THE UNIVERSITY OF TEXAS
M. D. ANDERSON CANCER CENTER

DIVISION OF MEDICINE

FLUDARABINE, MITOXANTRONE, AND DEXAMETHASONE (FND) PLUS CHIMERIC ANTI-CD20 MONOCLONAL ANTIBODY (RITUXIMAB) FOR STAGE IV INDOLENT LYMPHOMA

STUDY CHAIRMAN: _____
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PROTOCOL ABSTRACT

PROTOCOL: (Abbreviated title) (2 lines/75 characters per line) (USE 12 PT ONLY)

Fludarabine, Mitoxantrone, and Dexamethasone (FND) Plus Anti-CD20 Monoclonal Antibody (rituximab) for Stage IV Indolent Lymphoma

STUDY CHAIRMAN | Peter McLaughlin, MD

OBJECTIVES:

1. To compare molecular response rates with the FND regimen followed by rituximab (chimeric anti-CD20 antibody) and interferon versus FND plus rituximab concurrently, followed by interferon, for patients with stage IV indolent lymphoma.
2. To compare the toxicity of these two regimens, including their effects on B- and T- cell subsets, immunoglobulins, and patterns of infections.
3. To compare failure-free and overall survival rates with these two regimens.
4. To identify and treat with a separate strategy those follicular lymphoma patients without bcl-2 mbr or mcr gene rearrangement ("germline" patients) because of their adverse outcome with FND alone in our prior experience.

RATIONALE: (Be as concise as possible)

For all stage IV indolent lymphomas (with one exception; see Appendix B), the FND regimen appears to be comparable to the more intensive ATT regimen, in terms of remission rates, failure-free survival, and even molecular remission rates. The anti-CD20 monoclonal antibody rituximab is a promising agent with modest toxicities, none of which should overlap with the toxicities of FND. Hence, we propose to combine FND + rituximab, either concurrently or with rituximab as post-FND adjuvant therapy.

ELIGIBILITY: (List Major Criteria)

- Previously untreated stage IV indolent B-cell lymphoma [Amendment May 2001: eligibility restricted to follicular lymphoma]
- Age <76

TREATMENT PLAN:

I. FND

Fludarabine	25 mg/m^2	IV	qd x 3 d1-3	(d2-4 in conjunction with IDEC)
Novantrone	10 mg/m^2	IV	day 1 only	(day 2 only in conjunction with IDEC)
Decadron	20 mg	IV	qd x 5	d1-5

II. Rituximab 375 mg/m^2 per dose

Dosing and schedule integrated with FND (see Section 5.3) or after FND (see section 5.2.3)

III. Interferon alfa-2b maintenance 3 x 10^6 U/m^2/d x 14 days 1-14 of each 28 day maintenance cycle for 12 cycles, with decadron 8 mg qd x 3, days 1-3.
(see Section 5.7.3 for integration of IFN cycles with rituximab)

STATISTICAL CONSIDERATIONS:

The average yearly accrual rate for the current stage IV trial has been 33 patients per year. About 75% of patients can be expected to have a positive PCR. It will take 64 PCR positive patients in each arm to detect a difference of 25% in the twelve month molecular CR rate, assuming that the higher response rate was 85%. This assumes a two-sided alpha level of 0.05 and a power of 0.90.

Allowing for some inevaluable cases, approximately 210 patients will be accrued, which will probably take a little over 5 years.

PATIENT EVALUATION: (Pretreatment and Interim Testing)

	PRE STUDY	WEEKLY	EVERY 2 COURSES	EVERY 3 COURSES	EVERY 6 MONTHS	POST-THERAPY
H&P	X		X			q 3-6 mo
PS	X					
CBC	X	X				q 3-6 mo
U/A	X					
CXR	X					q 3-6 mo‡
SMA 12, K, Mg*	X		X			q 3-6 mo
B2M	X			X		q 3-6 mo
BX/FNA*	X					
BM BX	X			X		q 6 mo‡
LAG, CTs	X			X		q 6 mo‡
PB markers, Ig's	X			X***		
PB PCR	X				X**	
BM PCR	X				X**	
ECHO or MUGA	X					

♣ K, Mg, etc as indicated, mainly for pts on ATT (see App. B)
* when accessible; for phenotype, gene rearrangement
** PCR for bcl-2 q 6 mo yr 1-3, q 12 mo thereafter. Contingency for PCR monitoring at 9 and/or 15 months for selected patients (see 7.2).
*** PB markers, Ig's: until recovery to normal
‡ Restaging off therapy (see section 7.7): at least q 6 mo until relapse or through year 5; then at least yearly

MISCELLANEOUS INFORMATION: (Include any other information that you feel is pertinent to the study) (Three lines not to exceed 75 characters per line)

- PCP prophylasix: TMP/SMX, 2 DS tabs PO twice weekly (q Sat & Sun). For allergy , see section 5.4.3.2
- If PCP pneumonia occurs, subsequent chemotherapy cycles will be given without dexamethasone.

ESTIMATED ACCRUAL:

It is estimated that accrual will be ___2___ participants per month.

SITE OF STUDY: (please circle the appropriate answer)

This protocol is performed on an:

_____INPATIENT ___X___ OUTPATIENT _____ BOTH basis

LENGTH OF STAY: (What is the length and frequency of hospitalization)

RETURN VISITS: (How often must participants come to MDACC)

HOME CARE: (specify what (if any) treatment may be given at home)

WHERE THE STUDY WILL BE CONDUCTED:

A) ONLY AT MDACC B) MDACC + COMMUNITY PROGRAMS (CCOP, NETWORK) C) INDEPENDENT MULTICENTER ARRANGEMENTS

NAME OF SPONSOR/FUNDING SOURCE:

COMPETING PROTOCOLS: (Protocol number(s))

NONE

NAME OF RESEARCH NURSE/DATA MANAGER RESPONSIBLE FOR PROTOCOL:

SUBMIT PROTOCOL TO CLINICAL RESEARCH CENTER REVIEW COMMITTEE:

YES ❑ NO ❑

IF YOUR PROTOCOL HAS A DIAGNOSTIC STEP REQUIRING INFORMED CONSENT AND REGISTRATION ON THE PROTOCOL (E.G., A BLOOD TEST OR BIOPSY) THAT WILL DETERMINE WHETHER OR NOT THE PATIENT WILL SUBSEQUENTLY RECEIVED OR NOT RECEIVED EXPERIMENTAL THERAPY. PLEASE CHECK THE APPROPRIATE BOX(ES) SO THAT THE APPROPRIATE FIELDS MAY BE ESTABLISHED IN PDMS:

BLOOD TEST:	**YES**	**NO**	**BIOPSY:**	**YES**	**NO**	**OTHER:**	**YES**	**NO**

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STUDY CHAIRMAN: _____
Peter McLaughlin, M.D.

1.0 OBJECTIVES

1.1 To compare molecular response rates with the FND regimen followed by rituximab (chimeric anti-CD20 antibody) and interferon versus FND plus rituximab concurrently, followed by interferon, for patients with stage IV indolent lymphoma.

1.2 To compare the toxicity of these two regimens, including their effects on B- and T-cell subsets, immunoglobulins, and patterns of infections.

1.3 To compare failure-free and overall survival rates with these two regimens.

1.4 To identify and treat with a separate strategy those follicular lymphoma patients without bcl-2 mbr or mcr gene rearrangement ("germline" patients) because or their adverse outcome with FND alone in our prior experience.

2.0 BACKGROUND

2.1 The Disease

The indolent lymphomas are characterized by a slow pace, typically by responsiveness to at least the initial therapy, but by inevitable relapse following standard therapy.

The histologic categories that comprise the majority of cases of indolent lymphoma are small lymphocytic lymphoma (SL), follicular small cleaved (FSC), and follicular mixed (FM) lymphoma as defined in the Working Formulation[1]. However, it is notable that the recent Revised European American Lymphoma (REAL) scheme has: (a) created a scheme that more precisely categorizes several subsets of SL, including mantle cell lymphoma (MCL) which is considered <u>not</u> indolent; (b) challenged the concept that follicular large cell lymphoma (FLC) is intermediate grade and classifies FLC (follicle center lymphoma, follicular, grade III) along with the other follicular lymphomas.

Concerning subsets that have previously been categorized as SL: (a) we currently have a separate treatment strategy for MCL; (b) MALT lymphomas, when they present with localized disease, have a separate appropriate treatment strategy; but (c) when the marginal cell lymphomas present with disseminated disease, they are just as relentless as other advanced stage indolent lymphomas[3] and therefore deserve, in our opinion, the same treatment strategy as other advanced stage indolent lymphomas.

Concerning FLC, inter-institutional and inter-pathologist differences in classification are well known for subclassification of follicular lymphomas[4]. At MDACC, the distinction between follicular large non-cleaved versus cleaved lymphoma has been emphasized in recent years[5], the latter being considered indolent and thus eligible for this protocol, while the former is considered aggressive and such cases are triaged to other protocols. It is acknowledged that the distinction among precise cell types among the follicular lymphomas is at times arbitrary. Pertinent to therapy considerations (see below), FLC is unique among the intermediate grade lymphomas in that responsiveness to fludarabine is typically good[6].

An important hallmark of the follicular lymphomas is the t(14;18) translocation which results in bcl-2 gene rearrangement in the majority of cases. Among other things, this breakpoint provides a marker that can be followed by PCR (see below). There is beginning to be evidence that the specific breakpoint site (mbr; mcr) may be prognostically important, and the "germline" (i.e., not mbr or mcr rearranged) cases may do poorly with FND chemotherapy[7]. Accordingly, in this protocol such patients are assigned to a separate treatment strategy

2.2 Chemotherapy Approaches

Using therapy based on alkylating agents such as cyclophosphamide and chlorambucil, depressingly little has changed in survival outcomes in the past 30 years[8]. In the intermediate grade lymphomas, the impact of doxorubicin is compelling[9]; but the impact of the addition of doxorubicin in indolent lymphoma is arguable [9,10]. To date, the impact of interferon (IFN) appears mainly on duration of remission rather than on survival[11]. The purine nucleoside analogs, especially fludarabine, are a new class of drugs that have appeared very promising in indolent lymphoma and chronic lymphocytic leukemia[6]. Fludarabine has been used extensively in relapsed indolent lymphoma, both singly and in combination regimens[6]. At MDACC, the FND regimen has been used successfully in front-line therapy, with early results showing it to be comparable to the more intensive "ATT" regimen[12,13]. One subset of follicular lymphoma for whom FND may be inferior to ATT are those with "germline" status for bcl-2[7].

2.3 PCR for bcl-2

The initial description of the utility of PCR for bcl-2 in detecting the subclinical presence of rearranged cells was here at MDACC. Since then, the role of this assay as a surrogate endpoint and marker of treatment success has generated worldwide interest[15-17].

The attainment of PCR-negativity with any therapy approach except bone marrow transplantation has been difficult[18,19]. In recent years, reversion to PCR-negativity has been accomplished with our "ATT" regimen[13]. Thus, it is possible to explore whether attaining PCR-negativity is a desirable goal that correlates with more durable remission, as has been observed with bone marrow transplantation and *ex vivo* purging[15,19]. Our preliminary results indicate that PCR-negativity does indeed correlate with longer remission following conventional dose chemotherapy[20].

Our recent experience (DM 92-103) with FND has shown that this regimen, too, can induce PCR-negativity[12]. The current protocol is a logical extension of that experience.

2.4 Anti-CD20 Monoclonal Antibody Therapy (rituximab)

Monoclonal antibodies are of tremendous theoretical appeal as therapeutic agents. Our understanding of the expression of surface antigens in B-cell malignancies has led to numerous trials of monoclonal antibodies in B-cell malignacies[21]. Stumbling blocks have been encountered, including the immunogenicity of rodent monoclonal antibodies and the myelosuppressive effects of radioimmunoconjugates.

A chimeric anti-CD20 antibody, rituximab, has emerged as a promising single agent. Since it is predominantly a human protein, host immune responses against the agent have been infrequent. Since it is not conjugated to a toxin or isotope, its spectrum of toxicity is relatively modest. And, most importantly, as a single agent

is has been shown to have promising activity in patients with relapsed B-cell lymphoma[22,23].

Rituximab has been used in conjunction with standard CHOP chemotherapy, with promising early results[24]. Other combination trials, including the current protocol, are planned.

The most extensive experience with rituximab, as a single agent, has utilized a schedule of weekly dosing for four weeks. Its relative lack of immunogenicity suggests that re-treatment or longer-term treatment schedules are feasible. This issue is to be explored in one arm of the current trial.

The experience with rituximab in conjunction with CHOP chemotherapy utilized a total of six doses of the antibody, integrated into the chemotherapy cycles in a fashion similar to the other proposed arm of our current protocol. This integration of rituximab with chemotherapy has already been shown feasible and effective with CHOP. The current protocol will be the initial experience of the integration of rituximab with the FND regimen.

