

The latter two references by Little et al and Cianfrocca et al published in 1998 do not discuss the use of topical therapy.

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of designing clinical trials for AIDS-related Kaposi's sarcoma. Oncology 1998; 12:871-883; Cianfrocca M, Von Roenn JH. Epidemic Kaposi's sarcoma. Oncology 1998; 12:1375-1385.

4. THE FIRST PIVOTAL TRIAL: RANDOMIZED PHASE 3
VEHICLE CONTROLLED TRIAL OF ALRT1057 TOPICAL
GEL IN PATIENTS WITH AIDS-RELATED CUTANEOUS
KAPOSI'S SARCOMA (Protocol L1057T-31)

Started: 4/4/96

Last Patient Accrued: 7/14/97 -

n= 134 patients in each treatment arm (total of 268 patients in the study).

Sites: 35 centers in the US and Canada

Number of Investigators: 19

4.1 PROTOCOL REVIEW

A. OBJECTIVES:

1. to evaluate the anti-tumor effects of ALRT1057 topical gel compared to vehicle gel when applied topically to cutaneous KS lesions.
2. to evaluate the safety and cutaneous tolerance of ALRT1057 topical gel compared to vehicle gel when applied topically to cutaneous KS lesions

B. ELIGIBILITY

1. inclusion criteria

- Diagnosis of KS proven by biopsy (repeat biopsy was not required for entry if KS has been previously confirmed histologically and the histopathology report has been reviewed)
- Serum HIV antibody positive by ELISA (confirmed by review of laboratory report)
- A minimum of **six (6) cutaneous KS lesions** including at least **three (3) raised lesions**, each of which has been present for at least thirty (30) days OR has a longest dimension of at least 10 mm, AND was accessible to the patient for self-application of study drug. These KS

index lesions must not have received any prior topical or local therapy within sixty (60) days of entry in the study

- Age > 18 years
- Karnofsky performance score > 60
- Acceptable organ function defined as follows:
 - Hepatic Function: Bilirubin <1.5 x the upper limit of normal; SGOT (AST) and SGPT (ALT) < 5 x the upper limit of normal
 - Renal Function: creatinine < 2.0 x the upper limit of normal
 - Hematology: hemoglobin > 8.0 g/dL (without being transfusion dependent), neutrophil count > 700/mm³ and platelet count >50,000/mm³;
- No concurrent, serious, uncontrolled infections including, but not limited to: *Mycobacterium avium intracellulare* or other mycobacterium infection; *Pneumocystis carinii* pneumonia; CMV retinitis or colitis; Toxoplasma brain abscess; Cryptococcal meningitis
- Women of child-bearing potential must have a negative serum beta-HCG pregnancy test within seven (7) days prior to the initiation of treatment and must have used an effective means of contraception or must have been sexually abstinent from at least four (4) weeks prior to the negative pregnancy test through to the time of entry in the study.
- Female patients with child-bearing potential must have agreed to use an effective means of contraception and male patients with female sexual partners with child-bearing potential must have agreed to use condoms during sexual intercourse during the entire period of treatment and for at least three (3) months after treatment was discontinued.

2. Exclusion criteria

- Systemic treatment for KS < 30 days of entry in this study
- Systemic therapy with either Vitamin A in doses greater than 15,000 IU (5,000 mcg) per day (equivalent to approximately three times the RDA) or other retinoid class drug for any indication within thirty (30) days of entry to this study
- Previous local or topical therapy of any KS index lesion such as, but not limited to, Vitamin A, tretinoin (all-trans-retinoic acid), other retinoid class drugs, cryotherapy, radiotherapy, intralesional (injection) therapy, photodynamic therapy and/or laser therapy within sixty (60) days of entry in this study
- Pregnancy or active breast-feeding
- Serious intercurrent medical illness or infection, including (but not limited to) KS for which systemic therapy is indicated, which would interfere with the ability of the patient to carry out the treatment program
- Known allergy or sensitivity to retinoid class drugs
- Patient participation in any other Ligand study of topical therapy of KS

C. DOSE AND SCHEDULE

- ALRT1057 (9-cis-retinoic acid) 0.1% topical gel vs. vehicle gel
- Patients applied the study drug three times daily. The frequency of application was increased according to protocol specifications to four times daily as tolerated, and was decreased to twice daily, once daily or every other day according to toxicity.

