New Agents and Therapeutic Strategies in CTCL

Youn H Kim, MD

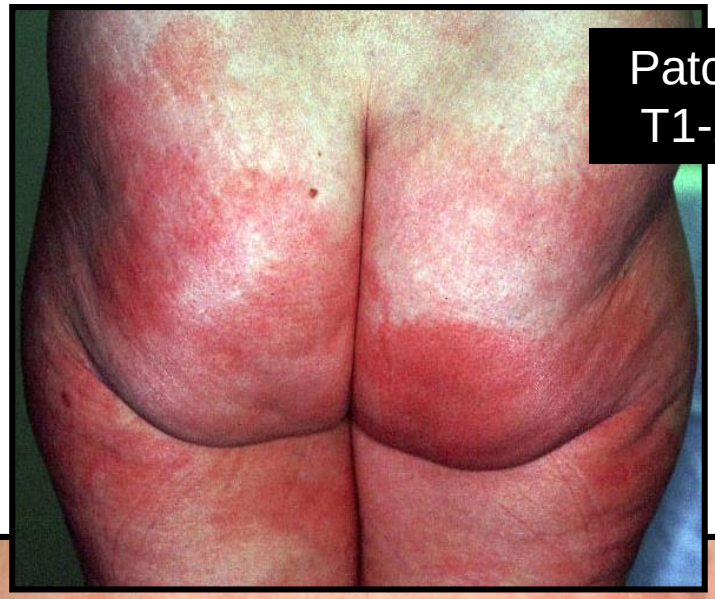
Department of Dermatology
Multidisciplinary Cutaneous Lymphoma Group
Stanford Cancer Institute & School of Medicine

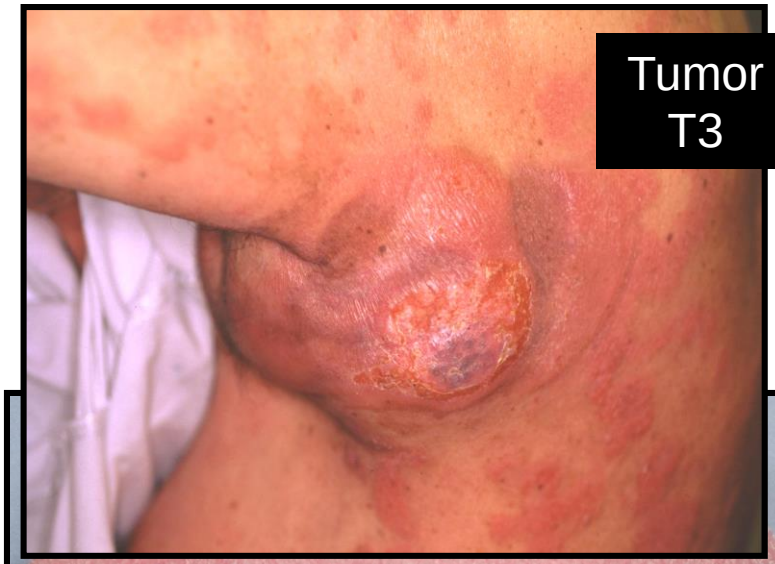
Cutaneous T- and NK/T-cell Lymphomas

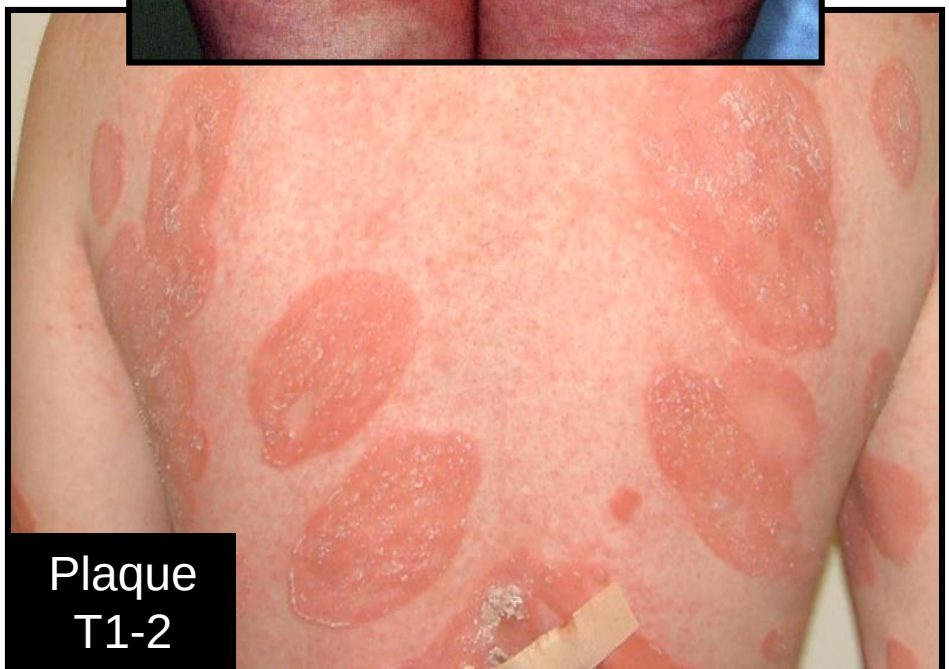
New WHO-EORTC Classification
Mycosis fungoides and variants/subtypes
Sézary syndrome
PC CD30+ lymphoproliferative disorders
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Cutaneous γ/δ T-cell lymphoma
Adult T-cell leukemia/lymphoma
PC peripheral T-cell lymphoma,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

