10th POSTGRADUATE

# Lymphoma Conference

## WILL WE HAVE THE OPPORTUNITY TO RAPIDLY DEVELOP THERAPEUTIC MODALITIES (SEQUENTIAL/COMBINED) THAT COULD RAISE THE BAR IN TERMS OF OS, PFS AND POTENTIAL CURE IN CTCL?”

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Memorial Sloan Kettering Cancer Center

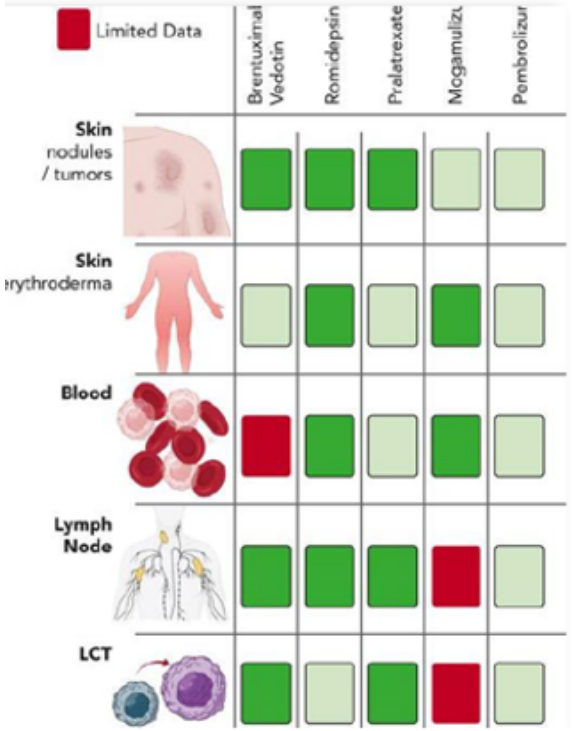
Venice,
March 12-13, 2026

Hotel Monaco & Grand Canal

President:
P.L. Zinzani

# Disclosures

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board |
|---|---|---|---|---|---|---|
| Dren Bio | No | No | Yes | No | No | Yes |
| Kiowa Kirin | Yes | No | Yes | No | Yes | Yes |
| Bioinvent | Yes | No | No | No | No | No |
| Secura Bio | No | No | Yes | No | No | No |
| Corvus | Yes | No | No | No | No | No |

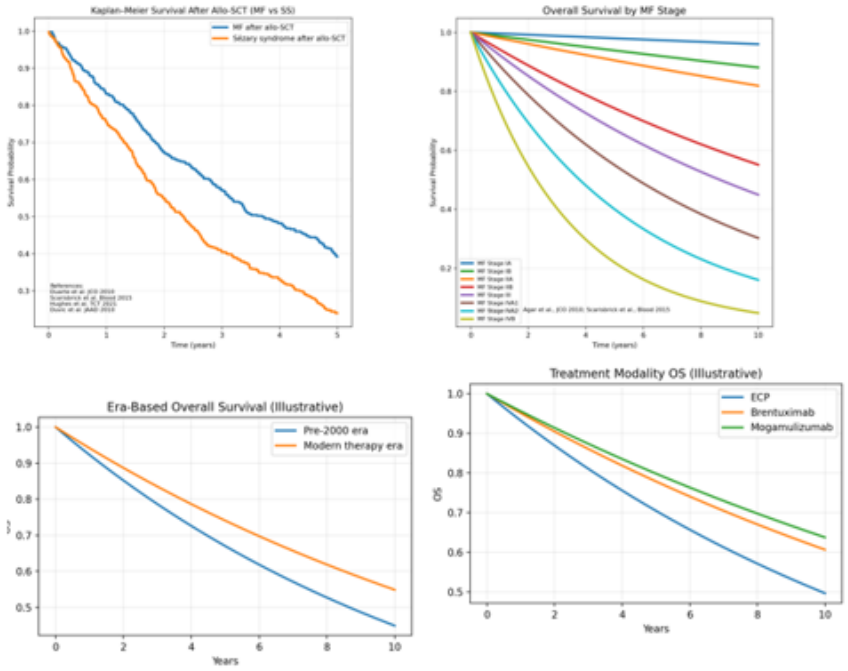



Inherent challenges in treating and evaluating MF/SS

Treatment is stage based – also consider compartmental burden of disease

Agents have differing effects in different compartments

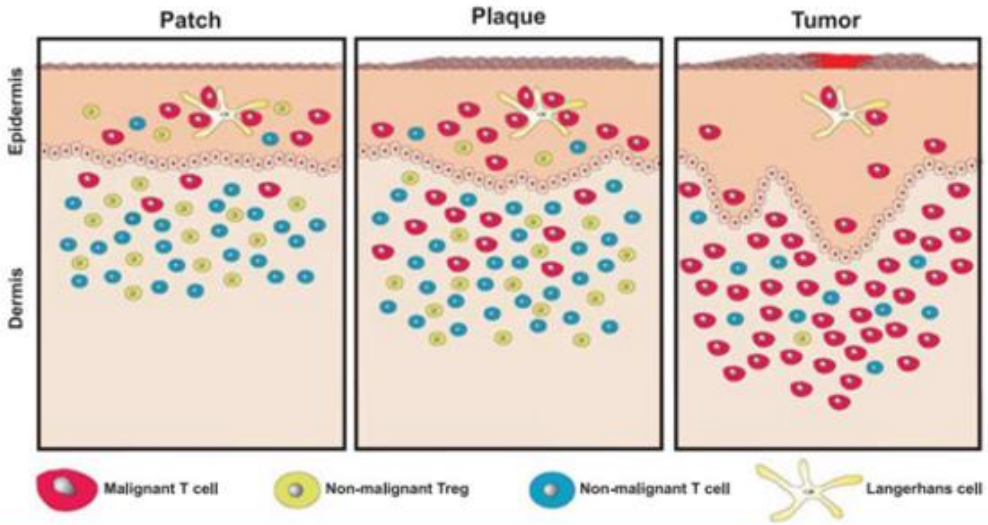
Disease can wax and wane/ cutaneous drug reactions

