Activation of the Innate Immune Response as Therapy for CTCL

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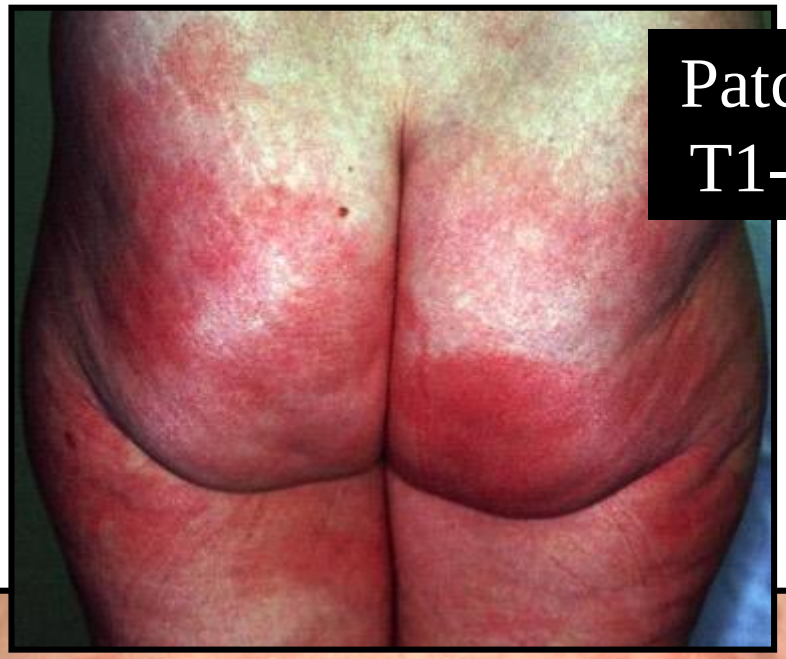
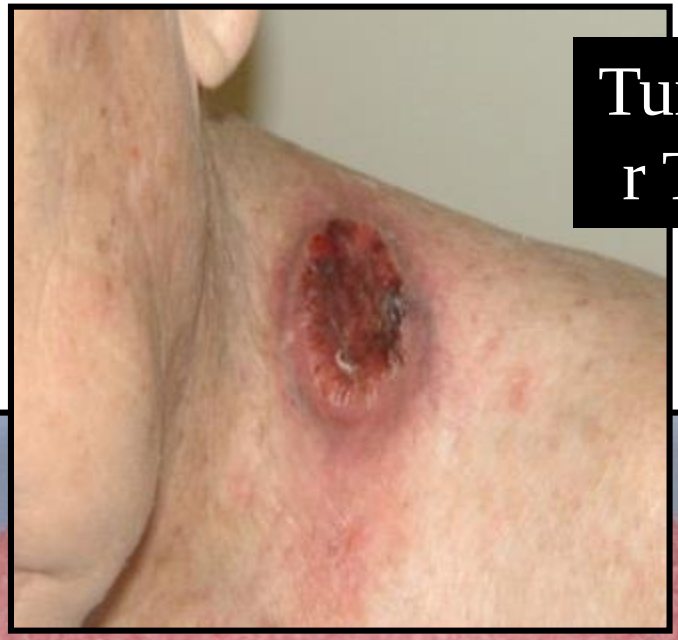
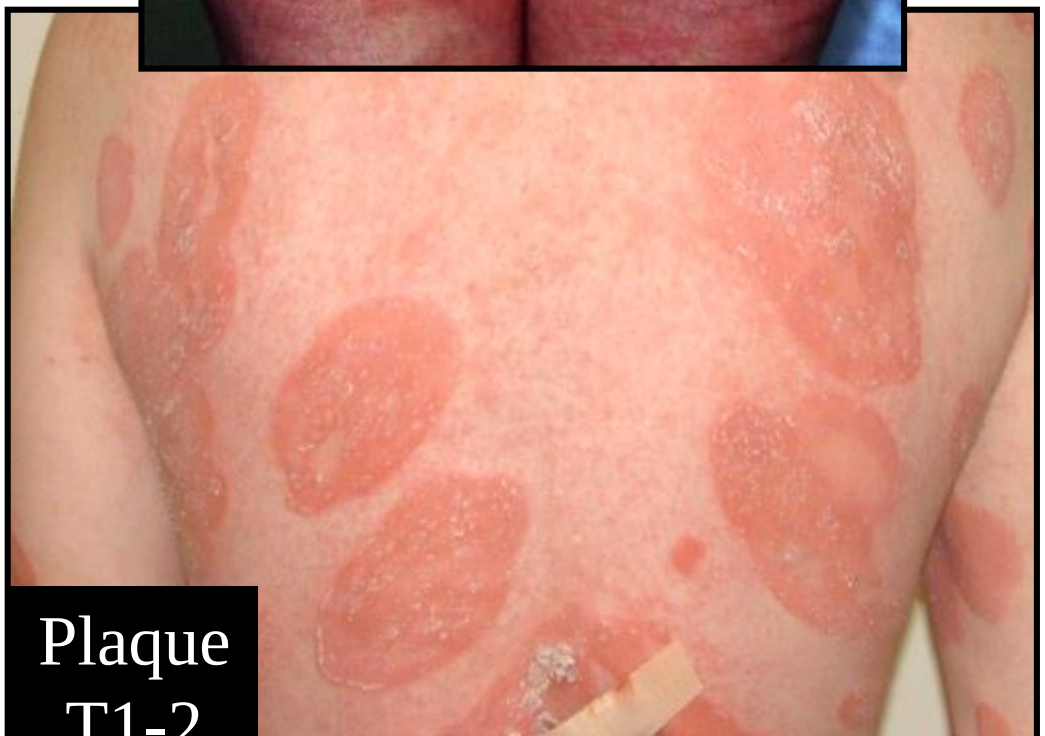
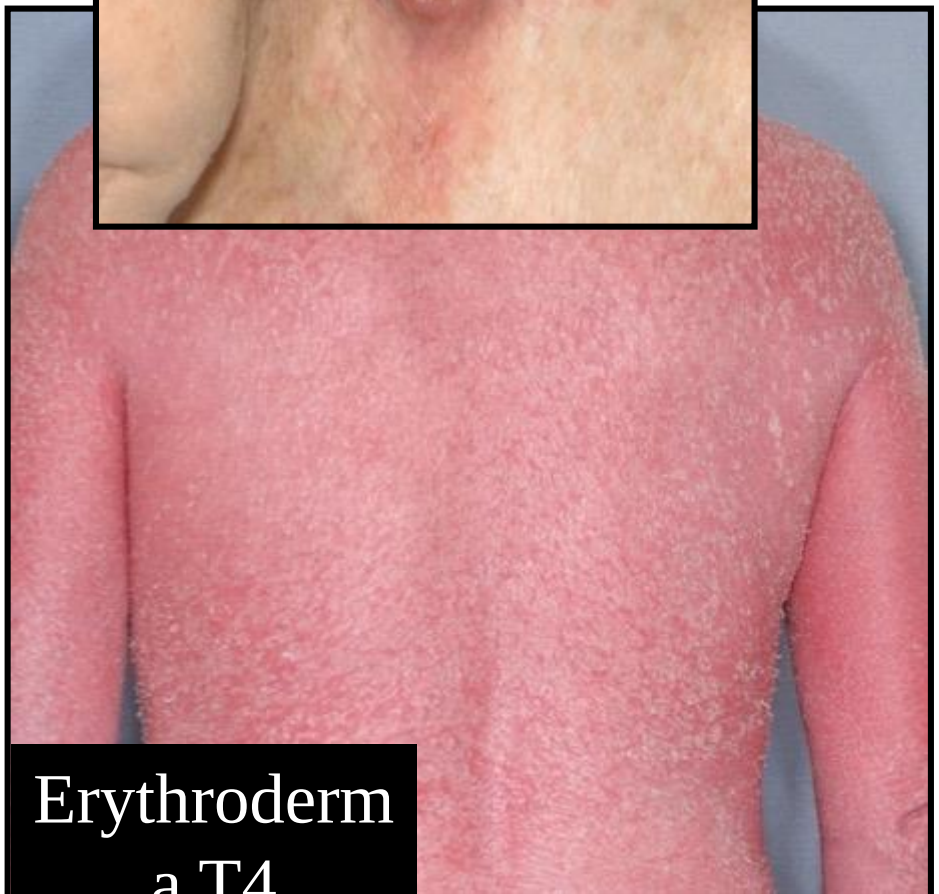
GREETINGS FROM PENN

