

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 21055**

**STATISTICAL REVIEW(S)**

## Statistical Review and Evaluation

DEC 17 1998

**NDA#:** 21-055  
**Applicant:** Ligand Pharmaceuticals  
**Name of Drug:** Targretin Capsules  
**Indication:** Treatment of patients with all clinical stages (IA-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 or persistent early stage CTCL, and patients with refractory advanced stage CTCL.  
**Documents Reviewed:** Vols. 1, 189-193, 196, 205, 212-214, 227, 229, 240 and 242  
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### 1. BACKGROUND AND OVERVIEW

In support of a first-line treatment of patients with cutaneous T-cell lymphoma (CTCL) the sponsor submitted an NDA which includes a Phase I trial and two Phase II-III pivotal trials. A total of 200 patients with CTCL were treated with Targretin capsules. Nine of these patients were in the Phase I study and the remaining 191 were enrolled into one of the two Phase II-III studies - L1069-23 and L1069-24. 152 of these 191 patients were enrolled in the study as of 31 July 1998 and were included in the database. This review will focus on the efficacy aspects of the two Phase II-III trials based on the results from these 152 patients.

In addition, 14 Phase I-II, II and II-III clinical studies in patients with non-CTCL cancers or benign diseases were conducted.

### 2. BRIEF DESCRIPTION OF STUDIES

#### Study L1069-23

Study L1069-23 was a Phase II-III, open-label, multicenter, multinational, historically-controlled, single-arm study to evaluate the safety, tolerability and antitumor efficacy of Targretin capsules in patients with refractory or persistent early stage (I-IIA) CTCL, and to evaluate two different dose levels of Targretin capsules in patients with refractory or persistent early stage (I-IIA) CTCL.

Initially, patients were randomly assigned to one of two dose groups - 6.5 mg/m<sup>2</sup>/day or 650 mg/m<sup>2</sup>/day. Patients were given Targretin capsules once daily. The 650 mg/m<sup>2</sup>/day level was reduced to 500 mg/m<sup>2</sup>/day and later to 300 mg/m<sup>2</sup>/day. Six out of fifteen patients in the 6.5 mg/m<sup>2</sup>/day group crossed over to 500 mg/m<sup>2</sup>/day under a protocol amendment. A later protocol amendment established the initial dose of 300 mg/m<sup>2</sup>/day. Five of the remaining patients in the 6.5 mg/m<sup>2</sup>/day group crossed over to 300 mg/m<sup>2</sup>/day. Fourteen patients who were randomly assigned to either the low or high dose (nine patients and five patients respectively) were assigned to the 300 mg/m<sup>2</sup>/day

dose. If a patient remained on 300 mg/m<sup>2</sup>/day and no response was observed for that patient within eight or more weeks of therapy, the dose may be increased to 400 mg/m<sup>2</sup>/day after Week 8 provided that no unacceptable toxicity occurred. The 300 mg/m<sup>2</sup>/day dosage level could be reduced to 200 mg/m<sup>2</sup>/day and then 100 mg/m<sup>2</sup>/day as necessitated by toxicity.

A total of 65 patients were screened and 58 patients were entered into the study at 18 enrolling study centers through 31 July 1998. For the purpose of analysis, patients are grouped in this study report by three initial dose groups: 6.5 mg/m<sup>2</sup>/day (N=15), 300 mg/m<sup>2</sup>/day (N=28) and >300 mg/m<sup>2</sup>/day (N=15).

The primary efficacy endpoints are response rates according to Physician's Global Assessment of Clinical Condition (PGA), Composite Assessment of Index Lesion Disease Severity (CA) and the Primary Endpoint Classification (PEC). The CA is determined by a summation of the grades for each index lesion erythema, scaling, plaque elevation, hypopigmentation or hyperpigmentation, and area of involvement of up to five index lesions, and also considered the presence or absence of all extracutaneous disease manifestations. The PGA considers index and non-index cutaneous lesions, clinically abnormal lymph nodes, cutaneous tumors, pathologically positive lymph nodes, visceral disease, and other tumor manifestations. The PGA is an assessment of the extent of improvement/worsening of the patient's overall disease compared to the condition at entry (at baseline). Except in cases of intervening progressive disease by either endpoint, the PEC is the best response according to either the Composite Assessment of Index Lesion Disease Severity (CA) or the Physician's Global Assessment of Clinical Condition (PGA).

For PGA and CA primary measures of efficacy, responses required confirmation over at least two assessments that were at least four study weeks apart, and a partial response required at least 50% improvement.

The sponsor deems the study successful for an initial dose group if that group's observed response rate for (CCR+PR) was at least 20% with the corresponding 95% confidence interval lying entirely above 5%.

Secondary endpoints include (1) times to first and best response, (2) duration of disease control, (3) durability of response, (4) time to disease progression, (5) total body surface area involvement, (6) individual index lesions signs and symptoms, (7) clinically abnormal lymph nodes, (8) cutaneous CTCL tumors (if present), (9) visceral involvement (if present), (10) quality of life (questionnaires), (11) responses of patients who crossed over to higher doses (see above) and (12) comparison of responses in the low and high dose groups.

#### **Study L1069-24**

Study L1069-24 is a phase II-III, open-label, multicenter, multinational, historically-controlled study to evaluate the safety, tolerability and antitumor efficacy of Targretin capsules in patients with refractory advanced stage (IIB-IVB) CTCL.