Rituximab appears to be capable of effecting reversion of PCR for bcl-2 in the peripheral blood and bone marrow from positive to negative. Using the antibody alone, the peripheral blood became PCR-negative in 68% and the bone marrow in 50% [23]. In conjunction with CHOP, the peripheral blood became PCR-negative in almost 80% [24]. Since CHOP alone appears to result in PCR-negativity only infrequently, the expectation of higher rates of PCR negativity, coupled with in vitro evidence of synergism between rituximab and some chemotherapeutic agents [25], warrants further experience with concurrent antibody plus chemotherapy.

Given the potential of rituximab to produce, as a single agent, PCR negativity in the blood and marrow [26], and since some chemotherapy-treated patients do <u>not</u> achieve PCR negativity, the adjuvant use of the antibody may result in higher molecular remission rates (although at a later time point than 12 months). This potential for eradication of minimal residual disease, and extrapolation from our previous favorable experience with adjuvant interferon, provide the rationale for the adjuvant antibody strategy.

As previously discussed, a small subset of patients with follicular lymphoma are germline for bcl-2, and our experience suggests that these patients may be prognostically unfavorable, in that an intensive regimen such as ATT appears necessary for best results. For these patients, we propose integration of rituximab with ATT.

3.0 BACKGROUND DRUG INFORMATION

3.1 For fludarabine, mitoxantrone, dexamethasone, interferon alfa-2b (Intron A), and the agents in the CHOD-Bleo/ESHAP/NOPP program, data available on request (713-792-2860).

3.2 Rituximab chimeric anti-CD20 antibody.

3.2.1 Investigational Drug Nomenclature

- IDEC Pharmaceuticals code designation: IDEC-C2B8 (IDEC-102)
- Generic name: Rituximab
- CAS Registry number: 174722-31-7
- IND number: BB-IND 4904

3.2.2 Origin of the IDEC-C2B8 cell line.
The chimeric mouse/human anti-CD20 monoclonal antibody, rituximab (IDEC-C2B8 [IDEC-102]), is a human gamma 1 kappa antibody with mouse variable regions isolated from a murine anti-CD20 monoclonal antibody (2B8). This chimeric antibody, which is secreted by the Chinese hamster ovary (CHO) transfectoma clone 8-8F12-5E5-50C9, binds with high affinity to CD20-positive cells, performs human effector functions in *in vitro* assays, and specifically depletes B cells *in vivo*. The CHO transfectoma was produced by inserting DNA coding for the chimeric immunoglobulin chains into the CHO cell line DG44 by electroporation, and selecting for a clone resistant to G418 (Genetecin) that secreted chimeric immunoglobulin (Clone 8-8F12). Subsequently, the immunoglobulin production was enhanced through selection of a clone resistant to 5 nM methotrexate (MTX) (clone 8-8F12-5E5); Phase I and Phase II material was produced using this clone. Immunoglobulin production was further enhanced through selection of a clone resistant to 50nM MTX (clone 8-8F12-5E5-50C9). Material produced from this clone has been used in a Phase II combination study with CHOP.

3.2.2.1 Development Code: IDEC-C2B8 (IDEC-102)

3.2.2.2 Other Designations: Mouse/human chimeric monoclonal antibody for CD20 antigen; anti-CD20 antibody, chimeric pan-B.

3.2.3 Clinical Formulation
Clinical supplies for this study will be manufactured by either IDEC Pharmaceuticals in San Diego, CA or Genentech Incorporated in South San Francisco, CA.

Rituximab from either source will be provided to the clinical sites packaged in single use 10 mL (100 mg) and 50mL (500 mg) Type I glass vials at a concentration of 10 mg of protein per mL. The product is formulated in 7.35 mg/mL sodium citrate buffer, containing 7 mg/mL polysorbate 80, 9.0 mg/mL sodium chloride and Sterile Water for Injection. The pH is adjusted to 6.5.

Rituximab may be produced by the mammalian (Chinese Hamster Ovary) cell suspension culture in a nutrient medium containing 100 mg/mL of the antibiotic gentamicin. The antibiotic is not detectable in the final product.

3.2.4 Storage
Rituximab for clinical use should be stored in a secure refrigerator at 2-8° C.

3.2.5 Reconstitution and Dilution of rituximab

Using a sterile syringe and a 21 gauge or larger needle, transfer the necessary amount of rituximab from the vial into a partially filled IV pack containing sterile, pyrogen-free 0.9% Sodium Chloride, USP (saline solution). The final concentration of Rituximab should be approximately 1 mg/mL. Mix by inverting the bag gently.

For lots 0122-0125 the final preparation should be administered through a 0.22 micron low-protein binding in line filter, such as IMED 9216, into the outflow port of the bag containing the infusion solution. For other lots this will not be required.

Caution should be taken during the preparation of the drug. (See Appendix I). Parenteral drug products should be inspected visually for particulate matter prior to administration, Preparations of rituximab containing visible particles should note be used. As with all parenteral drug products, aseptic procedures should be used during the preparation and administration of rituximab.

NOTE: DO NOT USE A VACUUM APPARATUS to transfer rituximab from the syringe to the infusion pack. DO NOT USE evacuated glass container which require vented administration sets, because this causes foaming when air bubbles pass through the solution.

3.2.6 Product Administration

In calculating body surface area, actual height and weight should be used, that is, there will be no downward adjustment to "ideal" weight. Dosage calculations for all treatments will be calculated using the patient's body surface area as determined during the screening evaluation. The dose level of rituximab will not be adjusted.

3.2.7 Pre-Clinical Experience

Rituximab (IDEC-102) is a chimeric IgG1 kappa monoclonal antibody, with mouse variable and human constant regions, that recognizes the CD20 antigen expressed on normal B cells and most malignant B-cell lymphomas[1]. The antigen, important in cell cycle initiation and differentiation, is expressed strongly in over 90% of B-cell lymphomas. Rituximab shows specificity for the CD20 antigen and binds with an apparent affinity of 5.2×10^{-9}M.

In vitro mechanism of action studies have demonstrated that this antibody binds human complement and lyses lymphoid B cell lines. It has significant activity in assays for antibody-dependent cellular cytotoxicity (ADCC). High dose safety studies in cynomolgus monkeys revealed a decrease in platelet levels between 7 and 33% at the two higher doses on day 1 with recovery between days 7 and 14. A reduction in white blood cells between 13 and 31% was seen in 5 of 6 monkeys studied with recovery beginning by day 8. In 4 of 6 monkeys at 12 to 34% decrease in segmented neutrophils was observed; recovery occurred by day 14 in one animal. Hematologic changes were not dose-dependent. In this study and during other rituximab testing in cynomolgus monkeys, vomiting

was noted in a minority of monkeys. Dose levels of 20 mg/kg weekly for up to eight weeks showed no significant adverse reactions, toxicological events or any abnormal histopathology. The biologic effect of four weekly doses of rituximab in cynomolgus monkeys resulted in B-cell depletion in peripheral blood (PB), lymph nodes (LN) and bone marrow (BM). Three weeks after 4 weekly doses there was a >75% decrease of B cells in the bone marrow. Recovery of the B cells in the peripheral blood (to >75% of baseline) usually occurred within 60 days following the last dose.

3.2.8 Clinical Experience

Previous clinical trials have shown that outpatient therapy with rituximab, completed within 22 days, is safe and effective in the treatment of patients with relapsed low-grade/follicular non-Hodgkin's lymphoma.

Phase I/II Trials

Two previous Phase I/II dose-escalation studies of rituximab were conducted (IDEC Protocols 102-01 and 102-02) in patients with relapsed or recurrent non-Hodgkin's lymphoma [Maloney, 1994#1537;[3]. Fifteen patients were enrolled in a single-dose study (IDEC 102-01), (10 to 500 mg/m^2 of rituximab) and 47 patients in a multiple-dose study (IDEC 102-02) (125, 250, or 375 mg/m2 once weekly times four). Clinical activity was noted in seven of 15 patients in the single-dose trial with two partial responses lasting 8.1 and 8.5 months, and five minor responses lasting between 0.9 and 6 months. In the multiple-dose study, three complete responses and 14 partial responses were noted in 34 evaluable patients (375 mg/m^2 rituximab) with a median response duration of 8.6 months. Median time to progression (TTP) in responders was 10.2 months; TTP exceeded 20 months in five patients, two of whom have ongoing responses of 30+ months. No correlation between pharmacokinetic parameters clinical response was apparent in the single-dose study; however, a positive correlation was observed between clinical response and antibody serum levels prior to the second infusion in the multiple-dose study.

Overall, adverse experience were mostly Grades 1 and 2 and consisted primarily of infusion-related events (fever, asthenia, chills, headache, and less commonly, bronchospasm, hypotention and agioedema[subjective sensation of tongue and throat swelling). Hematologic toxicity was usually mild and reversible. In both trials, a rapid an selective depletion of circulating B-cells was observed following treatment. In the Phase I/II study, mean serum immunoglobulin levels remained stable, although some patients experienced transient reductions of IgOs. In both studies, it was concluded that intravenous infusions of rituximab appeared safe and well tolerated and demonstrated significant activity in patients with relapsed B-cell lymphoma.

Phase III Open-Label Trial

A Phase III multicenter trial completed patient entry in March 1996 with a total enrollment of 166 patients [4]. Treatment consisted of weekly x four infusions at 375 mg/m^2. Analysis revealed that adverse events (AE) were primarily related to first infusion and consisted of fever, chills, nausea, and headache. There was a marked reduction in the incidence of AEs in

subsequent infusions. Overall, 6% of all events (72 of 1163) observed during study treatment and follow-up were Grade 3 and 4, and of those, 3% (39 of 1163) were related to study treatment. There were no incidences of human antichimeric antibody (HACA) during this trial. (The overall incidence of HACA in over 300 patients participating in all rituximab trials has been <1% and HACA was not clinically significant in those in whom it occurred).

Ninety-one percent of patients (151 of 166) were evaluable for efficacy and achieved an overall response rate of 50% with 6% CR and 44% of PR. The onset of response was as early as even weeks and responses were seen in patients with bulky and extranodal disease. CT scans of responders were reviewed and confirmed (blinded audit) by an independent panel of lymphoma experts following established response criteria. Median time to progression for responders had not been reached with 9+ months median follow-up.

4.0 ELIGIBILITY

4.1 Previously untreated patients, younger than 76 years old, with stage IV follicular lymphoma (including follicular large cleaved cell) or small lymphocytic lymphoma. [Amendment May 2001: Eligibility for last 25-30 patients restricted to <u>follicular</u> lymphoma (see section 10.2)]

4.1.1 Patients with chronic lymphocytic leukemia (absolute lymphocyte count >5000 μL) are excluded.

4.1.2 Patients with divergent histologies (intermediate grade in one site and low grade in another) will not be eligible.

4.1.3 It is known that there can be a continuum of histologies, spanning elements of indolent and aggressive. While patients with truly divergent histologies are specifically excluded (see 4.1.2), other variants can be eligible, as follows:

- F + DSC* - eligible.
- F + DM* - eligible.
- Sclerosing SCCL or mixed cell - eligible (even if follicular architecture not definite)
- Follicular large <u>non</u>cleaved cell -- the distinction between this entity and follicular large cleaved can be arbitrary and is of debatable significance. But it has been our practice to treat follicular large <u>non</u>cleaved as an intermediate grade lymphoma. Hence, if eligible, such patients should be treated on the appropriate intermediate grade protocol. However, both FND and rituximab have established efficacy in FLCL (without regard to cleaved or not), so if a patient is not eligible for an intermediate grade protocol (e.g., because of SCCL in the marrow), then registration on this trial is permitted.
- FSC or FM with areas of FLC – eligible.
- FSC or FM with areas of DLC – <u>not</u> eligible unless reviewed with P.I. and an addendum on the pathology report is issued stating that the disease is best categorized as an indolent lymphoma.

*- in F & D cases, any extent of follicular architecture is traditionally accepted, but in cases that are > 75% diffuse, please review with P.I. and Pathology as for 4.1.3 (f) above.

4.2 Patients must sign an informed consent indicating that they are aware of the invitational nature of the study, in keeping with the policies of the hospital.

4.3 Ineligible patients are:

4.3.1 Patients who are unable or unlikely to be able to adhere to the treatment plan or to return to Houston for follow-up visits because of geographical, economic, emotional, or social considerations are not eligible for this study.

4.3.2 Patients with an absolute peripheral granulocyte count of < 1,000 and platelet count < 100,000 unless due to marrow infiltration or hypersplenism.

4.3.3 Patients with hepatic dysfunction, defined as bilirubin of > 1.5 mg%, unless the alteration is due to lymphoma.

4.3.4 Patients with a serum creatinine level >1.5 mg% unless the alteration is due to lymphoma.

4.3.5 Patients with HIV infection should not be registered on this protocol.

4.3.6 Pts with an antecedent malignancy whose prognosis is poor (< 90% probability of surviving for 5 yrs).

4.3.7 All patients should have a cardiac ejection fraction of ≥ 50% by echocardiography or MUGA. If a patient without cardiac symptoms has an aberrant low LVEF (< 50%), please consult cardiology and discuss with P.I.

