Clinical Issues in Cutaneous T-cell Lymphoma

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Stanford, CA

Disclosure statement

- **Youn Kim, MD**
- Steering Committee
  - Eisai, Millennium
- Consultant or Advosory board
  - Kyowa, Celgene, Emergent, Medicis
- Investigator
  - Allos, Kyowa, Merck, Millennium, Seattle Genetics, SHAPE, Ceptaris/Yaupon, Eisai, Genentech

Key Clinical Questions in CTCL

- How can we optimize our diagnostic ability?
- What are the key prognostic factors or markers that can help guide clinical management?
- How do we make optimal treatment decisions with available therapies?
- How can we improve future therapeutics and outcome?

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NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Hodgkin's Lymphomas

Version 1.2013

NCCN.org

NHL => MFSS

Medicare and other insurances follow NCCN guidelines

Real time updates

Consensus if not evidence-based recommendations

NCCN Guidelines Version 1.2013
Mycosis Fungoides/Sezary Syndrome

NCCN Guidelines Index
NHL Table of Contents
Discussion

DIAGNOSIS

ESSENTIAL:

- Biopsy of suspicious skin sites
- Dermatopathology review of slides

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- IHC of skin biopsy[a,b,c] (CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD25, CD56, TIA1, granzyme B, βF1)
- Molecular analysis for TCR gene rearrangements (assessment of clonality) of skin biopsy;[a] PCR methods[d]
- Assessment of peripheral blood for Sezary cells (in cases where skin is not diagnostic, especially T4) including Sezary cell prep, flow cytometry, and PCR for TCR gene rearrangement
- Biopsy of suspicious lymph nodes (in absence of definitive skin diagnosis)
- Assessment of HTLV-1[e] serology in at-risk populations. HTLV-1 PCR if serology is indeterminate

WORKUP

ESSENTIAL:

- Complete physical examination
  - Examination of entire skin: assessment of %BSA (palm plus digits ≈1% BSA) and type of skin lesion (patch/plaque, tumor, erythroderma)
  - Palpation of peripheral lymph node regions
  - Palpation for organomegaly/masses
- Laboratory studies:[f]
  - CBC with Sezary screen (manual slide review, "Sezary cell prep")
  - Sezary flow cytometric study (optional for T1); CD3, CD4, CD7, CD8, CD26 to assess for expanded CD4+ cells with increased CD4/CD8 ratio or with abnormal immunophenotype, including loss of CD7 or CD26
  - TCR gene rearrangement of peripheral blood lymphocytes if blood involvement suspected
  - Comprehensive metabolic panel
  - LDH
- Imaging studies
  - Chest/abdominal/pelvic contrast-enhanced CT or integrated whole body PET-CT (≥T2, large cell transformed or folliculotropic MF, or with palpable adenopathy or abnormal laboratory studies)
- Pregnancy testing in women of child-bearing age[g]

USEFUL IN SELECTED CASES:

- Bone marrow biopsy (not required for staging but used to document visceral disease in those suspected to have marrow involvement including B2 blood involvement and in patients with unexplained hematologic abnormality)
- Biopsy of suspicious lymph nodes for identical clones (recommend assessment of clonality for all but particularly NCI LN 2-3) or suspected extracutaneous sites
- Rebiopsy if suspicious of large cell transformation
- Neck CT

STAGE
(MFSS-2 and MFSS-3)

Stage IA	See Primary Treatment (MFSS-4)
Stage IB-IIA	See Primary Treatment (MFSS-5)
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[a] Clinically or histologically non-diagnostic cases. Pimpinelli N, Olsen EA, Santucci M, et al., for the International Society for Cutaneous Lymphoma. Defining early mycosis fungoides. J Am Acad Dermatol 2005;53:1053-1063.

[b] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[c] Typical immunophenotype: CD2+ CD3+ CD5+ CD7- CD4+ CD8- (rarely CD8+) CD30-/+ cytotoxic granule proteins negative.

[d] TCR gene rearrangement results should be interpreted with caution. TCR clonal rearrangement can be seen in non-malignant conditions or may not be demonstrated in all cases of MF/SS. Demonstration of identical clones in skin, blood, and/or lymph node may be helpful in selected cases.

[e] See map for prevalence of HTLV-1 by geographic region.

[f] Sezary syndrome (B2) is as defined on MFSS-2.

[g] Many skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Refer to individual drug information.

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Current diagnostics, 1/2013

Dermatopathology review

CLINICAL-PATHOLOGIC CORRELATION REMAINS KEY

Tissue pathology +/- PB/LN flow cytometric data

Ancillary studies:

Immunohistochemistry (IHC)

- rule out histologic mimics

TCRR PCR for clonality

- demonstration of same clone > 1 site, relevant clone

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Exploratory diagnostics

How to better distinguish from inflammatory ddx and mimics?

- **New IHC markers, FISH to distinguish malignant cell vs. reactive/normal cells**
- **Gene, epigenetic modulation, miRNA expression profiles**

=> *NOT READY for clinical use*

(needs further validation, better/more controls)

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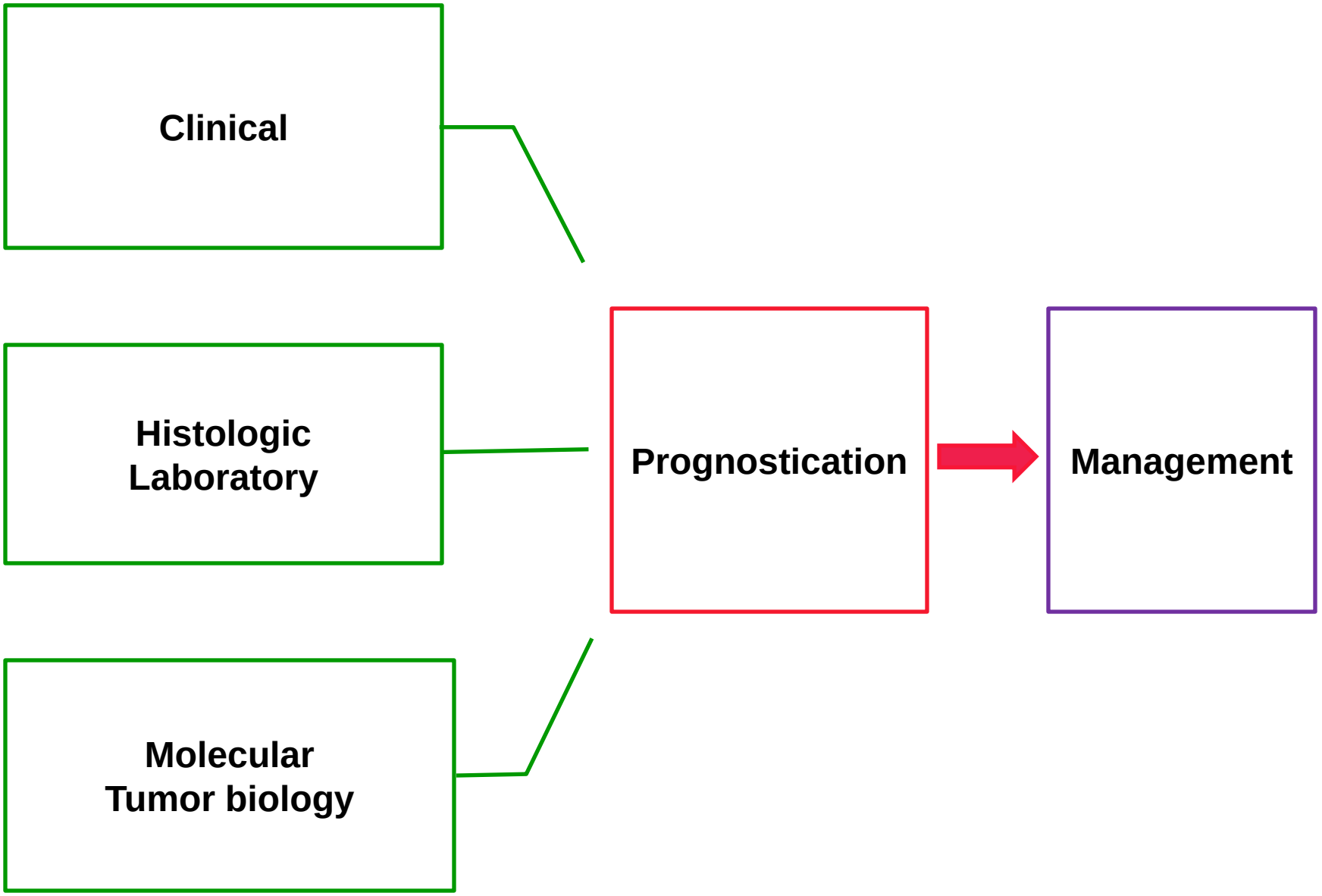
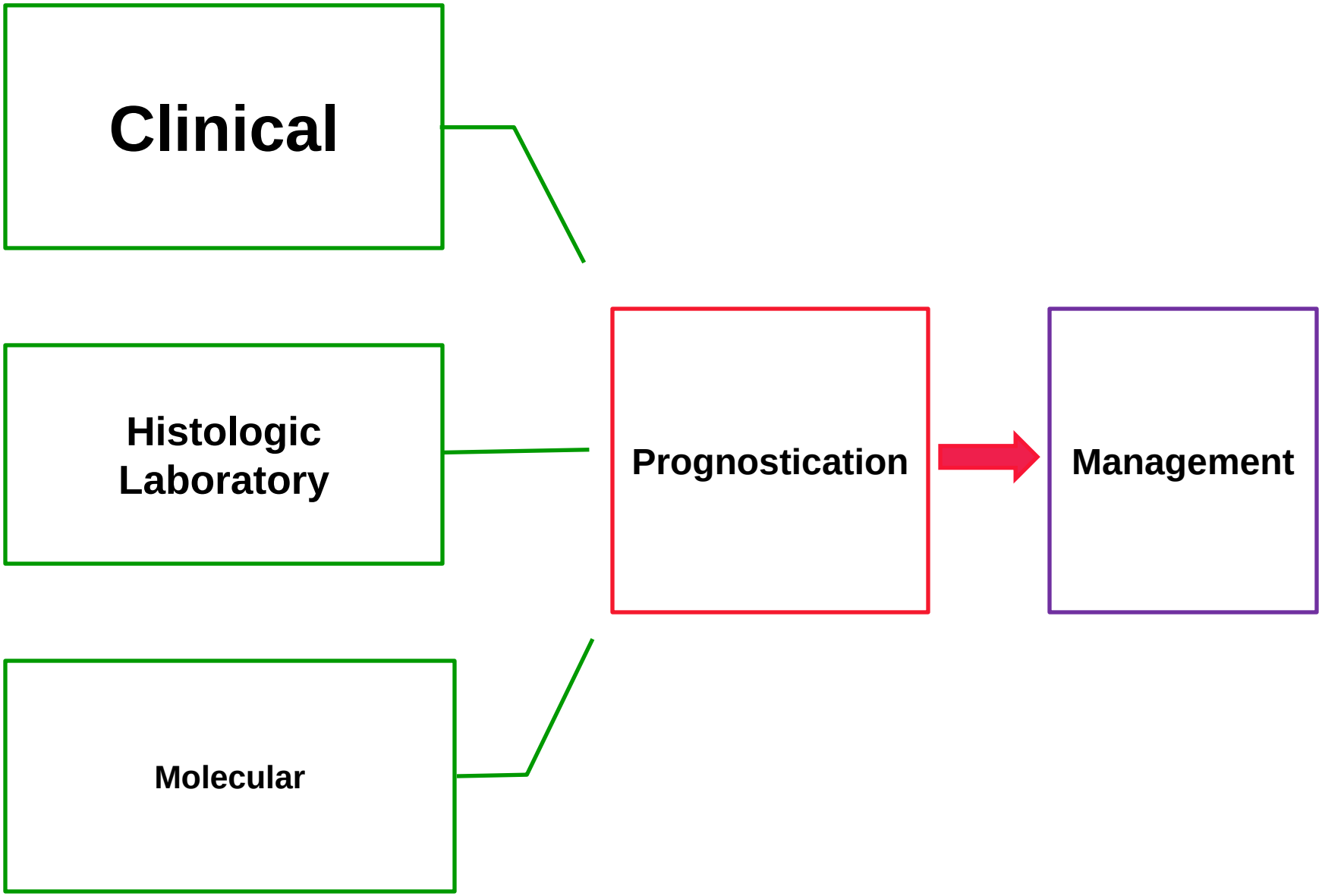
Prognostic factors in cancer management



Cutaneous T-cell lymphoma



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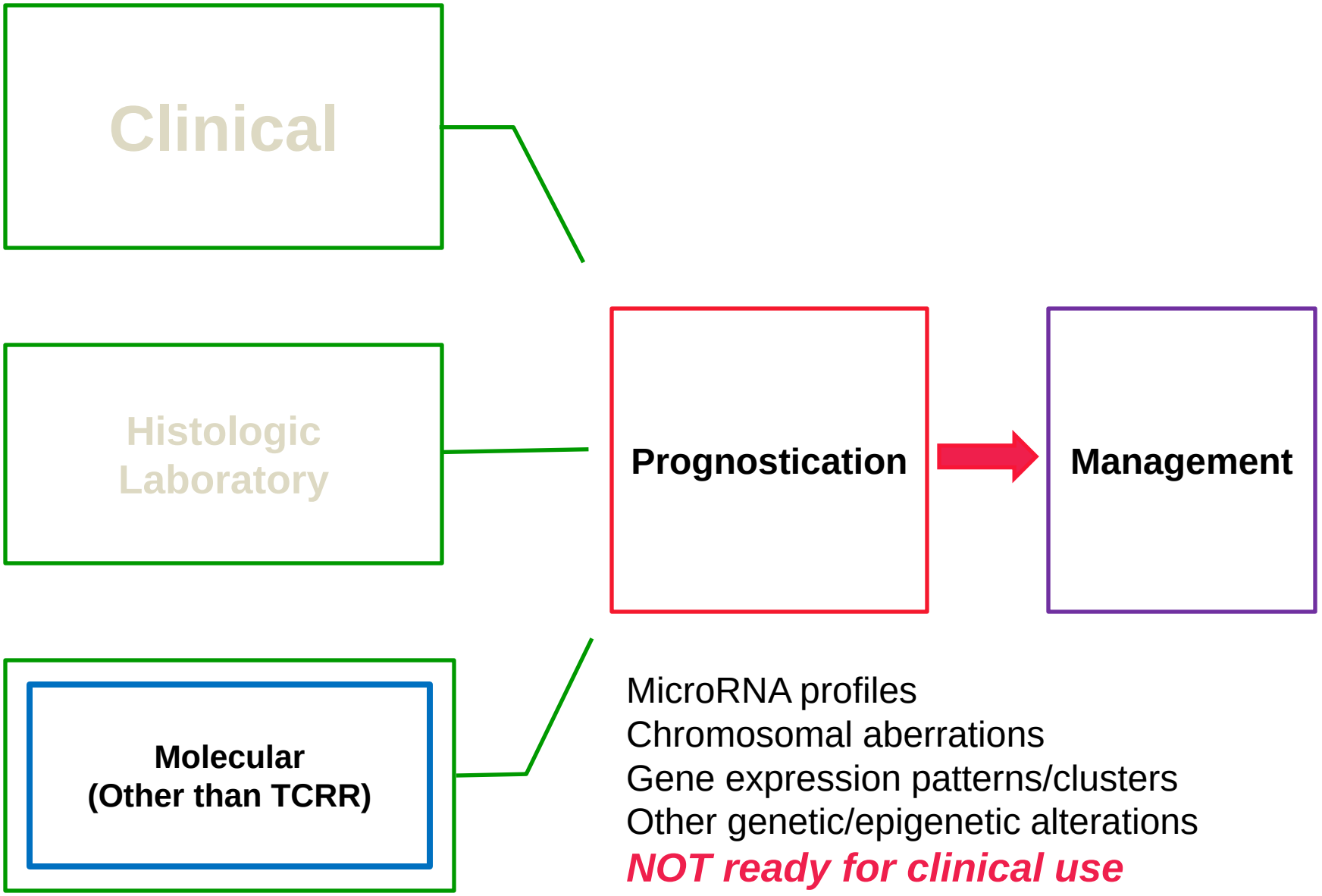


Key clinical factors in CTCL

- Age
  - Worse px in elderly (subset of young/non-cauc bad)
- TNMB/clinical stage
  - Worse with plaque vs. patch, extensive tumors, erythroderma (+ tumors)
  - LN: N0 v N1-2 (relevant clone pos vs neg) v N3 (frank LN dz)
  - Viscera/M (solid organ vs BM)
  - Blood/B0 (relevant clone pos) vs B1 vs B2 vs very high SC load
- MF clinical variants
  - WK (favorable), F-MF (unfavorable)
  - Poikilodermatous (favorable)
- Transformation to aggressive clinical behavior
- *Gender, ethnicity (geographic variation)*

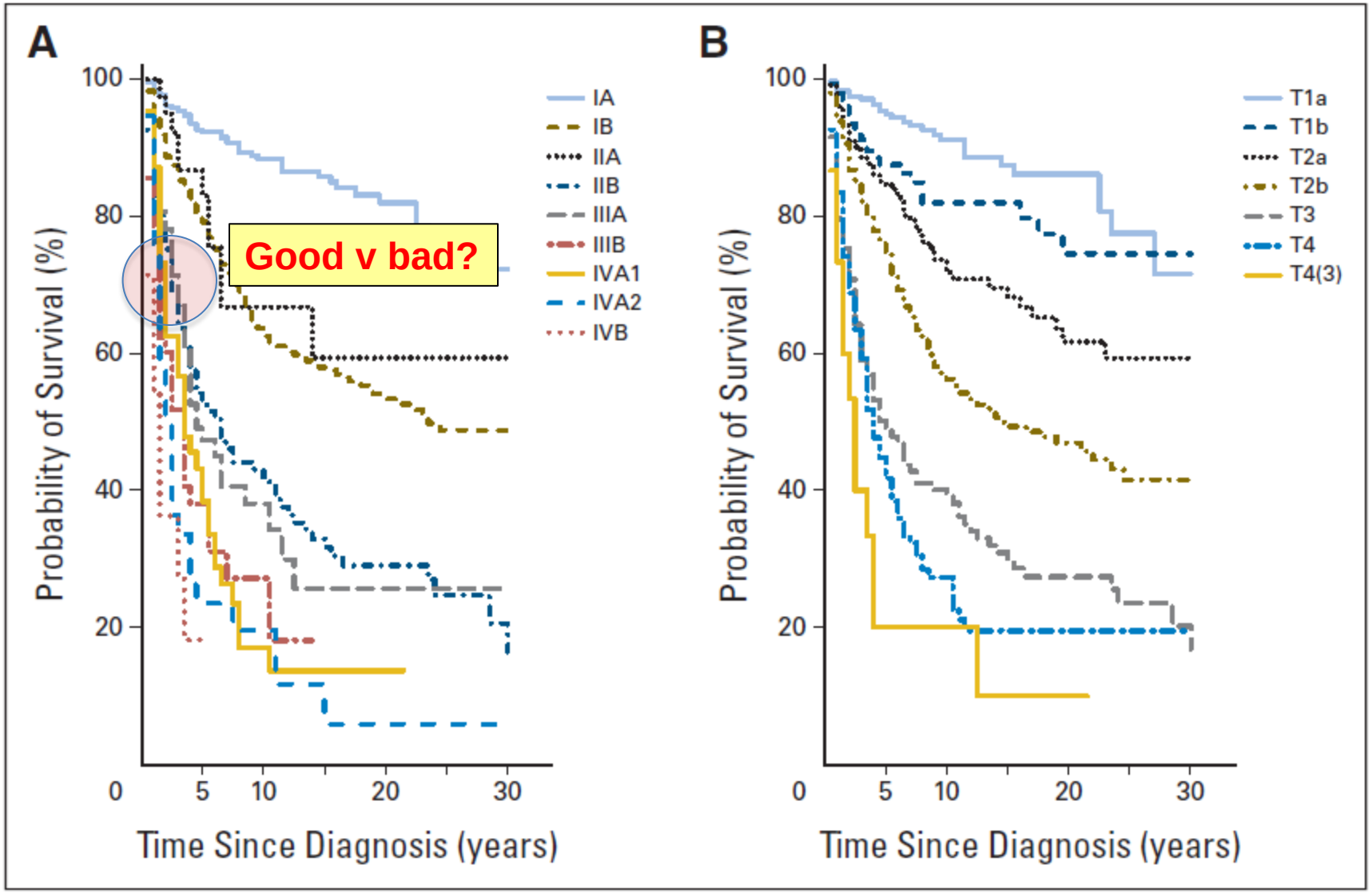
Arch Dermatol 2003;139:857, J Clin Oncol 2010;28:4730, J Am Acad Dermatol 2009:60:231, Int J Dermatol 2009;48:243, Clin Cancer Res 2012 18:5051

Histologic and laboratory factors in CTCL

- **Folliculotropism, large cell transformation**
- Tissue tumor cell features
  - Ki-67, CD30, CD25
- Tissue tumor microenvironment
  - TILs (CD8+ CTL), Tregs
- **LDH, beta-2 microglobulin**, eosinophilia/IgE
- Soluble CD25, CD30, cytokine/cytokine receptor levels

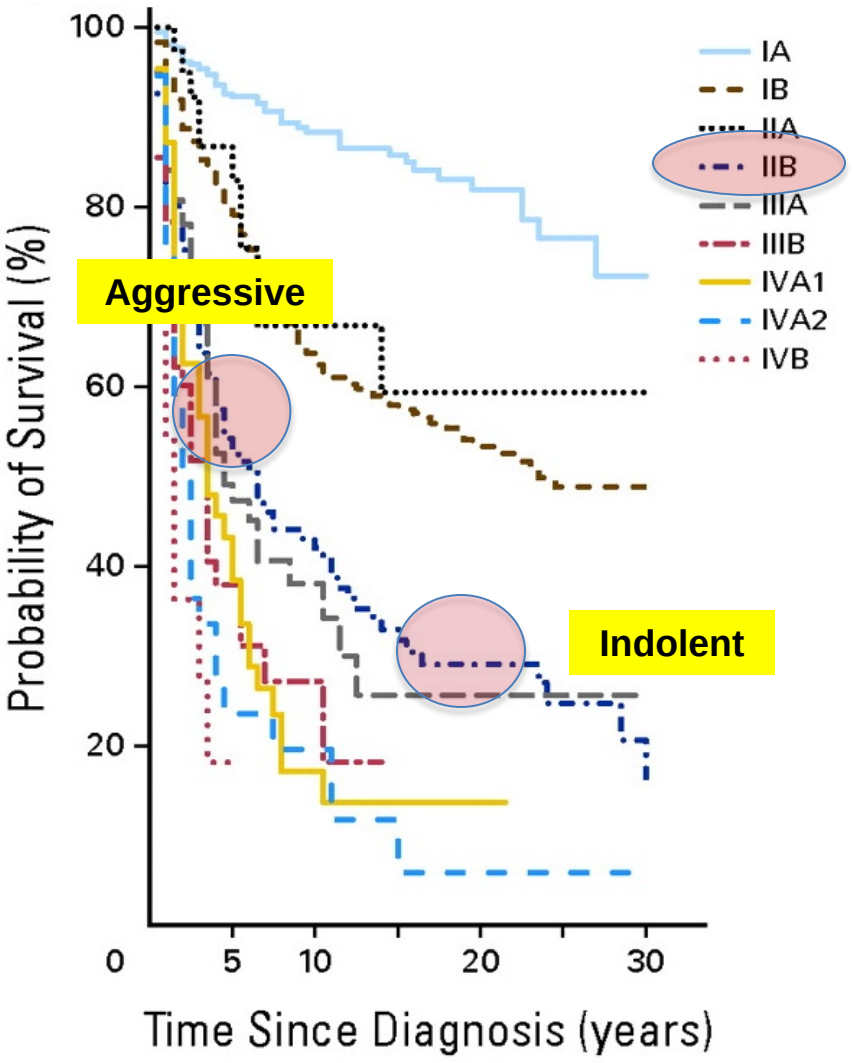
J Clin Oncol 2010;28:4730, Blood 2012;119:1643, Clin Cancer Res 2012 18:5051
J Am Acad Dermatol 1995;32:448, Leukemia 2007;21:2512, J Invest Dermatol 2012;132:703

Survival decreased with advancing skin disease (T-class) and overall clinical stage



Agar et al. J Clin Oncol 2010;28:4730

Beyond clinical factors: how can we predict the good from the bad within a stage/IIB?



- Are there clinical factors, biomarkers that distinguish between indolent and aggressive IIB?
- Can we predict which IIB patients will live longer?
- Are there biomarkers for cells in the aggressive disease?
- Are there drugs that target the dysregulated genes or biological pathways?

