New Systemic Immune Strategies in CTCL

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Multidisciplinary Cutaneous Lymphoma Group
Stanford Cancer Institute & School of Medicine
Disclosure statement

Youn Kim, MD

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

• **Consultant or Advisory Board**
  – Actelion, Seattle Genetics, Forty Seven, Medivir, Takeda

• **Investigator**
  – Kyowa, Merck, Millennium/Takeda, Seattle Genetics, Eisai, Tetralogic, Innate, Neumedicine, Soligenix, miRagen, Infinity, Forty Seven, Portola
Exploring & integrating new systemic immune strategies in CTCL

**Rationale and Status**

- **Rationale for immunotherapy in CTCL**
  - Evidence for immune dysregulation
  - Prolong/sustain clinical responses, induction of immune memory?

- **Limited SoC immunotherapy choices in CTCL**

- **Great promising immunotherapies in clinical development, expanding our options and strategies**

- **Rational partnering, combine approaches more sensibly**
  - Avoid combinations with conflicting or counteractive MOA
  - Optimize efficacy while minimize toxicity

- **Newer tools to improve our understanding of biology/mechanisms and allow more rational partnering**
Why is immunotherapy important in CTCL?

Need of therapies with reliable responses that last

*Partnering with immunotherapy*
Local and systemic immune dysregulation in CTCL

Overcome immune suppression

- PD-1
- CD4
- CCR4
- CTLA4
- Malignant T-Cell
- TGF-β
- CLA

T\(_H\)2 Cytokines:
- IL-4
- IL-13
- IL-5
- IL-10

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

- IgE

Courtesy A Rook, modified from JCI 2005
Genomic analysis of mycosis fungoides and Sézary syndrome identifies recurrent alterations in TNFR2

Alexander Ungevikell et al., Aparna Bhaduri et al., Eric Rios, Jason Reuter, Carolyn Lee, Angela Mah, Ashley Zehnder I, Robert Ohgami, Shashikant Kulkarni, Randal Armstrong, Wen-Kai Weng, Dita Gratzinger, Mahkam Tavallaei, Alain Rook, Michael Snyder, Ysoon Kim & Paul A. Khavari

Genomic basis for immune dysregulation

JCO 2016;34:2698
A. Lesokhin, et al.
Nivolumab in Lymphoid Malignancies

PD-L2 Translocation in a Cutaneous T-cell Lymphoma

Genomic landscape of cutaneous T cell lymphoma

Nat Genetics 2015

Nat Genetics 2015
Improved tools & technology for correlative science

Microenvironment profiling

IHC  Multiplexed Ion Beam Imaging  Nanostring GEP

Systemic Profiling

Molecular Profiling

Flow  CyTOF  Luminex

Whole exome seq  TCR – high throughput seq

Courtesy M Khodadoust
Standard-of-care “immunotherapy” options in clinical management (NCCN guidelines):

- Top imiquimod (TLR-A)
- IFN-α, IFN-γ
- Photopheresis
- Allo-HSCT
- Clinical trial therapies

Need more immunotherapies!

<table>
<thead>
<tr>
<th>IA Limited patch/plaque</th>
<th>IB/IIA Generalized patch/plaque</th>
<th>IIB Tumors</th>
<th>III Erythroderma</th>
<th>IV Extracutan disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical steroid, retinoid (bex), NM phototherapy, local RT, imiquimod</td>
<td>Phototherapy + bexarotene or IFN</td>
<td>photopheresis + IFN, bexarotene</td>
<td>Combination chemo</td>
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</tr>
<tr>
<td>Alemtuzumab</td>
<td>TSEBT + IFN, photopheresis</td>
<td><strong>New targeted or cytotoxic systemic therapy</strong></td>
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</tr>
<tr>
<td>Bexarotene, methotrexate, IFN vorinostat, romidepsin</td>
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</tbody>
</table>

**brentuximab, pralatrexate, liposomal doxorubicin, gemcitabine, other**
### Standard-of-care combinations with immune therapies:

- **Phototherapy + IFNs**
- **Total skin electron beam (TSEBT) + IFNs**
- **Photopheresis + IFNs +/- bexarotene**
- **Bexarotene + IFNs**

### Need more combination strategies as clinical trials with correlative studies

### Current Clinical Management of CTCL, 2017

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

<table>
<thead>
<tr>
<th>IA</th>
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<th>IIB</th>
<th>III</th>
<th>IV</th>
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<td>Tumors</td>
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<td>Photopheresis + IFN, bexarotene</td>
<td></td>
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</tr>
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</table>

**Clinical Trials**

**brentuximab, pralatrexate, liposomal doxorubicin, gemcitabine, other**

**Allo-HSCT**
How to best combine? Concurrently vs sequentially? Both elements? Continuous vs intermittent dosing? Dose of each therapy?

