



# Skin Lymphomas

The Dermatologist's Perspective

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# Cutaneous Lymphomas

- Diverse group of lymphoma
- Localized to the skin
- T-cell and B-cell types
- Mycosis fungoides and Sezary syndrome most common types

# Epidemiology

- Most common between age of 50 to 60 years
- 6.4 per million people in the United States
- Male > female
- African American > Caucasian

SEER data: 1973 - 2002

# Etiology

- Unknown
- Some studies have shown links to
  - Infectious
  - Environmental
  - Genetics



# WHO-EORTC Classification

## **Indolent Behavior**

- ❑ Mycosis fungoides and MF variants
- ❑ Primary cutaneous CD30<sup>+</sup> lymphoproliferative disorders
  - ❑ Cutaneous anaplastic large cell lymphoma
  - ❑ Lymphomatoid papulosis
- ❑ Subcutaneous panniculitis-like T-cell lymphoma
- ❑ CD4<sup>+</sup> small/medium-sized pleomorphic T-cell lymphoma

# WHO-EORTC Classification

## **Aggressive Behavior**

- ❑ Sézary syndrome
- ❑ Extranodal NK/T-cell lymphoma, nasal type
- ❑ Cutaneous peripheral T-cell lymphoma, unspecified
  - ❑ Epidermotropic CD8<sup>+</sup> T-cell lymphoma
  - ❑ Gamma-delta T-cell lymphoma



CTCL – The problems:

- Rare
- Not known by many physicians
- Mistaken for common skin rashes
- Diagnosis may take up to years
- Multiple skin biopsies may be needed

- Mycosis fungoides can mimic other skin conditions
- Other skin conditions can mimic mycosis fungoides

- Psoriasis
- Eczema
- Ringworm
- Contact allergy
- Drug-rash
- Vitiligo



**Mycosis fungoides: The great imitator**

Zackheim et al. JAAD 2002

**Table I.** Dermatoses simulated clinically by mycosis fungoides (MF)

	Presence of other clinical manifestations of MF	Type	References
Acanthosis nigricans	Yes	PL	Willemze et al <sup>5</sup>
Alopecia	Yes	PA	Kossard et al <sup>6</sup>
Alopecia	No		Peris et al <sup>8</sup>
Bullous eruption	Yes	PA/PL, tumors	Roenigk and Castrovinci <sup>9</sup>
Comedones, epidermal cysts	No		Oliwiecki, Ashworth <sup>7</sup>
Comedones, epidermal cysts	No		Peris et al <sup>8</sup>
Comedones, epidermal cysts	Yes	PL	Lacour et al <sup>10</sup>
Cysts (epidermal)	Yes	PL	Radeff et al <sup>11</sup>
Cysts (epidermal), comedones	Yes	PA/PL	Aloi et al <sup>12</sup>
Dissecting cellulitis of the scalp	Yes	PA/PL	Giljam et al <sup>13</sup>
Dyshidrosis	Yes	PL	Soyer et al <sup>14</sup>
Erythema annulare centrifugum	Yes	PA	Zackheim and McCalmont (this report)
Erythema multiforme	No		Krebs et al <sup>15</sup>
Gangrene	No		Lund et al <sup>16</sup>
Ichthyosis, acquired	No		Kutting et al <sup>17</sup>
Invisible dermatosis	No		Pujol et al <sup>18</sup>
Ischemic foot	No		Goldstein et al <sup>19</sup>
Keratosis lichenoides chronica	No		Bahadoran et al <sup>20</sup>
Necrobiosis	Yes	PA/PL, tumors	Woolons et al <sup>21</sup>
Perioral dermatitis	Yes	PA/PL	Wolf et al <sup>22</sup>
Pigmented purpuric dermatitis	Yes	PA	Barnhill and Braverman <sup>23</sup>
Pigmented purpuric dermatitis	No		Cather et al <sup>24</sup>
Pigmented purpuric dermatitis	No		Martinez et al <sup>25</sup>
Pityriasis alba	No		Whitmore et al <sup>26</sup>
Porokeratosis	No		Hsu et al <sup>27</sup> (case 2)
Porokeratosis	Yes	PA	Breneman and Breneman <sup>28</sup>
Psoriasis, plaque-type	Yes	PL, tumor	Zackheim and McCalmont (this report)
Pustulosis, palmoplantar	Yes	PA/PL, tumors	Ohkohchi et al <sup>29</sup>
Pustulosis, palmoplantar	Yes	PA/PL, tumors	Moreno et al <sup>30</sup>
Pustulosis, palmoplantar	Yes	PA/PL	Camisa and Aulisio <sup>31</sup>
Pyoderma gangrenosum	Yes	PL	Ho et al <sup>32</sup>
Sarcoidosis	No		Bessis et al <sup>33</sup>
Sarcoma	Yes	PA/PL	Machler et al <sup>34</sup>
Vesicular eruption	Yes	PL	McBride et al <sup>35</sup>
Vesiculobullous eruption	Yes	PA/PL	Maeda et al <sup>36</sup>
Vesiculobullous eruption	Yes	PL, tumors	Cordoba et al <sup>37</sup>
Vitiligo	Yes	PA	Zackheim et al <sup>38</sup> (case 3)
Vitiligo	No		Cooper et al <sup>39</sup>
Vitiligo	No		Lambrzoza et al <sup>40</sup>

