Management Challenges in Sézary Syndrome

Youn H Kim, MD

Department of Dermatology
Director, Multidisciplinary Cutaneous Lymphoma Group
Stanford Cancer institute
Stanford University School of Medicine
Disclosure statement

Youn H Kim, MD

• **Steering Committee**
  – Eisai, Kyowa, Millennium/Takeda

• **Consultant or Advisory Board**
  – Innate, Seattle Genetics, Medivir, Takeda, Kyowa, Corvus, Portola

• **Investigator**
  – Kyowa, Merck, Millennium/Takeda, Seattle Genetics, Eisai, Innate, Neumedicine, Soligenix, miRagen, Forty Seven, Horizon, Portola, Trillium
Cutaneous T-cell lymphoma
*Mycosis fungoides & Sézary syndrome, very diverse in presentation*

- Rare/orphan disease, 1 in 100,000 annual incidence, 4% of NHLs
- Significant heterogeneity in clinical, histopathology, cellular/molecular features

**Early stage:**
Patch/plaque dz, T1, T2
Stages IA-IIA

**Advanced stage:**
Tumor T3
Erythroderma T4
Extracutan dz (IV)
Stages IIB-IV
Sézary syndrome—generalized erythroderma, keratoderma, severe itching; freq staph aureus infection

Significant blood dz (B2):
Sézary cells >1,000 per mm$^3$; expanded CD4, CD4+CD7- >40% or CD4+CD26- >30% of lymphocytes

Evaluation for erythrodermic patients

- Skin bx often non-diagnostic
- Sézary flow
- Relevant clone: same dominant TCR sequences in skin, blood, LN
- Imaging for LAD, H/S
- Skin culture
- Supportive care
Prognosis of early vs advanced stage MF and SS: Appropriate risk-stratification for treatment selection

Large-cell transformation (LCT) with worse clinical outcome, most often a/w tumor type skin disease

F-MF two prognostic subsets
(Hodak et al, 2016)
F-MF not sig independent factor in advanced MF/SS
(CLIC Scarisbrick et al, 2015)

Prognostic modeling beyond clinical stage

Retro-CLIPI:
Retrospective study of 10 parameters in advanced stage MF/SS, dx from 2007

• 29 international sites, N = 1,275
• 4 independent factors:
  Age >60, stage IV, LCT, ↑LDH
• Combined into prognostic index model => 3 risk groups
  - Low-risk, 67.8%
  - Intermediate-risk, 43.5%
  - High-risk, 27.6%

5-year OS rates of 3 risk groups

Prospective study (PROCLIPI) in progress- to validate old and identify new prognostic factors
• J Scarisbrick/UHB, EU lead
• Y Kim/Stanford, non-EU lead
Evaluation and management in MF/SS

- Clinical
- Histologic
- Laboratory Imaging
- Molecular (primarily TCRR)

Diagnosis
Prognostication

Management determined by:
- MF vs SS
- Clinical stage/TNMB
- F-MF, LCT, other

Treatment:
- skin-directed +/- systemic

Other key factors
- Age
- Comorbidities, PS
- Availability & accessibility

Chromosomal aberrations
Gene expression patterns
Genomic alterations by NGS
Epigenetic alterations/profiles
MicroRNA profiles
NOT ready for clinical use
Newer therapies in clinical development in CTCL

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., Bcl2/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, OX40, MDSC, Tregs)

CTCL

TILs

M

Brentuximab vedotin
Mogamulizumab
Denileukin diftitox/E7777
Anti-KIR3DL2 mab

Proteosome inhibitor
PI3K inhibitor
mTOR inhibitor
Jak inhibitor
Syk-Jak dual inhibitor
ITK inhibitor
Bcl2 inhibitor
Anti-miR-155
HDAC inhibitor
Demethylating agent
Improved anti-folate

Anti-PD-1/PD-L1 mAbs
Anti-CTLA-4 mAbs
Anti-CD47 mAb/SIRPα Fc decoy, anti-SIRPα mAb
OX40 agonistic mAb
Lenalidomide
Treg depleting agents

Multiple combination therapies (systemic and/or skin-directed strategies)

Brentuximab vedotin
Mogamulizumab
Denileukin diftitox/E7777
Anti-KIR3DL2 mab

Improved anti-folate
Do we have molecular data to guide management?

