scan with both diameters greater than the distance between cuts of the imaging study, or 3) palpation with both diameters 2 cm or greater.

05/30/02

b. *Evaluable Disease*: Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with both diameters less than 0.5 cm, lesions on scan with either diameter smaller than the distance between cuts, palpable lesions with either diameter less than 2 cm, bone disease.

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

d. *Objective Status, To Be Recorded at Each Evaluation*: If an organ has too many measurable lesions to measure at each evaluation, choose three to be followed before the patient is entered on study. The remaining measurable lesions in that organ will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when ALL is measurable and evaluable sites and lesions are assessed.

11.1 Complete Response (CR)

Complete disappearance of all measurable evidence of non-evaluable disease. No new lesions. No disease related symptoms. No evidence of non-evaluable disease, including normalization of markers and other abnormal lab values. All measurable, evaluable and non-evaluable lesions and sites must be assessed using the same techniques as baseline. Refers to clinical CR-when restaging surgery is required, a separate pathologic response variable is defined.

11.2 Partial Response (PR)

Applies only to patients with at least one measurable lesion. Greater than or equal to 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. All measurable and evaluable lesions and sites must be assessed using the same techniques as baseline.

11.3 Stable Disease (SD)

Does not qualify for CR, PR or Progression. All measurable and evaluable sites and lesions must be assessed using the same techniques as baseline.

11.4 Progressive Disease (PD)

50% increase or an increase of 10 cm^2 (whichever is smaller) in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same

techniques as baseline, OR clear worsening of any evaluable disease, OR reappearance of any lesion which had disappeared, OR appearance of any new lesion/site, OR failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer). For "scan only" bone disease, increased uptake does not constitute clear worsening. Worsening of existing non-evaluable disease not constitute progression.

11.5 Relapse

08/07/01 Relapse is defined as the re-appearance of any clinical evidence of lymphoma in a patient who has had a CR. Relapse for partial responders are defined as progressive disease relative to disease status during the partial remission.

11.6 Duration of Response

This is measured from the documented beginning of response (CR or PR)

11.7 Performance Status

Patients will be graded according to the current Performance Status Scales/Scores (Appendix IV).

11.8 Time to Progression

From date of registration to date of first observation of progressive disease or death due to any cause.

11.9 Time to Death

From date of registration to date of death due to any cause.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design and Justification of Sample Size

The definition of dose limiting toxicity is given in section 6.1. The maximum tolerated dose is defined in section 6.2. The number of patients to be treated at each dose level examined in the phase I trial as well as the rules for dose escalation is given in section 6.2.

The phase II portion of the study will follow a two-stage minimax design suggested by Simon (1). It is assumed that a true response rate less than 20% would not warrant further study of this agent. It is also assumed that a response rate of 40% would be considered promising for further studies in these patients. In the first stage, seventeen evaluable patients will be entered. If less than four responses are observed, the accrual will stop with the conclusion that the regimen is not promising for further study. If four or more responses are observed in the first 17 patients, additional 20 patients will be accrued during the second stage of the study. Eleven or more responses out of 37 patients will be considered as evidence warranting further study of the regimen providing other factors, such as toxicity and survival, also appear favorable. If less than 11 responses out of 37 patients are observed, further study of the regimen would not be warranted.

The probability of falsely declaring an agent with a 20% response probability as warranting further

study is 0.10 (alpha) and the probability of correctly declaring an agent with a 40% response probability as warranting further study is 0.90 (power). With 37 patients the true probability of response can be estimated with a maximum standard error equal to 0.08.

The phase I portion study is expected to accrue a minimum of 15-18 evaluable patients and a maximum of 30. The phase II portion of the study will accrue a minimum of 17 patients and a maximum of 37 patients, of which at least six of these patients will have been included in the phase I portion of the study. It should take approximately 24-36 months to complete both the phase I and phase II portions of this trial.

12.2 Analysis of Clinical Endpoints

Patients will be considered evaluable for response and evaluable for toxicity as outlined in section 11.0. The toxicities observed at each dose level will be summarized in terms of type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI Common Toxicity Criteria and nadir or maximum values for the laboratory measures), time of onset (i.e. course number), duration, and reversibility or outcome. Tables will be created to summarize these toxicities and side effects by dose and by course. Baseline information (e.g. the extent of prior therapy) and demographic information will be presented, as well, to describe the patients treated in the phase I portion of the study. All responses will be reported from the phase I portion of the study

Response rates and duration of response will be estimated for the phase II portion of survival. Confidence intervals for the response rate will be established by calculating exact 95% confidence limits for a binomial parameter. The duration of overall and disease-free survival of the patient will be estimated using the product-limit method of Kaplan and Meier.

13.0 REGISTRATION GUIDELINES

08/07/01 Once a signed, written informed consent has been obtained and all pretreatment evaluations have been performed, patients will be entered on study, after review of patient eligibility criteria by the assigned Data Manager from the City of Hope Department of Biostatistics. Patients may be screened for registration by calling the Department of Biostatistics, ext. 62468.

14.0 RECORDS TO BE KEPT AND DATA SUBMISSION SCHEDULE

14.1 Confidentiality of Records

The original data collection forms will be stored in secure cabinets in the Department of Biostatistics. All radioimmunotherapy associated data will be kept in the Department of Radioimmunotherapy.

14.2 Patient Consent Form

At the time of registration, signed and dated copies of the patient Informed Consent form with the Human Rights must be available (for patient, chart, and Biostatistics Office).

15.0 GENDER AND MINORITIES

15.1 Planned Gender and Minority Inclusion for Transplant Patients with Intermediate Grade Lymphoma at City of Hope

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	White, Hispanic or not-Hispanic Unknown	Other or Unknown	Total
Female	0%	9%	4%	16%	54%	17%	0%	100%
Male	0%	5%	2%	20%	60%	12%	1%	100%
Unknown	0%	0%	0%	0%	0%	0%	0%	0%

15.2 Actual Gender and Minority Inclusion for Transplant Patients with Intermediate Grade Lymphoma at City of Hope

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	White, Hispanic or not-Hispanic Unknown	Other or Unknown	Total
Female	0%	0%	0%	0%	0%	0%	0%	0%
Male	0%	0%	0%	0%	0%	0%	0%	0%
Unknown	0%	0%	0%	0%	0%	0%	0%	0%

16.0 DATA MANAGEMENT

Clinical Statistics maintains a patient database at City of Hope Medical Center, Department of Biostatistics to allow storage and retrieval of patient data collected from a wide variety of sources. The investigator will ensure that data collected conform to all established guidelines for coding, collection, key-entry, and verification. All patients are assigned a unique patient number to assure patient confidentiality. Any publications or presentations refer to patient by unique patient number, not name. The licensed medical records department, affiliated with the institution where the patient receives medical care, maintains all original inpatient and outpatient chart documents. Patient research files are kept in a locked room. They are maintained by the COHMC data collection staff. Access is restricted to personnel authorized by the Division of Clinical Research.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

This study is to be approved by the Institutional Review Board according to City of Hope ethical and regulatory guidelines. All patients will have signed an informed consent for participation in research activities, and will have been given a copy of the Experimental Subject's Bill of Rights.

When results of this study are reported in medical journals or at meetings, identification of those taking part will be withheld. Medical records of patients will be maintained in strictest confidence,

according to current legal requirements. However, they will be made available for review, as required by the Food and Drug Administration (FDA) or other authorized users such as the National Cancer Institute (NCI), under the guidelines established by the Federal Privacy Act, or IDEC Pharmaceuticals Corporation.

