Living with Cutaneous T-cell Lymphoma

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Living with Cutaneous T-cell Lymphoma

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Cutaneous T-cell Lymphoma Mycosis Fungoides/Sézary Syndrome

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Historical Perspective MF

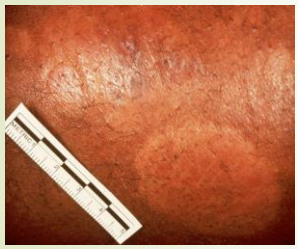
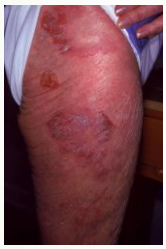
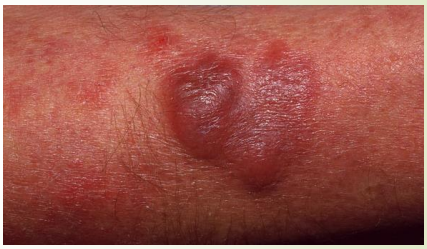
- Jean-Louis-Marc Alibert (1768 –1837) was a pioneer of French dermatology
- Originally planning to enter the priesthood, Alibert did not begin studying medicine until he was 26 years old
- In 1801 he was appointed médecin adjoint to the Hôpital Saint-Louis where he administered to patients with skin disorders, syphilis and leprosy. Following the Restoration of the French monarchy, Alibert became a personal physician to Louis XVIII
- Alibert was a prodigious writer, his best known work being the beautifully illustrated Descriptions des maladies de la peau
- In 1806, he was the first to describe a patient with mycosis fungoides.The disease was formerly referred to as "Alibert-Bazin syndrome", named in conjunction with dermatologist Pierre-Antoine-Ernest Bazin

Cutaneous T-cell and NK-cell lymphomas

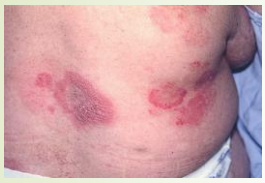
- Mycosis fungoides
- MF variants and subtypes
  - Folliculotropic MF
  - Pagetoid reticulosis
  - Granulomatous slack skin
- Sézary syndrome
- Adult T-cell leukemia/lymphoma
- Primary cutaneous $CD30^+$ lymphoproliferative disorders
  - Primary cutaneous anaplastic large cell lymphoma
  - Lymphomatoid papulosis
- Subcutaneous panniculitis-like T-cell lymphoma*
- Extranodal NK/T-cell lymphoma, nasal type
- Primary cutaneous peripheral T-cell lymphoma, unspecified
  - Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma (provisional)
  - Cutaneous γ/δ T-cell lymphoma (provisional)
  - Primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma (provisional)

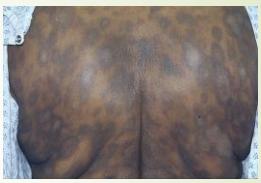
Willemze R, et al. *Blood*. 2005;105:3768-85.

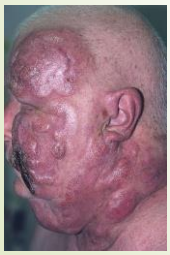
Mycosis Fungoides and Sézary Syndrome

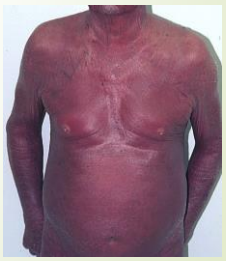




Skin Manifestations of CTCL


T1

T2



T3

T4


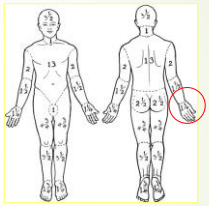
Recommended Staging of MF/SS

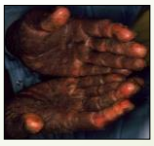
- **Skin staging**
  - Determination of stage T1-T4
  - Histological nuances: folliculotropism, large cell transformation
- **Blood analysis**
  - CBC, LFTs, LDH
  - T-cell gene rearrangements
  - Flow cytometry
  - CD4/CD8 ratio and/or Sézary cell prep
- **Radiology**
  - Early stage does not always need scanning
  - PET or CT scan for more advanced patients
- **Node biopsy**
  - Any ≥1.5 cm or fixed/firm may be biopsied

