Current Approach to the Management of Cutaneous T-Cell Lymphoma

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Medical Director, Photopheresis Service
Stanford Cancer Center
Disclosure statement

• **Advisory board**
  – Merck, Therakos, Eisai

• **Consultant**
  – Allos, Celgene, Gloucester, Kyowa, Seattle Genetics

• **Investigator**
  – Merck, Gloucester, BioCryst, Allos, Kyowa, Yaupon, Celgene, Eli Lilly
Cutaneous T-Cell Lymphoma

**Multidisciplinary approach to the management**

- Apply knowledge from pathogenesis
- Optimize diagnosis/Classification
  - Helpers for dx of MF/SS
  - Indolent vs. aggressive
- Utilize revised staging
- Manage with consensus, newer therapies
  - NCCN clinical practice guidelines
  - Romidepsin, [pralatrexate]
  - Clinical trials, investigative therapies
# Cutaneous T- and NK/T-cell Lymphomas

<table>
<thead>
<tr>
<th>New WHO-EORTC Classification</th>
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<td>Mycosis fungoides and variants/subtypes</td>
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<td>Adult T-cell leukemia/lymphoma</td>
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<td>PC peripheral T-cell lymphoma, unspecified</td>
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<td>• Aggressive epidermotropic CD8+ T-cell lymphoma</td>
</tr>
<tr>
<td>• CD4+ sm/med-sized pleomorphic T-cell lymphoma</td>
</tr>
<tr>
<td>• PTCL, other</td>
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</tbody>
</table>

*Blood 2005;105: 3768-85*  
*WHO monogram, 4th Ed, 2008*
Pathogenesis

Early Stages of Disease
- Defects in pro and anti-apoptotic signals
- Genomic and epigenetic changes

Accumulation of Molecular Abnormalities
- Defects in TCR and cytokine signalling
- Constitutive activation of STAT/NF-κB/AP1

Advanced Stages of Disease
- Large cell transformation
- Genomic instability

From S Whittaker, Semin Oncol 2006
Immune abnormalities

Malignancy of skin-homing/resident, CD45RO+ effector memory T-cells

**MF/SS cells**
- CD3+CD4+CD45RO+, CLA+, CXCR4+, CCR4+, CCR10+, Foxp3+
- CD4+CD7-, CD4+CD26-
- **↓ Th1 cytokines (IL2, IFN-γ)**
- **↑ Th2 cytokines (IL4, IL5, IL10)**
- **↓ IL12 production**
- **↓ Cytotoxic (CM, NK, LAK) activity**
- **↑ IL7, 15, 18 (skin/plasma)**

**TILs**
- CD4+CD8dim+, CD4+CD8-
- CD3+CD8+
- Cytotoxic activity
- **↑ Th1 cytokines**

Mycosis Fungoides & Sézary Syndrome

• Continued rising annual incidence in US (SEER)\textsuperscript{1}
  – 0.96 per 100,000
    • 3,000 new cases
  – 4% of NHLs

• Median age at diagnosis is 55 yrs
  – Two-thirds present with early stage disease

• Factors predictive of disease progression or survival\textsuperscript{2,3}
  – Advanced skin involvement
  – Extracutaneous disease
  – Older age, male gender, blacks
  – Folliculotropism
  – Large cell transformation
  – Increased LDH

\textsuperscript{1} Arch Dermatol 2007;143:184-189
\textsuperscript{2} Arch Dermatol 2003;139:857-866
\textsuperscript{3} JNCCN 2008;6:436-441
Cutaneous Manifestations, T-classification

- Patch, T1-2
- Plaque, T1-2
- Tumor, T3
- Erythroderma, T4
Sézary syndrome—generalized erythroderma, keratoderma, severe itching; freq. Staph infection
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)
- Follicular MF (+/- mucinosis)
  - Head and neck
- Granulomatous MF
  - Granulomatous slack skin
- Bullous MF
- PPE-like MF
- Interstitial MF
- Icthyiosiform MF
- Palmar plantar MF
- Hyperkeratotic/verrucous MF
- Misc. histo variants/mimics
  - Lichenoid, spongiotic, psoriasiform, syringotropism

Diagnosis of MF requires essential clinical-path correlation
Hypopigmented/vitiligenous
Mycosis fungoides
Pagetoid reticulosis
(Woringer Kolopp)
Folliculocentric presentation of mycosis fungoides
Granulomatous variants/subtypes of mycosis fungoides
Mycosis fungoides,

Pigmented purpuric eruption-like variant
Interstitial MF
Icthyiosiform MF
Diagnosis of MF, *essential* clin-path correlation

Suspect MF

Diamond symbol

Skin biopsy: select site, size, process

> 2 sites, off skin tx

Essential for Dx: **Dermatopathology review** of all slides

Only if indicated

Ancillary studies: immunophenotyping, molecular studies

Clinical-pathologic correlation for final interpretation
T-cell clonality analysis in biopsy specimens from two different skin sites shows high specificity in the diagnosis of patients with suggested mycosis fungoides

Stacy E. Thurber, MD, a Bing Zhang, MD, a Youn H. Kim, MD, b Iris Schrijver, MD, a James Zehnder, MD, a and Sabine Kohler, MD a,b
Stanford, California

Conclusion: These data suggest that dual TCR-PCR is a very promising technique with high specificity in distinguishing MF from inflammatory dermatoses. (J Am Acad Dermatol 2007;57:782-90.)

