How I (We) Treat CTCL

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Multidisciplinary Cutaneous Lymphoma Group

Stanford Cancer institute

School University School of Medicine

2015... 2018
T-Cell Lymphomas:
we are close to the
finalization

Bologna
ROYAL HOTEL CARLTON
May 7-9, 2018

President: Pier Luigi Zinzani
Co-President: Michele Cavo
Honorary President: Sante Tura

NCCN NHL TCL member

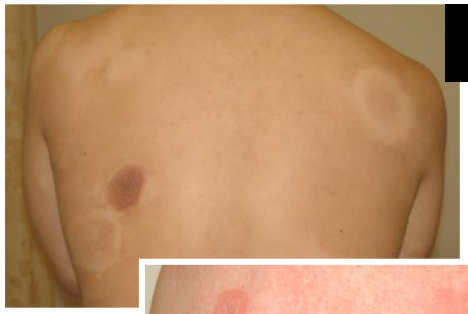
Disclosures of Youn Kim

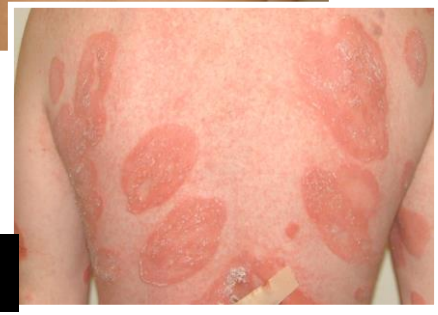
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Eisai	xx						SAC
Kyowa	xx					xx	SAC
Takeda	xx					xx	SAC
Seattle Gen	xx					xx	
Actelion						xx	
Merck	xx						
Portola	xx						
Medivir						xx	

Cutaneous T-cell lymphoma

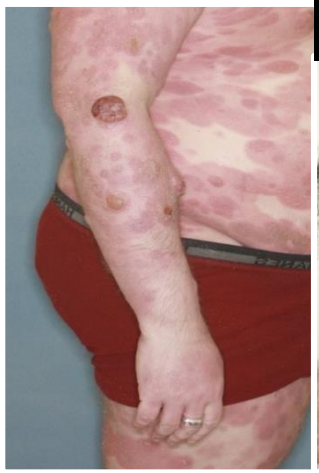
Mycosis fungoides & Sézary syndrome, very diverse in presentation

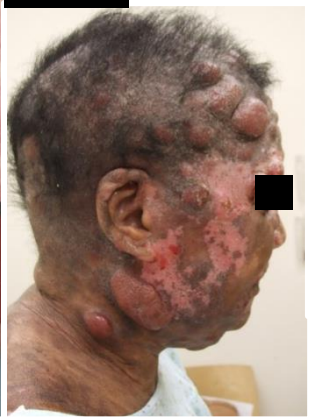
- Rare/orphan disease, 1 in 100,000 annual incidence, 4% of NHLs
- Significant heterogeneity in clinical, histopathology, cellular/molecular features

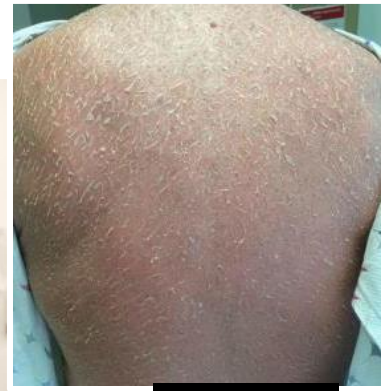


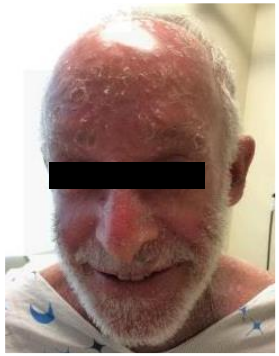


Early stage:
Patch/plaque dz,
T1, T2
Stages IA-IIA







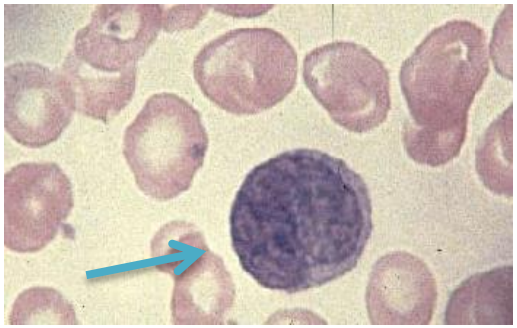


Advanced stage:
Tumor T3
Erythroderma T4
Extracutan dz (IV)
Stages IIB-IV

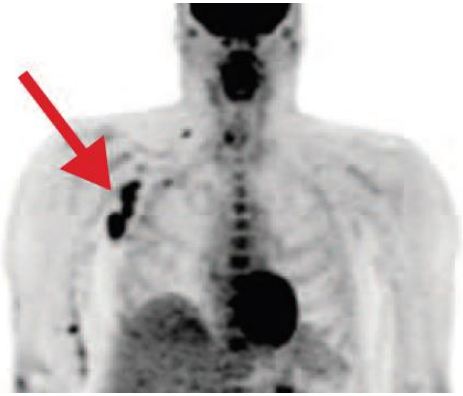
Management of extracutaneous disease, stage IV

Blood (B2)

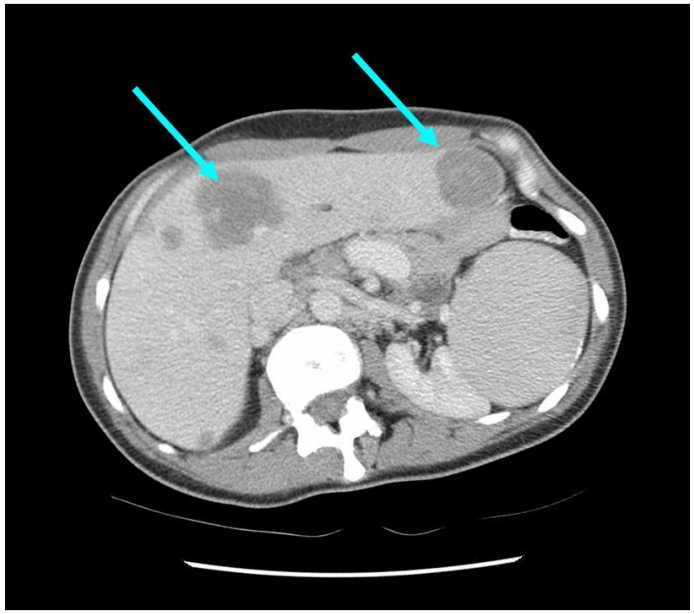
Sézary cells



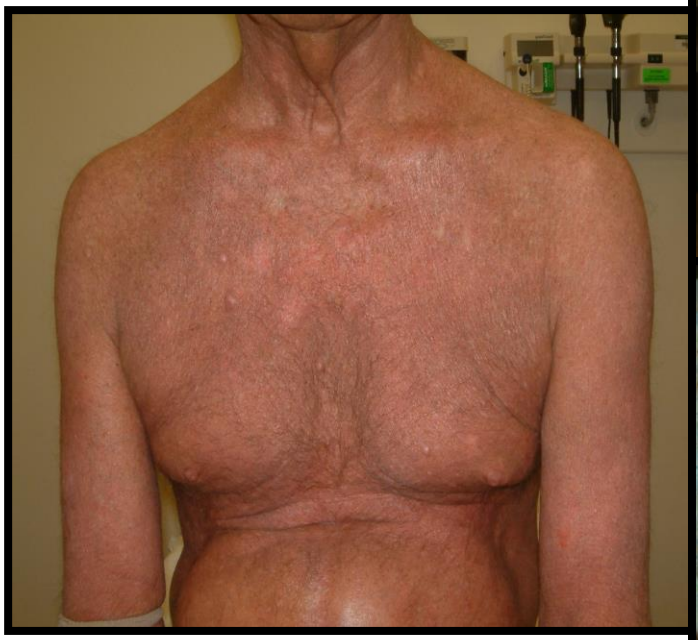
Lymph node (N3)

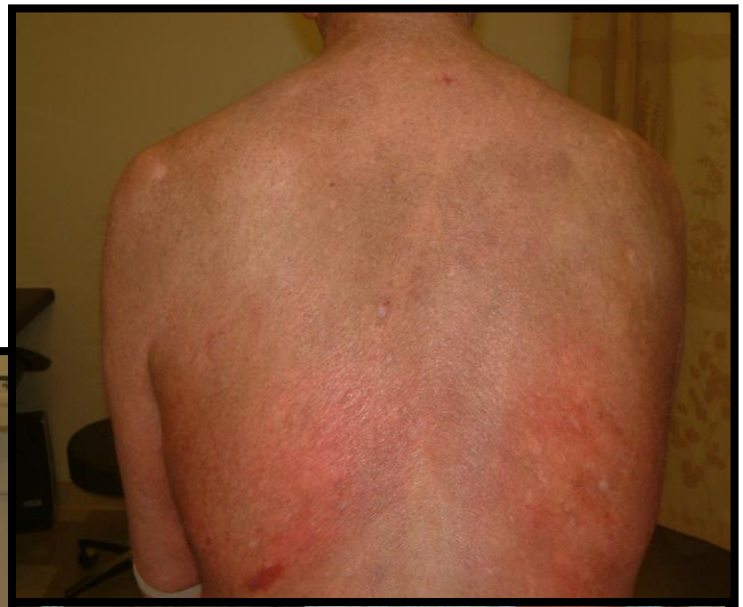


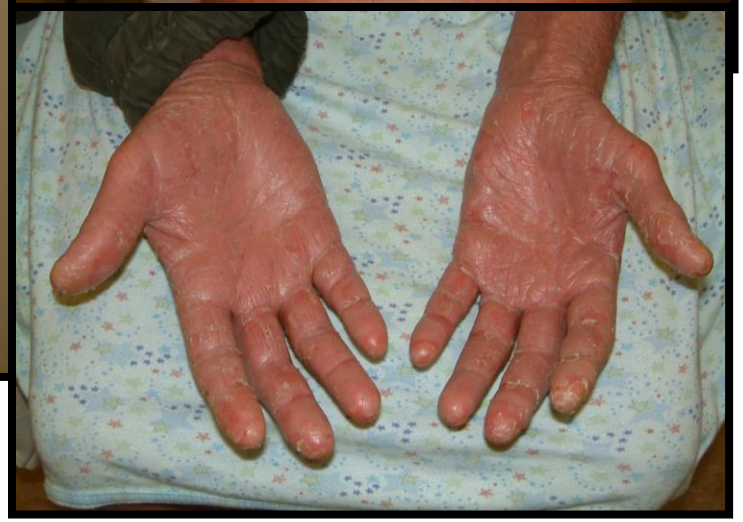
Viscera (M1)



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



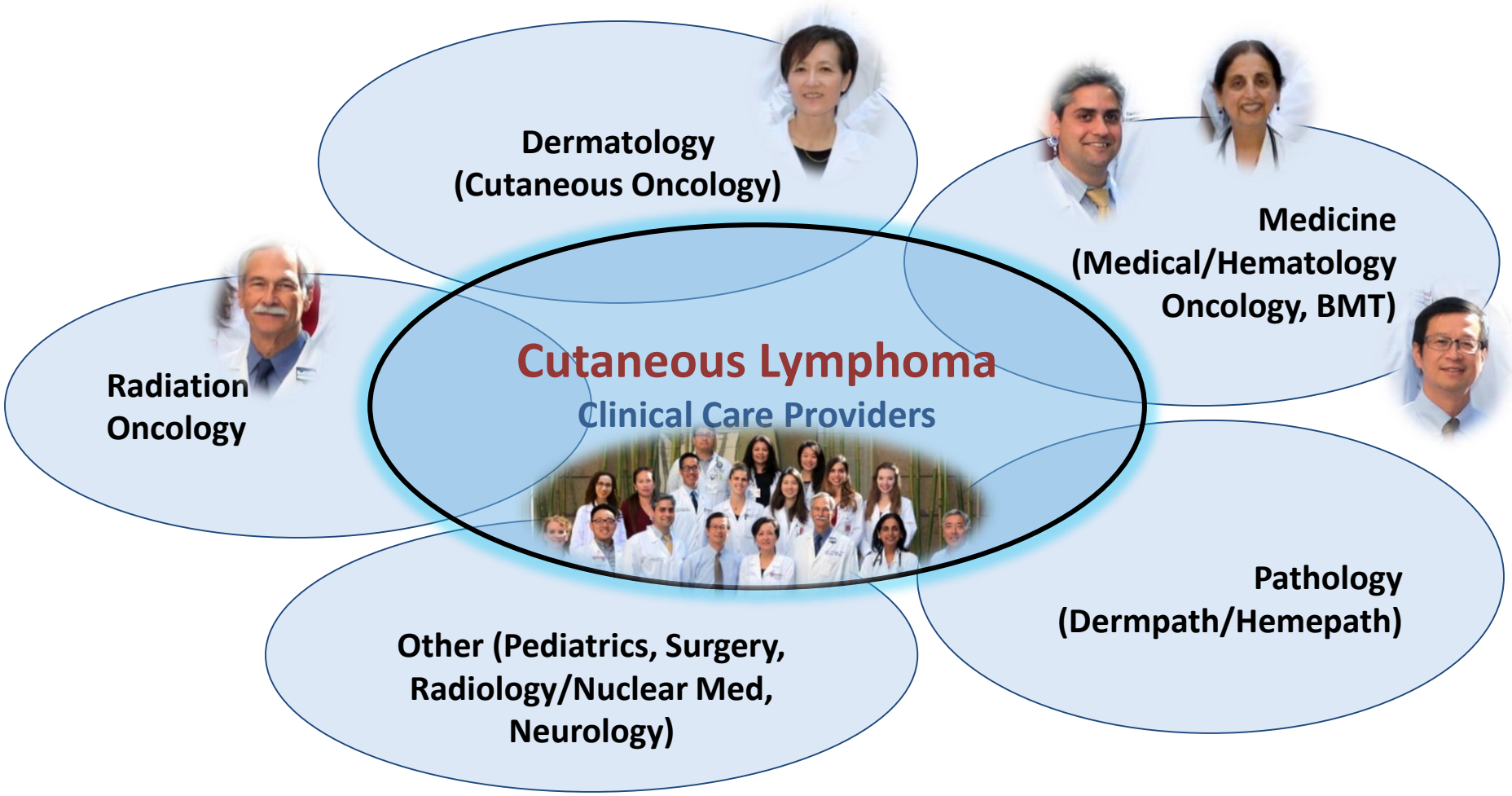




Evaluation for erythrodermic patients

- **Skin bx often non-diagnostic**
- **Sézary flow**
- **Relevant clone: same dominant TCR sequences in skin, blood, LN**
- **Imaging for LAD, H/S**
- **Skin culture**

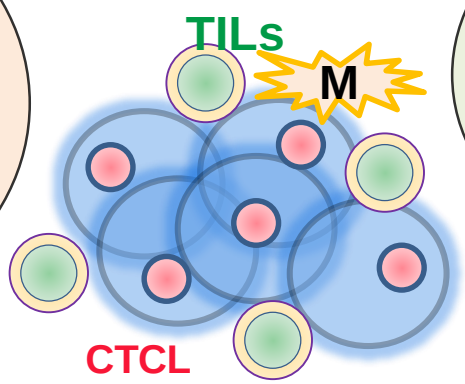
Multidisciplinary Teamwork for Optimal Comprehensive Care



Newer therapies in clinical development in CTCL

Tumor cell surface molecules (e.g., CD4, CD25, CD30, CD52, CCR4, CD158k/KIR3DL2)

Brentuximab vedotin
Mogamulizumab
Denileukin diftitox/E7777
Anti-KIR3DL2 mab



Microenvironment, immune mechanisms (e.g., PD-1, PD-L1, CTLA-4, SIRPα/CD47, OX40, IDO, MDSC, Tregs)

Anti-PD-1/PD-L1 mAbs
Anti-CTLA-4 mAbs
Anti-CD47 mAb/SIRPα Fc decoy, anti-SIRPα mAb
IDO inhibitor
OX40 agonistic mAb
Lenalidomide
Treg depleting agents

Proteosome inhibitor
PI3K inhibitor
mTOR inhibitor
Jak inhibitor
Syk-Jak dual inhibitor
ITK inhibitor
Bcl2 inhibitor
Anti-miR-155
HDAC inhibitor
Demethylating agent
Anti-folate (pralatrexate)

Tumor proliferation, metabolism, survival, progression mechanisms:
Signal transduction/transcription activation pathways *(e.g. TNFR2, proteasome, AKT/PI3K/mTOR, JAK/STAT, ITK)*
Apoptotic pathways *(e.g. Bcl2/Bax, TNFR, Fas, miRNAs)*
Epigenetics *(e.g., histone, non-histone proteins)*
Metabolic/survival pathways *(e.g., RFC-1, PARP)*

Multiple combination therapies under investigation

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2018
Mycosis Fungoides/Sezary Syndrome

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a]

SKIN-DIRECTED THERAPIES

For limited/localized skin involvement (Skin-Limited/Local)
- Topical corticosteroids[b]
- Topical chemotherapy (mechlorethamine [nitrogen mustard])
- Local radiation (8-12 Gy; 24-30 Gy for unilesional presentation)[c]
- Topical retinoids (bexarotene, tazarotene)
- Phototherapy (UVB, NB-UVB for patch/thin plaques; PUVA for thicker plaques)[d]
- Topical imiquimod

For generalized skin involvement (Skin-Generalized)
- Topical corticosteroids[b]
- Topical chemotherapy (mechlorethamine [nitrogen mustard])
- Phototherapy (UVB, NB-UVB, for patch/thin plaques; PUVA for thicker plaques)[d]
- Total skin electron beam therapy (TSEBT) (12–36 Gy)[c,e,f]

SYSTEMIC THERAPIES

Milder tx, indolent

Category A (SYST-CAT A)
- Retinoids (bexarotene, all-trans isotretinoin [13-cis-retinoic acid], acitretin)[i]
- Interferons (IFN-alpha, IFN-gamma)
- HDAC-inhibitors (vorinostat, romidepsin)[f]
- Extracorporeal photopheresis[g]
- Methotrexate (≤100 mg q week)
- Brentuximab vedotin[h]

Category B (SYST-CAT B)
- Preferred therapies (alphabetical order)
  - Brentuximab vedotin[h]
  - Gemcitabine
  - Liposomal doxorubicin
  - Low-dose pralatrexate
- Other therapies
  - Chlorambucil
  - Pentostatin
  - Etoposide
  - Cyclophosphamide
  - Temozolomide
  - Methotrexate (>100 mg q week)
  - Pembrolizumab[i] (category 2B)
  - Bortezomib (category 3)

Fail Cat A, more severe

SYSTEMIC THERAPIES (continued)

