Protocol Body

1.0 Objectives

1.1 To assess whether the time to progression for these high-risk patients can be prolonged to a median of 36 months, compared to the historical expectation of approximately 24 months.

1.2 To assess the tolerance and efficacy of Y2B8 (Zevalin) after R-FND (rituximab, fludarabine, mitoxantrone, dexamethasone) in patients with high-risk stage III-IV follicular lymphoma

1.3 To assess overall response, failure-free survival, and survival of this strategy compared to our historical experience with FND (fludarabine, mitoxantrone, dexamethasone) alone or R-FND

1.4 To assess the tolerance and efficacy of maintenance therapy with rituximab

1.5 To maximize the 12-month molecular remission rate for patients with high-risk stage III-IV follicular lymphoma

1.6 To correlate the results of quantitative PCR assay with classical PCR and with clinical outcome.

2.0 Background

2.1 Follicular Lymphoma

Numerous therapies can be effective for patients with follicular lymphoma, but virtually all patients eventually relapse after standard alkylating agent based therapies. Examples of standard therapy are COP (cyclophosphamide, vincristine, and prednisone), CHOP (cyclophosphamide, vincristine, prednisone, and doxorubicin), and FND (fludarabine, mitoxantrone, dexamethasone (1,2)). Increasingly, rituximab is being incorporated into front-line regimens, with promising results (3,4).

Prognostic models can identify subsets who are less likely to attain complete response (CR), or whose remissions are likely to be relatively brief (3, 5-7). A large multi-institutional collaboration has recently led to a prognostic model that identifies high-risk patients based on the presence of 3 or more of the following features: stage III-IV; age 60 or more; elevated LDH; Hgb < 12; and 5 or more involved nodal sites (8).

2.2 bcl-2.

The bcl-2 gene is rearranged in about 85% of patients with follicular lymphoma. The small fraction without bcl-2 gene rearrangement appear to have a worse outlook (9). For those with bcl-2 gene rearrangement, the polymerase chain reaction (PCR) provides an excellent way to monitor these patients for subclinical residual disease (10,11). Ultimately, a quantitative PCR technique may prove useful (12); currently, the literature that supports the use of PCR for bcl-2 is based on qualitative (positive or negative) PCR data.

2.3 Fludarabine and FND Combination

Fludarabine is an active agent for patients with indolent lymphomas; it has been used in the setting of relapse and up-front, and has been used alone and in combination (13,14). The FND combination has been particularly effective and well tolerated (11-13), and is capable of inducing molecular remission (18).

Our sequential experience with FND started with a phase I trial (15) that has defined a dose that has been adopted widely (16, 19-22). We subsequently conducted a phase II trial in the setting of relapse (17), then front-line trials including one in conjunction with rituximab (6, 23, 24). These latter trials (6, 23, 24) provide the framework for the questions to be addressed in the current trial. The FND front-line experience that has the longest follow-up is DM92-103 (23). Based on that trial, we expect a CR rate of about 80%, and a 5-year failure-free survival of about 40%. The R-FND experience (protocol DM97-261) has shorter follow-up; the DM97-261 experience provides the expectation of a molecular response rate of 80% (17,18).

2.4 Rituximab and other monoclonal antibodies

Rituximab is a chimeric anti-CD20 monoclonal antibody (25). As a single agent, it has been effective and well tolerated (26-28). In combination with chemotherapy, it has been well tolerated (24,29). Ongoing trials suggest that rituximab can add to the impact of chemotherapy (30). Rituximab is capable of inducing molecular remissions (31).

Zevalin is a radioimmunoconjugate that targets CD20, the same pan B antigen recognized by rituximab. It is a highly active single agent (32, 33).

The safety profile of Zevalin in five clinical trials revealed that AEs are primarily hematologic with Grade 4 neutropenia, thrombocytopenia, and anemia occurring in 30%, 10%, and 4% of patients, respectively. Most nonhematologic AEs were Grade 1 or 2 and the incidence was comparable to that seen with rituximab. Hematologic toxicity did not correlate with any of the dosimetric or pharmacokinetic parameters analyzed. Patients were effectively screened for safe treatment using clinical selection criteria including percent bone marrow involvement with NHL (<25%), baseline platelet count (> 100,000 cells/mm^3). Patients were treated safely using individualized dosing based on patient weight and platelet count. The incorporation of Zevalin, in sequence with chemotherapy, in the front-line strategy proposed in this protocol is investigational.

3.0 Background Drug Information

3.1 Fludarabine is commercially available.

3.2 Mitoxantrone is commercially available.

3.3 Dexamethasone is commercially available.

3.4 Rituximab (Rituxan®) is commercially available. Safety information is as follows:

Hematologic Events: In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with rituximab; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following rituximab therapy were reported.