Demonstration of identical clones at > 2 skin sites (dual TCR-PCR) can help in differentiating MF from clinical mimics (inflammatory dermatoses)

• sensitivity = 82.6%
• specificity = 95.7%
Combined use of PCR-based TCR-gamma and TCR-beta clonality tests on paraffin embedded skin tissue in the differential diagnosis of MF and inflammatory dermatoses


Can help in false negative or positive TCR-γ cases:

- highly suspicious, TCR-γ neg => TCR-β pos => c/w MF
- unlikely cases, TCR-γ pos => TCR-β neg => no support for MF
Challenge of the red person
Differential diagnosis of erythrodermas

- Psoriasis
- PRP
- Eczematous dermatitis
- Drug reaction
- Sarcoidosis
- GVHD
- Autoimmune
  - DM
  - Overlap

- CTCL (MF/SS)
- Other hematolymphoid processes
- Paraneoplastic
- GVHD
- Infectious
  - Staph toxin
- Scabies
- Misc. inflammatory

Skin biopsies often non-diagnostic from erythrodermic skin of CTCL

MUST ASSESS BLOOD (and/or LN if suspicious)
Folliculotropic, papular eruption
Diagnosis?
PRP, drug, CTCL?
Folliculotropic, papular eruption

Diagnosis?
MF/SS, the great masquerader

Clinical & histo mimic of benign skin disorders

• MF/SS unmasked with immunosuppressive therapies
  – Consider MF/SS when presumed benign dermatoses are refractory to conventional therapies or worsen with immunosuppressive agents (anti-TNF-\(\alpha\), cyclosporine)

• Importance of evaluating non-skin compartments for dx
  – Peripheral blood for Sézary cells
  – Imaging studies/LN bx whenever appropriate

• Comparative clonality studies of > 1 skin sample, blood, and/or LN as indicated
  – Consider TCR-beta test if TCR-gamma neg
Exacerbation of Undiagnosed Mycosis Fungoides During Treatment With Etanercept

Philippe Lafaille, MD
Danielle Bouffard, MD
Nathalie Provost, MD

Arch Dermatol
2009;145:94-95
Progression of Undiagnosed Cutaneous T-Cell Lymphoma During E talizumab Therapy

Claudia Hernandez, MD
Sophie M. Worobec, MD
Sujata S. Gaitonde, MD
Monika L. Kiripolsky, MD
Kristen Aquino, BS

Figure. Tumors developed on the face, ears, chest, and back despite bexarotene therapy. A, Generalized erythema is visible on the chest, face, abdomen, and arms, sparing the body folds; numerous firm erythematous nodules are present on the face. B, Multiple erythematous nodules are scattered on the patient’s back.
Question #1:
You suspect that your erythrodermic pt may have Sézary syndrome. What is the single most informative test to help confirm the diagnosis?

1. Skin biopsies
2. Whole body PET-CT
3. Contrast-enhanced CT of chest, abdomen, pelvis
4. Blood for Sézary cell assessment
5. Lymph node biopsy
Question #1:
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4. Blood for Sézary cell assessment
5. Lymph node biopsy
Treatment Alternatives in MF/SS (CTCL), 2010 update

• Topical (skin-directed) therapy
  – Topical steroid, nitrogen mustard, topical retinoid (bexarotene*), BCNU, phototherapy (UVB/PUVA), EBT, topical imiquimod

• Systemic therapy
  – Biologicals/targeted therapies:
    • photopheresis*, interferon, retinoid (bexarotene*), fusion protein/toxin (denileukin diftitox*)
  – HDAC inhibitors: vorinostat*, romidepsin* (11/09)
  – Cytotoxic chemotherapy:
    • MTX, lipo doxorub, gemcitabine, etoposide, pentostatin, combination regimens, pralatrexate (approved for PTCL, 9/09)

• Combined modality therapy
  – Topical + topical, topical + systemic, systemic + systemic

• Investigative therapy
  – Monoclonal antibodies (e.g., CD4, CD30, CCR4)
  – HDAC inhibitors (e.g., panobinostat, belinostat)
  – PNP inhibitors (e.g., forodesine) -- Kinase inhibitors
  – TLRA (e.g., CpG) -- Vaccine strategies
  – Improved chemo agents -- Allo-HSC transplantation

* FDA approved for CTCL
US Treatment Guidelines in MF/SS

www.nccn.org

- First available standard of care treatment guideline in cutaneous lymphoma in US
- Help with insurance auth and reimbursement; given lots of off-label use
- Lack of evidence-based help in CTCL → important role of consensus guidelines
MF and SS, Disease-Specific Survival by Clinical Stage,

Stanford data (n=525), Arch Dermatol 139:857-866, 2003
# Suggested Treatment Regimens

## Skin-Directed Therapies

For limited/localized skin involvement (Skin-Limited/Local):
- Topical corticosteroids
- Topical chemotherapy (nitrogen mustard, carmustine)
- Local radiation (particularly unilesional presentation, 24-36 Gy)
- Topical retinoids (bexarotene, tazarotene)
- Phototherapy (UVB, nbUVB for patch/thin plaques; PUVA for thicker plaques)
- Topical imiquimod

For generalized skin involvement (Skin-Generalized):
- Topical corticosteroids
- Topical chemotherapy (mechlorethamine, carmustine)
- Phototherapy (UVB, nbUVB, for patch/thin plaques; PUVA for thicker plaques)
- Total skin electron beam therapy (30-36 Gy) (reserved for those with severe skin symptoms or generalized thick plaque or tumor disease, or poor response to other therapies)

## 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)
- Extracorporeal photopheresis
- Denileukin diftitox
- Methotrexate (≤ 100 mg q week)

### Category B (SYST-CAT B)
- First-line therapies
  - Liposomal doxorubicin
  - Gemcitabine
- Second-line therapies
  - Chlorambucil
  - Pentostatin
  - Etoposide
  - Cyclophosphamide
  - Temozolomide
  - Methotrexate (>100 mg q week)
  - Bortezomib

## Combination Therapies

- Skin-directed + Systemic
- Phototherapy + retinoid
- Phototherapy + IFN
- Photopheresis + photopheresis
- Total skin electron beam + photopheresis

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

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*See references for regimens [MFSS-A 2 of 4](#), [MFSS-A 3 of 4](#), and [MFSS-A 4 of 4](#).