Agar N S et al. JCO 2010;28:4730-4739

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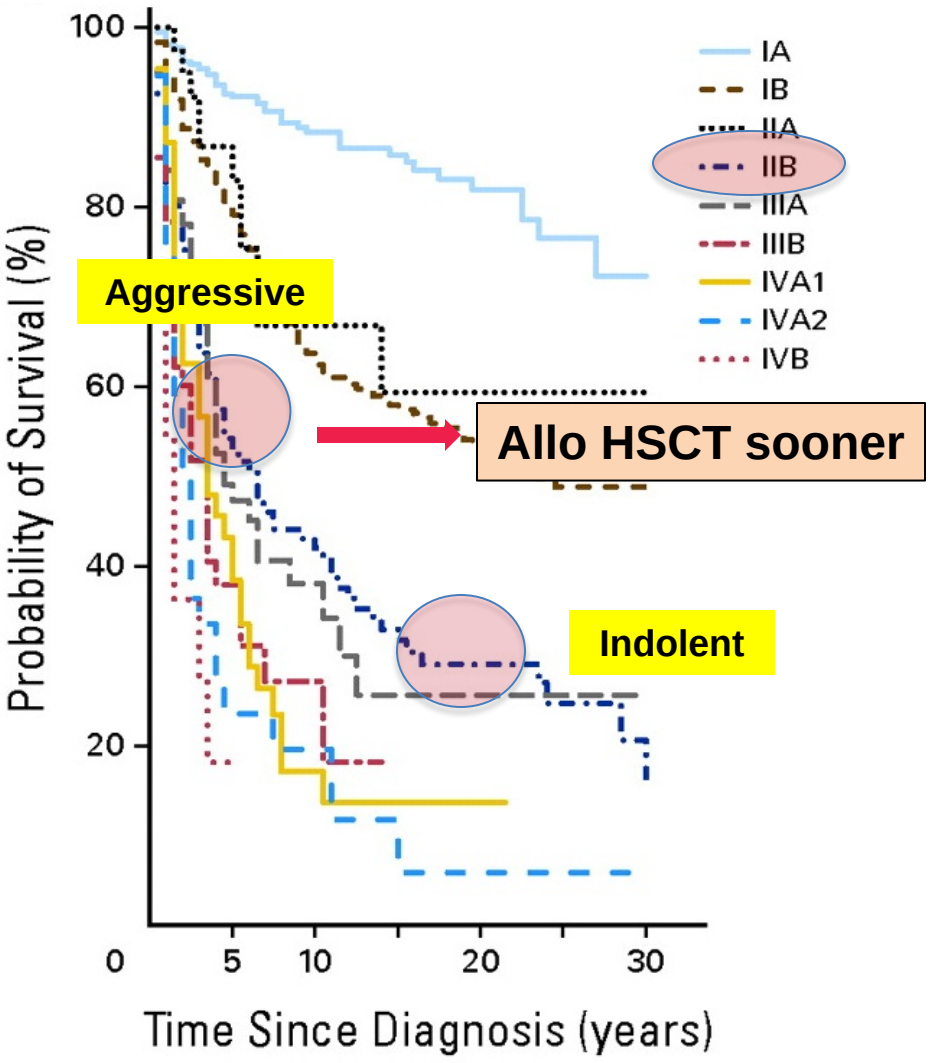

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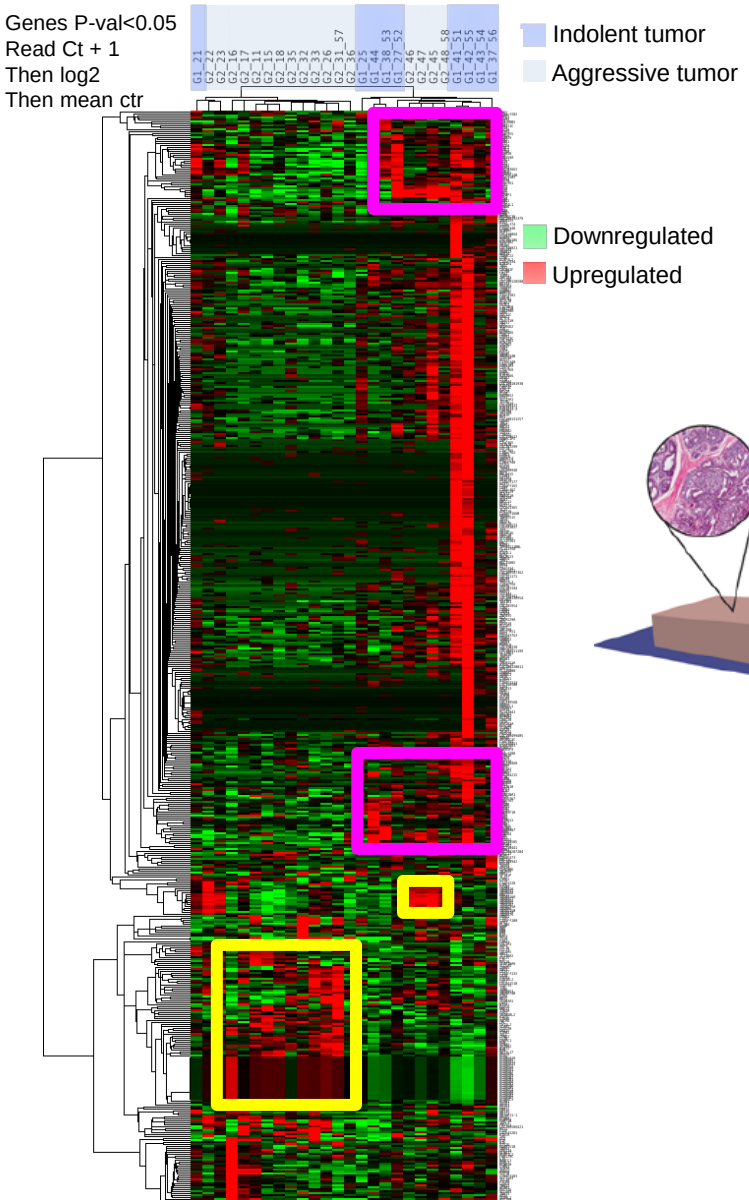
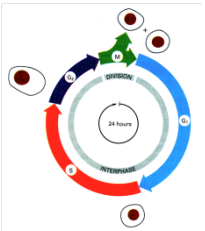
Gene expression pattern that distinguish indolent vs. aggressive MF tumors



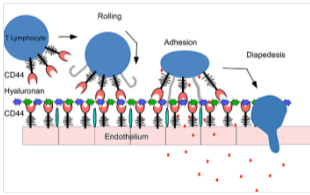
R Chen et al 2012

Key changes in aggressive MF tumors

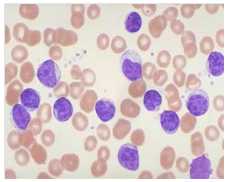
Genes regulating cell proliferation and survival including the MAPK, PI3K, AKT, Jak/Stat pathways



T cell adhesion and migration



Genes implicated in leukemias/ lymphomas and other cancers

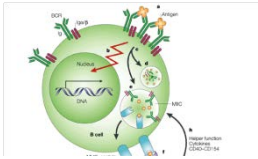


Aggressive MF Tumors

Breakdown of extracellular matrix, potentially favoring tumor invasion, metastasis

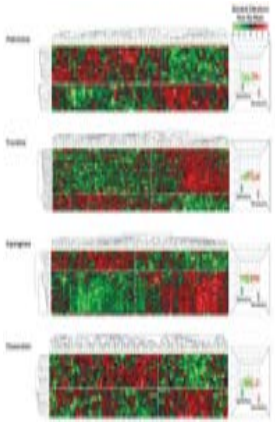
Inflammatory response genes including ones implicated in skin conditions such as psoriasis

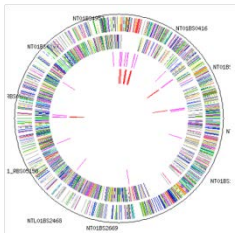
B cell differentiation, proliferation



R Chen et al 2012

Dreaming the future of personalized medicine
CTCL Bench to Bedside





- **Diagnosis**
- **Prognosis**
- **Personalized management**

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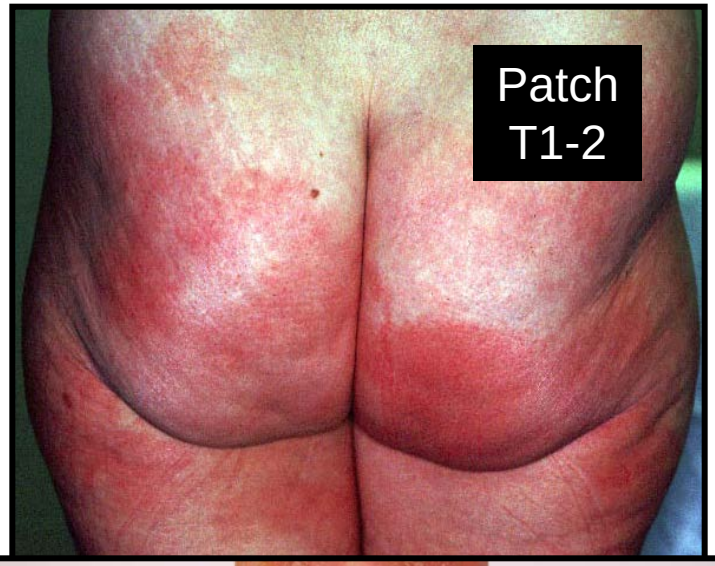
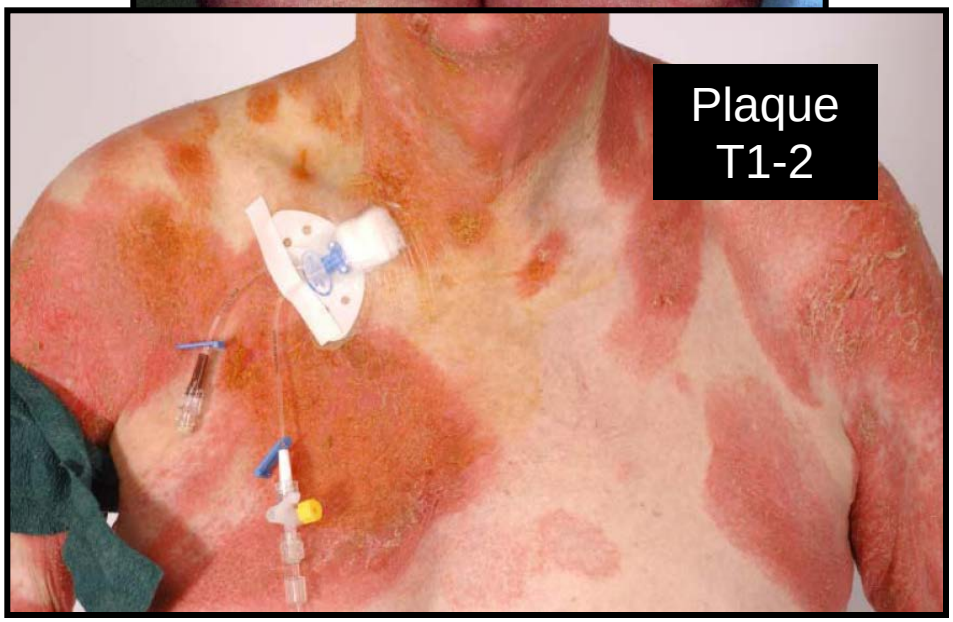
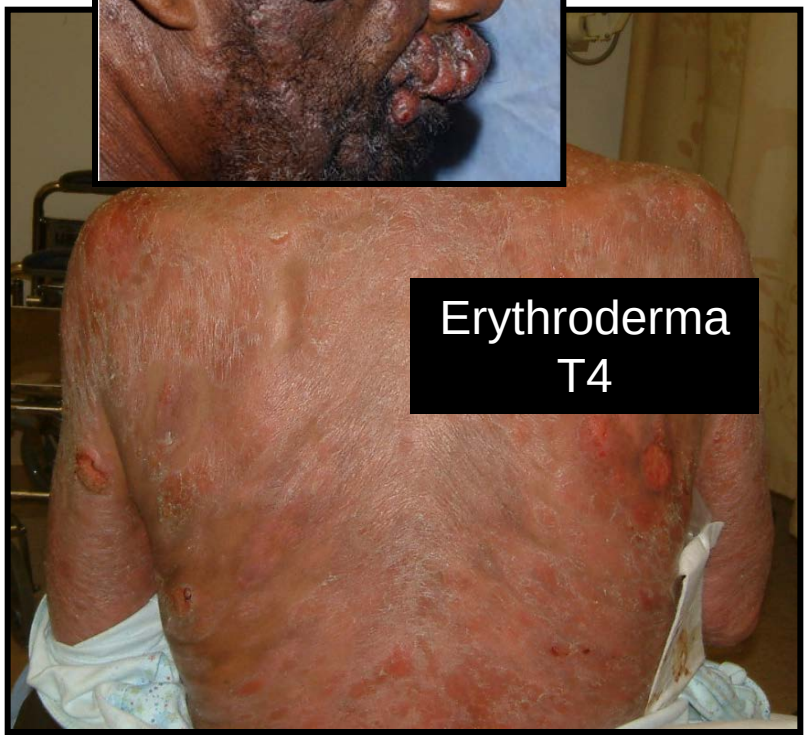
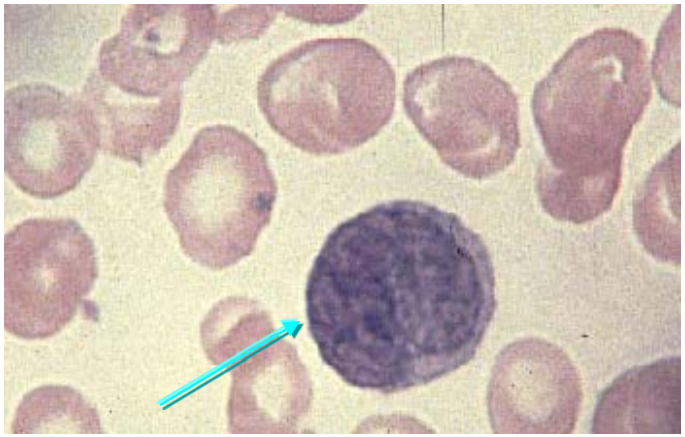
Mycosis Fungoides
Treatment of varying skin manifestations





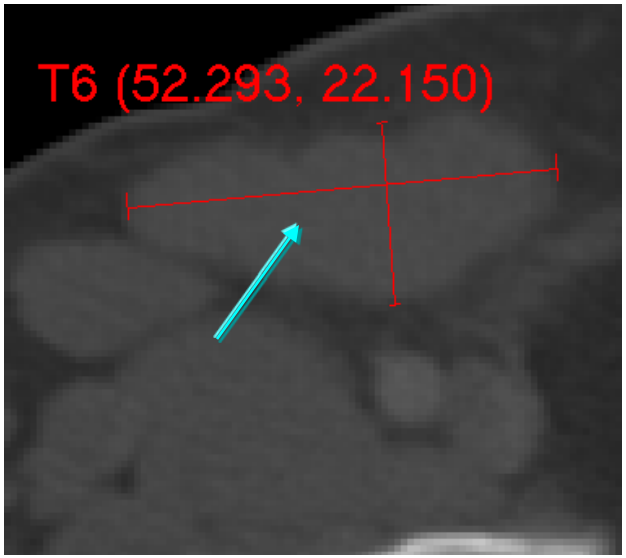


Management of extracutaneous disease

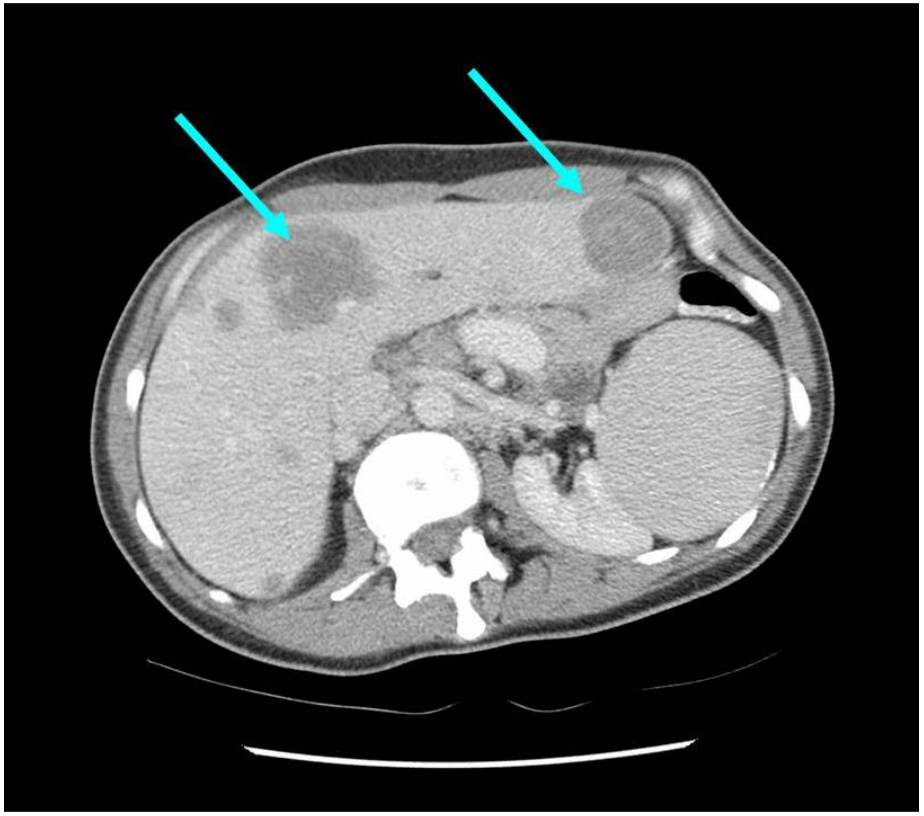


Blood

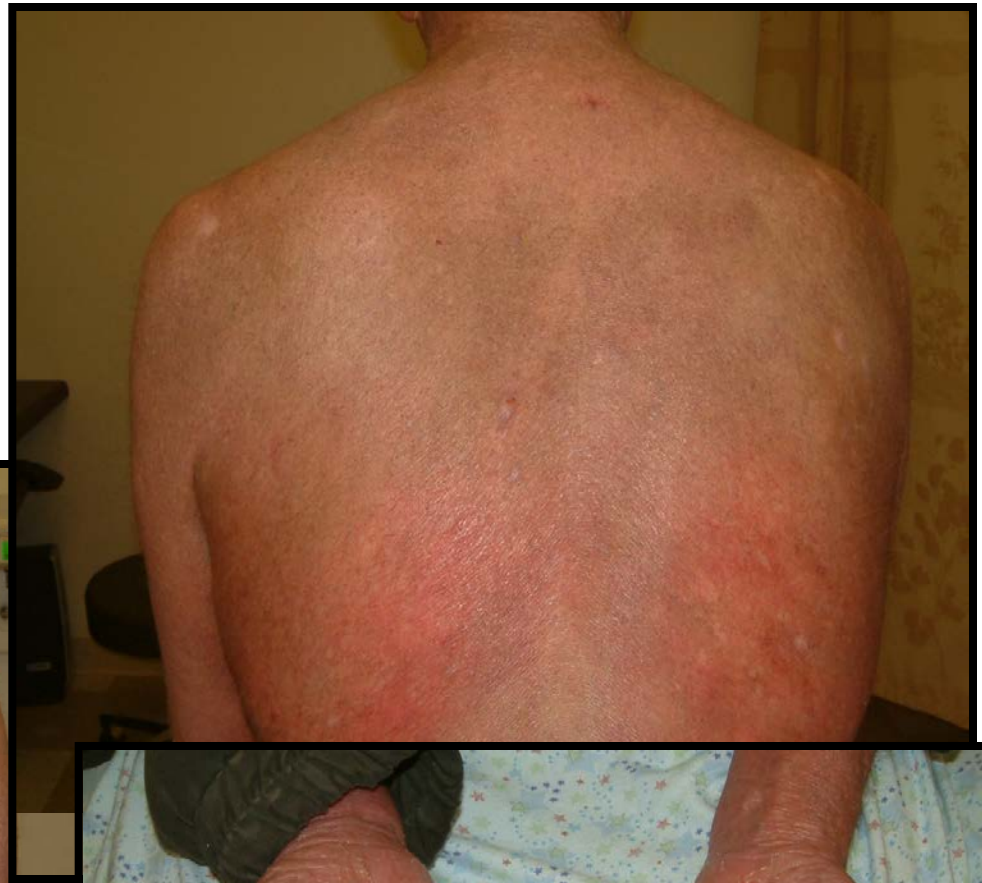
Lymph node

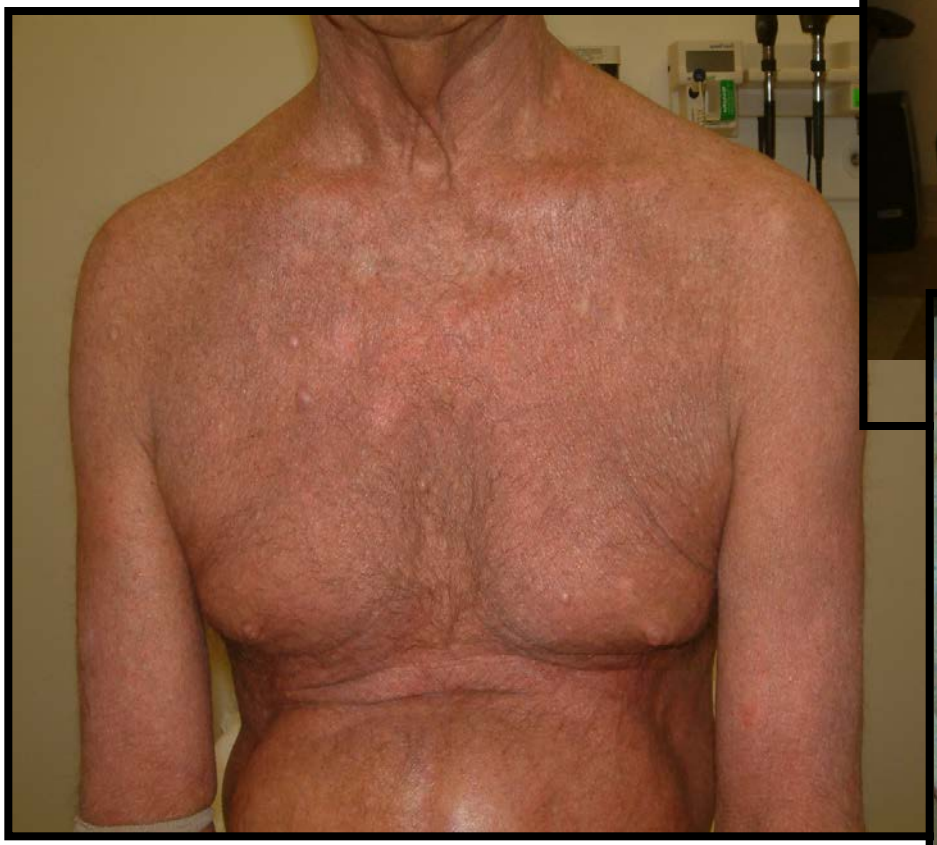


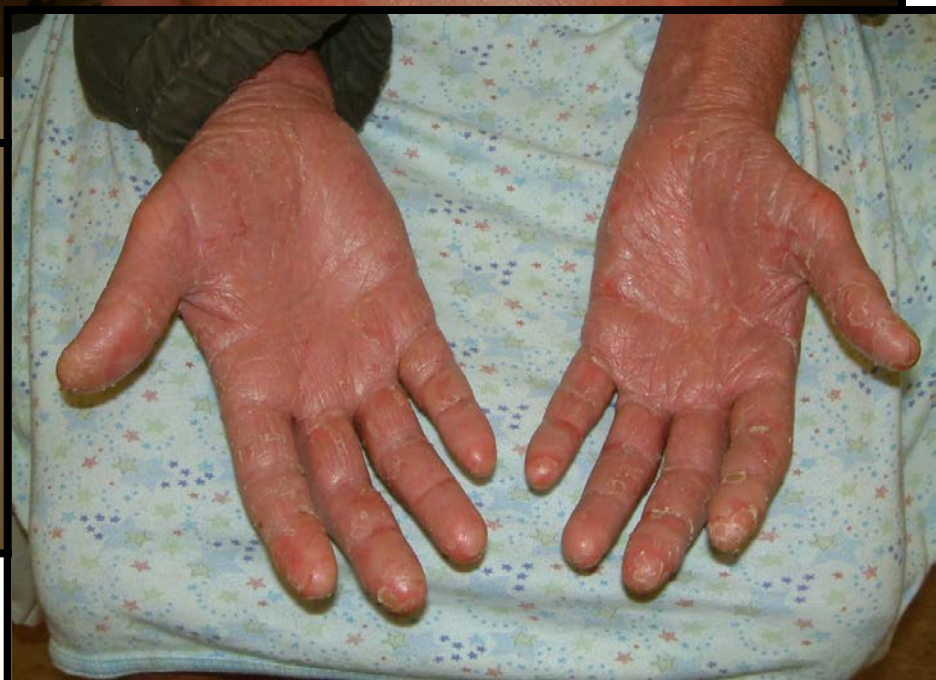
Viscera



Sézary syndrome- generalized erythroderma, keratoderma, severe itching; freq staph aureus infection







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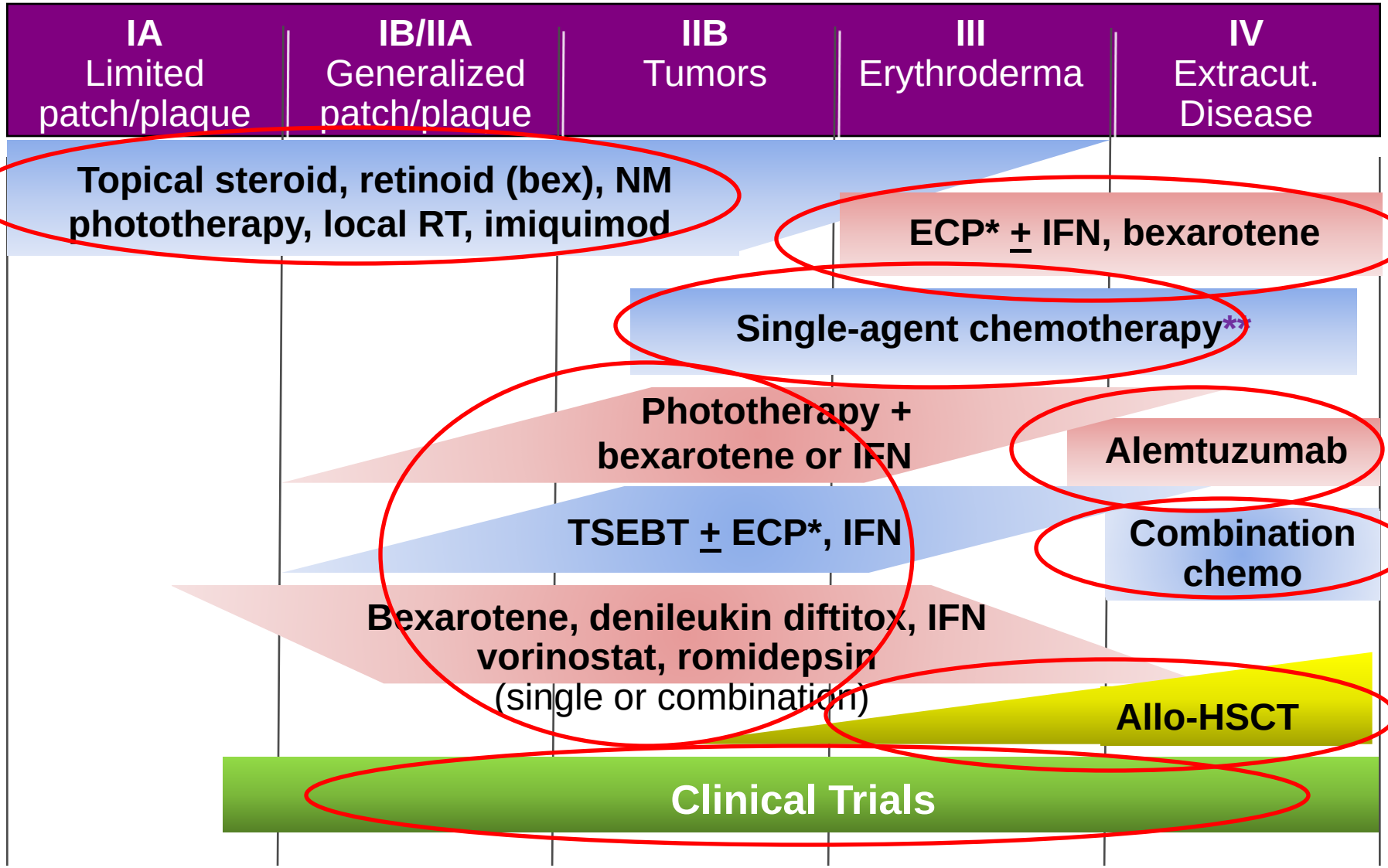
Stage-based treatment algorithm