18.0 REFERENCES

1. Parker SL, Tong T, Bolden S, Wingo PA: Cancer Statistics, 1997 [published erratum appears in CA Cancer J Clin 1997 Mar-Apr;47(2):68]. CA.Cancer J.Clin. 47:5, 1997
2. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, Glick JH, Coltman CAJ, Miller TP: Comparison of a Standard Regimen (CHOP) with Three Intensive Chemotherapy Regimens for Advanced Non-Hodgkin's Lymphoma [see comments]. N.Engl.J.Med. 328:1002, 1993
3. Vose JM, Anderson JR, Kessinger A, Bierman PJ, Coccia P, Reed EC, Gordon B, Armitage JO: High-Dose Chemotherapy and Autologous Hematopoietic Stem-Cell Transplantation for Aggressive Non-Hodgkin's Lymphoma [see comments]. J.Clin.Oncol. 11:1846, 1993
4. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, Sonneveld P, Gisselbrecht C, Cahn JY, Harousseau JL: Autologous Bone Marrow Transplantation as Compared with Salvage Chemotherapy in Relapses of Chemotherapy-Sensitive Non-Hodgkin's Lymphoma [see comments]. N.Engl.J.Med. 333:1540, 1995
5. Bierman PJ, Vose JM, Anderson JR, Bishop MR, Kessinger A, Armitage JO: High-Dose Therapy with Autologous Hematopoietic Rescue for Follicular Low-Grade Non-Hodgkin's Lymphoma. J.Clin.Oncol. 15:445, 1997
6. Nademanee A, Schmidt GM, O'Donnell MR, Snyder DS, Parker PM, Stein A, Smith E, Molina A, Wong KK, Stepan DE, Margolin KA, Somlo G, Raschko J, Sniecinski I, Lipsett JA, Dagis A, Niland JC, Forman SJ: Fractionated Total Body Irradiation (FTBI), High-Dose Etoposide (VP-16) and Cyclophosphamide (CY) Followed by Autologous Bone Marrow Transplantation (ABMT): The Results in 110 Patients with Non-Hodgkin's Lymphoma (NHL). Blood 82:143a (559), 1993 (abstr.)
7. Horning SJ, Negrin RS, Chao JC, Long GD, Hoppe RT, Blume KG: Fractionated Total-Body Irradiation, Etoposide, and Cyclophosphamide Plus Autografting in Hodgkin's Disease and Non-Hodgkin's Lymphoma. J.Clin.Oncol. 12:2552, 1994
8. Weaver CH, Petersen FB, Appelbaum FR, Bensinger WI, Press O, Martin P, Sandmaier B, Deeg HJ, Hansen JA, Brunvand M: High-Dose Fractionated Total-Body Irradiation, Etoposide, and Cyclophosphamide Followed by Autologous Stem-Cell Support in Patients with Malignant Lymphoma. J.Clin.Oncol. 12:2559, 1994
9. Maloney DG, Grillo-Lopez AJ, White CA, Bodkin D, Schilder RJ, Neidhart JA, Janakiraman N, Foon KA, Liles TM, Dallaire BK, Wey K, Royston I, Davis T, Levy R: IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients With Relapsed Low-Grade Non-Hodgkin's Lymphoma. Blood 90:2188, 1997
10. McLaughlin P, Grillo-López AJ, Link BK, Levy R, Czuczman MS, Williams ME, Heyman MR, Bence-Bruckler I, White CA, Cabanillas F, Jain V, Ho AD, Lister J, Wey K, Shen D, Dallaire BK: Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program. Journal of Clinical Oncology 16:2825, 1998
11. Czuczman M, Grillo-López AJ, White CA, Saleh M, Gordon L, LoBuglio AF, Jonas C, Dallaire B, Varns C: IDEC-C2B8/CHOP Chemoimmunotherapy in Patients With Low-

Grade Lymphoma: Clinical and BCL-2 (PCR) Final Results. Blood 88:453a (1799), 1996 (abstr.)

12. Kaminski MS, Zasadny KR, Francis IR, Milik AW, Ross CW, Moon SD, Crawford SM, Burgess JM, Petry NA, Butchko GM: Radioimmunotherapy of B-Cell Lymphoma with [^{131}I]Anti-B1 (Anti-CD20) Antibody. N.Engl.J.Med. 329:459, 1993
13. Stagg R, Wahl RL, Estes J, Tidmarsh G, Kroll S, Shochat D, Zasadny K, Kaminski MS: Phase I/II Study of Iodine-131 Anti-B1 Antibody for Non-Hodgkin's Lymphoma (NHL): Final Results. Proceedings of ASCO 17:39a (150), 1998 (abstr.)
14. Vose J, Saleh M, Lister A, Rohatiner A, Knox S, Radford J, Zelenetz AD, Stagg R, Tidmarsh G, Wahl R, Kaminski MS: Iodine-131 Anti-B1 Antibody for Non-Hodgkin's Lymphoma (NHL): Overall Clinical Trial Experience. Proceedings of ASCO 17:10a (38), 1998 (abstr.)
15. Press OW, Eary JF, Appelbaum FR, Martin PJ, Badger CC, Nelp WB, Glenn S, Butchko G, Fisher D, Porter B: Radiolabeled-Antibody Therapy of B-Cell Lymphoma With Autologous Bone Marrow Support [see comments]. N.Engl.J.Med. 329:1219, 1993
16. Press O, Eary J, Liu S, Petersdorf S, Bush S, Durack L, Martin P, Maloney D, Matthews D, Fisher D, Gooley T, Appelbaum F, Bernstein I: A Phase I/II Trial of High Dose Iodine-131-Anti-B1 (Anti-CD20) Monoclonal Antibody, Etoposide, Cyclophosphamide, and Autologous Stem Cell Transplantation for Patients With Relapsed B Cell Lymphomas. Proceedings of ASCO 17:3a (9), 1998 (abstr.)
17. Knox SJ, Goris ML, Trisler K, Negrin R, Davis T, Liles TM, Grillo-Lopez A, Chinn P, Varns C, Ning S, Fowler S, Deb N, Becker M, Marquez C, Levy R: Yttrium-90-Labeled Anti-CD20 Monoclonal Antibody Therapy of Recurrent B-Cell Lymphoma. Clin.Cancer Res. 2:457, 1996
18. Witzig T, Wiseman G, White CA, Solinger A, Gordon L, Raubitschek A, Emmanoulides C, Royston I, Parker E, Chinn P, Grillo-López A: IDEC-Y2B8 ^{90}Yttrium Anti-CD20 Radioimmunotherapy of Relapsed Non-Hodgkin's Lymphoma (NHL): Interim Results of a Phase I/II Trial. Blood 90:586a (2606), 1997 (abstr.)
19. Wiseman GA, Solinger AM, Grillo-López A, Stabin M, Dunn WL, Witzig TE, Spies S, Gordon L, Raubitschek A, Margolin K, Karvelis K, Janakiraman N, Silverman DH, Emmanoulides C, Royston I, Chinn P, Parker E, Carter W, White CA: IDEC-Y2B8 (^{90}Y Conjugated Anti-CD20) Dosimetry Calculated From ^{111}In Anti-CD20 in Patients With Low and Intermediate Grade B-Cell Non-Hodgkin's Lymphoma (NHL) Emphasis on Bone Marrow (BM). Blood 90:510a (2273), 1997 (abstr.)
20. Witzig TE, White CA, Wiseman GA, Gordon LI, Emmanoulides C, Raubitschek A, Janakiraman N, Gutheil J, Schilder RJ, Spies S, Silverman DH, Parker E, and Grillo-López A: Phase I/II Trial of Yttrium 90 Ibritumomab Tiuxetan (IDEC-Y2B8) Radioimmunotherapy for Treatment of Relapsed or Refractory CD20 Positive B-Cell Mon-Hodgkin's Lymphoma. Submitted 1999.

Appendix I
Common Toxicity Criteria (CTC)

FINAL 1/30/98

CTC Version 2.0

Toxicity	Grade 0	1	2	3	4
ALLERGY/IMMUNOLOGY					
Allergic reaction/ hypersensitivity (including drug fever)	none	transient rash, drug fever < 38°C (<100.4°F)	urticaria, drug fever ≥ 38°C (≥100.4°F), and/or asymptomatic bronchospasm	symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema	anaphylaxis
Note: Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN category.					
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	none	mild, not requiring treatment	moderate, requiring treatment	-	-
Autoimmune reaction	none	serologic or other evidence of autoimmune reaction but patient is asymptomatic (e.g., vitiligo), all organ function is normal and no treatment is required	evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism), requiring treatment other than immunosuppressive drugs	reversible autoimmune reaction involving function of a major organ or other toxicity (e.g., transient colitis or anemia), requiring short-term immunosuppressive treatment	autoimmune reaction causing major grade 4 organ dysfunction; progressive and irreversible reaction; long-term administration of high-dose immuno-suppressive therapy required
Also consider Hypothyroidism, Colitis, Hemoglobin, Hemolysis.					
Serum sickness	none	-	-	present	-
Urticaria is graded in the DERMATOLOGY/SKIN category if it occurs as an isolated symptom. If it occurs with other manifestations of allergic or hypersensitivity reaction, grade as Allergic reaction/hypersensitivity above.					
Vasculitis	none	mild, not requiring treatment	symptomatic, requiring medication	requiring steroids	ischemic changes or requiring amputation
Allergy/Immunology -Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling

