Overview of CTCL: Clinicopathologic Aspects, Diagnostic Pitfalls and Novel Immune Therapies

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Disclosures

- **Advisory Board**
  - MiRagen, Actelion, Medivir, Trillium Therapeutics, Kyowa

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

- **Grants**
  - Celgene
### The 2016 updated WHO Classification of Hematological Malignancies

#### Cutaneous T cell lymphomas

<table>
<thead>
<tr>
<th>Condition</th>
<th>Details</th>
</tr>
</thead>
</table>
| Mycosis fungoides                                                        | • Folliculotrophic type  
• Pagetoid reticulosis  
• Granulomatous slack skin                                              |
| Sézary syndrome                                                          |                                                                         |
| Primary cutaneous CD30+ lymphoproliferative disorders                    | • Lymphomatoid papulosis (type A-E)  
• Primary cutaneous anaplastic large cell lymphoma                      |
| Subcutaneous panniculitis-like T cell lymphoma                           |                                                                         |
| Primary cutaneous γδ T cell lymphoma                                      |                                                                         |
| Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T cell lymphoma |                                                                         |
| Primary cutaneous acral CD8+ T cell lymphoma                             |                                                                         |
| CD4⁺ small/medium-sized pleomorphic T-cell lymphoproliferative disorder   |                                                                         |
| Primary cutaneous peripheral T cell lymphoma, NOS                        |                                                                         |
Mycosis Fungoides/Sézary Syndrome

- Malignancy of 3 different T-cell populations:
  - Features of **T-regulatory** (CD25+FoxP3+), **Th**₂- and **Th**₁₇-cell phenotype
- **Th2-driven** immunosuppressive properties
  - Secretion of **IL-4, IL-5, IL-6, IL-10**
- Expression of skin homing ligands CLA, LFA1, CCR4, CCR7, CCR10, and CXCR4
  - MF: skin resident effector-memory T-cell: **CCR4⁺CCR7⁻**
  - SS: central memory T-cell: **CCR4⁺/CCR7⁺**
- Dysregulated/exhausted immunophenotype (**PD1, CTLA4, LAG3, TIM3**)
- Pro-tumorigenic role of macrophages and mast cells
  - Increased **CD68⁺** and **CD163⁺ cells** with increasing tumor burden
- Micro RNA profiling: ↑miRNA 155, ↓miRNA 203 & miRNA 205
- High SCNV: **STAT3, STAT5b, NFkB**, PI3K/AKT, TCR signaling (**CTLA4, CD28, PD1**)

Mimickers:

- Cutaneous epidermotropic aggressive CD8+ T cell lymphoma
- Cutaneous gamma delta T cell lymphoma
Cutaneous aggressive epidermotropic CD8⁺ cytotoxic T-cell lymphoma

- M > F
- Necrotic and hemorrhagic plaques
- CD2⁻, CD3⁺, CD4⁻, CD8⁺, CD45RA⁺, CD56⁺/⁻ phenotype
- Cytotoxic protein (TIA-1, gr B, perforin) expression
- αβ phenotype, TCR+
- EBV negative; T-bet +
- Non-responding to standard regimens for CTCL
- Aggressive with rapid systemic dissemination
Primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphomas: reappraisal of a provisional entity in the 2016 WHO classification of cutaneous lymphomas

Joan Guitart¹, M Estela Martinez-Escala¹, Antonio Subtil², Madeleine Duvic³, Melissa P Pulitzer⁴, Elise A Olsen⁵, Ellen Kim⁶, Alain H Rook⁶, Sara S Samimi⁶, Gary S Wood⁷, Michael Girardi², Jacqueline Junkins-Hopkins⁸, Doina S Ivan⁹, M Angelica Selim⁹, Kimberly A Sable¹, Pooja Virmani⁵, Laura B Pincus⁹, Michael T Tetzlaff³, Jinah Kim¹⁰ and Youn H Kim¹⁰

- 34 pts; median age 77 y (range, 19-89)
- Extensive annular necrotic plaques or tumor lesions
- Early skin signs of chronic patch/plaque lesions often misdiagnosed as MF
- Cases that lack CD8 expression and αβ phenotype
- 5-year survival of 32% with a median survival of 12 months
Phenotype:
  Positive: CD3, CD7, CD5 (partial), CD30 (large cells), TIA, granzyme B, TCR γδ
  Negative: CD4, CD8, Beta F1, CD56, EBER
Cutaneous gamma delta T cell lymphoma

