Mogamulizumab

Targeting CCR4 to Treat CTCL

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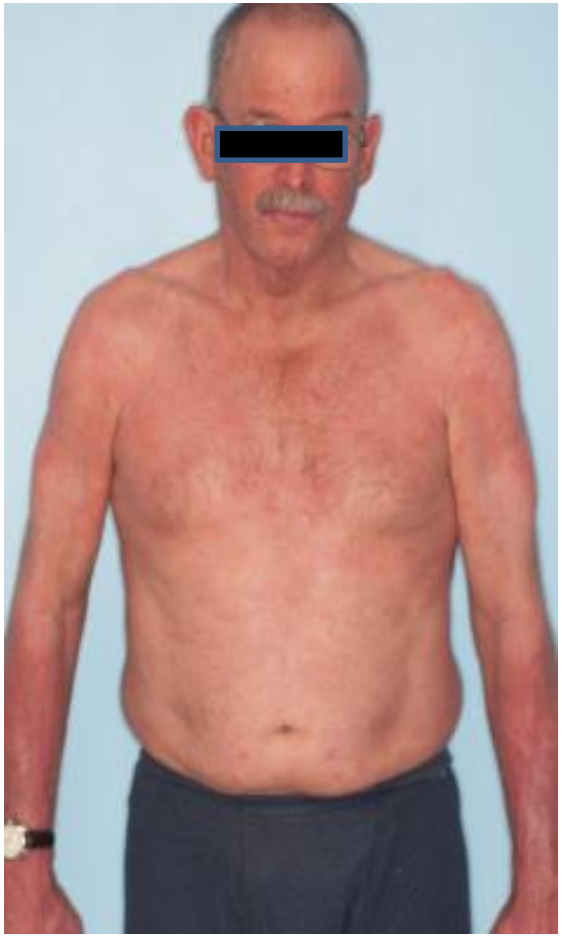
Case 1

- 2000 a healthy 60 year old WM developed pruritus and erythema on back & keratoderma
- 2006 diagnosis “Pityriaisis rubra pilaris”
- Narrow band UVB without improvement.

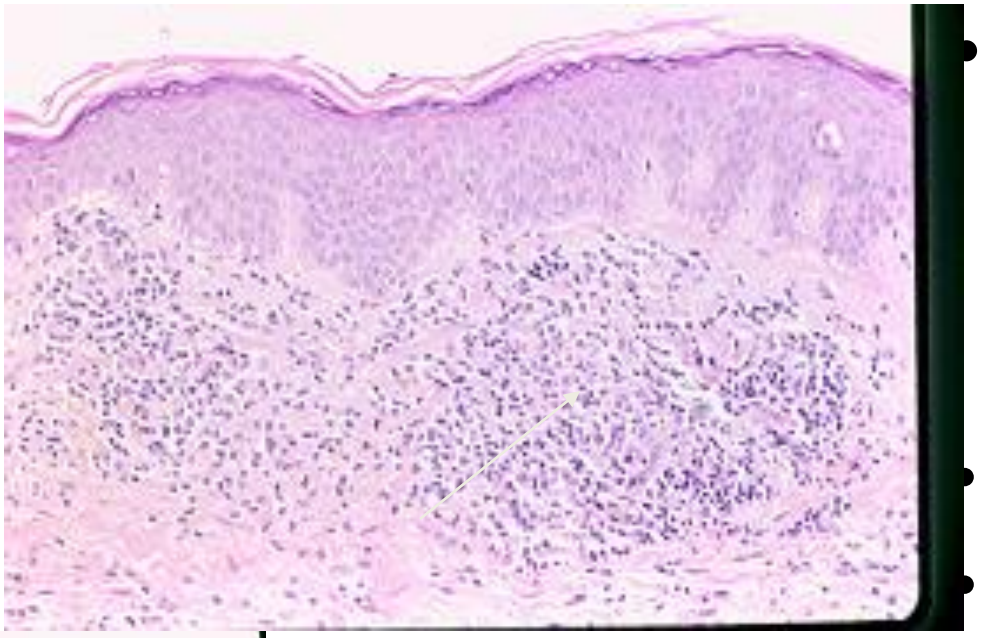
- 2007 - Sezary 80% erythroderma, pruritus, Increased CD4+CD26- by flow cytometry.

Erythroderma MRSA+ colonization
Pruritus, adenopathy, B2 (SS 9,000)



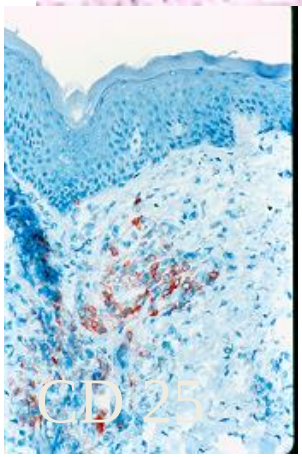
August 2012

Leukemic CTCL vs Sézary Syndrome

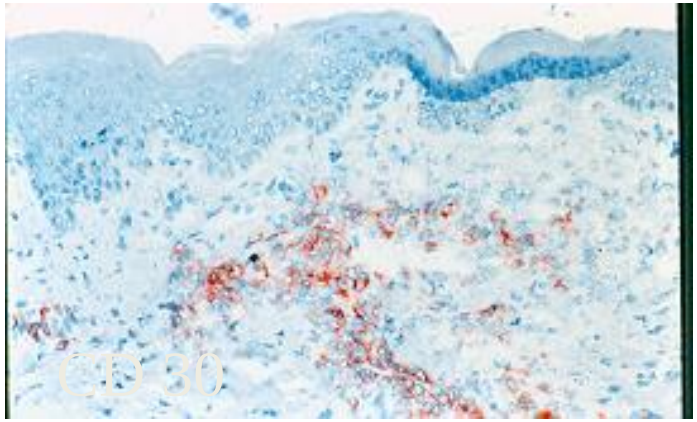


- Perivascular infiltrates without supporting epidermotrophism

- CD4+CD26- or CD4+CD7-
- Central memory T-cells
- By flow in blood



CD 25



CD 30

- CD4+ T cell infiltrate

Frontline Therapy

- 2007 – 2012 the patient received combined immunomodulatory therapy
- Extracorporeal photopheresis (ECP) q 4 weeks
- Interferon alpha 3 mil units x 3 x week

  with stable disease thru 2009.
- Acitretin added 2010 with stable disease
- 2010 - Gemcitabine x 6 months stopped for hemolytic uremic syndrome (HUS) 0.6%

Progression of SS

- Nov 2011-May 2012 restarted immunotherapy
- ECP/bexarotene/interferon
- 700- 900 SS cells (B1), pruritus, erythroderma
- May–August 2012 off therapy MF flared.

- Increased CD4+26- SS cells (4,000 to 9,000 /ul) adenopathy, severe erythroderma with MRSA, acral keratoderma, and fissures.

What second line therapy would you use for patient with Sézary Syndrome?

