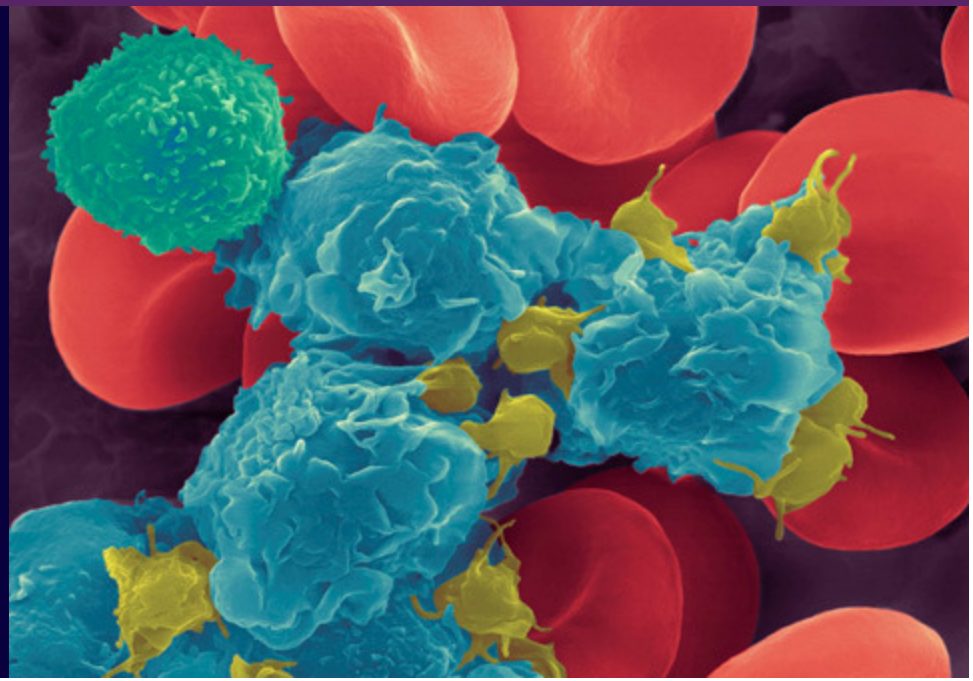
Tuesday September 28, 2015

Silencing the Elusive Sézary cell Past, Present, & Future

Madeleine Duvic, MD
Prof of Dermatology &
Internal Medicine
Blanche Bender Chair in
Cancer Research
Dept of Dermatology
MD Anderson Cancer Center
Houston, Texas



Disclosures

Clinical Trial or Research Support– Allos/Spectrum, Eisai, Galderma, Kyowa-Kirin, Merck, Millineum, Seattle Genetics, Rhizan, Innate Pharma, Tetrologics, Therakos, Valient

Consultant – Eisai, Galderma, Kyowa-Kirin, Ligand, Merck, Millennium, miRNA, Innate

Past Advisory Boards – Allos/Spectrum, Celgene, Eisai, Galderma, Seattle Genetics, Millinieum, Kyowa-Kirin



Albert Sézary

(1880-1956)

French Dermatologist - Venereologist.
Described "cellules monstrueuses" (monster cells) in skin and blood

Am J Dermatopathology
Aug 28(4):357-67, 2006

Sézary Patient



WHO-EORTC Classification of CTCL

Variants recognized by Clinical-Pathologic features

Cutaneous T-Cell and NK-Cell Lymphomas
Mycosis fungoides - effector skin memory cells
MF variants and subtypes
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome - central memory T cells – leukemia CD4+CD26- or CD7-
Adult T-cell leukemia/lymphoma ATCL (HTLV-1+)
Primary cutaneous CD30+ lymphoma (ALCL) & Lymphoproliferative disorder (LyP)
Extranodal NK/T-cell lymphoma, nasal type (EBV+)
Primary cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
Cutaneous γ/δ T-cell lymphoma (provisional)
Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)

Willemze R, et al. Blood. 2005;105:3768-3785.

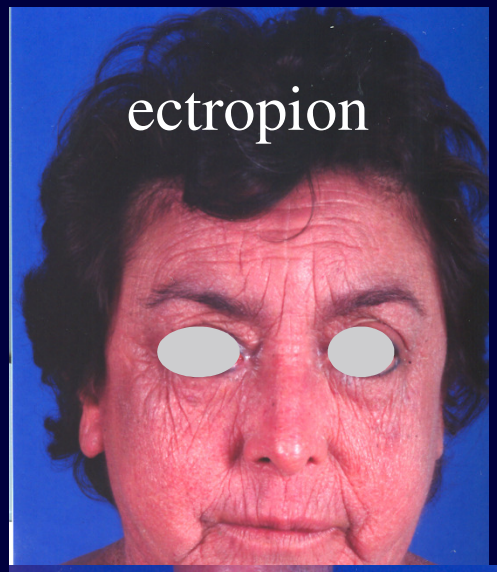
Questions about Sezary Syndrome

- Why are SS patients red and get keratoderma?
- Why are they itch?
- Why is the SS cell nucleus cerebriform?
- Why does photopheresis improve both SS and GVHD?
- Can Antiboides or drugs selectively kill malignant T cells?
- Next Gen Sequencing: What are the genetic or epigenetic drivers of T cell proliferation and genomic instability.
- How can we cure SS?

Clinical Findings of Sézary Syndrome

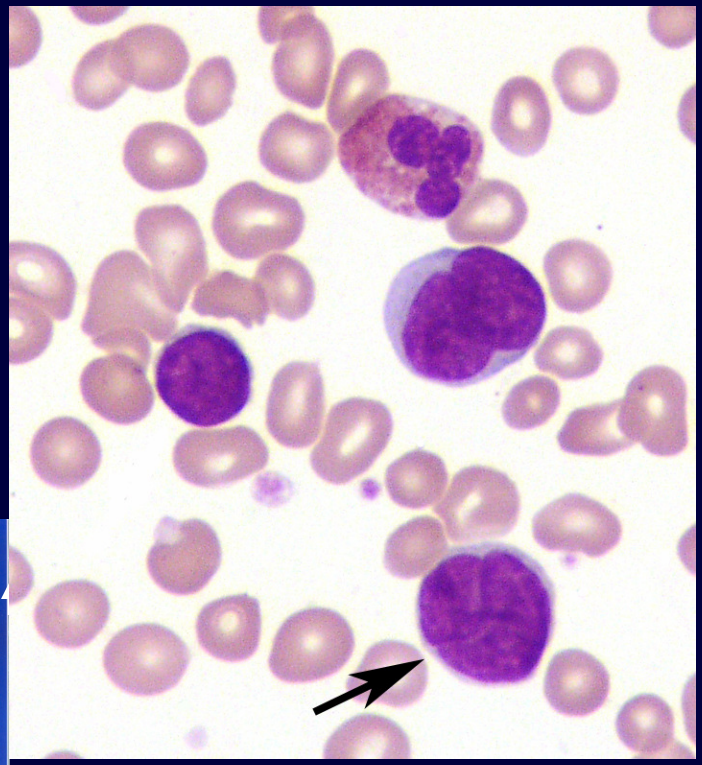


Erythroderma
> 80% BSA
Pruritus / staph colonization 60%





Keratoderma + Tinea pedis



CD4+26- or CD4+7-SS by flow cytometrhy
B0, B1 250-1000,
B2 >1000

Adenopathy – LN0-4
Bone marrow +/-

Why are SS patients red?

74 yo WF - Sézary Syndrome x 7 years. ECP, bexarotene, & gemcitabine.
Red with MRSA sepsis stopped on ampicillin. Ongoing CR x >10 years.



Baseline



Week 8

Staph and Sézary Syndrome

- Sepsis is most common cause of death in SS patients.
- 1992 - SS cells proliferate in response to bacterial superantigens according to Vb usage.
- 1995 – Catheter associated sepsis in 11/12 ECP pts noting that IV Abs improve EE. *Duvic JAAD 1996 35(4):573*
- 1997 - 76% enterotoxin+ S.Aureus- ETS-1 - TSST- assoc Vb2 - no fever. *Jackow CM, et al. Blood. 1997 Jan 1;89(1):32-40*
- 48% of 107 E/SS pts colonized with S.A. or MRSA. 85% decolonized w treatment - *Br J Dermatol 2008 Jul;159(1):105-12.*
- Standard of care: Atopic skin care w antibiotics improves redness, LDH, SS number, pruritus, and OS

Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC)

Elise Olsen, Eric Vonderheid, Nicola Pimpinelli, Rein Willemze, Youn Kim, Robert Knobler, Herschel Zackheim, Madeleine Duvic, Teresa Estrach, Stanford Lamberg, Gary Wood, Reinhard Dummer, Annamari Ranki, Gunter Burg, Peter Heald, Mark Pittelkow, Maria-Grazia Bernengo, Wolfram Sterry, Liliane Laroche, Franz Trautinger, and Sean Whittaker, for the ISCL/EORTC

Revised Blood and Node Staging - 2007

Clinical Evlauation MF/Sézary Syndrome

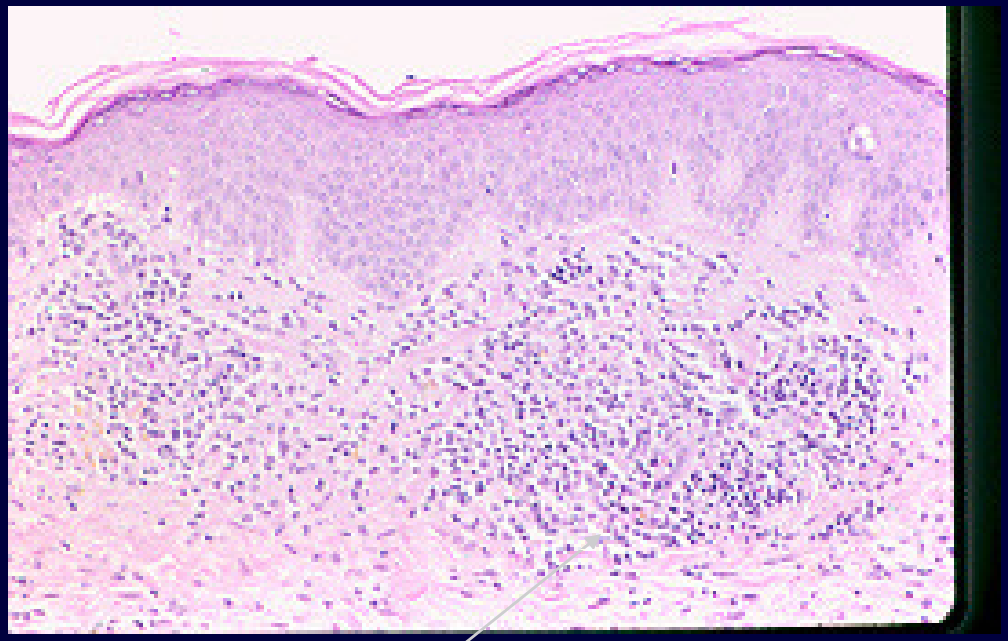
mSWAT Weighing Factors

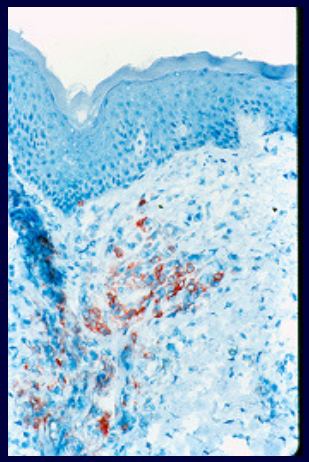
- % involvement with patch x 1
- % involvement with plaque x 2
- % involvement with tumors (ulcers) x 4

