New and emerging treatment strategies for mycosis fungoides & Sézary syndrome (MF/SS)

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S006 Updates in Cutaneous Oncology

DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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DISCLOSURES
Research/Grants: Eli Lilly, Soligenix, Helsinn, Eisai, Boehringer Ingelheim, Novartis, AbbVie, BMS, Celgene, Glenmark, Kyowa Kirin, Amgen, AnaptysBio, Innate Pharma
Advisory boards: Novartis, Boehringer Ingelheim, Helsinn, Kyowa Kirin, Regeneron
Consultant: OncoDerm LLC, Aptis Partners
Speaker: Helsinn, Kyowa Kirin
Background

The most common CTCLs are mycosis fungoides (MF) and Sézary syndrome (SS), which account for ~70% of all primary CTCLs.

Treatment of MF and SS remains a clinical challenge and there is no cure. Current clinical response to therapies are heterogenous and may reflect the molecular heterogeneity of MF/SS.

Identification of clinically relevant molecular targets is needed to help prioritize treatment selections and improve patient outcomes.

Molecular Targets for Therapy of CTCL

FDA-approved drugs

- Denileukin Diftitox
- Mogamulizumab
- Brentuximab vedotin
- Oncotarget
- CAR T-cell
- Pembrolizumab
- LMB-2
- Sipiluzumab
- Lacutamab
- CD2
- CD25
- CD158K (KIR3DL2)
- CCR4
- CD4
- CD30
- JAK/STAT
- CD52
- PI3K
- CD47
- MTX
- RFC1
- DHFR
- HDAC
- JAK/STAT
- RAR
- ATRA
- Etretinate
- RXR
- TLR7/8
- Resiquimod
- Vorinostat/Romidepsin
- Remetinostat
New and upcoming therapies for CTCL

**Antibodies**
1. Brentuximab vedotin [CD30]
2. Mogamulizumab [CCR4]
3. Alemtuzumab [CD52]
4. Pembrolizumab [PD-1]
5. Lacutamab [KIR3DL2 (CD158k)]
6. Ontorpacept or TTI-621 [CD47]

**Small molecules**
1. Duvelisib [PI3K]
2. Cobomarsen (MRG-106) [miR155]

**Immune-based therapies**
1. CAR-T-cell [CD4,CCR4, CD30]
2. BNZ-1 [γc IL-2, IL-15]

**Skin-directed therapies**
1. Topical SGX301 (synthetic hypericin) and fluorescent bulb-light irradiation
2. Remetinostat [HDAC]
3. Resiquimod [TLR7/8]

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**Brentuximab Vedotin (BV)**

- CD30 mediates signal transduction after interaction with TRAF2 and TRAF5, leading to NF-Kappa B activation.
- BV is an anti-CD30 antibody–drug conjugate that combines CD30 mAb with the microtubule inhibitor monomethylauristatin E (MMAE).

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Intervention Study design</th>
<th>n</th>
<th>Subtype</th>
<th>ORR4 (%)</th>
<th>CR (%)</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCA NZA</td>
<td>BV vs. physician's choice Phase III</td>
<td>64 vs. 64</td>
<td>CTCL BV: MF 48, pcALCL 18 PC: MF 49, pcALCL 17</td>
<td>56.3 vs. 12.5</td>
<td>16 vs. 2</td>
<td>PFS: 16.7 vs. 3.5 month</td>
<td>NR</td>
</tr>
</tbody>
</table>

References:
**Brentuximab vedotin (BV)**

**Dosing:**
- 1.8mg/kg IV q3 weeks (MAX: 180 mg/dose)

**Safety:**
- Peripheral neuropathy in ~ 67% of patients
- Anemia in ~ 62%
- Neutropenia in ~ 21%, thrombocytopenia in 15%
- GI disorders in 17-36%
- Fatigue 10%
- Warning: Progressive multifocal leukoencephalopathy has been reported with BV

**Laboratory monitoring:**
- CBC, CMP prior to each dose

**Notes:**
- Females with reproductive potential and males with female sexual partners of reproductive potential to use contraception during treatment and for at least 6 months after the final dose
- In a recent real-life retrospective study, BV appeared to be an effective therapy independently from CD30 positivity, LCT, SS and previous treatments.