Blood 2007;110:1713

www.nccn.org => NHL => MFSS

Current Clinical Management of CTCL, *2013*

www.nccn.org => NHL => MF/SS



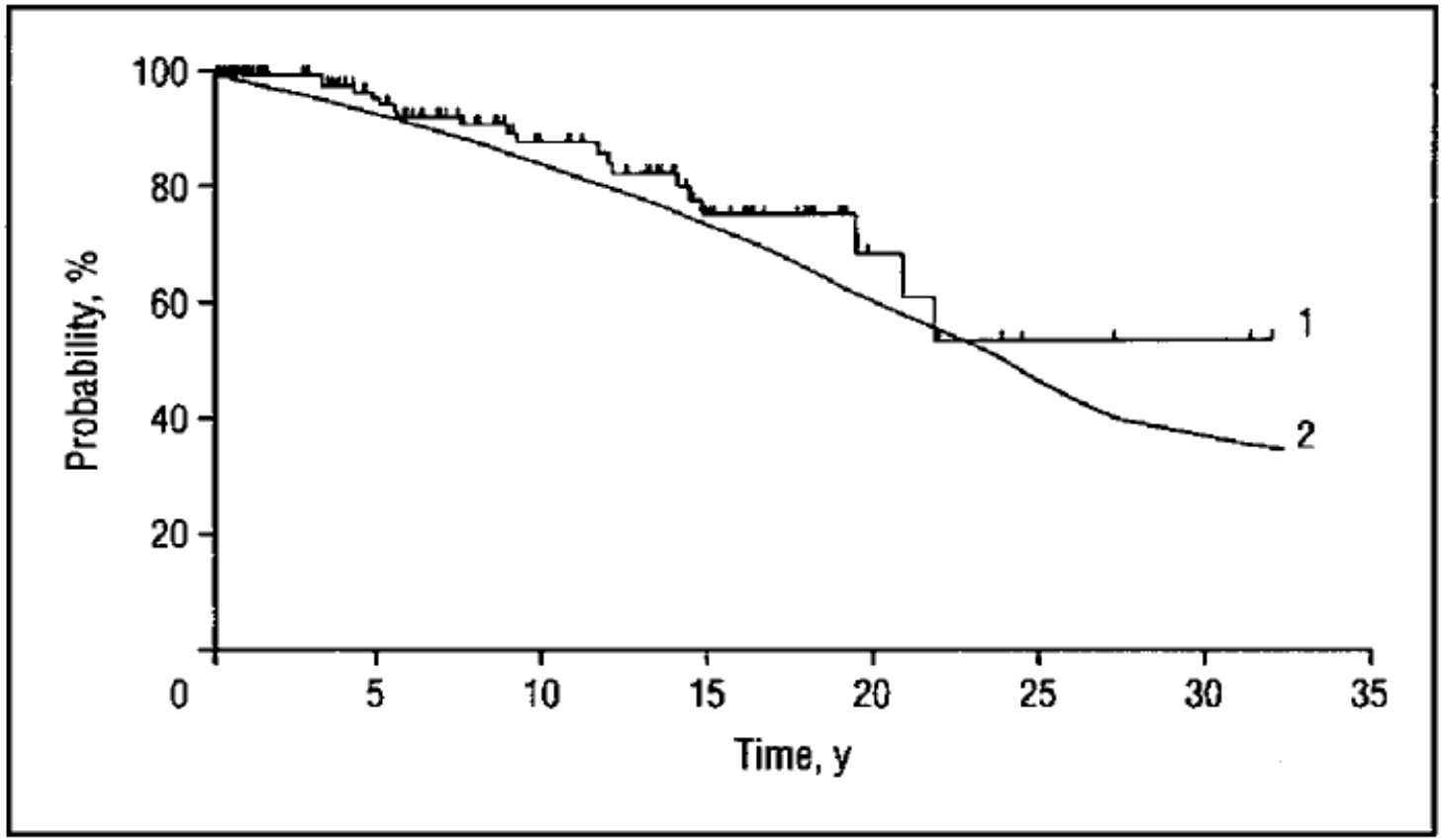
*ECP = photopheresis

** Methotrexate, liposomal doxorubicin, gemcitabine, pentostatin, chlorambucil, etoposide, **pralatrexate**

Key treatment selection factors

- **Clinical stage/TNMB**
  - MF vs. SS
- **Other prognostic factors**
  - Large cell transformation
  - Folliculotropic disease
- **Age, co-morbidities, concomitant meds**
- **Availability/access issues**
  - TSEBT, photopheresis
  - US vs. other countries
  - Insurance barriers

Actuarial survival of stage IA vs. control population: *Life-expectancy is not altered in patients with limited patch/plaque disease*



Kim et al, Arch Dermatol 1996;132:1309-13

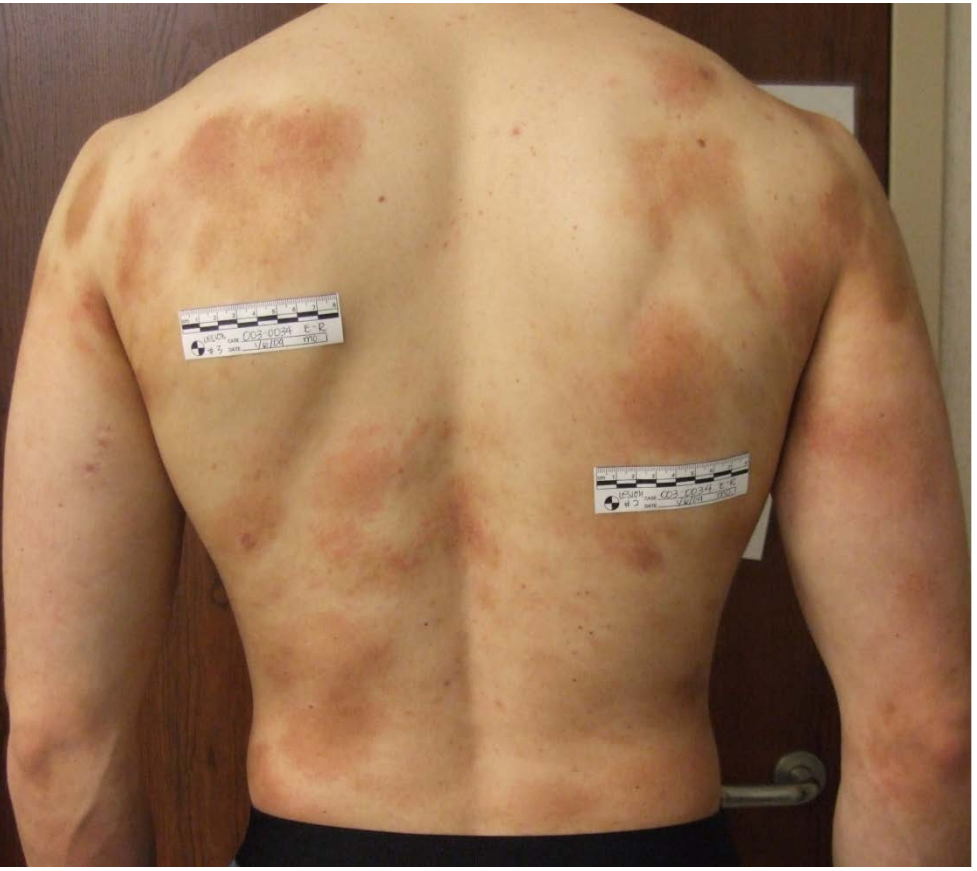
Reliable skin responses with skin-directed options as primary therapy in stages I-IIA (skin-limited, patch/plaque disease)

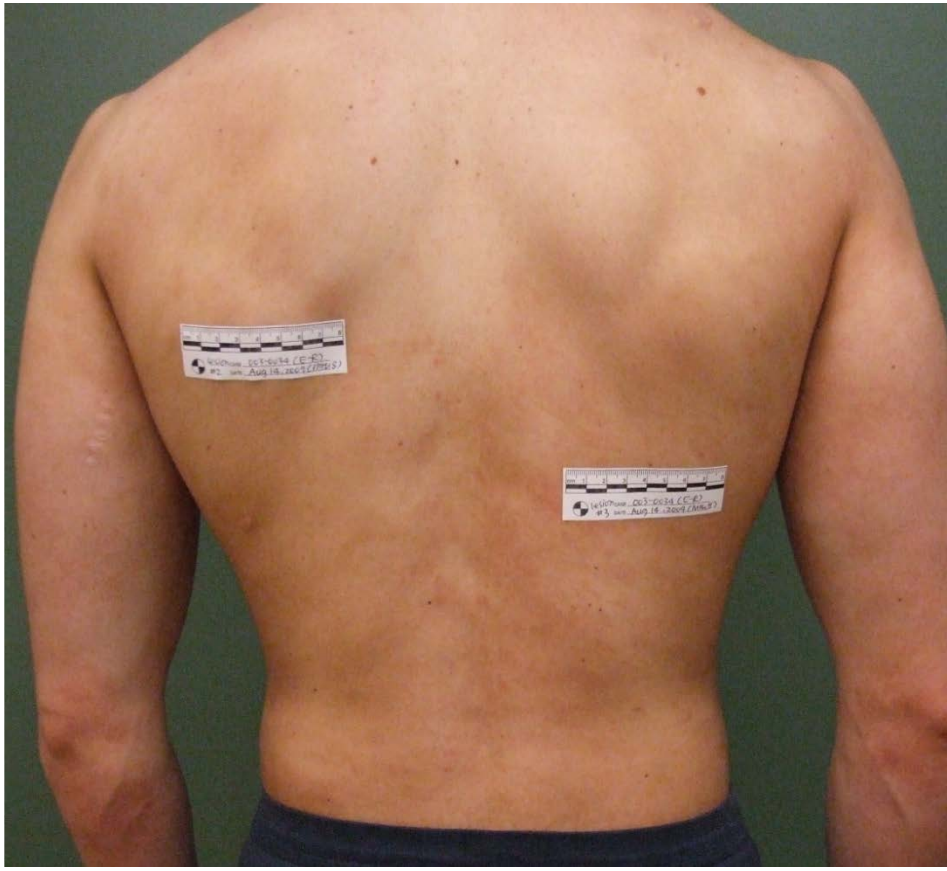
Skin Therapy	CR	ORR
Topical steroids	45-65%	75-95%
Bexarotene gel	20-35%	50-75%
Topical NM	25-70%	50-90%
nbUVB	45-75%	75-100%
PUVA	50-80%	85-100%
TSEBT (≥30 Gy)	80-90%	100%

- **Systemic agents (e.g., bexarotene, IFN, methotrexate, vorinostat, romidepsin) 30-45% RR in skin with low CR rates**

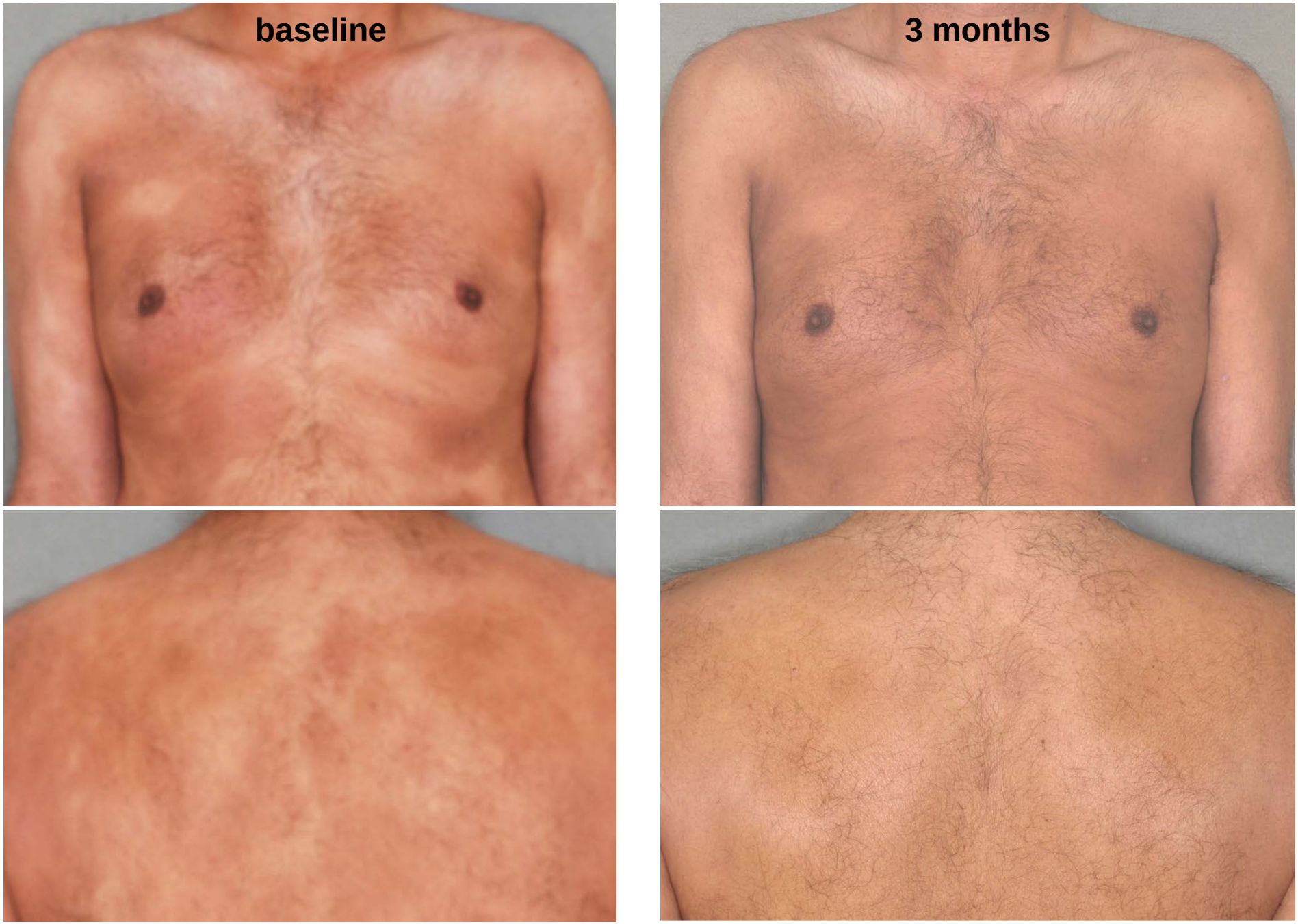
Arch Dermatol 2003;139:165, J Am Acad Dermatol 2003;49:801, J Am Acad Dermatol 2002;47:191, Arch Dermaol 2005;141:305, Arch Dermatol 2011;147:561, Arch Dermatol 2001;137:581, J Clin Oncol 2007;25:3109, J Clin Oncol 2010;28:4485

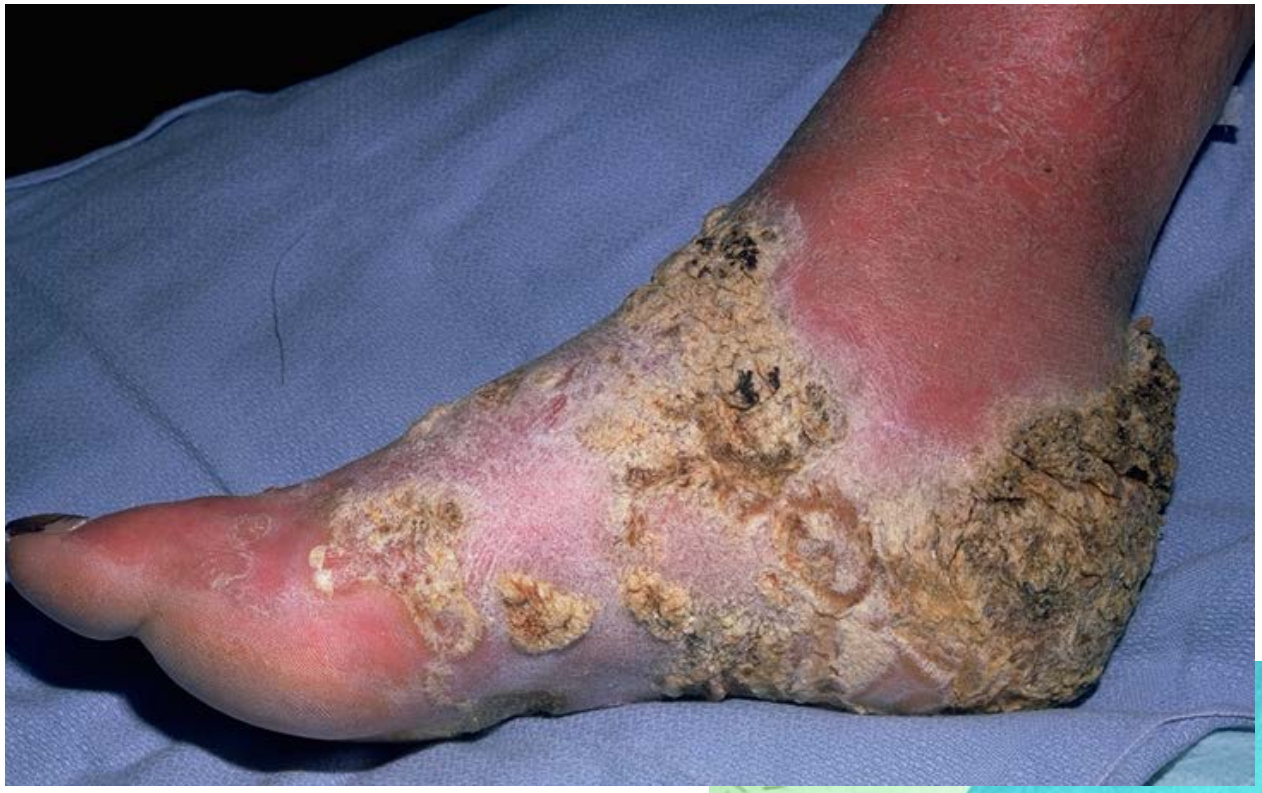
Clinical response to topical nitrogen mustard gel
NDA re-filed; expect approval end of 2013

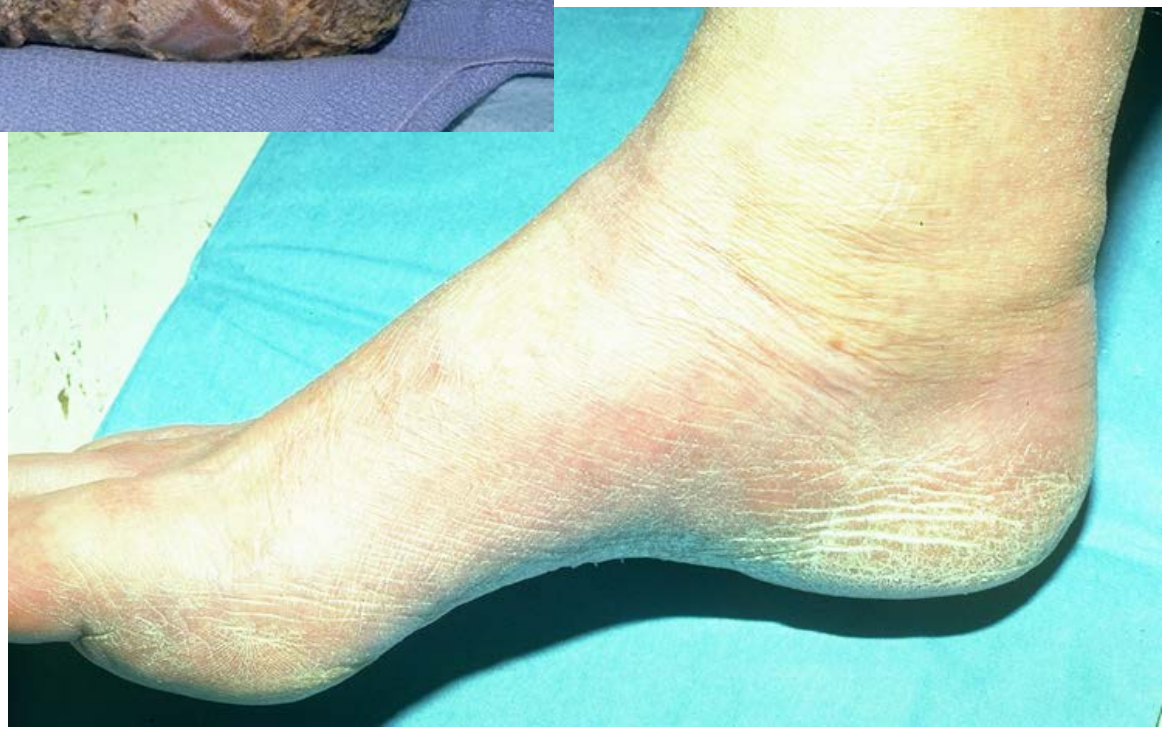




Narrow band UVB







Localized RT in Woringer Kolopp disease

When need to intensify therapy in MF/SS "Combination strategies" are utilized

- **Skin-directed + Systemic**
  - Phototherapy + retinoid
  - Phototherapy + IFN
  - Phototherapy + photopheresis*
  - TSEBT + photopheresis*

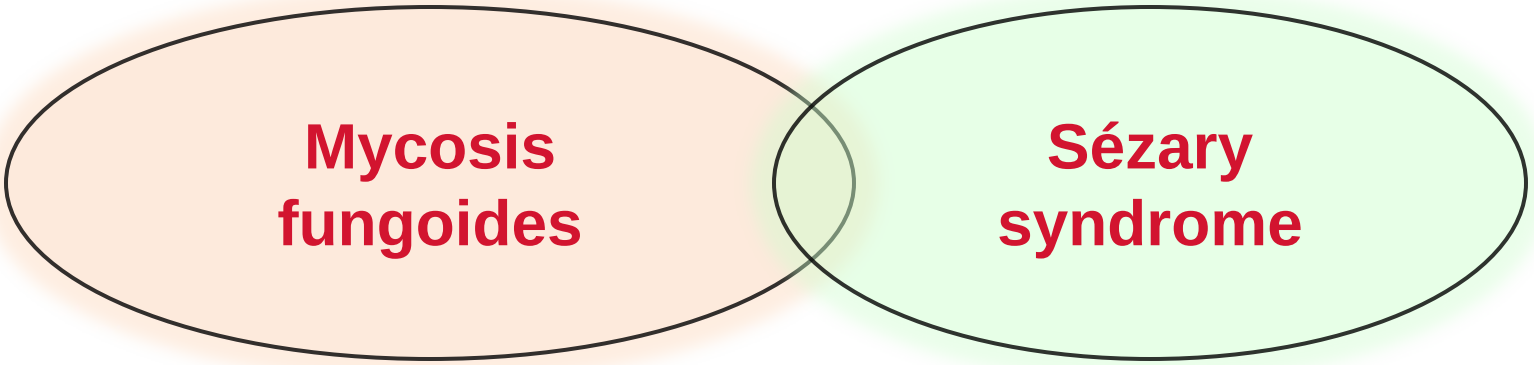
- **Systemic + Systemic**
  - Retinoid + IFN
  - Bexarotene + denileukin diftitox
  - Photopheresis* + retinoid
  - Photopheresis* + IFN
  - Photopheresis* + retinoid + IFN

Is combination therapy "better"?

- ***No comparative data***
- ***Lower doses of each (less toxicity)***
- ***Synergy?***

****Photopheresis comb more appropriate in pts with blood involvement,B1-2***

Appreciating biologic and clinical differences/overlap in MF vs. SS: translating into management



Oncogenomic analysis of mycosis fungoides reveals major differences with Sézary syndrome

Blood 2009 113:127-36

Brief report

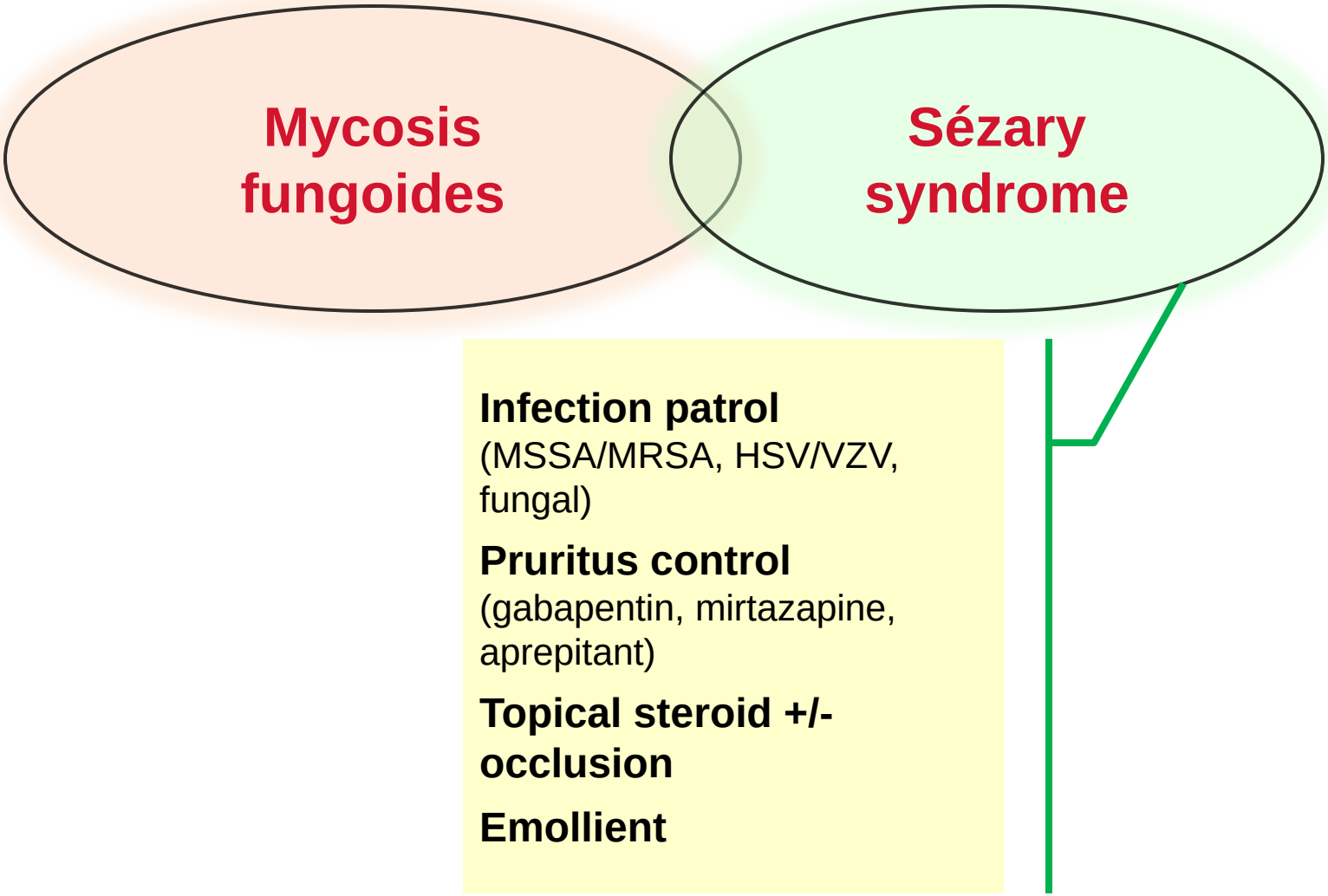
Sézary syndrome and mycosis fungoides arise from distinct T-cell subsets: a biologic rationale for their distinct clinical behaviors

*James J. Campbell,[1] *Rachael A. Clark,[1] Rei Watanabe,[1] and Thomas S. Kupper[1]

[1]Department of Dermatology, Brigham and Women's Hospital/Harvard, Boston, MA

Blood 2010;116:767-771

Distinctive supportive management in Sezary syndrome



Management of Sezary Syndrome, B2/stage IV

- Stratification based on blood Sezary burden
- Given risk for staph sepsis, utilize agents that spare further immune dysfunction
- **Low-intermediate Sezary burden**
  - "Milder" systemic therapies: biologics (bexarotene, photopheresis, interferon), methotrexate
- **High Sezary burden (> 5-10K/mm^3)**
  - Combination therapies
  - Romidepsin
  - Alemtuzumab
- Refractory disease
  - Alemtuzumab
  - **Clinical trials**

Allo HSCT

Key Clinical Questions in CTCL

- How can we optimize our diagnostic ability?
  - Better distinguish from inflammatory/benign mimics and specify type of CTCL
- What are the key prognostic factors or markers that can help guide clinical management?
- How do we make optimal treatment decisions with available therapies?
- How can we improve future therapeutics and outcome?

Why do we need better therapies?