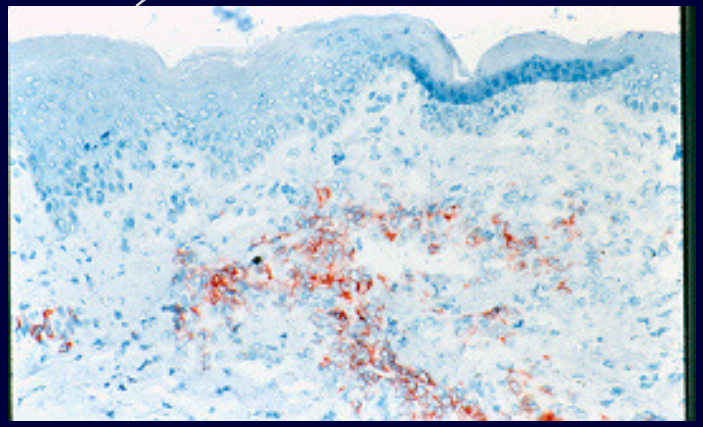
- mSWAT = sum of % lesions x factor

- BSA (body surface area) w/o weighing
- Sezary defined as >80% BSA or T4

Leukemic CTCL and Sezary Syndrome are perivascular







CD 25

CD 30

Perivascular infiltrates without diagnostic epidermotrophism

Sézary cells cerebriform morphology

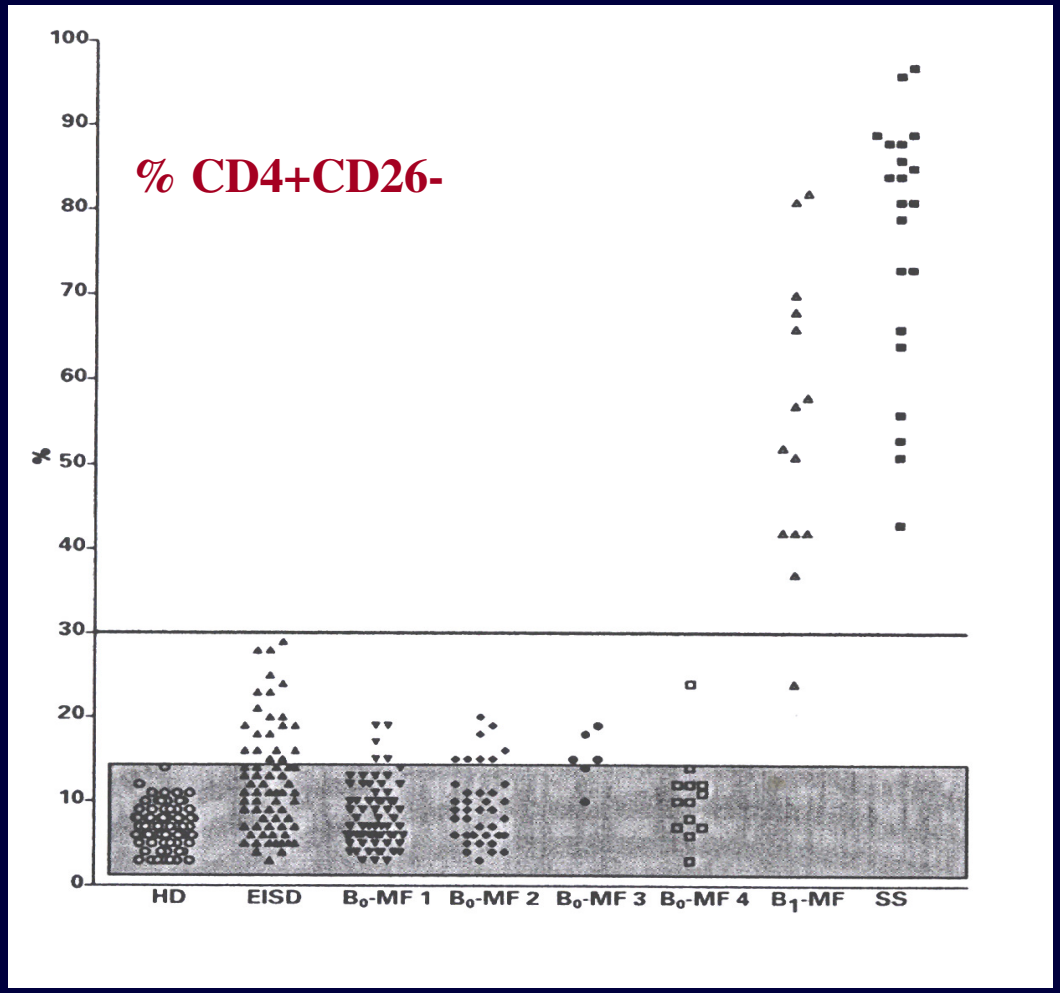
CD4+CD26-

CD4+CD7-

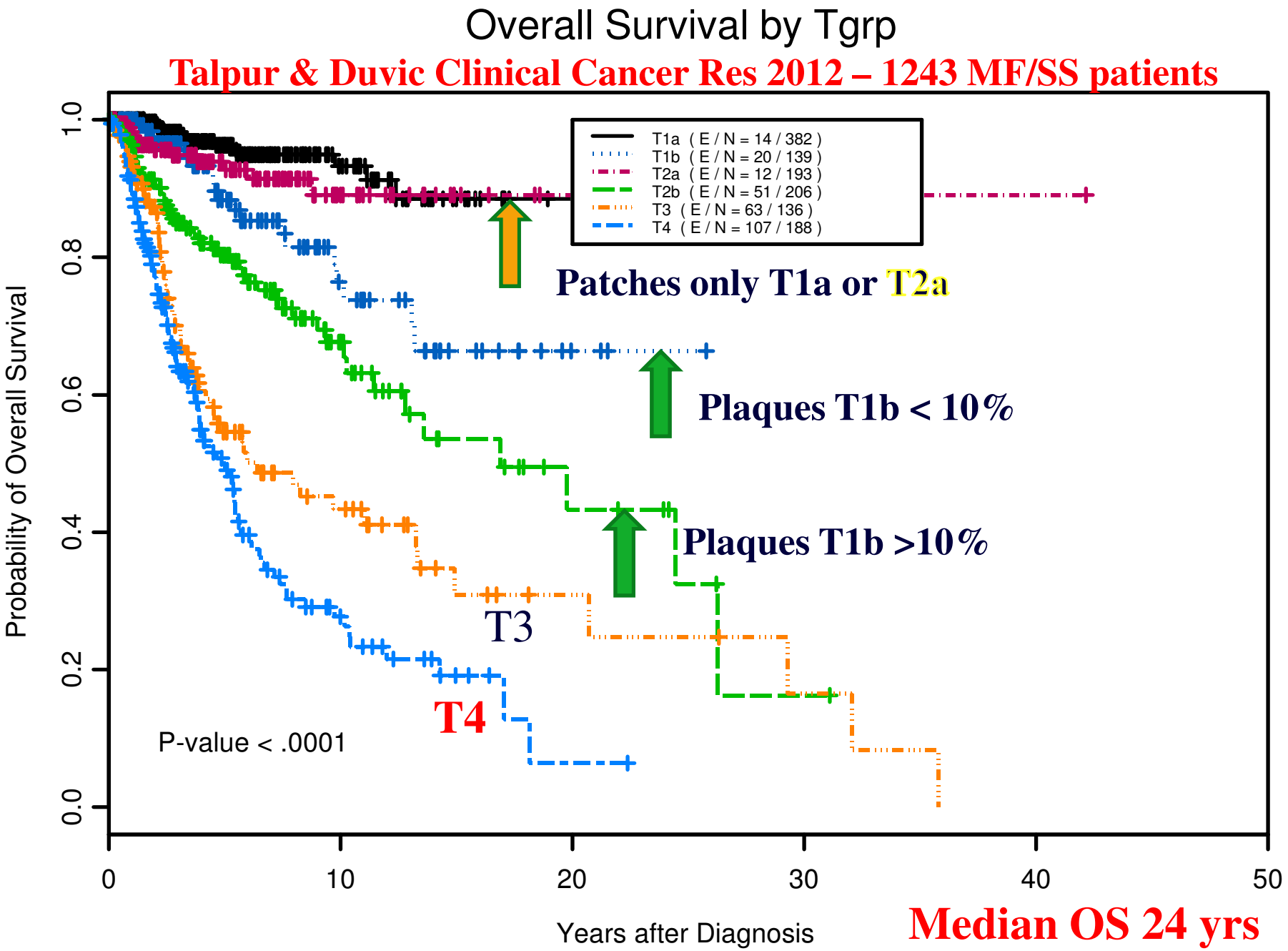
Central memory T-cells

Diwan AH, Prieto VG, Herling M, Duvic M, Jones D. Am J Clin Pathol. 2005 Apr;123(4):510-5

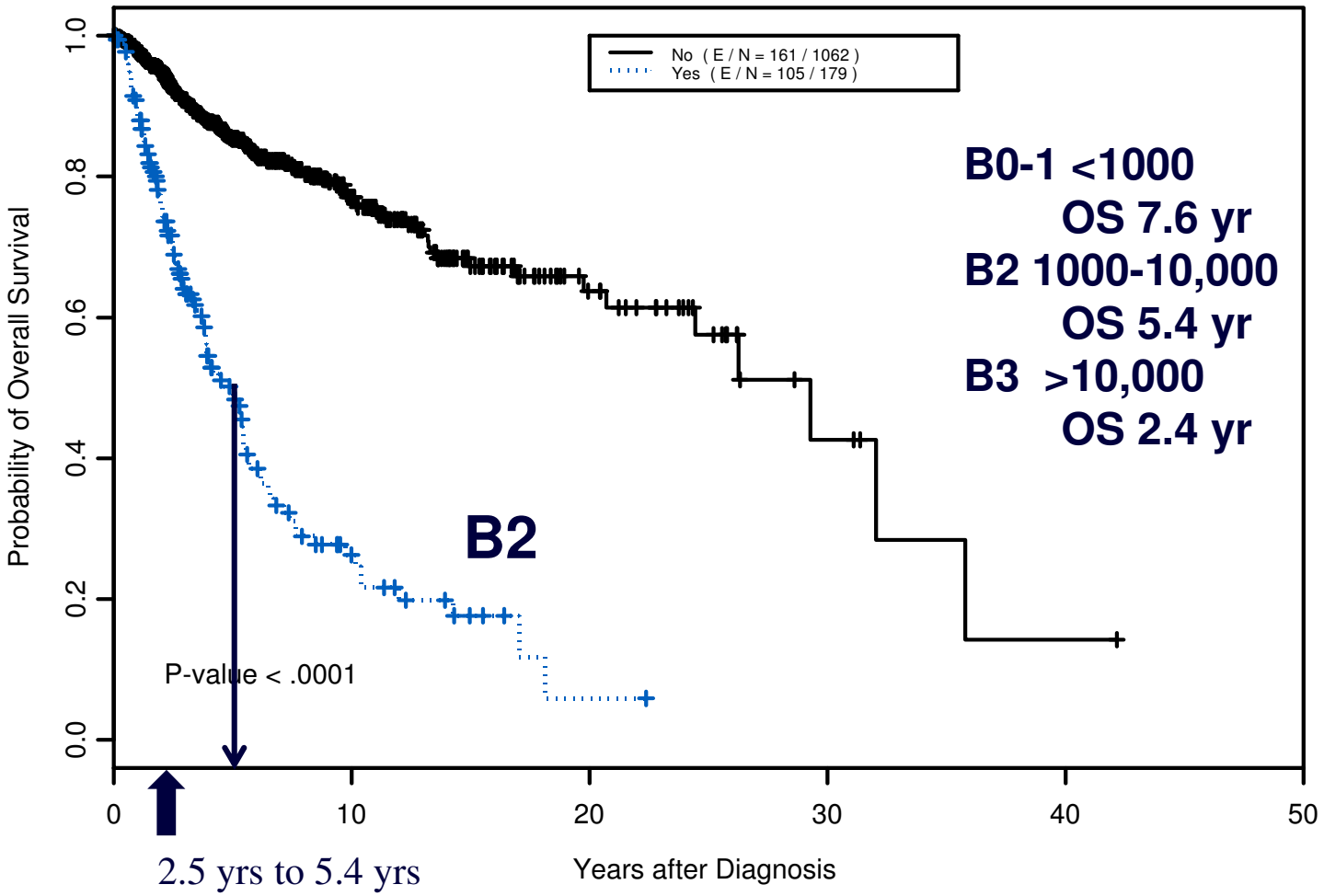
CD4+26- in blood by stage using flow



Bernengo, M.G. The relevance of the CD4+CD26- subset in the identification of circulating Sézary cells. Br J Dermatol 2001;144:125.


Overall Survival by Tgrp
Talpur & Duvic Clinical Cancer Res 2012 – 1243 MF/SS patients
T1a (E / N = 14 / 382)
T1b (E / N = 20 / 139)
T2a (E / N = 12 / 193)
T2b (E / N = 51 / 206)
T3 (E / N = 63 / 136)
T4 (E / N = 107 / 188)
Patches only T1a or T2a
Plaques T1b < 10%
Plaques T1b >10%
T3
T4
P-value < .0001
Probability of Overall Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
Years after Diagnosis
Median OS 24 yrs

Overall survival of 124 Erythrodemic CTCL



- *Talpur R et al. Clin Cancer Res 18(18):5051-60, 2012..*
- *Vidulich et al. 2009 Int J. Derm 48(3)243-252*

What Sezary saw

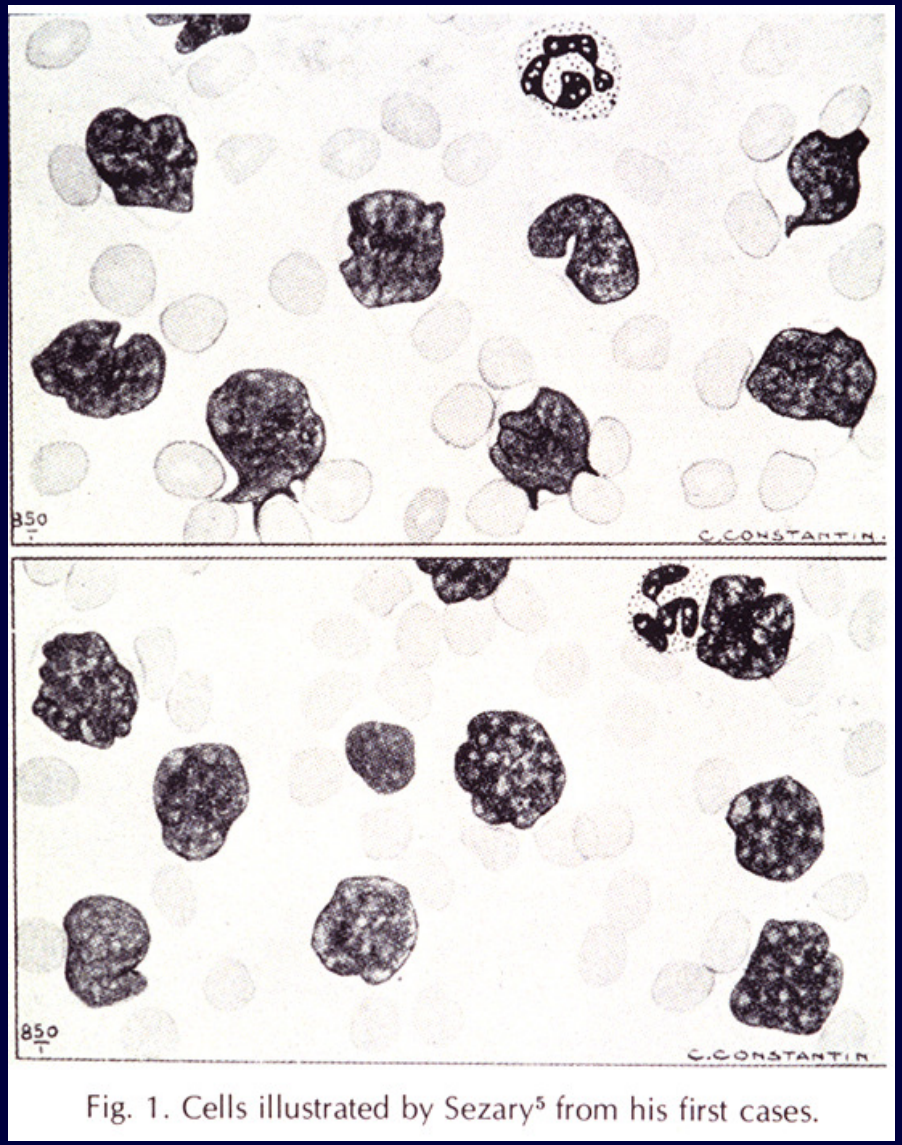
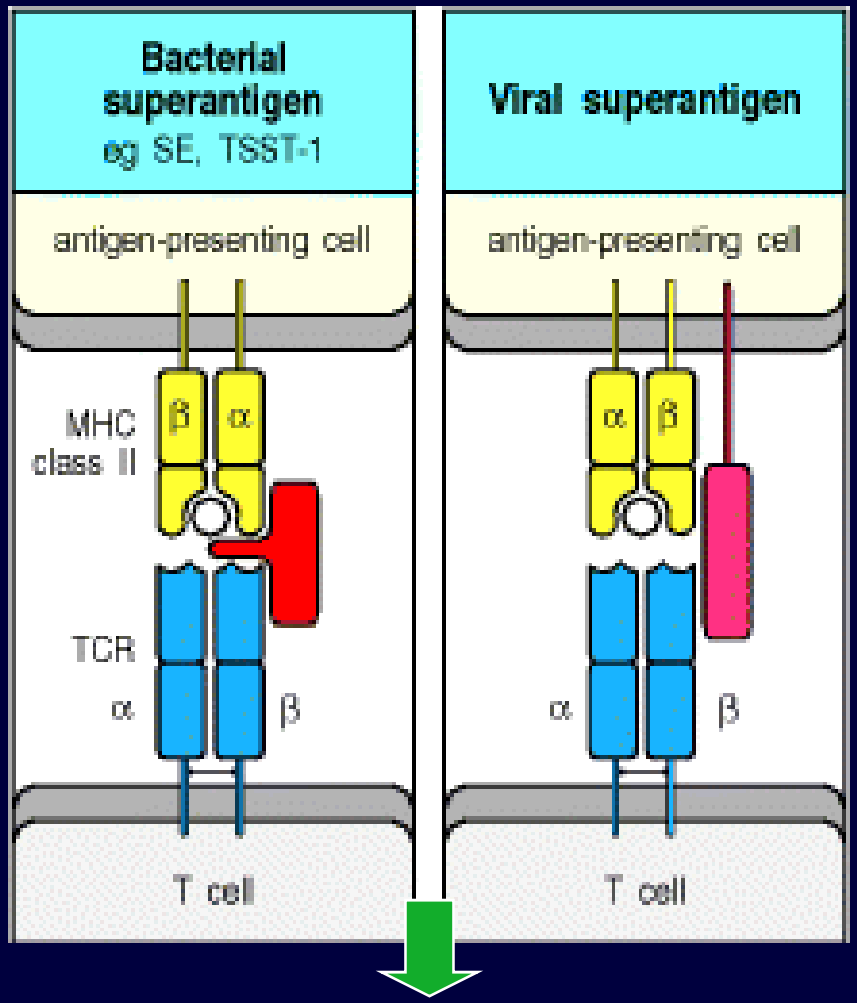


Fig. 1. Cells illustrated by Sezary[5] from his first cases.

