Cutaneous Lymphomas: Novel Immune Therapies for Cutaneous T-cell Lymphoma

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City of Hope

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How the Experts Treat Hematologic Malignancies
Las Vegas, NV
3/16/2018
Disclosures

- **Advisory Board**
  - MiRagen, Actelion, Kyowa, Mallinckrodt

- **Investigator**
  - Celgene, MiRagen, Trillium Therapeutics, Actelion, Kyowa, Soligenix, Bioniz, Esai

- **Grants**
  - Celgene
Learning Objectives

- Participants will be able to:
  - Discuss fundamental features of mycosis fungiodes
  - State treatment regiments for this disease
  - Understand expectations of risks and benefits in treatment options
### Cutaneous T cell lymphomas

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td><strong>Mycosis fungoides</strong></td>
<td>• Folliculotropic type&lt;br&gt;• Pagetoid reticulosis&lt;br&gt;• Granulomatous slack skin</td>
</tr>
<tr>
<td><strong>Sézary syndrome</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Primary cutaneous CD30+ lymphoproliferative disorders</strong></td>
<td>• Lymphomatoid papulosis (type A-E)&lt;br&gt;• Primary cutaneous anaplastic large cell lymphoma</td>
</tr>
<tr>
<td><strong>Subcutaneous panniculitis-like T cell lymphoma</strong></td>
<td></td>
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<tr>
<td><strong>Primary cutaneous γδ T cell lymphoma</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T cell lymphoma</strong></td>
<td></td>
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<td><strong>Primary cutaneous acral CD8+ T cell lymphoma</strong></td>
<td></td>
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<tr>
<td><strong>CD4+ small/medium-sized pleomorphic T-cell lymphoproliferative disorder</strong></td>
<td></td>
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<tr>
<td><strong>Primary cutaneous peripheral T cell lymphoma, NOS</strong></td>
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</tbody>
</table>
Mycosis Fungoides

- Prototype of CTCL
- Low-grade lymphoma
- Post-thymic T-cell malignancy (CD4+/CD45RO+)
- Malignancy of 3 different T-cell populations:
  - Features of **T-regulatory** (CD25+FoxP3+), **Th2**- and **Th17**-cell phenotype
- **Th2-driven** immunosuppressive properties
  - Secretion of IL-4, IL-5, IL-6, IL-10
  - Peripheral eosinophilia, elevated IgE
  - Decreased antigen-specific T-cell response
  - Impaired cell mediated cytotoxicity
- Patch, plaque, tumors and erythroderma

*Berger C et al. 2005; Dummer R et al. 1996; Krejsgaard T et al. 2010*
Mycosis Fungoides, folliculotropic type
MF/SS large cell transformation

Large cell morphology
CD30- > CD30+
Increased LDH, β2-microglobulin
Systemic symptoms
Poor prognosis
Transformation rate?
Sézary Syndrome

- Systemic and aggressive variant
- Exfoliative erythroderma
- Ectropion, alopecia, palmoplantar keratoderma
- Severe pruritus
- Circulating, atypical, malignant T-lymphocytes (Sézary cells)
**Mycosis Fungoides / Sézary Syndrome**

**Molecular Biology and Genetics**

- Expression of various skin homing ligands/receptors CLA, LFA1, CCR-4, CCR-7, CCR-10, and CXCR4
  - MF: skin resident effector-memory T-cell: **CCR7-/CCR4+**
  - SS: central memory T-cell: **CCR7+/CCR4+**
- Dysregulated/exhausted immunophenotype (**PD1, CTLA4, LAG3, TIM3**)
- Chromosomal aberrations (loss on 1p, 9p, 10q, 17p, and 19, gains on 4q, 17q, and 18)
- Diminished expression/activation of tumor suppressor genes TGF-β receptor II, FAS, p15, and p16
- Enhanced expression/activation of JUNB, **Bcl-2**, Bcl-2-related genes, STAT3, STAT5 and NF-κB,
- Microsatellite instability, promotor hypermethylation
- ↑ miRNA 155, ↓miRNA 203 & miRNA 205

Disease-specific survival according to (A) clinical stage and (B) T classification