Efficacy of Systemic Agents in CTCL

Efficacy data for FDA approval

Agent (Class)	Indication	Year	Study	N	ORR	DOR
Romidepsin (HDAC inhibitor)	CTCL with prior systemic therapy	2009	Pivotal	96	34%	15 mo
			Supportive	71	35%	11 mo
Denileukin diftitox (Fusion protein)	Tumors that express CD25	1999, 2008	Pivotal	71	30%	4 mo
Bexarotene (RXR activator)	Cutaneous manifestations	1999	Pivotal	62	32%	5+ mo
Vorinostat (HDAC inhibitor)					30%	6+ mo
					24%	4 mo

Need better therapies
More options

Era of targeted therapies

Huge impact in cutaneous oncology:

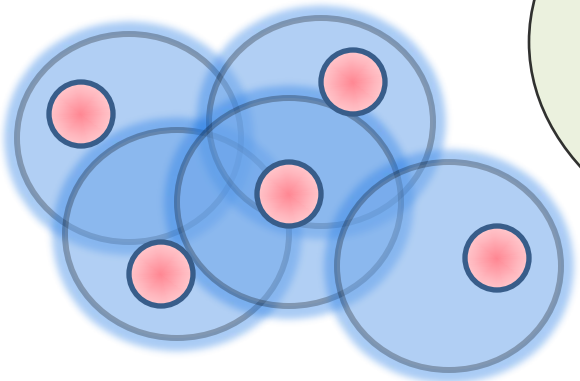
melanoma (vemurafenib), BCCs (vismodegib)

- **Need understanding of driver targets**
- **Kill tumor/bad cells but spare good cells**
- **Target the environment to enhance anti-tumor effects**
- Improved technology for increased potency
- Consider combination strategies as appropriate
  - Multiple targets/pathways
  - Complementary targets
  - How to optimize efficacy without additive toxicities

Targets for therapy in cutaneous T-cell lymphoma

Tumor cell surface molecules
(e.g., CD4, CD25, CD30, CD40, CD52, CD158k, CCR4)

CTCL



Microenvironment, immune mechanisms
(e.g., vasculature, immune modulation)

Tumor proliferation, metabolism, survival, progression mechanisms:
Signal transduction/transcription activation pathways
(e.g., ubiquitin-proteasome, AKT/PI3K/mTOR, RAS/RAF/MEK, MAPK)
Apoptotic pathways *(e.g. Bcl/Bax, TNFR, Fas, miRNAs)*
Epigenetics *(e.g., histone, non-histone proteins)*
Metabolic/survival pathways *(e.g., RFC-1, PARP)*

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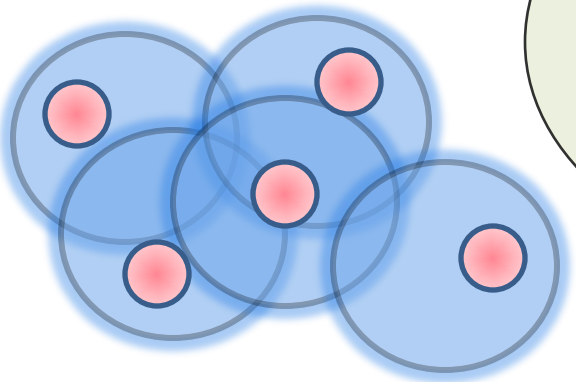

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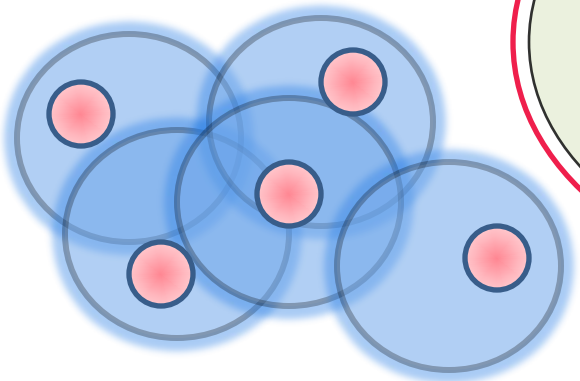

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Types of targeted therapies in lymphoma, 2013

- More and fancier **monoclonal antibodies**

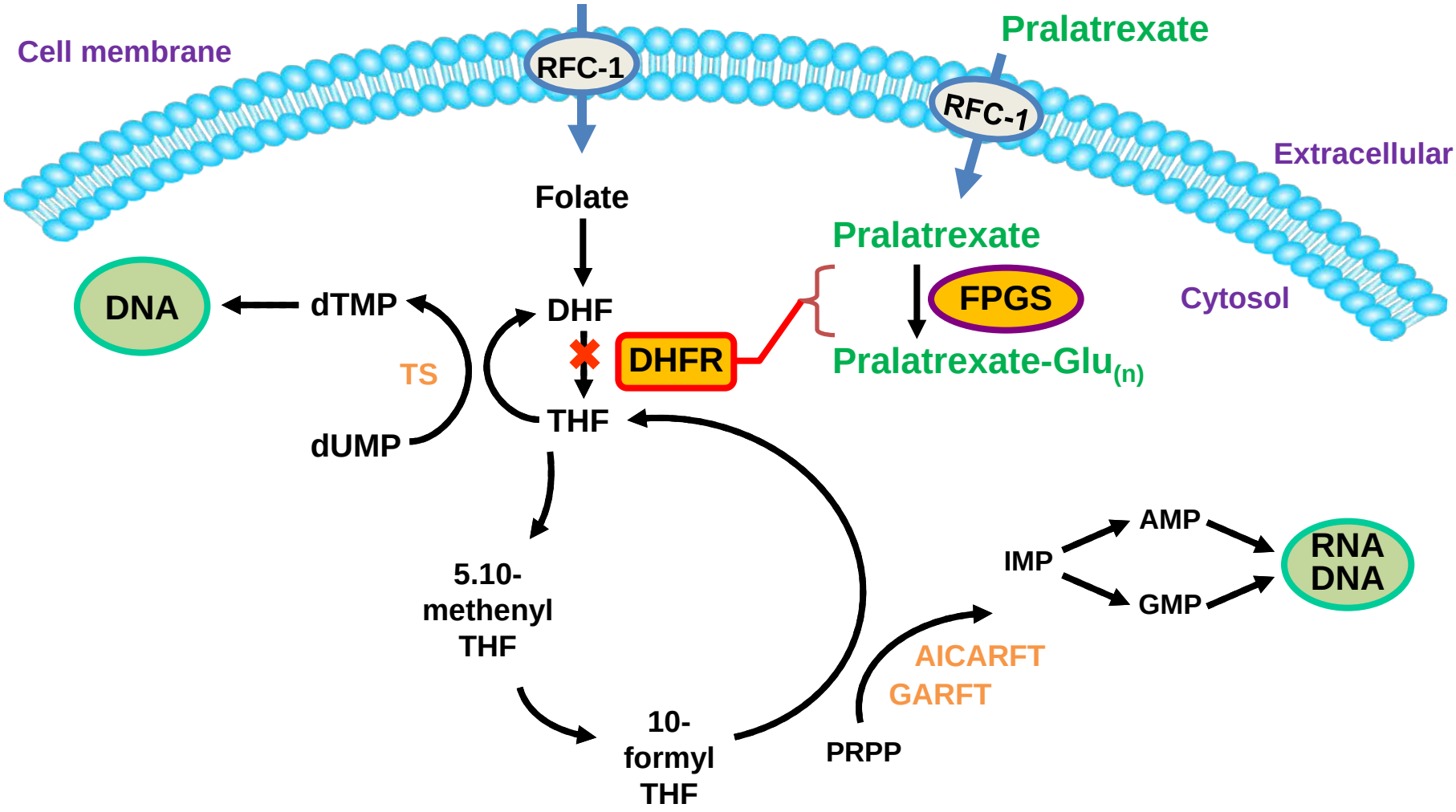
  Cell surface molecules

  – Naked mAbs
    - newer engineered, “high-tech” mAbs
  – MAb drug conjugates (ADCs)
  – Radiolabeled mAbs
- **Small molecule inhibitors/agonists**

  Multitude of potential targets/pathways, need disease relevance

Pralatrexate with improved tumor selectivity

- Improved **anti-folate** agent => ↑ **cellular uptake/retention, tumor > normal**
- High affinity for RFC-1; efficient substrate for polyglutamylation by FPGS
- Antifolate activity via the inhibition of DHFR.



Pralatrexate FDA-approved in systemic PTCL, 2009

blood

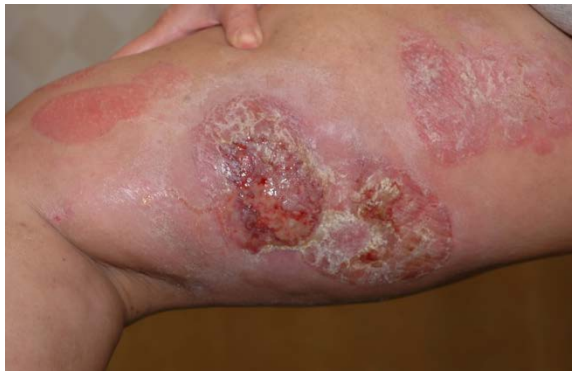
2012 119: 4115-4122
Prepublished online March 6, 2012;
doi:10.1182/blood-2011-11-390211

Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma

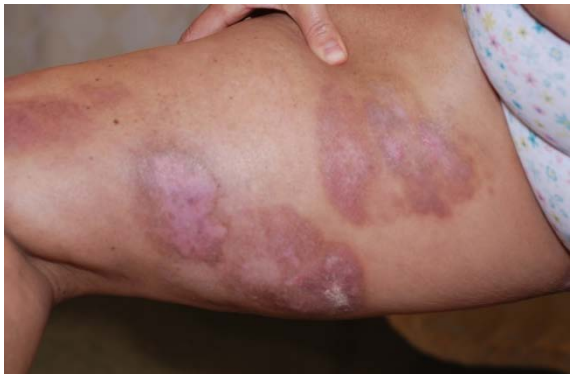
Steven M. Horwitz, Youn H. Kim, Francine Foss, Jasmine M. Zain, Patricia L. Myskowski, Mary Jo Lechowicz, David C. Fisher, Andrei R. Shustov, Nancy L. Bartlett, Maria L. Delioukina, Tony Koutsoukos, Michael E. Saunders, Owen A. O'Connor and Madeleine Duvic

Doses $\geq$15 mg/m^2 , 3/4 weeks (IV)	61% ORR
Optimal dose in CTCL, 15 mg/m^2 , 3/4 weeks (IV)	**45% ORR**
DOR at 6 mo	**73%**

Pralatrexate response in MF, stage IIB
Good option in MF with LCT



Pretreatment



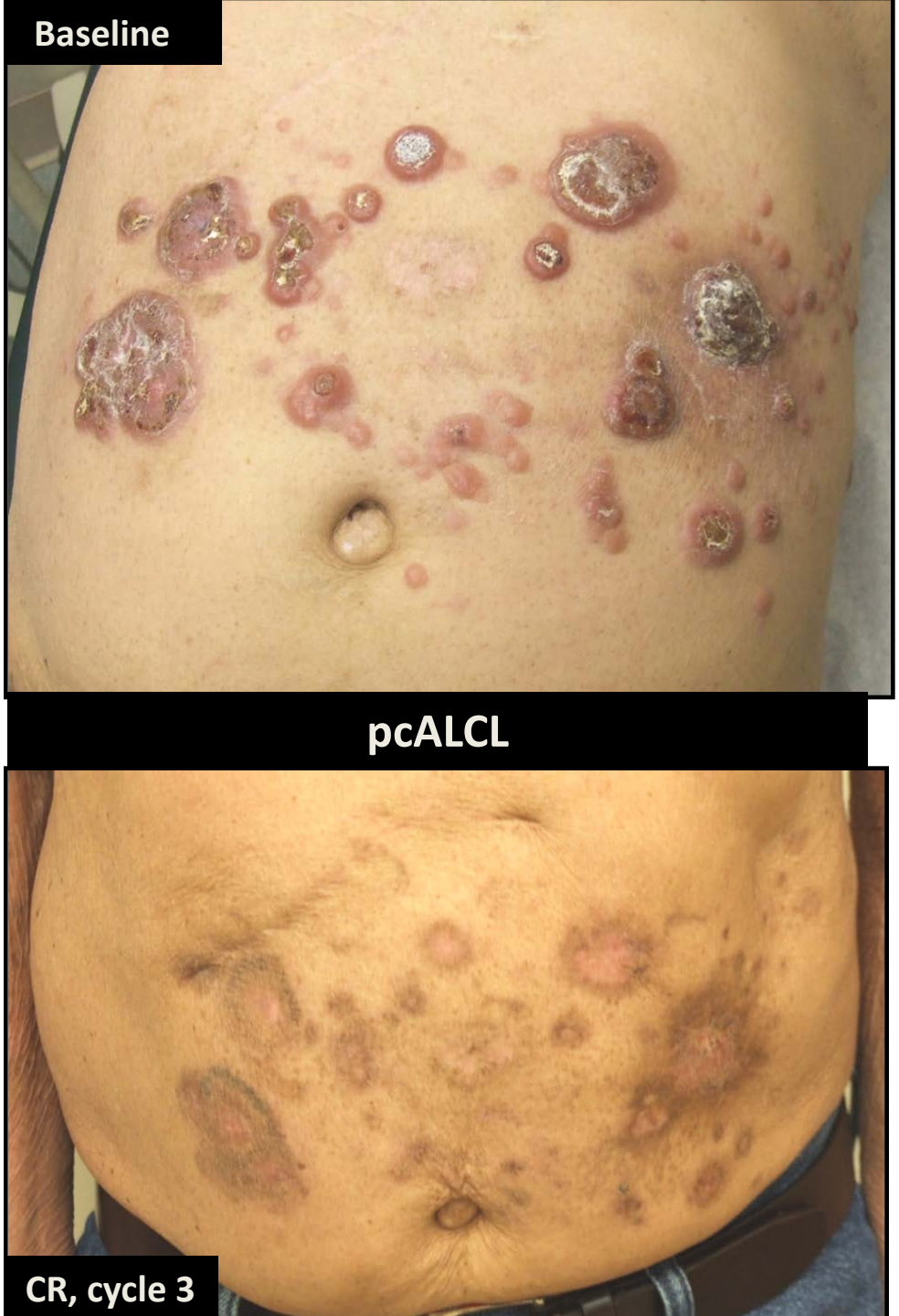
Partial Response post cycle 3

MD Anderson CC

Pralatrexate response,

Pc CD30+ ALCL

Stanford CC



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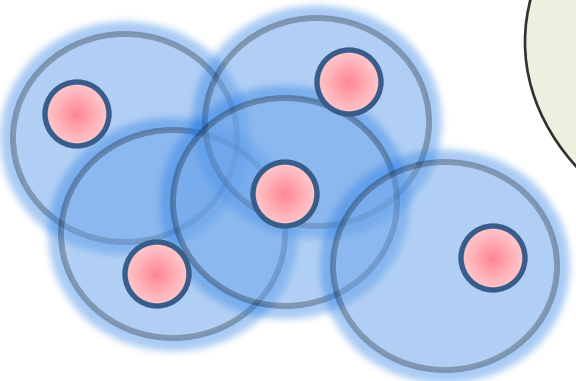

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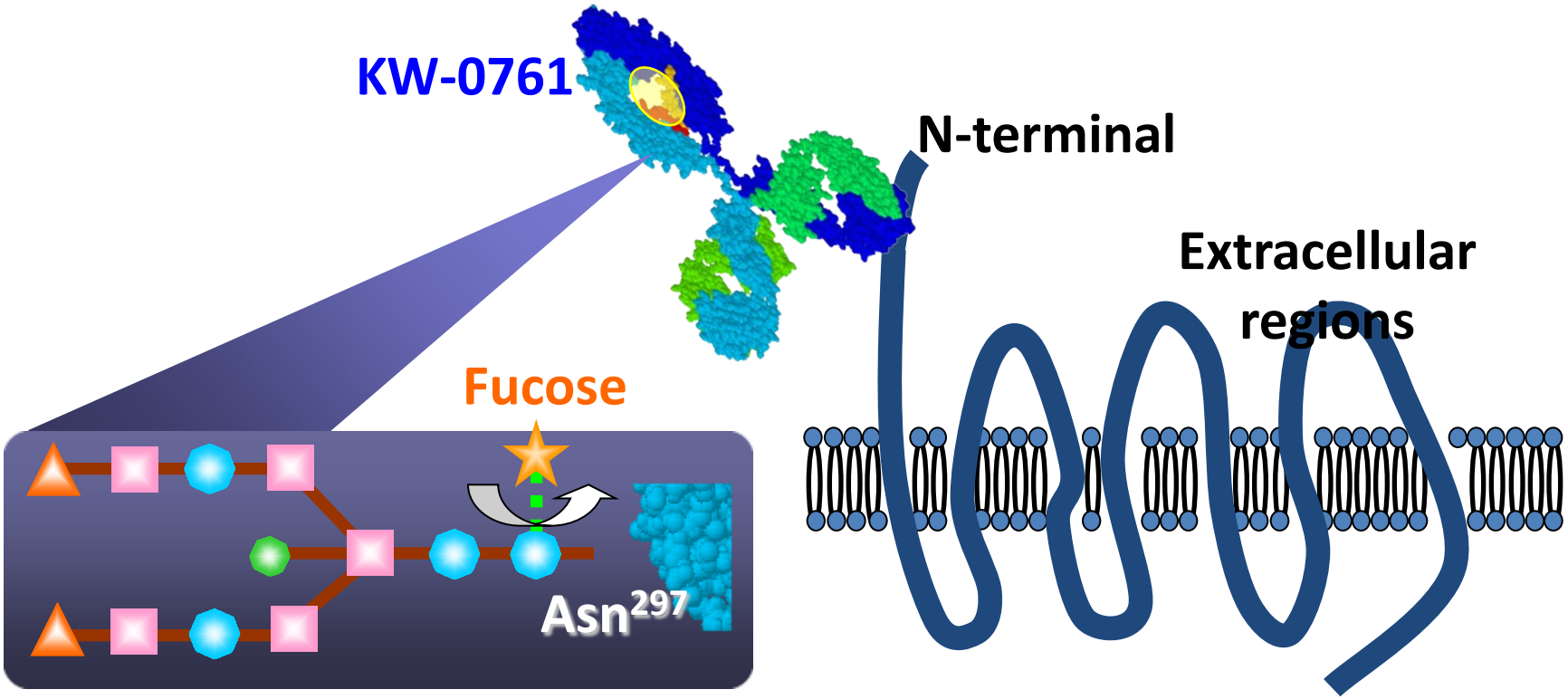
Newer generation monoclonal antibodies in cutaneous T-cell lymphoma

- Fully human mAbs
  - Anti-CD4 mAb (zanolimumab)
- Engineered mAbs, modified Fc portion to enhance biologic activity
  - **Defucosylated anti-CCR4 mAb, mogamulizumab (KW-0761)**
- Antibody drug conjugates
  - **Anti-CD30 ADC, brentuximab vedotin (SGN-35)**

Defucosylated humanized anti-CCR4 antibody, KW-0761



Higher ADCC due to a defucosylated Fc region by POTELLIGENT®

CCR4 (CC chemokine receptor 4)

Highly expressed (> 90%) in ATL
Great clinical response in skin/blood

Shinkawa et al, J Biol Chem 2003;278:3466
Ishii et al, Clin Cancer Res 2010;16:1520

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

Courtesy T. Ishida

VOLUME 30 · NUMBER 8 · MARCH 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Defucosylated Anti-CCR4 Monoclonal Antibody (KW-0761) for Relapsed Adult T-Cell Leukemia-Lymphoma: A Multicenter Phase II Study

Takashi Ishida, Tatsuro Joh, Naokuni Uike, Kazuhito Yamamoto, Atae Utsunomiya, Shinichiro Yoshida, Yoshio Saburi, Toshihiro Miyamoto, Shigeki Takemoto, Hitoshi Suzushima, Kunihiro Tsukasaki, Kisato Nosaka, Hiroshi Fujiwara, Kenji Ishitsuka, Hiroshi Inagaki, Michinori Ogura, Shiro Akinaga, Masao Tomonaga, Kensei Tobinai, and Ryuzo Ueda

Approved in Japan 2012 for pts with ATL

Phase II study in progress in the US- NCT01626664

KW 0761 or Investigator's Choice in Subjects With Previously Treated Adult T-cell Leukemia-Lymphoma (ATL)

KW-0761, a Monoclonal Antibody Directed against CC Chemokine Receptor type 4 (CCR4), in CTCL patients: Results of a Phase 1 /2 Study

Madeleine Duvic,[1] Lauren Pinter-Brown,[2] Francine Foss,[3] Lubomir Sokol,[4] Jeffrey Jorgensen,[5] George Spitalny,[6] and Youn H Kim[7]

[1]Department of Dermatology and [5]Department of Hematopathology, UT MD Anderson Cancer Center; [2] Geffen School of Medicine at UCLA; [3]Department of Medical Oncology, Yale Cancer Center; [4]Department of Malignant Hematology, H Lee Moffitt Cancer Center and Research Institute; [6]Kyowa Hakko Kirin Pharma, Inc.; [7]Department of Dermatology, Stanford Cancer Center

American Society of Hematology

52nd Annual Meeting

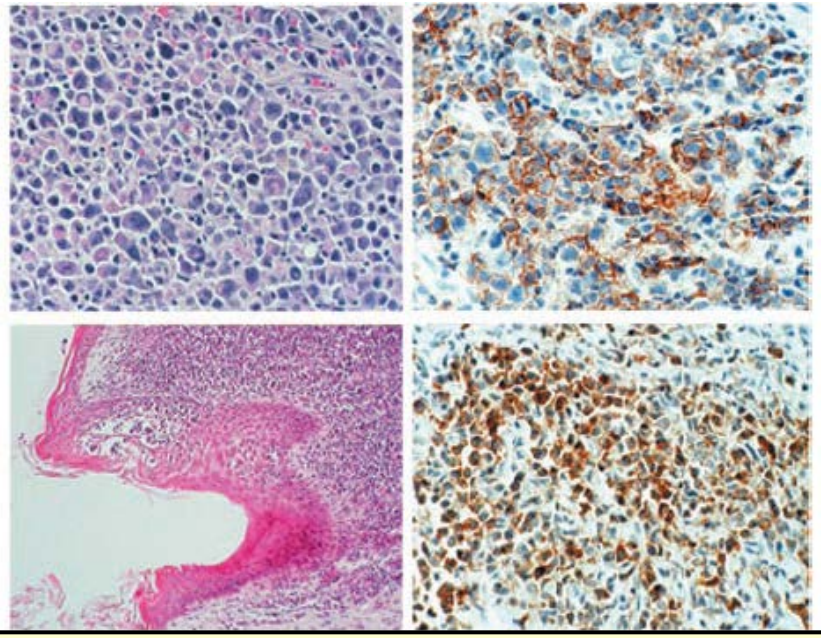
December 4–7, 2010

Expression of CCR4

Receptor for CC chemokines, MDC, TARC

ALK-negative ALCL

MF/SS



Greater proportion of CTCL cells have CCR4 expression than healthy T-cells

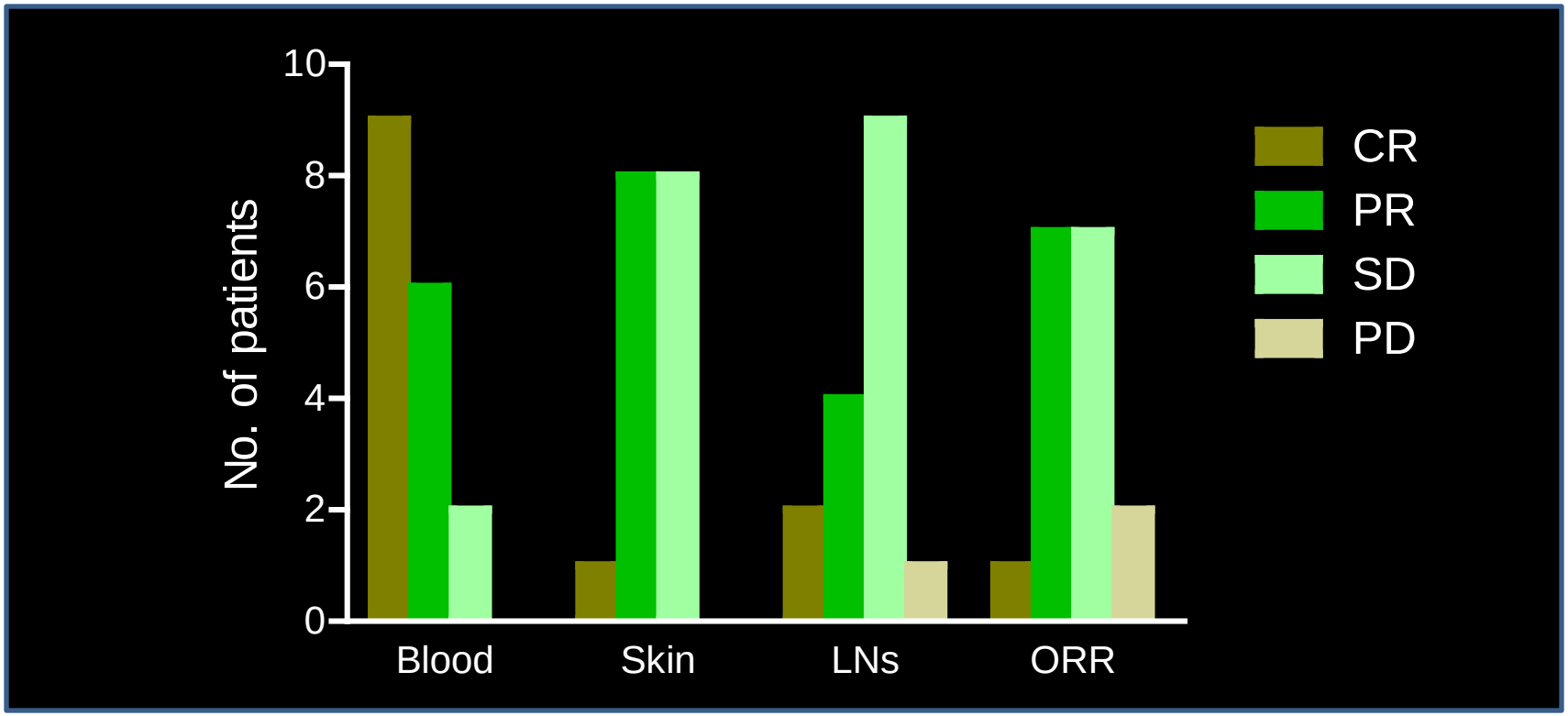
Ishida T, et al. Clin Cancer Res. 2004;10:7529,
Ferenczi K et al. J Invest Dermatol 2002;119:1405

Overall response rate in phase 1/2 study

	ORR	No. of patients			
		CR	PR	SD	PD
Sezary Syndrome (N=17)	47%	1	7	7	2
Mycosis Fungoides (N=21)	33%	1	6	10	4
TOTAL (N=38)	42%	2	13	17	6