4.3.8 Patients who will not accept transfusions of blood products or supportive care measures such as antibiotics are not eligible for this study.

4.3.9 Female patients must not be pregnant or lactating, and men and women of reproductive potential must follow accepted birth control methods.

4.4 Additional safety guidelines for use of interferon (see Appendix F): These considerations are not exclusions to eligibility since:

(1) Some abnormalities might change before IFN maintenance, e.g., organ dysfunction related to disease might likely improve with treatment; or
(2) some guidelines, e.g., a history of depression, might mitigate against IFN but would not exclude the patient's being treated on protocol with all the other elements of the program.

Please discuss any concerns about IFN with the P.I.

5.0 TREATMENT PLAN

5.1. All patients must be registered with Data Management at 792-2926. They will be interviewed first by the Research Nurse before registration.

5.1.1 Follicular lymphoma patients who are known not to have bcl-2 gene rearrangement will not be randomized -- they will proceed directly to therapy with the ATT regimen (see Appendix B).

If there is no threatening disease and the clinician judges that it is safe to wait for the bcl-2 data, the initiation of therapy may be delayed (This is encouraged.)

However, if therapy is needed, it will not be delayed just for the bcl-2 report. If bcl-2 status is not known or pending, patients will be randomized. If, after therapy with FND begins, a patient is found to be germline for bcl-2, the patient will be crossed over to ATT (see strategy outline in Appendix B).

5.1.2 Randomization will be stratified for: tumor mass size < 5 cm vs. ≥ 5 cm; age < 60; FLC histology; SL histology; and suitability for the watch-and-wait policy followed at other institutions.

5.2 ARM 1 (delayed anti-CD20 arm) will consist of consecutive courses of Fludarabine/Mitoxantrone/Dexamethasone (FND), followed by rituximab.

Agent	Dose	Days	Route	Time	Total Dose
Fludarabine	25 mg/m^2	1-3	IV	15 min	75 mg/m^2
Mitoxantrone	10 mg/m^2	1	IV	15 min	10 mg/m^2
Decadron	20 mg	1-5	IV or PO	15 min	100 mg

5.2.1 Duration of therapy and intervals between courses:

a) The courses should be repeated every 28 days according to recovery from myelosuppression.

b) The total length of treatment will be 8 courses unless cumulative myelosuppression is encountered, in which case the treatment will be finished after 6 courses. Cumulative myelosuppression is defined as recovery of granulocytes to ≥ 1,000 or platelets to >100,000 requiring more than 6 weeks.

5.2.2 Patients older than 60 years will receive full doses of chemotherapy. Anyone experiencing delayed recovery of granulocyte counts (>35 days) or neutropenic fever will be candidates for G-CSF (Neupogen), with the chemotherapy doses adjusted down one dose level. The G-CSF dose will consist of 300 mcg total dose daily, subcutaneously. The dose can be increased to 480 mcg daily at the clinician's discretion.

5.2.3 Rituximab Adjuvant Therapy
Starting at 12 months, after collection of the 12-month PCR samples (Sec 7.2), rituximab will be given monthly for 6 doses total.

The dose will be 375 mg/m^2 IV. Interferon maintenance will usually have commenced about 3-4 months before the rituximab doses start. When IFN and rituximab doses are given in the same month, the rituximab dose will be given first, with decadron permitted (but not mandatory) and the IFN will begin on day 2 of each cycle, or may be delayed for 1-2 days if needed (see 5.7.3).

When rituximab is given by itself (without IFN), decadron 8 mg IV or PO as a pre-medication is permitted but not mandatory (and see also 5.4).

5.3 ARM 2 (concurrent anti-CD20 arm) will consist of FND in conjunction with rituximab. Rituximab will be given on days 1 and 8 of course 1, then on day 1 only of courses 2-5, as outlined below:

- course 1:
  rituximab 375 mg/m^2 d.1 & 8 IV
  (see section 5.4 for details of administration)
  fludarabine 25 mg/m^2 d. 2-4 IV
  mitoxantrone 10 mg/m^2 d.2 IV
  dexamethasone 20 mg d. 1-5 IV or PO
  (note dexamethasone starts a day earlier than in the usual FND schedule, so that the first dose of rituximab is given in conjunction with steroid)

- courses 2-5:
  rituximab 375 mg/m^2 d.1 IV
  (see section 5.4 for details of administration)
  fludarabine 25 mg/m^2 d. 2-4 IV
  mitoxantrone 10 mg/m^2 d.2 IV
  dexamethasone 20 mg d. 1-5 IV or PO
  (note dexamethasone starts a day earlier than in the usual FND schedule, so that the first dose of rituximab is given in conjunction with steroid)

- courses 6 - 8:
  same as for arm 1 (i.e., FND without concurrent rituximab) -- see Section 5.2, especially 5.2.1 and 5.2.2 concerning interval (q28 d), guidelines for use of G-CSF (applicable for all courses), and guidelines for omitting courses 7 & 8 if there is cumulative myelosuppression

5.4 Details Pertaining to Rituximab Administration

5.4.1 Rituximab Dose

All patients enrolled into the study will receive fixed doses of rituximab at 375 mg/m^2. In calculating body surface area, actual height and weight should be used, that is, there will be no downward adjustment to "ideal" weight. Dosage for all treatments will be calculated using the patient's body surface area as determined during the baseline evaluation. The dose level of rituximab will not be adjusted thereafter.

5.4.2 Method of Administration

CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

Rituximab infusions will be administered to patients in an outpatient clinic setting. To decrease the incidence of infusion-related adverse events, oral premedication (650 mg of acetaminophen and 25-50 mg diphenhydramine hydrochloride) may be administered prior to starting

each infusion of rituximab. Decadron 8 mg IV or PO is also permitted. A peripheral or central intravenous (IV) line will be established. During the rituximab infusion, the patient's vital signs (blood pressure, pulse, respiration, temperature) should be monitored every 15 minutes x 4 or until stable and then hourly until the infusion is discontinued.

Available at the bedside prior to rituximab administration will be:

(a) epinephrine for subcutaneous injection;
(b) diphenhydramine hydrochloride for intravenous injection; and
(c) resuscitation equipment for the emergency management of anaphylactoid reactions.

The initial dose rate at the time of the first rituximab infusion should be 50 mg/hr for the first hour. If no toxicity is seen, the dose rate may be escalated gradually (50 mg/hr increments at 30-minute intervals) to a maximum of 400 mg/hr. If the first dose of rituximab is well tolerated, the starting flow rate for the administration of subsequent doses will be 100 mg/hour then increased gradually (100 mg/hr increments at 30-minute intervals) not to exceed 400 mg/hr.

Since transient hypotention has been reported during rituximab infusions, consideration should be given to withholding anti-hypertensive medications the day of the rituximab infusion. Patients may experience transient fever and rigors with rituximab. When these side effects are noted, the antibody infusion should be temporarily slowed or discontinued, the patient should be observed, and the severity of the side effects should be evaluated. The patient should be treated according to the best available local practices and procedures. Following observation, when the patient's symptoms improve, the infusion should be continued, initially at 1/2 the previous rate and gradually escalated to a maximum rate of 300 mg/hour (see table below). Following the antibody infusion, the IV line should be kept open for medications, as needed. If there are no complications, the IV line may be discontinued after one hour of observation. If complications occur during the rituximab infusion, the patient should be observed for two hours after the completion of the infusion.

In patients with detectable circulating lymphoma cells, it is strongly advised that the initial rate of infusion be reduced to 25 mg/hr. Patients with detectable circulating cells may experience more frequent and severe transient fever and rigors, shortness of breath, and hypotension with rituximab. When these side effects are noted, the antibody infusion should be temporarily slowed or discontinued, the patient should be observed, and the severity of the side effects should be evaluated. The patient should be treated according to the best available local practices and procedures. Following observation, when the patient's symptoms improve, the infusion should be continued, initially at 1/2 the previous rate and gradually escalated to a maximum rate of 300 mg/hour (see table below). Subsequent infusions may be carried out at a gradually increased infusion rate of up to 400 mg/hr maximum. If the first dose of rituximab

is well tolerated, the starting flow rate for the administration of subsequent doses will be 100 mg/hr then increased gradually.

Following the antibody infusion, the IV line should be kept open for medications, as needed. If there are no complications, the IV line may be discontinued after one hour of observation. If complications occur during the rituximab infusion, the patient should be observed for two hours after the completion of the infusion.

Dose Rate	Fever	or	Rigors	or	Mucosal congestion/ Edema	or	Drop in Systolic BP
Decrease to 1/2	> 38.5°C		Mild Moderate		Mild Moderate		> 30 mm Hg

5.4.3 Adverse Clinical Events - see Appendix E

5.5 Prophylaxis for Pneumocystis Carinii

5.5.1 all patients will receive prophylaxis with trimethoprim-sulfa (TMP/SMX) as follows:
Two DS tablets twice weekly on Saturday and Sunday.

5.5.2 for TMP/SMX allergy, patients will receive pentamidine aerosol therapy: 300 mg q 4 weeks using a Respigard II neubulizer

5.5.3 for any problems, please consult PI and/or ID

5.6 Dose Modification Guidelines

5.6.1 Recommended Guidelines for Hematological Toxicity

Lowest granulocyte	Lowest platelet	Modification
> 1000 and	>100,000	Increase one level
>200 but <1000 or <200 for ≥ days	>20,000 but <100,000	No change
<200 for > 5 days and/or	<20,000	Decrease one level
Documented infection with neutropenia	Mucosal bleeding	Decrease one level

5.6.2 For All Other Toxicities (see Appendix D)

Grade 0-2	No Change
3	Decrease one level
4	Stop Treatment

5.6.3 All courses will be held pending hematologic recovery to granulocytes >1,000 and platelets >100,000, and non-hematologic toxicities to grade <1.

5.6.4 Dose levels for FND

Level	-2	-1	0	+1
Fludarabine (qd x 3)	16/m^2	20/m^2	25/m^2	30/m^2
Mitoxantrone (d.1)	6.4/m^2	8/m^2	10/m^2	12/m^2
Dexamethasone (qd x 5)	20 mg	20 mg	20 mg	20 mg

5.7 Interferon alfa-2b (Intron A) Maintenance

5.7.1 After completion of FND ± rituximab, patients will receive interferon alfa-2b (Intron A) maintenance.

5.7.2 Maintenance (for CR, PR, and "CRu" patients)

day	1	2	3	4-14	
Dexamethasone (mg)	8	8	8	-	} Repeat q mo
Interferon (x 10^6 u/m^2)	3	3	3	3	} for 12 cycles

5.7.3 IFN maintenance schedule for these receiving rituximab adjuvant therapy on delayed anti-CD20 arm:.

The IFN will start 1 month after the final FND course. Usually this will be before 12 months, i.e., before rituximab maintenance for patients on the delayed anti-CD20 arm.

When IFN and rituximab are given in the same month, the schedule will be as follows (see also 5.2.3):

day	1	2$^+$	3	4-15
rituximab (mg/m^2)	375	-	-	-
dexamethasone (mg)	8*	8	8	-
Interferon alfa (x 10^6 u/m^2)	-	3	3	3

* decadron pre-med is optional but encouraged
\+ day 2 if possible, but delay of 1-2 days permitted between rituximab and IFN

5.7.4 Dose Modification Guidelines for Interferon

Level	-2	-1	0	+1
Interferon (x 10^6 u/m^2)	1	2	3	5

Interferon guidelines for hematologic toxicity same as for chemotherapy (see 5.6.1). For non hematologic toxicity:

Grade	
0-1	Increase 1 level if appropriate (escalation anticipated to be done infrequently)
2	No change
3	Decrease 1 level
4	Hold treatment; discuss with study chairman

6.0 PRETREATMENT EVALUATION (SEE APPENDIX A)

6.1 A complete history and physical to include performance status, recent weight loss, current weight and concurrent non-malignant disease and therapy. Detailed information on existing malignant lesions and sizes is required, within 2 weeks before starting therapy.

6.2 Laboratory studies shall include a CBC, platelet count, differential, urinalysis, chest x-ray, creatinine, electrolyte, bilirubin, SGOT, alkaline phosphate, and peripheral blood lymphocyte surface markers, LDH, assay for soluble CD20 if possible, and B2 microglobulin levels, to be done within 2 weeks before starting therapy.

6.3 Appropriate studies should be obtained to define fully the extent of disease. Bilateral bone marrow biopsy, chest x-ray and CAT scan of the area(s) of involvement should be performed within 2 months before therapy (within 1 month preferably, especially if there is any clinical evidence of rapidly changing adenopathy). Lymphangiogram is recommended but is optional. The measurements of masses detected by CT scan ideally should be recorded as the volume in cubic centimeters, or as the perpendicular diameters. All other masses should be recorded as the perpendicular diameter.

