Treatments for Advanced Stage Disease

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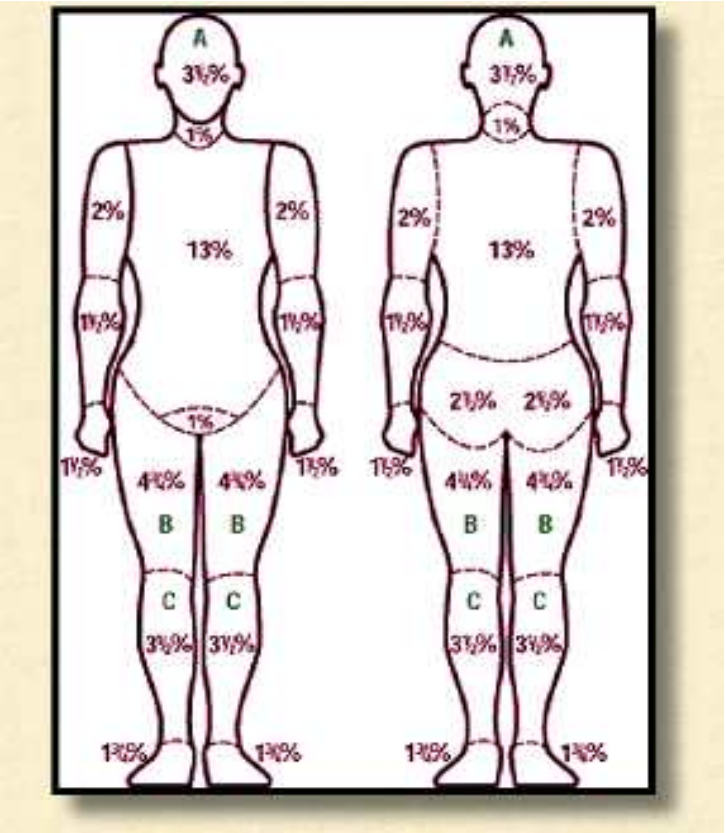
Staging of MF/CTCL involves the evaluation of skin, lymph nodes, viscera, and blood

Essential Workup				
Physical Exam	Labs	Imaging	Biopsy	Other
• Examination of entire skin • mSWAT • Palpation of peripheral lymph node regions • Palpation for organomegaly/ masses	• CBC with Sézary cell count • Flow cytometric analysis (CD4, CD8, CD7, CD26) • TCR gene rearrangement of peripheral blood • Comprehensive metabolic panel & LDH • Rule out other - ANA	• Contrast-enhanced CT scan of the neck/chest/ abdomen and pelvis **or** • Whole-body PET/CT scan	• Biopsy of suspicious skin sites • Dermatopathology/ Hematopathology review of biopsy	• For treatment consideration, women of childbearing age should be tested for pregnancy • Test Lipids & TSH/T4 if considering targretin

CBC: complete blood count; **CT**: computed tomography; **TCR**: t-cell receptor; **PET**: positron emission tomography; **LDH**: lactate dehydrogenase

%TSBA = (Total Body Surface Area)

- The body is divided into 12 regions with pre-assigned %TSBA based on methodology used to assess burns.
- The extent of skin disease is assessed for each region and quantified by using the patient's palm as the 'ruler' to measure the %TBSA involvement with each region.
  - Patient's palm with 4 fingers, excluding the thumb and measured from wrist to fingertips, is 1% of TBSA.
  - Patient's palm without fingers is 0.05% of TBSA



TNMB stages	Staging parameters
Skin (T)	
T_1	Patches and/or plaques covering <10% BSA; Further stratified into $T1_a$ (patch only) versus $T1_b$ (plaque ± patch)
T_2	Patches and/or plaques covering ≥10% BSA: Further stratified into $T2_a$ (patch only) versus $T2_b$ (plaque ± patch)
T_3	One or more tumors (≥1 cm diameter)
T_4	Coalescing erythema covering ≥80% of skin surface
LN (N)	
N_0	No clinically abnormal lymph nodes
N_1	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN0-2 Further stratified into N1a (TCR non clonal) versus N1b (TCR clonal)
N_2	Clinically abnormal lymph nodes; histopathology Dutch grade 2 or NCI LN3 Further stratified into N1a (TCR non clonal) versus N1b (TCR clonal)
N_3	Clinically abnormal lymph nodes; histopathology Dutch grades 3-4 or NCI LN4; clone positive or negative
N_x	Clinically abnormal lymph nodes; no histologic confirmation
Visceral (M)	
M_0	No visceral organ involvement
M_1	Visceral involvement, pathologically confirmed + organ involved specified)
Blood (B)	
B_0	No significant blood involvement: <5% Sézary cells. For clinical trials, B0 may also be defined as <250/mL Sézary cells CD4+CD26- or CD4+CD7- cells or CD4+CD26- and CD4+CD7- cells <15%
B_{0a}	Clone negative
B_{0b}	Clone positive
B_1	Low tumor burden. Does not fit B_0 or B_2 criteria
B_{1a}	Clone negative
B_{1b}	Clone positive
B_2	High blood tumor burden: Positive clone plus one of the following: >1000/mL Sézary cells; CD4/CD8 ≥10 CD4+CD7- cells ≥40 percent CD4+CD26- cells ≥30 percent For clinical trials, B_2 may also be defined as >1000/mL CD4+CD26- or CD4+CD7- cells.

Staging of MF Involves Evaluation of Skin (T), Lymph Nodes (N), Viscera (M), and Blood (B)

For skin, plaque is any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikilderma should be noted. Features such as folliculotropism (FT) or large-cell transformation (LCT; >25% large cells), CD30+, and ulceration are important to document. Tumor indicates at least one 1 cm solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, largest size lesion, region of body involved, and histologic features such as FT or LCT, CD30+.

For node, abnormal lymph node (LN) indicates any LN ≥1.5 cm.

For viscera, spleen and liver may be diagnosed by imaging criteria alone.

A T cell clone is defined by PCR or Southern blot analysis. For B_2 the clone in the blood should match that of the skin.

Modified from: Olsen E, Vonderheid E, Pimpinelli N, et al. Blood 2007; 110:1713; and, Olsen EA, Whittaker S, Kim YH, et al. J Clin Oncol 2011; 29:2598.

COMPOSITE ISCL/EORTC STAGING

2007 ISCL/EORTC Revision to the Staging System of MF and SS				
Stage	T (Skin)	N (Lymph Node)	M (Viscera)	B (Blood)
IA	1	0	0	0,1
IB	2	0	0	0,1
IIA	1,2	1,2	0	0,1
IIB	3	0-2	0	0,1
III	4	0-2	0	0,1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA_1	1-4	0-2	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

B0 Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes or <250/mcL Sezary cells or <15% CD4+CD26- or CD4+CD7-

B1 Low blood tumor burden: >5% of peripheral blood lymphocytes are Sezary cells but not meet criteria for B2

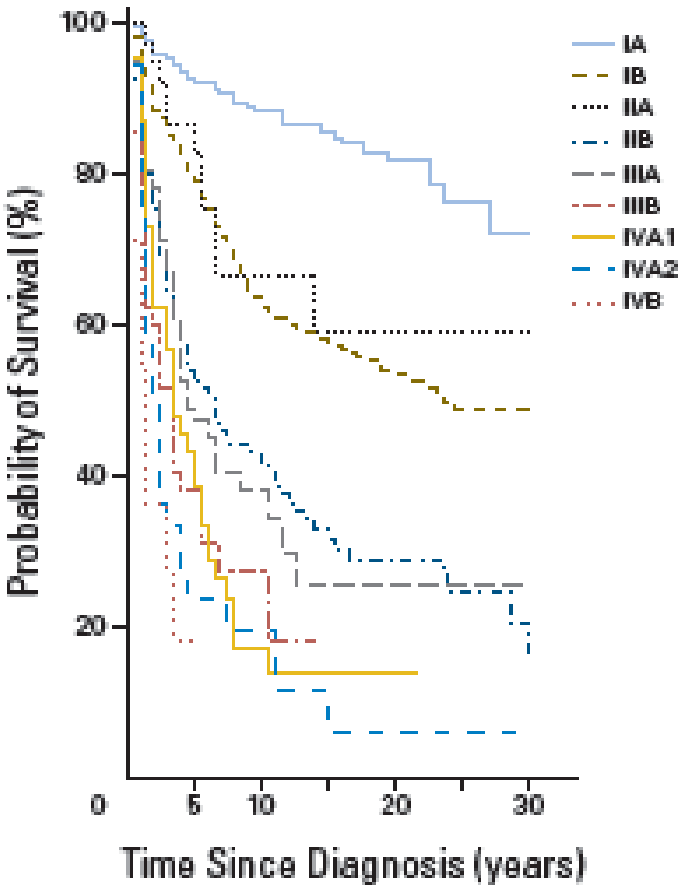
B2 High blood tumor burden: ≥1000/mcL Sezary cells or CD4/CD8 ≥10 or ≥40% CD4+CD7- or ≥CD4+CD26- cells

Prognosis in MF best predicted by TNMB staging

Clinical Stage	Median Survival (years)
IA	35.5
IB	21.5
IIA	15.9
IIB	4.7
IIIA	4.7
IIIB	3.4
IVA1	3.9
IVA2	2.1
IVB	1.4

Agar et al. JCO. 2010

Advanced Stage CTCL (Stage ≥ IIB) predicts a poor prognosis



IA: Limited patch <10%
IB-IIA: Patch/plaques >10%

<u>AS-CTCL (Stage ≥ IIB)</u>

- Tumor Stage (>1cm)
- Nodal, visceral, or blood involvement

Significant variability in AS-CTCL

- Teleological factors responsible for this variability are not well known.
- Prognostic markers include folliculotropism[1], large cell transformation (LCT)[2] & number of tumors[3]
- Easily quantifiable markers (e.g. LDH[2], elevated cell free EBV-DNA[4]) of advanced systemic disease are needed
- Independent px factors in large retrospective study:
  - Stage IV, Age >60yo, LCT, increased LDH
  - w/5 yr survival 68% (0-1 factor), 44% (2 factors), 28% (3-4 factors)

[1] Van Santen et al. JAMA Derm. 2016. [2] Scarisbrick et al. JCO. 2015. [3] Boonk et al. Br J Dermatol. 2014. [4] Haverkos et al. L&L. 2016.. [5] Scarsisbrick et al. JCO. 2015.

