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APPLICATION NUMBER: NDA 21055

MEDICAL REVIEW(S)

NDA MEDICAL REVIEW

NDA # 21-055

TARGRETIN (Bexarotene) 75mg Capsules

Applicant: Ligand Pharmaceutical Inc

Date Submitted: June 23, 1999

Date Completed: December 23 1999

1 TITLE AND GENERAL INFORMATION

- 1.1 Title/Heading - Medical Officer's Review
- 1.1.1 NDA #21-055 Targretin® (bexarotene) 75mg Capsule
- 1.1.2 M.O. Review #
- 1.1.3 Submission Date: June 23, 1999
- 1.1.4 Review completed: (date) November 25, 1999
- 1.2 Drug Name:
- 1.2.1 Generic Name: Bexarotene
- 1.2.2 Proposed trade name Targretin®
- 1.2.3 Chemical: 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)vinyl]benzenecarboxylic acid,
- 1.2.4 Molecular Formula $C_{24}H_{28}O_2$.
- 1.2.5 Molecular Weight: 348.48

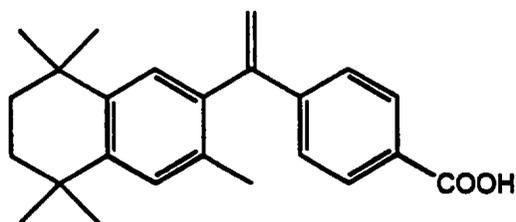
- 1.3 Applicant Ligand Pharmaceuticals Inc
10275 Science Center Dr
San Diego, California 92121-
- 1.4 Pharmacologic Category: Retinoids

1.4.1 Active Ingredient: Targretin® (bexarotene)

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.

- 1.4.2 Important Related Drugs: Panretin, Etretnate
ATRA, Accutane

1.5 Chemical Structure:



1.6 Proposed Indication(s) Treatment of patients with all clinical stages (1A-IVB) of Cutaneous T-Cell Lymphoma (CTCL) in the following categories: patients with early stage CTCL who have not tolerated other therapies, patients with refractory advanced stage CTCL therapies, and patients with refractory or persistent early stage CTCL.

1.7 Dosage Form(s) and Route(s) of Administration: : An off-white to white powder insoluble in water and slightly soluble in vegetable oils and ethanol, USP. Available in 10mg and 75mg capsules for oral administration.

1.8 NDA Drug Classification: 1 P

1.9 Related Reviews: Statistical Review
Biopharm Review

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3 MATERIAL REVIEWED

3.1 Paper Submission

The Clinical and Statistical Sections of a 450 volume paper submission was reviewed.

3.2 Electronic Submission

Electronic submission consisted of :

Access Database

Clinical Data in CD-ROM-WORD

CRF in PDF

3.3 Photographic Submission

Photographic Electronic Slide Viewer

4.0 CHEMISTRY/MANUFACTURING CONTROLS

See the review by Chemist.

5 NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY:

See a more detailed review by Pharmacologist.

5.1 MECHANISM OF ACTION:

5.1.1 RETINOIDS

Retinoids modulate cell growth, division, reproduction, differentiation, immune function, and apoptosis through interactions with intracellular retinoid receptors to modulate gene expression. There are two subfamilies of intracellular retinoid receptors: the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs). The RARs and RXRs each has three subtypes, designated α , β , and γ . Classical retinoic acid drugs such as all-*trans*-retinoic acid (ATRA, tretinoin) exert their activity in vitro primarily by modulation of RARs. 9-*cis*-Retinoic acid (alitretinoin) is an endogenous panagonist for both the RAR and RXR receptor families.

The presence of multiple retinoid receptors suggests that compounds selective for a receptor subfamily may have unique pharmacological properties, providing the potential for an improved therapeutic index and new clinical applications. Novel

synthetic compounds with RXR selectivity may regulate distinct gene pathways and thus elicit more specific physiological effects than classical retinoid drugs. Bexarotene (LGD1069, Targretin®) is one such novel synthetic retinoid that selectively activates the RXR subfamily receptor partners that are important in cellular function and in physiology indicates that the biological activities of bexarotene may be more diverse than those of compounds that activate the RARs.

The potential clinical utility of bexarotene was assessed by examining its effects in several in vitro and in vivo biological assays. In vitro, bexarotene inhibits the growth of tumor cell lines of squamous epithelial cell origin, and possibly modulates hematopoietic cell proliferation. In vivo, it causes tumor regression in some animal models and prevents tumor induction in others. However, the exact mechanism of action of bexarotene in the treatment of cutaneous T-cell lymphoma (CTCL) is unknown.

In contrast to ATRA, bexarotene does not induce the differentiation of human leukemic promyelocytes. Bexarotene can induce apoptosis in various cell systems in vitro. In vivo, bexarotene inhibits tumor growth and causes regression of two human primary squamous cell xenografts in nude mice. In addition, bexarotene is an effective chemopreventive agent in the development of mammary carcinoma and chemotherapeutic agent in naïve and in tamoxifen-resistant rodent models of mammary carcinogenesis.

The ability of bexarotene to modulate growth and apoptosis in cancer models and its selectivity for the RXR subfamily of retinoid receptors in vitro suggests the potential for unique biological activity in vivo, thus potentially providing therapeutic specificity, reduced toxicities or both. These unique features suggest that bexarotene may be useful clinically as an anti-cancer agent.

5.1.2 BEXAROTENE (Targretin®): Bexarotene is a synthetic compound that exerts its biological action through selective binding and activation of the three retinoid X receptors (RXRs): RXR α , β , and γ . Once activated, these receptors function as transcription factors that regulate many physiologic processes.

In Vitro and In Vivo Pharmacology.

The Applicant has explored the actions of bexarotene in multiple in vitro and in vivo models. The major findings are outlined below:

- **Bexarotene induces apoptosis in cell based assays.**
- **In contradistinction to ATRA, bexarotene is not a differentiating agent at levels that do not result in significant RAR activation.**
 - **Bexarotene displays potent antitumor activity when tested against several human head and neck squamous cell carcinoma lines and inhibits the growth and causes regression of squamous cell carcinoma xenografts in nude mice.**
 - **Neither bexarotene nor ATRA inhibits growth of ME-180 tumors in nude mice.**
 - **Bexarotene displays potent antitumor activity when tested against both estrogen receptor-positive and estrogen receptor-negative breast cancer cell lines in vitro.**
 - **Bexarotene has shown dramatic efficacy in the carcinogen-induced mammary carcinoma model in the rat, a model in which it acts as both an effective chemopreventive and an effective therapeutic.**
 - **Bexarotene has antikeratinizing effects in rhino mice.**
 - **Both preclinically in rodents, and clinically in humans, bexarotene has been shown to elevate triglycerides. The antilipemic agent fenofibrate acts as both a preventive agent and as a therapeutic agent, by reducing bexarotene-induced increases in plasma triglyceride levels in a mouse model of non-insulin dependent diabetes mellitus.**
 - **Bexarotene induces cellular triglyceride accumulation and adipocyte differentiation in the mouse preadipocyte cell line 3T3 L1. Furthermore, bexarotene acts as an insulin sensitizer, increasing triglyceride accumulation over treatment with insulin alone.**

- Bexarotene functions as an insulin sensitizer in three rodent models of non-insulin dependent diabetes mellitus.

5.2 TOXICOLOGY

5.2.1 Animal Studies

Bexarotene is developed for oral administration. Preclinical oral toxicity studies were therefore conducted in rats and beagle dogs treated with bexarotene to:

- i. identify target organs after oral administration
- ii. evaluate the relationship of treatment level and duration to toxicity produced.
- iii. assess pharmacokinetic parameters and toxicity.
- iv. determine the extent of reversibility of the toxicities produced.

Increases in serum triglyceride levels were noted in all species evaluated, including humans, where triglyceride elevations have been frequently observed and associated with pancreatitis.

Preclinically, relative liver weights increase and liver function test alterations occur simultaneously. The liver enzyme effects are dose-related and appear reversible upon cessation of treatment. The cytochrome P450 isozymes CYP2B and CYP3A are known to be induced by bexarotene treatment and appear to be involved in the metabolism of bexarotene in rats and dogs. An effect on liver enzymes is potentially related to enhanced or inhibited biotransformation of endogenous substances (cytochrome P450), bexarotene and other concomitantly administered therapeutic agents. Decreased plasma concentrations and AUCs of bexarotene after consecutive, repeated administration, were observed at the higher doses tested in rats and dogs. The reduction of C_{max} and AUC is attributed to an increase in the oral clearance. In general, the clinical once-daily pharmacokinetic database has not been consistent with these preclinical observations. Development of posterior subcapsular cataracts in growing rats and dogs has been documented with prolonged (two to six months) administration at exposures comparable to those seen in patients receiving Targretin capsules at the recommended initial human

dose of 300 mg/m²/day. These studies gave no indication of the mechanism or pathogenesis of lenticular opacification.

Testicular tubular degeneration occurred in immature dogs that were treated for three months with 30 mg/m² of bexarotene. Testicular atrophy has not been identified in sexually mature rats or dogs where treatment was started in adulthood. -

Adrenal gland hypertrophy has been observed in preclinical toxicology studies. Alterations in coagulation parameters resulting in elevations of PT and APTT are observed in animals.

Retinoids are known to have teratogenic potential if given orally to females during embryogenesis. In oral studies in rats, bexarotene was shown to have teratogenic and embryotoxic effects. The abnormalities noted in fetuses included cleft palate, depressed eye bulge/microphthalmia and delays in ossification. These findings are typical for retinoid compounds.

