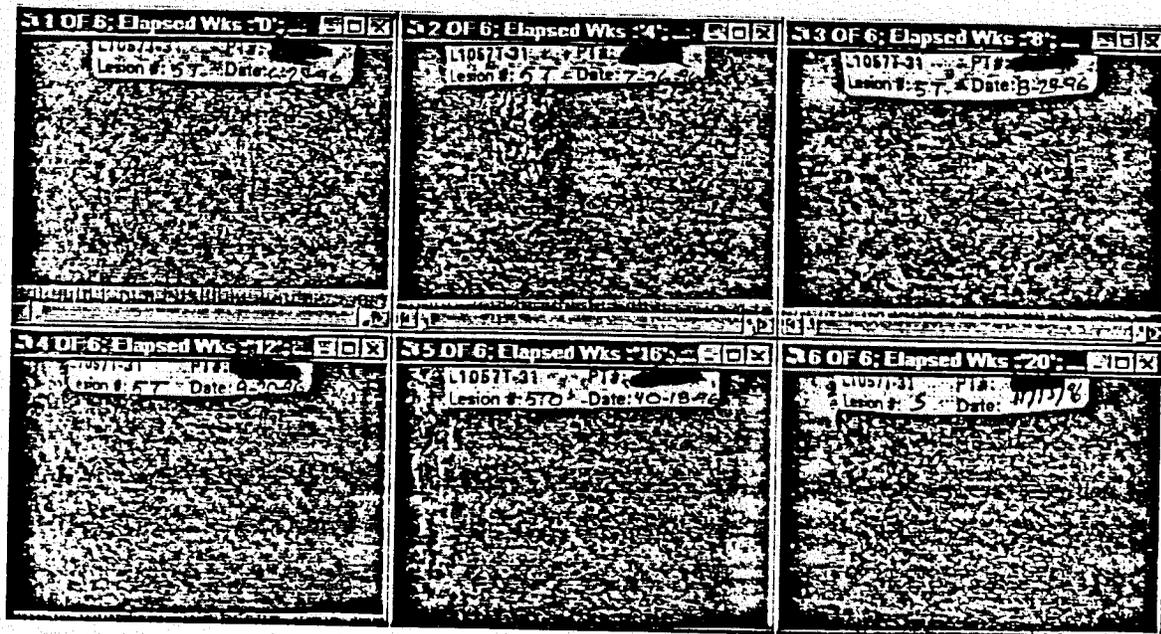


This is patient (lesion #5). This patient was considered a modified ACTG criteria responder to panretin (this patient was not a considered a cosmetically beneficial responder in the 1<sup>st</sup> 12 weeks of the blinded phase). This lesion was flat at baseline so was not counted as a responding lesions.

There was grade 1 erythema at 2, 4, and 12 wks. There was grade 2 erythema at 8 wks.



5. THE SECOND PIVOTAL CLINICAL TRIAL:  
RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED,  
12-WEEK CLINICAL TRIAL OF TOPICAL 9-CIS-  
RETINOIC ACID GEL (ALRT1057) IN THE PALLIATIVE  
TREATMENT OF CUTANEOUS AIDS-RELATED KAPOSI'S  
SARCOMA (Protocol ALRT 1057-503)

Started: 9/16/96

Last Patient Completed (9/7/97); date of Ligand report  
4/22/98

n = 82 total (planned 270); 36 panretin, 46 placebo

Sites: 17 centers in Europe, US, and Australia

5.1 PROTOCOL REVIEW

A. OBJECTIVES:

1. to compare the efficacy of 0.1% 9-cis-retinoic acid to placebo when applied topically in the palliative treatment of cutaneous Kaposi's sarcoma
2. to determine the safety and tolerability of the formulation in this patient group

B. ELIGIBILITY

1. inclusion criteria
  - Biopsy confirmed Kaposi's sarcoma (KS) which is localised and amenable to self-administered topical treatment. (The presence of systemic KS is allowed, but it should not be of a nature which is likely to require systemic therapy in the ensuing 12 weeks)
  - Presence of at least 3 lesions, each having minimum bidimensional diameters of 10mm x 2mm (Note: raised lesions were not required)
  - Confirmed ELISA-positive serum HIV antibody
  - Male or female, 18 years of age or older
  - ECOG Performance Status 0 - 2
  - Life expectancy >4 months
  - Hemoglobin 8.0g/dl, Neutrophils  $\geq 0.5 \times 10^9/l$ , Platelets  $50 \times 10^9/l$