Intravenous administration, weekly x 4, then every 2 wks

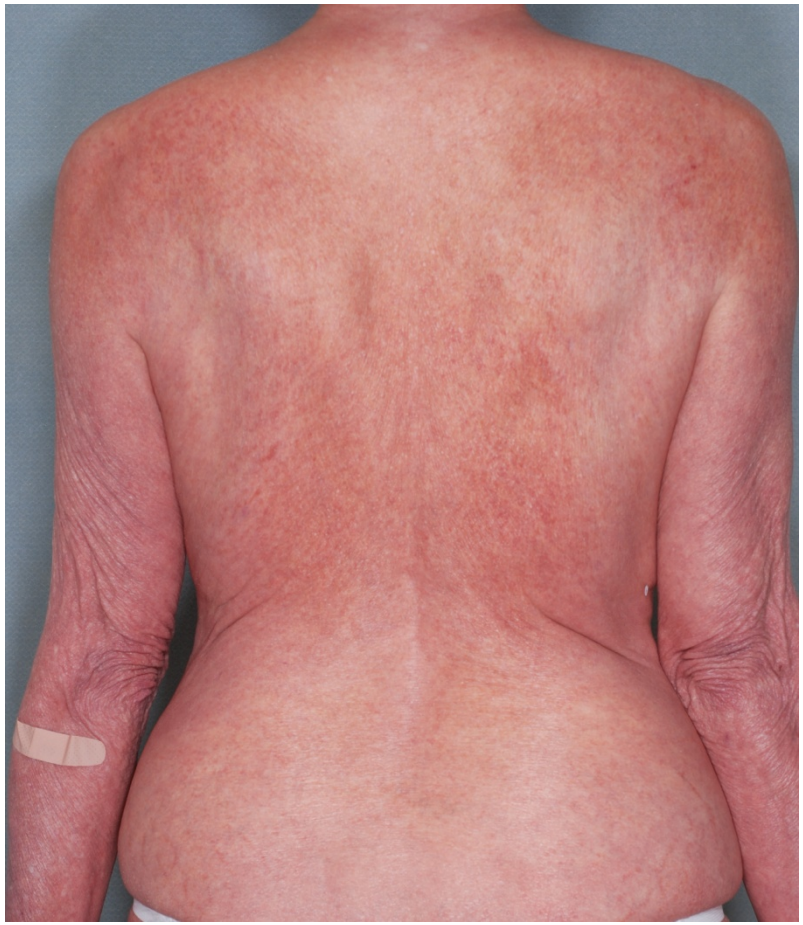
Best Response in SS Patients by Compartment



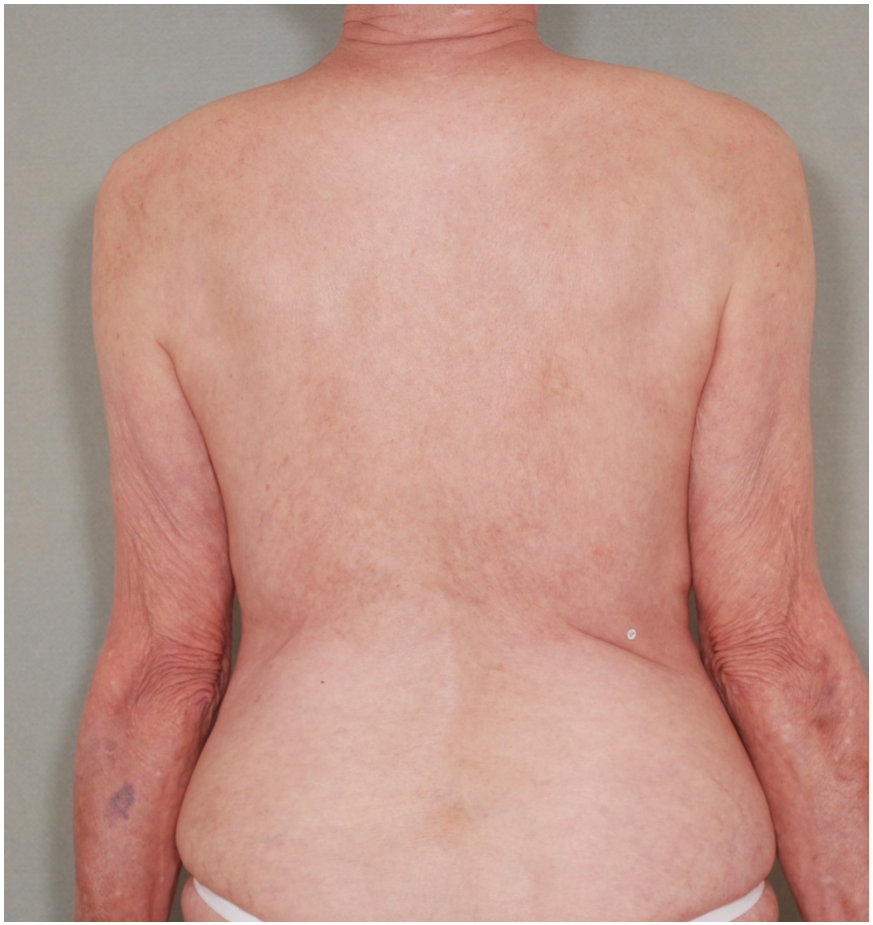
- 8/17 (47%) of SS patients with global response (ORR)
- 15/17 (88%) of SS patients had response in blood
  9/17 (53%) had CR in blood

Case Study: Patient 03-Stanford

(SS; Stage IVA; 6 Prior Therapies; 0.3 mg/kg)



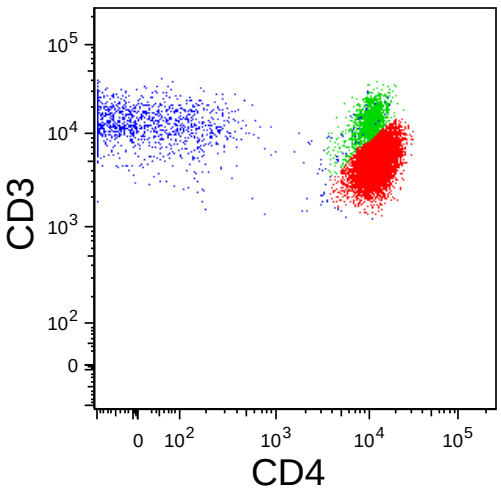
Pretreatment
Course 1 Day 1

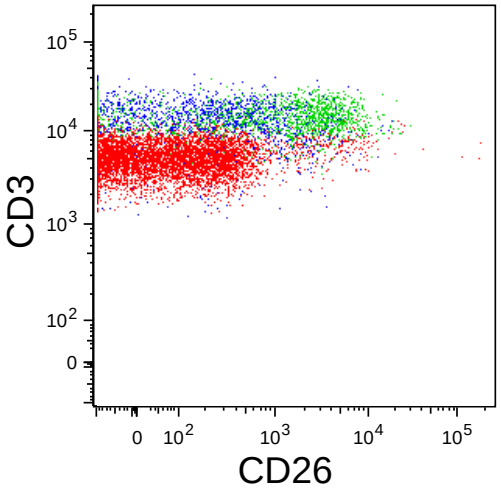


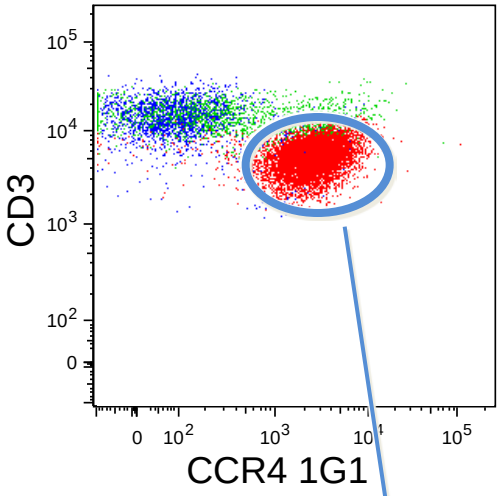
Post treatment
Post Course 11

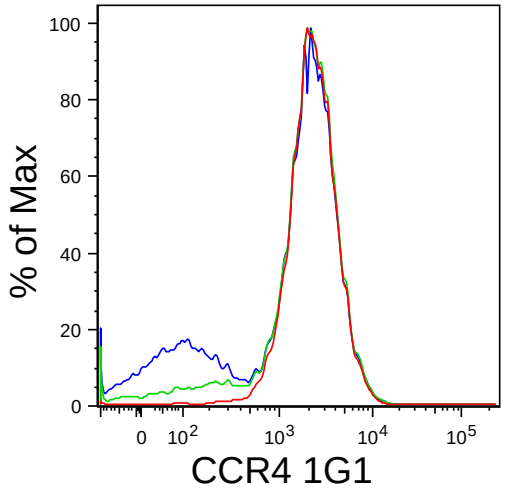
Response in Blood: Patient 01-Stanford (SS; Stage IVA; 6 prior therapies; 0.1 mg/kg)

Pre-treatment







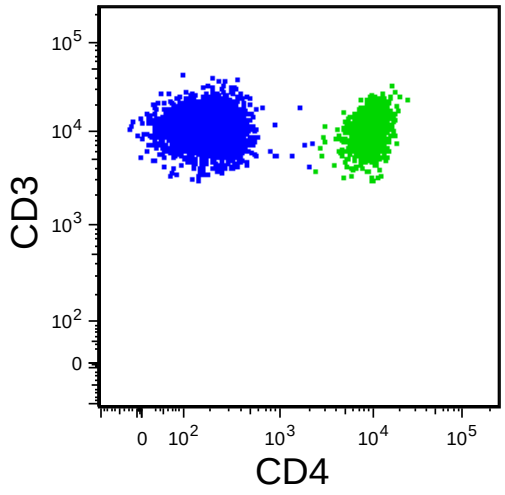


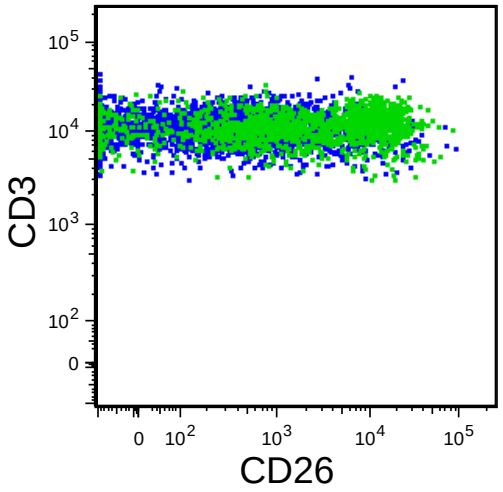
Lymphoma cells
Normal CD3+CD4+
CD3+CD4neg

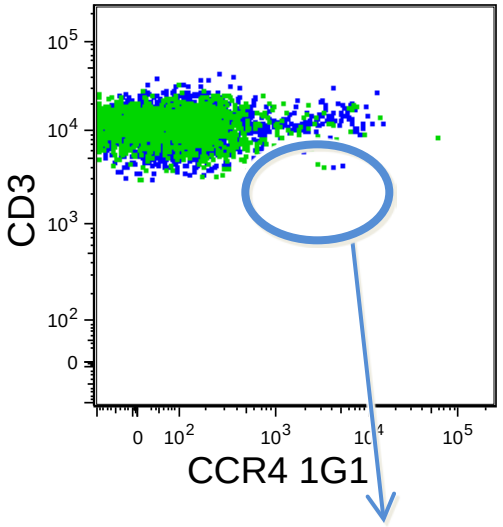
Lymphoma cells

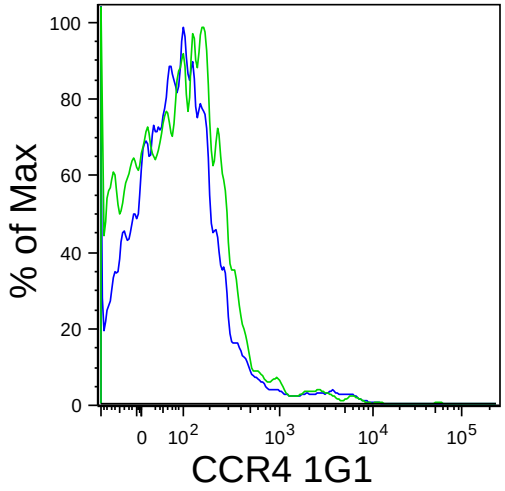
Response in Blood: Patient 01-Stanford

Post-treatment









Lymphoma cells
Normal CD3+CD4+
CD3+CD4neg

Lymphoma cells undetectable

Maintaining response >2 yrs

KW-0761 Clinical Development Summary

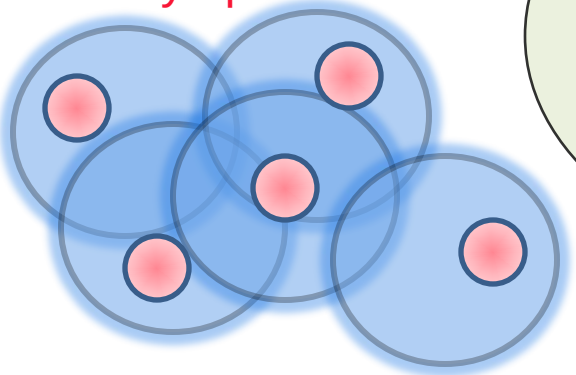
- Clinical responses are most impressive in the skin and blood compartments in ATL and CTCL
- Absence of severe infections (←→ alemtuzumab)

Phase III RCT in CTCL ongoing for FDA approval in the US

Targets for Therapy in Cutaneous Lymphoma

Tumor cell surface molecules
(e.g., CD4, CD19, CD20, CD22, CD25, **CD30**, CD40, CD52, CD158k, CCR4)

Cutaneous lymphoma



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CD30+ primary cutaneous lymphoproliferative disorders

- Lymphomatoid papulosis
- Pc CD30+ anaplastic large cell lymphoma

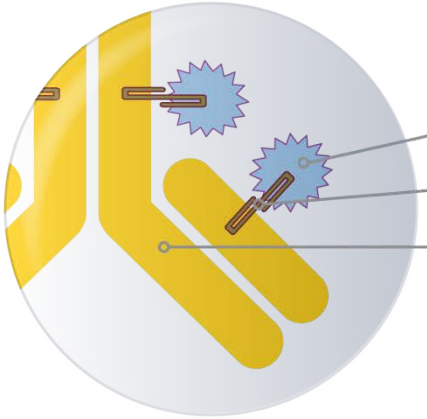
- *Mycosis fungoides with CD30 expression*
- *other TCLs and BCLs may express CD30*

Targeted therapy in CD30+ LPDs

- CD30, an attractive target, as CD30 expression is limited in normal cells, but increased in proliferative or malignant lymphocytes **=> good tumor selectivity**

Brentuximab Vedotin Mechanism of Action

Antibody Drug Conjugate



Monomethyl auristatin E (MMAE), microtubule-disrupting agent

Protease-cleavable linker

Anti-CD30 monoclonal antibody

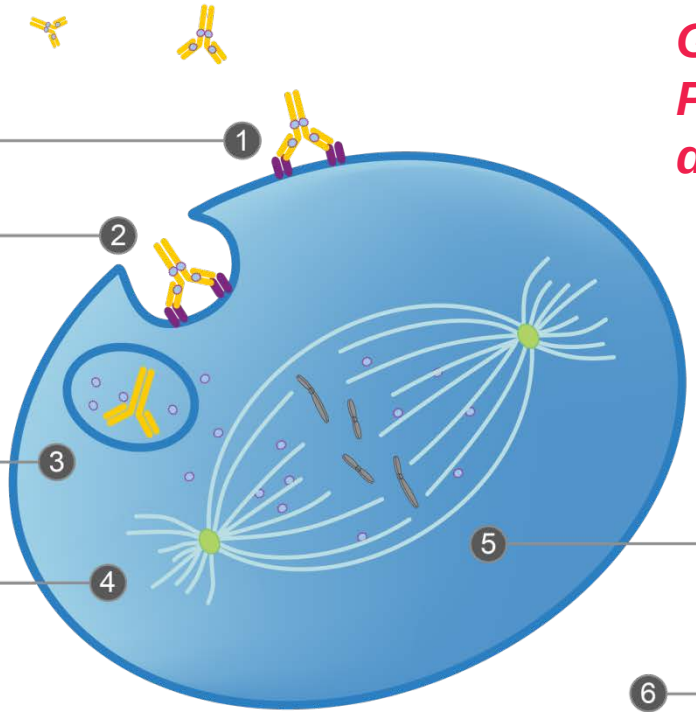
Given IV every 3 wks; Peripheral Neuropathy, dose-limiting

ADC binds to CD30

ADC-CD30 complex is internalized and traffics to lysosome

MMAE is released

MMAE disrupts microtubule network



G2/M cell cycle arrest

Apoptosis

Brentuximab vedotin (SGN-35) in systemic lymphoma

- Highly effective in relapsed/refractory HL and sALCL
- Adverse events were manageable including peripheral neuropathy (85% sig improved/reversible)

Received accelerated approval by FDA in HL and sALCL (8/2011) => 2nd mAb-drug-conjugate (ADC) to be approved

ASH abstract #797,
presented 12/10/2012

Brentuximab vedotin demonstrates clinical activity in mycosis fungoides / Sézary syndrome

Krathen M[1], Bashey S[1], Sutherland K[1], Sundram U[1], Nagpal S[1], Salva K[3], Wood G[3], Advani R[1], Hoppe RH[1], Reddy S[1], Pulitzer M[2], Horwitz S[2], Kim YH[1]

[1]Stanford Cancer Institute, Stanford, CA, USA
[2]Memorial Sloan-Kettering Cancer Center, New York, NY, USA
[3]University of Wisconsin, Madison, WI, USA

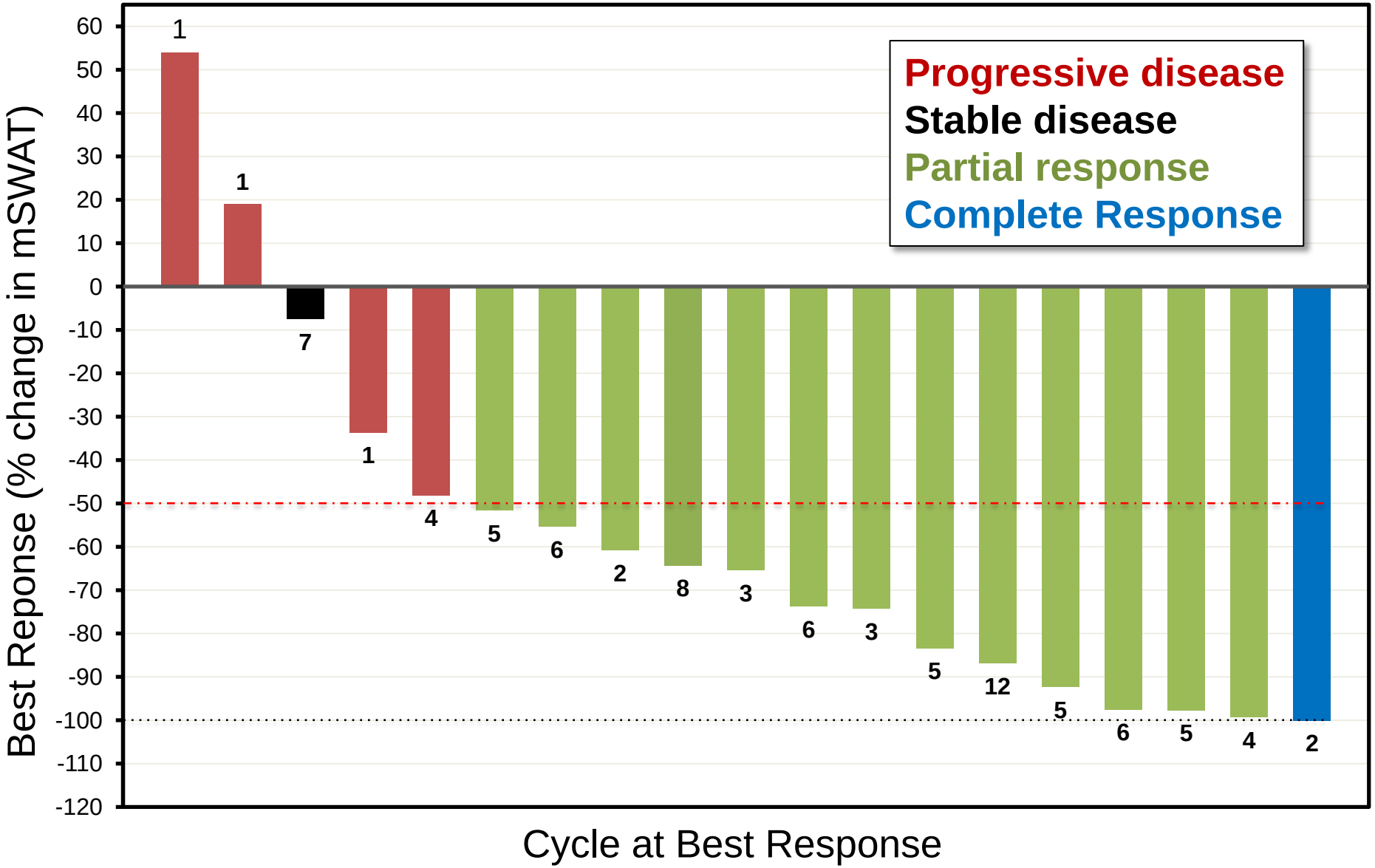
CD30: Target in MF/SS

- **HL and sALCL with consistent expression of CD30** on tumor cells and high response rates

- **Variable CD30 expression on neoplastic cells of MF**
  - Transformed MF with more frequent and greater CD30 expression, 30-50%
  - Non-transformed MF, 0-15% (majority of MF)

Am J Surg Pathol. 2009;33:1860
Clin Cancer Res 2004;10:5587, Blood. 2012;119;1643.

Percent Change in Skin mSWAT At Best Clinical Response



Clinical Response by Stage

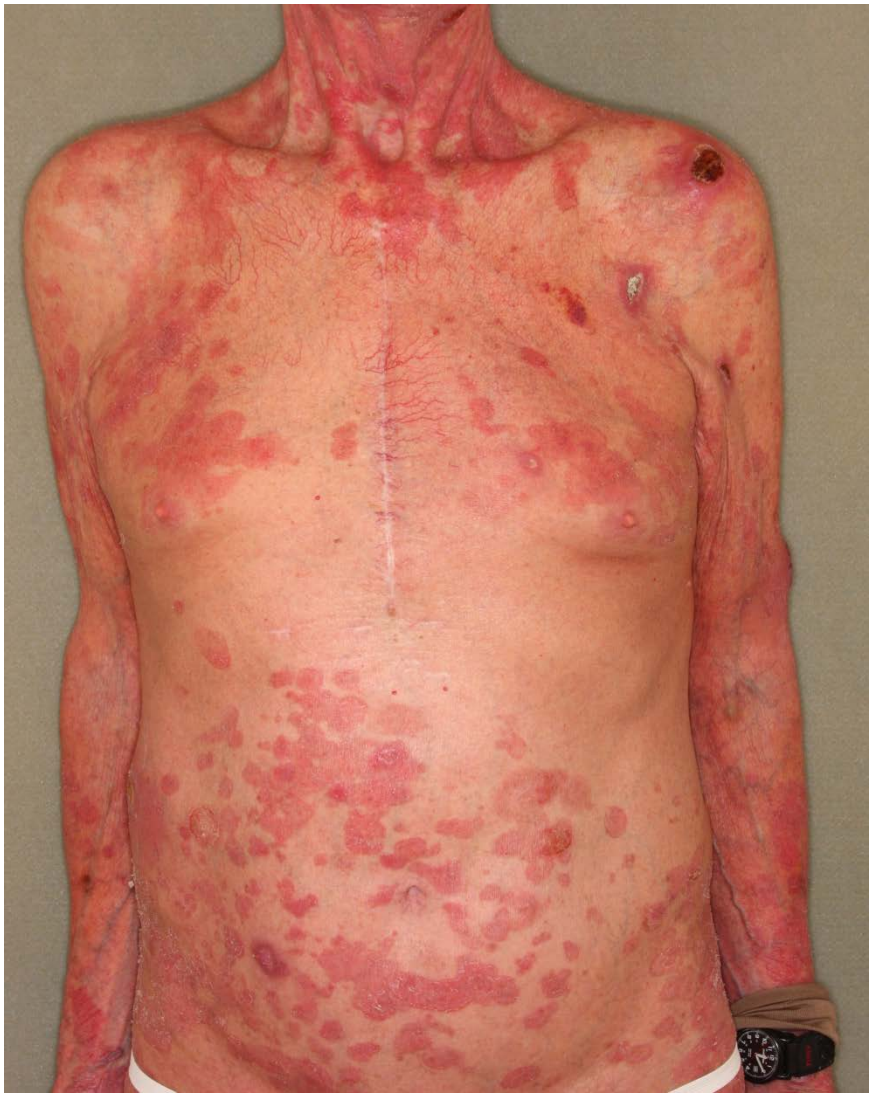
Stage	Response Rate	CR	PR	SD	PD
IB (n=2)	100%	0	2	0	0
IIB* (n=11)	91%	0	10	1	0
IVA**/B (n=6)	33%	1	1	0	4
Total n=19**	74%	1	13	1	4