Mycosis Fungoides
Treatment of varying skin manifestations

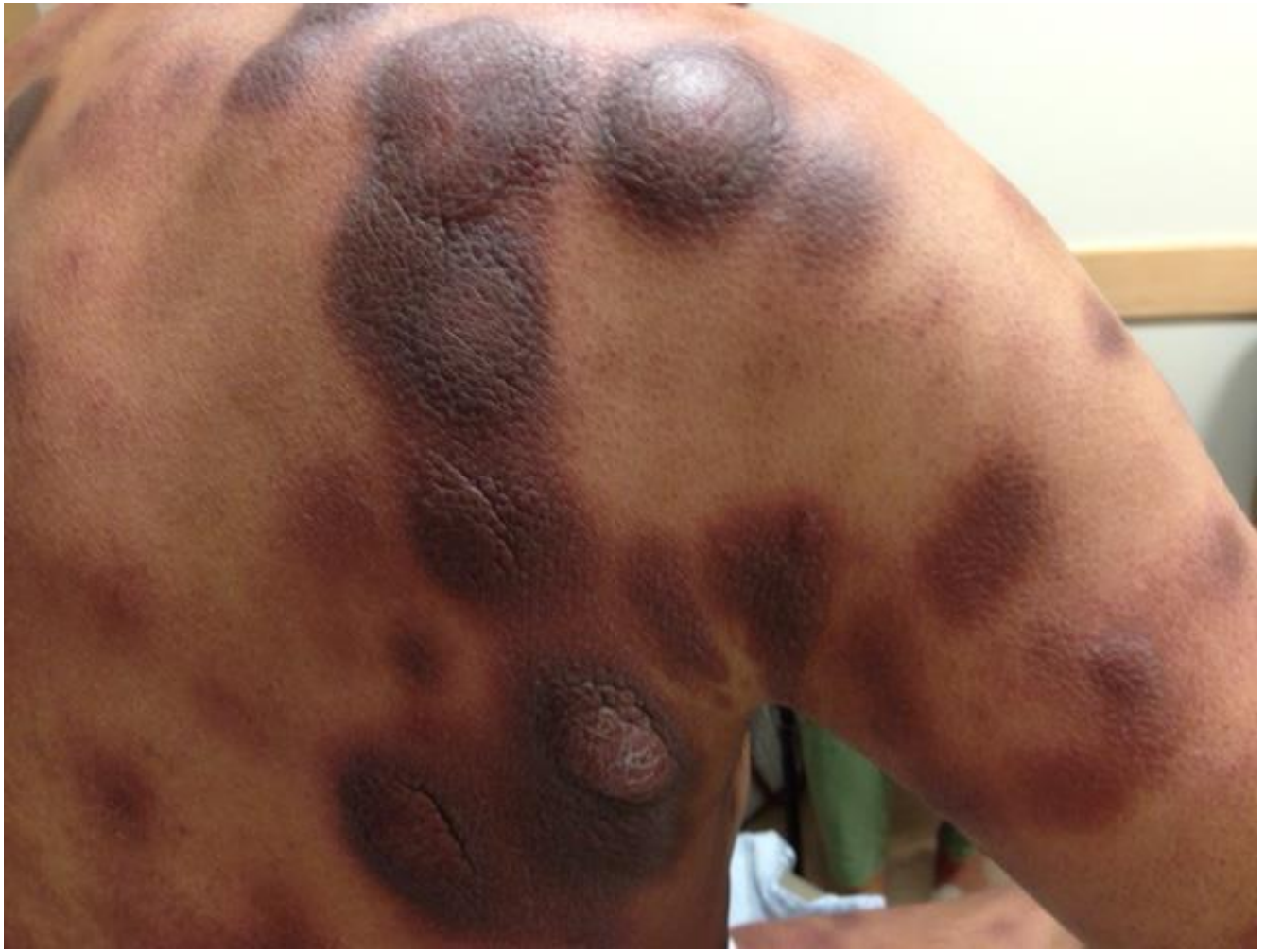




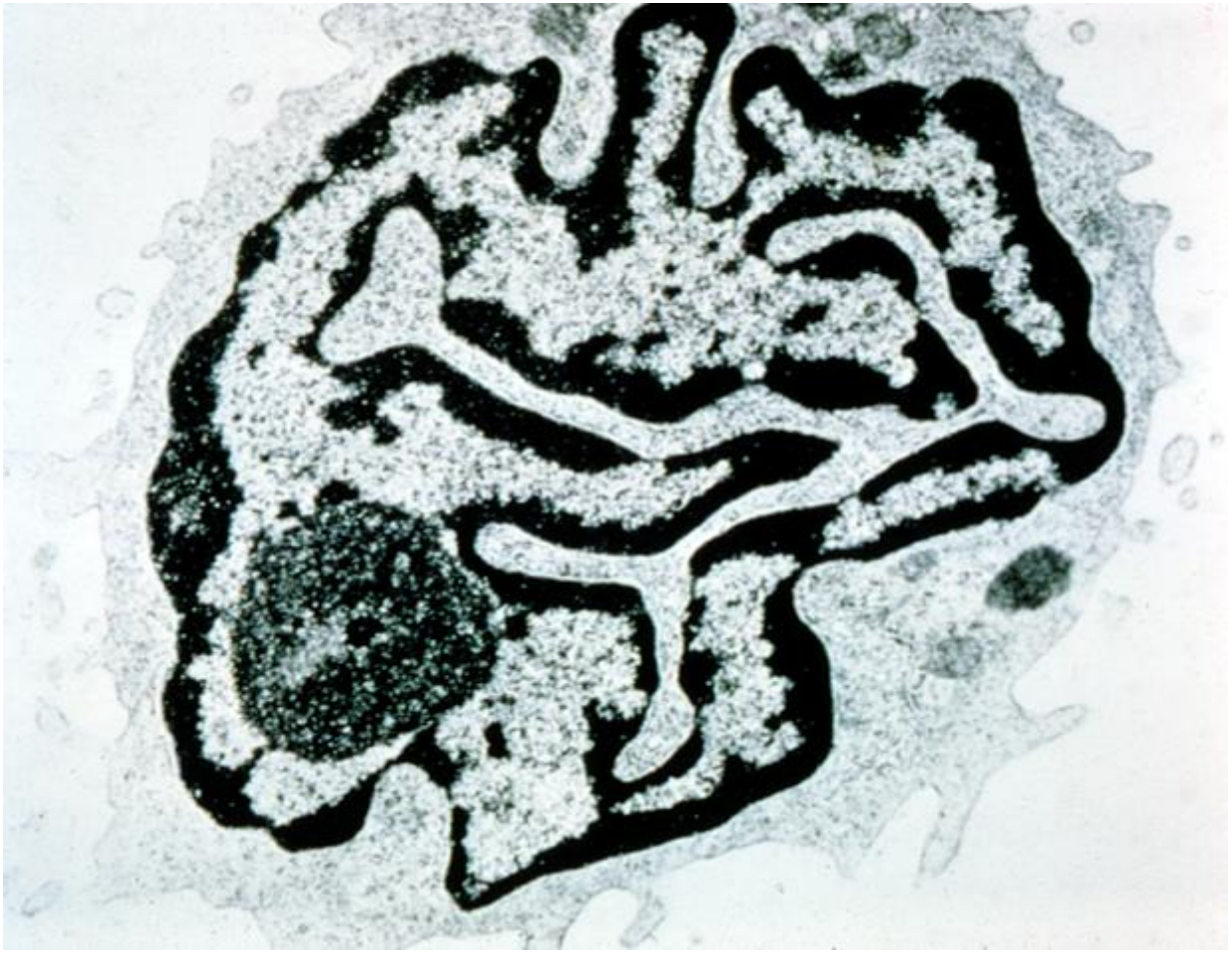




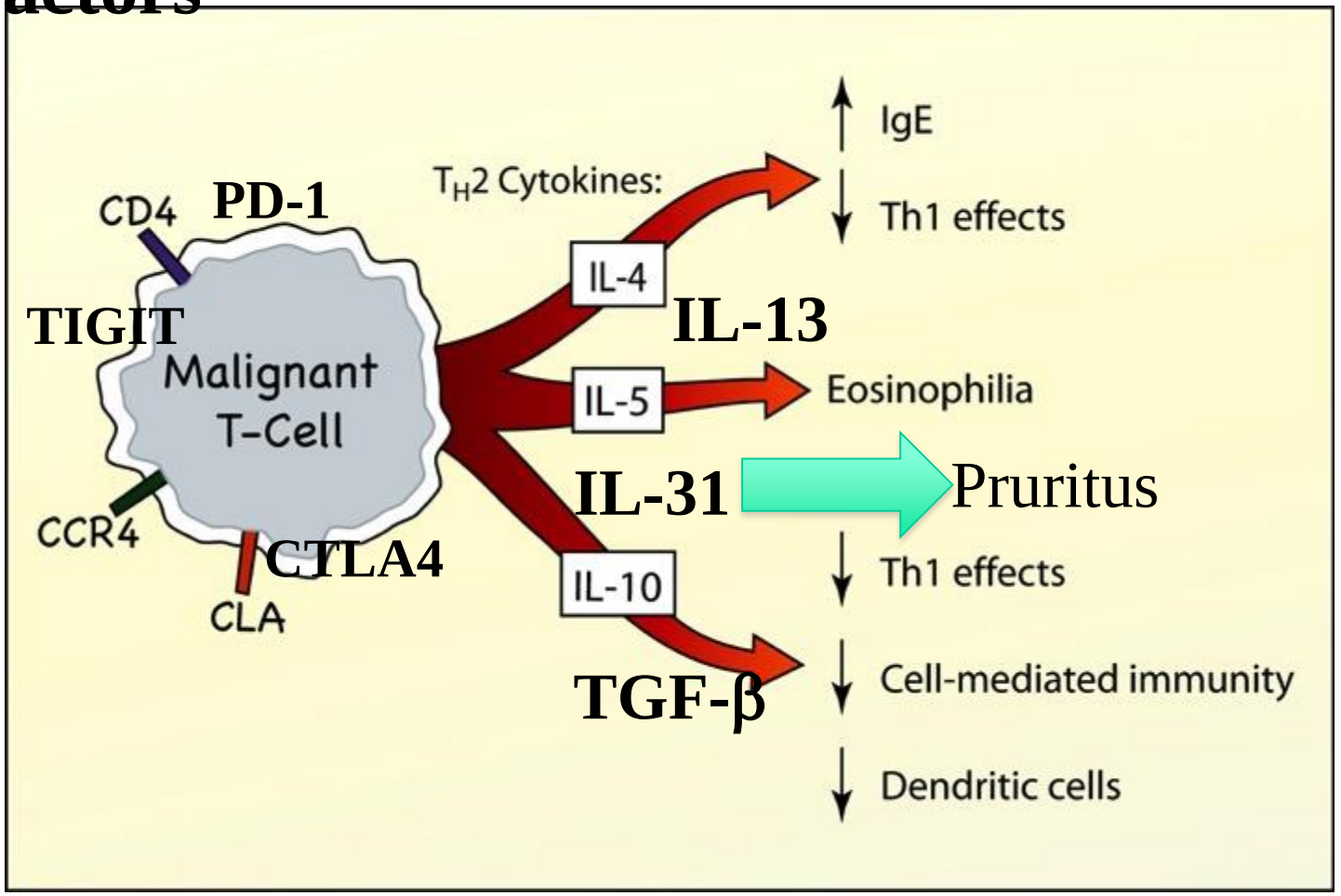
Refractory Tumor Stage CTCL



Sezary Cell



Sezary Cell: Receptors and Soluble Factors

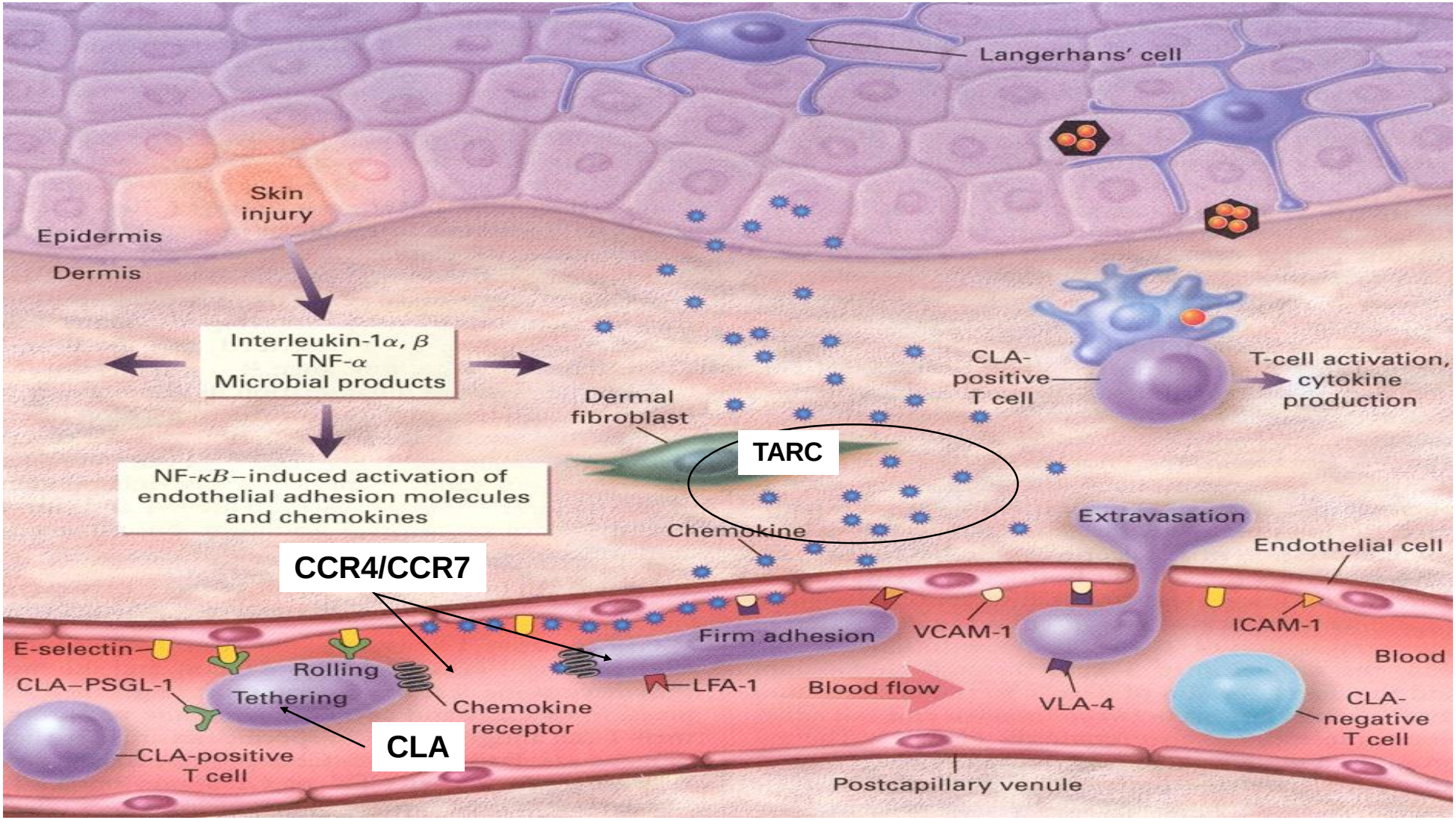


Anti-tumor Immunity Vs. Tumor Th2 and T-Reg Effects

Th1 immunity (anti-tumor)

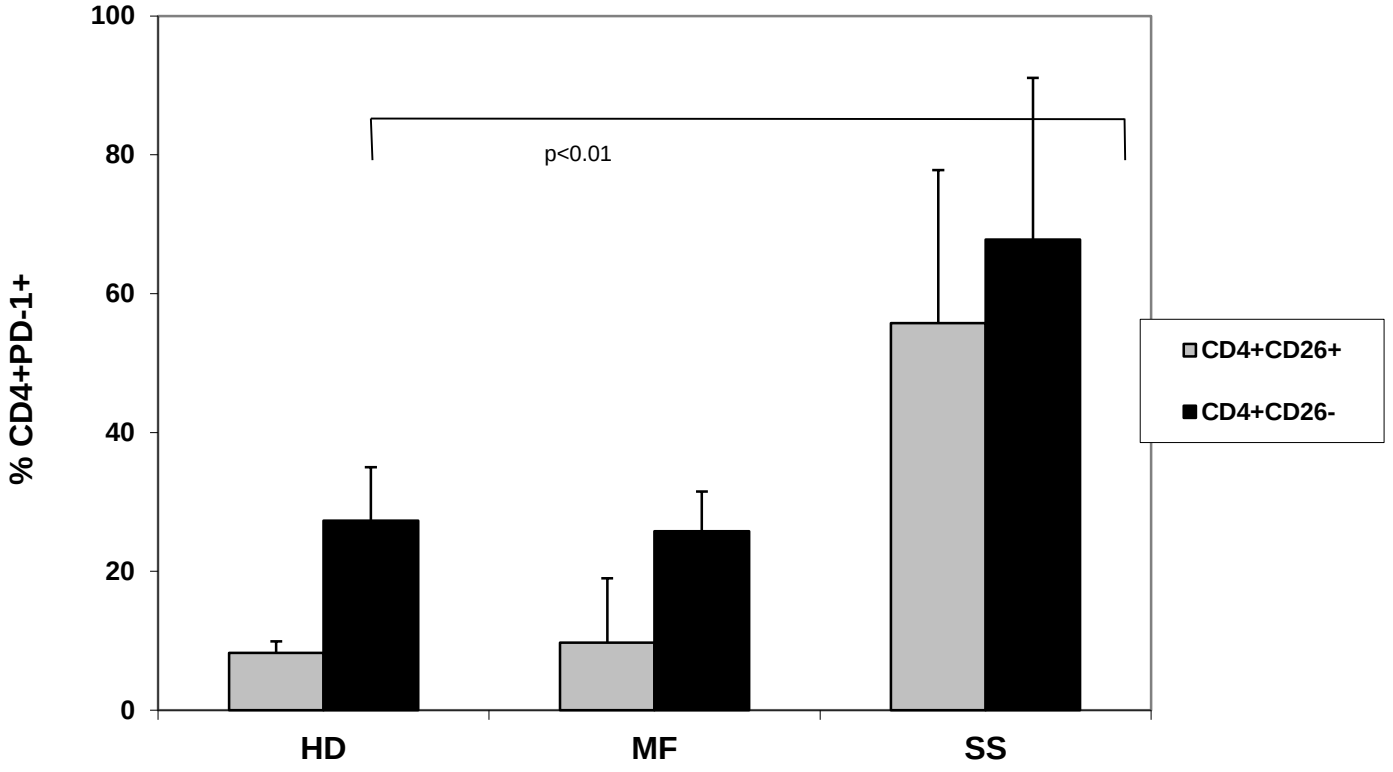
Tumor cells (Th2) and T-regulatory cells (allograft tolerance

Skin Trafficking T-Cells



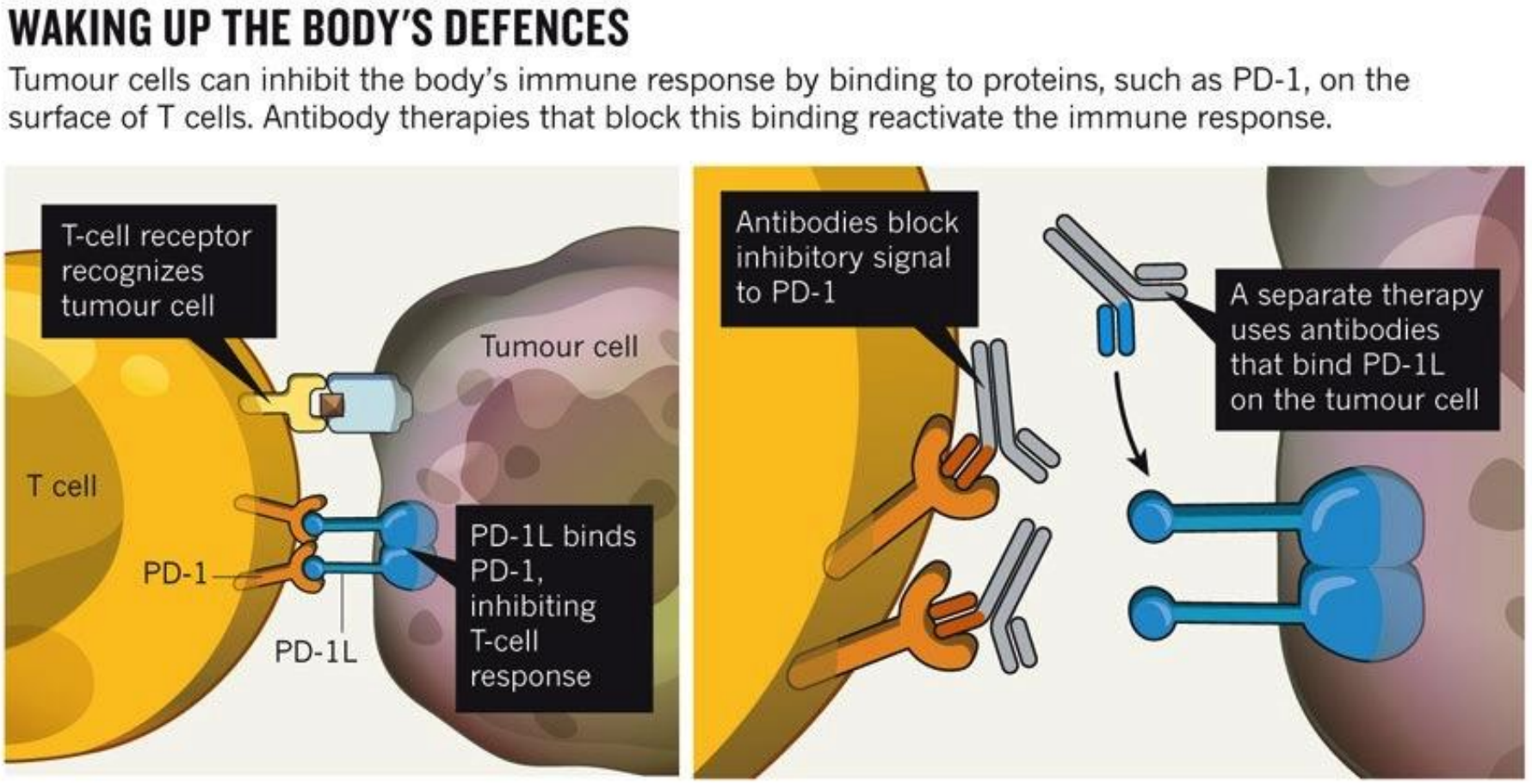
TS Kupper. Inflammatory Skin Diseases, T Cells, & Immunosurveillance. NEJM 2000 341:1817-28

Increased circulating PD-1+CD4+ T-cells in SS patients compared to MF patients or healthy volunteers



S. Samimi , et al

PD-1 Engagement Results in T-Cell "Anergy"



Cancer Immunotherapy Trials Network

NCI Protocol # CITN-10

A Phase 2 Study of MK-3475 (pembrolizumab) for the Treatment of Relapsed/Refractory MF/SS

Coordinating Center: M Cheever

CITN, Fred Hutchinson Cancer Research Center

Principal Investigator: H Kohrt

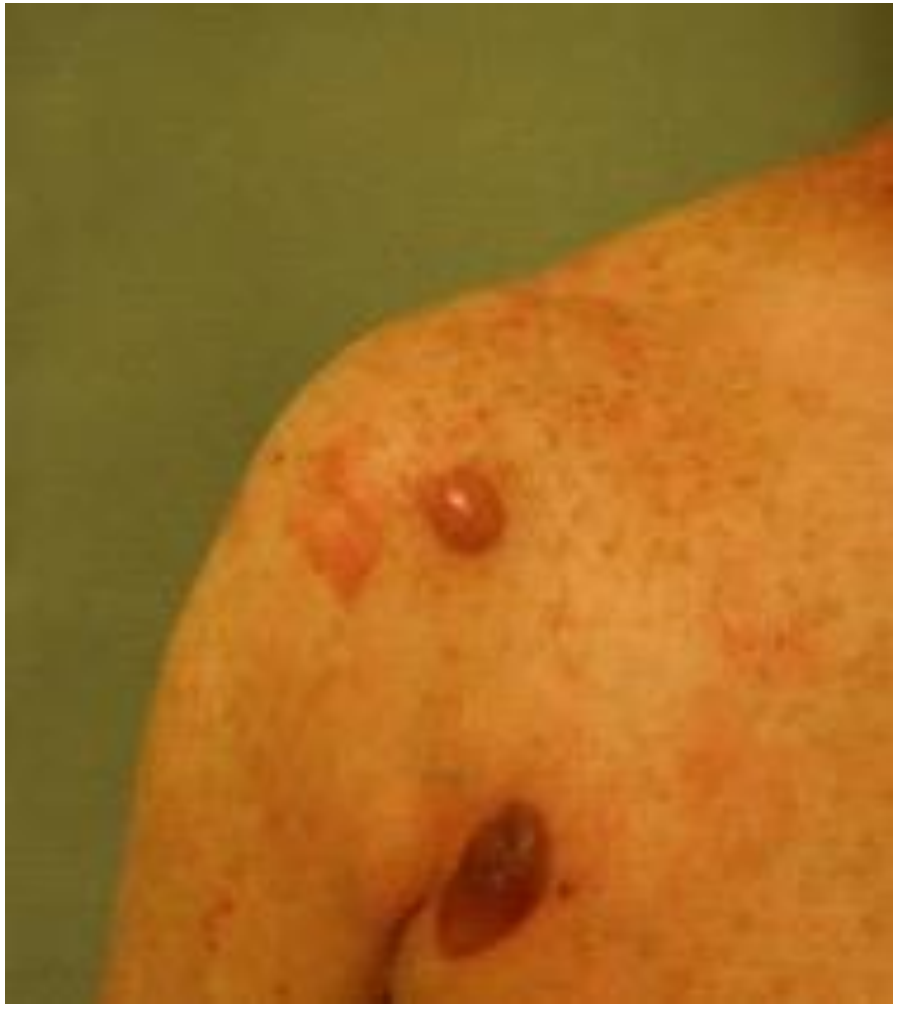
Y Kim (Co-PI)

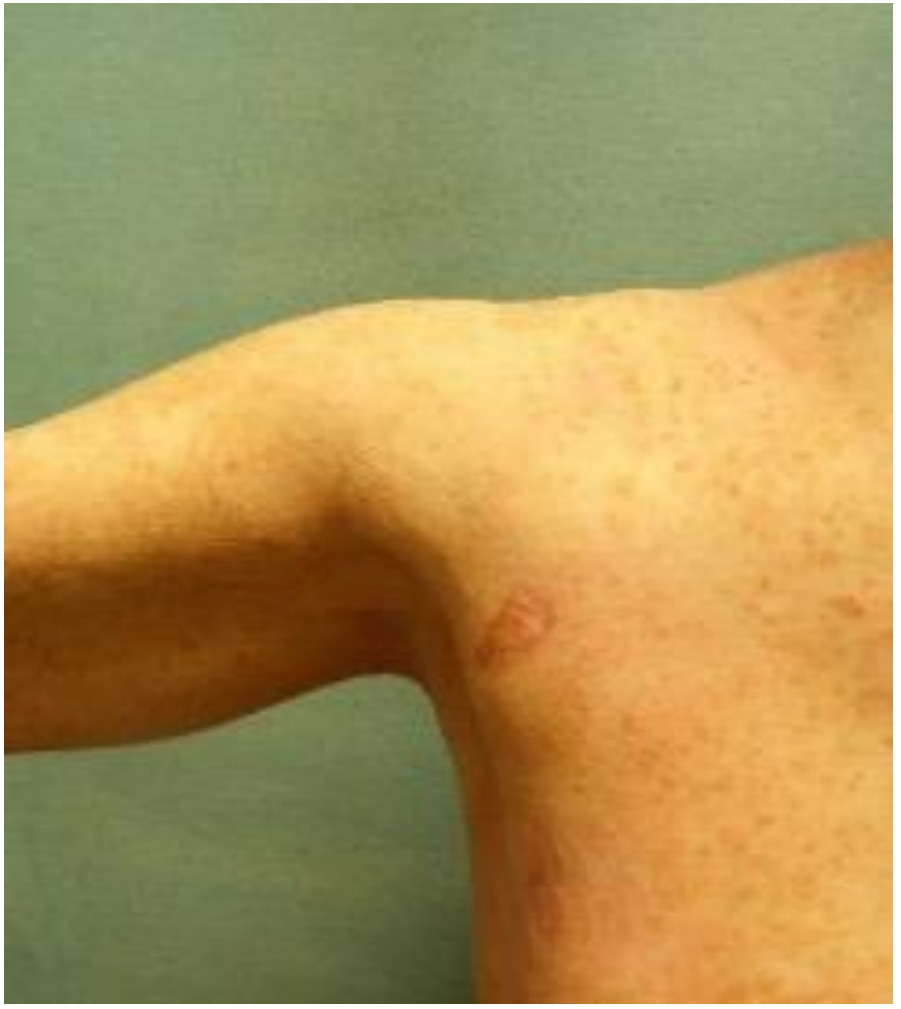
Stanford University SOM

Investigative sites/site PI:

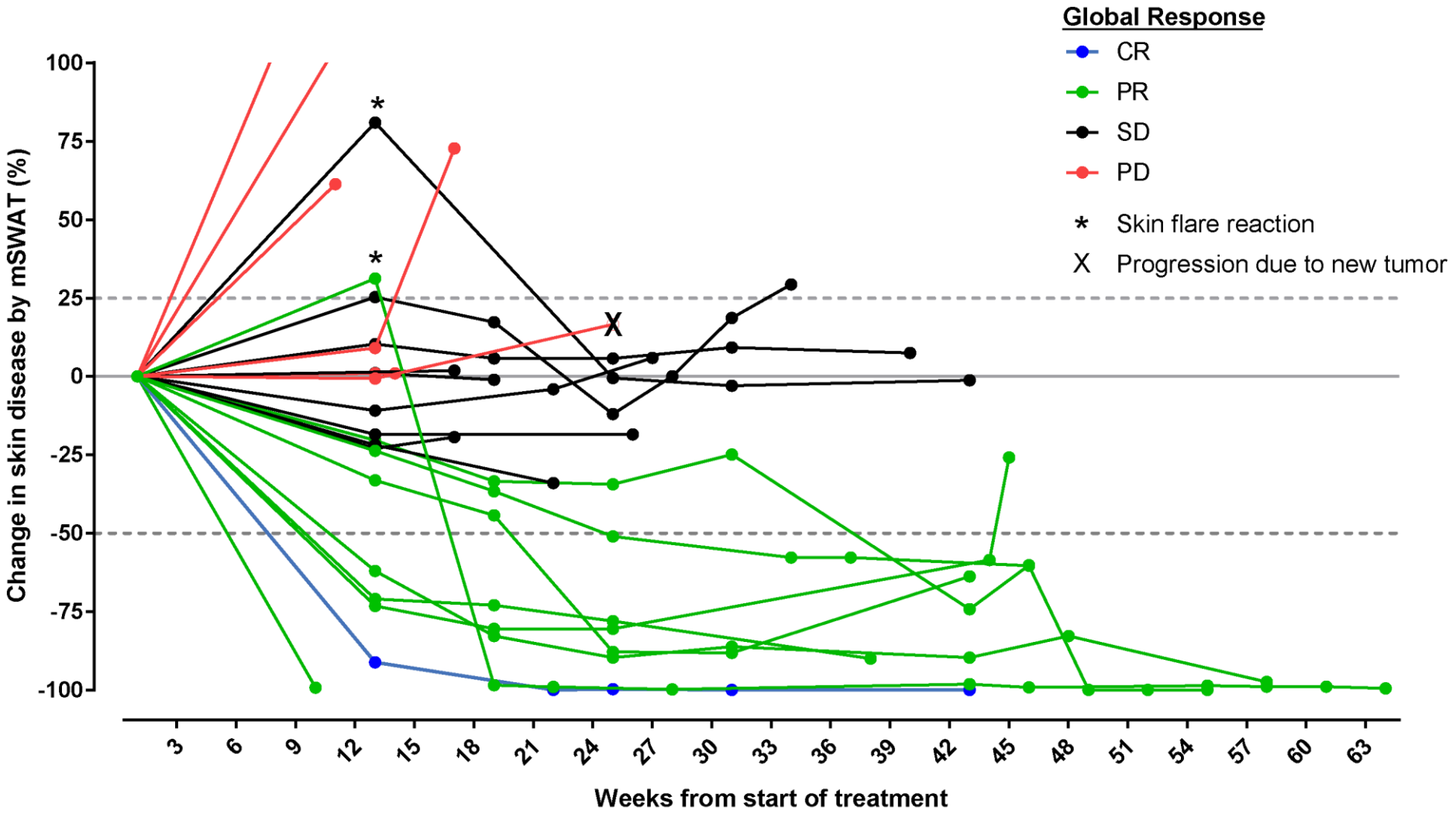
A Rook (U Penn), F Foss (Yale), PG Porcu (OSU), A Moskowitz (MSKCC), A Shustov (SCCA), L Sokol (Moffitt), S Shanbhag (Johns Hopkins)

Refractory Stage IIB: Response to Anti-PD-1 After Progression on 9 Previous Treatments





Change in Skin Disease from Baseline

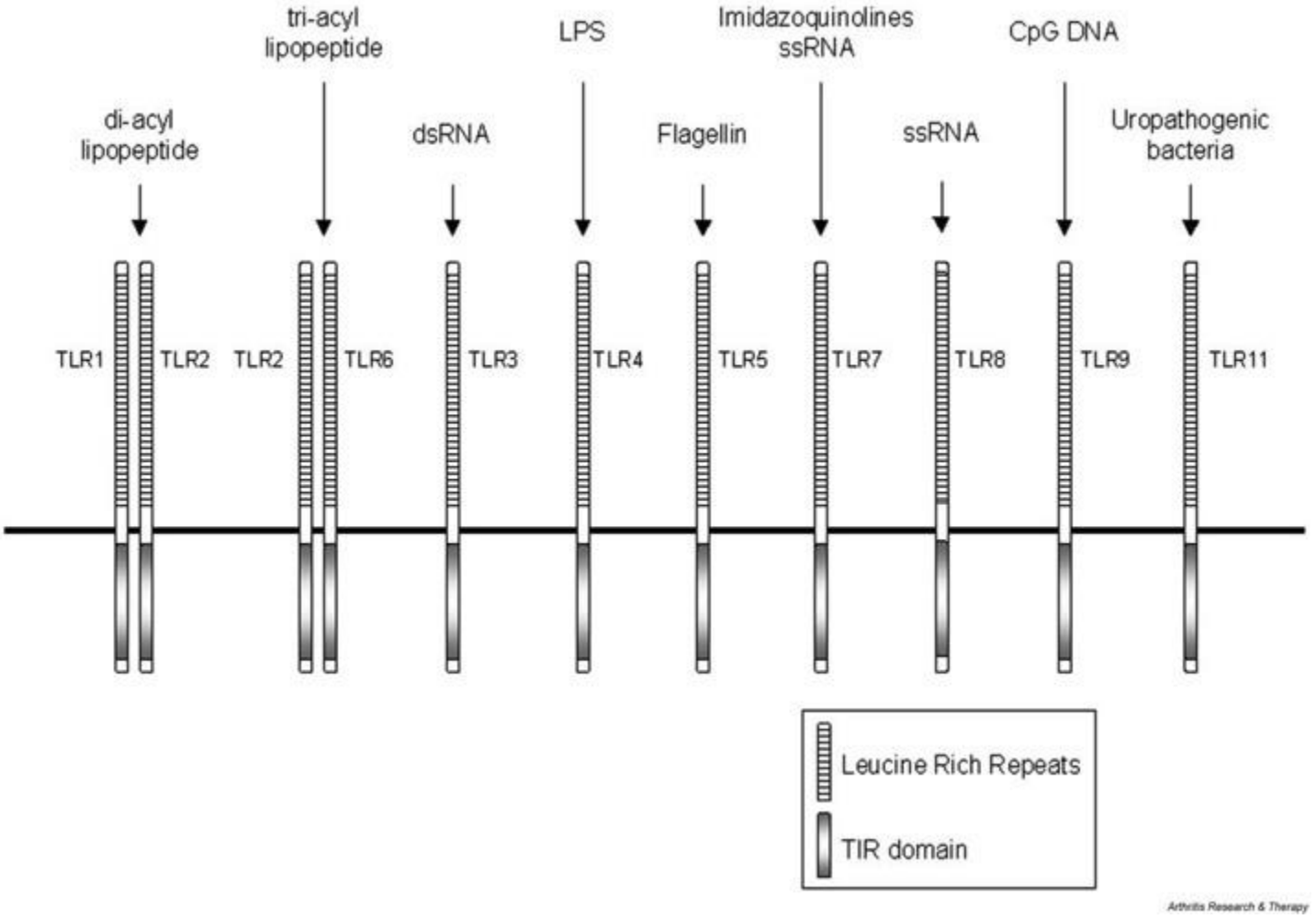


The Immune Response Plays a Critical Role in Control of Cutaneous T-Cell Lymphoma in Early Stage Disease, and, Likely, in Late Stage Disease

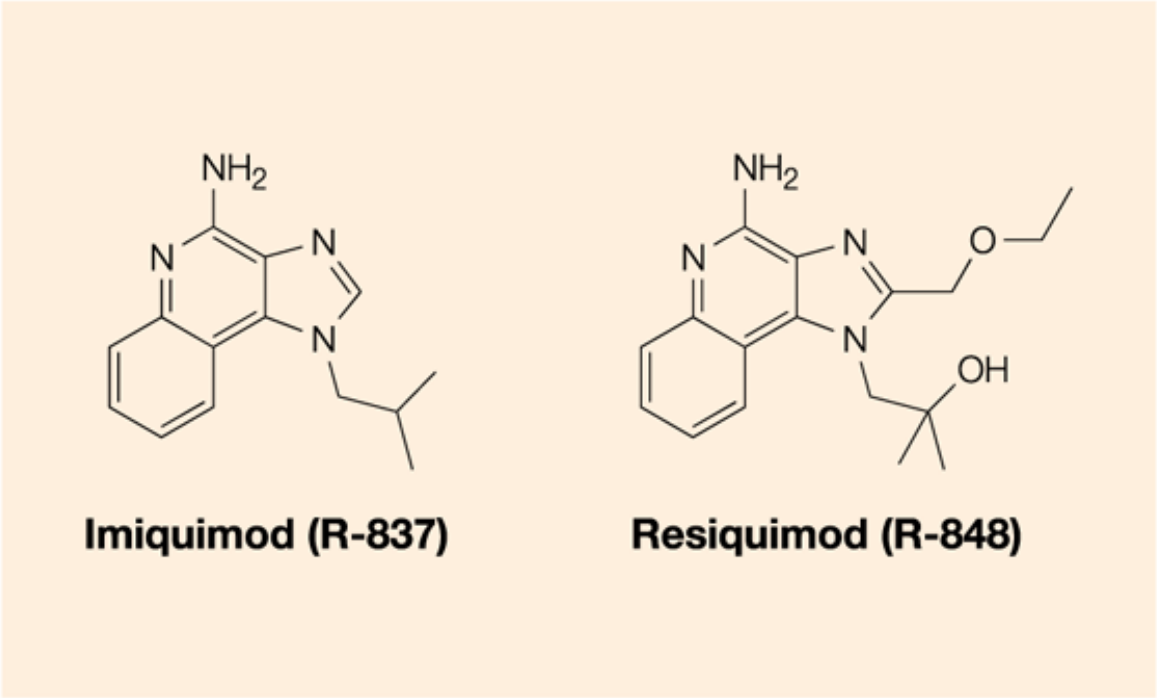
Products of the Innate Immune Response Are Active for CTCL

- **Interferon alpha (plasmacytoid DCs)**
- **Interleukin-12 (myeloid DCs)**
- **Interferon gamma (natural killer cells)**

Toll Like Receptors

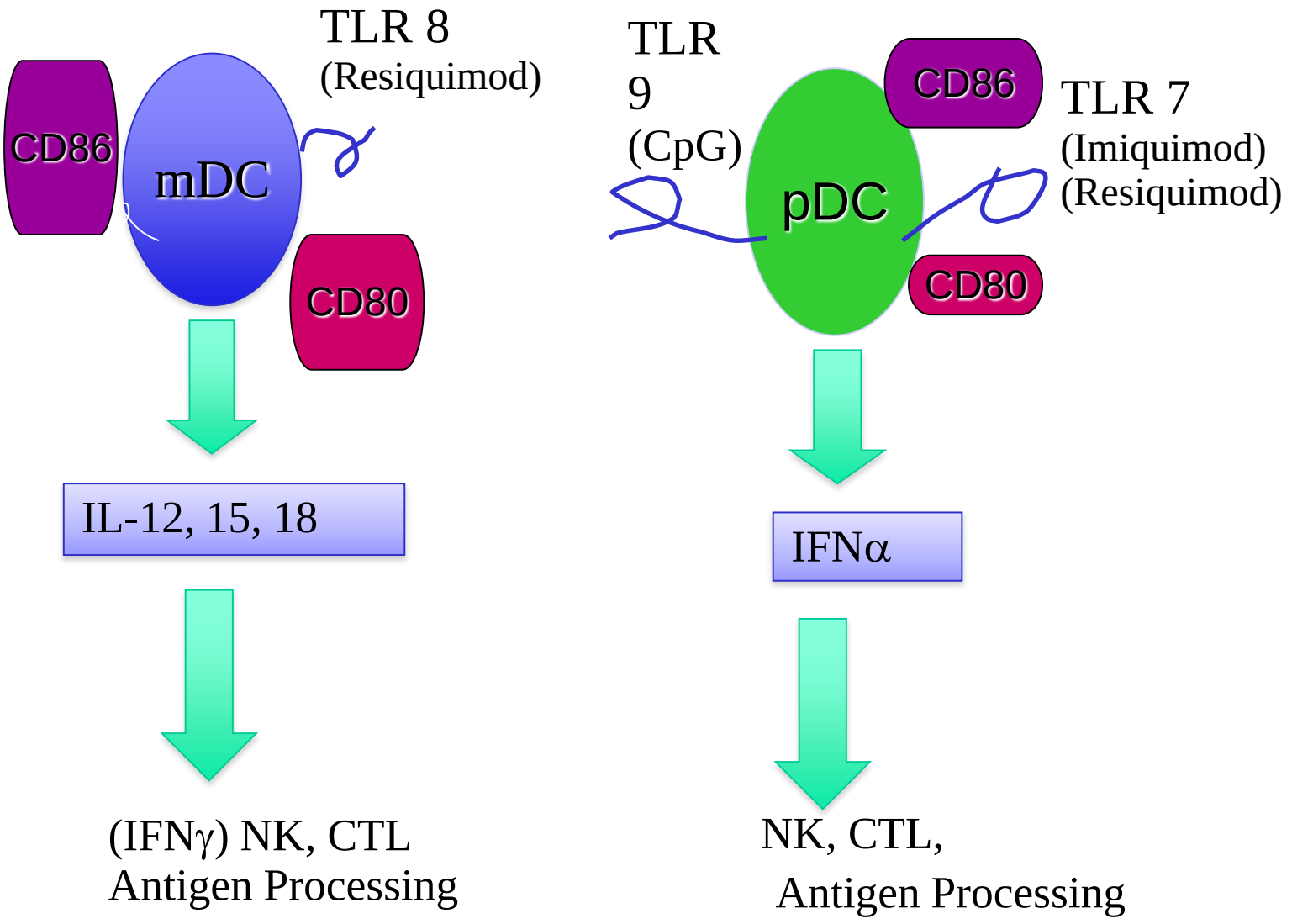


Imidazoquinolines Are Powerful TLR Agonists

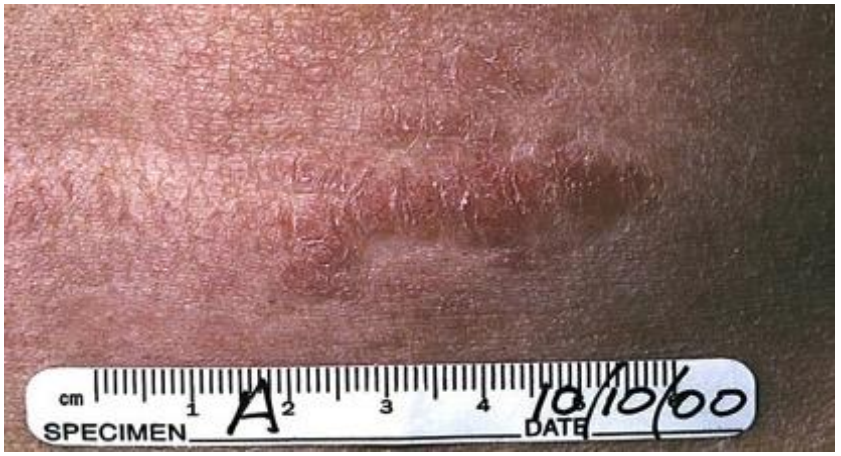


Nature Reviews | Drug Discovery

Toll Like Receptor Agonists Are Therapeutically Active for Cutaneous T-Cell Lymphoma

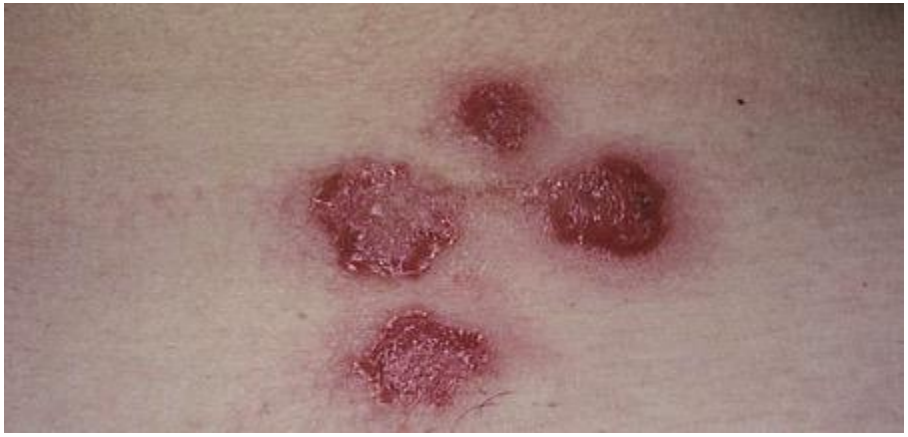


Site A before treatment measured 4.0 x 2.4 cm



Suchin, K. R. et al. Arch Dermatol 2002;138:1137-1139.