What guides/tools do we have to help optimize partnering?
- Pre-clinical models (cell lines, clinical samples, PDX/other animal system)
- GEP/NGS/other molecular data
- Epigenetic tools
- Single agent or combination human data
Immunotherapies in clinical development in CTCL

**Direct effects** against tumor cells

- Kills tumor cells, renders tumors immunogenic, stimulates immune mechanisms

**Indirect effects** on immune system microenvironment, systemic

- DCs
- CD8 T cells
- NK cells
- Tregs
- MDSCs
- Macrophages

**Direct + indirect effects**

- Cell surface targets
- Intracellular targets

TILs
Immunotherapies in clinical development in CTCL

**Direct effects** against tumor cells
- Anti-KIR3DL2 mAb
- Bispecific Ab
- CAR-T
- Allogeneic HSCT

**Direct + indirect effects**
- Anti-CCR4 Mab
- E7777
- Combination therapies/strategies

**Indirect effects** on immune system microenvironment, systemic
- Anti-PD-1/PD-L1 mAb
- Anti-KIR mAb
- Anti-CD137 mAb
- Anti-CD47 mAb
- TLR-agonists (resiquimod)
- Cytokines (IFNγ, IL-12)
Immunotherapies in clinical development in CTCL

Direct effects against tumor cells

Anti-KIR3DL2 mAb
Bispecific Ab
CAR-T
Allogeneic HSCT

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

Bagot et al

TILs
M
CTCL

M
M
M
M
Targeting **KIR3DL2** with IPH4102 in CTCL

*Member of the Killer Immunoglobulin-like Receptor (KIR) family*

In healthy individuals, there is limited expression of KIR3DL2 by normal blood cells (~25% NK cells and <15% T cells)

KIR3DL2 is expressed by up to 95% CTCL cells irrespectively of disease stage and CTCL subtype, ↑↑ T-MF and SS

→ KIR3DL2 is considered a specific marker of CTCL, high therapeutic index

IPH4102, an Fc modified humanized IgG1, ↑ADCC/ADCP

*Sicard et al, Oncoimmunology 2015*
KIR3DL2 expression in Sézary cells

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

Marie-Cardine et al, Cancer Res. 2014

IPH4102 First-In-Human dose-escalation study ongoing, led by Martine Bagot, at 6 EU/US sites
Phase 1 study of IPH4102, first-in-class, humanized anti-KIR3DL2 monoclonal antibody, in R/R CTCL: preliminary data

- **Accelerated 3+3 design (0.0001 to 10 mg/kg)**
- Regular safety and clinical activity assessments to decide on treatment extension and intra-patient dose-escalation
- Clinical global response assessed according to consensus response criteria
- Immuno-monitoring of blood cells: screening, weekly for 5 weeks and then Q4W after W10
- Skin biopsies taken at SCR, W5, W14 and End of Tx visit

### Key eligibility
- **All CTCL subtypes with at least 2 prior systemic therapies**
- **KIR3DL2 expression (>5%) on malignant T cells in blood (flow) or skin (IHC), assessed by central review**

### Patients (N)

<table>
<thead>
<tr>
<th>CTCL Subtype</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>MF</td>
<td>2</td>
</tr>
<tr>
<td>SS</td>
<td>13</td>
</tr>
<tr>
<td>CD4+ CTCL, NOS</td>
<td>1</td>
</tr>
</tbody>
</table>

19 pts screened, 3 screen failures for KIR3DL2-negativity

Currently at cohort 10, no DLT, concurrent intra-patient dose-escalations


**Preliminary clinical and correlative results: anti-KIR3DL2 mAb in CTCL**

<table>
<thead>
<tr>
<th></th>
<th>All pts</th>
<th>Best Global Response n=16</th>
<th>Sézary Syndrome pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best Response (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>PR</td>
<td>6</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>SD</td>
<td>10</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ORR</td>
<td>38 %</td>
<td>38 %</td>
<td>46 %</td>
</tr>
</tbody>
</table>

12 pts were still on treatment at data cut-off, including all responders

**Ex vivo ADCC assay**

Autologous NK-mediated death of KIR3DL2+CD4+ tumor cells induced by IPH4102

- NK cells from SS pt 11-005 mediate potent ADCC with IPH4102 against primary autologous tumor cells

**MRD in skin (biopsy #1) & blood**

- 2 dominant clones found pre-dose in skin and blood
- Both substantially decrease by W5 and W14 in skin biopsies and blood (still above detection limit)