In addition, there have been a limited number of post-marketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset n (defined as occurring 40 days after the last dose of rituximab) in patients with hematologic malignancies. In reported cases of late onset neutropenia (NCI-CTC Grade 3 and 4), the median duration of neutropenia was 10 days (range 3 to 148 days). Documented resolution of the neutropenia was described in approximately one-half of the reported cases; of those with documented recovery, approximately half received growth factor support. In the remaining cases, information on resolution was not provided. More than half of the reported cases of delayed onset neutropenia occurred in patients who had undergone a prior autologous bone marrow transplantation. In an adequately designed, controlled, clinical trial, the reported incidence of NCI-CTC Grade 3 and 4 neutropenia was higher in patients receiving rituximab in combination with fludarabine as compared to those receiving fludarabine alone (76% [39/51] vs.39% [21/53]).

3.4.1 Investigational Drug Nomenclature

- IDEC Pharmaceuticals code designation IDEC C2B8
- Generic Name: Rituximab
- IND Number: BB-IND 4904

3.4.2 Clinical Formulation

Clinical supplies for this study will be manufactured by Genentech Incorporated in South San Francisco, CA.

Rituximab will be provided to the clinical sites packaged in single use 10 mL (100mg) and 50 mL (500mg)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 is produced by a 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.

3.4.3 Storage

Rituximab for clinical use should be stored in a secure refrigerator at 2-8 degrees Celsius.

3.4.4 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 1 mg/mL. Mix by inverting the bag gently.

Caution should be taken during the preparation of the drug. Parenteral drug products should be inspected visually for particulate matter prior to administration. Preparations of rituximab containing visible particles should not 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 containers which require vented administration sets, because this causes foaming when air bubbles pass through the solution.

3.5 Zevalin: Zevalin is composed of the following: a murine IgG1 kappa monoclonal antibody IDEC-2B8 (ibritumomab); the linker chelator tiuxetan (isothiocyanatobenzyl MX-DTPA); and the radioisotope ^{90}Y that is securely chelated via the linker. Like its unlabeled chimeric counterpart, rituximab, Zevalin targets the CD20 antigen present on 95% of B cell lymphomas. IDEC-In2B8 is the ^{111}Indium-labeled murine monoclonal antibody used for imaging and dosimetry. Rituximab is given initially to clear peripheral B lymphocytes and optimize biodistribution of the radiolabeled antibody. Dosimetry studies have shown that normal organ and red marrow radiation doses were estimated to be well under 2000 cGy and 300 cGy, respectively. Estimated median tumor absorbed dose as determined by data from 18 tumors in 9 patients was 1712 cGy (range 575 – 6710). In a specific analysis of safety, estimated absorbed red marrow radiation dose (performed by blood-derived and sacral image-derived methods), blood $T_{1/2}$, blood AUC, plasma $T_{1/2}$, and plasma AUC did not predict severity of hematologic toxicity as demonstrated by the lack of clear correlation between these variables. In a multicenter phase II trial, adverse events were primarily hematologic, transient, and reversible. The median nadirs were 34,000/mm^3 for platelets, 60/mm^3 for ANC, and 10.0 g/dL for hemoglobin. Grade 4 neutropenia and thrombocytopenia occurred in 31% and 12% of patients.

3.5.1 Investigational Drug Nomenclature

- IDEC Pharmaceuticals code designation: Zevalin (IDEC-106); IDEC-2B8-MX-DPTA (IDEC-129)
- Generic name: ^{90}Y-Ibritumomab tiuxetan
- IND numbers: BB-IND 4850 – Zevalin
- MF number: BB-MF 7087 – Zevalin

3.5.2 Clinical Formulation

The radiolabeling kit is provided by IDEC and all components are tested to be sterile and pyrogen-free. The kit consists of the following components:

- 3 mL glass vial containing 2 mL (3.2 mg) of Zevalin at 1.6 mg/mL in low metal normal saline
- 3 mL glass vial containing 2 mL low-metal 50 mM sodium acetate
- 10 mL glass vial containing 10 mL formulation buffer (PBS containing 7.5% human serum albumin and 1 mM DTPA, pH 7.2)
- 10 mL glass vial (empty)

3.5.3 Storage

The radiolabeling kits should be stored in a secure refrigerator at 2-8 degrees Celsius. Zevalin solutions are stable at 2-8 degrees Celsius for up to 8 hours following preparation. Due to the relatively short half life of the 90Y isotope, if not used soon after calibration time, the actual dose will have decayed and will require recalculation.

4.0 Patient Eligibility

4.1 Patients with previously untreated Ann Arbor stage III-IV follicular lymphoma, grade 1 and 2, with high-risk features are eligible for this protocol. High-risk is defined according to the FL-IPI (4), based on the presence of advanced stage, plus any additional 2 of the following 4 features: age 60 or more; elevated LDH; Hgb < 12; or number of involved nodal sites 5 or more.

4.2 Follicular lymphoma, grade 3 (follicular large cell lymphoma): If eligible for a current large cell lymphoma protocol, that alternative protocol is recommended, particularly grade 3b or FLCL patients characterized as large non-cleaved cell. However, both FND and rituximab have established efficacy in FLCL, so if a patient is not eligible for a protocol for aggressive lymphoma (e.g., because of SCCL in the marrow), then registration on this trial is permitted.

4.3 Biopsy or FNA material is strongly recommended for bcl-2 studies to verify rearrangement status of all patients who are designated “germline” (see section 6.4). For other patients, tissue availability is desirable but not mandatory.