Risk of Progression

• T-stage
• Folliculotropic MF
• Large cell transformation

• Elevated LDH
• Peripheral blood clone
• Tumor distribution

Agar NS et al., J Clin Oncol 2010
## Stage-based Treatment Algorithm for Mycosis Fungoides and Sézary Syndrome

<table>
<thead>
<tr>
<th>Stage</th>
<th>IA</th>
<th>IB/IIA</th>
<th>IIIB</th>
<th>IIIA/B</th>
<th>IVA&lt;sub&gt;1/2&lt;/sub&gt;</th>
<th>IVB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions</td>
<td>Patches/Plaques (T&lt;sub&gt;1&lt;/sub&gt;/T&lt;sub&gt;2&lt;/sub&gt;N&lt;sub&gt;0&lt;/sub&gt;-N&lt;sub&gt;1&lt;/sub&gt;M&lt;sub&gt;0&lt;/sub&gt;B&lt;sub&gt;0&lt;/sub&gt;/B&lt;sub&gt;1&lt;/sub&gt;)</td>
<td>Tumors (T&lt;sub&gt;1&lt;/sub&gt;-T&lt;sub&gt;4&lt;/sub&gt;N&lt;sub&gt;0&lt;/sub&gt;-N&lt;sub&gt;2&lt;/sub&gt;M&lt;sub&gt;0&lt;/sub&gt;B&lt;sub&gt;0&lt;/sub&gt;/B&lt;sub&gt;1&lt;/sub&gt;)</td>
<td>Erythroderma (T&lt;sub&gt;4&lt;/sub&gt;N&lt;sub&gt;0&lt;/sub&gt;-N&lt;sub&gt;2&lt;/sub&gt;M&lt;sub&gt;0&lt;/sub&gt;B&lt;sub&gt;0&lt;/sub&gt;/B&lt;sub&gt;1&lt;/sub&gt;)</td>
<td>Erythroderma or Nodal (T&lt;sub&gt;1&lt;/sub&gt;-T&lt;sub&gt;4&lt;/sub&gt;N&lt;sub&gt;0&lt;/sub&gt;-N&lt;sub&gt;2&lt;/sub&gt;M&lt;sub&gt;0&lt;/sub&gt;B&lt;sub&gt;0&lt;/sub&gt;/B&lt;sub&gt;1&lt;/sub&gt;)</td>
<td>Visceral (T&lt;sub&gt;1&lt;/sub&gt;-T&lt;sub&gt;4&lt;/sub&gt;N&lt;sub&gt;0&lt;/sub&gt;-N&lt;sub&gt;2&lt;/sub&gt;M&lt;sub&gt;1&lt;/sub&gt;B&lt;sub&gt;0&lt;/sub&gt;/B&lt;sub&gt;1&lt;/sub&gt;)</td>
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</tbody>
</table>

**Topical therapy** (intermittent):
- Topical steroids
- Topical retinoids (bexarotene gel, tazarotene gel)
- Topical nitrogen mustard

**Phototherapy** (NB-UVB, PUVA), skin-directed investigational agents:
- Phototherapy +/- IFN-α and/or +/- bexarotene
- ECP +/- IFN-α and/or +/- bexarotene
- Romidepsin, alemtuzumab

**Spot radiation**, TSEBT
- Methotrexate, bexarotene, IFN-α, brentuximab
- HDACi (romidepsin, vorinostat)

**Investigational trials**
- Single or multi-agent chemotherapy (gemcitabine, pegylated doxorubicin, CHOP/CHOP-like regimens)
- Allogeneic transplant
Langerhans cells, dendritic cells

Macrophages

Fibroblasts (collagen, proteins)

NK cells

Favoring tumor growth:
- Cytokines
- Breakdown of tissue proteins

Escape mechanisms by cancerous cells
- Change in surface receptors/adhesion molecules
- Cytokines (IL-10; TGFβ)
- PD1, CTLA4 (immune tolerance)
- Death receptor: FAS; defective apoptosis

Chronic Antigen Stimulation

Adaptive immune response

CD8+ tumor infiltrating T-cells

Th1 T-cell functions (IFNγ, IL-12)

Regulatory T-cells (CD25+FOXP3+)

Tumor microenvironment
- Immune checkpoint blockade inhibitors
- MicroRNA inhibitors
- Targeted therapies
- CAR-T-Therapy
Cutaneous T-cell lymphoma and Microenvironment

