CITY OF HOPE NATIONAL MEDICAL CENTER
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Division of Hematology and Hematopoietic Cell Transplantation

TITLE: Phase II Study of IV Busulfan Combined with 12 Gy of Fractionated Total Body Irradiation (FTBI) and Etoposide (VP16) as a Preparative Regimen for Allogeneic Hematopoietic Stem Cell (HSC) Transplantation for Patients with Advanced Hematological Malignancies

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Amendment 2	11/08/01	Version 02
Amendment 3	03/11/02	Version 03
Amendment 4	06/13/02	Version 04
Amendment 5	08/12/02	Version 05
(Consent form change	10/16/02	Version 05)
Amendment 6	11/18/02	Version 06
Amendment 7	04/20/04	Version 07
Amendment 8	09/28/17	Version 08
Amendment 9	07/26/19	Version 09
Amendment 10 at Continuation	07/01/20	Version 10
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HISTOLOGY: Advanced Hematological Malignancies
STAGE: Advanced
MODALITY: Allogeneic BMT
TYPE: Phase II

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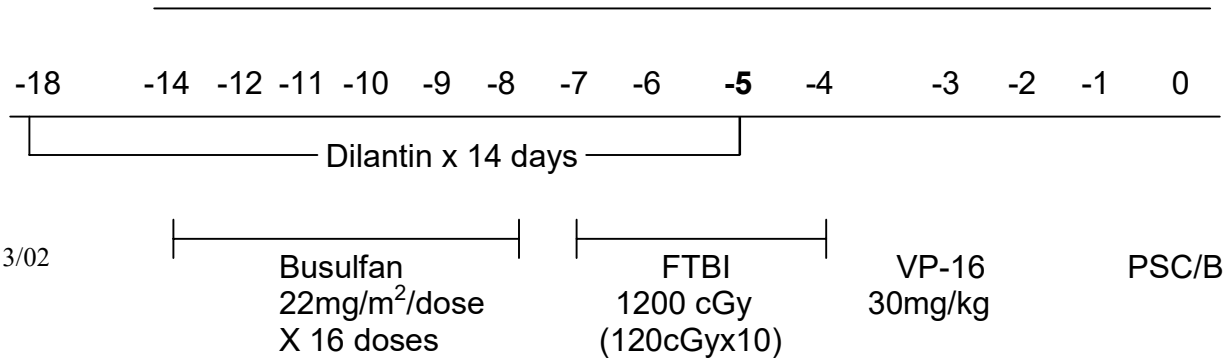
SCHEMA

Rev. 11/8/01



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1.0 OBJECTIVES

1.1 To determine the efficacy of intravenous busulfan, dose targeted to achieve AUC of 700-900 combined with fractionated total body irradiation and VP16 as a preparative regimen for marrow transplantation from an HLA-identical sibling in patients with advanced hematological malignancies (AML or ALL) beyond 2nd remission, induction failure, in relapse, chronic myelogenous leukemia in blast crisis and myelodysplasia (RAEB and RAEBIT).

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1.2 To determine the efficacy of this regimen in patients with AML in first remission with unfavorable cytogenetics.

1.3 To evaluate the early and late toxicities of this regimen.

2.0 BACKGROUND AND HYPOTHESIS

During the last 20 years clinical bone marrow transplantation from a histocompatible sibling donor has evolved into an important treatment modality for patients with acute lymphoblastic leukemia, acute myelogenous leukemia and chronic myelogenous leukemia. If the transplant procedure is performed in first complete remission of acute leukemia or during chronic phase or chronic myelogenous leukemia, approximately 50-70% of patients become disease free long-term survivors.[1-8] In contrast, the chances for an ultimately successful outcome of bone marrow transplantation drops to 10-40% if this is performed during second or subsequent complete remission, during relapse of acute leukemias, or while patients with chronic myelogenous leukemia are in accelerated or blast phase of this disease. In the latter group of patients the probability of leukemic relapse is in the range of 40-70%.[9-16] Many transplant centers have performed several phase I-II trials of preparative regimens using alternative chemotherapeutic agents or methods of administering TBI. Some of these studies suggest a decrease in the post-transplant relapse rate that are often associated with increased transplant related morbidity and mortality from regimen related toxicity.[17-20] At the City of Hope a phase I/II trial was conducted in 1986 to determine the efficacy of substituting etoposide (VP-16) for cyclophosphamide in combination with fractionated total body irradiation (FTBI). This trial was done in 33 patients with acute leukemia beyond first remission, and resulted in a 43% long-term disease free survivorship. Despite this improved survival compared to previous studies there still is significant relapse rate, particularly in patients with advanced leukemia. This regimen has subsequently been utilized to treat 100 patients with acute leukemia in remission. There was only one case of fatal veno-occlusive disease; otherwise the regimen was well tolerated. [21] Studies combining busulfan and cyclophosphamide as a preparative regimen for patients with advanced hematological malignancies have been reported to result in similar or superior outcomes when compared with standard cyclophosphamide and TBI regimens, suggesting that busulfan has important anti-leukemic effects. A randomized Southwest Oncology Group study (SWOG) comparing busulfan, cyclosphophamide with FTBI VP-16 showed 20% disease free survival for patients transplanted with advanced leukemia. [22] At City of Hope a phase I study was conducted utilizing escalating doses busulfan in combination with fixed doses of

FTBI and VP-16 in an attempt to decrease the relapse rate in those patients transplanted for advanced hematological malignancies. The rationale behind the study was that we combined three non-cross resistant anti-leukemic agents with non-overlapping extramedullary toxicities. An in vitro synergy has been demonstrated between busulfan/VP-16 and busulfan/VP-16 has been proven to be an effective regimen for relapsed leukemia and for ABMT for AML in first and second remission.[23,24] The dose limiting toxicity occurred at 12mg/kg the MTD was defined at 11mg/kg. At this dose level median first dose AUC for these patients was 892μM*min (460-1267). With a median follow-up of 11.5 months, the disease-free survival is 32%, and the probability of relapse is 40%. The only variable predictive of a disease-free survival and relapse was the busulfan dose of 7-8 mg/kg. In this phase I study there was a wide variability of the AUC of busulfan due to the variability of absorption of oral busulfan. An AUC of 700-950 showed a trend to a decreased relapse rate and improved disease free survival.

A phase II study utilizing IV busulfan was conducted at City of Hope which has resulted in FDA approval of IV busulfan and it is proposed to substitute IV busulfan which has been shown to have more predictable pharmacokinetic properties than the oral preparation resulting in a better toxicity profile. [25,26,27]

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*Patients with AML in first complete remission (CR1) with unfavorable cytogenetics have a relapse rate of 40% with our current transplant regimen consisting of fractionated radiation and etoposide. We propose to use this new preparative regimen to see if it can improve the DFS and relapse rate for this subset of patients with AML in first CR.

3.0 DRUG INFORMATION

3.1 Busulfan (Myleran)

3.11 Mechanism of Action: Busulfan is a bifunctional alkylating agent. In aqueous media, busulfan hydrolyses to produce reactive carbonium ions that can alkylate DNA.

3.12 Formulation and stability: Busulfan injection is a sterile, pyrogen-free solution provided in a mixture of dimethylacetamide (DMA) and polyethlyeneglycol 400 (PEG 400). It is supplied in 10-ml single use ampules at a concentration of 6-mg Busulfan per ml. Each ampule contains 60mg of Busulfan in 3.3 ml of DMA and 6.7 ml of PEG 400. When diluted in normal saline or D5W to a concentration of 0.5mg/mL, the resulting solution must be administered within eight (8) hours of preparation; including the 2 hours of infusion of the drug.

Stable at 4º C for at least twelve months. Ampules should be stored refrigerated at 2-8º C. Do not freeze. Ampules may be stored for up to seven days at room temperature.

Solution preparation: prepare the Busulfan solution as follows: Use sterile, non-pyrogenic, disposable containers, syringes, needles, stopcocks, and transfer tubing, etc. Calculate the amount of drug to be administrated based on the dosage and the patient's body weight.

Prepare a solution of 0.9% sodium chloride injection USP (normal saline) calculated Busulfan dose in ml from the step above.

Break off the top of the ampule and remove the calculated volume of Busulfan from the container by using a syringe fitted with a filter needle or equivalent. Transfer the contents of the syringe into the calculated amount of either normal saline or D5W making sure that the drug flows into and through the solution. Mix by inverting the bag.

3.13 Administration: Each dose of the drug will be given by slow central intravenous infusion over 2 hours. Caution: Do not administer as an intravenous push or bolus.

