Topic Area:
What's New in T and B cell Lymphoma Diagnostic and Therapeutic Landscapes

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What's New in T and B cell Lymphoma Diagnostic and Therapeutic Landscapes

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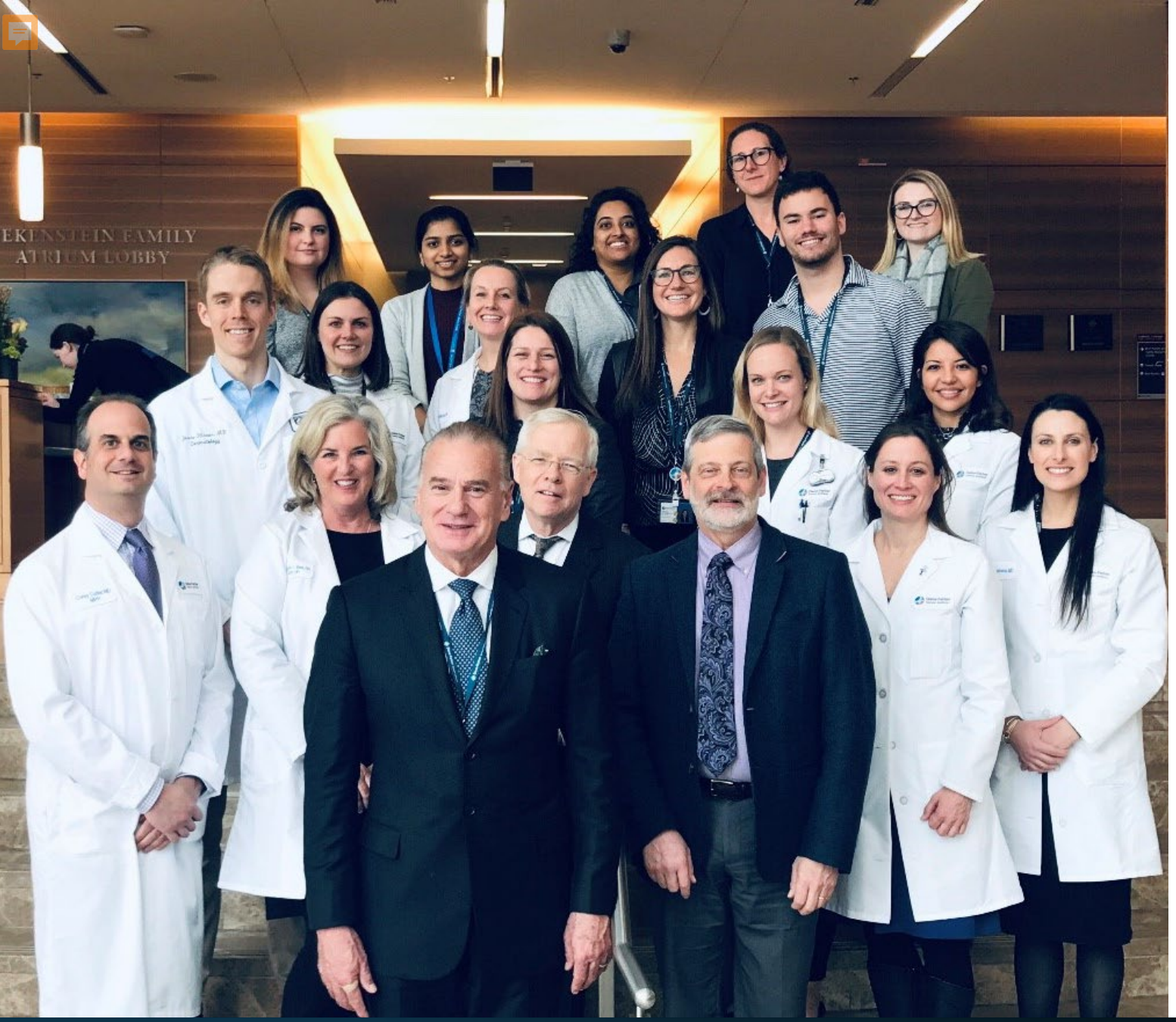
SDNP Annual Meeting 4/23

Dana-Farber Cancer Institute

No Conflcit of Interest to Disclose



DFCI CTCL Team

Dermatology (MDs, NP, PA, RNs, Fellows & Residents)

Medical Oncologist & Transplant Oncology

Infusion Service

Radiation Oncologist & RT Service

Pathology-Derm/Heme/Molecular

Radiology

Photopheresis & Phototherapy Centers

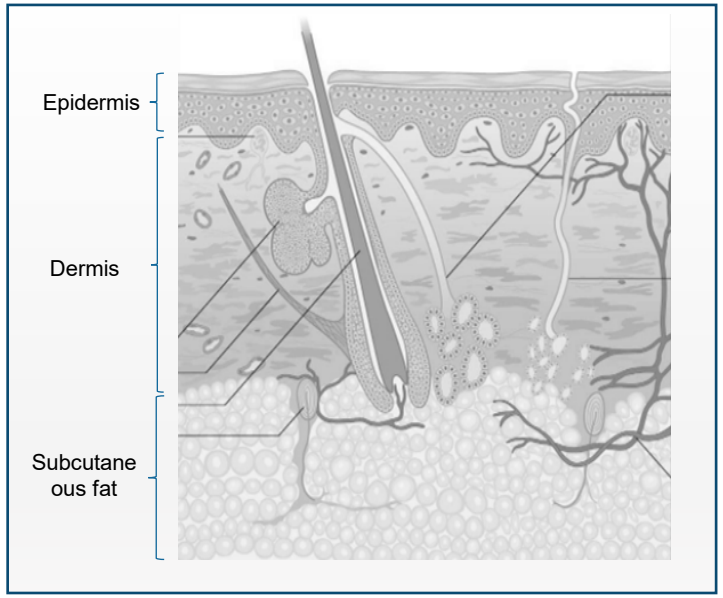
Research Teams- Clinical Trials & Bench

New Patient Coordinator

Medical Assistants & Scheduling Staff

Patient and Family

THE SKIN: More than a just physical barrier

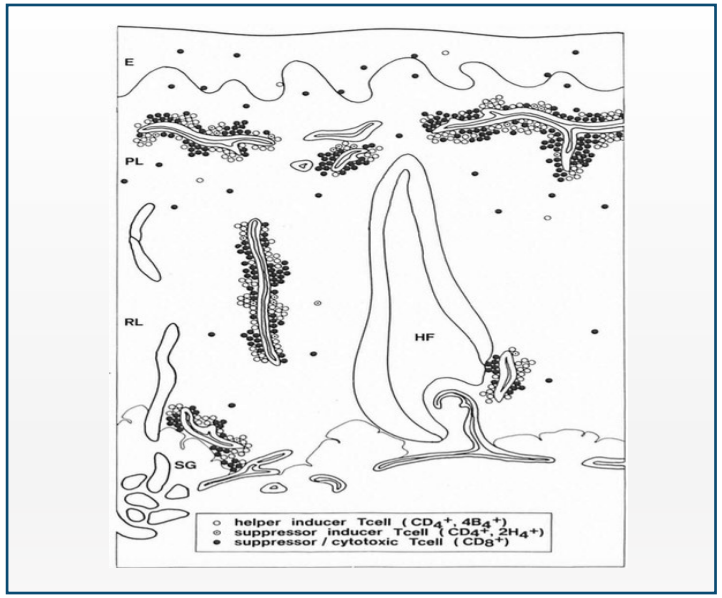


"Old View"

Current commonly held view

1922

First reported observation of lymphocytes in normal skin

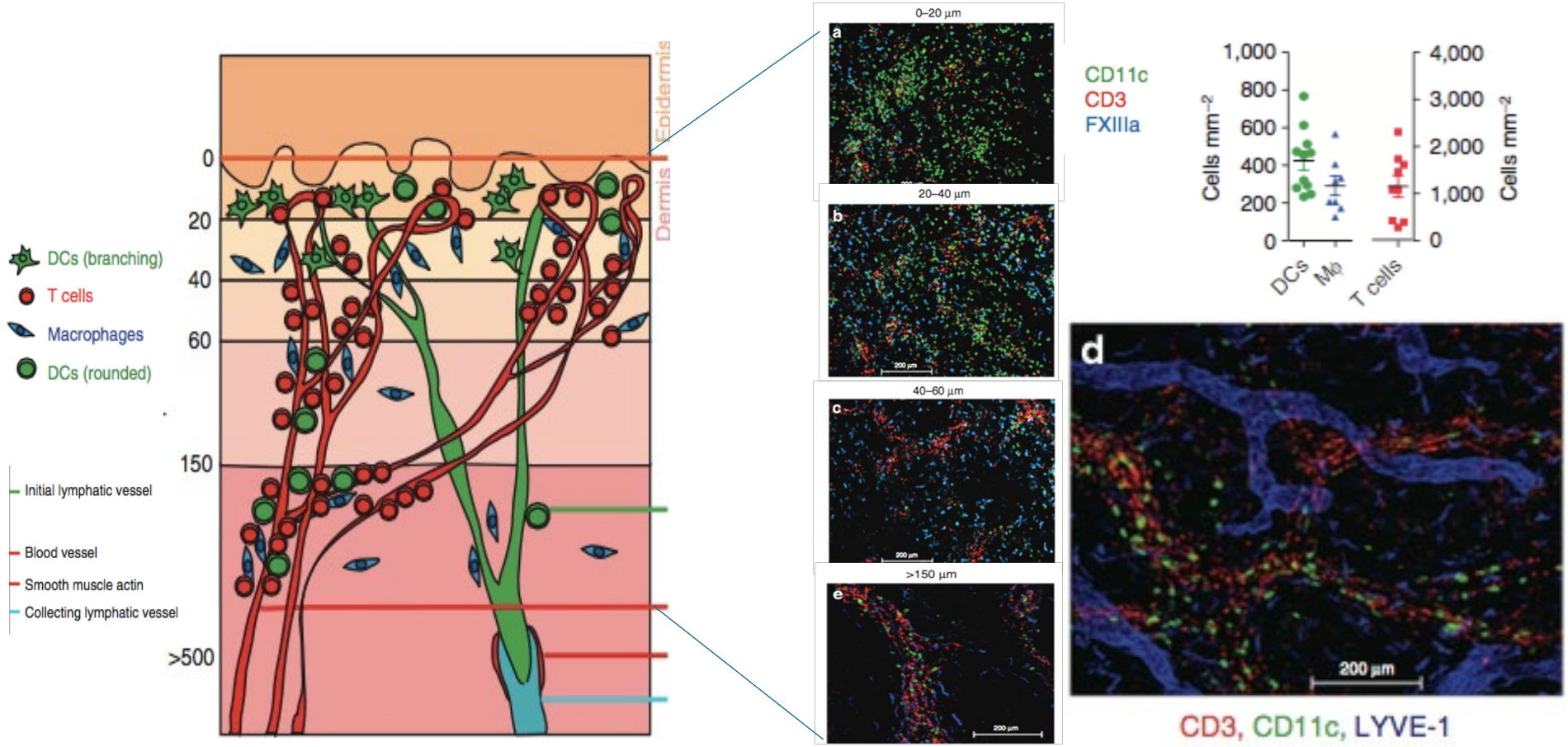


1970-1980's

Identification of the "Skin Immune System": presence of T cells in normal skin

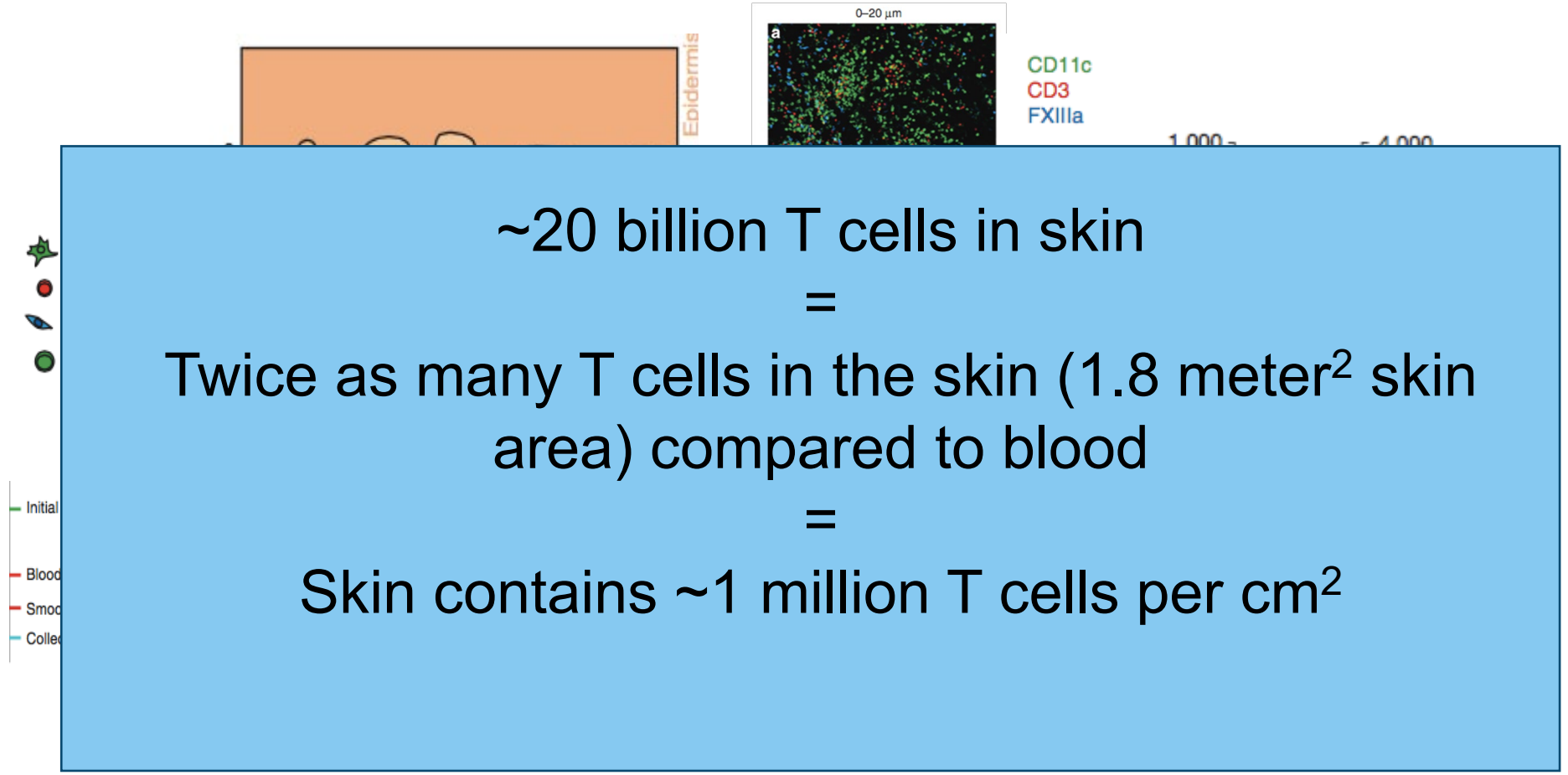
Bos et al. The Skin Immune System (SIS): Distribution and immunophenotype of lymphocyte subpopulations in normal human skin.

Skin contains a rich immune system



Wang XN et al. A three-dimensional atlas of human dermal leukocytes, lymphatics, and blood vessels. J Invest Dermatol. 2014 Apr;134(4):965-974.

Skin contains a rich immune system



~20 billion T cells in skin

=

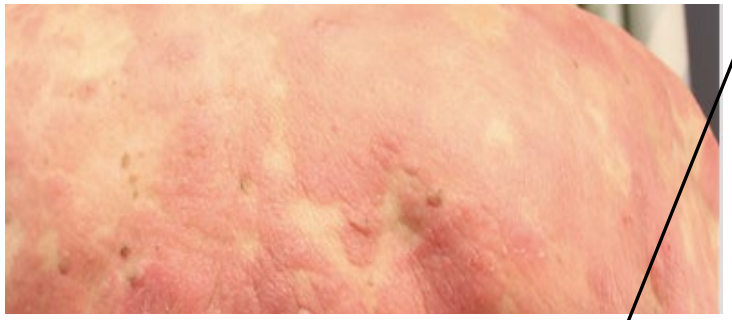
Twice as many T cells in the skin (1.8 meter^2 skin area) compared to blood

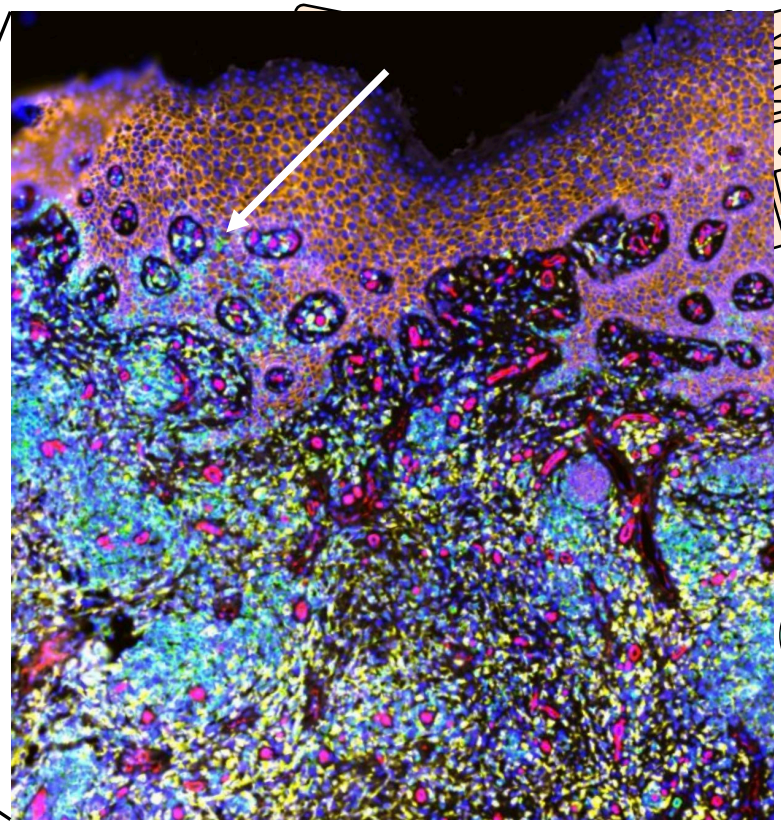
=

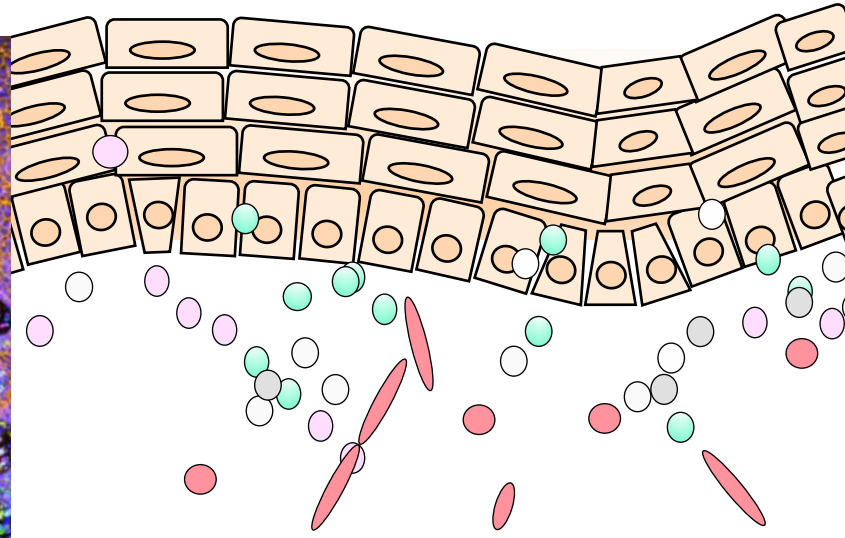
Skin contains ~1 million T cells per cm^2

Primary cutaneous T cell lymphomas (CTCL) are *rare cancers* of a skin-homing T cells

~10 cases per million in USA (Mycosis Fungoides and Sezary Syndrome subtypes)
<4% of all non-Hodgkin's lymphoma (NHL)



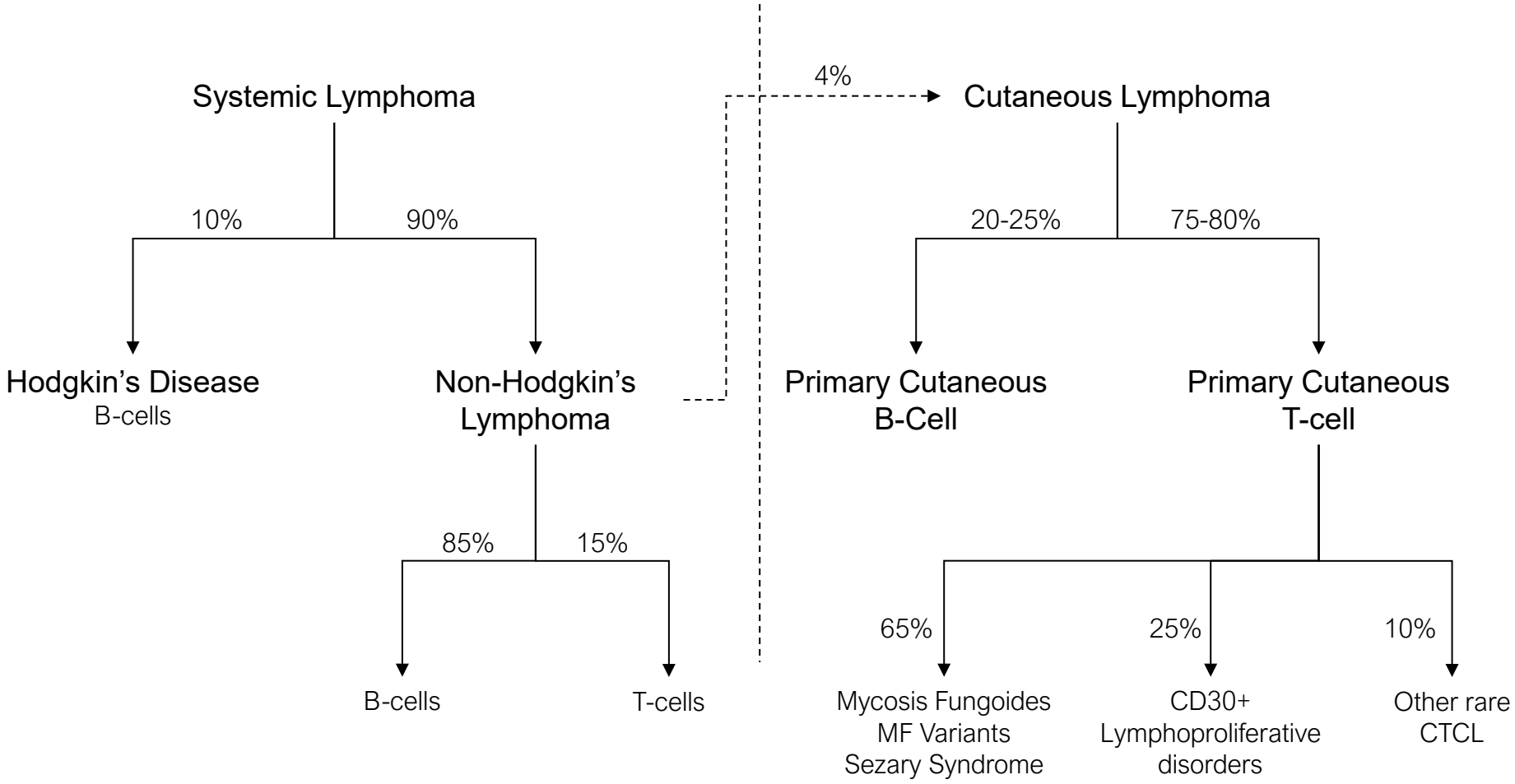




Cancerous skin-homing T cells

Benign reactive inflammatory cells

Breakdown of Lymphomas by Type



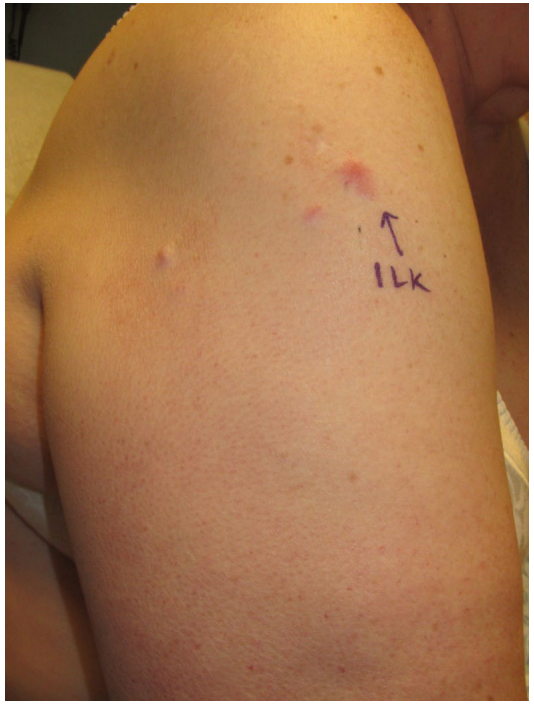
Primary Cutaneous B-Cell Lymphoma Update

