3rd Cuneo City ImmunoTherapy Conference (CCITC)

Immunotherapy in Hematological Malignancies 2023

CUNEO
May 18-20, 2023
Spazio incontri Fondazione CRC

Organized by Prof. Massimo Massaia, SC Ematologia AO S.Croce e Carle, Cuneo, Italy
and Centro Interdipartimentale di Ricerca in Biologia Molecolare (CIRBM), Torino, Italy

CCR4/CD30: mogamulizumab/brentuximab in CTCL and beyond

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Dermatologic Clinic, Dept Medical Sciences,
University of Turin Medical School

DICHIARAZIONE

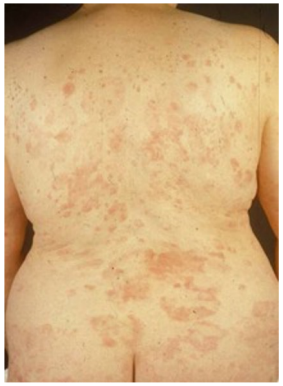
Relatore: PIETRO QUAGLINO

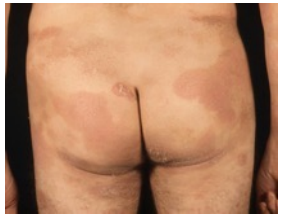
Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

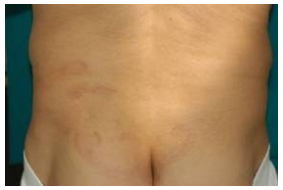
- Posizione di dipendente in aziende con interessi commerciali in campo sanitario (**NIENTE DA DICHIARARE**)
- Consulenza ad aziende con interessi commerciali in campo sanitario (**NIENTE DA DICHIARARE**)
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(TAKEDA, KYOWA-KIRIN, THERAKOS)**
- Partecipazione ad Advisory Board **(TAKEDA, KIOWA-KIRIN, THEAKOS, 4SC, CELLGENE, ROCHE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario (**NIENTE DA DICHIARARE**)
- Altro

PRESENTATION SUMMARY

1. PRINCIPLES OF THERAPY IN MYCOSIS FUNGOIDES/SEZARY SYNDROME



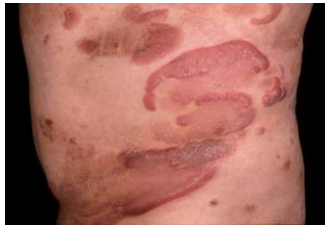


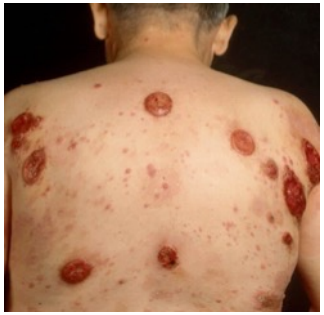


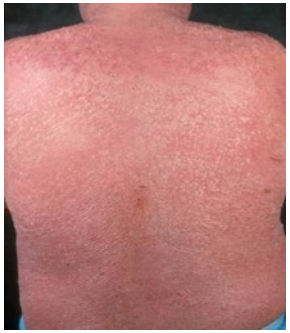
MYCOSIS FUNGOIDES

EARLY vs ADVANCED PHASE DISEASE

	EARLY	ADVANCED
% patients	70%	30%
Stage	IA – IB -IIA	IIB-III-IV
Lesion morphology	Patch plaque	Tumour erythroderma
Extracutaneous involvement	Extremely rare	Significant
Quality of life	Impaired	Severely impaired
Prognosis	Very good	Poor
Therapy	SDT	Systemic + SDT Chemo / HSCT

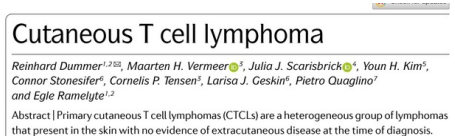






Images provided with the courtesy of Prof Quaglino and patient consent

Nat Rev Dis Primers
. 2021 Aug 26;7(1):61.
doi: 10.1038/s41572-021-00296-


Cutaneous T cell lymphoma

Reinhard Dummer[1,2✉], Maarten H. Vermeer[3], Julia J. Scarisbrick[4], Youn H. Kim[5], Connor Stonesifer[6], Cornelis P. Tensen[3], Larisa J. Geskin[6], Pietro Quaglino[7] and Egle Ramelyte[1,2]

Abstract | Primary cutaneous T cell lymphomas (CTCLs) are a heterogeneous group of lymphomas that present in the skin with no evidence of extracutaneous disease at the time of diagnosis.

MF/SS THERAPY AT A GLANCE: FIRST LINE

European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2017.

F. Trautinger, J. Eder, C. Assaf, M. Bagot, A. Cozzio, R. Dummer, R. Gniadecki, C.D. Klemke, P.L. Ortiz-Romero, E. Papadavid, N. Pimpinelli, P Quaglino, A. Ranki, J. Scarisbrick, R. Stadler, L. Väkevä, M.H. Vermeer, S. Whittaker, R. Willemze, R. Knobler

European Journal of Cancer (2017) 77: pp57-74

EORTC
European Organisation for Research and Treatment of Cancer

	Wait & see	Topical steroids	Photo therapy	Local RT	CHL gel	TSET	Interferon	Bexarotene	Mono-CT	MTX	PoliCT	ECP
IA												
IB												
IIA												
IIB												
III												
SS												
IVA - IVB												

… MULTIPLE FIRST LINE THERAPIES..

MF/SS THERAPY AT A GLANCE: SECOND LINE

European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2017.

F. Trautinger, J. Eder, C. Assaf, M. Bagot, A. Cozzio, R. Dummer, R. Gniadecki, C.D. Klemke, P.L. Ortiz-Romero, E. Papadavid, N. Pimpinelli, P Quaglino, A. Ranki, J. Scarisbrick, R. Stadler, L. Väkevä, M.H. Vermeer, S. Whittaker, R. Willemze, R. Knobler

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	Topical steroids	Photo therapy	Local RT	TSET	Interferon	Bexarotene	Mono-CT	MTX	PoliCT	ECP	HSCT
IA											
IB											
IIA											
IIB											
III											
SS											
IVA - IVB											

ESMO

CLINICAL PRACTICE GUIDELINES

Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

R. Willemze[1], E. Hodak[2], P. L. Zinzani[3], L. Specht[4] & M. Ladetto[5], on behalf of the ESMO Guidelines Committee*

[1]Department of Dermatology, Leiden University Medical Centre, Leiden, The Netherlands; [2]Department of Dermatology, Nahn Medical Centre, Belinson Hospital, Petach Tikva, Israel; [3]Institute of Hematology and Medical Oncology, University of Bologna, Bologna, Italy; [4]Department of Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [5]Divisione di Ematologia, Azienda Ospedaliera Santi Antonio e Biagio e Cesare Arrigo, Alessandria, Italy

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 6, 6900 Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee: December 2006, last update: January 2018. This publication supersedes the previously published version—Ann Oncol 2015; 26 (Suppl. 4): vi149–vi154.

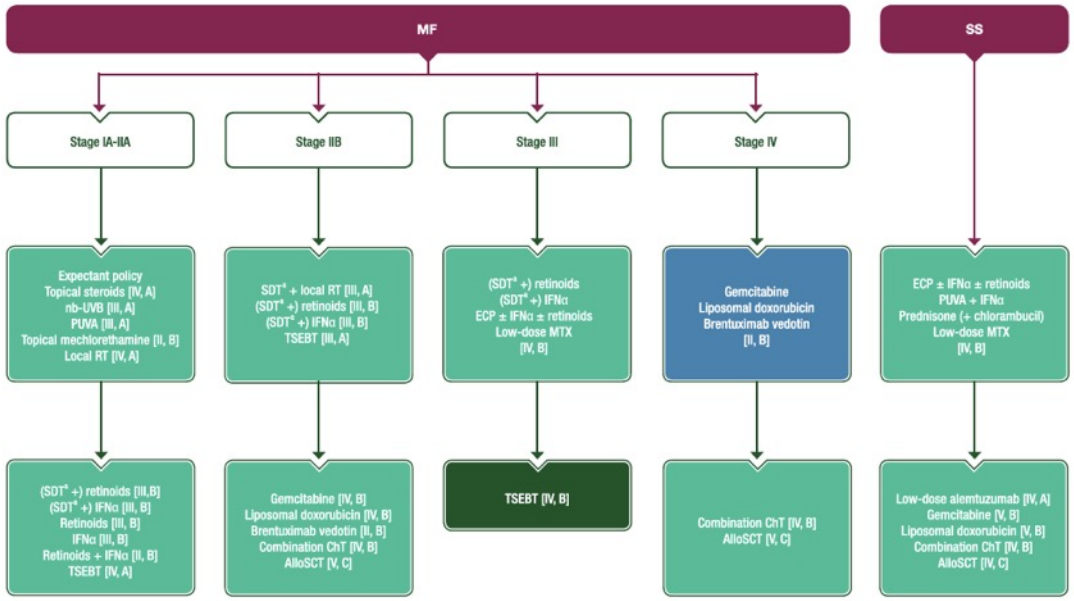


Figure 1. Recommendations for the treatment of MF/SS.
[a]Most commonly PUVA.
AlloSCT, allogeneic stem cell transplantation; ChT, chemotherapy; ECP, extracorporeal photopheresis; IFNα, interferon alpha; MF, mycosis fungoides; MTX, methotrexate; nb-UVB, narrow-band ultraviolet B; PUVA, psoralens plus ultraviolet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

Annals of Oncology
Clinical Practice d

Stage-base approach: treat what we see

Review of the Treatment of Mycosis Fungoides and Sézary Syndrome: A Stage-Based Approach

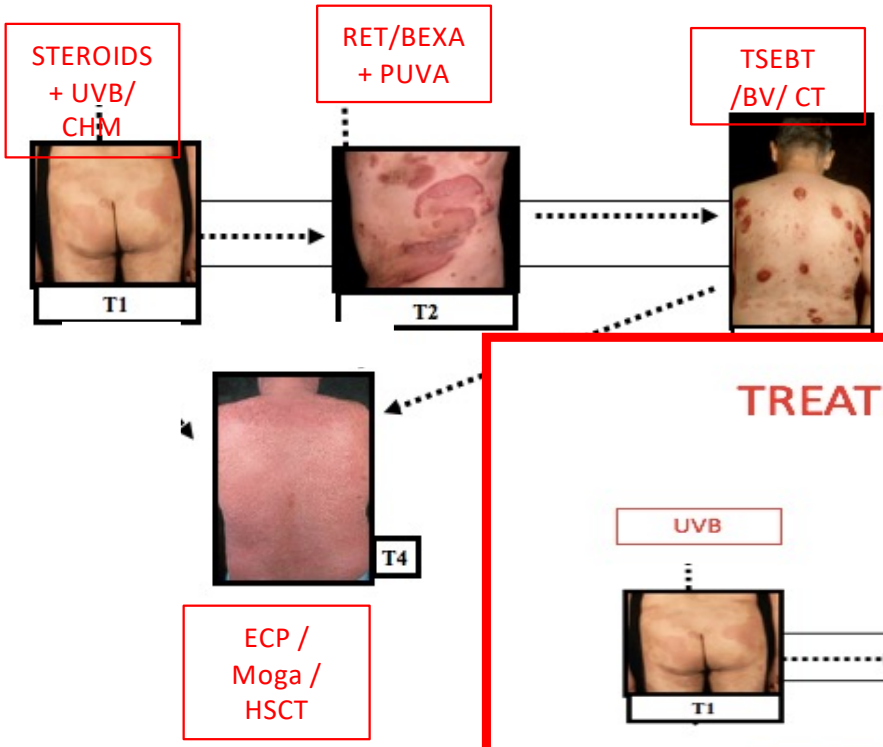
Steven M. Horwitz, MD;[a] Elise A. Olsen, MD;[b] Madeleine Duvic, MD;[c] Pierliugi Porcu, MD;[d] and Youn H. Kim, MD,[e]
New York, New York; Durham, North Carolina; Houston, Texas; Columbus, Ohio; and Stanford, California

Key Words
Mycosis fungoides, Sézary syndrome, cutaneous T-cell lymphoma

Abstract
The NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Disease were recently revised to include recommendations for treating mycosis fungoides and Sézary syndrome. These uncommon lym-

tients results in a much higher overall prevalence. In 2007, the NCCN created its first guidelines on MF/SS. There are not sufficient randomized studies to recommend a preferred treatment strategy for MF/SS, nor do universally accepted standard treatments exist. The chronicity of the disease results in many patients being

TREATMENT UP- GRADE



Nat Rev Dis Primers
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Cutaneous T cell lymphoma

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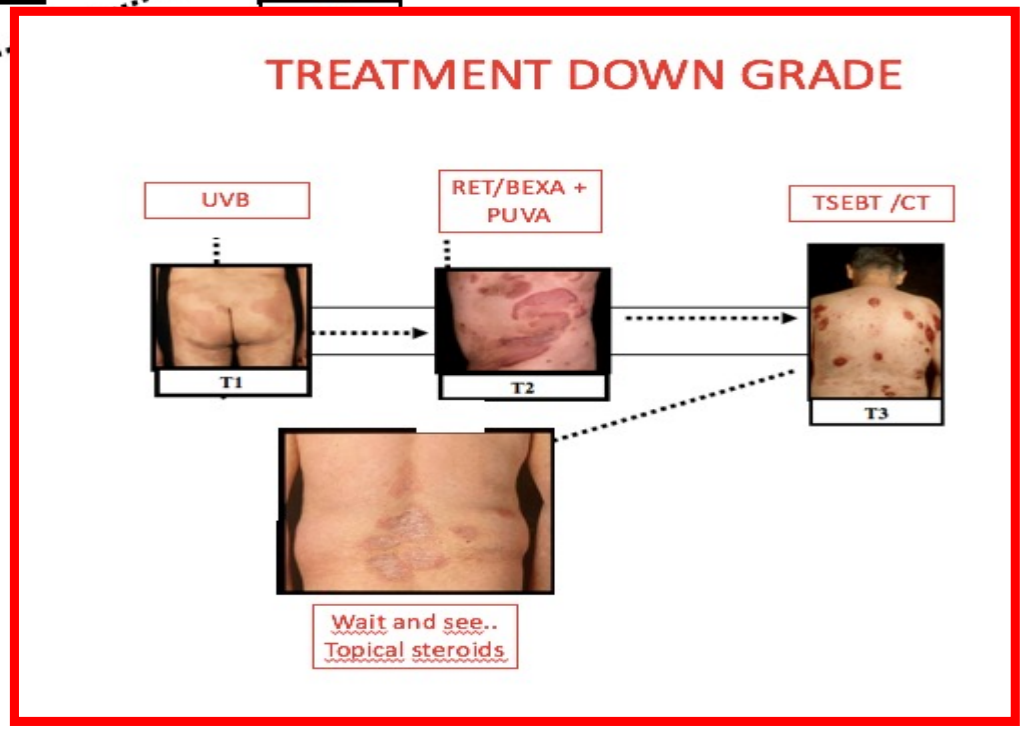

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Cutaneous T cell lymphoma

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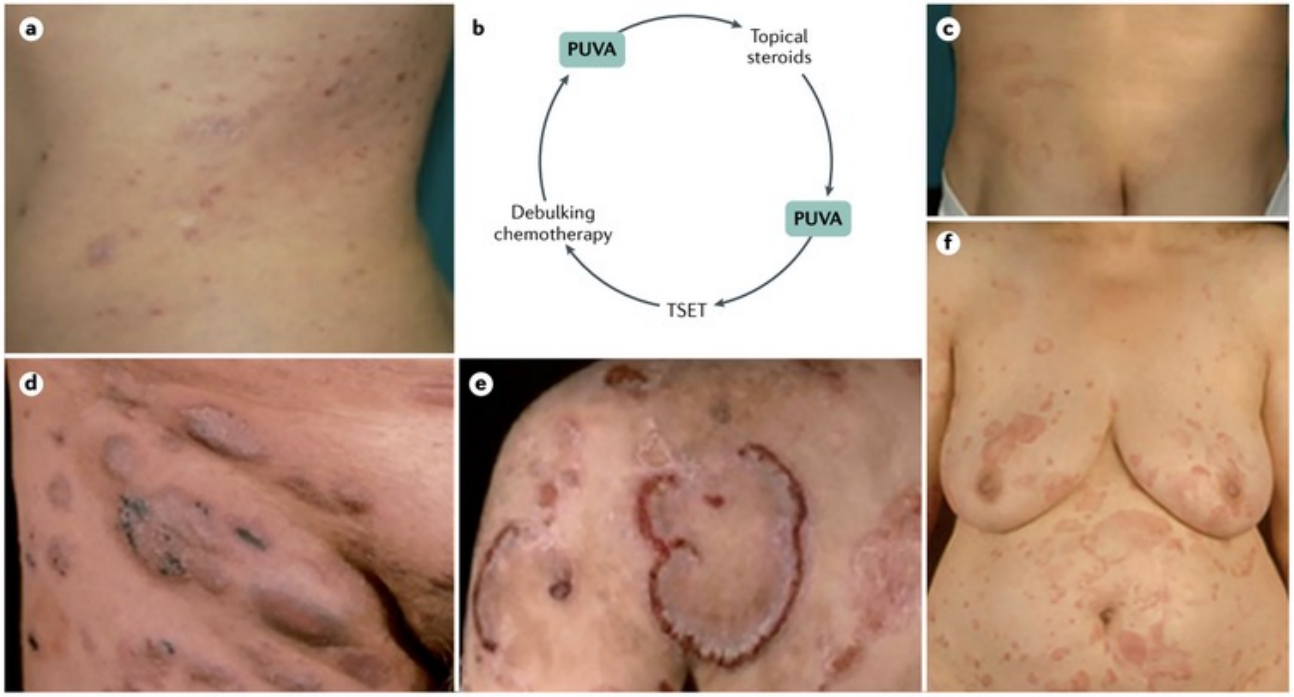


Stage-base approach: treat what we see

Treat-to-target requires physicians to measure a patient's disease activity every 1 to 3 months until the desired outcome is reached, and then disease activity is measured every 3 to 6 months.

