Cutaneous T-Cell Lymphoma: Exploring Therapeutic Options

Madeleine Duvic, MD
The University of Texas
MD Anderson Cancer Center
Houston, Texas

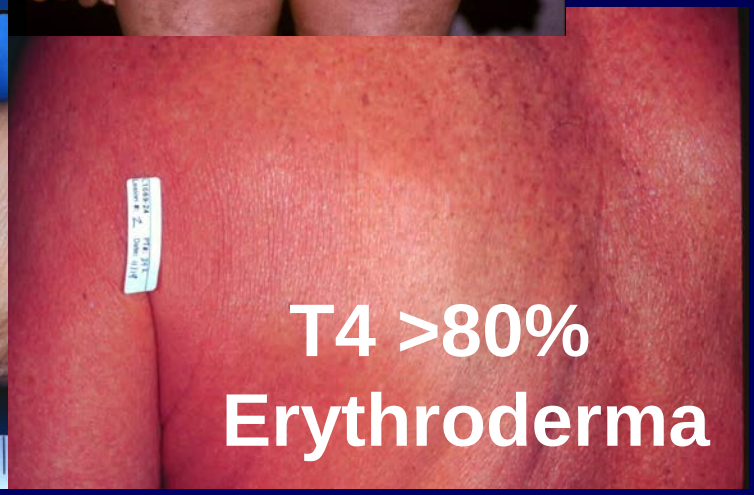
TNM-Staging of MF Patients

Patches & Plaques

T1
<10%

T2
>10%

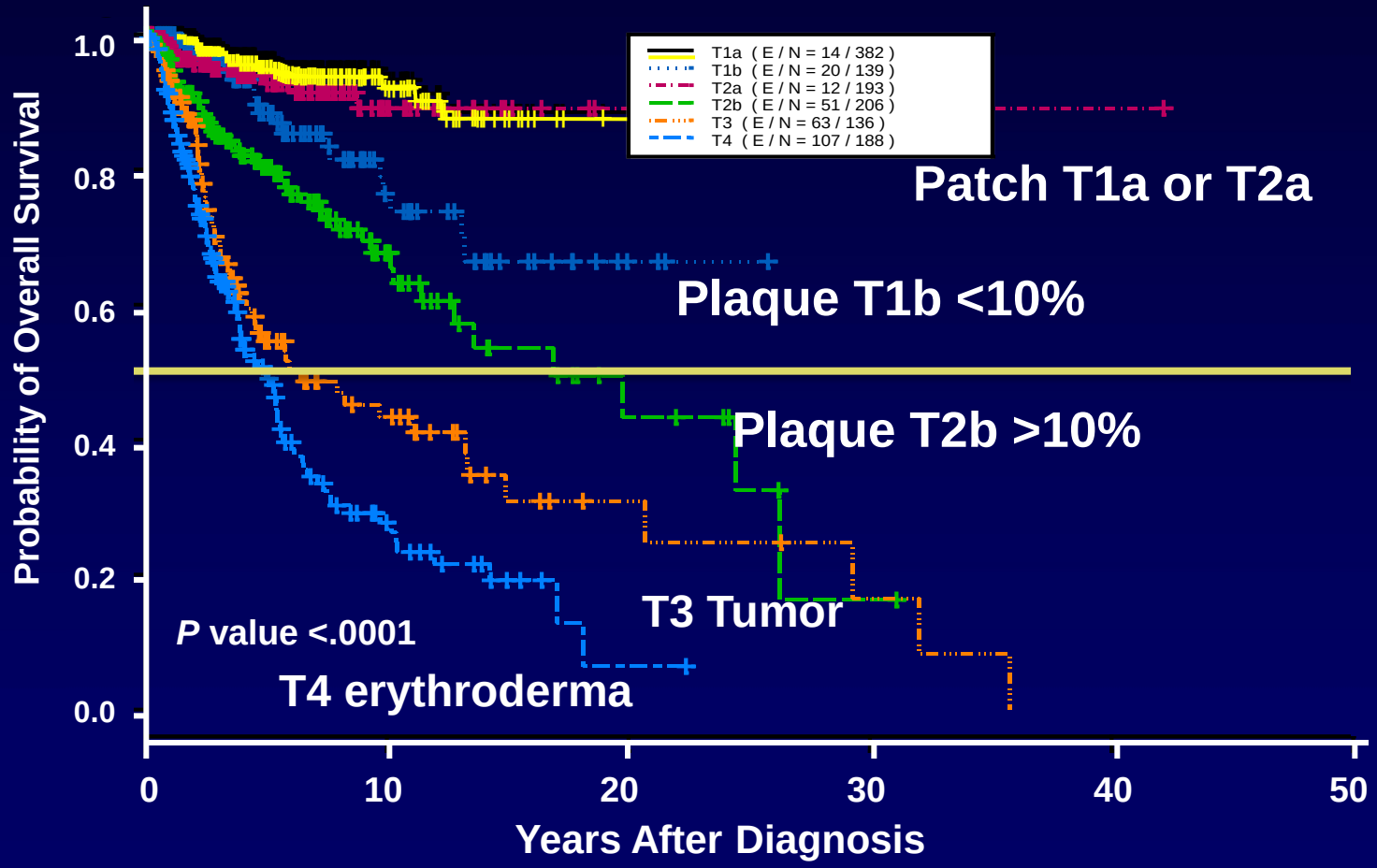
T3
tumor



MF, mycosis fungoides

Outcomes of 1263 Patients with MF/SS From 1982 to 2009

Median Overall Survival 24 Years



SS, Sézary syndrome

Talpur R, et al. *Clin Cancer Res.* 2012;18(18):5051-5060.