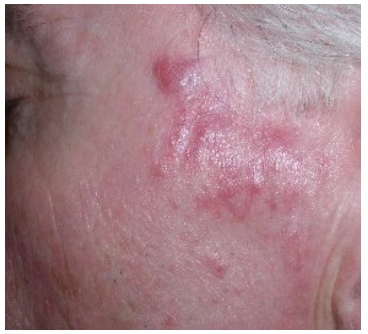
Primary B-Cell Lymphomas *Fast Facts*

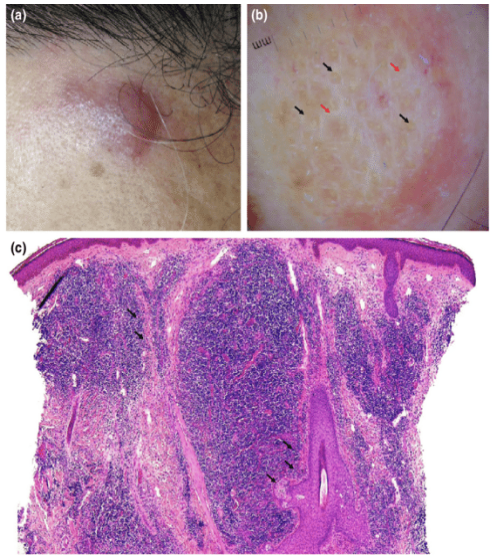
- Group of extranodal B-Cell non-Hodgkin Lymphomas B-cell derived
- Primarily involve skin without evidence extracutaneous disease at the time of DX (completion of staging w/u (scans/ blood/ bx)
- 25% of all Cutaneous Lymphomas
- Incidence 4 per million persons>unique entities/features/ pathology/prognosis
- WHO, 2018- **3** major subtypes
- Primary cutaneous marginal zone(pcMZL)
- Primary cutaneous follicle center lymphoma (pcFCL)
- Primary cutaneous large B cell lymphoma, leg type

pcMZL

2-7% of all primary cutaneous lymphomas	Cause unknown, but…pc MZL has been associated with tattoo pigments, tick bites and antigen injection.	Borrelia burgdorferi infection established in Europe, but not USA
Red-violaceous small, solitary or multiple papules or nodules.	INDOLENT course	Preferentially located on trunk, arms and occasionally the head
Pathology reveals dense dermal lymphocytic infiltrates arranged in nodular or diffuse pattern.	IHC stains+ CD20, +CD22,+ CD79a + BCL 2: absence of CD3	Genetic studies to document clonality



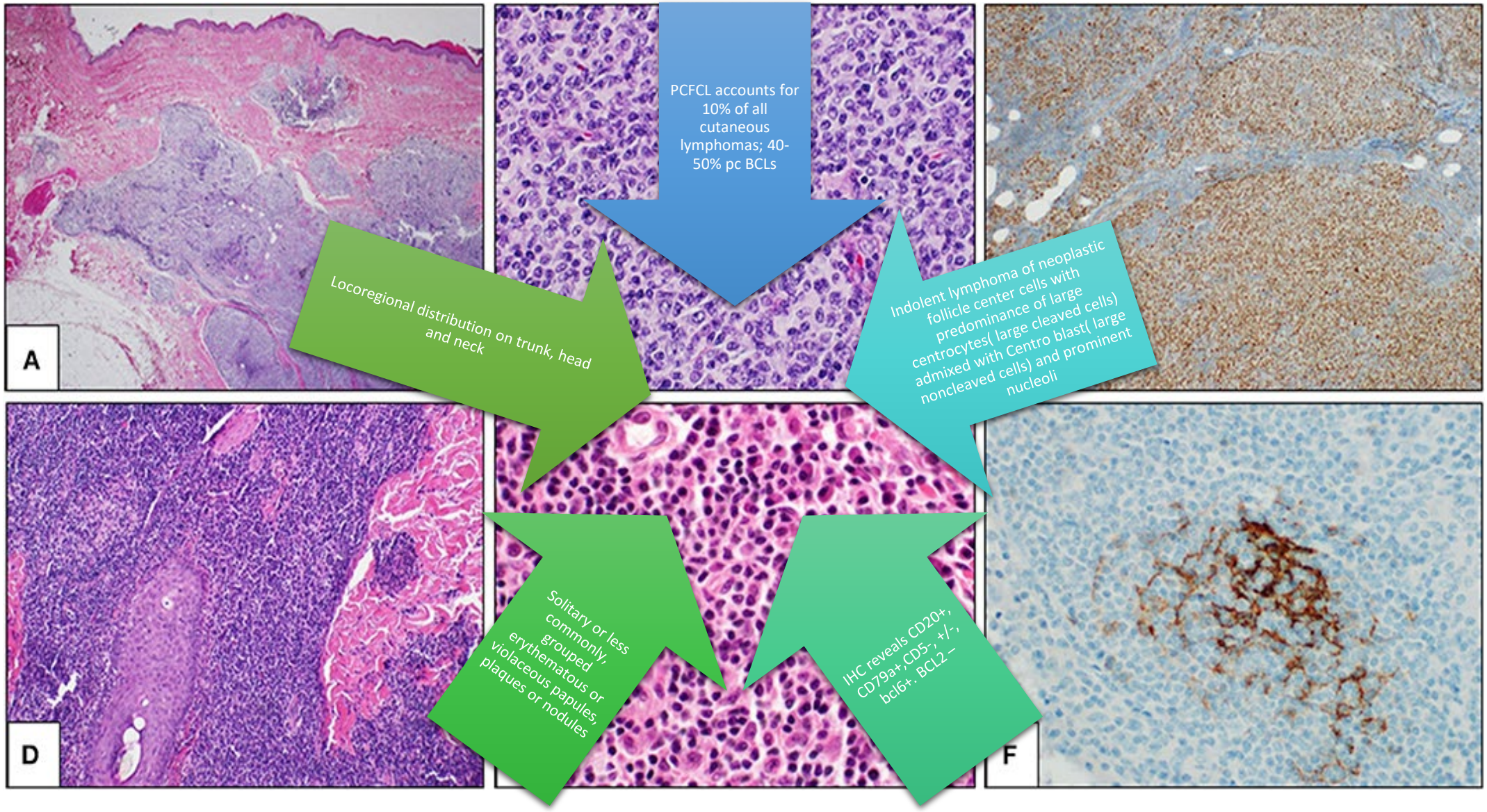




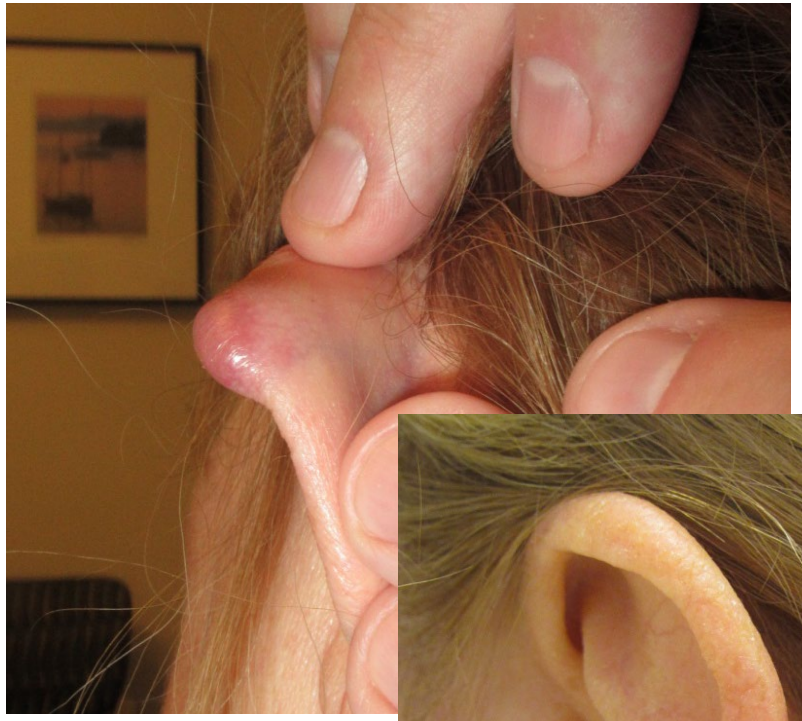
Establishing the DX and Planning TX

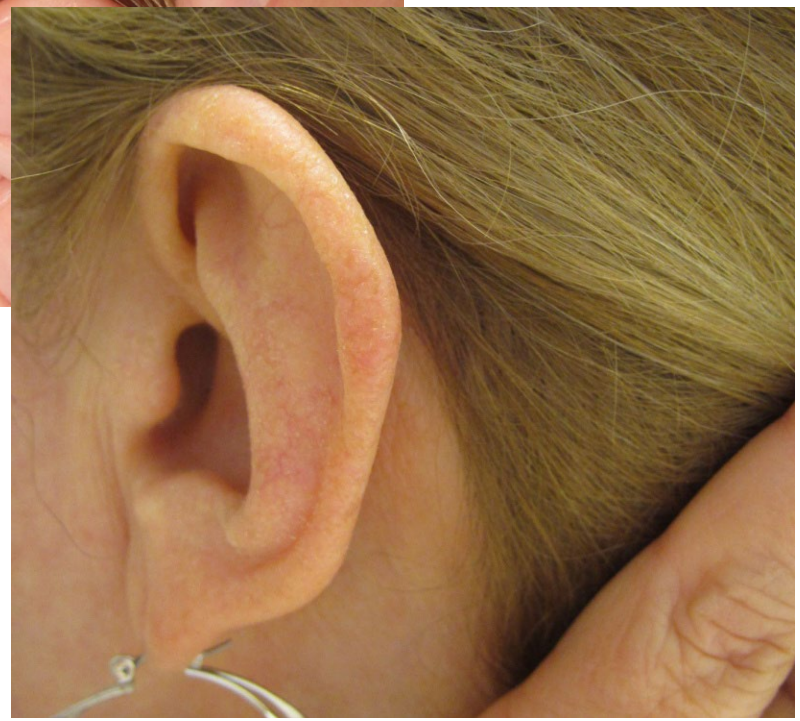
- Skin biopsy- 4mm at a minimum
- r/o systemic disease- absence of B sx/nl blood counts/ nl LDH/negative CAP or PET CT
- Differential DX- reactive hyperplasia/pseudo lymphomas= polyclonal
- **Excellent** prognosis
- Rare disorder, thus large trials lacking
- Treatment approach based on # lesions, location & presence of Sx (itch)
- Localized Radiation/ Excision/ Intralesional Tac/ Topical corticosteroids/ imiquimod
- IV Rituximab for multiple localized lesions

Primary Cutaneous Follicle Center Lymphoma



Making the DX and Planning TX



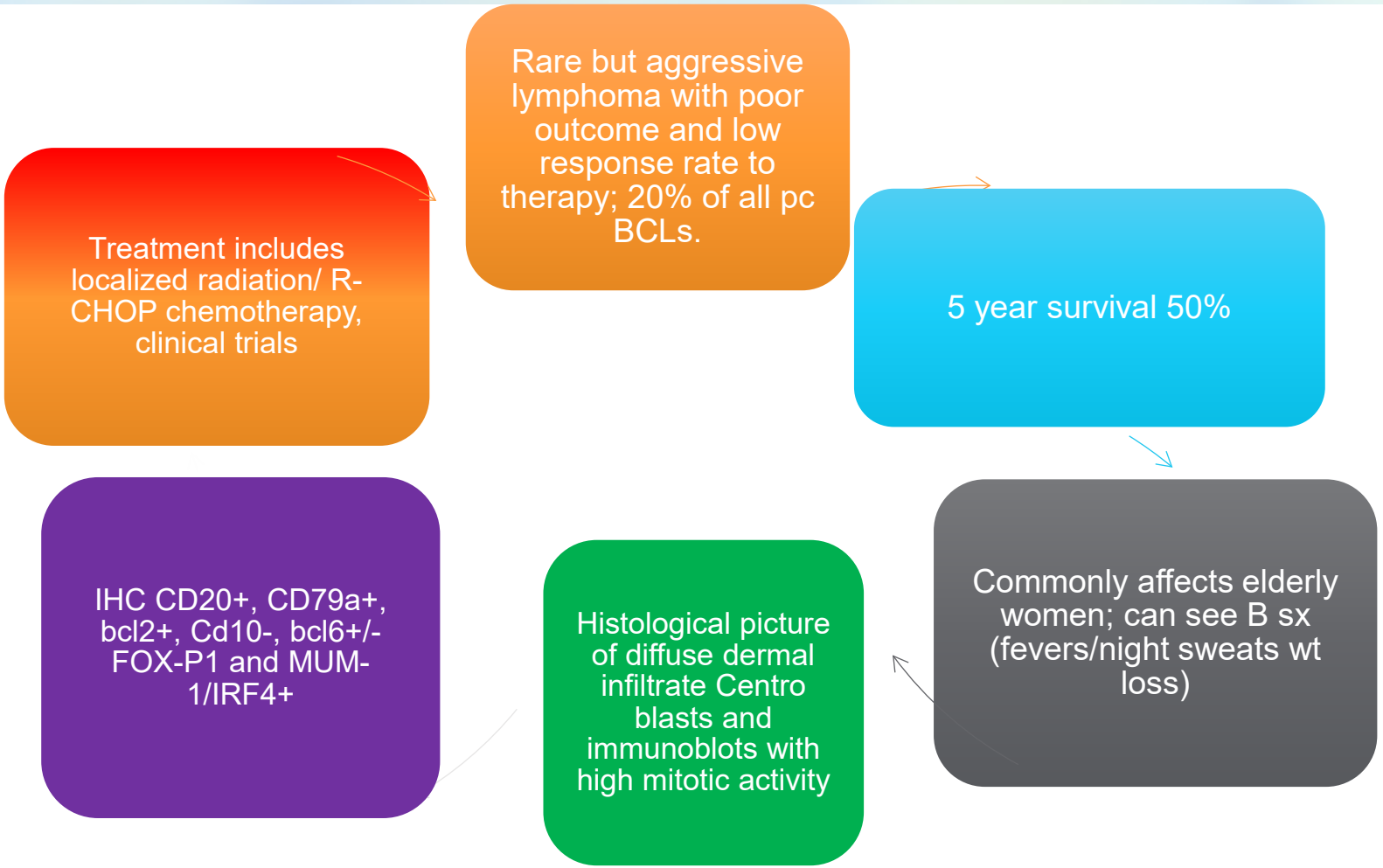


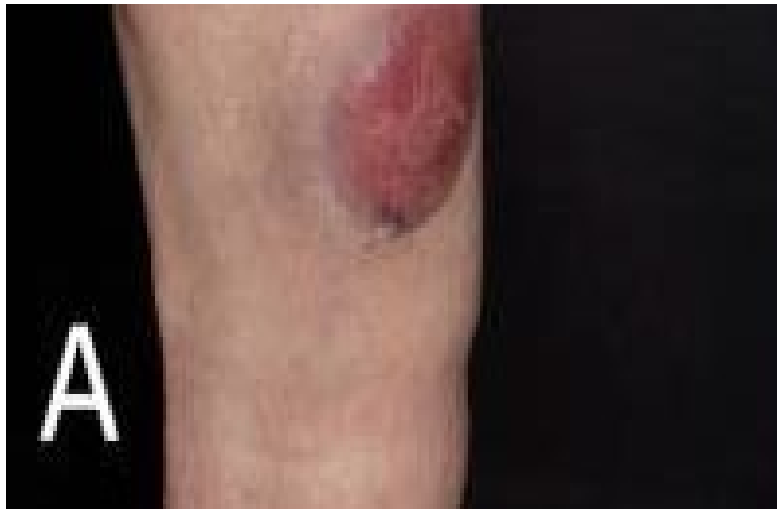
Punch Biopsy

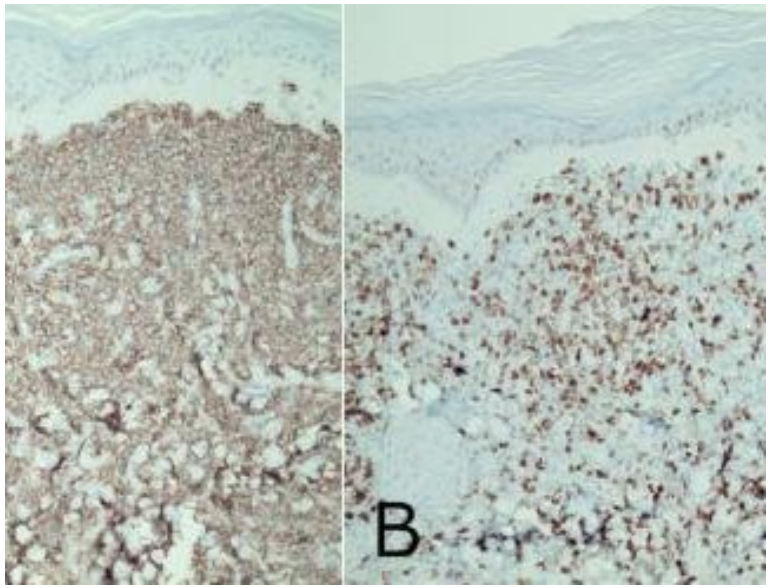
Treatment largely based on # and distribution of lesions

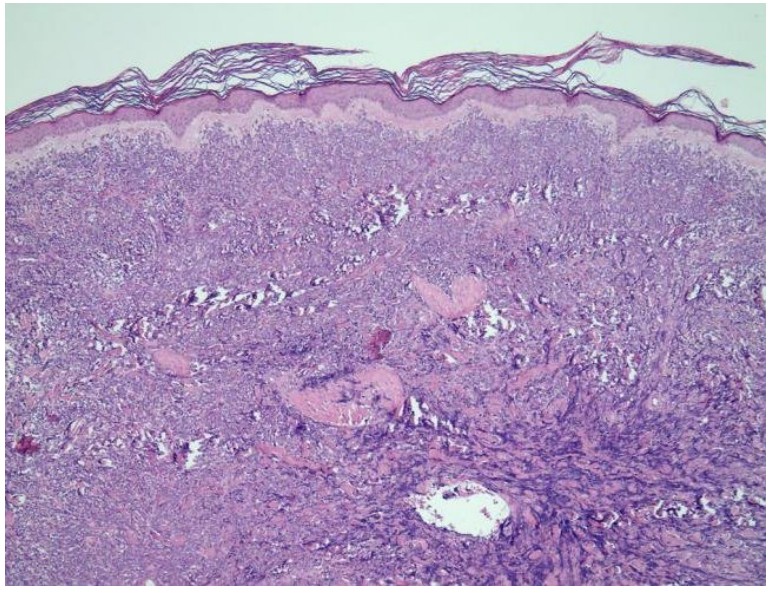
- Wait and watch
- Localized radiation
- IV Rituximab
- Cutaneous recurrences are common 30-46.6%

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type









Lower extremity infiltrative nodulo-tumors + B sx

What to do?