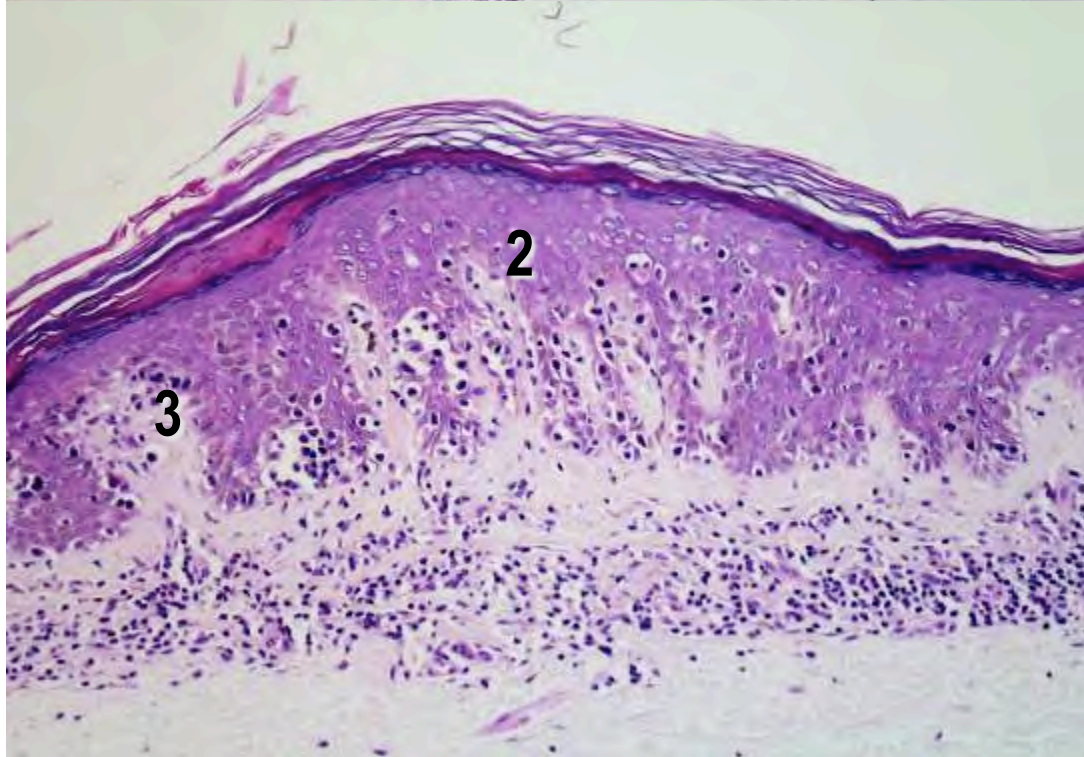
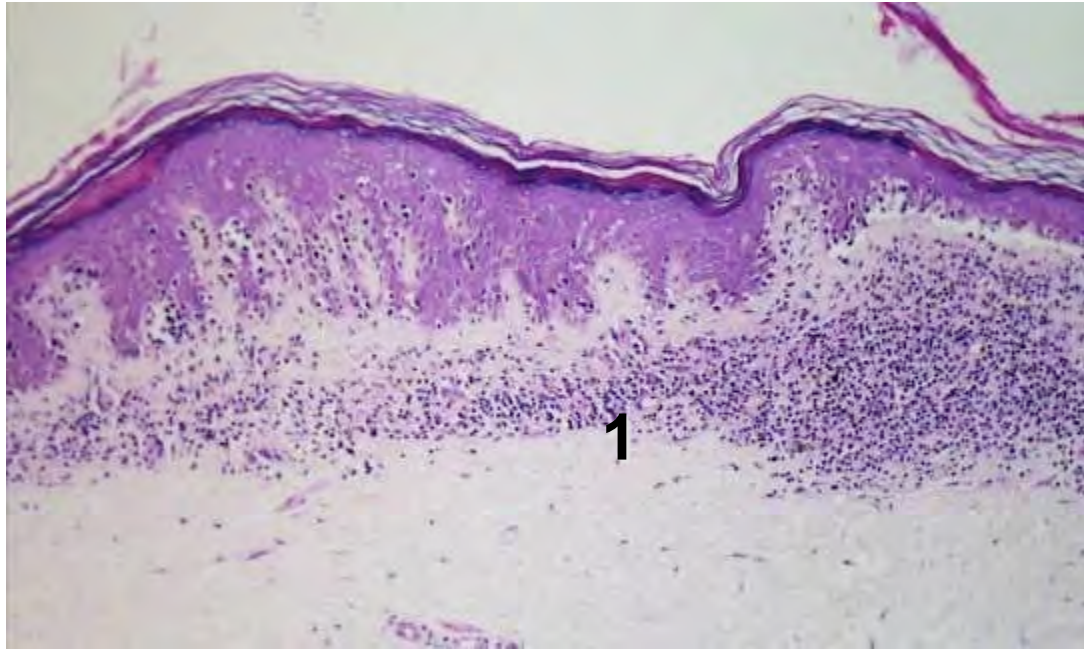
MF, Mycosis fungoides; PA, patch stage; PL, plaque stage.



