Clinical Issues in Cutaneous T-cell Lymphoma

Youn H Kim, MD

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Multidisciplinary Cutaneous Lymphoma Program
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Stanford, CA
Disclosure statement

- **Youn Kim, MD**
- **Steering Committee**
  - Eisai, Millennium
- **Consultant or Advisory board**
  - Kyowa, Celgene, Emergent, Medicis
- **Investigator**
  - Allos, Kyowa, Merck, Millennium, Seattle Genetics, SHAPE, Ceptaris/Yaupon, Eisai, Genentech
Key Clinical Questions in CTCL

• How can we optimize our diagnostic ability?
• What are the key prognostic factors or markers that can help guide clinical management?
• How do we make optimal treatment decisions with available therapies?
• How can we improve future therapeutics and outcome?
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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Hodgkin’s Lymphomas

Version 1.2013

NCCN.org

NHL => MFSS

Medicare and other insurances follow NCCN guidelines

Real time updates

Consensus if not evidence-based recommendations
NCCN Guidelines Version 1.2013
Mycosis Fungoides/Sezary Syndrome

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, $\beta$F1)
- 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 $\approx 1\%$ BSA) and type of skin lesion (patch/plaque, tumor, erythroderma)
  - Palpation of peripheral lymph node regions
  - Palpation for organomegaly/masses
- Laboratory studies:
  - 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

**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)

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$^{b}$ See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHQDGA).

$^{c}$ Typical immunophenotype: CD2+ CD3+ CD5+ CD7- CD4+ CD8- (rarely CD8+) CD30-/+ cytotoxic granule proteins negative.

$^{d}$ TCR gene rearrangement results should be interpreted with caution. TCR clonal rearrangement can be seen in non-malignant conditions or may not be demonstrated in all cases of MF/SS. Demonstration of identical clones in skin, blood, and/or lymph node may be helpful in selected cases.

$^{e}$ See map for prevalence of HTLV-1 by geographic region.

$^{f}$ Sezary syndrome (B2) is as defined on MFSS-2.

$^{g}$ Many skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Refer to individual drug information.
Current diagnostics, 1/2013

Dermatopathology review

CLINICAL-PATHOLOGIC CORRELATION REMAINS KEY

Tissue pathology +/- PB/LN flow cytometric data

Ancillary studies:

Immunohistochemistry (IHC)
- rule out histologic mimics

TCRR PCR for clonality
- demonstration of same clone > 1 site, relevant clone
Current diagnostics, 1/2013

Clinical-pathologic correlation remains key
Tissue pathology +/- PB/LN flow cytometric data

Ancillary studies:
Immunohistochemistry (IHC)
- rule out histologic mimics

TCRR PCR for clonality
- demonstration of same clone > 1 site, relevant clone

Exploratory diagnostics
How to better distinguish from inflammatory ddx and mimics?
- New IHC markers, FISH to distinguish malignant cell vs. reactive/normal cells
- Gene, epigenetic modulation, miRNA expression profiles

=> NOT READY for clinical use
(needs further validation, better/more controls)
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Clinical

Histologic Laboratory

Molecular Tumor biology

Prognostication

Management

Prognostic factors in cancer management
Cutaneous T-cell lymphoma

Clinical

Histologic Laboratory

Prognostication

Management

Molecular (Other than TCRR)

- MicroRNA profiles
- Chromosomal aberrations
- Gene expression patterns/clusters
- Other genetic/epigenetic alterations

*NOT ready for clinical use*
Key clinical factors in CTCL

- **Age**
  - Worse px in *elderly* (subset of young/non-cauc bad)

- **TNMB/clinical stage**
  - Worse with plaque vs. patch, extensive tumors, erythroderma (+ tumors)
  - LN: N0 v N1-2 (relevant clone pos vs neg) v N3 (frank LN dz)
  - Viscera/M (solid organ vs BM)
  - Blood/B0 (relevant clone pos) vs B1 vs B2 vs very high SC load

- **MF clinical variants**
  - WK (favorable), F-MF (unfavorable)
  - Poikilodermatous (favorable)

- **Transformation** to aggressive clinical behavior

- **Gender, ethnicity** (geographic variation)

Histologic and laboratory factors in CTCL

- Folliculotropism, large cell transformation
- Tissue tumor cell features
  - Ki-67, CD30, CD25
- Tissue tumor microenvironment
  - TILs (CD8+ CTL), Tregs
- LDH, beta-2 microglobulin, eosinophilia/IgE
- Soluble CD25, CD30, cytokine/cytokine receptor levels

Survival decreased with advancing skin disease (T-class) and overall clinical stage

Good v bad?
Beyond clinical factors: how can we predict the good from the bad within a stage/IIB?

