



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 05-098 A(6)

**Phase II Trial of Doxorubicin HCl Liposome injection (Doxil®) in Advanced Stage
Cutaneous T-Cell Lymphoma Followed by Bexarotene (Targretin®)**

THERAPEUTIC/DIAGNOSTIC PROTOCOL

Coordinating Center: Memorial Sloan-Kettering Cancer Center

Principal Investigator: David J. Straus, M.D.

Co-Principal Investigator(s): Steven M. Horwitz, M.D.
Patricia L. Myskowski, M.D..

Investigator(s): Andrew D. Zelenetz, M.D., Ph.D.
Craig H. Moskowitz, M.D.
Paul A. Hamlin, M.D.
Ariela Noy, M.D.
Carol S. Portlock, M.D.
Klaus J. Busam, M.D.
Howard T. Thaler, Ph.D.
Lia Palomba, M.D.
John Gerecitano, M.D., Ph.D.
Matthew Matasar, M.D

Consenting Professional(s): David J. Straus, M.D.
Steven M. Horwitz, M.D.
Andrew D. Zelenetz, M.D., Ph.D.
Craig H. Moskowitz, M.D.
Paul A. Hamlin, M.D.
Ariela Noy, M.D.
Carol S. Portlock, M.D.
Lia Palomba, M.D.
John Gerecitano, M.D., Ph.D.
Matthew Matasar, M.D

Please Note: A Consenting Professional must have completed the mandatory Human

**Memorial Sloan-Kettering Cancer Center
1275 York Ave. New
York, NY 10021**



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Subjects Education and Certification Program.

Collaborating Institution (s): Madeleine Duvic, M.D. (Co-Principal Investigator)
M.D. Anderson Cancer Center
The University of Texas
M.D. Anderson Cancer Center
1515 Holcombe Blvd., Box 434
Rm. FC5.3001
Houston, TX 77030-4009
Phone: (713)745-1113
Fax: (713) 745-3597
mduvic@mdanderson.org

Kenneth Hymes, M.D. (Co-Principal Investigator)
New York University Medical Center
School of Medicine, Hematology
Clinical Cancer Center
160 East 34th Street, 7th Floor
New York, NY 10016
Phone: (212)731-5189
Fax: (212)731-5540
Kenneth.hymes@med.nyu.edu



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André Goy, M.D. (Co-Principal Investigator)
Hackensack University Medical Center
The Cancer Center at Hackensack University Medical Center
360 Essex Street, Ste 302
Hackensack, NJ 07601
Phone: (201)336-8957
agoy@humed.com

Francisco J. Hernandez-Ilizaturri, MD (Co-Principal Investigator)
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, NY 14263
Phone: (201)716-845-3221
francisco.hernandez@roswellpark.org



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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Cutaneous T-cell lymphoma: TNM stages IB, IIA, IIB-IV, either newly diagnosed or previously treated with active measurable disease

Sample Size: 37 patients

Multi-Center Study : Participating sites include M.D. Anderson Cancer Center, Yale University School of Medicine, New York University Medical Center, Hackensack University Medical Center

IND Status: Non-IND

Criteria to be used for response evaluation:

The evaluation of cutaneous tumor burden in CTCL is an evolving process. Skin tumor and lymph node assessments will be performed prior to treatment and after eight cycles of Doxil® according the Severity-Weighted Assessment Tool (SWAT) for CTCL response that is currently employed in IRB 02-078 and 04-051. Also the completion of treatment, history and general physical examination, Karnofsky performance status, CBC with Sézary cell count for patients with Sézary syndrome, and CT scans of the chest, abdomen and pelvis for patients with TNM stage IV CTCL will be obtained. These studies will also be obtained prior to treatment. If clinical complete remission of target skin lesions is suspected, skin biopsies will be repeated following completion of treatment.

Dosing/Regimen:

1. Doxil®Dose: 20mg/m² intravenously. Frequency: 2 weeks. Number of Cycles: 8
2. Targretin®Dose: 300mg/m² orally Frequency: Daily for at least 16 weeks

Schema:

Doxil® every 2 weeks x 8→response assessment→Targretin® x 16 weeks→response assessment, CR/PR→continue Targretin® until relapse.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective: To determine the progression-free survival in patients with CTCL treated by Doxil® followed by Targretin®

Secondary Objective: To determine the major response rate (CR + PR) of Doxil® followed by Targretin® in the treatment of CTCL



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3.0 BACKGROUND AND RATIONALE

Cutaneous T-cell lymphoma (CTCL) is a chronic lymphoma that is not curable with systemic treatment. Doxorubicin is one of many single agents with activity in CTCL¹. Doxorubicin HCl liposome injection (Doxil®) is licensed for the treatment of Kaposi's sarcoma. High concentrations are attained in skin lesions of Kaposi's sarcoma following intravenous administration of Doxil®. At 48 and 96 hours post-infusion of Doxil® 20mg/m² in 11 patients, the concentrations of Doxil® in biopsies of skin lesions of Kaposi's sarcoma were several-fold higher than in those in normal skin. Adverse events led to discontinuation of Doxil® in only 5% of patients with Kaposi's sarcoma treated at this dose. Wollina et al.² treated 34 CTCL patients with Doxil; 27 received Doxil at a dose of 20 mg/m² every 2-4 weeks, 23 of whom were treated every 4 weeks. The major response rate was 88.2% with 15 patients achieving a CR or CRu (not confirmed by skin biopsy) and 15 a PR. Event-free survival was 12.0 months ± 9.5 months. Only 6 patients experienced grade 3 or 4 toxicities. Prince and colleagues³ reported on two patients with CTCL who failed to respond to Doxil®. Both were refractory to other previously administered intravenous chemotherapy. Although the Package Insert for Doxil® recommends a dose of 20 mg/m² administered every 3 weeks for Kaposi's sarcoma, the safety and efficacy of this dose administered every two weeks has been recently established for breast cancer^{4,5}.