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# How do we make a diagnosis?

- Clinical appearance
- Skin biopsies
- Additional tests
  - Special histologic stains for phenotype (surface markers)
  - Molecular tests (PCR, southern blot)



## Characteristic histology

1. Upper-dermal band-like lymphocytic infiltrate with atypical lymphocytes
2. Epidermotropism
3. Pautrier's microabscesses

# CTCL

- No single perfect test
- Biopsy
  - Untreated skin
  - Repeat biopsy if not diagnostic
- Determine lymphoma subtype



# Staging

- Localized versus widespread
- Skin
- Lymph nodes
- Blood
- Internal organs

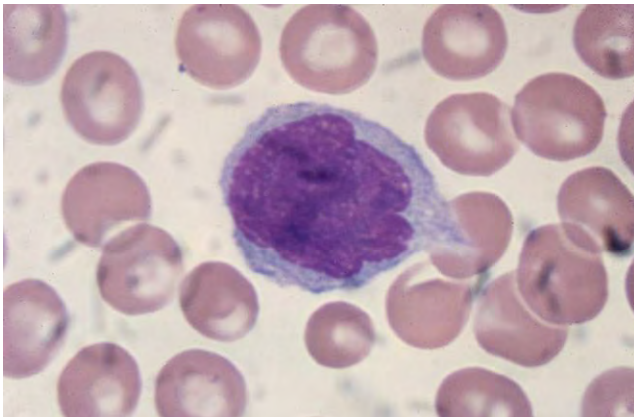
# CTCL Staging

## All patients

- Physical exam
- Skin biopsy
- Blood tests
- X-ray

## Selected patients

- Flow cytometry
- Molecular tests
- CT scan PET scan
- Lymph node biopsy
- Bone marrow biopsy



## Staging is:

- Important for prognosis
- Important to know for selecting the best treatment option



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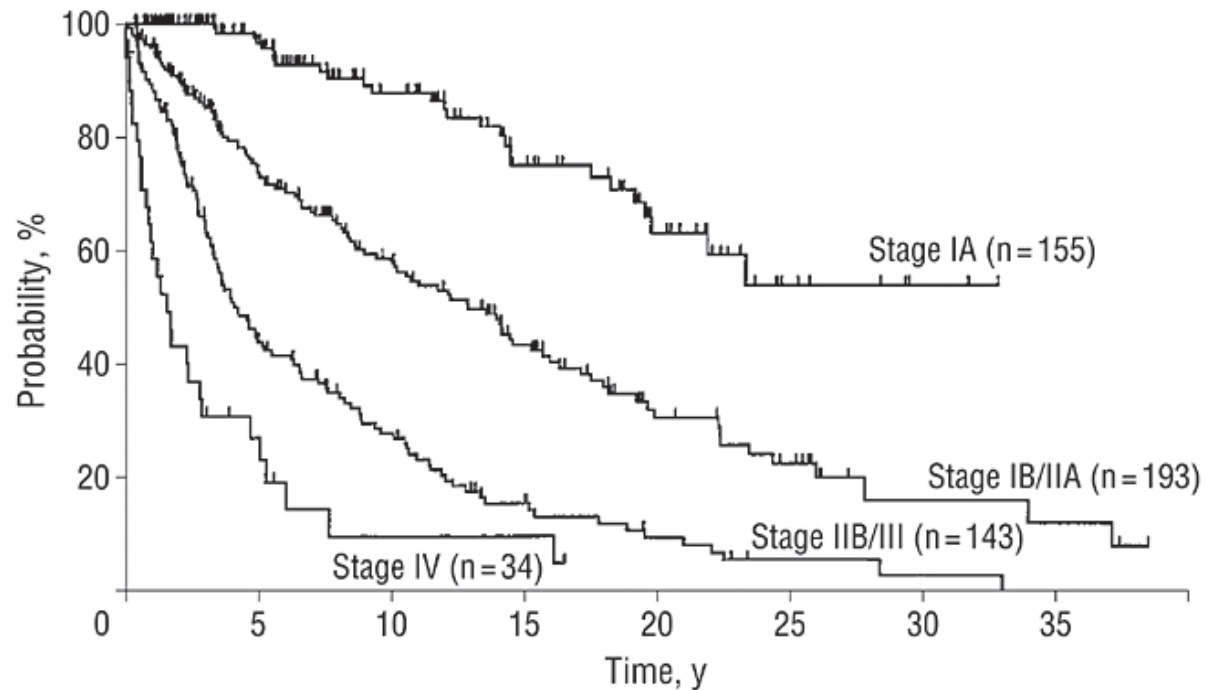
# CTCL - Prognosis

