CTCL Therapeutics in 2014: Are We Better Now?

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Director, Multidisciplinary Cutaneous Lymphoma Group
Stanford Cancer Center & School of Medicine
NCCN NHL Panel Member
Disclosure statement

Youn Kim, MD

• Steering Committee
  – Eisai, Kyowa, Millennium

• Consultant or Advisory Board
  – Actelion, Celgene, Galderma

• Investigator
  – Kyowa, Merck, Millennium, Seattle Genetics, Shape, Ceptaris, Eisai, Genentech
Why do we need better therapies?
Goals of therapies in MF/SS

**IDEAL**
- Cure
- Extend Life
- Alleviate symptoms
- Durable response
- High response rate
  *PLUS well-tolerated*

**REAL**
- Alleviate symptoms
- Variable response
- Variable response duration
- Variable toxicity
- Extend Life
- Cure

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Roadmap to improved therapeutics

Lymphomagenesis & progression

Tumor resistance, Interplay with microenvironment

Biomarkers, Integrative omics

Technologic advancement & knowledge

Tumor-selective therapies

Rational combination strategies

Personalized therapeutics

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Multidisciplinary Teamwork & Synergy

Cutaneous Lymphoma
Clinical Care Providers
Support Staff

- Dermatology (Cutaneous Oncology)
- Medicine (Medical/Hematology Oncology, BMT)
- Pathology (Dermpath/Hemepath)
- Radiation Oncology
- Other (Pediatrics, Surgery, Radiology/Nuclear Med)

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## Cutaneous T- and NK/T-cell Lymphomas

### New WHO-EORTC Classification

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis fungoides and variants/subtypes</td>
<td></td>
</tr>
<tr>
<td>Sézary syndrome</td>
<td></td>
</tr>
<tr>
<td>PC CD30+ lymphoproliferative disorders</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
<td></td>
</tr>
<tr>
<td>Cutaneous γ/δ T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma</td>
<td></td>
</tr>
<tr>
<td>PC peripheral T-cell lymphoma, unspecified</td>
<td></td>
</tr>
<tr>
<td>• Aggressive epidermotropic CD8+ T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>• CD4+ sm/med-sized pleomorphic T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>• PTCL, other</td>
<td></td>
</tr>
</tbody>
</table>

**Blood**

2005;105:3768-85

**WHO monogram, 4th Ed, 2008**
Mycosis Fungoides
Treatment of varying skin manifestations

Patch T1-2
Plaque T1-2
Erythroderma T4
Tumor T3

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Management of extracutaneous disease

Blood

Viscera

Lymph node

T6 (52.293, 22.150)
Sézary syndrome-generalized erythroderma, keratoderma, severe itching; freq staph aureus infection
Survival decreased with advancing T class and overall clinical stage
DSS utilizing revised staging system

Patch better than plaque disease, $P = .007/.002$

Agar et al. J Clin Oncol 2010;28:4730
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
General concepts in managing MF/SS-CTCL

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

NCCN guidelines

Y Kim, Stanford CC
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Hodgkin’s Lymphomas

Version 1.2014

NCCN.org

NHL => MFSS, CBCL, PCTLD
US Treatment Guidelines in MF/SS & CBCL

www.nccn.org => NHL => MFSS, CBCL, CD30+ LPD

- 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
**DIAGNOSIS**

**ESSENTIAL:**
- Biopsy of suspicious skin sites
- Dermatopathology review of slides

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- IHC panel of skin biopsy\(^a, b, c\)
  - CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD25, CD56, TIA1, granzyyme B, βF1, TCR-CyM1
- Molecular analysis of skin biopsy: TCR gene rearrangements (assessment of clonality)\(^a\) by 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 (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) 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):
  - 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 folliculotrophic 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

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**Stage-based treatment algorithm**

Blood 2007;110:1713

www.nccn.org => NHL => MFSS

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**Current Clinical Management of CTCL, 2014**

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

<table>
<thead>
<tr>
<th>IA</th>
<th>IB/IIB</th>
<th>IIB</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited patch/plaque</td>
<td>Generalized patch/plaque</td>
<td>Tumors</td>
<td>Erythroderma</td>
<td>Extracut. Disease</td>
</tr>
</tbody>
</table>

