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Southeastern Multidisciplinary Approaches to Cancer Symposium

Therapeutic Advances in Advanced Mycosis Fungoides

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Disclosures

- Grant/Research Support from Bioinvent, Dren Bio, Incyte, & Kiowa Kirin.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of DR-01, fenretinide, Darvalumab, CD70 bispecific, and CD5-CART will be addressed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

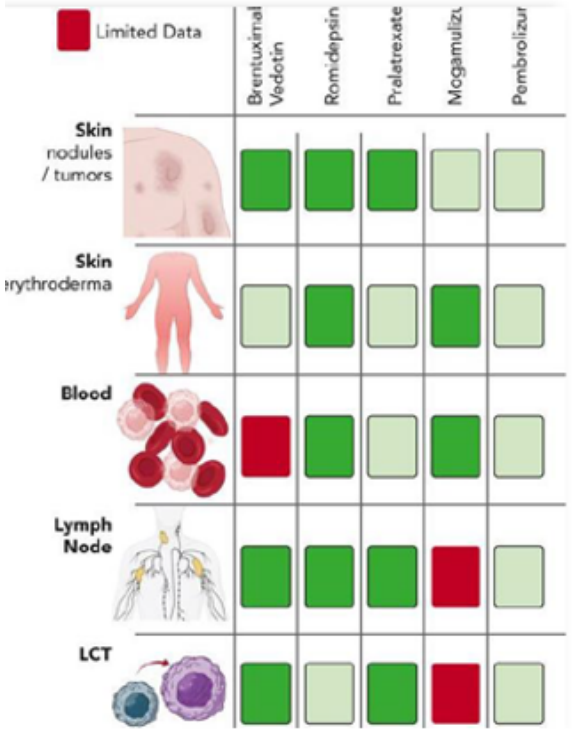
STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

TREATMENT CONSIDERATIONS AND OUTCOMES IN MF/SS

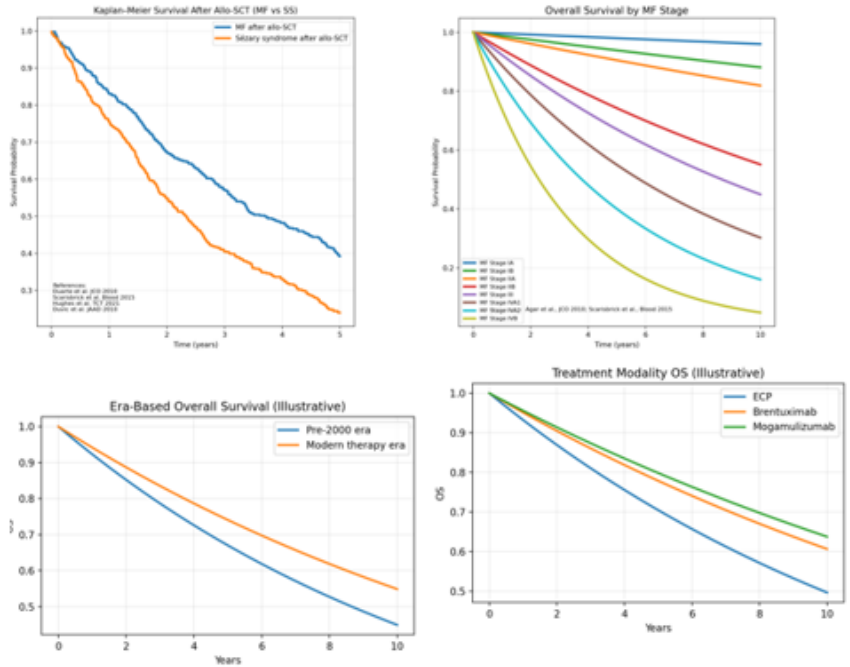


Inherent challenges in treating and evaluating MF/SS

Treatment is stage based – also consider compartmental burden of disease

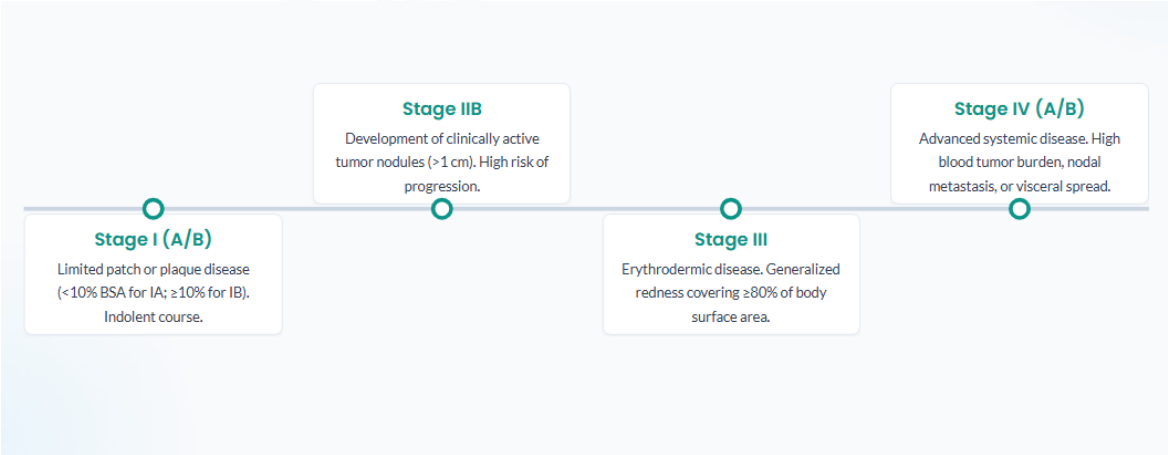
Agents have differing effects in different compartments

Disease can wax and wane/ cutaneous drug reactions

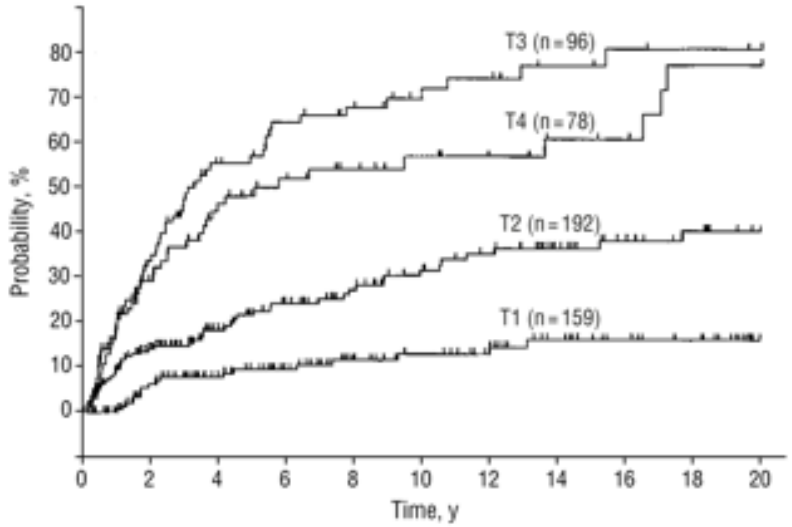


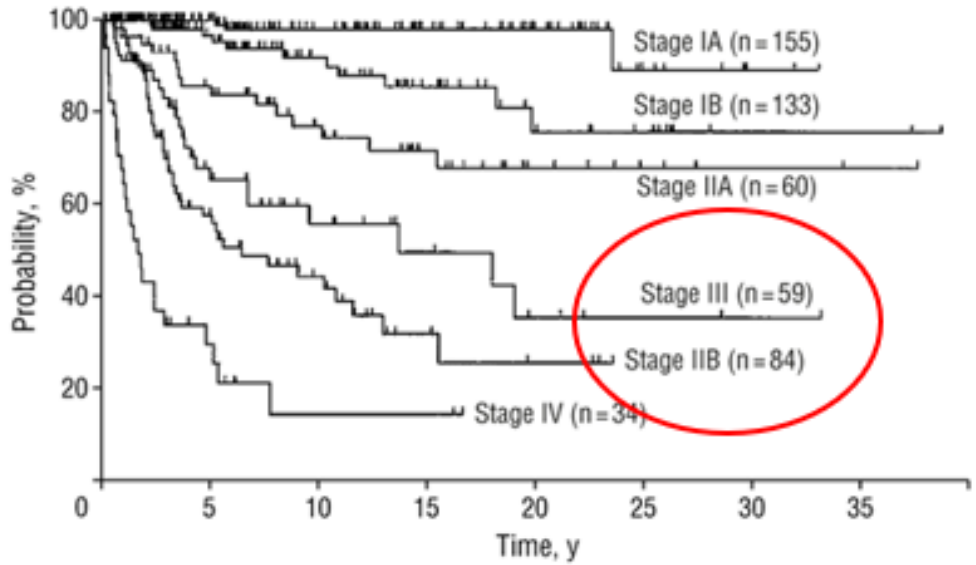
Outcomes of MF and Sezary syndrome

Classification	Definition
Stage	
T1	Patches, plaques, or both involving <10% of body-surface area
T2	Patches, plaques, or both involving ≥10% of body-surface area
T3	One or more cutaneous tumors
T4	Erythroderma
N0	Lymph nodes clinically uninvolved
N1	Lymph nodes clinically enlarged but not histologically involved
N2	Lymph nodes clinically nonpalpable but histologically involved
N3	Lymph nodes clinically enlarged and histologically involved
M0	No visceral disease
M1	Visceral disease
B0	No circulating atypical cells (Sézary cells)
B1	Circulating atypical cells (Sézary cells)
Stage groups	
IA	T1N0M0
IB	T2N0M0
IIA	T1–2N1M0
IIB	T3N0–1M0
IIIA	T4N0M0
IIIB	T4N1M0
IVA	T1–4N2–3M0
IVB	T1–4N0–3M1



Probability of survival





Kim et al: JAMA Dermatology 2003

CLIPI- A NEW PROGNOSTIC INDEX FOR ADVANCED STAGE CUTANEOUS LYMPHOMA

Context of Research

Advanced **mycosis fungoides (MF)** and **Sézary syndrome (SS)** have a poor prognosis, with an overall survival rate of less than 5 years. Studies have found the current clinical staging (IA-IVB) to be inadequate for risk stratification.