Risk Factors: Overall Survival

- **Beneficial**: T1a, T2a, poikiloderma, LyP
- **Negative**: Plaques T1-T2, node+, high LDH, large cell transformation and
- **Erythroderma**: SS-B2 or B3 **>10,000/uL**
- No difference: Sex, folliculotropic, CD25+, CD30+
- *TCR* gene rearrangement clonal at different sites or time associated with risk of progression

LDH, lactate dehydrogenase; LyP; lymphomatoid papulosis

Talpur R, et al. *Clin Cancer Res.* 2012;18(18):5051-5060. Vidulich KD, et al. *Int J Derm.* 2009;48(3):243-252. Vega F, et al. *Blood.* 2002;100(9):3369-3373.

Poor Prognostic Factors

- Young African American female
- Histology: folliculotropic, large cell
- Advanced stage IB to IVA to IVB
- Failure to respond to frontline skin and immunotherapy
- Bulky plaques, LCT tumors, nodes, blood and liver involvement.
- Staph colonization—risk of septic lines

Improved Survival in MF

- Earlier accurate diagnosis—immunophenotyping, clonality and flow cytometry
- Therapy based on T stage, multimodality approach
- FDA approved for CTCL-MF
  - Narrowband UVB phototherapy, mechlorethamine
  - Biologic response modifiers (BRM): Interferon (IFN) alpha/gamma, peg-IFN
  - Retinoids- bexarotene, acitretin
  - Photopheresis + BRM
  - HDAC inhibitors: Vorinostat, romidepsin
  - Pralatrexate
  - Proteosome inhibitors
  - Targeted antibodies & fusion proteins

CTCL, cutaneous T-cell lymphomas; FDA, US Food and Drug Administration; HDAC, histone deacetylase; UVB, ultraviolet B

Stage I MF: Skin-Directed Therapies

Active site therapies

- Topical steroids (class I, II)
- Topical retinoids
  - Bexarotene, tazarotene
- Topical nitrogen mustard
- Topical imiquimod
- Local radiation
- Local excision
- Excimer laser
- Topical carmustine
- SHP 141 topical vorinostat
- Topical resiquimod
- Topical hypericin

Total body treatments

- Topical steroid short term
- Topical nitrogen mustard
- Phototherapy
- NB-UVB - patches
- PUVA - plaques

Electron beam

- 12 Gy low dose

PUVA, psoralen plus ultraviolet A (UVA) treatment

Treatment of Stage IB/IIA MF

Refractory to topical, folliculotropic MF (F-MF), B1+ECP

Plaques, large cell transformation

SDT plus immunomodulators

systemic or multiple systemic

- **Interferon alpha or gamma or PEG**
- **Oral retinoids: Bexarotene,**
  13-cis retinoic acid,
  acitretin, ATRA
- **Methotrexate (low dose)**
- **HDAC inhibitors**
- **Denileukin diftitox – E777**

- **Total or local body electron beam—12-32 Gy**

ATRA, all-trans retinoic acid

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Non-Hodgkin's Lymphoma (v.5.2014). Available at: https://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf. Accessed December 4, 2014.

Treatment of Stage IIB Mycosis Fungoides

- **First line:** Local XRT (orthovoltage or EB) 12-32 Gy
- **Maintenance:** Resume skin-directed or systemic biologic therapy interferon, bexarotene/HDAC inhibitor (romidepsin, vorinostat)
- **If relapsed or biologic agents fail, use single or combination chemotherapy**
- **Relapse/second line:** HDAC-I, denileukin diftitox, TBSEB followed by allo SCT (CR) or maintenance, brentuximab vedotin
- **Third line:** Pralatrexate + bexarotene, gemcitabine, liposomal doxorubicin, methotrexate, bortezomib, etoposide, chemotherapy

CR, complete response; EC, external beam; SCT, stem cell transplant; TBSEB, total-body skin electron beam radiation; XRT, radiotherapy

Comparison of Systemic Therapies for MF

Treatment, %	CR, %	ORR (PR + CR)
Interferon	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