Site A after 2 months of therapy



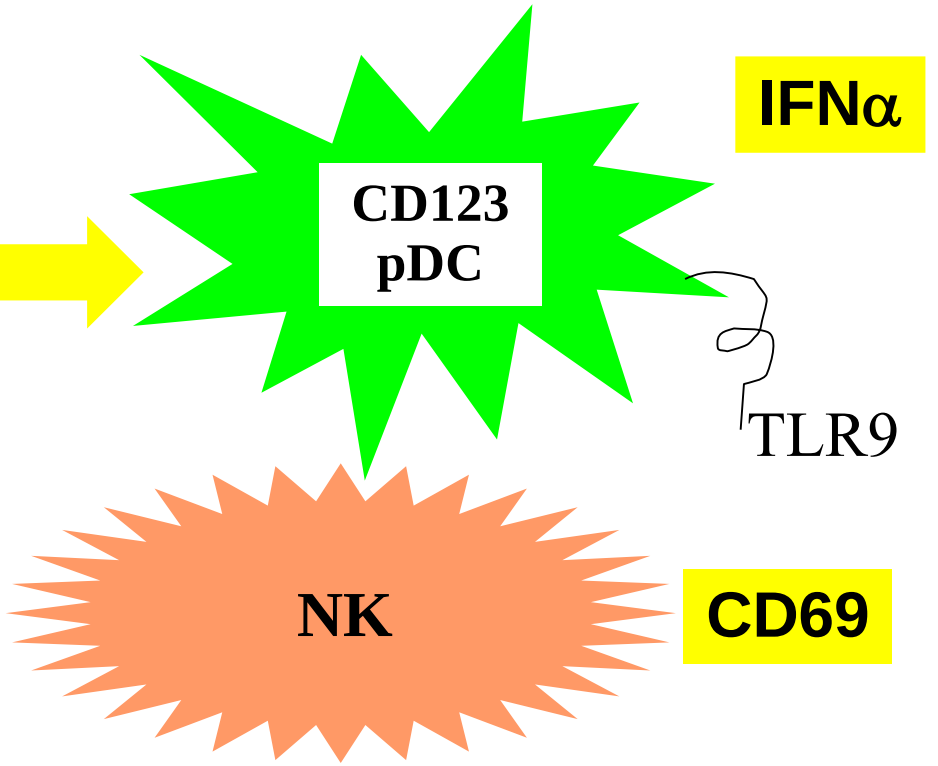
Suchin, K. R. et al. Arch Dermatol 2002;138:1137-1139.

Effects of Imiquimod

- **Low bioavailability**
- **Efficacy dependent upon duration of use**
- **Variable numbers of plasmacytoid DCs**
- **Topical steroids and other therapies can reduce pDCs**
- **Synergism *in vitro* with IFN gamma**

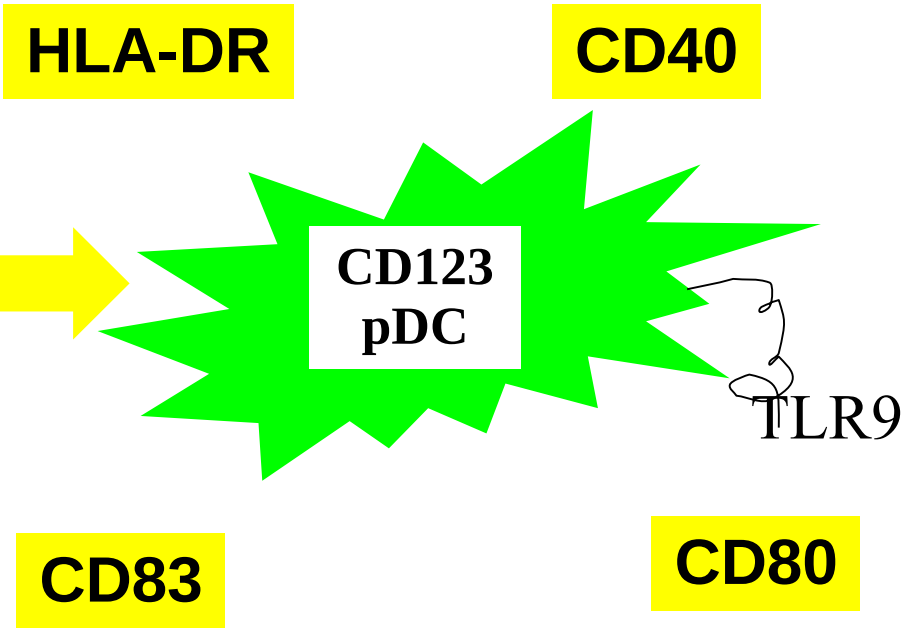
CpG A

CpG oligonucleotide 2216
(Phosphodiester bond)
Stimulates NK activity , IFNα production



CpG B

CpG oligonucleotide 2006
(Phosphorothioate bond)
Promotes survival and maturation



Phase I trial of a Toll-like receptor 9 agonist, PF-3512676 (CPG 7909), in patients with treatment-refractory, cutaneous T-cell lymphoma.

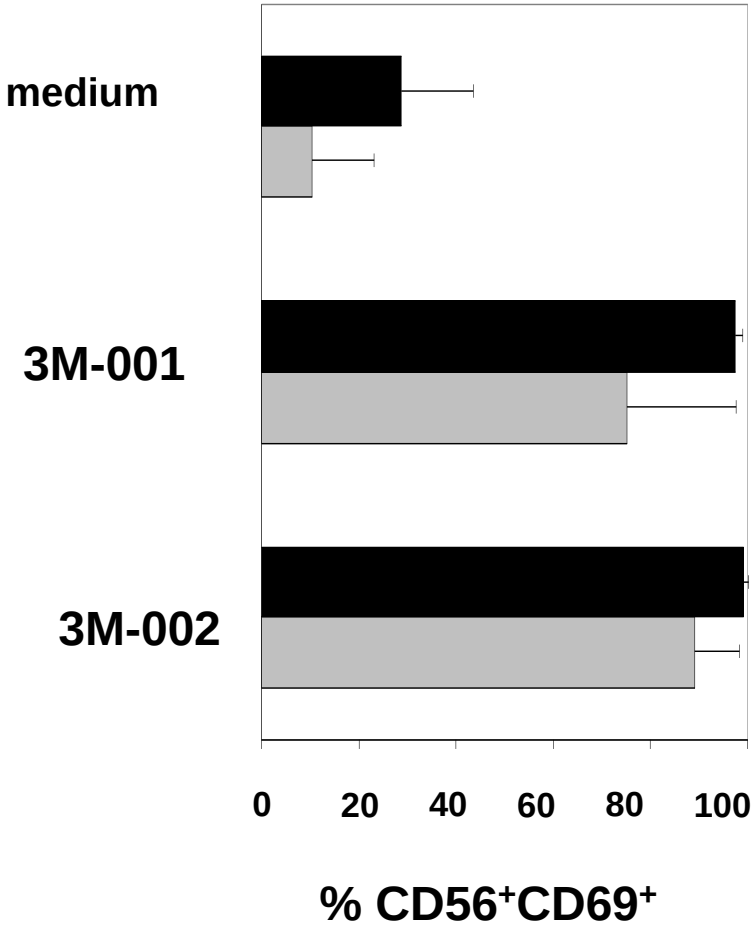
Kim YH1, Girardi M, Duvic M, Kuzel T, Link BK, Pinter-Brown L, Rook AH.

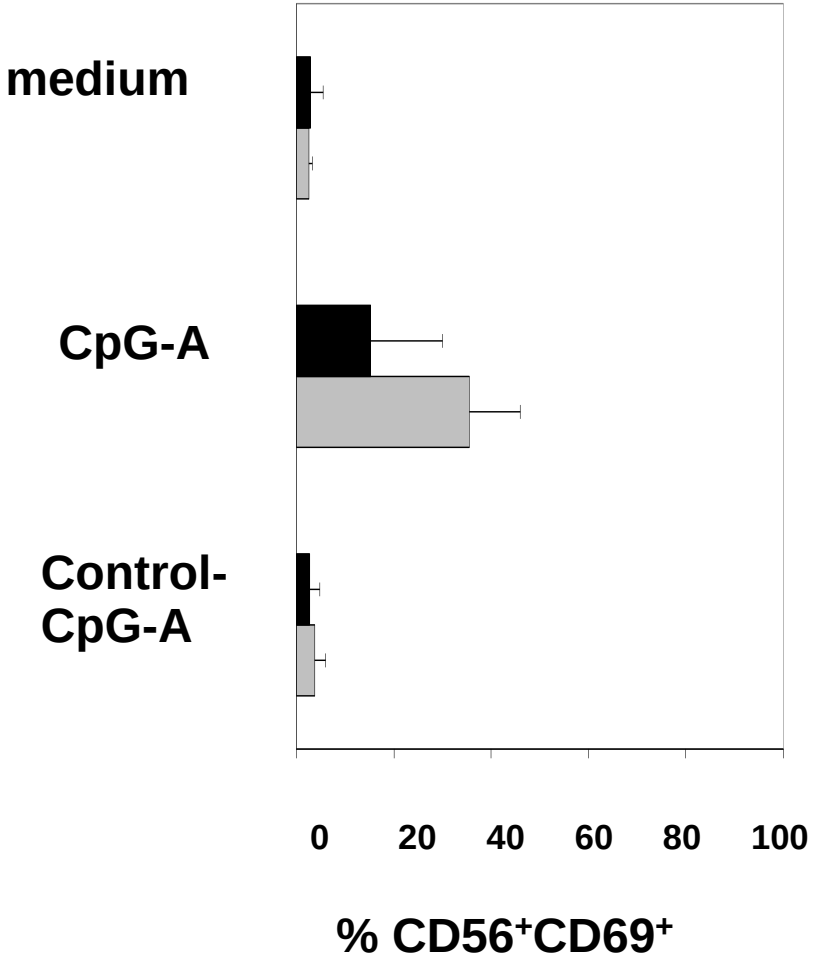
- **A phase I designed to test safety but not efficacy with weekly Sub Q injections**
- **Dose escalation trial with low concentrations not effective**
- **High concentrations produced responses even at stage IV**

Phase I Trial of CpG 7909

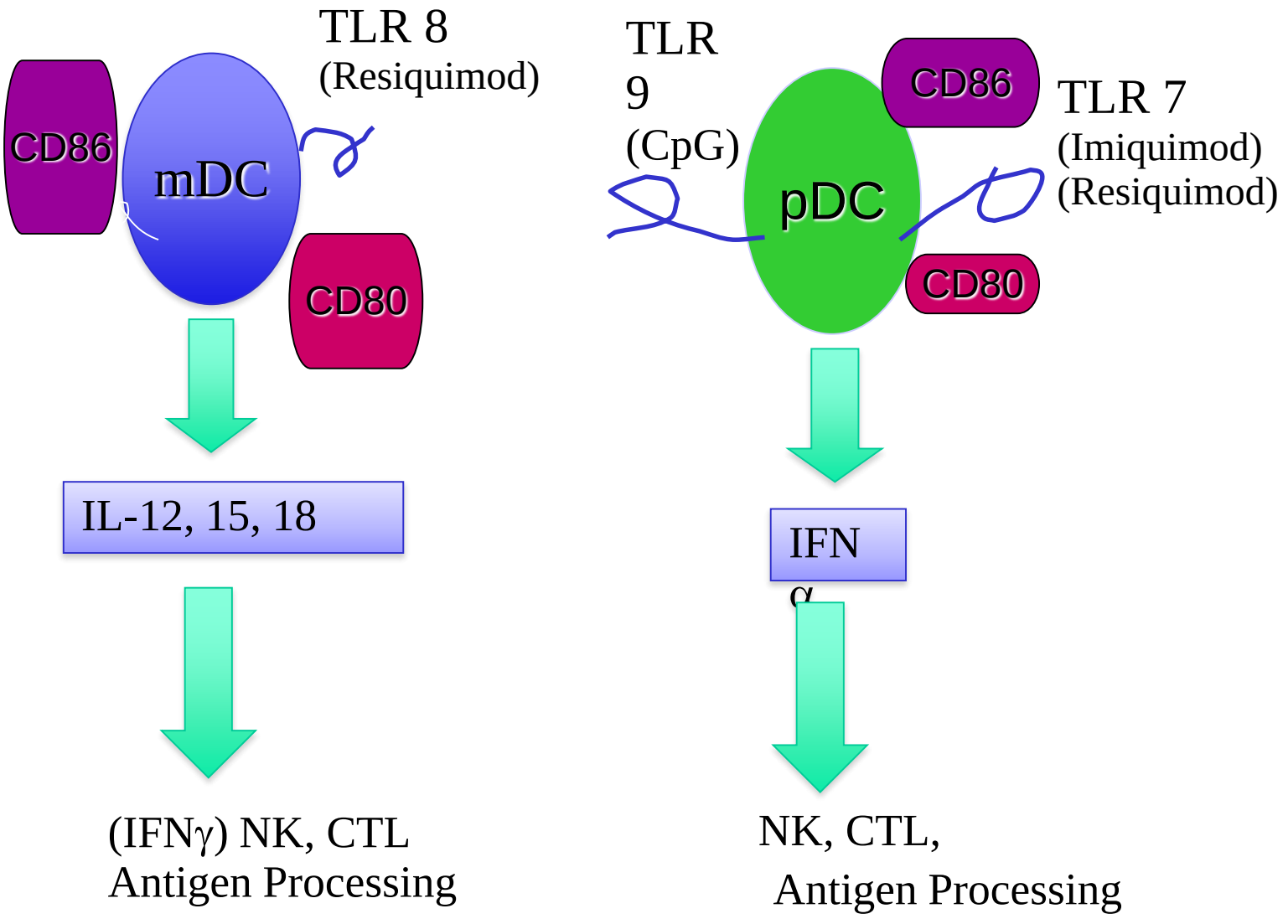
- **28 patients with highly refractory CTCL**
- **9 responses**
- **3 complete responses (including 2 with late stage disease)**
- **Significant activity in advanced CTCL:future trials are warranted**

3M-001 Is A Significantly More Potent Activator Of NK Cells Than Type A CpG





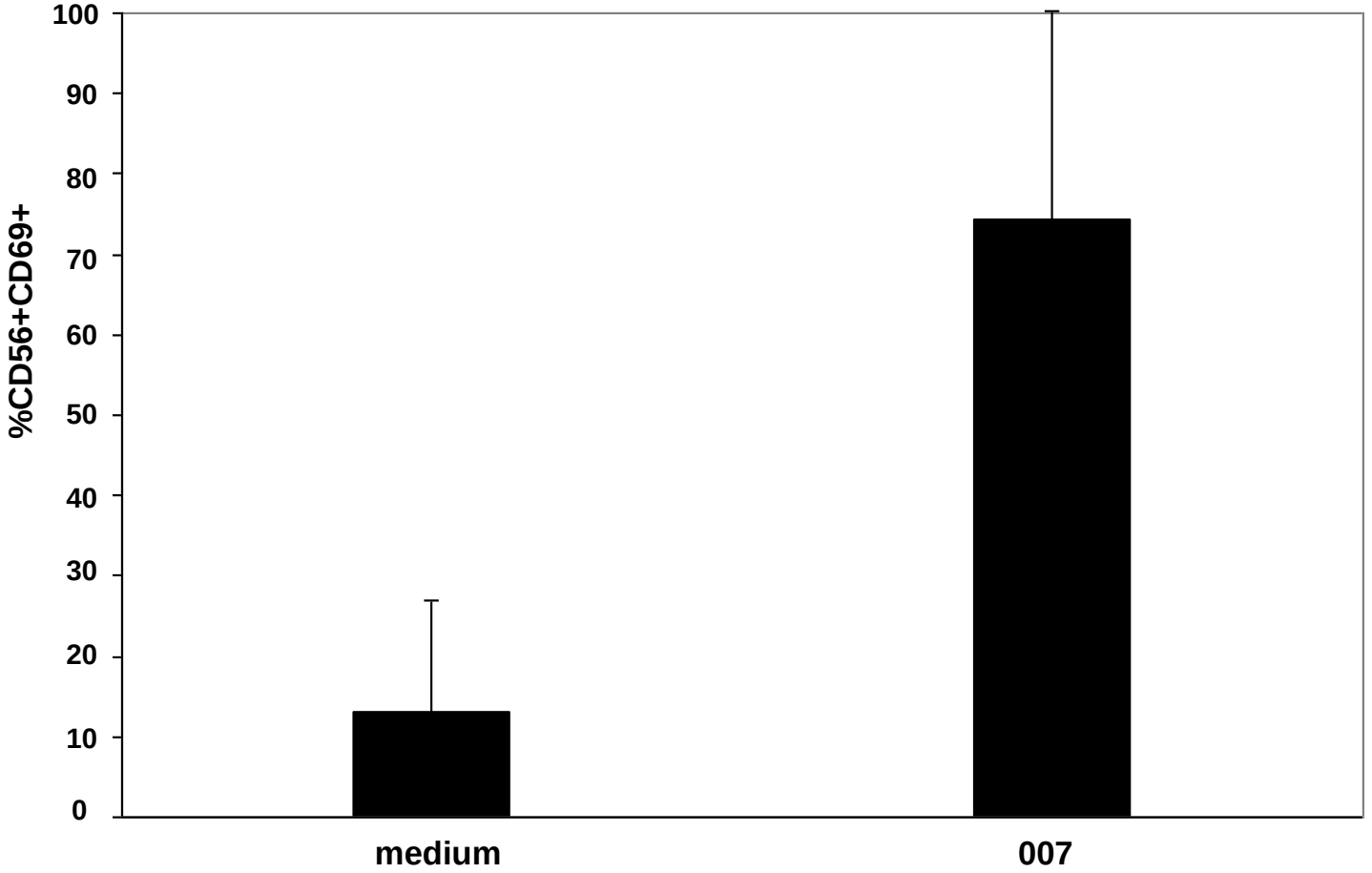
Toll Like Receptor Agonists Are Therapeutically Active for Cutaneous T-Cell Lymphoma