Initially, patients were assigned a dose of 650 mg/m<sup>2</sup>/day. The 650 mg/m<sup>2</sup>/day level was reduced to 500 mg/m<sup>2</sup>/day and later to 300 mg/m<sup>2</sup>/day. Patients were given Targretin capsules once daily. A later protocol amendment established the initial dose of 300 mg/m<sup>2</sup>/day. If a patient remained on 300 mg/m<sup>2</sup>/day and no response was observed for that patient within eight or more weeks of therapy, the dose may be increased to 400 mg/m<sup>2</sup>/day after Week 8 provided that no unacceptable toxicity occurred. The 300 mg/m<sup>2</sup>/day dosage level could be reduced to 200 mg/m<sup>2</sup>/day and then 100 mg/m<sup>2</sup>/day as necessitated by toxicity.

A total of 102 patients were screened and 94 patients were entered into the study at 26 enrolling study centers through 31 July 1998. For the purpose of analysis, patients are grouped in this study report by three initial dose groups: 300 mg/m<sup>2</sup>/day (N=56) and >300 mg/m<sup>2</sup>/day (N=38).

The primary endpoints are the same as those for study L1069-23. The secondary endpoints are the same as (1) to (10) for study L1069-23.

### 3. SUMMARY OF EFFICACY RESULTS AND COMMENTS

This section summarizes the primary and secondary efficacy analyses and baseline characteristics for studies L1069-23 and L1069-24.

#### Study L1069-23

An initial dose is deemed successful by the sponsor in the protocol if there is a response rate above 20% and the corresponding confidence interval lies entirely above 5%. Table 1 below lists the sponsor's determined response rates and this reviewer's calculations of exact 95% confidence intervals based on these rates.

**Table 1. Response Rates and 95% Confidence Intervals**

Efficacy Endpoint	Initial Dose (in mg/m <sup>2</sup> /day)		
	6.5 <sup>1</sup>	300	> 300
PEC	3/15 (0.0433, 0.4810)	15/28 (0.3387, 0.7249)	10/15 (0.3838, 0.8818)
CA	3/15 (0.0433, 0.4810)	10/28 (0.1864, 0.5594)	7/15 (0.2126, 0.7341)
PGA	1/15 (0.0017, 0.3195)	14/28 (0.3064, 0.6935)	9/15 (0.3228, 0.8366)

<sup>1</sup>Response rates for the 6.5 mg/m<sup>2</sup>/day initial dose group are prior to cross over to higher doses

According to the criteria in the Sponsor's statistical analysis plan, the study is deemed successful for each high dose group (300 mg/m<sup>2</sup>/day and > 300 mg/m<sup>2</sup>/day) – the rates are above 20% and the confidence intervals lie entirely above 5%. The corresponding response rates and exact 95% confidence intervals for the aggregate of the high initial dose groups are for PEC, 25/43 and (0.4213, 0.7299), for CA, 17/43 and (0.2498, 0.5559), and for PGA, 23/43 and (0.3765, 0.6882).

It was discussed at the Oncology Division Advisory Committee (ODAC) meeting that response rates by three months and by four months may be informative. Three month and four month response rates (PGA and CA) with the corresponding exact 95% confidence intervals are given in Tables 2a and 2b below. For the 6.5 mg/m<sup>2</sup>/day, the one PGA response occurred at 30 days and the three CA responses occurred at 16, 30 and 110 days.

**Table 2a. PGA 3-Month and 4-Month Response Rates and 95% Confidence Intervals**

Response Within	Initial Dose (in mg/m <sup>2</sup> /day)		Total
	300	> 300	
90 days	12/28 (0.2466, 0.6282)	5/15 (0.1182, 0.6161)	17/43 (0.2498, 0.5559)
120 days	13/28 (0.2751, 0.6613)	7/15 (0.2126, 0.7341)	20/43 (0.3118, 0.6234)

**Table 2b. CA 3-Month and 4-Month Response Rates and 95% Confidence Intervals**

Response Within	Initial Dose (in mg/m <sup>2</sup> /day)		Total
	300	> 300	
90 days	9/28 (0.1588, 0.5235)	4/15 (0.0779, 0.5510)	13/43 (0.1718, 0.4612)
120 days	10/28 (0.1864, 0.5594)	5/15 (0.1182, 0.6161)	15/43 (0.2101, 0.5093)

Eleven of the patients in the 6.5 mg/m<sup>2</sup>/day initial dose group crossed over to a higher dose. The response rates according to the sponsor's determinations are given in Table 3 below.

**Table 3. Response Rates Before and After Cross-Over**

Efficacy Endpoint	Dose (in mg/m <sup>2</sup> /day)		
	Before Cross-Over	After Cross-Over	
	6.5	300	> 300
PEC	2/11	3/5	5/6
CA	2/11	1/5	4/6
PGA	0/11	3/5	3/6

PGA, CA and PEC responses across all initial dose groups according to the sponsor's tabulations are given in Table 4 below.