If disease activity becomes unstable, it needs to be monitored more often, and treatment must be adjusted.

- HOW WE MEASURE DISEASE ACTIVITY ?
- WHICH ARE THE SUITABLE END POINTS?

ESMO

Annals of Oncology 00: 1–9, 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

CLIC
CUTANEOUS LYMPHOMA INTERNATIONAL CONSORTIUM

Quaglino P, Maule M, Prince HM, Porcu P, Horwitz S, Duvic M, Talpur R, Vermeer M, Bagot M, Guitart J, Papadavid E, Sanches JA, Hodak E, Sugaya M, Berti E, Ortiz-Romero P, Pimpinelli N, Servitje O, Pileri A, Zinzani PL, Estrach T, Knobler R, Stadler R, Fierro MT, Alberti Violetti S, Amitay-Laish I, Antoniou C, Astrua C, Chaganti S, Child F, Combalia A, Fabbro S, Fava P, Grandi V, Jonak C, Martinez-Escala E, Kheterpal M, Kim EJ, McCormack C, Miyagaki T, Miyashiro D, Morris S, Muniesa C, Nikolaou V, Ognibene G, Onida F, Osella-Abate S, Porkert S, Postigo-Llorente C, Ram-Wolff C, Ribero S, Rogers K, Sanlorenzo M, Stranzenbach R, Spaccarelli N, Stevens A, Zugna D, Rook AH, Geskin LJ, Willemze R, Whittaker S, Hoppe R, Scarisbrick J, Kim Y.

Ann Oncol. 2017 Oct 1;28(10):2517-2525.

853 patients stage IIB or higher diagnosed from January 2007 with treatment information retrospectively collected from 21 centres (14 European, 4 USA, 1 Australian, Brazilian and Japanese)

The objectives were:

- **to analyze treatment distribution according to geographical areas, stage and age of advanced-phase MF/SS patients;**
- **to ascertain the association between these parameters and survival.**

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
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

Most commonly used first approaches were extracorporeal photochemotherapy (ECP), bexarotene and phototherapy. As treatment numbers increased, they included poly-chemotherapy, total-skin-electron-beam therapy (TSEBT), histone-deacetylase inhibitors (HDACi), pegylated doxorubicin and allogeneic transplantation.

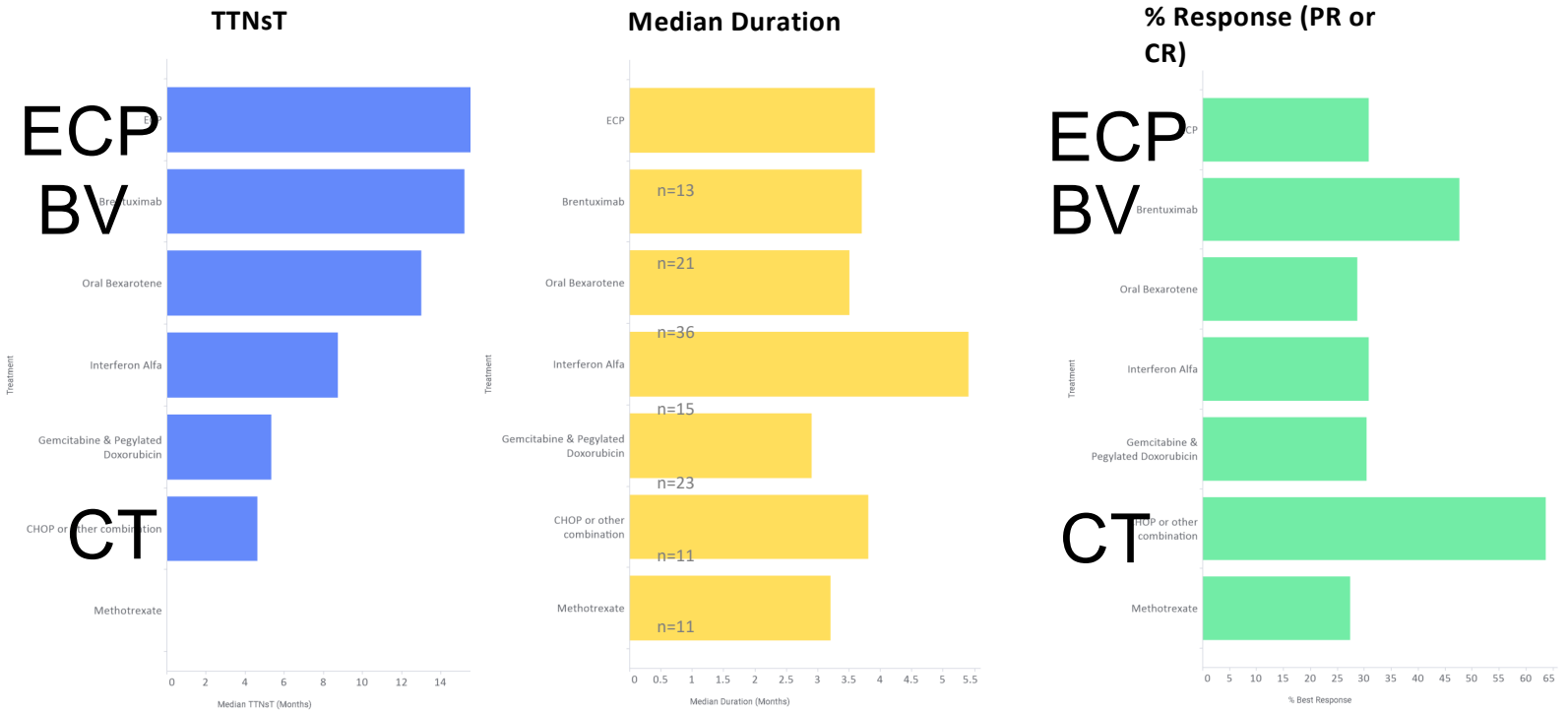
Global patterns of care in advanced stage mycosis fungoides/Sezary syndrome: a multicenter retrospective follow-up study from the Cutaneous Lymphoma International Consortium. Quaglino P, et al. Ann Oncol. 2017.

PROCLIPI DATA – EORTC MADRID CLTG 2022

Second line treatment options in advanced stages MF/SS

	N (%)	In Combination	Median Duration	TTNsT	Response Rate
Oral Bexarotene	44 (20.3%)	11 (25.0%)	3.5 (1.6-11.3)	13.0 (3.9-NR)	10 (28.6%)
Gemcitabine or Pegylated Doxorubicin	27 (12.4%)	5 (18.5%)	2.9 (1.4-4)	5.3 (3.2-11.8)	7 (30.4%)
Brentuximab	22 (10.1%)	2 (9.1%)	3.7 (2.1-5.3)	15.2 (6.2-NR)	10 (47.6%)
Anti-CCR4 - Mogamulizumab	20 (9.2%)	0 (0%)	7.5 (2.0-9.6)	NR	5 (71.4%)
ECP	20 (9.2%)	7 (35.0%)	3.9 (2.3-12.2)	16.8 (9.0-NR)	4 (30.8%)
Interferon Alpha	18 (6.8%)	4 (22.2%)	5.4 (1.6-14.9)	8.7 (5.3-NR)	4 (30.8%)
Methotrexate	17 (6.4%)	6 (35.3%)	3.2 (2.5-13.0)	NR	3 (27.3%)
CHOP or other combination	12 (5.5%)	2 (16.7%)	3.8 (2.1-7.0)	4.6 (3.3-80.3)	7 (63.6%)
Any other therapy	9 (4.2%)	2 (22.2%)	4.1 (0-7.2)	28.3 (12.6-NR)	4 (57.1%)
Other Retinoid	8 (3.7%)	2 (25.0%)	5.9 (2.5-8.4)	14.4 (8.4-16.7)	2 (40%)
Other oral chemotherapy	7 (3.2%)	4 (57.1%)	2.9 (2-4.6)	7.5 (2.0-9.1)	1 (33.3%)
Romidepsin	5 (2.3%)	0	4.6 (2.7-8.0)	5.4 (2.7-9.0)	5 (71.4%)
Pembrolizumab &/or Alemtuzumab	4 (1.8%)	0	2.0 (1.3-2.6)	3.3 (1.5-7.7)	2 (50%)
Other iv monchemotherapy	3 (1.4%)	1 (33.3%)	2.9 (1.8-3.9)	3.9 (3.9-4.2)	0

Second line treatments TTNsT, median duration & % with response (PR or CR)



HOW WE MEASURE DISEASE ACTIVITY AND CLINICAL RESPONSE??

- mSWAT and measurable parameters
- Presence of plaques
- TtNT
- Quality of Life

- … WHAT DO WE NEED?

What do we need?

VOLUME 33 · NUMBER 32 · NOVEMBER 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

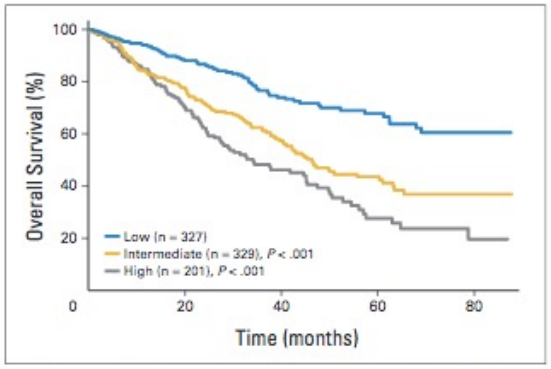


Fig 2. Kaplan-Meier plot showing prognostic index model for low-, intermediate-, and high-risk groups. Variables included in the prognostic index model were stage IV, elevated lactate dehydrogenase, age greater than 60 years, and large-cell transformation in skin (low risk = zero to one variable; intermediate risk = two variables; high risk = three to four variables).

- stage IV
- age>60years
- large-cell transformation
- increased LDH

Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sézary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model

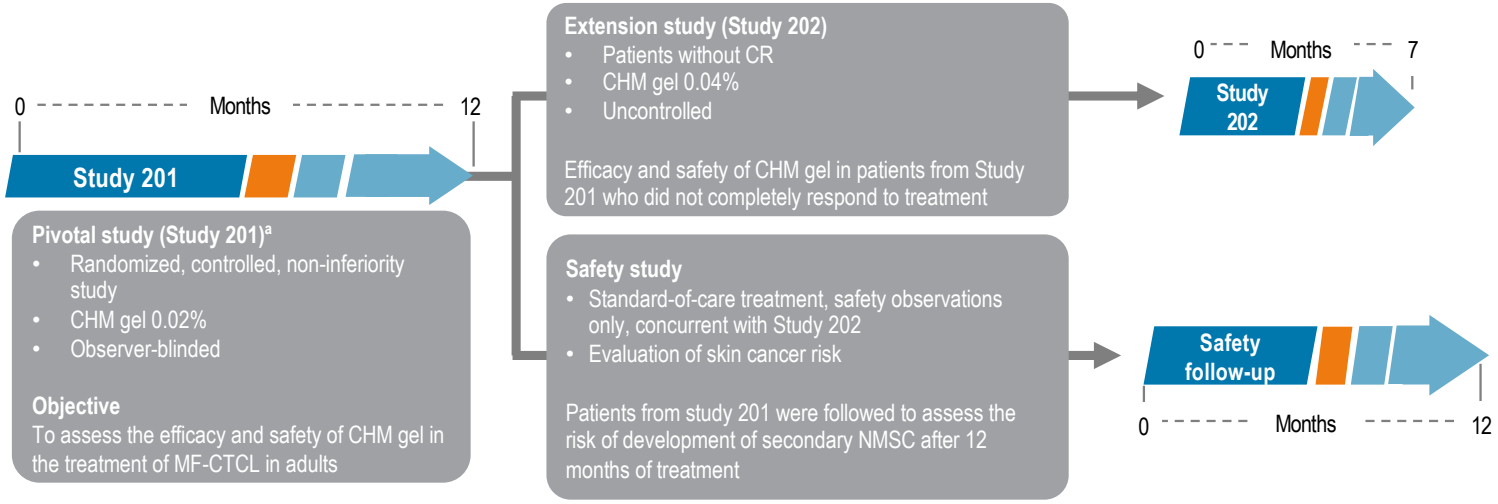
Julia J. Scarisbrick, H. Miles Prince, Maarten H. Vermeer, Pietro Quaglino, Steven Horwitz, Pierluigi Porcu, Rudolf Stadler, Gary S. Wood, Marie Beylot-Barry, Anne Pham-Ledard, Francine Foss, Michael Girardi, Martine Bagot, Laurence Michel, Maxime Battistella, Joan Guitart, Timothy M. Kuzel, Maria Estela Martinez-Escala, Teresa Estrach, Evangelia Papadavid, Christina Antoniou, Dimitis Rigopoulos, Vassilki Nikolaou, Makoto Sugaya, Tomomitsu Miyagaki, Robert Gniadecki, José Antonio Sanches, Jade Cury-Martins, Denis Miyashiro, Octavio Servitje, Cristina Muniesa, Emilio Berti, Francesco Onida, Laura Corti, Emilia Hodak, Iris Amitay-Laish, Pablo L. Ortiz-Romero, Jose L. Rodríguez-Peralto, Robert Knobler, Stefanie Porkert, Wolfgang Bauer, Nicola Pimpinelli, Vieri Grandi, Richard Cowan, Alain Rook, Ellen Kim, Alessandro Pileri, Annalisa Patrizi, Ramon M. Pujol, Henry Wong, Kelly Tyler, Rene Stranzenbach, Christiane Querfeld, Paolo Fava, Milena Maule, Rein Willemze, Felicity Evison, Stephen Morris, Robert Twigger, Rakhshandra Talpur, Jinah Kim, Grant Ognibene, Shufeng Li, Mahkam Tavallaee, Richard T. Hoppe, Madeleine Duvic, Sean J. Whittaker, and Youn H. Kim

Listen to the podcast by Dr Pinter-Brown at www.jco.org/podcasts

Chlormethine gel for the treatment of MF-CTCL

Pivotal study: study 201, Lessin trial

Phase 2, multicentre, randomized, observer-blinded, non-inferiority trial in 260 MF patients; stage I–IIA



[a] Patients were treated for 12 months except for: disease progression, treatment limiting toxicity, concomitant illness, or a change in health status necessitated discontinuation. Patients were free to withdraw consent at any time.

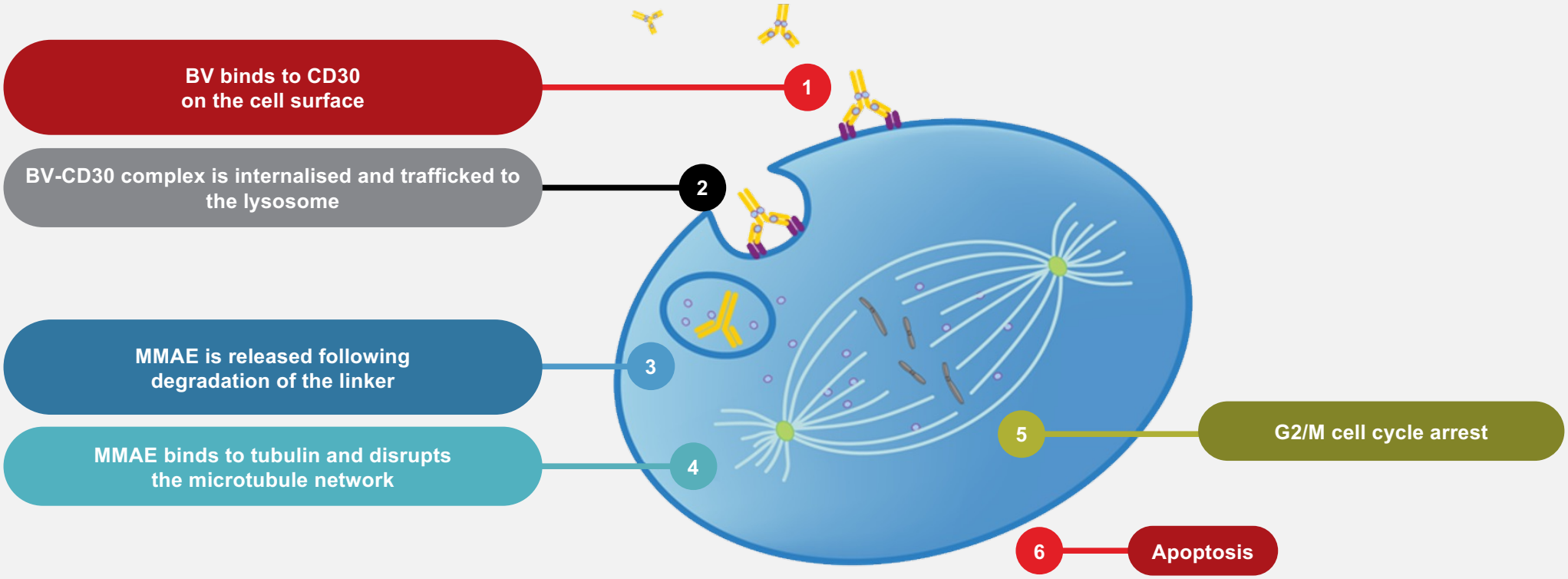
CR, complete response; NMSC, non-melanoma skin cancer.