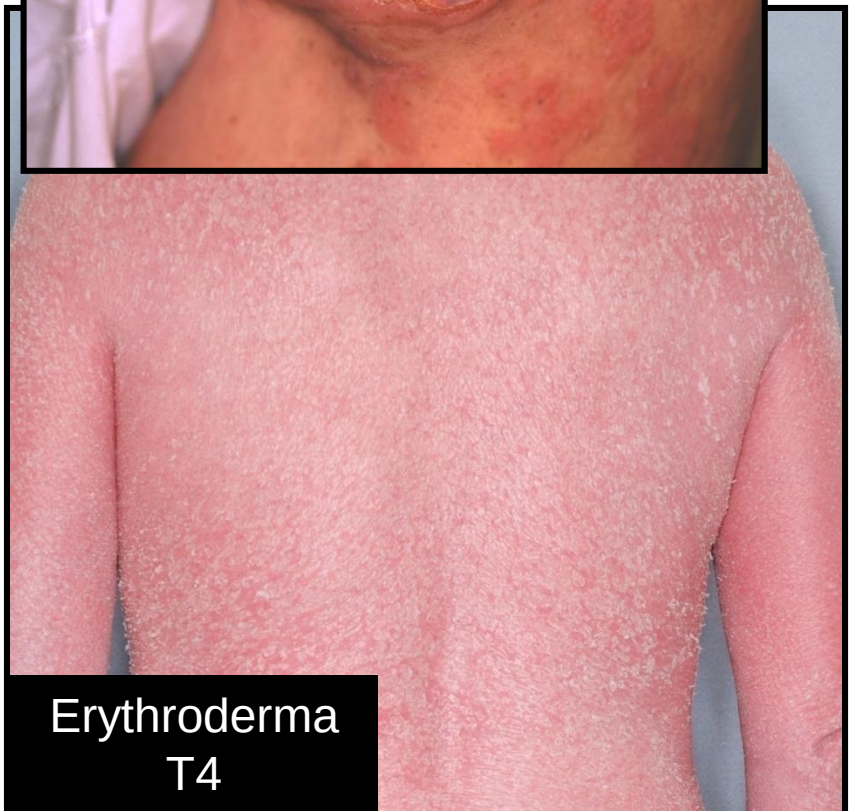
WHO monogram, 4th Ed, 2008

Mycosis Fungoides
Treatment of varying skin manifestations

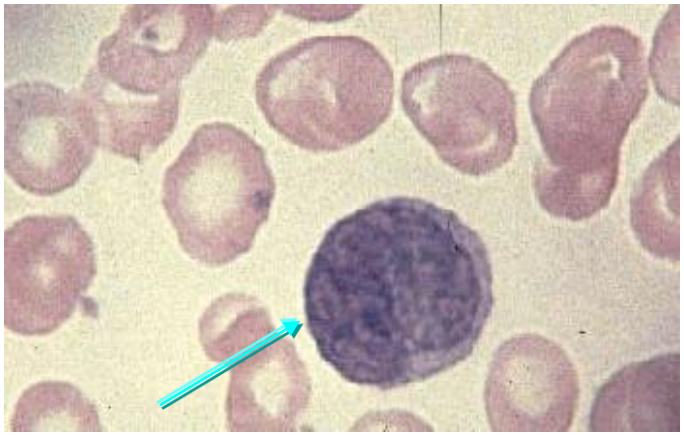






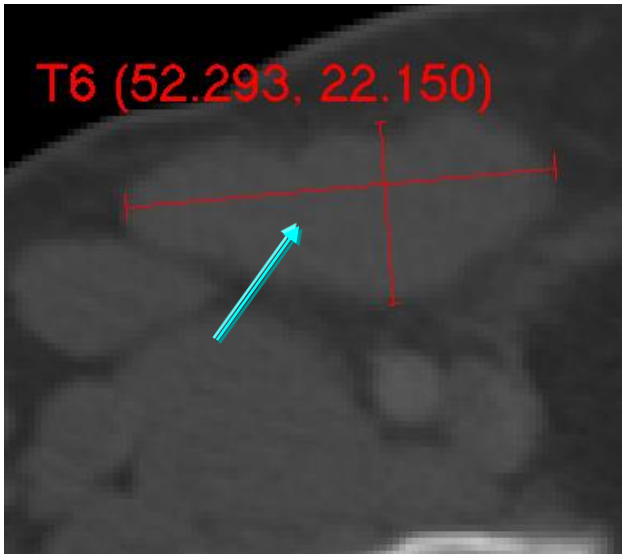


Management of extracutaneous disease

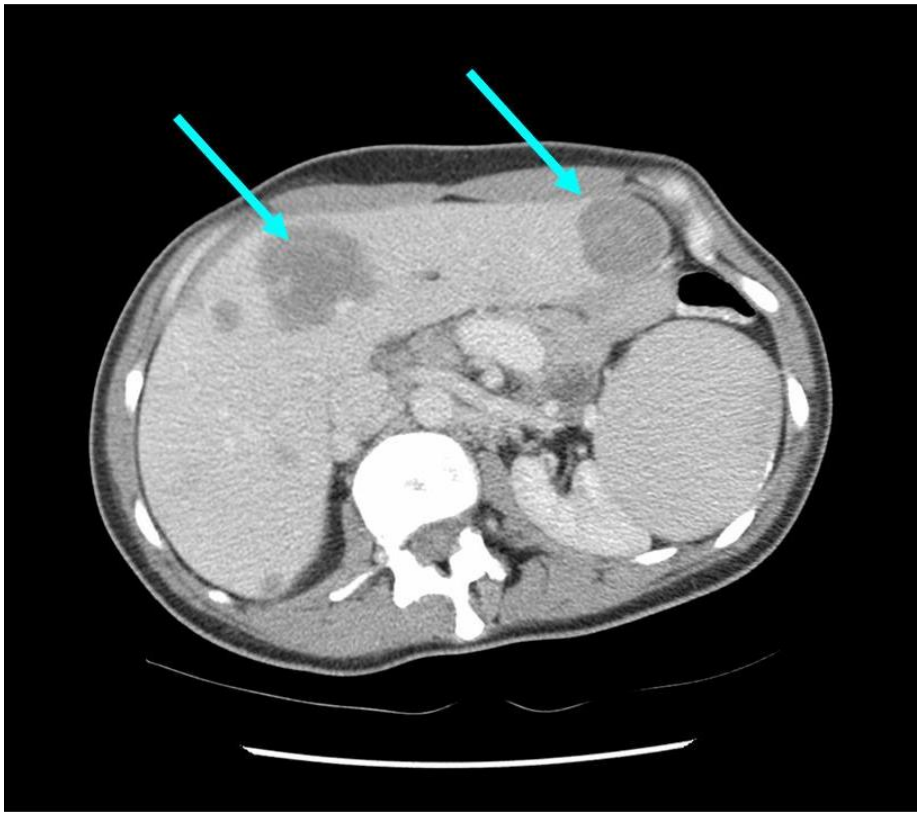


Blood

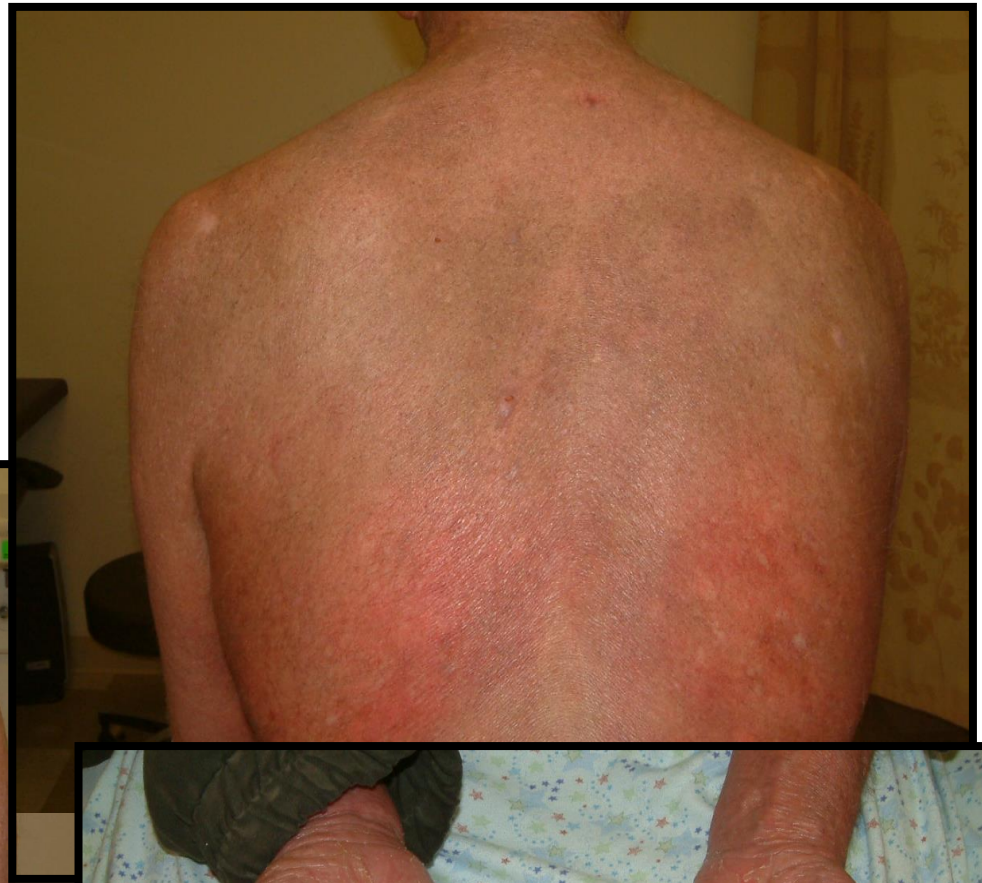
Lymph node

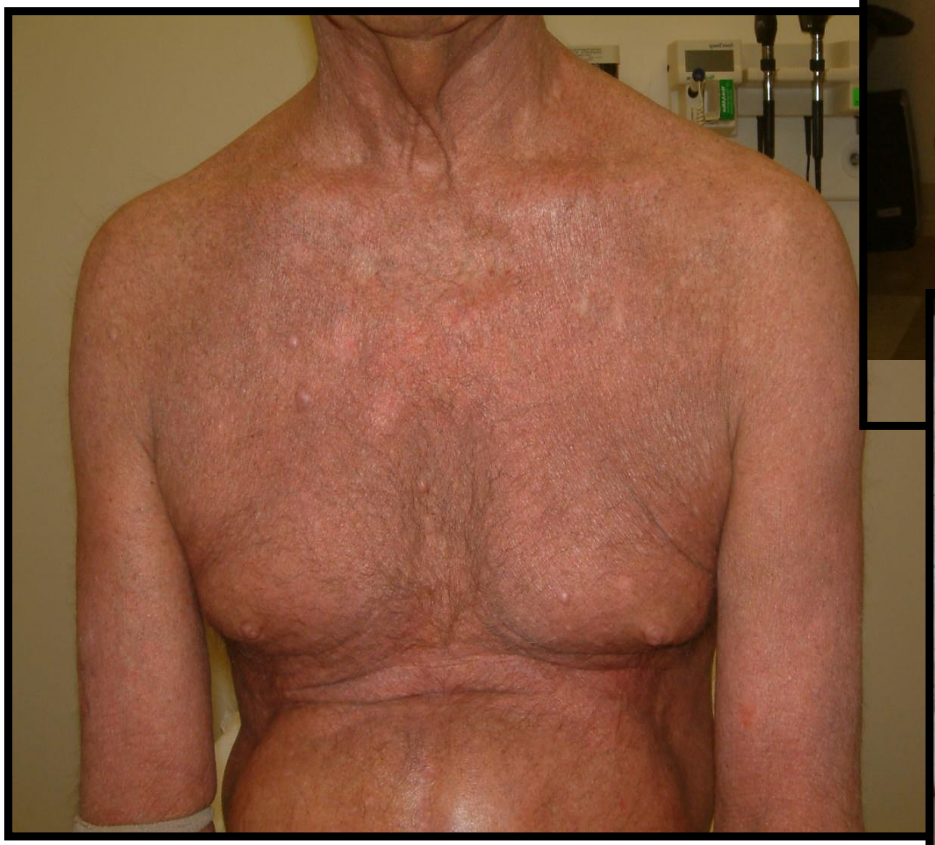


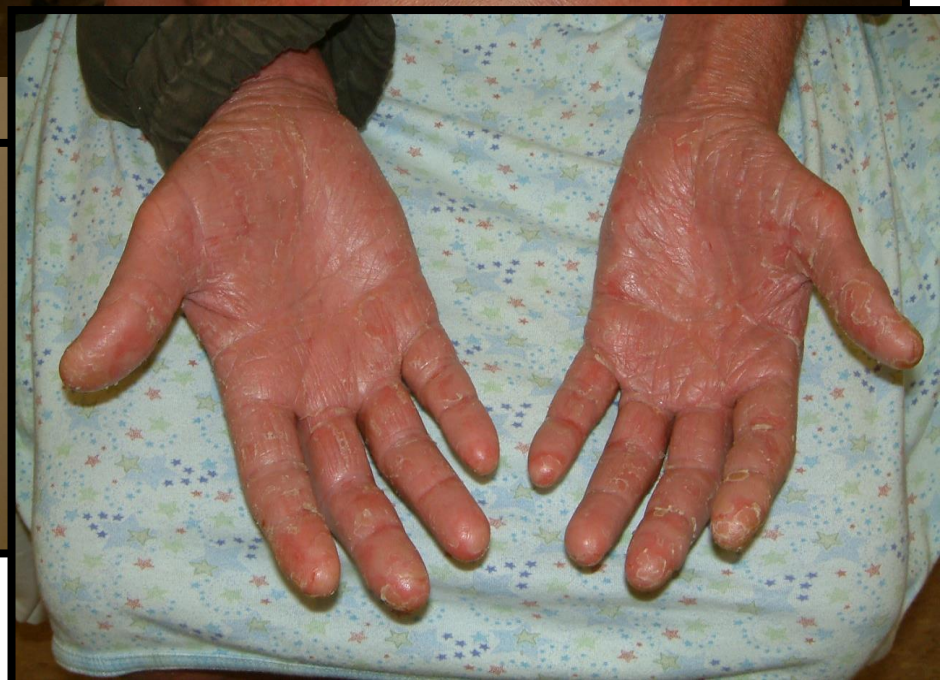
Viscera



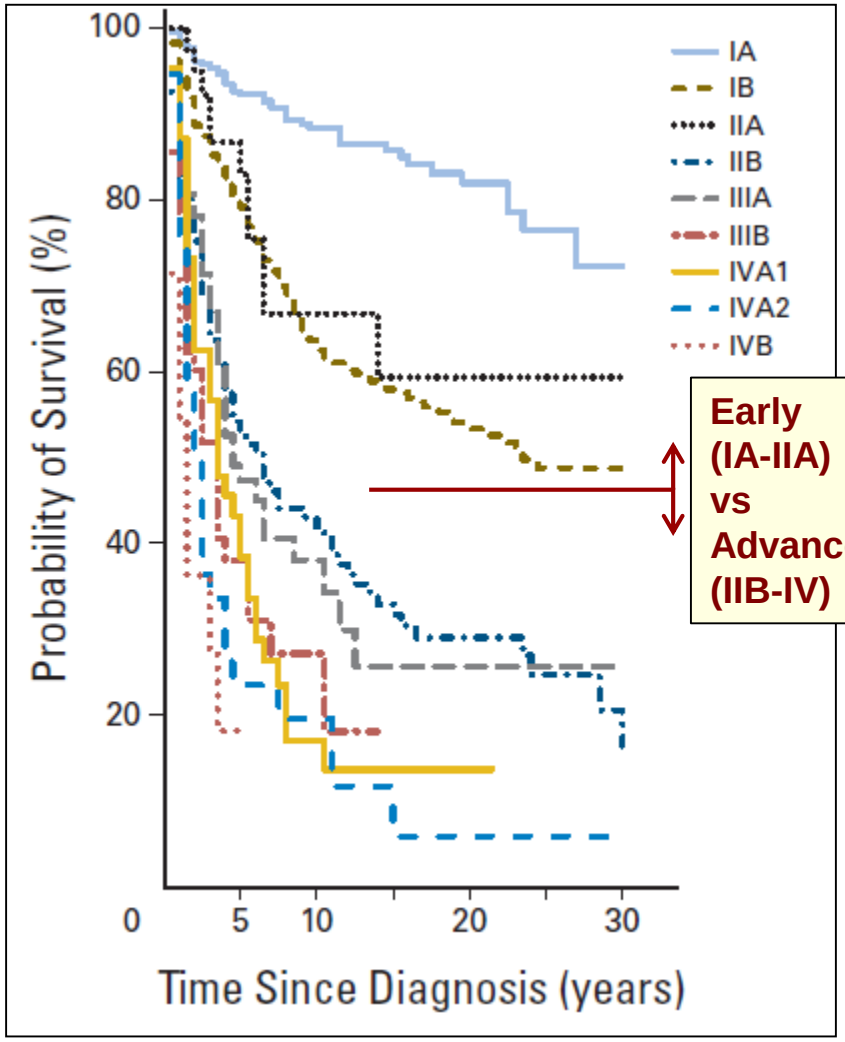
Sézary syndrome- generalized erythroderma, keratoderma, severe itching; freq staph aureus infection







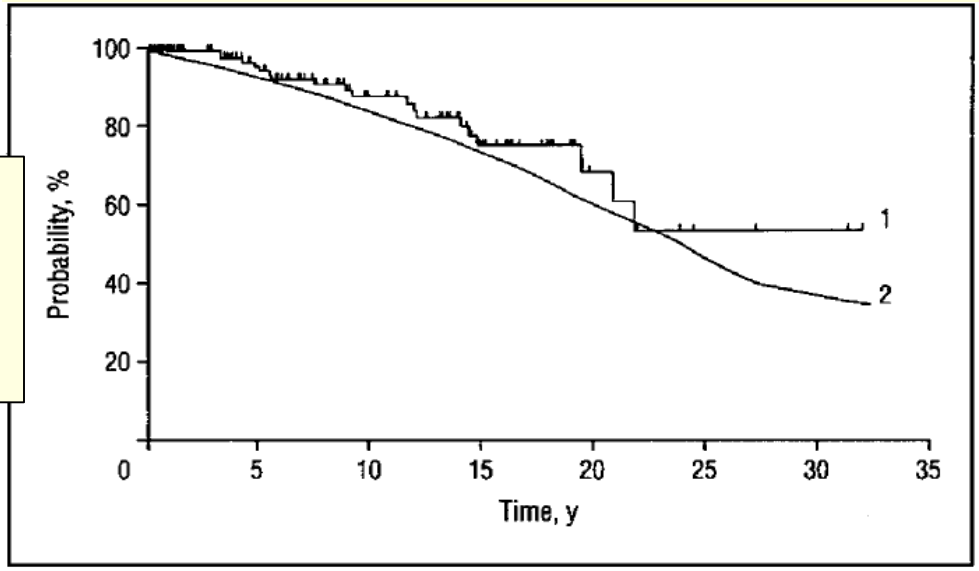
Prognosis of early vs advanced stage MF and SS:
Appropriate risk-stratification for treatment selection



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

General concepts in managing MF/SS-CTCL

Lack of evidence-based help

- **Consensus-based management**

NCCN, EORTC, other guidelines

Overall goal of treatment

- Good PRs that are durable, well-tolerated, and improve QoL
- Lasting CRs are great but hard to attain and often at risk of undesired AEs

Appreciate unique features of skin disease

- **Supportive therapy** is essential (barrier defect)
  - Chronic control of skin infections (staph, HSV)
  - Use anti-itch regimens, emollients/sealants
- Often observe **mixed responses**
- Can **re-cycle** treatments
- Optimize utility of **maintenance** therapy

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Mycosis Fungoides/Sezary Syndrome

What are the standard systemic agents in CTCL?

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)

=> Stage-based management

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

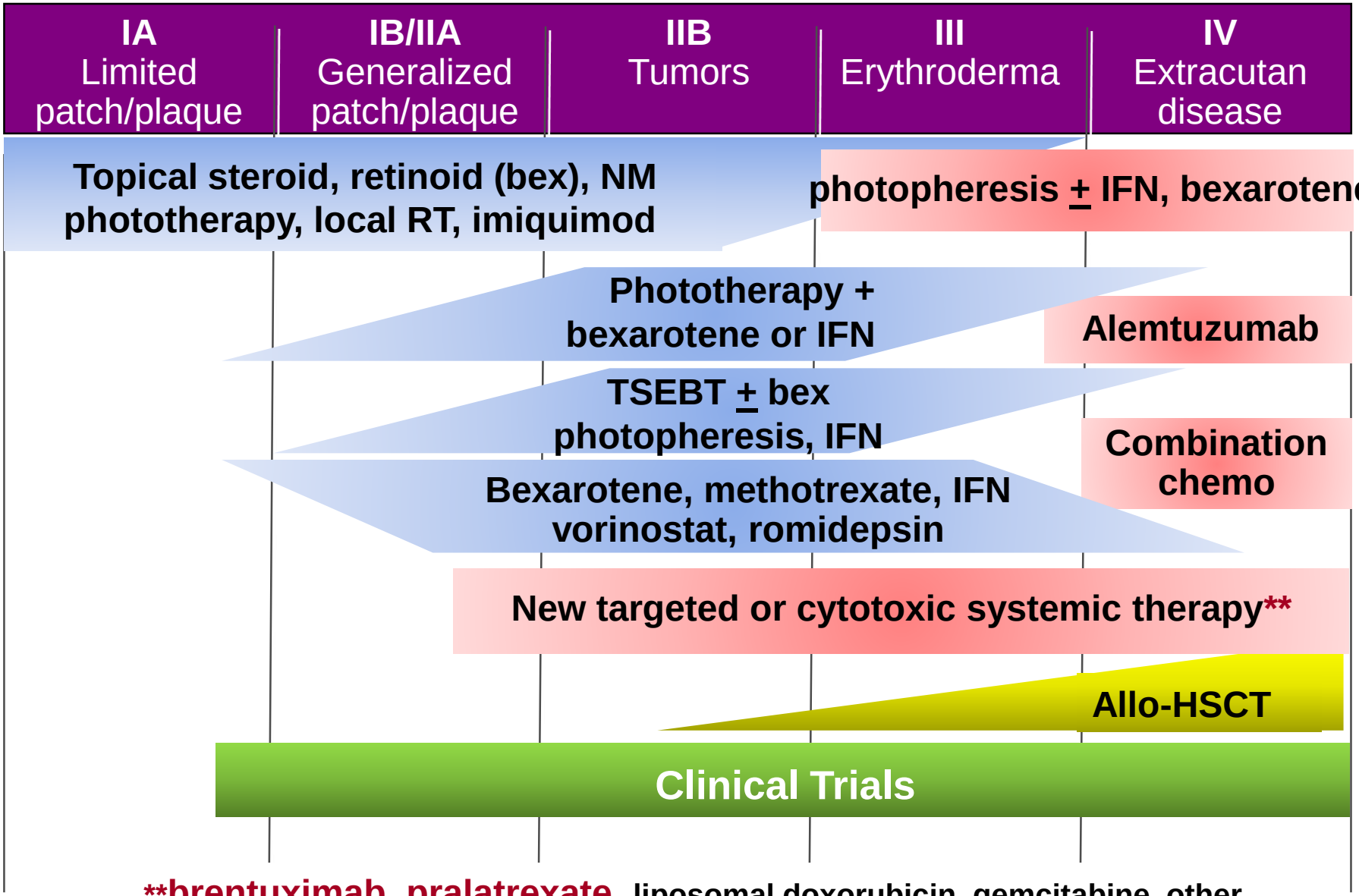
- Phototherapy + retinoid[e]
- Phototherapy + IFN
- Phototherapy + photopheresis[f]
- Total skin electron beam + photopheresis[f]

Systemic + Systemic

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

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**
- **Topical HDAC inhibitor (SHP-141/SHAPE)**
- **New PDT (hypericin)**

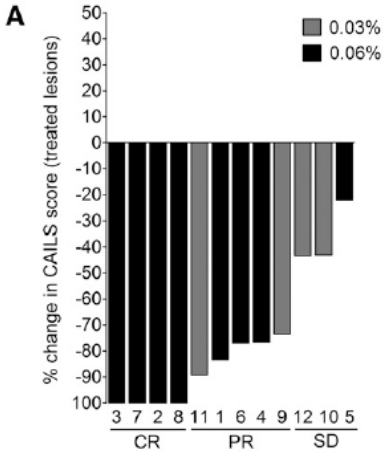
JAMA Dermatol 2013;149:25;
J Am Acad Dermatol 2015:72:286; Blood 2015;126:1452

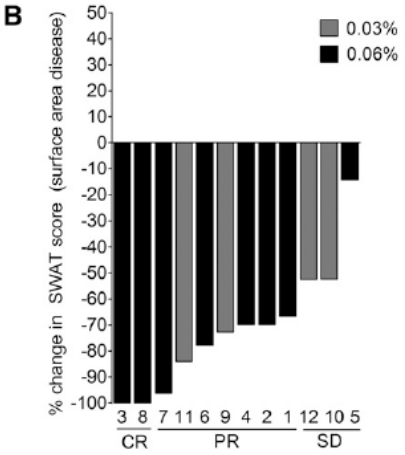
Blood 2015;126:1452

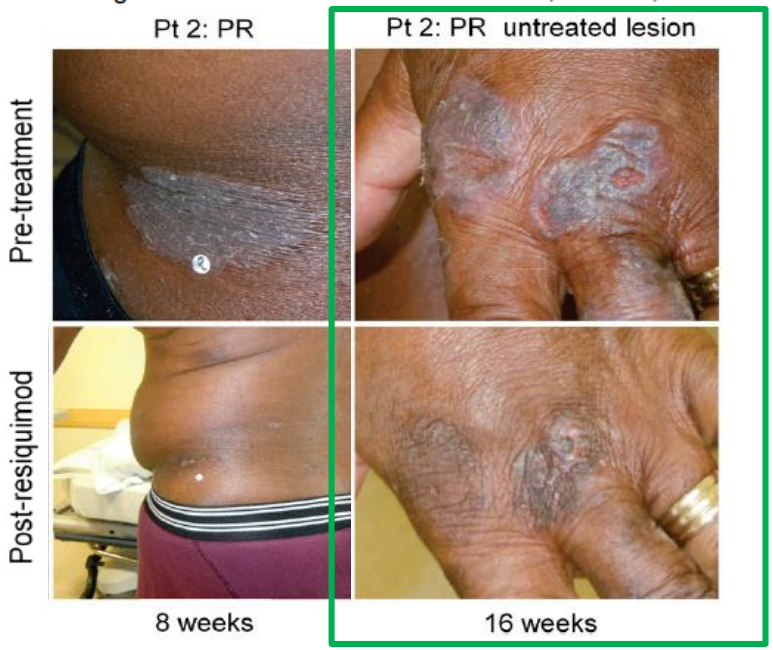
Topical resiquimod can induce disease regression and enhance T-cell effector functions in cutaneous T-cell lymphoma

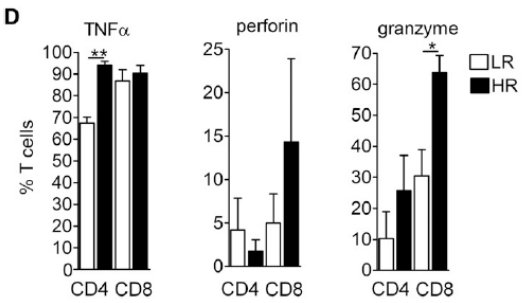
Alain H. Rook,[1] Joel C. Gelfand,[1] Maria Wysocka,[1] Andrea B. Troxel,[1] Bernice Benoit,[1] Christian Surber,[2,3] Rosalie Elenitsas,[1] Marie A. Buchanan,[1] Deborah S. Leahy,[1] Rei Watanabe,[4,5] Ilan R. Kirsch,[6] Ellen J. Kim,[1] and Rachael A. Clark[5,7]

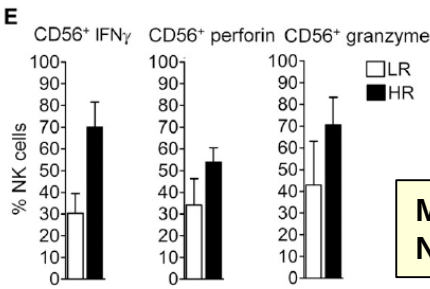
[1]Department of Dermatology and the Center for Clinical Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [2]Department of Dermatology, University Hospital, Zürich, Switzerland; [3]Department of Dermatology, University Hospital, Basel, Switzerland; [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





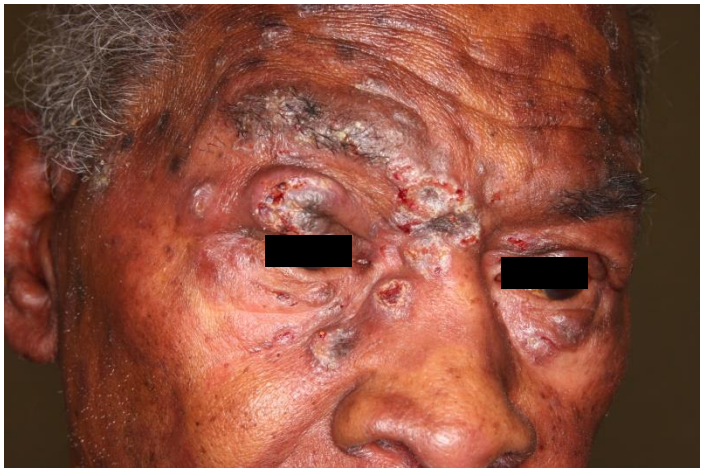


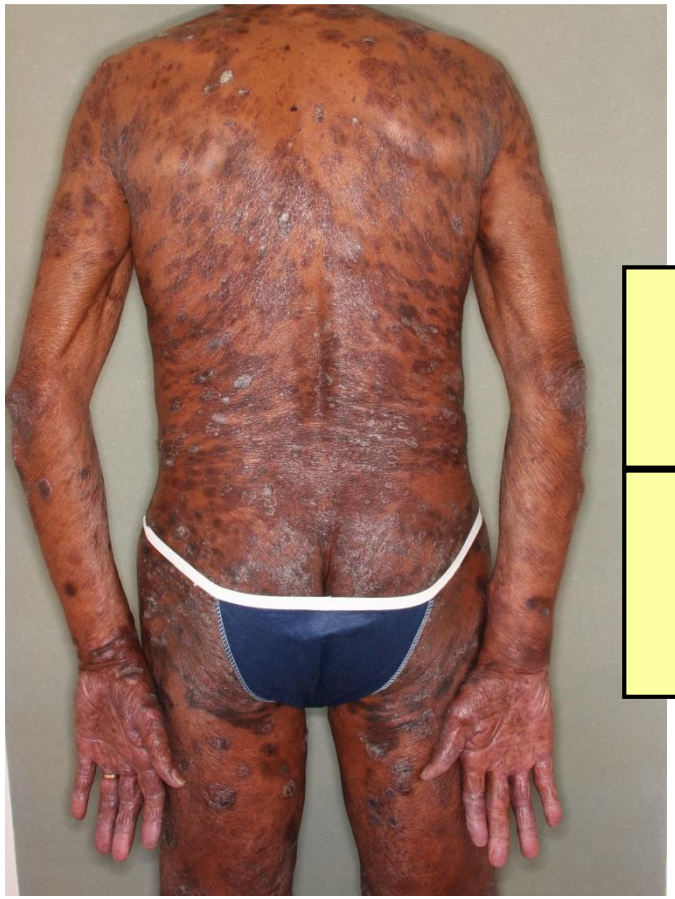




Malignant T cell eradication is a/w ↑T-cell and NK-effector functions in treated skin