The initial treatment period for KS index lesions was at least twelve weeks. Patients with documented progressive disease prior to Week 12 were continued to be blinded and were to be switched from their randomly assigned treatment arm to the other blinded treatment arm at the time that disease progression was confirmed. Patients meeting

criteria for response or disease progression that has not yet persisted for at least four weeks as of Week 12 of treatment were continued on their blinded assigned treatment arm for up to four additional weeks or until response or disease progression was confirmed, and then received open label ALRT1057 therapy. All other patients received open label ALRT1057 therapy after twelve weeks of blinded study drug.

D. CRITERIA TO REMOVE PATIENT FROM STUDY

- treatment was no longer deemed beneficial
- unacceptable toxicity
- deleterious changes in the patient's health
- patient's best interests as decided by the patient and/or the patient's physician
- occurrence of several instances of treatment-limiting toxicity
- intercurrent illness which prevented further study drug treatment
- general or specific changes in the patient's condition

E. TREATMENT ASSIGNMENT/RANDOMIZATION

- Patients were randomized in a 1:1 allocation ratio to either ALRT1057 0.1% topical gel or vehicle gel treatment in a blinded fashion.

F. CONCURRENT THERAPY

During the study, the following therapies are prohibited and must not be administered to patients being treated on this protocol:

- Local or topical therapy such as, but not limited to, Vitamin A, tretinoin (all-trans-retinoic acid), other retinoid class drugs, cryotherapy, radiotherapy, intralesional (injection) therapy, photodynamic therapy and/or laser therapy to any KS index lesion
- Systemic anticancer chemotherapy, systemic anticancer

hormonal therapy and/or systemic anticancer immunotherapy

- Systemic use of retinoid class drugs, beta-carotene compounds, or Vitamin A doses of more than 15,000 IU (5,000 mcg) per day (equivalent to approximately three times the RDA) for any indication.

H. KAPOSI SARCOMA ASSESSMENT

- Selection of KS Index Lesions

Six (6) KS cutaneous lesions, including at least three (3) raised lesions, were to be designated as "index" lesions. These index lesions were selected on the basis of being representative of the patient's overall KS cutaneous disease. Cutaneous lesions on all areas of the body, including exposed areas such as the face, were eligible for treatment providing that the patient can self-treat the lesions.

KS index lesions must, at baseline, have been present for at least thirty (30) days OR have a longest dimension of at least 10 mm. KS index lesions must not have received any prior local or topical treatment within sixty (60) days of entry in this study. These index lesions should have distinct and easily measurable borders. The anatomic location and the individual lesion characteristics such as lesion area, lesion height, lesion color and lesion-associated pain were considered.

Unless the patient had only raised cutaneous lesions, the group of index lesions selected should have contained both flat and raised lesions, preferably in a ratio approximating the proportion of the overall distribution of flat and raised lesions for that patient. It was recommended that an even number of raised lesions be designated as index lesions.

- The total number of KS lesions and the anatomic distribution of KS lesions for each patient was recorded
- Each KS index lesion was recorded on the anatomic chart in the Case Report Form with the appropriate lesion label designation.

- Non-index lesions could also be treated. These non-index treated KS lesions were also identified and recorded on the anatomic chart.
- Each KS index lesion was assessed for lesion area, height, color and lesion-associated pain at Day 1 (baseline), every two (2) weeks for the first four (4) weeks, every four (4) weeks thereafter for as long as the patient remains in the study, and again at the follow-up visits. Supplemental (non-index) treated lesions were not subjected to these detailed individual lesion assessments, but were nevertheless assessed at each clinic visit as part of the Investigator's Global Assessment.

- for lesion area:

- The longest diameter and the longest diameter perpendicular to this diameter of each KS index lesion were measured (in mm). The lesion area were the product of these the two diameters.