Bexarotene (Targretin®) is a synthetic retinoid that selectively activates retinoid X receptors (RXRs). These retinoid receptors have biologic activity distinct from that of retinoic acid receptors (RARs). Once activated, these receptors function as transcription factors that regulate the expression of genes that control cellular differentiation and proliferation. By mechanisms that are not known, activity has been found against CTCL, and the drug has been recently commercially released. The optimal dose was 300 mg/m²/day, and patients on the trials were treated for up to 97 weeks. At the optimal dose, in patients with refractory or persistent early stage CTCL, the overall response rate was 54% and was 45% for patients with refractory advanced stage disease^{6,7}. At this dose, most side effects were infrequent and included pruritus, headache, peripheral edema, leukopenia, hypothyroidism and rash. Grade 3 or 4 hypertriglyceridemia and hypercholesterolemia were seen in 25%-30% of patients. These elevations are reversible with cessation of the drug, and some patients were continued on treatment with the addition of antilipemic treatment.

There are no preclinical data on potential synergy of Doxil® and Targretin®. Sequential treatment with single agents in patients with CTCL has been as effective as and less toxic than the use of drug combinations⁸.



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Further organized phase II investigation of Doxil® followed by Targretin® treatment of CTCL seems warranted in view of the following considerations:

1. Treatment of patients with CTCL with both agents results in high response rates.
2. The high skin lesion concentrations and efficacy were seen in the treatment of Kaposi's sarcoma with Doxil®.
3. Severe adverse events were infrequent in patients with Kaposi's sarcoma or CTCL treated at the doses proposed in this study.
4. Although Doxil® alone results in a high overall response rate, the responses of at least 50% of the patients are incomplete, and progression-free survival can be relatively short.
5. Although cardiotoxicity is less with Doxil® than doxorubicin, concern about eventual cardiac toxicity might limit the continuous use of Doxil® as a maintenance drug. The responses with Doxil® might be more rapid than with Targretin®. The latter agent might improve on initial responses to Doxil® and maintain complete and partial remissions for a longer time than a brief course of Doxil® alone.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a phase II, multi-center, open-label, single arm trial. The goals are to prolong progression-free survival and improve response rate in patients with cutaneous T-cell lymphomas with the sequential use of Targretin after an optimal course of Doxil

4.2 Intervention

Patients will be treated with intravenous Doxil® every two weeks for 8 doses (16 weeks). Responses will be assessed. They will then receive Targretin® orally for at least 16 weeks. Patients who achieve a CR or PR may continue on Targretin® until relapse.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Doxil® (doxorubicin HCl liposome injection)

Doxil® (doxorubicin HCl liposome injection) is doxorubicin hydrochloride (HCl) encapsulated in STEALTH® liposomes for intravenous administration. The active ingredient of Doxil® is doxorubicin HCl, a cytotoxic anthracycline antibiotic isolated from *Streptomyces peucetius* var. *caesius*. The mechanism of action of doxorubicin HCl is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis. Cell structure studies have demonstrated rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations.

If at anytime the patient develops progressive disease he/she will be taken off study and referred for alternative therapy.



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If at anytime the patient develops unacceptable toxicity he/she will be removed from study.

If at anytime the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

Doxil[®] is doxorubicin HCl encapsulated in long-circulating STEALTH[®] liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The STEALTH[®] liposomes of Doxil[®] are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time.

Doxil[®] (doxorubicin HCl liposome injection) is indicated for:

DOXIL[®] (doxorubicin HCl liposome injection) is indicated for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy.

DOXIL[®] (doxorubicin HCl liposome injection) is also indicated for the treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy.

These indications are based on objective tumor response rates. No results are available from controlled trials that demonstrate a clinical benefit resulting from this treatment, such as improvement in disease-related symptoms or increased survival.

Doxil Study Drug Supplier/Accountability

Doxil will be provided by Ortho Biotech Products, L.P. The investigator agrees not to supply the study drug to any person other than investigators, designated staff and the subjects participating in the study. It is the responsibility of the clinical investigator to ensure that all study drug received at the site will be inventoried and accounted for throughout the study. Records must be kept by the institution. Administration of the study drug must be recorded in the patient's permanent record. The study drug provided may not be used for any purpose other than what is outlined in this protocol, including other human studies, animal investigations or in vitro testing. Study drug will be stored in a limited access or locked area and under refrigeration.

Doxil Storage and Handling

Refrigerate unopened vials of Doxil[®] at 2°C to 8°C (36°F to 46°F). Avoid freezing. Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on Doxil[®].



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Caution should be exercised in the handling and preparation of Doxil[®]. The use of gloves is required. If Doxil[®] comes into contact with skin or mucosa, immediately wash thoroughly with soap and water.

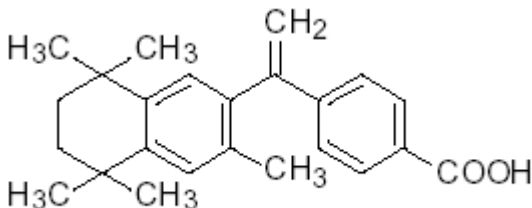
Doxil[®] should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of Doxil[®], extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. Doxil[®] must not be given by the intramuscular or subcutaneous route.

Doxil[®] should be handled and disposed of in a manner consistent with other anticancer drugs. Several guidelines on this subject exist.

Targretin[®] (bexarotene)

Targretin[®] (bexarotene) is a member of a subclass of retinoids that selectively activate retinoid X receptors (RXRs). These retinoid receptors have biologic activity distinct from that of retinoic acid receptors (RARs). Each soft gelatin capsule for oral administration contains 75 mg of bexarotene.

The chemical name is 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl] benzoic acid, and the structural formula is as follows:



Bexarotene is an off-white to white powder with a molecular weight of 348.48 and a molecular formula of C₂₄H₂₈O₂. It is insoluble in water and slightly soluble in vegetable oils and ethanol, USP.

Each Targretin[®] (bexarotene) capsule also contains the following inactive ingredients: polyethylene glycol 400, NF, polysorbate 20, NF, povidone, USP, and butylated hydroxyanisole, NF. The capsule shell contains gelatin, NF, sorbitol special-glycerin blend, and titanium dioxide, USP.

Bexarotene selectively binds and activates retinoid X receptor subtypes (RXRa, RXRb, RXRg). RXRs can form heterodimers with various receptor partners such as retinoic acid receptors (RARs), vitamin D receptor, thyroid receptor, and peroxisome proliferator activator receptors (PPARs). Once activated, these receptors function as transcription factors that regulate the expression of genes that control cellular differentiation and proliferation. Bexarotene inhibits the growth *in vitro* of some tumor cell lines of hematopoietic and squamous cell origin. It also induces tumor



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regression *in vivo* in some animal models. The exact mechanism of action of bexarotene in the treatment of cutaneous T-cell lymphoma (CTCL) is unknown.

