Two vehicle responders started protease inhibitors greater than 2 months prior to entry on study. Only two vehicle responders had a change in protease inhibitor therapy within a two month period prior to entry on-study. A determination of a protease inhibitor effect was inconclusive in one patient because the required follow up CD4-counts were not available; this patient started protease inhibitor therapy greater than two months prior to on-study.

VEHICLE RESPONDERS: PROTEASE INHIBITOR REVIEW

PID	TIMING OF PROTEASE INHIBITOR (PI)	CD4-LYMPHOCYTE COUNT @ BASELINE /UL	CD4-LYMPHOCYTE COUNT @ TIME OF RESPONSE CONFIRMATION /UL	TRIGLYCERIDES @ BASELINE MG/DL	TRIGLYCERIDES @ TIME OF RESPONSE CONFIRMATION MG/DL	COMMENTS
	Saquinavir started 6 mos. prior to on-study	12	Ligand: not done	206	not done	PI effect: INCONCLUSIVE
	Nelfinavir started 1 wk before on-study	66	49	311	516	No PI effect Base of tongue KS growing @ 4 wks
	Indinavir started 7 mos. prior to on-study	184	135	235	230	No effect

GENERAL RESPONSE EVALUATION

Only three index lesions were required for entry on study. Fifty-three percent of panretin responders had greater than 3 index lesions (median 4 lesions; range ; 76% of the panretin nonresponders had greater than 3 index lesions (median 5 lesions; range . Thirty-three percent of the vehicle responders had greater than 3 index lesions (median 3; range ; 63% of the vehicle nonresponders had greater than 3 index lesions (median 4; range .

The pattern of response to panretin and vehicle were comparable (see table below). For panretin, 33% (5/15) of the responders had reduction in the height of the index lesion alone as the criteria for response; for the vehicle responders, 33% (1/3) of

the patients met this criteria. For panretin, 67% of the responders had index lesion area reduction alone or in combination with height reduction as the criteria for response; for the vehicle responders, 67% of the responders met this criteria. In contrast to Study -31, the proportions for response by height reduction alone or by area reduction were reversed in Study -503, i.e., area reduction of lesions was the predominant mode of response[66]. Also, raised lesions were not a requirement for entry on study. Fifteen of 36 patients (42%) on panretin and 15 of 46 patients (32%) on vehicle had no raised lesions at baseline. The reduction of area--a more rigorous response criteria--was the only criteria available to score a response in these patients.

ACTG RESPONSE CRITERIA	PANRETIN 15 RESPONDERS	VEHICLE RESPONDERS
Plaque to macule	5 (33%)	1(33.3%)
Area	9 (60%)	1 (33.3%)
Area + plaque to macule	1 (7%)	1 (33.3%)

In a given responder, panretin and the vehicle gel were not as consistent in the flattening of lesions as in Study -31. The following table demonstrates the variability in the proportions of index lesion which became flat in responders. Between 0% to 100% of raised lesions--selected as index lesions--became flat in a panretin responder. Between 0% and 100% of raised lesions--selected as index lesions--became flat in a vehicle responder. The small number of raised lesions selected may have contributed to the variability.

RESPONDERS: VARIABLE FLATTENING OF RAISED LESIONS

LESION I.D. LETTER	PANRETIN # FLATTENED/# RAISED @ BASELINE (%)	VEHICLE # FLATTENED/# RAISED @ BASELINE (%)
A	2/5 (40%)	0/1 (0%)
B	5/6 (83%)	2/2 (100%)
C	7/7 (100%)	2/2 (100%)
D	3/7 (43%)	1/1 (100%)
E	0/2 (0%)	1/1 (100%)

[66] A high proportion of responses by criteria other than flattening of KS lesions has been reported for systemic therapy. In the DaunoXome labeling, twenty of 33 (61%) ABV responders responded to therapy by shrinkage of lesions and/or reduction in the number of lesions. Eleven of 27 (41%) DaunoXome responders responded to therapy by criteria other than flattening of lesions.