Category C (SYST-CAT C)[j] (alphabetical order)
- Bortezomib (category 3)
- Brentuximab vedotin[h]
- Gemcitabine
- Liposomal doxorubicin
- Low- or standard-dose pralatrexate
- Romidepsin
- See regimens listed on TCEL-B 2 of 5 (PTCL-NOS)[k]

LCT+ aggressive

COMBINATION THERAPIES

Need more combo studies

Skin-directed + Systemic
- Phototherapy + retinoid
- Phototherapy + IFN
- Phototherapy + photopheresis[g]
- Total skin electron beam* + photopheresis[g]

Systemic + Systemic
- Retinoid + IFN
- Photopheresis[g] + retinoid
- Photopheresis[g]+ IFN
- Photopheresis[g] + retinoid + IFN

Treatment “buckets”, category A, B, C; combinations of treatments

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

	Skin Therapy	CR	ORR
FDA approved	Topical steroids	45-65%	75-95%
FDA approved	Bexarotene gel	20-35%	50-75%
FDA approved	Topical NM	25-70%	50-90%
	nbUVB	45-75%	75-100%
	PUVA	50-80%	85-100%
	TSEBT (12-36 Gy)	30-90%	90-100%

- **Systemic agents (e.g., bexarotene, IFN, methotrexate, vorinostat, romidepsin) 15-45% 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

Selected Systemic Therapies for MF Stage ≥ IIB

Agent	ORR	CR	Comments
Bexarotene	45–55%	6%	≥Stage IIB
Vorinostat	29.5%	2%	≥Stage IIB
Denileukin diftitox	36%	12%	18ug/kg
Romidepsin	38%	7%	≥Stage IIB
Gemcitabine	68%	8%	1000 mg/m^2, 3–4 wk
Pralatrexate	53%	6%	Stage IIB
Liposomal doxorubicin	41%	6%	Stage IIB-IV
Brentuximab vedotin	68%	16%	Stage IIB, RCT against bex/mtx

First RCT in CTCL comparing new tx against standard therapy

Modified from Horwitz S. *Clin Lymphoma Myeloma*. 2008;8(suppl 5):S187

Lancet 390:555-566, 2017

FDA approval 11/2017 in MF

Clinical activity of systemic agents in Sezary Syndrome

Agent	N	ORR	DOR	comments
Bexarotene	17	24% (no CR)	ND	Phase 2-3 single arm
Photopheresis+, varying regimen	70 (>1 study)	20-89% (0-29% CR)	ND	Mostly retrospective studies
Vorinostat	30	33% (no CR)	6+ mo	Pivotal single arm
Romidepsin	13	31% (no CR)	> 1 year	Pivotal single arm
Methotrexate	10	50% (30% CR)	>1 year	Retrospective study
Chlorambucil	26	88%	ND	Retrospective study
Gemcitabine	11	73%	4 mo	Phase 2 single arm
Alemtuzumab, varying regimen	14/17	86%/82%	6 mo (n=17)	Phase 2 single arm Median OS 35 mo (n=14)
Mogamulizumab, phase 3 RCT	81	37%	17 mo	**Largest RCT,** PFS as primary; blood response in 83/122 (68%)
Pembrolizumab	15	27% (7% CR)	> 1 year	Phase 2 single arm

Brentuximab, ALCANZA RCT excluded SS; activity reported in ISTs

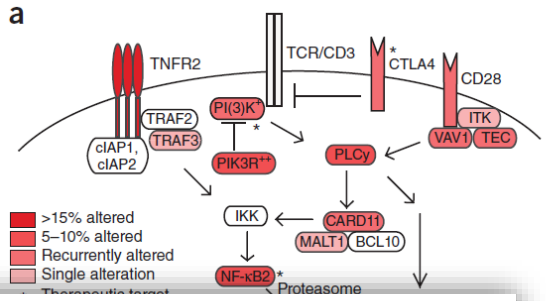
nature genetics

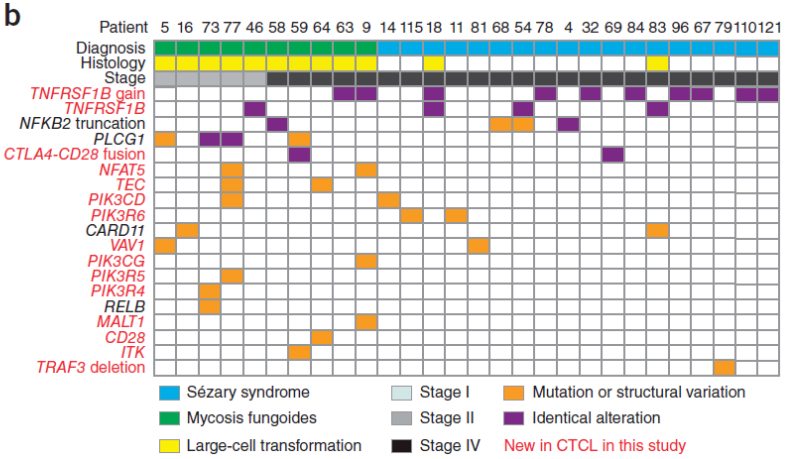
2015

Do we have molecular data to guide management?

Genomic analysis of mycosis fungoides and Sézary syndrome identifies recurrent alterations in TNFR2

Alexander Ungewickell[1,2,12], Aparna Bhaduri[1,12], Eon Rios[1], Jason Reuter[3], Carolyn S Lee[1], Angela Mah[1], Ashley Zehnder[1], Robert Ohgami[4], Shashikant Kulkarni[5–7], Randall Armstrong[8], Wen-Kai Weng[8], Dita Gratzinger[4], Mahkam Tavallaee[9], Alain Rook[10], Michael Snyder[3], Youn Kim[9] & Paul A Khavari[1,11]





The mutational landscape of cutaneous T cell lymphoma and Sézary syndrome

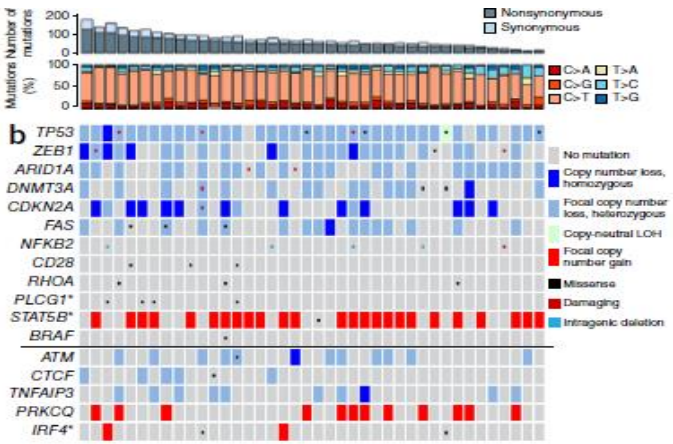
Ana Carolina da Silva Almeida[1,8], Francesco Abate[2,8], Hossein Khiabanian[2], Estela Martinez-Escala[3], Joan Guitart[3], Cornelis P Tensen[4], Maarten H Vermeer[4], Raul Rabadan[2,5], Adolfo Ferrando[1,6,7] & Teresa Palomero[1,6]

Genomic profiling of Sézary syndrome identifies alterations of key T cell signaling and differentiation genes

Linghua Wang[1], Xiao Ni[2], Kyle R Covington[1], Betty Y Yang[2], Jessica Shiu[2], Xiang Zhang[2], Liu Xi[1], Qingchang Meng[1], Timothy Langridge[2], Jennifer Drummond[1], Lawrence A Donehower[3], Harshavardhan Doddapaneni[1], Donna M Muzny[1], Richard A Gibbs[1], David A Wheeler[1] & Madeleine Duvic[2]

Genomic landscape of cutaneous T cell lymphoma

Jaehyuk Choi[1,2], Gerald Goh[3,4], Trent Walradt[1], Bok S Hong[1], Christopher G Bunick[1], Kan Chen[1], Robert D Bjornson[5], Yaakov Maman[3,6], Tiffany Wang[1], Jesse Tordoff[1], Kacie Carlson[1], John D Overton[7], Kristina J Liu[1], Julia M Lewis[1], Lesley Devine[8], Lisa Barbarotta[9], Francine M Foss[1,9], Antonio Subtil[1], Eric C Vonderheid[10], Richard L Edelson[1], David G Schatz[3,6], Titus J Boggon[11], Michael Girardi[1] & Richard P Lifton[3,4,12]

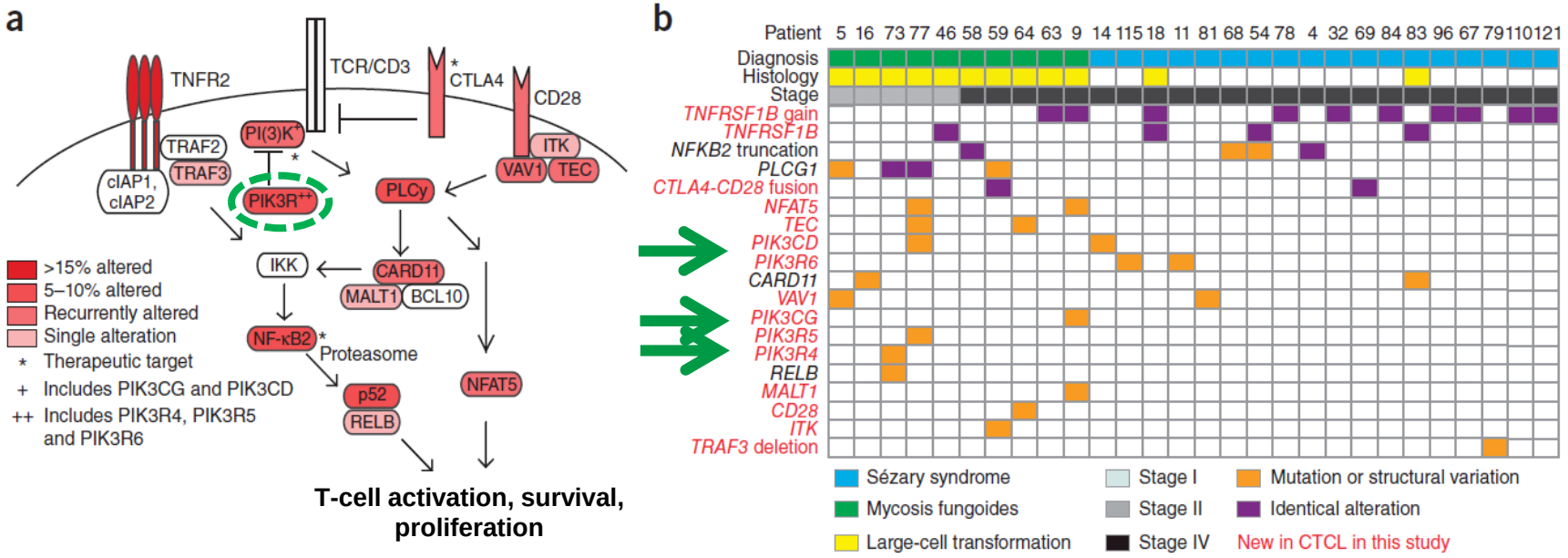


Many potential actionable targets/pathways
Translation into meaningful outcome needs to be established

nature genetics
2015;47:1056

Genomic analysis of mycosis fungoides and Sézary syndrome identifies recurrent alterations in TNFR2

Alexander Ungewickell[1,2,12], Aparna Bhaduri[1,12], Eon Rios[1], Jason Reuter[3], Carolyn S Lee[1], Angela Mah[1], Ashley Zehnder[1], Robert Ohgami[4], Shashikant Kulkarni[5–7], Randall Armstrong[8], Wen-Kai Weng[8], Dita Gratzinger[4], Mahkam Tavallaee[9], Alain Rook[10], Michael Snyder[3], Youn Kim[9] & Paul A Khavari[1,11]



Memorial Sloan Kettering Cancer Center

Horwitz et al, ASH 2014

Duvelisib (IPI-145), a Phosphoinositide-3-Kinase-δ,γ Inhibitor, Shows Activity in Patients with Relapsed/Refractory T-Cell Lymphoma

Steven Horwitz[1]; Pierluigi Porcu[2]; Ian Flinn[3]; Brad Kahl[4]; Howard Stern[5]; Mark Douglas[5]; Kerstin Allen[5]; Patrick Kelly[5]; and Francine Foss[6]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]The Ohio State University; [3]Sarah Cannon Research Institute, Nashville, TN, USA; [4]University of Wisconsin, Madison, WI, USA; [5]Infinity Pharmaceuticals, Inc., Cambridge, MA, USA; [6]Yale University Cancer Center, New Haven, CT, USA.

nature genetics
2015;47:1056

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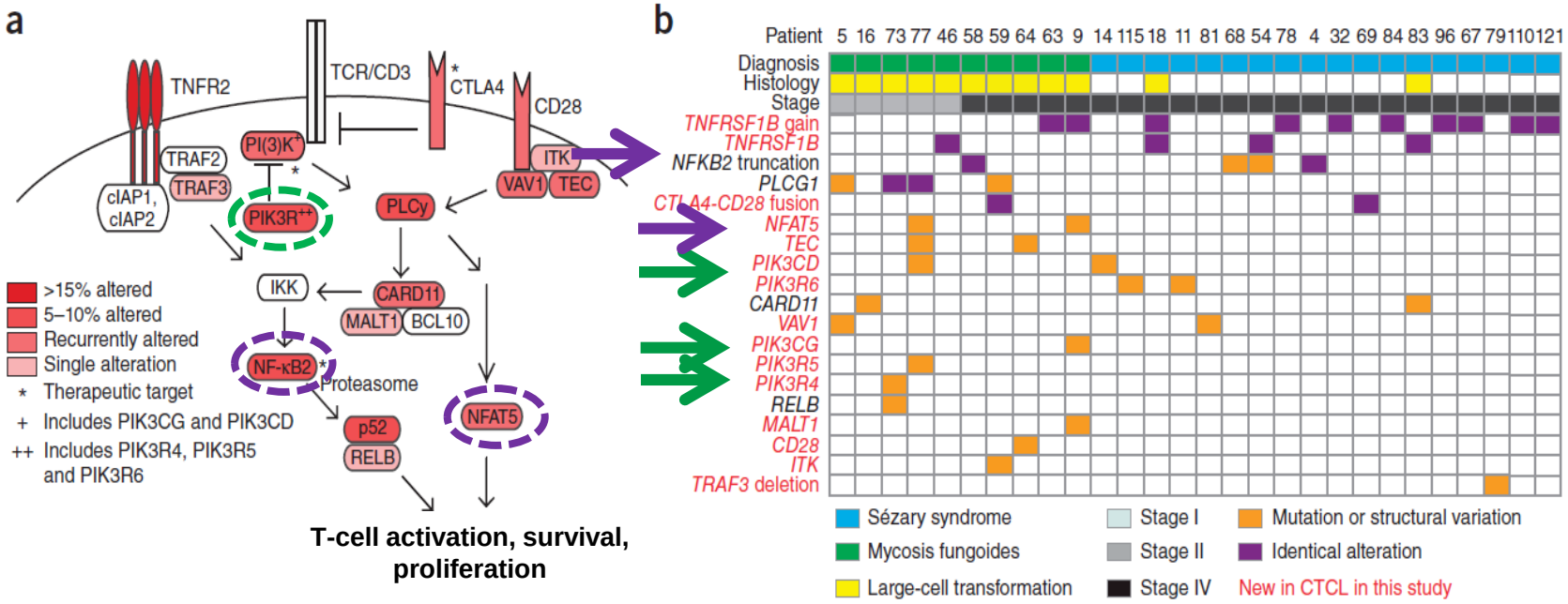
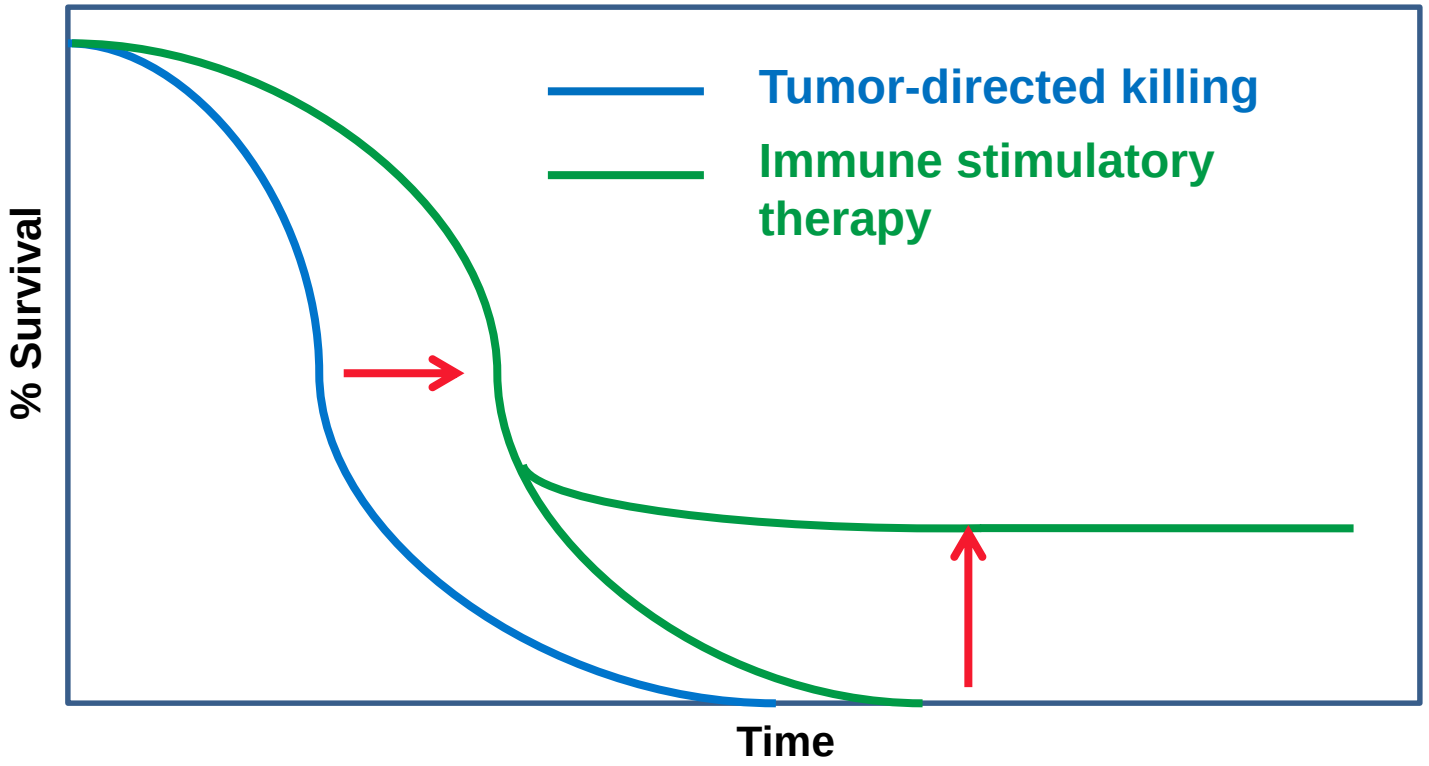


PI3k inhibitor combination strategies in CTCL: duvelisib + bortezomib vs. duvelisib + romidepsin (ongoing trial – MKSCC/Horwitz, DFCI, Stanford, other)

Why is immunotherapy important in CTCL?