6.4 Baseline blood and bone marrow aspirates will be obtained for bcl-2 PCR. Contact our research nurse to make these arrangements, at the same time that eligibility screening is done. Please make these contacts early, so that candidate patients can have these studies done in a timely and efficient manner.

6.5 Immunophenotyping and gene rearrangement studies (PCR studies for bcl-2 mbr and mcr; and JH for bcl-2 negative patients) also should be performed on lymph node tissue, whenever possible. For fresh tissue obtained here, please arrange, through our research nurse, to have the sample triaged appropriately.

For biopsies done outside, prior to referral here, please arrange, through our research nurse, to have this archival tissue analyzed by Dr. Mederios.

For cases whose diagnosis is based on limited tissue sample (e.g., FNA), it is strongly encouraged to obtain more tissue. Please discuss such cases with the P.I., if it is felt that treatment plans need to proceed despite suboptimal diagnostic material.

If fresh tissue is obtained, please also perform nucleic acid flow cytometry, if possible.

6.6 Required tests include ejection fraction by echocardiography or MUGA to be performed as baseline. Smokers as well as those with any significant history of pulmonary disease should also have pulmonary function testing. These should be done within 3 months before starting therapy.

6.7 Location, type and size of all measurable or evaluable lesions must be recorded prior to treatment.

7.0 EVALUATION DURING STUDY (SEE APPENDIX A)

7.1. Patients shall be followed at least weekly with CBC, platelet count and differential and will be seen in our clinic after the second and fourth courses.

7.2 PCR in the peripheral blood will be followed every 6 months during the first 3 years, then every 12 months. PCR in the bone marrow will be followed every 6 months during the first 3 years, and every 12 months subsequently. For patients who are positive at the 6 month time point an additional PCR assay at 9 months is requested. For such patients who are still positive at 9 months, but who are subsequently negative at 12 months, yet another additional assay at 15 months is requested.

7.3 An SMA-12 shall be performed at least every other course or as frequently as needed to define drug toxicity.

7.4 Peripheral blood lymphocyte surface markers and Ig's every 3 months during therapy, and at least every 6-12 months off therapy until any abnormalities resolve.

7.5. Appropriate restaging every 3 courses, to include at least CXR, CT abdomen and pelvis, and BM Bx, and other tests to assess baseline measurable and assessable disease sites.

7.6 Cardiac re-evaluation as clinically indicated.

7.7 Off therapy monitoring should include restaging assessments (as outlined in section 7.5) at least every 6 months until relapse, or through year 5, and at least yearly thereafter.

8.0 CRITERIA FOR RESPONSE AND TOXICITY

8.1 Tumor Measurements

a. Lesions will be measured bidimensionally in centimeters prior to each course of therapy. Masses detected by CT may be measured volumetrically in cubic centimeters.

b. The longest diameter and its perpendicular will be measured on bidimensionally measured lesions. Size will be reported as the product of the diameters.

c. Measurements should be made by the radiologist and/or clinician and recorded by the oncology research nurse under his/her supervision.

d. An estimate of overall objective and subjective response will be made and recorded at each visit.

8.2 Response Definitions:

I. A molecular complete remission is defined as a patient with an initially positive peripheral blood PCR who converts to negative on at least 2 consecutive occasions no less than 2 months apart. If, during the interval when 2 consecutive blood PCR's are negative, a marrow PCR is positive, such patients would not be considered a molecular complete responder. (Such cases of discordance are infrequent but can occur).

II. Clinical CR: defined as those who achieve a normal state which includes no detectable evidence of disease on x-rays.

III. Clinical CRu: defined as "CR unconfirmed" on the basis of minimal residual abnormalities on x-ray such as a residual mass <25% of original measurement (either by volume calculation or by the product of 2 diameters -- See Sect. 8.1) with no palpable disease on physical examination.

IV. Clinical PR: a) 50-75% reduction in the product of palpable tumor diameters of in the tumor volume measurements by radiologic criteria (See Sect. 8.1) or any palpable disease such as peripheral node(s) > 1 cm in diameter or palpable abdominal mass with histological evidence of lymphoma cells.

V. Clinical minor response or failure includes, <50% tumor shrinkage or > 50%, but with tumor regrowth between courses.

8.3 All toxicities encountered during the study will be evaluated according to the grading system (0-4) in Appendix D and recorded prior to each course of therapy. Duration and treatment will be recorded. Life-threatening toxicities should be reported immediately to the Study Chairman.

9.0 CRITERIA FOR REMOVAL FROM THE STUDY

9.1 Minor responses or failures to respond after delivering the first 4 courses of treatment in this protocol will be removed from the study.

9.2 Patients who relapse after achieving remission will be considered for ABMT or if not eligible will be treated with he salvage protocol of highest priority.

10.0 STATISTICAL CONSIDERATIONS

10.1 Design:
The study will consist of a randomized controlled trial comparing two schedules of the anti-CD20 antibody rituximab, integrated with an established effective front-line chemotherapy program, FND. The primary endpoint will be the molecular complete response rate 12 months after the start of treatment. Since molecular response requires 2 consecutive negative PCR's (see 8.2, part I), a 12-month negative PCR will be considered truly negative only if a 9 or 15 month (or both) are also negative.

10.2 Accrual Rate:
The average yearly accrual rate during the past 4 years on the current low grade lymphoma stage IV clinical trial has been 33 patients per year. Previous experience at M.D. Anderson Hospital has shown that the PCR positivity rate in these stages is in the neighborhood of 60% when tested with the mbr probe only. If the mcr probe is added, approximately 75% of patients can be expected to have a positive PCR at the time of diagnosis. Accrual of the target 128 evaluable patient (see 10.3 e) will therefore take just over 5 years (estimated 5 years, 2 months). Allowing for some inevaluable cases (9% on protocol 88-050), a total accrual of about 185 patients is planned. [Amendment May 2001: Planned accrual changed to 210 patients, with restriction of eligibility to <u>follicular lymphoma only</u> for the last 25-30 patients, so that adequate numbers are entered to fulfill the goal outlined in 10.3.a below. This amendment results from higher-than-expected numbers of patients with small lymphocytic (including MALT) lymphoma being entered.]

10.3 Adequacy of Sample Size:
Preliminary experience with the intensive regimen (CHOD-B/ESHAP/NOPP) has shown that a molecular CR rate in the neighborhood of 60-65% can be expected. Preliminary evidence indicates that a similar fraction of patients achieve molecular CR with FND.

An additional impact of rituximab is anticipated, since rituximab, when used singly, is capable of achieving blood and marrow molecular response, and rituximab has been integrated with CHOP chemotherapy with attainment of more molecular responses than would be expected with CHOP alone. Both the rapidity of attaining PCR-negative status, and the durability of the PCR-negative state, are additional molecular endpoints of interest. Thus, we intend to address if:

a. the addition of biotherapy with chimeric anti-CD20 antibody to FND chemotherapy can induce a higher molecular response rate at 12 months than FND alone. This is the primary endpoint of this trial. The delayed administration of anti-CD20 given after 12 months, as in arm #1, will allow us to investigate this point. Sixty-four PCR-positive patients would be required in each arm to detect a difference of 25% in the 12-month molecular CR rates, assuming that the higher response rate was 85%. This assumes a two-sided α level of 0.05 and a power of 0.90.

b. the addition of biotherapy with anti-CD20 to FND chemotherapy (arm #2) is capable of inducing a higher molecular response rate at 6 months, as well as the 12 month primary endpoint, when compared with FND chemotherapy alone (arm #1).

c. the addition of delayed anti-CD20 biotherapy after 12 months will then raise the molecular response rate at 18 months as compared with 12 months in the same patient. We will also compare the molecular response at 18 months with patients randomized to arm #2 (concurrent therapy) at the same timepoint.

d. either of the two arms is associated with a more prolonged or sustained molecular response (as measured at 2 years from initiation of chemotherapy).

e. the FFS of patients in the concurrent arm is different from the delayed arm. This is the secondary efficacy endpoint for which we can expect information on a reasonable time frame. (For survival, long-term follow-up is intended, but mature data requires 5-10 years follow-up -- which serves to emphasize the need to identify reliable surrogate endpoints). A 3-year FFS of 50% with standard therapy is typical. Assuming one FND plus rituximab scheme matches this standard expectation, and the other exceeds it by 20%, the trial will have power of 0.66 to detect a difference of this size at significance level of 0.05. This assumes that 128 patients will be entered at the rate of two patients per month, that FFS is distributed exponentially, and that all patients will be followed for a minimum of one year. Nonetheless, this data will: (a) be an important endpoint to correlate with the molecular remission data; and (b) hopefully provide hypothesis-generating information for future, larger-scale trials.

10.4 Other Statistical Considerations

a) Another secondary aim is to compare response rates, both CR (clinical CR plus CRu -- see Section 8.2) and CR + PR. It is anticipated to be high (approximately 80% CR and >90% CR + PR) in both arms; therefore it is unlikely that there will be significant differences between arms.

b) Molecular response rates will be compared to CR and CR + PR rates.

c) Other secondary aims, which are to compare the 5 year disease-free survival and overall survival for these 2 treatments, and to correlate the molecular complete remission rate with these endpoints, will require longer follow up. To attain these goals, we will follow the patients for at least 5 years to determine if a difference develops in disease-free survival. It might take 10 years or more of follow-up to establish statistically significant survival trends.

d) Patients who are PCR negative will also be entered in this trial. These are of 2 categories: (a) "germline" follicular lymphoma; and (b) DSL (i.e., not follicular lymphoma).

Our preliminary data indicates that "germline" follicular patients have not done as well with FND as with ATT, so they will receive ATT, with rituximab. This will be a small number of patients (about 15% of follicular patients, i.e., about 16 patients on DM92-103), for whom analysis will be mainly descriptive. Likewise for DSL, which also will be a small subset of patients (24 in 4 1/2 years on DM92-103), traditional endpoints, including CR, PR, FFS, and survival will be used.

11.0 DATA AND PROTOCOL MANAGEMENT

11.1 Protocol Compliance: The attending physician and oncology research nurse must see each patient at least every 2-3 cycles. All required interim and pretreatment data should be available and the physician must have made a designation as to tumor response and toxicity grade.

11.2 Data Entry: Data must be entered into the Clinical Data Management System. A brief explanation for required but missing data should be recorded as a comment.

11.3 Accuracy of Data Collection: The Study Chairman will be the final arbiter of response of toxicity should a difference of opinion exist.

12.0 REPORTING REQUIREMENTS

12.1 Any life-threatening and/or unexpected and serious (Grade 3 or 4) toxicity will be reported immediately to the Study Chairman who, in turn, must notify the Surveillance Committee and the sponsoring agency. Genentech Judith Canham 650-225-1000 x2330, Fax 650-225-4101.

13.0 REFERENCES:

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APPENDIX A

ACTIVITY FLOW CHART

	PRE STUDY	WEEKLY	EVERY 2 COURSES	EVERY 3 COURSES	EVERY 6 MONTHS	POST-THERAPY
H & P	X		X			q 3-6 mo
PS	X					
CBC	X	X				q 3-6 mo
U/A	X					
CXR	X					q 3-6 mo‡
SMA 12, K, MG♣	X		X			q 3-6 mo
B2M	X			X		q 3-6 mo
BX/FNA*	X					
BM BX	X			X		q 6 mo‡
LAG, CTs	X			X		q 6 mo‡
PB markers, Ig's	X			X***		
PB PCR	X				X**	
BM PCR	X				X**	
ECHO or MUGA	X					

♣ K, Mg, etc as indicated, mainly for pts on ATT (see App. B)
* when accessible; for phenotype, gene rearrangement
** PCR for bcl-2 q 6 mo yr 1-3, q 12 mo thereafter. Contingency for PCR monitoring at 9 and/or 15 months for selected patients (see 7.2)
*** PB markers, Ig's: until recovery to normal
‡ Restaging off therapy (see section 7.7): at least q 6 mo until relapse or through year 5; then at least yearly.

APPENDIX B

MANAGEMENT STRATEGY FOR FOLLICULAR LYMPHOMA PATIENTS WHO DO NOT HAVE BCL-2 MBR OR MCR GENE REARRANGEMENT ("GERMLINE" PATIENTS).

I. Since these patients appear to have an inferior outcome with FND compared courses to ATT, these patients will receive ATT, 9 courses total, and all will also receive rituximab, 6 doses total. This will include d.1 and 8 doses of rituximab during the first cycles of CHOD-Bleo and NOPP (but not ESHAP) courses, and d.1 only during the second cycles of CHOD-Bleo and NOPP.

All "germline" patients will also receive interferon maintenance, as outlined for FND + rituximab patients (see 5.7).