**Table 4. PGA, CA and PEC Responses for Each Initial Dose Group**

Response	Initial Dose (in mg/m <sup>2</sup> /day)		
	6.5 <sup>1</sup>	300	> 300
<b>PGA Response</b>			
CCR	0	1	2
PR	1	13	7
SD	6	10	5
PD	8	4	1
<b>CA Response</b>			
CCR	1	1	3
PR	2	9	4
SD	11	13	6
PD	1	5	2
<b>PEC Response</b>			
CCR	1	2	4
PR	2	13	6
SD	5	7	3
PD	7	6	2

<sup>1</sup>Responses for the 6.5 mg/m<sup>2</sup>/day initial dose group are prior to cross over to higher doses

Eleven of the patients in the 6.5 mg/m<sup>2</sup>/day initial dose group crossed over to a higher dose. A summary of the PEC response results according to the sponsor's tabulations is given in Table 5 below. For these eleven "cross-over" patients baseline is re-defined to the time of cross-over.

**Table 5. PEC Responses Before and After Cross-Over**

PEC Response	Dose (in mg/m <sup>2</sup> /day)		
	Before Cross-Over	After Cross-Over	
		6.5	300
CCR	0	0	0
PR	2	3	5
SD	2	1	0
PD	7	1	1

The relapse rates for each initial dose group according to the sponsor's calculations are given in Table 6 below.

**Table 6. Relapse Rates for Each Initial Dose Group**

	Initial Dose mg/m <sup>2</sup> /day		
	6.5	300	> 300
Relapse rate	0/3	2/15	5/10

Secondary endpoints (1) to (4) are summarized in Table 7 below for each initial dose group based on the sponsor's calculations. All medians are in days and determined by the Kaplan-Meier method.

**Table 7. Summary of Secondary Endpoints for Study L1069-23**

Characteristics	Initial Assigned Dose (mg/m <sup>2</sup> /day)		
	6.5	300	> 300
Total Patients	15	28	15
Number of PGA Responding Patients	1	14	9
PGA Time to First Response Median	NR <sup>1</sup>	114	117
PGA Time to First Response Responding Patients Only Median	NA <sup>2</sup>	33	NA
PGA Time to Best Response Median	NR	114	185
PGA Time to Best Response Responding Patients Only Median	NA	44	NA
<b>Duration of Disease Control According to PGA</b>			
Number of Patients Relapsed	0	0	3
Median disease control duration	NA	NA	NR
<b>PGA Durability of Response</b>			
Median	NA	NA	NR
<b>PGA Disease Progression</b>			
Median	113	NR	NR

<b>PGA Disease Progression</b>			
<b>Regardless of Confirmation</b>			
Number of patients progressing	10	4	1
Median time to onset	95	NR	NR
<b>PGA Disease Progression</b>			
<b>Progressing Patients Only</b>			
Number of patients progressing	8	4	1
Median time to onset	68	43	199
<b>Number of CA</b>			
<b>Responding Patients</b>	3	10	7
<b>CA Time to First Response</b>			
Median	NR	NR	152
<b>CA Time to First Response</b>			
<b>Responding Patients Only</b>			
Median	NA	29	NA
<b>CA Time to Best Response</b>			
Median	174	NR	372
<b>CA Time to Best Response</b>			
<b>Responding Patients Only</b>			
Median	NA	29	NA
<b>Duration of Disease</b>			
<b>Control According to CA</b>			
Number of patients relapsed	0	2	3
Median disease control duration	NA	210	516
<b>CA Durability of Response</b>			
Median	NA	176	425
<b>CA Disease Progression</b>			
Median	NR	NR	NR
<b>CA Disease Progression</b>			
<b>Regardless of Confirmation</b>			
Number of patients progressing	4	8	4
Median time to onset	124	210	516
<b>Progressing Patients Only</b>			
Number of patients progressing	1	5	2
Median time to onset	29	85	15

<b>Number of PEC Responding Patients</b>	3	15	10
<b>PEC Time to First Response Median</b>	NR	57	92
<b>PEC Time to First Response Responding Patients Only Median</b>	NA	29	NA
<b>PEC Time to Best Response Median</b>	174	87	152
<b>PEC Time to Best Response Responding Patients Only Median</b>	NA	31	NA
<b>Duration of Disease Control According to PEC</b>			
Number of patients relapsed	0	2	5
Median disease control duration	NA	NR	516
<b>PEC Durability of Response Median</b>	NA	NR	453
<b>PEC Disease Progression</b>			
Number of patients progressing	7	6	2
Median time to onset	113	NR	NR
<b>PEC Disease Progression Progressing Patients Only</b>			
Median time to onset	57	43	15
<b>PEC Disease Progression Regardless of Confirmation</b>			
Number of patients progressing	11	9	4
Median time to onset	95	210	516

<sup>1</sup> NR = "Not reached"

<sup>2</sup> NA = "Not available"

For the quality of life assessments in tables 8-11, patients who complete at least 16 weeks on study are defined as "completers." Thirty-six of the 58 patients were completers. The remaining 22 patients are considered as "non-completers."

Table 8 summarizes the changes in Spitzer quality of life assessments according to the sponsor's calculations. The first five questions of the Spitzer questionnaire concern respectively, activity, daily living, health, support and outlook. The choices for each question are scored - 2, 1 and 0 – from highest quality to lowest quality. Question 6 asks "Please mark with an X the appropriate place within the bar to indicate your rating of your quality of life during the past 4 weeks." The left-hand side represents "lowest quality" and the right-hand side represents "highest quality." These marks were then converted to a score to millimeter measurements from the left margin of the bar. The possible values range from 0 mm (lowest quality) to 100 mm (highest quality). All values are according to the sponsor's calculations.