What we know now

- Helper Central Memory CD4+CD45R0+CLA+4
- Perivascular infiltrate w/out epidermotropism
- Clonal TCR rearrangements
- Abnormal karyotypes
- Th2 cytokines, T-Plastin, Twist, CCR4, CXCR3. KIRDL2, Foxp3, IL2R, Jak/stat5, IL31 itch
- Accumulation – loss of fas induced apoptosis.
- Role of epigenetics HDACi

What antigens do T cells encounter?



Polyclonal Expansion of Vβ-bearing CD4+ T cells

- T-cells see peptides on dendritic cells in skin, LN
- CLASS 2 Antigens/APC
  - HLA-DR 5 –SS OR= 3
  - DQB1*03 – SS OR = 4.7
  - DQB1*0502 w SS
  - OR= 7.75
- Drug – HCTZ, SSI, gleevec, anti-convulsants

Jackow et al. J Invest Dermol 1996 Sept;107(3):373-6.
Jahn-thigh et al Cancer

FDA Approved Therapies

- PHOTOPHERESIS – Edelson- first immunotherapy 1988
- Denileukin diftitox - first fusion toxin – 1990s
- Bexarotene (Targretin) - first rexinoid in man 1990s
- Vorinostat first histone deacetylase inhibitor in man
- Romidepsin second HDACi, Belinostat (PTCL)
- Topical Nitrogen mustard in gel base – 2014
- Radiation – electron beam – lower doses 4 x 2, 12 v 36 Gy
- Not approved: Topical Steroids, topical retinoidsaoral soriataine, tazarotene, UVA and PUVA phototherapy, Interferons, methotrexate, TRL agonists, PD1/PDL1

Treatment of E-CTCL and SS

- Palliative skin directed care: culture for Staph, antibiotics, moisturize and use topical steroids wet wraps, NB-UVB, PUVA, TBSEB
- Itching: gabapentin – opiate antagonists
- First line: Rooks combination immunomodulatory therapy: photopheresis, bexarotene +/- interferon alpha or gamma, GM-CSF, avoid po stds
- Second line: HDAC-Inhibitors: Romidepsin, pentostatin, targeted therapies, antibodies (CCR4, CD52,CD30), TBSEB, chemotherapy
- allogeneic SCT —TBEB + non-ablative allo SCT 75% CRs in SS- submitted JCO

Olsen et al J Am Acad Dermatol 64(2):352-404, 2/2011.

Comparison of Systemic Therapies

Systemic Treatments	CR %	ORR (PR + CR)
Interferon +/- ECP	20-40	50-80
Bexarotene	5	50
Methotrexate low dose	Unk	33-58
Methotrexate high dose	64	82
Denileukin diftitox	10	44
Vorinostat	0	30
Romidepsin	6	34
Pralatrexate	6	45

Li JY, et al. Cancer Management Res. 2012;4:75-89.
Drews RE J Clin Oncol. 2012;30:4064-4070.

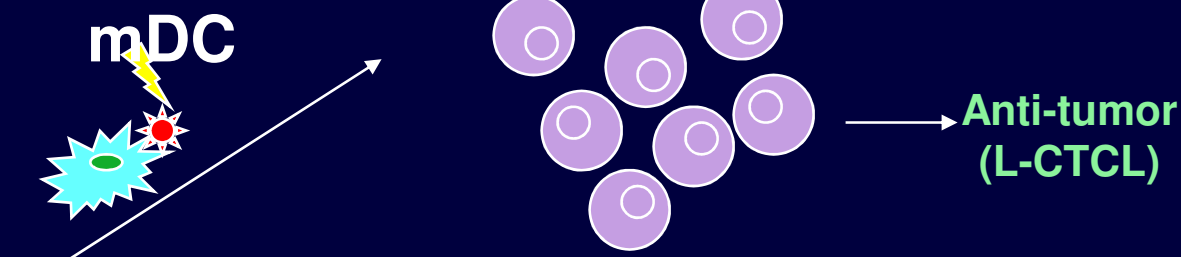
How can photopheresis work in SS and GVHD?

Proposed Mechanisms of Action of ECP

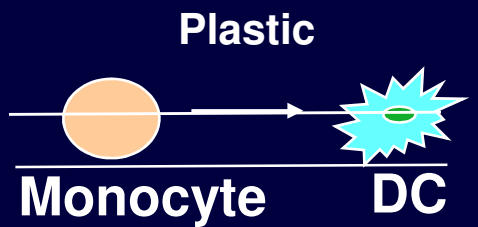
Cytokine modulation



Immunostimulation

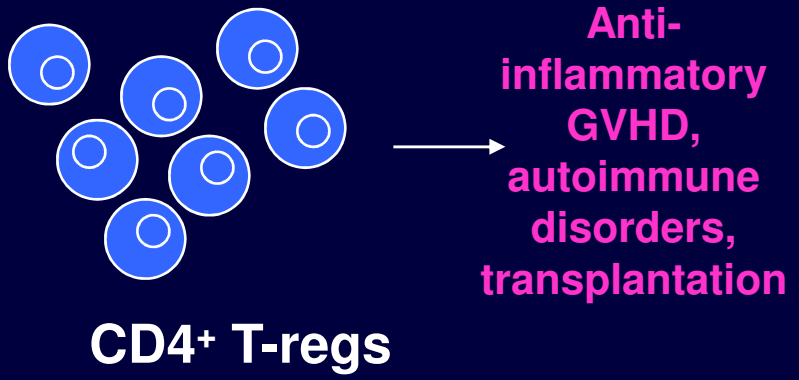


Dendritic cell (DC) differentiation



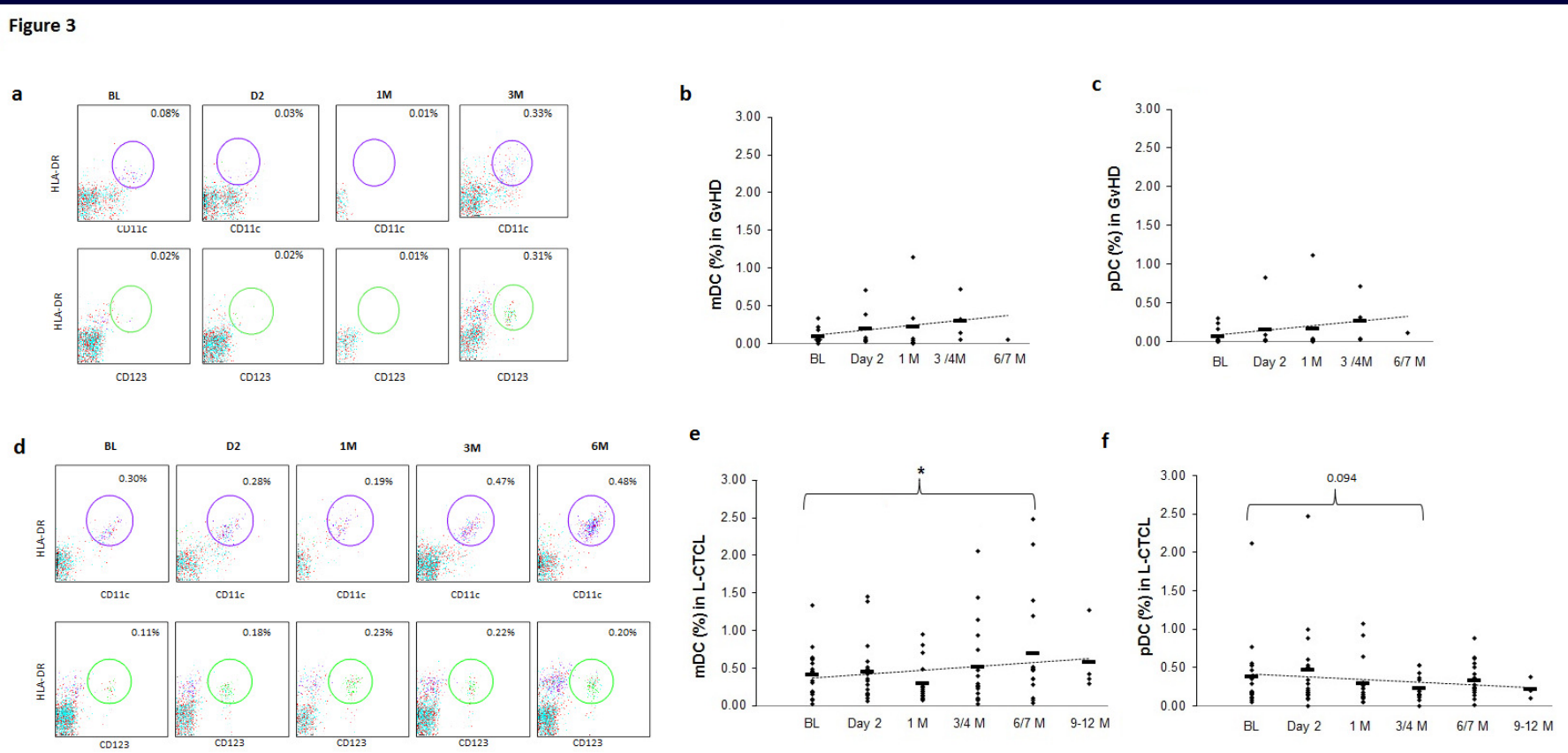


Immunosuppression



Shiue et al, JID, 2013 Aug;133(8):2098-100

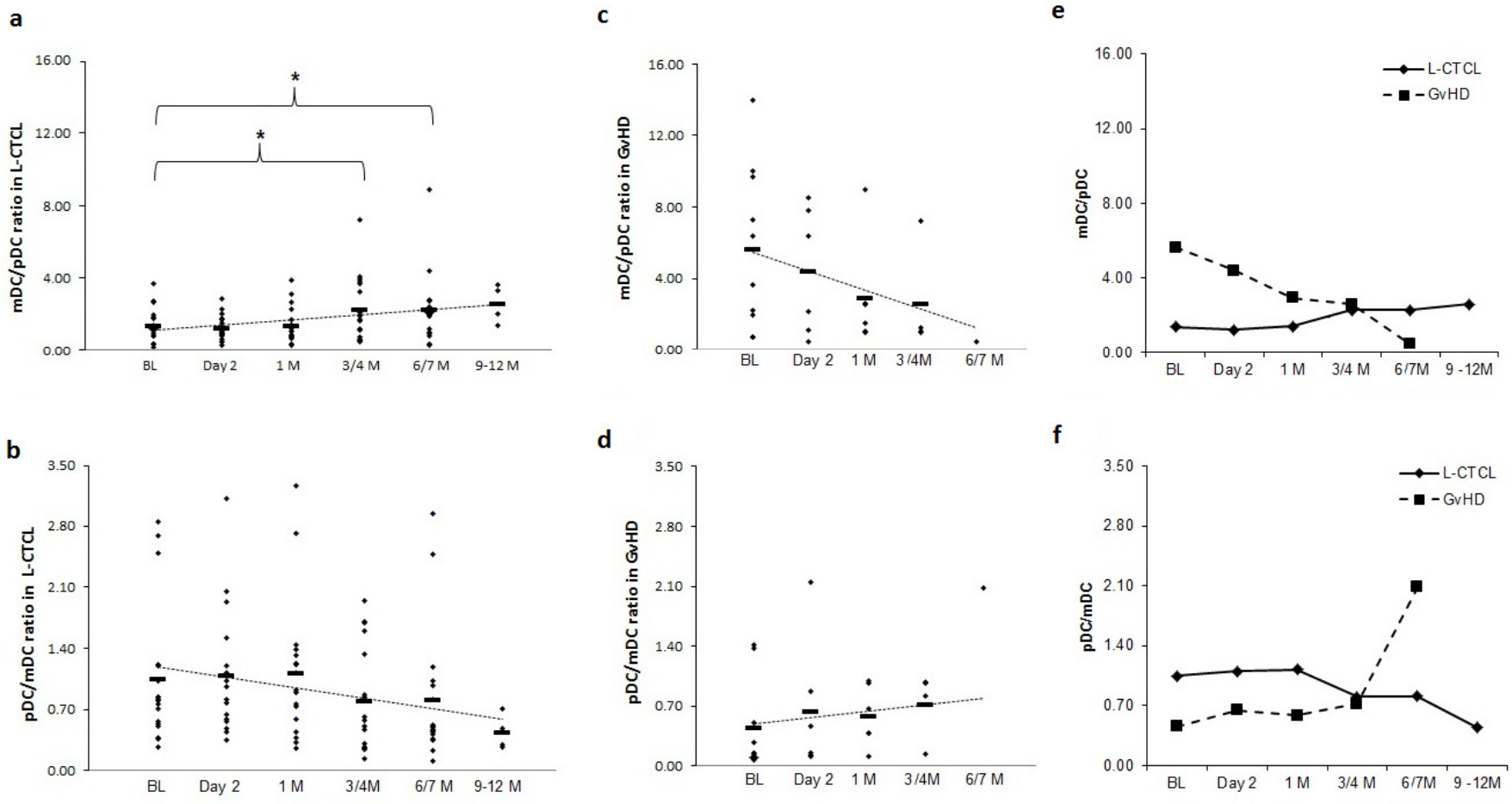
Monocytoid CD11c+ DCs increase in GVHD & SS
Plasmacytoid DC CD123+ up in GVHD, down in SS



Shiue L, Ni X et al, JID, 2013 Aug;133(8):2098-100.

DC ratios change **in opposite directions** in GVHD & SS after ECP treatment

Figure 4



Shiue L, Ni ,X et al, JID, 2013 Aug;133(8):2098-100.