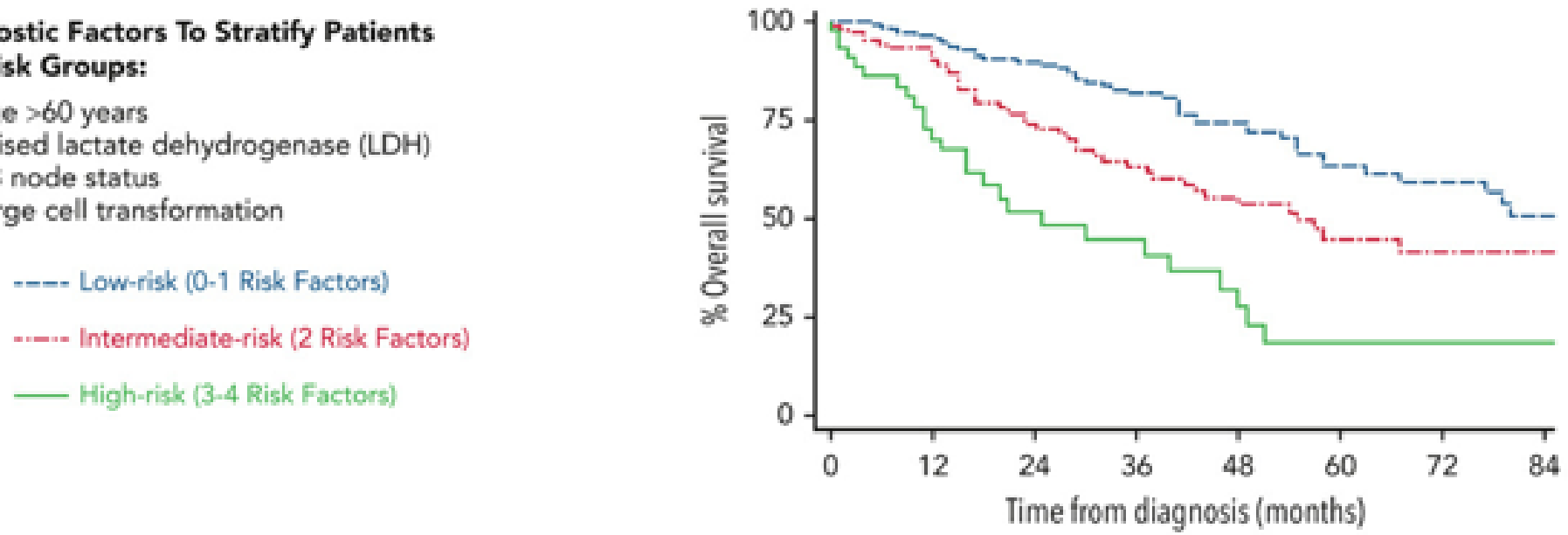
Aim of This Study

Our objective was to develop a **Cutaneous Lymphoma International Prognostic Index (CLIPI)** that could accurately identify MF/SS patients with poor outcomes, enabling better management decisions (**PROCLIPI study, NCT02848274**).

Findings

Prognostic Factors To Stratify Patients Into Risk Groups:

1. Age >60 years
2. Raised lactate dehydrogenase (LDH)
3. N3 node status
4. Large cell transformation

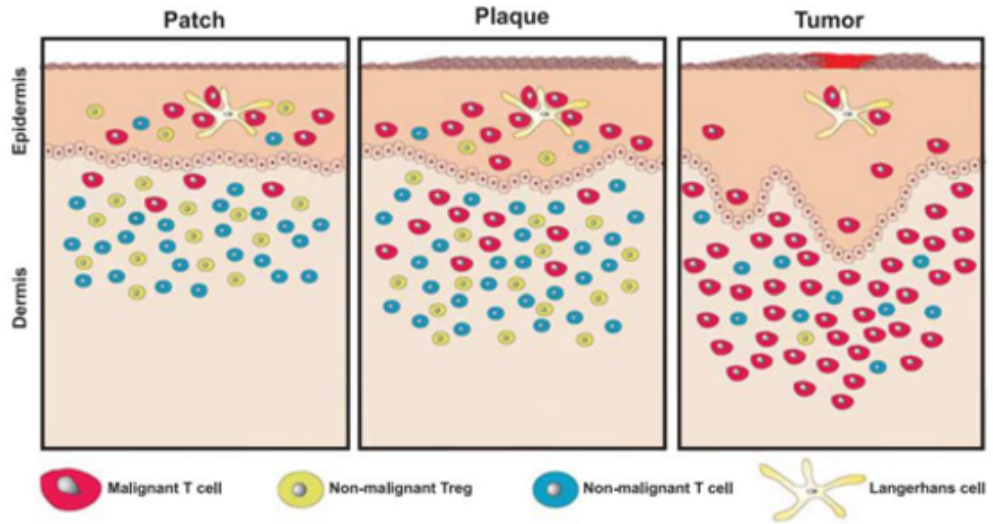


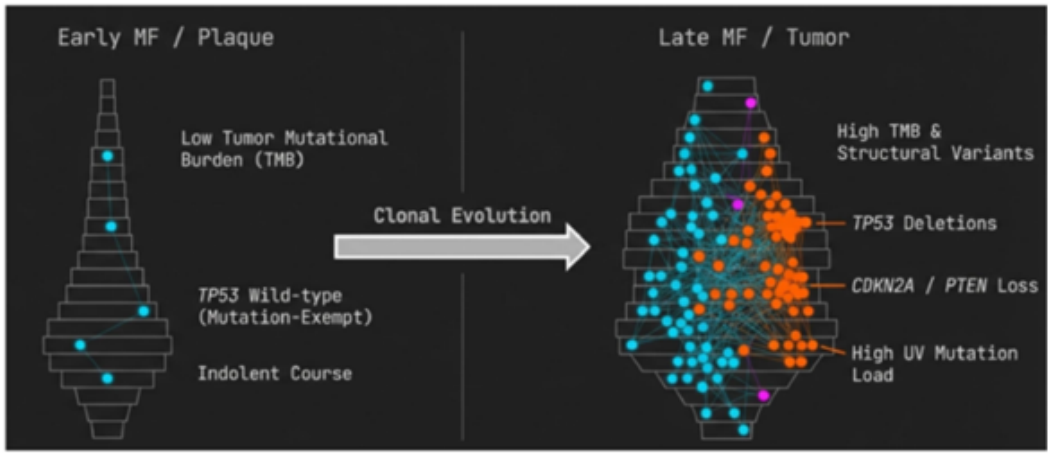
Scarisbrick et al: Blood 2025

STAGE BASED TREATMENT

Disease Stage	Preferred Clinical Focus	First-Line NCCN Regimen	Alternative Therapies
Stage IA–IIA	Symptom control, localized focus	Topical Steroids, Phototherapy	Mechlorethamine 0.02% Gel
Stage IIB	Active tumor management	Systemic Retinoids + Local RT	TSEBT, Oral Bexarotene
Stage III	Erythrodermic control	ECP or Mogamulizumab	LYMPHIR, Oral Methotrexate
Stage IVA–IVB	Systemic, cytoreductive intent	Targeted mAb / Allogeneic HCT	Romidepsin, Polychemotherapy

EARLY VS LATE MF





Mycosis Fungoides is the most common type of CTCL
Slow progression from Patch → Plaque → Tumor
Malignant clonal expansion of CD4+ T cells

Inherently chemo resistant
Genetic alterations drive the progression of disease
CTCL cells have skin homing properties
Increasingly immunosuppressive tumor microenvironment
Immunosuppressive cytokines
Loss of normal effector cells
Microbiome

