

PID	COMMENTS PROTEASE INHIBITOR (PI) EFFECT CHARACTER OF LESIONS & REPORTED RESPONSE <sup>M</sup> FDA REVIEW	BENEFICIAL RESPONSE
	lesions #1,#2,#3, #4 may be responses: nodular to raised (2), nodular to flat (1); global ant. upper suggests response in some of non-index lesions also; #4 may have satellite lesions that responded	
	no response in lesions #5,#6; #5: new lesion appears and grows; new lesion with lesion #5 shows on global (post. upper)	
	response is from nodular to raised	
	photos of lesions show benefit	
	No PI effect	Yes
	3 raised lesions: all became flat	
	new lesions appear on right leg @ 4.7 wks	
	Incorrect baseline photo for lesion #4; Ligand response: baseline photos for lesions #3 & #4 are incorrect—Ligand cannot identify baseline photo for #3	
	Photos of lesions show benefit	
	No PI effect	No
	4 raised lesions: all became flat; area	
	#1 is a response	
	Lesions #2, #3, #4 are not responses	
	photos of lesions do not show benefit	
	lesion #2 mislabeled in the baseline in-photo; wk 3.7 photo for lesion #2 also mislabeled;	
	none of the index lesion have the correct date @ baseline in-photo	

PID	COMMENTS PROTEASE INHIBITOR (PI) EFFECT CHARACTER OF LESIONS & REPORTED RESPONSE <sup>SM</sup> FDA REVIEW	BENEFICIAL RESPONSE
=	new lesions on neck @ 17 wks; most of lesions in upper anterior photo gone	
	No PI effect	Yes
	3 raised lesions: 2 became flat	
	Lesions #1 and #2 are questionable responses	
	Photos of lesions show benefit	
	lesion #3 @14.7 wks appears different than the other photos	
	Erythema and edema associated with flattening	
	PI effect	No
	6 raised lesions: 3 became flat	
	Lesions #1 & #4 are not responses	
	maybe lesion #5 is a late response but it is not confirmed	
	Photos of lesions do not show benefit	

In response to the above information about beneficial response, Ligand stated (Nov. 8, 1998), "This analysis could be presented by FDA at the Advisory Committee meeting as "another analysis" performed by the FDA on the information submitted in the NDA or it could be presented as an analysis calling into question the protocol-defined primary efficacy analysis conducted for these studies."

EXAMPLES OF COSMETICALLY BENEFICIAL RESPONSES TO PANRETIN

The first example of a patient with a beneficial response to panretin is case Out of the 6 index lesions, there were 3 plaque lesions at baseline. By the modified ACTG criteria, a partial response was scored when all 3 of these lesions became flat. Also the combined area of the 6 index lesions was reduced by 50%.

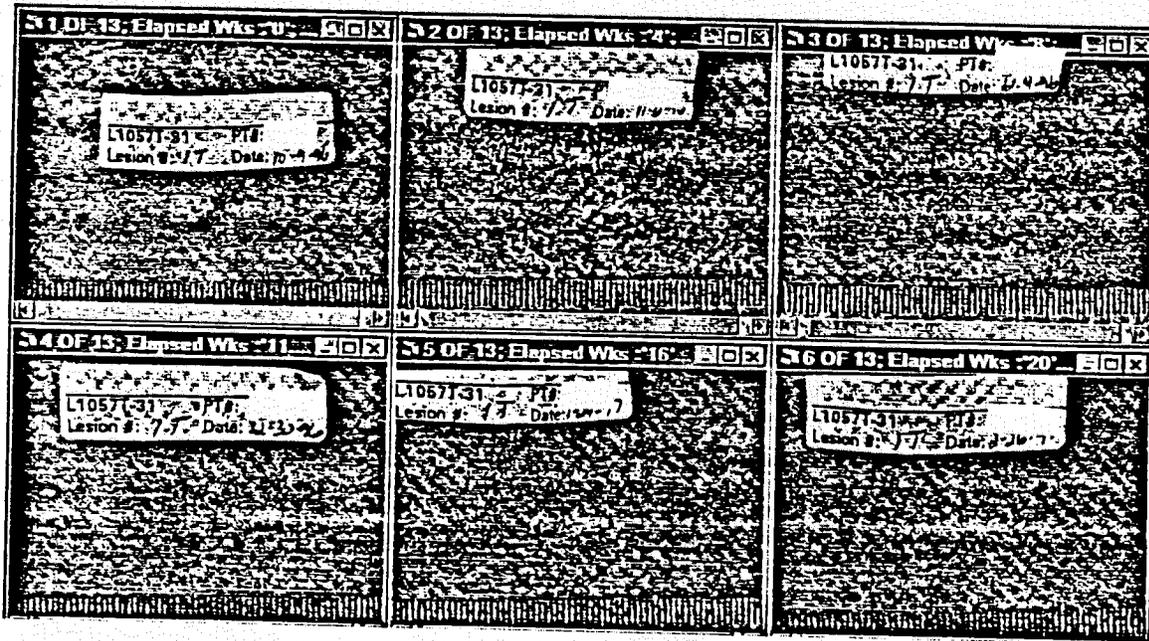
lesion #1:

plaque at baseline

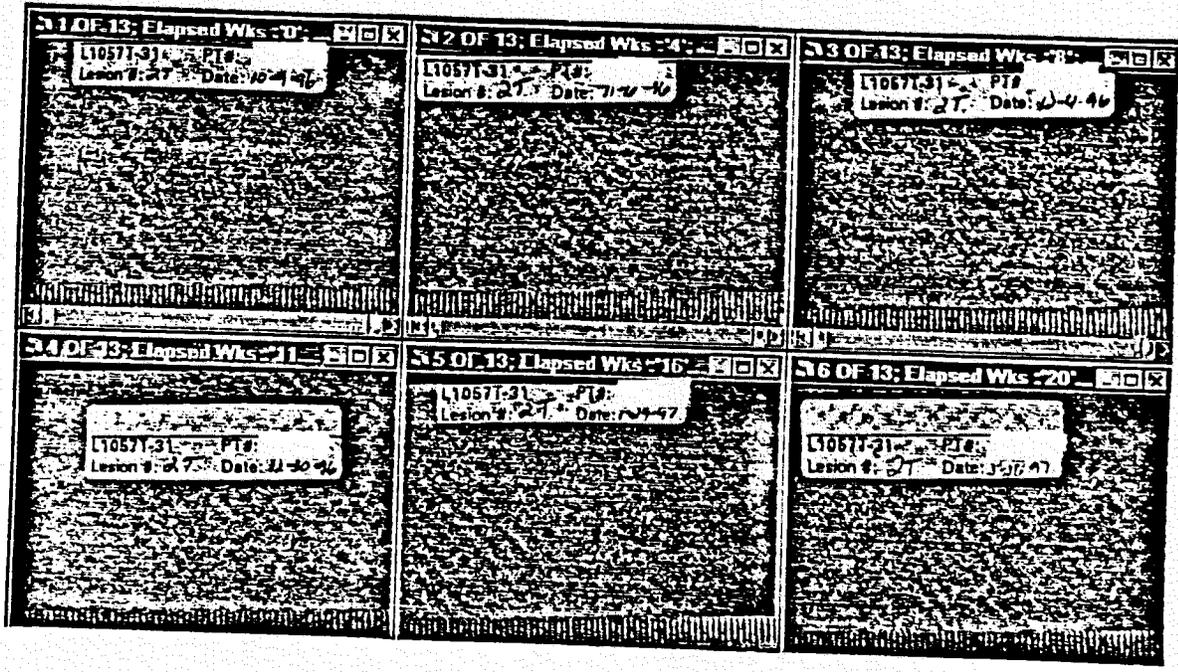
flat @ 4 wks, according to the CRF (this is the investigator assessment; FDA does not necessarily agree based on photos)