- CTCL develops from clonally expanded CD4$^+$ T cells in a background of chronic inflammation.
- Antigen presenting cells (e.g. dendritic cell subsets, macrophages) populate all cutaneous lesions and are critical tumorigenic regulators of the microenvironment.
- CD4$^+$ and CD8$^+$ T cells (malignant/non-malignant) display an exhausted/dysregulated phenotype.
- Tumor cells escape immune surveillance by manipulating immune checkpoint receptors like PD1, and activation of the PD1 receptor by PD-L1 transduces a signal that leads to the inhibition of T-cell functions.
- Mechanisms of PD-L1 regulation in CTCL is largely unknown.

Immature DC

CD1a+

Malignant T-cell

TCD4+

CD40L +

TCR +

MHC II+

Tumor specific antigens/self-peptides

CTCL cell growth, T-reg phenotype
DC activated phenotype

DC survival

IL-10

Immature DC CD1a+

CD40+

CD-40L +

DC activated phenotype

T-cell exhausted phenotype

CTLA-4 -

CD80/86-

PD-L1/L2-

MHC-II-

TIM-3 -

Galectin9-

ICOS +

ICOS-L+

T-cell exhausted phenotype
Multispectral Imaging for Immune Checkpoints: **PD1, PD-L1**

- **A:** Patch
- **B:** Plaque
- **C:** Tumor
Pembrolizumab for Treatment of Relapsed/Refractory Mycosis Fungoides and Sézary Syndrome: Clinical Efficacy in a Citn Multicenter Phase 2 Study

- 24 patients
- Median age was 67 (range 44-85); 18 were male
- 23 patients (96%) with advanced MF - stage IIB or higher
  - 15 patients (63%) with stage IVA SS
- Median follow-up time was 40 weeks (range 9-60 weeks)
- ORR was 38%, 1 CR and 8 PR
- There was no significant association between response and clinical characteristics including stage, disease type (MF vs. SS), and number of prior therapies, nor with skin tissue expression of PD-1, PD-L1, PD-L2, or infiltrating CD8+ T-cells as determined by IHC

Figure 1. Change in skin disease by mSWAT (%)
PD-L1 is Expressed on Antigen Presenting Cells

Multispectral imaging: PD-L1 and ICOS expressions correlate with advanced stage CTCL

PD-L1 correlates with advanced stage ($p=0.007$) and/or large cell transformation ($p=0.002$)

ICOS correlates with PD-L1 ($p=0.043$)

PD1 does not correlate with stage, transformation, response to regimens, or other checkpoints (data not shown)

Clinical Trial Design

Blockade of PD1/PD-L1 pathway with anti-PD-L1 (durvalumab) +/- lenalidomide
Phase I/II

- 1500 mg IV durvalumab q 4 weeks
- 10 mg lenalidomide starting dose

Phase I: durvalumab & lenalidomide: non-responder expresses high ICOS levels

Subject #1
Baseline | Cycle 2 Day 1 | H&E | PDL-1/ICOS | ICOS
---|---|---|---|---
---|---|---|---|---
Subject #2
CD47 - SIRPα Innate Immune Checkpoint Blockade for Anti-Cancer Therapy

- **CD47** is a transmembrane glycoprotein found in all human cells
- Can be overexpressed in cancer cells
  - AML, ALL, CLL, non-Hodgkin lymphoma, solid cancer
- Elevated CD47 expression has predicted poor survival in patients w/cancer
- **CD47** binds to *signal-regulatory protein (SIRPα)* - an inhibitory receptor expressed on myeloid cells (such as macrophages)
- CD47 elicits a “**don’t eat me**” signal through its effect on SIRPα
  - Inhibitory signal that prevents macrophage phagocytosis of cancer cells
- CD47 is an important mechanism in which malignant cells can escape immune-mediated clearance
- Regulates the natural clearance of erythrocytes and platelets by splenic macrophages
TTI-621: a dual function decoy receptor that blocks CD47 while engaging activating Fc receptors

CD47 binding domain of human SIRPα

Blocks the DO NOT EAT signal from CD47 but does not bind CD47+ erythrocytes

Delivers an EAT signal to macrophages through FcγRs; differentiated from IgG4 antibodies

- TTI-621 (SIRPαFc) is an immune checkpoint inhibitor consisting of SIRPα linked to an IgG1 Fc domain. It is designed to block the CD47 “do not eat” signal and deliver an activating signal through Fcγ receptors.