Lessin SR, et al. JAMA Dermatol. 2013;149:25-32.

PRESENTATION SUMMARY

1. PRINCIPLES OF THERAPY IN MYCOSIS FUNGOIDES/SEZARY SYNDROME
2. BRENTUXIMAB VEDOTIN

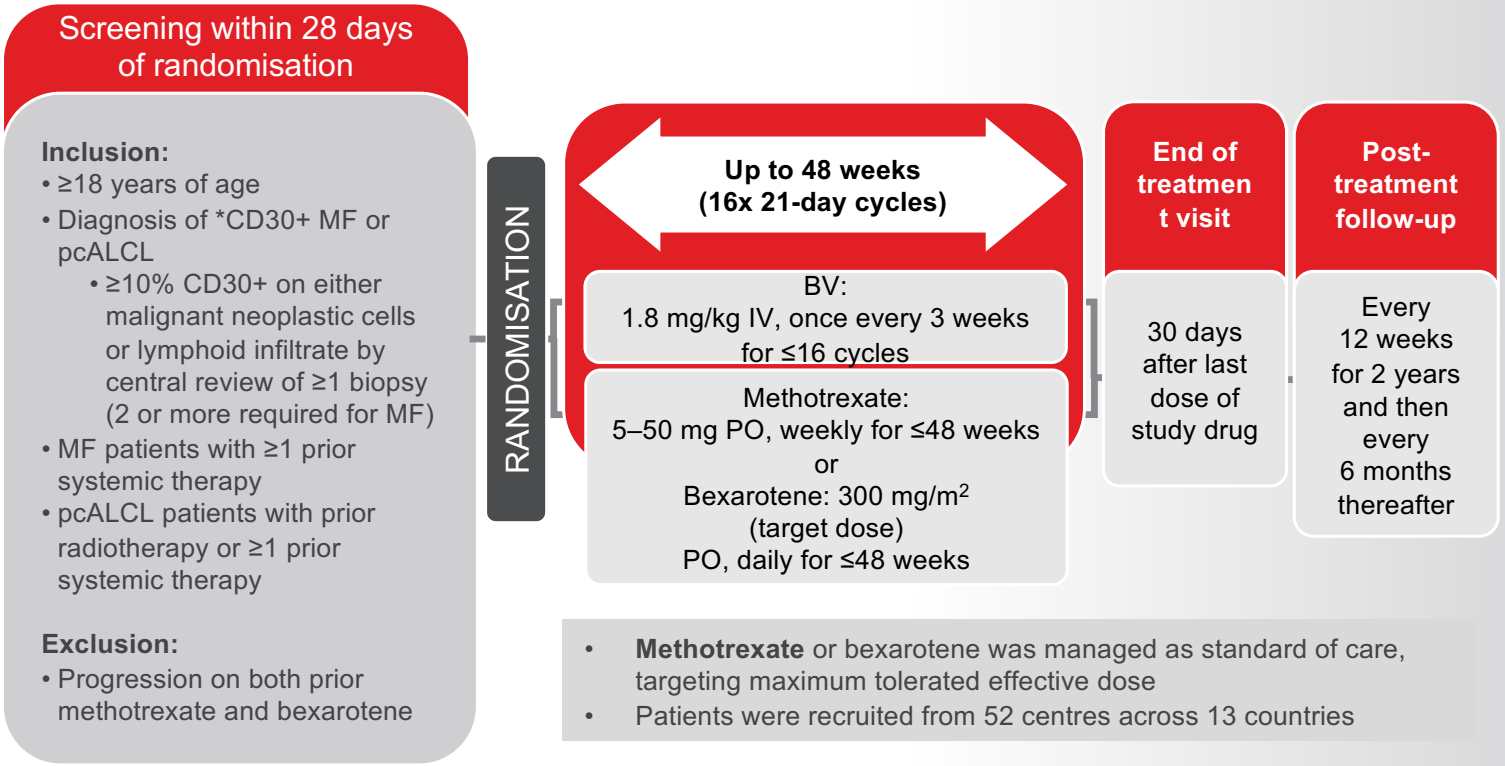
Brentuximab vedotin (BV) mode of action: Anti-CD30/MMAE ADC



ADC, antibody–drug conjugate; BV, brentuximab vedotin; CD30, cluster of differentiation 30; MMAE, monomethyl auristatin E.

1. van de Donk NWCJ and Dhimolea E. *Mabs.* 2012;4:458–65. 2. ADCETRIS (brentuximab vedotin). Summary of Product Characteristics. June 2022.

ALCANZA: An international, open-label, randomised, Phase III, multicentre trial to assess brentuximab vedotin versus conventional therapy in patients with CD30+ R/R MF or pcALCL



- **Methotrexate** or bexarotene was managed as standard of care, targeting maximum tolerated effective dose
- Patients were recruited from 52 centres across 13 countries

Objective:
To investigate the efficacy and safety of BV vs physician's choice of methotrexate or bexarotene in previously treated patients with CD30+ CTCL

Primary endpoint:
- Rate of objective response lasting ≥4 months (ORR4)
  - Response assessed by mSWAT for skin evaluation, radiographic assessment, and circulating Sézary cell assessment (for MF only) using consensus guidelines

Secondary endpoints:
- CR rate
- PFS
- Symptom burden/PRO (measure of QoL using Skindex-29)

*CD30+ on either neoplastic cells or lymphoid infiltrate by central review of ≥1 biopsy (2 biopsies required for MF). The global response score is a composite of skin evaluation per investigator; nodal and visceral radiographic assessment per IRF; and for patients with MF, Sézary cell count per IRF.
BV, brentuximab vedotin; CD30, cluster of differentiation 30; CR, complete response; CTCL, cutaneous T-cell lymphoma; IRF, independent review facility; IV, intravenously; MF, mycosis fungoides; mSWAT, modified severity weighted assessment tool; ORR4, objective response lasting at least 4 months; pcALCL, primary cutaneous anaplastic large cell lymphoma; PFS, progression-free survival; PO, orally; PRO, patient-reported outcome; QoL, quality of life; R/R, relapsed/refractory.
Prince HM, et al. *Lancet.* 2017;390:555–66.

Baseline patient characteristics

Patient characteristics		BV (n=64)	Physician's choice of methotrexate or bexarotene (n=64)	Overall (N=128)
Median age, years (range)		**62** (51–70)	**59** (48–67)	**60** (48–69)
Sex, n (%)	**Male**	**33** (52)	**37** (58)	**70** (55)
	Female	**31** (48)	**27** (42)	**58** (45)
Race, n (%)	**White**	**56** (88)	**53** (83)	**109** (85)
	Other	**5** (8)	**10** (16)	**15** (12)
	Not reported	**3** (5)	**1** (2)	**4** (3)
ECOG PS, n (%)	**0**	**43** (67)	**46** (72)	**89** (70)
	1	**18** (28)	**16** (25)	**34** (27)
	2	**3** (5)	**2** (3)	**5** (4)
Median CD30 expression,* % (range)		**32.5** (12.5–67.5)	**31.3** (12.0–47.5)	**31.3** (12.5–60.0)
Median time since initial diagnosis, months (range)		**42.2** (12.8–87.4)	**37.0** (12.3–102.7)	**40.9** (12.7–96.8)
Median time since progression on last therapy,† months (range)		**2.4** (1.4–7.9)	**1.3** (0.9–3.7)	**1.9** (1.1–3.8)
Lines of previous therapy, n (range)	**Total**	**4** (2.0–7.0)	**3.5** (2.0–5.5)	**4.0** (2.0–6.0)
	Skin-directed	**1.0** (1.0–2.0)	**1.0** (1.0–2.0)	**1.0** (1.0–2.0)
	Systemic	**2.0** (1.0–4.0)	**2.0** (1.0–3.0)	**2.0** (1.0–4.0)

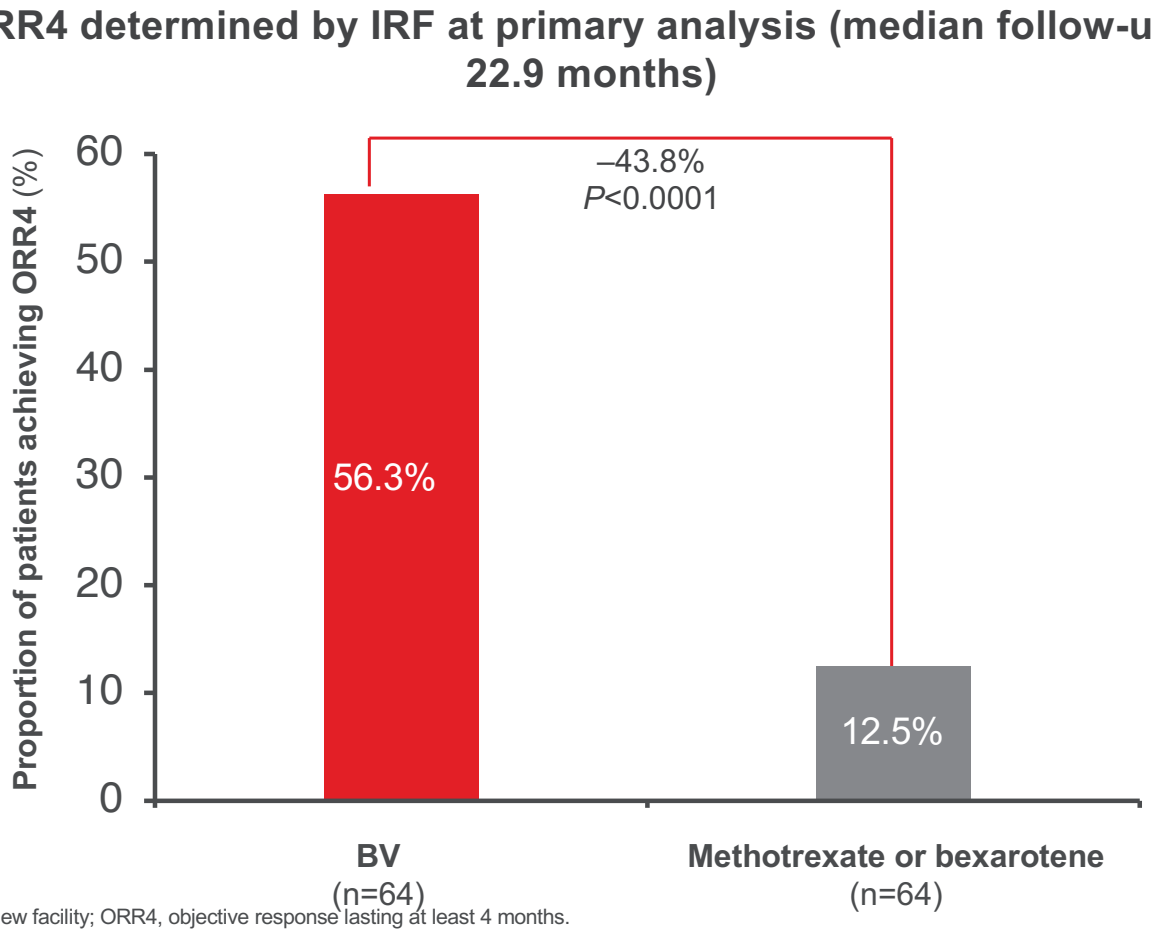
Disease characteristics		BV (n=64)	Physician's choice of methotrexate or bexarotene (n=64)	Overall (N=128)
Mycosis fungoides, n (%)		**48** (75)	**49** (77)	**97** (76)
Disease stage,‡§ n (%)	**IA–IIA**	**15/48** (31)	**18/49** (37)	**33/97** (34)
	IIB	**19/48** (40)	**19/49** (39)	**38/97** (39)
	IIIA–IIIB	**4/48** (8)	**2/49** (4)	**6/97** (6)
	IVA1	**0**	**1/49** (2)	**1/97** (1)
	IVA2	**2/48** (4)	**8/49** (16)	**10/97** (10)
	IVB	**7/48** (15)	0	**7/97** (7)
pcALCL, n (%)		**16** (25)	**15** (23)	**31** (24)
Disease stage,‡ n (%)	**Skin T_1**	**1/16** (6)	**4/15** (27)	**5/31** (16)
	Skin T_2	**3/16** (19)	**5/15** 33)	**8/31** (26)
	Skin T_3	**12/16** (75)	**6/15** (40)	**18/31** (58)
	Node N_0	**10/16** (63)	**11/15** (73)	**21/31** (68)
	Node N_1	**2/16** (13)	**1/15** (7)	**3/31** (10)
	Node N_2	**2/16** (13)	**1/15** (7)	**3/31** (10)
	Node N_3	**2/16** (13)	**2/15** (13)	**4/31** (13)
	Visceral M_0	**12/16** (75)	**14/15** (93)	**26/31** (84)
	Visceral M_1	**4/16** (25)	**1/15** (7)	**5/31** (16)

*Based on average CD30 expression among all biopsies for each patient's baseline visit. †Excluding radiotherapy. ‡Percentage in each subcategory in the total column is based on the number of patients in each disease subtype. §One patient in each group had incomplete staging data and are not included in the table.

BV, brentuximab vedotin; CD30, cluster of differentiation 30; ECOG PS, Eastern Cooperative Oncology Group Performance Status; M, metastasis; N, node; pcALCL, primary cutaneous anaplastic large cell lymphoma; T, tumour.

Prince HM, et al. *Lancet.* 2017;390:555–66.

Significantly more patients achieved durable response with brentuximab vedotin as measured by ORR4, versus physician's choice of therapy



BV, brentuximab vedotin; IRF, independent review facility; ORR4, objective response lasting at least 4 months.

Prince HM, et al. *Lancet.* 2017;390:555–66.

At last follow-up, patients with CD30-expressing R/R MF or pcALCL had superior response and longer PFS with brentuximab vedotin versus physician's choice

- Median overall follow-up was 45.9 months (95% CI: 41.0–49.4); median follow-up for PFS was 36.8 months

Patient outcomes	BV (n=64)	Physician's choice (n=64)	*P*-value
ORR4 per IRF, n (%)	35 (54.7)*	8 (12.5)	<0.001
Best response per IRF, n (%)			
ORR (CR + PR)	42 (65.6)	13 (20.3)	<0.001
CR	11 (17.2)	1 (1.6)	0.002
PR	31 (48.4)	12 (18.8)	
SD	10 (15.6)	18 (28.1)	
PD	5 (7.8)	22 (34.4)	
Median PFS per IRF, months (95% CI)	16.7 (15.4–21.6)	3.5 (2.4–4.6)	
HR for PFS (95% CI)	0.38 (0.25–0.58)		<0.001
3-year OS rate % (95% CI)	64.4 (50.7–75.2) [Median FU: 48.4 mos]	61.9 (47.3–73.6) [Median FU: 42.9 mos]	
HR for OS (95% CI)	0.75 (0.42–1.32)		0.310

*Based on additional information provided to the IRF after the 31st May, 2016 data cut-off, the IRF determined that one patient had not achieved ORR4 as was originally reported; the change in status was determined through a standard IRF adjudication process.