*Long-term use of topical steroid may be associated with skin atrophy and/or striae formation. This risk worsens with increased potency of the steroid. High-potency steroid used on large skin surfaces may lead to systemic absorption.

*Cumulative dose of UV is associated with increased risk of UV-associated skin neoplasms; thus, phototherapy may not be appropriate in patients with history of extensive squamousproliferative skin neoplasms or basal cell carcinomas or who have had melanoma.

*It is common practice to follow TSEBT with systemic therapies such as interferon or bexarotene to maintain response.

*Safety of combining TSEBT with systemic retinoids or HDAC-inhibitors, such as vorinostat or romidepsin or combining phototherapy with vorinostat or romidepsin is unknown.

*Photopheresis may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2).
For generalized skin involvement (Skin-Generalized)

- Topical corticosteroids
- Topical chemotherapy ( mechloretamine, carmustine)
- Phototherapy (UVB, nbUVB, for patch/thin plaques; PUVA for thicker plaques)
- Total skin electron beam therapy (reserved for those with severe skin, generalized thick plaque or tumor response to other therapies)

**SYSTEMIC THERAPIES**

Category A (SYS-T-CAT A)

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

For patients achieving a response should be considered for maintenance on the same treatment. Patients with a PR should be treated with the other systemic therapy for refractory disease. Patients with relapse or persistent disease after treatment failure, or refractory or intolerant to multiple previous therapies.

For patients with recalcitrant sites after generalized skin treatment, additional local treatment may be needed.
**STAGE**

- Limited extent tumor disease ± patch/plaque disease
- Generalized tumor disease or limited extent tumor disease with B1 or histologic evidence of folliculotropic or large cell transformed MF

**Primary Treatment**

- Local RT for limited tumor lesions + skin-directed therapies as in stages I-IIA
- **Systemic Therapies** (SYST-CAT A) (MFSS-A) ± RT
- TSEBT
- See Suggested Treatment Regimens
  - **Systemic Therapies**
  - Systemic Therapies (SYST-CAT A) (MFSS-A)
  - Systemic Therapies (SYST-CAT B) (MFSS-A)
  - Combination Therapies

**Systemic Therapies**

- **Category A** (SYST-CAT A)
  - Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13-cis-retinoic acid], acitretin)
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  - HDAC-inhibitors (vorinostat, romidepsin)
  - Extracorporeal photopheresis f
  - Denileukin difitox
  - Methotrexate (≤ 100 mg q week)

**Combination Therapies**

- Skin-directed + Systemic
- Phototherapy + retinoid e
- Phototherapy + IFN
- Photopheresis f + retinoid
- Photopheresis f + IFN
- Photopheresis f + retinoid + IFN

**Category B** (SYST-CAT B)

- First-line therapies
  - Liposomal doxorubicin
  - Gemcitabine
- Second-line therapies
  - Chlorambucil
  - Pentostatin
  - Etoposide
  - Cyclophosphamide
  - Temozolomide
  - Methotrexate (≥100 mg q week)
  - Bortezomib

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*It is preferred that treatment occur early in the diagnosis of this disease.
*Patients achieving a response should be considered for primary systemic regimens to optimize response duration. Patients may be offered further systemic treatment for disease recurrence. Additional systemic therapy may be considered in the primary treatment setting for refractory disease. Additional systemic therapy may also be considered as a second-line therapy, particularly in patients who are refractory or intolerant to multiple agents.
*Skin-directed therapies are for patients with limited extent disease only.
*Combination systemic regimens are for patients with advanced disease and are generally used as second-line therapy or for patients with recurrent disease.
*Photopheresis is an extracorporeal photopheresis process that is used to treat certain types of skin conditions.
*Photopheresis f is a combination therapy involving photopheresis and retinoid therapy.
*Photopheresis f + IFN is a combination therapy involving photopheresis, retinoid, and interferon therapy.
*Photopheresis f + retinoid + IFN is a combination therapy involving photopheresis, retinoid, and interferon therapy.*
- Preserve immune response whenever possible
- Low threshold to cover skin pathogens
- Supportive/combination care (topicals, anti-itch)
Supportive Care

Improve QoL factors

• Emollients
• Topical steroids +/- wraps
• Antibiotic therapy as needed
  – Bacterial, fungal, viral (HSV, VZV)
• Oral anti-itch measures
  – Anti-histamines
  – Tricyclics
  – Gabapentin
  – Mirtazapine
  – Aprepitant
Current Clinical Management of CTCL

**IA Limited Disease**
- Skin-directed*

**IB/IIA Generalized**
- ECP*** (single or combination)
- Single-agent chemotherapy**
- Phototherapy ± bexarotene or IFN
- TSEBT

**IIB Tumors**

**IIIB Erythroderma**
- Alemtuzumab

**IV Extracut. Disease**
- Combination chemo
- Bexarotene, denileukin diftitox, IFN, vorinostat, romidepsin (single or combination)
- Allo-HSCT