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
Many potential actionable targets/pathways need to be established for translation into meaningful outcomes.
Importance of supportive management in Sézary syndrome

**Mycosis fungoides**

**Sézary syndrome**

**Infection patrol**
(skin MSSA/MRSA, HSV/VZV, candida/dermatophyte)

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

**Topical steroid +/- occlusion**

**Emollient**
(sustain skin barrier)
Clinical activity of systemic agents in Sézary Syndrome, *NCCN 2019*

<table>
<thead>
<tr>
<th>Agent</th>
<th>N</th>
<th>ORR</th>
<th>DOR</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bexarotene</td>
<td>17</td>
<td>24% (no CR)</td>
<td>ND</td>
<td>Phase 2-3 single arm</td>
</tr>
<tr>
<td>Photopheresis+, varying regimen</td>
<td>70  (&gt;1 study)</td>
<td>20-89% (0-29% CR)</td>
<td>ND</td>
<td>Mostly retrospective studies</td>
</tr>
<tr>
<td>Vorinostat</td>
<td>30</td>
<td>33% (no CR)</td>
<td>6+ mo</td>
<td>Pivotal single arm</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>13</td>
<td>31% (no CR)</td>
<td>&gt; 1 year</td>
<td>Pivotal single arm</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>10</td>
<td>50% (30% CR)</td>
<td>&gt;1 year</td>
<td>Retrospective study</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>26</td>
<td>88%</td>
<td>ND</td>
<td>Retrospective study</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>11</td>
<td>73%</td>
<td>4 mo</td>
<td>Phase 2 single arm</td>
</tr>
<tr>
<td>Alemtuzumab, varying regimen</td>
<td>14/17</td>
<td>86%/82%</td>
<td>6 mo (n=17)</td>
<td>Phase 2 single arm; Median OS 35 mo (n=14)</td>
</tr>
<tr>
<td>Mogamulizumab, phase 3 RCT (vs vorinostat)</td>
<td>81</td>
<td>37%</td>
<td>17 mo</td>
<td>Largest RCT, PFS as primary; blood response in 83/122 (68%)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>15</td>
<td>27% (7% CR)</td>
<td>&gt; 1 year</td>
<td>Phase 2 single arm</td>
</tr>
</tbody>
</table>

Most recently FDA approved agent (8/2018) in MF/SS (LCT excluded); activity reported in ISTs

Brentuximab, ALCANZA RCT excluded SS; activity reported in ISTs

*Lancet Oncol 2018;19:1192*
Management of Sézary Syndrome, B2/stage IV

- **Stratification based on blood Sézary burden and LN status**
  - Given risk for staph sepsis, utilize agents that spare further immune dysfunction, importance of supportive care

- **Low-intermediate Sézary burden**
  - Combination therapies (e.g., photopheresis+, bex + IFN)
  - “Milder” Cat-A systemic therapies: biologics (bexarotene, photopheresis, HDAC-i (vorinostat, romidepsin), methotrexate

- **High Sézary burden (>5-10K/mm³)**
  - Combination therapies (e.g., photopheresis+, bex + IFN)
  - Mogamulizumab
  - Romidepsin +/- TSEBT
  - Alemtuzumab (low-dose sc, 3-10 mg short courses)
  - Clinical trials

- **Refractory disease**
  - Alemtuzumab
  - Pralatrexate, brentuximab (if CD30+), bortezomib, pembrolizumab
  - Chlorambucil, other TCL options
  - Clinical trials

---

**1st line, choice by blood-burden**

*single or combination therapy*

- Retinoids (bexarotene)
- IFNs
- HDAC-i (vorinostat, romidepsin)
- Methotrexate (25-35 mg)
- Photopheresis (if >B0)
- Mogamulizumab
  +/- skin-directed option