ORR, overall response rate; PR, partial response

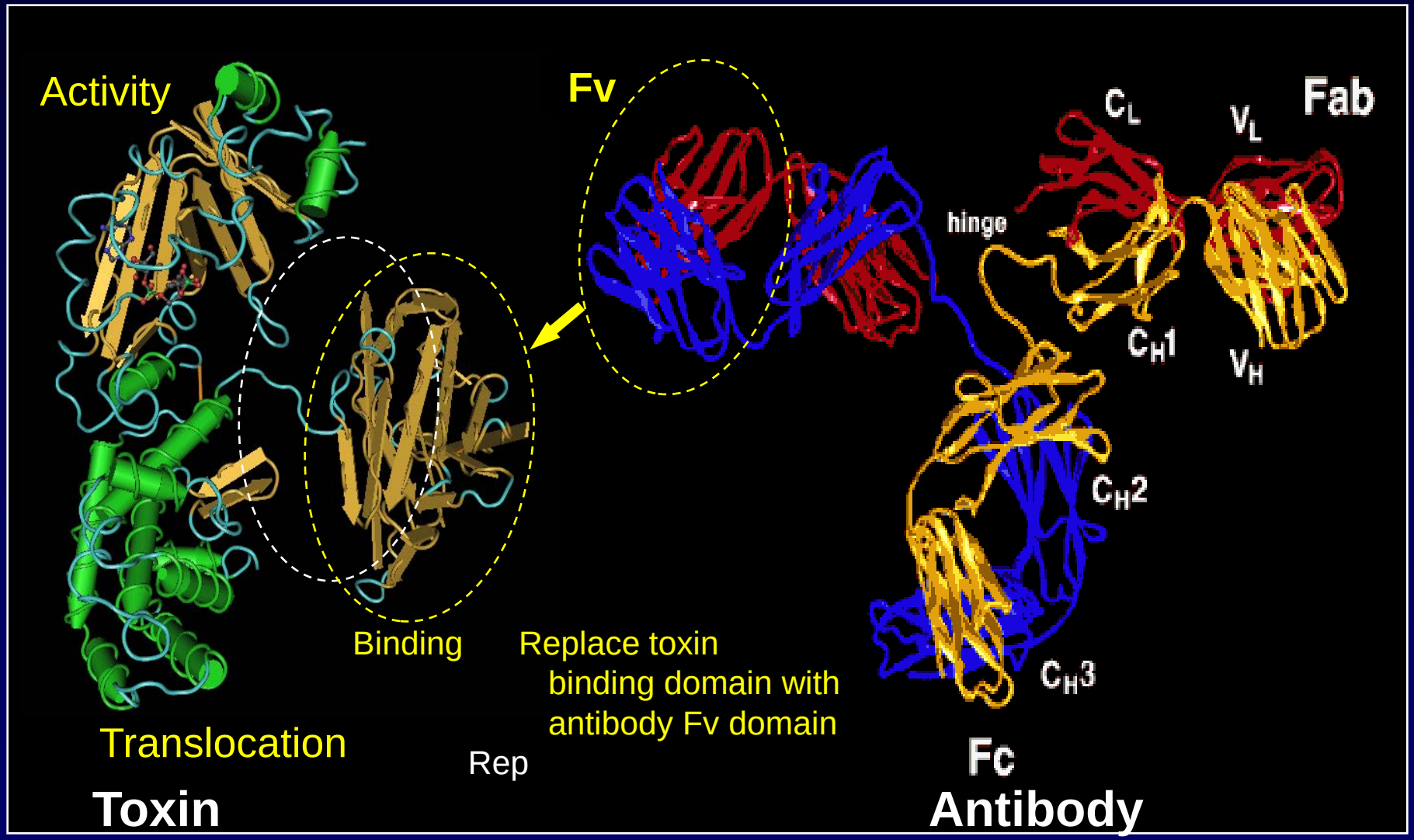
Li JY, et al. *Cancer Manag Res.* 2012;4:75-89. Drews RE. *J Clin Oncol.* 2012;30(33):4064-4070.

Investigational Agents

- **Inhibitors of HDAC: Belinostat, panobinostat**
- **Antifolate: Pralatrexate (plus bexarotene)**
- **Immunomodulators: Resiquimod, CpG, IL12, lenalidomide, PD-1**
- **Monoclonal antibodies TARGETED THERAPIES**
  - **Mogamulizumab (KW-0761; defucosylated, anti-CCR4)**
  - **Alemtuzumab (anti-CD52); Zanolimumab (anti-CD4)**
  - **Brentuximab vedotin—anti-CD30-auristatin E conjugate**
- **Fusion proteins—CD3 diphtheria toxin, CD25 E777 phase 1**
- **Proteasome inhibitors—bortezomib, carfilzomib +/- HDAC-1**

Jain S, et al. *J Hematol Oncol*. 2012;5:24. Li, JY, et al. *Cancer Manag Res*. 2012;4:75-89. Duvic M, et al. 2010;116: Abstract 962. Duvic M, et al. *J Invest Dermatol.* 2013;133(S1): Abstract 1058. Kaplan JB, et al. *Expert Rev Hematol*. 2014;7(4):481-493.

The Basic Design of Diphtheria Toxin–Based Recombinant Immunotoxins



Phase I—A-dmDT390-bisFv(UCHT1)
Anti-CD3ε Recombinant Diphtheria Immunotoxin

- DT catalytic and translocation domains fused to 2 single-chain antibody fragments reactive with extracellular domain of CD3ε
- Dose 2.5 ug/kg - 11.25 ug/kg dose escalation in 25 patients
- Response 41% (9 of 22) in evaluable patients
- Four CRs (18%) 72+, 72+, 60+, and 38+ months
- Stage IB/IIB and mSWAT <50 (8 of 10) had 80% ORR

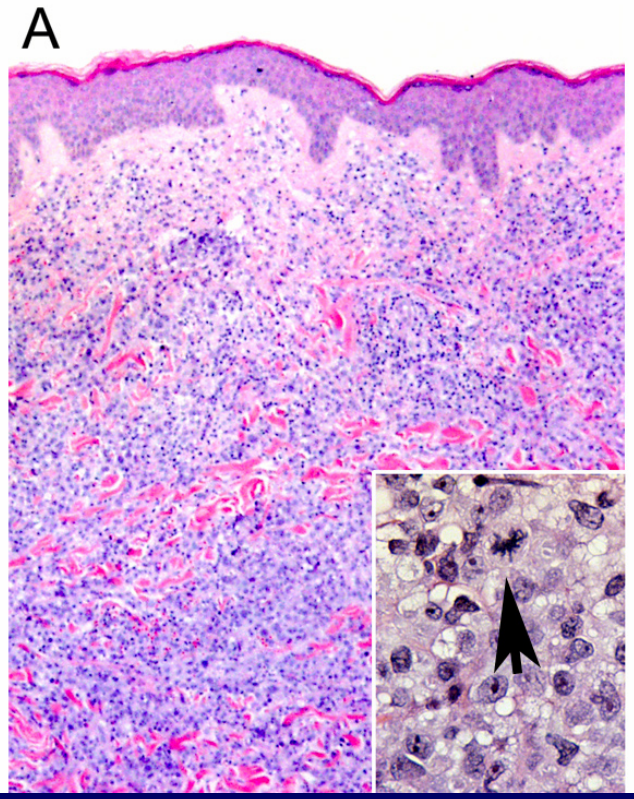
Frankel AE, et al. *Blood.* 2013;122: Abstract 4381. Frankel AE, et al. *Blood.* 2014;124: Abstract 3097.