**Table 8. Summary of Spitzer Quality of Life Assessments**

Characteristics	Initial Assigned Dose (mg/m <sup>2</sup> /day)		
	6.5	300	> 300
<b>Mean and SE of Changes from Baseline in General Status Quality of Life Questionnaire for Completers - Spitzer Items 1-5</b>			
(Number of Patients in Parentheses)			
Day 1 Baseline	9.5, 0.3 (6)	8.4, 0.4 (17)	9.2, 0.5 (11)
Week 4	0.0, 0.5 (6)	0.3, 0.4 (16)	-0.7, 0.5 (11)
Week 8	-0.3, 0.6 (6)	0.4, 0.4 (17)	-1.0, 0.4 (10)
Week 12	-0.2, 0.5 (6)	0.6, 0.4 (16)	-0.6, 0.5 (10)
Week 16	0.2, 0.4 (6)	0.8, 0.5 (14)	-0.6, 0.5 (9)
Week 20	0.0, 0.8 (4)	0.3, 0.5 (7)	-1.0, 0.5 (8)
<b>Mean and SE of Changes from Baseline in General Status Quality of Life Questionnaire for Non-Completers - Spitzer Items 1-5</b>			
(Number of Patients in Parentheses)			
Day 1 Baseline	8.8, 0.4 (9)	8.6, 0.6 (9)	7.8, 1.0 (4)
Week 4	0.0, 0.2 (8)	0.3, 0.6 (4)	-0.3, 0.3 (3)
Week 8	-0.7, 0.6 (6)	0.3, 1.2 (3)	2.0, NA (1)
Week 12	-5.0, 1.0 (2)		
<b>Mean and SE of Changes from Baseline in Overall Quality of Life for Completers - Spitzer Item 6</b>			
(Number of Patients in Parentheses)			
Day 1 Baseline	94.2, 1.5 (6)	84.3, 3.2 (16)	76.4, 5.3 (10)
Week 4	-10.3, 8.2 (6)	-8.3, 3.6 (14)	-8.7, 7.6 (7)
Week 8	-26.0, 12.0 (4)	-11.8, 4.4 (14)	-8.6, 6.6 (9)

Week 12	-24.3, 11.0 (4)	-5.2, 4.1 (15)	-8.0, 5.5 (9)
Week 16	-13.2, 9.7 (5)	-5.7, 3.0 (13)	-15.3, 12.2 (6)
Week 20	-16.3, 10.6 (4)	-13.3, 4.2 (7)	-14.1, 8.1 (7)

**Mean and SE of Changes from Baseline in Overall Quality of Life for Non-Completers -Spitzer Item 6**  
(Number of Patients in Parentheses)

Day 1 Baseline	79.6, 5.7 (8)	77.4, 7.6 (9)	74.3, 24.2 (3)
Week 4	-13.7, 13.0 (7)	2.0, 8.7 (3)	-9.5, 8.5 (2)
Week 8	-28.2, 22.2 (5)	-8.7, 17.3 (3)	-5.0, NA (1)
Week 12	-5.0, 1.0 (1)		

Table 9 summarizes the changes in the composite scores for question 1 of the CTCL-Specific Patient questionnaire according to the sponsor's calculations.

Question 1: On a scale from 1 to 10 (1 being the very worst and 10 being the very best), how have you been feeling on the average during the past 4 weeks? (This question has five parts.) a. Overall, in general? b. Physically? c. Emotionally? d. Personal/Social Life? e. About your job, work?

**Table 9. CTCL-Specific Patient Questionnaire: Composite Score of Feelings Change from Baseline**

Characteristics	Initial Assigned Dose (mg/m <sup>2</sup> /day)		
	6.5	300	> 300
<b>Mean and SE of Changes from Baseline for Completers</b> (Number of Patients in Parentheses)			
Day 1 Baseline	34.3, 1.1 (6)	30.3, 1.7 (17)	30.5, 2.5 (11)
Week 4	-1.5, 0.9 (6)	0.1, 1.5 (16)	-1.4, 1.3 (11)
Week 8	-2.2, 1.4 (6)	-0.6, 1.8 (17)	-3.5, 1.8 (10)
Week 12	-4.0, 1.8 (6)	0.9, 2.1 (16)	-2.4, 2.4 (10)
Week 16	-4.8, 2.1 (6)	2.1, 2.2 (14)	-3.2, 2.5 (9)
Week 20	-3.5, 3.0 (4)	-1.9, 1.6 (7)	-4.9, 2.5 (8)
<b>Mean and SE of Changes from Baseline for Non-Completers</b> (Number of Patients in Parentheses)			
Day 1 Baseline	24.8, 2.3 (9)	30.6, 2.9 (9)	24.0, 6.1 (4)
Week 4	4.1, 3.3 (8)	-1.0, 1.7 (4)	-1.3, 7.3 (3)
Week 8	1.5, 1.8 (6)	-1.0, 4.4 (3)	9.0, NA (1)
Week 12	-1.5, 7.5 (2)		

Tables 10a and 10b summarize the sponsor's tabulations of the responses to question 8 of the CTCL-specific patient questionnaire.