Overview of CTCL Treatments

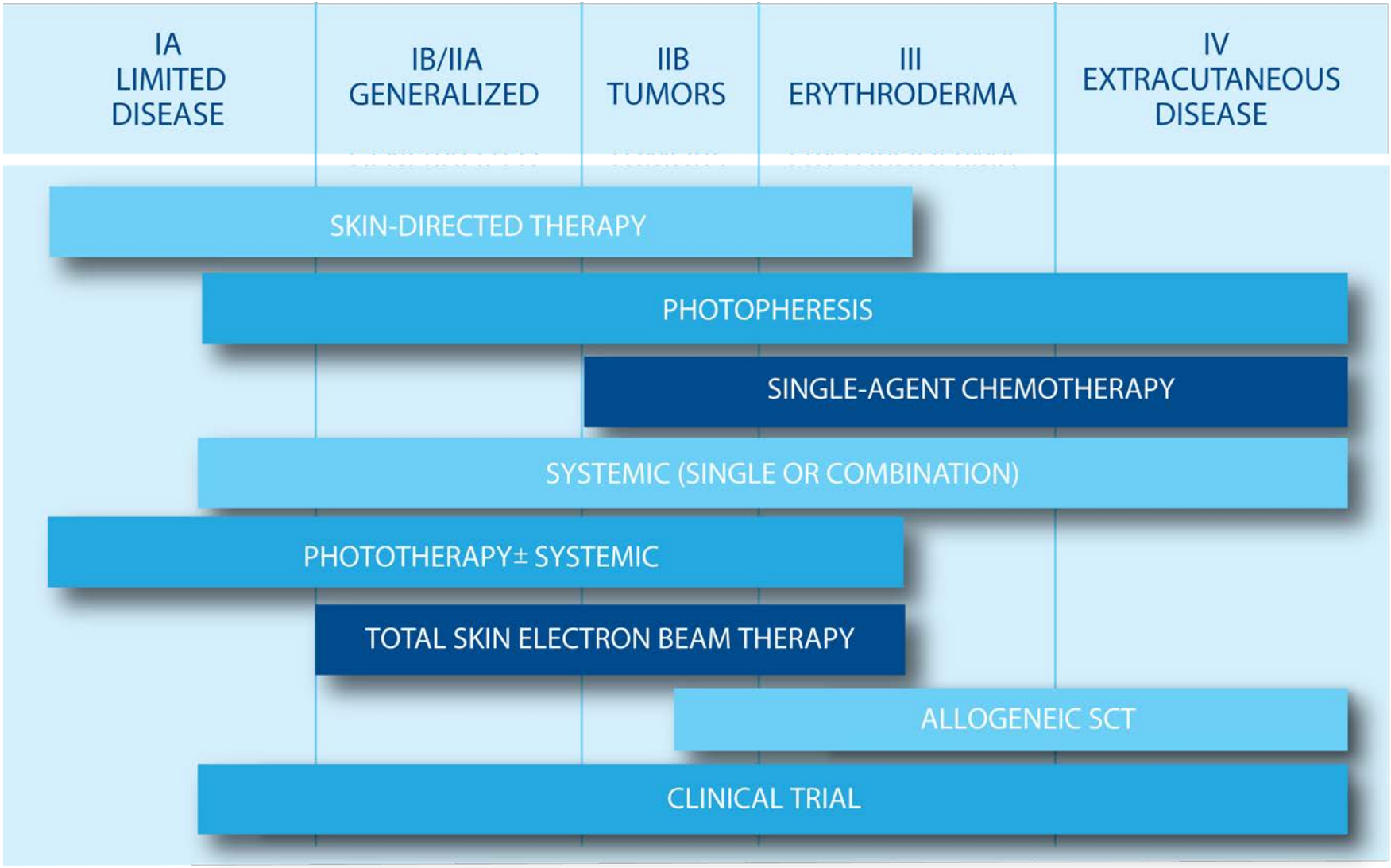
Skin Directed

- Topical corticosteroids
- Topical chemotherapy
  - Nitrogen mustard (*Mustargen*)
  - Carmustine (*BCNU*)
  - Mechlorethamine (*Valchlor*)
- Topical retinoids
  - Bexarotene gel (*Targretin* gel)
- Phototherapy
  - Narrow-band UVB (NBUVB)
  - Psoralen with UVA (PUVA)
- Radiation therapy
  - Total-skin electron beam therapy (TSEBT)
  - Site-directed radiation

Systemic

- Vorinostat (ZOLINZA™)
- Bexarotene capsules (*Targretin*)
- Romidepsin
- Pralatrexate
- Denileukin diftitox (*Ontak*)
- Alemtuzumab (*Campath*)
- Interferon
- Extracorporeal photopheresis
- Chemotherapy—single agent
  - Chlorambucil (*Leukeran*)
  - Cladribine (*Leustatin*)
  - Fludarabine (*Fludara*)
  - Methotrexate (*Trexall*, *Rheumatrex*)
  - Gemcitabine (*Gemzar*)
  - Pegylated doxorubicin (*Doxil*)
  - Pentostatin (*Nipent*)
- Combination chemotherapies
  - CHOP, EPOCH, Gem/Dox

Clinical Management of CTCL



National Comprehensive Cancer Network. www.nccn.org

General concepts in managing MF/SS-CTCL

- Lack of evidence-based help
- Consensus-based management **NCCN guidelines**
- Do no harm (refer to those who like skin or collaborate)
- Appreciate unique features of skin disease
  - Supportive therapy is essential (barrier defect)
    - Chronic control of skin infections (staph, HSV)
    - Use anti-itch regimens, emollients/sealants
  - Things that work in LNs may not work in skin
  - Often observe mixed responses
  - Can re-cycle treatments
  - Optimize utility of maintenance therapy

Key treatment selection factors

- **Clinical stage/TNMB**
  - MF vs. SS
- Other prognostic factors
  - **Large cell transformation**
    - limited vs. generalized
  - **Folliculotropic disease**
    - infiltrate deeper/thicker => refractory to topicals
- **Age, co-morbidities**, concomitant meds
- **Availability/access issues**
  - TSEBT, photopheresis
  - U.S. vs. other countries
  - Insurance barriers

Mycosis Fungoides - the greatest masquerader
Clinical & Histologic Variants/Subtypes
Unique Prognosis?

- Hypopigmented/vitiligenous MF
  - Children, African American, Indian; CD8+
- Pagetoid reticulosis (Woringer-Kolopp type only)
- **Folliculotropic MF (+/- FM)**
  - **Head and neck**
- Granulomatous MF
  - Granulomatous slack skin
- Bullous MF
- PPE-like MF
- Interstitial MF
- Icthyiosiform MF
- Palmar plantar MF
- Hyperkeratotic/verrucous MF
- Papular MF
- Invisible MF

Worse clinical outcome => separated out in NCCN guidelines
F-MF + LCT => even worse

Arch Dermatol 144:738, 2008
Arch Dermatol 146:607, 2010
JCO 28:4730, 2010
Blood 119:1643, 2012

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 + vorinostat
  - Photopheresis* + retinoid
  - Photopheresis* + IFN
  - Photopheresis* + retinoid + IFN

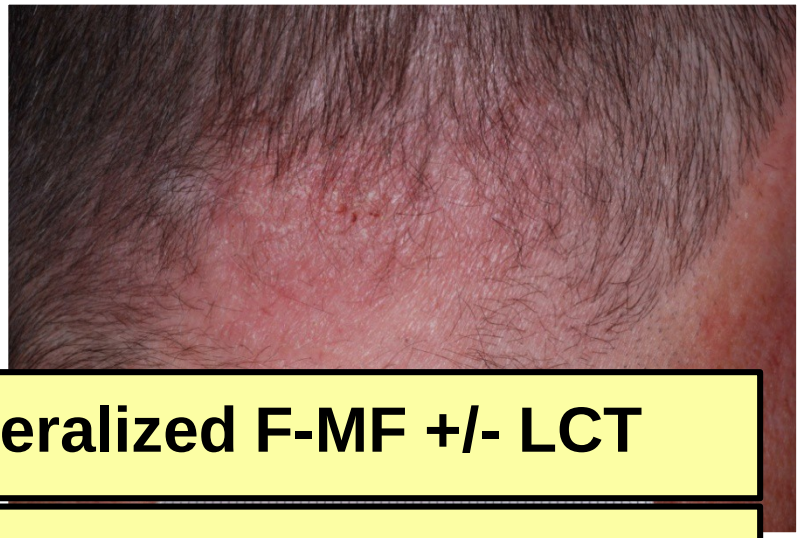
Is combination therapy "better"?