3.14 Supplier: This drug is commercially available; manufactured by Orphan Medical Inc.

3.15 Toxicity: Toxicity from busulfan includes:

a). Severe bone marrow hypoplasia, which would be fatal without administration of bone marrow, stem cells.

b). Nausea and vomiting which can be decreased by the use of sedation and anti-emetics.

c). Stomatitis and diarrhea which can be treated symptomatically with fluid replacement and atropine or diphenoxylate H C1.

d). Pulmonary fibrosis characterized by delayed onset of cough, shortness of breath and low-grade fever.

e). Hepatic damage, which can occur in combination with cytoxan or as a single agent and can result in significant hepatic toxicity which, can be fatal.

f). Temporary hyperpigmentation of the skin and nail bed changes.

g). Grand mal seizures which can be prevented by the prophylactic administration of Dilantin.

3.2 VP-16 (VP-16-213) (Etoposide) (Vepesid)

3.21 Chemistry: VP-16 is a semi-synthetic podophyllotoxin derivative from the plant podophyllum pletatum, has anti-neoplastic properties in experimental animals and in man. The empiric formula C_{29} H_{32} 0_{13} has a molecular weight of 588.

3.22 Mechanism of Action: The epipodophyllotoxin exert phase-specific spindle poison activity with metaphase arrest, but in contrast to the vinca alkaloids, have an additional activity of inhibiting cells from entering mitosis. Suppression of tritiated thymidine, uridine, and leucine incorporation in human cells in tissue culture suggest effects against DNA, RNA and protein synthesis.

3.23 Animal Tumor Data: Significant anti-tumor effect has been demonstrated in L-1210, mouse sarcoma 37 and 180, Walker carcinosarcoma and Erlich ascites tumor. With the L 1210 system,

activity was schedule-dependent, having greater effect with a twice a week administration than with daily dosing or the administration of single large doses. The drug is active given intraperitoneally or orally in L 1210. No effect was demonstrated intracerebrally inoculated L 1210.

3.24 Animal Toxicology: The predominant toxicities of VP-16 in animal studies involve the hematopoietic system, with toxicity to the liver and GI tract occurring only at doses producing profound myelosuppression. Anemia, leukopenia, and lymphoid involution occur in mice, rats and monkeys. Acute toxicity investigations have been complicated by the toxicity of the solvent system. The LD-50 of the solvent plus drug approached that of the solvent alone. Immuno-suppressive effects occur with an inhibition of antibody production in mice and monkeys, and prevention of experimental allergic encephalomyelitis in rats (cell mediated immunity).

3.25 Human Toxicology: Reversible myelotoxicity has been uniformly observed to be the major toxicity of VP-16 and to represent the only clinically significant side effect. Following a single IV injection, peak myelotoxicity occurs at 7 to 9 days. Following daily IV injections for 5 to 7 days, myelotoxicity is maximal between 12 to 16 days from the initiation of therapy. Bone marrow suppression is mainly manifested as granulocytopenia with thrombocytopenia and anemia occurring to a lesser extent. Transient, modest nausea, usually without vomiting, is common. Occasional alopecia is reported. VP-16 does not produce stomatitis, phlebitis, neurotoxicity, hepato-toxicity or nephro-toxicity. Hypotension and anaphylaxis are occasional side effects. Hypotension can be managed by infusing the drug over at least a 30 minute period. Occasionally, fever may be a result of VP-16 administration.

3.26 Pharmaceutical Data: Formulation: 100 mg of VP-16 is supplied as 5 ml of solution in clear ampules for injection. Each ampule also contains anhydrous citric acid 10 mg, benzylalcohol 150 mg, polysorbate 80 purified 400 mg, polyethylene glycol and absolute alcohol. The contents of the ampule are non-aqueous and must be diluted with 20 to 50 volumes of sodium chloride injection USP. The time before precipitation depends on concentration.

Dilution	Time
1:20	30 minutes
1:50	3 hours
1:100	6 hours

3.27 Storage and stability: The drug is available as a box of 10 ampules that are stored at room temperature. Each ampule should be kept in the box to protect it from light. VP-16 is less stable in 5% Dextrose injection and precipitation is reported. VP-16 has a minimum infusion time of 30 minutes to reduce hypotension.

3.28 Supplier: VP-16 is commercially available.

3.3 Cyclosporine:

3.31 Mechanism of Action: Cyclosporine is an immunosuppressant used to prevent the rejection of transplanted kidneys, hearts and livers. It is also effective in treating bone marrow recipients with acute graft vs host disease. The drug inhibits T lymphocyte function with minimal activity against B cells.

3.32 Human Toxicology: Nephrotoxicity is the most frequent side effect of cyclosporine. Other frequently observed side effects include hypertension, hirsutism, tremors, paresthesias, hepato-toxicity, hypomagnesemia and hyperkalemia. Transient gastrointestinal symptoms have also occurred, to include anorexia, nausea and ileus. The drug has demonstrated a relative lack of myelotoxicity.

3.33 Pharmaceutical Data: Formulation: Cyclosporine is available for oral and intravenous administration. Cyclosporine is an olive oil solution supplied in 50 ml bottles containing 100 mg/ml. The intravenous solution is available as 5 ml ampules containing 50 mg/ml. Cyclosporine is also available as 25mg and 100mg capsules.

3.34 Storage and Stability: The oral solution of cyclosporine should be stored and dispensed in the original container at temperatures below 86^{o}F and should be used within two months after opening bottle. Do not store in the refrigerator. The intravenous solution should be stored at temperatures below 86^{o}F and protected from light.

3.35 Administration: The oral solution may be mixed with whole milk, chocolate milk or fruit juice to mask the taste and should be taken immediately after mixing. Cyclosporine should be administered intravenously over 2 to 6 hours. Longer infusion times are acceptable and sometimes better tolerated. The contents of the ampule should be diluted with 50-250 ml of 0.9% sodium chloride injection or 5% dextrose injection.

3.36 Supplier: This drug is commercially available.

3.4 Methotrexate

3.41 Chemistry: Methotrexate is a well known antimetabolite which has been intensively studied.

3.42 Biochemistry: As a folic acid analog, methotrexate is considered to act as an inhibitor or dihydrofolate reductase to which it tightly binds.

3.43 Human Pharmacology: Methotrexate is well absorbed in low doses from the gastrointestinal tract and is well absorbed when given intramuscularly. Large doses are completely absorbed when given

orally. About 40-50% of small doses and about 90% of large doses are excreted unchanged in the urine within eight hours. Toxicity is directly related to the duration of blood levels and thus, renal insufficiency can significantly increase toxicity. In man, there is insignificant metabolism of methotrexate.

3.44 Human Toxicity: Human toxicity includes myelosuppression, mucositis, nausea and abdominal discomfort, generalized malaise, rashes, photosensitization, decreased renal function, fetal death, hepatic toxicity and pulmonary toxicity (methotrexate lung).

3.45 Pharmaceutical Data: Formulation; 50mg vials containing 25mg/cc.

3.46 Storage: Room temperature.

3.47 Administration: In this study, administered intravenously.

3.48 Supplier: Methotrexate is commercially available for purchase by the third party.

4.0 STAGING CRITERIA:

4.1 Definition of Disease Stages of Chronic Myelogenous Leukemia

Chronic Phase

1. No significant symptoms which are not readily controlled by conventional doses of hydroxyurea or busulfan.

2. None of the features of accelerated phase or blastic phase. (Note: Granulocytic hyperplasia and the Philadelphia chromosome may be present in the bone marrow).

Accelerated Phase (any one or more of the following criteria)

1. WBC difficult to control with conventional use of busulfan/hydroxyurea in terms of doses required or shortening of intervals between courses.

2. Rapid doubling of WBC ($\leq$ 5 days).

3. $\geq$ 10% blasts in blood or marrow.

4. $\geq$ 20% blasts plus promyelocytes in blood or marrow.

5. $\geq$ 20% basophils plus eosinophils in blood.

6. Anemia or thrombocytopenia unresponsive to busulfan/hydroxyurea.

7. Persistent thrombocytosis ($\geq$ 1,000,000/ 1) unresponsive to conventional doses of hydroxyurea or busulfan.

8. Additional chromosome changes (evolving new clone).

9. Increasing splenomegaly unresponsive to conventional doses of hydroxyurea or busulfan.

10. Development of chloromas or myelofibrosis.

11. Patients in a second (or subsequent) chronic phase after blast crisis.

Blastic Phase

1. ≥ 30% blasts plus promyelocytes in the blood or bone marrow.