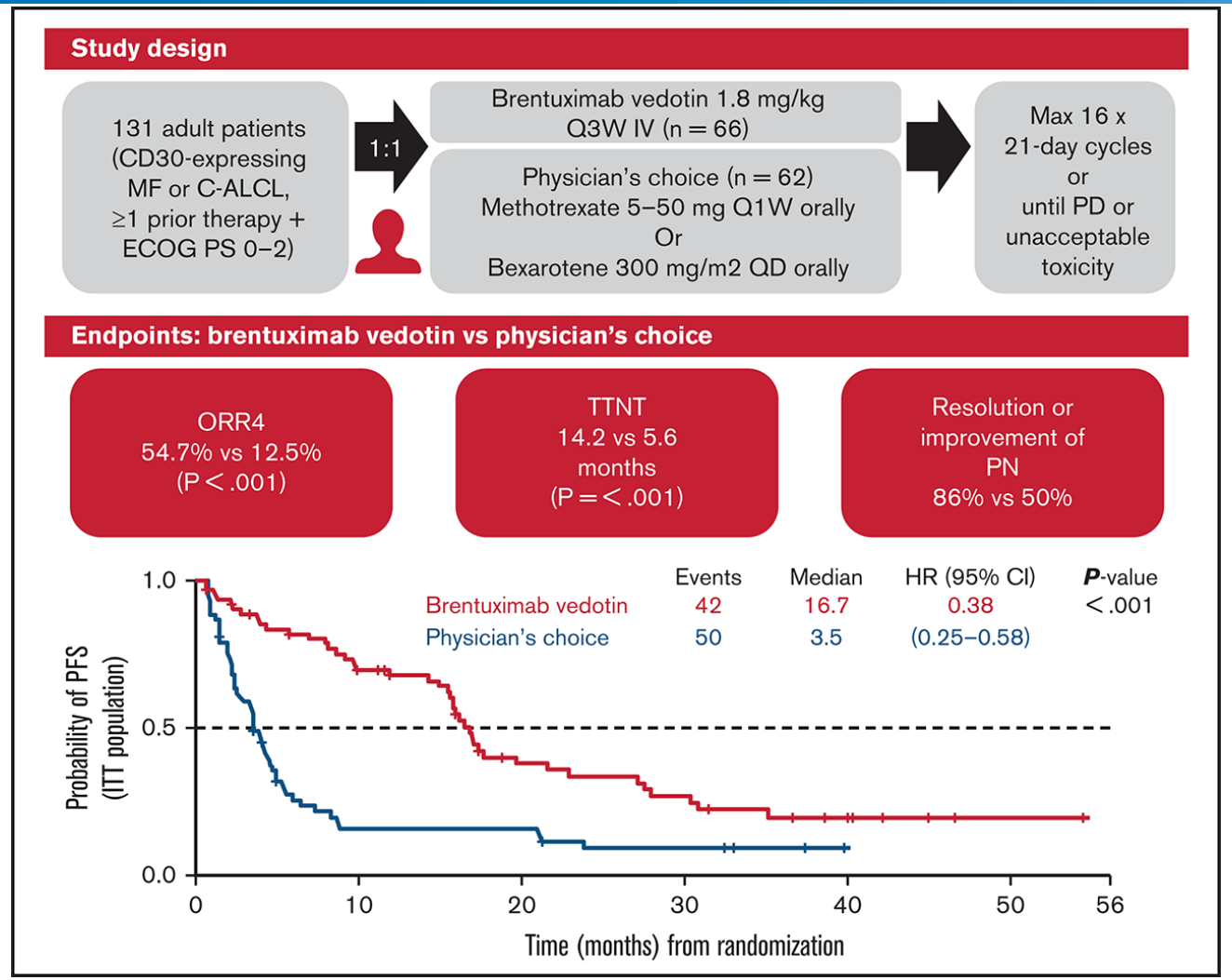
Kresisgaard et al : Leukemia 2012, , Gniadecki et al Cells 2023

KEY CLINICAL TRIALS IN ADVANCED STAG MF/SS

Study/Agent	CR	ORR	DoR	Median Survival
ALCANZA (BV)	16%	56.3%	13.2 mo	NR
MAVORIC (Moga)	0–1%	28%	14.1 mo	NR
Vorinostat	0–1%	30%	5–6 mo	NR
Romidepsin	6%	34%	14–15 mo	NR
Bexarotene	1–2%	45%	7–9 mo	NR
Denileukin diftitox	10%	30–44%	6–7 mo	NR
LYMPHIR (E7777)	15%	36%	9–10 mo	NR
Pralatrexate (CTCL)	6%	45%	4–5 mo	NR
Pembrolizumab (KN170)	2%	38%	11 mo	NR
Lacutamab TELLOMAK	3–5%	30–35%	10–12 mo	NR
Lacutamab IPH4102-101	0–1%	36%	11 mo	NR

Kim et al., Lancet 2017 (ALCANZA); Kim et al., Lancet Oncol 2018 (MAVORIC); Olsen et al., JCO 2007 (Vorinostat); Whittaker et al., JCO 2010 (Romidepsin); Duvic et al., JCO 2001 (Bexarotene); Olsen et al., JCO 2001 (Denileukin diftitox); KEYNOTE-170 JCO 2020; TELLOMAK & IPH4102 trials.

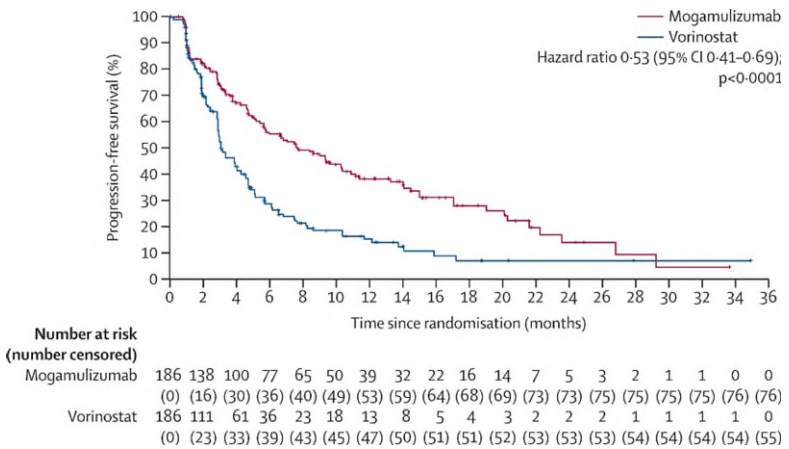
ALCANZA- PHASE III STUDY OF BRENTUXIMAB VEDOTIN VS PHYSICIAN CHOICE

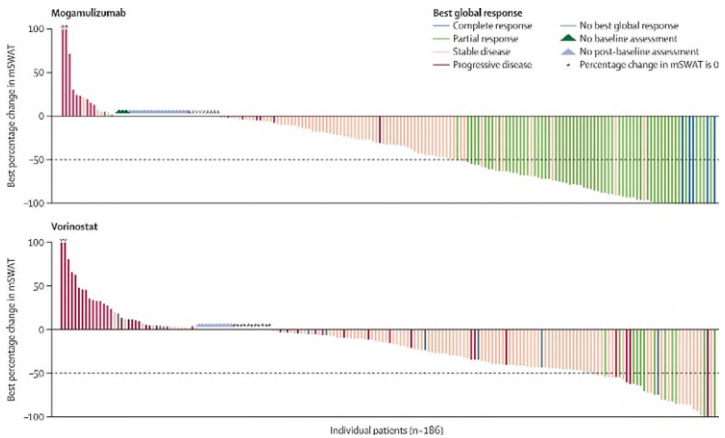


- Median follow up was 45.9 months
- CD30 was defined as > 10% of target lymphoid cells
- 1:1 randomization
- Patients with Sezary Syndrome were excluded
- Stage B1 were eligible
- ORR4 was defined as objective global response rate that lasted for 4 months
- Peripheral neuropathy was the main side effect – 67% vs 6%
- Exploratory analysis demonstrated that activity was observed across all levels of CD30 expression, regardless of LCT

Horwitz et al: Blood 2021

MAVORIC- MOGAMULIZUMAB VS VORINOSTAT



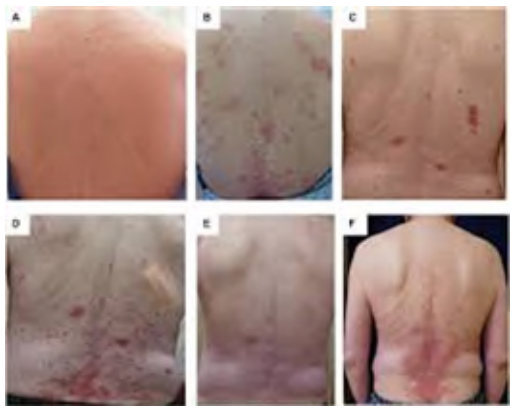


Kim et al: Lance Oncology 2018,

-Targets CCR4- defucosylated Humainzed IgG1 monoclonal antibody
-CCR4 is consistently expressed on tumor cells in MF and SS
-1:1 randomization
- Cross over was allowed for progression on Vorniostat
-Superior PFS compared to Vorinostat 7.7 months vs 3.1 month, ORR – 28% vs 5%
- Median time to respond was 3.3 months , **1.1 month for blood compartment**, 3.0 months for skin and 3.3 months for nodes
- IRR, RASH, diarrhea, nausea

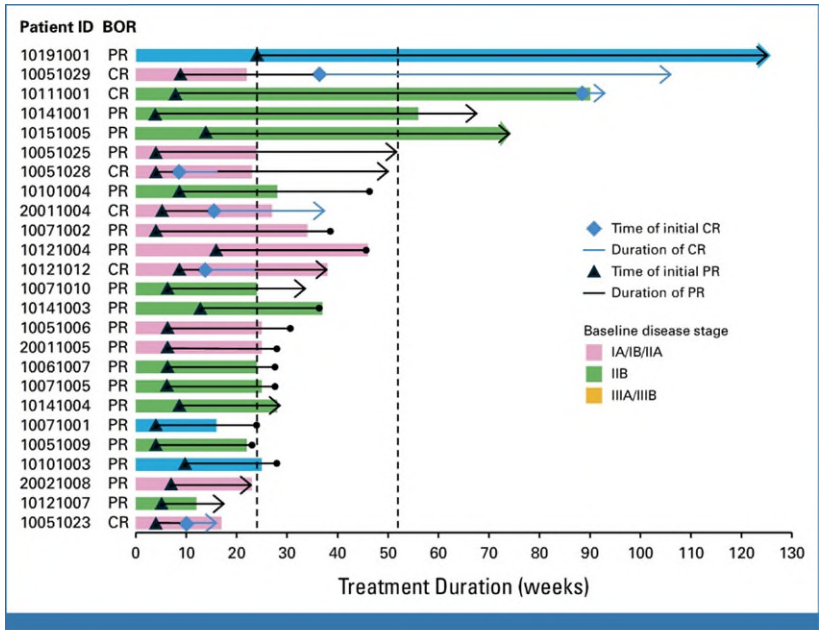
-Mogamulizumab – associated rash (MAR)

