21ST INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM™

Management of Advanced CTCL

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THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Disclosures

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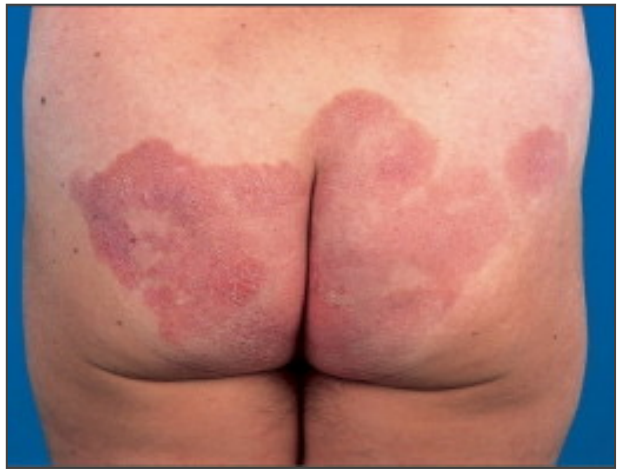
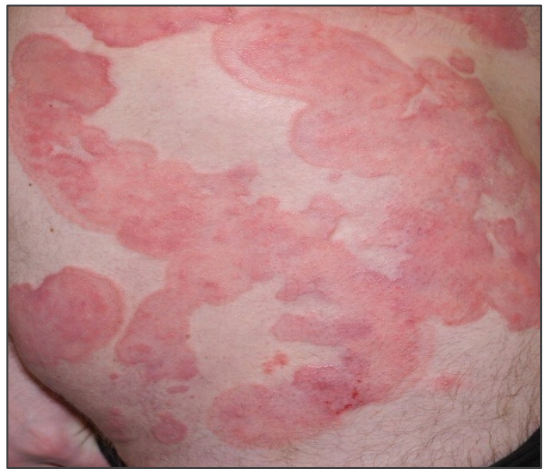
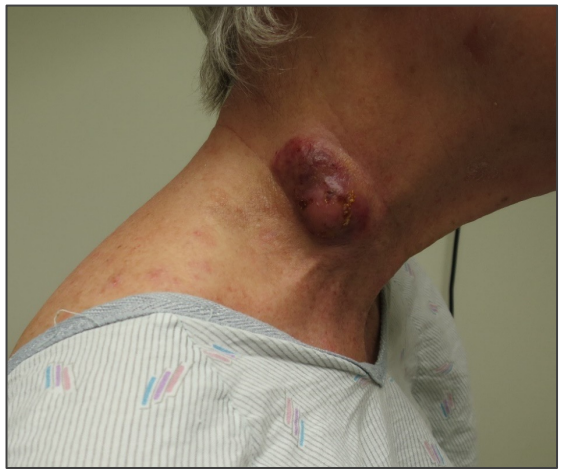
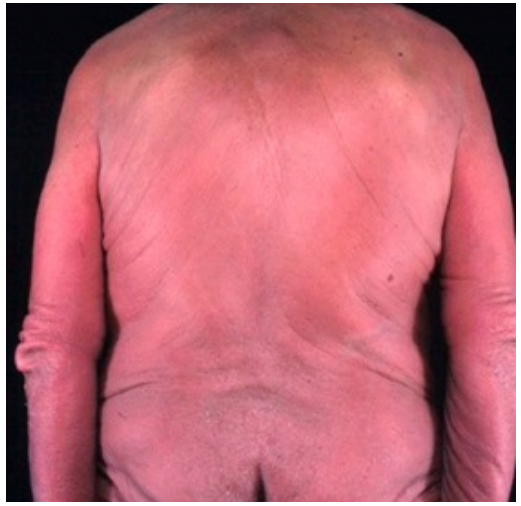
Consultancy: Kiowa Hakka Kirin, Karyopharma, Ono Pharmaceuticals, Secura Bio, Daiichi Sankyo, Genentech, Pfizer, Janssen

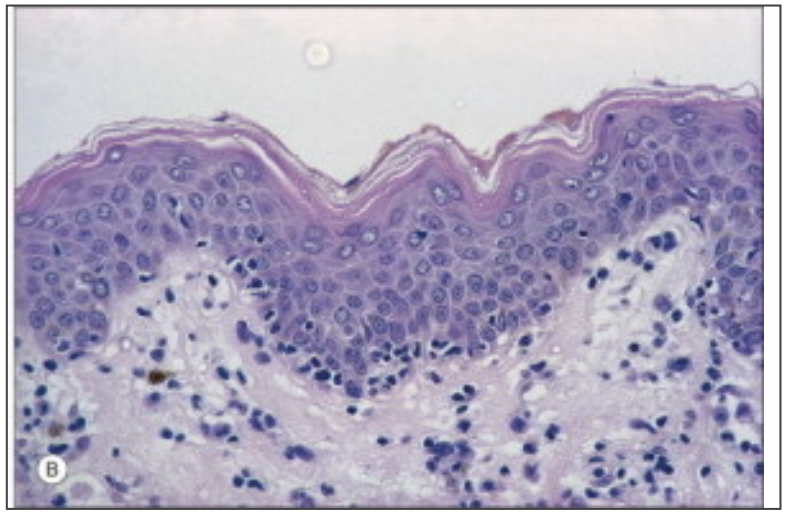
Many Forms of Mycosis Fungoides







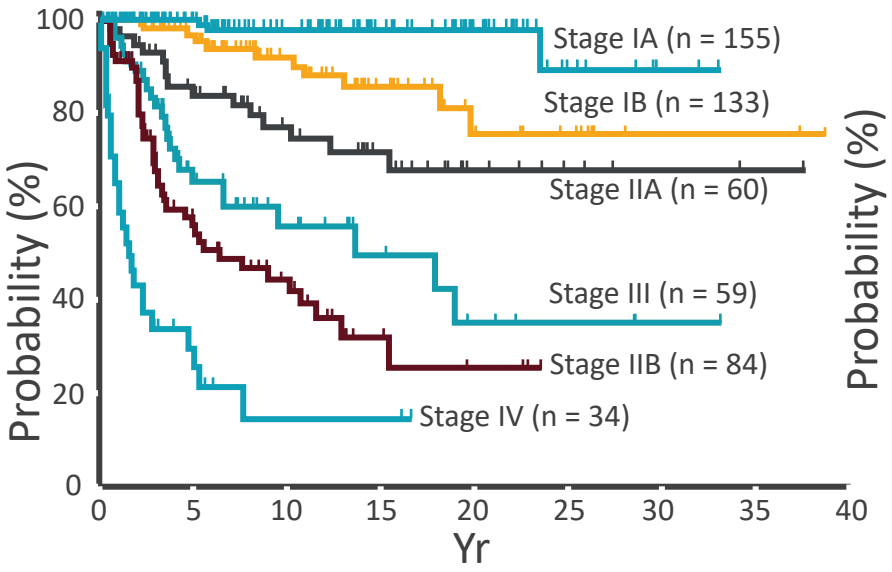




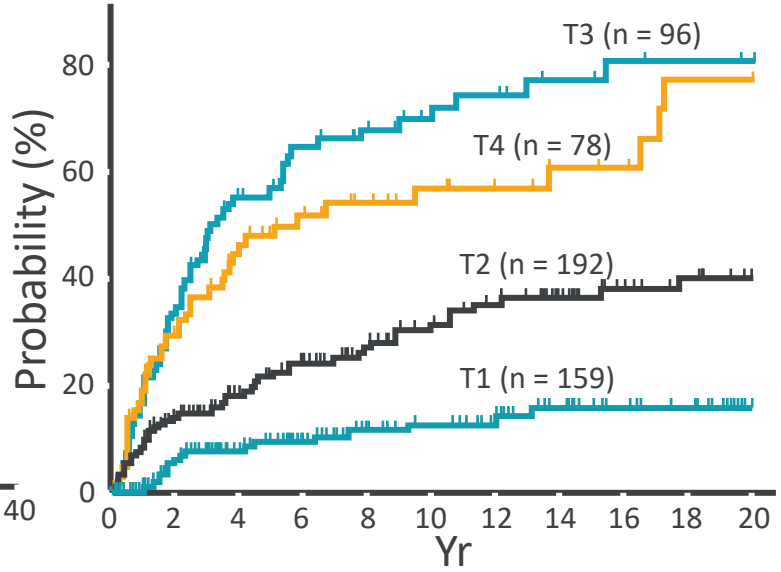
Photographs from A. Musiek M.D. and S. Horwitz M.D.

Prognosis in CTCL Is Heterogeneous

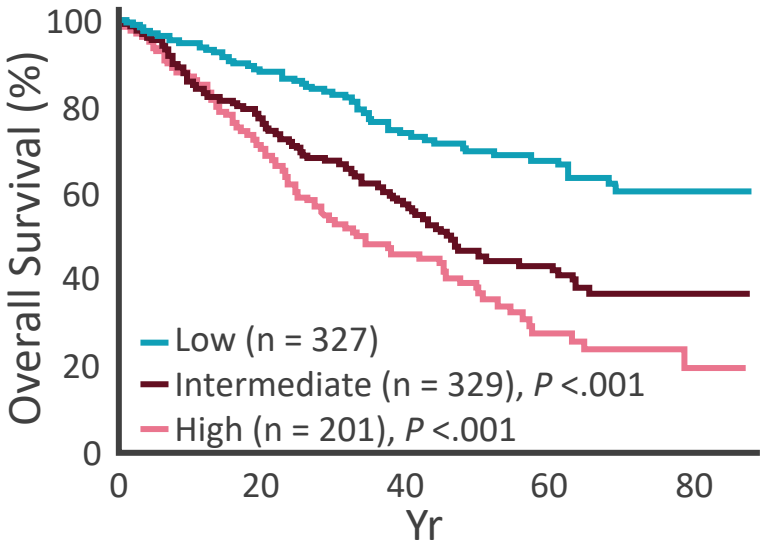
OS by Stage (N = 525)[1]



Risk of Progression (N = 525)[1]



OS by Risk Group (N = 1275)[2]



Prognostic factors associated with Worse Outcomes

- Stage IV
- LDH
- Age 60 yr or older
- Large-cell transformation in skin

1. Kim. Arch Dermatol. 2003;139:857. 2. Scarisbrick. JCO 2015;33:3766.

Strategies for Systemic Treatment in CTCL

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Guiding Principles for CTCL Management

- CTCLs are highly heterogeneous
- Prognosis is highly varied
- Early aggressive therapy tends not to change outcome
  - Most therapies have limited duration of response
  - Therapies often lead to partial, not complete, remissions
- Treatment is guided around patient quality of life

“Don’t make treatment worse than the disease”

NCCN. Clinical practice guidelines in oncology: primary cutaneous lymphomas. v.1.2024. nccn.org.

