Novel Investigational Agents & Clinical Trials

Youn H Kim, MD

Department of Dermatology

Multidisciplinary Cutaneous Lymphoma Program

Stanford Cancer Center & School of Medicine

Stanford, CA

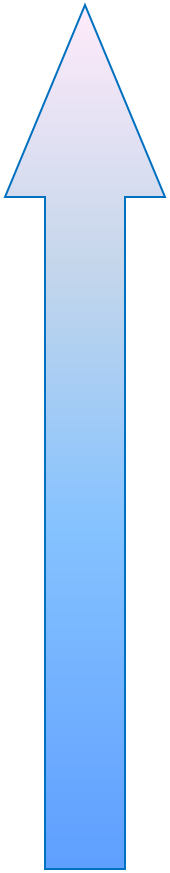
Disclosure statement

Youn Kim, MD

- Steering Committee
  - Eisai, Millennium, Kyowa
- Consultant or Advosory board
  - Kyowa, Celgene, Emergent, Medicis
- Investigator
  - Allos, Kyowa, Merck, Millennium, Seattle Genetics, SHAPE, Ceptaris/Yaupon, Eisai, Genentech

Why do we need better therapies?

Goals of therapies in MF/SS



IDEAL

Cure

Extend Life

Alleviate symptoms

Durable response

High response rate

PLUS well-tolerated

REAL

Alleviate symptoms

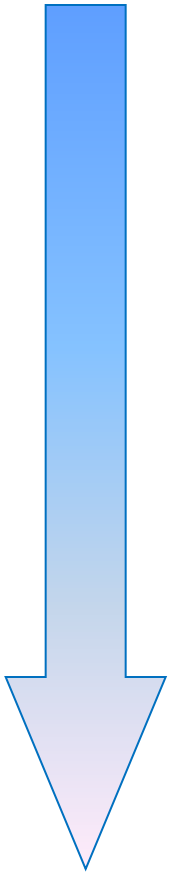
Variable response

Variable response duration

Variable toxicity

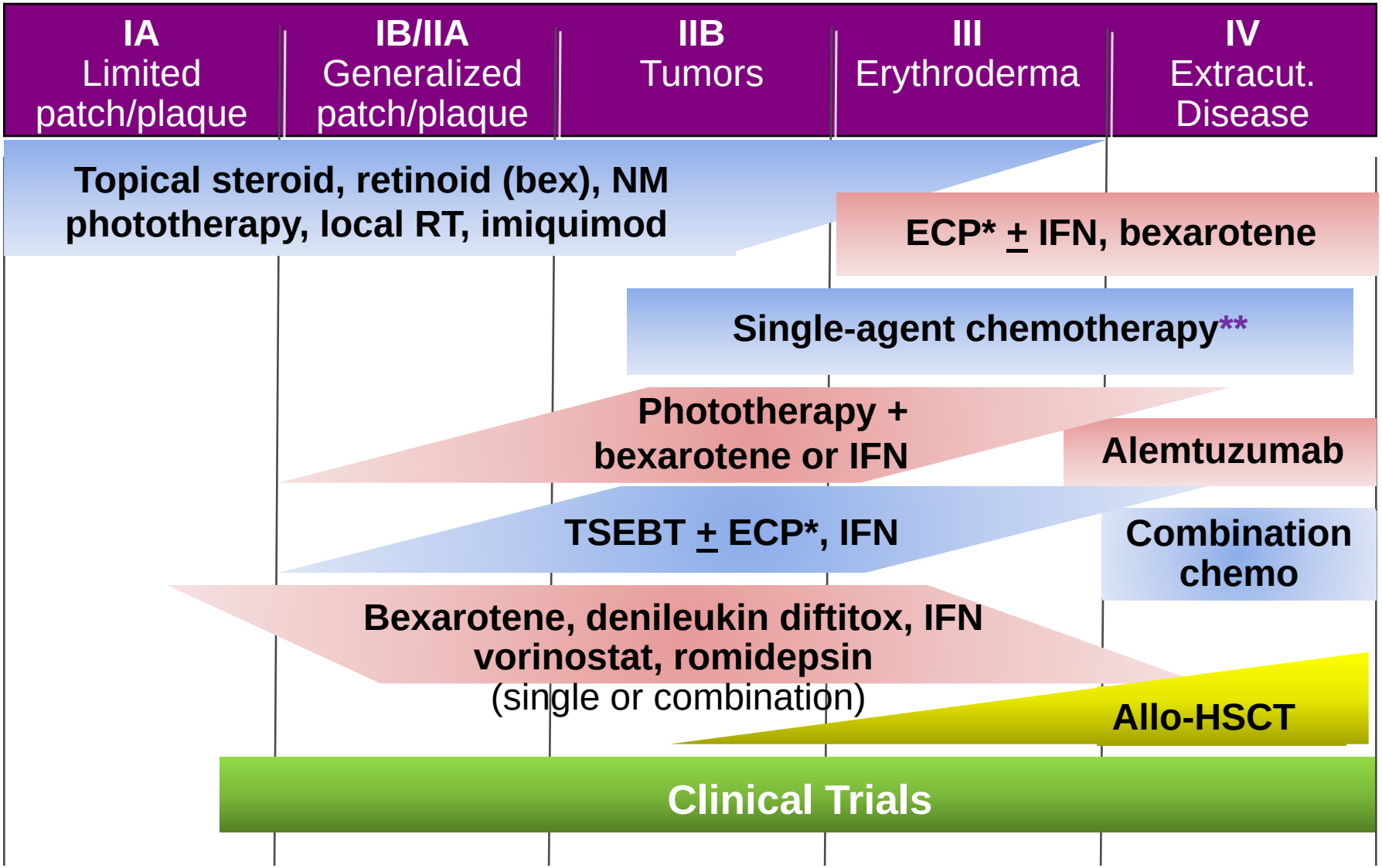
Extend Life

Cure



Current Clinical Management of CTCL, *2013*

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



*ECP = photopheresis

** Methotrexate, liposomal doxorubicin, gemcitabine, pentostatin, chlorambucil, etoposide, **pralatrexate**

Approved Systemic Agents in CTCL

Agent (Class)	Indication	Year	Efficacy data for FDA approval: Study	N	ORR	DOR
Romid (HDAC						15 mo 11 mo
Denile (Fusio						4 mo
Bexar (RXR a						6+ mo
Vorino (HDAC inhibitor)	manifestations	2006	Supportive	33	24%	6+ mo 4 mo

Need better therapies
More options

FDA no longer satisfied with ORR, single arm studies in CTCL

Need to show meaningful response duration and safety to claim overall clinical benefit

RCTs are strongly recommended

Era of targeted therapies

Huge impact in cutaneous oncology:

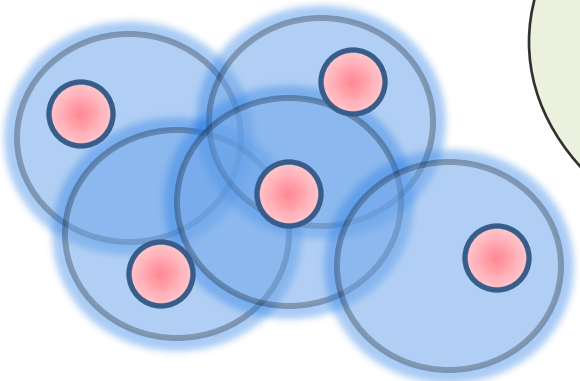
melanoma (vemurafenib), BCCs (vismodegib)

- **Need understanding of driver targets**
- **Kill tumor/bad cells but spare good cells**
- **Target the environment to enhance anti-tumor effects**
- Improved technology for increased potency
- Consider combination strategies as appropriate
  - Multiple targets/pathways
  - Complementary targets
  - How to optimize efficacy without additive toxicities

Targets for therapy in cutaneous T-cell lymphoma

Tumor cell surface molecules
(e.g., CD4, CD25, CD30, CD40, CD52, CD158k, CCR4)

CTCL



Microenvironment, immune mechanisms
(e.g., vasculature, immune modulation)

Tumor proliferation, metabolism, survival, progression mechanisms:
Signal transduction/transcription activation pathways
(e.g., ubiquitin-proteasome, AKT/PI3K/mTOR, RAS/RAF/MEK, MAPK)
Apoptotic pathways *(e.g. Bcl/Bax, TNFR, Fas, miRNAs)*
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Metabolic/survival pathways *(e.g., RFC-1, PARP)*

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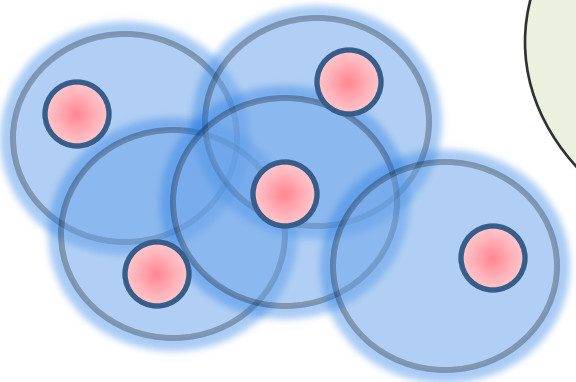

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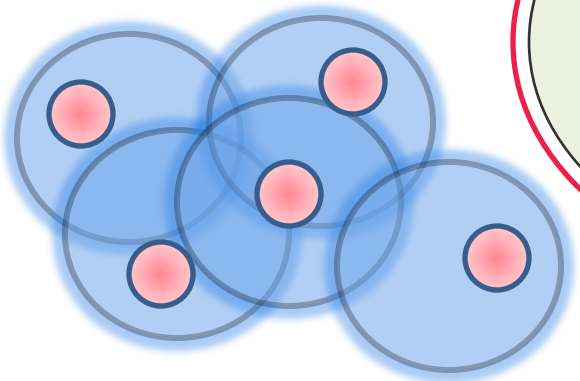

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Types of targeted therapies in lymphoma, 2013

- More and fancier **monoclonal antibodies**

  Cell surface molecules

  – Naked mAbs
    - newer engineered, “high-tech” mAbs
  – MAb drug conjugates (ADCs)
  – Radiolabeled mAbs
- **Small molecule inhibitors/agonists**

  Multitude of potential targets/pathways, need disease relevance

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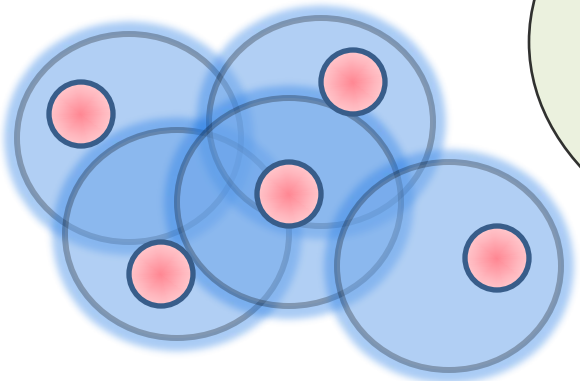

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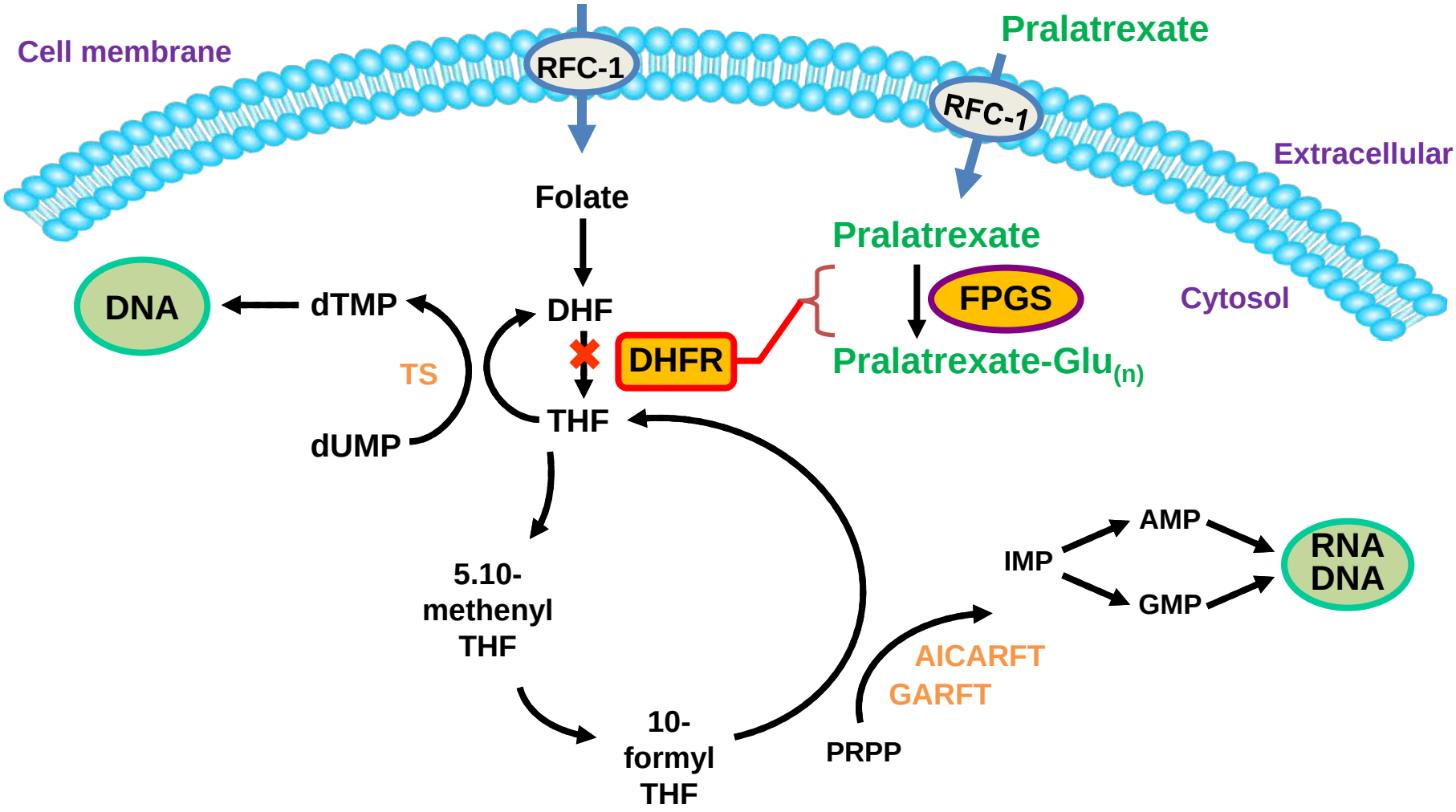
Metabolic/survival pathways *(e.g.,* ***RFC-1****, PARP)*

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 FDA-approved in systemic PTCL, 2009

blood

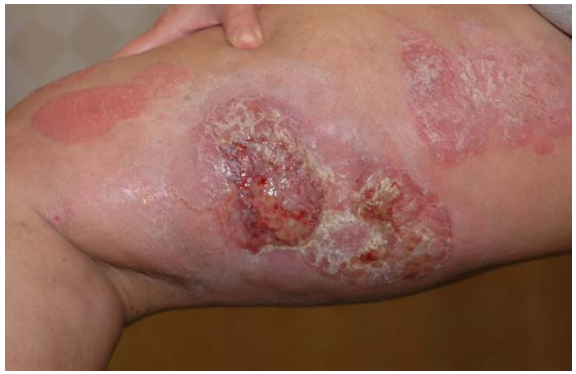
2012 119: 4115-4122
Prepublished online March 6, 2012;
doi:10.1182/blood-2011-11-390211

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

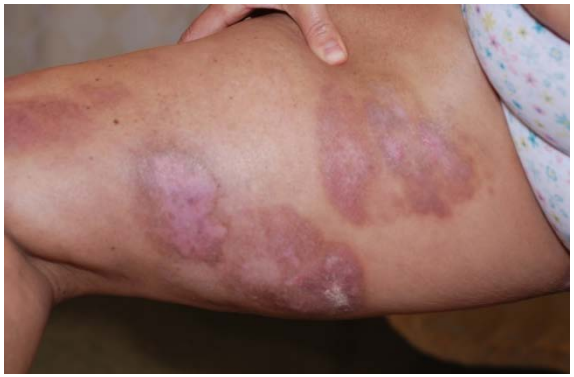
Steven M. Horwitz, Youn H. Kim, Francine Foss, Jasmine M. Zain, Patricia L. Myskowski, Mary Jo Lechowicz, David C. Fisher, Andrei R. Shustov, Nancy L. Bartlett, Maria L. Delioukina, Tony Koutsoukos, Michael E. Saunders, Owen A. O'Connor and Madeleine Duvic

Doses $\geq$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 at 6 mo	**73%**

Pralatrexate response in MF, stage IIB
Good option in MF with LCT



Pretreatment



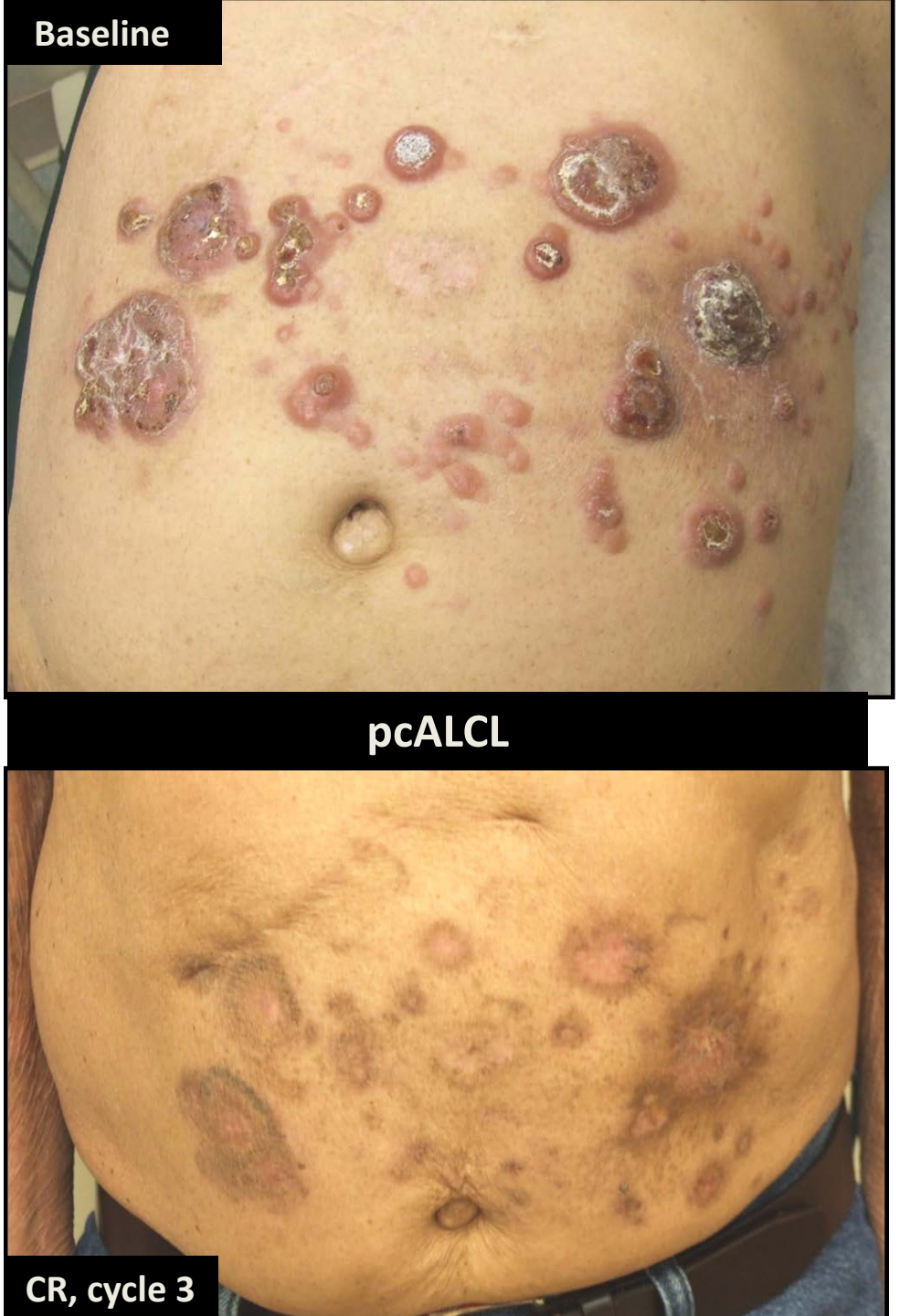
Partial Response post cycle 3

MD Anderson CC

Pralatrexate response,

Pc CD30+ ALCL

Stanford CC



Treatment-Related Adverse Events

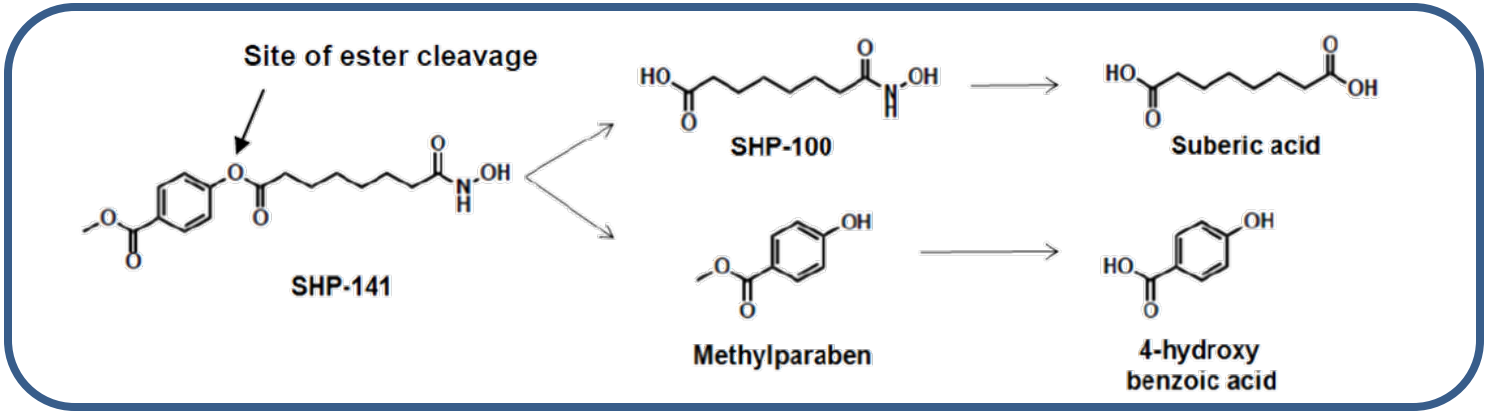
	Optimal Dose 15 mg/m^2 N=29		
Event	**ALL**	**Grade 1-2**	**Grade 3**
Stomatitis	**14 (48%)**	**9 (31%)**	**5 (17%)**
Fatigue	**11 (38%)**	**10 (34%)**	**1 (3%)**
Nausea	**9 (31%)**	**9 (31%)**	**0 (0%)**
Skin toxicity	**6 (21%)**	**4 (14%)**	**2 (7%)**
Vomiting	**4 (14%)**	**4 (14%)**	**0 (0%)**
Pyrexia	**2 (7%)**	**2 (7%)**	**0 (0%)**
Epistaxis	**7 (24%)**	**7 (24%)**	**0 (0%)**
Edema	**4 (14%)**	**4 (14%)**	**0**
Anemia	**1 (3%)**	**1 (3%)**	**0 (0%)**
Thrombocytopenia	**2 (7%)**	**1 (3%)**	**1 (3%)**

Horwitz et al Blood 2012; 119: 4115

Combination trials under way to minimize toxicity and assess synergy

SHP-141: topical HDAC inhibitor

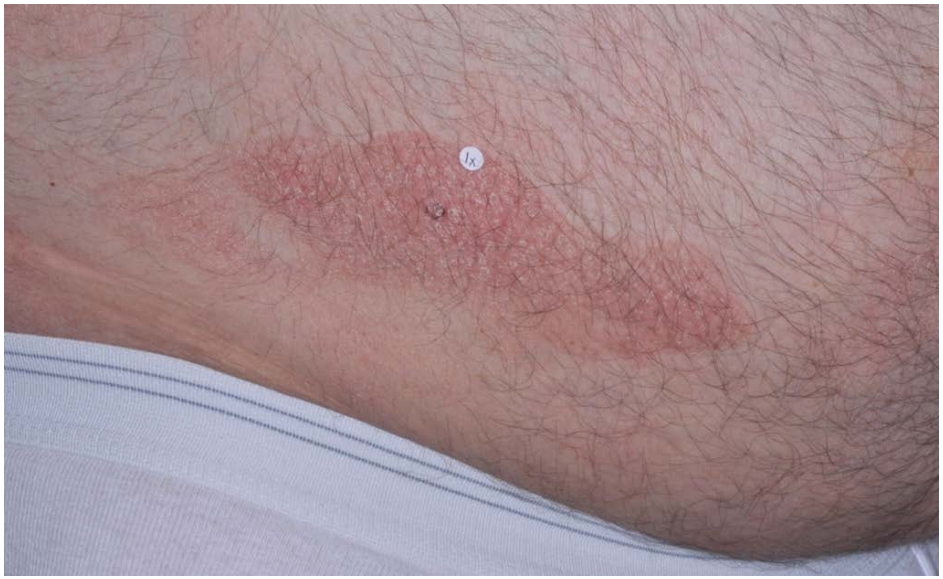
- Discovered at Harvard, the Dana-Farber Cancer Institute and the Broad Institute of Harvard and MIT
- Inhibits HDAC1, 2, 3, & 6 isoforms, similar to vorinostat
- Contains ester bond to promote presystemic metabolism by serum esterases
  - Breaks down to inactive primary metabolites SHP-100 and methylparaben, a common preservative in topical formulations
  - Negligible levels of systemic exposure translates to reduced risk of HDACi class-associated toxicities

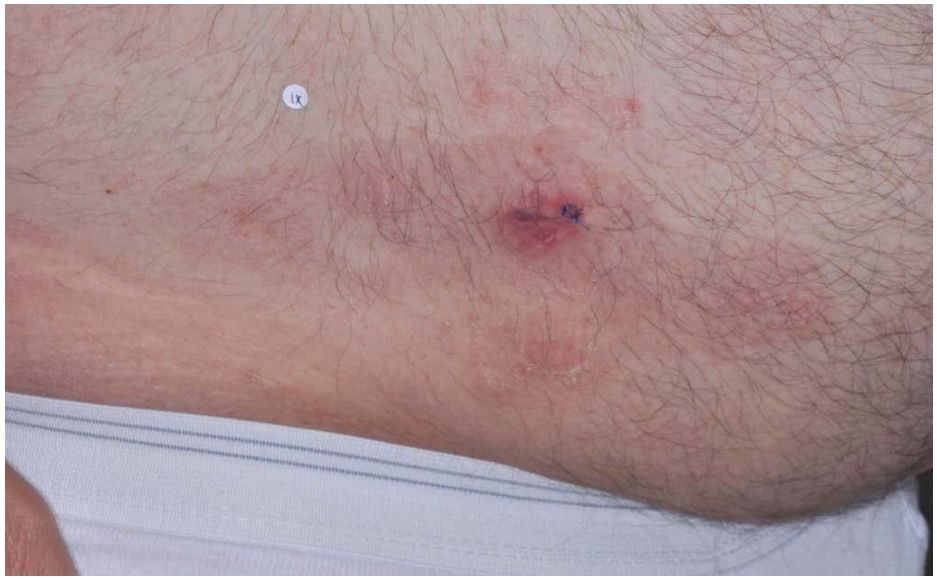


SHP-141: topical HDAC inhibitor

55 yo male stage IA MF

Right lower abdomen





Screening

Day 42

Targets for Therapy in Cutaneous Lymphoma

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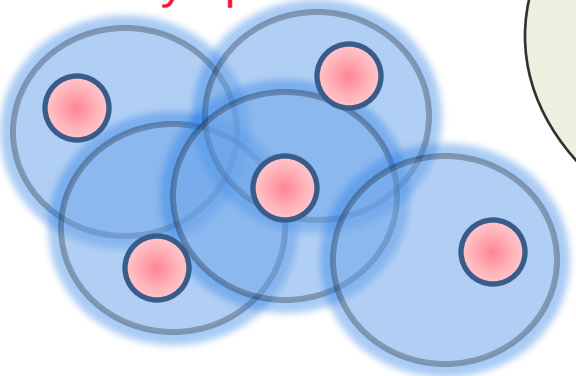
Cutaneous lymphoma



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Targeting tumor surface molecules in lymphoma