Targretin capsule therapy in clinical trials of patients with CTCL has been frequently associated with thyroid axis alterations.

5.2.2 Genotoxicity: Results were negative when bexarotene was tested in a battery of genotoxicity studies including, Ames *Salmonella* and *E. coli* assays, the mouse lymphocyte assay, the CHO/HRPT mammalian cell forward gene mutation assay, and the in vivo mouse micronucleus test.

5.3 Summary Toxicology

In summary, the preclinical adverse effects of bexarotene are serum triglyceride elevation, abnormal liver function and increased liver weight, cataract development, testicular tubule degeneration, adrenal gland hypertrophy, and coagulopathy. These adverse effects are dose- and duration-related and, with the exception of cataracts, are reversible.

In addition to the preclinical data and the cumulative human clinical experience with Targretin capsules, it is possible that at sufficiently high doses Targretin capsules may be

associated with any of the clinical toxicities observed with hypervitaminosis A syndrome. These include gastrointestinal distress, headache, dizziness, fatigue, irritability, pseudotumor cerebri, cheilitis, epidermal desquamation, xerosis, hyperostosis, bone resorption and hairline fractures, hepatosplenomegaly, elevated serum triglycerides and cholesterol, and ocular abnormalities.

Fetal abnormalities constitute a significant retinoid toxicity and Targretin is a potential teratogen.

6 HUMAN PHARMACOKINETICS PHARMACODYNAMICS AND BIOAVAILABILITY

6.1. Absorption/Dose Proportionality

In patients with advanced cancer receiving single doses of Targretin® capsules, bexarotene peak plasma concentrations (C_{max}) increased approximately proportionally from 67 ng/mL following a 18 mg/m² dose to 2792 ng/mL following a 650 mg/m² dose. Area under the plasma concentration-time curve (AUC) increased from ng·hr/mL to ng·hr/mL over the same dose range. Terminal elimination half-life values were generally between one and three hours over the six-hour sampling interval. Following repeat dose administration at dose levels 230mg/m², C_{max} and AUC in some patients were less than respective single dose values. The average repeat dose trough (C_{min}) level was 4% of C_{max} values. No evidence of prolonged accumulation was observed. Repeat dose half-life values were similar to single dose values, and were generally between one and three hours.

At the recommended initial daily-dose level (300 mg/m²) of Targretin® capsules, single-dose and repeated daily-dose bexarotene pharmacokinetic parameters were similar. Mean±SD C_{max} values were 922 ng/mL ± 339 ng/mL and 1130 ng/ml ± 269 ng/mL following single-dose and repeated daily-dose administration of Targretin® capsules, respectively. Mean±SD AUC values were 3877 ng·hr/mL ± 2640 ng·hr/mL and 3797 ng·hr/mL ± 1526 ng·hr/mL following single-dose and repeated daily-dose administration of Targretin® capsules, respectively. Pharmacokinetic profiles of

bexarotene in patients with CTCL were consistent with observations in patients with other advanced cancers.

6.2 Food Effects:

Formal studies to assess the effect of food on the absorption of bexarotene have not been conducted.

6.3 Protein Binding/Distribution:

Bexarotene is highly bound (>99%) to plasma proteins. The uptake of bexarotene by organs or tissues has not been evaluated. It is unknown if bexarotene crosses the placenta or blood/brain barrier.

6.4 Metabolism:

Bexarotene metabolites in plasma include 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene. In vitro studies suggest glucuronidation as a metabolic pathway, and that cytochrome P450 3A4 is the major cytochrome P450 isozyme responsible for formation of the oxidative metabolites. Based on the in vitro binding and the retinoid receptor activation profile of the metabolites, and on the relative amounts of individual metabolites in plasma, the metabolites appear to have little impact on the pharmacologic profile of retinoid receptor activation of bexarotene.

6.5 Excretion:

No formal studies to evaluate the routes of elimination of bexarotene and its metabolites in humans have been conducted. The renal excretion of bexarotene and its metabolites was examined in patients with Type II diabetes mellitus. Neither bexarotene nor its metabolites were excreted in urine in any appreciable amounts. In all evaluated patients, the renal clearance of bexarotene was less than 1mL/minute. Renal excretion is not a significant elimination pathway for bexarotene.

6.6 Drug-Drug Interactions

No formal studies to evaluate drug interactions with bexarotene have been conducted. Bexarotene oxidative metabolites appear to be formed through cytochrome P450 3A4.

Drugs that affect levels or activity of cytochrome P450 3A4 may potentially affect the disposition of bexarotene.

A population analysis of plasma bexarotene concentrations in patients with CTCL indicated that concomitant administration of gemfibrozil resulted in substantial increases in plasma concentrations of bexarotene. The mechanism of this interaction is unknown. Under similar conditions, bexarotene concentrations were not affected by concomitant administration of atorvastatin or levothyroxine.

6.7 Special Populations:

Elderly: Bexarotene C_{max} and AUC parameters were similar in advanced cancer patients <60 years old and in patients 60 years old, including a subset of patients 70 years old.

Pediatric: Studies to evaluate the pharmacokinetics of bexarotene in the pediatric population have not been conducted

Gender and Ethnicity ; There were no gender or ethnic differences noted in the pharmacokinetics of bexarotene in patients with advanced cancer.

Renal and hepatic Insufficiency: No formal studies have been conducted with Targretin® capsules in patients with renal or hepatic insufficiency. Clinical pharmacokinetic data indicate that urinary elimination of bexarotene and its metabolites is a minor excretory pathway for bexarotene. In all evaluated patients, the renal clearance of bexarotene was less than 1 mL/minute. Elimination of bexarotene appears to be primarily through hepatobiliary mechanisms. Although no evidence for altered bexarotene pharmacokinetics was noted in patients with elevated serum bilirubin, SGPT/ALT, SGOT/AST, or alkaline phosphatase, patients with hepatic insufficiency may theoretically have altered bexarotene pharmacokinetics.

7.0 Background on Cutaneous T-Cell Lymphoma (CTCL, Mycosis Fungoides)

7.1 History:

Aliberti in 1806 first described a severe skin disorder in which large necrotic tumors resembling mushrooms presented in the skin. He eventually named the disease mycosis fungoides. The different phases of the disease were subsequently described by others: In 1876, Bazin, Aliberti's student described the three clinical evolutionary phases of the disease; premycotic and patch, the infiltrative or plaque, and the tumor phase. Sezary and Bouvrain in 1938 noted what was later recognized to be an erythroleukemic variant called Sezary syndrome. Dermatologists and subsequently, pathologists determined that mycosis fungoides was a specific cutaneous lymphoma with distinctive extracutaneous histopathologic features similar to those in the skin. Cutaneous T-cell lymphoma (CTCL) is now the preferred name, and it has become the focus of intense interest by oncologists, dermatologists and hematopathologists.

7.2 Demographics and Natural History of CTCL: The incidence of CTCL is variously reported as 0.19 per 100,000 in 1973 and 0.42 per 100,000 in 1984, suggesting a possible rising incidence. About 1000 new cases are diagnosed every year in the U.S. The disease is typically found in mature adults (40-60 years old) in all races. The disease is twice as common in the black population compared to caucasians and twice as common in men compared to women. The incidence also rises with age, with the average age at presentation of 50 years. Children are rarely affected. There are racial and gender differences in predilection for the disease.

7.3 Causative agents of CTCL: The putative causative agents of CTCL include industrial or environmental exposure to metals and chemicals carcinogens, especially herbicides pesticides and organic solvents. Genetic predisposition is supported by family clusters of the disease, and by an association with some histocompatibility antigens. The role of viral carcinogenesis is inconclusive, but there are strong indicators of a possible role of the retroviruses in disease causation. The skin lesions in CTCL are very similar to those of adult T-cell lymphoma/ leukemia, which is caused by the human lymphotropic virus type 1 (HTLV-1). HTLV-1like retroviral particles were noted by electron microscopy

in 18 of 20 HTLV-1 seronegative patients with CTCL. Antibodies to HTLV-1/II are rarely found in mycosis fungoides or the Sezary variant. Lesions resembling those of CTCL are occasionally seen in patients with AIDS. Finally, a new retrovirus (HTLV-V) has been reported from several Italian patients with CTCL. This finding however requires further confirmation.

