

LIGAND PHARMACEUTICALS INC.

TARGRETIN[®] CAPSULES 75MG
BEXAROTENE

NDA 21-055

ONCOLOGIC DRUGS
ADVISORY COMMITTEE MEETING

13 December 1999

CONFIDENTIAL

**TARGRETIN® CAPSULES
(BEXAROTENE)
NDA 21-055**

Ligand Pharmaceuticals Incorporated
San Diego, CA

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Proposed Label Indication

Targretin® capsules are indicated for the treatment of cutaneous manifestations in patients with all clinical stages of CTCL (IA-IVB) in the following categories:

- Patients with early stage CTCL who have not tolerated other therapies,
- Patients with refractory or persistent early stage CTCL, and
- Patients with refractory advanced stage CTCL

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TARGRETIN CAPSULES

Ligand Presentation

- **Introductions and Background**
Howard T. Holden, Ph.D.
- **Overview of CTCL**
Francine M. Foss, M.D., New England Medical Center
- **Targretin Capsules Efficacy Results**
Richard C. Yocum, M.D.
- **Targretin Capsules Safety Findings**
Steven D. Reich, M.D.
- **Clinical Investigators' Perspectives**
Kenneth B. Hymes, M.D., New York University
Madeleine Duvic, M.D., M. D. Anderson Cancer Center
- **Summary and Questions**
Howard T. Holden, Ph.D.

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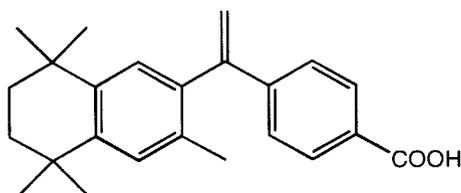
TARGRETIN CAPSULES

Regulatory History

- | | |
|--------------------------------|------------------|
| • IND Submitted | 28 December 1993 |
| • Phase II-III Protocols Filed | 4 October 1996 |
| • Orphan Drug Designation | 18 June 1999 |
| • NDA Submitted | 23 June 1999 |
| • Priority Review Granted | 18 August 1999 |

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BEXAROTENE (TARGRETIN®)



- LGD1069

- Formula:
 $C_{24}H_{28}O_2$

- MW: 348

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RECEPTOR BINDING PROFILES Bexarotene, Tretinoin and Alitretinoin

	RAR			RXR		
	α	β	γ	α	β	γ
Bexarotene (LGD1069)	-	-	-	+	+	+
Tretinoin (all- <i>trans</i> -RA)	+	+	+	-	-	-
Alitretinoin (9- <i>cis</i> -RA)	+	+	+	+	+	+

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CUTANEOUS T-CELL LYMPHOMA OVERVIEW

Francine M. Foss, M.D.

Assoc. Professor, Hematology-Oncology
New England Medical Center, Boston, MA

Co-Director, Skin Oncology Program

Former Chair for CTCL Studies,
NCI-Navy Medical Oncology Branch, NCI

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CTCL IMPORTANT ISSUES

- Chronic, highly symptomatic malignancy of mature CD4+ T-lymphocytes
- Disseminated from the onset
- Incurable (except perhaps in Stage IA)

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CTCL IMPORTANT ISSUES (continued)

- Cumulative, overlapping toxicities limit duration and intensity of long-term therapy
- Major cause of death is infection
- Disease palliation of significant benefit to patients, even without documented increased survival
- Novel, effective therapies without typical cytotoxic profiles are needed

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CTCL DISEASE DESCRIPTION

- **CTCL** defines a continuous spectrum of diseases, including mycosis fungoides, Sézary syndrome, and peripheral T-cell lymphomas
- **Mycosis fungoides:** skin involvement by patch, plaque and erythroderma +/- clinically detectable lymph nodes or visceral involvement
- **Sézary syndrome:** triad of generalized erythroderma, lymphadenopathy, and circulating Sézary cells

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CTCL EPIDEMIOLOGY

- ~1000 new cases annually in U.S.
 - Comprises 2.2% of all lymphomas
 - Incidence increasing
- Estimated prevalence 16,000 to 20,000 in U.S.
- Two times more common in men than women
- More common in blacks than whites
- Majority of patients 45 to 65 years of age at time of diagnosis

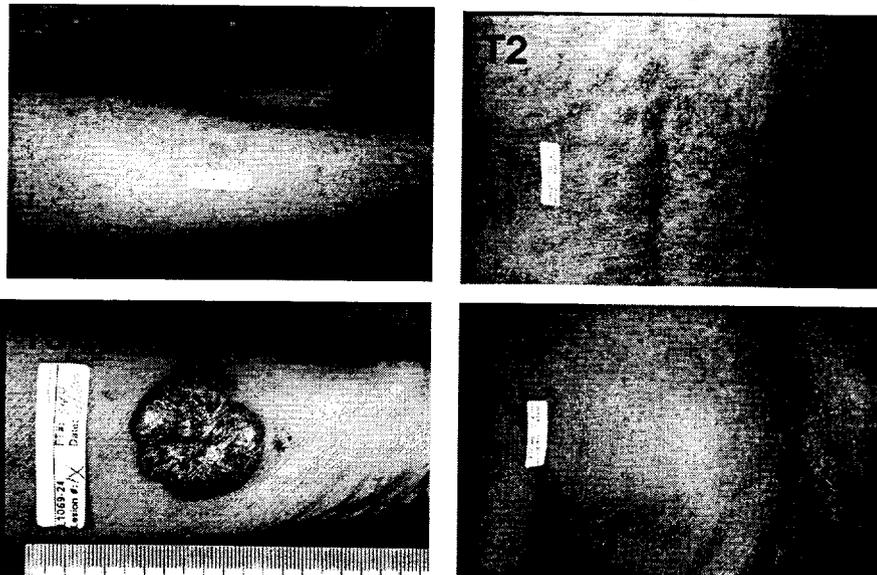
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CTCL TNM STAGING

- IA <10% BSA patch or plaque (T1)
- IB ≥10% BSA patch or plaque (T2)
- IIA Patch or plaque (T1-2) and clinical lymphadenopathy (node biopsy negative)
- IIB Cutaneous tumors (T3)
- III Erythroderma (T4)
- IVA Nodal involvement (node biopsy positive) and T1-4
- IVB Visceral involvement and T1-4

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EXAMPLES OF CTCL LESIONS BY TUMOR STAGING



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PROGNOSIS IN CTCL

(N = 489 Patients With CTCL)

<u>Skin Stage at Diagnosis</u>	<u>10-Year Relative Survival*</u>	<u>P-Value</u>
T1	100%	NS
T2	67%	0.002
T3	39%	<0.001
T4	41%	<0.001

* (Observed + expected survival) X 100, for age-, sex-, and race-matched controls

Zackheim *et al.*, JAAD 40:418, 1999

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GENERAL APPROACHES TO CTCL THERAPY

- **Early stage disease:**
Skin-directed therapies
- **Advanced/refractory disease:**
Skin-directed therapies and/or
systemic therapy

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CURRENT CTCL TREATMENT Major Toxicities

- Irradiation (PUVA, UVB, EBT): Skin aging, telangiectasia, skin cancer including basal and squamous cell and melanoma
- Topical Cytotoxics (Nitrogen mustard, BCNU): Hypersensitivity, skin cancer
- Interferon: Constitutional symptoms
- DAB₃₈₉IL-2: Hypersensitivity, vascular leak
- Systemic Cytotoxics: Immunosuppression with increased infection

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EVALUATION OF THERAPIES IN CTCL

- The majority of commonly used therapies have not been formally studied in CTCL and are not approved for CTCL
- Most studies are small (~15 patients) and uncontrolled
- Only one randomized, controlled trial in literature

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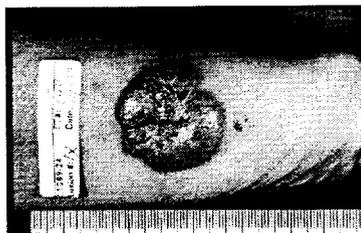
EVALUATION OF THERAPIES IN CTCL (continued)

- No standardized response criteria
- Response rates variable (19-58%) depending upon prior treatment and response criteria
- Responses not durable
- No impact on survival

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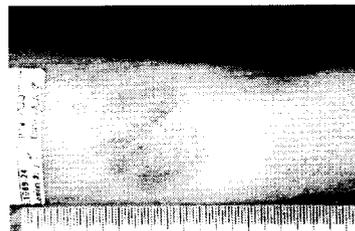
CHALLENGES IN MEASURING RESPONSES IN CTCL

Examples

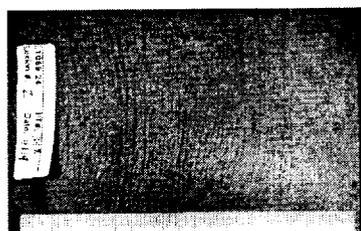


Tumor

to

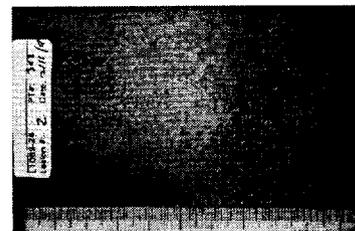


Patch



Erythroderma

to



Normal

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GOALS FOR MANAGEMENT OF ADVANCED/REFRACTORY DISEASE

- Alleviate symptoms, including pruritus and recurrent skin infections
- Slow or prevent further progression of disease
- Prevent further immunosuppression
- Use combination approaches of skin-directed and systemic therapies

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CTCL OVERVIEW Summary

- Highly symptomatic, debilitating, disfiguring disease
- Life-threatening in advanced stages
- No spontaneous remissions
- Incurable (except perhaps Stage IA)
- Novel therapies needed that are effective, easy to administer (due to chronicity of disease), and non-immunosuppressive

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PHASE II-III CTCL STUDIES

DESIGN, DEMOGRAPHICS AND EFFICACY RESULTS

Richard C. Yocum, M.D.
Project Physician and Senior Medical Director
Clinical Research
Ligand Pharmaceuticals Inc.

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TARGRETIN CAPSULES IN CTCL Phase II-III Clinical Trials

- Design and scope of studies
- Eligibility criteria
- Study patient population
- Efficacy endpoints and results
- Efficacy conclusions

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DESIGN AND SCOPE OF TARGRETIN CAPSULES CLINICAL TRIALS

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SCOPE OF TARGRETIN CAPSULES CLINICAL TRIALS

- 690 Patients from 16 clinical trials
- 200 CTCL patients treated with Targretin capsules
- 152 CTCL patients in Integrated Summary of Effectiveness Data (ISE)
- 84 CTCL patients in ISE treated at initial dose of 300 mg/m²/day

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TARGRETIN CAPSULES IN CTCL Rationale for Phase II-III Studies

- At least two non-RXR-selective retinoids (etretinate and isotretinoin) used in treating CTCL
- Targretin capsules were generally well-tolerated in Phase I-II program in various advanced cancers
- 2 of 9 patients with CTCL responded in a Phase I study in various advanced cancers
- Topically applied Targretin[®] gel induced responses in treated lesions in a Phase I-II program in early stage CTCL

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TARGRETIN CAPSULES IN CTCL Introduction to Phase II-III Studies

- Open-label
- Historically-controlled
- Multicenter, multinational, at 32 enrolling centers in the U.S., Canada, Europe, and Australia
- Previously-treated patients having adequate prior qualifying therapies
- Study L1069-23 in early stage CTCL (IA, IB and IIA) allocated to low or high dose
- Study L1069-24 in advanced stage CTCL (IIB, III, IVA, and IVB) high dose only

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TARGRETIN CAPSULES IN CTCL Statistical Design of Phase II-III Trials

- No spontaneous remission rate for CTCL
- Studies were historically-controlled in patients with refractory or persistent CTCL
- Statistical targets for a successful trial:
 - a point estimate response rate of at least 20%
 - the lower bound of the 95% confidence intervals excluding a conservative estimate 5% maximal theoretical spontaneous response rate

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TARGRETIN CAPSULES IN CTCL

Phase II-III Principal Objectives

Evaluate Targretin capsules in previously treated patients:

- Safety and tolerability in refractory or persistent early stage CTCL and refractory advanced stage CTCL
- Antitumor efficacy in refractory or persistent early stage CTCL and refractory advanced stage CTCL
- Different dose levels in refractory or persistent early stage CTCL

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TARGRETIN CAPSULES IN CTCL

Dose Regimens in Early Stage Study

- Low dose (6.5 mg/m²/day) approximated dose at which responses seen in Phase I study
- High dose (650 mg/m²/day) based on maximum tolerated doses (300 and 650 mg/m²/day) in Phase I-II dose escalation studies
- Patients to be randomized 1:1 to low or high dose
- Allowance for cross over from low to high dose if progression at 8 weeks or no response at 16 weeks

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TARGRETIN CAPSULES IN CTCL Dose Regimens in Phase II-III Studies

- Only high dose in advanced stage protocol
- High dose reduced by protocol amendment from 650 to 500 to 300 mg/m²/day because of dose-limiting toxicities (↑TG and ↓WBC)
- For high dose, dose reductions to 200 mg/m²/day and to 100 mg/m²/day as necessitated by toxicity
- For the purpose of analysis, three initial dose groups used (6.5, 300, >300 mg/m²/day)

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ELIGIBILITY CRITERIA

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MAIN ELIGIBILITY CRITERIA

Both Phase II-III CTCL Studies

- Clinical diagnosis of CTCL confirmed by current biopsy to be histologically consistent with CTCL
- Refractory or persistent CTCL despite prior therapy (specific to individual protocol)
- Adequate washout from prior CTCL therapy
- Karnofsky performance score ≥ 60
- Age ≥ 18 years
- Acceptable organ function
- Not pregnant and agree to use effective contraception