- What about cure?
- What means remission?
- What happens if the lymphoma comes back?
- What happens if the lymphoma progresses?
- How long will I live?

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- Most subtypes are indolent
- Chronic course
- Relapses are common
- Early stages have good prognosis

# Prognosis of 525 patients with mycosis fungoides and Sezary syndrome according to their stage.





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# Treatment Goals

- Cure?
- Complete remission
- Partial remission
- Preserve quality of life
- Reasonable risk-benefit ratio
- Consider treatment costs
- Treatment availability



# Treatment Principles

- **Early stage**
  - Potential for cure
  - Skin-directed therapies, combination therapies
- **Advanced stage**
  - Palliation and control of disease
  - Multidisciplinary approach
  - Systemic therapies and combinations
    - Immune enhancing therapies
    - Cytotoxic response in malignant cells



# Strategies:

- Treating infections
- Preserving skin barrier
- Targeting abnormal clone
- Preserving cytotoxic response
- Using skin-directed therapy early in the disease

## Skin manifestations of CTCL at diagnosis

<b>Stage at diagnosis</b>	<b>Patients at diagnosis (%)</b>
<b>T1: Patches/plaques covering &lt;10% of body surface</b>	<b>42</b>
<b>T2: Patches/plaques covering <math>\geq</math>10% of body surface</b>	<b>30</b>
<b>T3: Tumor(s)</b>	<b>15</b>
<b>T4: Erythroderma</b>	<b>12</b>

## Skin-directed Therapies

- Topical corticosteroids
- Topical chemotherapy
  - Nitrogen mustard (Mustargen)
  - Carmustine (BCNU)
- Topical retinoids/rexinoids
  - Bexarotene (Targretin)
  - Tazarotene
- Phototherapy
  - NB-UVB
  - PUVA
- Radiation
  - Electron beam radiation
  - Site-directed radiation

