# Research Update

**Youn H Kim, MD**

Department of Dermatology
Director, Multidisciplinary Cutaneous Lymphoma Group
Stanford Cancer Institute & School of Medicine
NCCN NHL Panel Member

# Disclosure statement

## Youn Kim, MD

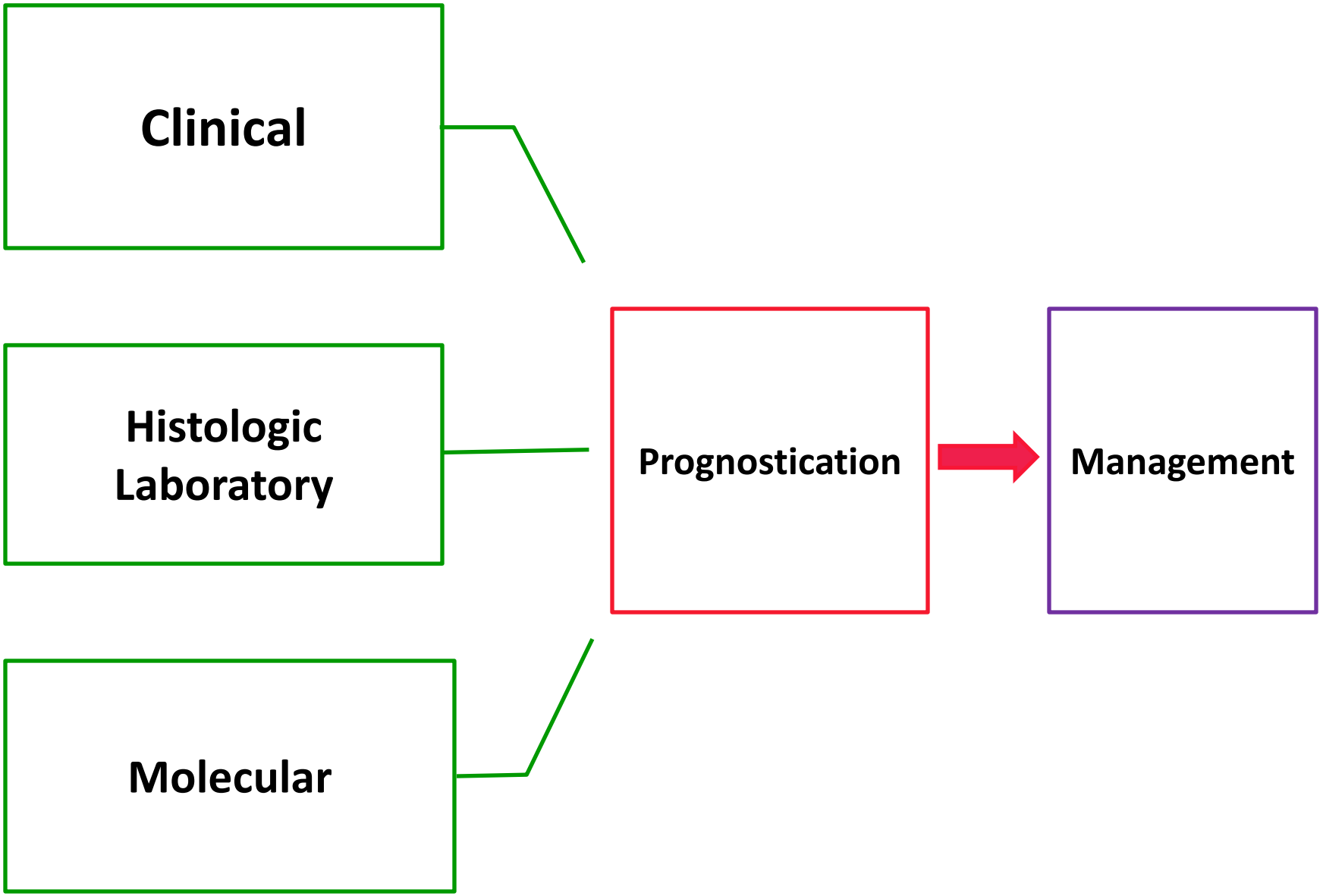
- **Steering Committee**
  - Eisai, Kyowa, Millennium/Takeda
- **Consultant or Advisory Board**
  - Actelion, Celgene, Galderma, Seattle Genetics, Horizon, Forty Seven, Portola
- **Investigator**
  - Kyowa, Merck, Millennium/Takeda, Seattle Genetics, Eisai, Tetralogic, Innate, Neumedicine, Soligenix, miRagen

CLIC
CUTANEOUS LYMPHOMA INTERNATIONAL CONSORTIUM

# Cutaneous Lymphoma International Consortium (CLIC): an International Alliance for Large-Scale Collaborative Investigations in Cutaneous Lymphoma

**55+ centers**
**Derm, Onc, Path**

# Management of Cutaneous Lymphoma



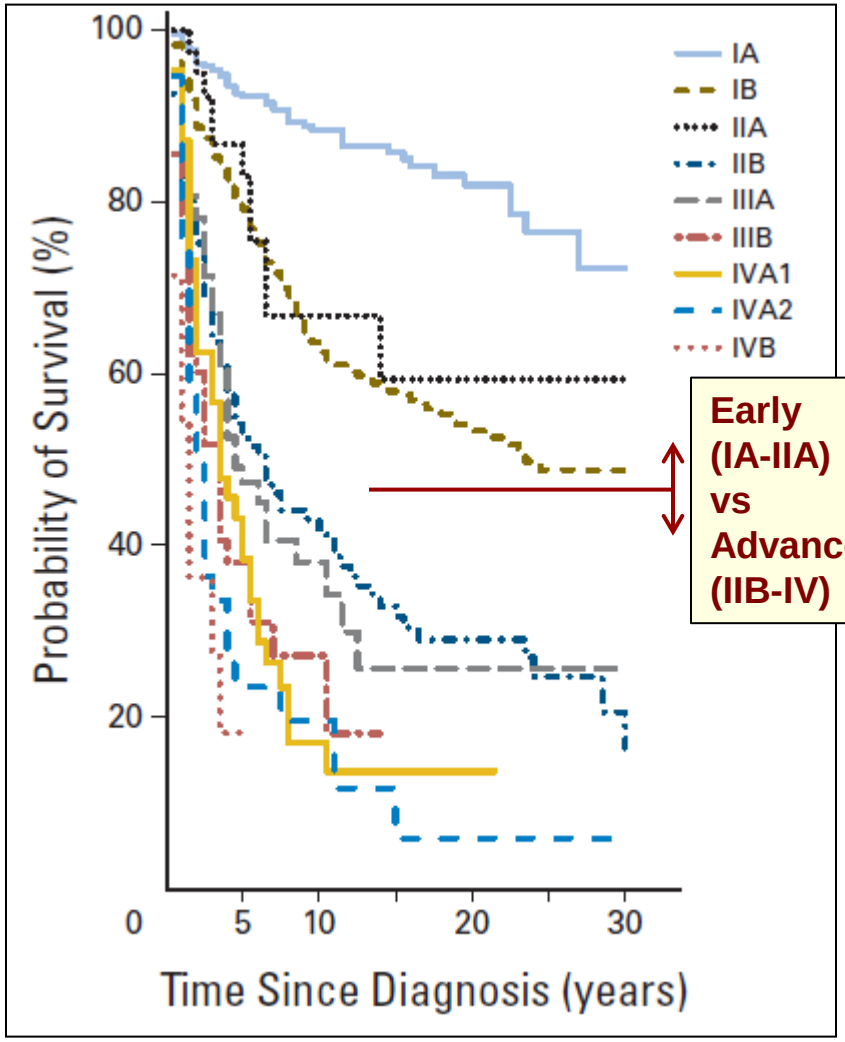
# New Agents and Therapeutic Strategies in CTCL

# Cutaneous T- and NK/T-cell Lymphomas

| New WHO-EORTC Classification |
| --- |
| Mycosis fungoides and variants/subtypes |
| Sézary syndrome |
| PC CD30+ lymphoproliferative disorders |
| Subcutaneous panniculitis-like T-cell lymphoma |
| Extranodal NK/T-cell lymphoma, nasal type |
| Cutaneous $\gamma/\delta$ T-cell lymphoma |
| Adult T-cell leukemia/lymphoma |
| PC peripheral T-cell lymphoma, unspecified<br>• Aggressive epidermotropic CD8+ T-cell lymphoma<br>• CD4+ sm/med-sized pleomorphic T-cell *lymphoma/LPD*<br>• PTCL, other |

WHO monogram, 4th Ed, 2008

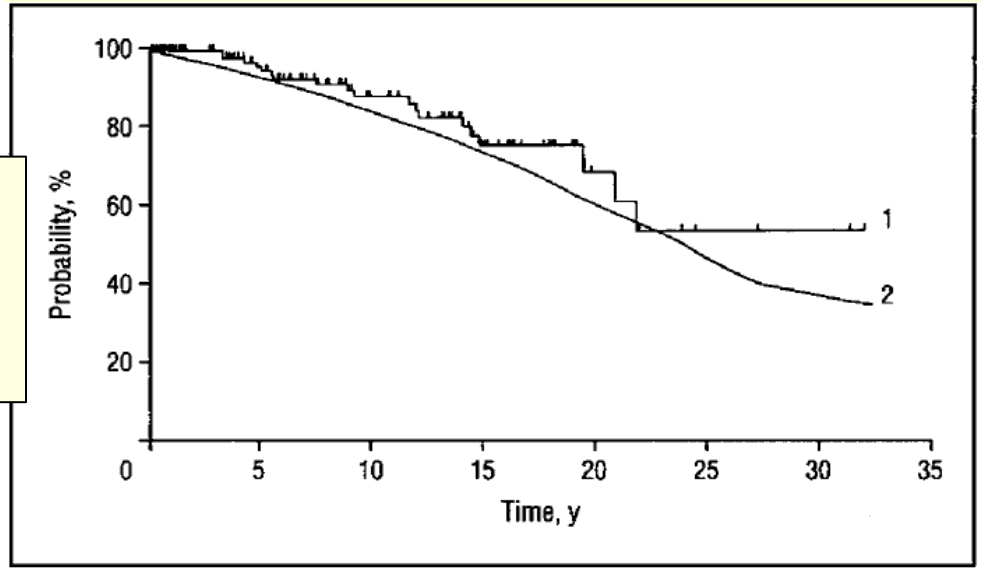
# Prognosis of early vs advanced stage MF and SS:
## *Appropriate risk-stratification for treatment selection*




**Early (IA-IIA) vs Advanced (IIB-IV)**

Agar et al. J Clin Oncol 2010;28:4730

**Stage IA vs. control population:**
***Life-expectancy is not altered in patients with limited patch/plaque disease***




**F-MF or LCT with worse clinical outcome**
***F-MF not sig independent factor in advanced MF/SS*** *(CLIC Scarisbrick et al, 2015)*

*Arch Dermatol 146:607, 2010, J Clin Oncol 28:4730, 2010, Blood 119:1643, 2012, J Clin Oncol 2015;33:3766*

# NCCN Guidelines Version 1.2016
# Mycosis Fungoides/Sezary Syndrome

NCCN Guidelines Index
NHL Table of Contents
Discussion

## SUGGESTED TREATMENT REGIMENS[a]

### SYSTEMIC THERAPIES

*Category A (SYST-CAT A)*

- Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13-cis-retinoic acid], acitretin)[e]
- Interferons (IFN-alpha, IFN-gamma)
- HDAC-inhibitors (vorinostat, romidepsin)[e]
- Extracorporeal photopheresis[f]
- Methotrexate (≤100 mg q week)

*Category B (SYST-CAT B)*

- First-line therapies (alphabetical order)
  - Brentuximab vedotin
  - Gemcitabine
  - Liposomal doxorubicin
  - Low-dose pralatrexate
- Second-line therapies
  - Chlorambucil
  - Pentostatin
  - Etoposide
  - Cyclophosphamide
  - Temozolomide
  - Methotrexate (>100 mg q week)
  - Bortezomib (category 3)

### SYSTEMIC THERAPIES (continued)

*Category C (SYST-CAT C)*[g] (alphabetical order)

- Bortezomib (category 3)
- Brentuximab vedotin
- Gemcitabine
- Liposomal doxorubicin
- Low- or standard-dose pralatrexate
- Romidepsin
- See regimens listed on TCEL-B 2 of 5 (PTCL-NOS)[h]

### COMBINATION THERAPIES

*Skin-directed + Systemic*

- Phototherapy + retinoid[e]
- Phototherapy + IFN
- Phototherapy + photopheresis[f]
- Total skin electron beam + photopheresis[f]

*Systemic + Systemic*

- Retinoid + IFN
- Photopheresis[f] + retinoid
- Photopheresis[f] + IFN
- Photopheresis[f] + retinoid + IFN

**=> Stage-based management**

SUGGESTED TREATMENT REGIMENS[a]

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TCEL-B 2 of 5 (PTCL-

IES

c
d[e]

pheresis[f]
m + photopheresis[f]

*Systemic + Systemic*

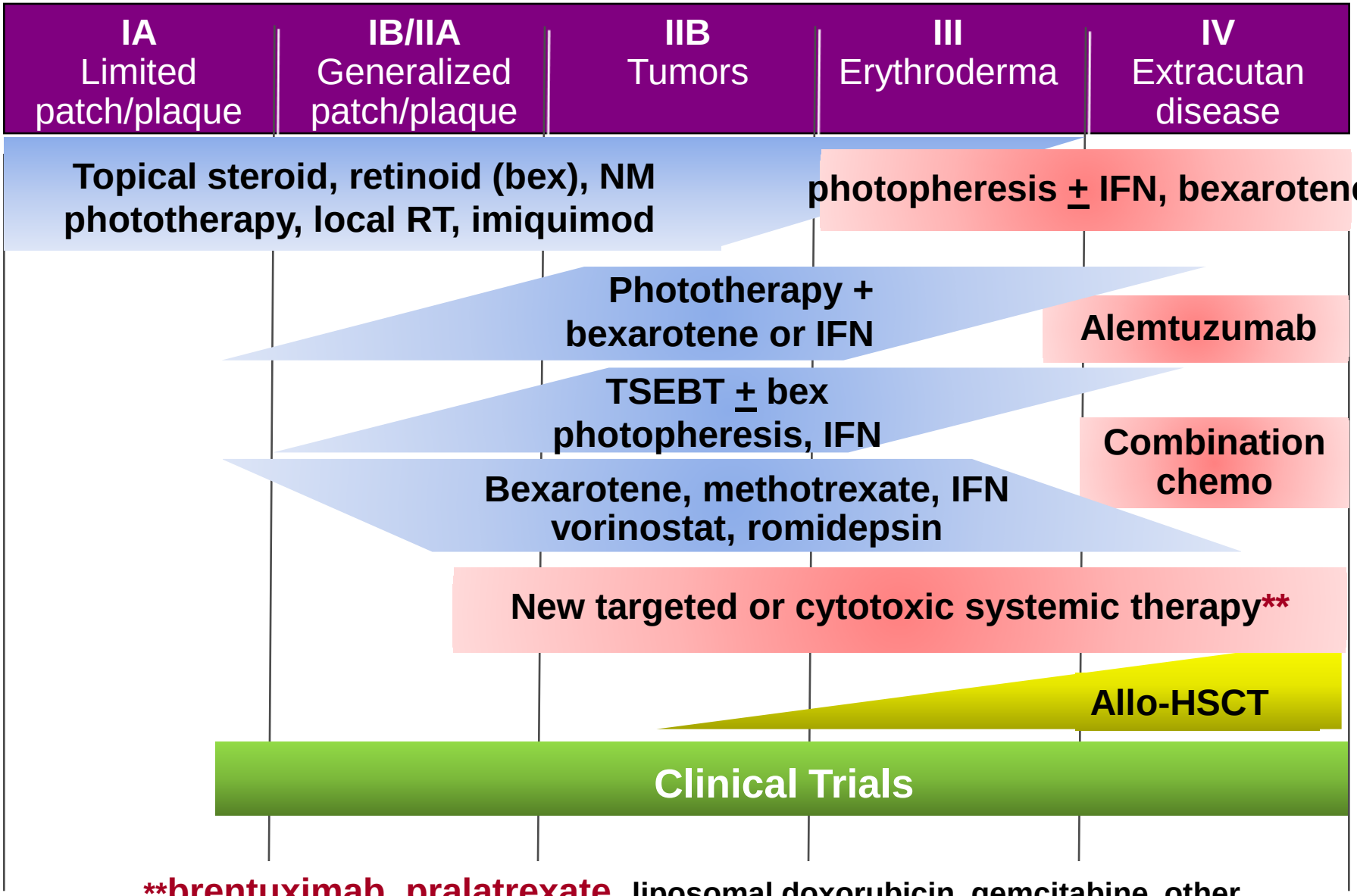
- Retinoid + IFN
- Photopheresis[f] + retinoid
- Photopheresis[f] + IFN
- Photopheresis[f] + retinoid + IFN

**What are the standard systemic agents in CTCL?**

**=> Stage-based management**

# Current Clinical Management of CTCL, *2016*

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




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

# What therapeutic advances have we made?

# Advances in skin-directed therapies, to partner with systemic agents in CTCL

- Topical steroids
- Topical chemotherapy
  - FDA approval of topical mechlorethamine gel
- Topical retinoids (bexarotene)
- Topical imiquimod
- Phototherapy
  - UVB (narrow band, broad band)
  - PUVA (psoralen + UVA)
- **Radiation, *less is more***
  - **Low-dose (12 Gy) total skin electron beam therapy**
  - **Combine with immune modulation**
- Excimer, photodynamic therapy (not in NCCN)

**New skin-directed therapies in clinical development:**

- **Resiquimod (TLR 7/8-A)**
- **Topical HDAC inhibitor (SHP-141/SHAPE)**
- **New PDT (hypericin)**

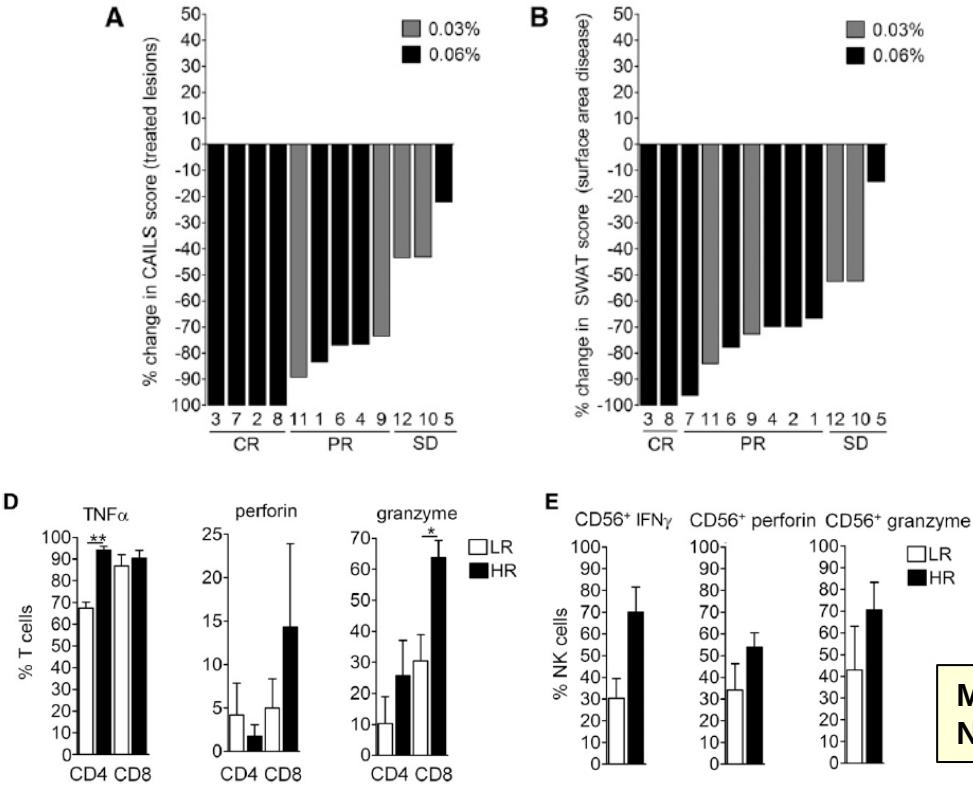
*JAMA Dermatol 2013;149:25;*
*J Am Acad Dermatol 2015:72:286; Blood 2015;126:1452*

