Linfomi cutanei a cellule T: nuove opportunità terapeutiche topiche e sistemiche

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Stadiazione

Pazienti con MF in stadio iniziale hanno generalmente una prognosi eccellente con sopravvivenza a 10 anni di oltre l'80% ma con un impatto sulla qualità di vita.

I pazienti con malattia in stadio tumorale (T3) mostrano una sopravvivenza a 5 anni fino al 45%.

Clinical Staging of MF and SS[l]

Clinical Stage[r]	T (Skin)	N (Node)	M (Visceral)	B (Blood Involvement)	Guidelines Page
IA (Limited skin involvement)	T1 (Patches, papules, and/or plaques covering <10% body surface area [BSA])	N0	M0	B0 or B1	MFSS-6
IB (Skin only disease)	T2 (Patches, papules, and/or plaques covering ≥10% BSA)	N0	M0	B0 or B1	MFSS-7
IIA	T1–2	N1–2	M0	B0 or B1	MFSS-7
IIB (Tumor stage disease)	T3 (One or more tumors [≥1 cm in diameter])	N0–2	M0	B0 or B1	MFSS-8
IIIA (Erythrodermic disease)	T4 (Confluence of erythema ≥80% BSA)	N0–2	M0	B0	MFSS-10
IIIB (Erythrodermic disease)	T4 (Confluence of erythema ≥80% BSA)	N0–2	M0	B1	MFSS-10
IVA_1 (Sézary syndrome)	T1–4	N0–2	M0	B2	MFSS-11
IVA_2 (Sézary syndrome or Non-Sézary)	T1–4	N3	M0	B0 or B1 or B2	MFSS-11
IVB (Visceral disease)	T1–4	N0–3	M1	B0 or B1 or B2	MFSS-11
	Large-cell transformation (LCT)[s]				MFSS-12

First Line

EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome – Update 2023

Johanna Latzka [a,b,*], Chalid Assaf [c,d,e], Martine Bagot [f], Antonio Cozzio [g], Reinhard Dummer [h], Emmanuella Guenova [i], Robert Gniadecki [j,k], Emmilia Hodak [l], Constanze Jonak [m], Claus-Detlev Klemke [n], Robert Knobler [m], Stephen Morrris [o], Jan P. Nicolay [p], Pablo L. Ortiz-Romero [q], Evangelia Papadavid [r], Nicola Pimpinelli [s], Pietro Quaglino [t], Annamari Ranki [u], Julia Scarisbrick [v], Rudolf Stadler [w], Liisa Väkevä [u], Maarten H. Vermeer [x], Ulrike Wehkamp [y,z], Sean Whittaker [aa], Rein Willemze [x], Franz Trautinger [a,b]

	Wait & see	Topical steroids	nbUVB	Topical chlormeti	Local RT	TSET	Interferon	Bexarotene	MonoCT	MTX	PoliCT	ECP
IA	✓	✓	✓	✓	✓							
IB	✓	✓	✓	✓	✓							
IIA		✓	✓	✓	✓							
IIB					✓	✓	✓	✓	✓	✓		
III						✓	✓	✓		✓		✓
SS							✓	✓	✓	✓		✓
IVA-IVB									✓		✓	

Second Line

EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome – Update 2023

Johanna Latzka [a,b,*], Chalid Assaf [c,d,e], Martine Bagot [f], Antonio Cozzio [g], Reinhard Dummer [h], Emmanuella Guenova [i], Robert Gniadecki [j,k], Emmilia Hodak [l], Constanze Jonak [m], Claus-Detlev Klemke [n], Robert Knobler [m], Stephen Morrris [o], Jan P. Nicolay [p], Pablo L. Ortiz-Romero [q], Evangelia Papadavid [r], Nicola Pimpinelli [s], Pietro Quaglino [t], Annamari Ranki [u], Julia Scarisbrick [v], Rudolf Stadler [w], Liisa Väkevä [u], Maarten H. Vermeer [x], Ulrike Wehkamp [y,z], Sean Whittaker [aa], Rein Willemze [x], Franz Trautinger [a,b]

	Wait & see	Topical steroids	nbUVB	Local RT	TSET	Interferon	Bexarotene	MonoCT	MTX	PoliCT	ECP
IA						✓	✓		✓		
IB					✓	✓	✓		✓		
IIA					✓	✓	✓		✓		
IIB										✓	
III										✓	
SS								✓		✓	
IVA-IVB								✓		✓	

Linee guida ESMO 2018

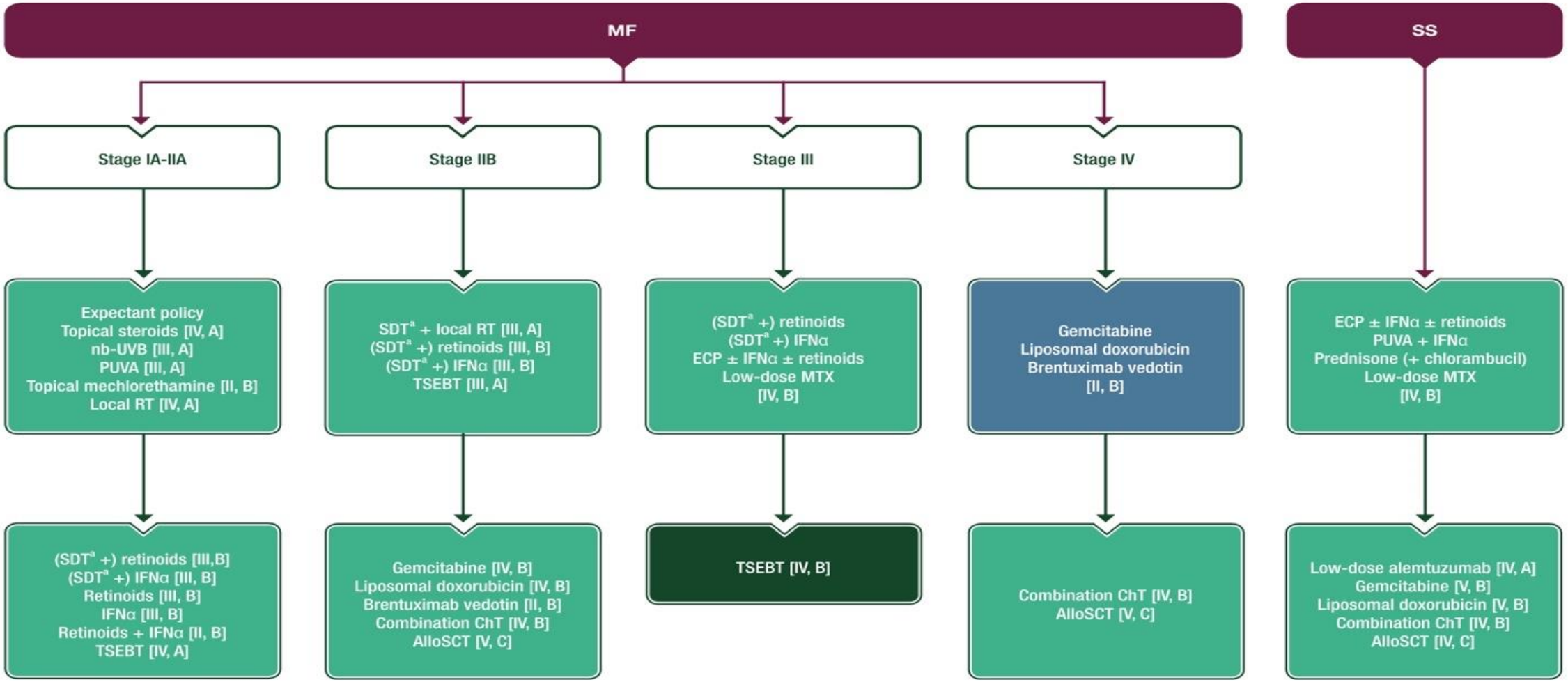


Figure 1. Recommendations for the treatment of MF/SS.
[a]Most commonly PUVA.
AlloSCT, allogeneic stem cell transplantation; ChT, chemotherapy; ECP, extracorporeal photopheresis; IFNα, interferon alpha; MF, mycosis fungoides; MTX, methotrexate; nb-UVB, narrow-band ultraviolet B; PUVA, psoralens plus ultraviolet A; RT, radiotherapy; SS, Sézary syndrome; SDT, skin-directed therapy; TSEBT, total skin electron beam therapy.

Multiple choises (Etereogeneità di trattamento)