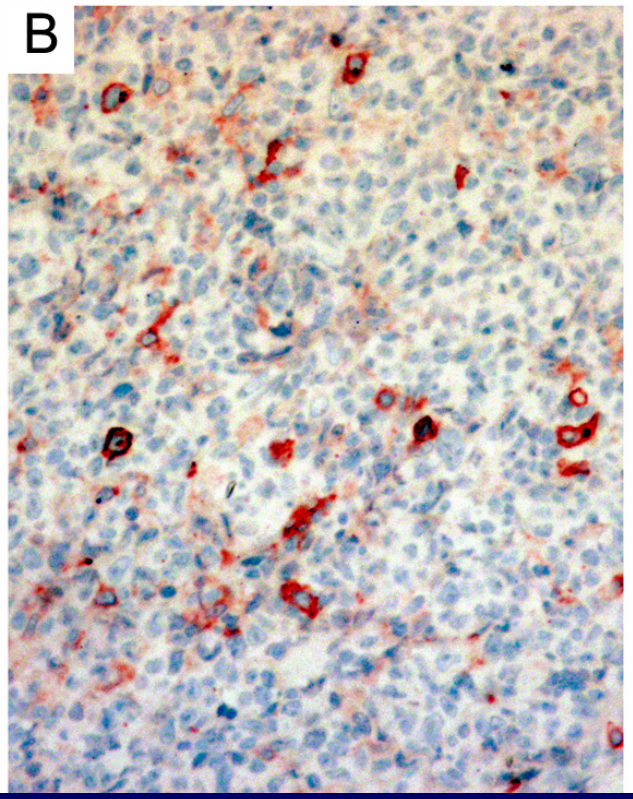
CD-30 + tumors

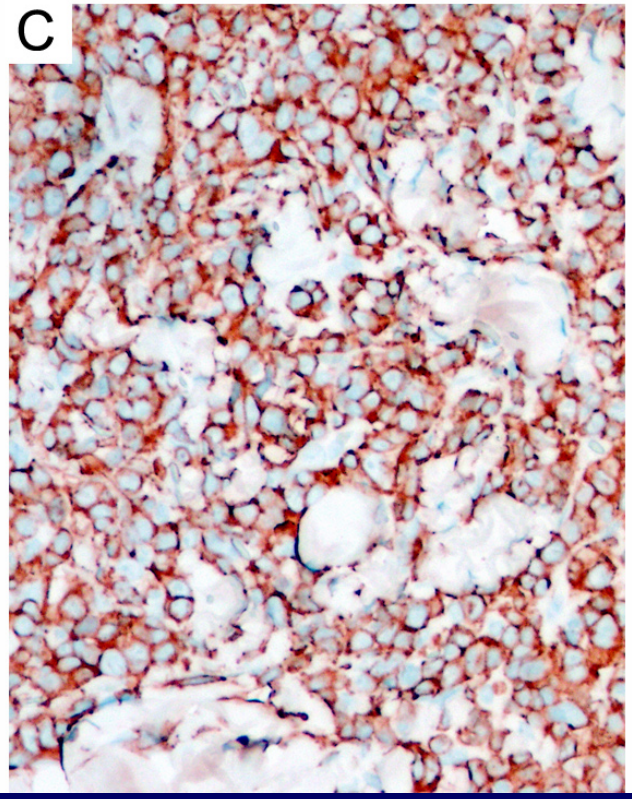
- Primary Cutaneous ALCL (C-ALCL)
- Lympho-matoid Papulosis (LyP)
- Transformed) Mycosis Fungoides (t-MF)
- Secondary Cutaneous ALCL
- PTCL, NOS ATLL
- Hodgkin Lymph-oma

ALCL, anaplastic large cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; NOS, not otherwise specified; PCTL, peripheral T-cell lymphoma.