- Histone deacetylase inhibitors- romidepsin or vorinostat?
- Targeted antibody therapy
  - Bretuximab vedotin- conjugate Mab to CD30 + MMAE
  - Zanolimumab - Mab to CD4+ T-cells
  - Alemtuzumab – Mab to CD52 on mature lymphocytes
  - Mogamulizumab - Mab to CCR4 (chemokine)
- TBSEB and non-ablative allogeneic SCT

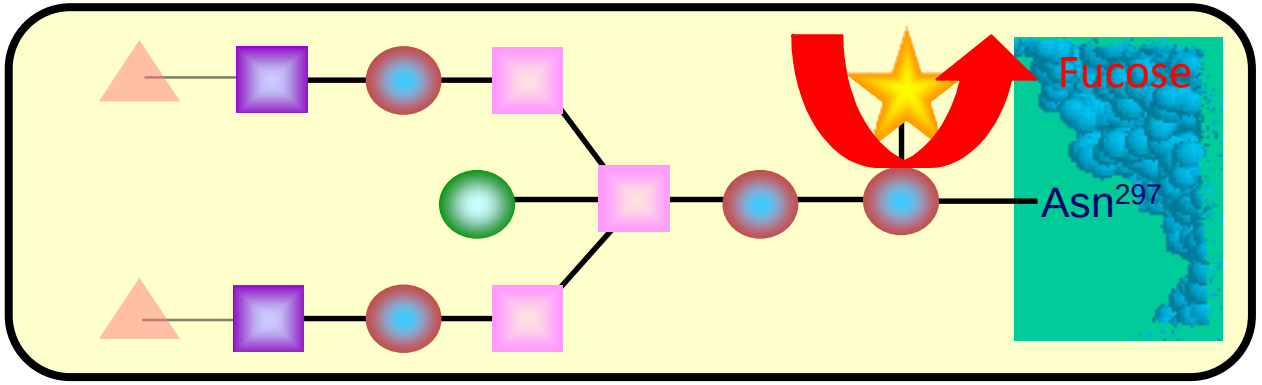
Mogamulizumab

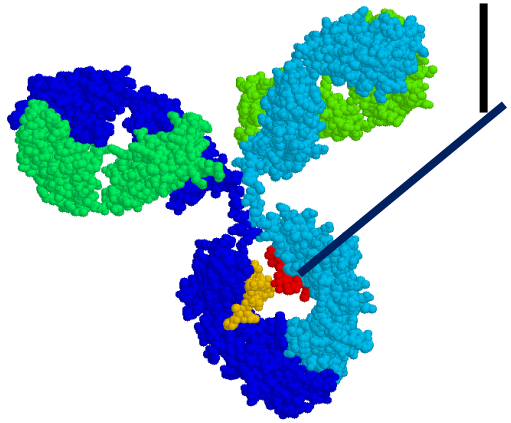
- CCR4 - chemokine receptor expressed on helper T cells and on T-regulatory cells.
- CCR4 binding to ligands TARC or MDC on endothelial cells promotes trafficking of T cells to skin.
- First glyco-engineered humanized mAb
- Approved for HTLV-1+ adult T cell lymphoma.
- Defucosylation of the antibody Fc backbone increases ADCC compared to other mAbs.
- Phase I/II clinical dose finding study
- Phase 3 randomized trial vs vorinostat for improved PFS

Remer et al. Immunotherapy 2014, 6(11): 1187-206

KW-0761: Humanized Defucosylated Monoclonal Antibody “Mogamulizumab”Enhanced ADCC (Potelligent®)

: N-acetylglucosamine
: bisec GlcNAc
: Mannose
: Galactose
: Sialic acid
: Fucose





- Antibody backbone lacks fucose
- Leads to an increase in ADCC activity compared to conventional antibodies

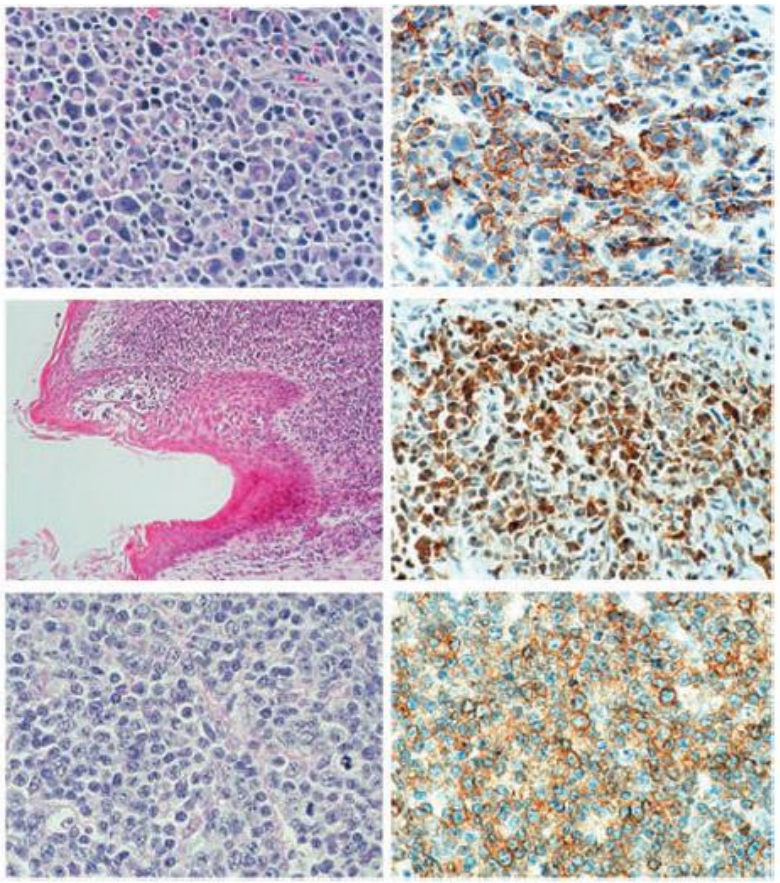
Ishida et al, Clin Cancer Res 2003;9:3625

Expression of CCR4 Receptor on skin homing CD4+ lymphocytes

ALK-negative ALCL

MF (transformed)

PTCL-U

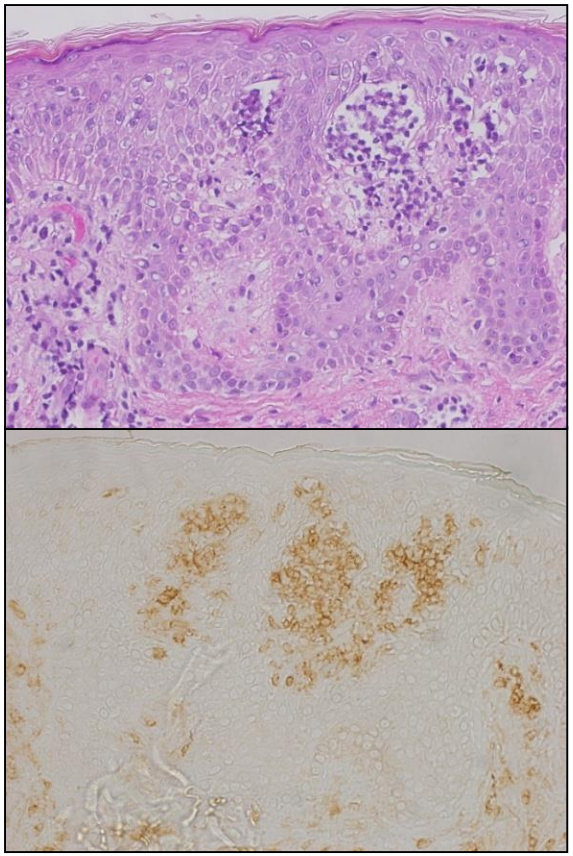


Ishida T, *et al.* Clin Cancer Res. 2004 Aug 15;10(16):5494-500.

CC chemokine receptor 4 (CCR4) in CTCL

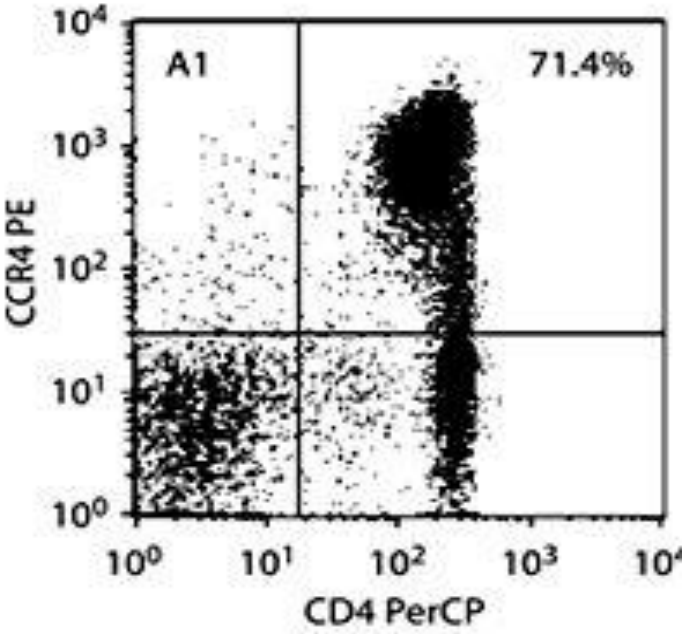
HE

CCR4



Immunohistochemistry staining: CCR4+ atypical T cells in Pautrier's microabscess of MF skin lesions