5.0 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

5.1.1 Patients with acute myelogenous or lymphocytic leukemia who are not in first remission or second remission i.e. after failing remission induction therapy or in relapse or beyond second remission, or patients with chronic myelogenous leukemia in blastic phase of the disease are eligible for the study. Patients with refractory anemia with excess blasts and in transformation will be eligible.

5.1.2 All candidates for this study must have a HLA (A,B,C,DR) identical siblings who is willing to donate bone marrow for marrow grafting. All ABO blood group combinations of the donor/recipient are acceptable since even major ABO compatibilities can be dealt with by various techniques. (Red cell exchange or plasma exchange). Peripheral blood stem cells or bone marrow can be used.

5.1.3 Prior therapy with VP-16 and busulfan is allowed.

5.1.4 Patients must be older than 16 and the upper age limit is physiological age of 50.

5.1.5 A cardiac evaluation with electrocardiogram and MUGA or echocardiogram is required in all patients. Patients must have an ejection fracture of greater than or equal to 50%.

5.1.6 Patients must have a serum creatinine of less than or equal to 1.2 or creatinine clearance > 80ml/min.

5.1.7 A bilirubin of less than or equal to 1.5. Patients should also have an SGOT and SGPT less than 5 times the upper limit of normal.

5.1.8 Pulmonary function tests including DLCO will be performed. FEV_1 and DLCO should be greater than 50% of predicted normal value.

5.1.9 The time from the last induction or reinduction attempt should be greater than or equal to 28 days.

5.1.10 Signed informed consent form approved by the IRB is required. The patient, family member and transplant staff physician (physician, nurse, and social worker) meet at least once prior to starting the transplant procedure. During this meeting all pertinent information with respect to risks and benefits to donor and recipient will be presented. Alternative treatment modalities will be discussed. The risks are explained in detail on the enclosed consent forms.

Revised 8/28/00
Revised 3/11/02

5.1.11 Patients with AML in first remission with poor risk cytogenetics (11q abnormalities, -7,-5, complex abnormalities i.e. > 3 abnormalities, 6;9 translocation and 3q abnormalities del (7q), del (5q), complex abn ≥ abnormalities, 9q, 20q, 21q, 17p, t(9;21).

Revised 6/13/02

5.2 Exclusion Criteria

5.2.1 Prior radiation therapy that will exclude the use of total body irradiation.

5.2.2 Patients who have undergone bone marrow transplantation previously and who have relapsed.

5.2.3 Patients with psychological or medical condition that patients physician deems unacceptable to proceed to allogeneic bone marrow transplant.

Revised 8/28/00

5.2.4 Pregnancy

5.3 Donors

5.3.1 Any sibling donors who are histocompatible with the prospective recipient will be considered as a suitable donor.

5.3.2 Donors will be excluded if for psychological or medical reasons they are unable to tolerate the procedure.

5.3.3 Donor should be able to donate peripheral blood stem cells or bone marrow.

6.0 TREATMENT PLAN

All patients will have a right atrial catheter, hickman type inserted. This catheter will be used for collection of blood specimens, administration of drug, bone marrow, blood components, and for hyperalimentation.

Revised 8/28/00

6.1 Pre-transplant evaluation *will be performed within four weeks of beginning treatment except for the following: 1) Bone marrow aspirate and biopsy + cytogenetics within 14 days of starting treatment, 2). CBC, differential, platelets, comprehensive metabolic panel within 5 days of starting treatment*.

a). Prior to admission patient will have a complete history and physical examination performed. Special attention will be given to prior

chemotherapy, height, weight and body surface area should also be noted.

b). Patients will have the following laboratory tests performed:
- i. CBC with diff platelets
- ii. Sodium, potassium, chloride, bicarbonate or total carbone dioxide, BUN, creatinine, Ca, Mg, Phosphorous, total bilirubin, total protein, albumin, SGPT, SGOT, LDH, alkaline phosphatase, cholesterol, glucose.
- iii. Urine analysis
  HIV test
  Hepatitis A,B + C
  24-hr urine for creatinine clearance
  CMV, HSV – HZV ab
  Immunoglobulin levels
- iv. 24-hour urine collection for creatinine clearance.
- v. Chest x-ray and EKG
- vi. CT scan chest, abdomen and pelvis.
- Revised 8/28/00 vii. Pregnancy test

c). Initial coagulation studies prothrombin time, APTT.

d). MUGA scan or echocardiogram

e). Pulmonary function tests

f). A bone marrow aspirate and biopsy, and cytogenetics needs to be done within 2 weeks of admission (if bone marrow not aspirable and > 20% blasts in blood this may be done on peripheral blood sample). Rev. 11/8/01

g). Patients with acute leukemia or chronic myelogenous leukemia in blast crisis will have a lumbar puncture performed. Methotrexate (10mg/m^2 but not more than a total dose of 12mg) will be administered intrathecally. The spinal fluid will be examined for the presence of malignant cells. Those patients who had leukemic CNS involvement prior to the time of admission before transplantation will receive five weekly intrathecal methotrexate injections with the dose described above from the time patients platelet count is greater than 75,000 to day 100, then monthly intrathecal methotrexate injections with the dose described above between day 100 and 12 months after transplantation. The initial spinal tap will only be performed if patients platelet count can be kept above 75,000. Revised 8/28/00

6.2 Preparative Chemotherapy Regimen

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* Patient to sign consent form before starting Dilantin.

Friday/Day -18 — Begin dilantin 300mg/p.o. t.i.d. times 1 day, then 300mg/p.o./IV daily times 14 days. Rev. 11/8/01

Tuesday/Day -14 — Admission or outpatient, dilantin blood levels will be checked and dose adjusted as needed to meet therapeutic range. Further adjustments if clinically indicated. Busulfan test dose administered at 6 a.m. as a single dose. The I/V dose is calculated as follows:

1. Body surface area (BSA) is calculated by the equation:

$$BSA = \sqrt{\frac{(\text{Actual body wt.(kg)} \times \text{height (cm)})}{3600}}$$

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2. 22mg/m^2 I/V Busulfan will be given over 2 hours. Blood levels will be obtained with the first dose as per appendix 1 and will be performed at City of Hope.

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Wednesday/Day -13

Busulfan AUC will be calculated by standard methods available in the City of Hope Analytical Pharmacology Core Facility (APCF). The resulting AUC will be used to determine the dose required to achieve an AUC of 800 μM* min according to the following formula:

$$\text{Adj dose} = \text{Current dose} \times \frac{800\mu\text{Mx min}}{\text{test dose AUC}}$$

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The maximum dose given will not exceed 32mg/m^2. There is no limit on dose reduction Busulfan dose will only be adjusted for AUC's <700 or >900 μM*min.

Thursday/Day -12

The adjusted dose Busulfan dose will be given at 6 a.m. and blood levels will be repeated. Further dose adjustments will be performed if AUC >1000.

Friday/Day -11

Patient admitted to BMT or receive further dose of Busulfan in clinic.

Busulfan dosing restarted at 6 p.m. and is repeated every 6 hours for a total of 14 doses.

Tuesday/Day -7

Fractionated TBI will be given at 120 cGy per fraction for a total of 4 days for a total of 10 fractions for a total dose of 1200 cGy. See Appendix II.

Saturday/Day -3

VP-16 30mg/kg based on adjusted ideal body weight will be administered.

Tuesday/Day 0

PSC reinfusion/or BM infusion

See Appendix 3 for PSC Collection

Toxicities of the marrow infusion are very rare. Volume overload may be prevented by removal of plasma from the marrow aspirate or by phlebotomy of the recipient prior to marrow infusion. Pulmonary emboli are theoretically possible and would require management with 02 or IPPB. However, our clinical observations over the last 20 years indicate that pulmonary embolism in this clinical setting does

not occur at any increased rate. The most frequently encountered problem is that of chills, hives, and fever. Those allergic reactions occur rarely (in 1 to 2%) and can be prevented by intravenous injections of dyphenhydrimine 25mg and hydrocortisone (50mg) prior to the bone marrow infusion.

6.3 Recommended

6.3 Graft Versus Host Disease Prophylaxis and Treatment

1. MMF

Both intravenous and oral doses of MMF will be calculated using adjusted ideal body weight. If actual body weight is less than ideal body weight, actual body weight will be used. All patients will initiate the intravenous formulation of MMF on the day of transplantation (Day 0), a minimum of 2 hours after the end of the stem cell infusion. MMF will be administered at 30mg/kg/day in two divided daily doses from day 0 until day 27. At day 27 the MMF will be tapered by 250mg to be off by Day 56. If patient does not develop evidence of GVH. The intravenous formulation will be administered until at least day 14 after transplant. MMF will be administered as a 2 hour IV infusion. MMF will be induced with 5% dextrose. When patients have recovered from radiation-induced gastroenteritis and are capable of taking the oral MMF, they will be converted at an oral to intravenous ratio of 1:1. This can be done because of the high bioavailability of MMF. The oral formulation of MMF is available in 250mg capsules. The prescribed dose will be rounded to the nearest dose possible with these capsules.