- TTI-621-02 (NCT02890368) is a multi center, open label, Phase 1 study for subjects with relapsed or refractory mycosis fungoides and Sézary syndrome or other percutaneously accessible solid tumors.
Intratumoral dosing trial has enrolled 16 patients

<table>
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<th>Dose Escalation</th>
<th>Cohort</th>
<th>N</th>
<th>Once Grade 2 Toxicity Occurs</th>
<th>If DLT Occurs</th>
<th>TTI-621 Dose (mg)</th>
<th>Injection Frequency</th>
<th>Total DLT Observation Interval from 1st dose (days)</th>
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<td>Expand to 6(^a)</td>
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<td>Expand to 6(^a)</td>
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<td>4</td>
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<td>M-W-F x 1 wk</td>
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<td>Expand to 3</td>
<td>Expand to 6(^a)</td>
<td>10</td>
<td>M-W-F x 2 wks</td>
<td>21</td>
</tr>
</tbody>
</table>

| Expansion       | 6      | 12 | NA                            | NA             | MTD\(^b\)        | MTD frequency     | NA                                            |
|                 | 7      | 12 | NA                            | NA             | MTD\(^c\)        | MTD frequency     | NA                                            |

a May include subject(s) previously added due to Grade 2 toxicity
b Dose injected into a single lesion
c Dose in a total volume of 1 mL that will be distributed across up to 3 lesions
M-W-F: Monday-Wednesday-Friday
NA-Not applicable

- Seattle Cancer Care Alliance
- Oregon Health Sciences Center
- City of Hope National Medical Center
- University of Pittsburgh
1 mg single injection of TTI-621; obtained a loco-regional CR with no additional treatments (Querfeld, City of Hope)
Patient 21-010 injected April 5
April 8: mild improvement to the injected plaque
May 17: marked improvement of ulcerated plaques/tumors on foot and stable disease on trunk and extremities

10 mg single injection of TTI-621 (Querfeld, City of Hope)
10 mg injection M-W-F x 2 wk of TTI-621 (Querfeld, City of Hope)

- Patient 21-019 1st injection on 21Aug2017
- Aug 28: marked improvement of injected and the adjacent tumor, as well as in the control tumor
- Aug 30: further improvement of the adjacent lesion (upper pole nodule is completely flat)
Treatment with anti-CD47 antibodies stimulates macrophage phagocytosis in vitro and suppresses tumor growth in vivo.

Blocking CD47 may further recruit macrophages to tumors > phagocytosis > cytokines > recruit additional immune cells to tumors (positive feedback mechanism).

Adapted from Veillette et al. 2017
- Immune checkpoint blockade inhibitors
- MicroRNA inhibitors
- Targeted therapies
- CAR-T-Therapy
MicroRNAs (miRNAs) are small non-coding RNAs that direct post-transcriptional regulation of gene expression.

Epigenetic alterations have been implicated in the pathogenesis of lymphomas and leukemias including CTCL.

miRNA profiling and RT-PCR discriminate CTCL and non-malignant inflammation with a high accuracy.

miR-155 is overexpressed; miR-203 & miR-205 are decreased in CTCL skin.

JAK/STAT, PI3K, and RAS pathways are activated in CTCL and regulated by miR-155 that lead to uncontrolled clonal cell expansion.

Targeting micro RNA
(Potential Target: miR155)
First-In-Human Phase 1 Study of MRG-106 in Patients with Mycosis Fungoides

- MRG-106 is an optimized oligonucleotide inhibitor of miR-155 formulated in saline
- Study objectives:
  - Primary objective: Safety and tolerability
  - Secondary objectives: PK profile, efficacy, recommended Phase 2 dose and route of administration
- Study Design:
  - Subjects permitted to continue CTCL therapy if stable dose ≥ 4 weeks prior to MRG-106 administration
  - Part A: Activity of MRG-106 through intralesional injection
  - Part B: Dose-escalation by systemic administration (subcutaneous or I.V.)
    - Dose schedule for systemic administration:
    - Three doses in the first week followed by weekly doses
miR-155 is Upregulated in MF Lesions and Inhibition Affects Cell Growth & Apoptosis