Since the bcl-2 status may not be available prior to starting therapy, some will have received one (or rarely two) cycles of FND, with or without rituximab, prior to crossover to ATT. In such cases, the final chemotherapy cycle of the ATT sequence (NOPP) will be omitted, so that the total number of chemotherapy cycles is nine.

If the patient had been randomized to receive FND + rituximab and thus already received doses of rituximab, the subsequent courses of ATT, with d.1 and 8 IDEC during each CHOD-Bleo and NOPP course, should complete all 6 planned doses of rituximab (see scenario B below). For any patient who does not complete nine courses of chemotherapy, any missed doses of rituximab can be completed after the last chemotherapy cycle.

If the patient had been randomized to receive FND without rituximab, see scenario C.

Scenarios:
A. When the bcl-2 status is known before therapy (i.e., those patients who are not randomized -- see section 5.1.1):

course 1:	CHOD-Bleo, plus rituximab d. 1 & 8
course 2:	ESHAP
course 3:	NOPP, plus rituximab d.1 & 8
course 4:	CHOD-Bleo, plus rituximab d.1 only
course 5:	ESHAP
course 6:	NOPP, plus rituximab d.1 only
courses 7-9:	CHOD-Bleo; ESHAP; NOPP (No more rituximab)

B. If patient had been randomized, and got FND with rituximab:

course 1:	FND + rituximab d. 1 & 8
course 2:	CHOD-Bleo, plus rituximab d.1 & 8
course 3:	ESHAP
course 4:	NOPP, plus rituximab d.1 & 8
course 5:	CHOD-Bleo without rituximab
course 6:	ESHAP
courses 7-9:	NOPP; CHOD-Bleo; ESHAP (No more rituximab)

C. If patient had been randomized, and got FND without rituximab:

course 1:	FND
course 2:	CHOD-Bleo, plus rituximab d. 1 & 8
course 3:	ESHAP
course 4:	NOPP, plus rituximab d. 1 & 8
course 5:	CHOD-Bleo, plus rituximab d. 1 & 8
course 6:	ESHAP
courses 7-9:	NOPP; CHOD-Bleo; ESHAP (no more rituximab)

For any questions about this sequence, consult P.I.

For all cycles given in conjunction with rituximab, the steroid will start on d. 1 along with the rituximab, and the remainder of the chemotherapy will start one day later than standard, analogous to the modified schedule of FND as outlined in Section 5.

II. ATT doses and schedule (with rituximab in CHOD-Bleo and NOPP courses):

1. Initial Dosing Regimen for CHOD-Bleo:

Agent	Dose	Days	Route	Time	Total Dose
Rituximab	375 mg/m^2	1 & 8	IV	approx 4 hr (Sec 5. 4)	750 mg/m^2
Adriamycin	25 mg/m^2/day	2-3	IV-CI	48 hrs	50mg/m^2
Oncovin	0.7 mg/m^2/day	2-3	IV-CI	48 hrs	1.4 mg/m^2
Bleomycin	5 u/m^2/day	2-3	IV-CI	48 hrs	10 u/m^2
Cytoxan	750 mg/m^2	2	IVPB	15 min	750 mg/m^2
Dexamethasone	40 mg/day	1-4	p.o.	--	160 mg

2. Initial Dosing Regimen for ESHAP:

Agent	Dose	Days	Route	Time	Total Dose
Etoposide	40 mg/m^2 (daily)	1-4	IV	30 min	160 mg/m^2
Cisplatin	25 mg/m^2 (daily)	1-4	IV-CI	96 hrs	100 mg/m^2
Ara-C	1.5 gm/m^2 (single dose)	5	IV	2 hrs	1.5 gm/m^2
Solu Medrol	500 mg (daily)	1-5	IV	15 min	2500 mg

3. Initial Dosing Regimen for NOPP:

Agent	Dose	Days	Route	Time	Total Dose
Rituximab	375 mg/m^2	1 & 8	IV	approx 4 hr (Sec 5.4)	750 mg/m^2
Novantrone	10 mg/m^2 (single dose)	2	IV	15 min	10 mg/m^2
Oncovin	1.4 mg/m^2	2	IVPB	15 min	1.4 mg/m^2
Procarbazine	100 mg/m^2	2-11	p.o.	--	1000 mg/m^2
Prednisone	100 mg	1-5	p.o	--	500 mg

III. Dose modifications related to myelotoxicity.

1. For CHOD-Bleo

Dose Level:	-2	-1	0	1
Adriamycin (total dose)	35 mg/m^2	40 mg/m^2	50 mg/m^2	60 mg/m^2
Cytoxan	500 mg/m^2	600 mg/m^2	750 mg/m^2	1000 mg/m^2
Oncovin (total dose)	1.4 mg/m^2	1.4 mg/m^2	1.4 mg/m^2	1.4 mg/m^2
Bleomycin (total dose)	10 u/m^2	10 u/m^2	10 u/m^2	10 u/m^2
Dexamethasone (daily dose)	40 mg	40 mg	40 mg	40 mg

2. For ESHAP

Dose Level:	-2	-1	0	1
Etoposide (daily dose)	25 mg/m^2	30 mg/m^2	40 mg/m^2	50 mg/m^2
Cisplatin (daily dose)	16 mg/m^2	20 mg/m^2	25 mg/m^2	25 mg/m^2
Ara-C x1	0.5 mg/m^2	1 g/m^2	1.5 mg/m^2	2 g/m^2
Solu Medrol (daily dose)	500 mg	500 mg	500 mg	500 mg

3. For NOPP

Dose Level:	-2	-1	0	1
Novantrone	6 mg/m^2	8 mg/m^2	10 mg/m^2	12 mg/m^2
Oncovin	1.4 mg/m^2	1.4 mg/m^2	1.4 mg/m^2	1.4 mg/m^2
Procarbazine (daily dose)	60 mg/m^2	80 mg/m^2	100 mg/m^2	120 mg/m^2
Prednisone (daily dose)	100 mg	100 mg	100 mg	100 mg

IV. Recommended Dose Modification Guidelines

1. For Hematologic Toxicity -- see Section 5.6
2. For Renal Toxicity

Serum Creatinine (mg%)		Creatinine Clearance (cc/min)	Modification of Cisplatin
0.6 - 1.4	or	> 75	None
1.5 - 2.0	or	60 - 74	33% reduction
2.1 - 2.5	or	40 - 59	50% reduction
>2.5 - 4.0	or	<39	Delete*

* Cisplatin could be given at 25% dose, after consultation with Study Chairman, if renal failure is secondary to lymphoma.

APPENDIX C

PERFORMANCE STATUS SCALES

Karnofsky Performance Scale (1)

Point	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self, unable to carry on normal activity or to do active work
60	Requires occasional assistance, but able to care for most of own needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization indicated. Death not imminent
20	Very sick, hospitalization indicated. Death not imminent
10	Moribund, fatal processes, progressing rapidly
0	Dead

Zubrod Performance Scale (2)

Point	Description
0	Normal activity; asymptomatic
1	Symptomatic; but ambulatory
2	Symptomatic; in bed 50% of time
3	Symptomatic; in bed 50% of time; not bedridden
4	100% bedridden
5	Dead

REFERENCES

1. Karnofsky, D.A: Meaningful Clinical Classification of Therapeutic Responses to Anti-Cancer Drugs. Editorial. Clin. Pharmacol and Therapeutics 2:709-712, 1961.

2. Stanley, K.E.: Prognostic Factors for Survival in Patients with Inoperable Lung Cancer. J. Natl. Can. Inst. 65:25-32, 1980.

APPENDIX D

NCI COMMON TOXICITY CRITERIA

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

Toxicity	Grade 0	1	2	3	4
Earache is graded in the PAIN category.					
External auditory canal	normal	external otitis with erythema or dry desquamation	external otitis with moist desquamation	external otitis with discharge, mastoiditis	necrosis of the canal soft tissue or bone
Note: Changes associated with radiation to external ear (pinnae) are graded under Radiation dermatitis in the DERMATOLOGY/SKIN category.					
Inner ear/hearing	normal	hearing loss on audiometry only	tinnitus or hearing loss, not requiring hearing aid or treatment	tinnitus or hearing loss, correctable with hearing aid or treatment	severe unilateral or bilateral hearing loss (deafness), not correctable
Middle ear/hearing	normal	serous otitis without subjective decrease in hearing	serous otitis or infection requiring medical intervention; subjective decrease in hearing; rupture of tympanic membrane with discharge	otitis with discharge, mastoiditis or conductive hearing loss	necrosis of the canal soft tissue or bone
Auditory/Hearing-Other (Specify, _____)	normal	mild	moderate	severe	life-threatening or disabling
BLOOD/BONE MARROW					
Bone marrow cellularity	normal for age	mildly hypocellular or 25% reduction from normal cellularity for age	moderately hypocellular or >25 - ≤ 50% reduction from normal cellularity for age or >2 but <4 weeks to recovery of normal bone marrow cellularity	severely hypocellular or >50 - ≤ 75% reduction in cellularity for age or 4 - 6 weeks to recovery of normal bone marrow cellularity	aplasia or >6 weeks to recovery of normal bone marrow cellularity
Normal ranges: children (≤ 18 years)	90% cellularity average				
younger adults (19-59)	60-70% cellularity average				
older adults (≥ 60 years)	50% cellularity average				
Note: Grade Bone marrow cellularity only for changes related to treatment not disease.					
CD4 count	WNL	< LLN - 500/mm^3	200 - < 500/mm^3	50 - < 200/mm^3	< 50/mm^3

Toxicity	0	Grade 1	2	3	4
Haptoglobin	normal	decreased	-	absent	-
Hemoglobin (Hgb)	WNL	< LLN - 10.0 g/dl < LLN - 100 g/L < LLN - 6.2 mmol/L	8.0 - < 10.0 g/dl 80 - < 100 g/L 4.9 - < 6.2 mmol/L	6.5 - < 8.0 g/dl 65 - 80 g/L 4.0 - < 4.9 mmol/L	< 6.5 g/dl < 65 g/L < 4.0 mmol/L
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic processes	WNL	10 - <25% decrease from pretreatment	25 - <50% decrease from pretreatment	50 - <75% decrease from pretreatment	≥75% decrease from pretreatment
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other)	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, Hgb.					
Leukocytes (total WBC)	WNL	< LLN - 3.0 x 10^9/L < LLN - 3000/mm^3	≥2.0 - < 3.0 x 10^9/L ≥2000 - < 3000/mm^3	≥1.0 - < 2.0 x 10^9/L ≥1000 - < 2000/mm^3	< 1.0 x 10^9/L < 1000/mm^3
For BMT studies:	WNL	≥2.0 - <3.0 X 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9/L ≥1000 - <2000/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	<0.5 x 10^9/L <500/mm^3
Note: The following criteria using age, race and sex normal values may be used for pediatric studies if the protocol so specifies.					
		≥75 - <100% LLN	*≥50 - <75% LLN*	*≥25 - 50% LLN*	*<25% LLN*
Lymphopenia	WNL	<LLN - 1.0 x 10^9/L <LLN - 1000/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	<0.5 x 10^9/L <500/mm^3	-
Note: The following criteria using age, race, and sex normal values may be used for pediatric studies if the protocol so specifies.					
		≥75-<100%LLN	*≥50-<75%LLN*	*≥25-<50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC)	WNL	≥1.5 - <2.0 x 10^9/L ≥1500 - <2000/mm^3	≥1.0 - <1.5 x 10^9/L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	< 0.5 x 10^9/L < 500/mm^3
For BMT:	WNL	≥1.0 - <1.5 x 10^9/L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	≥0.1 - <0.5 x 10^9/L ≥100 - <500/mm^3	<0.1 x 10^9/L <100/mm^3
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					

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

Toxicity	Grade 0	1	2	3	4
For BMT: Also consider Platelets.	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: Also consider Hemoglobin.	none none	- ≤2 u pRBC (≤*15cc/kg*) in 24 hours elective or planned	- 3 u pRBC (>*15* ≤*30cc/kg*) in 24 hours elective or planned	Yes ≥4 u pRBC (>*30cc/kg*) in 24 hours	- hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve 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)

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
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	-

Toxicity	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

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Edema	none	asymptomatic, not requiring therapy	symptomatic, requiring therapy	symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation	anasarca (severe generalized edema)
Hypertension	none	asymptomatic, transient increase by >20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	recurrent or persistent or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	requiring therapy or more intensive therapy than previously	hypertensive crisis
**Note: For pediatric patients, use age and sex appropriate normal values > 95th percentile ULN.*					
Hypotension	none	changes, but not requiring therapy (including transient orthostatic hypotension)	requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Also consider Syncope (fainting). Note: Angina or MI is graded as Cardiac- ischemia/infarction in the CARDIOVASCULAR (GENERAL) category. *For pediatric patients, systolic BP 65 mmHg or less in infants up to 1 year old and 70 mmHg or less in children older than 1 year of age, use two successive or three measurements in 24 hours.*					
Myocarditis	none	-	-	CHF responsive to treatment	severe or refractory CHF
Operative injury of vein/artery	none	primary suture repair for injury, but not requiring transfusion	primary suture repair for injury, requiring transfusion	vascular occlusion requiring surgery or bypass for injury	myocardial infarction; resection of organ (e.g., bowel, limb)
Pericardial effusion/ pericarditis	none	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and/or chest pain)	physiologic consequences resulting from symptoms	tamponade (drainage or pericardial window required)
Peripheral arterial ischemia	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., amputation)