Agent	Target	Conjugate/toxin	Disease
Siplizumab	CD2	--	T-, NK-cell lymphomas
Zanolimumab*	CD4	--	CTCL/PTCL
Denileukin diftitox**	CD25	Diphtheria toxin	CTCL/PTCL
UCHT1	CD3	Diphtheria toxin	T-cell malignancies
Brentuximab vedotin*	CD30	MMAE	CD30+ lymphoma
Alemtuzumab*	CD52	--	Hematolymphoid malignancy
Rituximab	CD20	--	CD20+ malignancy
Ofatumumab	CD20	--	CD20+ malignancy
Inotuzumab ozogamicin	CD22	Calicheamycin	B-cell malignancy
KW-0761*	CCR4	--	ATL/CTCL/PTCL

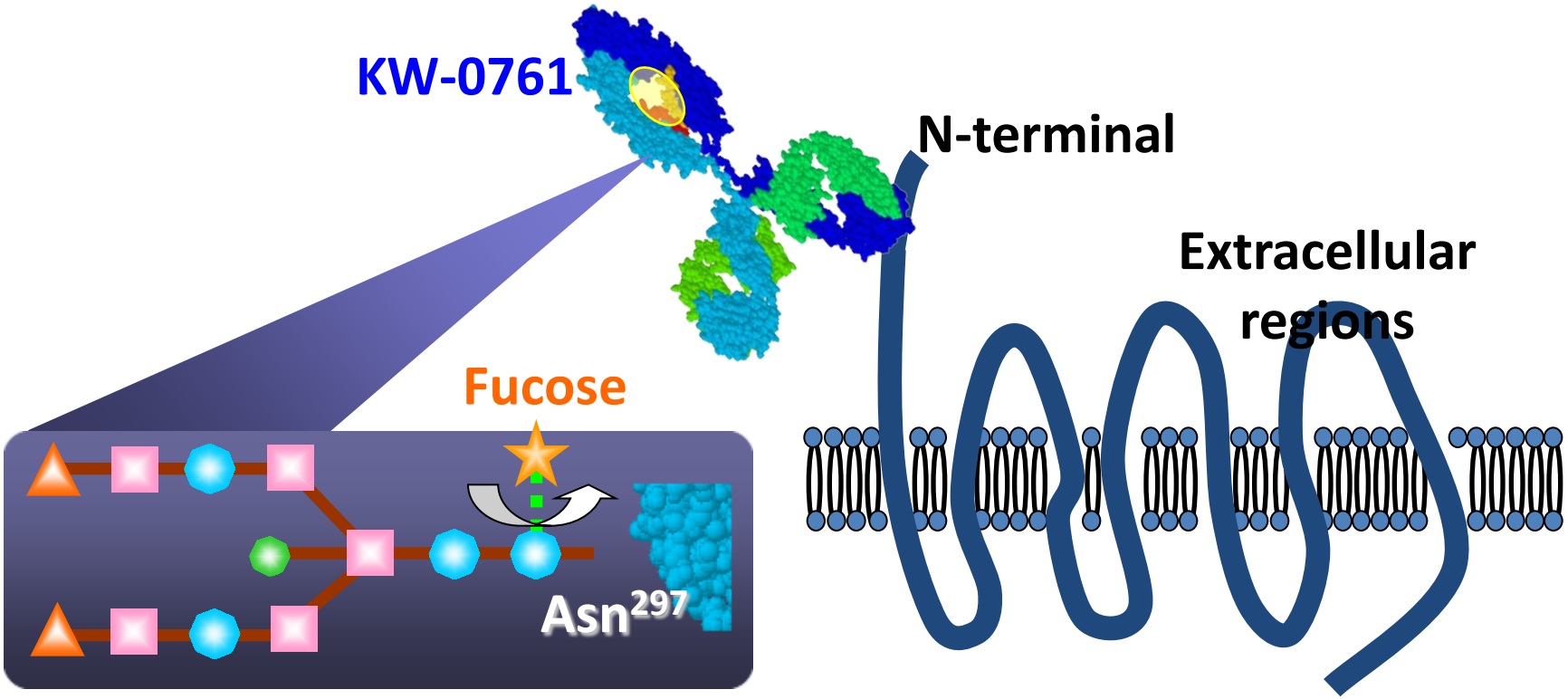
* Clinical studies or off-label use in CTCL
** FDA-approved for CTCL

Ann Oncol 2010;21:683, J Pathol 2010;220:404, 509, Lancet Oncol 2010;11:1074

Newer generation monoclonal antibodies in cutaneous T-cell lymphoma

- Fully human mAbs
- Engineered mAbs, modified Fc portion to enhance biologic activity
  - Defucosylated anti CCR4 Mab (KW-0761)
- Antibody drug conjugates
  - Anti CD30 ADC, brentuximab vedotin (SGN-35)

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

Approved in Japan 2012 for pts with ATL

Phase II study in progress in the US- NCT01626664

KW 0761 or Investigator's Choice in Subjects With Previously Treated Adult T-cell Leukemia-Lymphoma (ATL)

KW-0761, a Monoclonal Antibody Directed against CC Chemokine Receptor type 4 (CCR4), in CTCL patients: Results of a Phase 1/2 Study

Madeleine Duvic,[1] Lauren Pinter-Brown,[2] Francine Foss,[3] Lubomir Sokol,[4] Jeffrey Jorgensen,[5] George Spitalny,[6] and Youn H Kim[7]

[1]Department of Dermatology and [5]Department of Hematopathology, UT MD Anderson Cancer Center; [2] Geffen School of Medicine at UCLA; [3]Department of Medical Oncology, Yale Cancer Center; [4]Department of Malignant Hematology, H Lee Moffitt Cancer Center and Research Institute; [6]Kyowa Hakko Kirin Pharma, Inc.; [7]Department of Dermatology, Stanford Cancer Center

American Society of Hematology

52nd Annual Meeting

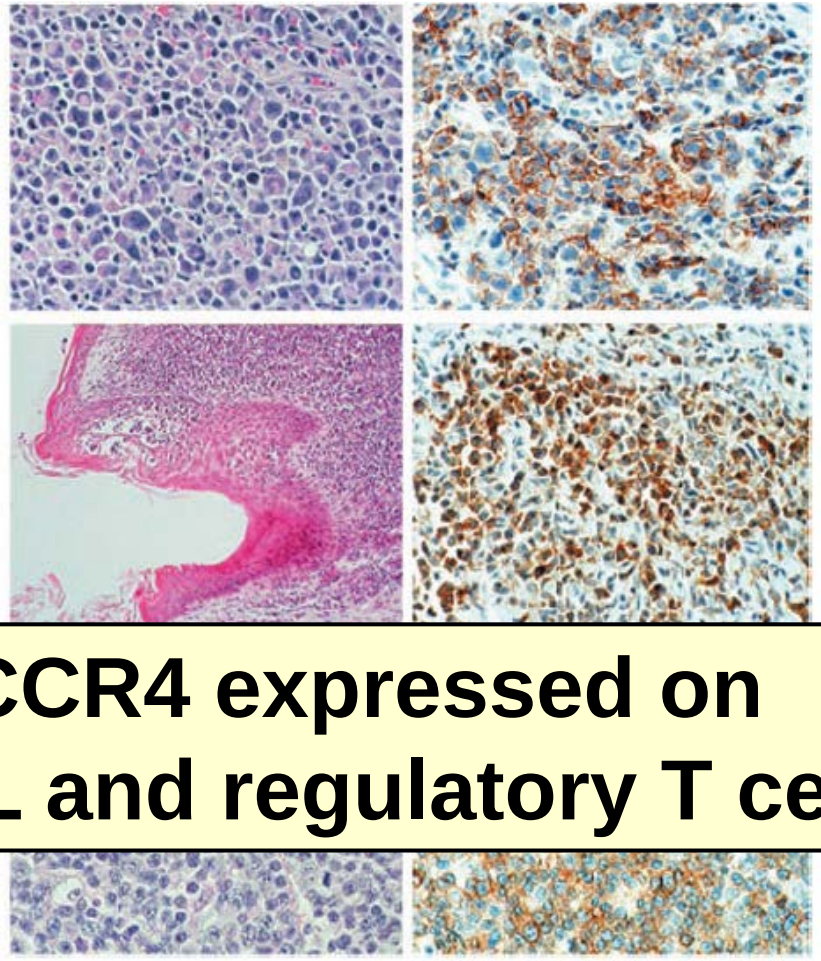
December 4–7, 2010

Expression of CCR4

Receptor for CC chemokines, MDC, TARC

ALK-negative ALCL

MF/SS



CCR4 expressed on CTCL and regulatory T cells

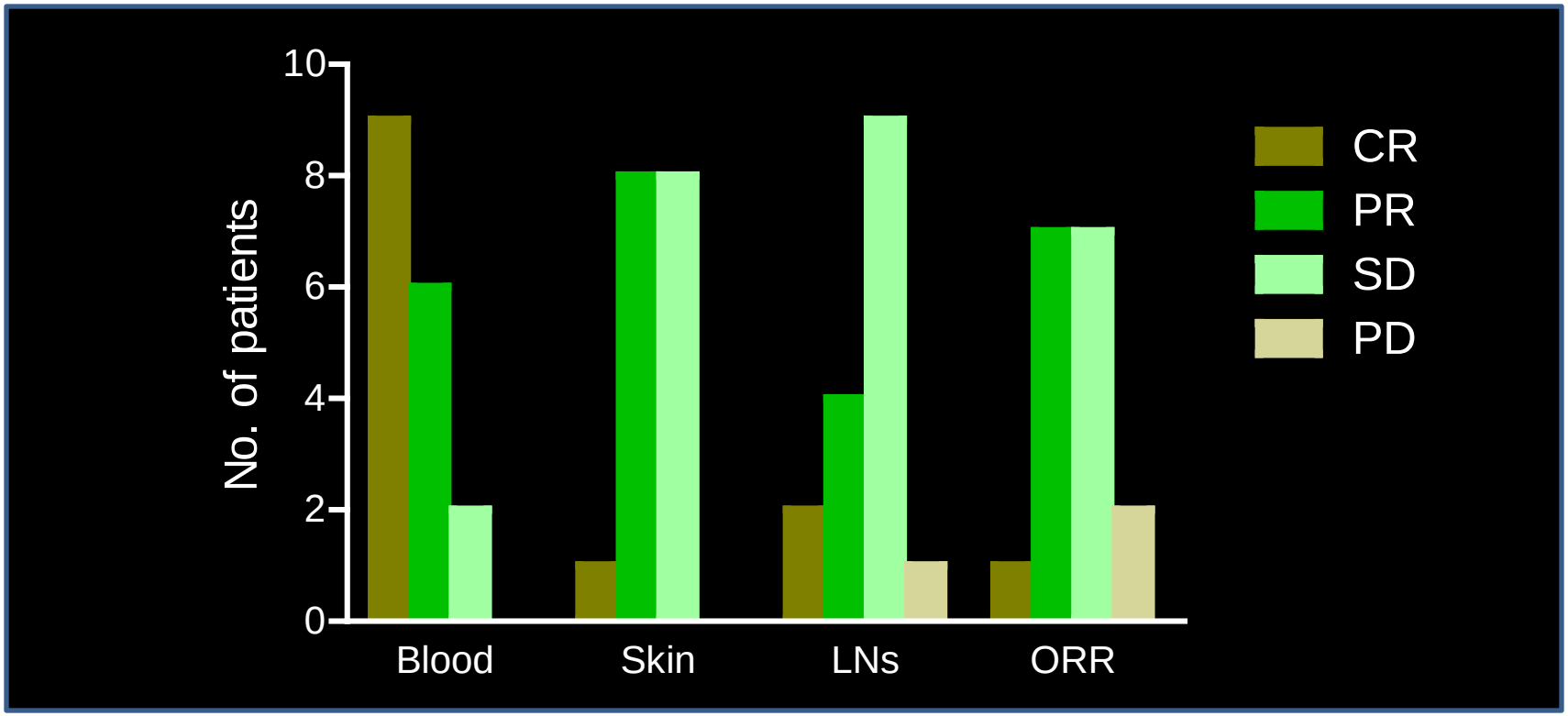
Ishida T et al. Clin Cancer Res. 2004;10:7529,
Ferenczi K et al. J Invest Dermatol 2002;119:1405
Chang D-K et al. Mol Cancer Ther 2012;11:2451

Overall response rate in phase 1/2 study

	ORR	No. of patients			
		CR	PR	SD	PD
Sezary Syndrome (N=17)	47%	1	7	7	2
Mycosis Fungoides (N=21)	33%	1	6	10	4
TOTAL (N=38)	42%	2	13	17	6

Intravenous administration, weekly x 4, then every 2 wks

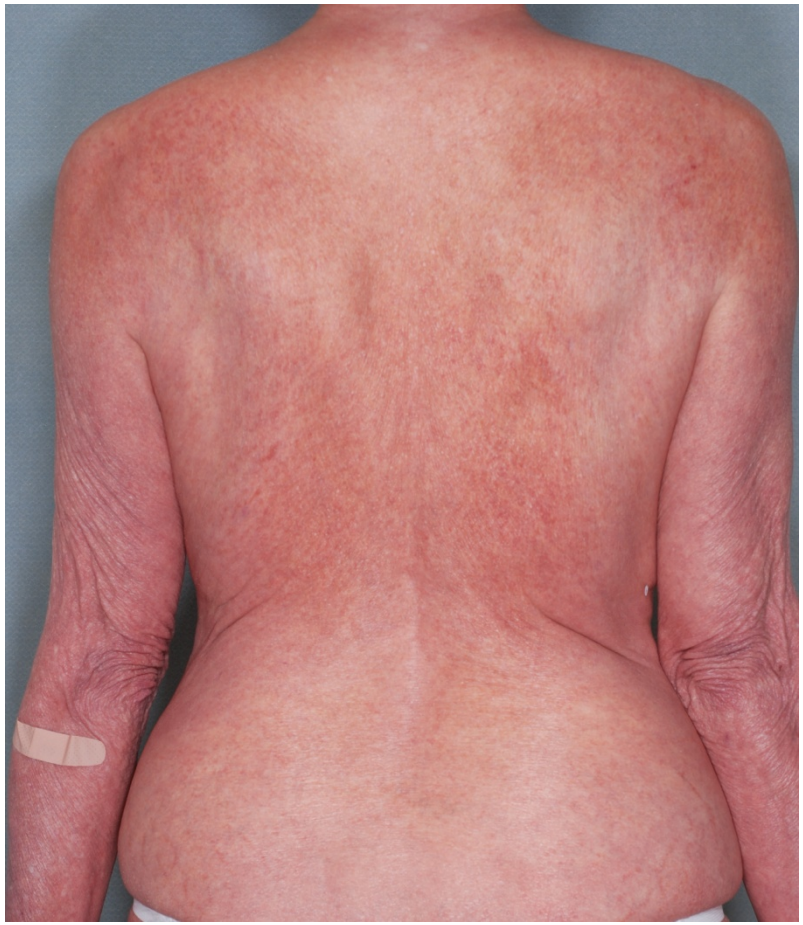
Best Response in SS Patients by Compartment



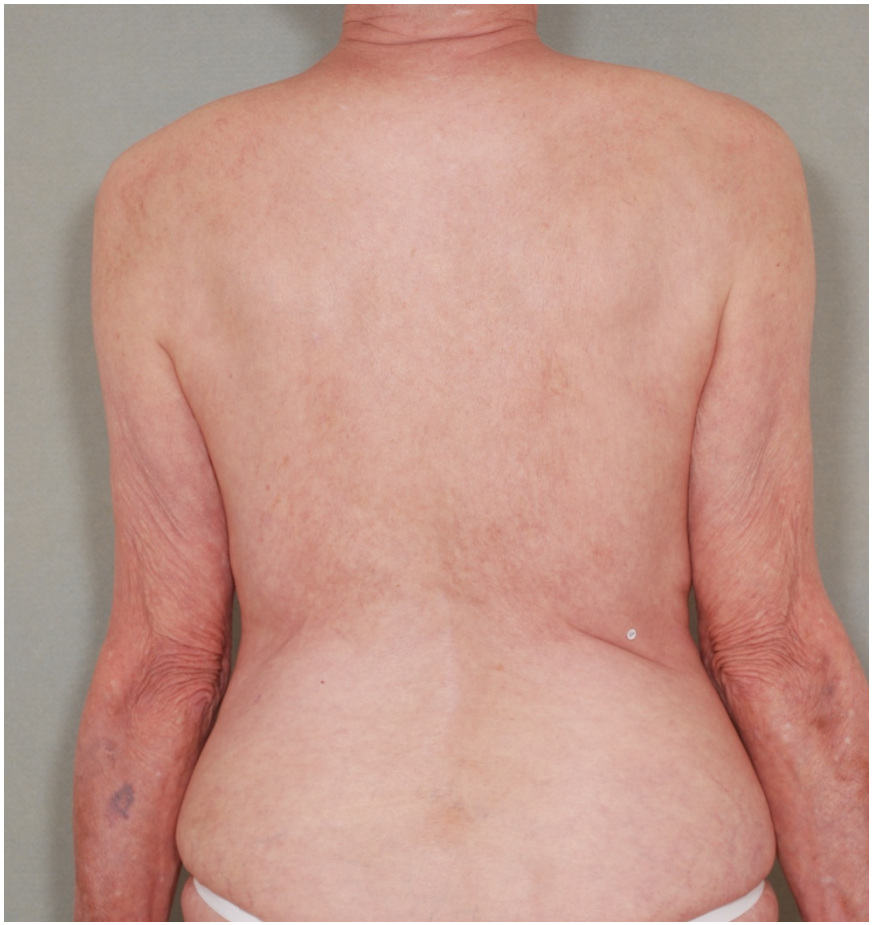
- 8/17 (47%) of SS patients with global response (ORR)
- 15/17 (88%) of SS patients had response in blood
  9/17 (53%) had CR in blood

Case Study: Patient 03-Stanford

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



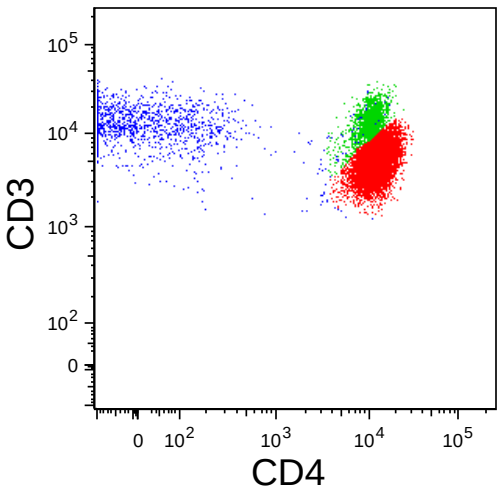
Pretreatment
Course 1 Day 1

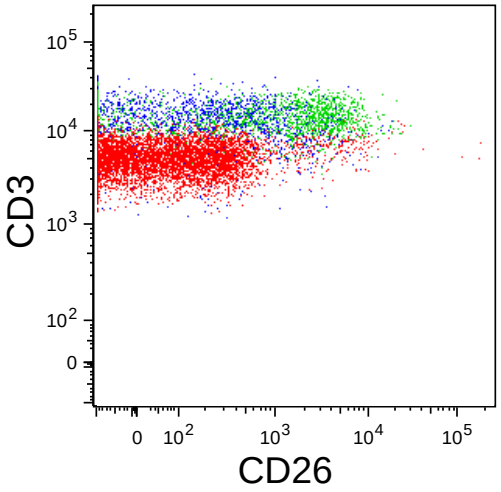


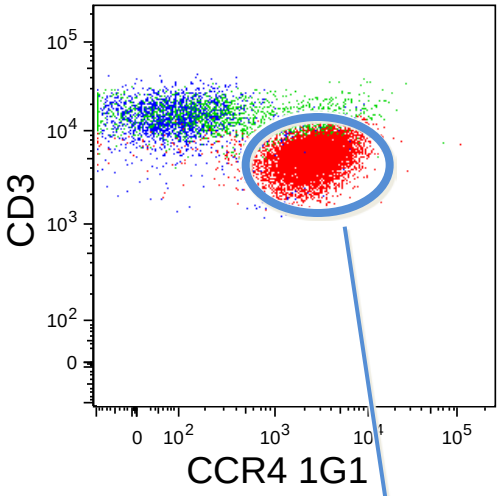
Post treatment
Post Course 11

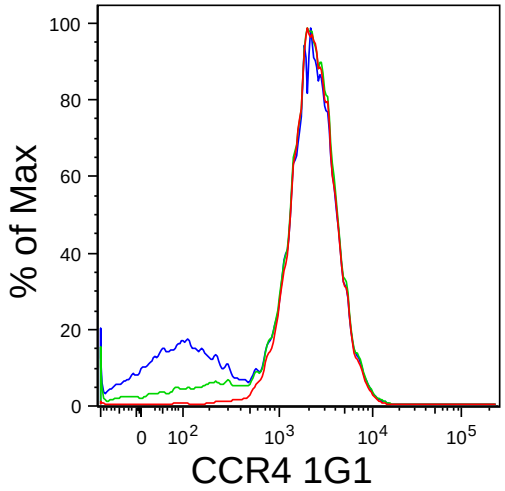
Response in Blood: Patient 01-Stanford (SS; Stage IVA; 6 prior therapies; 0.1 mg/kg)

Pre-treatment







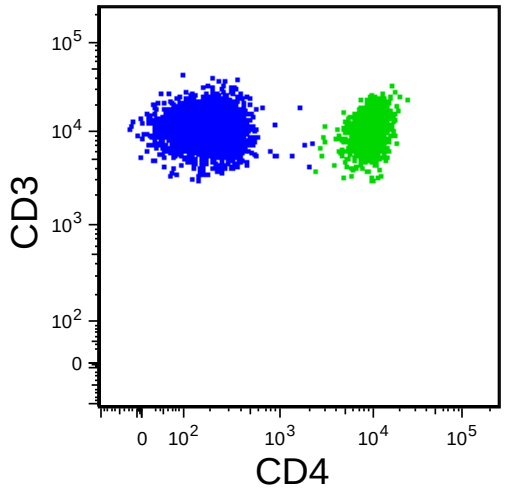


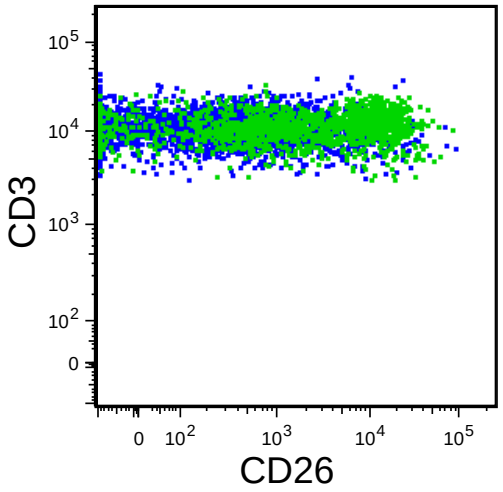
Lymphoma cells
Normal CD3+CD4+
CD3+CD4neg

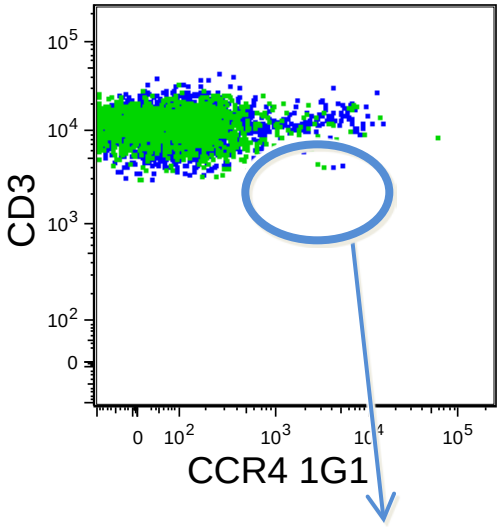
Lymphoma cells

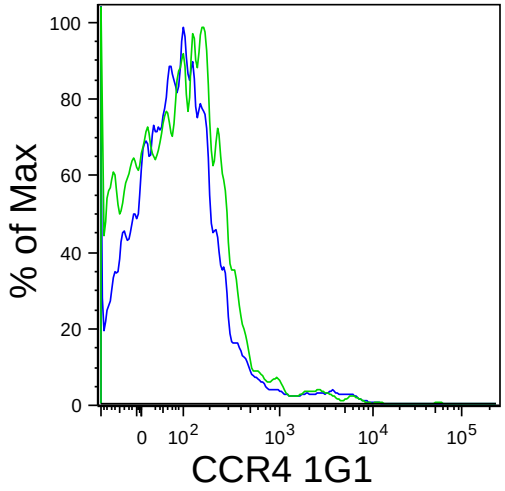
Response in Blood: Patient 01-Stanford

Post-treatment









Lymphoma cells
Normal CD3+CD4+
CD3+CD4neg

Lymphoma cells undetectable

Maintaining response >2 yrs

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 in CTCL ongoing for FDA approval in the US

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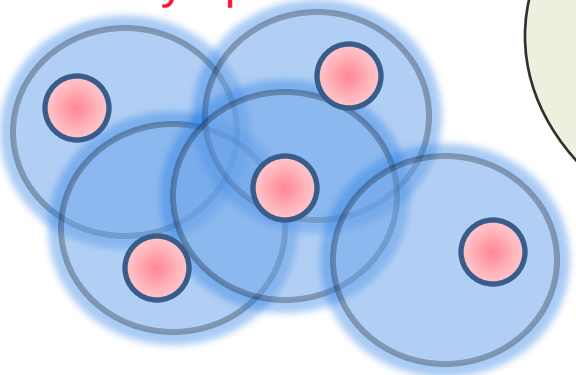
Cutaneous lymphoma



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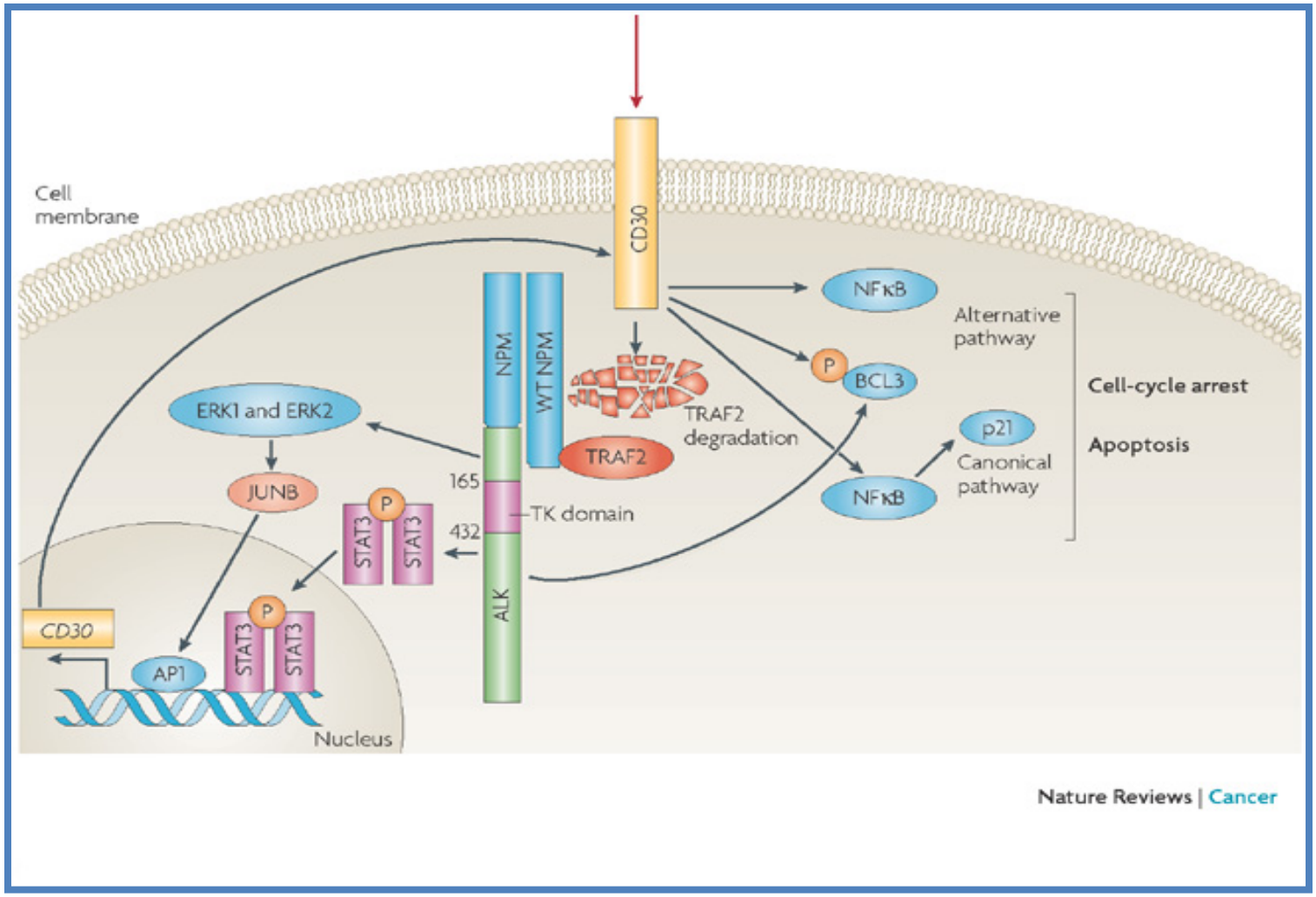
Targeted therapy in CD30+ LPDs