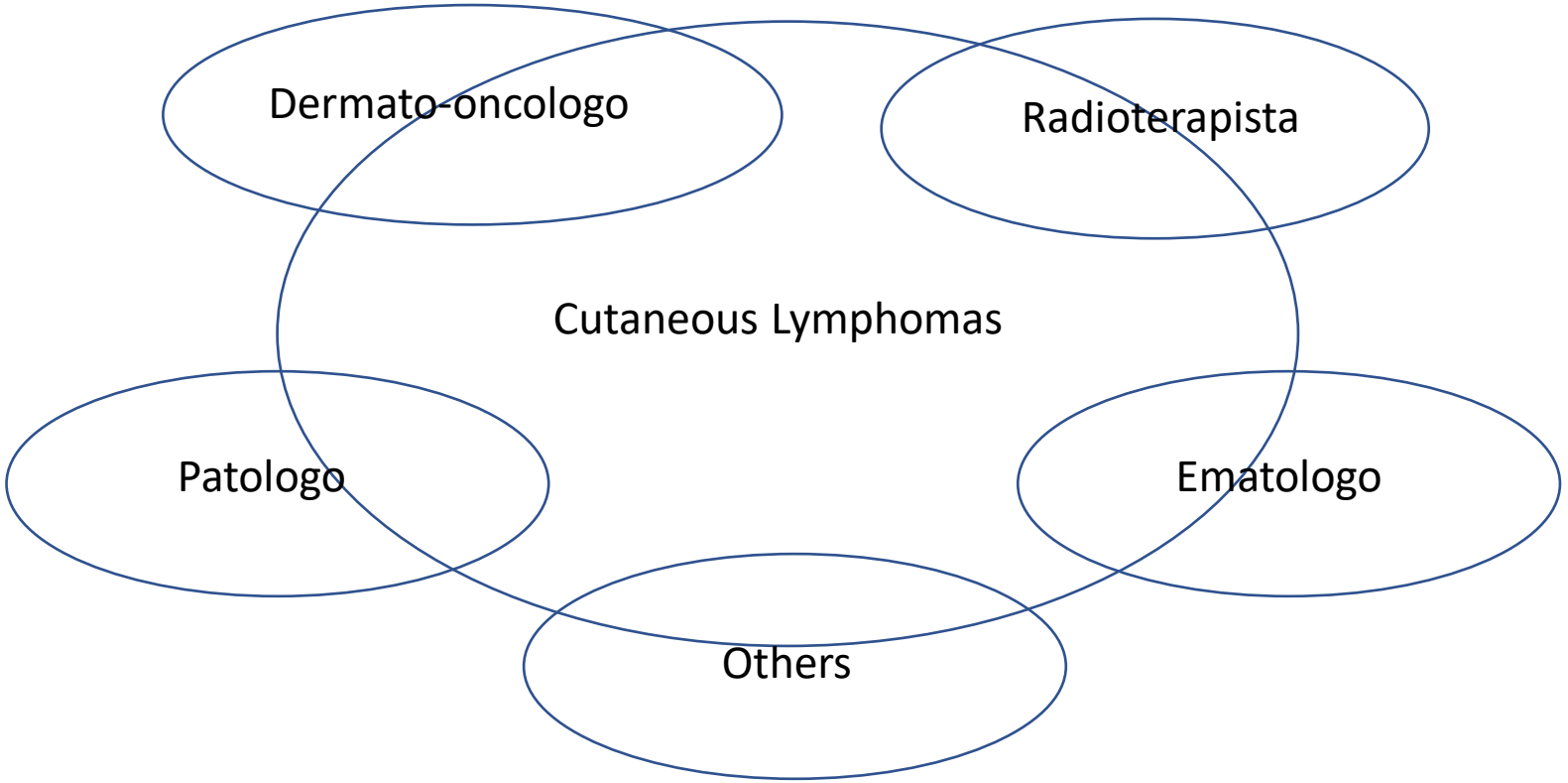
Libertà di scelta del medico

Accessibilità ai trattamenti

Comorbidità (performance status)

Compliance del paziente

Approccio multidisciplinare



Stage based therapy

STAGE	THERAPY
T1	STEROIDS+/- UVB
T2	RET/IFN/MTX/PUVA
T3	TSEBT/CT
T4	ECP/HSCT

blood®
Regular Article

LYMPHOID NEOPLASIA

Skin colonization by circulating neoplastic clones in cutaneous T-cell lymphoma

Aishwarya Iyer,[1] Dylan Hennessey,[1] Sandra O'Keefe,[1] Jordan Patterson,[2] Weiwei Wang,[2,3] Gane Ka-Shu Wong,[2,4] and Robert Gniadecki[1,5]

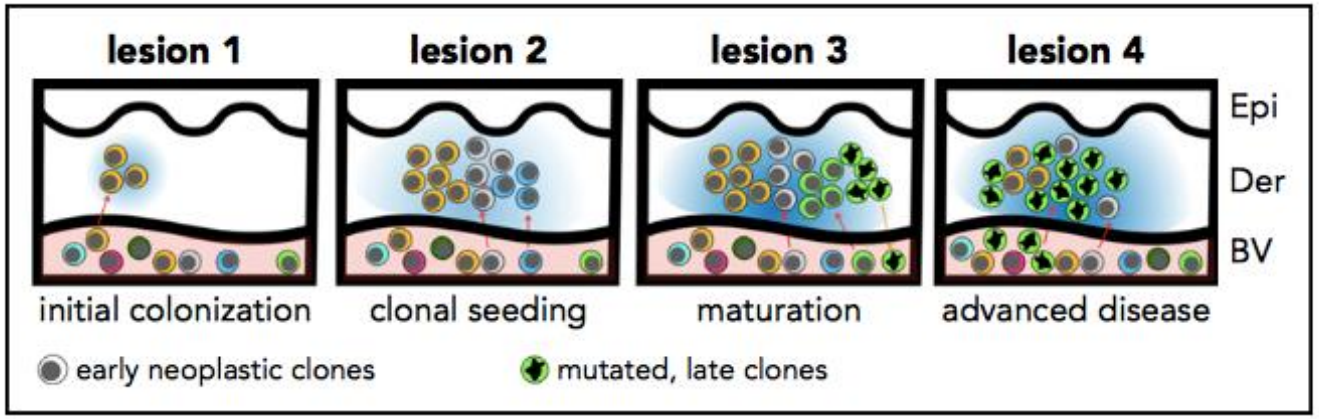


Figure 5. The hypothesis of tumor seeding in the pathogenesis of MF. Even in the early stages of the disease, patients have circulating neoplastic T-cell clones in peripheral blood. Early lesions are initiated by the pioneer clones and create a niche (blue-shaded area) that facilitates seeding of this area of the skin (lesion 1) with subsequent clones (lesion 2) (consecutive seeding model[43] and supplemental Figure 6). The clonal composition of different lesions may differ (lesion 3) due to the stochastic nature of cancer seeding. Some clones may have a higher proliferation capacity in the skin and may overgrow other clones (green clone in lesion 3), further mutate, reenter the circulation (orange arrow), and reseed another area of the skin (lesion 4). The figures represent symbolically the structure of the skin with the epidermis (Epi), dermis (Der), and a pink-shaded blood vessel (BV). Different clones of neoplastic T cells are marked with different colors.

MEDICAL DERMATOLOGY

BJD
British Journal of Dermatology

Treatment of early-stage mycosis fungoides: results from the PROspective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study*

P. Quaglino,[1] H.M. Prince,[2] R. Cowan,[3] M. Vermeer,[4] E. Papadavid,[5] M. Bagot,[6] O. Servitjie,[7] E. Berti,[8] E. Guenova,[9] R. Stadler,[10] C. Querfeld,[11] A.M. Busschots,[12] E. Hodak,[13] A. Patsatsi,[14] J. Sanches,[15] M. Maule,[16] J. Yoo,[17] M. Kevin,[17] P. Fava,[1] S. Ribero,[1] L. Zocchi,[1] M. Rubatto,[1] M.T. Fierro,[1] U. Wehkamp,[18] M. Marshalko,[19] C. Mitteldorf,[20] O. Akilov,[21] P. Ortiz-Romero,[22] T. Estrach,[23] L. Vakeva,[24] P.A. Enz,[25] M. Wobser,[26] M. Bayne,[27] C. Jonak,[28] M. Rubeta,[29] A. Forbes,[30] A. Bates,[31] M. Battistella,[6] R. Amel-Kashipaz,[17] B. Vydianath,[17] A. Combalia,[23] E. Georgiou,[14] E. Hauben,[12] E.K. Hong,[32] M. Jost,[18] R. Knobler,[28] I. Amitay-Laish,[13] D. Miyashiro,[15] J. Cury-Martins,[15] X. Martinez,[11] C. Muniesa,[7] H. Prag-Naveh,[13] A. Stratigos,[5] V. Nikolaou,[5] K. Quint,[4] C. Ram-Wolff,[6] K. Rieger,[32] R. Stranzenbach,[10] Á. Szepesi,[19] S. Alberti-Violetti,[8] E. Felicity,[17] L. Cerroni,[33] W. Kempf,[34] S. Whittaker,[35] R. Willemze,[4] Y. Kim[32] and J.J. Scarisbrick[17,36]

Objectives To identify (i) differences in first-line approaches according to tumour-nodes-metastasis-blood (TNMB) staging; (ii) parameters related to a first-line systemic approach and (iii) response rates and QoL measures.

Registro prospettico di casi di linfomi cutanei raccolti worldwide in cui sono stati analizzati I dati delle terapie in 395 pazienti con micosi fungoide early stage

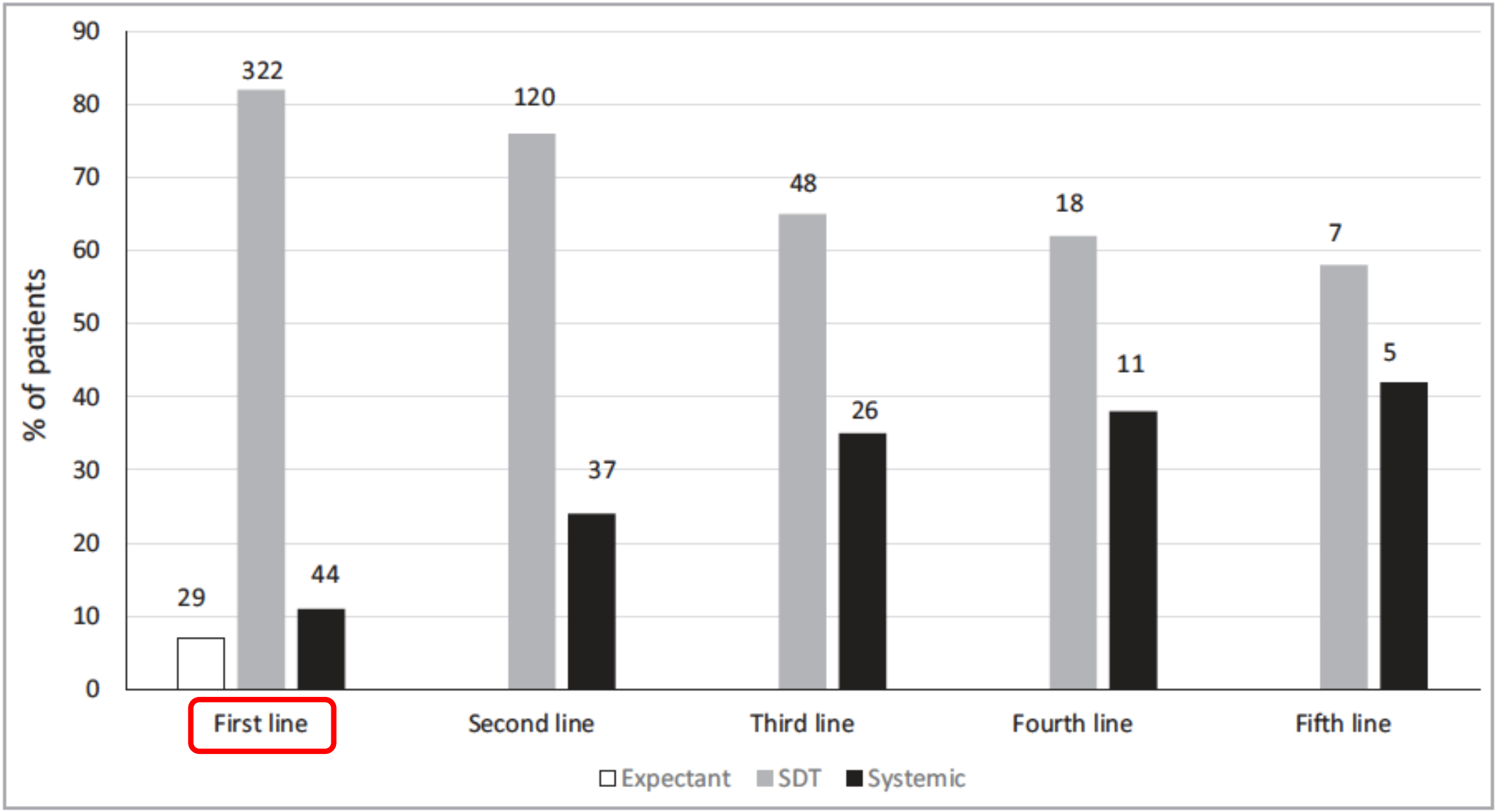


Figure 1 Percentages of patients treated according to different approaches [expectant policy, skin-directed therapy (SDT) and systemic therapy] across the therapy lines. The number at the top of each bar represents the absolute number of patients treated by the respective therapeutic approach.