**% of CD4+ T among lymphocytes in skin lesions**

- SCR: 98%
- W5: 95%
- W14: 90%

**% of CD8+ T among lymphocytes in skin lesions**

- SCR: 2%
- W5: 5%
- W14: 10%

- Treated skin lesions show ↓CD4 and ↑CD8 lymphocytes
- ↓%KIR3DL2+ in skin/blood; ↓MRD by HTS
- Potent NK function by autologous ADCC assay
- Potential for immune combination with agents ↑NK activity and/or cell phagocytosis
Immunotherapies in clinical development in CTCL

Direct effects against tumor cells

Anti-KIR3DL2 mAb
Bispecific Ab
CAR-T
Allogeneic HSCT

CAR-T cells targeting:
CD30
CCR4
TRBC1

TILs
M
M
M
M
CTCL
Immunotherapies in clinical development in CTCL

**Direct effects** against tumor cells

- Anti-KIR3DL2 mAb
- Bispecific Ab
- CAR-T

**Consolidative/additional tx**, hoping for permanent or lasting cellular anti-tumor activity

- Allogeneic HSCT

**Donor Cell Transplant**

Replacement of Host Blood System

- Donor Immune System to destroy lymphoma cells

TILs

CTCL

Donor Cell Transplant

Replacement of Host Blood System

Stem cell

Progenitor cells

Precursor cells

Mature cells

Lymphocytes

Sezary cells
Immunotherapies in clinical development in CTCL

**Direct effects** against tumor cells

**Indirect effects** on immune system microenvironment, systemic

Direct + indirect effects

Anti-CCR4 Mab E7777

Combination therapies/strategies
Immunotherapies in clinical development in CTCL

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

Daisuke Sugiyama, Hiroyoshi Nishikawa, Yuka Maeda, Megumi Nishikoa, Atsushi Tanemura, Ichiro Katayama, Sachiko Ezeo, Yuzuru Kanakura, Eiichi Sato, Yasuo Fukumonis, Julia Karbach, Elke Jäger, and Shimon Sakauchis

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

Direct + indirect effects

Anti-CCR4 Mab
E7777
Combination therapies/strategies

CCR4 is expressed in malignant T cells and Tregs
⇒ Tumor-directed (ADCC) and possible added immune modulatory effects
Approved in Japan for ATL (2012) and CTCL/PTCL (2014)

Phase 3 RCT against vorinostat in CTCL
PFS as primary endpoint
Completed enrollment 2016
Peripheral blood:
• CCR4 expression on malignant T cell = 21-100%
• CCR4 expression on Tregs = 59-100% (mean 88%)
• Significant reduction of CCR4+ cells after treatment
• Overall ↑ % CD8+ T cells; restoration of NK function

Lesional skin:
• ↓infiltrating CCR4+ and/or FoxP3+ T cells
Clinical trials using anti-CCR4 mAb for Treg depletion

Mogamulizumab for CCR4-negative advanced or recurrent solid tumors (NCT01929486), aiming to deplete effector Tregs, thus boosting anti-tumor immunity

2015 JSMO abstract, Ishida et al.

- 0.1 – 1.0 mg/kg
- Effective depletion of Tregs even at 0.1 mg/kg with augmentation of immune response
- Concern for development of new autoimmune disease

Bayry et al., Trends Pharm Sci 2014
Immunotherapies in clinical development in CTCL

**Direct effects** against tumor cells
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**Indirect effects** on immune system microenvironment, systemic
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- Cytokines (IFNγ, IL-12)

**Direct + indirect effects**
- Anti-CCR4 Mab E7777
- Combination therapies/strategies

**Release the brakes, step on the accelerator** => boost host immune system
Topical resiquimod can induce disease regression and enhance T-cell effector functions in cutaneous T-cell lymphoma

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

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

Resiquimod
Newer, potent TLR 7/8 agonist, available as topical therapy

Malignant T cell eradication is a/w ↑T-cell and NK-effector functions in treated skin

Clinical trial in MF to initiate in 2017
In situ vaccination against mycosis fungoides by intratumoral injection of a TLR9 agonist combined with radiation: a phase 1/2 study


CpG injections (6 mg) bracket RT Days 1 & 2 of immunization site #1, then Days 22 & 23 of immunization site #2, plus weekly until week 8

