Staging and Treatment of Cutaneous Lymphomas: Utility of NCCN Practice Guidelines

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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

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Hodgkin's Lymphomas

Version 1.2013

NCCN.org

NHL => MFSS

US Treatment Guidelines in MF/SS & CBCL

www.nccn.org => NHL => MFSS or CBCL

- First available standard of care treatment guideline in cutaneous lymphoma in US
- Real time updates
- Lack of evidence-based help in CL → important role of consensus guidelines
- Help with insurance auth and reimbursement; given lots of off-label use

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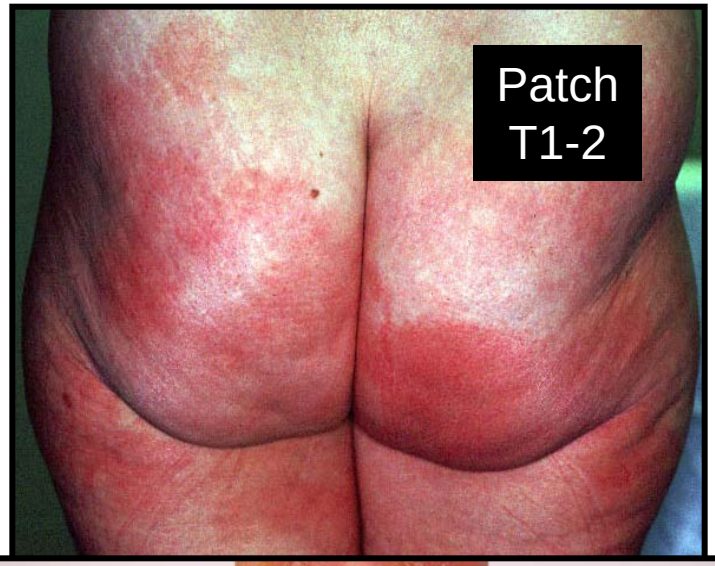
Cutaneous T- and NK/T-cell Lymphomas

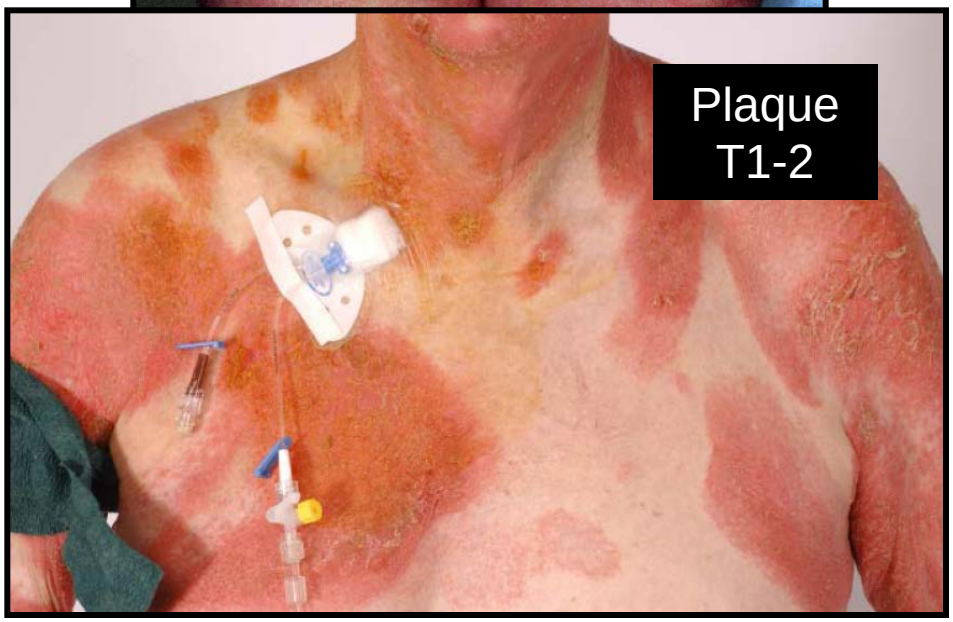
New WHO-EORTC Classification
Mycosis fungoides and variants/subtypes
Sézary syndrome
PC CD30+ lymphoproliferative disorders
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Cutaneous γ/δ T-cell lymphoma
Adult T-cell leukemia/lymphoma
PC peripheral T-cell lymphoma, unspecified • Aggressive epidermotropic CD8+ T-cell lymphoma • CD4+ sm/med-sized pleomorphic T-cell lymphoma • PTCL, other

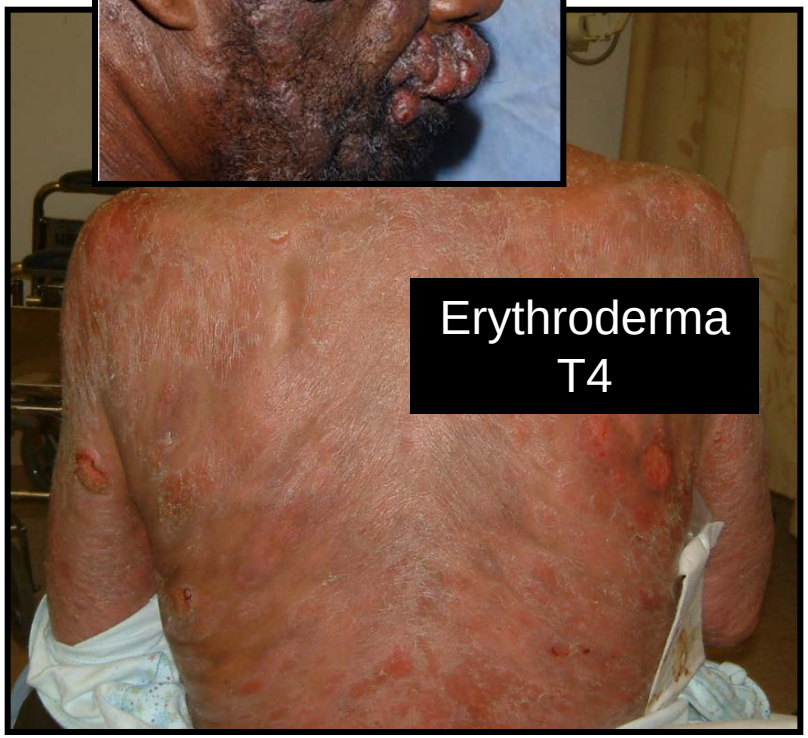
Blood 2005;105: 3768-85

WHO monogram, 4th Ed, 2008

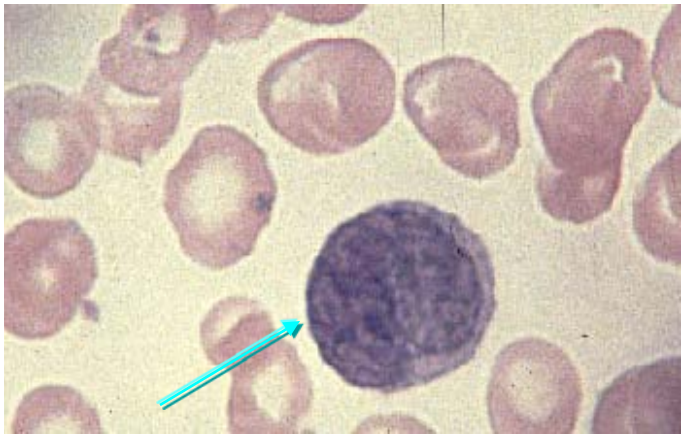
Mycosis Fungoides
Treatment of varying skin manifestations





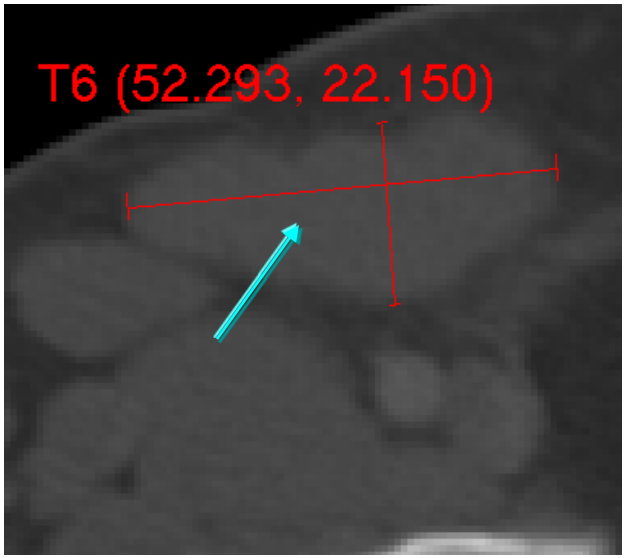


Management of extracutaneous disease

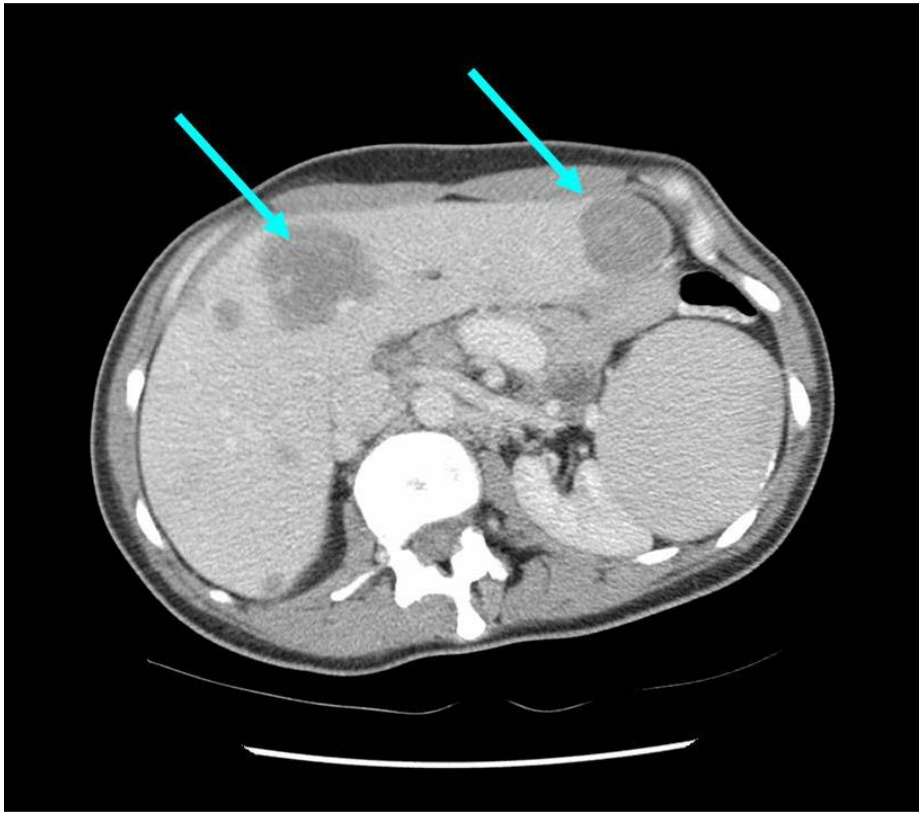


Blood

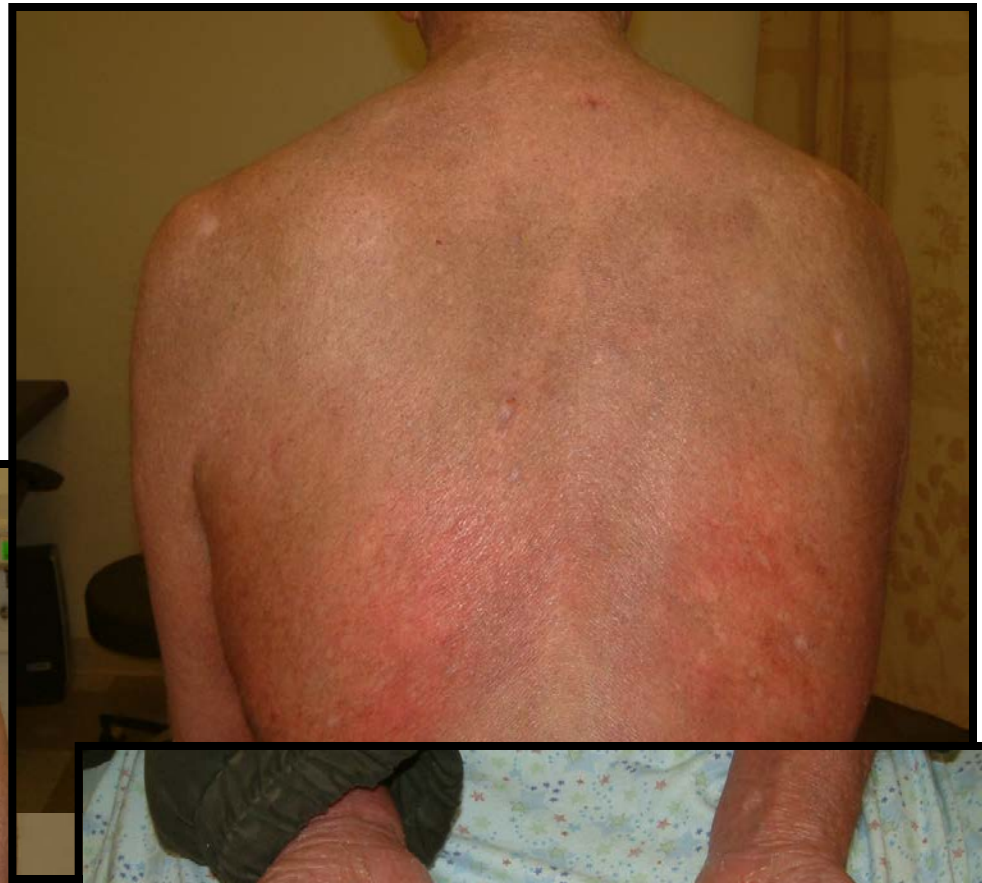
Lymph node

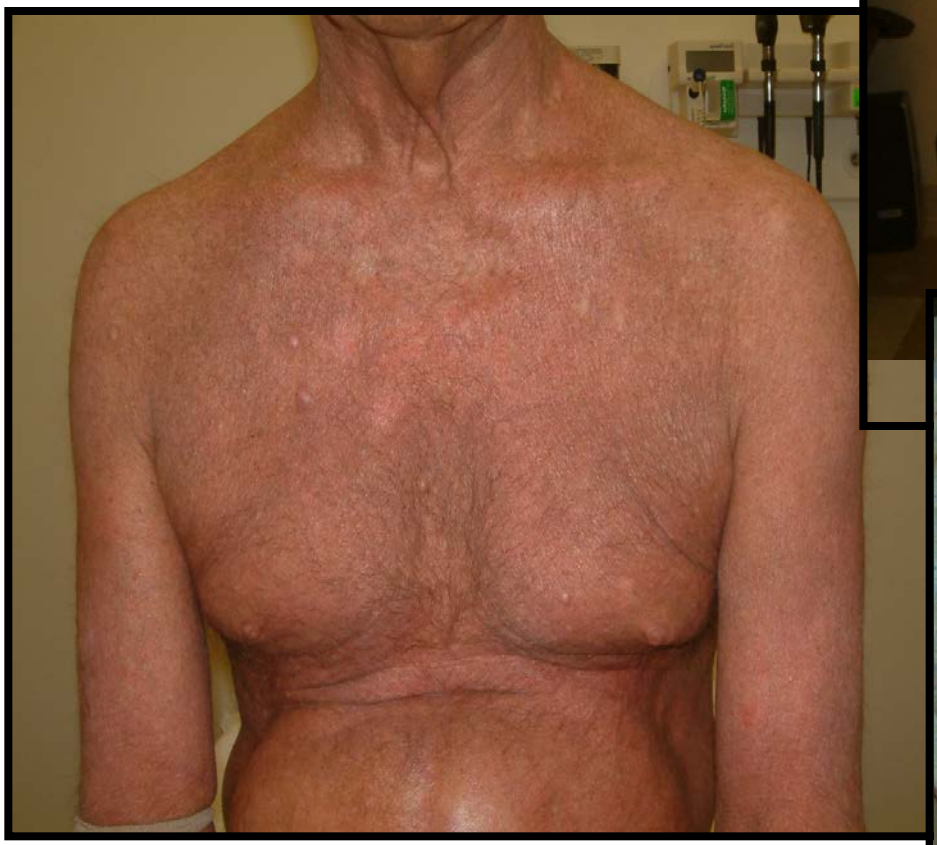


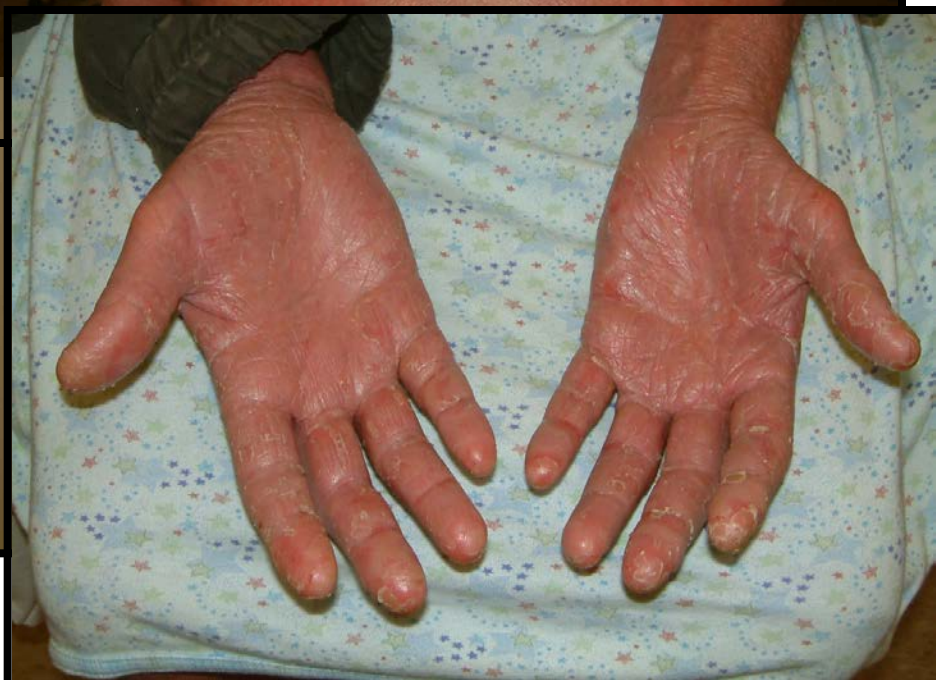
Viscera



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







General concepts in managing MF/SS-CTCL

- Lack of evidence-based help
- Consensus-based management

NCCN guidelines

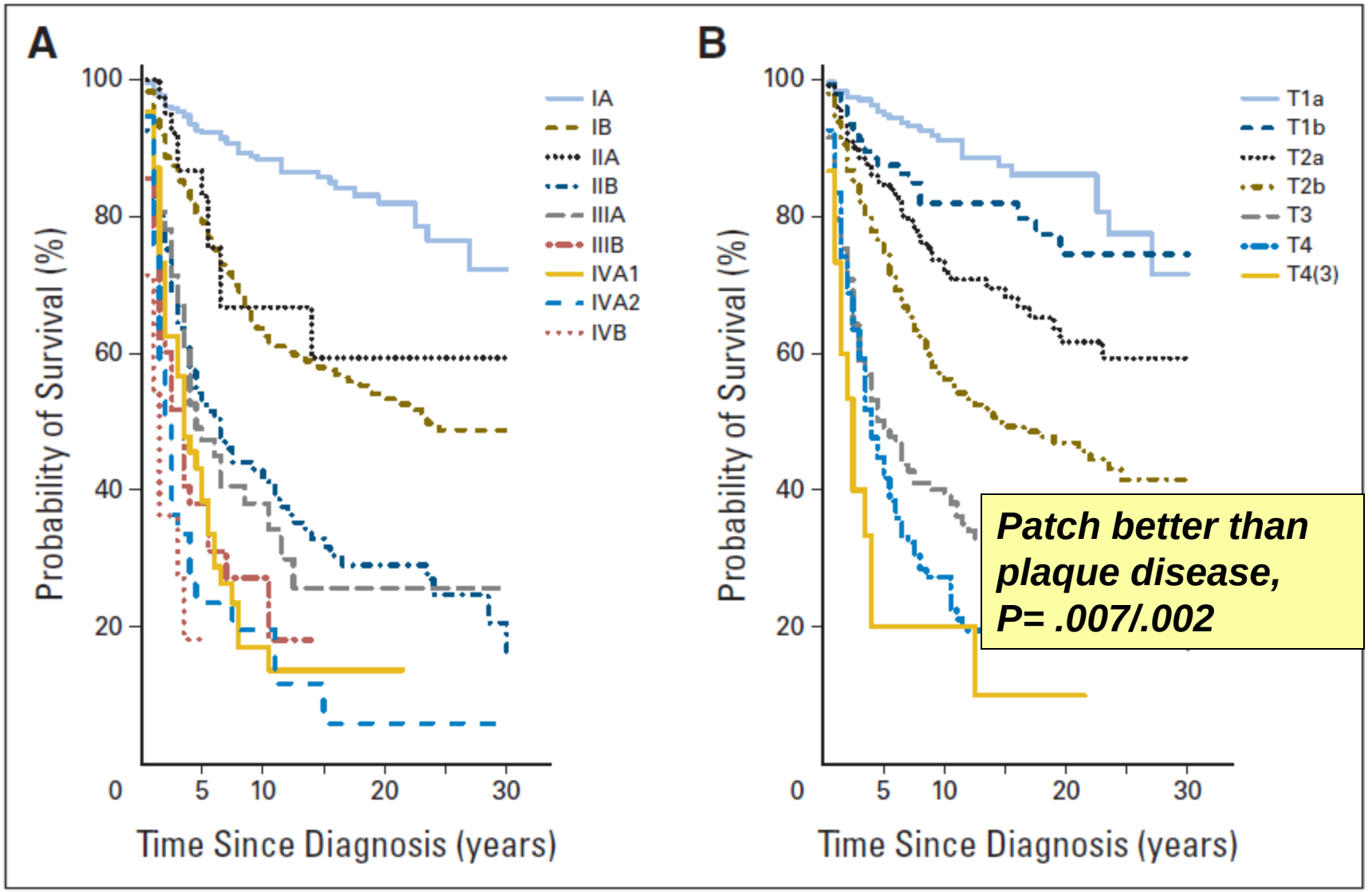
- Do no harm (refer to those who like skin or collaborate)
- Appreciate unique features of skin disease
  - Supportive therapy is essential (barrier defect)
    - Chronic control of skin infections (staph, HSV)
    - Use anti-itch regimens, emollients/sealants
  - Things that work in LNs may not work 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
  - US vs. other countries
  - Insurance barriers

Survival decreased with advancing T class and overall clinical stage

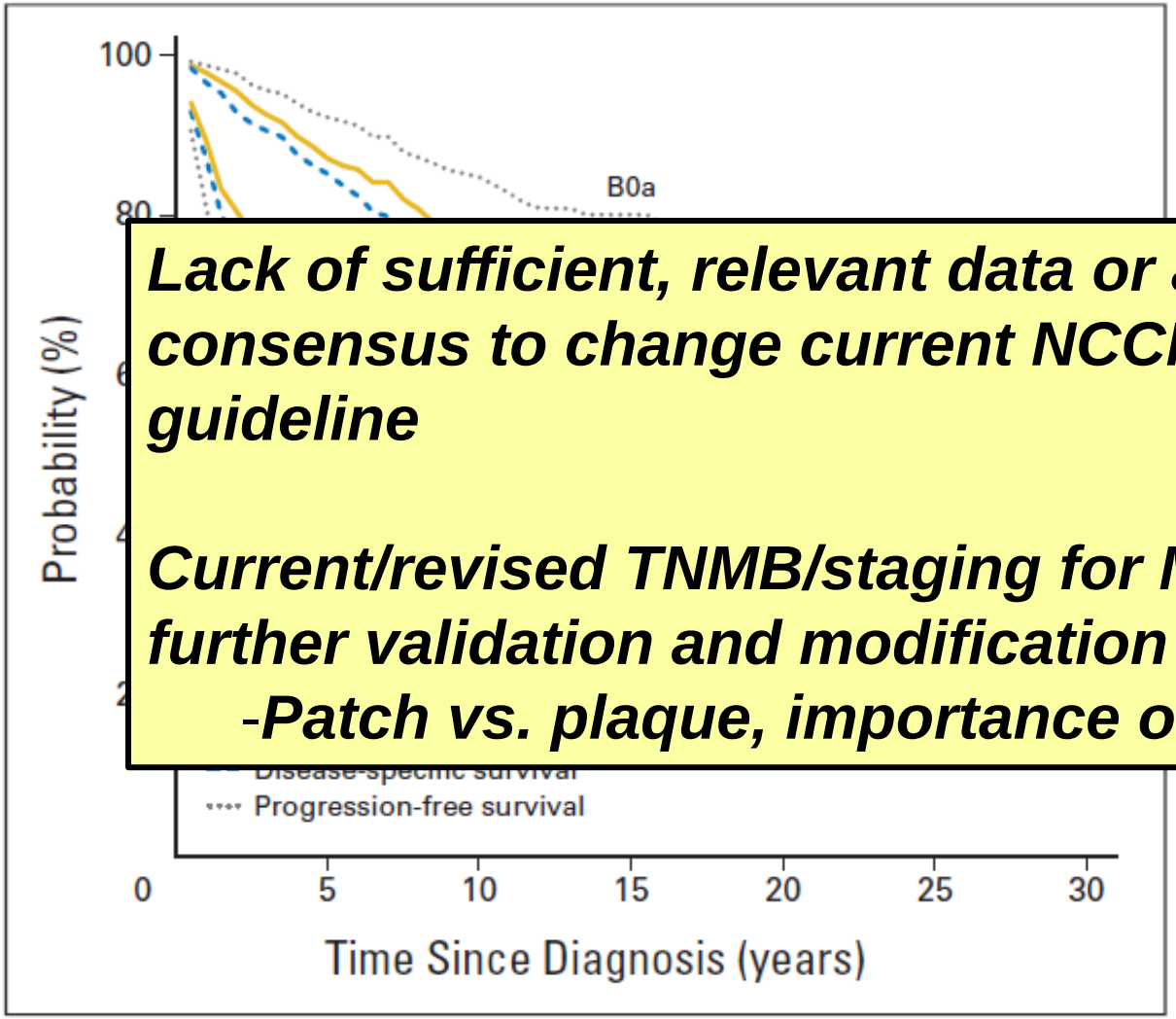
DSS utilizing revised staging system



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

B0 with positive clone (same as skin), B0b, a/w worse outcome

Impact of clonality data



Sig OS/DSS differences by increasing B-classification; *p < .001*

Lack of sufficient, relevant data or adequate consensus to change current NCCN practice guideline

Current/revised TNMB/staging for MF/SS needs further validation and modification

-Patch vs. plaque, importance of LN/B-clone

B1 vs. B2, *p=.040*

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

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Mycosis Fungoides/Sezary Syndrome

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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)
Stage IIB	See Primary Treatment (MFSS-6)
Stage III	See Primary Treatment (MFSS-7)
Stage IV	See Primary Treatment (MFSS-8)

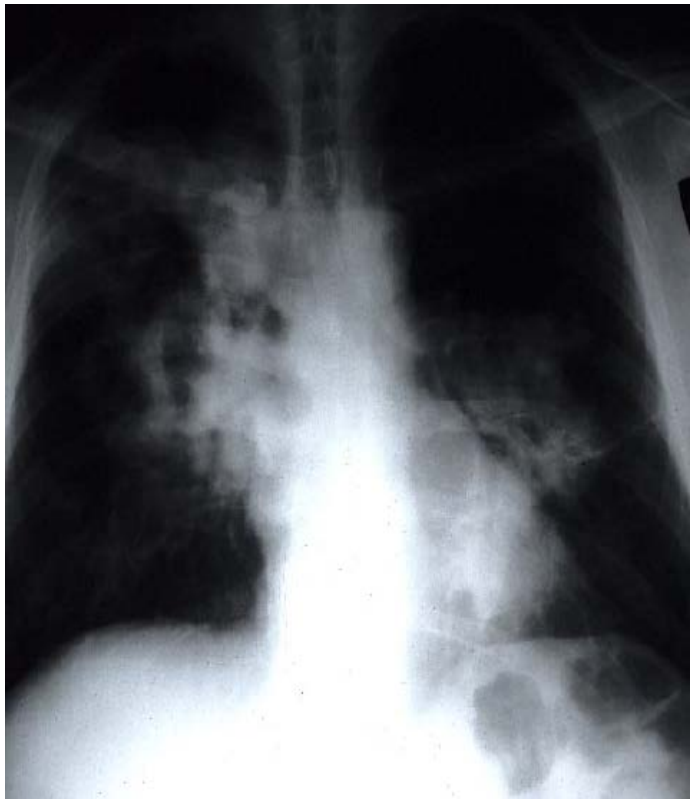
Stage-based treatment algorithm

Blood 2007;110:1713

www.nccn.org => NHL => MFSS

Staging Evaluation, Mycosis Fungoides/Sézary Syndrome

- Complete PE
  - Thorough skin exam (extent & type)
  - LN, organomeg/masses
- Laboratory studies
  - CBC with Sézary cell analysis
    - Sézary cell count (morphologic exam)
    - Flow cytometry: CD3, CD4, CD7, CD8, CD26 to assess for ↑CD4+, CD4/CD8 or abnormal phenotype (CD4+/CD7-%, CD4+/CD26-%, other)
  - Comp metabolic, LDH
- Imaging studies
  - Chest x-ray
  - Contrast-enhanced CT or whole body PET/CT: ≥T2, LCT, FMF, ↑LN/labs
- Biopsy of suspicious LNs (>1.5 cm or sig. PET+) or suspected visceral involvement
- *BM biopsy considered in B2 (not required)*



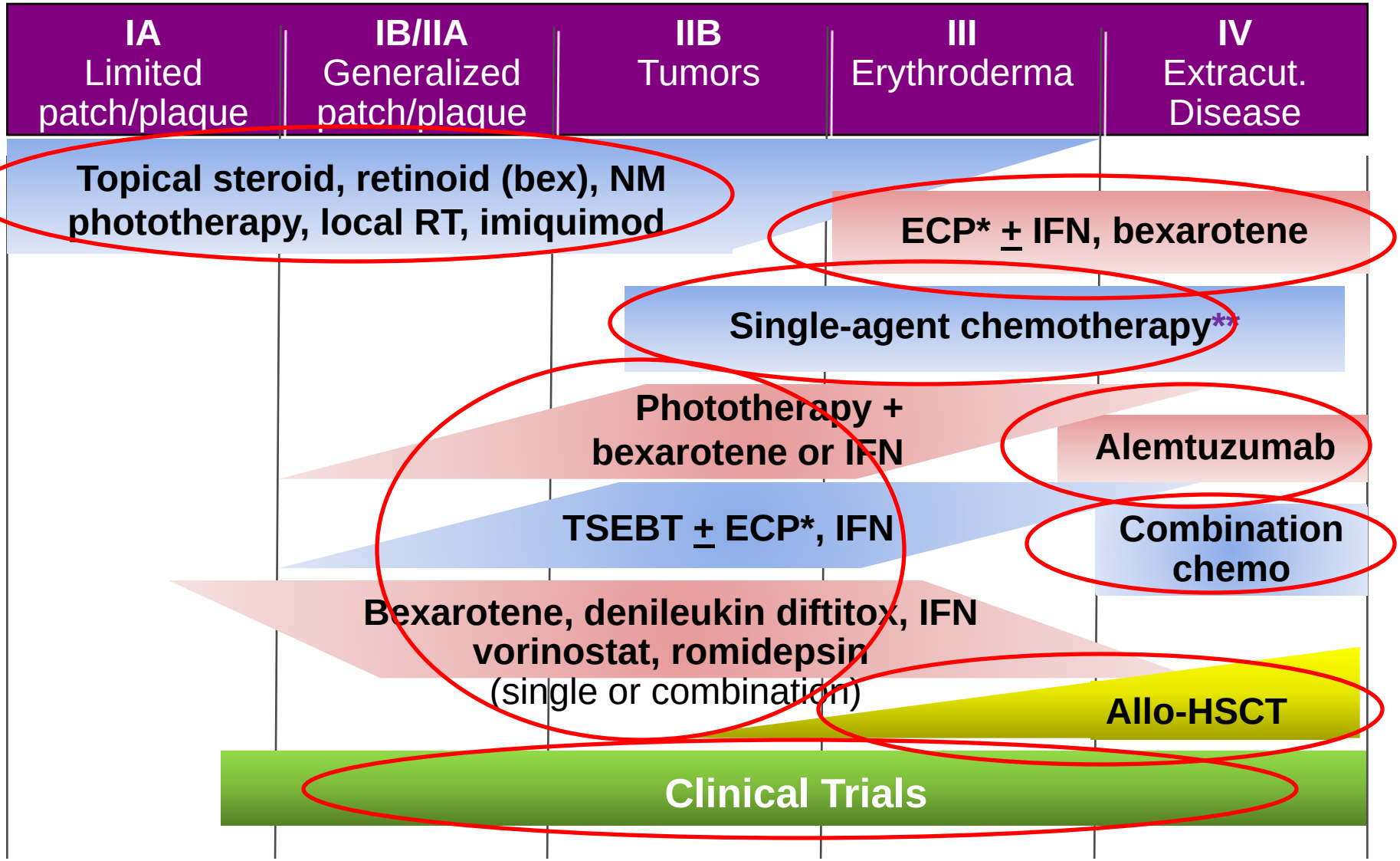
Revised MF/SS guidelines *Blood* 2007:110:1713-22.