Responses With Skin-Directed Primary Therapies for Stages I-IIA (Skin-Limited, Patch/Plaque Disease)

	Skin Therapy, %	CR	ORR
	Topical steroids	45-65	75-95
FDA approved	Topical bexarotene gel	20-35	50-75
FDA approved	Topical nitrogen mustard	34-65	72-93
	Narrowband UVB	45-75	75-90
	PUVA	50-80	85-92
	TSEBT	14-50	100

- Results are from different clinical trials/populations and should not be used for cross-comparison

Duvic. Arch Dermatol. 2001;137:581. Gathers. J Am Acad Dermatol. 2002;47:191. Heald. J Am Acad Dermatol. 2003;49:801. Kim. Arch Dermatol. 2003;139:165. Morgenroth. Curr Oncol Rep. 2023;25:1397. Navi. Arch Dermatol. 2011;147:561.

When to Add Systemic Therapies in CTCL

Early-stage disease refractory to skin directed treatment (stage IA/IIA)

- Consider higher-risk features: folliculotropism, large cell transformation

Advanced disease (stage IIB-IVB)

- Often combine skin-directed therapy with systemic therapy

"Don't make the treatment worse than the disease"

- Prefer less toxic therapy first
- Limit cumulative toxicity
- More likely to choose single agents sequentially

NCCN. Clinical practice guidelines in oncology: primary cutaneous lymphomas. v.1.2024. nccn.org.

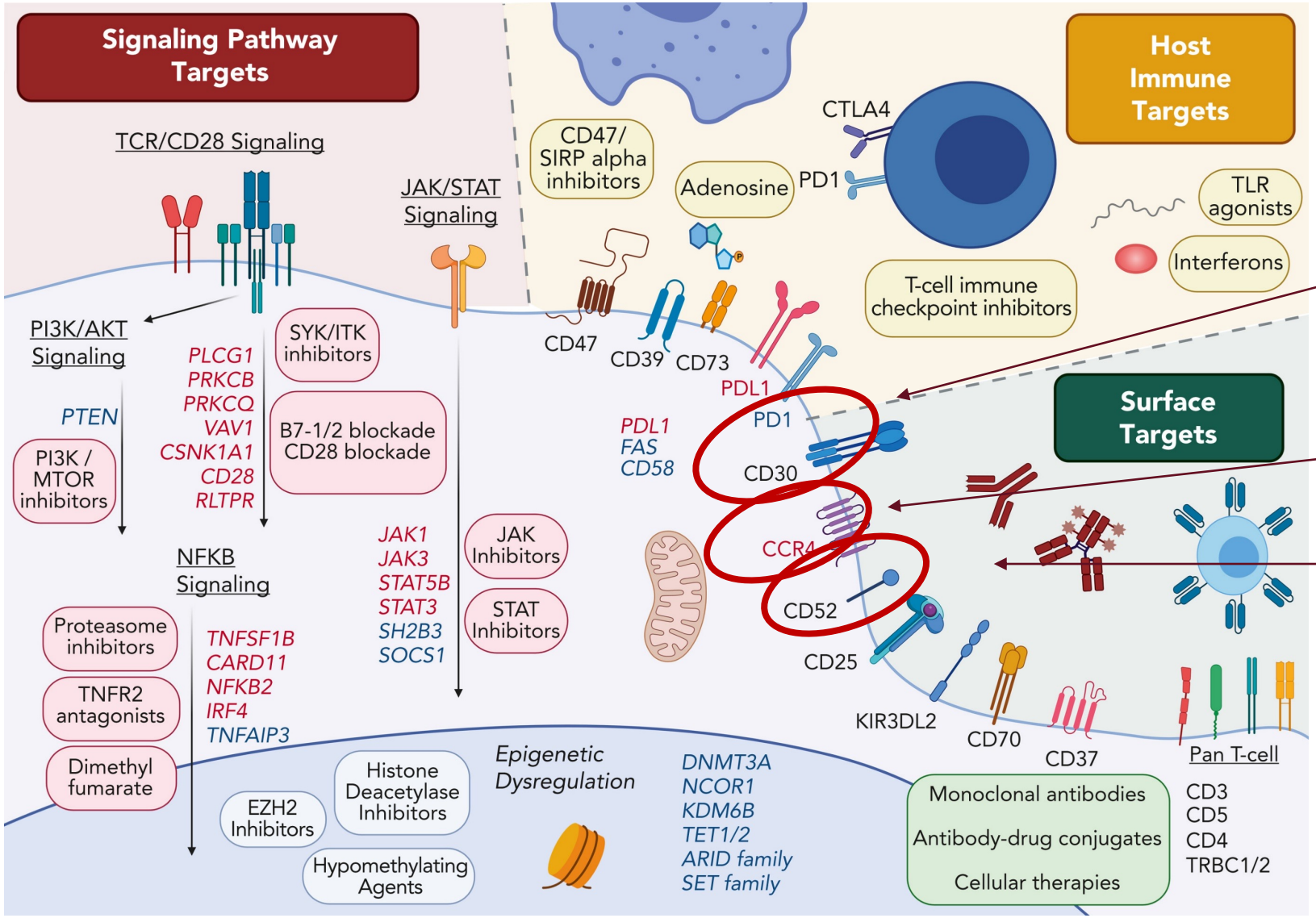
Selected Systemic Therapies for MF Stage > IIB

Agent	RR, %	CR, %	mDoR, Mo
Bexarotene	55	13	13
Brentuximab vedotin	50	10	15
CAVE + TSEB	88	31	12
Denileukin diftitox	27	7	2
Gemcitabine	68	8	4
Liposomal doxorubicin	41	6	6
Mogamulizumab	28	3	14
Pralatrexate	45	6	NR
Romidepsin	34	6	15
Vorinostat	30	<1	NR

- Results are from different clinical trials/populations and should not be used for cross-comparison

Duvic. Clin Lymphoma Myeloma. 2006;7:51. Horwitz. Clin Lymphoma Myeloma. 2008;8:187. Horwitz. Blood. 2012;199:4115. Kim. Lancet Oncol. 2018;19:1192. Morgenroth. Curr Oncol Rep. 2023;25:1397. Olsen. JCO. 2007;25:3109. Prince. Leuk Lymphoma. 2013;54:69. Prince. Lancet. 2017;390:555. Whittaker. JCO. 2010;28:4485.

Current Targets in CTCL



Khodadoust et al Blood 2023

Histone Deacetylase Inhibitors in CTCL

Romidepsin and vorinostat approved for CTCL

Romidepsin

- ORR: 34%
- Median duration of response: 15 mo

Vorinostat

- Original study ORR: 30%
- Later studies using modern response classification: ORR 5%

Kim. Lancet Oncol. 2018; 19:1192. Mann. Clin Cancer Res. 2007;13:2318.
Piekarz. JCO. 2009; 27:5410. Whittaker. JCO. 2010;28:4485.

ALCANZA: Brentuximab Vedotin vs Investigator's Choice for R/R CTCL

International, randomized, open-label phase III trial

Adults with previously treated CD30-positive MF or pcALCL and ECOG PS 0-2; 10% cutoff for enrollment* (N = 128)

Brentuximab Vedotin
1.8 mg/kg IV Q3W
(n = 64)

Choice
Methotrexate 5-50 mg PO weekly or
Bexarotene 300 mg/m^2 (target dose) PO daily
(n = 64) **Physician's**

Patients followed every 12 wk for 2 yr and then every 6 mo

*≥1 previous systemic therapy required for patients with MF; previous radiotherapy or ≥1 previous systemic therapy for patients with pcALCL.

Primary endpoint: ORR4 (objective global response lasting ≥4 mo)

Secondary endpoints: CR, PFS, QoL, PN

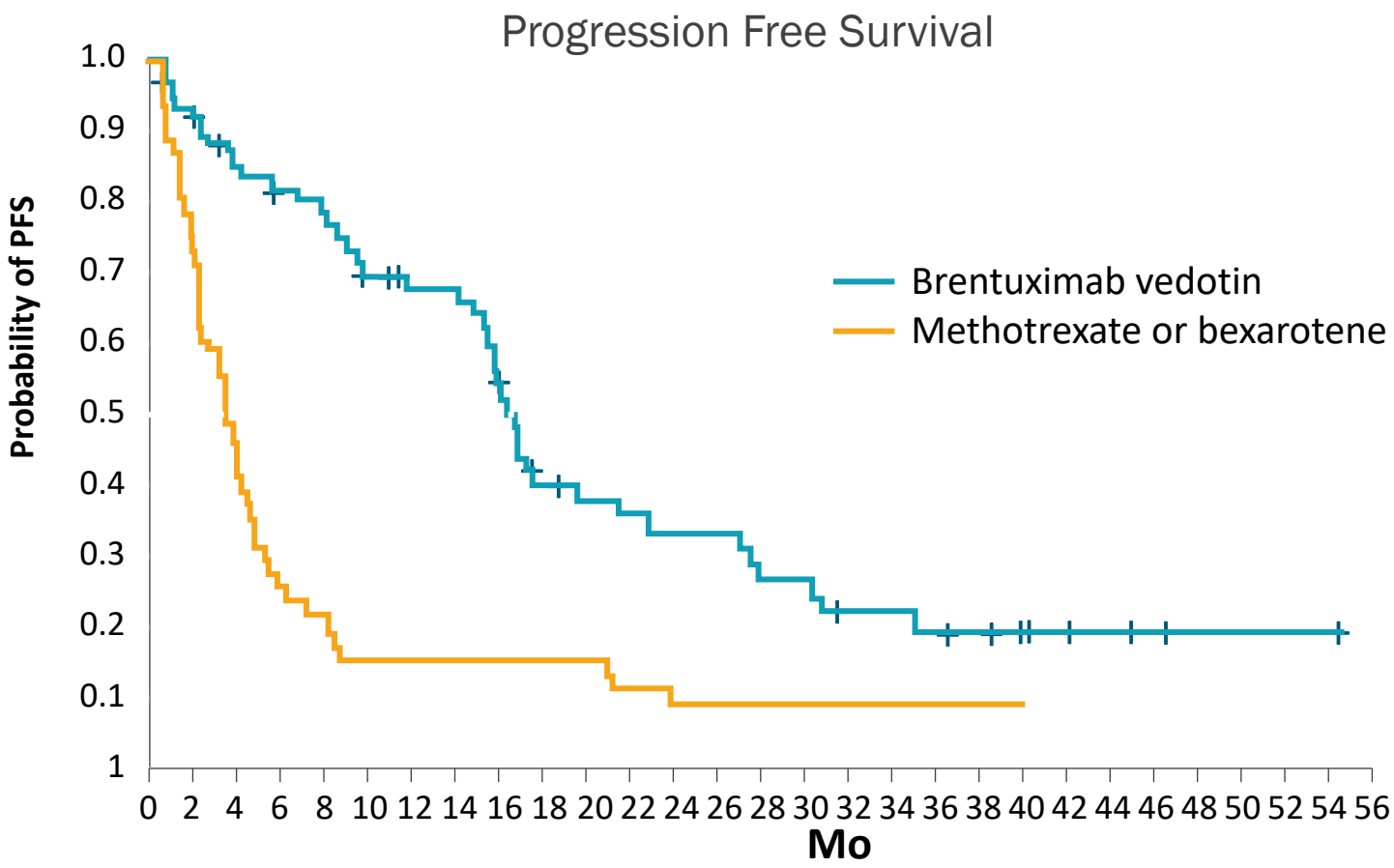
Not prespecified endpoints: TTNT, ORR

Prince. Lancet. 2017;390:555.