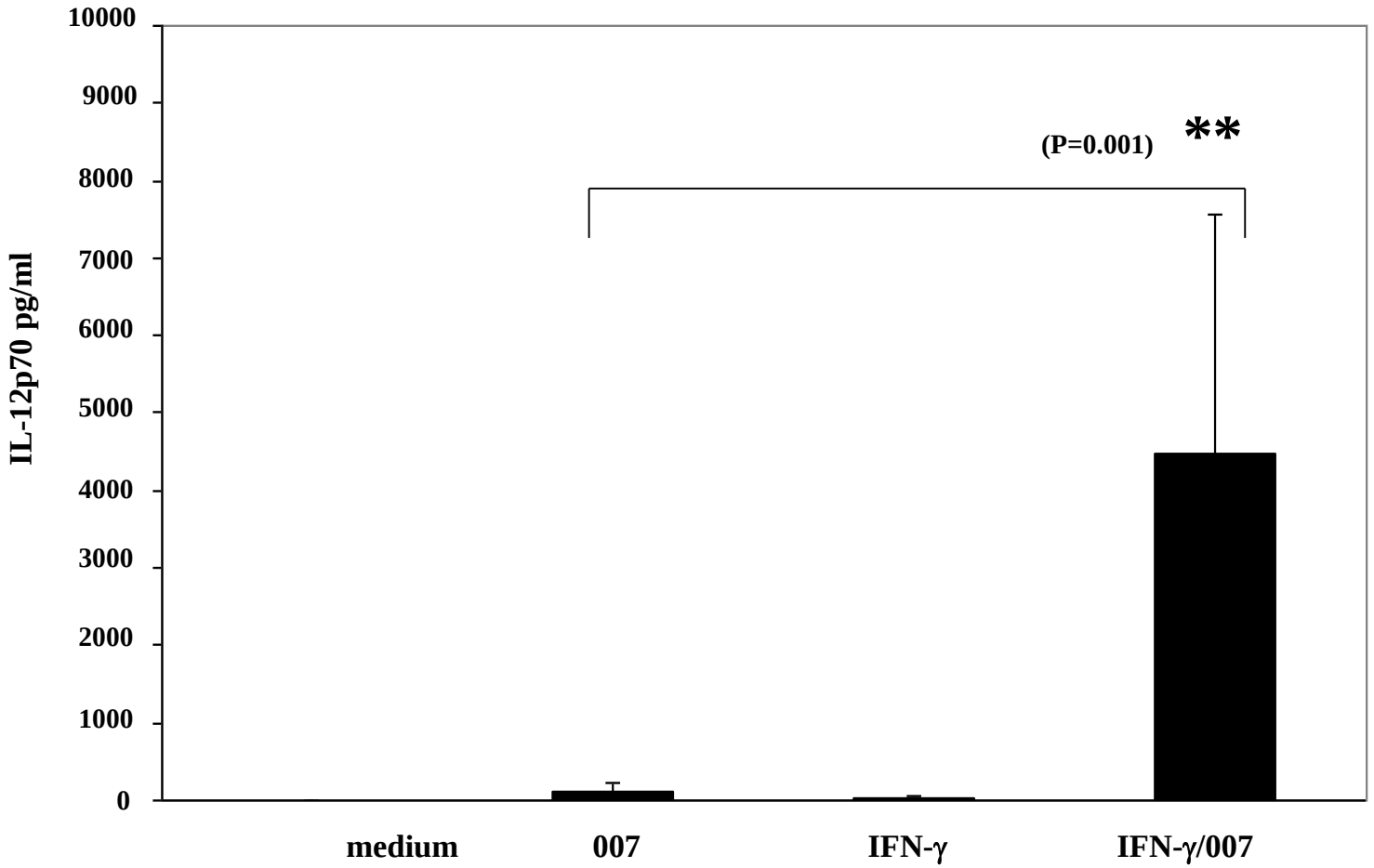


Resiquimod(007)

- **Combined TLR 7 & 8 agonist**
- **Bioavailability 10 times > imiquimod**
- **Potency up to 100 times > imiquimod**
- **1g application induces a systemic IFN alpha response**

Resiquimod Activates a High Percentage of NK Cells That are in the Blood of Sezary Syndrome Patients




10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
IL-12p70 pg/ml
(P=0.001)
**
medium
007
IFN-γ
IFN-γ/007

N=8

Resiquimod Protocol

- **Stage IA, IB, IIA cutaneous T-cell lymphoma**
- **Two cohorts: 0.06% and 0.03% topical gel**
- **Commence three times weekly and increase or decrease every 2 weeks based upon tolerance**
- **Treat for 8 weeks; 4 week hiatus; treat for 8 weeks; 4 week hiatus**
- **Those with partial response can restart drug for an additional 12 weeks**
- **Safety assessments every two weeks for AEs and SAEs and CBC and CMP**
- **Efficacy assessments every 4 weeks: Skin scores including SWAT, CAILS as well as Global Assessment and lesion photography**
- **Skin scores and photographs reviewed by CTCL expert (Dr. Ellen Kim)**
- **Data and safety monitoring committee evaluates data after each set of 4 patients**

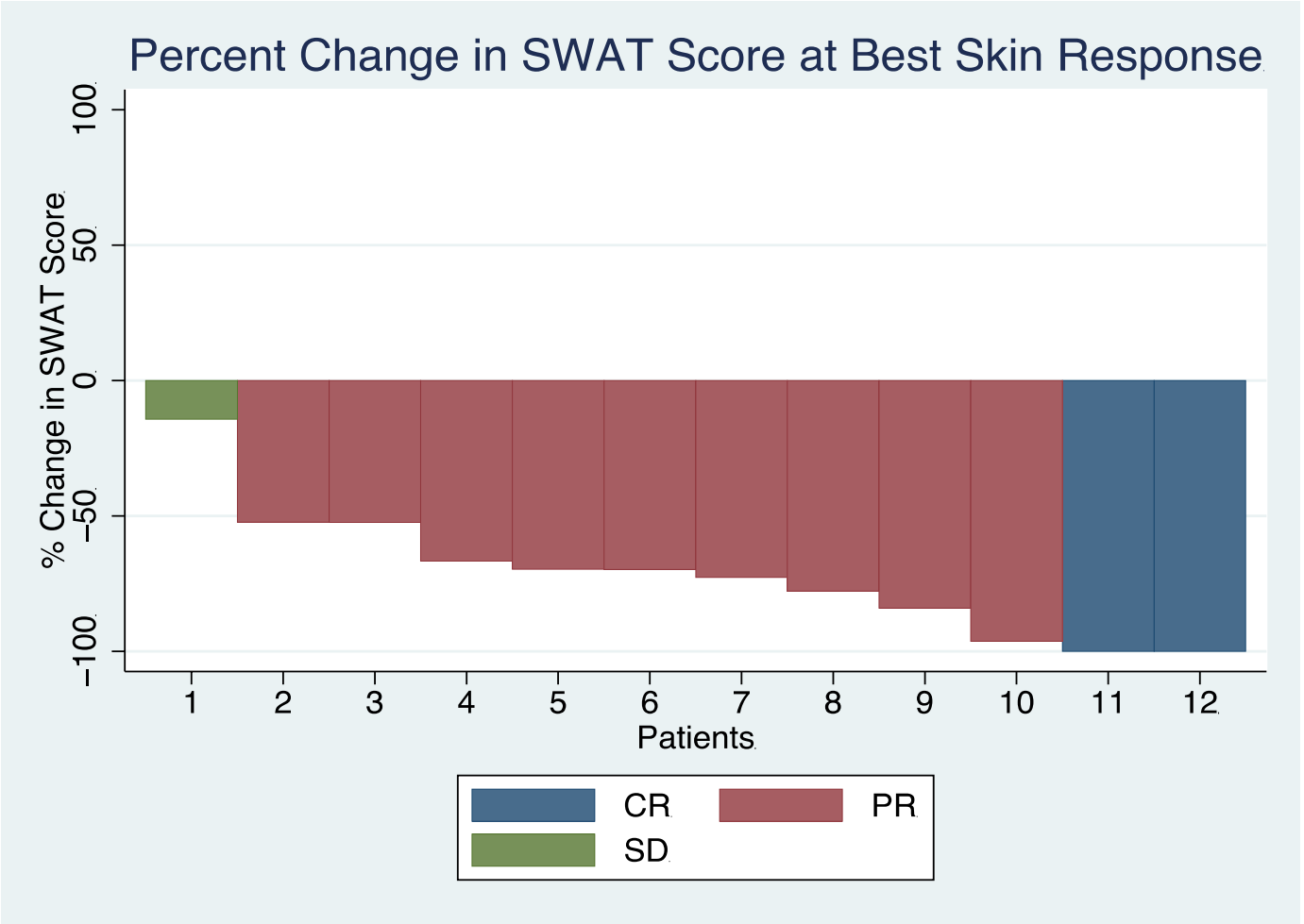
Patient Characteristics

- **1 Stage IA**
- **10 Stage IB (2 on treatment for only two weeks)**
- **1 Stage IIA**

(8 on 0.06% with 4 on 0.03%)