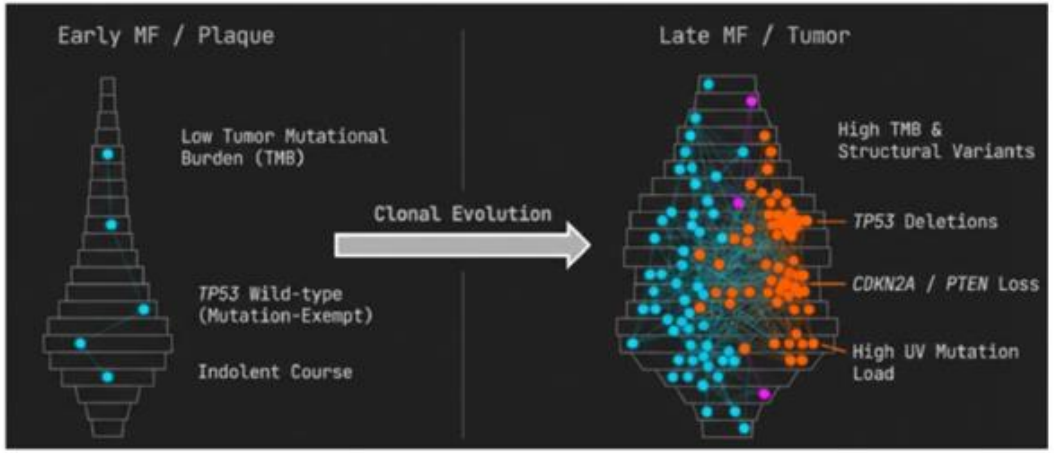



Outcomes of MF and Sezary syndrome

# EARLY VS LATE MF





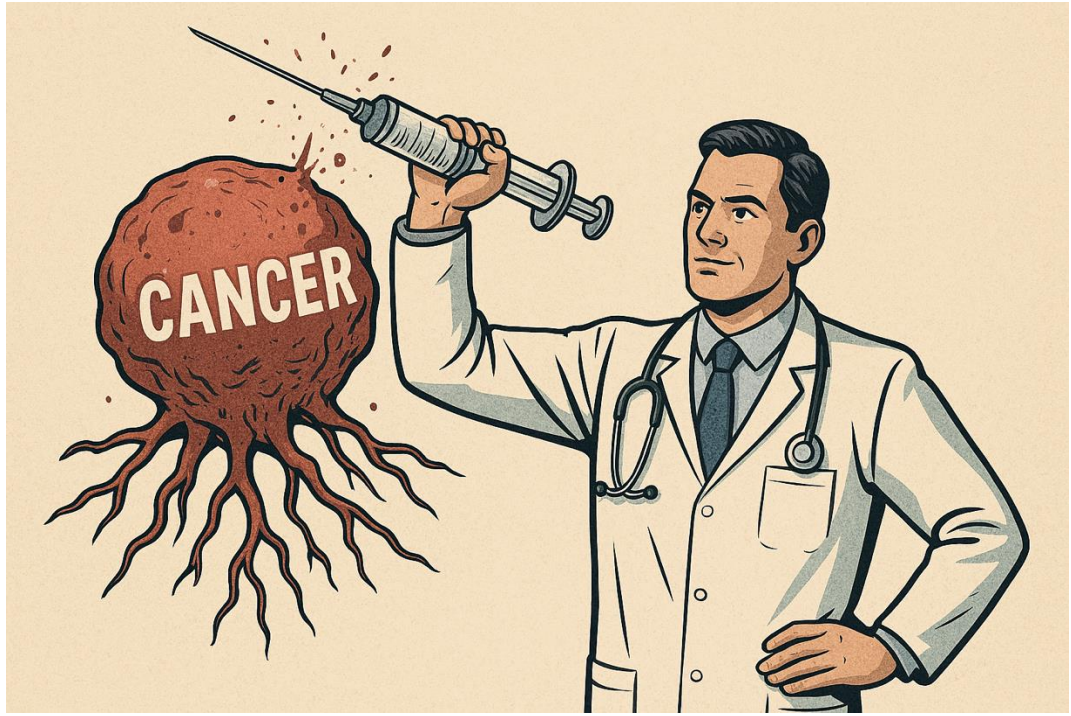

Mycosis Fungoides is the most common type of CTCL
Slow progression from Patch → Plaque → Tumor
Malignant clonal expansion of CD4+ T cells

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

# WHAT IT TAKES TO CURE CANCER

- Complete eradication of cancer (CR, pCR, MRD-negative)
- Higher intensity accepted for cure: definitive-dose surgery, chemo, radiation
- Time-limited, structured therapy with clear endpoints
- Recurrence prevention via adjuvant/consolidation/maintenance therapy
- Long-term surveillance for recurrence and late toxicities




Picture is AI generated

# CTCL KEY CLINICAL TRIALS SUMMARY



| 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.

# COMPARTMENTAL RESPONSE COMPARISON

| AGENT | GLOBAL ORR | SKIN ORR | BLOOD ORR | PRIMARY CLINIAL ROLE |
|---|---|---|---|---|
| Lacutamab | 42.95 | 33% | 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

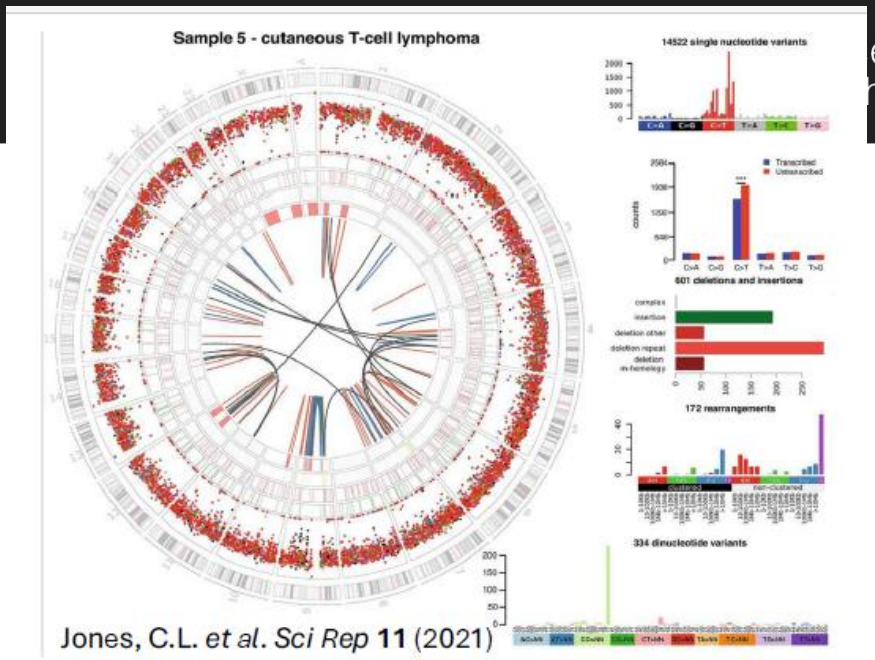
Non-synonymous variants (SNVs)

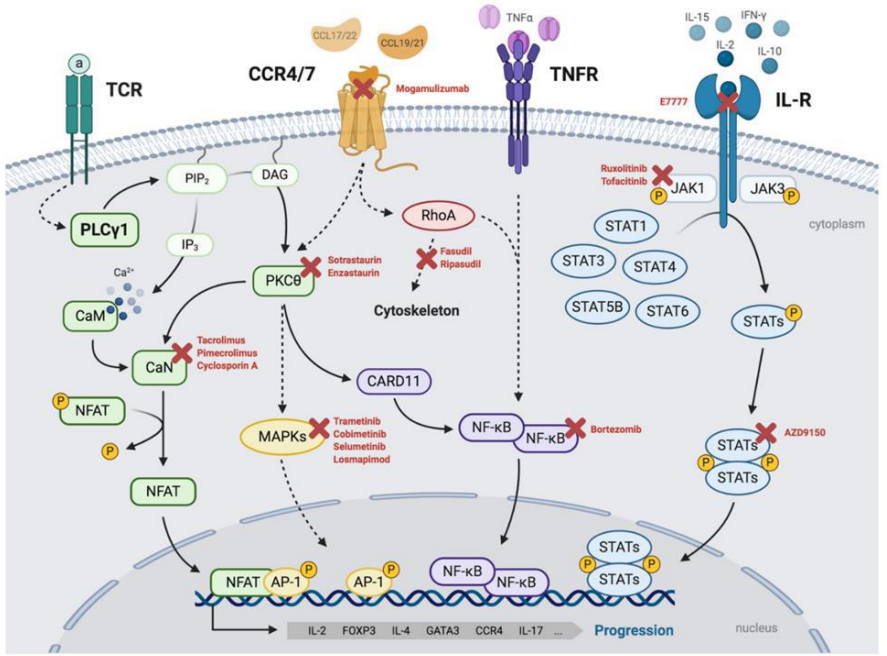
**Defined by pathway clustering rather than a single driver**