- Serum bilirubin  $<2.0 \times$  Upper Limit of Normal, AST/ALT  $<5.0 \times$  Upper Limit of Normal, Creatinine  $<3.0 \times$  Upper Limit of Normal
- Women of child-bearing potential must have negative serum pregnancy test (beta-HCG) within 7 days prior to initiation of treatment, and must have used barrier contraception for at least 4 weeks prior to the negative pregnancy test.
- Women of child-bearing potential, and all males with partners of child-bearing potential, must agree to practice barrier contraception to 3 months post-trial
- Signed informed consent must be obtained prior to any trial procedures

## 2. exclusion criteria

- Prior systemic treatment for KS within previous 4 weeks
- Prior systemic treatment for KS at any time with Vitamin A ( $>15,000$ IU or 5mg per day) or other retinoid class drug
- Prior local therapy to any indicator lesion
- Known allergy or sensitivity to retinoid class drugs or any components of the medication
- Concurrent enrollment or participation within the last 30 days in any investigational drug trial for KS. Participation in a trial of investigational treatments for AIDS/HIV was allowable, but the treatment should have been stable during the previous 3 months if possible
- Known or expected poor compliance
- Nursing females
- Concurrent acute infection requiring intravenous medication (antibiotic, antiviral (other than treatment for HIV), antifungal). The patient could enter the trial on resolution of active disease: maintenance treatment to prevent recurrence was allowed
- Concomitant malignancy (including visceral KS) likely to require systemic treatment during the course of the trial

## C. PROHIBITED TREATMENTS

Concurrent systemic administration of other anti-cancer chemotherapy, including cytotoxic, retinoid, hormonal, or

immunotherapy. (G-CSF to correct hematological abnormalities was be allowed.)

Concurrent administration of steroids e.g megestrol, testosterone and other male sex hormone analogues, corticosteroids.

Other local therapy (e.g. radiotherapy, intralesional cytotoxics, cryotherapy), with the exception to treat a specific, non-index, non-evaluated tumour site, e.g. metastatic lesion in lung (by radiotherapy), untreated superficial area.

Medications which have demonstrated activity against KS lesions in investigational studies, e.g. foscarnet. (The initiation of such medications would not preclude the patient from continuing in the trial, but was being avoided if possible).

#### D. DOSE AND SCHEDULE

0.1% gel formulation of 9-cis-retinoic acid versus placebo vehicle, each applied twice daily to cutaneous KS lesions. At 12 weeks or at disease progression, whichever was the shorter time period, patients were offered treatment with open-label 9-cis-retinoic acid.

#### E. CRITERIA TO REMOVE PATIENT FROM STUDY

- Clinically complete response (CCR), or partial response (PR): patient could withdraw from the trial upon request after response is confirmed over a period of 4 or more weeks
- Side-effects of treatment: serious or intolerable adverse event which was at least possibly related to trial medication
- Grade 3 local dermal irritation which did not resolve on dose reduction to minimum frequency allowed in protocol
- Disease progression (e.g., treated index lesion, treated non-index lesion, or untreated lesion)
- Patient's own request
- Any female patient who became or believed she may have become pregnant
- Loss to follow-up

- Investigator's opinion that it would be in the patient's best interests

**F. BASELINE & TREATMENT FOLLOW UP**

- at a screening visit prior to trial enrollment: onology history, physical examination and vital signs (pulse rate, blood pressure (sitting)), height and weight, assessment of ECOG PS, informed consent (prior to blood sampling), blood count: Hb, WBC (including differential count), platelets, biochemistry: electrolytes, creatinine, urea, LDH, AST, ALT, gamma-GT, alkaline phosphatase, total bilirubin, albumin, globulin, total protein, calcium, phosphorus, glucose, uric acid, total triglycerides, total cholesterol, CD4, CD8 counts, u/a (dipstick)
- **Pregnancy test for females of child-bearing potential**
- **trial enrollment visit**  
blood and biochemical evaluations, indicator lesion measurements by standardised ruler and photography; recording of concomitant medication; instruction in application of medication
- **weeks 2 & 8 visits:**  
physical examination and vital signs (pulse rate, blood pressure), weight, assessment of ECOG PS, indicator lesion measurements by standardised ruler (and photography if patient is withdrawn at this visit), and examination of all other treated lesions for safety evaluation; subjective assessment Scale to be completed both by Investigator and patient; tolerability assessment; recording of concomitant medication  
pregnancy test (optional) for females of child-bearing potential