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ELIGIBILITY CRITERIA

Prior CTCL Therapy in Early Stage Protocol

- 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)
- Topical steroids and systemic retinoids DO NOT qualify

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ELIGIBILITY CRITERIA

Prior CTCL Therapy in Advanced Stage Protocol

- Refractory to one or more systemic anticancer therapy(s) for CTCL

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ELIGIBILITY CRITERIA

Protocol Definition of Refractory and Intolerant

- “Refractory” defined as resistance to therapy due to lack of $\geq 50\%$ improvement or progression of disease on therapy after an initial response
- “Intolerant” defined as discontinuation of therapy due to side effects/toxicity of the therapy, whether or not a response occurred

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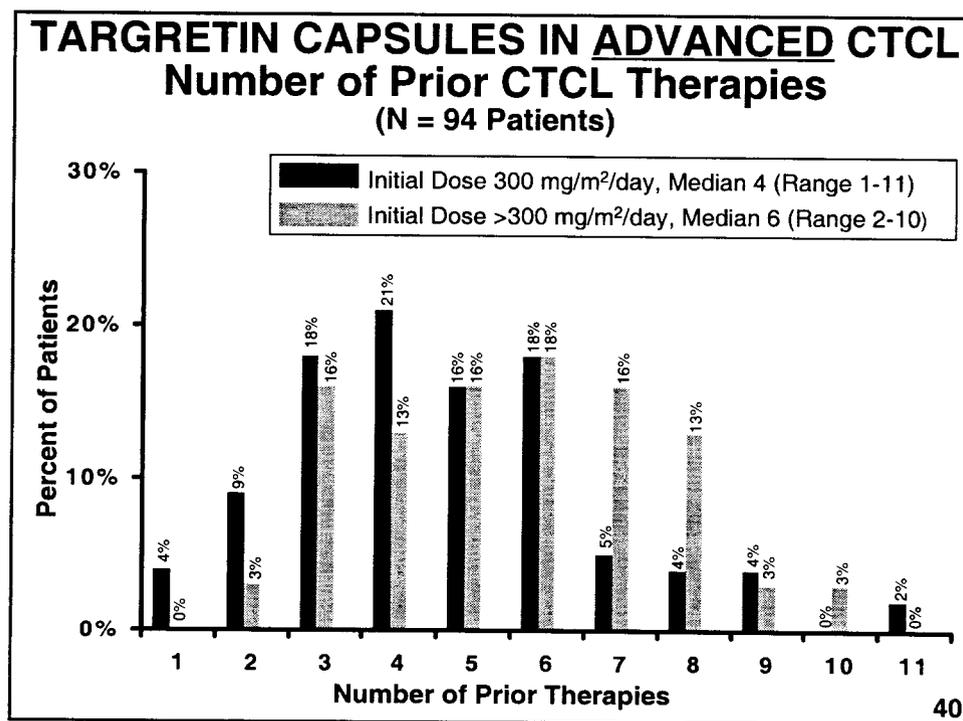
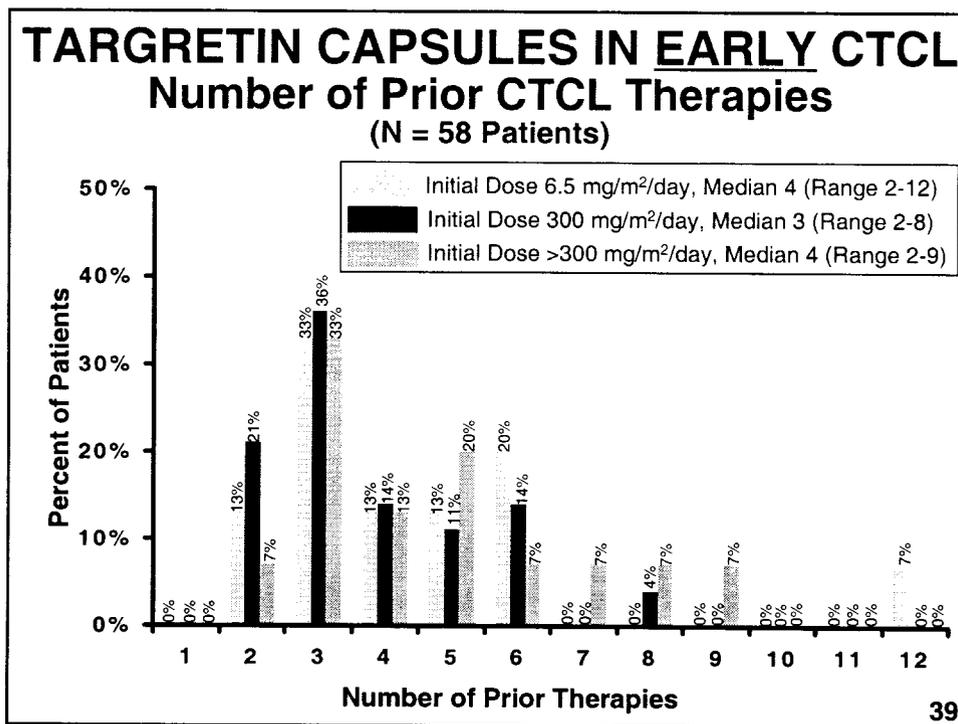
STUDY PATIENT POPULATION

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BASELINE TNM CLINICAL STAGE Phase II-III CTCL Studies

TNM Clinical Stage	Initial Dose Group (mg/m ² /day)			All Doses N = 152
	6.5 N = 15	300 N = 84	>300 N = 53	
IA	40%	5%	13%	11%
IB	47%	25%	11%	22%
IIA	7%	4%	6%	5%
IIB	7%	27%	32%	27%
III	0%	23%	19%	19%
IVA	0%	11%	11%	10%
IVB	0%	6%	8%	6%

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TARGRETIN CAPSULES IN CTCL

Most Common Prior Therapies (≥10% in Either Phase II-III Study)

Therapy (Approved and Unapproved)*	Early Stage (N = 58)	Advanced Stage (N = 94)
Interferon	38%	65%
Topical mustard	93%	56%
PUVA	62%	54%
EBT	47%	40%
Topical corticosteroid	22%	34%
Combination chemotherapy	7%	33%
Methotrexate	9%	33%
Photopheresis	5%	26%
Orthovoltage radiation	7%	25%
Systemic corticosteroid	9%	23%
Isotretinoin	10%	19%
UVB	28%	11%
DAB ₃₈₉ IL-2 (ONTAK [®])	14%	6%
Topical BCNU	16%	4%

* Multiple courses of the same therapy for a given patient counted only once.

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QUALIFYING PRIOR CTCL THERAPY

- **In early stage study, 100% met criteria**
 - 96% refractory to ≥1 prior therapy
 - 78% refractory to ≥2 prior therapies
 - Only 21% qualified, at least in part, on basis of "intolerance"
 - Only 3% qualified partially on basis of "response plateau"
- **In advanced stage study, 96% met criteria**
 - 96% refractory to ≥1 prior systemic therapy
 - 62% refractory to ≥2 prior systemic therapies
 - Refractory to median of 2 (range 0-6) prior systemic anticancer therapies

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TARGRETIN CAPSULES IN CTCL

Primary Efficacy Endpoints

- Physician's Global Assessment (PGA) of Clinical Condition
- Composite Assessment (CA) of Index Lesion Disease Severity
- Primary Endpoint Classification (PEC) of response for the study, derived from PGA and CA

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PHYSICIAN'S GLOBAL ASSESSMENT (PGA) OF CLINICAL CONDITION

Grade	Description	Response*
0 Completely clear	No evidence of disease; 100% improvement	CCR
1 Almost clear	Very significant clearance ($\geq 90\%$ to $< 100\%$); only traces of disease remains	PR
2 Marked Improvement	Significant improvement ($\geq 75\%$ to $< 90\%$); some evidence of disease remains	
3 Moderate Improvement	Intermediate between slight and marked improvement; ($\geq 50\%$ to $< 75\%$)	
4 Slight Improvement	Some improvement ($\geq 25\%$ to $< 50\%$); however, significant evidence of disease remains	SD
5 No change	Disease has not changed from baseline condition ($\pm < 25\%$)	
6 Worse	Disease is worse than at baseline evaluation by $\geq 25\%$ or more	PD

* Confirmation over at least four study weeks required except for a last assessment on study if progressive disease. CCR = Clinical Complete Response; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease

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COMPOSITE ASSESSMENT (CA) OF INDEX LESION DISEASE SEVERITY

Clinical Sign	Index Lesion:	Grading				
		1X	2X	3X	4X	5X
Erythema		a	b	c	d	e
Scaling		f	g	h	i	j
Plaque Elevation		k	l	m	n	o
Hypo/Hyperpigmentation		p	q	r	s	t
Area		u	v	w	x	y

$$\text{CA Ratio} = \frac{\sum(a-y)_{\text{post-baseline}}}{\sum(a-y^*)_{\text{baseline}}}$$

*For corresponding sign and index lesion

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COMPOSITE ASSESSMENT (CA) ENDPOINT (continued)

- **CCR: CA ratio = 0** (no evidence of index lesion disease), provided there is no other clinical evidence of disease
- **PR: CA ratio ≤0.5** (≥50% reduction in index lesion signs) provided that there is no new and no ≥25% increase in extra-cutaneous disease
- New or progressive extra-cutaneous disease overrides any degree of improvement in the CA ratio
- Improvement or resolution of adenopathy, cutaneous tumors, and other non-index disease manifestations could never constitute a response per se

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PHYSICIAN'S GLOBAL ASSESSMENT (PGA) ENDPOINT

- Allowed the clinician, applying expertise in assessing CTCL, to evaluate all of the varied disease manifestations that were important for each individual patient
- Allowed improvement/resolution in nodes, cutaneous tumors, pruritus, and visceral involvement to contribute to the classification of response
- PGA was independent of knowledge of CA classification (CA classification was determined by programmed algorithm and was not known to Investigators)

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PRIMARY ENDPOINT CLASSIFICATION FOR THE STUDY (PEC)

- Response criteria for either the PGA or the CA endpoint satisfied
- Except if the onset of confirmed progressive disease by either PGA or CA occurred on or before the confirmation date of response by the other endpoint, the patient was classified as progressive disease instead of response according to PEC

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Overview of Efficacy Endpoints in Phase II-III Studies

Study	Primary Endpoints	Secondary Endpoints
L1069-24 Advanced Stage CTCL	<ul style="list-style-type: none"> • Physician's Global Assessment of Clinical Condition (PGA) • Composite Assessment of Index Lesion Disease Severity (CA) • Primary Endpoint Classification (PEC) of Response 	<ul style="list-style-type: none"> • Time to response • Duration of disease control • Durability of response • Time to disease progression • Total body surface area involvement • Individual index lesions signs and symptoms* • Clinically abnormal lymph nodes • Cutaneous CTCL tumors, if present • Visceral involvement, if present • Quality of life questionnaires
L1069-23 Early Stage CTCL	Same as for L1069-24	Same as for L1069-24 plus: <ul style="list-style-type: none"> • Response for patients crossed over from low to high dose • Comparison of responses in the low and high dose groups

* Erythema, scaling, plaque elevation, hypo/hyperpigmentation, area of index lesions, and pruritus.

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PHOTOGRAPHS

FDA emphasis on photographs

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PHOTOGRAPHS

Role as Supporting Data

- Protocols prospectively defined photos as only **supporting** data
- Photos were neither a primary nor secondary endpoint
- Photographs were neither intended nor protocol-defined to serve as validation of efficacy endpoints
- Changes in photographic appearance of lesions generally followed the trend in primary endpoint response classifications

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PHOTOGRAPHS

“Global” Photographs

- The protocols specified close-up index lesion and “global photographs (half-body fields, anterior and posterior)”
- Prior to initiating either protocol at any center, technique changed to “regional index” (~8” x 10” cutaneous areas) instead of half-body photos
- Specific, detailed, written instructions for regional index technique provided to all centers
- An administrative amendment to the protocols was inadvertently not submitted to reflect change in technique
- Division of Oncology advised during 12/17/98 pre-NDA meeting

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PHOTOGRAPHS

Reasons for “Regional Index” Technique

- Faint and subtle lesions, common in CTCL, become indiscernible at greater focal distance
- Height of lesions especially difficult to capture at greater focal distance
- Regional index technique permits focus on intertriginous areas, which would be missed by half-body photos
- Half-body photos don't capture many areas that might be CTCL-involved (plantar, top head, axillae, groins, and sides of trunk and extremities)

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PHOTOGRAPHS

Summary

- PGA and CA endpoints based on all cutaneous and extracutaneous disease manifestations, but photos included only up to five index lesions
- Inferior to direct, hands-on clinical evaluation by Investigator
- Although photographs support the response assessments, response and patient benefit cannot be reliably determined in these studies from photographs alone