Lesion Type vs miR-155 Copy-Number

Cell Proliferation of HuT102 Cells

Apoptosis Pathway Activation in HuT102 Cells

Archived skin samples [M.Duvic; MD Anderson]

n=10  n=13  n=13  n=21
Gene expression changes with intratumoral injection of MRG-106 correlate to drug levels in MF lesion biopsies (Part A)

122 transcripts

![Heatmap graph showing gene expression changes with MRG-106 injection.](image)

Saline  MRG-106

**Up-regulated vs. untreated**

**Down-regulated vs. untreated**
MRG-106 treatment decreases key CTCL disease pathways including STAT and NFkB Pathways (Part A)

Saline-injected Lesions

MRG-106-injected Lesions

Activated

Inactivated
## Baseline Patient Characteristics:

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Part A  ( n = 6 )</th>
<th>Part B  ( n = 30 )</th>
<th>Total  ( n = 36 )</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Male (n, %)</td>
<td>5 (83%)</td>
<td>20 (67%)</td>
<td>25 (69%)</td>
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<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
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<tr>
<td>Median years (Min, Max)</td>
<td>61 (50,64)</td>
<td>63 (21,85)</td>
<td>63 (21,85)</td>
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<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
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<tr>
<td>Asian</td>
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<td>1 (3%)</td>
<td>1 (3%)</td>
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<tr>
<td>Black</td>
<td>1 (17%)</td>
<td>3 (10%)</td>
<td>4 (11%)</td>
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<td>Not reported</td>
<td>1 (17%)</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
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<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>4 (67%)</td>
<td>24 (80%)</td>
<td>28 (78%)</td>
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<tr>
<td><strong>Disease Stage at Screening</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Stage IA</td>
<td>0 (0%)</td>
<td>6 (20%)</td>
<td>6 (17%)</td>
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<tr>
<td>Stage IB</td>
<td>1 (17%)</td>
<td>8 (27%)</td>
<td>9 (25%)</td>
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<td>Stage IIA</td>
<td>2 (33%)</td>
<td>3 (10%)</td>
<td>5 (14%)</td>
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<td>Stage IIB</td>
<td>3 (50%)</td>
<td>9 (30%)</td>
<td>12 (33%)</td>
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<tr>
<td>Stage IIIA</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
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<tr>
<td>Stage IIIB</td>
<td>0 (0%)</td>
<td>3 (10%)</td>
<td>3 (8%)</td>
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<tr>
<td><strong>Prior Systemic Therapies</strong></td>
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<tr>
<td>No of pts. reporting</td>
<td>6</td>
<td>25</td>
<td>31</td>
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<tr>
<td>Median (range)</td>
<td>4 (1,6)</td>
<td>3 (1,13)</td>
<td>4 (1,13)</td>
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<tr>
<td><strong>Baseline mSWAT per Subject</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>3</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>23 (3,96)</td>
<td>45 (2,180)</td>
<td>43 (2,180)</td>
</tr>
</tbody>
</table>
23 of 26 Patients treated systemically with MRG-106 have mSWAT score improvement independent of treatment duration (Part B)

- 21 subjects were eligible for > 1 month of treatment
- 15 subjects chose to continue with additional months of treatment

6 doses = initial cycle
4 doses in subsequent cycles
64% Patients treated for > 1 month show ≥ 50% mSWAT score improvement

Once PR (≥50% mSWAT) is achieved, response is durable
Case Example (103-007): 300 mg IV Infusion Cohort

- Age: 51; Sex: Male
- Date of diagnosis: 2013
- CTCL stage at screening: IB
- Baseline mSWAT: 180
- Concomitant systemic therapy: weekly Methotrexate (started June 2015)
- Has skin (mSWAT) PR lasting > 4 months

