Managing MF and SS with Allogeneic HSCT

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Disclosure statement

Youn Kim, MD

- **Steering Committee**
  - Eisai, Kyowa, Millennium
- **Consultant or Advisory Board**
  - Actelion, Celgene, Galderma, Soligenix, Neumedicines, Seattle Genetics, Miragen
- **Investigator**
  - Kyowa, Merck, Millennium, Seattle Genetics, Actelion, Eisai, Genentech, Tetralogic

Allogeneic HSCT in MF/SS

Why?

Efficacy of Systemic Agents in CTCL

Efficacy data for FDA approval

Agent (Class)	Indication	Year	Study	N	ORR	DOR
Romidepsin (HDAC inhibitor)	CTCL with prior systemic therapy	2009	Pivotal	96	34%	15 mo
			Supportive	71	35%	11 mo
Deni… diftit… (Fus…						…4 mo
Bexa… (RXF…						…- mo
Vori… (HDA…						…- mo …4 mo

Need better therapies, more options:

Pralatrexate & belinostat approved for PTCL

Brentuximab vedotin (anti-CD30 ADC)

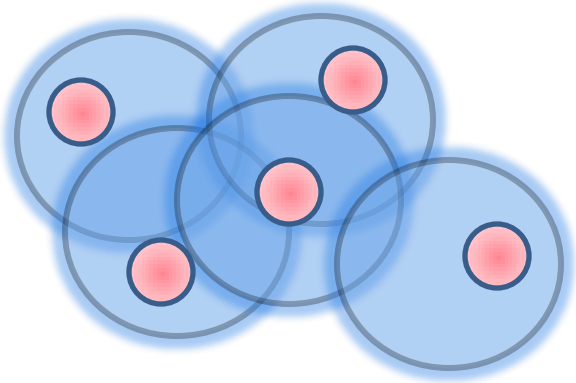
Mogamulizumab (anti-CCR4 mab)

Both in phase 3 trials in CTCL

New targeted therapies in clinical development in CTCL

Tumor cell surface molecules:
- CCR4
- CD158k/KIR3DL2
- CD164

CTCL

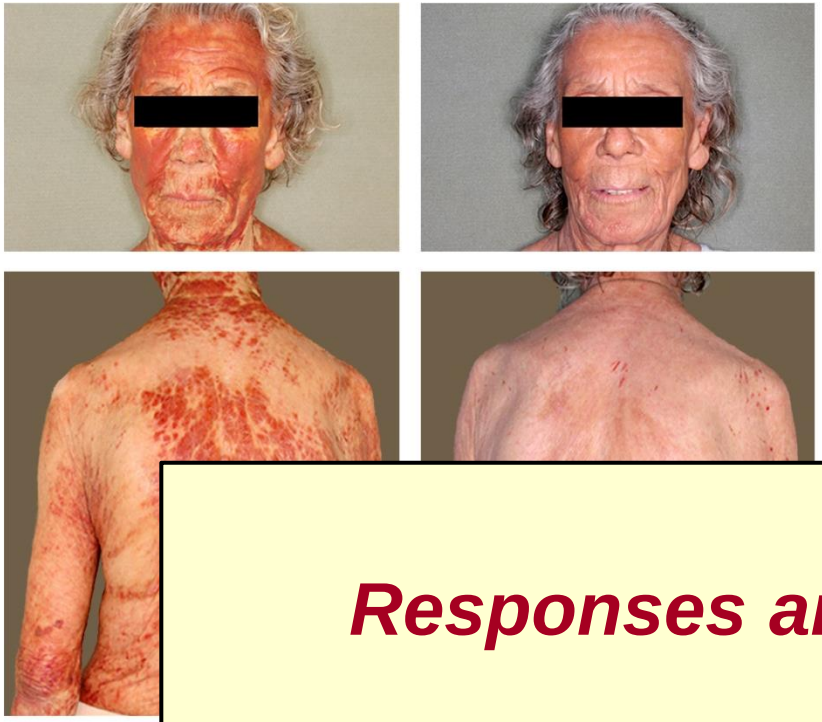


Microenvironment, immune mechanisms:
- Lenalidomide
- PD-1, PD-L1, IDO
- CD47/SIRP

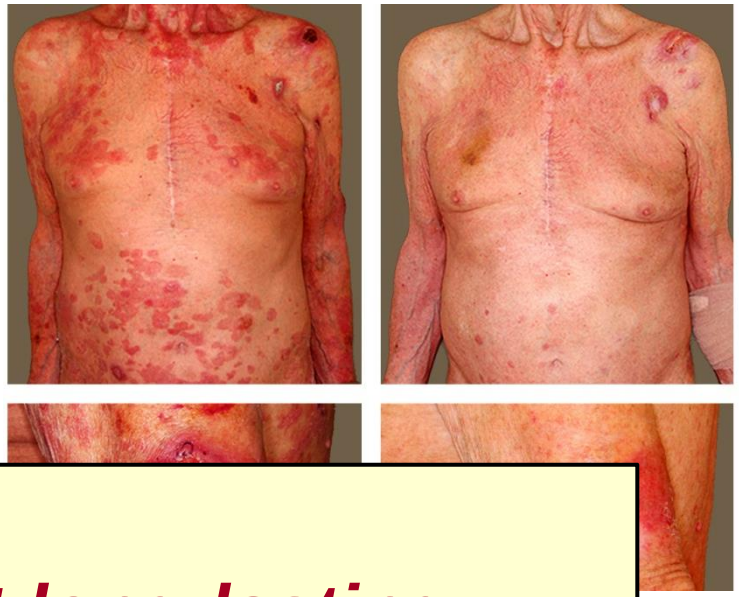
Tumor proliferation, metabolism, survival, progression mechanisms:
- *new proteasome inhibitors*
- *PI3K inhibitors*
- *mTOR inhibitors*
- *JAK inhibitors*
- *Oligonucleotide inhibitor of miR-155-5p (MRG-106)*
- *Inhibitors of Bcl-2 (ABT-263/199), MCL-1*
- *New epigenetic modulators*
- *PARP inhibitors*

