New Agents and Therapeutic Strategies in CTCL

Youn H Kim, MD

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Multidisciplinary Cutaneous Lymphoma Group
Stanford Cancer Institute & School of Medicine
## Cutaneous T- and NK/T-cell Lymphomas

<table>
<thead>
<tr>
<th>New WHO-EORTC Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis fungoides and variants/subtypes</td>
</tr>
<tr>
<td>Sézary syndrome</td>
</tr>
<tr>
<td>PC CD30+ lymphoproliferative disorders</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
</tr>
<tr>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
</tr>
<tr>
<td>Cutaneous $\gamma/\delta$ T-cell lymphoma</td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma</td>
</tr>
<tr>
<td>PC peripheral T-cell lymphoma, unspecified</td>
</tr>
<tr>
<td>• Aggressive epidermotropic CD8+ T-cell lymphoma</td>
</tr>
<tr>
<td>• CD4+ sm/med-sized pleomorphic T-cell lymphoma/LPD</td>
</tr>
<tr>
<td>• PTCL, other</td>
</tr>
</tbody>
</table>

WHO monogram, 4th Ed, 2008
Mycosis Fungoides
Treatment of varying skin manifestations
Management of extracutaneous disease

Blood

Viscera

Lymph node

T6 (52.293, 22.150)
Sézary syndrome—generalized erythroderma, keratoderma, severe itching; freq staph aureus infection
Prognosis of early vs advanced stage MF and SS: Appropriate risk-stratification for treatment selection

Stage IA vs. control population:
Life-expectancy is not altered in patients with limited patch/plaque disease

Early (IA-IIA) vs Advanced (IIB-IV)

F-MF or LCT with worse clinical outcome
F-MF not sig independent factor in advanced MF/SS (CLIC Scarisbrick et al, 2015)

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

General concepts in managing MF/SS-CTCL

Lack of evidence-based help
  – Consensus-based management

Overall goal of treatment
• Good PRs that are durable, well-tolerated, and improve QoL
• Lasting CRs are great but hard to attain and often at risk of undesired AEs

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
  – Often observe mixed responses
  – Can re-cycle treatments
  – Optimize utility of maintenance therapy
What are the standard systemic agents in CTCL?

**SYSTEMIC THERAPIES**

**Category A (SYST-CAT A)**
- Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13-cis-retinoic acid], acitretin[^8]
- Interferons (IFN-alpha, IFN-gamma)
- HDAC-inhibitors (vorinostat, romidepsin[^e])
- Extracorporeal photopheresis[^f]
- Methotrexate (≤100 mg q week)

**Category B (SYST-CAT B)**
- First-line therapies (alphabetical order)
  - Brentuximab vedotin
  - Gemcitabine
  - Liposomal doxorubicin
  - Low-dose pralatrexate
- Second-line therapies
  - Chlorambucil
  - Pentostatin
  - Etoposide
  - Cyclophosphamide
  - Temozolomide
  - Methotrexate (>100 mg q week)
  - Bortezomib (category 3)

**Category C (SYST-CAT C[^g]) (alphabetical order)**
- Bortezomib (category 3)
- Brentuximab vedotin
- Gemcitabine
- Liposomal doxorubicin
- Low- or standard-dose pralatrexate
- Romidepsin
- See regimens listed on TCEL-B 2 of 5 (PTCL-NOS)[^h]

**COMBINATION THERAPIES**

- **Skin-directed + Systemic**
  - Phototherapy + retinoid[^e]
  - Phototherapy + IFN
  - Phototherapy + photopheresis[^f]
  - Total skin electron beam + photopheresis[^f]

- **Systemic + Systemic**
  - Retinoid + IFN
  - Photopheresis[^f] + retinoid
  - Photopheresis[^f] + IFN
  - Photopheresis[^f] + retinoid + IFN

=> Stage-based management
Current Clinical Management of CTCL, 2016

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

IA
Limited patch/plaque

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

IB/IIA
Generalized patch/plaque

Photophoresis ± IFN, bexarotene

IIB
Tumors

Phototherapy + bexarotene or IFN

III
Erythroderma

TSEBT + bex photopheresis, IFN

IV
Extracutan disease

Bexarotene, methotrexate, IFN vorinostat, romidepsin

Photopheresis + bexarotene

New targeted or cytotoxic systemic therapy**

Alemtuzumab

Combination chemo

Allo-HSCT

Clinical Trials

**brentuximab, pralatrexate, liposomal doxorubicin, gemcitabine, other
What therapeutic advances have we made?
Advances in skin-directed therapies, to partner with systemic agents in CTCL

- Topical steroids
- Topical chemotherapy
  - FDA approval of topical mechlorethamine gel
- Topical retinoids (bexarotene)
- Topical imiquimod
- Phototherapy
  - UVB (narrow band, broad band)
  - PUVA (psoralen + UVA)
- Radiation, *less is more*
  - Low-dose (12 Gy) total skin electron beam therapy
  - Combine with immune modulation
- Excimer, photodynamic therapy (not in NCCN)