Toxicity	Grade 0	1	2	3	4
AUDITORY/HEARING					
Conductive hearing loss is graded as Middle ear/hearing in the AUDITORY/HEARING category.					
Earache is graded in the PAIN category.					
External auditory canal	normal	external otitis with erythema or dry desquamation	external otitis with moist desquamation	external otitis with discharge, mastoiditis	necrosis of the canal soft tissue or bone
Note: Changes associated with radiation to external ear (pinnae) are graded under Radiation dermatitis in the DERMATOLOGY/SKIN category.					
Inner ear/hearing	normal	hearing loss on audiometry only	tinnitus or hearing loss, not requiring hearing aid or treatment	tinnitus or hearing loss, correctable with hearing aid or treatment	severe unilateral or bilateral hearing loss (deafness), not correctable
Middle ear/hearing	normal	serous otitis without subjective decrease in hearing	serous otitis or infection requiring medical intervention; subjective decrease in hearing; rupture of tympanic membrane with discharge	otitis with discharge, mastoiditis or conductive hearing loss	necrosis of the canal soft tissue or bone
Auditory/Hearing-Other (Specify,)	normal	mild	moderate	severe	life-threatening or disabling
BLOOD/BONE MARROW					
Bone marrow cellularity	normal for age	mildly hypocellular or 25% reduction from normal cellularity for age	moderately hypocellular or >25 - ≤ 50% reduction from normal cellularity for age or >2 but <4 weeks to recovery of normal bone marrow cellularity	severely hypocellular or >50 - ≤ 75% reduction in cellularity for age or 4 - 6 weeks to recovery of normal bone marrow cellularity	aplasia or >6 weeks to recovery of normal bone marrow cellularity
Normal ranges:					
children (≤ 18 years)	90% cellularity average				
younger adults (19-59)	60-70% cellularity average				
older adults (≥ 60 years)	50% cellularity average				
Note: Grade Bone marrow cellularity only for changes related to treatment not disease.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
CD4 count	WNL	< LLN - 500/mm^3	200 - < 500/mm^3	50 - < 200/mm^3	< 50/mm^3
Haptoglobin	normal	decreased	-	absent	-
Hemoglobin (Hgb)	WNL	< LLN - 10.0 g/dl < LLN - 100 g/L < LLN - 6.2 mmol/L	8.0 - < 10.0 g/dl 80 - < 100 g/L 4.9 - < 6.2 mmol/L	6.5 - < 8.0 g/dl 65 - 80 g/L 4.0 - < 4.9 mmol/L	< 6.5 g/dl < 65 g/L < 4.0 mmol/L
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic processes	WNL	10 - <25% decrease from pretreatment	25 - <50% decrease from pretreatment	50 - <75% decrease from pretreatment	≥75% decrease from pretreatment
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other) Also consider Haptoglobin, Hgb.	none	only laboratory evidence of hemolysis [e.g., direct antiglobulin test (DAT, Coombs') schistocytes]	evidence of red cell destruction and ≥ 2gm decrease in hemoglobin, no transfusion	requiring transfusion and/or medical intervention (e.g., steroids)	catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
Leukocytes (total WBC)	WNL	< LLN - 3.0 x 10^9 /L < LLN - 3000/mm^3	≥2.0 - < 3.0 x 10^9 /L ≥2000 - < 3000/mm^3	≥1.0 - < 2.0 x 10^9 /L ≥1000 - < 2000/mm^3	< 1.0 x 10^9 /L < 1000/mm^3
For BMT studies:	WNL	≥2.0 - <3.0 X 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9 /L ≥1000 - <2000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3
Note: The following criteria using age, race and sex normal values may be used for pediatric studies if the protocol so specifies.					
		≥75 - <100% LLN	*≥50 - <75% LLN*	*≥25 - 50% LLN*	*<25% LLN*
Lymphopenia	WNL	<LLN - 1.0 x 10^9 /L <LLN - 1000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3	-
Note: The following criteria using age, race, and sex normal values may be used for pediatric studies if the protocol so specifies.					
		≥75-<100%LLN	*≥50-<75%LLN*	*≥25-<50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC)	WNL	≥1.5 - <2.0 x 10^9 /L ≥1500 - <2000/mm^3	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	< 0.5 x 10^9 /L < 500/mm^3
For BMT:	WNL	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	≥0.1 - <0.5 x 10^9 /L ≥100 - <500/mm^3	<0.1 x 10^9 /L <100/mm^3

Toxicity	Grade 0	1	2	3	4
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Platelets	WNL	< LLN - <75.0 x 10^9 /L < LLN - 75000/mm^3	≥50.0 - < 75.0 x 10^9 /L ≥50000 - < 75000/mm^3	≥10.0 - < 50.0 x 10^9 /L ≥10000 - < 50000/mm^3	< 10.0 x 10^9 /L < 10000/mm^3
For BMT:	WNL	≥50.0 - <75.0 x 10^9 /L ≥50000 - <75000/mm^3	≥20.0 - <50.0 x 10^9 /L ≥20000 - <50000/mm^3	≥10.0 - <20.0 x 10^9 /L ≥10000 - <20000/mm^3	<10.0 x 10^9 /L <10000/mm^3
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Transfusion: Platelets	none	-	-	yes	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
For BMT:	none	1 platelet transfusion in 24 hours	2 platelet transfusions in 24 hours	≥3 platelet transfusions in 24 hours	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Also consider Platelets.					
Transfusion: pRBCs	none	-	-	Yes	-
For BMT:	none	≤2 u pRBC (*≤15cc/kg*) in 24 hours elective or planned	3 u pRBC (*>15 ≤30cc/kg*) in 24 hours elective or planned	≥4 u pRBC (*>30cc/kg*) in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
Also consider Hemoglobin.					
Blood/Bone Marrow-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
CARDIOVASCULAR (ARRHYTHMIA)					
Conduction abnormality/ Atrioventricular heart block	none	asymptomatic, not requiring treatment (e.g., Mobitz type I second-degree AV block, Wenckebach)	symptomatic, but not requiring treatment	symptomatic and requiring treatment (e.g., Mobitz type II second-degree AV block, third-degree AV block)	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Nodal/junctional arrhythmia/dysrhythmia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Palpitations	none	present	-	-	-
Note: Grade palpitations only in the absence of a documented arrhythmia.					

Toxicity	Grade 0	1	2	3	4
Prolonged QTc interval (QTc > 0.48 seconds)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus bradycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus tachycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment of underlying cause	-
Supraventricular arrhythmias (SVT/atrial fibrillation/ flutter)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Syncope (fainting) is graded in the NEUROLOGY category.					
Vasovagal episode	none	-	present without loss of consciousness	present with loss of consciousness	-
Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ ventricular tachycardia)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Cardiovascular/ Arrhythmia-Other (Specify, _____)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic, and requiring treatment of underlying cause	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
		CARDIOVASCULAR (GENERAL)			
Acute vascular leak syndrome	absent	-	symptomatic, but not requiring fluid support	respiratory compromise or requiring fluids	life-threatening; requiring pressor support and/or ventilatory support
Cardiac-ischemia/infarction	none	non-specific T-wave flattening or changes	asymptomatic, ST- and T- wave changes suggesting ischemia	angina without evidence of infarction	acute myocardial infarction

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Cardiac left ventricular function	normal	asymptomatic decline of resting ejection fraction of ≥ 10% but < 20% of baseline value; shortening fraction ≥ 24% but < 30%	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction ≥ 20% of baseline value; < 24% shortening fraction	CHF responsive to treatment	severe or refractory CHF or requiring intubation
CNS cerebrovascular ischemia is graded in the NEUROLOGY category.					
Cardiac troponin I (cTnI)	normal	-	-	levels consistent with unstable angina as defined by the manufacturer	levels consistent with myocardial infarction as defined by the manufacturer
Cardiac troponin T (cTnT)	normal	≥ 0.03 - < 0.05 ng/ml	≥ 0.05 - < 0.1 ng/ml	≥ 0.1 - < 0.2 ng/ml	≥ 0.2 ng/ml
Edema	none	asymptomatic, not requiring therapy	symptomatic, requiring therapy	symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation	anasarca (severe generalized edema)
Hypertension **Note: For pediatric patients, use age and sex appropriate normal values > 95th percentile ULN.*	none	asymptomatic, transient increase by >20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	recurrent or persistent or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	requiring therapy or more intensive therapy than previously	hypertensive crisis
Hypotension Also consider Syncope (fainting). Note: Angina or MI is graded as Cardiac- ischemia/infarction in the CARDIOVASCULAR (GENERAL) category. *For pediatric patients, systolic BP 65 mmHg or less in infants up to 1 year old and 70 mmHg or less in children older than 1 year of age, use two successive or three measurements in 24 hours.*	none	changes, but not requiring therapy (including transient orthostatic hypotension)	requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Myocarditis	none	-	-	CHF responsive to treatment	severe or refractory CHF