0 x 0 at 8 wks, according to the CRF

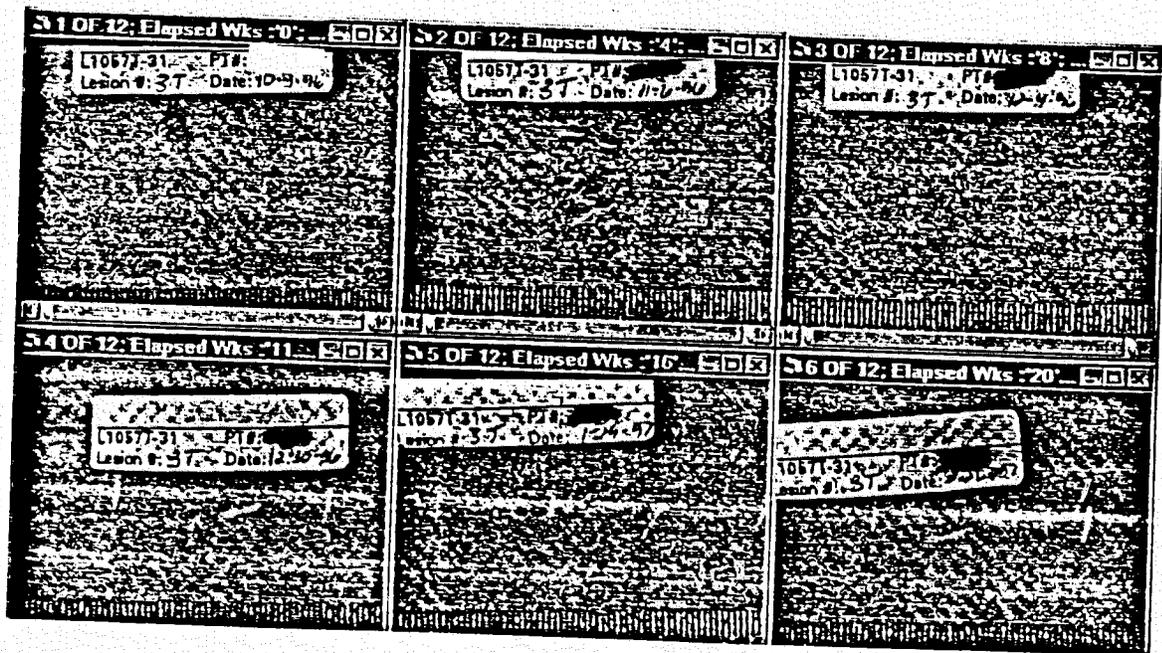
grade 2 erythema @ 4 wks



lesion #2:  
 plaque at baseline  
 flat at 4 wks  
 0 x 0 at 12 wks

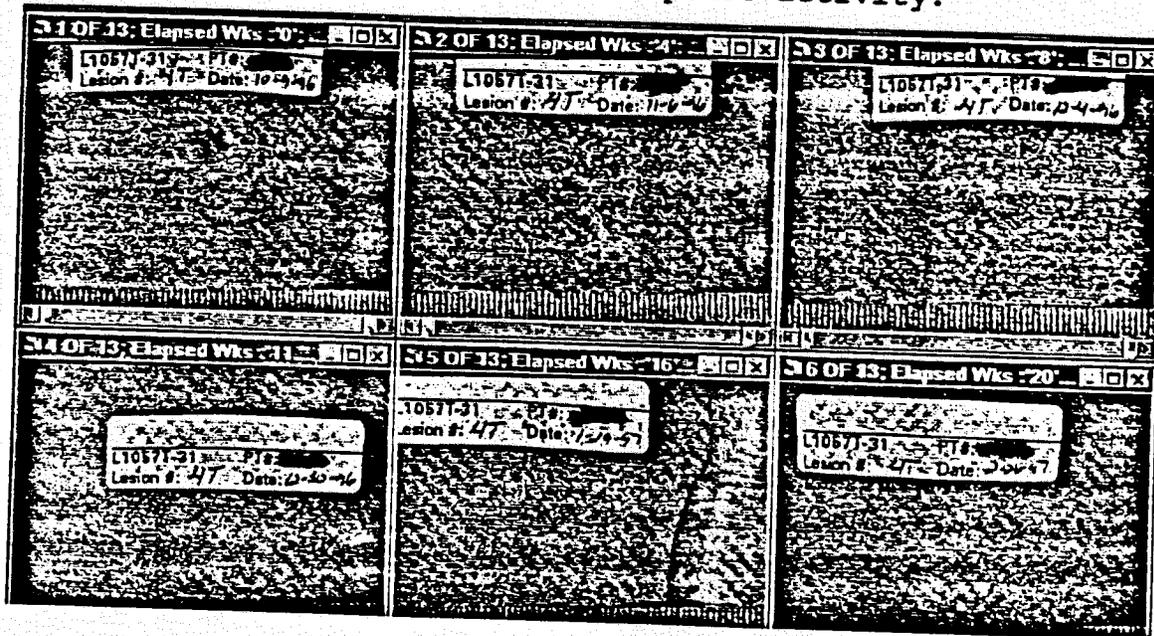


lesion #3:  
 plaque at baseline  
 flat at 4 wks  
 grade 1 erythema

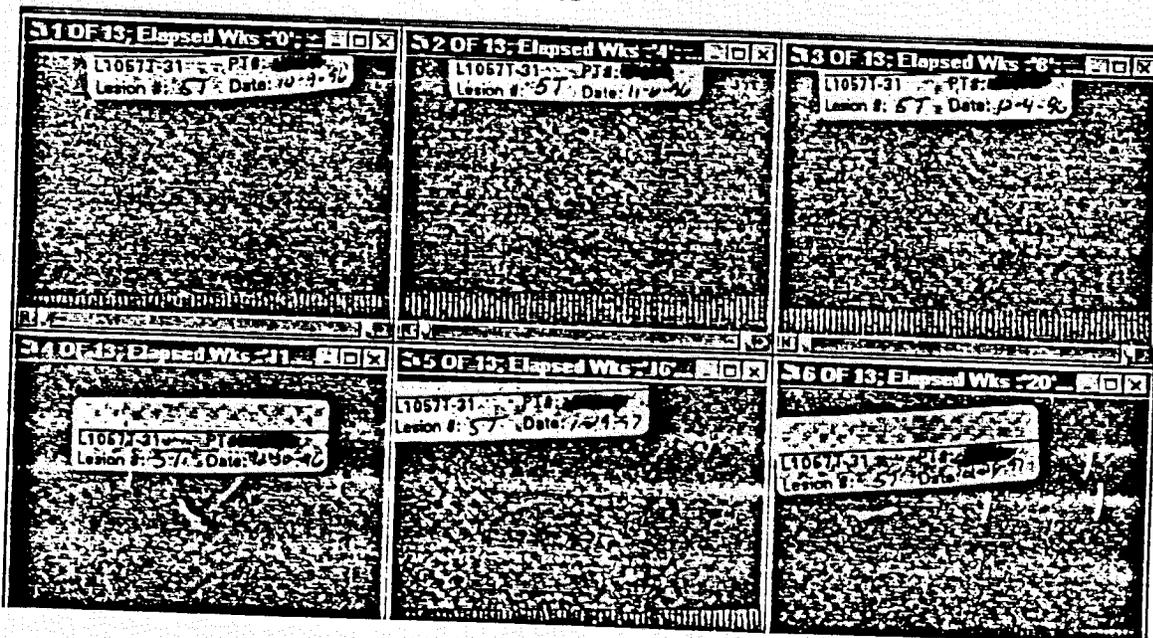


lesion #4:  
flat at baseline  
grade 1 erythema

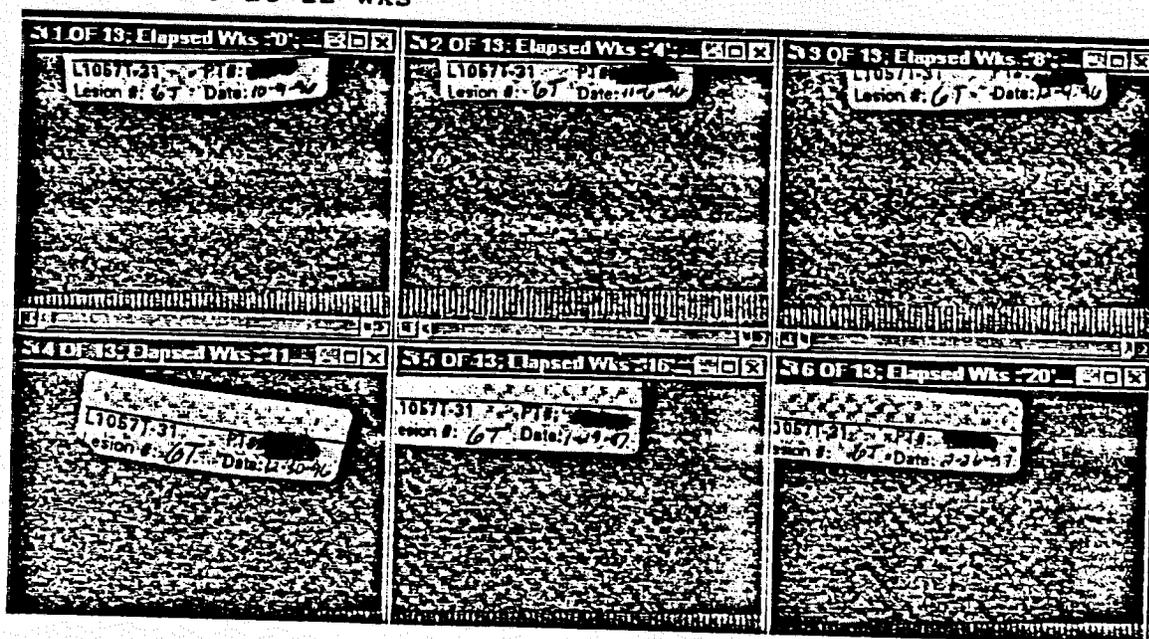
There was no other evidence of response activity.



lesion #5:  
flat at baseline  
0 x 0: wk 12  