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2. Cyclosporine

All patients will receive cyclosporine 3mg/kg/day IV or 12.5 mg/kg/day orally from day –1 until day 50. Dosing should be based on adjusted ideal body weight. If GVHD is absent, cyclosporine will then be tapered by 5% week until day 180 when the drug is discontinued. Cyclosporine whole blood levels will be monitored.

6.31 If moderate to severe graft-versus-host disease occurs (Grade II-IV), patients will be treated with the administration of higher doses of methyl-prednisolone, anti-thymocyte globulin, etc.

6.32 Graft-versus-host disease will be graded according to previously defined criteria (Appendix IV,V).

6.4 Supportive Care during Transplant

On the day of admission menstruating females will start Provera 10mg p.o. daily and Nystatin vaginal suppositories 1 b.i.d. In addition, all patients will start, levofloxacin 500mg/p.o or I/V q daily, Bactrim DS 1 tablet p.o. b.i.d. or IV will be started and continue until day –2.

Hyperalimentation will be given while patient is unable to eat.

It is recommended that platelet transfusions will be given to maintain platelet count greater than 20,000/µl at all times. Single donor platelets will be used with an attempt to use family members when possible. All platelets will be filtered to remove contaminated leukocytes which may harbor cytomegalovirus (CMV). Packed RBC transfusions will be used to keep the hemoglobin greater than 8.5gm/dl. All blood products will be irradiated with 2500cGy prior to tranfusions.

The management of infections in these immunocompromised patients must by necessity be individualized, but the following general approach will be utilized. If a specific infection is documented, patients will be placed on specific anti-microbial agents to treat that infection. For temperatures greater than 38.5°C without an obvious source in patients with less than 1000granulocytes/l, cultures of blood will be obtained. Following this, a third generation cephalosporin will be used as initial empiric antibiotic coverage. For persistent or recurrent fevers an aminoglycoside and or ancef will be added. Prophylactic intravenous amphotericin B will be used and the dose can be increased as clinically indicated. If a specific organism or site of infection is identified after starting empiric antibiotic coverage, therapy will be changed as needed.

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While hospitalized, patients will have daily CBC's with platelet count, and SMA-7 (Na, K, C1, CO_2, BUN, creatinine, glucose). SMA12 (total protein, albumin, phosphatase, Ca, SGPT, SGOT, alkaline phosphatase, total bilirubin, cholesterol) determinations will be performed on Monday, Wednesday and Fridays and chest x-rays will be done weekly. CSA levels q Mon & Thurs, and CMV blood cultures q Mon & Thurs when WBC >2000.

7.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

7.1 Radiation toxicities: The short term complications of TBI are: a). nausea and vomiting. This problem will be managed symptomatically. b) Oral mucositis is expected in all patients. All patients will receive oral care with hydrogen peroxide and clotrimazole. Only sponge toothbrushes will be allowed. Pain will be managed with morphine and dilaudid, c) Temporary alopecia will also be expected in all patients. Long-term complications of TBI include: a) cataracts, these can be managed successfully in the same way as cataracts unrelated to radiation. b) Solid tumors have been seen following TBI. c) Radiation fibrosis of the lungs, d) hypothyroidism and patient will be required to take supplemental thyroid medication, e). Sterility.

7.2 Chemotherapy Toxicities:

7.2.1 Toxicities of VP-16

a) VP-16 may cause nausea, vomiting lasting for a few hours.

b). Occassionally VP16 can cause allergic reactions, hemorrhagic cystitis and hepatotoxicity.

b) Can cause mucositis, and dermatitis.

7.2.2 Busulfan Toxicities are myelosuppression, pulmonary fibrosis, increased pigmentation, grand mal seizures and temporary or permanent alopecias have also been seen.

If 2 of first 6 patients develop grade 3 liver or lung toxicity related to the preparative regimen the Busulfan dose will be decreased to the equivalent of 9mg/kg of the oral dose and AUC range will be changed to 600-800.

If 2 of first 6 patients require ventilator support for mucositis the VP-16 will be omitted.

7.3 The dose of methotrexate will be modified for impaired liver function based on serum direct bilirubin as follows:

Direct Bilirubin mg/dl	% MTX dose
≤ 2	100%
2.1 – 3.0	50%
> 3.0	0%

7.4 The dose of cyclosporine and methotrexate will be modified for impaired renal function based on serum creatinine.

Creatinine mg/dl	% CSA + MTX
< 1.5	100%
1.6 – 1.7	75%
1.8 – 2.0	50%
> 2.0	0%

8.0 Toxicities will be graded per CTC 2.0 (Appendix VII) publish date April 30, 1999. Rev. 11/8/01

9.0 STUDY CALENDAR SEE APPENDIX VI.

10.0 CRITERIA FOR EVALUATION AND DEFINITION

10.1 Achievement of a lymphohematopoietic graft is defined as recovery from post-transplant.

10.2 Complete remission is defined as attainment of M-1 marrow status, and no evidence of recurrent extramedullary disease.

10.3 Length of survival is measured from entry on study to death or time of last contact.

10.4 Treatment failure is defined as death from toxicities associated with transplant procedure of recurrence of malignancy.

10.5 All registered patients including those removed from the treatment protocol will be followed for survival every six months.

11.0 CRITERIA FOR REMOVAL FROM STUDY

There are two situations that will determine removal of a patient from the study:

11A. The patient may always be removed from the study whenever he/she wishes.

11B. If the scheduled bone marrow donor decides not to provide bone marrow.

12.0 STATISTICAL CONSIDERATIONS

12.1 Primary and Secondary Endpoints: The primary endpoint of the Phase II study is to evaluate the efficacy of FTBI/BU/VP-16 with a targeted Busulfan dose of AUC 700-900 as a preparative regimen for allogeneic BMT in patients with advanced hematological malignancies (AML or ALL beyond second remission, in induction

failure, or in relapse; CML in blast crisis; and myelodysplasia, RAEB and RAEBIT). Secondary endpoints will include early and late toxicities of this regimen.

Efficacy will be estimated based on 2 and 5 year disease-free survival (DFS). The effects of cytogenetics, WBC at presentation, and number of courses of induction therapy to achieve remission will be evaluated as possible prognostic factors for relapse, DFS, and overall survival.

12.2 Sample size Estimation and Length of Accrual: A total of 50 patients with advanced malignancies and less than 50 years old (physiological age) will be accrued to this trial, so that in estimating the engraftment and relapse rates the maximum standard error will be 0.7. We expect to accrue approximately 10-12 patients per year so that this trial will require 4-5 years of completion.

12.3 If at any time the severe treatment related complication rate (e.g. severe VOD, interstitial pneumonia, neurotoxicity at day 100 post BMT) or regimen related mortality exceeds 20% with a high probability (i.e. >95%) then further accrual to the trial will be terminated. This would occur if the following numbers of events have been observed, monitoring after every set of 10 patients is accrued:

Number of Patients Accrued	Number of Events Leading to Early Termination
10	5
20	8
30	11
40	14

12.4 Statistical Analyses: The rate of engraftment and median time to engraftment will be estimated, defined as time to ANC > 500 and platelets >20,000.

The Kaplan-Meier method will be used to estimate time to relapse, DFS, and overall survival, and 95% confidence intervals will be calculated using Greenwood's variance.

The intent-to-treat group will include all patients receiving the preparative regimen for BMT. For overall survival, failure time will be calculated from the day of first treatment to the day of death due to any cause for those patients who fail. For DFS, the failure time will be calculated from the day of first treatment to the day of disease relapse or death due to any cause. For patients who remain alive and well at the time of analysis, the survival time will be censored as of the date of last contact. The Cox proportional hazard regression model will be used to analyze possible prognostic factors for relapse, DFS and overall survival.

Revised 9/26/00

12.5 Patients with AML with unfavorable cytogenetics will be a subset analysis that will include approximately 12 patients. This number is too small for formal hypothesis testing. It will give us some experience with this population of patients and descriptive analysis will be used along with estimation of relapse rate and 95% C.I.