7.4 Clinical Staging and Prognosis of CTCL: CTCL encompasses a somewhat heterogeneous constellation of related diseases of malignant, generally mature, clonal, T-lymphocytes that are generally of help/inducer (CD4) phenotype and usually have an initial presentation in the skin. Although recent and ongoing developments in immunogenotyping and immunophenotyping have provided new insight, the etiology of CTCL remains unknown. CTCL is typically a chronic, slowly progressive disease of 10 to 20 years duration classified into four clinical stages. according to the TNM staging system initially developed by the Mycosis Fungoides Cooperative Group in 1979

(Table 1). Skin patches and plaques occur in stage I, the presence of clinical lymphadenopathy with negative pathology and/or cutaneous tumors characterize stage II, generalized erythroderma characterizes stage III, and pathologically positive lymph nodes and/or visceral disease characterize stage IV

The prognosis of CTCL varies with the clinical stage of disease at the time of diagnosis. CTCL lesions may remain as patches or plaques confined to the skin for many years before development of cutaneous tumors or visceral disease. Cutaneous lesions are present for an average of 2 to 10 years prior to biopsy confirmation of disease. CTCL patients with superficial skin involvement (stages I and IIA) have a median survival of more than twelve years. Patients with plaque disease, tumors, erythroderma (Sezary syndrome), and lymph node or blood involvement but no visceral involvement (stages IIB, III and IVA) have a median survival of five years. Patients with visceral involvement (stage IVB) have a median survival of 2.5 years or less

Sezary syndrome is the erythrodermic leukemic variant of CTCL, historically defined by the triad of generalized erythroderma, lymphadenopathy, and circulating neoplastic abnormal T-lymphocytes (i.e., Sezary cells). This syndrome involves pruritic exfoliation or infiltrated erythroderma, often with lymphadenopathy, alopecia, onychodystrophy, and

palmoplantar hyperkeratosis. The circulating Sezary cells are characterized by markedly convoluted, cerebriform nuclei. There is no consensus regarding the number of

TABLE I Staging System for Cutaneous T-Cell Lymphoma

Stage	TNM Groupings	Description
IA	T1, N0, M0	Eczematous patches, papules, or limited plaques covering less than 10% of skin surface. No clinically abnormal peripheral lymph nodes, pathology negative for CTCL. No involvement of visceral organs.
IB	T2, N0, M0	Erythematous patches, papules, or generalized plaques covering 10% or more of the skin surface. No clinically abnormal peripheral lymph nodes, pathology negative for CTCL. No involvement of visceral organs.
IIA	T1 or T2, N1, M0	Eczematous patches, papules, limited or generalized plaques. Clinically abnormal peripheral lymph nodes with pathology negative for CTCL. No involvement of visceral organs.
IIB	T3, N0 or N1, M0	One or more cutaneous tumors. Clinically normal or abnormal peripheral lymph nodes with pathology negative for CTCL. No involvement of visceral organs.
III	T4, N0 or N1, M0	Generalized erythroderma. Clinically normal or abnormal peripheral lymph nodes with negative pathology for CTCL. No involvement of visceral organs.
IVA	T1-T4, N2 or N3*, M0	Eczematous patches, papules, limited or generalized plaques; and/or one or more cutaneous tumors; and/or generalized erythroderma. Clinically normal or abnormal peripheral lymph nodes with pathology positive for CTCL. No involvement of visceral organs.
IVB	T1-T4, N0-N3*, M1	Eczematous patches, papules, limited or generalized plaques; and/or one or more cutaneous tumors; and/or generalized erythroderma. Clinically normal or abnormal peripheral lymph nodes with pathology negative or positive for CTCL. Visceral involvement (must have confirmation of pathology; organ involved must be specified).

*Pathological staging of a lymph node as LN3 or LN4 will constitute N3.

Note: Staging according to Sezary cells on blood smear (i.e., B+ = Positive blood smear or B- = Negative blood smear) does not alter the TNM stage classification.

circulating Sezary cells required for the diagnosis of Sezary syndrome, and various criteria ranging from 5% to 20%, and 1000 cells/mm³, are used. The presence of Sezary cells generally increases with more advanced stages of CTCL, from about 10% to 12% of patients with generalized plaque stage disease, to 16% to 25% of patients with cutaneous tumor stage disease, to nearly 100% of patients with generalized erythroderma

7.5 Currently Available Treatments for Cutaneous T-Cell Lymphoma

Therapy for cutaneous T-cell lymphoma is frequently given topically, especially in the earlier stages of the disease. Therapies such as topical glucocorticoids, nitrogen mustard (mechlorethamine), carmustine (BCNU), psoralen plus ultraviolet-A radiation (PUVA) and electron beam radiation therapy (EBT) can improve the skin manifestations and induce temporary remissions, but do not alter the patient's long term prognosis. The currently approved therapies for non-advanced CTCL are photopheresis (methoxsalen plus extracorporeal long wave radiation of white blood cells), for the palliative treatment of skin manifestations of CTCL in persons who have not been responsive to other forms of treatment, and systemic mechlorethamine (Mustargen®), for the palliative treatment of mycosis fungoides (MF).

Nitrogen mustard, BCNU and radiation therapies (EBT and PUVA) carry significant epidermal carcinogenic risk. Environmental exposure of household contacts and health care workers to nitrogen mustard and BCNU is also a concern. Radiation therapies may induce skin aging changes, telangiectasia, edema, radiation dermatitis, permanent alopecia and chronic blepharitis. The incidence of drug hypersensitivity is reported to occur in up to 45% or more of patients treated with topical nitrogen mustard and up to 5% of patients treated with BCNU.

Systemic therapies are generally reserved for more advanced stages of CTCL due to the greater potential for toxicity. In addition to photopheresis as approved therapy, systemic mechlorethamine (Mustargen®) is approved for the palliative treatment of mycosis fungoides (MF), vinblastine (Velban®) is approved for advanced stages of MF and methotrexate is approved in combination with other anticancer agents in the treatment of advanced MF. For broader lymphoma indications, Carmustine [BCNU] is approved for

palliative treatment of non-Hodgkin's lymphoma as secondary therapy in combination with other approved drugs for relapsed and refractory patients and vincristine (Oncovin®) has been shown to be useful in combination therapy with other oncolytic agents for treatment of non-Hodgkin's malignant lymphomas.

Newer therapies have been explored using biological regulators, including interferon α and γ , 13-*cis*-retinoic acid, etretinate and others. Interferons have been shown to be nearly as active in CTCL as single-agent chemotherapy with less toxicity when used on low doses. Clinical responses have been observed with treatment with retinoids, including 13-*cis*-retinoic acid, acotinoic acid and etretinate. Various combinations of treatments have also been explored. Interferon α has been used in combination with deoxycoformycin, PUVA and retinoids with good results. Etretinate has also been successfully used in combination with bleomycin, cyclophosphamide, PUVA and interferon α . Many patients in advanced stages of cutaneous T-cell lymphoma are cleared temporarily with combination therapy, but there are no documented effects on the progression of the disease or the patient's prognosis. 13-*cis*-Retinoic acid has been shown to be successful in clearing CTCL plaques either alone or in combination with PUVA. Etretinate and PUVA was effective and allowed a lower dose of PUVA for induction and remission of CTCL, as did PUVA plus either etretinate or 13-*cis*-retinoic acid).

8.0 PIVOTAL STUDY #1 Protocol # L1069-23

Title: A Multicenter International Phase 2-3 Evaluation of TARGRETIN™ Capsules in Patients with Refractory or Persistent Early Stage Cutaneous T-Cell Lymphoma

Number of Clinical Study Sites: 18 centers in the US, Europe and Australia.

Number of Investigators:

Number of patients: A total of 80 patients were enrolled to provide for at least 30 evaluable patients starting at 300 mg/m²/day in the higher dose level arm and at least 15 patients in the lower dose arm of 6.5 mg/m²/day.

8.1 Study Protocol # L 1069-23

8.1.1. OBJECTIVES:

1. To evaluate the safety and tolerability of TARGRETIN capsules in patients with refractory or persistent early stage Cutaneous T-cell lymphoma. -
2. To evaluate the antitumor efficacy of TARGRETIN capsules in patients with refractory or persistent early stage cutaneous T-cell lymphoma.
3. To evaluate two different dose levels of TARGRETIN capsules in patients with refractory or persistent early stage cutaneous T-cell lymphoma.

8.1.2 RATIONALE:

TARGRETIN activity in both the gel and capsule formulation had demonstrated activity in previous Phase 1-2 studies of CTCL patients, conducted by the Sponsor using different dose schedules. The presumed lack of other available therapies for patients who have exhausted current standard therapy constitutes the rationale for conducting a phase II-III study in this disease.

8.1.3 EXPERIMENTAL DESIGN

An open label phase II-III study of patients who have failed at least two prior therapies and had been exposed to a median of 3.5 (range two to at least 12) therapies.

8.1.4 PATIENT POPULATION

8.1.4.1. Inclusion Criteria

- i.A clinical diagnosis of cutaneous T-cell lymphoma (CTCL, mycosis fungoides), stage IA, IB or IIA and confirmed by a current biopsy (within 30 days prior to entry) to be histologically consistent with CTCL by a dermatopathologist.

ii. Refractory to, intolerant to, or have reached a response plateau for at least six months on at least two prior therapies from the following list: PUVA, UVB, EBT, photopheresis, interferon, systemic cytotoxic chemotherapy, topical nitrogen mustard or topical carmustine (BCNU). At least one of these qualifying prior treatments must have been topical nitrogen mustard, topical carmustine or a phototherapy (UVB, PUVA, or EBT)

Definitions: a) Refractory is defined as resistance to therapy due to lack of response of at least 50% improvement or progression of disease on therapy after an initial response.

b) Intolerant is defined as discontinuation of therapy due to side effects/toxicity of the therapy, whether or not a response occurred.)

iii. Systemic therapy indicated.

iv Complete avoidance of all antipruritic agents for at least one (1) week, or, in unavoidable cases, a stable dose regimen should be used for at least one week prior to initiation of study drug treatment and throughout the study.,

v. A Karnofsky performance score ≥ 60 (see Appendix 4).

vi Age ≥ 18 years.

vii Acceptable bone marrow, renal and hepatic function.

viii. Serum calcium ≤ 11.5 mg/dL.

ix. Fasting serum triglyceride within normal limits with or without use of antilipemic agents.

x. Must be free of serious concurrent illness.

xi. Negative serum pregnancy test (β -HCG) within seven (7) days prior to the initiation of treatment in women of child-bearing potential. In female patients and male patients with female partners of child-bearing potential, use of an effective means of contraception or sexual abstinence for at least four (4) weeks prior to entry in the study, during the entire period of treatment and for at least three (3) months after treatment is discontinued.

xii. Willingness to give informed consent, comply with study instructions and commit to all study visits.