LESION I.D. LETTER	PANRETIN # FLATTENED/# RAISED @ BASELINE (%)	VEHICLE # FLATTENED/# RAISED @ BASELINE (%)
F	1/1 (100%)	

However, the nonresponders did fare similar to the nonresponders in Study -~~31~~. Fifteen panretin nonresponders did not have one index lesions become flat. Two panretin nonresponders had at least 1 raised index lesion become flat. One panretin nonresponder had raised lesions become flat but an increase in area of the lesions intervened. Three panretin nonresponders had marginal reductions in area. Thirty vehicle nonresponders did not have one index lesions become flat. Two vehicle nonresponders had at least 1 raised index lesion become flat. One vehicle nonresponder had raised lesions become flat but an increase in area of the lesions intervened. Eight panretin nonresponders had marginal reductions in area.

Two panretin patients had face lesions treated--three (cheek x 3) and four (cheek, neck, nose, suborbital) lesions respectively. These two panretin patients were not scored as overall responders. Only one lesion out of the seven facial lesions was a partial response by area reduction.

Five vehicle patients had face lesions treated--one (forehead), one (nose), one (neck), two (forehead, eyelid), and three (cheek, nostril, temple) lesions, respectively. These five patients were not scored as overall responders. Only one lesion out of the eight facial lesions was a partial response by height reduction.

FDA REVIEW OF THE PANRETIN & VEHICLE RESPONDERS

The FDA reviewed all the panretin and the placebo responders in Study -503. The nonresponders of the placebo arm have not been reviewed.

The primary efficacy endpoint was KS cutaneous tumor response during the 12 week initial blinded phase of the study. The review concentrated on this time period.

A. Per Protocol Review of Index Lesions

The FDA reviewed Listing 25 (Response Chronology–Initial Blinded

Treatment) and ACCESS Database (response data tabulation on index lesions [height, area]).

FDA disagreed with two Ligand panretin responders. One patient was disqualified as a responder and one patient was disqualified as a complete responder (but remained a partial responder). The table below comments on these patients. The FDA did not disagree with per protocol evaluations of the vehicle responders.

PID	COMMENTS
	2 more raised lesions added @ 2 wks according to CRF 2 of original 3 raised lesions became flat; 2 of the late added lesions became flat but not confirmed Were 3 lesions or 5 lesions (or more) assessed? Ligand states that "the number of lesions raised at baseline (all three)" and "The photos for all Lesions A,B,C,D, and E were label as Week 0 (baseline)" (10/15/98). Only 3 index lesions @ baseline on CRF;3 measurable lesions on Listing 25; CRF: 2 more lesions added @ 2 wks; Ligand: acknowledges that lesions D & E are correctly labeled as week 0; Ligand: response based on 3 lesions not 5 lesions.
	Ligand states that only lesions A thru G were treated and no photos for a Lesion H were available (10/15/98). Photos for H & I (12 wks elapsed) submitted electronically & in hard copy. CRF: lesions H & I marked on figure and recorded but crossed out No activity for lesions H & I--> overall response cannot be CR.

B. Cosmetically Beneficial Panretin & Vehicle Responses Based on Photographs

The FDA determination of cosmetically beneficial tumor responses in panretin patients reported by Ligan as responders by the modified ACTG criteria was based primarily on the photographs. This assessment included beneficial tumor responses in the blinded phase of the study in patients initially randomized to either the panretin or the vehicle arms of the study. In assessing the photographs for beneficial response, the FDA looked for a 50% improvement in appearance from baseline, considering the KS lesion and dermal toxicity at the lesion site. 50% of the index lesions were required to improve in appearance. For the blinded phase analysis (12 wks) if the response started by 12 weeks, the response confirmation could occur after 12 weeks. The improvement was to be maintained 3-4 weeks. The FDA assessment also included comments on other

aspects of the tumor response evaluation. Specifically, the FDA reviewed: 1. Listing 25: Response Chronology–Initial Blinded Treatment; 2. ACCESS Database: a. concurrent medications, especially protease inhibitors, b. CD4-lymphocyte counts @ baseline and @ response confirmation, c. triglycerides @ baseline and @ response confirmation, d. Patient's Subjective Assessment (treated index and non-index lesions) @ response confirmation, e. Physician's Subjective Assessment (treated index and non-index lesions)@ response confirmation, f. response data tabulation on index lesions (height, area); 3. photographs (index lesions only), especially a comparison of baseline and @ response confirmation; and 4. Case Report Forms of responders.