- **IA** Limited patch/plaque
  - Topical steroid, retinoid (bex), NM phototherapy, local RT, imiquimod

- **IB/IIB** Generalized patch/plaque
  - Phototherapy + bexarotene or IFN
  - TSEBT + ECP*, IFN
  - Bexarotene, denileukin diftitox, IFN
  - Vorinostat, romidepsin (single or combination)

- **III** Erythroderma
  - ECP* + IFN, bexarotene
  - Single-agent chemotherapy**

- **IV** Extracut. Disease
  - Alemtuzumab
  - Combination chemo
  - Allo-HSCT

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*ECP = photopheresis

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

Y Kim, Stanford CC
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)

<table>
<thead>
<tr>
<th>Skin Therapy</th>
<th>CR</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical steroids</td>
<td>45-65%</td>
<td>75-95%</td>
</tr>
<tr>
<td>Bexarotene gel</td>
<td>20-35%</td>
<td>50-75%</td>
</tr>
<tr>
<td>Topical NM</td>
<td>25-70%</td>
<td>50-90%</td>
</tr>
<tr>
<td>nbUVB</td>
<td>45-75%</td>
<td>75-100%</td>
</tr>
<tr>
<td>PUVA</td>
<td>50-80%</td>
<td>85-100%</td>
</tr>
<tr>
<td>TSEBT (≥30 Gy)</td>
<td>80-90%</td>
<td>100%</td>
</tr>
</tbody>
</table>

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

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

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Clinical response with low-dose (12 Gy) TSEBT
69 yo M, stage IIB, folliculotrophic MF
Management of advanced stages, those with adverse prognostic profile remain a challenge
# Efficacy of Systemic Agents in CTCL

<table>
<thead>
<tr>
<th>Agent (Class)</th>
<th>Indication</th>
<th>Year</th>
<th>Study</th>
<th>N</th>
<th>ORR</th>
<th>DOR</th>
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<tr>
<td>Romidepsin (HDAC inhibitor)</td>
<td>CTCL with prior systemic therapy</td>
<td>2009</td>
<td>Pivotal</td>
<td>96</td>
<td>34%</td>
<td>15 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Supportive</td>
<td>71</td>
<td>35%</td>
<td>11 mo</td>
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<tr>
<td>Denileukin diftitox (Fusion protein)</td>
<td>Tumors that express CD25</td>
<td>1999, 2008</td>
<td>Pivotal</td>
<td>71</td>
<td>30%</td>
<td>4 mo</td>
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<tr>
<td>Bexarotene (RXR activator)</td>
<td>Cutaneous manifestations</td>
<td>1999</td>
<td>Pivotal</td>
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<td>5+</td>
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<td>2006</td>
<td>Pivotal</td>
<td>74</td>
<td>30%</td>
<td>6+</td>
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<tr>
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<td></td>
<td>Supportive</td>
<td>33</td>
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<td>4</td>
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**Need better therapies, more options:**

- **Brentuximab vedotin (anti-CD30 ADC)**
- **Mogamulizumab (anti-CCR4 mab)**

*Both in phase 3 trials*
# Efficacy of Systemic Agents in CTCL

## Efficacy data for FDA approval

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Era of targeted therapies

**Huge impact in cutaneous oncology:** melanoma (vemurafenib), BCCs (vismodegib)

- Need understanding of driver targets
- Kill tumor/bad cells but spare good cells
- Target the environment to enhance anti-tumor effects
- Consider combination strategies as appropriate
  - Multiple targets/pathways
  - Complementary targets
  - How to optimize efficacy without additive toxicities
Targets for therapy in cutaneous T-cell lymphoma

- **Tumor cell surface molecules** (e.g., CD4, CD25, CD30, CD40, CD52, CD158k, CCR4)
- **Tumor proliferation, metabolism, survival, progression mechanisms:**
  - *Signal transduction/transcription activation pathways* (e.g., ubiquitin-proteasome, AKT/PI3K/mTOR, RAS/RAF/MEK, MAPK)
  - *Apoptotic pathways* (e.g., Bcl/Bax, TNFR, Fas, miRNAs)
  - *Epigenetics* (e.g., histone, non-histone proteins)
  - *Metabolic/survival pathways* (e.g., RFC-1, PARP)
- **Microenvironment, immune mechanisms** (e.g., vasculature, immune modulation)