- Are there clinical factors, biomarkers that distinguish between indolent and aggressive IIB?
- Can we predict which IIB patients will live longer?
- Are there biomarkers for cells in the aggressive disease?
- Are there drugs that target the dysregulated genes or biological pathways?
Beyond clinical factors: how can we predict the good from the bad within a stage/IIB?

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- Are there drugs that target the dysregulated genes or biological pathways?
Gene expression pattern that distinguish indolent vs. aggressive MF tumors

Genes $P\text{-val}<0.05$
Read Ct + 1
Then log2
Then mean ctrl

Indolent tumor
Aggressive tumor

Downregulated
Upregulated

R Chen et al 2012
Key changes in aggressive MF tumors

- Genes regulating cell proliferation and survival including the MAPK, PI3K, AKT, Jak/Stat pathways
- Genes implicated in leukemias/lymphomas and other cancers
- Inflammatory response genes including ones implicated in skin conditions such as psoriasis
- Breakdown of extracellular matrix, potentially favoring tumor invasion, metastasis
- T cell adhesion and migration
- B cell differentiation, proliferation

R Chen et al 2012
Dreaming the future of personalized medicine

CTCL Bench to Bedside

- Diagnosis
- Prognosis
- Personalized management
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Mycosis Fungoides
Treatment of varying skin manifestations

Patch T1-2

Tumor T3

Plaque T1-2

Erythroderma T4
Management of extracutaneous disease
Sézary syndrome—generalized erythroderma, keratoderma, severe itching; freq staph aureus infection
**Stage-based treatment algorithm**

**Diagnosis**
- Biopsy of suspicious skin sites
- Dermatopathology review of slides

**Workup**
- Complete physical examination
  - Assessment of %BSA (palm plus digits ≈1% BSA) and type of skin lesion (patch/plaque, tumor, erythroderma)
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**Stage**
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- Stage III → See Primary Treatment (MFSS-7)
- Stage IV → See Primary Treatment (MFSS-8)

**References**
- Blood 2007;110:1713
- www.nccn.org => NHL => MFSS
# Current Clinical Management of CTCL, 2013

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

<table>
<thead>
<tr>
<th>IA</th>
<th>IB/IIA</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>

- **Topical steroid, retinoid (bex), NM phototherapy, local RT, imiquimod**

- **Combination chemo**
  - Bexarotene, denileukin diftitox, IFN vorinostat, romidepsin (single or combination)

- **Allo-HSCT**

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

- **Phototherapy + bexarotene or IFN**

- **TSEBT + ECP*, IFN**

- **Alemtuzumab**

- **Combination chemo**

- **Clinical Trials**

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*ECP = photopheresis

** Methotrexate, liposomal doxorubicin, gemcitabine, pentostatin, chlorambucil, etoposide, pralatrexate
Key treatment selection factors

- Clinical stage/TNMB
  - MF vs. SS

- Other prognostic factors
  - Large cell transformation
  - Folliculotropic disease

- Age, co-morbidities, concomitant meds

- Availability/access issues
  - TSEBT, photopheresis
  - US vs. other countries
  - Insurance barriers
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 to topical nitrogen mustard gel
NDA re-filed; expect approval end of 2013
Narrow band UVB

baseline

3 months
Localized RT in Woringer Kolopp disease
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

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

Is combination therapy “better”?