13.0 WOMEN AND MINORITIES GUIDELINES

All eligible patients from both genders and from all racial/ethnic groups will be recruited equally into this trial, with the only exclusionary criteria being those stated in Section 5.0. Based on our patient populations and previous experience with BMT for advanced hematological malignancies, the anticipated rates of entry into this study by gender and race/ethnicity are as follows:

Race/Ethnicity by Gender for Advanced Malignancy Patients Receiving BMT at City of Hope

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or unknown
Female	0%	8%	1%	32%	58%	1%
Male	<1%	8%	3%	33%	54%	3%
Total	<1%	8%	2%	33%	55%	2%

14.0 GUIDELINES FOR REPORTING ADVERSE EVENTS (AE) ADVERSE DRUG REACTIONS ADR OCCURRING WITH COMMERCIAL AGENTS. APPENDIX VIII.

Rev. 11/8/01

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APPENDIX I

IV BUSULFAN KINETICS FORM

IRB#: _____ DATE: _____ (CIRCLE WEIGHT USED)

PATIENT _____ DOSE #_____ Actual Body Weight _____

Medical Record #_____ Start time: _____ Ideal Body Weight _____

MD/Pager # _____ Stop Time: _____ Adjusted IBW _____

Coordinator/Pager #_____ DOSE: _____mg

INFUSION TO RUN OVER 2 HOURS

Tube #	Collection Schedule	Proposed Collection Time	Actual Collection Time
1	Immediately prior to beginning of infusion	APPROX. 0555	
2	Immediately prior to end of infusion	APPROX. 0755	
3	15 minutes post infusion	APPROX. 0815	
4	30 minutes post infusion	APPROX. 0830	
5	60 minutes post infusion (1 hour)	APPROX. 0900	
6	180 minutes post infusion (3 hours)	APPROX. 1100	
7	240 minutes post infusion (4 hours)	APPROX. 1200	

** ALL samples to be obtained in 7cc green top tubes (Sodium Heparin) and kept on ice at Nurses Station.

Then send to Clinical Pathology.

RN SIGNATURE _____

Appendix II

FRACTIONATED TOTAL BODY IRRADIATION SCHEMA

Session	Day	Time	Beam Direction	Energy (MeV)	Dose (rads)	Notes
1	-7	0730	AP	8/10X	120	TLD
			AP	Electron		Testes male (ALL only)
2	-7	1200	AP	Electron	400	TLD
3	-7	1630	PA	8/10X	120	
4	-6	0730	AP	8/10X	120+	(PA Chestwall Boost) 300
5	-6	1200	PA	8/10X	120+	(AP Chestwall Boost) 300
6	-6	1630	AP	8/10X	120	
7	-5	0730	AP	8/10X	120	
			AP	electron	300	Chest wall boost
8	-5	1200	PA	8/10X	120+	(PA Chestwall Boost –300)
9	-5	1630	PA	8/10X	120	
10	-4	0730	PA	8/10X	120	

Photon dose is calculated at mid-depth, central axis. Electron chest wall dose is calculated at 90% isodose level, where electron energy is selected to place 90% isodose level at pleural surface. At the first AP and PA sessions for total body irradiation, portal films with the treatment beam will be obtained prior to treatment to assure proper lung block placement. The x-ray total body irradiation dose given during portal film will be subtracted from the total dose planned for that session. Subsequent placement of lung blocks at the remaining sessions will be documented by verification films obtained during the actual treatment.

During the first AP and PA sessions for total body irradiation, the radiation dose received by the patient will be monitored by means of thermoluminescent dosimeters placed on the anterior surface of the patient's skin at the following anatomic locations: forehead, supra-sternal notch, xiphoid process, umbilicus, pelvis, mid-thigh, knee, mid-calf, and ankle. The midline dose to the patient can be calculated from the sum of entrance and exit doses recorded by the thermoluminescent dosimeter. If thermoluminescent dosimeter indicates a deviation of greater than $\pm$ 10% in the planned dose, either the compensating filter, the machine monitor units, or both may be modified for subsequent sessions.

Appendix III

1). G-CSF Administration to Donors: All donors will receive G-CSF 10 µg/kg/day for 6 consecutive days from day –5 to day 0. G-CSF will be administered by a subcutaneous injection daily beginning 5 days prior to day 0 (defined as the day marrow would ordinarily be given).

2). PBSC Collection: Donors may undergo vein to vein collections or may receive an appropriate catheter inserted on or before day of the treatment regimen. Donors will receive -5 daily doses of G-CSF, 10µg/kg/day by subcutaneous injection commencing on day –5. These doses will be administered each day in the Outpatient Department or at home.

Treatment Schema for Donor

Days	**-5**	**-4**	**-3**	**-2**	**-1**	**0**
G-CSF 10µg/kg/SQ	X	X	X	X	X	
PBSC Collection					X	X

PBSC's will be collected in the afternoon of day -1 and reinfused on day 0. *If the collection on day -1 contains less than 5.0 x 10^6 CD34+ cells per kg recipient weight, a second collection will be performed the following morning and transfused on day 0.

If PBSC's cannot be collected by a vein to vein technique, a percutaneous Mahurkar catheter will be inserted.

General procedures will include the use of a standard apheresis machined (COBE Spectra, Lakewood Colo.), and processing up to 16 l of whole blood during the collection. (Refer to Standard Practice Manual for collection procedure).

APPENDIX IV

Acute Graft Versus Host Disease Staging and Grading Table

Clinical Stage of acute GVHD according to Organ System

Stage	Skin	Liver	Intestine
+	Maculopapular rash <25% of body surface	Bilirubin 2-3mg/dl	>500-1000 ml diarrhea per day or (nausea, anorexia or vomiting with biopsy (EGD) confirmation of upper GI GVHD
++	Maculopapular rash 25-50% of body surface	Bilirubin 3-6mg/dl	>1000-1500 ml diarrhea per day
+++	Maculopapular rash >50% body surface area or Generalized erythroderma	Bilirubin 6-15mg/dl	>1500 ml diarrhea per day
++++	Generalized erythroderma with bullous formation and desquamation	Bilirubin >15mg/dl	>1500 ml diarrhea per day plus severe abdominal pain with or without ileus

Overall Clinical Grading of Severity of acute GVHD

Grade	Skin	Liver	GI
I	1-2	0	0
II[A]	0	0-1	1
	0	1	0-1
	1-3	0-1	1
	1-3	1	0-1
	3	0	0
III[A]	0-3	2-3	0-2
	0-3	0-3	2-3
	0-3	4[B]	0-3
IV[A]	0-3	0-4	4
	4	0-4	0-4

A. Grade II-IV GVHD with only single organ involvement should be biopsy confirmed.
B. If Karnofsky performance status is $\leq$ 30%, then Grade IV.

APPENDIX V

Grading of Chronic Graft Versus Host Disease

Definitions:

Progressive: Direct continuation from preceding acute GVHD.

Quiescent: Arising after complete resolution of acute GVHD.

de Novo: No preceding GVHD.

Subclinical disease: Characteristic pathology findings on both blind oral and skin biopsies in absence of clinical signs or symptoms.

Clinical disease: Multi-organ clinical manifestations and positive skin and oral biopsies

Limited cGVHD: Either or both of the following:

1. Localized skin involvement
2. Hepatic dysfunction due to cGVHD

Extensive cGVHD: Either

1. Generalized skin involvement
2. Localized skin involvement and/or hepatic dysfunction due to chronic GVHD

PLUS

3. Liver histology showing chronic aggressive hepatitis, bridging necrosis or cirrhosis, OR
4. Eye involvement with Schirmer's test with less than 5 mm wetting, OR
5. Positive lip biopsy
6. Involvement of any other target organ

Reference: Chronic Graft Versus Host Disease: Pathology, diagnosis, treatment and prognostic factors, BMT – Exp Hem Today 1988

APPENDIX VI

HD Therapy/Transplant therapy (All testing (except BM bx 4 weeks) has to be completed no more than 28 days prior to starting treatment)

Required studies	Pre admit	Day -17	Day -13	Day -12	Day -11	Day -10	Day -9	Day -8	Day -7	Day -6	Day -5	Day –4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 6	Day 7	Day 100	Day 180	Yearly X 2 years
CBC,Diff, PLT++*	X	X	X	X	X	X				X				X		X	X	X	X	X			X		X
Sma- 7	X	X	X	X	X	X				X				X		X	X	X	X	X			X		X
SMA-12 ++	X	X		X		X								X			X		X				X		X
MG ++	X	X		X		X								X				X							
Hepatitis a,b,c	X																								
HIV	X																								
PT,PTT	X																								
UA	X																								
24hr Crea cl	X																								
Pregnancy test	X																								
CMV,HSV/HZV	X																								
Immunoglobulin	X																								
PFT	X																								
EKG	X																								
++CXR	X																								
CT Scan Chest, ABD	X																								
ECHO or MUGA	X																								
LP see 6.1g	X																								
BM asp, bx, cytogenetics	X																						X		X
Dilantin level			X																						
Busulfan levels			XX		XX* *																				
TREATMENT																									
Dilantin		X	X	X	X	X	X	X	X	X	X	X													
Busulfan			X	**X****	X	X	X	X	X																
FTBI										X	X	X	~~X~~												
VP-16													**X**	~~X~~											
PSC's or BM																X									
CNS Disease patients see section 6.53																									

$ Dilantin will be given daily consecutively until day –14
++ Every Monday, Wednesday, Friday during hospitalization, CXR to be done weekly
XX blood sample shipment

** If required

COMMON TOXICITY CRITERIA (CTC)

Adverse Event	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 adverse event (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
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.					