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TARGRETIN CAPSULES IN CTCL

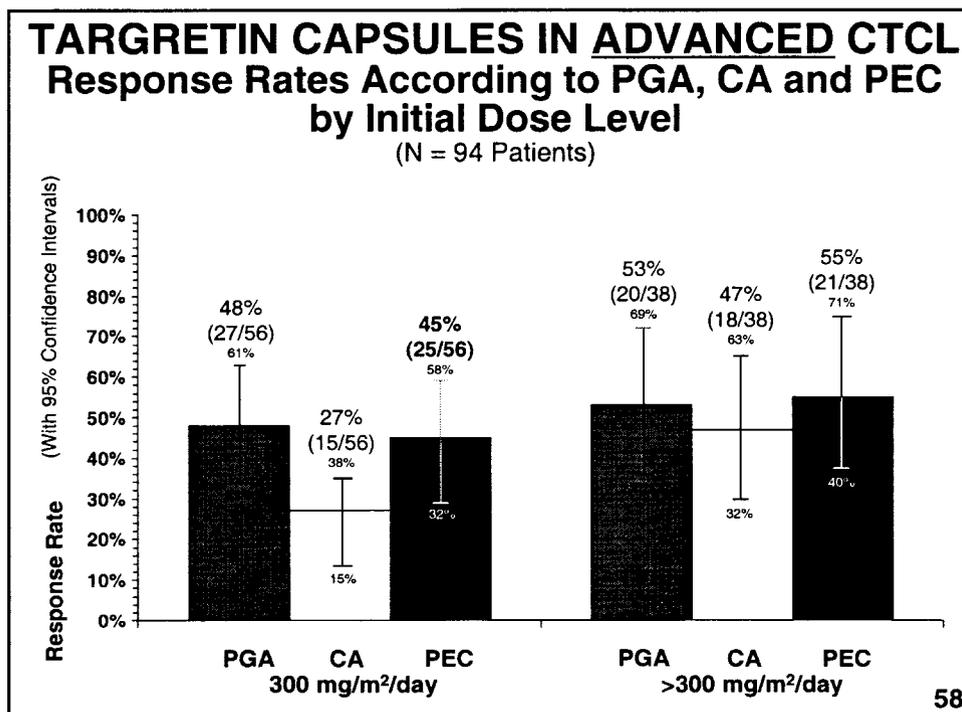
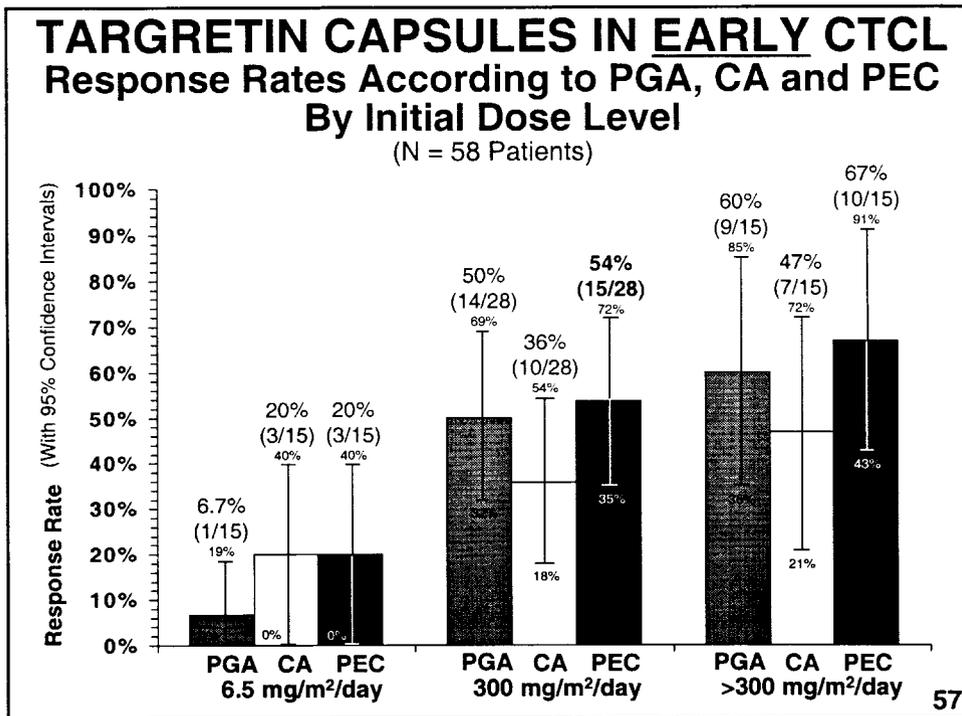
Acknowledgement of FDA Input Into Study Design

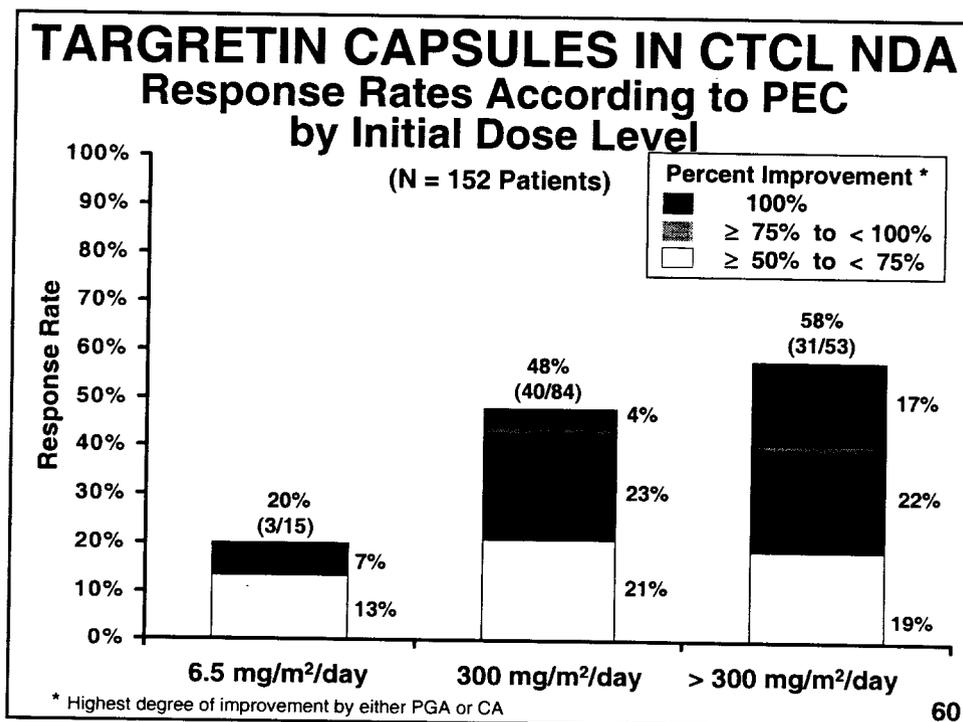
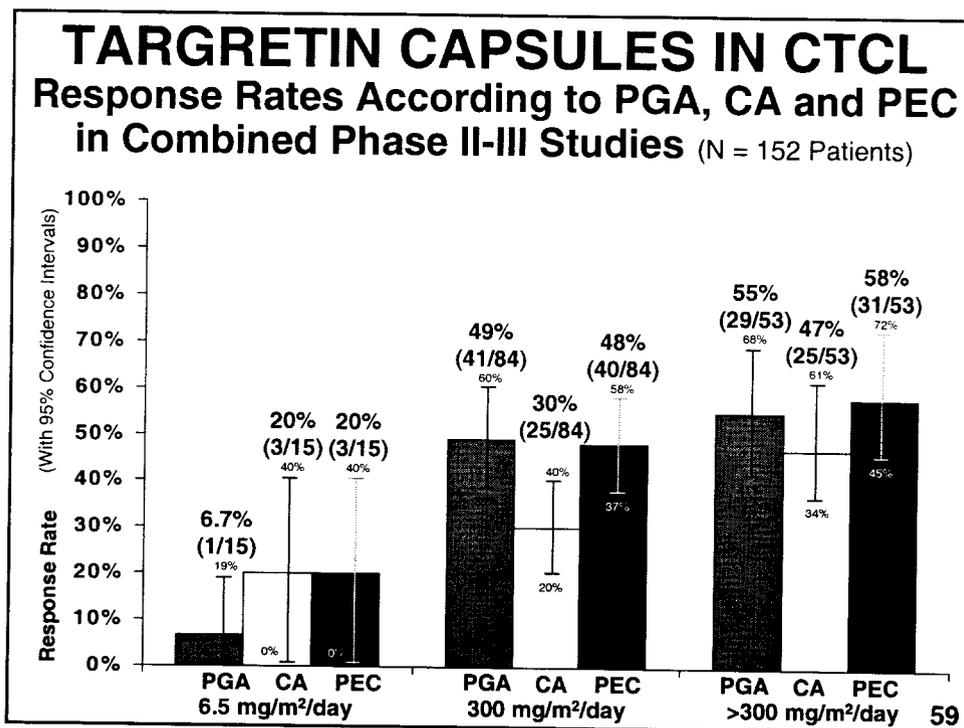
- The Division of Oncology provided in-depth review and attention to detail during protocol development and design
- With regard to the protocol-defined endpoints, Ligand proceeded with confidence knowing that neither the Division nor CTCL disease experts could identify more relevant oncology criteria
- The Division confirmed that single-arm, historically-controlled studies in refractory patients would support an NDA depending upon the results

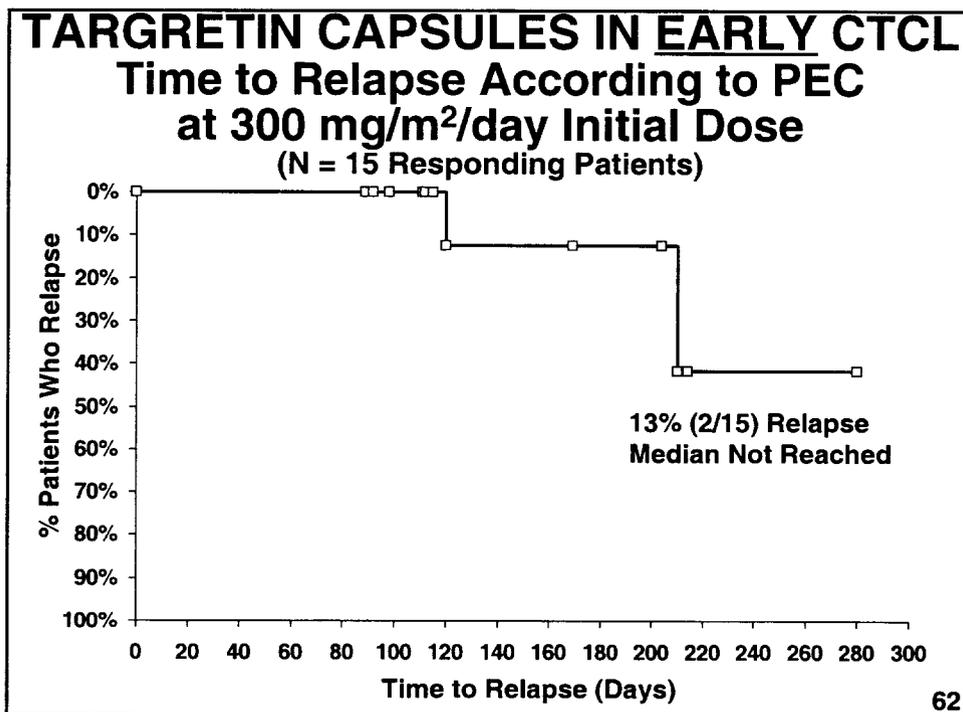
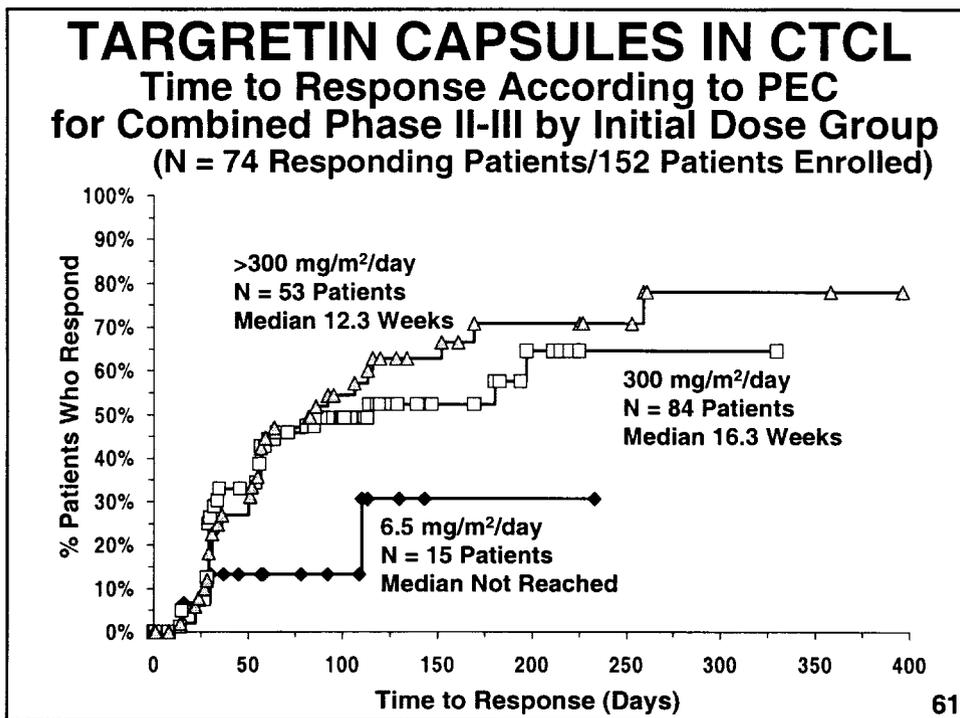
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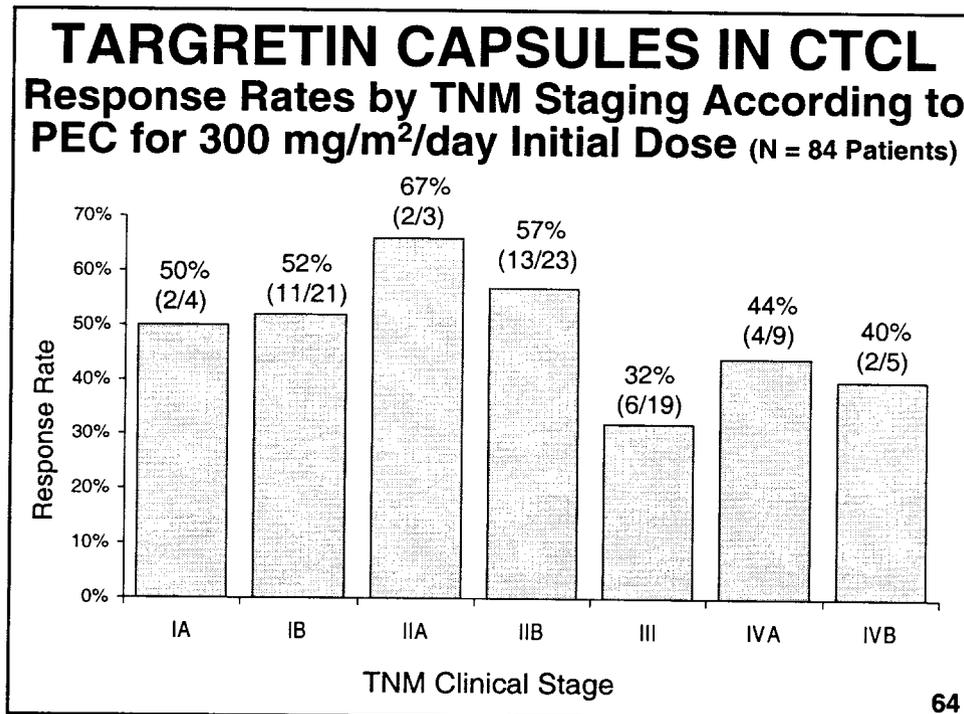
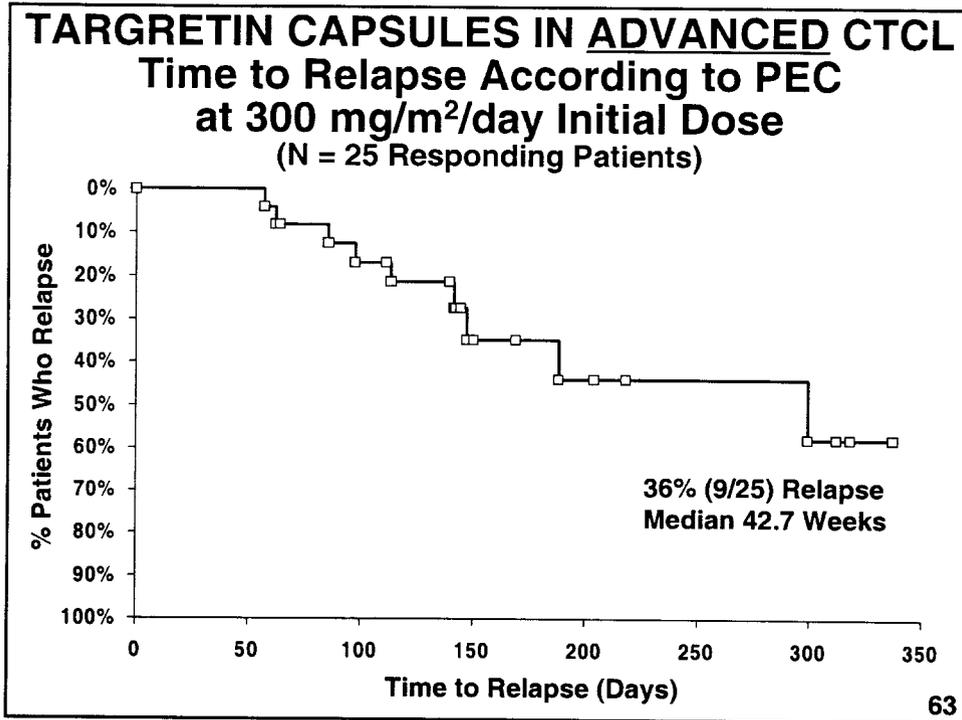
EFFICACY RESULTS