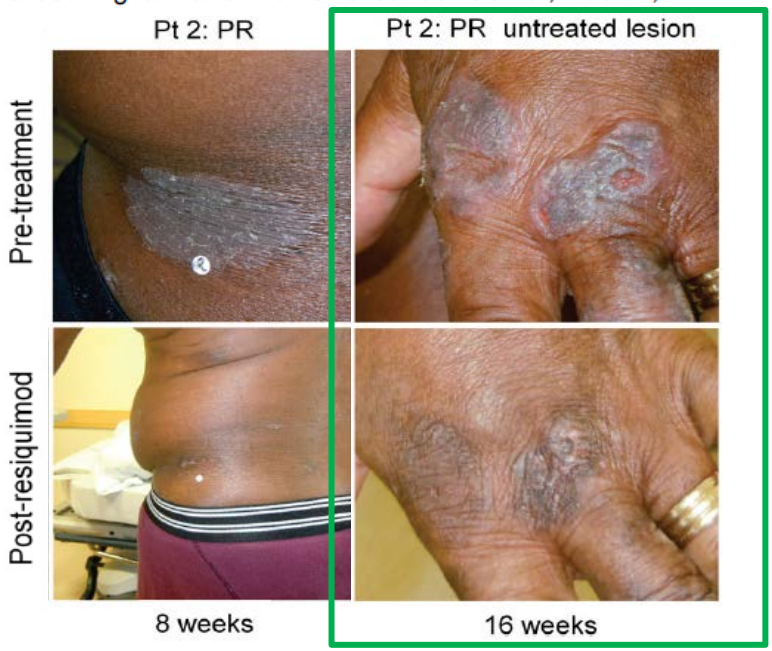
*Blood 2015;126:1452*

# Topical resiquimod can induce disease regression and enhance T-cell effector functions in cutaneous T-cell lymphoma

Alain H. Rook,[1] Joel C. Gelfand,[1] Maria Wysocka,[1] Andrea B. Troxel,[1] Bernice Benoit,[1] Christian Surber,[2,3] Rosalie Elenitsas,[1] Marie A. Buchanan,[1] Deborah S. Leahy,[1] Rei Watanabe,[4,5] Ilan R. Kirsch,[6] Ellen J. Kim,[1] and Rachael A. Clark[5,7]

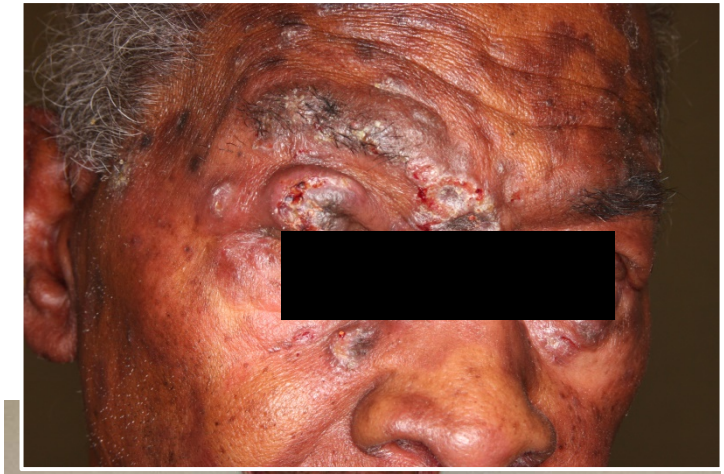
[1]Department of Dermatology and the Center for Clinical Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [2]Department of Dermatology, University Hospital, Zürich, Switzerland; [3]Department of Dermatology, University Hospital, Basel, Switzerland;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

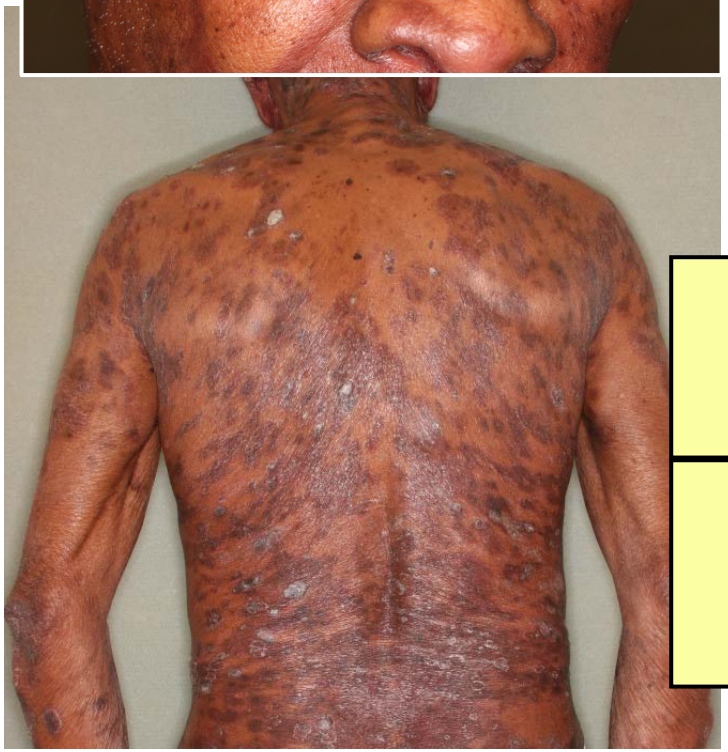



**Malignant T cell eradication is a/w ↑T-cell and NK-effector functions in treated skin**

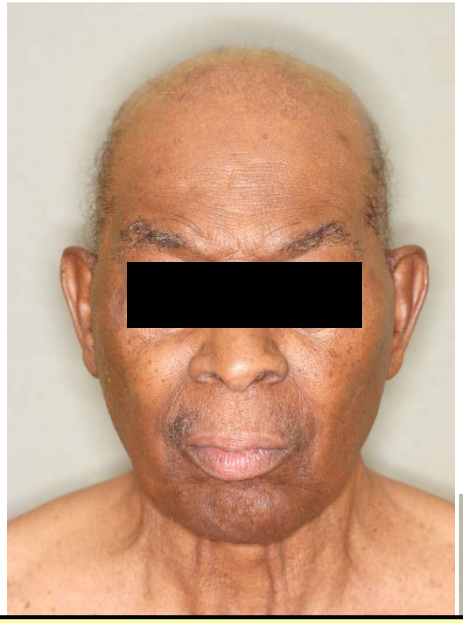
# MF stage IIB with LCT

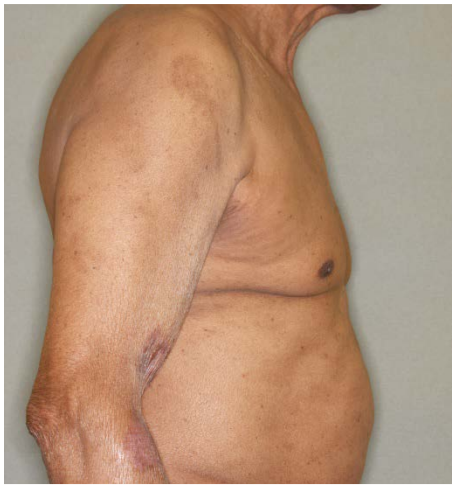


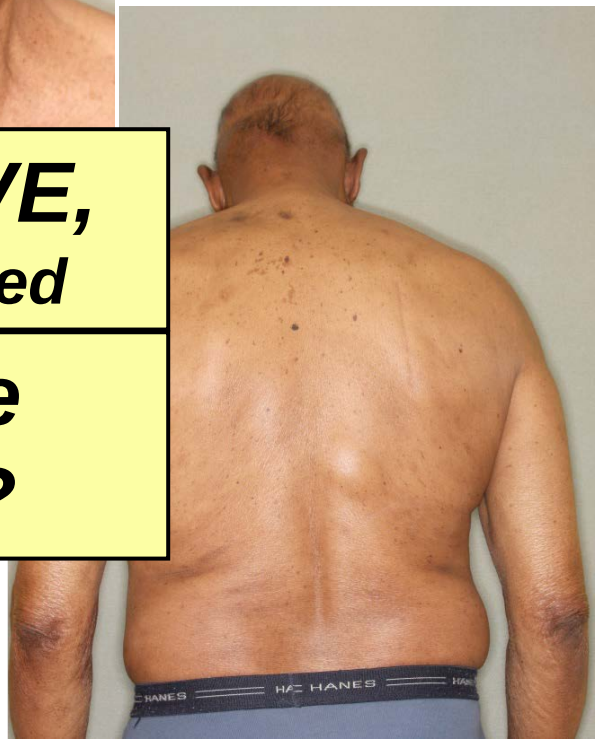


**Standard dose TSEBT**

**36 Gy**







***NOT CURATIVE,***
***Retreatment limited***

***Why not use lower dose?***

# 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,[a] Cameron Harrison, MD,[b] Mahkam Tavallaee, MD, MPH,[b] Sameer Bashey, MD,[b] Uma Sundram, MD, PhD,[b,c] Shufeng Li, MS,[b] Lynn Million, MD,[a] Bouthaina Dabaja, MD,[d] Pamela Gangar, MD,[e] Madeleine Duvic, MD,[e] and Youn H. Kim, MD[b]
*Stanford, California, and Houston, Texas*

*JAAD 2015; 72:286-92*

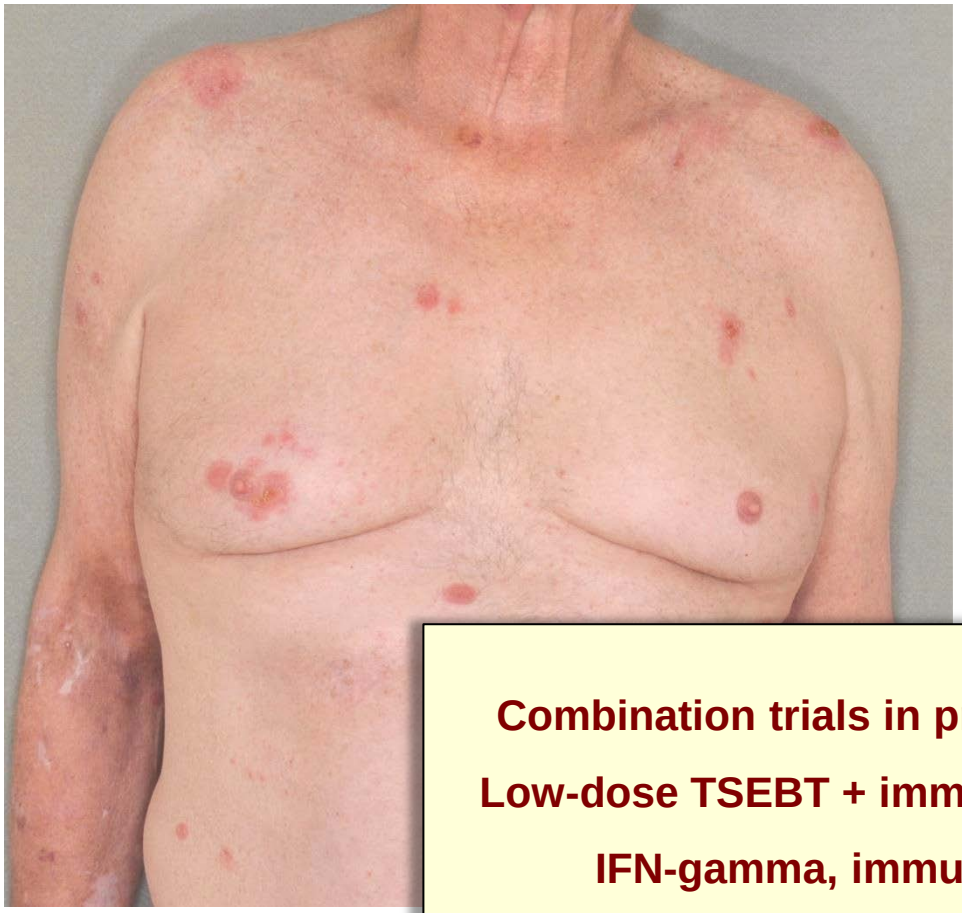
- **Low-dose, 12 Gy (3 wks)** vs. standard, 36 Gy (10 wks)
- **Reliable/efficient reduction** in skin disease => **near 90% ORR, ~30% CR**
- **Less side effects:** no permanent hair loss, less skin toxicity
- **Can be given repetitively** in pt's course
- Low-dose can be followed or combined with other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

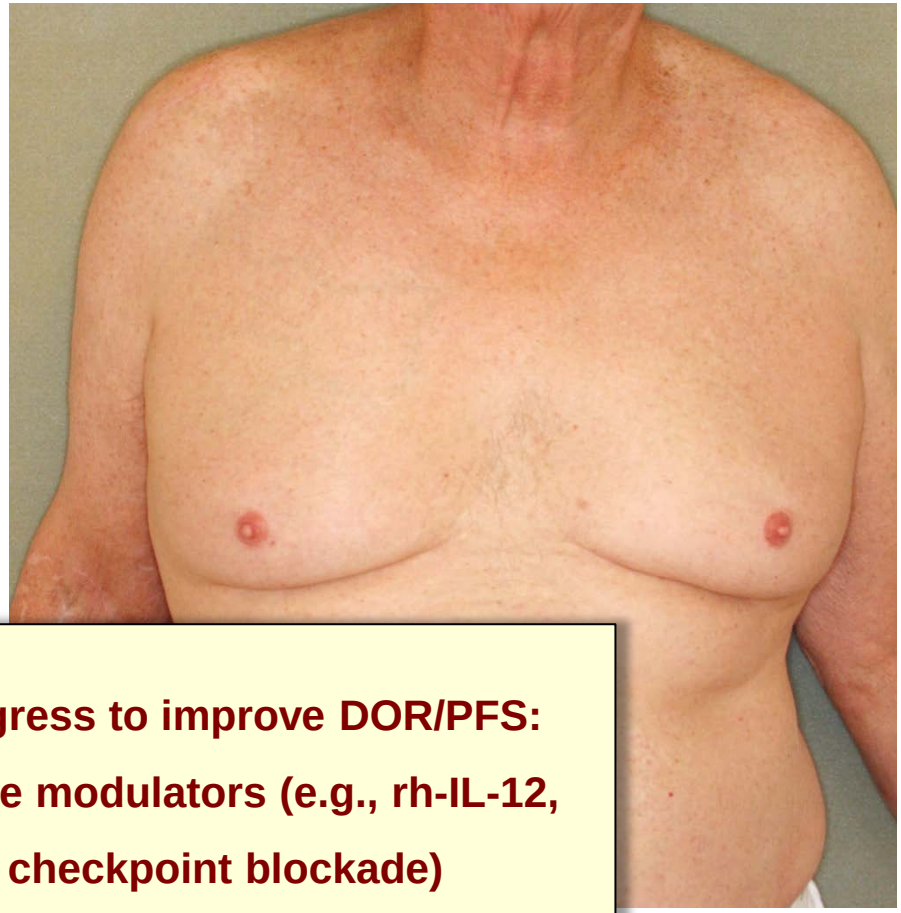
**Table II.** Best overall response to treatment at study termination, total time to response, and duration of clinical response

| | | Response data | | | | ORR |
|---|---|---|---|---|---|---|
| Characteristic | n (%) | CR | PR | SD | PD | n (%) |
| Clinical stage | | | | | | |
| All | 33 (100) | 9 (27) | 20 (61) | 4 (12) | 0 | 29 (88) |
| IB | 22 (67) | 7 | 13 | 2 | 0 | 20 (91) |
| IIA | 2 (6) | 0 | 2 | 0 | 0 | 2 (100) |
| IIB | 7 (21) | 2 | 4 | 1 | 0 | 6 (96) |
| IIIA | 2 (6) | 0 | 1 | 1 | 0 | 1 (50) |
| Median time to response (range) | | 7.6 (3-12.4) wk | | | | |
| Median duration of clinical benefit (95% CI) | | 70.7 (41.8-133.8) wk | | | | |

**F-MF, n=8 (24%)**
**LCT , n=4 (12%)**

# Clinical response with low-dose (12 Gy) TSEBT
# 69 yo M, stage IIB, folliculotropic MF, multiple comorbidities





**Combination trials in progress to improve DOR/PFS:**

**Low-dose TSEBT + immune modulators (e.g., rh-IL-12, IFN-gamma, immune checkpoint blockade)**

**Screening**
**mSWAT 133**
**Pruritus 8/10**

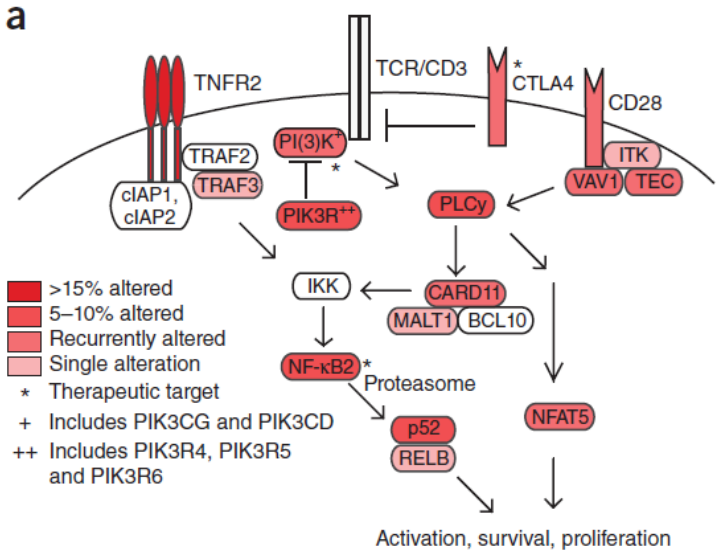
**Wk 16**
**mSWAT 0 (CR)**
**Pruritus 0/10**

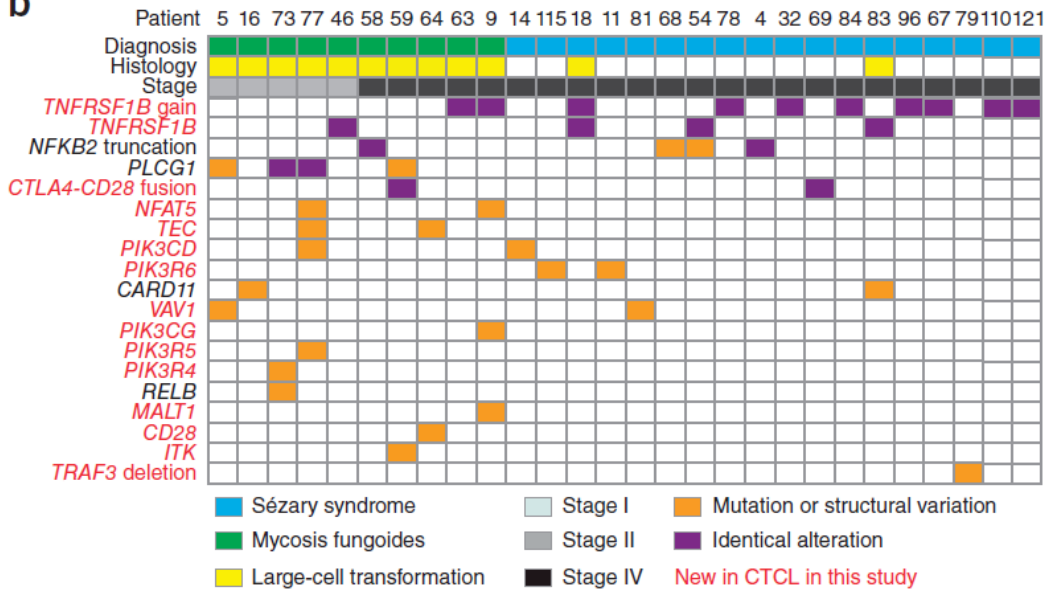
nature genetics

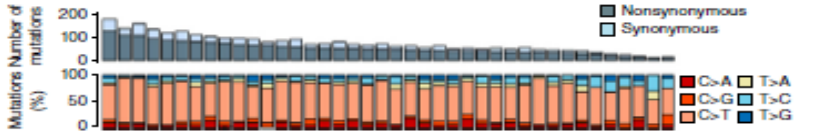
2015

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

Alexander Ungewickell[1,2,12], Aparna Bhaduri[1,12], Eon Rios[1], Jason Reuter[3], Carolyn S Lee[1], Angela Mah[1], Ashley Zehnder[1], Robert Ohgami[4], Shashikant Kulkarni[5–7], Randall Armstrong[8], Wen-Kai Weng[8], Dita Gratzinger[4], Mahkam Tavallaee[9], Alain Rook[10], Michael Snyder[3], Youn Kim[9] & Paul A Khavari[1,11]

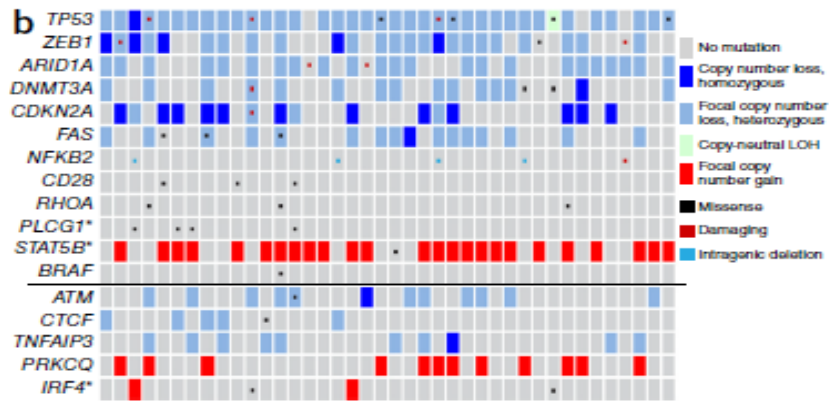



# Genomic landscape of cutaneous T cell lymphoma

Jaehyuk Choi[1,2], Gerald Goh[3,4], Trent Walradt[1], Bok S Hong[1], Christopher G Bunick[1], Kan Chen[1], Robert D Bjornson[5], Yaakov Maman[3,6], Tiffany Wang[1], Jesse Tordoff[1], Kacie Carlson[1], John D Overton[7], Kristina J Liu[1], Julia M Lewis[1], Lesley Devine[8], Lisa Barbarotta[9], Francine M Foss[1,9], Antonio Subtil[1], Eric C Vonderheid[10], Richard L Edelson[1], David G Schatz[3,6], Titus J Boggon[11], Michael Girardi[1] & Richard P Lifton[3,4,12]