Adverse Event	Grade 0	1	2	3	4
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 conducive 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.					
CD4 count	WNL	<LLN - 500/mm^3	200 - <500/mm^3	50 - <200/mm^3	<50/mm^3
Haptoglobin	normal	decreased	-	absent	-
Hemoglobic (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
For leukemia studies or bone marrow infiltrative / myelophthisic processes, if specified in the protocol	*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)	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)
Also consider Haptoglobin, Hemoglobin.					

Adverse Event	Grade 0	1	2	3	4
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, if specified in the protocol	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
For pediatric BMT studies (using age, race and sex normal values), if specified in the protocol		*≥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	-
For pediatric BMT studies (using age, race and sex normal values), if specified in the protocol		*≥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 studies, if specified in the protocol	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
For leukemia studies or bone marrow infiltrative/ myelophthisic process, if specified in the protocol	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 - 75,000/mm^3	≥50.0 - <75.0 x 10^9/L ≥50,000 - <75,000/mm^3	≥10.0 - <50.0 x 10^9/L ≥10,000 - <50,000/mm^3	<10.0 x 10^9/L <10,000/mm^3
For BMT studies, if specified in the protocol	WNL	≥50.0 - <75.0 x 10^9/L ≥50,000 - <75,000/mm^3	≥20.0 - <50.0 x 10^9/L ≥20,000 - <50,000/mm^3	≥10.0 - <20.0 x 10^9/L ≥10,000 - <20,000/mm^3	<10.0 x 10^9/L <10,000/mm^3
For leukemia studies or bone marrow infiltrative/ myelophthisic process, if specified in the protocol	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)
For BMT studies, if specified in the protocol	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.

Adverse Event	Grade 0	1	2	3	4
Transfusion: pRBCs	none	-	-	yes	-
For BMT studies, if specified in the protocol	none	≤2 u pRBC in 24 hours elective or planned	3 u pRBC in 24 hours elective or planned	≥4 u pRBC in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
For pediatric BMT studies, if specified in the protocol	none	≤15ml/kg in 24 hours elective or planned	>15 <30ml/kg in 24 hours elective or planned	>30ml/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.					
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	-

Adverse Event	Grade 0	1	2	3	4
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
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.

Adverse Event	Grade 0	1	2	3	4
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).					
Notes: 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
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)	with physiologic consequences	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	-	-
Notes: 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

Adverse Event	0	1	Grade 2	3	4
COAGULATION					
Note: See the HEMORRHAGE category for grading the severity of bleeding events.					
DIC (disseminated intravascular coagulation) Also consider 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
For leukemia studies or bone marrow infiltrative/ myelophthisic process, if specified in the protocol	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	-
Phlebitis 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 studies, if specified in the protocol	-	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, 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) Note: See Appendix III for performance status scales.	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

Adverse Event	Grade 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 (non-malignant).					
Weight gain associated with Veno-Occlusive Disease (VOD) for BMT studies, if specified in the protocol	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascites	≥10% or fluid retention resulting in pulmonary failure
Also consider Ascites, Edema, Pleural effusion (non-malignant).					
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.					
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	-

Adverse Event	Grade 0	1	2	3	4
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.					
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 and 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 and 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 pruritus 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
Also consider Allergic reaction/hypersensitivity.					
Note: Stevens-Johnson syndrome is graded separately as Erythema multiforme in the DERMATOLOGY/SKIN category.					
Rash/dermatitis associated with high-dose chemotherapy or BMT studies	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 and 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
Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol	None	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms	macular or papular eruption or erythema with pruritus 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: Stevens-Johnson syndrome is graded separately as Erythema multiforme in the DERMATOLOGY/SKIN category.					

Adverse Event	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 fasciitis
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, 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
Ascites (non-malignant)	none	asymptomatic	symptomatic, requiring diuresis	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

Adverse Event	Grade 0	1	2	3	4
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 Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis), Hypotension.					
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
Diarrhea associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol: *For pediatric BMT studies, if specified in the protocol:*	None	>500 - ≤1000mL of diarrhea/day *>5 - ≤10 mL/kg of diarrhea/day*	>1000 - ≤1500mL of diarrhea/day *>10 - ≤15 mL/kg of diarrhea/day*	>1500mL of diarrhea/day *>15 mL/kg of diarrhea/day*	severe abdominal pain with or without ileus
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain, Dehydration, Hypotension.					
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)	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
Note: If the adverse event is radiation-relate.., grade either under Dysphagia-esophageal related to radiation or Dysphagia-pharyngeal related to radiation.					
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 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
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

	Grade				
Adverse Event	0	1	2	3	4
Fistula-pharyngeal	none	-	-	present	requiring surgery
Fistula-rectal/anal	none	-	-	present	requiring surgery
Flatulence	none	mild	moderate	-	-
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 Notes: 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 Vaginitis. 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 - pain; includes bleeding not induced by minor trauma or abrasion
Also consider Pain due to radiation. Notes: 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. Note: Amylase is graded in the METABOLIC/LABORATORY category.					
Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis).					

Adverse Event	Grade 0	1	2	3	4
Proctitis	none	increased stool frequency, occasional blood-streaked stool; 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, Pain due to radiation.					
Notes: 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 IV)					
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 prophylactic intubation
For BMT studies, if specified in the protocol	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	-	-
Typhlitis (inflammation of the cecum)	none	-	-	abdominal pain, diarrhea, fever, and radiographic or biopsy 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

Adverse Event	Grade 0	1	2	3	4
HEMORRHAGE					
Notes: 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 grading severity by grading 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: platelets, Transfusion: pRBCs, site or type of bleeding. If the site is not listed, grade as Hemorrhage-Other (Specify site, _____). Note: This adverse event must be graded for any bleeding with grade 3 or 4 thrombocytopenia.					
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: platelets, Transfusion: pRBCs, Hemorrhage - Other (Specify site, _____). 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
Hemorrhage/bleeding associated with surgery	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Note: Expected blood loss at the time of surgery is not graded as an adverse event.					
Melena/GI bleeding	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention

Adverse Event	Grade 0	1	2	3	4
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 associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol	normal	≥1 - <3 mg/100 mL	≥3 - <6 mg/100 mL	≥6 - <15 mg/100 mL	≥15 mg/100 mL
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 Note: Grade Hepatic enlargement only for treatment related adverse event including Veno-Occlusive Disease.	absent			present	
Hypoalbuminemia	WNL	<LLN - 3 g/dL	≥2 - <3 g/dL	<2 g/dL	-
Liver dysfunction/ failure (clinical)	normal	-	-	asterixis	encephalopathy or coma
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)

Adverse Event	Grade 0	1	2	3	4
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C) Also consider Neutrophils. Note: Hypothermia instead of fever may be associated with neutropenia and is graded here.	none	-	-	Present	Life-threatening sepsis (e.g., septic shock)
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L) Also consider Neutrophils. Notes: Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection grade 3 or 4 neutropenia with fever is graded as Febrile neutropenia.	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection with unknown ANC Note: This adverse event criterion is used in the rare case when ANC is unknown.	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection without neutropenia Also consider Neutrophils.	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)
Wound-infectious is graded in the DERMATOLOGY/SKIN category.					
Infection/Febrile Neutropenia - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
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					
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

Adverse Event	Grade 0	1	2	3	4
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 acidosis
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
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, Hyperkalemia.					
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

Adverse Event	Grade 0	1	2	3	4
Muscle weakness (not due to neuropatay)	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 [tenderness or pain in muscles] 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.					
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*

Adverse Event	Grade 0	1	2	3	4
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	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
Note: Syncope (fainting) is graded in the NEUROLOGY category.					
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 th PAIN category.					
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 adverse event 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

Adverse Event	Grade 0	1	2	3	4
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
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)
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) Also consider CARDIOVASCULAR (ARRHYTHMIA), Vasovagal episode, CNS cerebrovascular ischemia.	absent	-	-	present	-

Adverse Event	Grade 0	1	2	3	4
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)
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	-

	Grade				
Adverse Event	0	1	2	3	4
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					
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
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

Adverse Event	Grade 0	1	2	3	4
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
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 flare 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

Adverse Event	Grade 0	1	2	3	4
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	-
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 IV)					
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
Notes: 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

Adverse Event	Grade 0	1	2	3	4
RENAL/GENITOURINARY					
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmodic	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	-
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 dip stick 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

Adverse Event	Grade 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 metastasis from initial primary	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	-
Feminization 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.					
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.					