* Clinical Trial

* Topical steroid, retinoid gel, nitrogen mustard, phototherapy, radiation therapy.
** Methotrexate, liposomal doxorubicin, gemcitabine, pentostatin, chlorambucil, etoposide, temozolomide.  ***ECP = photopheresis
## Cutaneous T- and NK/T-cell Lymphomas

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**Blood**

2005;105: 3768-85

WHO monogram, 4th Ed, 2008
Spectrum of pc lymphoproliferative disorders characterized by cell surface CD30 expression

- CD30 is transmembrane glycoprotein receptor, member of TNF-R superfamily
- Expressed in proliferative or malignant processes (e.g. HD, ALCL, MF, subset of BCLs) and activated leukocytes (T, B, macrophages)
- CD30 expression upregulated by select virus (EBV, HHV, HTLV1/2)
- Implicated in cell death and proliferation

LyP === borderline === pc CD30+ ALCL

Proapoptotic anti-apoptotic
sensitive to TGF-β escapes TGF-β
Differential diagnosis of CD30+ lymphoid infiltrates in the skin

Reactive
- Arthropod reaction
- Lymphomatoid drug reaction
- Misc. inflammatory dermatoses
- Infection

Neoplastic
- pc CD30+ LPD
  - Lymphomatoid papulosis
  - pc CD30+ ALCL
- MF
  - Large cell transformation
  - Woringer-Kolopp
- PTCL, nos
- Secondary skin involvement of sALCL, HD or other LPD

Clinico-pathologic correlation is essential
### PC CD30+ Lymphoproliferative Disorders

#### Survival Data

<table>
<thead>
<tr>
<th>Type</th>
<th>No. of Pts.</th>
<th>Overall Survival 5-yr, 10-yr</th>
<th>Disease-specific Survival 5-yr, 10-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>LyP</td>
<td>118</td>
<td>98%, 95%</td>
<td>100%, 100%</td>
</tr>
<tr>
<td>PC ALCL</td>
<td>79</td>
<td>83%, 78%</td>
<td>96%, 96%</td>
</tr>
<tr>
<td>PC ALCL + reg LN</td>
<td>11</td>
<td>76%, 76%</td>
<td>91%, 91%</td>
</tr>
</tbody>
</table>

Great prognosis

- Subset of pcALCL associated with worse outcome

Dutch Cutaneous Lymphoma Group, Blood 2000;95:3653-61
PC CD30+ ALCL

Nodules or tumors, singly or in groups, less tendency for self-regression than LyP
PC CD30+ ALCL

Nodules or tumors, limited regional presentation
Subset of pcALCL with worse outcome?

- Extensive limb disease (ELD) presentation
  - Single extremity (lower > upper) extensive involvement with multiple tumor nodules
  - Histo, IHC similar to “typical” presentation (vs. DLBCL-leg type)
  - Refractory to local radiation therapy and systemic therapies
  - Associated with worse survival outcome
Prognostic Factors in Primary Cutaneous Anaplastic Large Cell Lymphoma

Characterization of Clinical Subset With Worse Outcome

Denise K. Woo, MD, MS; Christopher R. Jones, MD; Monique N. Vanoli-Storz, MD; Sabine Kohler, MD; Sunil Reddy, MD; Ranjana Advani, MD; Richard T. Hoppe, MD; Youn H. Kim, MD


Table 2. Adjusted Hazard Ratios (HRs) From Multivariate Cox Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>All-Cause Mortality</th>
<th>Disease-Specific Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR^a (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age at diagnosis (per 10 y)</td>
<td>1.83 (1.02-3.26)</td>
<td>.04</td>
</tr>
<tr>
<td>ELD</td>
<td>3.48 (0.72-16.74)</td>
<td>.12</td>
</tr>
<tr>
<td>Progression to extracutaneous disease^b</td>
<td>6.42 (1.39-29.68)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ELD, extensive limb disease.

^a Adjusted for other variables listed.

^b Treated as time-dependent variable.
PC CD30+ ALCL

Extensive limb disease (ELD) with worse outcome,

Woo et al, Arch Dermatol 2009
PC CD30+ ALCL

Extensive limb disease (ELD)

Woo et al, Arch Dermatol 2009
PC CD30+ ALCL

Extensive limb disease (ELD), a subset with worse outcome and differential gene expression profile,

Woo et al, Arch Dermatol 2009
Management Algorithm in PC CD30+ ALCL

“Typical” pcALCL

- Solitary / Regional (T1-2a)
- Generalized (T3a)

- Radiotherapy (RT)
- Excision
- Topical tx: NM, imiq, retinoid
- Observation

RT for symptomatic lesions

- Topical tx: NM, imiq, retinoid
- Phototherapy +/- biologics
- Biologics: bexarotene, interferons, denileukin diftitox
- HDAC inhibitors: vorinostat, romidepsin
- Chemotherapy: methotrexate, pralatrexate

Clinical trials

ELD, unfavorable subsets (T2b,c; T3b)

- Systemic biologics
  - bexarotene
  - denileukin diftitox ± bex
- HDAC inhibitors
  - vorinostat, romidepsin
  (RT adjuvant/combo role)
- Chemotherapy + RT