The FDA had comments about most of the panretin responders. These included: 1. poor photographic evidence of response (5 pts.); 2. additional lesions added and/or treated (5 pts.); 3. incomplete CD4-count follow up (4 pts.); 4. questionable protease inhibitor effect on KS response (2 pts.); 5. missing follow up photos (4 pts.); 6. no baseline photos (2 pts.); 7. new lesions (2 pts.); and 8. unable to find lesion in photo (1 pt.).

Among the 15 panretin responders reported by Ligand, the FDA believed that 7 patients had beneficial responses. One of these panretin responders was one of the three patients with symptoms related to mucocutanous KS at baseline; the symptom of an itchy KS lesion remissed.

FDA REVIEW OF THE PANRETIN RESPONDERS

PID	COMMENTS PI EFFECT CHARACTER OF LESIONS & REPORTED RESPONSE[67] FDA REVIEW	BENEFICIAL RESPONSE
	No PI effect	No
	4 lesions, 2 raised: 2 became flat	
	no follow up photos—protocol violation	
	PI effect: INCONCLUSIVE No CD4s done @ 12 wk	No
	3 lesions @ baseline, 2 raised: 2 lesions became flat 2 more flat lesions added @ 2 wks	
	Only 3 index lesions @ baseline on CRF;3 measurable lesions on Listing 25; 2 more lesions added @ 2 wks; ACCESS database documents 2 more lesions added @ 2wks; lesions D & E submitted as photos	
	All the photos started after 2 wks of therapy, i.e., no baseline photos—protocol violation	
	Photos do not show benefit	
	MD saw complete clearing, pt saw almost complete clearing and withdrew from study @ 12 wks; Ligand: no KS biopsies	
	No biochemistry or CD4 done @ wk 12—protocol violation	

[67] Lesion (plaque or nodule) reduction in height = flat; lesion area reduction = area

PID	COMMENTS PI EFFECT CHARACTER OF LESIONS & REPORTED RESPONSE[67] FDA REVIEW	BENEFICIAL RESPONSE
	PI effect: INCONCLUSIVE No other CD4s done	Yes
	3 lesions @ baseline, 2 raised: 2 lesions became flat 1 more flat lesion added @ 2 wks	Were 3 lesions or 4 lesions (or more) assessed? The physician saw almost clearing of lesions and the patients saw a marked response.
	Only 3 index lesions @ baseline on CRF;3 measurable lesions on Listing 25; 1 more lesion added @ 2 wks; ACCESS database documents lesion D; lesion D photo submitted	
	No biochemistry or CD4 done @ wk 12—protocol violation	
	pt withdrew from trial after 12 wks: MD saw almost clearing & pt saw a marked response	
	lesion A & C are responses; lesion D is marginal—lesion? @ left upper corner unchanged, satellite lesions @ upper border of lesion resolved	
	PI effect: INCONCLUSIVE No other CD4s done	No
	3 lesions @ baseline, 3 raised: 2 of original 3 raised lesions became flat; 2 of the late added lesions became flat but not confirmed 2 more raised lesions added @ 2 wks according to CRF	Were 3 lesions or 5 lesions (or more) assessed? Ligand states that "the number of lesions raised at baseline (all three)" and "The photos for all Lesions A,B,C,D, and E were label as Week 0 (baseline)" (10/15/98).

PID	COMMENTS PI EFFECT CHARACTER OF LESIONS & REPORTED RESPONSE[67] FDA REVIEW	BENEFICIAL RESPONSE
	Only 3 index lesions @ baseline on CRF;3 measurable lesions on Listing 25; CRF: 2 more lesions added @ 2 wks; Ligand: acknowledges that lesions D & E are correctly labeled as week 0; Ligand: response based on 3 lesions not 5 lesions.	Both the physician and the patient saw a slight response
	On Oncology History CRF:last thalidomide 3 wks prior to on-study & PI appears to have evaluated pt for response—protocol violation but PI denies thalidomide was for KS	
	Efficacy data in ACCESS database includes up to 8 wks; efficacy data from 16 wks crossed-out on CRFs & not reported in ACCESS; Ligand: data should have been reported in Study –504	
	PD of untreated lesions: reason for withdrawal; appears that treated lesions also progressed if information crossed-out @ 16 wks is correct (but on the wrong form). Why wouldn't the patient conveniently apply the gel to untreated lesions?	
	no follow up photos—protocol violation	
	photos for lesions D & E are labeled as wk 0 and dated 11/11/96. Ligand states that this is correct. The Listing and CRF cite only 3 lesions @ baseline; the 2 additional lesions have surrounding erythema; they were suppose to have been added @ wk 2	
	No PI new lesions appearing	No