Need of therapies with reliable responses that last

Partnering with immunotherapy, induction of anti-tumor memory

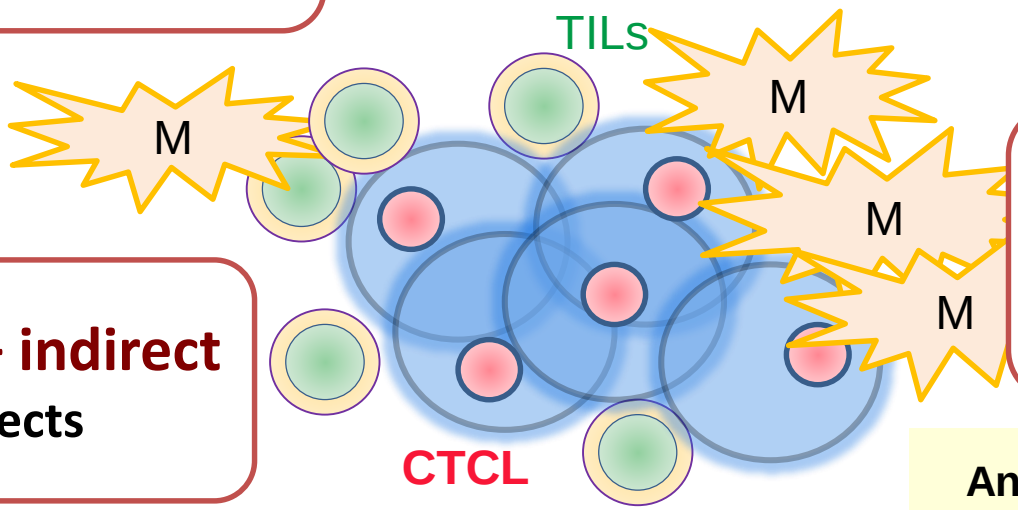


Immunotherapies in clinical development in CTCL

Partner with immune therapies

Direct effects against tumor cells

Anti-KIR3DL2 mAb
Bispecific Ab
CAR-T
Allogeneic HSCT



Indirect effects on immune system microenvironment, systemic

Direct + indirect effects

Anti-CCR4 Mab
E7777

Combination therapies/strategies

Anti-PD-1/PD-L1 mAb
Anti-KIR mAb
Anti-CD137 mAb
Anti-CD47 mAb
TLR-agonists (resiquimod)
Cytokines (IFNγ, IL-12)

General concepts in managing MF/SS-CTCL

NCCN, EORTC, ESMO, other regional guidelines

Lack of evidence-based help

- **Consensus-based guidelines to enable access/insurance coverage**
  (management by stage, MF v SS, indolent v aggressive, dz burden, etc)

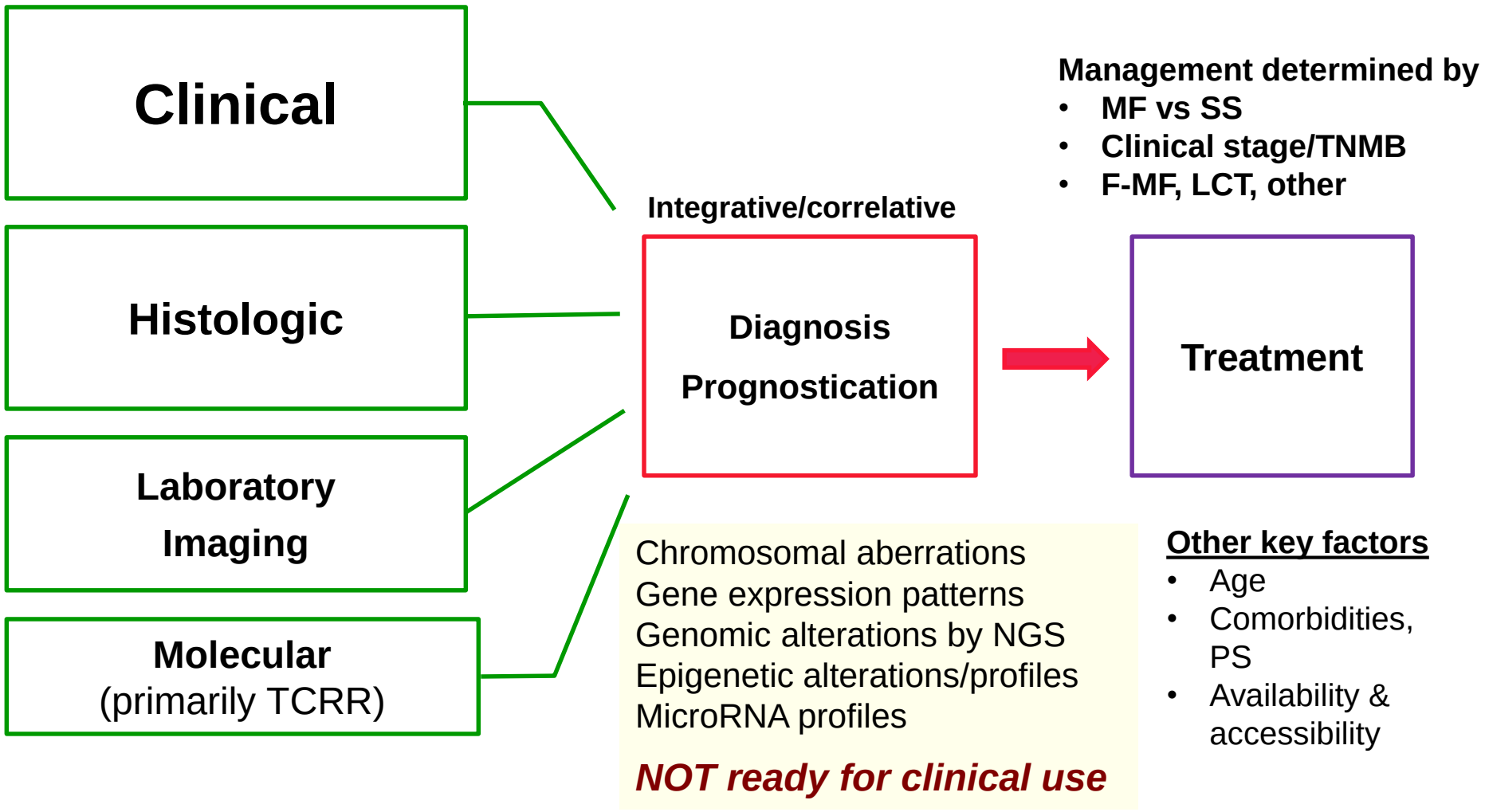
Overall goal of treatment (other than allo-HSCT)

- Not curative intent: good PRs that are durable, well-tolerated, and improve QoL
- Lasting CRs are great but hard to attain and often at risk of undesired AEs

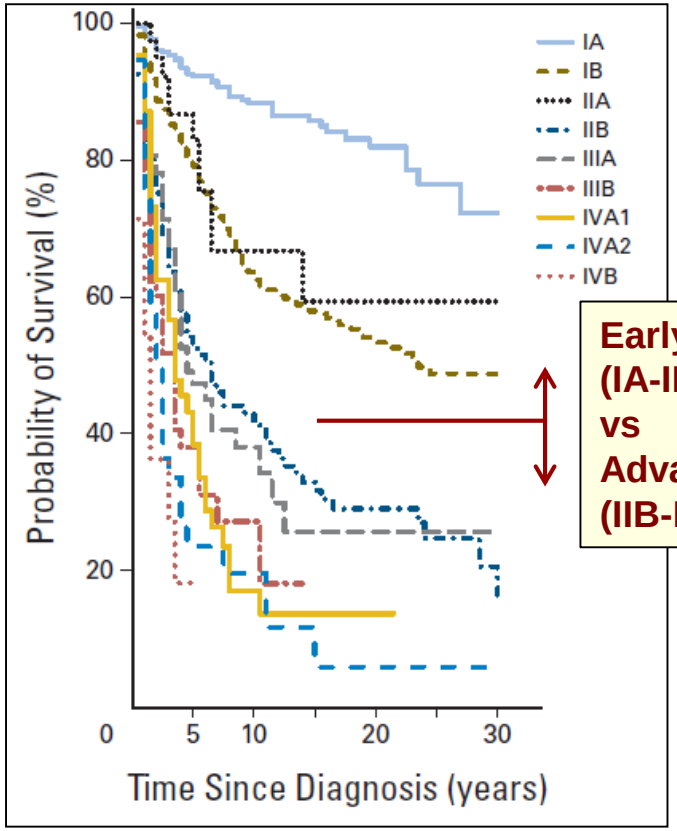
Appreciate unique approaches in MF/SS

- Optimize use of **skin-directed and biologic agents**
- **Single agent chemotx** (chronic tx) **over combination chemotx** (PTCL regimens short-lived; best for extensive EC dz and/or prior to allo HSCT)
- Often observe **mixed responses** (within and across compartments)
- Can **re-cycle** treatments
- Optimize utility of **maintenance therapy to sustain response**
- **Supportive therapy** is essential
  - Chronic control of skin infections (staph, HSV)
  - Use anti-itch regimens, emollients/sealants

Evaluation and management in MF/SS



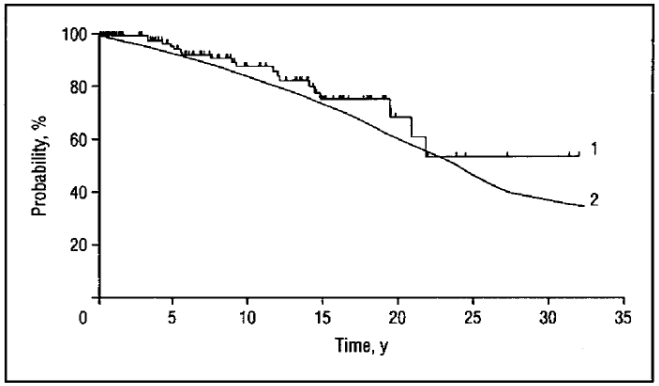
Prognosis of early vs advanced stage MF and SS:
Appropriate risk-stratification for treatment selection



Early (IA-IIA) vs Advanced (IIB-IV)

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

Stage IA vs. control population:
Life-expectancy is not altered in limited patch/plaque disease



Kim et al, Arch Dermatol 1996;132:1309

Large-cell transformation (LCT) with worse clinical outcome;
F-MF two prognostic subsets *(Hodak et al, 2016)*
F-MF not sig independent factor in advanced MF/SS *(CLIC Scarisbrick et al, 2015)*

J Am Acad Dermatol 2016;75:347, J Clin Oncol 2010;28:4730, Blood 2012;119:1643, J Clin Oncol 2015;33:3766

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

CLIC
CUTANEOUS LYMPHOMA INTERNATIONAL CONSORTIUM

Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sézary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model

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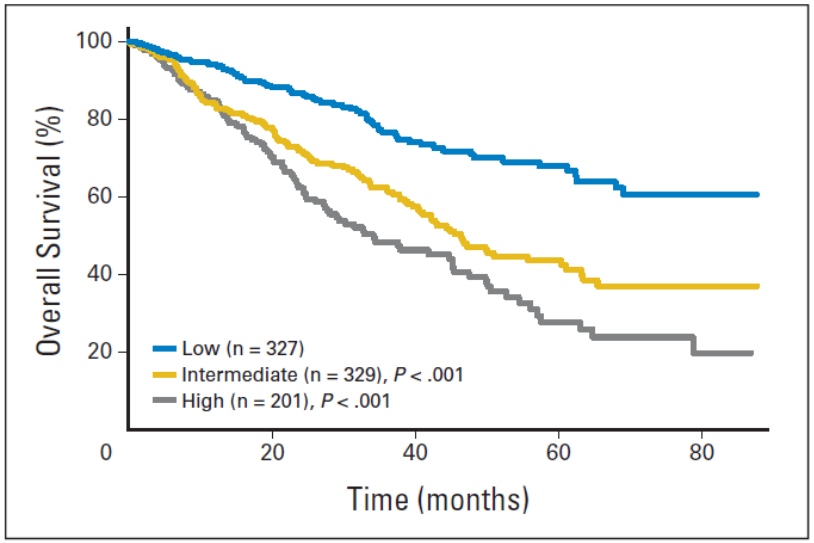


Prognostic modeling beyond clinical stage

Retro-CLIPI:

Retrospective study of 10 parameters in advanced stage MF/SS, dx from 2007

- **29 international sites, N = 1,275**
- **4 independent factors:**
  Age >60, stage IV, LCT, ↑LDH
- **Combined into prognostic index model**
  => 3 risk groups

5-year OS rates of 3 risk groups

- **Low-risk, 67.8%**
- **Intermediate-risk, 43.5%**
- **High-risk, 27.6%**

Prospective study (PROCLIPI) in progress- to validate old and identify new prognostic factors

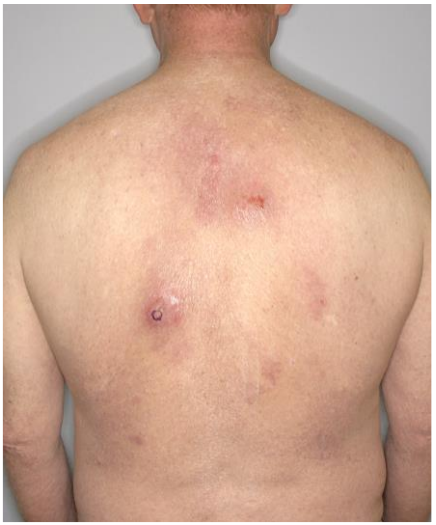
- **J Scarisbrick/UHB, EU lead**
- **Y Kim/Stanford, non-EU lead**

Two extremes of tumor/T3 disease:

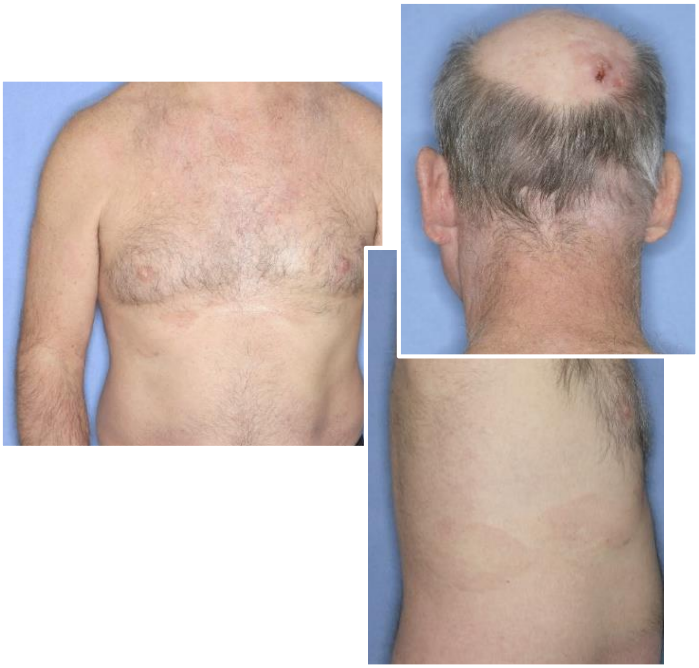
both with “LCT+”

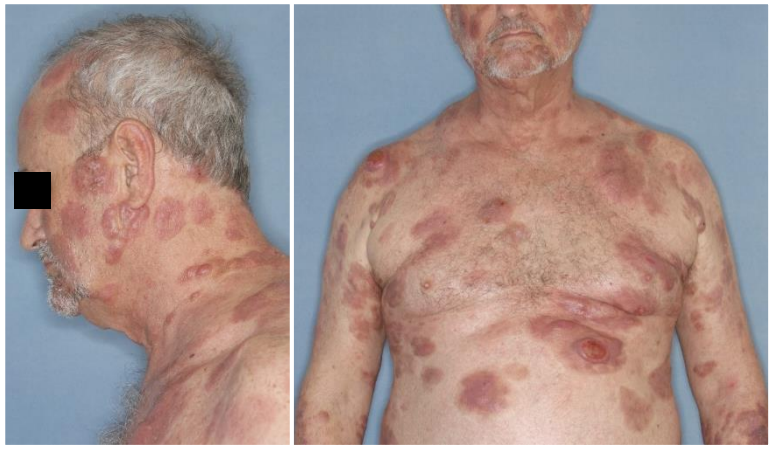
Indolent vs aggressive

Managed differently

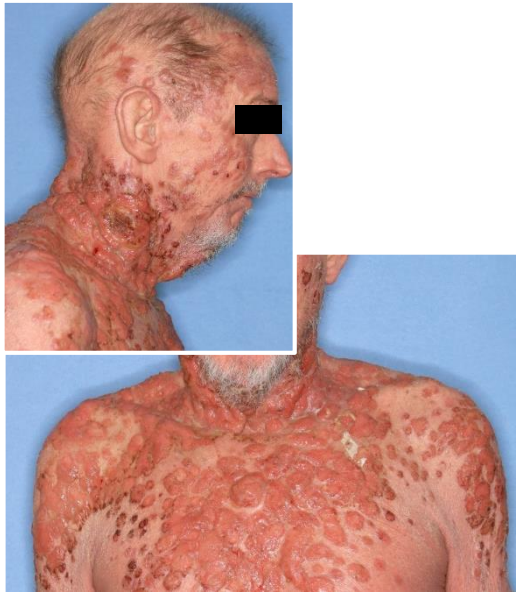


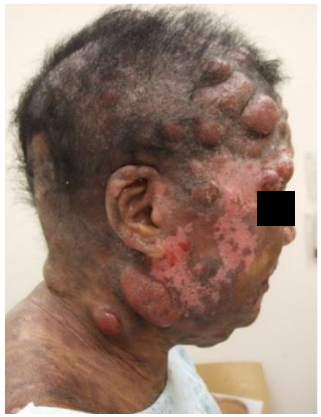
Localized, indolent Tumor/T3 disease





Generalized, aggressive Tumor/T3 disease





Management of skin "tumor" disease (stage IIB)

- **Limited vs. generalized** extent tumor disease
- **Intensify therapy for** aggressive growth pattern, e.g., **la cell transformation (LCT)**

- **Limited extent tumor disease**
  - **Local RT for limited tumor disease**
  - "Milder" systemic options (Cat-A)