- Aggressive course
- Longstanding indolent (MF-like) course in a subset
- Ulcerated plaques and tumors
- May mimic autoimmune disorder
- Associated with autoimmune disease, pregnancy

- Aggressive multi-agent regimens and allogeneic transplantation
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+
- 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, EphA4, Twist
- Genomic gains/point mutations TNFR2, CTLA4-CD28 fusions
- Enhanced expression/activation of JUNB, Bcl-2, Bcl-2-related genes, CCR-4, TOX, IL2-RA, STAT3, STAT5 and NF-kB
- Microsatellite instability, promotor hypermethylation
- ↑ miRNA 155, ↓ miRNA 203 & miRNA 205
<table>
<thead>
<tr>
<th>Mutated Pathway</th>
<th>Gene (SCNV)</th>
<th>Agents</th>
</tr>
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<tbody>
<tr>
<td>JAK/STAT pathway</td>
<td>JAK1/3</td>
<td>Ruxolitinib; tofacitinib STAT inhibitors</td>
</tr>
<tr>
<td></td>
<td>STAT3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>STAT5B</td>
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<tr>
<td>NF-κB pathway</td>
<td>TNFR2</td>
<td>Bortezomib</td>
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<td>CARD11</td>
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<tr>
<td>TCR signaling &amp; skin homing</td>
<td>CTLA4/CD28</td>
<td>Iplimumab</td>
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<tr>
<td></td>
<td>PDCD1</td>
<td>Pembrolizumab, nivolumab</td>
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<td>ZEB1</td>
<td>Anti-CCR4/mogamulizumab</td>
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<tr>
<td></td>
<td>CCR4</td>
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<td>PI3K/AKT pathway</td>
<td>PI3K</td>
<td>PI3 Kinase inhibitor</td>
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<td>CTLA4/CD28</td>
<td>Iplimumab</td>
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<tr>
<td>Epigenetic regulators</td>
<td>ARID1A</td>
<td>HDAC inhibitors</td>
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<tr>
<td></td>
<td>DNMT3A</td>
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<tr>
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<td>KMT2C</td>
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<td>MAPK pathway</td>
<td>KRAS, BRAF, MAPK1</td>
<td>BRAF /MEK inhibitors</td>
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<td>DNA damage repair</td>
<td>ATM</td>
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<td>TP53</td>
<td></td>
</tr>
<tr>
<td>Cell cycle</td>
<td>CDKN2A</td>
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</tr>
<tr>
<td>Apoptosis</td>
<td>FAS</td>
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<tr>
<td></td>
<td>TNFRSF10A</td>
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</tr>
</tbody>
</table>

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 (B0b)
- Tumor distribution
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 CD4+ Malignant T-cell growth, T-reg phenotype DC activated phenotype Tumor specific antigens/self-peptides

CD-40+ PD-L1/L2+ PD-1- ICOS+ ICOS-L+ CD40L + CD80/86- CTLA-4 - TIM-3 - Lag-3 - MHC IIL-10 IL-10 T-cell exhausted phenotype

DC survival

DC
These results justify identification of antigens driving T-cell exhaustion and development of immunotherapeutic interventions to reverse T-cell exhaustion in CTCL.

Querfeld et al. Cancer Immunol Res, 2018
MF - tumor lesion

Querfeld et al. Cancer Immunol Res, 2018
PD-L1 is Expressed on Antigen Presenting Cells
Inflammatory response
T cell activation:
CD3, CD8A&B, CD4, CD25, CD80, CD86, LAT, ICOS, IFNG
T cell inhibition/exhaustion:
LILRB, PILRA, PDCD1 (PD1), CD274 (PD-L1), CD233 (LAG3), CD152 (CTLA4), KIR2DL1-4, SLA2, FOXP3, IL10
Extracellular matrix assembly
Regulation of cell migration
Innate immune response
Epidermis development
Keratinocyte differentiation
Extracellular matrix assembly
Regulation of cell migration
Neutrophil degranulation
Neg. regul. of transcription
Innate immune response
mRNA-seq analysis shows elevated transcript levels of immune checkpoints and inflammatory cytokines

Sample categories
- Healthy
- Patch lesion, MF
- Plaque lesion, MF
- Tumor lesion, MF
- Sézary syndrome

n = 50 patients
Multispectral imaging: PD-L1 and ICOS expressions correlate with advanced stage CTCL