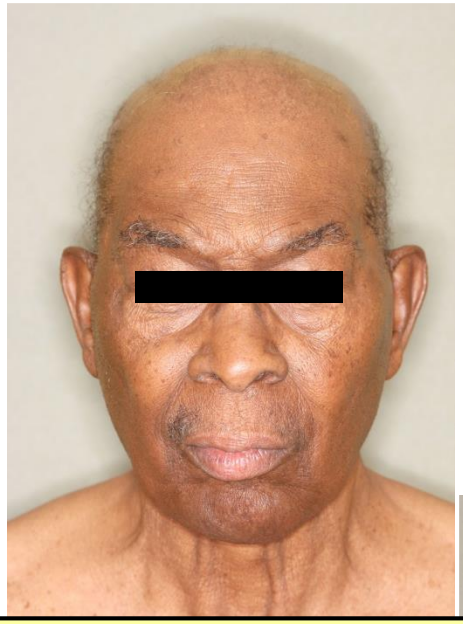
MF IIB with LCT

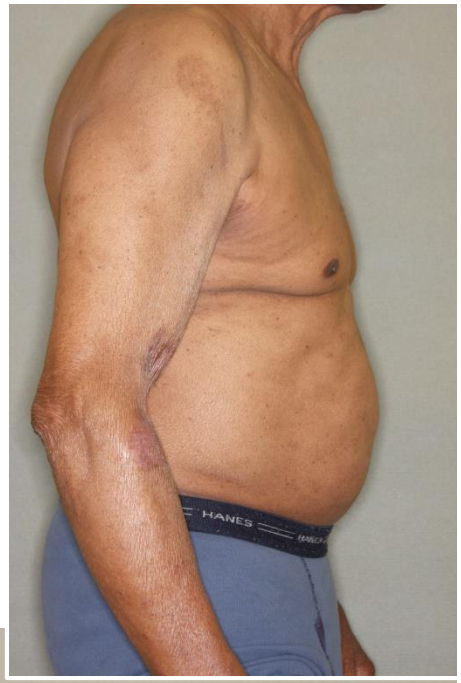


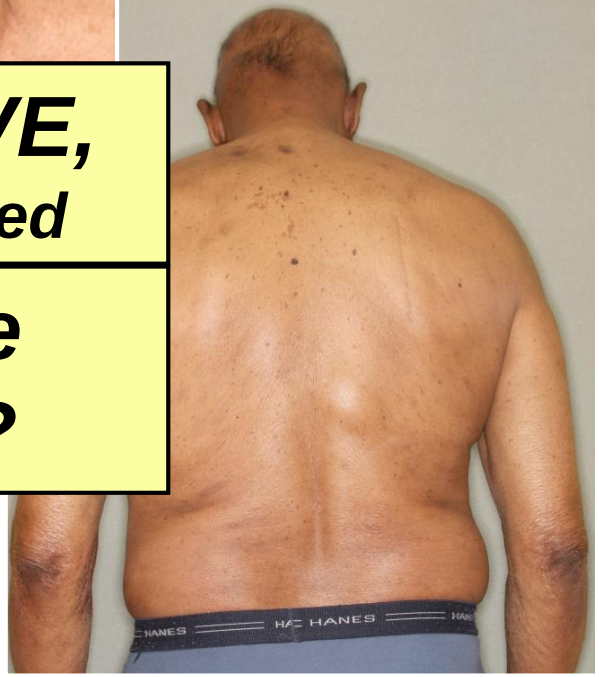


Standard dose TSEBT

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

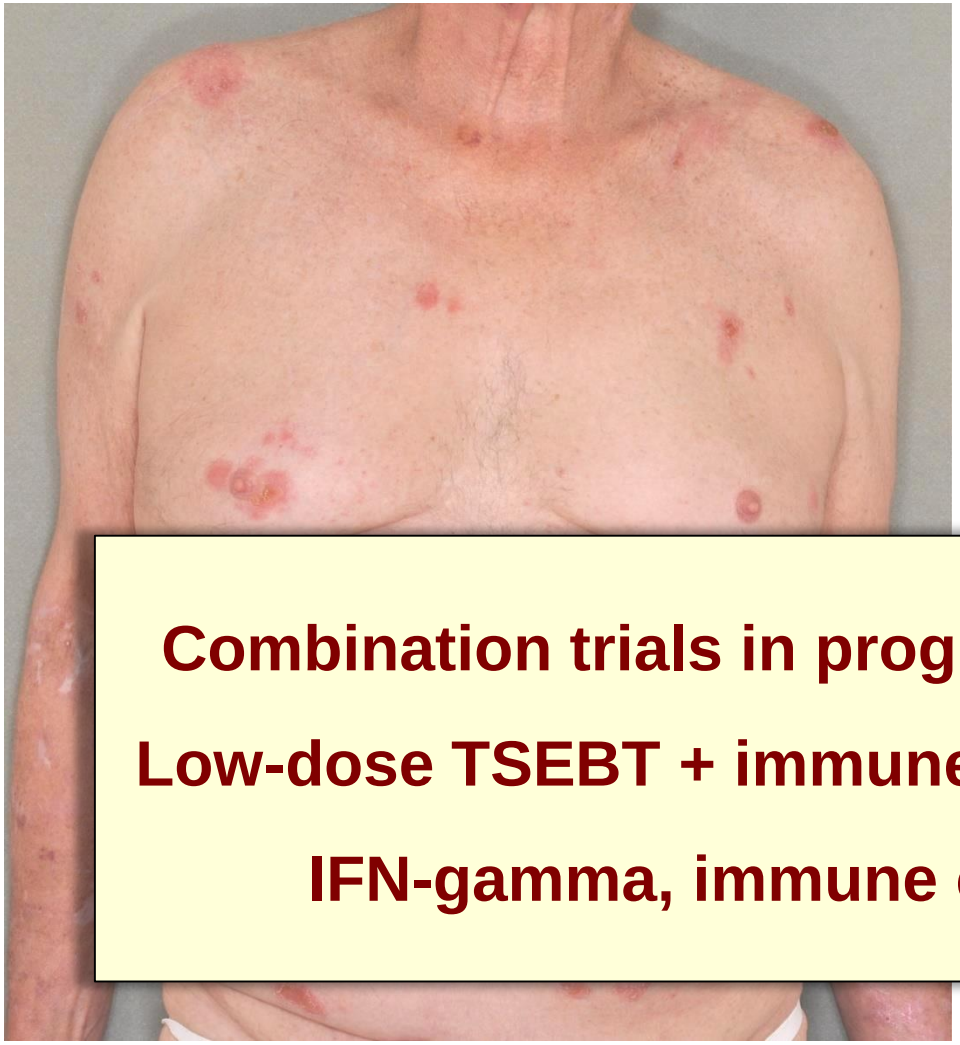
- **Low-dose, 12 Gy (3 wks)** vs. standard, 36 Gy (10 wks)
- **Reliable/efficient reduction** in skin disease => **near 90% ORR, ~30% CR**
- **Less side effects:** no permanent hair loss, less skin toxicity
- **Can be given repetitively** in pt's course
- Low-dose can be followed or combined with other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

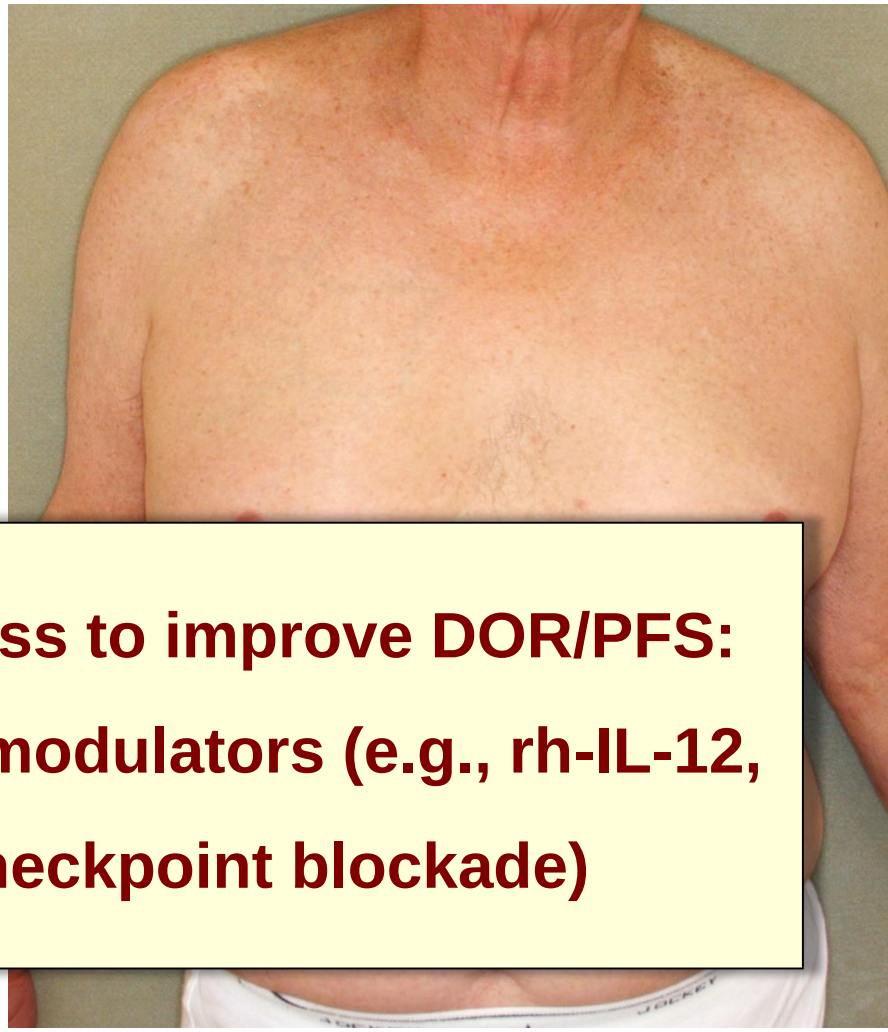
Table II. Best overall response to treatment at study termination, total time to response, and duration of clinical response

		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

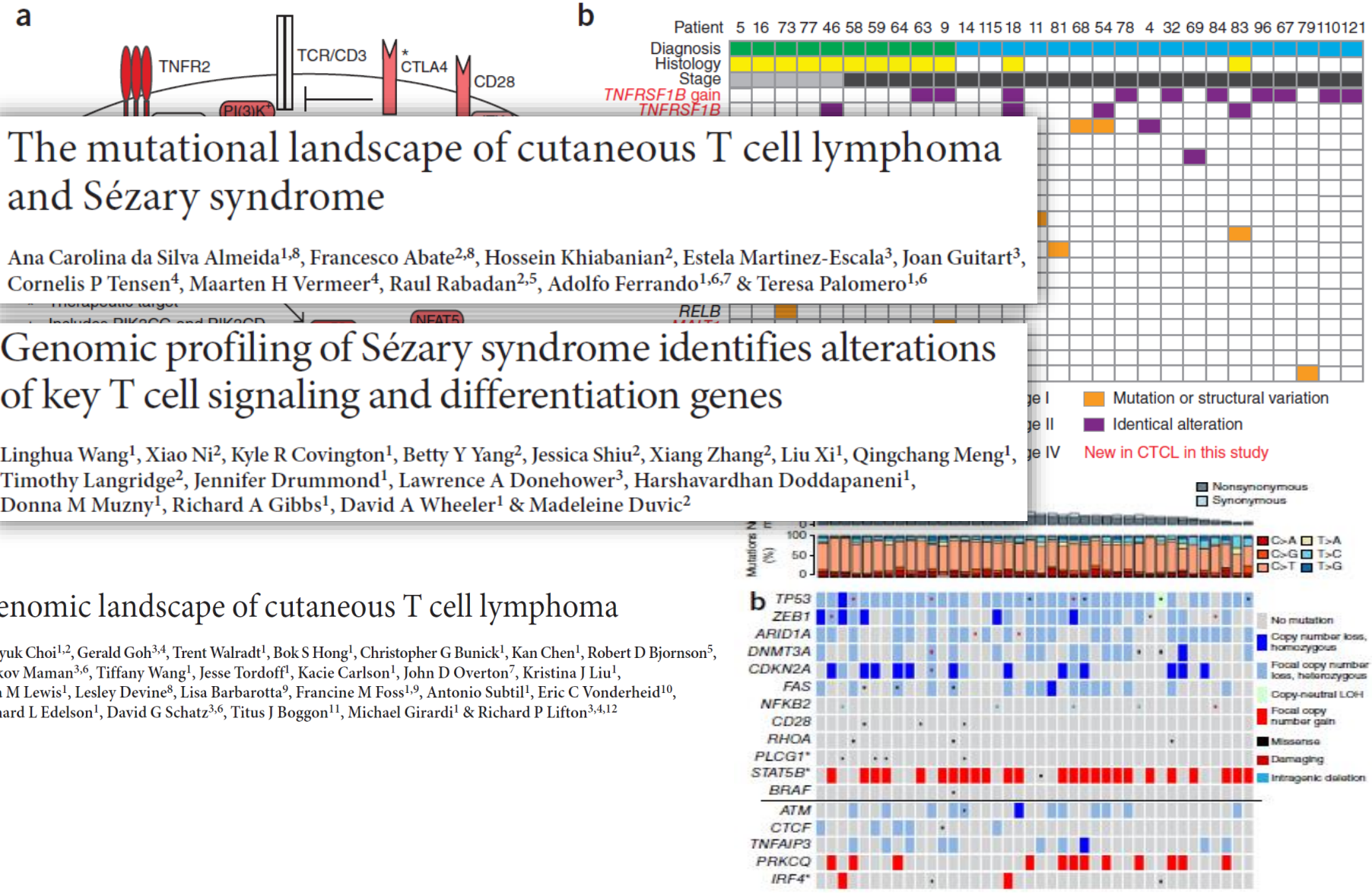
Wk 16
mSWAT 0 (CR)
Pruritus 0/10

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]



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]

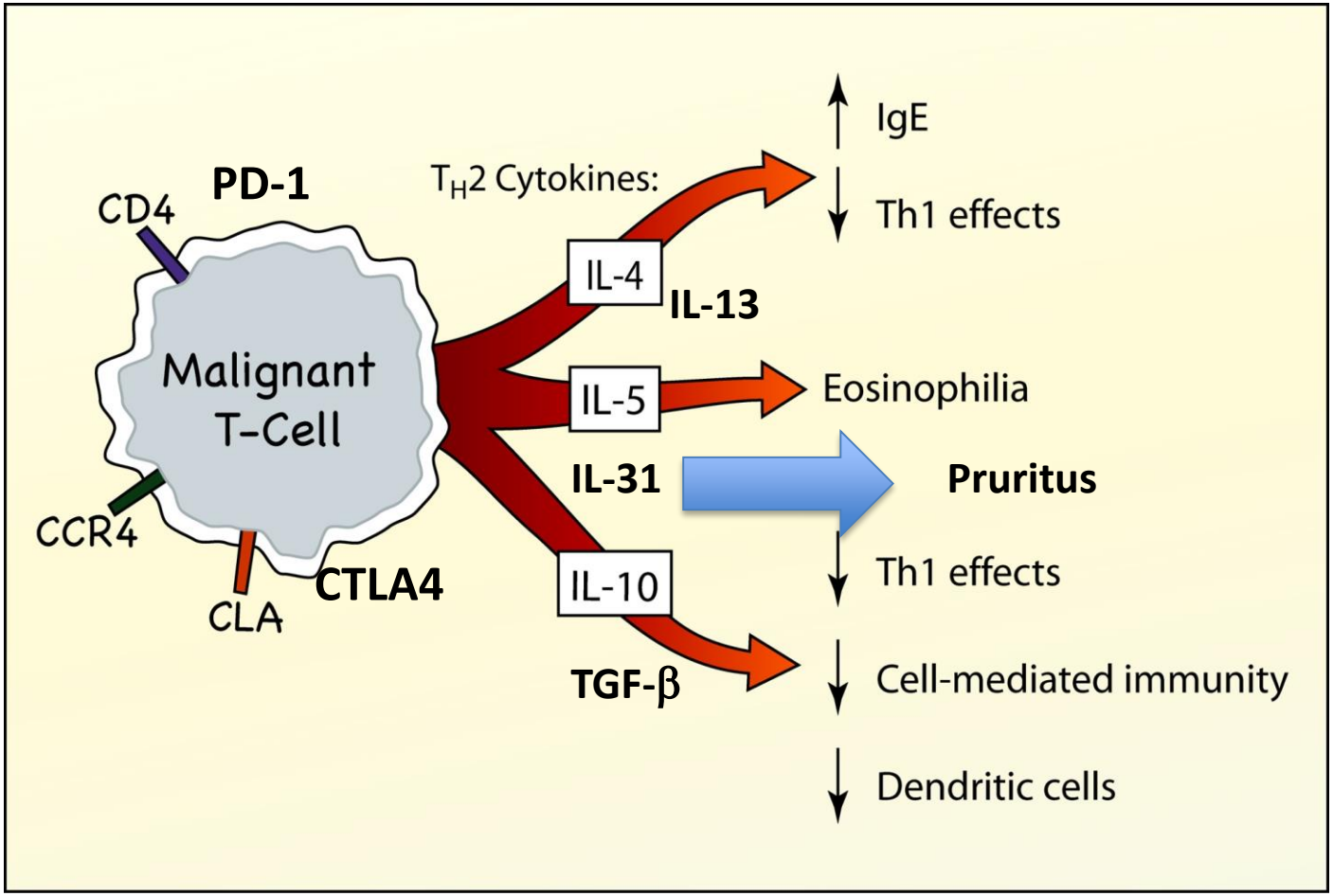
Genomic profiling of Sézary syndrome identifies alterations of key T cell signaling and differentiation genes

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]

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]

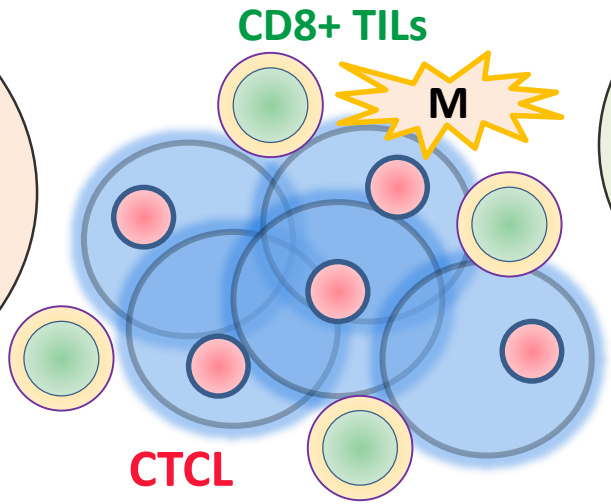
Effects of soluble factors, immune dysregulation in MF/SS