Updated in NCCN Practice Guidelines, www.nccn.org

Stage-based management

Current Clinical Management of CTCL, *2013*

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



*ECP = photopheresis

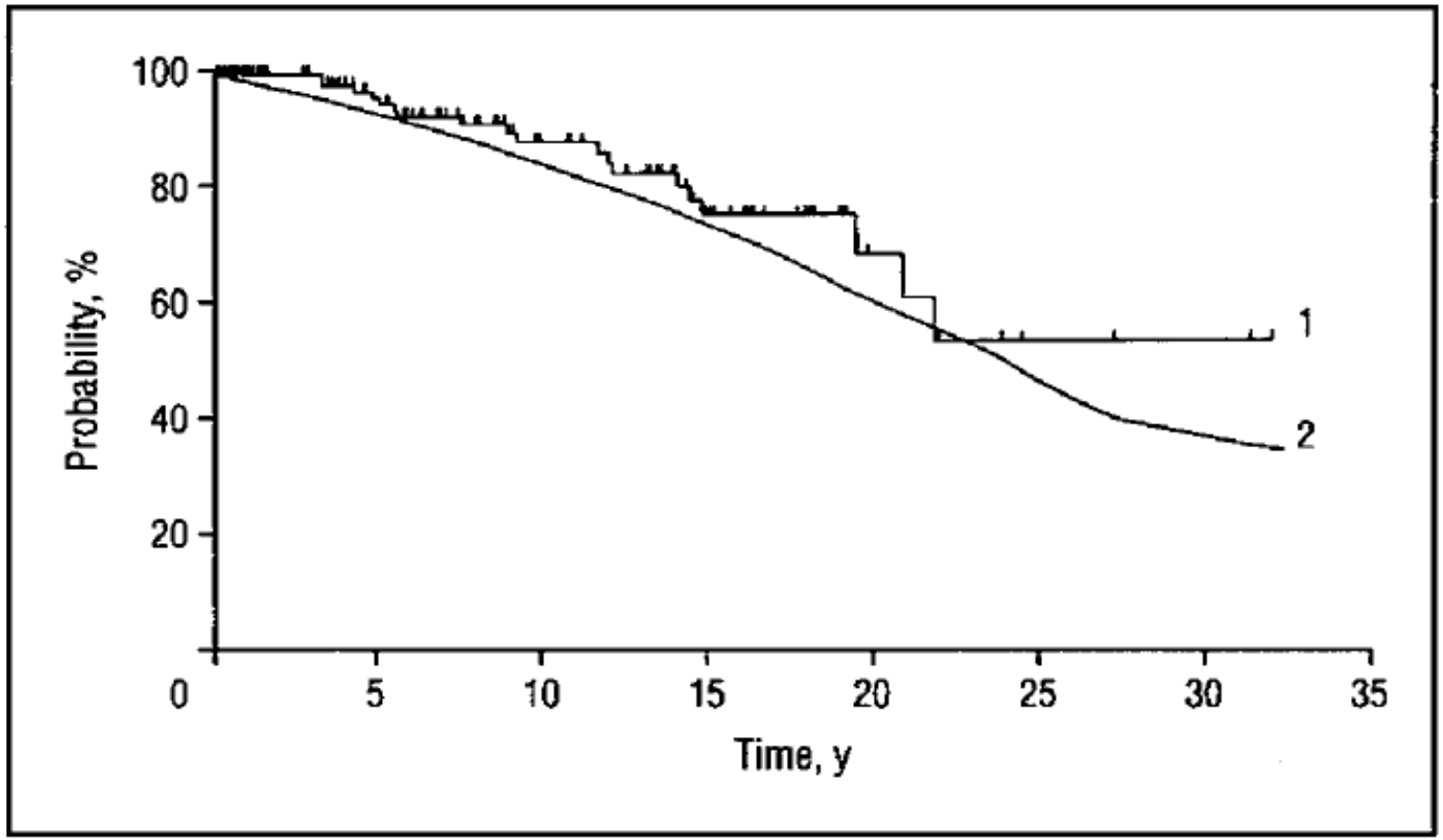
** Methotrexate, liposomal doxorubicin, gemcitabine, pentostatin, chlorambucil, etoposide, **pralatrexate**

Skin-directed therapies

- Topical steroids
- Topical chemotherapy (mechlorethamine, carmustine)
- Topical retinoids (bexarotene)
- Topical imiquimod
- Phototherapy
  - UVB (narrow band, broad band)
  - PUVA (psoralen + UVA)
- Radiation
  - Local (12-36 Gy)
  - Total skin electron beam therapy (12-36 Gy)
- *Excimer, photodynamic therapy (not in NCCN)*

Derm Ther 2003;16:283-302, Arch Dermatol 2003;139:165, Arch Dermatol 2002;138:325, J Am Acad Dermatol 2005;52:275, Arch Dermatol 2005;141:305, Arch Dermatol 2011;147:561

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

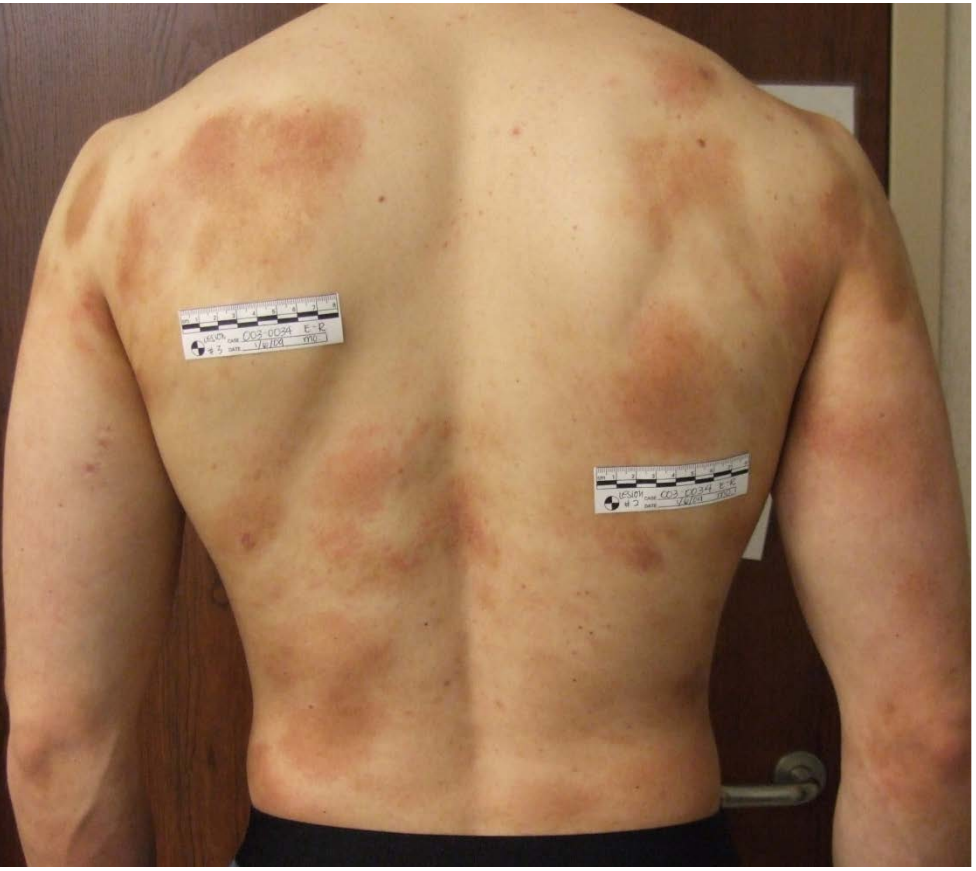
Reliable skin responses with skin-directed options as primary therapy in stages I-IIA (skin-limited, patch/plaque disease)

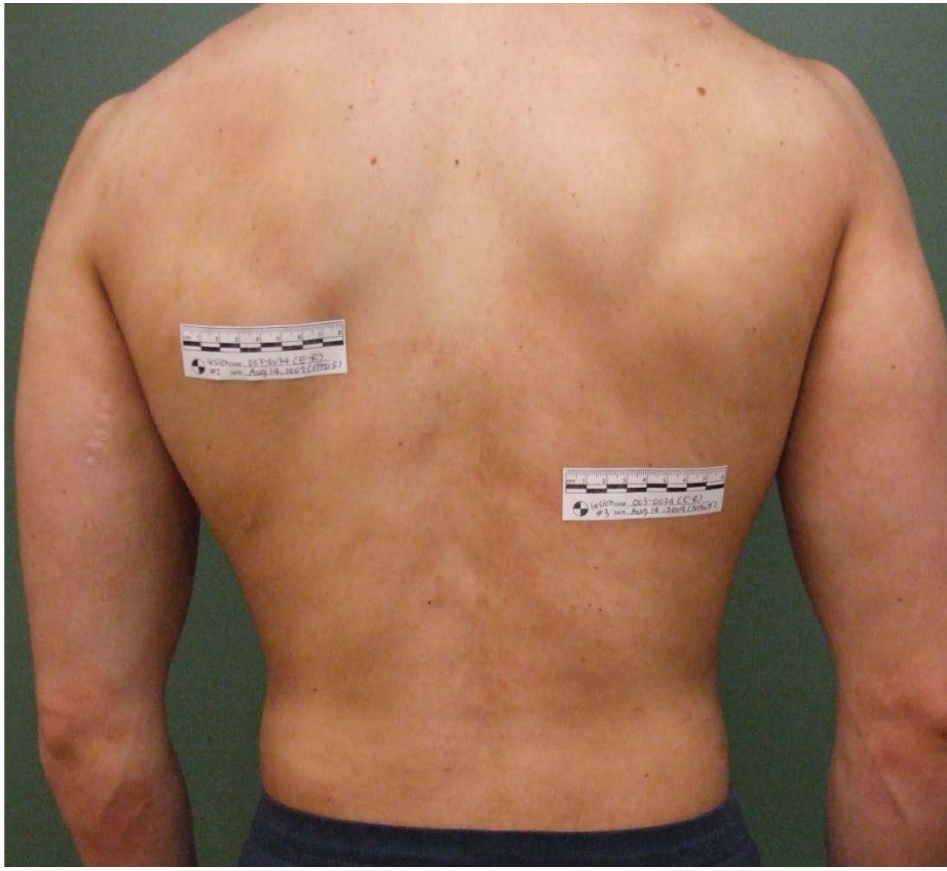
Skin Therapy	CR	ORR
Topical steroids	45-65%	75-95%
Bexarotene gel	20-35%	50-75%
Topical NM	25-70%	50-90%
nbUVB	45-75%	75-100%
PUVA	50-80%	85-100%
TSEBT (≥30 Gy)	80-90%	100%

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

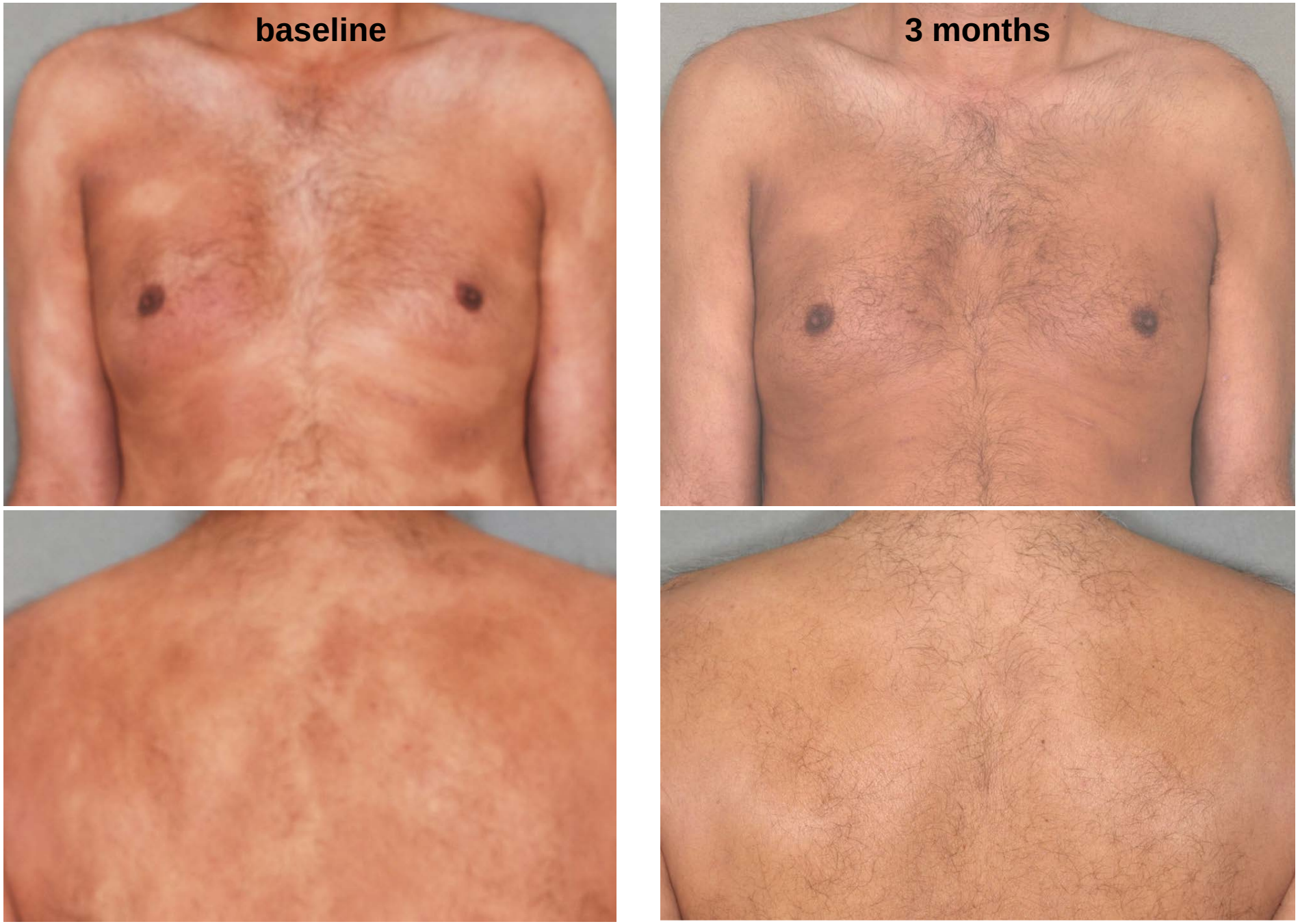
Arch Dermatol 2003;139:165, J Am Acad Dermatol 2003;49:801, J Am Acad Dermatol 2002;47:191, Arch Dermaol 2005;141:305, Arch Dermatol 2011;147:561, Arch Dermatol 2001;137:581, J Clin Oncol 2007;25:3109, J Clin Oncol 2010;28:4485

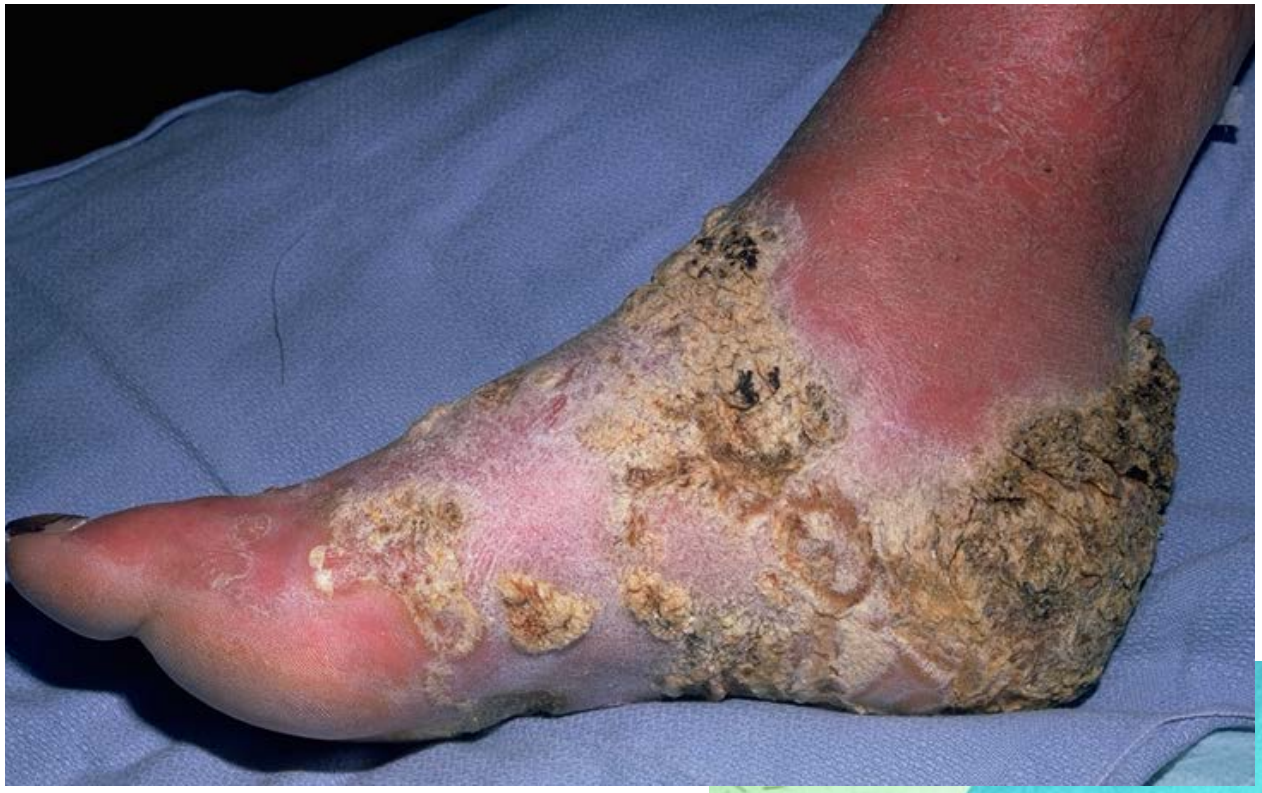
Clinical response to topical nitrogen mustard gel

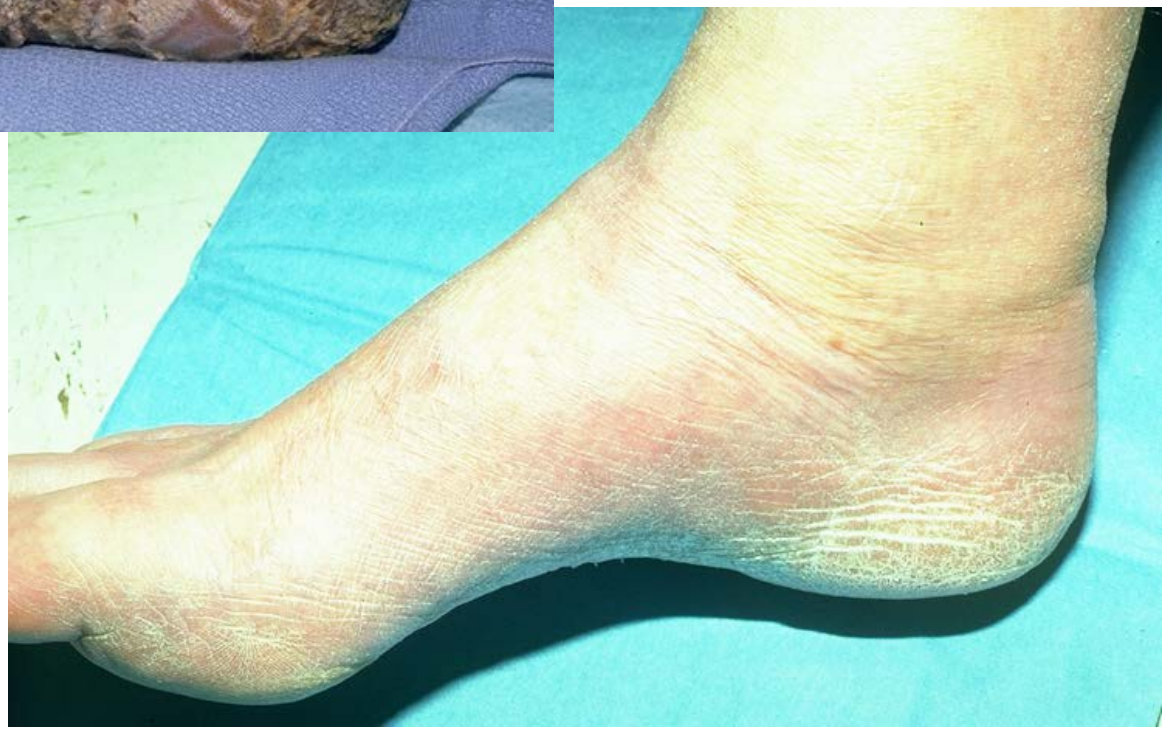




Narrow band UVB







Localized RT in Woringer Kolopp disease

Systemic therapies for MF/SS-CTCL

- **“Milder” therapies => “Category A in NCCN”**
  - First-line systemic tx in refractory early dz, IA-IIA
  - Bexarotene, IFNs, HDAC-inhibitors (vorinostat, romidepsin), photopheresis, denileukin diftitox, low-dose methotrexate
- **Single-agent cytotoxic therapies => “Category B in NCCN”**
  - Refractory to Category A agents
  - First-line: liposomal doxorubicin, gemcitabine
  - Second-line: other single agent cytotoxic
- Frontline systemic therapies **for aggressive growth pattern** (large cell transformation, stage IV non-Sezary) **=> “Category C in NCCN”**
  - Liposomal doxorubicin, gemcitabine, denileukin diftitox, romidepsin, pralatrexate, regimens for PTCL (stage IV)

NCCN Practice Guidelines 1.2013

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

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

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

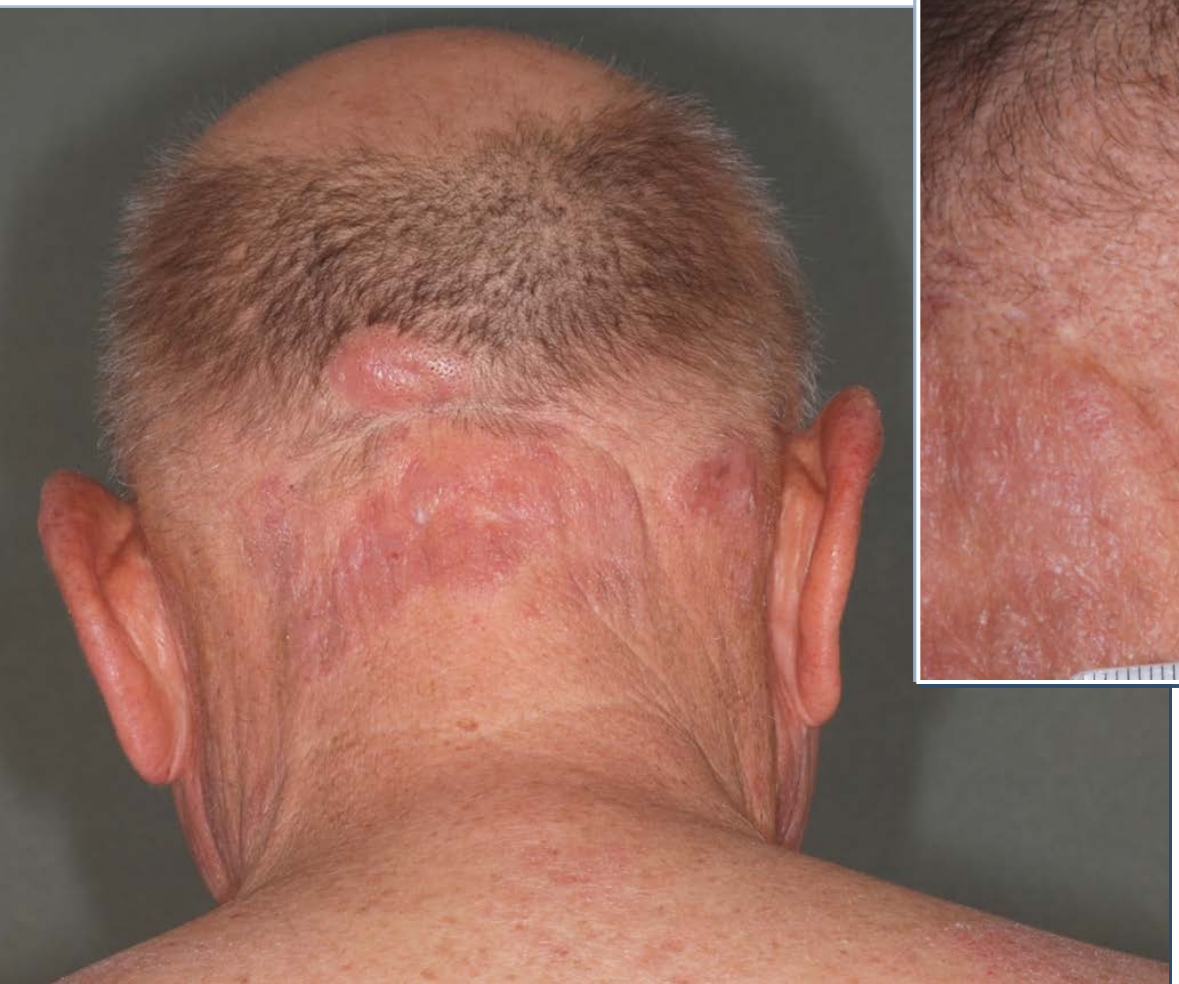
- **Systemic + Systemic**
  - Retinoid + IFN
  - Bexarotene + denileukin diftitox
  - Photopheresis* + retinoid
  - Photopheresis* + IFN
  - Photopheresis* + retinoid + IFN

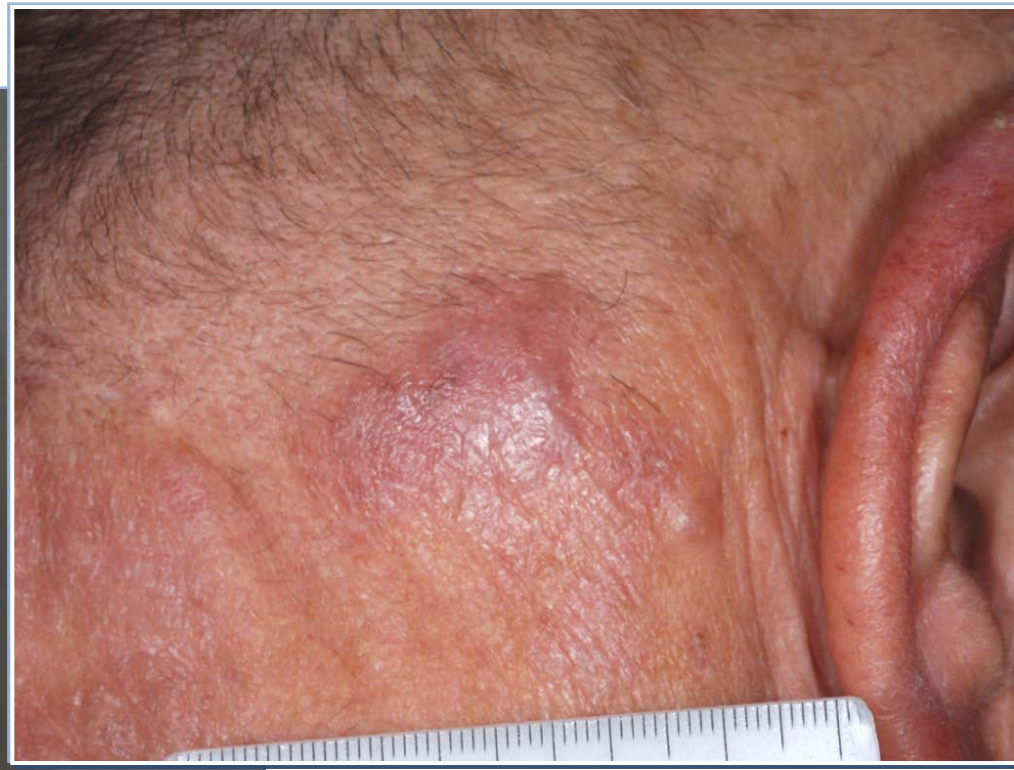
Is combination therapy "better"?

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

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

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.