- CD30, an attractive target, as CD30 expression is limited in normal cells, but increased in proliferative or malignant lymphocytes **=> good tumor selectivity**

Rationale for Targeting CD30

ALK and CD30 Signaling closely linked



CD30 engagement leads to activation of NFkB pathways and p21 mediated cell cycle arrest and apoptosis

Chiarle 2008

A Phase II Study of SGN-30 in Cutaneous Anaplastic Large Cell Lymphoma and Related Lymphoproliferative Disorders

Madeleine Duvic,[1] Sunil A. Reddy,[2] Lauren Pinter-Brown,[4] Neil J. Korman,[5] John Zic,[6] Dana A. Kennedy,[7] Jennie Lorenz,[7] Eric L. Sievers,[7] and Youn H. Kim[3]

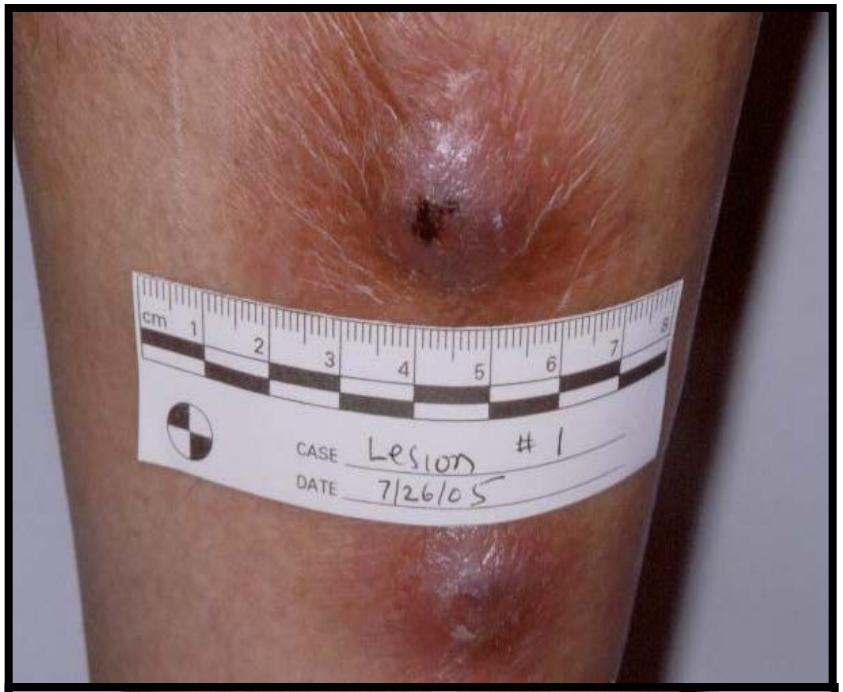
Clin Cancer Res 2009;15:6217-24

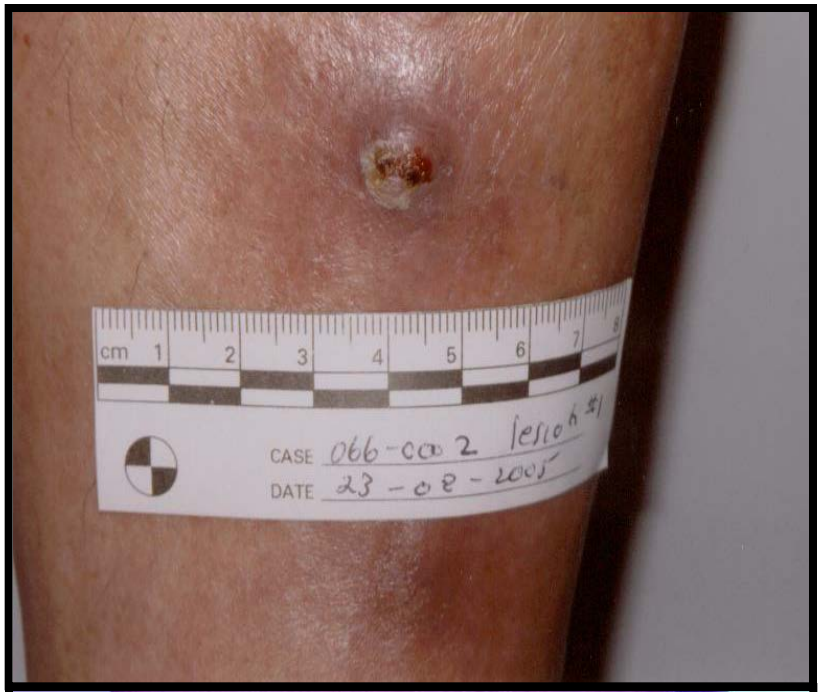
Table 2. Best clinical response

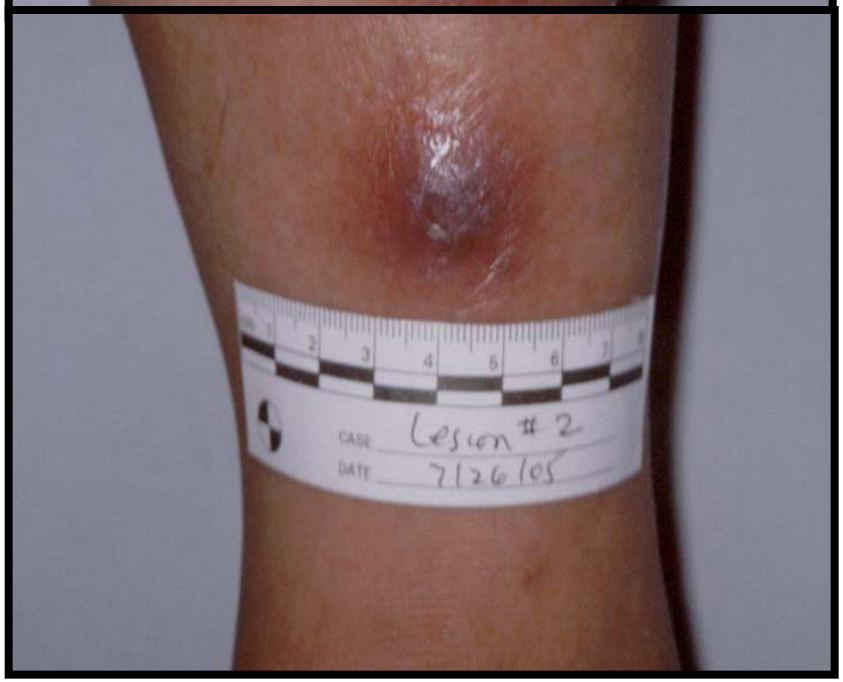
	Diagnosis				Total (*N* = 23), *n* (%)
	pc-ALCL (*n* = 11), *n* (%)	LyP (*n* = 3), *n* (%)	T-MF (*n* = 3), *n* (%)	Multiple (*n* = 6), *n* (%)	
CR	6 (55%)	1 (33%)	0	3 (50%)	10 (43%)
PR	3 (27%)	1 (33%)	1 (33%)	1 (17%)	6 (26%)
CR or PR	9 (82%)	2 (67%)	1 (33%)	4 (67%)	16 (70%)
SD	2 (18%)	1 (33%)	1 (33%)	0	4 (17%)
Progressive disease	0	0	1 (33%)	2 (33%)	3 (13%)

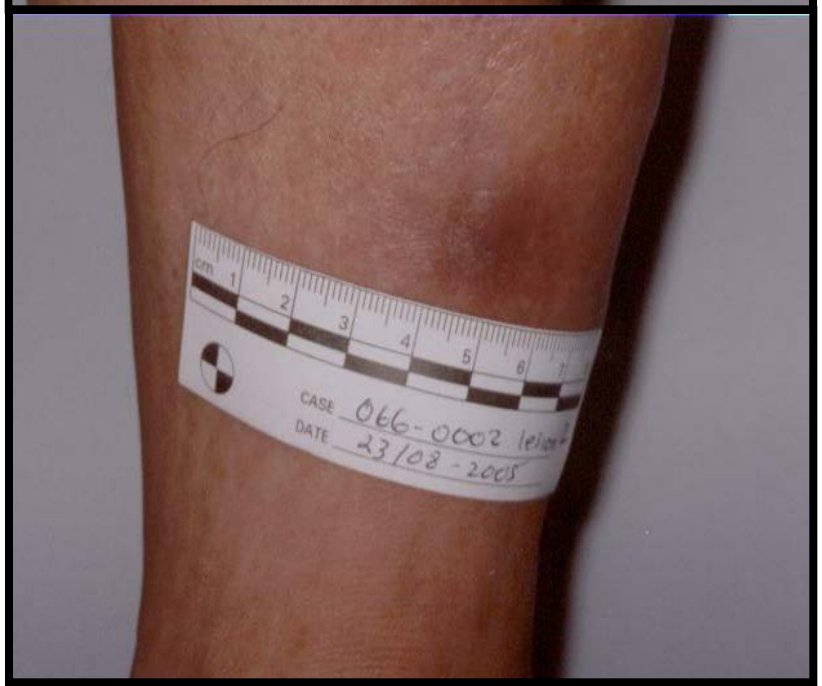
- *Very well tolerated, no drug-related SAE or AEs leading to discontinuation*

Day 1, Dose #1 SGN-30 **pc ALCL** **Day 28, Pre-Dose #2**







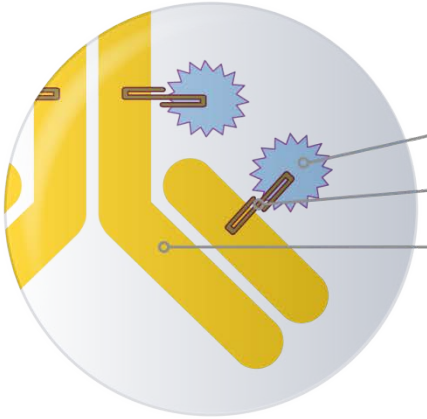


Naked anti-CD30 MAbs in CD30+ LPDs

- Naked anti-CD30 mAb well tolerated but variable efficacy
  - High responses in pcALCL/LyP
  - Efficacy in MF minimally explored
  - Disappointing efficacy in HL/sALCL

Brentuximab Vedotin Mechanism of Action

Antibody Drug Conjugate



Monomethyl auristatin E (MMAE), microtubule-disrupting agent

Protease-cleavable linker

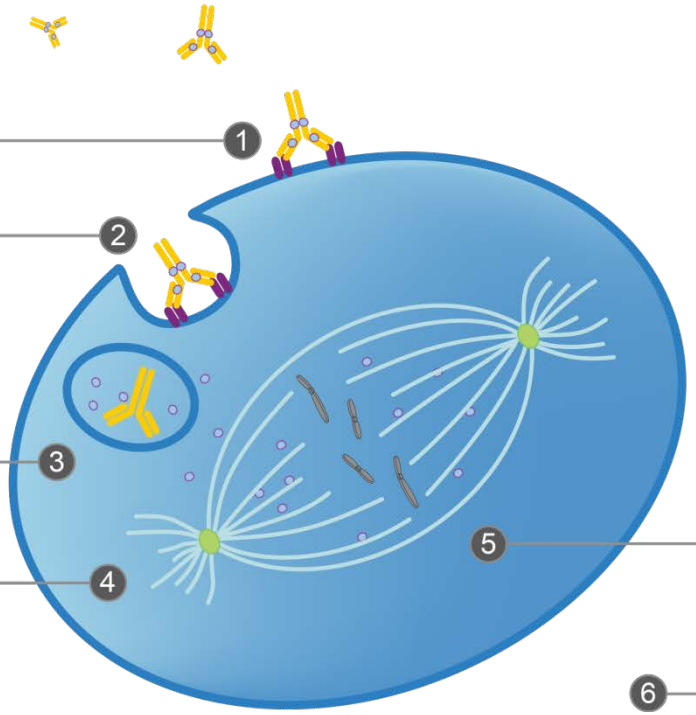
Anti-CD30 monoclonal antibody

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

ASH abstract #797,
presented 12/10/2012

Brentuximab vedotin demonstrates clinical activity in mycosis fungoides / Sézary syndrome

Krathen M[1], Bashey S[1], Sutherland K[1], Sundram U[1], Nagpal S[1], Salva K[3], Wood G[3], Advani R[1], Hoppe RH[1], Reddy S[1], Pulitzer M[2], Horwitz S[2], Kim YH[1]

[1]Stanford Cancer Institute, Stanford, CA, USA
[2]Memorial Sloan-Kettering Cancer Center, New York, NY, USA
[3]University of Wisconsin, Madison, WI, USA

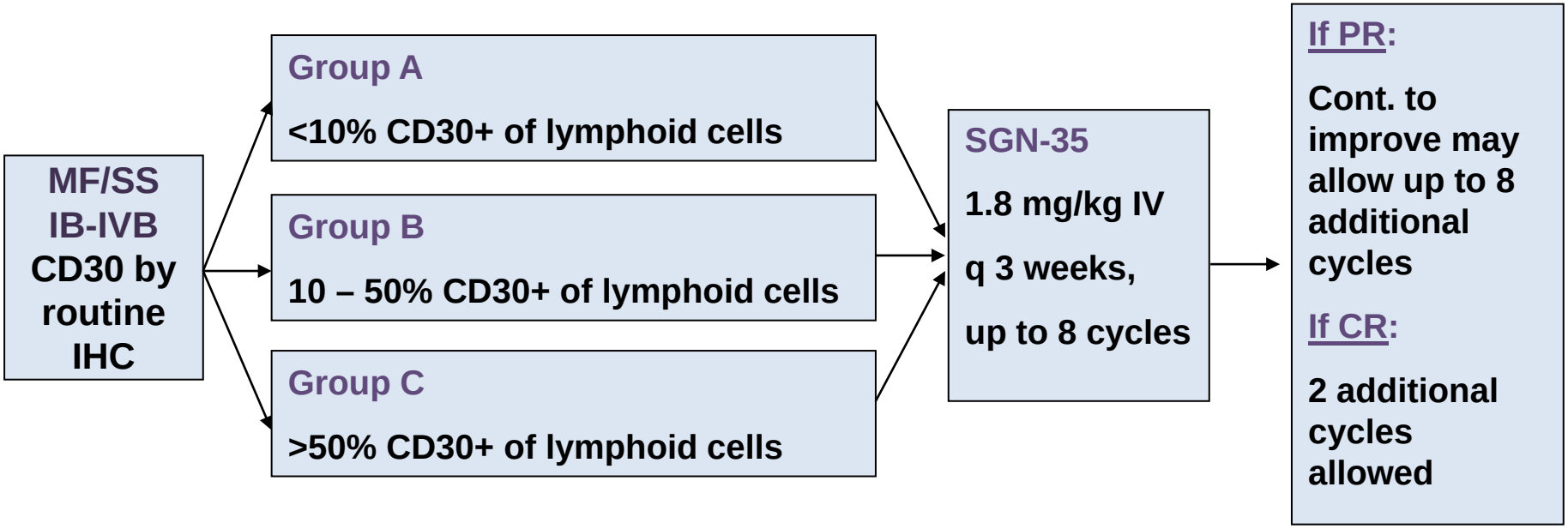
Brentuximab Vedotin (SGN-35)

- High response rates in relapsed/refractory HL and sALCL with consistent expression of CD30 on tumor cells
  - Accelerated FDA approval 8/2011

- Variable CD30 expression in neoplastic cells of MF
  - Transformed MF with more frequent and greater CD30 expression, 30-50%
  - Non-transformed MF, 0-15%

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

Study Design

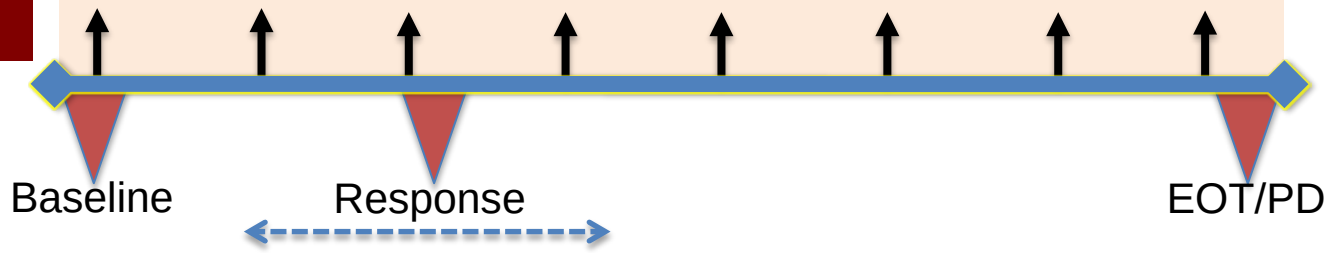


*Responses confirmed subsequent cycle and IRG

Clinical Assessments

Physical exam + Flow q cycle
Imaging at baseline, q2 cycles (extracutaneous), q 3 cycles, EOT

Correlative Tissue/Blood



Patient Characteristics, N=20

Age (y), median (range)		59.5 (20 – 88)	
Sex (n)		Men	13
		Women	7
Stage (n)		IB	2
		IIA	0
		IIB	11
		III	0
		IVA2	4
		IVB	1
		SS	2
Large cell transformation (LCT) / Folliculotropic MF (FMF)		13/20 LCT 8/20 FMF LCT & FMF 2/20	
Prior systemic therapies		4 (1-15)	
CD30 baseline, % of lymphoid cells (skin, via IHC)	A: < 10%	7	
	B: 10-50%	10	
	C: >50%	3	

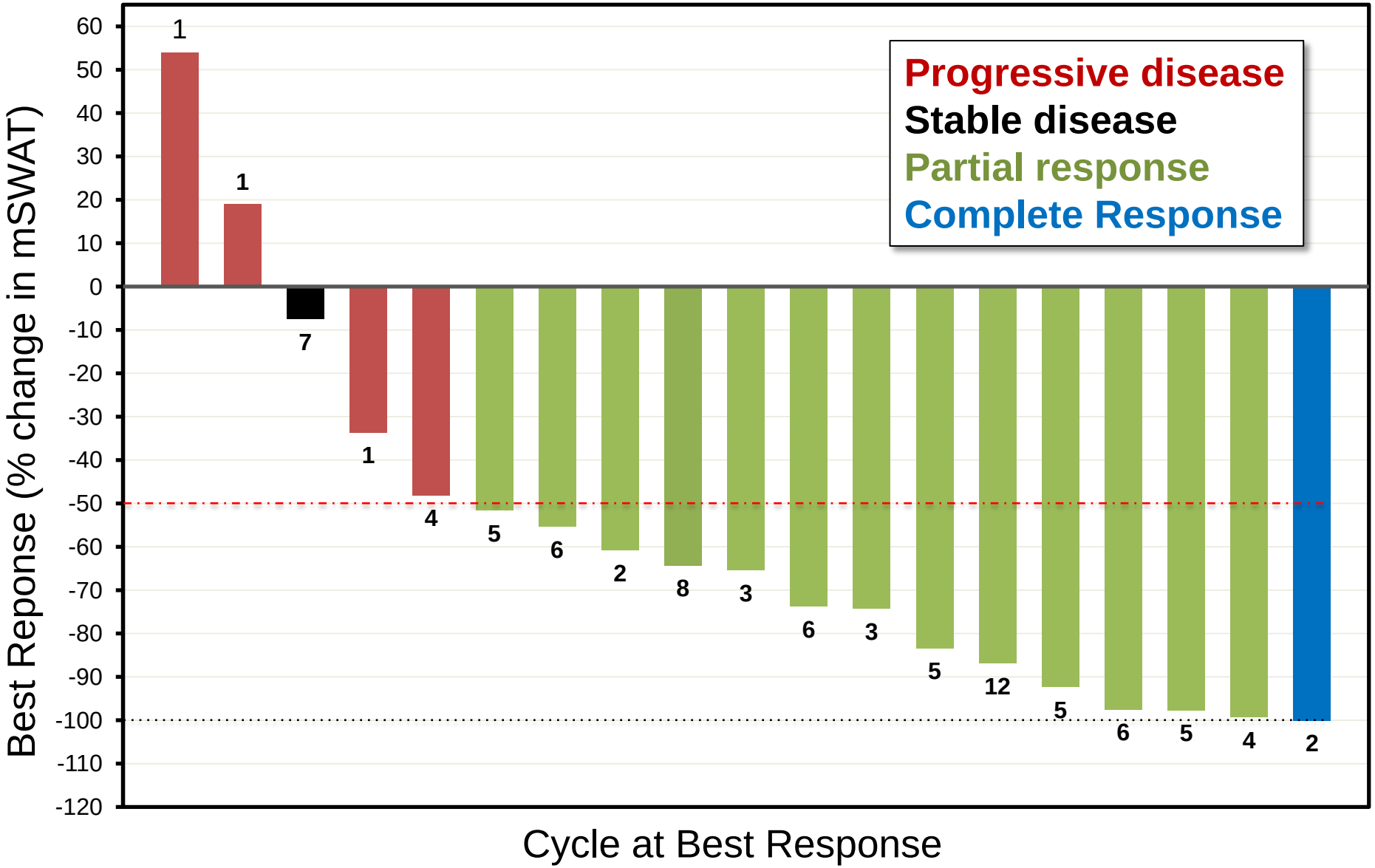
Advanced stage

Variable expression

Patient Characteristics, N=20

Age (y), median (range)		59.5 (20 – 88)		
Sex (n)		Men	13	
		Women	7	
Stage (n)		IB	2	
		IIA	0	
		IIB	**6/11**	**Advanced stage**
		III	0	
		IVA2 **IVB**	**4/4** **1/1**	
		SS	**2/2**	
Large cell transformation (LCT) / Folliculotropic MF (FMF)		**13/20 LCT** 8/20 FMF **LCT & FMF 2/20**		
Prior systemic therapies		4 (1-15)		
CD30 baseline, % of lymphoid cells (skin, via IHC)	A: < 10%	7		**Variable expression**
	B: 10-50%	10		
	C: >50%	3		

Percent Change in Skin mSWAT At Best Clinical Response



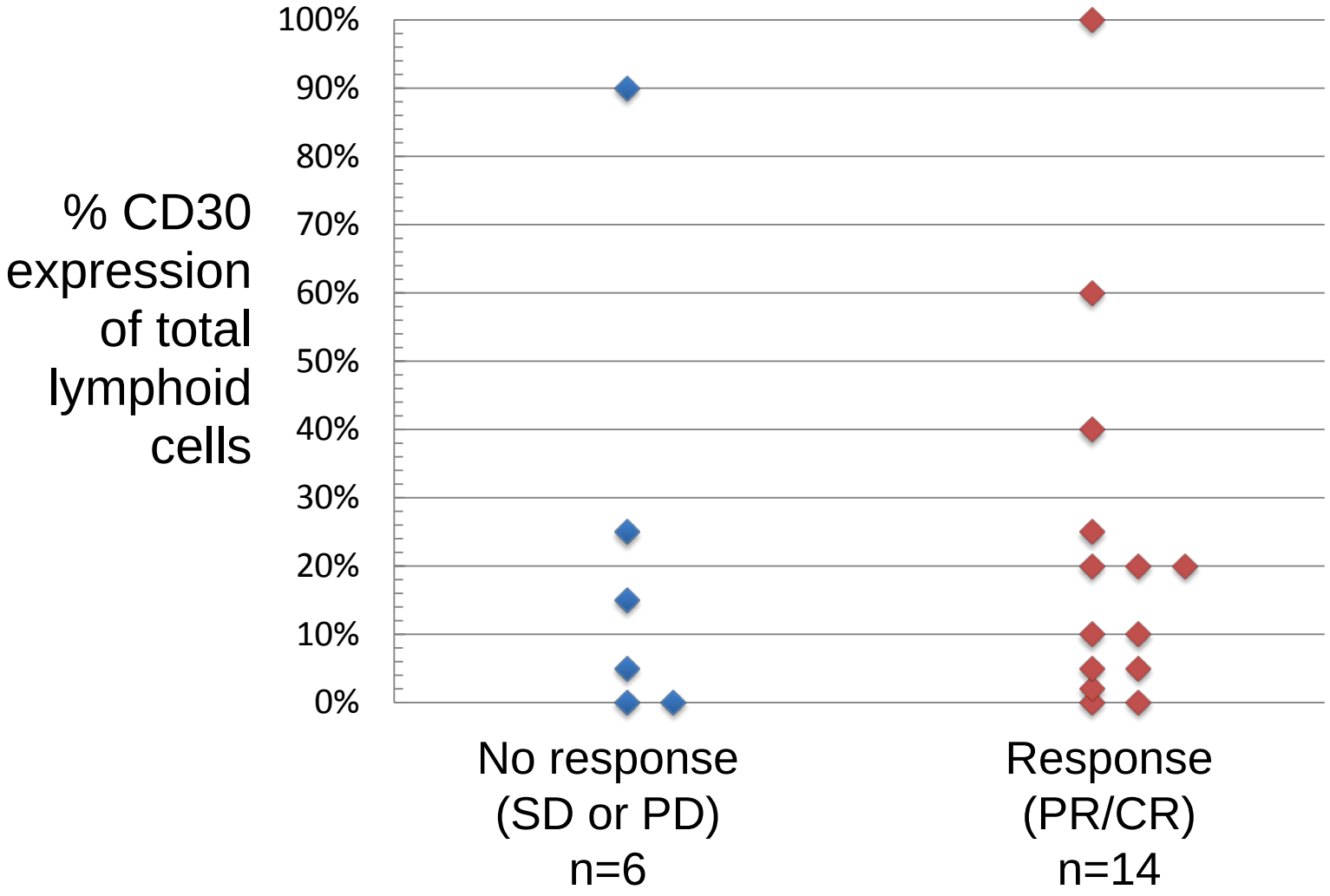
Clinical Response by Baseline CD30 Expression

CD30 Expression Group	Response Rate % (n)	CR	PR	SD	PD
Group A (<10%) n=7	71% (5)	0	5	1	1
Group B (10-50%) n=10	70% (7)	0	7	0	3
Group C (>50%) n=2*	100% (2)	1	1	0	0
TOTAL n=19*	74% (14)	1	13	1	4

If > 1 skin biopsy at baseline, maximum CD30% designated grouping

* 1 subject non-evaluable for response

No Correlation of Clinical Response and CD30 Expression by Routine IHC



Clinical Response by Stage

Stage	Response Rate	CR	PR	SD	PD
IB (n=2)					
IIB* (n=11)					
IVA**/B (n=6)					
Total n=19**					

No correlation with response:

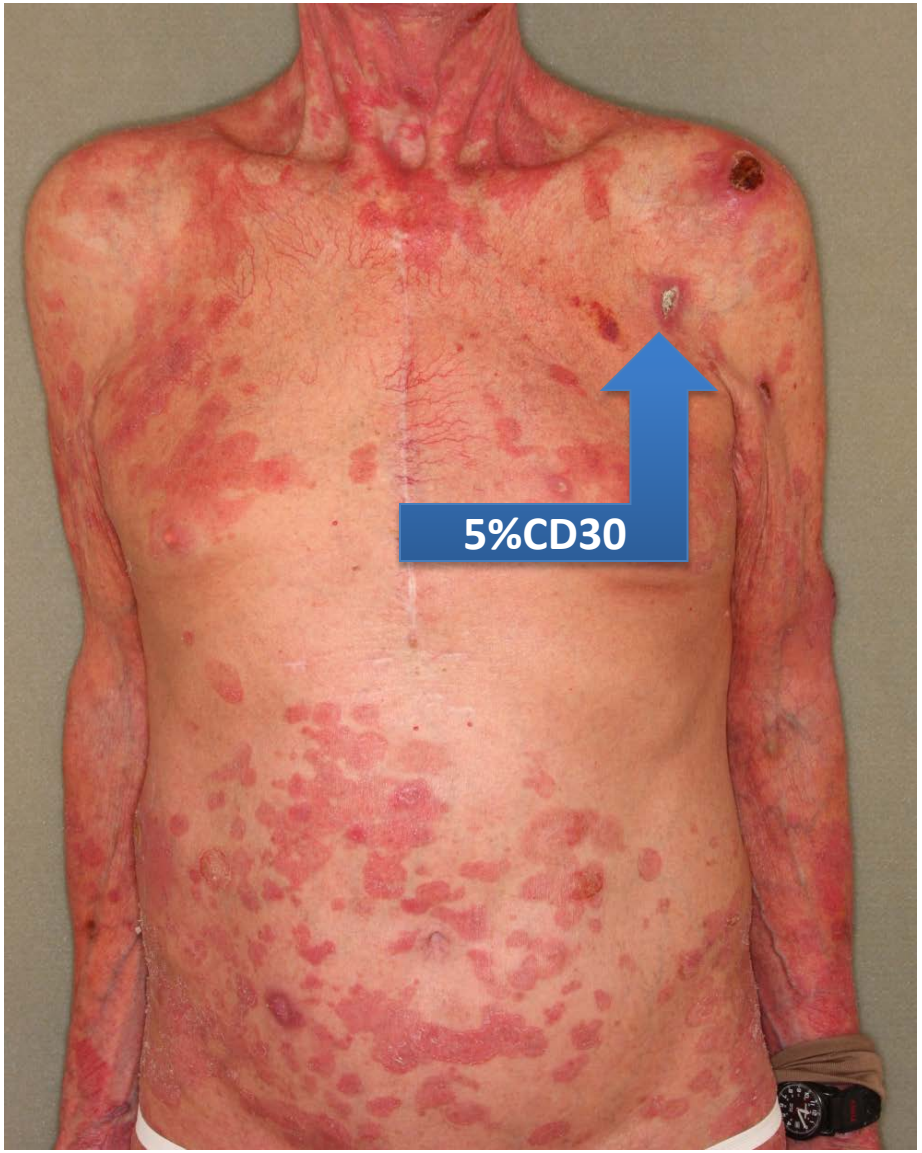
- **Gender (p=0.62)**
- **Age (p=0.44)**
- **Large cell transformation (p=0.35)**
- **Folliculotropism (p=0.64)**
- **Baseline soluble CD30 (p=0.90)**