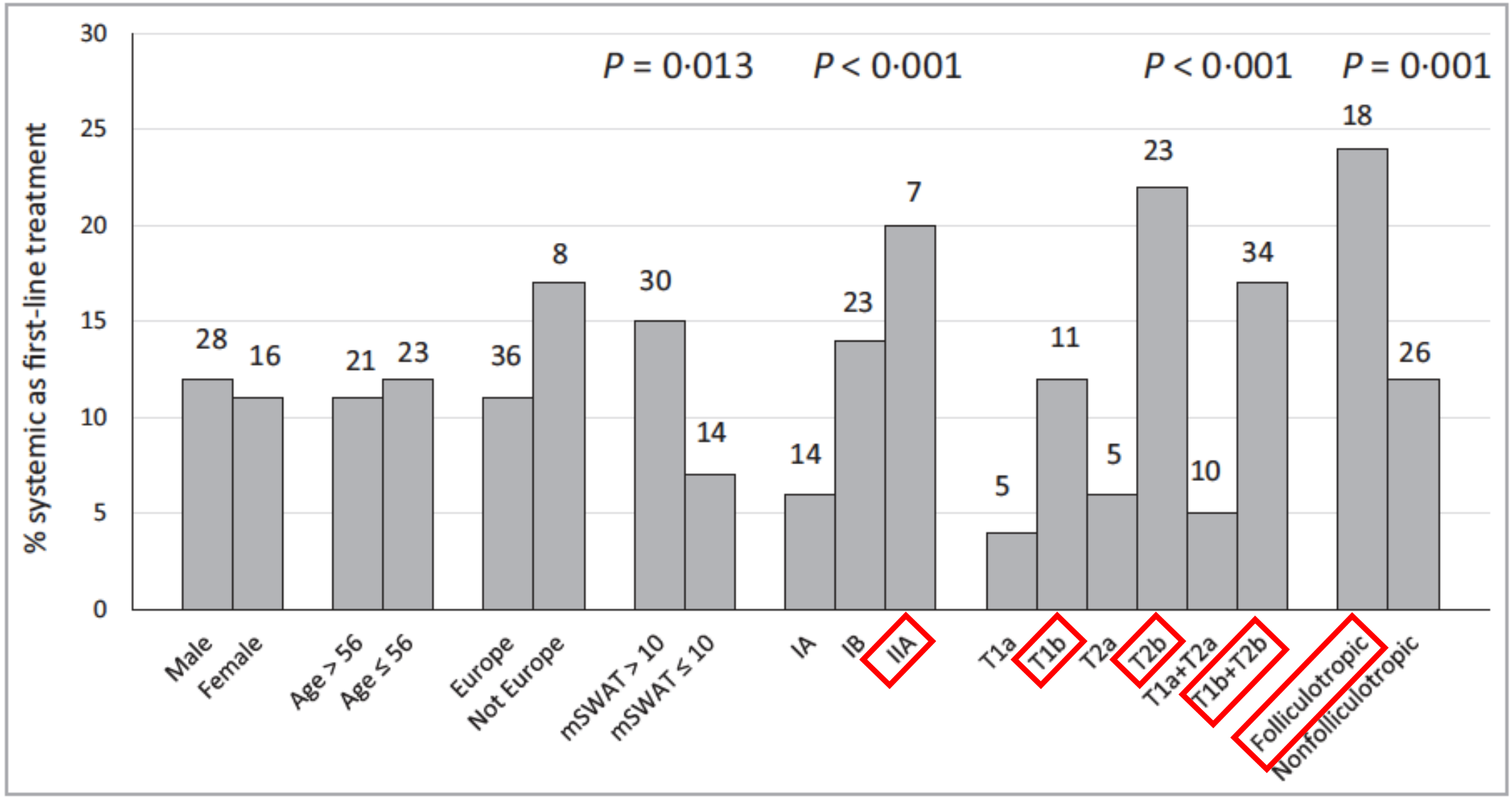


Figure 2 Clinicopathological characteristics associated with first systemic approach. The bars represent the percentages of patients treated with a first-line systemic approach according to the different clinicopathological characteristics. The number at the top of each bar represents the absolute number of patients. P-values of parameters with a statistically significant difference are reported at the top of the graph. mSWAT, modified Severity Weighted Assessment Tool.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 2517–2525, 2017
doi:10.1093/annonc/mdx352
Published online 24 July 2017

ORIGINAL ARTICLE

Global patterns of care in advanced stage mycosis fungoides/Sezary syndrome: a multicenter retrospective follow-up study from the Cutaneous Lymphoma International Consortium

- Studio retrospettivo su 853 pazienti provenienti da 21 diversi centri nel mondo
- L'obiettivo era quello di analizzare la distribuzione dei trattamenti in base alle aree geografiche, lo stadio e l'età in pazienti con CTCL in stadio avanzato

Table 3. Distribution of treatments performed in time (percentage of patients treated with that therapy out of the total no. of patients treated in a given treatment line) in the first 10 treatment lines

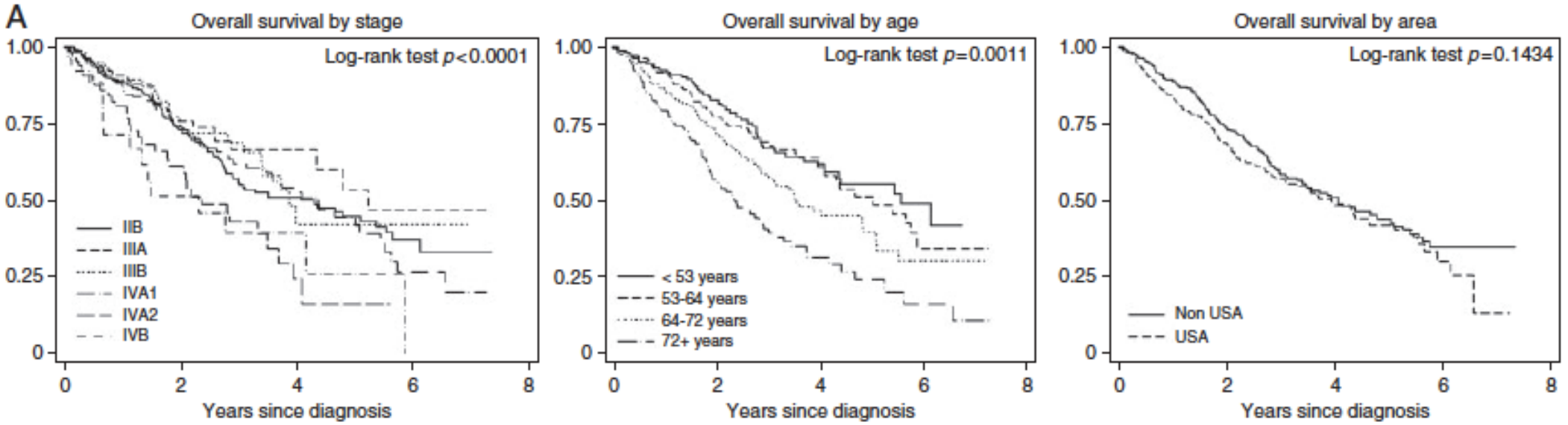
Therapy	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	*P* for trend
ECP (alone or in combination)	18.6	13.3	6.3	5.8	6.4	4.8	2.8	7.7	9.4	5.3	0.952
Bexarotene	11.3	12.8	10.3	7.4	7.4	5.6	4.2	1.9	6.3	10.5	0.001
Phototherapy (alone or in combination)	9.5	5.9	3.5	3.4	3.5	2.4	2.8	1.9		5.3	0.949
Methotrexate	8.8	5.9	7.0	6.8	4.5	9.6	6.9	9.6	6.3	10.5	0.232
Interferon	7.7	7.7	10.8	8.5	8.4	4.8	5.6	1.9	3.1	5.3	0.616
Local RT	7.3	5.7	7.0	5.1	5.0	8.0	6.9	7.7	6.3	5.3	0.442
Gemcitabine	6.2	5.6	6.8	6.1	4.0	8.8	1.4	1.9			0.378
Polychemotherapy	5.3	9.2	9.8	9.8	10.4	10.4	16.7	13.5	9.4	26.3	<0.0001
TSEBT	4.5	7.9	7.0	5.7	9.4	6.4	6.9	9.6	6.3	5.3	0.028
Chlorambucil	3.6	2.5	2.1	2.7	2.0	1.6		1.9			0.067
HDACi	2.9	5.6	5.4	12.5	5.5	8.8	11.1	1.9	9.4		<0.0001
Other Retinoids	2.7	2.7	1.9	1.0			1.4		3.1		0.029
Pegylated Doxorubicin	1.8	4.7	4.4	3.7	10.9	4.8	5.6	5.8	12.5	5.3	<0.0001
Alemtuzumab	1.3	2.9	3.5	3.4	2.0	2.4	5.6	1.9	3.1	15.8	0.006
Interferon plus Bexarotene or Other Retinoids	0.8	0.5	0.7	0.3							0.020
Other Monochemotherapy	0.7	1.7	2.1	2.0	3.0	3.2	5.6	5.8	6.3		<0.0001
Denileukin Diftitox	0.5	0.3	0.7	0.7	1.0		1.4	3.9	6.3		0.008
Brentuximab vedotin	0.4	0.7	4.0	2.4	3.0	5.6	5.6	1.9			<0.0001
Pralatrexate	0.2	0.8	1.4	2.0	1.0	1.6	1.4	5.8	3.1		<0.0001
Topical Nitrogen Mustard (Mechlorethamine)	0.1	0.2	0.5			1.6		1.9			0.001
Bevacizumab					0.5						–
Lenalidomide				0.7	1.5						–
Mogamulizumab		1.2	0.9	2.4	2.5	2.4	2.8	5.8	3.1		<0.0001
Transplantation		1.0	2.3	6.4	6.4	4.8	4.2	5.8	6.3	5.3	<0.0001
Zanolimumab		0.2	0.2	0.3				1.9			0.003