- Multi-agent chemotherapy
- Rarely localized radiation- *if single site*

The World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC) Classification of CTCL

Cutaneous T cell Lymphoma

Indolent clinical behavior

- **Mycosis fungoides**: variants include
  - Folliculotropic mycosis fungoides
  - Pagetoid reticulosis
  - Granulomatous slack skin
- **Subcutaneous panniculitis-like-T-cell lymphoma**
- **CD30+ Lymphoproliferative disorders**
  - Primary cutaneous anaplastic large cell lymphoma
  - Lymphomatoid papulosis

Aggressive clinical behavior

- **Sezary Syndrome**
- **Primary cutaneous CD8+ aggressive epidermotropic T cell lymphoma**
- **Primary cutaneous gamma/delta T cell lymphoma**
- **Extra-nodal natural killer/T cell, nasal type**

Variable clinical behavior

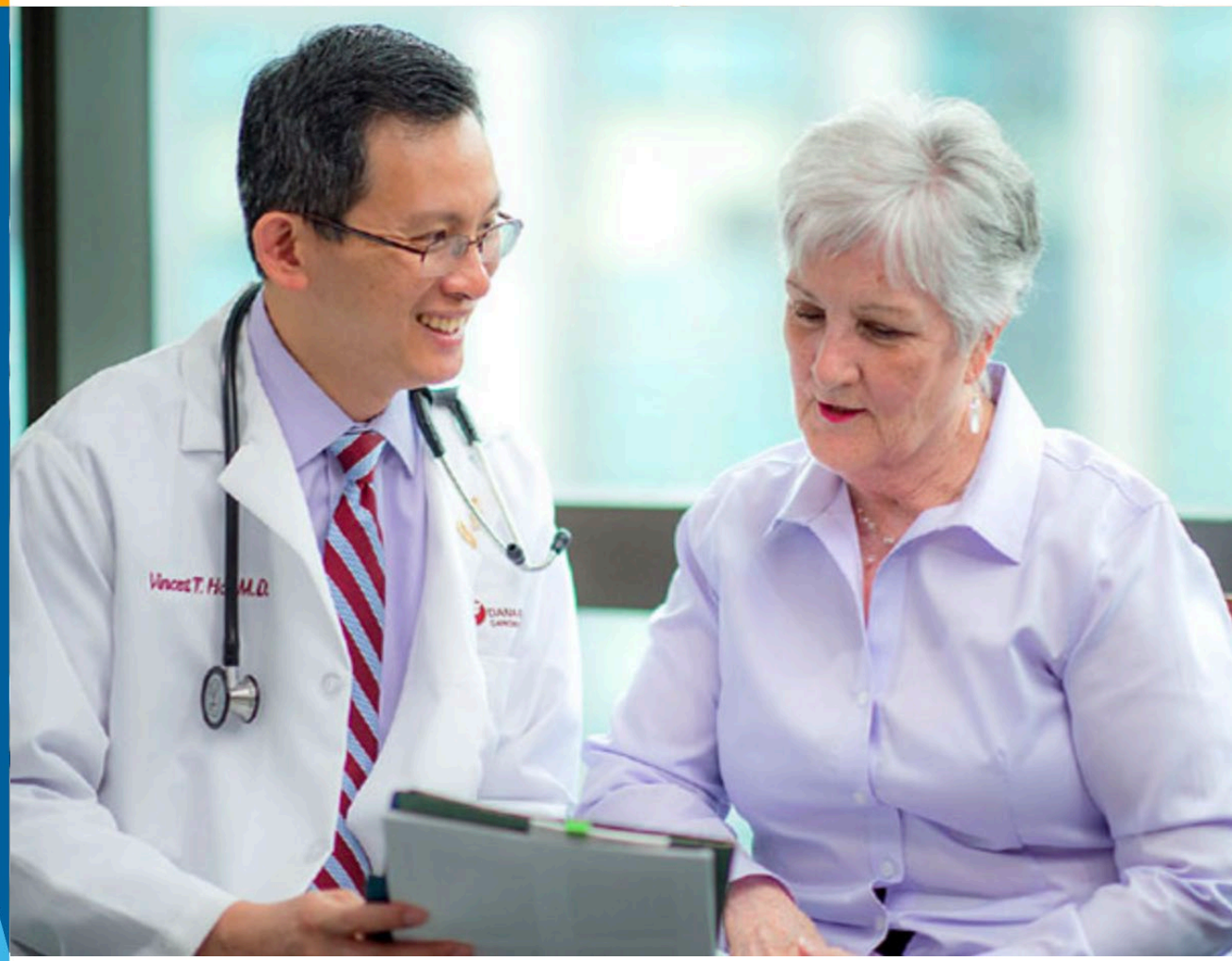
- **Primary cutaneous peripheral T cell lymphoma, Not Otherwise Specified**

Aggressive clinical behavior will be seen in patients with advance-stage MFor in those with LCT. Follculotropic MF has also been shown to have worse prognosis.

Affected Populations

- CTCL affected males twice as often as females.
- One study estimated that from.5 to 5% of CTCLs occur in children.
- Occurs twice as often in African American vs. European/ Asian decent.
- ~1,000 new cases/yr of skin lymphoma diagnosed in the US

Is this CTCL?



Making the diagnosis: Requires clinical-pathologic correlation

Morphology

Distribution

Evolution

Epidermotropism

CD4>CD8 (~6)

Loss of CD7 (CD2, 3, 5)

Dermal/epidermal discordance

Cytologic atypia

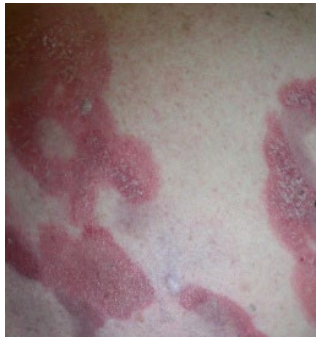
Presence of a T cell clone (TCR gene rearrangement) in

Skin and/or
Blood (SS) (also Flow cytometry)

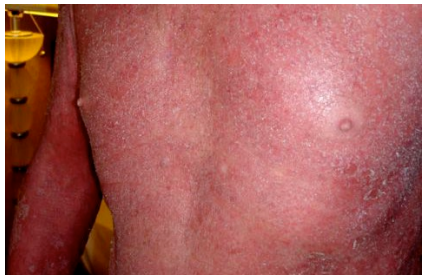
CTCL is a malignancy of skin homing T cells with distinct clinical presentations that correlate with molecular T cell subtype

Diagnosis	T cell origin	Surface Markers	Histology
Mycosis fungoides	Resident Memory (T_{RM})	CCR4+ CLA+ CCR7- L Selectin -	Epidermotropism Pautrier microabsceses
MF/SS	Migratory Memory (T_{MM})	CCR4+ CLA + CCR7+ L Selectin +/-	Intermediate phenotype
Sézary Syndrome	Central Memory (T_{CM})	CCR4+ CCR7+ L Selectin +	Spongiosis

Clinical presentation



Malignant T cells:
Confined to fixed plaques in skin



Malignant T cells:
-Found in all areas of skin
-Accumulate in blood and lymph nodes

Clinical presentation

Typical Patient Presentation (MF/SS)

Fixed, persistent or progressive, patch

Size/shape variation

Often sun-protected sites

Other: Poikiloderma

PATCH

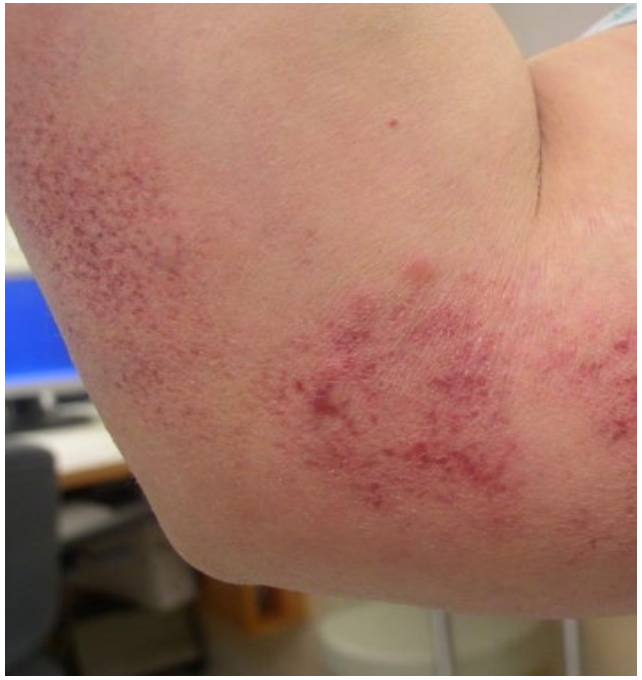
PLAQUE

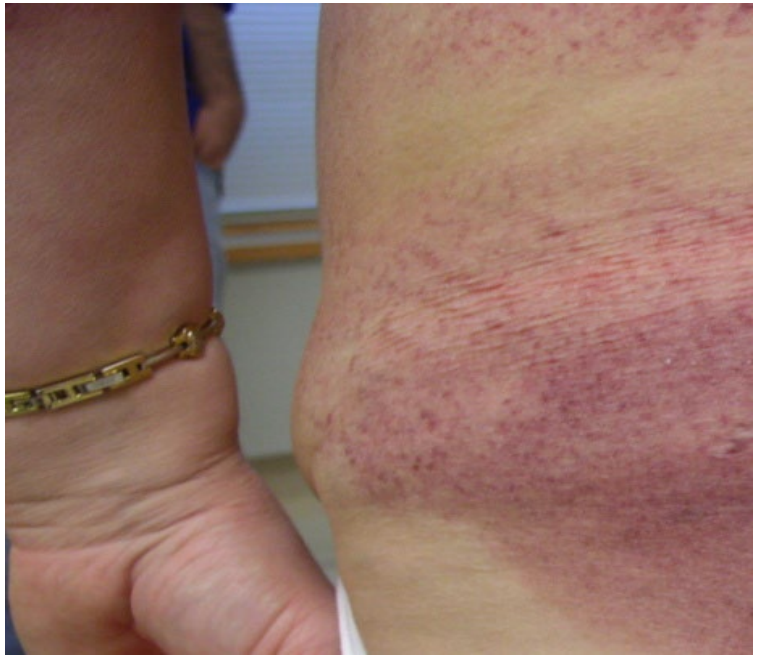
TUMOR

ERYTHRODERMA

Most often misdiagnosed as chronic contact dermatitis, atopic dermatitis psoriasis or drug eruption; conflicting clinical presentations and pathology