Assess systemic clinical response

Pre-treatment biopsy | Week 9

Immunization site #1 (CpG + RT) | Immune response monitoring

Immunization site #2 (CpG + RT) | MF lesions assessed for response

Low-dose radiation plus TLR-A +

Immunization site: left thigh
Immunotherapies in clinical development in CTCL

**Direct effects**
- Anti-KIR3DL2 mAb
- Bispecific Ab
- CAR-T
- Allogeneic HSCT

**Indirect effects**
- on immune system microenvironment, systemic
  - Anti-PD-1/PD-L1 mAb
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  - Anti-CD47 mAb
  - TLR-agonists (resiquimod)
  - Cytokines (IFNγ, IL-12)

**Direct + indirect effects**
- Anti-CCR4 Mab E7777
- Combination therapies/strategies

**Release the brakes, step on the accelerator**
- => boost host immune system
Combination of IL-12 with radiation therapy for efficient cytoreduction + lasting response
Low-dose total skin electron beam therapy as an effective modality to reduce disease burden in patients with mycosis fungoides: Results of a pooled analysis from 3 phase-II clinical trials

Richard T. Hoppe, MD, Cameron Harrison, MD, Mahkam Tavallaei, MD, MPH, Sameer Bashey, MD, Uma Sundram, MD, PhD, Shufeng Li, MS, Lynn Million, MD, Bouthaina Dabaja, MD, Pamela Gangar, MD, Madeleine Dugic, MD, and Youn H. Kim, MD
Stanford, California, and Houston, Texas

JAAD 2015; 72:286-92

- **Low-dose, 12 Gy (3 wks) vs. standard, 36 Gy (10 wks)**
- **Reliable/efficient reduction** in skin disease => near 90% ORR, ~30% CR
- ~ 1.5 yr median duration of benefit
- **Less side effects:** no permanent hair loss, less skin toxicity
- Can be given repetitively in pt’s course
- Low-dose can be followed or combined with other therapies to boost response and duration of benefit
- Great option for folliculotropic disease or pts with multiple co-morbidities

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>ORR n (%)</th>
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<tbody>
<tr>
<td>All</td>
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<td>9 (27)</td>
<td>20 (61)</td>
<td>4 (12)</td>
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<td>20 (91)</td>
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<tr>
<td>II A</td>
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<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1 (100)</td>
</tr>
<tr>
<td>II B</td>
<td>7 (21)</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>6 (96)</td>
</tr>
<tr>
<td>III A</td>
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<td>1</td>
<td>1</td>
<td>0</td>
<td>1 (50)</td>
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<tr>
<td>Median time to response</td>
<td>7.6 (3-12.4) wk</td>
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<tr>
<td>Median duration of clinical benefit</td>
<td>70.7 (41.8-133.8) wk</td>
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F-MF, n=8 (24%)
LCT, n=4 (12%)

Combination trial in progress:
Low-dose TSEBT + rh-IL-12 to prolong the clinical response

Low-dose (12 Gy) Total Skin EBT

CR
A Single-arm Phase 2A Study of NM-IL-12 (rHu-IL-12) In Patients with Mycosis Fungoides-Type CTCL (MF) Undergoing Low-Dose Total Skin Electron Beam Therapy

YH Kim, RT Hoppe, AH Rook, A Maity, L Geskin, D Horowitz, G Finnegan, M Khodadoust, WK Weng, A Lares, EK Hong, M Buchanan, V Ma, H Kha, C Lawrence, V Vainstein, LA Basile

Collaborative study by Stanford, U Penn, Columbia, and Neumedicine
Single-arm phase 2A study of rHu-IL-12 + low-dose TSEBT in MF

- Single arm, open-label, non-randomized study for patients with MF
- N=10; Clinical Stage IB-IIIB, >18 years old

Patient 001-03, 54M with MF, stage IB (plaques), CR confirmed at Week 11
Sustained CR at Week 27, continues to receive treatment q 4 weeks
Immunotherapies in clinical development in CTCL

**Direct effects**
against tumor cells

**Direct + indirect effects**

**Indirect effects**
on immune system microenvironment, systemic

- Anti-PD-1/PD-L1 mAb
- Anti-KIR mAb
- Anti-CD137 mAb
- Anti-CD47 mAb
- TLR-agonists (resiquimod)
- Cytokines (IFNγ, IL-12)

Release the brakes, unleash anti-tumor T cells
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)
Z Rahbar, 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
Anti-PD1 therapy restores a natural anti-tumor immune response

“releases the brakes”
Immune Checkpoints in MF / SS

The PD1/PDL1 immune checkpoint axis appears central to MF/SS biology

Hypothesis:
Disruption of PD1/PDL1 immune checkpoint will be an effective treatment strategy in CTCL