Question 8: Taking into account the appearance and all symptoms related to your cutaneous t-cell lymphoma (mycoses), how has your cutaneous t-cell lymphoma (mycoses) changed as compared to before your participation in this study? (1= 'Much worse' to 5= 'Much improved')

**Table 10a. CTCL-Specific Patient Questionnaire: Change in CTCL (Question 8) Compared to Baseline for Completers**

Initial Dose (mg/m <sup>2</sup> /day)	Study Visit	Total No.Pts.	Much Worse	Moderately Worse	About the Same	Moderately Improved	Much Improved
6.5	Week 4	6	0	1	3	1	1
	Week 8	6	0	0	2	1	3
	Week 12	6	1	0	1	3	1
	Week 16	6	0	3	0	2	1
	Week 20	4	0	0	1	2	1
300	Week 4	18	0	1	3	6	8
	Week 8	18	0	0	3	7	8
	Week 12	17	0	0	2	9	6
	Week 16	16	0	0	0	7	9
	Week 20	9	0	0	1	5	3
>300	Week 4	10	0	0	3	4	3
	Week 8	10	0	1	3	4	2
	Week 12	10	1	0	1	5	3
	Week 16	9	1	0	1	3	4
	Week 20	8	0	0	3	2	3

**Table 10b. CTCL-Specific Patient Questionnaire: Change in CTCL (Question 8) Compared to Baseline for Non-Completers**

Initial Dose (mg/m <sup>2</sup> /day)	Study Visit	Total No.Pts.	Much Worse	Moderately Worse	About the Same	Moderately Improved	Much Improved
6.5	Week 4	8	0	1	1	5	1
	Week 8	5	0	1	1	3	0
	Week 12	2	0	0	1	0	1
300	Week 4	4	0	0	0	3	1
	Week 8	3	0	1	0	2	0
>300	Week 4	3	0	0	0	1	2
	Week 8	1	0	0	0	1	0

Tables 11a and 11b summarize the sponsor's tabulations of the responses to question 9 of the CTCL-specific patient questionnaire.

Question 9: What has been your overall level of satisfaction or dissatisfaction with the drug treatment in this study? (1= 'Very dissatisfied' to 5= 'Very satisfied')

**Table 11a. CTCL-Specific Patient Questionnaire: Satisfaction/Dissatisfaction with Study Drug Treatment (Question 9) Compared to Baseline for Completers**

Initial Dose (mg/m <sup>2</sup> /day)	Study Visit	Total No.Pts.	Very Dissatisfied	Moderately Dissatisfied	Neutral	Moderately Satisfied	Very Satisfied
6.5	Week 4	6	0	0	4	2	0
	Week 8	6	0	0	2	1	3
	Week 12	6	0	1	0	4	1
	Week 16	6	0	1	2	3	0
	Week 20	4	0	0	1	2	1
300	Week 4	18	0	0	2	8	8
	Week 8	18	1	0	4	5	8
	Week 12	17	0	0	3	11	3
	Week 16	16	0	0	0	10	6
	Week 20	9	0	0	0	7	2
>300	Week 4	11	0	0	3	4	4
	Week 8	10	1	2	1	4	2
	Week 12	10	1	0	3	4	2
	Week 16	9	1	1	2	3	2
	Week 20	8	0	1	2	2	3

**Table 11b. CTCL-Specific Patient Questionnaire: Satisfaction/Dissatisfaction with Study Drug Treatment (Question 9) Compared to Baseline for Non-Completers**

Initial Dose (mg/m <sup>2</sup> /day)	Study Visit	Total No.Pts.	Very Dissatisfied	Moderately Dissatisfied	Neutral	Moderately Satisfied	Very Satisfied
6.5	Week 4	8	0	0	2	3	3
	Week 8	5	0	1	2	1	1
	Week 12	2	0	0	0	1	1
300	Week 4	3	0	0	0	2	1
	Week 8	3	0	0	2	0	1
>300	Week 4	3	0	1	1	0	1
	Week 8	1	0	0	0	1	0

Table 12 summarizes some of the baseline demographics and disease characteristics.

**Table 12. Baseline Characteristics and Prior Therapies**

Characteristics	6.5	300	>300
<b>Recorded Index Lesion Area</b>			
0-25	4	6	5
> 25-50	6	4	4
> 50-75	3	8	3
> 75-100	2	10	2
<b>If prior topical therapy given, unresponsive (SD or PD) to at least one therapy</b>			
Yes	9	16	12
No	1	9	1
<b>Frequency of Prior EBT</b>			
Yes	10	9	8
No	5	19	7
<b>If prior irradiation therapy given, unresponsive (SD or PD) to at least one therapy</b>			
Yes	13	8	8
No	2	19	5
<b>Number of Prior Anti CTCL Irradiation Therapies</b>			
0	0	1	1
1	4	18	5
2	10	7	9
3	1	2	0
<b>Stage of CTCL</b>			
I-A	6	4	7
I-B	7	21	6
II-A	1	3	2
II-B	1	0	0

**Reviewer's Comments:**

[1] The changes from baseline in overall quality of life are in opposite directions for question 6 of the Spitzer questionnaire and questions 8 and 9 of the CTCL-specific questionnaire (see tables 8, 10 and 11).

[2] The relapse rates and their differences should be considered when making conclusions about the proper dosage.

[3] Since this is a single arm study, the definition of "completers" and "non-completers" is quite arbitrary and subjective.

**Study L1069-24**

An initial dose is deemed successful by the sponsor in the protocol if there is a response rate above 20% and the corresponding confidence interval lies entirely above 5%. Table 13 below lists the sponsor determined response rates and this reviewer's calculations of exact 95% confidence intervals based on these rates.