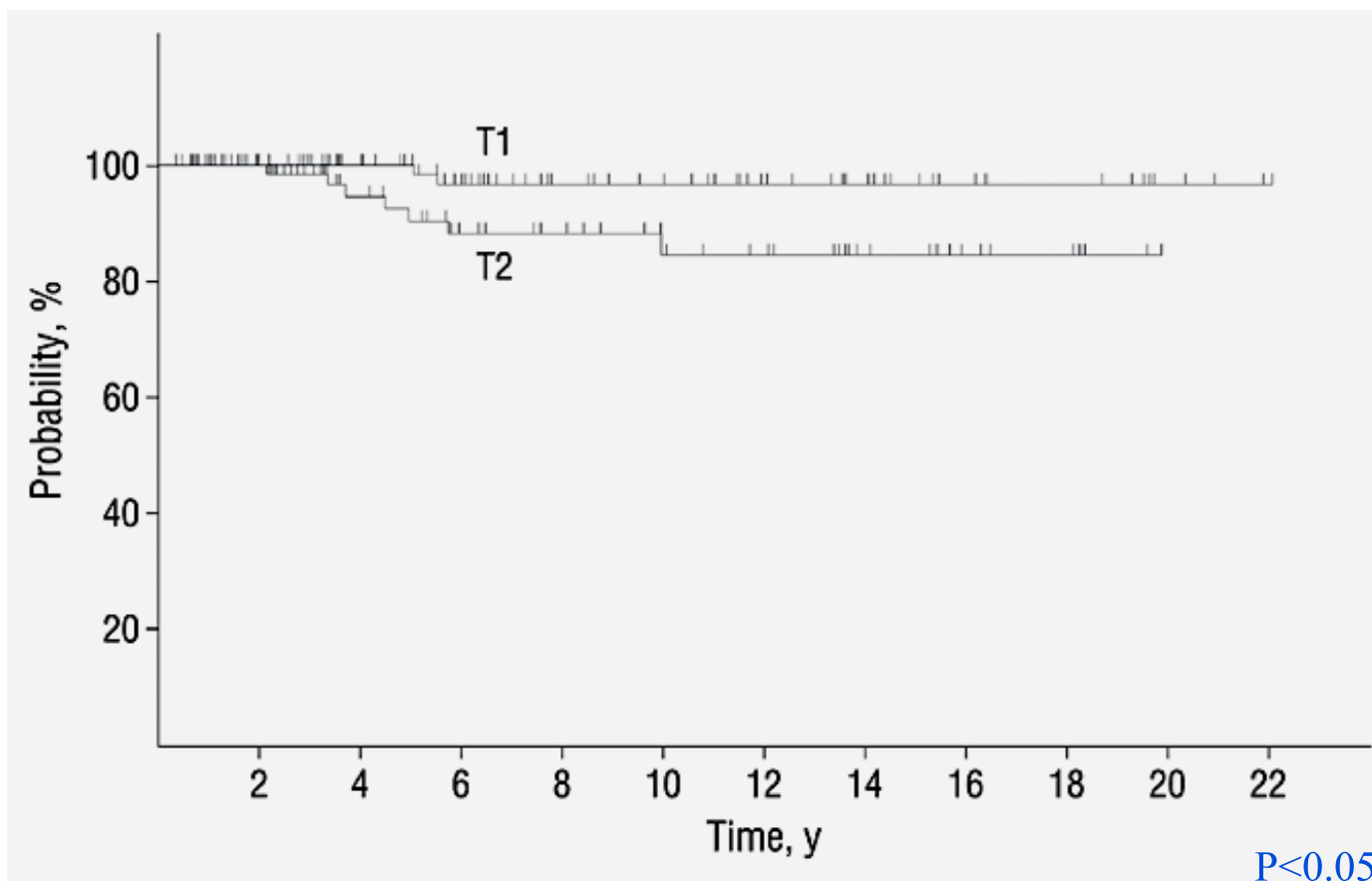
## Topical steroids

- ❑ Cream or ointment, once or twice daily
- ❑ High response rates
- ❑ Convenient
- ❑ Less expensive
- ❑ Skin irritation, allergy
- ❑ Skin thinning, stretch marks
- ❑ Systemic absorption

## Nitrogen mustard (Mustargen)

- ❑ Topical chemotherapy
- ❑ High response rates
- ❑ 0.1% – 0.2% aqueous or ointment formulation
- ❑ Mechanism of action?  
Immunostimulation?
- ❑ No increased risk of skin cancer
- ❑ Skin irritation
- ❑ Darkening of skin
- ❑ May take 6 months or longer to clear skin

Actuarial disease-specific survival rates of 195 patients with early disease treated with topical nitrogen mustard