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
Operative injury of vein/artery	none	primary suture repair for injury, but not requiring transfusion	primary suture repair for injury, requiring transfusion	vascular occlusion requiring surgery or bypass for injury	myocardial infarction; resection of organ (e.g., bowel, limb)
Pericardial effusion/ pericarditis	none	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and/or chest pain)	physiologic consequences resulting from symptoms	tamponade (drainage or pericardial window required)
Peripheral arterial ischemia	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., amputation)
Phlebitis (superficial)	none	-	present	-	-
Note: Injection site reaction is graded in the DERMATOLOGY/SKIN category. Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Syncope (fainting) is graded in the NEUROLOGY category.					
Thrombosis/embolism	none	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the CARDIOVASCULAR (GENERAL) category.					
Visceral arterial ischemia (non-myocardial)	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., resection of ileum)
Cardiovascular/ General-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
COAGULATION					
Note: See the HEMORRHAGE category for grading the severity of bleeding events.					
DIC (disseminated intravascular coagulation) Also grade Platelets. Note: Must have increased fibrin split products or D-dimer in order to grade as DIC.	absent	-	-	laboratory findings present with no bleeding	laboratory findings and bleeding
Fibrinogen	WNL	≥0.75 - <1.0 x LLN	≥0.5 - <0.75 x LLN	≥0.25 - <0.5 x LLN	<0.25 x LLN
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					

Toxicity	Grade 0	1	2	3	4
For leukemia studies:	WNL	<20% decrease from pretreatment value or LLN	≥20 - <40% decrease from pretreatment value or LLN	≥40 - <70% decrease from pretreatment value or LLN	<50 mg%
Partial thromboplastin time (PTT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Phelbitis is graded in the CARDIOVASCULAR (GENERAL) category.					
Prothrombin time (PT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS)	absent	-	-	laboratory findings present without clinical consequences	laboratory findings and clinical consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure) requiring therapeutic intervention
For BMT:	-	evidence of RBC destruction (schistocytosis) without clinical consequences	evidence of RBC destruction with elevated creatinine (≤3 x ULN)	evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy
Also consider Hemoglobin (Hgb), Platelets, Creatinine. Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).					
Coagulation-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia)	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities	bedridden or disabling
Note: See Appendix IV (http://ctep.info.nih.gov/ctc3/ctc.htm) for performance status scales.					

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x 10^9/L)	none	38.0 - 39.0°C (100.4 - 102.2°F)	39.1 - 40.0°C (102.3 - 104.0°F)	> 40.0°C (>104.0°F) for < 24hrs	> 40.0°C (>104.0°F) for > 24hrs
Also consider Allergic reaction/hypersensitivity. Note: The temperature measurements listed above are oral or tympanic.					
Hot flashes/flushes are graded in the ENDOCRINE category.					
Rigors, chills	none	mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication	severe and/or prolonged, requiring narcotic medication	not responsive to narcotic medication	-
Sweating (diaphoresis)	normal	mild and occasional	frequent or drenching	-	-
Weight gain	< 5%	5 - <10%	10 - <20%	≥ 20%	-
Also consider Ascites, Edema, Pleural effusion.					
Weight gain - veno-occlusive disease (VOD) Note: The following criteria is to be used ONLY for weight gain associated with Veno-Occlusive Disease.					
	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascities	≥10% or fluid retention resulting in pulmonary failure
Weight loss	< 5%	5 - <10%	10 - <20%	≥20%	-
Also consider Vomiting, Dehydration, Diarrhea.					
Constitutional Symptoms-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
DERMATOLOGY/SKIN					
Alopecia	normal	mild hair loss	pronounced hair loss	-	-
Bruising (in absence of grade 3 or 4 thrombocytopenia)	none	localized or in dependent area	generalized	-	-
Note: Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura and Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, not in the DERMATOLOGY/SKIN category.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Dermatitis, focal (associated with high-dose chemotherapy and bone marrow transplant)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding not induced by minor trauma or abrasion
Dry skin	normal	controlled with emollients	not controlled with emollients	-	-
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	absent	-	scattered, but not generalized eruption	severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Flushing	absent	present	-	-	-
Hand-foot skin reaction	none	skin changes or dermatitis without pain (e.g., erythema, peeling)	skin changes with pain, not interfering with function	skin changes with pain, interfering with function	-
Injection site reaction	none	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-
Nail changes	normal	discoloration or ridging (koilonychia) or pitting	partial or complete loss of nail(s) or pain in nailbeds	-	-
Petechiae is graded in the HEMORRHAGE category.					
Photosensitivity	none	painless erythema	painful erythema	erythema with desquamation	-
Pigmentation changes (e.g., vitiligo)	none	localized pigmentation changes	generalized pigmentation changes	-	-
Pruritus	none	mild or localized, relieved spontaneously or by local measures	intense or widespread, relieved spontaneously or by systemic measures	intense or widespread and poorly controlled despite treatment	-
Purpura is graded in the HEMORRHAGE category.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Radiation dermatitis	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Note: Pain associated with radiation dermatitis is graded separately in the PAIN category as Pain due to radiation.					
Radiation recall reaction (reaction following chemotherapy in the absence of additional radiation therapy that occurs in a previous radiation port)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Rash/desquamation	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritis or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis
For BMT:	none	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms	macular or papular eruption or erythema with pruritis or other associated symptoms covering ≥25 - <50% of body surface or localized desquamation or other lesions covering ≥25 - <50% of body surface area	symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation
Also consider Allergic reaction/hypersensitivity. Note: Erythema multiforme (Stevens-Johnson syndrome) is graded separately as Erythema multiforme.					

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
Urticaria (hives, welts, wheals)	none	requiring no medication	requiring PO or topical treatment or IV medication or steroids for <24 hours	requiring IV medication or steroids for ≥24 hours	-
Wound- infectious	none	cellulitis	superficial infection	infection requiring IV antibiotics	necrotizing fascitis
Wound- non-infectious	none	incisional separation	incisional hernia	fascial disruption without evisceration	fascial disruption with evisceration
Dermatology/Skin-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
ENDOCRINE					
Cushingoid appearance (e.g., moon face with or without buffalo hump, centripetal obesity, cutaneous striae) Also consider Hyperglycemia, Hypokalemia.	absent	-	present	-	-
Feminization of male	absent	-	-	present	-
Gynecomastia	none	mild	pronounced or painful	pronounced or painful and requiring surgery	-
Hot flashes/flushes	none	mild or no more than 1 per day	moderate and greater than 1 per day	-	-
Hypothyroidism	absent	asymptomatic,TSH elevated, no therapy given	symptomatic or thyroid replacement treatment given	patient hospitalized for manifestations of hypothyroidism	myxedema coma
Masculinization of female	absent	-	-	present	-
SIADH (syndrome of inappropriate antidiuretic hormone)	absent	-	-	present	-
Endocrine-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
GASTROINTESTINAL					
Amylase is graded in the METABOLIC/LABORATORY category.					
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Ascites (non-malignant)	none	asymptomatic	symptomatic, requiring diuretics	symptomatic, requiring therapeutic paracentesis	life-threatening physiologic consequences
Colitis	none	-	abdominal pain with mucus and/or blood in stool	abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	perforation or requiring surgery or toxic megacolon
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension.					
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Dehydration	none	dry mucous membranes and/or diminished skin turgor	requiring IV fluid replacement (brief)	requiring IV fluid replacement (sustained)	physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Hypotension, Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Diarrhea Patients without colostomy:	none	increase of < 4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
Patients with a colostomy:	none	mild increase in loose, watery colostomy output compared with pretreatment	moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	physiologic consequences, requiring intensive care; or hemodynamic collapse
For BMT	none	>500 - ≤1000ml of diarrhea/day	>1000 - ≤1500ml of diarrhea/day	>1500ml of diarrhea/day	severe abdominal pain with or without ileus
For Pediatric BMT:		*>5 - ≤10 ml/kg of diarrhea/day*	*>10 - ≤15 ml/kg of diarrhea/day*	*>15 ml/kg of diarrhea/day*	-
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain, Dehydration, Hypotension.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Duodenal ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	uncontrolled by outpatient medical management; requiring hospitalization	perforation or bleeding, requiring emergency surgery
Dyspepsia/heartburn	none	mild	moderate	severe	-
Dysphagia, esophagitis, odynophagia (painful swallowing) Note: If toxicity is radiation-related, grade either under Dysphagia- esophageal related to radiation or Dysphagia-pharyngeal related to radiation.	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring IV hydration	complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support, or perforation
Dysphagia- esophageal related to radiation Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula- esophageal.	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly liquid, pureed or soft diet	dysphagia requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Dysphagia - pharyngeal related to radiation Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula- pharyngeal.	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Fistula- esophageal	none	-	-	present	requiring surgery
Fistula- intestinal	none	-	-	present	requiring surgery
Fistula- pharyngeal	none	-	-	present	requiring surgery
Fistula- rectal/anal	none	-	-	present	requiring surgery
Flatulence	none	mild	moderate	-	-