Targretin® capsules were evaluated in 152 patients with advanced and early stage cutaneous T-cell lymphoma (CTCL) in two multicenter, open-label, historically controlled clinical studies conducted in the U.S., Canada, Europe, and Australia.

The advanced disease patients had disease refractory to at least one prior systemic therapy (median of two, range one to six prior systemic therapies) and had been treated with a median of five (range 1 to 11) prior systemic, irradiation, and/or topical therapies. Early disease patients were intolerant to, had disease that was refractory to, or had reached a response plateau of six months on, at least two prior therapies. The patients entered had been treated with a median of 3.5 (range 2 to 12) therapies (systemic, radiation, and/or topical).

The two clinical studies enrolled a total of 152 patients, 102 of whom had disease refractory to at least one prior systemic therapy, 90 with advanced disease and 12 with early disease. This is the patient population for whom Targretin® capsules are indicated. Patients were initially treated with a starting dose of 650 mg/m²/day with a subsequent reduction of starting dose to 500 mg/m²/day. Neither of these starting doses were tolerated, and the starting dose was then reduced to 300 mg/m²/day. If, however, a patient on 300 mg/m²/day of Targretin® capsules showed no response after eight or more weeks of therapy, the dose could be increased to 400 mg/m²/day. Tumor response was assessed in both studies by observation of up to five baseline defined index lesions using a Composite Assessment of Index Lesion Disease Severity (CA). This endpoint was based on a summation of the grades, for all indexes lesions, of erythema, scaling, plaque elevation, hypopigmentation or hyperpigmentation, and area of involvement. Also considered in response assessment was the presence or absence of cutaneous tumors and extracutaneous disease manifestations.

All tumor responses required confirmation over at least two assessments separated by at least four weeks. A partial response was defined as an improvement of at least 50% in the index lesions without worsening, or development of new cutaneous tumors or non-cutaneous manifestations. A complete clinical response required complete disappearance of all manifestations of disease, but did not require confirmation by biopsy.

At the initial dose of 300 mg/m²/day, 1/62 (1.6%) of patients had a complete clinical tumor response and 19/62 (30%) of patients had a partial tumor response. The rate of relapse (25% increase in CA or worsening of other aspects of disease) in the 20 patients who had a tumor response was 6/20 (30%) over a median duration of observation of 21 weeks, and the median duration of tumor response had not been reached. Responses were seen as early as 4 weeks and new responses continued to be seen at later visits.



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Targretin® capsules are supplied as 75-mg off-white, oblong soft gelatin capsules, imprinted with “Targretin,” in high density polyethylene bottles with child-resistant closures.

Bottles of 100 capsules..... NDC 64365-502-01

Store at 2°-25°C (36°-77°F). Avoid exposing to high temperatures and humidity after the bottle is opened. Protect from light.

Manufactured for: Ligand Pharmaceuticals Incorporated
San Diego, CA 92121
by: R.P. Scherer
St. Petersburg, FL 33716

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Patient \geq 18 years of age.
- Cutaneous T-cell lymphoma: TNM stages IB, IIA, IIB-IV with biopsy documentation within six weeks before treatment. Repeat biopsies are not required within six weeks before treatment for patients with Sézary syndrome and objective evidence of circulating cells.
- KPS \geq 60
- Acceptable organ function: absolute neutrophil count \geq 1500/ μ L, platelet count \geq 100,000/ μ L, bilirubin \leq 1.5x upper limit of normal, creatinine \leq 1.5x upper limit of normal, SGOT (AST) and SGPT (ALT) \leq 2.5x upper limit of normal
- MUGA or 2-d echocardiogram indicating an ejection fraction of \geq 50% within 42 days prior to first dose of study drug. The method used at baseline must be used for later monitoring.
- Patients previously treated with doxorubicin or epirubicin are eligible if the total cumulative dose does not exceed 300 mg/m² for doxorubicin or 540 mg/m² for epirubicin.
- Negative pregnancy test. Effective birth control measures.
- Topical corticosteroids, with the exception of those with high potency (class 1), will be allowed for patients with erythroderma-Sézary syndrome (T4) and tumor stage (T3) with intense pruritus. Therapy with non-prescription emollients will also be allowed on study.



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6.2 Subject Exclusion Criteria

- Pregnant or lactating women
- No acute intercurrent disease including active potentially life-threatening infection or heart disease, with New York Heart Association Class II or greater, or clinical evidence of congestive heart failure.
- History of hypersensitivity reactions attributed to a conventional formulation of doxorubicin HCL or components of Doxil
- No demonstrated resistance to prior treatment with Targretin®.
- Patients using class 1 high potency topical therapy will not be allowed on to the study.

Please note copies of source documentation confirming eligibility for patients enrolling at outside institutions must be provided to the MSKCC CTO registrar at the time of registration. Please fax to 212-557-0786.

7.0 RECRUITMENT PLAN

The trial will require 37 patients to meet study endpoints. With the targeted annual accrual of 10-15 patients, this study will require about 3 years to complete accrual.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC-Lead Center), M. D. Anderson Cancer Center, New York University Medical Center, Hackensack University Medical Center, and Roswell Park Cancer Institute. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

Consent Process

Participation is voluntary. The patient must be aware of the nature of his/her disease and willingly consent after being informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks and discomforts. All patients will be required to sign a statement of informed consent that conforms to IRB guidelines. Informed consent will be documented by the use of a written consent form that has been approved by the institution's IRB. Three copies of the informed consent will be signed and dated by the patient or the patient's legally authorized representative. One copy will be given to the patient, one copy will be filed in the patient's medical record, and one copy will be retained in the Protocol Participant Registration (PPR) Office. Written consent will be obtained by either the principal investigators or participating investigators.