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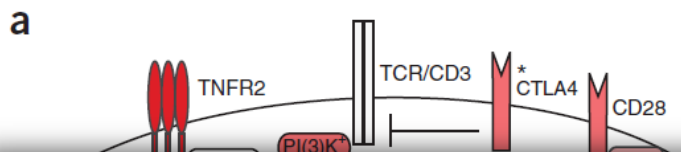
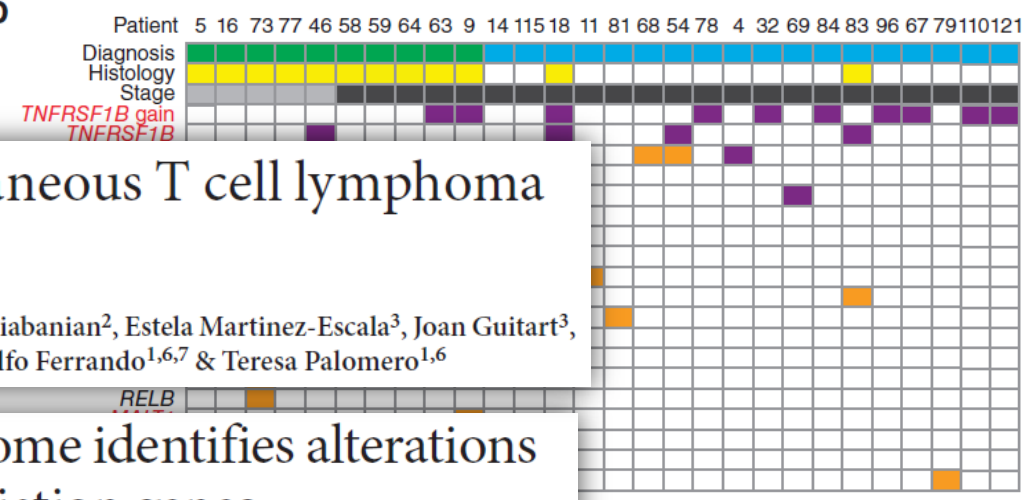


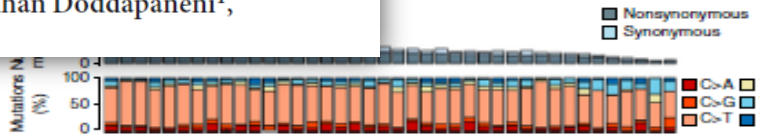




# The mutational landscape of cutaneous T cell lymphoma and Sézary syndrome

Ana Carolina da Silva Almeida[1,8], Francesco Abate[2,8], Hossein Khiabanian[2], Estela Martinez-Escala[3], Joan Guitart[3], Cornelis P Tensen[4], Maarten H Vermeer[4], Raul Rabadan[2,5], Adolfo Ferrando[1,6,7] & Teresa Palomero[1,6]

# Genomic profiling of Sézary syndrome identifies alterations of key T cell signaling and differentiation genes

Linghua Wang[1], Xiao Ni[2], Kyle R Covington[1], Betty Y Yang[2], Jessica Shiu[2], Xiang Zhang[2], Liu Xi[1], Qingchang Meng[1], Timothy Langridge[2], Jennifer Drummond[1], Lawrence A Donehower[3], Harshavardhan Doddapaneni[1], Donna M Muzny[1], Richard A Gibbs[1], David A Wheeler[1] & Madeleine Duvic[2]

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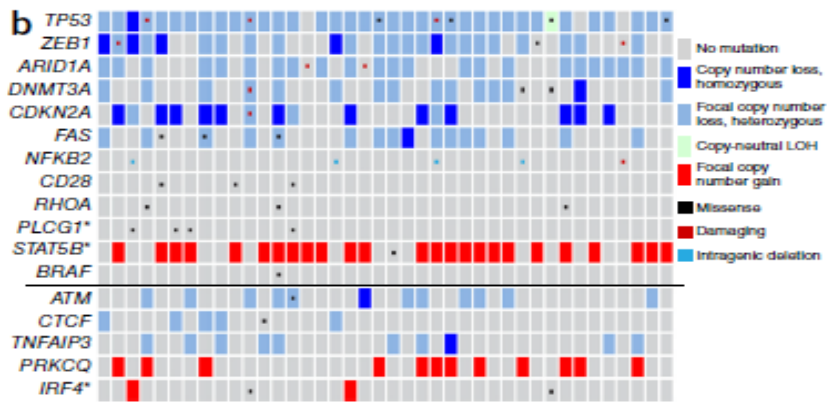
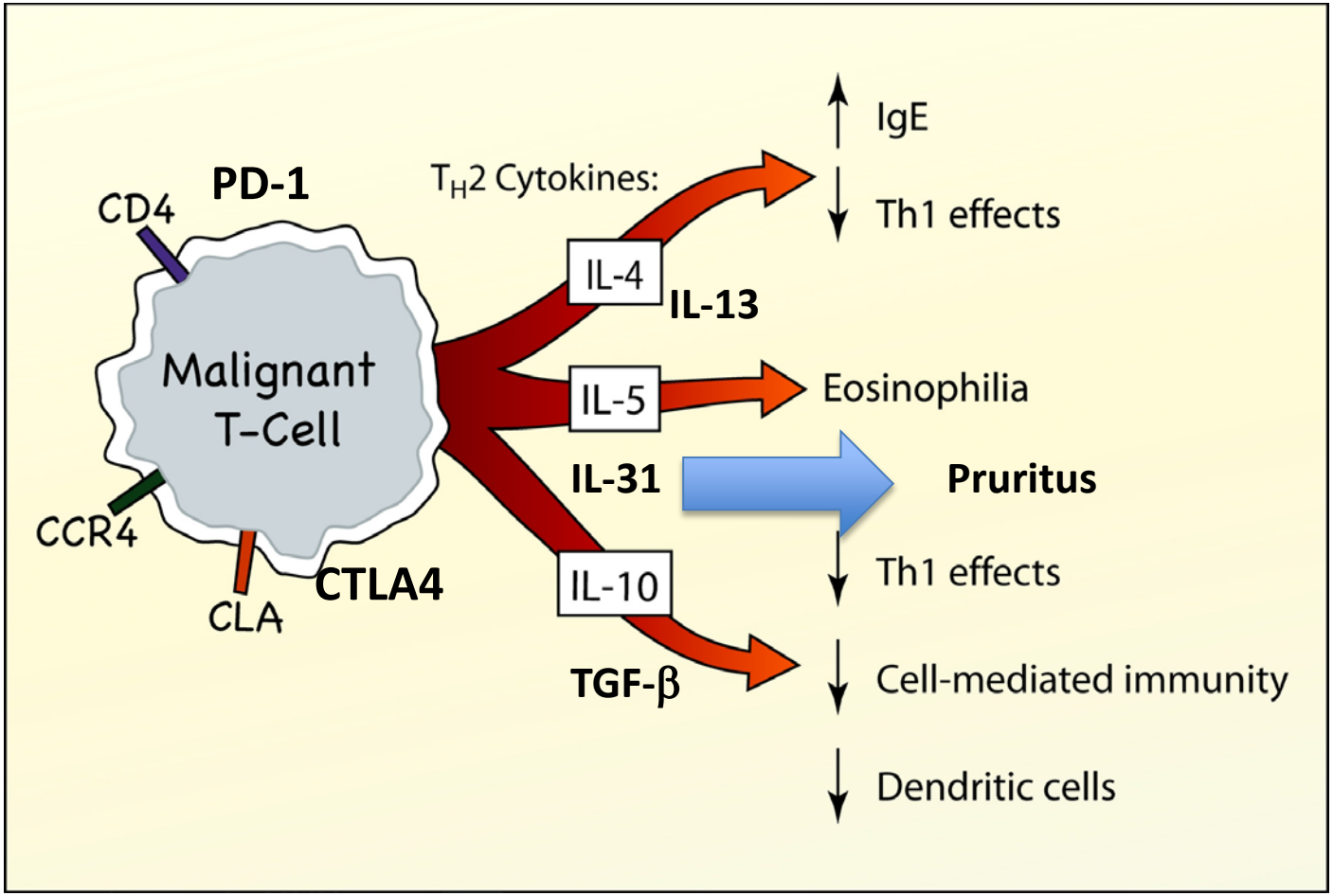


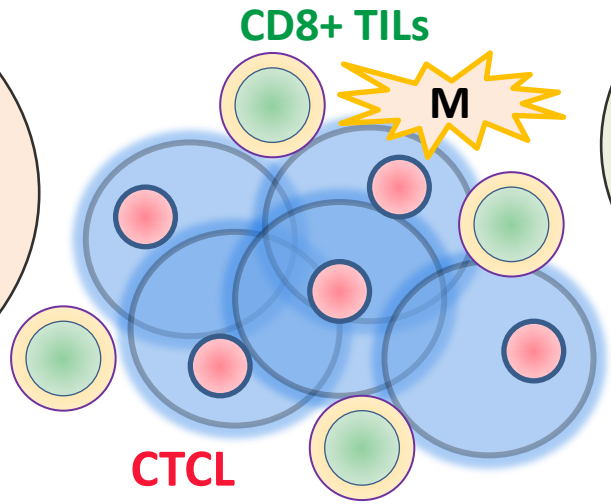
# Effects of soluble factors, immune dysregulation in MF/SS




*Courtesy A Rook, J Clin Invest 2005:115:798*

# Targets for therapy in cutaneous T-cell lymphoma

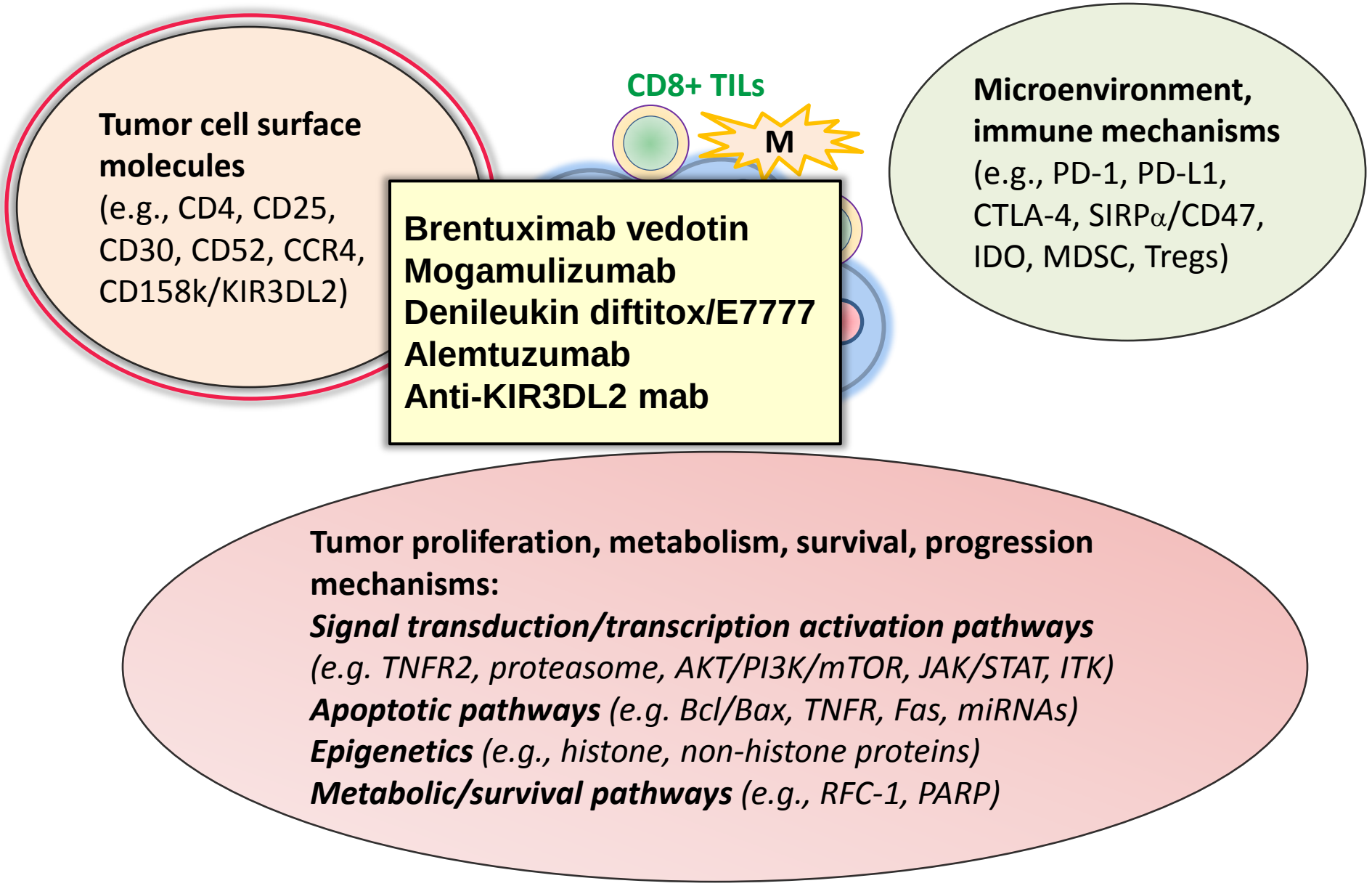
**Tumor cell surface molecules**
(e.g., CD4, CD25, CD30, CD52, CCR4, CD158k/KIR3DL2)




**Microenvironment, immune mechanisms**
(e.g., PD-1, PD-L1, CTLA-4, SIRP$\alpha$/CD47, IDO, MDSC, Tregs)

**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. Bcl/Bax, TNFR, Fas, miRNAs)*
***Epigenetics*** *(e.g., histone, non-histone proteins)*
***Metabolic/survival pathways*** *(e.g., RFC-1, PARP)*

# Targets for therapy in cutaneous T-cell lymphoma



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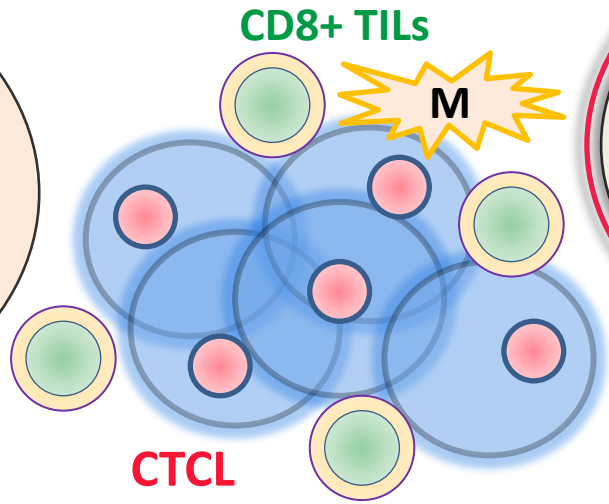


**Microenvironment, immune mechanisms**
(e.g., PD-1, PD-L1, CTLA-4, SIRPα/CD47, IDO, MDSC, Tregs)

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

**Tumor proliferation, metabolism, survival, progression mechanisms:**
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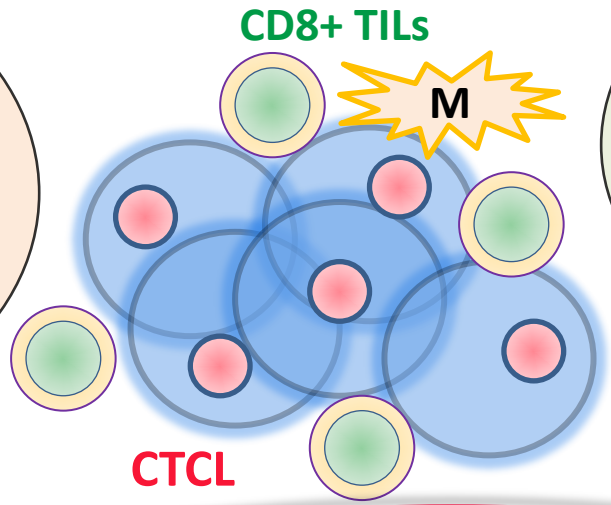



**Microenvironment, immune mechanisms**
(e.g., PD-1, PD-L1, CTLA-4, SIRP$\alpha$/CD47, IDO, MDSC, Tregs)

**Bortezomib, carfilzomib**
**Duvelisib, idelalisib**
**Sirolimus, everolimus**
**Jak inhibitors**
**Syk-Jak dual inhibitor**
**ITK inhibitor**
**Anti-apoptotic agents**
**Anti-miR-155**
**HDAC inhibitors**
**Demethylating agents**
**Anti-folates (pralatrexate)**

**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. Bcl/Bax, TNFR, Fas, miRNAs)*
***Epigenetics*** *(e.g., histone, non-histone proteins)*
***Metabolic/survival pathways*** *(e.g., RFC-1, PARP)*

*Need better therapies, more options:*

*Brentuximab vedotin (anti-CD30 ADC)*

*Mogamulizumab (anti-CCR4 mab)*

*Both phase 3 RCT*
*(superior DOR/PFS or impressive ORR)*

# Efficacy of Systemic Agents in CTCL

## Efficacy data for FDA approval

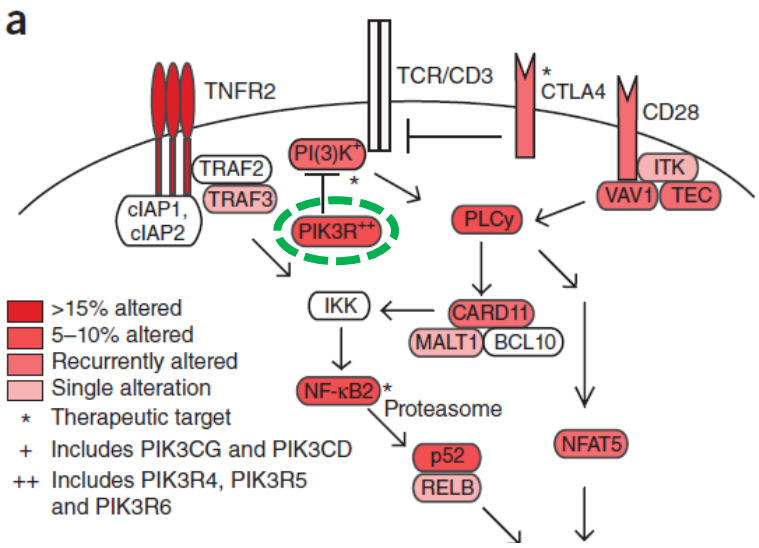
| Agent (Class) | Indication | Year | Study | N | ORR | DOR |
|---|---|---|---|---|---|---|
| Romidepsin (HDAC inhibitor) | CTCL with prior systemic therapy | 2009 | Pivotal | 96 | 34% | 15 mo |
| | | | Supportive | 71 | 35% | 11 mo |
| Denileukin diftitox (Fusion protein) | Tumors that express CD25 | 1999, 2008 | Pivotal | 71 | 30% | 4 mo |
| Bexarotene (RXR activator) | Cutaneous manifestations | 1999 | Pivotal | 62 | 32% | 5+ mo |
| Vorinostat (HDAC inhibitor) | Cutaneous manifestations | 2006 | Pivotal | 74 | 30% | 6+ mo |
| | | | Supportive | 33 | 24% | 4 mo |

nature genetics

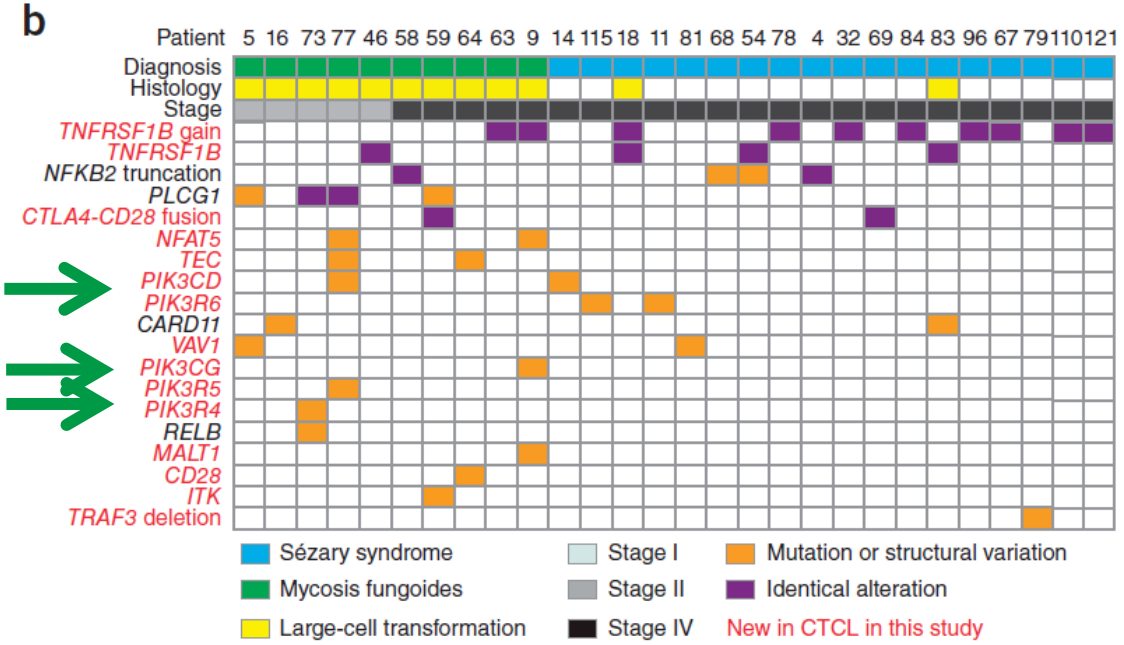
2015;47:1056

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

Alexander Ungewickell[1,2,12], Aparna Bhaduri[1,12], Eon Rios[1], Jason Reuter[3], Carolyn S Lee[1], Angela Mah[1], Ashley Zehnder[1], Robert Ohgami[4], Shashikant Kulkarni[5–7], Randall Armstrong[8], Wen-Kai Weng[8], Dita Gratzinger[4], Mahkam Tavallaee[9], Alain Rook[10], Michael Snyder[3], Youn Kim[9] & Paul A Khavari[1,11]




**T-cell activation, survival, proliferation**



Memorial Sloan Kettering Cancer Center

*Horwitz et al, ASH 2014*

# Duvelisib (IPI-145), a Phosphoinositide-3-Kinase-δ,γ Inhibitor, Shows Activity in Patients with Relapsed/Refractory T-Cell Lymphoma

Steven Horwitz[1]; Pierluigi Porcu[2]; Ian Flinn[3]; Brad Kahl[4]; Howard Stern[5]; Mark Douglas[5]; Kerstin Allen[5]; Patrick Kelly[5]; and Francine Foss[6]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]The Ohio State University; [3]Sarah Cannon Research Institute, Nashville, TN, USA; [4]University of Wisconsin, Madison, WI, USA; [5]Infinity Pharmaceuticals, Inc., Cambridge, MA, USA; [6]Yale University Cancer Center, New Haven, CT, USA.