If a KS lesion's borders were not well-demarcated due to study drug-induced erythema, discoloration or other skin changes and the lesion was suspected to have had a clinical complete response, then study drug treatment may be withheld for up to two (2) weeks for this lesion in order to allow for at least partial resolution of any drug-induced changes and to facilitate a more accurate lesion area measurement.

Evaluation of individual lesion responses to treatment would be derived from these data and according to the response criteria discussed. The Investigator were not asked to make determinations of individual lesion responses to treatment in the Case Report Forms.

- PHOTOGRAPHS OF KS LESIONS

On Day 1 (baseline), every four (4) weeks thereafter for the duration of treatment, and again at the post treatment follow-up visits, all KS index lesions were to be photographed. The KS lesions to be photographed were to be marked on the anatomic chart in the patient's Case Report Form. Global photographs of each patient's KS disease were to be obtained on Day 1 (baseline), every four (4) weeks during treatment and again at the

patient's post treatment follow-up visits.

Ligand Pharmaceuticals Inc. provided a standardized photographic system, film, processing and development along with detailed instructions and training. Each area to be photographed was photographed with the patient in a consistent pose and with a technique using a consistent combination of camera, film, light, angle and distance from the patient.

All lesion areas which were photographed at baseline were to be re-photographed every four (4) weeks, even if the lesions have cleared, until the patient completed the follow-up study visits.

- KS Tumor Biopsies

This study did not require a repeat biopsy for patient entry if KS has been histologically confirmed by previous evaluation and the histopathology report has been reviewed. As an optional procedure, KS tumor biopsies (generally using standard skin punch biopsy techniques) of selected KS lesions were obtained from consenting patients before, during and after study drug treatment. One purpose of these biopsies would be to evaluate cellular response to topical ALRT1057 treatment. If a biopsy sample of the patient's KS tumor was obtained, laboratory studies were performed on tissue derived from that biopsy sample.

KS tumor biopsies were to be limited to supplemental treated (non-index) lesions until after treatment is discontinued; unless clinically indicated, no designated KS index lesion that was still on treatment was biopsied. These biopsies, if performed for the sole purpose of this investigational study, were to be done at no charge to the patient.

- ULTRASOUND MEASUREMENTS OF KS LESIONS

As an optional procedure, ultrasound measurement of selected KS index lesions were to be obtained from consenting, selected patients before, during and after study drug treatment. The purpose of the ultrasound evaluation would be to provide an additional objective measure of tumor depth/volume change in response to study drug treatment. Any ultrasound measurements would be performed in addition to, and not in place of, the lesion area and height assessments. The ultrasound evaluation, if

performed for the sole purpose of this investigational study, would be done at no charge to the patient.

- PHYSICIAN'S GLOBAL ASSESSMENT

The Physician's Global Assessment was completed at Week 4, every four (4) weeks thereafter during the study, and at the first post treatment follow-up visit to evaluate the extent of improvement or worsening of all of the patient's treated lesions (index and non-index) relative to the condition at baseline.

- PATIENT QUALITY OF LIFE QUESTIONNAIRE

A patient quality of life questionnaire was designed to collect subjective information, including the patient's own assessment of KS lesions and other information. The questionnaires were completed at Day 1 (baseline), every four (4) weeks for as long as the patient remained on treatment, and again at the post treatment follow-up visits.

I. STUDY VISITS DURING TREATMENT

Throughout the study and upon discontinuation of study drug, patients had multiple evaluations performed at various timepoints. Each patient returned for evaluation every two (2) weeks for the first four (4) weeks of treatment, every four (4) weeks thereafter for as long as the patient remains in the study, and again at the follow-up visits, for a targeted history and physical examination, KS lesions assessments, and adverse event and toxicity recordation. The anatomic chart of the KS lesions was updated. The patient quality of life questionnaire, photographs of KS lesions and global photographs, and the Physician's Global Assessment were performed every four (4) weeks during the study.