4.4 No age limit. Any pediatric candidate (age <16) will be discussed with Pediatrics.

4.5 Women must not be pregnant.

4.6 Patients must have a performance status of Zubrod 3 or better (Appendix H).

4.7 Patients must have adequate renal and hepatic function (creatinine < 2mg%; bilirubin < 2 mg%). Patients with renal or liver dysfunction due to organ infiltration by lymphoma may be eligible after discussion with the study chairman.

4.8. Patients may not receive other concurrent chemotherapy, radiotherapy, or immunotherapy.

4.9 Patients must sign an informed consent indicating that they are aware of the investigational nature of this study in keeping with the policies of the hospital.

4.10 Exclusions:

4.10.1 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. Note: some follow-up care may be provided by outside physicians as long as the MDACC protocol for outside physician participation is strictly adhered to (see Appendix G).

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

4.10.3 Patients with organ dysfunction, including bilirubin of > 2 mg% or serum creatinine level > 2 mg%, unless the alteration is due to lymphoma.

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

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

4.10.6 All patients should have a cardiac ejection fraction of 50% or more by echocardiography or MUGA.

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

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

4.10.9 Patients who have received prior murine antibody therapy will be excluded.

4.10.10 Patients with evidence of active or prior infection of Hepatitis B are excluded. (Note: Persons vaccinated for Hepatitis B who have + antibodies are not excluded).

5.0 Treatment Plan (see Appendix D)

All patients will start with R-FND.

5.1 R-FND

5.1.1 Initial Dose Regimen of R-FND - Course 1: *please note that there are 2 doses of rituximab for course 1 only:*

AGENT	*DOSE*	*DAY*	*ROUTE*	*TIME*
Fludarabine	25 mg/m²/day	2-4	I.V.	5-30 minutes
Mitoxantrone	10 mg/m²	2	I.V.	5-30 minutes
Dexamethasone	20 mg/day	2-6	PO or I.V.	
Rituximab*	375 mg/m²/dose	1* & 8	I.V.	4-6 hours

*For leukemic patients, because of the risk of lysis, rituximab Day 1 dose will be deferred to Day 3 (or later at clinician's discretion). Missed rituximab doses will be made up in subsequent courses; discuss with P.I.

Subsequent Monthly Dose Regimen of R-FND – Courses 2 and beyond: *please note that there is only 1 dose of rituximab:*

AGENT	*DOSE*	*DAY*	*ROUTE*	*TIME*
Fludarabine	25 mg/m²/day	1-3	I.V.	5-30 minutes
Mitoxantrone	10 mg/m²	1	I.V.	5-30 minutes
Dexamethasone	20 mg/day	1-5	PO or I.V.	
Rituximab	375 mg/m²	1	I.V.	4-6 hours

5.1.2 Rituximab is recommended to start two hours before fludarabine. Mitoxantrone is recommended to be given after the first dose of fludarabine. Courses are recommended to be repeated each four weeks, after documentation of recovery from the prior course, including platelets > 100,000, and granulocytes > 1500.

5.1.3 Dose Levels

	-2	-1	0
Fludarabine	16 x 3	20 x 3	25 x 3
Mitoxantrone	6	8	10

Dose Reduction of rituximab is discouraged, but may be discussed with the P.I.

5.1.4 Patients are recommended to receive fludarabine phosphate I.V. over 5-30 minutes daily for 3 days. Mitoxantrone is recommended to be given I.V. over 5-30 minutes. Rituximab will be given as in section 5.1. Courses are recommended to be repeated every 4 weeks. Restaging on R-FND is recommended to be conducted after completion of 2 and 4 courses.

5.1.5 Patients achieving a stable partial response or demonstrating continued response after 4 courses may be given an additional 2 courses. Discuss with P.I.

5.1.6 Patients demonstrating progressive disease or no response after 2-4 courses will come off study. See section 9.1.

5.1.7 Dose adjustment to the next lower level will be made if pneumonia, septicemia, or other life-threatening infection occurs with any course. If recovery of the WBC or platelet count to the level prior to treatment exceeds 35 days, the dose may be decreased 1 level. If grade 3 or 4 toxicities to other organ systems develops, the dose level may be lowered 1 or 2 levels respectively.

5.1.8 Four courses is the intended limit for R-FND. For patients with substantial (>20%) ongoing shrinkage of measurable disease between courses 2 and 4 will receive additional R-FND, if their hematologic tolerance has been good. If such special circumstances warrant consideration of additional R-FND, please discuss with P.I.

5.2 GUIDELINES FOR RITUXIMAB ADMINISTRATION:
CAUTION: DO NOT ADMINISTER RITUXIMAB AS AN INTRAVENOUS PUSH OR BOLUS

5.2.1 Recommended: Premedication (two tablets [375mg or 500 mg] of acetaminophen orally and 25 to 100 mg diphenhydramine hydrochloride orally or intravenously) to be administered 30 to 60 minutes prior to starting each infusion of rituximab.