- No comparative data
- Lower doses of each (less toxicity)
- Synergy?
Appreciating biologic and clinical differences/overlap in MF vs. SS: translating into management

Oncogenic analysis of mycosis fungoides reveals major differences with Sézary syndrome

Brief report

Sézary syndrome and mycosis fungoides arise from distinct T-cell subsets: a biologic rationale for their distinct clinical behaviors

*James J. Campbell,1 *Rachael A. Clark,1 Rei Watanabe,1 and Thomas S. Kupper1

1Department of Dermatology, Brigham and Women’s Hospital/Harvard, Boston, MA
Distinctive supportive management in Sézary syndrome

- **Mycosis fungoides**
- **Sézary syndrome**

**Infection patrol**
(MSSA/MRSA, HSV/VZV, fungal)

**Pruritus control**
(gabapentin, mirtazapine, aprepitant)

**Topical steroid +/- occlusion**

**Emollient**
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/mm³)**
  - Combination therapies
    - Romidepsin
    - Alemtuzumab
- **Refractory disease**
  - Alemtuzumab
  - Clinical trials

Clinical trials
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Why do we need better therapies?
# Efficacy of Systemic Agents in CTCL

Efficacy data for FDA approval

<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>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td>Denileukin difftitox (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>
</tr>
<tr>
<td>Bexarotene (RXR activator)</td>
<td>Cutaneous manifestations</td>
<td>1999</td>
<td>Pivotal</td>
<td>62</td>
<td>32%</td>
<td>5+ mo</td>
</tr>
<tr>
<td>Vorinostat (HDAC inhibitor)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30%</td>
<td>6+ mo</td>
</tr>
</tbody>
</table>

*Need better therapies*  
*More options*
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
- Improved technology for increased potency
- 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)
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**CTCL**

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Types of targeted therapies in lymphoma, 2013

- 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
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.

![Diagram showing the mechanism of pralatrexate and its interaction with cellular pathways.](image)
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

<table>
<thead>
<tr>
<th>Doses &gt;15 mg/m², 3/4 weeks (IV)</th>
<th>61% ORR</th>
</tr>
</thead>
<tbody>
<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
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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*Signal transduction/transcription activation pathways* (e.g., ubiquitin-proteasome, AKT/PI3K/mTOR, RAS/RAF/MEK, MAPK)

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

*Metabolic/survival pathways* (e.g., RFC-1, PARP)
Newer generation monoclonal antibodies in cutaneous T-cell lymphoma

• Fully human mAbs
  – Anti-CD4 mAb (zanolimumab)

• Engineered mAbs, modified Fc portion to enhance biologic activity
  – Defucosylated anti-CCR4 mAb, mogamulizumab (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 POTELIGENT®

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
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, Kazuhito 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 Tomonaga, 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

Greater proportion of CTCL cells have CCR4 expression than healthy T-cells

Ferenczi K et al. J Invest Dermatol 2002;119:1405
<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><strong>Sezary Syndrome</strong></td>
<td>47%</td>
<td>1</td>
<td>7</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>(N=17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mycosis Fungoides</strong></td>
<td>33%</td>
<td>1</td>
<td>6</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>(N=21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>42%</td>
<td>2</td>
<td>13</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>(N=38)</td>
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</table>

Intravenous administration, weekly x 4, then every 2 wks
• 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)
Response in Blood: Patient 01-Stanford
(SS; Stage IVA; 6 prior therapies; 0.1 mg/kg)

Pre-treatment

![CD3+CD4neg](image1)
![Normal CD3+CD4+ Lymphoma cells](image2)
![Lymphoma cells](image3)

Lymphoma cells

![CD4](image4)
![CD26](image5)
![CCR4 1G1](image6)
Response in Blood: Patient 01-Stanford
Post-treatment

Lymphoma cells undetectable
Maintaining response >2 yrs
KW-0761 Clinical Development Summary

• Clinical responses are most impressive in the skin and blood compartments in ATL and CTCL
• Absence of severe infections (↔ alemtuzumab)

Phase III RCT in CTCL ongoing for FDA approval in the US
Tumor cell surface molecules (e.g., CD4, CD19, CD20, CD22, CD25, CD30, CD40, CD52, CD158k, CCR4)

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

Cutaneous lymphoma

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

Microenvironment, immune mechanisms (e.g., vasculature, immune modulation)
CD30+ primary cutaneous lymphoproliferative disorders

- Lymphomatoid papulosis
- Pc CD30+ anaplastic large cell lymphoma
- *Mycosis fungoides with CD30 expression*
- *other TCLs and BCLs may express CD30*
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
Monomethyl auristatin E (MMAE), microtubule-disrupting agent
Protease-cleavable linker
Anti-CD30 monoclonal antibody