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**PATIENTS CROSSED OVER
FROM LOW TO HIGH DOSE THERAPY
Early Stage CTCL Study
(N = 11 Patients Crossed Over)**

Response Classification*	Before Cross Over	After Cross Over
	6.5 mg/m ² /day N (%)	300 and >300 mg/m ² /day N (%)
CCR + PR	2 (18%)	8 (73%)
SD	2 (18%)	1 (9%)
PD	7 (64%)	2 (18%)

*Responses according to PEC.

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**TARGRETIN CAPSULES IN CTCL
Correlation of Efficacy Endpoints**

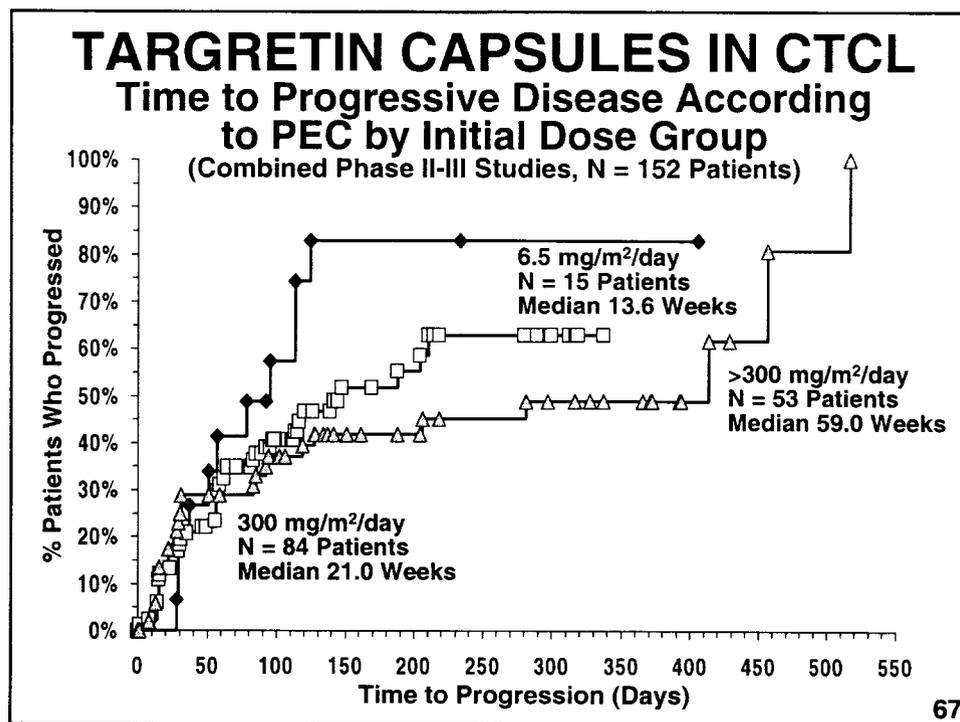
Multiple measures of efficacy present a cohesive body of data reinforcing primary efficacy endpoint (PGA, CA and PEC) findings:

- Dose-response relationship by various measures

and additional measures of clinical benefit:

- Body surface area
- Index lesion individual signs (erythema, scaling, plaque elevation, hypo/hyperpigmentation, and area)
- Index lesion pruritus
- CTCL-specific questions on quality of life questionnaires

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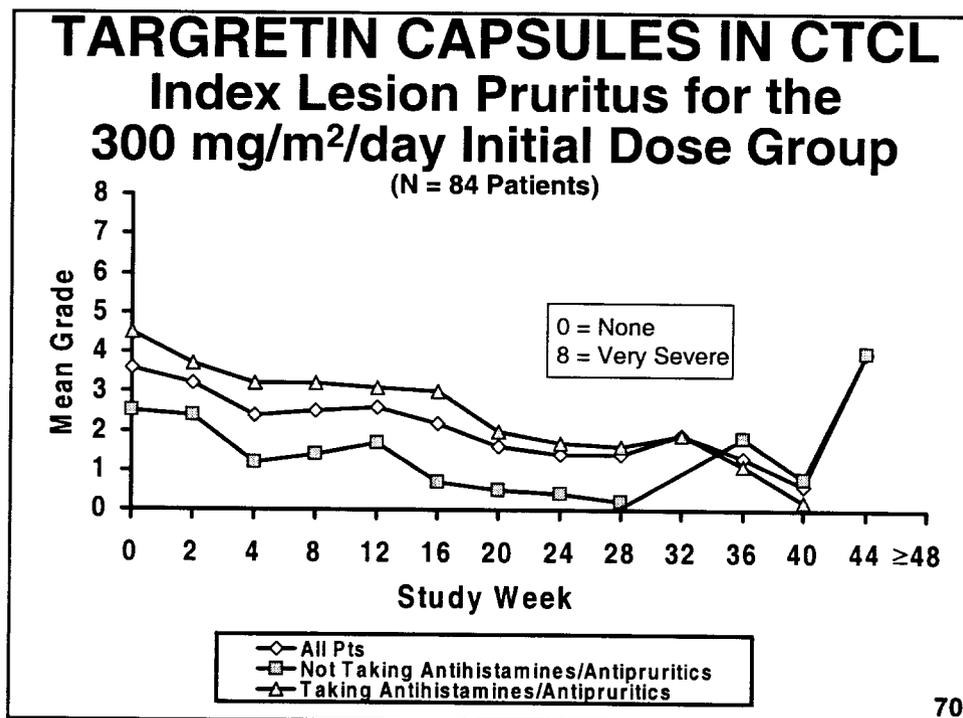
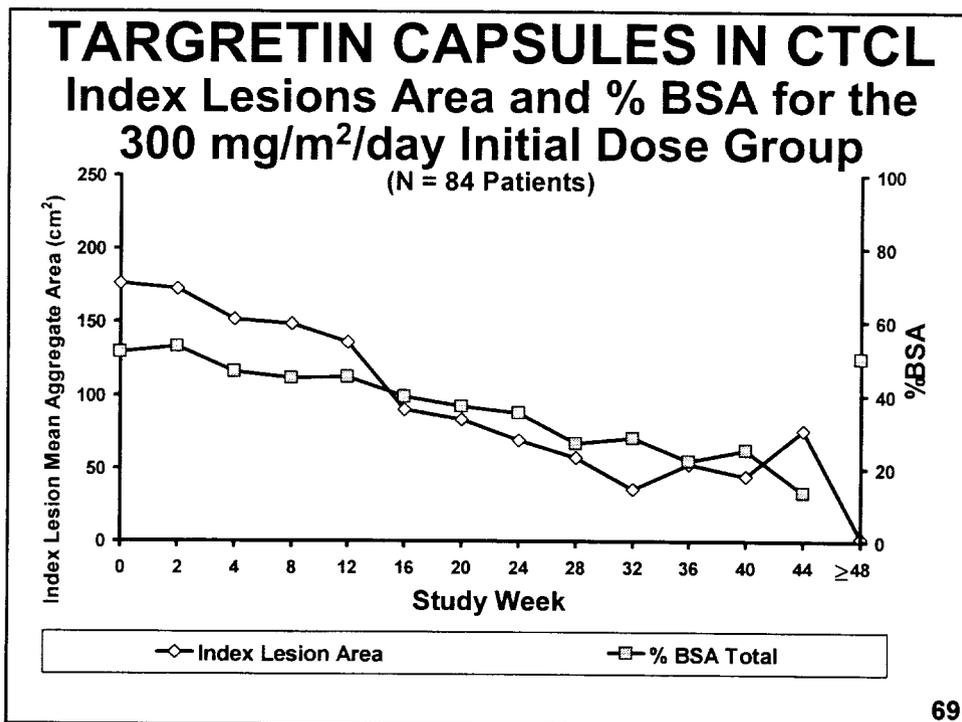


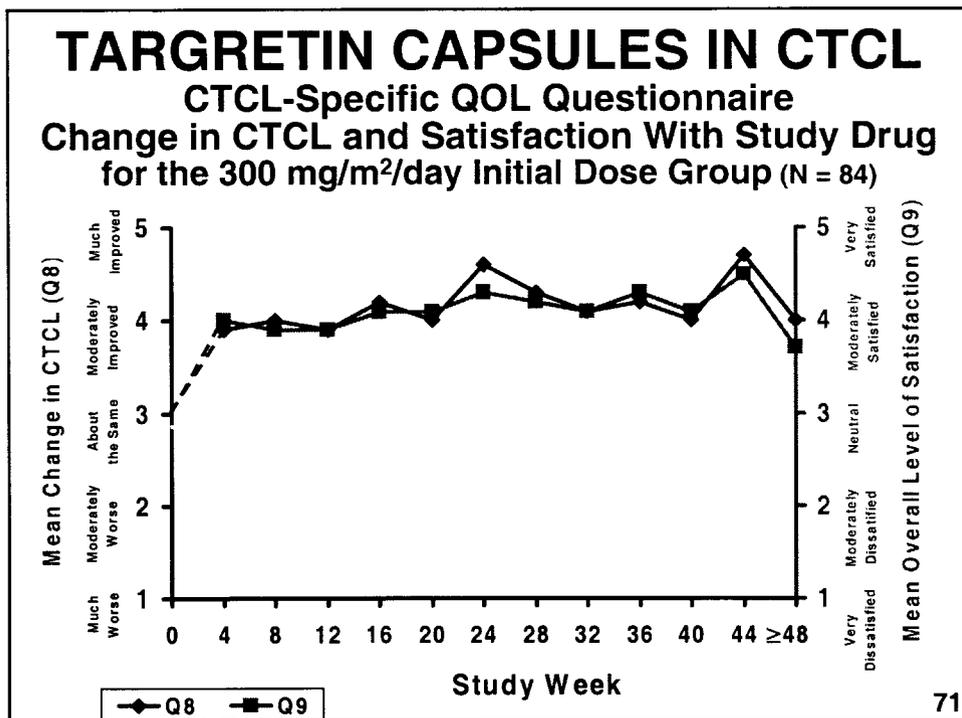
TARGRETIN CAPSULES IN CTCL
Cutaneous Tumors
 in 300 and >300 mg/m²/day Initial Dose Groups
 (24 [16%] of 137 patients had ≥ 1 cutaneous tumor at baseline)

Response Classification	Patient Responses	
	N	%
Responder ¹	9	38%
Complete	4	17%
Partial	5	21%
Stable Disease ²	11	46%
Progressive Disease	4	17%

1. Response required $\geq 50\%$ reduction in aggregate tumor volume or area.
 2. One patient had no post-baseline tumor measurements.