Day 1
mSWAT: 180

Day 93
mSWAT: 68 (62% reduction)
- Immune checkpoint blockade inhibitors
- MicroRNA inhibitors
- Targeted therapies
- CAR-T-Therapy
- 30 (32) pts eligible
- ORR: 21 (70%) of 30
- Highly variable CD30 expression
- Lower response with < 5% CD30 expression ($P \ .005$)
- CD163 positive tumor-associated macrophages express CD30
- Most common AE: peripheral sensorial neuropathy
Brentuximab Vedotin Demonstrates Significantly Superior Clinical Outcomes in Patients with CD30-Expressing Cutaneous T Cell Lymphoma Versus Physician's Choice (Methotrexate or Bexarotene): The Phase 3 Alcanza Study

N=131 pts

<table>
<thead>
<tr>
<th>Table 1. Clinical characteristics and responses</th>
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<td><strong>Brentuximab Vedotin</strong></td>
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<td>Total N=64 n (%)</td>
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<tr>
<td>MF</td>
</tr>
<tr>
<td>48 (75%)</td>
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<tr>
<td>ORR4+</td>
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<tr>
<td>50%</td>
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<td>65%</td>
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<td><strong>Physician’s Choice</strong></td>
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<td><strong>Stage</strong>, n (%)</td>
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<td>IVB</td>
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<td>7 (15%)</td>
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<tr>
<td>Disease involvement**, n (%)</td>
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<td>pCALCL</td>
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<td>16 (25%)</td>
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<td>Skin-only</td>
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<td>9 (56%)</td>
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<tr>
<td>Extracutaneous disease</td>
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<tr>
<td>7 (44%)</td>
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</table>

*ORR4 is defined as response lasting at least 4 months.

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<th>Figure 2: PFS per IRF</th>
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<tbody>
<tr>
<td>Log-rank test p-value: &lt; 0.001</td>
</tr>
<tr>
<td>Median (months): 18.7 MTX or Bex. 9.5</td>
</tr>
<tr>
<td>Number of events: 36 MTX or Bex. 50</td>
</tr>
</tbody>
</table>

Prince HM et al; Lancet 2017
Anti-CCR4 Monoclonal Antibody, Mogamulizumab, Demonstrates Significant Improvement in PFS Compared to Vorinostat in Patients with Previously Treated Cutaneous T-Cell Lymphoma: Results from the Phase 3 MAVORIC Study

Youn H. Kim, MD1; Martine Bagot, MD2; Lauren Pinter-Brown, MD3; Alain H. Rook, MD4; Pierluigi Porcu, MD5; Steven Horwitz, MD6; Sean Whittaker, MD7; Yoshiki Tokura, MD, PhD8; Maarten Vermeer, MD9; Pier Luigi Zinzani, MD10; Lubomir Sokol, MD, PhD11; Stephen Morris, MD7; Ellen J. Kim, MD4; Pablo L. Ortiz-Romero, MD12; Herbert Eradat, MD13; Julia Scarisbrick, MBChB, FRCP, MD14; Athanasios Tsianakas, MD15; Craig Elmets, MD16; Stephane Dalle, MD, PhD17; David Fisher, MD, PhD18; Ahmad Halwani, MD19; Brian Poligone, MD, PhD20; John Greer, MD21; Maria Teresa Fierro, MD22; Amit Khot, MD23; Alison J. Moskowitz, MD6; Karen Dwyer24; Junji Moriya24; Jeffrey Humphrey, MD24; Stacie Hudgens25; Dmitri O. Grebennik24; Kensei Tobinai, MD, PhD26; Madeleine Duvic, MD27 for the MAVORIC Investigators
### Patient baseline characteristics: ITT population, N=372

<table>
<thead>
<tr>
<th></th>
<th>Mogamulizumab (N=186)</th>
<th>Vorinostat (N=186)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>63 (25, 101)</td>
<td>65 (25, 89)</td>
</tr>
<tr>
<td><strong>Male gender (n, %)</strong></td>
<td>109 (59)</td>
<td>107 (58)</td>
</tr>
<tr>
<td><strong>ECOG performance status (n, %)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>106 (57)</td>
<td>104 (56)</td>
</tr>
<tr>
<td>1</td>
<td>78 (42)</td>
<td>82 (44)</td>
</tr>
<tr>
<td>2</td>
<td>2 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Disease type (n, %)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MF</td>
<td>105 (56)</td>
<td>99 (53)</td>
</tr>
<tr>
<td>SS</td>
<td>81 (44)</td>
<td>87 (47)</td>
</tr>
<tr>
<td><strong>Clinical stage (n, %)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IB-IIA</td>
<td>36 (19)</td>
<td>49 (26)</td>
</tr>
<tr>
<td>IIB</td>
<td>32 (17)</td>
<td>23 (12)</td>
</tr>
<tr>
<td>IIIA-IIIB</td>
<td>22 (12)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>IVA1</td>
<td>73 (39)</td>
<td>82 (44)</td>
</tr>
<tr>
<td>IVA2</td>
<td>19 (10)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>IVB</td>
<td>4 (2)</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>