New skin-directed therapies in clinical development:

- Resiquimod
- Topical HDAC inhibitor (SHP-141/SHAPE)
- New PDT (hypericin)
Topical resiquimod can induce disease regression and enhance T-cell effector functions in cutaneous T-cell lymphoma

Alain H. Rook, Joel C. Gelfand, Maria Wysocka, Andrea B. Troxel, Bernice Benoit, Christian Surber, Rosalie Elenitsas, Marie A. Buchanan, Deborah S. Leahy, Rei Watanabe, Ilan R. Kirsch, Ellen J. Kim, and Rachael A. Clark

1Department of Dermatology and the Center for Clinical Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; 2Department of Dermatology, University Hospital, Zürich, Switzerland; 3Department of Dermatology, University Hospital, Basel, Switzerland; 4Department of Dermatology, University of Tokyo, Tokyo, Japan; 5Department of Dermatology, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; 6Adaptive Biotechnologies, Seattle, WA; and 7Dana-Farber/Brigham and Women’s Cancer Center, Boston, MA

Malignant T cell eradication is a/w ↑T-cell and NK-effector functions in treated skin
Standard dose TSEBT 36 Gy

NOT CURATIVE, Retreatment limited

Why not use lower dose?
Low-dose total skin electron beam therapy as an effective modality to reduce disease burden in patients with mycosis fungoides: Results of a pooled analysis from 3 phase-II clinical trials

Richard T. Hoppe, MD,a Cameron Harrison, MD,b Mahkam Tavallae, MD, MPH,b Sameer Bashey, MD,b Uma Sundram, MD, PhD,b,c Shufeng Li, MS,b Lynn Million, MD,a Bouthaina Dabaja, MD,d Pamela Gangar, MD,e Madeleine Duvic, MD,e and Youn H. Kim, MDb
Stanford, California, and Houston, Texas

**Table II.** Best overall response to treatment at study termination, total time to response, and duration of clinical response

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>ORR n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>33 (100)</td>
<td>9 (27)</td>
<td>20 (61)</td>
<td>4 (12)</td>
<td>0</td>
<td>29 (88)</td>
</tr>
<tr>
<td>IIB</td>
<td>22 (67)</td>
<td>7</td>
<td>13</td>
<td>2</td>
<td>0</td>
<td>20 (91)</td>
</tr>
<tr>
<td>IIA</td>
<td>2 (6)</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2 (100)</td>
</tr>
<tr>
<td>IIIA</td>
<td>7 (21)</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>6 (96)</td>
</tr>
<tr>
<td>Median time to response (range)</td>
<td></td>
<td>7.6 (3-12.4) wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration of clinical benefit (95% CI)</td>
<td></td>
<td>70.7 (41.8-133.8) wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Low-dose, 12 Gy (3 wks)** vs. standard, 36 Gy (10 wks)
- **Reliable/efficient reduction** in skin disease => **near 90% ORR, ~30% CR**
- **Less side effects:** no permanent hair loss, less skin toxicity
- **Can be given repetitively** in pt’s course
- Low-dose can be followed or combined with other therapies to boost response and duration of benefit
- **Great option for folliculotropic disease or pts with multiple co-morbidities**
Clinical response with low-dose (12 Gy) TSEBT
69 yo M, stage IIB, folliculotropichc MF, multiple comorbidities

Screening
mSWAT 133
Pruritus 8/10

Wk 16
mSWAT 0 (CR)
Pruritus 0/10

Combination trials in progress to improve DOR/PFS:
Low-dose TSEBT + immune modulators (e.g., rh-IL-12, IFN-gamma, immune checkpoint blockade)
Genomic analysis of mycosis fungoides and Sézary syndrome identifies recurrent alterations in TNFR2

The mutational landscape of cutaneous T cell lymphoma and Sézary syndrome

Genomic profiling of Sézary syndrome identifies alterations of key T cell signaling and differentiation genes

Genomic landscape of cutaneous T cell lymphoma
Effects of soluble factors, immune dysregulation in MF/SS

- IL-13
- TGF-β
- IL-31

IC\_31 Cytokines:
- IL-4
- IL-13
- IL-5
- IL-10
- IgE

Th1 effects
- Eosinophilia
- Pruritus
- Cell-mediated immunity
- Th1 effects
- Dendritic cells

Tumor cell surface molecules (e.g., CD4, CD25, CD30, CD52, CCR4, CD158k/KIR3DL2)

Tumor proliferation, metabolism, survival, progression mechanisms:
- Signal transduction/transcription activation pathways (e.g., TNFR2, proteasome, AKT/PI3K/mTOR, JAK/STAT, ITK)
- 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., PD-1, PD-L1, CTLA-4, SIRPα/CD47, IDO, MDSC, Tregs)