Transformed MF vs CD30+ ALCL vs Lymphomatoid Papulosis







Large cell transformation of MF can be CD30+ or CD30-
ALCL of skin is CD30+

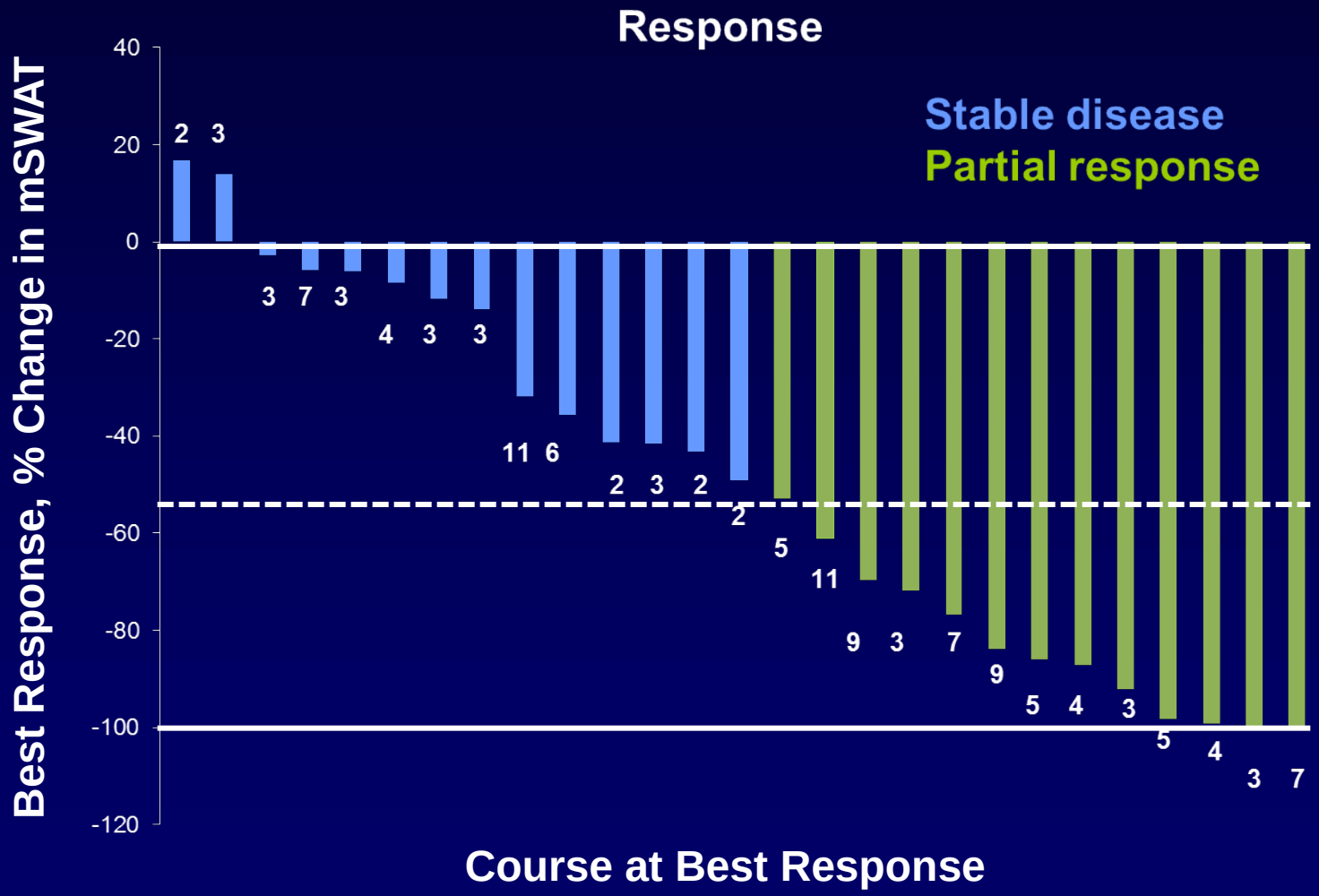
Brentuximab Vedotin: ORR 54% for Patients With MF

59-year-old black female with F-MF cells expressed 50% CD30

Baseline C2 D1 C7D1

Tumor response with brentuximab vedotin is rapid

Percent Change in MF mSWATs at Time of Best Skin Response to Brentuximab Vedotin



Duvic M, et al. *Blood.* 2013;122: Abstract 367.

Response to Brentuximab Vedotin

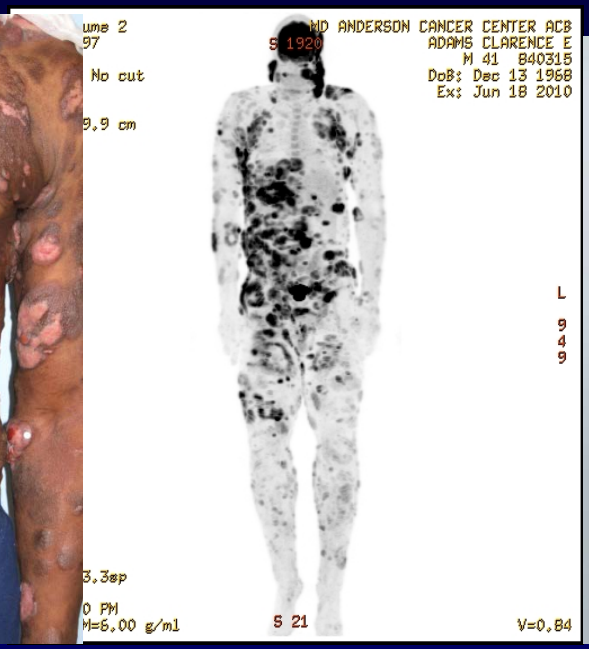
73% OR 35 of 48 Patients	Overall Response	Time to Response	Duration of Response (DOR)
MF (n = 28)	54%	12 weeks (3-39 weeks)	32 weeks (3-39 weeks)
Lyp (n = 9) Lyp+ (n = 11)	100%	3 weeks	26 weeks
Pc-ALCL (n = 2)	100%	(3-9 weeks)	(6-44 weeks)

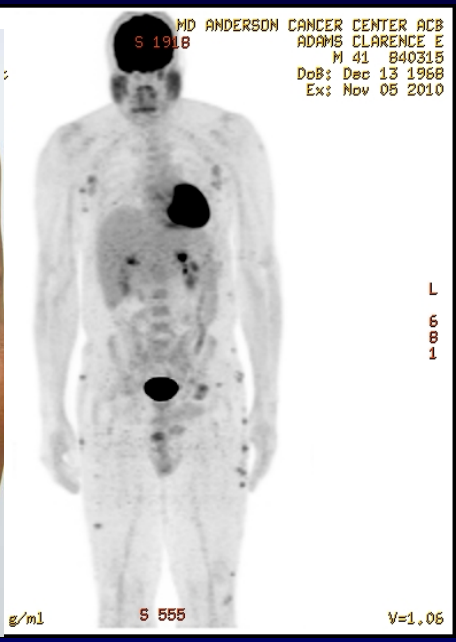
Grade 1-2 neuropathy 65% (31/48); ongoing in 55% (17/31)

Duvic M, et al. *Blood.* 2013;122: Abstract 367.