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EFFICACY CONCLUSIONS

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TARGRETIN CAPSULES IN CTCL

Efficacy Conclusions

- Prospective statistical targets for successful trial exceeded by each of primary endpoints (PGA, CA and PEC) for each of two studies independently
- Efficacious in cutaneous manifestations in all TNM stages
- Dose-response relationship for rate of overall response and for CCR, rate of progression, time to progression, and reversal of disease progression upon cross over from low to high dose

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TARGRETIN CAPSULES IN CTCL

Efficacy Conclusions (continued)

- 300 mg/m²/day is optimal initial dose, when dose-related safety profile considered
- Primary endpoint results reinforced by positive findings in secondary endpoints further documenting clinical benefit
- Prompt and durable responses remarkable in heavily pretreated population with few if any remaining treatment options

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PHASE II-III CTCL STUDIES

SAFETY FINDINGS

Steven D. Reich, M.D.
Senior Vice President
Clinical Research
Ligand Pharmaceuticals Inc.

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SCOPE OF TARGRETIN CAPSULES CLINICAL TRIALS

- 690 patients from 16 clinical trials
- 651 patients in Integrated Summary of Safety (ISS)
- 152 CTCL patients treated prior to NDA cutoff treated for a mean of 166 days (maximum 97 weeks)
- 84 CTCL patients in ISS treated at initial dose of 300 mg/m²/day
- MTD 300 to 650 mg/m²/day (QD)

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TARGRETIN CAPSULES IN CTCL

Most Common Adverse Events in Phase II-III ($\geq 20\%$ Incidence Regardless of Relatedness)

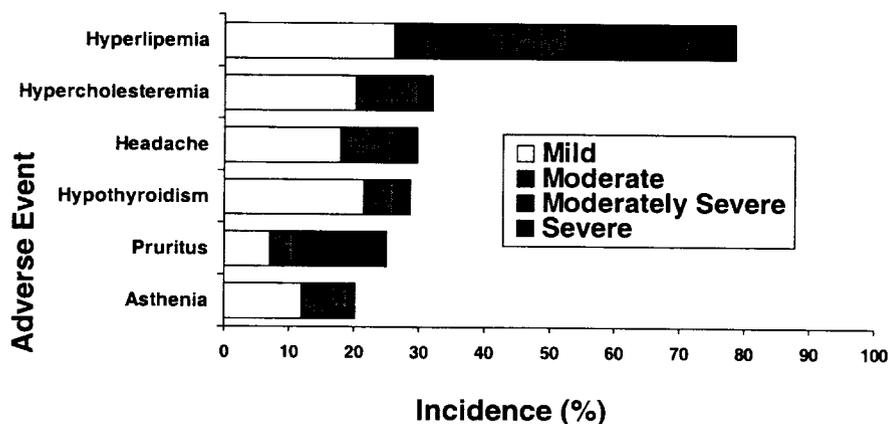
Adverse Event*	Incidence by Initial Dose (mg/m ² /day)	
	300 (N = 84)	>300 (N = 53)
Hyperlipemia	79%	79%
Hypercholesteremia	32%	62%
Headache	30%	42%
Hypothyroidism	29%	53%
Pruritus	25%	15%
Asthenia	20%	45%
<i>Pain</i>	<i>18%</i>	<i>26%</i>
<i>Leukopenia</i>	<i>17%</i>	<i>47%</i>
<i>Rash</i>	<i>17%</i>	<i>23%</i>
<i>Infection</i>	<i>13%</i>	<i>23%</i>
<i>Exfoliative Dermatitis</i>	<i>10%</i>	<i>28%</i>
<i>Diarrhea</i>	<i>7%</i>	<i>42%</i>
<i>Anemia</i>	<i>6%</i>	<i>25%</i>
<i>Anorexia</i>	<i>2%</i>	<i>23%</i>

*COSTART 5 Dictionary Preferred Terms.

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TARGRETIN CAPSULES IN CTCL

Severity of Most Frequent ($\geq 20\%$ Incidence) AEs for 300 mg/m²/day Initial Dose Group in Phase II-III (N = 84 Patients)



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TARGRETIN CAPSULES IN CTCL

Most Common Laboratory Abnormalities

- Hypertriglyceridemia and Hypercholesterolemia
- Thyroid axis alteration (central hypothyroidism)
- Leukopenia/Neutropenia
- Elevation liver function tests

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TARGRETIN CAPSULES IN CTCL

Hypertriglyceridemia in Phase II-III Studies

for 300 mg/m²/day Initial Dose Group (N = 84)

- AEs: 79% of patients had ≥ 1 event of hyperlipemia
 - 26% incidence moderately-severe or severe
- Labs: 21% incidence Grade 3 (>1065 mg/dL) and 7% Grade 4 (>2130 mg/dL) by NCI toxicity
- Reversible
 - 100% (5/5) of patients with Grade 4 (>2130 mg/dL) had resolution as of database closure
- Dose-related

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TARGRETIN CAPSULES IN CTCL
Hypertriglyceridemia in Phase II-III Studies
 for 300 mg/m²/day Initial Dose Group (continued)

- 43% of patients had ≥1 dose-limiting event of ↑TG or ↑Chol
- 60% took a concurrent antilipid drug
- 1.2% (1 patient) primarily withdrawn for hypertriglyceridemia and 1.2% (1 patient) for pancreatitis
- No clinical sequelae except 4 patients (for all dose groups) with pancreatitis (all recovered)
- No drug-related cardiovascular AEs

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TARGRETIN CAPSULES IN CTCL
Pancreatitis in Phase II-III Studies (N = 152)

- 2.6% (4/152) incidence of pancreatitis
- All 4 patients hospitalized, and fully recovered without clinical sequelae
- Associated with TG levels 771 to 2960 mg/dL
- 2 patients at 650, 1 at 500, and 1 at 300 mg/m²/day
- All 4 had ≥1 prestudy risk factor: 3 patients with hyperlipidemia, 1 diabetes mellitus, 1 alcohol, 1 omeprazole, 1 enalapril
- No pancreatitis observed after institution of stricter TG monitoring and management guidelines

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TARGRETIN CAPSULES IN CTCL
Thyroid Axis Alterations in Phase II-III Studies
for 300 mg/m²/day Initial Dose Group (N = 84)

- Consistent with central hypothyroidism (↓TSH, ↓T4), easily detected, reversible with discontinuation of Targretin therapy, and without clinical sequelae
- Mildly symptomatic in most, but not all, patients with biochemical changes
- Labs: 59% with TSH <0.75xLLN and 45% with T4 <0.75xLLN
- As of database closure, 73% with T4 <0.75xLLN resolved

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TARGRETIN CAPSULES IN CTCL
Thyroid Axis Alterations in Phase II-III Studies
for 300 mg/m²/day Initial Dose Group (continued)

- 2.4% (2 patients) ≥1 dose-limiting thyroid event
- No withdrawals for hypothyroidism
- 37% started thyroxine replacement on study
- Patients become euthyroid on replacement therapy
- Recovery to normal TSH occurred as early as 7 days after discontinuation of Targretin capsules

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TARGRETIN CAPSULES IN CTCL Leukopenia in Phase II-III Studies for 300 mg/m²/day Initial Dose Group (N = 84)

- Leukopenia was primarily due to neutropenia
- Labs: 16% Grade 2, 12% Grade 3, and 3.6% Grade 4 NCI neutropenia
- As of database closure, 81% resolved (median 12-28 days)
- 3.6% of patients had ≥ 1 dose-limiting event of leukopenia
- No withdrawals primarily for leukopenia
- 2.4% (2 patients) took concurrent filgrastim
- No drug-related neutropenic fever or sepsis or other infectious clinical sequelae

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TARGRETIN CAPSULES IN CTCL Liver Abnormalities in Phase II-III Studies for 300 mg/m²/day Initial Dose Group (N = 84)

- Labs: No Grade 3 or 4 NCI toxicity LFT abnormalities except 1.2% (1 patient) each Grade 3 hyperbilirubinemia, ALT, and alkaline phosphatase
- Resolved in 75% (3/4) of patients with SGOT/AST $> 2.5 \times \text{ULN}$ and 100% (2/2) with SGPT/ALT $> 2.5 \times \text{ULN}$ as of database closure
- No dose-limiting liver toxicities
- No withdrawals primarily for liver toxicities except 1.2% (1 patient) for hyperbilirubinemia
- One death due to cholestatic "liver failure," associated coagulopathy, and hemorrhage, all assessed as "possibly related" by Investigator

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TARGRETIN CAPSULES

Slit-Lamp Eye Examination Conclusions

(N = 393 patients with ≥ 1 slit-lamp exam)

- No signal is apparent, with two years intensive surveillance including serial examinations
- Only sporadic examples of the normal sequence of increasing lens opacity as expected in a population of similar age, number, and lens status
- No unexpected loss of visual acuity
- No pattern or consistency in reports of new or changed (improved or worsened) lens opacities
- Therefore, no evidence of lens opacity from Targretin capsule therapy

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TARGRETIN CAPSULES IN CTCL

Primary Reasons for Withdrawal From Phase II-III Studies

Primary Reason for Withdrawal	Initial Dose Group (mg/m ² /day)	
	300 (N = 84)	>300 (N = 53)
Did Not Withdraw	38%	23%
CTCL Disease Status		
Progressive Disease	30%	21%
Stable Disease	1%	6%
Partial Response	4%	2%
Clinical Complete Response	0%	2%
Adverse Event	13%	26%
Withdraw Consent	10%	13%
Death	1%	4%
Noncompliance	2%	0%
Lost to Follow-up	1%	0%
Administrative	0%	4%

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TARGRETIN CAPSULES IN CTCL AEs as Primary Reason for Withdrawal From Phase II-III Studies

- AEs (related and not related) cited as primary reason for withdrawal in 13% for 300 mg/m²/day and 26% for >300 mg/m²/day initial dose groups
- For 300 mg/m²/day, 10 of 11 events cited as primary reason were at least possibly drug-related:

Abdominal pain	Hypercholesteremia and
Allergic reaction	hyperlipidemia
Chest pain (not related)	Neuropathy
Diarrhea	Pancreatitis
Headache, tachycardia, vomiting	Pruritus
Hyperbilirubinemia	Skin disorder

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TARGRETIN CAPSULES IN CTCL Deaths and SAEs in Phase II-III Studies

- Only one death (0.7%, 1/152) among CTCL patients judged at least possibly related to drug: liver failure with associated coagulation disorder and hemorrhage
- Non-fatal SAE judged at least possibly related in 5.9% (9/152) of CTCL patients
 - 2.6% (4/152) incidence pancreatitis (all recovered)
 - 0.7% (1/152) incidence: cholestatic jaundice, bilirubinemia, diarrhea, dehydration, herpes zoster, fever, pruritus, and chest pain

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BEXAROTENE PHARMACOKINETICS

- At intended 300 mg/m²/day initial dose level:
 - Half-life generally 1-3 hours
 - Systemic exposure over the daily dosing interval
 - Minimal accumulation
- Metabolized through oxidation by P450 3A4 and glucuronidation
- No observed interaction with P450 3A4 inhibitors
- Gemfibrozil increased bexarotene plasma levels and is not recommended for use with Targretin capsules

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SAFETY CONCLUSIONS

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TARGRETIN CAPSULES IN CTCL Safety Summary and Conclusions

- Generally well-tolerated over a mean of 166 days (maximum 97 weeks)
- No confirmed drug-related deaths*
- Drug-related SAEs uncommon
- No new toxicities with longer term treatment

* One death judged "possibly related" by Investigator but judged not related upon independent expert review.

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TARGRETIN CAPSULES IN CTCL Safety Summary and Conclusions (continued)

- Common toxicities (↑TG, ↓TSH, ↓WBC) often warrant pharmacologic intervention, but
 - concomitant therapies easily administered and monitored
 - these toxicities generally well-tolerated; easily managed; nearly always lacked clinical sequelae; and reversible upon dose reduction, suspension or discontinuation

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TARGRETIN CAPSULES IN CTCL

Rationale for Recommended Dose Regimen

- **Dose-response relationship** supported by rate of response, rate of progression, time to progression, and reversal of progression after cross over from low to high dose therapy
- **Dose relationship for toxicity** based on DLTs, many adverse events, and laboratory abnormalities
- **Dose level best titrated on a patient-by-patient basis** due to wide variation in individual patient tolerance
- **Risk-benefit ratio optimal at 300 mg/m²/day initial dose level**, with provisions for upward and downward dose adjustments

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TARGRETIN CAPSULES IN CTCL

Dose Regimen Proposed for Labeling

- Initial dose 300 mg/m²/day PO
- Adjust to 200 mg/m²/day then to 100 mg/m²/day, or suspend, if necessitated by toxicity
- With appropriate clinical monitoring, individual patients may benefit from doses above 300 mg/m²/day
- Doses greater than 650 mg/m²/day have not been evaluated in CTCL patients

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TARGRETIN CAPSULES IN CTCL Conclusion

The clinical data support the safety and efficacy of Targretin capsules at the dose regimen recommended for labeling in patients with refractory or persistent CTCL.