grade 2 erythema at 4 wks



lesion #6:  
 flat at baseline  
 0 x 0 at 12 wks



It is also of note that the response of the KS lesions in this patient may have possibly been due to a protease inhibitor effect. It appears that KS Lesions started to disappear after crixivan started.

#### SUMMARY of Patient

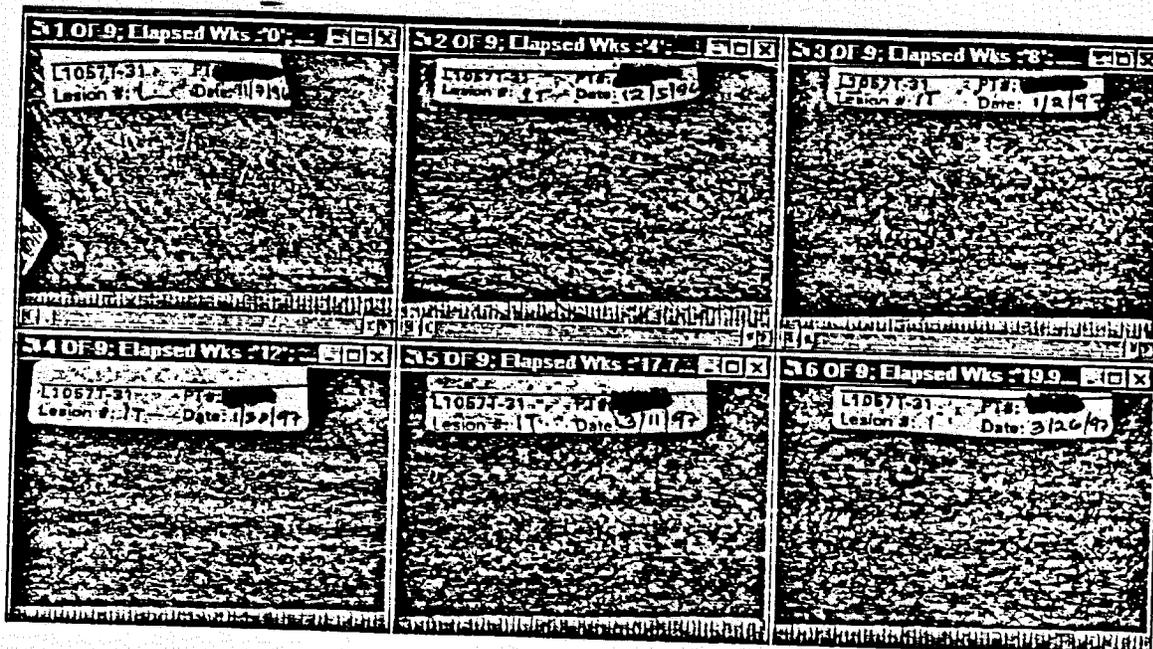
- Modified ACTG response: PR
- Physician's global assessment: PR
- Patient satisfaction with the KS lesions treated: moderately satisfied
- Cosmetically beneficial response: YES