<table>
<thead>
<tr>
<th>PD-L1</th>
<th>Early</th>
<th>Advanced</th>
<th>Total</th>
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<tr>
<td>Neg.-Low</td>
<td>17 (63)</td>
<td>4 (20)</td>
<td>21</td>
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<tr>
<td>Medium-High</td>
<td>10 (37)</td>
<td>16 (80)</td>
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<tr>
<td>Total</td>
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<td>20</td>
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</table>

\( p = 0.007 \)

<table>
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<tr>
<th>ICOS</th>
<th>Low</th>
<th>High</th>
<th>Total</th>
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<tr>
<td>Low</td>
<td>13 (62)</td>
<td>8 (31)</td>
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<tr>
<td>High</td>
<td>8 (38)</td>
<td>18 (69)</td>
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<tr>
<td>Total</td>
<td>21</td>
<td>26</td>
<td>47</td>
</tr>
</tbody>
</table>

\( p = 0.043 \)

- 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
Preliminary Results from Phase I Trial of Durvalumab and Lenalidomide
Phase I: durvalumab & lenalidomide: non-responder expresses high ICOS levels

Patient #1
Baseline | Cycle 2 Day 1 | H&E | PD-L1/ICOS | ICOS

Patient #2
Baseline | Cycle 2 Day 1 | H&E | PD-L1/ICOS | ICOS

Patient #3
Baseline | Cycle 2 Day 1 | H&E | PD-L1/ICOS | ICOS
Super Resolution Imaging of CTCL Patient Samples

Comparison of T cells in PD-L1 Treatment Response

**Patient 1 (non-responder)**

**Patient 3 (responder)**

![Graph showing PD-1 and PD-L1 molecules per cluster frequency for Patient 1 and Patient 3.](image)

![Images showing PD-1 expression in patient samples.](image)
PD-L1 Regulation by IFNγ, IL6 and IL 10 through STAT Signaling

- Upregulation is possibly a consequence of pro-inflammatory/ immunosuppressive cytokine production by tumor-infiltrating immune cells and tumor cells
- IFN-γ produced by inflammatory cells acts as a potent PD-L1 up-regulator
PD-L1 Up-Regulation by IFN-γ and IL6 through STAT1 and STAT3 Signaling in Cutaneous T-Cell Lymphoma

<table>
<thead>
<tr>
<th></th>
<th>INF γ</th>
<th>IL6</th>
<th>CP-690550</th>
<th>PBMCs/72hrs</th>
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<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100 ng/mL</td>
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<tr>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>10 ng/mL</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Western Blot Analysis**

- **PDL-1**
- **p-STAT-3**
- **p-STAT-1**
- **GADPH**
PD-L1 and pSTAT3 Co-localize on Macrophages in the CTCL microenvironment
IFN-γ induces PD-L1 and ICOS Upregulation in CTCL that can be Abrogated by Lenalidomide and Durvalumab
**CD47 - SIRPα Innate Immune Checkpoint Blockade for Halting Cancer Progression**

**Result:**

No phagocytosis
Tumor cells protected from immune response
Progression of cancer

**Result:**

Phagocytosis of tumor cells
Tumor cells are not protected from immune response
Impaired progression of cancer

*CD47* binds to **signal-regulatory protein (SIRPα)** - an inhibitory receptor expressed on phagocytic cells
Intratumoral dosing trial has enrolled 16 patients

<table>
<thead>
<tr>
<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 3</td>
<td>Expand to 6a</td>
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<td>7</td>
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<td>1</td>
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<td>Expand to 6a</td>
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<td>7</td>
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<tr>
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<td>1</td>
<td>Expand to 3</td>
<td>Expand to 6a</td>
<td>3</td>
<td>Single</td>
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<td>Expand to 6a</td>
<td>10</td>
<td>Single</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1</td>
<td>Expand to 3</td>
<td>Expand to 6a</td>
<td>10</td>
<td>M-W-F x 1 wk</td>
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<td>5</td>
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<td>Expand to 6a</td>
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<td>M-W-F x 2 wks</td>
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<tr>
<td>Expansion</td>
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<td>NA</td>
<td>MTD^</td>
<td>MTD frequency</td>
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<td></td>
<td>7</td>
<td>12</td>
<td>NA</td>
<td>NA</td>
<td>MTD^</td>
<td>MTD frequency</td>
<td>NA</td>
</tr>
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</table>

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
10 mg single injection of TTI-621 (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

Baseline: April 5

Started PI3K inhib: May 17

Long term follow up: July 10
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)
Left lateral lower leg
Baseline 4.11.18

6.19.18
Phase I/II Clinical Trial of BNZ 1 for Patients with Refractory Cutaneous T cell Lymphoma

- Open Label first in human study
- CTCL and LGL pts
- Multi-cytokine inhibitor targeting Interleukin (IL)-2, IL-9 and IL-15

<table>
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<tr>
<th>Dose Level</th>
<th>Weekly IV Dose of BNZ-1</th>
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<tr>
<td>1</td>
<td>0.5 mg/ kg</td>
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<tr>
<td>2</td>
<td>1 mg/ kg</td>
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<tr>
<td>3</td>
<td>2 mg/ kg</td>
</tr>
<tr>
<td>4</td>
<td>4 mg/ kg</td>
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</table>
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)
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
122 transcripts

A.