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

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

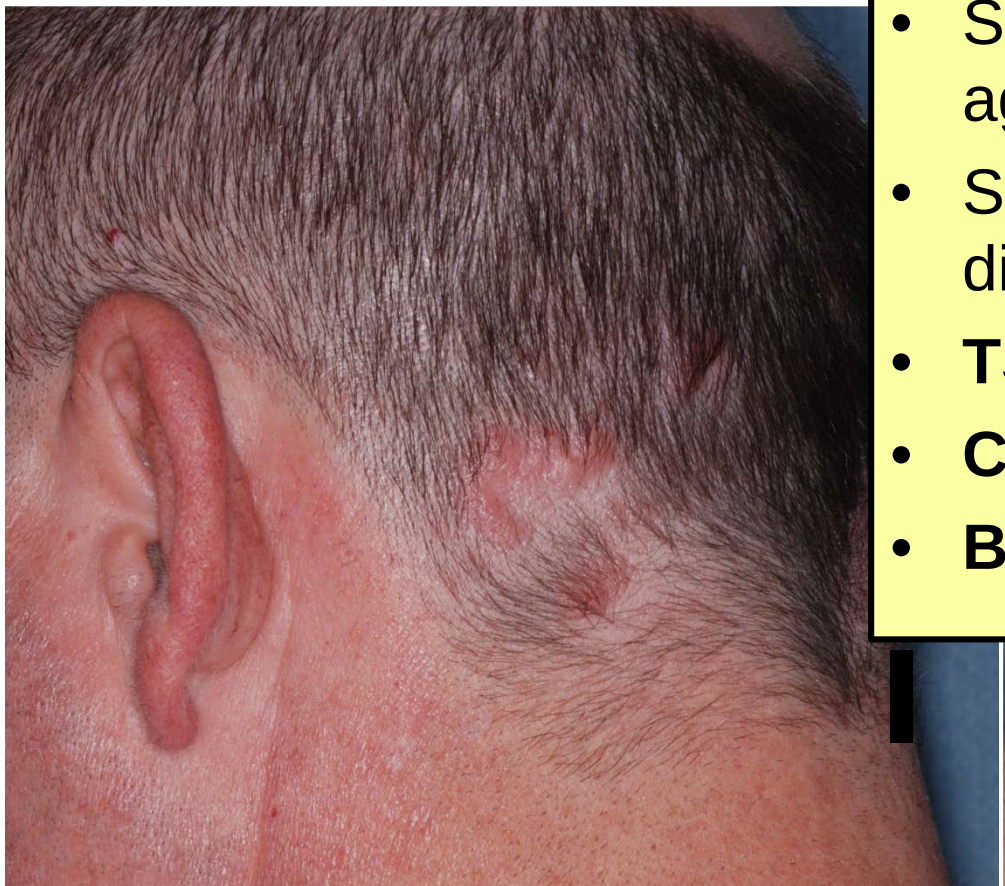
Clinical Cases

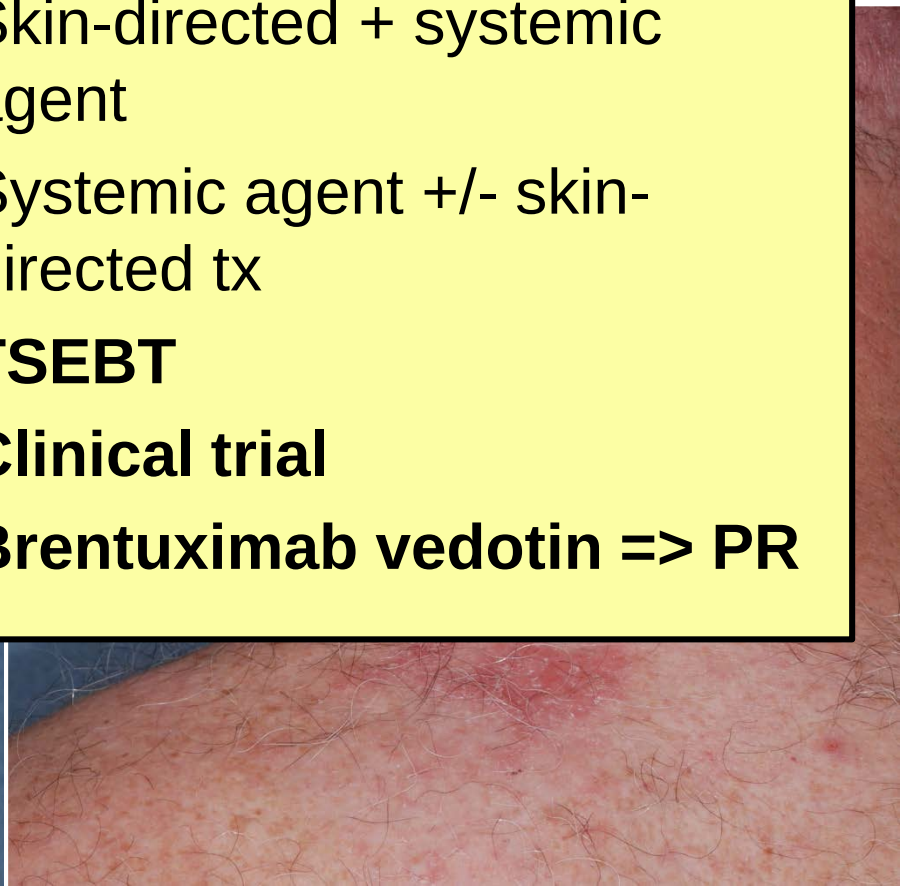
50 yo male, generalized disease, progressive with increasing nodular lesions, IIB. Prior therapies: topical steroids, NM, local RT, nbUVB.
=> Failed oral bex, IFN, MTX



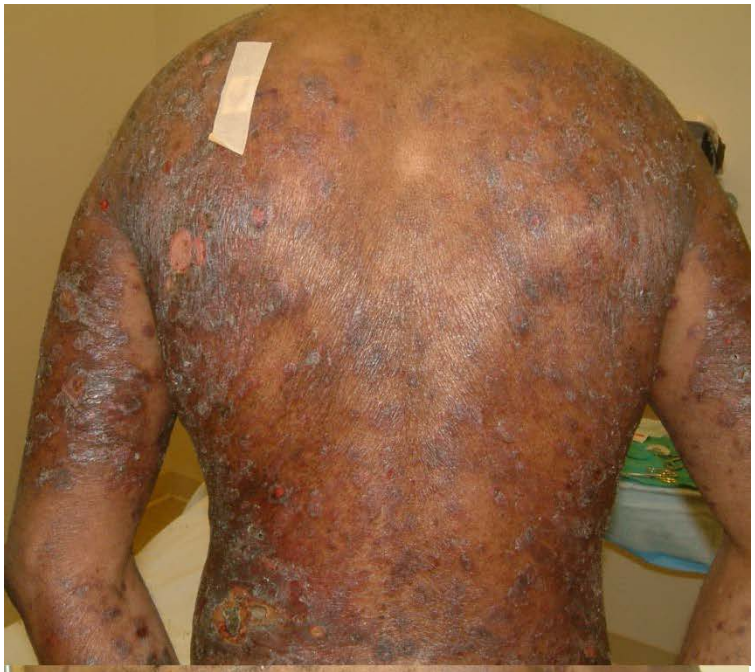
- **Generalized F-MF +/- LCT**

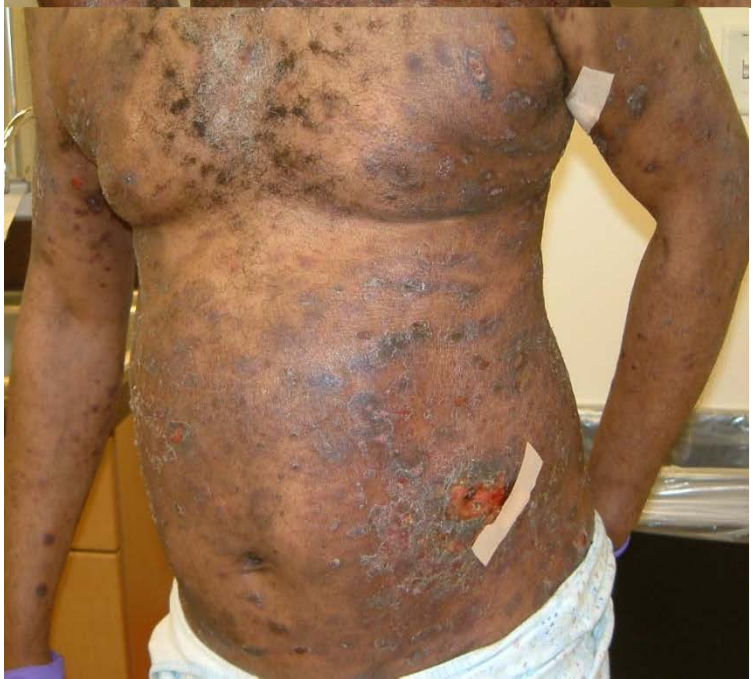
- Skin-directed + systemic agent
- Systemic agent +/- skin-directed tx
- **TSEBT**
- **Clinical trial**
- **Brentuximab vedotin => PR**





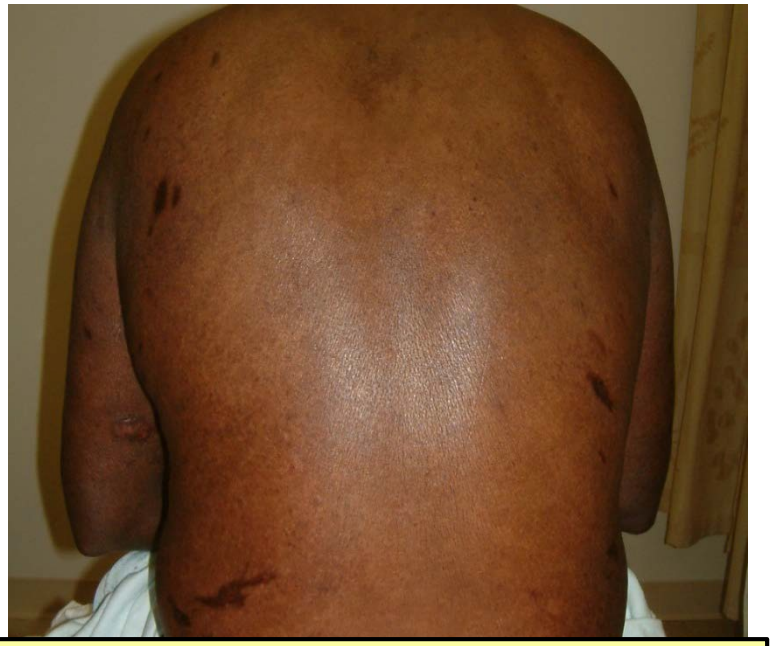
Severely symptomatic folliculotropic MF

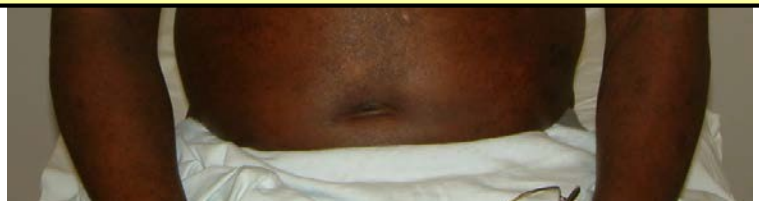




Standard dose TSEBT

36 Gy





NOT CURATIVE,

Relapse within 2 yrs,
Retreatment limited

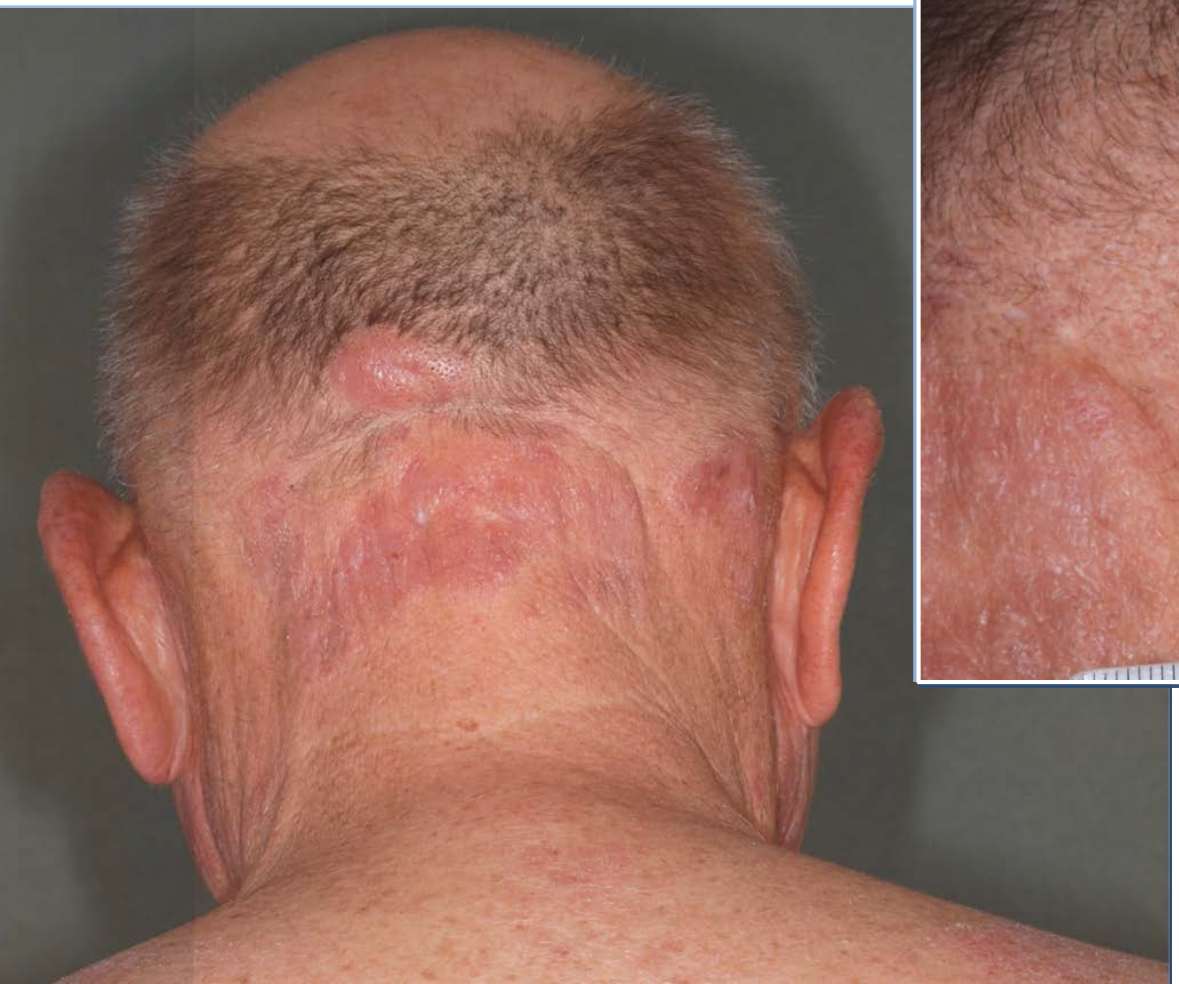
Why not use lower dose?