Great clinical response to brentuximab vedotin in MF/SS

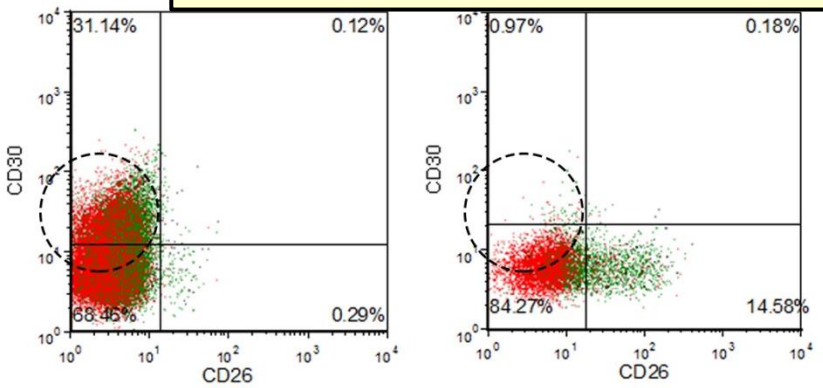
Sézary syndrome, IVA_1

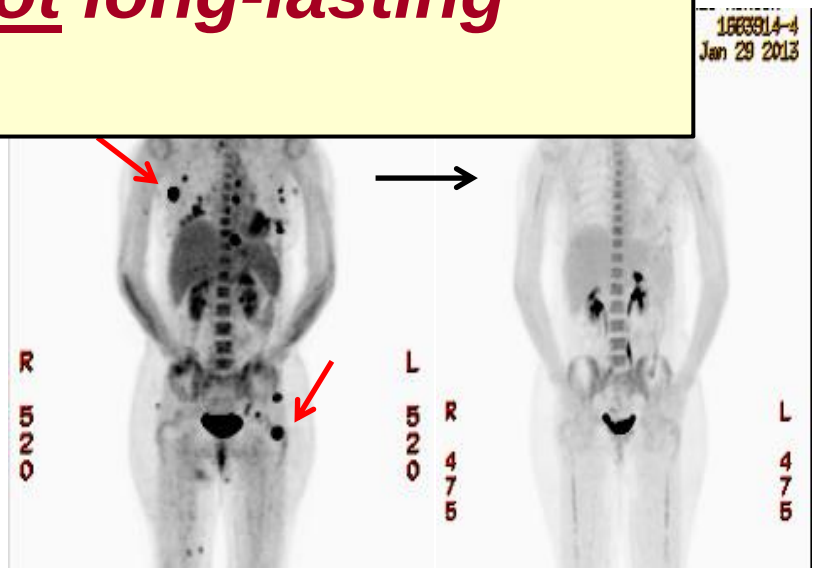


MF IVA_2 LN with LCT



Responses are <u>not</u> long-lasting

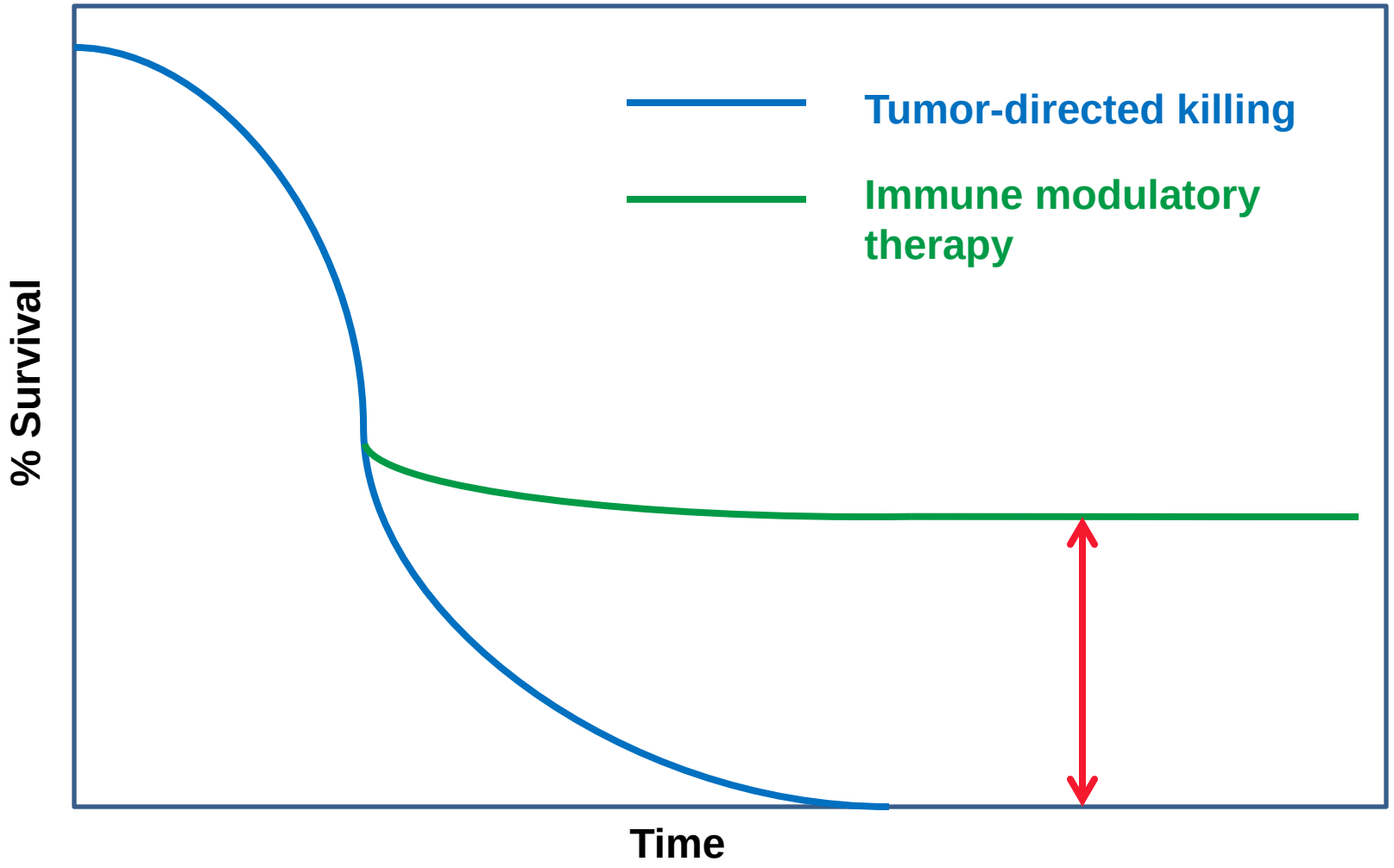




Road to a CURE

How do we make the nice responses last?

Partnering with immunotherapy



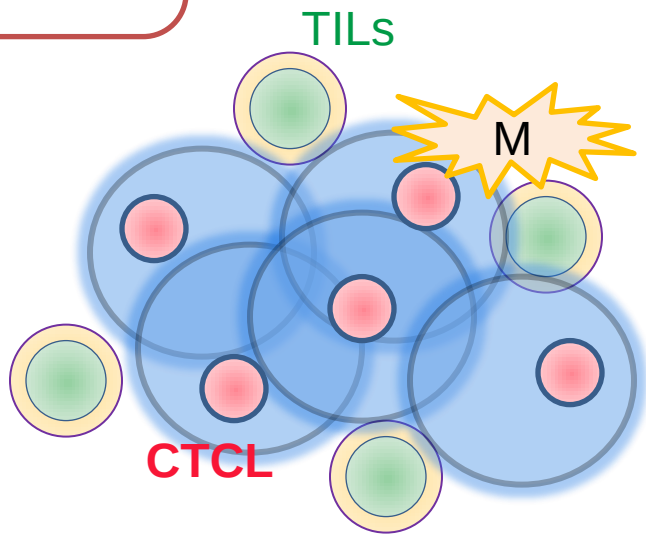
Immunotherapy strategies in CTCL

Tumor-specific monoclonal antibodies

CD25,
CD30,
CCR4,
KIR3DL2

Cytokine therapy

IFNs, IL2,
IL12



Adoptive T-cell transfer

Immune-modulating agents or antibodies

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

Allogeneic HSCT

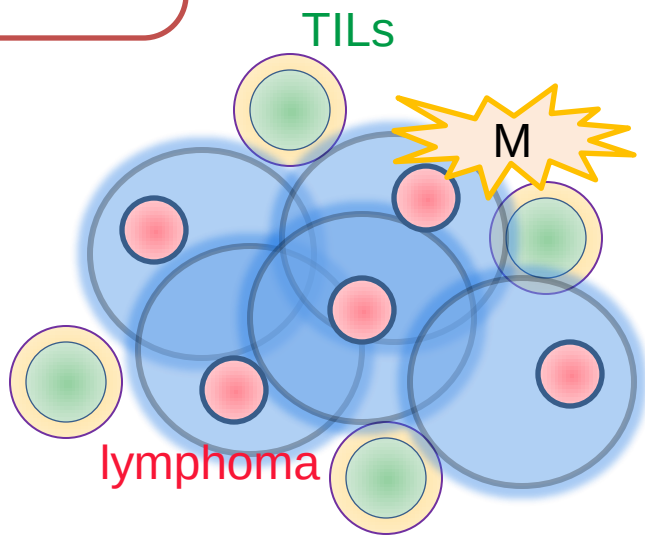
Vaccine-based approaches

ECP
DC-based
Idiotype
In situ strategy

Immunotherapy strategies in CTCL

Tumor-specific monoclonal antibodies

Cytokine therapy



Adoptive T-cell transfer

Immune-modulating agents or antibodies

Allogeneic HSCT

Vaccine-based approaches

Can we cure our patients with MF or SS?

Autologous → High-dose therapy followed by stem cell rescue

Benefit of no GVHD

No durable response in MF/SS, not recommended

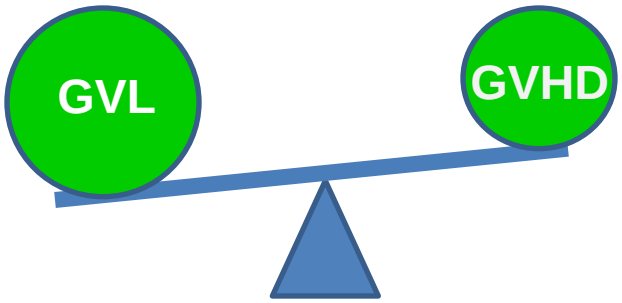
Unable to eliminate all tumor cells

Allogeneic → **Graft vs. lymphoma effect**

Risk of GVHD

Increasing evidence of durable clinical, cytogenetic, molecular remissions in MF/SS

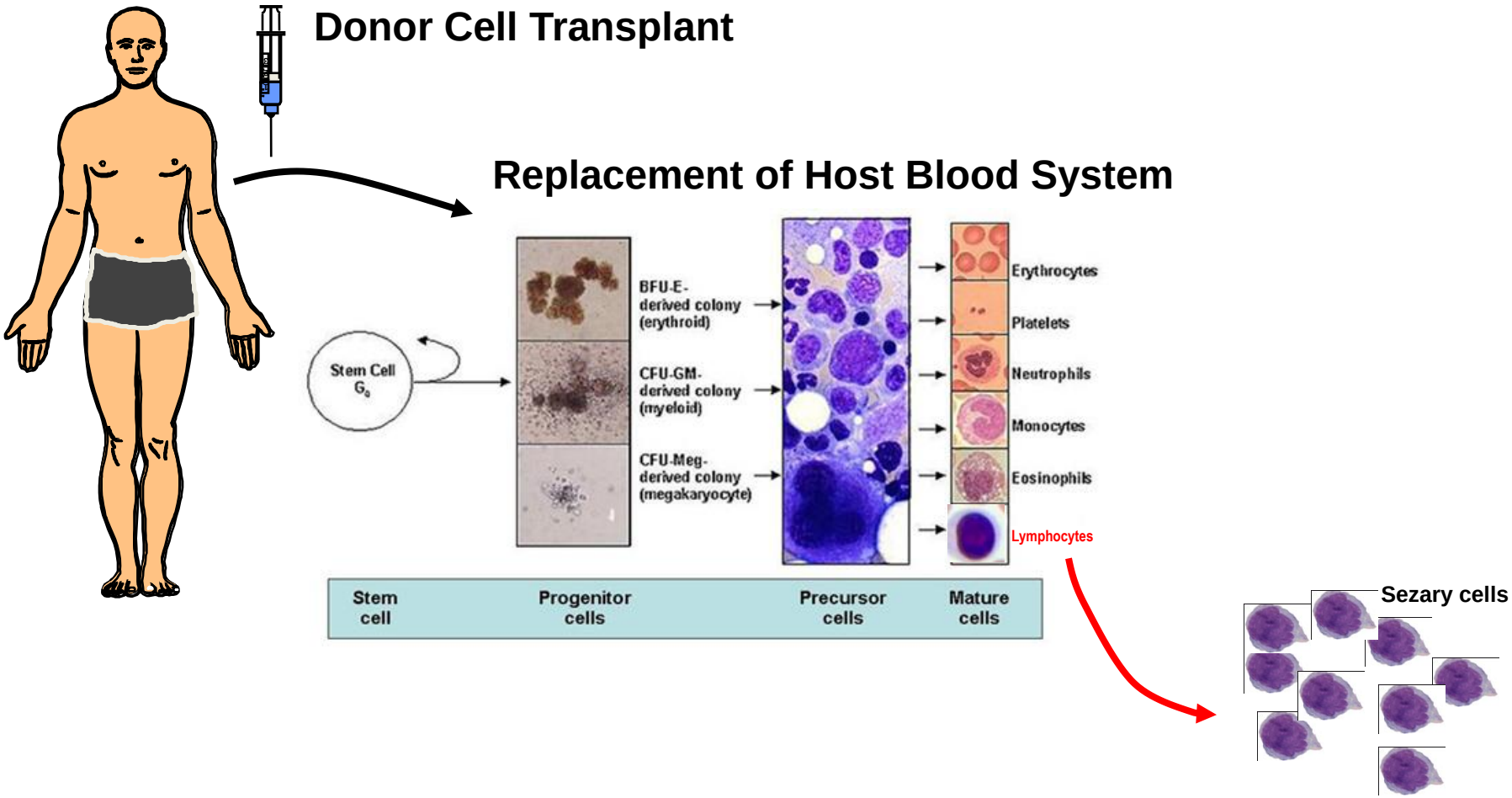
Able to eliminate residual tumor cells



How to maximize GVL effect while minimizing GVHD risk

P Wu, Y Kim, et al. Biol Blood Marrow Transplant 2009;15:982

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



Allogeneic HSCT in MF/SS

Who, When, and How

Current Clinical Management of CTCL, *2015*

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

IA Limited patch/plaque	IB/IIA Generalized patch/plaque	IIB Tumors	III Erythroderma	IV Extracutan disease