Adverse Event	Grade 0	1	2	3	4
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., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/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 in the RENAL/GENITOURINARY category.					
Syndromes - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

Adverse Event 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.

Adverse Event:	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 adverse event resolve? If so, date of resolution of adverse event:	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 adverse event not currently in CTC, please provide definitions for adverse event grading:

Grade 0 = _____

Grade 1 = _____

Grade 2 = _____

Grade 3 = _____

Grade 4 = _____

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 _____

Performance Status Scales/Scores

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

Use for adverse event occurring greater than 90 days after radiation therapy.

Adverse Event	Grade 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 mL)	Necrosis/contracted bladder (capacity <100 mL)/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; dilation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilation required	Necrosis/ perforation; fistula
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
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 limitation of movement	Severe joint stiffness; pain with severe limitation of movement	Necrosis/complete fixation
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

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

Use for adverse event occurring greater than 90 days after radiation therapy.

Adverse Event	Grade 0	1	2	3	4
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 or bleeding	Moderate diarrhea and colic; bowel movement >5 x daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/perforation fistula
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
Radiation - Other (Specify, _____)	None	Mild	Moderate	Severe	Life-threatening or disabling

BMT-Specific Adverse Events

Summary of BMT-Specific Adverse Events that may be used if specified by the protocol. These differ from the standard CTC and may be more relevant to the transplant setting. They are listed here for the convenience of investigators writing transplant protocols. They are also included in the CTC document.

		Grade			
Adverse Event	**0**	**1**	**2**	**3**	**4**
Bilirubin associated with graft versus host disease for BMT studies.	normal	≥2 - <3 mg/100 mL	≥3 - <6 mg/100 mL	≥6 - <15 mg/100 mL	≥15 mg/100 mL
Diarrhea associated with graft versus host disease (GVHD) for BMT studies.	none	>500 - ≤1000mL of diarrhea/day	>1000 - ≤1500mL of diarrhea/day	>1500mL of diarrhea/day	severe abdominal pain with or without ileus
Diarrhea for pediatric BMT studies.		*>5 - ≤10 mL/kg of diarrhea/day*	*>10 - ≤15 mL/kg of diarrhea/day*	*>15 mL/kg of diarrhea/day*	-
Hepatic enlargement	absent	-	-	present	-
Leukocytes (total WBC) 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
Leukocytes (total WBC) for pediatric BMT studies (using age, race and sex normal values).		*≥75 - <100% LLN*	*≥50 - <75% LLN*	*≥25 - 50% LLN*	*<25% LLN*
Lymphopenia for pediatric BMT studies (using age, race and sex normal values).	mm^3	*≥75-<100%LLN*	*≥50-<75%LLN*	*≥25-<50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC) for BMT studies.	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
Platelets for BMT studies.	WNL	≥50.0 - <75.0 x 10^9/L ≥50,000 - <75,000/mm^3	≥20.0 - <50.0 x 10^9/L ≥20,000 - <50,000/mm^3	≥10.0 - <20.0 x 10^9/L ≥10,000 - <20,000/mm^3	<10.0 x 10^9/L <10,000/mm^3
Rash/dermatitis associated with high-dose chemotherapy or BMT studies.	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
Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies.	none	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms	macular or papular eruption or erythema with pruritus 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

BMT-Specific Adverse Events

Summary of BMT-Specific Adverse Events that may be used **if specified by the protocol**. These differ from the standard CTC and may be more relevant to the transplant setting. They are listed here for the convenience of investigators writing transplant protocols. They are also included in the CTC document.

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Stomatitis/pharyngitis (oral/pharyngeal mucositis) for BMT studies.	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
Transfusion: Platelets for BMT studies.	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)
Transfusion: pRBCs for BMT studies.	none	≤2 u pRBC in 24 hours elective or planned	3 u pRBC in 24 hours elective or planned	≥4 u pRBC in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
Transfusion: pRBCs for pediatric BMT studies.	*none*	*≤15mL/kg in 24 hours elective or planned*	*>15 - ≤30mL/kg in 24 hours elective or planned*	*>30mL/kg in 24 hours*	*hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin*
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS) for BMT studies.	-	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
Weight gain associated with Veno-Occlusive Disease (VOD) for BMT studies.	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascites	≥10% or fluid retention resulting in pulmonary failure

BMT Complex/Multicomponent Events

Adverse Event	Grade 0	1	2	3	4
Note: The grading of Complex/Multicomponent 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 (adverse events).					
Failure to engraft	absent	mild	moderate	severe	life-threatening
Also consider Hemoglobin, Neutrophils/granulocytes (ANC/AGC), Neutrophils/granulocytes (ANC/AGC) for BMT studies, if specified in the protocol, Platelets, Platelets for BMT studies, if specified in the protocol					
Graft versus host disease	absent	mild	moderate	severe	life-threatening
Also consider Fatigue, Rash/desquamation, Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Diarrhea for patients without colostomy, Diarrhea for patients with colostomy, Diarrhea associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Diarrhea for pediatric BMT studies, if specified in the protocol, Bilirubin, Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol					
Stem cell infusion complications	absent	mild	moderate	severe	life-threatening
Also consider Allergic reaction/hypersensitivity, Conduction abnormality/Atrioventricular heart block, Nodal/junctional arrhythmia/dysrhythmia, Prolonged QTc interval (QTc >0.48 seconds), Sinus bradycardia, Sinus tachycardia, Supraventricular arrhythmias (SVT/atrial fibrillation/flutter), Vasovagal episode, Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ventricular tachycardia), Cardiovascular/Arrhythmia - Other (Specify, _____), Hypertension, Hypotension, Fever (in the absence of neutropenia, where neutropenia is defined as AGC <1.0 x 10^9/L), Rigors/chills, Sweating (diaphoresis), Rash/desquamation, Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Urticaria (hives, welts, wheals), Diarrhea for patients without colostomy, Diarrhea for patients with colostomy, Diarrhea associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Diarrhea for pediatric BMT studies, if specified in the protocol, Nausea, Vomiting, Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hemoptysis, Alkaline phosphatase, Bilirubin, Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, GGT, SGOT (AST), SGPT (ALT), Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L), Infection without neutropenia, Hyperkalemia, Hypernatremia, Hypokalemia, Depressed level of consciousness, Seizures, Abdominal pain, Headache, Creatinine, Hemoglobinuria					
Veno-Occlusive Disease (VOD)	absent	mild	moderate	severe	life-threatening
Also consider Weight gain associated with Veno-Occlusive Disease (VOD) for BMT studies, if specified in the protocol, Bilirubin, Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Depressed level of consciousness, Hepatic pain, Renal failure, Hepatic enlargement					

APPENDIX VIII

GUIDELINES FOR REPORTING OF
ADVERSE EVENTS (AE)/ ADVERSE DRUG REACTIONS (ADR)
OCURRING WITH **COMMERCIAL** AGENTS

1. WITHIN 10 DAYS, SEND TO THE CITY OF HOPE IRB AND DATA SAFETY MONITORING BOARD C/O CPRMC.

a) **A COPY OF THE FDA FORM 3500**

2. IN ADDITION, FOLLOW THE GUIDELINES BELOW

The following guidelines for reporting an AE/ADR apply to this protocol which uses commercial anticancer agents. The following AE/ADR experienced by patients accrued to this protocol and attributed to the commercial agent should be reported:

(a) Any AE/ADR which is life threatening (Grade 4) or fatal (Grade 5) and unknown.[1,2,3] Any occurrence of secondary AML or MDS must also be reported.

(b) Any increased incidence of a known AE/ADR reported in the protocol.

(c) Any AE/ADR which if fatal (Grade 5), even though known.[3]

The AE report, documented on Form FDA-3500 should be mailed to the address below within 10 working days:

or Fax to:
1-800-FDA-0178

Medwatch
5600 Fishers Lane
Rockville, MD 20852-9787

[1] For grading reactions, see App V, VI.

[2] All known toxicities can be found in either the drug Information, Background or in the consent form sections of the protocol.