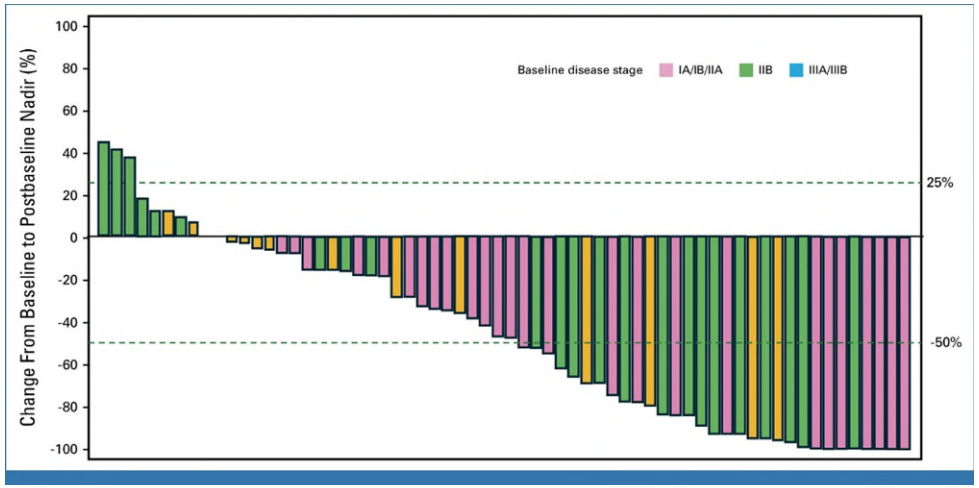
-Manifests as papular, maculopapular, lichenoid, or eczematous/psoriasiform rashes
-Skin Biopsy is crucial to differentiate from CTCL.
-MAR is often associated with a significantly better tumor response to the medication
Managed by temporary drug cessation, steroids and low dose MTX



Hu et al: Blood 2022

DENILEUKIN DIFTITOX –CXDL

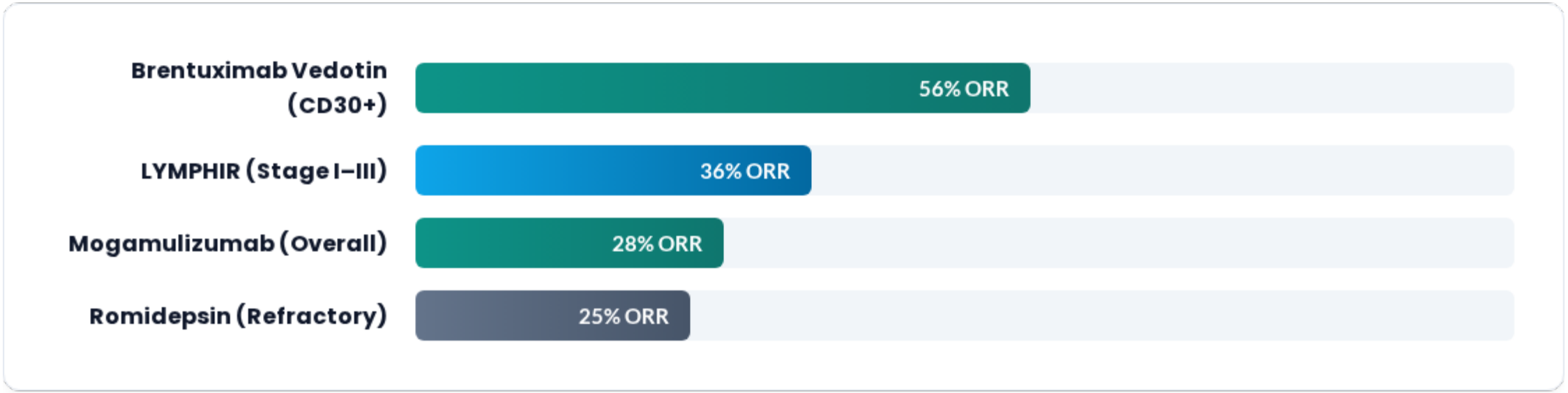




Efficacy and Safety of Denileukin Diftitox-Cxdl, an Improved Purity Formulation of Denileukin Diftitox, in Patients With Relapsed or Refractory Cutaneous T-Cell Lymphoma

Foss et al ;JCO 2025

SYSTEMIC EFFICACY COMPARISON



COMPARTMENTAL RESPONSE COMPARISON

AGENT	GLOBAL ORR	SKIN ORR	BLOOD ORR	PRIMARY CLINIAL ROLE
Lacutamab	42.95	52.45	50.85	Post mogamulizumab - high nodal response
Lymphir	36.25	48.4%	30-40%	Rapid relief for stage I-IIIMF
Mogamulizumab	28.0%	42.05%	68%	Ist line treatment for SS
Brentuximab vedotin	56.3%	High	Low	CD30+ tumor – transfomred dz
Pembrolizumab	45%	High	Variable	Cytotoxic aggressive MF
Lenalidomide	28%	30%	Low	Immunomodulation for late – line MF

Genetic Landscapes in MF/SS

Complexity & Heterogeneity

High structural variations / Copy number variations

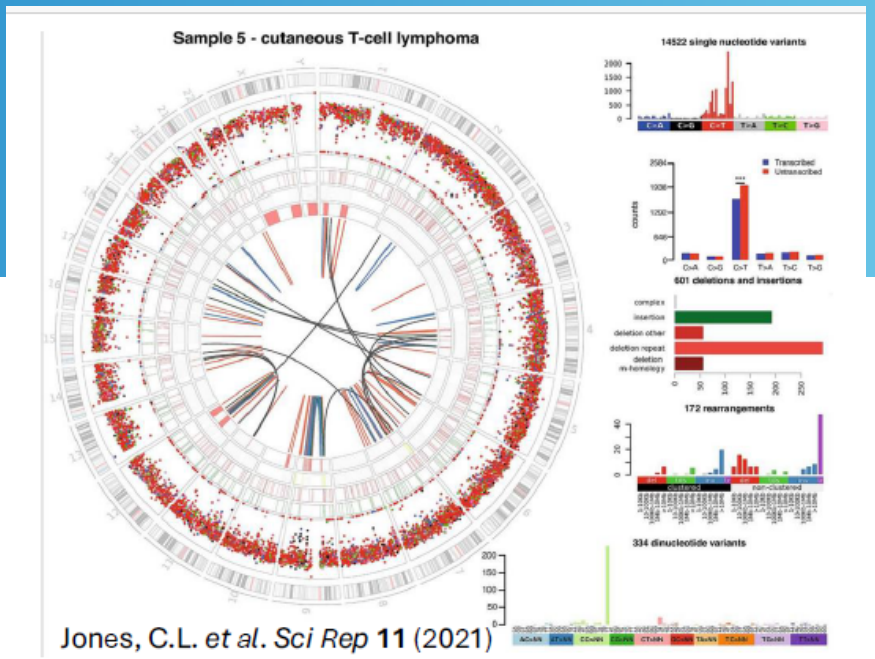
Non-synonymous variants (SNVs)

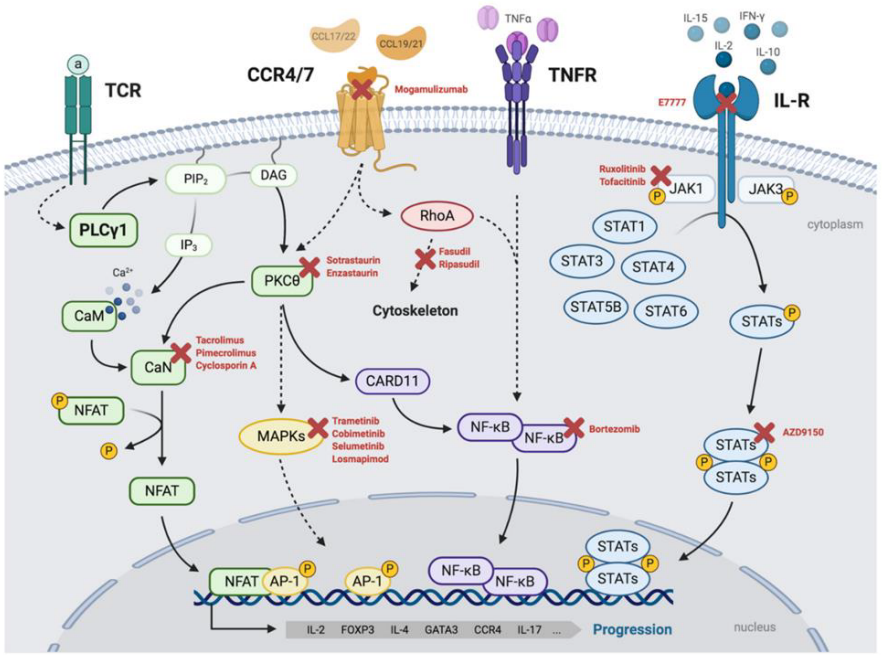
Defined by pathway clustering rather than a single driver

Major dysregulated pathways:

- TCR Signaling: PLCG1, CARD11, and CD28.
- NF-κB Pathway: High selection pressure for activation; TNFRSF1B and RLTPR
- JAK/STAT Signaling: STAT3 and STAT5B copy number gains
- DNA Damage Response (DDR): TP53, ATM, and POT1

Genomic overlap between MF and SS



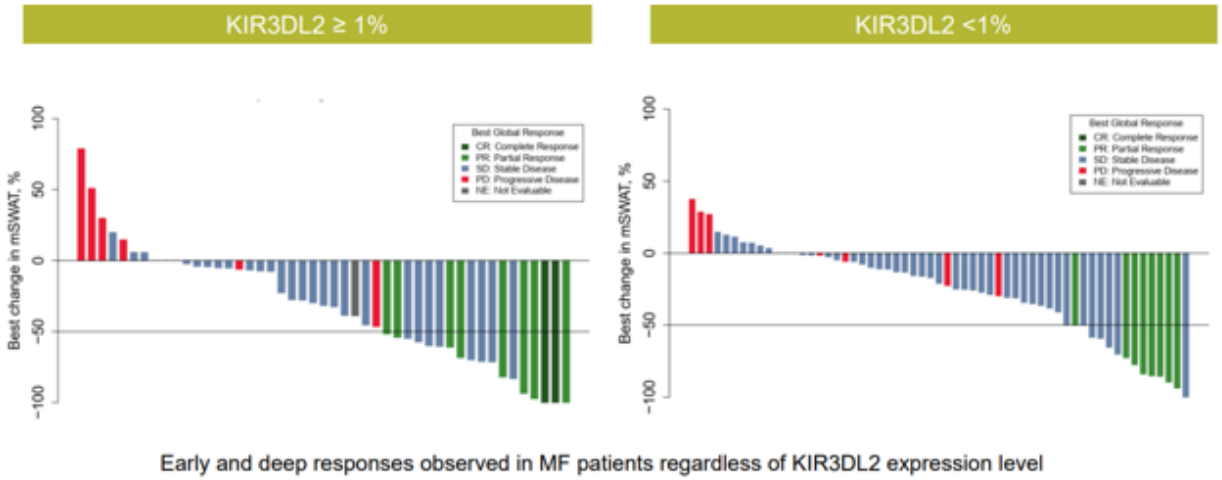


EMERGING THERAPEUTIC TARGETS IN CTCL

TARGET / PATHWAY	RATIONALE	REPRESENTATIVE AGENTS	DEVELOPMENT STAGE
STAT3 / STAT5	Constitutive activation	JAK Inhibitors, TTI-101, STAT3 PROTACs	Preclinical/Early
PI3K-δ/γ	Survival signaling	Duvelisib, Tenalisib	Phase I–II
KIR3DL2	Sézary-specific expression	Lacutamab	Phase II
CCR8	SS & Treg expression	Anti-CCR8 Abs	Preclinical
CD47	Macrophage checkpoint	Magrolimab	Phase I–II
TIGIT/LAG-3	Alternative checkpoints	Tiragolumab, Relatlimab	Early clinical
EZH2	Epigenetic silencing	Tazemetostat, Tulmimetostat	Phase II in MF/SS
BET proteins	MYC regulation	Birabresib	Preclinical
IL-15/CD25	Cytokine-driven growth	Camidanlumab	Phase I–II
PTX-100	GGTase-1 Inhibitor	Blocks geranylgeranyl transferase-1;	granted FDA Fast Track status in 2025 for R/R MF.

LACUTAMAB

ITT set	All MF N=107	KIR3DL2 ≥ 1% N=48	KIR3DL2 <1% N=59
Olsen 2011 Global ORR % (95%CI)	**16.8% (10.9, 25.0)**	**20.8% (11.7, 34.3)**	**13.6% (7.0, 24.5)**
CR n (%)	2 (1.9)	2 (4.2)	0 (0.0)
PR n (%)	16 (15.0)	8 (16.7)	8 (13.6)
SD* n (%)	74 (69.2)	30 (62.5)	44 (74.6)
PD n (%)	13 (12.1)	6 (12.5)	7 (11.9)
NE n (%)	2 (1.9)	2 (4.2)	0 (0.0)
Time to global response (mo) median (range)	1.0 (1-5)	1.0 (1-5)	1.9 (1-4)
Skin response (n=107) % (95%CI)	29.0% (21.2, 38.2)	33.3% (21.7, 47.5)	25.4% (16.1, 37.8)
Olsen 2022 Global ORR % (95%CI)	**22.4% (15.6, 31.2)**	**29.2% (18.2, 43.2)**	**16.9% (9.5, 28.5)**



Early and deep responses observed in MF patients regardless of KIR3DL2 expression level

Bagot et al : Lancet 2019. Porcu et al EHA2025

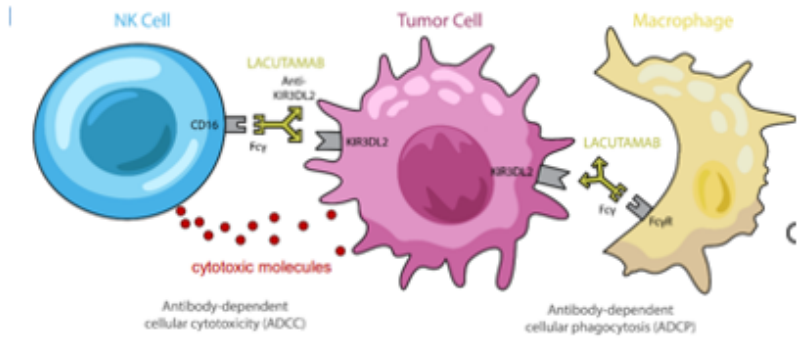


Figure 1: Lacutamab Mechanism of Action

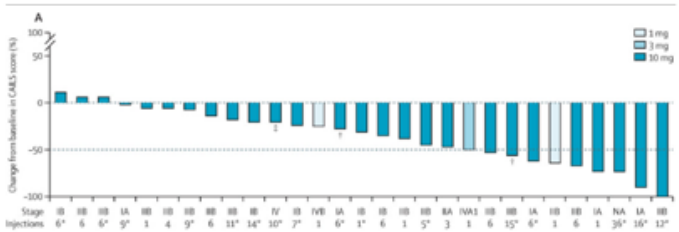
- **TELLOMAK 3** trial (randomizing patients against Mogamulizumab or Romidepsin) is actively enrolling as of early 2026.
- **Efficacy:** Phase 2 data showed an Overall Response Rate (ORR) of roughly **43%** in heavily pre-treated SS patients.

- Orphan drug designation for the treatment of CTCL (EMA and FDA)
- PRIME (EMA) and Fast Track (FDA) designation for SS patients who have received at least 2 prior systemic therapies

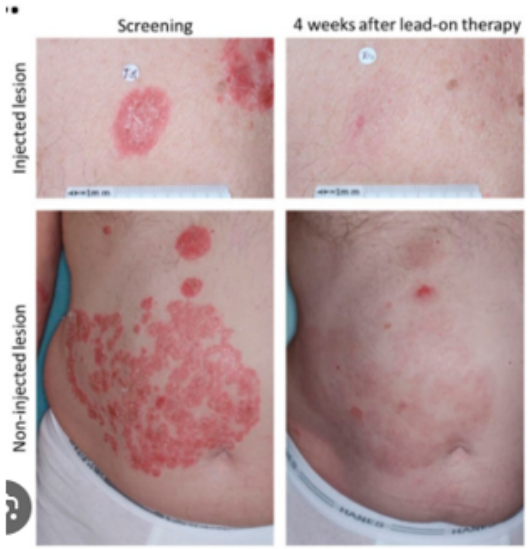
TARGETING THE SIRP-α–CD47 AXIS

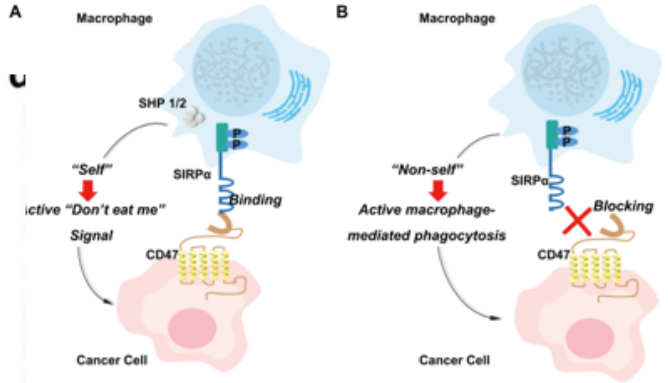
-Sezary syndrome cells express higher levels of CD47 than normal T cells
CD47 blockade increases macrophage mediated killing of CTCL cells in vitro

- Intralesional TTI-621- ORR 40-60% with durable responses , abscopal responses in non- injected lesions



Querfeld et al Lancet Hematology 2021, Wong et al J Invest Ferm 2013





- 67 patents (as of 2023)
- CD47 monoclonal antibodies
- CD47 directed bispecific
- SIRP alpha/Fc fusion protein antibody
- CD47 small molecule inhibitor
- CD47- ADC
- Combination trials
  - CD-47 blocker plus PD1 inhibitor
  - D-47 blocker plus KIR 3DL2 targeted therapy
  - CD47 blocker plus ADC

TARGETING THE JAK/STAT PATHWAY

JAK/STAT pathway is constitutively activated in CTCL

Dysregulated JAKs (especially JAK1/3) phosphorylate STAT proteins (notably STAT3/5), which translocate to the nucleus, driving tumor growth