5.2.2 The drug may be administered via a peripheral or central intravenous line.

5.2.3 Recommended: During the rituximab infusion, the patient's vital signs (blood pressure, pulse, respiration, temperature) are recommended to 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 it is recommended to have epinephrine for subcutaneous injection, diphenhydramine hydrochloride for intravenous injection, and resuscitation equipment for emergency management of anaphylactoid reactions.

5.2.4 Recommended: The initial dose rate at the time of the first rituximab infusion is recommended to be 50 mg/hr for the first half hour. If no toxicity is seen, the dose rate may be escalated gradually **(50 mg/hour increments at 30-minute intervals)** to a maximum of 500 mg/hr. If the first dose of rituximab is well tolerated, the starting flow rate for the administration of doses 2-4 will be 100 mg/hour then increased gradually **(100 mg/hour increments at 30-minute intervals)** not to exceed 600 mg/hr.

5.2.5 Patients may experience transient fever and rigors with infusion of chimeric anti-CD20 (rituximab) antibody. When these side effects are noted, the antibody infusion is recommended be slowed or interrupted. 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 may be resumed, initially at half the previous rate (see table below). Upon resolution of all side effects and in the judgement of the investigator, the patient's dose may be gradually escalated (50 mg/hr increments at 30 minute intervals) to a maximum rate of 300 mg/hr. Following the antibody infusion, it is recommended that the IV line be kept open for medications, as needed. 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

5.2.6 Since transient hypotension has been reported during rituximab infusions, consideration should be given to withholding anti-hypertensive medications the day of the rituximab infusion.

5.3 Antibiotic prophylaxis

5.3.1 Prophylaxis for pneumocystis carinii

5.3.1.1 All patients are recommended to receive prophylaxis with trimethoprim-sulfa (TMP-SMX) as follows: 2 DS tablets twice daily, on Sat. & Sun.

5.3.1.2 For TMP-SMX allergy, patients are recommended to receive pentamidine aerosol therapy: 300 mg q 4 wks using a Respigard II nebulizer.

5.3.1.3 For any problems, please consult P.I. and/or Infectious Disease

5.3.2 Viral prophylaxis

5.3.2.1 Valacyclovir 500 mg po qd x 10d, days 8-17 of each cycle, is recommended.

5.4 Zevalin Radioimmunotherapy (see Appendices I and J)

5.4.1 Candidate patients: PR or CR after R-FND x 4

5.4.2 Exclusions:

- persistent marrow infiltrate > 25% -- n.b., most such patients will not meet PR criteria anyway.
- Hypocellular bone marrow (cellularity less than 15%)
- Marked reduction in bone marrow precursors of one or more cell lines (granulocytic, megakaryocytic, erythroid)
- Platelet count <100,000/mm^3
- creatinine, bilirubin, AST/ALT or alkaline phosphatase > 2 x the upper limit of normal.
- Active infection
- pleural effusion

- G-CSF or GM-CSF within 2 weeks
- Performance status 3 or more

5.4.3 Schedule: Zevalin to start approximately 12-16 weeks after last course of R-FND, pending hematologic recovery as outlined above in 5.4.2

5.4.3.1 The ^{90}Y isotope order form must be completed and faxed to the designated isotope vendor preceding the initial rituximab infusion. Patients will receive an initial infusion of 250 mg/m^2 rituximab. One week later, patients must receive a second infusion of 250 mg/m^2 of rituximab and 0.3 mCi/kg of ZEVALIN. The exact dose of ZEVALIN will be based on the patient's weight during the baseline evaluation. **The maximum dose is not to exceed 32 mCi of ^{90}Y.**

5.4.3.2 Rituximab Administration (See 5.2)

5.4.3.3 Zevalin Administration

The Zevalin phase of the treatment program is a coordinate schedule of two rituximab doses, a single therapeutic Zevalin dose, and an imaging ^{111} In Zevalin dose (see sections 5.4.31. and 5.4.3.4). The therapeutic dose of Zevalin will be administered approximately one week after the first 250 mg/m^2 rituximab infusion (see 5.4.3.1 above), and following the second rituximab infusion.

Each patient will receive one therapeutic dose of ZEVALIN according to the dosing schema in Section 5.4.3.1, not to exceed 32 mCi of ^{90}Y. Zevalin will be administered intravenously as a slow IV push over 10 minutes. Zevalin may be directly infused by stopping the flow from the IV bag and injecting the radiolabeled antibody directly into the infusion port. A **0.22 micron filter** must be on line between the syringe and the infusion port. (The 0.22 micron filter is not provided by IDEC Pharmaceuticals). Flush the line with at least 10 mLs of normal saline after ZEVALIN has been infused.

There is no provision for additional treatment courses for patients entered into this protocol.

CAUTION WILL BE TAKEN IN THE HANDLING OF ALL RADIOACTIVE SAMPLES ACCORDING TO STANDARD PROCEDURES AND PRACTICES AT THE CLINICAL SITE.

ALL DOSES WILL BE CALCULATED USING ACTUAL BODY WEIGHT.

5.4.3.4 Indium-111 Imaging:

All patients will have imaging studies using ^{111}In Zevalin antibody before the therapeutic course. The plan is as follows:

Day 1: A course of 250 mg/m^2 rituximab infusion, followed by 5.0 mCi of ^{111}In Zevalin (for details please see Appendix I).