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
Gastric ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery	perforation or bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Gastritis	none	-	requiring medical management or non-surgical treatment	uncontrolled by out-patient medical management; requiring hospitalization or surgery	life-threatening bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Hematemesis is graded in the HEMORRHAGE category.					
Hematochezia is graded in the HEMORRHAGE category as Rectal bleeding/hematochezia.					
Ileus (or neuroconstipation)	none	-	intermittent, not requiring intervention	requiring non-surgical intervention	requiring surgery
Mouth dryness	normal	mild	moderate	-	-
Mucositis Note: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginititis. Radiation-related mucositis is graded as Mucositis due to radiation.					
Mucositis due to radiation	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally ≤ 1.5 cm in diameter and non-contiguous)	confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
Also consider Pain due to radiation. Note: Grade radiation mucositis of the larynx here. Dysphagia related to radiation is also graded as either Dysphagia- esophageal related to radiation or Dysphagia-pharyngeal related to radiation, depending on the site of treatment.					
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Pancreatitis	none	-	-	abdominal pain with pancreatic enzyme elevation	complicated by shock (acute circulatory failure)
Also consider Hypotension.					

Toxicity	Grade 0	1	2	3	4
Note: Asymptomatic amylase and Amylase are graded in the METABOLIC/LABORATORY category.					
Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Proctitis	none	increased stool frequency, occasional blood-streaked stools, or rectal discomfort (including hemorrhoids), not requiring medication	increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	increased stool frequency/diarrhea, requiring parenteral support; rectal bleeding, requiring transfusion; or persistent mucus discharge, necessitating pads	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, and Pain due to radiation. Note: Fistula is graded separately as Fistula- rectal/anal. Proctitis occurring more than 90 days after the start of radiation therapy is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. (See Appendix V, http://ctep.info.nih.gov/ctc3/ctc.htm)					
Salivary gland changes	none	slightly thickened saliva/may have slightly altered taste (e.g., metallic); additional fluids may be required	thick, ropy, sticky saliva; markedly altered taste; alteration in diet required	-	acute salivary gland necrosis
Sense of smell	normal	slightly altered	markedly altered	-	-
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylatic intubation
For BMT:	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
Note: Radiation-related mucositis is graded as Mucositis due to radiation.					
Taste disturbance (dysgeusia)	normal	slightly altered	markedly altered	-	-

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Typhlitis (inflammation of the cecum)	none	-	-	abdominal pain, diarrhea, fever, or radiographic documentation	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile/neutropenia.					
Vomiting	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Dehydration.					
Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category.					
Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category.					
Gastrointestinal-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
HEMORRHAGE					
Note: Transfusion in this section refers to pRBC infusion. For <u>any</u> bleeding with grade 3 or 4 platelets (< 50,000), <u>always</u> grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider platelets, transfusion- pRBCS, and transfusion-platelets in addition to the grade that incorporates the site or type of bleeding. If the site or type of hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: CNS hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/hematochezia, Vaginal bleeding. If the platelet count is ≥50,000 and the site or type of bleeding is listed, grade the specific site. If the site or type is <u>not</u> listed and the platelet count is ≥50,000, grade Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia and specify the site or type in the OTHER category.					
Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs.					
Note: This toxicity must be graded for any bleeding with grade 3 or 4 thrombocytopenia. Also grade the site or type of hemorrhage/bleeding. If the site is not listed, grade as Other in the HEMORRHAGE category.					

Toxicity	Grade 0	1	2	3	4
Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs. Note: Bleeding in the absence of grade 3 or 4 thrombocytopenia is graded here only if the specific site or type of bleeding is not listed elsewhere in the HEMORRHAGE category. Also grade as Other in the HEMORRHAGE category.					
CNS hemorrhage/bleeding	none	-	-	bleeding noted on CT or other scan with no clinical consequences	hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms
Epistaxis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematemesis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematuria (in the absence of vaginal bleeding)	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Hemoptysis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention

Toxicity	Grade 0	1	2	3	4
Hemorrhage/bleeding associated with surgery Note: Expected blood loss at the time of surgery is not graded as a toxicity.	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Melena/GI bleeding	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	none	rare petechiae of skin	petechiae or purpura in dependent areas of skin	generalized petechiae or purpura of skin or petechiae of any mucosal site	-
Rectal bleeding/ hematochezia	none	mild without transfusion or medication	persistent, requiring medication (e.g., steroid suppositories) and/or break from radiation treatment	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Vaginal bleeding	none	spotting, requiring < 2 pads per day	requiring ≥ 2 pads per day, but not requiring transfusion	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage-Other (Specify site, _____)	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
HEPATIC					
Alkaline phosphatase	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Bilirubin	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Bilirubin- graft versus host disease (GVHD) Note: The following criteria are used only for bilirubin associated with graft versus host disease.	normal	≥2 - <3 mg/100 ml	≥3 - <6 mg/100 ml	≥6 - <15 mg/100 ml	≥15 mg/100 ml

Toxicity	Grade 0	1	2	3	4
GGT (γ - Glutamyl transpeptidase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic enlargement	absent	-	-	present	-
Note: Grade Hepatic enlargement only for changes related to VOD or other treatment related toxicity.					
Hypoalbuminemia	WNL	<LLN - 3 g/dl	≥2 - <3 g/dl	<2 g/dl	-
Liver dysfunction/failure (clinical)	normal	-	-	asterixis	encephalopathy or coma
Note: Documented viral hepatitis is graded in the INFECTION category.					
Portal vein flow	normal	-	decreased portal vein flow	reversal/retrograde portal vein flow	-
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
SGPT (ALT) (serum glutamic pyruvic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
INFECTION/FEBRILE NEUTROPENIA					
Catheter-related infection	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment or hospitalization	life-threatening sepsis (e.g., septic shock)
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC < 1.0 x 10^9/L, fever ≥38.5°C)	none	-	-	Present	Life-threatening sepsis (e.g., septic shock)
Note: Hypothermia instead of fever may be associated with neutropenia and is graded here.					