6 JAK inhibitors have been evaluated in CTCL (Ruxolitinb, Cerdulatinib, Tofacitnib, Upadacitinb and Abrocacitinib)- responses not very high in CTCL (trials were not focused on CTCL)

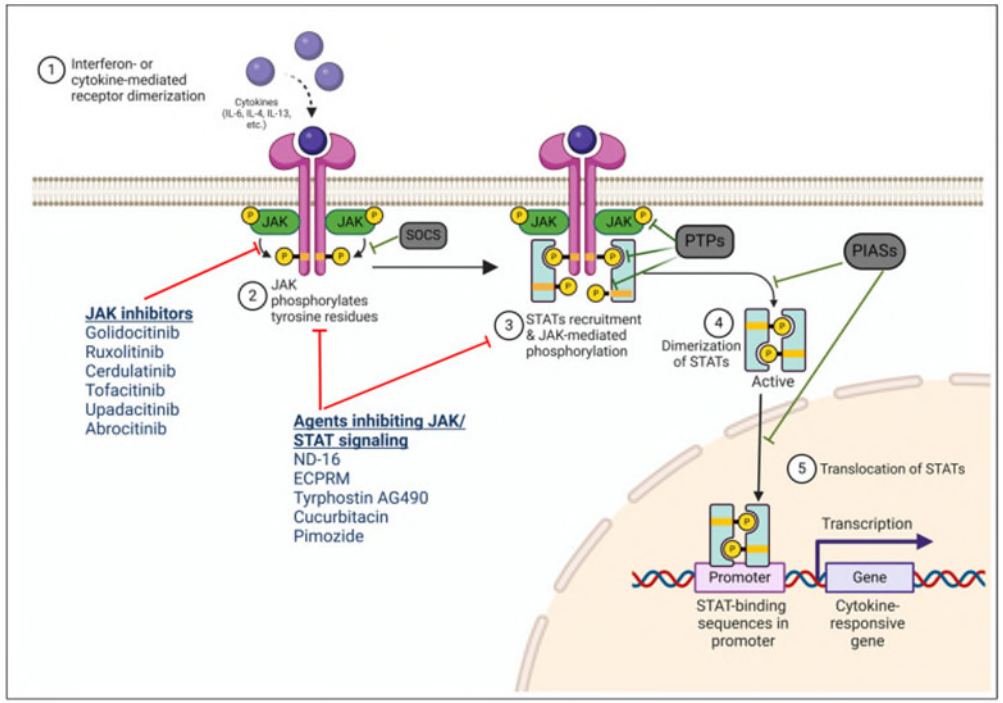
Combination with epigenetic agents – Ruxolitinib plus Resiminostat – synergistic in cell lines , Tofacitinib plus Chidamide is an ongoing study

Combination with modulators of apoptosis- Ruxolitnib plus Navitoclax (in vitro synergy in ATLL)

Concern about potential worsening of CTCL after JAK inhibitor therapy (case reports) - TBD
Potential concern for bioavailability in skin tissue

STAT3 inhibitors- TTI-101 (C188-9)- direct STAT3 inhibitor- preclinical data shows apoptosis in CTCL lines

- STAT3 degrader(PROTACS) under development



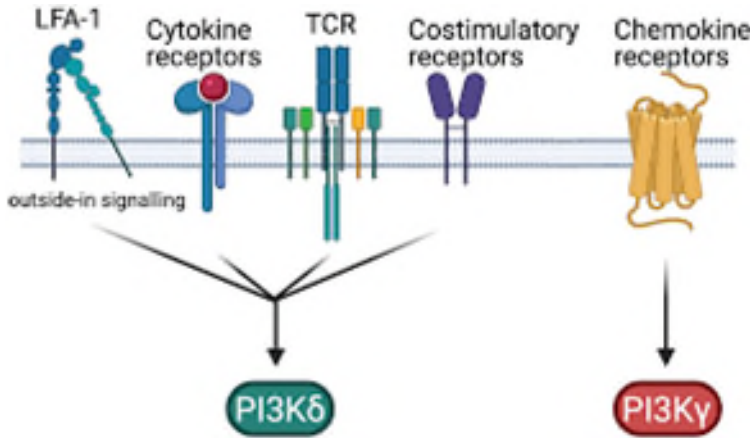
Kashyap et al: Cancers 2025

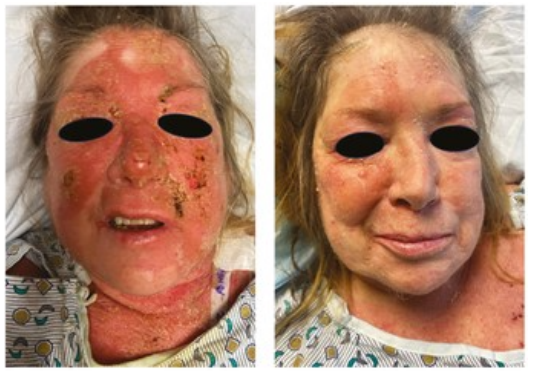
PI3K ISOFORM – SELECTIVE INHIBITORS

- Duvelisib – ORR of 31,6% in CTCL, 48% in PTCL- now a category 2A in the NCCN guidelines
-
- Linperlisib – ORR 48% in PTCL

- Tenalisib- ORR 45% , 53% when combined with Romidepsin, granted orphan drug designation for CTCL in 2018

- Notable combinations
  - HDAC inhibitors
  - JAK inhibitors
  - CPI





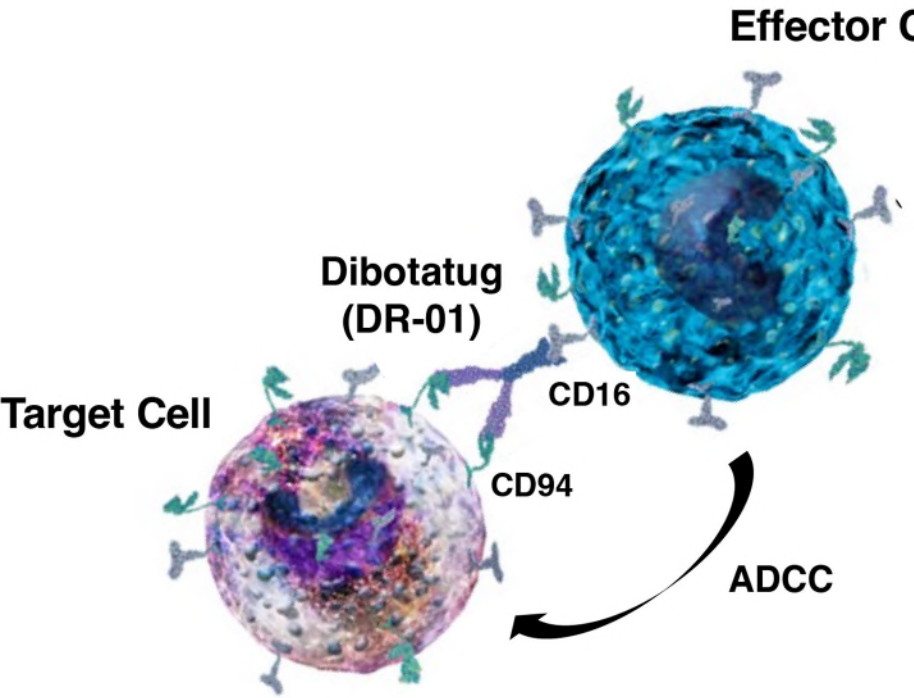
Before duvelisib 2 months after duvelisib

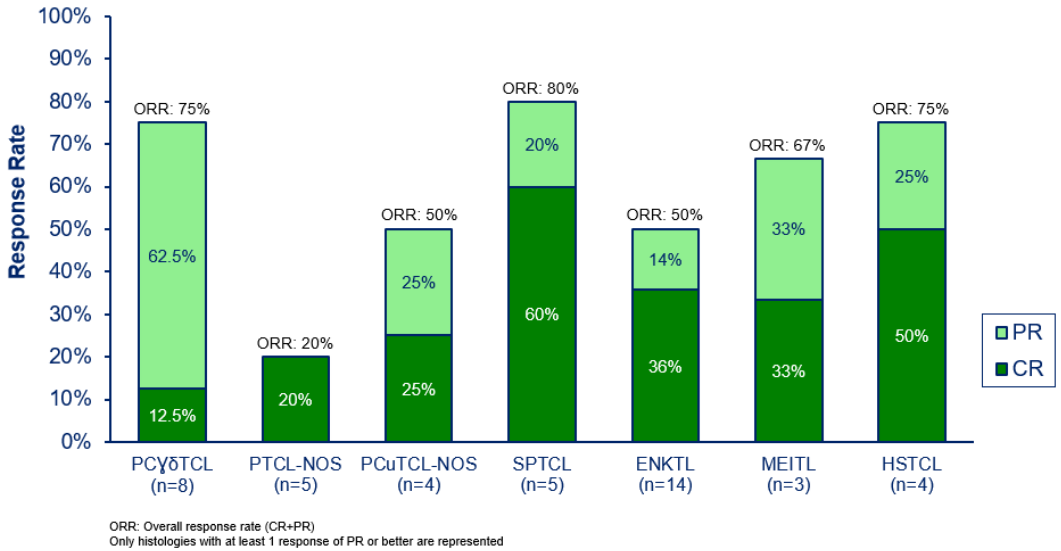
Shah et al; ASH2025 Bazewicz et al: The oncologist 2024, Iyer el al Cancers 2020