ALCANZA: Final Update of BV vs MTX or Bexarotene in CTCL

	Brentuximab Vedotin (n=64)	Physicians Choice (n=64)
ORR4, %	54.7	12.5
Median PFS, mo	16.7	3.5
Median TTNT, mo	14.2	5.6
3-y OS, %	64.4	61.9
Peripheral Neuropathy Resolution, n/N, (%)	38/44 (86)	2/4 (50)

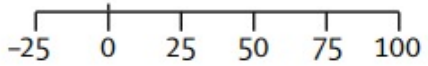
- BV improved patient-reported burden of symptoms, measured by Skindex-29 (adjusted *P* <.0001)



Horwitz. Blood Adv. 2021;5.23: 5098. Prince. Lancet. 2017;390:555.

ALCANZA: Improved ORR4 Across Key Subgroups

	Brentuximab vedotin, n/N (%)	Physician's choice of methotrexate or bexarotene, n/N (%)	Difference in percentages (95% CI)
Mycosis fungoides	24/48 (50·0%)	5/49 (10·2%)	39·8 (19·9 to 56·2)
pcALCL	12/16 (75·0%)	3/15 (20·0%)	55·0 (19·7 to 80·4)
Baseline ECOG PS=0	29/43 (67·4%)	6/46 (13·0%)	54·4 (37·3 to 71·5)
Baseline ECOG PS≥1	7/21 (33·3%)	2/18 (11·1%)	22·2 (–10·2 to 51·2)
Men	19/33 (57·6%)	5/37 (13·5%)	44·1 (21·3 to 63·3)
Women	17/31 (54·8%)	3/27 (11·1%)	43·7 (18·5 to 64·7)
Age <65 years	20/36 (55·6%)	2/40 (5·0%)	50·6 (29·3 to 68·3)
Age ≥65 years	16/28 (57·1%)	6/24 (25·0%)	32·1 (6·9 to 57·4)
Europe	23/37 (62·2%)	3/35 (8·6%)	53·6 (32·7 to 71·3)
Non-Europe	13/27 (48·1%)	5/29 (17·2%)	30·9 (4·2 to 53·5)
Bexarotene	36/64 (56·3%)	6/38 (15·8%)	40·5 (23·7 to 57·3)
Methotrexate	36/64 (56·3%)	2/26 (7·7%)	48·6 (26·7 to 67·7)
Skin only	21/31 (67·7%)	5/30 (16·7%)	51·1 (27·3 to 71·0)
Skin and other involvement	15/33 (45·5%)	3/34 (8·8%)	36·6 (12·3 to 56·3)
Baseline skin tumour score >0	26/41 (63·4%)	2/38 (5·3%)	58·2 (38·1 to 74·1)
Baseline skin tumour score =0	10/23 (43·5%)	6/26 (23·1%)	20·4 (–5·5 to 46·3)
Overall	**36/64 (56·3%)**	**8/64 (12·5%)**	**43·8 (29·1 to 58·4)**



Favors brentuximab vedotin

Prince. Lancet. 2017;390:555.

Brentuximab Vedotin at Variable CD30 Levels in CTCL

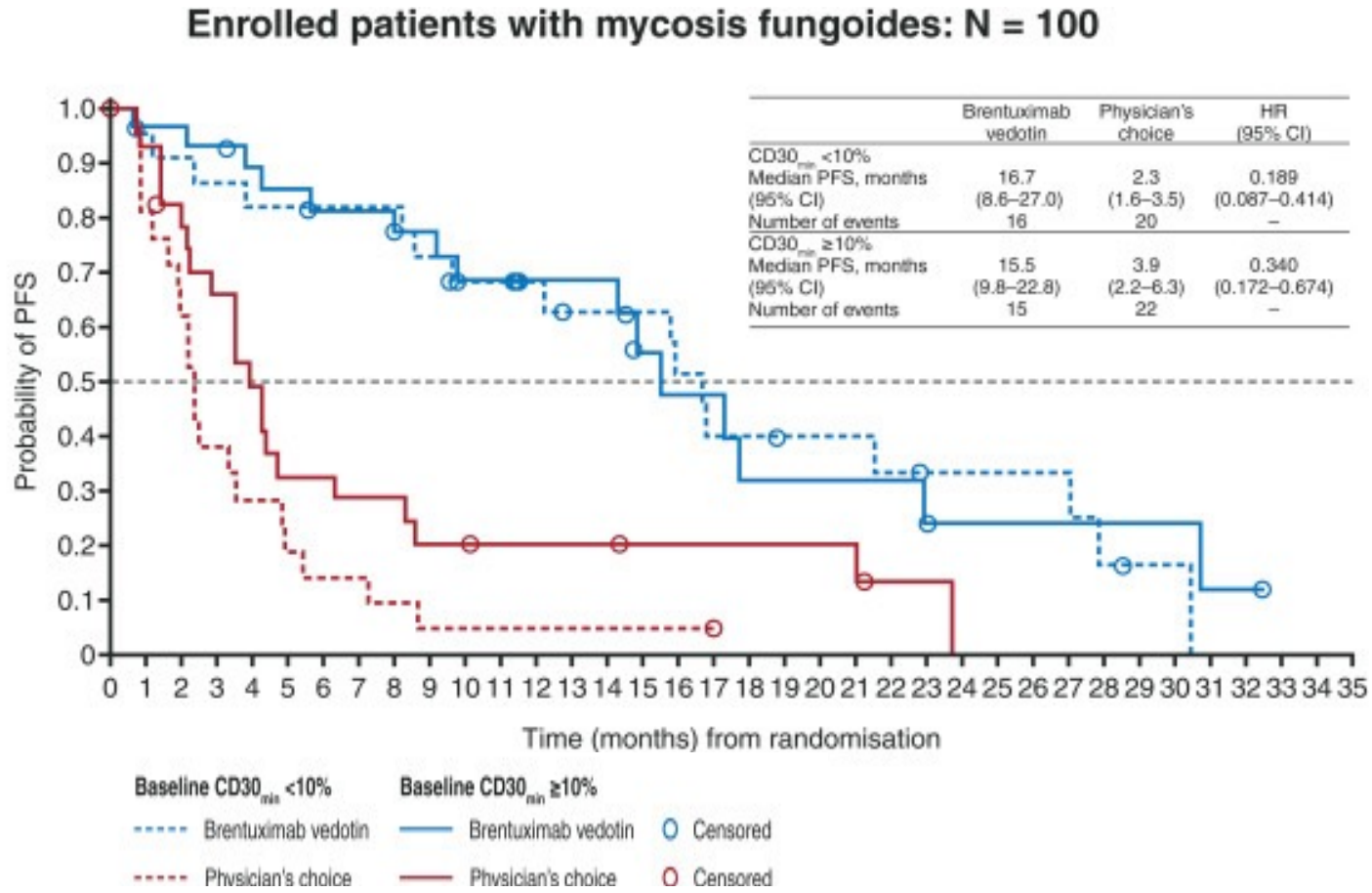
CD30 expression is variable in MF/SS[1]

- Median of 13% expression (n = 30)
- By more sensitive techniques, >90% of samples were CD30+

Response rate by CD30 level[1]

- ORR 70% (total population)
- CD30 <5% less likely to respond
- 17% ORR <5% expression
- 83% ORR >5% expression

PFS With BV vs Choice by Baseline CD30 Expression Level[2]



	Brentuximab vedotin	Physician's choice	HR (95% CI)
$CD30_{min}$ <10%			
Median PFS, months	16.7	2.3	0.189
(95% CI)	(8.6–27.0)	(1.6–3.5)	(0.087–0.414)
Number of events	16	20	–
$CD30_{min}$ ≥10%			
Median PFS, months	15.5	3.9	0.340
(95% CI)	(9.8–22.8)	(2.2–6.3)	(0.172–0.674)
Number of events	15	22	–

1. Kim. JCO. 2015;33: 3750. 2. Kim. Eur J Cancer. 2021; 148:411.

Neuropathy with Brentuximab Vedotin

Neuropathy remains limitation of brentuximab vedotin

ALCANZA: 67% of patients in the BV arm developed neuropathy

- Grade 2: 32%; grade 3: 10%

Neuropathy can be reversible but can take years to resolve

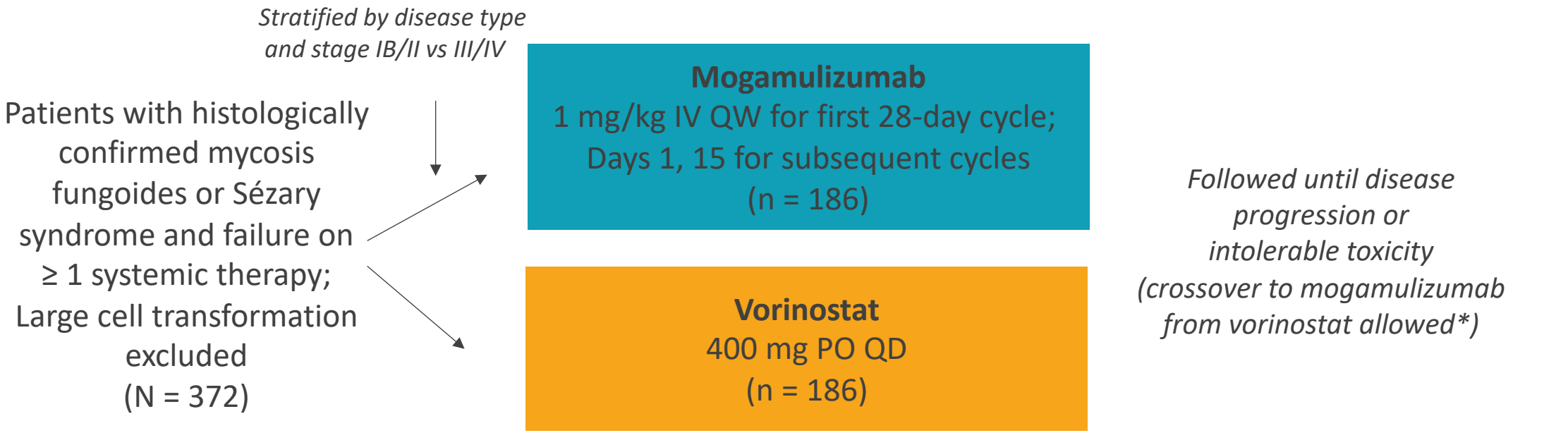
Phase II evaluation of lower brentuximab vedotin doses

- 0.9mg/kg: ORR 42% (n=19) median duration of response 19.6 mo
- 1.2mg/kg: ORR 57% (n=14) median duration of response NR
  - Neuropathy: 56% patients
    - Grade 2: 24%, grade 3: 0%
  - Observed improved quality of life

Geller. WCCL 2024. Abstr 1702. Prince. Lancet. 2017;390:555.