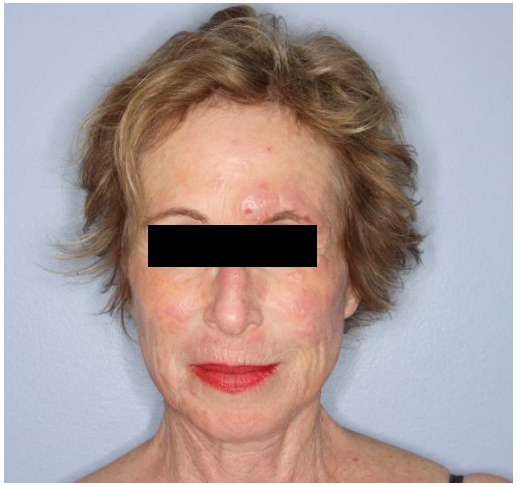
  } +/- Skin-directed therapie

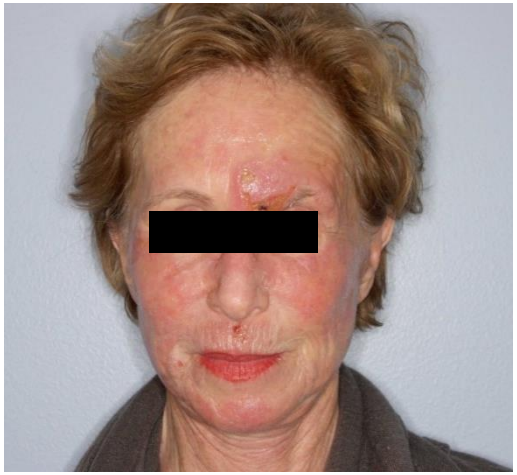
- **Generalized extent tumor disease**
  - **Indolent (no LCT)**
    - TSEBT (low-dose/12 Gy)
    - Category A systemic +/- skin-directed tx
  - **Aggressive (+ LCT)**
    - TSEBT (12-36 Gy) + Cat-A systemic
    - Category B or C systemic options +/- skin-directed tx
  - Refractory dz => clinical trials, multi-agent therapies

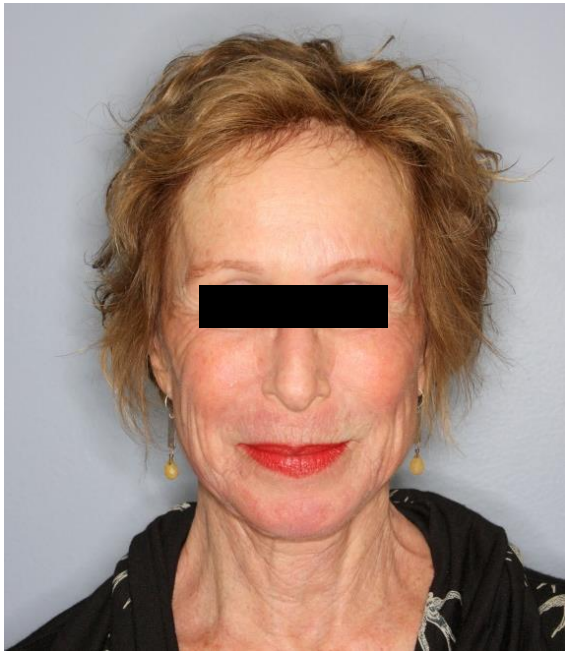
Category A, "milder"
- Retinoids
- IFNs
- HDAC-i
- Methotrexate (low-dose)
- Brentuximab
- Clinical trial

Category B or C "more intensive"
- Brentuximab vedotin
- Pralatrexate (15-30 mg/m2)
- HDAC-i (romidepsin)
- Liposomal doxorubicin
- Gemcitabine
- Other single agents
- Clinical trial
- Options for PTCL-NOS

Radiation is highly effective in CTCL, so use it when appropriate for reliable disease reduction, +/- maintenance strategies





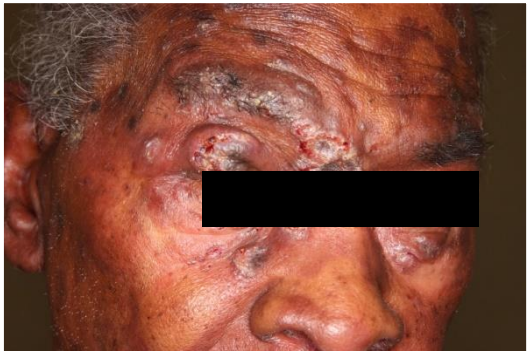


RT highly effective for localized refractory tumor (T3) disease:

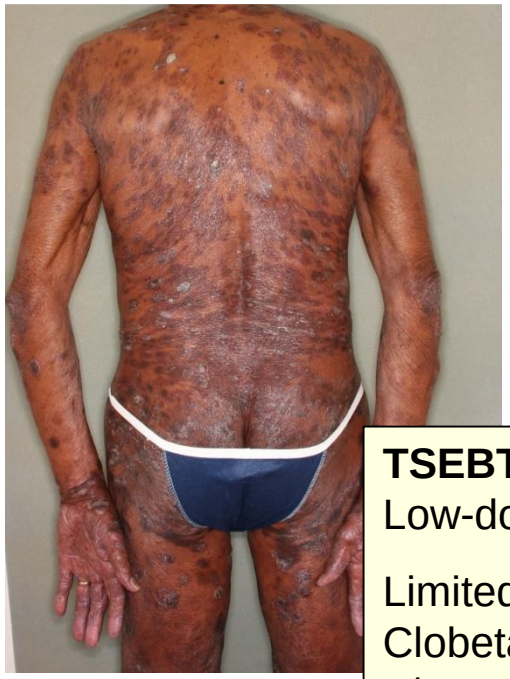
Predominantly face, refractory to oral bexarotene, MTX, IFN

<u>67 F with F-MF</u>
Bexarotene, MTX, IFN, topical steroid, excimer

EBT 15 Gy "face technique" => CR, sustained 2+ years

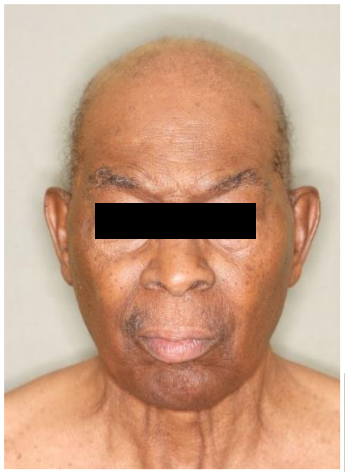


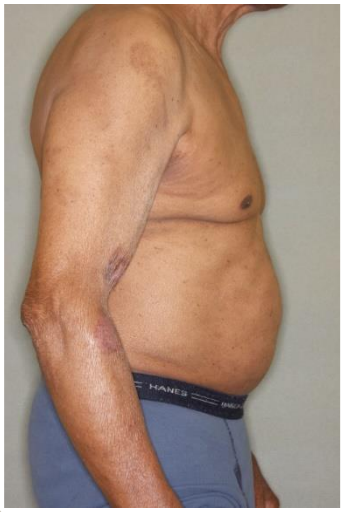
76 M MF IIB with LCT

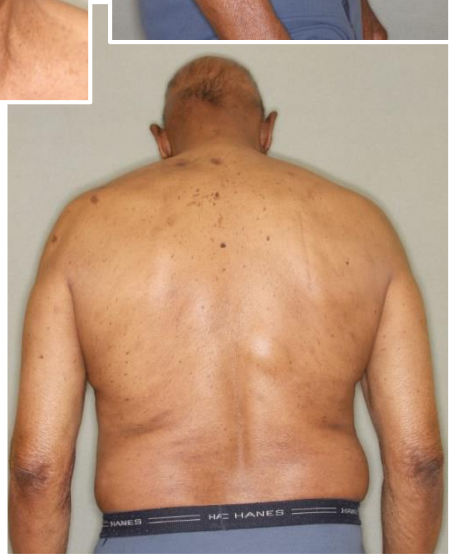


Generalized aggressive tumors

Multiple comorbidites







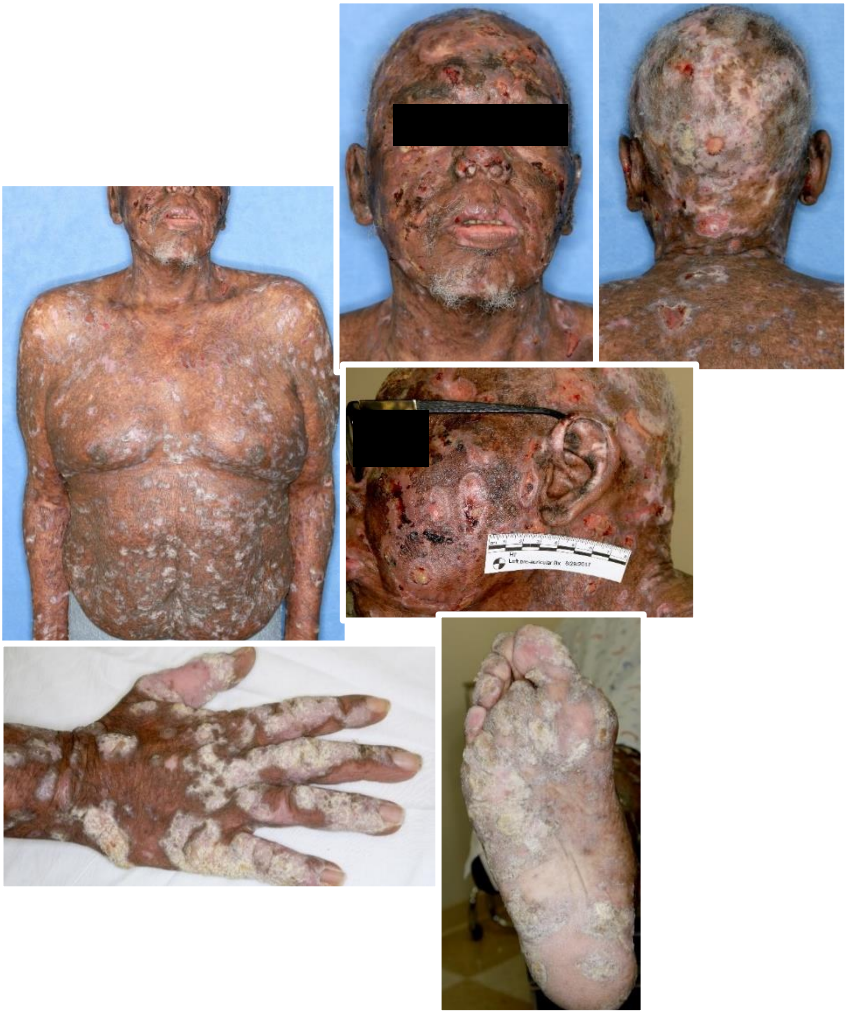
TSEBT 36 Gy => near CR
Low-dose bex + IFN

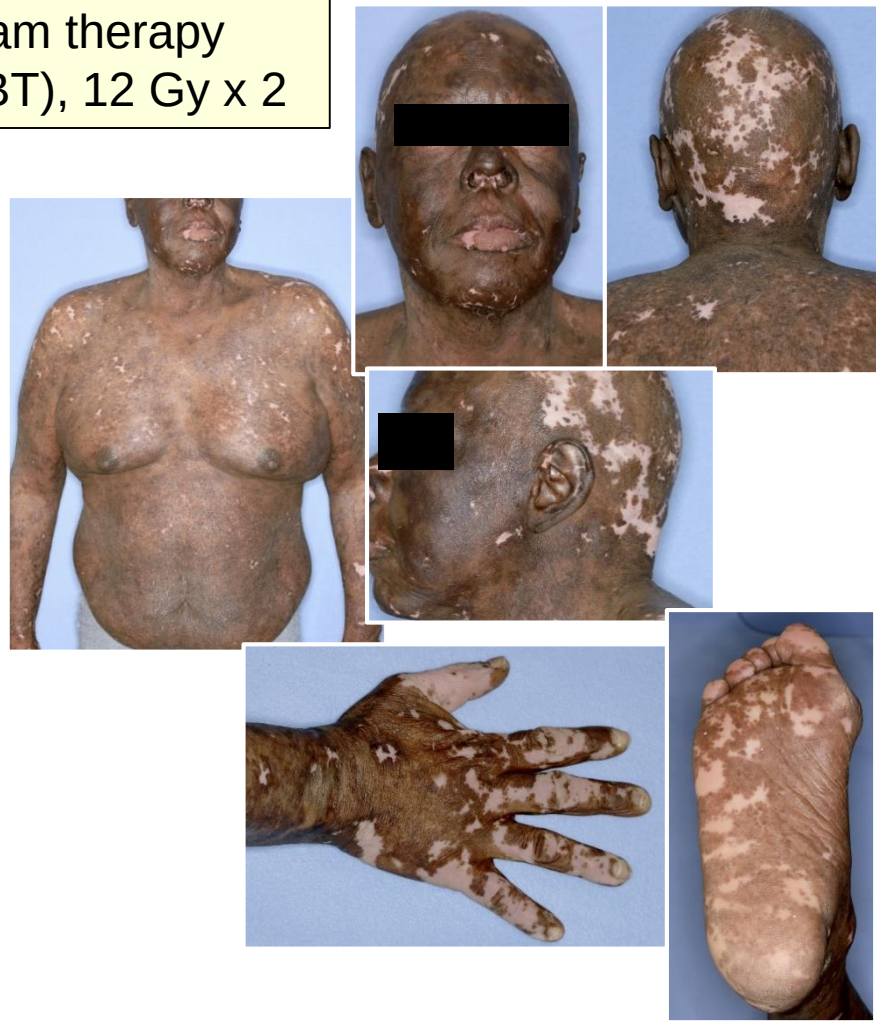
Limited dz x 7+ yrs with Clobetasol and Valchlor gel +/- occ local RT

However, most others need subsequent systemic therapy

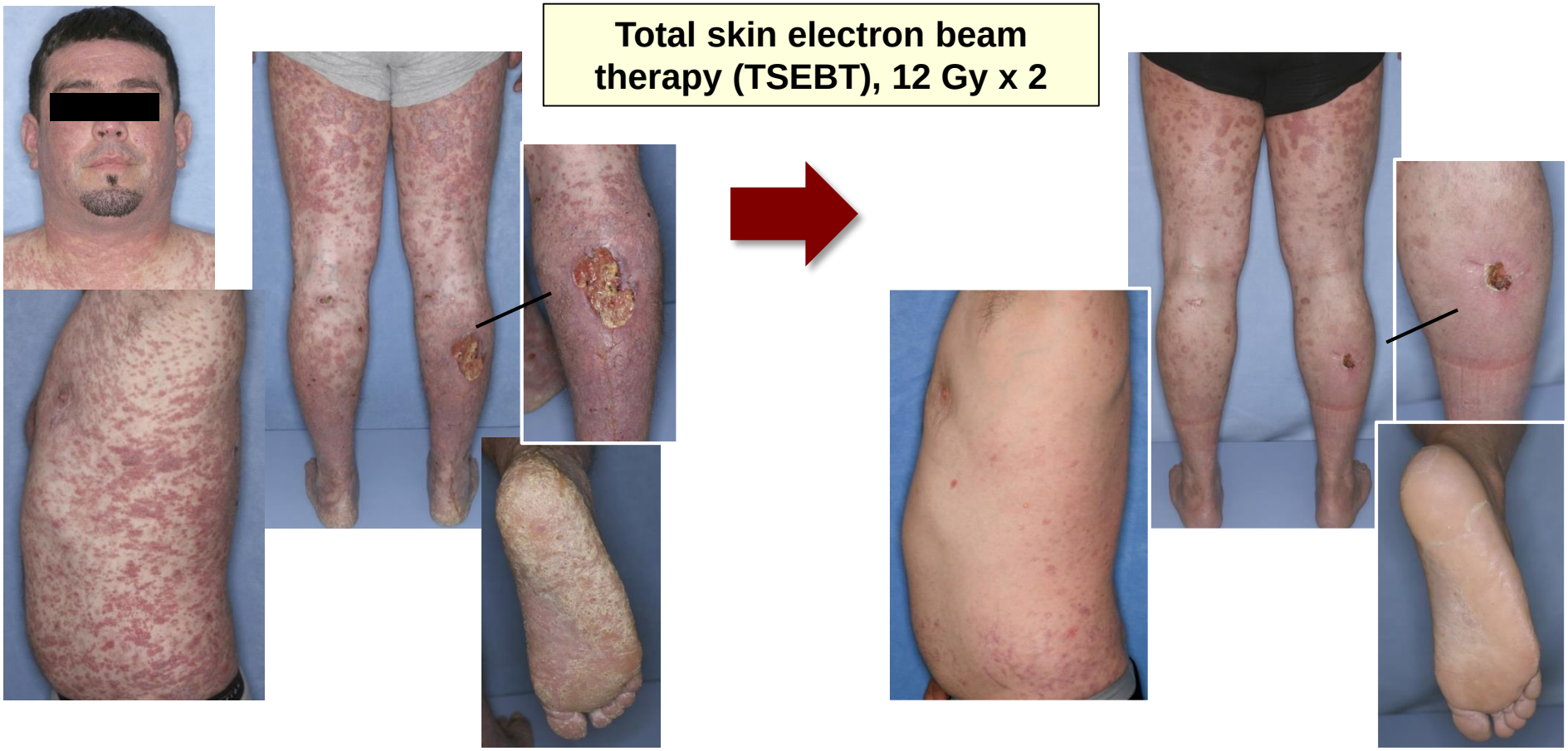
Radiation effective therapy for rapid disease reduction

Total skin electron beam therapy (TSEBT), 12 Gy x 2





Management with lower dose total skin electron beam therapy, followed by milder systemic therapies and/or skin-directed therapies



Low-dose total skin electron beam therapy as an effective modality to reduce disease burden in patients with mycosis fungoides: Results of a pooled analysis from 3 phase-II clinical trials

Richard T. Hoppe, MD,[a] Cameron Harrison, MD,[b] Mahkam Tavallaee, MD, MPH,[b] Sameer Bashey, MD,[b] Uma Sundram, MD, PhD,[b,c] Shufeng Li, MS,[b] Lynn Million, MD,[a] Bouthaina Dabaja, MD,[d] Pamela Gangar, MD,[e] Madeleine Duvic, MD,[e] and Youn H. Kim, MD[b]
Stanford, California, and Houston, Texas

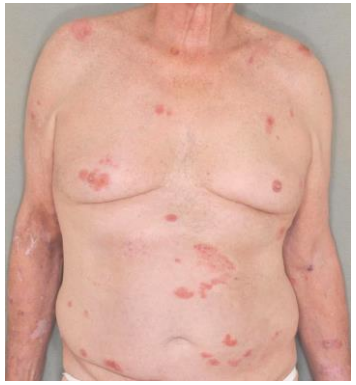
JAAD 2015; 72:286-92

- **Low-dose, 12 Gy (3 wks)** vs. standard, 36 Gy (10 wks)
- **Reliable/efficient reduction** in skin disease => **near 90% ORR, ~30% CR**
- **~ 1.5 yr median duration of benefit**
- **Less side effects:** no permanent hair loss, less skin toxicity
- **Can be given repetitively** in pt's course
- Low-dose can be followed or combined with other therapies to boost response and duration of benefit
- **Great option for folliculotropic disease, generalized thick plaques o indolent tumor disease, esp pts with multiple co-morbidities**