- **Median number of previous treatments 6**
- **Range 2-11 treatments**

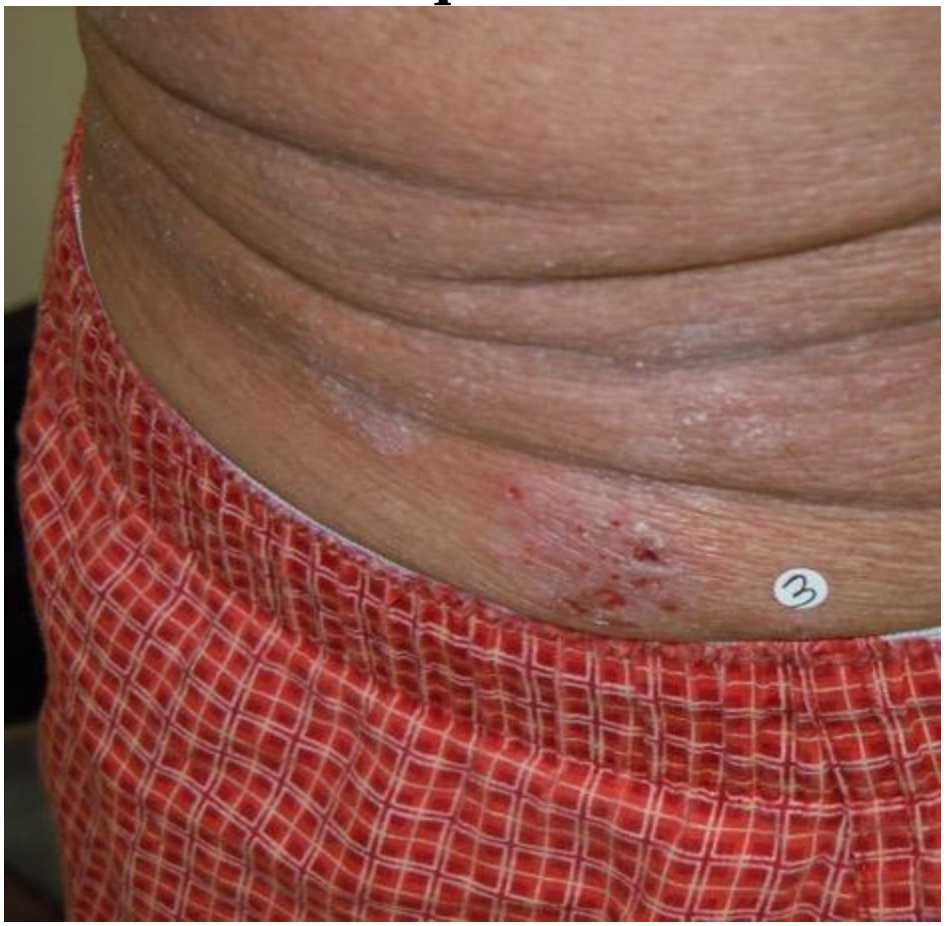
Resiquimod Phase I Trial Responses



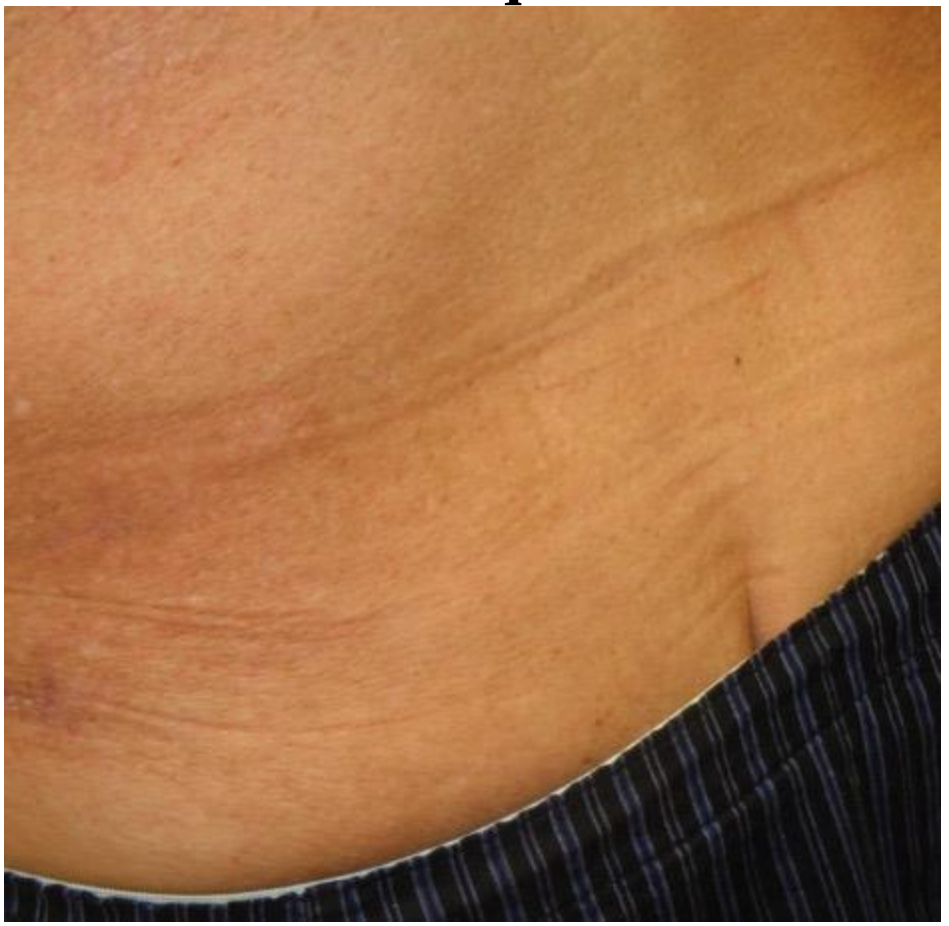
Rook, et al. Blood. Sept 17, 2015

Clinical Response to Resiquimod

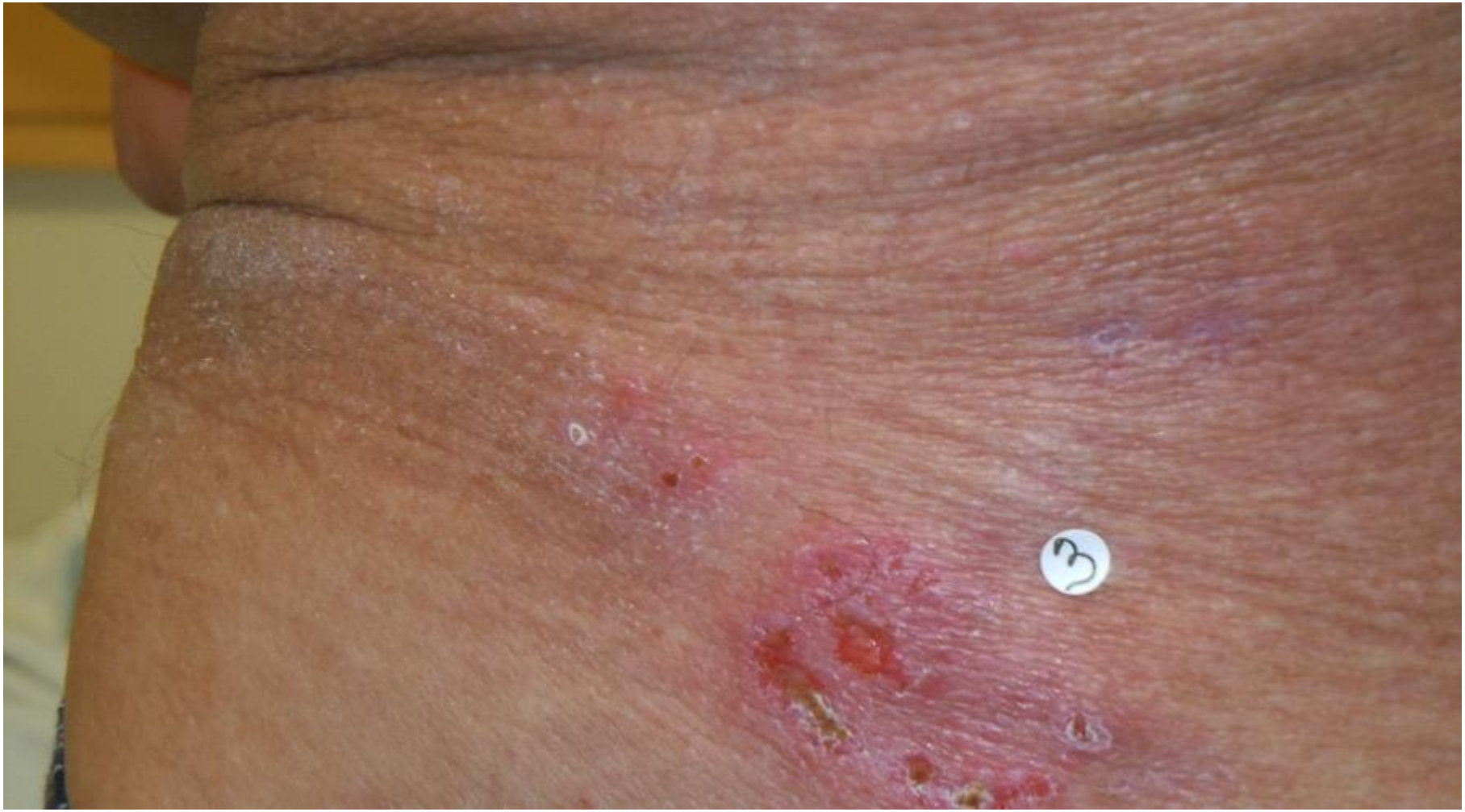
Pre-Resiquimod

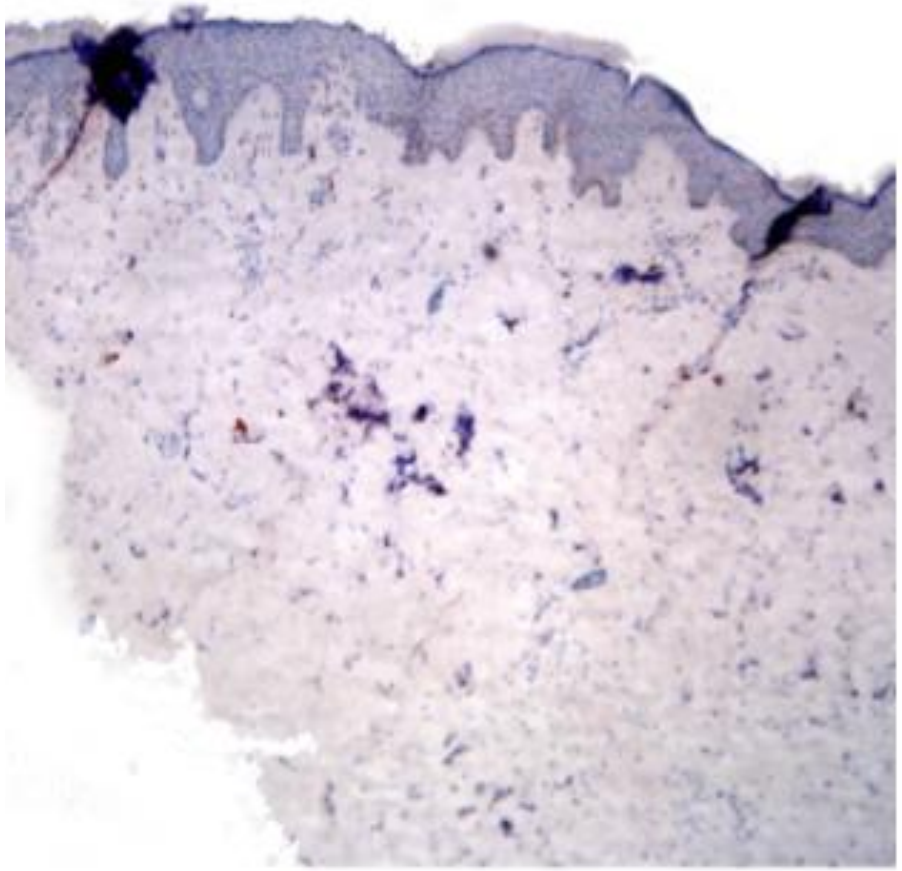


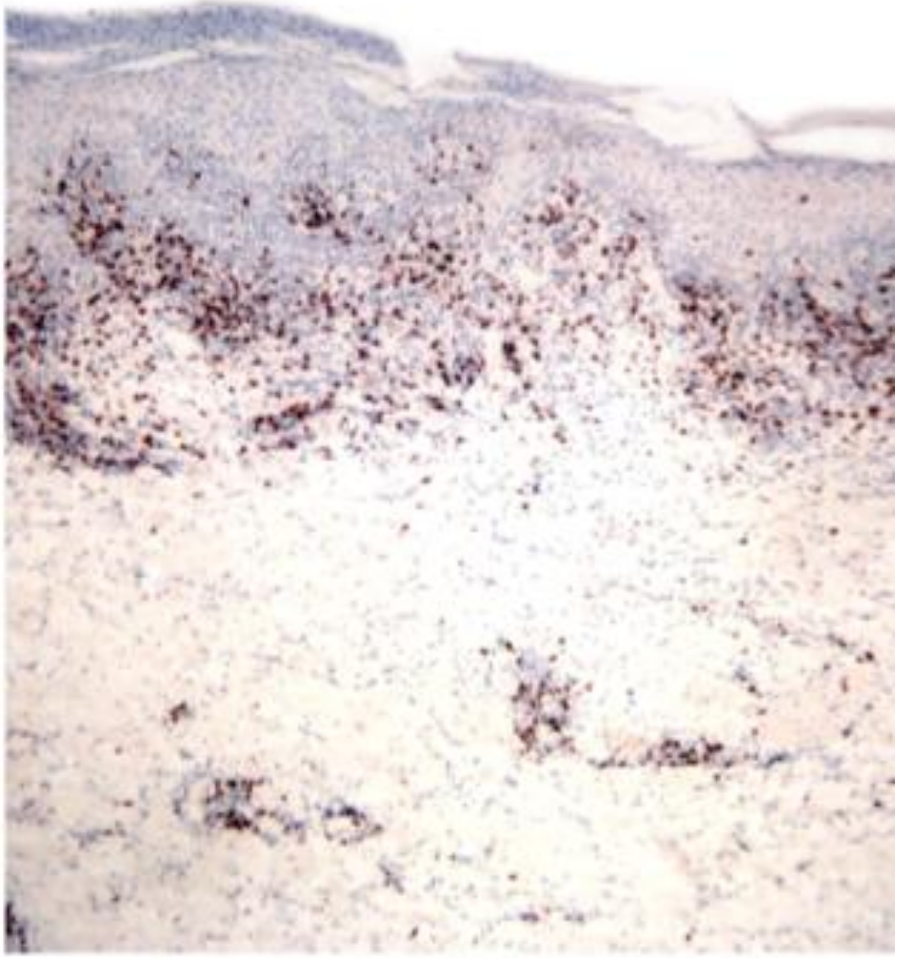
Week 12 Resiquimod



Proinflammatory Effects of Resiquimod:Week 8

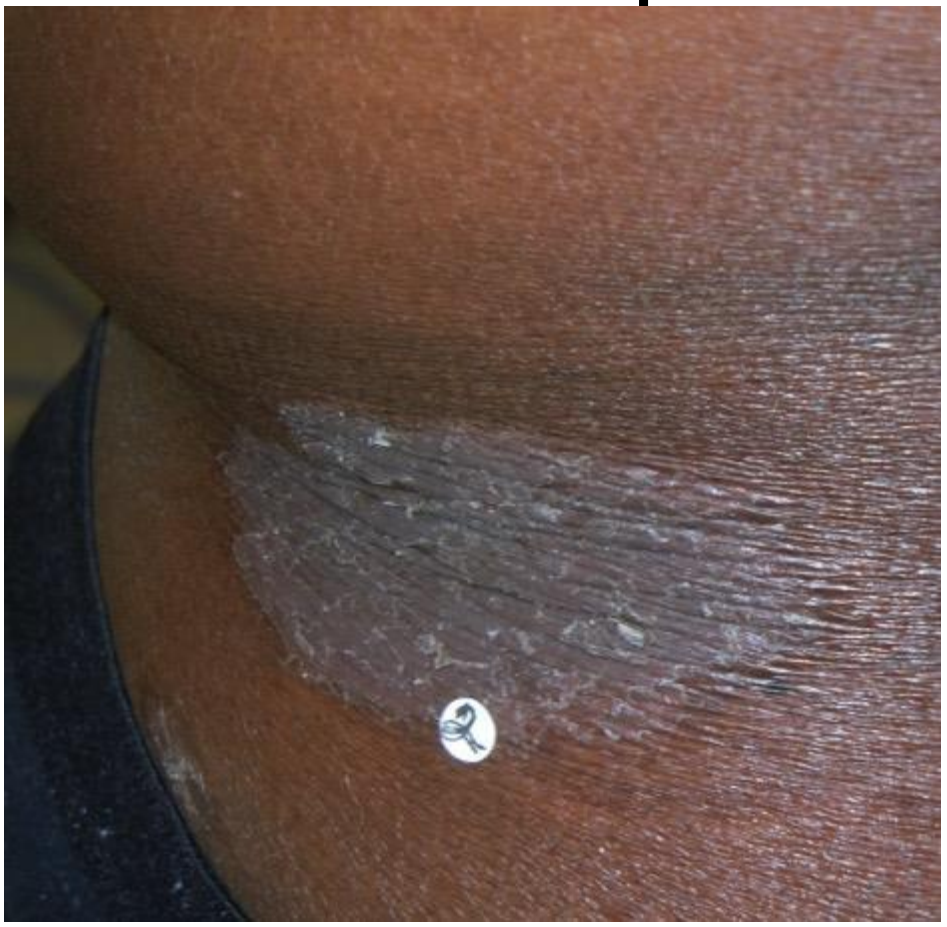




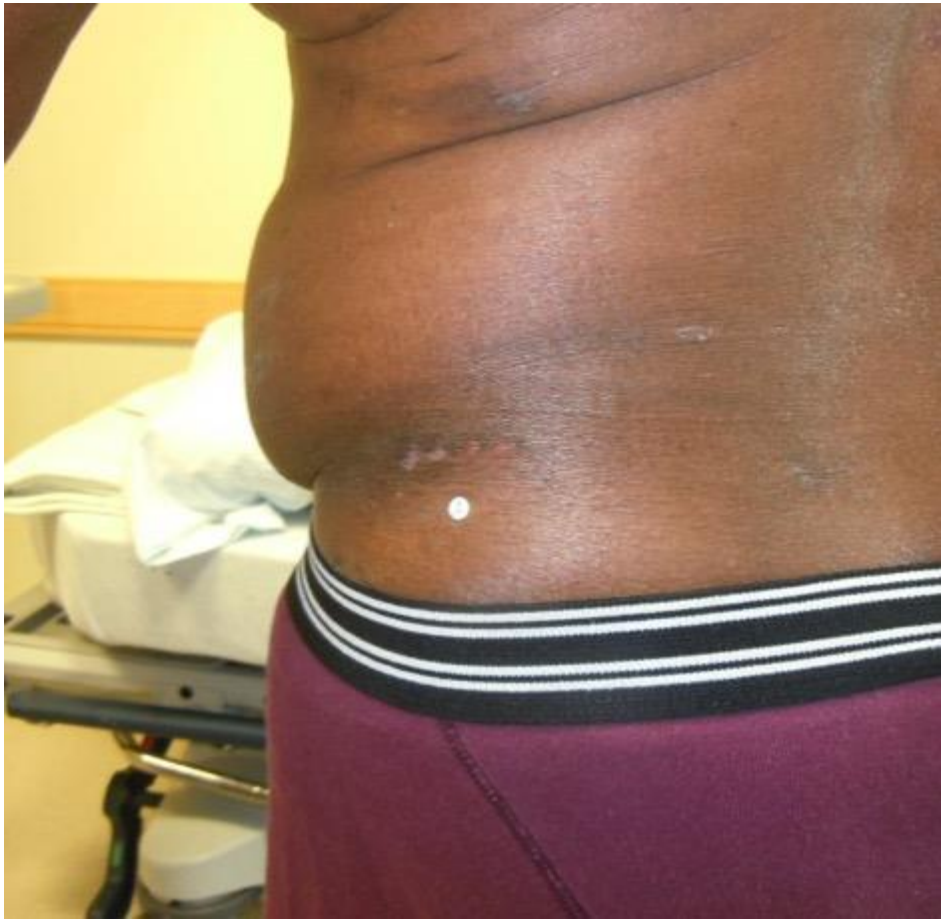