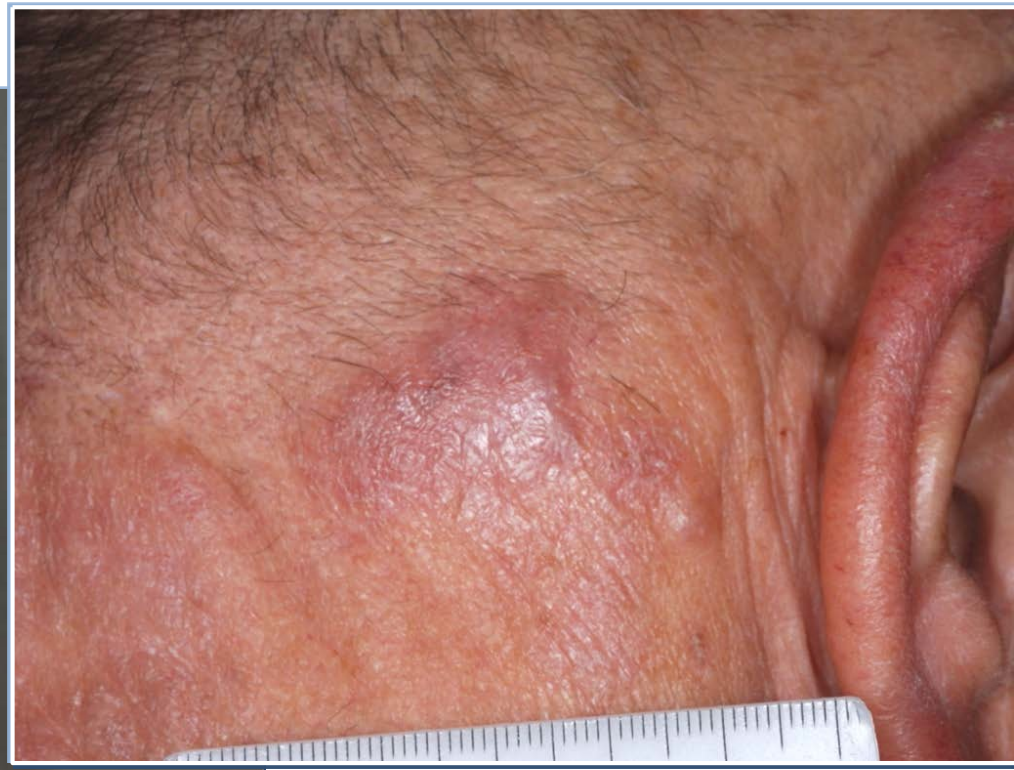
Low-Dose TSEBT Regimen
Less is better?

- Low-dose, 12 Gy (3 wks) vs. standard, 36 Gy (10 wks)
- Standard dose not-curative, protracted tx course, sig skin toxicity
- Reliable/efficient reduction in skin disease
- Less side effects
  - No permanent hairloss, 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

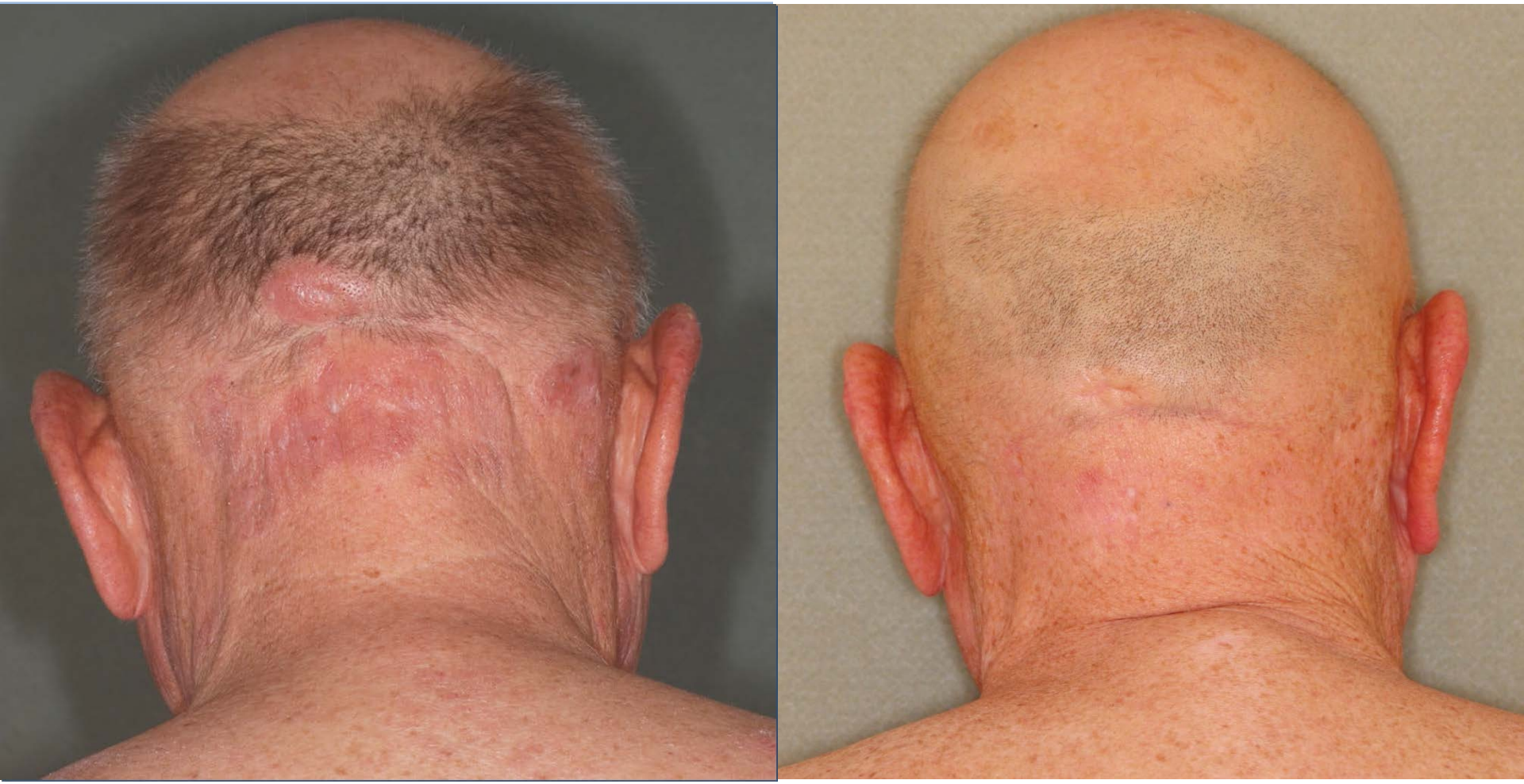
69 yo male w/ 5 yr h/o scaly plaques on face/scalp, trunk, extremities, progressive worsening. Partial response to topical steroids, NM, and nbUVB. Recently noted scalp tumor nodules; multiple comorbidities.

Case F-MF, stage IIB





Clinical response with low-dose (12 Gy) TSEBT
69 yo M, stage IIB, folliculotropic MF



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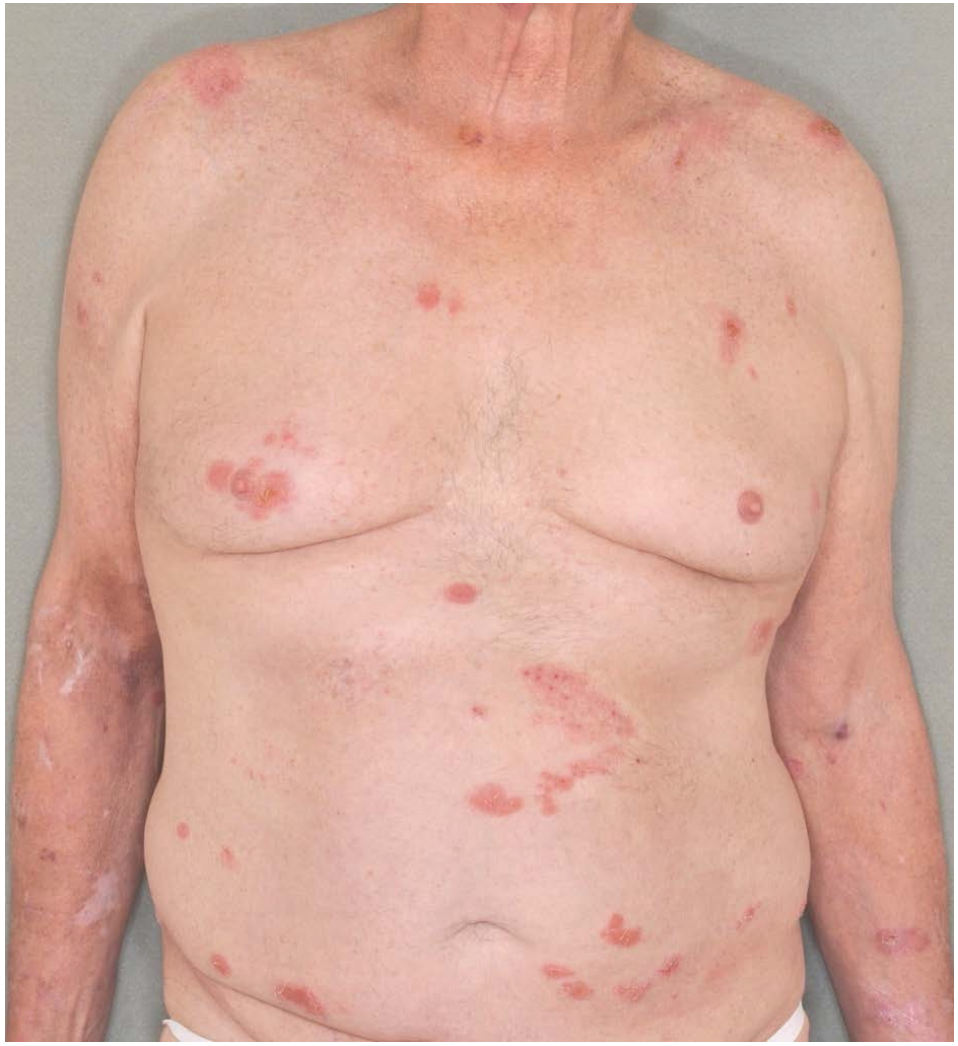
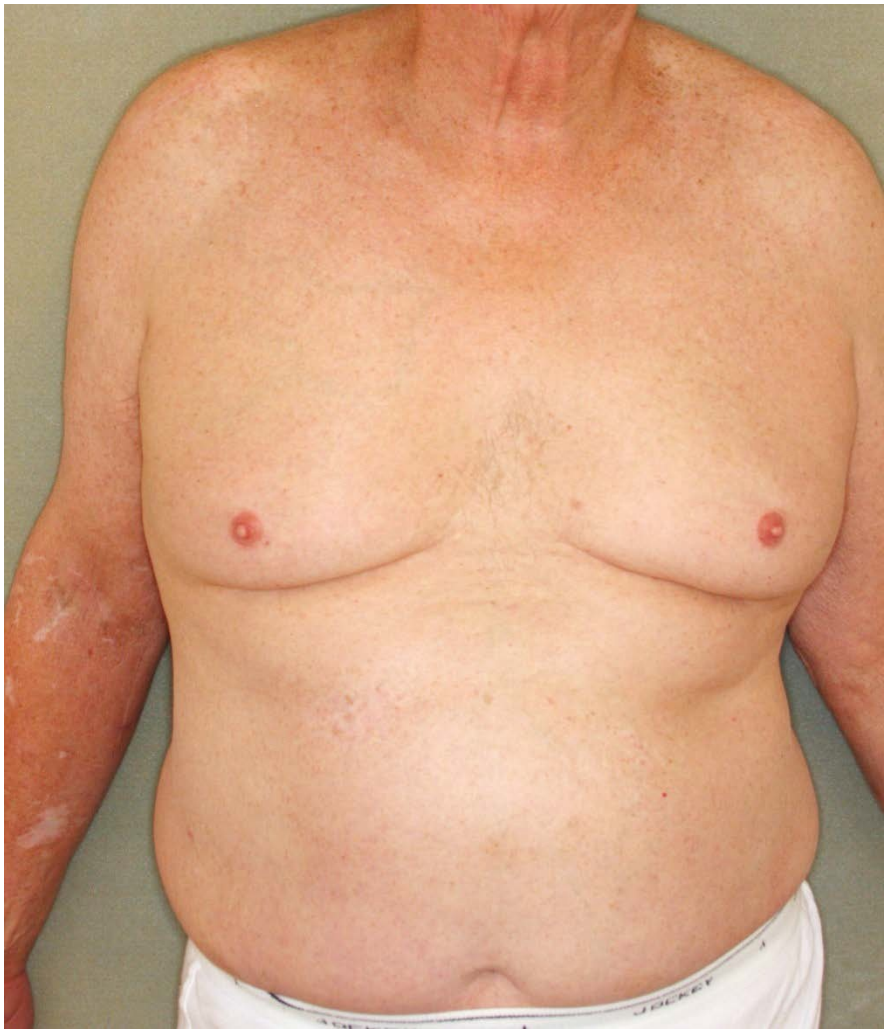