ADC binds to CD30
ADC-CD30 complex is internalized and traffics to lysosome
MMAE is released
MMAE disrupts microtubule network

Given IV every 3 wks; Peripheral Neuropathy, dose-limiting

G2/M cell cycle arrest
Apoptosis
Brentuximab vedotin (SGN-35) in systemic lymphoma

- Highly effective in relapsed/refractory HL and sALCL
- Adverse events were manageable including peripheral neuropathy (85% sig improved/reversible)

Received accelerated approval by FDA in HL and sALCL (8/2011) => 2nd mAb-drug-conjugate (ADC) to be approved
Brentuximab vedotin demonstrates clinical activity in mycosis fungoides / Sézary syndrome

Krathen M¹, Bashey S¹, Sutherland K¹, Sundram U¹, Nagpal S¹, Salva K³, Wood G³, Advani R¹, Hoppe RH¹, Reddy S¹, Pulitzer M², Horwitz S², Kim YH¹

¹Stanford Cancer Institute, Stanford, CA, USA
²Memorial Sloan-Kettering Cancer Center, New York, NY, USA
³University of Wisconsin, Madison, WI, USA
CD30: Target in MF/SS

- HL and sALCL with consistent expression of CD30 on tumor cells and high response rates

- Variable CD30 expression on neoplastic cells of MF
  - Transformed MF with more frequent and greater CD30 expression, 30-50%
  - Non-transformed MF, 0-15% (majority of MF)

Percent Change in Skin mSWAT
At Best Clinical Response

Best Response (% change in mSWAT)
Progressive disease
Stable disease
Partial response
Complete Response

Cycle at Best Response
### Clinical Response by 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=2)</td>
<td>100%</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIB* (n=11)</td>
<td>91%</td>
<td>0</td>
<td>10</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>IVA**/B (n=6)</td>
<td>33%</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total n=19**</td>
<td>74%</td>
<td>1</td>
<td>13</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

*All 11 either LCT or FMF

** 1 subject non-evaluable for response
87 yo M with MF IIB, LCT

Screening

Cycle 6
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

20% CD30
Summary of clinical development of brentuximab vedotin in CTCL

• Two separate investigator-initiated studies (Stanford, MD Anderson) show consistent data of promising responses
  – MF (regardless of tissue CD30), LyP, pcALCL

• Acceptable toxicities
  – PN most common, concern of PML being observed

Phase III RCT in CTCL ongoing in the US and Europe for approval
Immunotherapy strategies in cancer

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

TILs, lymphoma
Induction of long-lasting responses and improving survival with partnering with immune strategies
Immunotherapy strategies in cutaneous lymphoma

- Tumor-specific monoclonal antibodies
- Cytokine therapy (IFNs, IL2, IL12)
- Adoptive cell transfer
- Allogeneic HSCT
- Immune-modulating agents or antibodies
- Vaccine-based approaches
- TLR-A, IMiDs, Tregs, CTLA4, PD-1, PD-L1
- ECP, DC-based, Idiotype, In situ strategy
Immunotherapy strategies in cutaneous lymphoma

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

Key molecules:
- TLR-A
- IMiDs
- Tregs
- CTLA4
- PD-1
- PD-L1
- Imiquimod
- Resiquimod
- TILs
- lymphoma M
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)

Monoclonal antibodies

Microenvironment Immune modulation (e.g. CTLA4, PD-1, PD-L1, IDO, Tregs)

Cutaneous lymphoma

TILs
# Modulating microenvironment & immune mechanisms

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Conjugate</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>--</td>
<td>lymphoma</td>
</tr>
<tr>
<td>Endostatin</td>
<td>Endothelial cell</td>
<td>--</td>
<td>lymphoma</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>--</td>
<td>Solid tumor/lymphoma</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Multiple</td>
<td>--</td>
<td>Hematologic malignancies</td>
</tr>
<tr>
<td>TLR agonists</td>
<td>TLR</td>
<td>--</td>
<td>lymphoma</td>
</tr>
<tr>
<td>Anti-PD-1 mAbs</td>
<td>PD-1</td>
<td>--</td>
<td>Solid tumor/hematolymph</td>
</tr>
<tr>
<td>Anti-PD-L1 mAbs</td>
<td>PD-L1</td>
<td>--</td>
<td>Solid tumor/hematolymph</td>
</tr>
<tr>
<td>IDO inhibitors</td>
<td>IDO+ DCs, tumor</td>
<td>--</td>
<td>Solid tumor/hematolymph</td>
</tr>
</tbody>
</table>

Renewed interest in immunotherapy

Programmed Death-1 (PD-1) and ligands B7-H1/PD-L1 and B7-DC/PD-L2: Pivotal role in maintaining immunosuppressive tumor microenvironment

Curr Opin Immunol 2012;24:207
Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthy, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.