2007 ISCL/EORTC Staging for Mycosis Fungoides and Sézary Syndrome: Skin

T_1	Patches, papules and plaques covering < 10% of the skin surface
T_2	Patches, papules or plaques covering ≥ 10% of the skin surface
T_3	Tumors (≥ 1)
T_4	Confluence of erythematous lesions covering ≥ 80% BSA

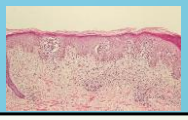
Olsen E, et al. Blood. 2007;110:1713-1722





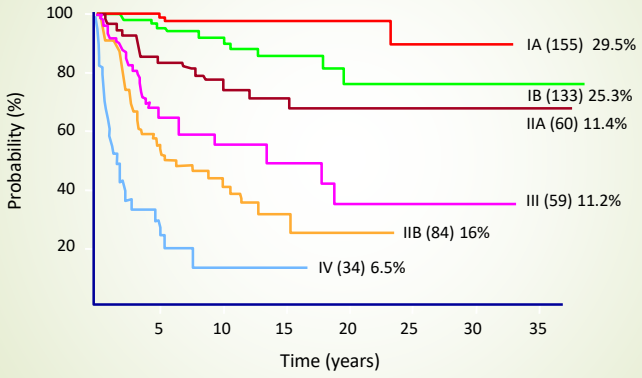
1% BSA: patient's palm plus all 5 fingers

Diagnosis of Early Mycosis Fungoides (4 Points Required)

CRITERIA	Major (2 points)	Minor (1 point)
CLINICAL Persistent and/or progressive patches/thin plaques plus 1) Non-sun exposed location 2) Size/shape variation 3) Poikiloderma	Any 2	Any 1
HISTOPATHOLOGICAL Superficial lymphoid infiltrate plus* 1) Epidermotropism 2) Atypia *Implies no spongiosis	Both 	Either 

Pimpinelli N, et al. J Am Acad Dermatol. 2005;53:1053-1063.

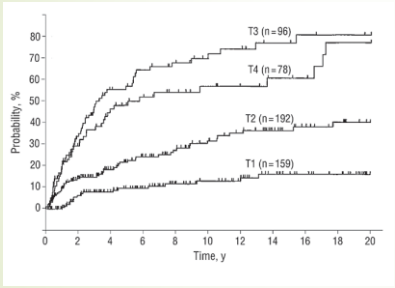
Survival by Clinical Stage in MF and SS Before Modern Era



Total N = 525

Kim YH, et al. *Arch Dermatol.* 2003;139:857-66.

MF/SS Patients Require Many Treatments Over Duration of the Disease



Risk of Progression:

Stage IA (T1N0): < 10%

Stage IB: (T2N0): ~25%

Stage IIA (T1N1-2 or T2N1-2): ~40%

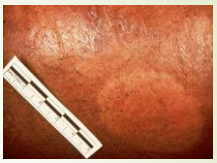
Kim YH, et al. Arch Dermatol. 2003;139:857-866.

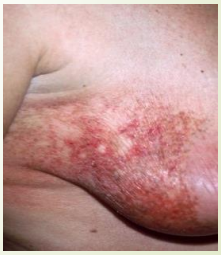
MF/SS: General Treatment Guidelines

- For patch/plaque skin lesions with no extracutaneous involvement, use skin-directed therapies first (if possible), then immunomodulatory agents
- For more extensive disease, combination of treatments, skin directed with immunomodulators (retinoids, IFN,HDAC) is generally more effective than single agent therapy and should be considered early in treatment algorithm
- Avoid chemotherapy in patients with early stage disease (stage I-IIA) and utilize with caution in those with later stage disease. Use single agent chemotherapy if possible

Patch-Stage Disease

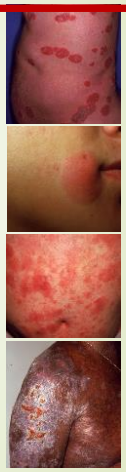
- Lesions may be hypopigmented, hyperpigmented or erythematous
- Biopsy: performed off topical steroids
- Differential diagnosis includes tinea corporis, eczema, drug reaction
- Skin involvement measured based on % of BSA
- T1= < 10% BSA
- T2=> 10% BSA