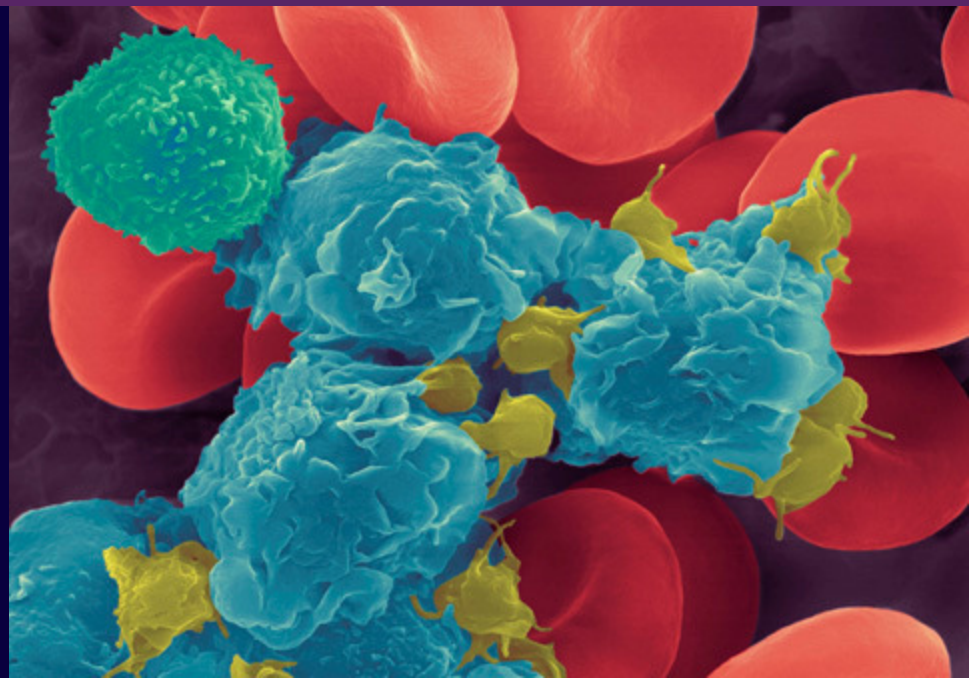
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

CLINICAL CARE OPTIONS®
ONCOLOGY

Allogeneic Stem Cell Transplantation for Cutaneous T-cell Lymphoma: Updated results from a single center

Journal of Clinical Oncology
First 19 patients

Update on 48 patients from 2001 to present



Demographics of 48 allo SCT patients

Age (y), median (range)	**51.5 years (19-72 years)**	
Sex	Male	22 (46%)
	Female	26 (54%)
Ethnicity	Caucasians	33 (69%)
	African American	11 (23%)
	Hispanics	4 (8%)
Clinical and Pathologic Diagnosis	Sezary Syndrome	17
	MF with LCT	24
	SS + LCT	7
	Stage IVA LN+ or IIB	4 nodal; 1 tumor
	Folliculotropic MF	4

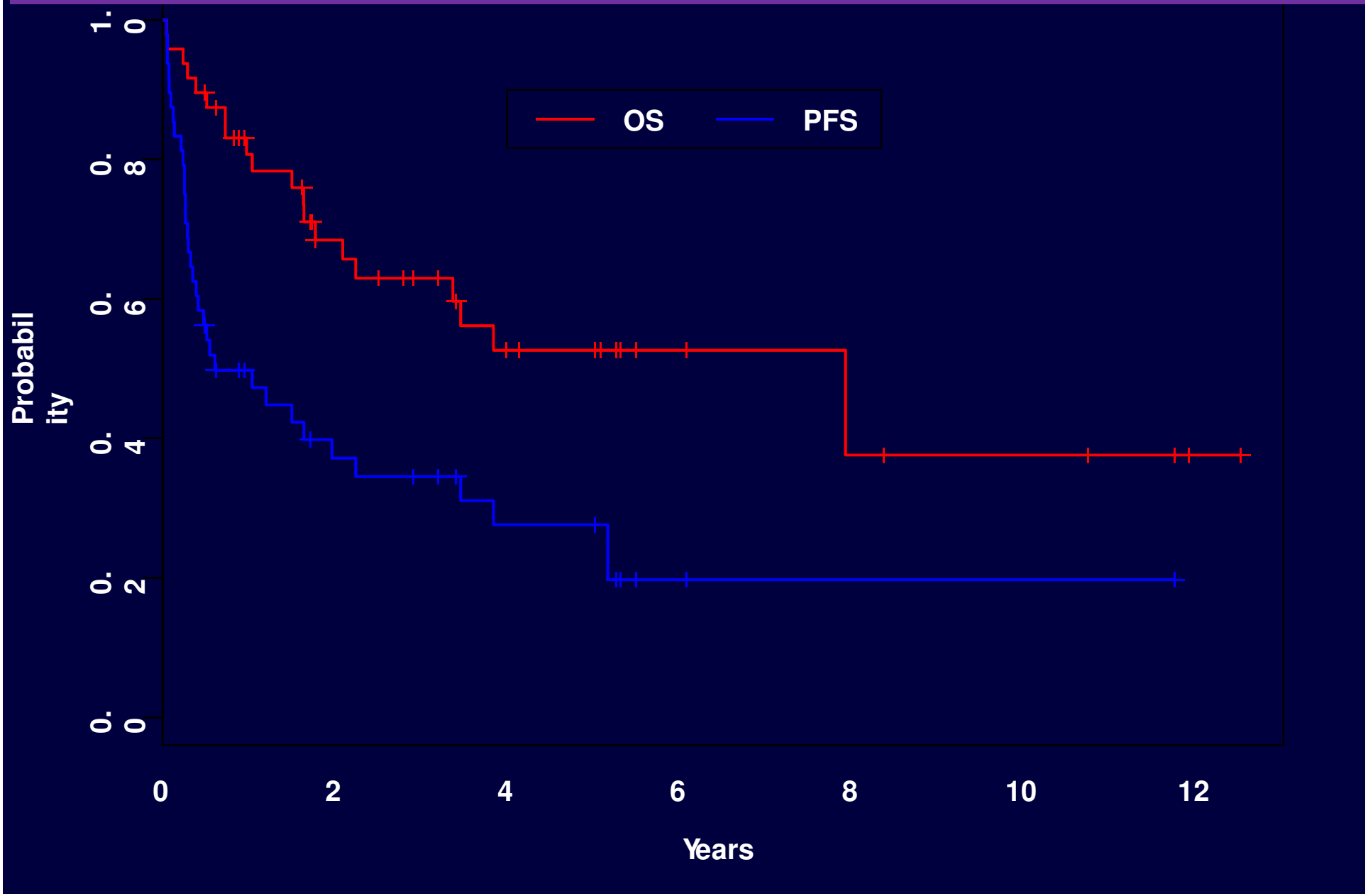
Prior systemic Therapies

Parameter	Patients (N=48)
Median Therapies	6 (range 2-11)
Bexarotene	31 (65%)
Interferon	24 (50%)
ECP	20 (42%)
Chemotherapy	32 (67%)
TBSEB	43 (90%)

Overall Complete Response 58% (28 of 48)
Relapse rate 33% (16 of 48) Mortality rate 44% (21/48)

Clinical Variant	N	Responders 58% (28/48)		Relapsed 33% (16/48)		Non-engraftment 8% (4/48)		Dead/Alive 44% (21/48)
SS	14	11	79%	3	21%			3/11
LCT	16	9	56%	4	25%	3	19%	6/10
SS + LCT	9	4	44%	5	56%			4/9
IVA (LN+) IIB	4 1	2	40%	2	40%	1	20%	1/4
Fol -MF	4	2	50%	2	50%			2/2

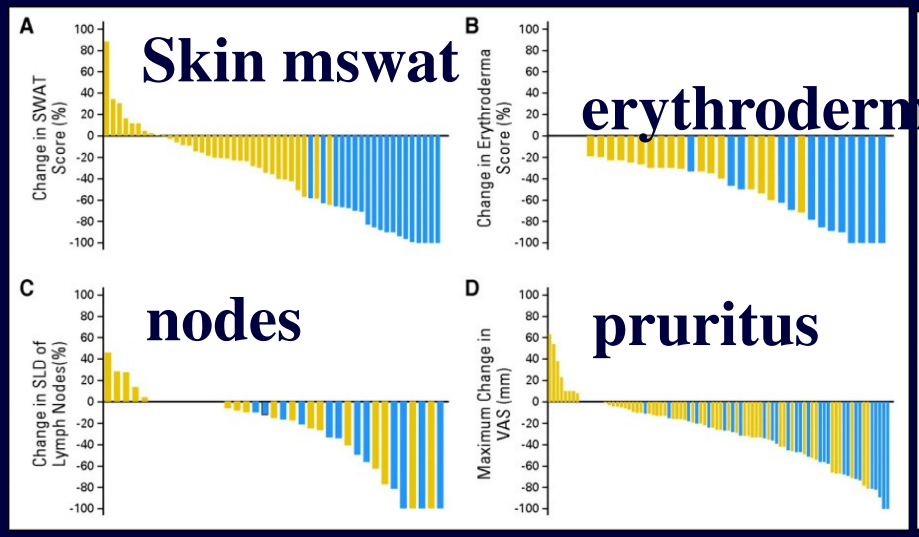
Overall and Progression–Free Survival all 48 pts from Transplant date - 4 yr OS 53%

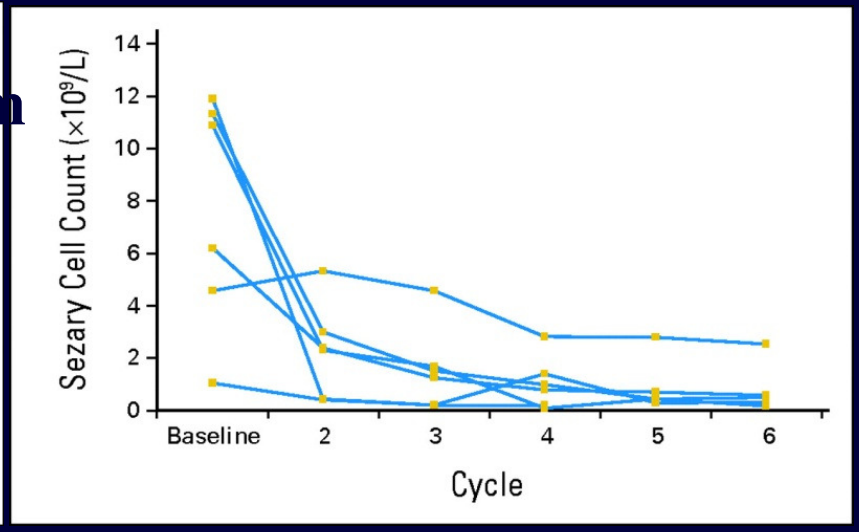


Pan histone deacetylase inhibitor Romidepsin

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 37 pts with B1 or B2 involvement
- 31% (4 of 13) w B2 responded





Whittaker et al JCO October 2010 vol 28, 4485

Targeted Therapies

TARGETED FUSION PROTEINS:

- Denileukin diftox – IL2 plus diptheria toxin –now E7777
- CD3 –diptheria toxin – phase I/II clinical trial

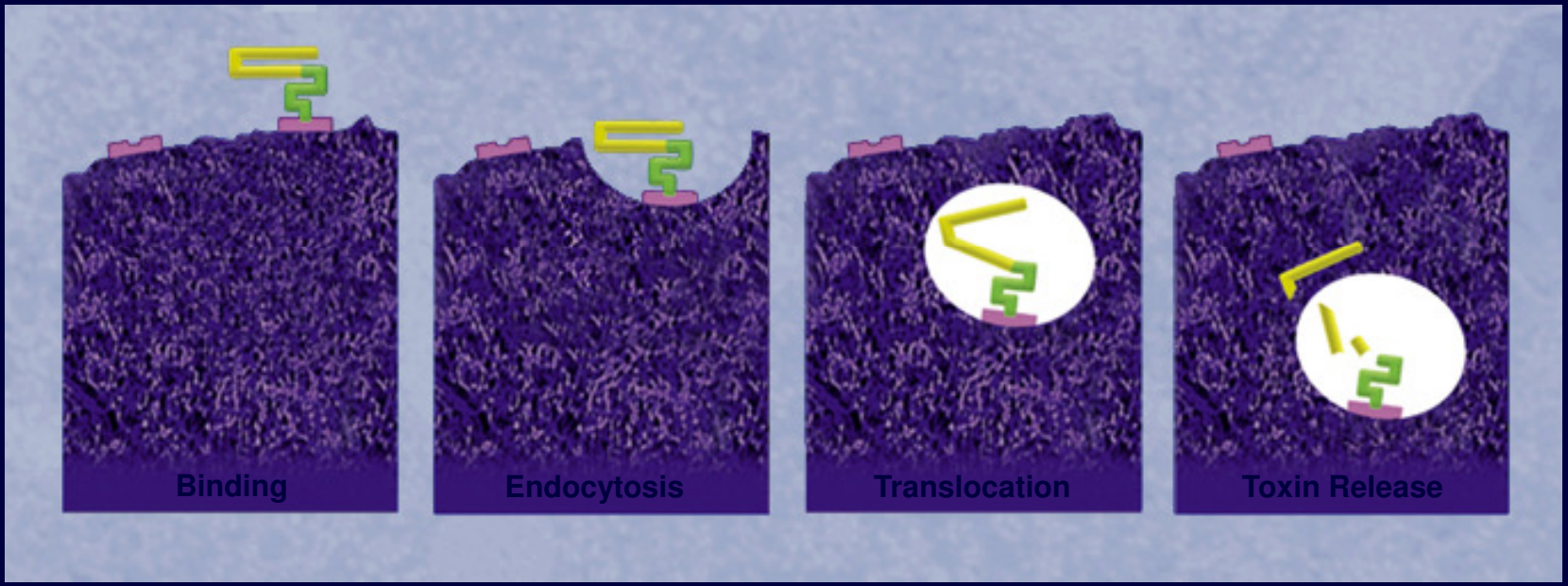
TARGETED ANTIBODIES

- Brentuximab vedotin–anti-CD30-auristatin E conjugate P3
- CCR4 defucosylated Antibody - approved for ATL Japan
- Anti -KIR3DL2 (LPH-4012) killer immunoglobulin like MHC receptors - Orphan status 2014, trial 2015
- Targeting miRNA 155

Duvic et al. Blood 2010 and JID 2013
Kaplan et al Expert Rev Hematol. 2014 Aug;7(4):481-93