Clinical trials

- Bone marrow / HSC transplantation: auto vs. allo

Clinical trials
Promising therapies in clinical development

• Modified radiation therapy strategies
• More HDAC inhibitors and other agents targeting epigenetics
• Monoclonal antibodies (enhanced potency, immunoconjugates)
  – CD4, CD30, CCR4
• New immunotherapies
  – TLR-agonists
  – Gene delivery-based immunotherapy
• Signal transduction and kinase inhibitors
• Novel apoptosis inhibitors
• Newer nucleoside analogs
  – Forodesine
• Improved anti-folate agents
  – Pralatrexate (approved 9/09 in PTCL)
• Novel vaccine strategies
• HSC transplant strategies
# HDAC Inhibitors in clinical investigation in CTCL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Chemical structure</th>
<th>Route</th>
<th>Disease</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vorinostat</td>
<td>Hydroxamate</td>
<td>Oral</td>
<td>CTCL</td>
<td>FDA approved in CTCL, 10/06</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>Cyclic peptide</td>
<td>IV</td>
<td>CTCL/PTCL</td>
<td>FDA approved in CTCL, 11/09</td>
</tr>
<tr>
<td>LBH589</td>
<td>Hydroxamate</td>
<td>Oral</td>
<td>CTCL</td>
<td>Phase II</td>
</tr>
<tr>
<td>Belinostat</td>
<td>Hydroxamate</td>
<td>IV, oral</td>
<td>CTCL/PTCL</td>
<td>Phase II</td>
</tr>
</tbody>
</table>
HDAC Inhibitors: Multifunctional Anticancer Agents

Acetylation of Histone and Non-Histone Proteins

Altered Gene Expression And Protein Function

- Cell Cycle Arrest
  - p21, p27, Cyclin A & D
- Apoptosis
  - Hsp90, Bcl-2, Bcl-XL, Bax, Fas, Caspase-3 & 9
- Angiogenesis
  - VEGF, VEGFR, MMPs, Activin A, Ang2, eNOS

- Cellular Differentiation
  - MDR-1, Na-I Symporter, CD25, CAR (Adenovirus Receptor), RARα & β
- Cellular Transformation
  - C-myc, Ras, Raf, Bcl-6, p53
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
Romidepsin

- Novel bicyclic peptide
- Potent pan-histone deacetylase (HDAC) inhibitor
  
  Greatest activity against:
  - Class I (HDACs 1, 2, 8)
  - Class II (HDACs 4, 5, 6)
  - Class IV (HDAC 11)

- In vitro efficacy
  - HUT-78 (TCL cell line)
    \[ IC_{50} = 1.4 \times 10^{-9} \text{M} \]
### GPI and NCI Studies

#### Similar Design & Conduct

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GPI/Pivotal study</th>
<th>NCI study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Open-label, multicenter, international</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>N=96</strong></td>
<td><strong>N=71</strong></td>
</tr>
<tr>
<td>Treatment regimen</td>
<td>14 mg/m² 4-hr infusion on Day 1, 8, 15 of a 28 day cycle</td>
<td></td>
</tr>
</tbody>
</table>

## Patient Characteristics

### As-Treated

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GPI study</th>
<th>NCI study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>57 (21 to 89) yrs</td>
<td>57 (28 to 84) yrs</td>
</tr>
<tr>
<td>Sex, Men, n (%)</td>
<td>59 (61)</td>
<td>48 (68)</td>
</tr>
<tr>
<td>ECOG, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>49 (51)</td>
<td>16 (23)</td>
</tr>
<tr>
<td>1</td>
<td>47 (49)</td>
<td>41 (58)</td>
</tr>
<tr>
<td>2</td>
<td>NA</td>
<td>10 (14)</td>
</tr>
<tr>
<td>Disease stage, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>NA</td>
<td>1 (1)</td>
</tr>
<tr>
<td>IB</td>
<td>15 (16)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>IIA</td>
<td>13 (14)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>IIB</td>
<td>21 (22)</td>
<td>14 (20)</td>
</tr>
<tr>
<td>III</td>
<td>23 (24)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>IVA</td>
<td>24 (25)</td>
<td>27 (38)</td>
</tr>
<tr>
<td>IVB</td>
<td>NA</td>
<td>12 (17)</td>
</tr>
<tr>
<td>Blood involvement, n (%)</td>
<td>37 (39)</td>
<td>21 (30)</td>
</tr>
</tbody>
</table>

- 71% Stage ≥ IIB
- 87% Stage ≥ IIB
## Responses by Clinical Stage

### As-Treated

<table>
<thead>
<tr>
<th>Stage</th>
<th>GPI study</th>
<th>NCI study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>ORR</td>
</tr>
<tr>
<td>All stages</td>
<td>96</td>
<td>33 (34%)</td>
</tr>
<tr>
<td>IA - IIA</td>
<td>28</td>
<td>7 (25%)</td>
</tr>
<tr>
<td>IIB</td>
<td>21</td>
<td>9 (43%)</td>
</tr>
<tr>
<td>III</td>
<td>23</td>
<td>9 (39%)</td>
</tr>
<tr>
<td>IV</td>
<td>24</td>
<td>8 (33%)</td>
</tr>
<tr>
<td>≥ IIB</td>
<td>68</td>
<td>26 (38%)</td>
</tr>
</tbody>
</table>
Stage IVA, PR, Prior: Methotrexate, Retinoids, PUVA, Interferon Alpha

Baseline

Cycle 2

Cycle 3
Stage IVB, PR, Prior: CVP

Baseline

Cycle 5
Stage III, PR, Prior: Photopheresis, Bexarotene, IFN Gamma, Denileukin Diftitox, Vaccine Therapy, Chlorambucil, Cyclophosphamide, Radiation

Baseline

45% Sézary cells

Cycle 6

4% Sézary cells
Stage: IVB
Prior Therapies: azathioprine, methotrexate
Best Response: PR
Liver Nodules: 80% Decrease
Response to Romidepsin

Stage IIB, PR, Prior bexarotene, denileukin diftitox, ECP

Baseline Cycle 3
Response to Romidepsin
Patient 37-018 (Stage III, CCR, failed 3 chemotherapy regimens)