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8.0 PRETREATMENT EVALUATION

- History and physical examination. Karnofsky Performance Status. A dermatologist will make skin score determination. A two item self-reported pruritus questionnaire will be administered. (to be done within 14 days prior to entry into the study)
- Laboratory Evaluations:
 - f* CBC, platelet count, differential count with absolute neutrophil count (to be done within 14 days prior to entry into the study)
 - f* Serum chemistry panel: electrolytes, BUN, creatinine, SGOT (AST), SGPT (ALT), alkaline phosphatase, LDH, total bilirubin, albumin, total protein, calcium, amylase, uric acid. After at least an eight-hour fast: glucose, cholesterol, triglycerides (to be done within 14 days prior to entry into the study)
 - f* T4, TSH (to be done within 14 days prior to entry into the study)
 - f* Patients must have a MUGA scan or 2-d echocardiogram indicating an ejection fraction of $\geq 50\%$ within 42 days prior to first dose of study drug. The method used at baseline must be used for later monitoring.
- Urinalysis (to be done within 7 days prior to entry into the study)
- Patients with stage IV disease (TNM): CT of chest, abdomen and pelvis (to be done within 6 weeks prior to entry into the study)
- For women of child bearing potential: beta-HCG pregnancy test (to be done within 7 days prior to entry into the study)
- Patients with Sézary syndrome will have a Sézary cell count and/or flow cytometry panel (to be done within 14 days prior to entry into the study)

9.0 TREATMENT/INTERVENTION PLAN

Dosing/Regimen:

Doxil@Dose: 20mg/m² intravenously. Frequency: 2 weeks. Number of Cycles: 8 (16 weeks)

To minimize the risk of infusion-related reactions, the first infusion of DOXIL should be administered over 90 minutes as follows:

10 mL over 1st 10 minutes



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20mL over next 10 minutes
 40mL over next 10 minutes
 then, complete the infusion over a total of 90 minutes

Targretin® Dose: 300mg/m² orally Frequency: Daily for at least 16 weeks to be started within 2 weeks of tumor assessment (It is recommended that patients be treated prophylactically with an agent to lower triglycerides such as fenofibrate or atorvastatin)

Schema:

Doxil® every 2 weeks x 8 → response assessment → within 2 weeks of tumor assessment:
 Targretin® x 16 weeks → response assessment, CR/PR → continue Targretin® until relapse.

Dose Modification Guidelines

Patients should be carefully monitored for toxicity. Adverse events, such as palmar-plantar erythrodyesthesia (hand-foot syndrome), hematologic toxicities, and stomatitis may be managed by dose delays and adjustments. Following the first appearance of Grade 1 toxicity, patients will be prescribed topical betamethasone dipropionate (Diprolene) 0.05% gel to use twice daily on hands and feet only until signs and symptoms resolve. Following the first appearance of a Grade 2 or higher adverse event, the dosing should be adjusted or delayed as described in the following tables. Once the dose has been reduced, it should not be increased at a later time.

PALMAR – PLANTAR ERYTHRODYESTHESIA	
Toxicity Grade	Dose Adjustment
1 (mild erythema, swelling, or desquamation not interfering with daily activities)	Redose unless patient has experienced previous Grade 3 or 4 toxicity. If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.
2 (erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter.)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. If after 2 weeks there is no resolution, Doxil® should be discontinued.



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3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, Doxil® should be discontinued.
4 (diffuse or local process causing infectious complications, or a bed ridden state or hospitalization)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, Doxil® should be discontinued.

HEMATOLOGICAL TOXICITY			
GRADE	ANC	PLATELETS	MODIFICATION
1	1500 – 1900	75,000 - 150,000	Resume treatment with no dose reduction
2	1000 - <1500	50,000 - <75,000	Wait until ANC > 1,500 and platelets > 75,000; redose with no dose reduction
3	500 – 999	25,000 - <50,000	Wait until ANC > 1,500 and platelets > 75,000; redose with no dose reduction
4	<500	<25,000	Wait until ANC > 1,500 and platelets > 75,000; redose at 25% dose reduction or continue full dose with cytokine support.

STOMATITIS	
Toxicity Grade	Dose Adjustment
1 (painless ulcers, erythema, or mild soreness)	Redose unless patient has experienced previous Grade 3 or 4 toxicity. If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.
2 (painful erythema, edema, or ulcers, but can eat)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. If after 2 weeks there is no resolution, Doxil® should be discontinued.



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3 (painful erythema, edema, or ulcers, and cannot eat)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, Doxil® should be discontinued.
4 (requires parenteral or enteral support)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, Doxil® should be discontinued.

Myeloid and erythroid growth factor support will be permitted according to institutional or National Comprehensive Cancer Network (NCCN) guidelines.

In the event of Targretin® dose-limiting toxicity (NCI toxicity grade 3 or 4 or serum triglycerides ≥ 800 mg/dL), the 300 mg/m²/day dose may be reduced to 200 mg/m²/day, or a 200 mg/m²/day dose may be reduced to 100 mg/m²/day. Suspension of Targretin capsules treatment may accompany dose reductions for up to 14 days, if necessary for recovery from toxicity. Patients with dose-limiting toxicities at the 100 mg/m²/day dose level should be withdrawn from the study.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Treatment visits every 2 weeks for Doxil® administration for 16 weeks. At each visit: history, physical exam, KPS, toxicity assessment, CBC, platelet count.

10.2 Tumor assessment within 2 weeks following the last dose of Doxil®, optimally between 7 and 14 days. For patients with stage IV disease (TNM) with baseline lymphadenopathy on CT scans of chest, abdomen and pelvis: repeat CT scans of chest, abdomen and pelvis. Patients with Sezary syndrome will have Sézary cell count and/or flow cytometry. Patients who have a CCR should have a biopsy to document a pathological CR. Two item self-reported pruritus questionnaire will be administered at time of tumor assessment. The details for tumor assessments at 16 and 32 weeks are described in Section 12.0 and in the Table in Appendix 3.

10.3 Cardiac Safety Monitoring

All patients will be monitored for a decrease in LVEF based on the criteria below: Baseline Left Ventricular Ejection Fraction (LVEF) determinations will be performed on all patients prior to enrollment in the trial. Patients will not be enrolled if LVEF <50%. If during treatment the LVEF falls to $\leq 45\%$, or the ejection fraction (LVEF) falls by 20% from the baseline level, Doxil® will be discontinued. The investigator



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may verify the LVEF from a MUGA by obtaining an ECHO with cardiac consultation. If there is no evidence of cardiac damage determined by ECHO the patient may continue on treatment.

MUGA or ECHO (LVEF) Schedule for all patients:

- f* Cumulative anthracycline dose of $< 350\text{mg}/\text{m}^2$: physicians discretion
- f* Cumulative anthracycline dose of $\geq 350\text{mg}/\text{m}^2$: every two cycles

10.4 Within 2 weeks of tumor assessment: history, physical exam, KPS, CBC, platelet count, total bilirubin, SGOT (AST), SGPT (ALT), creatinine, uric acid, fasting triglycerides and cholesterol, T4, TSH.