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

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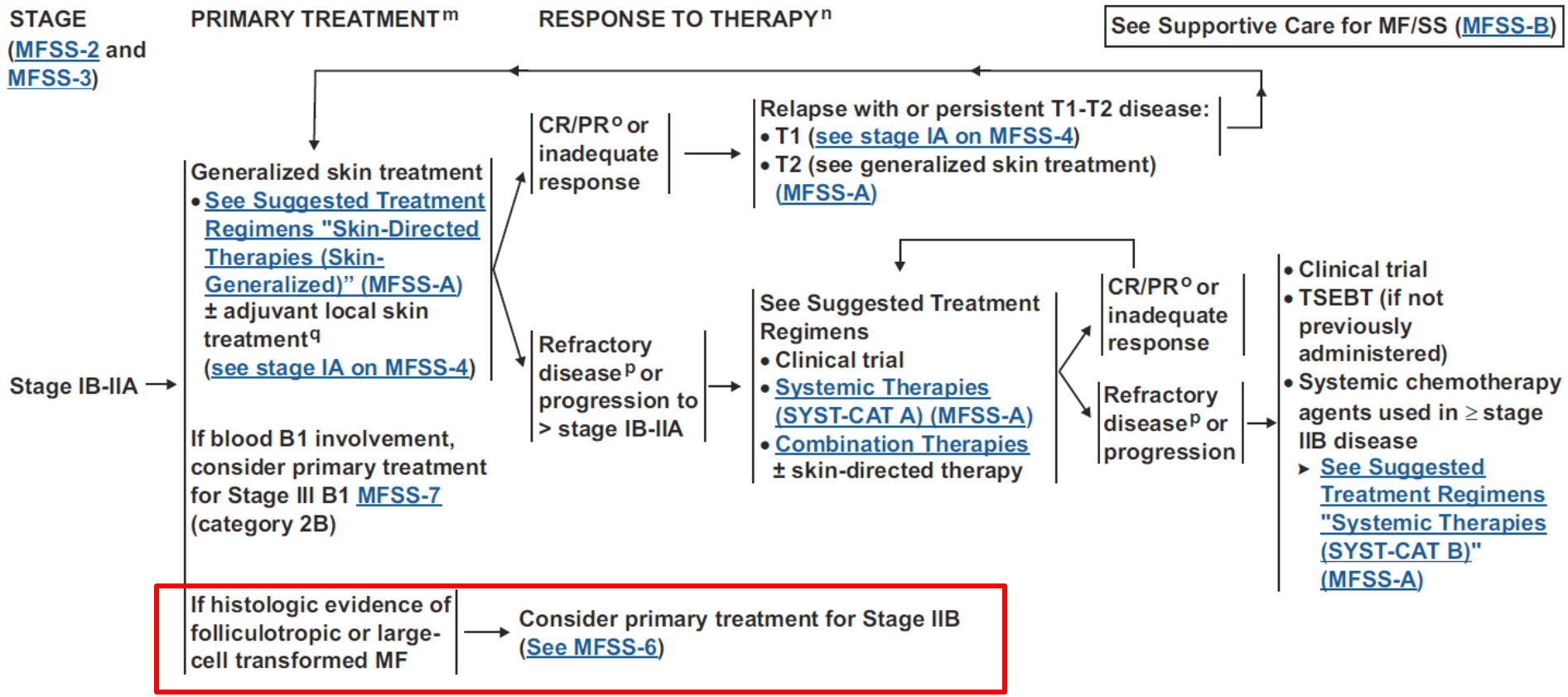


Approach to the management of F-MF based on extent/severity of folliculotropic lesions

Limited or mild sx

- Top/IL steroids
- Imiquimod
- Bexarotene gel
- Topical NM
- Local RT
- Phototherapy
- “milder” systemic therapy (bexarotene, mtx)
- Clinical trial

Generalized or severe sx

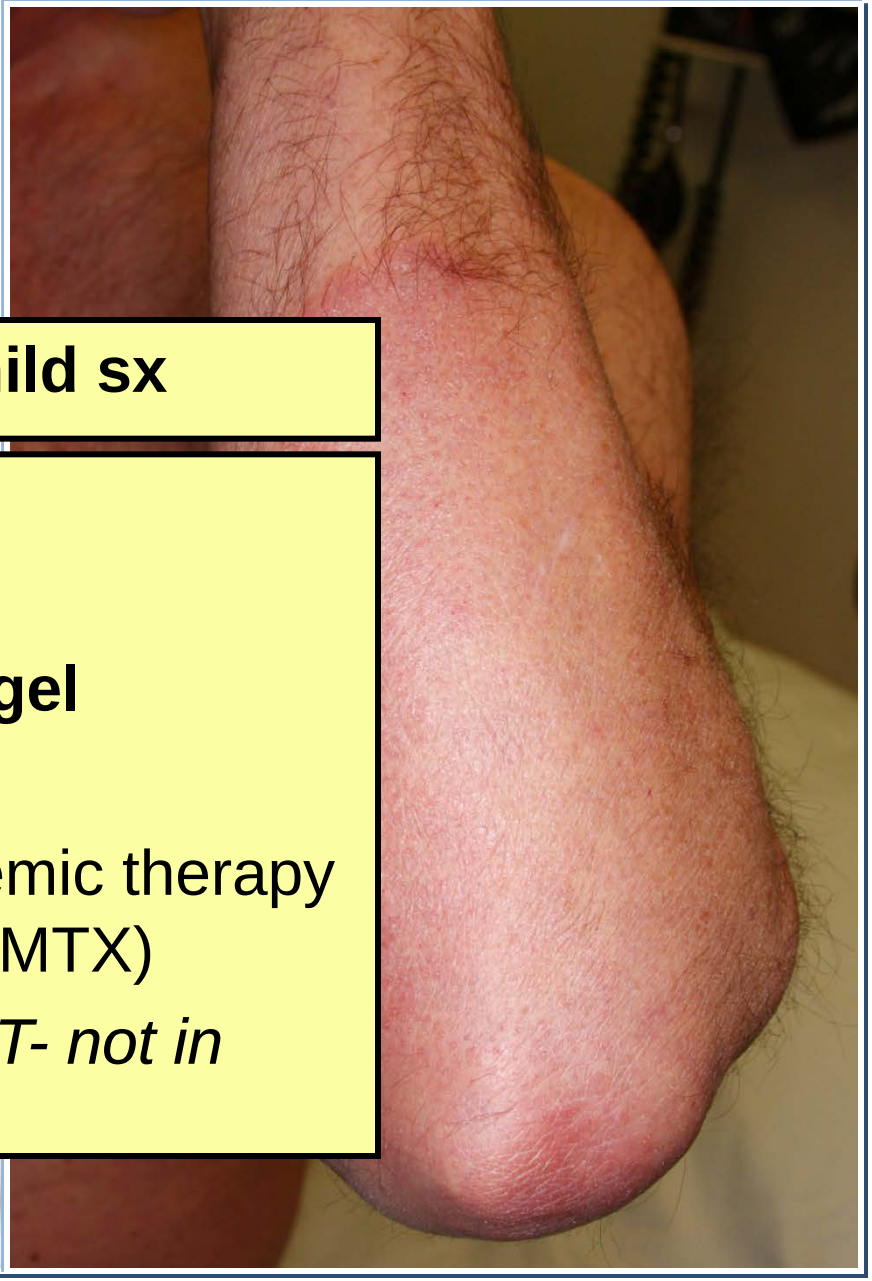
- Skin-directed + systemic agent
  - Phototherapy + bex or IFN
- Systemic agent +/- skin-directed tx
  - Bex, IFN, MTX, vori, romi
- If LCT+, Cat-B/C NCCN
- TSEBT
- Clinical trial

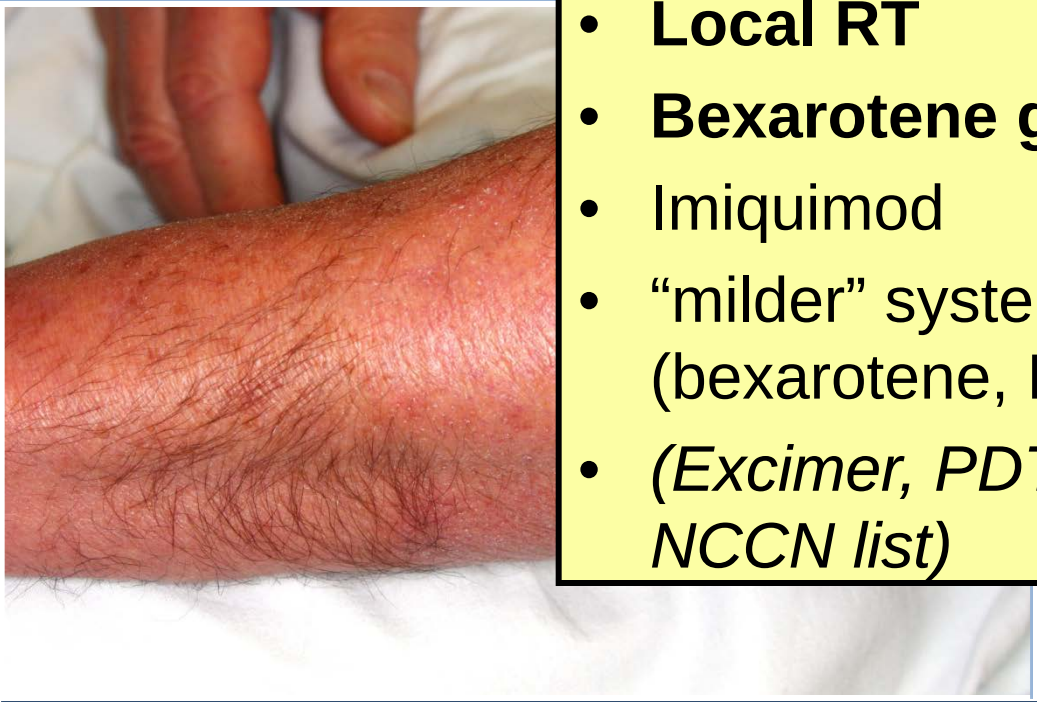
Combination strategies in refractory folliculotropic patch/plaque or tumor disease

Skin + systemic Therapy	Systemic + systemic Therapy
PUVA + IFN	Bexarotene + IFN
PUVA or nbUVB + bexarotene	Bex + denileukin diftitox
PUVA or nbUVB + photopheresis	Methotrexate + IFN
PUVA + [Photopheresis + bexarotene +/- IFN]	Methotrexate + bexarotene
TSEBT + photopheresis	Vorinostat + IFN
Low-dose TSEBT + HDAC inhibitors	Vorinostat + bexarotene

Hoping for improved synergistic efficacy and/or less toxicity by allowing lower doses of each

7 yr h/o very slowly enlarging patch/plaque, localized to left forearm, failed top ster

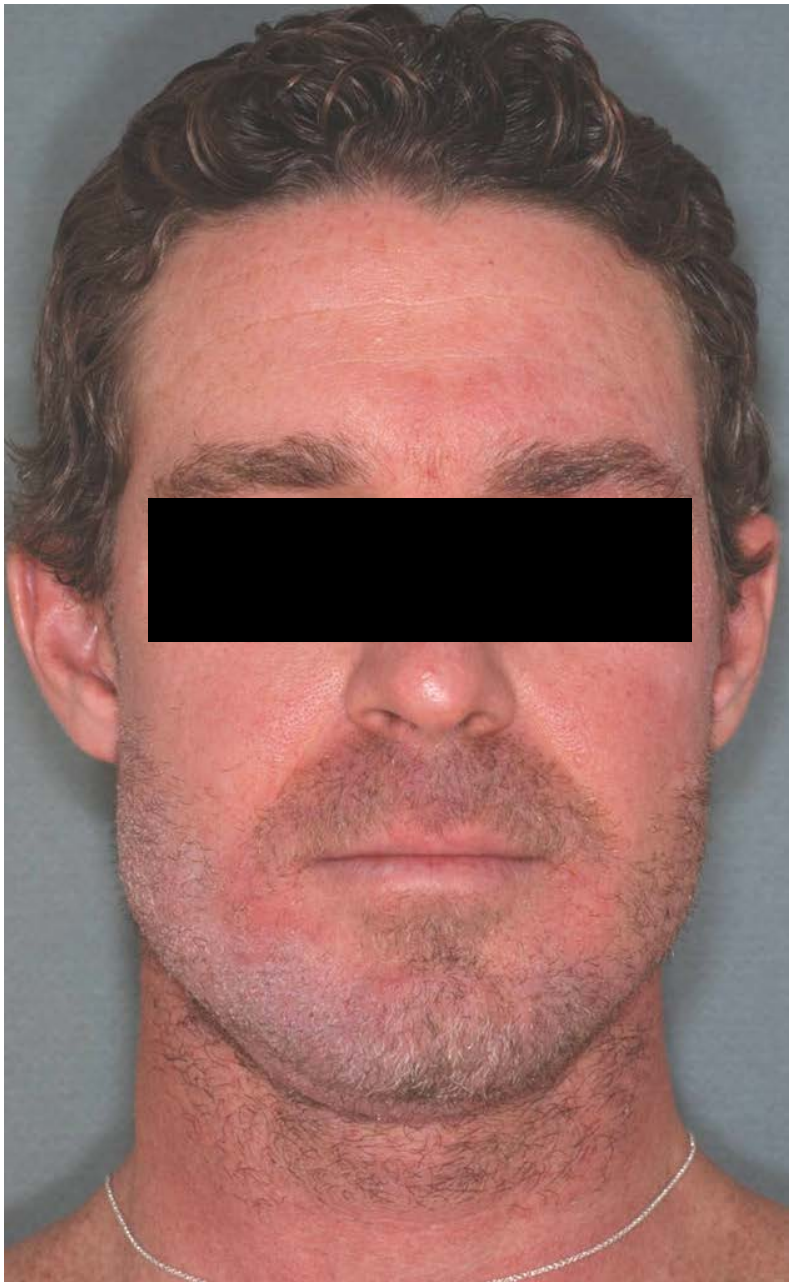


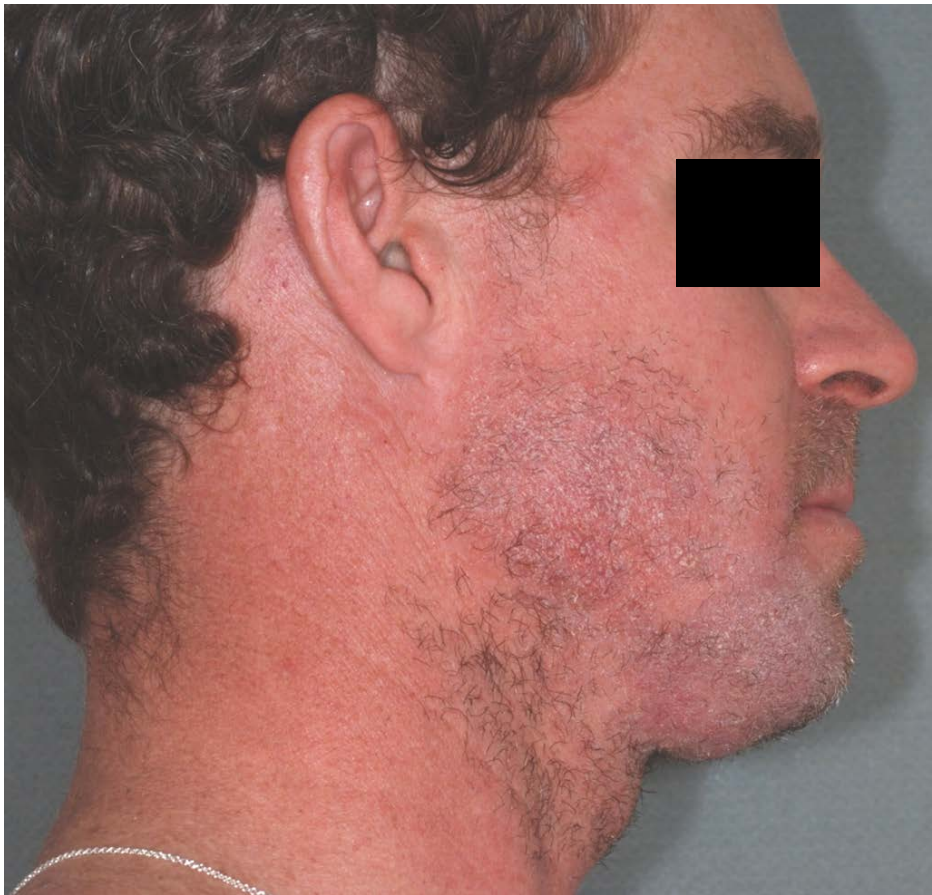


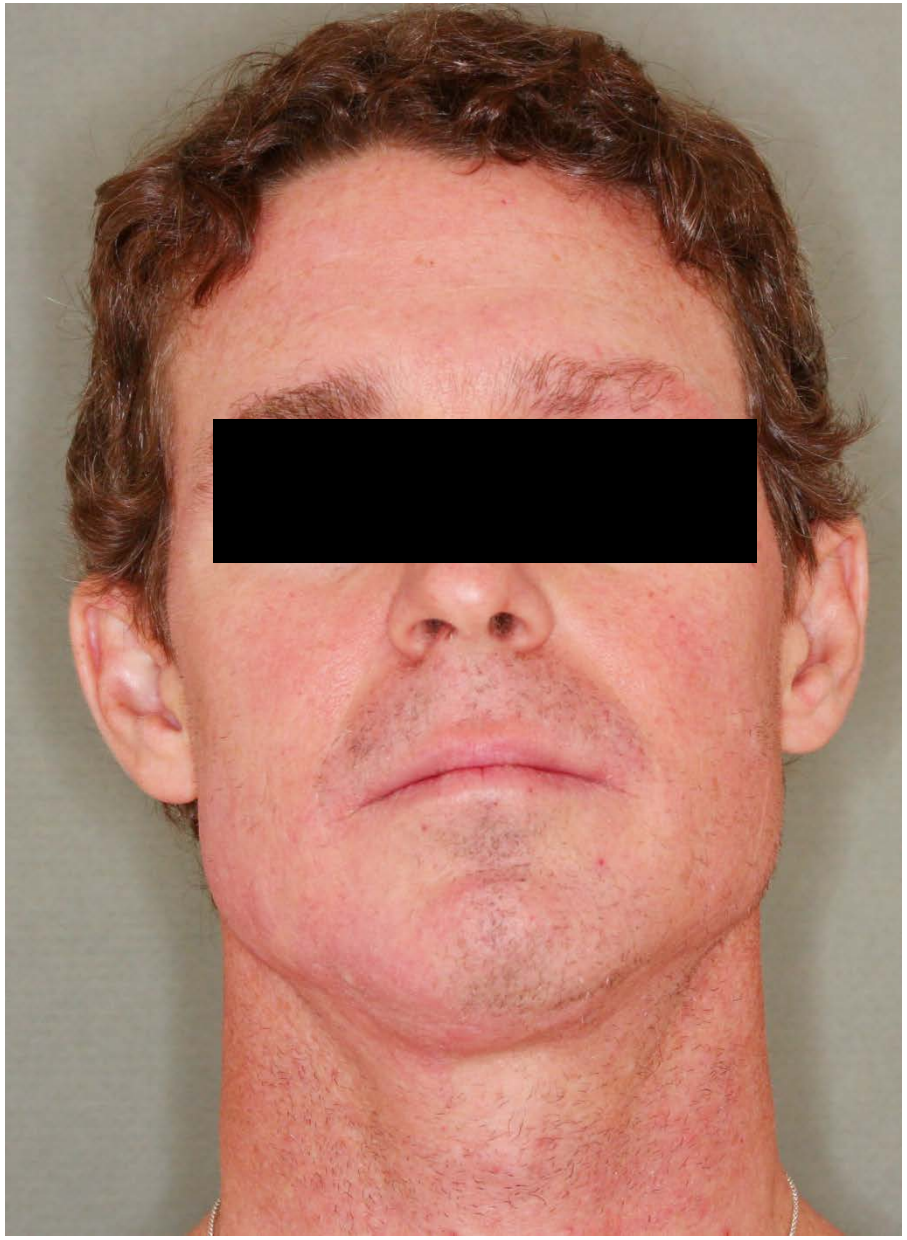
- **Limited or mild sx**

- **Topical NM**
- **Local RT**
- **Bexarotene gel**
- Imiquimod
- “milder” systemic therapy (bexarotene, MTX)
- *(Excimer, PDT- not in NCCN list)*

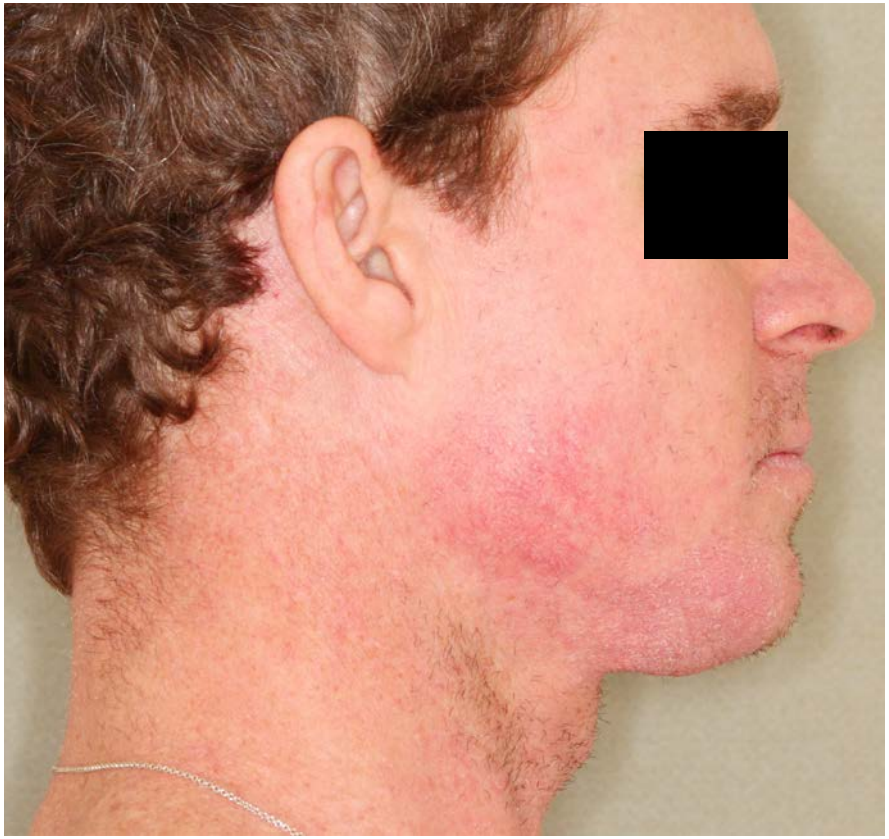
Localized refractory disease: Predominantly face, refractory to oral bex, MTX, IFN



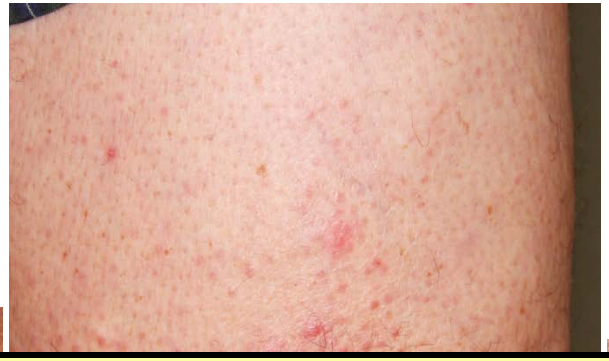


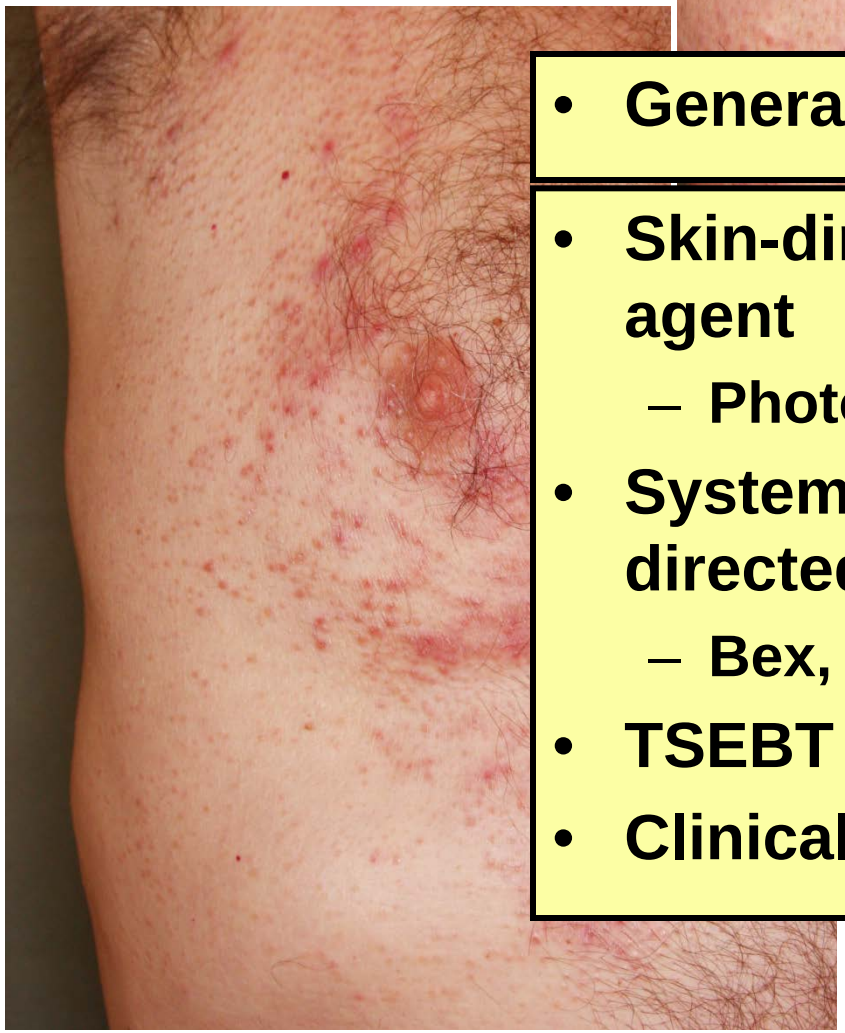


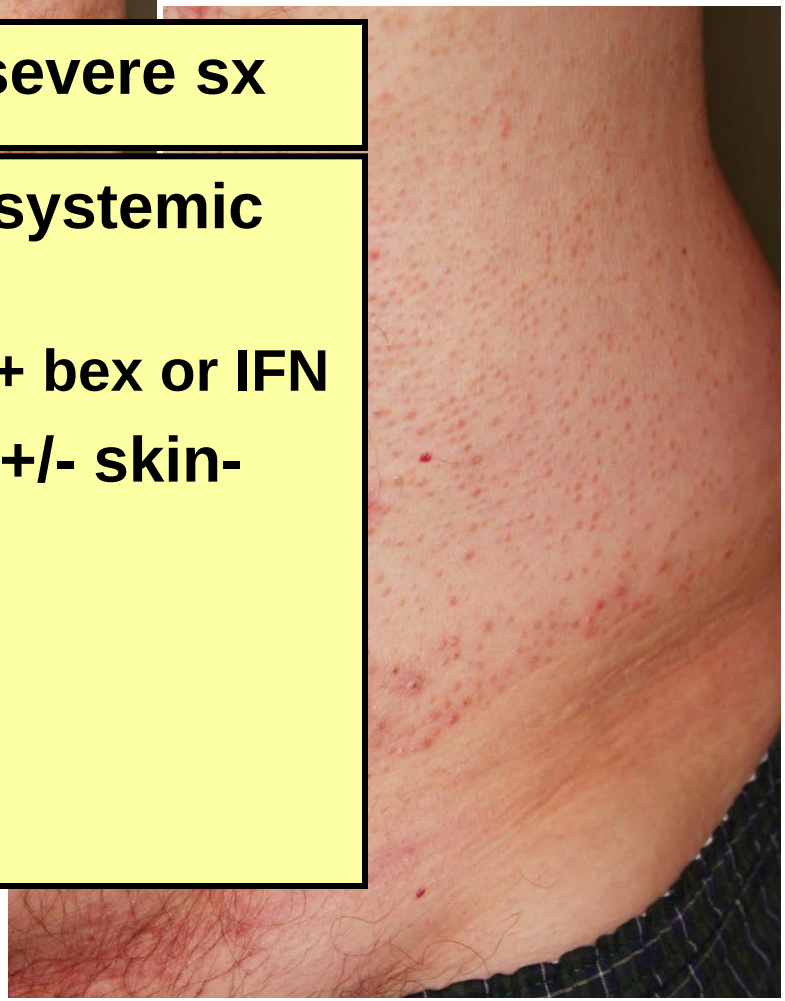
Durable local control w/ local electron beam therapy (tailored-made “face technique”)



Generalized folliculotropic disease



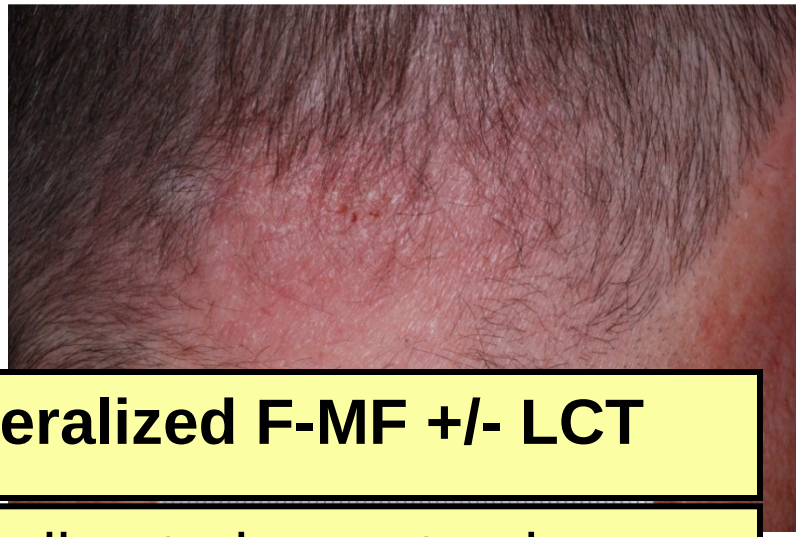




- **Generalized or severe sx**

- **Skin-directed + systemic agent**
  - **Phototherapy + bex or IFN**
- **Systemic agent +/- skin-directed tx**
  - **Bex, IFN, MTX**
- **TSEBT**
- **Clinical trial**

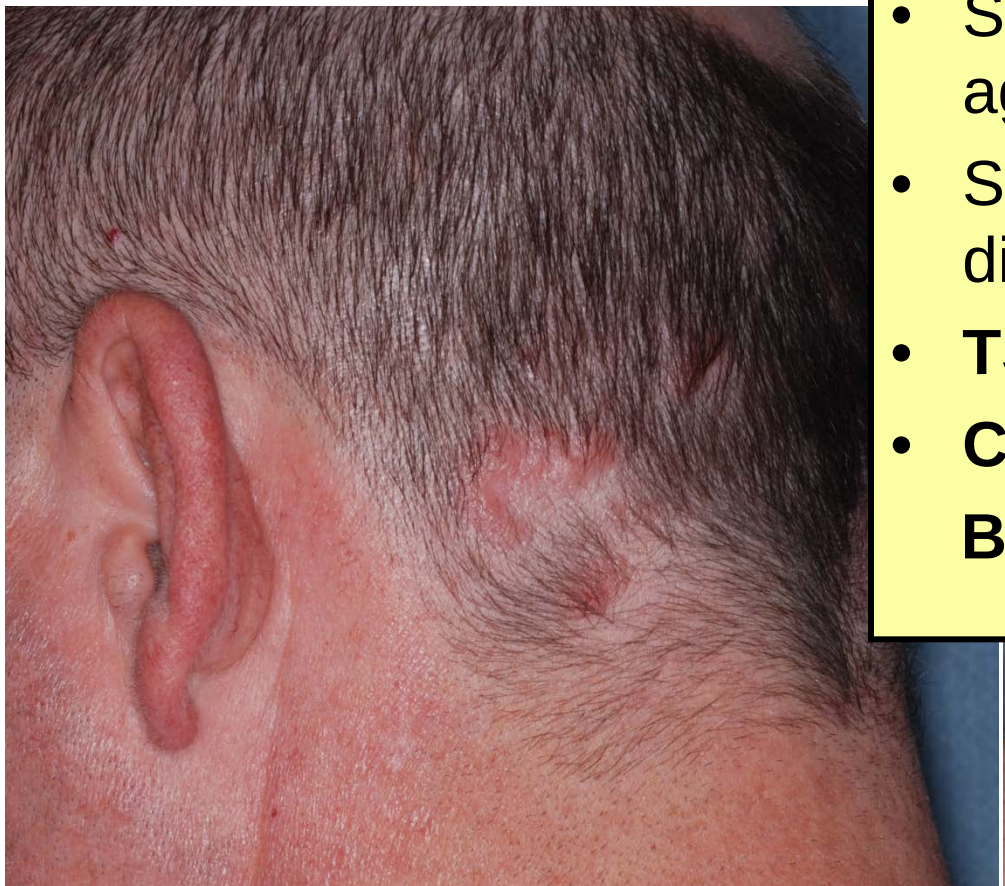
50 yo male, generalized disease, progressive with increasing nodular lesions, IIB. Prior therapies: topical steroids, NM, local RT, nbUVB.
=> Failed oral bex, IFN, MTX

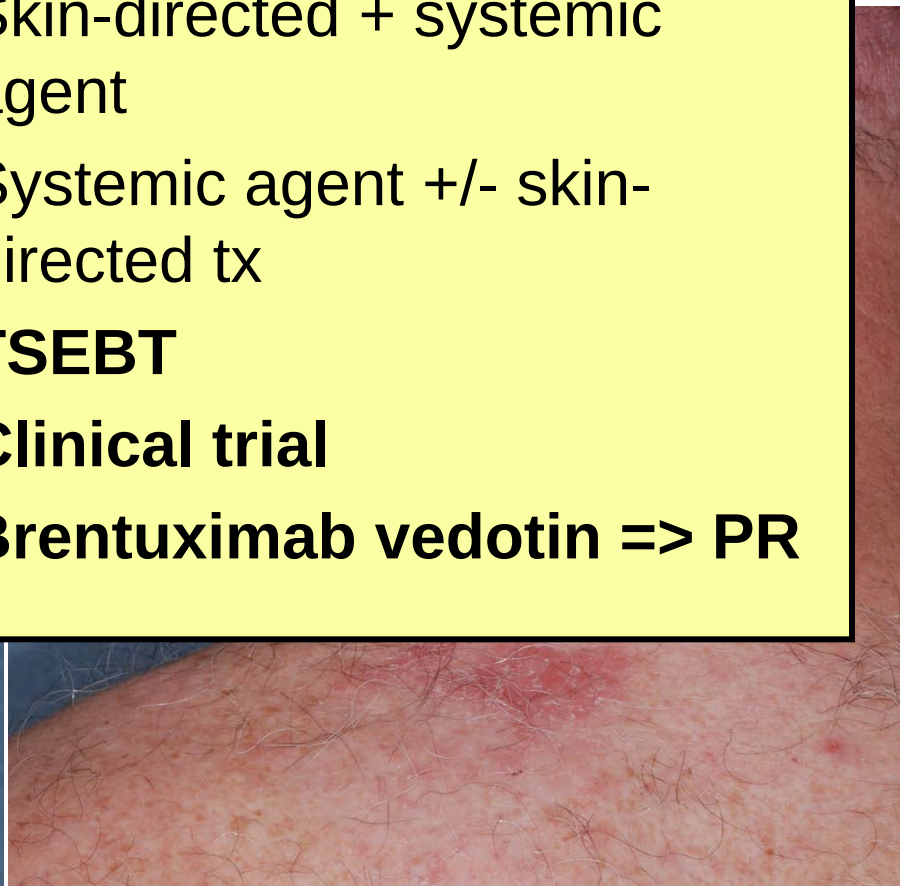


- **Generalized F-MF +/- LCT**

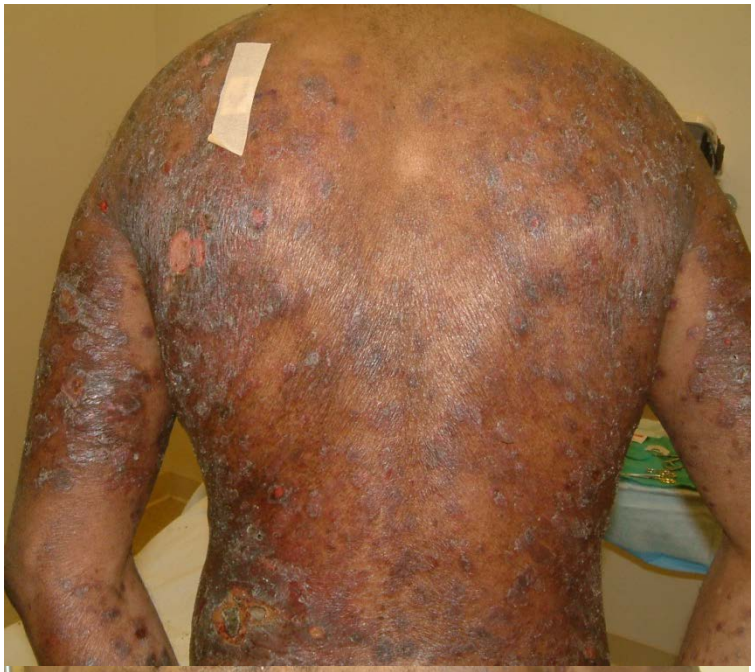
- Skin-directed + systemic agent
- Systemic agent +/- skin-directed tx
- **TSEBT**
- **Clinical trial**