Targets for therapy in cutaneous T-cell lymphoma
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**Microenvironment, immune mechanisms**
- PD-1, PD-L1, CTLA-4, SIRPα/CD47, IDO, MDSC, Tregs

**Brentuximab vedotin**
**Mogamulizumab**
**Denileukin diftitox/E7777**
**Alemtuzumab**
**Anti-KIR3DL2 mab**

**CD8+ TILs**
Targets for therapy in cutaneous T-cell lymphoma

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Microenvironment, immune mechanisms (e.g., PD-1, PD-L1, CTLA-4, SIRPα/CD47, IDO, MDSC, Tregs)

Anti-PD-1/PD-L1 mAbs
Anti-CTLA-4 mAbs
Anti-CD47 mAb/SIRPα Fc decoy, anti-SIRPα mAb
IDO inhibitor
Treg depleting agents

CD8+ TILs
Tumor cell surface molecules (e.g., CD4, CD25, CD30, CD52, CCR4, CD158 k/KIR3DL2)

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- Signal transduction/transcription activation pathways (e.g., TNFR2, proteasome, AKT/PI3K/mTOR, JAK/STAT, ITK)
- Apoptotic pathways (e.g., Bcl/Bax, TNFR, Fas, miRNAs)
- Epigenetics (e.g., histone, non-histone proteins)
- Metabolic/survival pathways (e.g., RFC-1, PARP)

Targets for therapy in cutaneous T-cell lymphoma

Bortezomib, carfilzomib, Duvelisib, idelalisib, Sirolimus, everolimus, Jak inhibitors, Syk-Jak dual inhibitor, ITK inhibitor, Anti-apoptotic agents, Anti-miR-155, HDAC inhibitors, Demethylating agents, Anti-folates (pralatrexate)

Microenvironment, immune mechanisms (e.g., PD-1, PD-L1, CTLA-4, SIRPα/CD47, IDO, MDSC, Tregs)
# 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 diftitox (Fusion</td>
<td>Tumors that express CD25</td>
<td>1999,</td>
<td>Pivotal</td>
<td>71</td>
<td>30%</td>
<td>4 mo</td>
</tr>
<tr>
<td>protein)</td>
<td></td>
<td>2008</td>
<td></td>
<td></td>
<td></td>
<td></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>Cutaneous manifestations</td>
<td>2006</td>
<td>Pivotal</td>
<td>74</td>
<td>30%</td>
<td>6+ mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Supportive</td>
<td>33</td>
<td>24%</td>
<td>4 mo</td>
</tr>
</tbody>
</table>

**Need better therapies, more options:**

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

**Both phase 3 RCT**

(superior DOR/PFS or impressive ORR)
Phase II Multi-Institutional Trial of the Histone Deacetylase Inhibitor Romidepsin As Monotherapy for Patients With Cutaneous T-Cell Lymphoma


J Clin Oncol 2009;27:5410

Romidepsin administration
14 mg/m² IV D1, 8, 15 of 28d cycle

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 Yoon H. Kim

J Clin Oncol 2010;28:4485

<table>
<thead>
<tr>
<th>Pivotal study</th>
<th>NCI study</th>
</tr>
</thead>
<tbody>
<tr>
<td>As-treated N = 96</td>
<td>Evaluable N = 72</td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>33 (34%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>[25, 45]</td>
</tr>
<tr>
<td>CCR, n (%)</td>
<td>6 (6%)</td>
</tr>
</tbody>
</table>

Table 2. Disease Response (All Patients N = 96)

<table>
<thead>
<tr>
<th>Response</th>
<th>No.</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR + PR)</td>
<td>33</td>
<td>34</td>
<td>25 to 45</td>
</tr>
<tr>
<td>CR</td>
<td>6</td>
<td>6</td>
<td>2 to 13</td>
</tr>
<tr>
<td>PR</td>
<td>27</td>
<td>28</td>
<td>19 to 38</td>
</tr>
<tr>
<td>SD</td>
<td>45</td>
<td>47</td>
<td>37 to 57</td>
</tr>
<tr>
<td>PD</td>
<td>10</td>
<td>10</td>
<td>5 to 18</td>
</tr>
<tr>
<td>Stage IIA (n = 28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>7</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Stage IIB (n = 21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>9</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>2</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Stage IIIA (n = 23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>9</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Stage IVA (n = 24)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>8</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Stage IIA to IVA (n = 68)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>26</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

When patients with blood involvement (n = 37)

<table>
<thead>
<tr>
<th>ORR in patients with blood involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
</tr>
<tr>
<td>12</td>
</tr>
</tbody>
</table>