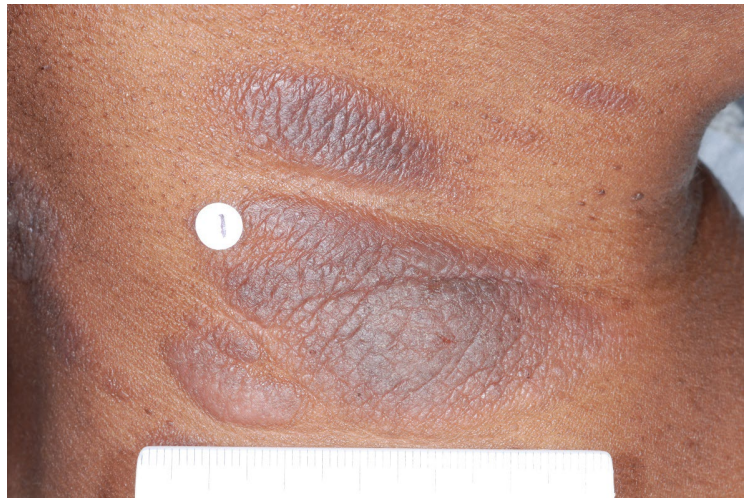
Regression within Lesion Poikiloderma

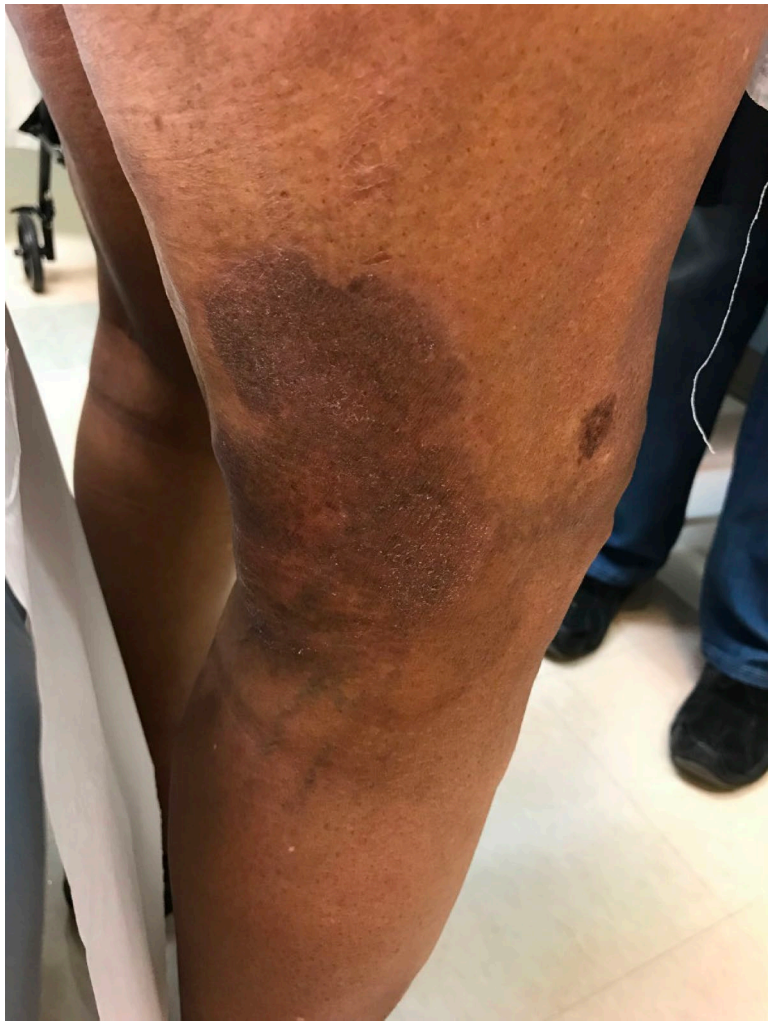


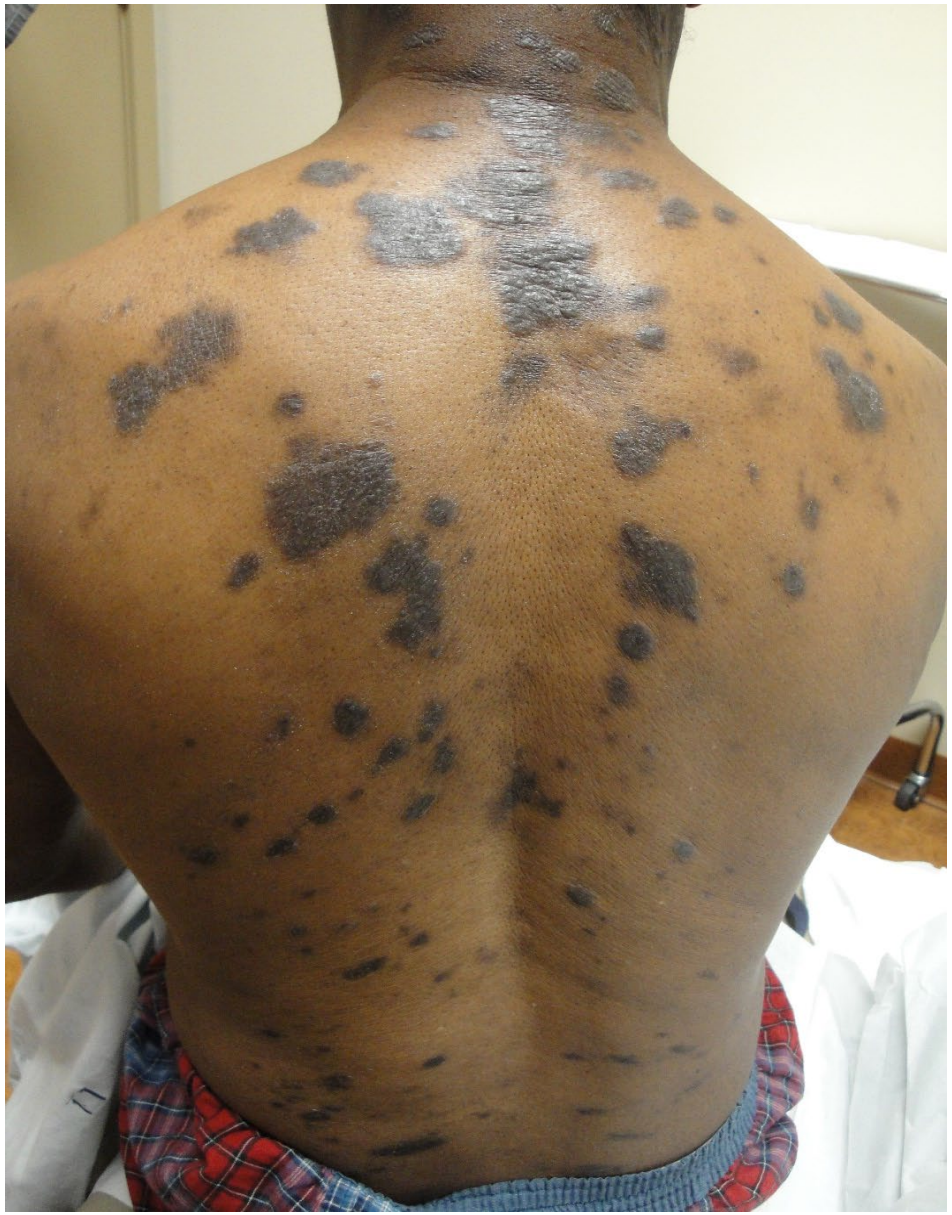


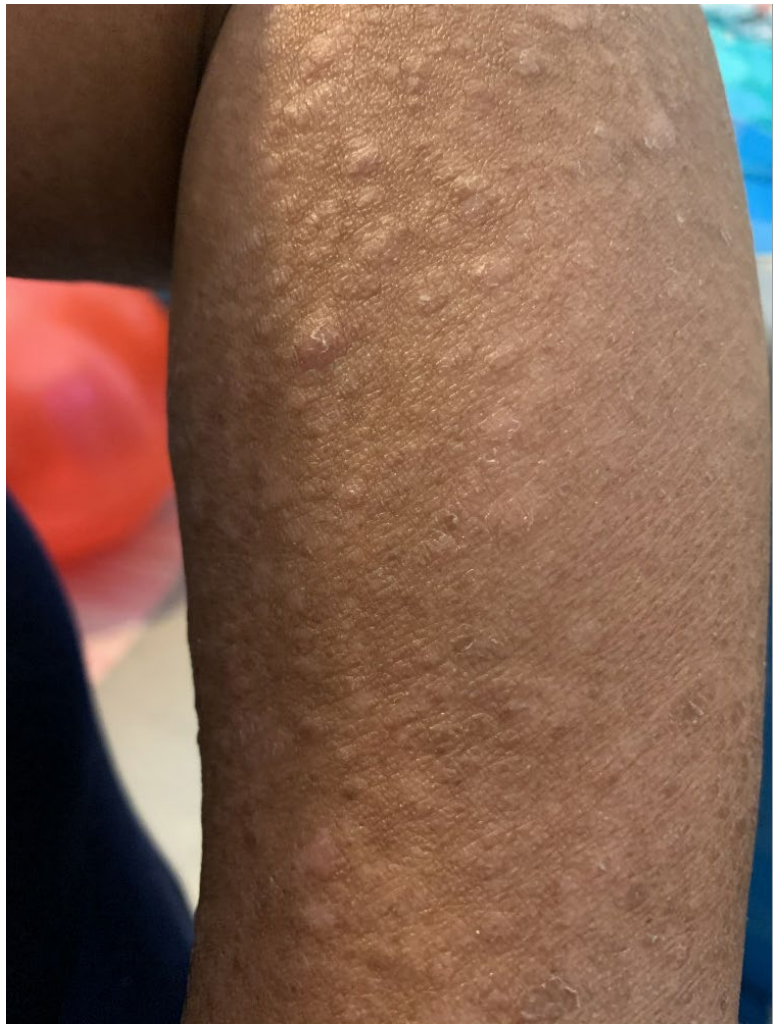
Excellent prognosis

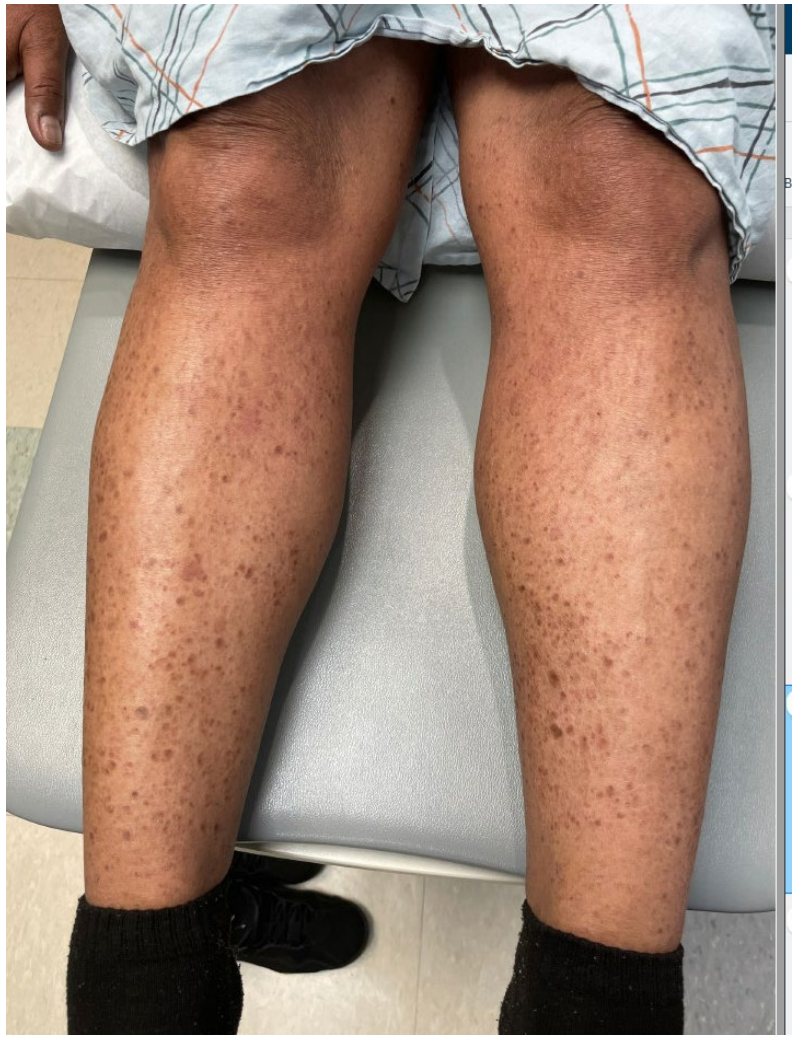
MF in skin of color

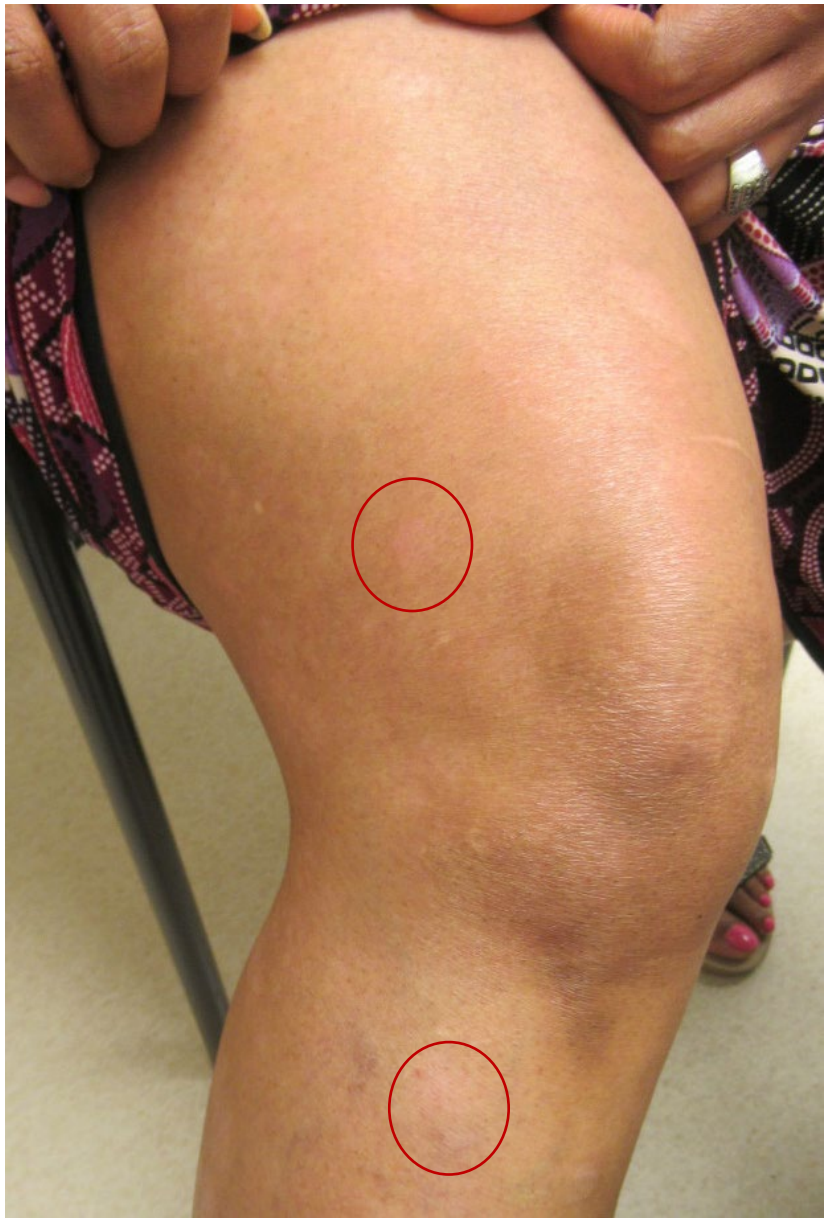




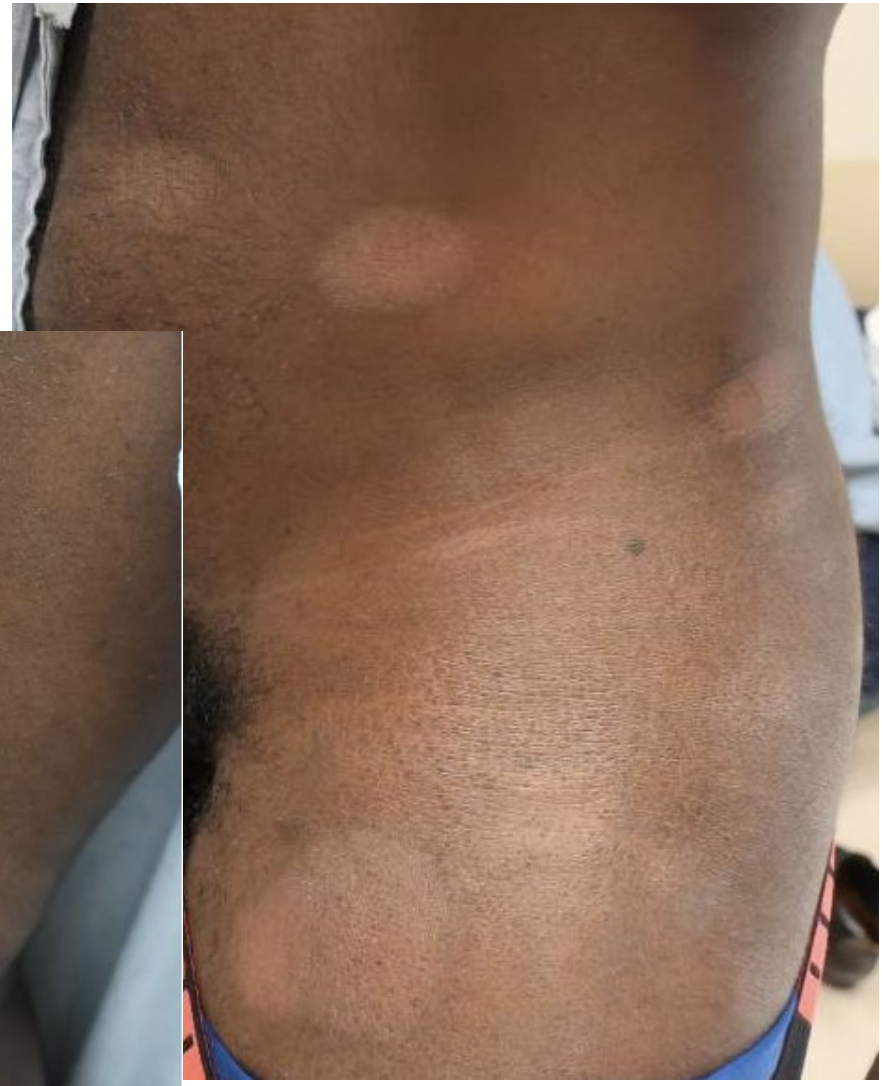


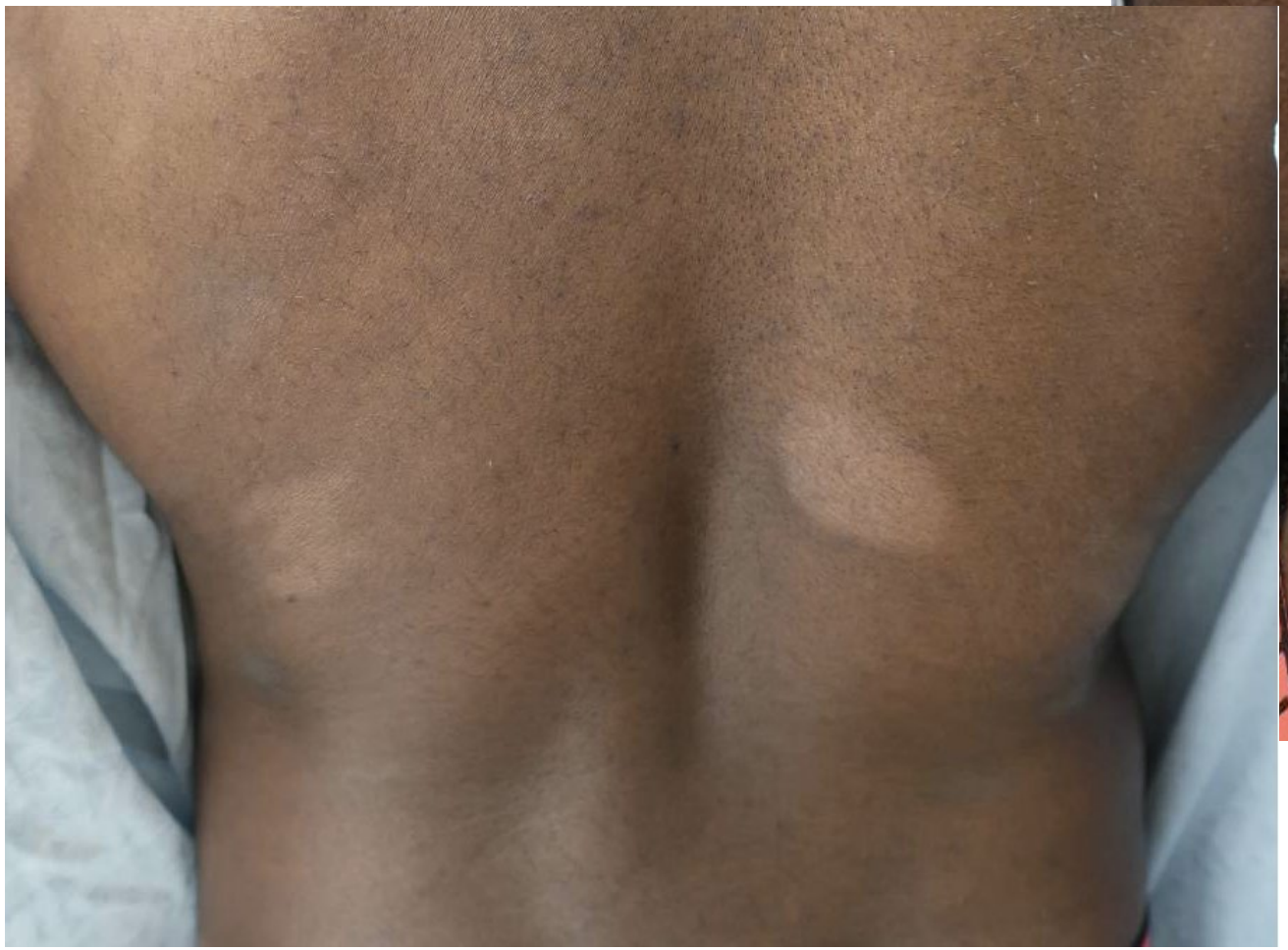






Hypopigmented MF





However, consider other rare subtypes when patients present with:

Tumors first, no patch/plaque stage
→ cutaneous PTCL, NOS, γδ TCL, ALCL

Wide-spread ulceration
→ primary cutaneous aggressive epidermotropic CD8+ TCL

Infiltration into fat
→ γδ TCL

Making the diagnosis: Pathology

Ahhhh the biopsy……

Biopsy site selection is paramount (aim for 6 mm punch)

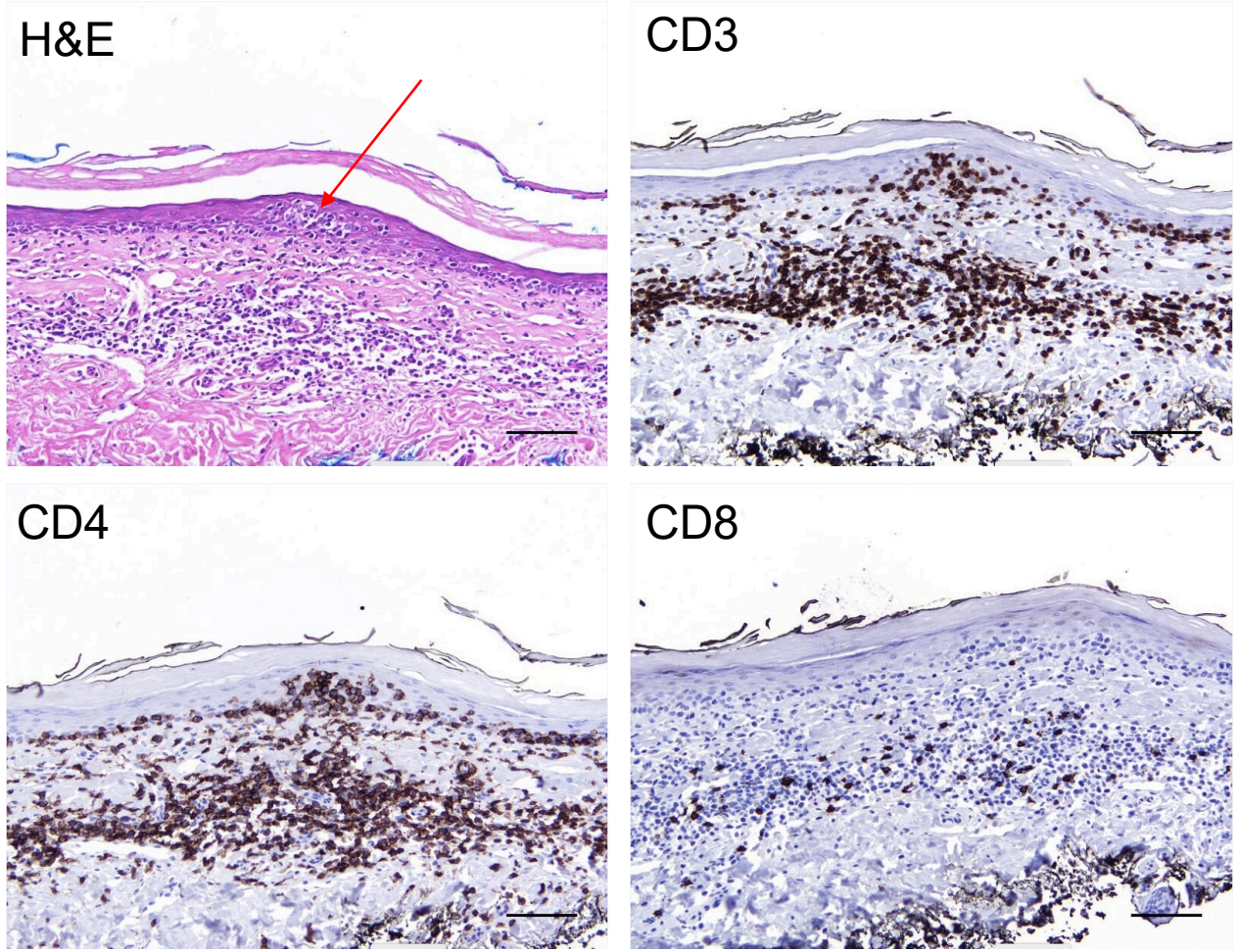
May need more than 1 biopsy from different lesion types
(look for matching clones in different sites)

Untreated skin preferred aka no topical steroids (> 2 weeks, > 4 weeks from phototherapy)

Key pathology findings

- **Pathology report will say…**
  - Superficial perivascular → dense band-like infiltrates of lymphocytes
  - Epidermotropism (and tagging DEJ), without spongiosis (but in SS spongiosis/eos typical)
  - Pautrier micro abscesses (<25% of cases)
  - Cytologic atypia?

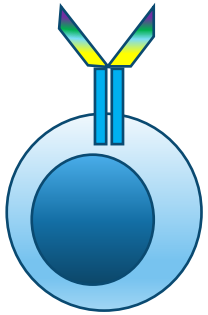
- **Immunophenotyping**
  - <50% CD2,CD3,CD4,CD5+ T cells
  - <10% CD7+ T cells
  - *Other: CD30 (for subtyping)*



Making the diagnosis: Molecular tests

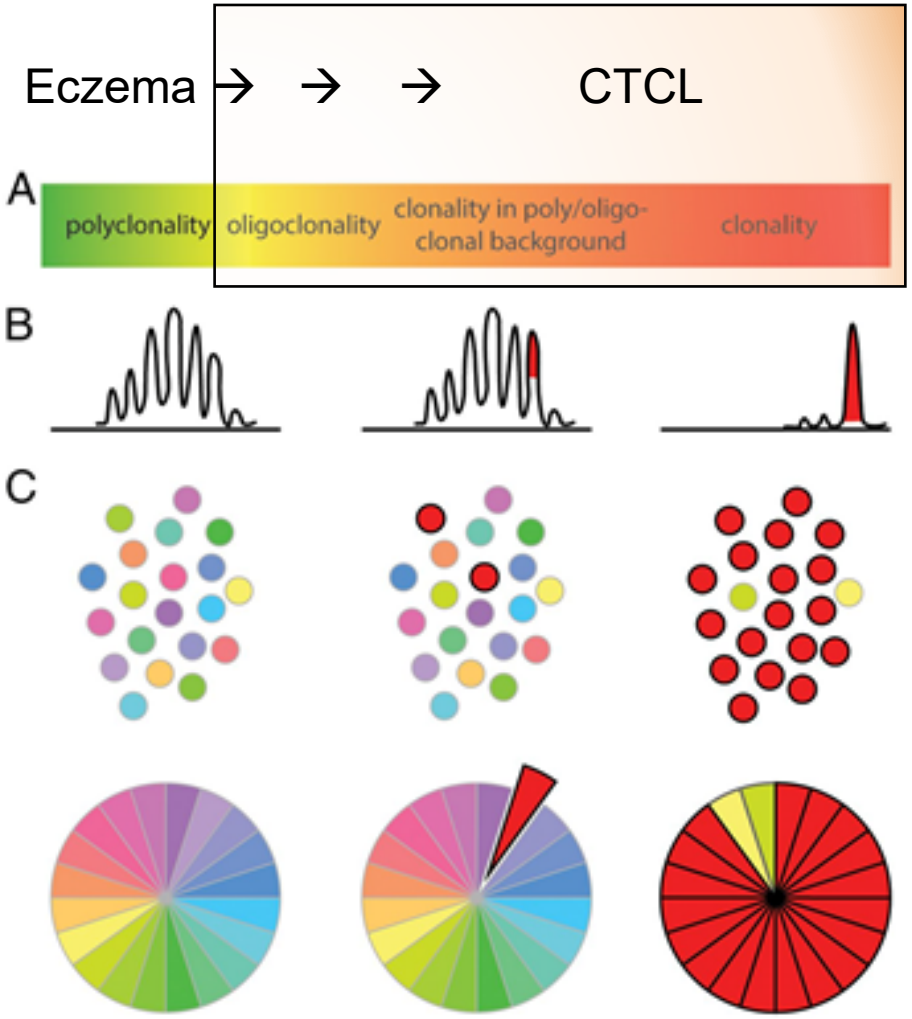
Is there a T cell clone?

TCR is like a fingerprint



Unique antigen receptor serves as a specific marker for that cell and its clonal progeny

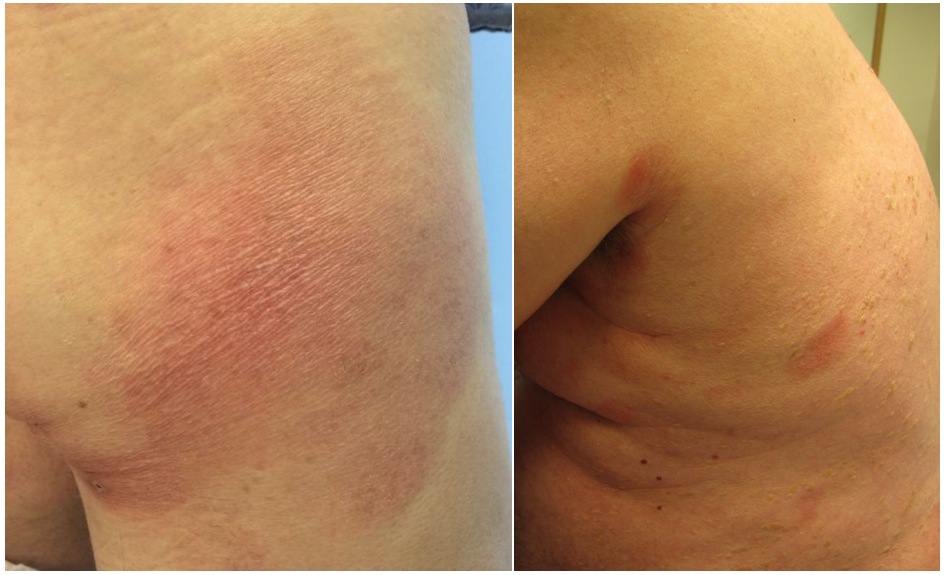
What is clonality?

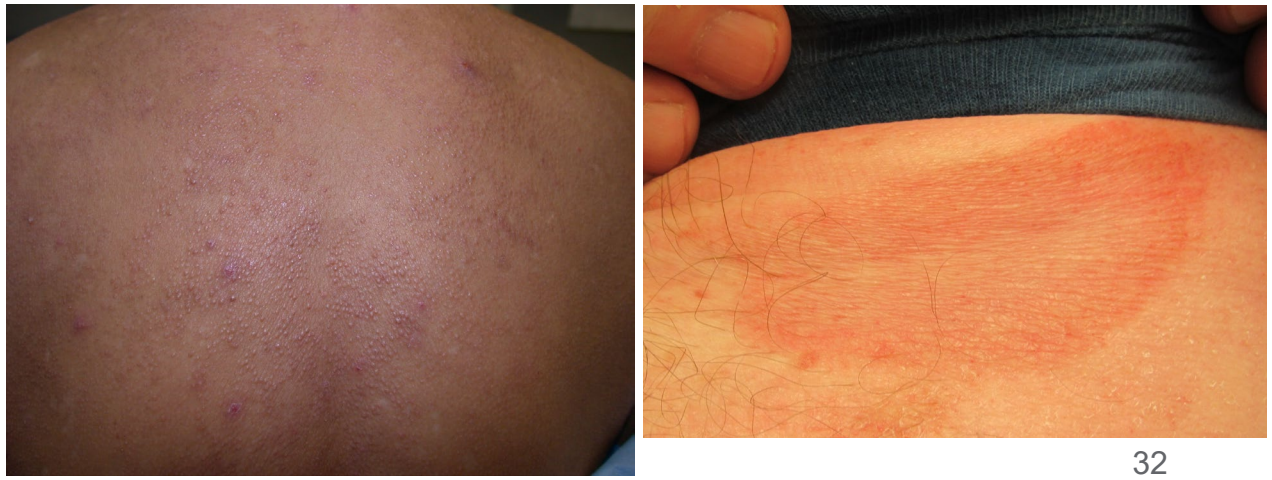


Anton W. Langerak et al. J Immunol 2017;198:3765-3774

Diagnosing early MF is challenging!

- Average 3-6 years from symptom onset to dx
- Average 6 bx prior to dx
- Lack of cytologic atypia
- TCR clone + in ~50% of patches of MF (PCR 80% sensitivity)





Dupilumab-associated CTCL

- Risk:
  - CTCL diagnosed after dupilumab started for presumed AD (bx neg)
  - Rapid disease progression with mortality reported

  - 23 cases of CTCL diagnosed after dupilumab given for presumed AD
    - 83% had NO personal/family history of atopy (adult-onset AD)
    - Only 56% had pre-tx skin biopsies
    - NONE had TCR gene rearrangement studies
    - No peripheral flow cytometry was obtained in erythrodermic patients
    - 7/23 had initial improvement with dupi
    - 82% dx with MF, 18% with SS
    - CTCL diagnosed 1-15 months after initiation of dupi

Rule out CTCL BEFORE started dupi (flow cytometry for erythrodermic pt)
and
Re-evaluate for CTCL if patients are not improving or getting worse!