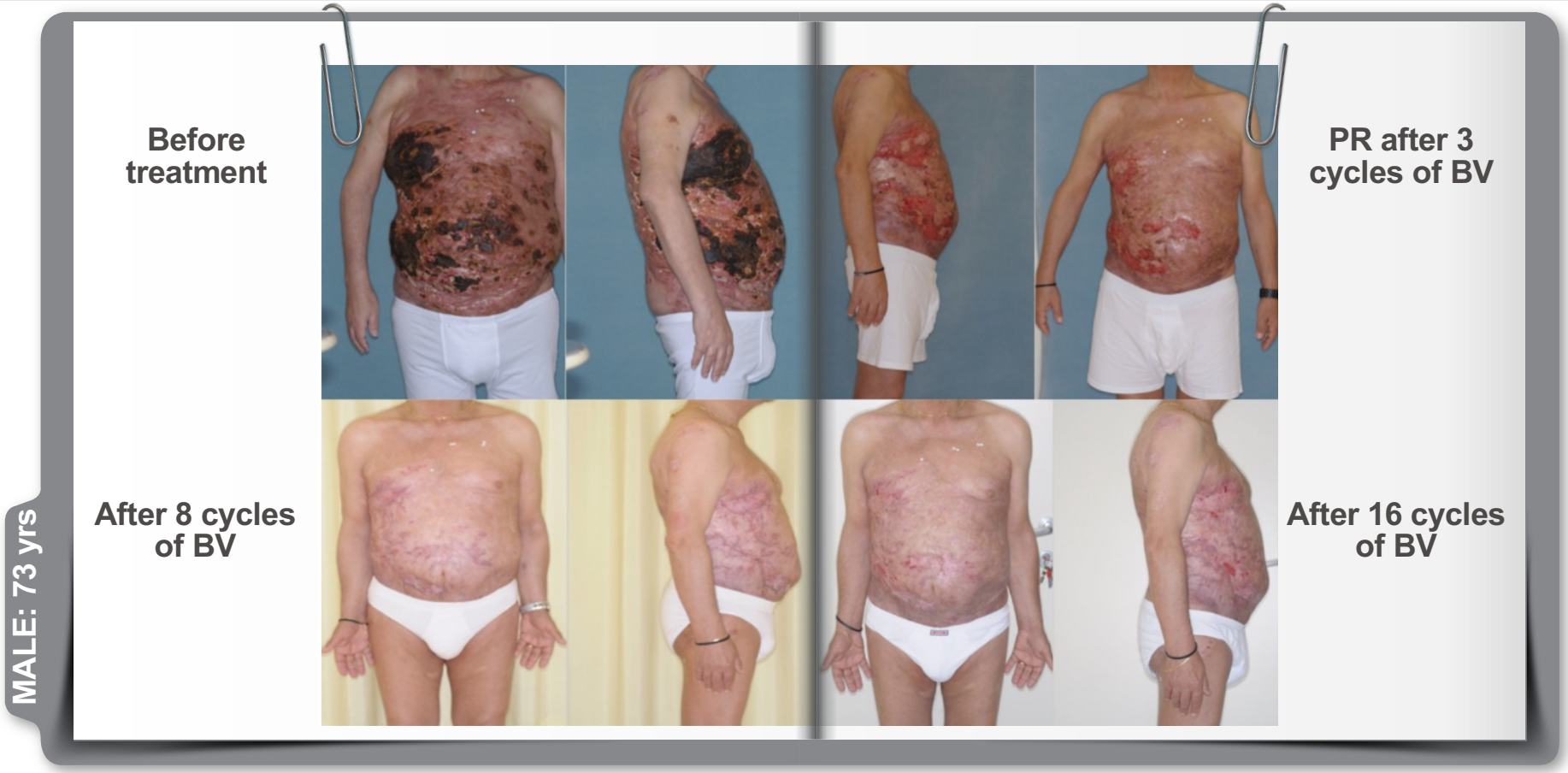
BV, brentuximab vedotin; CD30, cluster of differentiation 30; CI, confidence interval; CR, complete response; FU, follow-up; HR, hazard ratio; IRF, independent review facility; MF, mycosis fungoides; mos, months; ORR, objective response rate; ORR4, objective response lasting at least 4 months; OS, overall survival; PD, progressive disease; pcALCL, primary cutaneous anaplastic large cell lymphoma; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; SD, stable disease.

Horwitz S, et al. *Blood Adv.* 2021;5:5098–106.

ORR4 and response rates by disease type and extent

	Brentuximab Vedotin				Bexarotene or Methotrexate			
	Total N = 64 n (%)	**ORR4 (%)**	ORR (%)	CR (%)	Total N = 64 n (%)	**ORR4 (%)**	ORR (%)	CR (%)
ITT population	64 (100)	56	67	16	64 (100)	13	20	2
MF	48 (75)	**50**	65	10	49 (77)	**10**	16	0
Stage								
IA-IIA	15 (31)	40	53	7	18 (37)	22	28	0
IIB	19 (40)	63	68	16	19 (39)	5	16	0
IIIA-IIIB	4 (8)	50	75	0	2 (4)	0	0	0
IVA	2 (4)	100	100	50	9 (18)	0	0	0
IVB	7 (15)	29	57	0	0	NA	NA	NA
pcALCL	16 (25)	**75**	75	31	15 (23)	**20**	33	7
Disease involvement								
Skin-only	9 (56)	89	89	44	11 (73)	27	45	9
Extracutaneous disease	7 (44)	57	57	14	4 (27)	0	0	0

Brentuximab vedotin activity in a patient with MF stage IIB



The outcomes presented are for the treatment of a single patient; other patient experiences with this treatment may differ.

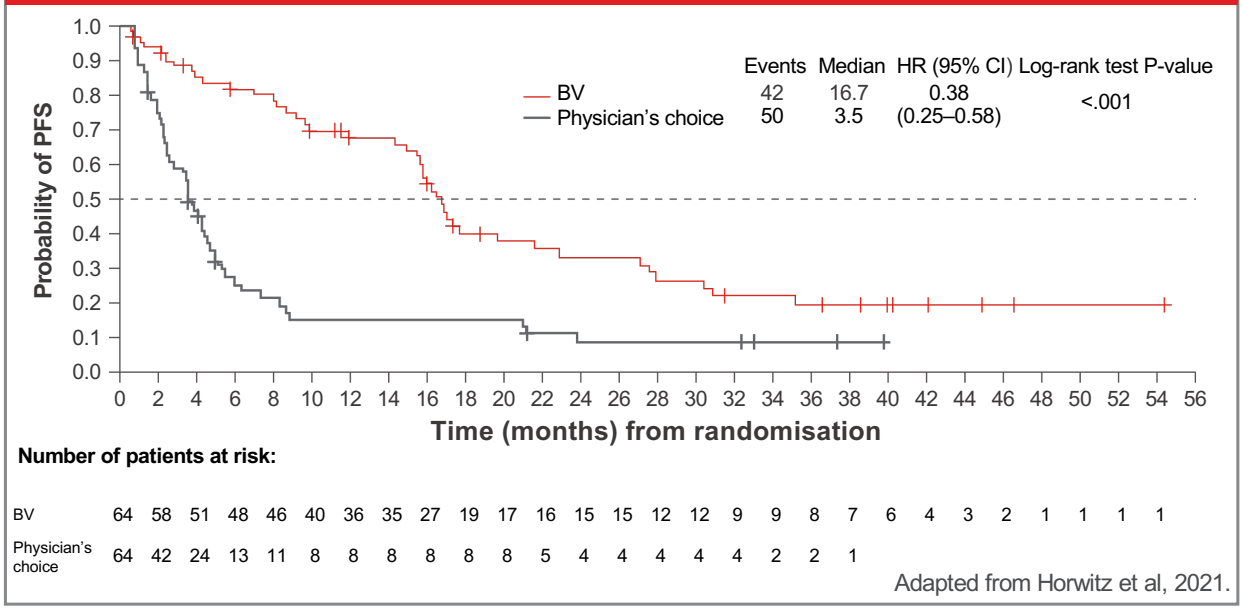
Images courtesy of the speaker. Patient from the ALCANZA trial. All patient images have been used with informed consent from the patient.

BV, brentuximab vedotin; MF, mycosis fungoides; PR, partial response.

PFS per IRF in ITT population and by number of brentuximab vedotin treatment cycles at final analysis

- Patients exposed to longer BV therapy were more likely to remain progression-free at multiple time points

PFS per IRF in ITT population



Adapted from Horwitz et al, 2021.

PFS per IRF by number of BV treatment cycles in ITT population

	Number of BV treatment cycles		
	1–5 (n=19)	6–12 (n=17)	13–16 (n=28)
Median PFS, months	3.8	15.4	21.6
PFS for extended follow-up, %*			
12 months	27.3	58.8	96.0
18 months	18.2	32.7	57.3
24 months	18.2	26.1	46.9

*Kaplan–Meier estimates

Adapted from Horwitz et al, 2021.

PFS was defined as the time from randomisation until disease progression per IRF or death of any cause, whichever occurred first.

Patients who were lost to follow-up, withdrew consent, or discontinued treatment because of undocumented disease progression after the last adequate disease assessment were censored at the last disease assessment.

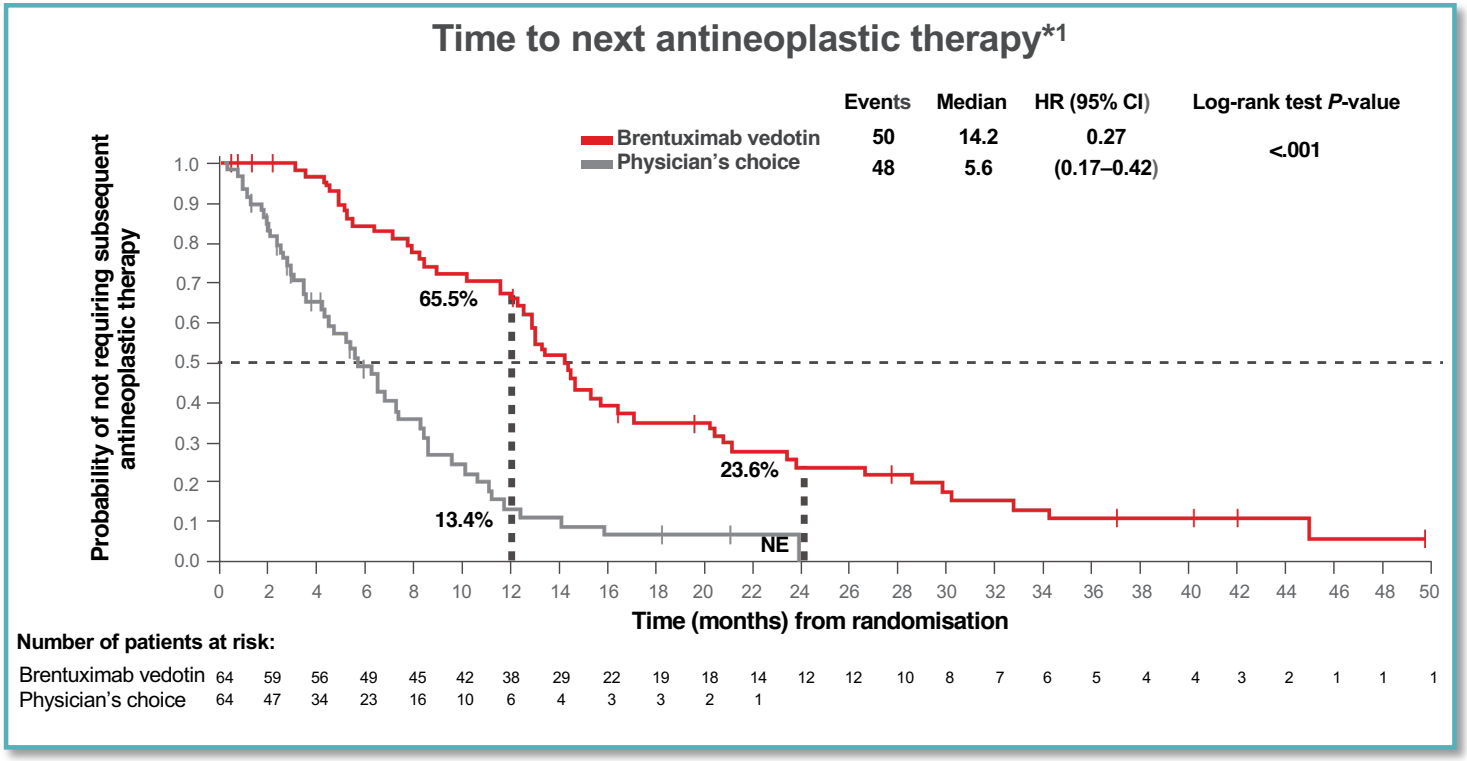
BV, brentuximab vedotin; CI, confidence interval; HR, hazard ratio; IRF, independent review facility; ITT, intention-to-treat; PFS, progression-free survival.

Horwitz S, et al. *Blood Adv.* 2021;5:5098–106.

At median follow-up of 37.3 months, TTNT was significantly longer with brentuximab vedotin versus physician's choice

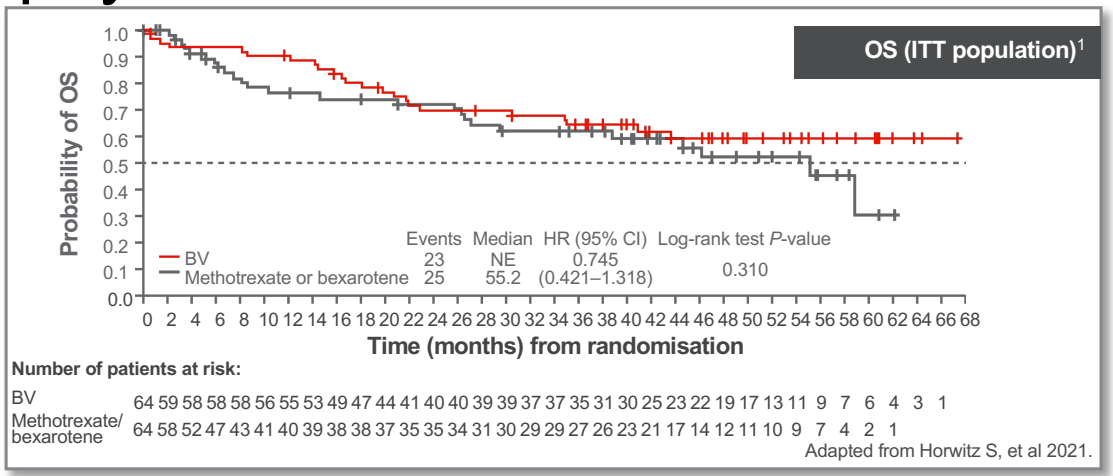
Median TTNT was improved with BV vs physician's choice:[1]
14.2 months vs 5.6 months; HR 0.27
(95% CI: 0.17–0.42; *P*<0.001)

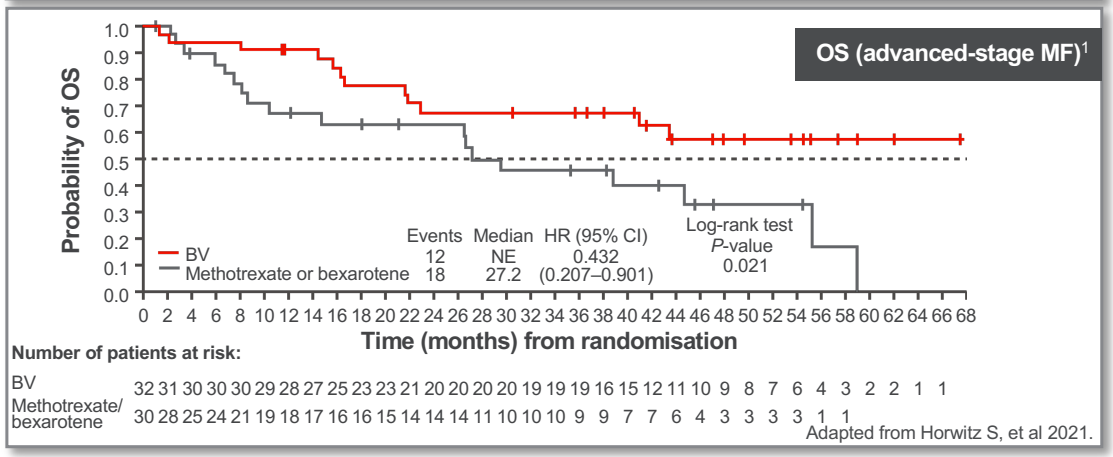
- **Median TTNT in the BV arm:**[1]
  - **MF group:** 13.4 months (95% CI: 11.4–15.3)
  - **pcALCL group:** 20.6 months (95% CI: 7.0–32.8)
- 24% (12/64) of the BV arm were **retreated with BV**; 69% (33/64) of the physician's choice arm received **subsequent BV therapy**†[1,2]
- Probability of not requiring **subsequent antineoplastic therapy** in the BV arm:[1]
  - **Year 1**: 65.5%
  - **Year 2**: 23.6%



*Defined as the time from randomisation to the date of the first documentation of antineoplastic therapy or last contact date for subjects who never took antineoplastic therapy, over a median follow-up of 37.3 months. TTNT was shorter than PFS, possibly due to patients with CTCL requiring treatment for symptomatic deterioration without meeting the criteria for PD.
†Percentages are based on the number of patients with ≥1 subsequent antineoplastic treatment in the ITT population in each arm.
BV, brentuximab vedotin; CI, confidence interval; CTCL, cutaneous T-cell lymphoma; HR, hazard ratio; MF, mycosis fungoides; NE, not evaluable; pcALCL, primary cutaneous anaplastic large cell lymphoma; PD, progressive disease; PFS, progression-free survival; TTNT, time to next therapy.
1. Horwitz S, et al. *Blood Adv.* 2021;5:5098–106. 2. Horwitz S, et al. *Blood Adv.* 2021;5:5098–106.Supplemental material.

OS improvement was observed in patients with advanced stages of MF treated with brentuximab vedotin versus physician's choice





OS was not a prespecified endpoint in ALCANZA

Median follow-up was 45.9 months[2]

3-year estimates of OS:[2]

- BV 64.4% and physician's choice 61.9%
  - (HR 0.75; 95% CI: 0.42–1.32; *P*=0.310)
- 23 deaths in the BV arm and 25 in the physician's choice arm[2]
- **OS improvement** observed in the subgroup of **patients with advanced stages of MF** (post hoc analysis) with BV vs physician's choice
  - (HR 0.43; 95% CI: 0.207–0.901; *P* =0.021)[1]

Subgroup analyses are not powered to draw definitive conclusions and, therefore, results should be interpreted with caution.