**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**




Garcia Diaz et al cancers 2021

# EMERGING THERAPEUTIC TARGETS IN CTCL

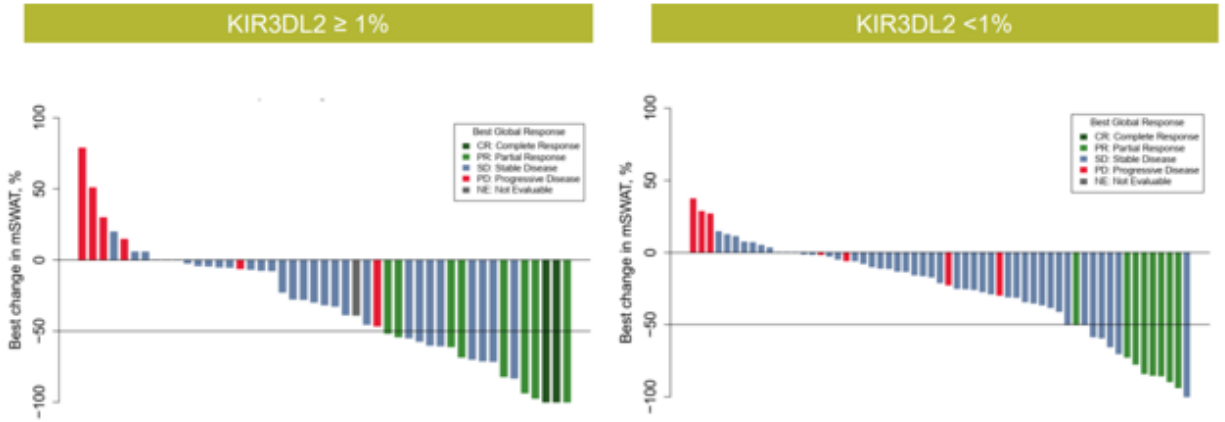


| TARGET / PATHWAY | RATIONALE | REPRESENTATIVE AGENTS | DEVELOPMENT STAGE |
|---|---|---|---|
| **STAT3 / STAT5** | Constitutive activation | JAK Inhibitors, TTI-101, STAT3 PROTACs | Preclinical/Early |
| **PI3K-δ/γ** | Survival signaling | Duvelisib, Tenalisib | Phase I–II |
| **KIR3DL2** | Sézary-specific expression | Lacutamab | Phase III |
| **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 -KIR3DL2 TARGETED TREATMENT IN T-CELL LYMPHOMA



| 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

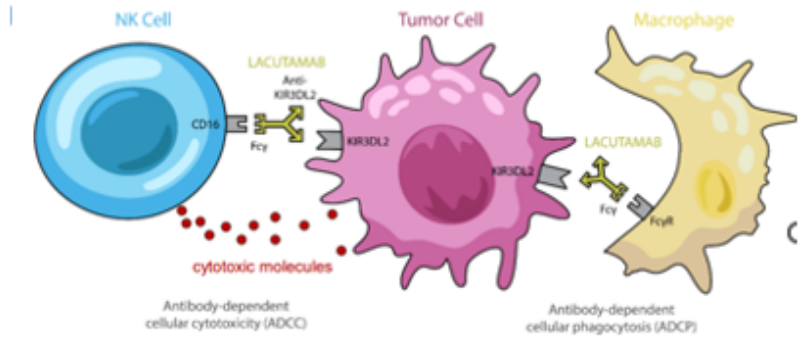


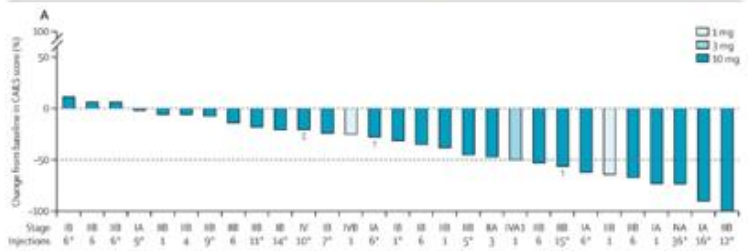

*Figure 1: Lacutamab Mechanism of Action*

- **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.

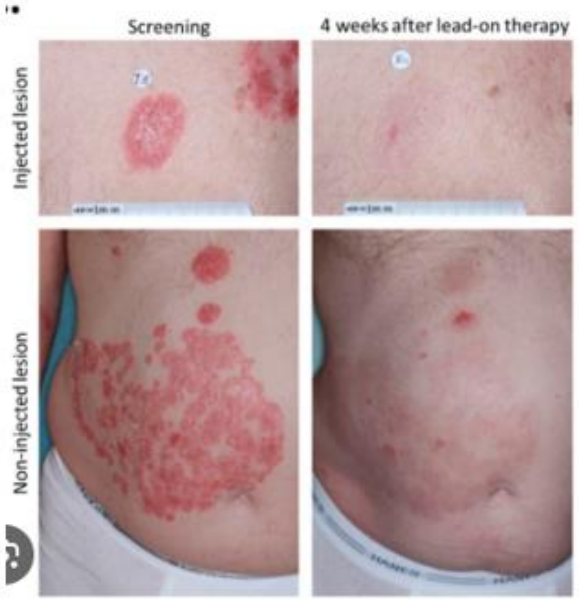
- Orphan drug designation for the treatment of CTCL (EMA and FDA)
- PRIME (EMA) and Fast Track (FDA) designation for SS patients who have received at least 2 prior systemic therapies

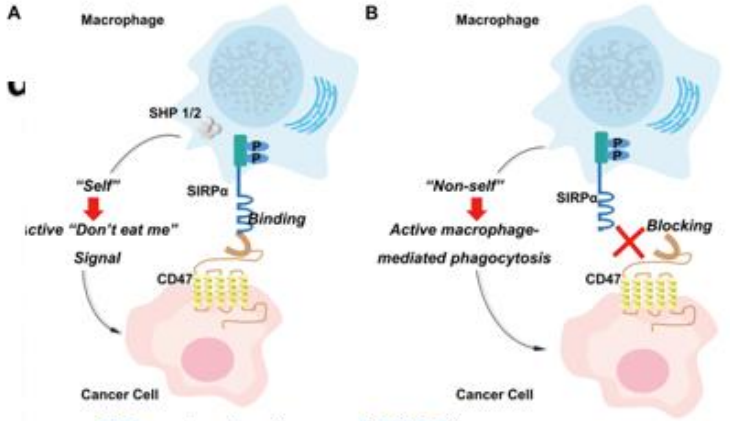
-Sezary syndrome cells express higher levels of CD47 than normal T cells CD47 blockade increases macrophage mediated killing of CTCL cells in vitro

- 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

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)

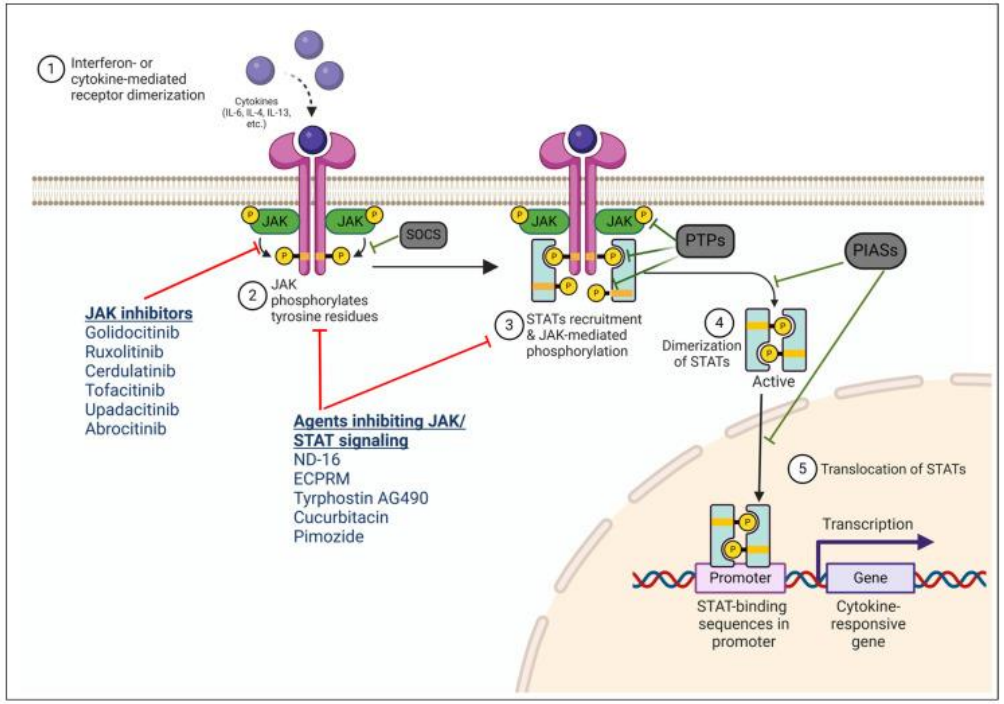
Combination with epigenetic agents – Ruxolitinib plus Resiminostat – synergistic in cell lines , Tofacitinib plus Chidamide is an ongoing study