PID	COMMENTS PI EFFECT CHARACTER OF LESIONS & REPORTED RESPONSE[67] FDA REVIEW	BENEFICIAL RESPONSE
	3 lesions, 1 raised: area -	Were 3 lesions or 4 lesions (or more) assessed? Both the physician and patient saw a marked response.
	lesion D 12 wk photo; no lesion D data in ACCESS; hard copy of photos: No Subsequent Photos Were Taken	
	3 new KS lesions on chest @ wk 8	
	New KS lesion on eyelid & leg @ 12 wk; eyelid lesion Rx'ed with intralesional interferon	
	pt has history of recurrent genital warts; 2 of index lesions on penis	
	pt continued on panretin	
	Lesions B & C responses	
	No PI effect	Yes
	6 raised lesions: area [criteria for response]; 2 became flat	Symptoms of patches of KS on hard palate, eye, foot, back, and arms @ baseline No change in Sxs: mild and continuous thru-out study
	New KS lesions on right leg @ wk 8	
	Radiotherapy to foot & leg lesions @ or about wk 12	
	pt continued on panretin	
	no photos for lesion F; Ligand does not have photos for lesion F—protocol violation	
	photos show benefit	
	No PI effect	Yes

PID	COMMENTS PI EFFECT CHARACTER OF LESIONS & REPORTED RESPONSE[67] FDA REVIEW	BENEFICIAL RESPONSE
	7 lesions, all flat @ baseline: area; CR -	Were 7 lesions or 9 lesions (or more) assessed? Both the physician and patient saw complete clearing of treated lesions.
	photos provide adequate evidence of response for lesions A thru G? No activity for lesions H & I--> overall response cannot be CR.	
	Ligand states that only lesions A thru G were treated and no photos for a Lesion H were available (10/15/98). Photos for H & I (12 wks elapsed) submitted electronically & in hard copy. CRF: lesions H & I marked on figure and recorded but crossed out	
	Ligand: no indication that a Lesion H was ever treated for Pt. 438 in either study -503 or study -504 (10/15/98). CRF (hand-written):Photos taken for roll-over Study 504, Lesions H and I. Lesions H & I have surrounding erythema-->Rx with panretin?	
	pt continues on panretin	
	No PI effect	No
	4 flat lesions @ baseline: area	
	photos do not show benefit for lesions A,B,D	
	lesion C may be a response	
	pt continues on panretin	
	No PI effect	Yes

PID	COMMENTS PI EFFECT CHARACTER OF LESIONS & REPORTED RESPONSE[67] FDA REVIEW	BENEFICIAL RESPONSE
	3 flat lesions @ baseline: area -	
	all 3 lesions photographically show response	
	pt continues on panretin	
	No PI effect	Yes
	4 lesions, 2 raised: area	Lesion A pruritus @ baseline (mild & intermittent) Sx gone by wk 8
	Photographic evidence of responses; decreases in area	
	pt continue on panretin	
	No PI effect	No
	4 lesions, 1 raised: area; 1 lesion became flat	
	Photos do not show benefit for lesions or activity	
	*wk 2 CRF declares all lesions as PR??	
	Pt continues on panretin	
	PI effect??	Yes
	4 flat lesions @ baseline: area	
	Photographic evidence of response matches data in ACCESS for lesions A,B,C; non-response of lesion D (by ACCESS data) matches photos	

PID	COMMENTS PI EFFECT CHARACTER OF LESIONS & REPORTED RESPONSE[47] FDA REVIEW	BENEFICIAL RESPONSE
	pt continues on panretin	
	PI effect?	Yes
	5 flat lesions @ baseline: area	
	responses in lesions A, C, & D	
	Identification of lesion E difficult	
	pt continues on panretin	
	No PI effect	No
	3 flat lesions @ baseline: area	
	The follow up photos (@ 12.9 wks) are at a time when progressive disease was declared. Ligand has no photos for 4 & 8 wks.	
	Measurements in photos do not match measurements in ACCESS: no 50% reduction in area	
	A: 1/22/97, 6x15 4/22/97, 6x17 B:1/22/97,5x9 4/22/97,6x6 C:1/22/97,6x9 4/22/97,5x7	
	pt continues on panretin	