Other retinoids: etretinate, acitretin. Other monochemotherapy: mainly cyclophosphamide, etoposide. First treatment unknown in 5.6% of patients. ECP combos: ECP plus Interferon, ECP plus Bexarotene, ECP plus Other Retinoids, ECP plus IFN plus Bexarotene, ECP plus Methotrexate, ECP plus Phototherapy. Phototherapy combos: Phototherapy plus IFN, Phototherapy plus Other Retinoids, Phototherapy plus Bexarotene, ECP plus Phototherapy, Phototherapy plus IFN plus Bexarotene, Phototherapy plus Other Retinoids.

ECP, extracorporeal photochemotherapy; RT, radiotherapy; TSEBT, total-skin-electron-beam therapy; HDAC, histone deacetylase inhibitors.

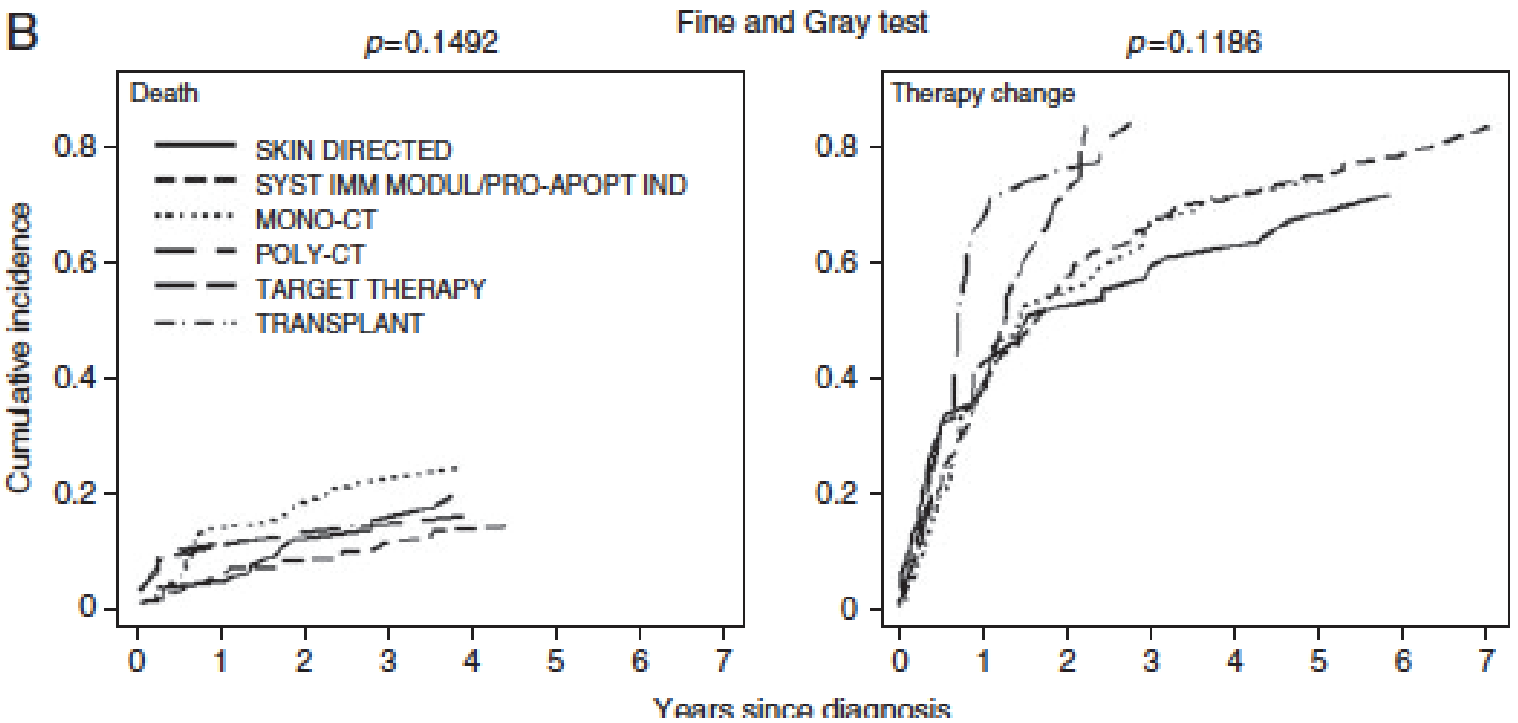
- La prima linea più comunemente utilizzata è stata la fotoferesi, sia da sola(10%) o in combinazione (8,6%), seguita da bexarotene e fototerapia.
- Le chemioterapie più frequentemente utilizzate come trattamento di prima linea sono state la gemcitabina (6,2%) e la polichemioterapia (5,3%).

Overall survival



- La prognosi, indipendentemente dalla sede geografica, è determinata dallo stadio e dall'età.

Overall survival



Sia la monochemioterapia che la polichemioterapia hanno mostrato un'elevata associazione con un maggior rischio di cambio di terapia e una ridotta OS.

Chemotherapy as first treatment is associated with a higher risk of death and thus other therapeutic options should be preferable as first treatment approach.

Obiettivi dello studio

ORIGINAL ARTICLE

DERMATOLOGIC THERAPY WILEY

Continuous low-dose gemcitabine in primary cutaneous T cell lymphoma: A retrospective study

Cosimo Di Raimondo[1,2] | Sara Vaccarini[3] | Andrea Nunzi[3] | Vito Rapisarda[3] | Annagiulia Zizzari[3] | Federico Meconi[3] | Alessandro Monopoli[2] | Maria Grazia Narducci[2] | Enrico Scala[2] | Luca Bianchi[1] | Cristiano Tesei[3] | Maria Cantonetti[3]

Comunemente, nei CTCL la gemcitabina si somministra ad una dose di 1200mg/m² di al giorno 1-8-15 di ciascun ciclo di 28 giorni. Questo schema garantisce la massima efficacia MA con un profilo di tossicità che ne limita l'uso prolungato

- Valutazione **retrospettiva** dell'efficacia di una terapia con Gemcitabina **a un basso dosaggio** in pazienti affetti da micosi fungoide e sindrome di Sézary

- Abbiamo dimostrato che una dose ridotta di gemcitabina (1000 mg una volta ogni 15 giorni) ha portato a un tasso di risposta globale del 59,5% con un miglior profilo di sicurezza nei pazienti con CTCL refrattario in stadio avanzato.

Mecloretamina

- La mecloretamina è un agente alchilante che agisce sulle cellule in rapida moltiplicazione ed in particolare sui linfociti.
- In uso per via sistemica già dal 1947 (Goodman e Gilman) per la cura dei Linfomi Cutanei a Cellule T (CTCL), solo nei primi anni ’60, Richardson e Haserick la usarono topicamente su un paziente con MF in fase avanzata con brillanti risultati.
- Sono seguite sperimentazioni in tutto il mondo e questo farmaco è diventato una terapia consolidata per la MF in fase precoce.

Management of Mycosis Fungoides with Topical Chlormethine/ Mechlorethamine Gel: A Columbia University Cutaneous Lymphoma Center Experience

Tiffany J. GARCIA-SALEEM[1], Connor J. STONESIFER[2], Alexandra E. KHALEEL[2] and Larisa J. GESKIN[1]
[1]Department of Dermatology, Columbia University, and [2]Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA

Use of chlormethine 0.04% gel for mycosis fungoides after treatment with topical chlormethine 0.02% gel: A phase 2 extension study

Article

Real-life experience with chlormethine gel for early-stage mycosis fungoides with emphasis on types and management of cutaneous side-effects#

Hadas Prag Naveh, Iris Amitay-Laish, Omri Zidan, Yael A. Leshem, Shany Sherman, Yehonatan Noyman,

A Little Experience Goes a Long Way: Chlormethine/Mechlorethamine Treatment Duration as a Function of Clinician-Level Patient Volume for Mycosis Fungoides Cutaneous T-Cell Lymphoma (MF-CTCL)—A Retrospective Cohort Study

Christiane Querfeld[1*], Theresa Pacheco[2], Bradley Haverkos[3], Gary Binder[4], James Angello[4] and Brian Poligone[5]