8.1.4.2 Exclusion Criteria for Definition of Study Population

Patients meeting any one of the following exclusion criteria must be excluded:

i. Systemic antibiotic therapy within two (2) weeks of entry in the study.

- ii. Topical therapy for CTCL including nitrogen mustard, carmustine (BCNU), corticosteroids and others within two (2) weeks of entry in the study.
- iii. . Psoralen plus UV-A radiation therapy (PUVA) or UVB therapy within three (3) weeks of entry in the study.
- iv. Electron beam therapy (EBT) or photopheresis therapy within 30 days of entry in the study.
- v. . Systemic anticancer therapy of any kind (e.g., methotrexate, mechlorethamine, vinblastine, corticosteroid, etc.) within thirty (30) days of entry in the study.
- vi. . Systemic therapy with Vitamin A in doses of greater than 15,000 IU (5,000 mcg) per day (equivalent to approximately three times the RDA) or other retinoid class drugs within thirty (30) days of entry in this study.
- vii. Participation in any other investigational drug study within thirty (30) days of entry in this study.
- viii. Oral retinoid therapy for any indication within three (3) months of entry in the study, or
- ix. oral etretinate therapy for any indication within one (1) year of entry in the study.
- x. Participation in any other study of TARGRETIN capsules.
- xi. Serious known intercurrent medical illness or infection
- xii. History of pancreatitis or clinically significant risk factors for pancreatitis, pre-existing hypertriglyceridemia, hypercalcemia, uncontrolled diabetes mellitus, excessive alcohol use, biliary tract disease, and medications known to increase triglycerides.
- xiii. . Unwillingness or inability to avoid prolonged exposure to the sun or UV light sufficient to produce a mild erythema or thought by the Investigator likely to modify the patient's disease.
- xiv. Known allergy or sensitivity to retinoid class drugs.

8.1.5 Concomitant Medications or Therapy:

The following therapies are prohibited and may not be administered to patients being treated on this protocol:

- i. Systemic anti-psoriatic and systemic anticancer drugs and therapies (e.g., methotrexate, bleomycin, cyclophosphamide, prednisone, etc.).
- ii. Topical medications (such as corticosteroids or tar baths). However, mineral oil, baby oil, and simple moisturizing lotions may be used as emollients.
- iii. Systemic use of other retinoid class drugs, beta-carotene compounds, or Vitamin A doses of more than 15,000 IU (5,000 mcg) per day (equivalent to approximately three times the RDA) for any indication.
- iv. If systemic and dermatologically-applied antihistamine and antipruritic agents cannot be avoided, such agents must be administered using a stable dose regimen for at least one (1) week prior to initiation of study drug treatment and throughout the study, unless it is determined that a discontinuation or reduction in dose is indicated.
- v. Localized radiation therapy of specific lesions while patient is a study candidate.

8.1.6 TREATMENT PLAN

Patients were assigned to one of two treatment groups based on dose regimens; a once daily dose of Targretin capsules given as low dose (6.5 mg/m²/day) or high dose of 650 mg/m²/day, but subsequently reduced to 300mg/m²/day because of unacceptable toxicity. Patients initially assigned to the 6.5 mg/m²/day dose level were crossed over to the higher dose of 300mg/m² following disease progression after eight or more weeks of therapy or if no response is observed for that patient after sixteen or more weeks of therapy, and no unacceptable toxicity is occurring.

Patients were to continue treatment for at least 16 weeks. Treatment could be continued as long as the study remains open and active, provided the Investigator deems treatment is of potential benefit to the patient and no unacceptable toxicity occurs.

If a patient reaches a confirmed complete clinical response or a partial response plateau with a duration of at least twelve weeks, and decides to

discontinue treatment with TARGRETIN capsules, the patient should continue to be evaluated every four weeks for at least an additional twelve weeks after treatment discontinuation and continue to be considered an active patient in the study, and can resume treatment as needed, even though treatment has been discontinued.

8.1.6.1 Dose-Limiting Toxicities

A dose-limiting toxicity (DLT) is defined as a clinical observation that is, in the judgment of the Investigator, both attributable to the administration of study drug and necessitates a reduction or discontinuation in dose of study drug. DLTs will generally be Grade 3 and/or 4 level toxicities in the NCI Common Toxicity Criteria.

8.1.6.2.1 Dose Modifications

The dose of Targretin may be adjusted because of toxicity based on criteria established in Table 2

TABLE 2 Dose Modification for Toxicities

<p>No Dose-Limiting Toxicity (DLT)</p>	<ul style="list-style-type: none"> • Continue treating the patient at the current dose. Use appropriate supportive care for mild to moderate toxicities.
<p>Patient Experiences a DLT (Dose-limiting toxicity) attributable to TARGRETIN capsules.</p>	<ul style="list-style-type: none"> • If the patient is receiving 300 mg/m²/day, stop treatment until DLT resolves or improves to NCI Grade 1 or 0 (up to four weeks), then resume TARGRETIN capsules at 200 mg/m²/day. • If the patient is receiving 200 mg/m²/day, stop treatment until DLT resolves or improves to NCI Grade 1 or 0 (up to four weeks), then resume TARGRETIN capsules at 100 mg/m²/day. • If the patient is receiving 100 mg/m²/day, restart the patient at 100 mg/m²/day or withdraw patient from the study.

A patient who experiences a DLT should be monitored at least weekly until the DLT resolves or improves to NCI Grade 1 or 0 on the NCI Toxicity Table. Symptoms, physical examination and pertinent laboratory parameters must be closely monitored.

8.1.6.3 Therapeutic prevention/interventions for hypertriglyceridemia

Pharmacologic levels of TARGRETIN capsules is associated with altered blood lipid profiles including increased serum triglycerides. Significant elevation of serum triglyceride levels is associated with an increased risk for acute pancreatitis, especially in the presence of other risk factors for pancreatitis (e.g., prior history of pancreatitis, pre-existing hypertriglyceridemia, hypercalcemia, uncontrolled diabetes mellitus, excessive alcohol use, biliary tract disease, and medications known to increase triglycerides.)

TABLE 3 : MANAGEMENT OF HYPERTRIGLYCERIDEMIA

<p>FASTING SERUM TRIGLYCERIDE</p>	<p>ANTILIPEMIC MEASURES</p>
--	------------------------------------

LEVEL	
GREATER THAN 400 mg/DL, BUT LESS THAN 800MG/DL	<p>Adequate hydration and avoidance of additional risk factors:</p> <ul style="list-style-type: none"> • alimentary factors: foods and substances that increase endogenous VLDL output, such as alcohol must be avoided; • -concomitant medications leading to hypertriglyceridemia and/or associated with the development of pancreatitis must be avoided.
GREATER THAN 800 MG/DL, BUT LESS THAN 1200MG/DL	<ul style="list-style-type: none"> • Same as above • Antilipemics*: Atorvastatin, Fibrate or statin. (gemfibrozil has been found to be of only limited benefit)
800-1200 MG/DL	<ul style="list-style-type: none"> • Suspend Targretin treatment. • Initiate antilipemic treatment until level is below 400mg/dl. Resume treatment at same dose
ABOVE 1200 MG/DL.	Same as above, but resume treatment at a lower dose

*(Atorvastatin calcium, LIPITOR®) has been reported to have the greatest triglyceride lowering effect, and is strongly recommended as the antilipemic of choice for the treatment of elevated fasting triglycerides in this study. CAUTION must be taken when considering using any antilipemic drug along with investigational TARGRETIN capsule treatment, especially since no formal drug-drug interaction data are available. Additionally, please recall the potential for the development of rhabdomyolysis syndrome when either statin-class drugs or fibrate-class drugs are used, and especially the contraindication for their combination use.

If the patient is unable to resume TARGRETIN capsule treatment after four weeks of suspension of treatment, then the patient must be discontinued from the study.

Therapeutic Intervention for other retinoid-associated, non-threatening toxicities and adverse events.:

- For mild to moderate symptoms such as headache and mucocutaneous dryness: mild to moderate such as headache and mucocutaneous dryness, treat with supportive therapy (e.g., analgesics, nonsteroidal anti-inflammatory agents, skin and eye lubricants and moisturizers, etc.).
- Dose adjustment for patients who cannot tolerate the assigned dose according to the guidelines in Table 2 above.

8.1.6.4 .Withdrawal from study or Treatment Termination:

Criteria for terminating study therapy include, but are not limited to, the following:

- i. Disease progression
- ii. DLT (attributable to study medication) that does not resolve or improve to NCI Grade 1 or 0 within four (4) weeks after stopping the study medication responsible for the toxicity.
- iii. Intercurrent illness which prevents further treatment with TARGRETIN capsules.
- iv. General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the Investigator.
- v. The patient or patient's physician is free to discontinue treatment and take the patient off study at any time, especially if this is believed to be in the patient's best interest.