Follow-Up Visits

All patients who entered the study and received at least one dose of study drug, regardless of the reason for withdrawal or study termination, were, if at all possible, had a follow-up evaluation at least four (4) weeks following their last application of study drug and then two additional follow-up visits at three (3) month intervals. Follow-up evaluation was to consist of a history and physical examination, adverse

event recordation, assessment of KS index lesions, completion of the patient quality of life questionnaire, photographs of KS index lesions and global photographs, the Physician's Global Assessment and determination of adverse events that may have been ongoing at the time when therapy was discontinued. The required blood and urine tests would be performed at the first follow-up visit.

Pre-study/baseline laboratory studies: CBC (hgb, neutrophils, platelets, total bilirubin, SGOT & SGPT, creatinine, triglycerides, amylase, U/A; pregnancy test; CD4/CD8

Every 2 weeks x 2 then every 8 weeks: CBC (hgb, neutrophils, platelets, total bilirubin, SGOT & SGPT, creatinine, triglycerides, amylase, U/A

CD4/CD8 @ 4 weeks then every 8 weeks

QOL @ baseline, @ 4 weeks then every 8 weeks

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SUMMARY OF THE REQUIRED ASSESSMENTS

TABLE 5. SUMMARY OF REQUIRED STUDY ASSESSMENTS

ASSESSMENT TO BE COMPLETED	At Any Time Prior to Entry	Pre-Study (1) Up to 14 Days Before Day 1	Day 1 "Baseline" Test Rx/Day	Every 2 Weeks for 4 Weeks, then Every 4 Weeks During Treatment	Follow-Up Visits
KS Confirmed by Biopsy	X				
HIV Ab by ELISA	X				
Age ≥ 18 years		X	X		
Women - Neg. β-HCG		X (2)	✓		
Symptoms and/or AEs		X	X	X	X
KS and Med History/Physical Exam, Weight and Height		X (include height)	X	X	X
Karnofsky Performance			≥ 60	✓	✓
No Serious Uncontrolled Infection			X	✓	✓
Agree to Use Contraception (2)		X (2)	✓	✓	✓
Patient QOL Questionnaire			X	X (5)	X (5)
Physician's Global Assessment				X (5)	X (5)
Laboratory					
CD4/CD8 Counts			X	X (3)	X (3)
Chemistry Panel and CBC, including tests below: (5)		X (1)	X (1)	X (5)	X (5)
Total Bilirubin		≤ 1.5 X LLN	X	X (5)	X (5)
SGOT and SGPT		≤ 5.0 X LLN	X	X (5)	X (5)
Creatinine		≤ 2.0 X LLN	X	X (5)	X (5)
Total Triglycerides (4)			X (4)	X (5)	X (5)
Hemoglobin		≥ 8.0 g/dL	X	X (5)	X (5)
Absolute Neutrophils		≥ 700/mm ³	X	X (5)	X (5)
Platelets		≥ 50,000/mm ³	X	X (5)	X (5)
Amylase			X		
Urinalysis			X	X (5)	X (5)
Efficacy					
KS Lesion Photographs			X	X (6)	X (6)
KS Lesion Assessments			X	X	X

X = Required *✓* = Check on Status LLN = Upper Limit of Normal

NOTE 1: "Pre-study" assessments must be obtained and results known within two (2) weeks prior to the first dose of ALRT1057. A set of "baseline" labs must be obtained just prior to the application of the first dose (results do not need to be available to start therapy).

NOTE 2: For women of childbearing potential, a serum (β-HCG) pregnancy test must be negative within seven (7) days before starting treatment. Pregnancy is strictly contraindicated during treatment and within three (3) months after treatment discontinuation. All female patients must agree to use an effective contraceptive method or remain sexually abstinent during those periods.

NOTE 3: Completed at baseline (Day 1), at Week 4, every eight (8) weeks thereafter during the study, and at the first follow-up visit.

NOTE 4: Lipids should be obtained fasting at baseline, and at any other times when lipid levels are found to be significantly elevated.

NOTE 5: Chemistry panel and CBC will be obtained pre-study, and Chemistry panel, CBC and urinalysis will be obtained at baseline (Day 1), at Week 2, Week 4 and every 8 weeks thereafter during treatment, and at the first follow-up visit.