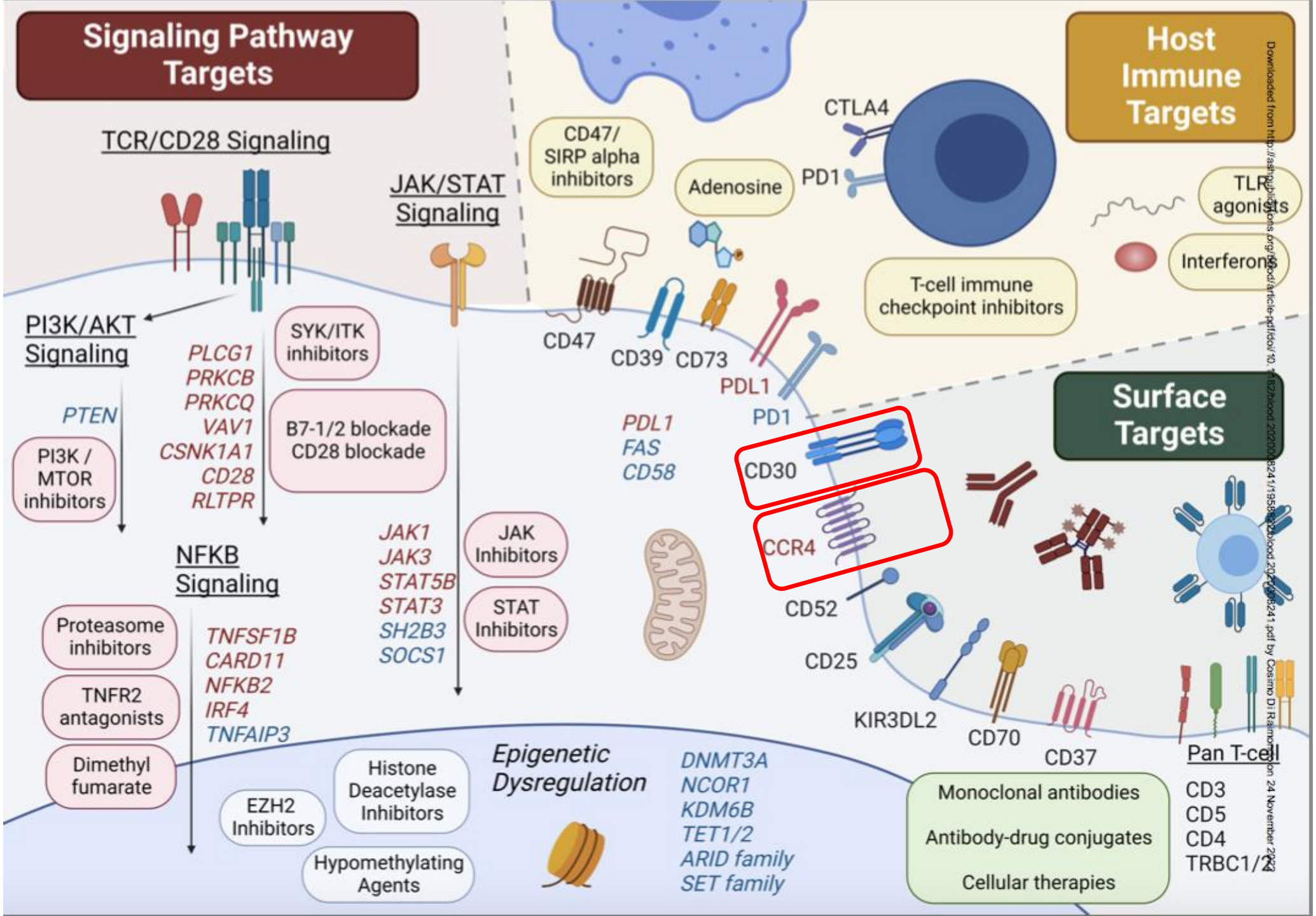
Real-world experience with mechlorethamine gel in patients with mycosis fungoides-cutaneous lymphoma: Preliminary findings from a prospective observational study

Optimizing Care and Compliance for the Treatment of Mycosis Fungoides Cutaneous T-Cell Lymphoma With Mechlorethamine Gel

Allister Benjamin Chase Kristen Markel Marianne C. Tawa Lymphoma

Integrating Novel Agents into the Treatment of Advanced Mycosis Fungoides and Sézary Syndrome

Michael S Khodadoust , Eric Mou , Youn H Kim



MAVORIC: Graphical representation of study design

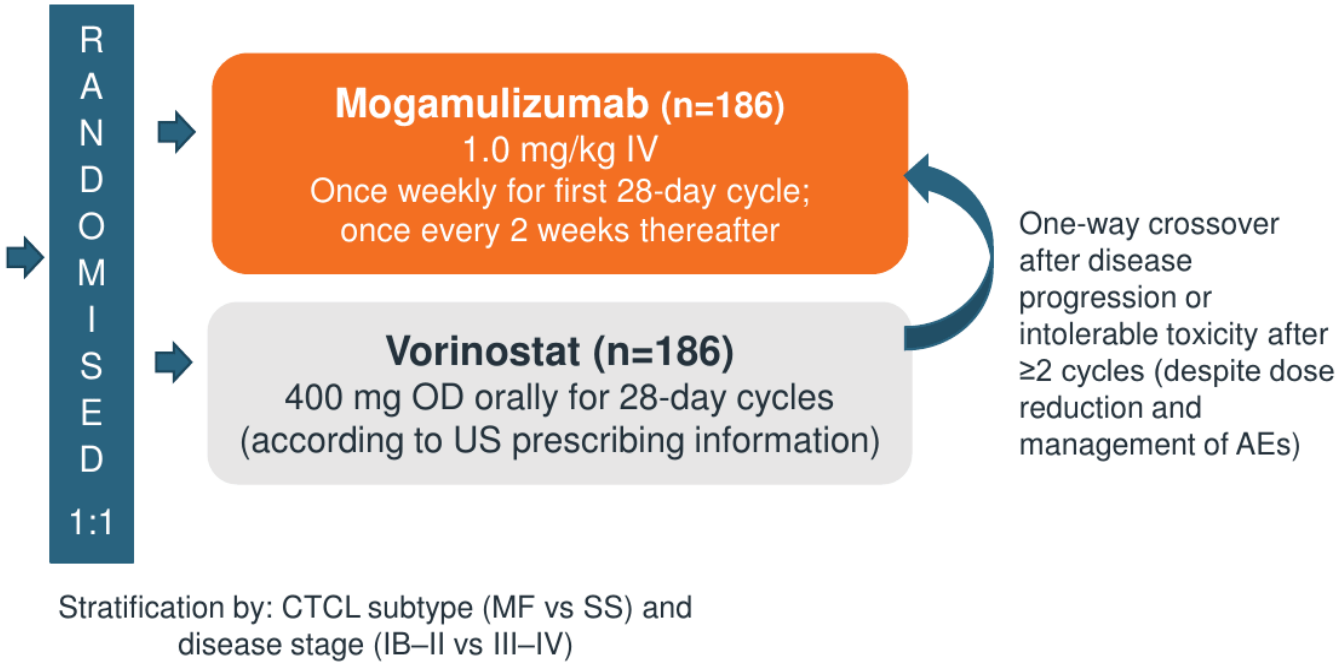
Patient population (N=372)

Key inclusion criteria

- Adults with Stage IB–IVB[a], histologically confirmed MF or SS
- At least one prior course systemic treatment
- ECOG PS ≤1

Key exclusion criteria

- Large cell transformation
- Previous mogamulizumab or vorinostat[b] treatment
- Previous CTCL skin-directed therapy within 2 weeks or systemic therapy within 4 weeks of randomisation; previous allogeneic transplant
- CNS metastasis, active autoimmune disease, clinically significant uncontrolled intercurrent illness



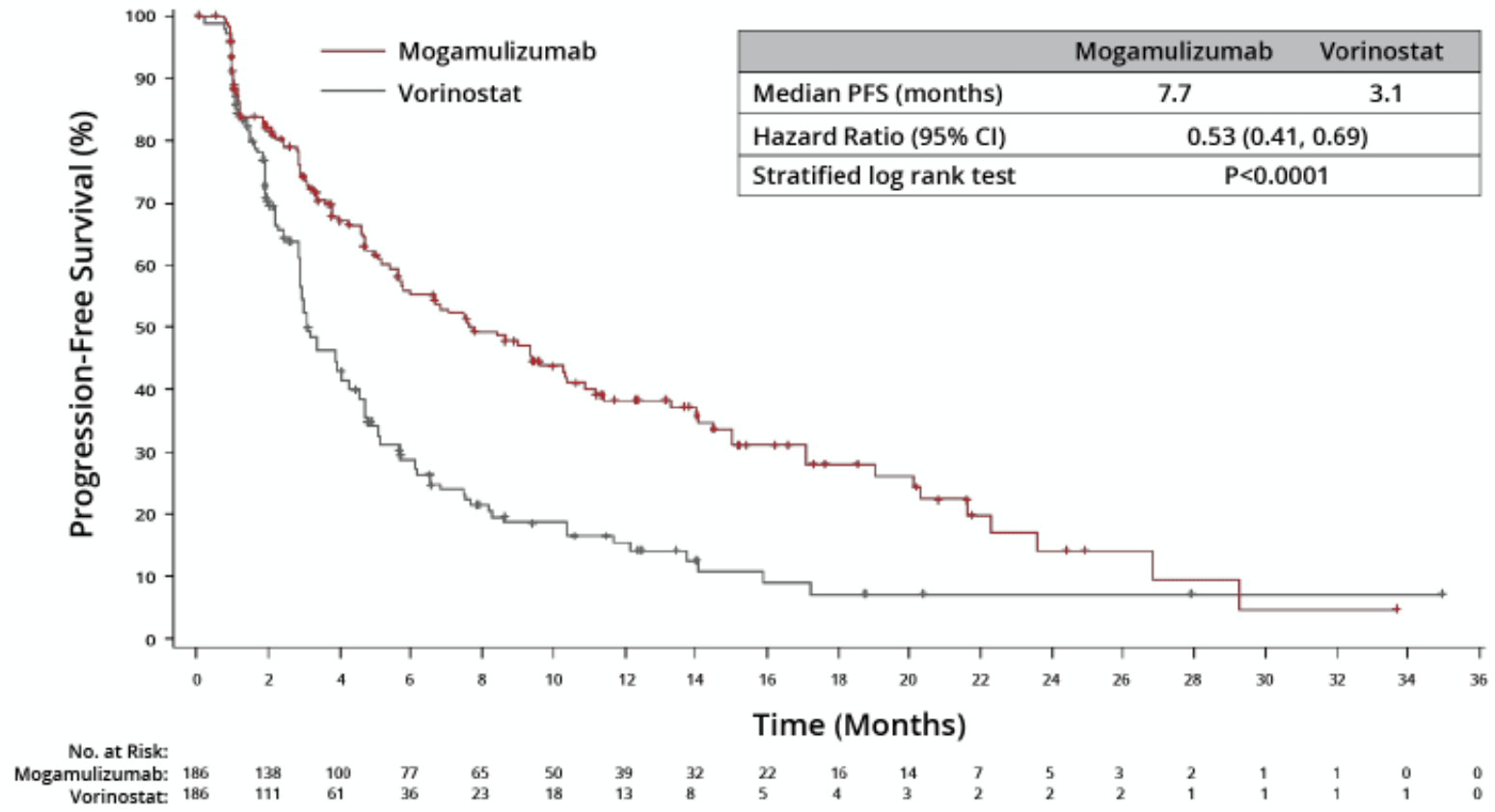
Abbreviations: AE, adverse event; CTCL, cutaneous T-cell lymphoma; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance score; IV, intravenous; MF, mycosis fungoides; OD, once daily; SS, Sézary syndrome.