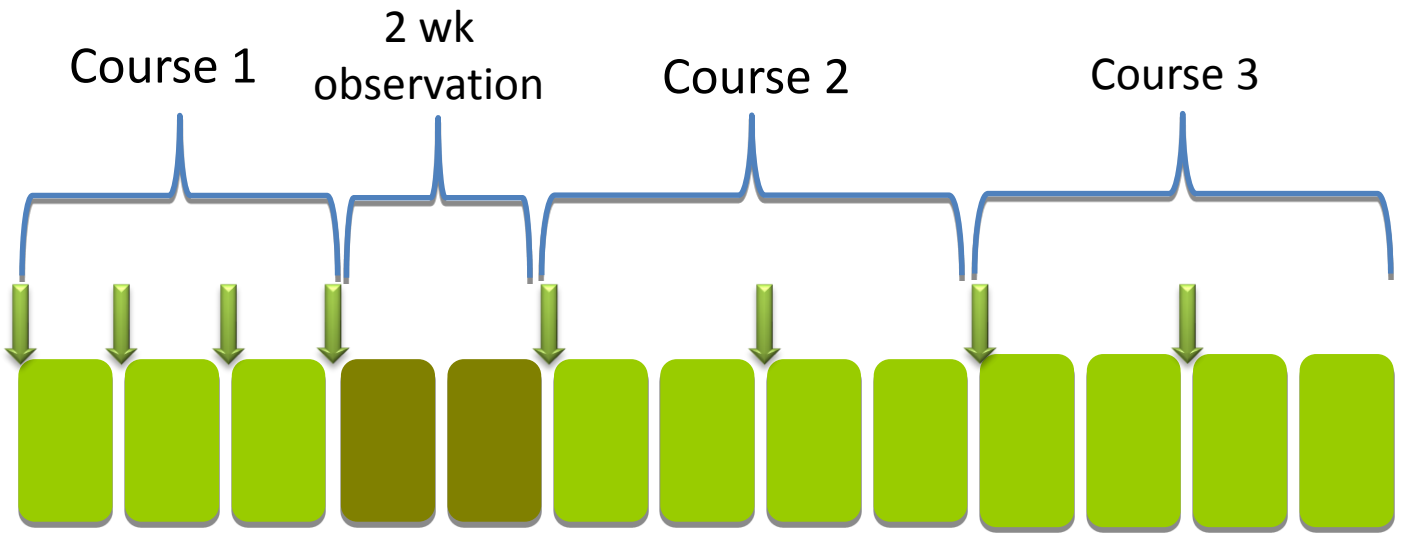
(Ni and Duvic, unpublished data)



Flow cytometry: CD4+CCR4+ T cells in Sézary syndrome patient's blood

Fierro et al, Dermatology, 2006, 213: 284-292

CCR4 Treatment Schedule Phase I/II
0.1,0.5,1 mg/kg q week x 4 then every 2 weeks



- Patients with CR are given up to 2 additional courses
- Patients with PR/SD given infusion every other week until disease progression or withdrawal
- No DLT – 1 mg/kg chosen for Phase II

Results of Phase I/II Multi-center trial CCR4 Global Composite Response

Patient Subgroups	ORR	Number of patients			
		CR	PR	SD	PD
Mycosis Fungoides (N=21)	**29%**	**1**	**5**	**11**	**4**
Sezary Syndrome (N=17)	**47%**	**1**	**7**	**7**	**2**
TOTAL (N=38)	**37%**	**2**	**12**	**18**	**6**

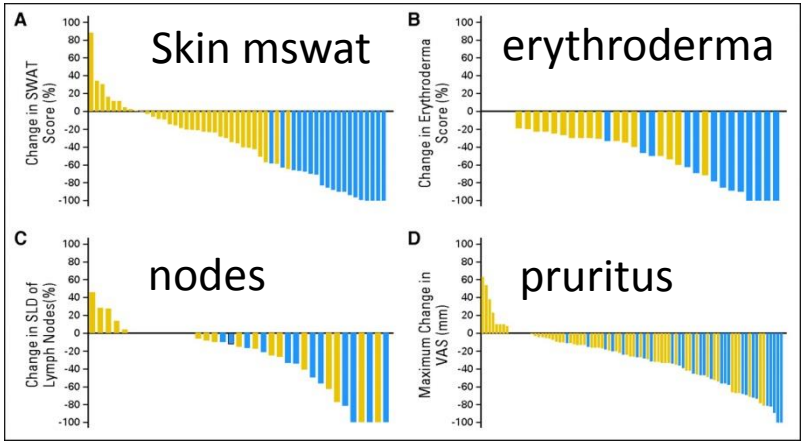
- Overall ORR of 37% vs 47% in Sezary patients
- Multi-center Phase III CCR4 vs vorinostat trial

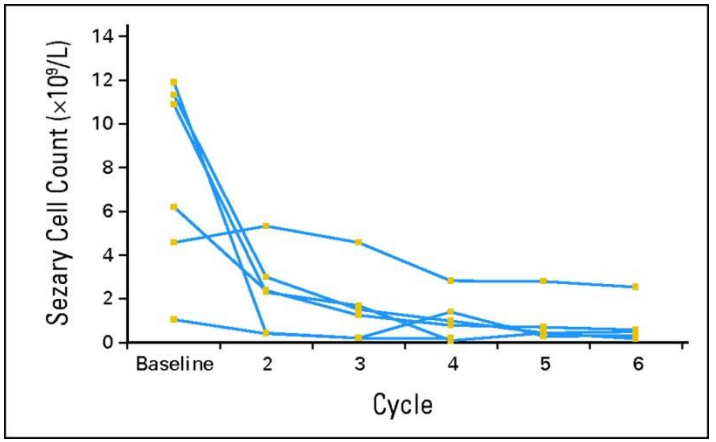
Duvic et al. Blood Jan 20 epub 2015

Pan histone deacetylase inhibitor Romidepsin

ORR 34% (6 CRs) in 95 treated patients

- Time to response 2 mos, duration 15 months
- 40% (38 pts) >50% decrease in mSWAT or EE
- 43% had improved pruritus
- 39% OR in 37pts with B1 or B2 involvement
- 31% (4 of 13) w B2 responded





Whittaker et al JCO October 2010 vol 28, 4485

Phase III Multicenter Trial
CCR4 antibody (Mogamulizumab) vs vorinostat

March 2013 CCR4-mAb

July 2013 cycle 5

SS cells gone, nodes smaller

Mswat = partial response

October 2013 CR skin, blood, pruritus resolved

Photodermatitis:

Fishing on Bactrim and

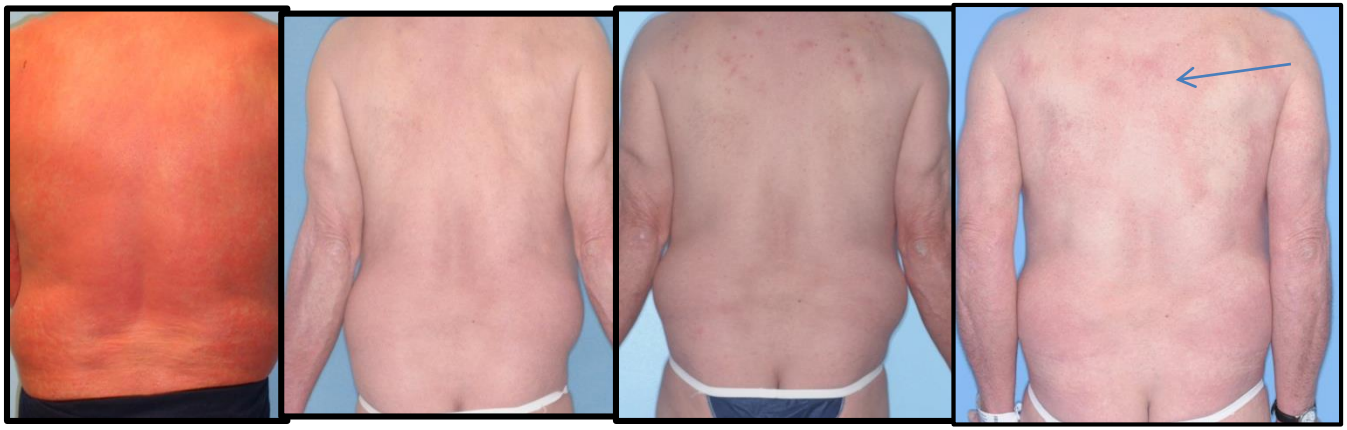
Drug rash course 14 -23

Complete response: 3/2014

3/2015 - ongoing off drug

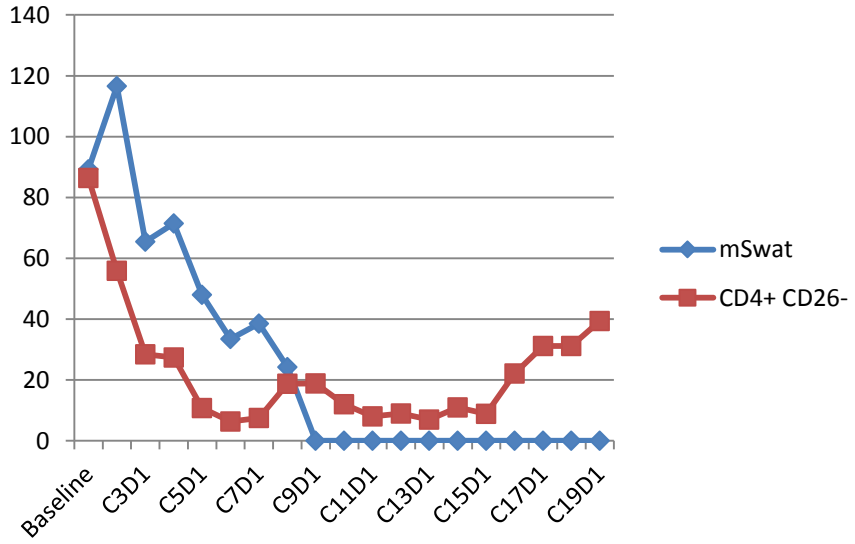
66 y/o male treated > one year: PR blood C1D29 and CR at C3D1, PR in skin at C8D1, CR at C9D1. New hypersensitivy pruritic rash with eos at C14- C23