Duration of response (OR; n = 33), months:
- Median: 15.0
- Range: 0.0-19.8+

TTR (OR; n = 33), months:
- Median: 2.0
- Range: 0.9-4.8

TTR (CR; n = 6), months:
- Median: 4
- Range: 0.9-6.9

TTP (n = 33), months:
- Median: 8
- Range: 0-21.7+

Rapid and sustained blood Sez cell response
39 F, subcutaneous panniculitis-like TCL with HPS
Rapid improvement with romidepsin therapy

Pre-treatment

After 2 cycles

Bashey, Kim, J Clin Oncol 2012; 30:e221-5
Improvement demonstrated by PET/CT

Pre-romidepsin

After 2 cycles

J Clin Oncol 2012; 30:e221-5
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:**
- Cell membrane
- RFC-1
- Folate
- DHF
- THF
- DHFR
- dUMP
- dTMP
- DNA
- Extracellular
- Cytosol
- PRPP
- AMP
- GMP
- RNA
- DNA
- IMP
- AICARFT
- GARFT
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 ≥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, estimate rate at 6 mo</td>
<td>73%</td>
</tr>
<tr>
<td>Median PFS not reached; estimate rate at 6 mo</td>
<td>70%</td>
</tr>
</tbody>
</table>

<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>
</tbody>
</table>

No great data that combinations is more meaningful over single agent PDX in CTCL patients:

PDX + bex (Duvic et al ASH 2015)
- MTD = PDX 15 mg/m² + bex 150 mg/m²
- ORR 60%, 4 CR, 14 PR
- DOR estimate at 6 mo 67%
- Median PFS = 12.8 mo

↑toxicity related terminations
Genomic analysis of mycosis fungoides and Sézary syndrome identifies recurrent alterations in TNFR2

Alexander Ungewickell¹,²,¹², Aparna Bhaduri¹,¹², Eon Rios¹, Jason Reuter³, Carolyn S Lee¹, Angela Mah¹, Ashley Zehnder¹, Robert Ohgami⁴, Shashikant Kulkarni⁵–⁷, Randall Armstrong⁸, Wen-Kai Weng⁸, Dita Gratzinger⁴, Mahkam Tavallaee⁹, Alain Rook¹⁰, Michael Snyder³, Youn Kim⁹ & Paul A Khavari¹,¹¹

T-cell activation, survival, proliferation
Duvelisib (IPI-145), a Phosphoinositide-3-Kinase-δ,γ Inhibitor, Shows Activity in Patients with Relapsed/Refractory T-Cell Lymphoma

Steven Horwitz¹; Pierluigi Porcu²; Ian Flinn³; Brad Kahl⁴; Howard Stern⁵; Mark Douglas⁵; Kerstin Allen⁵; Patrick Kelly⁵; and Francine Foss⁶

¹Memorial Sloan Kettering Cancer Center, New York, NY, USA; ²The Ohio State University; ³Sarah Cannon Research Institute, Nashville, TN, USA; ⁴University of Wisconsin, Madison, WI, USA; ⁵Infinity Pharmaceuticals, Inc., Cambridge, MA, USA; ⁶Yale University Cancer Center, New Haven, CT, USA.
## Clinical Activity in TCL

<table>
<thead>
<tr>
<th>Population</th>
<th>Best Response, n (%)</th>
<th>Median Time to Response, months (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>CR</td>
</tr>
<tr>
<td>All TCL</td>
<td>33</td>
<td>2 (6)</td>
</tr>
<tr>
<td>PTCL</td>
<td>15</td>
<td>2 (13)</td>
</tr>
<tr>
<td>CTCL</td>
<td>18</td>
<td>0</td>
</tr>
</tbody>
</table>

Includes evaluable patients = at least 1 on-treatment response assessment or PD without assessment
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
ORR = CR + PR

- Clinical trials with duvelisib combination strategies in CTCL
  - CTCL: PRs in 4 MF, 1 Sézary syndrome, and 1 MF-LCT

*Horwitz et al, ASH 2014*
Tumor cell surface molecules (e.g., CD4, CD25, CD30, CD52, **CCR4**, CD158k/KIR3DL2)

**Tumor proliferation, metabolism, survival, progression mechanisms:**
- Signal transduction/transcription activation pathways (e.g., TNFR2, 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., RFC1, PARP)

**Microenvironment, immune mechanisms** (e.g., PD-1, PD-L1, CTLA-4, SIRPα/CD47, IDO, MDSC, Tregs)

**Targets for therapy in cutaneous T-cell lymphoma**

**CCR4, an attractive target:**
- CCR4 is expressed in malignant T cells and T_{regs}
  ⇒ Tumor-directed and possible added immune modulatory effects

**Anti-CCR4 mAb selectivity depletes effector-type FoxP3^+CD4^+ regulatory T cells, evoking antitumor immune responses in humans**