MAJOR ADVANCE IN CTCL DIAGNOSIS

- High throughput TCR sequencing of **COMPLEMENTARITY DETERMINING REGION 3** (CDR3) region of TCR

clonoSEQ®

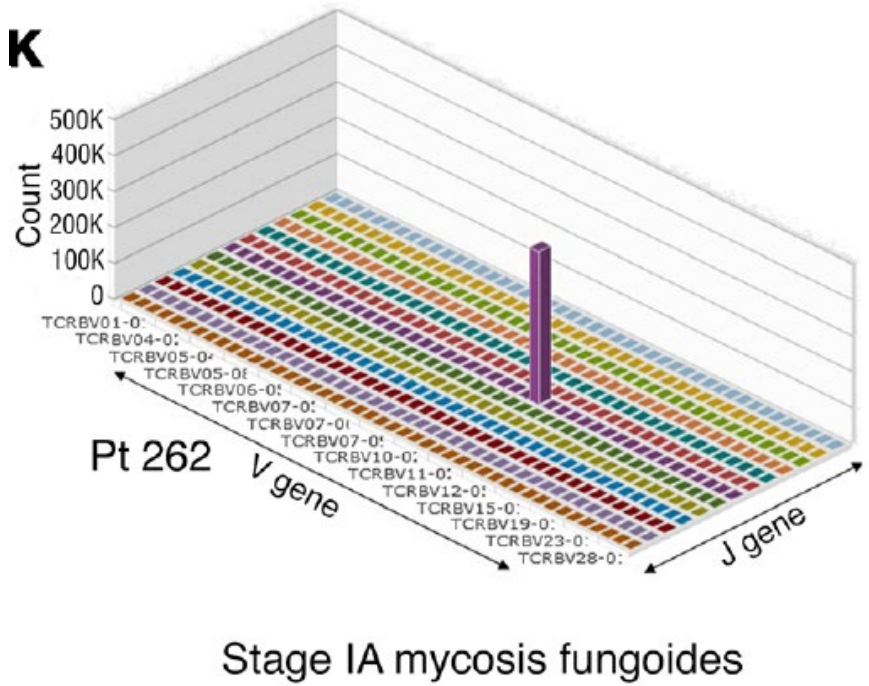
Next generation high throughput sequencing technology

Fancy and enormous # of PCR primers
(corrected for amplification bias)

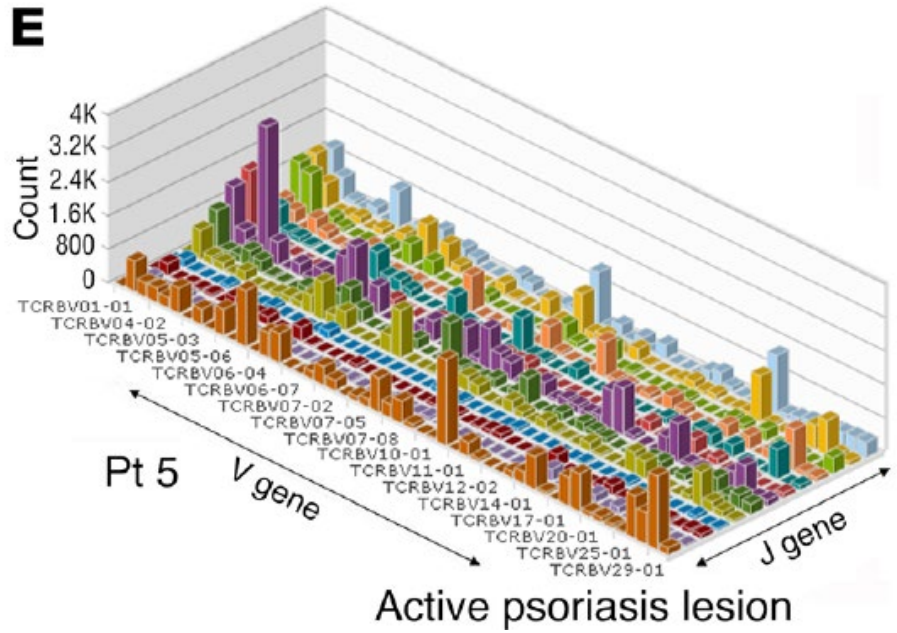
TCRB and TCRG genes evaluated

Sophisticated bioinformatic analysis

Monoclonal expansions predominate in early-stage MF compared to psoriasis



Stage IA mycosis fungoides

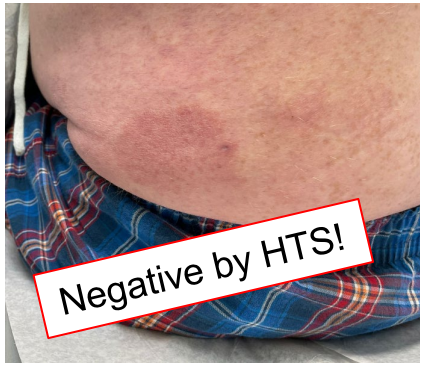


Active psoriasis lesion

Important applications of HTS of TCR

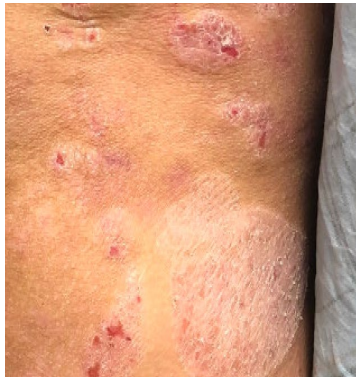
1	2	3	4
Diagnosing early MF	Prior to starting dupilumab	Skin rash from cancer Tx?	Monitor disease

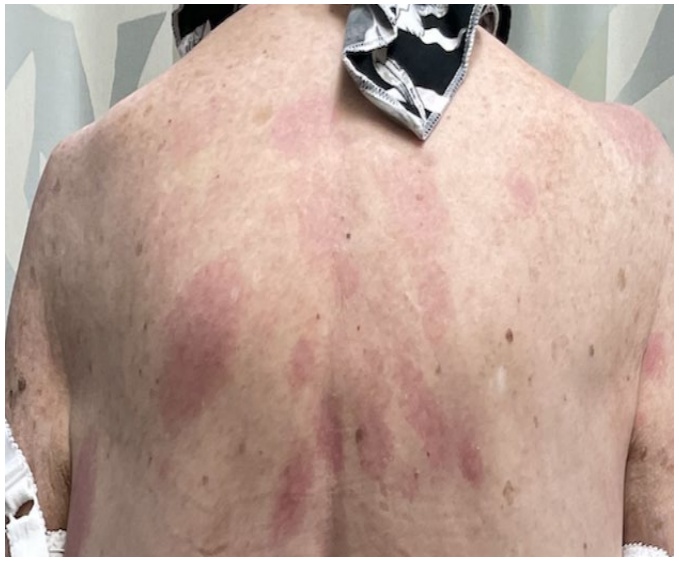
• Start treatment sooner
• Prognostic tool
	• Dupilumab may unmask CTCL or lead to rapid disease progression in previously undiagnosed CTCL	• Helps distinguish disease progression from treatment side effect	• Prior to transplant
			  • Clearance of disease in skin/blood?
			• Following transplant
			  • Relapse vs GVHD?



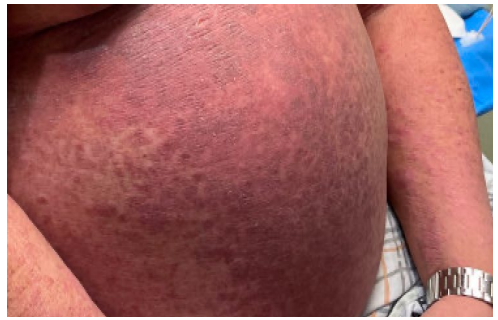
What is my prognosis?

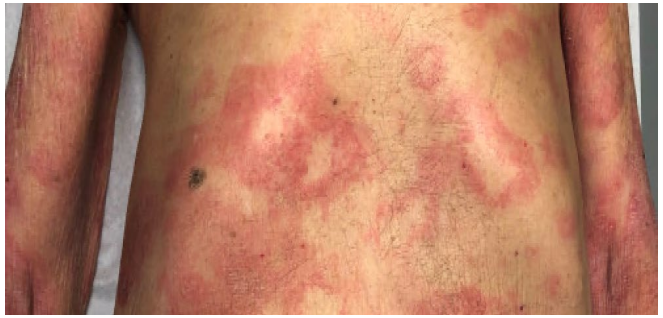
Cutaneous manifestations (TNMB stage) directly linked with prognosis





T1: <10% Body Surface Area Affected





T2: >10% Body Surface Area Affected

Patients can experience indolent (chronic) or aggressive (fatal) disease

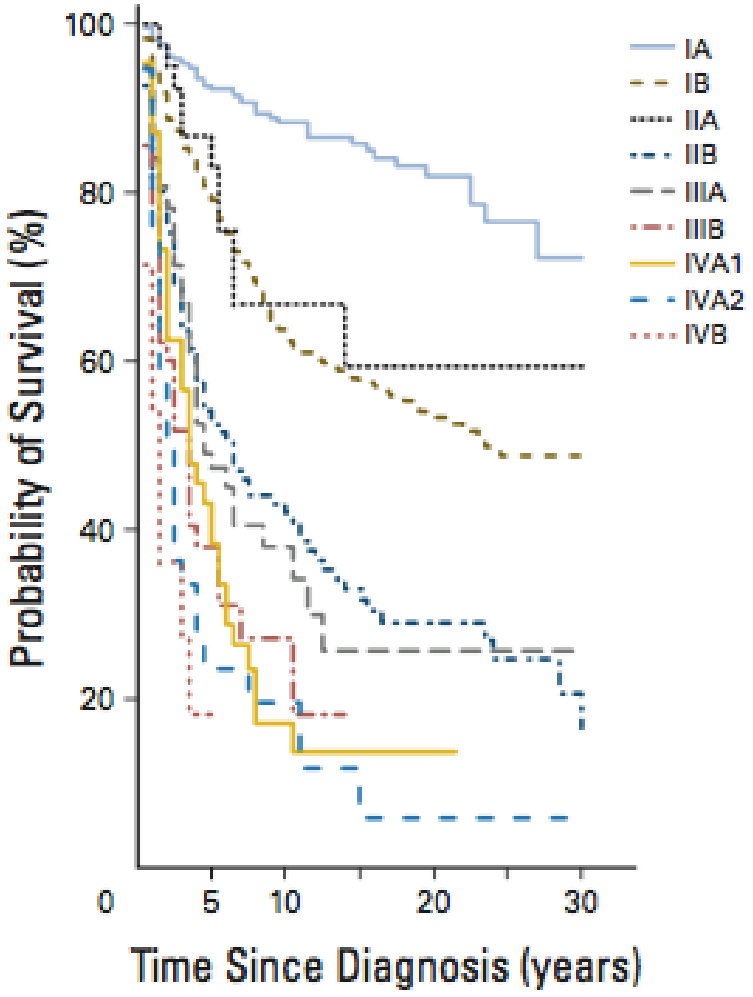
Excellent prognosis in early stage, consider a chronic illness

Indolent → Aggressive

Stage	Median OS (years)	10-year[6] OS (%)	10-year[6] DSS (%)	10-year[6] RDP (%)
IA	35.5	88	95	12
IB	21.5	70	77	38
IIA	15.8	52	67	33
IIB	4.7	34	42	58
IIIA	4.7	37	45	62
IIIB	3.4	25	45	73
IVA1	3.8	18	20	83
IVA2	2.1	15	20	80
IVB	1.4	18 (5 year)	18 (5 year)	82 (5 year)

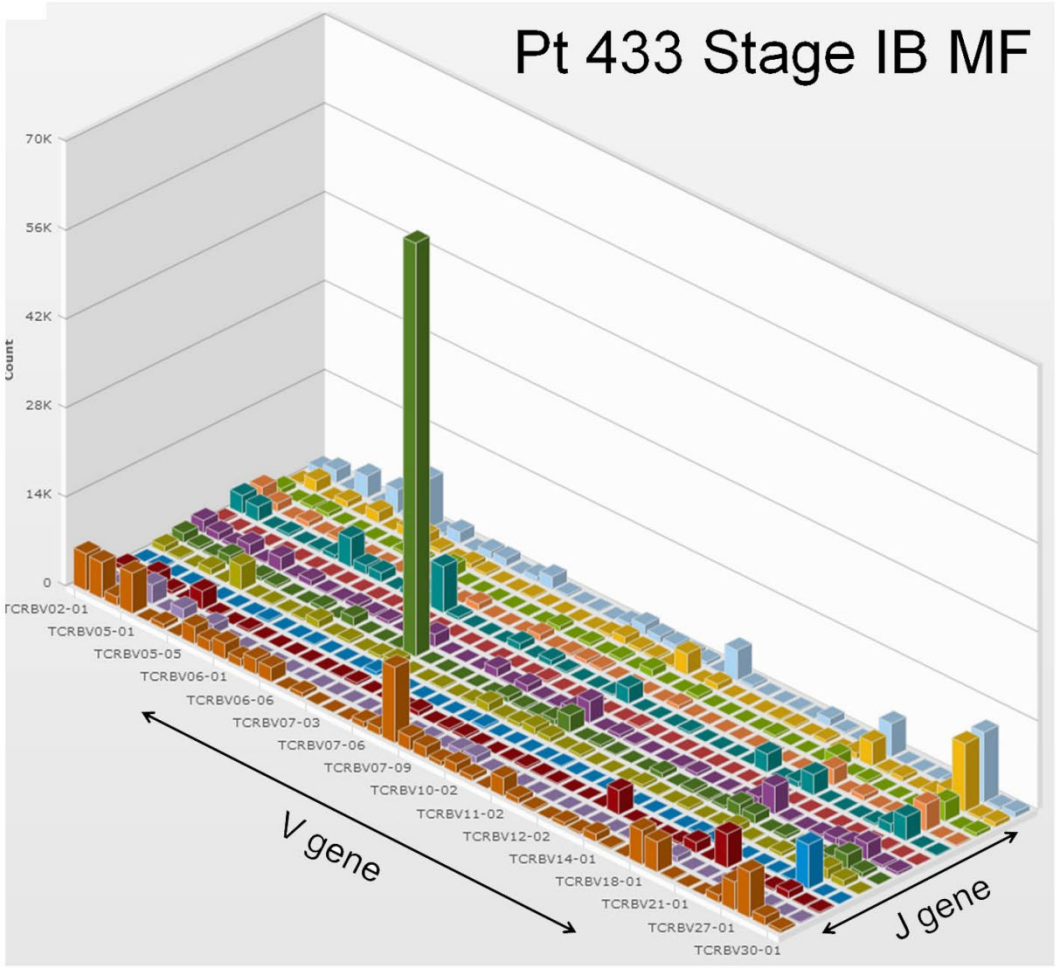
Risk of disease progression *even for early-stage patients*

Increasing risk of mortality across stages

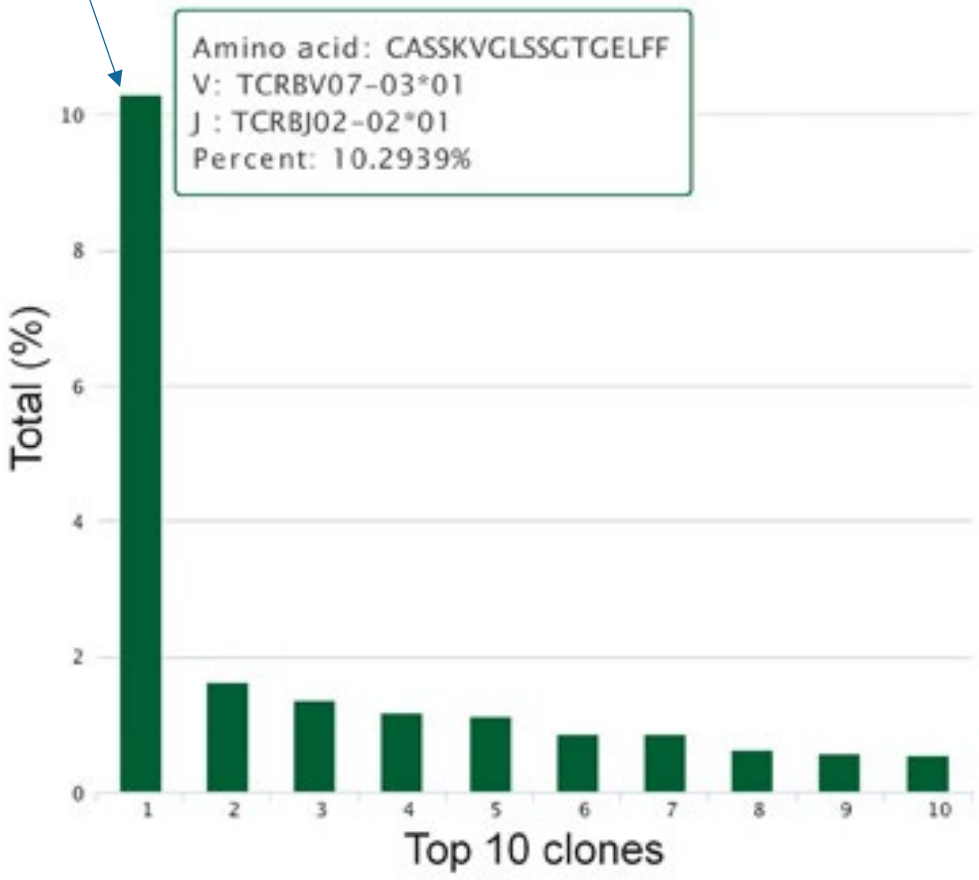


Agar JCO 110;28931) 4730

Determining the malignant clone and **tumor clone frequency (TCF)**



$$TCF = \frac{\text{\# of reads of top TCRB gene sequence}}{\text{\# of reads of all rearranged TCRB gene sequences}}$$

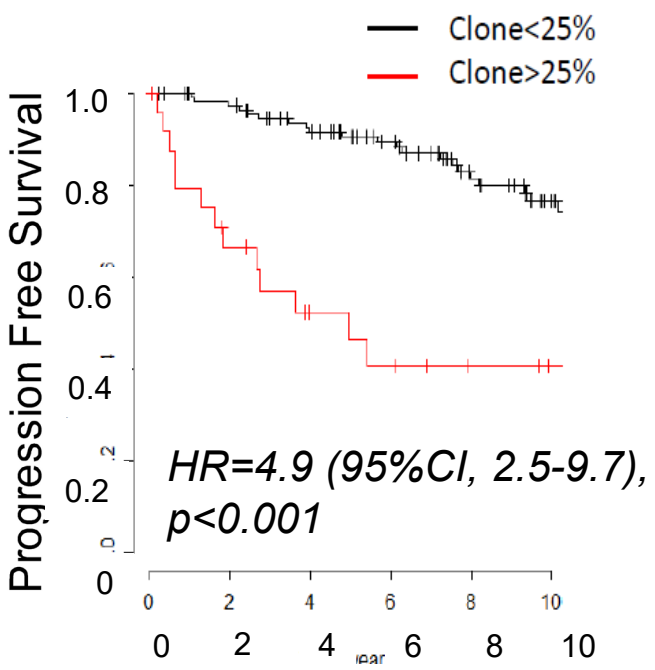


Dana-Farber Cancer Institute

de Masson, O'Malley, et al. 2018. *Science Translational Medicine*. 2018 May 9;10(440).

The skin TCF is highly predictive of disease progression in early-stage MF patients

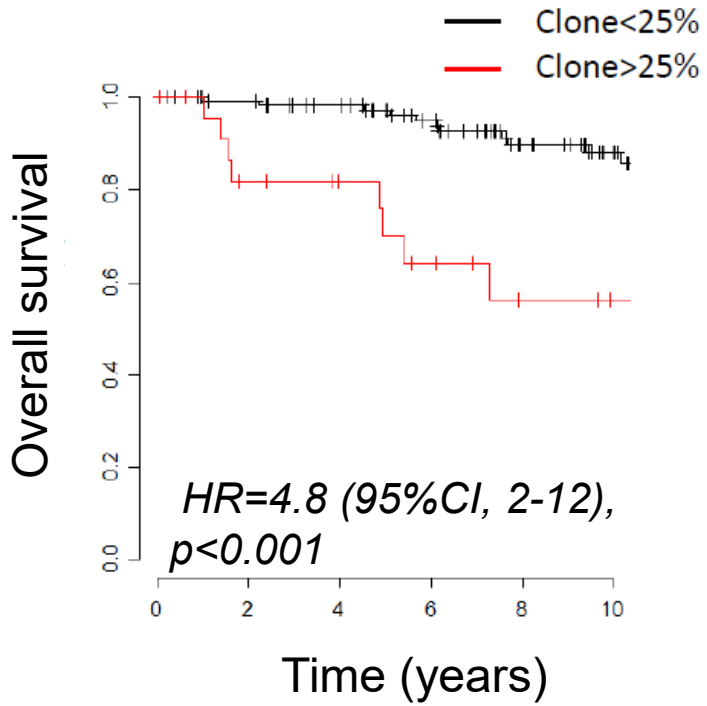
Discovery set
Early-stage mycosis fungoides



Number at risk

Clone<25%	116	107	94	78	56	37
Clone>25%	25	15	9	7	4	2

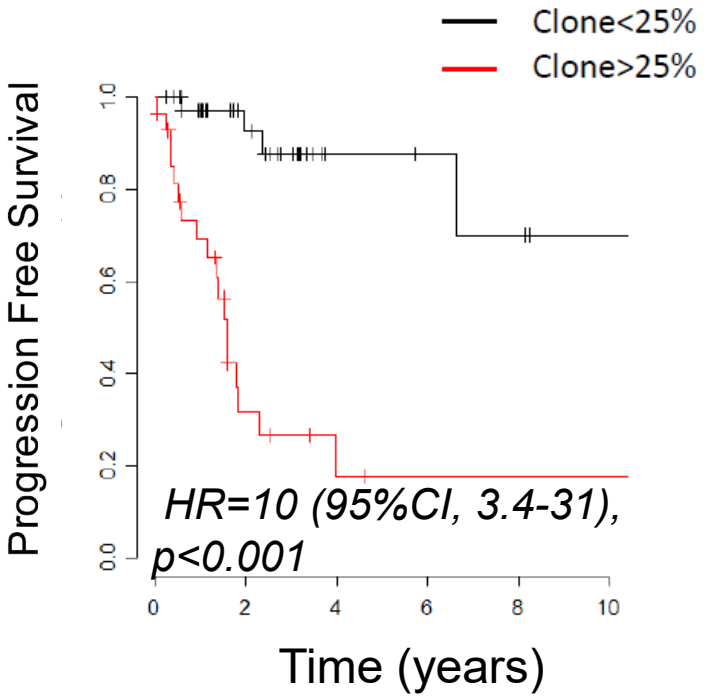
Discovery set
Early-stage mycosis fungoides



Number at risk

Clone<25%	116	108	100	83	59	41
Clone>25%	25	17	14	10	6	4

Validation set
Early-stage mycosis fungoides



Number at risk

Clone<25%	41	20	6	5	4	2
Clone>25%	28	6	2	1	1	1

Dana-Farber Cancer Institute

de Masson, O'Malley, et al. 2018. *Science Translational Medicine*. 2018 May 9;10(440).

We are better at diagnosing CTCL but are we better at treating it?

What factors impacts decision making on treatment selection?

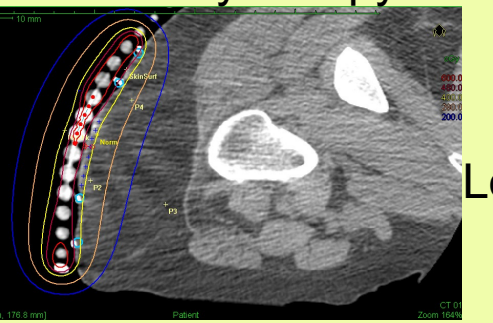
- What is the tenor and pace of the disease?
- What is observed under the microscope e.g. folliculotropism/ LCT
- B sx/ elevated LDH
- Degree of immunosuppression associated
- Pruritus level
- $ and access to therapies
- CTCL MF/ SS are chronic diseases requiring chronic courses of therapy
- **HRQOL**

Treatment is Multidisciplinary

Phototherapy
nbUVB
PUVA

Topical agents

Brachytherapy



Local XRT

TSEBT

Dermatology

Retinoids
Bexarotene
MTX
IFN a

Extracorporeal photopheresis

Radiation Oncology

Medical Oncology

Targeted therapy
Chemotherapy
Stem cell transplant

Where?