MAVORIC: Mogamulizumab vs Vorinostat in previously Treated CTCL

Multicenter, international, open-label, randomized phase III trial



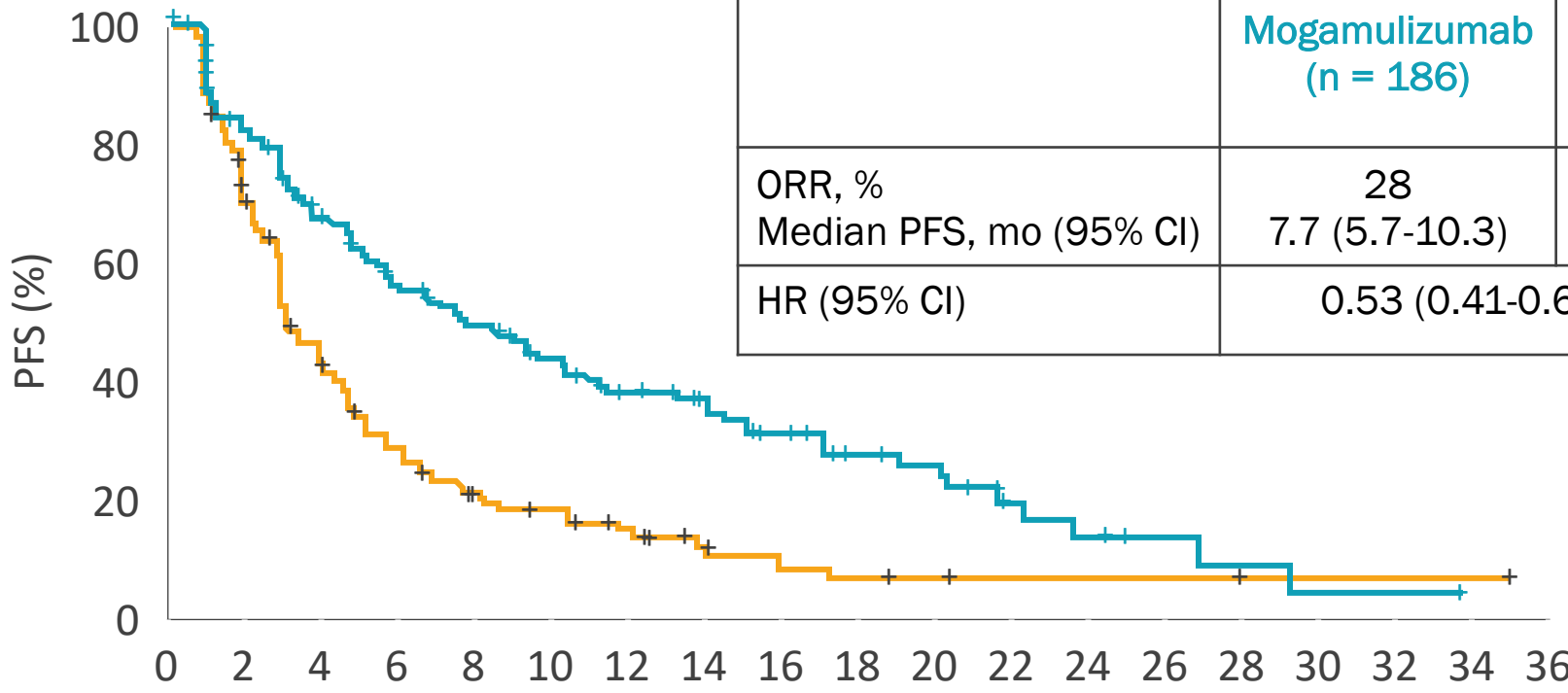
*Crossover in 136 (109 PD; 27 intolerance)

- Primary endpoint: PFS, using global composite response score based on skin, blood, lymph nodes, and viscera

Kim. Lancet Oncol. 2018;19:1192.

MAVORIC: Mogamulizumab vs Vorinostat in previously Treated CTCL

Progression Free survival



	Mogamulizumab (n = 186)	Vorinostat (n = 186)
ORR, % Median PFS, mo (95% CI)	28 7.7 (5.7-10.3)	5 3.1 (2.9-4.1)
HR (95% CI)	0.53 (0.41-0.69); P <.0001	

Patients at Risk, n

Mogamulizumab	186	138	100	77	65	50	39	32	22	16	14	7	5	3	2	1	1	0	0
Vorinostat	186	111	61	36	23	18	13	8	5	4	3	2	2	2	1	1	1	1	0

Kim. Lancet Oncol. 2018;19:1192.

MAVORIC: Clinical Activity by Compartment

Compartment Response*	Mogamulizumab (n = 186)	Vorinostat (n = 186)
Skin, n/N (%) ▪ ORR (CR + PR), n (%) ▪ mDoR, mo	78/186 (42) 8 (4) 10.7	29/186 (16) 1 (1) 10.7
Blood ▪ ORR (CR + PR), n (%) ▪ mDoR, mo	83/122 (68) 54 (44) 25.5	23/123 (19) 5 (4) N/A
Lymph nodes ▪ ORR (CR + PR), n (%) ▪ mDoR, mo	21/124 (17) 10 (7) 15.5	5/122 (4) 2 (2) N/A
Viscera	0/3 (0)	0/3 (0)

*Proportion of patients with confirmed complete response or confirmed partial response.

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Mogamulizumab-Associated Rash

Rash occurs in at least 25% patients

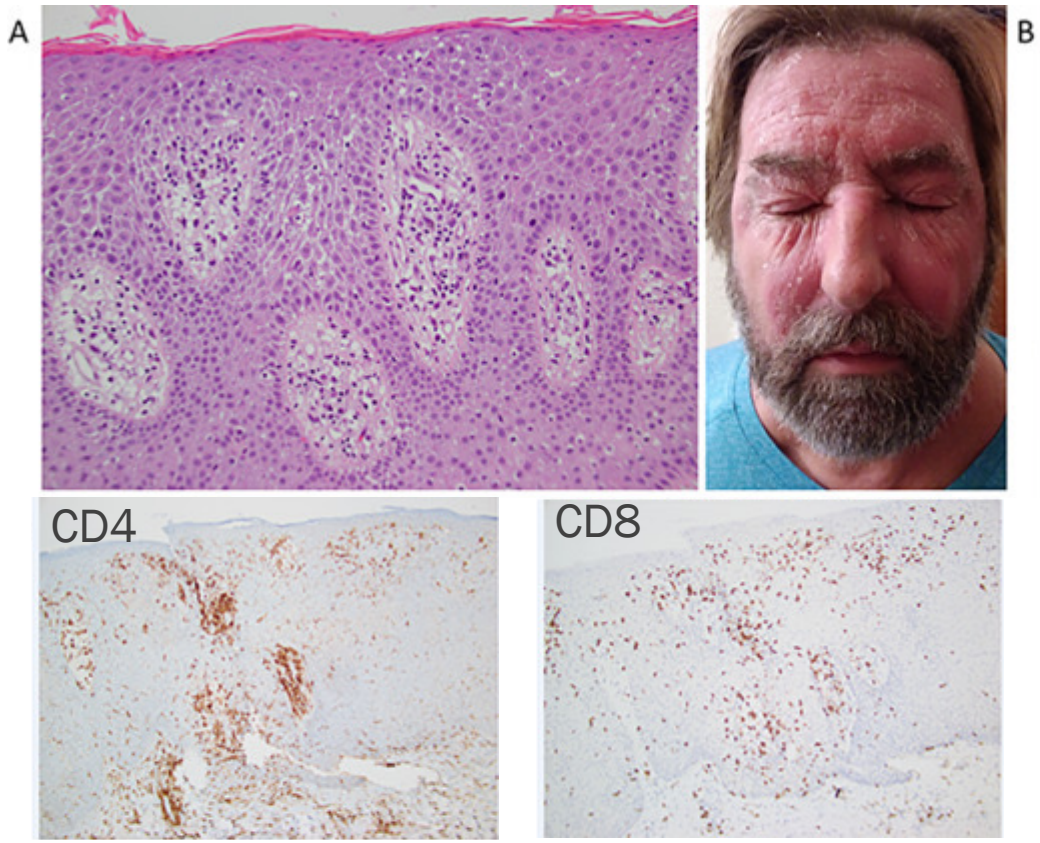
Rash can be clinically indistinguishable from disease progression

Onset 2-6 mo after treatment

Appearance variable:

- Plaques, macules, or photosensitive rash

Skin biopsy should be performed to distinguish rash from disease progression



Chen. JAMA Dermatol. 2019;155: 968. Hirotsu. JAMA Dermatol. 2021;157:700. Musiek. Dermatol Ther 2022;12:29.

Mogamulizumab-Associated Rash Predictive of Outcomes

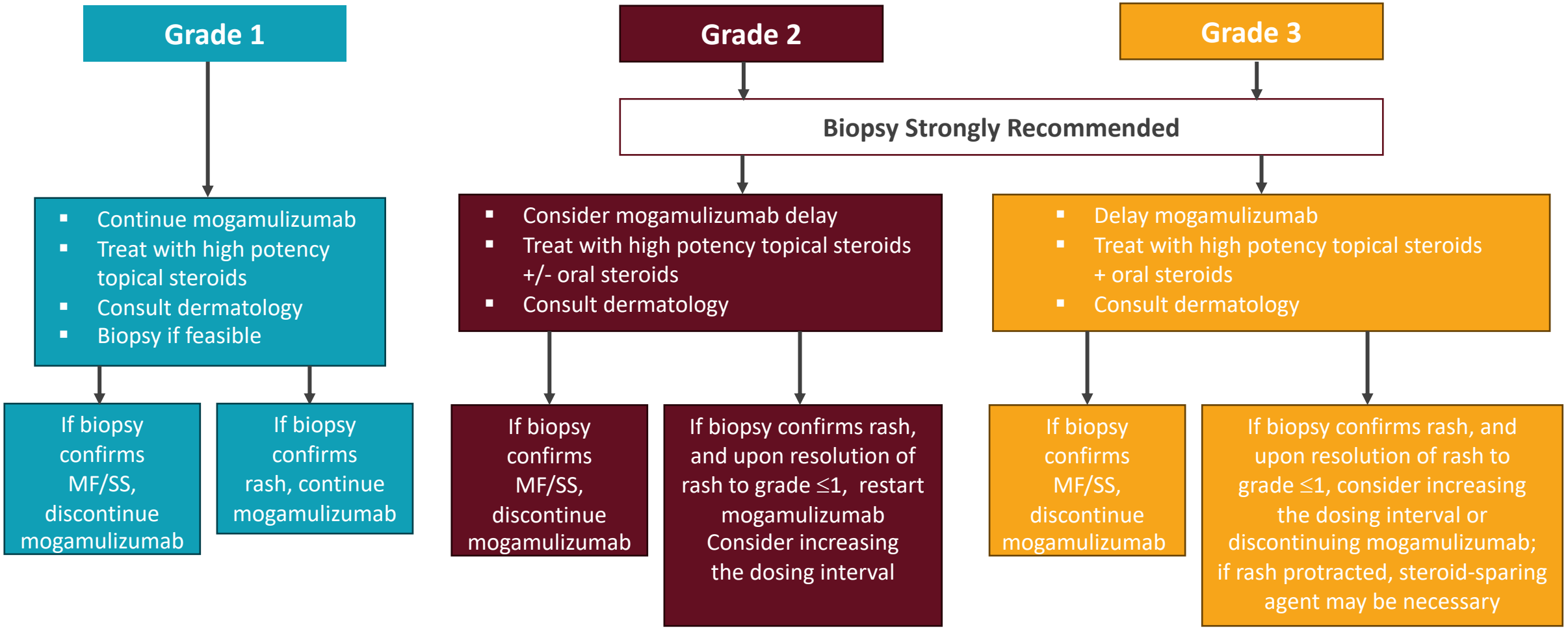
- Retrospective series (n = 24) showed rash associated with higher ORR with mogamulizumab (88% vs 28%)

- Multi-institutional retrospective series (n = 159) showed rash associated with longer progression-free survival and overall survival

Outcome	Rash (n = 72)	No Rash (n = 77)
CR, %	64	26
	Odds ratio: 4.64 (2.37-10.25) P <.0001	
ORR, %	85	54
	P <.0001	
PFS, mo	30.5	8.6
	P <.0001	
3-yr survival, %	84	55
	P = .00077	

Hui. ASH 2022. Abstr 617. Trum. Br J Dermatol. 2022;186:153.