Y Kim, Stanford CC
Targets for therapy in cutaneous T-cell lymphoma

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

CTCL

Microenvironment, immune mechanisms (e.g., vasculature, immune modulation)

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Microenvironment, immune mechanisms (e.g., vasculature, immune modulation)

Y Kim, Stanford CC
Types of targeted therapies in lymphoma, 2014

• **More and fancier monoclonal antibodies**
  
  *Cell surface molecules*
  
  – Naked mAbs
    
    • newer engineered, “high-tech” mAbs
  
  – MAb drug conjugates (ADCs)
  
  – Radiolabeled mAbs

• **Small molecule inhibitors/agonists**
  
  *Multitude of potential targets/pathways, need disease relevance*
Targets for therapy in cutaneous T-cell lymphoma

Tumor cell surface molecules (e.g., CD4, CD25, CD30, CD40, CD52, CD158k, CCR4)

CTCL

Microenvironment, immune mechanisms (e.g., vasculature, immune modulation)

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*Epigenetics* (e.g., histone, non-histone proteins)

*Metabolic/survival pathways* (e.g., RFC-1, PARP)

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Pralatrexate with improved tumor selectivity

- Improved **anti-folate** agent => ↑ cellular uptake/retention, tumor > normal
- High affinity for RFC-1; efficient substrate for polyglutamylation by FPGS
- Antifolate activity via the inhibition of DHFR.
Pralatrexate FDA-approved in systemic PTCL, 2009

Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma

Steven M. Horwitz, Youn H. Kim, Francine Foss, Jasmine M. Zain, Patricia L. Myskowski, Mary Jo Lechowicz, David C. Fisher, Andrei R. Shustov, Nancy L. Bartlett, Maria L. Delioukina, Tony Koutsoukos, Michael E. Saunders, Owen A. O'Connor and Madeleine Duvic

<table>
<thead>
<tr>
<th>Doses</th>
<th>61% ORR</th>
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</thead>
<tbody>
<tr>
<td>&gt;15 mg/m², 3/4 weeks (IV)</td>
<td></td>
</tr>
<tr>
<td>Optimal dose in CTCL, 15 mg/m², 3/4 weeks (IV)</td>
<td>45% ORR</td>
</tr>
<tr>
<td>DOR at 6 mo</td>
<td>73%</td>
</tr>
</tbody>
</table>
Pralatrexate response in MF, stage IIB
Good option in MF with LCT

Pretreatment

Partial Response post cycle 3

MD Anderson CC
Pralatrexate response,
Pc CD30+ ALCL
Stanford CC
# Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>ALL</th>
<th>Grade 1-2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomatitis</td>
<td>14 (48%)</td>
<td>9 (31%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (38%)</td>
<td>10 (34%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (31%)</td>
<td>9 (31%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Skin toxicity</td>
<td>6 (21%)</td>
<td>4 (14%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (14%)</td>
<td>4 (14%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (7%)</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>7 (24%)</td>
<td>7 (24%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Edema</td>
<td>4 (14%)</td>
<td>4 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (7%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Optimal Dose
15 mg/m²
N=29

Combination trials under way to minimize toxicity and assess synergy

Horwitz et al
Blood
2012; 119: 4115

Y Kim, Stanford CC
Tumor cell surface molecules (e.g., CD4, CD25, CD30, CD52, CD158k, CCR4)

Tumor proliferation, metabolism, survival, progression mechanisms:
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- **Metabolic/survival pathways** (e.g., RFC-1, PARP)

Microenvironment, immune mechanisms (e.g., vasculature, immune modulation)

Targets for therapy in cutaneous T-cell lymphoma (CTCL)
Newer generation monoclonal antibodies in cutaneous T-cell lymphoma