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A CLINICAL INVESTIGATOR'S PERSPECTIVE

Kenneth B. Hymes, M.D.
Associate Professor of Medicine
Division of Hematology
NYU Medical Center

98

KENNETH B. HYMES, M.D.

- Board-certified in Hematology and Medical Oncology
- CTCL Practice with >200 active patients
- Director, Bellevue Hospital Hematology Clinic
- Member of ECOG
- NIH Career Development Award

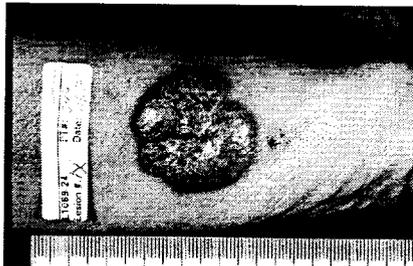
99

TARGRETIN CAPSULES IN CTCL **Profile of L1069-24 (282) Patient 544**

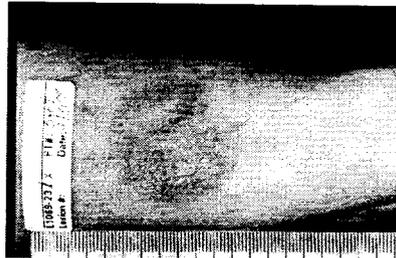
- 67-year-old woman with Stage IIB CTCL
- 10 1/2-year duration of disease
- 70% BSA involvement
- 3 cutaneous tumors
- Previous CTCL therapy:
 - Refractory following partial response to topical nitrogen mustard
 - Refractory following partial response with relapse to interferon

100

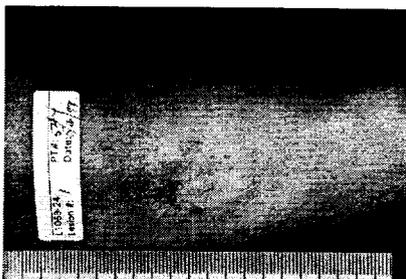
L1069-24 (282) PATIENT 544 Lesion 1X, Forearm



Baseline



Week 12



Week 28

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L1069-24 (282) PATIENT 544 Lesion 3X, Scalp



Baseline



Week 12



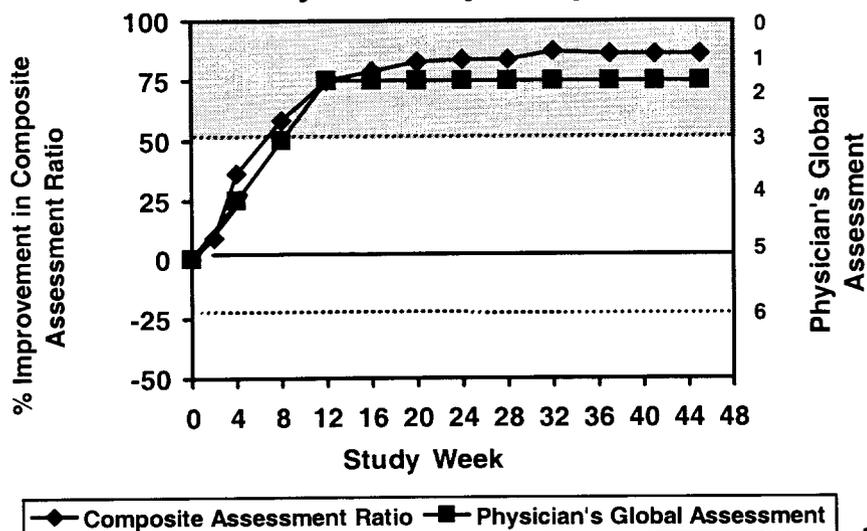
Week 41

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TARGRETIN CAPSULES IN CTCL

Patient Profile L1069-24 (282) 544

Primary Efficacy Endpoints



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TARGRETIN CAPSULES IN CTCL

Profile of L1069-24 (282) Patient 544

Summary

- $\geq 75\%$ response, duration 2.1 years and continuing
- BSA reduction from 70% to 12%
- 3 cutaneous tumors at baseline, all completely resolved
- 1 new tumor appeared (only 1.1 cm³) with dose reduction, then resolved with dose increase
- Dose reduction and concomitant medications were required to control \uparrow TG

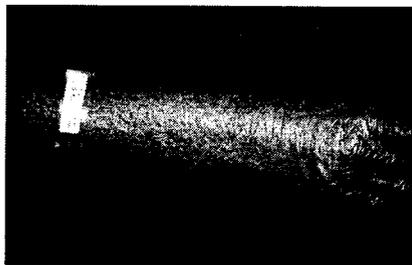
104

TARGRETIN CAPSULES IN CTCL Profile of L1069-24 (282) Patient 541

- 58-year-old woman with Stage III CTCL
- 2-year duration of disease
- 100% BSA involvement
- 2 clinically abnormal lymph nodes
- Previous CTCL therapy:
 - Refractory to interferon
 - Refractory following partial response to high dose methotrexate

105

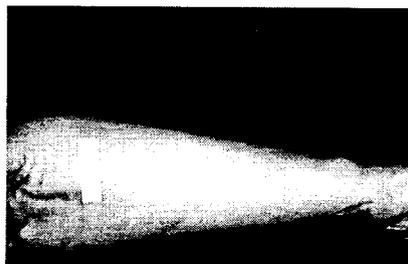
L1069-24 (282) PATIENT 541 Lesion G1X, Forearm



Baseline

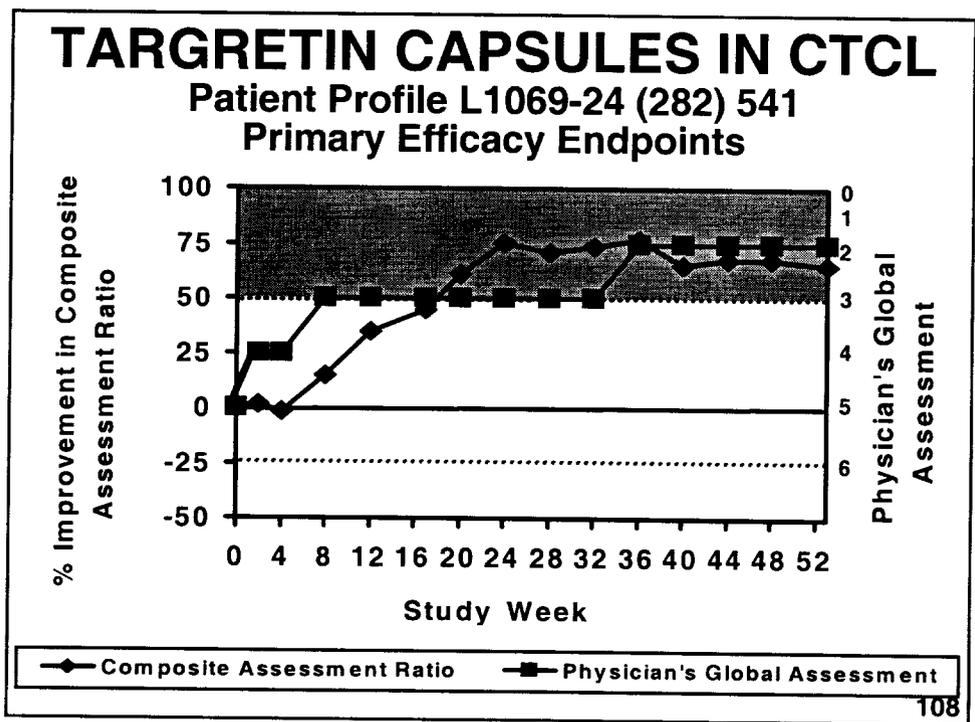
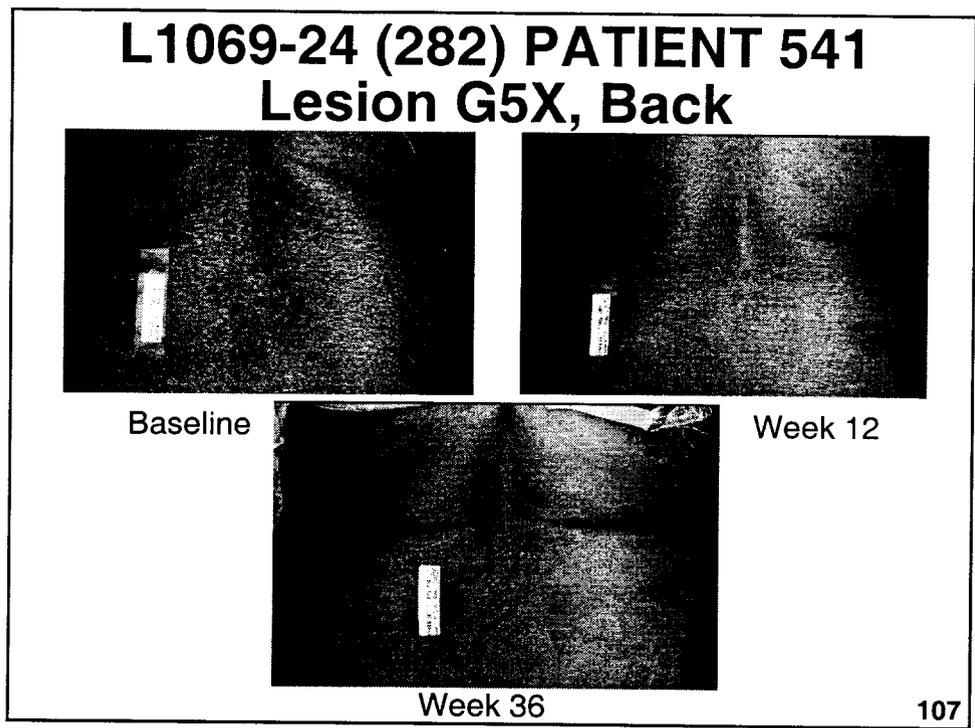


Week 12



Week 36

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TARGRETIN CAPSULES IN CTCL

Profile of L1069-24 (282) Patient 541

Summary

- 65%-75% response, duration 2.2 years and continuing
- Pruritus, alopecia and nail changes fully resolved
- The 2 nodes at baseline completely resolved (↓total 17 to 0 cm²)
- Dose reduction and concomitant medication were required to control ↑TG

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TARGRETIN CAPSULES IN CTCL

Potential Benefits of Targretin Capsules

- CTCL is a chronic, symptomatic, incurable and relapsing disease; therefore, patients require a sequence of multiple different treatments
- Impressive response rate for orally administered single agent therapy in refractory patients
- Safety profile of Targretin capsules is qualitatively different from other CTCL treatments, providing an advantage in avoiding cumulative and overlapping toxicities

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TARGRETIN CAPSULES IN CTCL
Potential Benefits of Targretin Capsules
(continued)

- Common toxicities can be easily controlled
- Ease of oral administration and lack of required travel to specialized referral treatment centers are benefits
- Long duration of response to Targretin capsules is impressive

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**A CLINICAL INVESTIGATOR'S
PERSPECTIVE**

Madeleine Duvic, M.D.
Chief, Section of Dermatology
M.D. Anderson Cancer Center

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MADELEINE DUVIC, M.D.

- Professor of Medicine and Dermatology
- Chief, Section of Dermatology
- Director Multidisciplinary CTCL Clinic
- Co-Director Melanoma and Skin Center, MD Anderson Cancer Center, Houston
- Lead accruing study center in Targretin capsules in CTCL Phase II-III studies

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MADELEINE DUVIC, M.D.

- International Society of Cutaneous Lymphomas - Task Force to define Sézary Syndrome
- American Academy of Dermatology- NCI Liaison Member and CTCL Guidelines Task Force
- NCI grant - Molecular Markers of Retinoid Action in CTCL
- Lymphoma Research Foundation of America - Webcast Moderator on CTCL

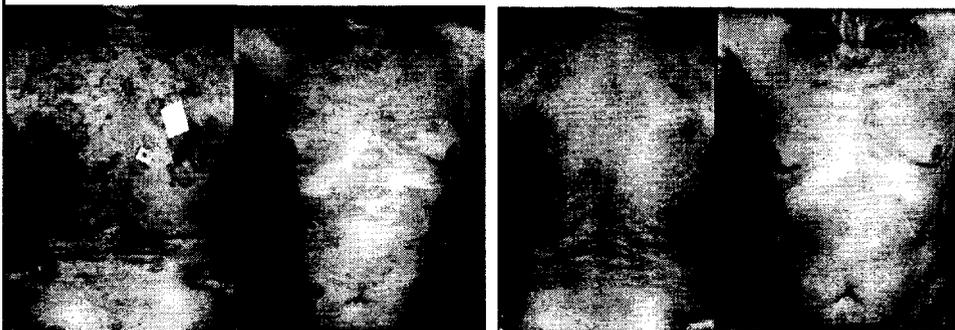
114

TARGRETIN CAPSULES IN CTCL L1069-23 (014) Patient 1171

- 71-year-old man
- Stage IIA CTCL for >13 years
- Baseline 59% BSA involvement
- Failed 9 previous CTCL therapies:
 - Relapsed after responding to: interferon, isotretinoin, topical nitrogen mustard, PUVA, and TBSEB
 - Refractory to CHOP, prednisone and pentostatin
 - Intolerant to interferon; ifosfamide + MTX + VP16 + dexamethasone; PUVA; and TBSEB