SKIN **BLOOD** **LYMPH NODE** **VISCERA**

Severity?

Body Surface area?

Tumors?

High risk features?

Folliculotropism?

Large cell transformation?

Special site?

Difficult to treat locations?
(e.g. eyelids, feet)

Severity?

LOW?

Sezary count

HIGH?

Goals?

PALLIATION

Or

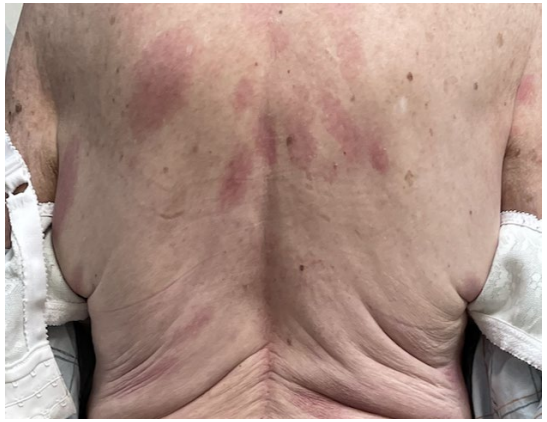
Transplantation?

SKIN-DIRECTED THERAPY FOR EARLY CTCL

Treatments in CTCL are rarely if ever a cure (except for allogenic transplantation)

Treatment goals

- Symptomatic relief (decrease itch)
- Prevented disease progression
- Aim for disease improvement/stable disease (may not be spotless)



Patient counseling

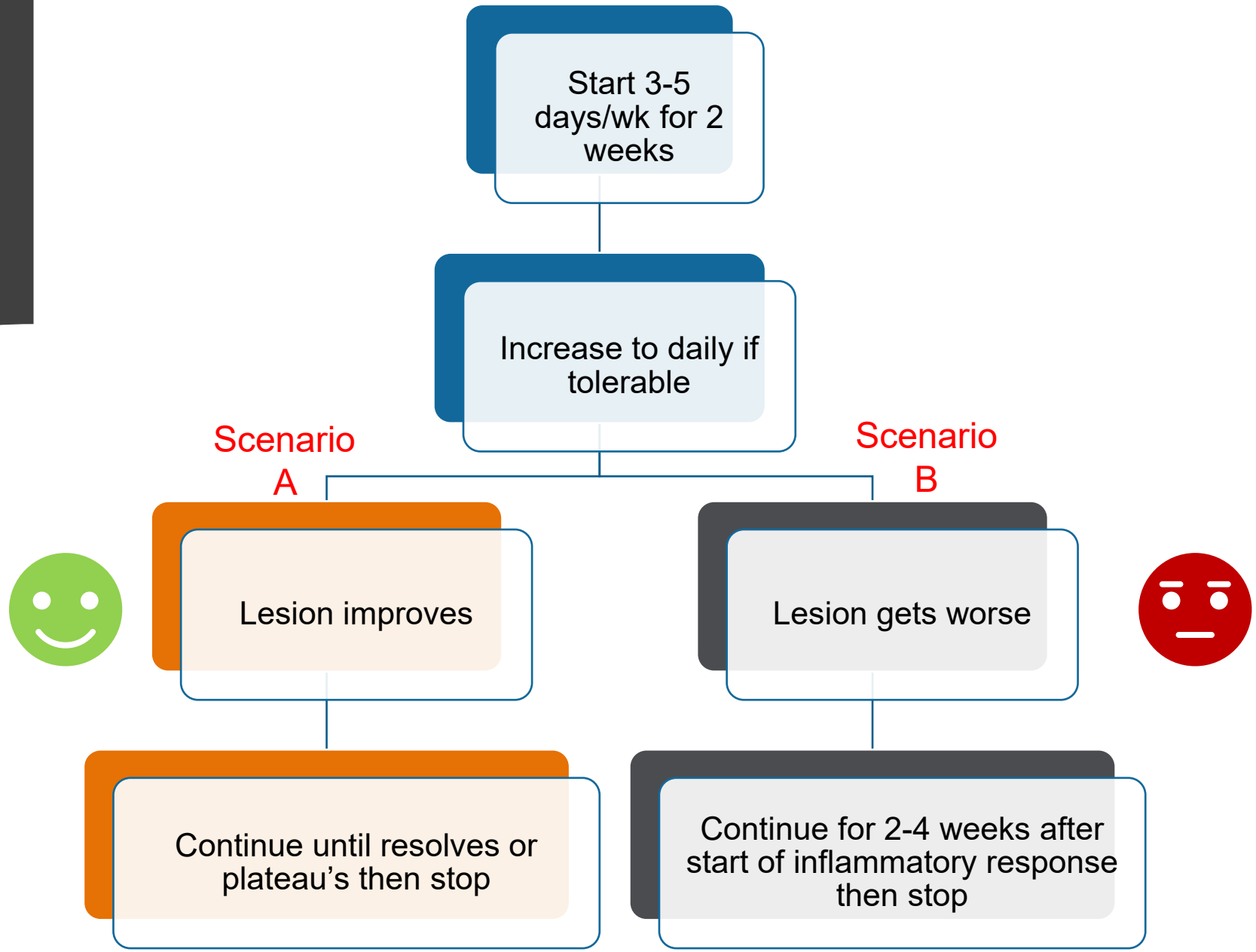
- Can take time to be effective
- May appears worse before it improves
- May experience transient disease flares

Topical treatments for Mycosis Fungoides

Type	Anti-inflammatory	Chemotherapy	Targeted: Retinoid/Rexinoid	Immunotherapy
Agent	**Topical steroids**	**Nitrogen mustard** (mechlorethamine HCl)	**Bexarotene*** **Tazarotene[t]**	**Imiquimod**
ORR	75-95%	50-90%	*50-75% [t]58%	50%
Pros	Very effective against itch Does not cause irritation	Whole body application	No risk of atrophy Safe for face	Thicker plaques tx/FMF Safe for face Lasting remission?
Cons	Steroid atrophy etc.	Not for use on genitals Not w/ phototx Irritating/allergy	Irritating	Inflammation (mild) Limited to small BSA
Onset of response	n/a (~1 month)	~ 6 months	~ 5 months	n/a (~2 months)

Arch Dermatol 2003:139:165 , J AM Acad Dermatol 2003;49;801. J AM Acad Dermatol2002:47;191 Arch Dermatol 2005: 141;305, Arch Dermatol 2011:147;561, Arch Dermatol 2001:2001: 137:581, J Clin Oncol 2007,25:3109, J Clin Oncol 2010: 28:4485

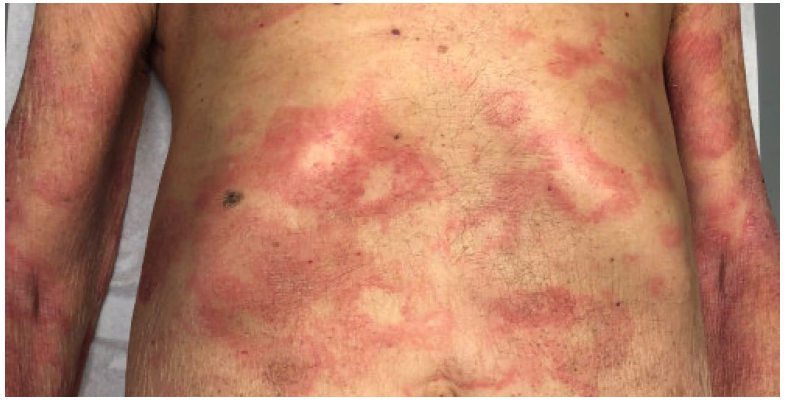
Imiquimod


Start 3-5 days/wk for 2 weeks
Increase to daily if tolerable
Scenario A
Scenario B
Lesion improves
Lesion gets worse
Continue until resolves or plateau's then stop
Continue for 2-4 weeks after start of inflammatory response then stop

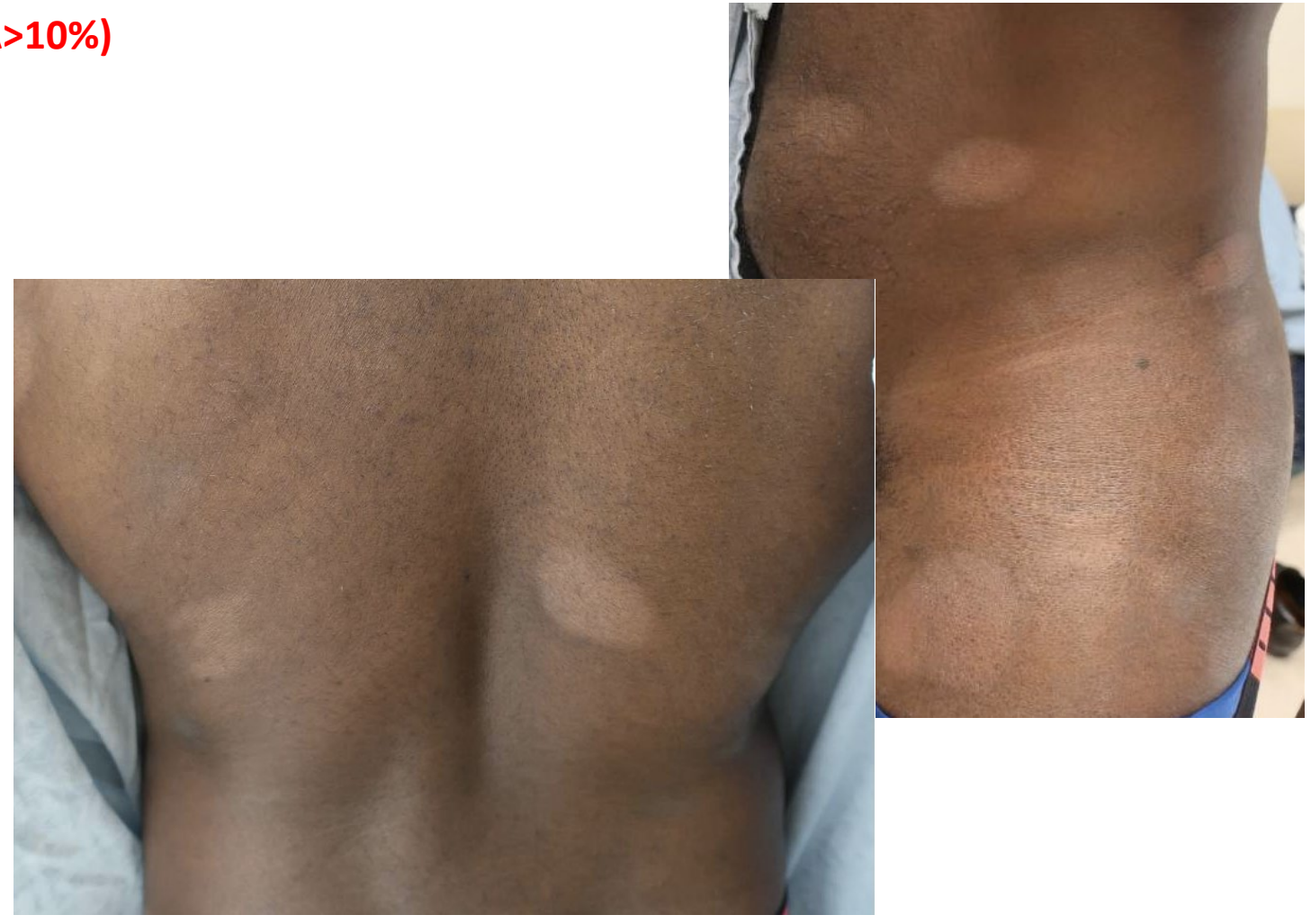
When topicals are not enough….. Phototherapy

Excellent candidates:

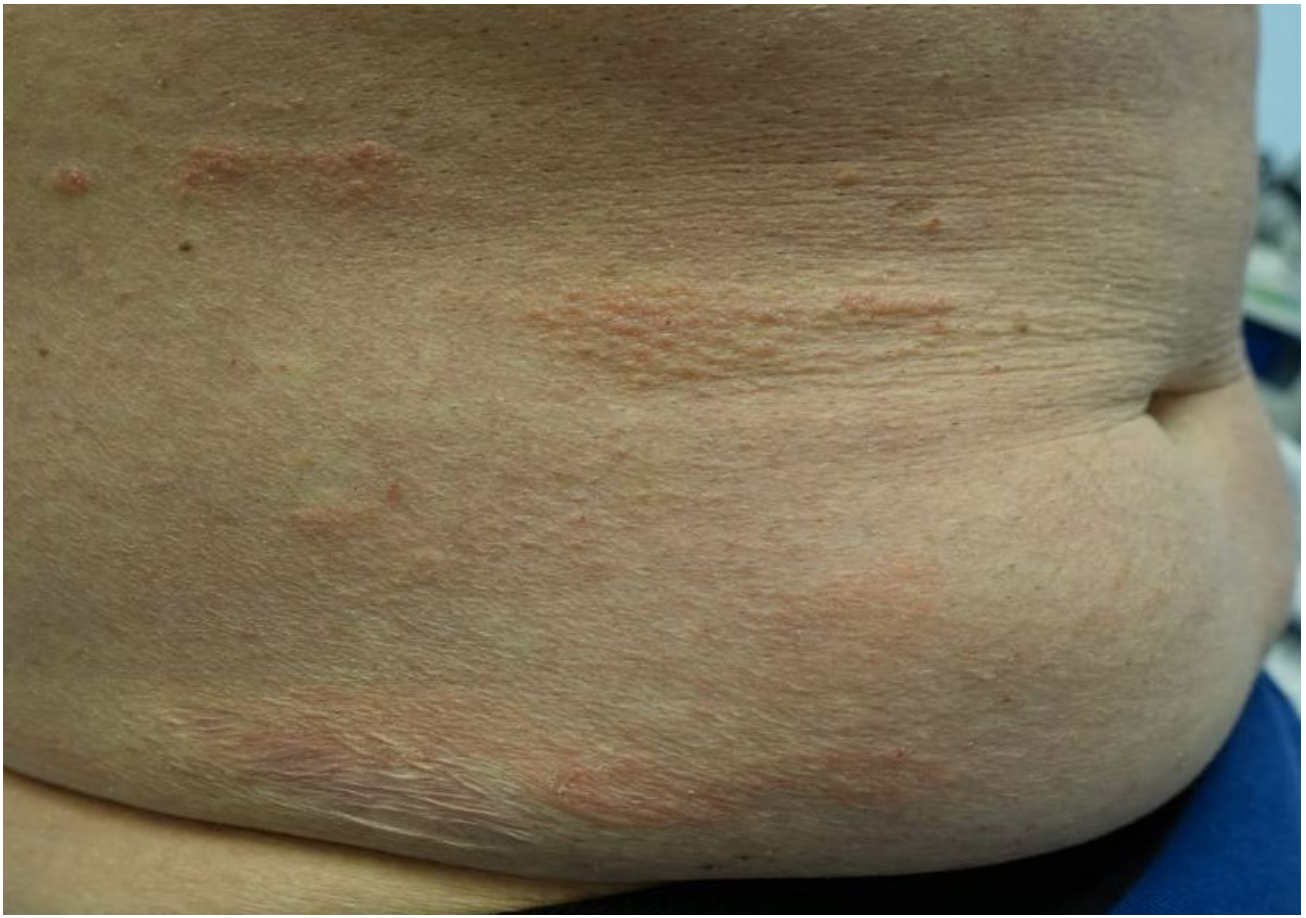
Stage IB: Numerous, scattered lesion (e.g. BSA>10%)

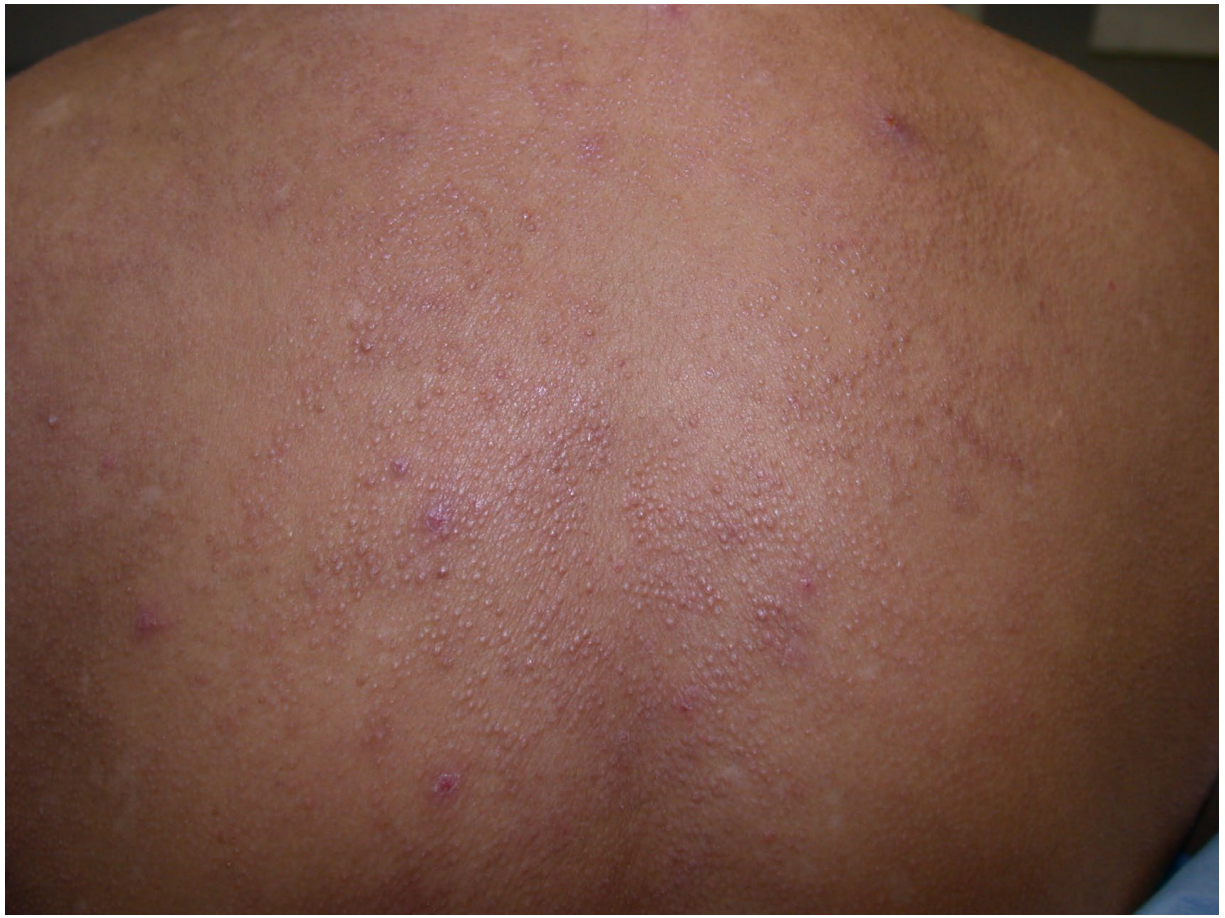


Hypopigmented mycosis fungoides



Folliculotropic disease: *some FMF patients have indolent behavior*





Thinner disease is amenable to treatment with nbUVB, PUVA preferred for thicker lesions

Phototherapy Guidelines

Goal: long-lasting remission off therapy or minimize active disease

Induction/clearing phase:	Increasing dose, 3/week to achieve CR	Time variable
Consolidation phase:	Maintain dose/frequency after CR	1-3 months
Maintenance phase:	Taper down phototherapy	3 months

nbUVB

- ORR 54-90%
- May be used in combination with other tx

PUVA

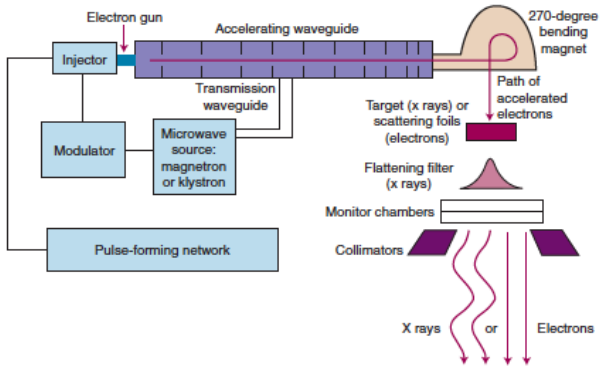
- ORR 85-100%
- May be used in combination with other tx
- Better for thicker disease/FMF
- Increased risk of skin cancer

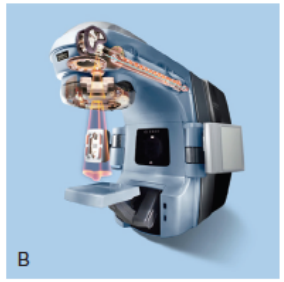
Olsen et al. JAAD 2016

Low-Dose Radiation is Highly Effective for MF

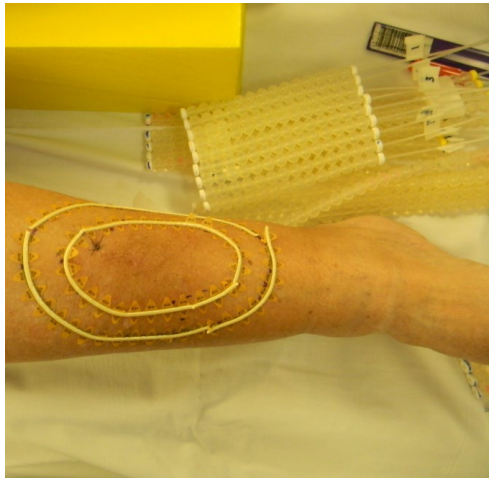
Localized therapy (8-12 Gy)

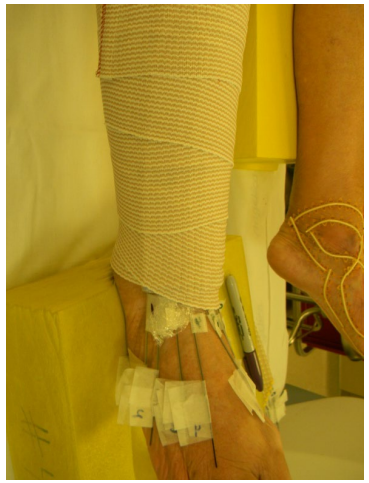
- External beam (electron)