Expression of PD-1 and PD-L1 in MF skin tissue: Inverse correlation of PD-1 and PD-L1 with disease severity

Am J Dermatopathol 2012:34:126
**TABLE I. PD-1 Expression in CTCL Determined by Immunohistochemistry**

<table>
<thead>
<tr>
<th>Disease subtype</th>
<th>PD-1-positive cases (%)</th>
<th>Mean (range) percentage of PD-1-positive tumor cells&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch/plaque mycosis fungoides (n = 15)</td>
<td>6 (40)</td>
<td>78 (60–95)</td>
</tr>
<tr>
<td>Generalized or tumor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Differential Expression of Programmed Death-1 (PD-1) in Sézary Syndrome and Mycosis Fungoides**

Fatma Çetinözm, MD; Patty M. Jansen, MD, PhD; Maarten H. Vermeire, MD, PhD; Rein Willemze, MD, PhD

PD-1 blockade enhanced IFN-gamma production

*Rook’s group*
Anti-PD1/PD-L1 mAbs in clinical development

- MDX-1105/BMS-936559, MDX-1106/BMS-936558 (Medarex/Bristol-Myers Squibb), MK-3475 (Merck), CT-011 (Cure Tech/Teva), AMP-224 (Amplimmune/GSK)

Anti-PD-L1 mAb opened for enrollment at Stanford:

- A phase I, open-label, dose-escalation study of the safety and pharmacokinetics of MPDL3280A administered intravenously as a single agent to patients with locally advanced or metastatic solid tumors or hematologic malignancies (Genentech)
- MPDL3280A, a phage-derived human IgG1 mAb
- Targets PD-L1 on APCs or tumor cells, prevents interaction with PD-1 on T-cells
Stage IB MF (h/o phototx, bexarotene, anti-CD4 mAb, forodesine, CpG+RT, lenalidomide, sapacitabine, enzastaurin, TSEBT)

11/20/2012 (pre-treatment)
mSWAT 36 (20 plaque, 16 patch)

2/19/2013 (C5D1)
mSWAT 12 (6 patch, 6 plaque)
Stage IB MF (h/o phototx, bexarotene, anti-CD4 mAb, forodesine, CpG+RT, lenalidomide, sapacitabine, enzastaurin, TSEBT)

pre-treatment (11/20/2012)  C5D1 (2/19/2013)
Harnessing the graft-versus-lymphoma effect in allo HSCT as the ultimate cellular immune therapy
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%)
Mycosis fungoides, stage IVA w/ LCT in skin/LNs: CR

Pre-TSEBT

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

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

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

Pre-transplant

1.5+ yr (NED, no GVHD)
Reconstitution of TCRβ repertoire after non-myeloablative allogeneic HSCT
Immunotherapy strategies in cutaneous lymphoma

- Immune-modulating agents or antibodies
- Vaccine-based approaches
- Combination with molecular targeted therapies, chemotherapies, radiation therapy
- Adoptive cell transfer
- Allogeneic HSCT
- Cytokine therapy
- Long-lasting, curative outcome
Key Clinical Issues in CTCL: Take home summary

• How can we optimize our diagnostic ability?
  => Utilize appropriate ancillary studies for optimal clinical-pathologic diagnosis

• What are the key prognostic factors or markers that can help guide clinical management?
  => Integration of clinical, path, standard molecular studies for overall prognosis, to guide management

• How do we make optimal treatment decisions with available therapies?
  => Stage-based decision, MF v SS, other prog, availability, co-morbidity related selection; utilize NCCN guidelines

• How can we improve future therapeutics and outcome?
  => Pursue targeted/tumor selective tx + partnership with immune strategies to improve long-term outcome