Toxicity	Grade 0	1	2	3	4
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC < 1.0 x 10^9/L)	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Note: Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection with grade 3 or 4 neutropenia, grade as Febrile neutropenia.					
Infection with unknown ANC Note: This toxicity criterion is used in the rare case when ANC is unknown.	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection without neutropenia	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)
Infection/Febrile Neutropenia-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
Wound-infectious is graded in the DERMATOLOGY/SKIN category.					
LYMPHATICS					
Lymphatics	normal	mild lymphedema	moderate lymphedema requiring compression; lymphocyst	severe lymphedema limiting function; lymphocyst requiring surgery	severe lymphedema limiting function with ulceration
Lymphatics-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
METABOLIC/LABORATORY					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Acidosis (metabolic or respiratory)	normal	pH < normal, but ≥7.3	-	pH < 7.3	pH < 7.3 with life-threatening physiologic consequences
Alkalosis (metabolic or respiratory)	normal	pH > normal, but ≤7.5	-	pH > 7.5	pH > 7.5 with life-threatening physiologic consequences
Amylase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	>5.0 x ULN
Bicarbonate	WNL	< LLN - 16 mEq/dl	11 - 15 mEq/dl	8 - 10 mEq/dl	< 8 mEq/dl
CPK (creatine phosphokinase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5 x ULN	> 5 - 10 x ULN	> 10 x ULN
Hypercalcemia	WNL	> ULN - 11.5 mg/dl > ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dl > 2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dl > 3.1 - 3.4 mmol/L	> 13.5 mg/dl > 3.4 mmol/L
Hypercholesterolemia	WNL	> ULN - 300 mg/dl > ULN - 7.75 mmol/L	> 300 - 400 mg/dl > 7.75 - 10.34 mmol/L	> 400 - 500 mg/dl >10.34 - 12.92 mmol/L	> 500 mg/dl > 12.92 mmol/L
Hyperglycemia	WNL	> ULN - 160 mg/dl > ULN - 8.9 mmol/L	> 160 - 250 mg/dl > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dl > 13.9 - 27.8 mmol/L	> 500 mg/dl > 27.8 mmol/L or ketoacidosis
Hyperkalemia	WNL	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Hypermagnesemia	WNL	> ULN - 3.0 mg/dl > ULN - 1.23 mmol/L	-	> 3.0 - 8.0 mg/dl > 1.23 - 3.30 mmol/L	> 8.0 mg/dl > 3.30 mmol/L
Hypernatremia	WNL	> ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hypertriglyceridemia	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10 x ULN	> 10 x ULN

Toxicity	0	1	2	3	4
			Grade		
Hyperuricemia	WNL	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L without physiologic consequences	-	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dl > 0.59 mmol/L
Also consider Tumor lysis syndrome, Renal failure, Creatinine, Potassium.					
Hypocalcemia	WNL	<LLN - 8.0 mg/dl <LLN - 2.0 mmol/L	7.0 - < 8.0 mg/dl 1.75 - < 2.0 mmol/L	6.0 - < 7.0 mg/dl 1.5 - < 1.75 mmol/L	<6.0 mg/dl < 1.5 mmol/L
Hypoglycemia	WNL	<LLN - 55 mg/dl <LLN - 3.0 mmol/L	40 - < 55 mg/dl 2.2 - < 3.0 mmol/L	30 - < 40 mg/dl 1.7 - < 2.2 mmol/L	< 30 mg/dl < 1.7 mmol/L
Hypokalemia	WNL	<LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L
Hypomagnesemia	WNL	<LLN - 1.2 mg/dl <LLN - 0.5 mmol/L	0.9 - <1.2 mg/dl 0.4 - < 0.5 mmol/L	0.7 - < 0.9 mg/dl 0.3 - < 0.4 mmol/L	< 0.7 mg/dl < 0.3 mmol/L
Hyponatremia	WNL	<LLN - 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
Hypophosphatemia	WNL	<LLN -2.5 mg/dl <LLN - 0.8 mmol/L	≥2.0 - <2.5 mg/dl ≥0.6 - <0.8 mmol/L	≥1.0 - <2.0 mg/dl ≥0.3 - <0.6 mmol/L	< 1.0 mg/dl <0.3 mmol/L
Hypothyroidism is graded in the ENDOCRINE category.					
Lipase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Metabolic/Laboratory-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
			MUSCULOSKELETAL		
Arthralgia is graded in the PAIN category.					
Arthritis	none	mild pain with inflammation, erythema or joint swelling but not interfering with function	moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living	severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living	disabling

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Muscle weakness (not due to neuropathy)	normal	asymptomatic with weakness on physical exam	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	bedridden or disabling
Myalgia is graded in the PAIN category.					
Myositis (inflammation/damage of muscle) Also consider CPK. Note: Myositis implies muscle damage (i.e., elevated CPK).	none	mild pain, not interfering with function	pain interfering with function, but not interfering with activities of daily living	pain interfering with function and interfering with activities of daily living	bedridden or disabling
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic; or disabling
Musculoskeletal-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
NEUROLOGY					
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Arachnoiditis/meningismus/ radiculitis Also consider Headache, Vomiting, Fever.	absent	mild pain not interfering with function	moderate pain interfering with function, but not interfering with activities of daily living	severe pain interfering with activities of daily living	unable to function or perform activities of daily living; bedridden; paraplegia
Ataxia (incoordination)	normal	asymptomatic but abnormal on physical exam, and not interfering with function	mild symptoms interfering with function, but not interfering with activities of daily living	moderate symptoms interfering with activities of daily living	bedridden or disabling
CNS cerebrovascular ischemia	none	-	-	transient ischemic event or attack (TIA)	permanent event (e.g., cerebral vascular accident)
CNS hemorrhage/bleeding is graded in the HEMORRHAGE category.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Cognitive disturbance/ learning problems	*none*	*cognitive disability; not interfering with work/school performance; preservation of intelligence*	*cognitive disability; interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones*	*cognitive disability; resulting in significant impairment of work/school performance; cognitive decline > 2 SD*	*inability to work/frank mental retardation*
Confusion	normal	confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living	confusion or delirium interfering with activities of daily living	harmful to others or self; requiring hospitalization
Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.					
Delusions	normal	-	-	present	toxic psychosis
Depressed level of consciousness Note: Syncope (fainting) is graded in the NEUROLOGY category.	normal	somnolence or sedation not interfering with function	somnolence or sedation interfering with function, but not interfering with activities of daily living	obtundation or stupor; difficult to arouse; interfering with activities of daily living	coma
Dizziness/lightheadedness	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Dysphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Extrapyramidal/ involuntary movement/ restlessness	none	mild involuntary movements not interfering with function	moderate involuntary movements interfering with function, but not interfering with activities of daily living	severe involuntary movements or torticollis interfering with activities of daily living	bedridden or disabling
Hallucinations	normal	-	-	present	toxic psychosis
Headache is graded in the PAIN category.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Insomnia	normal	occasional difficulty sleeping not interfering with function	difficulty sleeping interfering with function, but not interfering with activities of daily living	frequent difficulty sleeping, interfering with activities of daily living	-
Note: This toxicity is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia.					
Irritability *(children <3 years of age)*	*normal*	*mild; easily consolable*	*moderate; requiring increased attention*	*severe; inconsolable*	-
Leukoencephalopathy associated radiological findings	*none*	*mild increase in SAS (subarachnoid space) and/or mild ventriculomegaly ; and/or small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or < 1/3 of susceptible areas of cerebrum*	*moderate increase in SAS; and/or moderate ventriculomegaly ; and/or focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum*	*severe increase in SAS; severe ventriculomegaly ; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)*	*severe increase in SAS; severe ventriculomegaly ; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)*
Memory loss	normal	memory loss not interfering with function	memory loss interfering with function, but not interfering with activities of daily living	memory loss interfering with activities of daily living	amnesia
Mood alteration-anxiety agitation	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-depression	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Mood alteration-euphoria	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	danger to self
Neuropathic pain is graded in the PAIN category.					
Neuropathy- cranial	absent	-	present, not interfering with activities of daily living	present, interfering with activities of daily living	life-threatening, disabling
Neuropathy- motor	normal	subjective weakness but no objective findings	mild objective weakness interfering with function, but not interfering with activities of daily living	objective weakness interfering with activities of daily living	paralysis
Neuropathy-sensory	normal	loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paresthesia interfering with activities of daily living	permanent sensory loss that interferes with function
Nystagmus Also consider Vision-double vision.	absent	present	-	-	-
Personality/behavioral	normal	change, but not disruptive to patient or family	disruptive to patient or family	disruptive to patient and family; requiring mental health intervention	harmful to others or self; requiring hospitalization
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	normal	asymptomatic with abnormality on physical examination	symptomatic or interfering with function but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling; paralysis
Seizure(s)	none	-	seizure(s) self-limited and consciousness is preserved	seizure(s) in which consciousness is altered	seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)

Toxicity	Grade 0	1	2	3	4
Speech impairment (e.g., dysphasia or aphasia)	normal	-	awareness of receptive or expressive dysphasia, not impairing ability to communicate	receptive or expressive dysphasia, impairing ability to communicate	inability to communicate
Syncope (fainting)	absent	-	-	present	-
Also consider CARDIOVASCULAR (ARRHYTHMIA), Vasovagal episode, CNS cerebrovascular ischemia.					
Tremor	none	mild and brief or intermittent but not interfering with function	moderate tremor interfering with function, but not interfering with activities of daily living	severe tremor interfering with activities of daily living	-
Vertigo	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Neurology-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
OCULAR/VISUAL					
Cataract	none	asymptomatic	symptomatic, partial visual loss	symptomatic, visual loss requiring treatment or interfering with function	-
Conjunctivitis	none	abnormal ophthalmologic changes, but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Dry eye	normal	mild, not requiring treatment	moderate or requiring artificial tears	-	-
Glaucoma	none	increase in intraocular pressure but no visual loss	increase in intraocular pressure with retinal changes	visual impairment	unilateral or bilateral loss of vision (blindness)