10.5 Within 2 weeks after tumor assessment begin oral Targretin® for 16 weeks.

10.6 Followup visits: at 2 weeks, 4 weeks, 8 weeks, 12 weeks, 16 weeks: history, physical examination, KPS, CBC, platelet count, total bilirubin, SGOT (AST), SGPT (ALT), creatinine, uric acid, fasting triglycerides and cholesterol, T4, TSH. Tumor assessment at 16 weeks on Targretin® including self-reported pruritus questionnaire. Imaging with CT scans of the chest, abdomen and pelvis will be repeated at 16 weeks for stage IV patients if initial lymphadenopathy was present. Patients with Sézary syndrome will also have Sézary cell counts and/or flow cytometry repeated at 16 weeks. Responding patients may continue on Targretin® until progression. Followup visits will be at least every 3 months for 5 years or until signs or symptoms of tumor progression.

11.0 TOXICITIES/SIDE EFFECTS

Toxicity will be described according to NCI Common Toxicity Criteria (Version 3.0)

11.1 Doxil®

- f* Cardiac toxicity: cardiomyopathy and/or congestive heart failure. Possibly non-specific arrhythmias
- f* Myelosuppression. Leukopenia more common than thrombocytopenia and anemia
- f* Infusion reactions: shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea and/or hypotension, anaphylaxis
- f* Palmar-plantar erythrodysesthesia (hand-foot syndrome)
- f* Stomatitis
- f* Pregnancy, Category D risk
- f* Injection site reactions. An irritant, not a vesicant.
- f* Asthenia
- f* Nausea/vomiting

11.2 Targretin®



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- f* Hyperlipidemia: hypertriglyceridemia more common than hypercholesterolemia
- f* Hypothyroidism
- f* Headache
- f* Fever
- f* Asthenia, myalgia, arthralgia
- f* Rash
- f* Pancreatitis (associated with hypertriglyceridemia)
- f* Reversible liver function abnormalities
- f* Leukopenia/neutropenia
- f* Anemia
- f* Pregnancy, Category X risk

11.2.1 Serious Adverse Event (SAE) Reporting

For Participating Sites:

Any SAE will be reported to the local institution's IRB. In addition, it will need to be sent to MSKCC as the coordinating center and Ortho Biotech as soon as possible but no later than 5 days from the onset of the event.

Ortho Biotech will be notified of SAEs within 24 hours by faxing a completed MedWatch 3500 form to 908-541-4565; this form must also be faxed to the MSKCC principal investigator, David Straus, MD (phone: 212-639-8365; fax :646-422-2291; email: strausd@mskcc.org). The sites should fax to Ortho Biotech and MSKCC at the same time.

The Study PI will fax a copy of all SAE's within 5 days to outside site principal investigators to report to their own local IRB's.

Participating sites should send the following information to the coordinating center:

1. The initials of the subjects, patient MRN #, MSKCC protocol# and title
2. The date the event occurred
3. A description of the SAE
4. An explanation of how the SAE was handled
5. A description of the subject's condition
6. Indication if the subject remains on the study
7. Indication if the event is considered related to the treatment (drug, device, intervention)
8. Indication if an amendment will need to be made to the protocol and/or consent form as a result of the SAE.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

- 12.1 At 16 weeks (completion of Doxil® treatment) and after 16 weeks of Targretin® treatment: CT scans of chest, abdomen and pelvis for TNM stage IV patients who had positive findings prior to treatment.



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- 12.2 History and physical examination including skin assessment
- 12.3 Karnofsky performance status.
- 12.4 CBC with Sézary cell count and/or flow cytometry in patients with Sézary syndrome.
- 12.5 Assessment of response status and any residual toxicity will be performed 4 weeks after completion of treatment.
- 12.6 Biopsy of residual lesions 4 weeks after the completion of treatment if clinical complete remission is suspected.
- 12.7 Dermatologic evaluation of response

Dermatologic responses will be determined by the Severity-Weighted Assessment Tool (SWAT), a standardized approach to measuring the extent and severity of overall skin disease in patients with CTCL. It will be briefly described and full details are provided in an appendix. The purpose of this description is to optimize intra-observer objectivity and to minimize the potential for intra-observer and inter-observer variability in the measurement of overall skin disease. Only physicians who received training will be permitted to conduct SWAT assessments during the clinical study. It is essential that physicians adhere as closely as possible to the prescribed procedures so as to reduce measurement error and variability. All efficacy assessments should be performed by the same physician for each patient whenever possible. Physicians will be instructed not to examine previous SWAT assessments and full body photographs prior to conducting the current SWAT assessment.

1. Total Body Surface Area (TBSA) Involvement by Skin Disease

The body is divided into 12 regions with pre-assigned %TBSA based on the burn literature. The extent of skin disease in each region is quantified by using the patient's palm to measure the %TBSA involvement within region:
Patient's palm with 4 fingers (excluding the thumb) is 1% of TBSA
Patient's palm without fingers is 0.5% of TBSA.

The patient's palm with 4 fingers is traced on a transparency sheet at the baseline visit, using a permanent marker that will not rub off or smear. The transparency of the patient's palm should be used in all SWAT assessments during the course of the clinical study. The transparency will be labeled with the patient's study ID number kept in the patient's study file on site. Using the baseline visit transparency of the patient's palm, the investigator will measure and record on the case report form (Example of table from CRF is given below) the %TBSA for each lesion type within each of the 12 regions.

2. Severity Weighting Factor

The severity weighting factors will be the following:



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1= patch (flat erythema or erythema with mild infiltration)
2=plaque (e levated erythema or erythema with moderate infiltration)

4= tumor or ulceration (erythema with fissuring, ulceration or tumor)

Patch is defined as abnormal skin not elevated from normal skin. A plaque is defined as abnormal skin elevated from normal skin by < 5 mm. A plaque elevated ≥5 mm is a tumor.