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

Targets for therapy in cutaneous T-cell lymphoma

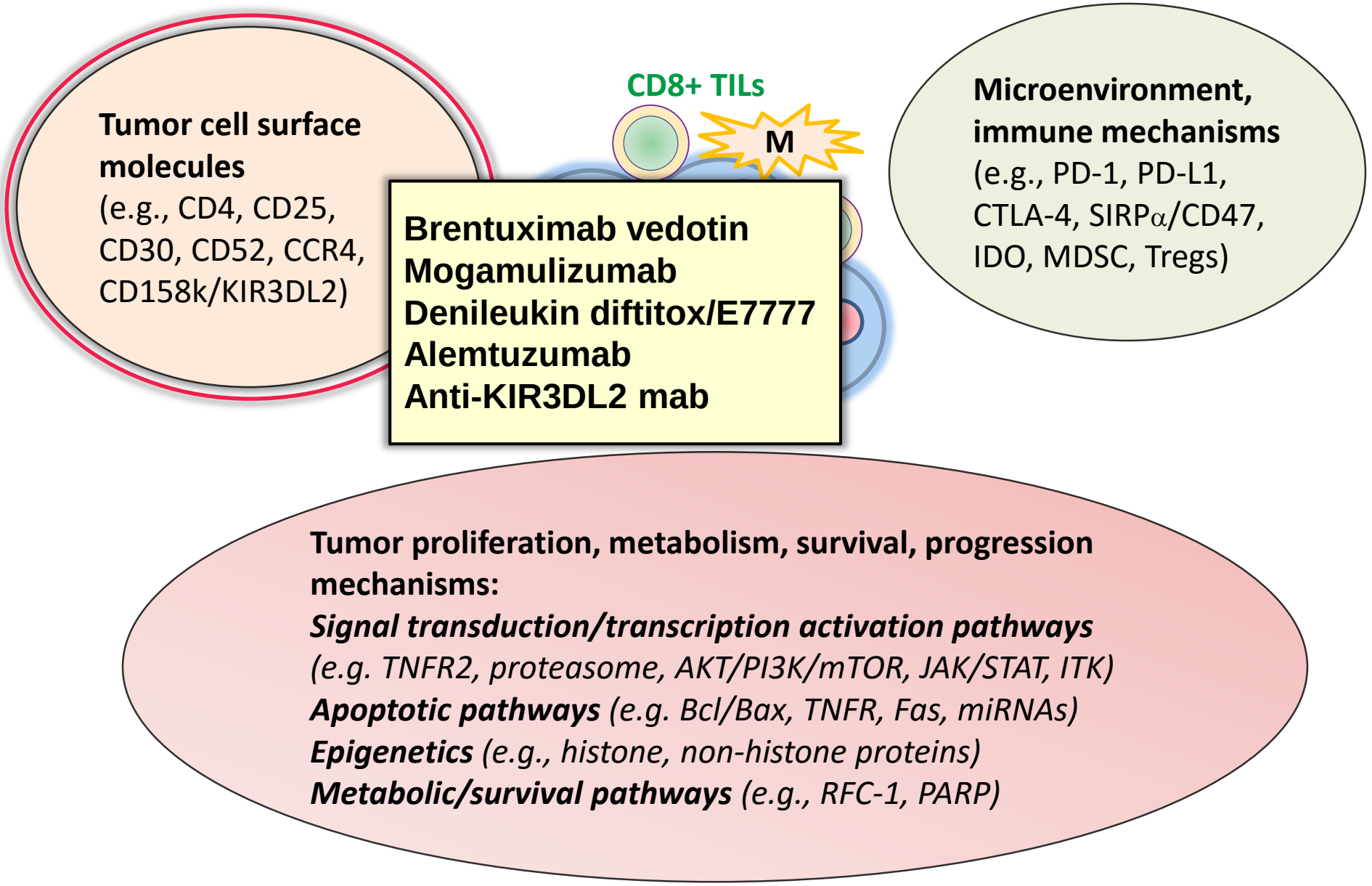
Tumor cell surface molecules
(e.g., CD4, CD25, CD30, CD52, CCR4, CD158k/KIR3DL2)



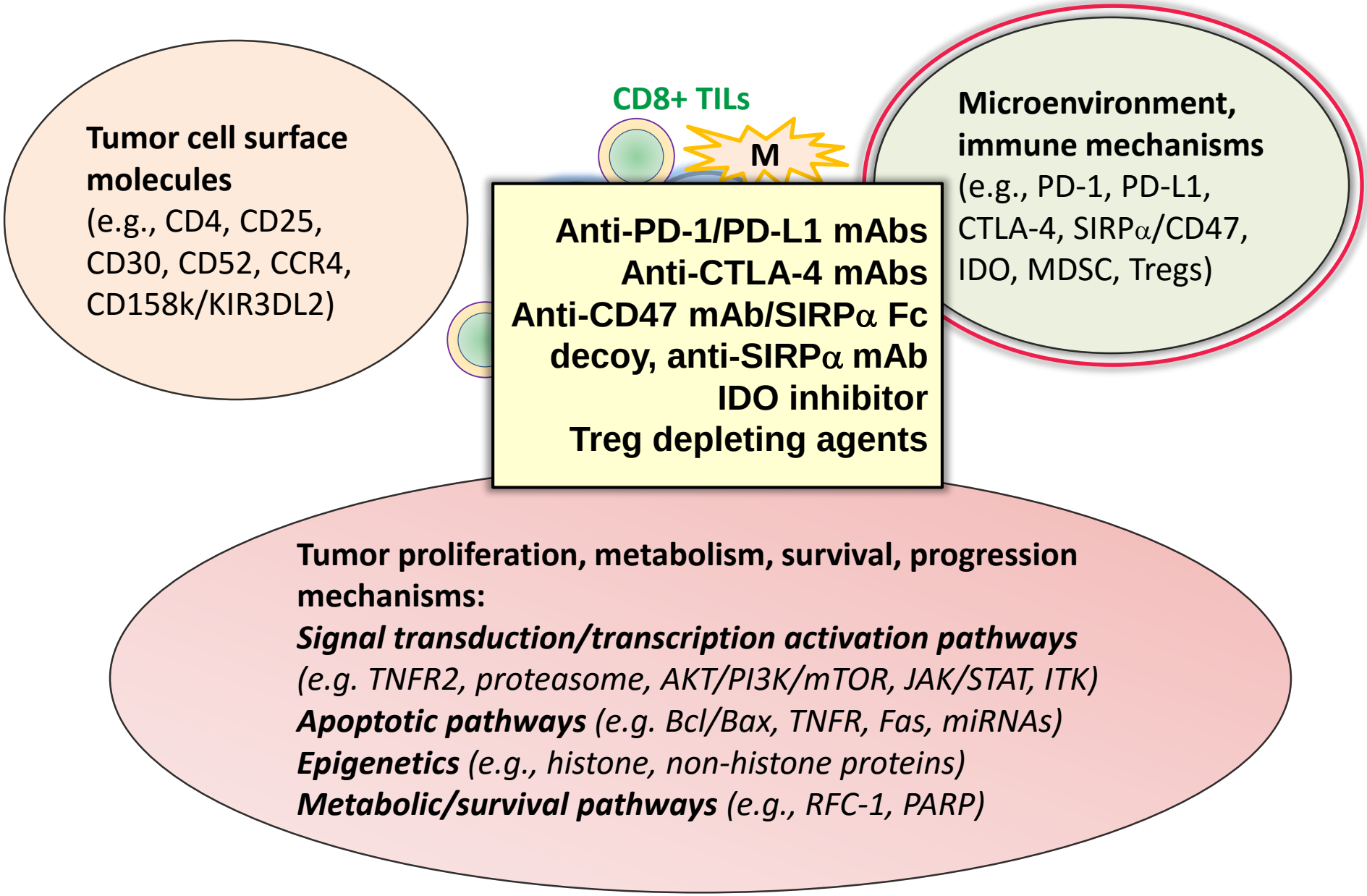
Microenvironment, immune mechanisms
(e.g., PD-1, PD-L1, CTLA-4, SIRPα/CD47, IDO, MDSC, Tregs)

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

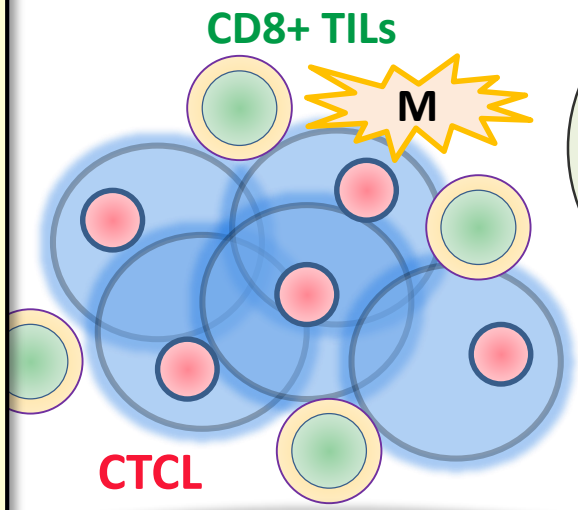


Targets for therapy in cutaneous T-cell lymphoma



Targets for therapy in cutaneous T-cell lymphoma

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)



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

Efficacy of Systemic Agents in CTCL

Agent (Class)	Indication	Year	Efficacy data for FDA approval: Study	N	ORR	DOR
Romidepsin (HDAC inhibitor)	CTCL with prior systemic therapy	2009	Pivotal	96	34%	15 mo
			Supportive	71	35%	11 mo
Denil diftito (Fusi						4 mo
Bexar (RXR						5+ mo
Vorin (HDAC inhibitor)						6+ mo
			Supportive	33	24%	4 mo

Need better therapies, more options:

Brentuximab vedotin (anti-CD30 ADC)

Mogamulizumab (anti-CCR4 mab)

Both phase 3 RCT

(superior DOR/PFS or impressive ORR)

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II Multi-Institutional Trial of the Histone Deacetylase Inhibitor Romidepsin As Monotherapy for Patients With Cutaneous T-Cell Lymphoma

Richard L. Piekarz, Robin Frye, Maria Turner, John J. Wright, Steven L. Allen, Mark H. Kirschbaum, Jasmine Zain, H. Miles Prince, John P. Leonard, Larisa J. Geskin, Craig Reeder, David Joske, William D. Figg, Erin R. Gardner, Seth M. Steinberg, Elaine S. Jaffe, Maryalice Stetler-Stevenson, Stephen Lade, A. Tito Fojo, and Susan E. Bates

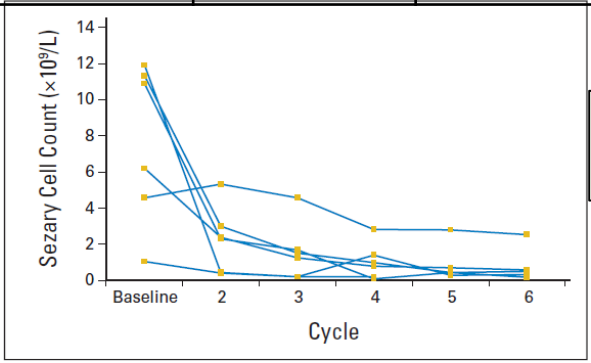
J Clin Oncol 2009;27:5410

Final Results From a Multicenter, International, Pivotal Study of Romidepsin in Refractory Cutaneous T-Cell Lymphoma

Sean J. Whittaker, Marie-France Demierre, Ellen J. Kim, Alain H. Rook, Adam Lerner, Madeleine Duvic, Julia Scarisbrick, Sunil Reddy, Tadeusz Robak, Jürgen C. Becker, Alexey Samtsov, William McCulloch, and Youn H. Kim

J Clin Oncol 2010;28:4485

	Pivotal study		NCI study	
	As-treated N = 96	Evaluable N = 72	As-treated N = 71	Evaluable N = 63
ORR, n (%)	33 (34%)	30 (42%)	25 (35%)	25 (40%)
95% CI	[25, 45]	[30, 54]	[25, 49]	[28, 53]
CCR, n (%)	6 (6%)	6 (8%)	4 (6%)	4 (6%)



Rapid and sustained blood Sez cell response

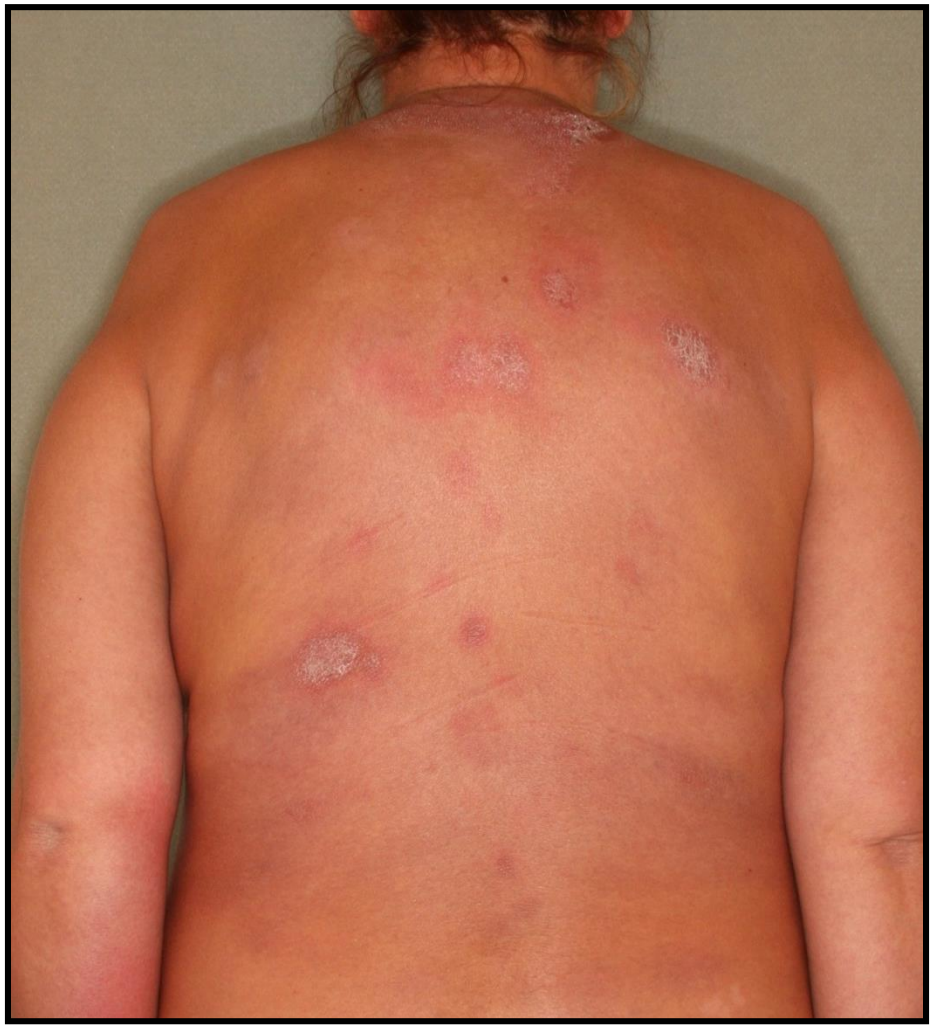
Romidepsin administration
14 mg/m^2 IV D1, 8, 15 of 28d cycle

Table 2. Disease Response

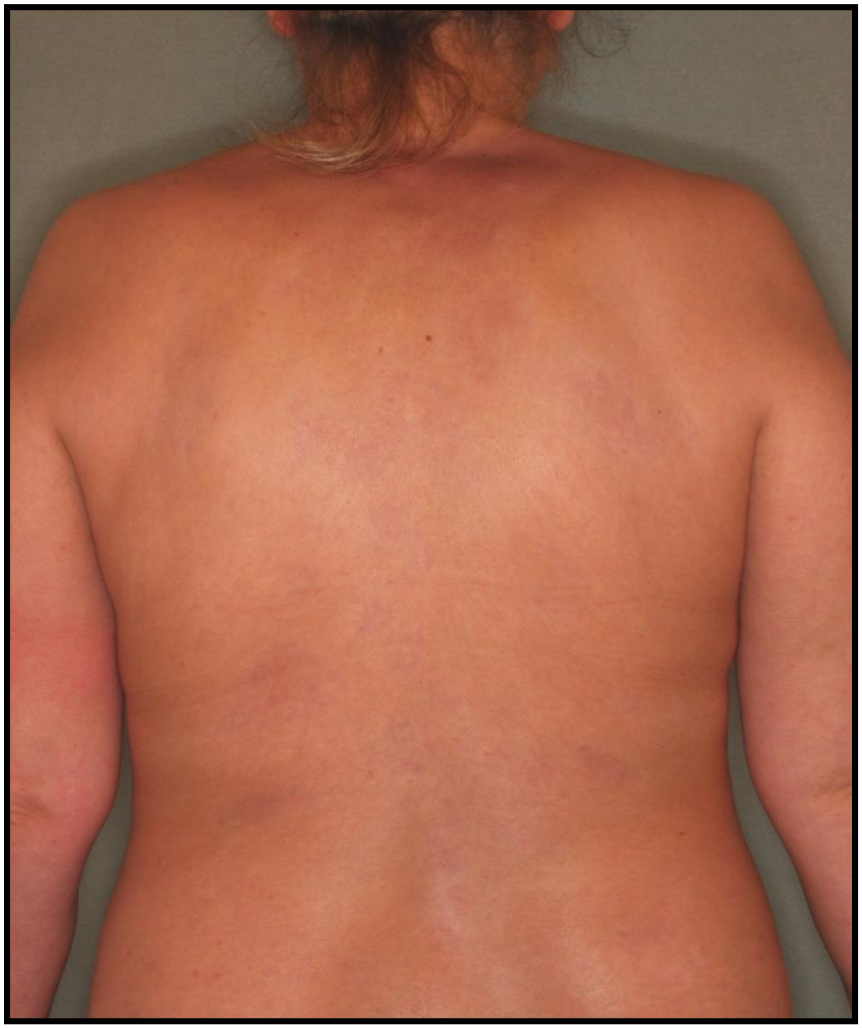
Response	All Patients (N = 96) No.	%	95% CI
ORR (CR + PR)	33	34	25 to 45
CR	6	6	2 to 13
PR	27	28	19 to 38
SD	45	47	37 to 57
PD	10	10	5 to 18
Stage IB and IIA (n = 28)			
ORR	7	25	
CR	1	4	
Stage IIB (n = 21)			
ORR	9	43	
CR	2	10	
Stage III (n = 23)			
ORR	9	39	
CR	1	4	
Stage IVA (n = 24)			
ORR	8	33	
CR	2	8	
Stage IIB to IVA (n = 68)			
ORR	26	38	
CR	5	7	
ORR in patients with blood involvement (n = 37)	12	32	
Duration of response (OR; n = 33), months*			
Median	15.0		
Range	0.0+-19.8+		
TTR (OR; n = 33), months			
Median	2.0		
Range	0.9-4.8		
TTR (CR; n = 6), months			
Median	4		
Range	0.9-6.9		
TTP (n = 33), months			
Median	8		
Range	0+-21.7+		