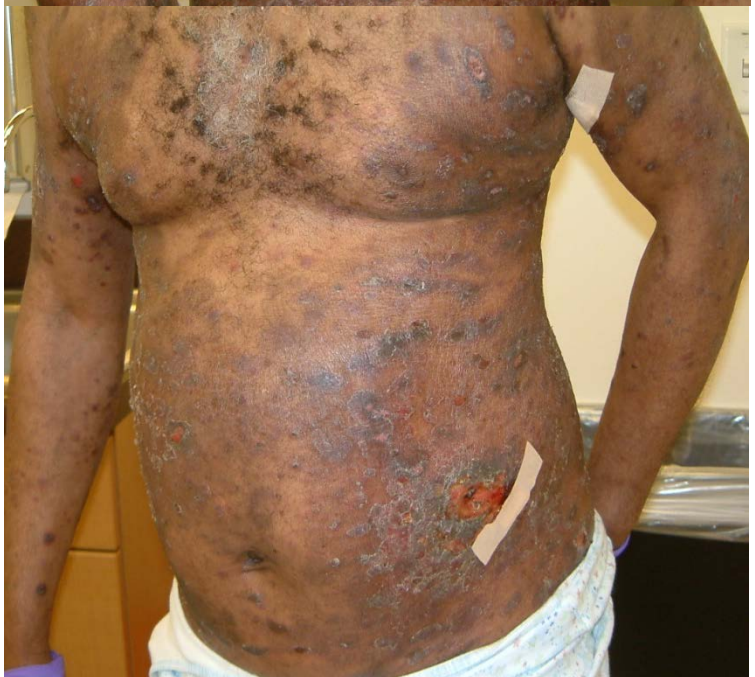
  Brentuximab vedotin => PR





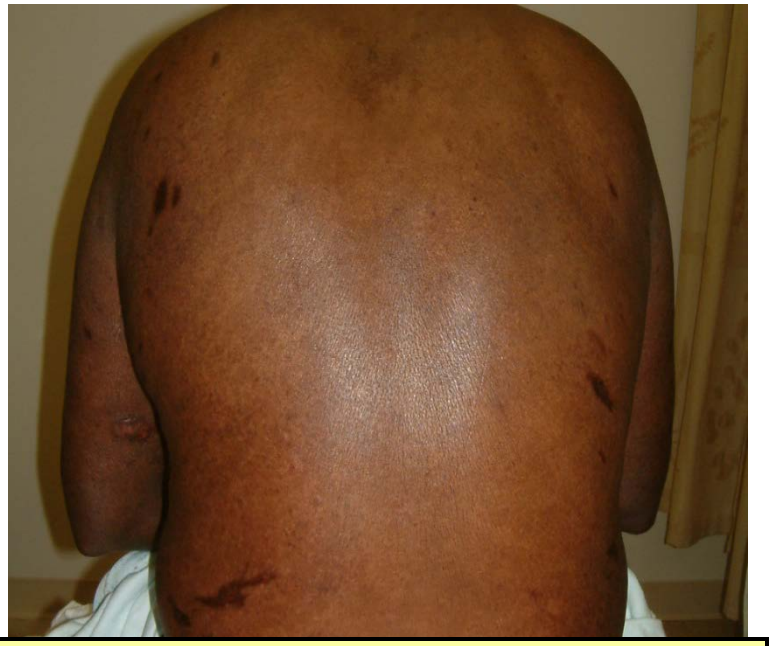
Severely symptomatic folliculotropic MF

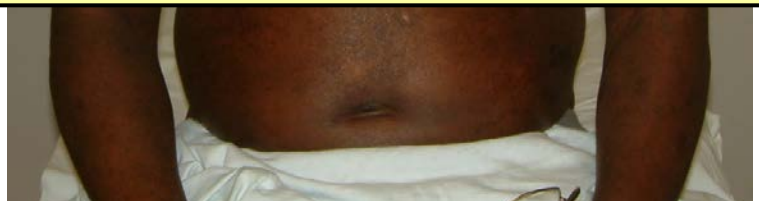




Standard dose TSEBT

36 Gy





NOT CURATIVE,

Relapse within 2 yrs,
Retreatment limited

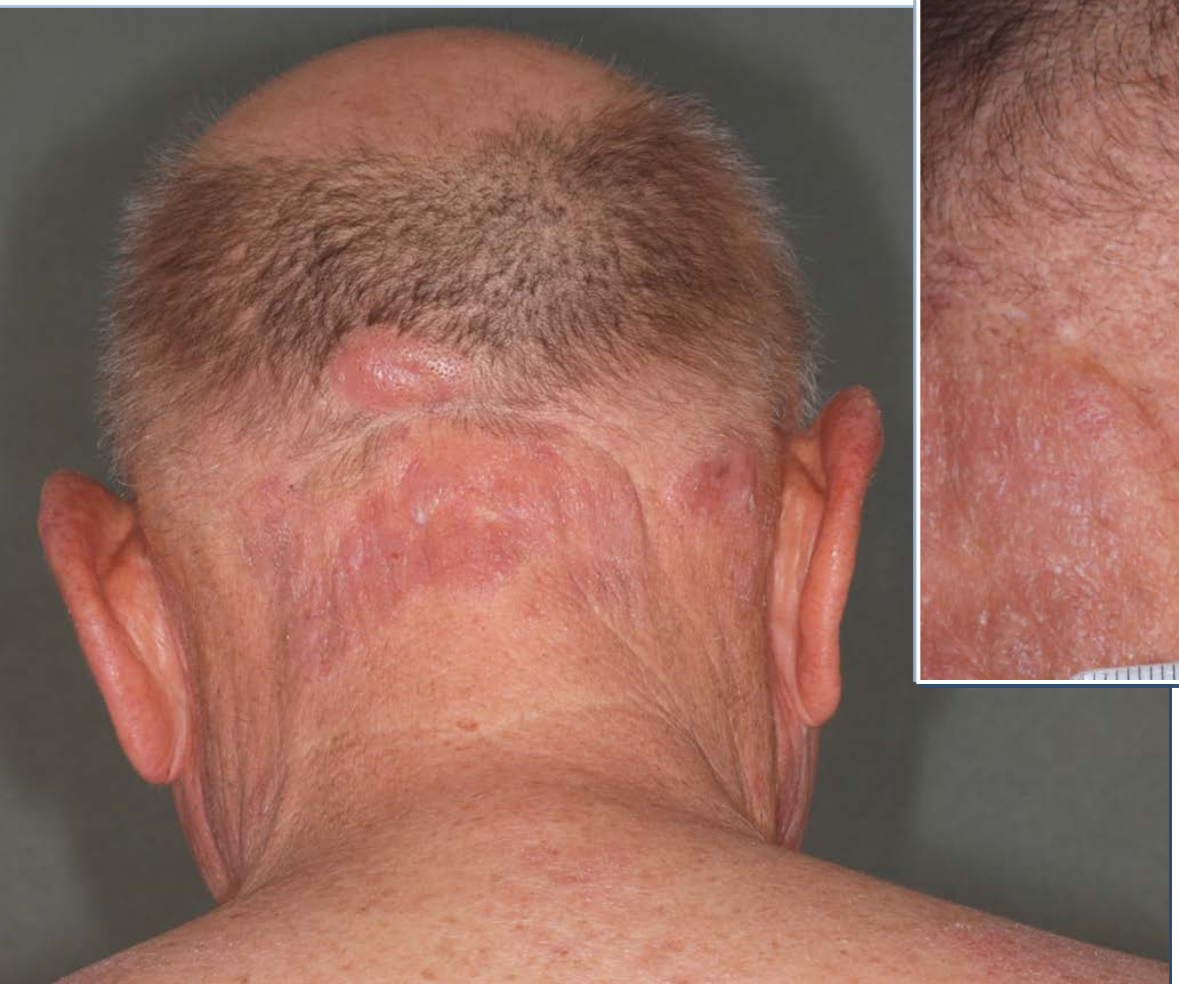
Why not use lower dose?

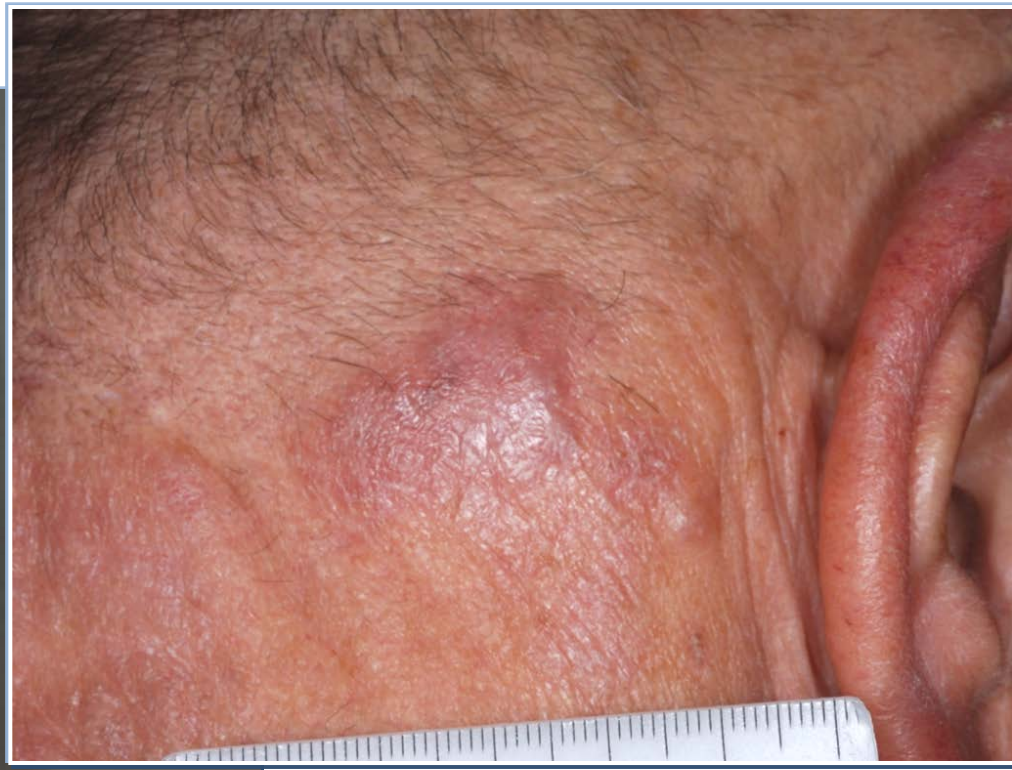
Low-Dose TSEBT Regimen
Less is better?

- 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

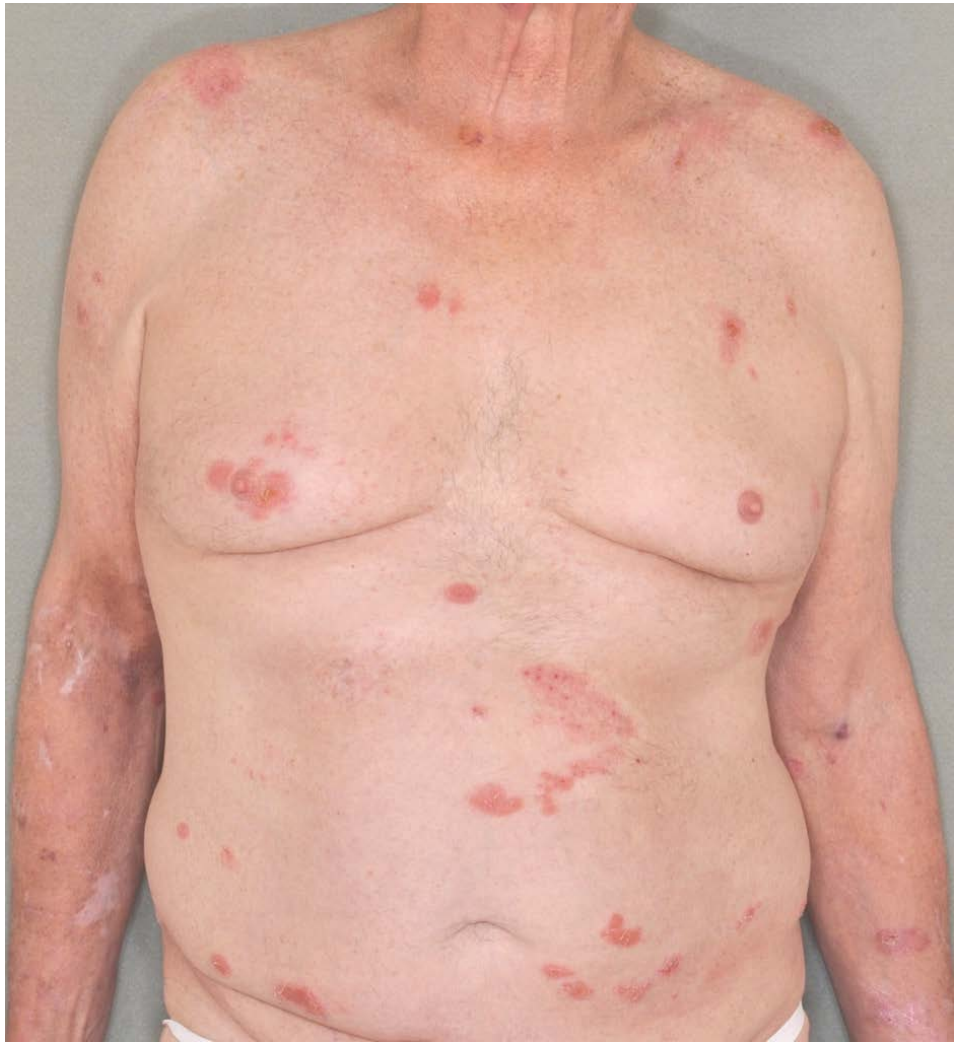
69 yo male w/ 5 yr h/o scaly plaques on face/scalp, trunk, extremities, progressive worsening. Partial response to topical steroids, NM, and nbUVB. Recently noted scalp tumor nodules; multiple comorbidities.

Case F-MF, stage IIB

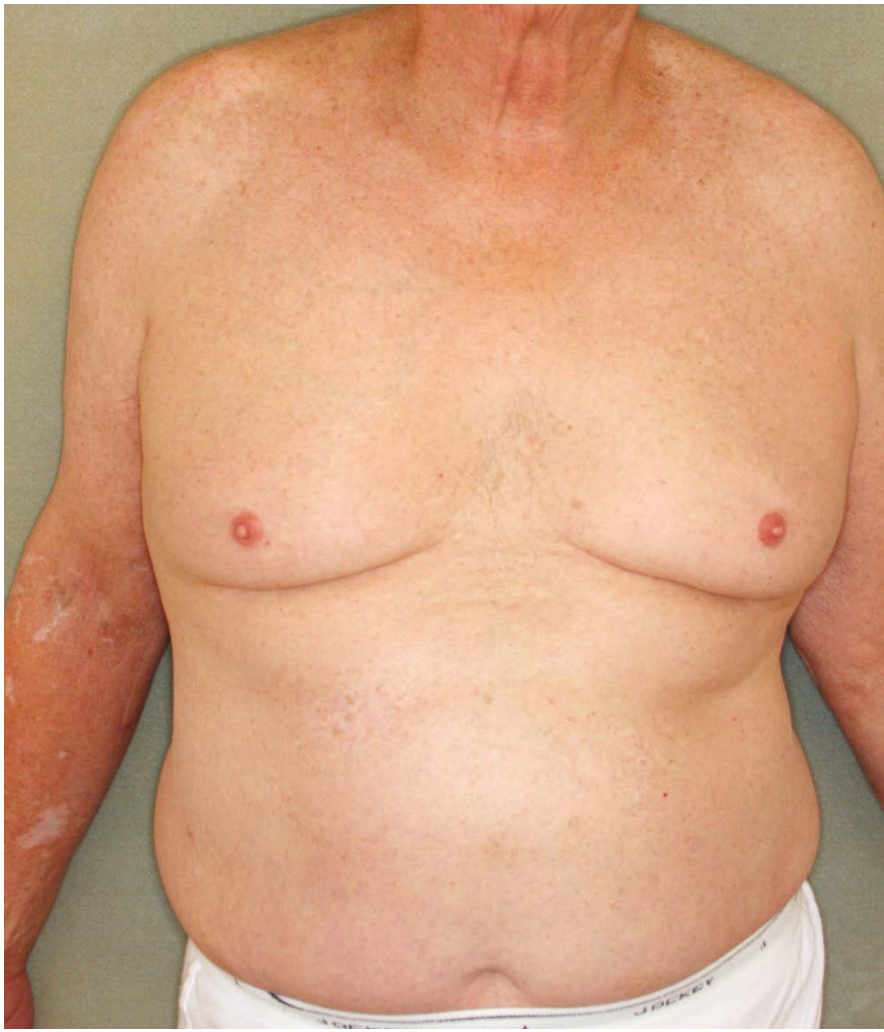




Clinical response with low-dose (12 Gy) TSEBT
69 yo M, stage IIB, folliculotropic MF

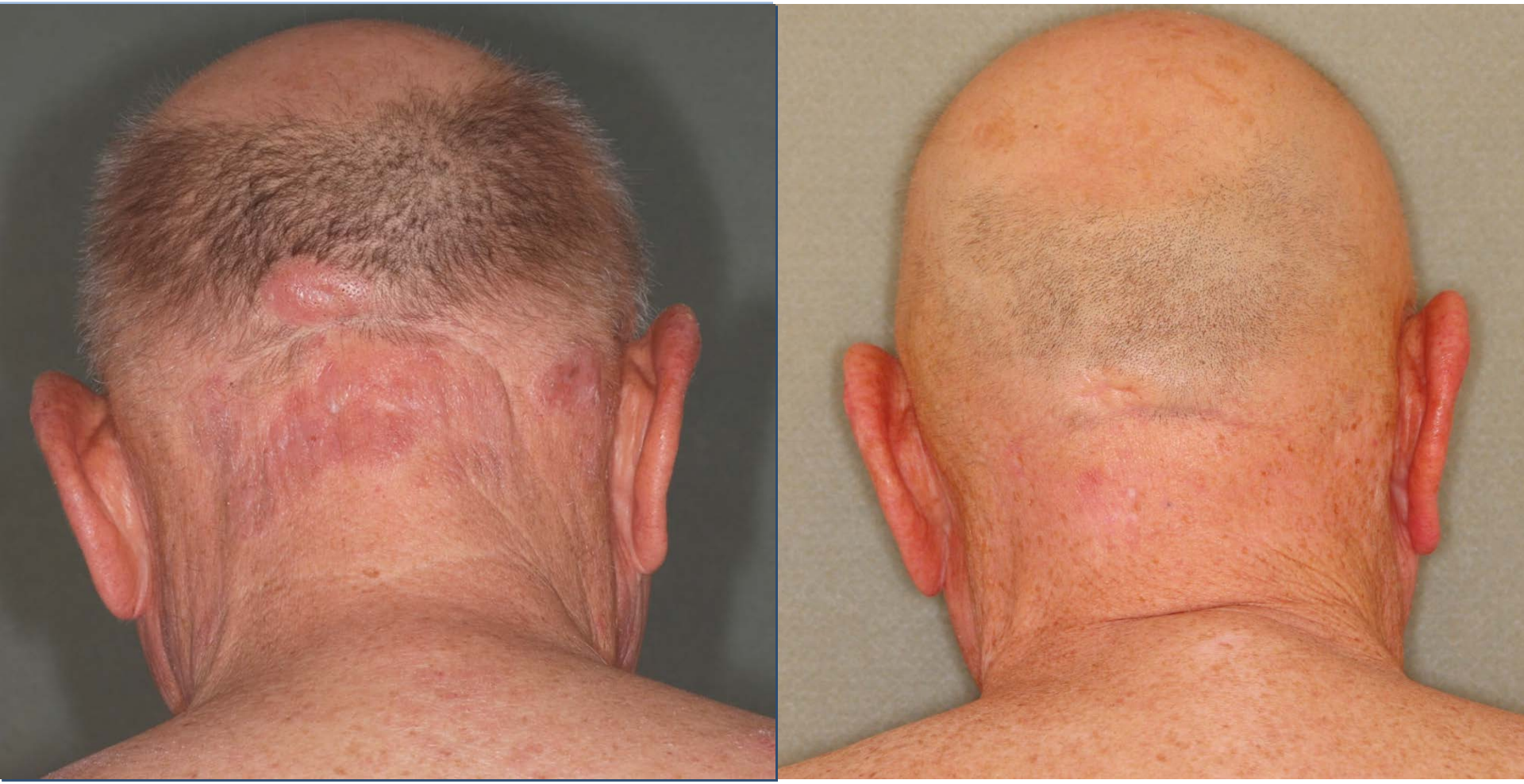


Screening
mSWAT 133
Pruritus 8/10



Wk 16
mSWAT 0 (CR)
Pruritus 0/10

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



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 (Cat-A) +/- skin-directed tx
- **Generalized extent tumor disease**
  - **Indolent (no LCT)**
    - TSEBT
    - Category A systemic +/- skin-directed tx
  - **Aggressive (+ LCT)**
    - TSEBT + Cat-A systemic
    - Category B or C systemic options +/- skin-directed tx
- Refractory disease => clinical trials, combo

Consider Allo HSCT

NCCN Guidelines Version 1.2013
Mycosis Fungoides/Sezary Syndrome

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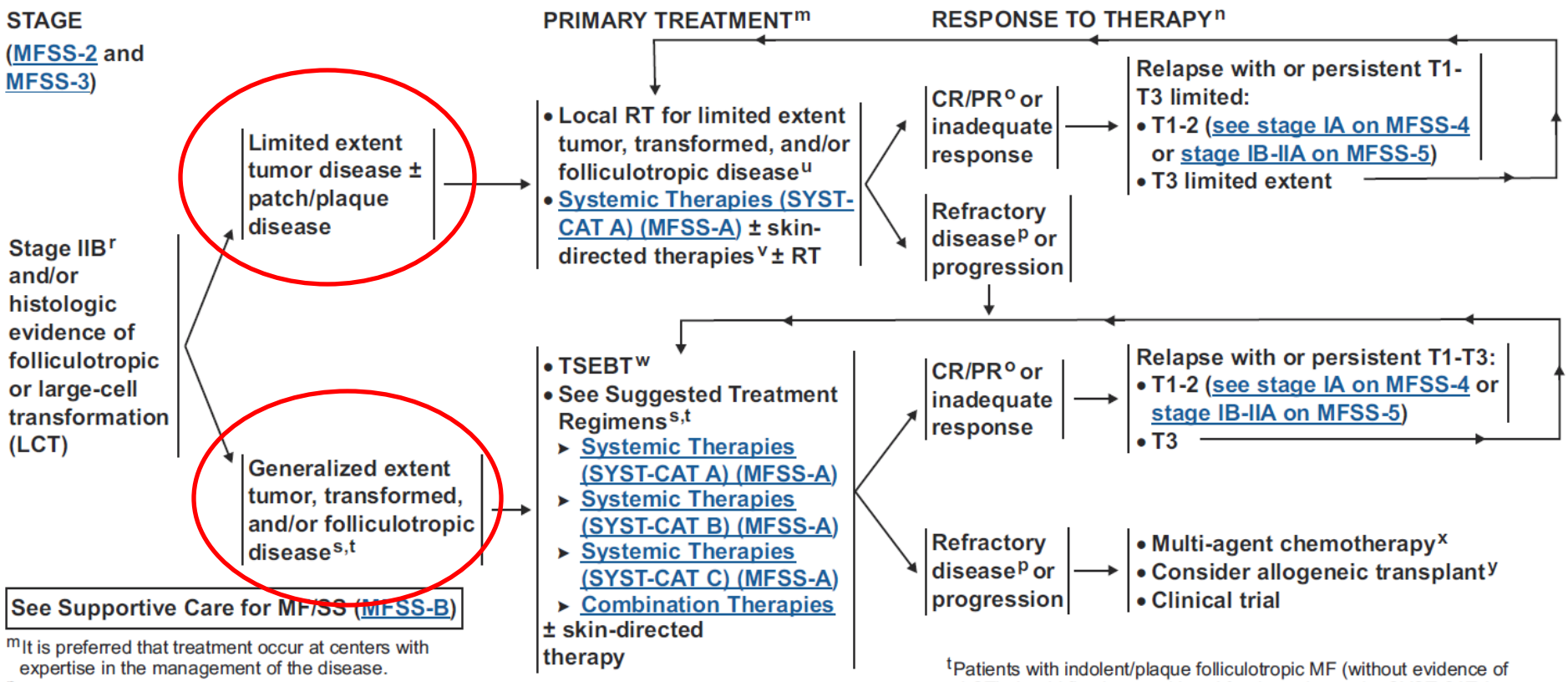


[m] It is preferred that treatment occur at centers with expertise in the management of the disease.

[n] Unlike other NHL subtypes, response criteria for MF/SS has not been demonstrated to correlate with prognosis. Often decisions to continue or switch therapy are on a clinical basis. However, a proposal for detailed response criteria has been published (Olsen E, Whittaker S, Kim YH, et al. J Clin Oncol 2011;29:2598-2607).

[o] Patients achieving a response and/or a clinical benefit should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

[p] Refractory or intolerant to multiple previous therapies.

[r] Rebiopsy if suspect large cell transformation.

[s] Histologic evidence of LCT often, but not always corresponds to a more aggressive growth rate. If there is no evidence of more aggressive growth, choosing systemic therapies from SYST-CAT A or SYST-CAT B are appropriate. If aggressive growth is seen, then agents listed in SYST-CAT C are preferred.

[t] Patients with indolent/plaque folliculotropic MF (without evidence of LCT) should first be considered for therapies under SYST-CAT A before resorting to treatments listed in SYST CAT B or SYST CAT C.

[u] For non-radiated sites, see Stage I-IIA. After patient is rendered disease free by RT, may consider adjuvant systemic biologic therapy (SYST-CAT A) after RT to improve response duration.

[v] Skin-directed therapies are for patch or plaque lesions and not for tumor lesions.

[w] May consider adjuvant systemic biologic therapy (SYST-CAT A) after TSEBT to improve response duration.

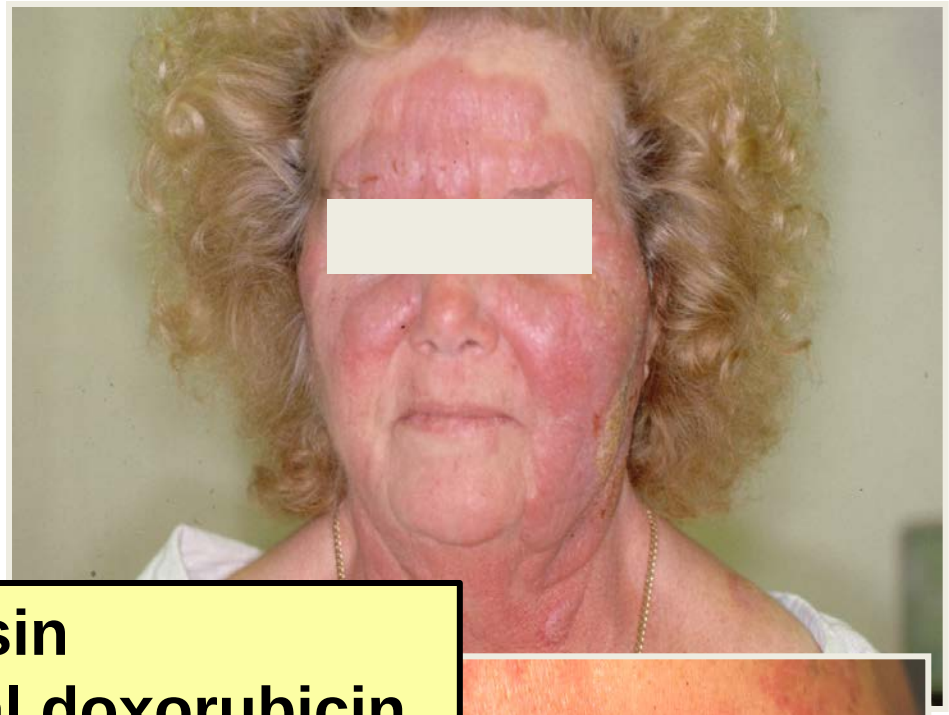
[x] Most patients are treated with multiple SYST-CAT A/B or combination therapies before receiving multiagent chemotherapy.

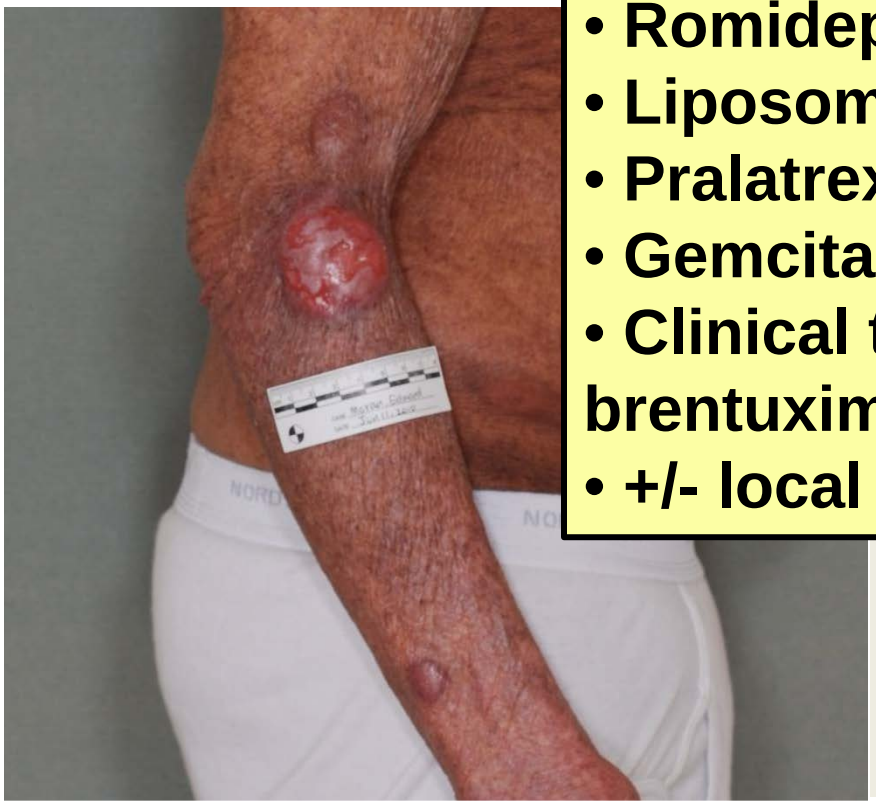
[y] The role of allogeneic HSCT is controversial. See Discussion for further details.