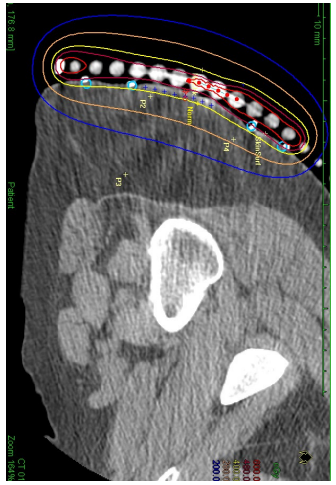




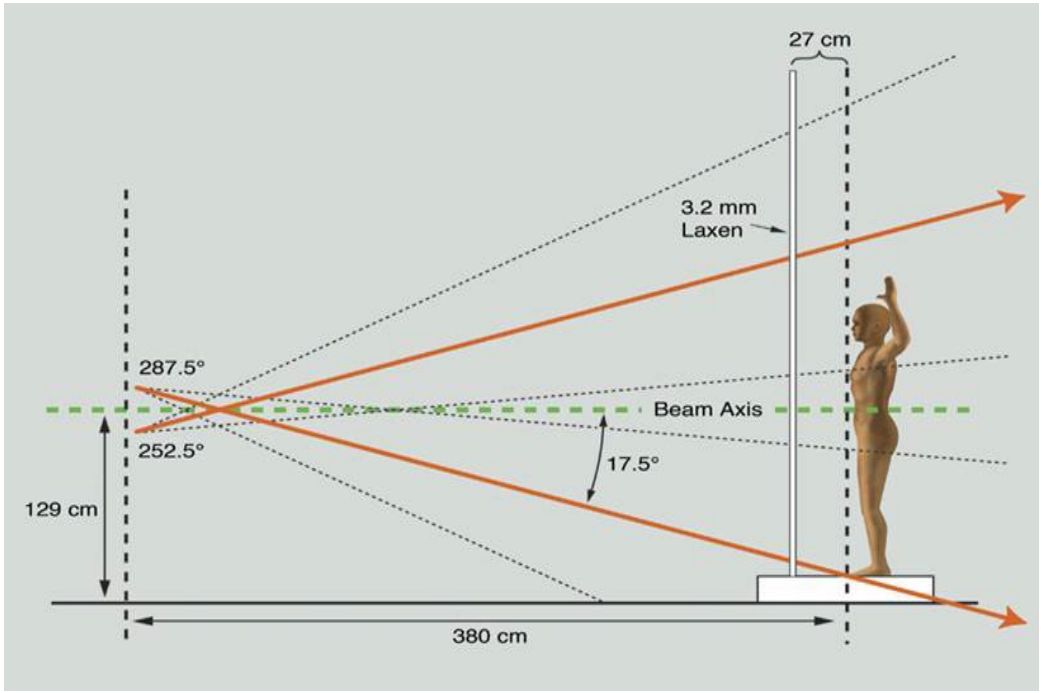
- Brachytherapy (photons)



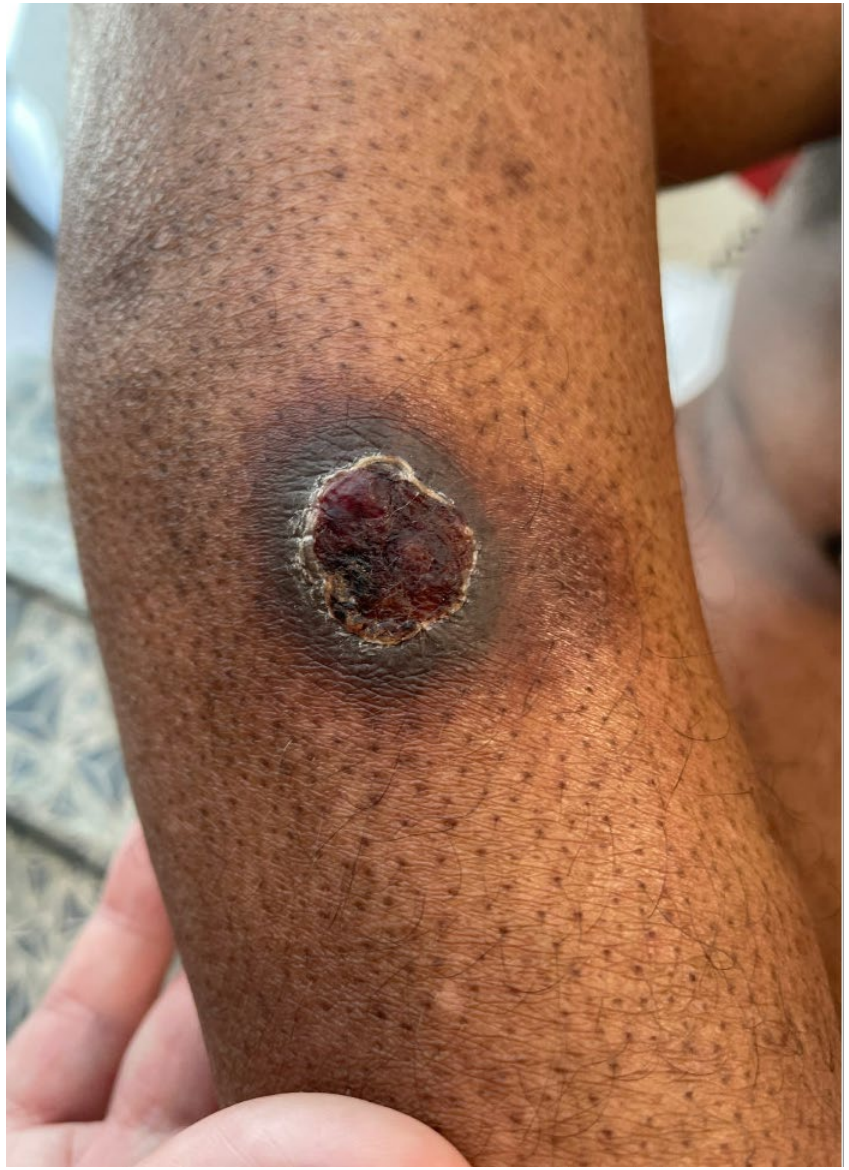




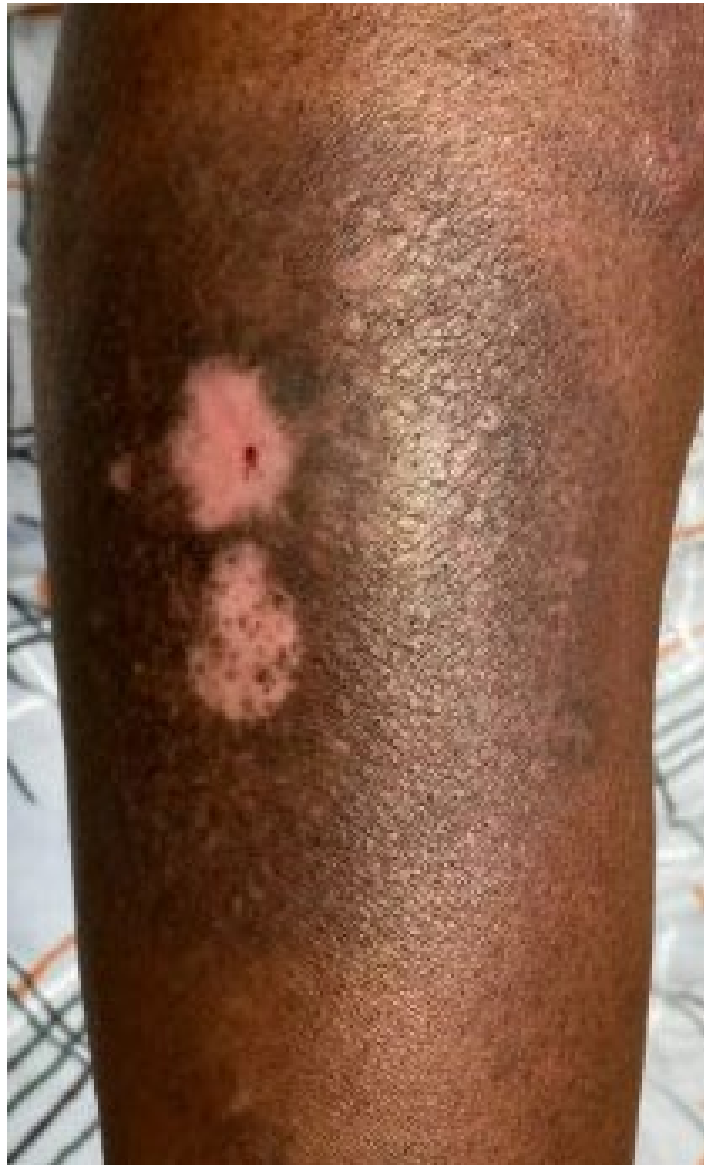
Total skin electron beam therapy (10-12 Gy)



Local external electron beam XRT



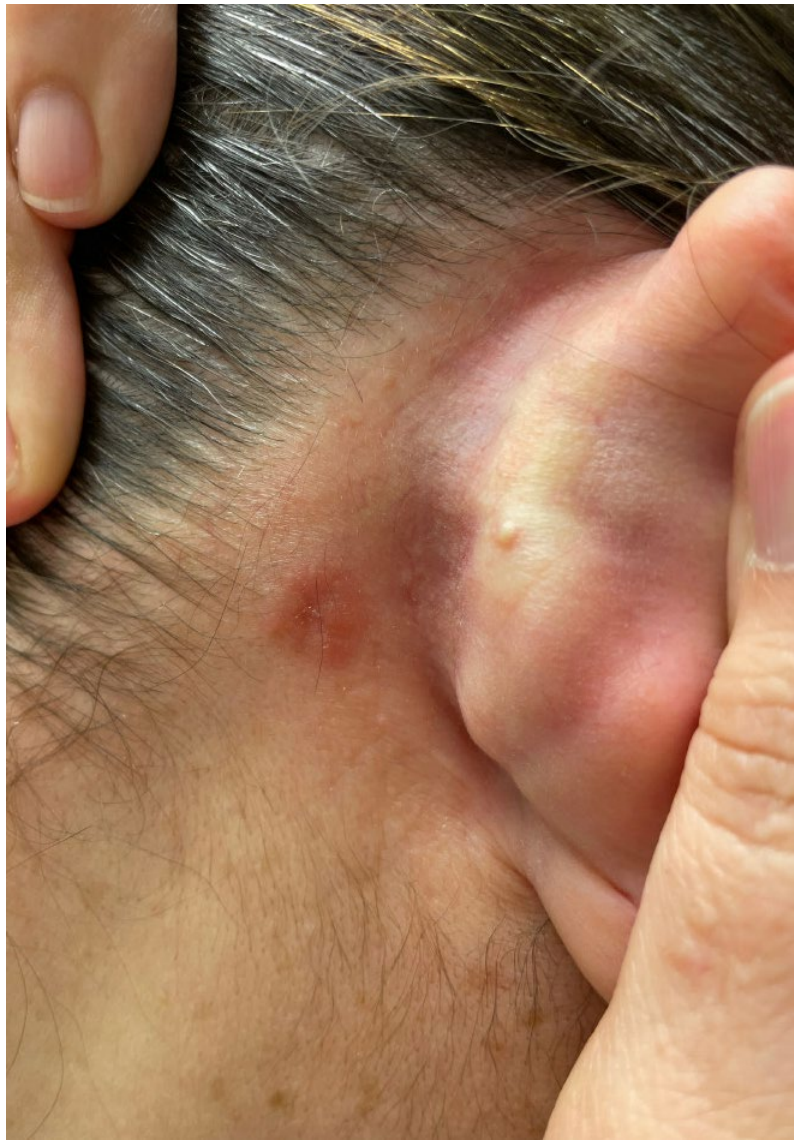
Before



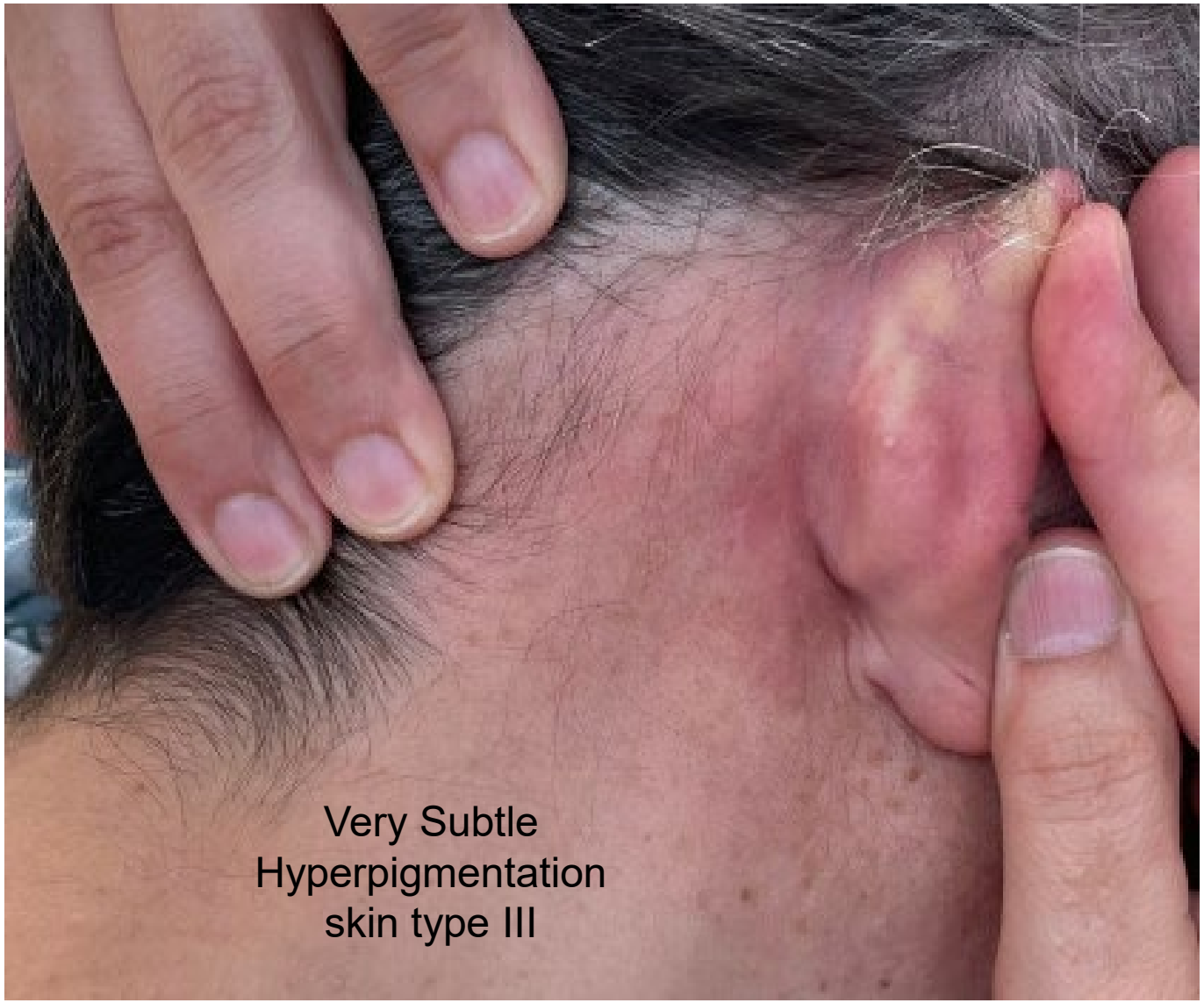
After 30 Gy (PCALCL)