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**Mogamulizumab**

- CCR4 is expressed on skin-homing malignant T-cells in MF/SS and in a subset of Th2 and T-reg cells.
- Mogamulizumab is a humanized IgG1 monoclonal antibody that selectively binds to CCR4 which triggers the recruit effector cells and their release of cytotoxic mediators that kill the malignant T-cell.

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</tr>
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<tbody>
<tr>
<td>MAV ORIC Moga vs. vorinostat Phase III</td>
<td>3</td>
<td>NF 204, SS 168</td>
<td>28 (21 MF, 37 SS) vs 5 NR</td>
<td>7.7 vs. 3.1 month</td>
<td>Median OS not reached</td>
<td></td>
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</table>

Mogamulizumab

Dosing:
- 1mg/kg IV weekly for the first 5 infusions then Q2 weeks

Safety:
- Infusion reaction ~ 30%
- Rash 24 - 63%
- Infections (URI ~ 22%, skin ~ 19%)
- GI disorders 12-28%
- Pyrexia 17%
- Lymphopenia 31%
- Hypoalbuminemia ~34%
- Other: abnl calcium, uric acid, magnesium, phosphate

Laboratory monitoring:
- CBC, CMP, Ca, Mg, uric acid

Notes:
- Females of reproductive potential and males with female sexual partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the final dose
- Consider premedication (such as diphenhydramine and acetaminophen) for the first infusion

Mogamulizumab - rash

- Onset: median 110 days, after 5 cycles
- Most patients had CR/PR in skin and CR in blood at the time of new rash onset
- Clinical presentations can mimic CTCL and include morbilliform eruption, papules/plaques, photodistributed eruption, and folliculotrop-like scalp plaques with alopecia
- Localized or widespread, most common location scalp> trunk> arms> legs
- Associated with pruritus

Management:
1. Depends on severity of drug-rash, consider:
   - Topical steroids
   - Phototherapy
   - 4-week systemic steroid taper
   - ECP
   - MTX
2. Consider holding for one cycle and resuming when grade of rash decreases or resolves

References:
Alemtuzumab

- CD52 can be expressed on more than 95% of peripheral blood lymphocytes, monocytes, and macrophages and cells from B- and T- malignancies.
- Alemtuzumab is a humanized IgG1 anti-CD52 monoclonal antibody targeting CD52, a glycosylphosphatidylinositol-anchored glycoprotein.

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<th>PFS</th>
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</tr>
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<tbody>
<tr>
<td>Lundin et al.</td>
<td>Alemtuzumab</td>
<td>Phase II, single arm</td>
<td>22</td>
<td>CD52 + MF/SS</td>
<td>Relapsed/Refractory</td>
<td>55</td>
<td>32</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Querfeld et al.</td>
<td>Alemtuzumab</td>
<td>Phase II, single arm</td>
<td>19</td>
<td>Erythrodermic MF 2, SS 17</td>
<td>Relapsed/Refractory</td>
<td>84</td>
<td>47</td>
<td>6 months</td>
<td>41 months</td>
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</table>

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Alemtuzumab

Dosing:
- Loading dose (3mg on day1, 10mg day 3, and 30mg day 5), then 30 mg IV 3x/week

Safety:
- Infusion-related reactions
- Neutropenia (3 deaths) ~ 18%
- Infections ~ 50% [26 – 62%] (CMV reactivation 18%)

Laboratory monitoring:
- CBC, CMP

Notes:
- May induce long-term remission in SS but seems ineffective in MF and transformed CTCL

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The genes for the programmed cell death protein 1 (PD-1) and its ligands PD-L1 and PD-L2 are frequently altered in advanced MF/SS. Pembrolizumab is a monoclonal antibody that blocks PD-1, which is a cell surface receptor expressed in malignant T-cells in patients with MF/SS.