**Median number of prior systemic therapies (range)**  
- Mogamulizumab: 3 (1, 18)  
- Vorinostat: 3 (0, 14)

*There are two patients (one on each arm) who are noted to be Stage IVB at baseline but who did not have measurable visceral disease at baseline.*
## Response outcomes

<table>
<thead>
<tr>
<th></th>
<th>Mogamulizumab</th>
<th>Vorinostat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR(^{a,b}), n/N (%)</strong></td>
<td>52/186 (28)</td>
<td>9/186 (5)</td>
</tr>
<tr>
<td>MF(^c)</td>
<td>22/105 (21)</td>
<td>7/99 (7)</td>
</tr>
<tr>
<td>SS(^b)</td>
<td>30/81 (37)</td>
<td>2/87 (2)</td>
</tr>
<tr>
<td><strong>Stage IB/IIA</strong></td>
<td>7/36 (19)</td>
<td>5/49 (10)</td>
</tr>
<tr>
<td><strong>Stage IIB</strong></td>
<td>5/32 (16)</td>
<td>1/23 (4)</td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td>5/22 (23)</td>
<td>0/16 (0)</td>
</tr>
<tr>
<td><strong>Stage IV</strong></td>
<td>35/96 (36)</td>
<td>3/98 (3)</td>
</tr>
<tr>
<td><strong>DOR, median, months</strong></td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>MF</td>
<td>13 (n=22)</td>
<td>9 (n=7)</td>
</tr>
<tr>
<td>SS</td>
<td>17 (n=30)</td>
<td>7 (n=2)</td>
</tr>
<tr>
<td><strong>ORR(^a) n/N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mogamulizumab after crossover</td>
<td>41/136 (30)</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\)ORR is the percentage of patients with confirmed CR or confirmed PR; \(^{b}\)\(P<0.0001\); \(^{c}\)\(P=0.004\).

- Median relative dose intensities for mogamulizumab were 97.5% and for vorinostat was 95.1%
Mogamulizumab with greater reduction in mSWAT score and superior best global response

Mogamulizumab

Vorinostat
The CC chemokine receptor 4 (CCR4) is expressed on malignant T cells in cutaneous T-cell lymphoma (CTCL) as well as on regulatory T cells.
- Immune checkpoint blockade inhibitors
- MicroRNA inhibitors
- Targeted therapies
- CAR-T-Therapy
Adoptive Therapy using CAR-Engineered T cells

1. Leukapheresis (Remove immune cells from blood)
2. Isolate and activate T cells
3. Genetically engineer T cells with tumor-specific chimeric antigen receptor (CAR)
4. Stimulate replication of tumor-specific engineered CAR T cells
5. Infuse engineered CAR T cells
Potential Targets in CTCL

- IL-13
- CCR-4
- CD4
- CD30
Conclusions

- Treatment outcomes in CTCL is characterized by high rates of relapses.
  - Although overall survival is not significantly affected in early stages, it is shortened in tumor/advanced stages of CTCL
- Understanding the role of the CTCL microenvironment is aimed to develop treatment strategies that enhance anti-tumor potency
- Recent advances have been made on several levels of CTCL biology:
  - Whole genome sequencing has resulted in novel strategies of NF-κB, JAK/STAT, PI3K/AKT and TCR signaling pathways
  - Translational research has revealed new targets including CD30 or CCR4
  - Recent research focusing on impaired immunosurveillance and T cell dysfunction has led to development of immunotherapies
  - Epigenetic changes (microRNAs) have lead to micro-RNA therapeutics
- More encouraging treatment options including CAR-T cell therapy are on the horizon
Thank You

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