Duvic et al. JCO 28: No 14 MAY 10, 2010

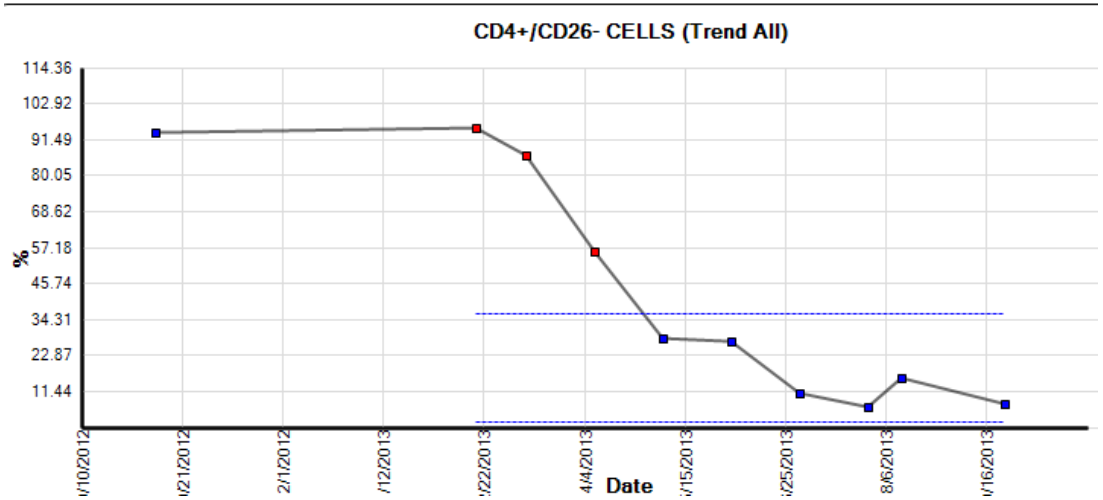


Baseline C8D1- PR C18 D1- CR C24 D28- CR

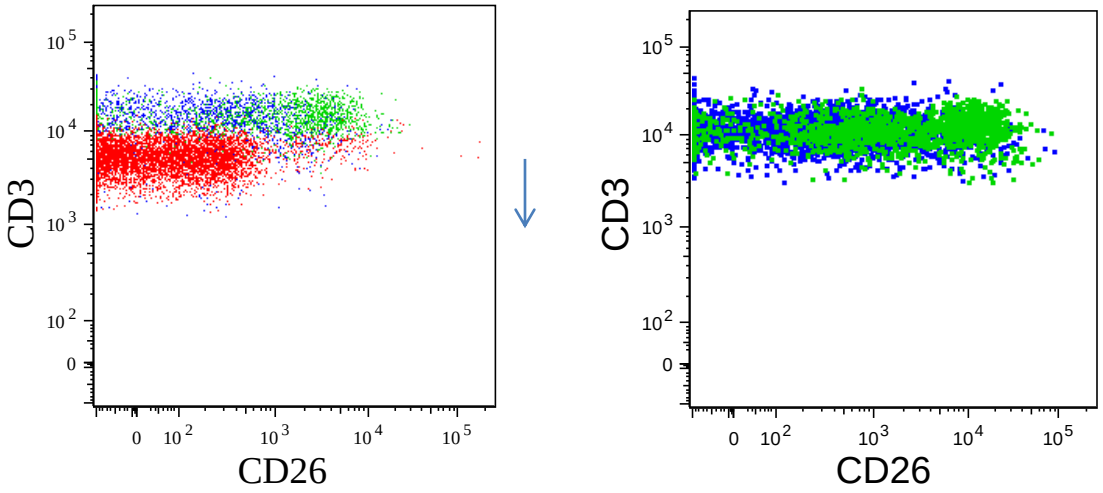
BL C8D1-PR C18 D1-CR C24 D28 CR



CCR4 Antibody normalizes Sézary cells in blood

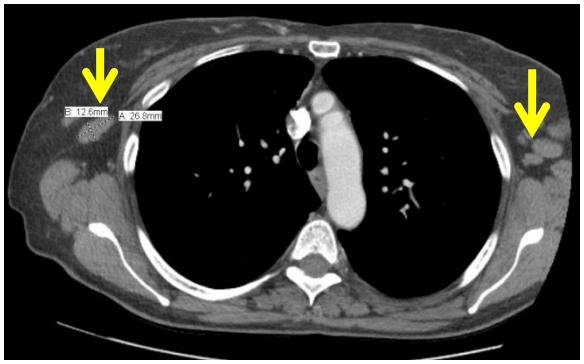


%CD4+CD26-

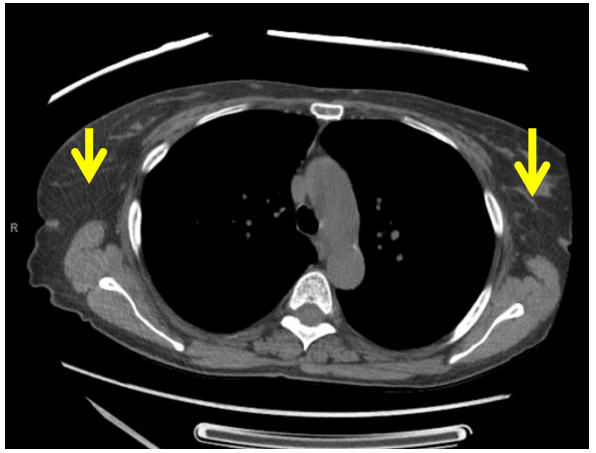


Lymphoma cells
Normal CD3+CD4+
CD3+CD4neg

Absolute
CD3+CD26-



Baseline

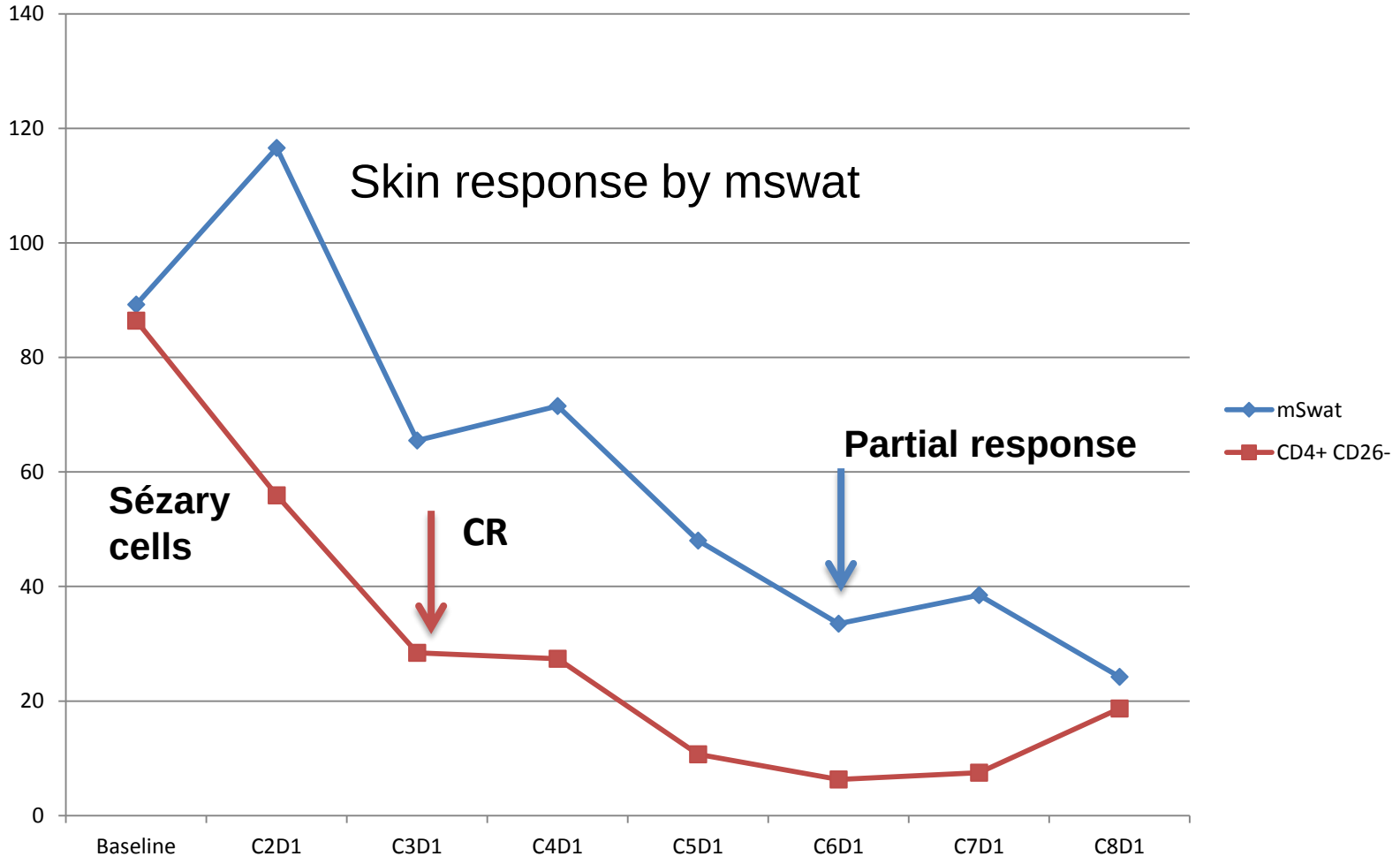


Baseline **Cycle 5 D1- PR** **Cycle 10 D1-CR** **Cycle 10 D1- CR nodes**

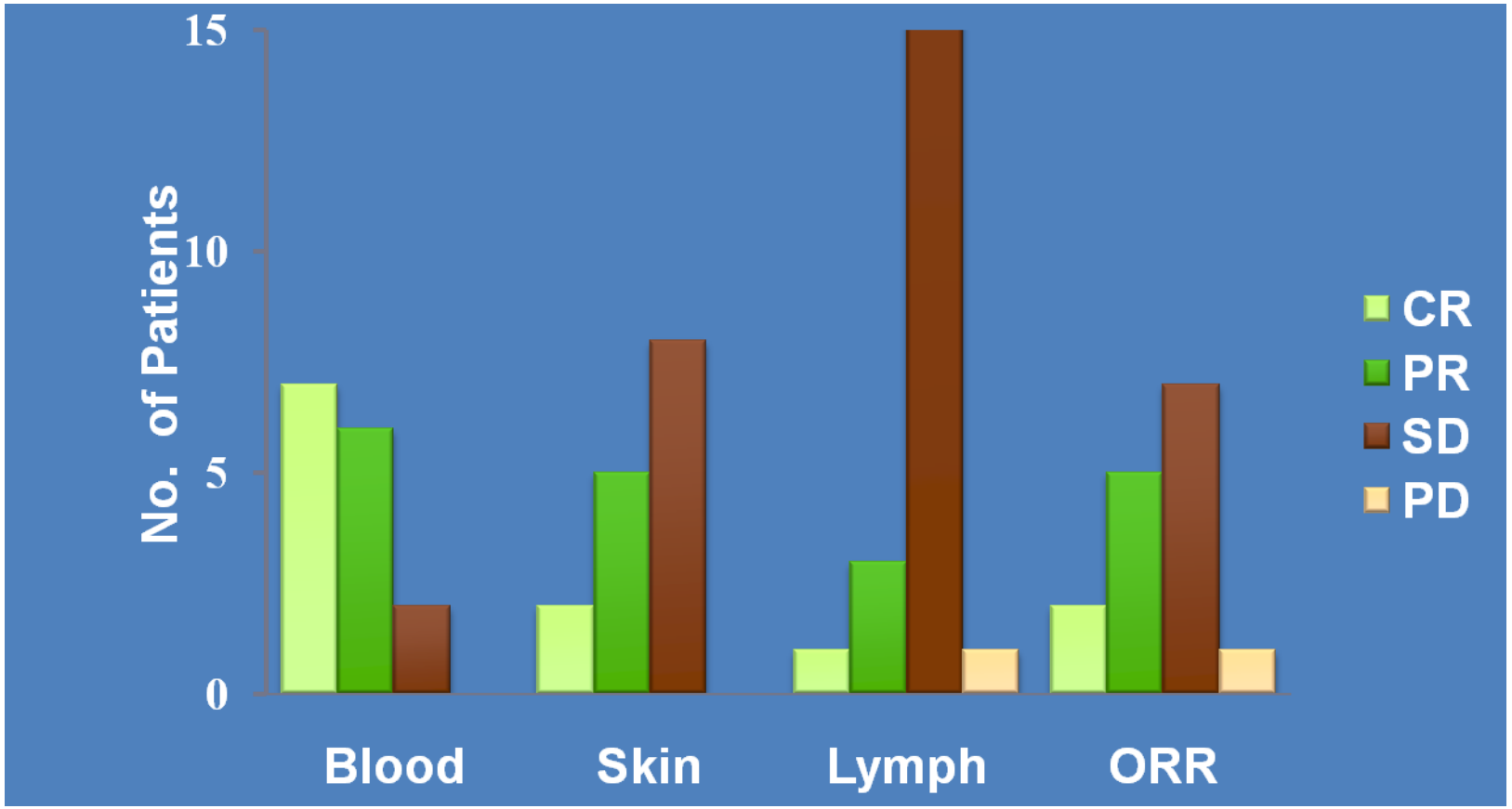
CCR4 in Female patient cleared skin, nodes, blood and BM