# Clinical Activity in TCL

| Population | | Best Response, n (%) | | | | | Median Time to Response, months (Range) |
|---|---|---|---|---|---|---|---|
| | n | CR | PR | SD | PD | ORR | |
| All TCL | 33 | 2 (6) | 12 (36) | 7 (21) | 12 (36) | **14 (42)** | 1.9 (1.5, 3.8) |
| PTCL | 15 | 2 (13) | 6 (40) | 1 (7) | 6 (40) | **8 (53)** | 1.9 (1.5, 3.5) |
| CTCL | 18 | 0 | 6 (33) | 6 (33) | 6 (33) | **6 (33)** | 2.4 (1.6, 3.8) |

Includes evaluable patients = at least 1 on-treatment response assessment or PD without assessment
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
ORR = CR + PR

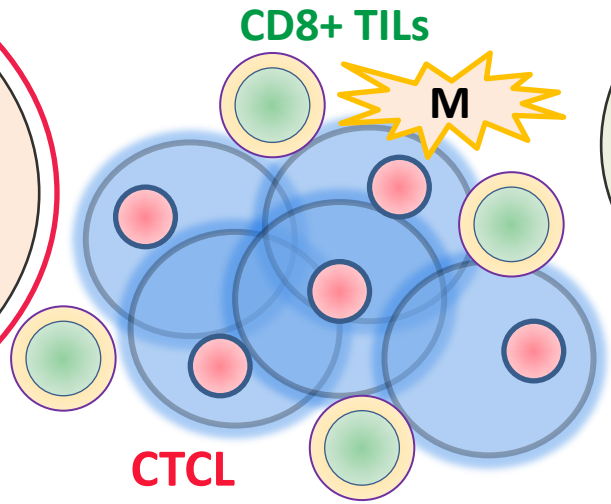
**Clinical trials with duvelisib combination strategies in CTCL**

- Clinical activity observed across PTCL and CTCL subtypes
  - PTCL: CRs in 1 EATCL and 1 PTCL NOS
    PRs in 2 AITCL, 2 SPTCL, 1 PTCL NOS, 1 ALCL (ALK-negative)
  - CTCL: PRs in 4 MF, 1 Sézary syndrome, and 1 MF-LCT

*Horwitz et al, ASH 2014*

# Targets for therapy in cutaneous T-cell lymphoma

**Tumor cell surface molecules**
(e.g., CD4, CD25, CD30, CD52, **CCR4**, CD158k/KIR3DL2)

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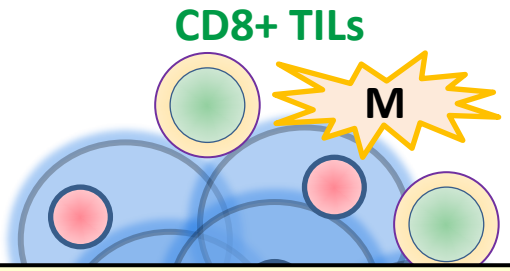



**Microenvironment, immune mechanisms**
(e.g., PD-1, PD-L1, CTLA-4, SIRPα/CD47, IDO, MDSC, Tregs)

**CCR4, an attractive target:**
**CCR4 is expressed in malignant T cells and $T_{regs}$**
**⇒ Tumor-directed and possible added immune modulatory effects**

Tumo
mech

*ways*
*R,*
*IAs)*

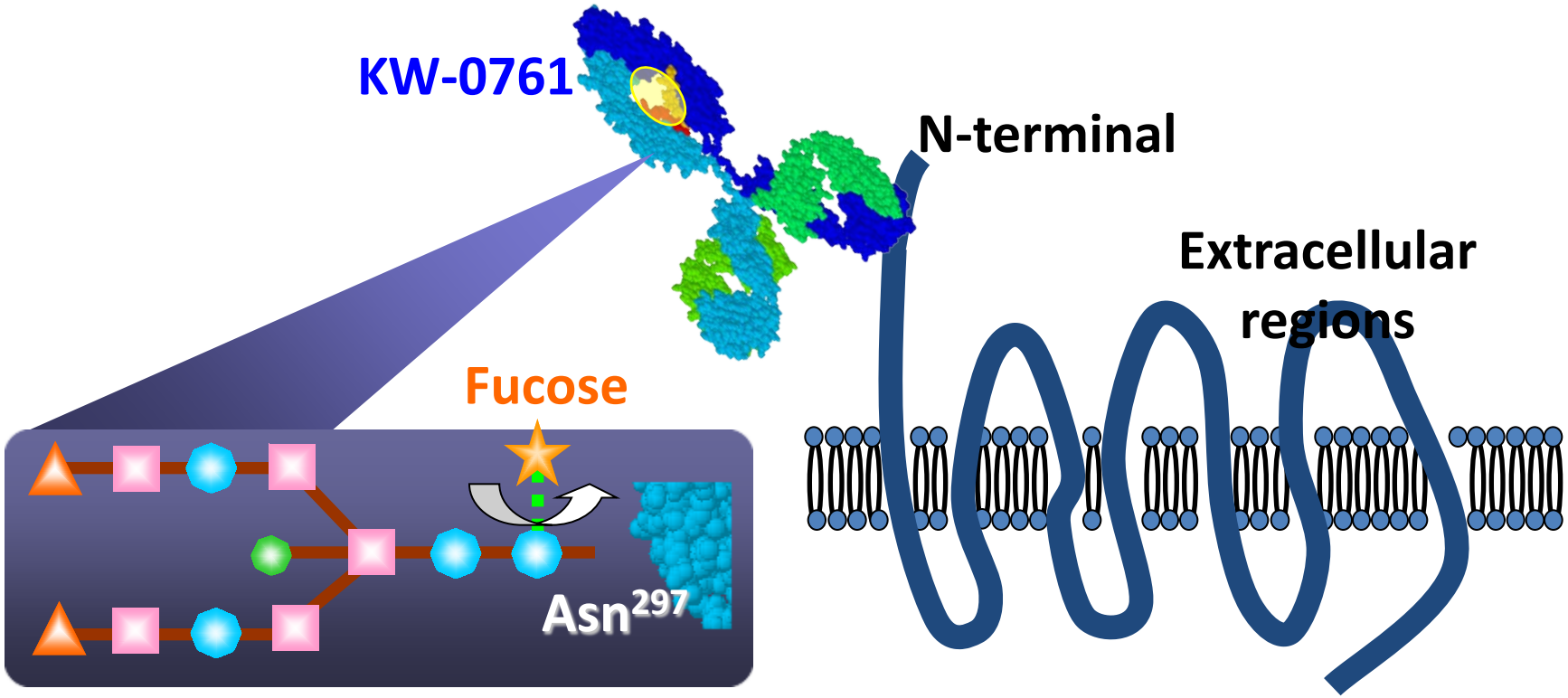
PNAS

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

Daisuke Sugiyama[a], Hiroyoshi Nishikawa[a,1], Yuka Maeda[a], Megumi Nishioka[a,b], Atsushi Tanemura[b], Ichiro Katayama[b], Sachiko Ezoe[c], Yuzuru Kanakura[c], Eiichi Sato[d], Yasuo Fukumori[e], Julia Karbach[f], Elke Jäger[f], and Shimon Sakaguchi[a,1]

[a]Experimental Immunology, World Premier International Research Center, Immunology Frontier Research Center, [b]Department of Dermatology, and [c]Department of Hematology and Oncology, Graduate School of Medicine, Osaka University, Osaka 565-0871, Japan; [d]Department of Anatomic Pathology, Tokyo Medical University, Tokyo 160-8402, Japan; [e]The Third Section of Clinical Investigation, Kinki Blood Center, Osaka 536-8505, Japan; and [f]Department of Hematology and Oncology, Krankenhaus Nordwest, Frankfurt 60488, Germany

# Defucosylated humanized anti-CCR4 antibody, KW-0761




**Higher ADCC due to a defucosylated Fc region by POTELLIGENT®**

**CCR4 (CC chemokine receptor 4)**

**Highly expressed (> 90%) in ATL**
**Great clinical response in skin/blood**

*Shinkawa et al, J Biol Chem 2003;278:3466*
*Ishii et al, Clin Cancer Res 2010;16:1520*

*Ishida et al, Clin Cancer Res 2003;9:3625*

*Courtesy T. Ishida*

VOLUME 30 · NUMBER 8 · MARCH 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Defucosylated Anti-CCR4 Monoclonal Antibody (KW-0761) for Relapsed Adult T-Cell Leukemia-Lymphoma: A Multicenter Phase II Study

*Takashi Ishida, Tatsuro Joh, Naokuni Uike, Kazuhito Yamamoto, Atae Utsunomiya, Shinichiro Yoshida, Yoshio Saburi, Toshihiro Miyamoto, Shigeki Takemoto, Hitoshi Suzushima, Kunihiro Tsukasaki, Kisato Nosaka, Hiroshi Fujiwara, Kenji Ishitsuka, Hiroshi Inagaki, Michinori Ogura, Shiro Akinaga, Masao Tomonaga, Kensei Tobinai, and Ryuzo Ueda*

VOLUME 32 · NUMBER 11 · APRIL 10 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Multicenter Phase II Study of Mogamulizumab (KW-0761), a Defucosylated Anti-CC Chemokine Receptor 4 Antibody, in Patients With Relapsed Peripheral T-Cell Lymphoma and Cutaneous T-Cell Lymphoma

*Michinori Ogura, Takashi Ishida, Kiyohiko Hatake, Masafumi Taniwaki, Kiyoshi Ando, Kensei Tobinai, Katsuya Fujimoto, Kazuhito Yamamoto, Toshihiro Miyamoto, Naokuni Uike, Mitsune Tanimoto, Kunihiro Tsukasaki, Kenichi Ishizawa, Junji Suzumiya, Hiroshi Inagaki, Kazuo Tamura, Shiro Akinaga, Masao Tomonaga, and Ryuzo Ueda*

**Approved in Japan 2012 for pts with ATL and in 2014 for CTCL and PTCL**

*Blood 2015;125:1883*

# Phase 1/2 study of mogamulizumab, a defucosylated anti-CCR4 antibody, in previously treated patients with cutaneous T-cell lymphoma

Madeleine Duvic,[1] Lauren C. Pinter-Brown,[2] Francine M. Foss,[3] Lubomir Sokol,[4] Jeffrey L. Jorgensen,[1] Pramoda Challagundla,[1] Karen M. Dwyer,[5] Xiaoping Zhang,[5] Michael R. Kurman,[5] Rocco Ballerini,[5] Li Liu,[6] and Youn H. Kim[7]

[1]MD Anderson Cancer Center, Houston, TX; [2]University of California, Los Angeles, CA; [3]Smilow Cancer Center at Yale New Haven Hospital, New Haven, CT; [4]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; [5]Kyowa Hakko Kirin Pharma Inc, Princeton, NJ; [6]ReSearch Pharmaceutical Services, Inc, Fort Washington, PA; and [7]Stanford Cancer Center, Stanford, CA

**Cancer Therapy: Clinical**

*Clin Cancer Res 2015;21:274*

## Reduction of Regulatory T Cells by Mogamulizumab, a Defucosylated Anti-CC Chemokine Receptor 4 Antibody, in Patients with Aggressive/Refractory Mycosis Fungoides and Sézary Syndrome

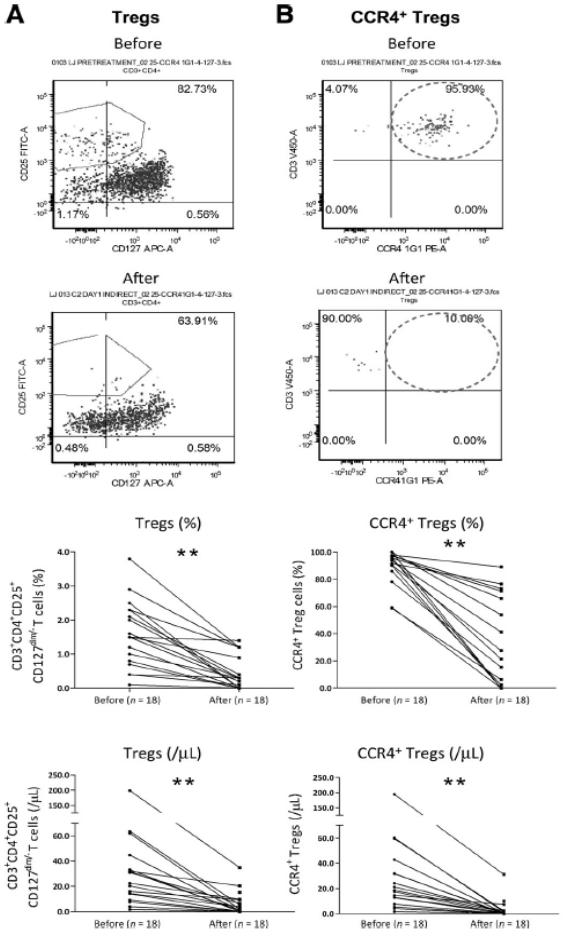
Xiao Ni[1], Jeffrey L. Jorgensen[2], Meghali Goswami[1], Pramoda Challagundla[2], William K. Decker[3], Youn H. Kim[4], and Madeleine A. Duvic[1]

**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; ↑NK cells after treatment with restoration of NK function**

**Lesional skin:**

- **↓infiltrating CCR4+ and/or FoxP3+ T cells**



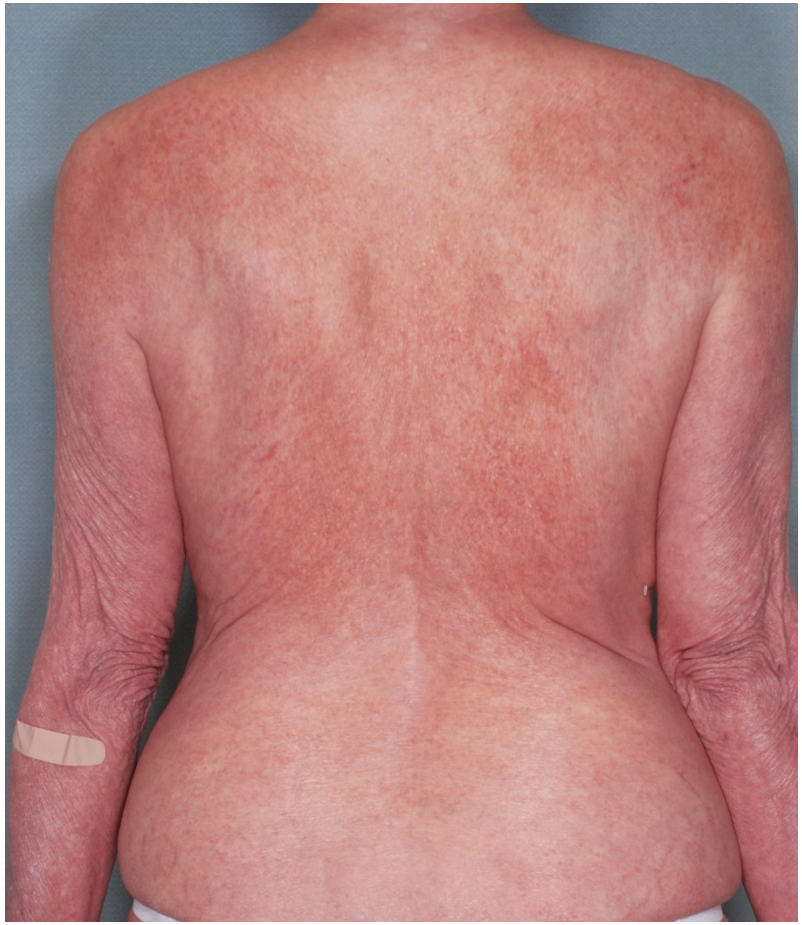
# Overall response rate in phase 1/2 study

| | ORR | No. of patients | | | |
|---|---|---|---|---|---|
| | | CR | PR | SD | PD |
| Sezary Syndrome (N=17) | 47% | 2 | 6 | 7 | 2 |
| Mycosis Fungoides (N=21) | 29% | 1 | 5 | 12 | 3 |
| TOTAL (N=38) | 37% | 3 | 11 | 19 | 5 |

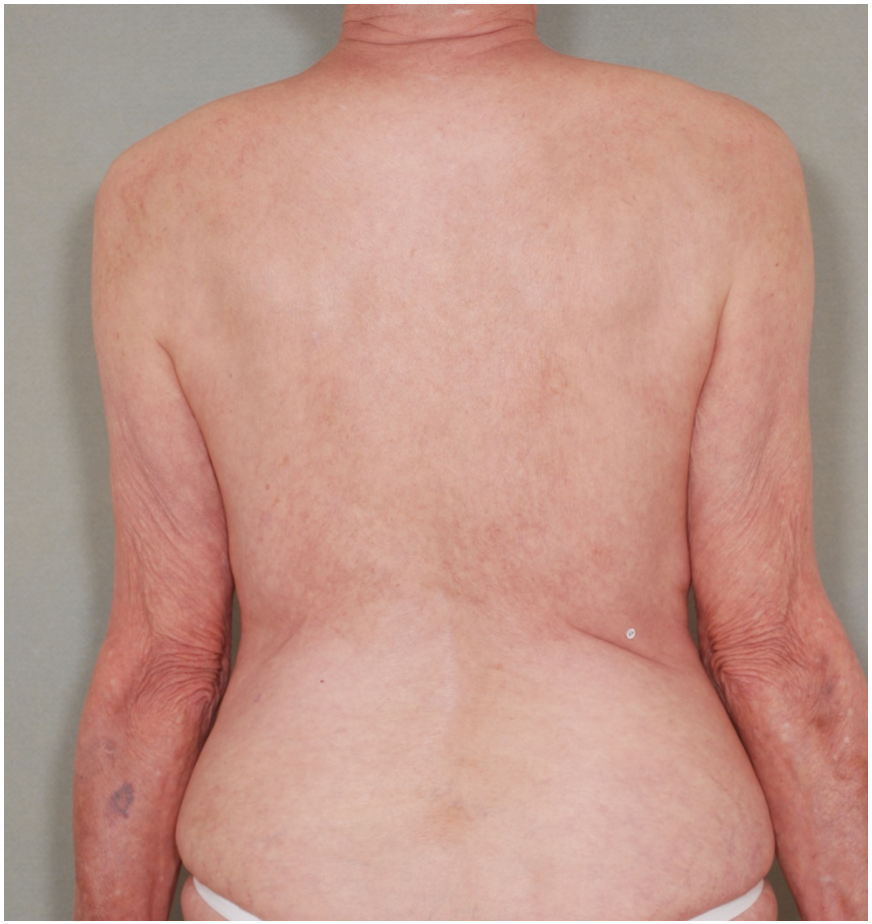
Intravenous administration, weekly x 4, then every 2 wks