39 F, subcutaneous panniculitis-like TCL with HPS
Rapid improvement with romidepsin therapy

Pre-treatment



After 2 cycles

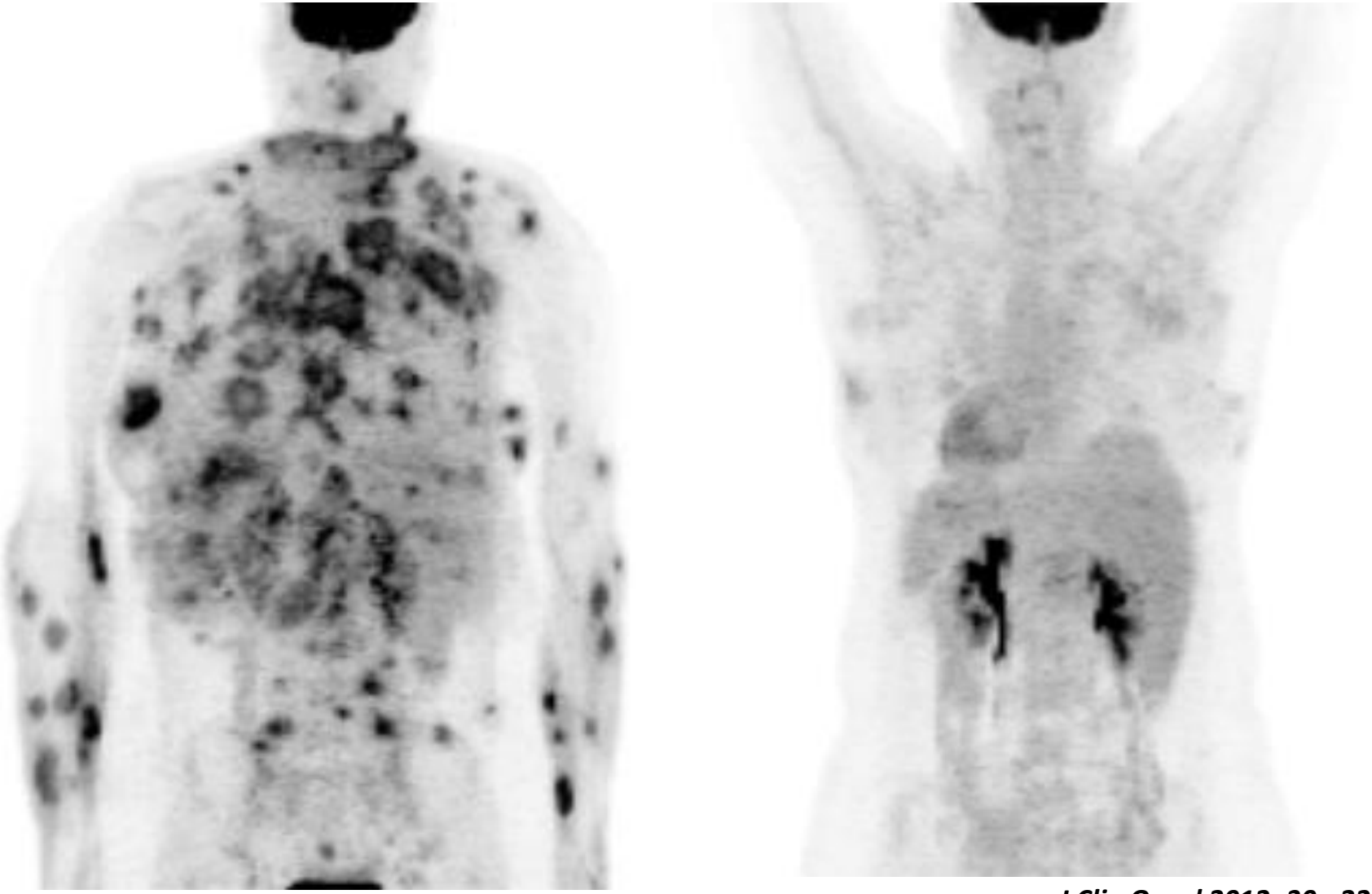


Bashey, Kim, J Clin Oncol 2012; 30:e221-5

Improvement demonstrated by PET/CT

Pre-romidepsin

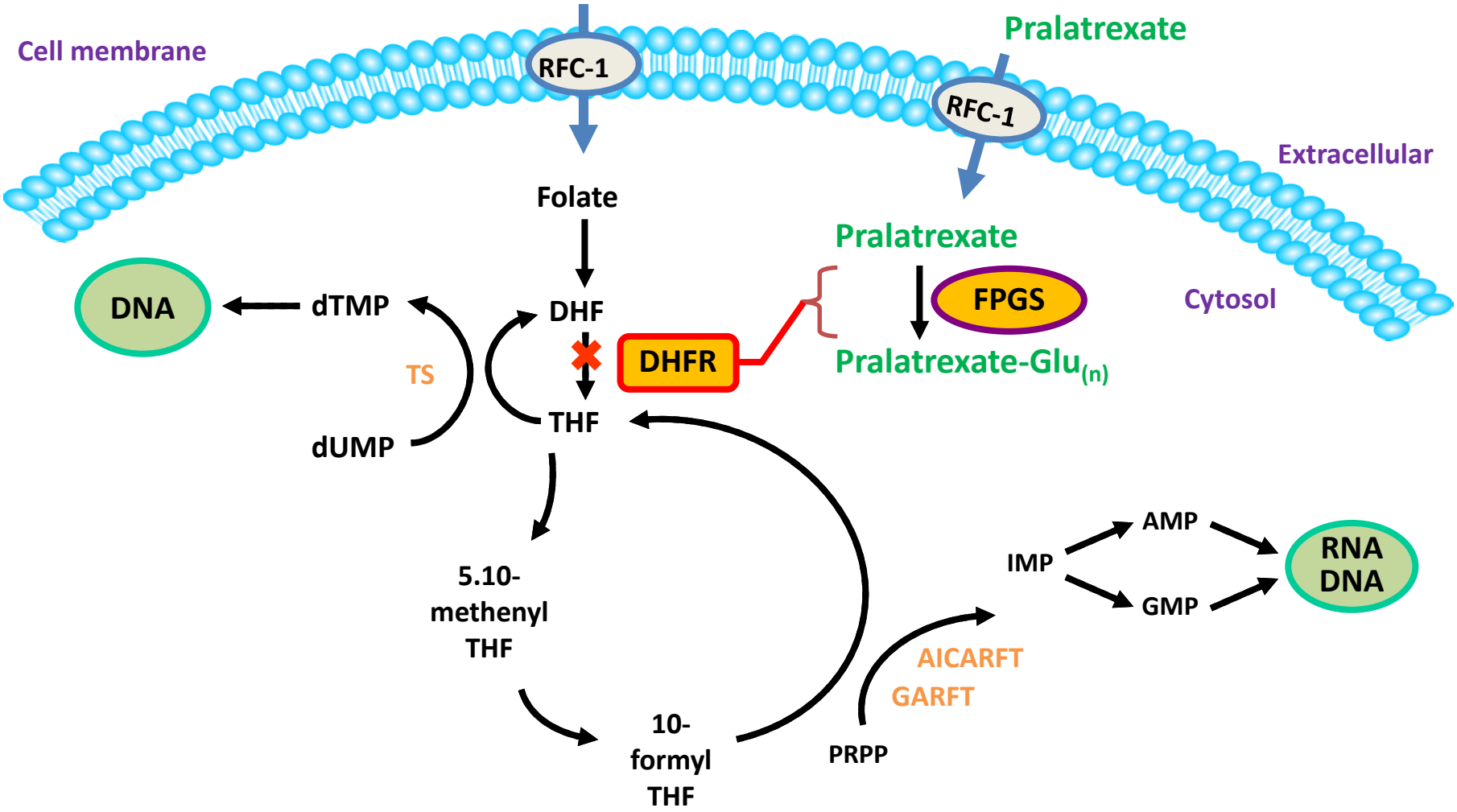
After 2 cycles



J Clin Oncol 2012; 30:e221-5

Pralatrexate with improved tumor selectivity

- Improved **anti-folate** agent => **↑ cellular uptake/retention, tumor > normal**
- High affinity for RFC-1; efficient substrate for polyglutamylation by FPGS
- Antifolate activity via the inhibition of DHFR.



Pralatrexate (PDX) FDA-approved in systemic PTCL, 2009

blood

2012 119: 4115-4122
Prepublished online March 6, 2012;
doi:10.1182/blood-2011-11-390211

Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma

Steven M. Horwitz, Youn H. Kim, Francine Foss, Jasmine M. Zain, Patricia L. Myskowski, Mary Jo Lechowicz, David C. Fisher, Andrei R. Shustov, Nancy L. Bartlett, Maria L. Delioukina, Tony Koutsoukos, Michael E. Saunders, Owen A. O'Connor and Madeleine Duvic

Doses ≥15 mg/m^2 , 3/4 weeks (IV)	61% ORR
Optimal dose in CTCL, 15 mg/m^2 , 3/4 weeks (IV)	**45% ORR**
DOR, estimate rate at 6 mo **Median PFS not reached; estimate rate at 6 mo**	**73%** **70%**

	Optimal Dose, 15 mg/m^2 N=29		
Event	**ALL**	**Grade 1-2**	**Grade 3**
Stomatitis	**14 (48%)**	**9 (31)**	**5 (17%)**
Fatigue	**11 (38%)**	**10 (34%)**	**1 (3%)**
Nausea	**9 (31%)**	**9 (31%)**	**0 (0%)**
Skin toxicity**	**6 (21%)**	**4 (14%)**	**2 (7%)**

No great data that combinations is more meaningful over single agent PDX in CTCL patients:

PDX + bex *(Duvic et al ASH 2015)*

- **MTD = PDX 15 mg/m2 + bex 150 mg/m2**
- **ORR 60%, 4 CR, 14 PR**
- **DOR estimate at 6 mo 67%**
- **Median PFS = 12.8 mo**

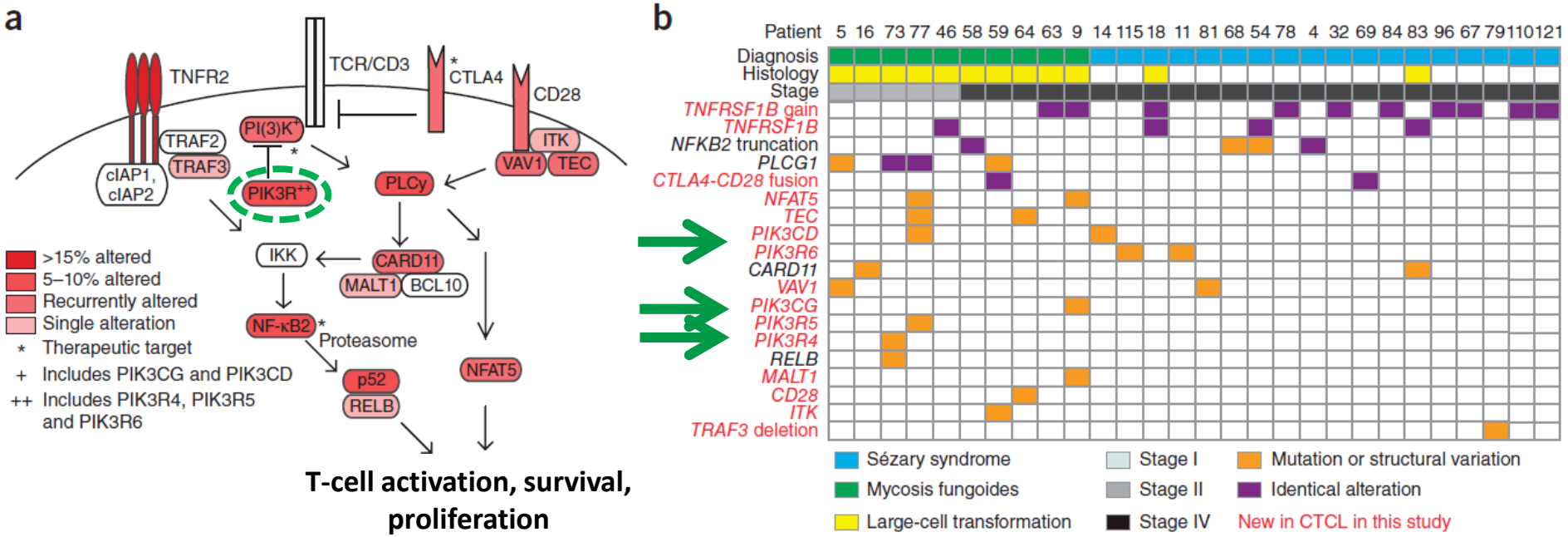
↑toxicity related terminations

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

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

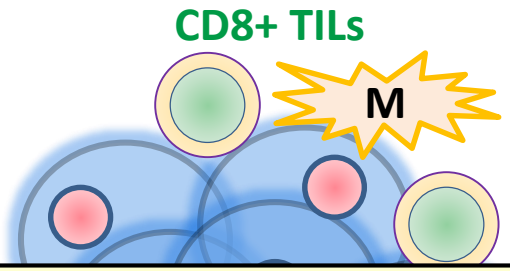
- C
  - CTCL: PRs in 4 MF, 1 Sézary syndrome, and 1 MF-LCT

Clinical trials with duvelisib combination strategies in CTCL

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)



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

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

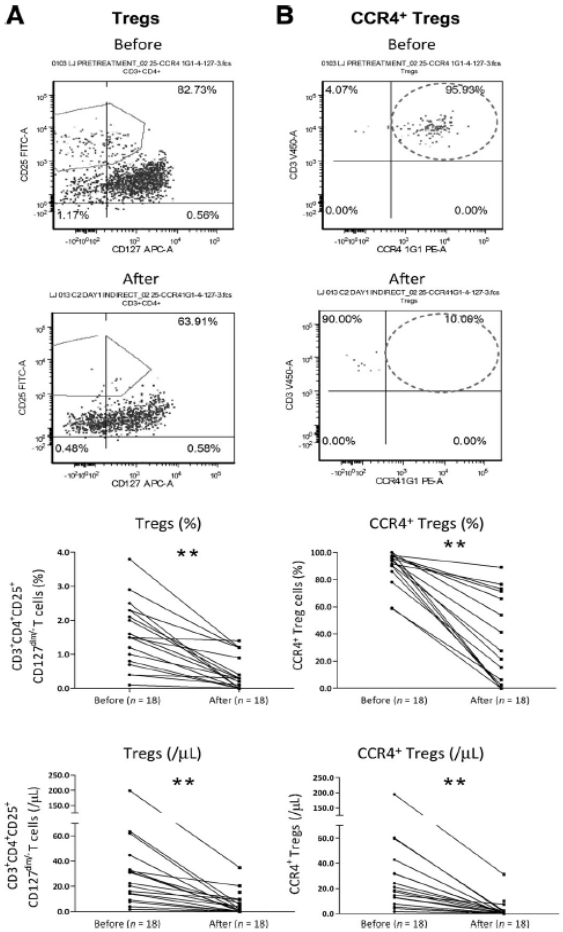
Xiao Ni[1], Jeffrey L. Jorgensen[2], Meghali Goswami[1], Pramoda Challagundla[2],

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**



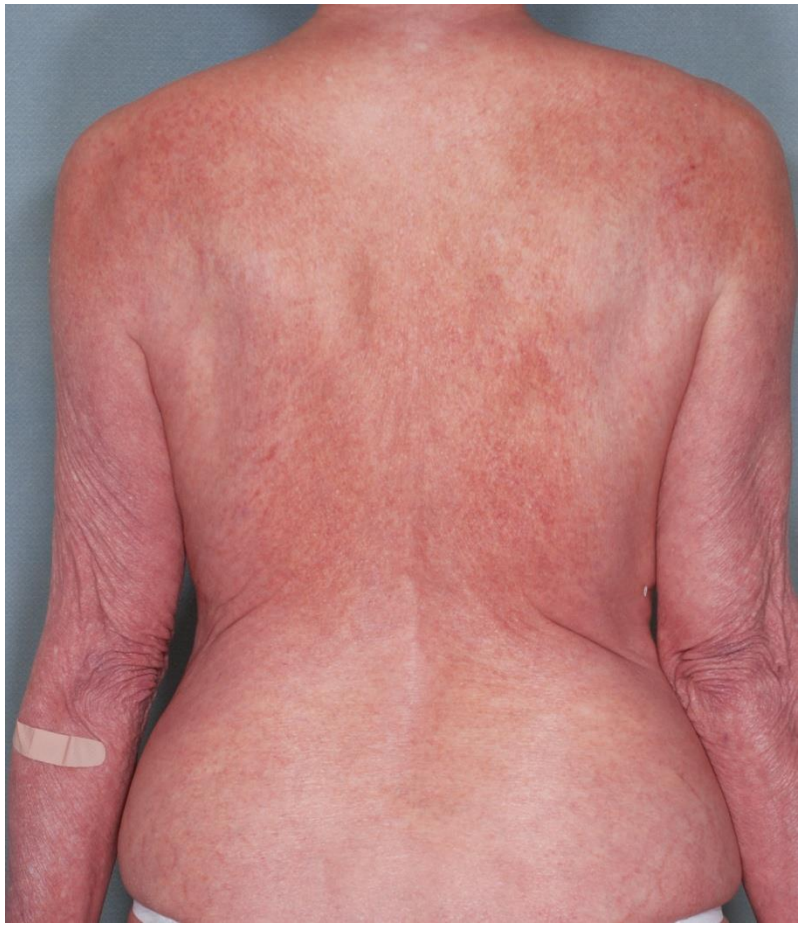
Overall response rate in phase 1/2 study