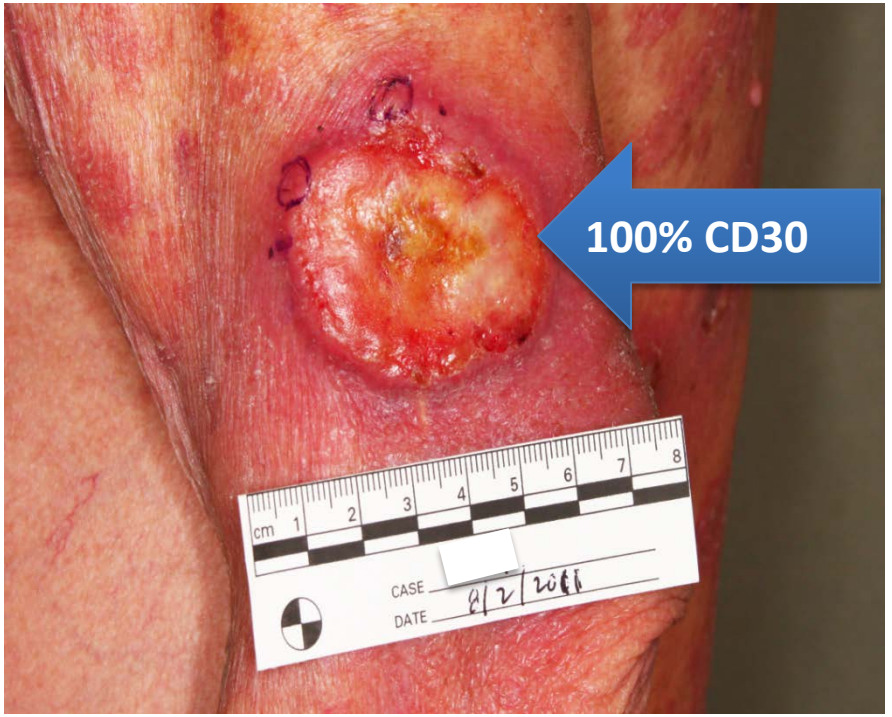
*All 11 either LCT or FMF

** 1 subject non-evaluable for response

87 yo M with MF IIB, LCT

Screening biopsies (L chest plaque and L arm tumor)



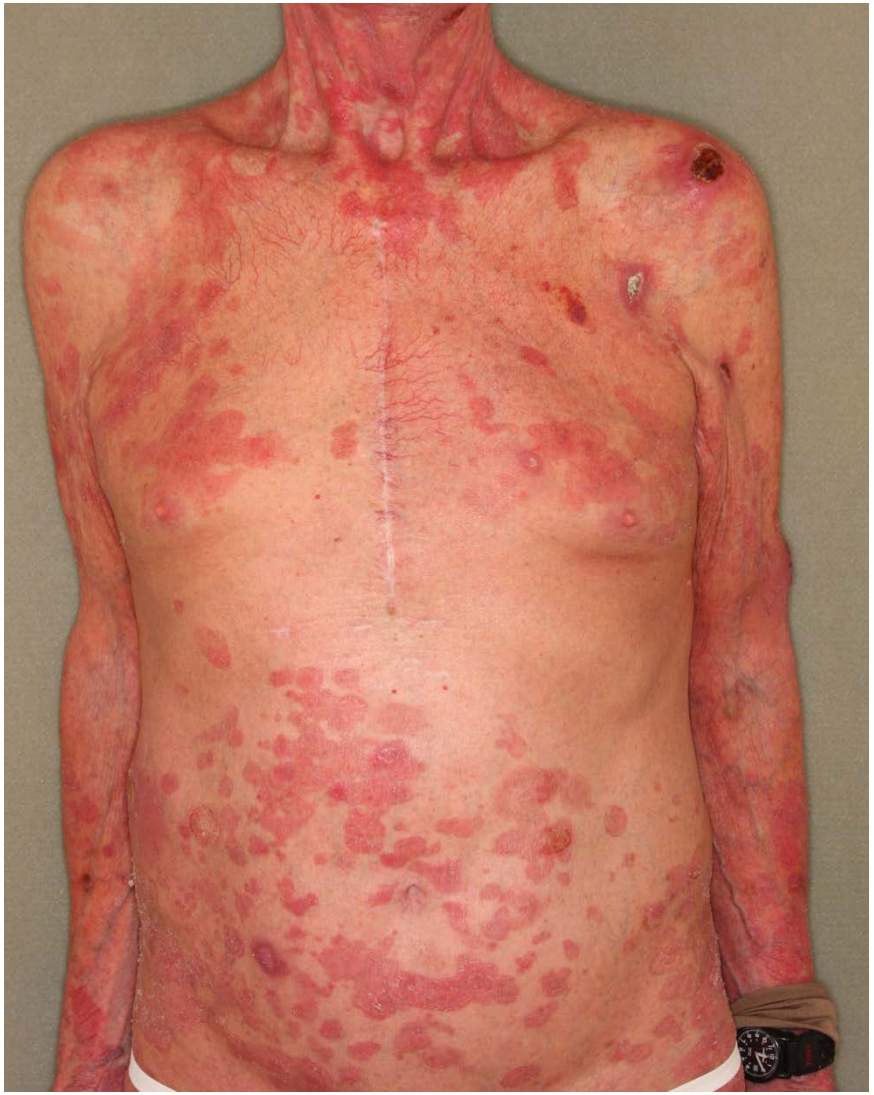


Max CD30 TLI 100%

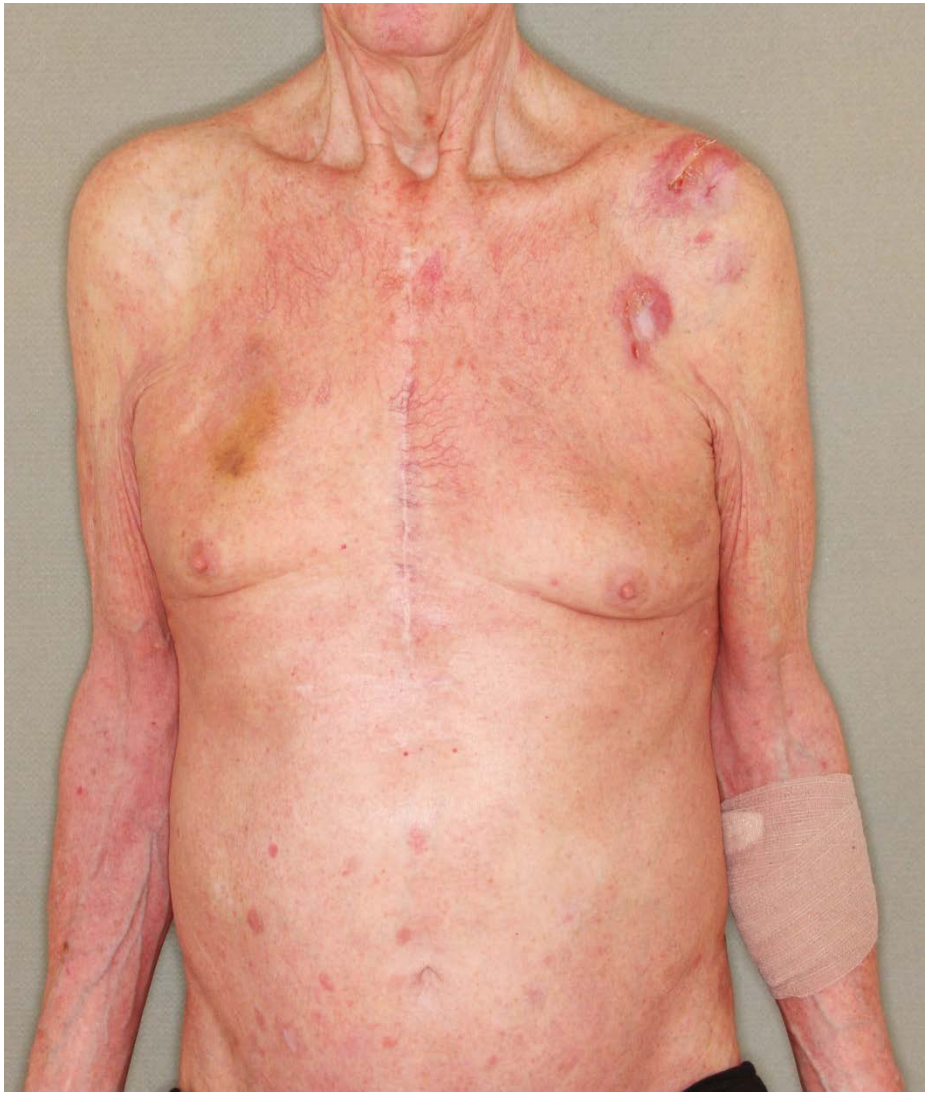
Group C (>50%)

87 yo M with MF IIB, LCT

Screening

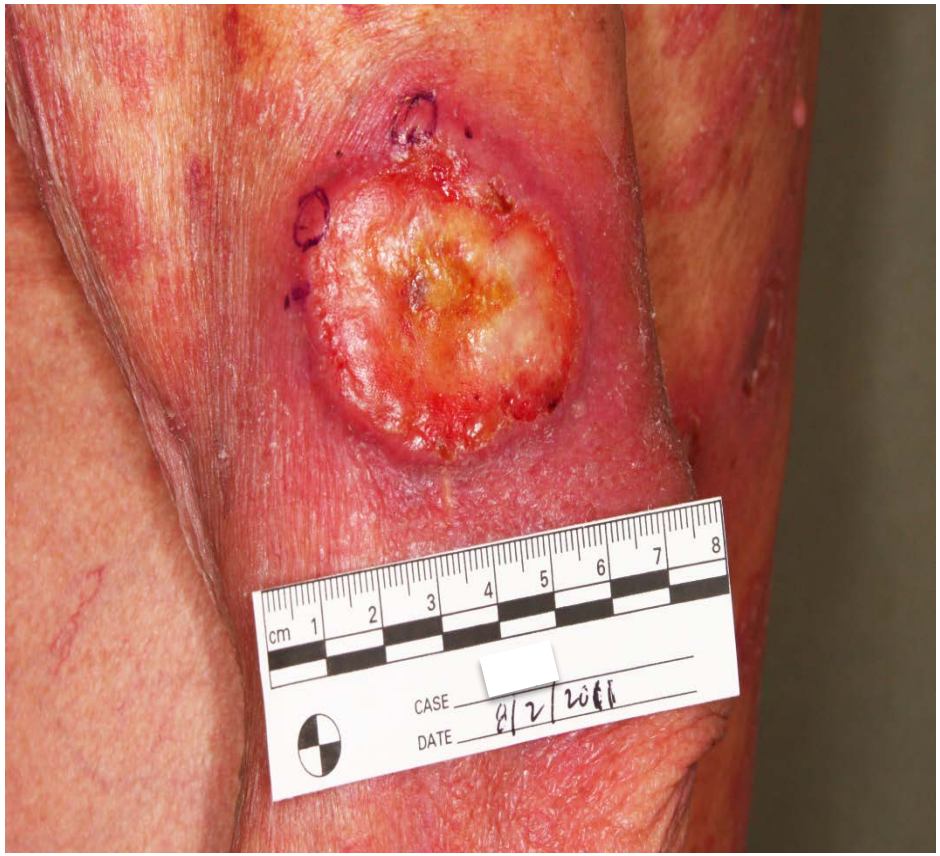


Cycle 6

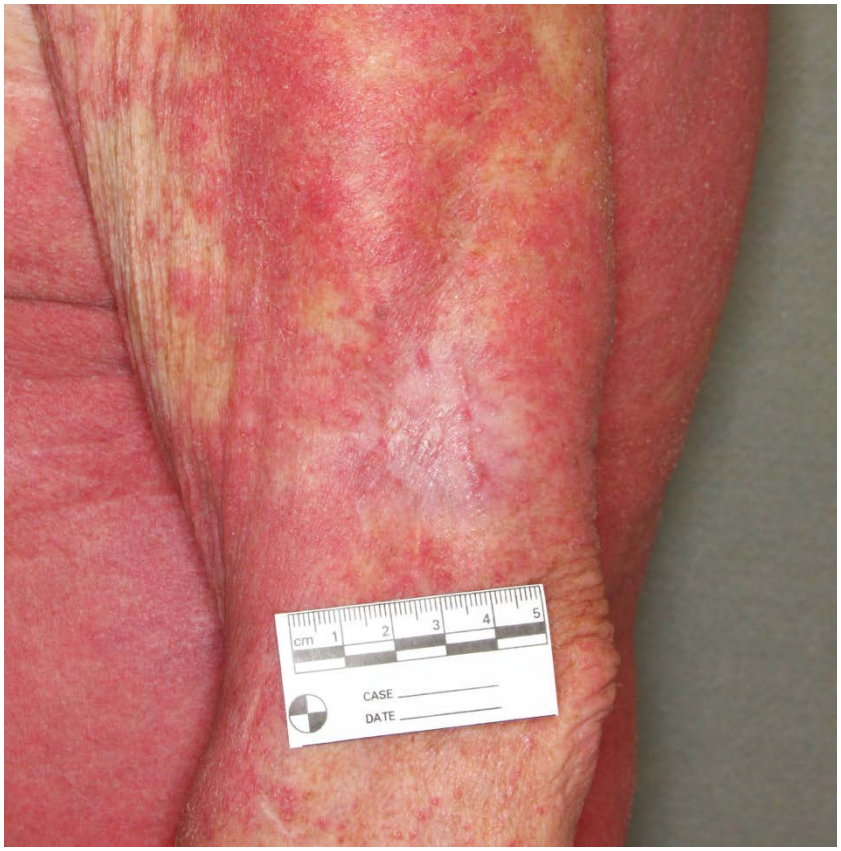


87 yo M with MF IIB, LCT

Screening



Cycle 6

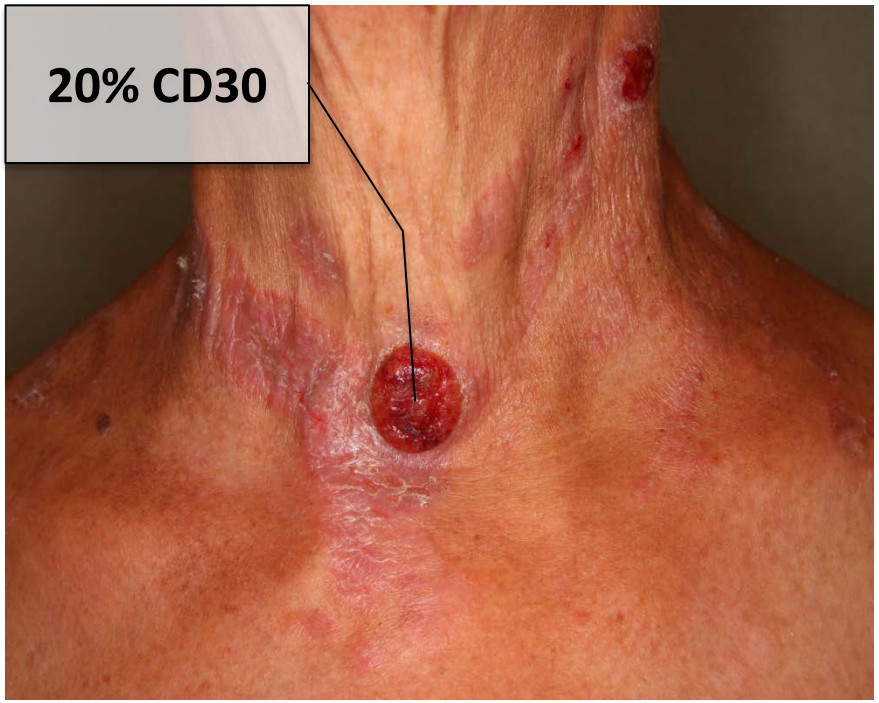


Subject 12: 66 yo F with MF IVB, LCT w/ oropharyngeal involvement

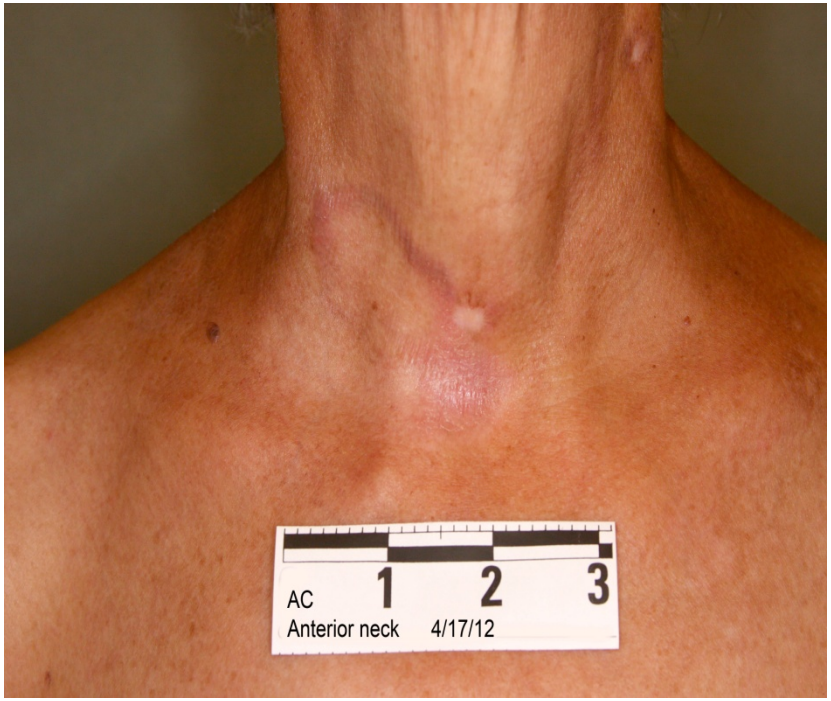
Group B (10-50%): Max CD30 TLI 20%

Best Response: PR

Screening

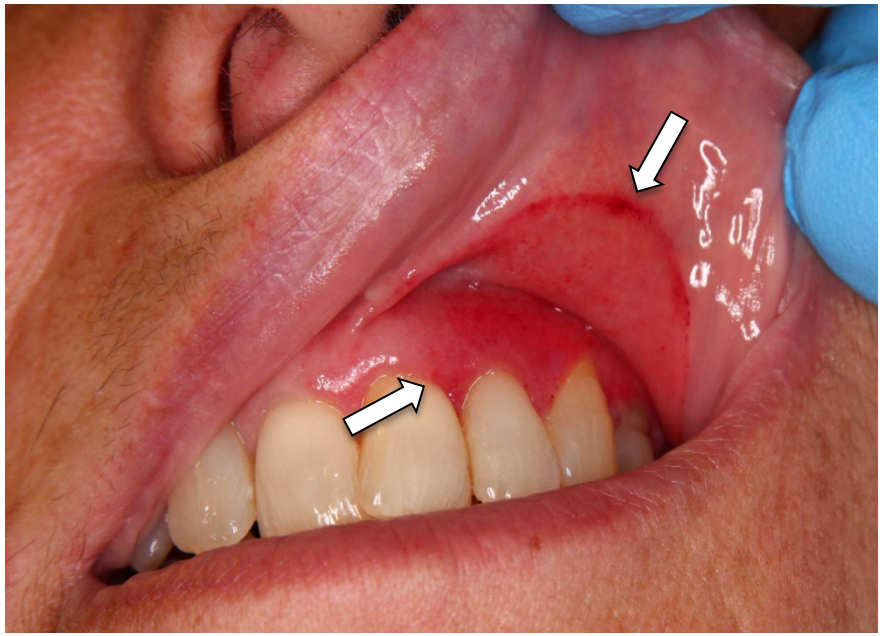


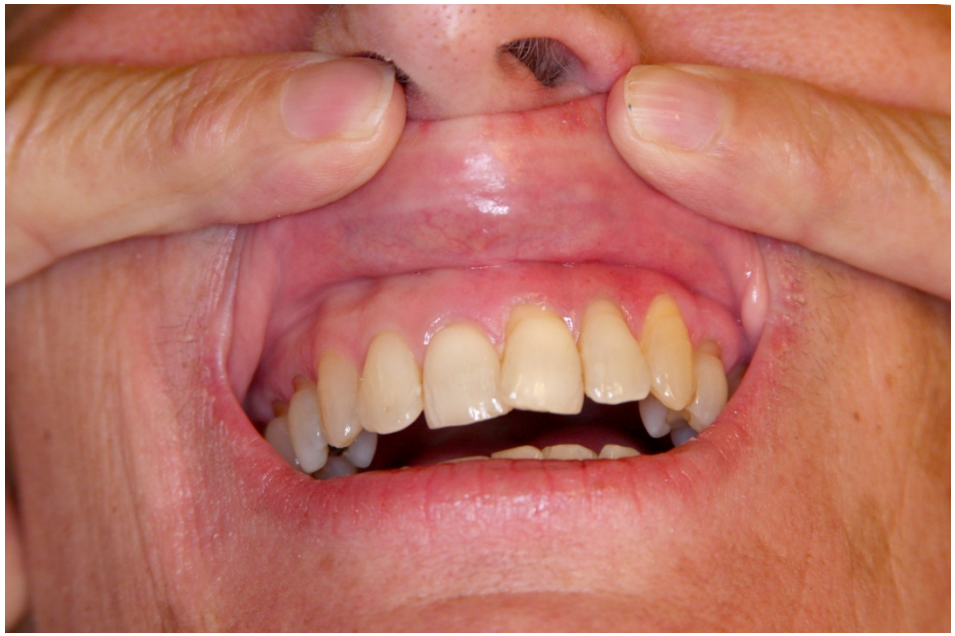
Cycle 10

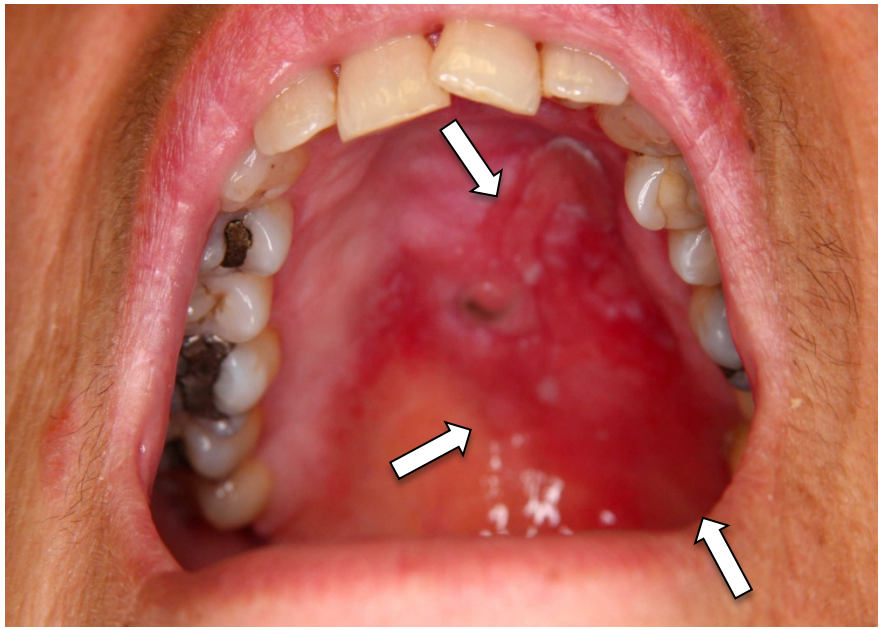


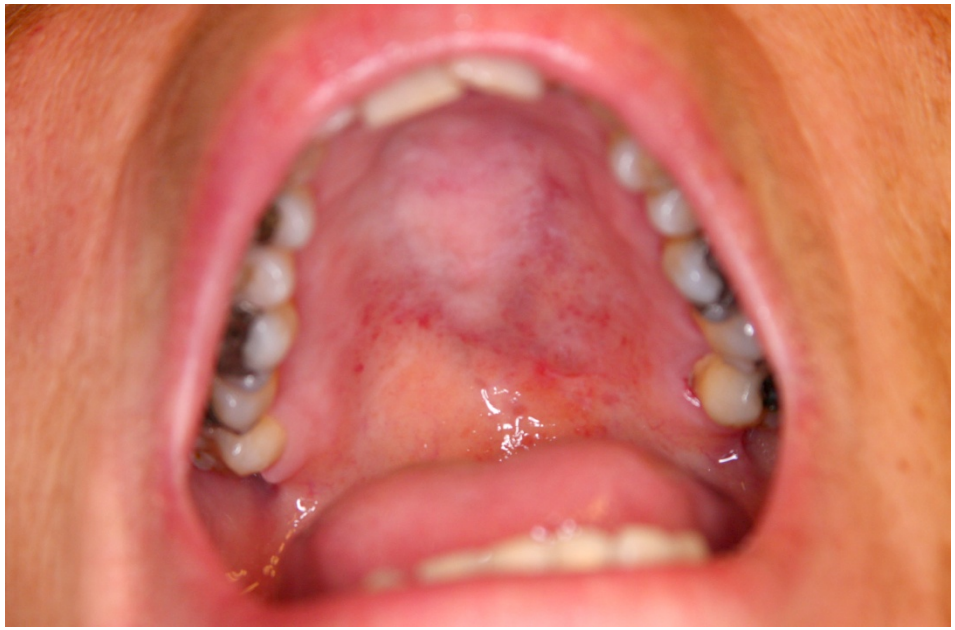
Screening

Cycle 10





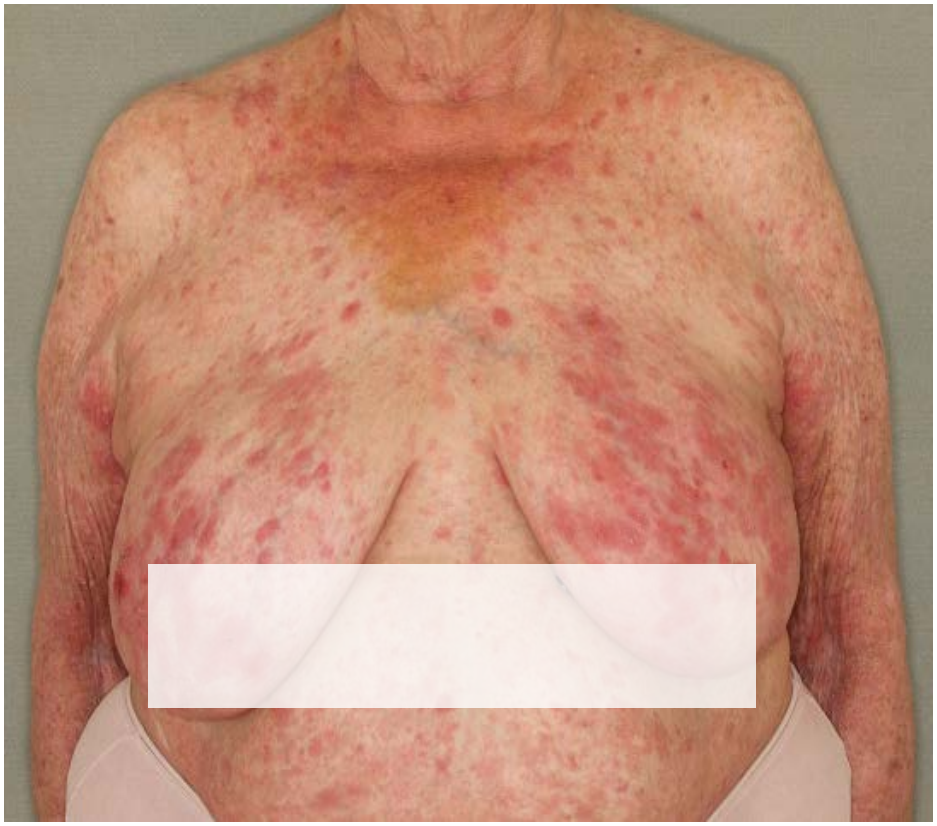




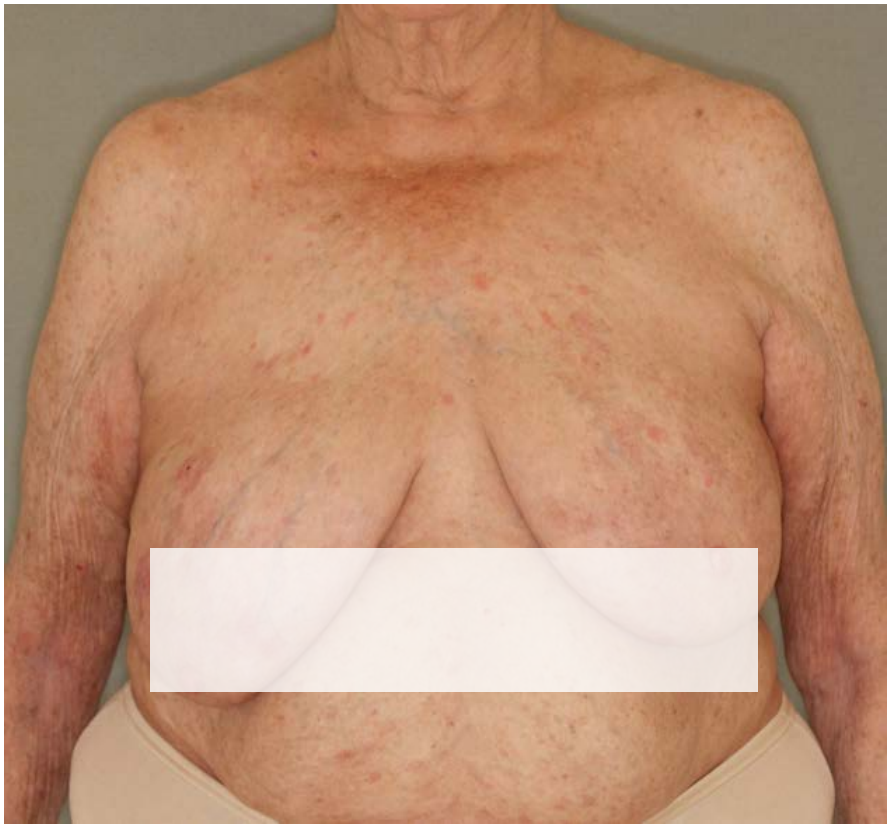
78 yo F, IVA1 (SS)