*Experimental Immunology, World Premier International Research Center, Immunology Frontier Research Center, Department of Dermatology, and Department of Hematology and Oncology, Graduate School of Medicine, Osaka University, Osaka 565-0871, Japan; ‡Department of Anatomic Pathology, Tokyo Medical University, Tokyo 160-8402, Japan; §The Third Section of Clinical Investigation, Kinki Blood Center, Osaka 536-8505, Japan; and †Department of Hematology and Oncology, Krankenhaus Nordwest, Frankfurt 60488, Germany*
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, Yoshi 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

Multicenter Phase II Study of Mogamulizumab (KW-0761), a Defucosylated Anti-CC Chemokine Receptor 4 Antibody, in Patients With Relapsed Peripheral T-Cell Lymphoma and Cutaneous T-Cell Lymphoma

Michinori Ogura, Takashi Ishida, Kiyohiko Hatake, Masafumi Taniwaki, Kiyoshi Ando, Kensei Tobinai, Katsuya Fujimoto, Kazuhito Yamamoto, Toshihiro Miyamoto, Naokuni Uike, Mitsune Tanimoto, Kunihiro Tsukasaki, Kenichi Ishizawa, Junji Suzumiya, Hiroshi Inagaki, Kazuo Tamura, Shiro Akinaga, Masao Tonomaga, and Ryuzo Ueda

Approved in Japan 2012 for pts with ATL and in 2014 for CTCL and PTCL
Phase 1/2 study of mogamulizumab, a defucosylated anti-CCR4 antibody, in previously treated patients with cutaneous T-cell lymphoma

Madeleine Duvic,1 Lauren C. Pinter-Brown,2 Francine M. Foss,3 Lubomir Sokol,4 Jeffrey L. Jorgensen,1 Pramoda Challagundla,1 Karen M. Dwyer,5 Xiaoping Zhang,5 Michael R. Kurman,5 Rocco Ballerini,5 Li Liu,6 and Youn H. Kim7

1MD Anderson Cancer Center, Houston, TX; 2University of California, Los Angeles, CA; 3Smilow Cancer Center at Yale New Haven Hospital, New Haven, CT; 4H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; 5Kyowa Hakko Kirin Pharma Inc, Princeton, NJ; 6ReSearch Pharmaceutical Services, Inc, Fort Washington, PA; and 7Stanford Cancer Center, Stanford, CA

Peripheral blood:
• CCR4 expression on malignant T cell = 21-100%
• CCR4 expression on Tregs = 59-100% (mean 88%)
• Significant reduction of CCR4+ cells after treatment
• Overall ↑ % CD8+ T cells; ↑NK cells after treatment with restoration of NK function

Lesional skin:
• ↓infiltrating CCR4+ and/or FoxP3+ T cells
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>2</td>
<td>6</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>12</td>
<td>3</td>
</tr>
<tr>
<td>TOTAL (N=38)</td>
<td>37%</td>
<td>3</td>
<td>11</td>
<td>19</td>
<td>5</td>
</tr>
</tbody>
</table>

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

CD3 vs CD4
CD3 vs CD26
CD3 vs CCR4 1G1

Lymphoma cells
Normal CD3+CD4+
CD3+CD4neg
Lymphoma cells
Response in Blood: Patient 01- Stanford Post-treatment

Lymphoma cells undetectable
Maintaining response >2 yrs

CD3

CD26

CCR4 1G1

Lymphoma cells
Normal CD3+CD4+
CD3+CD4neg

% of Max
Table 2. Nonhematologic adverse events regardless of relationship to treatment reported by >10% of patients in the safety population \((N = 42)\)

<table>
<thead>
<tr>
<th>Preferred term*</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (26.2)</td>
</tr>
<tr>
<td>Chills</td>
<td>10 (23.8)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>9 (21.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (21.4)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 (19.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (16.7)</td>
</tr>
<tr>
<td>Cutaneous drug eruption</td>
<td>6 (14.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (7.1)</td>
</tr>
</tbody>
</table>
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 (vs. vorinostat) in CTCL completed enrollment**  
**First CTCL trial to use PFS as primary endpoint for approval**
Targets for therapy in cutaneous T-cell lymphoma

- **Tumor cell surface molecules**
  - (e.g., CD4, CD25, **CD30**, CD52, CCR4, CD158k/KIR3DL2)

- **Tumor proliferation, metabolism, survival, progression mechanisms**
  - Signal transduction/transcription activation pathways
    - (e.g., TNFR2, 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., PD-1, PD-L1, CTLA-4, SIRPα/CD47, IDO, MDSC, Tregs)

**CD30**, an attractive target: CD30 expression is increased in proliferative or malignant lymphocytes

=> good tumor selectivity
Phase II Investigator-Initiated Study of Brentuximab Vedotin in Mycosis Fungoides and Sézary Syndrome With Variable CD30 Expression Level: A Multi-Institution Collaborative Project