Screening

Cycle 6, Day 1
Response to Romidepsin
Patient 37-018

Screening

Cycle 6, Day 1
Romidepsin Activity in Blood

GPI Study, Patients with High Blood Tumor Burden*

GPI study
- All (> 5%, n = 37), ORR 32%
- High (> 1000 /µl and/or > 20%, n = 13), ORR 31%

* > 1,000 Sézary cells/µl
**Consistent Results GPI and NCI Studies**

*Duration of Response, As-Treated*

- **Median duration of response**
  - GPI study: 14.9 mo
  - NCI study: 11.1 mo

Cumulative proportion of patients who have not progressed:
- 0.1
- 0.2
- 0.3
- 0.4
- 0.5
- 0.6
- 0.7
- 0.8
- 0.9
- 1.0

Events:
- > 19 mo
- > 65 mo

Censored:
- O O O Censored
Change in Pruritus by VAS
GPI Study, As-Treated

Clinically meaningful change: ≥ 30 mm decrease
- 43% patients
- 5.6 mo median duration

Maximum change in VAS (mm)

Responders
Non-responders
<table>
<thead>
<tr>
<th>Event</th>
<th>All Grades n (%)</th>
<th>Grade 3 n (%)</th>
<th>Grade 4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>54 (56%)</td>
<td>2 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenic conditions</td>
<td>42 (44%)</td>
<td>6 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25 (26%)</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>19 (20%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13 (14%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (14%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aguesia</td>
<td>12 (13%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (11%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dysguesia</td>
<td>11 (11%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>10 (10%)</td>
<td>2 (2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3. Most common drug-related adverse events (N = 96)

No clinically significant ECG changes or QTc prolongation
Romidepsin Summary

• Clinically meaningful ORR in 2 studies
  – ORR: GPI - 34%, NCI - 35%
  – Responses across all stages, including advanced stage disease
  – Included 10 CCRs

• Activity in all disease compartments

• Durable responses
  – Median GPI - 14.9 mo, NCI - 11.1 mo

• Clinically relevant improvement in pruritus

• Toxicities are acceptable, familiar, and manageable

=> Romidepsin, FDA-approved 11/2009 for CTCL in patients who have received at least 1 systemic therapy
# Current Clinical Management of CTCL

*Derived from NCCN Practice Guidelines 2010*

<table>
<thead>
<tr>
<th>IA Limited Disease</th>
<th>IB/IIA Generalized</th>
<th>IIB Tumors</th>
<th>III Erythroderma</th>
<th>IV Extracut. Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin-directed*</td>
<td></td>
<td></td>
<td>ECP (single or combination)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Single-agent chemotherapy**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phototherapy ± bexarotene or IFN</td>
<td></td>
<td></td>
<td>Alemtuzumab</td>
</tr>
<tr>
<td></td>
<td>TSEBT</td>
<td></td>
<td></td>
<td>Combination chemo</td>
</tr>
<tr>
<td></td>
<td>Bexarotene, denileukin diftitox, IFN vorinostat, romidepsin (single or combination)</td>
<td></td>
<td></td>
<td>Allo-HSCT</td>
</tr>
</tbody>
</table>

* Topical steroid, retinoid gel, nitrogen mustard, phototherapy, radiation therapy.
** Methotrexate, liposomal doxorubicin, gemcitabine, pentostatin, chlorambucil, etoposide, temozolomide.
Question #2:
All of the following statements about HDAC inhibitors in the management of MF/SS are true except

1. Vorinostat and romidepsin are the 2 HDAC inhibitors currently approved in CTCL
2. Overall clinical response rates in MF/SS with these agents range from 30-35%
3. Every patient should get a baseline ECG and follow-up ECGs monthly for 6 months
4. Potassium and magnesium should be within normal range before administration of drug
5. Subset of patients can experience clinically meaningful reduction in pruritus
Question #2: All of the following statements about HDAC inhibitors in the management of MF/SS are true except

1. Vorinostat and romidepsin are the 2 HDAC inhibitors currently approved in CTCL
2. Overall clinical response rates in MF/SS with these agents range from 30-35%
3. Every patient should get a baseline ECG and follow-up ECGs monthly for 6 months
4. Potassium and magnesium should be within normal range before administration of drug
5. Subset of patients can experience clinically meaningful reduction in pruritus
Newer targeted therapies in CTCL
Zanolimumab

*Anti-CD4 MoAb*

- Generated from Ig-Transgenic mice
- Human IgG1, κ
Mechanism of Action

Inhibition of T- cell activation (proliferation and cytokine production)

Inhibition of TCR signal transduction

Reduced TCRζ ITAM and ZAP70 phosphorylation → inhibition of Erk1/2, p38 and AKT pathways.

Increased p56lck tyrosine kinase → phosphorylation of Dok-1 and SHIP-1.