# Case Study: Patient 03-Stanford

## (SS; Stage IVA; 6 Prior Therapies; 0.3 mg/kg)



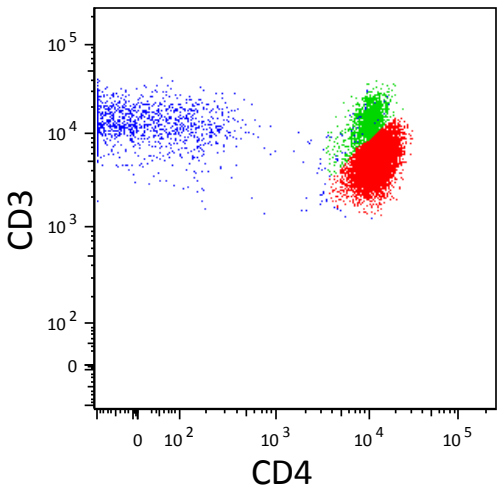
Pretreatment
Course 1 Day 1

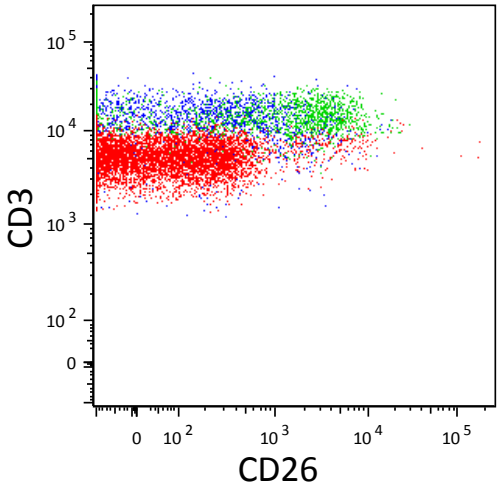


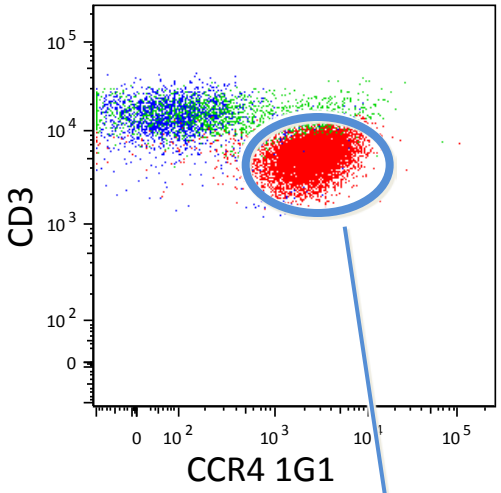
Post treatment
Post Course 11

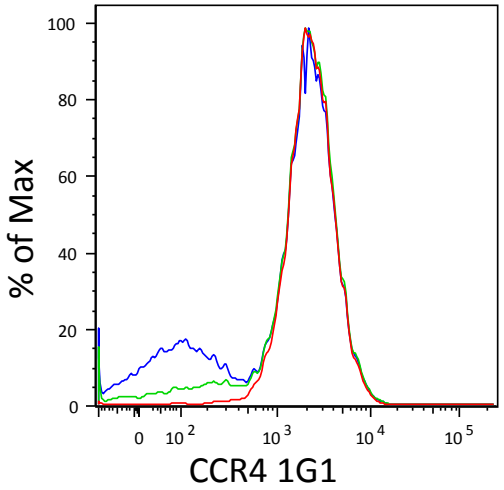
# Response in Blood: Patient 01-Stanford (SS; Stage IVA; 6 prior therapies; 0.1 mg/kg)

## Pre-treatment




Lymphoma cells

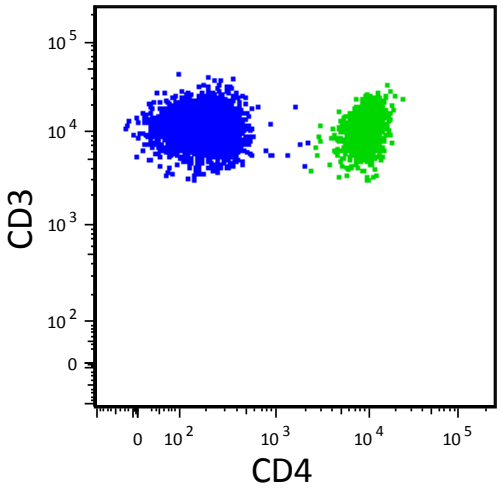
Normal CD3+CD4+

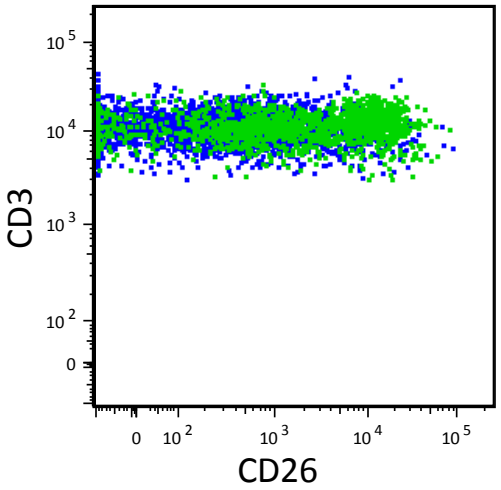
CD3+CD4neg

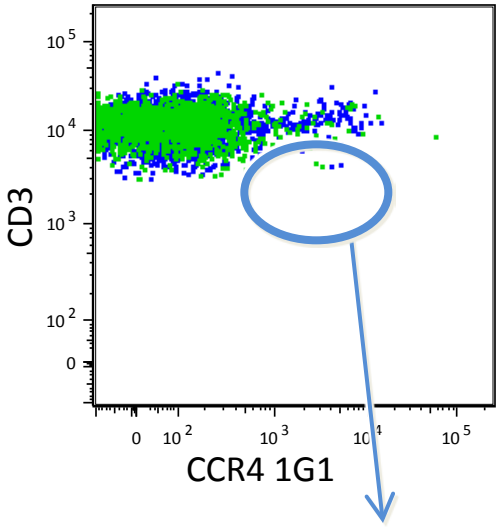
**Lymphoma cells**

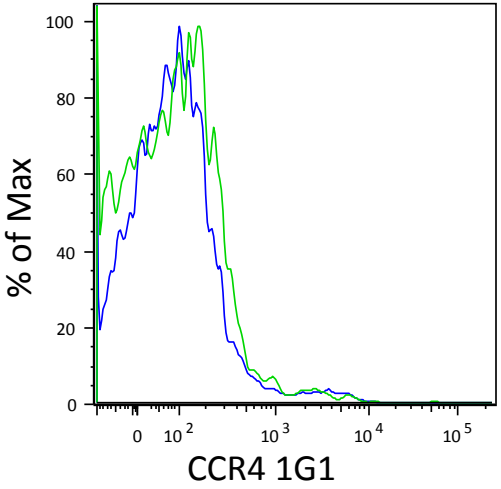
# Response in Blood: Patient 01-Stanford

## Post-treatment




Lymphoma cells
Normal CD3+CD4+
CD3+CD4neg

**Lymphoma cells undetectable**

**Maintaining response >2 yrs**

**Table 2. Nonhematologic adverse events regardless of relationship to treatment reported by >10% of patients in the safety population (N = 42)**

| Preferred term* | Patients, n (%) | | | |
|---|---|---|---|---|
| | Grade 1-2 | Grade 3 | Grade 4-5 | Total |
| Nausea | 11 (26.2) | 2 (4.8) | 0 (0) | 13 (31.0) |
| Chills | 10 (23.8) | 0 (0) | 0 (0) | 10 (23.8) |
| Infusion-related reaction | 9 (21.4) | 0 (0) | 0 (0) | 9 (21.4) |
| Headache | 9 (21.4) | 0 (0) | 0 (0) | 9 (21.4) |
| Pyrexia | 8 (19.0) | 0 (0) | 0 (0) | 8 (19.0) |
| Fatigue | 7 (16.7) | 0 (0) | 0 (0) | 7 (16.7) |
| Cutaneous drug eruption | 6 (14.3) | 1 (2.4) | 0 (0) | 7 (16.7) |
| Diarrhea | 5 (11.9) | 1 (2.4) | 0 (0) | 6 (14.3) |
| Pruritus | 5 (11.9) | 0 (0) | 0 (0) | 5 (11.9) |
| Upper respiratory tract infection | 5 (11.9) | 0 (0) | 0 (0) | 5 (11.9) |
| Vomiting | 3 (7.1) | 2 (4.8) | 0 (0) | 5 (11.9) |

*Blood 2015;125:1883*

# KW-0761 (mogamulizumab, anti-CCR4) Clinical Development Summary

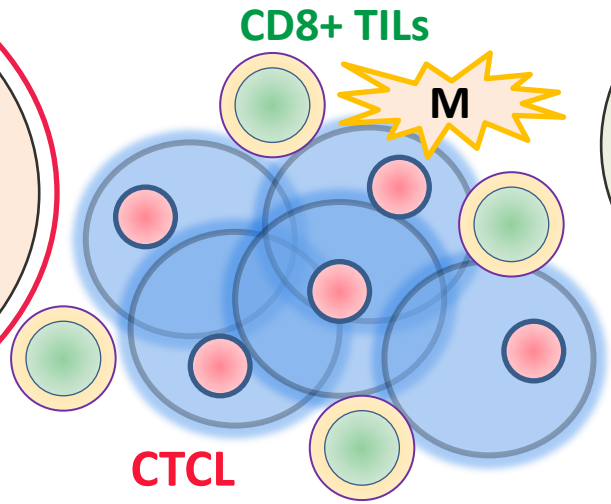
- Clinical responses are most impressive in the skin and blood compartments in ATL and CTCL
- Absence of infections with chronic therapy, no need for antimicrobial prophylaxis (←→ alemtuzumab)

***Phase III RCT (vs. vorinostat) in CTCL completed enrollment***

***First CTCL trial to use PFS as primary endpoint for approval***

# Targets for therapy in cutaneous T-cell lymphoma

**Tumor cell surface molecules**
(e.g., CD4, CD25, **CD30**, CD52, CCR4, CD158k/KIR3DL2)

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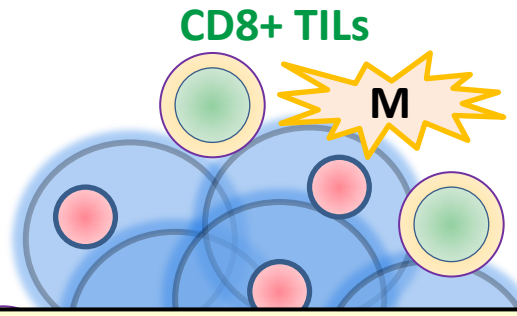
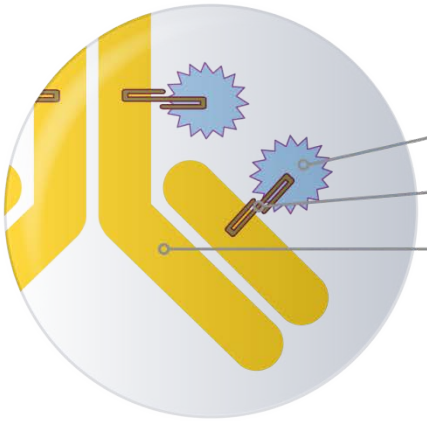



**Microenvironment, immune mechanisms**
(e.g., PD-1, PD-L1, CTLA-4, SIRP$\alpha$/CD47, IDO, MDSC, Tregs)

**CD30, an attractive target:**
**CD30 expression is increased in proliferative or malignant lymphocytes**
**=> good tumor selectivity**

**Tumo**
**mecha**
***Signal***
*(e.g.,*
*RAS/R*
***Apoptotic pathways*** *(e.g. Bcl/Bax, TNFR, Fas, miRNAs)*
***Epigenetics*** *(e.g., histone, non-histone proteins)*
***Metabolic/survival pathways*** *(e.g., RFC-1, PARP)*

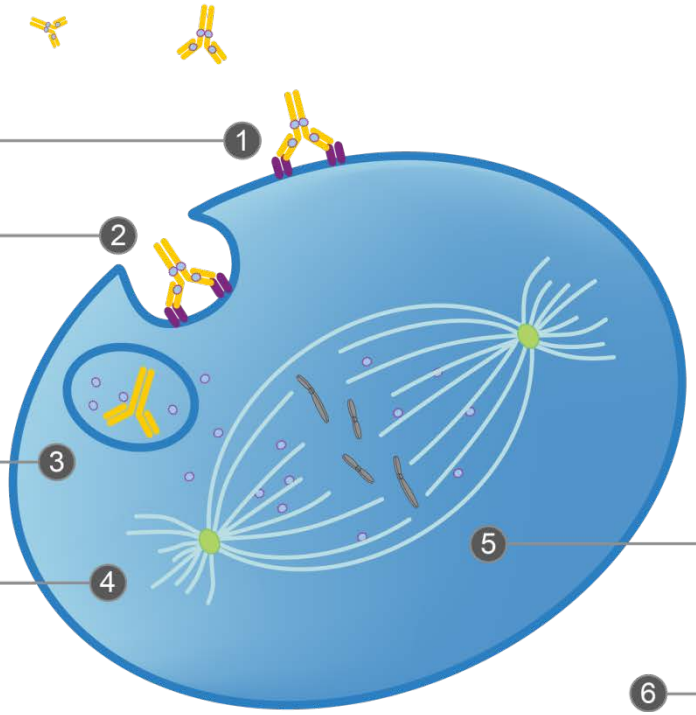
# Brentuximab Vedotin
## *Antibody Drug Conjugate*



Monomethyl auristatin E (MMAE), microtubule-disrupting agent

Protease-cleavable linker

Anti-CD30 monoclonal antibody




ADC binds to CD30

ADC-CD30 complex is internalized and traffics to lysosome

MMAE is released

MMAE disrupts microtubule network

G2/M cell cycle arrest

Apoptosis

Published Ahead of Print on July 20, 2015 as 10.1200/JCO.2014.60.3969
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2014.60.3969

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

# Phase II Investigator-Initiated Study of Brentuximab Vedotin in Mycosis Fungoides and Sézary Syndrome With Variable CD30 Expression Level: A Multi-Institution Collaborative Project

*J Clin Oncol 2015;33:3750*

*Youn H. Kim, Mahkam Tavallaee, Uma Sundram, Katrin A. Salva, Gary S. Wood, Shufeng Li, Sima Rozati, Seema Nagpal, Michael Krathen, Sunil Reddy, Richard T. Hoppe, Annie Nguyen-Lin, Wen-Kai Weng, Randall Armstrong, Melissa Pulitzer, Ranjana H. Advani, and Steven M. Horwitz*

Published Ahead of Print on August 10, 2015 as 10.1200/JCO.2014.60.3787
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2014.60.3787

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

# Results of a Phase II Trial of Brentuximab Vedotin for CD30$^+$ Cutaneous T-Cell Lymphoma and Lymphomatoid Papulosis

*Madeleine Duvic, Michael T. Tetzlaff, Pamela Gangar, Audra L. Clos, Dawen Sui, and Rakhshandra Talpur*

# Patient characteristics, n=32

| | | | |
|---|---|---|---|
| Age (y), median (range) | | 62 (20-87) | |
| Sex, n (%) | | Men | 19 (59) |
| | | Women | 13 (41) |
| Stage, n (%) | | IB | 4 (13) |
| | | IIA | 0 |
| | | IIB | 18 (56) |
| | | III | 0 |
| | | IV/SS | 10 (31) |
| Large cell transformation (LCT) Folliculotropic MF (FMF), n (%) | | LCT | 16 (50) |
| | | FMF | 8 (25) |
| | | LCT & FMF | 5 (15) |
| Prior systemic therapies, median (range) | | 3 (1-13) | |
| CD30 baseline, % of skin infiltrate, n (%) | A: < 10% | 14 (43) | |
| | B: 10-50% | 14 (43) | |
| | C: >50% | 4 (13) | |

Advanced stage (88%)

F-MF, LCT (90%)

Variable CD30

*Kim et al, J Clin Oncol 2015;33:3750*

# Global response by clinical stage

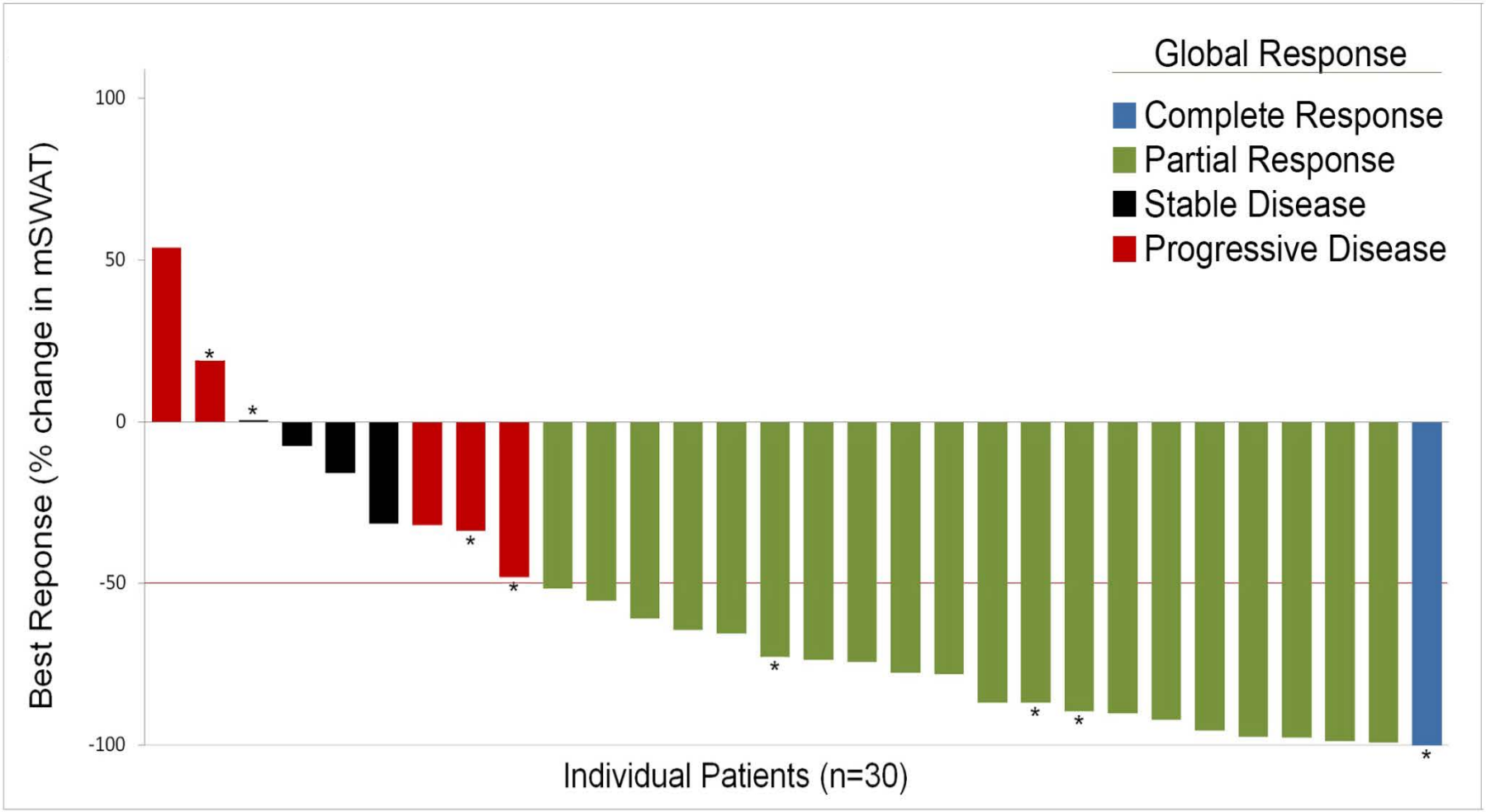
| Stage | Response Rate | CR | PR | SD | PD |
|---|---|---|---|---|---|
| IB (n=4) | 75% | 0 | 3 | 1 | 0 |
| IIB (n=18) | 78% | 0 | 14 | 2 | 2 |
| IV/SS (n=8)* | 50% | 1 | 3 | 1 | 3 |
| Total n= 30* | 70% | 1 | 20 | 4 | 5 |