Results of a Phase II Trial of Brentuximab Vedotin for CD30⁺ Cutaneous T-Cell Lymphoma and Lymphomatoid Papulosis

Madeleine Duvic, Michael T. Tetzlaff, Pamela Gangar, Audra L. Clos, Dawen Sui, and Rakhshandra Talpur
CD30 as a target in MF/SS

- HL and sALCL with consistent expression of CD30 on tumor cells and high response rates
  - accelerated FDA-approval 8/2011
  - Similarly, good clinical activity in cutaneous CD30+ ALCL expected

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

### Patient characteristics, n=32

<table>
<thead>
<tr>
<th>Age (y), median (range)</th>
<th>62 (20-87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>19 (59)</td>
</tr>
<tr>
<td>Women</td>
<td>13 (41)</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>18 (56)</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
</tr>
<tr>
<td>IV/SS</td>
<td>10 (31)</td>
</tr>
<tr>
<td>Large cell transformation (LCT)</td>
<td></td>
</tr>
<tr>
<td>Folliculotrophic MF (FMF), n (%)</td>
<td></td>
</tr>
<tr>
<td>LCT</td>
<td>16 (50)</td>
</tr>
<tr>
<td>FMF</td>
<td>8 (25)</td>
</tr>
<tr>
<td>LCT &amp; FMF</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Prior systemic therapies, median (range)</td>
<td>3 (1-13)</td>
</tr>
<tr>
<td>CD30 baseline, % of skin infiltrate, n (%)</td>
<td></td>
</tr>
<tr>
<td>A: &lt; 10%</td>
<td>14 (43)</td>
</tr>
<tr>
<td>B: 10-50%</td>
<td>14 (43)</td>
</tr>
<tr>
<td>C: &gt;50%</td>
<td>4 (13)</td>
</tr>
</tbody>
</table>
# Global 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=18)</td>
<td>78%</td>
<td>0</td>
<td>14</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>IV/SS (n=8)*</td>
<td>50%</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total n= 30</strong>*</td>
<td>70%</td>
<td>1</td>
<td>20</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

*Unable to evaluate response in 2 patients

1.8 mg/kg every 3 wks x 8, cont only if ongoing benefit, max 16; dose-modification with Gr 2 PN

Kim et al, J Clin Oncol 2015;33:3750
Median TTR = 6.6 wk (3.0-27.0)
At 6, 12 mo, 90%, 79% are continuing responses by KM estimate

Time course in 21 patients with objective/global clinical responses

- Time to response
- Duration of response
- Last BV dose on study
- Still responding
- Progressive disease
- Another systemic therapy started
- Deceased due to other reasons

J Clin Oncol 2015;33:3750
Great clinical response to brentuximab vedotin in MF/SS

Sézary syndrome, IVA₁

MV IVA₂ LN with LCT

BV demonstrates clinical activity in all compartments
Correlation of skin/global response with skin CD$_{30\text{max}}$ by IHC

Global ORR by CD$_{30\text{max}} <5\%$ vs $\geq 5\%$, 17\% vs. 83\%, $P = .0046$

Significance of 5\% threshold confirmed in matured, pooled analysis (n=71)
Summary and Conclusions

• Brentuximab vedotin showed significant clinical activity in refractory/advanced MF/SS, majority with F-MF/LCT
  – Primary endpoint met: ORR 70% (90% CI, 53%-83%), sig greater than 35% ORR recent FDA-approved agents
  – Responses seen across all stages/compartment
  – Encouraging duration of clinical benefit

Included in the 2015 NCCN NHL practice guidelines

Phase III RCT (vs MD choice- oral bex or MTX)
completed, pending FDA submission:
Included MF and pcALCL, excluded SS
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](image)
Immunotherapy strategies in CTCL

- **Vaccine-based approaches**
  - Tumor-specific antibodies (direct effects)
  - CD25, CD30, CCR4, KIR3DL2
  - Immune-modulating agents or antibodies (indirect effects)
  - TLR-A, IMiDs, Treg, CTLA4, PD-1/PD-L1, SIRPα/CD47