- CCR4 expression was not a requirement for participation.[1]
- Patients could continue treatment until disease progression, drug intolerance, or unacceptable toxicity.[1]

1. Kim YH, et al. *Lancet Oncol.* 2018;19(9):1192-1204.

Primary endpoint (PFS)

Investigator-assessed PFS[1]



	Mogamulizumab	Vorinostat
Median PFS (months)	7.7	3.1
Hazard Ratio (95% CI)	0.53 (0.41, 0.69)	
Stratified log rank test	P<0.0001	

1. Kim YH, et al. *Lancet Oncol.* 2018;19(9):1192-1204.

Compartmental responses

Compartmental responses[1]	Mogamulizumab	Vorinostat
Skin ORR (CR + PR), n/N[a] (%) CR, n (%)	78/186 (42) 8 (4)	29/186 (16) 1 (1)
Blood ORR (CR + PR), n/N[a] (%) CR, n (%)	83/122 (68) 54 (44)	23/123 (19) 5 (4)
Lymph nodes ORR (CR + PR), n/N[a] (%) CR, n (%)	21/124 (17) 10 (8)	5/122 (4) 2 (2)
Viscera ORR (CR + PR), n/N[a] (%) CR, n (%)	0/3 (0) 0	0/3 (0) 0

[a] Denominator includes patients with compartmental disease at baseline.
Abbreviations: CR, complete response; ORR, overall response rate; PR, partial response. Table elaborated from reference 1.

Time to Compartmental Response (mogamulizumab)[2]	
Blood	1.1 months
Skin	3.0 months
Lymph nodes	3.3 months

Table elaborated from textual data from Ref 2

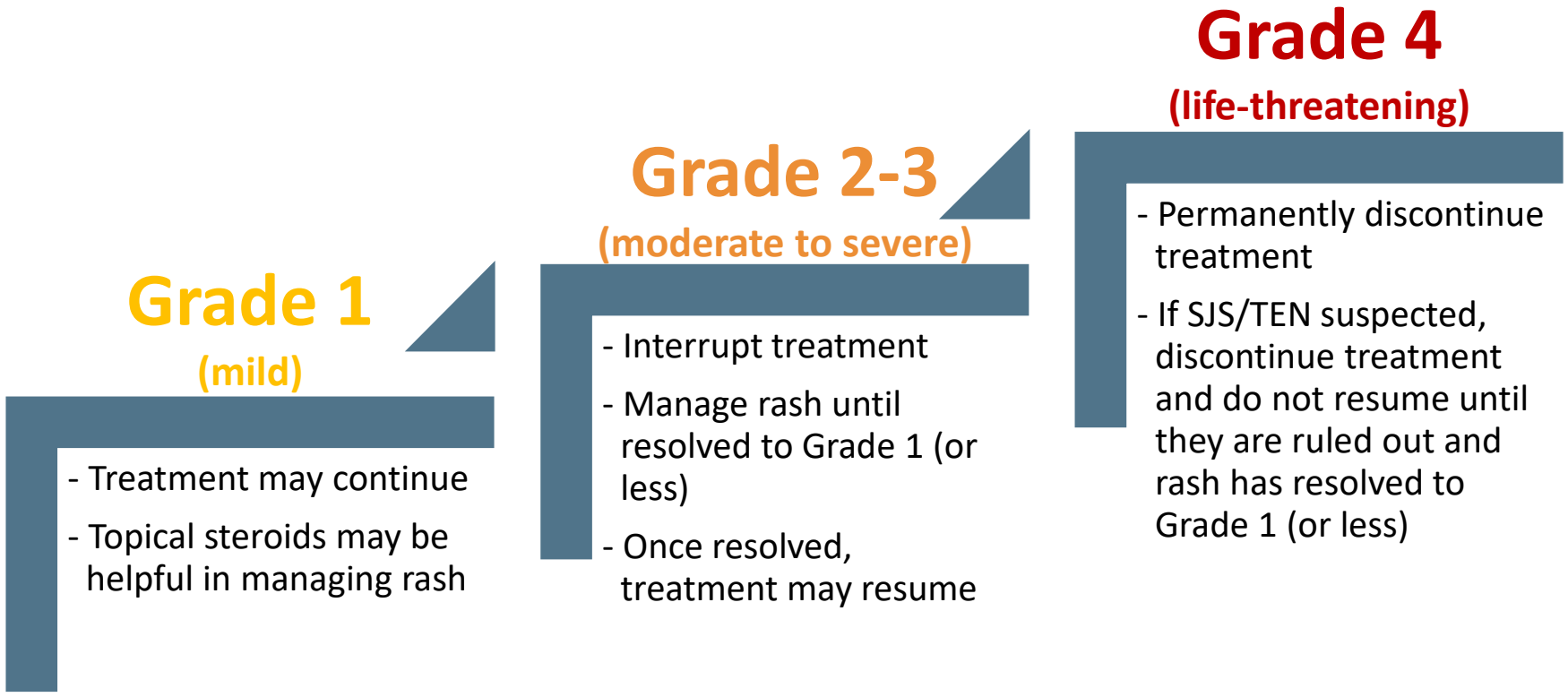
Compartmental Duration of Response (mogamulizumab)[2]	
Blood	25.5 months
Skin	20.6 months
Lymph nodes	15.5 months

Table elaborated from textual data from Ref 2

1. Kim YH, et al. *Lancet Oncol.* 2018;19(9):1192-1204; **2.** Cowan R, et al. JEADV 2021, 35, 2225-2238

Management of MAR: Dose Modifications per SmPC

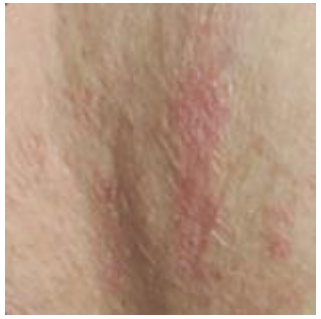
- MAR may be clinically indistinguishable from disease progression; skin biopsy with clinicopathological correlation may help to distinguish between the two



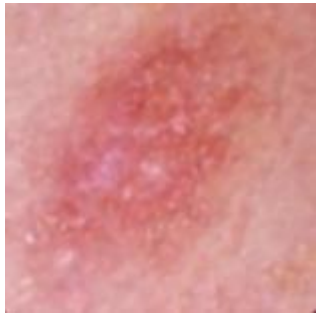
1. POTELIGEO® (mogamulizumab) Summary of Product Characteristics (SmPC). Published: 28-Jan-2019. Updated: 10-Jan-2020. Accessed: 03-Mar-2021.

Identifying Skin Rash from Real-World Experience

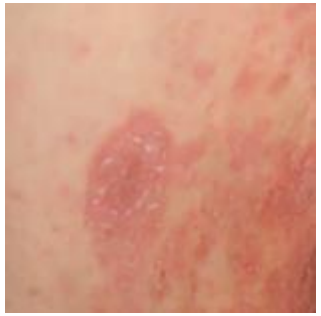
- Additional awareness and education may be critical to accurately distinguish MAR from disease and to minimise unnecessary treatment interruption or discontinuation[1]
- **MAR can mimic CTCL lesions and may be mistaken for disease progression,[2-5] which can lead to premature discontinuation of mogamulizumab treatment**



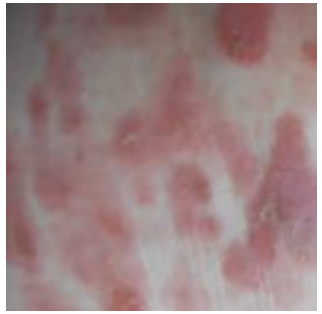
Drug eruption[a]



MF patch[b]



Drug eruption[a]



MF plaque[c]

[a]Image used with permission from *JAMA Dermatology* [b]Image used with permission from *Seminars in Radiation Oncology* [c]Image used with permission from *Dove Medical Press*

- **Monitor patients for rash throughout the treatment course. Skin biopsies are recommended to determine whether a rash is drug- or disease-related[2]**
- While awaiting results of biopsy, dermatologic toxicity should be treated as a rash

1. Wang JY, et al. Am J Surg Pathol. 2020;44(12):1666-1676.
2. Chen L, et al. JAMA Dermatol. 2019;155(8):968-971.
3. Poligone B, et al. Br J Dermatol. 2015;173:1081-1083.
4. Smith BD, Wilson LD. Cutaneous lymphomas. Semin Radiat Oncol. 2007;17(3):158-68.
5. Denis D, et al. Cancer Manag Res. 2019;11:2241-2251.