	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

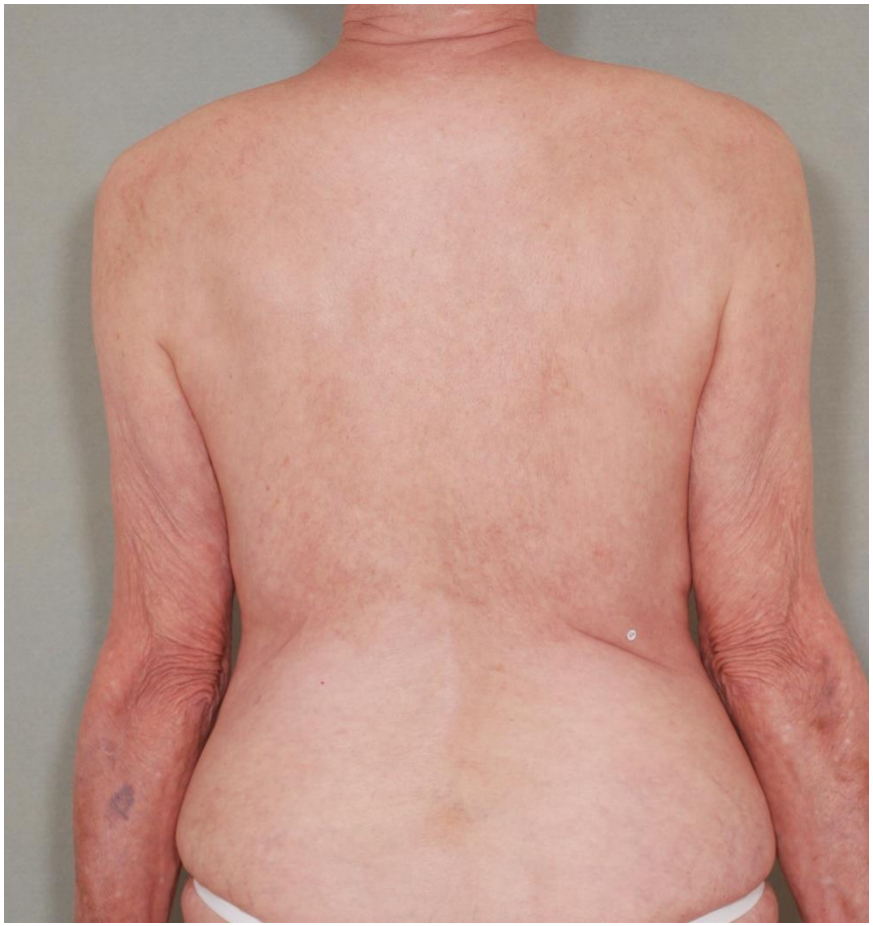
Intravenous administration, weekly x 4, then every 2 wks

Case Study: Patient 03-Stanford

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



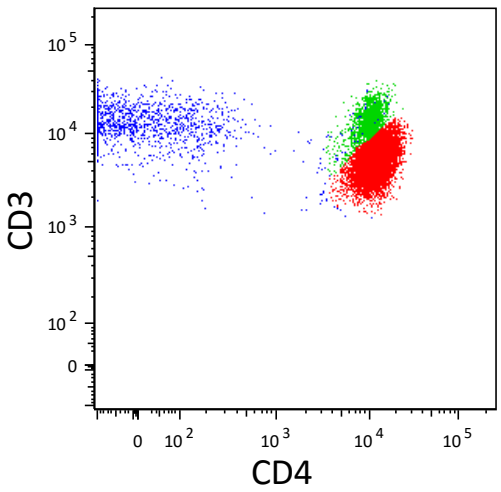
Pretreatment
Course 1 Day 1

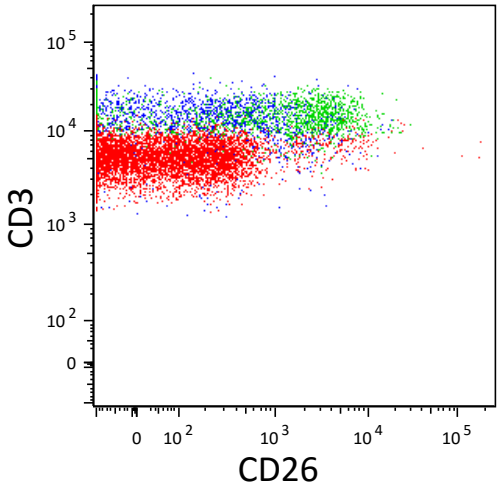


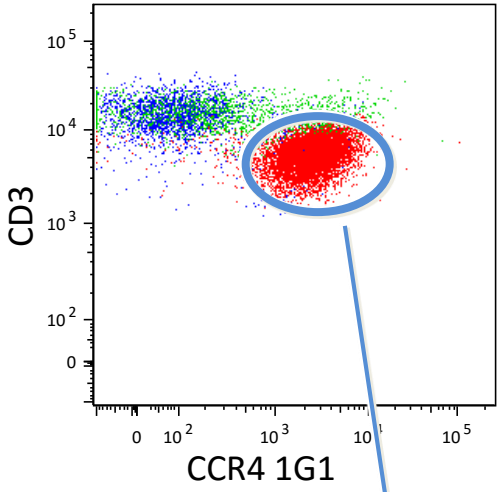
Post treatment
Post Course 11

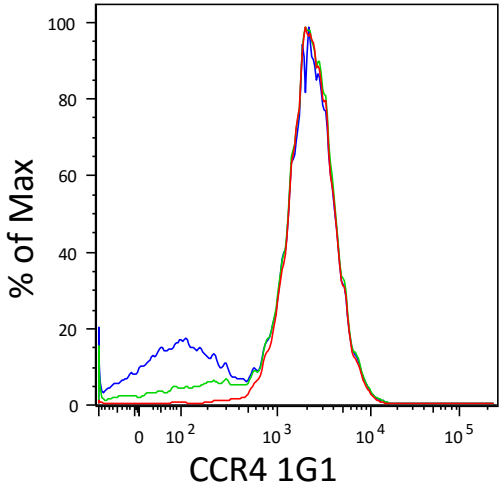
Response in Blood: Patient 01-Stanford (SS; Stage IVA; 6 prior therapies; 0.1 mg/kg)

Pre-treatment







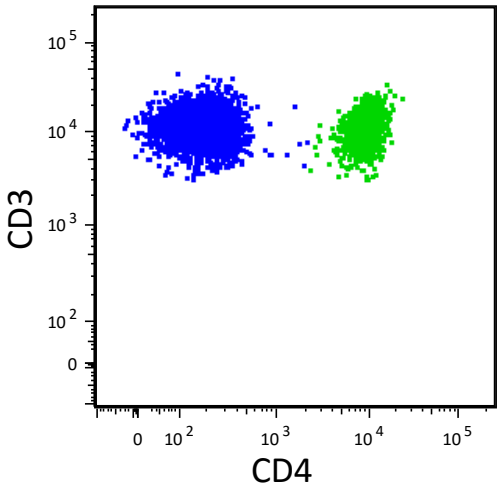


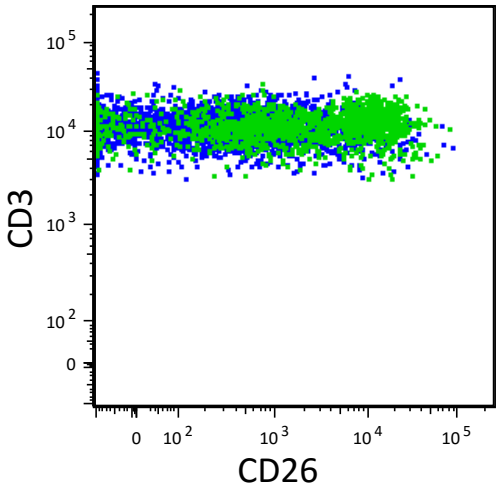
Lymphoma cells
Normal CD3+CD4+
CD3+CD4neg

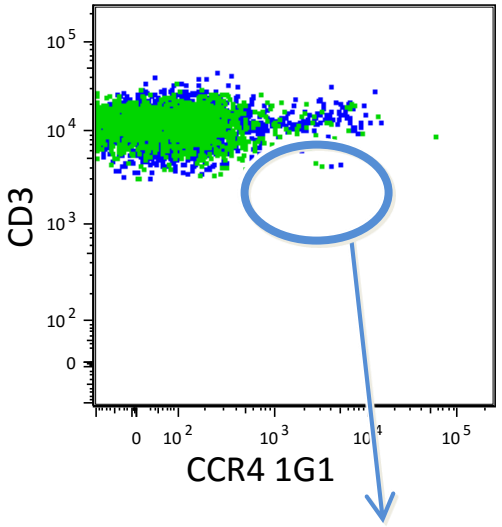
Lymphoma cells

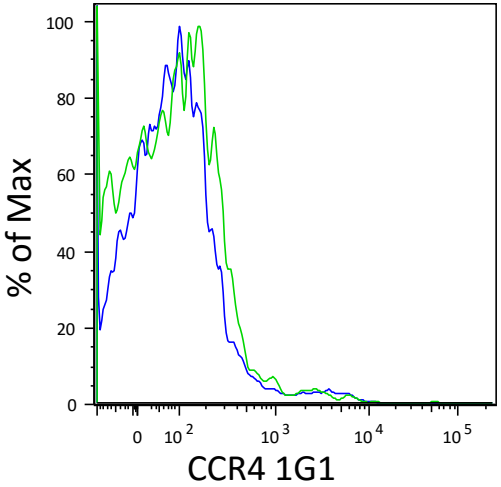
Response in Blood: Patient 01-Stanford

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

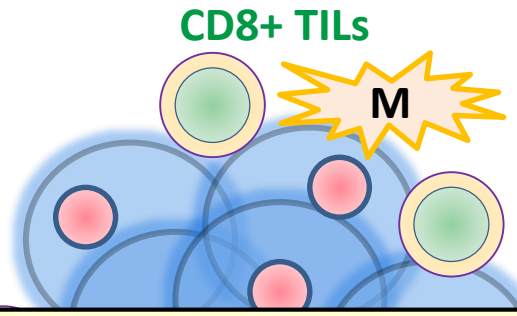
- Clinical responses are most impressive in the skin and blood compartments in ATL and CTCL
- Absence of infections with chronic therapy, no need for antimicrobial prophylaxis (←→ alemtuzumab)

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)



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

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

CD30 as a target in MF/SS

- **HL and sALCL with consistent expression of CD30 on tumor cells and high response rates**
  - accelerated FDA-approval 8/2011
  - Similarly, good clinical activity in cutaneous CD30+ ALCL expected
- **MF/SS with variable CD30 expression in neoplastic cells**
  - Transformed MF with more frequent and greater CD30 expression, 30-50%
  - Non-transformed MF, 0-15% (majority of MF)

Am J Surg Pathol. 2009;33:1860
Clin Cancer Res 2004;10:5587, Blood. 2012;119;1643.

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)	Advanced stage (88%)
		III	0	
		IV/SS	10 (31)	
Large cell transformation (LCT) Folliculotropic MF (FMF), n (%)		LCT	16 (50)	F-MF, LCT (90%)
		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)		Variable CD30
	B: 10-50%	14 (43)		
	C: >50%	4 (13)		

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

Global response by clinical stage

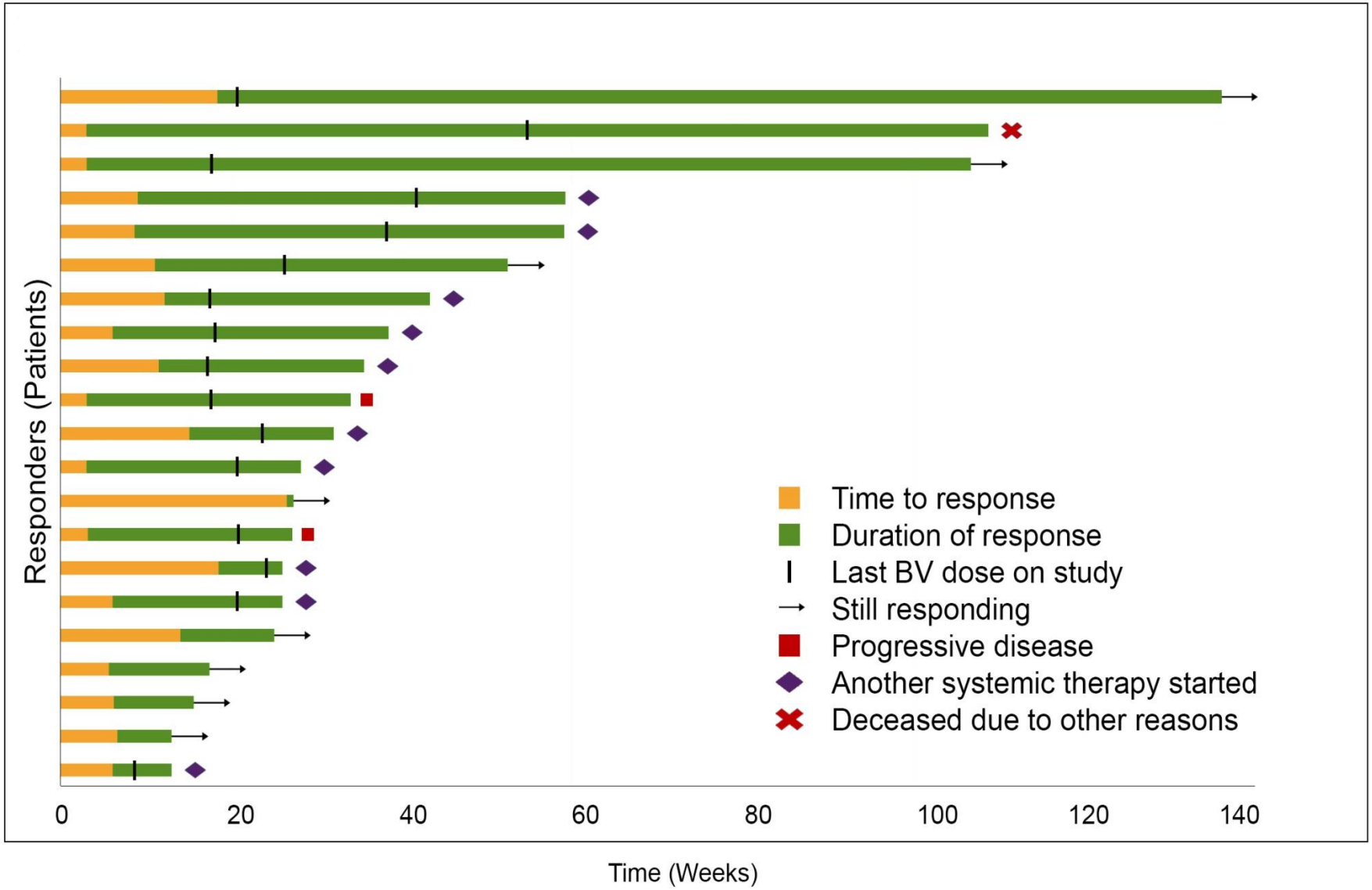
Stage	Response Rate	CR	PR	SD	PD
IB (n=4)	75%	0	3	1	0
IIB (n=18)	78%	0	14	2	2
IV/SS (n=8)*	50%	1	3	1	3
Total n= 30*	70%	1	20	4	5

*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

Time course in 21 patients with objective/global clinical responses

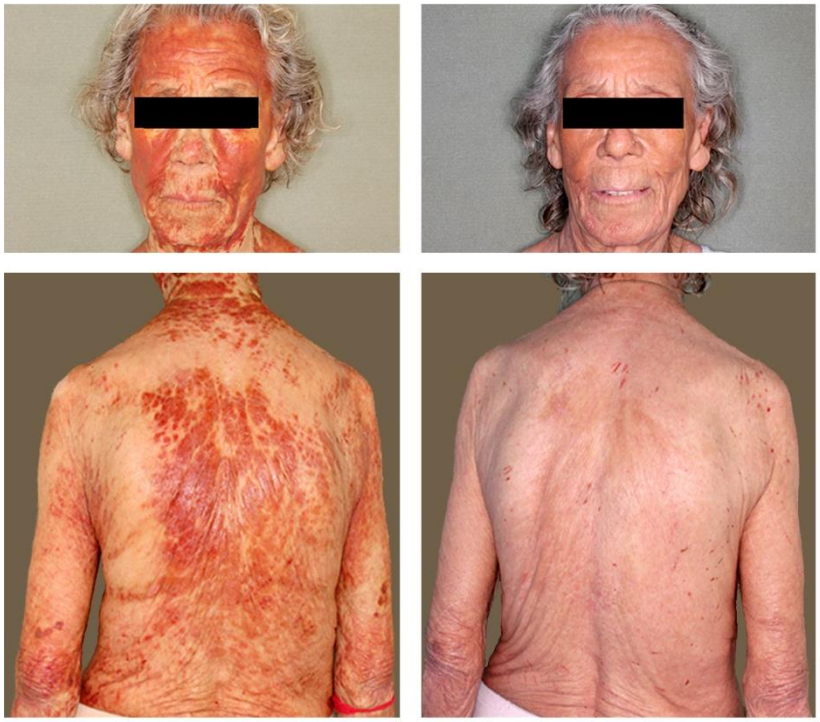


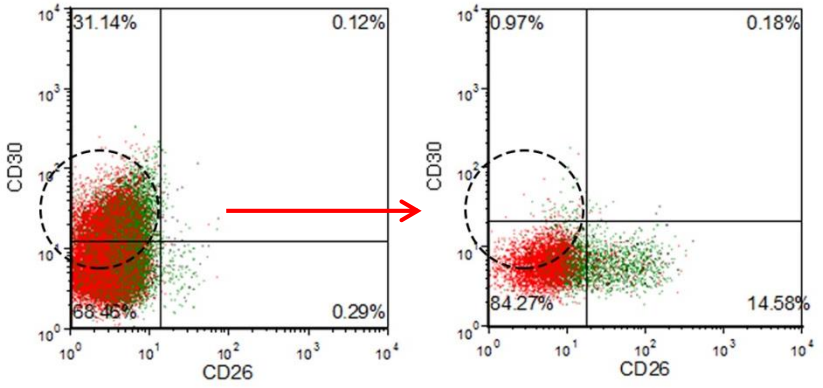
- **Median TTR = 6.6 wk (3.0-27.0)**
- **At 6, 12 mo, 90%, 79% are continuing responses by KM estimate**

J Clin Oncol 2015;33:3750

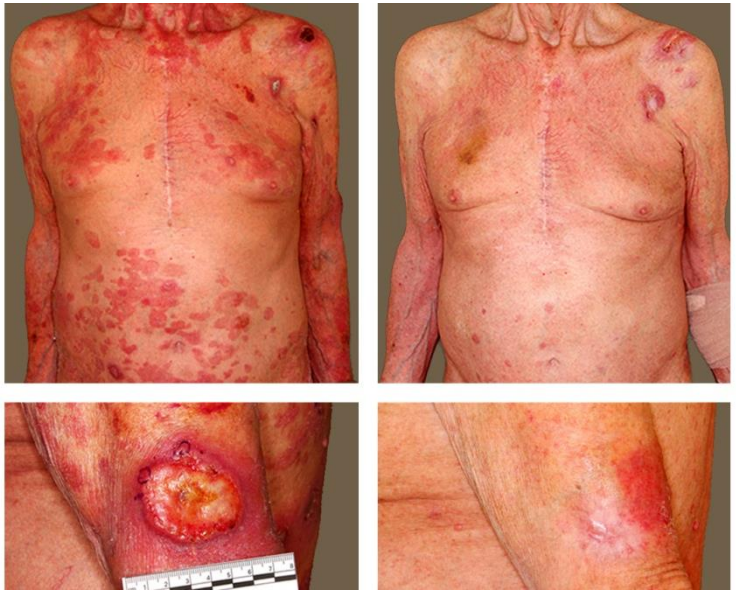
Great clinical response to brentuximab vedotin in MF/SS