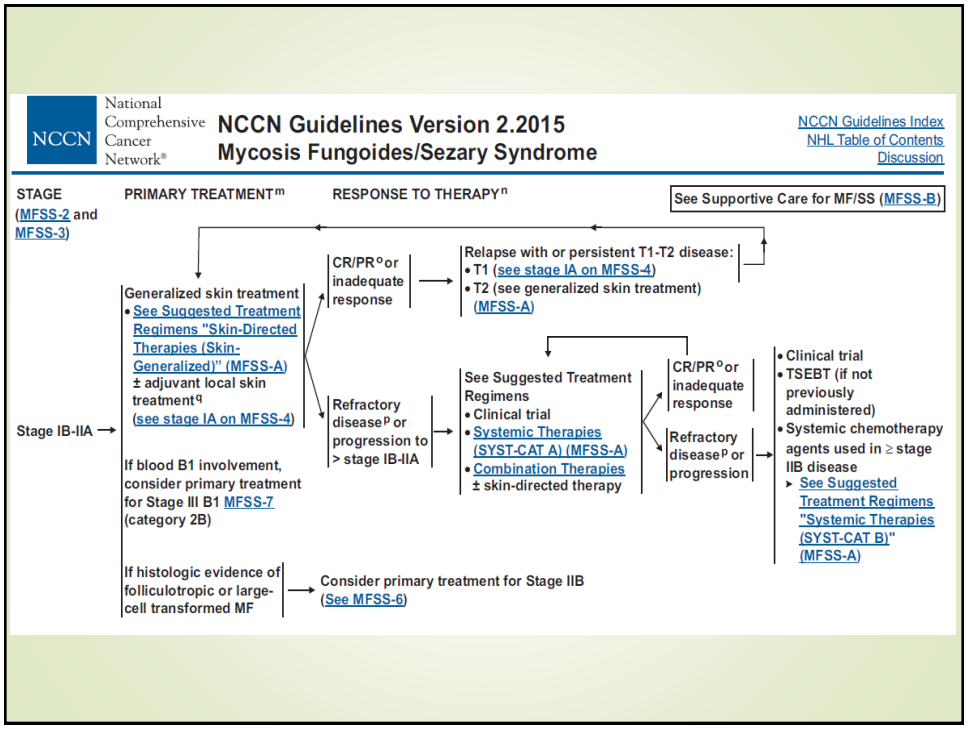




Plaque Stage Disease

- Skin directed therapy alone could be considered if no folliculotropism or LCT. Total body electron beam therapy reserved for extensive plaque disease
- Systemic immunomodulators
  - Interferon alfa and gamma
  - Oral retinoids (bexarotene, 13-cis retinoic acid, acitretin, all-trans RA)
  - Methotrexate (low dose)
  - HDAC inhibitors
- Combination SDT and systemic therapy or two systemic agents
- ECP +/- other systemic or skin-directed therapies if ≥B1 blood involvement





Skin Directed and Systemic Agents for Early Stage CTCL

Topicals

Steroids

Mustargen (Valchlor)

Radiation- electron beam

Retinoids

Imiquimod

Phototherapy (UVA, UVB)

Combinations

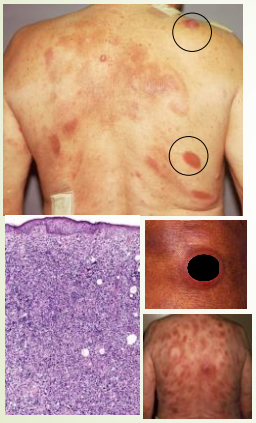
Retinoids IFN

UVA/UVB + retinoids,IFN

ECP + Retinoids

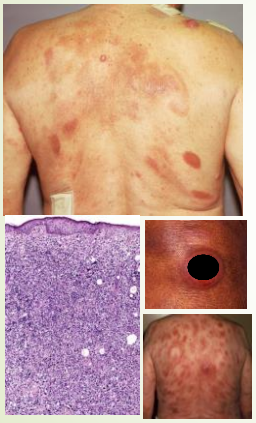
ECP + Retinoids + IFN

Tumor-stage Disease



- Tumor stage (T3): ≥ 1 nodular lesion > 1 cm
- Biopsy: representative non-ulcerated tumor
  - If large cells, record %
- Perform both T and B clonality studies
- Differential diagnosis includes all types of primary cutaneous lymphoma, pseudolymphoma (B cell) or lymphocytoma cutis (T cell), secondary cutaneous lymphoma, leukemic lesions, and for single lesions, metastatic cancer