*Unable to evaluate response in 2 patients

**1.8 mg/kg every 3 wks x 8, cont only if ongoing benefit, max 16; dose-modification with Gr 2 PN**

*Kim et al, J Clin Oncol 2015;33:3750*

# Percent change in skin mSWAT score at best skin response

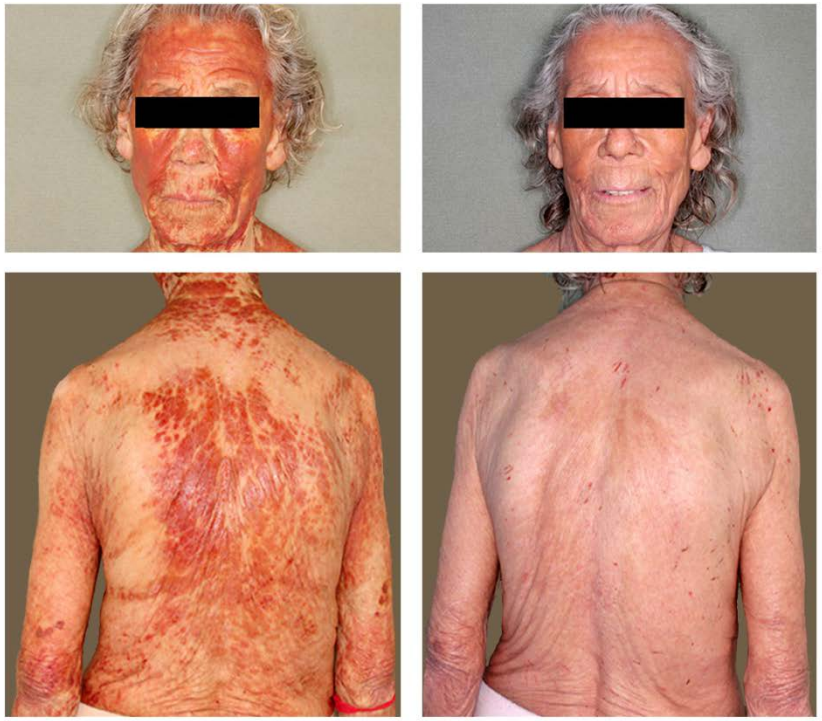


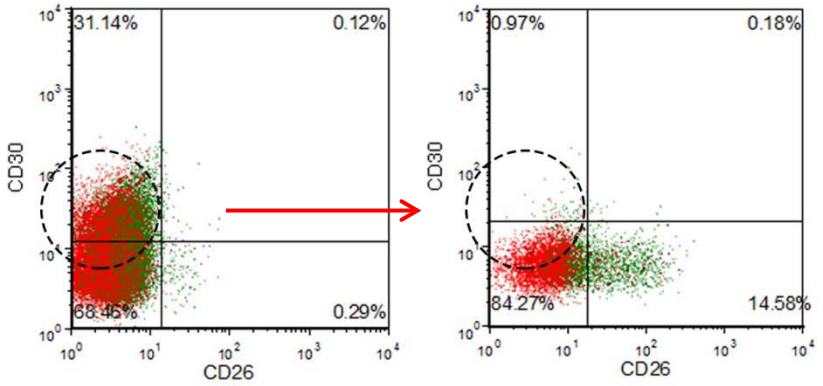

* Stage IV

**Median best mSWAT reduction 73% (100% to -54%)**
**8 pts with mSWAT reduction >90%**

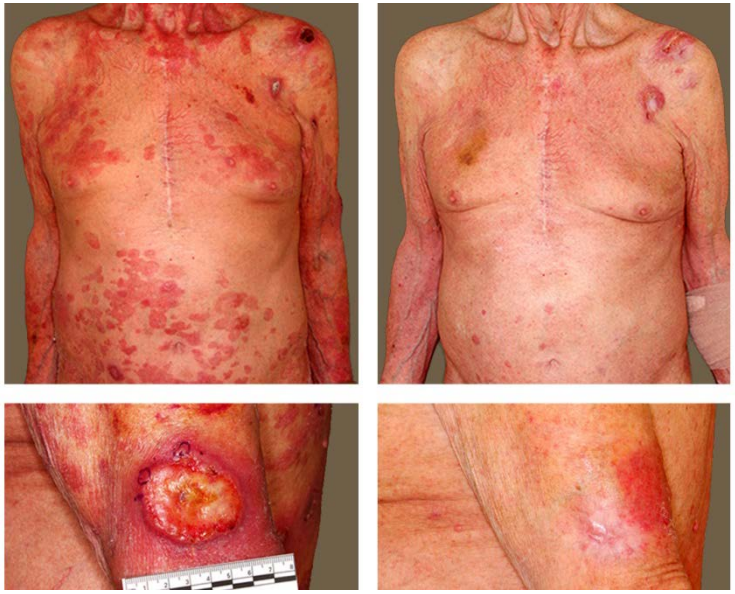
# Great clinical response to brentuximab vedotin in MF/SS

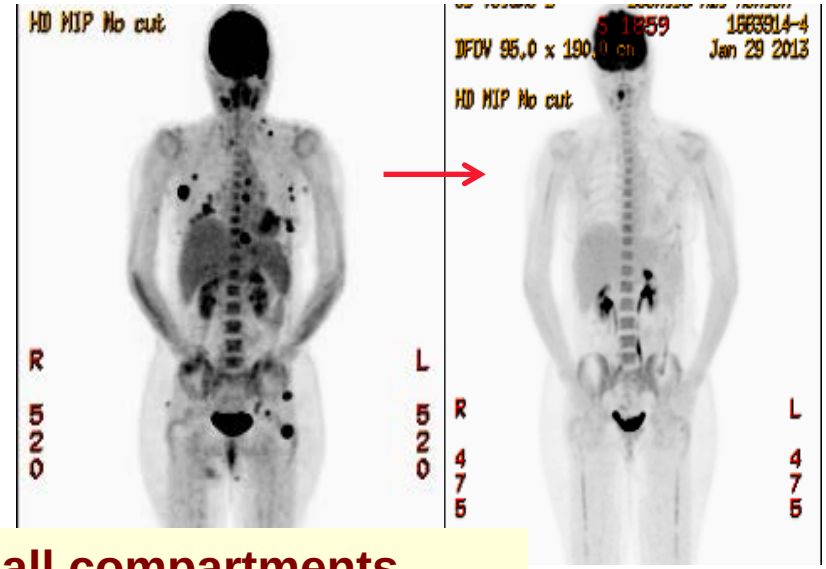
## Sézary syndrome, $IVA_1$






## MF $IVA_2$ LN with LCT






**BV demonstrates clinical activity in all compartments**

# Summary and Conclusions

- Brentuximab vedotin showed significant clinical activity in refractory/advanced MF/SS, majority with F-MF/LCT
  - Primary endpoint met: ORR 70% (90% CI, 53%-83%), sig greater than 35% ORR recent FDA-approved agents
  - Responses seen across all stages/compartments
  - Encouraging duration of clinical benefit
- Anticipated toxicity profile
  - Not all PN is reversible
- Clinical responses were observed in all CD30 groups but reliability or depth of response correlates with $CD30_{max}$ expression

# Summary and Conclusions

- Brentuximab vedotin showed significant clinical activity in refractory/advanced MF/SS, majority with F-MF/LCT
  - Primary endpoint met: ORR 70% (90% CI, 53%-83%), sig greater than 35% ORR recent FDA-approved agents
  - Responses seen across all stages/compartments
  - Encouraging duration of clinical benefit

**Included in the 2015 NCCN NHL practice guidelines**

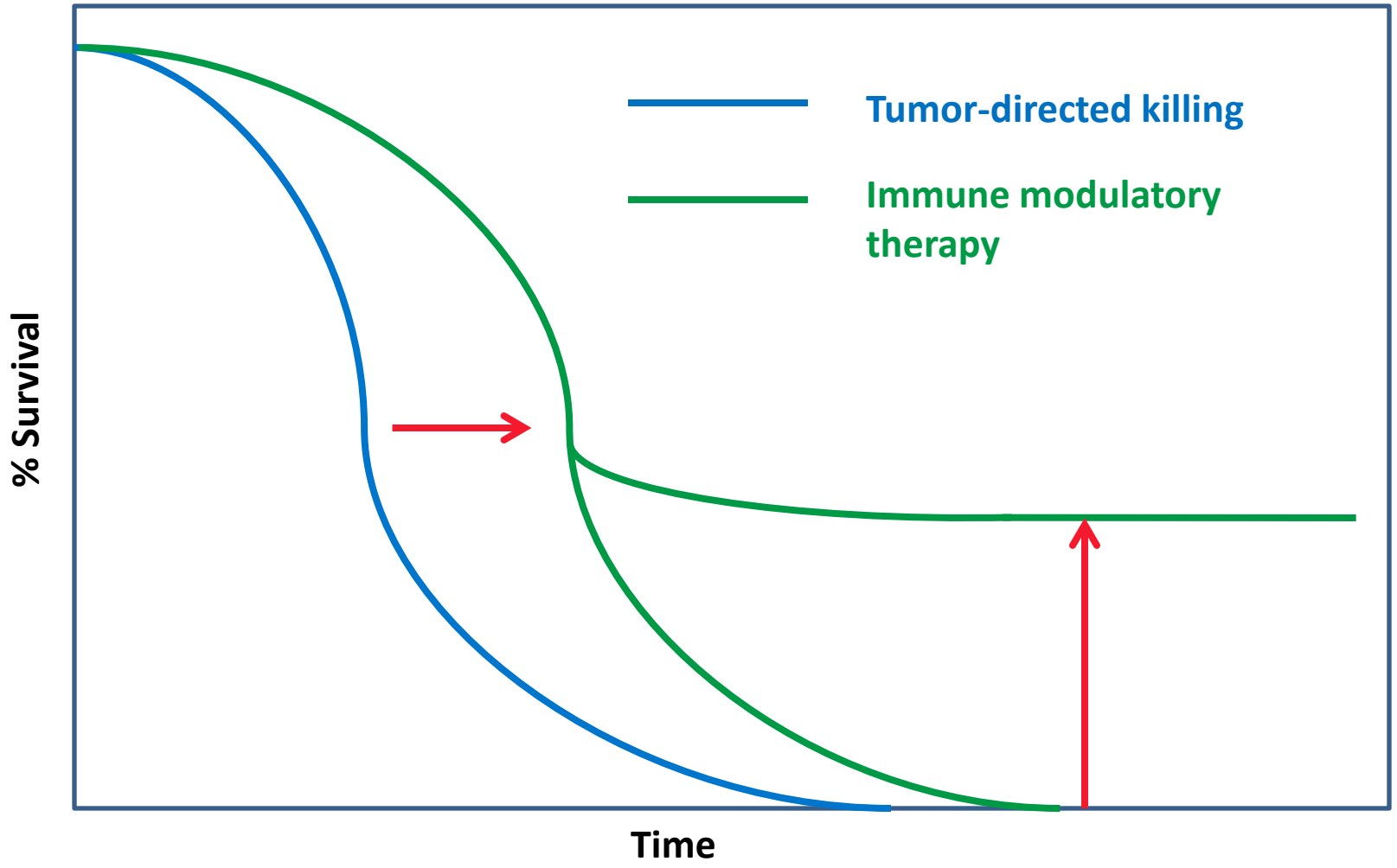
**Phase III RCT (vs MD choice- oral bex or MTX) completed, pending FDA submission: Included MF and pcALCL, excluded SS**

expression

# Road to a CURE

## How do we make the nice responses last?

## *Partnering with immunotherapy*



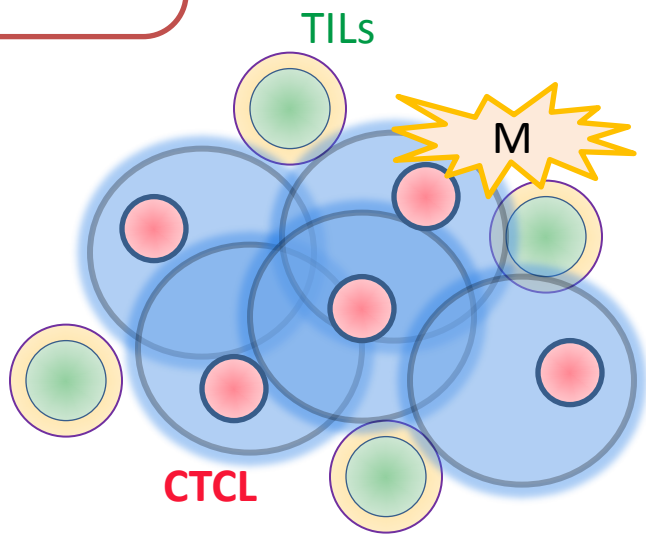
# Immunotherapy strategies in CTCL

CD25,
CD30,
CCR4,
KIR3DL2

**Tumor-specific antibodies (direct effects)**

**Cytokine therapy**

IFNs, IL2,
IL12




**Adoptive T-cell transfer, CAR-T**

**Immune-modulating agents or antibodies (indirect effects)**

TLR-A
IMiDs
$T_{reg}$
CTLA4
PD-1/PD-L1
SIRP$\alpha$/CD47

**Allogeneic HSCT**

**Vaccine-based approaches**

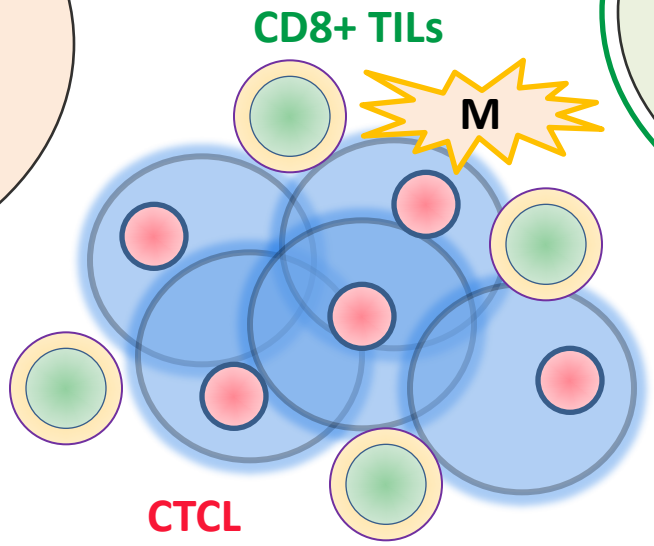
ECP
DC-based
Idiotype
*In situ* strategy

# Targeting T-cell immune checkpoints in MF/SS

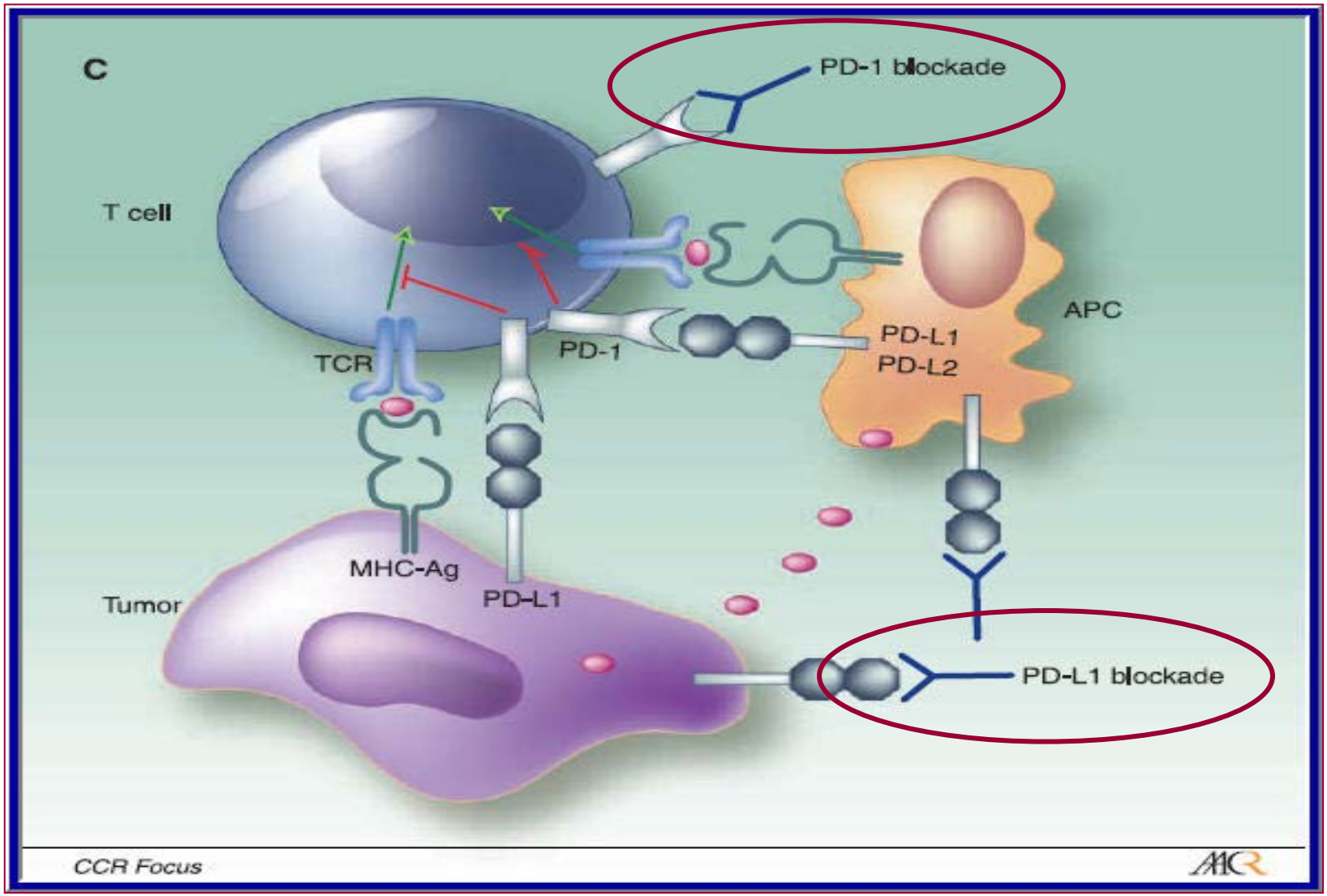
**Monoclonal antibodies**

**Tumor cell-specific:**
tumor surface molecules
(e.g., CD4, CD25, CD30, CD52, CCR4, CD158k/KIR3DL2)

**Microenvironment Immune modulation**
(e.g. **PD-1, PD-L1, CTLA-4,** IDO, CD40, TLRs, SIRP$\alpha$/CD47, CD137, MDSC, Tregs)



# PD-1 and ligands B7-H1/PD-L1 & B7-DC/PD-L2: Pivotal role in maintaining immunosuppressive tumor microenvironment




*Curr Opin Immunol 2012;24:207*

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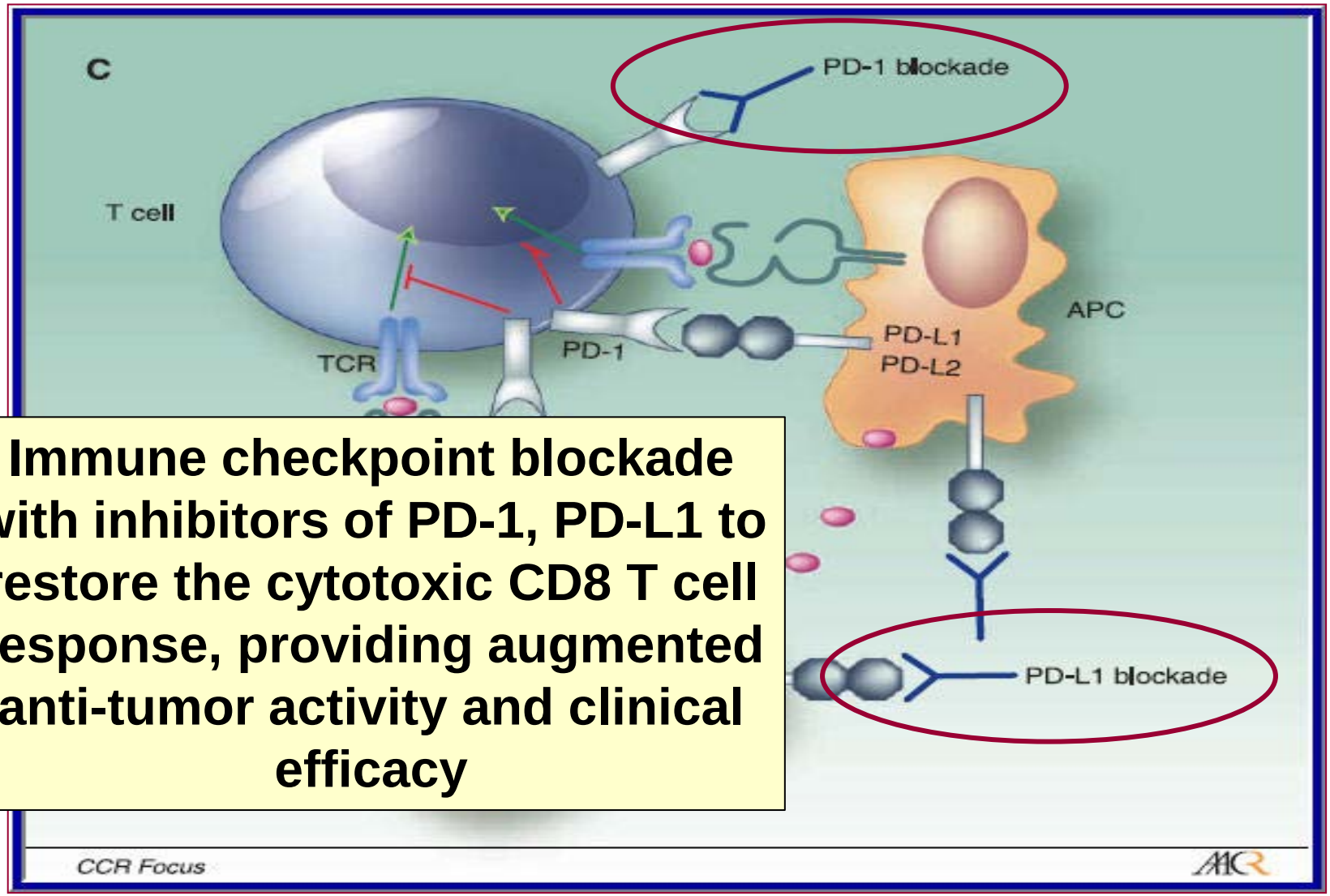