BV, brentuximab vedotin; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; MF, mycosis fungoides; NE, not evaluable; OS, overall survival.

1. Horwitz S, et al. *Blood Adv.* 2021;5:5098–106 (Supplement); 2. Horwitz S et al. *Blood Adv.* 2021;5:5098–106.

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Original Research

Response to brentuximab vedotin versus physician's choice by CD30 expression and large cell transformation status in patients with mycosis fungoides: An ALCANZA sub-analysis

Youn H. Kim [a,*], H. Miles Prince [b], Sean Whittaker [c], Steven M. Horwitz [d], Madeleine Duvic [e], Oliver Bechter [f], Jose A. Sanches [g], Rudolf Stadler [h], Julia Scarisbrick [i], Pietro Quaglino [j], Pier Luigi Zinzani [k], Pascal Wolter [l], Herbert Eradat [m], Lauren C. Pinter-Brown [n], Pablo L. Ortiz-Romero [o], Oleg E. Akilov [p], Judith Trotman [q], Kerry Taylor [r], Michael Weichenthal [s], Jan Walewski [t], David Fisher [u], Marise McNeeley [v], Alejandro A. Gru [w], Lisa Brown [x,1], M. Corinna Palanca-Wessels [x], Julie Lisano [x], Matthew Onsum [x], Veronica Bunn [y], Meredith Little [y], Willi [illegible], Reinhard Dummer [z]

Table 2
Efficacy of brentuximab vedotin and PC by CD30 expression and LCT status.

Treatment	$CD30_{min} < 10\%$ (n = 43)		$CD30_{min} \geq 10\%$ (n = 57)	
	Brentuximab vedotin (n = 22)	Physician's choice (n = 21)	Brentuximab vedotin (n = 28)	Physician's choice (n = 29)
ORR4, n (%)	9 (40.9)	2 (9.5)	16 (57.1)	3 (10.3)
Δ versus PC, % (95% CI)	31.4 (2.8–58.1)		46.8 (20.6–67.0)	
Median PFS, months (95% CI)	16.7 (8.6–27.0)	2.3 (1.6–3.5)	15.5 (9.8–22.8)	3.9 (2.2–6.3)
HR (95% CI)	0.189 (0.087–0.414)		0.340 (0.172–0.674)	
Treatment	LCT present (n = 34)		LCT absent (n = 62)	
	Brentuximab vedotin (n = 17)	Physician's choice (n = 17)	Brentuximab vedotin (n = 31)	Physician's choice (n = 31)
ORR4 per IRF, n (%)	11 (64.7)	3 (17.6)	12 (38.7)	2 (6.5)
Median PFS, months (95% CI)	15.5 (9.1–22.8)	2.8 (1.4–7.3)	16.1 (8.6–21.6)	3.5 (2.2–4.3)
Median $CD30_{min}$, % (range)	30.0 (0–95.0)	20.0 (0–95.0)	5.0 (0–60.0)	8.0 (0–50.0)

$CD30_{min}$, minimum CD30 levels; CI, confidence interval; HR, hazard ratio; IRF, independent review facility; LCT, large cell transformation; ORR4, objective response rate lasting ≥4 months; PC, physician's choice; PFS, progression-free survival.

PRESENTATION SUMMARY

1. PRINCIPLES OF THERAPY IN MYCOSIS FUNGOIDES/SEZARY SYNDROME
2. BRENTUXIMAB VEDOTIN
3. MOGAMULIZUMAB

Importance of CCR4

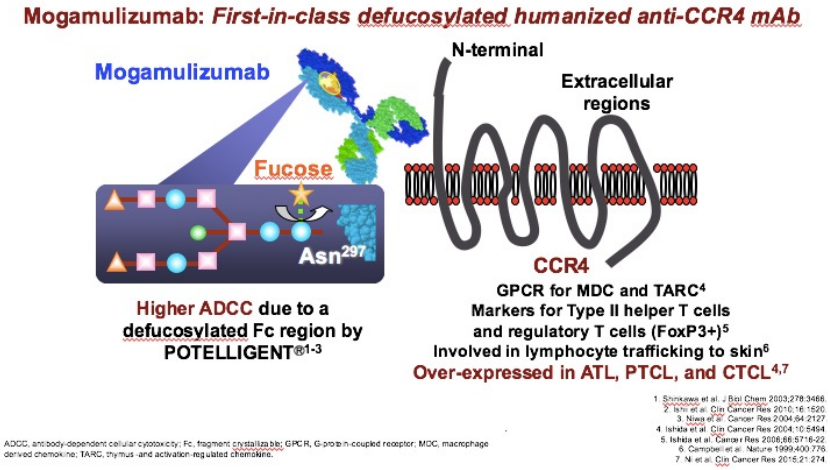
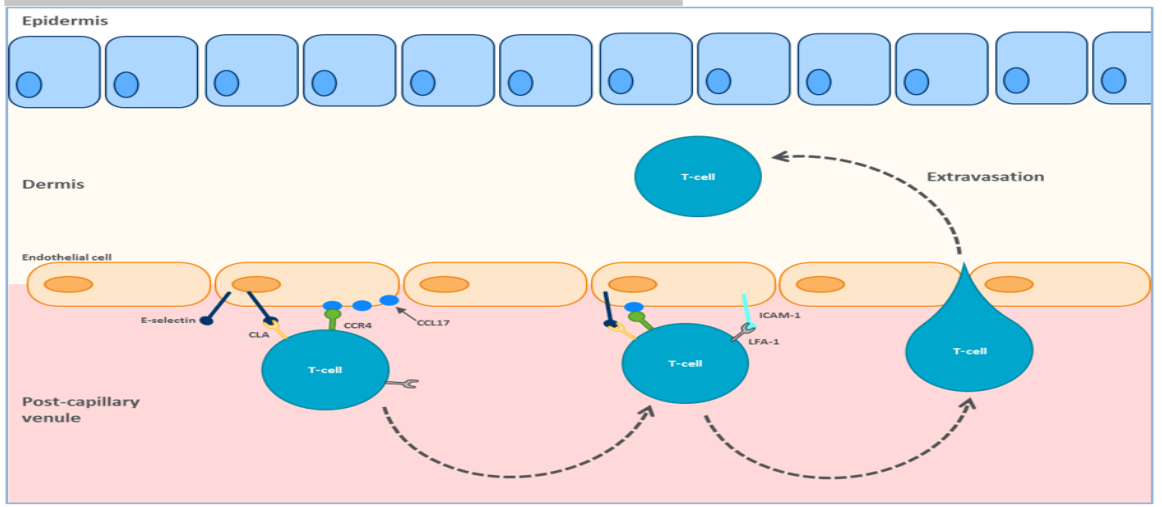
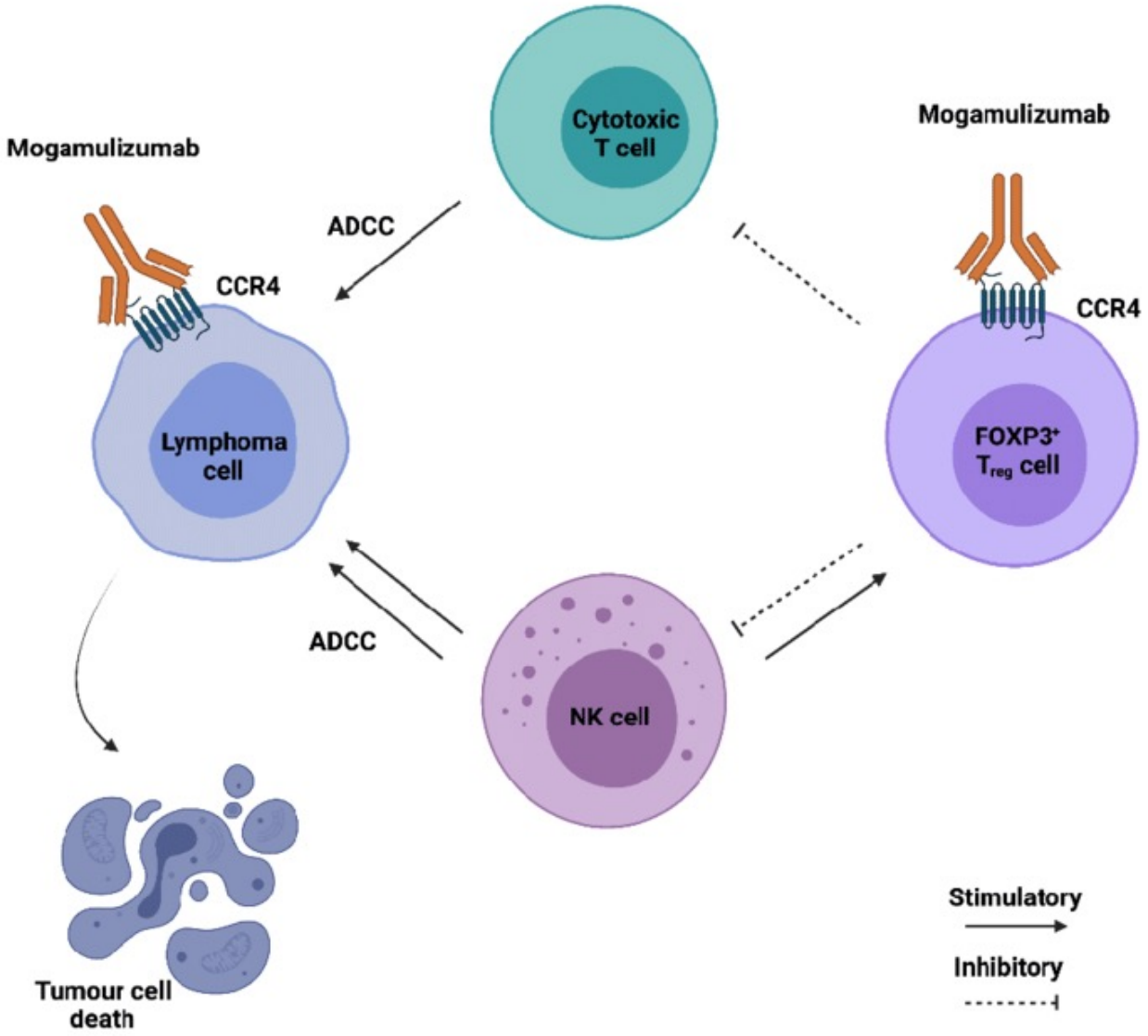


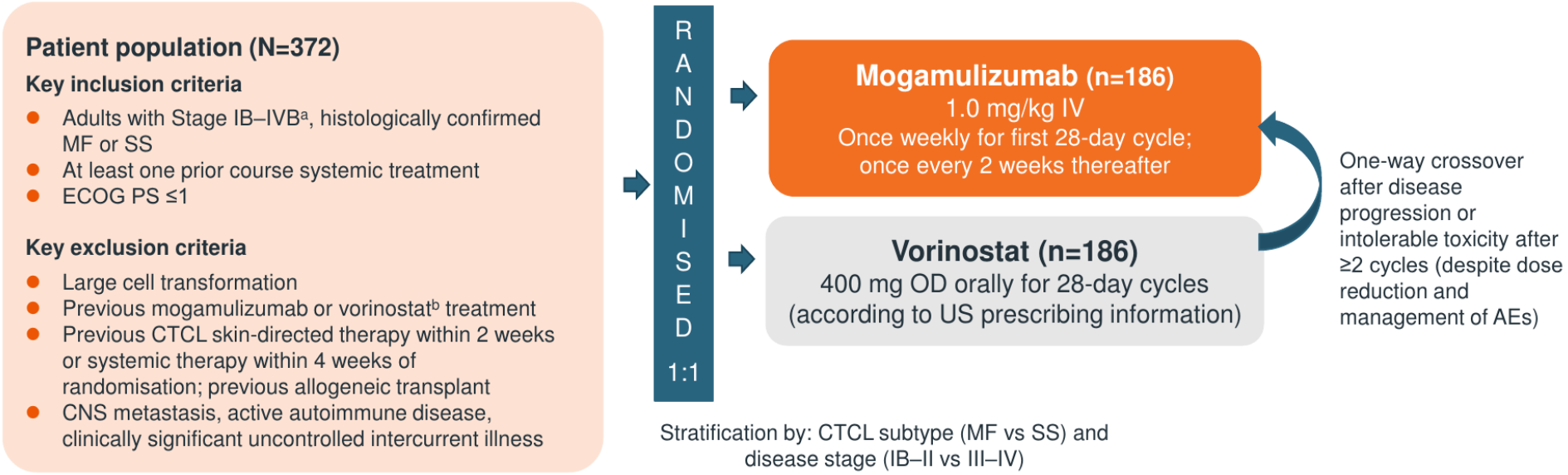
Figure 1. Extravasation of a T-cell into the dermis[6]



CCL17: chemokine (C-C motif) ligand 17, CCR4: CC chemokine receptor 4, CLA: cutaneous lymphocyte antigen, ICAM-1 intracellular adhesion molecule-1, LFA-1: leukocyte function antigen-1.


Mogamulizumab
CCR4
Lymphoma cell
ADCC
Cytotoxic T cell
Mogamulizumab
CCR4
FOXP3+ Treg cell
ADCC
NK cell
Tumour cell death
Stimulatory
Inhibitory

MAVORIC: Graphical representation of study design



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, Bagot M, Pinter-Brown L, et al. *Lancet Oncol.* 2018;19(9):1192-1204.

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Study endpoints

Primary endpoint[1]

- **Investigator-assessed progression-free survival (PFS)**
- Time from randomisation until documented disease progression or death due to any cause
- Based on Global Composite Response score based on responses (complete and partial) in each compartment (skin, blood, lymph nodes, and viscera)
- 90% power to detect a 50% increase in PFS vs. vorinostat

PFS by independent review was also performed and consisted of an independent radiological evaluation of all CT scans (two-reader paradigm) and a comprehensive review of all compartmental data.

Secondary endpoints[1]

- **Overall response rate (ORR)**
- Proportion of patients with confirmed global response at ≥2 successive evaluations ≥8 weeks apart
- Based on Global Composite Response score based on responses (complete and partial) in each compartment (skin, blood, lymph nodes, and viscera)
- **Duration of response (DOR)**
- Time from first achievement of an overall response to progression or death
- **Patient-reported assessment of quality of life (QoL)**
- Skindex-29, Functional Assessment of Cancer Therapy-General (FACT-G), 3-level EQ-5D, pruritus evaluation (Likert scale), and ItchyQoL instruments
- **Overall response rate (ORR) in crossover population**
- **Safety and immunogenicity**

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

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Patient baseline characteristics

Baseline characteristics (ITT set)	Mogamulizumab (n=186)	Vorinostat (n=186)
Median age (range), years	63.5 (25-101)	65 (25-89)
Male gender, n (%)	109 (58.6)	107 (57.5)
ECOG performance status, n (%)		
0	106 (57.0)	104 (55.9)
1	78 (41.9)	82 (44.1)
2[a]	2 (1.1)	0 (0)
Disease type, n (%)		
MF	105 (56.5)	99 (53.2)
SS	81 (43.5)	87 (46.8)
Clinical stage, n (%)		
IB-IIA	36 (19)	49 (26)
IIB	32 (17)	23 (12)
IIIA-IIIB	22 (12)	16 (9)
IVA_1	73 (39)	82 (44)
IVA_2	19 (10)	12 (6)
IVB[b]	4 (2)	4 (2)
Number of prior systemic therapies, median (range)	3 (1-18)	3 (0-14)

[a] Two patients in the mogamulizumab group had an ECOG performance status <2 at screening but equal to 2 at baseline.

[b] There were two patients (one in each arm) that were noted to be Stage IVB at baseline, but that had no measurable visceral disease at baseline.