- Fully human mAbs
- Engineered mAbs, modified Fc portion to enhance biologic activity
  - Defucosylated anti CCR4 Mab (KW-0761)
- Antibody drug conjugates
  - Anti CD30 ADC, brentuximab vedotin (SGN-35)
Defucosylated humanized anti-CCR4 antibody, KW-0761

Higher ADCC due to a defucosylated Fc region by POTELLIGENT®

KW-0761

N-terminal

Extracellular regions

Fucose

Asn²⁹⁷

Higher ADCC due to a defucosylated Fc region by POTELLIGENT®

CCR4 (CC chemokine receptor 4)

Highly expressed (> 90%) in ATL
Great clinical response in skin/blood

Shinkawa et al, J Biol Chem 2003;278:3466
Ishii et al, Clin Cancer Res 2010;16:1520

Ishida et al, Clin Cancer Res 2003;9:3625

Courtesy T. Ishida

Y Kim, Stanford CC
Defucosylated Anti-CCR4 Monoclonal Antibody (KW-0761) for Relapsed Adult T-Cell Leukemia-Lymphoma: A Multicenter Phase II Study

Takashi Ishida, Tatsuro Joh, Naokuni Uike, Kazuhiro Yamamoto, Atae Utsunomiya, Shinichiro Yoshida, Yoshio Saburi, Toshihiro Miyamoto, Shigeki Takemoto, Hitoshi Suzushima, Kunihiro Tsukasaki, Kisato Nosaka, Hiroshi Fujiwara, Kenji Ishitsuka, Hiroshi Inagaki, Michinori Ogura, Shiro Akinaga, Masao Tonomaga, Kensei Tobinai, and Ryuzo Ueda

Approved in Japan 2012 for pts with ATL

Phase II study in progress in the US- NCT01626664
KW 0761 or Investigator's Choice in Subjects With Previously Treated Adult T-cell Leukemia-Lymphoma (ATL)
KW-0761, a Monoclonal Antibody Directed against CC Chemokine Receptor type 4 (CCR4), in CTCL patients: Results of a Phase 1/2 Study

Madeleine Duvic,1 Lauren Pinter-Brown,2 Francine Foss,3 Lubomir Sokol,4 Jeffrey Jorgensen,5 George Spitalny,6 and Youn H Kim7

1Department of Dermatology and 5Department of Hematopathology, UT MD Anderson Cancer Center; 2Geffen School of Medicine at UCLA; 3Department of Medical Oncology, Yale Cancer Center; 4Department of Malignant Hematology, H Lee Moffitt Cancer Center and Research Institute; 6Kyowa Hakko Kirin Pharma, Inc.; 7Department of Dermatology, Stanford Cancer Center

American Society of Hematology
52nd Annual Meeting
December 4–7, 2010
Expression of CCR4
Receptor for CC chemokines, MDC, TARC

ALK-negative ALCL

MF/SS

CCR4 expressed on CTCL and regulatory T cells

Ishida T et al. Clin Cancer Res. 2004;10:7529,
Ferenczi K et al. J Invest Dermatol 2002;119:1405
Chang D-K et al. Mol Cancer Ther 2012;11:2451
### Overall response rate in phase 1/2 study

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sezary Syndrome (N=17)</td>
<td>47%</td>
<td>1</td>
<td>7</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Mycosis Fungoides (N=21)</td>
<td>29%</td>
<td>1</td>
<td>5</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>TOTAL (N=38)</td>
<td>37%</td>
<td>2</td>
<td>12</td>
<td>18</td>
<td>6</td>
</tr>
</tbody>
</table>

Intravenous administration, weekly x 4, then every 2 wks

Y Kim, Stanford CC
• 8/17 (47%) of SS patients with global response (ORR)
• 15/17 (88%) of SS patients had response in blood
  9/17 (53%) had CR in blood
Case Study: Patient 03-Stanford
(SS; Stage IVA; 6 Prior Therapies; 0.3 mg/kg)

Pretreatment Course 1 Day 1

Post treatment Post Course 11

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Response in Blood: Patient 01-Stanford (SS; Stage IVA; 6 prior therapies; 0.1 mg/kg)