The next example of a patient with a beneficial response to panretin is case -a complete responder by the modified ACTG criteria. There were 3 plaques + 1 nodular lesion at baseline. All the raised lesions became flat. The area of the index lesions was reduced by > 50%. By the modified ACTG criteria, a complete response was scored.

lesion #1:

#1: nodular @ baseline  
flat @ wk 8  
0 x 0: wk 8

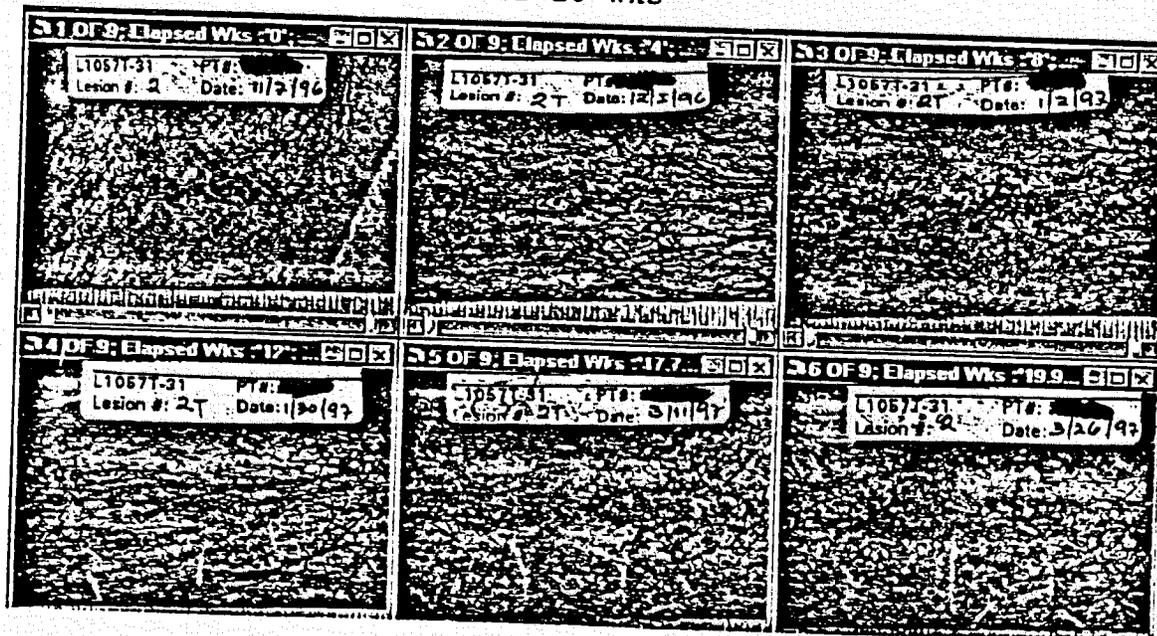
grade 2 erythema at 8 wks  
grade 1 erythema at 12 & 16 wks



lesion #2:

#2: plaque @ baseline  
flat @ 4 wks  
0 x 0: wk 4

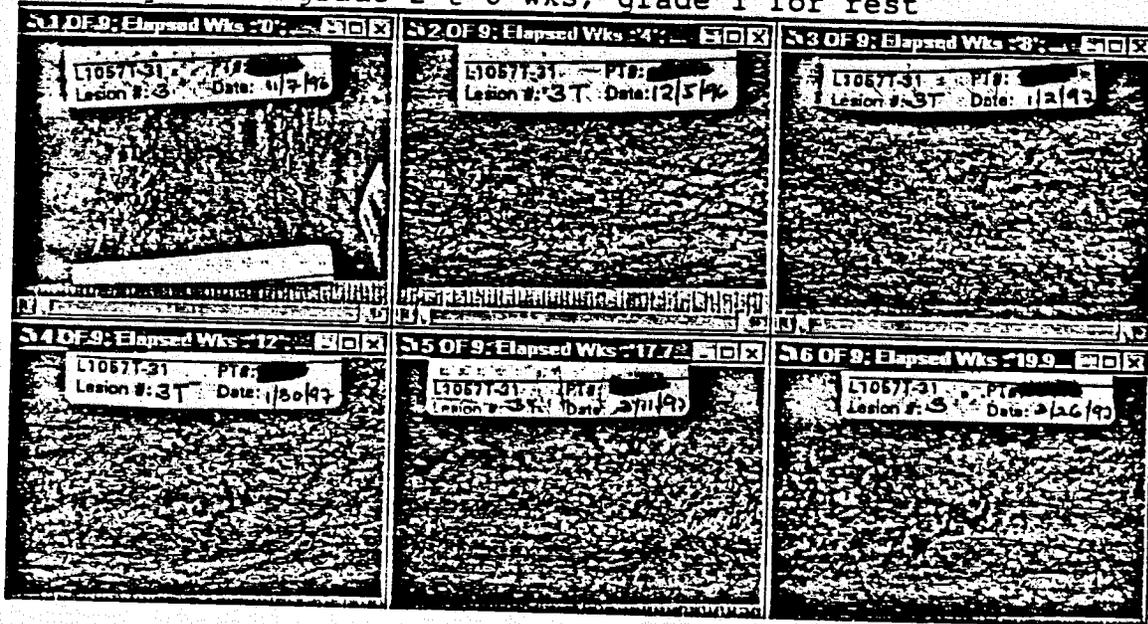
grade 2 erythema at 8 wks  
grade 1 erythema at 12-28 wks