Table elaborated from reference 1

1. Kim YH, Bagot M, Pinter-Brown L, et al. *Lancet Oncol.* 2018;19(9):1192-1204; **2.** European Medicines Agency (EMA). POTELIGEO European Public Assessment Report (EPAR). [EMA/698539/2018]. Accessed: November 2020

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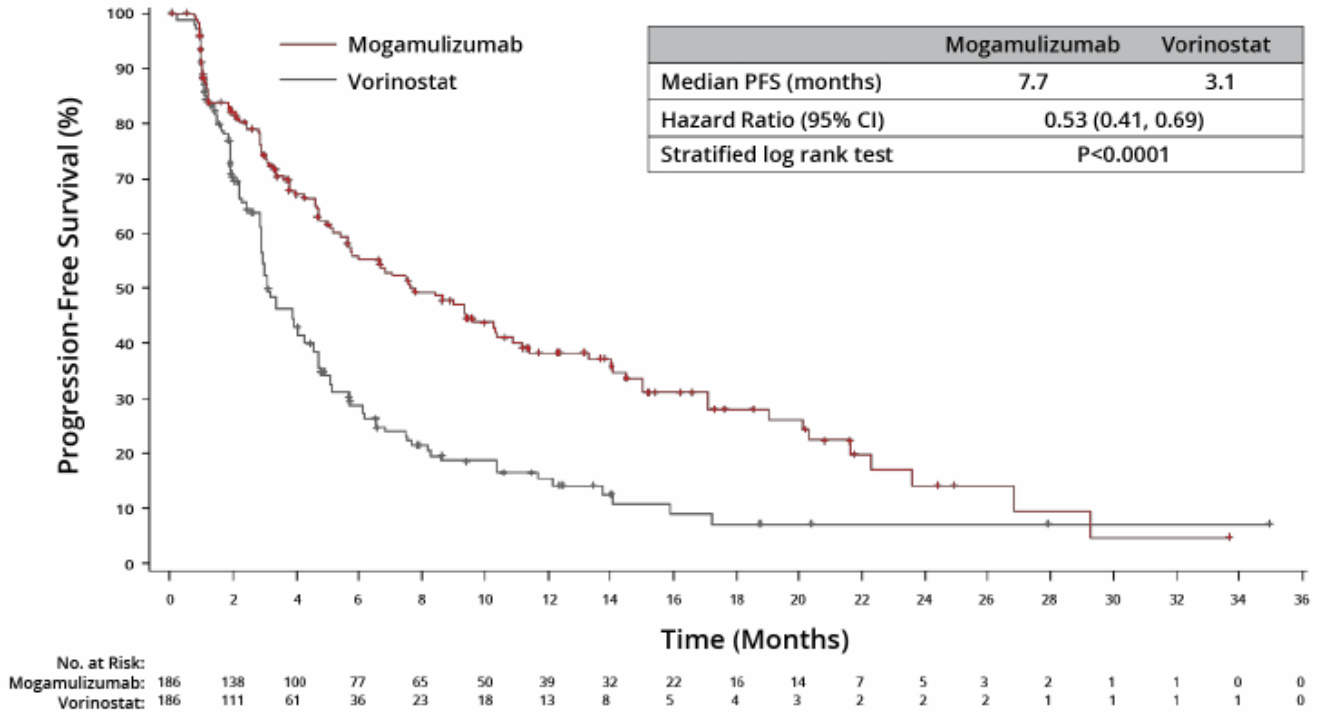
Primary endpoint (PFS)

Investigator-assessed PFS



	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, Bagot M, Pinter-Brown L, et al. *Lancet Oncol.* 2018;19(9):1192-1204.

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Other response outcomes

Measures of response by investigator assessment		
	Mogamulizumab	**Vorinostat**
ORR (CR + PR)[a], n/N (%)		
ITT set	52/196 (28)	9/186 (4.8)
MF[b] SS[a]	22/105 (21.0) 30/81 (37.0)	7/99 (7.1) 2/87 (2.3)
Stage IB-IIA Stage IIB Stage III Stage IV	7/36 (19.4) 5/32 (15.6) 5/22 (22.7) 35/96 (36.4)	5/49 (10.2) 1/23 (4.3) 0/16 (0) 3/98 (3.1)
DOR, median, months		
ITT set	14.1	9.13
MF SS	13.1 17.3	9.1 6.9
ORR (CR + PR) in crossover population, n/N (%)	41/133 (31)	
Median relative dose intensity (%)	97.5	95.1

[a] $P<0.0001$

[b] $P=0.004$

Abbreviations: CR, complete response; DOR, duration of response; ITT, intent-to-treat; MF, mycosis fungoides; ORR, overall response rate; PR, partial response; SS, Sézary syndrome.. Table elaborated from 1)

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

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Compartmental responses

Compartmental responses	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)	
Blood	1.1 months
Skin	3.0 months
Lymph nodes	3.3 months

Table elaborated from reference 2

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

Table elaborated from reference 2

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

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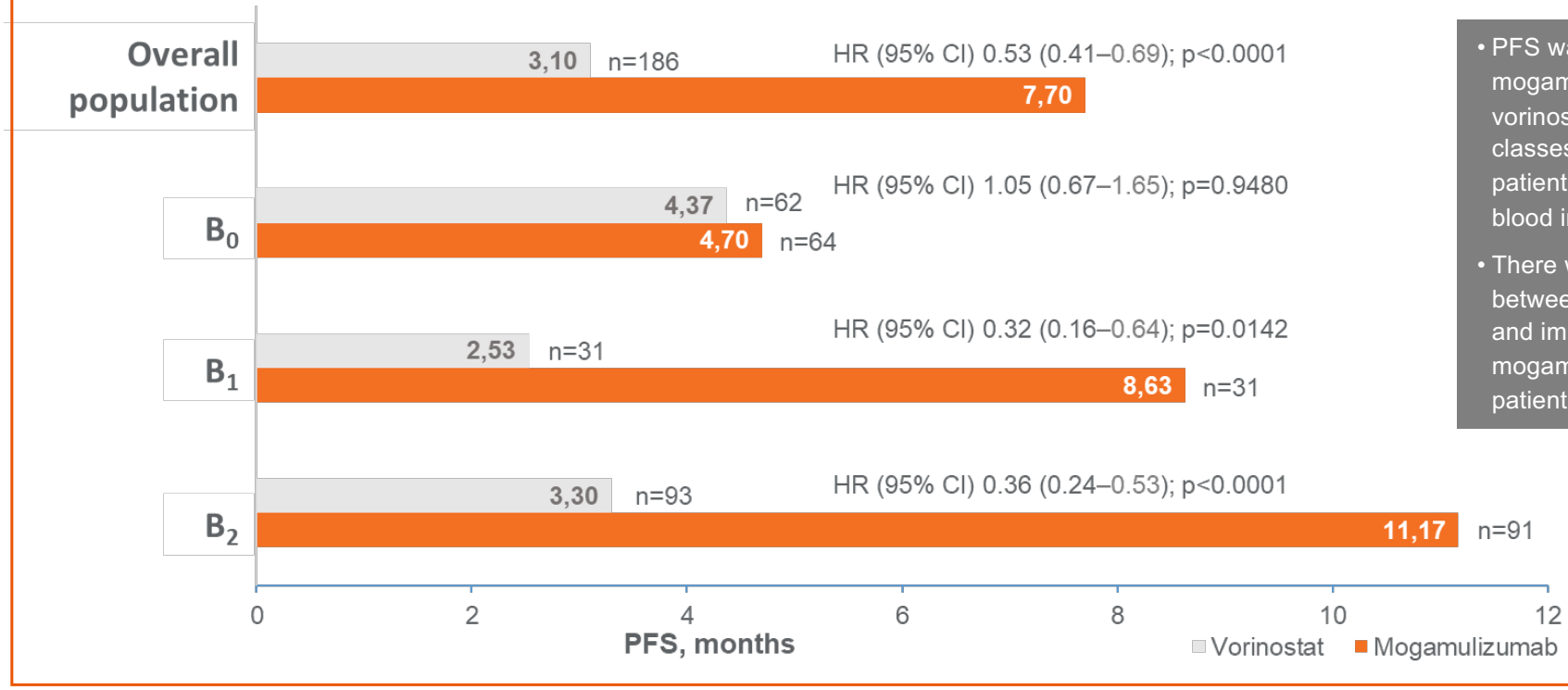
Mogamulizumab: progression-free survival (PFS) by blood tumour burden

Investigator-assessed PFS in the overall population and by patient blood tumour burden[1]



- PFS was higher with mogamulizumab than with vorinostat across all B-classes; significantly so for patients with B1 and B2 blood involvement.[1]
- There was a correlation between increasing B-class and improved PFS in mogamulizumab-treated patients.[1]

1. Cowan R, et al. JEADV 2021, 35, 2225-2238

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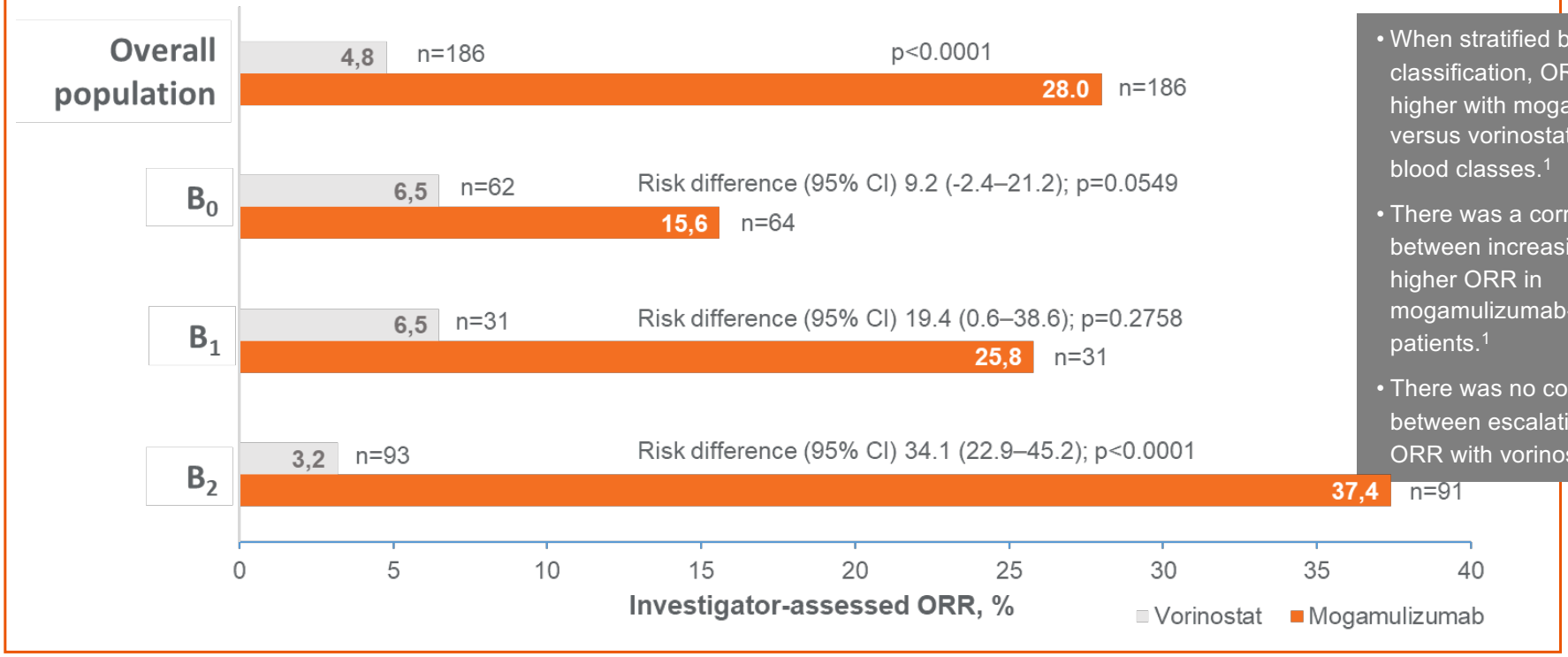
Mogamulizumab: ORR by blood tumour burden

Investigator-assessed ORR in the overall population and by patient blood tumour burden[1]



- When stratified by patient blood classification, ORRs were higher with mogamulizumab versus vorinostat across all blood classes.[1]
- There was a correlation between increasing B-class and higher ORR in mogamulizumab-treated patients.[1]
- There was no correlation between escalating B-class and ORR with vorinostat.[1]

1. Cowan R, et al. JEADV 2021, 35, 2225-2238

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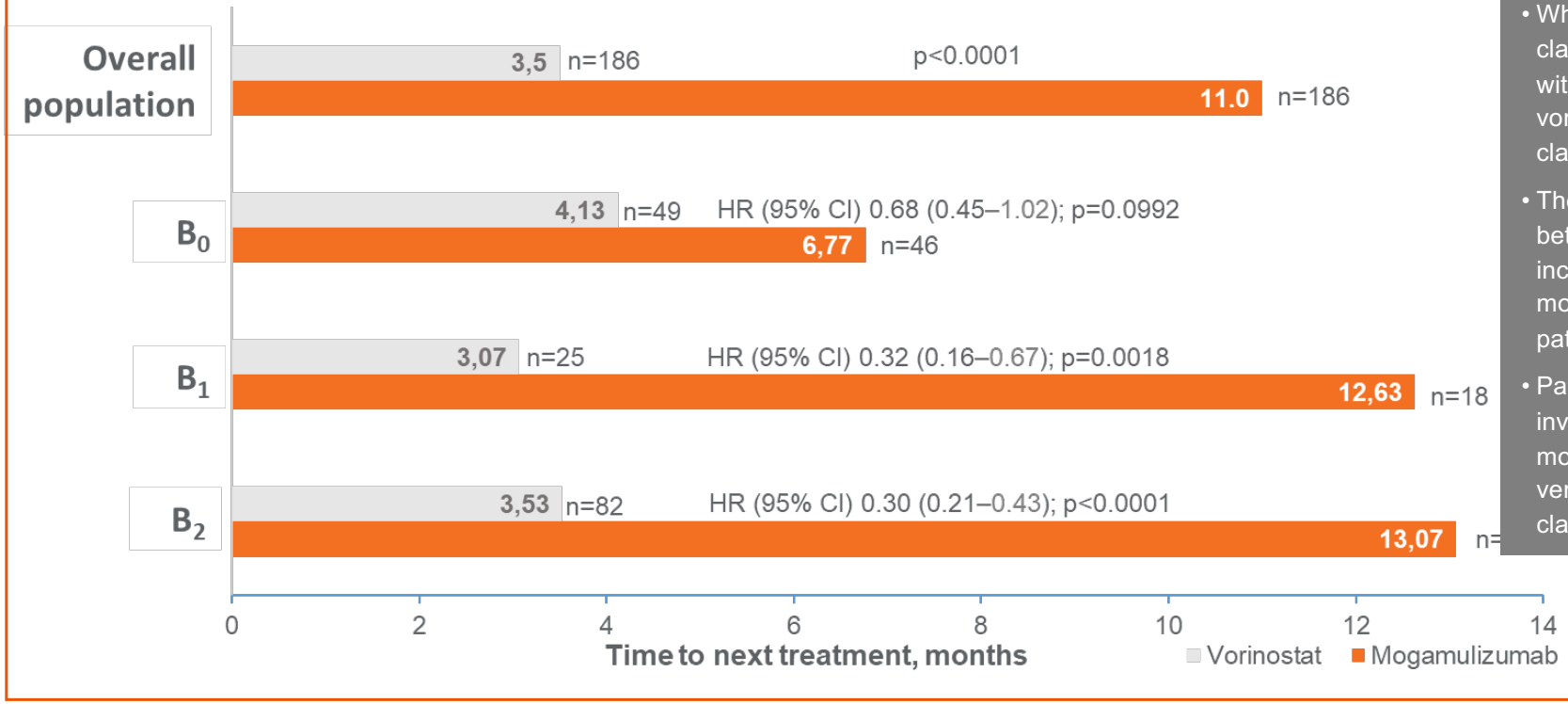
Mogamulizumab: time to next treatment (TTNT) by blood tumour burden

TTNT in the overall population and by patient blood tumour burden[1]



- When stratified by patient blood classification, TTNT was higher with mogamulizumab versus vorinostat across all blood classes.[1]
- There was a correlation between increasing B-class and increased TTNT in mogamulizumab-treated patients.[1]
- Patients with B1 blood involvement treated with mogamulizumab had a TTNT very similar to those patients classed as B2.[1]

1. Cowan R, et al. JEADV 2021, 35, 2225-2238

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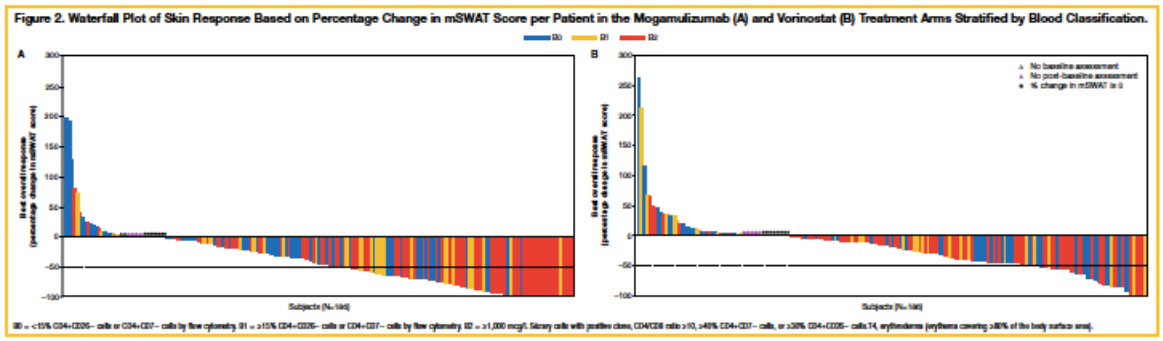
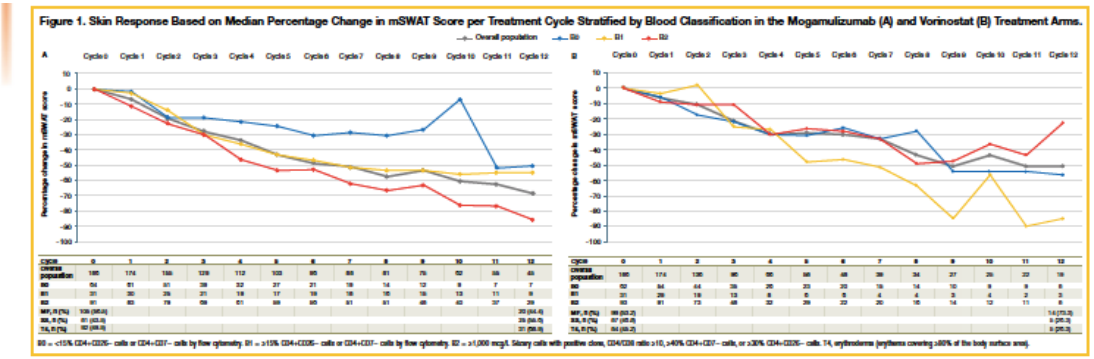
> J Eur Acad Dermatol Venereol. 2021 Jul 17. doi: 10.1111/jdv.17523. Online ahead of print.