8.1.7 STUDY PROCEDURES

Prior to entry into the study, throughout the study, and at follow-up evaluation(s), various clinical and diagnostic laboratory evaluations as displayed in Table 4:

Table 4: FLOW CHART OF STUDY ACTIVITIES

ASSESSMENT TO BE COMPLETED	At Any Time Prior to Entry	Pre-Study (1) Up to 14 Days Before Day 1	Day 1 "Baseline" 1st Rx Day	Weekly Until Week 4, Every 2 Weeks Until Week 8, then Monthly	Every 2 Wks to Week 4, then every 4 Weeks	Every 12 weeks	Follow Up Visit
Med History/Physical Exam, Weight		x (include height)	x		x		x
Slit Lamp Eye Examination		x				x	x
Karnofsky Performance		≥60	x		x		x
Chest X-Ray		x					
Electrocardiogram		x					
Abdomen and Pelvis CT Scan		x)			x		x
LABORATORY							
Drug Monitoring Samples			x		x		
CBC, Including Tests Below		x	x		x		x
Hemoglobin		≥9.0 g/dL	x		x		x
WBC		≥2000/mm ³	x		x		x

Chemistry Panel, Including Tests Below		x	x	x	x		
Total Bilirubin		<1.5 X ULN	x	x			x
SGOT and SGPT		≤2.5 X ULN	x	x			x
Creatinine		≤2.0 X ULN	x	x			x
Total Triglycerides		≤800 mg/dL	x	x			x
Serum Calcium		≤11.5 mg/dL	x		x		x
Serum Amylase		≤1.5 X ULN			x		
Electrolytes, BUN and Glucose			x		x		x
Urinalysis			x		x		x
HDL, LDL, Total Cholesterol (5)			x	x			
CPK			x				
TSH, T4			x		x		x
PT, APTT			x				
EFFICACY							
Index Lesion Signs & Symptoms			x		x		x
Body Surface Area Involvement			x		x		x
Global Assessment					x		x
Lymph Node and Other Tumor Assessments			x		x		x
Patient QOL Questionnaires			x		x		x
CTCL Lesion Photographs			x		x		x

- i. History and Physical Examination
- ii. Laboratory, Radiographic and Electrocardiographic Evaluations
- iii. **CBC** to include counts of RBCs, WBCs, platelets, hematocrit, hemoglobin, RBC morphology, and WBC differential with absolute neutrophil count.
- iv. **Urinalysis** Baseline samples for serum lipids pretreatment must be obtained with the patient **fasting**. If the lipids are elevated, samples for serum lipids during the study should be obtained with the patient fasting, as well.
- v. Chemistry panel which includes fasting total serum triglycerides, fasting HDL, LDL and total cholesterol of treatment. Thyroid stimulating hormone (TSH) and thyroxine (T4);
- vi. Serum amylase; creatine phosphokinase (CPK)
- vii. **Coagulation parameters** which include prothrombin time (PT) and activated partial thromboplastin time (APTT). Any of these tests may be repeated during the study when clinically indicated.

- viii. The serum chemistry panel test must include, at a minimum, electrolytes (sodium, calcium, chloride, bicarbonate, potassium, magnesium, and phosphate), BUN, creatinine, glucose, SGOT(AST), SGPT(ALT), alkaline phosphatase, LDH, total bilirubin, albumin, total protein, calcium, phosphorous, uric acid,
- ix. A current skin biopsy (within 30 days prior to entry) to confirm the diagnosis of CTCL is necessary for entry to the study. The lesion site being biopsied must not have had topical steroid treatment for at least four (4) weeks prior to the biopsy.
- x. A representative biopsy(s) of clinically abnormal lymph nodes that are ≥ 2 cm diameter should be obtained at screening whenever feasible in order to accurately stage each patient and to assure eligibility for this protocol.
- xi. A baseline chest x-ray is required on all patients within 30 days prior to entry in the study.
- xii. A resting 12-lead electrocardiogram is required on all patients within six (6) months prior to entry in the study.

8.1.8 Response Assessments:

There are no standardized, or uniform criteria for evaluating response to therapy in patients with CTCL. The sponsor utilized efficacy endpoints designed specifically for this study. Measures of efficacy were determined on the basis of primary and secondary efficacy assessments by the on site investigators. These measures were recorded on the patient' case report forms. The sponsor then analyzes and scores the information provided. Responses, duration of responses and other measures of efficacy were calculated.

The Primary and Secondary Efficacy Instruments are as follows:

8.1.8.1 Primary Efficacy Assessments:

- PGA (Physician Global Assessment Of Clinical Condition)
- CA (Composite Assessment of Index Lesion)
- PEC (Primary End Point Classification of Response)

Secondary Efficacy Assessments:

- Time to Response
- Duration of Response
- Durability of Response

- Time to Disease Progression
- Total Body Surface Area involved
- Individual Index Lesions signs & symptoms
- Clinically abnormal nodes
- CTCL tumors present
- Visceral Involvement
- QOL Questionnaires

8.1.8.2 Physician's Global Assessment of Clinical Condition (PGA):

The Physician's Global Assessment is an assessment of the overall extent of improvement/worsening of the patient's overall disease compared to the condition at baseline. The Assessment considers both index and non-index cutaneous lesions, clinically and pathologically abnormal lymph nodes and palpable tumors, visceral disease or other tumor manifestations in any location where prior evaluation for disease was conducted in a manner that documented the absence of disease.

8.1.8.3 Composite Assessment of Index Lesions (CA):
was defined as the summation of the grades for all index lesions for the following clinical signs:

- erythema (Grade: 0-8),
- scaling (Grade: 0-8),
- plaque elevation (Grade: 0-8),
- hypopigmentation or hyperpigmentation (Grade: 0-8), and
- index lesion area involvement (Grade: 0-18).

Up to a maximum of five (5) cutaneous T-cell lymphoma lesions will be designated as index lesions. If the patient has five or fewer CTCL lesions, then all CTCL lesions will be designated as index lesions. If the patients has more than five CTCL lesions, then five lesions that are representative of the patient's overall cutaneous disease will be designated as index lesions. The index lesions should preferably be separate and distinct from other lesions in order to minimize the chance of lesion confluence. The index lesions will be designated by the letter "X" and numbered in sequence, starting with 1 (i.e., 1X, 2X, 3X, 4X and 5X). The location of all index lesions will be clearly noted on the anatomic chart in the patient's Case Report Form.

Composite Assessment of Index Lesion Disease Severity grade is the ratio of post-baseline study visit assessment divided by the assessment at baseline. If any index lesion measurements were missing at a post-baseline visit, the sum of lesion measurements at baseline that was to be used for calculating the ratio was and based only on those clinical signs for those index lesions which have measurements at that particular post-baseline visit.

8.1.8.4 Photographic support of Primary and Secondary Efficacy Assessments

Photographs of Lesions

The five (5) designated index lesions will be serially photographed. On Day 1 (baseline), every four (4) weeks thereafter for the duration of treatment, and again at the follow-up visit, these five index lesions must be photographed. Global photographs (half-body fields, anterior and posterior) of each patient's CTCL disease will be obtained on Day 1 (baseline), every four (4) weeks during treatment and again at the patient's follow-up visit. All index lesion and global areas which are photographed at baseline must be re-photographed every four (4) weeks, even if the lesions have cleared, until the patient completes the follow-up study visit.

8.1.8.5 RESPONSE CRITERIA:

Clinical Complete Response (CCR)

Composite Assessment was to have met two criteria:

- i. Ratio of the Composite Assessment of Index Lesion Disease Severity grades of 0 and
- ii. No clinically abnormal lymph nodes (and no cutaneous tumors, or known pathologically abnormal lymph nodes or visceral disease, or other tumor manifestations).
Physician's Global Assessment of Clinical Condition was to have been grade of 0.

Complete Response (CR)

CCR criteria plus a cutaneous biopsy documenting absence of histologic signs of CTCL from a cleared lesion.

Physician's Global Assessment of Clinical Condition was to have been a grade of 0 and a cutaneous biopsy was to have documented the absence of histologic signs of CTCL from a cleared lesion

Partial Response (PR)

- i. Ratio of the Composite Assessment of Index Lesion Disease Severity grades of ≤ 0.5 , and
- ii. a $< 25\%$ increase in the number of and aggregate area of clinically abnormal lymph nodes, no new cutaneous tumors, and no known pathologically abnormal lymph nodes or visceral disease in a location where prior evaluation for disease was to have been conducted in a manner that documented the absence of disease within 14 days of entry in the study.

Physician's Global Assessment of Clinical Condition was to have been a grade of one, two or three.

Progressive Disease (PD)

Ratio of Composite Assessment of Index Lesion Disease Severity grades ≥ 1.25 .

- $\geq 25\%$ increase in the discrete number of or aggregate area of clinically abnormal lymph nodes.
 - New cutaneous tumor.
 - New pathologically abnormal lymph nodes or new visceral disease in an area documented to be free of disease within 14 days of entry into the study.
- Physician's Global Assessment of Clinical Condition was to have been a grade of six.

Stable Disease (SD)

Composite Assessment of Index Lesion Disease Severity would not have met the response classification criteria for CR, CCR, PR, or PD.

Physician's Global Assessment of Clinical Condition was to have been a grade of four or five.

Response Confirmation

For the Composite Assessment and the Physician's Global Assessment, evaluation a confirmed response status is based on a patient's response persisting for two or more consecutive study visits over at least four study weeks. A response is defined as the

highest confirmed response status divided by the lowest numerical (best) response hierarchy of the assessment. The best response hierarchy was defined as CR, CCR, PR, SD, and PD. CR was the highest and PD was to have been the lowest.