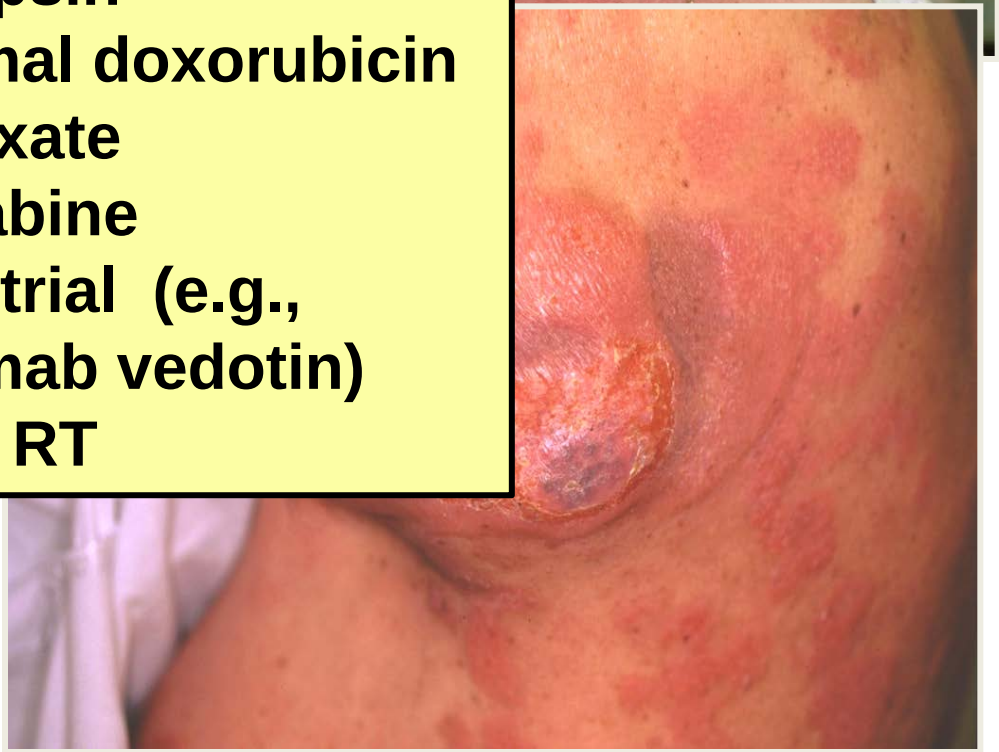
MF w/ large cell transformation with worse prognosis

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

Cat-B or C NCCN options, trials







- Romidepsin
- Liposomal doxorubicin
- Pralatrexate
- Gemcitabine
- Clinical trial (e.g., brentuximab vedotin)
- +/- local RT

Management of erythrodermic (T4) disease

- Approach **based on peripheral blood Sezary burden**
  - B0, B1, vs. B2 (Sezary syndrome)
- Erythrodermic (T4) MF, stage III
  - B0 => generalized skin-directed options or Cat-A
  - B1 => “milder” systemic options (NCCN Cat-A)
- Refractory disease
  - Combination therapies
    - Skin tx + Cat-A, Cat-A + Cat-A
  - Alemtuzumab
- Essential to optimize support
  - Emollients, topical steroids -
  - Vigilant infection control (sta
  - Anti-itch support (gabapanti

SYSTEMIC THERAPIES

Category A (SYST-CAT A)

- **Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13-cis-retinoic acid], acitretin)**
- **Interferons (IFN-alpha, IFN-gamma)**
- **HDAC-inhibitors (vorinostat, romidepsin)[e]**
- **Extracorporeal photopheresis[f]**
- **Methotrexate (≤100 mg q week)**

Evidence for treatment stratification by blood tumor burden in SS

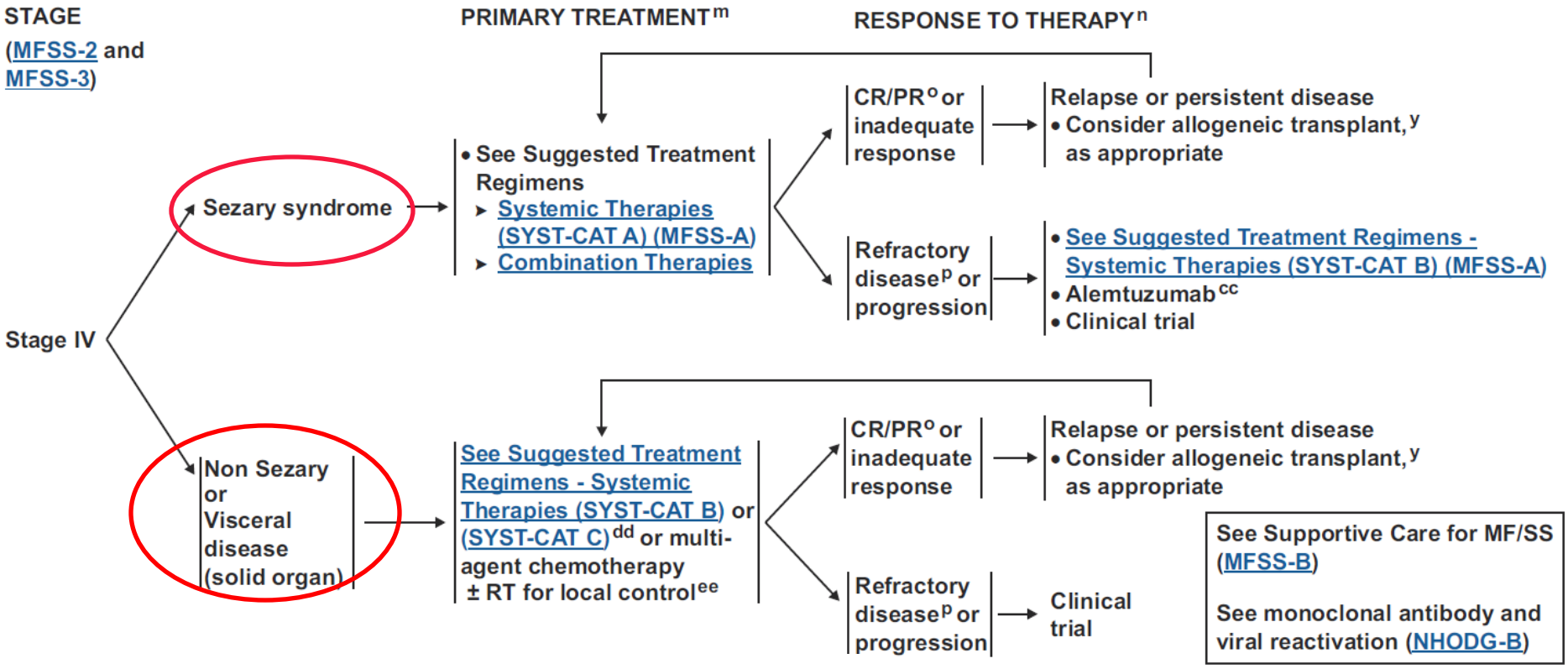
- Current B2 $\geq$ 1,000 SC/mm^3
- Evidence that $\geq$ 5K or $\geq$ 10K are important prognostic or therapy outcome SC levels
  - SC $\geq$ 5K as worse px group
    (Vonderheid et al. leukemia Lymph 2006;47:1841)
  - ↑death rate in SC $\geq$ 10K
    (ScarisbricK et al. Blood 2001;97:624)
  - Reduced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

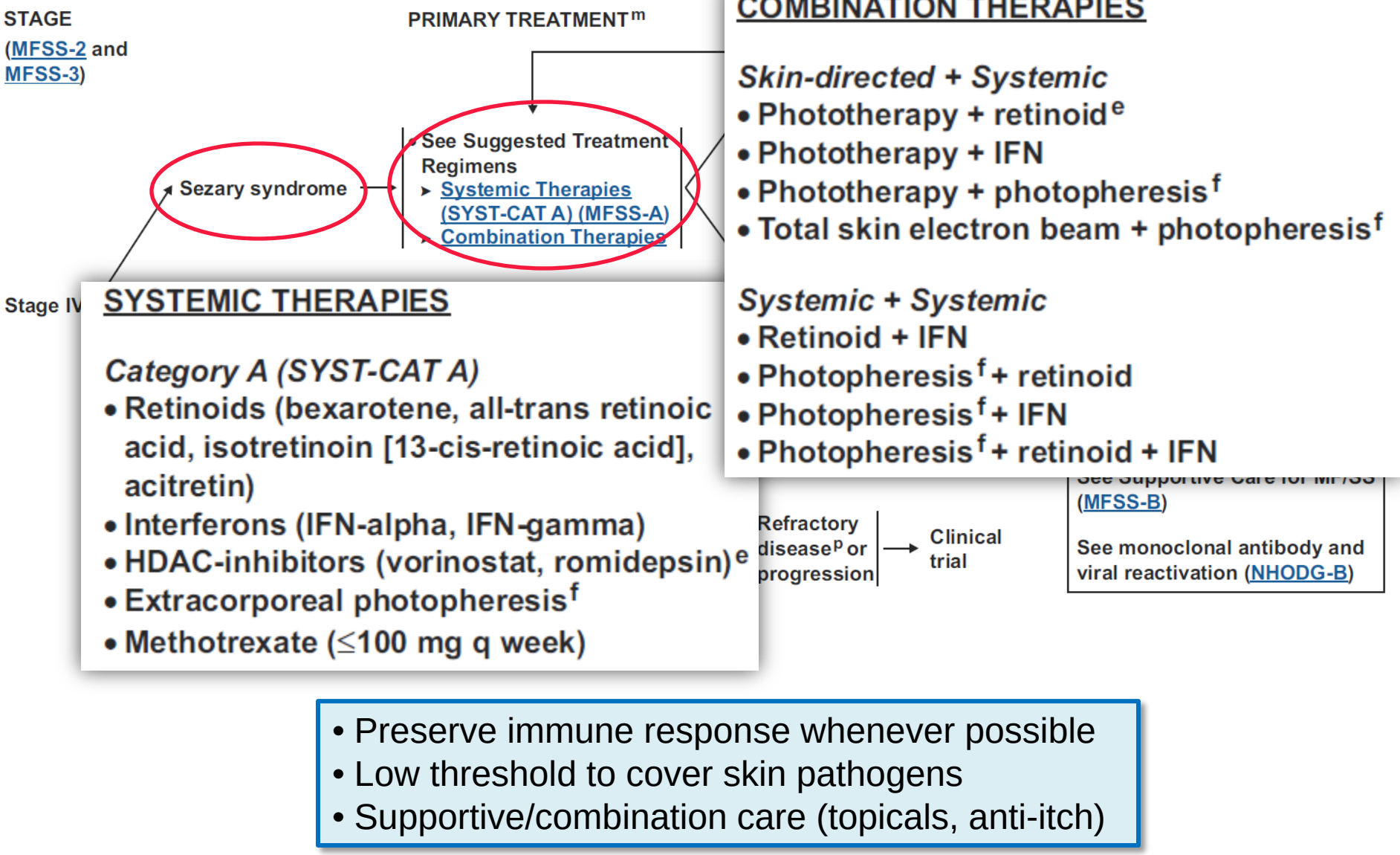
Management of Sezary Syndrome, B2/stage IV

- 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
  - Romidepsin
  - Alemtuzumab
- Refractory disease
  - Alemtuzumab
  - Clinical trials

Allo HSCT

NCCN Guidelines Version 1.2013
Mycosis Fungoides/Sezary Syndrome





- Preserve immune response whenever possible
- Low threshold to cover skin pathogens
- Supportive/combination care (topicals, anti-itch)

NCCN Guidelines Version 1.2013
Mycosis Fungoides/Sezary Syndrome

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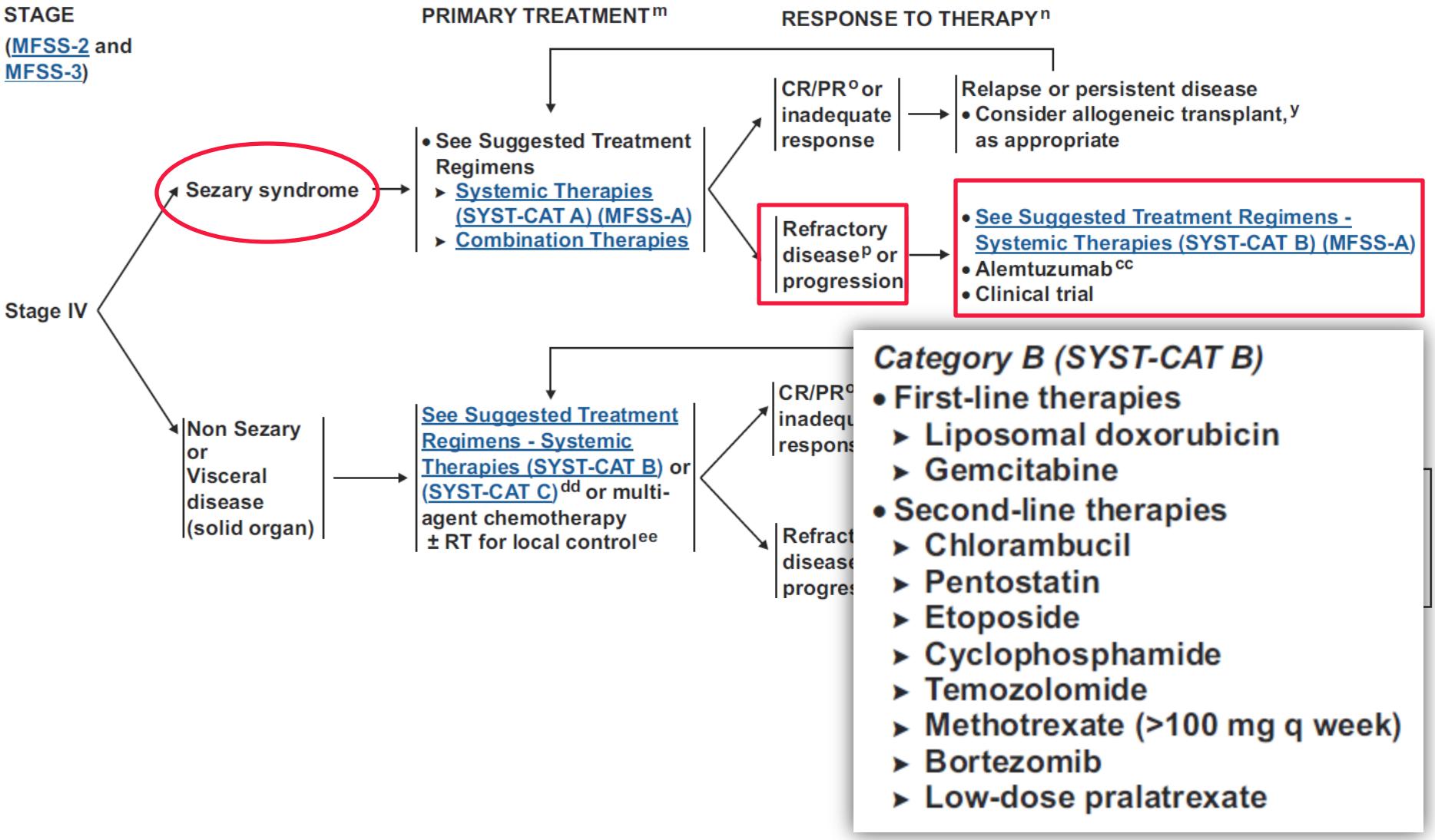


JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

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

J Clin Oncol. 2009;27:5410-5417

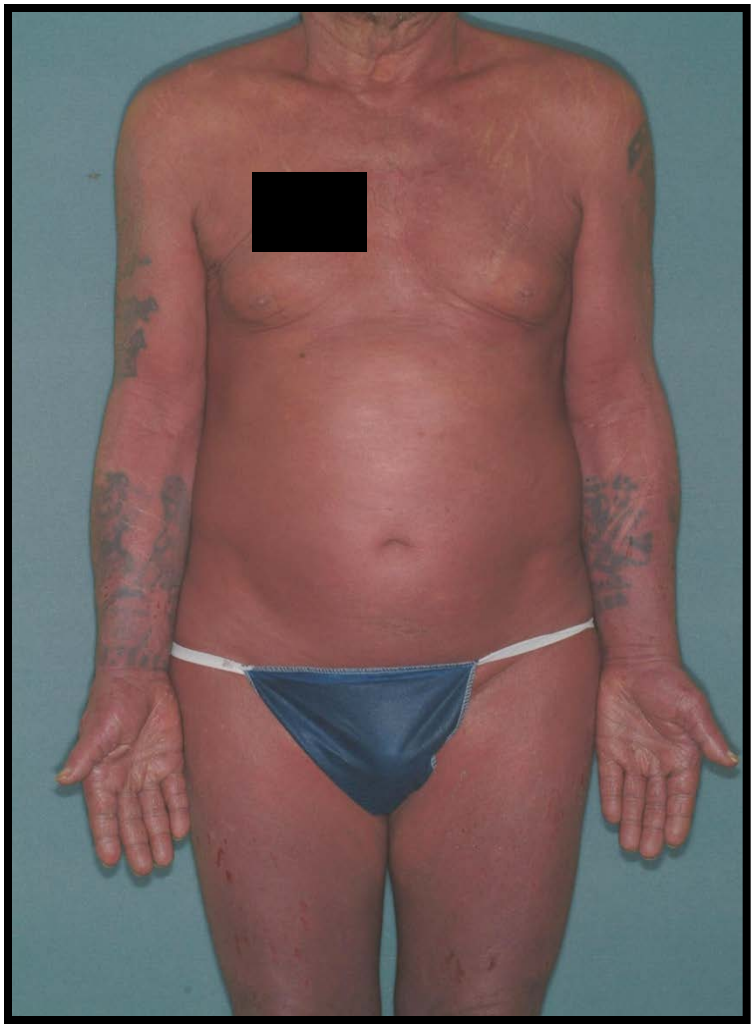
Final Results From a Multicenter, International, Pivotal Study of Romidepsin in Refractory Cutaneous T-Cell Lymphoma

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

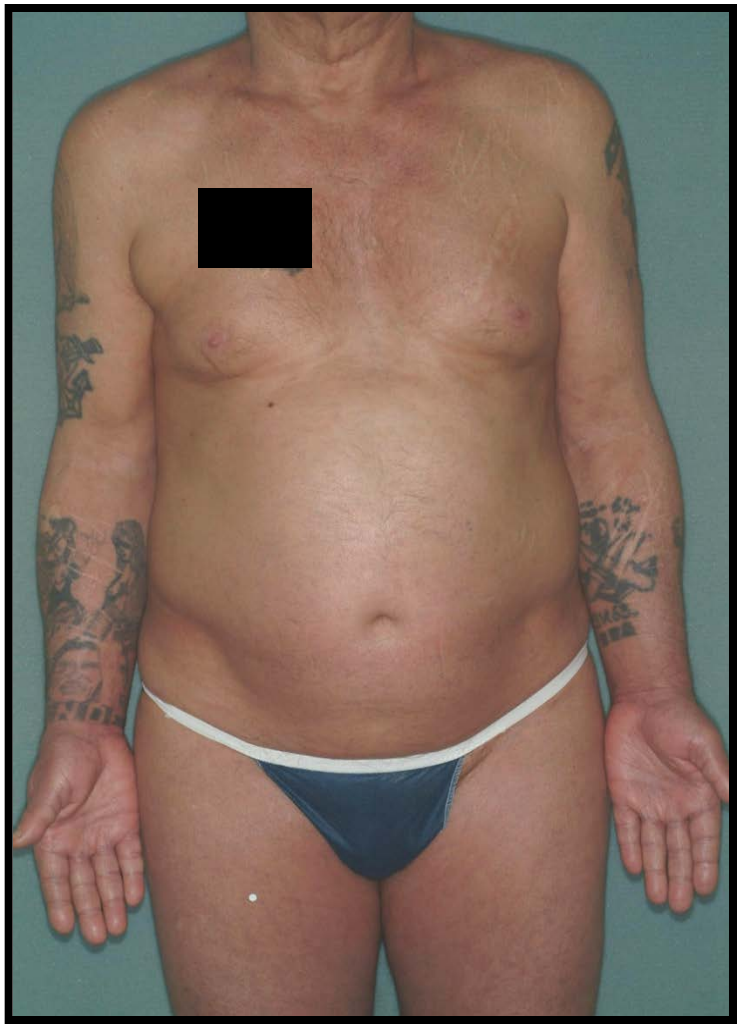
J Clin Oncol, 2010;28:4485-4491

Sezary syndrome response to romidepsin

Patient 37-018 (failed 3 chemo regimens)



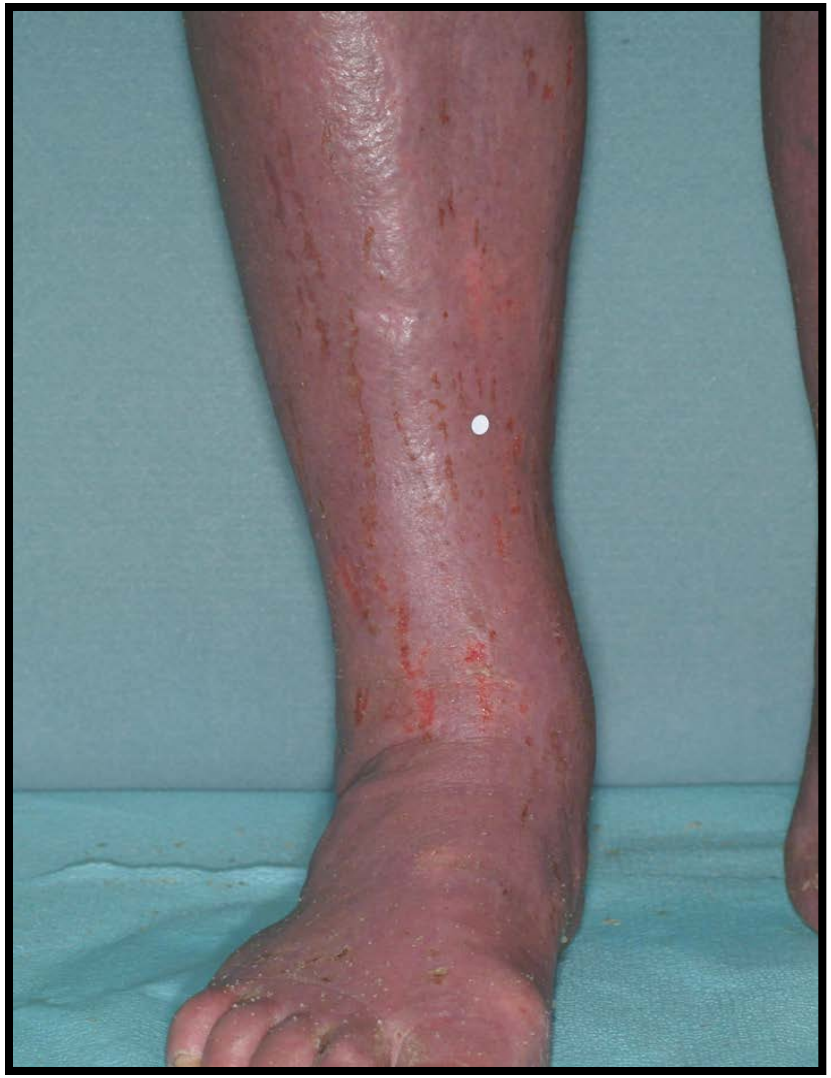
Screening



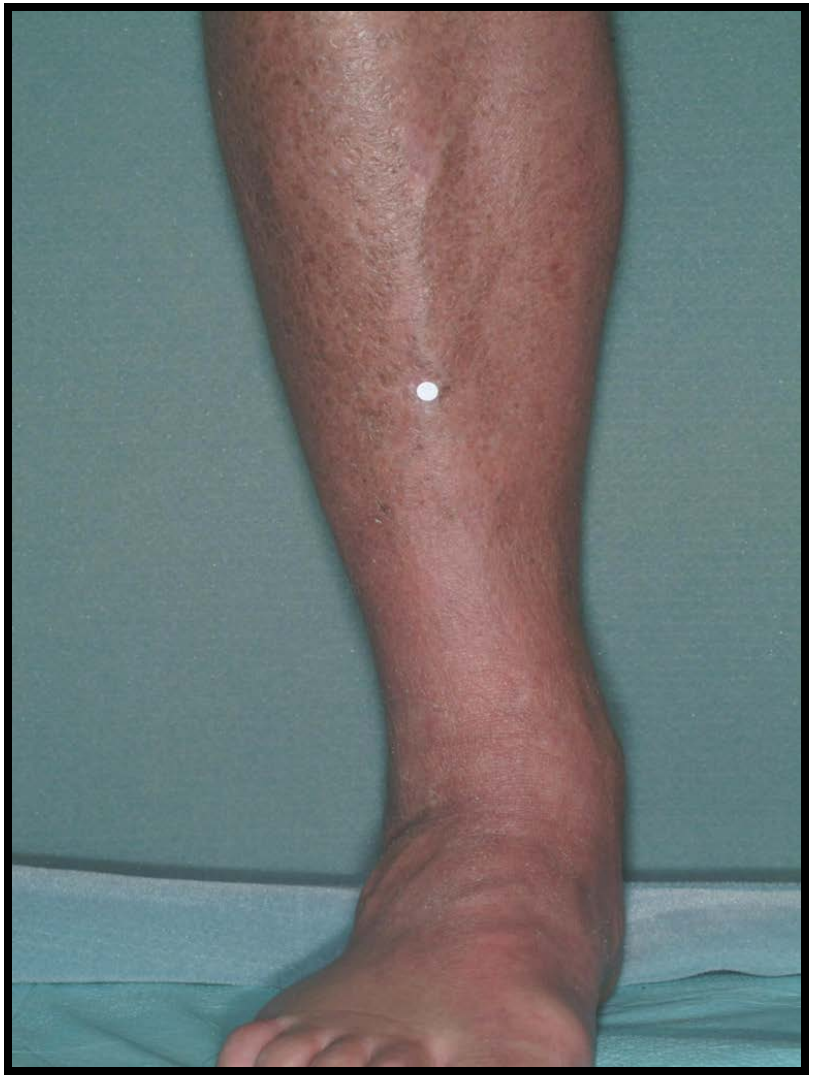
Cycle 6, Day 1

Sezary syndrome response to romidepsin

Patient 37-018



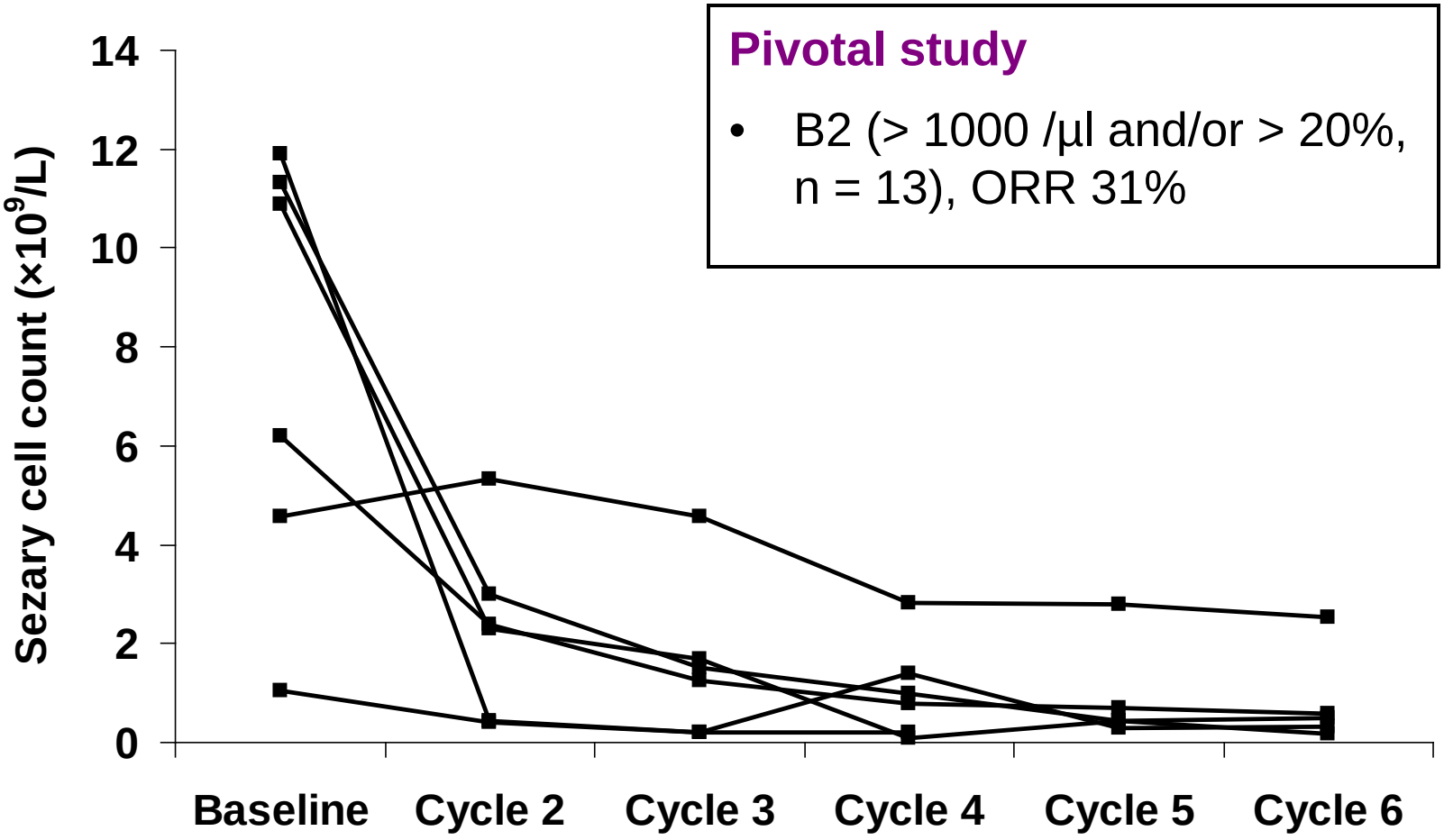
Screening



Cycle 6, Day 1

Romidepsin Activity in Blood

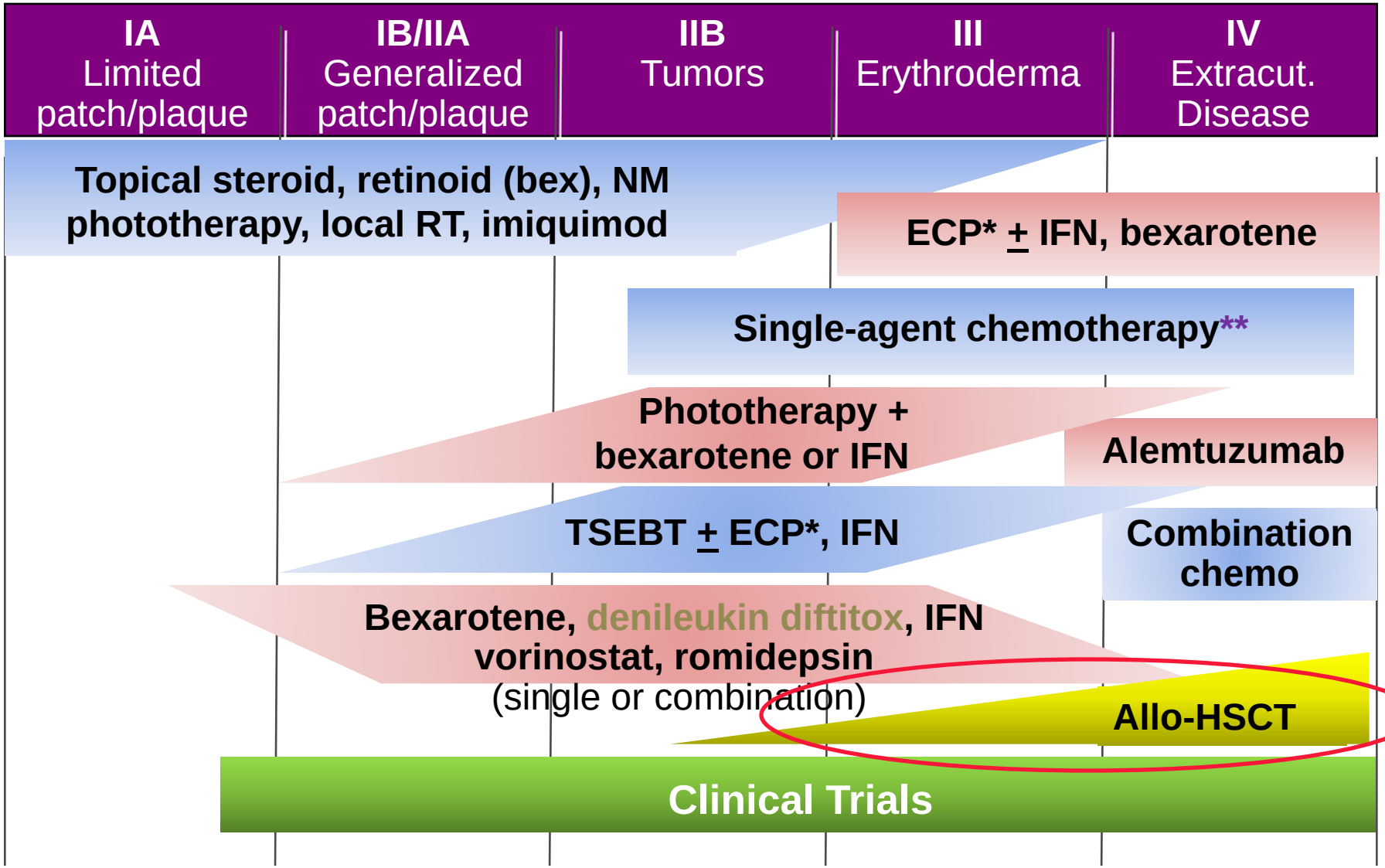
Pivotal Study, Patients with Significant Blood Sezary Burden*