*Kim YH et al. Arch Dermatol 2003*

# Light therapy

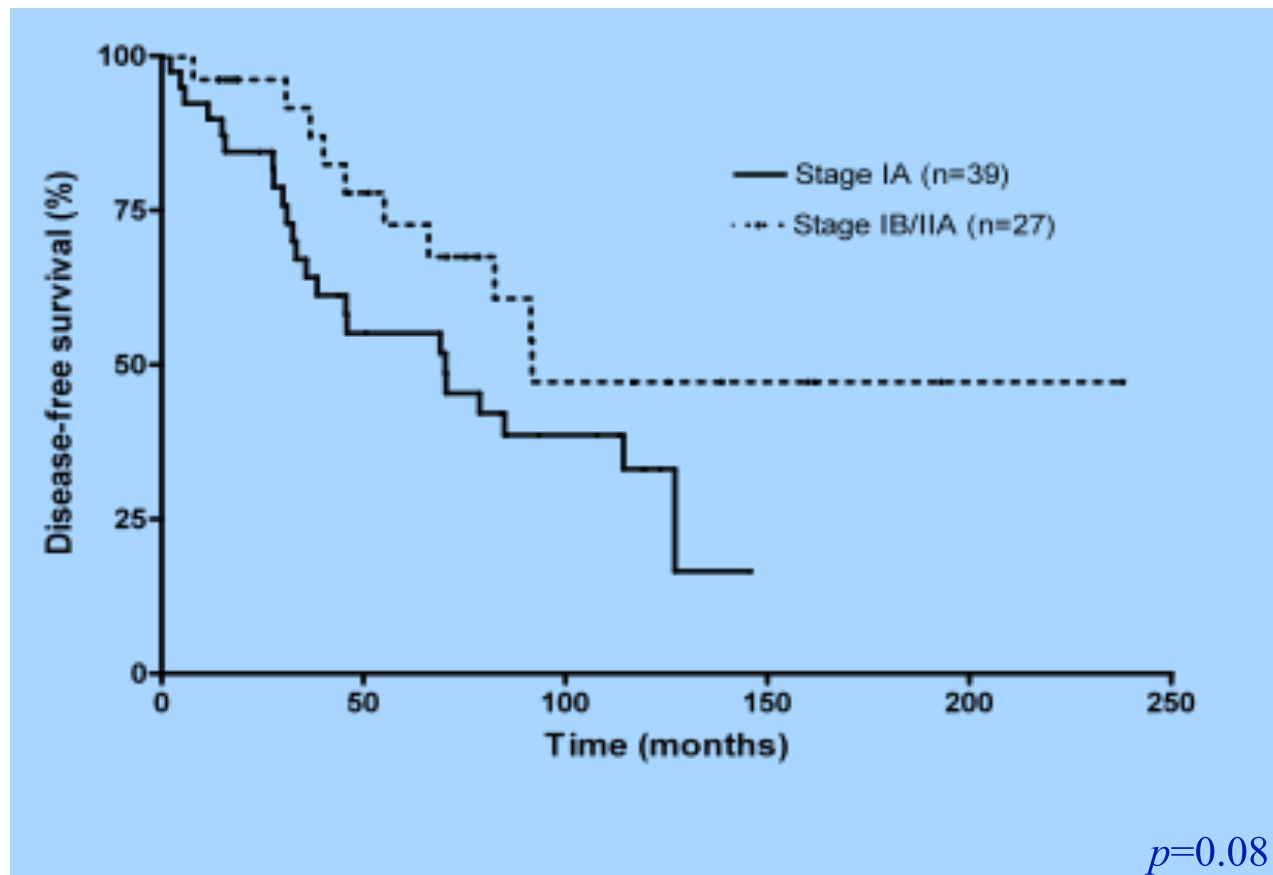
- ❑ Narrowband UVB
- ❑ Broadband-UVB
- ❑ PUVA



## Phototherapy: PUVA or Narrowband-UVB

- ❑ 2-3 x week
- ❑ Stops the abnormal proliferation of malignant T-cells in the skin by preventing the cells from duplicating their DNA
- ❑ Highly effective, with 70-90% of patients experiencing partial or complete response
- ❑ Long-term responses
- ❑ Skin burn
- ❑ Itch
- ❑ Nausea (psoralen)
- ❑ Risk of skin cancer with long-term exposure of PUVA