Targeted Therapies

ONTAK
Mechanism of Action - Ex-Vivo Studies



1. IL-2 receptor binding

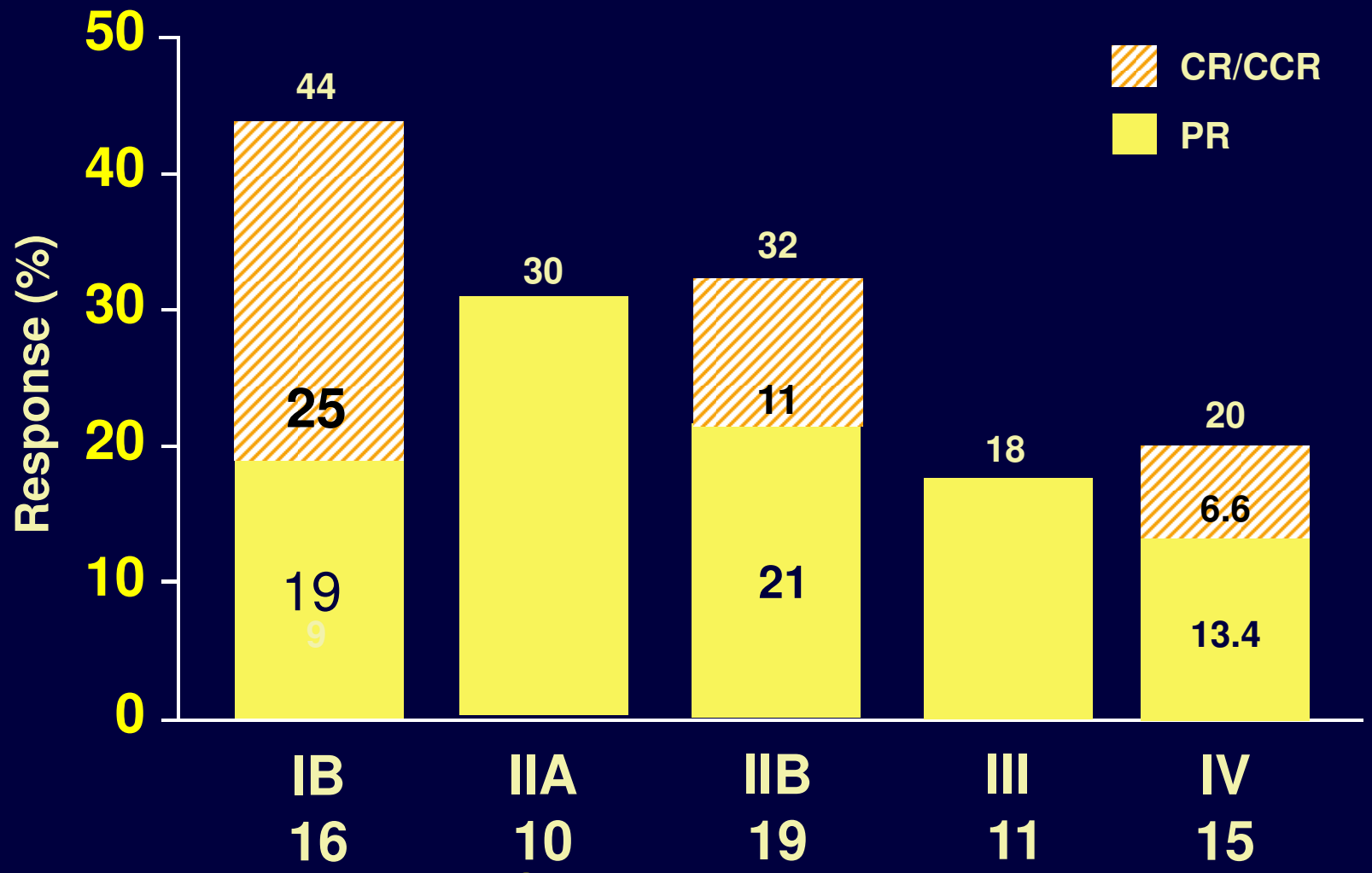
2. Internalization via endocytosis

3. Active fragment released into cytosol

4. Inhibition of protein synthesis, resulting in cell death

Targeted Therapies

Pivotal Phase 3 Trial of Denileukin Diftitox in CTCL: Response Rates by Stage



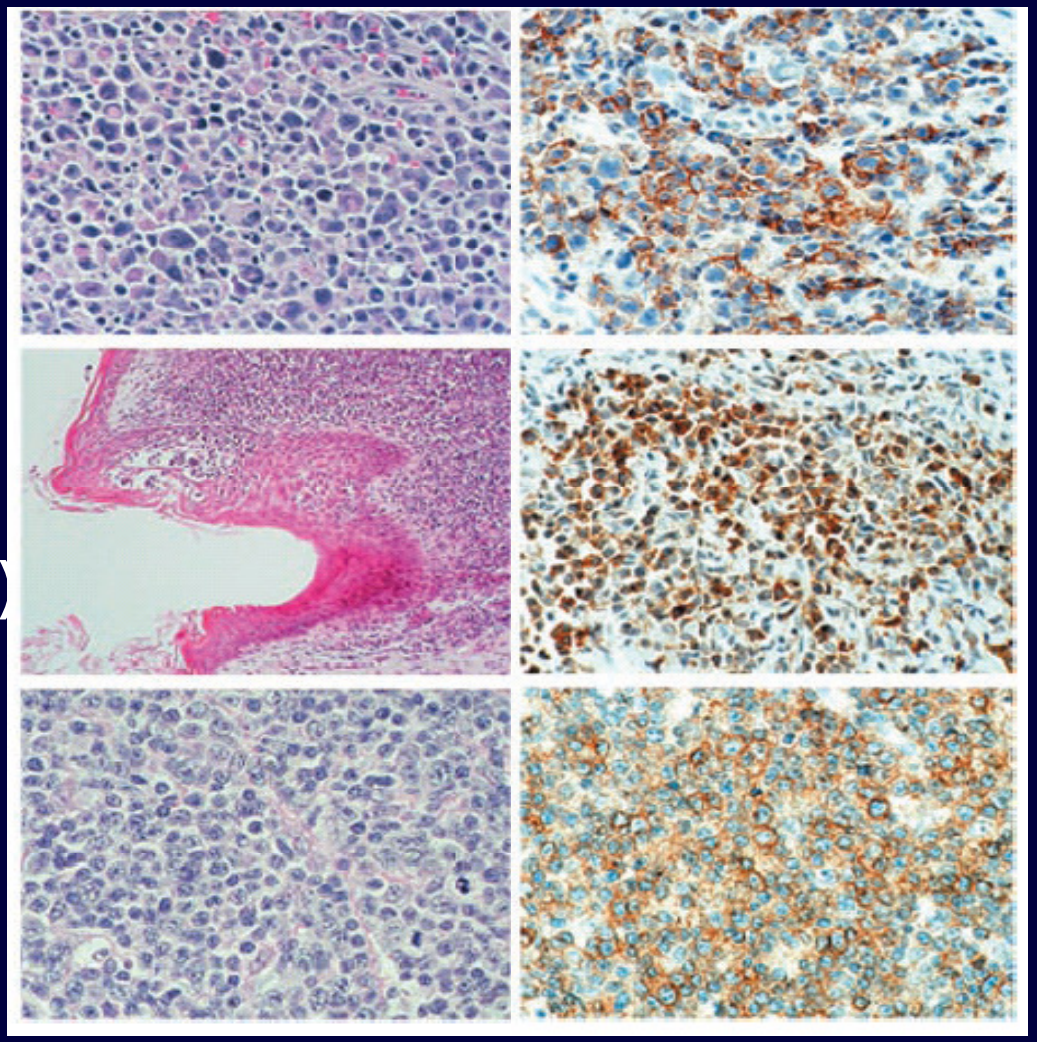
Olsen *et al. J Clin Oncol. 2001;19:376–388.*

CCR4 Receptor on CD4+ lymphocytes

ALK-negative ALCL

MF (transformed)

PTCL-U

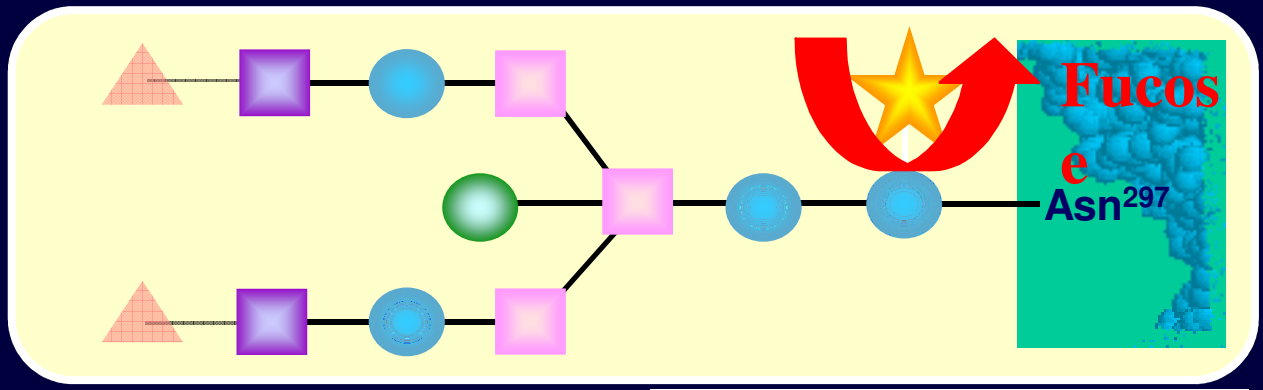


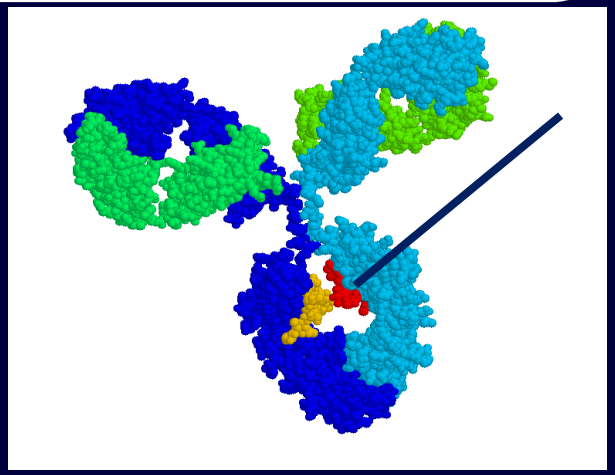
Ishida T, et al. Clin Cancer Res. 2004 Aug 15;10(16):5494-500.

Targeted Therapy to CCR4 chemokine

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

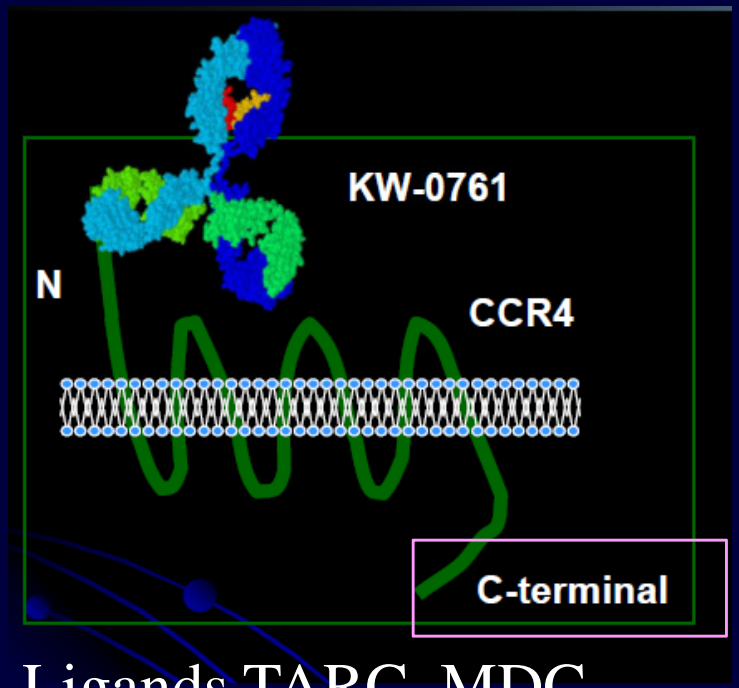
Ishida et al, Clin Cancer Res 2003;9:3625

Humanized Anti-CCR4 Antibody: KW-0761

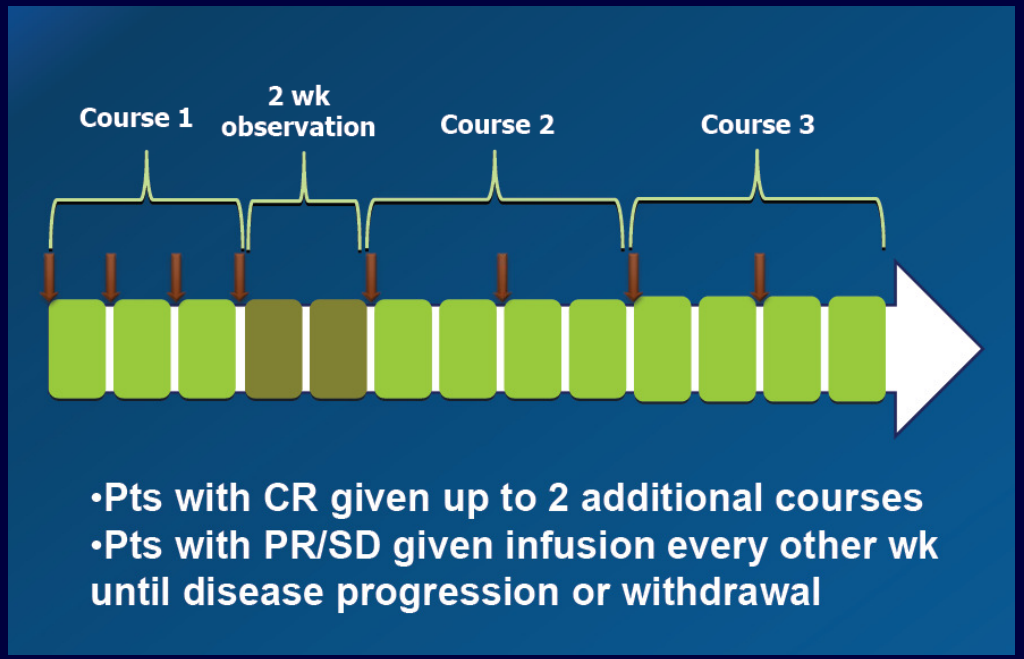
Mogamulizumab (KW-0761)

Schedule q two weeks then q week IV

- Phase I/II studies in ATLL in Japan – approved
- Phase I/II US and Phase III Randomized Trial



Ligands TARC, MDC
on endothelial cells.
Helper CD4 and T-regs



Yano H, et al. Clin Cancer Res. 2007;13:6494-6500.
Duvic M et al. Blood - March 19; 125 (12):1883-9

Mogamulizumab – Anti-CCR4

Case Study: Patient 05-MDACC (MF; Stage IVA ; 4 Prior Therapies)