Pre-treatment

- CD3+CD4neg Normal CD3+CD4+
- Lymphoma cells

Y Kim, Stanford CC
Lymphoma cells undetectable
Maintaining response >2 yrs

Lymphoma cells
Normal CD3+CD4+
CD3+CD4neg

Response in Blood: Patient 01-Stanford Post-treatment

Y Kim, Stanford CC
KW-0761 (mogamulizumab, anti-CCR4)
Clinical Development Summary

• Clinical responses are most impressive in the skin and blood compartments in ATL and CTCL
• Absence of infections with chronic therapy, no need for antimicrobial prophylaxis (↔ alemtuzumab)

Phase III RCT in CTCL ongoing for FDA approval in the US
Targets for Therapy in Cutaneous Lymphoma

Tumor cell surface molecules (e.g., CD4, CD19, CD20, CD22, CD25, CD30, CD40, CD52, CD158k, CCR4)

Cutaneous lymphoma

Microenvironment, immune mechanisms (e.g., vasculature, immune modulation)

Tumor proliferation, metabolism, survival, progression mechanisms:

*Signal transduction/transcription activation pathways* (e.g., ubiquitin-proteasome, AKT/PI3K/mTOR, RAS/RAF/MEK, MAPK)

*Apoptotic pathways* (e.g. Bcl/Bax, TNFR, Fas, miRNAs)

*Epigenetics* (e.g., histone, non-histone proteins)

*Metabolic/survival pathways* (e.g., RFC-1, PARP)

Y Kim, Stanford CC
Targeted therapy in CD30+ LPDs

- CD30, an attractive target, as CD30 expression is limited in normal cells, but increased in proliferative or malignant lymphocytes => good tumor selectivity
Rationale for Targeting CD30

ALK and CD30 Signaling closely linked

CD30 engagement leads to activation of NFkB pathways and p21 mediated cell cycle arrest and apoptosis

Chiarle 2008

Y Kim, Stanford CC
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
Naked anti-CD30 MAbs in CD30+ LPDs

- Naked anti-CD30 mAb well tolerated but variable efficacy
  - High responses in pcALCL/LyP
  - Efficacy in MF minimally explored
  - Disappointing efficacy in HL/sALCL
Monomethyl auristatin E (MMAE), microtubule-disrupting agent
Protease-cleavable linker
Anti-CD30 monoclonal antibody

1. ADC binds to CD30
2. ADC-CD30 complex is internalized and traffics to lysosome
3. MMAE is released
4. MMAE disrupts microtubule network
5. G2/M cell cycle arrest
6. Apoptosis
Brentuximab Vedotin (SGN-35)

• High response rates in relapsed/refractory HL and sALCL with consistent expression of CD30 on tumor cells
  – Accelerated FDA approval 8/2011

• Variable CD30 expression in neoplastic cells of MF
  – Transformed MF with more frequent and greater CD30 expression, 30-50%
  – Non-transformed MF, 0-15%

Phase II Study of Brentuximab Vedotin in MF/SS with Variable CD30 Expression (Stanford-initiated trial)

**Clinical Assessments**

**Correlative Tissue/Blood**

**Physical exam + Flow q cycle**
**Imaging at baseline, q2 cycles (extracutaneous), q 3 cycles, EOT**

**MF/SS IB-IVB CD30 by routine IHC**

**Group A**
- <10% CD30+ of lymphoid cells

**Group B**
- 10 – 50% CD30+ of lymphoid cells

**Group C**
- >50% CD30+ of lymphoid cells

**SGN-35**
- 1.8 mg/kg IV
- q 3 weeks, up to 8 cycles

If PR:
- Cont. to improve may allow up to 8 additional cycles

If CR:
- 2 additional cycles allowed

*Responses confirmed subsequent cycle and IRG

Y Kim, Stanford CC
# Patient Characteristics, N = 30

<table>
<thead>
<tr>
<th>Age (y), median (range)</th>
<th>60.5 (20-88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>18 (60)</td>
</tr>
<tr>
<td>Women</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>4 (13)</td>
</tr>
<tr>
<td>IIA</td>
<td>0</td>
</tr>
<tr>
<td>IIB</td>
<td>16 (53)</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
</tr>
<tr>
<td>IVA</td>
<td>9 (29)</td>
</tr>
<tr>
<td>IVB</td>
<td>1 (3)</td>
</tr>
<tr>
<td>SS</td>
<td>3 (10)</td>
</tr>
<tr>
<td>LCT</td>
<td>19 (63)</td>
</tr>
<tr>
<td>FMF</td>
<td>11 (37)</td>
</tr>
<tr>
<td>LCT &amp; FMF</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Prior systemic therapies, median (range)</td>
<td>3 (1-13)</td>
</tr>
<tr>
<td>Large cell transformation (LCT) / Folliculotropic MF (FMF), n (%)</td>
<td></td>
</tr>
</tbody>
</table>