**Table 13. Response Rates and 95% Confidence Intervals**

Efficacy Endpoint	Initial Dose (in mg/m <sup>2</sup> /day)		Total
	300	> 300	
PEC	25/56 (0.3134, 0.5853)	21/38 (0.3830, 0.7138)	46/94 (0.3848, 0.5946)
CA	15/56 (0.1583, 0.4030)	18/38 (0.3098, 0.6418)	33/94 (0.2554, 0.4564)
PGA	27/56 (0.3466, 0.6197)	20/38 (0.3582, 0.6902)	47/94 (0.3950, 0.6050)

According to the criteria in the Sponsor's statistical analysis plan, the study is deemed successful for each dose group (300 mg/m<sup>2</sup>/day and > 300 mg/m<sup>2</sup>/day) – the rates are above 20% and the confidence intervals lie entirely above 5%.

It was discussed at the ODAC meeting that response rates by three months and by four months may be informative. Three month and four month response rates (PGA and CA) with the corresponding exact 95% confidence intervals are given in Tables 14a and 14b below.

**Table 14a. PGA 3-Month and 4-Month Response Rates and 95% Confidence Intervals**

Response Within	Initial Dose (in mg/m <sup>2</sup> /day)		Total
	300	> 300	
90 days	23/56 (0.2810, 0.5502)	15/38 (0.2404, 0.5662)	38/94 (0.3042, 0.5105)
120 days	26/56 (0.3299, 0.6026)	17/38 (0.2862, 0.6170)	43/94 (0.3542, 0.5634)

**Table 14b. CA 3-Month and 4-Month Response Rates and 95% Confidence Intervals**

Response Within	Initial Dose (in mg/m <sup>2</sup> /day)		Total
	300	> 300	
90 days	13/56 (0.1298, 0.3642)	14/38 (0.2181, 0.5400)	27/94 (0.1986, 0.3898)
120 days	14/56 (0.1439, 0.3837)	16/38 (0.2631, 0.5918)	30/94 (0.2267, 0.4233)

PGA, CA and PEC responses across each initial dose groups according to the sponsor's calculations are given in Table 15 below.

**Table 15. PGA, CA and PEC Responses for Each Initial Dose Group**

Response	Initial Dose (mg/m <sup>2</sup> /day)	
	300	> 300
<b>PGA Response</b>		
CCR	0	2
PR	27	18
SD	19	14
PD	10	4
<b>CA Response</b>		
CCR	1	5
PR	14	13
SD	21	9
PD	20	11
<b>PEC Response</b>		
CCR	1	5
PR	24	16
SD	9	5
PD	22	12

Endpoints (1) to (4) are summarized in table 16 below for each initial dose group based on the sponsor's calculations. All medians are in days and determined by the Kaplan-Meier method.

**Table 16. Summary of Secondary Endpoints for Study L1069-24**

Characteristics	Initial Assigned Dose (mg/m <sup>2</sup> /day)	
	300	> 300
<b>Total Patients</b>	56	38
<b>Number of PGA Responding Patients</b>	27	20
<b>PGA Time to First Response Median</b>	100	113
<b>PGA Time to Best Response Median</b>	100	121
<b>Duration of Disease Control According to PGA Number of Patients Relapsed</b>	5	5
<b>Median</b>	NR <sup>1</sup>	385
<b>PGA Durability of Response Median</b>	NR	306
<b>PGA Disease Progression Number of patients progressing</b>	10	4
<b>Median</b>	NR	NR
<b>PGA Disease Progression Regardless of Confirmation Number of patients progressing</b>	18	11
<b>Median time to onset</b>	NR	413
<b>Number of CA Responding Patients</b>	15	18
<b>CA Time to First Response Median</b>	NR	106
<b>CA Time to Best Response Median</b>	NR	140

<b>Duration of Disease</b>		
<b>Control According to CA</b>		
Number of patients relapsed	5	7
Median	NR	456
<b>CA Durability of Response</b>		
Median	NR	372
<b>CA Disease Progression</b>		
Number of patients progressing	20	11
Median	NR	NR
<b>CA Disease Progression</b>		
<b>Regardless of Confirmation</b>		
Number of patients progressing	26	18
Median time to onset	147	281
<b>Number of PEC</b>		
Responding Patients	25	21
<b>PEC Time to First Response</b>		
Median	180	59
<b>PEC Time to Best Response</b>		
Median	180	106
<b>Duration of Disease</b>		
<b>Control According to PEC</b>		
Number of patients relapsed	9	8
Median	299	385
<b>PEC Durability of Response</b>		
Median	159	306
<b>PEC Disease Progression</b>		
Number of patients progressing	22	12
Median time to onset	NR	NR
<b>PEC Disease Progression</b>		
<b>Regardless of Confirmation</b>		
Number of patients progressing	31	22
Median time to onset	97	206

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<sup>†</sup> NR = "Not reached"

For the quality of life assessments in tables 17-20, patients who complete at least 16 weeks on study are defined as "completers." Sixty-three of the 94 patients were completers. The remaining 31 patients are considered as "non-completers."

Table 17 summarizes the changes in Spitzer quality of life assessments according to the sponsor's calculations.