---

**2nd line/other options**

- Alemtuzumab
- Pralatrexate
- Pembrolizumab
- Bortezomib
- Brentuximab (if SC CD30+)
- Clinical trials
- Other TCL options

---

**Allo HSCT**
63 F with Sézary syndrome, stage IVA, (T4NxM0B2) with low Sézary burden

Consider safety; spare immune function

- PB flow showed expanded CD4+ T cells, CD4+/CD26- 65% of lymphs, abs cnt of 1,270 /mm3
- Photopheresis + IFNα => PR in blood, SD in skin
- Added bexarotene => global PR x 1 yr, but ↑lipid issues
- Methotrexate => PD in blood and skin; reactive LNs

Blood ↑CD4+/CD6- 95%, abs cnt 7,500 /mm3
- CR with mogamulizumab (anti-CCR4 mAb) x 3 years

Relapse in skin and blood
- Romidepsin => global PR but tolerability problem
- Anti-KIR3DL2 mAb => near CR

Supportive care:
- Topical steroids
- Oral anti-itch meds
- Antimicrobials (staph aureus), dilute bleach baths esp if MRSA
Mogamulizumab: First-in-class defucosylated humanized anti-CCR4 mAb

Higher ADCC due to a defucosylated Fc region by POTELLIGENT®

ADCC, antibody-dependent cellular cytotoxicity; Fc, fragment crystallizable; GPCR, G-protein-coupled receptor; MDC, macrophage derived chemokine; TARC, thymus- and activation-regulated chemokine.

MAVORIC: Open-label, randomized study of anti-CCR4 monoclonal antibody, mogamulizumab (KW-0761), vs vorinostat in patients with previously treated CTCL

**Inclusion:**
- Stage IB – IVB, MF or SS (B2)
- At least one prior course of systemic therapy

**Exclusion:**
- Patients with large cell transformation

**1:1 Randomization**

**Mogamulizumab**
- 1.0 mg/kg i.v.
  - Weekly for first 28-day cycle; days 1 and 15 of subsequent cycles

**Vorinostat**
- 400 mg PO daily

- Patients could remain in the treatment phase up until progression or intolerable toxicity
- Vorinostat was administered in accordance with US prescribing information, targeting maximum tolerated effective dose; crossover allowed with approval
- CCR4 expression was not a requirement for participation
- Patients were enrolled at 61 centers across 11 countries

i.v., intravenously; PD, disease progression; PO, orally.

12/2017 ASH #817
Lancet Oncol, 2018
FDA approval 8/2018
Primary endpoint: Progression-free survival (PFS)

- Median PFS (months): Mogamulizumab 7.7 (5.67, 10.33) vs. Vorinostat 3.1 (2.87, 4.07)
- Hazard Ratio (95% CI): Mogamulizumab 0.53 (0.41, 0.69)
- Stratified log rank test: P<0.0001
## 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</td>
<td>22/105 (21)</td>
<td>7/99 (7)</td>
</tr>
<tr>
<td>SS</td>
<td>30/81 (37)</td>
<td>2/87 (2)</td>
</tr>
<tr>
<td>Stage IB/IIA</td>
<td>7/36 (19)</td>
<td>5/49 (10)</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>5/32 (16)</td>
<td>1/23 (4)</td>
</tr>
<tr>
<td>Stage III</td>
<td>5/22 (23)</td>
<td>0/16 (0)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>35/96 (36)</td>
<td>3/98 (3)</td>
</tr>
<tr>
<td><strong>DOR, median, months (IQR)</strong></td>
<td>14 (8-19)</td>
<td>9 (6-NE)</td>
</tr>
<tr>
<td>MF</td>
<td>13 (5-18)</td>
<td>9 (6-NE)</td>
</tr>
<tr>
<td>SS</td>
<td>17 (9-20)</td>
<td>7 (7-7)</td>
</tr>
<tr>
<td><strong>ORRa, n/N (%)</strong> mogamulizumab after crossover</td>
<td>41/133 (31)</td>
<td></td>
</tr>
</tbody>
</table>