Pretreatment
Course 1 Day 1



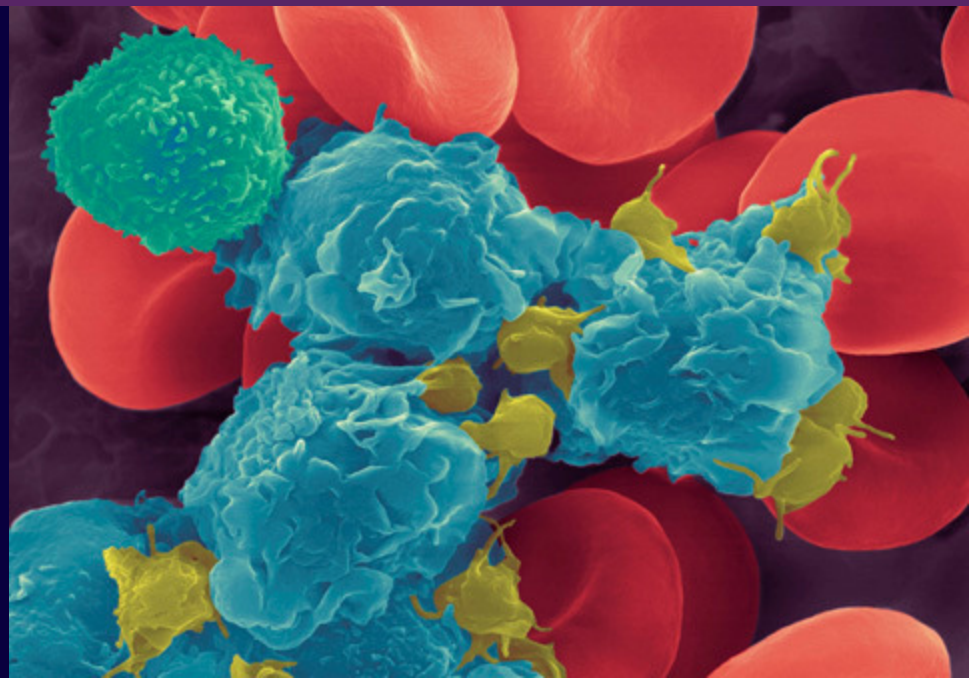
Post Course 6
CR- 3 years

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

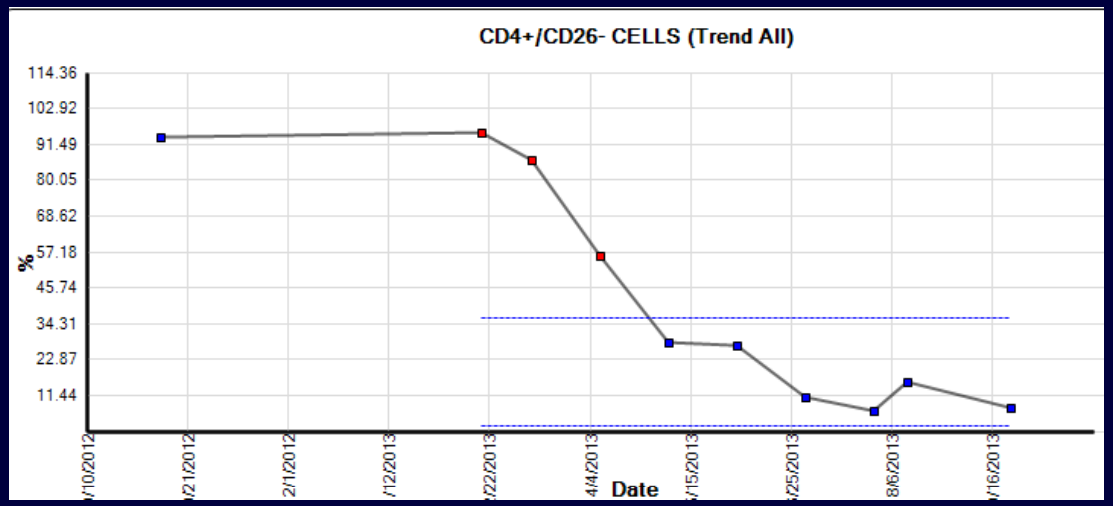
Patient Subgroups	ORR	Number of patients			
		CR	PR	SD	PD
Mycosis Fungoides (N=21)	29%	1	5	11	4
Sezary Syndrome (N=17)	47%	1	7	7	2
TOTAL (N=38)	37%	2	12	18	6

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

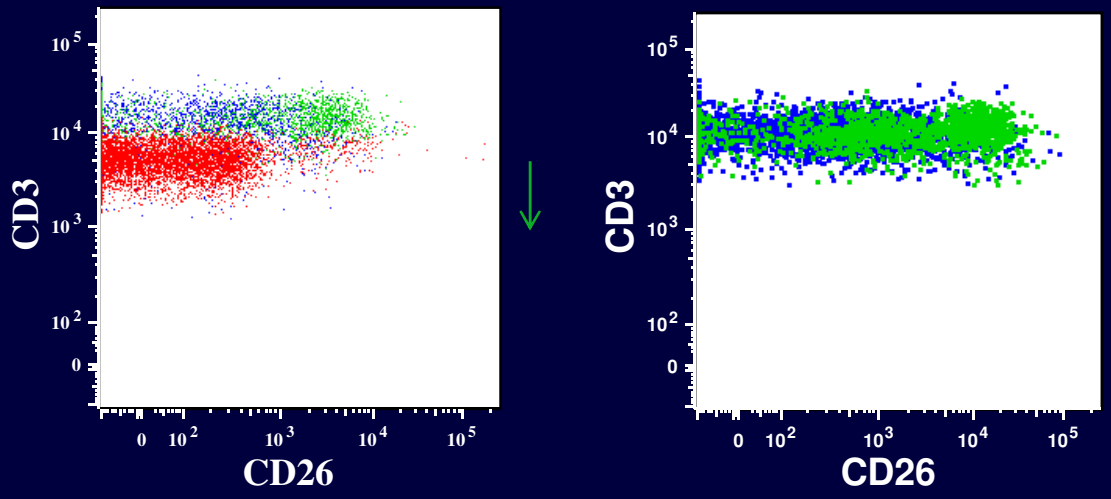
CLINICAL CARE OPTIONS®
ONCOLOGY



CCR4 Antibody normalizes Sézary cells in blood



%CD4+CD26-



Lymphoma cells
Normal CD3+CD4+
CD3+CD4neg

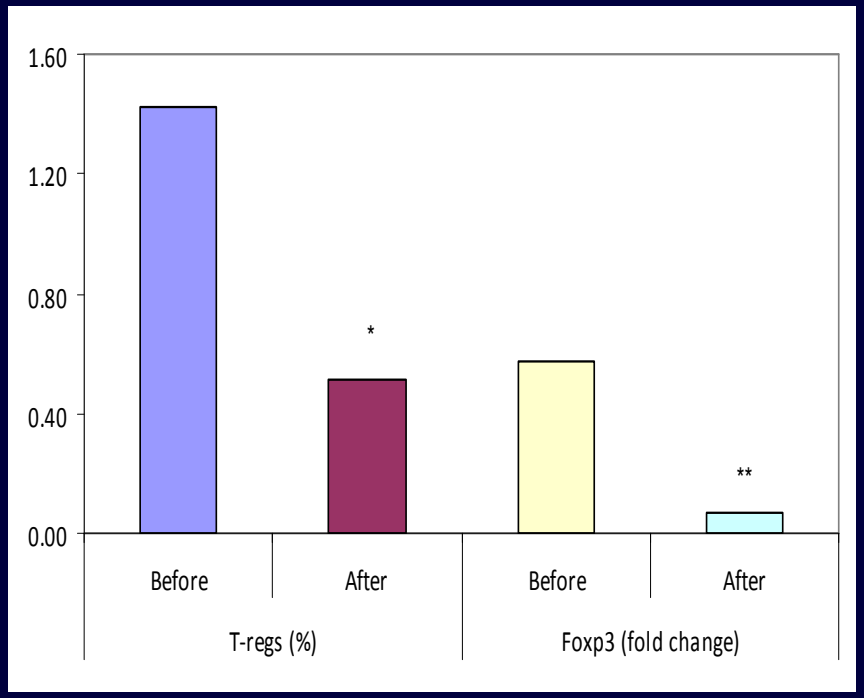
Absolute CD3+CD26-

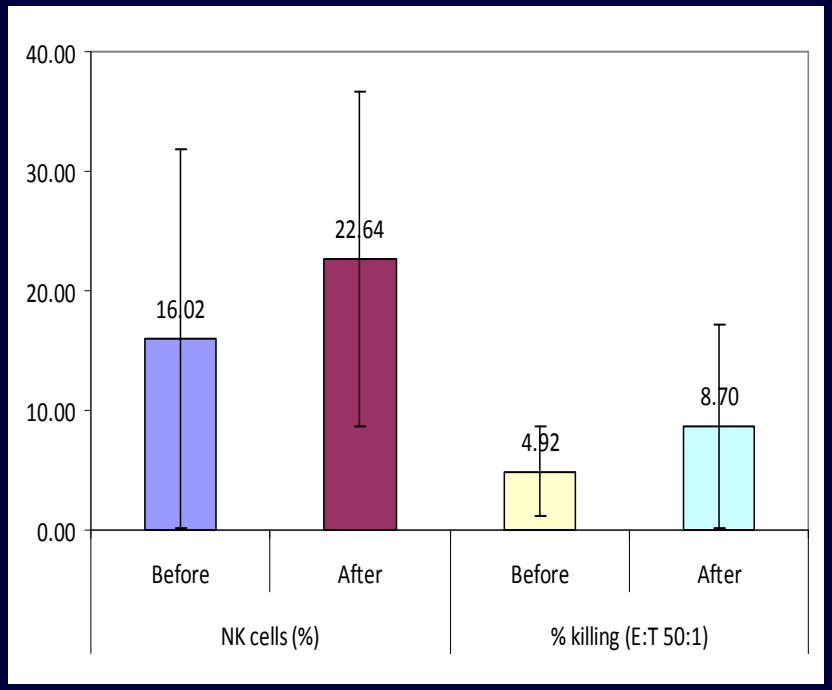
Reduction of regulatory T cells by Mogamulizumab, a defucosylated anti-CC chemokine receptor 4 antibody, in patients with aggressive/refractory mycosis fungoides and Sézary syndrome.

Ni X, Jorgensen JL, Goswami M, Challagundla P, Decker WK, Kim YH, Duvic M.

Clin Cancer Res. 2015 Jan 15;21(2):274-85. doi: 10.1158/1078-0432.CCR-14-0830. Epub 2014 Nov 5

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



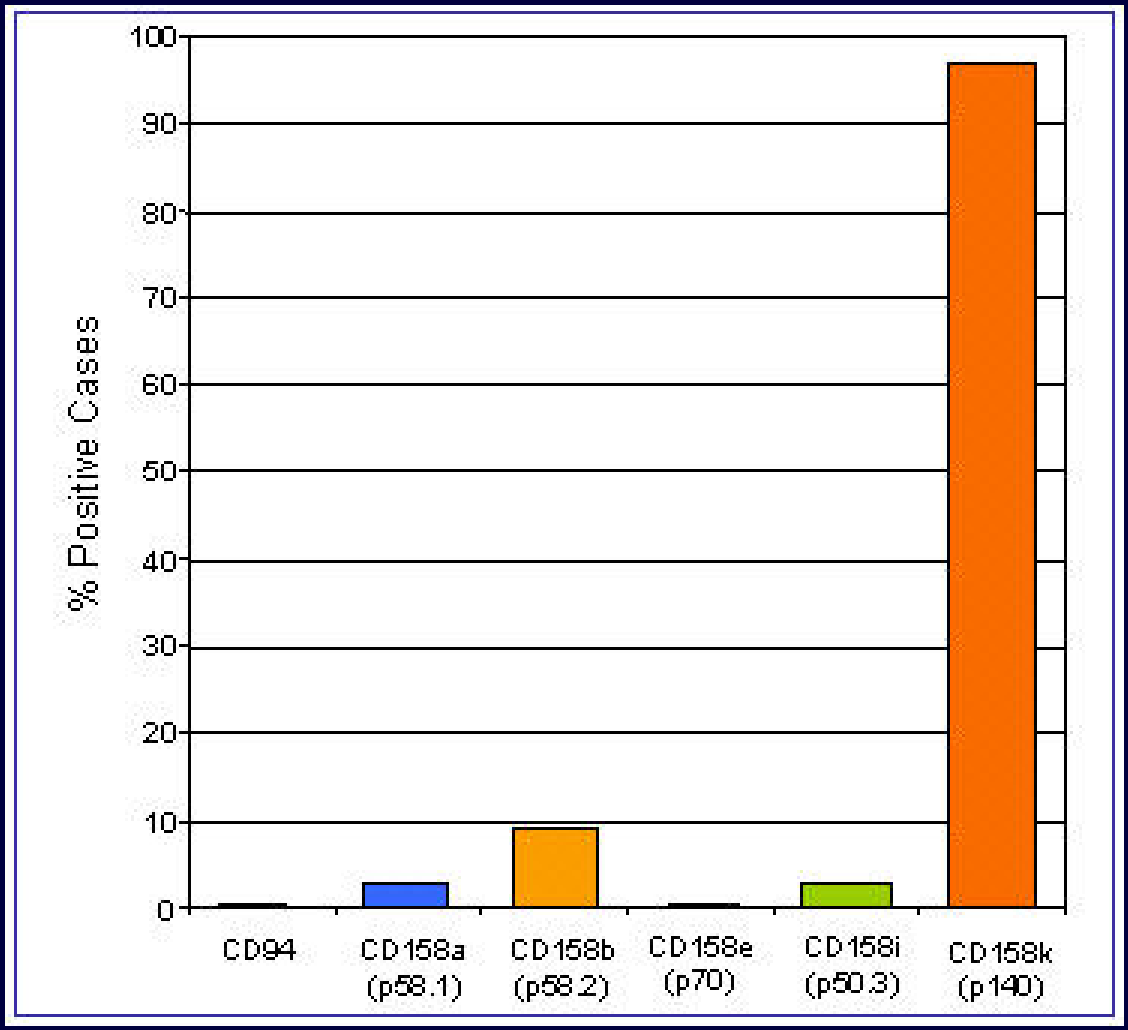


% T-regs **Foxp3** **%NK** **% Killing**

Xia Ni et al. Clin Cancer Res. 2015 Jan 5;21(2):274-85

Targeted Therapy: KIR3D2L mAb

Expression in 33 Patients with Sézary Syndrome

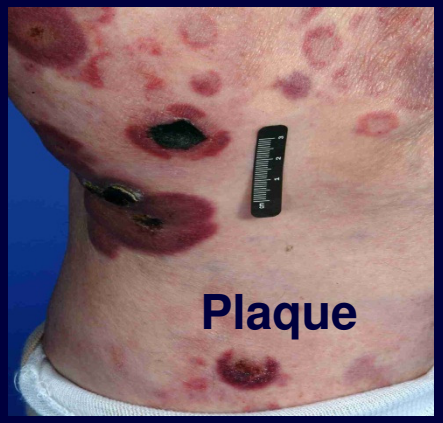


Poszepczynska-Guigne, E., J Invest Dermatol 2004;122,820

The different presentations of CTCL











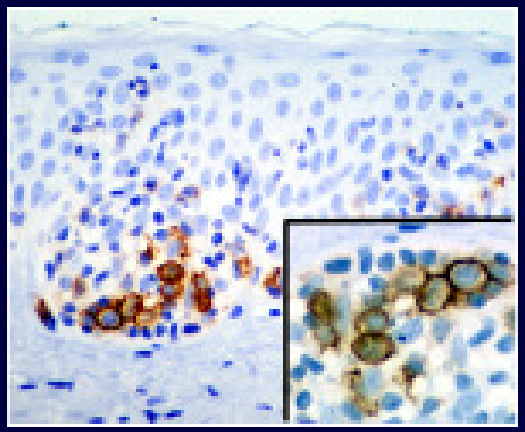








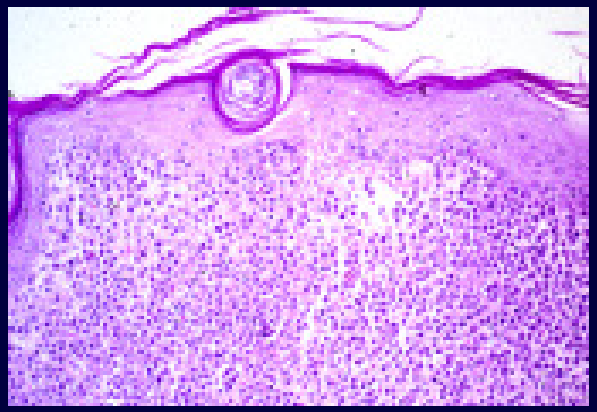
Advanced ≥IIB: Tumors (LCT), Nodes, Blood, Viscera



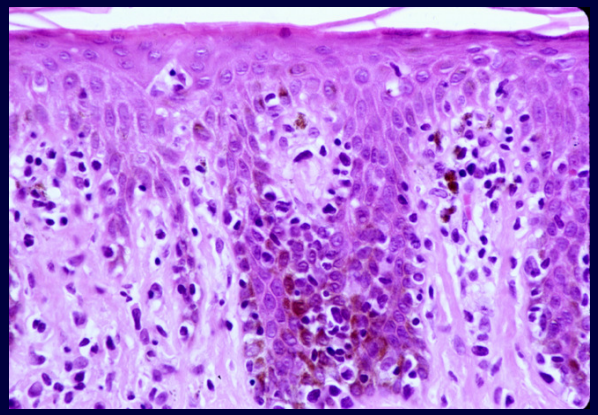
Epidermotropic
Large cell

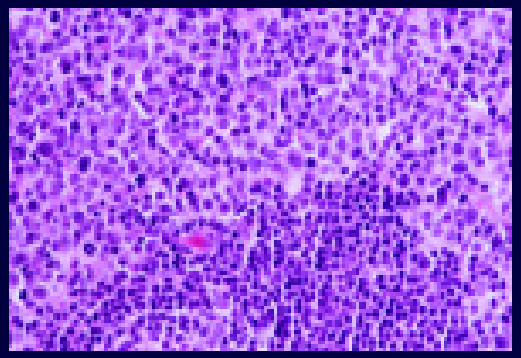
Large cell

Transformation?