Suggested Management for Mogamulizumab-Associated Rash



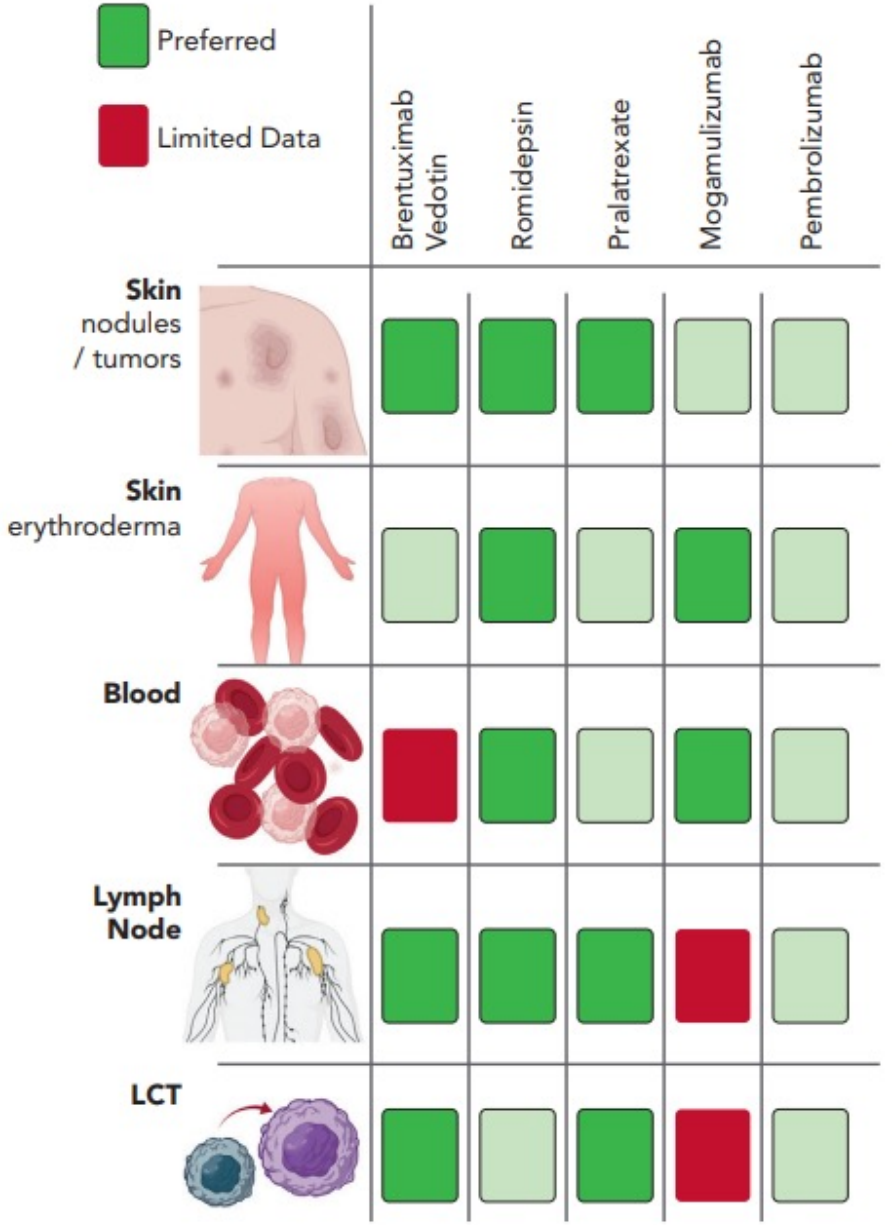
Musiek. Dermatol Ther 2022;12:29.

CTCL Whack-a-mole

Treatments are often directed towards what compartment at play

- Not all agents work equally in all situations

Sequential therapy with emphasis on quality of life



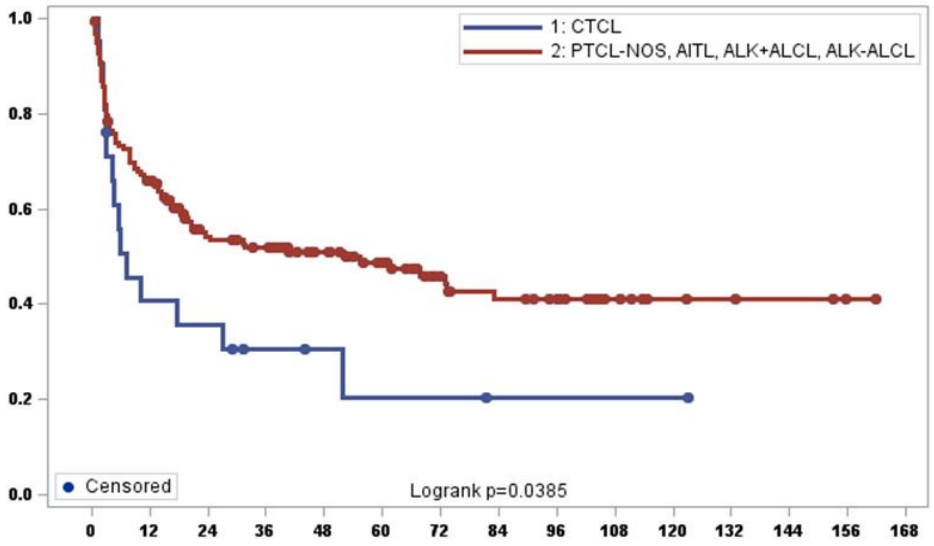
Khodadoust et al Blood 2023

Allogeneic Stem Cell Transplant

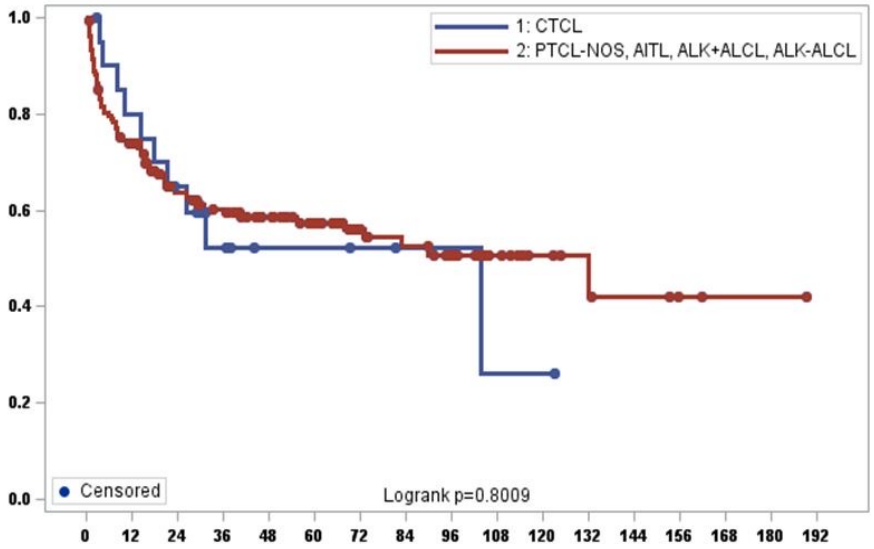
Real-world experience of allogeneic transplant in PTCL vs CTCL

CTCL has similar OS to PTCL but inferior PFS

Progression-Free Survival



Overall Survival



Survival		
		% (95% CI)
OS	1 year	51% (39-64)
	3+ year	40% (32-49)
PFS	1 year	42% (31-53)
	3+ year	33% (25-42)

Mehta-Shah. Blood. 2017;130(Suppl 1):4597. Foss WCCL 2024

CUTALLO: Allogeneic Stem Cell Transplant in Advanced CTCL

Prospective multicenter, matched control study (N = 99)

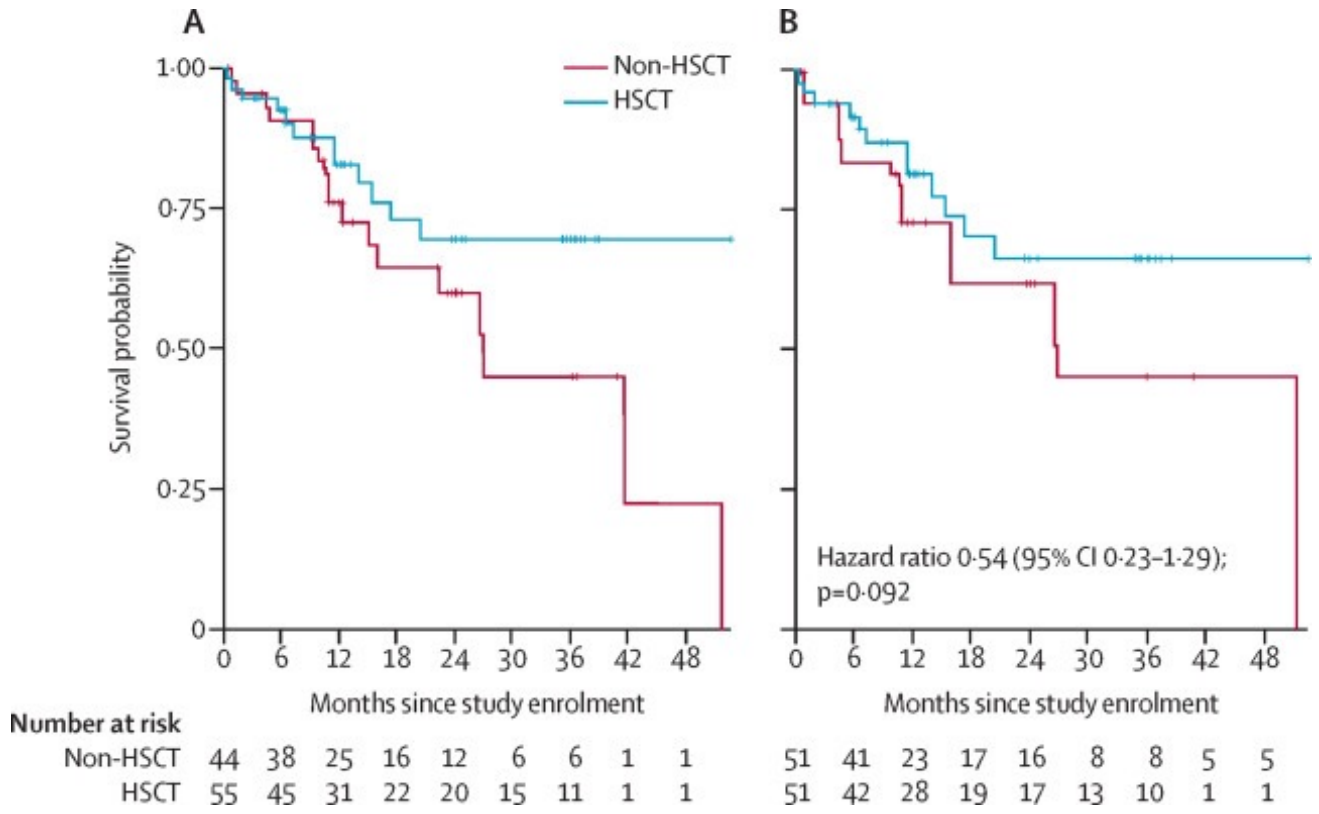
- Transplant group (n = 55)
  - mPFS: 9 mo (95% CI: 6.6-30.5)
  - mOS: NR
- No transplant (n = 44)
  - mPFS: 3 mo (95% CI 2.0-6.3)
  - mOS: 26.9 mo

Eligible patients with high-risk disease should be considered for transplant

- Decision is nuanced

OS in Original ITT Population

OS in Matched ITT Population



deMasson. Lancet. 2023. 401:1941.