3. Calculating Skin Scores

The sum of %TBSA by lesion is derived by summing the %TBSA from all regions affected by the lesion. The sum of %TBSA across lesion types (patches, plaques and tumors) within each region can not exceed the %TBSA for the region. For example, the %TBSA for the head region is 7%. The sum of %TBSA across lesion types from head can only range from 0-7%. The skin score subtotal by lesion type are derived by multiplying the sum of %TBSA for patches from all regions by 1, sum of %TBSA of plaques from all regions by 2, and the sum of %TBSA of tumors or ulcers from all regions by 4. The skin score total is derived from summing the skin score subtotals for patches, plaques and tumors or ulcers. The skin score total is dimensionless with a scale of 0 to 400.

Region	% TBSA for the region	% TBSA Patch (or flat erythema)	% TBSA Plaque (or elevated/indurated erythema)	% TBSA Tumor/ Ulceration (or erythema w/fissuring, ulceration)
Head	7			
Neck	2			
Anterior Trunk	13			
Posterior Trunk	13			
Buttocks	5			
Genitalia	1			
Upper Arms	8			
Forearms	6			
Hands	5			
Thighs	19			
Lower Leg	14			
Feet	7			
% BSA by category	100			
Severity Weighting Factor		X 1	X 2	X 4
Skin Score Subtotal				



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Responses will be determined by the criteria described in the table below. Progression of disease while on treatment should be confirmed by a second assessment 1-4 weeks later so that patients who experience a temporary flare of disease due to skin infection or other intercurrent illnesses are not removed from the study prematurely.

Assessment	Description	Status
Completely clear	No evidence of disease; 100% improvement	CCR
Marked Improvement	Greater than or equal to 50% decrease in skin scores compared to baseline and improvement is maintained for 4 weeks	PR
Slight Improvement	Less than 50% decrease in skin scores compared to baseline	SD
Worse	$\geq 25\%$ increase in skin scores compared to baseline while the patient is actively taking the study drug or $\geq 50\%$ increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes (should be documented by biopsy) compared to baseline while the patient is actively taking the study drug.	PD

Assessment of Overall Skin Disease

Pruritus Relief (Appendix 1)

The intensity of pruritus will be evaluated by the patient at baseline, at the week 16 (end of treatment with Doxil®) and week 32 (after 16 weeks of treatment with Targretin®) using a 1-10 point scale, where 0 is no pruritus and 10 is the worst imaginable pruritus. A 3-point decrease in pruritus intensity confirmed by a second assessment at least 4 weeks later without an increase in the use of anti-pruritic medications is considered clinically significant in those whose pruritus score is ≥ 3 on the 0-10 point scale at baseline.

4. As a secondary goal, index lesion severity will be evaluated by a modified Composite Assessment Scale (Appendix 2). These are measurements of skin disease that have been employed and validated in the phase II-III studies of Targretin® and in the current MSKCC trial of Targretin® of Intron-A® (IRB #01-128) in CTCL. Up to 4 index skin lesions will be chosen from representative patch, plaque and tumor lesions, and erythrodermic lesions. For erythrodermic patients, a 10x10 cm. area, easily identified by anatomic landmarks will be chosen and assessed by the same scale. These index lesions will be photographed and assessed at the same time as the SWAT assessment.

In the Phase II-III studies of Targretin capsules in CTCL, the Composite Assessment (CA) of Index Lesion Disease Severity was based on a core element of the summation of index lesion



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clinical signs . Up to a maximum of five (5) cutaneous T-cell lymphoma lesions were designated as index lesions. If the patient had five or fewer CTCL lesions, then all CTCL lesions were designated as index lesions. If the patients had more than five CTCL lesions, then five lesions that were representative of the patient's overall cutaneous disease were designated as index lesions. The index lesions were preferably separate and distinct from other lesions in order to minimize the chance of lesion confluence. Individual index lesion clinical signs and symptoms were to have been graded at each visit according to a 0-to-8 point scale (see Table). A CA summation was generated by summing the grades for each index lesion for each clinical sign. To determine the area of each index lesion, the longest diameter and the longest diameter perpendicular to this diameter of each index lesion were to have been measured to the nearest millimeter. The area in square centimeters was then converted to a 0-to-18 scale in order to provide a means for integrating the area into the CA summation of grades (see Table). The summation of CA grades at baseline was divided into the summation of CA grades at each subsequent post-baseline study visit to determine the CA ratio to provide an objective measure of the patient's response to treatment (e.g., a CA ratio <1.0 indicated improvement in disease and a ratio >1.0 indicated a worsening of disease). This CA score was found to correlate with the Physicians Global Assessment, which is replaced by SWAT in this study.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at anytime the patient develops progressive disease he/she will be taken off study and referred for alternative therapy.

If at anytime the patient develops unacceptable toxicity he/she will be removed from study. If

at anytime the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

14.0 BIOSTATISTICS

This is a phase II, multi-center, open-label, single arm trial. The goal of this trial is to improve response rate and prolong progression-free survival in patients with cutaneous T-cell lymphomas with the sequential use of Targretin® after an optimal course of Doxil®. The primary endpoint is progression-free survival at 12 months. Based on historical data, the median progression-free is 12 months for treatment of CTCL with Doxil®. With the new treatment, this trial will be considered as promising if the probability of progression-free at 12 months is 70%. Thirty seven patients are needed in this trial with conventional type I error 0.05 and power 0.8. This trial would be considered to be promising for further study if 24 or more patients are progression free at one year. There is 80% chance of observing 24 or more progression-free out of 37 patients if the true rate is 70% or better.



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The second endpoints are complete response and partial response rates.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Subject Registration (at Memorial Sloan-Kettering Cancer Center)

The following person(s) can obtain informed consent: MSKCC: David J. Straus, M.D., Steven M. Horwitz, M.D., Andrew D. Zelenetz, M.D., Ph.D., Craig H. Moskowitz, M.D., Paul A. Hamlin, M.D., Ariela Noy, M.D., Carol S. Portlock, M.D., Lia Palomba, M.D., John Gerecitano, M.D., Ph.D., and Matthew Matasar, M.D.

Confirm with electronic medical record that the patient has received the Notice of Privacy Practice. This must be obtained before the eligibility confirmation and obtaining of the research informed consent.

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain written informed consent, by following procedures defined in section entitled Informed Consent Procedures.

All patients must be registered through the Protocol Patient Registration (PPR) at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am - 5:30pm at telephone (646)735-8000, fax (646) 735-0008. The completed signature page of the informed consent form, the completed signature page of the Research Authorization and a completed Eligibility Checklist must be faxed to PPR at the time of registration.