Max CD30 TLI 60%: Group C (>50%)

PR; mSWAT reduction 81% post 1 cycle



Screening

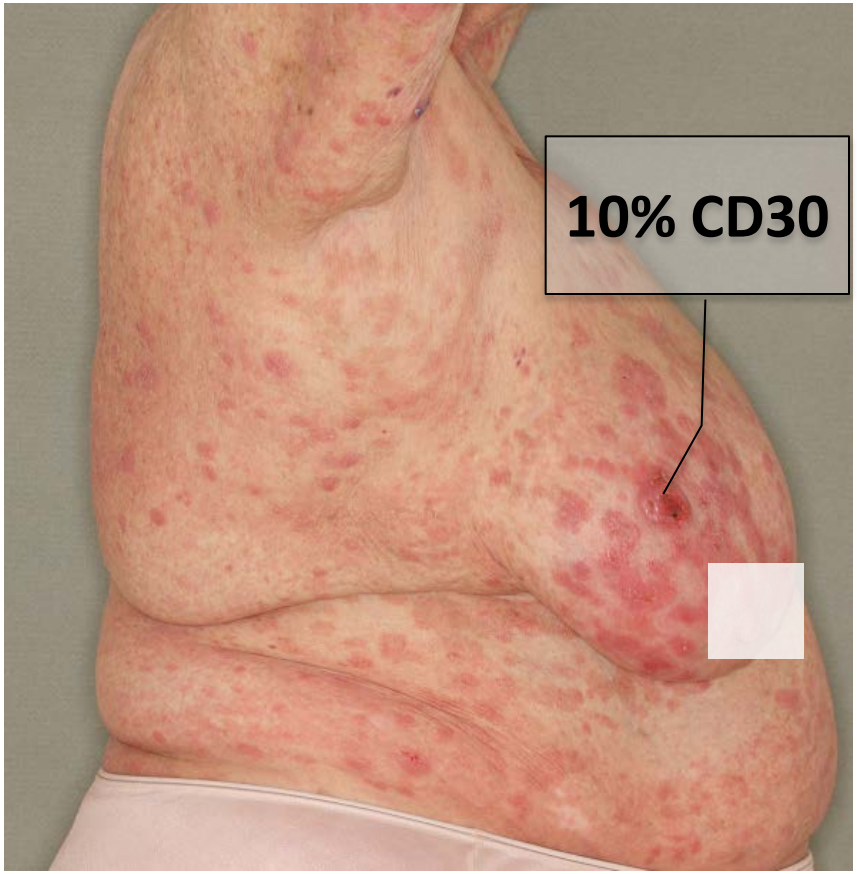


Pre Cycle 2

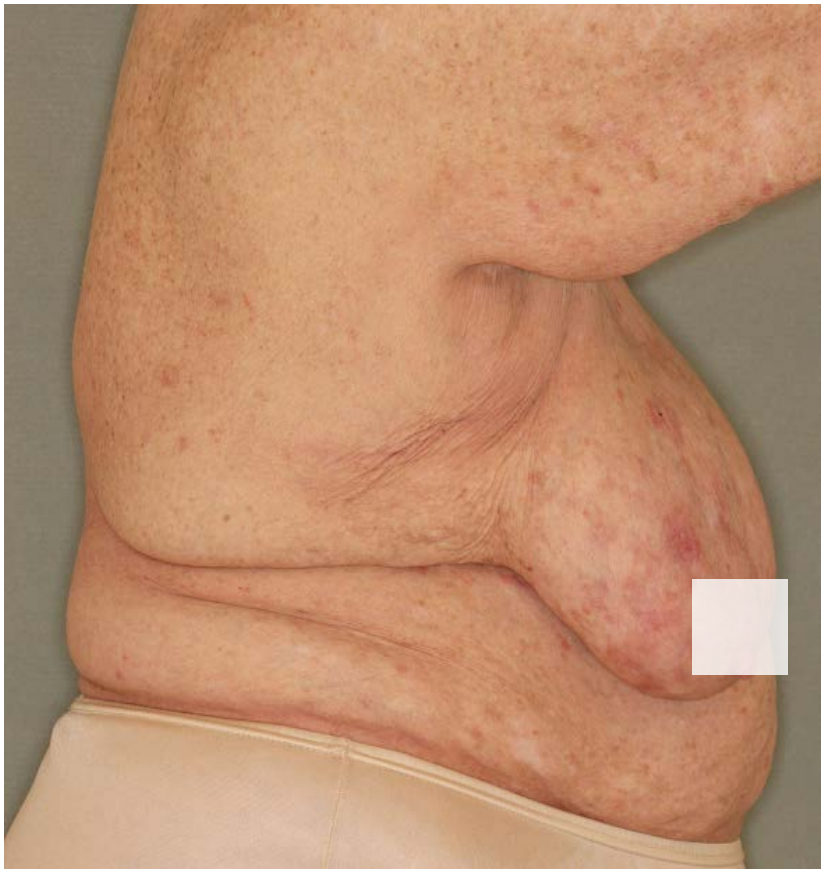
78 yo F, IVA1 (SS)

Max CD30 TLI 60%: Group C (>50%)

PR; mSWAT reduction 81% post 1 cycle



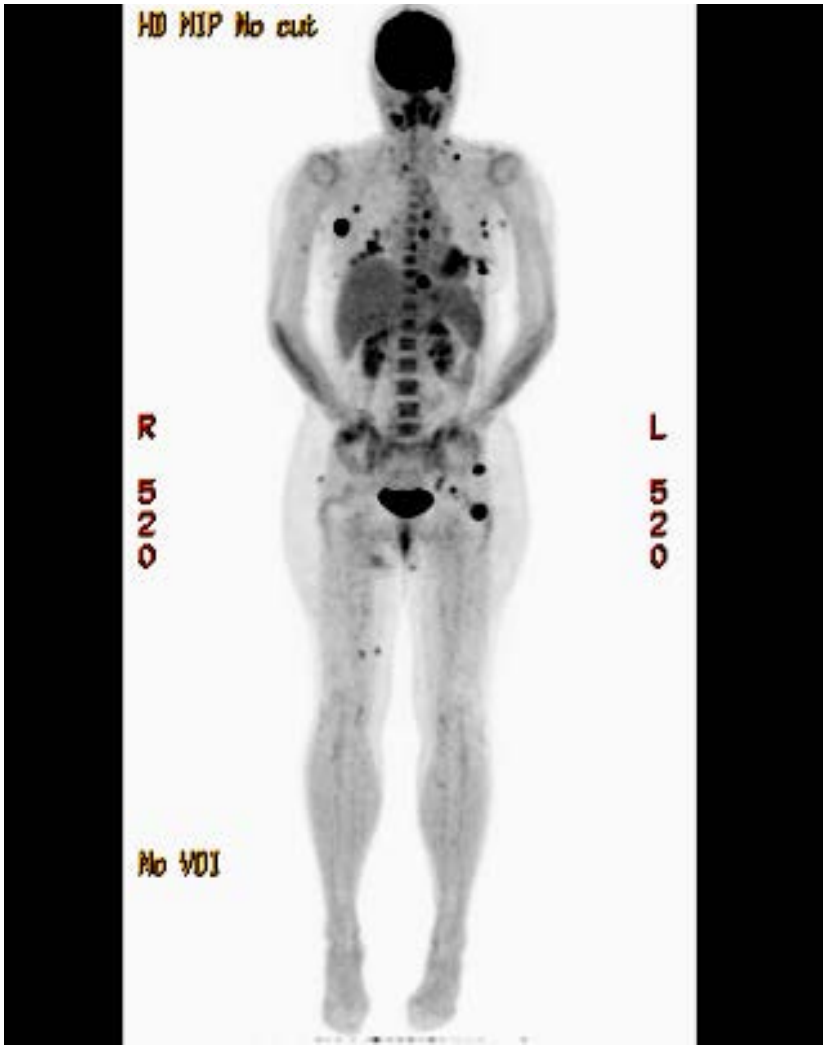
Screening



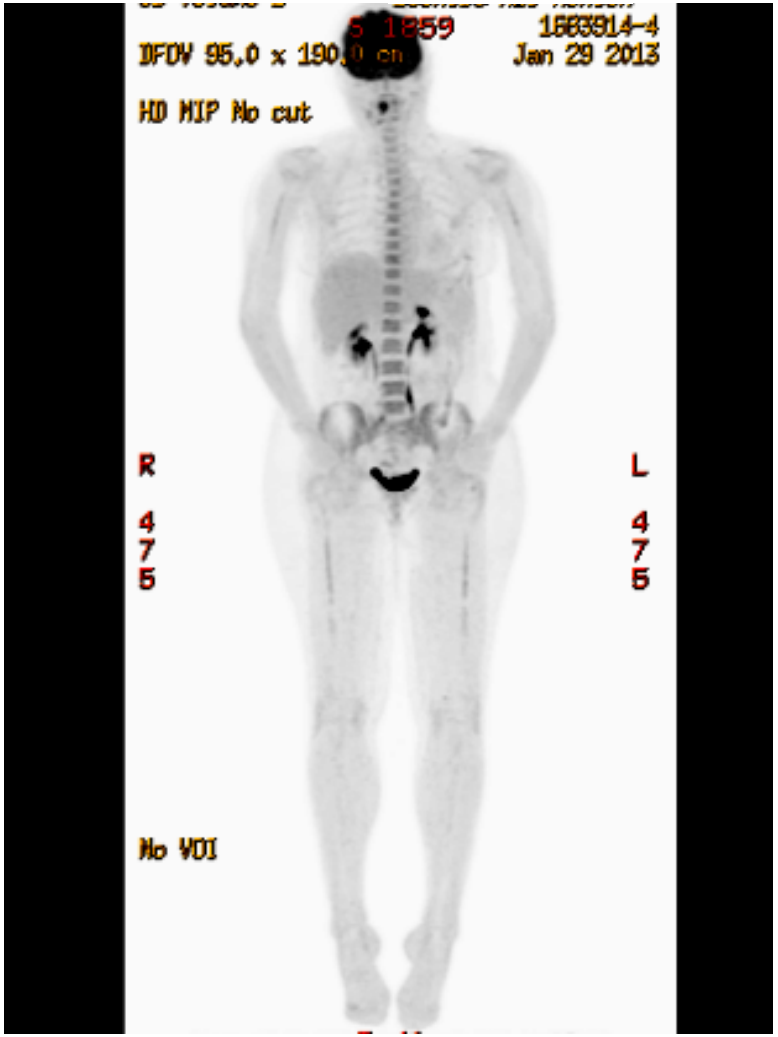
Pre Cycle 2

51 yo F stage IVA2 MF with LCT in skin/LNs: response to brentuximab vedotin

Pre-treatment 12/20/2012



Post 2 cycles 1/29/2013



Common Related Adverse Events; n= 20 (≥20%)

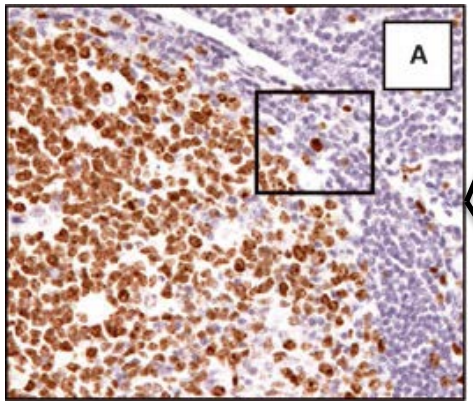
Adverse Event	Rate
Peripheral Neuropathy	75%
Fatigue	60%
Decreased Appetite	30%
Nausea	25%
Alopecia	20%
Dyspepsia	20%
Skin eruption	20%

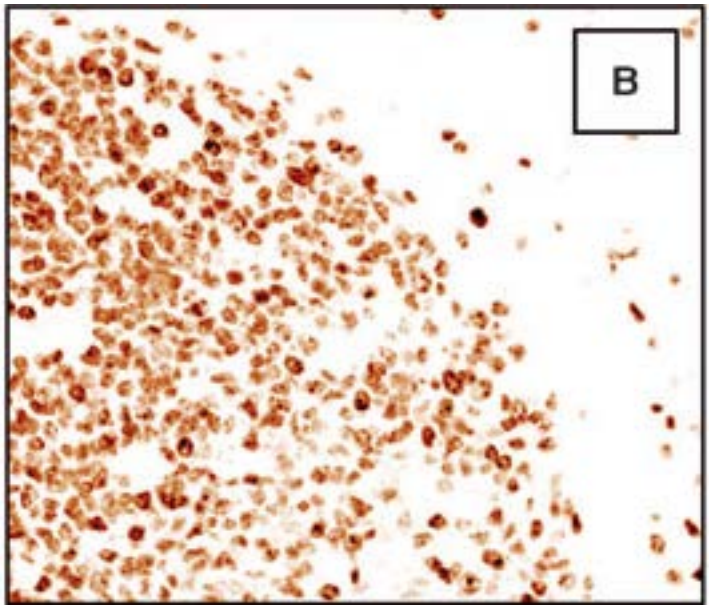
Mostly grade 1-2
2 pts with CLA+, CCR4+ lymphocytosis
1 death, grade 4 neuropathy
No PML

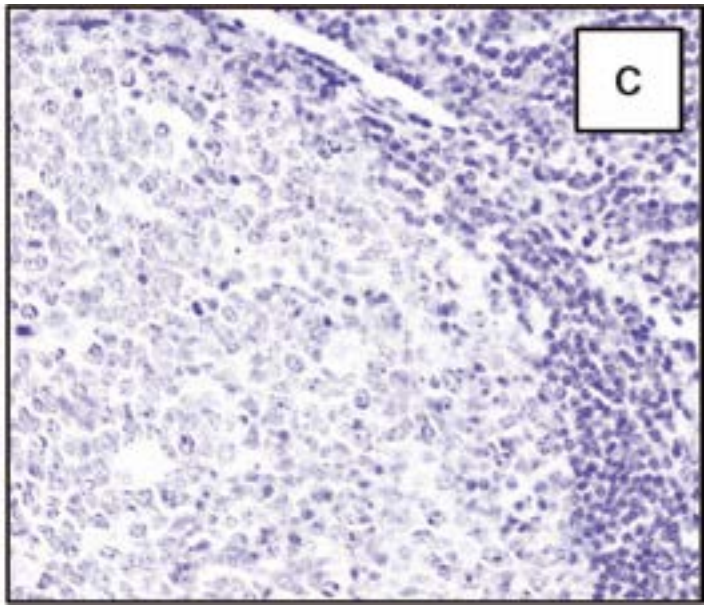
Tissue CD30 expression: key findings

- Response rate independent of CD30% by routine IHC (FFPE)
- CD30 expression variable - even within same patient
- Clinical response observed in subjects w/ non-detectable CD30 via routine IHC
- Question:
  - Can we assess target molecule with improved sensitivity over IHC?

Multispectral Imaging Analysis (Nuance™)





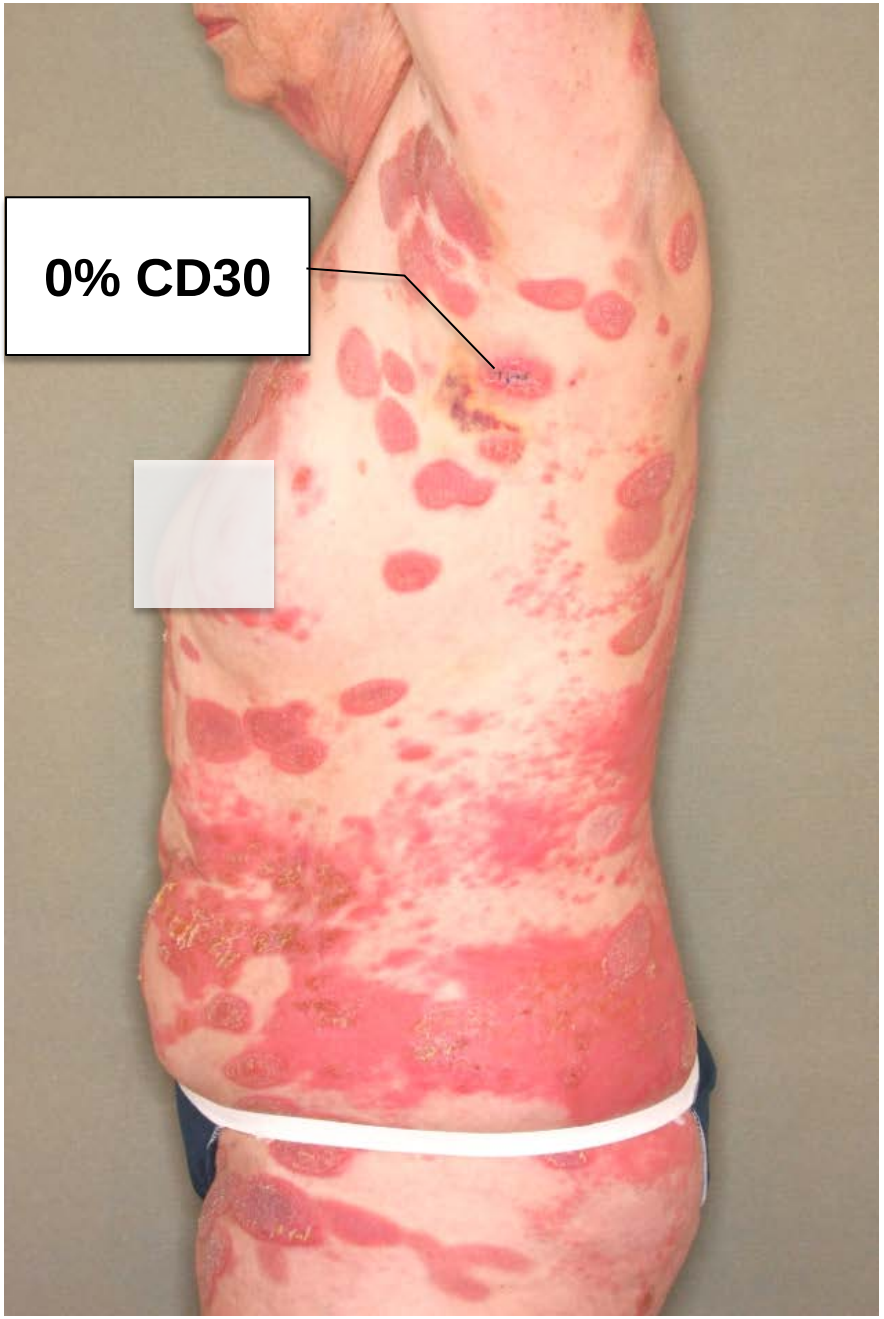


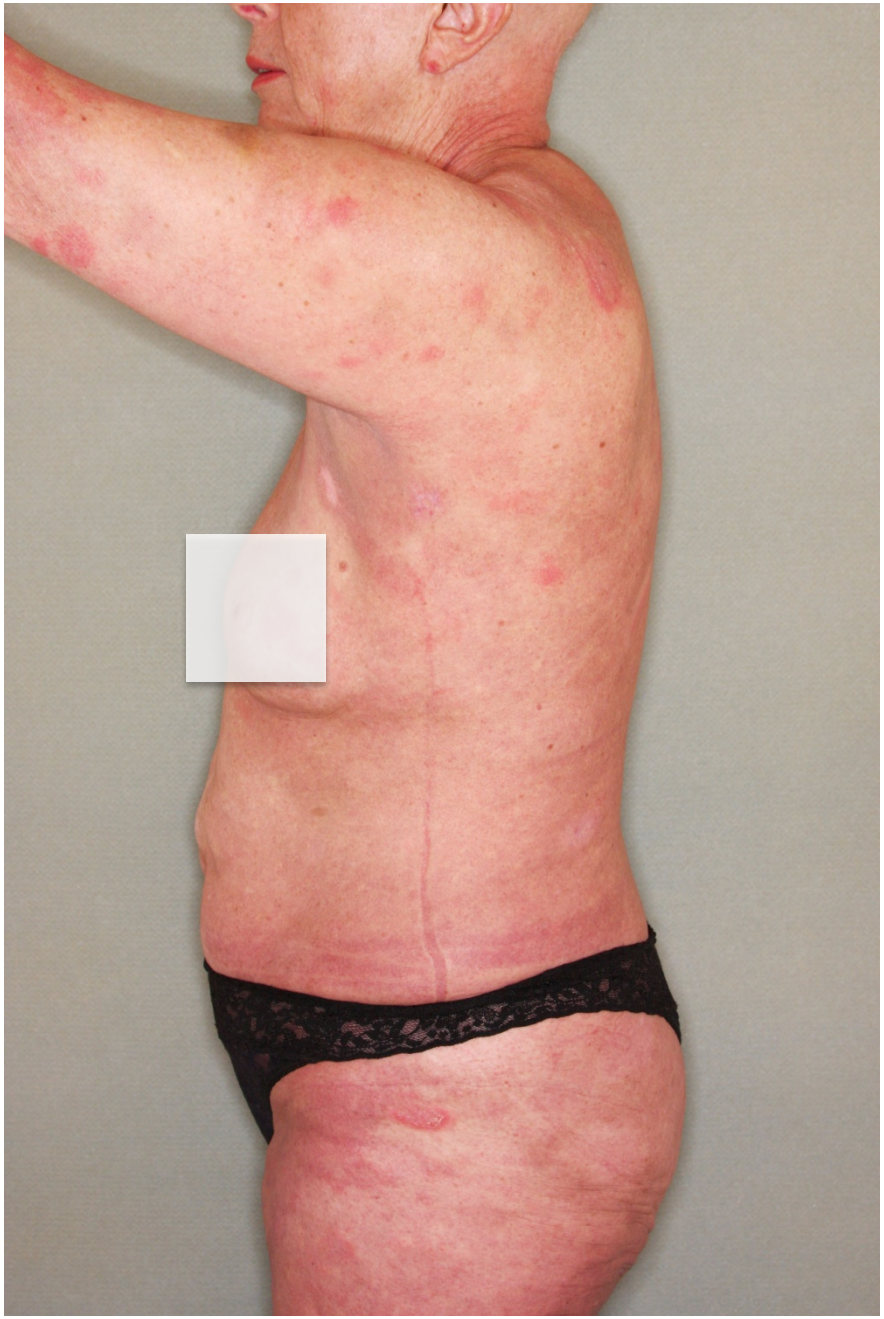
- Quantitative:
  - Optical Density (OD)
- Multispectral imaging
- Up to 14 channels

Taylor & Levenson: Quantification of Immunohistochemistry, Histopathology 2006, 49, 411-424.