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<tbody>
<tr>
<td>Khodadoust et al.</td>
<td>Pembrolizumab</td>
<td>Phase II, single arm</td>
<td>24</td>
<td>MF 9, SS 15</td>
<td>Relapsed/Refractory 38 (44 MF, 33 SS)</td>
<td>8.3 (all SS)</td>
<td>65% at 1-year</td>
<td>95% at 1-year</td>
<td></td>
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Lacutamab

- KIR3DL2 (CD158k) is a member of the family of killer-cell immunoglobulin-like receptors that binds to HLA-class I ligands and negatively modulates immune cell functions.
- It is expressed in malignant T-cells in CTCL patients, and in >85% of SS patients.
- Lacutamab is a humanized monoclonal antibody that depletes KIR3DL2-expressing cells via antibody-dependent cell cytotoxicity and phagocytosis.

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<th>PFS</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Bagot et al.</td>
<td>Lacutamab</td>
<td>Phase I, first-in-human</td>
<td>44</td>
<td>MF 8 (5 LCT), SS 35, CTCL NOS 1</td>
<td>Relapsed/Refractory</td>
<td>36 (43 SS)</td>
<td>NR(6 SS)</td>
<td>8.2 months (3.9 MF/13.8 SS)</td>
<td>NR</td>
</tr>
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Dosing:
- 750 mg IV Q1wk for the first month, Q2wks x 10 administrations, and then Q4wks until disease progression or unacceptable toxicity.

Safety:
- Peripheral edema 27%
- Fatigue 20%
- Lymphopenia 14%
- Infusion reactions 7%
- Other: abnl liver function test, hypotension, sepsis, peripheral neuropathy

Laboratory monitoring:
- CBC, CMP
Ontorpacept (TTI-621)

- CD47 is a transmembrane protein overexpressed in hematological malignancies that helps them to escape immune surveillance. It binds SIRPα on myeloid cells, generating a “don’t eat me” signal that suppresses phagocytosis.
- Ontorpacept is a fusion protein consisting of the CD47-binding domain of human signal regulatory protein alpha (SIRPα) and the Fc region of human IgG1, that binds to CD47 and blocks its interaction with SIRPα, promoting phagocytosis.

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<th>CR (%)</th>
<th>PFS</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Ansell et al.</td>
<td>TTI-621 IV</td>
<td>Phase I, open-label</td>
<td>29</td>
<td>24 MF, 5 SS</td>
<td>Relapsed/Refractory</td>
<td>21</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Querfeld et al.</td>
<td>TTI-621 intralesional</td>
<td>Phase I, open-label, ongoing</td>
<td>22</td>
<td>18 MF, 3 MF with LCT, 1 SS</td>
<td>Relapsed/Refractory</td>
<td><strong>88% improvement on CAILS score</strong></td>
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Ontorpacept (TTI-621)

**Dosing:**
- 0.2mg/kg IV weekly

**Safety (in all hematological malignancies):**
- Infusion reaction 43%
- Thrombocytopenia 26%, anemia 13%, neutropenia 9%
- Chills 18%, fatigue 15%, pyrexia 10%
- Nausea 12%, diarrhea 10%, vomiting 9%
- Headache 8%
- Hypotension 5%

**Laboratory monitoring:**
- CBC, CMP

**Notes:**
- Use prophylactic acetaminophen and diphenhydramine to prevent infusion-related reactions
Duvelisib

- The PI3K-δ and PI3K-γ isoforms are preferentially expressed in leukocytes, and modulate innate and adaptive immune function, as well as suppress antitumor immune responses.
- PI3K-δ/γ inhibition may directly inhibit malignant T-cell growth, activate antitumor immune responses, and affect M1 macrophage polarization in the tumor microenvironment.
- Duvelisib is an oral inhibitor of phosphatidylinositol 3-kinase (PI3K)–δ/γ isoforms.