PET-CT—Response of F-MF IVA

Liposomal doxorubicin 20 mg/m² q2 week x 16 weeks
Bexarotene 300 mg/m² x 32 week maintenance
ORR 41% (14/34)





Day 1 - Dox **Dose 5 - Dox** **Dose 8 BL Bex** **Wk 8 + Bex**

Straus DJ, Duvic M, et al. *Ann Oncol.* 2014;25(1):206-210.

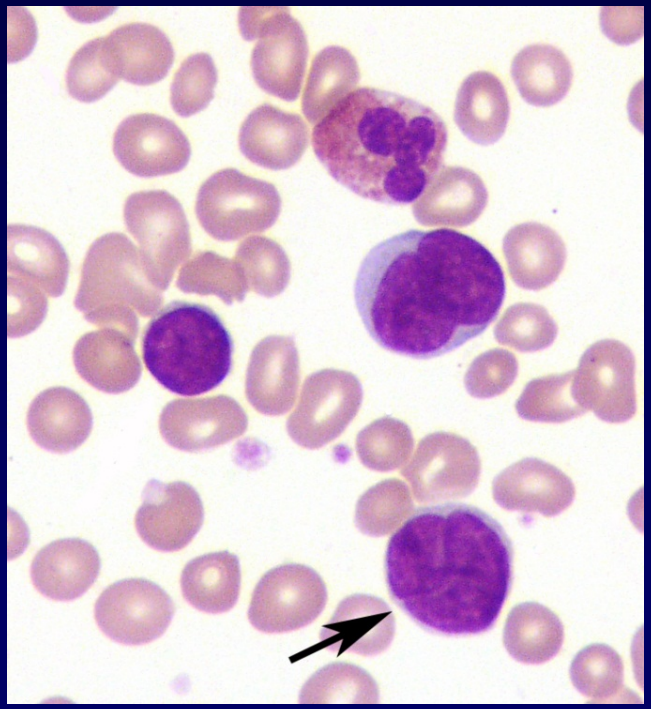
Pralatrexate for MF

	No. Patients	Dose	Overall Response
Phase I/II[1]	54	15 mg/m^2 3 of 4 weeks	41%
Phase I[2]	26	15 mg/m^2 Bex 150 mg	50% DOR 27 week

1. Horwitz SM, et al. *Blood*. 2012;119(18):4115-4122. 2. Talpur R, et al. *Clin Lymphoma Myeloma Leuk.* 2014;14(4):297-304.