B.

C.

<table>
<thead>
<tr>
<th>DOWN regulated gene clusters</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation of immune response</td>
<td>CXCR5, ICAM3, CD44, LCK, IL17A, IL17RA, IL10, IL6R, IL1R</td>
</tr>
<tr>
<td>Inflammatory response</td>
<td></td>
</tr>
<tr>
<td>T cell receptor signaling pathway</td>
<td></td>
</tr>
<tr>
<td>Coagulation, response to wound healing, hemostasis</td>
<td>SMAD3, TGFBR2, PIK3R5, LCK, VAV1, IL10</td>
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<td>Adaptive immune response</td>
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<tr>
<td>Regulation of T cell activation</td>
<td>CD28, IL17A, PIK3R5, ICOS, IL5R, IL10, CXCR5, LCK, VAV1</td>
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<tr>
<td>T cell costimulation, lymphocyte costimulation</td>
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<tr>
<td>Positive regulation of interleukin-6 production</td>
<td>IL6R, IL10, IL1R, IL17A</td>
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<td>Ribonucleotide binding, ATP binding, RNA binding, nucleic acid binding</td>
<td>RP72, CDK7, NARS, ALGKHS5</td>
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<td>Apoptotic process, programmed cell death</td>
<td>CASP3, TNFRSF6, BNP30L, APAF1, PUMA, MAPK7</td>
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<td>Apoptotic signaling pathway</td>
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<tr>
<td>Immune response</td>
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<td>Cytokine-mediated signaling pathway</td>
<td>VEGFA, SMAD7</td>
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### Baseline Patient Characteristics:

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<th>Part B n = 30</th>
<th>Total n = 36</th>
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<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>
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<td></td>
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<td>Median years (Min, Max)</td>
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<td>63 (21,85)</td>
<td>63 (21,85)</td>
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<td><strong>Race</strong></td>
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<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>24 (80%)</td>
<td>28 (78%)</td>
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<td>Stage IA</td>
<td>0 (0%)</td>
<td>6 (20%)</td>
<td>6 (17%)</td>
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<td>Stage IB</td>
<td>1 (17%)</td>
<td>8 (27%)</td>
<td>9 (25%)</td>
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<td>5 (14%)</td>
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<td>1 (3%)</td>
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<td>Stage IIIB</td>
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<td>3 (10%)</td>
<td>3 (8%)</td>
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<td>3 (1,13)</td>
<td>4 (1,13)</td>
</tr>
</tbody>
</table>

**Baseline mSWAT per Subject**

<table>
<thead>
<tr>
<th></th>
<th>Part A</th>
<th>Part B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>3</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>33 (2.96)</td>
<td>45 (2.189)</td>
<td>43 (2.189)</td>
</tr>
</tbody>
</table>
Clinical presentation of patient with MF (stage 1B) at baseline and during treatment (300 mg IV MRG-106). Patient achieved PR with a 62% reduction in skin disease burden; response is ongoing.

Maximum percent improvements in skin from baseline in severity-weighted assessment tool (SWAT) scores (26 patients).
Summary

- T cells in CTCL express an exhausted/dysregulated immunophenotype that correlates with the immune gene expression profile.
- PD-L1 is expressed on antigen presenting cells (dendritic cells; macrophages) and can be induced in (circulating) T cells.
- High PD-L1 levels correlate with advanced stage and large cell transformation.
- ICOS expression correlates with high PD-L1 levels in advanced stage and large cell transformation and may affect response to PD1/PD-L1 blockade.
- PD-L1 is regulated by proinflammatory cytokines IFN-γ and IL-6 in a STAT-dependent manner.
- miRNAs are involved in PD-L1 regulation.
- Mouse xenograft model for CTCL to study effects.
- Understanding the role of the CTCL microenvironment is aimed to develop treatment strategies that enhance anti-tumor potency.
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