Resiquimod Clears Treated Lesions and Induces Resolution of Distant Lesions

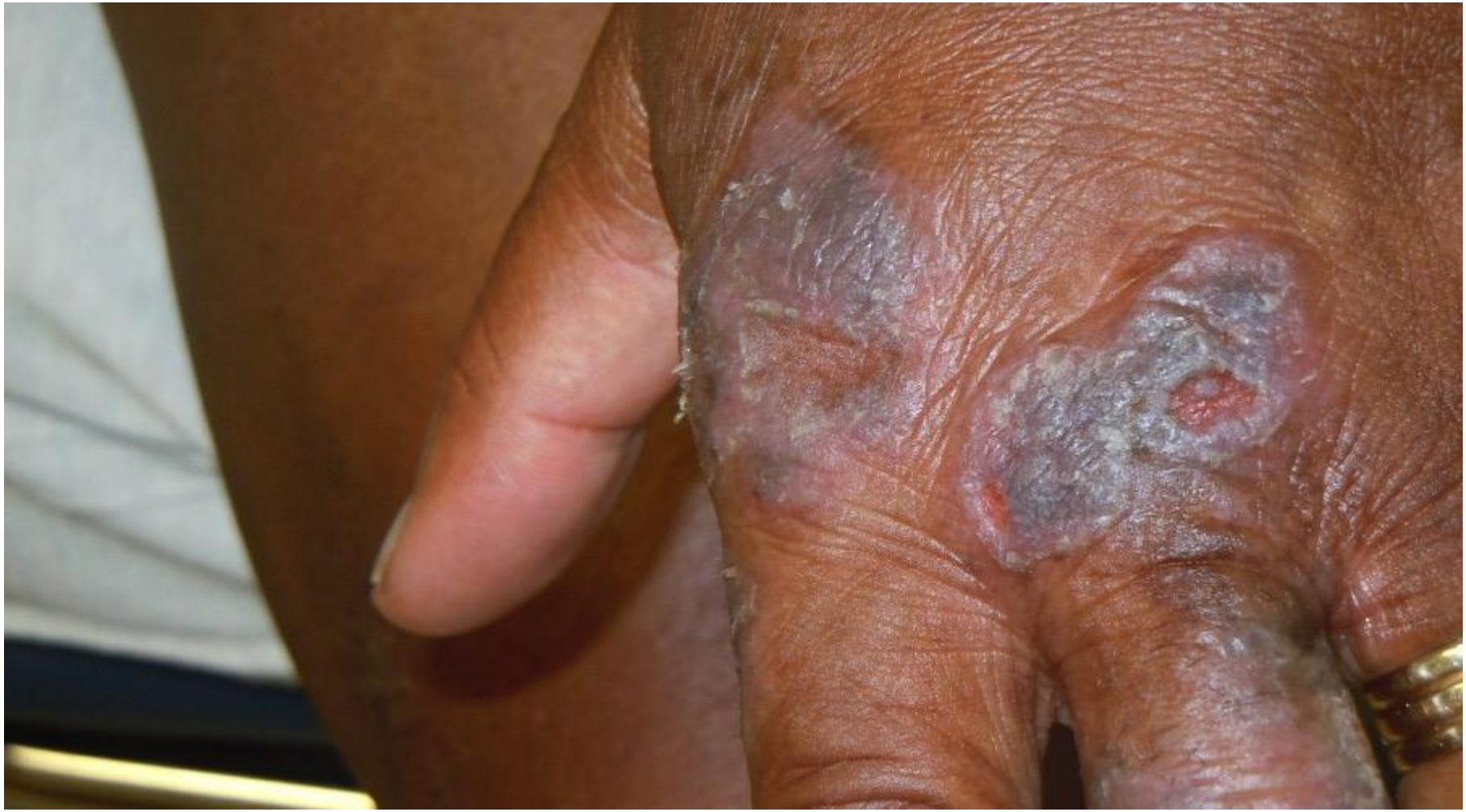
Pre-Resiquimod



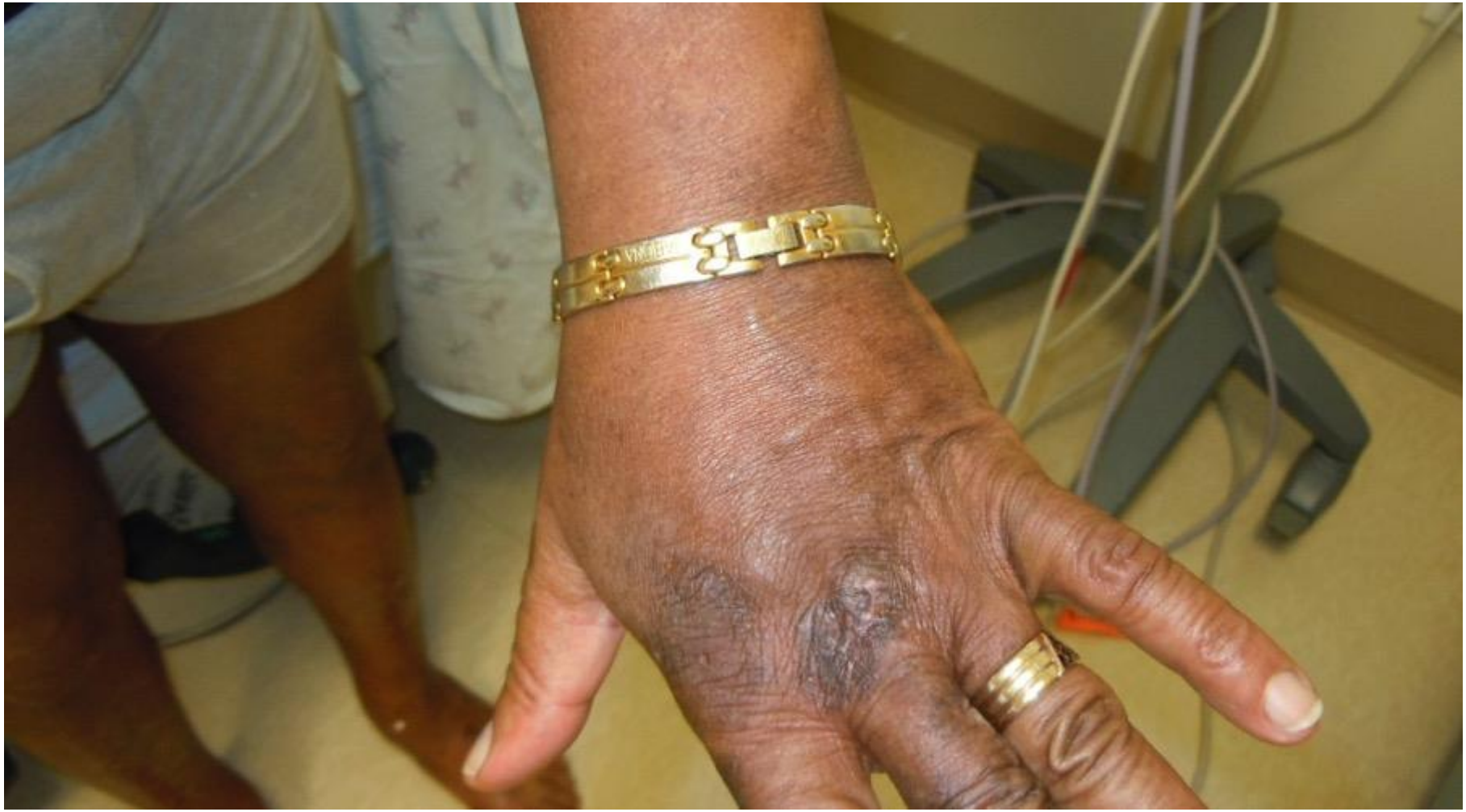
Week 8



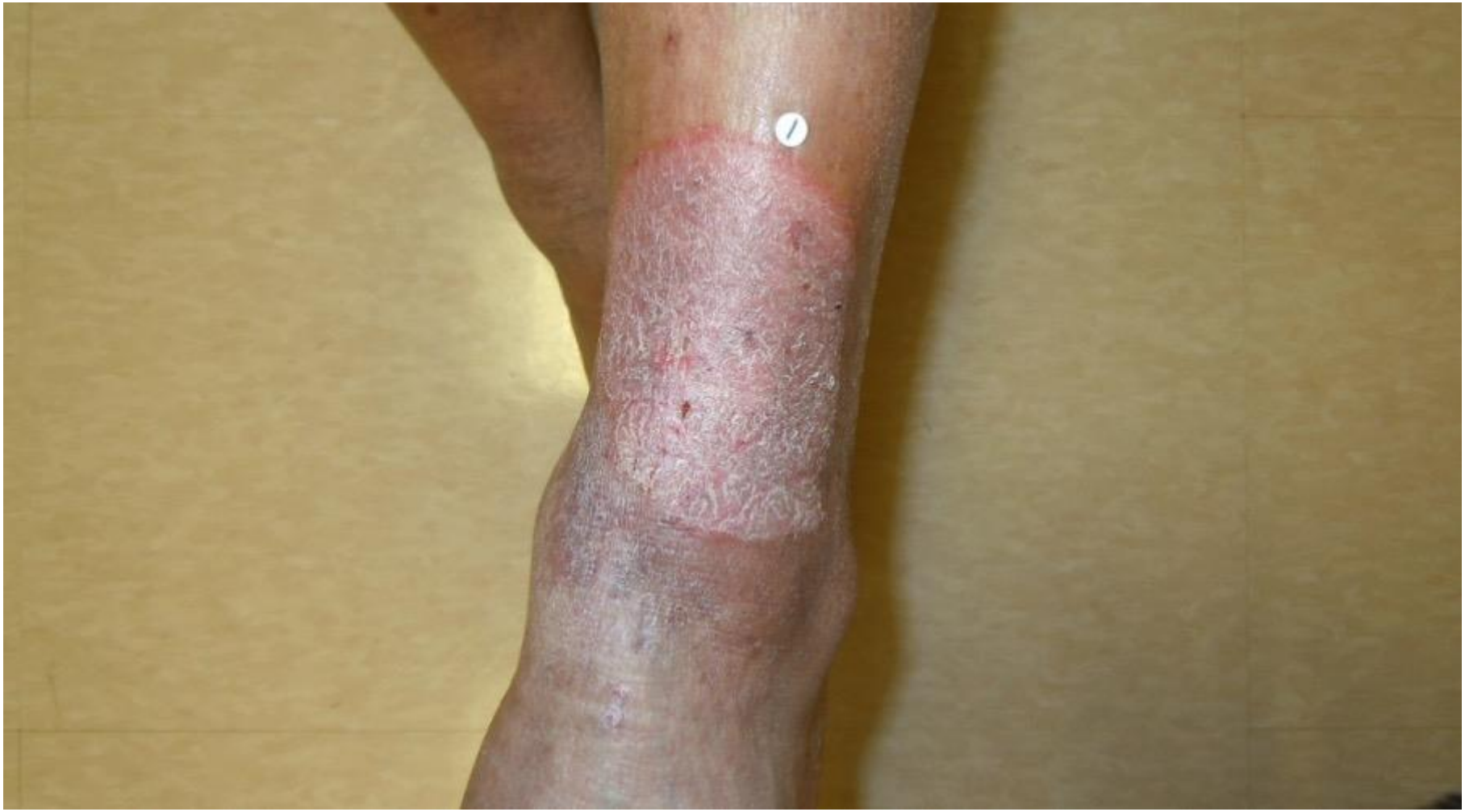
Patient #2 Baseline



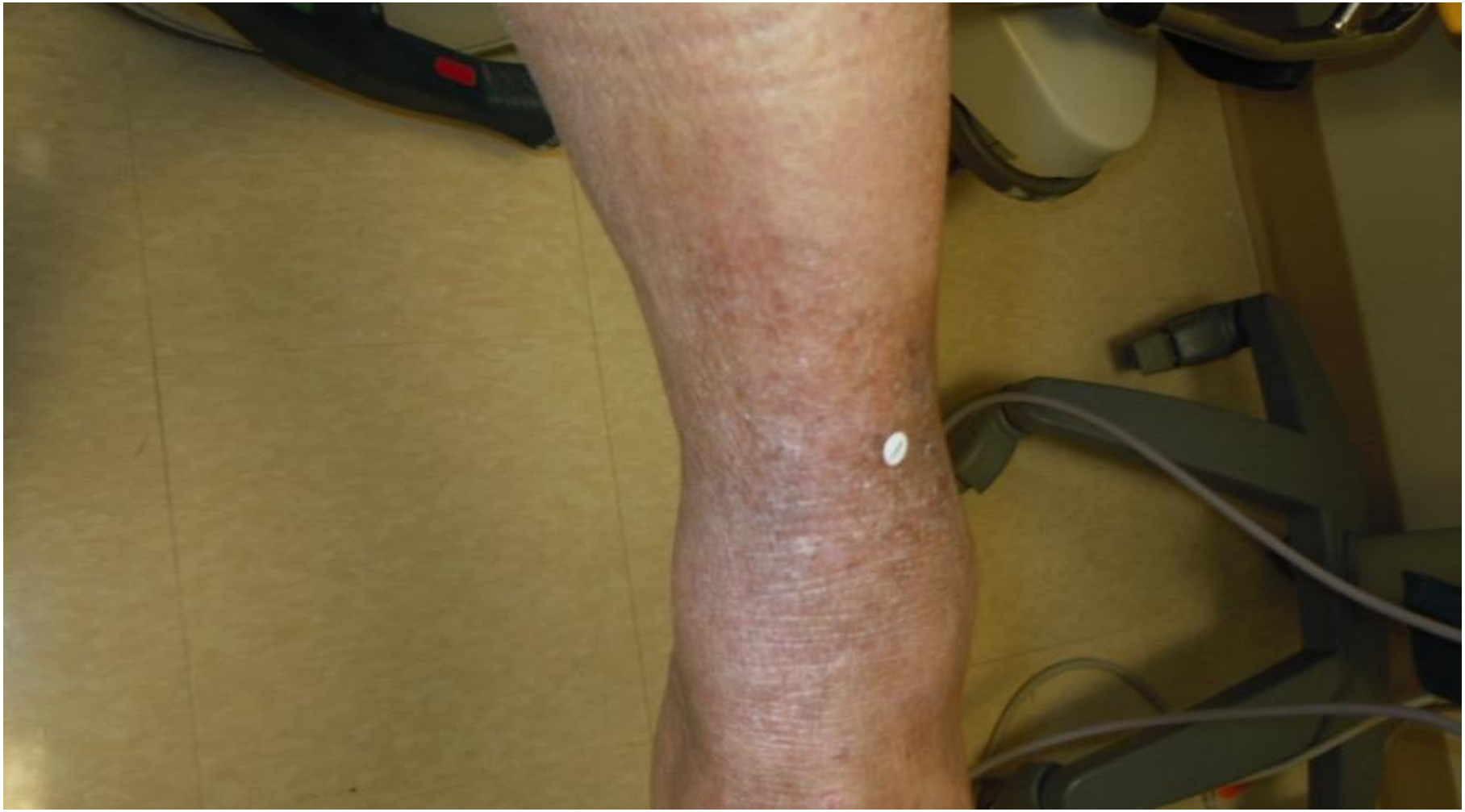
Patient #2 Week 16 (Response In Untreated Lesion)



Patient #3 Baseline



Patient #3 Week 24



Activation of Circulating Dendritic Cells by Topical Resiquimod

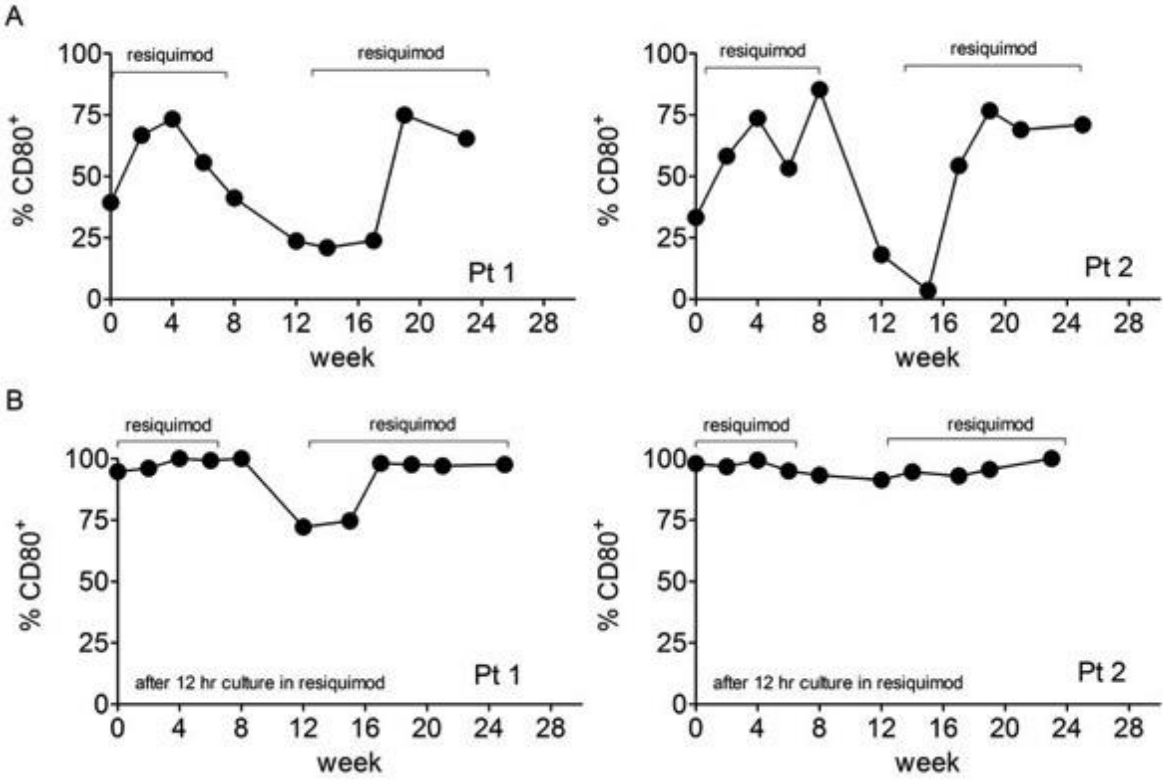
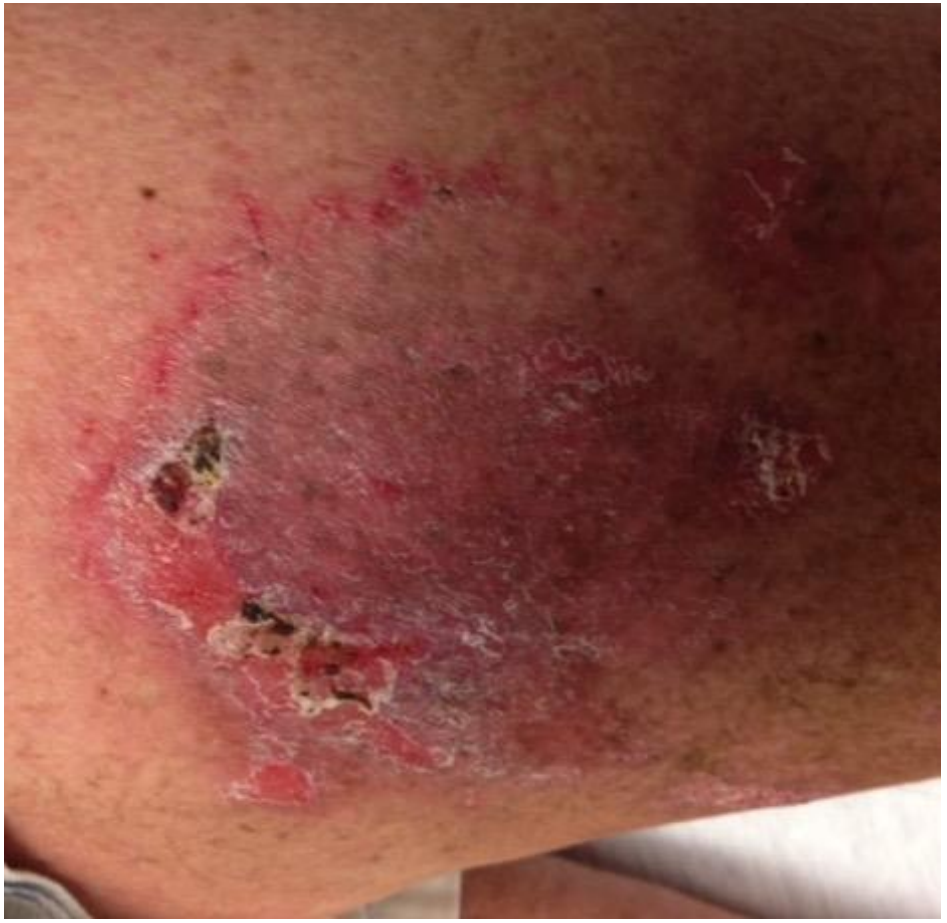