*All 11 either LCT or FMF

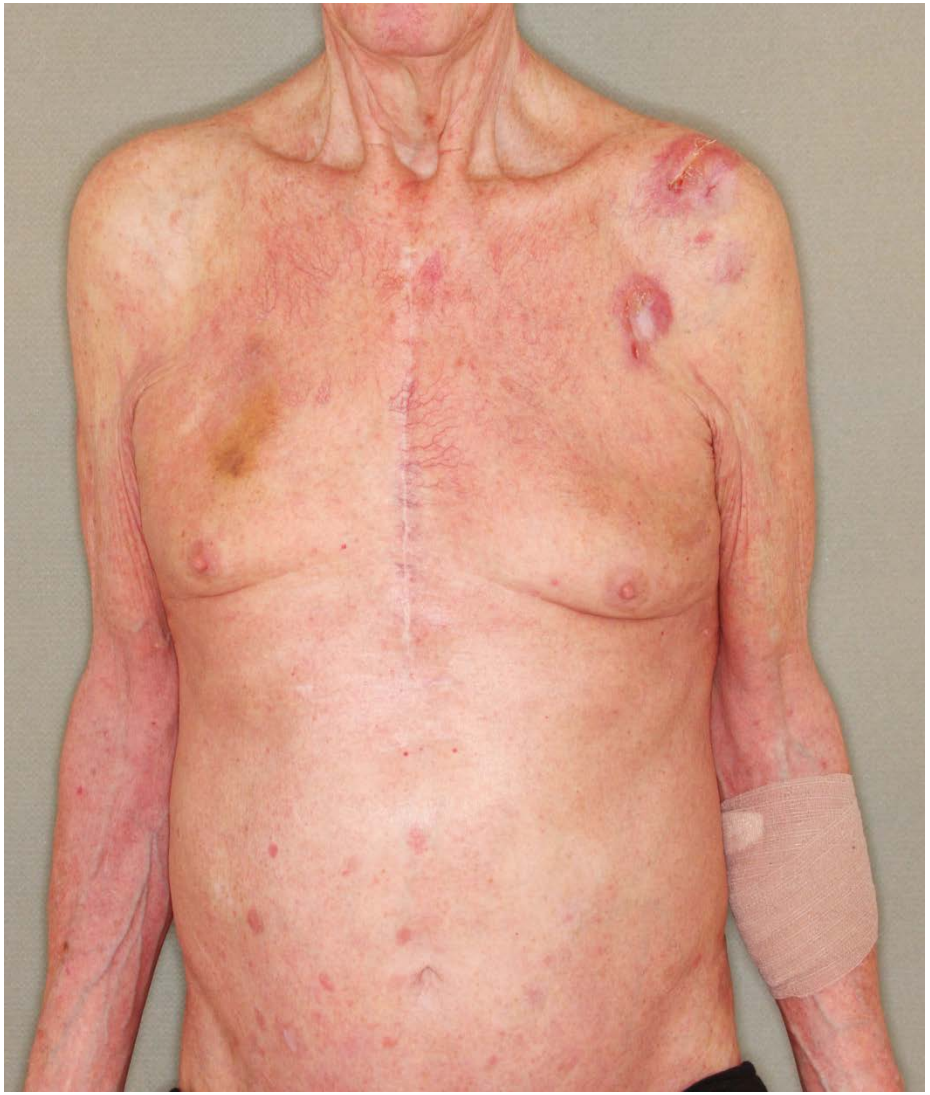
** 1 subject non-evaluable for response

87 yo M with MF IIB, LCT

Screening

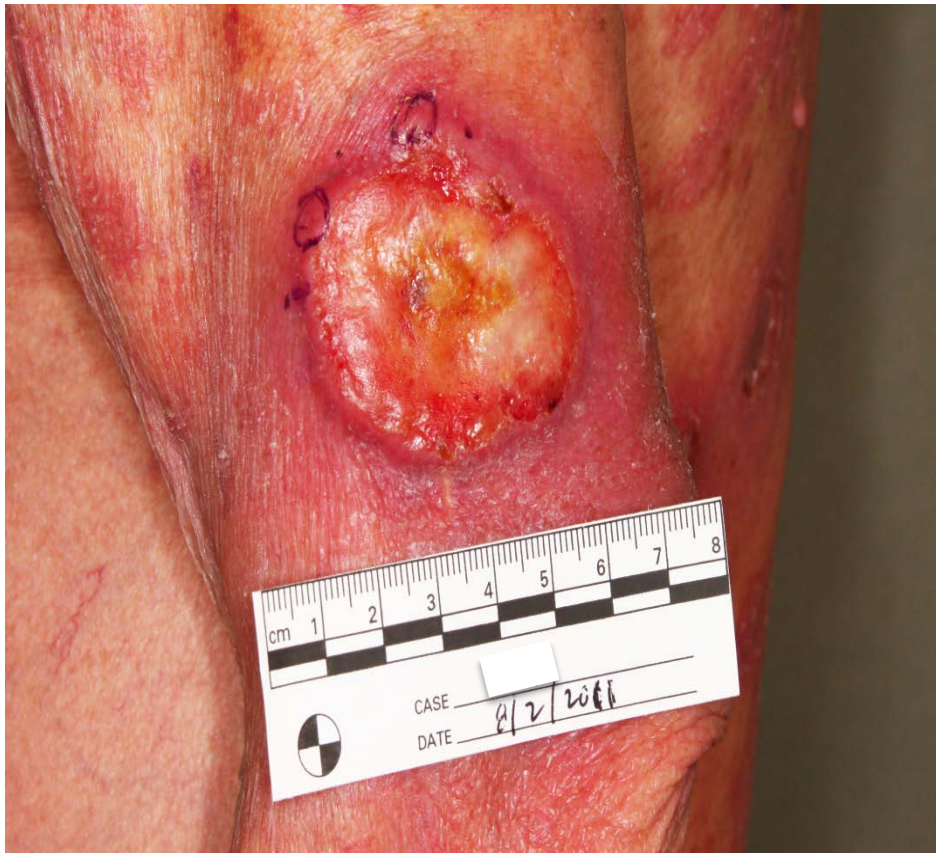


Cycle 6

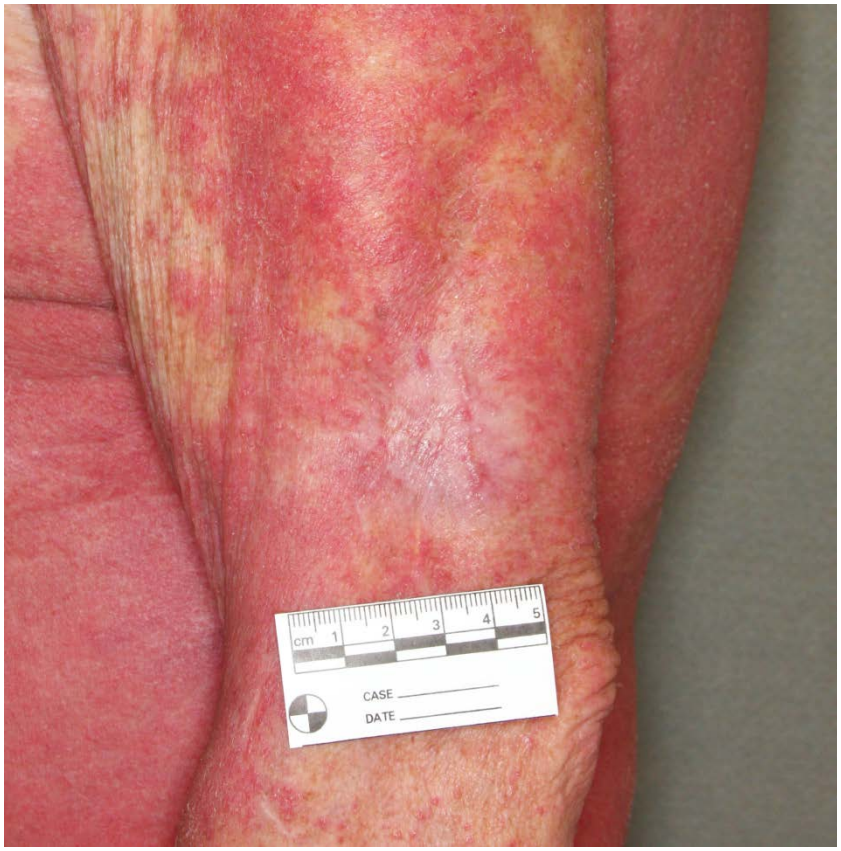


87 yo M with MF IIB, LCT

Screening



Cycle 6

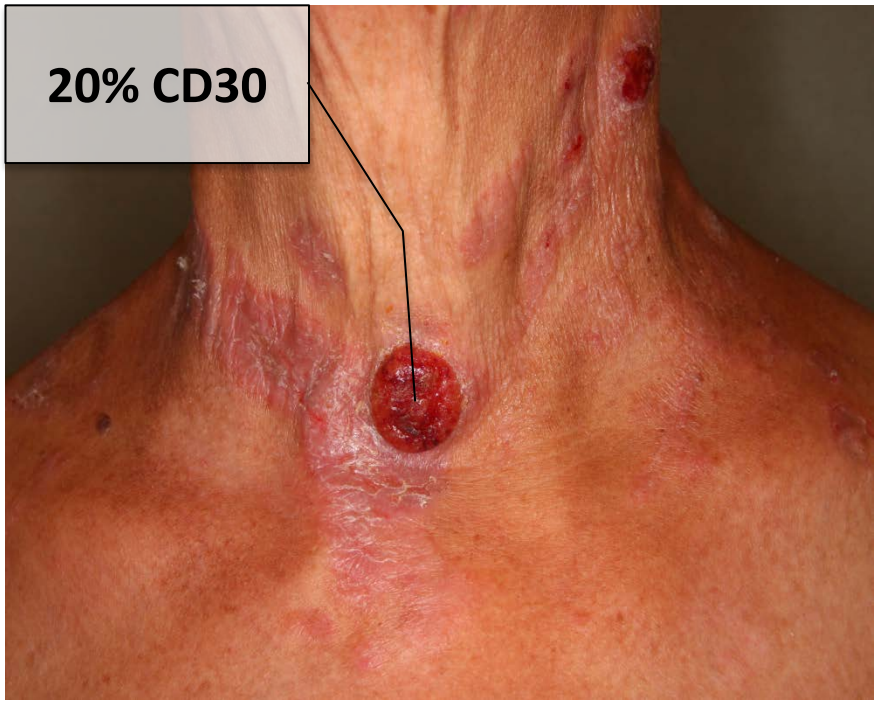


Subject 12: 66 yo F with MF IVB, LCT w/ oropharyngeal involvement

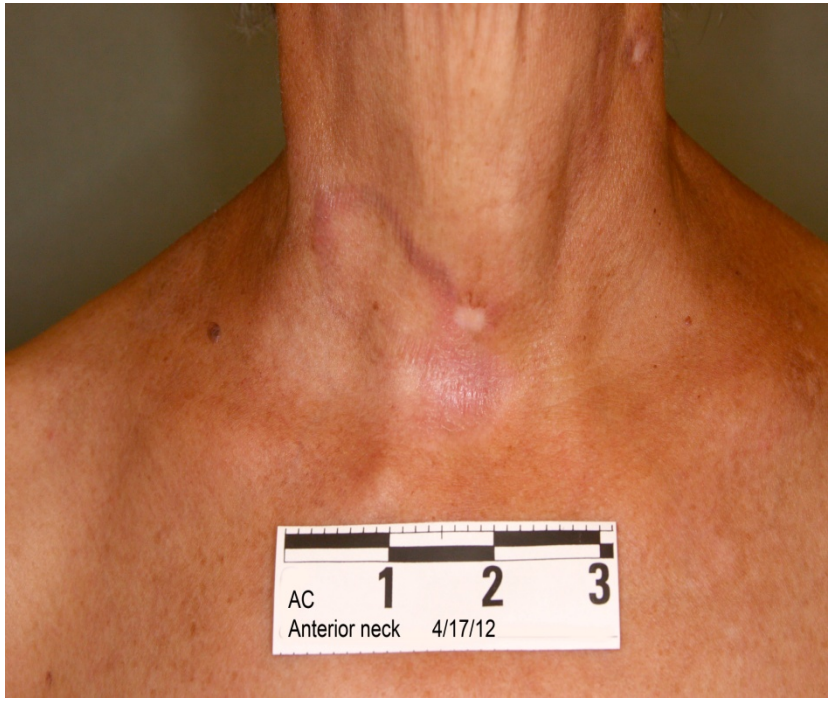
Group B (10-50%): Max CD30 TLI 20%

Best Response: PR

Screening

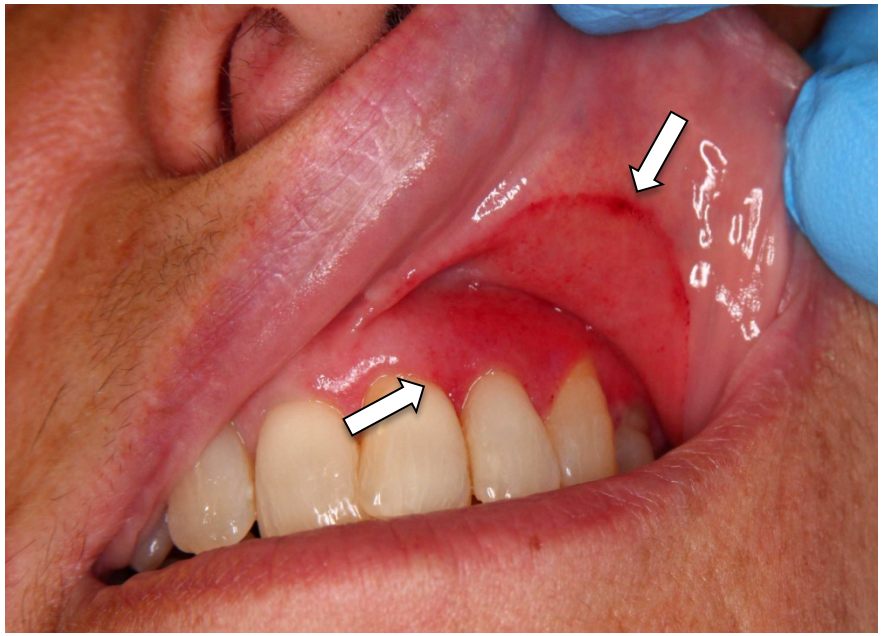


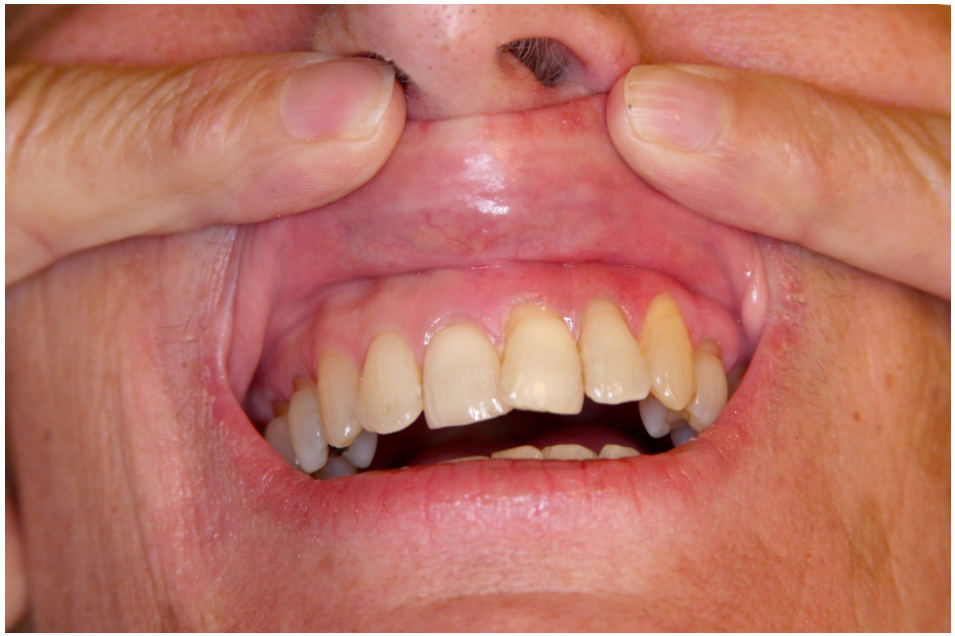
Cycle 10

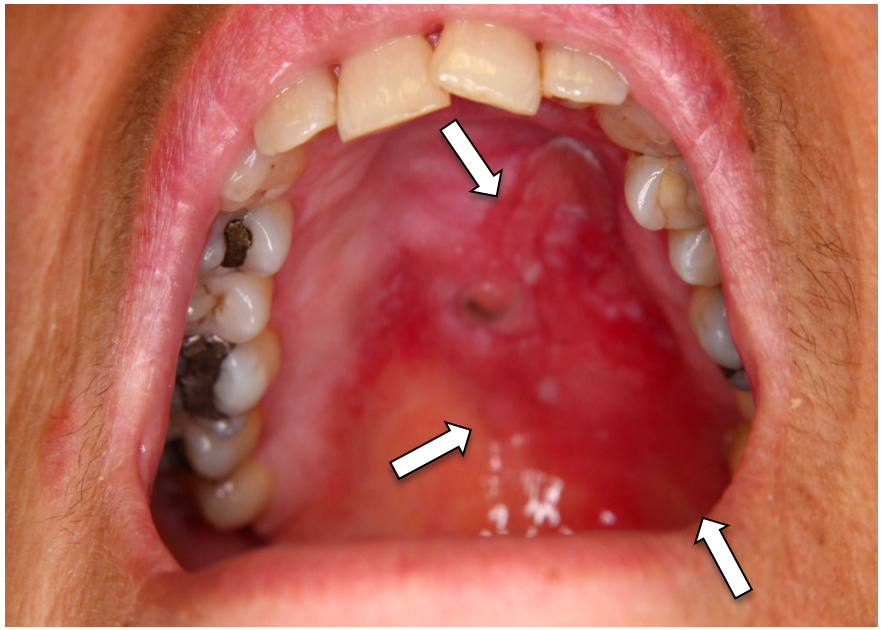


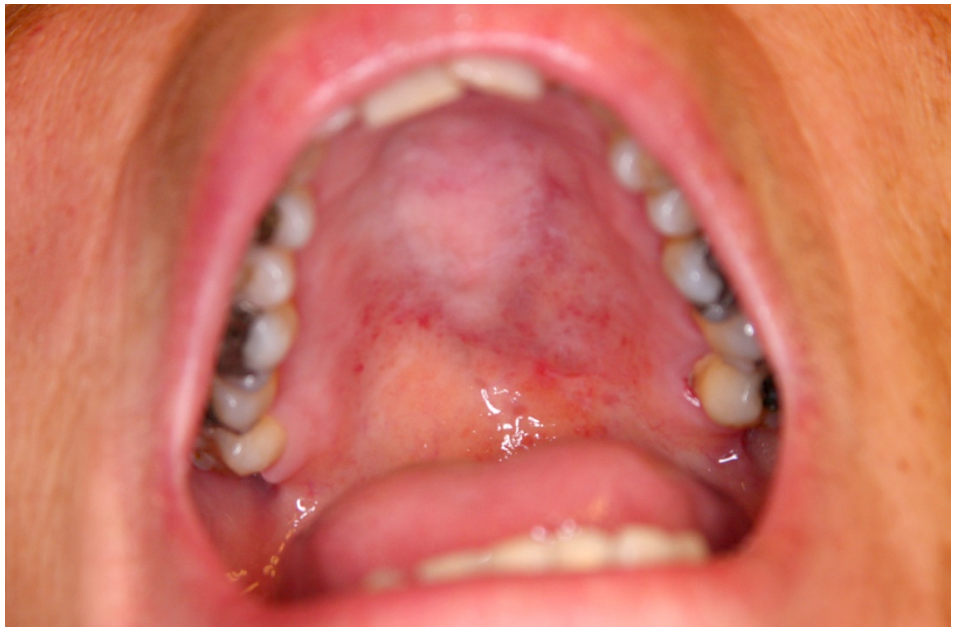
Screening

Cycle 10









Summary of clinical development of brentuximab vedotin in CTCL

- Two separate investigator-initiated studies (Stanford, MD Anderson) show consistent data of promising responses
  - MF (regardless of tissue CD30), LyP, pcALCL

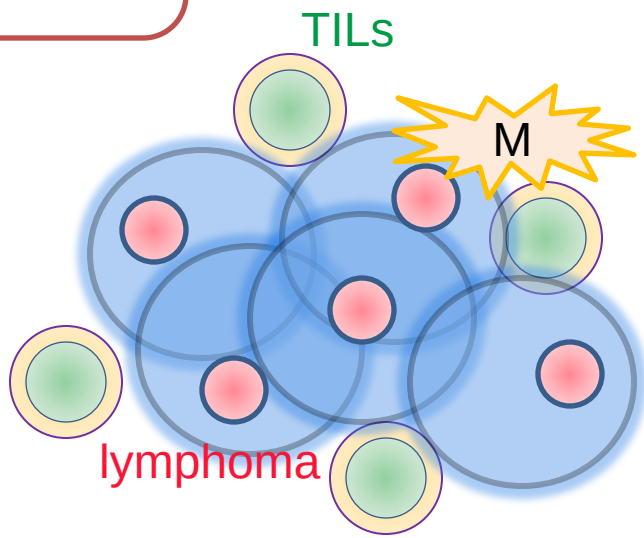
- Acceptable toxicities
  - PN most common, concern of PML being observed

Phase III RCT in CTCL ongoing in the US and Europe for approval

Immunotherapy strategies in cancer

Tumor-specific monoclonal antibodies

Cytokine therapy



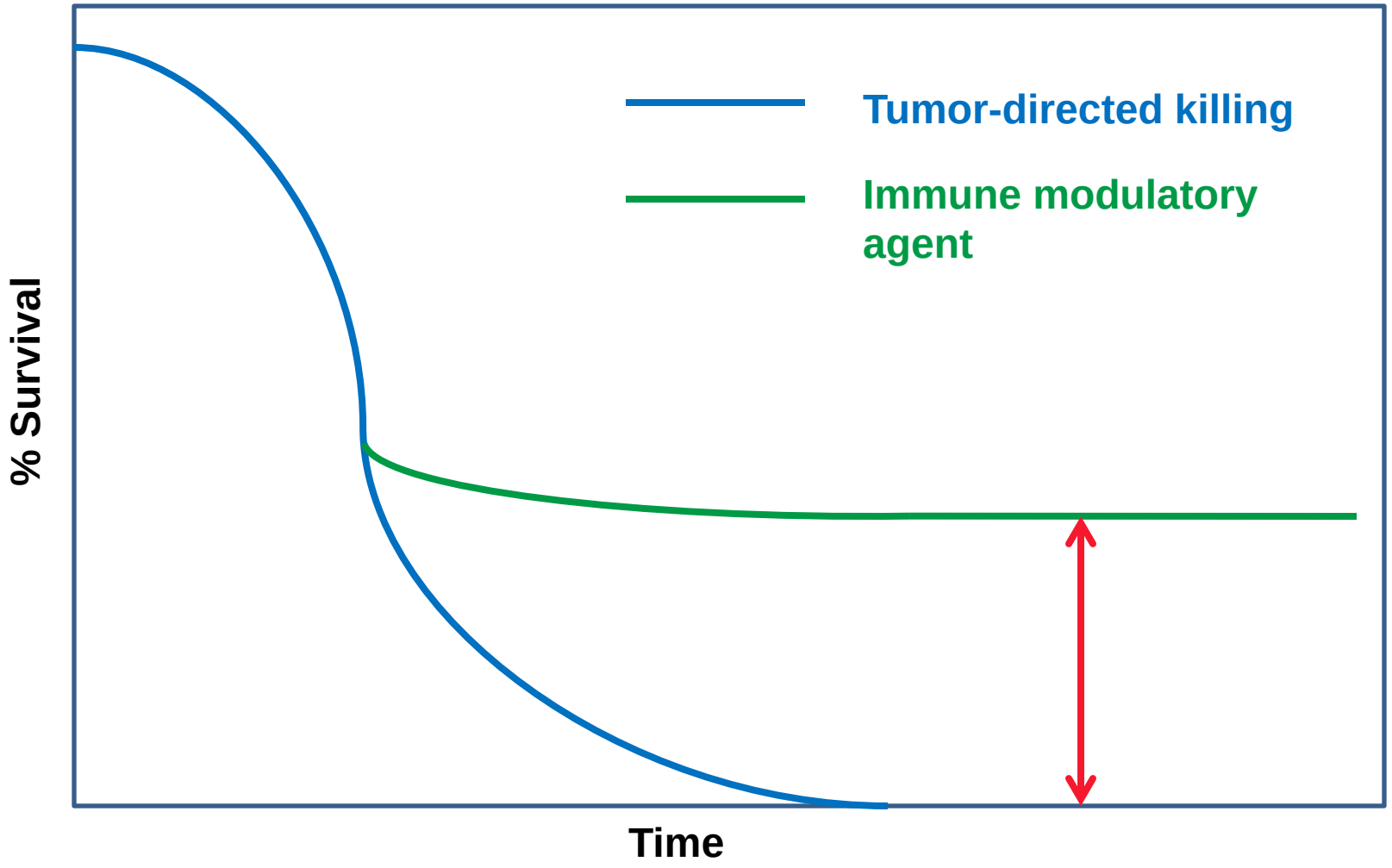
Adoptive T-cell transfer

Immune-modulating agents or antibodies

Allogeneic HSCT

Vaccine-based approaches

Induction of long-lasting responses and improving survival with partnering with immune strategies



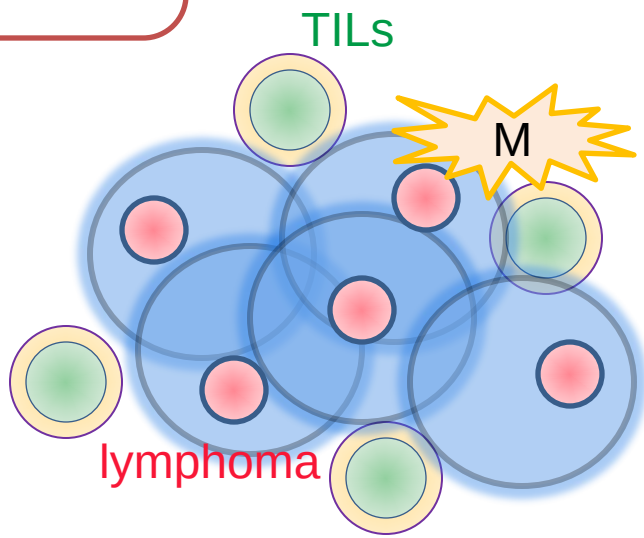
Immunotherapy strategies in cutaneous lymphoma

CD4,
CD20,
CD25,
CD30,
CCR4

Tumor-specific monoclonal antibodies

Cytokine therapy

IFNs, IL2,
IL12



Adoptive cell transfer

Immune-modulating agents or antibodies

TLR-A
IMiDs
Tregs
CTLA4
PD-1
PD-L1

Allogeneic HSCT

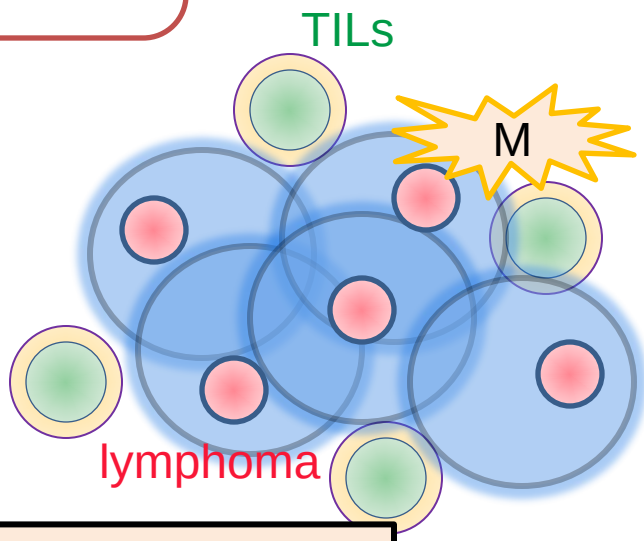
Vaccine-based approaches

ECP
DC-based
Idiotype
In situ strategy

Immunotherapy strategies in cutaneous lymphoma

Tumor-specific monoclonal antibodies

Cytokine therapy



Adoptive cell transfer

Immune-modulating agents or antibodies

Allogeneic HSCT

TLR-A
IMiDs
Tregs
CTLA4
PD-1
PD-L1

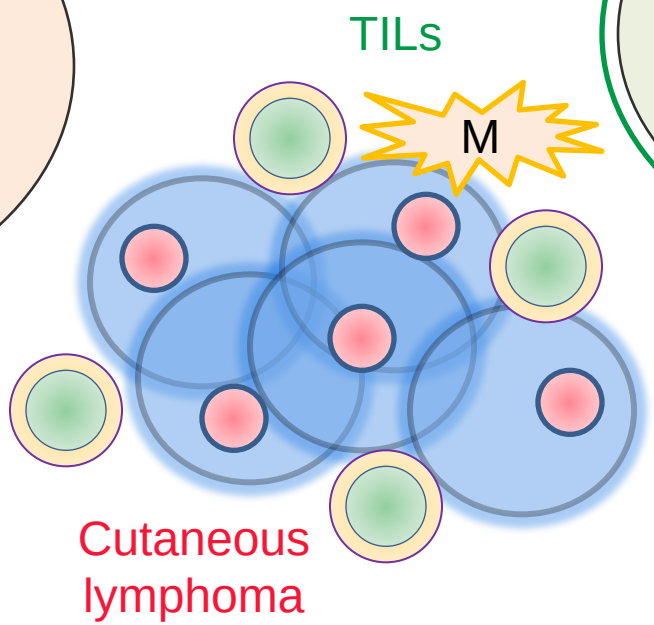
Imiquimod
Resiquimod

Immune modulation of tumor microenvironment with mAbs

Monoclonal antibodies

Tumor cell-specific:
tumor surface molecules
(e.g., CD4, CD19, CD20, CD22, CD25, CD30, CD40, CD52, CD158k, CCR4)