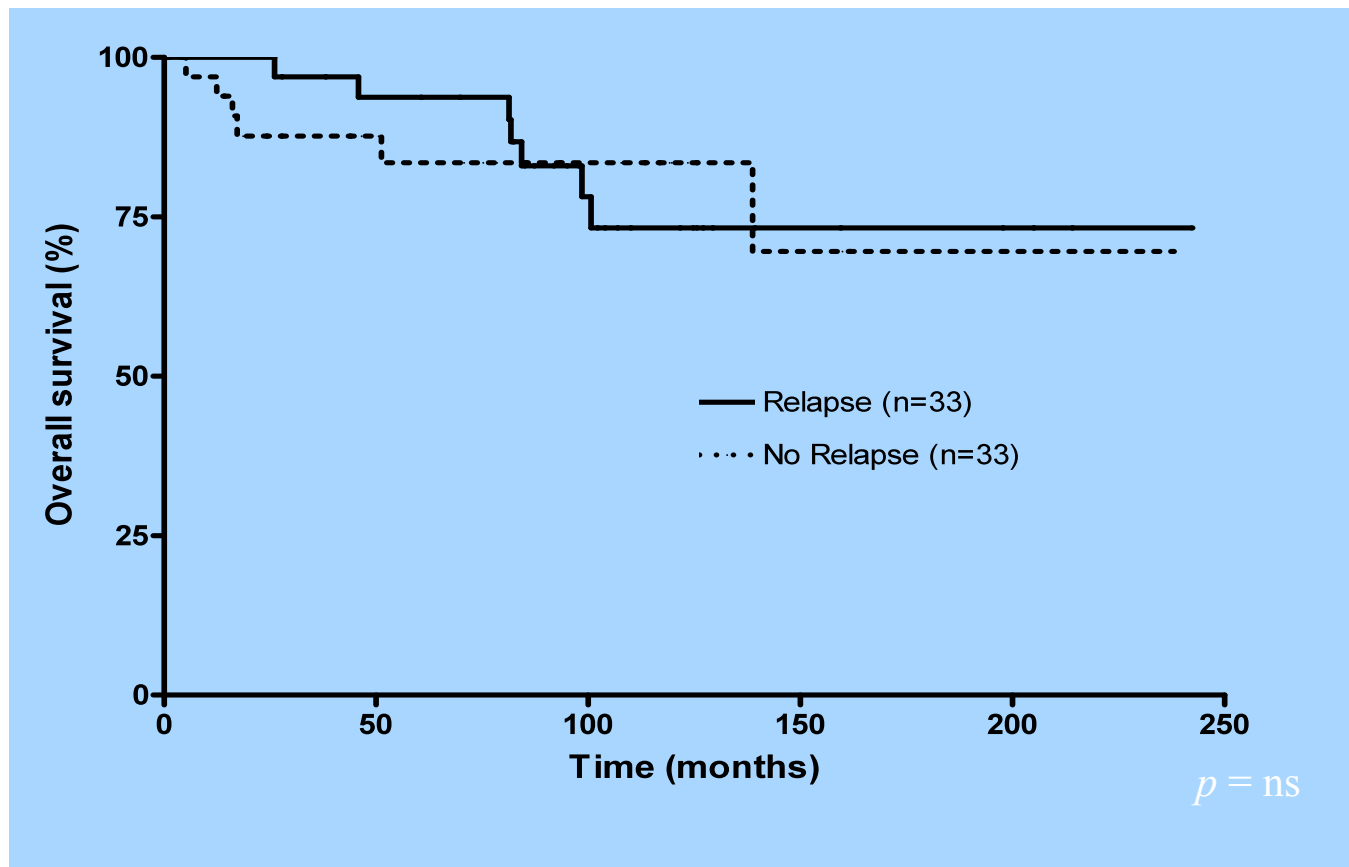
## Relapse-free survival



Querfeld et al. Arch Dermatol 141: 305-11; 2005

# Overall Survival

Relapsed/non-relapsed patients = ns



Querfeld et al. Arch Dermatol 141: 305-11; 2005

## Retinoids

- ❑ Vitamin A derivatives
- ❑ Applied once daily
- ❑ 1% gel
  - ❑ Bexarotene gel (Targretin)
  - ❑ Tazorac 0.1% gel
- ❑ Response rates between 63% and 75%
- ❑ Inhibits growth of tumor cells
- ❑ Redness, itching, warmth, swelling, burning, scaling, or other irritation
- ❑ Increase sensitivity to light
- ❑ Expensive



## Off-label Therapies

- Imiquimod (Aldara)
- Pimecrolimus (Elidel)
- Tacrolimus (Protopic)
- Excimer laser therapy
- Photodynamic therapy



## Clinical trials

1. Nitrogen mustard 0.02% aquaphor versus propylene glycol ointment
  - Possibly equally effective
2. Lenalidomide
3. Pegylated interferon- $\alpha$  2b

# Treatment recommendations

- Lymphomatoid papulosis:
- Observation vs. palliative treatment
- PUVA, NB-UVB, low-dose methotrexate
- ALCL:
- Radiation (localized)
- Systemic chemotherapy (dissem.)
- Investigational:
- Monoclonal antibody:
  - anti-CD30