Screening
mSWAT 133
Pruritus 8/10



Wk 16
mSWAT 0 (CR)
Pruritus 0/10

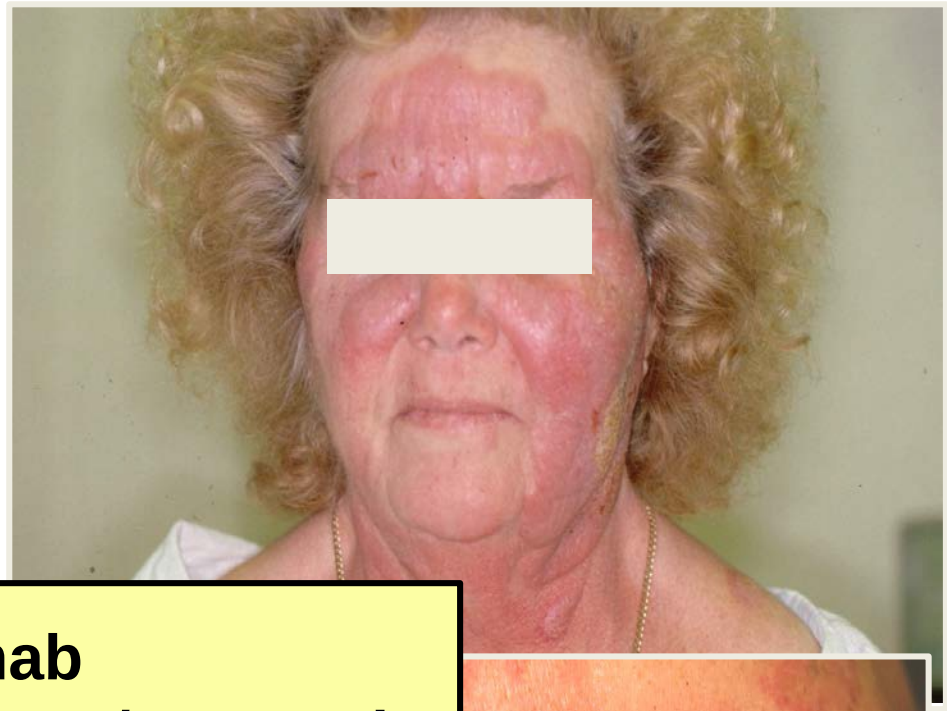
Management of skin “tumor” disease (IIB)

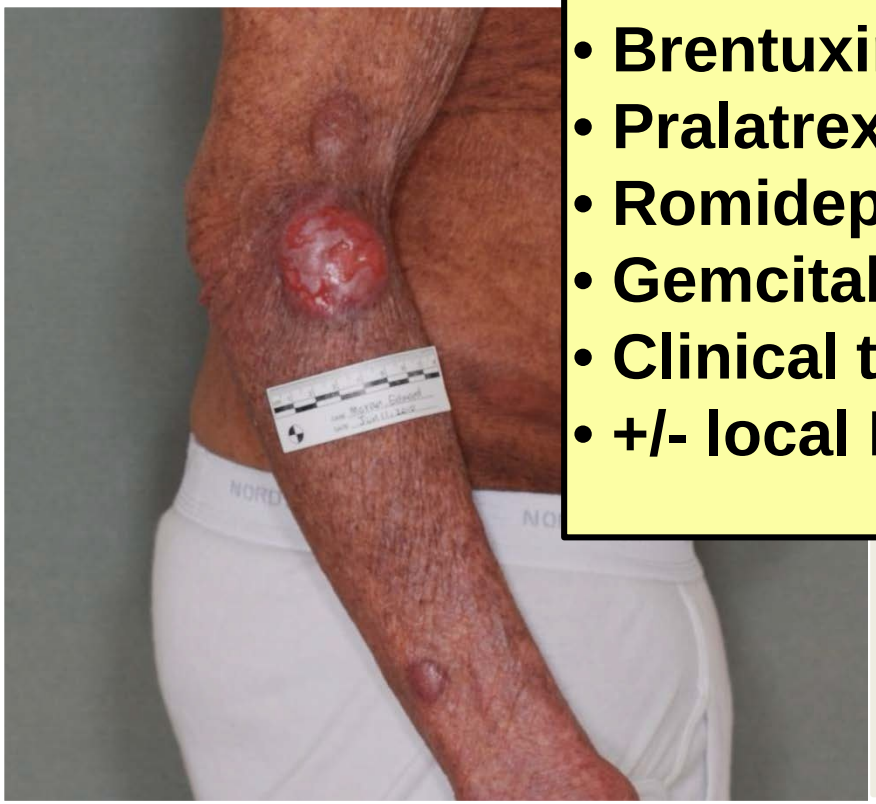
- **Limited vs. generalized** extent tumor disease
- **Intensify therapy for** aggressive growth pattern, e.g., large cell transformation (LCT)
- **Limited extent tumor disease**
  - Local RT for limited tumor disease +/- skin-directed therapy for patch/plaque disease
  - “Milder” systemic options +/- skin-directed tx
- **Generalized extent tumor disease**
  - **Indolent (no LCT) and <4 tumors**
    - Systemic (e.g. targretin) +/- skin-directed tx
  - **Aggressive (+** LCT) or ≧4 tumors
    - Systemic options +/- skin-directed tx
- Refractory disease => clinical trials, combo

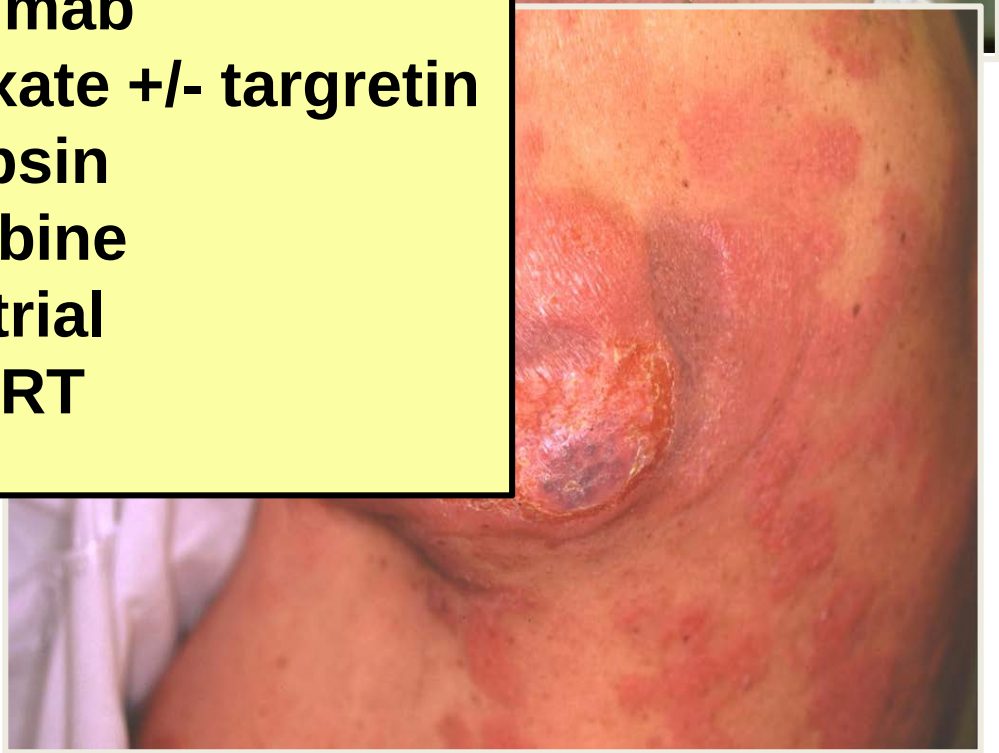
Consider Allogeneic transplant

MF w/ large cell transformation with worse prognosis

NOTE: CD30+ pcALCL should be differentiated from MF with large cell transformation (T-MF) with CD30+ tumor cells







- **Brentuximab**
- **Pralatrexate +/- targretin**
- **Romidepsin**
- **Gemcitabine**
- **Clinical trial**
- **+/- local RT**