For Participating Centers:

The following person(s) can obtain informed consent:

M.D. Anderson Cancer center: Madeleine Duvic, M.D., New York University Medical Center:: Kenneth Hymes, M.D.; Hackensack University Medical Center: André Goy, M.D., Roswell Park Cancer Institute: Francisco J. Hernandez-Ilizaturri, M.D.

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center. To complete registration and enroll a patient from an outside center, the study coordinator will fax to Clinical Trials Office at MSKCC the completed MSKCC eligibility checklist, the last page of the signed informed consent, the signature page of the Research Authorization, and supporting source documentation for eligibility questions. If the patient meets all criteria, the patient will be enrolled and then the patient will be assigned a MSKCC study number. The MSKCC registrar will fax back an enrollment confirmation. Patients from all sites must be registered with the Protocol Patient Registration (PPR) at MSKCC before starting therapy, Telephone 646-735-



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8000, Fax 646-735-0008, Hours of operation 8:30 am to 5:30 pm (Eastern Time) Monday through Friday.

During the registration process registering individuals will be required to answer specific eligibility questions and provide the following information:

Registering Individual	[Last, First Name]
Notice of Privacy Status	[Yes, No, N/A]
Research Authorization	[Date]
MSKCC IRB Protocol#	
Attending of Record (if applicable)	[Last, First Name]
Consenting Professional	[Last, First Name]
Informed Consent Date	
Patient's Full Name	[Last, First Name]
Patient MRN	

15.2 Protocol Patient Number

Once eligibility has been established, the patient is assigned an MSKCC Clinical Research Database (CRDB) patient number. This number is unique to the patient and must be written on all data and correspondence for the patient.

15.3 Randomization

NA

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secured database (Clinical Research Database, CRDB) at Memorial Sloan-Kettering Cancer Center.

Standardized Case Report Forms (CRFs) have been generated for this study. Affiliate sites will be responsible for filling out these MSKCC case report forms. Blank case report forms will be sent to the data managers at each site (for photocopying and use). These forms and the



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required source documentation must be submitted to MSKCC in a timely fashion (please see Appendix 4 for schedule of data collection forms). When a patient goes off-study all CRFs are required to be sent to MSKCC no later than 4 weeks after the off-study date. Participating sites must fax case report forms bimonthly to: (212) 557-0787 to the attention of the RSA. Forms can also be mailed to the address below.

Memorial Sloan-Kettering Cancer Center
Clinical Trials Office
Dorothy Lin
633 Third Avenue – 15th floor
New York, NY 10017

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of once a year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: <http://cancertrials.nci.nih.gov/researchers/dsm/index.html>. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: <http://mskweb2.mskcc.org/irb/index.htm>

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and



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II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation
Inclusion of Children in Research

This protocol/project does not include children because the number of children is limited and because the majority are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

17.0 PROTECTION OF HUMAN SUBJECTS

Inclusion of Children in Research

This protocol/project does not include children because the number of children is limited and because the majority are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

17.1 Privacy

It is the responsibility of the Research Staff to ensure that protocol patients have received the Center's Notice of Privacy Practices. If the subject has not already done so, MSK personnel must try to obtain acknowledgment before the patient participates in this study.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2 Serious Adverse Event (SAE) Reporting

At Memorial Sloan-Kettering Cancer Center:

Any SAE must be reported to the IRB as soon as possible but no later than 5 calendar days. The IRB requires a Clinical Research Database (CRDB) AE report to be delivered to the Institutional SAE Manager (307 East 63rd Street, 1st Floor) containing the following information:



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Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
 - A explanation of how the AE was handled
 - A description of the subject's condition
 - Indication if the subject remains on the study
 - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

All serious adverse events regardless of severity or relationship must be reported to Ortho Biotech Products, L.P. within 24 hours of the investigational staff's knowledge.

SAE Fax Number: 908-541-4565

***Serious Adverse Event (SAE):**

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (The patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.),
- requires inpatient hospitalization or prolongation of existing hospitalization,

Hospitalizations that do not meet these criteria are:

- reasons described in the protocol, e.g., drug administration, protocol-required testing
- social reason in the absence of an AE
- surgery or procedure planned prior to entry into the trial
- results in persistent or significant disability/incapacity,
or
- is a congenital anomaly/birth defect.

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be



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immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above.

18.0 INFORMED CONSENT PROCEDURES

All Patients will be required to sign a statement of informed consent that has been approved by both the sponsor and by the local Institutional Review Board. The principal investigator is responsible for verifying compliance with all aspects of both the protocol and the informed consent process, which must indicate that the patient has received adequate information to make such informed consent.

Patients willing to enroll will be required to sign three copies of the consent form; one will be returned to the patient, one will be filed in the patient's chart, and one copy will be filed with Protocol Patient Registration (PPR) at the Office of Clinical Research.

18.1 Research Authorization

Procedures for obtaining Research Authorization: Before any protocol-specific procedures are carried out, investigators and/or designated staff will fully explain the details of the protocol, study procedures, and the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must sign the Research Authorization component of the informed consent form. The Research Authorization requires a separate set of signatures from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents.



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19.0 REFERENCE(S)

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8. Kaye FJ, Bunn PA, Jr., Steinberg SM, et al: A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. *N Engl J Med* 321:1784-90, 1989



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Appendix 1: Patient Questionnaire

Patient Name _____

Study Site Name: _____

In this questionnaire, you will be asked about your itching and the use of anti-itching medications over the past week. Please complete this questionnaire before seeing your doctor.

(1) Overall, how badly has your skin itched over the past week? Please circle only one number.

0 1 2 3 4 5 6 7 8 9 10

No Itching

Itching as
bad as it
can be

(2) Overall, how has your use of prescribed or over the counter medications against itching, e.g., pills, creams, changed in the past week compared to the previous week? Please circle only one item.

- (A) I did not use any medications against itching in the past week
- (B) I used medication against itching in the past week, but the use is less than the previous week
- (C) I used medication against itching in the past week, but there is no change in the use
- (D) I used medication against itching in the past week, but the use is more than the previous week

Patient Signature: _____

Month _____ Day _____ Year _____

Study staff: This questionnaire must be completed, signed and dated by the patient before the patient is seen by the treating physician.