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

- Median relative dose intensities for mogamulizumab were 97.5% and for vorinostat was 95.1%
## Clinical activity by compartment

<table>
<thead>
<tr>
<th>Compartments</th>
<th>Mogamulizumab</th>
<th>Vorinostat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Compartment response rate</strong> (confirmed), n/N\textsuperscript{a} (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (CR+PR)</td>
<td>78/186 (42)</td>
<td>29/186 (16)</td>
</tr>
<tr>
<td>CR</td>
<td>8 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (CR+PR)</td>
<td>83/122 (68)</td>
<td>23/123 (19)</td>
</tr>
<tr>
<td>CR</td>
<td>54 (44)</td>
<td>5 (4)</td>
</tr>
<tr>
<td><strong>Lymph nodes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (CR+PR)</td>
<td>21/124 (17)</td>
<td>5/122 (4)</td>
</tr>
<tr>
<td>CR</td>
<td>10 (8)</td>
<td>2 (2)</td>
</tr>
<tr>
<td><strong>Viscera</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (CR+PR)</td>
<td>0/3 (0)</td>
<td>0/3 (0)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Denominator includes patients with compartmental disease at baseline

CR=complete response; PR=partial response.

Potential combination with treatments with activity in the skin compartment
Commonly reported treatment-emergent adverse events (≥ 20% of patients in either group)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Mogamulizumab</th>
<th>Vorinostat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-related reaction</td>
<td>31%</td>
<td>5%</td>
</tr>
<tr>
<td>Drug eruption</td>
<td>23%</td>
<td>5%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29%</td>
<td>44%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26%</td>
<td>36%</td>
</tr>
<tr>
<td>Nausea</td>
<td>23%</td>
<td>33%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19%</td>
<td>29%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15%</td>
<td>23%</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>6%</td>
<td>12%</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>4%</td>
<td>7%</td>
</tr>
</tbody>
</table>

- Mogamulizumab group: Commonly reported grade ≥ 3 TEAEs ranged from 0%-4.3% of patients
- Vorinostat group: Commonly reported grade ≥ 3 TEAEs ranged from 0%-5.9% of patients

---

a One patient had an infusion reaction on Day 1 of crossover to mogamulizumab treatment (17 days after the last dose of vorinostat) that was indicated as possibly related to vorinostat (and mogamulizumab).
b Skin rashes that were assessed by investigator or sponsor as possibly, probably, or definitely related to study drug.
Rashes/skin eruptions with mogamulizumab treatment

SS, IVA₁
Skin near CR after C4, worsening rash with C5; Skin bx with TCR HTS confirmed new rash

Often delayed, Photo-accentuated rash

Topical steroids allowed in trials; post-approval, systemic steroid use expected

SS, IVA₁
Skin CR after C2, worsening rash from C4; Skin bx with TCR HTS confirmed new rash
Drug Eruption in MAVORIC

- Drug eruption was defined as a skin rash that was assessed by the investigator or sponsor as possibly, probably, or definitely related to study drug.
- N=45 patients randomized to mogamulizumab experienced drug eruption; 9 Gr 3, the remainder Gr 1-2.
- Median time to onset of a drug eruption event was 107 days (Q1, 43 days; Q3, 256 days).

Note: As the number of patients remaining on treatment decreases over time, the number of patients at risk decreases.

Bagot M. et al., ASH Dec 2018; Abstract 2901.
Is there an increased risk of severe, steroid-refractory GVHD with mogamulizumab exposure in patients receiving allogeneic transplant?
5.5 Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) after POTELIGEO

- Increased risks of transplant complications have been reported in patients who receive allogeneic HSCT after POTELIGEO including severe (Grade 3 or 4) acute graft-versus-host disease (GVHD), steroid-refractory GVHD, and transplant-related death. Among recipients of pre-transplantation POTELIGEO, a higher risk of transplant complications has been reported if POTELIGEO is given within a shorter time frame (approximately 50 days) before HSCT. Follow patients closely for early evidence of transplant-related complications.