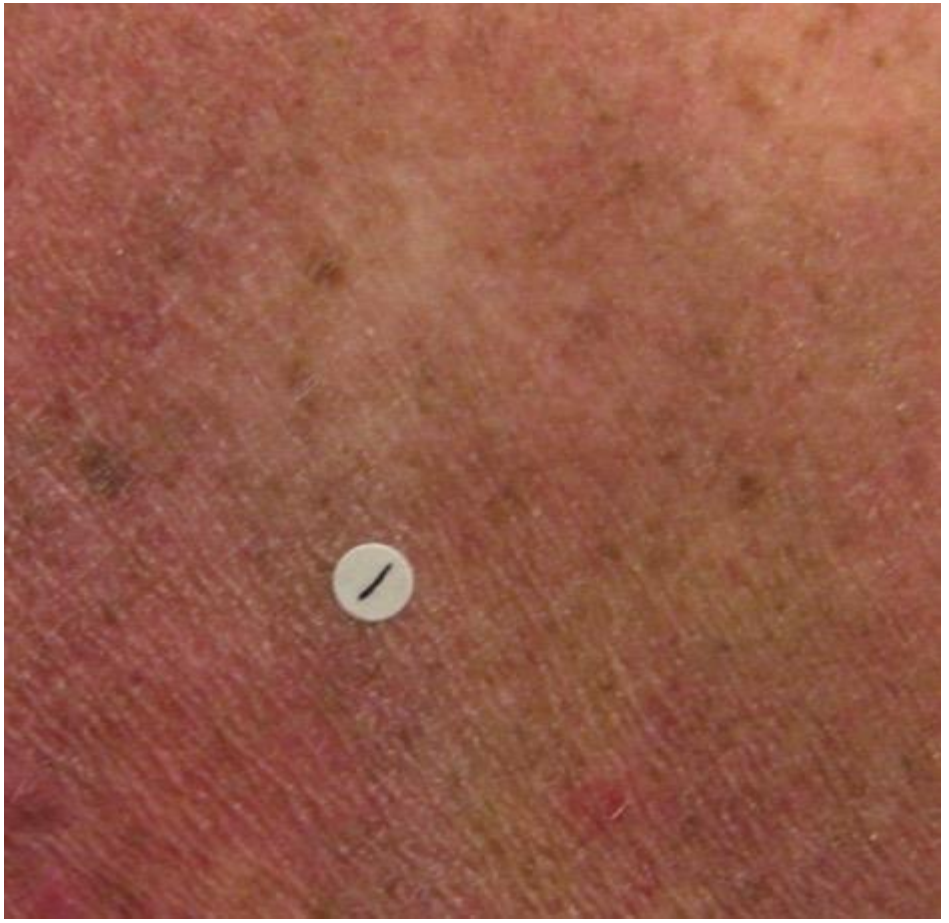
Figure 8

Patient #11

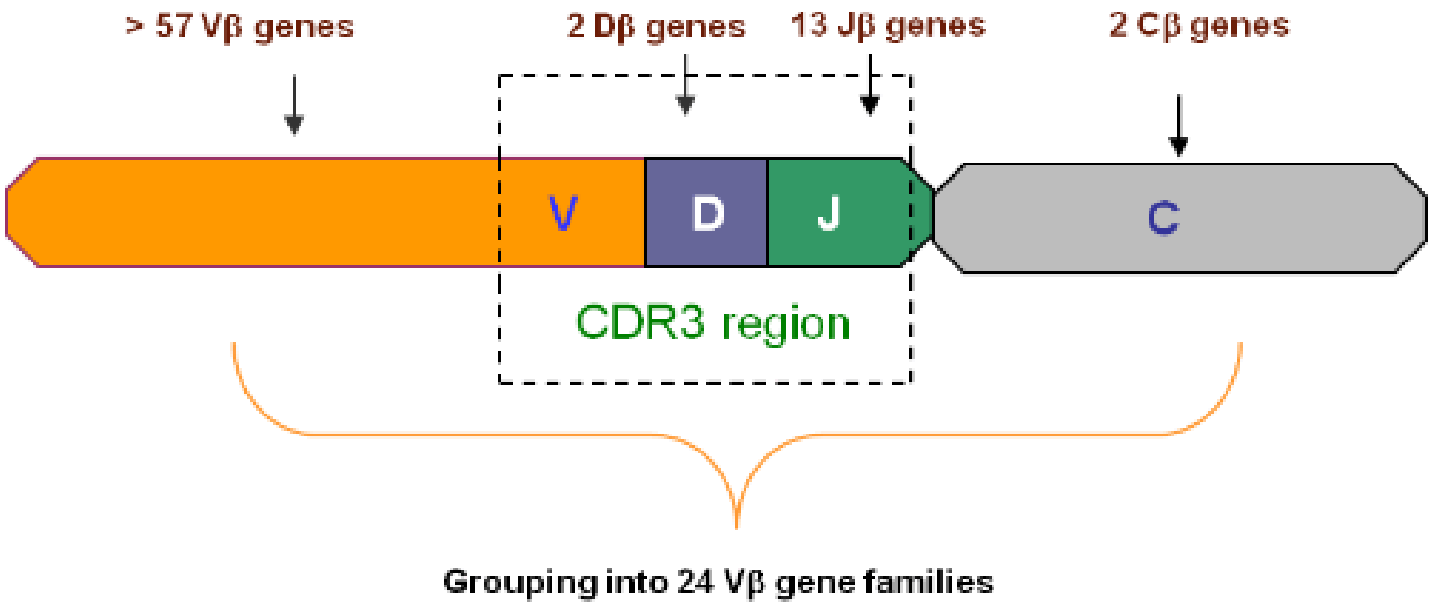
Baseline Pre-Treatment



Week 8 of Treatment



High throughput TCR CDR3 Sequencing (HTS): T cell fingerprinting

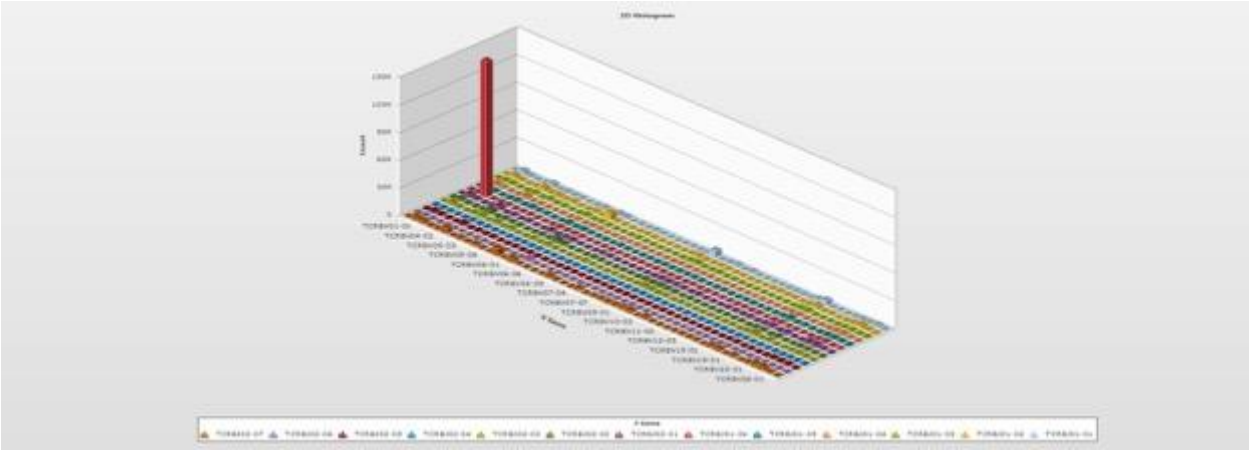


Every T cell has a unique CDR3 sequence

Patient 11

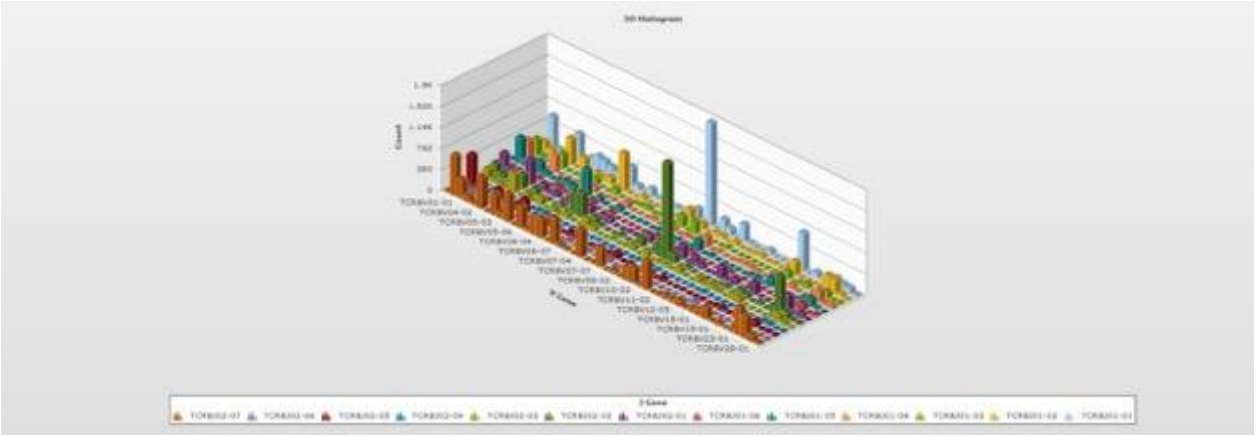
Clearance of Malignant Clone and Restoration of Clonal Diversity

Pre-treatment



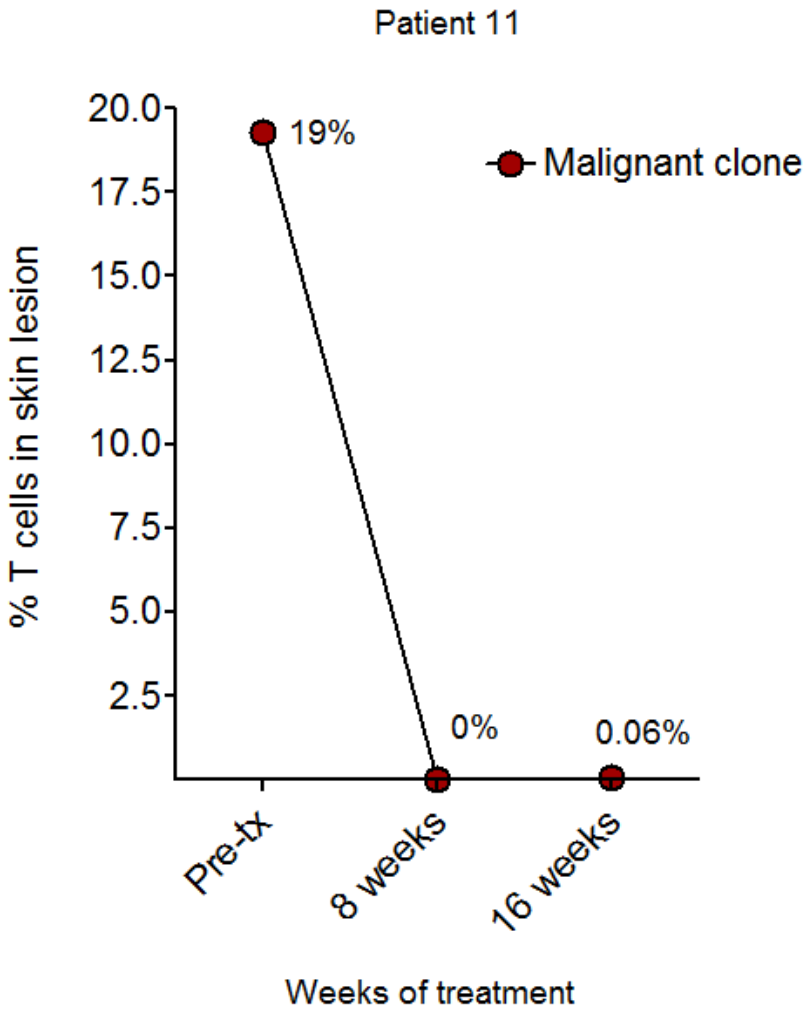
Clone:
19% T cells

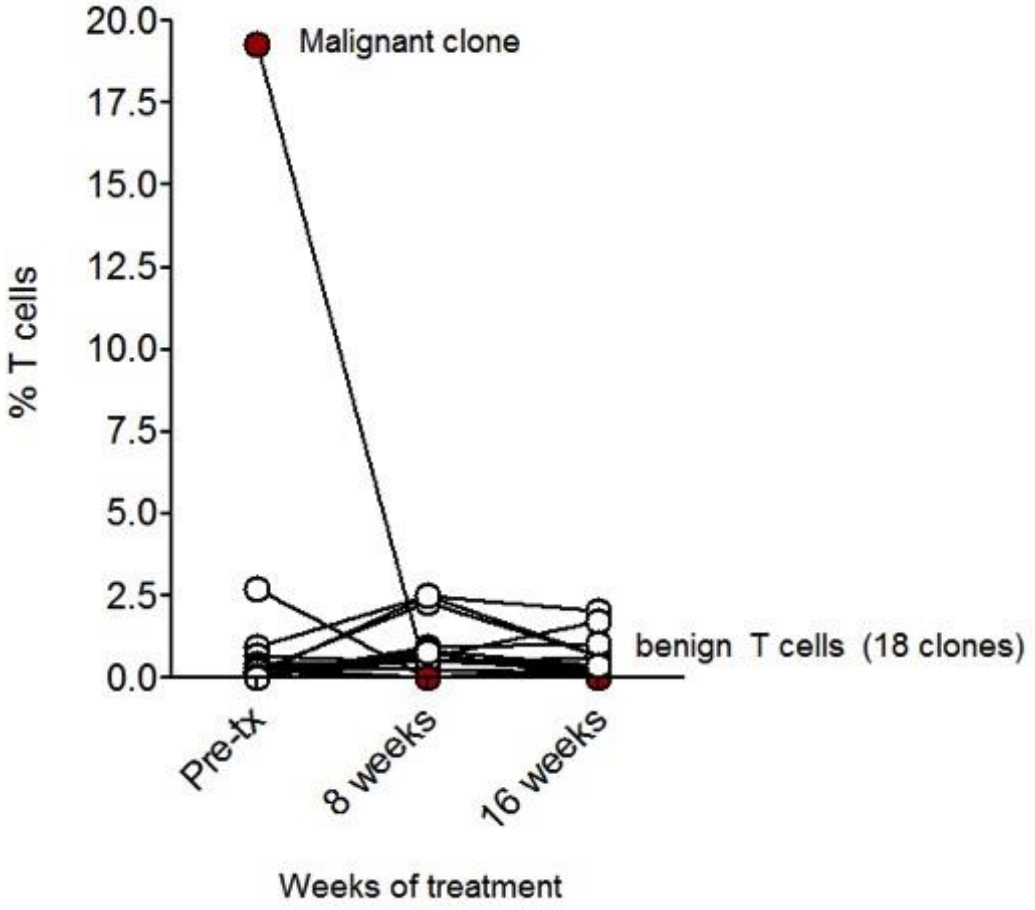
8 weeks



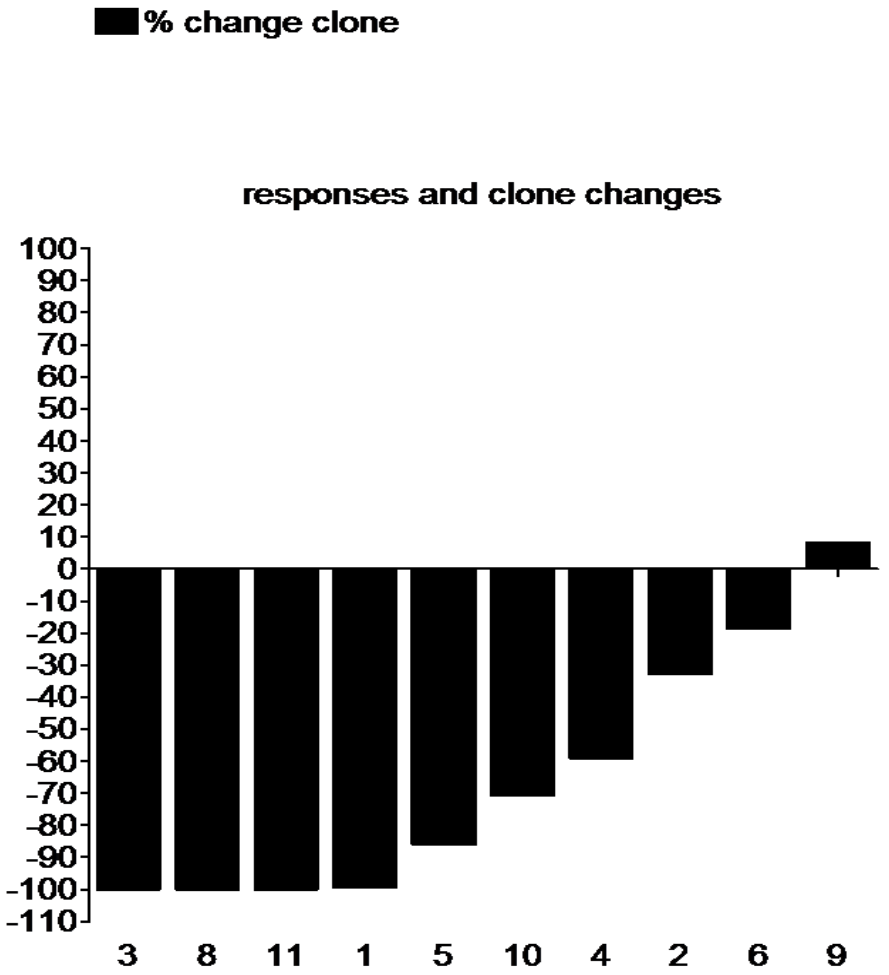
Clone:
0% T cells

Patient 11


Patient 11
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
% T cells in skin lesion
19%
Malignant clone
0%
0.06%
Pre-tx
8 weeks
16 weeks
Weeks of treatment


20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.0
% T cells
Malignant clone
benign T cells (18 clones)
Pre-tx
8 weeks
16 weeks
Weeks of treatment

Percent Change in Malignant Clone During Therapy



Patients

Resiquimod Trial for CTCL

- **Well tolerated topical drug with grade I skin toxicity**
- **Ease of application**
- **High clinical response rates of both treated and untreated lesions among refractory early stage CTCL**
- **Among 12 patients 10/12 responses (7 PR; 3CR; 2 stable disease)**
- **Evidence for systemic immune activation**
- **Phase II, multicenter, placebo controlled trial planned**

Adverse Events (CTCAE Version 4.0)

- **No serious adverse events recorded**
- **No patient drop outs**
- **11 patients with grade I skin AEs which resolved within 3-7 days (inflammation; pain; erosions).**
- **2 patients (both on 0.06%) with less than grade I fever for two days**

Potential Role of TLR Agonists in CTCL Therapy

Single-agent immunostimulator

Effective agent in combination regimens

- **Photopheresis**
- **Cytokines (particularly IFN gamma)**
- **Retinoids**
- **PUVA**
- **Electron beam**
- **Anti-PD-1**

***In situ* vaccination therapy**

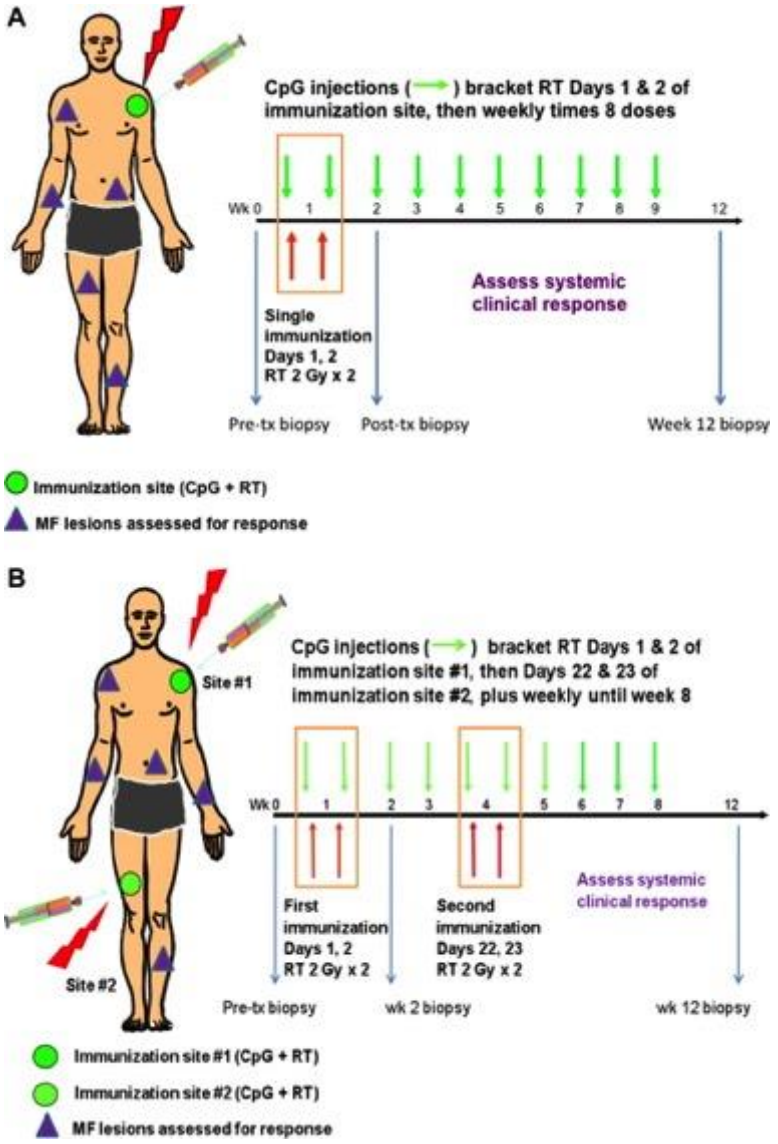
- **Low-dose RT + intratumoral CPG**

  (Ongoing clinical trial at Stanford)

IN SITU VACCINATION AGAINST MYCOSIS FUNGOIDES BY INTRATUMORAL INJECTION OF A TLR9 AGONIST COMBINED WITH RADIATION: A PHASE 1/2 STUDY

Youn H. Kim, Blood, 2012

Treatment schema.



Kim Y H et al. Blood 2012;119:355-363