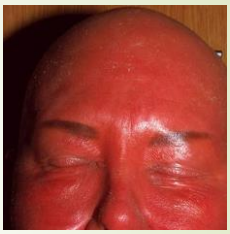
Tumor-stage Disease Treatment

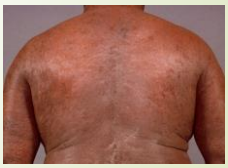


- Local XRT (orthovoltage or EB) plus systemic biologic therapies
- Total skin electron beam radiation:
  - If persistent lesions: skin-directed or systemic therapy with single or combination biologic agents
  - If remission achieved: single or combination biologic agents for maintenance therapy
- Single or combination chemotherapy
  - Consider BMT or experimental therapy if failed above

Erythrodermic Disease

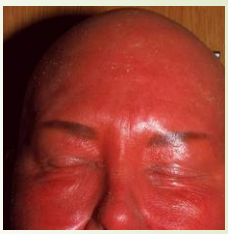
- Erythroderma (T4) defined as at least 80% BSA with erythematous confluence of lesions
- May be infiltrated or flat
- Hair loss in areas of involvement
- Diagnosis often difficult by skin biopsy alone—must be off topical steroids, it may require multiple biopsies, and requires immunophenotyping and TCR GR analysis—blood and nodal evaluation key
- Differential diagnosis includes atopic dermatitis, hyper IgE, psoriasis, drug reaction

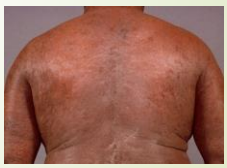




Erythrodermic Disease

- Total body skin-directed therapy may be considered for those with B0 disease
  - Topical nitrogen mustard
  - PUVA or UVB
  - Total skin electron beam
- Single or combination immunomodulators (interferon , retinoids, photopheresis) ± skin-directed therapy
- Single agent therapy
  - Methotrexate
  - HDAC inhibitors
  - Brentuximab vedotin





Systemic Chemotherapy Agents for CTCL

Brentuximab vedotin

Gemcitabine

Liposomal doxorubicin

Pralatrexate

Romidepsin

Vorinostat

Chlorambucil

Pentostatin

Cytoxan

Temozolimide

Methotrexate >100 mg

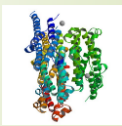
Bortezomib

Interferon Alfa in the Treatment of MF

Usual dose
- 3-6 MU IFN a2a/b SQ TIW to QD or low dose pegylated interferon alfa

Efficacy
- ORR: 50% to 80%; CR 20% to 41% including 25% stage I-IIA
- Maximum response usually by 6 months
- Long-lasting remissions, long-term maintenance well tolerated

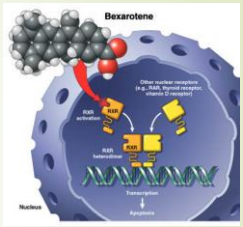
Expected side effects
- Common (dose related): anorexia, fatigue, depression
- Uncommon (dose related): leukopenia and elevated LFTs
- Adjuvant treatment with phototherapy ± retinoid
- Post TSEB therapy or adjuvant to local XRT with tumor-stage disease



Olsen EA, et al. Dermatol Ther. 2003;16:311-321.

Bexarotene in the Treatment of MF

- Retinoid X receptor-selective retinoid
- Monotherapy
  - Dose (target): 300 mg/m^2
  - Efficacy
    - IA-IIA: 53% ORR, 7% CR, better with higher dose
    - IIB-IVB: 46% ORR, 5% CR, better with higher dose
- Safety
  - Hyperlipidemia and secondary hypothyroidism - TSH markedly decreased
  - Leukopenia 28%, headache 47%, asthenia 36% at target dose

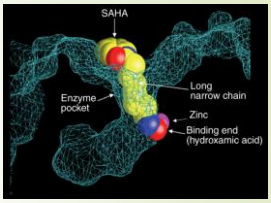


Duvic M. Haematological Rep. 2006;2:75-76.

HDAC Inhibitors in MF/SS

Vorinostat*

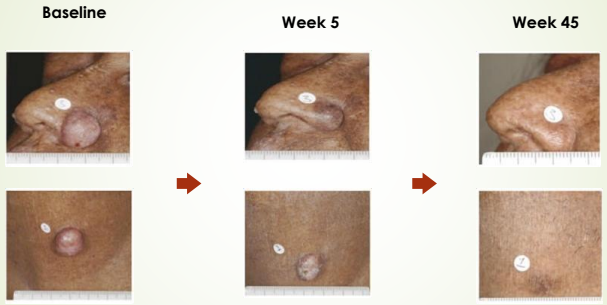
- Orally bioavailable
- 30% PR across all stages at 400 mg per day
- Adverse effects: diarrhea most disabling and dose related. Anemia, thrombocytopenia, increased creatinine less common



*Olsen et al JCO 2007.