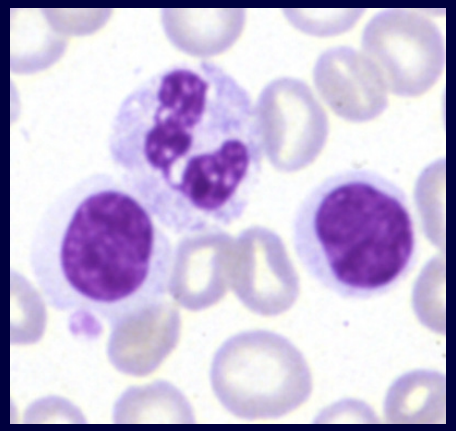
Tumor stage
+/- large cell



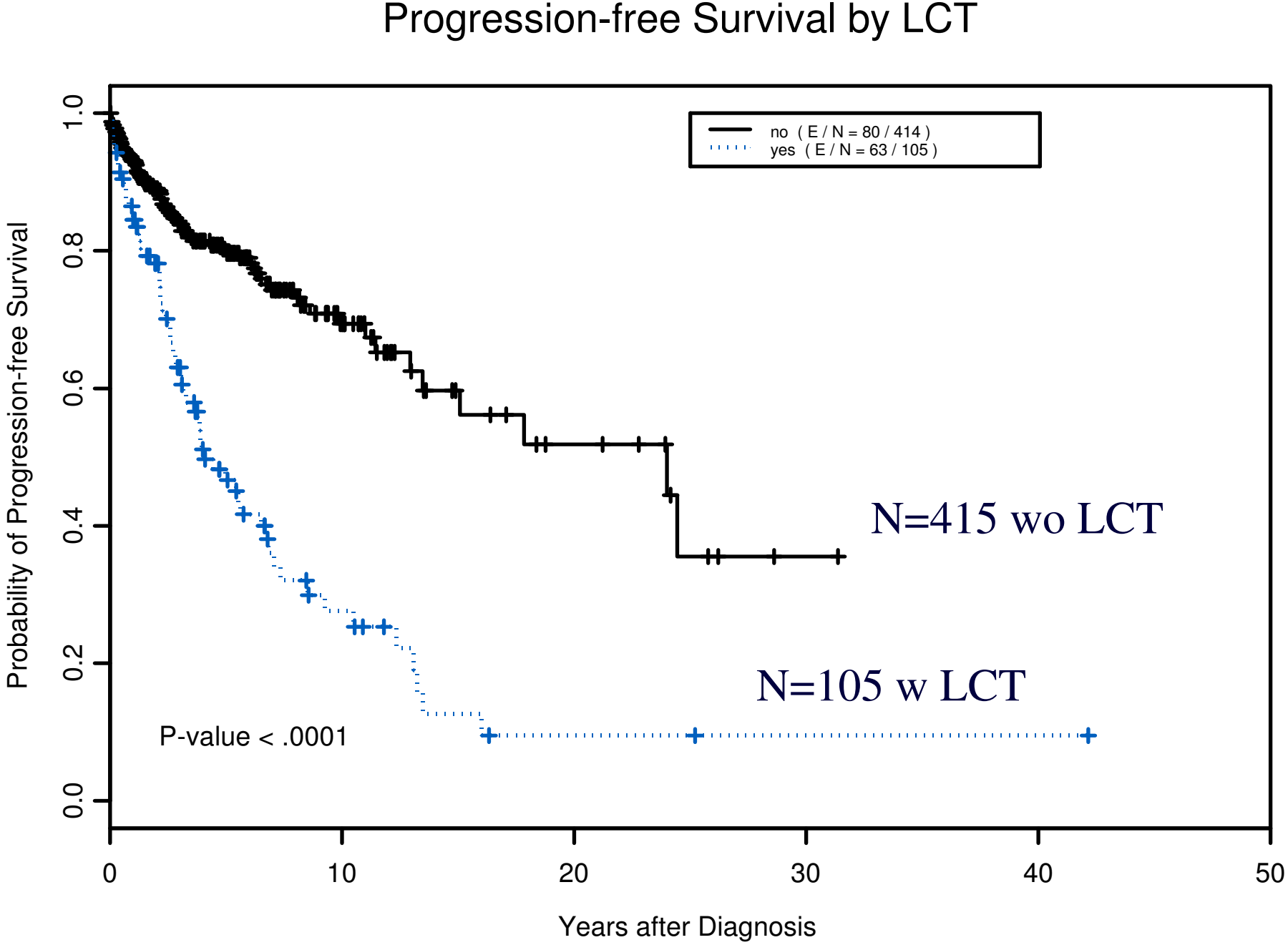


Systemic Large Cell
Transformation (LN)

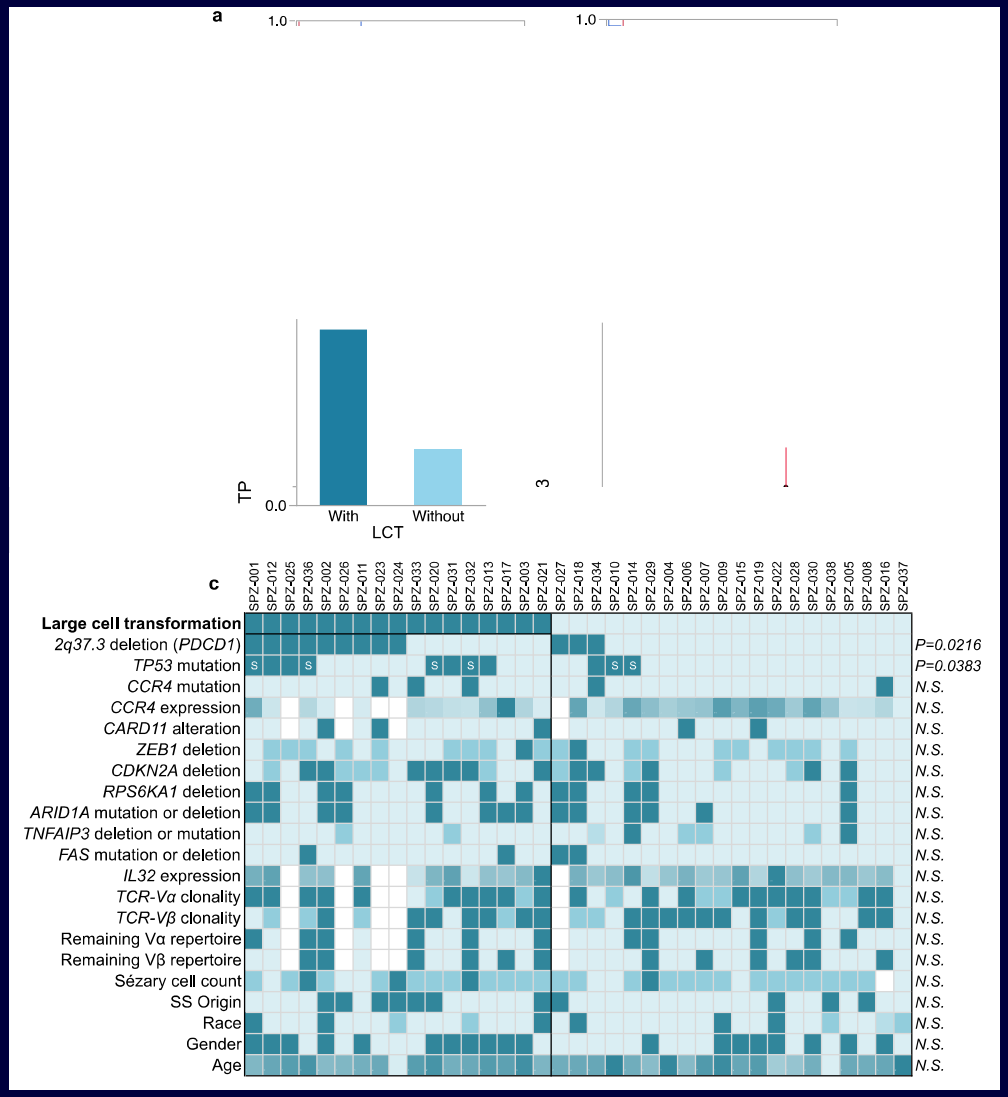
Refractory
Disease



Spread to Blood
Sezary syndrome


Progression-free Survival by LCT
no (E / N = 80 / 414)
yes (E / N = 63 / 105)
N=415 wo LCT
N=105 w LCT
P-value < .0001
Probability of Progression-free Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
Years after Diagnosis

Analysis of Mutations associated with Large Cell Transformation



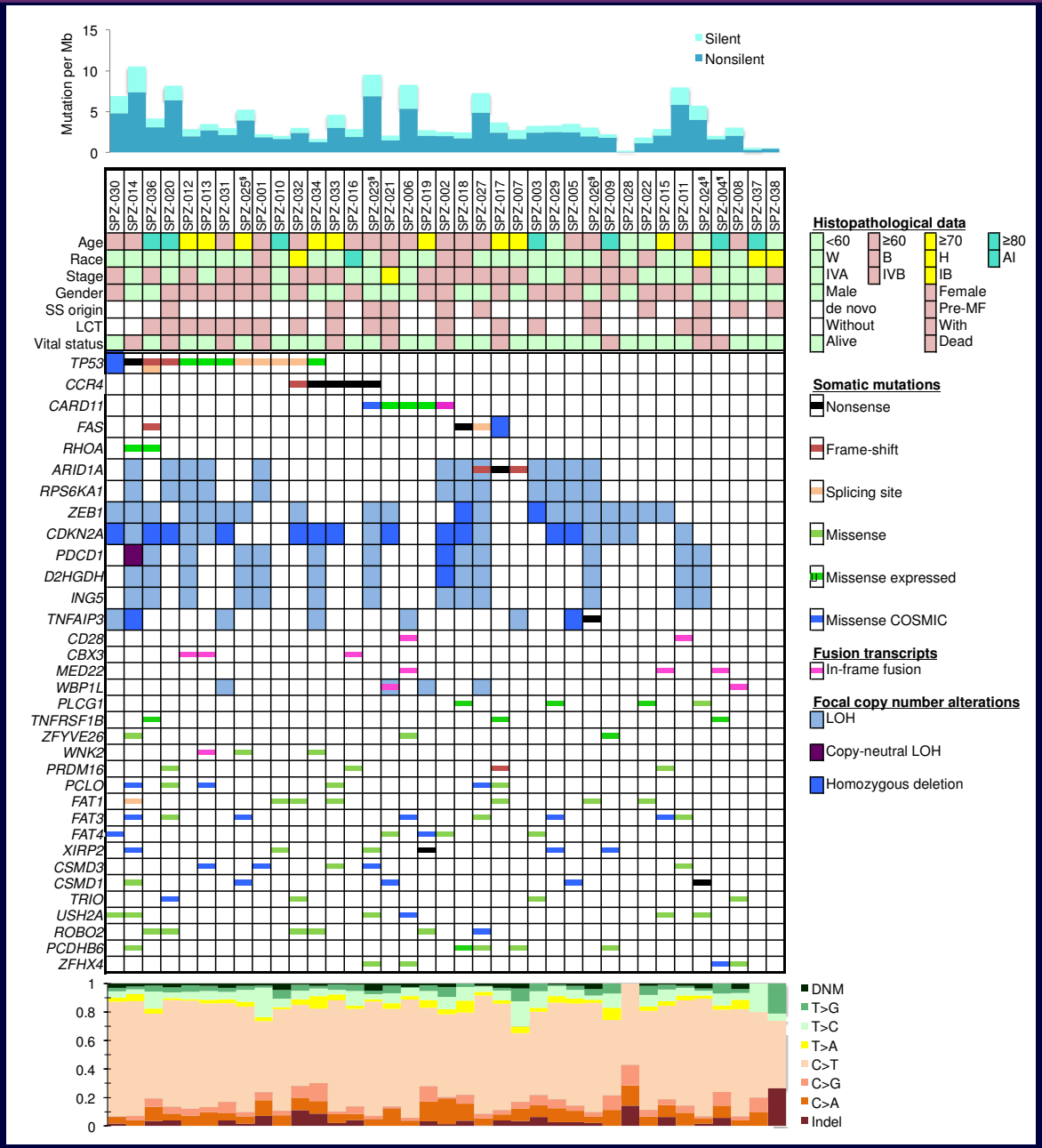
Large Cell Transformation is associated with