Clinical efficacy of zanolimumab (HuMax-CD4): two phase 2 studies in refractory cutaneous T-cell lymphoma

Youn H. Kim,1 Madeleine Duvic,2 Erik Obitz,3 Robert Gniadecki,4 Lars Iversen,3 Anders Österborg,5 Sean Whittaker,6 Timothy M. Illidge,7 Thomas Schwarz,8 Roland Kaufmann,9 Kevin Cooper,10 Kim M. Knudsen,11 Steen Lisby,11 Ole Baadsgaard,11 and Susan J. Knox12

1Multidisciplinary Cutaneous Lymphoma Program, Stanford Comprehensive Cancer Center, CA; 2M.D. Anderson Cancer Center, Houston, TX; 3Aarhus University Hospital, Denmark; 4Bispebjerg Hospital, Copenhagen, Denmark; 5Karolinska Hospital, Stockholm, Sweden; 6St Thomas’ Hospital, London, United Kingdom; 7Manchester University, Christie Hospital, United Kingdom; 8Department of Dermatology, University Kiel, Germany; 9Universitätshautklinik, Frankfurt aM, Germany; 10Case Western Reserve University Hospital of Cleveland, OH; 11Genmab, Copenhagen, Denmark; 12Department of Radiation Oncology, Stanford Comprehensive Cancer Center, CA


- Promising clinical efficacy
- Effective CD4+ T-cell depletion
- Acceptable safety profile

=> Phase III multicenter pivotal trial
Zanolimumab (HuMax-CD4), fully human anti-CD4 antibody

Baseline

Week 4

Kim et al, Blood
2007;109:4655
Targeted therapy in CD30+ LPDs

- **CD30**, an attractive target, as CD30 expression is limited in normal cells, but increased in proliferative or malignant lymphocytes
- **Anti-CD30 monoclonal antibody**
  - SGN-30
    - Chimeric form of a novel murine mAb w/ distinct specificity for CD30
    - Anti-tumor activity by promoting growth arrest and apoptosis
A Phase II Study of SGN-30 in Cutaneous Anaplastic Large Cell Lymphoma and Related Lymphoproliferative Disorders

Madeleine Duvic,¹ Sunil A. Reddy,² Lauren Pinter-Brown,⁴ Neil J. Korman,⁵ John Zic,⁶ Dana A. Kennedy,⁷ Jennie Lorenz,⁷ Eric L. Sievers,⁷ and Youn H. Kim³


Table 2. Best clinical response

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>pc-ALCL (n = 11), n (%)</th>
<th>LyP (n = 3), n (%)</th>
<th>T-MF (n = 3), n (%)</th>
<th>Multiple (n = 6), n (%)</th>
<th>Total (N = 23), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>6 (55%)</td>
<td>1 (33%)</td>
<td>0</td>
<td>3 (50%)</td>
<td>10 (43%)</td>
</tr>
<tr>
<td>PR</td>
<td>3 (27%)</td>
<td>1 (33%)</td>
<td>1 (33%)</td>
<td>1 (17%)</td>
<td>6 (26%)</td>
</tr>
<tr>
<td>CR or PR</td>
<td>9 (82%)</td>
<td>2 (67%)</td>
<td>1 (33%)</td>
<td>4 (67%)</td>
<td>16 (70%)</td>
</tr>
<tr>
<td>SD</td>
<td>2 (18%)</td>
<td>1 (33%)</td>
<td>1 (33%)</td>
<td>0</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>0</td>
<td>1 (33%)</td>
<td>2 (33%)</td>
<td>3 (13%)</td>
</tr>
</tbody>
</table>

• Very well tolerated, no drug-related SAE or AEs leading to discontinuation
Day 1, Dose #1 SGN-30

pc ALCL

Day 28, Pre-Dose #2
Response of multiple pc-ALCL tumors on the leg of an 80-year-old male with known aortic stenosis and coronary artery disease who had previously been treated with 2 courses of CHOP and local radiation before receiving SGN-30 for 18 months. The patient expired from an unrelated myocardial infarction.
Enhancing potency with immune conjugates
*Brentuximab vedotin, SGN-35 (Seattle Genetics)*

**Anti-CD30 antibody conjugated to auristatin E (MMAE)**

Selectively induces apoptosis in CD30+ LPDs:
- Bind to CD30
- Internalize
- Release MMAE
- Anti-tubulin activity
Immune abnormalities

Malignancy of skin-homing/resident, CD45RO+ effector memory T-cells

MF/SS cells
- CD3+CD4+CD45RO+, CLA+, CXCR4+, CCR4+, CCR10+, Foxp3+, CD25+
- CD4+CD7-, CD4+CD26-
- ↓ Th1 cytokines (IL2, IFN-γ)
- ↑ Th2 cytokines (IL4, IL5, IL10)
- ↓ IL12 production
- ↓ Cytotoxic (CM, NK, LAK) activity
- ↑ IL7, 15, 18 (skin/plasma)

TILs
- CD4+CD8dim+, CD4+CD8-
- CD3+CD8+
- Cytotoxic activity
- ↑ Th1 cytokines

CCR4 as a target on T-cells

- CCR4: Receptor for CC chemokines, MDC and TARC
- **CCR4 expression present in all stages of CTCL**
  - Intensity and overall % of expressing cells increase with stage
- CCR4 expressed on sub-population of $T_{reg}$ and Th2 cells
- CCR4 expressed to varying degrees in most other types of PTCL

*Phase 1/2 study in CTCL ongoing*
Reduced-fucose technology enhances ADCC activity

- The antibody backbone lacks fucose due to knock out of the FUT8 gene
- This leads to an increase in ADCC activity

*Kyowa Hakko Pharma, Inc.*
POTELLI GENT® Technology enhances ADCC

- Enhanced ADCC has been confirmed using multiple antibodies (> 20)
Drug profile for KW-0761

• A first-in-class reduced-fucose humanized CCR4 antibody
• Enhanced Antibody Dependent Cellular Cytotoxicity (ADCC) activity
  – No neutralizing activity of ligand, no CDC activity, no direct apoptosis induction
• Initial indication in US trials: CTCL and PTCL
KW-0761, a Monoclonal Antibody Directed Against CCR4 in CTCL Patients: Preliminary Results of a Phase 1/2 Study

M Duvic, F Abdulla, R Talpur, S Reddy, S Daulat, G Spitalny, Y Kim
MD Anderson, Stanford,
Kyowa Hakko Pharma, Inc.