Baseline

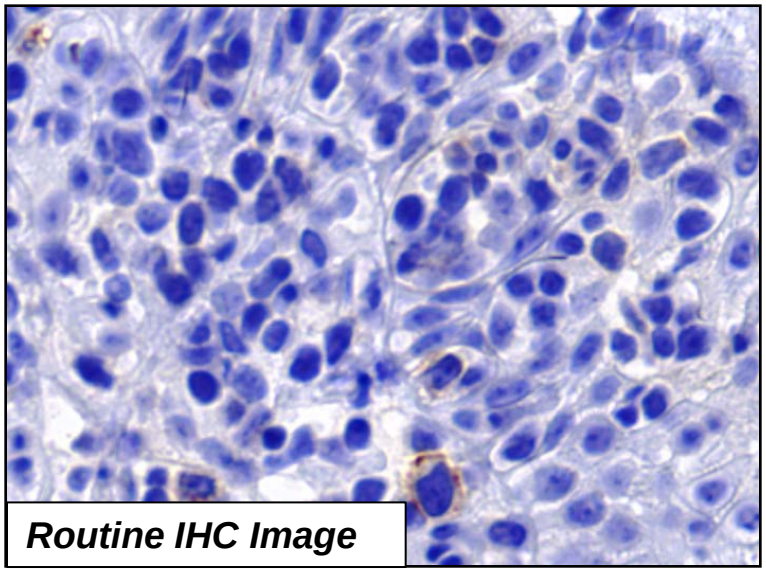
Cycle 8



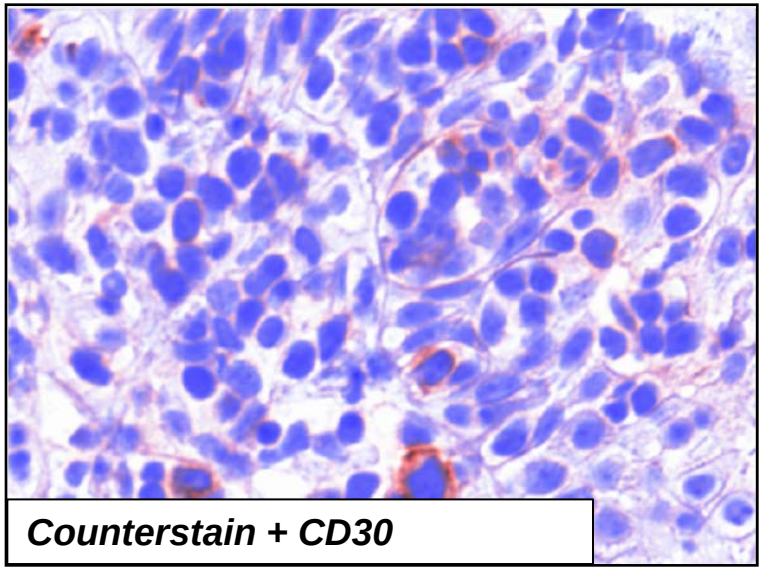


Subject 1, Screening Bx, Left Chest

IHC: TLI 0 Nuance: Avg. OD/cell: 0.042; Avg. Max OD/cell: 0.111

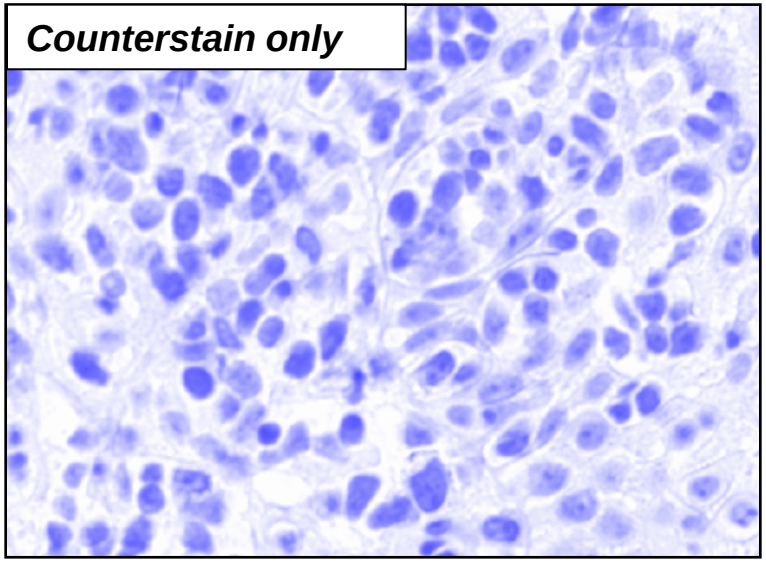


Routine IHC Image

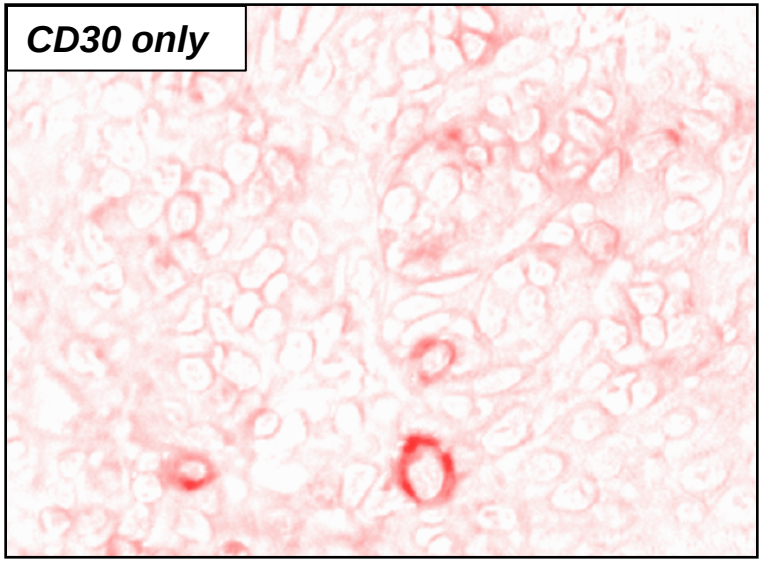


Counterstain + CD30

Counterstain only



CD30 only



Summary and Conclusions

- Brentuximab vedotin shows significant clinical activity (RR 74%) in refractory and advanced MF/SS
- Encouraging DOR with KM estimates at 6 mo 78% maintaining response & EFS median 31 weeks (range 4-61+)
- Well tolerated with mostly G1/2 AEs

Summary and Conclusions

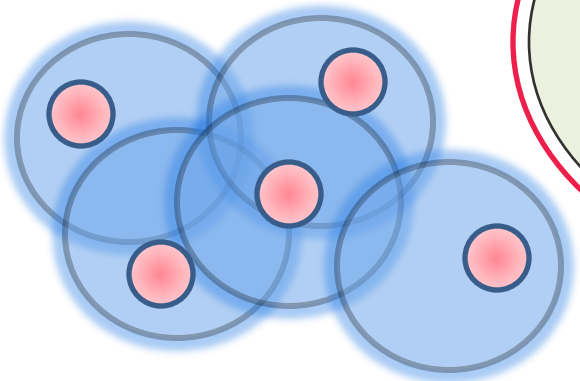
- No correlation w/ CD30 expression assessed by routine IHC and clinical response
- CD30 target identified in non-detectable tissue samples (routine IHC) via computerized detection software analysis (improved sensitivity)

Phase III RCT in CTCL for approval in US and Europe in progress (Millennium)

Targets for therapy in cutaneous T-cell lymphoma

Tumor cell surface molecules
(e.g., CD4, CD25, CD30, CD40, CD52, CD158k, CCR4)

CTCL



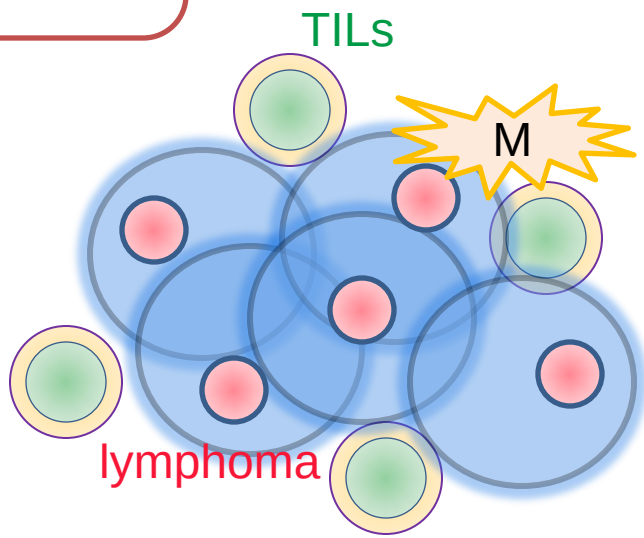
Microenvironment, immune mechanisms
(e.g., vasculature, immune modulation)

Tumor proliferation, metabolism, survival, progression mechanisms:
Signal transduction/transcription activation pathways *(e.g., ubiquitin-proteasome, AKT/PI3K/mTOR, RAS/RAF/MEK, MAPK)*
Apoptotic pathways *(e.g. Bcl/Bax, TNFR, Fas, miRNAs)*
Epigenetics *(e.g., histone, non-histone proteins)*
Metabolic/survival pathways *(e.g., RFC-1, PARP)*

Immunotherapy strategies in cancer

Tumor-specific monoclonal antibodies

Cytokine therapy



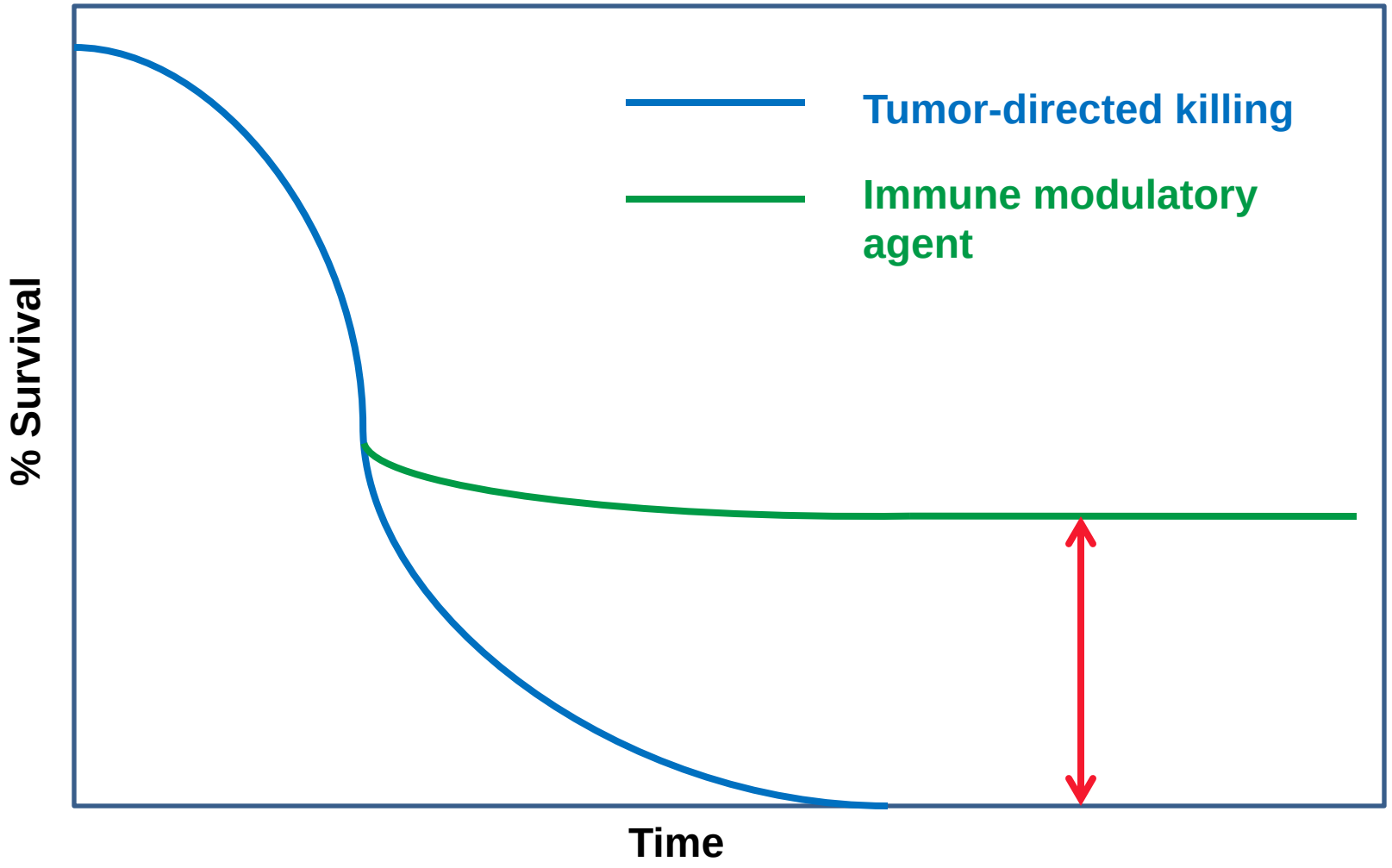
Adoptive T-cell transfer

Immune-modulating agents or antibodies

Allogeneic HSCT

Vaccine-based approaches

Induction of long-lasting responses and improving survival with partnering with immune strategies



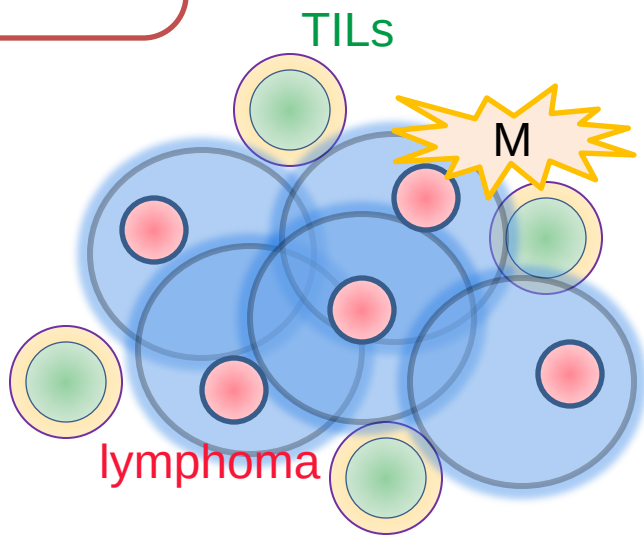
Immunotherapy strategies in cutaneous lymphoma

CD4,
CD20,
CD25,
CD30,
CCR4

Tumor-specific monoclonal antibodies

Cytokine therapy

IFNs, IL2,
IL12



Adoptive cell transfer

Immune-modulating agents or antibodies

TLR-A
IMiDs
Tregs
CTLA4
PD-1
PD-L1

Allogeneic HSCT

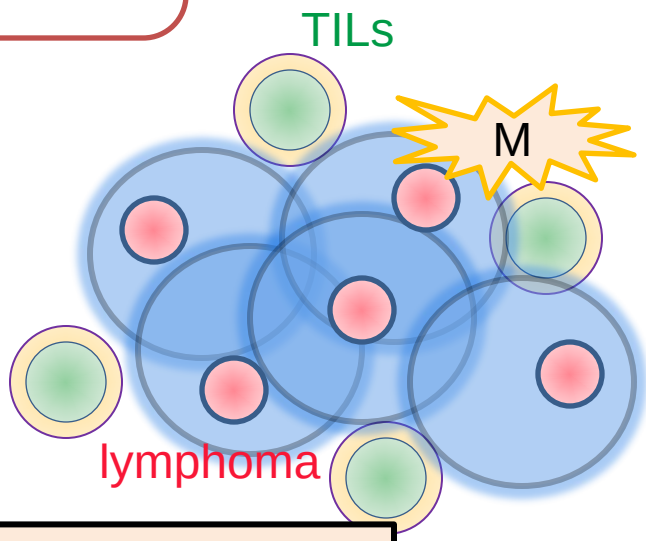
Vaccine-based approaches

ECP
DC-based
Idiotype
In situ strategy

Immunotherapy strategies in cutaneous lymphoma

Tumor-specific monoclonal antibodies

Cytokine therapy



Adoptive cell transfer

Immune-modulating agents or antibodies

Allogeneic HSCT

TLR-A
IMiDs
Tregs
CTLA4
PD-1
PD-L1

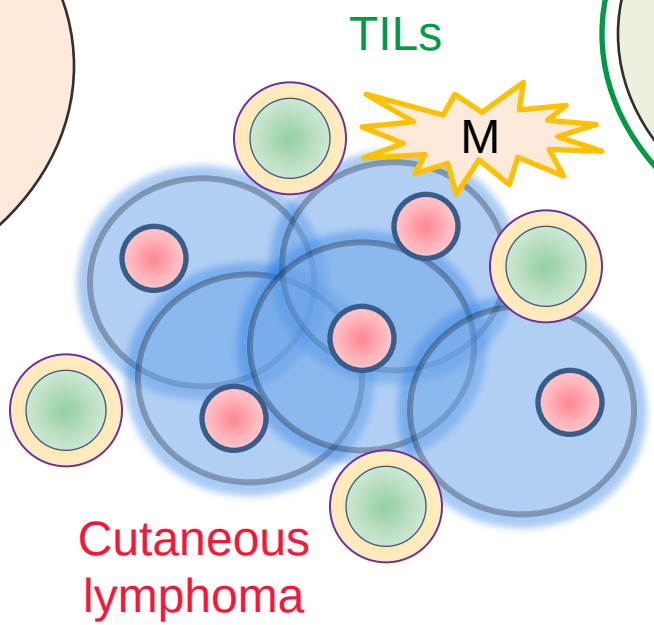
Imiquimod
Resiquimod
Lenalidomide

Immune modulation of tumor microenvironment with mAbs

Monoclonal antibodies

Tumor cell-specific:
tumor surface molecules
(e.g., CD4, CD19, CD20, CD22, CD25, CD30, CD40, CD52, CD158k, CCR4)

Microenvironment Immune modulation
(e.g. CTLA4, PD-1, PD-L1, IDO, Tregs)



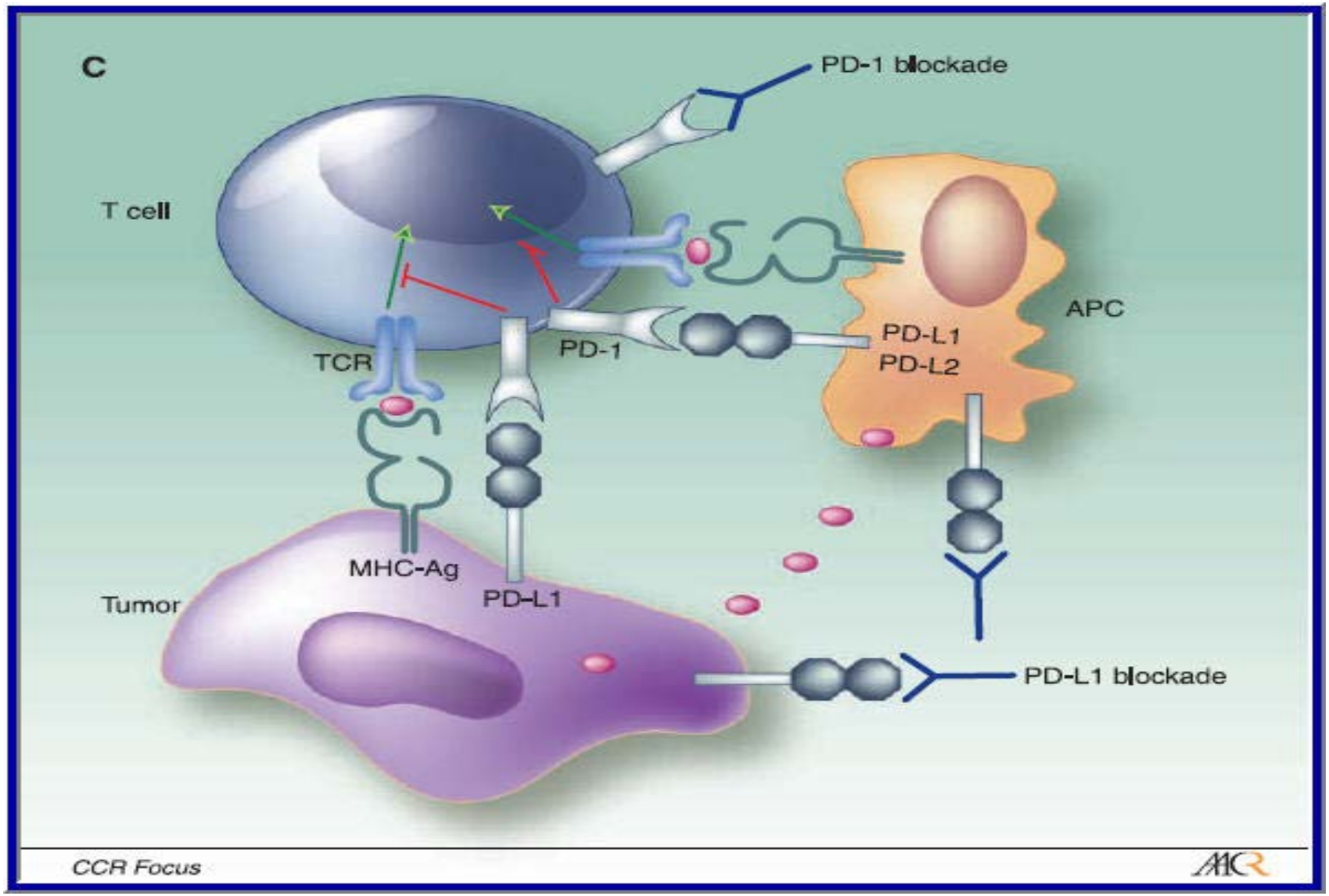
Modulating microenvironment & immune mechanisms

Agent	Target	Conjugate	Disease
Bevacizumab	VEGF	--	lymphoma
Endostatin	Endothelial cell	--	lymphoma
Ipilimumab	CTLA-4	--	Solid tumor/lymphoma
Lenalidomide	Multiple	--	Hematologic malignancies
TLR agonists	TLR	--	lymphoma
Anti-PD-1 mAbs	PD-1	--	Solid tumor/hematolymph
Anti-PD-L1 mAbs	PD-L1	--	Solid tumor/hematolymph
IDO inhibitors	IDO+ DCs, tumor	--	Solid tumor/hematolymph

Renewed interest in immunotherapy

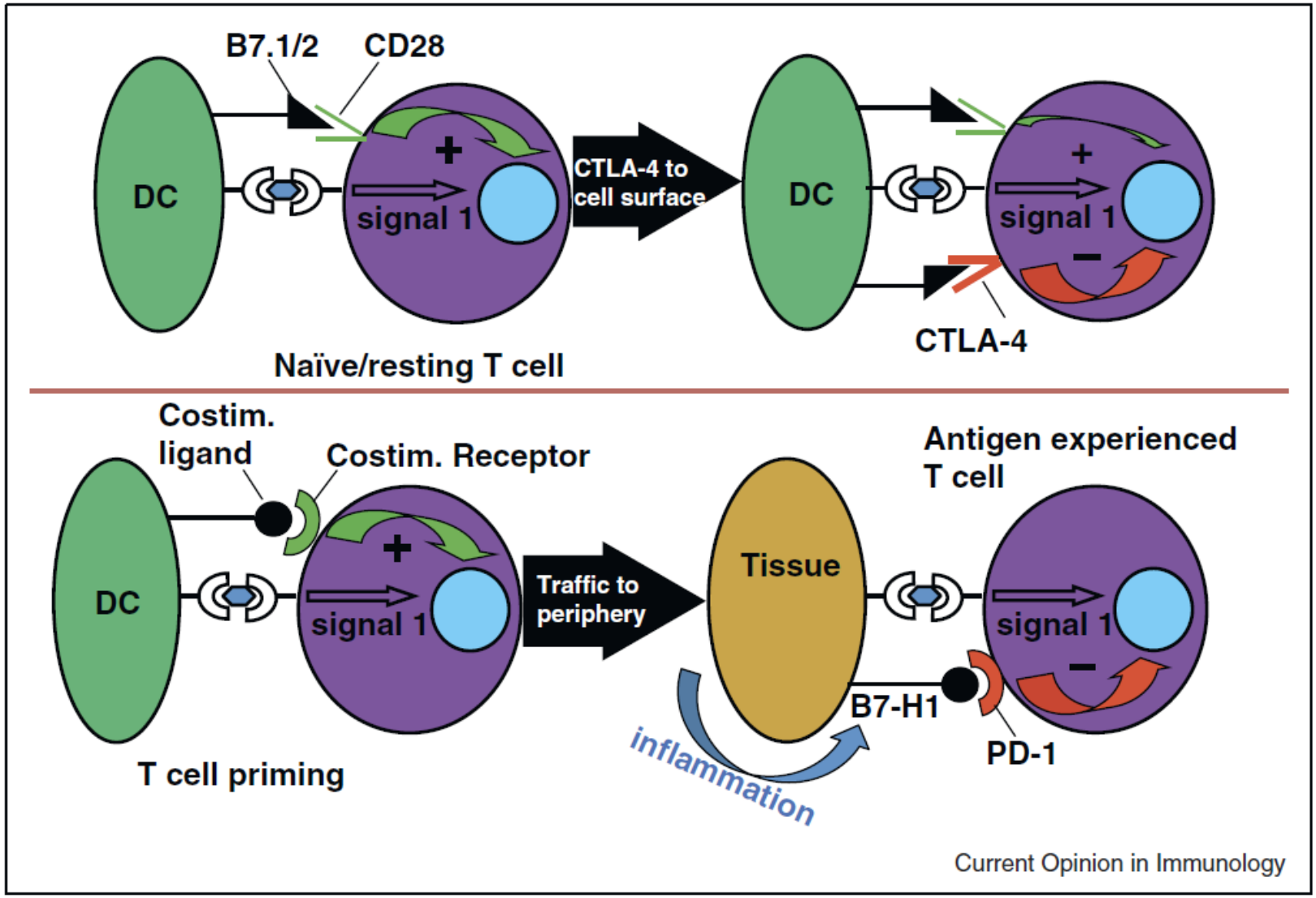
Ann Oncol 2010;21:683, J Pathol 2010;220:404, 509, Lancet Oncol 2010;11:1074

Programmed Death-1 (PD-1) and ligands B7-H1/PD-L1 and B7-DC/PD-L2: Pivotal role in maintaining immunosuppressive tumor microenvironment



Curr Opin Immunol 2012;24:207

Immune checkpoint blockades: CTLA-4 vs. PD-1



Topalian et al, Curr Opinion Immunol 2012;24:207

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

Safety,
of A

Suzanne L. Topalian, M.D.
David C. Smith, M.D., Davi
Jeffrey A. Sosman, M.D.,
Scott J. Antonia, M.D., Ph.D., L
Lieping Chen, M.D., Ph.D., Wil
Tracee L. McMiller, M.S., Haiying
Daniel McDonald, M.B.A., C

The NEW ENGLAND JOURNAL of MEDICINE

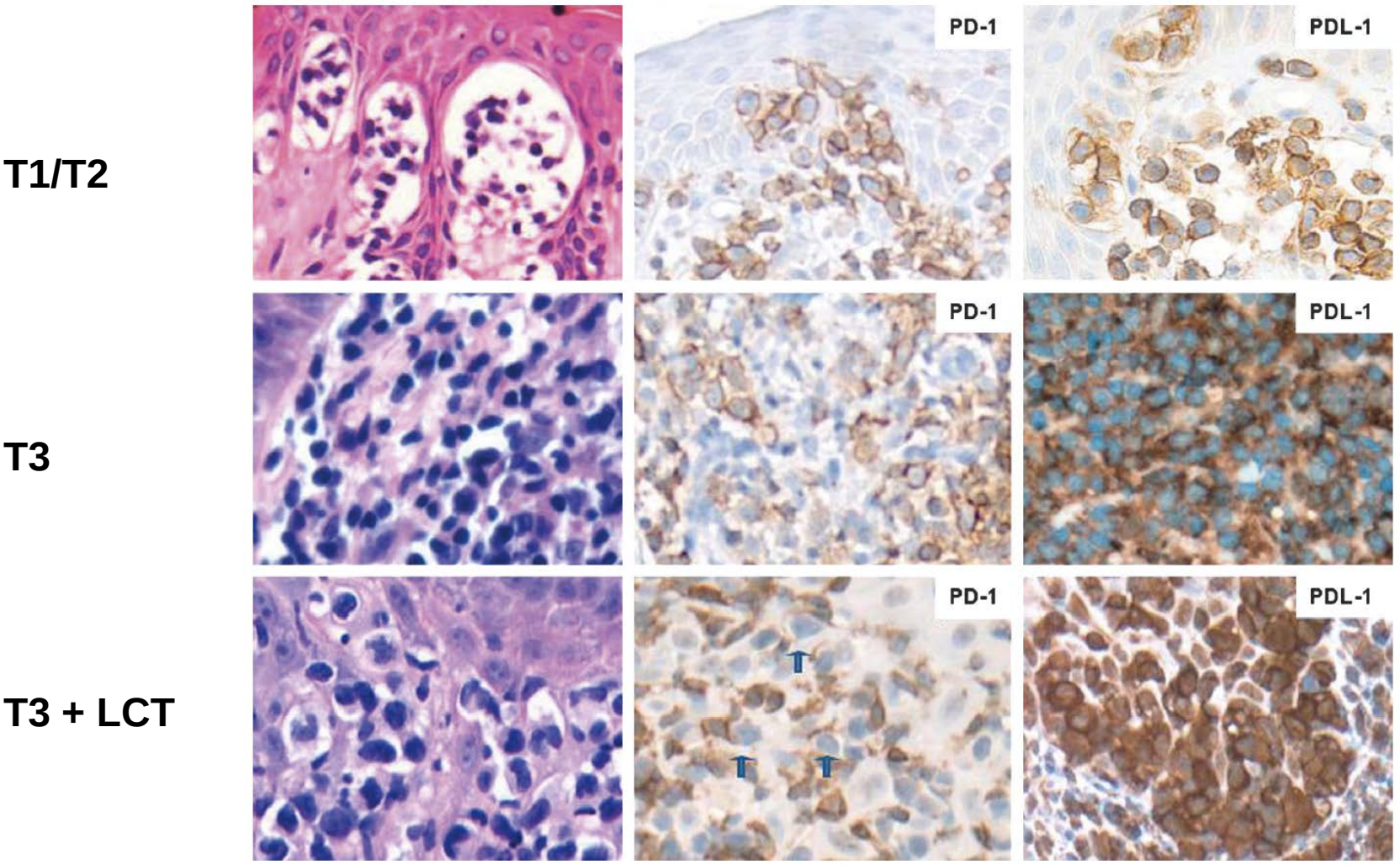
ORIGINAL ARTICLE

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthy, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.

N Engl J Med 2012;366:2455-65.