Vorinostat– Visible Improvements in Skin Lesions

Baseline: Stage IIB MF



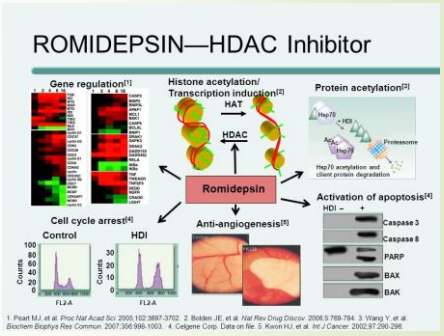
Patient remained on vorinostat for >4 years having received 4 prior therapies

[a]Sample responses during treatment with vorinostat

Duvic M et al. Clin Lymphoma Myeloma; 2009;9:412–416.

Romidepsin

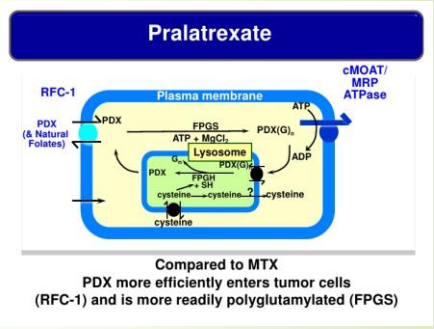
- IV preparation only
- 34% response rate
- Dose is 14 mg/m2 over 4 hr infusion days 1,8,and 15 q 28 days
- Adverse effects
  - EKG shows QT prolongation
  - Nausea, fatigue, vomiting and anorexia, low blood counts



[#]Piekarz et al. JCO 2009;Whittaker et al JCO 2010.

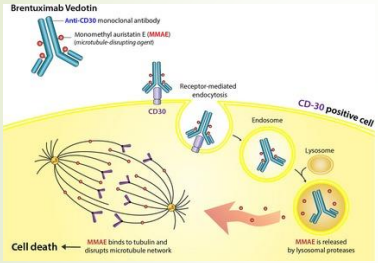
Pralatrexate

- Approved for relapsed/refractory PTCL and MF with LCT
- Open label Phase I clinical research study in CTCL*
  - 54 patients who failed at least one prior systemic therapy
  - Treated with maximum (and optimal) dose of 15 mg/m2 weekly for 3 weeks of a 4 week cycle
  - **Objective response rate of 41% (including 35% PR, 6% CR)**
  - Most frequent AEs: fatigue, mucositis, nausea, epistaxis, edema and vomiting. Grade 3-4AEs: mucositis (17%), thrombocytopenia (3%)



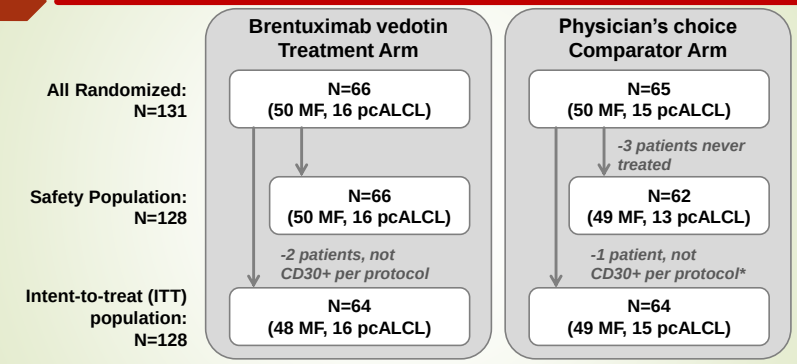
*Horwitz et al Blood 2012.

Brentuximab vedotin



- Targets CD30 receptor on T cells
- CD30 expression in most MF patients
- Major side effects are neurotoxicity (paresthesias)
- Drug is given IV once every 3 weeks

ALCANZA Study- Brentuximab Vedotin



3 patients on brentuximab vedotin are still on treatment at the time of analysis

*CD30 assay changed during the study, patients were CD30+ under original assay

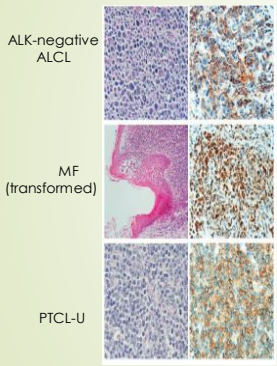
Prince et al, Lancet 2017.