Topical steroid, retinoid (bex), NM phototherapy, local RT, imiquimod

ECP ± IFN, bexarotene

Phototherapy + bexarotene or IFN

Alemtuzumab

TSEBT ± ECP, IFN

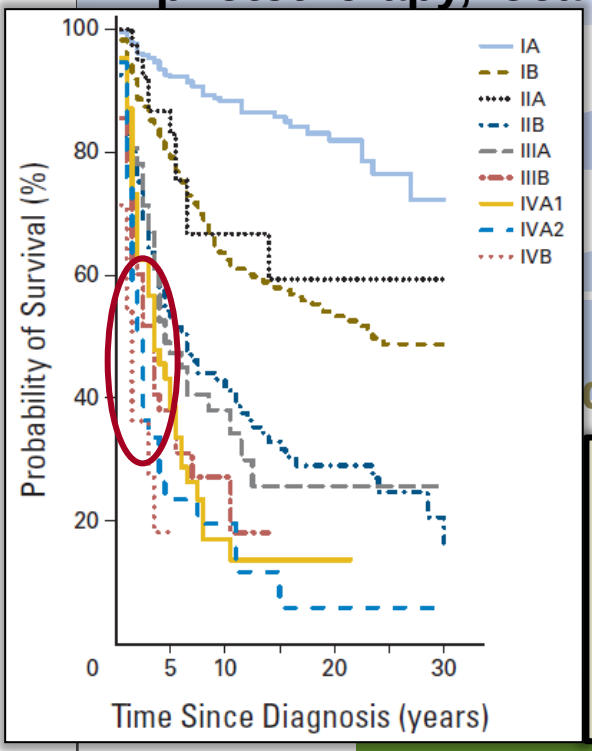
Combination chemo

Bexarotene, methotrexate, IFN; denileukin diftitox, vorinostat, romidepsin

cytotoxic systemic therapy**

Allo-HSCT

Clinical Trials



Overall life-expectancy < 5 yrs

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

Elements to consider for allogeneic HSCT

- Age, comorbidities/PS profile
- MF vs SS
- Clinical stage/TNMB (dz burden)
- Additional prognostic factors
  - Folliculotropism, LCT (skin vs EC sites), other
- Prior therapies and responses/DOR
- Available donor (type, source)
- Adequate disease control
- Preparatory/conditioning regimens
- GVHD prophylaxis & management
- Management of disease progression post-transplant

Overall life-expectancy < 5 yrs

Cumulating evidence of durable GVL in MF/SS

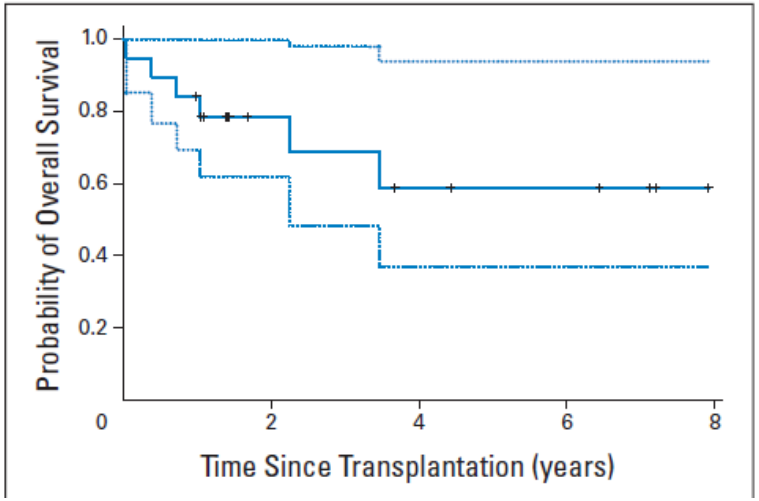
VOLUME 28 · NUMBER 14 · MAY 10 2010

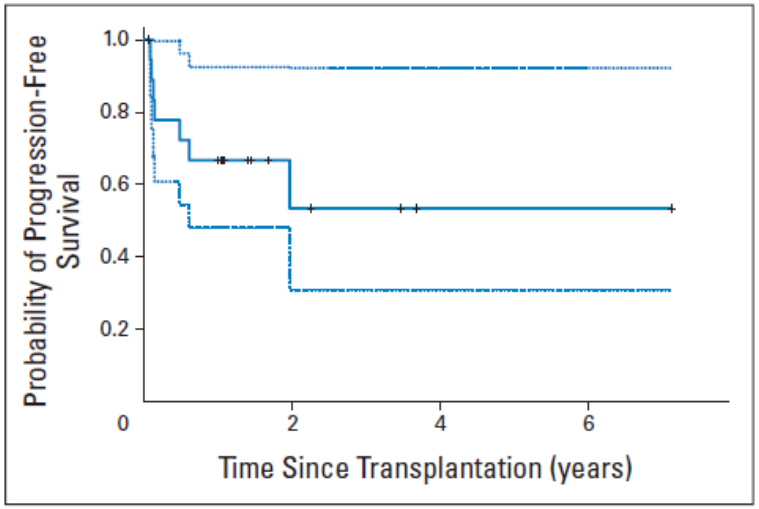
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Total Skin Electron Beam and Non-Myeloablative Allogeneic Hematopoietic Stem-Cell Transplantation in Advanced Mycosis Fungoides and Sézary Syndrome

Madeleine Duvic, Michele Donato, Bouthaina Dabaja, Heather Richmond, Lotika Singh, Wei Wei, Sandra Acholonu, Issa Khouri, Richard Champlin, and Chitra Hosing





N = 19 MF or SS, 2001-2008
Median f/u 19 mo (1.3-8.3 yrs)
OS 79% at 2 yrs
PFS 53% at 2 yrs

GVHD:
- **Acute, 12 of 18 (67%), 5 Gr II-IV (28%)**
- Chronic, 12 (67%)

Failure post-transplant:
- 7 of 18 evaluable with relapse or progression, median time to event 50 d (28-718)
- **TRM at 2 yrs 12%**

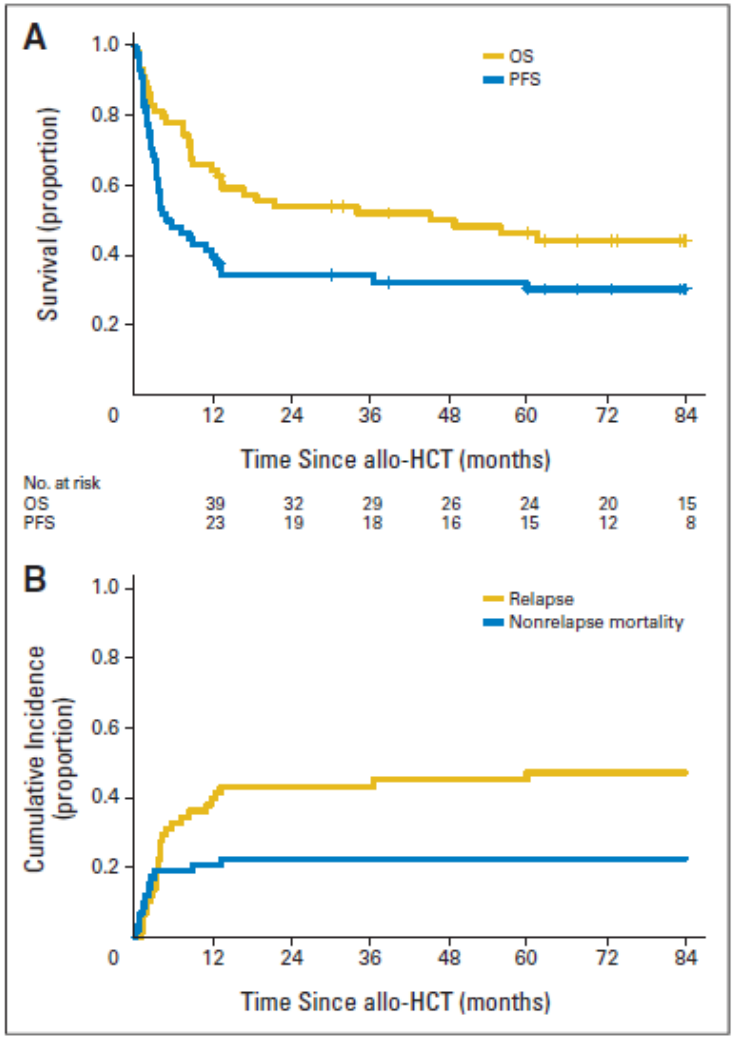
6 deaths, 2 due to dz

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Allogeneic Hematopoietic Cell Transplantation for Patients With Mycosis Fungoides and Sézary Syndrome: A Retrospective Analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation

Rafael F. Duarte, Carmen Canals, Francesco Onida, Ian H. Gabriel, Reyes Arranz, William Arcese, Augustin Ferrant, Guido Kobbe, Franco Narni, Giorgio Lambertenghi Deliliers, Eduardo Olavarría, Norbert Schmitz, and Anna Sureda

2010;28:2365



CORRESPONDENCE

Long-Term Outcome of Allogeneic Hematopoietic Cell Transplantation for Patients With Mycosis Fungoides and Sézary Syndrome: A European Society for Blood and Marrow Transplantation Lymphoma Working Party Extended Analysis

2014;32:3347

RF Duarte, A Boumendil, F Onida, I Gabriel, R Arranz, W Arcese, X Poire, G Kobbe, F Narni, A Cortelezzi, E Olavarria, N Schmitz, A Sureda, P Dreger

EBMT N= 60; 36 MF, 24 SS; 1997-2007
Median age, 46.5 (22-66); 73% stage IV
45 MRD; 73% RIC/NMA; 67% “advance dz phase”

Long-term outcome data:
Median f/u = 7 yrs
OS 46% at 5 yrs, 44% at 7 yrs **(2-yr 54%)**
PFS 32% at 5 yrs, 30% at 7 yrs **(2-yr 34%)**

GVHD: aGVHD 40%; Gr II-IV 28%; cGVHD 27%

Failure post-transplant:
- Disease progression/relapse, 27 (45%), median 3.8 mo after HCT (only 2 events after 2 yrs)
- **7-yr TRM 22%, latest event at 14 mo (22% 2-yr)**

Factors a/w adverse outcome:
- Advanced phase dz at HCT (RFS/PFS, OS)
- URD (NRM, PFS, OS)
- Myeloablative (NRM, OS)