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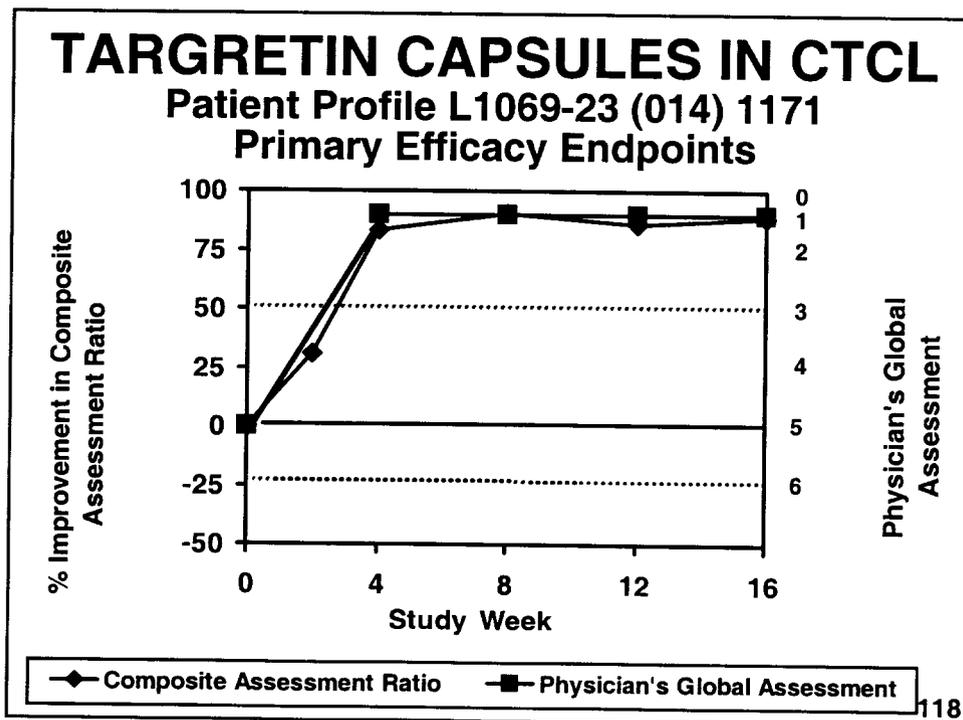
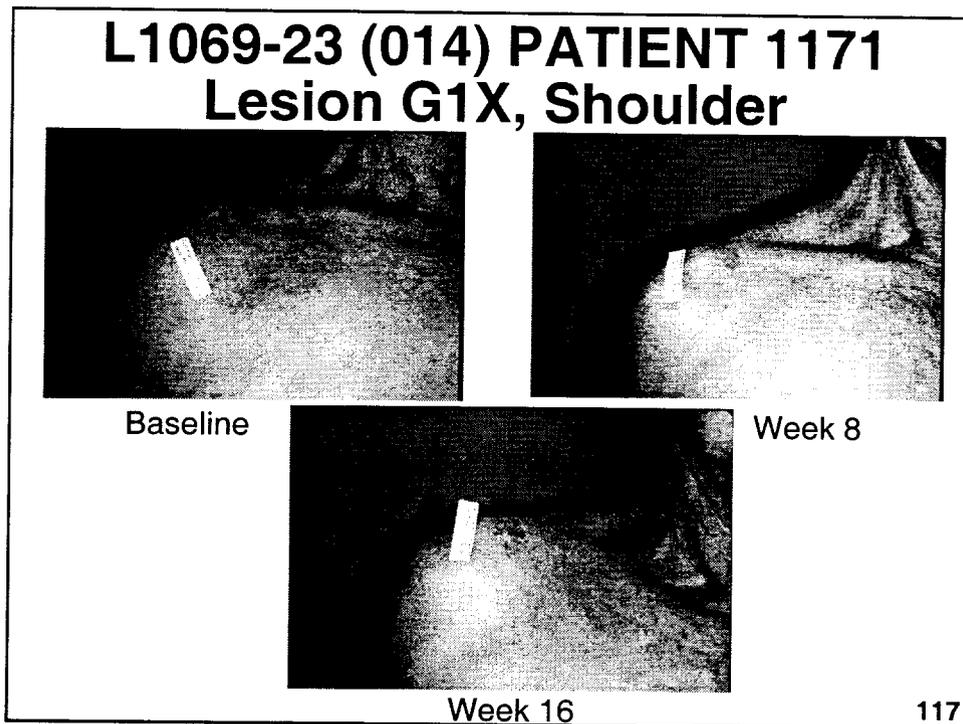
TARGRETIN CAPSULES IN CTCL L1069-23 (014) Patient 1171



Baseline (6-98)

1 Year (5-99)

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TARGRETIN CAPSULES IN CTCL **L1069-23 (014) Patient 1171**

- 98% response (all except one lesion)
 - ↓ BSA 59% to 0.2%
 - 1 baseline lymph node disappeared
 - Sézary cells ↓ from 20% → 0% by Week 12
- Dose reduction and concomitant medication were required to control ↑TG
- DURATION of almost CCR = 17+ MONTHS

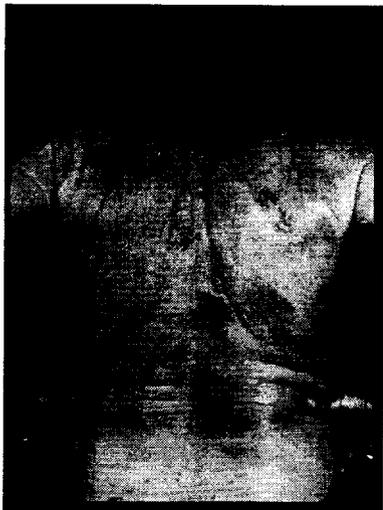
119

TARGRETIN CAPSULES IN CTCL **L1069-23 (014) Patient 1172**

- 81-year-old man
- Stage IIA CTCL for 7 years
- 48% BSA involvement at baseline
- 7 Previous CTCL therapies:
 - Prednisone - response and relapse
 - PUVA (response, but intolerant)
 - Topical nitrogen mustard - allergic, intolerant
 - Refractory to CVP chemotherapy, chlorambucil, interferon, and PUVA

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**TARGRETIN CAPSULES IN CTCL
L1069-23 (014) Patient 1172**



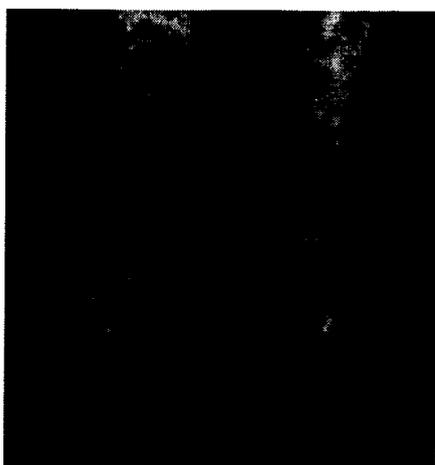
Baseline (6-98)



9 Months (3-99)

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**TARGRETIN CAPSULES IN CTCL
L1069-23 (014) Patient 1172**



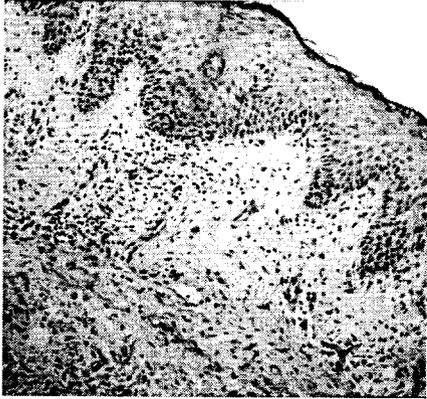
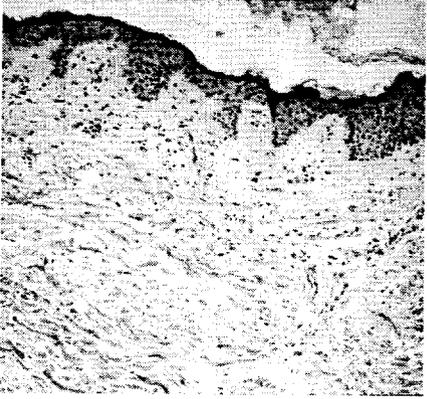
Baseline (6-98)



9 Months (3-99)

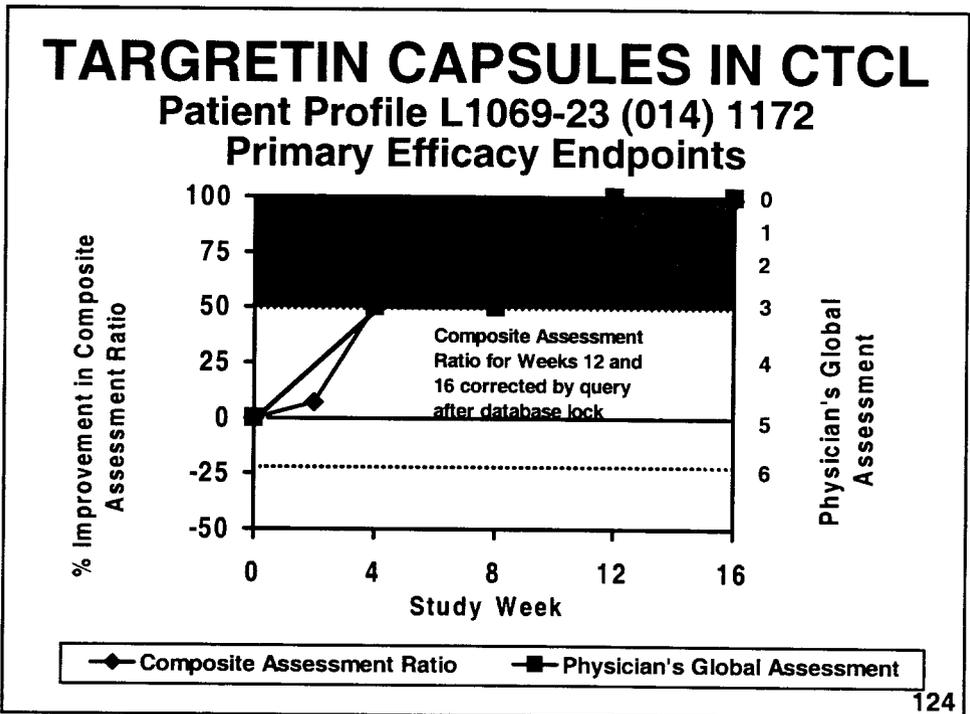
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TARGRETIN CAPSULES IN CTCL L1069-23 (014) Patient 1172 Skin Biopsies

Baseline
Week 8

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TARGRETIN CAPSULES IN CTCL

Profile of L1069-23 (014) Patient 1172

Summary

- Complete Response:
 - BSA ↓ 48% to 0% with confirmatory biopsy
 - Pruritus resolved
 - Two baseline nodes, both disappeared
 - Sézary cells ↓ from 9% at Week 4 to 0% at Weeks 12 - 20
- No dose-limiting toxicity
- Dose reduction and concomitant medication were required to control ↑TG
- RESPONSE DURATION = 17+ MONTHS (CR 14+ MONTHS)

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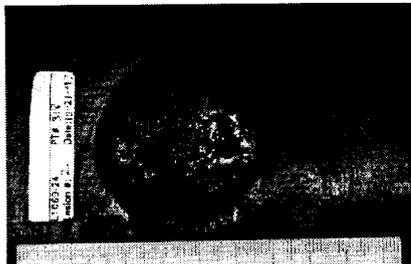
TARGRETIN CAPSULES IN CTCL

Profile of L1069-24 (014) Patient 318

- 63-year-old man with Stage IIB CTCL
- 5-year duration of disease
- 39% BSA involvement
- 1 cutaneous tumor (large-cell transformation)
- Previous CTCL therapy:
 - Partial response to CMED, ESHAP, with relapse to both
 - Refractory to interferon, isotretinoin, topical mustard

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L1069-24 (014) PATIENT 318 Lesion 2X, Elbow



Baseline



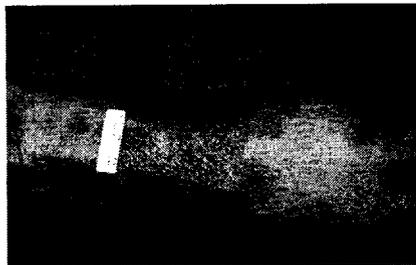
Week 4



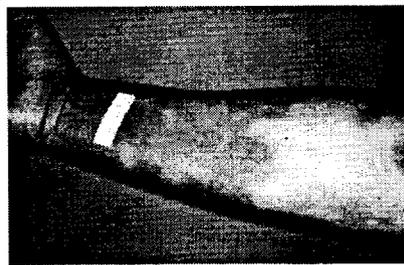
Week 13

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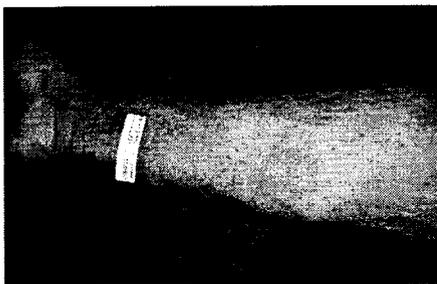
L1069-24 (014) PATIENT 318 Lesion G5X, Forearm