Partial Response Case 2

SS cells at C3D1 - Skin at C6D1

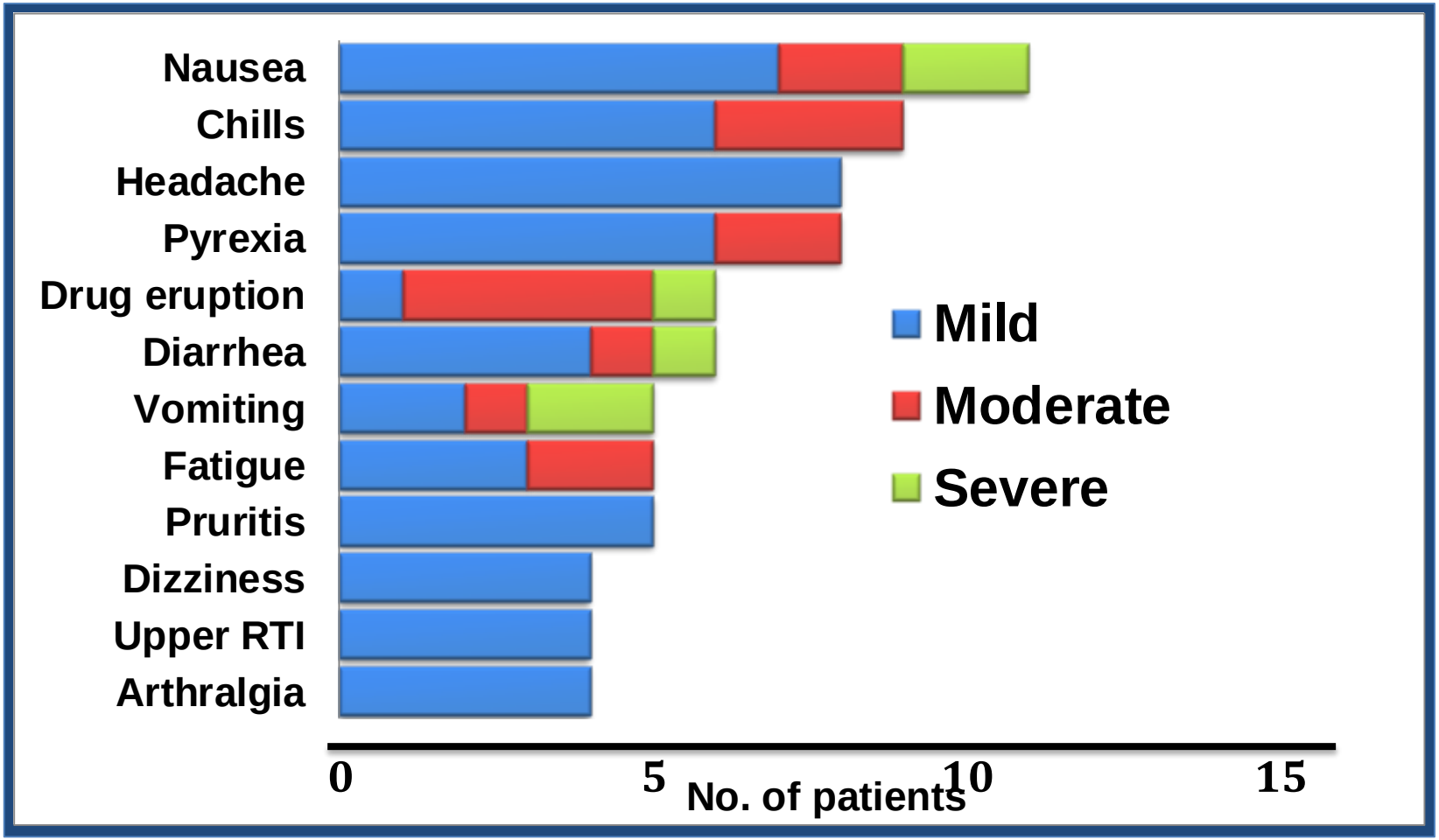


Best Response by Compartment: Patients with ≥B1 Blood Involvement



- 7/15 (47%) of patients responded to treatment
- 13/15 (87%) had response in blood
  - 7/15 (47%) had CR in blood

Severity of Most Frequent AEs



Duvic et al. Blood Jan 20 epub 2015

Drug Eruption

Pt. 02-MDACC

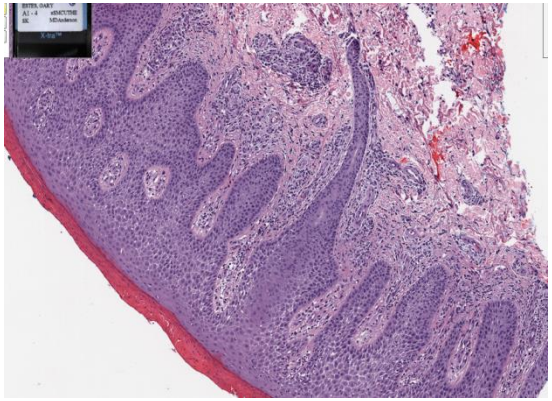
Pt. 05-MDACC

Six patients had drug eruptions not consistent with underlying disease

- Four patients discontinued treatment due to rash
- Use of systemic steroids for treatment of rash not permitted by protocol

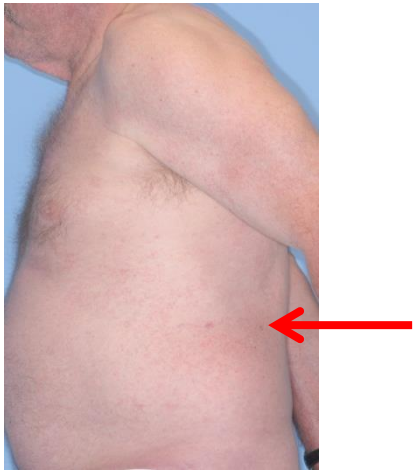
Rash at different cycles during CCR4

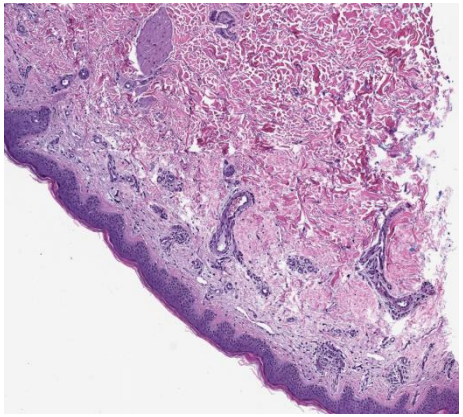
C14 D28



Spongiotic and psoriasiform dermatitis

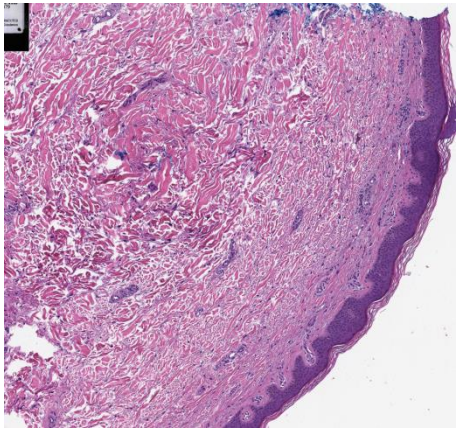
C20D28





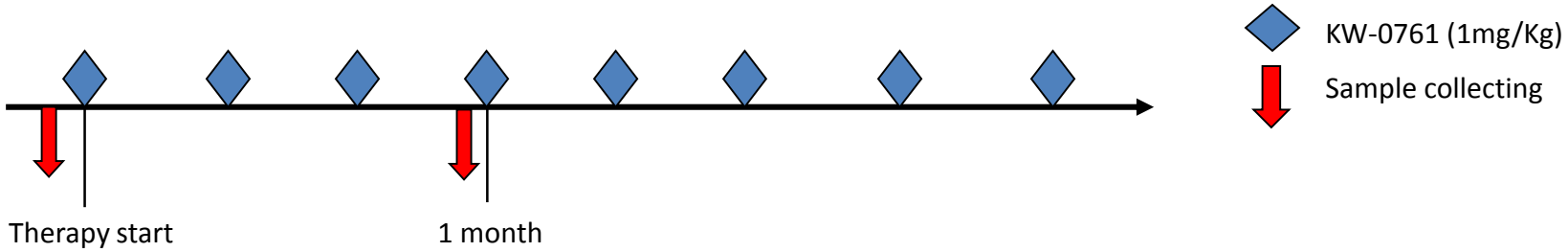
Skin with mild superficial perivascular lymphocytic infiltrate; perivascular dermatitis