Toxicity	Grade 0	1	2	3	4
Phlebitis (superficial)	none	-	present	-	-
Note: Injection site reaction is graded in the DERMATOLOGY/SKIN category. Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Syncope (fainting) is graded in the NEUROLOGY category.					
Thrombosis/embolism	none	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the CARDIOVASCULAR (GENERAL) category.					
Visceral arterial ischemia (non-myocardial)	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., resection of ileum)
Cardiovascular/ General-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
COAGULATION					
Note: See the HEMORRHAGE category for grading the severity of bleeding events.					
DIC (disseminated intravascular coagulation) Also grade Platelets.	absent	-	-	laboratory findings present with no bleeding	laboratory findings and bleeding
Note: Must have increased fibrin split products or D-dimer in order to grade as DIC.					
Fibrinogen	WNL	≥0.75 - <1.0 x LLN	≥0.5 - <0.75 x LLN	≥0.25 - <0.5 x LLN	<0.25 x LLN
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies:	WNL	<20% decrease from pretreatment value or LLN	≥20 - <40% decrease from pretreatment value or LLN	≥40 - <70% decrease from pretreatment value or LLN	<50 mg%
Partial thromboplastin time (PTT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Phelbitis is graded in the CARDIOVASCULAR (GENERAL) category.					
Prothrombin time (PT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS)	absent	-	-	laboratory findings present without clinical consequences	laboratory findings and clinical consequences, (e.g., CNS hemorrhage / bleeding or thrombosis/ embolism or renal failure) requiring therapeutic intervention
For BMT:	-	evidence of RBC destruction (schistocytosis) without clinical consequences	evidence of RBC destruction with elevated creatinine (≤3 x ULN)	evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy
Also consider Hemoglobin (Hgb), Platelets, Creatinine. Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).					
Coagulation-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia)	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities	bedridden or disabling
Note: See Appendix III for performance status scales.					

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

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

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

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

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

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

Toxicity	Grade 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 Note: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginititis. Radiation-related mucositis is graded as Mucositis due to radiation.					
Mucositis due to radiation	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally ≤ 1.5 cm in diameter and non-contiguous)	confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
Also consider Pain due to radiation. Note: Grade radiation mucositis of the larynx here. Dysphagia related to radiation is also graded as either Dysphagia- esophageal related to radiation or Dysphagia- pharyngeal related to radiation, depending on the site of treatment.					
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-

Toxicity	Grade 0	1	2	3	4
Pancreatitis	none	-	-	abdominal pain with pancreatic enzyme elevation	complicated by shock (acute circulatory failure)
Also consider Hypotension. Note: Asymptomatic amylase and Amylase are graded in the METABOLIC/LABORATORY category.					
Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Proctitis	none	increased stool frequency, occasional blood-streaked stools, or rectal discomfort (including hemorrhoids), not requiring medication	increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	increased stool frequency/diarrhea, requiring parenteral support; rectal bleeding, requiring transfusion; or persistent mucus discharge, necessitating pads	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, and Pain due to radiation. Note: Fistula is graded separately as Fistula- rectal/anal. Proctitis occurring more than 90 days after the start of radiation therapy is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. (See Appendix 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 prophylatic intubation
For BMT:	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia

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

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

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

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

Toxicity	Grade 0	1	2	3	4
Infection without neutropenia	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)
Infection/Febrile Neutropenia-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
Wound-infectious is graded in the DERMATOLOGY/SKIN category.					
LYMPHATICS					
Lymphatics	normal	mild lymphedema	moderate lymphedema requiring compression; lymphocyst	severe lymphedema limiting function; lymphocyst requiring surgery	severe lymphedema limiting function with ulceration
Lymphatics-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
METABOLIC/LABORATORY					
Acidosis (metabolic or respiratory)	normal	pH < normal, but ≥7.3	-	pH < 7.3	pH < 7.3 with life-threatening physiologic consequences
Alkalosis (metabolic or respiratory)	normal	pH > normal, but ≤7.5	-	pH > 7.5	pH > 7.5 with life-threatening physiologic consequences
Amylase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	>5.0 x ULN
Bicarbonate	WNL	< LLN - 16 mEq/dl	11 - 15 mEq/dl	8 - 10 mEq/dl	< 8 mEq/dl
CPK (creatine phosphokinase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5 x ULN	> 5 - 10 x ULN	> 10 x ULN
Hypercalcemia	WNL	> ULN - 11.5 mg/dl > ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dl > 2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dl > 3.1 - 3.4 mmol/L	> 13.5 mg/dl > 3.4 mmol/L
Hypercholesterolemia	WNL	> ULN - 300 mg/dl > ULN - 7.75 mmol/L	> 300 - 400 mg/dl > 7.75 - 10.34 mmol/L	> 400 - 500 mg/dl >10.34 - 12.92 mmol/L	> 500 mg/dl > 12.92 mmol/L
Hyperglycemia	WNL	> ULN - 160 mg/dl > ULN - 8.9 mmol/L	> 160 - 250 mg/dl > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dl > 13.9 - 27.8 mmol/L	> 500 mg/dl > 27.8 mmol/L or ketoacidosis

Toxicity	Grade 0	1	2	3	4
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, Potassium.					
Hypocalcemia	WNL	<LLN - 8.0 mg/dl <LLN - 2.0 mmol/L	7.0 - < 8.0 mg/dl 1.75 - < 2.0 mmol/L	6.0 - < 7.0 mg/dl 1.5 - < 1.75 mmol/L	<6.0 mg/dl < 1.5 mmol/L
Hypoglycemia	WNL	<LLN - 55 mg/dl <LLN - 3.0 mmol/L	40 - < 55 mg/dl 2.2 - < 3.0 mmol/L	30 - < 40 mg/dl 1.7 - < 2.2 mmol/L	< 30 mg/dl < 1.7 mmol/L
Hypokalemia	WNL	<LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L
Hypomagnesemia	WNL	<LLN - 1.2 mg/dl <LLN - 0.5 mmol/L	0.9 - <1.2 mg/dl 0.4 - < 0.5 mmol/L	0.7 - < 0.9 mg/dl 0.3 - < 0.4 mmol/L	< 0.7 mg/dl < 0.3 mmol/L
Hyponatremia	WNL	<LLN - 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
Hypophosphatemia	WNL	<LLN -2.5 mg/dl <LLN - 0.8 mmol/L	≥2.0 - <2.5 mg/dl ≥0.6 - <0.8 mmol/L	≥1.0 - <2.0 mg/dl ≥0.3 - <0.6 mmol/L	< 1.0 mg/dl <0.3 mmol/L
Hypothyroidism is graded in the ENDOCRINE category.					
Lipase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Metabolic/Laboratory-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
MUSCULOSKELETAL					
Arthralgia is graded in the PAIN category.					
Arthritis	none	mild pain with inflammation, erythema or joint swelling but not interfering with function	moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living	severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living	disabling

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

Toxicity	Grade 0	1	2	3	4
Cognitive disturbance/ learning problems	*none*	*cognitive disability; not interfering with work/school performance; preservation of intelligence*	*cognitive disability; interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones*	*cognitive disability; resulting in significant impairment of work/school performance; cognitive decline > 2 SD*	*inability to work/frank mental retardation*
Confusion	normal	confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living	confusion or delirium interfering with activities of daily living	harmful to others or self; requiring hospitalization
Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.					
Delusions	normal	-	-	present	toxic psychosis
Depressed level of consciousness	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 the 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 toxicity is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia.					

Toxicity	Grade 0	1	2	3	4
Irritability (children <3 years of age)	*normal*	*mild; easily consolable*	*moderate; requiring increased attention*	*severe; inconsolable*	-
Leukoencephalopathy associated radiological findings	*none*	*mild increase in SAS (subarachnoid space) and/or mild ventriculomegaly; and/or small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or < 1/3 of susceptible areas of cerebrum*	*moderate increase in SAS; and/or moderate ventriculomegaly; and/or focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum*	*severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)*	*severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)*
Memory loss	normal	memory loss not interfering with function	memory loss interfering with function, but not interfering with activities of daily living	memory loss interfering with activities of daily living	amnesia
Mood alteration-anxiety agitation	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-depression	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
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

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
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	-

Toxicity	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	-

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Vision- blurred vision	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- double vision (diplopia)	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- flashing lights/floaters	normal	mild, not interfering with function	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- night blindness (nyctalopia)	normal	abnormal electro-retinography but asymptomatic	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- photophobia	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Ocular/Visual-Other (Specify, _____)	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)
			PAIN		
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.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
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

	Grade				
Toxicity	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

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

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest, requiring supplemental oxygen	decreased O_2 saturation, requiring pressure support (CPAP) or assisted ventilation
Pleural effusion (non-malignant)	none	asymptomatic and not requiring treatment	symptomatic, requiring diuretics	symptomatic, requiring O_2 or therapeutic thoracentesis	life-threatening (e.g., requiring intubation)
Pleuritic pain is graded in the PAIN category.					
Pneumonitis/pulmonary infiltrates	none	radiographic changes but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation
Pneumothorax	none	no intervention required	chest tube required	sclerosis or surgery required	life-threatening
Pulmonary embolism is graded as Thrombosis/embolism in the CARDIOVASCULAR (GENERAL) category.					
Pulmonary fibrosis	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	requiring steroids or diuretics	requiring oxygen	requiring assisted ventilation
Note: Radiation-related pulmonary fibrosis is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme- Lung. (See Appendix 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
Note: Cough from radiation is graded as cough in the PULMONARY category. Radiation-related hemoptysis from larynx/pharynx is graded as Grade 4 Mucositis due to radiation in the GASTROINTESTINAL category. Radiation-related hemoptysis from the thoracic cavity is graded as Grade 4 Hemoptysis in the HEMORRHAGE category.					
Pulmonary-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

Toxicity	Grade 0	1	2	3	4
			RENAL/GENITOURINARY		
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmotic	severe symptoms requiring narcotic	-
Creatinine	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Note: Adjust to age-appropriate levels for pediatric patients.					
Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	-
Fistula or GU fistula (e.g., vaginal, vesicovaginal)	none	-	-	requiring intervention	requiring surgery
Hemoglobinuria	-	present	-	-	-
Hematuria (in the absence of vaginal bleeding) is graded in the HEMORRHAGE category.					
Incontinence	none	with coughing, sneezing, etc.	spontaneous, some control	no control (in the absence of fistula)	-
Operative injury to bladder and/or ureter	none	-	injury of bladder with primary repair	sepsis, fistula, or obstruction requiring secondary surgery; loss of one kidney; injury requiring anastomosis or re-implantation	septic obstruction of both kidneys or vesicovaginal fistula requiring diversion
Proteinuria	normal or < 0.15 g/24 hours	1+ or 0.15 - 1.0 g/24 hours	2+ to 3+ or 1.0 - 3.5 g/24 hours	4+ or > 3.5 g/24 hours	nephrotic syndrome
Note: If there is an inconsistency between absolute value and uristix reading, use the absolute value for grading.					
Renal failure	none	-	-	requiring dialysis, but reversible	requiring dialysis and irreversible
Ureteral obstruction	none	unilateral, not requiring surgery	-	bilateral, not requiring surgery	stent, nephrostomy tube, or surgery
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	none	asymptomatic, not requiring treatment	mild, reversible and manageable with oral replacement	reversible but requiring IV replacement	irreversible, requiring continued replacement
Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia.					
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x normal	increase > 2 x normal but < hourly	hourly or more with urgency, or requiring catheter	-

Toxicity	Grade 0	1	2	3	4
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
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 metastastic tumors	none	-	-	-	present
SEXUAL/REPRODUCTIVE FUNCTION					
Dyspareunia is graded in the PAIN category.					
Dysmenorrhea is graded in the PAIN category.					
Erectile impotence	normal	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for intercourse)	no erections	-
Female sterility	normal	-	-	sterile	-
Femininization of male is graded in the ENDOCRINE category.					
Irregular menses (change from baseline)	normal	occasionally irregular or lengthened interval, but continuing menstrual cycles	very irregular, but continuing menstrual cycles	persistent amenorrhea	-

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

Toxicity Module

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

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

Additional Comments:

_____

_____

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

Grade 0 = _____
Grade 1 = _____
Grade 2 = _____
Grade 3 = _____
Grade 4 = _____

Infection Module

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

1. Use the Common Toxicity Criteria definitions to grade the severity of the infection.
2. Specify type of infection from the following (CHOOSE ONE):

   BACTERIAL FUNGAL PROTOZOAL VIRAL UNKNOWN

3. Specify site of infection from the following (CHOOSE ALL THAT APPLY):
   BLOOD CULTURE POSITIVE
   BONE INFECTION
   CATHETER (intravenous)
   CATHETER (intravenous), tunnel infection
   CENTRAL NERVOUS SYSTEM INFECTION
   EAR INFECTION
   EYE INFECTION
   GASTROINTESTINAL INFECTION
   ORAL INFECTION
   PNEUMONIA
   SKIN INFECTION
   UPPER RESPIRATORY INFECTION
   URINARY TRACT INFECTION
   VAGINAL INFECTION
   INFECTION, not otherwise specified (Specify site, _____)
4. Specify organism, if known: _____.
5. Prophylactic antibiotic, antifungal, or antiviral therapy administration
   Yes_____ No_____
   If prophylaxis was given prior to infection, please specify below:

   Antibiotic prophylaxis _____

   Antifungal prophylaxis _____

   Antiviral prophylaxis _____

   Other prophylaxis _____

APPENDIX E

DISPENSING AND OTHER INFORMATION FOR IDEC-C2B8 (Rituximab)

DESCRIPTION: IDEC-C2B8 is a mouse/human chimeric antibody. The IDEC-C2B8 antibody is produced by a Chinese hamster ovary transfectoma.