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**Appendix 2: Grading Scales for Composite Assessment (CA)
of Index Lesion Disease Severity**

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SCALING	0 - No evidence of scaling on the lesion 1* 2 - Mild: Mainly fine scales; lesion partially covered 3* 4 - Moderate: Somewhat coarser scales; lesion partially covered 5* 6 - Severe: Coarse, thick scales; virtually all of the lesion covered; rough surface 7* 8 - Very severe: Coarse, very thick scales; all of the lesion covered; very rough surface
ERYTHEMA	0 - No evidence of erythema, possible brown hyperpigmentation 1* 2 - Mild: Light red lesion 3* 4 - Moderate: Red lesion 5* 6 - Severe: Very red lesion 7* 8 - Very severe: Extremely red lesion
PLAQUE/TUMOR ELEVATION	0 - 0 mm: No evidence of plaque above normal skin level 1 - ≥ 0 to < 0.5 mm: Minimal but definite plaque elevation above normal skin level 2 - ≥ 0.5 to < 1 mm: Slight but definite plaque elevation 3 - ≥ 1 to < 1.5 mm: Mild elevation 4 - ≥ 1.5 to < 2 mm: Moderate elevation 5 - ≥ 2 to < 2.5 mm: Moderate to marked elevation 6 - ≥ 2.5 to < 3 mm: Marked elevation 7 - ≥ 3 to < 3.5 mm: Very marked elevation 8 - ≥ 3.5 mm: Extreme elevation

* For scaling and erythema, intermediate intervals 1, 3, 5 and 7 were to serve as mid-points between the defined grades 0, 2, 4, 6 and 8.



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Table Grading Scales for Composite Assessment (CA)
of Index Lesion Disease Severity (continued)

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HYPO-/HYPER-PIGMENTATION	<p>To have been used only when hypopigmentation or hyperpigmentation was the clinical manifestation of CTCL.</p> <p>0 - No evidence of pigmentation change.</p> <p>1*</p> <p>2 - Mild: 25% lighter pigmentation or noticeably darker pigmentation compared to the patient's normal skin pigmentation.</p> <p>3*</p> <p>4 - Moderate: 50% lighter pigmentation or twice as dark pigmentation compared to the patient's normal skin pigmentation.</p> <p>5*</p> <p>6 - Severe: 75% lighter pigmentation or three times as dark pigmentation compared to the patient's normal skin pigmentation.</p> <p>7*</p> <p>8 - Very severe: Nearly complete absence of pigmentation or nearly as dark a pigmentation as could be observed compared to the patient's normal skin pigmentation.</p>
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* Intermediate intervals 1,3,5 and 7 are to serve as mid-points between the defined grades 0, 2, 4, 6 and 8.

INDEX LESION AREA	<p>0 - 0 cm² (no measurable area)</p> <p>1 - > 0 and ≤ 4 cm²</p> <p>2 - > 4 and ≤ 10 cm²</p> <p>3 - >10 and ≤ 16 cm²</p> <p>4 - >16 and ≤ 25 cm²</p> <p>5 - >25 and ≤ 35 cm²</p> <p>6 - >35 and ≤ 45 cm²</p> <p>7 - >45 and ≤ 55 cm²</p> <p>8 - > 55 and ≤ 70 cm²</p> <p>9 - >70 and ≤ 90 cm²</p> <p>10 - >90 and ≤ 110 cm²</p> <p>11 - >110 and ≤ 130 cm²</p> <p>12 - >130 and ≤ 155 cm²</p> <p>13 - >155 and ≤ 180 cm²</p> <p>14 - >180 and ≤ 210 cm²</p> <p>15 - >210 and ≤ 240 cm²</p> <p>16 - >240 and ≤ 270 cm²</p> <p>17 - >270 and ≤ 300 cm²</p> <p>18 - >300 cm²</p>
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**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 05-098 A(6)

Appendix 3: Schedule of Protocol Events																
Week	PreRx	W .2	W .4	W .6	W .8	W .10	W .12	W .14	W .14-16	W .14-16	W .16-18	W .18-20	W .22-24	W .26-28	W .30-32	
	Rx Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8		Rx Day 1	Rx W .2	Rx W .4	Rx W .8	Rx W .12	Rx W .16	
Resp. Eval.									X						X	
Rx	Do xil	Do xil	Do xil	Do xil	Do xil	Do xil	Do xil	Do xil		Targ retin	Targ retin	Targ retin	Targ retin	Targ retin	Targ retin	
Hx/Px	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
KPS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Toxicity assess.		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tumor measurements	X								X***						X***	
Skin score																
Pruritus questionnaire	X								X						X	
CBC	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fasting: Trigl.*** Cholest.	X								X		X	X	X	X	X	
Lytes, BUN, Cr., AST, ALT, alk. phos., bili., TP, alb., Ca, amylase, UA, gluc	X								X		X	X	X	X	X	
Urinal.	X															
T4, TSH	X								X		X	X	X	X	X	
Echo/MUGA	X															
CT c/a/p*	X								X						X	
Sézary cell CT/Flow	**** X								X						X	
beta-HCG**	X								X							
*Pts. with stage IV (TNM)																
**premenopausal women within 7 days																
***biopsy of residual lesions if CCR																
****fasting triglyc. obtained at each MD visit																
*****Pts. with Sézary syndrome																

Schedule of Protocol Events



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Appendix 4

DATA COLLECTION FORM SCHEDULE

FORM	BASELINE	CYCLE	OFFSTUDY	WHEN APPLICABLE
Demographic, Disease & Prior Treatment Form	X			
Comorbidity Form	X			
Original Pathology Reports*	X			
Original Radiology Reports	X			
Treatment & Treatment Modification Form		X	X	
Physical Exam Form		X	X	
Laboratory Form	X			
Toxicity Form		X	X	
Concomitant Drug Form	X	X	X	
Hospitalization Form				X
Patient Status & Outcome Form				X

* Pathology report must be faxed to the MSKCC Clinical Trials Office (212) 557-0786 at the same time as patient registration that confirms patient has Cutaneous T-Cell Lymphoma.

Schedule:

Baseline: Forms to be submitted within two weeks of registration.

Cycle: To be completed after each cycle and submitted every 4 weeks.

Off-study: To be submitted within four weeks of the protocol completion.

Please submit forms to:

**Dorothy Lin, Research Study Assistant
Memorial Sloan-Kettering Cancer Center
633 3rd Avenue, 15th Floor
New York, NY 10017
Fax: 212-557-0787**