**Immune checkpoint blockade with inhibitors of PD-1, PD-L1 to restore the cytotoxic CD8 T cell response, providing augmented anti-tumor activity and clinical efficacy**

*Curr Opin Immunol 2012;24:207*

# Rationale for immune checkpoint blockade in MF/SS

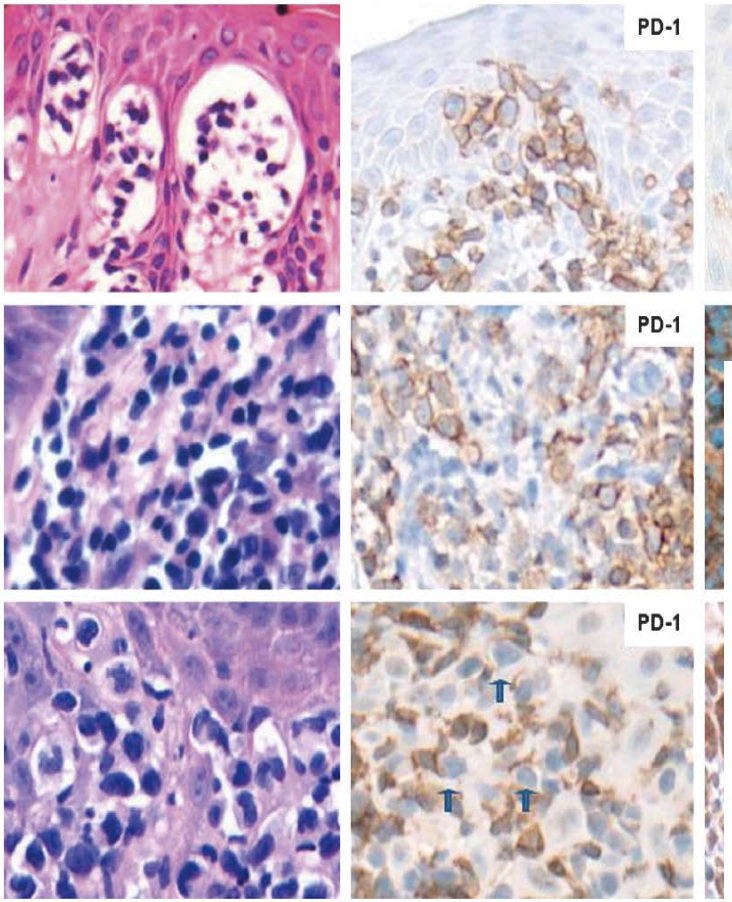
- Systemic and local tissue immune impairment is observed
- Mounting evidence that T cell immunity is critical for meaningful antitumor response
- Tumor-infiltrating CD8+ T cells have been associated with improved survival and therapies which augment their function are effective in MF/SS
- Allogeneic HSC transplantation can result in sustained remissions suggesting immune response to tumor may be curative
- Significant expression of PD-1 and PD-L1 has been demonstrated in the skin and peripheral blood in MF/SS
- Reports of 9p24.1/PD-L2 translocation, breakpoints in PD-L1 (CD274), recurrent SNV in CD28, or CTLA4-CD28 fusion in MF/SS support a genomic basis for immune evasion

# Expression of PD-1 and PD-L1 in CTCL
# Mycosis fungoides & Sézary syndrome

**MF skin plaque**

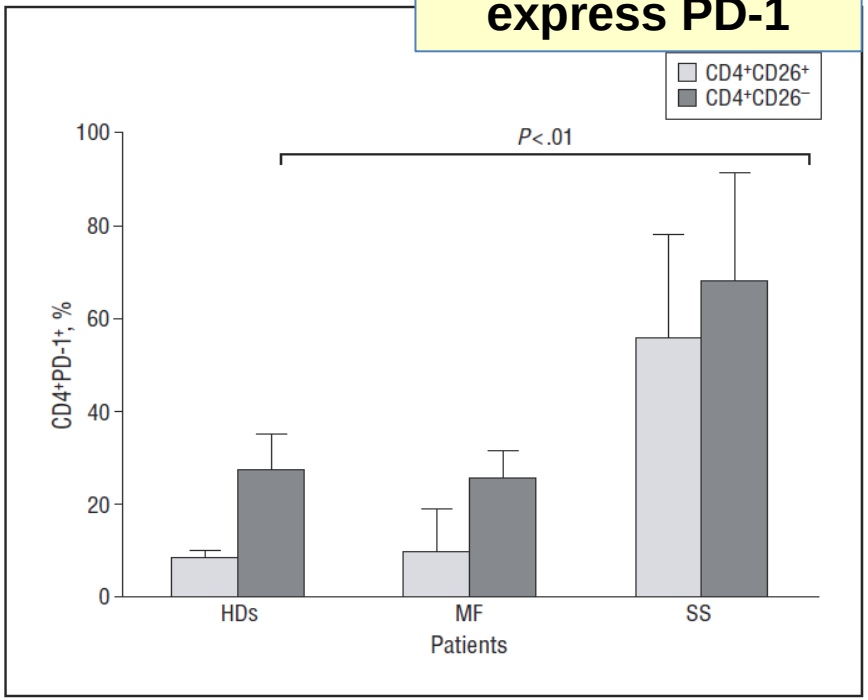
**tumor**

**T-MF**




*Am J Dermatopathol 2012:34:126*

**PB Sézary cells express PD-1**



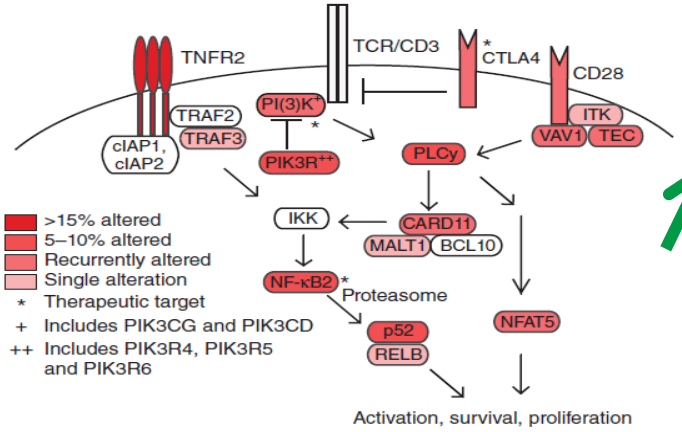

*Samimi, Rook, Arch Dermatol 2010;146:1382*

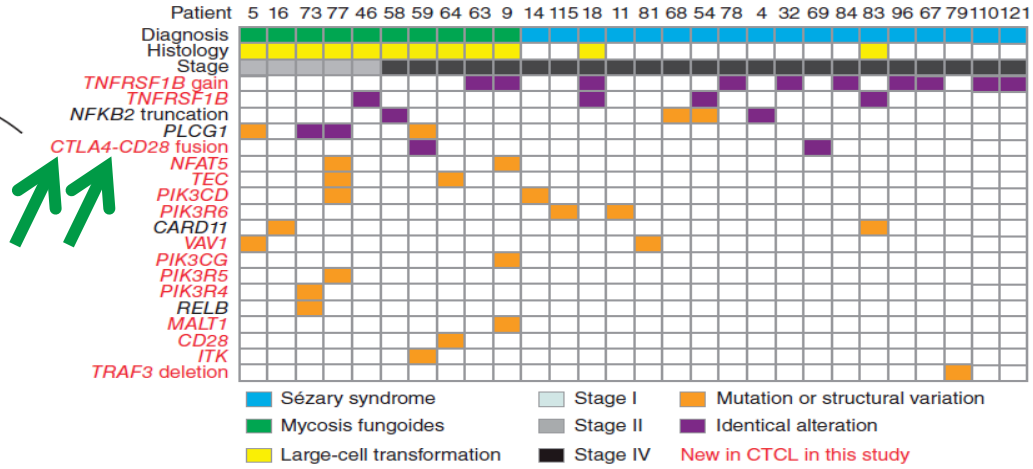
nature genetics

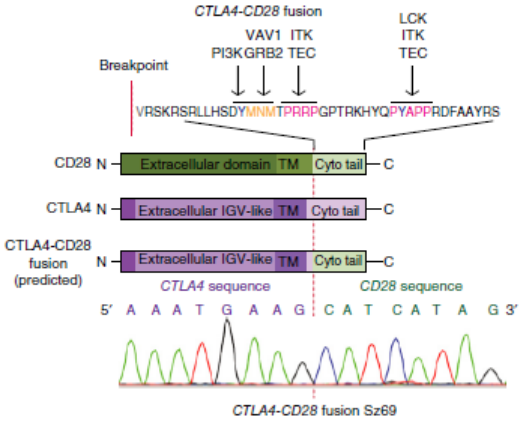
2015;47:1056

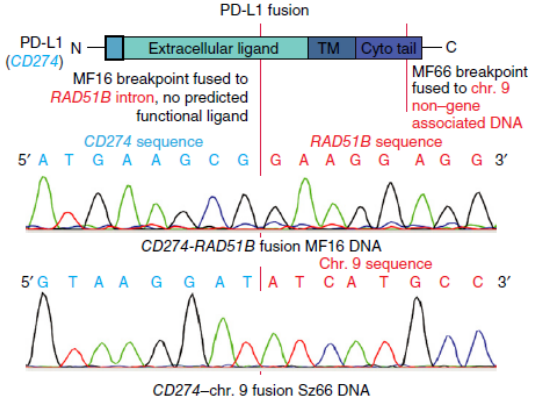
# Genomic analysis of mycosis fungoides and Sézary syndrome identifies recurrent alterations in TNFR2

Alexander Ungewickell[1,2,12], Aparna Bhaduri[1,12], Eon Rios[1], Jason Reuter[3], Carolyn S Lee[1], Angela Mah[1], Ashley Zehnder[1], Robert Ohgami[4], Shashikant Kulkarni[5–7], Randall Armstrong[8], Wen-Kai Weng[8], Dita Gratzinger[4], Mahkam Tavallaee[9], Alain Rook[10], Michael Snyder[3], Youn Kim[9] & Paul A Khavari[1,11]

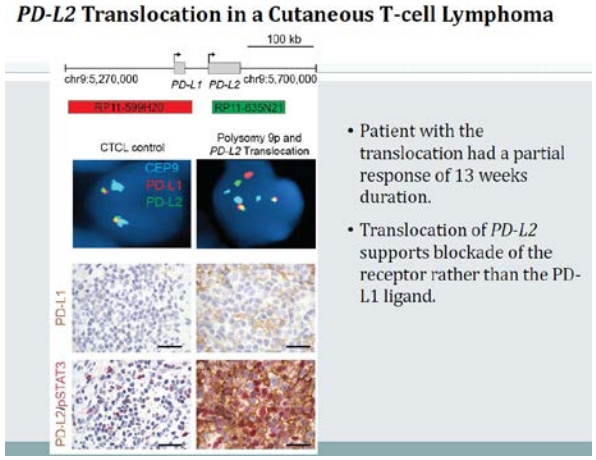


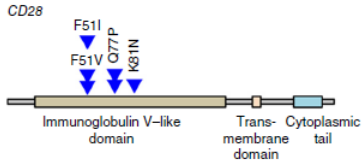

ASH 12/2014
Abstract 291, ***A Lesokhin, et al.***
***Nivolumab in Lymphoid Malignancies***




# Genomic landscape of cutaneous T cell lymphoma

*Nat Genetics 2015*

Jaehyuk Choi[1,2], Gerald Goh[3,4], Trent Walradt[1], Bok S Hong[1], Christopher G Bunick[1], Kan Chen[1], Robert D Yaakov Maman[3,6], Tiffany Wang[1], Jesse Tordoff[1], Kacie Carlson[1], John D Overton[7], Kristina J Liu[1], Julia M Lewis[1], Lesley Devine[8], Lisa Barbarotta[9], Francine M Foss[1,9], Antonio Subtil[1], Eric C Vonderhe Richard L Edelson[1], David G Schatz[3,6], Titus J Boggon[11], Michael Girardi[1] & Richard P Lifton[3,4,12]



cancer immunotherapy trials network

# Cancer Immunotherapy Trials Network

# 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)

CITN, Fred Hutchinson Cancer Research Center

**Principal Investigator:** Y Kim, H Kohrt (Co-PI)

S Li (biostatistician), M Khodadoust, Z Rahbar, J Kim

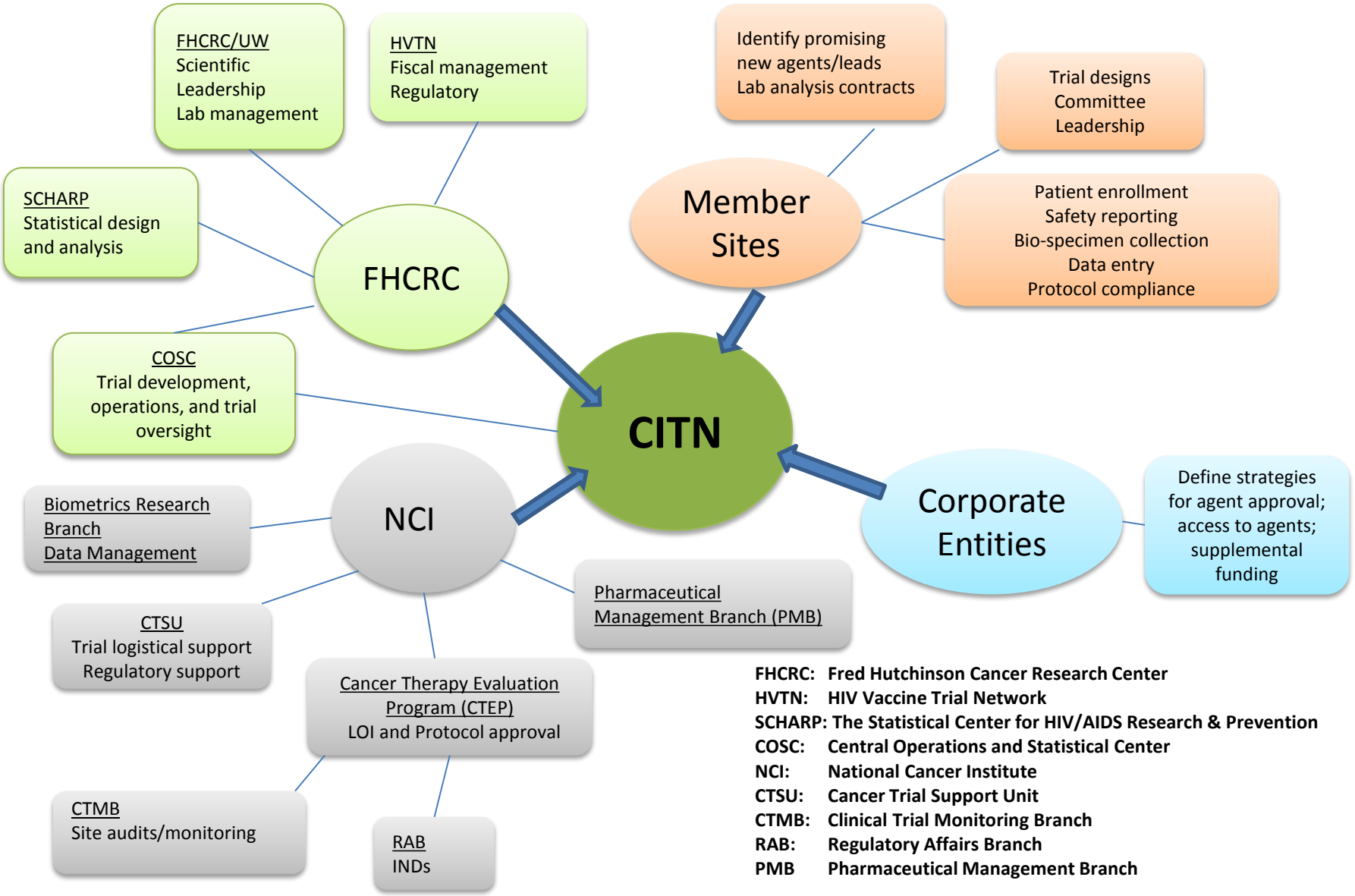
Stanford University SOM

**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)

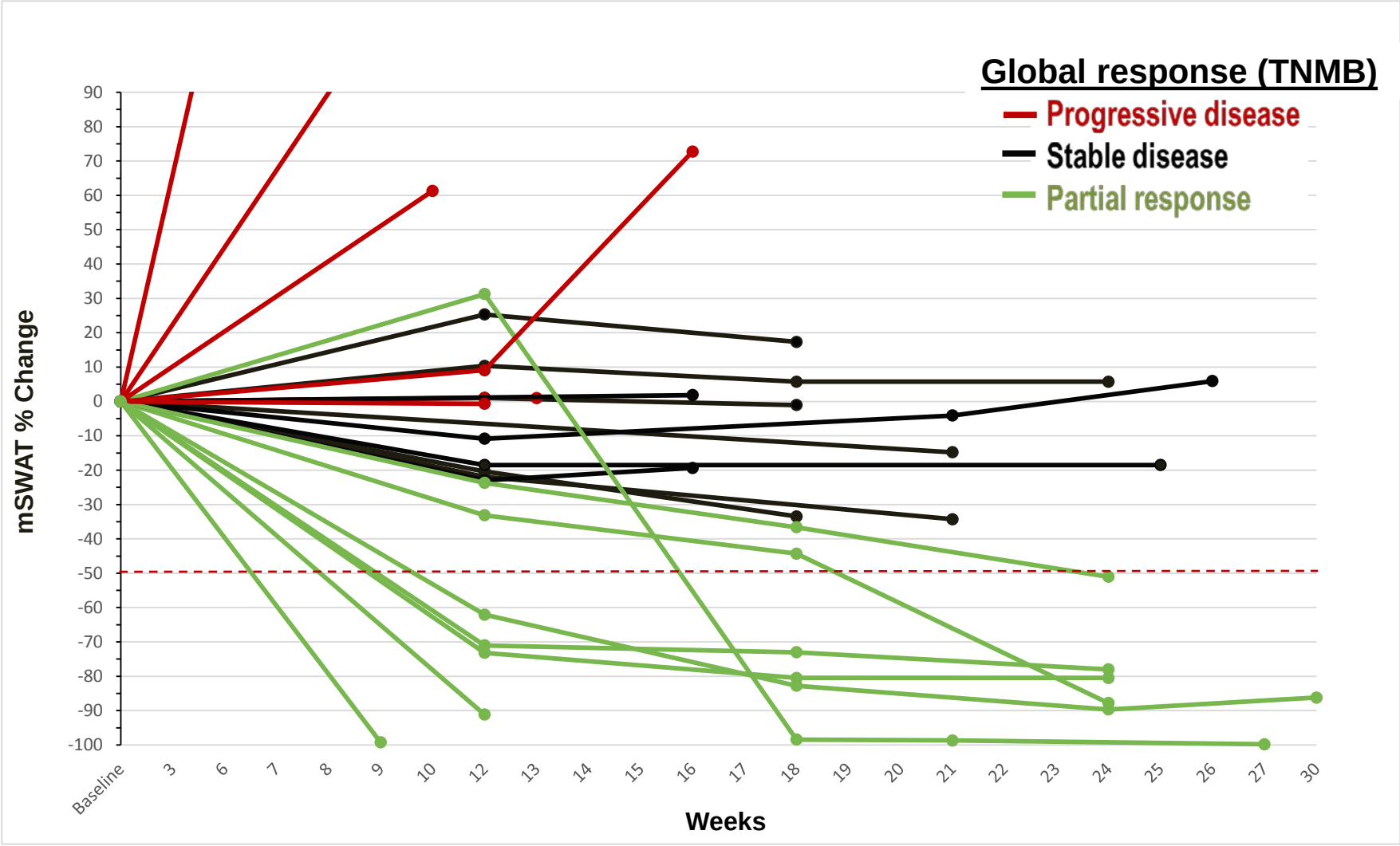
**NCI Collaboration:** Elad Sharon

# Cancer Immunotherapy Trials Network (CITN)




**FHCRC:** Fred Hutchinson Cancer Research Center
**HVTN:** HIV Vaccine Trial Network
**SCHARP:** The Statistical Center for HIV/AIDS Research & Prevention
**COSC:** Central Operations and Statistical Center
**NCI:** National Cancer Institute
**CTSU:** Cancer Trial Support Unit
**CTMB:** Clinical Trial Monitoring Branch
**RAB:** Regulatory Affairs Branch
**PMB** Pharmaceutical Management Branch

# Activity of pembrolizumab in skin (mSWAT %change) and global response



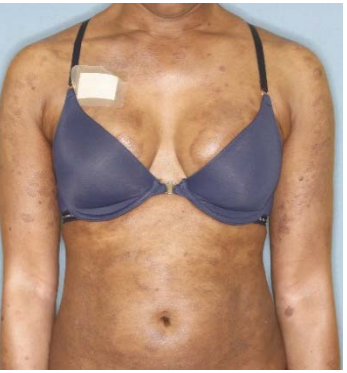

Median best mSWAT reduction 16.0% (99.8% to -198.5%)