Sézary Syndrome

Erythoderma >80% and
>1000 SS cells
Adenopathy
Pruritus *Staphylococcus aureus*



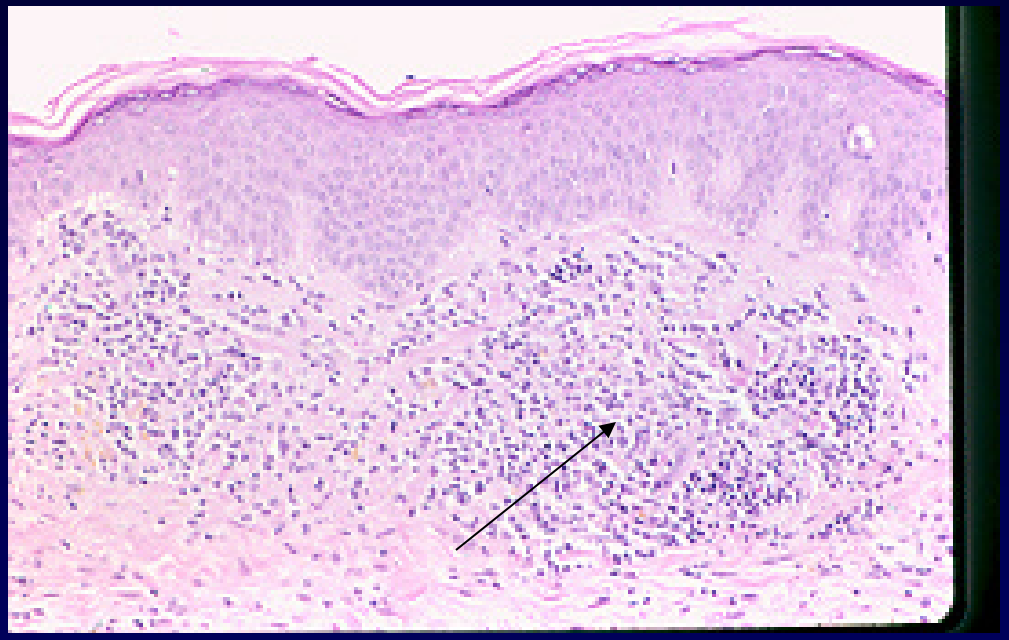
Keratoderma

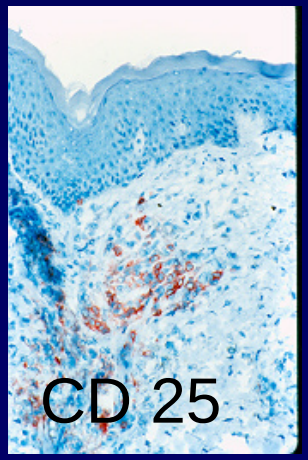
Ectropion

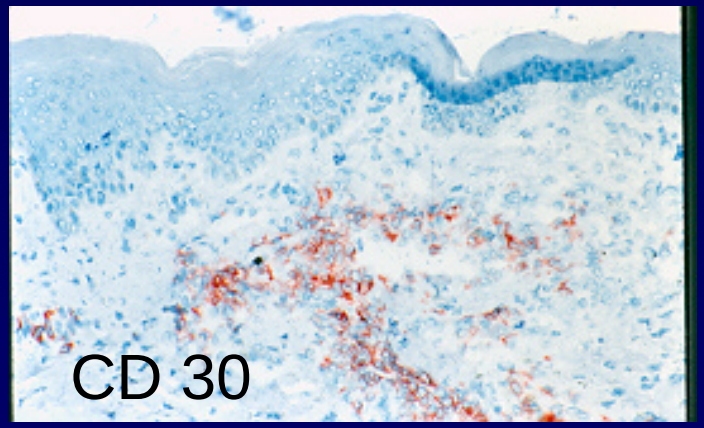
Hand/foot keratoderma tinea 60%

Vidulich KA, et al. *Int J Dermatol.* 2009;48(3):243-252.

Leukemic CTCL/SS

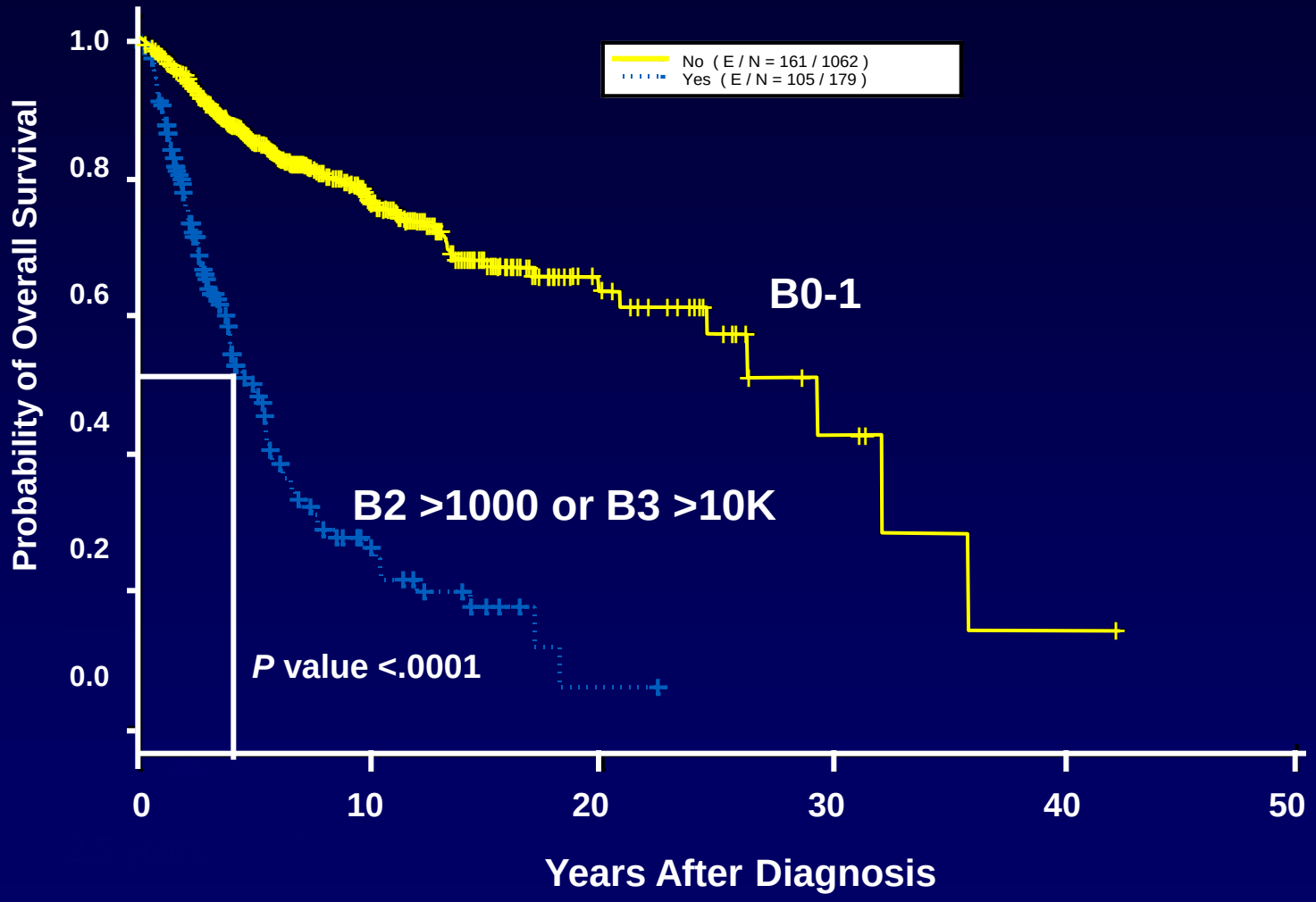






- Perivascular infiltrates without diagnostic epidermotrophism
- Sézary cells cerebriform morphology
- CD4+CD26-
- CD4+CD7-
- Central memory T-cells

Overall Survival by SS



Talpur R, et al. *Clin Cancer Res.* 2012;18(18):5051-5060.