PID	COMMENTS PI EFFECT CHARACTER OF LESIONS & REPORTED RESPONSE[67] FDA REVIEW	BENEFICIAL RESPONSE
	PI effect: INCONCLUSIVE No CD4-count follow up	No
	3 raised lesions: all became flat	L & R arm pruritus @ baseline (mild & intermittent) By 12 wk: substituted sxs for dry/peeling skin (moderate-severe & intermittent-continuous)
	*wk 2 CRF declares all lesions as PR??	
	Measurements in photos: good match with measurements in ACCESS (area reduction was not criteria for response	
	A:1/20/97,18x21 4/23/97,13x14 (response) B:1/20/97,43x24 4/23/97,40x29 C:1/20/97,24x12 4/23/97,22x10	
	Photos do not show benefit for lesions or activity	
	patient did not continue on panretin	

The FDA had comments about the vehicle responders. These included: 1. poor photographic evidence of response (2 pts.); 2. incomplete CD4-count follow up (1 pt.); and 3. missing follow up

photos (1 pt).

Among the 3 vehicle responders reported by Ligand, the FDA believed that 1 patient had a beneficial response.

FDA REVIEW OF THE VEHICLE RESPONDERS

PID	COMMENTS PI EFFECT CHARACTER OF LESIONS & REPORTED RESPONSE FDA REVIEW	FDA EVALUATION OF RESPONSE
	PI effect: INCONCLUSIVE CD4-counts not repeated	Yes
	3 flat lesion @ baseline: area	
	wk 4: enlarging of non-indicator lesions	
	Stinging and warmth of lesions B & C	
	Discontinued from study because of PD of untreated lesions	
	wk 8:lesions B & C not measured; photos demonstrated reduction in size	
	pt continued on follow up protocol	
	No PI effect	No
	5 raised lesions: area; 4 became flat	
	photos for lesions A,B,C are uninterpretable	
	No follow up photo for lesion D	
	Photos for lesion E demonstrate a response; although follow up photo is marginal	
	pt continued on follow up protocol	
	No PI effect	No
	3 lesions, 2 raised: 2 lesions became flat	
	Photos do not show benefit for lesions or activity	
	pt continued on follow up protocol	

5.3.3 SUMMARY OF RESPONSE EFFICACY IN STUDY -503

DURING INITIAL BLINDED PHASE (12 WEEKS) INTERIM ANALYSIS

	PANRETIN	PLACEBO
Ligand Modified ACTG Response (index lesions only)	41.7% (15/36) 1 CR	6.5% (3/46) p=0.00027
FDA Modified ACTG Response Analysis (index lesions only)	39% (14/36) 0 CR	6.5% (3/46) (p=0.00062)
Ligand Physician's Subjective Assessment (all rxed lesions)	47% (17/36)	11% 5/46 (p=0.0003)
FDA Beneficial Response Photographs (index lesions only)	19% (7/36)	2.2% (1/46) (p=0.019)
Ligand Patient's Subjective Assessment (all rxed lesions)	47% (17/36)	11% (5/46)

In contrast to Study -31, Study -503 did not have the disparity between the modified ACTG response and the physician's subjective assessment. The tables below suggested that among the responders, area reduction as a response criteria matches what the physicians saw during their subjective assessments of the patients. The physicians saw reduction of the height of lesions as stable disease.

ACTG RESPONSE CRITERIA PANRETIN 15 RESPONDERS	# MATCH WITH PHYSICIAN'S SUBJECTIVE ASSESSMENT
HEIGHT REDUCTION only N=5 Plaque to macule	3 (60%)
AREA REDUCTION alone or area plus height reduction N=10 Area Area + plaque to macule	9 (90%) 95% CI for diff: -17%, 77%

ACTG RESPONSE CRITERIA VEHICLE 3 RESPONDERS	# MATCH WITH PHYSICIAN'S SUBJECTIVE ASSESSMENT
HEIGHT REDUCTION only N=1 Plaque to macule	0 (0%)
AREA REDUCTION alone or area plus height reduction N=2 Area Area + plaque to macule	1 (50%) 95% CI for diff: -19%, 119%