**Advanced stage**

**Variable expression**

<table>
<thead>
<tr>
<th>CD30 baseline, % of lymphoid cells (skin, via IHC), n (%)</th>
<th>A: &lt; 10%</th>
<th>14 (47)</th>
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<td>B: 10-50%</td>
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Y Kim, Stanford CC
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<tr>
<td>Women</td>
<td>12 (42)</td>
</tr>
<tr>
<td>Stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>4 (13)</td>
</tr>
<tr>
<td>IIB</td>
<td>16 (53)</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
</tr>
<tr>
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<td>9 (30)</td>
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<td>IVB</td>
<td>1 (3)</td>
</tr>
<tr>
<td>SS</td>
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</tr>
<tr>
<td>LCT</td>
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| Prior systemic therapies, median (range) | 3 (1-13) |

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<td></td>
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</tr>
</tbody>
</table>

**Advanced stage**

**Variable expression**

Y Kim, Stanford CC
Percent Change in Skin mSWAT Score at Best Skin Response

Global Response

- Progressive disease
- Stable disease
- Partial response
- Complete response

% change in mSWAT

*Final response pending

Y Kim, Stanford CC
Percent Change in Skin mSWAT Score at Best Skin Response

Large Cell Transformation
NO Transformation

Y Kim, Stanford CC
Clinical response by clinical stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Response Rate</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB (n=4)</td>
<td>75%</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>IIB* (n=15)</td>
<td>73%</td>
<td>0</td>
<td>11</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>IVA**/B (n=8)</td>
<td>25%**</td>
<td>1</td>
<td>1</td>
<td>3**</td>
<td>3</td>
</tr>
<tr>
<td>Total n= 27</td>
<td>59%</td>
<td>1</td>
<td>15</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

No correlation with response:
- Gender (p=0.67)
- Age (p=0.78)
- Large cell transformation (p=0.40)
- Folliculotropism (p=1.0)
- Baseline soluble CD30 (p=0.90)

*All 15 either LCT or FMF
**Final response pending
87 yo M with MF IIB, LCT
Screening biopsies (L chest plaque and L arm tumor)

Max CD30 TLI 100%
Group C (>50%)

Y Kim, Stanford CC
87 yo M with MF IIB, LCT
87 yo M with MF IIB, LCT

Screening

Cycle 6
Subject 12: 66 yo F with MF IVB, LCT w/ oropharyngeal involvement

Group B (10-50%): Max CD30 TLI 20%

Best Response: PR

Screening

Cycle 10
Screening

Cycle 10
78 yo F, IVA1 (SS)
Max CD30 TLI 60%: Group C (>50%)
PR; mSWAT reduction 81% post 1 cycle
Screnning

78 yo F, IVA1 (SS)
Max CD30 TLI 60%: Group C (>50%)
PR; mSWAT reduction 81% post 1 cycle

Screening

Pre Cycle 2

Y Kim, Stanford CC
Clinical Response by Baseline CD30 Expression

<table>
<thead>
<tr>
<th>CD30 Expression Group</th>
<th>Response Rate % (n)</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (&lt;10%) n=13*</td>
<td>46% (6)</td>
<td>0</td>
<td>6</td>
<td>5*</td>
<td>2</td>
</tr>
<tr>
<td>Group B (10-50%) n=12*</td>
<td>67% (8)</td>
<td>0</td>
<td>8</td>
<td>1*</td>
<td>3</td>
</tr>
<tr>
<td>Group C (&gt;50%) n=2</td>
<td>100% (2)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL n=27</td>
<td>59% (16)</td>
<td>1</td>
<td>15</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