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

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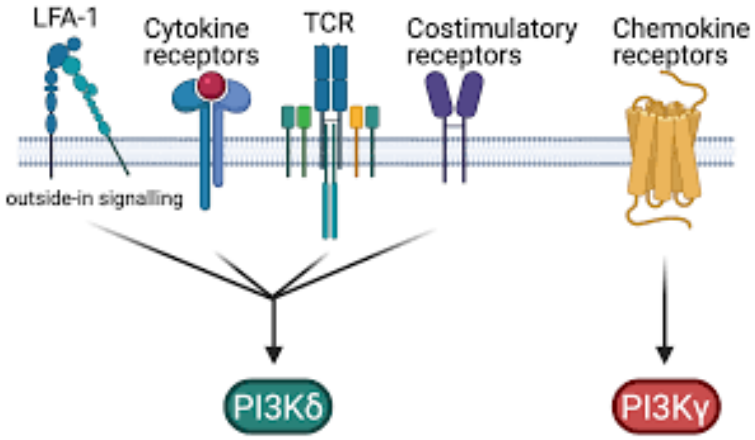
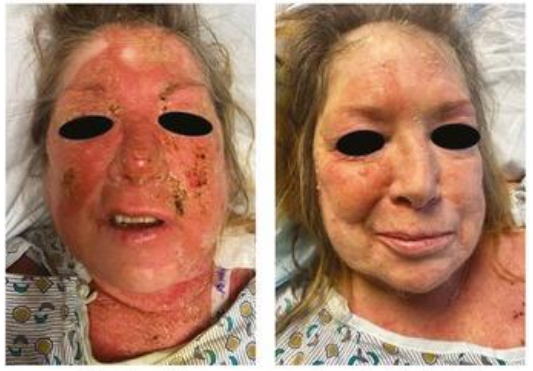


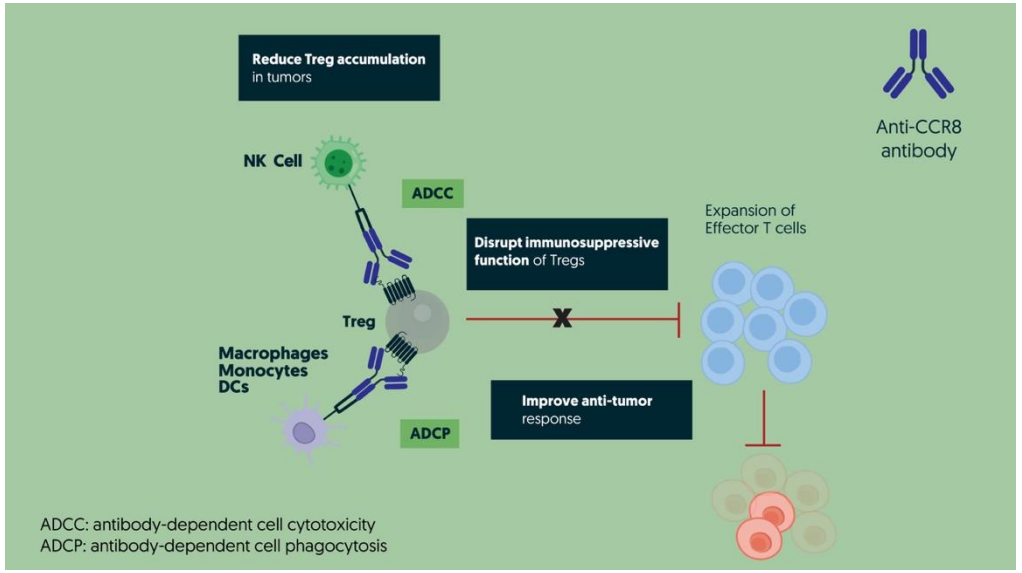



Before duvelisib | 2 months after duvelisib

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

# CCR8 – TARGET AGAINST TUMOR INFILTRATING T- REGS

- Tumor infiltrating T regs maintain a tumorigenic microenvironment
- CCR8 expressed on effector T1- Tregs with minimal expression on normal T regs-
- CCR8 is overexpressed at the cell surface of CTCL and SS
- Anti – CCR8 agents ,monoclonal antibodies (mAbs), antagonists, and bispecific antibodies, have been developed and demonstrate encouraging antitumor activity without obvious severe irAEs in preclinical models and Phase 1/2 clinical trials across various cancer types
- Phase I trials (e.g., NCT05690581) show that anti-CCR8 antibodies like ICP-B05 are safe and effective. They reduce tumor-infiltrating malignant T cells (average ~80% reduction) and Tregs (~68% reduction) in skin lesions.
- Other agents in development - DT 7012




Li et al ASCO abstract 2025

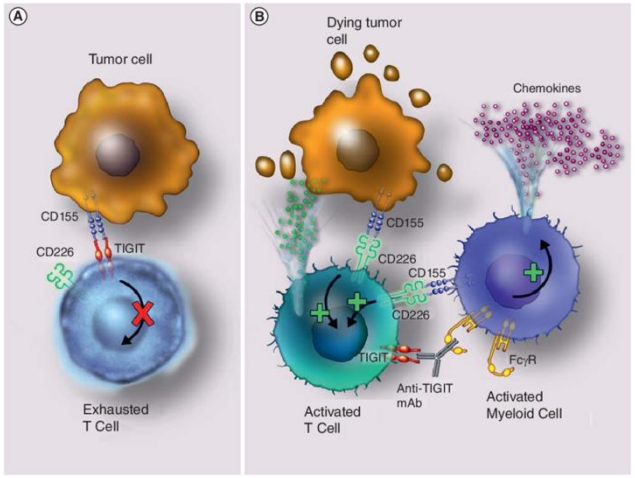
# NEXT GENERATION IMMUNE CHECK POINT INHIBITORS

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)