Microenvironment Immune modulation
(e.g. CTLA4, PD-1, PD-L1, IDO, Tregs)



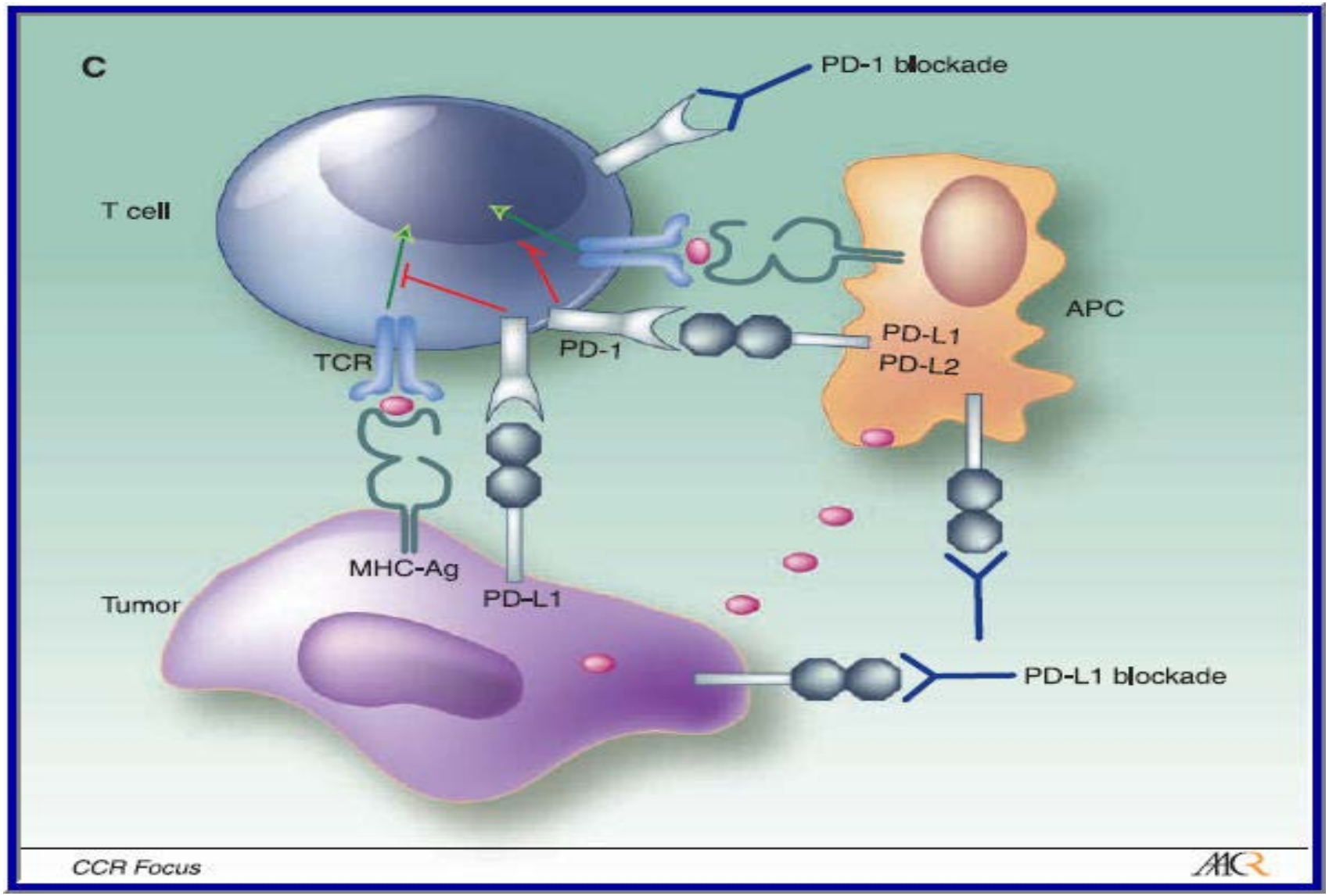
Modulating microenvironment & immune mechanisms

Agent	Target	Conjugate	Disease
Bevacizumab	VEGF	--	lymphoma
Endostatin	Endothelial cell	--	lymphoma
Ipilimumab	CTLA-4	--	Solid tumor/lymphoma
Lenalidomide	Multiple	--	Hematologic malignancies
TLR agonists	TLR	--	lymphoma
Anti-PD-1 mAbs	PD-1	--	Solid tumor/hematolymph
Anti-PD-L1 mAbs	PD-L1	--	Solid tumor/hematolymph
IDO inhibitors	IDO+ DCs, tumor	--	Solid tumor/hematolymph

Renewed interest in immunotherapy

Ann Oncol 2010;21:683, J Pathol 2010;220:404, 509, Lancet Oncol 2010;11:1074

Programmed Death-1 (PD-1) and ligands B7-H1/PD-L1 and B7-DC/PD-L2: Pivotal role in maintaining immunosuppressive tumor microenvironment



Curr Opin Immunol 2012;24:207

The NEW ENGLAND JOURNAL of MEDICINE

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Safety,
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Daniel McDonald, M.B.A., C

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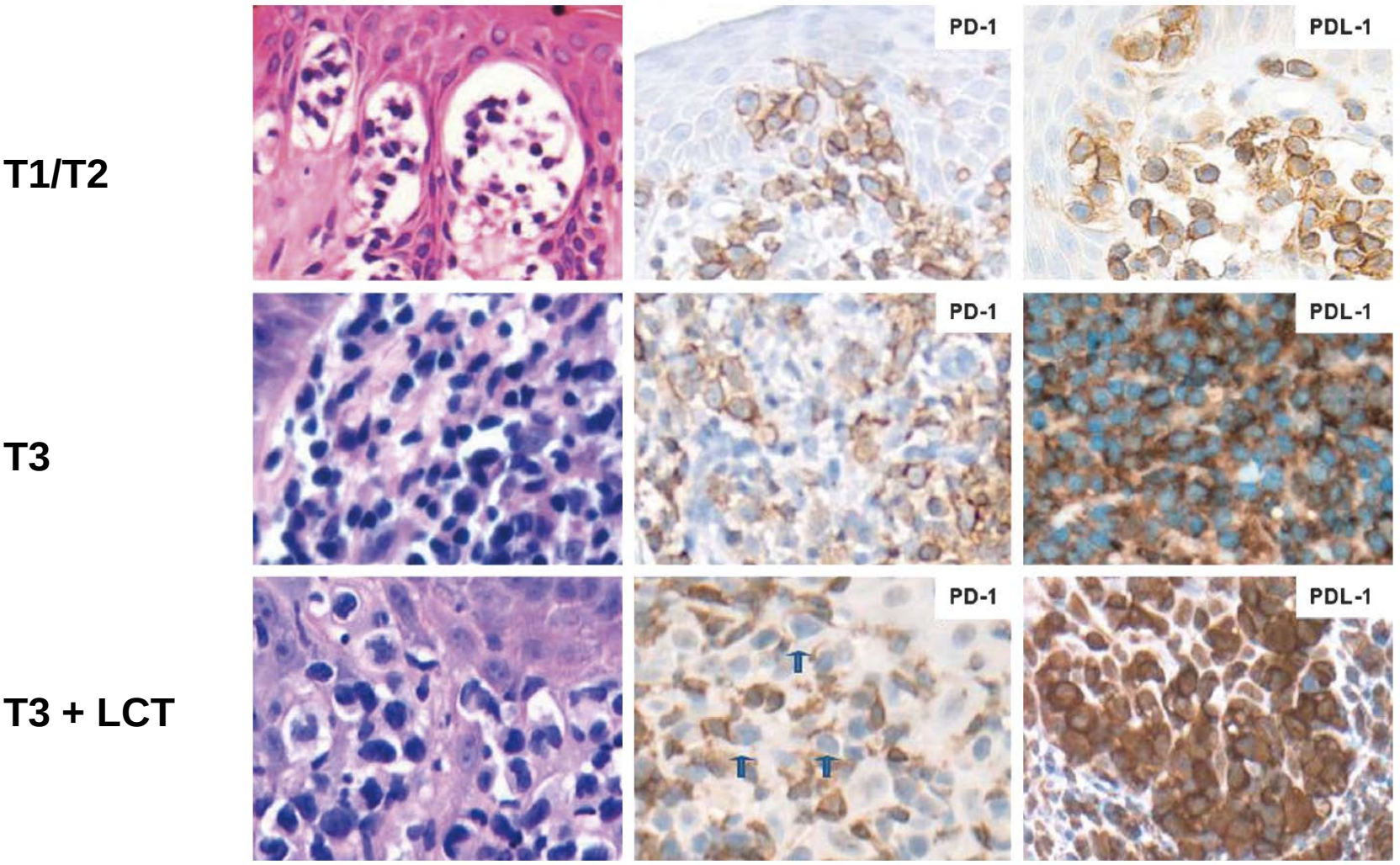
ORIGINAL ARTICLE

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthy, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.

N Engl J Med 2012;366:2455-65.

Expression of PD-1 and PD-L1 in MF skin tissue: Inverse correlation of PD-1 and PD-L1 with disease severity



Am J Dermatopathol 2012:34:126

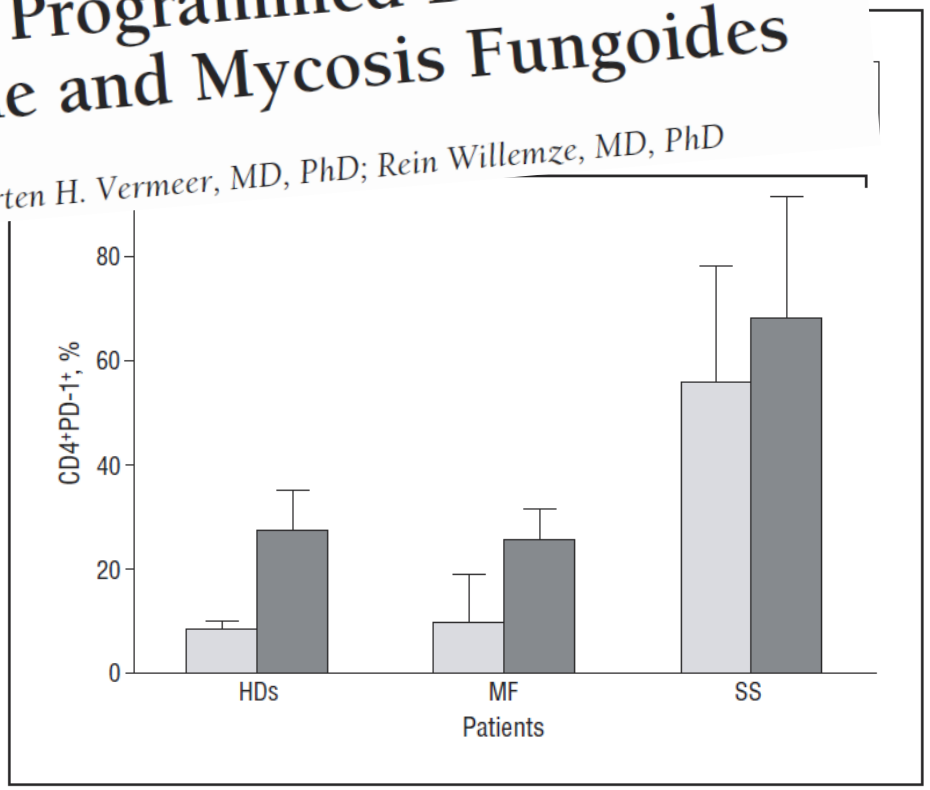
TABLE I. PD-1 Expression in CTCL Determined by Immunohistochemistry

Disease subtype	PD-1-positive cases (%)	Mean (range) percentage of PD-1-positive tumor cells[a]
Patch/plaque mycosis fungoides (n = 15)	6 (40)	78 (60–95)
Generalized or tumor		

STUDY

Differential Expression of Programmed Death-1 (PD-1) in Sézary Syndrome and Mycosis Fungoides

Fatma Çetinözman, MD; Patty M. Jansen, MD, PhD; Maarten H. Vermeer, MD, PhD; Rein Willemze, MD, PhD



PD-1 blockade enhanced IFN-gamma production

Rook's group

Arch Dermatol 2010;146:1382

Anti-PD1/PD-L1 mAbs in clinical development

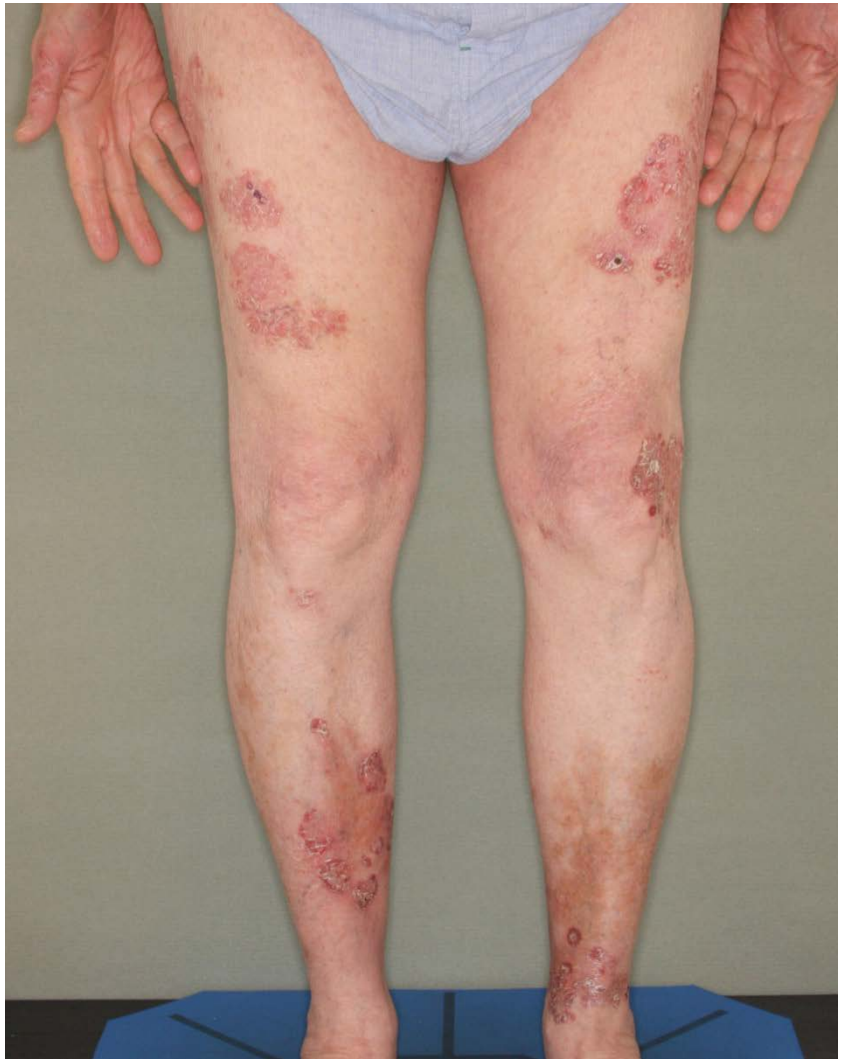
- MDX-1105/BMS-936559, MDX-1106/BMS-936558 (Medarex/Bristol-Myers Squibb), MK-3475 (Merck), CT-011 (Cure Tech/Teva), AMP-224 (Amplimmune/GSK)

Anti-PD-L1 mAb opened for enrollment at Stanford:

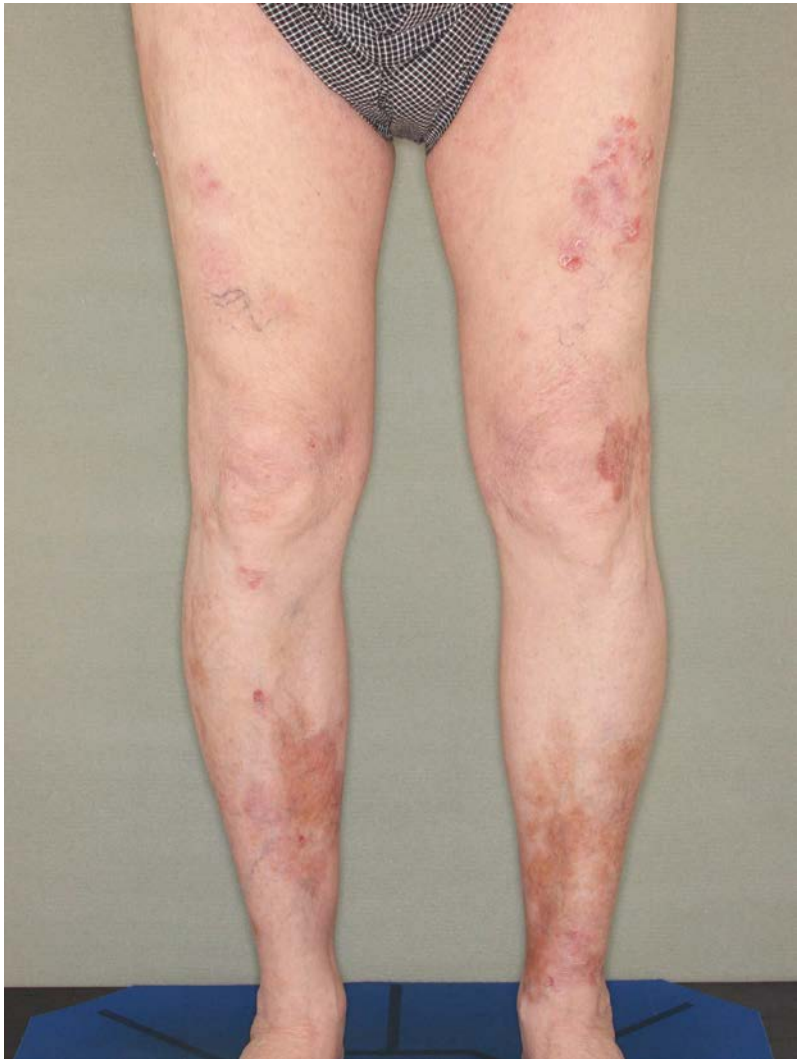
- A phase I, open-label, dose-escalation study of the safety and pharmacokinetics of MPDL3280A administered intravenously as a single agent to patients with locally advanced or metastatic solid tumors or **hematologic malignancies** (Genentech)
- MPDL3280A, a phage-derived human IgG1 mAb
- Targets PD-L1 on APCs or tumor cells, prevents interaction with PD-1 on T-cells

Stage IB MF (h/o phototx, bexarotene, anti-CD4 mAb, forodesine, CpG+RT, lenalidomide, sapacitabine, enzastaurin, TSEBT)

11/20/2012 (pre-treatment)
mSWAT 36 (20 plaque, 16 patch)

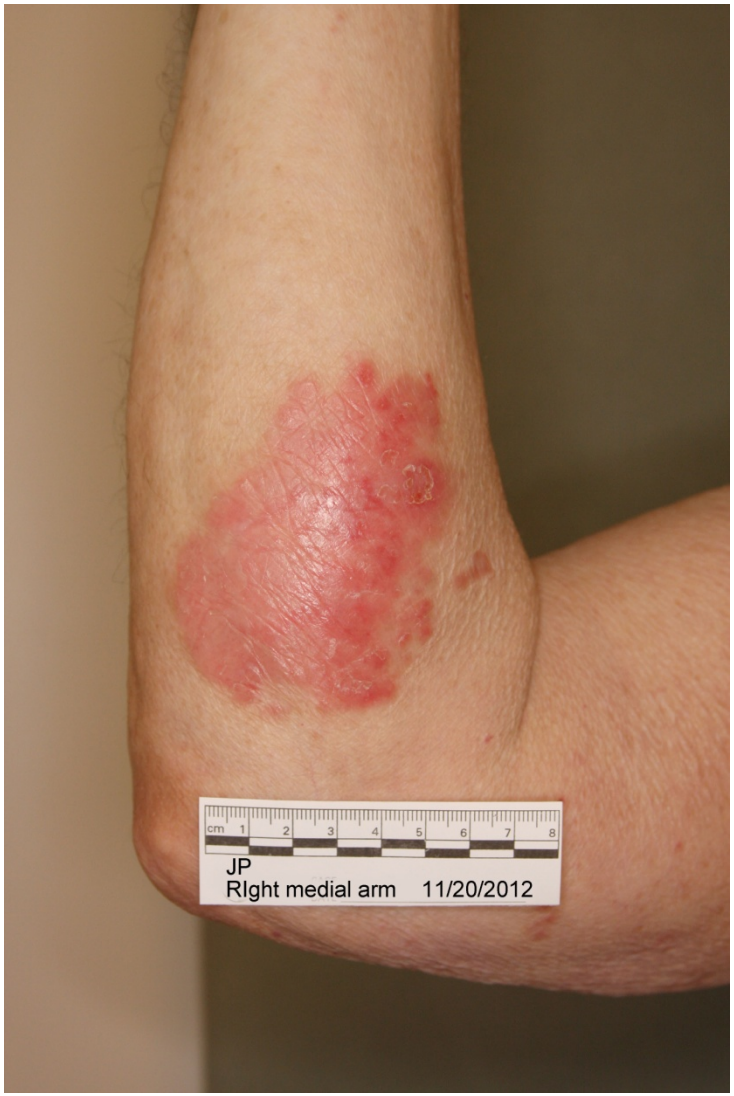


2/19/2013 (C5D1)
mSWAT 12 (6 patch, 6 plaque)

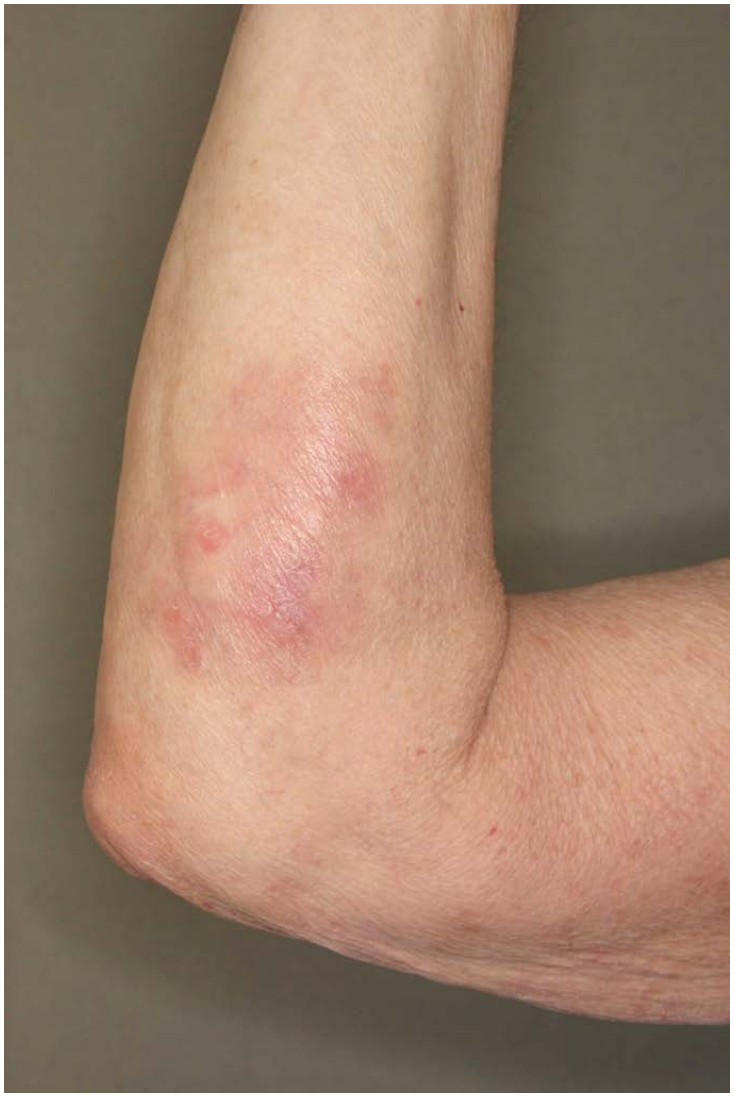


Stage IB MF (h/o phototx, bexarotene, anti-CD4 mAb, forodesine, CpG+RT, lenalidomide, sapacitabine, enzastaurin, TSEBT)

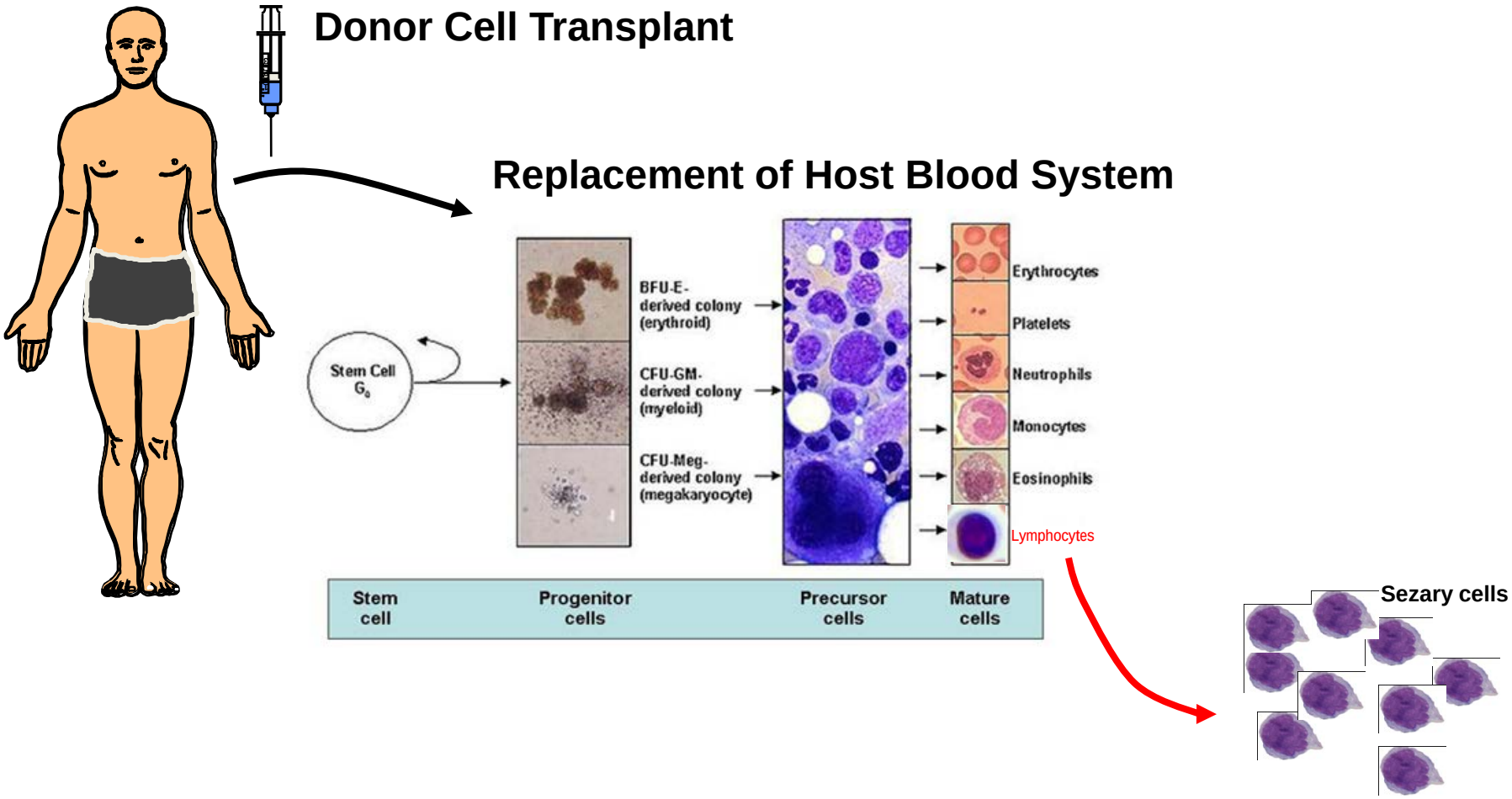
pre-treatment (11/20/2012)