Efficacy and safety of mogamulizumab by patient baseline blood tumour burden: a post hoc analysis of the MAVORIC trial

R A Cowan [1], J J Scarisbrick [2], P L Zinzani [3 4], J P Nicolay [5], L Sokol [6], L Pinter-Brown [7], P Quaglino [8], L Iversen [9], R Dummer [10], A Musiek [11], F Foss [12], T Ito [13], J-P Rosen [14], M C Medley [14]

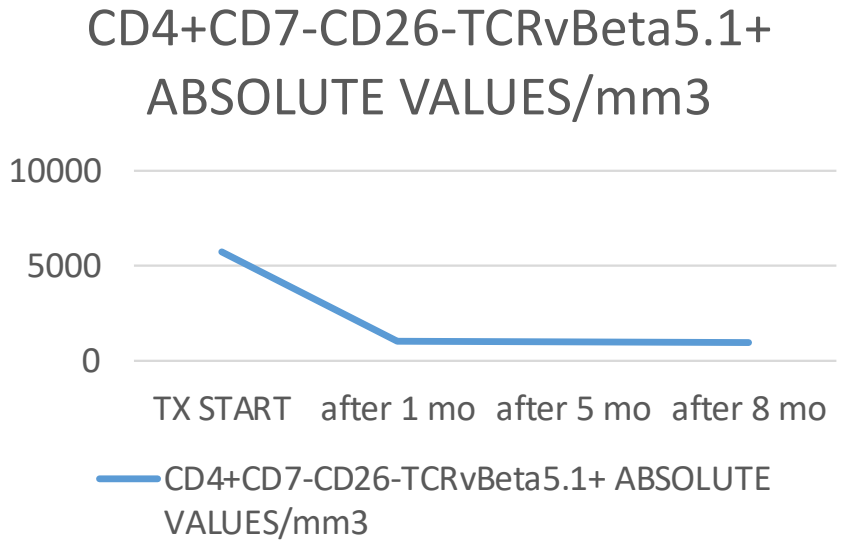
OVERALL POPULATION B0 B1 B2

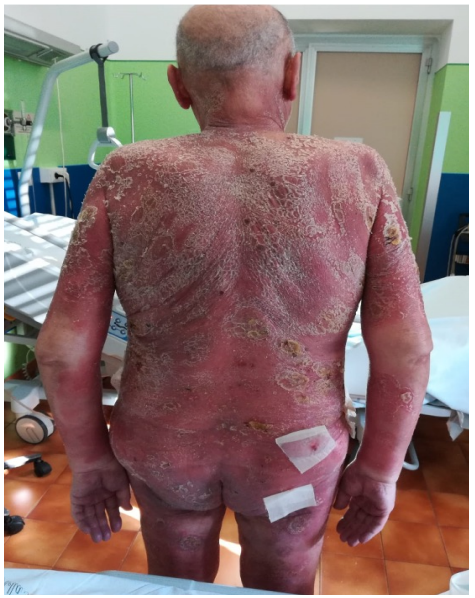


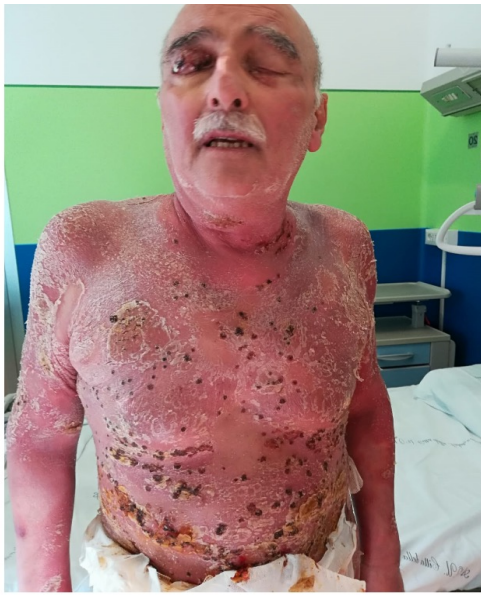


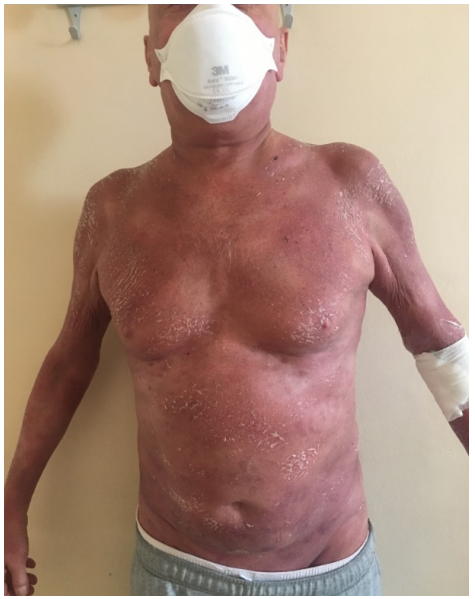
CASE PRESENTATION

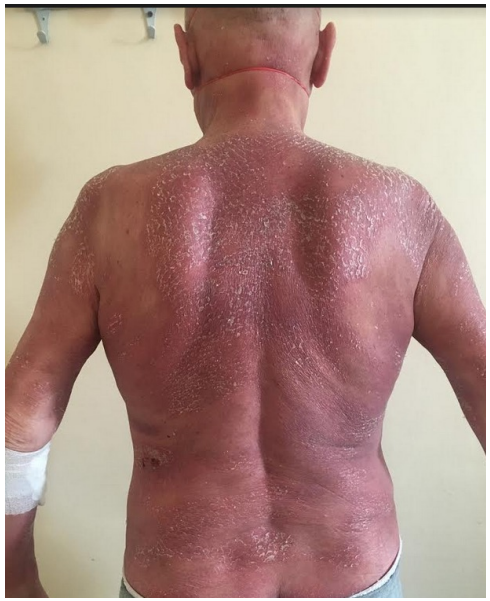
- Male patient, 70 years old
- Associated comorbidities: hypothyroidism, hypertension
- July 2019: diagnosis of Sézary syndrome, treated with ECP plus retinoids without response
- April 2020: worsening of the clinical picture with erythroderma and ulcerated lesions, circulating atypical blood cells CD3+CD5h, CD4+CD7-CD26-TCRvBeta5.1pos: 5,733/mmc
- Started Mogamulizumab May, 28, 2020 in nominate use











blood® Perspective

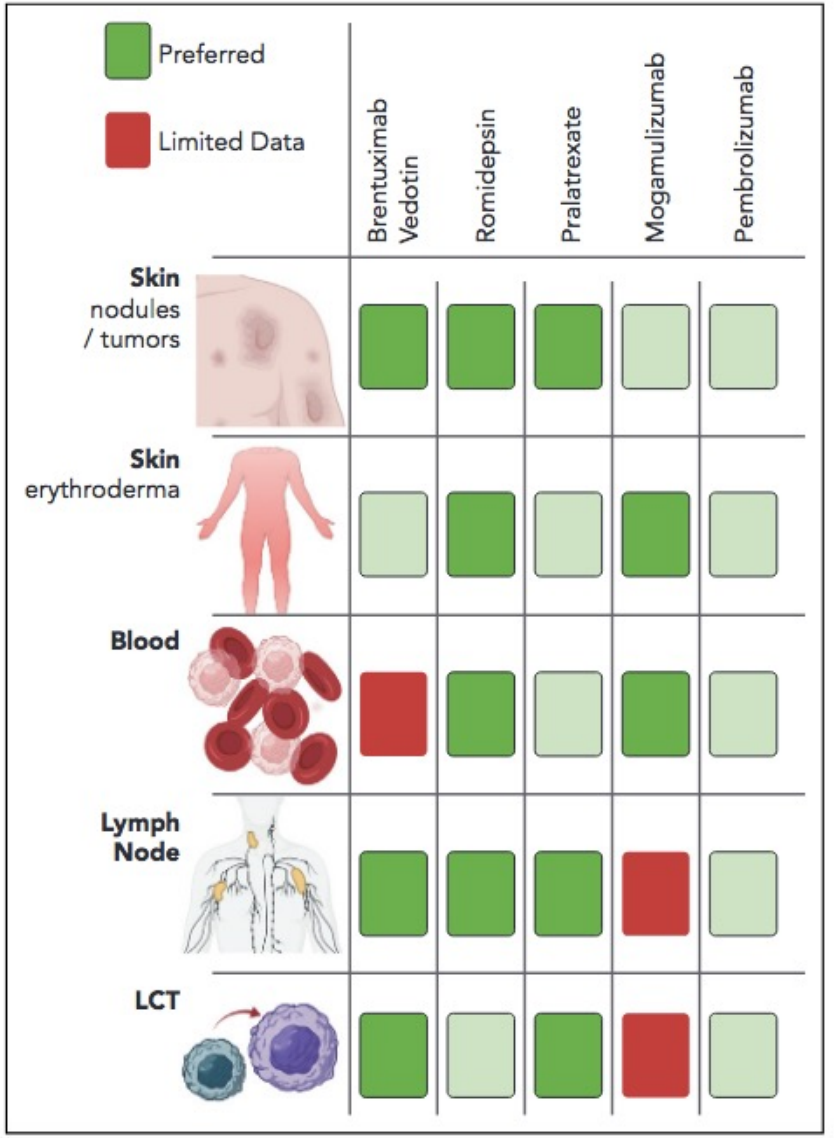
Integrating novel agents into the treatment of advanced mycosis fungoides and Sézary syndrome

Michael S. Khodadoust,[1,2] Eric Mou,[3] and Youn H. Kim[1,2]

[1]Division of Oncology, Stanford University, Stanford, CA; [2]Department of Dermatology, Stanford University, Stanford, CA; [3]Division of Hematology, Oncology, and Blood & Marrow Transplantation, University of Iowa, Iowa City, IA

Agents targeting the unique biology of mycosis fun-

increase, we are now challenged with selecting treat-



Received: 19 October 2020 | Revised: 7 December 2020 | Accepted: 8 December 2020

DOI: 10.1002/hon.2832

REVIEW

WILEY

Critical concepts and management recommendations for cutaneous T-cell lymphoma: A consensus-based position paper from the Italian Group of Cutaneous Lymphoma

Pier Luigi Zinzani[1,2] | Pietro Quaglino[3] | Silvia Alberti Violetti[4] | Maria Cantonetti[5] | Gaia Goteri[6] | Francesco Onida[7] | Marco Paulli[8] | Serena Rupoli[9] | Giovanni Barosi[10] | Nicola Pimpinelli[11]

[1]IRCCS, Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

[2]Institute of Hematology "L. e A. Seràgnoli", DIMES University of Bologna, Bologna, Italy

[3]Department Medical Sciences, Dermatologic Clinic, University of Turin, Italy

[4]UOC Dermatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milano, Milano, Italy

[5]Onco-Hematology Department, University "Tor Vergata", Roma, Italy

[6]Anatomo-Pathology Unit, DISBSP University Politecnica delle Marche, Ospedali Riuniti di Ancona, Ancona, Italy

[7]Hematology–Bone Marrow Transplantation Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico - University of Milan, Italy

[8]Anatomo-Pathology Unit, University of Pavia, Pavia, Italy

[9]Clinic of Hematology, Ospedali Riuniti Ancona, Ancona, Italy

[10]Center for the Study of Myelofibrosis, Laboratory of Biochemistry, Biotechnology and Advanced Diagnostics, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy

[11]Dermatology Department, University of Firenze, Firenze, Italy

Hematological Oncology [0278-0232] Zinzani, Pier anno:2020

Goals of therapy for CTCLs are to control symptoms, warranting a better QoL, and to improve survival by maximally reducing the tumor burden.

Key issues for the choice of therapy for CTCLs are: stage of disease, age/life expectancy, and availability of specific treatment procedures (e.g., total skin electron beam irradiation [TSEBI], extra-corporeal photo-chemotherapy [ECP]).

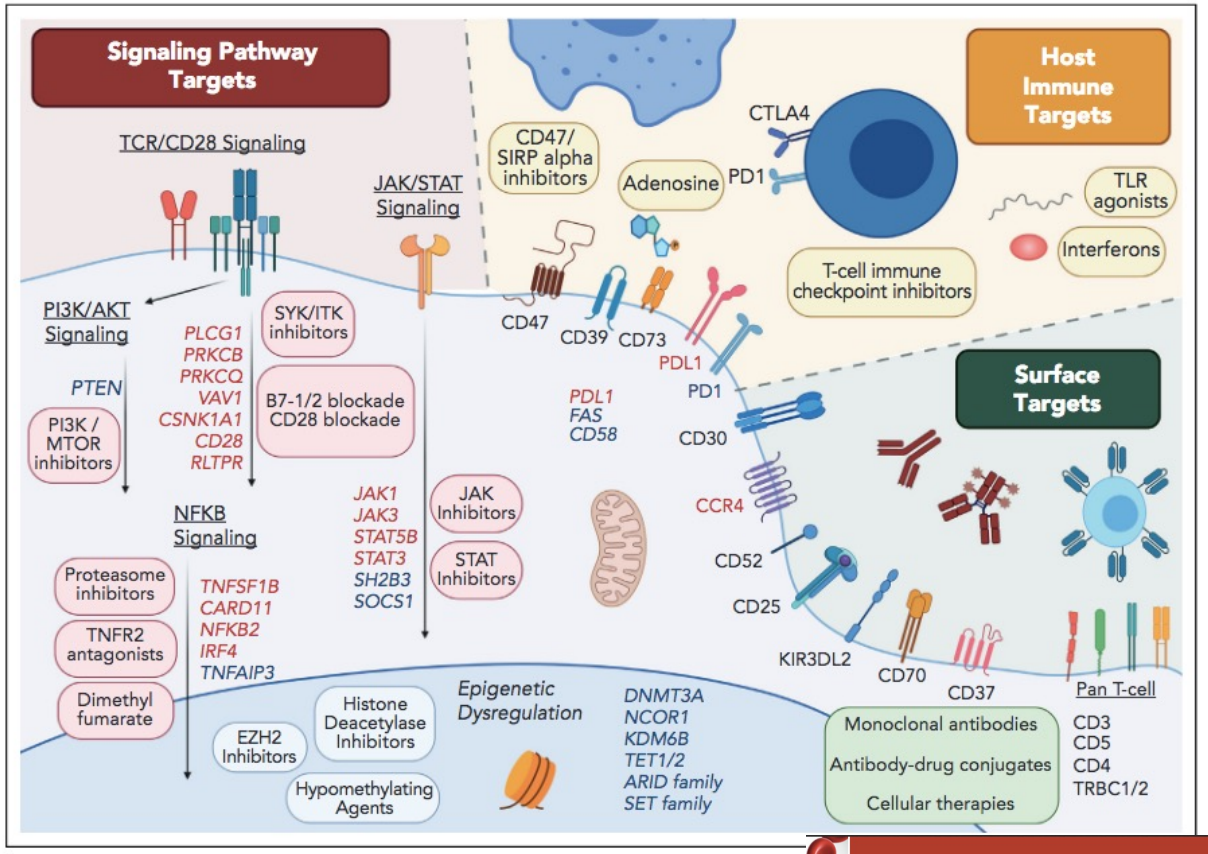
Skin-directed therapy (SDT) should be considered for early stages of disease and at disease relapse with early lesions after CR in advanced stages.

SDT associated with immunomodulating agents should be considered both for early stages refractory to/relapsing after SDT alone and for disease relapse with early lesions after CR in advanced stages.

Radiotherapy, limited field and/or total skin (TSEBI, where available), is indicated in early stages refractory to/relapsing after SDT associated with immunomodulating agents.

PRESENTATION SUMMARY

1. PRINCIPLES OF THERAPY IN MYCOSIS FUNGOIDES/SEZARY SYNDROME
2. BRENTUXIMAB VEDOTIN
3. MOGAMULIZUMAB
4. ..BEYOND



igure 2. Therapeutic targets in cutaneous T-cell lymphoma. Genes recurrently affected by gain-of-function g
hown with each altered pathway.