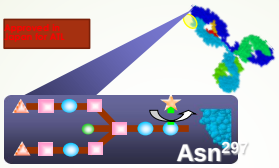
ALCANZA STUDY: ORR4 and Response Rates by Disease Type

	Brentuximab Vedotin				Bexarotene or Methotrexate			
	Total N = 64 n (%)	ORR4 (%)	ORR (%)	CR (%)	Total N = 64 n (%)	ORR4 (%)	ORR (%)	CR (%)
ITT population	64 (100)	56	67	16	64 (100)	13	20	2
MF	48 (75)	50	65	10	49 (77)	10	16	0
Stage								
IA-IIA	15 (31)	40	53	7	18 (37)	22	28	0
IIB	19 (40)	63	68	16	19 (39)	5	16	0
IIIA-IIIB	4 (8)	50	75	0	2 (4)	0	0	0
IVA	2 (4)	100	100	50	9 (18)	0	0	0
IVB	7 (15)	29	57	0	0	NA	NA	NA
pcALCL	16 (25)	75	75	31	15 (23)	20	33	7
Disease involvement								
Skin-only	9 (56)	89	89	44	11 (73)	27	45	9
Extracutaneous disease	7 (44)	57	57	14	4 (27)	0	0	0

NA, not applicable.

Mogamulizumab: Anti-CCR4 Monoclonal Antibody





Approved in Japan for HTLV-1 associated T cell leukemia/lymphoma

Lymphoma Subtype	N	ORR(%)	[95% CI]
PTCL	29	34	[18 - 54]
PTCL-NOS	16	19	
AITL	12	50	
ALCL ALK(-)	1	100	
CTCL	8	38	[9 - 76]

Ishida T, *et al.* Clin Cancer Res. 2004 Aug 15;10(16):5494-500.

MAVORIC: Open-label, randomized study of anti-CCR4 monoclonal antibody, mogamulizumab (KW-0761) vs vorinostat in patients with previously treated CTCL

Inclusion:
- Stage IB – IVB, MF or SS (B2)
- At least one prior course of systemic therapy

Exclusion:
- Patients with large cell transformation

1:1 Randomization

Mogamulizumab
1.0 mg/kg i.v.
Weekly for first 28-day cycle; days 1 and 15 of subsequent cycles

Vorinostat
400 mg PO daily

One-way crossover after PD or intolerable toxicity

- Patients could remain in the treatment phase up until progression or intolerable toxicity
- Vorinostat was administered in accordance with US prescribing information, targeting maximum tolerated effective dose; crossover allowed with approval
- CCR4 expression was not a requirement for participation
- Patients were enrolled at 61 centers across 11 countries

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One-way crossover after PD or intolerable toxicity

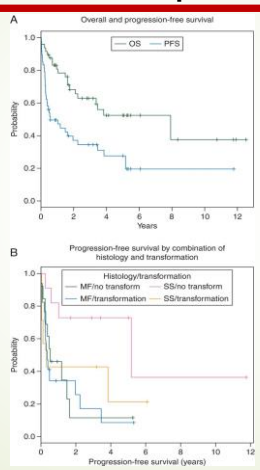
Response outcomes

	Mogamulizumab	Vorinostat
ORR[a,b], n/N (%)	**52/186 (28)**	**9/186 (5)**
MF[c]	**22/105 (21)**	**7/99 (7)**
SS[b]	**30/81 (37)**	**2/87 (2)**
Stage IB/IIA	7/36 (19)	5/49 (10)
Stage IIB	5/32 (16)	1/23 (4)
Stage III	5/22 (23)	0/16 (0)
Stage IV	35/96 (36)	3/98 (3)
DOR, median, months	**14**	**9**
MF	13 (n=22)	9 (n=7)
SS	17 (n=30)	7 (n=2)