DIBOTATAUG- DR-01

- Non-fucosylated IgG antibody targeting CD94 expressed on terminal effector $CD8^+$ T subsets, and NK cells
- Dibotatug engages Fc-gamma receptors, such as CD16a and triggers antibody-dependent cellular cytotoxicity (ADCC) by effector cells, resulting in rapid target cell depletion

CD94 expression on CD8 T cell subsets and NK cells in healthy donor PBMCs





Across all CTL histologies, ORR: 53% (25 of 47)

CR: 30% (14 of 47)

Poh et al: TCLF 2026

COMBINATION THERAPIES IN CTCL

Regimen	Population	ORR	CR	DOR	Median Survival (PFS/OS)
Interferon Plus retinoids (+/- ECP)	**CTCL/SS**	**39%- 60%**	**Variable**		
Romidepsin + Lenalidomide	R/R CTCL/SS	**56%**	**~22%**	NR	**PFS:** ~7.5 mo / **OS:** NR
Romidepsin + Duvelisib	R/R T-cell	**58–61%**	**34–42%**	~21 mo	**PFS:** 11 mo / **OS:** 16 mo
Romidepsin + Ruxolitinib	R/R T-cell	**~25%**	**~6%**	~7.3 mo	Data Limited
Moga + ECP	R/R MF/SS	**~72%**	Varies	~12.3 mo*	**PFS:** 9.2 mo

Strauss et al Cancer 2007, Mehta-Shah N, *Blood*, 2018 / *Blood Advances*, 2024, Horwitz S, *Blood Advances*, 2025. Moskowitz A, *Blood*, 2019. Khodadoust M, *Journal of Clinical Oncology*, 2020. Pilkington J, *Frontiers in Hematology*, 2025. Porcu P, *Journal of Clinical Oncology*, 2025.

DARVALUMAB PLUS LENALIDOMIDE

Phase 2 randomized study of combination vs Darvalumab alone

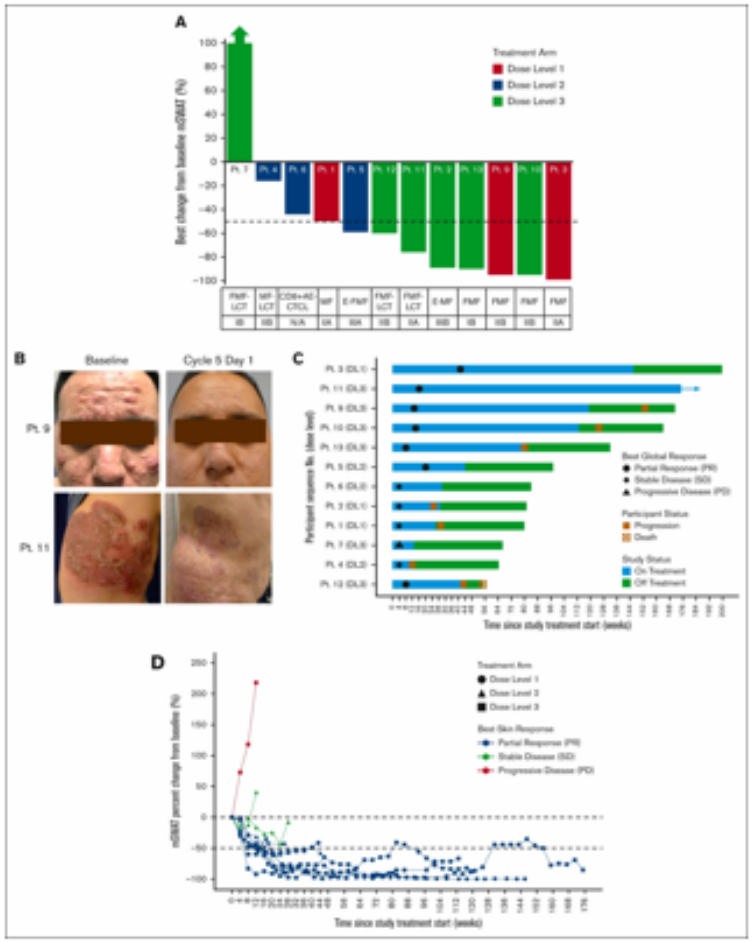
ORR of the combination arm 75% vs 42% for the single-agent arm

12-month progression-free survival rate was 73% vs 36%

The median progression-free survival was 6.2 months for durvalumab monotherapy and not reached for the combination of durvalumab plus lenalidomide.

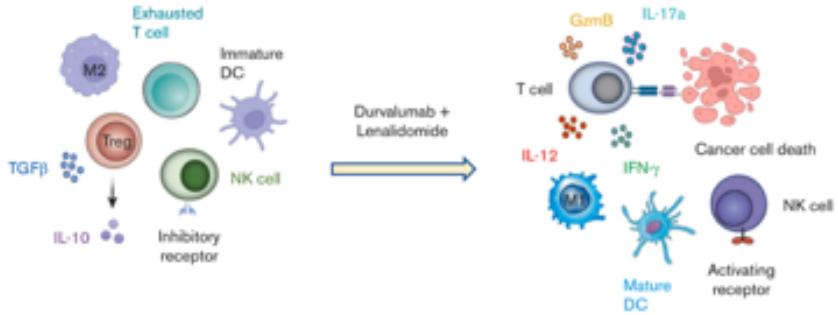
No major safety concerns

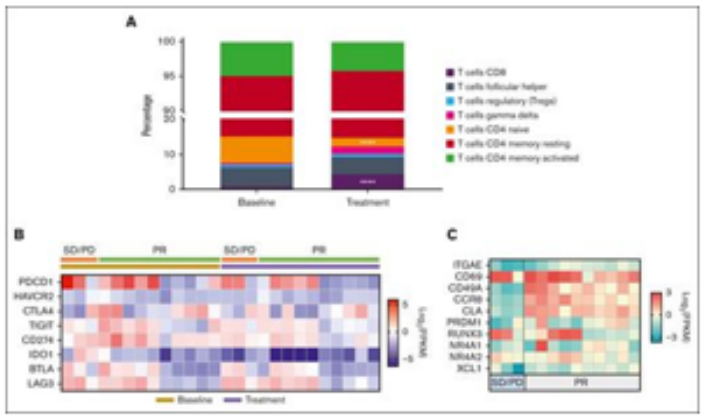
Querfeld et al: ASH 2024, SOHO 2025



Phase I data

Durvalumab (anti–PD-L1) combined with lenalidomide in relapsed/refractory cutaneous T-cell lymphoma – changes in TME