C5D1 (2/19/2013)

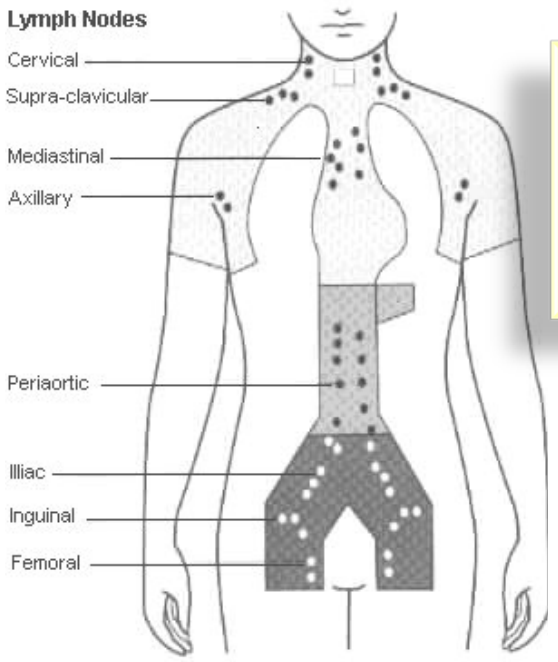


Harnessing the graft-versus-lymphoma effect in allo HSCT as the ultimate cellular immune therapy



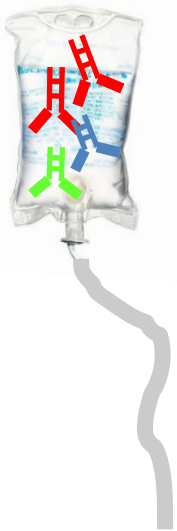
A New Approach in Donor Cell Transplant
Non-Myeloablative Regimen with TLI/ATG
"Protective conditioning"

NEJM 353:1321, 2005
Stanford study on going



TSEBT

+



Inverted Y field

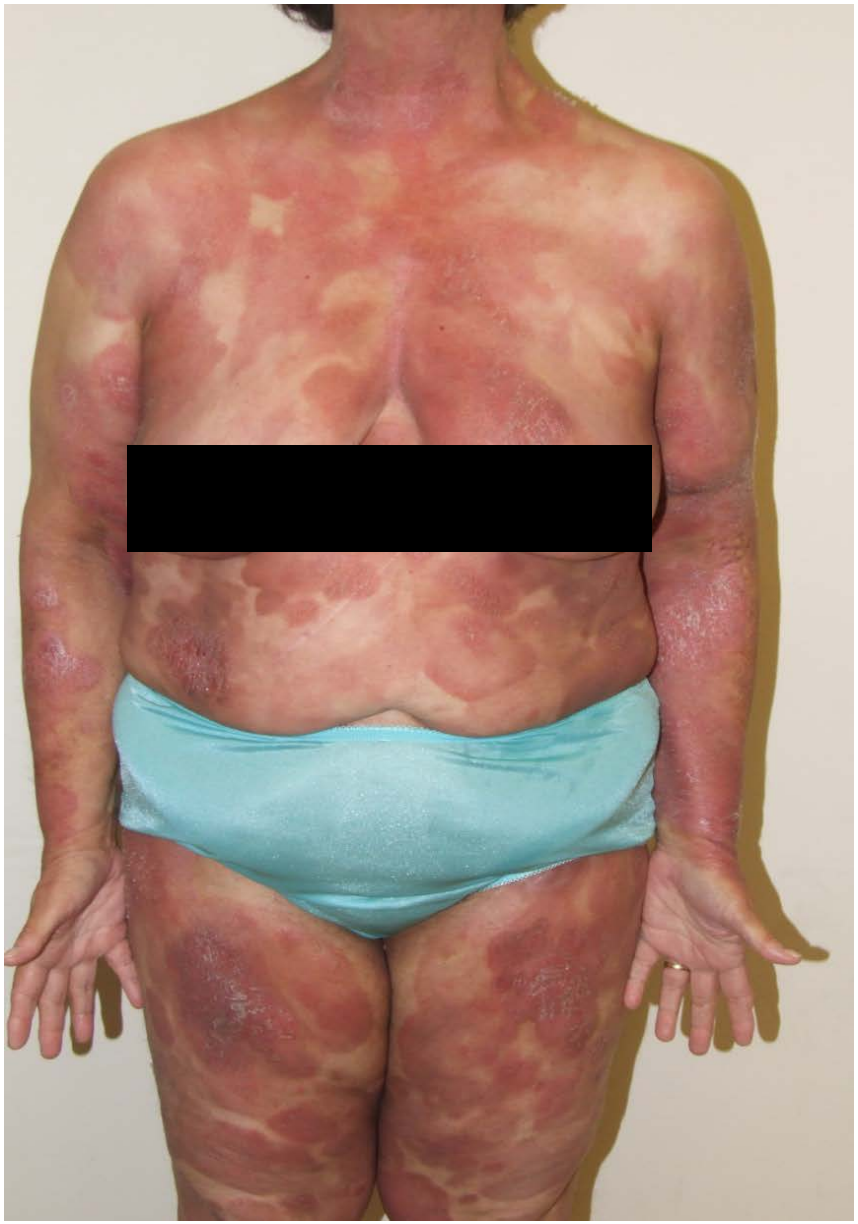
Total Lymphoid Irradiation (TLI)

Anti-Thymocyte Globulin (ATG, Rabbit anti-T cell antibodies)

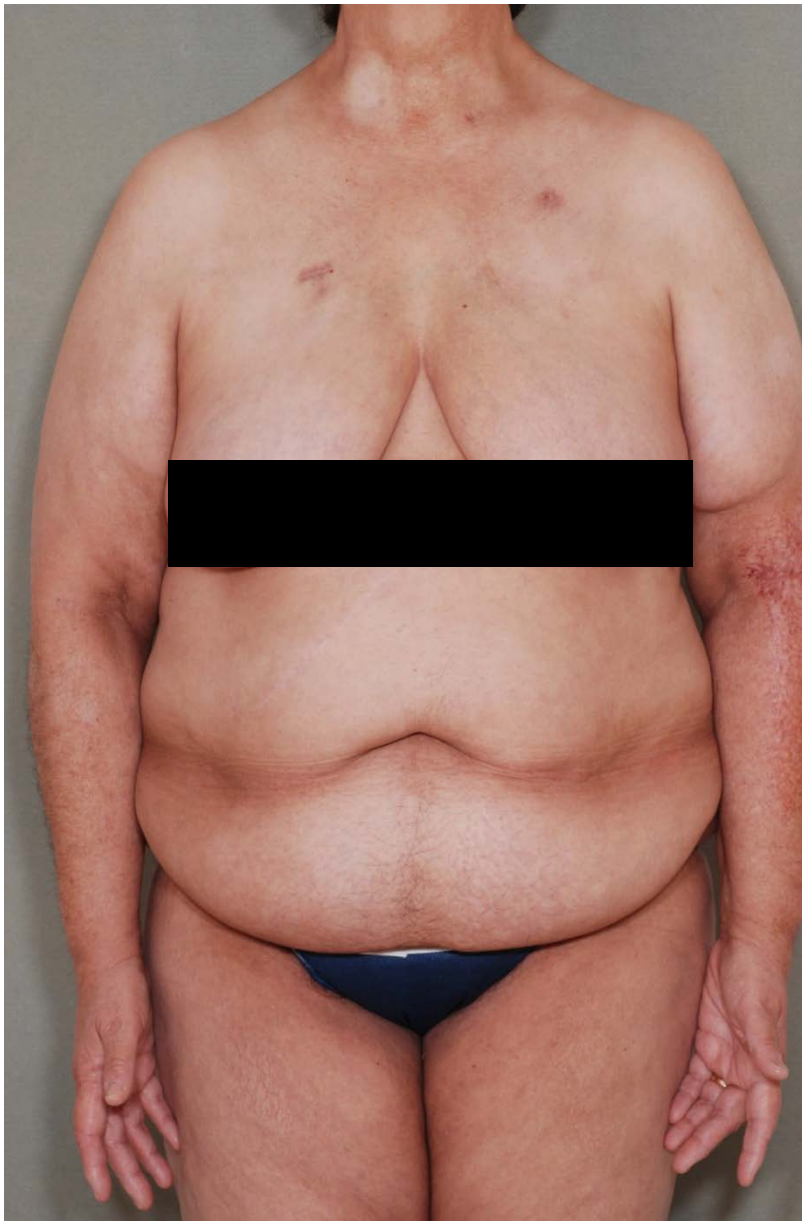
Enable Donor Cells to Engraft
aGVHD reduced to 2-5% (vs. 20-65%)

Mycosis fungoides, stage IVA w/ LCT in skin/LNs: CR

Pre-TSEBT



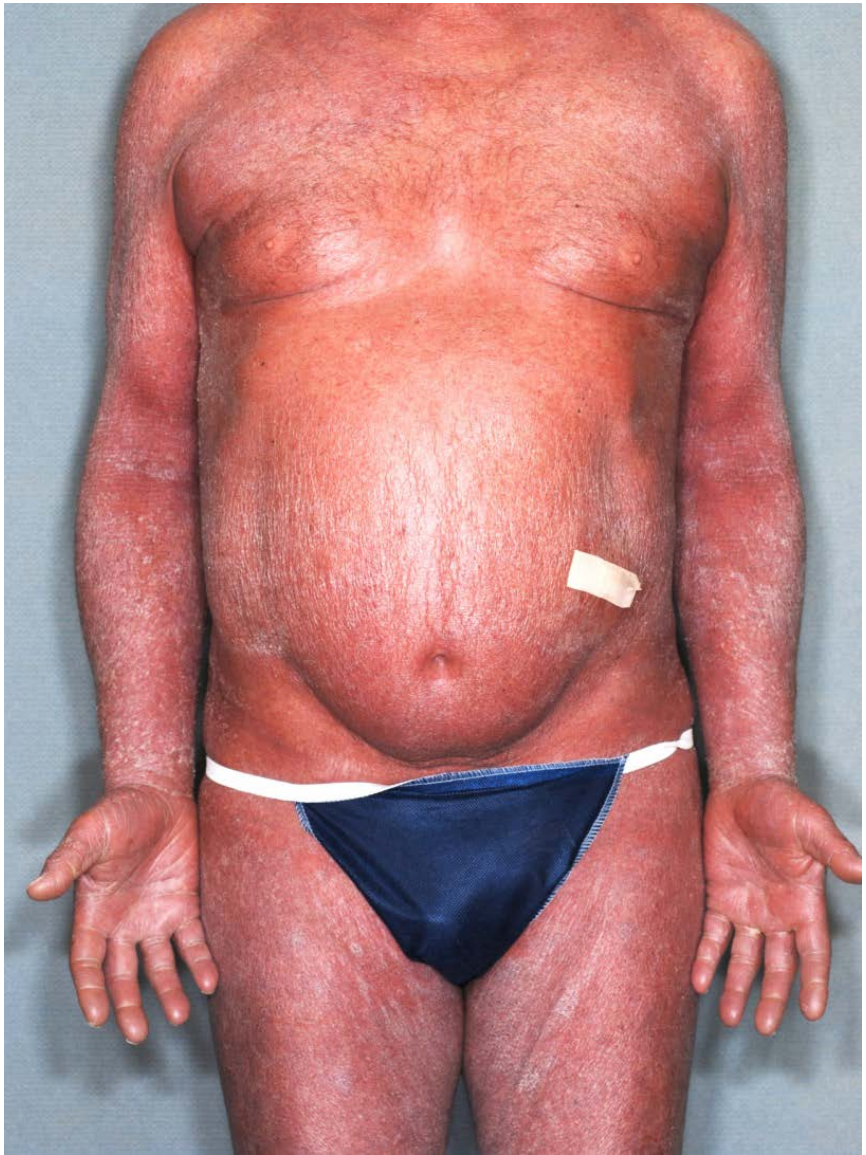
2.0+ yr (NED, no GVHD)



Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR

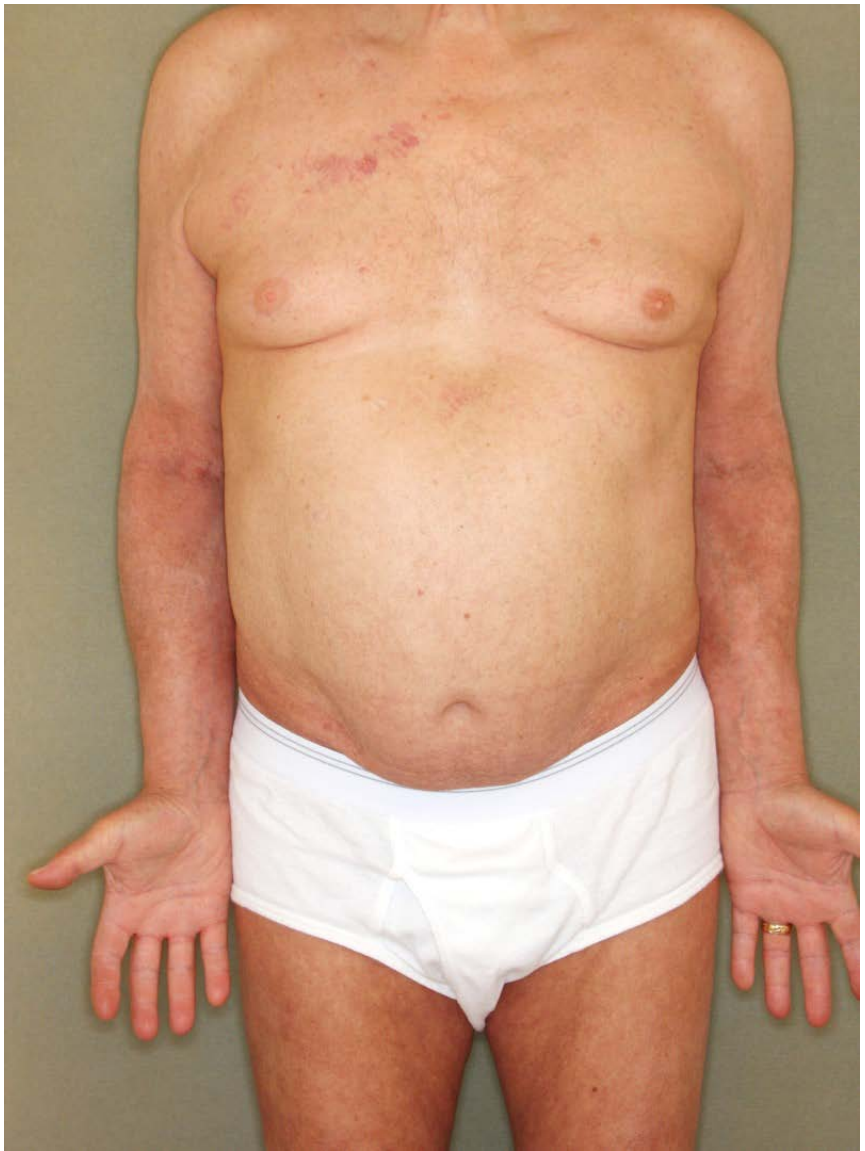
Pre-TSEBT

CD4+/CD26-: 99%, abs 19,780



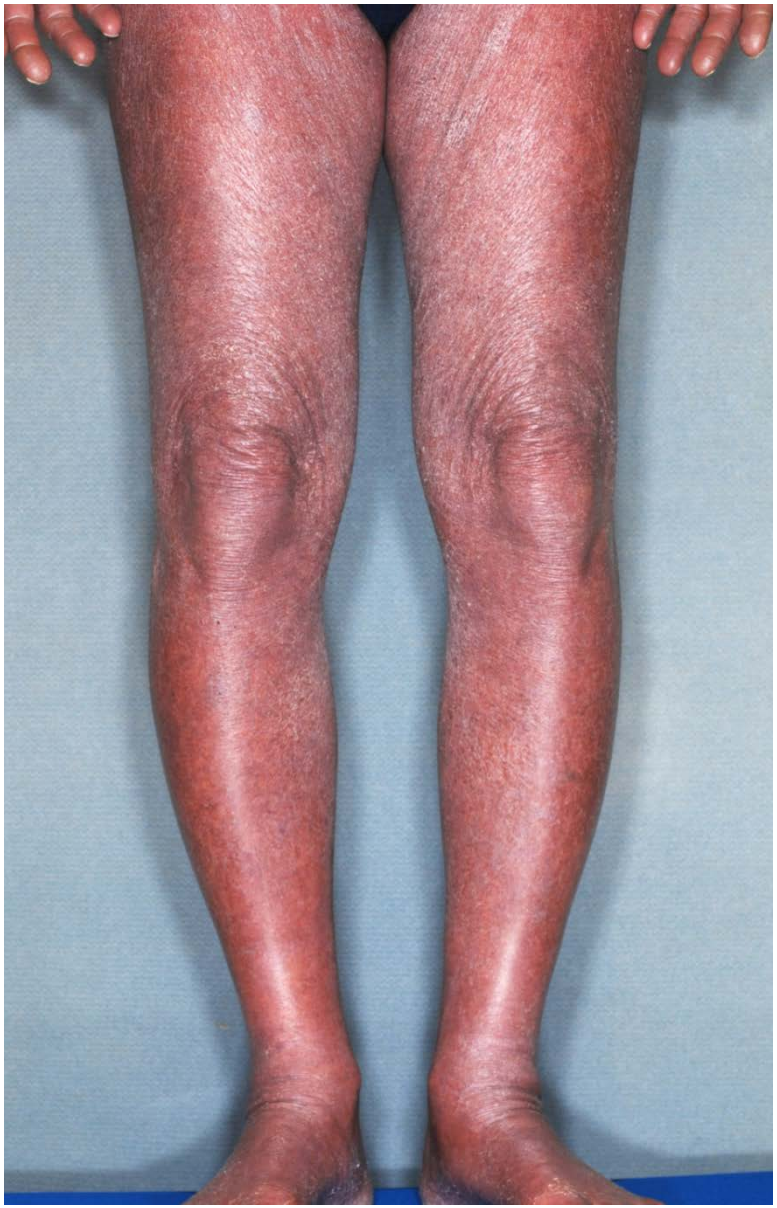
1.5+ yr (NED, no GVHD)

CD4+/CD26-: normalized

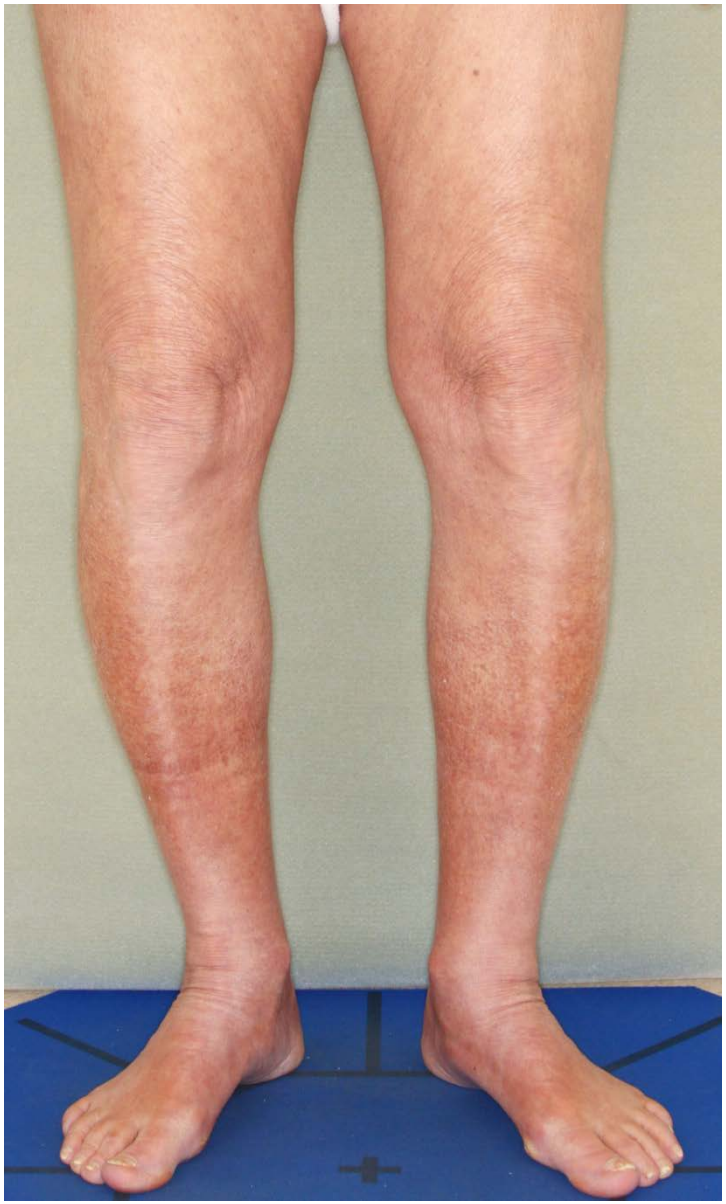


Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR

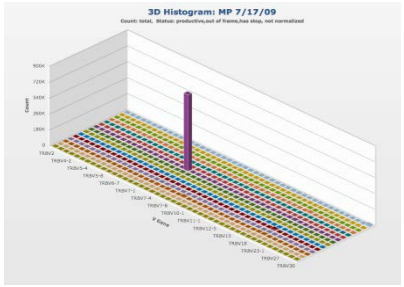
Pre-transplant



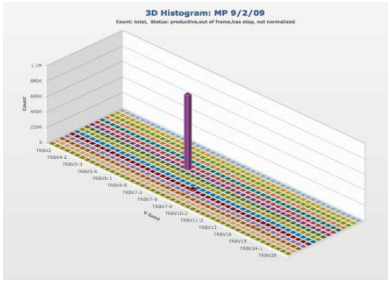
1.5+ yr (NED, no GVHD)



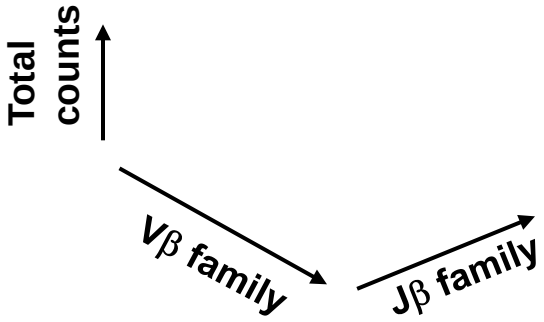
Reconstitution of TCRβ repertoire after non-myeloablative allogeneic HSCT

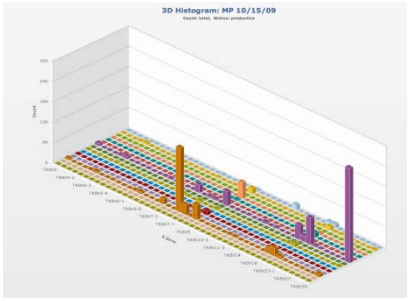


Pre-TSEBT

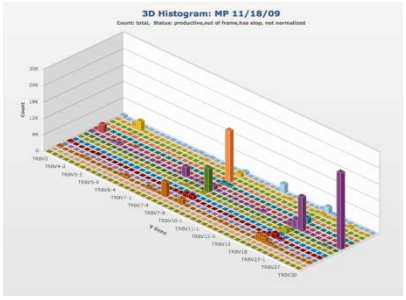


Pre-TLI/ATG

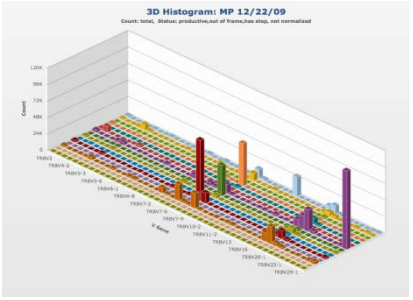




Day +30



Day +60



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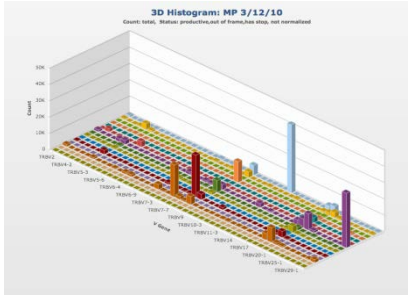

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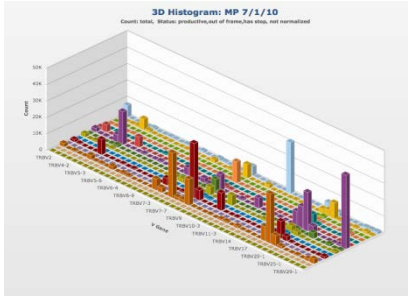

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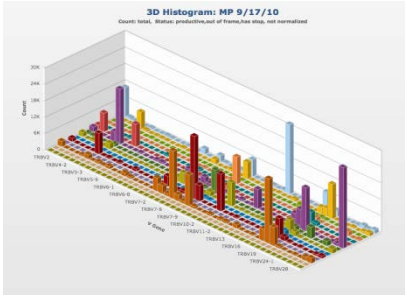
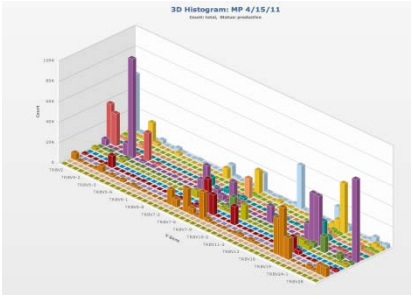


Day +360



Day +540

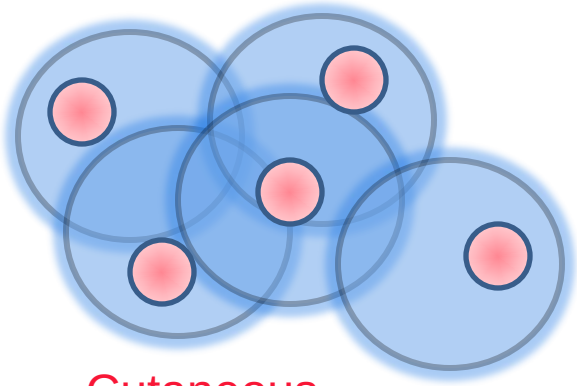
Immunotherapy strategies in cutaneous lymphoma

Combination with molecular targeted therapies, chemotherapies, radiation therapy

long-lasting, curative outcome

Adoptive cell transfer

Immune-modulating agents or antibodies



Cutaneous lymphoma

Vaccine-based approaches

Allogeneic HSCT

Key Clinical Issues in CTCL: Take home summary

- How can we optimize our diagnostic ability?

  => Utilize appropriate ancillary studies for optimal clinical-pathologic diagnosis

- What are the key prognostic factors or markers that can help guide clinical management?

  => Integration of clinical, path, standard molecular studies for overall prognosis, to guide management

- How do we make optimal treatment decisions with available therapies?

  => Stage-based decision, MF v SS, other prog, availability, co-morbidiity related selection; utilize NCCN guidelines

- How can we improve future therapeutics and outcome?

  => Pursue targeted/tumor selective tx + partnership with immune strategies to improve long-term outcome

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