33 deaths, 19 due to dz
26 or 27 alive remain in CR

Bone Marrow Transplantation (2014) **49**, 1360–1365
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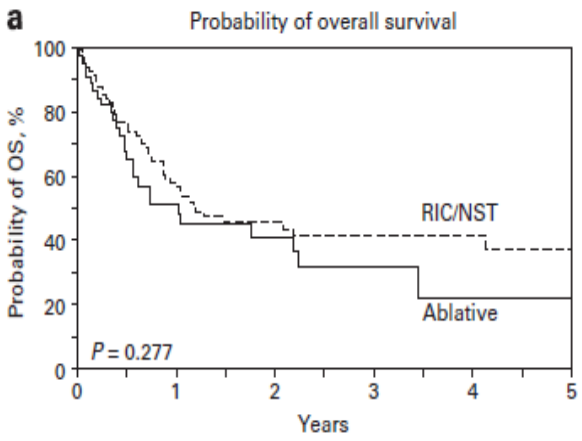
Significant % missing detail data

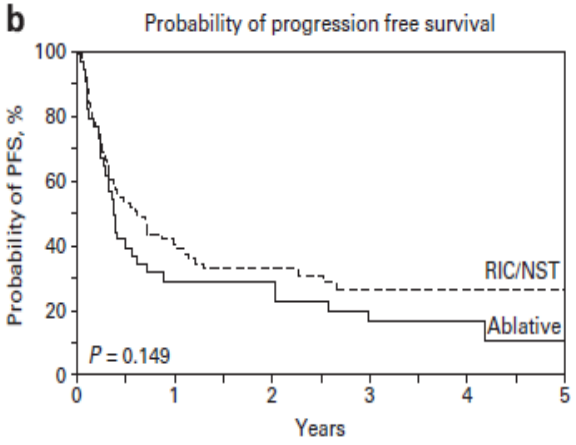
ORIGINAL ARTICLE

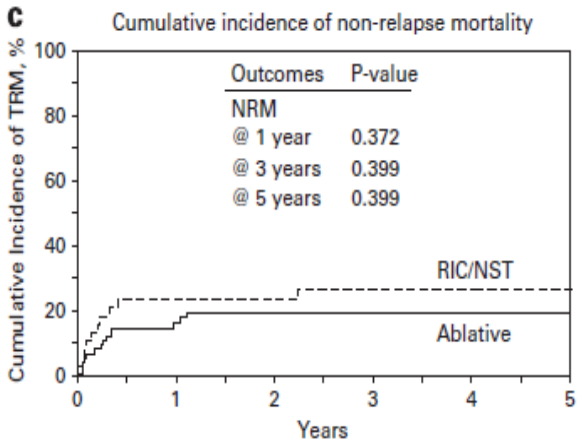
Allogeneic hematopoietic cell transplantation for mycosis fungoides and Sezary syndrome

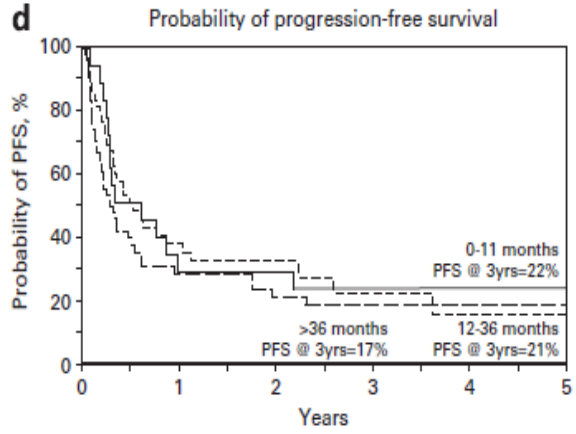
By CIBMTR

MJ Lechowicz[1], HM Lazarus[2], J Carreras[3], GG Laport[4], CS Cutler[5], PH Wiernik[6], GA Hale[7], D Maharaj[8], RP Gale[9], PA Rowlings[10], CO Freytes[11], AM Miller[12], JM Vose[13], RT Maziarz[14], S Montoto[15], DG Maloney[16] and PN Hari[3]









<u>Total N= 129; 2001-2009</u>
Age, median 52 (27-72)
Median f/u 36 mo (3-97)
OS 54%, 38% at 1, 3 yrs
PFS 31%, 19% at 1, 3 yrs

<u>Subset N=52 w/ higher level data:</u>
- 39% stage IV, 20% stage I at dx
- From dx → tx, median 38 mo
- Dz status at transplant;
  - Never CR n=33 (63%)

NMA/RIC 83, MAC 46
No sig diff in PFS/OS/NRM
Acute GVHD 74%, II-IV, 41%
Chronic GVHD at 2 yr, 43%

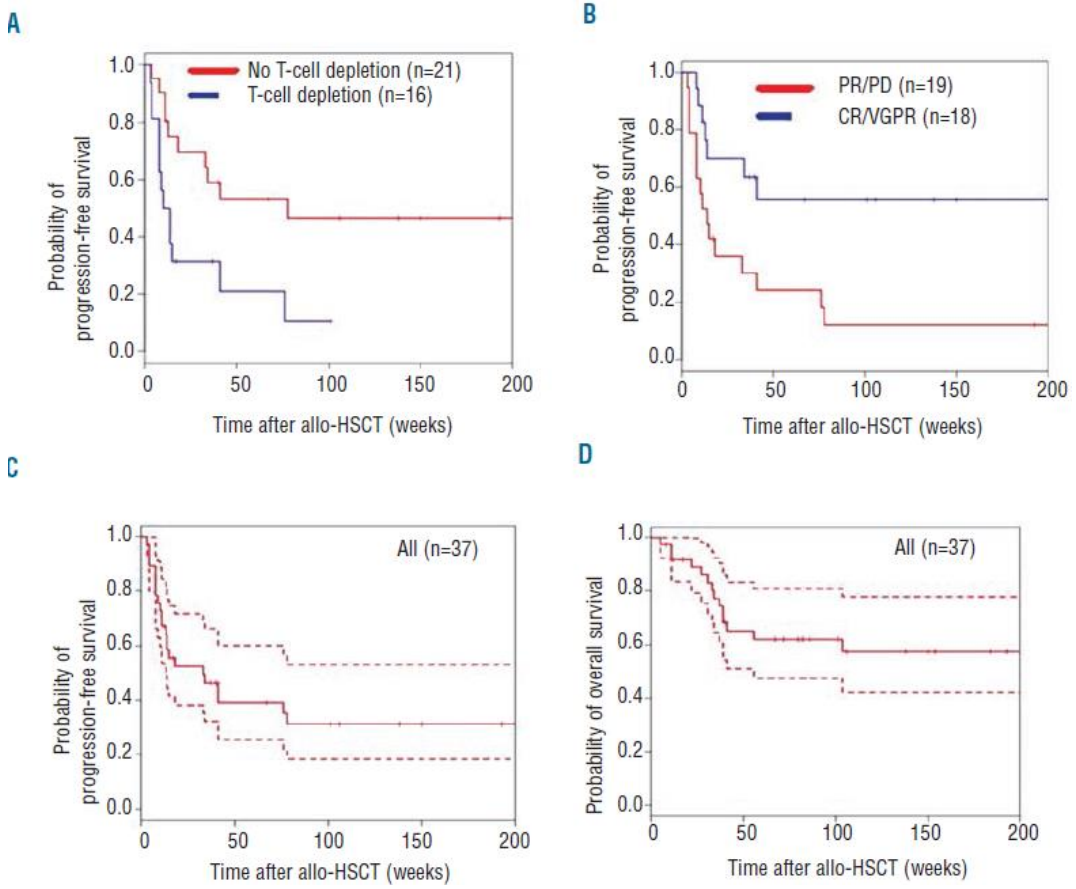
<u>Failure post-transplant:</u>
- **TRM 19%, 22% at 1, 3 yrs**
- RDP 50%, 58% at 1, 3 yrs

69 deaths, 35 due to dz

Allogeneic stem cell transplantation for advanced cutaneous T-cell lymphomas: a study from the French Society of Bone Marrow Transplantation and French Study Group on Cutaneous Lymphomas

Adèle de Masson,[1] Marie Beylot-Barry,[2] Jean-David Bouaziz,[1*] Régis Peffault de Latour,[3*] François Aubin,[4] Sylvain Garciaz,[5] Michel d'Incan,[6] Olivier Dereure,[7] Stéphane Dalle,[8] Anne Dompmartin,[9] Felipe Suarez,[10] Maxime Battistella,[11] Marie-Dominique Vignon-Pennamen,[11] Jacqueline Rivet,[11] Henri Adamski,[12] Pauline Brice,[13] Sylvie François,[14] Séverine Lissandre,[15] Pascal Turlure,[16] Ewa Wierzbicka-Hainaut,[17] Eolia Brissot,[18] Rémy Dulery,[19] Sophie Servais,[20] Aurélie Ravinet,[21] Reza Tabrizi,[22] Saskia Ingen-Housz-Oro,[23] Pascal Joly,[24] Gérard Socié,[3**] and Martine Bagot;[1**] French Study Group on Cutaneous Lymphomas and Société Française de Greffe de Moëlle et Thérapie Cellulaire

Haematologica 2014;99:527



N= 37, 2002-2013

31 (84%) MF/SS, 18 stage IV

Median f/u 29 mo (3-120)

OS 57% at 2 yrs

PFS 31% at 2 yrs

MRD 46%; 2 cord blood

GVHD:

- **Acute: 26 (70%)** median time to GVHD 24 d; 18 **Gr II-IV (49%)**
- Chronic: 15 (44% at 2-yr)

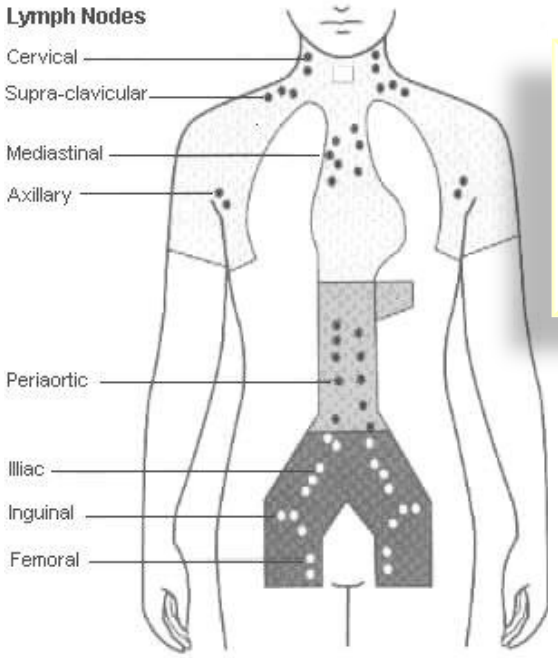
Failure post-transplant:

- **TRM 18% at 1, 2 yrs**
- 51% with PD

14 deaths, 8 due to dz, 6 TRM

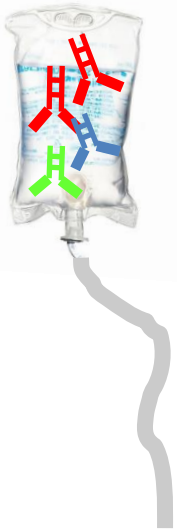
A New Approach in Donor Cell Transplant
Non-Myeloablative Regimen with TLI/ATG
"Protective conditioning"

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 cell engraftment
aGVHD reduced to <10% (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 suppresses GVHD by:

Altering host immune profile to favor regulatory NKT cells

➔ Polarization of donor T cells toward secretion of non-inflammatory Th2 cytokines (IL4)

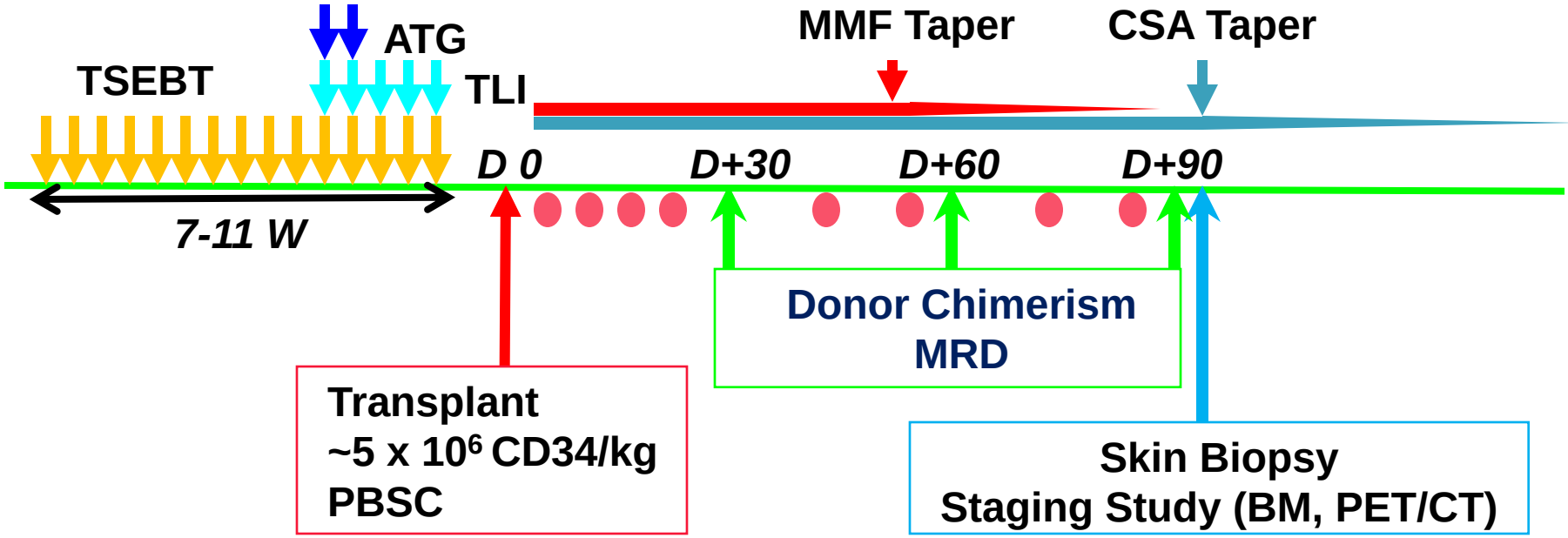
➔ Promotes expansion of donor CD4+CD25+FoxP3+ Treg cells

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

JI 2007;178:6242, Blood 2009;113:4458

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

Study Design



TSEBT, 30-36 Gy

TLI, total lymphoid irradiation, 8 Gy (80 cGy x 10)

ATG, rabbit anti-thymocyte globulin (1.5 mg/kg x 5)

Derm evaluation

Clinical data, n=32 Stanford NMA allo regimen
TSEBT with TLI + ATG

- **32 patients transplanted (over 5.5 years)**
  - 12 MF (all LCT+), 20 SS
  - Stage IV 81% (26/32)
    - 6 IIB, 23 IVA, 3 IVB
  - Median age, 62 yrs (range 20-74)
  - Median prior systemic tx, 5 (range 2-14)
- **Active disease at time of TSEBT, 100% (32/32)**
  - Skin 100%, Blood 44%, LN 63%, Visceral 16%
- **Donor**
  - Sibling 32%
  - Unrelated 68% (15 full-match, 5 one-mismatch)

Clinical outcome update (median f/u 36 mo)

- **Transplant course**
  - Outpatient allograft infusion, 100%
  - Re-admission within 100 days, 69%
    - **Median hospital stay, 4 days**
- **Graft-versus-host disease**
  - **Acute GVHD (22%)**
    - Grade I, n=2
    - Grade II, n=4
    - Grade IV, n=1
    - **Cumulative incidence of grade II-IV, 17%**
  - **Chronic GVHD**
    - Extensive, n=7
    - Cumulative incidence of extensive, 24%

Clinical outcome update (median f/u 36 mo)

- **Best clinical response at 3-month**

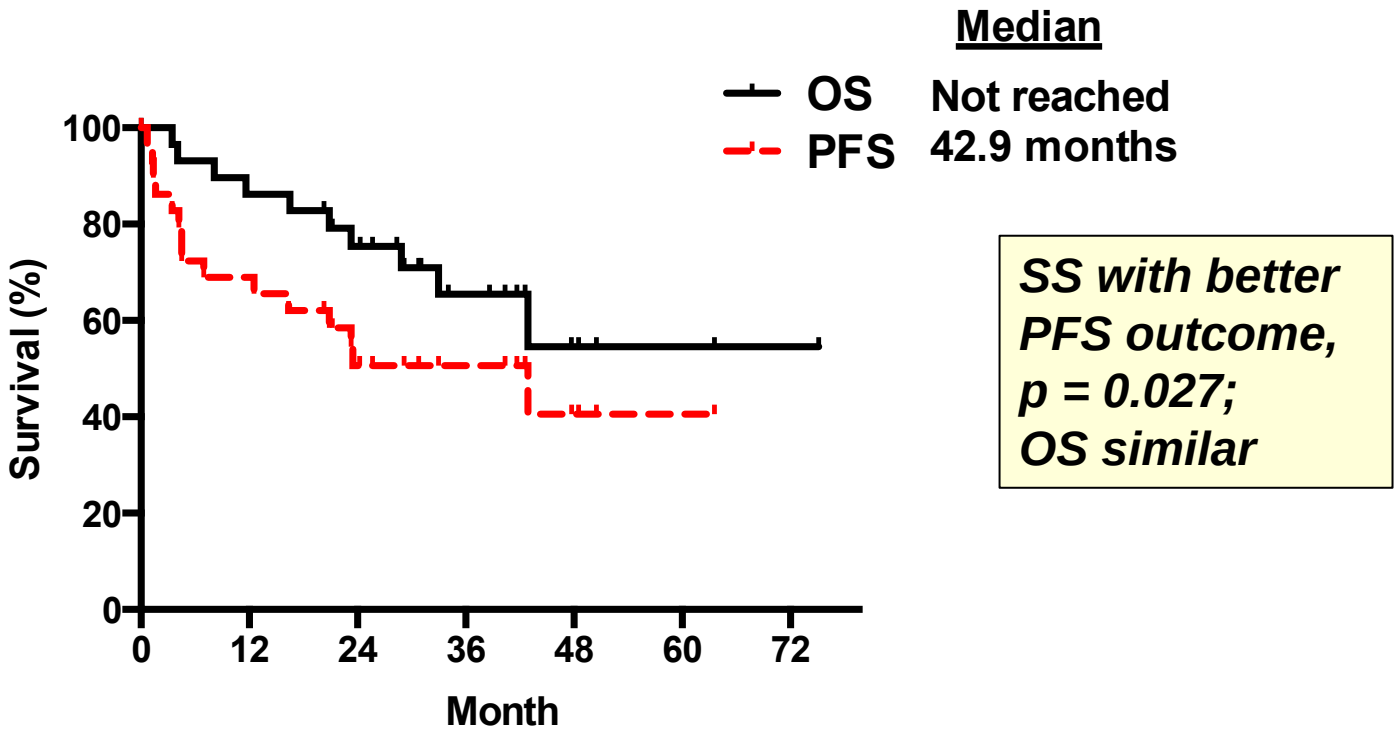
CR	19
PR	7 (near CR)
SD	1
PD	2
ORR	**90%**

- **Transplant-related mortality (TRM)**

Acute GVHD	1
Chronic GVHD	1
2nd malignancy	1
Hepatitis B	1
1-yr NRM	**3.4%**
2-yr NRM	**9.4%**

- Graft loss in 6 pts (3 received 2nd allo HSCT)