[3] **A report shall be submitted if there is only a reasonable suspicion of drug effect.**
Reactions judged definitely not treatment related should not be reported, except that all deaths while on treatment or within 30 days after treatment must be reported. Any death more than 30 days after treatment which is felt to be treatment related must also be reported.

Appendix IX

Eligibility Checklist #99041

Inclusion Criteria (circle yes or No)

1. Subject has acute myelogenous or lymphocytic leukemia who are not in first remission or second remission i.e. after failing remission induction therapy or in relapse or beyond second remission, or patients with chronic myelogenous leukemia in blastic phase of the disease are eligible for the study. Patients with refractory anemia with excess blasts and in transformation will be eligible.

   YES **NO**

2. Subject has a HLA (A,B,C,DR) identical siblings who is willing to donate bone marrow for marrow grafting. All ABO blood group combinations of the donor/recipient are acceptable since even major ABO compatibilities can be dealt with by various techniques.

   YES **NO**

3. A cardiac evaluation with electrocardiogram and MUGA or echocardiogram is required in all subjects and must have an ejection fracture of greater than or equal to 50%.

   YES **NO**

4. Subject is older than 16 and the upper age limit are physiological age of 50.

   YES **NO**

5. Subject has a serum creatinine of less than or equal to 1.2 or creatinine clearance > 80ml/min and a bilirubin of less than or equal to 1.5. Subjects should also have an SGOT and SGPT less than 5 times the upper limit of normal.

   YES **NO**

6. The time from the last induction or reinduction attempt is greater than or equal to 28 days.

   YES **NO**

7. Signed informed consent form approved by the IRB.

   YES **NO**

8. Pulmonary function tests including DLCO is performed and FEV_1 and DLCO are greater than 50% of predicted normal value.

YES NO

Donors

9. Is sibling donor histocompatible with the prospective recipient?

YES NO

10. Donor does not have psychological or medical reasons and they are able to tolerate the procedure.

YES NO

Are all answers YES? YES NO

*Note: If all answers have been circled YES then the subject is eligible to go on the study.

Exclusion Criteria

All answers must be NO (circle YES or NO)

11. Prior radiation therapy that will exclude the use of total body irradiation.

NO YES

12. Patients who have undergone bone marrow transplantation previously and who have relapsed.

NO YES

13. Patients with psychological or medical condition that the physician deems unacceptable to proceed to allogeneic bone marrow transplant.

NO YES

Are all answers NO? YES NO

*Note: If all answers were NO then the subject is eligible for study entry

***Note:** If all the answers are not YES or NO in appropriate sections then go over this case with the PI. If the PI approves an eligibility waiver then the reasons why must be documented in the subject's medical record or research record and a protocol deviation form must be filled out. Per regulatory policy, the PI can only make one waiver of the same criteria without amending the study and getting IRB approval prior to entry.

CRA signature_____ Date __/__/__

IRB # 99041 (BU, FTBI, VP-16, BM
Eligibility Checklist

Patient Name:_____ MR#_____

	YES	NO	DATE / RESULT
CONSENT FORM SIGNED?			
All questions must be answered "YES" to be eligible.			
1. Patient has Acute Myelogenous Leukemia or lymphocytic Leukemia who is not in first remission or second remission, i.e. after failing remission induction therapy or in relapse or beyond second remission, or diagnosed with Chronic Myelogenous Leukemia in blastic phase of the disease is eligible. *Patients with refractory anemia with excess blasts and in transformation will be eligible.			
2. Patient has a HLA (A,B,C,DR) identical sibling who is willing to donate bone marrow for marrow grafting. (All ABO blood group combinations of the donor/recipient are acceptable)			
3. Ejection fraction of greater than or equal to 50%.			
4. Patient is older than 16 and the upper age limit are physiological age of 50.			
5. Serum Creatinine of less than or equal to 1.2 or creatinine clearance > 80 ml/min.			
6. Bilirubin of less than or equal to 1.5			
7. SGOT and SGPT less than 5 times the ULN			
8. The time of the last induction or reinduction attempt is greater than or equal to 28 days.			
9. Pulmonary function tests are greater than 50% of predicted normal value.			
10. Is the sibling donor histocompatable wit the recipient			
11. Donor does not have psychological or medical problems and they are able to tolerate the procedure?			
All answers must be answered "NO" to be eligible.			
1. Prior radiation therapy that will exclude the use of total body irradiation.			
2. The patient has undergone bone marrow transplantation previously and who have relapsed.			
3. Patient with psychological or medical condition that the physician deems unacceptable to proceed to ALLO BMT?			
4. Is the patient pregnant or lactating?			
BASELINE TESTS: All testing must be completed 14 days prior to starting treatment.			
CBC, DIFF, PLT			
Complete Chemistry panel			
Magnesium			
Hepatitis panel			
HIV test			
PT, PTT			
Urinalysis			
Pregnancy test			
24 hour creatinine clearance			
CMV			
HSV/HZV			
Immunoglobulin level			
Pulmonary function test			
EKG			
Chest x-ray			
CT Scan of the: a. Chest b. Abdomen			
ECHO or MUGA			
Lumbar puncture (see 6.1g for conditions)			
Bone marrow: * can be done within 4 weeks* a. aspiration b. biopsy c. cytogenetics			

Eligibility completed by (signature & printed):_____
Date completed:_____

After all eligibility has been met, fax this form, the consent form and all outside test results **before** the patient starts treatment to: Kim Gilfillan, CCRA at City of Hope, Dept. of Biostatistics
FAX: 626-256-8736 Telephone: 626-359-8111 ext. 3811

Eligibile: YES / NO **COH CRA SIGNATURE:**

IRB # 99041 (BU, FTBI, VP-16, BMT)
Eligibility Checklist

Patient Name:_____ MR#_____

	YES	NO	DATE / RESULT
CONSENT FORM SIGNED?			
All questions must be answered "YES" to be eligible.			
1. Patient has Acute Myelogenous Leukemia or lymphocytic Leukemia who is not in first remission or second remission, i.e. after failing remission induction therapy or in relapse or beyond second remission, or diagnosed with Chronic Myelogenous Leukemia in blastic phase of the disease is eligible. *Patients with refractory anemia with excess blasts and in transformation will be eligible.			
2. Patient has a HLA (A,B,C,DR) identical sibling who is willing to donate bone marrow for marrow grafting. (All ABO blood group combinations of the donor/recipient are acceptable)			
3. Ejection fraction of greater than or equal to 50%.			
4. Patient is older than 16 and the upper age limit are physiological age of 50.			
5. Serum Creatinine of less than or equal to 1.2 or creatinine clearance > 80 ml/min.			
6. Bilirubin of less than or equal to 1.5			
7. SGOT and SGPT less than 5 times the ULN			
8. The time of the last induction or reinduction attempt is greater than or equal to 28 days.			
9. Pulmonary function tests are greater than 50% of predicted normal value.			
10. Is the sibling donor histocompatable wit the recipient			
11. Donor does not have psychological or medical problems and they are able to tolerate the procedure?			
All answers must be answered "NO" to be eligible			
1. Prior radiation therapy that will exclude the use of total body irradiation.			
2. The patient has undergone bone marrow transplantation previously and who have relapsed.			
3. Patient with psychological or medical condition that the physician deems unacceptable to proceed to ALLO BMT?			
4. Is the patient pregnant or lactating?			
BASELINE TESTS: All testing must be completed 14 days prior to starting treatment.			
CBC, DIFF, PLT			
Complete Chemistry panel			
Magnesium			
Hepatitis panel			
HIV test			
PT, PTT			
Urinalysis			
Pregnancy test			
24 hour creatinine clearance			
CMV			
HSV/HZV			
Immunoglobulin level			
Pulmonary function test			
EKG			
Chest x-ray			
CT Scan of the: a. Chest b. Abdomen			
ECHO or MUGA			
Lumbar puncture (see 6.1g for conditions)			
Bone marrow: * can be done within 4 weeks* a. aspiration b. biopsy c. cytogenetics			

Eligibility completed by (signature & printed):_____
Date completed:_____

After all eligibility has been met, fax this form, the consent form and all outside test results before the patient starts treatment to: Kim Gilfillan, CCRA at City of Hope, Dept. of Biostatistics
FAX: 626-256-8736 Telephone: 626-359-8111 ext. 2811

IRB#: 99041

APPENDIX X

Time points to grade toxicities and collect data.

Day 30 after PBSCT/BMT CTC form.

Day 31 – 100 CTC form and IBMTR booklet.

101 – 365 LT Follow up form.

Every year LT follow up form.