Allogeneic Stem Cell Transplantation in CTCL

Table 2. Disease stage at diagnosis

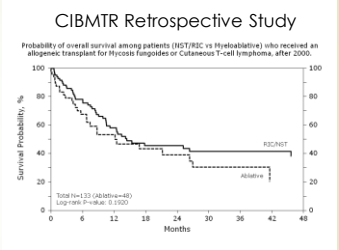
Disease stage	No. of patients (*N* = 47)
Clinicopathologic stage at diagnosis	
Mycosis fungoides	12
MF with large-cell transformation	18
Mycosis fungoides with Sézary syndrome	9
Mycosis fungoides with Sézary syndrome and	8
Large-cell transformation	4 nodal; 1 tumor
Folliculotropic mycosis fungoides	4
TNMB stage at diagnosis	
IB–IIA Refractory IB	2
IIB Tumors (includes tumors with large-cell transformation)	12
IIIA Erythrodermic mycosis fungoides (<B2)	1
IVA Sézary syndrome (B2) and/or nodes	18
IVB Bone marrow positive, liver (*n* = 2)	15



C. Hosing et al. Ann Oncol 2015;26:2490-2495.

Lechowicz et al, BMT 2014.

CIBMTR Retrospective Study

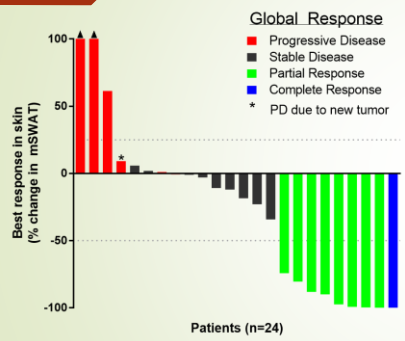


- 133 pts in registry with CTCL
- RI regimens in 64%
- Only 8 were in CR
- 100 day TRM 16%
- PFS and OS 36% and 44% at 2 yrs

Yale Allogeneic HSCT Guidelines

- Indications for HSCT
  - Mycosis fungoides (MF):
    - Tumor stage or folliculotropic MF, refractory to multiple therapies
    - MF with large cell transformation or visceral involvement
  - Sezary Syndrome that is chemo-resistant to multiple agents
- Conditioning Treatment
  - Pentostatin + low dose TBI- activity in refractory T cell lymphoma
  - Total skin electron beam as part of conditioning
  - Haploidentical transplants

CITN-10: Phase 2 Trial of Pembrolizumab in Relapsed or Refractory CTCL



Overall response rate: 38%

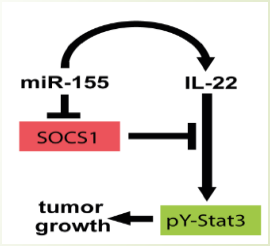
Characteristics	Total, n=24	Response				ORR, n (%)
	n(%)	CR	PR	SD	PD	
Gender						
Male	18 (75)	0	6	8	4	6/18 (33)
Female	6 (25)	1	2	1	2	3/6 (50)
Diagnosis						
MF	9 (38)	0	5	2	2	5/9 (56)
SS	15 (63)	1	3	7	4	4/15(27)
Stage						
IB	1 (4)	0	0	0	1	0/1 (0)
IIB	2 (8)	0	2	0	0	2/2 (100)
IIIA	3 (12)	0	2	1	0	2/3 (67)
IIIB	3 (12)	0	1	0	2	1/3 (33)
IVA	15 (63)	1	3	8	3	4/15 (27)
Number of prior systemic therapies						
<4	9 (38)	0	4	3	2	4/9 (44)
≥4	15 (63)	1	4	6	4	5/15 (33)

Follow up time (wks) - median(range): 40(9 - 60)
TTR (wks): 11(8-41) DOR: Median not reached; 89% ongoing
PFS: Median not reached 1-year PFS: 69%
Overall Response Rate: 38% (9 patients)

Khodadoust, Kim, and CITN investigators.

Inhibitors of Micro RNA: miR-155

- Highly expressed in ALK- ALCL and in MF/SS
- Drives growth of ALCL xenografts
- Directly targets SOCS1 and C/EBPb
  - Supresses IL-8, induces IL-22
  - Induces py-Stat3 activation
  - Phase I trial in MF/SS
    - Intralesion
    - subcutaneous



The United States Cutaneous Lymphoma Consortium (USCLC.org)

- Nonprofit, physician run organization founded in September 2007
- Mission Statement: To foster a multidisciplinary approach to patient care, education and clinical and basic research in the area of cutaneous lymphomas
- Goals: To establish an organization of physicians with expertise in cutaneous lymphomas to :
  1. Create a national registry of patients with cutaneous lymphomas
  2. Develop and participate in cooperative clinical trials of cutaneous lymphomas and/or other collaborative/cooperative research projects
  3. Develop guidelines of therapy and standardization of clinical trials for cutaneous lymphomas
  4. Develop a national virtual tissue bank for cutaneous lymphomas
- **Will have a patient portal for patient registry**