RECOMMENDED PREPARATION AND ADMINISTRATION:

1) Refer to the clinical trial protocol for details about the dose and dose schedule.

2) Storage:
IDEC-C2B8 should be stored at 2-8 °C. Do not freeze or store at room temperature. The products is a protein -- HANDLE GENTLY AND AVOID FOAMING. The avoidance of foaming during product handling, preparation and administration is important, as foaming may lead to the de-naturing of the product proteins.

3) All transfer procedures require strict adherence to aseptic techniques, preferably in a laminar flow hood.

4) Reconstitution and Dilution of IDEC-C2B8 (rituximab):

   a. Refrigerate (2-8 °C) all materials and solutions prior to use.

   b. Use sterile, non-pyrogenic, disposable containers, syringes, needles, stopcocks and transfer tubing, etc.

   c. Using a sterile syringe and a 21 gauge or larger needle, transfer the necessary amount of rituximab from the vial into a partially filled IV pack containing sterile, pyrongen free 0.9% Sodium Chloride, USP (saline solution). The final concentration of rituximab should be approximately 1 mg/mL. Mix by inverting the bag gently.

      For lots 0122-0125 the final preparation should be administered through a 0.22 micron low-protein binding in line filter, such as IMED 9216, into the outflow port of the bag containing the infusion solution. For other lots this will not be required.

      Caution should be taken during the preparation of the drug. (see Appendix I). Parental drug products should be inspected visually for particulate matter prior to administration, Preparations of rituximab containing visible particles should note be used. As with all parenteral drug products, aseptic procedures should be used during the preparation and administration of rituximab.

      NOTE: DO NOT USE A VACUUM APPARATUS to transfer IDEC-C2B8 from the syringe to the infusion pack. DO NOT USE evacuated glass container which require vented administration sets, because this causes foaming when air bubbles pass through the solution.

5) The administration of IDEC-C2B8 will be accomplished by slow IV infusion. CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

6) IV pumps such as the IMED 960 may be used with the IDEC-C2B8 infusion. DO NOT INFUSE CONCURRENTLY with another IV solution or IV medications. Prime the line with the IDEC-C2B8 solution such that approximately 30 mL are delivered. This will saturate the filter and tubing.

7) If a delay in administration of the infusion occurs after the product is prepared, the properly identified container may be kept refrigerated at 2-8 °C for up to six hours.

OCCUPATIONAL SAFETY

Study medication are not expected to pose significant occupational safety risks to investigational staff under normal conditions of use and administration. However, precautions should be taken to avoid direct contact with study medication.

ADVERSE CLINICAL EVENTS:

Throughout the course of the study, every effort should be made to remain alert to possible adverse experiences. Adverse events should be recorded using the toxicity criteria as stated in Appendix D. In the event of an adverse experience, appropriate medical intervention should be provided and necessary, the investigational agent (IDEC-C2B8 [rituximab]) should be discontinued.

1) Infusion Related Adverse Events

An infusion-related symptom complex consisting primarily of fever and chills/rigors can occur predominantly during the first IDEC-C2B8 infusion, usually within the first two hours. Other infusion-related symptoms include nausea, urticaria/rash, fatigue, headache, pruritus, sensation of tongue or throat swelling, rhinitis, vomiting, flushing, and pain at disease site. The incidence of infusion-related events decreases dramatically with subsequent infusions.

Transient hypotention and bronchospasm have occurred in association with IDEC-C2B8 infusion as a component of an infusion-related symptom complex. Patients with preexisting pulmonary disease may have an increased risk of bronchospasm. These symptoms are usually reversible with temporary interruption of the IDEC-C2B8 infusion and administration of acetaminophen, diphenhydramine intravenous saline or bronchodilators. The infusion may be completed when symptoms abate.

Patients with a history of cardiac disease (i.e., angina, cardiac arrhythmias, or congestive heart failure) should be monitored closely.

Anaphylactoid and other hypersensitivity reactions can occur following the IV administration of proteins to patients. Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines, should be available for immediate use in the event of an allergic reaction during administration.

2) Hematologic

Following are the results of an integrated safety analysis with 282 patients treated with single agent IDEC-C2B8 at 375 mg/m2.

¥ Neutropenia

During treatment, AGC nadirs were 1000 - 1500/mm3 in 9.2% of patients, 500 - 999/mm3 in 1.4% of patients, and <500 mm3 in 1.1% of patients. During a one year follow-up period, nadirs were 1000 - 1500/mm3 in 6.7% of patients, 500 - 999/mm3 in 5.0% of patients, and <500 mm3 in 2.5% of patients.

¥ Thrombocytopenia
During treatment, platelet values were 50,000-75,000/mm3 in 2.8% of patients and <50,000 in 1.1% of patients. During a one year follow-up period, platelet values were 50,000 - 75,000/mm3 in 1.8% of patients and <50,000 in 0.4% of patients. Two patients received platelet transfusions.

¥ Anemia
During treatment, hemoglobin values were 8-10 gm/dL in 7.8% of patients <8 gm/dL in 2.8% of patients. During a one year follow-up period, hemoglobin values were 8 -10 gm/dL in 3.2% of patients and <8 gm/dL in 0.7% of patients. Only four patients required transfusions and two received erythropoietin for anemia. Pure red cell aplasia was reported in one patient.

3) Infection

Although IDEC-C2B8 induces B-cell depletion and can be associated with decrease serum immunoglobulins, the incidence of infection does not appear to be greater than expected in this patient population and serious infections were considerably less common than report with conventional chemotherapy [1-7]. During treatment and for up to one year following therapy, approximately 17% an 12%, respectively, of patients developed infections which were usually common, nonopportunistic and Grade 1 or 2.

4) Other
There are no known drug interaction with IDEC-C2B8. Patients with HAMA/HACA titers may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic antibodies. Positive HACA results were reported in <1% of the patients receiving IDEC-C2B8.

IDEC-C2B8 has not been associated with clinically significant hepatic or renal toxicity, through mild, transient increases in liver function tests have occurred.

Bronchiolitis obliterans was reported in one patient.

FOR ADDITIONAL INFORMATION CONTACT:
Clinical Trials Management, IDEC Pharmaceuticals Corporation, 11011 Torreyana Road, San Diego, CA 92121. Telephone: (800)447-4131.

Appendix F

Additional Safety Guidelines for Use of Interferon

Consider for exclusion from interferon therapy, or dose modification, according to these guidelines (discuss with P.I.):

Inclusion Criteria

Patients should be assessed for adequate organ function as follows:

Hematologic: WBC ≥ 3,000/mm^2 (Neutrophils ≥ 1500/mm^3); platelets ≥ 70,000/mm^3; Hemoglobin 10.0 gm% or 8.21 mmol/L. For hematologic malignancies these inclusion criteria are at the discretion of the investigator

Hepatic: Bilirubin < 2.0 mg% cr 34.2 umol/L; SGOT or SGPT < 3.0 X's upper limit of normal; alkaline phosphatase < 3.0 X's upper limit of normal. Patients whose SGOT, SGPT or alkaline phosphatase are elevated as a result of metastatic disease are eligible.

Renal Serum creatinine: within normal limits.

- There should be no acute infection requiring systemic antibiotics.
- Patients with diabetes or hypertension should be considered for a baseline ocular examination.

Exclusion Criteria

1) Patients with a history of hypersensitivity to interfeorn alfa or any component of the injection.

2) Patient with pre-existing psychiatric condition, especially depression or a history of severe psychiatric disorder.

3) Patients with a history of severely debilitating cardiovascular disease, such as unstable angina or uncontrolled congestive heart failure.

4) History of severely debilitating pulmonary disease, such as chronic obstructive pulmonary disease.

5) Patients with history of diabetes mellitus prone to ketoacidosis.

6) Patients with coagulation disorders, such as thrombophlebitis or pulmonary embolism.

7) Patients with severe myelosuppression.

8) Patients with decompensated liver disease, autoimmune hepatitis or history of autoimmune disease.

9) Patients with pre-existing thyroid abnormalities, whose thyroid function cannot be maintained in the normal range.

10) Patients with clinically significant retinal abnormalities.

Appendix G

Guidelines for Filing Reports of Adverse Experience at MDACC

The administration of agents for which MDACC holds the IND confers increased requirements for reporting Adverse Experiences. The responsibility for reporting an AE to the FDA rests with the sponsor of the IND. As holder of the IND, MDACC becomes responsible for the reporting of all Adverse Experiences. It is the responsibility of the individual clinical investigator to report these to the Office of Protocol Research, who in turn is responsible for reporting to the FDA.

1.0 Types of Adverse Experiences

Two types of Adverse Experience requiring reporting to the IRB and IND sponsor are recognized:

1. Serious Adverse Experiences
2. Unexpected Adverse Experiences

The FDA definitions of these two types are included in Addendum A.

2.0 Serious Adverse Experience

For the majority of trials performed at MDACC, a serious adverse experience is a clinical event occurring subsequent to the administration of an agent or intervention classified as an Investigational New Drug (IND) which can be characterized as fatal, life-threatening, permanently disabling, requiring hospitalization, or an overdose.

It is recognized that in many instances it may not be possible to absolutely determine whether a clinical event is due to the IND or to progressive cancer. In these instances, a report should be filed, indicating the unlikelihood of a causal relationship.

2.1. Fatal Reactions

Although no specific time period is specifically defined in the regulations, historically, an AE report has been required if a patient expires within 30 days of receiving an investigational new drug or treatment. Although the clinical scenario may suggest an early death secondary to rapidly progressing disease, this event should be reported since the possibility of the agent contributing to this adverse event cannot be excluded.

2.2 Life-threatening

By definition, any grade 4 toxicity using the Common Toxicity Scale is life-threatening and should be reported when they occur in a patient receiving an investigational new drug. A grade 3 reaction, associated with significant co-morbid conditions, might also be life-threatening and should be reported, e.g. grade 3 vomiting leading to renal failure in a patient with compromised kidneys.

2.3 Permanently Disabling

If an IND agent is administered in a situation where prolonged survival is possible, and permanent damage or sequelae occurred sufficient to significantly compromise normal function an adverse experience report should be filed. Example might include marrow aplasia resulting in transfusion-dependency, or pulmonary fibrosis leading to symptomatic restrictive pulmonary disease.

2.4 Hospitalization

Although no time period is specified in the regulations, hospitalization or prolongation of hospital stay within 30 days or receiving an IND agent or intervention must be reported. If the hospitalization is incidental to an event unrelated to the drug administration or the underlying disease, e.g. fracture secondary to a fall, an AE report should still be filed.

2.5 Overdose

Any dose greater than 25% above the protocol specified dose should be reported with a description of the resultant side-effects or toxicity.

3.0 Unexpected Adverse Experience

An unexpected adverse experience is a clinical event that is not identified in nature, severity, or frequency in the investigator's brochure, protocol, or other pertinent supporting literature. At times, the occurrence of an unexpected adverse experience might not be suspected until more than one event has occurred, e.g. multiple cases of herpes zoster in a small phase II trial. Once the clinical event has been identified, all cases should be reported. No degree of unexpected toxicity is specified, but practically, it is unusual to be able to discern < grade 2 toxicity.

4.0 Schedule of Required Reports of Adverse Experiences

A. Serious and/or Unexpected AE

Submit a written report to the Office of Protocol Research within 10 working days of the adverse experience.

Unexpected fatal or life-threatening experiences must be phoned immediately to the Office of Protocol research at ext. 2-2933. OPR will notify the FDA within 3 working days. A follow-up written report should be submitted to OPR within 10 working days.