*Bekkenk et al. Blood 2000;*  
*Querfeld et al. Oncology 2007*

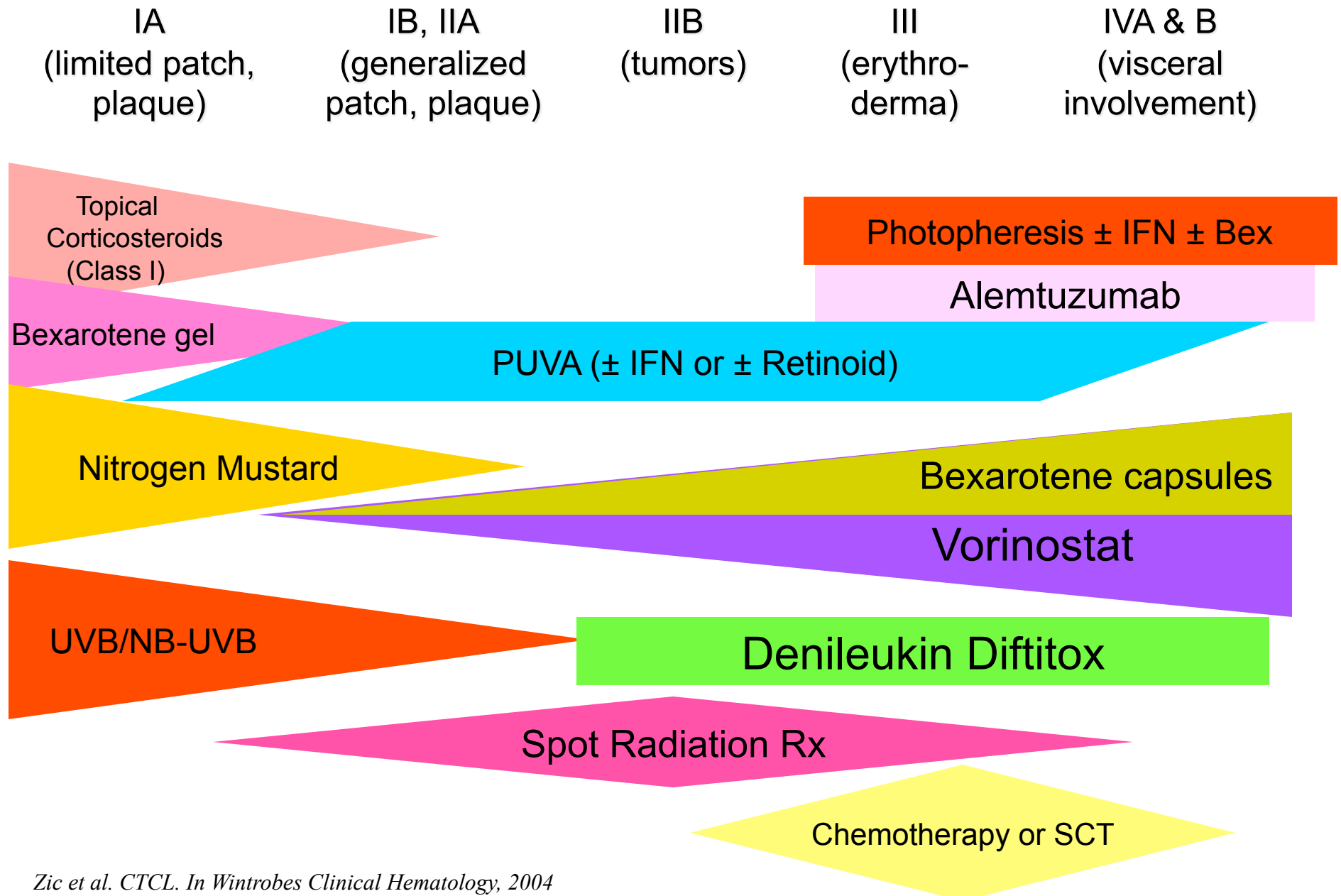
## Reference Guide

### Therapeutic Agents Mentioned in This Article

Bexarotene (Targretin)  
Carmustine (BCNU)  
Chlorambucil (Leukeran)  
CHOP, CHOP-like regimens  
Dapsone  
Doxorubicin, pegylated liposomal (Doxil)  
Doxycycline  
Imiquimod (Aldara)  
Interferon-alpha  
Interferon alfa-2a (Roferon-A)  
Interferon-gamma (Actimmune)  
Methotrexate  
Nitrogen mustard  
Phototherapy (UVB, PUVA, UVA-1)  
SGN-30

Brand names are listed in parentheses only if a drug is not available generically and is marketed as no more than two trademarked or registered products. More familiar alternative generic designations may also be included parenthetically.

# Mycosis Fungoides/Sézary Syndrome Treatment Algorithm



# Mycosis fungoides / Sézary syndrome

## *Systemic Therapies*

- ❑ Steroids
- ❑ Biological therapies
  - ❑ Interferon- $\alpha$
  - ❑ Retinoids/Rexinoids
  - ❑ Histone deacetylase inhibitors (Vorinostat)
  - ❑ Extracorporeal photochemotherapy
- ❑ Targeted modalities
  - ❑ Interleukin-2 fusion protein (denileukin diftitox, Ontak)
  - ❑ Alemtuzumab (Campath-1H)
- ❑ Systemic chemotherapy
  - ❑ purine analogs, temozolomide, pegylated doxorubicin, CHOP
- ❑ Stem cell transplantation (autologous, allogeneic)

■



# Mycosis fungoides / Sézary syndrome

## *Investigational Therapies*

- Interleukin-12
- Histone-deacetylase inhibitors
  - ✧ Depsipetide
  - ✧ Belinostat
- Anti-CD4 (HuMax-CD4)
- Anti-CD30 (SGN-30)
- Lenalidomide (Revlimid)
- Enzastaurin

# Care and Quality of Life

- Monitor for cutaneous infections
  - bacterial, viral (herpes, shingles)
- Monitor for other skin cancers
- Pruritus, pain
- Nutritional deficiencies
- Psychological needs





## Take Home Message

- Cutaneous lymphoma is not curable, but there is much to feel hopeful about
- There are many available treatment options
- Research is invaluable and ongoing
- Ultimate goal to improve survival and quality of life