Hyperpigmentation
skin type V

Local external electron beam XRT



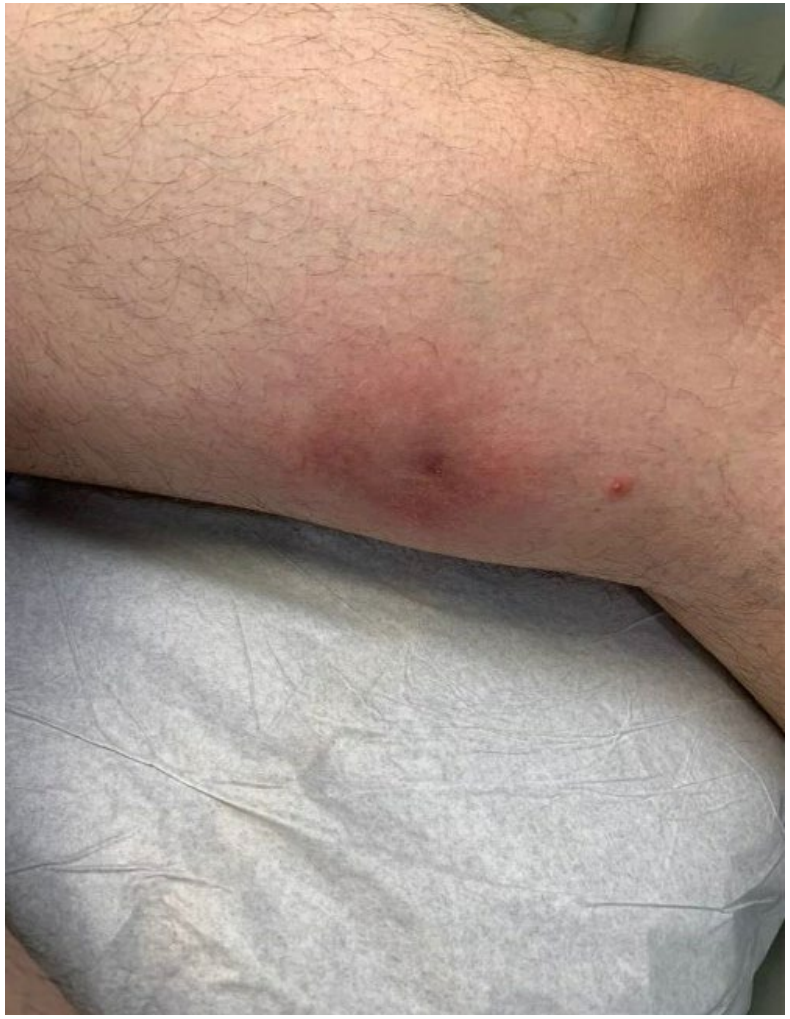
Before



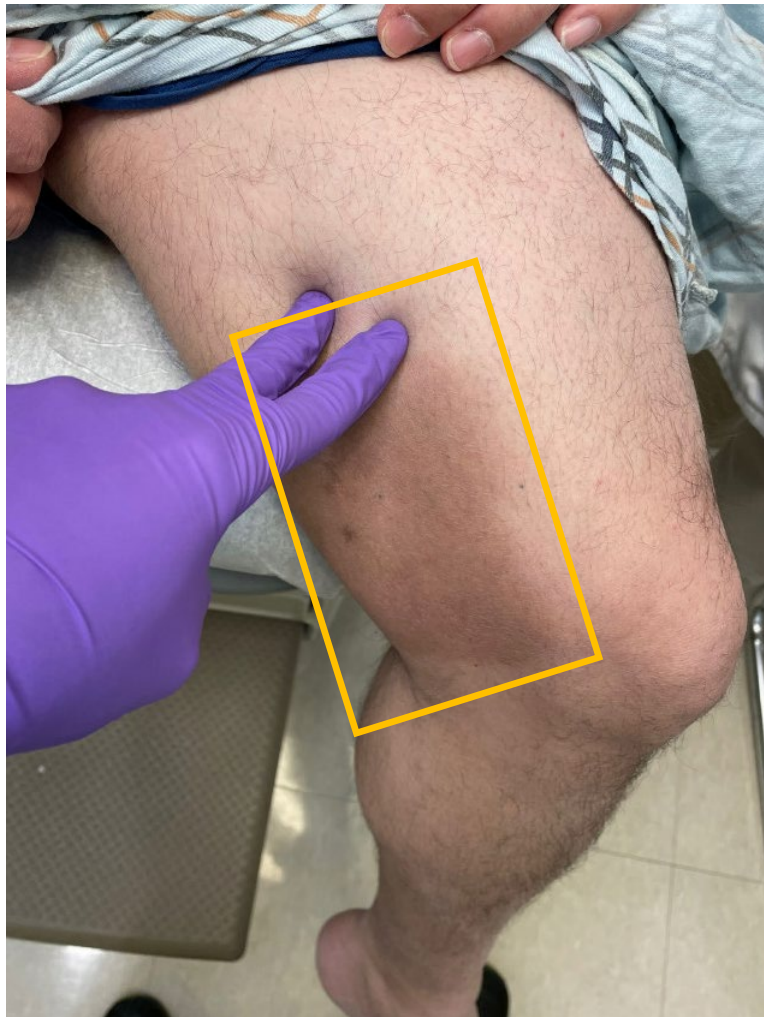
8 weeks after

Local external electron beam XRT

Subcutaneous panniculitis-like TCL



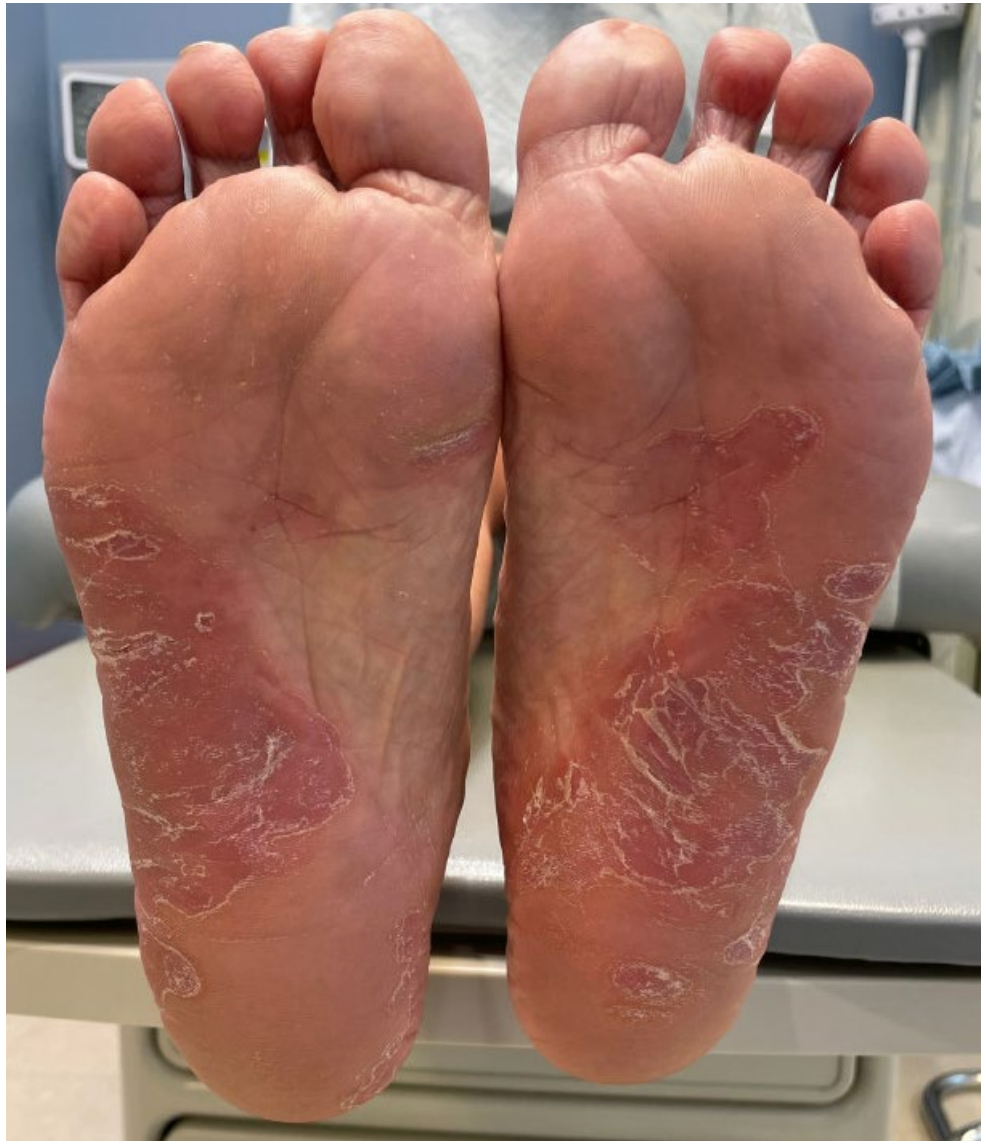
Before

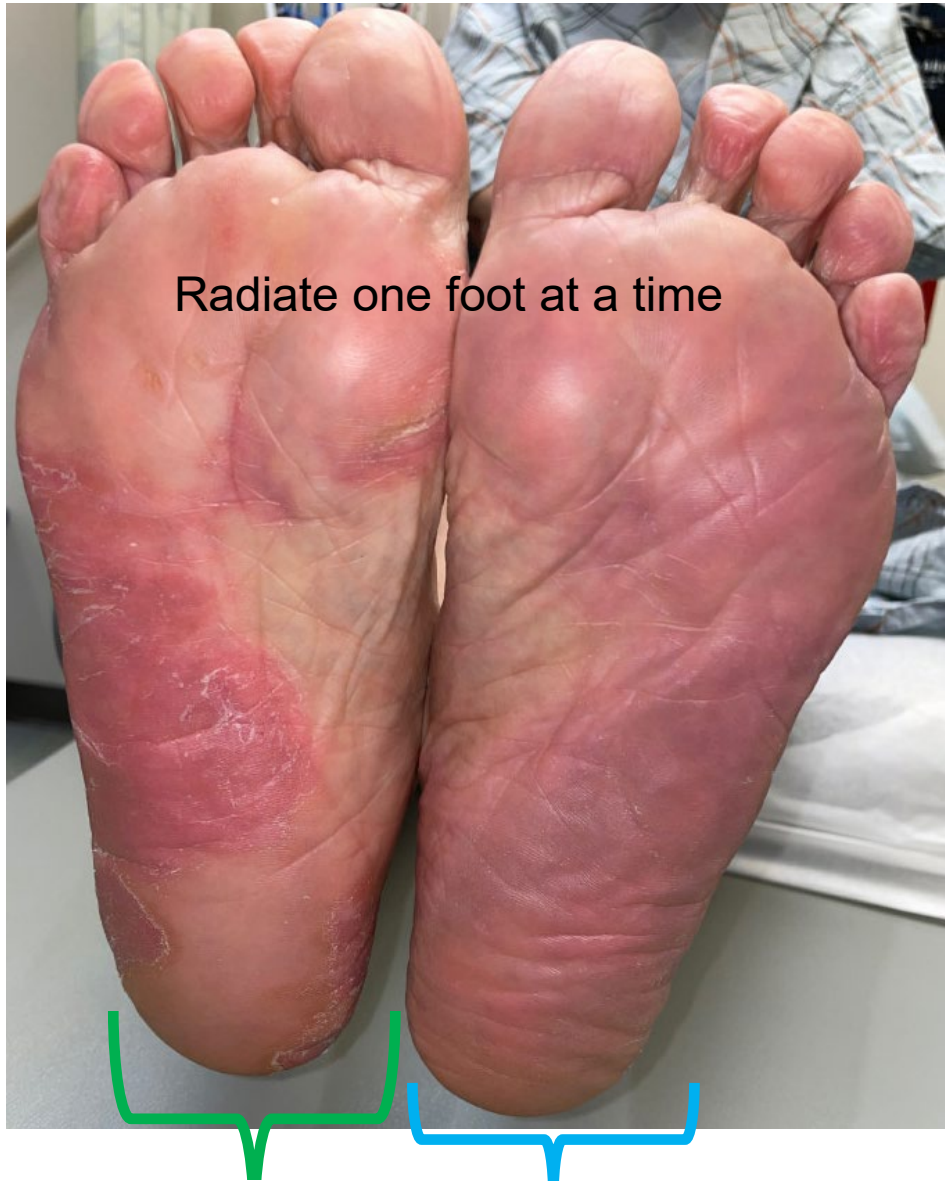


After

Subtle Hyperpigmentation skin type III (~20 Gy)

Brachytherapy (surface mold, photons)





Low dose
no significant
erythema/pain

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Before

During

8 weeks **After** 8 Gy

Radiation is a powerful tool

How good is it?

Low dose radiation vs. Topical steroids

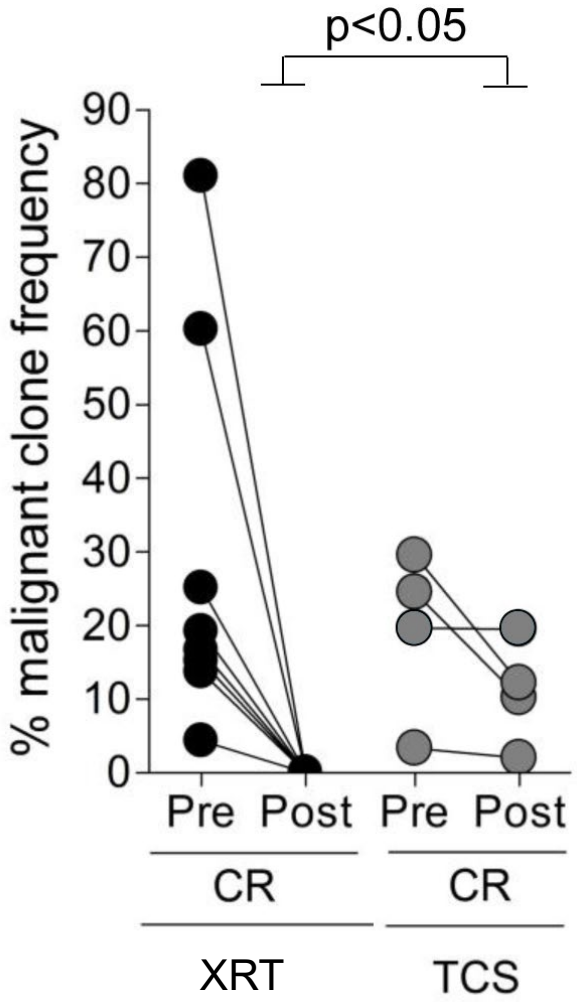
John O'Malley
MD, PhD

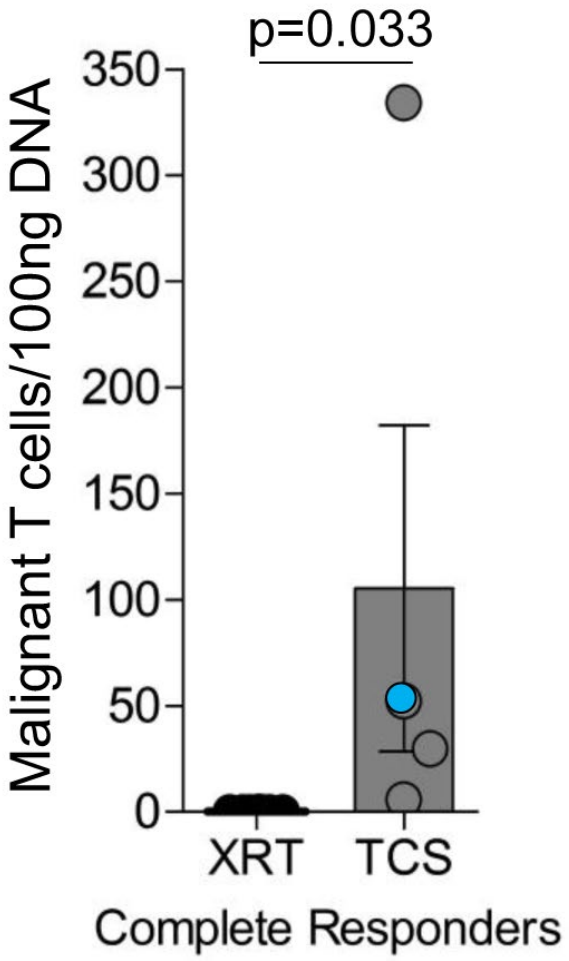
- Class 1 alternating with Class 4 steroids q2weeks (total 12 weeks)

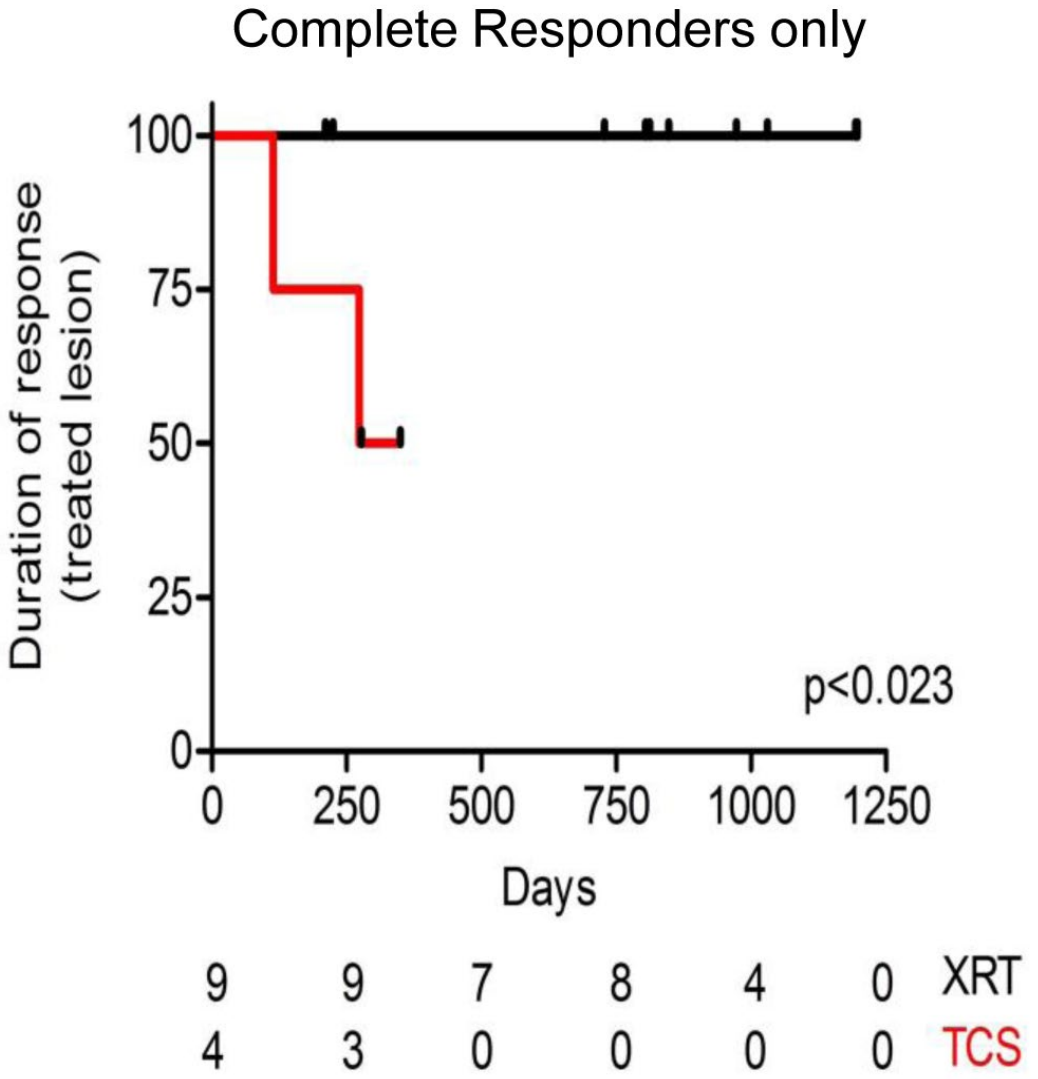
vs.

- Low dose radiation (4 Gy x 2)

Radiation eradicates clone but topical steroids do not







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BUT….

….skin-directed therapy is not for everyone!

Currently Available Systemic Treatments (Pivotal publication)

<1980's	1990's	2000-2010	2010-present
Multi-agent chemo	Methotrexate	Single agent chemo	Pralatrexate (2011)
ECP	Interferons	-Gemcitabine (2000)	Brentuximab Vedotin (2015)
	*Denileukin Diftitox (1999)**	-Doxil (2002, 2012)	Pembrolizumab (PII, 2018)
	*taken off market 2014	Bexarotene (2001)	Mogamulizumab (2018)
		Alemtuzumab (2003)	
		Bortezomib (2007)	
		Vorinostat (2007)	
		Romidepsin (2009)	

Systemic therapies recognized by NCCN guidelines for MF/SS

First-line

- Bexarotene
- Methotrexate
- Interferon alpha/gamma
- Retinoids (acitretin, isotretinoin)

Second-line*

- Brentuximab (LCT, CD30+, skin)
- Pralatrexate (skin)
- Mogamulizumab (blood)
- Alemtuzumab (blood)
- Romidepsin/vorinostat (both)
- Pembrolizumab (both)
- Gemcitabine (both)
- Doxil (both)

Complete Response rates ~30%

*May be 1st line in select cases

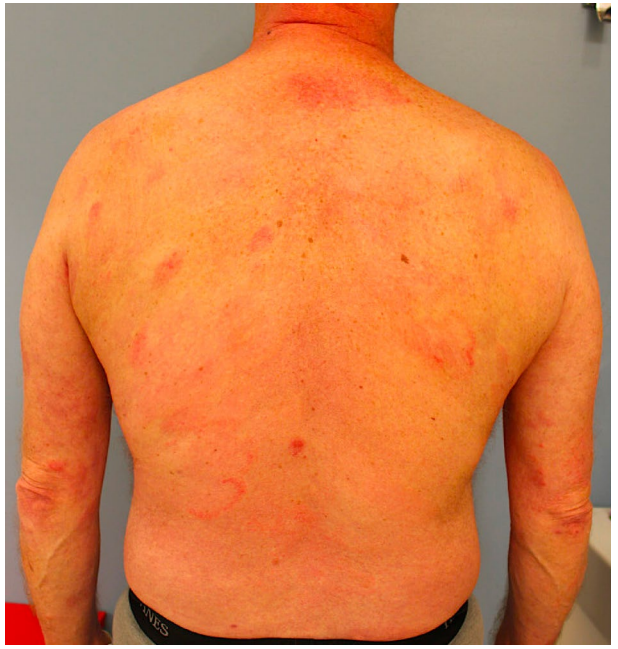
Oral Bexarotene

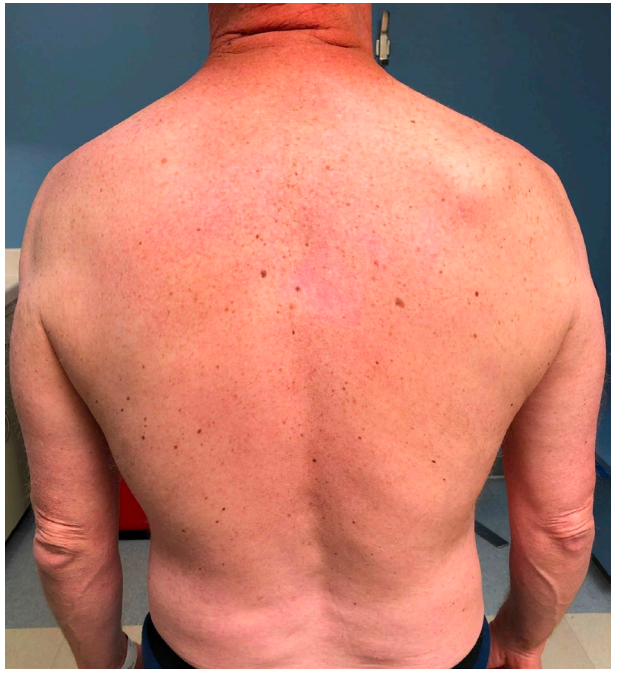
RXR agonist-selectively inhibits cell growth and induces apoptosis
Category X
Oral, titratable daily dosing up to 300mg/m2 **(= 300-600mg daily)**

Side effects usually dose dependent
→elevated TG, hypothyroidism (follow Free T4 only), HA, fatigue, neutropenia

- Start Bexarotene 150mg daily→ increase by 75mg q2-12 weeks
- Start synthroid and statin in everyone (can be before, at initiation, or after)
- Labs q2 weeks with dose changes, then q3 months

- AVOID gemfibrozil (inc. dose of bex): USE omega 3 fatty acids or fenofibrate
- Risk of hypoglycemia with certain diabetes medications





Systemic therapy have different response across disease compartments (and disease subtypes)

Skin	Blood	LN
• Brentuximab • Pralatrexate • Romidepsin	• ECP • Mogamulizumab • Romidepsin • Alemtuzumab	• Brentuximab • Chemotherapy

Consider combination therapy when need to escalate therapy in MF/SS (or skin + blood)

Skin-Directed + Systemic

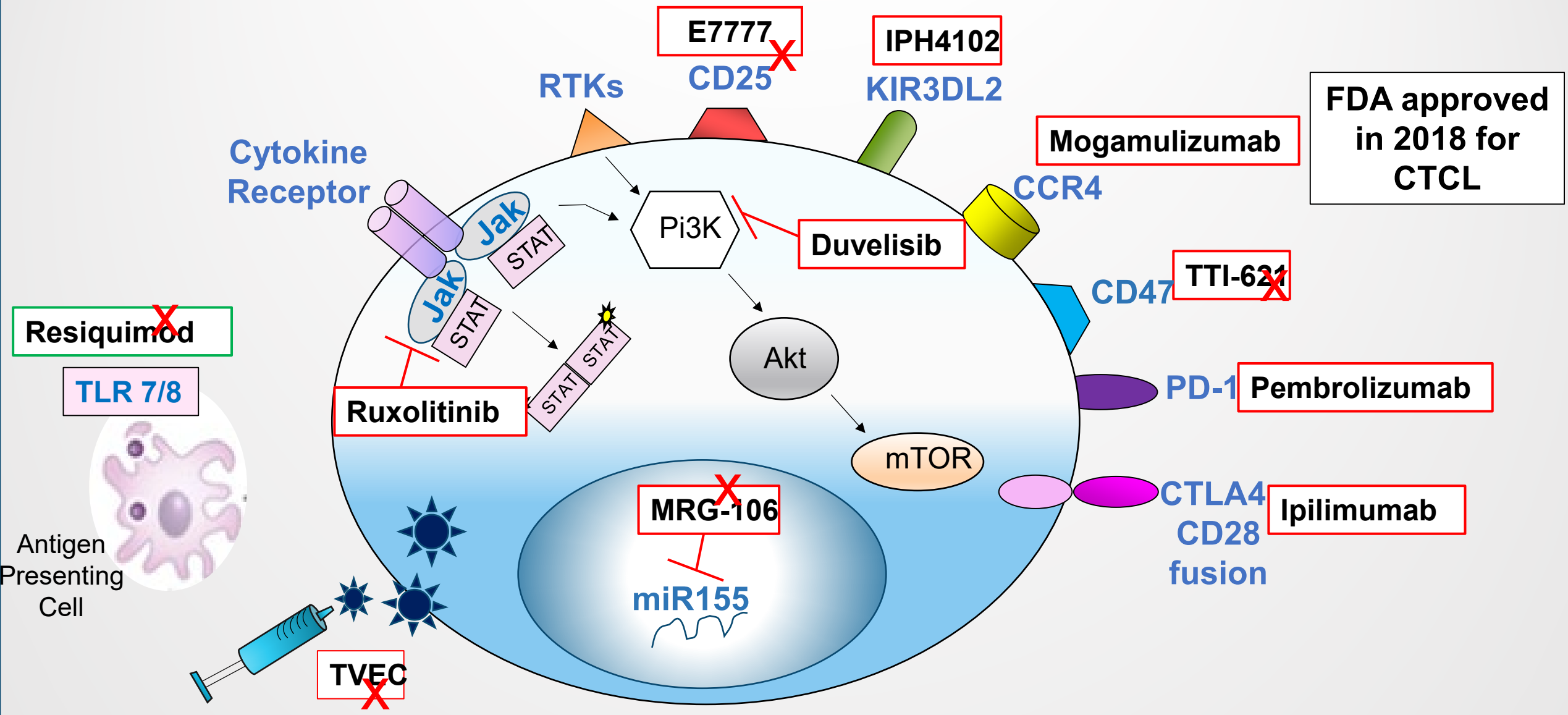
- Phototherapy + Retinoid
- Phototherapy + IFN
- Phototherapy +Photopheresis
- TSEBT + Photopheresis

Systemic + Systemic

- Retinoid + IFN
- Photopheresis + retinoid
- Photopheresis + IFN
- Photopheresis + retinoid + IFN

No clear data that any one combination therapy is better

Therapies in clinical development for CTCL



CTCL Management considerations

- CRs are rare: PRs more likely
- Can take 4-24 months to achieve full response
- Maintenance therapy; may return to prior therapies
- Monitor for secondary infections
- Assess and manage pruritus
- Immunosuppression
- Manage long term sequelae of skin TX (NMSC/ MM/ atrophy)
- Body Image and relationship challenges
- QOL compromise

The Trials and Tribulations of Designing CTCL Interventions

Progress underway

- Greater number of therapeutic options
- Finely tuned diagnostic measures e.g. IHC/TCR HTS
- Oncopanel/genomic sequencing
- Clinical trial landscape expanding
- US and international CTCL collaborations e.g. USCL/ISCL/EORTC/CLIC/Proclipi/ IDEOM
- Patient advocacy via CLF/ LRF/ LSS

Ongoing struggles

- CTCL is a heterogeneous disease

→*One size does not fit all*

- Many of the therapeutic interventions are at risk of extinction e.g. IFN/ PUVA
- Pricy disease to be diagnosed with= $$ cost
- HRQOL CTCL- current tools do not capture
- Lingering pandemic environment of care

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Thank you to the SDNP for this kind invitation

Questions and comments welcomed!