## Clinical Trial Intervention Study Design n Subtype Inclusion criteria ORR (%) CR (%) PFS OS

| Horwitz et al. | Duvelisib | Phase I, open-label | 19 | MF/S | MF 9, MF with LCT 4, SS 5, pcALCL 1 | Relapsed/Refractory PTCL or CTCL | 31.6 | 0 | 4.5 months | Median OS not reached |

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**Dosing:**
- 75 mg PO BID

**Safety (PTCL and CTCL):**
- Increase in AST/ALT 34%
- Infections 29%
- Rash 3%
- Diarrhea 3%
- Pyrexia 3%
- Other: decreased lymphocytes, decreased neutrophils

**Laboratory monitoring:**
- CBC, CMP

**Notes:**
- PCP prophylaxis is needed
- *Moderate and strong inhibitors or inducers of cytochrome P450 (CYP)3A should be avoided*

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Cobomarsen (MRG 106)

- The microRNA miR-155 regulates immune cell function and is overexpressed in numerous hematological malignancies, particularly CTCL.
- miR-155 simultaneously regulates multiple parallel survival pathways (including JAK/STAT, MAPK/ERK and PI3K/AKT) previously associated with the pathogenesis of MF.
- Cobomarsen (MRG-106) is an oligonucleotide inhibitor of miR-155.

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<th>CR (%)</th>
<th>PFS</th>
<th>OS</th>
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<tbody>
<tr>
<td>Foss et al.</td>
<td>Cobomarsen IL (75mg/dose), SC or IV</td>
<td>Phase I, open-label</td>
<td>36</td>
<td>MF/SS</td>
<td>Relapsed/Refractory CTCL</td>
<td>In the SC/IV cohorts, 26/29 evaluable subjects had improvement in mSWAT score</td>
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</table>

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Cobomarsen (MRG 106)

**Dosing:**
- Depending on administration route

**Safety (CTCL):**
- Fatigue, neutropenia, injection site pain, nausea, pruritus, and headache

**Laboratory monitoring:**
- CBC, CMP

**Notes:**
- A phase II study comparing cobomarsen vs vorinostat in subjects with MF was terminated early (Dec 2020) for business reasons.

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BNZ-1

- IL-2 and IL-15 inhibition block cytokine-driven propagation/survival of tumor cells and IL-2 and IL-9 inhibition decrease regulatory T-cells activity that may impede the anti-lymphoma immune response.
- BNZ-1 is a pegylated peptide, multi-cytokine inhibitor that selectively inhibits IL-2 and IL-15, and to a lesser degree, IL-9 signaling through the γc receptor, inactivating downstream targets (eg., STAT1/3/5, ERK and Akt pathways), thus, modulating immune responses in CTCL.

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<th>PFS</th>
<th>OS</th>
</tr>
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<tbody>
<tr>
<td>Querfeld et al.</td>
<td>BNZ-1 IV (0.5 mg/kg, 1mg/kg, 2 mg/kg, and 4 mg/kg)</td>
<td>Phase I/II, open-label</td>
<td>19</td>
<td>MF/SS</td>
<td>Relapsed/Refractory CTCL</td>
<td>63</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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Querfeld C, et al. Co-Inhibition of IL-2, IL-9 and IL-15 By the Novel Immunomodulator, BNZ-1, Provides Clinical Efficacy in Patients with Refractory Cutaneous T Cell Lymphoma in a Phase 1/2 Clinical Trial. 43. ASH Dec. 2020.

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CAR-T-cell

- Chimeric Antigen Receptor (CAR) T-cell therapy is a type of immunotherapy approach called adoptive cell transfer, which collects and uses patients own immune cells to treat their cancer.
- CARs are fusion proteins consisting of an antigen-recognition domain (which is an antibody-derived ScFv) and T-cell intracellular signaling domains.