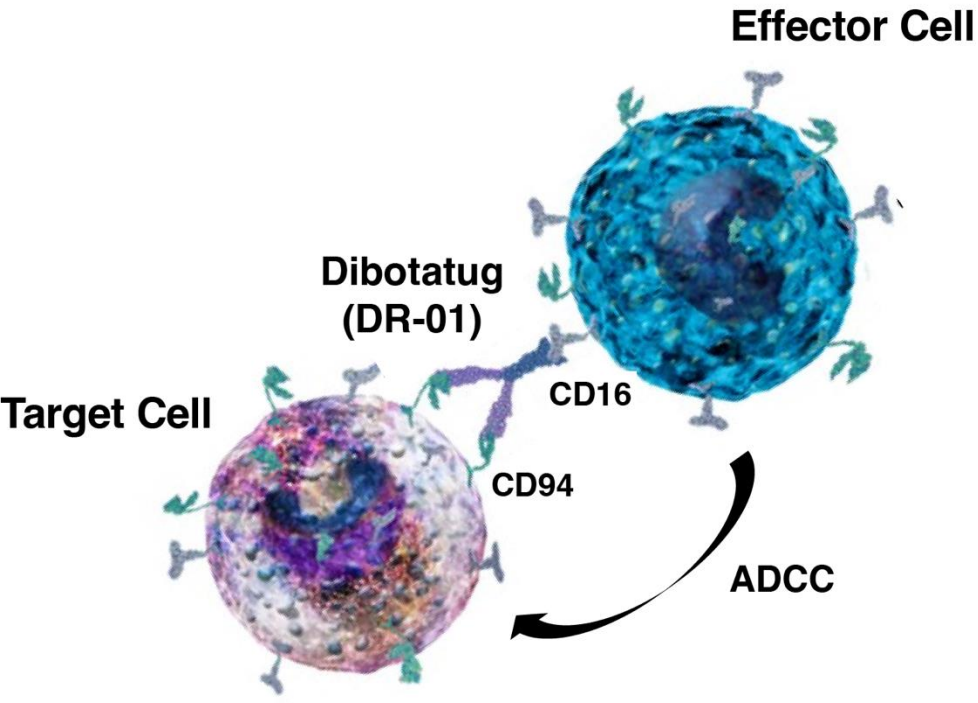

Beygi et al Blood advances 2021, Querfeld et al; Clin Lymphoma, Myeloma and leukemia 2025, Anzengruberet al: EJC 2018

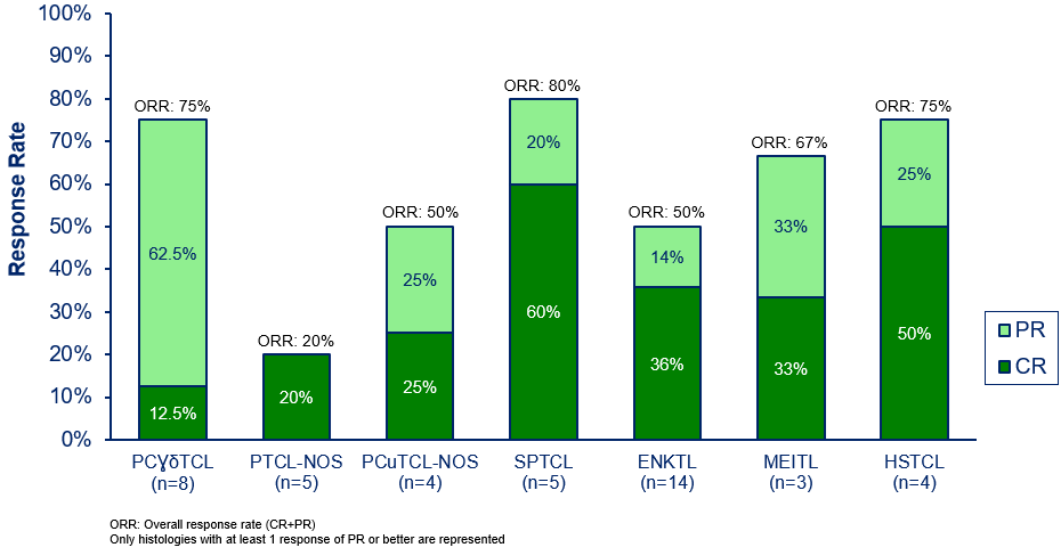
# DIBOTATUG (DR-01)



- 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.

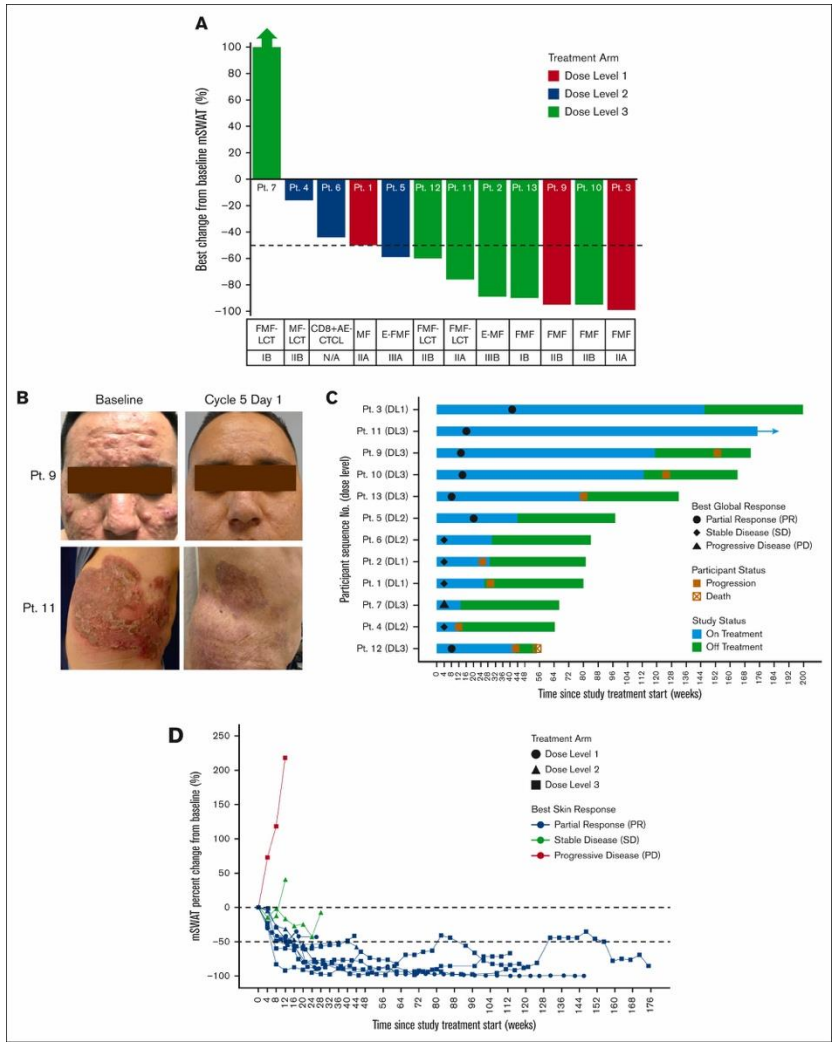
Phase 2 randomized study of combination vs Darvalumab alone

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.

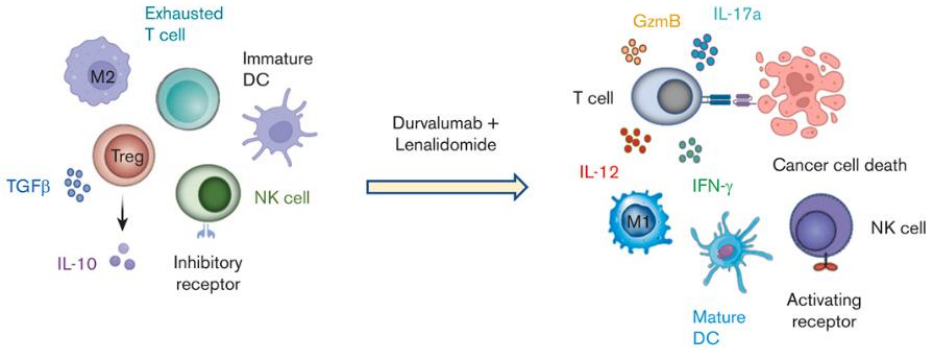
No major safety concerns

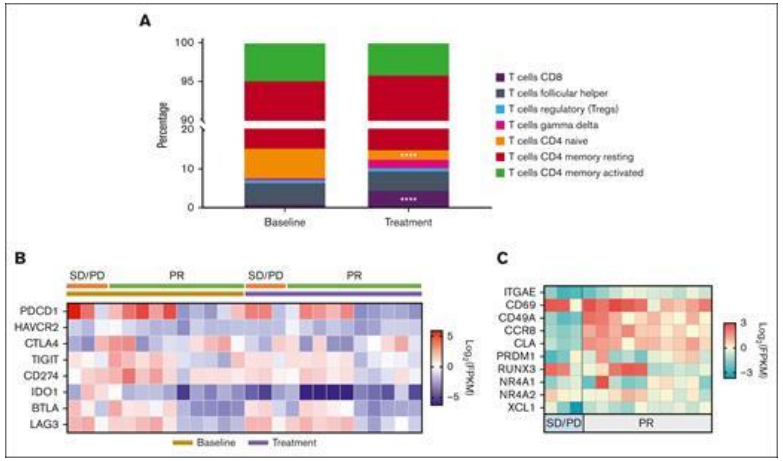



Phase I data

Querfeld et al: ASH 2024, SOHO 2025

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



# UPCOMING STUDIES IN EARLY MF



**(Synthetic Hypericin)**

Focusing on early-stage MF, this agent is a photodynamic therapy (PDT) alternative.