Management of erythrodermic (T4) disease

- Approach **based on peripheral blood burden**
  - B0, B1, vs. B2 (Sezary syndrome)
- Erythrodermic (T4) MF, stage III
  - B0 => generalized skin-directed options
  - B1 => “milder” systemic options
  - Refractory disease
  - Combination therapies
    - Skin tx + Systemic
  - Photopheresis, Romidepsin
- Essential to optimize supportive care
  - Emollients, topical steroids +/- occlusion
  - Vigilant infection control (staph, HSV/VZV
  - Anti-itch support (gabapentin, doxepin)

Evidence for treatment stratification by blood tumor burden

- Current B2 ≥ 1,000 /mm^3
- Evidence that ≥ 5K or ≥ 10K are important prognostic or therapy outcome levels
  - ≥ 5K as worse px group
    (Vonderheid et al. leukemia Lymph 2006;47:1841)
  - ↑death rate in ≥ 10K
    (Scarisbrick et al. Blood 2001;97:624)
  - Reduced survival in ≥ 10K
    (Vidulich et al. Int J Dermatol 2009;48:243)
  - Combination biologics less effective in ≥ 10K *(Stanford group, WCCL abstract 2010)*
- ≥ 10K /mm^3 may be important prognostic threshold

Management of Sezary Syndrome, B2/stage IV

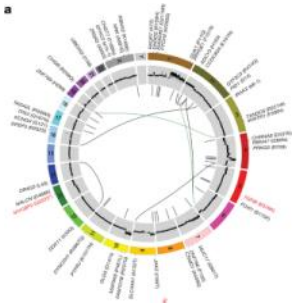
- Stratification based on blood Sezary burden
- Given risk for staph sepsis, utilize agents that spare further immune dysfunction
- **Low-intermediate Sezary burden**
  - "Milder" systemic therapies: biologics (bexarotene, photopheresis, interferon), methotrexate
- **High Sezary burden (> 5-10K/mm^3)**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

Allo HSCT

The Future of Lymphoma Treatment

Genomic Analysis

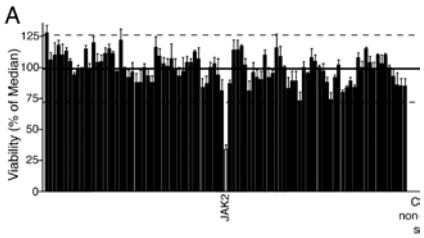
- Exome Sequencing
- RNA Seq



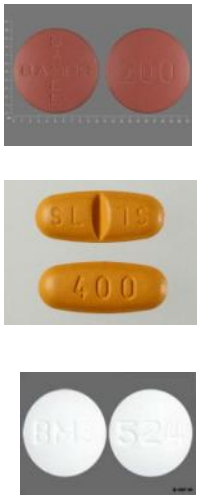
Functional Analysis

<u>In vitro</u>

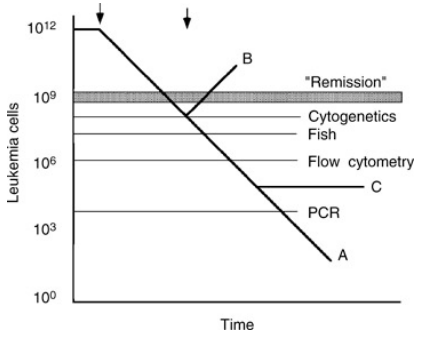
- Compound screen



Analysis → Choosing the Right Drug(s)



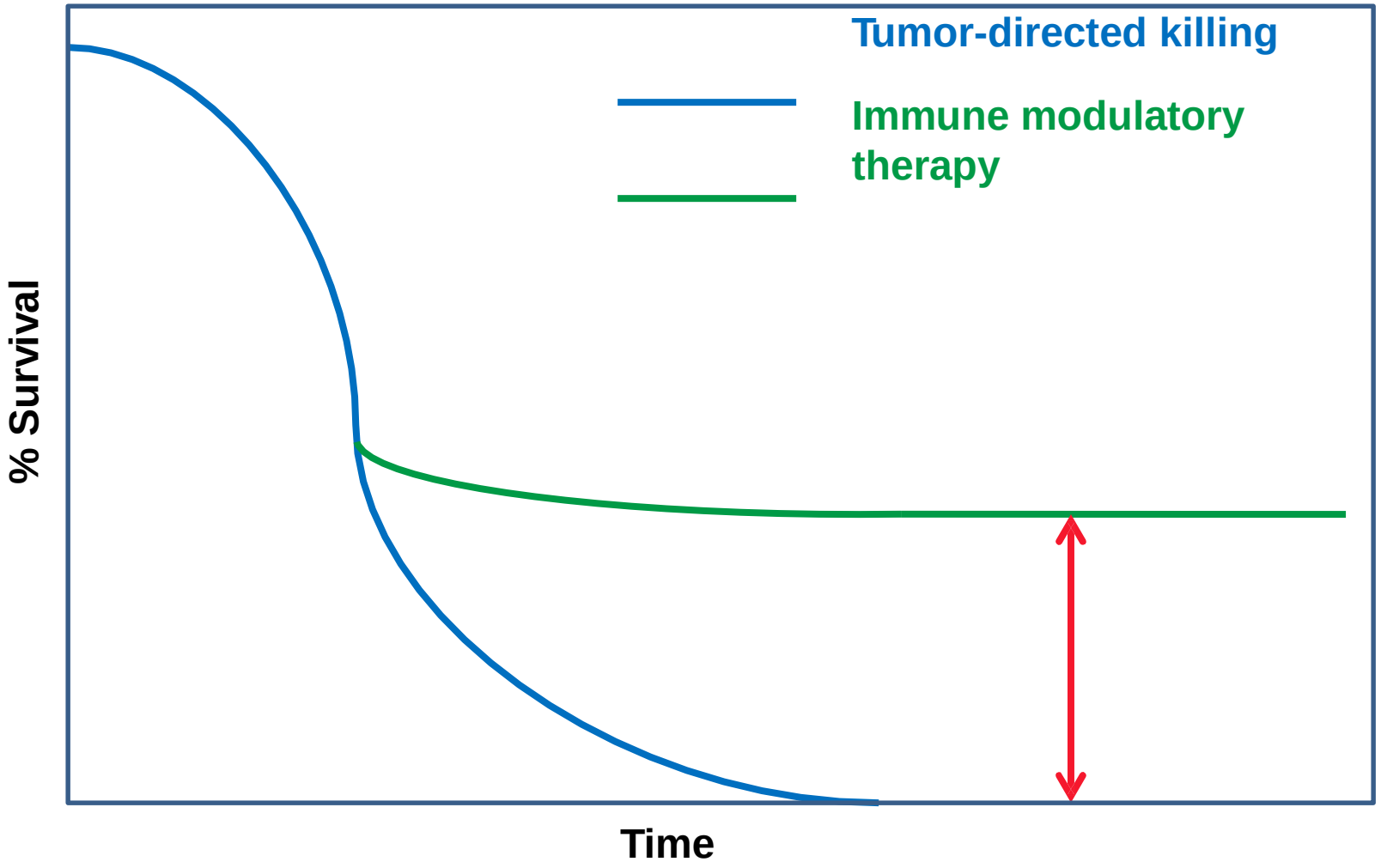
Minimal Residual Disease Testing



Road to a CURE

How do we make the nice responses last?

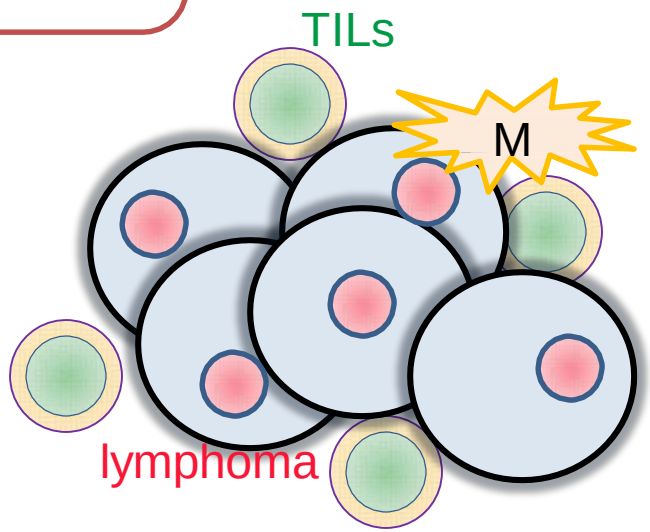
Partnering with immunotherapy



Immunotherapy strategies in CTCL

Tumor-specific monoclonal antibodies

Cytokine therapy



Adoptive T-cell transfer

Immune-modulating agents or antibodies

Allogeneic HSCT

Vaccine-based approaches

Hematopoietic cell transplantation in mycosis fungoides and Sézary syndrome

Considered for patients with refractory/advanced disease (stages IIB-IV)