If > 1 skin biopsy at baseline, maximum CD30% designated grouping
* 1 subject each in Group A, B pending response
Response versus max CD30 expression by routine IHC

% CD30 expression of total lymphoid cells

No Response (SD/PD)  
n=9

Response (PR/CR)    
n=16

Y Kim, Stanford CC
## Common related adverse event (≥10% incidence)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Neuropathy</td>
<td>62%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>48%</td>
</tr>
<tr>
<td>Nausea</td>
<td>28%</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>21%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>17%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>17%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>14%</td>
</tr>
<tr>
<td>Skin eruption</td>
<td>14%</td>
</tr>
</tbody>
</table>
Summary and Conclusions

• Brentuximab vedotin shows significant clinical activity (ORR 59%) in refractory and advanced MF/SS

• Time to response is early (median 7.3 wks; range 3-18)

• Encouraging DOR with KM estimates at 12 mo 76% maintaining response

• Well tolerated with mostly G1/2 AEs
  – Most patients with PN improve but not all resolve

Y Kim, Stanford CC
51 yo F stage IVA2 MF with LCT in skin/LNs: response to brentuximab vedotin

Pre-treatment 12/20/2012

Post 2 cycles 1/29/2013

Phase III RCT in CTCL ongoing for FDA approval

Most responses are not durable
Road to a CURE

How do we make the nice responses last?

*Partnering with immunotherapy*

![Graph showing survival over time with Tumor-directed killing and Immune modulatory therapy lines.](image)
Immunotherapy strategies in cancer

- Tumor-specific monoclonal antibodies
- Cytokine therapy
- Immune-modulating agents or antibodies
- Adoptive T-cell transfer
- Vaccine-based approaches
- Allogeneic HSCT

TILs

Lymphoma

M

Y Kim, Stanford CC
Targets for therapy in cutaneous T-cell lymphoma

- Tumor cell surface molecules (e.g., CD4, CD25, CD30, CD40, CD52, CD158k, CCR4)
- Tumor proliferation, metabolism, survival, progression mechanisms:
  - Signal transduction/transcription activation pathways (e.g., ubiquitin-proteasome, AKT/PI3K/mTOR, RAS/RAF/MEK, MAPK)
  - Apoptotic pathways (e.g., Bcl/Bax, TNFR, Fas, miRNAs)
  - Epigenetics (e.g., histone, non-histone proteins)
  - Metabolic/survival pathways (e.g., RFC-1, PARP)
- Microenvironment, immune mechanisms (e.g., vasculature, immune modulation)

Y Kim, Stanford CC
Immune modulation of tumor microenvironment with mAbs

Tumor cell-specific: tumor surface molecules (e.g., CD4, CD19, CD20, CD22, CD25, CD30, CD40, CD52, CD158k, CCR4)

Microenvironment Immune modulation (e.g. PD-1, PD-L1, CTLA-4, IDO, Tregs)

Monoclonal antibodies

CD8+ TILs

CTCL
PD-1 and ligands B7-H1/PD-L1 & B7-DC/PD-L2: Pivotal role in maintaining immunosuppressive tumor microenvironment

Immune checkpoint blockade with inhibitors of PD-1, PD-L1 to restore the cytotoxic CD8 T cell response, providing augmented anti-tumor activity and clinical efficacy
Expression of PD-1 and PD-L1 in CTCL Mycosis fungoides & Sezary syndrome

PD-1 expressed in PB Sezary cells

MF skin plaque tumor T-MF

Am J Dermatopathol 2012:34:126
Arch Dermatol 2010;146:1382

Y Kim, Stanford CC
Immune checkpoint blockade with anti-PD-L1 mAb (MPDL3280A) in lymphoma (H Kohrt Stanford PI)

- Expression of PD-1, PDL-1 in CTCL, a major mechanism of down-regulating the anti-tumor CD8 T cell response
- Targets PD-L1 on APCs or tumor cells, prevents interaction with PD-1 on T-cells

Encouraging clinical activity in MF/CTCL

A phase II study with anti-PD-1 mAb (MK-3745) in CTCL (MF/SS) planned (Kohrt, Kim)