Clinical outcome update, median f/u 36 mo

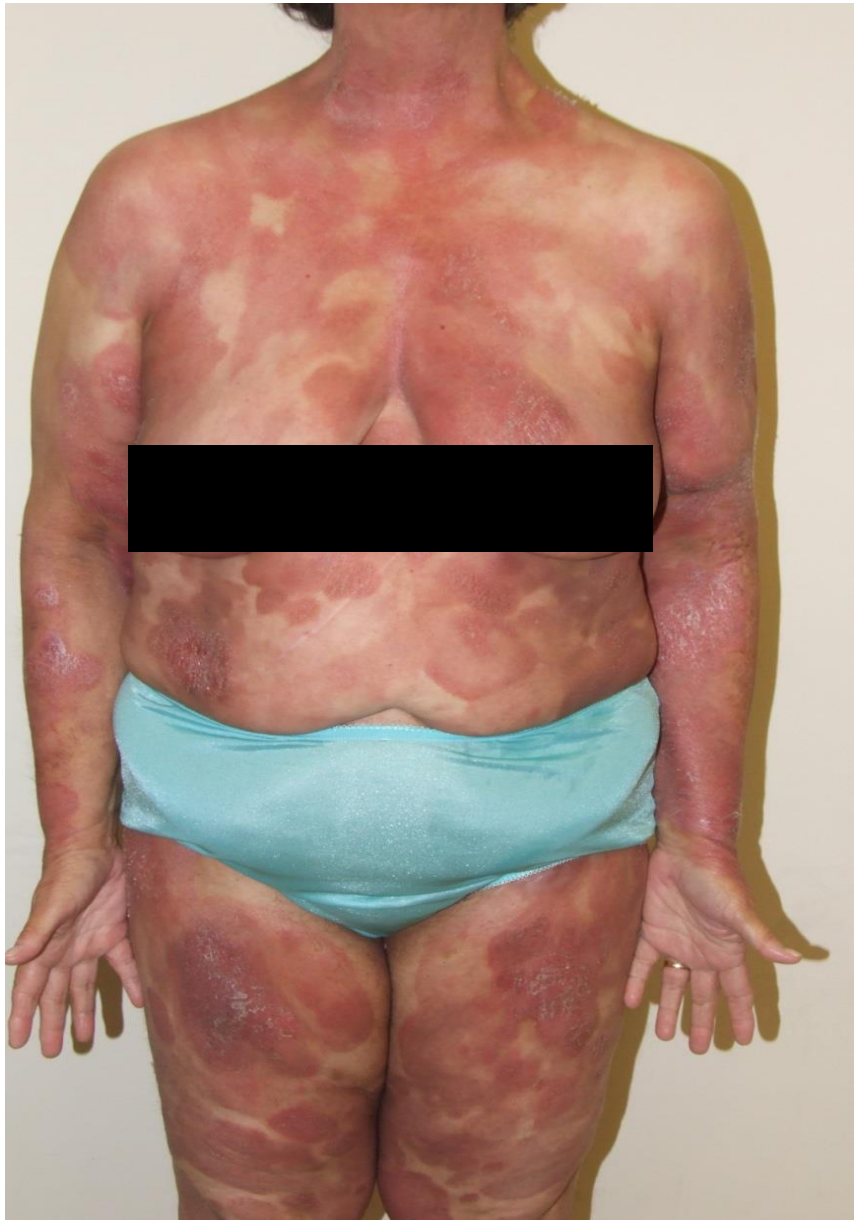


SS with better PFS outcome, p = 0.027; OS similar

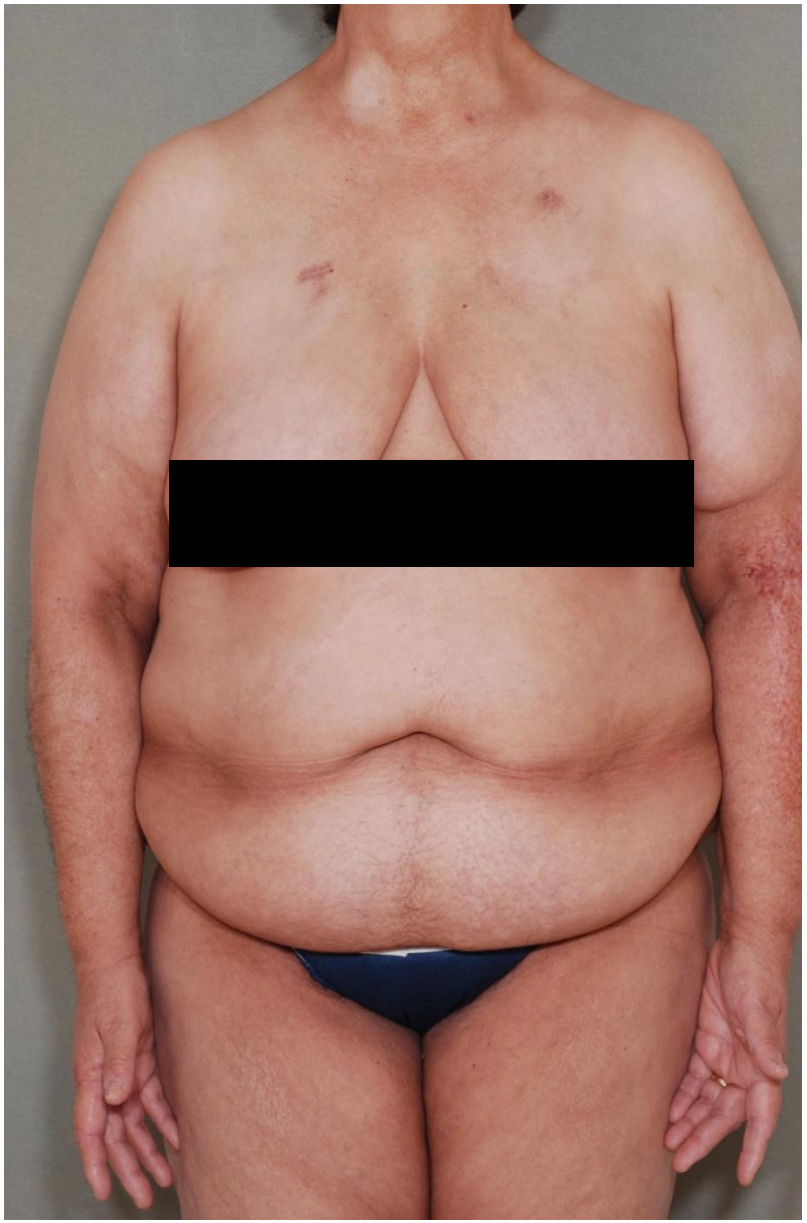
OS 75% at 2-years
PFS 51% at 2-years

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

Pre-TSEBT

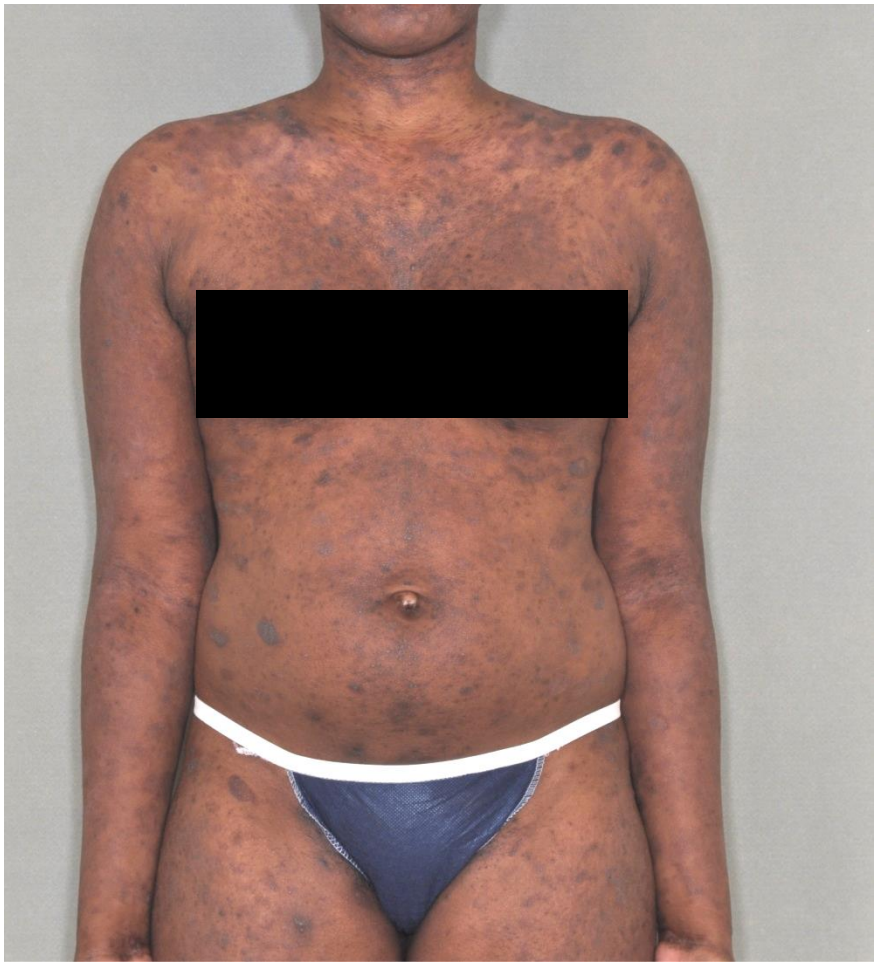


5.0+ yr (NED, no GVHD)

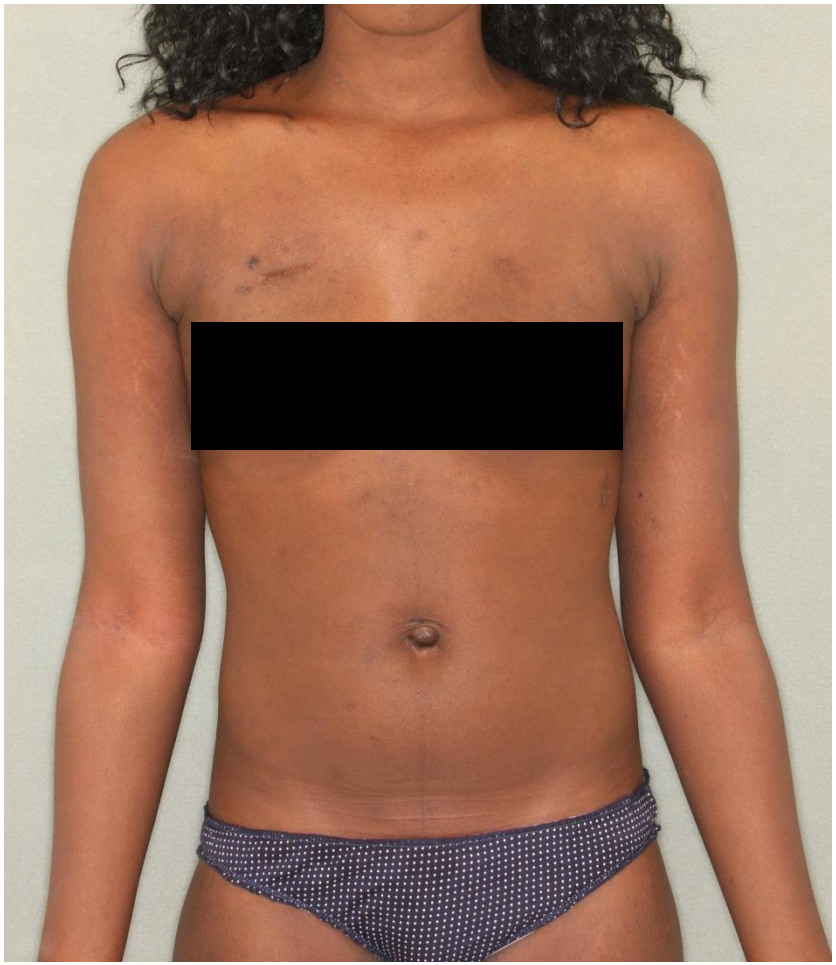


Mycosis fungoides, stage IVA w/ LCT in skin, LN+: CR

Pre-TSEBT



3.5+ yr (NED*)