Novel Agents for Mycosis Fungoides and Sézary Syndrome

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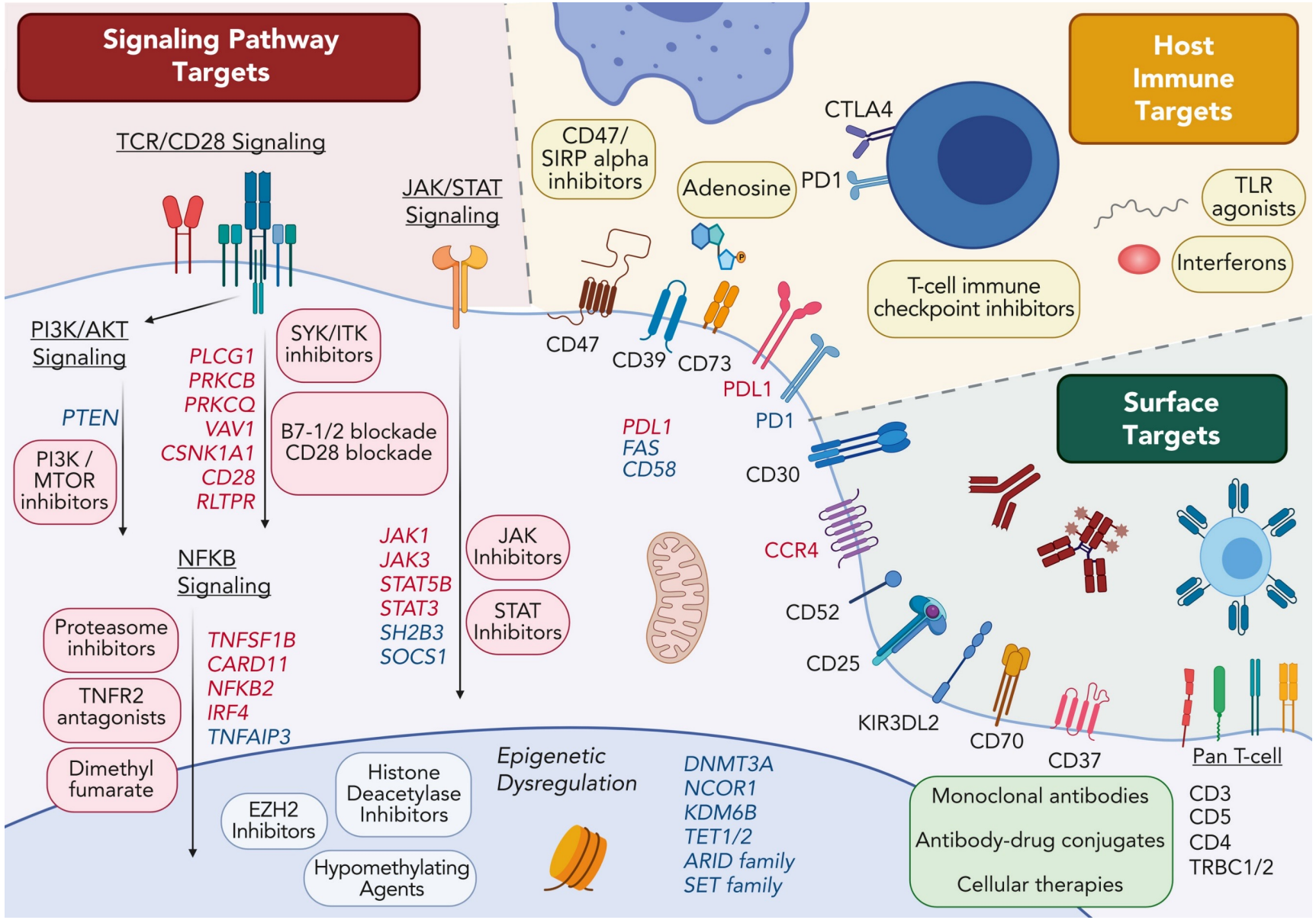
Novel Targets in CTCL



Khodadoust et al Blood 2023

Lacutamab: Phase I/II Study in Advanced MF/SS

Mechanism: mAb targeting KIR3DL2 cell surface protein expressed in CTCL and SS

Study:

- Phase I: n = 44 (35 SS, 8 MF, 1 CTCL, NOS)
- Phase II: KIR3DL2 positive (cohort 2 = 21); KIR3DL2 negative (cohort 3 = 18)

Adverse events:

- Peripheral edema (12 [27%])
- Fatigue (9 [20%]), grade 1/2
- Lymphopenia most common grade ≥ 3 AE (3 [7%])

Efficacy:

- Cohort 1 Global ORR 16/44 (36.4%), ***43% in SS***
- Cohort 2 ORR 28.6%
- Cohort 3 ORR 11.1%

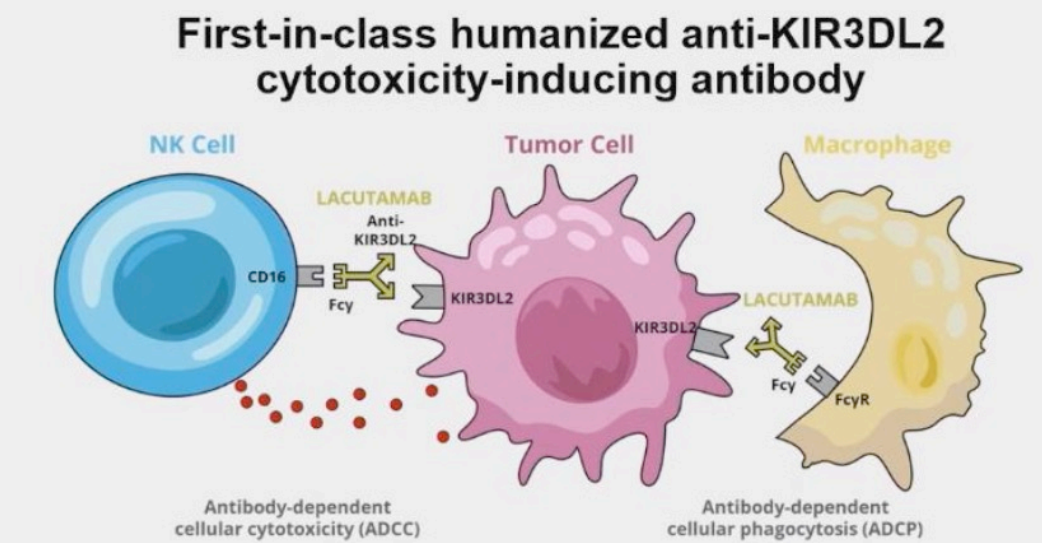
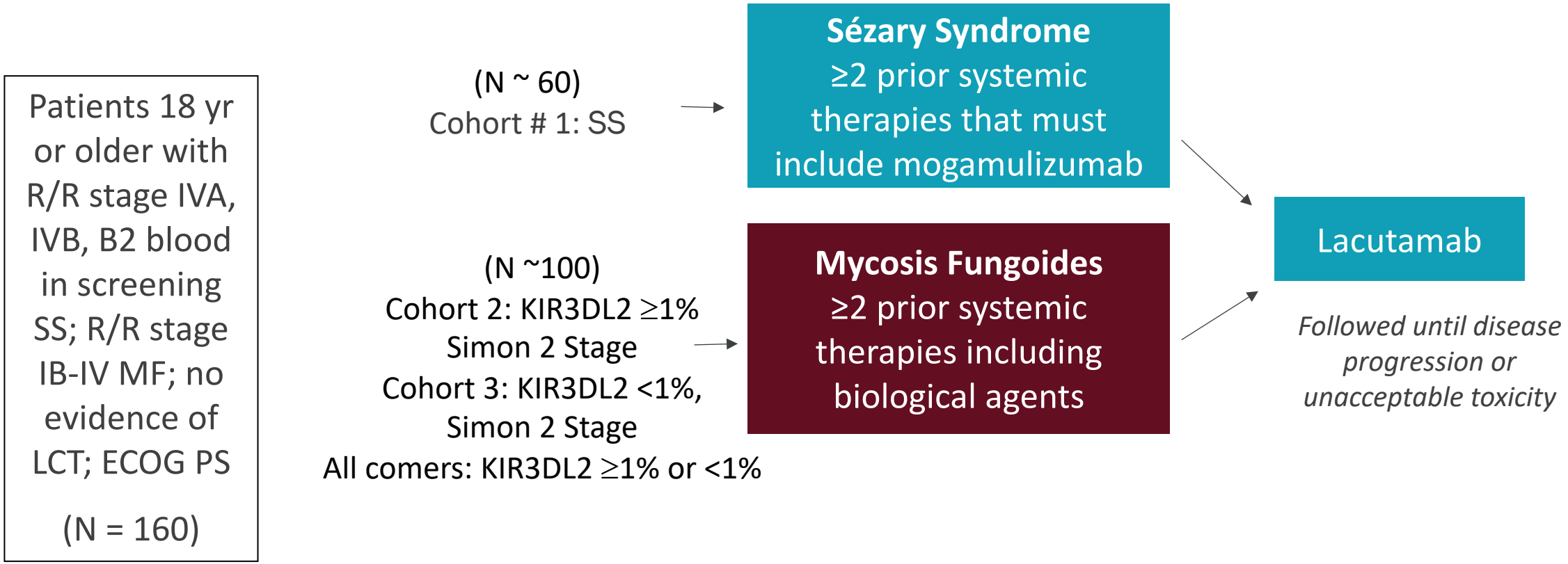


Figure 1: Lacutamab Mechanism of Action

Bagot. Lancet Oncol. 2019;20:1160. Bagot. EORTC CTLG 2022. Battistella. Blood. 2017;130:2900.