Immune correlative studies to assess local tissue/systemic immunologic activity and biomarkers of response
Immunotherapy strategies in cancer

- Tumor-specific monoclonal antibodies
- Cytokine therapy
- Immune-modulating agents or antibodies
- Adoptive T-cell transfer
- Vaccine-based approaches
- Allogeneic HSCT

Y Kim, Stanford CC
Harnessing the graft-versus-lymphoma effect in allo HSCT as the ultimate cellular immune therapy

Donor Cell Transplant

Replacement of Host Blood System

Donor Immune System to destroy lymphoma cells

Y Kim, Stanford CC
A New Approach in Donor Cell Transplant
Non-Myeloablative Regimen with TLI/ATG
“Protective conditioning”

Enable Donor Cells to Engraft
aGVHD reduced to 2-5% (vs. 20-65%)

Y Kim, Stanford CC
Mycosis fungoides, stage IVA w/ LCT in skin/LNs: CR

Pre-TSEBT

3.0+ yr (NED, no GVHD)
Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR

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

3.0+ yr (NED, no GVHD)
CD4+/CD26-: normalized
Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR

Pre-transplant

3.0+ yr (NED, no GVHD)
Monitoring minimal residual disease by High-throughput sequencing of T-cell receptor

Peripheral blood mononuclear cells and skin biopsy

Extracted of genomic DNA

High-throughput sequencing of rearranged TCRβ CDR3 using solid phase PCR (Illumina GA2 system)

Robins et al, Blood 2009;114:4099
WK Weng, Y Kim, Sci Transl Med 2013 in press

Y Kim, Stanford CC
## Minimal Residual Disease (MRD) in Blood Post Transplant

<table>
<thead>
<tr>
<th>Malignant Sequence</th>
<th>Total Read</th>
<th>% of Malignant Clone</th>
<th>% of Donor T Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-TSEBT</td>
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<td>69.029</td>
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<tr>
<td>Pre-TLI/ATG</td>
<td>1,057,097</td>
<td>1,356,526</td>
<td>77.926</td>
</tr>
<tr>
<td>Day+30</td>
<td>1,188</td>
<td>132,874</td>
<td>0.894</td>
</tr>
<tr>
<td>Day+60</td>
<td>2,946</td>
<td>184,495</td>
<td>1.596</td>
</tr>
<tr>
<td>Day+90</td>
<td>4,666</td>
<td>1,094,254</td>
<td>0.426</td>
</tr>
</tbody>
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Y Kim, Stanford CC
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<td>Day+90</td>
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<td>Day+180</td>
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<tr>
<td>Day+270</td>
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<td>877,242</td>
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<tr>
<td>Day+360</td>
<td>0</td>
<td>764,859</td>
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<tr>
<td>Day+540</td>
<td>0</td>
<td>2,263,923</td>
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*Monitoring MRD by HTS may predict true molecular and clinical cure and may predict disease relapse*

Y Kim, Stanford CC
CTCL Therapeutics: Are we better now?

YES!

• Consensus guidelines; use older therapies smarter
• **New/improved technology** allowing us to learn more, help **identify actionable targets**, and modify/render agents **more effective/safe**
• More approved treatment options (more in the pipeline)
• Improved targeted, **tumor-selective therapies** with more reliable responses that are well-tolerated
• Learning to **better partner** with immune microenvironment to boost anti-tumor potency
• **Can cure advanced disease** w/ allo HSCT, more safely
• Best therapies will be from recognizing the complexity of MF-SS and offer/allow **personalized strategy**

Y Kim, Stanford CC
Immunotherapy strategies in cutaneous lymphoma

- Immune-modulating agents or antibodies
- Vaccine-based approaches
- Adoptive cell transfer
- Allogeneic HSCT
- Combination with newer targeted therapies, chemotherapies, radiation therapy
  - long-lasting, curative outcome
Stanford Multidisciplinary Cutaneous Lymphoma Group

Holbrook Kohrt
Sunil Reddy
Ron Levy

Ranjana Advani
Med Onc partners

Wen-Kai Weng
Sally Arai
Katherine Wolpin
BMT partners