• KW-0761 is well tolerated in 9 pts in phase 1 study
• 5 of 9 ORR (>50%) in heavily pre-treated pts including 1 CR in SS

Phase 2 portion in progress

Presented at TCLF Maui, 2010
Pralatrexate Is Active in Cutaneous T-Cell Lymphoma (CTCL): Results of a Multicenter, Dose-Finding Trial

Steven M. Horwitz, Madeleine Duvic, Youn Kim, Jasmine M. Zain, Mary Jo Lechowicz, Nancy Bartlett, Patricia Myskowski, Steven Fruchtman, and Owen A. O'Connor
Pralatrexate Mechanism of Action

- Improved anti-folate agent => ↑ cellular uptake and retention
- High affinity for RFC-1; efficient substrate for polyglutamylation by FPGS
- Antifolate activity via the inhibition of DHFR.
Efficacy Results

- At pralatrexate dose intensity $\geq 15$ mg/m$^2$ q3/4w ORR was 61% (11/18)
- In this dose de-escalation trial, $\geq 15$ mg/m$^2$ q 3/4 appeared as the dose threshold for substantial activity in CTCL

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Pralatrexate Dose mg/m$^2$ Schedule</th>
<th>Response Rate</th>
<th>Response Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30- 3/4 weeks</td>
<td>100% (2/2)</td>
<td>2 PR</td>
</tr>
<tr>
<td>2</td>
<td>20- 3/4 weeks</td>
<td>67% (2/3)</td>
<td>2 PR</td>
</tr>
<tr>
<td>3</td>
<td>20- 2/3 weeks</td>
<td>57% (4/7)</td>
<td>1 CR/3 PR</td>
</tr>
<tr>
<td>4</td>
<td>15- 3/4 weeks</td>
<td>50% (3/6)</td>
<td>3 PR</td>
</tr>
<tr>
<td>5</td>
<td>15- 2/3 weeks</td>
<td>0 (0/3)</td>
<td>---</td>
</tr>
<tr>
<td>6</td>
<td>10- 3/4 weeks</td>
<td>10% (1/10)</td>
<td>1 CR</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>39% (12/31)</td>
<td>2 CR/10 PR</td>
</tr>
<tr>
<td>Doses $\geq 15$ mg/m$^2$, 3/4 weeks</td>
<td>61% (11/18)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Response by Subtype and Stage

<table>
<thead>
<tr>
<th>CTCL Subtype</th>
<th>Stage</th>
<th>N</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis fungoides/Sèzary syndrome</td>
<td>IB</td>
<td>5</td>
<td>2 PR</td>
</tr>
<tr>
<td></td>
<td>IIA</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>IIB</td>
<td>13</td>
<td>1 CR 5 PR</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>2</td>
<td>1 PR</td>
</tr>
<tr>
<td></td>
<td>IVA</td>
<td>8</td>
<td>1 PR</td>
</tr>
<tr>
<td></td>
<td>IVB</td>
<td>1</td>
<td>1 PR</td>
</tr>
<tr>
<td>Primary cutaneous anaplastic large cell</td>
<td>IIB</td>
<td>1</td>
<td>1 CR</td>
</tr>
</tbody>
</table>

| Doses $\geq 15 \text{ mg/m}^2$, 3/4 weeks (IV) | 61% (11/18) |
## Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>All Cohorts N=31</th>
<th>Optimal Dose 15 mg/m² N=6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-3 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>18 (58%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (52%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (48%)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7 (23%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (19%)</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>5 (16%)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Combination trials under way to minimize toxicity and assess synergy.
Pralatrexate response in MF, stage IIB

Pretreatment

Partial Response post cycle 3

Pretreatment

Partial Response post cycle 3
Pralatrexate response, Pc ALCL
Hematopoietic Stem Cell or BM Transplantation

Considered for patients with advanced disease (stage IIB-IV)

**Autologous** → High-dose chemo and RT (cytoreduction) followed by stem cell rescue

No durable response in MF/SS

**Allogeneic** → Cytoreduction + *graft vs. tumor effect*

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

*Studies ongoing to maximize GVL effect while minimizing GVHD risk*
Strategies in CTCL Treatment with Newer Options

How do we best design/utilize combinations?
What agents? What dose-regimen?

Skin-directed Therapies
(Topicals, Phototherapy, XRT)

Systemic Biologic Therapies
(IFN, Retinoids, ECP)

Cytotoxic Chemotherapy
(Single-agent, Combination)

HDAC-i, TLRA, MoAb, PNPI, IMiD, PKC-i

MF/SS IA-IIA
Primary
Salvage
Adjuvant
Primary
MF/SS IIB-IV

Primary Salvage Adjuvant Primary

HSCT
Stanford Multidisciplinary Cutaneous Lymphoma Clinic/Program

Youn Kim, Director, Cutaneous Oncology/Dermatology
Richard Hoppe, Co-Director, Radiation Oncology
Ranjana Advani, Sunil Reddy, Medical Oncology
Uma Sundrum, Jinah Kim, Dermatopathology
Cameron Harrison, Cutaneous Lymphoma Fellow
Natalie Viakhireva, Katherine Sutherland, Physician Assistants
Carol Bruce, Michelle Callejas, Chris Suk, Claudia Rivetta,
Leon Xing, Clinical Research & Database Administrators
Laura Morris, RN Coordinator

Dermatology, Radiation Oncology Residents

URL: Cutaneouslymphoma.stanford.edu