**•week 4 visit:**

physical examination and vital signs (pulse rate, blood pressure), weight, assessment of ECOG PS, blood count (as at baseline), biochemistry (as at baseline), U/A, indicator lesion measurements by standardised ruler (and photography if patient is withdrawn at this visit), and examination of all other treated lesions for safety evaluation, subjective assessment scale to be completed both by Investigator and patient, tolerability assessment, recording of concomitant medication

Pregnancy test (optional) for females of child-bearing potential

**•week 12 visit:**

final on-protocol visit

Patients who wish to continue on medication, and for whom the investigator considers it would be in their best interests to do so, were to be enrolled in a follow-up protocol, 192013-504, in which they were to receive 9-cis-retinoic acid 0.1% gel in an open-label trial for as long as it continues to be of benefit.

**It was essential that patients with response or stable disease who are transferred to protocol 192013-504 are assessed on the same indicator lesions as in this protocol and that continuity of drug treatment and lesion assessments were maintained.**

Patients--not entered into the F/U protocol: returned in 4 weeks: assessment for response and resolution of side-effects, physical examination and vital signs (pulse rate, blood pressure (sitting)), weight, assessment of ECOG PS, blood count (as at baseline), biochemistry (as at baseline), CD4, CD8 counts, U/A, indicator lesion measurements by standardised ruler and photography, and examination of all other treated lesions for safety evaluation, subjective assessment scale to be completed both by Investigator and patient, tolerability assessment, recording of concomitant medication

Pregnancy test (optional) for females of child-bearing potential

**•Follow-up visit (Exit visit)**

Patients withdrawn from the trial prior to week 12 for any of the reasons listed in Sec 8.5 and patients who discontinued trial medication at week 12. should return 4 weeks following cessation of medication and have the following procedures carried out: indicator lesion measurements by standardised ruler, examination of all other treated lesions for safety evaluation, and subjective assessment scale were to be completed both by Investigator and patient.

Trial Period	Screening 5 (Days -7 to 0)	Week 0 (Day 1)	Week 2 (Day 15)	Weeks 4, 8, & 12 (Days 29, 57, 85)	Follow-up visit (for pts. who do not enter follow- up protocol)
History <sup>1</sup>	X				
Physical Examination/Vital Signs <sup>2</sup>	X		X	X	
Height	X				
Weight	X		X	X	
ECOG Performance Status <sup>3</sup>	X		X	X	
Informed Consent	X				
Blood count <sup>4</sup>	X			Weeks 4 & 12	
Biochemistry <sup>4a</sup>	X			Weeks 4 & 12	
CD4/CD8 counts	X			Week 12	
Urine analysis (dipstick/bands/leu)	X			Weeks 4 & 12	
Pregnancy test	X		(30)	(30)	
Lesion Assessment (Ruler)		X	X	X	X
Lesion Assessment (Photography) <sup>4b</sup>		X		Week 12	
Subjective Assessment (Investigator)			X	X	X
Subjective Assessment (Patient)			X	X	X
Tolerability Assessment			X	X	X
Concomitant Medication		X	X	X	

**Key to Abbreviations**

1. Comprehensive physical examination, and oncology history
2. Vital signs (pulse, blood pressure, etc) to be measured every 4 weeks
3. See Appendix 12J
4. Hb, WBC (including differential), platelets
5. To include: electrolytes, creatinine, urea, LDH, AST, ALT, gamma-GT, alkaline phosphatase, total bilirubin, albumin, glucose, total protein, calcium, phosphate, glucose, uric acid, total triglycerides, total cholesterol
6. The investigator should comment on any clinically significant abnormalities or changes in haematological or biochemical tests
7. Optional for females of child-bearing potential
8. Photography of indicator lesions at baseline and at 12 weeks (or prior to this if patient is withdrawn due to progressive disease or toxicity). Full or photography to confirm response may be made at the discretion of the investigator

## G. RESPONSE MEASURES

Objective response criteria were to be based upon Aids Clinical Trial Group Criteria. In addition, a Subjective Assessment Scale<sup>41</sup> was to be completed by both Investigator and patient, each remaining as far as practicable blinded to the others assessment.

Baseline assessment of disease was to be made immediately prior to receiving the first dose of trial medication.

### Target Lesions

Response to treatment would be assessed on the basis of sequential measurement by standardised ruler of a set of indicator lesions: these were to include representative major lesions. All lesions meeting the minimum size criteria of 10mm x 2mm must would be evaluated, to a maximum of 8 lesions. Other lesions, which were also treated with medication, would be examined for safety evaluation, but not measured.