TELLOMAK: Phase II Trial of Lacutamab in R/R SS and MF

- International, multicenter, multicohort, multicenter trial, report on Cohort 1



- Primary endpoint: ORR
- Secondary endpoints: safety, QoL, PFS, OS, DoR, PK parameters

Porcu. ASH 2023. Abstr 185.

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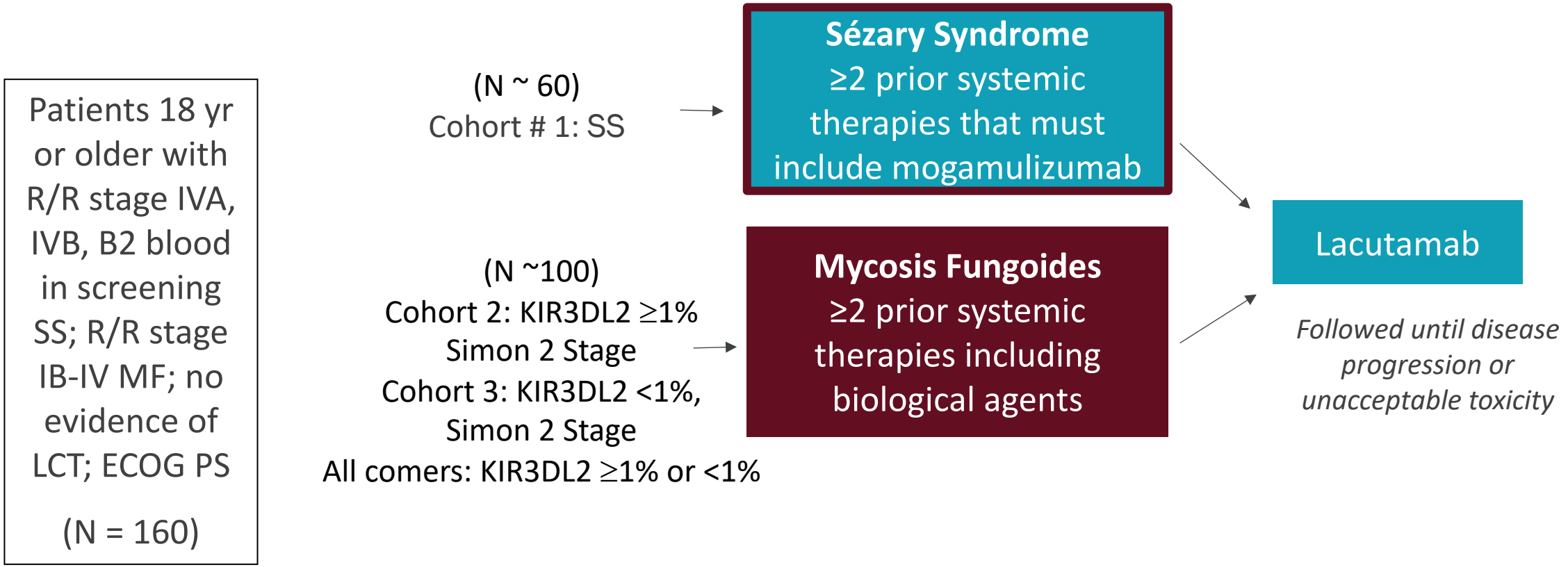

- Primary endpoint: ORR
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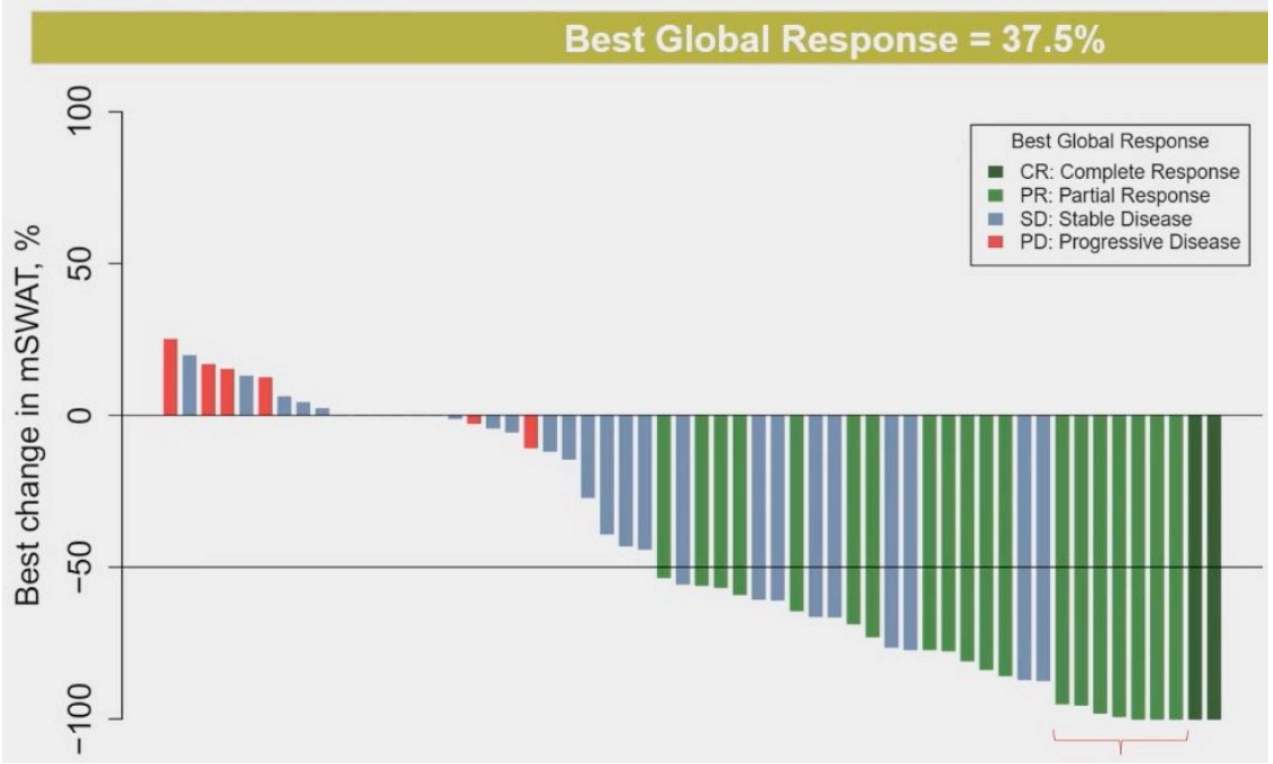
Porcu. ASH 2023. Abstr 185.

TELLOMAK: Lacutamab in R/R Sèzary Syndrome

- Best global response: 37%
  - Best skin response: 46%
  - Best blood response: 48%
  - Best LN response: 19%
- Median DoR: 12.3 mo
- Median PFS: 8.0 mo
- Most frequent AE: fatigue (12.5%), rash (12.5%), GI (10.7%)
- Grade 3 or higher AEs: 17.9%



Porcu. ASH 2023 Abstr. 185.

CITN-10: Phase II Study of Pembrolizumab in R/R MF/SS

Adults with advanced stage (IIB-IV) relapsed /refractory MF/SS (N = 24)

→ **Pembrolizumab**
2 mg/kg IV Q3W up to 24 mo

- 8/15 patients with SS had transient skin toxicity
  - 3/8 with toxicity had a response
  - 1/7 without skin toxicity achieved response
- 40% of patients had a skin flare reaction which was believed to be an immune-mediated AE
- Skin flare is clinically indistinguishable from progression

- PD1 expression was associated with increased risk of skin flare

Parameter, n (%)	MF/SS (N = 24)
ORR	**9 (38)**
CR	2 (8.3)
PR	7 (29.1)
mDOR	NR (@58 w)

Khodadoust. JCO. 2020;38:20.

Improving Outcomes With Checkpoint Inhibitors

Selection of patients

- Structural variants in PD-L1 reported in outstanding responders
  - Seen in Large Cell transformation

Studies exploring combination strategies

- Pembrolizumab + interferon-gamma (NCT03063632)
- Nivolumab + duvelisib (NCT04652960)
- Pembrolizumab + mogamulizumab (NCT05956041)
- Durvalumab + lenalidomide (NCT03011814)

Beygi. Blood Adv. 2021;9:771.

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Phase I Trial of Duvelisib Monotherapy:Efficacy in CTCL

ORR 32% in R/R MF/SS (n=19)

Safety:

- Treatment interruptions and/or dose reductions most commonly required for AST/ALT elevation, rash, diarrhea, and pyrexia.
- Neutropenia in 20%. Grade ≥ 3 infections in 29%.

- Low dose duvelisib (15mg BID to QOD) tried in CTCL with promising efficacy/safety

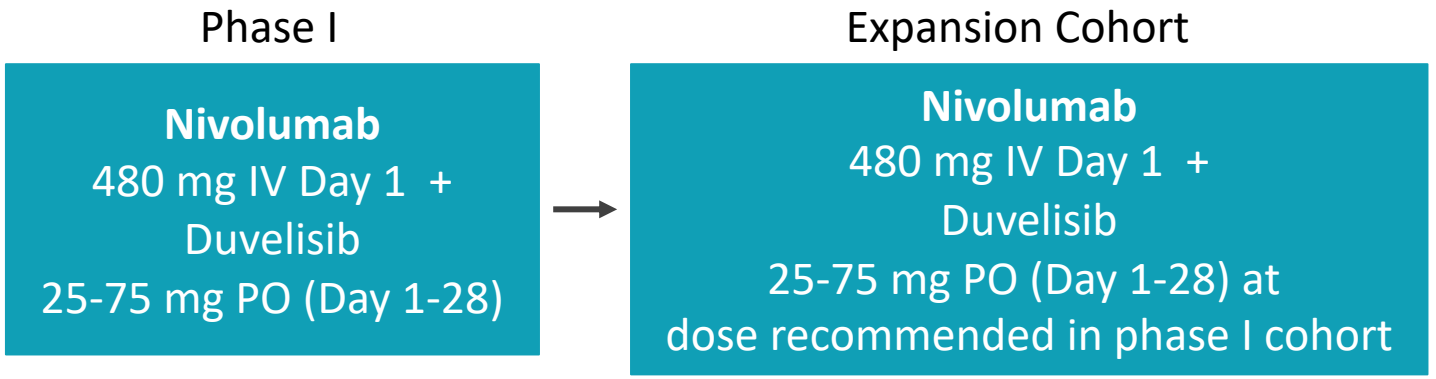
Parameter	CTCL (N = 19)
ORR, n (%)	6 (31.6)
Best overall response, n (%)	
▪ CR	0
▪ PR	6 (31.6)
▪ SD	6 (31.6)
▪ PD	6 (31.6)
▪ Unknown	1 (5.3)

Horwitz. Blood. 2018;131:888. Bazewicz The Oncologist 2024

Phase I Study of Duvelisib + Nivolumab in R/R MF and SS

28-day cycles

Adults with advanced stage (IIB-IVB) R/R MF/SS with ≥1 line of prior systemic therapy, adequate organ function, no history of autoimmune disorders



Followed until disease progression or intolerable toxicity

Primary endpoint: RP2D or MTD of combination, safety

Secondary endpoints: ORR, CR rate, DoR

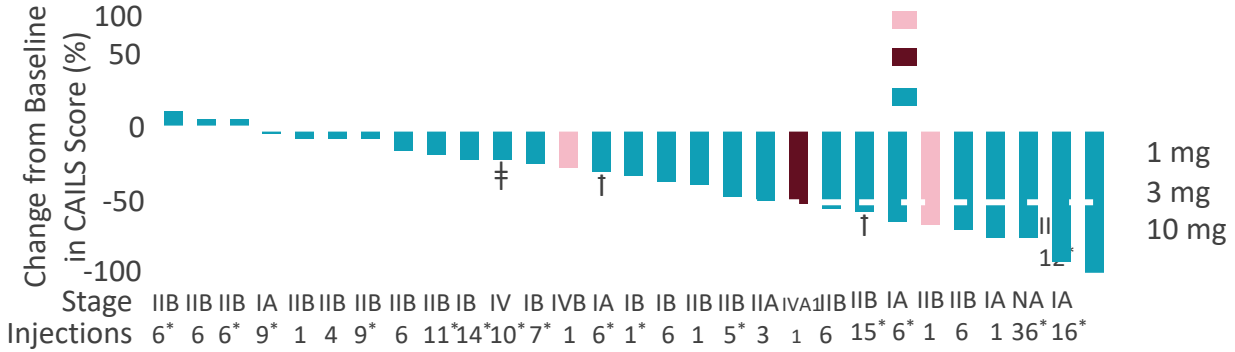
NCT04652960.