**Mechanism: Hypercin is a photosensitizer.**An ointment that is applied to the skin and then activated by visible light.

**Status:** The confirmatory Phase 3 **FLASH2** trial is ongoing, with top-line results expected in late 2026. Early data showed a 75% "treatment success" rate after 18 weeks of therapy.

# 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 | | |

# CONCLUSION

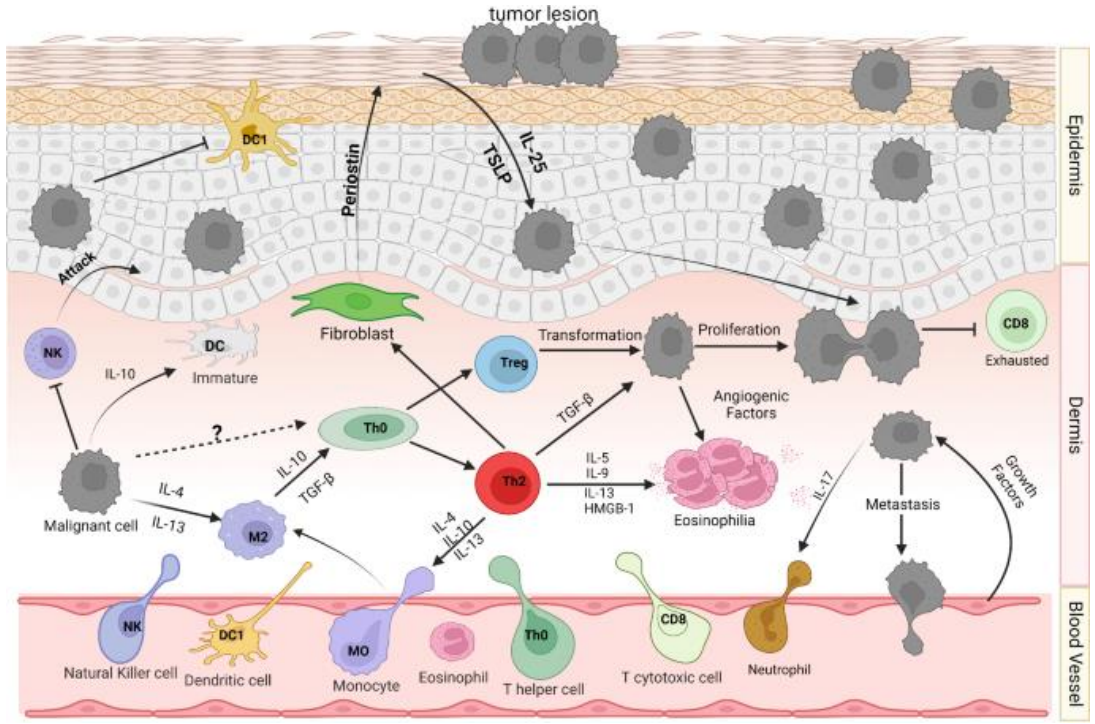


- CTCL is a heterogenous groups of diseases
- MF progression correlates with mutational burden and increasing immunosuppressive state
- Treatment should be based on compartmental approach with current therapies
- Chemo resistant
- High risk disease can be identified (Tp53, 7q gain, CDKN2A/B) – offer early aggressive approach, allogeneic transplant
- 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

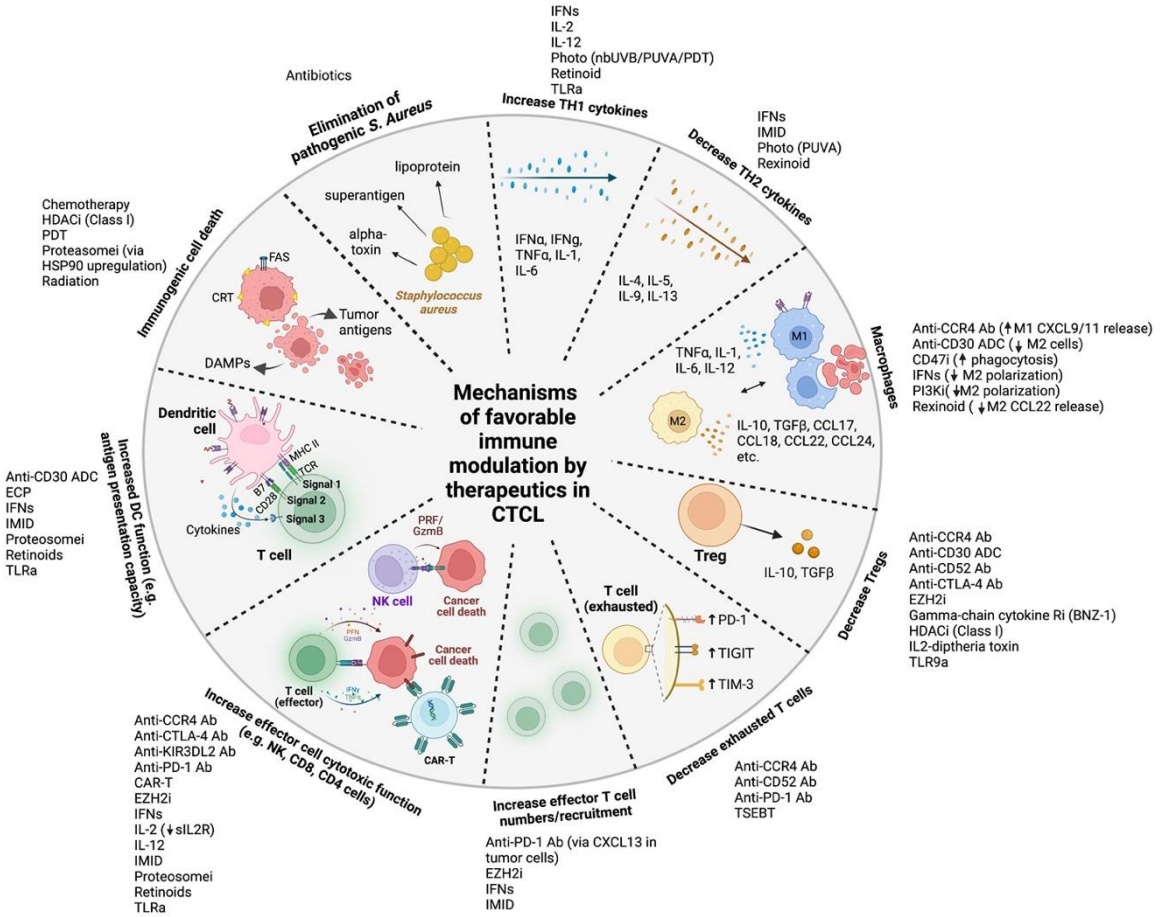
# THANKYOU



Memorial Sloan Kettering Cancer Center




Inherently chemo resistant
CTCL cells have skin homing properties
Immunosuppressive cytokines
Loss of normal effector cells
Microbiome
Genetic and epigenetic changes