Results: Mogamulizumab-associated rashes correlate with mogamulizumab efficacy and increased survival in CTCL

Patients' and rashes' characteristics

Table 1. Baseline characteristics of the patients

32%

	All Patients (n=44)	Patients with RAM (n=14)	Patients without RAM (n=30)	p
Age (years)	65.8 [33-87]	67.8 [33-83]	65 [33-87]	0.33
Sex				
Male	23 (52%)	6 (43%)	17 (57%)	
Female	21 (48%)	8 (57%)	13 (43%)	0.52
ECOG performance status				
0	28 (64%)	12 (86%)	16 (53%)	
1	10 (23%)	0 (0%)	10 (33%)	
2	2 (4%)	0 (0%)	2 (7%)	
3	1 (2%)	0 (0%)	1 (3%)	
NA	3 (7%)	2 (14%)	1 (3%)	0.06
Disease type				
Mycosis fungoides	9 (20%)	0 (0%)	9 (30%)	
Sézary syndrome	35 (80%)	14 (100%)	21 (70%)	**0.04**
mSWAT	85 [0-200]	74 [13.5-174]	90 [0-200]	0.52
LDH (UI/L)	372 [181-603]	384.5 [253-589]	365 [181-603]	0.50
Number of previous treatment lines	5.2 [1-11]	4 [1-10]	5.8 [1-11]	0.19
Number of previous systemic treatment lines	4 [1-9]	3 [1-6]	4 [1-9]	**0.04**
Time from diagnosis (days)	1393 [142-41632]	762 [238-41423]	1904 [142-41632]	**0.02**
Latest treatment before mogamulizumab				
Bexarotene	15 (34%)	7 (50%)	8 (27%)	
Interferon	2 (4%)	0 (0%)	2 (7%)	
Methotrexate	1 (2%)	1 (7%)	0 (0%)	
HDAC inhibitor	11 (25%)	3 (21%)	8 (27%)	
Conventional chemotherapy	11 (25%)	3 (21%)	8 (27%)	
Brentuximab vedotin	2 (4%)	0 (0%)	2 (7%)	
Lacutamab (anti-KIR3DL2)	2 (4%)	0 (0%)	2 (7%)	0.35

Abbreviations: HDAC: histone desacetylase; LDH: lactate dehydrogenase; mSWAT: modified severity weighted assessment tool; NA: not available; RAM: rash associated with mogamulizumab. Data are given as number (percentage) among patients, or as mean (range).
Table 1: Baseline characteristics of the 44 patients

Table 2. Clinical and histological characteristics of mogamulizumab-associated rashes

	Rash associated with mogamulizumab
Number of rash episodes/patient (n=14 patients)	
1	10 (71%)
2	4 (29%)
Mean time to first skin rash, days (n=14 patients)	100 [15-336]
Rash CTCAE grade (n=18 rashes)	
1	4 (22%)
2	11 (61%)
3	2 (11%)
NA	1 (6%)
Clinical presentation (n=18 rashes)	
Papules or plaques	13 (72%)
Macules without papules or plaques	5 (28%)
Facial edema	5 (28%)
Mucosal involvement	3 (17%)
Erythroderma	2 (11%)
Scaling of the scalp	2 (11%)
Pustules	1 (6%)
Histopathological patterns (n=18 rashes)	
Granulomatous	10 (56%)
Lichenoid	9 (50%)
Psoriasiform/spongiotic	13 (72%)
Immunohistochemical analysis (n=18 rashes)	
Intraepidermic CD8+ T-cells	**13 (72%)**
CD4+/CD8+ T-cell ratio	**3.5 [0.25-10]**
PD1+ cells (% lymphoid cells)	**28.9 [0-80]**
Associated findings (n=14 patients)	
Pruritus	6 (43%)
Fever	2 (14%)
Elevated serum creatinin	1 (7%)
Auto-immune disease (vitiligo, alopecia areata, auto-immune hepatitis, auto-immune thyroiditis)	5 (36%)
Management (n=18 rashes)	
Hospital admission	1 (6%)
Class III topical steroids	12 (67%)
Class IV topical steroids	4 (22%)
Antihistamines	2 (11%)
No specific treatment	1 (6%)
Discontinuation of mogamulizumab (n=18 rashes)	
No	8 (44%)
Yes, temporarily	6 (33%)
Yes, permanently	4 (22%)
Recurrence after rechallenge (n=6 rechallenges)	4 (66%)

NA: not available; HTS-TCRb: high throughput sequencing of the T-cell receptor gene beta. Data are given as number (percentage) among patients, or as mean (range).

de Masson A, et al. *Blood*. 2022 Mar 24;139(12):1820-1832

Study design

131 adult patients (CD30-expressing MF or C-ALCL, ≥1 prior therapy + ECOG PS 0–2)

1:1

Brentuximab vedotin 1.8 mg/kg Q3W IV (n = 66)

Physician's choice (n = 62)
Methotrexate 5–50 mg Q1W orally
Or
Bexarotene 300 mg/m2 QD orally

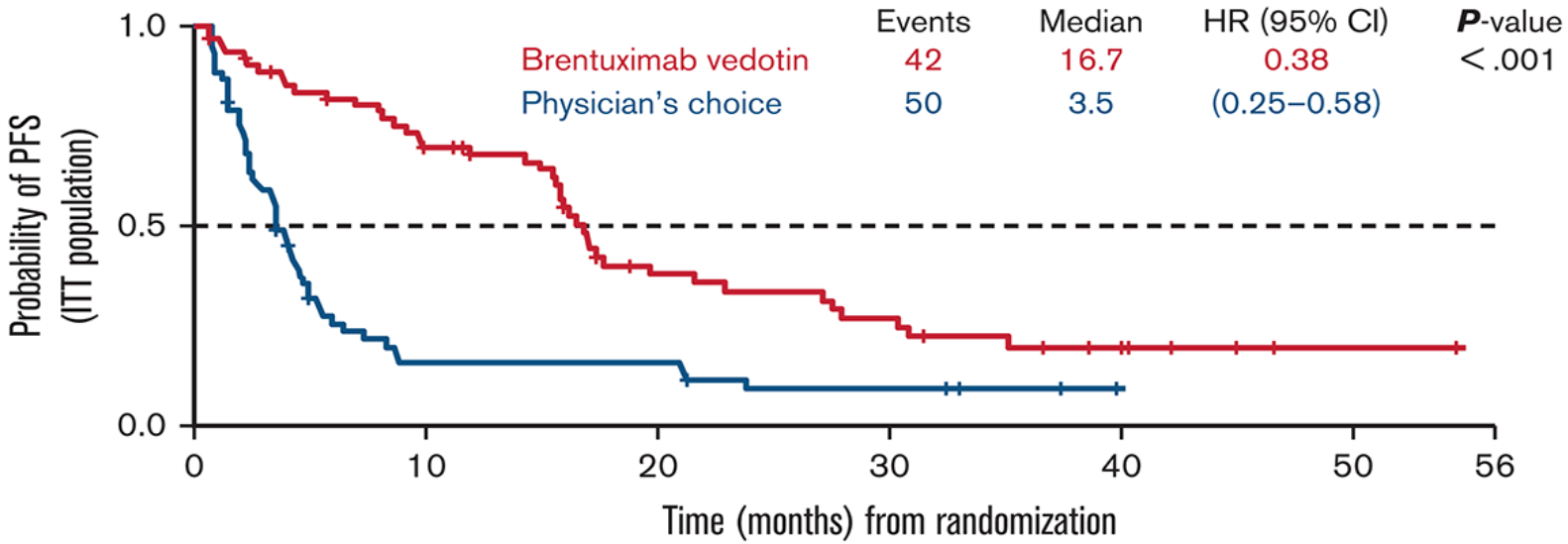
Max 16 x 21-day cycles or until PD or unacceptable toxicity

Endpoints: brentuximab vedotin vs physician's choice

ORR4
54.7% vs 12.5%
(P < .001)

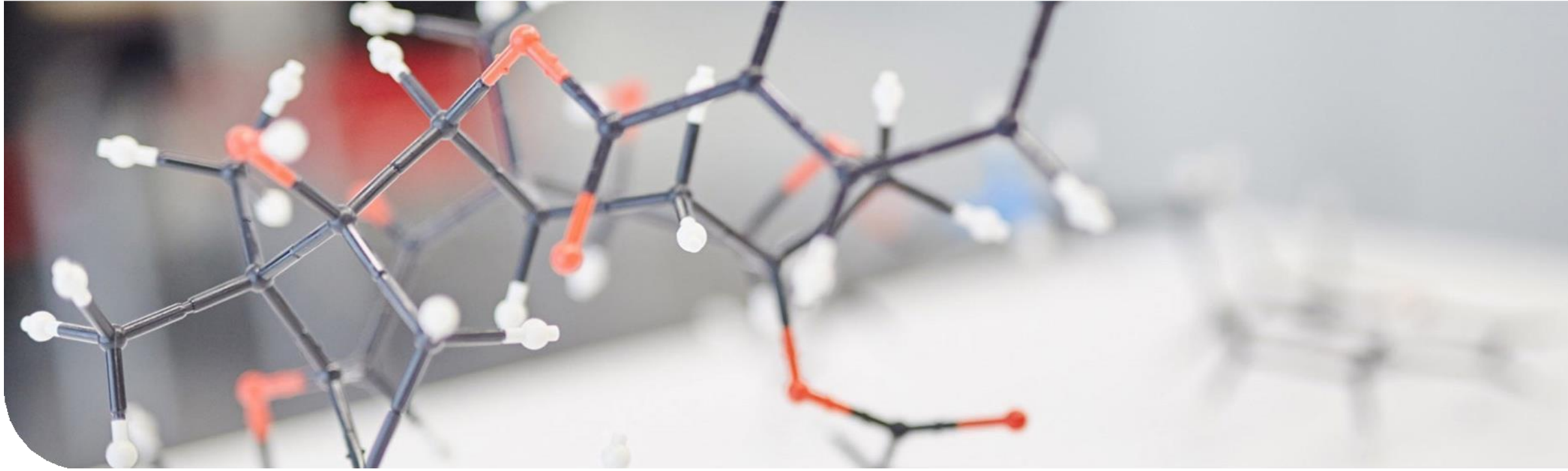
TTNT
14.2 vs 5.6 months
(P = < .001)

Resolution or improvement of PN
86% vs 50%



- **Peripheral neuropathy** in 67% of patients

	Brentuximab vedotin (n = 44)		Physician's choice (n = 4)	
Data cutoff	**31 May 2016**	**28 September 2018**	**31 May 2016**	**28 September 2018**
Patients with resolution or improvement of PN events, n (%)	36 (82)	38 (86)	1 (25)	2 (50)
Patients with resolution of all PN events, n (%)	22 (50)	26 (59)	1 (25)	2 (50)
Median time to resolution, wk	27.0	33.0	2.0	10.5
Patients with improvement in PN events by ≥1 grade, n (%)	14 (32)	12 (27)	0	0
Median time to improvement, wk	8.0	15.0	—	—
Patients with ongoing PN events, n (%)	22 (50)	18 (41)	3 (75)	2 (50)
Maximum severity grade 1, n (%)	17 (39)	15 (34)	1 (25)	1 (25)
Maximum severity grade 2, n (%)	5 (11)	3 (7)	2 (50)	1 (25)



BV or other SoC in CTCL: Real World Data from US Centers (#2265)

Barta S. et al. Real-World Treatment Patterns and clinical Outcomes with Brentuximab Vedotin or Other Standard Therapies in Patients with Previously Treated Cutaneous T-Cell Lymphoma (CTCL): A Retrospective Chart Review Study in The United States

Abstract #2265

Presented at the 64th American Society of Hematology Annual Meeting 2022, December 10–13, 2022, New Orleans, LA, USA.