C23D28



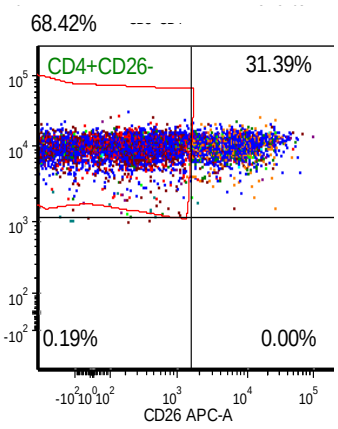
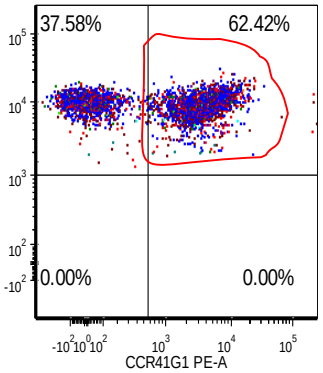
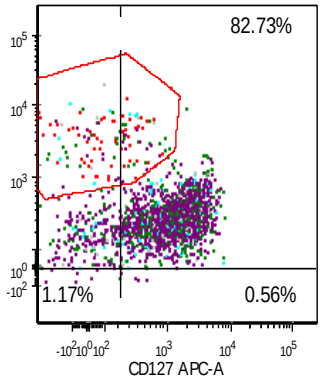
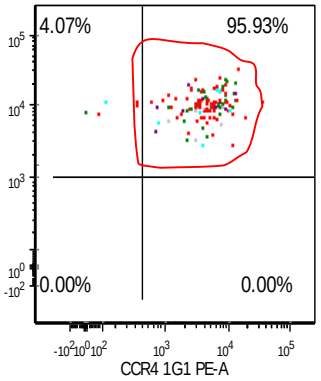
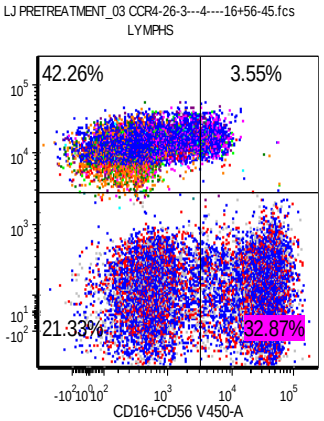
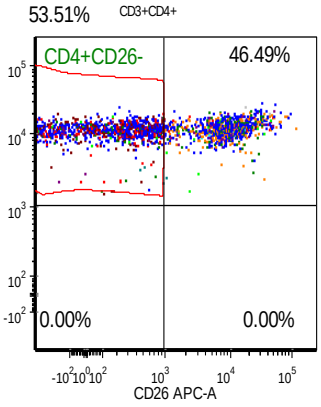
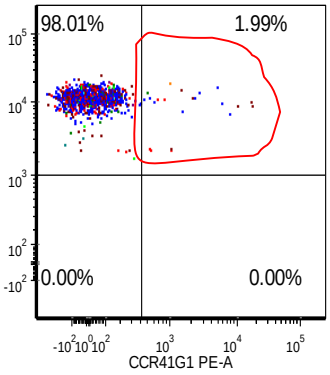
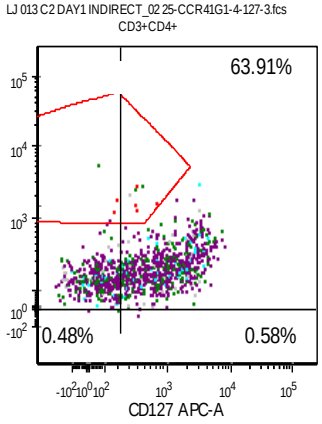
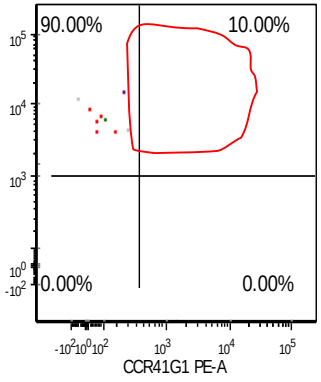
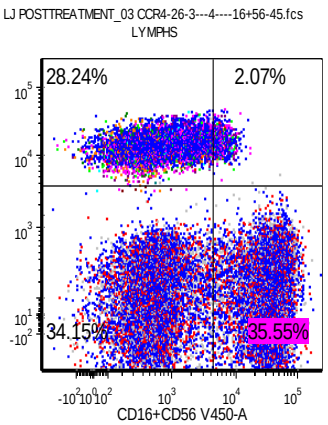
Superficial perivascular dermatitis, consistent with a dermal hypersensitivity reaction.

Translational Study
Materials & Methods



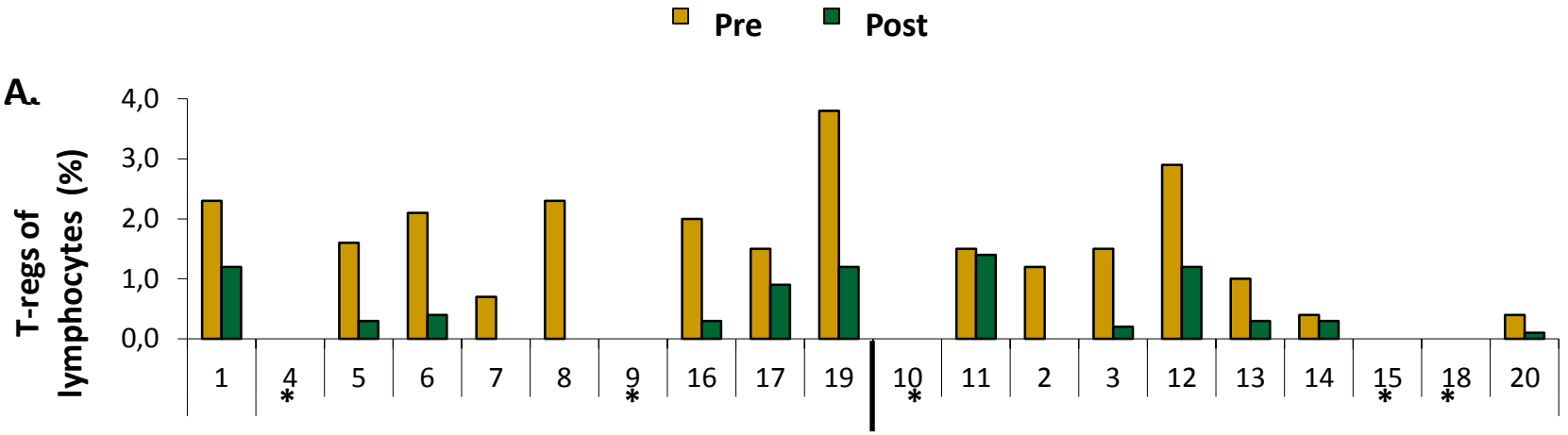
- Peripheral blood mononuclear cells (PBMCs) were collected from 20 patients (10 with MF and 10 with SS) pre- and 4-6 weeks post-KW-0761 at two centers.
- Flow cytometry analysis: T-regs: CD3+CD4+CD25+CD127-
  CCR4+ T-regs: CD3+CD4+CD25+CD127-CCR4+
  NK cells: CD3-CD56+CD16+
- Real-time PCR: The relative fold changes of foxp3 and CCR4 mRNA in PBMCs before and after treatment
- The standard 4-hour ^{51}Cr release assay: the cytotoxicity of NK cells in PBMCs before and after treatment