**Table 17. Summary of Spitzer Quality of Life Assessments.**

Characteristics	Initial Assigned Dose (mg/m <sup>2</sup> /day)	
	300	> 300
<b>Mean and SE of Changes from Baseline in General Status Quality of Life Questionnaire for Completers - Spitzer Items 1-5</b>		
(Number of Patients in Parentheses)		
Day 1 Baseline	8.0, 0.3 (35)	8.2, 0.4 (26)
Week 4	0.3, 0.2 (34)	-0.1, 0.4 (25)
Week 8	0.5, 0.3 (35)	0.1, 0.3 (25)
Week 12	-0.1, 0.3 (32)	-0.2, 0.4 (24)
Week 16	0.2, 0.3 (28)	0.0, 0.3 (22)
Week 20	0.0, 0.3 (21)	0.7, 0.4 (18)
<b>Mean and SE of Changes from Baseline in General Status Quality of Life Questionnaire for Non-Completers - Spitzer Items 1-5</b>		
(Number of Patients in Parentheses)		
Day 1 Baseline	7.3, 0.4 (18)	5.6, 0.6 (10)
Week 4	0.0, 0.4 (15)	0.2, 0.9 (6)
Week 8	0.6, 0.5 (8)	-0.3, 1.2 (3)
Week 12	0.0, 0.7 (4)	0.0, 4.0 (2)
<b>Mean and SE of Changes from Baseline in Overall Quality of Life for Completers - Spitzer Item 6</b>		
(Number of Patients in Parentheses)		
Day 1 Baseline	78.9, 3.6 (33)	75.9, 5.0 (26)
Week 4	-3.7, 3.5 (31)	-1.5, 3.3 (21)
Week 8	-5.4, 4.2 (31)	-6.4, 5.3 (23)
Week 12	-7.6, 3.2 (28)	-1.9, 5.6 (24)
Week 16	-10.7, 5.0 (26)	-1.4, 4.9 (22)
Week 20	-12.7, 5.0 (20)	4.6, 4.7 (19)

**Mean and SE of Changes from  
Baseline in Overall Quality of  
Life for Non-Completers - Spitzer Item 6**  
(Number of Patients in Parentheses)

Day 1 Baseline	69.1, 5.8 (18)	51.4, 8.3 (10)
Week 4	-3.0, 9.5 (15)	-12.2, 11.6 (6)
Week 8	7.5, 8.5 (6)	-37.0, 14.6 (3)
Week 12	-30.5, 28.8 (4)	-2.0, NA (1) -

Table 18 summarizes the changes in the composite scores for question 1 of the CTCL-Specific Patient questionnaire according to the sponsor's calculations.

**Table 18. CTCL-Specific Patient Questionnaire: Composite Score of Feelings  
Change from Baseline**

Characteristics	Initial Assigned Dose (mg/m <sup>2</sup> /day)	
	300	> 300
<b>Mean and SE of Changes from Baseline in Composite Score of Feelings for Completers – CTCL-Specific Questionnaire</b> (Number of Patients in Parentheses)		
Day 1 Baseline	28.1, 1.3 (35)	27.9, 1.6 (26)
Week 4	1.5, 1.1 (34)	0.5, 1.2 (25)
Week 8	0.8, 0.9 (35)	-0.7, 1.6 (25)
Week 12	0.4, 1.2 (32)	-1.5, 1.4 (24)
Week 16	-0.8, 1.5 (28)	0.7, 1.4 (23)
Week 20	-1.0, 1.3 (21)	1.7, 1.7 (19)
<b>Mean and SE of Changes from Baseline in Composite Score of Feelings for Non-Completers – CTCL-Specific Questionnaire</b> (Number of Patients in Parentheses)		
Day 1 Baseline	22.6, 2.1 (18)	19.8, 1.5 (10)
Week 4	2.4, 2.3 (15)	-0.4, 3.3 (7)
Week 8	5.6, 2.4 (8)	-3.0, 2.0 (3)
Week 12	-1.0, 5.0 (4)	10.0, NA (1)

Tables 19a and 19b summarize the sponsor's tabulations of the responses to question 8 of the CTCL-specific patient questionnaire.

**Table 19a. CTCL-Specific Patient Questionnaire: Change in CTCL (Question 8) Compared to Baseline for Completers**

Initial Dose (mg/m <sup>2</sup> /day)	Study Visit	Total No.Pts.	Much Worse	Moderately Worse	About the Same	Moderately Improved	Much Improved
300	Week 4	35	1	2	6	16	10
	Week 8	35	0	2	3	21	9
	Week 12	33	0	3	6	14	10
	Week 16	29	1	1	4	12	11
	Week 20	21	1	2	2	9	7
>300	Week 4	24	0	1	5	11	7
	Week 8	26	1	0	5	11	9
	Week 12	24	0	1	2	12	9
	Week 16	22	0	1	3	9	9
	Week 20	19	0	0	2	10	7

**Table 19b. CTCL-Specific Patient Questionnaire: Change in CTCL (Question 8) Compared to Baseline for Non-Completers**

Initial Dose (mg/m <sup>2</sup> /day)	Study Visit	Total No.Pts.	Much Worse	Moderately Worse	About the Same	Moderately Improved	Much Improved
300	Week 4	15	1	1	5	5	3
	Week 8	8	0	1	4	1	2
	Week 12	4	1	1	2	0	0
>300	Week 4	7	0	0	0	5	2
	Week 8	3	0	1	0	0	2
	Week 12	1	0	0	0	1	0

Tables 20a and 20b summarize the sponsor's tabulations of the responses to question 9 of the CTCL-specific patient questionnaire.