Methods:

Study Design

- A retrospective physician panel-based chart review was conducted from October 2021 through January 2022

Patient Eligibility

- Adults with pcALCL or MF
- Previously treated with ≥1 systemic therapy and subsequently treated with BV or OST from November 2017 through March 2021
- ≥6 months of follow-up after initiating 2L systemic therapy except in the event of death

Outcomes

- Treatment patterns were assessed from CTCL diagnosis to the end of the observation period
- Clinical outcomes for second-line systemic therapy and HRU were assessed during the observatio period; treatment response was calculated via the Global Response Score[1]
- Median times-to-event were computed using Kaplan-Meier (KM) methods
- Since median times-to-event were not reached (NR) in both cohorts for multiple outcomes, restricted mean survival time (RMST), a measure of the average event-free survival time during a specific period estimated by the area under the KM curve, at 1 and 2 years was estimated

Barta S. et al. Abstract #2265
Presented at the 64th American Society of Hematology Annual Meeting 2022, December 10–13, 2022, New Orleans, LA, USA.

Efficacy: Real World Response Rates

	Real-World Response Rates, % (95% CI)	
	BV, n=134[a]	OST, n=164[b]
rwORR	82.1 (74.5-88.2)	66.5 (58.7-73.6)
Complete response	38.8 (30.5-47.6)	27.4 (20.8-34.9)
Partial response	43.3 (34.8-52.1)	39.0 (31.5-46.9)
Stable disease	13.4 (8.2-20.4)	21.3 (15.3-28.4)
Progressive disease	4.5 (1.7-9.5)	12.2 (7.6-18.2)
rwORR4[c]	42.5 (34.0-51.4)	25.0 (18.6-32.3)

[a]5 patients were excluded from analysis of clinical outcomes due to being treated with BV as third line or later. [b]The OST cohort consisted of patients who did not receive BV as a second or later line of systemic therapy. Systemic therapies included alemtuzumab, bendamustine, bexarotene, bortezomib, chlorambucil, cisplatin, cyclophosphamide, cytarabine, doxorubicin, etoposide, fludarabine, gemcitabine, interferon alpha, interferon gamma, lenalidomide, methotrexate, mogamulizumab, pembrolizumab, pentostatin, extracorporeal photopheresis, pralatrexate, prednisone, romidepsin, vinblastine, vincristine, vorinostat, and 8-methoxypsoralen. Systemic therapies with or without skin-directed therapies were included. Skin-directed therapies included topical carmustine, topical corticosteroids, topical imiquimod, topical mechlorethamine, topical retinoids (eg, bexarotene, tazarotene), phototherapy (UVB or PUVA), and radiation therapy. [c]Defined as the proportion of patients achieving a global response (complete or partial response) lasting at least 4 months. Abbreviations: 2L, second-line; BV, brentuximab vedotin; CTCL, cutaneous T-cell lymphoma; OST, other standard therapies; rwORR, real-world objective response rate; rwORR4, real-world objective response rate lasting at least 4 months

Barta S. et al. Abstract #2265
Presented at the 64th American Society of Hematology Annual Meeting 2022, December 10–13, 2022, New Orleans, LA, USA.

Conclusions

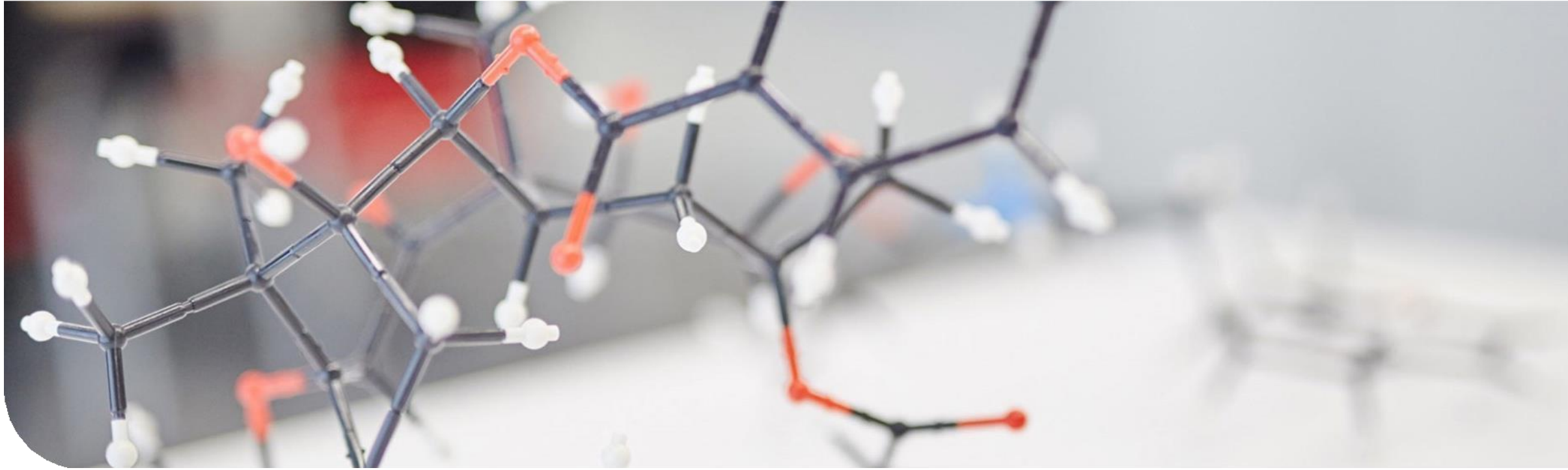
Limitations

- Results should be interpreted with caution due to differences in patient clinical profiles across the two treatment cohorts and the treatment heterogeneity of the OST cohort
- The study is limited by short duration of follow-up
- Participation in the study was subject to selection bias as panel members may differ from physicians who are not members or decline to participate; in addition, the majority of participating physicians represented community-based settings and results may not be generalizable to all patients and practice settings
- Although physicians may have selected specific patients for inclusion; selection bias was mitigated by implementing a randomization scheme

Conclusions

- This retrospective, physician panel-based chart review study addresses the gap in the literature by assessing patient characteristics, treatment patterns, clinical outcomes, and HRU outcomes among patients with CTCL who received 2L BV or OST in real-world clinical practice
- Real-world outcomes with BV in patients with CTCL who received ≥1 prior systemic therapy were consistent with results from ALCANZA, demonstrating favorable clinical outcomes with BV

Barta s. et al. Abstract #2265
Presented at the 64th American Society of Hematology Annual Meeting 2022, December 10–13, 2022, New Orleans, LA, USA.



BV + Romidepsin in r/r CTCL: Phase 1 Study (#2911)

Barta S. et al A Phase I Trial Assessing the Feasibility of Romidepsin Combined with Brentuximab Vedotin for patients Requiring Systemic Therapy for Cutaneous T-Cell Lymphoma

Abstract #2911

Presented at the 64th American Society of Hematology Annual Meeting 2022, December 10–13, 2022, New Orleans, LA, USA.

Methods: Patient eligibility and objectives

Patient eligibility

- Patients aged ≥18 years with stage ≥IB CTCL, good organ function, ECOG PS ≤2, Grade <2 neuropathy, who required systemic treatment
- Any degree of CD30 expression was allowed
- Prior use of HDAC inhibitors and/or BV were permitted

Primary objective:

- To determine the MTD of romidepsin + BV in patients with CTCL

Secondary objectives included:

- Overall safety and tolerability
- Response as measured by Global Response Score[1]
- Duration of response

Exploratory objectives included:

- Association of CD30 expression and treatment response
- Changes in CD30 expression after one dose of romidepsin

BV, brentuximab vedotin; CD30, cluster of differentiation 30; CTCL, cutaneous T-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HDAC, histone deacetylase; MTD, maximum tolerated dose

1. Olsen EA et al. J Clin Oncol 2011;29:2598–607

Barta S, et al. Poster Presentation 2911. Presented at the 64th American Society of Hematology Annual Meeting, December 10–13, 2022

Results: Efficacy

- Response assessment at data cut-off* was available for 13 of 15 patients

The ORR by GRS was **69%** (9/13; n=1 CR)

Both patients with prior **HDACi exposure**, and 2 of 3 with **prior BV exposure**, responded to treatment

RESPONSE CATEGORY	OVERALL RESPONSE	STABLE DISEASE	PARTIAL RESPONSE	COMPLETE RESPONSE
Global response	9/13 (69%)	4 (31%)	8 (62%)	1 (7%)
Skin	10/13 (77%)	3 (23%)	8 (62%)	2 (15%)
Blood	6/6 (100%)	0 (0%)	2 (33%)	4 (67%)
Lymph nodes/ Viscera	5/7 (71%)	2 (29%)	2 (29%)	3 (42%)

*Data cut-off: Oct 10, 2022

BV, brentuximab vedotin; CR, complete response; GRS, global response score; HDACi, histone deacetylase inhibitor; ORR, overall response rate

Barta S, et al. Poster Presentation 2911. Presented at the 64th American Society of Hematology Annual Meeting, December 10–13, 2022

Authors' conclusions

- In this Phase 1 study, the combination of romidepsin and BV was assessed for the treatment of patients with advanced CTCL
- The maximum tolerated dose was identified as:
  - Romidepsin at 14 mg/m^2 on Days 1 and 15
  - BV at 1.2 mg/kg (maximum 120 mg) on Days 1 and 15

  } Given every 28 days for up to 16 cycles
- The regimen was well tolerated and efficacious in MF/SS, including heavily pretreated participants with advanced disease and prior exposure to HDACi and BV
- Responses occurred in every disease compartment
- Correlative studies, including analysis of changes in CD30 expression after one dose of romidepsin, and association of response with CD30 expression, are pending

BV, brentuximab vedotin; CD30, cluster of differentiation 30; CTCL, cutaneous T-cell lymphoma; HDACi, histone deacetylase inhibitor; MF/SS, mycosis fungoides/Sézary syndrome

Barta S, et al. Poster Presentation 2911. Presented at the 64th American Society of Hematology Annual Meeting, December 10–13, 2022

Open Questions

- Maggiori studi per le fasi precoci
- Terapie di associazione
- Team multidisciplinare

GRAZIE!!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