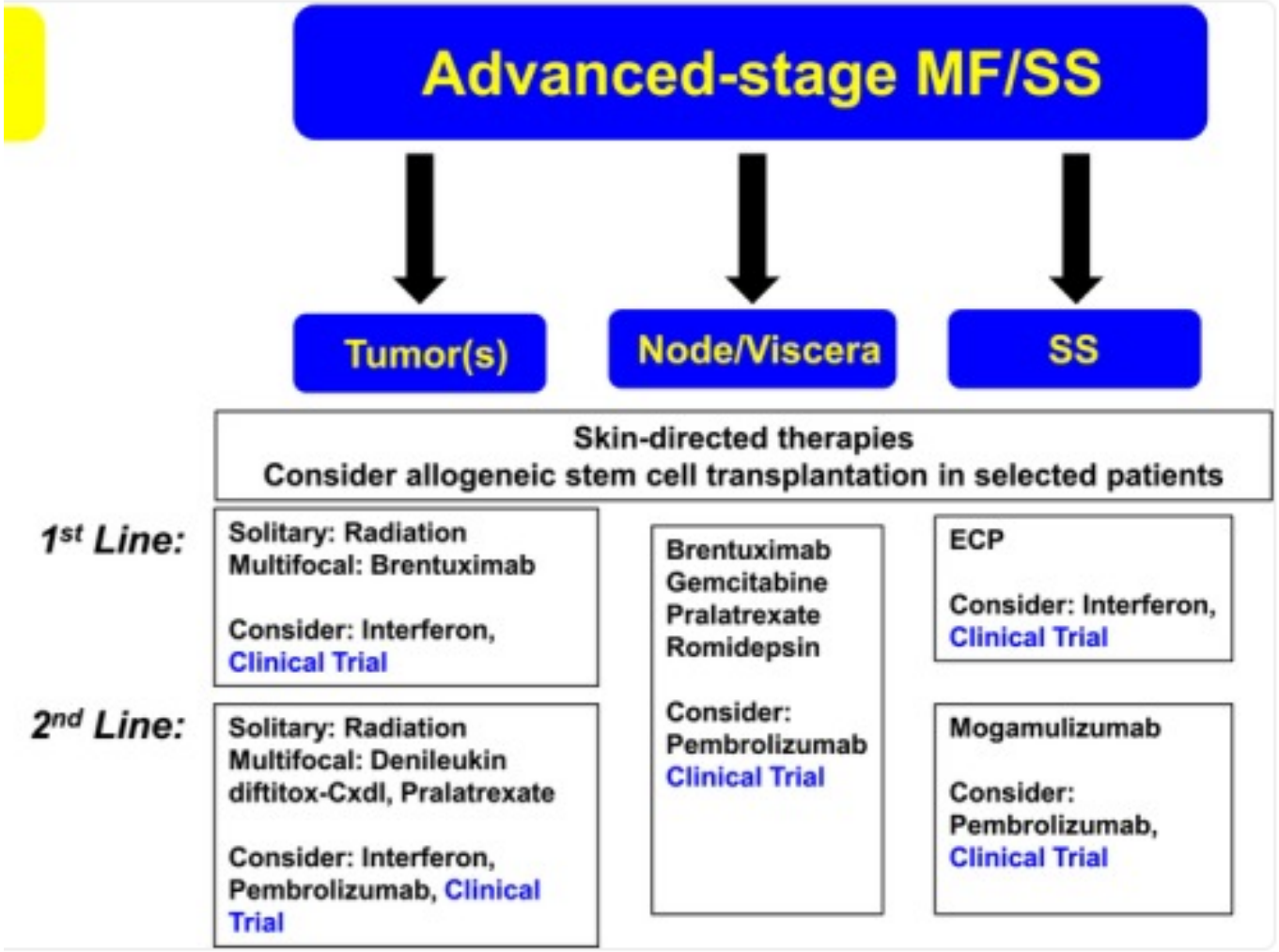




CAR T CELL THERAPY IN CTCL

CART/ TARGET	AUTO/ALLO	TRIAL	REPONSES	NEXT STEPS
CTX130/CD70	ALLO	COBALT/LYM PTCL//CTCL	51.3%	TERMINATED,AWAITING PRODUCT MODIFICATION
MB105.CD5	AUTO	PHASE 1 REPORTED	ORR 44%	PHASE 2 ONGOING
CD30	AUTO	TERMINATED BUT RESPONSES SEEN		ONGOING TRIALS WITH DIFFERENT PRODUCTS
CD30 CAR WITH CO EXPRESSION OF CCR4	AUTO	PHASE 1 COMPLETED	ORR 67% MEDIAN PFS 6.4 MONTHS	PHASE 2 IS ONGOING-PCALCL
AUTO4/TRBC1	AUTO	PHASE 1 COMPLETED	ORR 66.6%, DURABLE RESPONSES	
KIR13DL2 CAR-T	AUTO	XENOGRAFT DATA IS ENCOURAGING		
CD94	AUTO	PHASE 1 STARTED FOR CYTOTOXIC T CELL LYMPHOMAS		

TREATMENT ALGORITHIM FOR ADVANCES STAGE MF



Transformed disease – best approaches- skin vs LN, single site vs systemic

When to refer for AND perform allogeneic transplant

High risk features – CLIPI, genetic features (Tp53, 7q gain, CDKN2A/B)- how should the treatment paradigm be modified

Pruritis

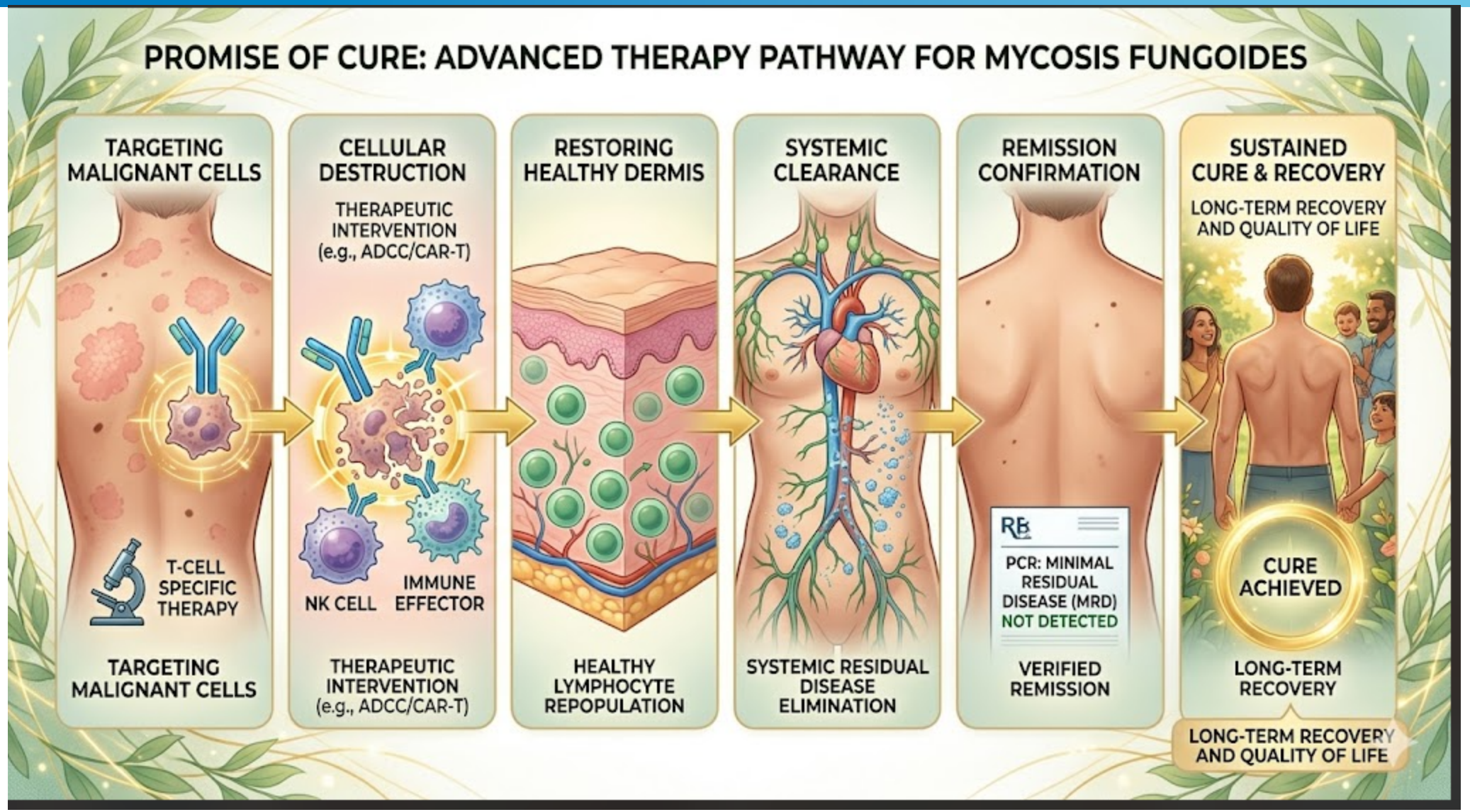
Quality of life

Wilcox et al
Am J of Hemtology 2025

CONCLUSION

- CTCL is a heterogenous groups of diseases
- MF progression correlates with mutational burden and increasing immunosuppressive state
- Treatment should be based on compartmental approach with current therapies
- Targeted therapies are more effective
- Combination treatments are increasing RR and longer DOR
- Need to build on these principles to define optimal treatments for patients

THANK YOU VERY MUCH



PROCLIPI- propsoective Cutaneous Lymphoma International Prognostic index

Launchd in 2015

PROCLIPI prospectively collects predefined datasets including clinical, hematological, pathological, imaging, treatment/response, quality of life, and survival data from patients with newly diagnosed MF/SS. All patients undergo central clinicopathological review to confirm diagnosis. As of the most recent reports, **1,916 patients have been recruited from 52 centers across 19 countries on 6 continents**. [2]

Key Findings

CLIPI (Cutaneous Lymphoma International Prognostic Index) for advanced-stage disease: Among 552 patients with advanced-stage MF/SS (stages IIB–IVB), the 5-year overall survival (OS) was notably poor and varied by stage (e.g., 50.0% for stage IIB, 25.9% for stage IVA2). Importantly, increasing stage was not consistently associated with worsening survival. Four independent risk factors were identified: **N3 nodal status, age >60 years, elevated serum LDH, and large-cell transformation in skin**. These were modeled into the CLIPI, which stratifies patients into low-, intermediate-, and high-risk groups with 5-year OS of **63.3%, 44.7%, and 18.3%**, respectively. [1]

PRINCIPLES OF TREATING MYCOSIS FUNGOIDES

Early-Stage Primary Management

Skin-Directed Therapies (SDT) remain the absolute cornerstone of Stage IA–IIA Cutaneous Lymphomas, aimed at optimizing quality of life while minimizing systemic toxicity.
NCCN preferred options include highly active topical corticosteroids (clobetasol), topical mechlorethamine gel (0.02%), topical retinoids, and targeted phototherapy (narrowband UVB or oral PUVA).

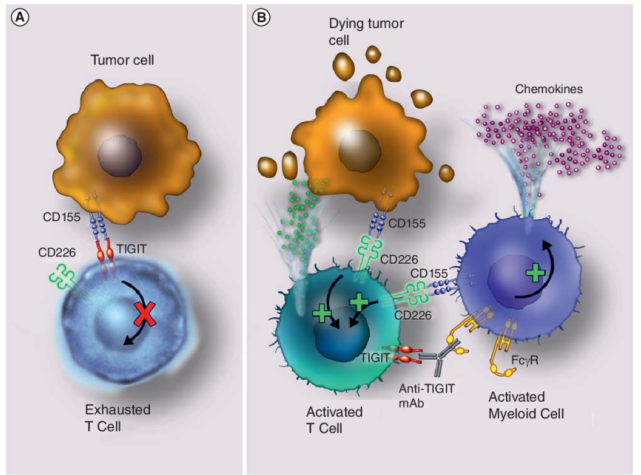
NEXT GENERATION IMMUNE CHECK POINT INHIBITORS

PD-1 inhibitors have shown limited success in CTCL

PD-L1 inhibitor in combination with Lenalidomide showed promising outcomes in RR CTCL- ORR 71% vs 42% for single agent Darvalumab- Median DOR not reached

TIGIT,LAG3, TIM-3 are overexpressed in CTCL

Combinatorial blockade (anti- TIGIT + anti KIR3DL2)



Beygi et al Blood advances 2021, Querfeld et al; Clin Lymphoma, Myeloma and leukemia 2025, Anzengruberet al: EJC 2018