First whole body imaging: between 2-24 hours after infusion of ^{111}In Zevalin and prior to urination (for details refer to Appendix I).

Second whole body imaging: 48-72 hours after the initial infusion of Indium.

Third whole body imaging: Only necessary if scan 2 showed a potential complication of biodistribution and would be used to make a treat or no treat decision.

5.4.3.5 Evaluations During the ^{111}In Zevalin Imaging Period

During the imaging period, vital signs will be obtained every 15 minutes for the first hour during the Rituxan infusion, hourly during the remainder of the infusion, and immediately following the indium labeled Zevalin infusion. If vital signs are unstable, they will be monitored at 5-minute intervals until stable.

The purpose of the indium labeled imaging is two fold:
- To evaluate biodistribution of whole body gamma camera images
- To assess whether biodistribution is acceptable to proceed with 90Y Zevalin radioimmunotherapy.

The biodistribution of 111In Zevalin is to be determined from a visual evaluation of whole body gamma images during the first day (2-24 hours) and the second or third day (48-72 hours) after injection.

The expected biodistribution is as follows:
- Easily detectable uptake in the blood pool areas (including but not limited to the heart, major abdominal blood vessels, vascular areas of the head, lungs and pelvis) on the first day image, with less activity in the blood pool areas on the second or third day image.
- Moderately high to high uptake in normal liver and spleen during the first day and the second or third day images.
- Moderately low or very low uptake in normal kidneys, urinary bladder, and normal bowel on the first day image and the second or third day image.
- Tumor uptake may be visualized in soft tissue as areas of the increased intensity, and tumor bearing areas in normal organs may be seen as areas of increased or decreased intensity.

Altered biodistribution would be as follows:
- Diffuse uptake in normal lung more intense than the cardiac blood pool on the first day image, or more intense than the liver on the second or third day image.
- Kidneys with greater intensity than the liver on the posterior view of the second or third day image.

Biodistribution of 111In Zevalin should be assessed on the first day image and second or third day image. If desired, a third image can be obtained at 90 - 120 hrs to support the decision. If the patient has an altered biodistribution, the patient will be taken off study before proceeding to 90Y Zevalin radioimmunotherapy. (See Appendix I for additional details regarding data acquisition for 111In Zevalin).

5.4.4 Subsequent monitoring:
- For toxicity: see sections 7.7 (CBC, etc) and 7.6 (marrow cytogenetics), and Appendices A and L.
- For efficacy: see section 7.2 and 7.3

5.5 Maintenance Rituximab

5.5.1 Candidate patients:
All responders (CR/CRu/PR), to start 6-8 weeks after Zevalin.

5.5.2 Schedule:

- Rituximab: 375 mg/m^2 IV, a single dose every other month for 12 mo (6 doses total). Start 6-8 weeks after Zevalin, at approximately month 7.

NOTE: Rituximab maintenance can and should start on schedule, even if there is delayed hematologic recovery after Zevalin.

5.6. Chemotherapy Dose Modification Guidelines

5.6.1 Recommended Guidelines for Hematological Toxicity: for fludarabine and mitoxantrone (see 5.1.3):

Lowest granulocytes	**Lowest Platelets**	**Modification**
>200	> 20,000	No change
<200 for > 5 days and/or	< 20,000	Decrease one level
documented infection with neutropenia	Bleeding	Decrease one level

5.6.2 For all other toxicities (see Appendix B)

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

5.6.3 Duration of therapy and intervals between courses:
a) R-FND courses are recommended to repeated every 28 days, after verification of hematologic recovery.
b) Total length of R-FND treatment will be 4 courses for most patients. Exceptions should be discussed with PI, e.g. give more if response is slow (see sections 5.1.5 and 5.1.8), or stop early if there is evidence of cumulative myelosuppression, with more than 6 weeks before recovery of granulocytes to 1000 or more or platelets to 100,000 or more.

5.6.4 Patients older than 60 years will receive full doses of chemotherapy.

5.6.5 Anyone experiencing delayed recovery of granulocyte counts (>35 days) or neutropenic fever will be candidates for colony stimulating factor support, with the chemotherapy doses adjusted down one dose level.

6.0 Pretreatment evaluation (see Appendix E)

6.1 A complete history and physical, including documentation of performance status, all measurable disease, screening for active or prior hepatitis B, as well as signs and symptoms shall be necessary.

6.2 Laboratory studies:

6.2.1 Mandatory (within 30 days of study entry): CBC, differential, and platelet count, chemical survey. Women of child-bearing potential will have a pregnancy test (serum HCG).

6.2.2 Recommended: Beta-2 microglobulin, quantitative immunoglobulins, serum protein electrophoresis, and immunofixation if monoclonal peak is identified. Plasma for soluble CD20 if possible.

6.3 Bone marrow aspirate and biopsy (bilateral biopsy; unilateral aspirate).

6.3.1 Marrow cytogenetics recommended. For exceptions, discuss with PI.

6.4 PCR for bcl-2

6.4.1 Mandatory: 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.

6.4.2 Optional: 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. Medeiros (713-794-5446).

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.