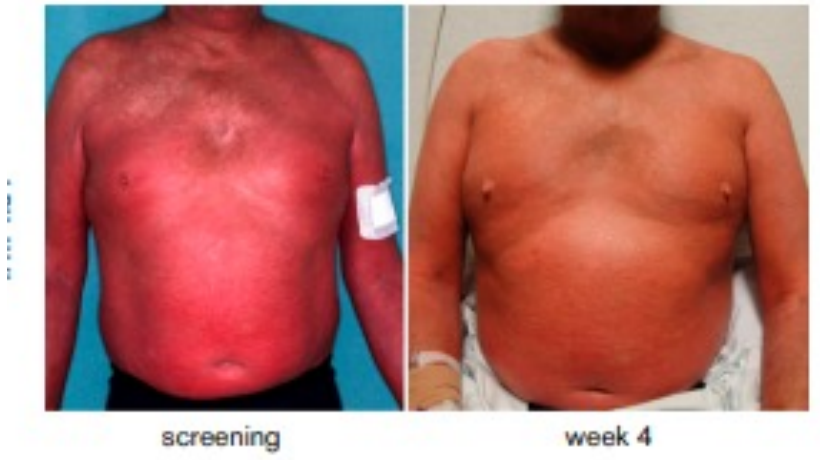
Multicenter Phase I Study of Intralesional TTI-621, in Patients With MF and SS

CD47 functions as a “don’t eat me” signal to block phagocytosis by macrophages

TTI-621 is a decoy CD47 receptor

- TTI-621 injected intralesionally in patients with MF and SS (n=34)
  - Cohorts 1–5; single 1-mg, 3-mg, or 10-mg injection or three 10-mg injections weekly for 1 or 2 wk
- ORR 34%, 10/34
- Reduction in non-injected lesions in 8/10 patients





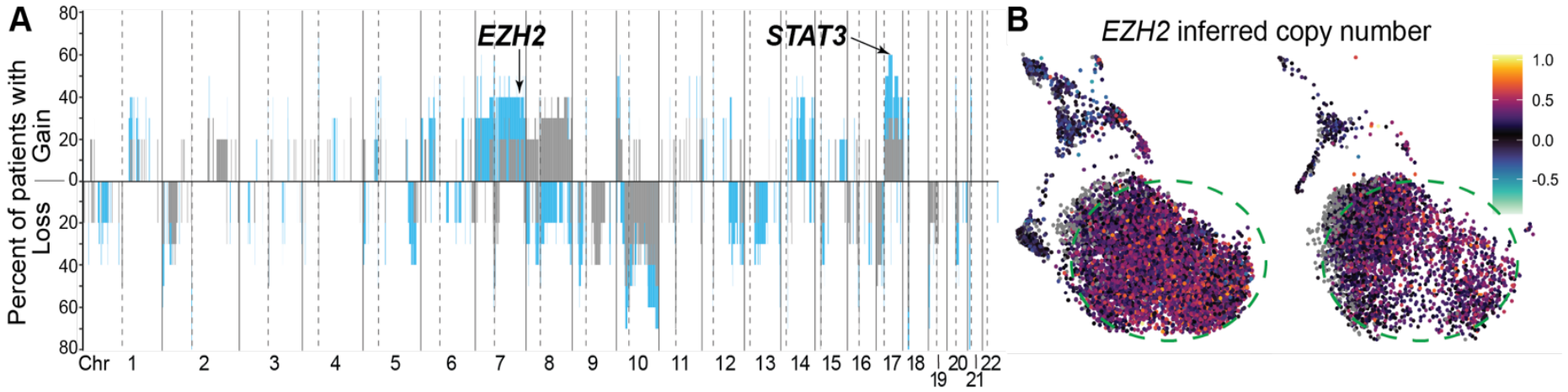
Querfeld. Lancet Hematol. 2021;8:e808.

Alterations in EZH2 with Clonal Evolution in CTCL

EZH2 inhibitors have shown efficacy, durability and tolerability in PTCL

EZH2 mutations not common in CTCL, however

Advanced stage CTCL associated with copy number gains and increased *EZH2* expression



Dorando. Blood. 2022;140(Suppl 1):754. Payton Laboratory (Washington University)

Phase I Study of Tulmimetostat in R/R MF and SS

Tulmimetostat = EZH2/EZH1 inhibitor

Adults with advanced stage (IB-IVB) R/R MF/SS with ≥1 line of prior systemic therapy, adequate organ function

28-day cycles

Dose-Escalation Cohort

Tulmimetostat → Expansion Cohort **Tulmimetostat**

Until disease progression or intolerable toxicity

Primary endpoint: RP2D, safety

Secondary endpoints include ORR, CRR, DoR

Evaluating tools for quality of life

NCT05944562

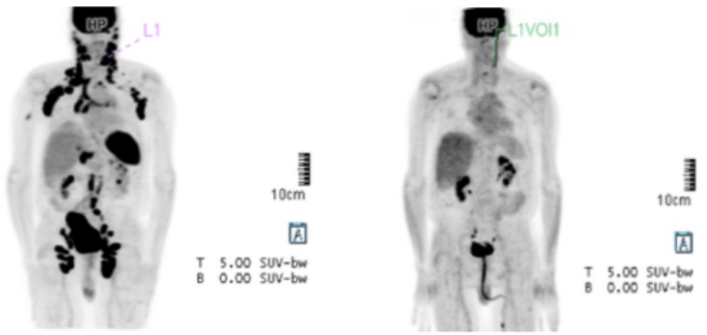
CAR T-Cells in T-Cell Lymphomas

CAR Type	Comments
CD5 CAR	Baylor; NCT03081910 CR seen in PTCL, AITL
CD30 CAR	Baylor: NCT02917083 UNC: NCT02690545 UNC: NCT03602157
CD7 CAR	Baylor NCT03690011
CD70 Allo CAR	NCT04502446 ORR 80% PTCL (n=4), 60% CTCL (n=3)
CD7 Allo CAR	WUSTL: NCT05377827

Difficulty in identifying T-cell specific target antigens expressed on malignant and not healthy T-cells

Several targets under investigation in T-cell lymphomas

Pre-CD5 CAR T => CR @ 4 wk post CD5 CAR-T



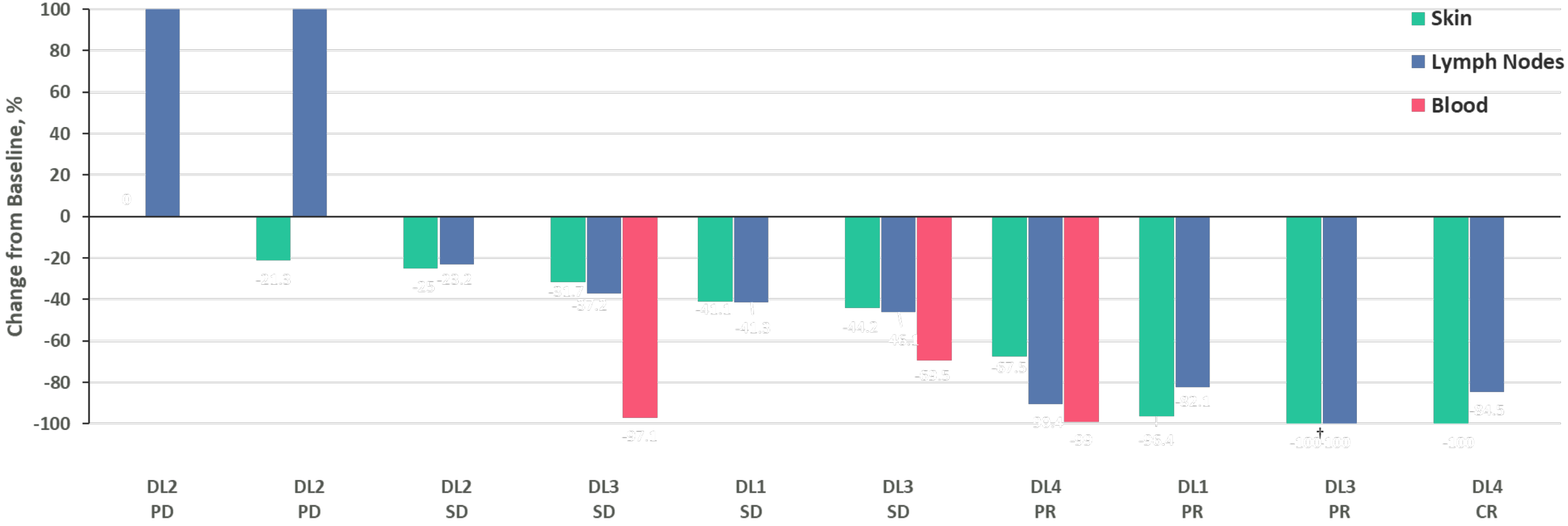
Hill. Blood. 2019;134 (Suppl 1):199. Iyer. EHA 2022. Abstr S262. Karsten. Front Immunol. 2023:14:1285406

CD70 Allogeneic CART (CTX130)

18 patients with TCL:

- - 70% ORR and 30% CR rate at DL≥3 (≥3x10^8 cells)

- Durable remissions seen



Iyer EHA 2022

Key Takeaways

- Mogamulizumab has improved efficacy compared to vorinostat in Sézary syndrome and mycosis fungoides
  - Compartmental responses can help guide patient care
- Differentiation of mogamulizumab associated rash from disease progression is part of an optimal management strategy
- Novel therapies have potential for CTCL management, including epigenetic regulators, targeted antibodies, small molecule inhibitors, and cellular therapy, but additional studies to confirm efficacy are necessary

Thank you!