Patient T-cells are collected → CAR is designed *ex vivo* → T-cells are transduced with an expression vector containing a gene encoding the CAR protein → CAR T-cells are grown in culture → Patient receives CAR-T infusion
CAR-T-cell

- CAR-T therapies for cutaneous cancers and autoimmune diseases (e.g., pemphigus vulgaris) are in preclinical testing.
- For CTCL, it remains a challenge to identify targets uniquely expressed on malignant but not on normal T-cells.
- On going clinical trials have targeted molecules expressed by a subpopulation of T-cells, or which are downregulated when T-cells are activated, including CD4, CD5, CD7, CD30, CD37, CCR4, and the 2 alleles of the T cell receptor beta chains (TRBC1/TRBC2)

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Zeng E, et al. Preclinical analysis of an autologous CD4-targeted chimeric antigen receptor T-cell (CAR-T) immunotherapy for relapsed or refractory peripheral T-cell lymphoma (PTCL) or cutaneous T-cell lymphoma (CTCL). Journal of Clinical Oncology 2021 39:15_suppl, e14510-e14510

Topical SGX301 (synthetic hypericin) and fluorescent bulb-light irradiation

- SGX301, synthetic hypericin, tends to accumulate in T-cells.
- Once in the T-cell it is activated by visible light (500-650 nm).
- When activated it creates oxygen radicals which subsequently cause cellular toxicity, killing the targeted T-cells.
- It has been previously tested as treatment for psoriasis.

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Topical SGX301 (synthetic hypericin) and fluorescent bulb-light irradiation

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<tr>
<th>Clinical Trial</th>
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<th>Treatment responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rook et al.</td>
<td>Lesions were treated biweekly for 6 weeks with hypericin or placebo followed 24 hours later by exposure to visible light at 8 to 20 J/cm²</td>
<td>Phase II</td>
<td>12</td>
<td>MF (IA, IB, IIA)</td>
<td>58.3%</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Cycle 1 - same as in the phase II study. In cycle 2, all subjects received treatment. In cycle 3, all lesions were treated.</td>
<td>Phase III, placebo-controlled</td>
<td>169</td>
<td>MF (IA, IB, IIA)</td>
<td>After cycle 1, ORR: 16% vs 4% In cycle 2 &amp; 3, all patients received SGX301, ORR: 40% &amp; 49%</td>
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Remetinostat, a topical histone deacetylase inhibitor

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<th>Subtype</th>
<th>Treatment responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duvic et al.</td>
<td>0.5% BID, 1% daily or 1% BID</td>
<td>Phase II</td>
<td>61</td>
<td>MF</td>
<td>Interim analysis (28 patients), when 50% of the patients reached 6 months: 24-32% responded [Treatment Response if any disease response (&gt; 50%) was noted in CAILS or mSWAT] 89% had reduction in itch</td>
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</tbody>
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Resiquimod, a topical a TLR7/8 agonist

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<tbody>
<tr>
<td>Rook et al.</td>
<td>0.03% or 0.06% gel Lesions treated initially 3 times per week. Dosing frequency (1, 2, 3, 5, or 7 times per week) was adjusted in a stepwise manner every 2 weeks</td>
<td>Phase I</td>
<td>12</td>
<td>MF</td>
<td>Analysis at 24 weeks: 11 of 12 patients (92%) experienced significant improvement by the end of the treatment period. Resiquimod therapy was associated with migration of CD8 T cells into treated skin lesions and decrease of lesional malignant cells</td>
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Summary

**CTCL is an incurable cancer with limited treatment options.**

Brentuximab vedotin (BV) and mogamulizumab are new FDA-approved antibodies for the treatment of CTCL and ORRs ~20-50%. Peripheral neuropathy is the most common side effect of BV. Rash, that may mimic CTCL, is the most common side effect of mogamulizumab.

Several antibodies, small molecules, and immunotherapies that target the TCR–PLCG1, CCR4/7–MAPK, TNFR/NF-κB, PI3K/AKT, and JAK/STAT signaling pathways are under study for CTCL.

Skin-directed therapies on the horizon for MF include topical resiquimod, remetinostat and SGX301.