* > 1,000 Sézary cells/µl

Current Clinical Management of CTCL, *2013*

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



*ECP = photopheresis

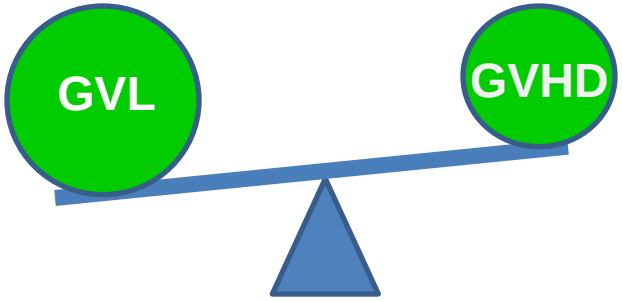
** Methotrexate, liposomal doxorubicin, gemcitabine, pentostatin, chlorambucil, etoposide, **pralatrexate**

Hematopoietic stem 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

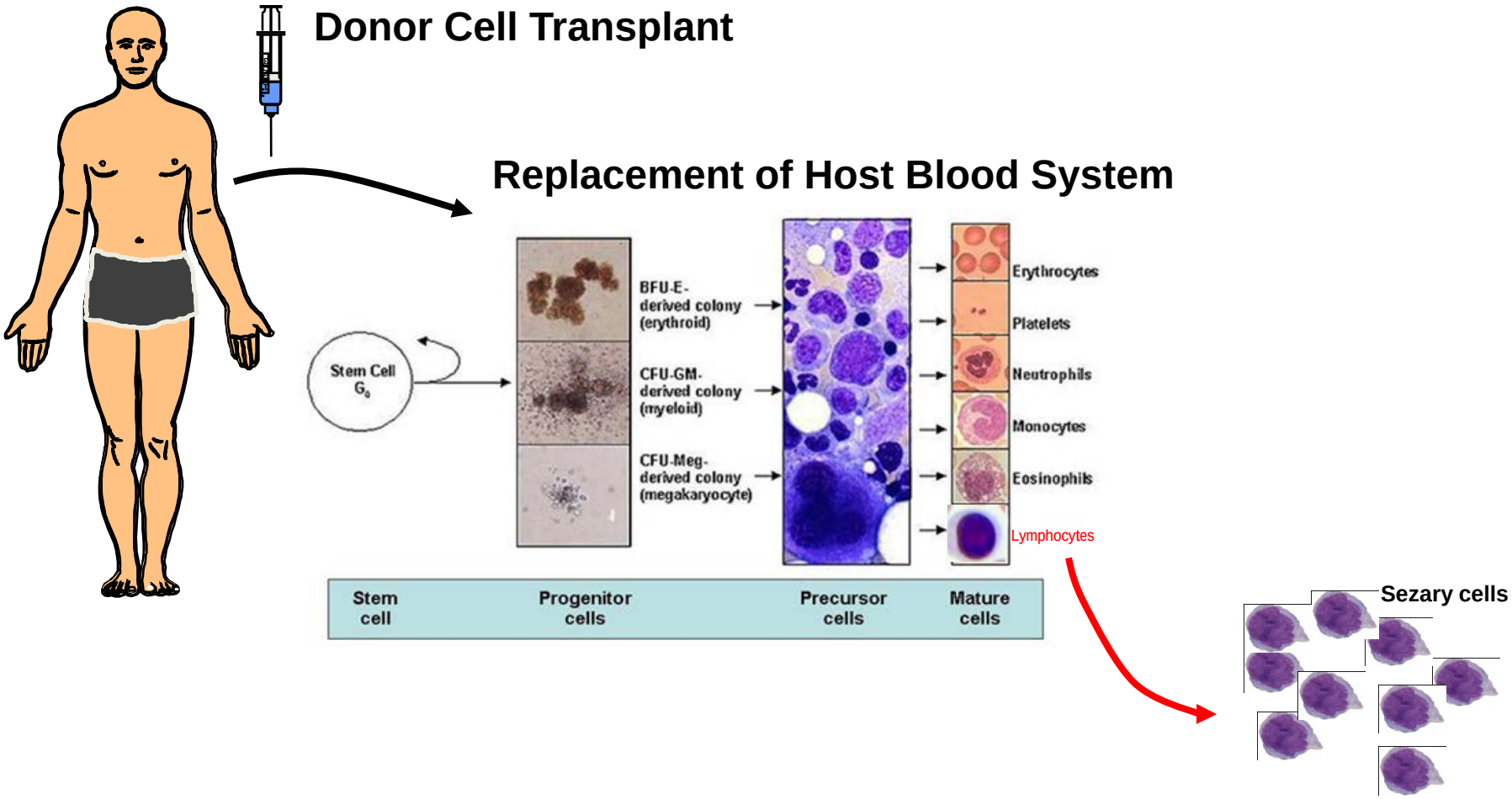
Allogeneic → **Graft vs. lymphoma (GVL) effect**
Risk of GVHD
Increasing evidence of durable clinical, cytogenetic, molecular remissions in MF/SS



How to maximize GVL effect while minimizing GVHD risk

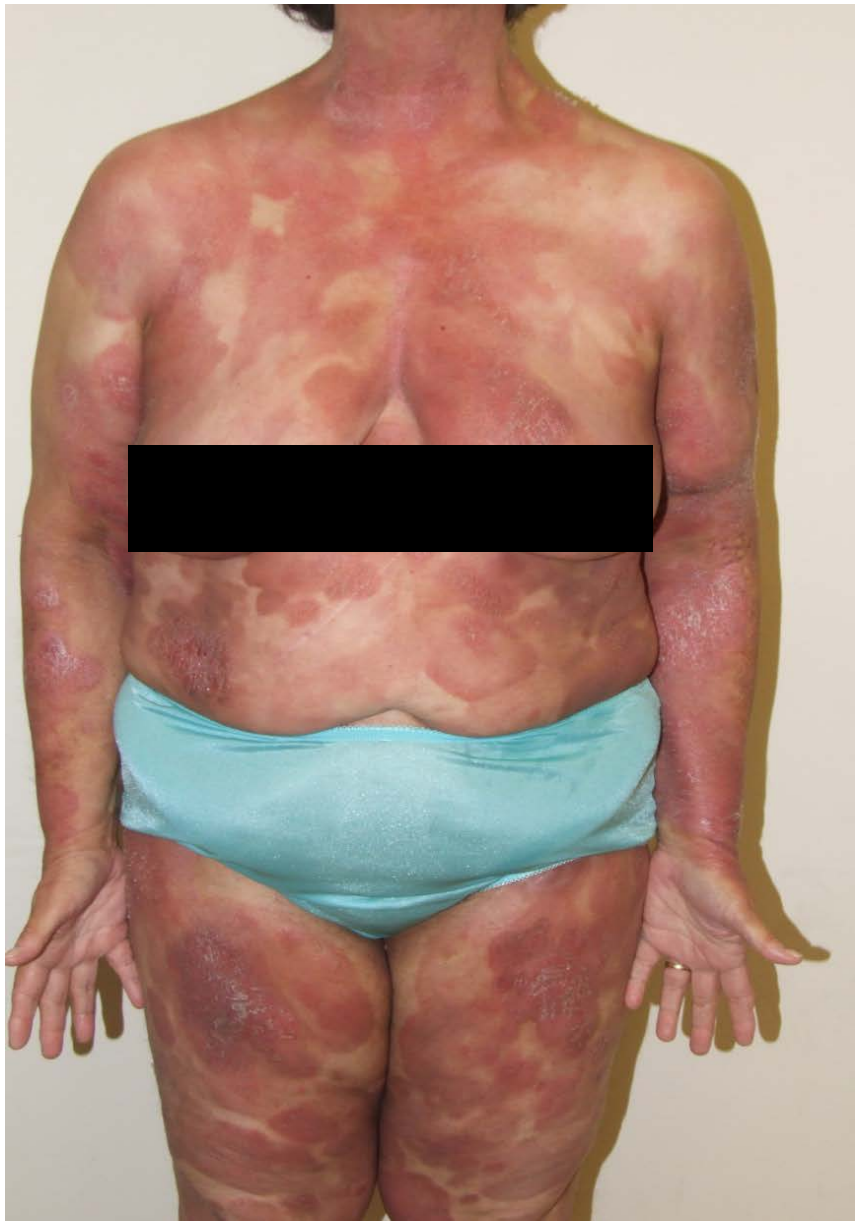
Biol Blood Marrow Transplant 15: 982-990 (2009); J Clin Oncol 29:2365-72 (2010); J Clin Oncol 28:4492-99 (2010); Bone Marrow Transplant ePub (2011)

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

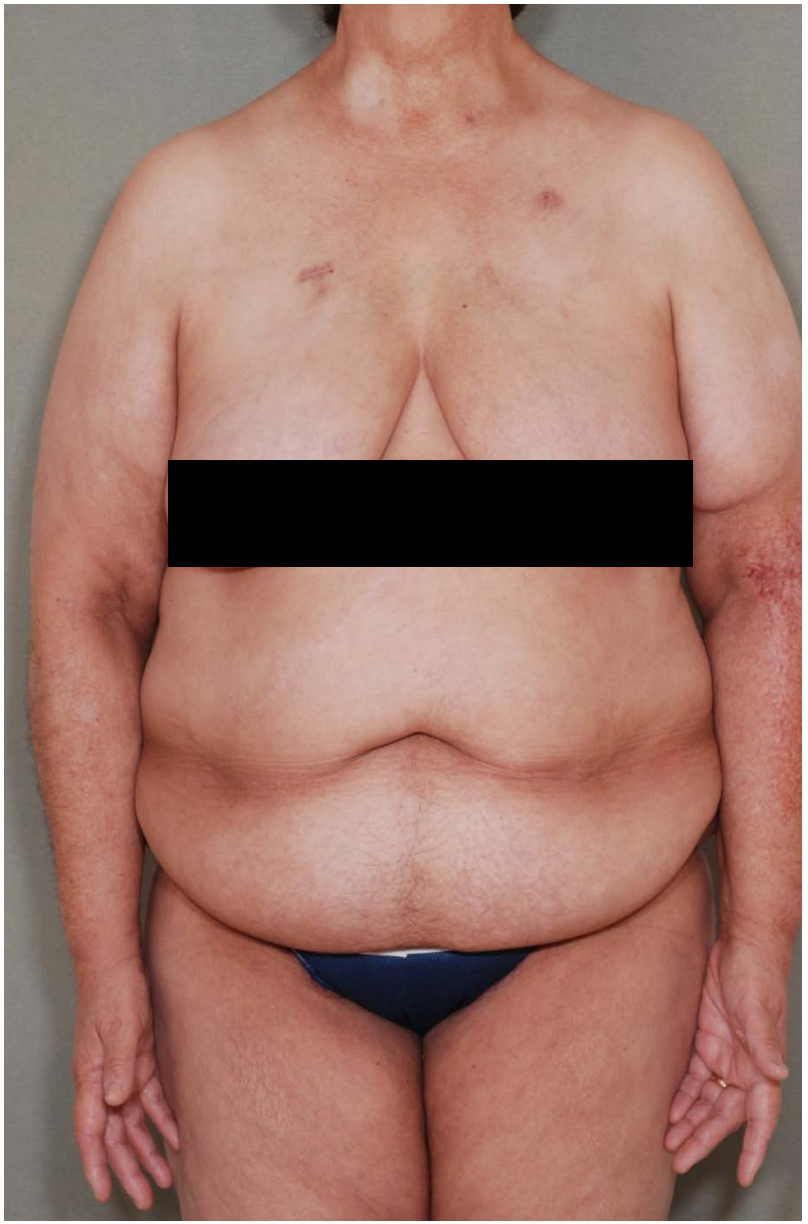


Mycosis fungoides, stage IVA w/ LCT in skin/LNs: CR

Pre-TSEBT



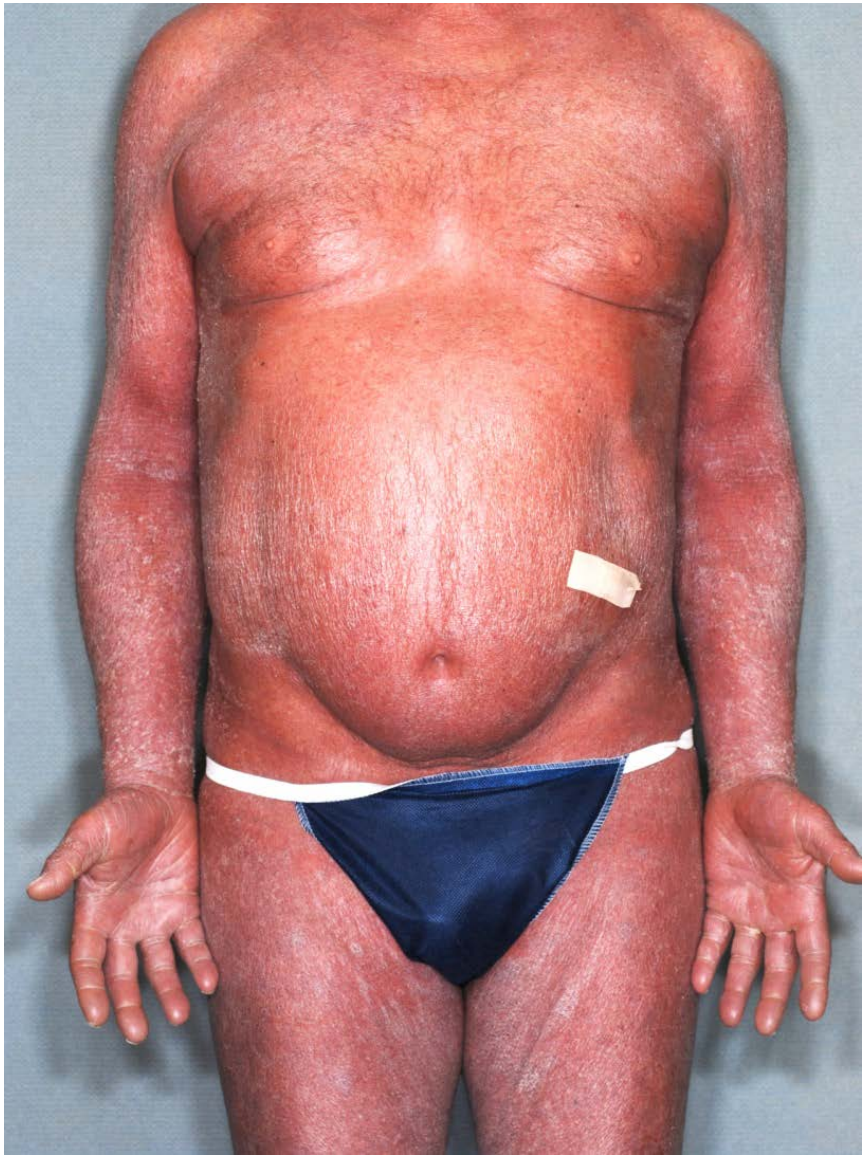
3 yr (NED, no GVHD)



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

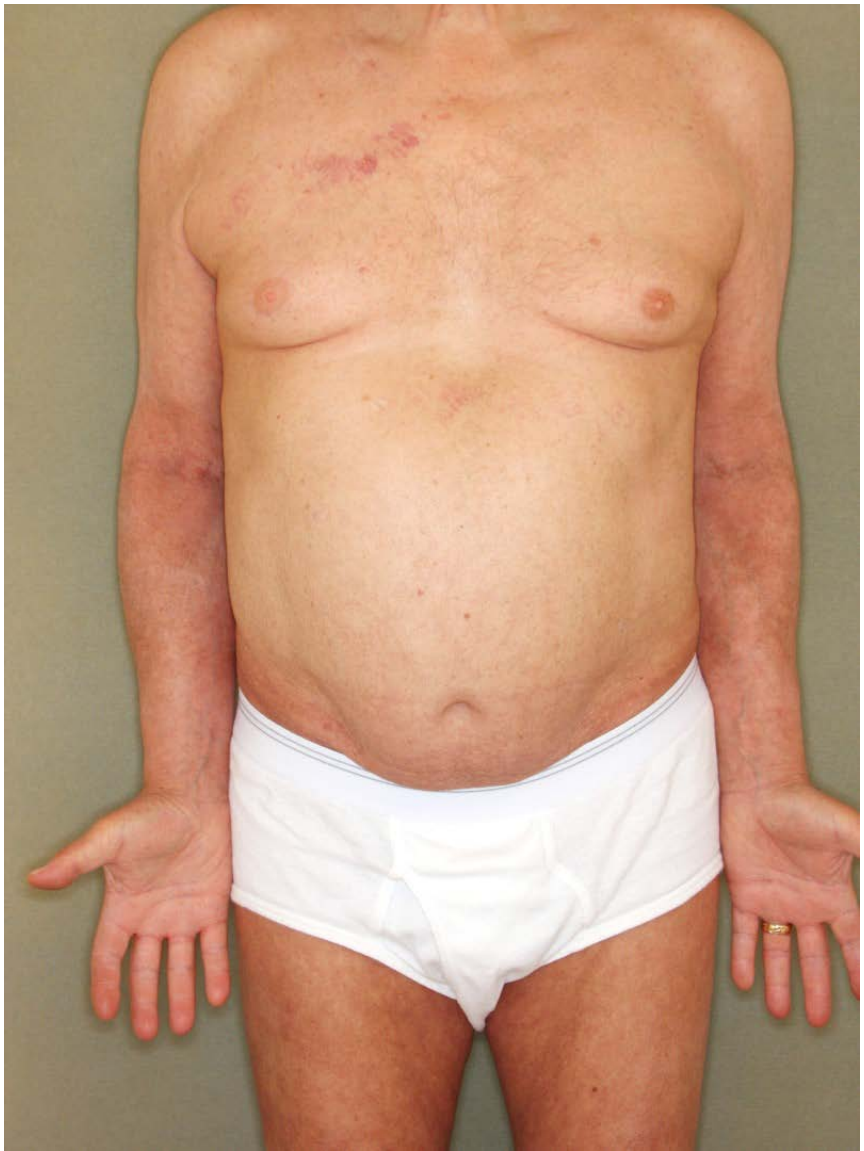
Pre-TSEBT

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



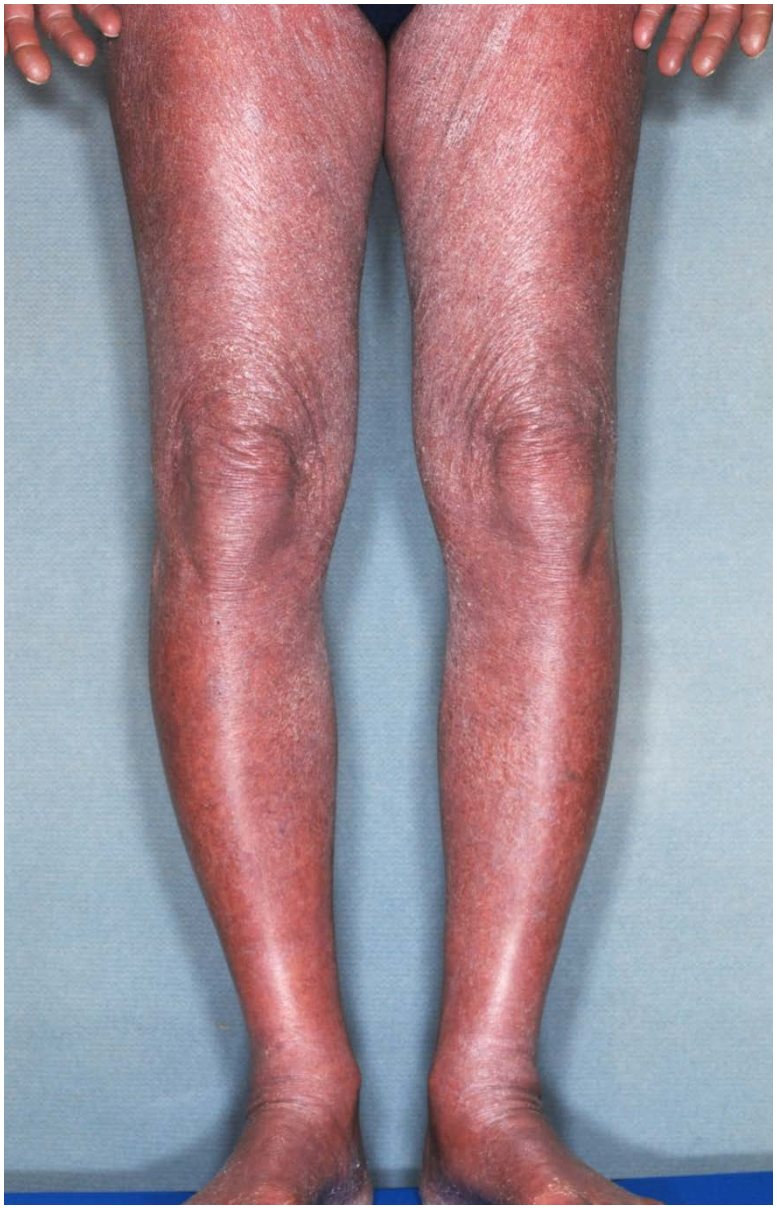
2 yr (NED, no GVHD)

CD4+/CD26-: normalized

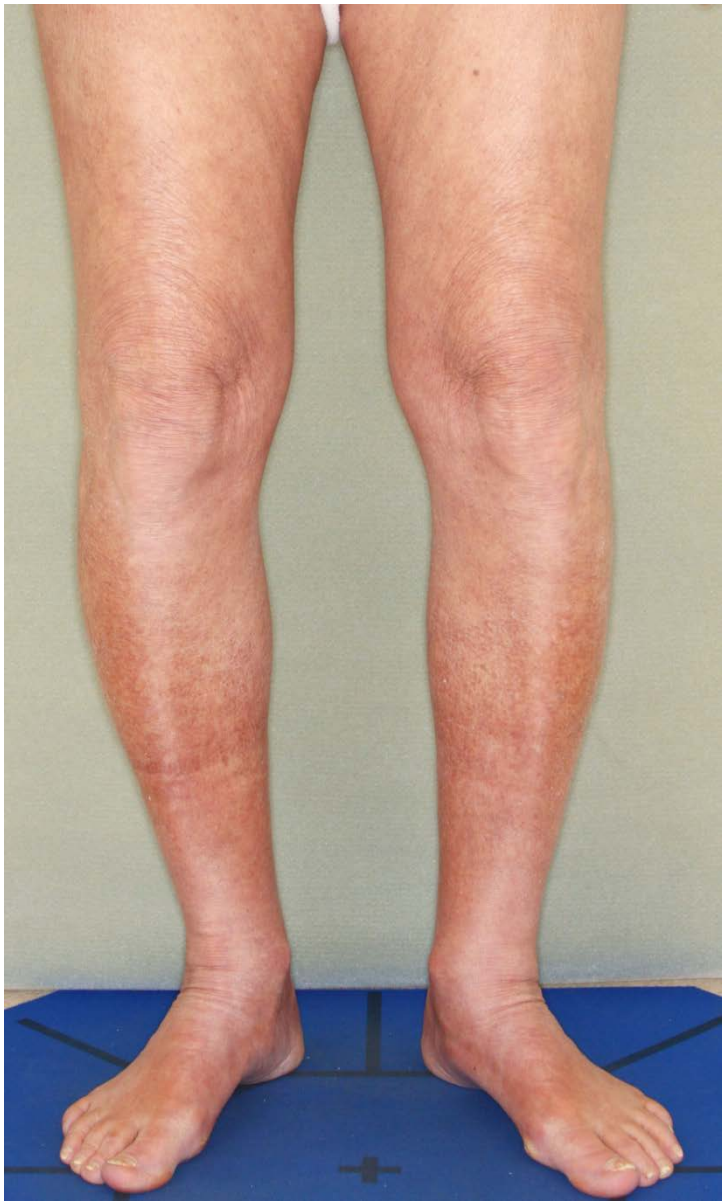


Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR

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

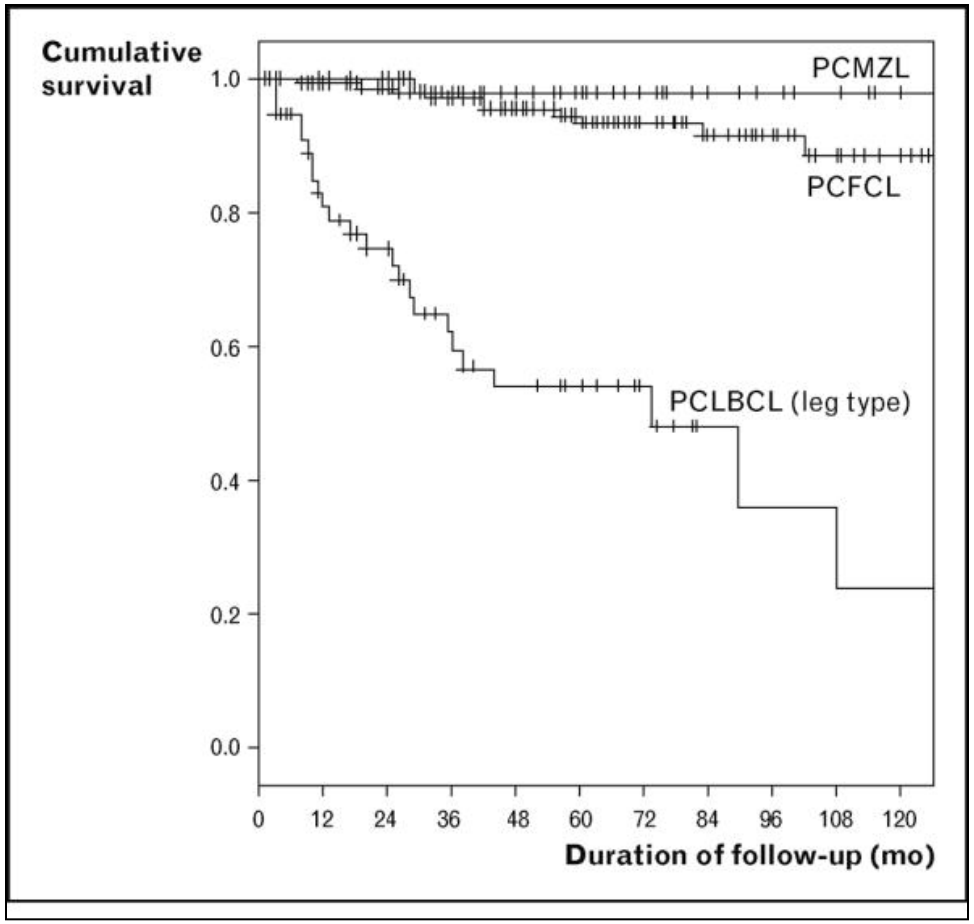
Primary Cutaneous B-cell Lymphomas

	New WHO-EORTC Classification
Indolent	Marginal zone B-cell lymphoma
Indolent	Follicle center lymphoma
Intermediate Aggressive	Diffuse large B-cell lymphoma, leg-type
Intermediate Aggressive	Diffuse large B-cell lymphoma, other

Blood 2005;105: 3768-85

WHO monogram, 4th Ed, 2008

Most primary cutaneous CBCL are "good" except DLBCL, leg-type/other

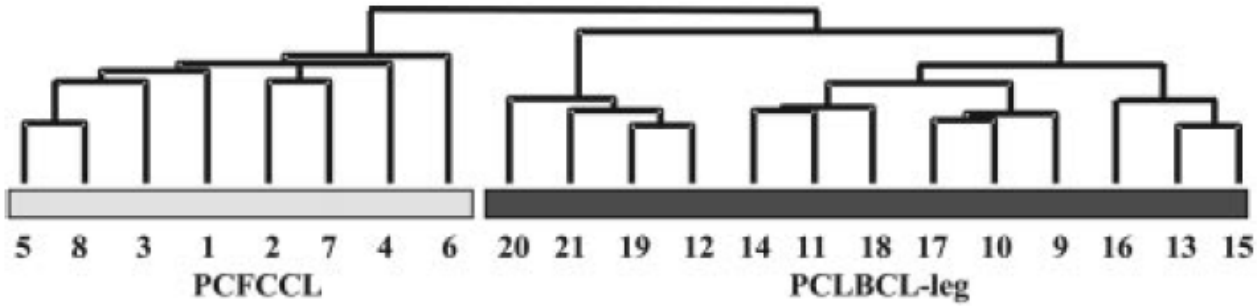


DSS, n = 280 Dutch patients

Willemze, Curr Op Oncol 18:425, 2006

Differential gene expression patterns, PCFCL vs. DLBCL leg-type

Hoefnagel et al, Blood 105;3674, 2005



PCBCL, Stanford Experience, *n = 222*

	Follicle Center Lymphoma (n=115)	Marginal Zone Lymphoma (n=96)	Diffuse Large Cell Lymphoma-leg type (n=11)
Age median	52 (17-88)	49 (14-80)	71 (41-90)
% Male/Female	72/28	61/39	63/37
OS, 5-year	95%	100%	33%
RFS, 5-year	44%	38%	17%
Sites for localized disease	H/N 54% Arm 11% Torso 27%	H/N 31% Arms 37% Torso 23%	Leg 100%

In indolent CBCL (MZL/FCL), when relapse occurs, majority are limited to skin and respond well to salvage therapy

PC Marginal-Zone B-cell Lymphoma

“Immunocytoma”, part of extranodal MZL of MALT (GI tract, salivary gland, lung, H/N, ocular adnexa, skin, thyroid, breast)

Precursor lesions of MALT lymphomas

- Pre-existing chronic inflammatory disorder resulting in accumulation of extranodal lymphoid tissue
- Infectious cause
  - H pylori (gastric MALT lymphoma)
  - Chlamydia psittaci (ocular adnexal MALT)
  - Campylobacter jejuni (IPSID- small intestine)
  - Borrelia burgdorferi (cutaneous- geographic diversity)
- Autoimmune based inflammation
  - Sjögren's (salivary gland MALT lymphoma)
  - Hashimoto's thyroiditis (thyroid gland MALT)

Within European margins

Elisabeth Aberer, Volker Fingerle, Nora Wutte, Regina Fink-Puches, Lorenzo Cerroni

Lancet 2011; 377: 178

Department of Dermatology, Medical University of Graz, Graz, Austria (Prof E Aberer MD, N Wutte MD, Prof R Fink-Puches MD, Prof L Cerroni MD); and National Center for Borrelia, Bavarian Health and Food Safety Authority, Oberschleissheim, Germany (V Fingerle PhD)

Acrodermatitis chronica atrophicans, B-cell LPDs in Europe is primarily caused by *B afzelii*