8.1.9 STATISTICAL CONSIDERATIONS

Response Rates

The response rate analysis was an intent-to-treat and evaluable patient analysis. Response rate was defined as the sum of the number of patients with CR, CCR, or PR divided by the total number of patients in the data set. The highest response between the Composite Assessment and the Physician's Global Assessment for each patient was to have been used for response calculation, except for the following condition :

When a patient has a confirmed PD from one assessment (e.g., PGA) and a higher response (i.e., CR, CCR or PR) from the other assessment (e.g., CA), the final classification between these two assessments was to be determined by the confirmation time of the PD classification. If the onset of confirmed PD occurred on or before the confirmation date of other assessment classification confirmation, the patient was to be classified as PD. If the onset of the confirmed PD occurred later than the other assessment confirmation date, the patient was to be classified according to the confirmed response by the other assessment.

Primary Endpoint Classification of Response (PEC)

The overall response rate, considering response according to either PGA or CA, is known in this report as the Primary Endpoint Classification for the study. Response rate and its 95% confidence interval were to be provided for each dose treatment group. The response

rates for Physician's Global Assessment and for Composite Assessment were also to be presented individually.

Secondary Efficacy Endpoints

Secondary efficacy endpoints included individual index lesion signs and symptoms, body surface area involvement, lymph node and other tumor assessment, patient quality of life questionnaires (QoL), and other response measurements. These secondary efficacy results were to have been evaluated by dose treatment group.

Photographs of Lesions as supporting documentation of efficacy:

The five designated index lesions used for CA and PGA assessments will be serially photographed. On Day 1 (baseline), every four (4) weeks thereafter for the duration of treatment, and again at the follow-up visit, these five index lesions must be photographed.

Global photographs (half-body fields, anterior and posterior) of each patient's CTCL disease will be obtained on Day 1 (baseline), every four (4) weeks during treatment and again at the patient's follow-up visit. All index lesion and global areas which are photographed at baseline must be re-photographed every four (4) weeks, even if the lesions have cleared, until the patient completes the follow-up study visit.

8.4.5 Quality of Life Questionnaire: General Status QoL (Spitzer) and CTCL-Specific Patient Questionnaire

In these questionnaires, there was a six-item general status QoL questionnaire (Spitzer) and a nine-item CTCL-specific questionnaire. The questionnaires were to be administered at baseline and every four weeks during the study, except CTCL Questions 8 and 9 which were not applicable at baseline. These two questions (8 and 9) were to be administered every four weeks during the study period.

Change from baseline of individual question scores was to be summarized using descriptive statistics. For composite score, percent of improvement from baseline was to be calculated by utilizing contingency distribution of baseline scores against the scores at each on-study clinic visit. The sum of the frequency from the cells above the main diagonal of this contingency table was to be the numerator and total frequency of the table was to be the denominator for improvement from baseline calculation. The subsections were to be analyzed individually. Summary statistics were to be provided at baseline and each study visit for each dose group. Sum of the scores of the subsections was to be summarized as a composite score. Summary statistics for the composite scores were to be presented for each study visit and for each dose group. Change from baseline of the individual question score and composite score was to be summarized using descriptive statistics for each visit and each dose group. For the composite score, percent improvement from baseline was to be calculated using the contingency table approach for each study visit and each dose group.

Completer and Non-Completer Analysis

A "completer" was defined as a patient who completes a specified number of weeks on study (e.g., 16 weeks). The number of weeks used for defining a completer was to be determined by utilizing the time-on-study distribution of all patients across study time, until a specified cutoff point. This cutoff point was based on number of weeks on study. Patients who were to have been on study for the specified number of weeks or longer were defined as completers, while others were defined as non-completers.

Evaluable Patient Analysis:

The evaluable patient analyses were intended to assess the efficacy of the study drug when the study drug was administered in compliance with the protocol-specified criteria for the evaluable patient data set. The evaluable patient data set included all patients who met the following protocol-specified criteria.

8.2 RESULTS: Reported by Applicant: Protocol L-1069-23

Demographic and Other Baseline Characteristics

Demographics

Patients enrolled in the study were as identified in TABLE 5. The median age of patients at the time of entry in the study was 64 years, with a range from 27 to 89 years. The ratio of male to female patients is 2:1

Table 5. Baseline Demographics

Demographics		Initial Assigned Dose (mg/m ² /day)			All Patients N = 58 N (%)
		6.5 N = 15 N (%)*	300 N = 28 N (%)	>300 N = 15 N (%)	
Age (Years)	<30	0 (0.0)	1 (3.6)	0 (0.0)	1 (1.7)
	30 – 39	1 (6.7)	4 (14.3)	1 (6.7)	6 (10.3)
	40 – 49	1 (6.7)	3 (10.7)	1 (6.7)	5 (8.6)
	50 – 59	1 (6.7)	5 (17.9)	2 (13.3)	8 (13.8)
	60 – 69	6 (40.0)	6 (21.4)	8 (53.3)	20 (34.5)
	≥70	6 (40.0)	9 (32.1)	3 (20.0)	18 (31.0)
	Min / Median / Max	39 / 66 / 80	24 / 62 / 88	39 / 64 / 73	24 / 64 / 88
Sex	Male	10 (66.7)	18 (64.3)	12 (80.0)	40 (69.0)
	Female	5 (33.3)	10 (35.7)	3 (20.0)	18 (31.0)
Race	White	12 (80.0)	23 (82.1)	14 (93.3)	49 (84.5)
	Black	3 (20.0)	3 (10.7)	0 (0.0)	6 (10.3)
	Hispanic	0 (0.0)	1 (3.6)	1 (6.7)	2 (3.4)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	1 (3.6)	0 (0.0)	1 (1.7)

* Percent based on number of patients in each treatment group.

Stage and Duration of CTCL at Study Entry

The majority of the patients enrolled in the study were in early Stage I disease, 87.9% and the remainder 10.3% in stage II.

The data on the duration of CTCL for the overall study population are provided in terms of length of clinical manifestation of disease and time of first histopathologic diagnosis prior to entry in the study are summarized for all three initial dose groups in Table. 6

The median time since first clinical manifestation of CTCL was 10.5 years, range (2.0 to 59 years) the median time since first histopathological determination consistent with CTCL was 6.6 years, range (0 days to 49 years).

These data indicate the very indolent and protracted nature of this disease. The patients have received an average of 3.5 different treatments prior to entry on study.

TABLE 6 BASELINE DISEASE CHARACTERISTICS

	Initial Assigned Dose (mg/m ² /day)			All Patients N = 58 N (%)
	6.5 N = 15 N (%)*	300 N = 28 N (%)	>300 N = 15 N (%)	
<u>Stage of CTCL</u>				
I (A and B)	13 (86.7%)	25 (89.3%)	13 (86.7%)	51 (87.9%)
II(A and B)	2 (13.3%)	3 (10.7)	2 (13.3)	6 (10.3%)
<u>Duration of CTCL</u>				
1 st Manifestation Min/Median/Max (in months)	157.9 60 / 134 / 316	150.4 24 / 120 / 588	184.5 29 / 156 / 706	161.2 24 / 126 / 706
1 st Path. Dx Min/Median/Max (in months)	95.9 5 / 75 / 206	102.7 0 / 85 / 588	116.9 13 / 84 / 314	101.0 0 / 79 / 588

*Percent based on number of patients in each treatment group.

Disposition of Patients:

Patients Screened	65
Patients Enrolled	58
Patients Not Enrolled	7
Study Drug Dispensed	58
Study Drug Not Dispensed	0
6.5mg/m ² /day Group	
# of patients	15
Completed 16 weeks without Cross-Over	3
Completed 16 weeks and Cross-Over	4
Completed < 16 weeks and Cross-Over	5
Withdrawn Prior to 16 weeks	3
300mg/m ² /day Group	

# of patients	28
Completed 16 weeks	18
Withdrawn Prior to 16 weeks	10
> 300mg/m ² /day Group	
# of patients	15
Completed 16 weeks	11
Withdrawn Prior to 16 weeks	4

Patient Withdrawal from study:

Total Number of Patients withdrawn throughout duration of the study (week 0 to > 24)	42
6.5 mg/m ²	12
300 mg/m ²	17
> 300 mg/m ²	13
Withdrawal of Consent or due to adverse events:	19
6.5 mg/m ²	4
300 mg/m ²	5
> 300 mg/m ²	10

The above data reveal a progressive diminution in the number of evaluable patients.

Protocol Revisions and amendments.

The original version of the protocol dated July 8, 1996, was amended nine times in the course of the study. Several of the revisions were necessitated by safety concerns noted by the FDA and the applicant in the course of the trial.

Protocol Deviations:

Table 7 shows the number of protocol deviations and the reasons for deviation. 75% of the enrolled patients had at least one protocol deviation. The majority of the deviations were for receiving prohibited drug therapy and deviation from Inclusion Criteria considerations.

TABLE 7 Protocol Deviations by Category of Deviation

Category of Deviation ¹	Initial Assigned Dose (mg/m ² /day)		
	6.5 N = 15 N (%) ⁽²⁾	300 N = 28 N (%)	>300 N = 15 N (%)
Deviation From Inclusion Criteria	6 (40.0)	9 (32.1)	8 (53.3)
Deviation From Exclusion Criteria	3 (20.0)	4 (14.3)	1 (6.7)
Received Incorrect Treatment or Dose	0 (0.0)	1 (3.6)	4 (26.7)
Received Prohibited Drug/Therapy	9 (60.0)	8 (28.6)	11 (73.3)
Other Deviation	2 (13.3)	2 (7.1)	4 (26.7)
Total Number of Deviations ¹	36	31	45
Total Number of Patients with at Least One Deviation	11 (73.3)	18 (64.3)	15 (100)

EFFICACY RESULTS

The Intent to treat (ITT) analysis of response findings by the applicant are as presented in Table 8 below. A total of 65 patients were screened and 58 patients were entered into the study at 18 study centers through a cut off date of July 31, 1998.