6.5 Optional: Cell surface markers (CD5, CD20, CD4, CD8, SIg, Kappa, Lambda) on peripheral blood and bone marrow. It is encouraged but not required that cells or extracted DNA be stored for future PCR studies.

6.6 Chest x-ray

6.7 CT and other scans:

6.7.1 Mandatory: CT scans of the abdomen & pelvis, within 2 months

6.7.2 Optional: CT scans of the head & neck and/or chest, as clinically indicated

6.7.3 Recommended: PET scan

6.8 Any additional appropriate radiologic and radioisotopic examinations should be performed as indicated.

7.0 Evaluation During Study (see Appendix E)

7.1 Recommended: Patients are recommended to be followed with CBC, platelet count and differential weekly for the first course, and q 2 wk thereafter. An SMA is recommended every month during chemotherapy.

7.2 After two courses, after four courses, 6-8 weeks after Zevalin,(i.e. approximately month 8 and 9), and 3 months later (approximately month 11-12), a full re-evaluation is to be performed, including:

7.2.1 Mandatory: CBC, differential, and platelet count, SMA-12, bone marrow aspiration and biopsy, CT scan of abdomen and pelvis, chest x-ray, and any other studies that were positive at baseline, such as CT head and neck or CT chest.

7.2.2 Optional: quantitative immunoglobulins. Surface marker studies on peripheral blood and bone marrow.

7.2.3 Prior to Zevalin therapy:

- CBC, chemistries, marrow, CXR; and
- Optional: Serum rituximab level

7.3 PCR for bcl-2

7.3.1 PCR in the peripheral blood will be followed every 3-4 months during the first 18 months, then every 6 months until month 36, then every 12 months. PCR in the bone marrow will be followed at times of bone marrow sampling, (see Section 7.2.1 and Appendix E), i.e., baseline, before Zevalin, 6-8 weeks after Zevalin, at months 9 and 12, and then every 4-6 months during the first 3 years, and every 12 months subsequently.

7.3.2 For patients who are still PCR positive after Zevalin: proceed to rituximab and explore alternative (off this protocol) treatment options, especially stem cell transplant, which is recommended to be pursued at first evidence of progressive disease by clinical (x-ray, marrow, physical exam) criteria.

7.4 Recommended: Restaging after month 12: every 4 months for 1 year (while on maintenance), then every 4-6 months for 2 years, then yearly (see Appendix E). Beyond year 5, it is recognized that these recommended assessments may not be realistic (due to age, distance, or cost issues). We will nonetheless strive to get this data.

7.5 Optional: Peripheral blood lymphocyte surface markers and Ig's every 3-4 months during therapy, and every 6-12 months off therapy until any abnormalities resolve.

7.6 Marrow cytogenetics: after 4 courses R-FND (before Zevalin): and 12-18 months after Zevalin.

7.7 During Zevalin phase:

- CBC, diff, platelets weekly x 12 wks;
- chemistries monthly x 3 mo;
- urinalysis at 1 and 3 mo;
- immunoglobulins at 3 mo;
- HAMA at times of lab testing/clinic visits post-Zevalin (see Section 7.2), i.e., at about 6-8 weeks after Zevalin, and at months 9 and 12.

7.8 During rituximab maintenance: CBC with differential and SMA every 1-3 months during maintenance
7.9 Outside Physician Participation During Treatment (Some general information regarding outside physician participation can also be found in Appendix G).
7.9.1 MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record
7.9.2 A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix M) and a copy of the chemotherapy instructions will also be sent to the outside physician (Appendix N).
7.9.3 Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
7.9.4 Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
7.9.5 A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
7.9.6 Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnositic studies and documentation of hospitalizations.
7.9.7 The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.
7.9.8 Patients will return to MDACC at least every 2-3 cycles for evaluation.
7.9.9 Physician to physician communication regarding protocol enrollment is required prior to the patient returning to the home physician and documentation of these conversations must be documented in the patient record.
7.9.10 A letter to the home physician outlining the patient's participation and requesting the home physician agreement to supervise the patient's care. The letter will be approved by the IRB as part of the protocol and a copy will be provided to the patient. (a copy of this letter can be found in Appendix M, and a copy of the chemotherapy instructions will also be sent to the outside physician (Appendix N).
7.9.11 The following documents are to be provided to the outside physician:
- a copy of the informed consent
- the protocol abstract
- the protocol treatment schema
- the protocol "Evaluation During Treatment" section
7.9.12 Commumication of protocol required evaluations to MDACC investigators can be by telephone (dictation documentation required), fax, or e-mail. Authentication of fax and/or e-mail documents requires date and physician signature. This becomes part of the source documentation in the medical record.
7.9.13 The informed consent will describe the outside physician participation.

8.0 Criteria for Response and Toxicity

8.1 Tumor Measures Protocol

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 (34):

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, 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. CRu: defined as "CR unconfirmed" on the basis of minimal residual abnormalities on x-ray such as a residual mass <25% of original measurement, and or residual indeterminate bone marrow aggregates.