Need prospective studies with larger sample size
Use of targeted NGS panels

- NGS assay for hematolymphoid neoplasms
- SNVs, Indels, CNVs*, Fusions
- Genes for therapy, diagnosis or prognosis

Effective therapies a/w superior outcome:
Activating CCR4 mutations as predictive biomarker for mogamulizumab in ATLL

CCR4 mutations associated with superior outcome of adult T-cell leukemia/lymphoma under mogamulizumab treatment

Blood 2018;132:759
Summary: mogamulizumab in SS, *the new kid on the block*

- New option with promising activity and great safety/tolerability profile
  - Particularly higher responses in the blood compartment
  - Incorporated into NCCN practice guidelines (MF/SS, CAT-A listing, preferred option in high-burden SS; ATL, 2nd line option)

- Direct (ADCC) and indirect (depletes Tregs) dual mode of immune therapy

- Explore rational combination or sequential therapies to improve clinical efficacy (LCT, non-blood compartments) and/or mitigate toxicity (rash)

- Great translational research platforms to incorporate in trials and to help personalize management
  - Guide treatment selection (e.g., activating CCR4 mutation by NGS)
  - Establish biomarkers of response, resistance, escape, and toxicities
  - Identify optimal partners for combination approaches
37 AA F Sézary syndrome, stage IVA2 (N3), high blood Sézary burden. Romidepsin with PR x 10 mo, then global near CR with pembrolizumab x 2+ yrs.

**Treatment options for high SC**
- Bex/retinoids +/- IFN
- Photopheresis + IFN, bex
- HDAC inhibitors (romidepsin)
- Mogamulizumab
- Clinical trials

**2nd line/other options for high SC**
- Anti-folates (pralatrexate)
- Brentuximab vedotin (if SC CD30+)
- Gemcitabine
- Liposomal doxorubicin
- Alemtuzumab (low-dose sc)
- Pembrolizumab
- Clinical trials

**Supportive care: address infection risk**
- Antimicrobials (staph aureus, dilute bleach baths esp if MRSA)
- Topical steroids, anti-itch meds

- **PET/CT**
  - Multiple PET avid LAD
  - Bx revealed LN4, N3
- **Sézary flow (high SC burden)**
  - CD4+/CD26- 95%, 5000+ SCs
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); Steven Fling (correlative core)
CITN, Fred Hutchinson Cancer Research Center

Principal Investigator: Y Kim (PI)

Lead Sub-I: M Khodadoust (correlative science lead)
J Kim (path), S Li (biostatistician)
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)

Correlative Studies: S Fling, Y Yang, J Yearley, E Chartash,
P Balsubrahmanyam, H Maecker

NCI Collaboration: Elad Sharon
Can PD-1 blockade be used safely and effectively to target a PD-1 expressing, T-cell malignancy?

- PD1 – commonly expressed
- PD-L1 - may be expressed
- PD1 – may be deleted
- PD-L1/L2 translocations reported
Primary outcome: Overall response rate

Overall response rate: 38%
Deep and Durable responses with pembrolizumab
*CITN-13 trial of pembrolizumab + IFN-g in MF/SS ongoing

Overall response rate: 38%

Responses are durable

Global Response
- CR
- PR
- SD
- PD

* Skin flare reaction
X Progression due to new tumor

Khodadoust et al. CITN-10 trial
ASH 12/2016
Abstract #181
KIR3DL2 as a promising therapeutic target in CTCL, esp Sézary syndrome

- KIR3DL2 belongs to the Killer Ig-like Receptor family that modulate NK and T cell activity
- KIR3DL2 is expressed on ~30% of normal NK and <10% normal T cells
- KIR3DL2 is widely expressed on CTCL cells (skin lesions and blood aberrant cells)
  - Irrespective of disease clinical stage
  - With a higher prevalence in Sézary syndrome (SS), CD30+ LPD and Mycosis fungoides with large-cell transformation
  - KIR3DL2 may have prognostic significance in SS

\[\text{Sézary syndrome} \quad \text{Transformed MF}\]

\[\text{Correlation between KIR3DL2 and TCR-Vβ expression in Sézary syndrome (n = 32)}\]

\[\text{Spearman r = 0.6609, p < 0.0001}\]

\[\text{KIR3DL2 is considered a specific marker of CTCL, high therapeutic index}\]