Physician's Global Assessment Response Rate

According to the PGA primary endpoint, a CCR or PR was seen in 50% (14/28) of patients in the 300 mg/m²/day initial dose group and 60% (9/15) of patients in the >300 mg/m²/day initial dose group. The CCR response rate was 4% (1/28) in the 300 mg/m²/day initial dose group and 13% (2/15) in the >300 mg/m²/day initial dose group. Considering data for the 6.5 mg/m²/day initial dose group only through the date of cross-over to high dose for those patients crossed over, only one patient (7%, 1/15) in the 6.5 mg/m²/day initial dose group experienced a CCR or PR. A substantial difference in the rate of progressive disease was noted in the 6.5 mg/m²/day dose group (53%, 8/15) compared to the 300 mg/m²/day initial dose group (14%, 4/28) and >300 mg/m²/day initial dose group (7%, 1/15). The CTCL disease status failed to meet criteria for either

CCR, PR or PD and therefore was classified as stable in a comparable percentage of patients in the 300 and >300 mg/m²/day initial dose groups (36% and 33%, respectively).

Table 8 Physician's Global Assessment Response Rate

	Initial Assigned Dose(mg/m ² /day)		
	6.5 N=15 N (%)	300 N=28 N (%)	>300 N=15 N (%)
Response			
CCR + PR	1 (6.7)	14 (50.0)	9 (60.0)
CCR	0 (0.0)	1 (3.6)	2 (13.3)
PR	1 (6.7)	13 (46.4)	7 (46.7)
SD	6 (40.0)	10 (35.7)	5 (33.3)
PD	8 (53.3)	4 (14.3)	1 (6.7)

Composite Assessment Response Rate

According to the CA primary endpoint, a CCR or PR was seen in 36% (10/28) of patients in the 300 mg/m²/day initial dose group and 47% (7/15) of patients in the >300 mg/m²/day initial dose group. The CCR response rate was 4% (1/28) in the 300 mg/m²/day initial dose group and 20% (3/15) in the >300 mg/m²/day initial dose group. For the pre-cross-over 6.5 mg/m²/day initial dose group, 20%, (3/15) of patients experienced a CCR or PR. Progressive disease ranged from 7% to 18% and stable disease ranged from 40% to 73% across the three initial dose groups.

Table 9 summarizes the CA response rates for the three initial dose groups.

CR or PR according to the CA endpoint was seen in 36% (10/28) of patients in the 300 mg/m²/day initial dose group and 47% (7/15) of patients in the >300 mg/m²/day initial dose group. Based on the 95% confidence intervals, the response rates for CA were statistically indistinguishable for the 300 and >300 mg/m²/day initial dose groups. The CCR response rate was 4% (1/28) in the 300 mg/m²/day initial dose group and 20% (3/15) in the >300 mg/m²/day initial dose group.

Considering data for the 6.5 mg/m²/day initial dose group only through the date of cross-over to high dose for those patients crossed over, 20%, (3/15) of patients in the 6.5 mg/m²/day initial dose group experienced a CCR or PR.

Progressive disease ranged from 7% to 18% and stable disease ranged from 40% to 73% across the three initial dose groups.

Table 9 Composite Assessment Response Rate

Response	Initial Assigned Dose(mg/m ² /day)		
	6.5 N=15 N (%)	300 N=28 N (%)	>300 N=15 N (%)
CCR + PR	3 (20.0)	10 (35.7)	7 (46.7)
CCR	1 (6.7)	1 (3.6)	3 (20.0)
PR	2 (13.3)	9 (32.1)	4 (26.7)
SD	11 (73.3)	13 (46.4)	6 (40.0)
PD	1 (6.7)	5 (17.9)	2 (13.3)

Primary Endpoint Classification Response Rate

According to the Primary Endpoint Classification Response criteria (PEC), there were no Complete Responders (CR), 7 Clinical Complete Responders (CCR) and 21 Partial Responders (PR). The CCR response rate was 7% (2/28) in the 300 mg/m²/day initial dose group and 27% (4/15) in the >300 mg/m²/day initial dose group. For the pre-cross-over 6.5 mg/m²/day initial dose group, 20%(3/15) of patients had a CCR or PR.

These findings represent a compilation of the PGA and CA criteria.

TABLE 10 Primary Endpoint Classification Response Rate

Response Classification	Initial Assigned Dose (mg/m ² /day)		
	6.5 N=15 N (%) ⁽²⁾	300 N=28 N (%)	>300 N=15 N (%)
CR	0	0	0
CCR	1 (6.7)	2 (7.1)	4 (26.7)
PR	2 (13.3)	13 (46.4)	6 (40.0)
SD	5 (33.3)	7 (25.0)	3 (20.0)
PD	7 (46.7)	6 (21.4)	2 (13.3)

Analysis of Cross-Over Patients

Patients who were enrolled and randomized into the 6.5 mg/m²/day initial dose group were allowed to cross over to a higher dose if protocol-specified conditions were met. For

the primary efficacy endpoints, these patients' data are analyzed in two periods: from baseline (Day 1) through the cross-over visit, and from post-cross-over with the baseline reset at the time of the cross-over visit. Only the pre-cross-over data as defined above are included in the primary efficacy analyses. The post-cross-over data, for all patients who were crossed over, are analyzed and summarized separately as a secondary efficacy endpoint. In addition, the post-cross-over response rates on high dose therapy for these cross-over patients are displayed in comparison to their pre-cross-over response rates on the 6.5 mg/m²/day dose level.

11 of 15 patients starting therapy at the low dose of 6.5 mg/m²/day crossed over to the high dose arm. Five patients were crossed over to 300 mg/m²/day and six were crossed over to >300 mg/m²/day. For the 11 patients crossed over, the response rate according to the Primary Endpoint Classification for the study was 18% (2/11) on the 6.5 mg/m²/day initial dose level prior to cross-over, and 73% (8/11) after cross-over to high dose therapy. The rates of PD prior to cross-over for these 11 patients are 73% (8/11) by PGA, 9% (1/11) by CA, and 64% (7/11) by the Primary Endpoint Classification for the study. The corresponding rates of PD after cross-over (with a reset baseline at the time of cross-over) for these same 11 patients for the 300 and >300 mg/m²/day initial dose groups respectively are 20% (1/5) and 50% (3/6) for PGA, 20% (1/5) and 17% (1/6) for CA, and 20% (1/5) and 17% (1/6) for the Primary Endpoint Classification for the study. The ability of high dose Targretin capsule therapy to reverse the disease progression observed on low dose therapy suggests that the drug has antitumor activity in CTCL.

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Table 11 Primary Endpoint Classification Response Rate Before and After Cross-Over for Cross-Over Patients (N=11 Patients Crossed Over)

Response Classification	<u>Before Cross-Over</u>		<u>After Cross-Over</u>	
	6.5 mg/m ² /day (N = 11 Pts.)	300 mg/m ² /day (N = 5 Pts.)	>300 mg/m ² /day (N = 6 Pts.)	
	N (%)	N (%)	N (%)	
CCR + PR	2 (18.2)	3 (60.0)	5 (83.3)	
CCR	0 (0.0)	0 (0.0)	0 (0.0)	
PR	2 (18.2)	3 (60.0)	5 (83.3)	
SD	2 (18.2)	1 (20.0)	0 (0.0)	
PD	7 (63.6)	1 (20.0)	1 (16.7)	

Secondary Efficacy Endpoints

Time to Response

The time to response for a given patient is the time interval from the first day of Targretin capsule treatment to the time of the first observation when the patient meets criteria for CR, CCR or PR. All patients were included in the calculation, with patients not achieving a response censored at their date of last clinical evaluation of lesions available in the database for this report.

The projected time to onset of first response and best response based on the PGA, CA and Primary Endpoint Classification for the study for the 300 mg/m²/day are summarized in **Table 12**.