Expression of PD-1 and PD-L1 in MF skin tissue: Inverse correlation of PD-1 and PD-L1 with disease severity



Am J Dermatopathol 2012:34:126

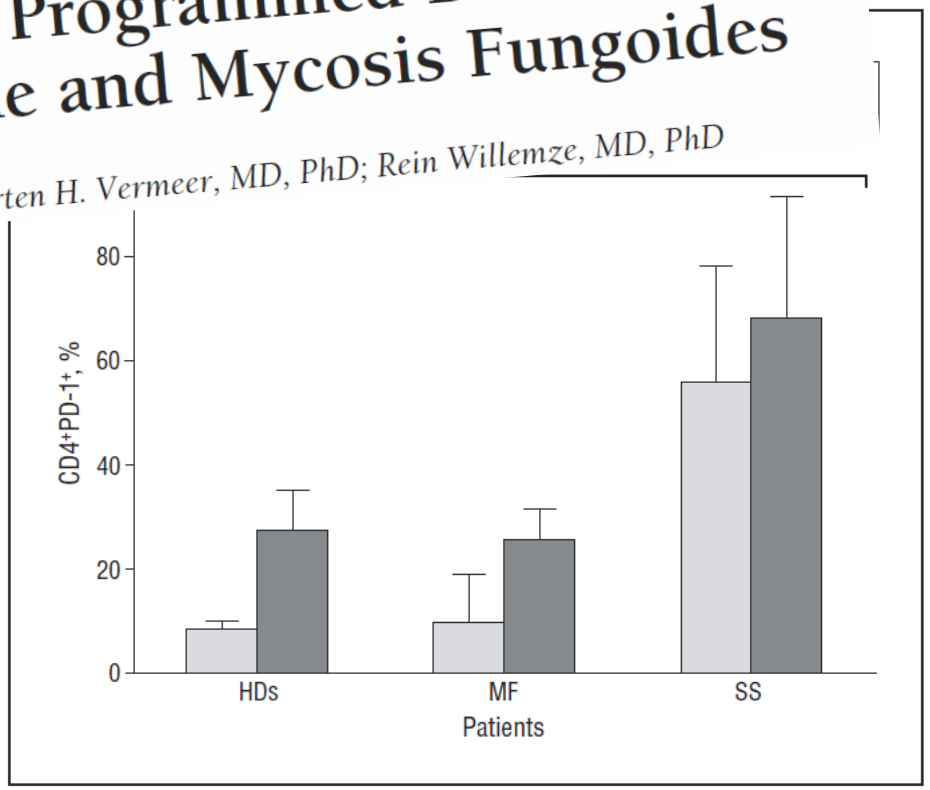
TABLE I. PD-1 Expression in CTCL Determined by Immunohistochemistry

Disease subtype	PD-1-positive cases (%)	Mean (range) percentage of PD-1-positive tumor cells[a]
Patch/plaque mycosis fungoides (n = 15)	6 (40)	78 (60–95)
Generalized or tumor		

STUDY

Differential Expression of Programmed Death-1 (PD-1) in Sézary Syndrome and Mycosis Fungoides

Fatma Çetinözman, MD; Patty M. Jansen, MD, PhD; Maarten H. Vermeer, MD, PhD; Rein Willemze, MD, PhD



PD-1 blockade enhanced IFN-gamma production

Rook's group

Arch Dermatol 2010;146:1382

Anti-PD1/PD-L1 mAbs in clinical development

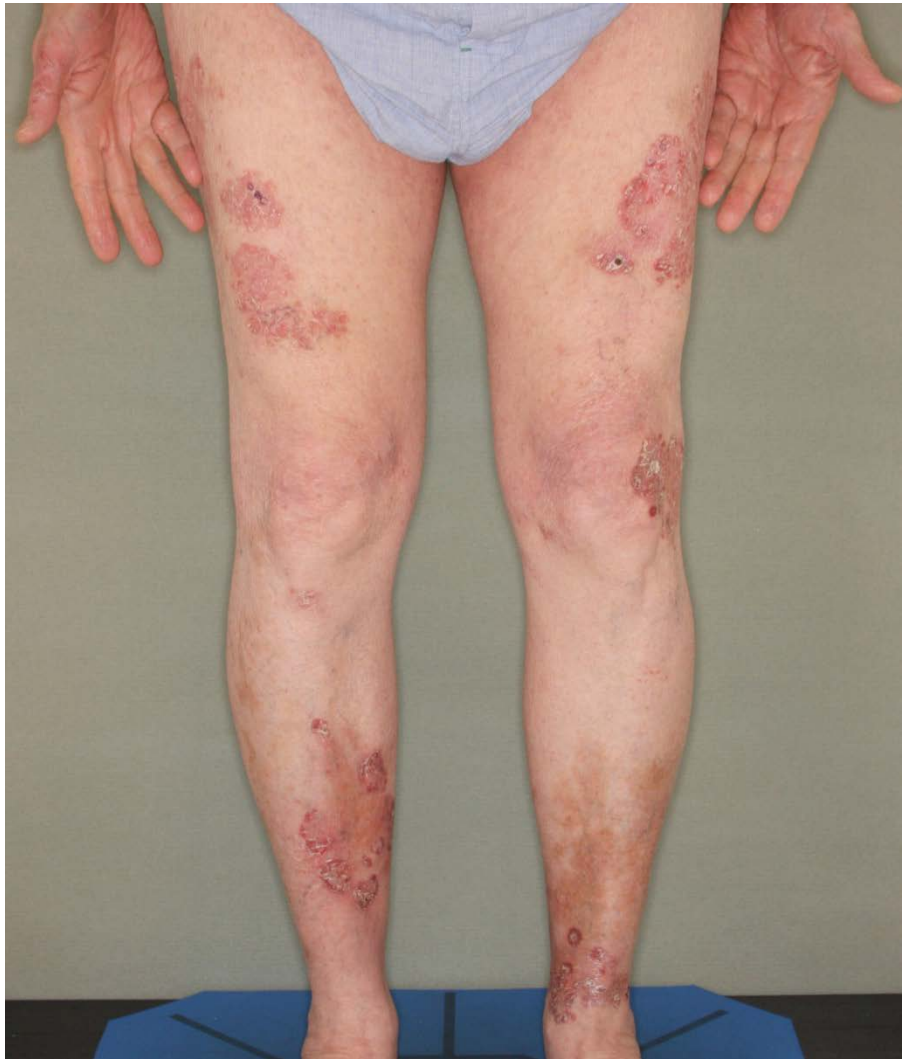
- MDX-1105/BMS-936559, MDX-1106/BMS-936558 (Medarex/Bristol-Myers Squibb), MK-3475 (Merck), CT-011 (Cure Tech/Teva), AMP-224 (Amplimmune/GSK)

Anti-PD-L1 mAb opened for enrollment at Stanford:

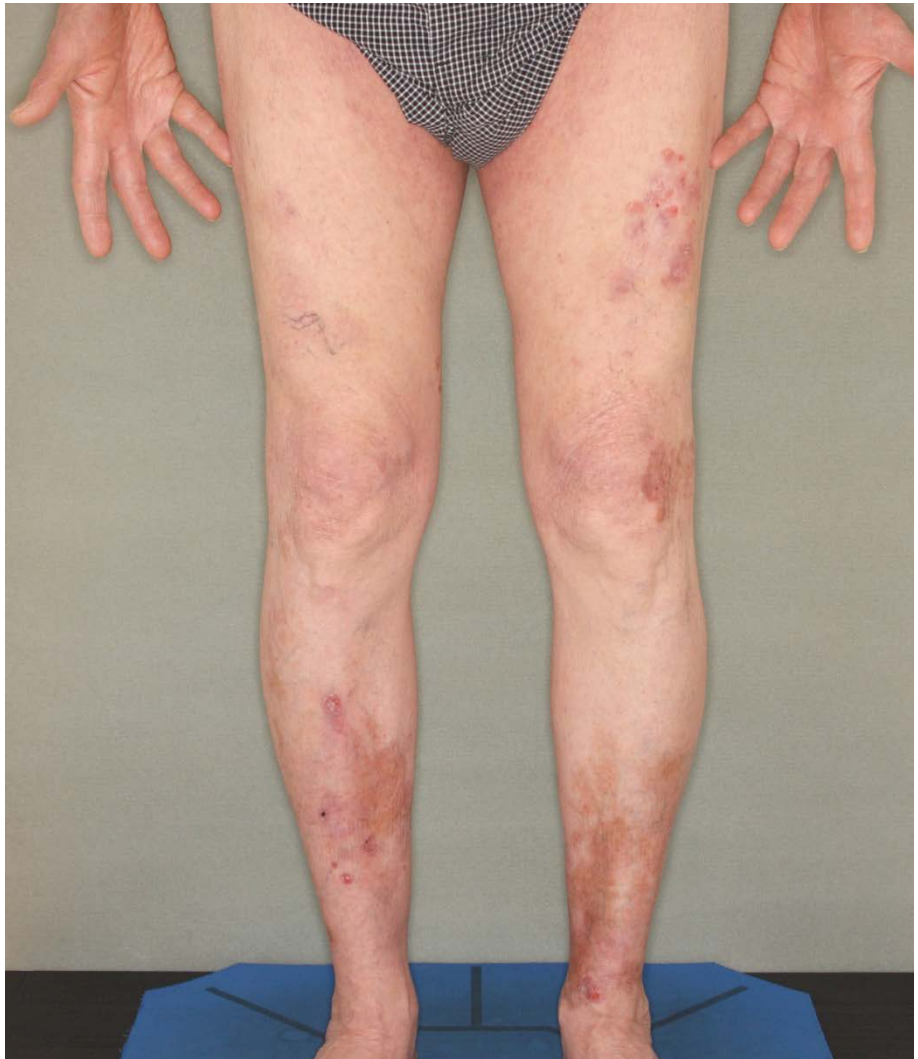
- A phase I, open-label, dose-escalation study of the safety and pharmacokinetics of MPDL3280A administered intravenously as a single agent to patients with locally advanced or metastatic solid tumors or **hematologic malignancies** (Genentech)
- MPDL3280A, a phage-derived human IgG1 mAb
- Targets PD-L1 on APCs or tumor cells, prevents interaction with PD-1 on T-cells

Stage IB MF (h/o phototx, bexarotene, anti-CD4 mAb, forodesine, CpG+RT, lenalidomide, sapacitabine, enzastaurin, TSEBT)

pre-treatment (11/20/2012)

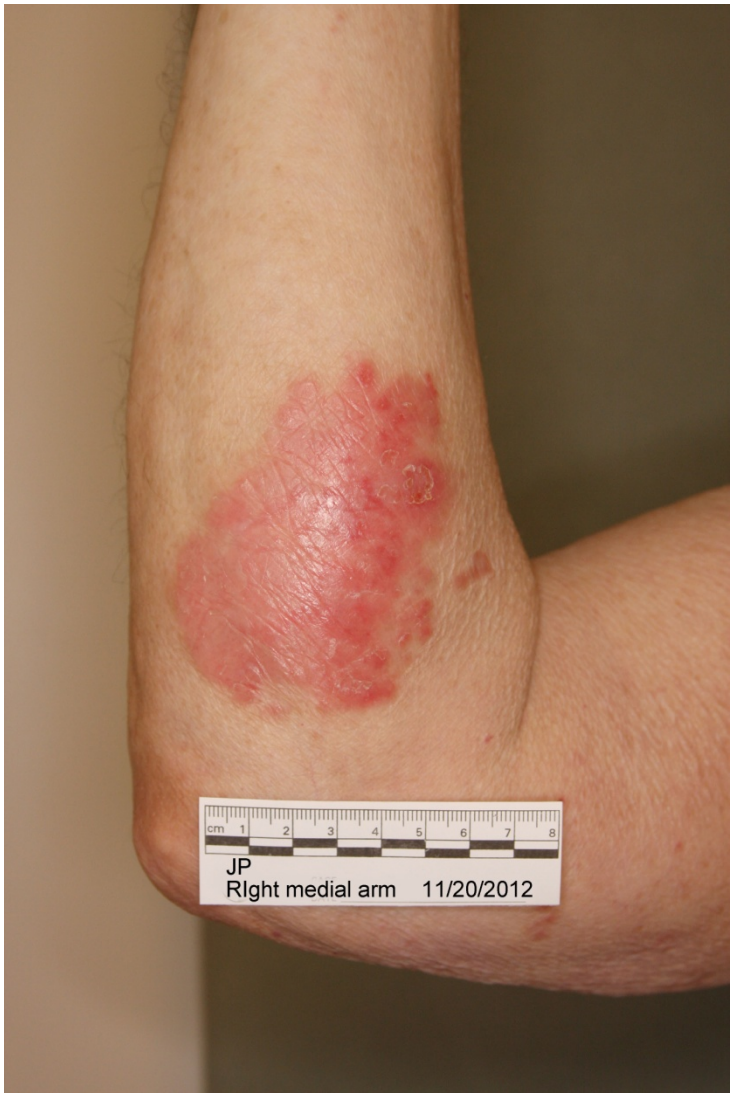


C8D1 (4/23/2013)

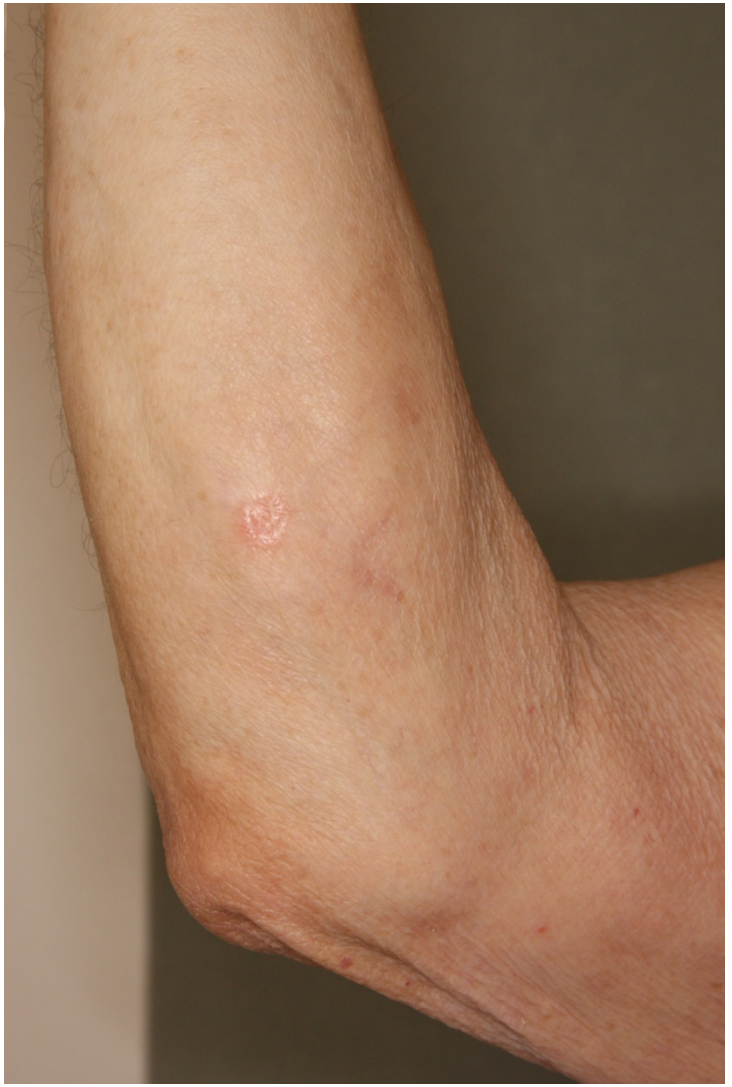


Stage IB MF (h/o phototx, bexarotene, anti-CD4 mAb, forodesine, CpG+RT, lenalidomide, sapacitabine, enzastaurin, TSEBT)

pre-treatment (11/20/2012)



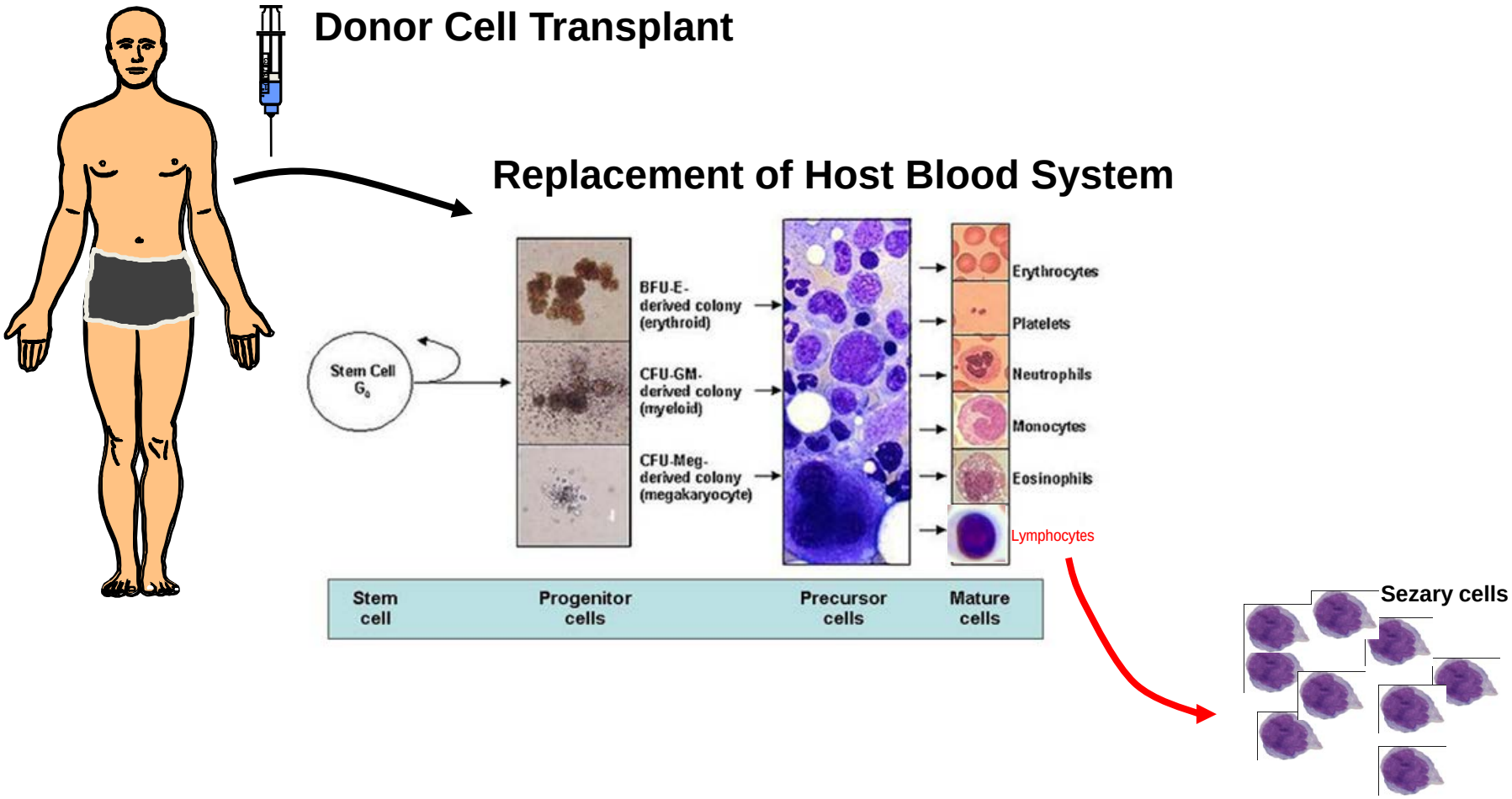
C8D1 (4/23/2013)



Cellular therapy strategies

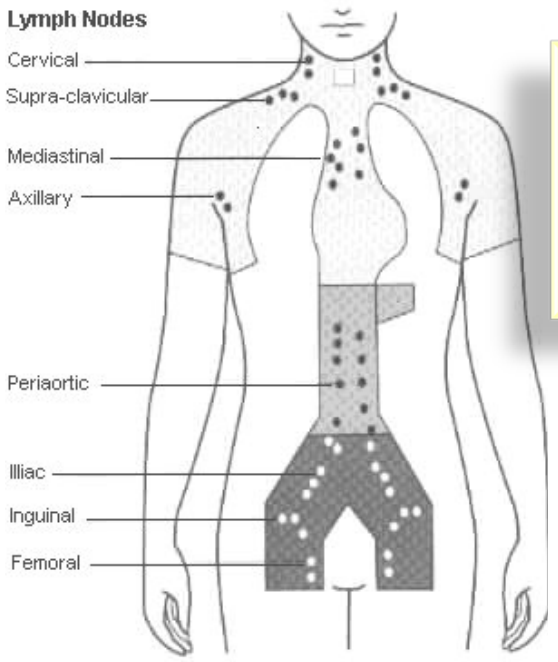
- Adoptive T-cell transfer (autologous)
- **Allogeneic HSCT (graft versus lymphoma)**
- Combination strategies

Harnessing the graft-versus-lymphoma effect in allo HSCT as the ultimate cellular immune therapy



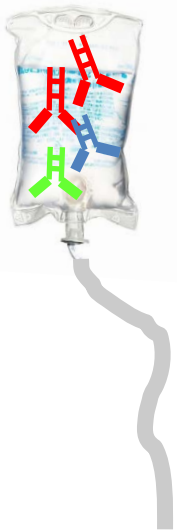
A New Approach in Donor Cell Transplant
Non-Myeloablative Regimen with TLI/ATG
"Protective conditioning"

NEJM 353:1321, 2005
Stanford study on going



TSEBT

+



Inverted Y field

Total Lymphoid Irradiation (TLI)

Anti-Thymocyte Globulin (ATG, Rabbit anti-T cell antibodies)

Enable Donor Cells to Engraft
aGVHD reduced to 2-5% (vs. 20-65%)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 29, 2005 VOL. 353 NO. 13

Protective Conditioning for Acute Graft-versus-Host Disease

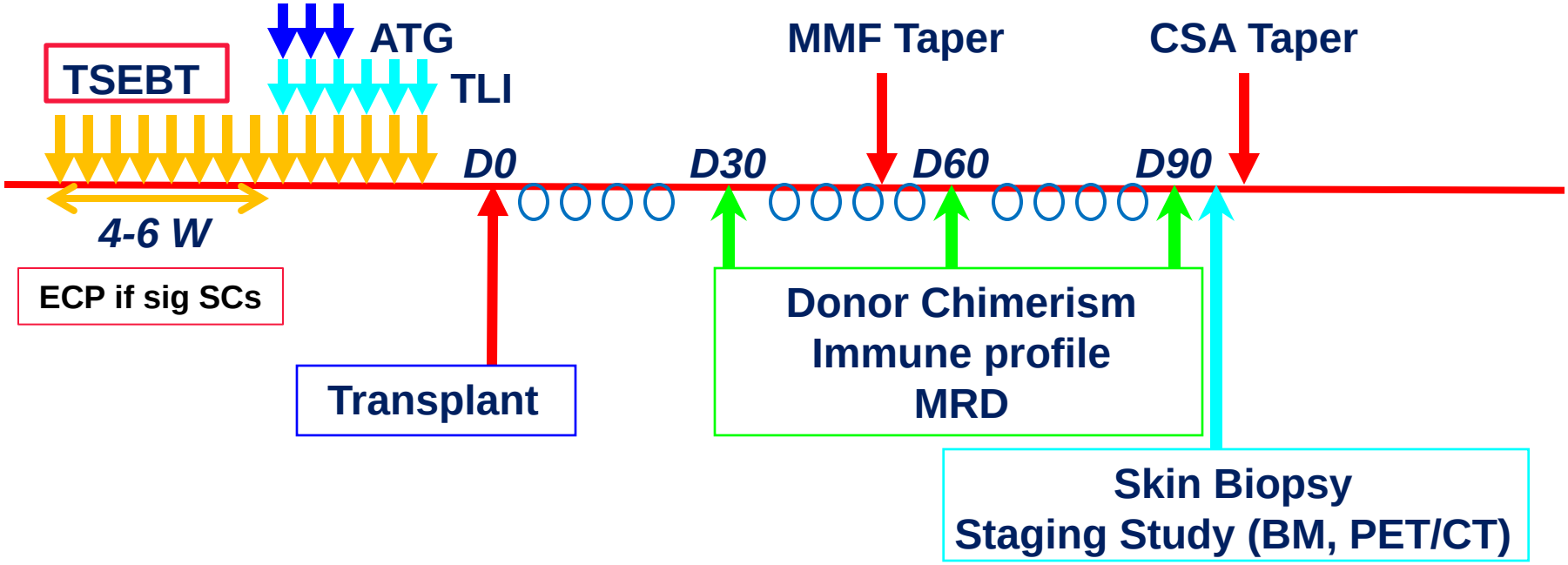
Robert Lowsky, M.D., Tsuyoshi Takahashi, M.D., Ph.D., Yin Ping Liu, M.D., Sussan Dejbakhsh-Jones, M.S., F. Carl Grumet, M.D., Judith A. Shizuru, M.D., Ph.D., Ginna G. Laport, M.D., Keith E. Stockerl-Goldstein, M.D., Laura J. Johnston, M.D., Richard T. Hoppe, M.D., Daniel A. Bloch, Ph.D., Karl G. Blume, M.D., Robert S. Negrin, M.D., and Samuel Strober, M.D.

TLI/ATG conditioning alters host immune profile to favor regulatory NKT cells that suppress GVHD by polarizing donor T cells toward secretion of noninflammatory cytokines (IL4) and by promoting expansion of donor CD4+CD25+FoxP3+ Treg cells

Does not affect donor CD8+ T-cell cytolytic function and graft antitumor activity

Phase II study of non-myeloablative allogeneic transplantation using TLI-ATG in MF/SS

Study Design



TSEBT (24-36 Gy)

TLI (8 Gy)

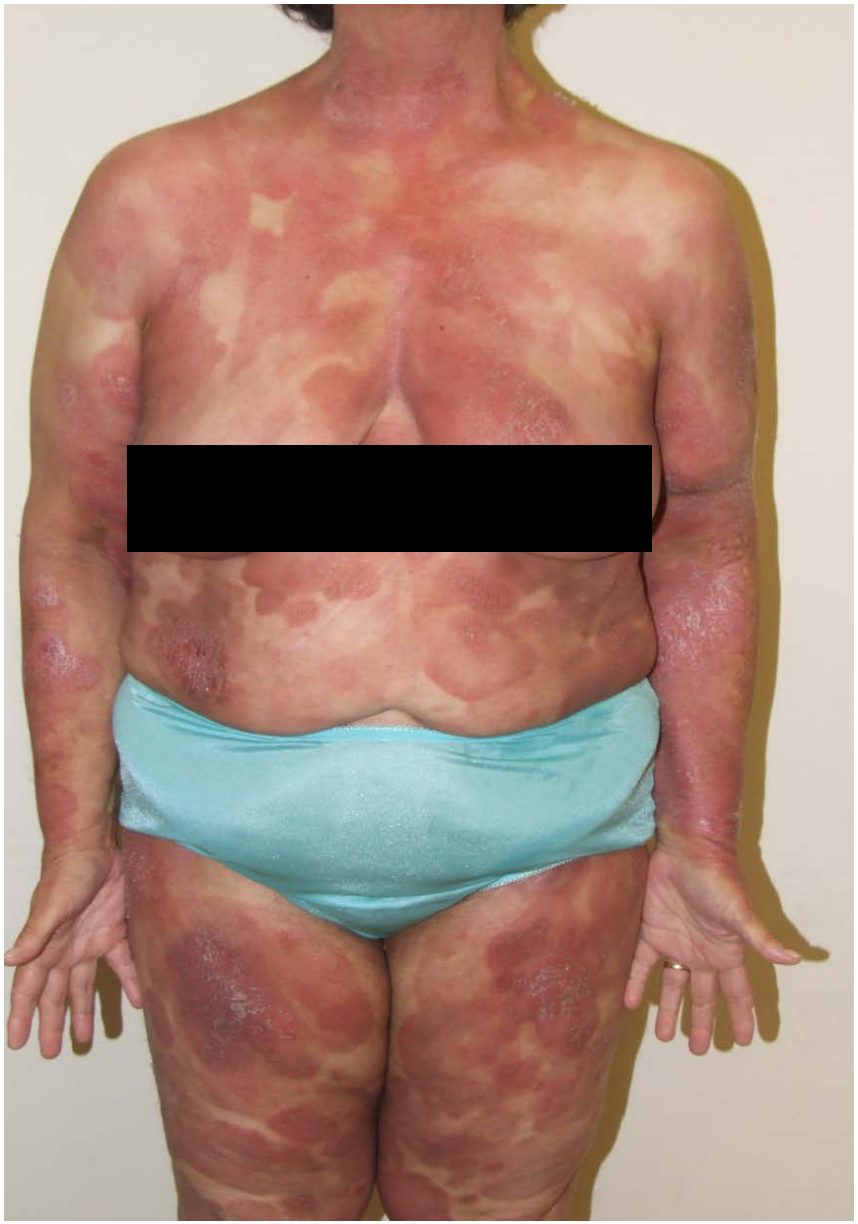
ATG (1.5 mg/kg x 5)