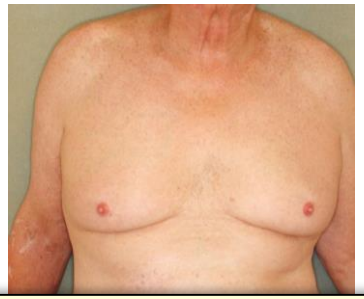
Table II. Best overall response to treatment at study termination, total time to response, and duration of clinical response

Characteristic	n (%)	Response data CR	PR	SD	PD	ORR n (%)
Clinical stage						
All	33 (100)	9 (27)	20 (61)	4 (12)	0	29 (88)
IB	22 (67)	7	13	2	0	20 (91)
IIA	2 (6)	0	2	0	0	2 (100)
IIB	7 (21)	2	4	1	0	6 (96)
IIIA	2 (6)	0	1	1	0	1 (50)
Median time to response (range)		7.6 (3-12.4) wk				
Median duration of clinical benefit		70.7 (41.8-133.8) wk				

Low-dose (12 Gy)
Total Skin EBT
Over 2-3 wks



CR



Combination with immunotherapy trials in progress to improve/prolong clinical response:

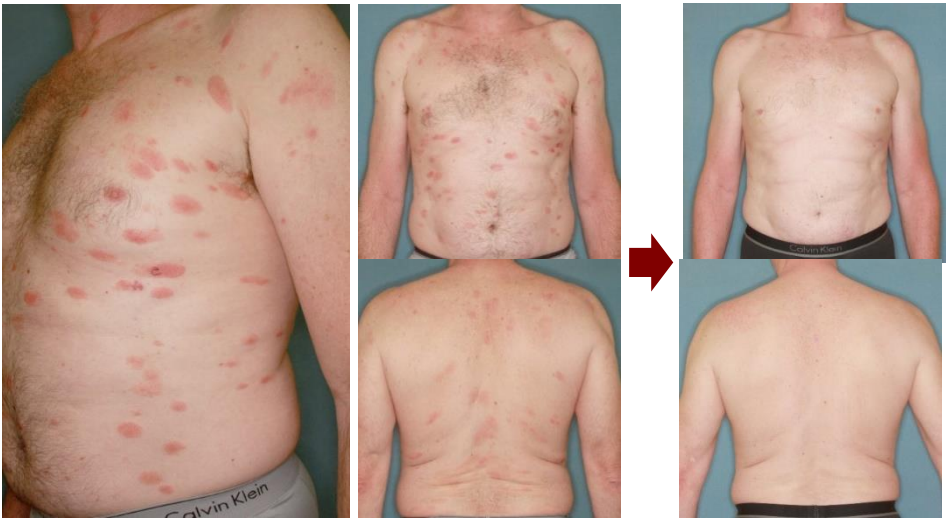
Low-dose TSEBT +
rh-IL-12, IFN-g, checkpoint inhibitors, other

Single-arm phase 2A study of rHu-IL-12 + low-dose TSEBT in MF

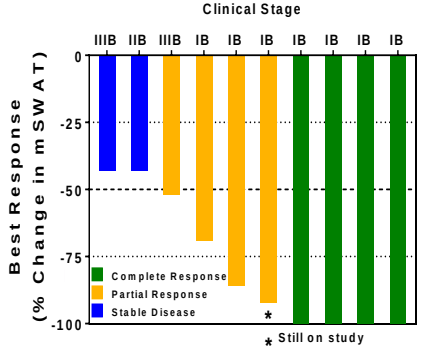
- **Single arm, open-label, non-randomized study for patients with MF**
- **N=10; Clinical Stage IB-IIIB, ≥18 years old**

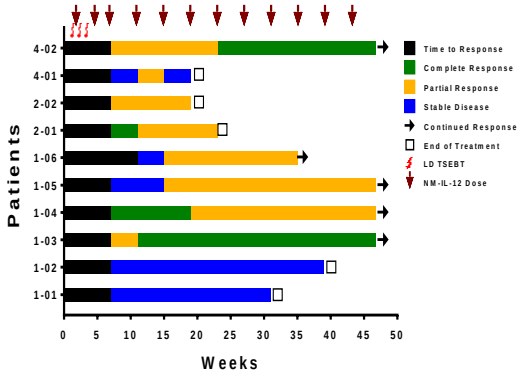
ASH 12/2016
EORTC 10/2017
Kim, Hoppe, Rook Geskin, Neumedicine

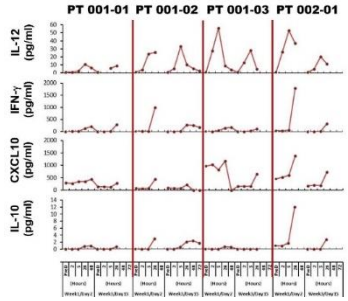
Patient 001-03, 54M with MF, stage IB (plaques), CR confirmed at Week 11
Sustained CR at Week 52, continues to receive treatment q 4 weeks

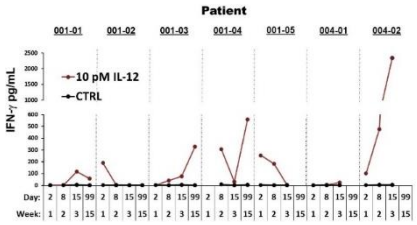


Pre-treatment **LD-TSEBT + IL-12, Week 11**







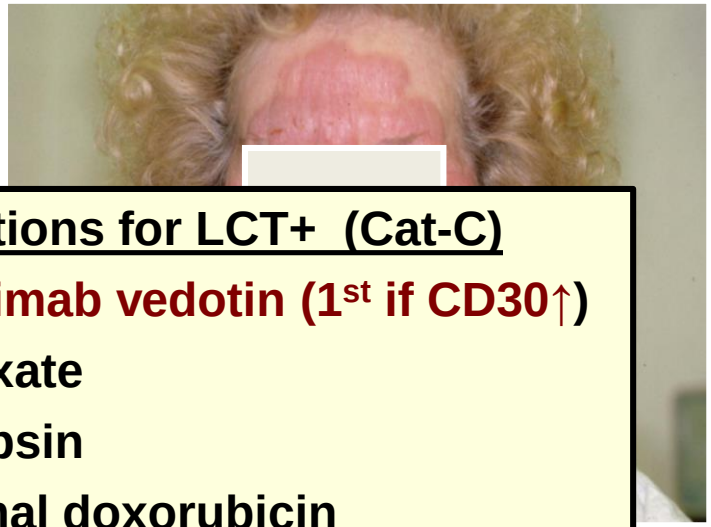


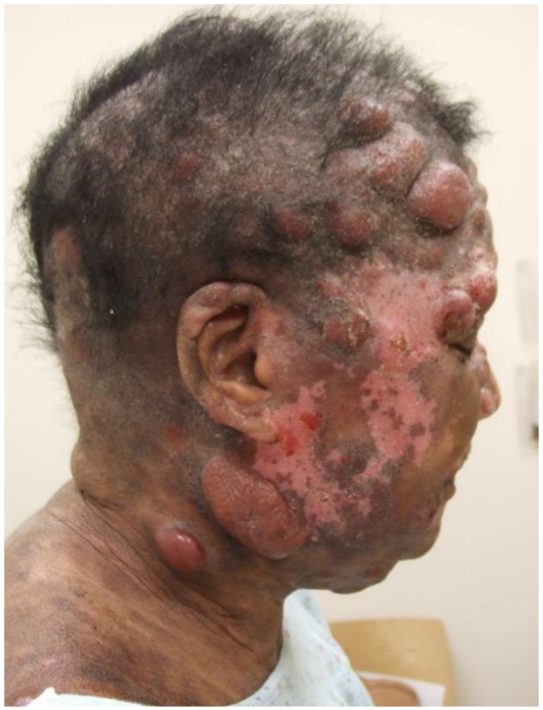
Stage IIB

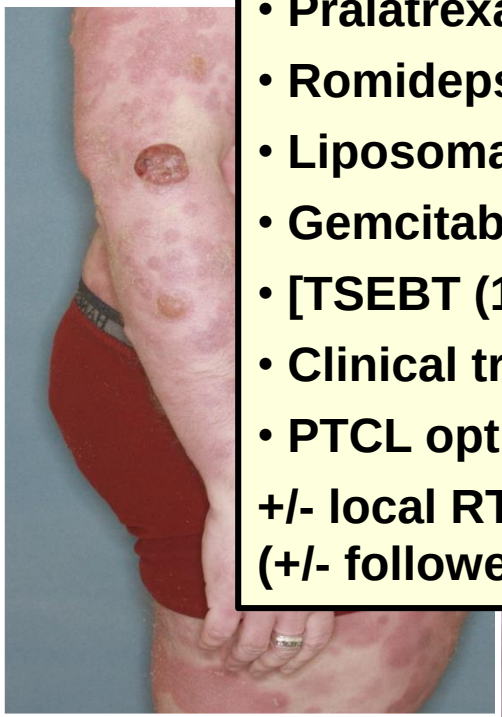
MF w/ large cell transformation with aggressive clinical behavior

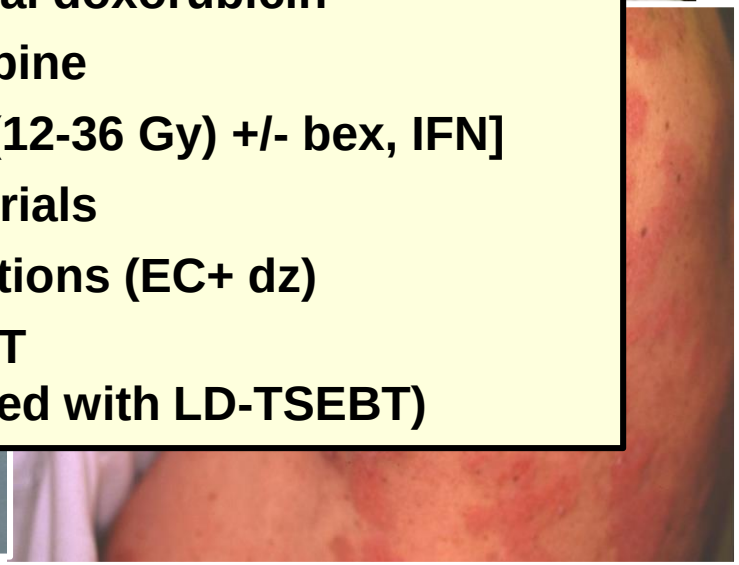
Need therapies with rapid activity

LCT+ treatment options, trials









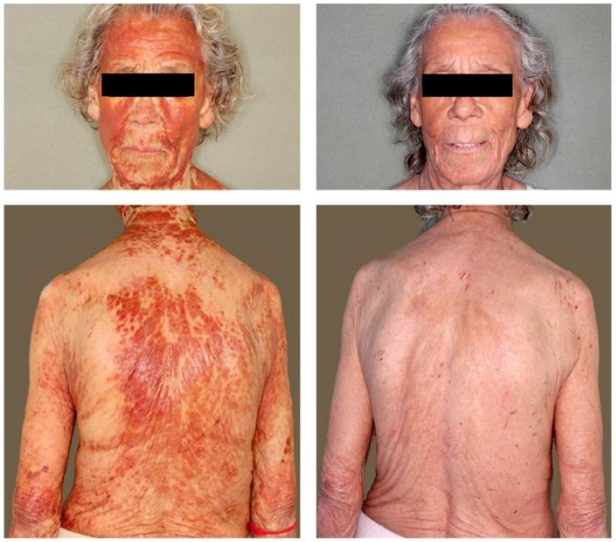
NCCN options for LCT+ (Cat-C)

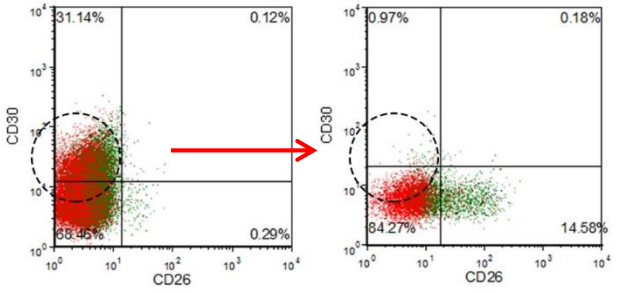
- **Brentuximab vedotin (1st if CD30↑)**
- **Pralatrexate**
- **Romidepsin**
- **Liposomal doxorubicin**
- **Gemcitabine**
- **[TSEBT (12-36 Gy) +/- bex, IFN]**
- **Clinical trials**
- **PTCL options (EC+ dz)**

+/- local RT
(+/- followed with LD-TSEBT)

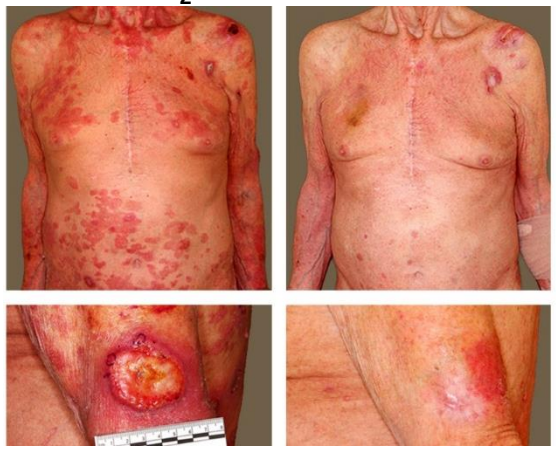
Great clinical response to brentuximab vedotin (BV) in MF/SS

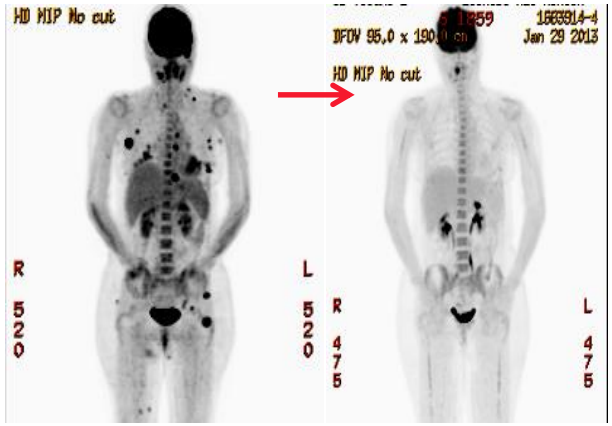
Sézary syndrome, IVA$_1$



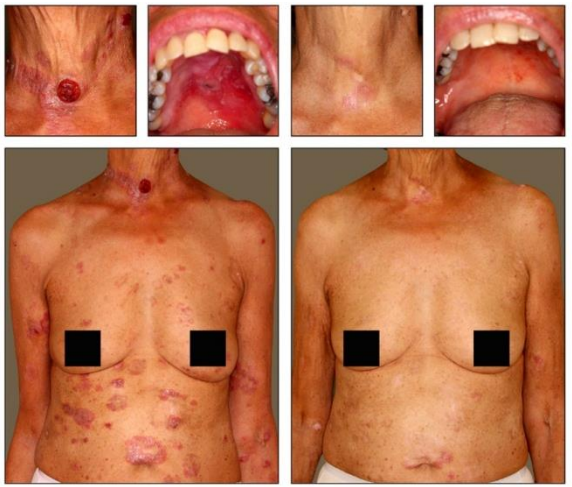


MF IVA$_2$ LN with LCT





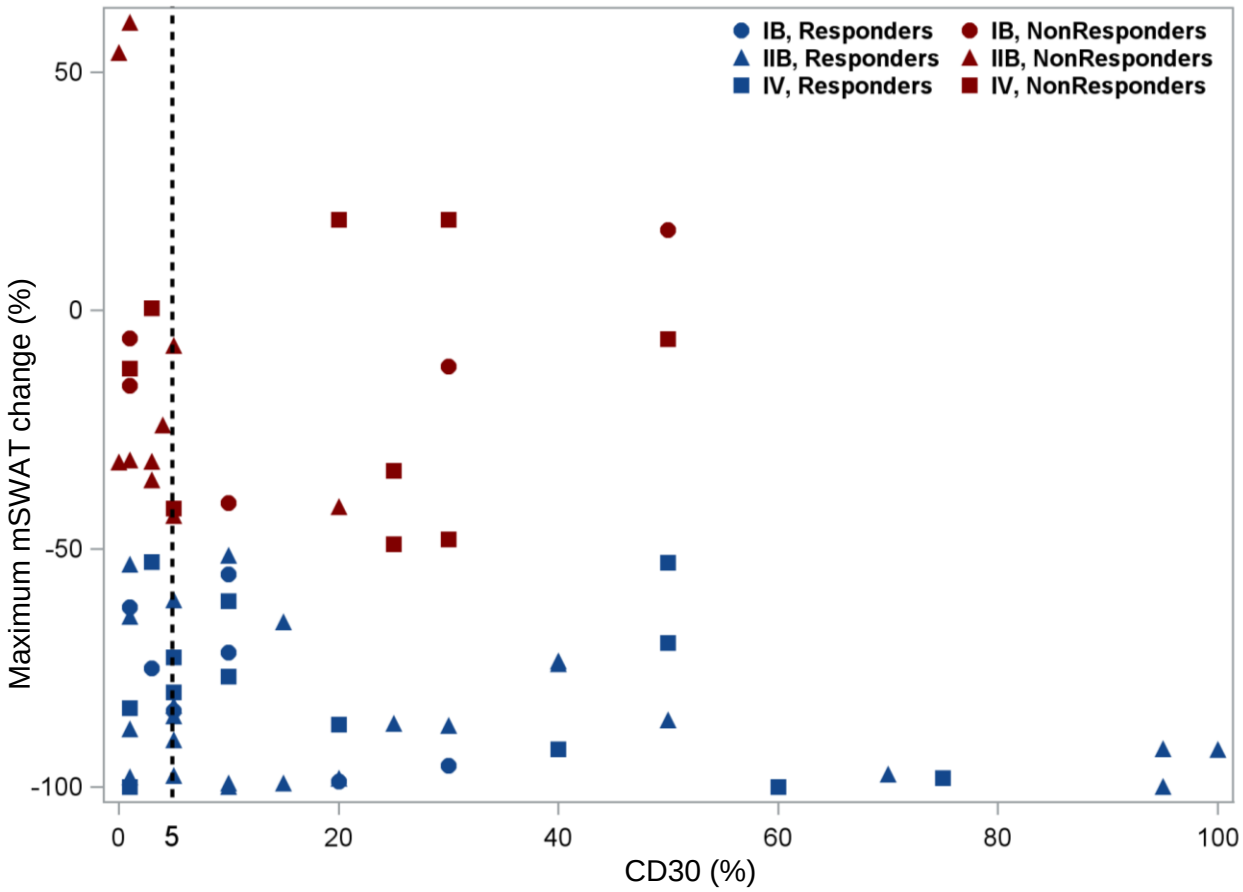
MF IVB with LCT



Kim Y, et al, J Clin Oncol 2015;33:3750

BV demonstrates clinical activity in all compartments

Correlation of skin/global response with tissue CD30 by IHC: Clinical activity observed with all CD30 expression levels