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Keratitis (corneal inflammation/ corneal ulceration)	none	abnormal ophthalmologic changes but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	unilateral or bilateral loss of vision (blindness)
Tearing (watery eyes)	none	mild: not interfering with function	moderate: interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	-
Vision- blurred vision	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- double vision (diplopia)	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- flashing lights/floaters	normal	mild, not interfering with function	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- night blindness (nyctalopia)	normal	abnormal electro-retinography but asymptomatic	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- photophobia	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Ocular/Visual-Other (Specify,)	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)
PAIN					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Abdominal pain or cramping	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthralgia (joint pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthritis (joint pain with clinical signs of inflammation) is graded in the MUSCULOSKELETAL category.					
Bone pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Chest pain (non-cardiac and non-pleuritic)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dysmenorrhea	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dyspareunia	none	mild pain not interfering with function	moderate pain interfering with sexual activity	severe pain preventing sexual activity	-
Dysuria is graded in the RENAL/GENITOURINARY category.					
Earache (otalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Hepatic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pain due to radiation	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pelvic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pleuritic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

Toxicity	Grade 0	1	2	3	4
Rectal or perirectal pain (proctalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor pain (onset or exacerbation of tumor pain due to treatment)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor flair is graded in the SYNDROME category.					
Pain-Other (Specify,)	none	mild	moderate	severe	disabling
PULMONARY					
Adult Respiratory Distress Syndrome (ARDS)	absent	-	-	-	present
Apnea	none	-	-	present	requiring intubation
Carbon monoxide diffusion capacity (DL_{CO})	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	-
Dyspnea (shortness of breath)	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support
FEV_1	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Hiccoughs (hiccups, singultus)	none	mild, not requiring treatment	moderate, requiring treatment	severe, prolonged, and refractory to treatment	-

Toxicity	Grade 0	1	2	3	4
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest, requiring supplemental oxygen	decreased O_2 saturation, requiring pressure support (CPAP) or assisted ventilation
Pleural effusion (non-malignant)	none	asymptomatic and not requiring treatment	symptomatic, requiring diuretics	symptomatic, requiring O_2 or therapeutic thoracentesis	life-threatening (e.g., requiring intubation)
Pleuritic pain is graded in the PAIN category.					
Pneumonitis/pulmonary infiltrates	none	radiographic changes but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation
Pneumothorax	none	no intervention required	chest tube required	sclerosis or surgery required	life-threatening
Pulmonary embolism is graded as Thrombosis/embolism in the CARDIOVASCULAR (GENERAL) category.					
Pulmonary fibrosis	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	requiring steroids or diuretics	requiring oxygen	requiring assisted ventilation
Note: Radiation-related pulmonary fibrosis is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme-Lung. (See Appendix V, http://ctep.info.nih.gov/ctc3/ctc.htm)					
Voice changes/stridor/larynx (e.g., hoarseness, loss of voice, laryngitis)	normal	mild or intermittent hoarseness	persistent hoarseness, but able to vocalize; may have mild to moderate edema	whispered speech, not able to vocalize; may have marked edema	marked dyspnea/stridor requiring tracheostomy or intubation
Note: Cough from radiation is graded as cough in the PULMONARY category. Radiation-related hemoptysis from larynx/pharynx is graded as Grade 4 Mucositis due to radiation in the GASTROINTESTINAL category. Radiation-related hemoptysis from the thoracic cavity is graded as Grade 4 Hemoptysis in the HEMORRHAGE category.					
Pulmonary-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
RENAL/GENITOURINARY					
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmotic	severe symptoms requiring narcotic	-
Creatinine	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Note: Adjust to age-appropriate levels for pediatric patients.					
Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	-

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Fistula or GU fistula (e.g., vaginal, vesicovaginal)	none	-	-	requiring intervention	requiring surgery
Hemoglobinuria	-	present	-	-	-
Hematuria (in the absence of vaginal bleeding) is graded in the HEMORRHAGE category.					
Incontinence	none	with coughing, sneezing, etc.	spontaneous, some control	no control (in the absence of fistula)	-
Operative injury to bladder and/or ureter	none	-	injury of bladder with primary repair	sepsis, fistula, or obstruction requiring secondary surgery; loss of one kidney; injury requiring anastomosis or re-implantation	septic obstruction of both kidneys or vesicovaginal fistula requiring diversion
Proteinuria	normal or < 0.15 g/24 hours	1+ or 0.15 - 1.0 g/24 hours	2+ to 3+ or 1.0 - 3.5 g/24 hours	4+ or > 3.5 g/24 hours	nephrotic syndrome
Note: If there is an inconsistency between absolute value and uristix reading, use the absolute value for grading.					
Renal failure	none	-	-	requiring dialysis, but reversible	requiring dialysis and irreversible
Ureteral obstruction	none	unilateral, not requiring surgery	-	bilateral, not requiring surgery	stent, nephrostomy tube, or surgery
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	none	asymptomatic, not requiring treatment	mild, reversible and manageable with oral replacement	reversible but requiring IV replacement	irreversible, requiring continued replacement
Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia.					
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x normal	increase > 2 x normal but < hourly	hourly or more with urgency, or requiring catheter	-
Urinary retention	normal	hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period	hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for < 6 weeks	requiring frequent in/out catheterization (≥ 4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy)	bladder rupture

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria)	normal	asymptomatic, change in urine color	-	-	-
Vaginal bleeding is graded in the HEMORRHAGE category.					
Vaginitis (not due to infection)	none	mild, not requiring treatment	moderate, relieved with treatment	severe, not relieved with treatment, or ulceration not requiring surgery	ulceration requiring surgery
Renal/Genitourinary-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
SECONDARY MALIGNANCY					
Secondary Malignancy-Other (Specify type, _____) excludes metastatic tumors	none	-	-	-	present
SEXUAL/REPRODUCTIVE FUNCTION					
Dyspareunia is graded in the PAIN category.					
Dysmenorrhea is graded in the PAIN category.					
Erectile impotence	normal	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for intercourse)	no erections	-
Female sterility	normal	-	-	sterile	-
Femininization of male is graded in the ENDOCRINE category.					
Irregular menses (change from baseline)	normal	occasionally irregular or lengthened interval, but continuing menstrual cycles	very irregular, but continuing menstrual cycles	persistent amenorrhea	-
Libido	normal	decrease in interest	severe loss of interest	-	-
Male infertility	-	-	Oligospermia (low sperm count)	Azoospermia (no sperm)	-
Masculinization of female is graded in the ENDOCRINE category.					

Toxicity	Grade 0	1	2	3	4
Vaginal dryness	normal	mild	requiring treatment and/or interfering with sexual function, dyspareunia	-	-
Sexual/Reproductive Function-Other (Specify,)	none	mild	moderate	severe	disabling
SYNDROMES (not included in previous categories)					
Acute vascular leak syndrome is graded in the CARDIOVASCULAR (GENERAL) category.					
ARDS (Adult Respiratory Distress Syndrome) is graded in the PULMONARY category.					
Autoimmune reactions are graded in the ALLERGY/IMMUNOLOGY category.					
DIC (disseminated intravascular coagulation) is graded in the COAGULATION category.					
Fanconi's syndrome is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Renal tubular acidosis is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Stevens-Johnson syndrome (erythema multiforme) is graded in the DERMATOLOGY/SKIN category.					
SIADH (syndrome of inappropriate antidiuretic hormone) is graded in the ENDOCRINE category.					
Thrombotic microangiopathy (e.g., thromboitic thrombocytopenic purpura/TTP or hemolytic uremic syndrom/HUS) is graded in the COAGULATION category.					
Tumor flare Also consider Hypercalcemia. Note: Tumor flare is characterized by a constellation of symptoms and signs in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances.	none	mild pain not interfering with function	moderate pain; pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain; pain or analgesics interfering with function and interfering with activities of daily living	Disabling
Tumor lysis syndrome Also consider Hyperkalemia, Creatinine.	absent	-	-	present	-
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) is graded under the RENAL/GENITOURINARY category.					
Syndromes-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling

Appendix II
Toxicity Module

To be implemented at the request of the study sponsor or principal investigator in the protocol or by protocol amendment when more detailed information is considered pertinent.