GVHD prophylaxis: CSA, MMF

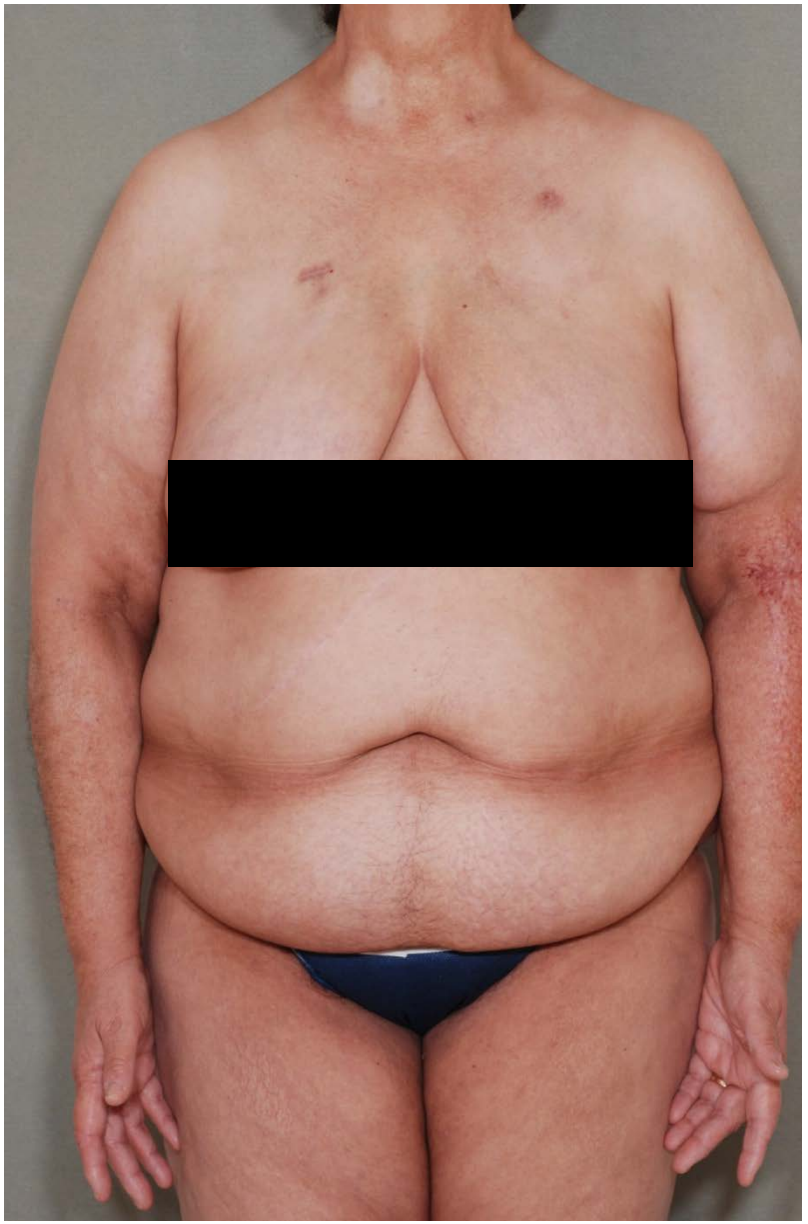
Efficacy/safety evaluation

Mycosis fungoides, stage IVA w/ LCT in skin/LNs: CR

Pre-TSEBT



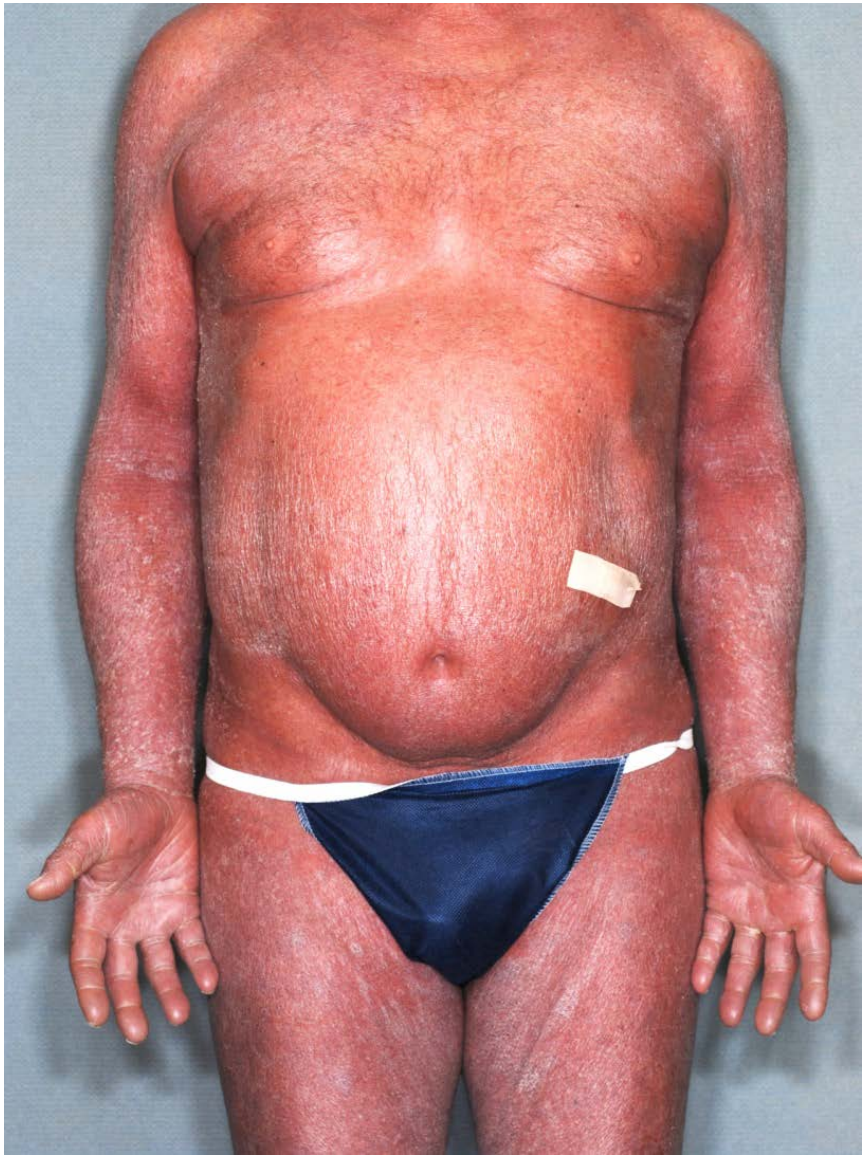
2.0+ yr (NED, no GVHD)



Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR

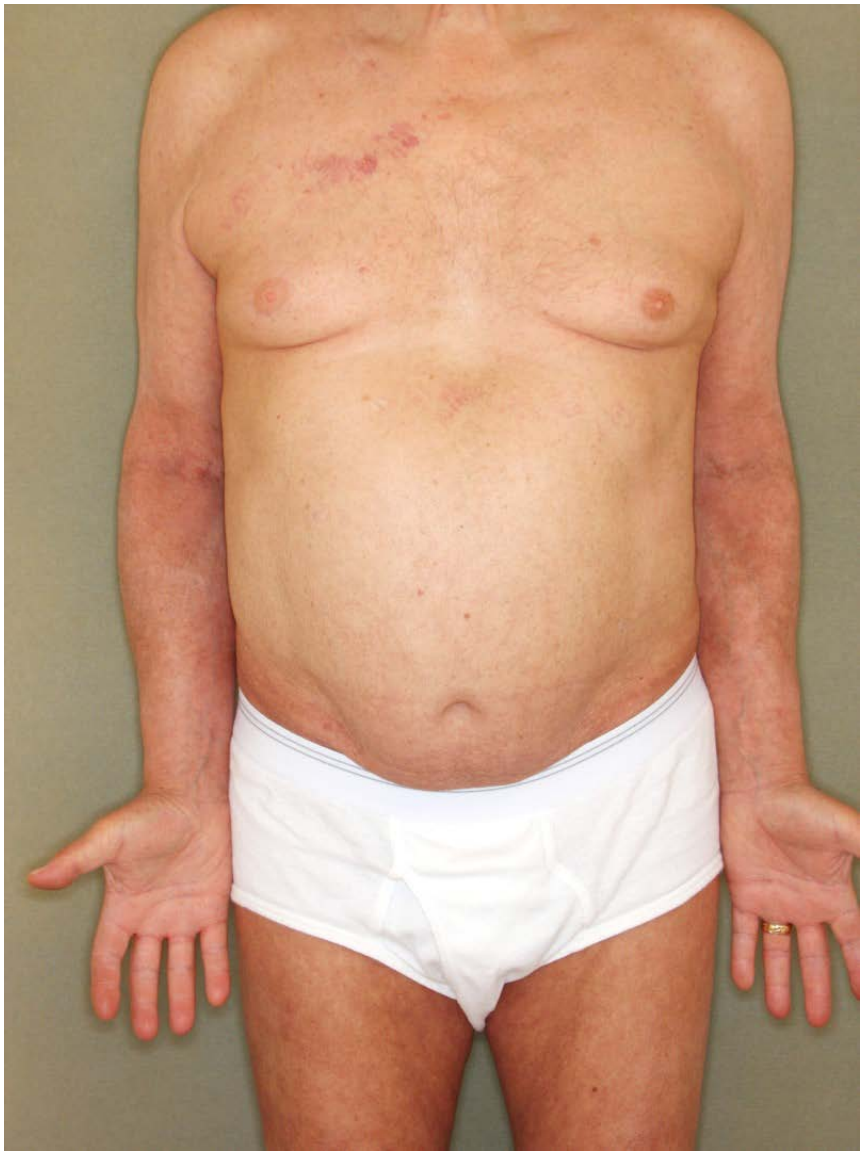
Pre-TSEBT

CD4+/CD26-: 99%, abs 19,780



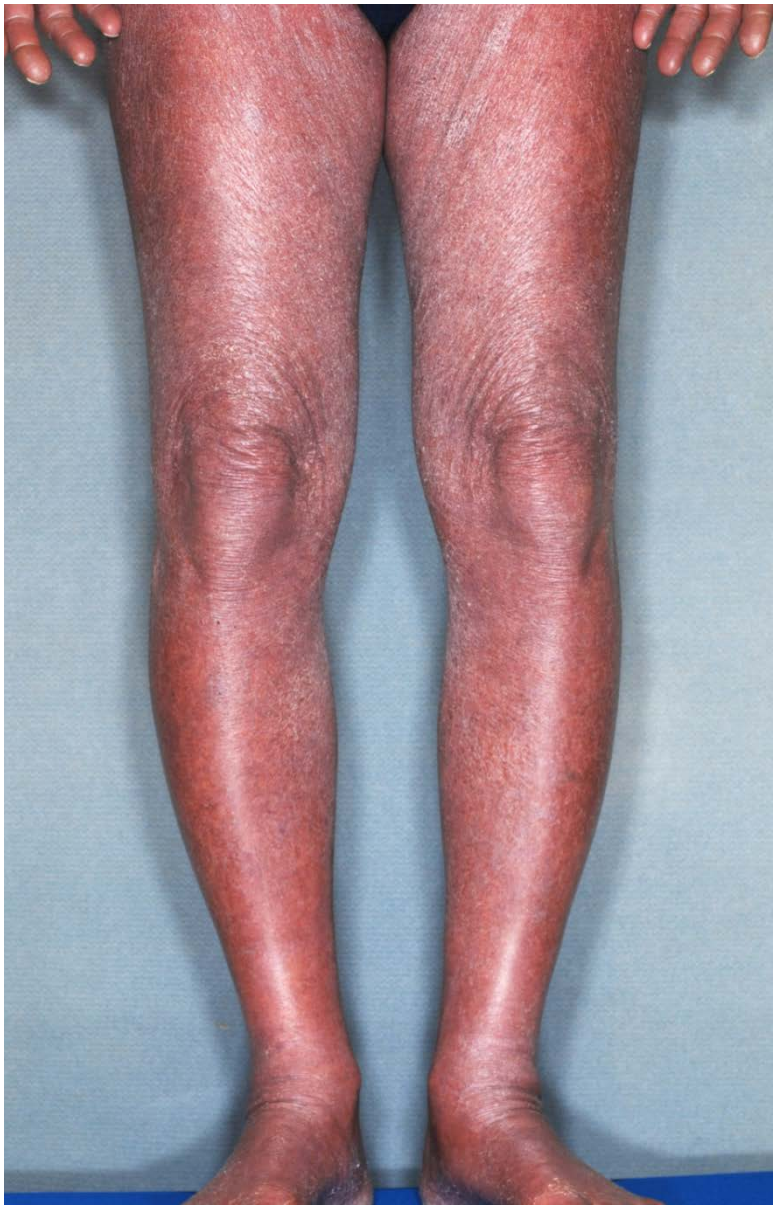
1.5+ yr (NED, no GVHD)

CD4+/CD26-: normalized

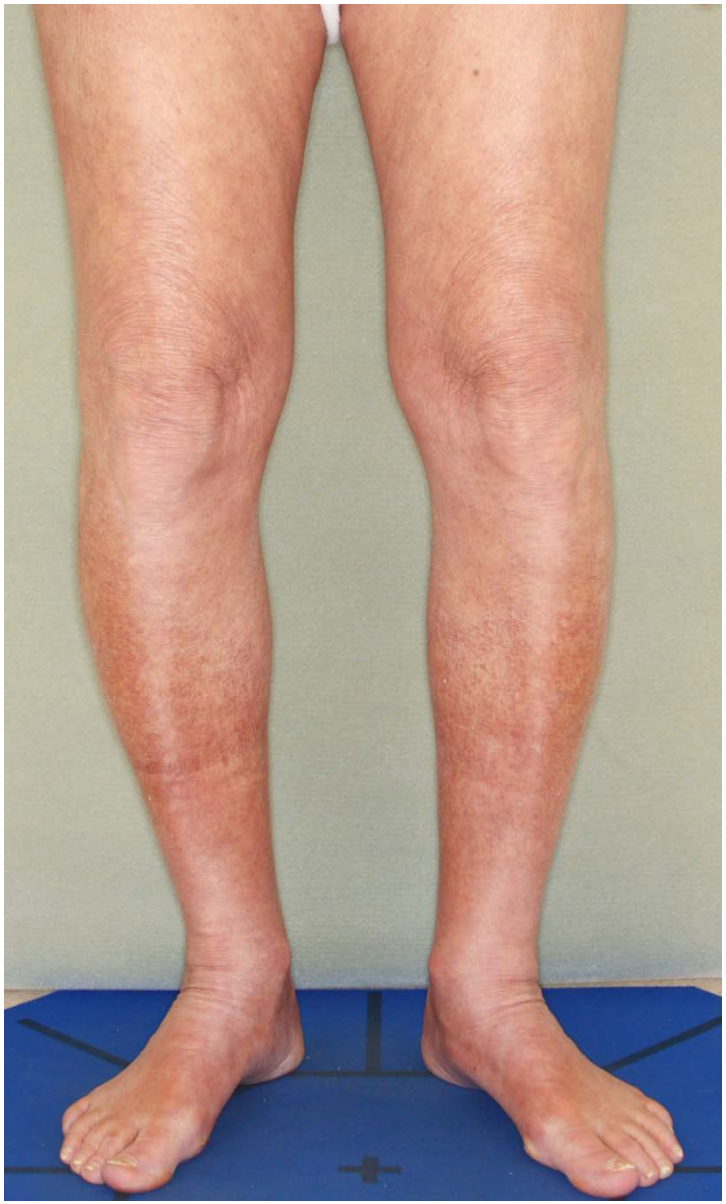


Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR

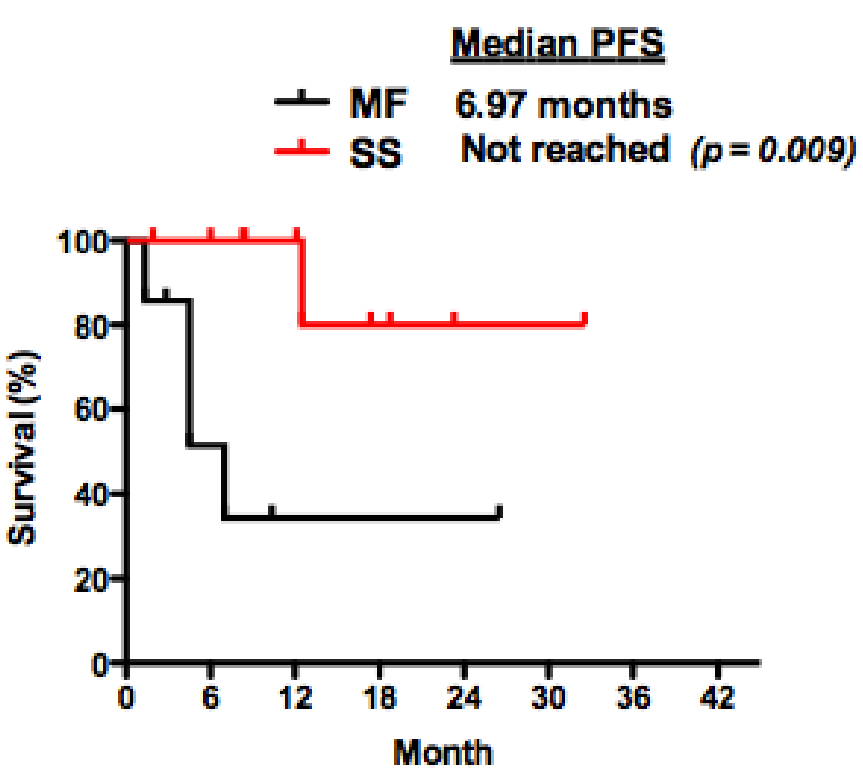
Pre-transplant

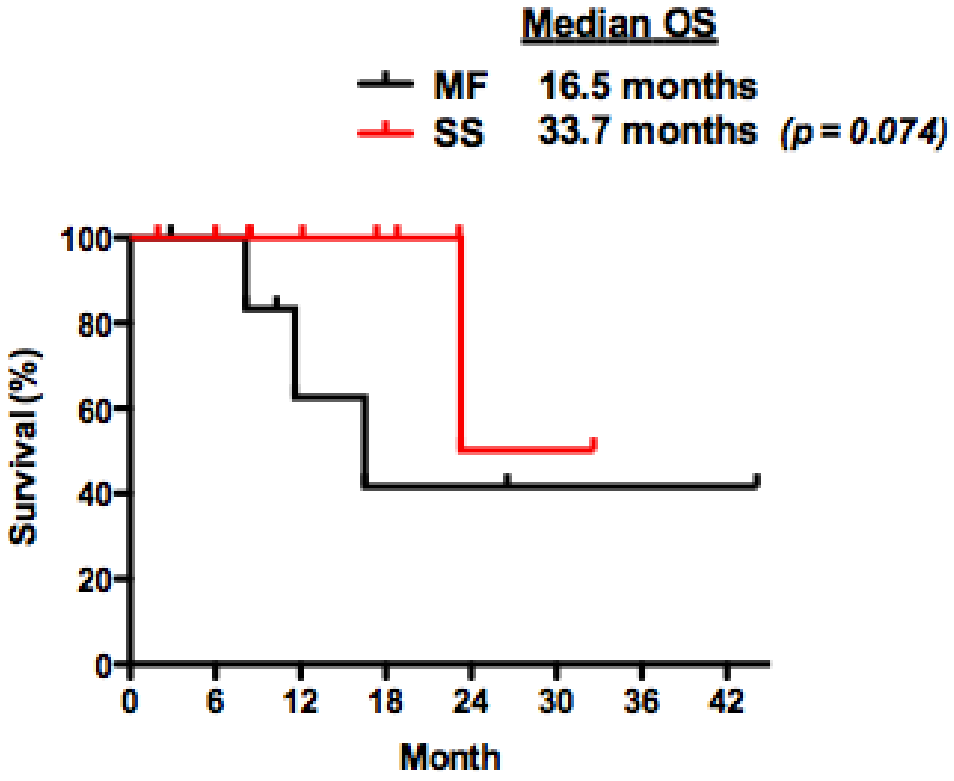


1.5+ yr (NED, no GVHD)



PFS and OS outcome in Sézary syndrome is better than in mycosis fungoides





Median follow up: 12 months

Monitoring minimal residual disease by High-throughput sequencing of T-cell receptor

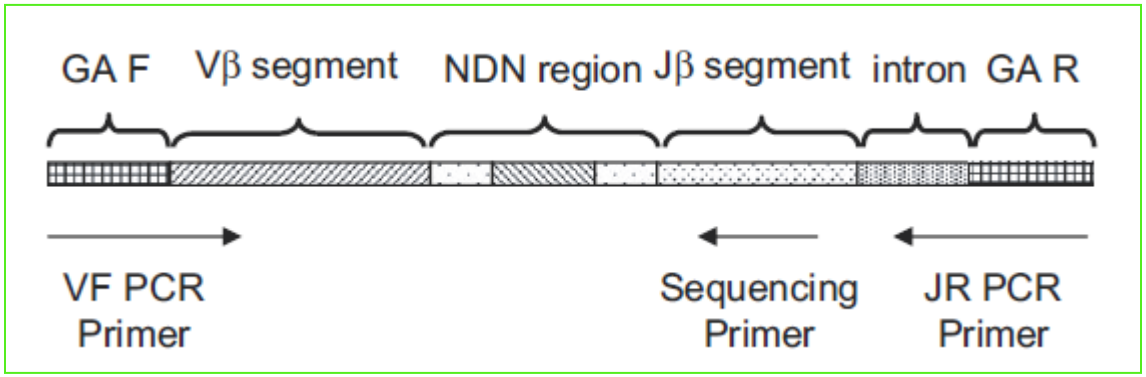
Peripheral blood mononuclear cells and skin biopsy

↓

Extraction of genomic DNA

↓

High-throughput sequencing of rearranged TCRβ CDR3 using solid phase PCR (Illumina GA2 system)



Robins et al, Blood 2009;114:4099

Minimal Residual Disease (MRD) in Blood Post Transplant

	Malignant Sequence -TCCGGGACGGCCCC-	Total Read	% of Malignant Clone	% of Donor T Cells
Pre-TSEBT	848,393	1,229,026	69.029	0%

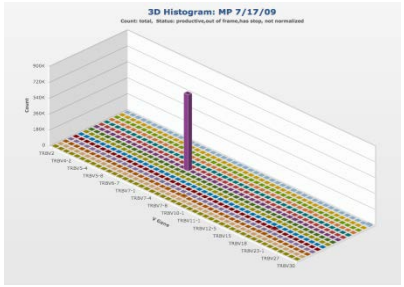
Minimal Residual Disease (MRD) in Blood Post Transplant

	Malignant Sequence -TCCGGGACGGCCCC-	Total Read	% of Malignant Clone	% of Donor T Cells
Pre-TSEBT	848,393	1,229,026	69.029	0%
Pre-TLI/ATG	1,057,097	1,356,526	77.926	0%
Day+30	1,188	132,874	0.894	94%
Day+60	2,946	184,495	1.596	92%
Day+90	4,666	1,094,254	0.426	92%

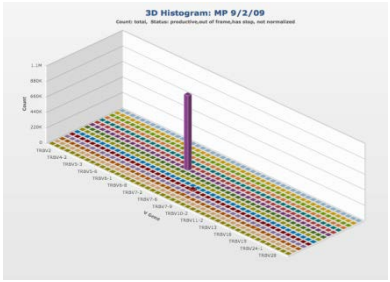
Minimal Residual Disease (MRD) in Blood Post Transplant

	Malignant Sequence -TCCGGGACGGCCCC-	Total Read	% of Malignant Clone	% of Donor T Cells
Pre-TSEBT	848,393	1,229,026	69.029	0%
Pre-TLI/ATG	1,057,097	1,356,526	77.926	0%
Day+30	1,188	132,874	0.894	94%
Day+60	2,946	184,495	1.596	92%
Day+90	4,666	1,094,254	0.426	92%
Day+180	154	416,277	0.036	93%
Day+270	0	877,242	0.000	97%
Day+360	0	764,859	0.000	98%
Day+540	0	2,263,923	0.000	97%

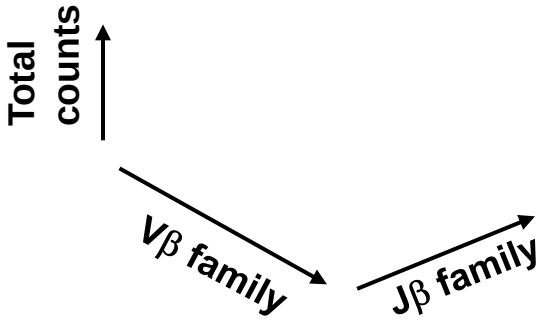
Reconstitution of TCRβ repertoire after non-myeloablative allogeneic HSCT

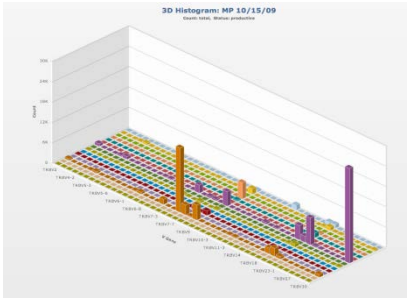


Pre-TSEBT

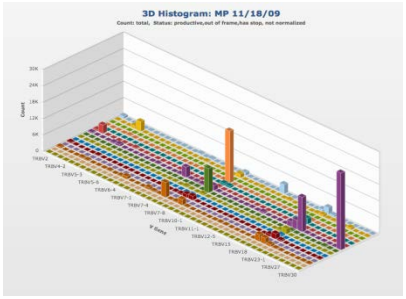


Pre-TLI/ATG

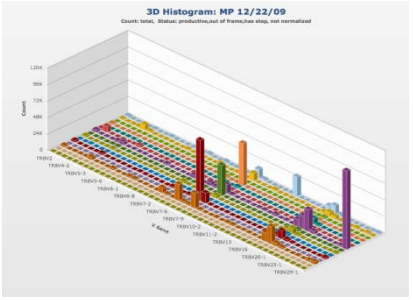




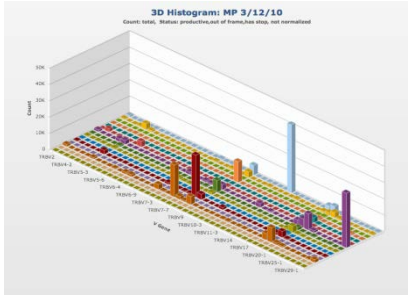
Day +30



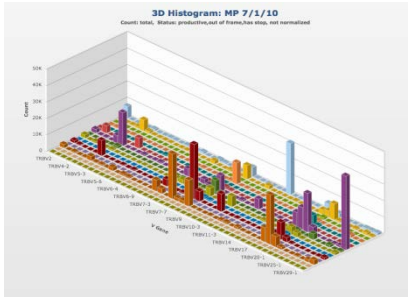
Day +60



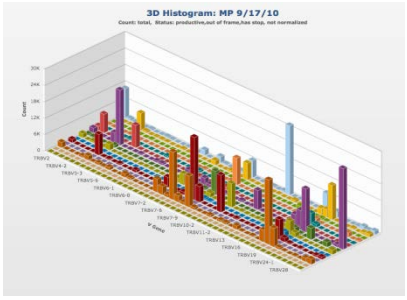
Day +90



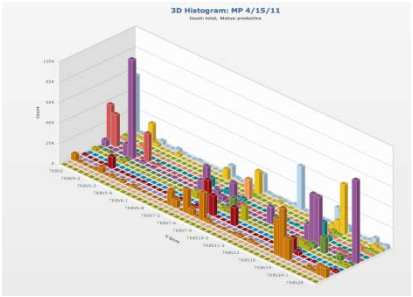
Day +180



Day +270



Day +360



Day +540

Allo HSCT with TSEBT+TLI/ATG

Clinical benefit demonstrated

- Novel non-myeloablative preparatory regimen of TSEBT-TLI/ATG was successful with meaningful outcome
  - 14/17 (82%) CR, 12 mo PFS, OS rates of 73%, 84%
  - SS better outcome than MF
    (PFS, *p=0,009*; OS, *p=0.074*)
- **Well-tolerated with TRM 1/17 (6%, 1 death at ~2 yrs due to cGVHD) pts, sig aGVHD 2*/17, 0% 100-day non-relapse mortality**

May support value of earlier transplant w/ TSEBT-TLI/ATG

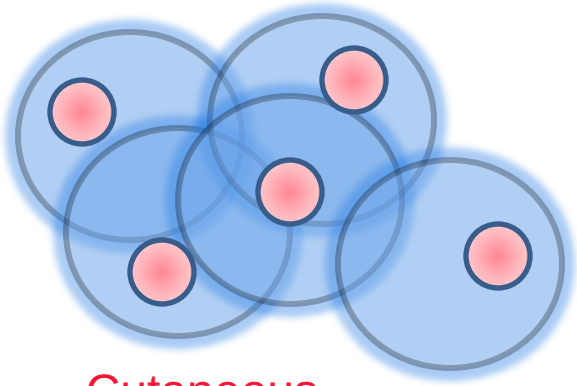
Immunotherapy strategies in cutaneous lymphoma

Combination with molecular targeted therapies, chemotherapies, radiation therapy

long-lasting, curative outcome

Adoptive cell transfer

Immune-modulating agents or antibodies



Cutaneous lymphoma

Vaccine-based approaches

Allogeneic HSCT

Novel Agents & Clinical Trials in CTCL: Take home summary

- New/improved technology allowing us to learn more, help identify ideal targets, and modify/render agents more effective/safe
- New therapies in CTCL are actively in clinical development
- Should further delineate actionable targets and better understand the role of the microenvironment and immune modulation partners
- Optimal clinical trial design should consider demonstrating meaningful benefit (objective and QoL elements) and incorporate appropriate correlative science to maximize discovery (mechanisms, dynamics, biomarkers, resistance) and help investigators optimize the design of the pivotal trial
- Best therapies/targets will be from exploring/appreciating the complexity of MF - SS and offer/allow personalized strategy

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