In addition to ruler measurements, the same indicator lesions would be photographed at baseline and at 12 weeks (or prior to 12 weeks if patient was withdrawn due to toxicity or progressive disease). Photography would be carried out with the patient in a consistent pose and using a consistent combination of camera, film, light, angle, and distance from the patient, and with mm rule placement beside each lesion. The Medical Photography Department of the Hospital or a suitably qualified individual would carry out this function.

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<sup>41</sup> This is the same as the Physician's Global Assessment used in Study -31.

## Objective Response Criteria

	Individual Lesion Response	Overall Response
<b>Clinical Complete Response (CCR)</b>	Disappearance of all clinical signs and symptoms of an indicator lesion, determined by 2 evaluations not less than 4 weeks apart.	Disappearance of all clinical signs and symptoms of all indicator lesions, determined by 2 evaluations not less than 4 weeks apart.
<b>Partial Response (PR)</b>	A 50% or greater decrease in the product of the longest perpendicular diameters of an indicator lesion, determined by 2 evaluations not less than 4 weeks apart, and no concurrent increase in the height of the lesion if flat at baseline. OR Complete flattening of the lesion raised at baseline without concurrent increase in area by 25% or more from baseline.	A 50% or greater decrease in the sum of the products of the longest perpendicular diameters of all indicator lesions, determined by 2 evaluations not less than 4 weeks apart. Not more than 25% of indicator lesions flat at baseline may become raised. OR Complete flattening of at least 50% of all indicator lesions raised at baseline without increase by 25% or more from baseline of the sum of the areas of the indicator lesions
<b>Stable Disease (SD)</b>	Any classification not meeting the criteria for CCR, PR, or PD.	Any classification not meeting the criteria for CCR, PR, or PD.
<b>Progressive Disease (PD)</b>	A 25% or more increase from baseline in the product of the longest perpendicular diameters of an indicator lesion OR A change in the character of the lesion from "flat" to "raised".	A 25% or more increase from baseline in the sum of the products of the longest perpendicular diameters of all indicator lesions OR A change in the character of 25% or more of all previously "flat" indicator lesions to "raised".

Investigators and patients<sup>42</sup> evaluated all treated lesions (i.e. both indicator and non-indicator lesions) with the subjective assessment scale below.

Score	Definition
0	Completely cleared except for pigmentation from residual hemosiderin
1	Almost cleared; very significant clearance in disease, with only traces of disease remaining (approximately 90% improvement)
2	Marked response; significant improvement with some disease remaining (approximately 75% improvement)
3	Moderate response; intermediate improvement, between slight and marked improvement (approximately 50% improvement)
4	Slight response; some improvement but significant disease remains (approximately 25% improvement)
5	Condition unchanged
6	Condition worsened

#### H. STATISTICAL DESIGN AND ANALYSIS OF RESULTS:

Statistical hypothesis and level of significance

Null Hypothesis: There was no difference between the two treatment groups in mean / success rate / frequency distribution with respect to all efficacy and safety variables.

Alternative Hypothesis: There was a difference between the two treatment groups in mean / success rate / frequency distribution with respect to all efficacy and safety variables.

A two-sided type I error less than or equal to 0.05 would be considered statistically significant.

**Sample size determination and methods of power calculation.**

The target response rate difference of clinical interest for the "active" treatment arm compared to the "placebo" arm is 15%

Postulating a response rate of 10% in the placebo group (as observed in the control arm of the Phase I trial), a response rate of 25% would be required in the "active" group. Thus to demonstrate this difference at standard

<sup>42</sup> There was no quality of life instrument used in this study.

significance levels (80% power, 2-sided test, type I error of 0.05), 113 patients will be required in each arm (i.e. a total of 226 patients). It was anticipated that approximately 270 patients would be required to be enrolled in order to achieve this aim.

#### **Subgroup analyses**

Subgroup analysis of response of patients having possibly different prognostic factors, (e.g. length of time elapsed since appearance of KS, size of lesion), would be carried out, although the statistical information obtained would be limited due to small sample sizes. This information would be used as a guide to the design of future studies.

#### **Interim analysis**

If there was a large benefit for the active treatment it was important (by Ligand) to stop the trial early. Therefore one interim analysis was undertaken. If the results showed a clear benefit for the active treatment they were to be submitted to European Regulatory Authorities for early Product Registration. If the decision was favourable the trial would then be stopped with fewer patients enrolled than originally proposed.