For a given patient, the best response would differ from the first response in the event that the patient first met response criteria for PR, and then later met response criteria for CCR. A projected median time to response for the CA endpoint for the 300 mg/m²/day initial dose group could not be made because the percent of patients responding as a function of the number of patients still on study did not reach 50% at any given time point. However an alternate analysis an alternative analysis was performed, based on only those patients responding. Based on only the patient responders in the 300 mg/m²/day initial dose group, the time to response is shown in **Table 13**. The median time to response for this group of patients was in the range of 29 to 31 days for both the CA

endpoint and Primary Endpoint Classification for the study, and slightly longer at 33 to 44 days for the PGA endpoint. According to the PGA endpoint, the projected median time to both first and best response was 114 days (range 27 to 186). According to the Primary Endpoint Classification for the study, the projected median time to first response was 57 days (range 27 to 114) and the median time to best response was 87 days (range 27 to 153)

Table 12 Time to Onset of First and Best Response According to PGA, CA and Primary Endpoint Classification for All Patients in the 300 mg/m²/day Initial Dose Group (N = 28 Patients)

Response Category	Time to Response (Days)					
	PGA (N=14 Responders)		CA (N=10 Responders)		Primary Endpoint Classification (N=15 Responders)	
	Median	Min-Max	Median	Min-Max	Median	Min-Max
First Response	114	27 - 186	-	27 - 110	57	27 - 114
Best Response	114	27 - 186	-	27 - 153	87	27 - 153

The projected median time to response was longer for the >300 mg/m²/day initial dose group than for the 300 mg/m²/day initial dose group. According to the PGA, the projected median time to first response was 114 days for the 300 mg/m²/day initial dose group compared to 117 days for the >300 mg/m²/day initial dose group, and the projected median time to best response was 114 days for the 300 mg/m²/day initial dose group compared to 185 days for the >300 mg/m²/day initial dose group. According to the Primary Endpoint Classification for the study, the projected median time to first response was 57 days for the 300 mg/m²/day initial dose group compared to 92 days for the >300 mg/m²/day initial dose group, and the projected median time to best response was 87 days for the 300 mg/m²/day initial dose group compared to 152 days for the >300 mg/m²/day initial dose group

Table 13 Time to Onset of First and Best Response According to PGA, CA and Primary Endpoint Classification for Responding Patients in the 300 mg/m²/day Initial Dose Group (N = 28 Patients)

Response Category	Time to Response (Days)					
	PGA (N=14 Responders)		CA (N=10 Responders)		Primary Endpoint Classification (N=15 Responders)	
	Median	Min-Max	Median	Min-Max	Median	Min-Max
First Response	33	27-186	29	27-110	29	27-114
Best Response	44	27-186	29	27-153	31	27-153

Too few patients responded at the 6.5 mg/m²/day initial dose group to provide a meaningful comparison of time to response.

Duration of Response/ Duration of Disease control

The protocol defined the time to response for a given patient as the time interval from the first day of Targretin capsule treatment to the time of the first observation when the patient meets criteria for CR, CCR or PR. The time to onset of response was calculated as the date of onset of the patient's first confirmed response (CCR, CR, or PR) or the date of last clinical evaluation of lesions for those patients not responding minus the date of first day of study (Day 1), plus one day. All patients were included in the calculation, with patients not achieving a response censored at their date of last clinical evaluation of lesions available in the database for this report.

The accompanying information provided by the FDA reviewer are analyses of data provided by the sponsor with confirmation.

For the analysis in this report, the sponsor assessed response duration both as duration of disease control, and as durability of response. Duration of disease control among responding patients was calculated as the date of onset of the patient's relapse minus the date of first day on study (Day 1), plus one day. All responding patients were included in the calculation, with patients not relapsing censored at their date of last clinical evaluation of lesions available in the database.

The sponsor reports, the duration of disease control based on the PGA, CA and PEC as summarized in Tables 14 A, B, C. As of the database closure for this report, neither the one responding patient at the 6.5 mg/m²/day initial dose group nor any of the 14 responding patients at the 300 mg/m²/day initial dose group had relapsed. Only 33% (3/9) of the nine responding patients at the >300 mg/m²/day initial dose group had relapsed. The numbers of days to relapse for these three patients, from Day 1, were 269 days (Patient 106 at Center 168), 327 days (Patient 105 at Center 168), and 337 days (Patient 008 at Center 014). Given this very low rate of relapse according to PGA, the sponsor was unable to project a median duration of response for any initial dose group.

Table 14A Duration of Disease Control According to Physician's Global Assessment

Initial Assigned Dose (mg/m ² /day)	Total Patients		Patients Responding		Responding Patients Relapsed		Projected Duration of Disease Control (Days)					
	N	%	N	%	N	%	Min	25th pctl	Median	75th pctl	Max	
6.5	15	25.9	1	6.7	0	0.0						0.0
300	28	48.3	14	50.0	0	0.0						0.0
>300	15	25.9	9	60.0	3	33.0	269.0	327.0				337.0

For the duration of disease control based on the CA endpoint, none of the three responding patients at the 6.5 mg/m²/day initial dose group had relapsed as of the database closure for this report. Only 20% (2/10) of the ten responding patients at the 300 mg/m²/day initial dose group had relapsed, with the numbers of days to the time to relapse for these two patients, from Day 1, being 120 days (Patient 010 at Center 014) and 210 days (Patient 032 at Center 348). The sponsor projected the median duration of response according to CA based on these two relapses as 210 days.

A total of 43% (3/7) of the seven responding patients at the >300 mg/m²/day initial dose group had relapsed. The numbers of days to relapse for these three patients, from Day 1, were 92 days (Patient 103 at Center 168), 309 days (Patient 008 at Center 014), and 516 days (Patient 003 at Center 014). The projected median duration of response according to CA based on these three relapses was 516 days.

Table 14B Duration of Disease Control According to Composite Assessment

Initial Assigned Dose (mg/m ² /day)	Total Patients		Patients Responding		Responding Patients Relapsed		Projected Duration of Disease Control (days)					
	N	%	N	%	N	%	Min	25th pctl	Median	75th pctl	Max	
6.5	15	25.9	3	20.0	0	0.0						0.0
300	28	48.3	10	35.7	2	20.0	120.0	165.0	210.0			210.0
>300	15	25.9	7	46.7	3	42.9	92.0	309.0	516.0	516.0	516.0	516.0

According to the Primary Endpoint Classification, none of the three responding patients at the 6.5 mg/m²/day initial dose group had relapsed. Only 13% (2/15) of the 15 responding patients at the 300 mg/m²/day initial dose group had relapsed, with the numbers of days to the time to relapse for these two patients, from Day 1, being 120 days (Patient 010 at Center 014) and 210 days (Patient 032 at Center 348). The projected median duration of response according to the Primary Endpoint Classification for the study based on these three relapses was 516 days. A total of 50% (5/10) of the ten responding patients at the >300 mg/m²/day initial dose group had relapsed. The number of days to relapse for these five patients who responded and then relapsed, from Day 1, ranged from 92 days to 516 days. The projected the median duration of response according to Primary Endpoint Classification for the study based on these five relapses was 516 days.

Table 14 C Duration of Disease Control According to Primary Endpoint Classification of Response

Initial Assigned Dose (mg/m ² /day)	Total Patients		Patients Responding		Responding Patients Relapsed		Projected Duration of Disease Control (Days)					
	N	%	N	%	N	%	Min	25th pctl	Median	75th pctl	Max	
6.5	15	25.9	3	20.0	0	0.0						0.0
300	28	48.3	15	53.6	2	13.3	120.0	210.0				210.0
>300	15	25.9	10	66.7	5	50.0	92.0	309.0	516.0	516.0	516.0	516.0

Overall, the rate of relapse for the patient responders in the 300 mg/m²/day initial dose group was lower than the rate of relapse for the >300 mg/m²/day initial dose group responders based on PGA, CA

Durability of Response

Response duration for a given patient is the time interval from the first observation when the patient meets criteria for CR, CCR or PR to the time that the patient relapses

The durability of response based on the PGA endpoint is based on information available on one responding patient at the 6.5 mg/m²/day initial dose group and of the 14 responding patients at the 300 mg/m²/day initial dose group in which there are not yet relapses. 33% (3/9) of the nine responding patients at the >300 mg/m²/day initial dose group had relapsed. The numbers of days to relapse for these three patients, from the onset of response, were 69 days (Patient 105 at Center 168), 213 days (Patient 106 at Center 168), and 246 days (Patient 008 at Center 014).

The durability of response by CA endpoint is based on information on this report, three responding patients at the 6.5 mg/m²/day initial dose group, none of whom had relapsed. Only 20% (2/10) of the ten responding patients at the 300 mg/m²/day initial dose group had relapsed, with the numbers of days to the time to relapse for these two patients, from the onset of response, of 92 days (Patient 010 at Center 014) and 176 days (Patient 032 at Center 348). The projected median duration of response according to CA based on these two relapses was 176 days. A total of 43% (3/7) of the seven responding patients at the >300 mg/m²/day initial dose group had relapsed. The numbers of days to relapse for these three patients, from the onset of response, were 59 days (Patient 103 at Center 168), 183 days (Patient 008 at Center 014), and 425 days (Patient 003 at Center 014). The projected the median duration of response according to CA based on these three relapses as 425 days.

The durability of response based on the Primary Endpoint Classification for the study is summarized in **Table 15**

As of the database closure for this report, none of the three responding patients at the 6.5 mg/m²/day initial dose group had relapsed. Only 13% (2/15) of the 15 responding patients at the 300 mg/m²/day initial dose group had relapsed, with the numbers of days

to the time to relapse for these two patients, from the onset of response, of 92 days (Patient 010 at Center 014) and 176 days (Patient 032 at Center 348). A median durability of response for the 300 mg/m²/day initial dose group cannot be projected for this group.

A total of 50% (5/10) of the ten responding patients at the >300 mg/m²/day initial dose group had relapsed. The numbers of days to relapse for these five patients who responded and then relapsed, from the onset of response, ranged from 59 days to 453 days. The projected the median durability of response according to Primary Endpoint Classification for the study based on these five relapses was 453 days.

Table 15 Durability of Response According to Primary Endpoint Classification of Response

Initial Assigned Dose (mg/m ² /day)	Total Patients		Patients Responding		Responding Patients Relapsed		Projected Durability of Response (Days)				
	N	%	N	%	N	%	Min	25th pctl	Median	75th pctl	Max
6.5	15	25.9	3	20.0	0	0.0					0.0
300	28	48.3	15	53.6	2	13.3	92.0	176.0			176.0
>300	15	25.9	10	66.7	5	50.0	59.0	213.0	453.0	453.0	453.0

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