KIR3DL2 is expressed on most CTCL subtypes

>85% cases KIR3DL2+
Targeting KIR3DL2 with IPH4102 in CTCL

- IPH4102, first-in-class Fc modified humanized IgG1 mAb
- Its modes-of-action include ADCC and ADCP
- IPH4102 has shown potent pre-clinical efficacy:
  - In mouse models of KIR3DL2-positive tumor cells
  - In ex vivo autologous assays using patient-derived NK and Sézary cells
**Dose-escalation**
- 10 dose levels – accelerated 3+3 design
- ≥ 2 prior systemic therapies
- ≥ 5% KIR3DL2pos aberrant cells in skin or blood
- if Mycosis Fungoides/Sézary Syndrome (MF/SS) stage ≥ IB

**Cohort expansion**
- Recommended Phase 2 dose (RP2D)
- ≥ 2 prior systemic therapies
- Irrespective of KIR3DL2 expression

**Dosing regimen**, until progression or unacceptable toxicity

- 4 admin. weekly
- W5 10 admin. Q2W
- W26 N admin. Q4W

- Intra-patient dose-escalation allowed after Week 5 (W5) in the dose-escalation portion
**Adverse event** | **All grades, N (%)** | **Grade 3-4, N (%)**
--- | --- | ---
Peripheral edema | 12 (27%) | 0 (0%)
Asthenia | 9 (20%) | 0 (0%)
Fatigue | 9 (20%) | 0 (0%)
Cough | 7 (16%) | 0 (0%)
Pyrexia | 7 (16%) | 0 (0%)
Diarrhea | 7 (16%) | 0 (0%)
Arthralgia | 7 (16%) | 0 (0%)
Fall | 6 (14%) | 0 (0%)
Headache | 6 (14%) | 0 (0%)
Lymphopenia | 6 (14%) | 2 (5%)
Constipation | 5 (11%) | 0 (0%)
Dyspnea | 5 (11%) | 0 (0%)
Chills | 5 (11%) | 0 (0%)
Anemia | 5 (11%) | 1 (2%)
Hypertension | 5 (11%) | 2 (5%)

Five patients developed 6 possibly related grade ≥ 3 AEs:
- grade 5 hepatitis (n=1)
- grade 4 sepsis (n=1)
- grade 3 AST elevation (n=1)
- grade 3 lymphopenia (n=2)
- grade 3 hypotension (n=1).

Only 3 patients (7%) stopped treatment for an AE.
Neither skin rash nor other immune-mediated reactions related to IPH4102 were reported.
# Clinical Efficacy Results (cut-off June, 28 2018)