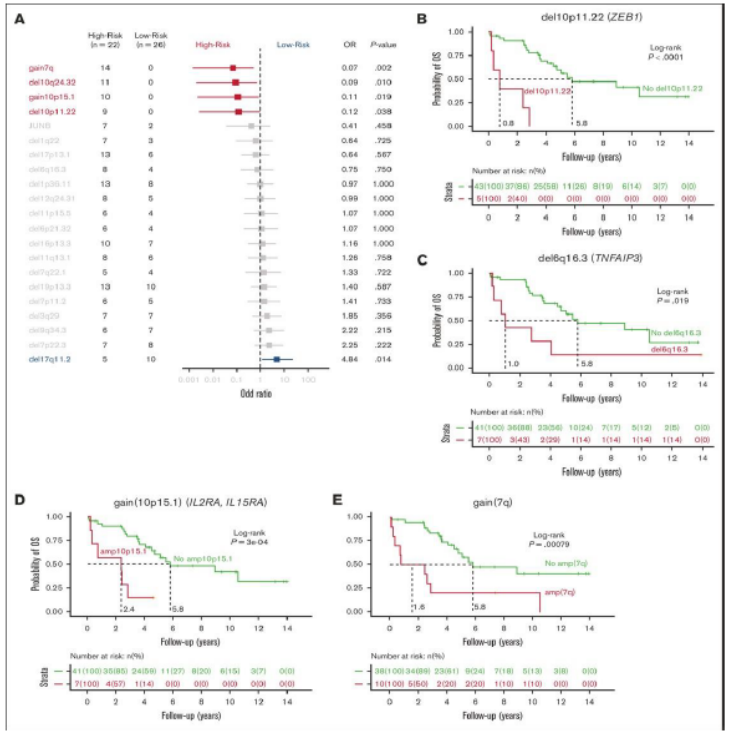



Faye et al : Front. Oncol., 11 January 2023, Chinas et al: Current oncology reports 2025

# Summary

- MF  progression correlates with mutational load
- Advanced MF is associated with a higher proportion of subclonal neoantigens (immunotherapy response remains unclear)
- CD30 status
- UV signature  is unique in primary CTCL
- Compartment approach to treatment
- High risk disease genomic profilw ( TP53, 7q gain,CDKN2A/B), treatment decision – remains to be define
- Next line of therapy ? plenty of options.. Allo-HSCT  ?

# Genomic profiling of MF identifies patients at high risk of disease progression

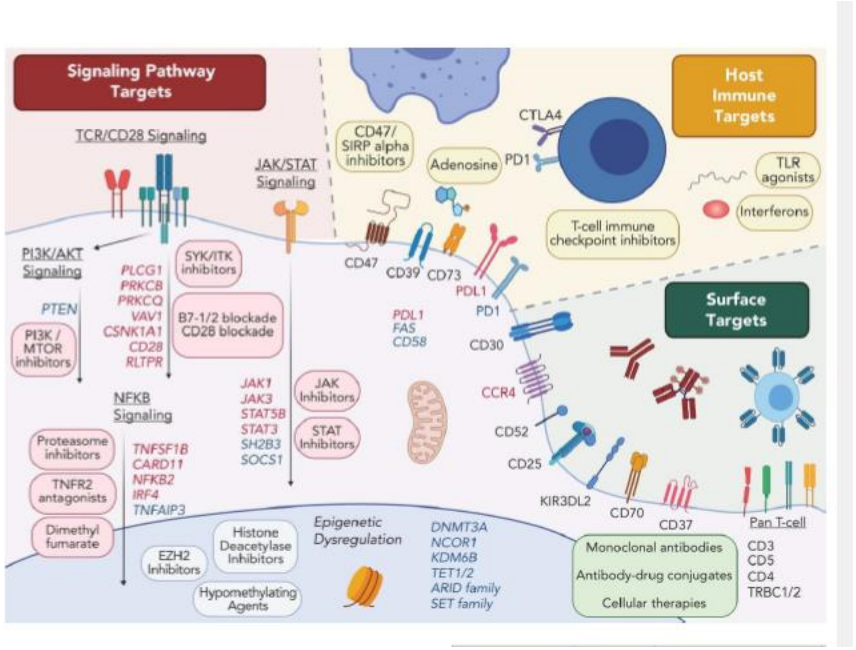



*Blood Adv* 2024; 8 (12): 3109–3119.

- Low risk vs. High risk disease :(IA–IIA) patch/plaque stages vs. high-risk (IIB–IVB) tumor or erythrodermic stages.
- WES performed on 67 skin samples from 48 patients (including sequential LR→HR samples) to define genomic drivers and clonal evolution.
- SCNAs in HR disease :
  - **7q gain ( in this case)**
  - 10p15.1 gain (IL2RA, IL15RA)
  - 10q24 deletion (NFKB2)
  - 10p11 deletion (ZEB1)
- SCNA in LR disease
  - 17q11.2 deletion (SUZ12, NF1)
- Remains significant for HR disease in MVA ( driver mutations )
- Inferior OS in all 4 SCNAs (7q gain mOS of 2.6 vs. 8.9 years, p=0.01)

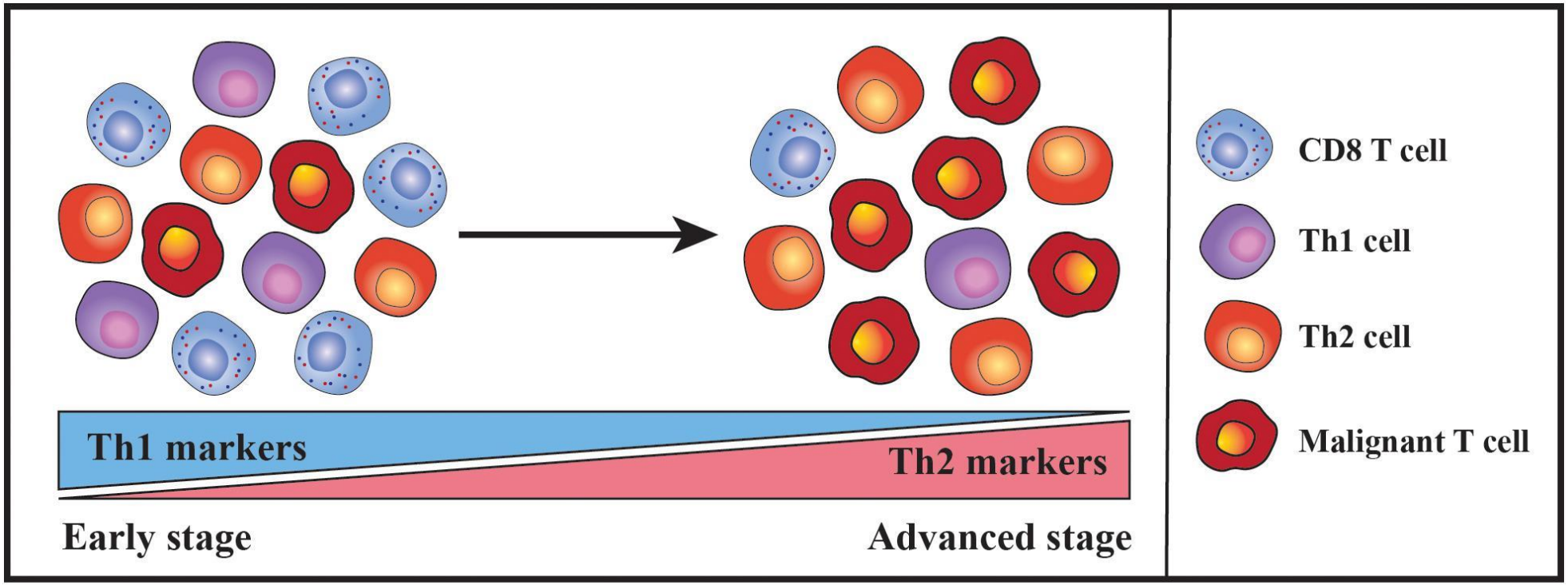
# Integrating Novel agents in advanced MF/SS based on mutational status and compartment