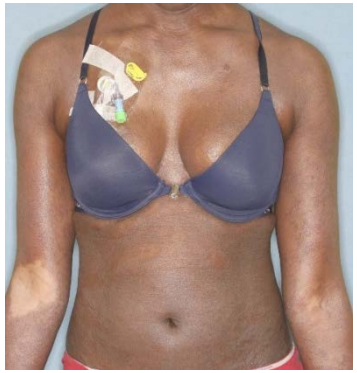
**2 pts with near CR in skin**

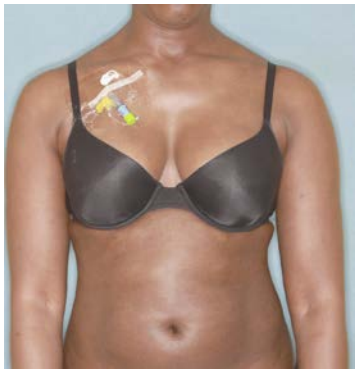
8/24 objective responses, median TTR = 11 wks (8-22)

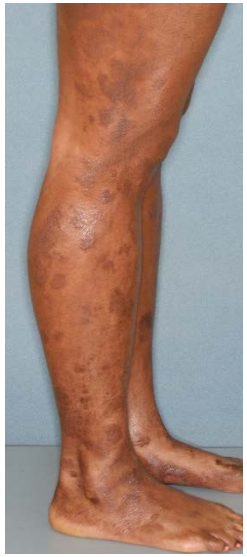
# 44 yo AA F with Sézary syndrome, stage IVA2, global PR

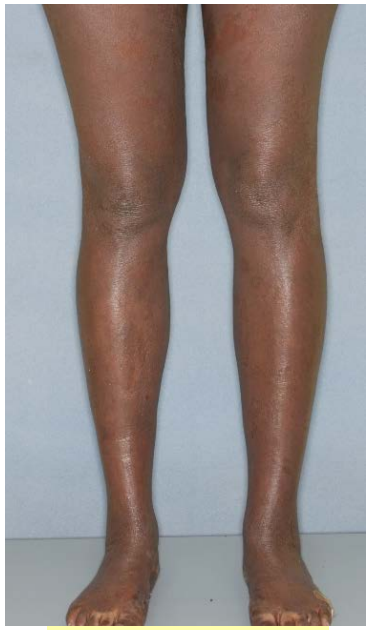
(h/o phototherapy, romidepsin)

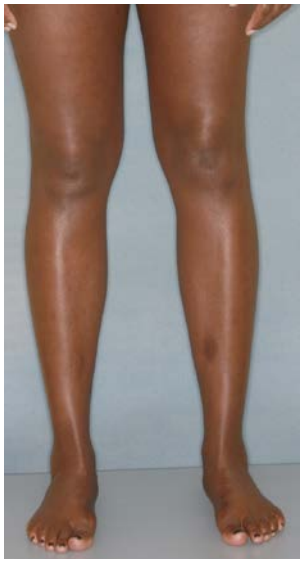










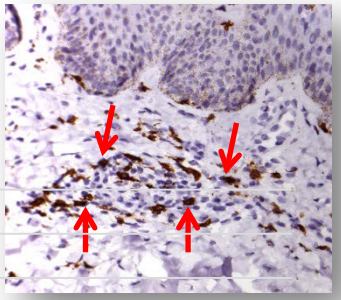


**Baseline**

**Immune mediated flare Gr 2 erythroderma**

**C13D1**

CD8+ T cells






**Global PR**

**Skin/PR C6D1, Blood/CR C5D1, LN/SD**

C2D1: skin/blood worsened with immune mediated flare

C5D1: concurrent AGEP due to IV contrast, mSWAT included AGEP

Numerous molluscum lesions on romidepsin, regressed with anti-PD-1 mab therapy

SU # 110-41-004

# Drug-related adverse events, ≥ 2 occurrence

| | All grades | | Grade 1/2 | | Grade 3/4 (Severe AE) | |
|---|---|---|---|---|---|---|
| **Adverse Event** | N | % | N | % | N | % |
| **Skin eruption** | **5** | **21** | **3** | **13** | **2** | **8** |
| **Anemia** | **3** | **13** | **1** | **4** | **2** | **8** |
| **WBC decreased** | **2** | **8** | **2** | **8** | **0** | **0** |
| **LFT (AST/ALT) elevated** | **2** | **8** | **1** | **4** | **1** | **4** |
| **Diarrhea** | **2** | **8** | **2** | **8** | **0** | **0** |
| **Fever** | **2** | **8** | **2** | **8** | **0** | **0** |
| **Face edema** | **2** | **8** | **1** | **4** | **1** | **4** |

* Exfoliative dermatitis (n=2), immune-mediated skin flare (n=2), excessive peeling/edema (n=1)

# Anti-PD-1 mab, pembrolizumab, in MF/SS *Summary*

- **Objective clinical responses observed in 8/24 (33%)**
  - MF (IIB/III, 4/9, 44%) and SS (IVA, 4/15, 20%)
  - Range of prior therapies, responses in heavily treated pts (3 of 8 responders with 6-7 prior systemic txs)
- **Well-tolerated and toxicity was manageable**
  - Skin reactions as most common AE, probably due to flare reaction
- **Biomarker/biology/molecular data pending, to better understand tumor/immune escape mechanisms**
  - Guide enrichment of response subset

***Combination immune strategies to improve ORR and DOR/PFS, being developed***

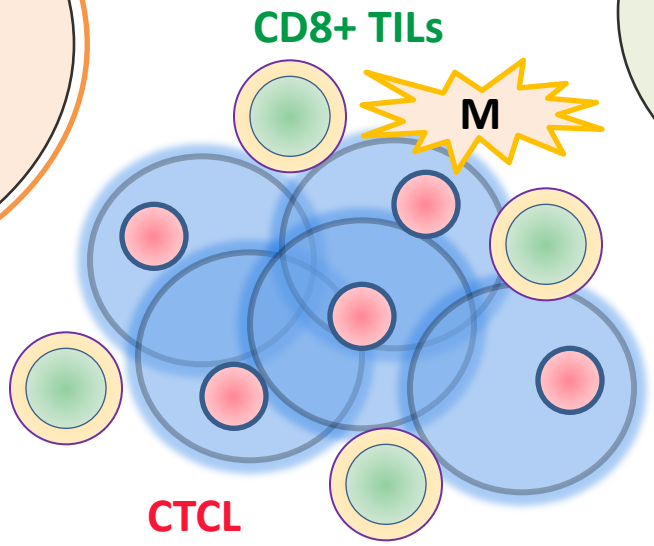
***Anti-PD-1 mAb + IFN-gamma***
***+/- low-dose TSEBT***

# New targets/novel approaches for immune modulation in CTCL

**Monoclonal antibodies**

**Tumor cell-specific:**
tumor surface molecules
(e.g., CD4, CD25, CD30, CD52, CCR4, **CD158k/KIR3DL2**)

**Microenvironment Immune modulation**
(e.g. PD-1/PD-L1, CTLA-4, IDO, CD40, TLRs, SIRP$\alpha$/CD47, CD137, MDSC, Tregs)

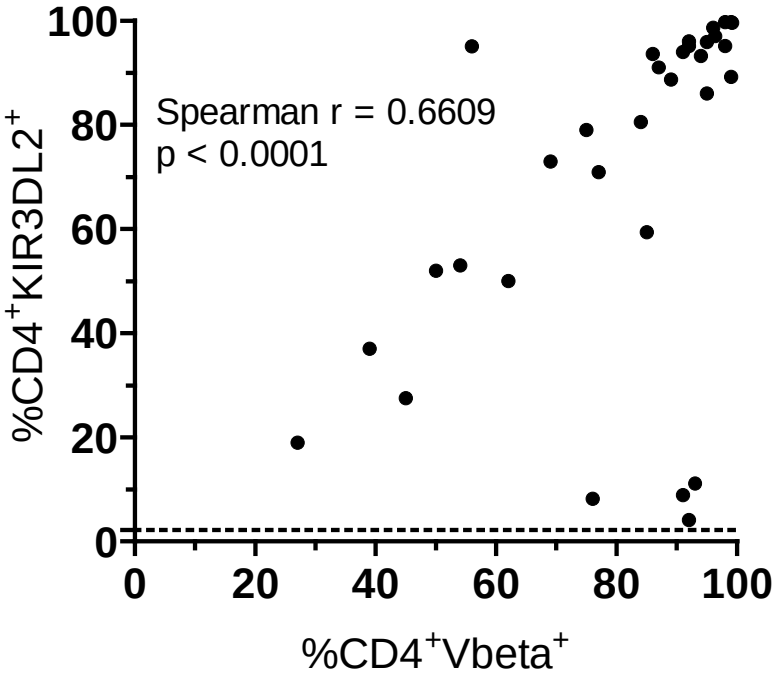



**<u>CD158k/KIR3DL2</u>**
**Consistently expressed in MF/LCT and Sézary syndrome**

**IPH4102 MOA by ADCC and ADCP**

# 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*

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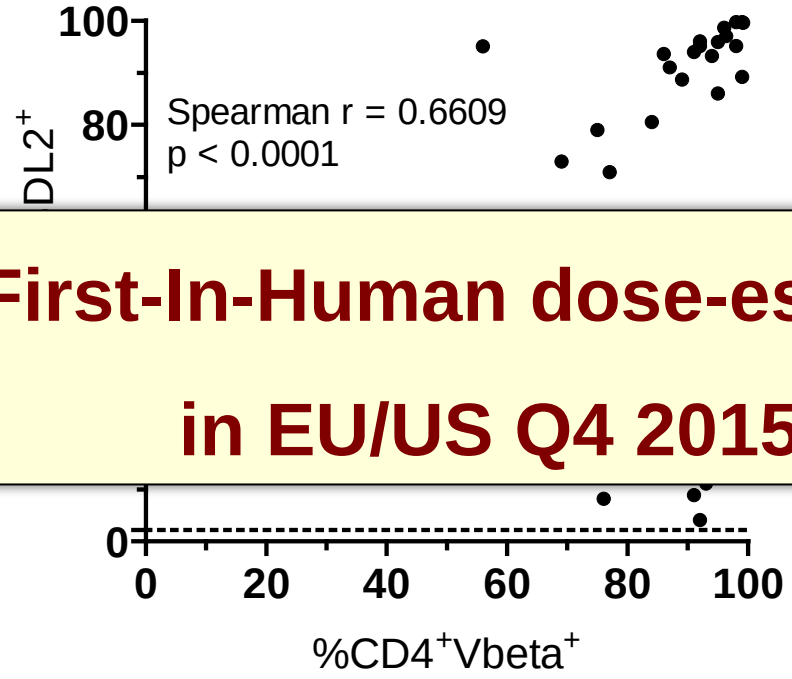


**IPH4102 First-In-Human dose-escalation study in EU/US Q4 2015**

*Marie-Cardine et al, Cancer Res. 2014*

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**Monoclonal antibodies**

**Tumor cell-specific:**
tumor surface molecules
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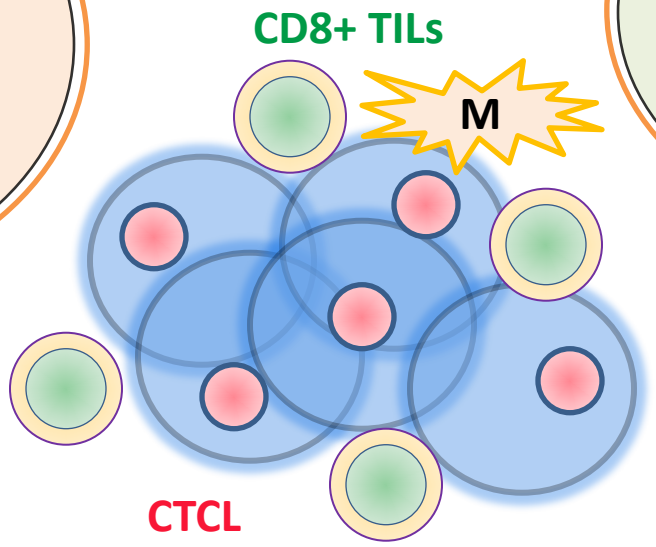
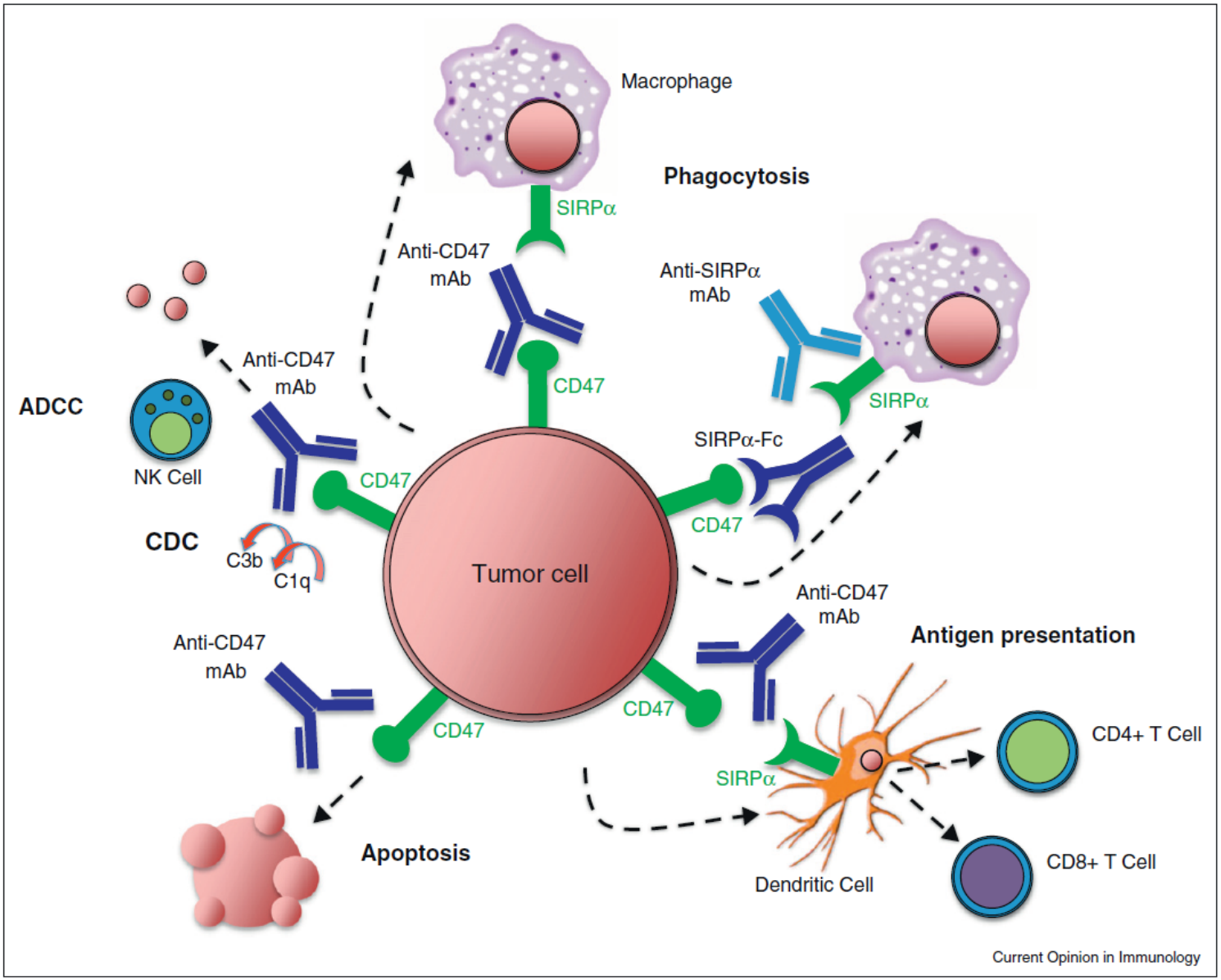



**SIRPα/CD47 axis**
**"Don't eat me" signal by tumor cells**

**Evasion of macrophage phagocytosis**

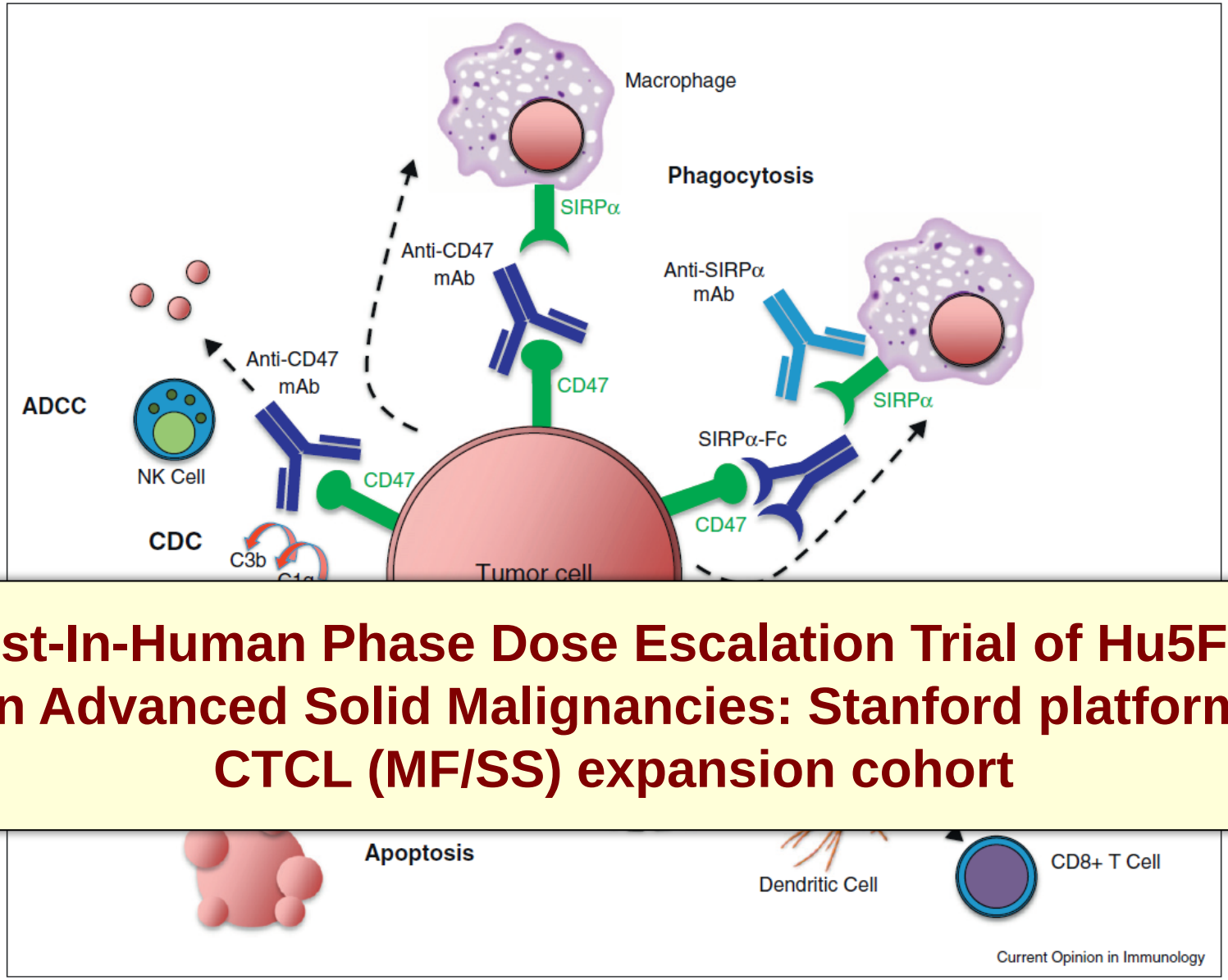
*Weissman group, Stanford*

# Targeting CD47–SIRPα axis in cancer immunotherapy: converting "don't eat me" ➔ "eat me" signal and more




*Curr Opinion Immunol 2012;24:225*

# Targeting CD47–SIRPα axis in cancer immunotherapy: converting "don't eat me" ➔ "eat me" signal and more




## A First-In-Human Phase Dose Escalation Trial of Hu5F9-G4 in Advanced Solid Malignancies: Stanford platform CTCL (MF/SS) expansion cohort

*Curr Opinion Immunol 2012;24:225*

# New agents and improved therapeutic strategies in CTCL

- **New/improved technology** allowing us to learn more, help identify actionable targets, and modify/render agents more effective/safe
- **More encouraging treatment options** (more in the pipeline)
- **Use old therapies smarter** (e.g., low-dose TSEBT+ immunotherapy)
- **Improved/more tumor-selective** therapies, less toxicity
- Learning to **partner with immune/microenvironment modulators**
- **Can cure advanced stage MF/SS** with allogeneic HSCT
- **Molecular/biomarker platforms integrated into clinical trials** to learn predictive value for response/resistance/escape, toxicity, or survival outcomes
- Taking steps **towards personalized, precision medicine**

Columbia University
College of Physicians and Surgeons

ISCL

# 3rd World Congress of Cutaneous Lymphomas

Wednesday - Friday | October 26 - 28, 2016
New York City, NY, USA

## *3WCCL Participating organizations:*

ISCL
USCLC
EORTC CLTF
Columbia University
New York City

October 26-28, 2016

*View website for details*
www.columbiacme.org