The interim analysis was based upon the method of O'Brien and Fleming<sup>12</sup> for 80% power and alpha 0.005 (two-sided test). If this level of significance was not reached, then the trial would continue to 270 patients as planned. In order to maintain the overall alpha level of 0.05, the p-value of the difference between the "active" and "placebo" treatments at completion of the trial was to be less than or equal to 0.048. Postulating an overall response rate of 50% in the "active" group and 10% in the placebo group, 39 patients would be needed in each group for the interim analysis, i.e. 78 patients in total.

In view of the fact that there was no available estimate of the placebo control response rate or the additive tumor response rate of 9-cis-RA over placebo control, this interim analysis was also to serve the purpose of estimating the placebo treatment effect. If it was determined to be higher than the postulate of 10%, then the sample size would have been adjusted upward to provide sufficient statistical power (0.80) to detect the postulated additive response rate with 9-cis-RA. However the sample size would not be adjusted downward.

The analysis was to be undertaken by identified personnel within Parexel who would have no further involvement with the trial until the complete database was closed. If it was recommended that the trial continued as planned to 270 patients, they would not reveal the treatment identification, directly or indirectly, to any other Parexel personnel or the sponsors or the investigators.

APPEARS THIS WAY  
ON ORIGINAL

## 5.2 RESULTS REPORTED BY THE SPONSOR

### 5.2.1 Study Population

This was a multicenter, randomized, double-blind, vehicle-controlled study of topical panretin (0.1%) applied to cutaneous KS lesions; approximately 0.5 g of gel was applied to each 1% of body surface area to be treated. After 12 weeks of treatment or progressive disease, all patients were offered open-label panretin.

The median age of the enrolled patients was 37 years (range: . . . . .). The racial composition was white (89%), Hispanic (4.9%), black (3.7%), and Asian or other (2.4%). All the patients were men. Eighty-nine percent (32/36) of the panretin patients and 85% (39/46) of the vehicle patients had poor risk disease according to TIS staging. There was more visceral disease in the panretin arm--19% (7/36) compared to 13% (6/46) in the vehicle arm. Seventy-two percent (72%) of the panretin patients and 85% of the vehicle patients had received at least three antiretroviral agents prior to entry on study. Twenty-eight percent (28%) (23/82) of the patients had received prior systemic therapy of KS and 10% (8/82) had received prior topical/local therapy for KS.

The following table provides additional demographic information on the two study arms.

	PANRETIN, N=36	PLACEBO, N=46
Age, median (range)	36	39
Male	36	46
Race		
White	33	40
Black	1	2
Asian	0	1
Hispanic	1	3
Other	1	0
ECOG performance status		
0	25 (69%)	30 (65%)
1	6 (17%)	11 (24%)
2	5 (14%)	5 (11%)
CD4+ lymphocytes Cells/mm <sup>3</sup>		
0-50	10 (27.8%)	13 (28.3%)
51-100	2 (5.6%)	7 (15.2%)
101-200	10 (27.8%)	13 (28.3%)
> 200	14 (38.9%)	13 (28.3%)

	PANRETIN, N=36	PLACEBO, N=46
Prior antiretroviral Rx		
None	3 (8.3%)	1 (2.2%)
1 drug protease inhibitor (PI) not including PI	0 1 (2.8%)	0 0
2 drugs including PI not including PI	1 (2.8%) 5 (13.9%)	4 (8.7%) 2 (4.3%)
>= 3 drugs including PI not including PI	25 (69.4%) 1 (2.8%)	36 (78.3%) 3 (6.5%)
Prior anti-cancer therapy		
None <sup>43</sup>	23 (63.9%)	32 (69.6%)
Systemic only	10 (27.8%)	9 (19.6%)
Topical/local only	1 (2.8%)	3 (6.5%)
Systemic and topical/local	2 (5.6%)	2 (4.3%)
OIs		
None <sup>44</sup>	9 (25%)	16 (34.8%)
1	5 (13.9%)	5 (10.9%)
2	12 (33.3%)	8 (17.4%)
> 3	10 (27.8%)	17 (37%)
Visceral KS		
None	29 (81%)	40 (87%)
Number raised, index		
0	15 (41.7%)	15 (32.6%)
1-4	14 (39.8%)	24 (52.2%)
5	2 (5.6%)	4 (8.7%)
6	2 (5.6%)	0
7-8	3 (8.3%)	3 (6.5%)
Tis poor risk	32/36 (89%)	39/46 (85%)

Among the 36 patients enrolled on the panretin arm, 9 or 25% withdrew prior to completion of the blinded treatment; only 1 enrolled in the open-label Study -504. Among the 46 patients enrolled on the vehicle arm, 10 or 22% withdrew

<sup>43</sup> These data are from Table 13 (vol. 1.91, p. 076). Table 14 (Prior Systemic Anti-Cancer Therapy) has for "Any systemic" under None, 24 and 35 patients for panretin and vehicle, respectively.