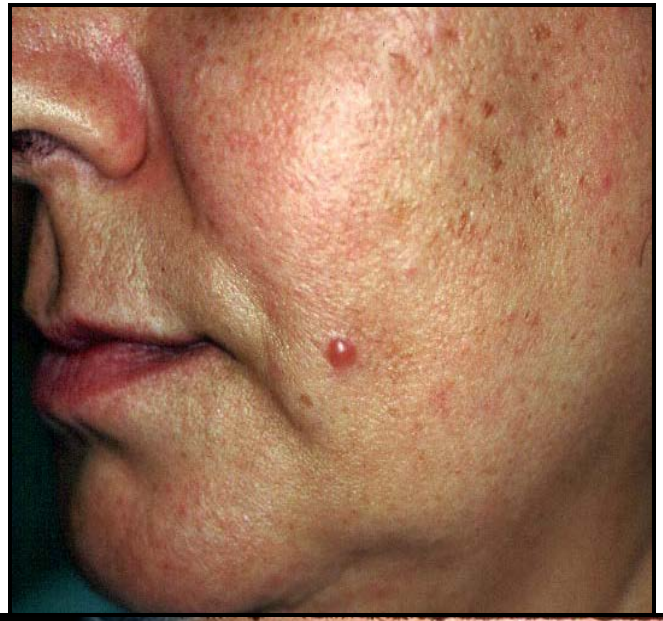
***B afzelli* is NOT found in the US**

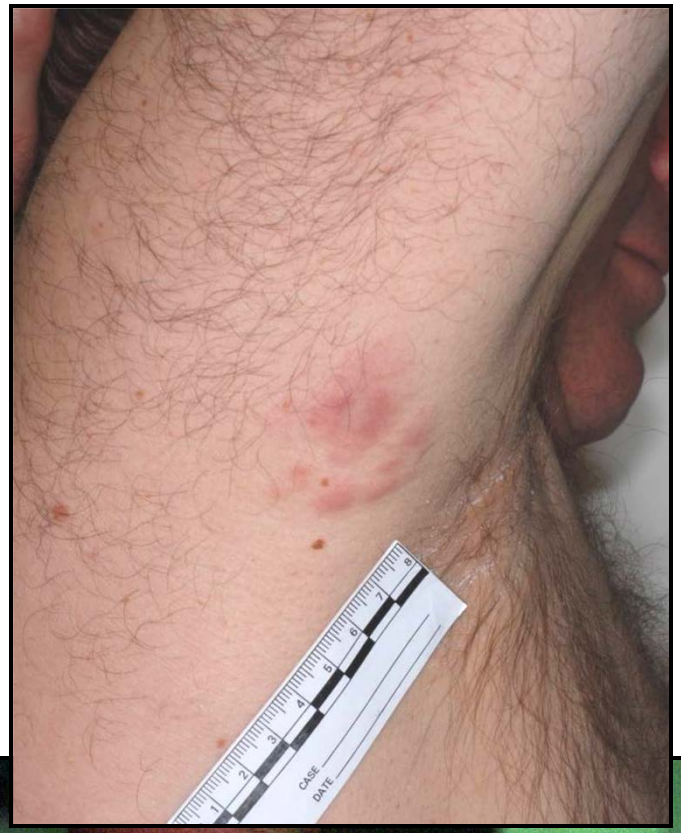
=> CBCL a/w borrelia is most likely a European phenomenon as *B burgdorferi* sensu lato, either *B burgdorferi* or *B afzelli*, has NOT been demonstrated by PCR in affected tissue in the US cases

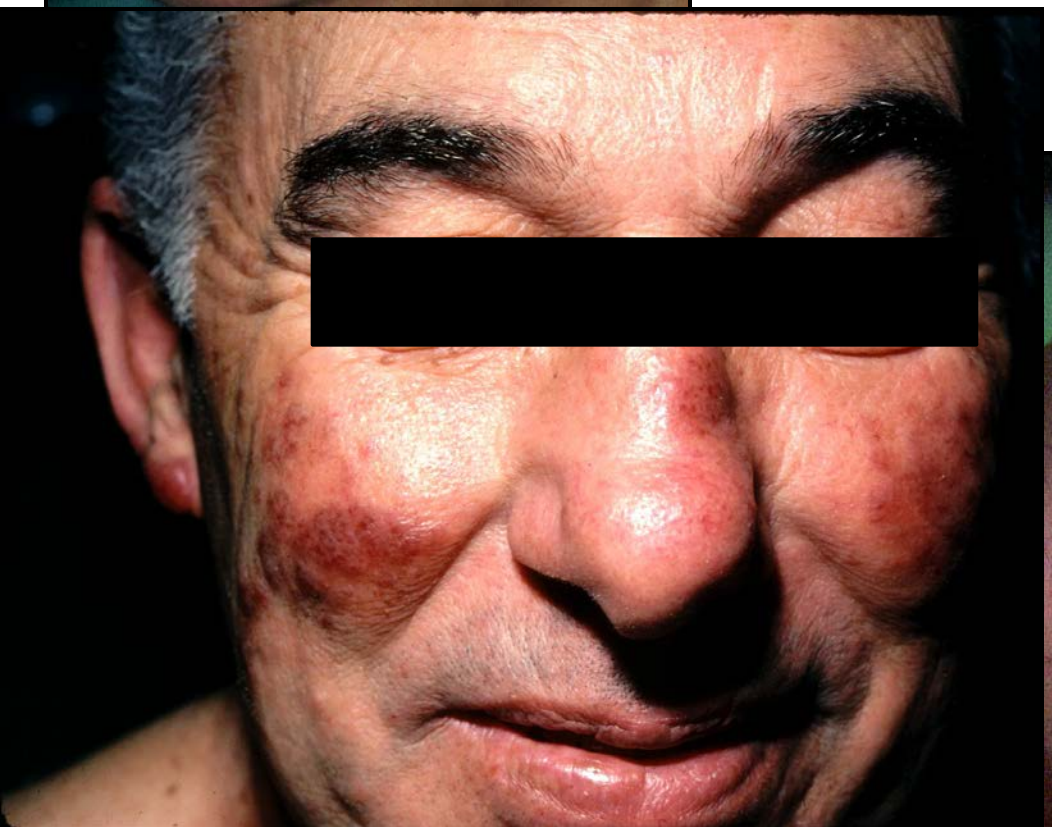
Aberer et al. Lancet 2011;377:178

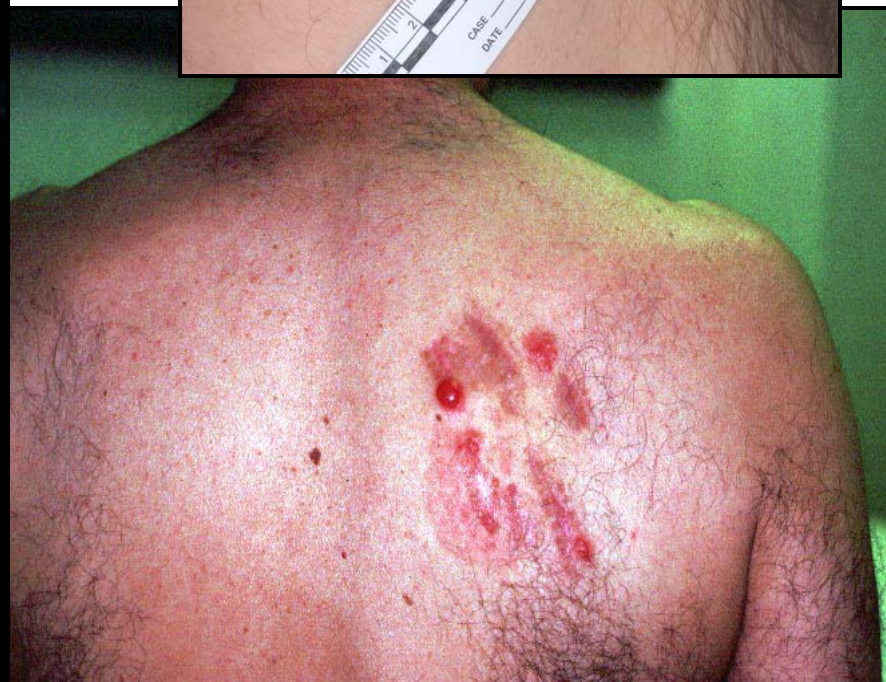
Checking borrelia serology or treating with oral antibiotics for borrelia is NOT in the NCCN guidelines

PCMZL



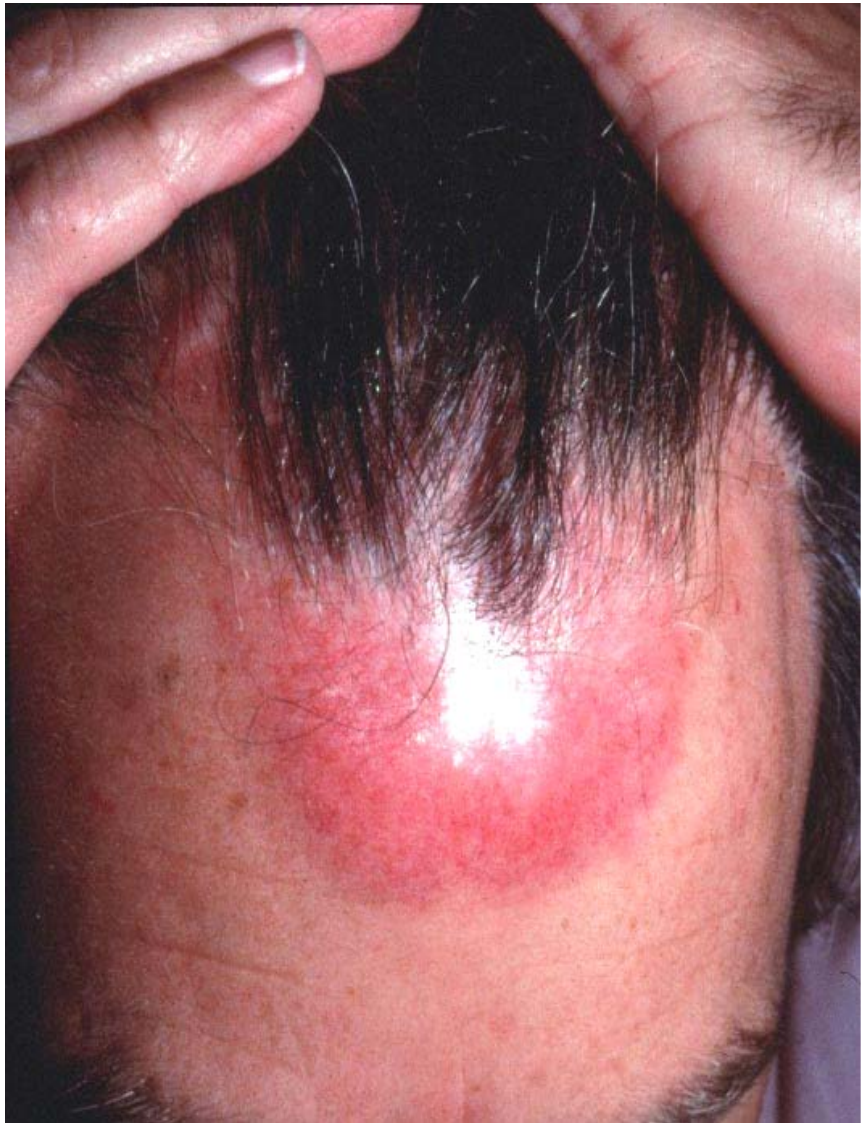




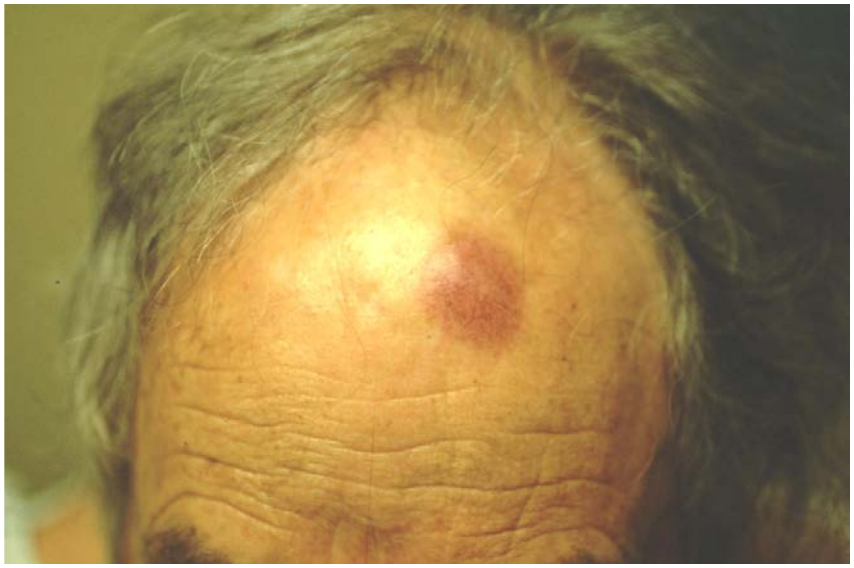


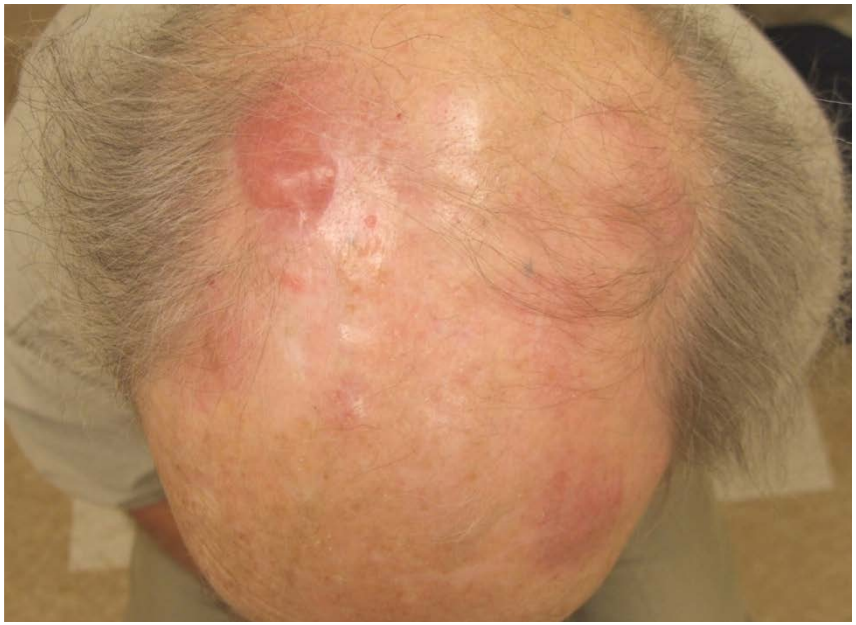
PC Follicle Center Lymphoma

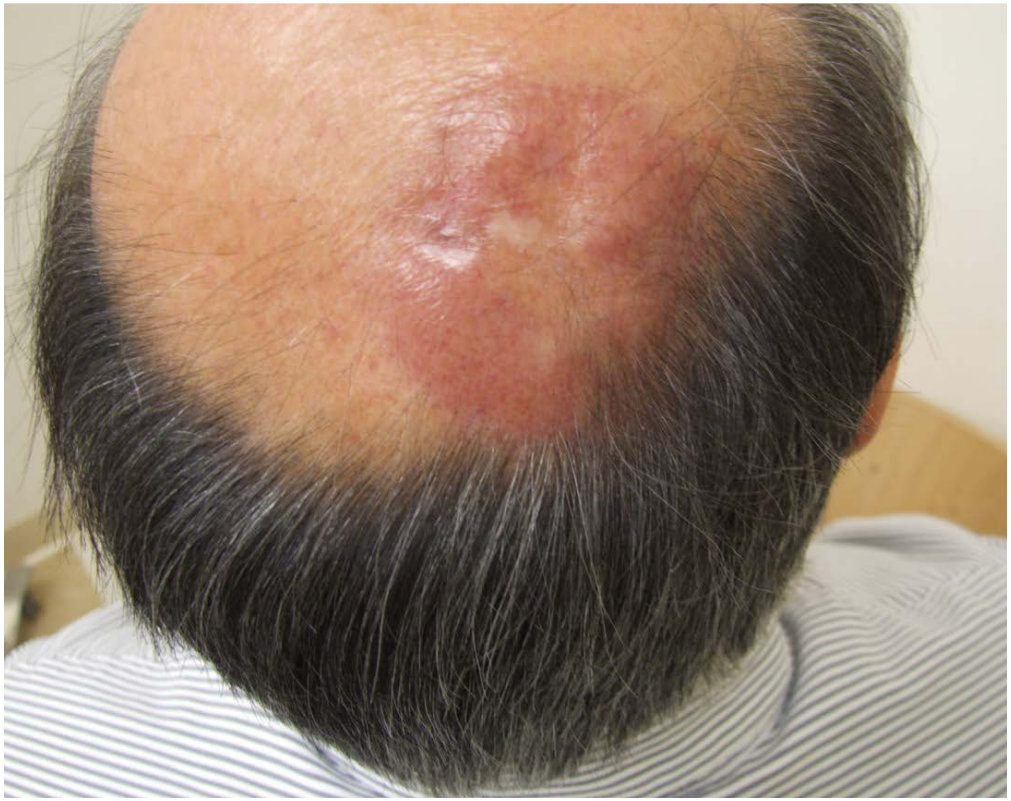
45M with 1 yr h/o slowly enlarging tumors on scalp/forehead

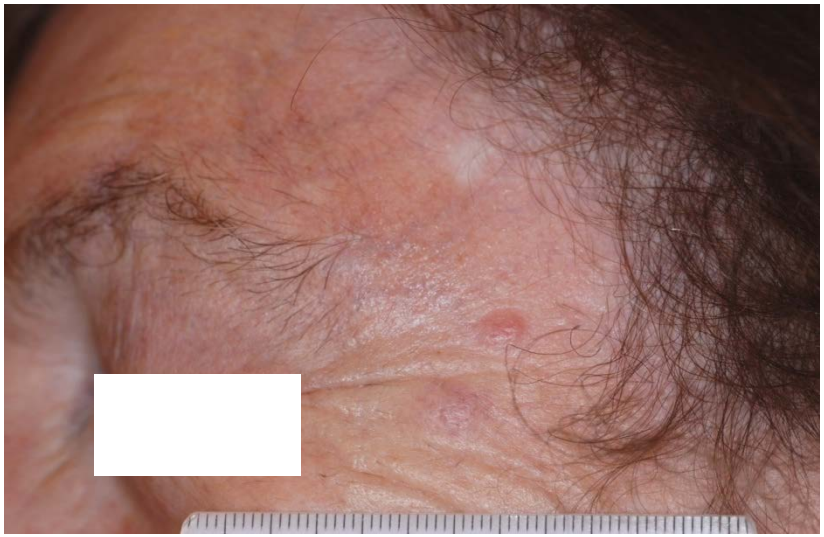


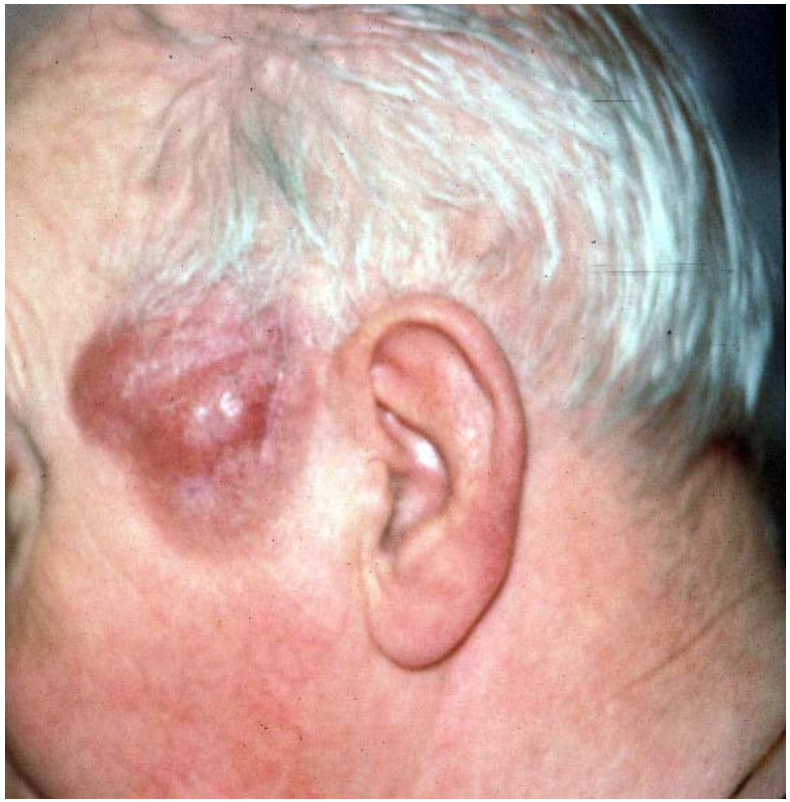
25 yrs later









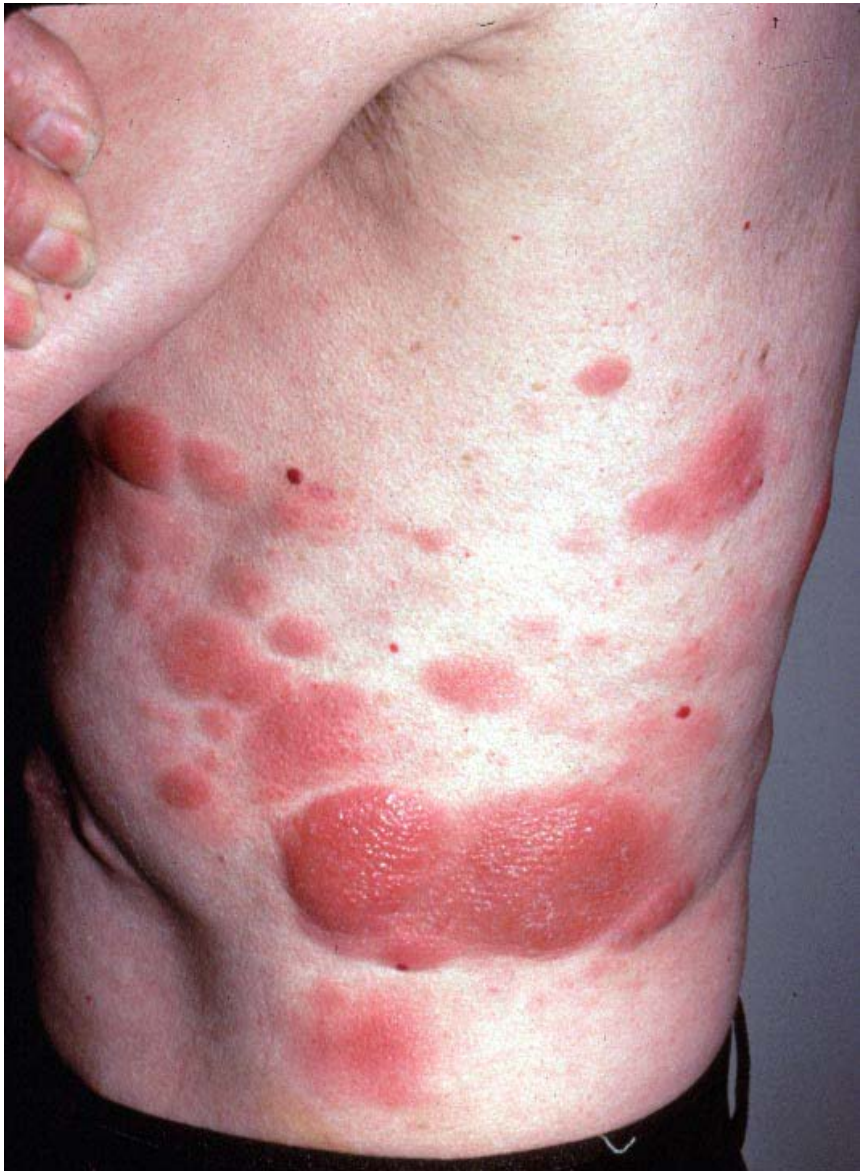


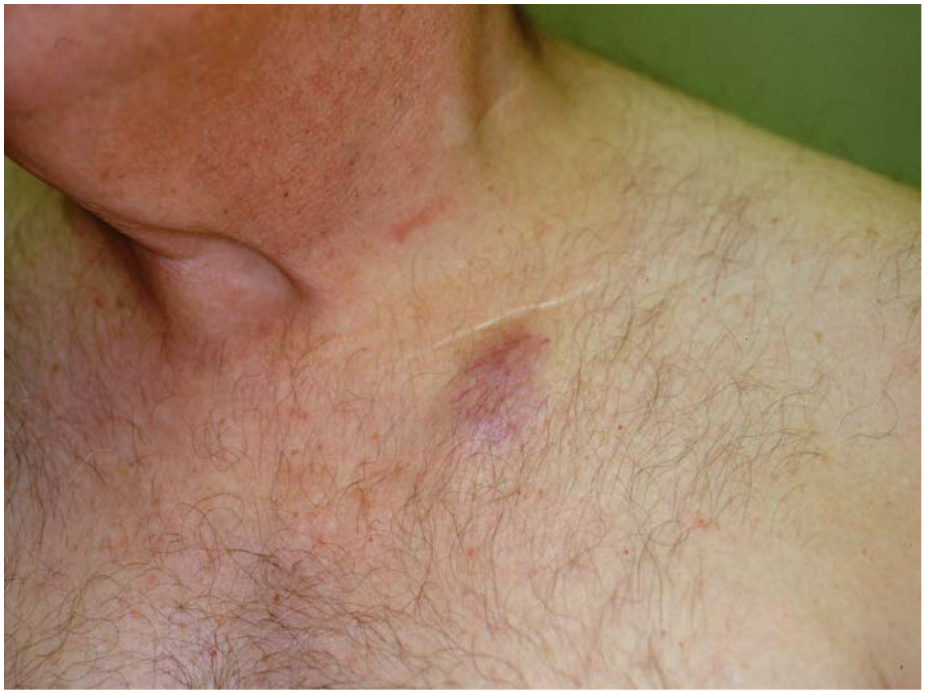
PCFCL

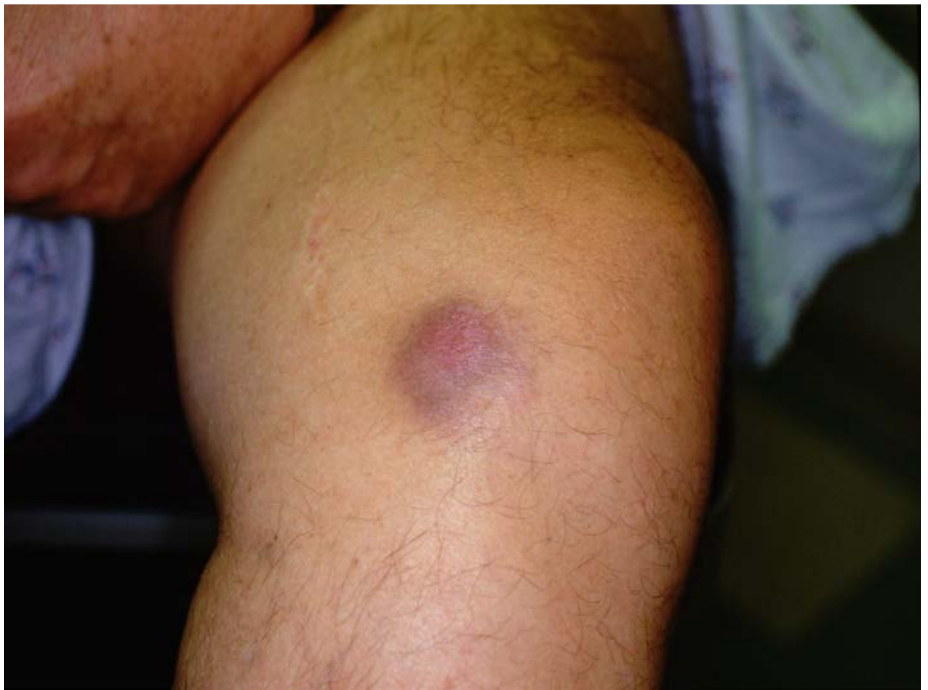
Localized T1, 2

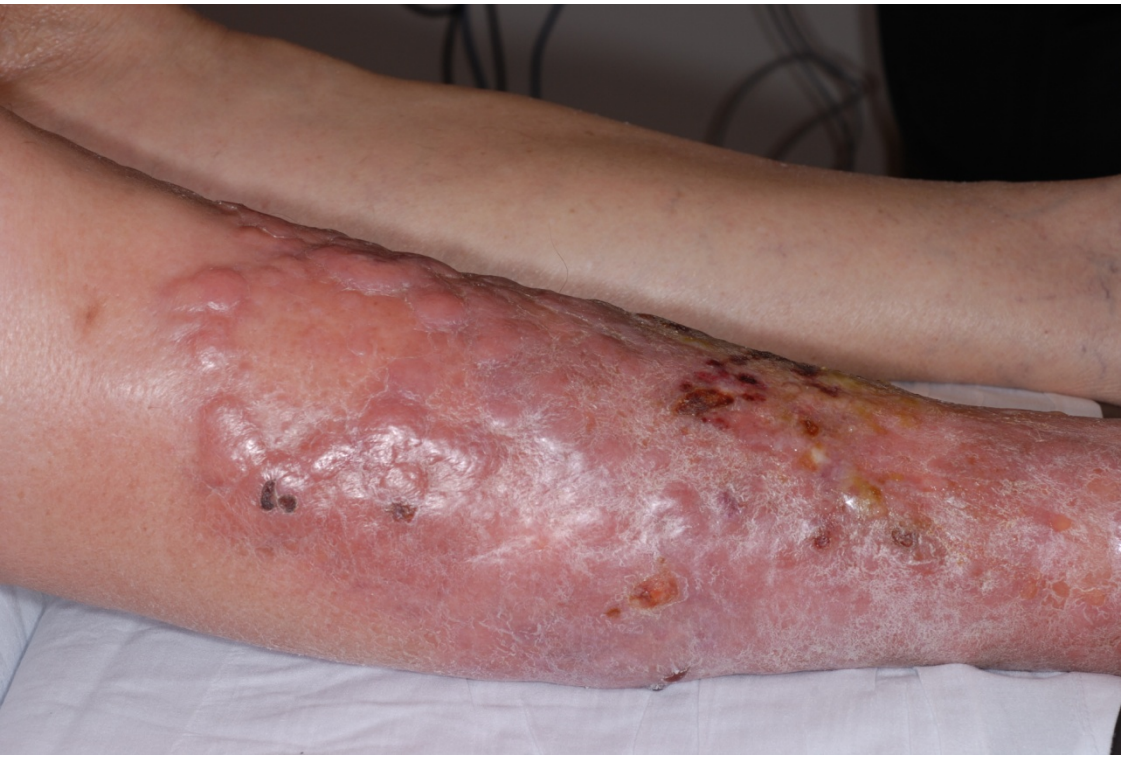
PCFCL

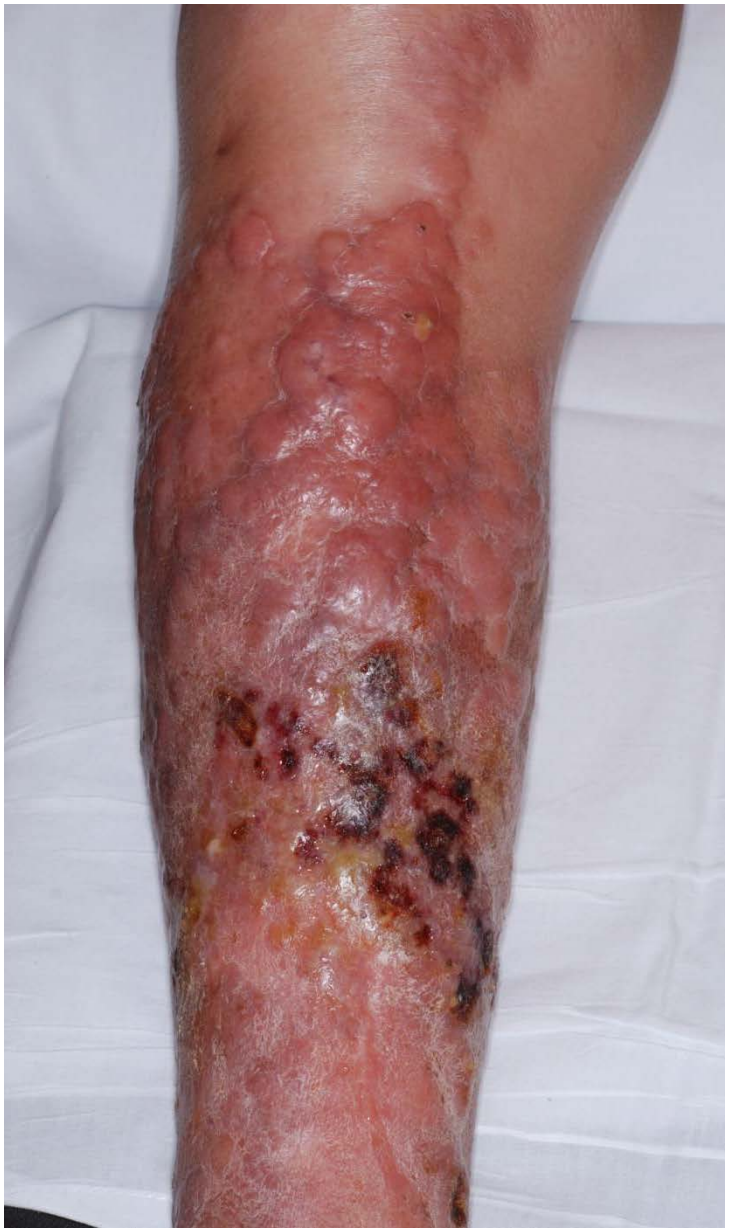
Multifocal/generalized, T3











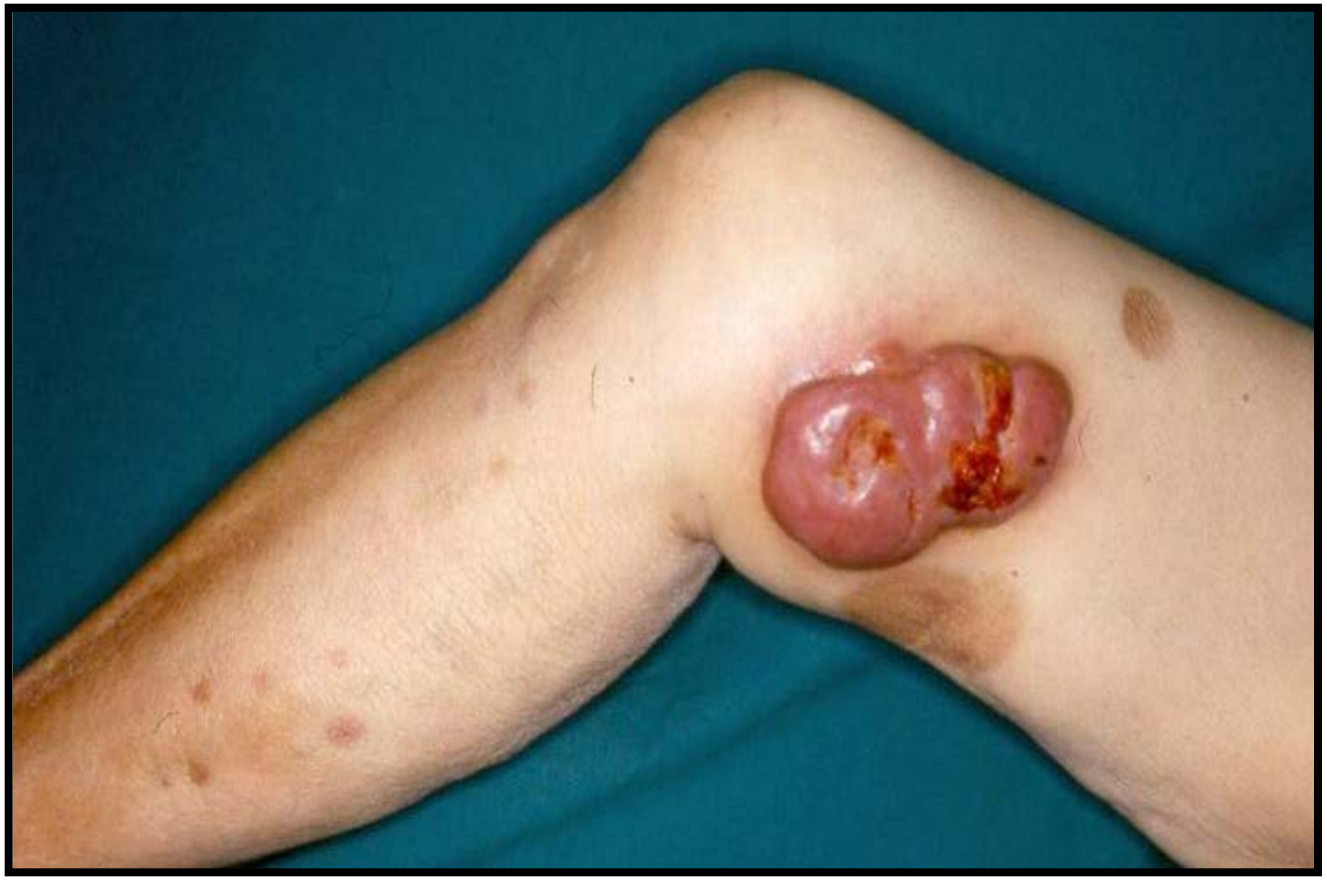
72 yo M initially noted R ankle swelling, then 5 mo h/o rapidly progressive tumor nodules along the R lower leg