- **PD1** – highly expressed
- **PD-L1** – can be expressed
- **PD-L1** – can be translocated
- **PD-L2** – can be translocated
Durable responses with pembrolizumab in MF/SS

Overall response rate: 38%

- IFN-γ
- IL-12
- CD40
- TLR-A
- Radiation
- Actionable pathway targets by genomic data
- Tumor cell directed mAb
Anti-PD-1 mAb plus IFN-γ combination strategy

- Rationale
  - IFN-γ with broad immune activation, but ↑PD-1 or PD-L1 expression may contribute towards immune escape
  - Anti-PD-1 may abrogate the potential immune escape induced by IFN-γ
  - Synergistic or complementary in immune activation
  - Apply correlative discovery, enrich response subset
- Similar combination regimen is well-tolerated in solid tumor trial

Immune combination therapy schema:
- IFN-γ lead-in treatment x 1 week = > correlative biomarkers after IFN-γ monotherapy
- Combination of pembro 200mg every 3 weeks and IFN-γ 50 mcg/m² 3 doses per week for 12 weeks
- Followed by pembro continued every 3 wks up to 2 yrs. IFN-γ boost (3 wks) every 2 cycles of pembro
- Intra-patient dose for IFN-γ by 25 mcg/m² allowed
Immunotherapies in clinical development in CTCL

A First-In-Human Phase Dose Escalation Trial of Anti-CD47 mAb (Hu5F9-G4) in Advanced Solid Malignancies: Stanford

CTCL (MF/SS) expansion cohort

CD47-SIRPα axis
“Don’t eat me” signal by tumor cells
Evasion of macrophage phagocytosis
Weissman group, Stanford

Indirect effects on immune system microenvironment, systemic

Release the brakes, unleash phagocytic macrophages

Anti-PD-1/PD-L1 mAb
Anti-KIR mAb
Anti-CD137 mAb
Anti-CD47 mAb
TLR-agonists (resiq)
Cytokines (IFNγ, IL-12)
CD47-SIRPα: A Universal Cancer Macrophage Immune Checkpoint

- CD47 sends a “don’t eat me” signal through its receptor SIRPα to macrophages and other immune cells
- Antibodies that block CD47:SIRPα stimulate macrophage phagocytosis of cancer cells
- Normal cells do not express “eat me” signals and are not affected by anti-CD47 mAbs
- Hu5F9-G4: humanized IgG4 anti-CD47 antibody developed at Stanford
Anti-CD47 Antibody Enables Phagocytosis of Cancer Cells

Control IgG treatment

Anti-CD47 mAb treatment

Macrophages
Cancer cells
Targeting CD47–SIRPα axis in cancer immunotherapy: converting “don’t eat me” → “eat me” signal and more
Hu5F9-G4 synergizes with other anti-cancer antibodies

- Monoclonal cancer antibodies such as rituximab provide a strong extrinsic “eat me” signal through the Fc receptor (ADCC, ADCP)
- Hu5F9-G4 blocks the “don’t eat me signal”
- Synergistic activity occurs through releasing the brakes (don’t eat me blockade) and stepping on the gas (eat me signal)
Hu5F9-G4 Synergizes with Rituximab to Eliminate NHL In Vivo

**B-cell lymphoblastic lymphoma (Raji)**

- Anti-CD47 Ab therapy with Hu5F9-G4 in combination with rituximab enables durable complete remissions in NHL-engrafted mice

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Liu et al., PLoS One 2015
Chao et al., Cell 2010
CTCL – Hu5F9-G4 and anti-CCR4 combination therapy

Other great combination potential with newer CTCL-directed mAbs, such as anti-KIR3DL2
Agents that can target new genomic discoveries + added anti-tumor immune effects

Genomic analysis of mycosis fungoides and Sézary syndrome identifies recurrent alterations in TNFR2

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T-cell activation, survival, proliferation

Targeting TNFR2 with antagonistic antibodies inhibits proliferation of ovarian cancer cells and tumor-associated Tregs

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Integrating immunotherapy approaches in CTCL

**Summary**

- **Immunotherapy approaches** to directly target malignant cell and/or stimulate the host immune activity to improve clinical activity
- **New/improved technology** allowing us to learn more, help identify actionable targets, and modify/render agents more effective/safe
- **More encouraging treatment options** (many in the pipeline)
- Develop combination/sequential strategies to optimize anti-tumor activity and to address immune escape/evasion, *so much to learn*
- Be mindful of immune-mediated toxicities
- **Molecular/biomarker platforms integrated into clinical trials** to learn predictive value for response/resistance/escape, flare reactions, toxicity, or survival outcomes
- Taking steps **towards how to combine and integrate** to improve outcome