IV. PR: a 50% or more reduction in the sum of the products of the diameters of the 6 largest measurable lesions. No new sites of disease.

V. Minor response or failure includes < 50% tumor shrinkage or > 50%, but with tumor regrowth between courses. Progressive disease (PD) is also defined by the appearance of new lymph nodes, of other new or worsening sites of disease, such as $\geq$ 50% increase in the size of liver and/or spleen, or a $\geq$ 50% increase in absolute number of circulating lymphocytes. An unimproved bone marrow, i.e., failure too attain the criteria for PR as defined above, will also be considered to be a failure/non-response (NR).

8.3 All toxicities encountered during the study will be evaluated according to the grading system (0-4) in Appendix B and recorded prior to each course of therapy. Duration and treatment will be recorded.

8.4 **Reporting of Serious Adverse Events to the Principal Investigator, the IRB and, if necessary, the FDA** any serious or unexpected adverse event (including death) due to any cause whether or not related to the study drug(s) must be immediately reported to the principal investigator.

It is the responsibility of the Investigator-Sponsor as the IND holder to **IMMEDIATELY REPORT ALL SERIOUS OR UNEXPECTED ADVERSE EVENTS IMMEDIATELY TO THE IRB CHAIR (AS PER INSTITUTION POLICY) AND, IF APPROPRIATE, TO THE FDA BY COMPLETING AND SUBMITTING A MEDWATCH FORM (FDA FORM 3500A).** The Investigator-Sponsor must promptly provide a copy of the MedWatch form to IDEC Pharmaceutical Corporation at the same time it is submitted to the FDA. **Completed FDA 3500A reports should be faxed to the Pharmacovigilance Department of IDEC Pharmaceuticals Corporation (877-462-1532).** See Appendix A and M for additional information and a blank copy of the MedWatch form.

Serious adverse events occurring after initiation of other anti-cancer therapy do not need to be reported, unless the therapy is initiated and the event occurs within 30 days following the infusion of the study drug or the event is felt to be related to the study drug. All written IND Safety Reports submitted to the FDA by the Sponsor-Investigator must also be faxed to:

Genentech Drug Safety
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4683

9.0 Removal From Study

9.1 Failure to respond after 2 courses, or only minor response after 4 courses. Discuss with P.I.

9.2 Progressive or relapsed disease

9.3 Patients whose maximum response is only PR, particularly if there is biopsy-proven or metabolically active disease, should be considered strongly for alternative therapy, such as stem cell transplantation. CR/CRu patients who do not attain molecular response after Zevalin and 3-6 months of rituximab should also be considered for alternative therapy options.

9.4 Unacceptable toxicity.

9.5 Patient request.

9.6 Noncompliance with requirements of the protocol (at the discretion of the PI).

10.0 Statistical Consideration

10.1.Primary objective and sample size

The objective of this trial is to determine if R-FND followed by Zevalin and rituximab maintenance therapy, is sufficiently efficacious in the treatment of high-risk follicular lymphoma to merit further study in this disease. Although tumor response can be achieved with standard therapy in the majority of patients, these responses are short-lived. Among 729 high-risk patients treated with standard therapy in a multicenter study (including MDACC), the median time to progression (TTP) was 24 months (8). The new regimen would be regarded as a success if median TTP can be prolonged to 36 months or greater. A maximum of 50 patients will be entered on this single arm trial, at an expected accrual rate of 2 patients per month. The trial will require approximately 25 months for patient accrual and an additional 8 months for patient follow-up. If the trial continues to maximum accrual and sufficient follow-up to observe 30 progression events, then a 95% credible interval for median TTP (assumed to be 36 months) would extend from 27.9 to 52.9 months.

10.2. Secondary objectives

Additional endpoints are achievement of response (CR + CRu + PR), as defined in Section 8, overall survival, and safety. Toxicity will be recorded for all patients, separately by grade, type of toxicity, and chemotherapy cycle. For patients treated with Zevalin, subsequent toxicity, including HAMA, will be tabulated separately.

Concerning safety, the R-FND therapy program is known to be safe (24). The use of Zevalin is safe (33,35). The sequential use of Zevalin shortly after chemotherapy is innovative, but not unprecedented (P. Multani, personal communication). The potential for marrow toxicity will be monitored carefully following Zevalin (see Section 7.7).

Treatment related mortality is expected to be rare. Any such events will be reported (see Section 11.4); if 2 or more treatment related deaths occur, the study will be temporarily placed on hold, and discussion about early closure will take place.

10.3. Analysis

The distribution of TTP will be estimated by the method of Kaplan and Meier, and accompanied by 95% confidence interval. Summary statistics will be computed for response and toxicity endpoints. All patients who receive any chemotherapy will be included in calculation of these endpoints. Patients lost to follow-up are regarded as failures if response has not been measured, and as censored observations at date of loss for purpose of estimating TTP.