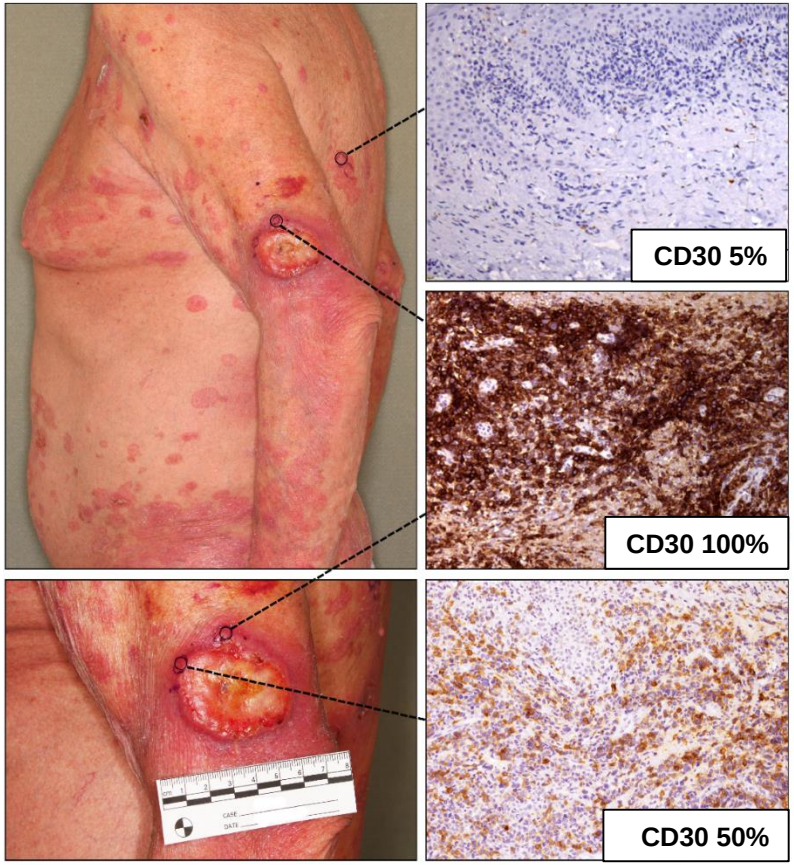


- Global composite response by skin $CD30_{exp}$ ≥5% vs. <5%, 69% vs. 45%, *P = 0.065*
- Skin response (by mSWAT) by skin $CD30_{exp}$ ≥ 5% vs. <5%, 74% vs. 34%, *P = 0.026*
- Median $CD30_{exp}$ in >90% vs. ≤90% mSWAT reduction (20% vs. 8%, *P = 0.018*)
- No difference between in TTR, DOR, and PFS by skin $CD30_{exp}$ ≥5% vs. <5%

Pooled analysis of Stanford/MDACC ISTs
***Huen, Rahbar, et al. in progress; partially presented at SID 2016*
Duvic et al. J Clin Oncol 2015;33:3750
Kim et al. J Clin Oncol 2015;33:3759

Inter- and intra-lesional variability in CD30 expression levels by IHC

Patient examples from Stanford BV IST

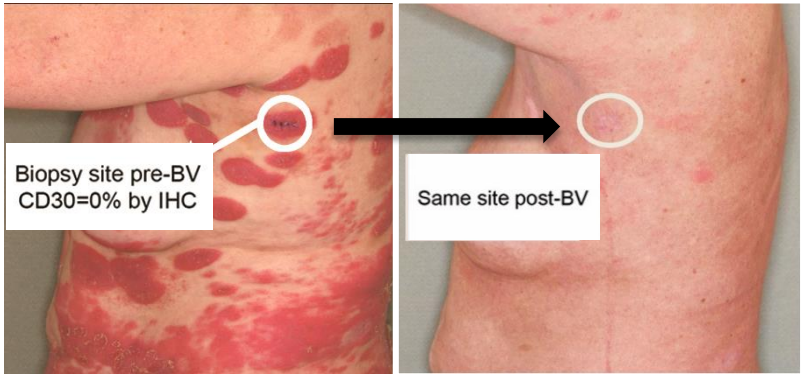


Rahbar et al. J Invest Dermatol., 2017 Dec, Epub ahead of print

MF stage IIB with LCT

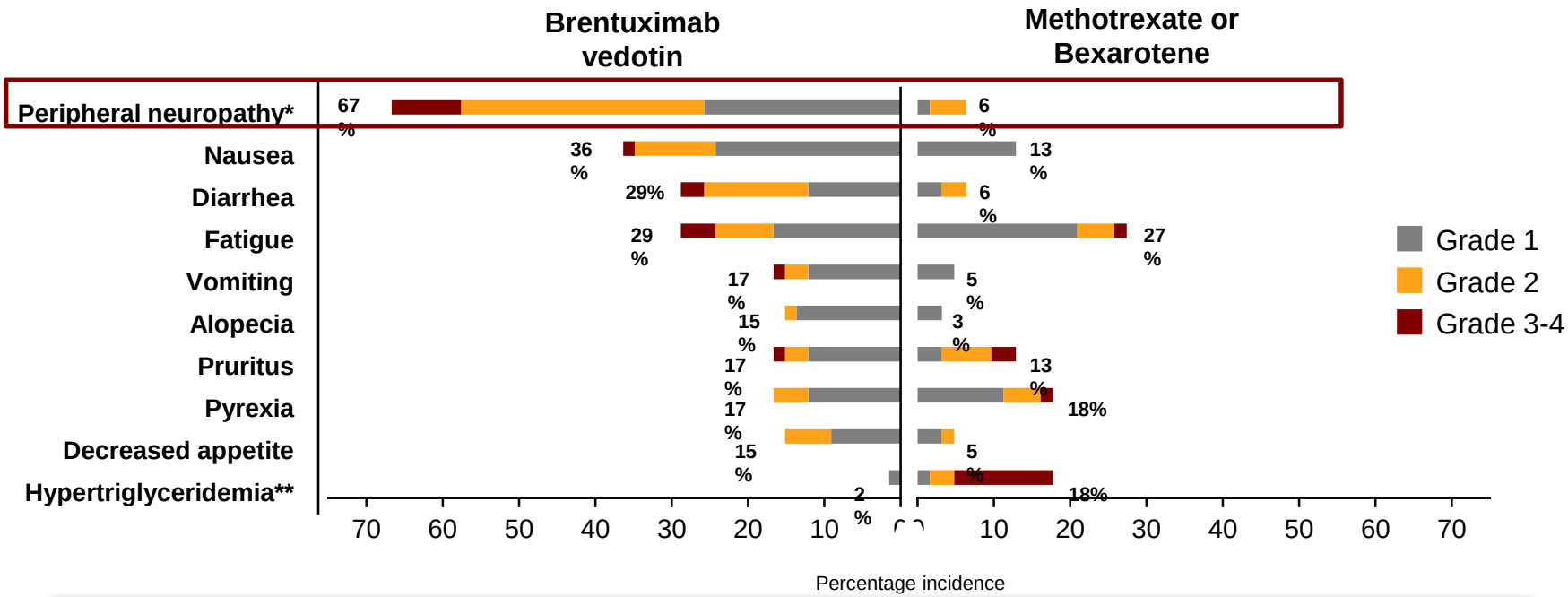
- **Inter-lesional** biopsies:
  Plaque, left back, CD30% = 5%
  Tumour, left arm, CD30% = 100%
- **Intra-lesional** paired biopsies:
  Same tumour lesion, CD30% = 100%, 50%

MF stage IIB with $CD30_{min}$ = 0%



Kim YH, et al. J Clin Oncol 2015;33:3750
Rahbar et al. J Invest Dermatol., Accepted 2017
Stanford SGN-35 IST

ALCANZA: Commonly reported (≥15% of patients) treatment-emergent AEs



BV use in CTCL population:

- **Important to not prolong use of BV to avoid irreversible neuropathy, aim for 6-8 cycles and transition to treatments with better long-term tolerability**
- **Can retreat with disease progression**
- **Explore alternative dose/schedules in MF/SS**

Lancet 390:555-566, 2017

FDA approval 11/2017

Management of non-Sezary, stage IV disease

- **Management based LN dz burden (+/- LCT), visceral disease**

  Cat B or C options

  – Single agents “more intensive”: brentuximab, pralatrexate, romidepsin, liposomal doxorubicin, gemcitabine; etoposide

  – Multi-agent chemotherapy/PTCL-NOS for high-burden LN dz or visceral dz, especially if followed by allo HSCT

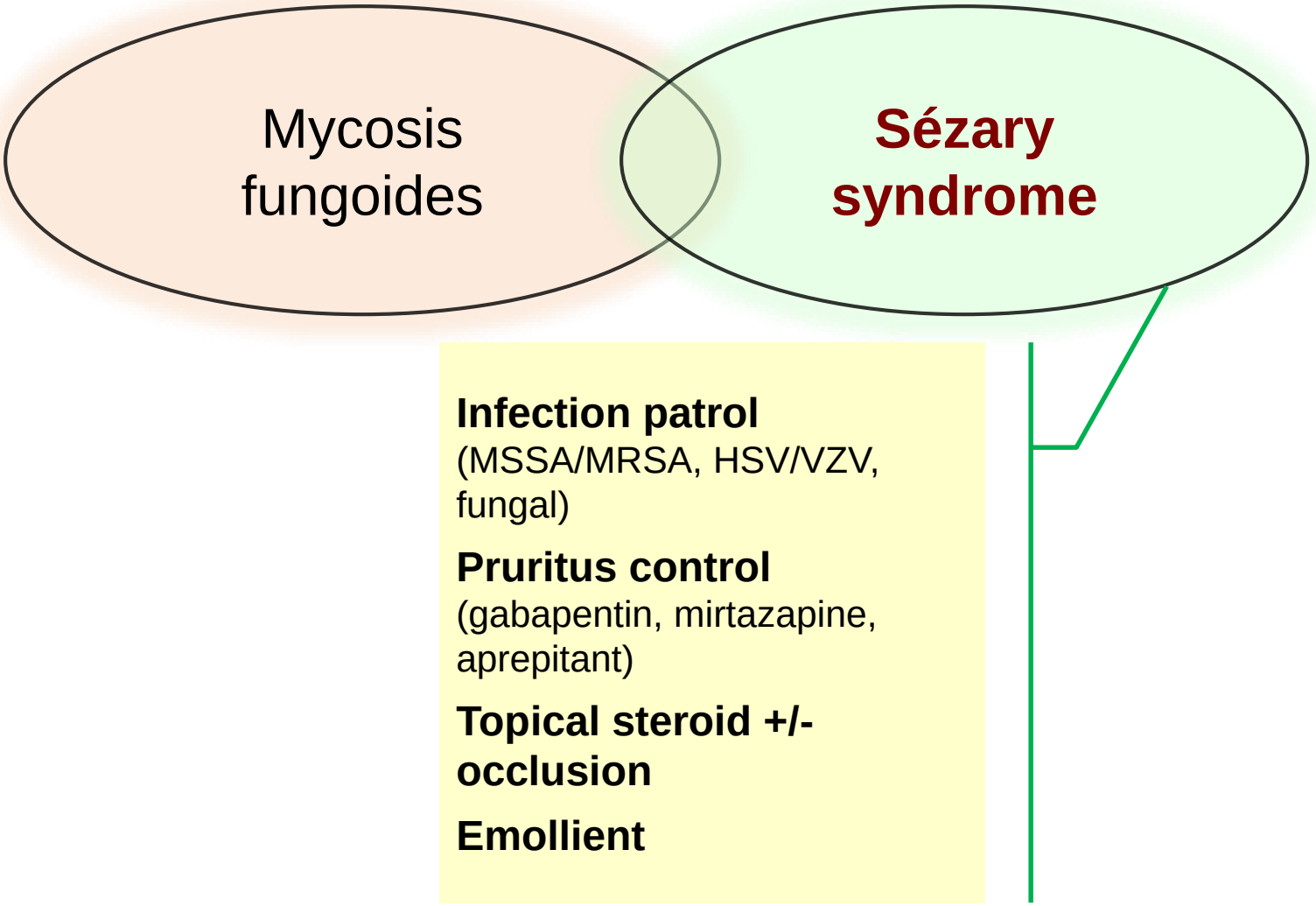
  – Clinical trials

  – RT for local control

  – **Consider allo HSCT**

Category B or C (intensive tx)
- Brentuximab vedotin
- Pralatrexate (15-30 mg/m2)
- HDAC-i (romidepsin)
- Liposomal doxorubicin
- Gemcitabine
- Other single agents
- Clinical trial
- Options for PTCL-NOS

Importance of supportive management in Sezary syndrome



Clinical activity of systemic agents in Sezary Syndrome

Agent	N	ORR	DOR	comments
Bexarotene	17	24% (no CR)	ND	Phase 2-3 single arm
Photopheresis+, varying regimen	70 (>1 study)	20-89% (0-29% CR)	ND	Mostly retrospective studies
Vorinostat	30	33% (no CR)	6+ mo	Pivotal single arm
Romidepsin	13	31% (no CR)	> 1 year	Pivotal single arm
Methotrexate	10	50% (30% CR)	>1 year	Retrospective study
Chlorambucil	26	88%	ND	Retrospective study
Gemcitabine	11	73%	4 mo	Phase 2 single arm
Alemtuzumab, varying regimen	14/17	86%/82%	6 mo (n=17)	Phase 2 single arm Median OS 35 mo (n=14)
Mogamulizumab, phase 3 RCT	81	37%	17 mo	Largest RCT, PFS as primary; blood response in 83/122 (68%)
Pembrolizumab	15	27% (7% CR)	> 1 year	Phase 2 single arm

Brentuximab, ALCANZA RCT excluded SS; activity reported in ISTs

Management of Sezary Syndrome, B2/stage IV

- **Stratification based on blood Sézary burden and LN status**
- Given risk for staph sepsis, utilize agents that spare further immune dysfunction, importance of supportive care
- **Low-intermediate Sezary burden (spare immune syster**
  - "Milder" Cat-A systemic therapies: biologics (bexarotene, photopheresis, interferon), HDAC-I, methotrexate
  - Mogamulizumab pending FDA approval
- **High Sezary burden (>5-10K/mm^3) (need fast working)**
  - Romidepsin +/- TSEBT
  - Combination biologics (e.g., photopheresis+, bex + IFN)
  - Alemtuzumab (low-dose sc, 3-10 mg short courses)
  - Clinical trials (mogamulizumab pending FDA approval)
- Refractory disease
  - Alemtuzumab
  - Pralatrexate, brentuximab (if CD30+), bortez, pembrolizumab
  - Chlorambucil, other TCL options
  - Clinical trials

1st line, choice by blood-burden

single or combination therapy

- Retinoids
- IFNs
- HDAC-i
- Methotrexate (25-35 mg)
- Photopheresis (if >B0)
- *Mogamulizumab pending FDA approval*

+/- skin-directed option

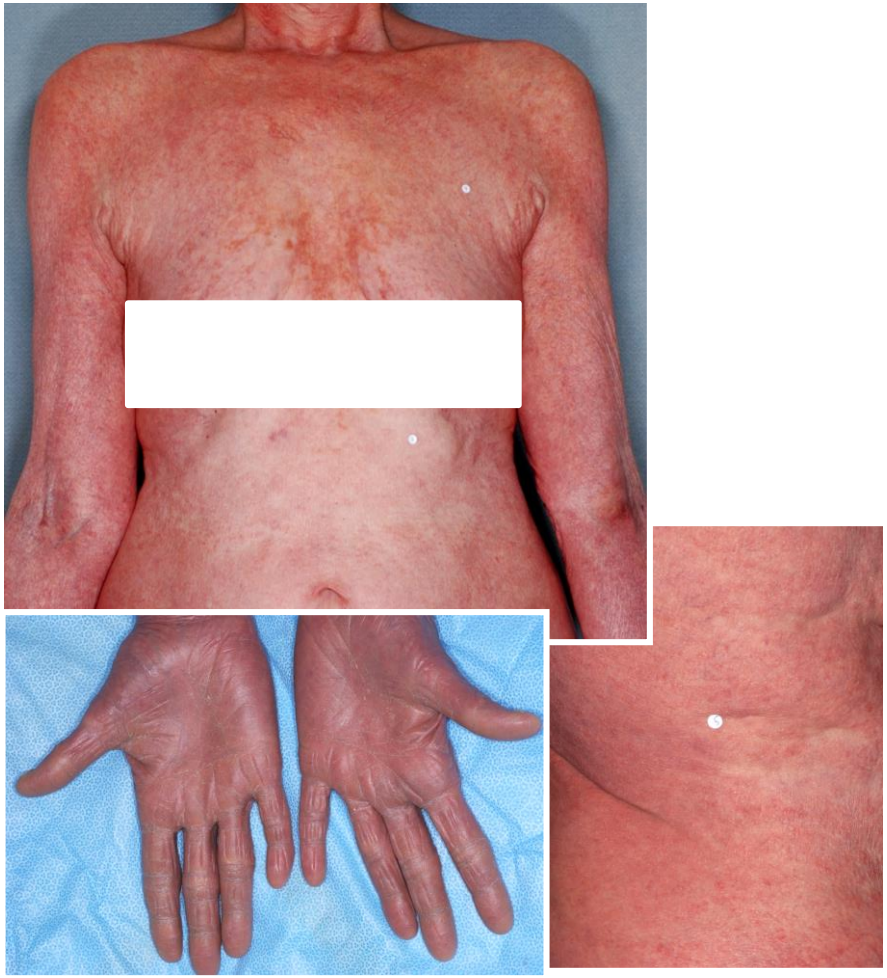
2nd line

- Alemtuzumab
- Pralatrexate
- Pembrolizumab
- Bortezomib
- Brentuximab (if SC CD30+)
- Clinical trials
- Other TCL options

Consider Allo HSCT

63 F with Sezary syndrome, stage IVA_1 (T4NxM0B2) with low Sezary burden

Consider safety and spare immune function



⇒ PB flow showed expanded CD4+ T cells, CD4+CD26- 65% of lymphs, abs cnt of 1,270 /mm3