Significant decrease overall survival in all LCT patients & in African Americans

Mutations in

T53, PD1, CCR4

Genomic Exon Sequencing



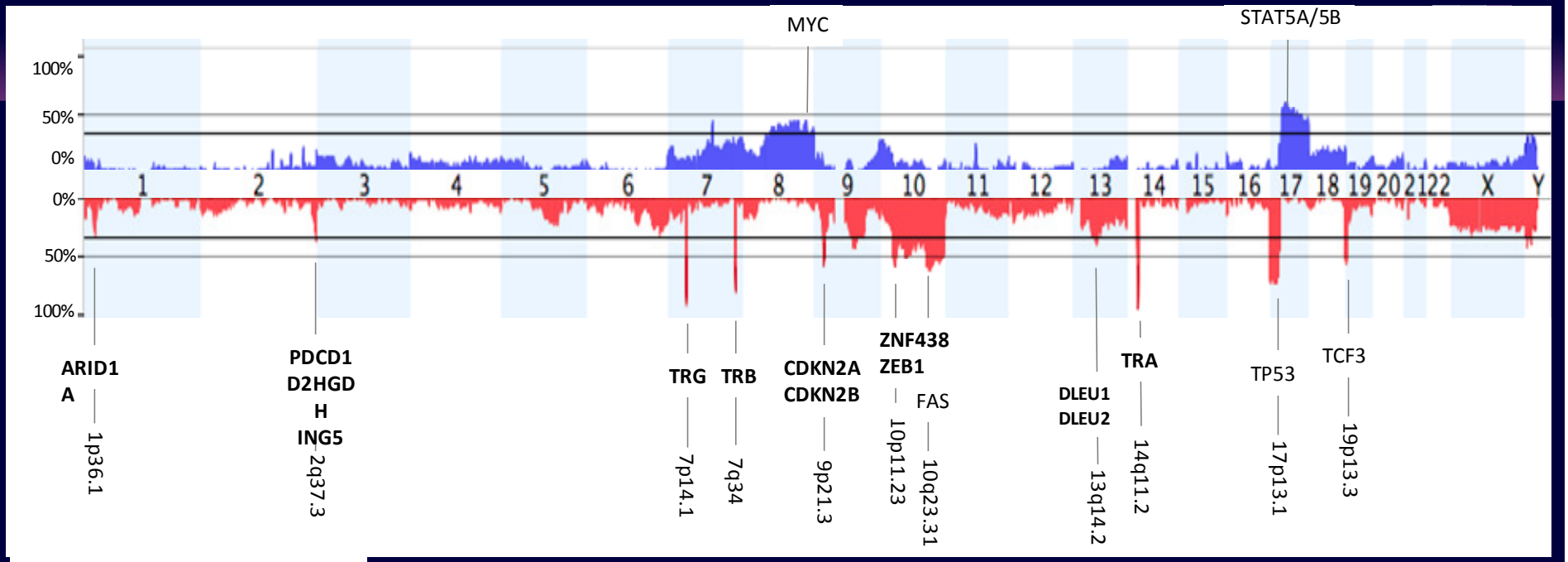
2 mutations/Mb

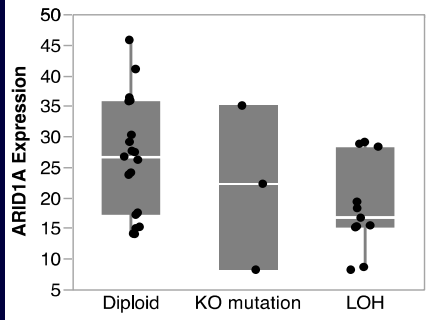
Mutations heterogeneous

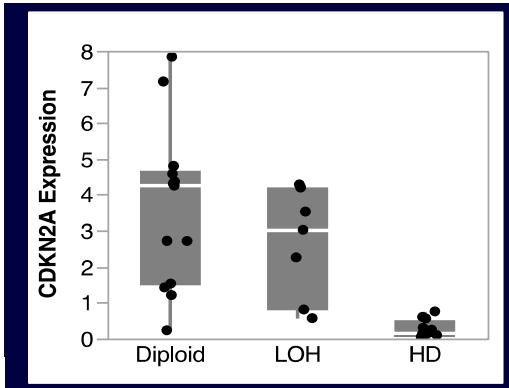
Tumor suppressors
P53
LOH – blue

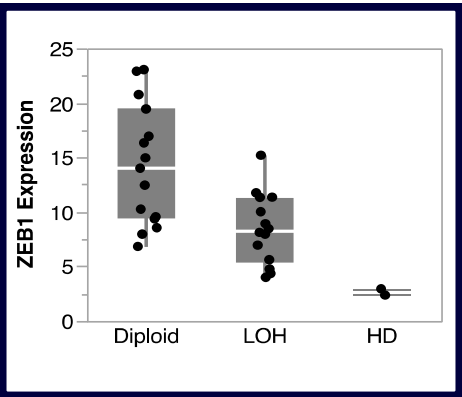
UV Signature

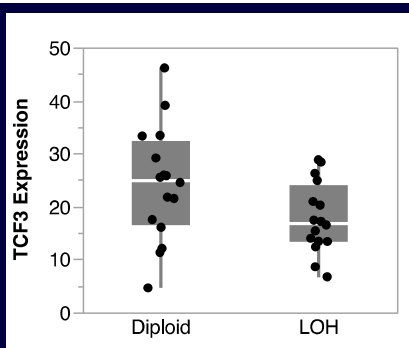
Methylation

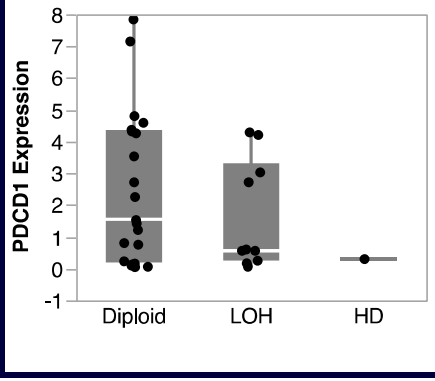




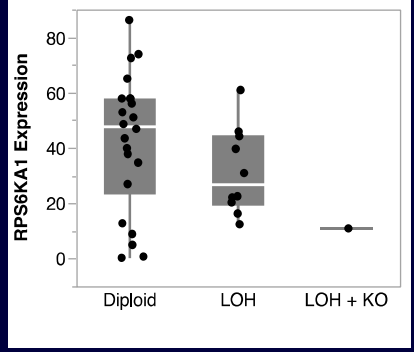




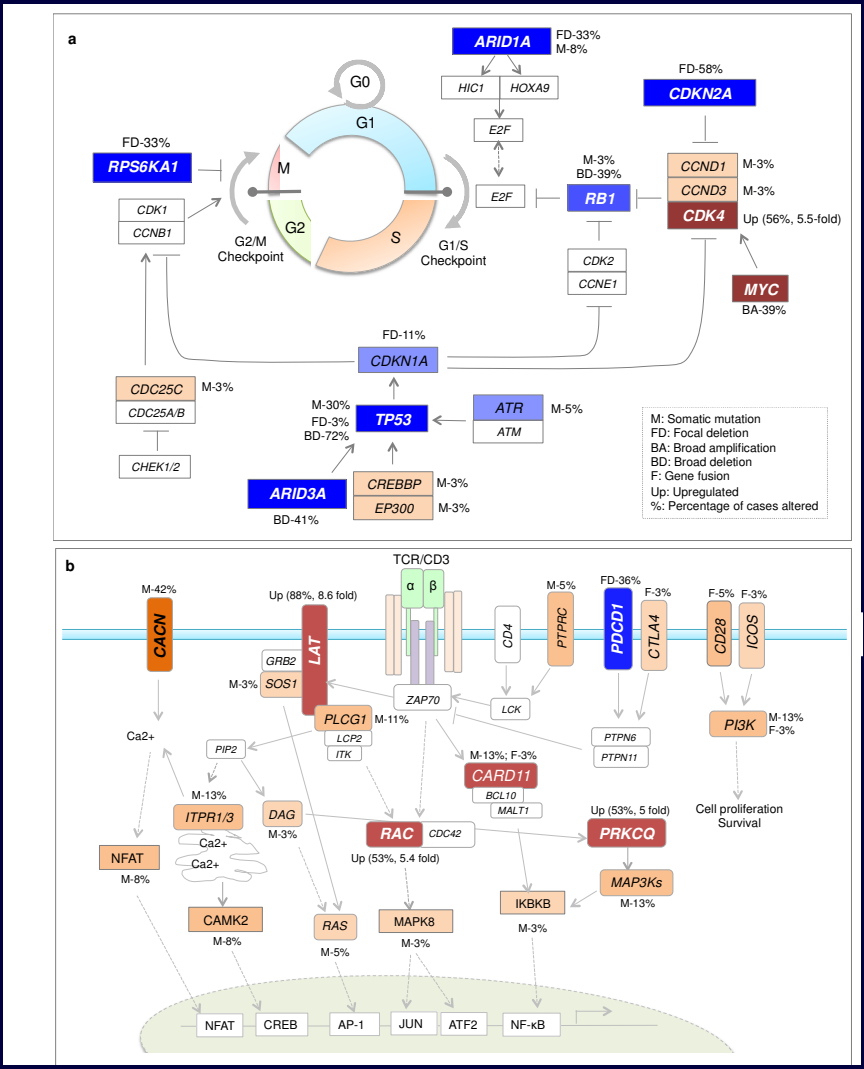




The Sezary Genome - Loss or Gain Chromosome & Expression by RNA seq



PATHWAYS TO THE FUTURE



- Precision medicine allows discovery prior to treatment for each patient.
- Knowledge based targeted therapies
- Rational combinations may prevent early resistance.
- Onc 201 – Trail inhibitor – pill every 3 weeks – inhibits several key

Questions Remaining

- Why is the SS cell nucleus cerebriform?
- Why are SS patients red? Staph toxins? AMPs?
- Why do they acquire keratoderma? 60% Tinea+
- Why are they cold? Vasodilation, VEGF, low TSH
- Why to they itch? opiate receptor mediated, IL-31 from CCR4+ cells killed by HDAC-inhibitors
- What genes or epigenetic changes drive T cell proliferation? Making progress – T cell signalling
- Can we cure SS? 79% SS cured with TBSEB and non-ablative allogeneic transplant and target therapy for others.

Acknowledgments

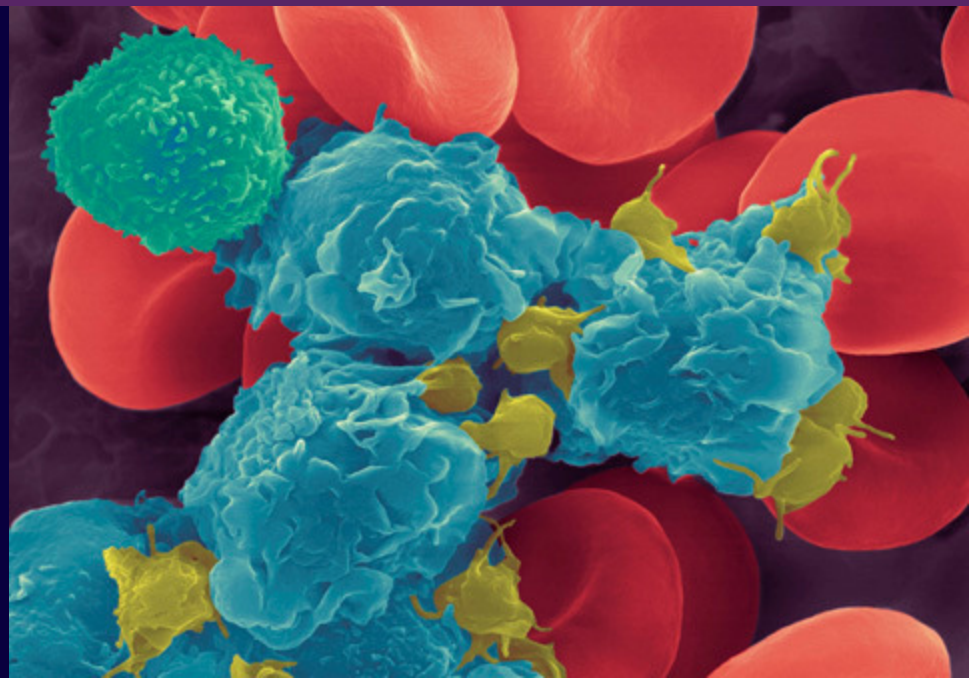
- Spatz & Anderson Foundations, Blanche Bender Chair, NCI, Dermatology Foundation, companies for financial support for trials and translational research.
- Lab and Clinical Research: Xia Ni, Lisa Shuie, R Talpur, C-L Zhang, Clinical Research Fellows, Derm Residents, medical students.
- Baylor Genome Center- D. Wheeler, Linghua Zhang
- CTCL family – colleagues/friends throughout the world who take care of CTCL patients and support each other: USCLC, EORTC, ISCL, CLIC



Naomi Kanof Lecture
75th SID Meeting May 8, 2015

Silencing the Sézary cell Past, Present, & Future

Madeleine Duvic, MD
Prof of Dermatology &
Internal Medicine
Blanche Bender Chair in
Cancer Research
Dept of Dermatology
MD Anderson Cancer Center
Houston, Texas



Who was Naomi Kanof?

- Attended NYU medical school, mentored by Dr Sulzberger and became editor of the Journal of Investigative Dermatology x 17 years. She married a lawyer, had two children in Washington DC.
- Dedicated to her patients, Chief of Pediatric Dermatology at Washington Hosp Center
- She knew political figures – Wilber Mills' Fanny Fox. She and Scoop Jackson raised funds for Sulzberger chair & start the Military Dermatology Program- John Stanley first job.
- (S. Katz, unpublished data)

Pathway Analysis

- Duke Medical School - Duke Triple Threats: Lowell Goldsmith, Gerald Lazarus, S. Pinnell & Brian Jegasothy. Master clinicians: J Lamar Callaway, Robert Gilgor, Mike Tharp, Janet Hickman.
- Elizabeth Kanoff (Naomi's cousin) taught "how to run an office and divert curbside consults."
- NIH immunology 3rd year elective- Fauci, Anderson, Waldmann. First scientific paper – improved the lives of NZB/W mice w estrogen inhibitor. Saw first SS pt.
- Clinical Research can help more people than a private practice and collaborate with interesting people.

Clinical End Points and Response Criteria in Mycosis Fungoides and Sézary Syndrome: A Consensus Statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer

Elise A. Olsen, Sean Whittaker, Youn H. Kim, Madeleine Duvic, H. Miles Prince, Stuart R. Lessin, Gary S. Wood, Rein Willemze, Marie-France Demierre, Nicola Pimpinelli, Maria Grazia Bernengo, Pablo L. Ortiz-Romero, Martine Bagot, Teresa Estrach, Joan Guitart, Robert Knobler, José Antonio Sanches, Keiji Iwatsuki, Makoto Sugaya, Reinhard Dummer, Mark Pittelkow, Richard Hoppe, Sareeta Parker, Larisa Geskin, Lauren Pinter-Brown, Michael Girardi, Günter Burg, Annamari Ranki, Maartan Vermeer, Steven Horwitz, Peter Heald, Steve Rosen, Lorenzo Cerroni, Brigette Dreno, and Eric C. Vonderheid

ABSTRACT

Mycosis fungoides (MF) and Sézary syndrome (SS), the major forms of cutaneous T-cell lymphoma, have unique characteristics that distinguish them from other types of non-Hodgkin's lymphomas. Clinical trials in MF/SS have suffered from a lack of standardization in evaluation, staging, assessment, end points, and response criteria. Recently defined criteria for the diagnosis of early MF, guidelines for initial evaluation, and revised staging and classification criteria for MF and SS now offer the potential for uniform staging of patients enrolled in clinical trials for MF/SS. This article presents consensus recommendations for the general conduct of clinical trials of patients with MF/SS as well as methods for standardized assessment of potential disease manifestations in skin, lymph nodes, blood, and visceral organs, and definition of end points and response criteria. These guidelines should facilitate collaboration among investigators and collation of data from sponsor-generated or investigator-initiated clinical trials involving patients with MF or SS.

J Clin Oncol 29:2598-2607. *© 2011 by American Society of Clinical Oncology*