**Update**

<table>
<thead>
<tr>
<th></th>
<th>Escalation (n=25)</th>
<th>Escalation SS only (n=20)</th>
<th>Expansion SS (n=15)</th>
<th>Total (N=44)$</th>
<th>Total without LCT (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best global response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CR</td>
<td>1 (4%)</td>
<td>1 (5%)</td>
<td>1 (6.7%)</td>
<td>2 (4.5%)</td>
<td>2 (6.9%)</td>
</tr>
<tr>
<td>- PR</td>
<td>10 (40%)</td>
<td>9 (45%)</td>
<td>4 (26.7%)</td>
<td>14 (31.8%)</td>
<td>13 (44.8%)</td>
</tr>
<tr>
<td>- SD</td>
<td>12 (48%)</td>
<td>8 (40%)</td>
<td>8 (53.3%)</td>
<td>24 (54.5%)</td>
<td>12 (41.4%)</td>
</tr>
<tr>
<td>- PD</td>
<td>2 (8%)</td>
<td>2 (10%)</td>
<td>2 (13.3%)</td>
<td>4 (9%)</td>
<td>2 (6.9%)</td>
</tr>
<tr>
<td><strong>Follow up</strong>*</td>
<td>18.2 (2–31+)</td>
<td>19.3 (2–31+)</td>
<td>8.1 (2–11+)</td>
<td>12.7 (2–31+)</td>
<td>14.9 (1.9–31+)</td>
</tr>
<tr>
<td><strong>Time to Response</strong>*</td>
<td>4.9 (0.9–26.8)</td>
<td>4.9 (0.9–26.8)</td>
<td>5.8 (0.8–9)</td>
<td>NR (0.8–26.8)</td>
<td>4.8 (0.9–25.8)</td>
</tr>
<tr>
<td><strong>Duration of Response</strong>*</td>
<td>9.9 (2.1–26.4+)</td>
<td>11.9 (2.1–26.4+)</td>
<td>NR (1.4–9+)</td>
<td>13.8 (1.4–26.4+)</td>
<td>13.8 (2.1–26.4+)</td>
</tr>
<tr>
<td><strong>Progression Free Survival</strong>*</td>
<td>8.1 (0.9–31.3+)</td>
<td>11.3 (0.9–31.3+)</td>
<td>NR (0.8–11.1+)</td>
<td>8.2 (0.8–31.3+)</td>
<td>12.9 (0.8–31.2+)</td>
</tr>
</tbody>
</table>

*All in months, median (range)*

NA: Not Applicable; NR: Not Reached
LCT: Large-Cell Transformation

Nine patients are still on treatment at cut-off date.

$Four tMF (MF with LCT) were enrolled in the expansion. All have best response of SD.
Change in Skin Disease (mSWAT) for All Patients (n=44)

Best global response

Best mSWAT change relative to baseline

Patients with Large Cell Transformation
Anti-KIR3DL2 antibody: representative pictures of responders

Patient 11-024: Stanford site
- 75-year old male
- Sézary Syndrome diagnosed in AUG 2011
- 6 lines of previous therapies (incl. MTX, INFα, vorinostat then mogamulizumab, BEX, pembrolizumab)

- Started at 3 mg/kg on 16OCT16
- Global PR since W14 (3 mg/kg)

Patient 11-005: Stanford site
- 77-year old female
- Sézary Syndrome diagnosed in NOV 2008
- 6 lines of previous therapies (incl. ECP + BEX + INFα, MTX, mogamulizumab, ECP + INFα + MTX, romidepsin, BEX+ INFα)

- Started at 0.05 mg/kg on 25JAN16
- Global PR since W10 (0.05 mg/kg)
• Retrospective study of 10 parameters in advanced stage MF/SS, dx from 2007
• 29 international sites, N = 1,275
• 4 independent factors: Age >60, stage IV, LCT, ↑LDH
• Combined into prognostic index model => 3 risk groups

5-year OS rates of 3 risk groups
• Low-risk, 67.8%
• Intermediate-risk, 43.5%
• High-risk, 27.6%

Highest priority for allogeneic HSCT
Take home: Management challenges in Sézary syndrome

- Overall management is based on compartmental disease burden and biologic activity, with recognition of additional prognostic factors (e.g., age, LCT) and risk-stratification.

- Optimize/maximize use of single agent therapies (biologics+, targeted therapies, chemotherapies), consider maintenance regimen to sustain response.

- Combination regimens if single agents fail, great combo rationale, primary disease is bulky extracutaneous, or optimizing for allogeneic HSCT.
  - Explore combination/sequential strategies, to optimize anti-tumor activity, reduce toxicity, and address resistance/escape/evasion; partner with immune therapies to improve/sustain response.

- Optimize use of skin-directed therapies and supportive care (↓infection, ↑QoL, ↑ORR).

- Participation in clinical trials is encouraged to develop improved therapies/regimens; integrate molecular/biomarker platforms into trials to learn biomarkers for response/resistance/escape, flare reactions, toxicity, or survival outcomes.

- Targeted/actionable NGS panels can be useful for personalizing treatment, though not ready for routine use in the clinics; and relevance for targeting unclear in SS, need more data.

- Taking steps towards personalized, precision medicine for optimal outcome.