lesion #3:

plaque @ baseline  
flat @ 4 wks  
0 x 0: wk 4

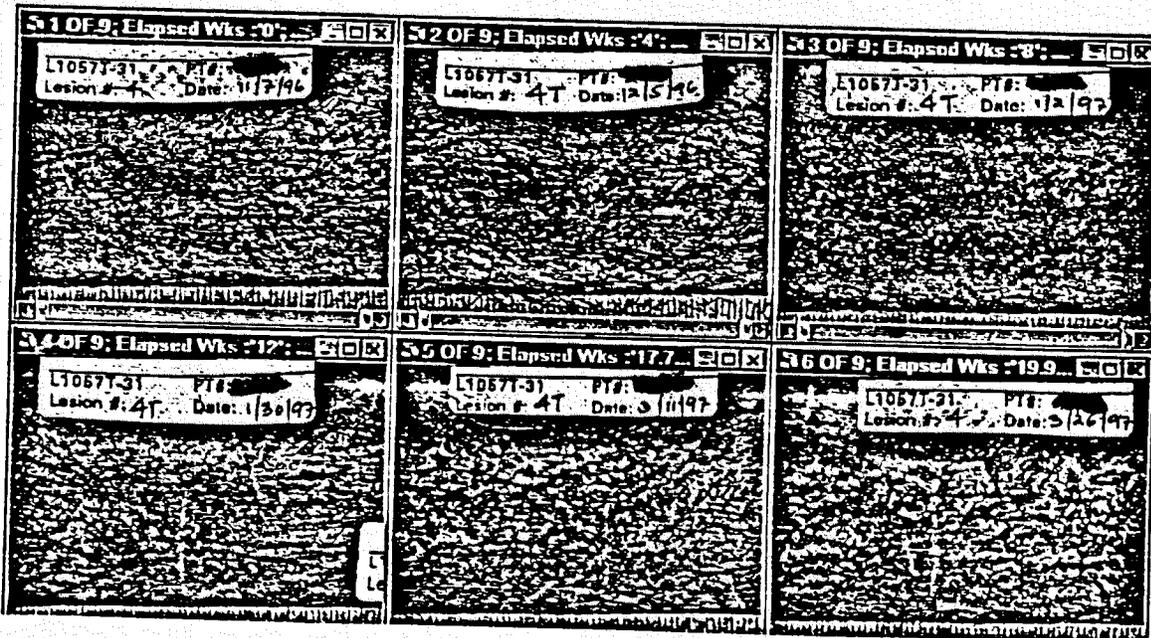
grade 2 erythema at 8 wks  
grade 1 erythema at 4, 12-28 wks  
erythema: grade 2 @ 8 wks; grade 1 for rest



lesion #4:

flat @ baseline  
0 x 0: wk 8

grade 2 erythema: wk 4  
grade 3: wk 8  
rest grade 1: 12-28 wks



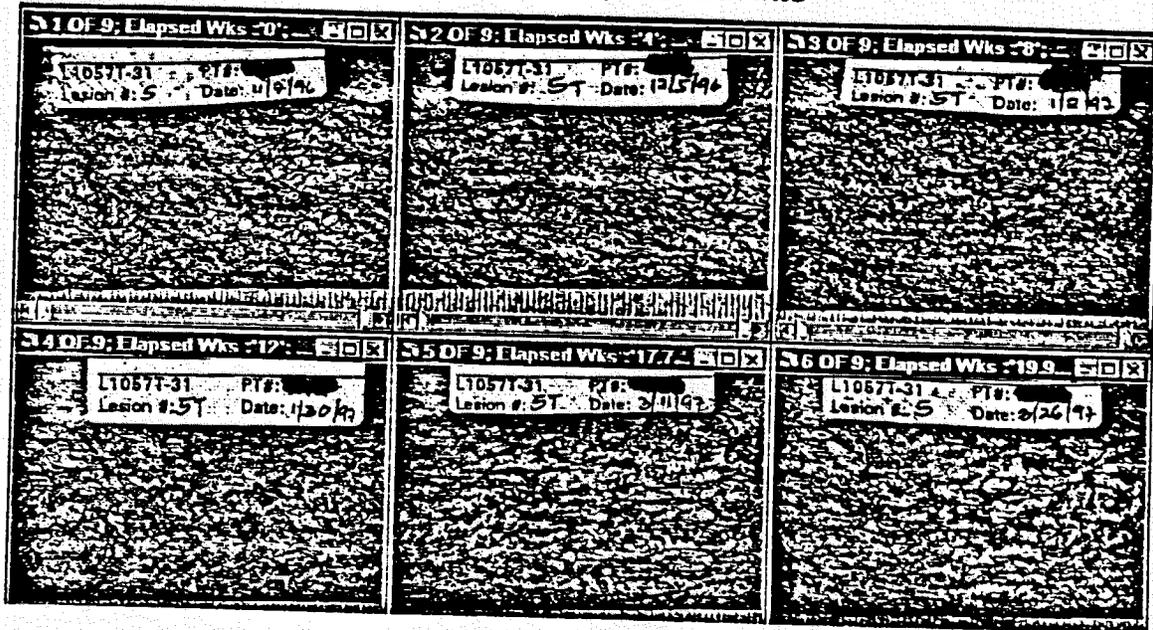
lesion #5:

flat @ baseline

0 x 0 @ 4 wks

grade 2 erythema @ 8 wks

grade 1 for the rest: 4 wks, 12-28 wks



lesion #6:

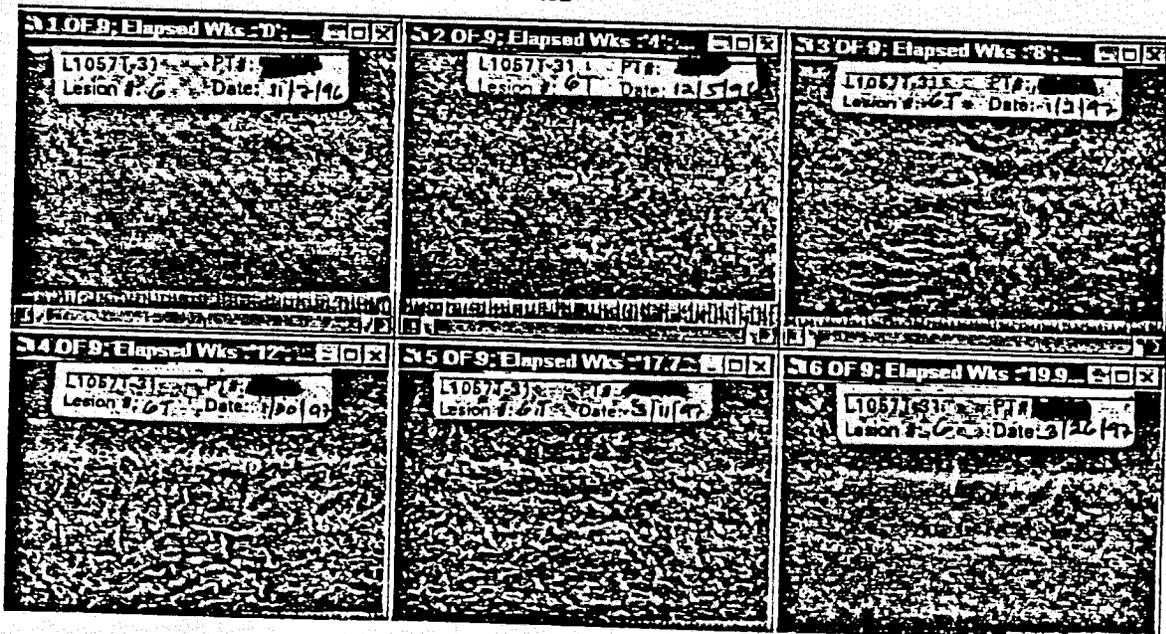
plaque at baseline

flat by wk 4

0 x 0 by wk 4

grade 2 erythema: wk 8

grade 1: 4 wks, 12-16 wks



SUMMARY of Patient :

- Modified ACTG: CCR
- Physician's global assessment: CCR
- Patient satisfaction with the KS lesions treated: very satisfied Cosmetically beneficial response: Yes