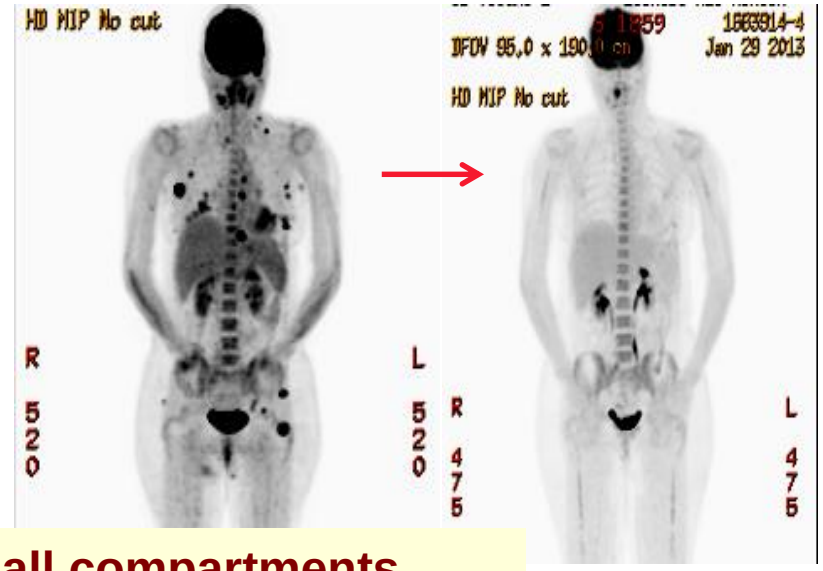
Sézary syndrome, IVA_1





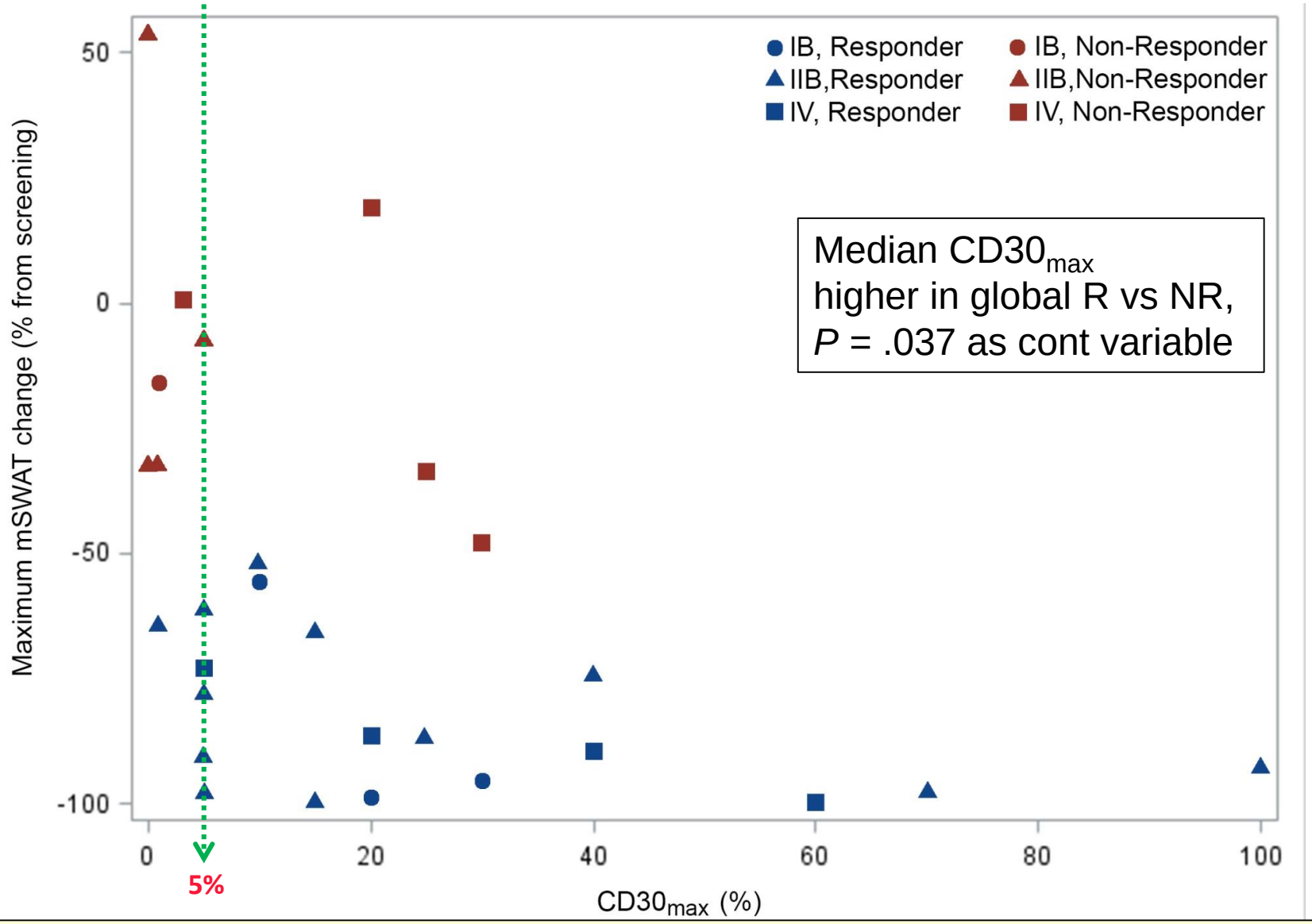
MF IVA_2 LN with LCT





BV demonstrates clinical activity in all compartments

Correlation of skin/global response with skin $CD30_{max}$ by IHC



Global ORR by $CD30_{max}$ <5% vs ≥5%, 17% vs. 83%, *P = .0046*

Significance of 5% threshold confirmed in matured, pooled analysis (n=71)

J Clin Oncol 2015;33:3750

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

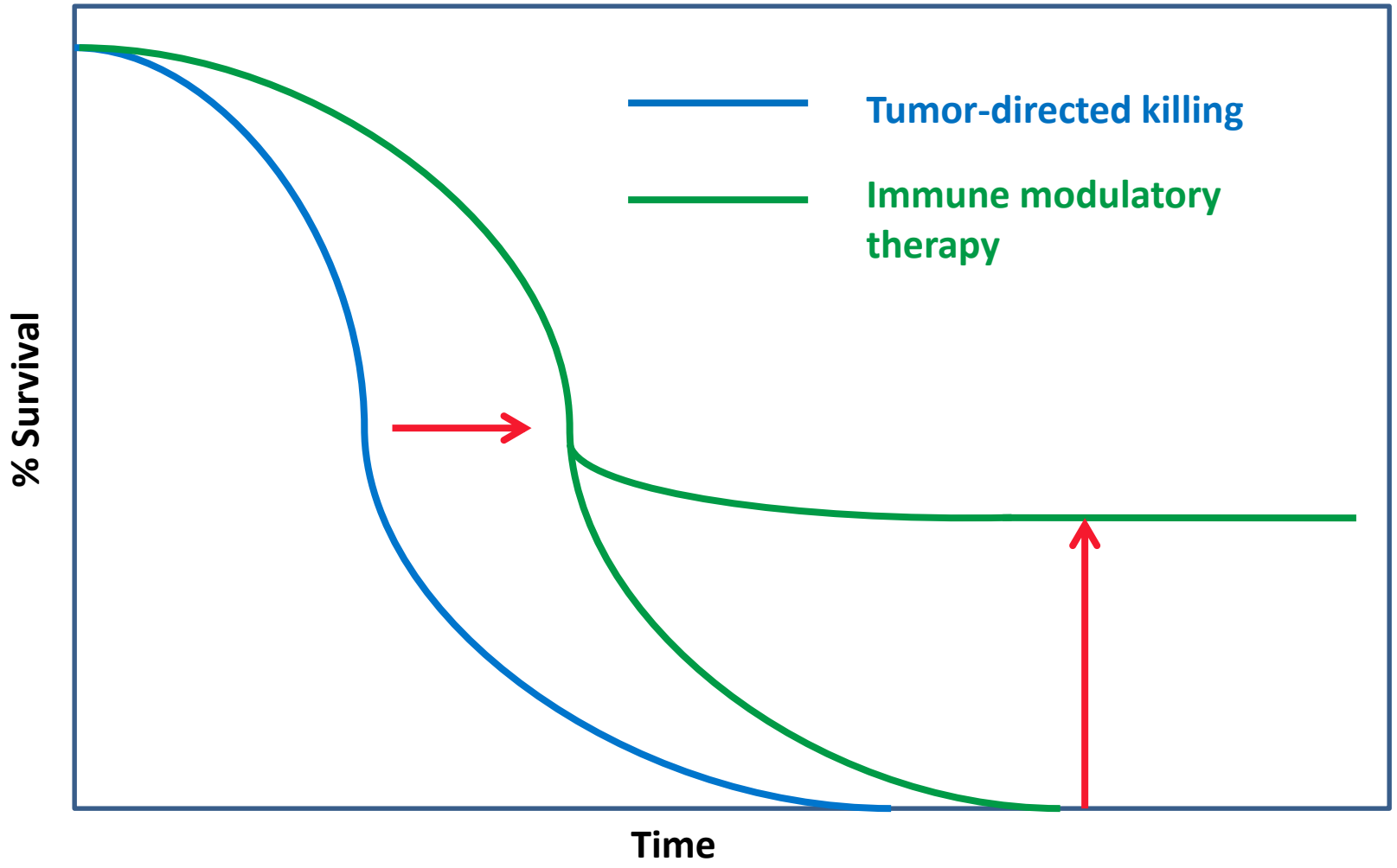
Phase III RCT (vs MD choice- oral bex or MTX) completed, pending FDA submission: Included MF and pcALCL, excluded SS

expression

Road to a CURE

How do we make the nice responses last?

Partnering with immunotherapy



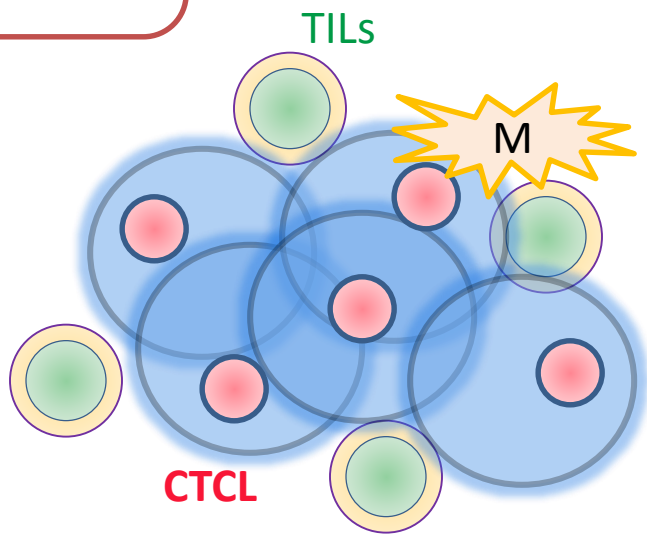
Immunotherapy strategies in CTCL

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
SIRPα/CD47

Allogeneic HSCT

Vaccine-based approaches

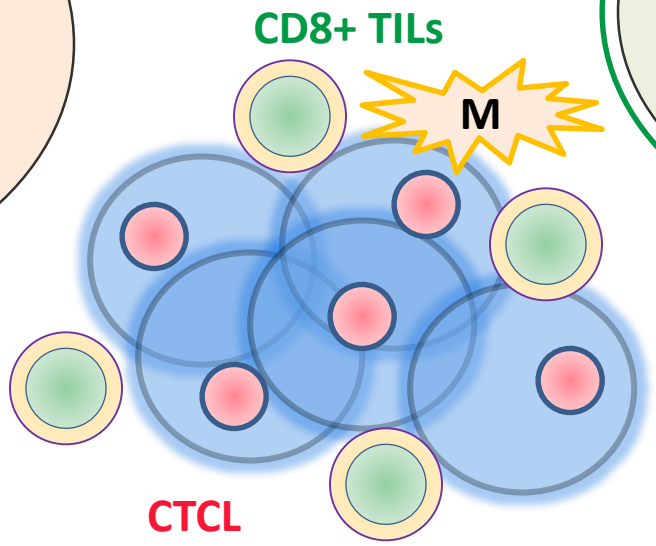
ECP
DC-based
Idiotype
In situ strategy

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, SIRPα/CD47, CD137, MDSC, Tregs)



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

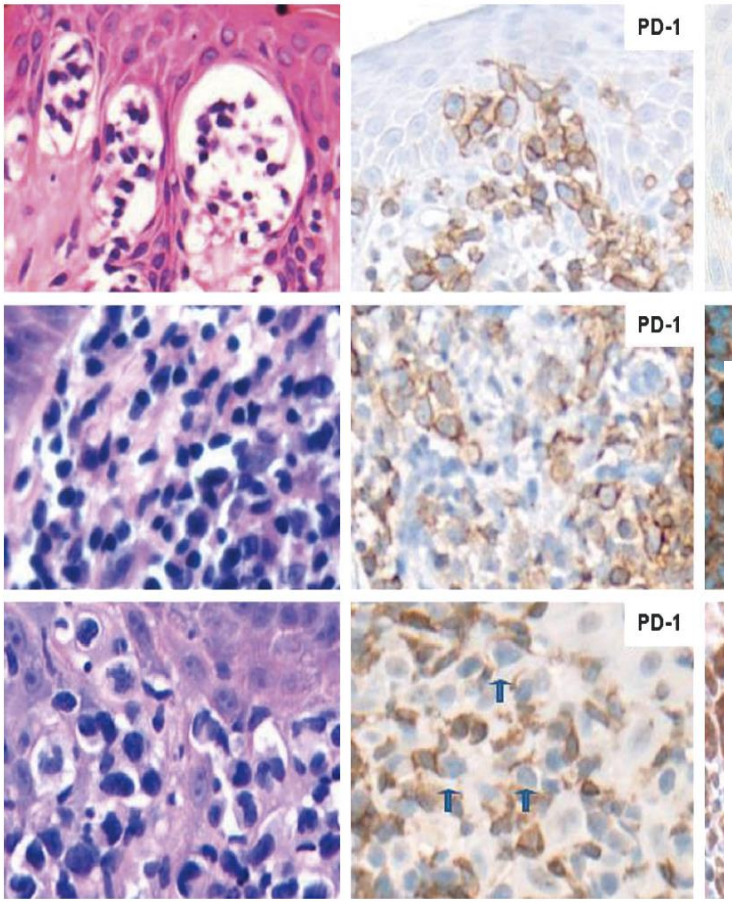
Expression of PD-1 and PD-L1 in CTCL
Mycosis fungoides & Sézary syndrome

MF skin

plaque

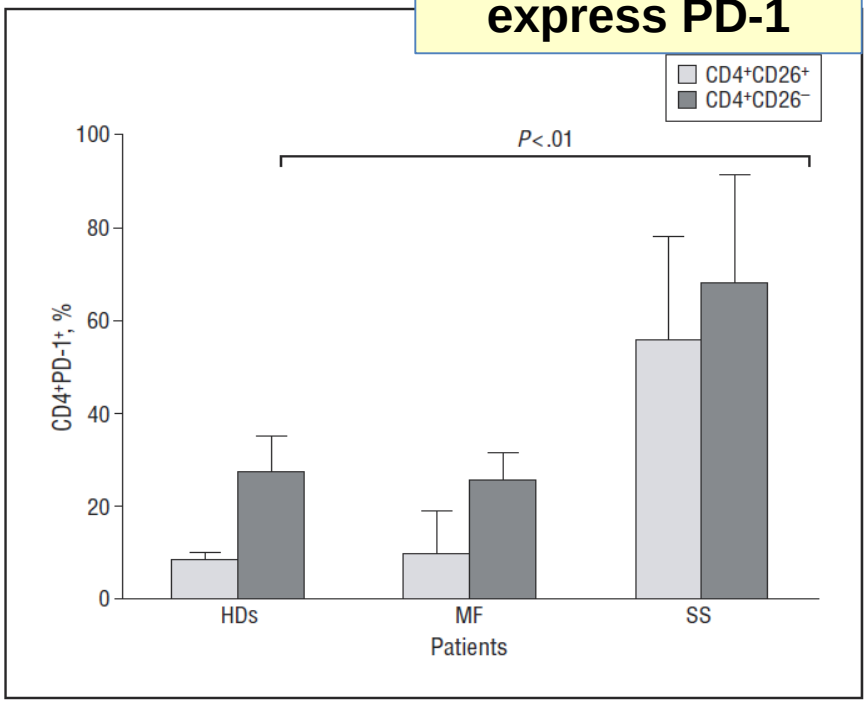
tumor

T-MF



Am J Dermatopathol 2012:34:126

PB Sézary cells express PD-1



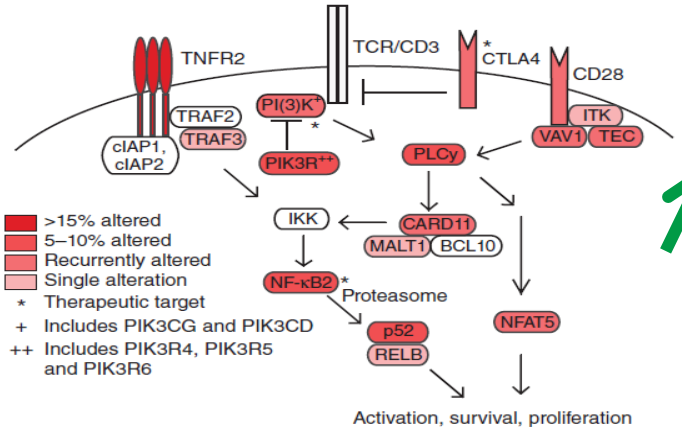
Samimi, Rook, Arch Dermatol 2010;146:1382