- **Cytokine therapy**
  - IFNs, IL2, IL12

- **Adoptive T-cell transfer, CAR-T**
  - Allogeneic HSCT

- **In situ strategy**
  - ECP, DC-based Idiotype

- **M**

- **CTCL**

  - TILs
Targeting T-cell immune checkpoints in MF/SS

**Tumor cell-specific:**
tumor surface molecules
(e.g., CD4, CD25, CD30, CD52, CCR4, CD158k/KIR3DL2)

**Monoclonal antibodies**

**Microenvironment Immune modulation**
(e.g. PD-1, PD-L1, CTLA-4, IDO, CD40, TLRs, SIRPα/CD47, CD137, MDSC, Tregs)

- CD8+ TILs
- CTCL
Rationale for immune checkpoint blockade in MF/SS

- Systemic and local tissue immune impairment is observed
- Mounting evidence that T cell immunity is critical for meaningful antitumor response
- Tumor-infiltrating CD8+ T cells have been associated with improved survival and therapies which augment their function are effective in MF/SS
- Allogeneic HSC transplantation can result in sustained remissions suggesting immune response to tumor may be curative
- Significant expression of PD-1 and PD-L1 has been demonstrated in the skin and peripheral blood in MF/SS
- Reports of 9p24.1/PD-L2 translocation, breakpoints in PD-L1 (CD274), recurrent SNV in CD28, or CTLA4-CD28 fusion in MF/SS support a genomic basis for immune evasion
Expression of PD-1 and PD-L1 in CTCL
Mycosis fungoides & Sézary syndrome

MF skin
plaque
tumor
T-MF

Am J Dermatopathol 2012;34:126

PB Sézary cells express PD-1

Samimi, Rook, Arch Dermatol 2010;146:1382
Genomic analysis of mycosis fungoides and Sézary syndrome identifies recurrent alterations in TNFR2

Alexander Ungevickell, Aparna Bhaduri, Eon Rios, Jason Reuter, Carolyn S Lee, Angela Mah, Ashley Zehnder, Robert Oghani, Shashikant Kulkarni, Randall Armstrong, Wen-Kai Weng, Dita Gratzing, Mahkam Tavallae, Alain Rook, Michael Snyder, Youn Kim & Paul A Khavari

Nat Genetics 2015

ASL 12/2014
Abstract 291, A Lesokhin, et al.
Nivolumab in Lymphoid Malignancies

PD-L2 Translocation in a Cutaneous T-cell Lymphoma

• Patient with the translocation had a partial response of 13 weeks duration.
• Translocation of PD-L2 supports blockade of the receptor rather than the PD-L1 ligand.

Genomic landscape of cutaneous T cell lymphoma

Nat Genetics 2015
Cancer Immunotherapy Trials Network
NCI Protocol # CITN-10

A Phase 2 Study of Pembrolizumab for the Treatment of Relapsed/Refractory MF/SS

Coordinating Center: M Cheever
R Shine (project manager)
CITN, Fred Hutchinson Cancer Research Center

Principal Investigator: Y Kim, H Kohrt (Co-PI)
S Li (biostatistician), M Khodadoust, Z Rahbar, J Kim
Stanford University SOM

Investigative sites/site PI:
A Rook (U Penn), F Foss (Yale), PG Porcu (OSU), A Shustov (SCCA),
A Moskowitz (MSKCC), L Sokol (Moffitt), S Shanbhag (Johns Hopkins)

NCI Collaboration: Elad Sharon
Special considerations for immunotherapeutics

- **Treatment beyond initial PD** in recognition of immune mediated flare reaction, at investigator’s discretion
  - Clinically “stable” vs “unstable”
  - If true PD is confirmed by subsequent mSWAT (each cycle) or scheduled global response assessment (q 12 wks/4 cycles), then go off study; hard stop is 25% worse in any compartment beyond initial PD data
  - **Biopsy** is recommended to help distinguish pseudoprogression vs true progression, and to characterize immune/TCR profile (TCR CDR3 high throughput sequencing)
Planned biomarker and correlative studies

CITN (Fred-Hutch CC), Merck, Stanford

- Chromogenic (single-color) IHC for PD-L1
  - PD-L1 as potential biomarker of response

- Multiparametric (two-color) IHC
  - Characterize spatial association of PD-1+ TILs and PD-L1+ cells

- Multiplexed ion beam imaging (MIBI)
  - Enhanced visualization/mapping of protein expression using metal-conjugated Abs

- Transcriptional and NGS analysis
  - Nanostring platform use to profile mRNA expression
  - Correlation of mutational burden

- Immunophenotyping and T cell function assays
  - CyTOF and multiparametric flow cytometry

- Cytokine/chemokine analysis (ELISA)
### Patient characteristics, n=24

<table>
<thead>
<tr>
<th>Age (y), median (range)</th>
<th>67 (44-85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (75)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>1 (4)</td>
</tr>
<tr>
<td>IIB</td>
<td>2 (8)</td>
</tr>
<tr>
<td>IIIA</td>
<td>3 (13)</td>
</tr>
<tr>
<td>IIIB</td>
<td>3 (13)</td>
</tr>
<tr>
<td>IVA</td>
<td>15 (62)</td>
</tr>
<tr>
<td>MF, n (%)</td>
<td>9 (38)</td>
</tr>
<tr>
<td>Sézary syndrome, n (%)</td>
<td>15 (62)</td>
</tr>
<tr>
<td>Large cell transformation (LCT)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Prior systemic therapies, median (range)</td>
<td>4 (1-10)</td>
</tr>
</tbody>
</table>
### Global response (skin+LN+blood), n=24