<sup>44</sup> Taken from Table 16 (vol. 1.91, p.80). Matches Table 50 (vol. 1.91, p. 181).

prior to completion of the blinded treatment; 5 patients enrolled in the open-label Study -504. Among the 27 panretin patients who completed the blinded treatment, 22 or 81% enrolled in the open-label Study -504. Among the 36 vehicle patients who completed the blinded treatment, 35 or 97% enrolled in the open-label Study -504.

REASONS FOR WITHDRAW FROM THE STUDY

	PANRETIN, n=9	VEHICLE, n=10
Protocol violation	0	1 (10%)
Grade 3 local dermal irritation	1 (11%) <sup>45</sup>	0
Disease progression	3 (33%)	7 (70%)
Rx'ed index lesions	1	6
Rx'ed non-index lesions	1	4
UnRx'ed lesions	3	5
Lost to F/U	4 (44%)	1 (10%)
Investigator's opinion	1 (11%)	1 (10%)

Lost to follow up was the most common reason for withdrawal for panretin patients; disease progression was the most common reason for withdrawal for vehicle patients.

5.2.2 Efficacy Results

The 82 patient interim analysis for the primary efficacy endpoint of response, according to ACTG criteria applied to topical therapy of index lesions, resulted in early stopping based on a response rate of 41.7% (15/36) for the panretin gel arm compared to 6.5% (3/46) for the vehicle gel arm (p=0.00027). One patient on panretin gel had a

<sup>45</sup> Patient : 8 measurable lesions; photos for only 6 lesions: no baseline photo for lesion F, F/U photos to only wk 2.7; cannot see and follow treatment limiting grade 3 dermal toxicity.

clinical complete response. Fifty-two additional patients<sup>46</sup> were accrued during the interim analysis; the total patient accrual was 134. The response rate on panretin gel was 37.1% (23/62) and 6.9% (5/72) on vehicle gel (p=0.00003).

The superiority of panretin over vehicle was corroborated by the Physician's Subjective Assessment and the Patient's Subjective Assessment. Both showed a response rate of 47% (17/36) for panretin and 11% (5/46) for vehicle (p=0.0003). The superiority of panretin over vehicle was maintained after adjusting for age, gender, race, baseline aggregate area of index lesions, number of raised index lesions at baseline, baseline performance status, baseline CD4+ lymphocyte counts, and history of OIs, or other AIDS-related illnesses. Responses to panretin were documented in 3 patients refractory to prior systemic anti-KS therapy (vinblastine = 2 pts; interferon = 1 pt).

Patients that completed Study 503 were eligible to continue therapy on Study ALRT-504 that was a follow-on study.

All 36 of the panretin gel patients administered the gel BID. At least 19% (31/167) of the panretin gel treated index lesions were on sun exposed area, such as face, hands, neck, and forearms. The lower legs (16%, 27/167), chest (17%, 28/167), and back (6%, 10/167) were the other areas of the body exposed where index lesions were exposed to panretin.

	PANRETIN	PLACEBO
Response @ interim analysis	41.7% <sup>47</sup> (15/36)	6.5% (3/46)
		p=0.00027
Response after 52 additional patients accrued <sup>48</sup>	37.1% (23/62) ((15+8)/(36+26))	6.9% (5/72) ((3+2)/(46+26))
		(p=0.00003)
Physician's Subjective	47% <sup>49, 50</sup> (17/36)	11% (5/46)

<sup>46</sup> Summary data (enrollment date, response [yes/no], and criteria for response) submitted 10/13/98. No reviewable data submitted.

<sup>47</sup> This includes a patient who had a clinical complete response.

<sup>48</sup> Full reviewable data not submitted.

<sup>49</sup> This is more concordant in favor of panretin with the objective response than the results in Study -31.

<sup>50</sup> ACTG criteria vs. Physician's Subjective Assessment: correlation statistic 0.2151, kappa statistic 0.4447.