B. Not serious and/or not Unexpected AE **For MDACC sponsored INDs only**

Submit written reports to OPR every month. OPR will submit this information in the annual IND report submitted to the FDA.

Addendum A

A. Serious Adverse Experience

"Any experience that suggests a significant hazard, contradiction, side effect or precaution, including any experience that is fatal, life-threatening, is permanently disabling, requires inpatient hospitalization or is a congenital anomaly, cancer or overdose. This definition also encompasses results obtained from tests in lab animals suggesting a significant risk for human subjects, including any finding mutagenicity, teratogenicity or carcinogenicity".

B. Unexpected Adverse Experience

"Any adverse experience that is not identified in nature, severity or frequency in the current investigator brochure or if an investigator's brochure is not required, that is not identified innature, severity or frequency in the risk information described in the general investigational plan or elsewhere in the current application".

Addendum B

A. Reporting requirements: Genentech requires certain events to be reported to Genentech (MedWatch 3500 form),attached.

APPENDIX H

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Page ____ of ____

Form Approved. OMB No. 0910-0291 Expires 12/31/94
See OMB statement on reverse

Mfr report #

UF/Dist report #

FDA use only

A. Patient Information

1. Patient Identifier — In Confidence

2. Age at time of event: ____ or Date of birth: ____

3. Sex ☐ female ☐ male

4. Weight ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse Event and/or ☐ Product Problem (e.g. defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
☐ death: ____
☐ life-threatening
☐ hospitalization - initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event (mo/day/yr)

4. Date of this report (mo/day/yr)

5. Describe event or problem

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1:
#2:

2. Dose, frequency & route used
#1:
#2:

3. Therapy dates (if unknown, give duration) from/to or best estimate
#1:
#2:

4. Diagnosis for use (indication)
#1:
#2:

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot# (if known)
#1:
#2:

7. Exp date (if known)
#1:
#2:

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC# - for product problems only (if known)
— —

10. Concomitant medical products and therapy dates (exclude treatment of event)

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)

2. Phone number

3. Report Source (check all that apply)
☐ foreign
☐ study
☐ literature
☐ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer mo/day/yr

5. A(NDA) # ____
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☐ periodic
☐ initial ☐ follow-ups

8. Adverse event term(s)

9. Mfr. report number

E. Initial Reporter

1. Name, address & phone #

2. Health professional?
☐ yes ☐ no

3. Occupation

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☐ unk

FDA Form 3500A (6/93)

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

IDEC Safety Review Officer: ____

Date: ____

The University of Texas
M.D. ANDERSON CANCER CENTER

INFORMED CONSENT FOR PARTICIPATION IN RESEARCH

PROTOCOL TITLE: **FLUDARABINE, MITOXANTRONE, AND DEXAMETHASONE (FND) PLUS ANTI-CD20 MONOCLONAL ANTIBODY (IDEC-C2B8) FOR STAGE IV INDOLENT LYMPHOMA**

1. _____ _____
Participant's Name I.D. Number

You are being asked to take part in this clinical research study at The University of Texas M.D. Anderson Cancer Center (hereinafter referred to as "UTMDACC"). Clinical studies include only individuals who choose to take part. This consent form explains why we are performing this research study and what your role would be should you choose to participate. This form also describes the possible risks linked with being in this study. After reviewing this information with the registering personnel, you should know enough about this study to be able to make an informed decision on whether you want to be in the study. This study complies with all laws and regulations that apply.

You are being asked to take part in this study because you have Stage IV indolent lymphoma.

DESCRIPTION OF RESEARCH

2. **PURPOSE OF STUDY:** The goal of this clinical research study is to compare chemotherapy given with rituximab to chemotherapy followed by rituximab. The safety of both treatment schedules will be studied. Laboratory tests of genetic changes in blood and bone marrow before and during the study will also be monitored.

3. **DESCRIPTION OF RESEARCH:** Rituximab seeks out and helps destroy cancer cells.

Before treatment starts, patients will have a complete exam, including blood and urine tests. Chest x-rays and CT scans will be done. Bone marrow samples will be taken; this is done with a large needle. Tests of heart function and lung function will be done. Tumors and lesions will be measured.

Patients in this study will be assigned at random (as in the toss of a coin) to 1 of 2 groups. Each group will receive 8 cycles of treatment. One cycle will last 28 days.

Most of the drugs are given by vein. A catheter (a tube) will be placed in a vein to decrease the number of needle sticks. Dexamethasone may be taken by mouth instead of given by vein.

Patients in group 1 will receive the drug rituximab on Days 1 and 8 of the first course, and on Day 1 only of Cycles 2-5 of FND. Fludarabine will be given on Days 2-4, mitoxantrone on Day 2, and dexamethasone on Days 1-5 of each 28-day cycle (FND). Patients in group 1 will not receive rituximab in Cycles 6 - 8. When the 8 cycles are finished, patients will begin receiving the drug interferon on Days 1-14 each month for 1 year. Dexamethasone will be given on Days 1-3 every month for 1 year.

Patients in group 2 will receive fludarabine on Days 1-3, mitoxantrone on Day 1, and dexamethasone on Days 1-5 of each 28-day cycle. When 8 cycles of treatment are finished, patients will begin receiving the drug interferon on Days 1-14 each month for 1 year. Dexamethasone will be given on Days 1-3 every month for 1 year. About 4 months after interferon treatment starts, patients in group 2 will begin receiving rituximab once a month for 6 months.

Other drugs may be given to help decrease the risk of or ease side effects. Treatment may be delayed or stopped if side effects are severe.

Some patients in this study, with changes in certain genes will receive different chemotherapy drugs than other patients in the study will. The patients will, like all the other patients, receive rituximab and interferon. But instead of the FND chemotherapy regimen, they will receive a sequence of three regimens, CHOD-Bleo, ESHAP, and NOPP. The drugs in these regimens include: cyclophosphamide, doxorubicin, vincristine, bleomycin, VP-16, Ara-C, cisplatin, mitoxantrone, procarbazine, and corticosteroids (prednisone, methylprednisolone, dexamethasone).

During the study, patients will have blood tests every week. Complete exams will be given in Cycles 2 and 4; patients will return to the clinic for these. Every 2 or 3 cycles, patients will have a chest x-ray and CT scans of the abdomen and pelvis. Bone marrow samples will be taken. Heart function tests (EKG) will be done as needed.

After the study ends, patients will return for checkups every 3 months in the first year, every 4 months in years 2 and 3, and every 6 months in years 4 and 5. After that, checkups will be needed once a year. Blood and bone marrow samples will be taken at these visits.

This is an investigational study. Rituximab is approved by FDA for commercial use. The other drugs used in the study are also approved for commercial use. About 210 patients will take part in the study. All will be enrolled at UTMDACC. Genentech, Inc., the makers of rituximab, will work with patients or their insurance companies to insure that no one is excluded from the study for money reasons. The protocol is partially funded by research grants from Genentech, Inc., Integrated Therapeutics Group, Inc., and Immunex Corporation.

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4. **RISKS, SIDE EFFECTS AND DISCOMFORTS TO PARTICIPANTS:** Fludarabine, mitoxantrone, dexamethasone, and interferon may cause low blood cell counts (white blood cells, red blood cells, and platelets). This means that while participants take the drugs, there is more of a chance of getting an infection, including pneumonia. Participants may become anemic and/or have problems with bleeding, bruising, fatigue, and/or shortness of breath. Participants may need a blood transfusion. Participants may die. These drugs may cause upset stomach, nausea, vomiting, diarrhea, mouth ulcers, and/or hair loss. The drugs may cause heart damage. The patient may have a fever, bone pain, and/or fluid retention, causing swelling.

Rituximab may cause fever, chills, nausea, and vomiting. The patient may have a rash, headache, muscle aches, and/or swelling from fluid buildup. The patient may feel dizzy and/or tired. Hives, breathing trouble, low blood pressure, and/or sweating may occur. There may be tenderness and/or swelling at tumor or lesions sites. Allergic reactions, including low blood pressure, shortness of breath, and/or wheezing, which can be fatal, may occur. These severe reactions have occurred with the first dose of rituximab, so this dose (especially) is monitored carefully and given slowly. Severe skin rashes, which can be fatal, may occur.

Rituximab does temporarily decrease one normal blood cell element (B-cells), and this can result in some decreased resistance to certain types of infections, such as viruses. There is also a temporary decrease of immunoglobulin levels, which can also lower the resistance of the body to infections.

Using these drugs together may cause other side effects that are not seen when each drug is given alone.

Participants may experience pain, bleeding, and/or bruising from the blood draws or bone marrow tests. Participants may faint and/or develop an infection with inflammation of the vein at the site where blood is drawn.

This clinical research study may involve unpredictable risks to the participant.

4a. Participants must practice birth control during the study if they are sexually active. There could be unknown risks to an unborn child or the patient. If the patient is pregnant, she may not participate in this study. Mothers should refrain from breast-feeding during the study to avoid injury to their children.

5. **POTENTIAL BENEFITS:** Treatment on this study may shrink or slow the growth of the tumor. There may be no benefits at all for patients in the study. Future patients may benefit from what is learned.

6. **ALTERNATE PROCEDURES OR TREATMENTS:** Individuals may choose not to take part in this study. Individuals may choose to be treated with a standard chemotherapy drug such as chlorambucil or combinations such as CVP or CHOP. If the tumors are not large or threatening, individuals may choose only to be observed by their doctors. Individuals may choose to receive other investigational therapy, if available. Individuals

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can choose not to have treatment for cancer at all. In all cases, individuals will receive care for symptoms and pain.

I understand that the following statements about this study are true:

7. According to the M.D. Anderson Cancer Center conflict of interest policy, the principal investigator of this study and the participant's primary physician cannot have a financial interest in any aspect of this research. However, because of the unconditional priority of patient care, a circumstance may arise wherein a participant may need to be cared for by a physician and/or administrator who does have some form of financial interest in the sponsor of this study.

8. If at any time I wish to acquire further updated information regarding the financial interests of any physician and/or administrator here who has cared for me, I may call the Office of Research Administration at (713) 745-1697. Upon request, I will be given access to information disclosing the identity of all physicians and/or administrators who have a financial interest in the sponsor of this study.

9. My participation is voluntary.

10. I may ask any questions I have about this study, including financial considerations, of my physician Dr. _____. I may also contact the principal investigator for this study Dr. Peter McLaughlin at (713) 792-2860 or the Chairman of UTMDACC's Surveillance Committee at (713) 792-2933 with any questions that have to do with my rights.

11. I may withdraw at any time without any penalty or loss of benefits. I should first discuss leaving the study with my physician. Should I withdraw from this study, I may still be treated at UTMDACC by my physician.

12. This study may be changed or stopped at any time by my doctor, the principal investigator, the study sponsor, or the Surveillance Committee of UTMDACC.

13. I will be informed of any new findings that might affect my willingness to continue participating in the study.

14. UTMDACC will take appropriate steps to keep my personal information private. However, there is no guarantee of absolute privacy. The Food and Drug Administration ("FDA"), Genentech, Inc., Integrated Therapeutics Group, Inc., and Immunex Corporation might review my record to collect data or to see that the research is being done safely and correctly.

    Under very rare circumstances, the FDA could be required to reveal the names of participants.

15. If I suffer injury as a result of participation in this study, the institution will provide reasonable medical care. I cannot expect to receive reimbursement of expenses or financial compensation from the institution, the sponsor, or the

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manufacturer for this injury. I may also contact the Chairman of UTMDACC's Surveillance Committee at 713-792-2933 with questions about study related injuries.

16. Unless I am told otherwise, all of the costs linked with this study are to be paid by me or the 3rd party payer (HMO, Health Insurance company, etc.) responsible for my health care expenses. If medications or devices are provided for free or at a reduced cost, I will not be charged or will pay a reduced charge for that item.

17. I recognize that there are no plans to provide any compensation to me for any patents or discoveries that may result from my participation in this research.

18. All participants must practice birth control. Female participants should not breast feed their infants. If a female participant becomes pregnant, or suspects that she is pregnant, she must notify her physician immediately. Getting pregnant may result in my removal from participation in this study.

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CONSENT

Having read and understood the above, and having had the chance to ask all my questions about this study and reflect and consult with any others that I might like to, I give Dr. _____ permission to enroll me on this study. I have been given a copy of this consent.

_____ _____
DATE SIGNATURE OF PARTICIPANT

_____ _____
WITNESS OTHER THAN PHYSICIAN OR INVESTIGATOR SIGNATURE OF PERSON RESPONSIBLE & RELATIONSHIP

I have discussed this clinical research study with the participant and/or his or her authorized representative, using a language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and I believe the participant understood this explanation.

_____
PHYSICIAN/INVESTIGATOR

I have translated the above informed consent into _____ for this participant.
(Name of Language)

_____ _____
NAME OF TRANSLATOR SIGNATURE OF TRANSLATOR & DATE

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* Date of Approved 1-29-03
*Signature