<table>
<thead>
<tr>
<th>Stage</th>
<th>Response Rate</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB (n=1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>IIB (n=2)</td>
<td>100%</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIIA (n=3)</td>
<td>33%</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>IIIIB (n=3)</td>
<td>33%</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>IVA (n=15)</td>
<td>27%</td>
<td>4</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>MF (n=9)</td>
<td>44%</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>SS (n=15)</td>
<td>20%</td>
<td>4*</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>LCT (n=3)</td>
<td>33%</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total n= 24</strong></td>
<td><strong>33%</strong></td>
<td><strong>8</strong></td>
<td><strong>10</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>

*1 (stage IVA2) of 4 possible CR
**4 SDs continuing on treatment
Activity of pembrolizumab in skin (mSWAT %change) and global response

Global response (TNMB)
- Progressive disease
- Stable disease
- Partial response

Median best mSWAT reduction 16.0% (99.8% to -198.5%)
2 pts with near CR in skin
8/24 objective responses, median TTR = 11 wks (8-22)
## Drug-related adverse events, ≥ 2 occurrence

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All grades</th>
<th>Grade 1/2</th>
<th>Grade 3/4 (Severe AE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Skin eruption</td>
<td>5</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>WBC decreased</td>
<td>2</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>LFT (AST/ALT) elevated</td>
<td>2</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Face edema</td>
<td>2</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

* Exfoliative dermatitis (n=2), immune-mediated skin flare (n=2), excessive peeling/edema (n=1)
Anti-PD-1 mab, pembrolizumab, in MF/SS

Summary

• Objective clinical responses observed in 8/24 (33%)
  – MF (IIB/III, 4/9, 44%) and SS (IVA, 4/15, 20%)
  – Range of prior therapies, responses in heavily treated pts (3 of 8 responders with 6-7 prior systemic txs)

• Well-tolerated and toxicity was manageable
  – Skin reactions as most common AE, probably due to flare reaction

• Biomarker/biology/molecular data pending, to better understand tumor/immune escape mechanisms
  – Guide enrichment of response subset

Combination immune strategies to improve ORR and DOR/PFS, being developed

Anti-PD-1 mAb + IFN-gamma
+/- low-dose TSEBT
New targets/novel approaches for immune modulation in CTCL

Tumor cell-specific:
tumor surface molecules
(e.g., CD4, CD25, CD30, CD52, CCR4, CD158k/KIR3DL2)

Monoclonal antibodies

Microenvironment
Immune modulation
(e.g. PD-1/PD-L1, CTLA-4, IDO, CD40, TLRs, SIRPα/CD47, CD137, MDSC, Tregs)

CD158k/KIR3DL2
Consistently expressed in MF/LCT and Sézary syndrome

IPH4102 MOA by ADCC and ADCP

CTCL

CD8+ TILs

M
KIR3DL2 expression in Sézary cells

Correlation between KIR3DL2 and TCR-Vβ expression in flow cytometry on blood CTCL cells in Sézary syndrome patients (n = 32)

Spearman r = 0.6609
p < 0.0001

IPH4102 First-In-Human dose-escalation study in EU/US Q4 2015

Marie-Cardine et al, Cancer Res. 2014
New targets/novel approaches for immune modulation in CTCL

Tumor cell-specific: tumor surface molecules (e.g., CD4, CD25, CD30, CD52, CCR4, CD158k/KIR3DL2)

Monoclonal antibodies

Microenvironment Immune modulation (e.g. PD-1/PD-L1, CTLA-4, IDO, CD40, TLRs, SIRPα/CD47, CD137, MDSC, Tregs)

SIRPα/CD47 axis “Don’t eat me” signal by tumor cells
Evasion of macrophage phagocytosis

Weissman group, Stanford
Targeting CD47–SIRPα axis in cancer immunotherapy: converting “don’t eat me” \(\rightarrow\) “eat me” signal and more

A First-In-Human Phase Dose Escalation Trial of Hu5F9-G4 in Advanced Solid Malignancies: Stanford platform CTCL (MF/SS) expansion cohort
New agents and improved therapeutic strategies in CTCL

- **New/improved technology** allowing us to learn more, help identify actionable targets, and modify/render agents more effective/safe
- **More encouraging treatment options** (more in the pipeline)
- **Use old therapies smarter** (e.g., low-dose TSEBT+ immunotherapy)
- **Improved/more tumor-selective** therapies, less toxicity
- Learning to **partner with immune/microenvironment modulators**
- **Can cure advanced stage MF/SS** with allogeneic HSCT
- **Molecular/biomarker platforms integrated into clinical trials** to learn predictive value for response/resistance/escape, toxicity, or survival outcomes
- Taking steps **towards personalized, precision medicine**