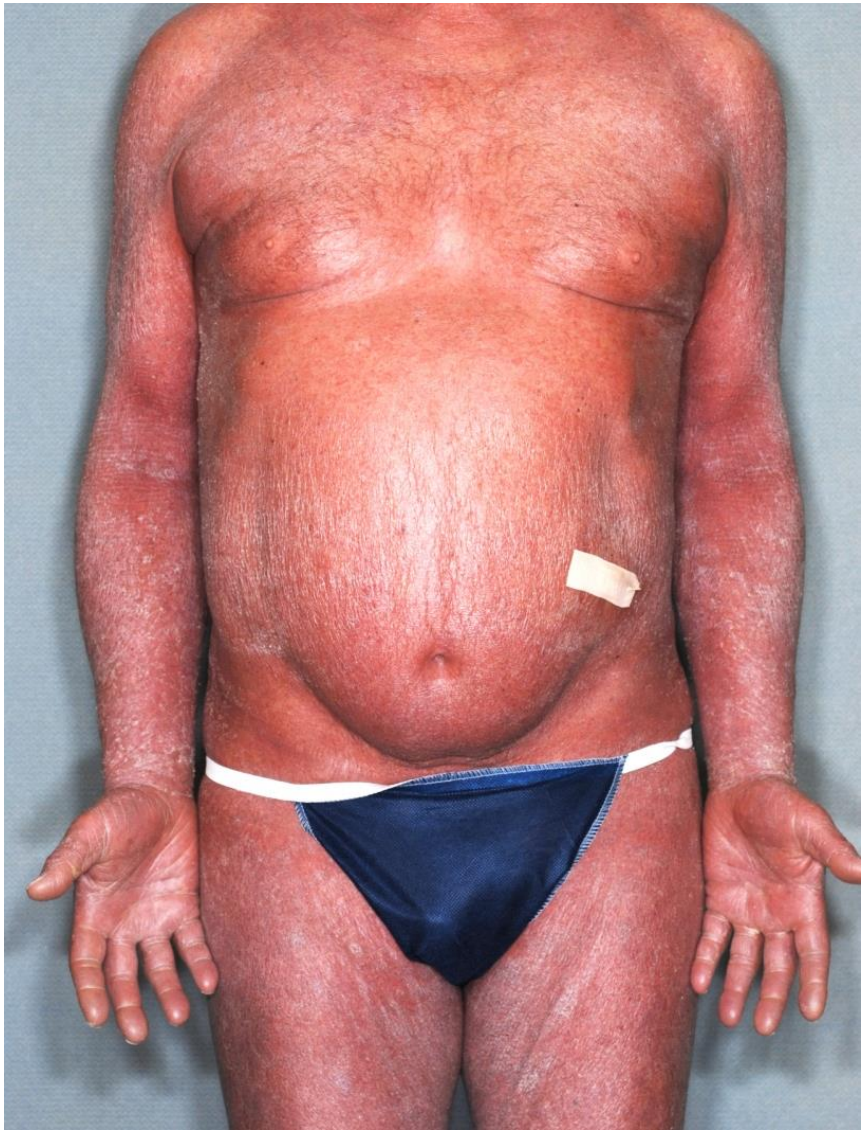


*Late onset aGVHD with pregnancy and non-compliance with GVHD prophylaxis

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

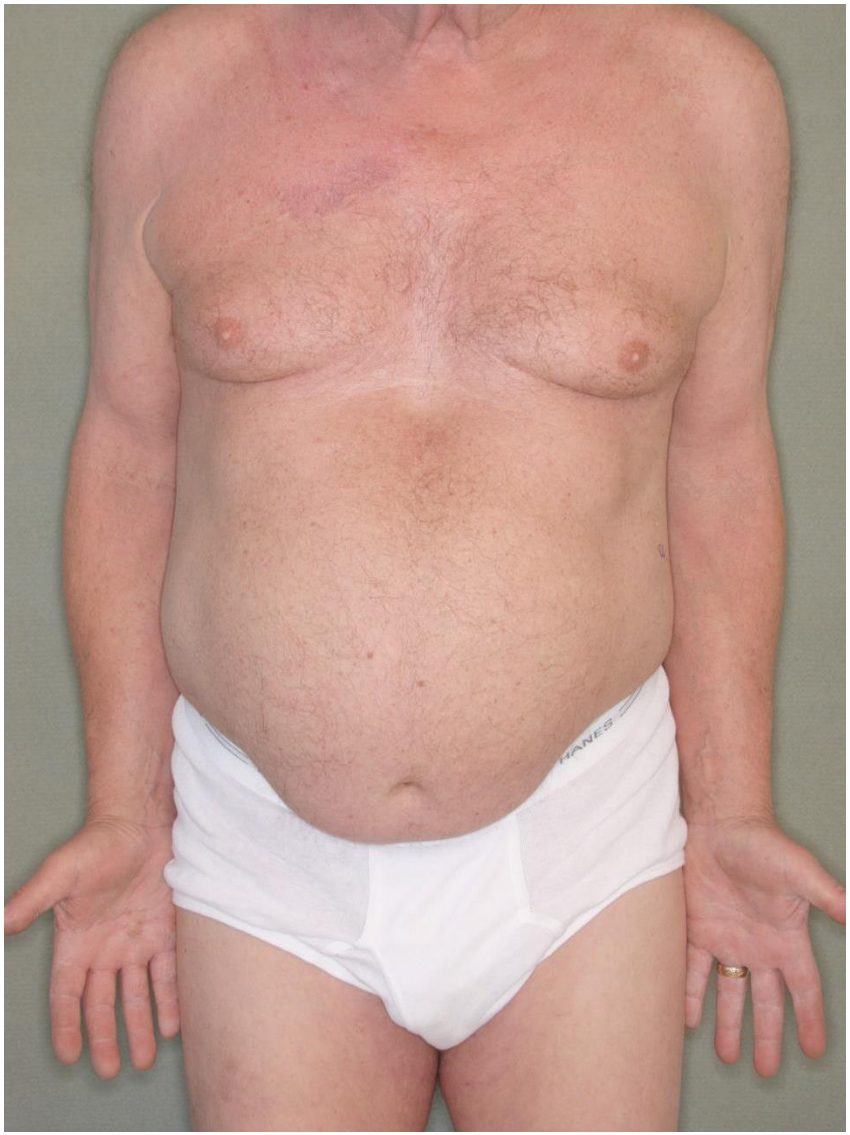
Pre-TSEBT

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



4.0+ yr (NED, no GVHD)