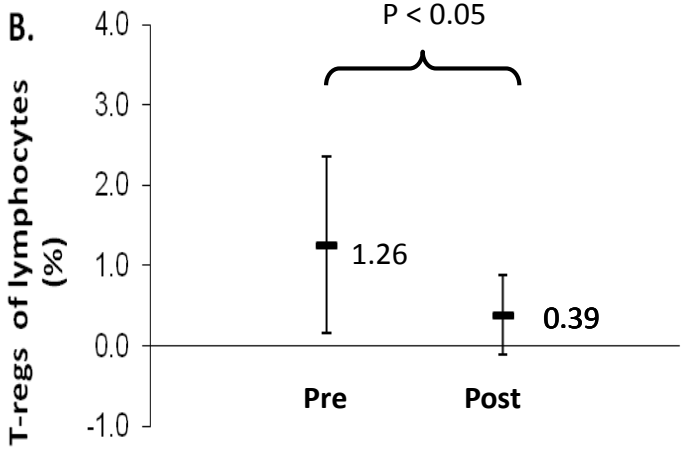
Flow cytometry analysis of tumor cells, T-regs, and NK cells in PBMCs of one CTCL patient pre- and post-treatment x 1 course

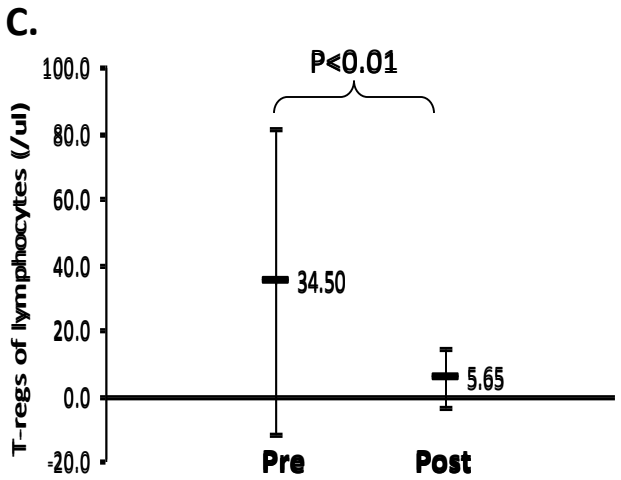
	A. CD3+CD4+CD26- tumor cells	B. CCR4+ tumor cells	C. CD3+CD4+CD25+ CD127- T-regs	D. CCR4+ T-regs	E. CD3-CD16+ CD56+ NK cells
Pre-Treatment					
Post-Treatment					

A representative of flow plots from Pt #8, MF, stable disease, after one course treatment

Anti-CCR4 decreased CD3+CD4+CD25+CD127- T-regs





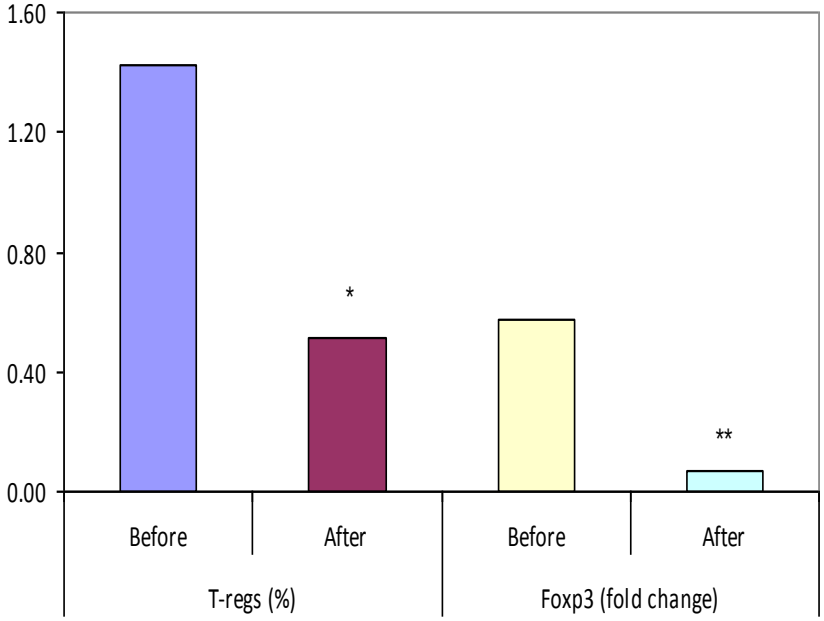


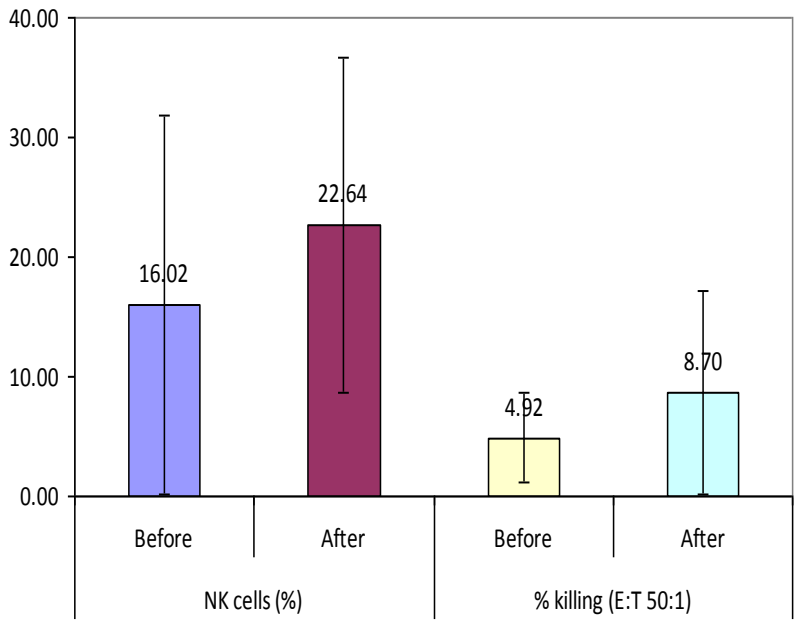
- 15/20 (75%) patients had detectable T-regs at baseline
- 15/15 (100%) patients had decreased T-regs in percentages (Figure B) and absolute #(Figure C) after treatment

* Patients who had no detectable T-regs (Figure A)

Ni et al. Clin Cancer Res. 2015 Jan 15;21(2):274-85.

Effects of anti-CCR4 antibody (KW-0761) on regulatory T cells and natural killer cells in CTCL patients





% T-regs Foxp3 %NK % Killing

Ni et al. Clin Cancer Res. 2015 Jan 15;21(2):274-85

Conclusions

- Mogamulizimab - humanized defucosylated mAb to skin homing chemokine receptor CCR4
- OR is 47% in SS, 29% in MF, and 37% MF/SS
- Flow cytometry to diagnose SS and monitor response of blood to CCR4 therapy.
- Mogamulizimab depletes malignant T memory SS cells and T-regulatory cells rapidly
- Ongoing Phase III Randomized International Trial of Mogamulizimab vs vorinostat PFS

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Alemtuzumab Anti-CD52 mAb

Outcome, %	Phase II Study: Sweden[1] Advanced MF/SS (n = 22)	Phase II Study: Northwestern[2] E-CTCL (N = 19)	Open label: Chicago[3] Heavily pre-tx E-CTCL (n = 19)
ORR	55	79	84
CR	32	47	47
PR	23	32	37
TTF, mo (range)	12 (5 - 32+)	NR	NR
DOR, mo (range)	NR	7 (1 – 39)	NR
PFS, mo	NR	NR	6
OS, mo	NR	NR	41

1. Lundin J, et al. Blood. 2003;101:4267-4272. 2. Querfeld C, et al. 2006 Ash Annual Meeting. Abstract 2732.
3. Querfeld C, et al. Leuk Lymphoma. 2009;50:1969-1976.

Start with skin care for SS patients

- Staph colonization induces pruritus, erythroderma, LDH, and elevated SS cells
  - Oral dicloxicillin or IV vancomycin (MRSA)
  - Bleach baths & antibacterial soap or
  - Acetic acid rinse to lower pH
  - Mupiricin for nares, fissures
- Repair barrier: Ceravé, Cetaphil, Restoraderm
- Topical triamcinolone with wet wraps
- Pruritus: Gabapentin 300 mg TID