⇒ **ECP + IFNa** => PR in blood, SD in skin

⇒ Added **bexarotene** => PR, but lipid problems

⇒ **MTX** => PD in blood and skin; reactive LNs

Blood ↑CD4+CD6- 90%, abs cnt 4,500 /mm3

⇒ **CR with mogamulizumab (anti-CCR4 mAb) x 3 years**

Relapse in skin and blood

⇒ Bex + IFN => PR x 6 mo,

⇒ **Romidepsin** => global PR but tolerability problem

⇒ **Anti-KIR3DL2 mAb** => near CR

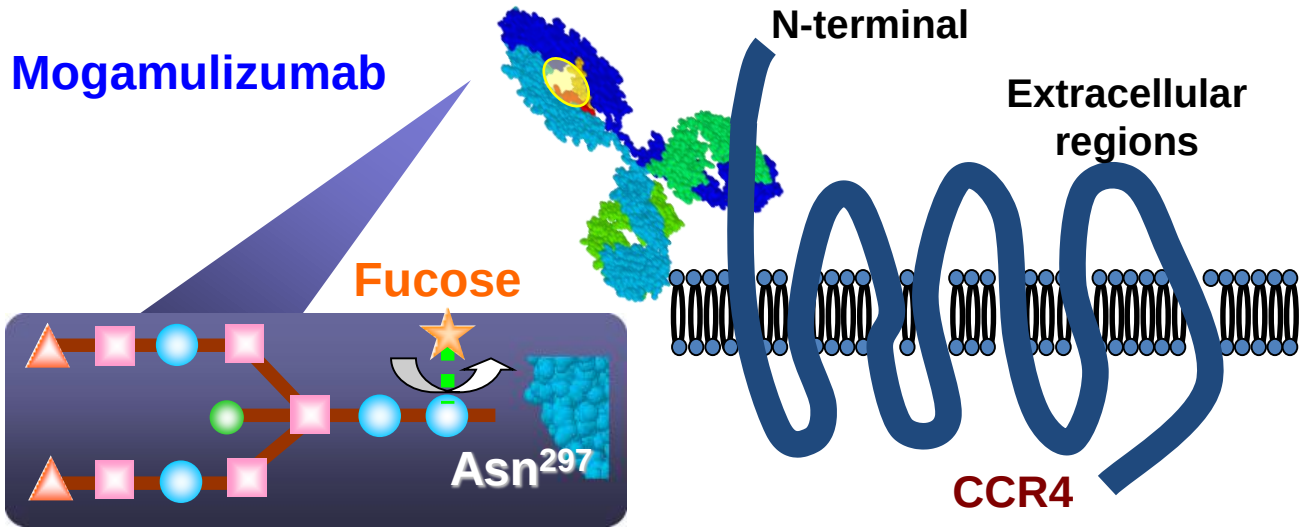
Supportive care:
Topical steroids
Oral anti-itch meds
antimicrobials (staph aureus)

Anti-CCR4 Monoclonal Antibody, Mogamulizumab, Demonstrates Significant Improvement in PFS Compared to Vorinostat in Patients with Previously Treated Cutaneous T-Cell Lymphoma: Results from the Phase 3 MAVORIC Study

Youn H. Kim, MD[1]; Martine Bagot, MD[2]; Lauren Pinter-Brown, MD[3]; Alain H. Rook, MD[4]; Pierluigi Porcu, MD[5]; Steven Horwitz, MD[6]; Sean Whittaker, MD[7]; Yoshiki Tokura, MD, PhD[8]; Maarten Vermeer, MD[9]; Pier Luigi Zinzani, MD[10]; Lubomir Sokol, MD, PhD[11]; Stephen Morris, MD[7]; Ellen J. Kim, MD[4]; Pablo L. Ortiz-Romero, MD[12]; Herbert Eradat, MD[13]; Julia Scarisbrick, MBChB, FRCP, MD[14]; Athanasios Tsianakas, MD[15]; Craig Elmets, MD[16]; Stephane Dalle, MD, PhD[17]; David Fisher, MD, PhD[18]; Ahmad Halwani, MD[19]; Brian Poligone, MD, PhD[20]; John Greer, MD[21]; Maria Teresa Fierro, MD[22]; Amit Khot, MD[23]; Alison J. Moskowitz, MD[6]; Karen Dwyer[24]; Junji Moriya[24]; Jeffrey Humphrey, MD[24]; Stacie Hudgens[25]; Dmitri O. Grebennik[24]; Kensei Tobinai, MD, PhD[26]; Madeleine Duvic, MD[27] for the MAVORIC Investigators

[1]Stanford University, Stanford, CA, USA; [2]Hôpital Saint Louis, APHP, Inserm U976, Université Paris 7, France; [3]University of California Irvine, Orange, CA, USA; [4]University of Pennsylvania, Philadelphia, PA, USA; [5]Thomas Jefferson University, Philadelphia, PA, USA; [6]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [7]Guy's and St Thomas' Hospital, London, UK; [8]Hamamatsu University School of Medicine, Hamamatsu, Japan; [9]Leiden University, Leiden, The Netherlands; [10]Institute of Hematology "Seràgnoli," University of Bologna, Bologna Italy; [11]Moffitt Cancer Center, Tampa, FL, USA; [12]Department of Dermatology, Institute i+12, Hospital 12 de Octubre Medical School, University Complutense Madrid; [13]UCLA Medical Center, Santa Monica, CA, USA; [14]University Hospital Birmingham, Birmingham, UK; [15]University Hospital Münster, Münster, Germany; [16]University of Alabama, Birmingham, AL, USA; [17]Hospices Civils de Lyon, Claude Bernard Lyon 1 University, Lyon, France; [18]Dana-Farber Cancer Institute, Boston, MA, USA; [19]University of Utah, Salt Lake City, UT, USA; [20]Rochester Skin Lymphoma Center, Fairport, NY, USA; [21]Vanderbilt University Medical Center, Nashville, TN, USA; [22]University of Turin, Turin, Italy; [23]Peter MacCallum Cancer Centre, Melbourne, Australia; [24]Kyowa Kirin Pharmaceutical Development, Inc., Princeton, NJ, USA; [25]Clinical Outcome Solutions, Tucson, AZ, USA; [26]National Cancer Center Hospital, Chuo-ku, Tokyo, Japan; [27]University of Texas MD Anderson Cancer Center, Houston, TX, USA.

Mogamulizumab: *First-in-class defucosylated humanized anti-CCR4 mAb*



Higher ADCC due to a defucosylated Fc region by POTELLIGENT®[1-3]

GPCR for MDC and TARC[4]
Markers for Type II helper T cells and regulatory T cells (FoxP3+)[5]
Involved in lymphocyte trafficking to skin[6]
Over-expressed in ATL, PTCL, and CTCL[4,7]

ADCC, antibody-dependent cellular cytotoxicity; Fc, fragment crystallizable; GPCR, G-protein-coupled receptor; MDC, macrophage derived chemokine; TARC, thymus -and activation-regulated chemokine.

1. Shinkawa et al. J Biol Chem 2003;278:3466.
2. Ishii et al. Clin Cancer Res 2010;16:1520.
3. Niwa et al. Cancer Res 2004;64:2127.
4. Ishida et al. Clin Cancer Res 2004;10:5494.
5. Ishida et al. Cancer Res 2006;66:5716-22.
6. Campbell et al. Nature 1999;400:776.
7. Ni et al. Clin Cancer Res 2015;21:274.

Response outcomes

	Mogamulizumab	Vorinostat
ORR[a,b], n/N (%)	**52/186 (28)**	**9/186 (5)**
MF[c]	**22/105 (21)**	**7/99 (7)**
SS[b]	**30/81 (37)**	**2/87 (2)**
Stage IB/IIA	7/36 (19)	5/49 (10)
Stage IIB	5/32 (16)	1/23 (4)
Stage III	5/22 (23)	0/16 (0)
Stage IV	35/96 (36)	3/98 (3)
DOR, median, months	**14**	**9**
MF	13 (n=22)	9 (n=7)
SS	17 (n=30)	7 (n=2)
ORR[a] n/N (%) mogamulizumab after crossover	**41/136 (30)**	

[a]ORR is the percentage of patients with confirmed CR or confirmed PR; [b]P<0.0001; [c]P=0.004.

- Median relative dose intensities for mogamulizumab were 97.5% and for vorinostat was 95.1%

ORR=overall response rate; DOR=duration of response.

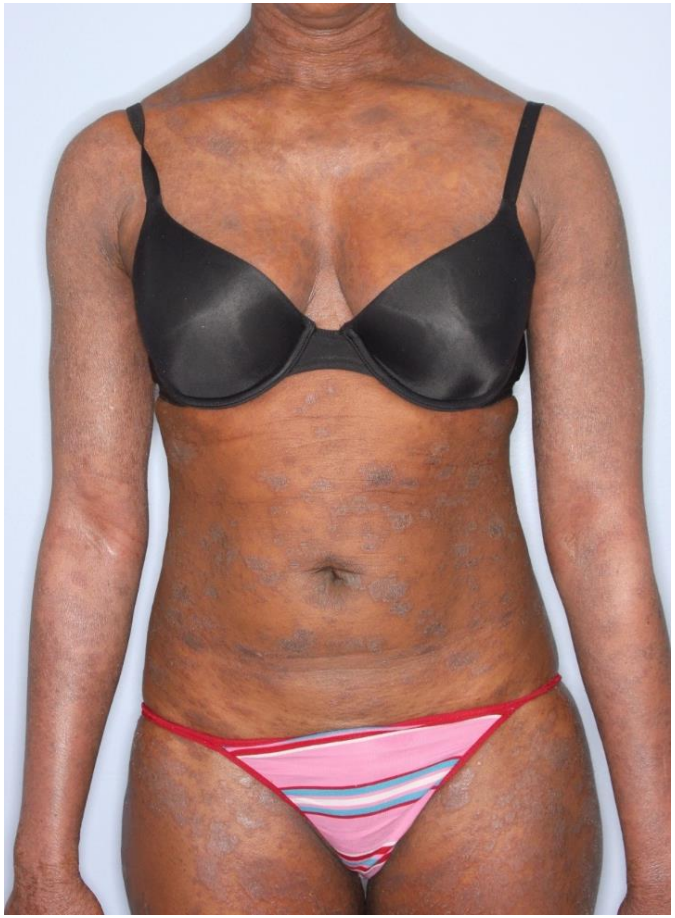
Clinical activity by compartment

	Mogamulizumab	Vorinostat
Compartment response rate (confirmed), n/N[a] (%)		
Skin		
ORR (CR+PR)	78/186 (42)	29/186 (16)
CR	8 (4)	1 (1)
Blood		
ORR (CR+PR)	**83/122 (68)**	23/123 (19)
CR	**54 (44)**	5 (4)
Lymph nodes		
ORR (CR+PR)	21/124 (17)	5/122 (4)
CR	10 (8)	2 (2)
Viscera		
ORR (CR+PR)	0/3 (0)	0/3 (0)
CR	0	0

[a]Denominator includes patients with compartmental disease at baseline

ORR=overall response rate; CR=complete response; PR=partial response.

37 AA F >7 yr h/o “atopic dermatitis” treated with phototherapy/steroids => Sezary syndrome, stage IVA2 (N3, no LCT), higher blood Sezary burden



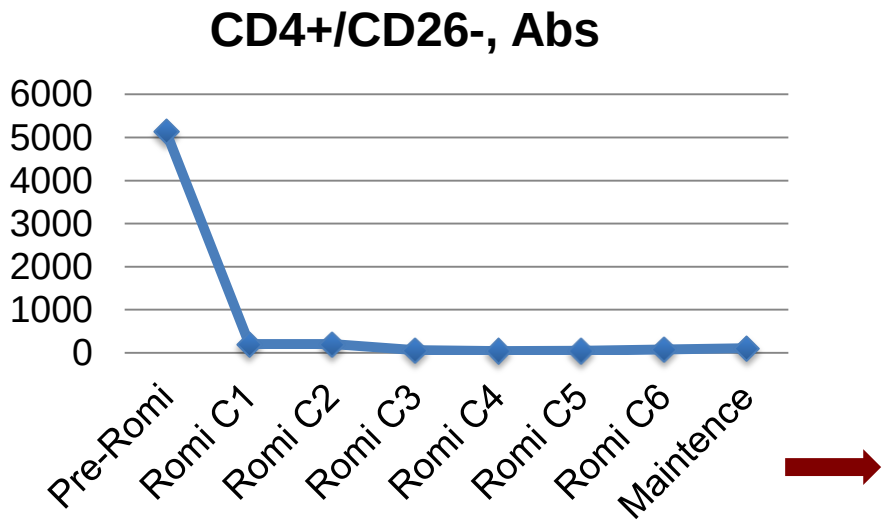
- PET/CT
  - Multiple PET avid LAD
  - Bx revealed LN4, N3
- Sezary flow (higher SC burden)
  - CD4+/CD26- 95%, 7000+ SCs, B2

Treatment options for higher SC

- Bex/retinoids +/- IFN
- Photopheresis + IFN, bex
- Anti-folates (pralatrexate)
- HDAC inhibitors (romidepsin)
- Liposomal doxorubicin
- Brentuximab vedotin (if SC CD30+)
- *Mogamulizumab (pending FDA)*
- Clinical trials

=> Consider allogeneic HSCT

37 AA F Sezary sydrome, stage IVA2
Romidepsin 6 cycles => near global CR (skin near CR, blood CR)
No donor available for allo-HSCT

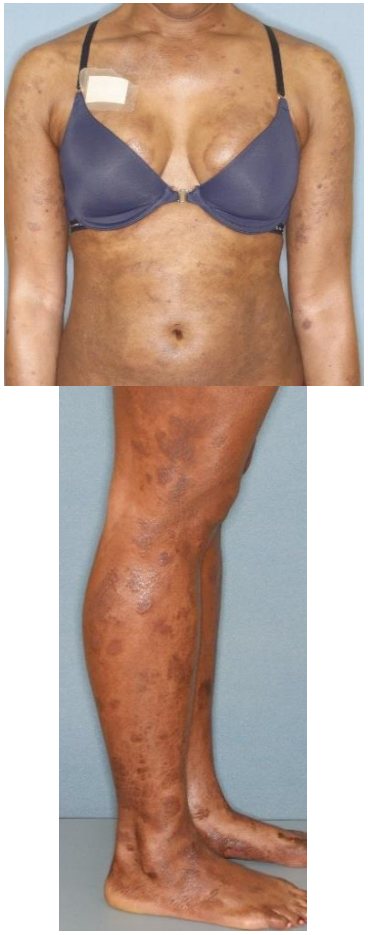


Global PR (near CR):
CR/Blood at C3D1, PR/Skin at C4D1, CR/LN at C7D1, then q 2 wks maintenance schedule, worsening dz

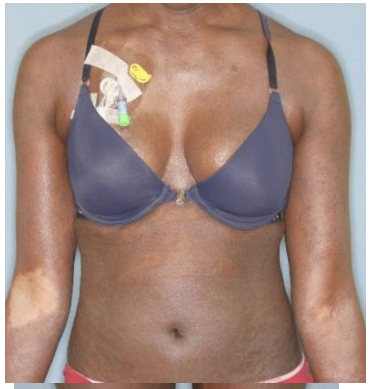
Ongoing donor search for allo-HSCT
Transitioned to anti-PD-1 mab clinical trial

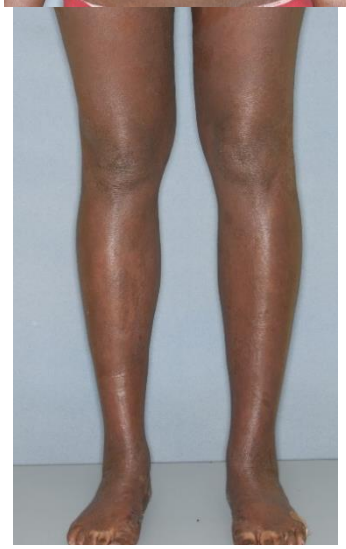
Pembrolizumab: 37 yo AA F with Sézary syndrome, stage IVA_2, global CR

(h/o phototherapy, romidepsin)

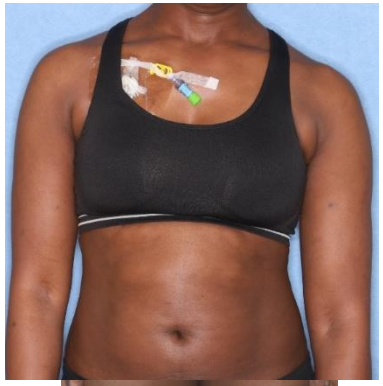


Baseline

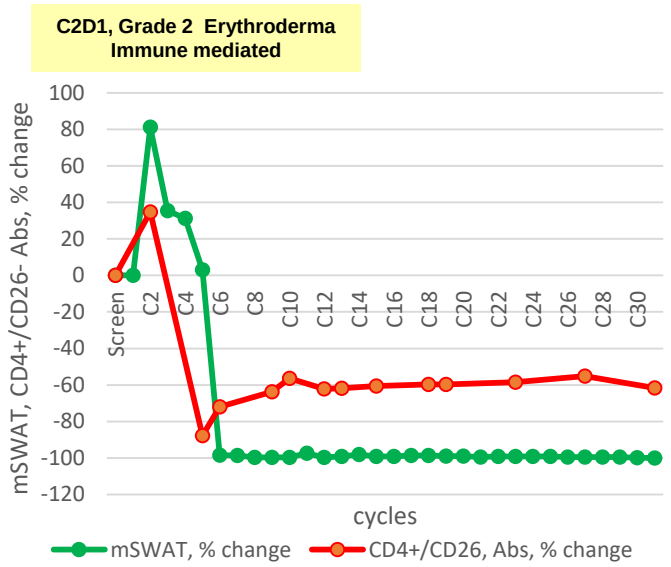




Immune mediated flare Gr 2 erythroderma



C31D1



Global PR C6 => CR

(Skin/PR C6D1, Blood/CR C5D1, LN/CR C12D1)

C2D1: skin/blood worsened with immune mediated flare

SU # 110-41-004

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Final Results From a Multicenter, International, Pivotal Study of Romidepsin in Refractory Cutaneous T-Cell Lymphoma

Sean J. Whittaker, Marie-France Demierre, Ellen J. Kim, Alain H. Rook, Adam Lerner, Madeleine Duvic, Julia Scarisbrick, Sunil Reddy, Tadeusz Robak, Jürgen C. Becker, Alexey Samtsov, William McCulloch, and Youn H. Kim

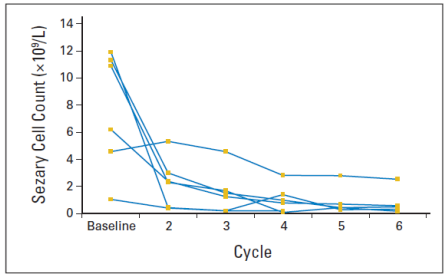
J Clin Oncol 2010;28:4485

Phase II Multi-Institutional Trial of the Histone Deacetylase Inhibitor Romidepsin As Monotherapy for Patients With Cutaneous T-Cell Lymphoma