Conclusions

- Multiple treatment approaches for patients with CTCL
- Focus on improvement in quality of life
- Stem cell transplant has led to cures
- New agents and mechanisms are being identified
- 53 studies on Clinical Trials.gov for mycosis fungoides
- Advocacy through Cutaneous Lymphoma Foundation, The Leukemia & Lymphoma Society, and Lymphoma Research Foundation

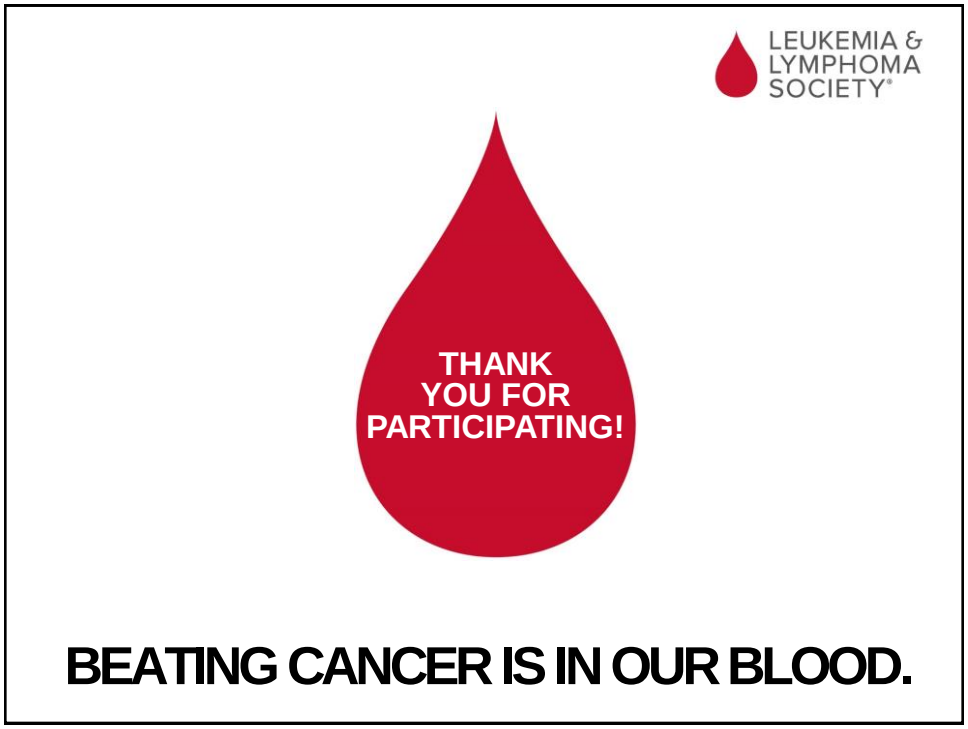
Q&A Session

The Leukemia & Lymphoma Society Offers:

- **Information Specialists:** Master's level oncology professionals available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
  - ➢**TOLL-FREE PHONE: 1-800-955-4572**
  - ➢**EMAIL:** infocenter@LLS.org
- **Free Education Booklets:**
  - ➢ www.LLS.org/booklets
- **Free Telephone/Web Programs:**
  - ➢www.LLS.org/programs
- **Live, weekly Online Chats:**
  - ➢www.LLS.org/chat

The Leukemia & Lymphoma Society Offers:

- **LLS Podcast, *The Bloodline with LLS:*** Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: www.LLS.org/thebloodline
  - **'CTCL: Skin Lymphoma, Not Skin Cancer' episode**
- **Education Video:** Free education videos about survivorship, treatment, disease updates and other topics**:** www.LLS.org/educationvideos
- **Patti Robinson Kaufmann First Connection Program:** Peer-to-peer program that matches newly diagnosed patients and their families: www.LLS.org/firstconnection
- **Free Nutrition Consults:** Telephone and email consultations with a Registered Dietitian: www.LLS.org/nutrition
- **What to ask:** Questions to ask your treatment team: www.LLS.org/whattoask
- **Support Resources**: LLS Community, discussion boards, blogs, support groups, financial assistance and more: www.LLS.org/support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