Autologous → High-dose therapy followed by stem cell rescue

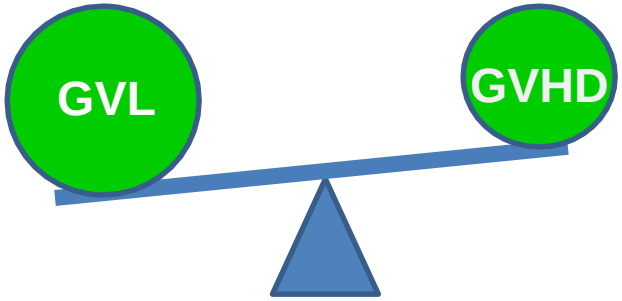
Benefit of no GVHD

No durable response in MF/SS, not recommended

Allogeneic → **Graft vs. lymphoma (GVL) effect**

Risk of GVHD

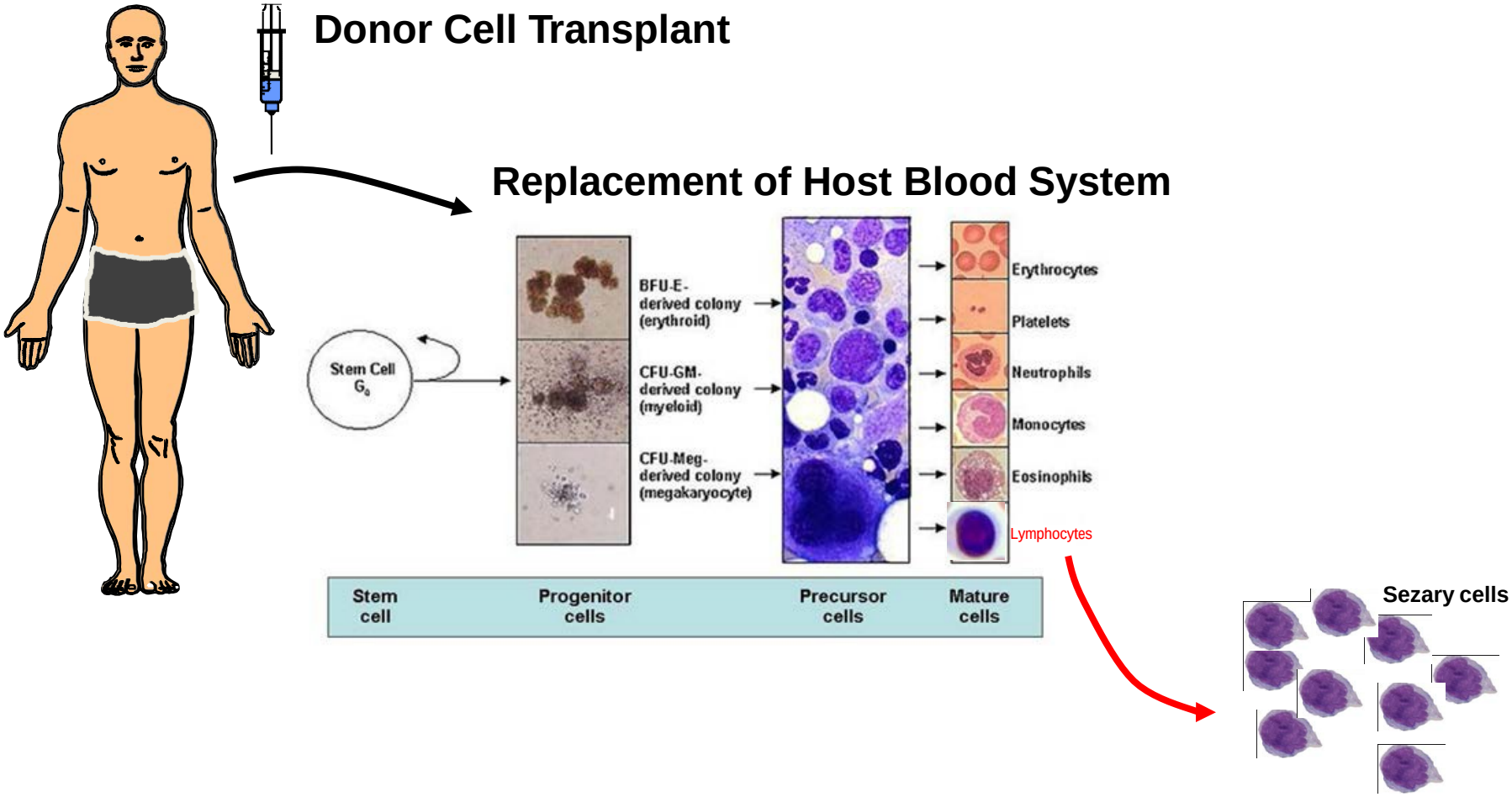
Increasing evidence of durable clinical, cytogenetic, molecular remissions in MF/SS



How to maximize GVL effect while minimizing GVHD risk

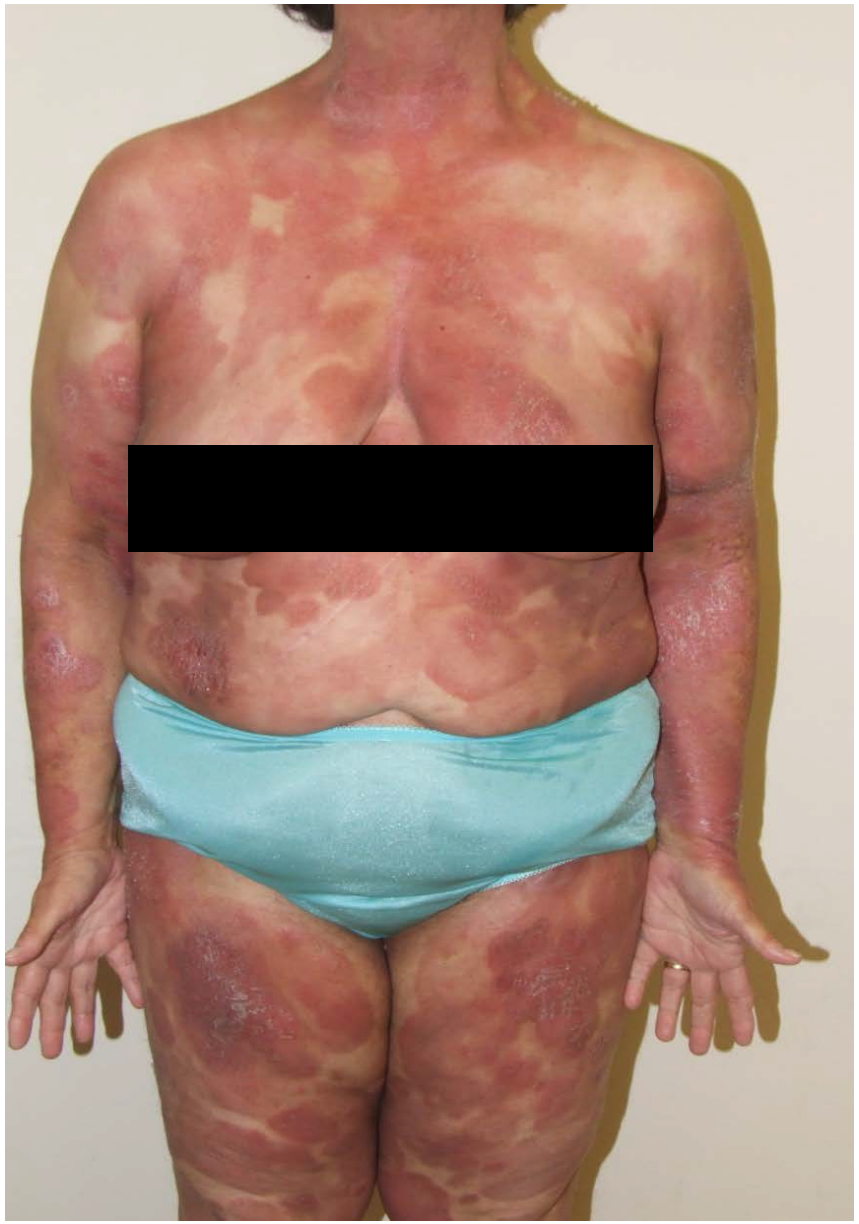
Biol Blood Marrow Transplant 15: 982-990 (2009); J Clin Oncol 29:2365-72 (2010); J Clin Oncol 28:4492-99 (2010); Bone Marrow Transplant ePub (2011)

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

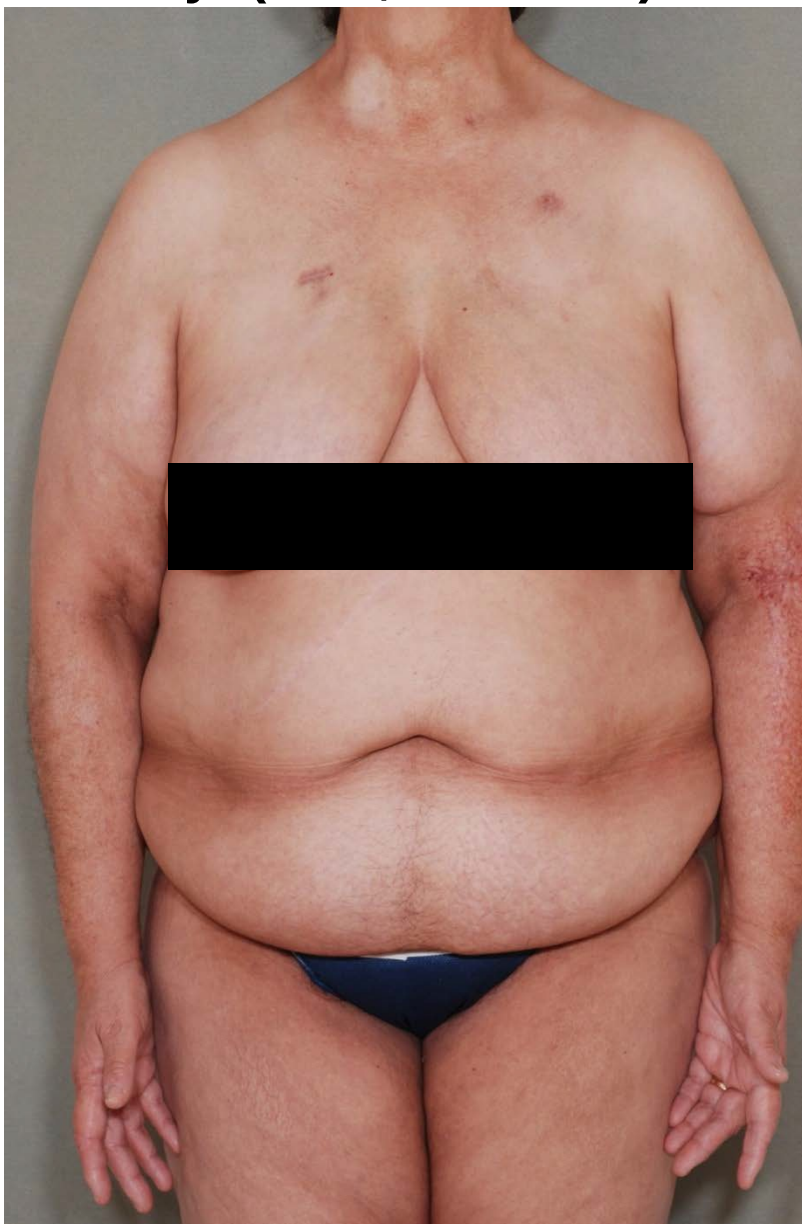


Mycosis fungoides, stage IVA w/ LCT in skin/LNs: CR

Pre-TSEBT



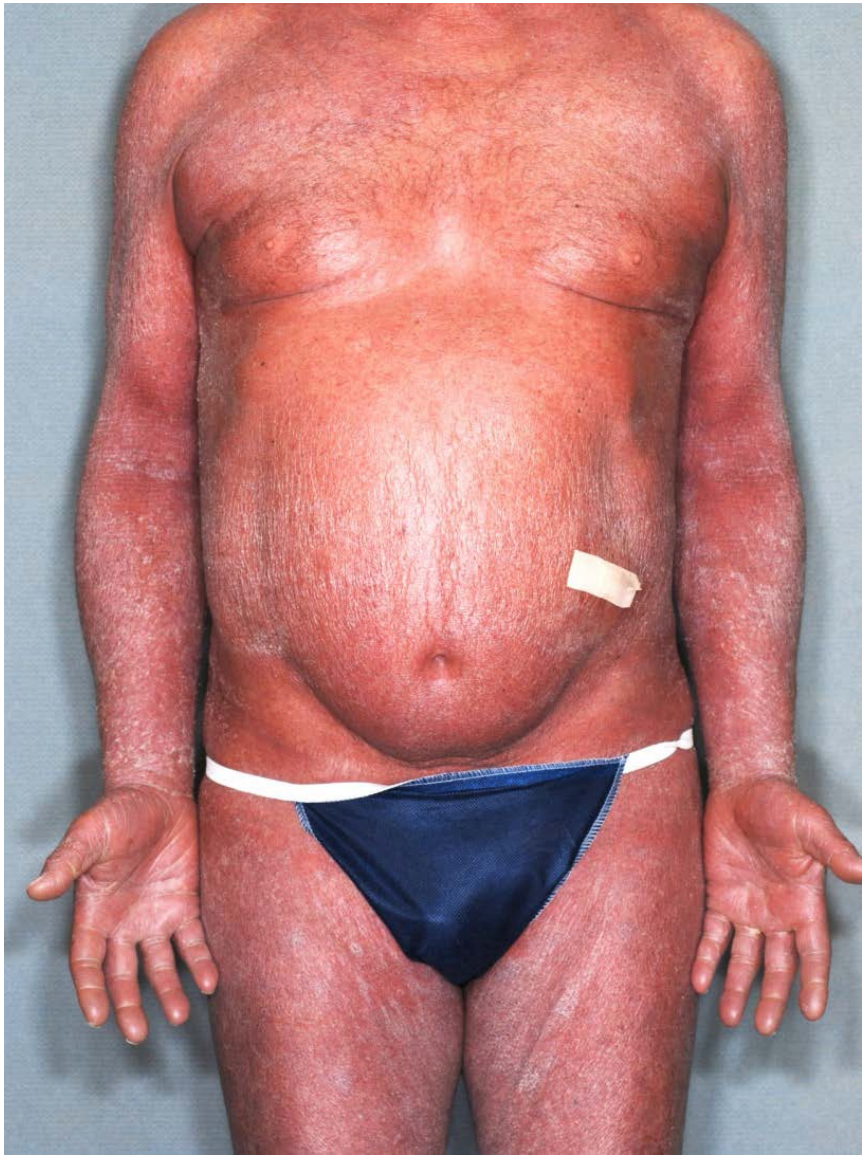
3 yr (NED, no GVHD)