J Clin Oncol 2009;27:5410

Richard L. Piekarz, Robin Frye, Maria Turner, John J. Wright, Steven L. Allen, Mark H. Kirschbaum, Jasmine Zain, H. Miles Prince, John P. Leonard, Larisa J. Geskin, Craig Reeder, David Joske, William D. Figg, Erin R. Gardner, Seth M. Steinberg, Elaine S. Jaffe, Maryalice Stetler-Stevenson, Stephen Lade, A. Tito Fojo, and Susan E. Bates

	Pivotal study		NCI study	
	As-treated N = 96	Evaluable N = 72	As-treated N = 71	Evaluable N = 63
ORR, n (%)	33 (34%)	30 (42%)	25 (35%)	25 (40%)
95% CI	[25, 45]	[30, 54]	[25, 49]	[28, 53]
CCR, n (%)	6 (6%)	6 (8%)	4 (6%)	4 (6%)



Rapid and sustained blood Sez cell response

Great option for Sézary syndrome

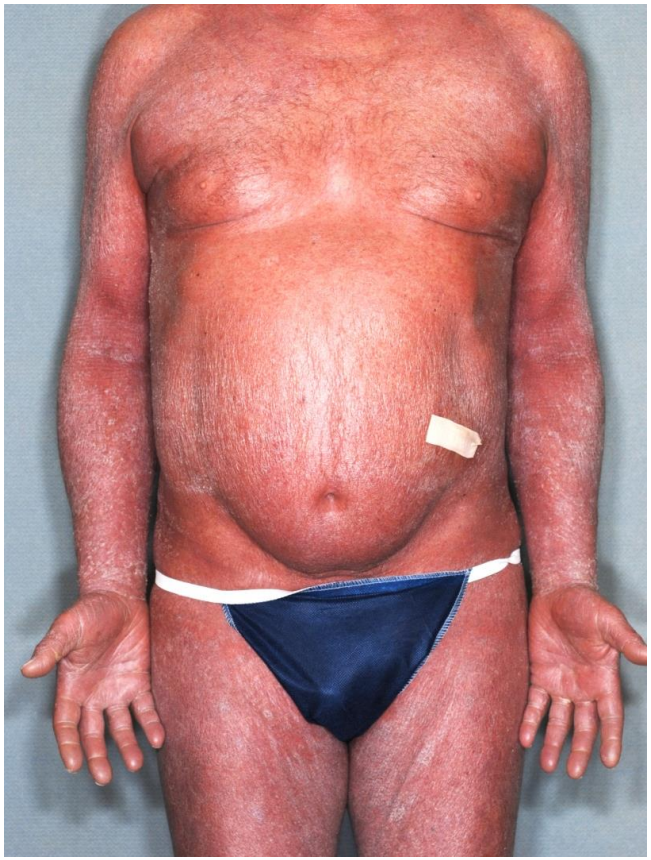
Romidepsin administration
14 mg/m² IV D1, 8, 15 of 28d cycle

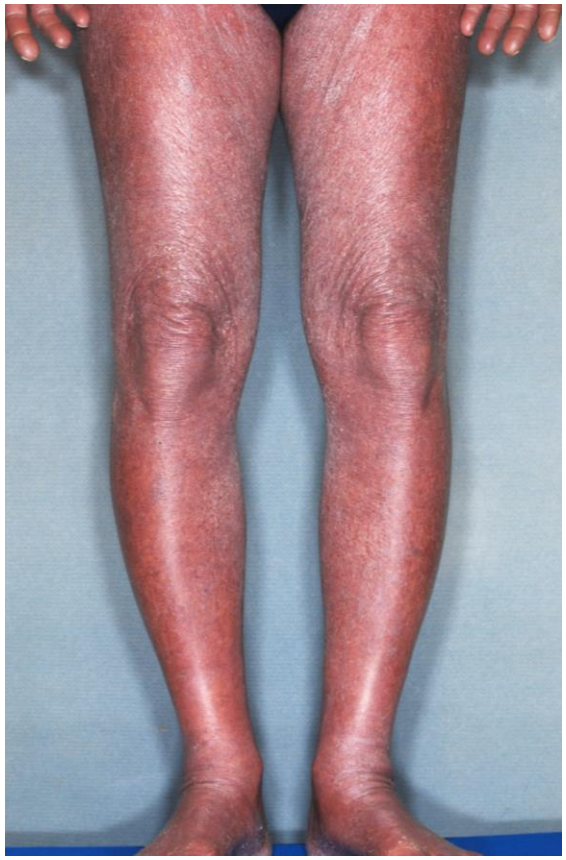
Table 2. Disease Response

Response	All Patients (N = 96) No.	%	95% CI
ORR (CR + PR)	33	34	25 to 45
CR	6	6	2 to 13
PR	27	28	19 to 38
SD	45	47	37 to 57
PD	10	10	5 to 18
Stage IB and IIA (n = 28)			
ORR	7	25	
CR	1	4	
Stage IIB (n = 21)			
ORR	9	43	
CR	2	10	
Stage III (n = 23)			
ORR	9	39	
CR	1	4	
Stage IVA (n = 24)			
ORR	8	33	
CR	2	8	
Stage IIB to IVA (n = 68)			
ORR	26	38	
CR	5	7	
ORR in patients with blood involvement (n = 37)	12	32	
Duration of response (OR; n = 33), months*			
Median	15.0		
Range	0.0+-19.8+		
TTR (OR; n = 33), months			
Median	2.0		
Range	0.9-4.8		
TTR (CR; n = 6), months			
Median	4		
Range	0.9-6.9		
TTP (n = 33), months			
Median	8		
Range	0+-21.7+		

Romidepsin FDA approval 11/2009
Single-arm studies

Sézary syndrome with thick skin involvement, LN (N3, LCT+), and blood compartments (high Sézary burden, >10,000 per mm^3), stage IVA_2 failed biologic combinations (ECP+, Bex + IFN), MTX + IFN, mogamulizumab





Treatment options: high SC

- **HDAC inhibitors (romidepsin)**
- **Pralatrexate**
- **Gemcitabine**
- **Liposomal doxorubicin**
- **Brentuximab vedotin**
- **PTCL NOS regimens**
- **Clinical trials (pembro+, E7777, PI3K+, other)**

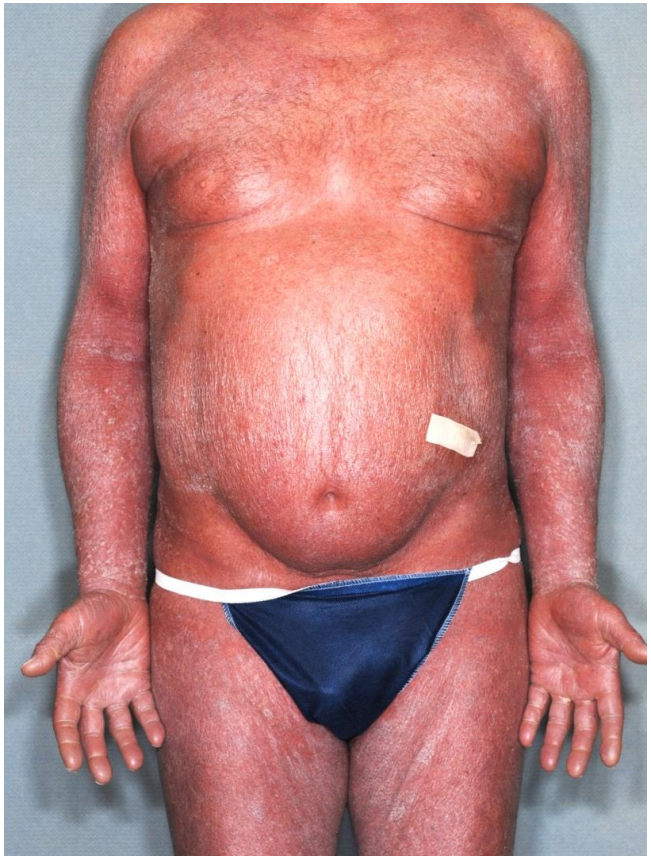
=> allogeneic HSCT

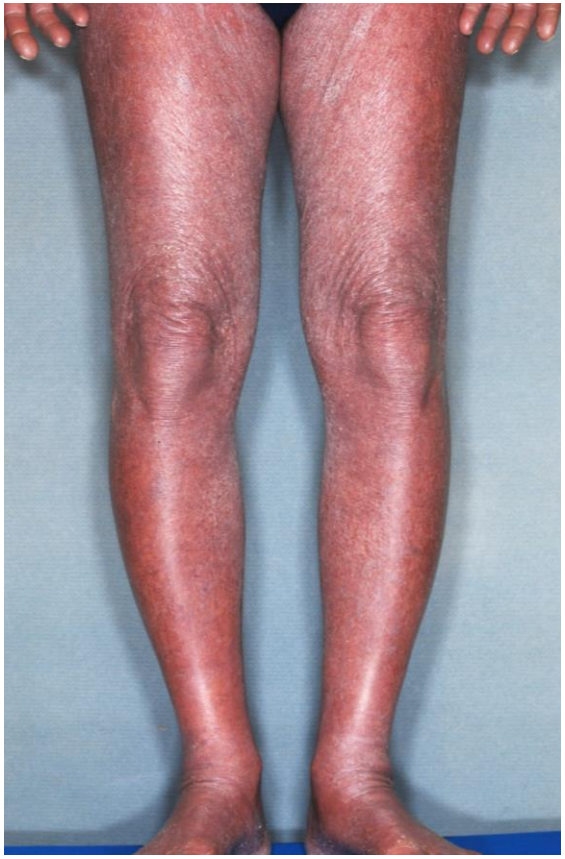
+/- skin-directed tx (low-dose TSEBT if indicated

Importance of supportive care to prevent staph infection

HSV/VZV prophylaxis

Sézary syndrome with thick skin involvement (LCT+), LN (N3, LCT+), and blood compartments (high Sézary burden, >10,000 per mm^3), stage IVA_2 failed biologic combinations (ECP+, Bex + IFN), MTX + IFN, mogamulizumab; preparation towards allo HSCT





GDP (gemcitabine, dexamethasone, cisplatin) only short-lived skin and LN response

Denileukin diftitox

Global CR

Consider immune therapies in chemo-resistant pts

NMA allo-HSCT, MUD

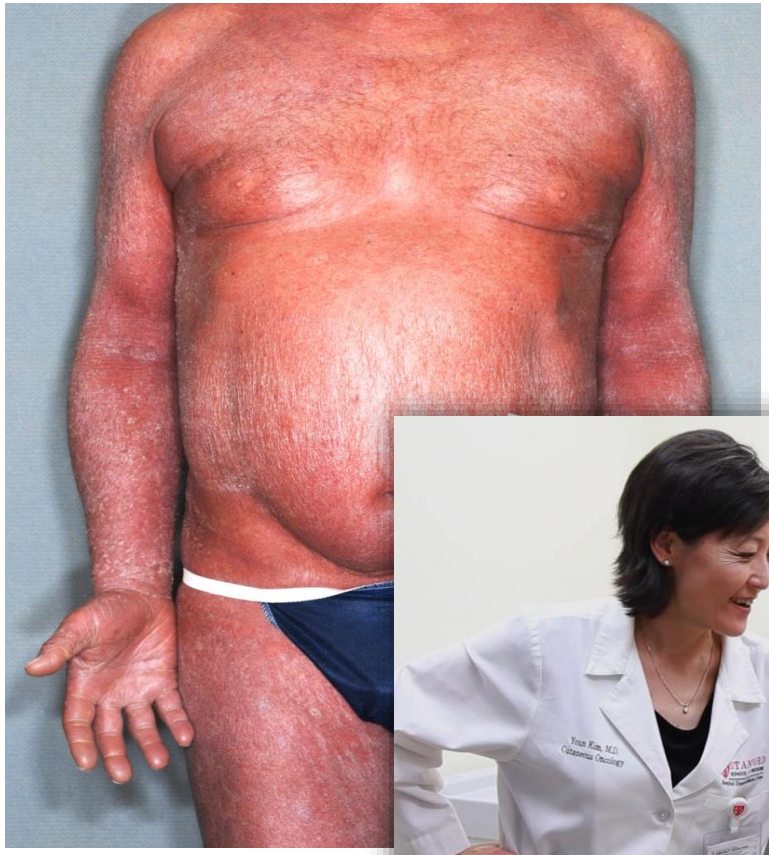
Sustained CR >8+ yrs

No GVHD

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

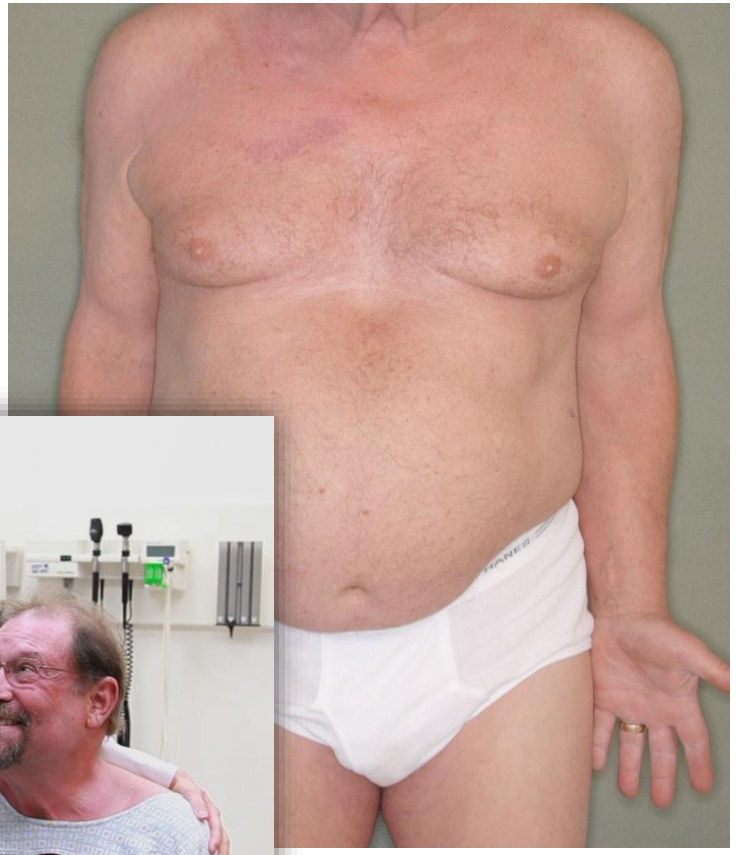
Pre-TSEBT

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



8.0+ yr (NED, no GVHD)

CD4+/CD26-: normalized



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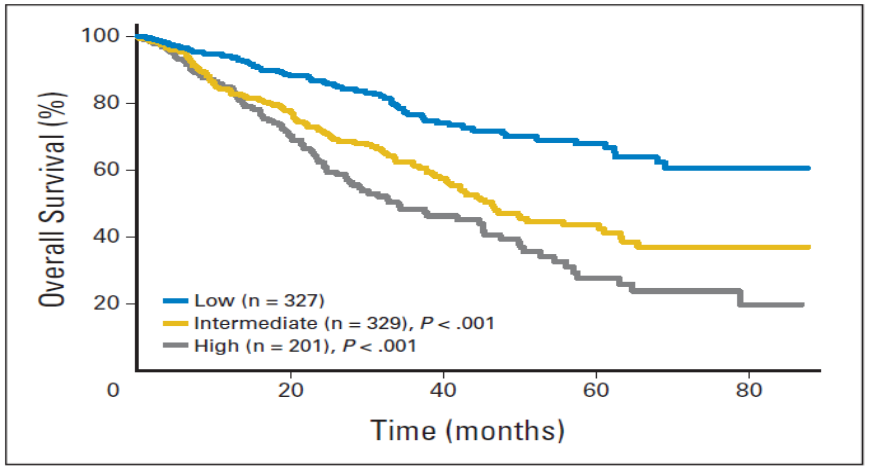
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sézary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model

Julia J. Scarisbrick, H. Miles Prince, Maarten H. Vermeer, Pietro Quaglino, Steven Horwitz, Pierluigi Porcu, Rudolf Stadler, Gary S. Wood, Marie Beylot-Barry, Anne Pham-Ledard, Francine Foss, Michael Girardi, Martine Bagot, Laurence Michel, Maxime Battistella, Joan Guitart, Timothy M. Kuzel, Maria Estela Martinez-Escala, Teresa Estrach, Evangelia Papadavid, Christina Antoniou, Dimitis Rigopoulos, Vassilki Nikolaou, Makoto Sugaya, Tomomitsu Miyagaki, Robert Gniadecki, José Antonio Sanches, Jade Cury-Martins, Denis Miyashiro, Octavio Servitje, Cristina Muniesa, Emilio Berti, Francesco Onida, Laura Corti, Emilia Hodak, Iris Amitay-Laish, Pablo L. Ortiz-Romero, Jose L. Rodríguez-Peralto, Robert Knobler, Stefanie Porkert, Wolfgang Bauer, Nicola Pimpinelli, Vieri Grandi, Richard Cowan, Alain Rook, Ellen Kim, Alessandro Pileri, Annalisa Patrizi, Ramon M. Pujol, Henry Wong, Kelly Tyler, Rene Stranzenbach, Christiane Querfeld, Paolo Fava, Milena Maule, Rein Willemze, Felicity Evison, Stephen Morris, Robert Twigger, Rakhshandra Talpur, Jinah Kim, Grant Ognibene, Shufeng Li, Mahkam Tavallaee, Richard T. Hoppe, Madeleine Duvic, Sean J. Whittaker, and Youn H. Kim



- Retrospective study of 10 parameters in **advanced stage MF/SS**, dx from 2007
- 29 international sites, N = 1,275
  - 4 independent factors **(age >60, stage IV, LCT, ↑LDH)**
  - Combined into prognostic index model => 3 risk groups

5-year OS rates of 3 risk groups

- **Low-risk, 67.8%**
- **Intermediate-risk, 43.5%**
- **High-risk, 27.6%**

Highest priority for allogeneic HSCT

Take home: How I Treat MF/SS-CTCL

- **Overall management is stage-based**, with recognition of additional prognostic factors (e.g., disease burden, LCT) and risk-stratification
- Despite recent advances in molecular findings, not ready for use in the clinics; and relevance for targeting unclear, need more data
- **Optimize/maximize use of skin-directeds, biologics, and single agent chemotherapy, maintenance tx to sustain response**
- **Optimal use of supportive care** to minimize risk for infection and improve QoL
- **Explore combination/sequential strategies, to optimize anti-tumor activity, reduce toxicity, and address resistance/escape/evasion**
- ***Partner with immune therapies to sustain response,*** including cellular therapies such as allogeneic HSCT
- **Integrate molecular/biomarker platforms into clinical trials and with new therapies** to learn predictors for response/resistance/escape, flare reactions, toxicity, or survival outcomes
- Taking steps **towards personalized, precision medicine**