NOTE 6: Completed every four (4) weeks during the study and at the first follow-up visit.

J. KS Index Lesion Response Evaluations

All KS index lesions were evaluated based on the lesion area and height measurements in the Case Report Forms at each timepoint for which data were available. The lesion area was calculated by multiplying the two lesion diameters recorded in the patient's Case Report Form for each lesion at each timepoint. The evaluation of each KS index lesion at each timepoint was classified according to the following system:

Complete Response (CR):

Decrease in lesion area to zero and biopsy documenting absence of KS cells. The lesion registered CR or CCR at two or more consecutive timepoints persisting over at least four.

Clinical Complete Response (CCR):

Decrease in lesion area to zero. The lesion registered CCR at two or more consecutive timepoints persisting over at least four weeks.

Partial Response Area (PRA):

Decrease in lesion area by 50% or more from baseline without concurrent increase in height of a lesion from flat (macular) at baseline to raised (plaque-like or nodular). The lesion registered, at two or more consecutive timepoints, the required reduction in area persisting over at least four weeks.

Partial Response Height (PRH):

Complete flattening of a lesion raised at baseline (decrease in height from nodular or plaque-like to macular) without concurrent increase in lesion area by 25% or more from baseline. The lesion registered, at two or more consecutive timepoints, the reduction in height persisting over at least four weeks.

TABLE 6. HEIGHT ASSESSMENT OF KS LESIONS

Description	Lesion Height
Macular	0mm
Plaque-Like	Up to 2mm
Nodular	Greater than 2mm

Stable Disease (SD):

Lesions that did not meet evaluation criteria for CR, CCR, PR or PD.

Increase in lesion area by 25% or more from baseline area, or an increase in height of a lesion from flat (macular) at baseline to raised (plaque-like or nodular). The lesion registered PD at two or more consecutive timepoints persisting over at least four weeks.

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Non-index lesions were not to be evaluated by the detailed ACTG criteria but their evaluation was to be included with the index lesions with the Physician's Global Assessment.

TABLE 9. PHYSICIAN'S GLOBAL ASSESSMENT

Assess only lesions treated with study drug (index and non-index treated lesions).

GRADE	DESCRIPTION
0 Completely Cleared	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	Condition has not changed from BASELINE evaluation.
6 Condition Worsened	Condition is worse than at BASELINE evaluation. (Approximately $\geq 25\%$ worsening)

K. STATISTICAL DESIGN AND ANALYSIS

The evaluation of the primary efficacy endpoint will be performed on a per-patient basis. The observed tumor response rates by patient for the group of control lesions in previous studies using intra-patient untreated control lesions have been in the range of 3% to 12%. Assuming a combined response rate (CCR and PR) in the vehicle control treatment arm in the range of 5% to 10%, a difference in combined response rate with ALRT1057 treatment over vehicle control treatment of 15% (overall response rate in the ALRT1057 treatment arm of 20% to 25%), a power of 0.80 and an overall Type I error of 0.05, 115 patients per treatment arm (total of 230 patients in the study) was required to demonstrate this primary efficacy endpoint using a two-sided test on proportions.

One interim analysis was to be performed after 100 patients (50 patients per treatment arm) have completed the planned initial 12 weeks of blinded study drug treatment. The stopping rule was based on the method developed by O'Brian and Fleming for a two-sided alpha level of 0.05; i.e., the trial would be declared statistically significant if the significance level at the interim analysis was less than or equal to 0.005. If this level of significance was not reached, then the study was continued until at least 230 patients have completed the blinded study drug treatment. In order to maintain the overall alpha level of 0.05, the p-value of the difference between the ALRT1057 and vehicle control treatment arms at completion of the study must have been less than or equal to 0.048.

If at this interim analysis the vehicle control response rate was determined to be higher than the initial estimate of 5% to 10%, then the sample size was to be adjusted upward to provide sufficient statistical power (0.80) to detect the revised estimated additive response rate with ALRT1057 treatment. However, the sample size was not to be adjusted downward.

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