**Table 20a. CTCL-Specific Patient Questionnaire: Satisfaction/Dissatisfaction with Study Drug Treatment (Question 9) Compared to Baseline for Completers**

Initial Dose (mg/m <sup>2</sup> /day)	Study Visit	Total No.Pts.	Very Dissatisfied	Moderately Dissatisfied	Neutral	Moderately Satisfied	Very Satisfied
300	Week 4	34	1	2	5	12	14
	Week 8	34	0	1	4	20	9
	Week 12	33	0	1	5	17	10
	Week 16	29	1	2	5	10	11
	Week 20	21	0	2	2	9	8

>300	Week 4	24	0	0	7	9	8
	Week 8	26	1	2	4	12	7
	Week 12	25	0	1	2	14	8
	Week 16	22	0	0	2	12	8
	Week 20	19	0	1	2	7	9

**Table 20b. CTCL-Specific Patient Questionnaire: Satisfaction/Dissatisfaction with Study Drug Treatment (Question 9) Compared to Baseline for Non-Completers**

Initial Dose (mg/m <sup>2</sup> /day)	Study Visit	Total No.Pts.	Very Dissatisfied	Moderately Dissatisfied	Neutral	Moderately Satisfied	Very Satisfied
300	Week 4	15	1	1	5	4	4
	Week 8	9	0	3	3	1	2
	Week 12	4	0	3	1	0	0
>300	Week 4	7	0	0	3	3	1
	Week 8	3	0	1	0	1	1
	Week 12	1	0	0	0	1	0

Table 21 below summarizes the number of prior anti-CTCL therapies and the number of prior anti-CTCL systemic agents/therapies according to the sponsor's tabulations.

**Table 21. Prior Therapies and Prior Responses**

Characteristics	Initial Dose	
	300	> 300
<b>Number of Prior Anti CTCL Therapies (Systemic, Topical/ Local and Irradiation Combined):</b>		
0	0	0
1	2	0
2	5	1
3	10	6
4	12	5
5	9	6
6	10	7
7	3	6
8	2	5
9	2	1
10	0	1
11	1	0

**Number of Prior Anti-CTCL  
Systemic Agents/Therapies**

0	2	0
1	18	4
2	12	10
3	15	9
4	5	5
5	3	7
6	1	3

**At least one prior response  
to systemic therapy**

Yes	20	25
No	34	13

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**Reviewer's Comments:**

[1] The changes from baseline in overall quality of life are in opposite directions for question 6 of the Spitzer questionnaire and questions 8 and 9 of the CTCL-specific questionnaire (see tables 17, 19 and 20).

[2] There is a much greater difference in the number of PGA responses and CA responses in the 300 mg/m<sup>2</sup>/day initial dose group (27 vs. 15) than in the > 300 mg/m<sup>2</sup>/day initial dose group (20 vs. 18).

[3] Since this is a single arm study, the definition of "completers" and "non-completers" is quite arbitrary and subjective.

**SUMMARY AND CONCLUSIONS**

Summary: These are single armed studies, which use historical controls. In each study after protocol amendments all new patients were given orally an initial dose of 300 mg/m<sup>2</sup>/day of Targretin. The sponsor deemed both studies successful for the 300 mg/m<sup>2</sup>/day and > 300 mg/m<sup>2</sup>/day initial dose groups; the response rates (whether PGA, CA or PEC) were above 20% with confidence intervals which lied entirely above 5%. In each study different quality of life instruments had changes from baseline in opposite directions. In the L1069-24 study there is a much larger difference in PGA responses and CA responses in the 300 mg/m<sup>2</sup>/day initial dose group (27 vs. 15) than in the > 300 mg/m<sup>2</sup>/day initial dose group (20 vs. 18). Based on a Kappa test for the combined studies, the agreement between the two response instruments, PGA and CA, is acceptable (kappa =0.517 with a 95% C.I. of (0.378, 0.656)).

The FDA informed the sponsor of the benefits of comparative randomized trials. The following FDA response is from the minutes of an August 7, 1996 meeting with the sponsor: *"While indicating that single-arm studies in refractory patients might support an NDA (depending on the results obtained) the FDA emphasized the advantages of*

comparative randomized trials and suggested that the sponsor consider conducting randomized trials in early disease comparing Targretin with the current accepted therapies. It was emphasized that response would have to [be, sic] meticulously documented. The sponsor may propose that a 20% response rate is indicative of efficacy but the FDA cannot guarantee that this will be adequate until the data is reviewed. ... The proposed use of historical control response rate of no more than 5% in two of the studies was discussed. The sponsor restated that this indicated that no more than [sic] 5% of the patients will have a spontaneous response. Dr. DeLap noted the advantages of comparative trials and emphasized to the sponsor that it is always risky to conduct uncontrolled trials." The FDA re-emphasized the advantages of comparative randomized trials in a October 7, 1996 letter to the sponsor.

**Conclusions:** In each study the response rates (whether PGA, CA or PEC) for the 300 mg/m<sup>2</sup>/day and > 300 mg/m<sup>2</sup>/day initial dose groups were above 20% with confidence intervals which lied above 5%. The results of one-armed studies are exploratory. Conclusions should be based on clinical judgement.

/S/  
Mark D Rothmann, Ph.D.  
Mathematical Statistician

Concur: Dr. Chen

Dr. Chi

*lhc* /S/

12/16/99

cc:

Archival NDA #21-055  
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HFD-150/Dr. Johnson  
HFD-150/Dr. Odujinrin  
HFD-710/Dr. Chi  
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This review consists of twenty-three pages of text.