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

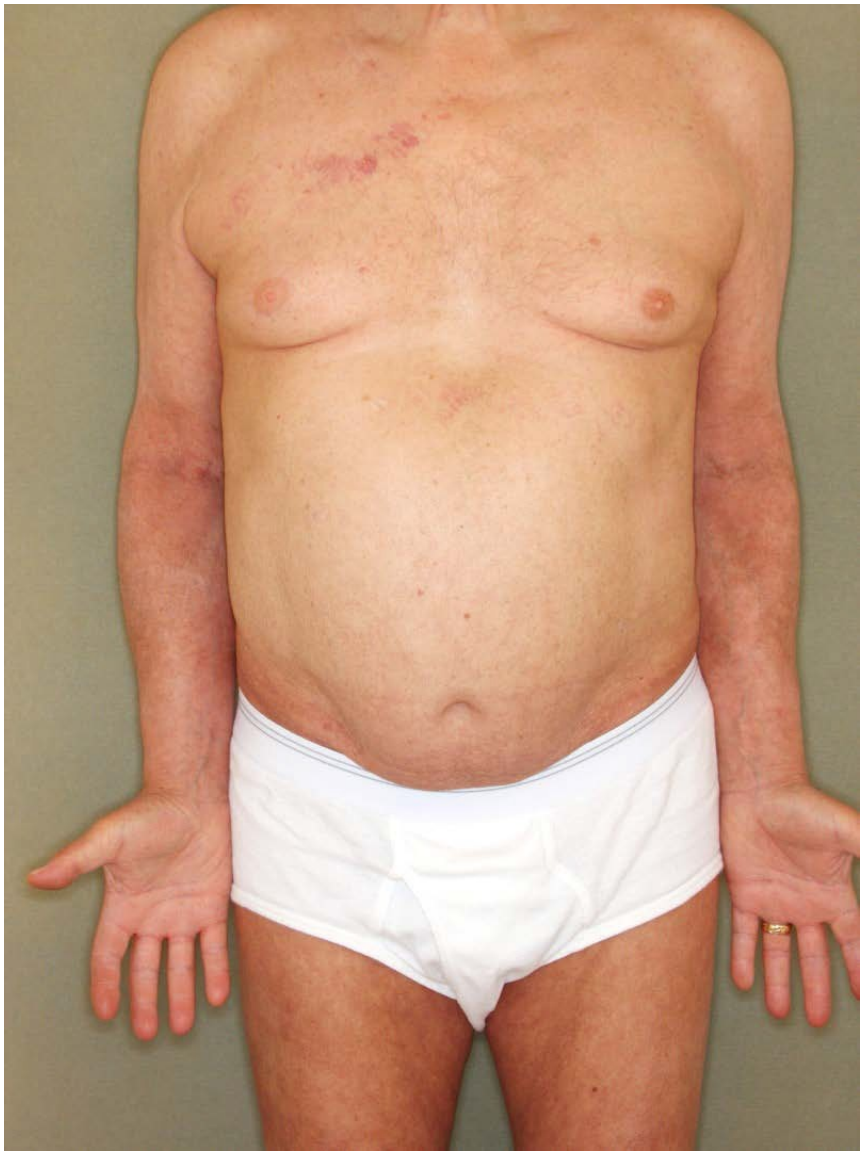
Pre-TSEBT

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



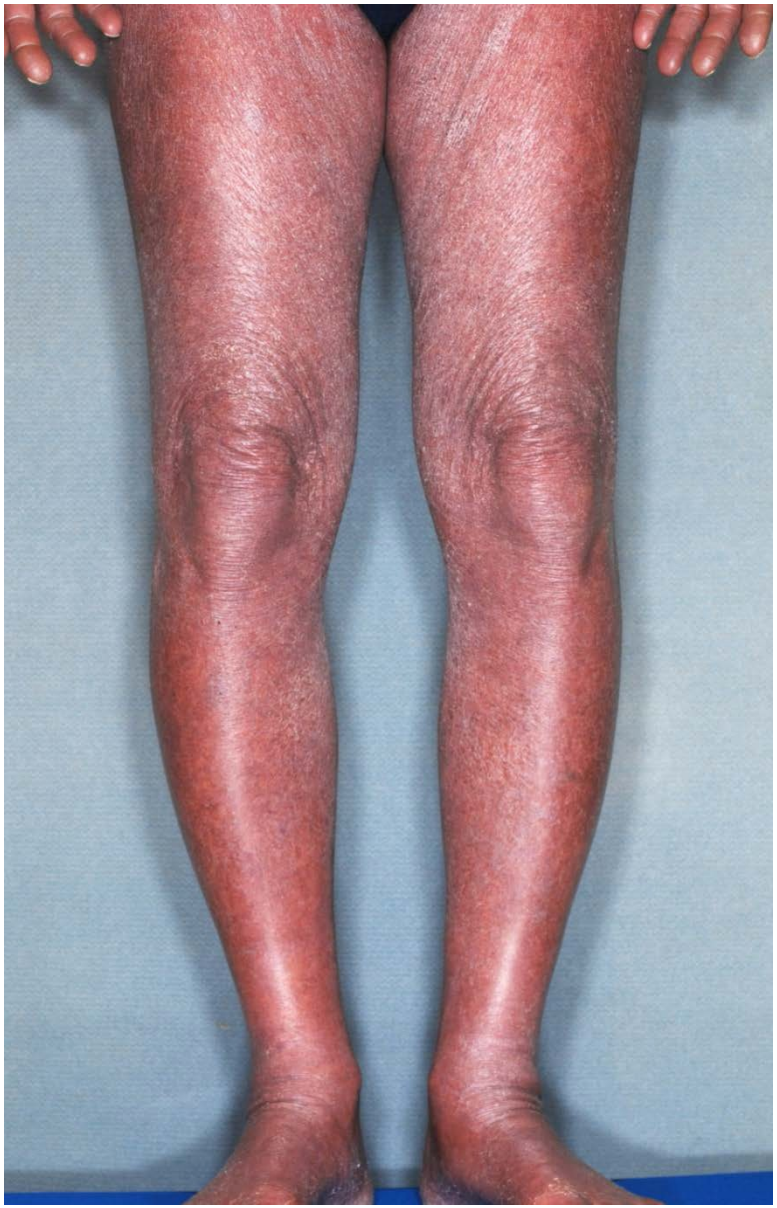
2 yr (NED, no GVHD)

CD4+/CD26-: normalized

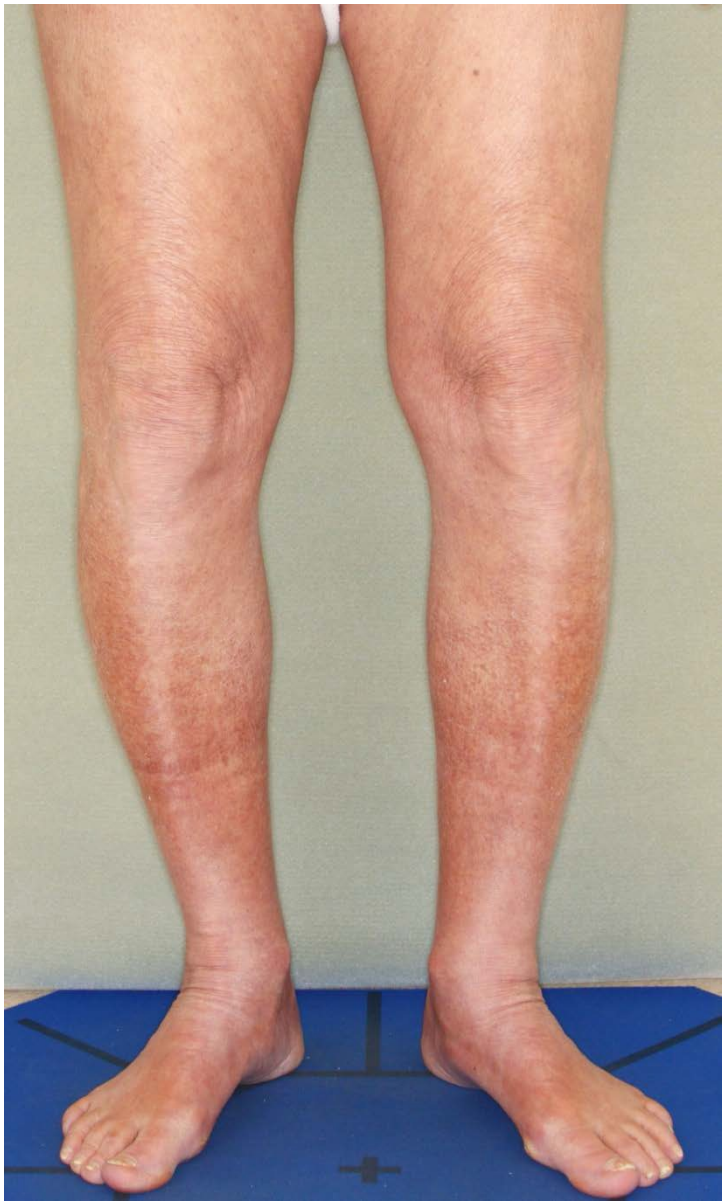


Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR

Pre-transplant



2 yr (NED, no GVHD)



Management of CTCL

Summary & Take-Home Messages

- MF and SS is very heterogeneous in clinical disease and responses to therapies- important to individualize
- With lack of evidence based help, utilization of consensus guidelines, such as NCCN, is important
- Stage-based management is essential, esp. not to over-treat early stages of MF
- Systemic or combination therapies are for refractory early stage or more advanced stages of MF and SS
- Given no curative therapies, participation in clinical trials should be considered whenever appropriate, and allogeneic HSCT considered in patients with advanced/aggressive/refractory disease

Questions