Treatment of Erythodermic CTCL and SS

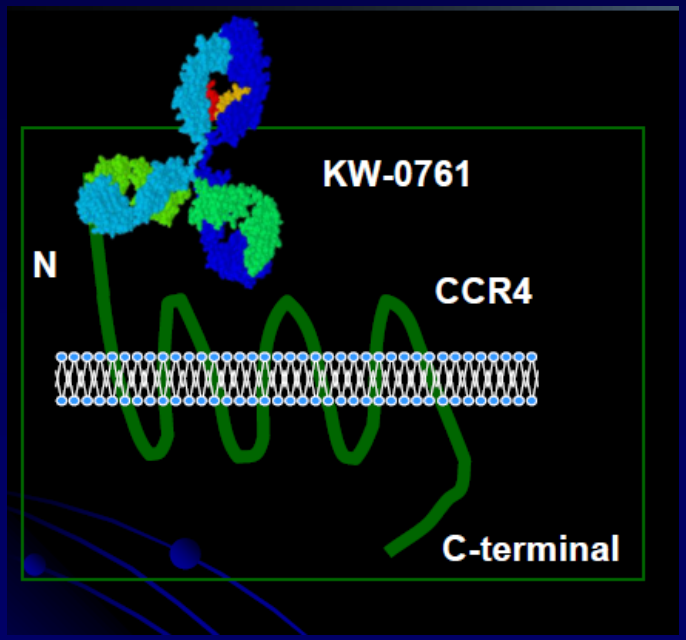
- **Palliative skin-directed care:** Culture for *Staph*, antibiotics, moisturize and use topical steroids, NB-UVB, PUVA, TBSEB
- **Itching**: Gabapentin – opiate antagonists
- **First-line combination immunomodulatory therapy**
  Photopheresis, bexarotene +/- interferon alpha
  Interferon gamma, GM-CSF
- **Second-line:** HDAC-inhibitors, pentostatin, targeted antibodies (CCR4, CD52,CD30), TBSEB
- **Allogeneic SCT:** CR in 50% SS –TBEB + nonablative allo

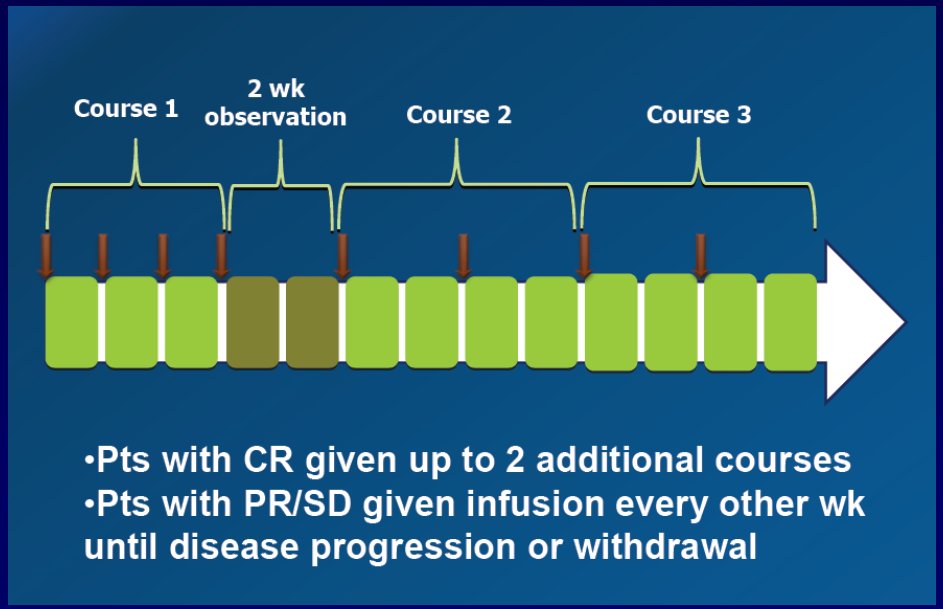
TBEB, total body electron beam

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

Humanized Anti-CCR4 Antibody: Mogamulizumab (KW-0761)

- Defucosylated antibody—increased ADCC
- Phase I/II studies in ATLL in Japan—approved
- Phase I/II US and phase III randomized trial





Yano H, et al. *Clin Cancer Res.* 2007;13(21):6494-6500.

Global Composite Response

Patient Subgroups	ORR	Number of Patients			
		CR	PR	SD	PD
MF (N = 21)	29%	1	5	11	4
SS (N = 17)	47%	1	7	7	2
TOTAL (N = 38)	37%	2	12	18	6

- Overall ORR of 37%
- ORR was higher in SS patients compared to MF

Duvic M, et al. *Blood.* 2012; Abstract 3697.

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

Pretreatment
Course 1 Day 1

Post Course 6
CR- 8+months

Review of Treatment 1-2-3

- Remove antigen/infection —*S aureus*, drug, tinea
- Skin-directed therapy for T1-2, radiation T3
- SDT plus systemic biologic response modifiers (retinoids, interferon) for refractory IB or new EE/SS
- Targeted therapy over chemotherapy and immunosuppressive therapy
- Chemotherapy reserved for nodal or transformed MF
- Explore allo- transplantation donor early in high-risk, advanced-stage, young patients
- Recycle previous therapies, alleviate symptoms, keep treating with maintenance therapy