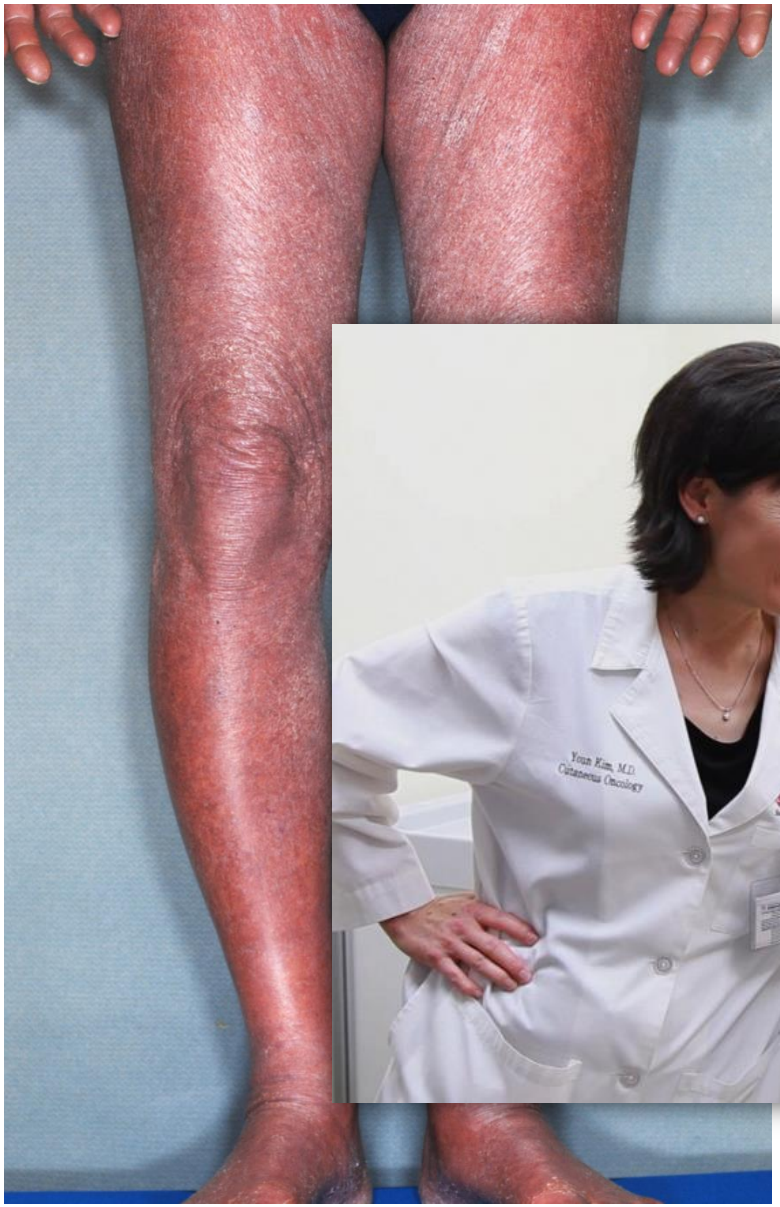
CD4+/CD26-: normalized

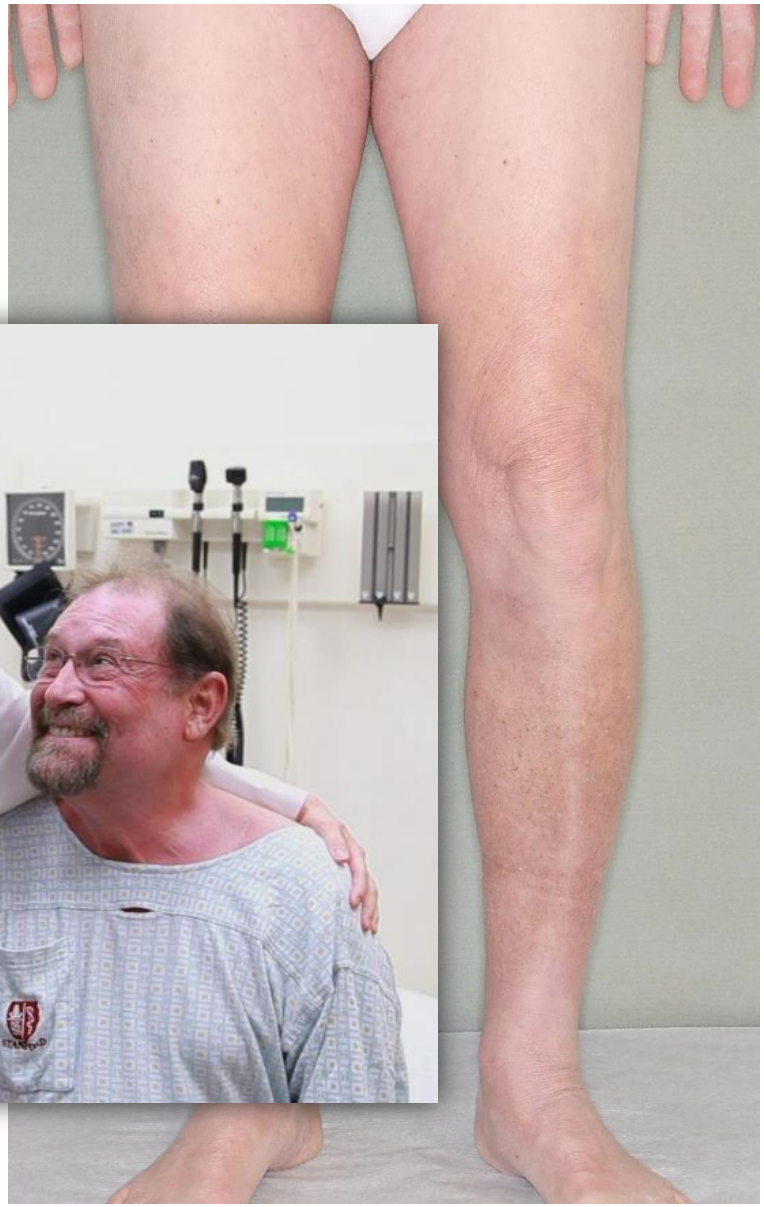


Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR

Pre-transplant

4.0+ yr (NED, no GVHD)





CANCER

Minimal Residual Disease Monitoring with High-Throughput Sequencing of T Cell Receptors in Cutaneous T Cell Lymphoma

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

Peripheral blood mononuclear cells and skin biopsy

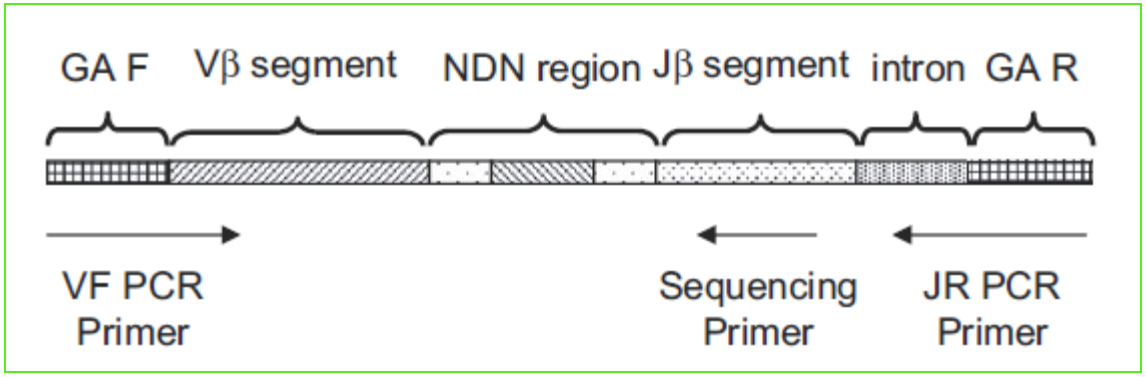
↓

Extraction of genomic DNA

↓

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

Up to 1,000,000 reads in blood; 200,000 reads in skin



Robins et al, Blood 2009;114:4099
WK Weng, Y Kim. Sci Transl Med 2013 5:214ra171

Detection of tumor specific malignant clonal sequence

TABLE 1. CHARACTERISTICS OF MALIGNANT TCR CLONAL SEQUENCE

PATIENT	% of Malignant Clone	TCRB CDR3 Sequence (5'-3')	V Gene	J Gene	CDR3 Length	Tissue Source	Vβ Usage by Flow
#1	69.03 %	TGTGCCAGCAGCTTA TCC *GGGAC* GGCCCC CAATGAGCA	TRBV 7-3	TRBJ 2-1	36	PBMC	n/a
#2	31.89 %	TGTGCCAGCAGCAGTTACTC *GGGACTAGCG* AGG AATGAGCA	6	TRBJ 2-1	36	PBMC	Vb 13.1 (TRBV6-5, 6-6, 6-9)
#3	51.67 %	TGTGCCAGCAGTGA GGTTA *GGACAG* TA TCACCCCT	TRBV 6-1	TRBJ 1-6	36	Skin	n/a
#4	81.52 %	TGTGCCAGCTCACCACC G *GGGACAGGGG* CAGATACGCA	TRBV 18	TRBJ 2-3	36	PBMC	Vb 18 (TRBV 18)
#5	78.09 %	TGCGCCAGCAGCTTGG CC *GGGGC* TCGG GATACGCA	TRBV 5-1	TRBJ 2-3	33	PBMC	n/a
#6	78.70 %	TGTGCCAGTAGTATAG GTT *CTAGCGGG* AC TAGCACAGATACGCA	TRBV 19	TRBJ 2-3	42	PBMC	Vb 17 (TRBV 19)
#7	91.72 %	TGCGCCAGCA TCG *GCGG* AA CGAACACCGGGGAGCT	TRBV 5-1	TRBJ 2-2	36	Skin	n/a
#8	76.09 %	TGTGCCAGCAGTGAAG *GGACAGGGGG* A AATTCACCCCT	TRBV 2	TRBJ 1-6	39	PBMC	Vb 22 (TRBV 2)
#9	59.66 %	TGTGCCAGCAGCGTAG TT *GGGA* GGGTTGACG CTGAAGC	TRBV 9	TRBJ 1-1	39	PBMC	Vb 1 (TRBV 9)
#10	18.33 %	TGCAGTGCTAG CC *GGACAGGGG* GCACAGATACGCA	TRBV 20.1	TRBJ 2-3	42	PBMC	Vb 2 (TRBV 20.1)

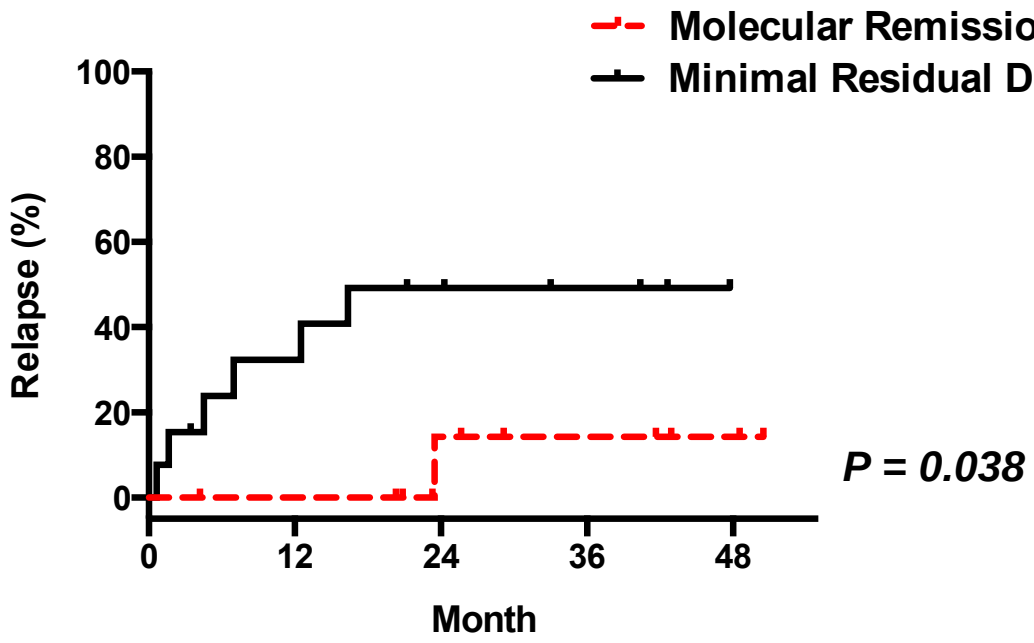
Sci Transl Med 2013, 5:214ra171

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				
Day+60				
Day+90				
Day+180				
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%

Monitoring MRD by HTS may predict true molecular and clinical cure and may predict disease relapse

Fewer relapse with molecular remission



42% of patients achieved molecular remission

Allogeneic HSCT
MRD monitoring with TCR HTS

Clinical benefit demonstrated in advanced stage MF/SS

- Can cure with allo HSCT, more safely, and provide lasting anti-tumor effect
  - SS better outcome than MF regardless of +/- LCT
- Regardless of center preference of transplant regimens, similar PFS, OS
- Longer follow-up needed to better assess post transplant complication issues and management

TCR HTS is a valuable means to monitor MRD after allo HSCT

- Molecular remission may predict better long-term outcome

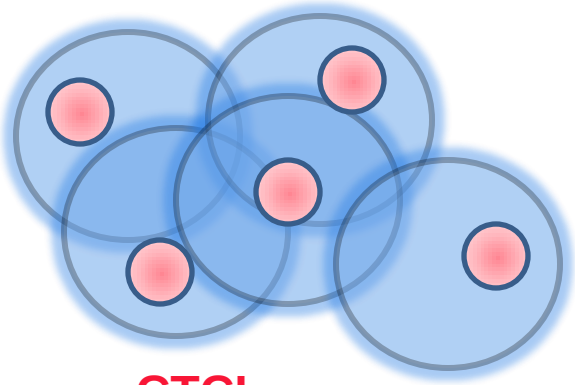
Allogeneic HSCT as ultimate immunotherapy in CTCL

Combined newer targeted therapies, chemotherapies, radiation therapy, followed by allogeneic HSCT

long-lasting, curative outcome

Adoptive cell transfer

Immune-modulating agents or antibodies



CTCL

Vaccine-based approaches

Allogeneic HSCT

Stanford Multidisciplinary Cutaneous Lymphoma Group