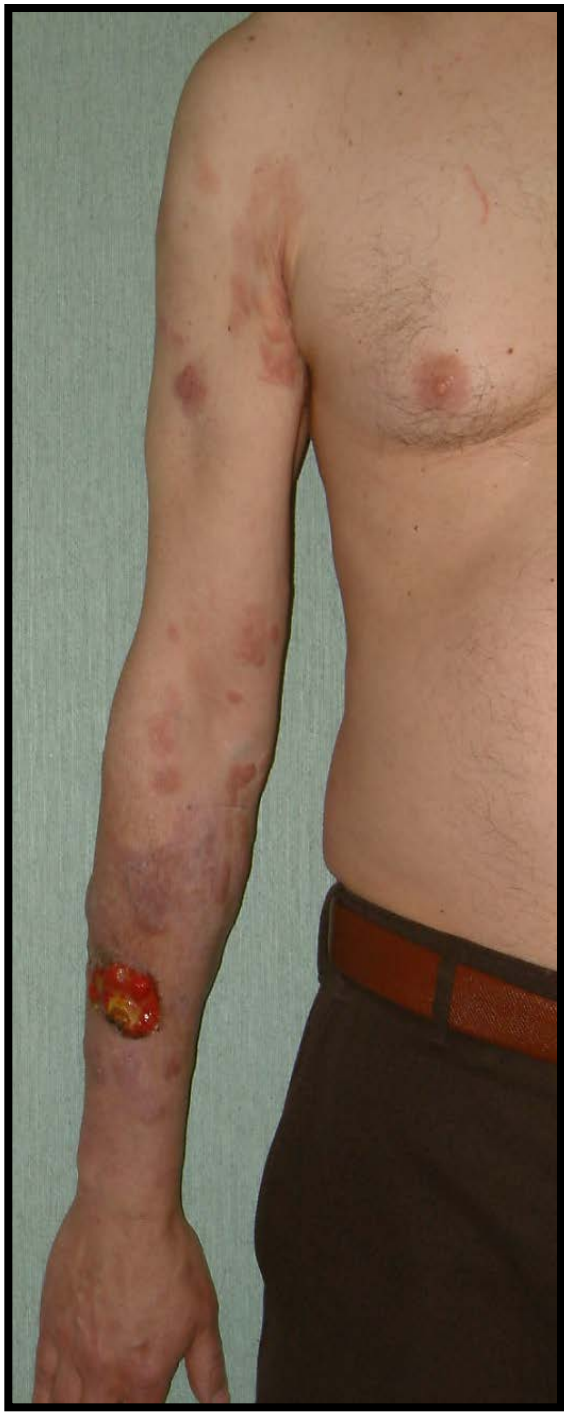
PC Diffuse Large B-cell Lymphoma, Leg-Type

- PCLBCL w/ predominance or confluent sheets of centroblasts and immunoblasts
  - CD20+, CD79a+, monotypic light chain expression
  - Bcl-2+ (strong), Bcl-6+/-, CD10-, IRF4/MUM1+, FOXP1+, IgM+, IgD+/-
  - Lack t(14;18) despite strong Bcl-2; lack IRF4 rearrangement
  - Inactivation of p15, p16 in 11%, 44%; chromosomal imbalances in 85% w/ gains of 18q, 7p, loss of regions of 9p21.3 (CDKN2A/B); translocations of myc, bcl-6, IgH
  - Frequent clonal IgH gene rearrangement by PCR
- Rapidly growing red-violaceous tumor(s), most commonly on leg(s), but can affect non-leg sites (10-15%)
  - Common in elderly
  - Less favorable prognosis w/ increased risk of development of extracutaneous disease => 5-yr OS 35-50%

DLBCL leg-type,

leg or non-leg location





IgM Expression on Paraffin Sections Distinguishes Primary Cutaneous Large B-cell Lymphoma, Leg Type From Primary Cutaneous Follicle Center Lymphoma

Lianne Koens, MD, Maarten H. Vermeer, MD, PhD,† Rein Willemze, MD, PhD,† and Patty M. Jansen, MD, PhD**

Am J Surg Pathol 2010;34:1043-48

- ***100% (40/40) of DLBCL leg type => cytoplasmic IgM+; 18/40 IgD+***
- ***10% (5/53) of FCL are IgM+ and/or IgD+***

IHC for IgM, IgD can be very helpful in distinguishing FCL vs. DLBCL leg type

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2013
Primary Cutaneous B-Cell Lymphomas[a]

NCCN Guidelines Index
NHL Table of Contents
Discussion

DIAGNOSIS

ESSENTIAL:

- Review of all slides with at least one paraffin block representative of the tumor should be done by a pathologist with expertise in the diagnosis of primary cutaneous B-cell lymphoma. Rebiopsy if consult material is nondiagnostic.
- Histopathology review of adequate biopsy (punch, incisional, excisional).
- Adequate immunophenotyping to establish diagnosis[b,c]
  - IHC panel: CD20, CD79a, CD3, CD5, CD10, BCL2, BCL6, kappa/lambda, IRF4/MUM1

USEFUL IN CERTAIN CIRCUMSTANCES:

- Additional immunohistochemical studies to establish lymphoma subtype
  - IHC panel: Ki-67, CD43, CD21, CD23
  - Paraffin panel: Cyclin D1
  - Assessment of IgM and IgD expression (to further help in distinguishing DLBCL, leg type from follicle center lymphoma)
- Molecular analysis to detect: antigen receptor gene rearrangements; *IG* gene rearrangement by PCR
- Cytogenetics or FISH: t(14;18)
- If adequate biopsy material available, flow cytometry can be useful in determining B-cell clonality.

NOTE: A germinal (or follicle) center phenotype and large cells in a skin lesion is *not* equivalent to DLBCL but is consistent with primary cutaneous germinal/follicle center lymphoma.

WORKUP

ESSENTIAL:[d]

- History and physical exam, including complete skin exam
- CBC, differential, comprehensive metabolic panel
- LDH
- Hepatitis B testing[e] if rituximab considered
- Chest/abdominal/pelvic CT
- Bone marrow biopsy, if PC-DLBCL, Leg type
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:

- PET-CT scan
- Bone marrow biopsy
  - Consider if PCFCL
  - Optional if PCMZL
- Peripheral blood flow cytometry, if CBC demonstrates lymphocytosis
- SPEP/quantitative immunoglobulins for PCMZL

See Initial Therapy for Primary Cutaneous Marginal Zone Lymphoma (CUTB-2)

See Initial Therapy for Primary Cutaneous Follicle Center Lymphoma (CUTB-2)

See Initial Therapy for Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg Type (CUTB-4)

PCMZL: Primary Cutaneous Marginal Zone Lymphoma
PCFCL: Primary Cutaneous Follicle Center Lymphoma
PC-DLBCL, Leg type: Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg type

Management of PCBCL

Indolent (MZL/FCL)

Solitary / Regional (T1-2)

- **RT**
- **Excision**
- **Observation**
- **Topical tx**
  - -NM, imiq, retinoid
- **IL steroids**

Generalized (T3)

- **Observation**
- **RT for sx+ lesions**
- **Topical tx**
  - - NM, imiq, retinoid
- **IL steroids**
- **Biologics**
  - - Rituximab
- **Chemotherapy ± R**
  Single or Combination
- **Clinical Trials**

Aggressive (DLBCL leg-type)

Solitary (T1)

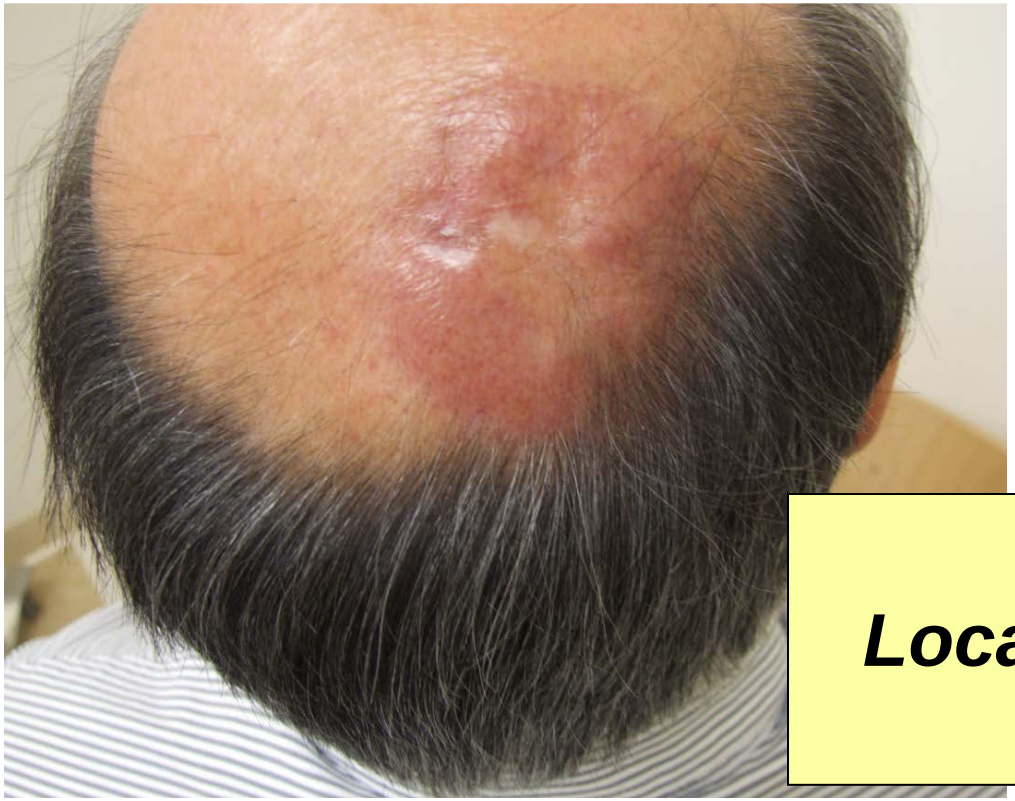
- **RT (caution)**
- **R-CHOP ± IFRT**
- **Clinical Trials**

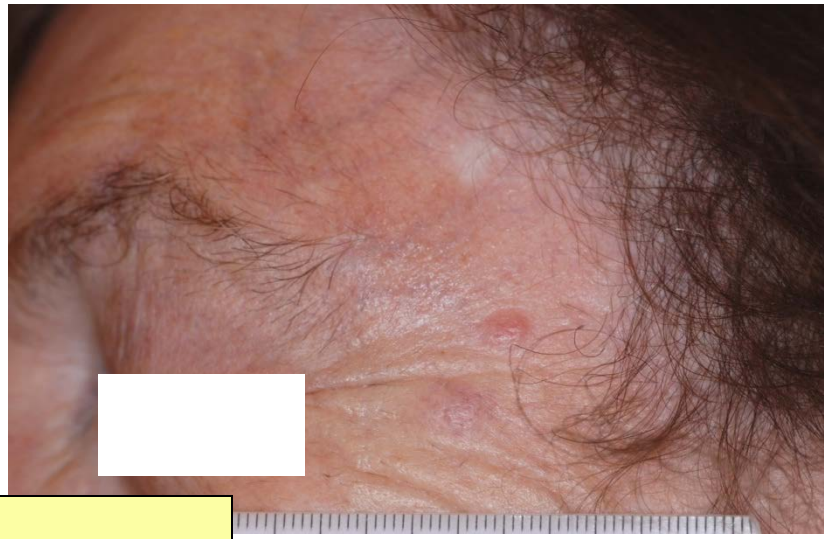
Multiple (T2-3)

- **R-CHOP ± IFRT**
- **Clinical Trials**

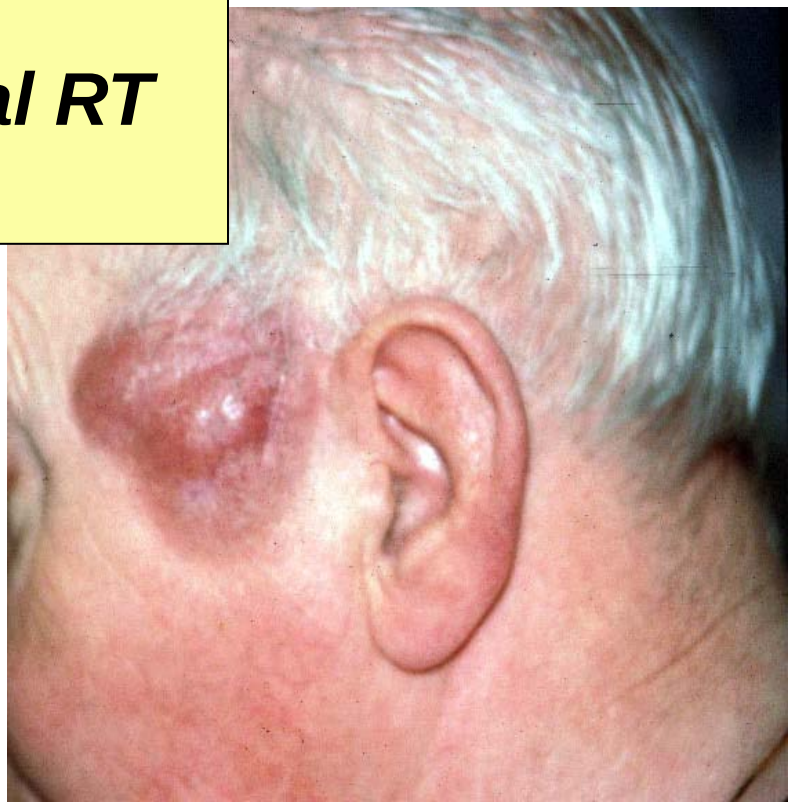
Intralesional rituximab, IFN-α in indolent CBCLs more common in Europe

www.nccn.org => NHL => PCBCL
Blood 2008;112:1600-1609





Local RT

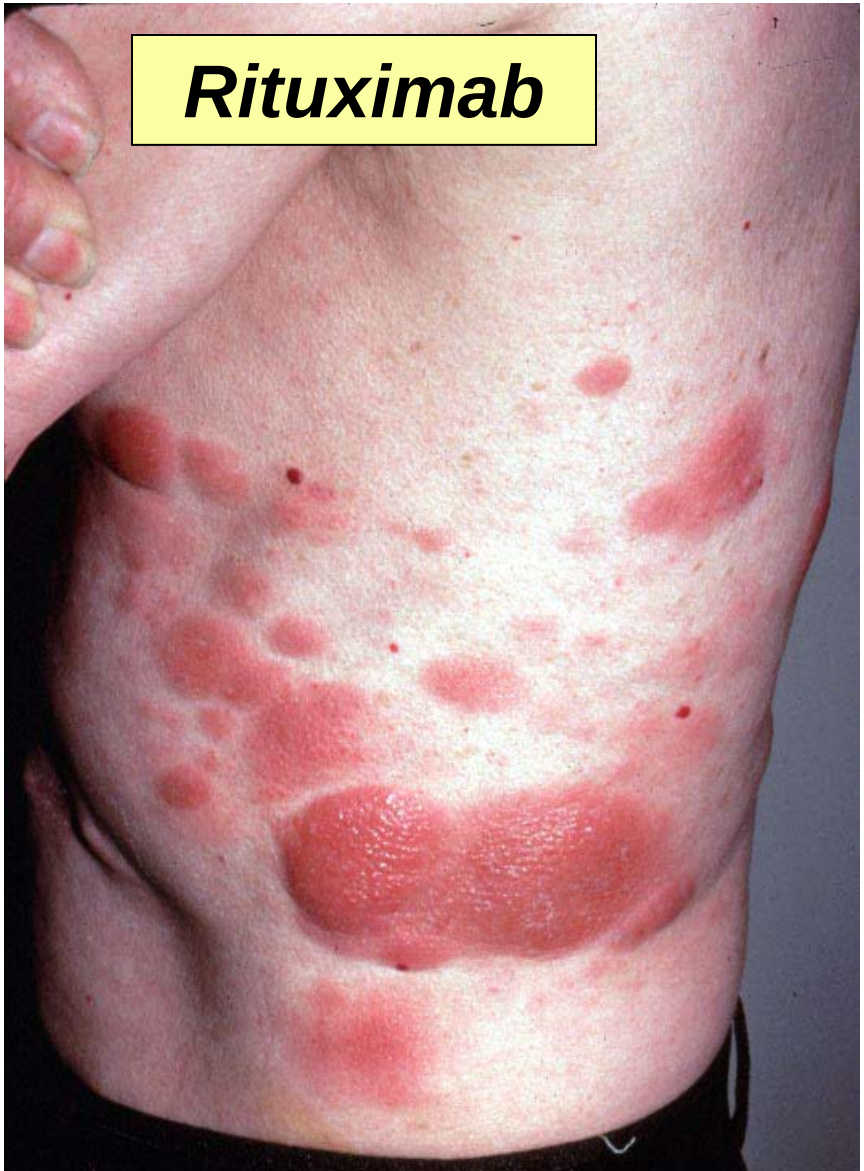


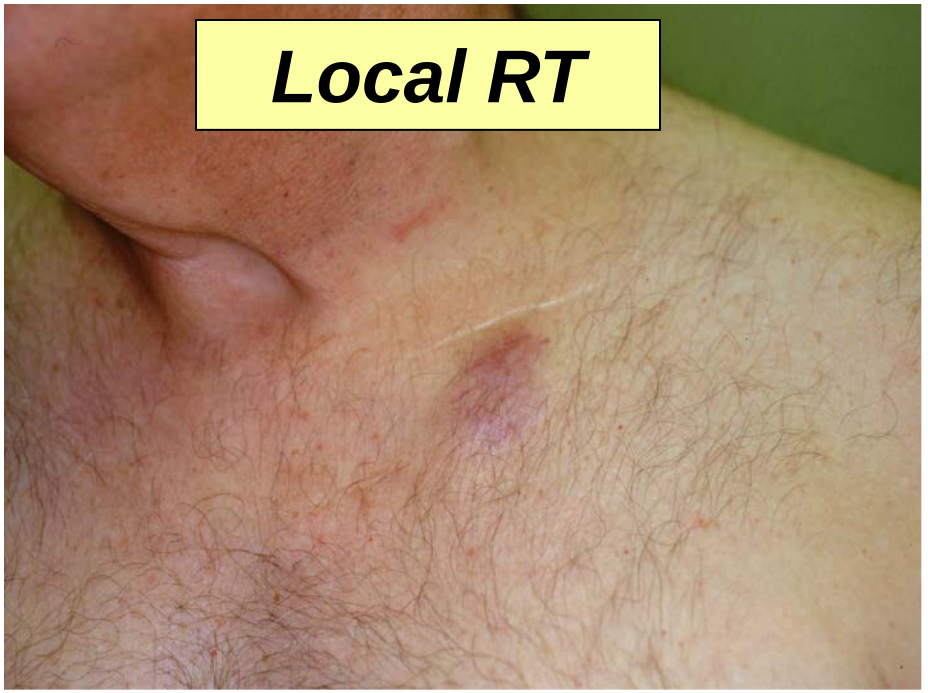
PCFCL

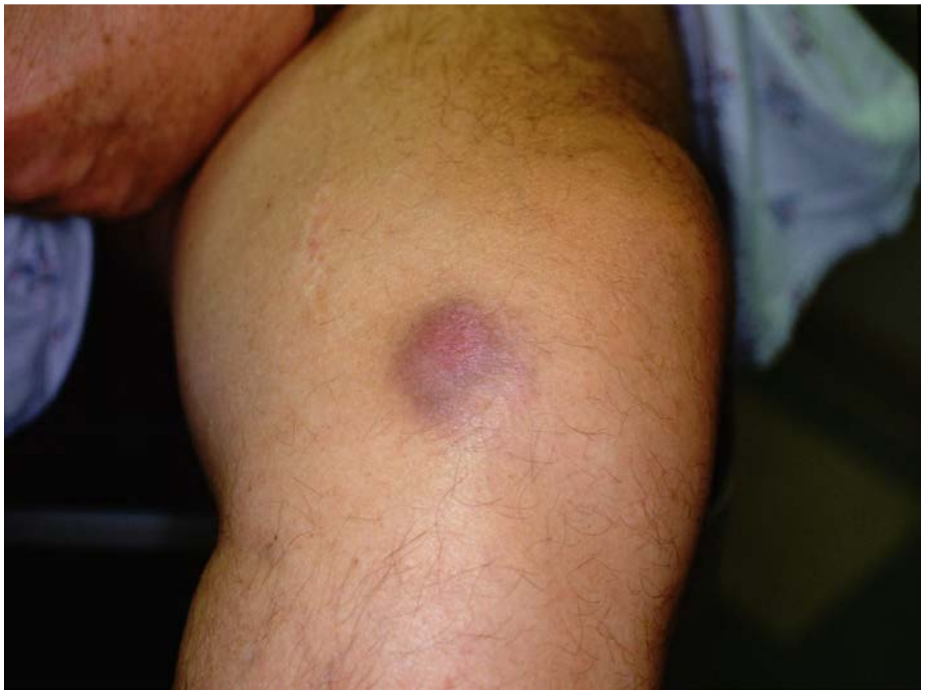
Localized T1, 2

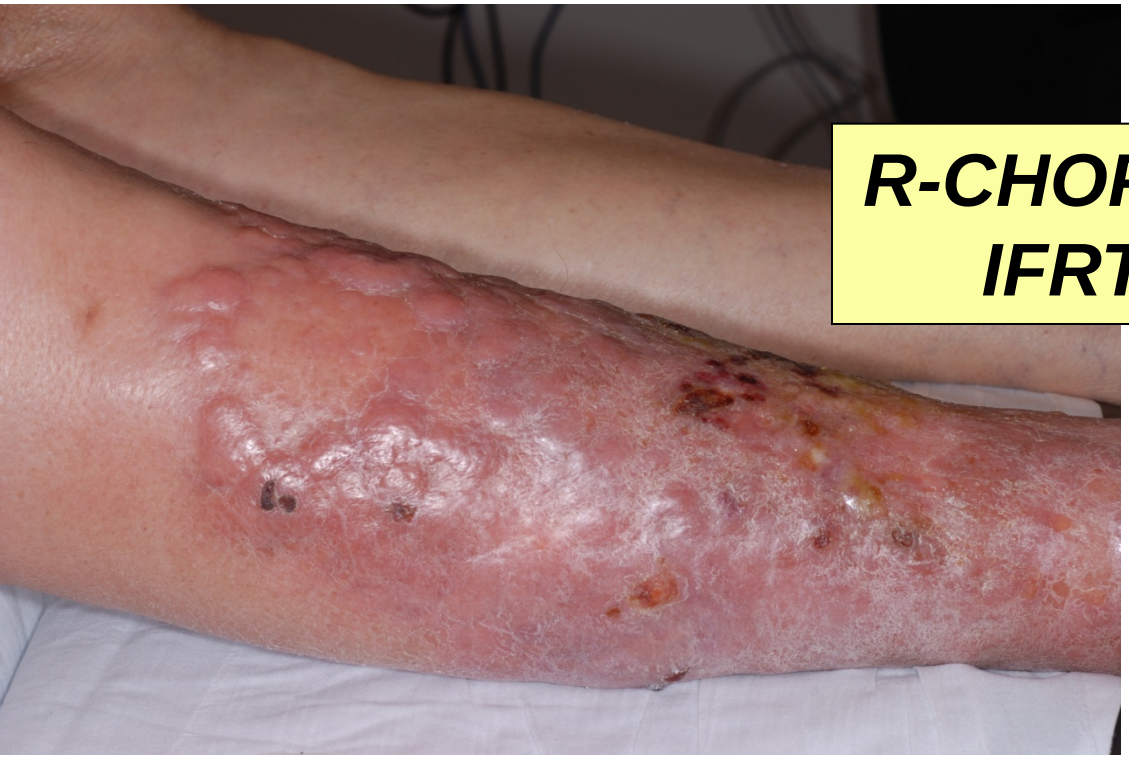
PCFCL

Multifocal/generalized, T3

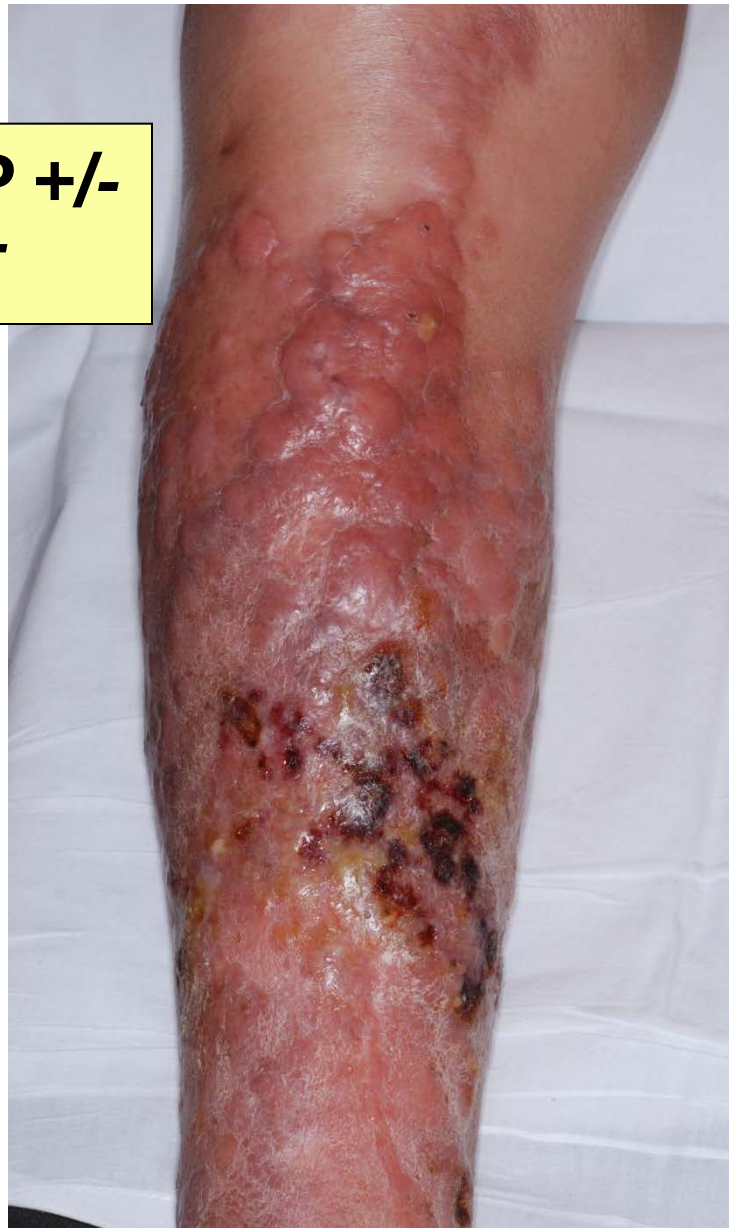








R-CHOP +/- IFRT



72 yo M initially noted R ankle swelling, then 5 mo h/o rapidly progressive tumor nodules along the R lower leg

PC CBCL - Take Home Summary

- **Indolent** (FCL/MZL) vs. **aggressive** (DLBCL leg-type)
- Need more specific molecular and/or tissue markers to differentiate CBCLs or prognosticate => aid in management
- **Do not over treat the indolent cases**
- **Do not under treat aggressive cases** (age appropriate)
- If precise classification difficult, manage according to clinical behavior
- **Utilize NCCN practice guidelines**
  - **NCCN.org => NHL => CBCL**

Other than MF/SS CTCL treatment strategy (not in NCCN)

Indolent clinical behavior (pcALCL, CD4+ sm/med pleomorphic T-cell LPD, SPTCL w/o HPs)

Solitary or regional (T1-2) ⟷ **Multi-focal/generalized (T3)**

Observation

Localized therapies
- Radiation
- Topicals (NM, bex, imiquimod)
- Intralesional steroid

Systemic therapies
- Systemic steroids (SPTCL)
- Methotrexate
- Bexarotene
- HDAC inhibitors
- Clinical trials

Aggressive clinical behavior (SPTCL w/ HPS, γ/δ TCL, PTCL NOS)

- Romidepsin
- single-agent chemo (liposomal doxorubicin, gemcitabine, pralatrexate)
- Upfront intensive combination chemotherapy
- HSC transplantation
- Clinical trials

Stanford Multidisciplinary Cutaneous Lymphoma Group

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