10.4. Interim monitoring

The trial will be monitored as often as feasible and will be stopped early if, based on current data, it is unlikely that the median TTP following R-FND followed by Zevalin and rituximab maintenance is at least 12 months longer than that achieved with standard therapy (see section 10.5). The probability criterion is recomputed prior to each patient entry (or as often as possible) and requires updating of TTP information for each patient previously entered. This will be accomplished through a web-based computer program and data entry screen provided by the Department of Biostatistics. In the event of insufficient evidence of the superiority of R-FND followed by Zevalin and rituximab maintenance with regard to TTP, the program will print a statement that no further patients should be accrued to the trial.

To obtain operating characteristics of these monitoring procedures, the trial was simulated using several assumed medians for time to progression, with computer generated patients arriving according to a Poisson process at the rate of 2 patients per month. Results follow:

Median TP (months)	Pr (stop early)	# of Patients	Average trial length (months)
12	0.999	23	11.3
24	0.433	43	21.4
36	0.054	49	24.4
48	0.015	50	24.9

In addition to the ongoing monitoring, a planned interim analysis will be performed on the first 25 patients, to be conducted 13 months after registration of patient 25.

Preliminary reviews of safety will also be done: (a) after the enrollment of 10 patients; and (b) after the first 10 patients complete Zevalin therapy.

10.5 At any point in the trial, TTP can be calculated for each patient, with the time interval regarded as censored at the date of last follow-up if progression has not been observed for a patient. At each interim analysis, we will apply a Bayesian method of updating prior information with TTP data observed to that time. It is assumed that the TTP for each patient is exponentially distributed with median, λ_{NEW}, for the R-FND followed by Zevalin and rituximab maintenance group and λ_H for standard treatment. Based on historical data, λ_H is assumed to follow an inverse gamma distribution with mean 24 and variance 16.7. To reflect the little prior knowledge of λ_{NEW} , we assume an inverse gamma distribution with the same mean and variance 100. Since the goal of the study is to increase the median TTP by 12 months, the trial will be stopped early if, based on current data, Pr ($\lambda_{NEW} > \lambda_H$ + 12 month data) < 0.03. The probability cutoff of 0.03 was chosen to obtain a 0.054 false negative (early stopping) probability if the true median TTP is 36 months.

11.0 Data and Protocol Management, and Reporting

11.1 Protocol Compliance: The attending physician and oncology research nurse must be in contact with (and preferably 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. All requirements of the MDACC protocol for outside physician participation must be adhered to (see Appendix G).

11.2 Data Entry: Data must be entered into the Protocol 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.

11.4 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 sponsors.

12.0 References

1. McLaughlin, P et al, in: Newland A, et al, eds: Haematological Oncology, vol. 1 Cambridge Univ. Press, 1991
2. Horning SJ Semin Oncol 1993; 20 (Suppl 5): 75-88
3. Rambaldi A, et al Blood 2002; 99: 856-62
4. McLaughlin P, et al Proc ASCO 2003; 22: 564 (abstr)
5. Solal-Celigny P et al J Clin Oncol 1998; 16: 2332-38
6.Romaguera JE, et al J Clin Oncol 1991; 9: 762-769
7. Solal-Celigny P et al Ann Oncol 2002; 13 (suppl 2): 18 (abstr)
8. Lopez-Guillermo A, et al Blood 1999; 93:3081-87
9. Gribben J, et al Blood 1994; 83: 3800-07
10. Lopez-Guillermo A, et al Blood 1998; 91: 2955-60
11. Luthra R et al Am J Pathol 1998; 153:63-68
12. McLaughlin P, et al, in: Cabanillas F, et al, eds: Advances in Lymphoma Research, Kluwer, 1997
13. Hagenbeek A et al Blood 1998; 92 (Suppl 1) 315a (abstr)
14. McLaughlin P, et al J Clin Oncol 1994; 12: 575-579
15. Velasquez W, et al Proc ASCO 1998; 18: 9a (abstr)
16. McLaughlin P, et al J Clin Oncol 1996; 14: 1262-68
17. Cabanillas F, et al Blood 2000; 96 (Suppl 1): 331a
18. Zinzani PL, et al Ann Oncol 1997; 8: 379
19. Gregory S, et al Leuk. Lymphoma 2001; 40: 315-24
20. Emmanouilides C, et al: Hematol Oncol 1998; 16: 107-116
21. Seymour JF, et al: Blood 1997; 10 (Suppl 1) 343a (abstr)
22. Tsimberidou A, et al Blood 2002; 100: 4351
23.McLaughlin P, et al Semin Oncol 2000; 27 (Suppl 12): 37-41
24. Reff M et al Blood 1994; 83: 435-45
25. Maloney D et al Blood 1994; 84: 2457-66
26. Maloney D et al Blood 1997; 90: 2188-95
27. McLaughlin P, et al J Clin Oncol 1998; 16: 2825-33
28. Czuczman M, et al J Clin Oncol 1999; 17:268-70
29. Coiffier B et al N Eng J Med 2002; 346: 235-42
30. Czuczman M et al Ann Oncol 2001; 12: 109-114
31. Knox SJ et al Clin Cancer Res 1996; 2: 457-70
32. Witzig T et al J Clin Oncol 1999; 17: 3793-803

33. Cheson B et al J Clin Oncol 1999; 17: 1244-53
34. Czuczman, Blood 2002 (abstr); 100 (Suppl 1)