Baseline

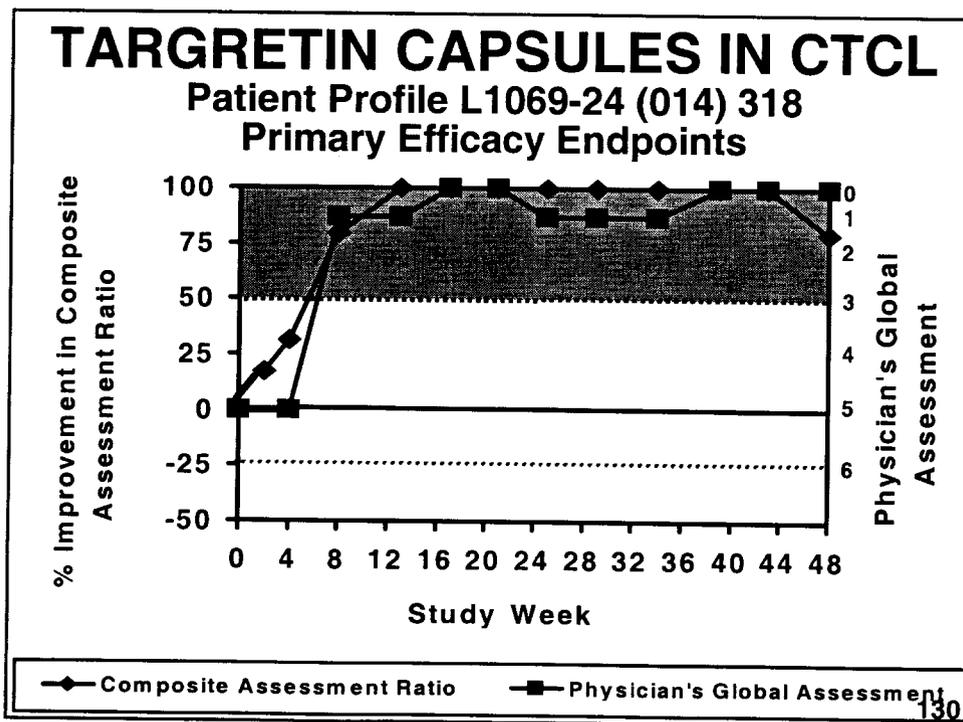
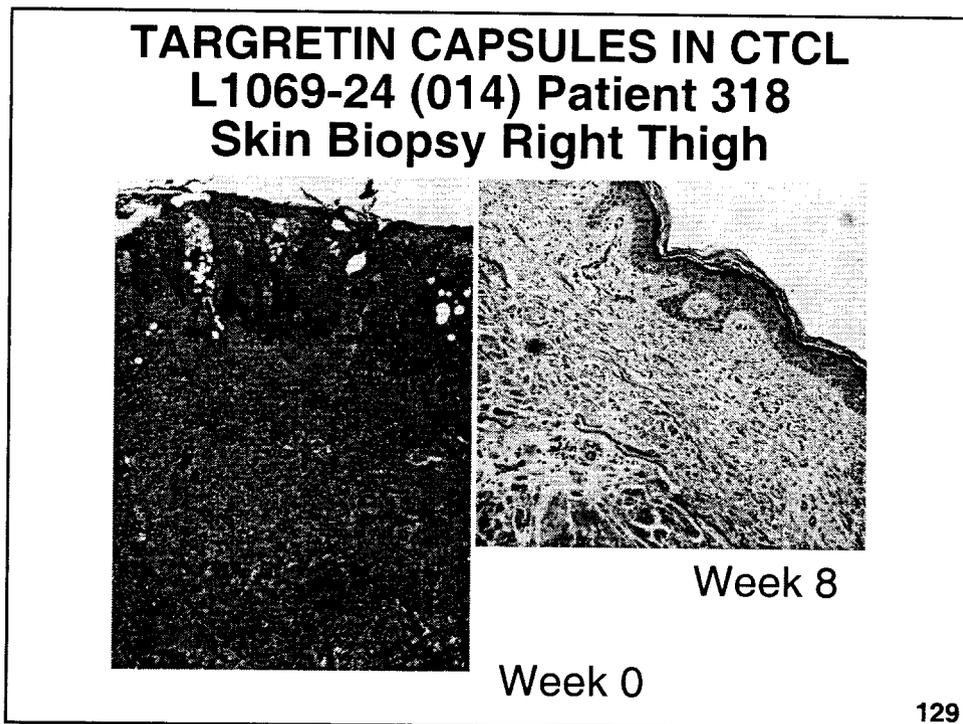


Week 17



Week 43

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TARGRETIN CAPSULES IN CTCL

Profile of L1069-24 (014) Patient 318

Summary

- 90% -100% response:
 - BSA ↓ 39% to 0%
 - 1 cutaneous tumor resolved (↓20 to 0 cm³)
- Dose reduced from 500→300→200→100→25→50→25 mg/m²/day due to ↑TG
- Dose reduction and concomitant medication were required to control ↑TG
- RESPONSE DURATION 2+ YEARS

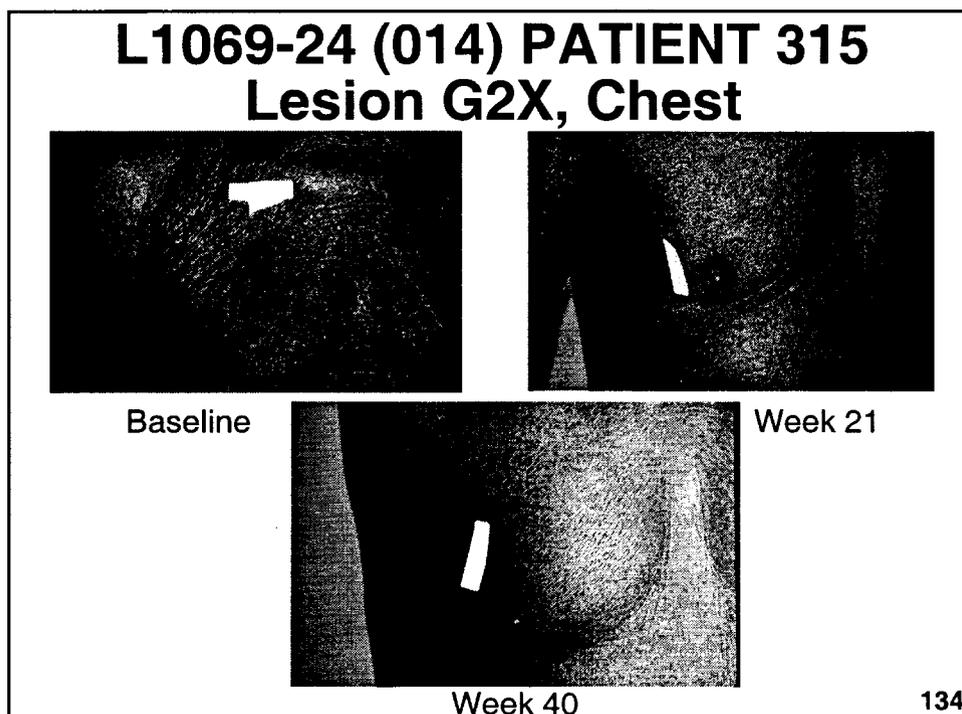
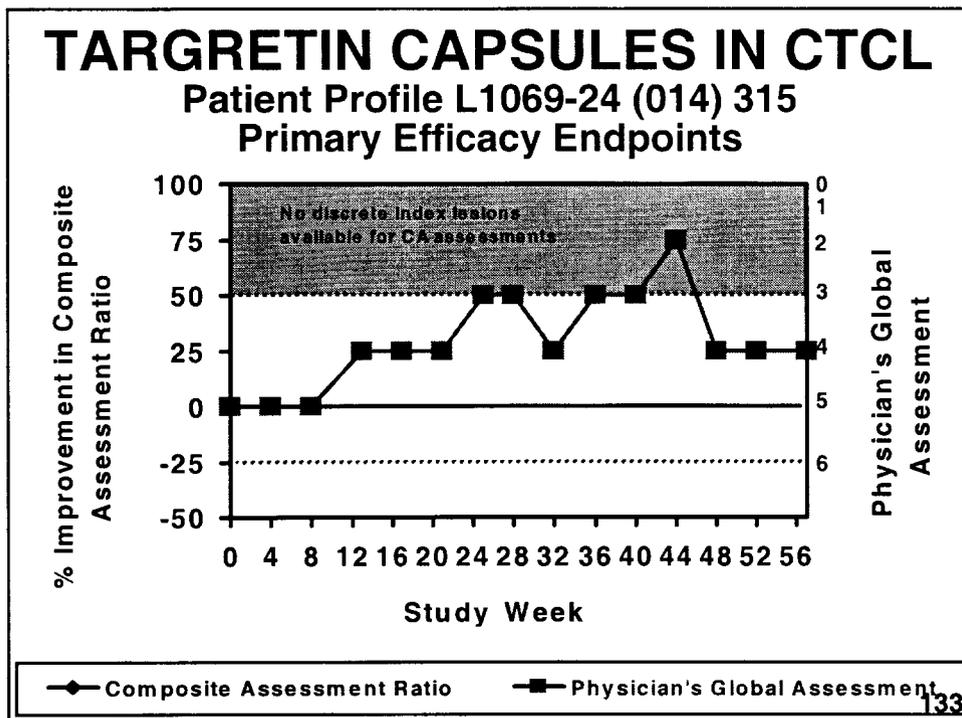
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TARGRETIN CAPSULES IN CTCL

L1069-24 (014) Patient 315

- 71-year-old man with Sézary Syndrome (Stage IVA) of 7-years duration
- 100% BSA involvement, lichenified skin
- Previous CTCL therapy:
 - Refractory to interferon, photopheresis, and topical nitrogen mustard
 - Intolerant to photopheresis (no venous access)
- Patient classified as progressive disease according to PEC and CA due to missed nodes on baseline exam (but PR by PGA)

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TARGRETIN CAPSULES IN CTCL

Potential Benefits of Targretin Capsules

- Targretin capsules produce excellent responses in cutaneous manifestations of all TNM stages of CTCL, even the more difficult to treat patients with Stage III-IV, including erythrodermic MF/Sézary syndrome and large-cell transformation.
- The CA endpoint used in these studies was conservative and underestimated the true response rate and clinical benefit.

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TARGRETIN CAPSULES IN CTCL

Potential Benefits of Targretin Capsules (continued)

- Targretin is an oral therapy and does not require venous access.
- It is non-immunosuppressive.
- Thus, Targretin capsules do not expose the patient to increased risk of infection/sepsis, the most common cause of death in CTCL patients.

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TARGRETIN CAPSULES IN CTCL

Potential Benefits of Targretin Capsules

(continued)

- Targretin capsules work quickly and responses are dose related and durable.
- The side effects are reversible, generally mild, easily monitored by blood work, and controllable with oral medication.
- Targretin capsules are an important novel therapy, controlling the disease in patients with all stages of CTCL.

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TARGRETIN CAPSULES IN CTCL

Summary/Questions

Howard T. Holden, Ph.D.
Vice President
Regulatory Affairs and Compliance
Ligand Pharmaceuticals Inc.

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TARGRETIN CAPSULES

Summary of Clinical Results

Efficacy for the Treatment of CTCL:

Demonstrated by two clinical studies showing clinically meaningful response rates in patients who failed one or more prior therapies in

- Early stage disease response rate of 54% at 300 mg/m²/day by PEC
- Advanced stage disease response rate of 45% at 300 mg/m²/day by PEC

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TARGRETIN CAPSULES

Summary of Clinical Results

Further Evidence Supporting Efficacy

Dose-Response Relationship

	Dose (mg/m ² /day)		
	6.5	300	>300
• Rate of overall response	20%	48%	58%
• Time to response	*	16 wks	12 wks
• Time to progression	14 wks	21 wks	59 wks
<p>• Reversal of disease progression upon cross-over from low dose to high dose with an increase in response rate from 18% to 73%</p>			

* Median not reached

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TARGRETIN CAPSULES

Clinical Benefit

- Positive response in several measures of clinical benefit included in CA, PGA and PEC:
 - Index lesion clinical signs
 - Index lesion pruritus
- Additional clinical benefit assessment recorded:
 - Body surface area
 - CTCL-specific questions on QOL questionnaires
- Positive effects seen across all stages of the disease
- Generally mild to moderate side effects, easily managed

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TARGRETIN CAPSULES

Clinical Benefit (continued)

- Safety profile is distinct from other available systemic therapies for CTCL
- Oral therapy does not require venous access or specialized treatment at referral centers
- These patients were heavily pretreated and have few if any remaining viable treatment options

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TARGRETIN CAPSULES IN CTCL

Conclusions

Data from two adequate and well-controlled clinical trials support the safe and effective use of Targretin® capsules for the treatment of cutaneous manifestations in patients with all clinical stages of CTCL (IA-IVB) in the following categories:

- Patients with early stage CTCL who have not tolerated other therapies,
- Patients with refractory or persistent early stage CTCL, and
- Patients with refractory advanced stage CTCL

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TARGRETIN® CAPSULES

(BEXAROTENE)

NDA 21-055

Ligand Pharmaceuticals Incorporated
San Diego, CA

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Summary of Targretin Capsules Clinical Results in CTCL

<u>Early Disease</u>	<u>PGA</u>	<u>CA</u>	<u>PEC</u>
6.5 mg/m ² /day (N = 15)	7%	20%	20%
300 mg/m ² /day (N = 28)	50%	36%	54%
>300 mg/m ² /day (N = 15)	60%	47%	67%
<u>Advanced Disease</u>			
300 mg/m ² /day (N = 56)	48%	27%	45%
>300 mg/m ² /day (N = 38)	53%	47%	55%

PEC Response Rate (CCR + PR)

<u>Crossover Patients</u>	<u>6.5 mg/m²/day</u>	<u>300 + >300 mg/m²/day</u>	
(Early Stage) (N = 11)	18%	73%	145

Summary of Targretin Capsules Clinical Results in CTCL (continued)

<u>Dose Response</u> (PEC)		
<u>Dose</u>	<u>CCR + PR</u>	<u>CCR</u>
6.5 mg/m ² /day	20%	7%
300 mg/m ² /day	48%	4%
>300 mg/m ² /day	58%	17%

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