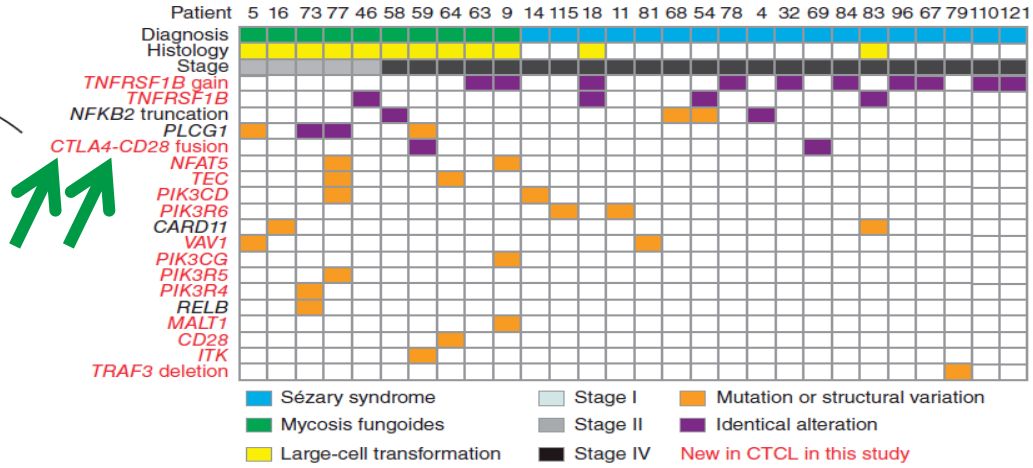
nature genetics

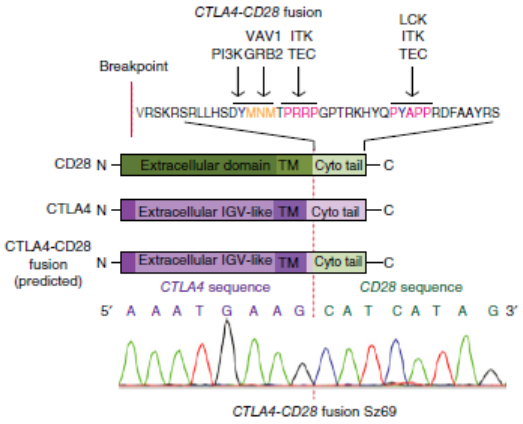
2015;47:1056

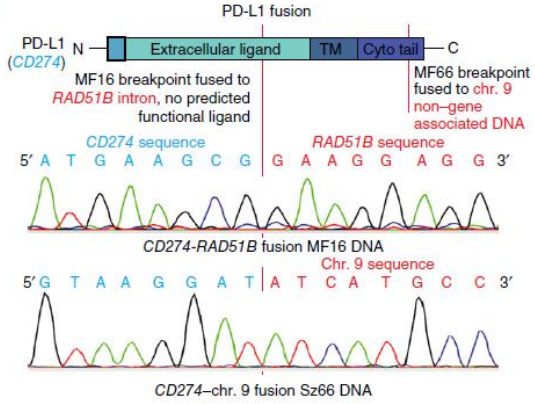
Genomic analysis of mycosis fungoides and Sézary syndrome identifies recurrent alterations in TNFR2

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]

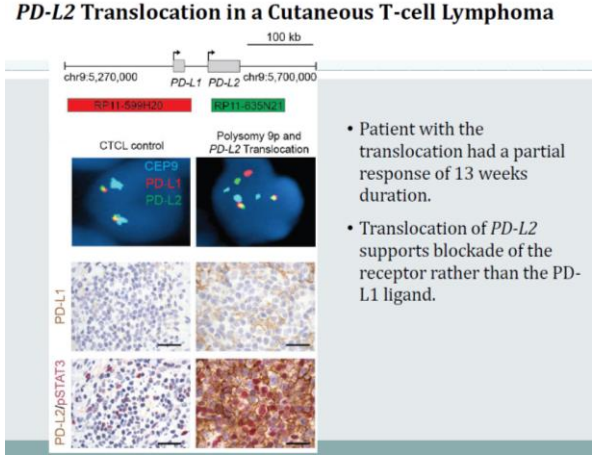








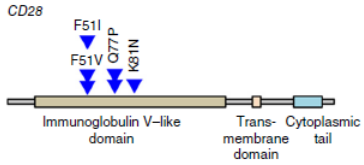
ASH 12/2014
Abstract 291, ***A Lesokhin, et al.***
Nivolumab in Lymphoid Malignancies



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

Special considerations for immunotherapeutics

- **Treatment beyond initial PD** in recognition of immune mediated flare reaction, at investigator's discretion
  - Clinically "stable" vs "unstable"
  - If true PD is confirmed by subsequent mSWAT (each cycle) or scheduled global response assessment (q 12 wks/4 cycles), then go off study; hard stop is 25% worse in any compartment beyond initial PD data
  - **Biopsy is recommended to help distinguish pseudoprogression** vs true progression, and **to characterize immune/TCR profile (TCR CDR3 high throughput sequencing)**

Planned biomarker and correlative studies

CITN (Fred-Hutch CC), Merck, Stanford

- Chromogenic (single-color) IHC for PD-L1
  - PD-L1 as potential biomarker of response
- Multiparametric (two-color) IHC
  - Characterize spatial association of PD-1+ TILs and PD-L1+ cells
- Multiplexed ion beam imaging (MIBI)
  - Enhanced visualization/mapping of protein expression using metal-conjugated Abs
- Transcriptional and NGS analysis
  - Nanostring platform use to profile mRNA expression
  - Correlation of mutational burden
- Immunophenotyping and T cell function assays
  - CyTOF and multiparametric flow cytometry
- Cytokine/chemokine analysis (ELISA)

Patient characteristics, n=24

Age (y), median (range)	67 (44-85)	
Sex, n (%)	Male	18 (75)
	Female	6 (25)
Stage, n (%)	IB	1 (4)
	IIB	2 (8)
	IIIA	3 (13)
	IIIB	3 (13)
	IVA	15 (62)
MF, n (%)	9 (38)	
Sézary syndrome, n (%)	15 (62)	
Large cell transformation (LCT)	3 (12)	
Prior systemic therapies, median (range)	4 (1-10)	

Advanced stage 96%

Global response (skin+LN+blood), n=24

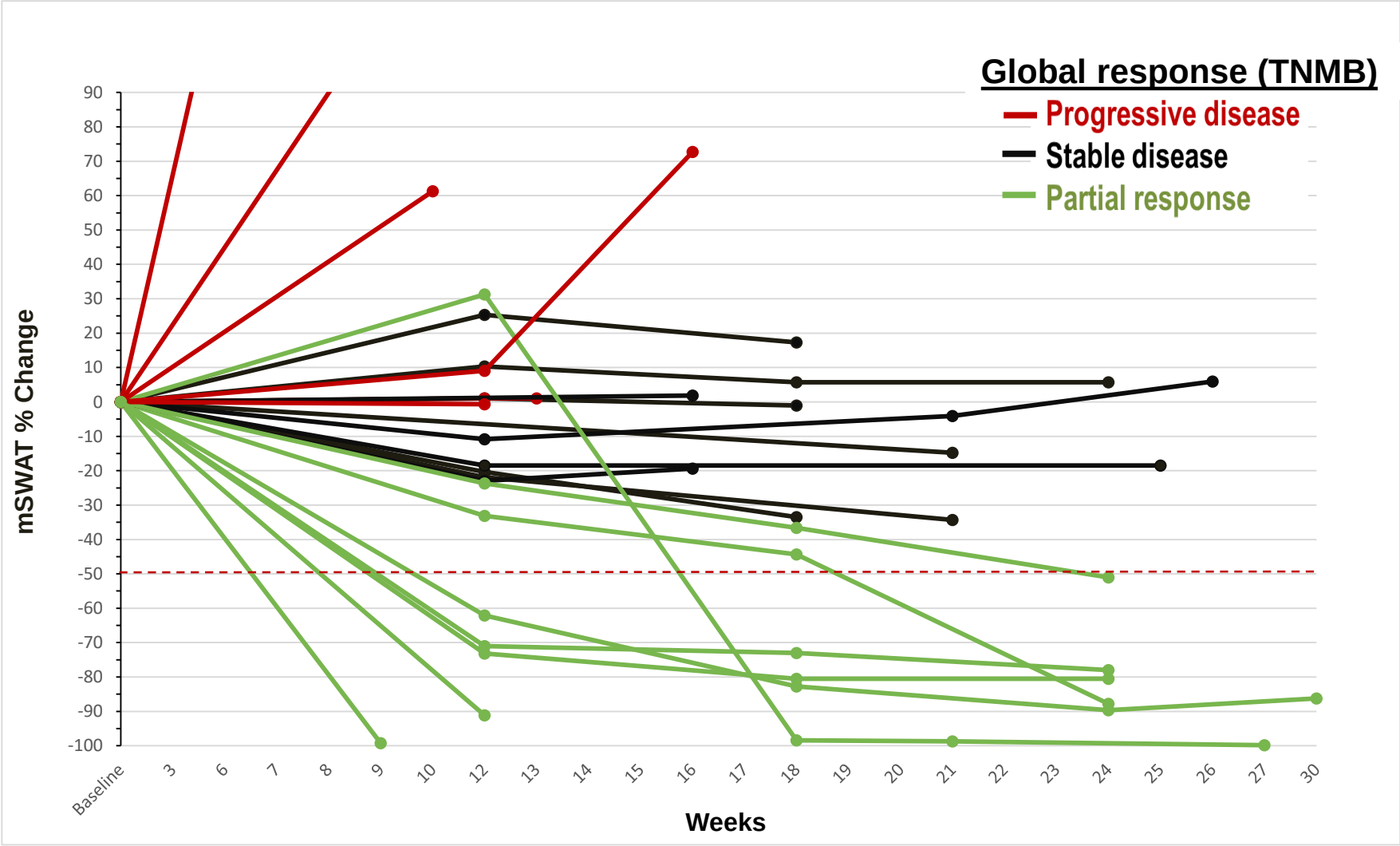
Stage	Response Rate	PR	SD	PD
IB (n=1)	0	0	0	1
IIB (n=2)	100%	2	0	0
IIIA (n=3)	33%	1	2	0
IIIB (n=3)	33%	1	0	2
IVA (n=15)	27%	4	8	3
MF (n=9)	44%	4	3	2
SS (n=15)	20%	4*	7	4
LCT (n=3)	33%	1	1	1
Total n= 24	33%	8	10**	6

Advanced stage 96%

SS 62%

*1 (stage IVA2) of 4 possible CR
**4 SDs continuing on treatment

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)

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

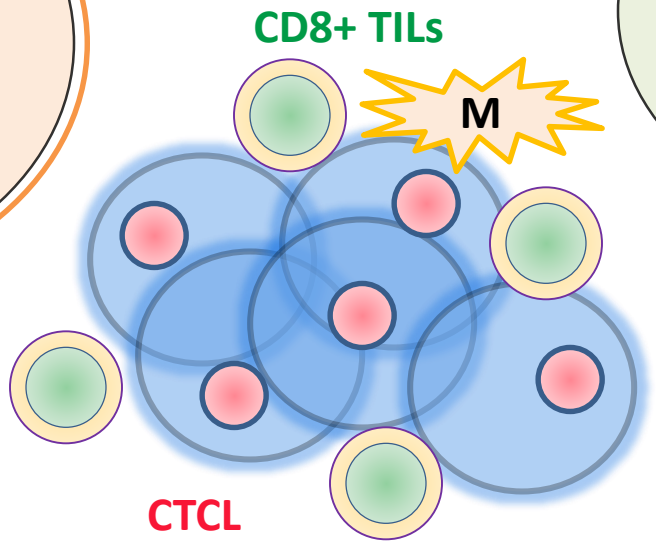
Anti-PD-1 mAb + IFN-gamma
+/- low-dose TSEBT

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, SIRPα/CD47, CD137, MDSC, Tregs)

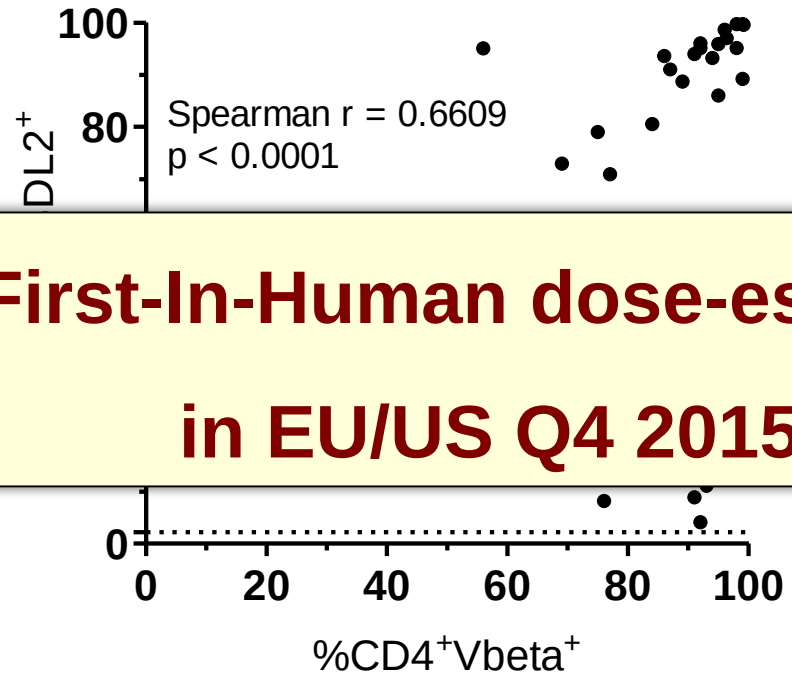


<u>CD158k/KIR3DL2</u>
Consistently expressed in MF/LCT and Sézary syndrome

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)



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

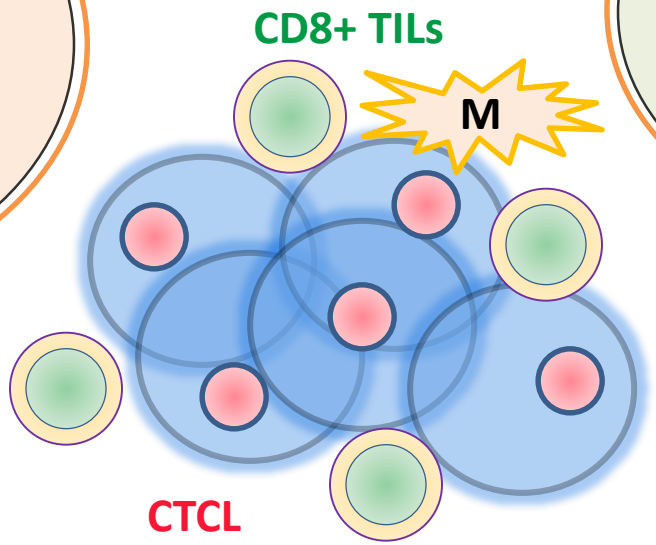
Marie-Cardine et al, Cancer Res. 2014

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, **SIRPα/CD47,** CD137, MDSC, Tregs)

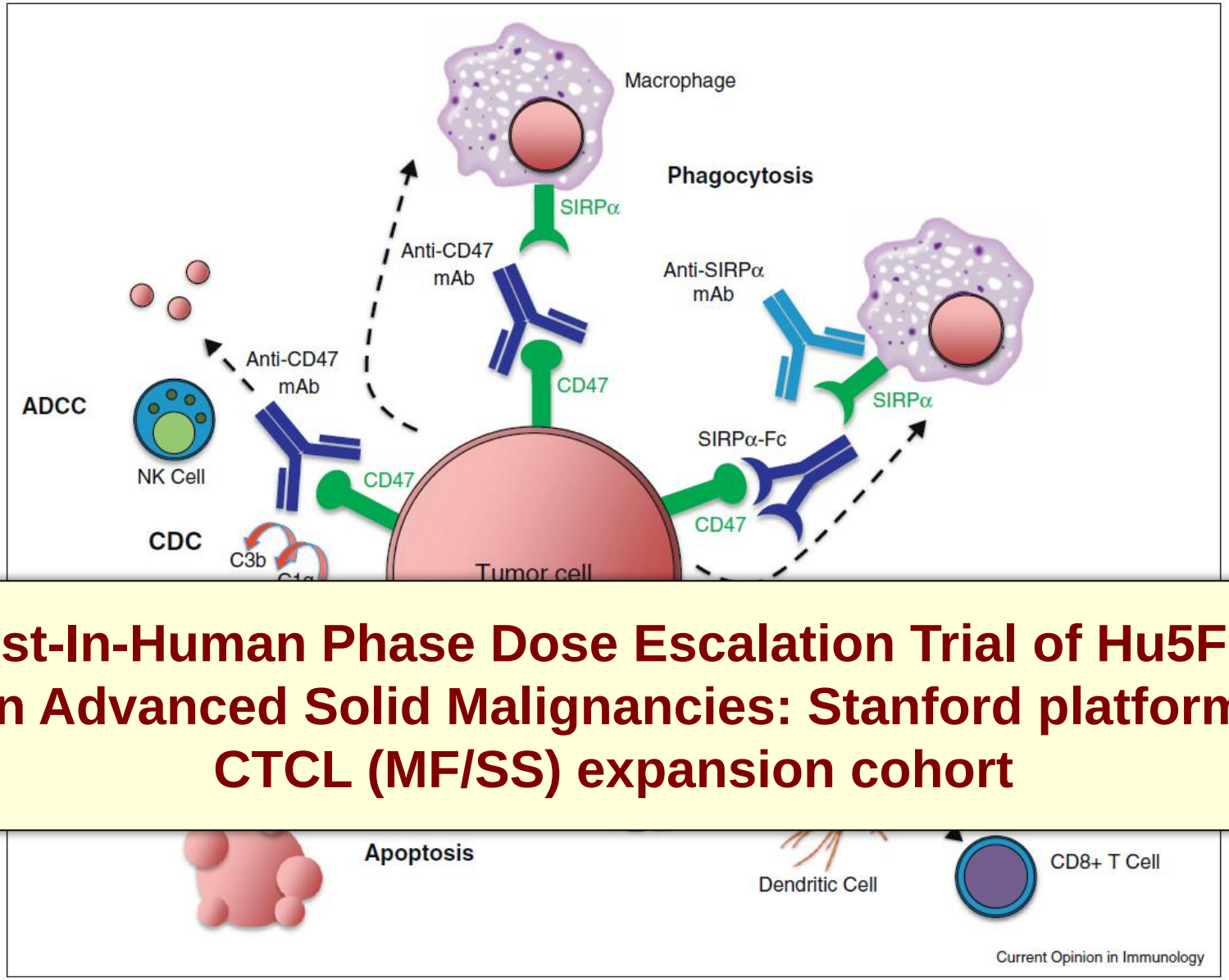


SIRPα/CD47 axis
"Don't eat me" signal by tumor cells

Evasion of macrophage phagocytosis

Weissman group, Stanford

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



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**