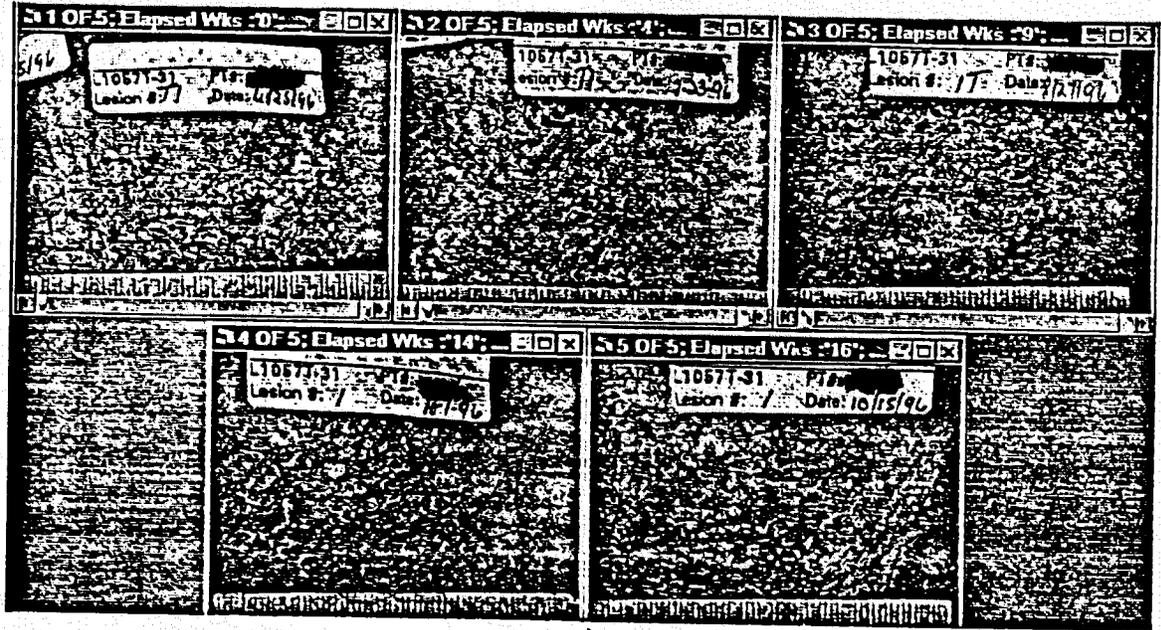
EXAMPLES OF RESPONSES TO PANRETIN NOT COSMETICALLY BENEFICIAL

The first example of a patient who did not have a beneficial response to panretin is case All 6 index lesions were nodular at baseline. By the modified ACTG criteria, a partial response was scored when all 6 of these lesions became plaques.

lesion #1:

nodular lesion at baseline  
plaque by 4 wks, according to the CRF

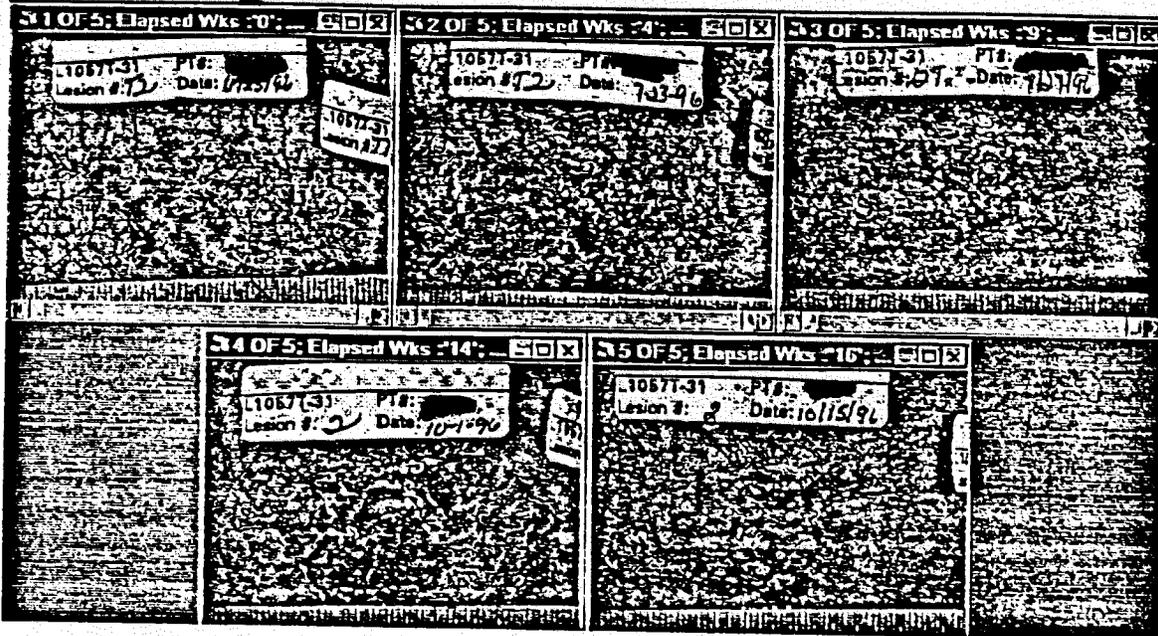
grade 2 erythema: wks 4 & 8  
grade 1 at 2 & 12 wks  
grade 0 erythema at 14 wks



lesion #2:

nodular lesion at baseline  
plaque by 4 wks

grade 2 erythema: wks 4 & 8  
grade 1 at 2 & 12 wks  
grade 0 erythema at 14 wks



lesion #3:

nodular lesion at baseline  
plaque by 4 wks

grade 2 erythema: wks 4 & 8  
grade 1 at 2 & 12 wks  
grade 0 erythema at 14 wks