| Drug | Mechanism | Approval[a] | ORR[b] | Compartmental effect (ORR)[a] | Notable adverse reaction(s) |
|---|---|---|---|---|---|
| Brentuximab vedotin[7] | Anti-CD30 ADC | R/R CD30+ MF after 1 prior systemic therapy | 65.6% | ≤IIA: 53%<br>IIB: 68%<br>IIA-IIIB: 75%<br>IVA: 100% (2/2)[c]<br>IVB: 57% | Peripheral sensory and motor neuropathy |
| Mogamulizumab[8] | Anti-CCR4 Ab | R/R MF/SS after 1 prior systemic therapy | MF: 21%<br>SS: 37% | Skin: 42%<br>Node: 17%<br>Blood: 68%<br>Viscera: 0%[d] | Infusion-related reaction, rash (see text for discussion) |
| E7777[10] | Recombinant IL2-diptheria toxin protein | R/R MF/SS after 1 prior systemic therapy | 36.2% | — | Infusion-related reaction, capillary leak syndrome, visual impairment |
| Lacutamab[14-16] | Anti-KIR3DL2 Ab | No | SS: 37.5%[e] | Skin: 46.4%<br>Node: 19.6%<br>Blood: 48.2%<br>Viscera: NR | Peripheral edema |
| Pembrolizumab[17] | Anti–PD-1 therapy | No (NCCN) | 38% | IB: 0% (0/1)<br>IIB: 100% (2/2)<br>IIIA: 100% (2/2)<br>IIIB: 33% (1/3)<br>IVA: 25% (4/16) | Rash/flare, immune-related toxicity |
| Tislelizumab[41] | Anti–PD-1 therapy | No | 46% | — | Rash/flare, immune-related toxicity (observed in only 1 patient with SS in study, recovered within 4 days) |
| DR-01 (NCT05475925) | Anti-CD94 Ab targeting cytotoxic TCLs, including MF, PCAETCL, PCGDTCL | No | Ongoing study, with data to be reported | | |

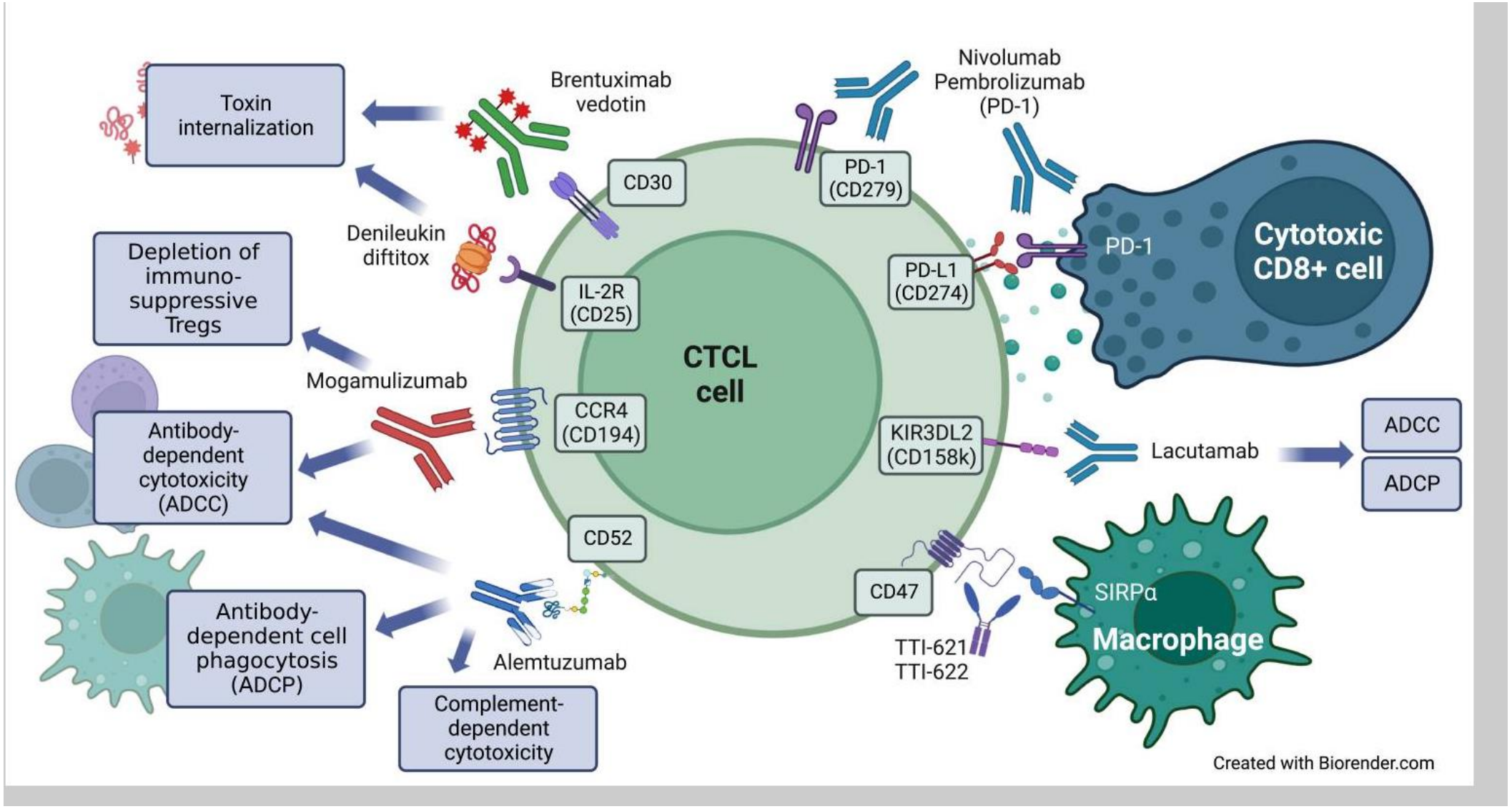



Khodadoust et al Blood 2023, Stuver et al ASH 2024

# Pathogenesis of CTCL




Stolearenco et al Cell Dev Bio 2020




Pelcovits e al : Cancer Manag Res 2023

| Class | MOA | Specific genetic vulnerability | Data in CTCL | Future direction | Ref |
|---|---|---|---|---|---|
| **EZH2 inhibitors** | Overexpressed in CTCL | PRC2 mutations | Tulmimetostat- phase -1 in CTCL<br>Valemetostat<br>Tazemetostat | Combinations – HDACI, Immunotherapies, CAR-T | Mehta Shah et al- 2025 |
| **BRD4/BET protein Inhibitors** | Inhibitors bromodomain-containing proteins (BRD2, 3, 4, and T), preventing them from reading acetylated histones and activating oncogenes like MYC | | BET inhibitors shoe repression of c-MYC and TCR singalling in CTCL lines | Combinaiotn with BCL2 inhibiton nd HDACi are promising | Kim et al Oncotarget 2018 |
| **TCR ? co stimulatory signaling targets** | CTCL cells depend on ch TCR signaling | ITK inhibitors Th1 skewing | ITK inhibitors, SYK inhibitors | Soquelitinib – phase 1 data shows a oRR of 39% and CR 25% | Reneau et al<br>2025 |
| **CD74 ADC** | Widely expressed in CTCL and SS | | ADC STRO-001 ( payload matansnoid conjugated ADC) efficiently killed CTCL-derived cell lines. | synergized with conventional chemotherapy in vitro and eradicated murine xenotransplants of CTCL cell lines in vivo | Costanza et al: B J of Dermatology 2025 |
| **Bipspecifics** | | | | | |
| **CD3 x KIR3DL2, CCR4 x CD3** | | | | | |