Toxicity:	Date of Treatment:		Course Number:
Date of onset:			Grade at onset:
Date of first change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Did toxicity resolve? If so, date of resolution of toxicity:	Yes_____	No_____	
Date of last observation (if prior to recovery):			
Reason(s) observations stopped (if prior to recovery):			
Was patient retreated?	Yes_____	No_____	
If yes, was treatment delayed for recovery?	Yes_____	No_____	
Date of next treatment?			
Dose reduced for next treatment?	Yes_____	No_____	

Additional Comments:

_____

_____

If module is being activated for new toxicity, not currently in CTC, please provide definitions for toxicity grading:

Grade 0 =

_____

Grade 1 =

_____

Grade 2 =

_____

Grade 3 =

_____

Grade 4 =

_____

Appendix III
Infection Module

To be implemented at the request of the study sponsor or principal investigator in the protocol or by protocol amendment when more detailed information is considered pertinent.

1. Use the Common Toxicity Criteria definitions to grade the severity of the infection.
2. Specify type of infection from the following (CHOOSE ONE):
   BACTERIAL FUNGAL PROTOZOAL VIRAL UNKNOWN
3. Specify site of infection from the following (CHOOSE ALL THAT APPLY):
   BLOOD CULTURE POSITIVE
   BONE INFECTION
   CATHETER (intravenous)
   CATHETER (intravenous), tunnel infection
   CENTRAL NERVOUS SYSTEM INFECTION
   EAR INFECTION
   EYE INFECTION
   GASTROINTESTINAL INFECTION
   ORAL INFECTION
   PNEUMONIA
   SKIN INFECTION
   UPPER RESPIRATORY INFECTION
   URINARY TRACT INFECTION
   VAGINAL INFECTION
   INFECTION, not otherwise specified (Specify site, _____)
4. Specify organism, if known: _____.
5. Prophylactic antibiotic, antifungal, or antiviral therapy administration
   Yes_____ No_____
   If prophylaxis was given prior to infection, please specify below:
   Antibiotic prophylaxis _____
   Antifungal prophylaxis _____
   Antiviral prophylaxis _____
   Other prophylaxis _____

Appendix IV
Performance Status Scales/Scores

ECOG or Zubrod Scale		Karnofsky Score
0	Asymptomatic and fully active	100%
1	Symptomatic; fully ambulatory; restricted in physically strenuous activity	80-90%
2	Symptomatic; ambulatory; capable of self-care; more than 50% of waking hours are spent out of bed	60-70%
3	Symptomatic; limited self-care; spends more than 50% of time in bed, but not bedridden	40-50%
4	Completely disabled; no self-care; bedridden	20-30%

Appendix V

RTOG/EORTC Late Radiation Morbidity Scoring Scheme
Use for toxicities occurring greater than 90 days after radiation therapy.

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Bladder- Late RT Morbidity Scoring	No change from baseline	Slight epithelial atrophy/minor telangiectasia (microscopic hematuria)	Moderate frequency/ generalized telangiectasia/ intermittent macroscopic hematuria	Severe frequency and dysuria/severe generalized telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (< 150 cc)	Necrosis/contracted bladder (capacity < 100 cc)/severe hemorrhagic cystitis
Bone- Late RT Morbidity Scoring	No change from baseline	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis/ spontaneous fracture
Brain- Late RT Morbidity Scoring	No change from baseline	Mild headache; slight lethargy	Moderate headache; great lethargy	Severe headaches; severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; coma
Esophagus- Late RT Morbidity Scoring	No change from baseline	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semi-solid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilation required	Necrosis/ perforation; fistula
Heart- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms; transient T wave inversion and ST changes; sinus tachycardia > 110 (at rest)	Moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low QRS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities	Tamponade/severe heart failure/severe constrictive pericarditis
Joint- Late RT Morbidity Scoring	No change from baseline	Mild joint stiffness; slight limitation of movement	Moderate stiffness; intermittent or moderate joint pain; moderate	Severe joint stiffness; pain with severe limitation of movement	Necrosis/complete fixation

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
			limitation of movement		
Kidney- Late RT Morbidity Scoring	No change from baseline	Transient albuminuria; no hypertension; mild impairment of renal function; urea 25 - 35 mg%; creatinine 1.5 - 2.0 mg%; creatinine clearance > 75%	Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function; urea > 36 - 60 mg%; creatinine clearance > 50 - 74%	Severe albuminuria; severe hypertension; persistent anemia (< 10 g%); severe renal failure; urea > 60 mg%; creatinine > 4 mg%; creatinine clearance < 50%	Malignant hypertension; uremic coma/urea > 100%
Larynx- Late RT Morbidity Scoring	No change from baseline	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis
Liver- Late RT Morbidity Scoring	No change from baseline	Mild lassitude; nausea; dyspepsia; slightly abnormal liver function	Moderate symptoms; some abnormal liver function tests; serum albumin normal	Disabling hepatic insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites	Necrosis/hepatic coma or encephalopathy
Lung- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms (dry cough); slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); low grade fever; patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; dense radiographic changes	Severe respiratory insufficiency/ continuous O2/assisted ventilation
Mucous membrane- Late RT Morbidity Scoring	No change from baseline	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucus	Marked atrophy with complete dryness; severe telangiectasia	Ulceration
Salivary glands- Late RT Morbidity Scoring	No change from baseline	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
Skin- Late RT Morbidity Scoring	No change from baseline	Slight atrophy; pigmentation change; some hair loss	Patchy atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Small/Large intestine- Late RT Morbidity Scoring	No change from baseline	Mild diarrhea; mild cramping; bowel movement 5 x daily slight rectal discharge	Moderate diarrhea and colic; bowel movement > 5 x daily; excessive	Obstruction or bleeding, requiring surgery	Necrosis/ perforation fistula

Toxicity	Grade 0	1	2	3	4
		or bleeding	rectal mucus or intermittent bleeding		
Spinal cord- Late RT Morbidity Scoring	No change from baseline	Mild Lhermitte's syndrome	Severe Lhermitte's syndrome	Objective neurological findings at or below cord level treatment	Mono-, para-, quadriplegia
Subcutaneous tissue- Late RT Morbidity Scoring	No change from baseline	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; < 10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture > 10% linear measurement	Necrosis
Eye- Late RT Morbidity Scoring	No change from baseline	Asymptomatic cataract; minor corneal ulceration or keratitis	Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment; severe glaucoma	Panophthalmitis; blindness
Radiation-Other (Specify,)	None	Mild	Moderate	Severe	Life-threatening or disabling

A Phase I/II Trial of Escalating Dose of Yttrium-90-labeled Anti-CD20 Monoclonal Antibody in Combination with High-Dose Etoposide and Cyclophosphamide followed by Autologous Stem Cell Transplantation for Patients with Relapsed B-Cell Non-Hodgkin's Lymphoma

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Appendix VI
BMT Complex/Multi-Component Events

Toxicity	Grade 0	1	2	3	4
Note: The grading of Complex/Multi-Component Events in bone marrow transplant will be defined in the protocol. The grading scale must use the CTC criteria for grading the specific component events (toxicities).					
Failure to engraft Also consider Hemoglobin (Hgb), Neutrophils/granulocytes (ANC/AGC), Platelets	absent	mild	moderate	severe	life-threatening
Graft versus host disease Also consider Fatigue, Rash/desquamation, Diarrhea, Bilirubin-GVHD	absent	mild	moderate	severe	life-threatening
Stem cell infusion complications Also consider Allergic reaction/hypersensitivity, Arrhythmia, Hypertension, Hypotension, Fever, Rigors/chills, Sweating, Rash/desquamation, Urticaria, Diarrhea, Nausea, Vomiting, Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hemoptysis, Alkaline phosphatase, Bilirubin, GGT, SGOT, SGPT, Infection, Hyperkalemia, Hypernatremia, Hypokalemia, Depressed level of consciousness, Seizures, Abdominal pain, Headache, Creatinine, Hemoglobinuria	absent	mild	moderate	severe	life-threatening
Veno-Occlusive Disease (VOD) Also consider Weight gain-VOD, Bilirubin, Depressed level of consciousness, Hepatic pain, Renal failure, Hepatic enlargement.	absent	mild	moderate	severe	life-threatening