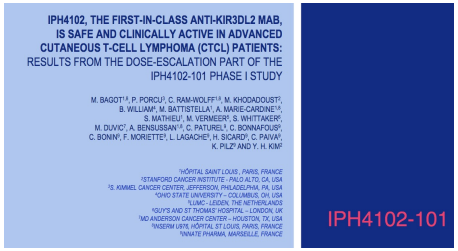
blood Perspective

Integrating novel agents into the treatment of advanced mycosis fungoides and Sézary syndrome

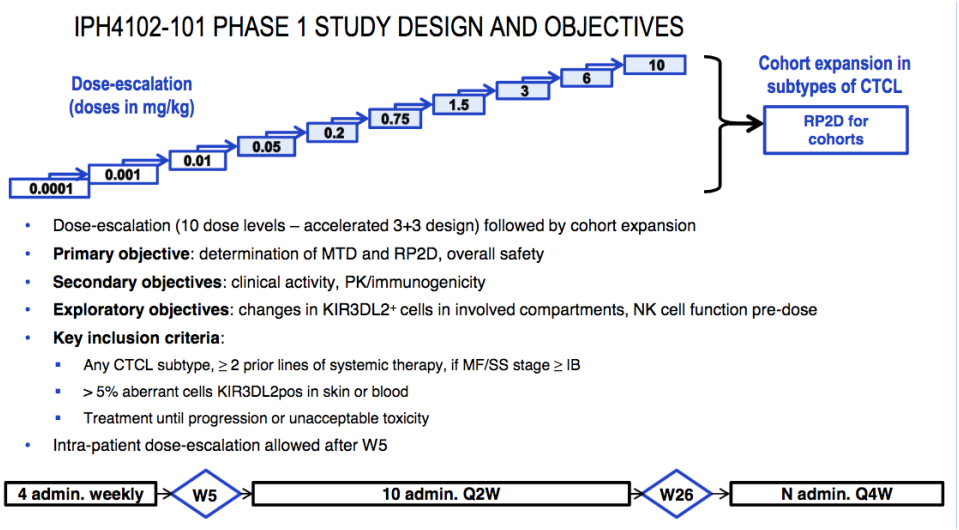
Michael S. Khodadoust,[1,2] Eric Mou,[3] and Youn H. Kim[1,2]

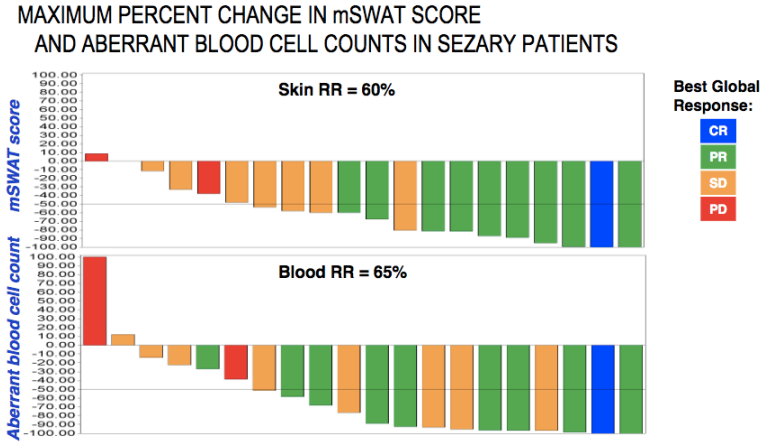
[1]Division of Oncology, Stanford University, Stanford, CA; [2]Department of Dermatology, Stanford University, Stanford, CA; [3]Division of Hematology, Oncology, and Blood & Marrow Transplantation, University of Iowa, Iowa City, IA

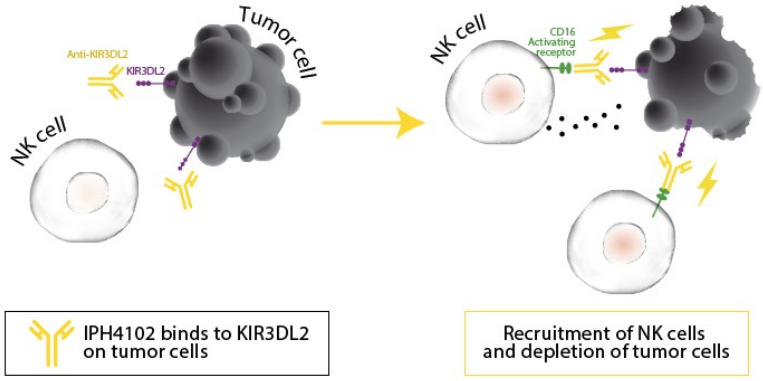
Agents targeting the unique biology of mycosis fungoides and Sézary syndrome are quickly being incorporated into clinical management. With these new increase, we are now challenged with selecting treatments from a growing list of options. To gain the full benefit of these novel agents, we must develop stra-



Lancet Oncol. 2019 Aug;20(8):1160-1170. 2045(19)30320-1. Epub 2019 Jun 25.







Immune Check Point Inhibitors in Primary Cutaneous T-Cell Lymphomas: Biologic Rationale, Clinical Results and Future Perspectives

frontiers in Oncology

REVIEW
published: 16 August 2021
doi: 10.3389/fonc.2021.733770

Gabriele Roccuzzo[1†], Silvia Giordano[1†], Paolo Fava[1], Alessandro Pileri[2,3], Alba Guglielmo[2,3], Luca Tonella[1], Martina Sanlorenzo[4], Simone Ribero[1], Maria Teresa Fierro[1] and Pietro Quaglino[1]*

OPEN ACCESS

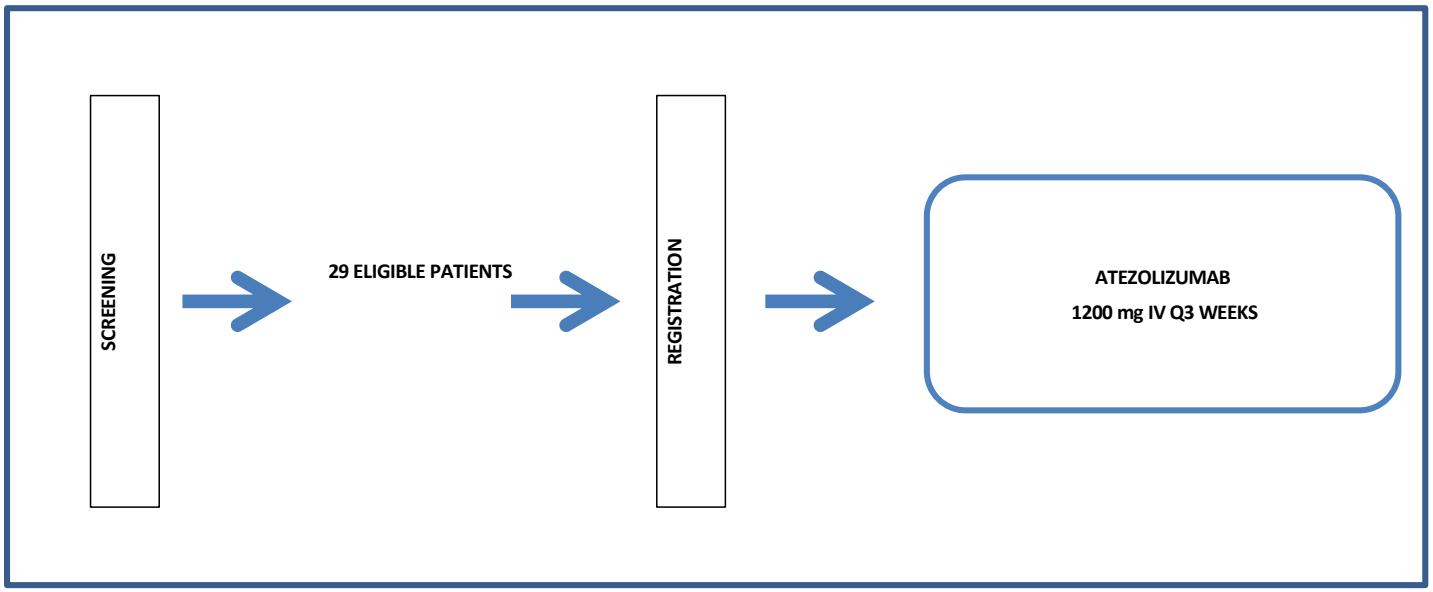
TABLE 1 | Summary of the published results from the main studies on immunotherapy in CTCL.

Target	Drug	Study Type	N° of pts	Inclusion	ORR	Disease outcome
PD-1 (Lesokhin)	Nivolumab	Phase I open-label dose-escalation, cohort-expansion basket	13	Heavily pretreated MF	15%	Duration of response up to 81 weeks
PD-1 (Khodadoust)	Pembrolizumab	Phase II	24	MF/SS patients (23 of 24 with stage IIB to IV) and heavily pretreated	38%	8 durable responses (median DOR not reached > 58 weeks)
PD-1 (Marchi)	Pembrolizumab in combination with epigenetic drugs	Phase 1b Three arms (4 patients per arm): **A**: pembrolizumab + pralatrexate **B:** pembrolizumab + pralatrexate + decitabine **C:** pembrolizumab + decitabine	12	Relapsed/refractory TCL (5 PCTL, 3 AITL*, 1 ATLL°, 2 MF and 1 SS). **Angioimmunoblastic T-cell lymphoma* *°Adult-T-cell lymphoma/ leukemia*	6 out of 12 patients evaluable for response at the time of analysis	*Arm B*: 2/4 (CR, PR)
PD-1 (Beygi)	Pembrolizumab	Case report on 3 patients **Pt.1** Pembrolizumab + IFNg 6 cycles, Pembrolizumab alone 36 cycles; **Pt.2** Pembrolizumab 2 cycles **Pt.3** Pembrolizumab 6 cycles	3	Pt.1 Stage IIB MF Pt.2 Stage IVB MF Pt.3 Stage IIB MF	***Duration of response:*** Pt.1 12 weeks (first round), 110 weeks (second round in combination with RT) Pt.2 12 weeks Pt.3 9 weeks	Pt.1 SD Pt.2 Discontinuation due to immune-related pneumonitis Pt.3 PD
CTLA-4 (Bar-Sela)	Ipilimumab	Case report	1	Stage IA MF	CR	–
CTLA-4 (Sekulic)	Ipilimumab	Case report	1	Stage IVA SS	PR 6 weeks	Death 3 months after last dose

ORR, Overall response rate; Pt, patient; Arm A, Arm B, Arm C.

EORTC – CLTF Study 1652:

Phase II trial of atezolizumab (anti-PD-L1) in the treatment of stage IIb-IV mycosis fungoides/sezary syndrome patients relapsed/refractory after a previous systemic treatment



Eur J Cancer. 2021 Oct;156 Suppl 1:S22-S23.doi: 10.1016/S0959-8049(21)00668-7.Phase II trial of atezolizumab (anti-PD-L1) in the treatment of stage IIb-IVB mycosis fungoides/Sézary syndrome patients relapsed/refractory after a previous systemic treatment (PARCT)Rudolf Stadler 1 , Pablo Ortiz Romero 2 , Martine Bagot 3 , Pietro Quaglino 4 , Emmanuella Guenova 5 , Constanze Jonak 6 , Evangelina Papadavid 7 , René Stranzenbach 8 , Delphine Sartori 9 , Jammbe Z Musoro 9 , Claudette Falato 9 , Sandrine Marreaud 9 , Julia Jane Scarisbrick 10 , Robert Knobler 6

- A total of 26 patients were registered by 7 institutions in 7 countries between 23rd October 2018 and 16th September 2019 (17 eligible)
- The proportion of responders (CR or PR) observed within 1 year since registration was 15.4% (4 patients) in the intention-to-treat population. Ten (38.5%) patients showed stable disease, 6 progression (23.1%), 3 were not evaluable and 3 (11.5%) experienced early death.
- The per-protocol population, median PFS was 3 months (95% CI 1.4–4.9), median time to next systemic treatment was 5.9 months (95% CI 2.8–NE) and median OS was not reached.
- The most frequent grade ≥3 AE was sepsis, affecting four patients (15.4%), including two leading to death, one of them considered to be possibly related to protocol treatment.

New drugs and studies on molecular targets in CTCL: HDAC inhibitors

Target	Drug	Phase	No pts	Inclusion	ORR	Disease outcome
HDAC	Vorinostat	MAVORIC III randomized moga vs vorinostat [32]	372	MF/SS stage Ib to IV with at least one systemic therapy.	28% vs 5%; RR in SS 37%; 68% in the blood	PFS median 7.7 vs 3.1; p<0.0001
HDAC	Vorinostat	Open-label phase IIb trial [119]	74	IB-IVA MF/SS, at least two prior systemic therapies, at least one of which bexarotene	29.7% (32% pruritus relief)	Median DOR NR (>185 days). Median TTP 4.9 mo, 9.8 months stage IIB or higher responders.
HDAC	Vorinostat	II [120]	33	Refractory CTCL	24% RR; 14/31 pruritus relief (45%)	Median DOR: 15.1 weeks; median TTP: 30.2 weeks
HDAC	Romidepsin	pivotal, single-arm, open-label, phaseII [122]	96	stage IB-IVA CTCL at least 1 prior systemic therapy	RR=34%, 38% IIB-IV;pruritus relief 43%	Median DOR 15 months
HDAC	Romidepsin	II [121]	84	relapsed or refractory CTCL stage-IA to IVB and ECOG 0–2	RR 35% and 31% with/out prior chemo	Median DOR 23 months
HDAC	Resminostat	III maintenance randomized vs placebo	190	MF/SS IIB-IV response or SD after a previous therapy.	-	-

A multicentre, double blind, randomized, placebo controlled, Phase II trial to evaluate resminostat for maintenance treatment of patients with advanced stage (Stage IIB-IVB) mycosis fungoides (MF) or Sézary syndrome (SS) that have achieved disease control with systemic therapy – the RESMAIN Study

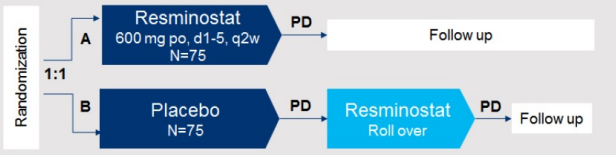
RESMAIN - Study Design

Patients

- Mycosis fungoides (advanced stages IIB – IV) or Sézary Syndrome
- CR, PR or SD 2-12 weeks after prior systemic therapy

Design

- Maintenance treatment
  - Primary endpoint: Progression free survival (PFS)
  - Secondary endpoints: TTSW (pruritus), ORR, PFS2, Safety, HrQoL, etc.



PD: progressive disease; po: per os; q2w: every 2 weeks
PFS: progression free survival; TTSW: time to symtom worsening
ORR: overall response rate; HrQoL: health related quality of life

RESMAIN Monthly Recruitment Flyer

4SC-201-6-2015

January 2019
Figures as of 01-Feb-2019

Please find below the current screening and enrolment status for the RESMAIN study and a breakdown of activity with top performing countries and sites globally.

GLOBAL RECRUITMENT	
Target number of patients:	150
Current number of patients screened:	137
Current number of patients randomized:	116

8 PATIENTS RANDOMIZED DURING JANUARY

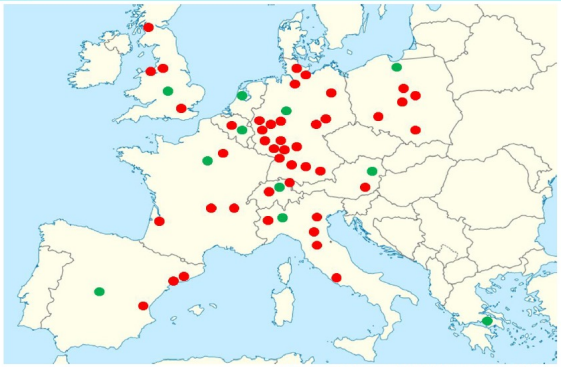
NEW ENROLLING COUNTRIES/SITES:

FR04 (Dr Michel D'Incan) screened their first patient; JP05 (Dr Youji Hirai) screened and randomised their first patient

TOP ENROLLING SITES

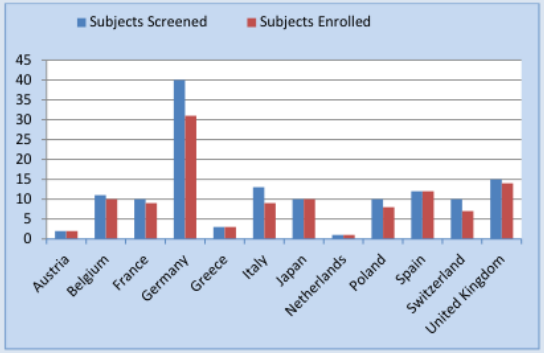
# Pts enrolled	PI name
9	BE01 Dr Woei A Jin
9	UK01 Dr Scarisbrick
7	CH01 Dr Dummer
5	ES01 Dr Ortiz Romero
5	IT01 Dr Quaglino
4	FR01 Dr Bagot
4	JP02 Dr Fujimura
4	DE01 Dr Stadler
3	DE03 Dr Dippel
3	DE04 Dr Gambichler
3	DE12 Dr Reidel
3	DE22 Dr Mitteldorf
3	ES02 Dr Gonzalez-Barca
3	GR01 Dr Papadavid
3	FR05 Dr Grange
3	PL05 Dr Romejko-Jarosinska
3	PL07 Dr Wozniacka
2	AT01 Dr Jonak
2	DE02 Dr Assaf

RESMAIN Sites and Status Update



NCI site ; NCI = national coordinating investigator

SCREENED & ENROLLED SUBJECTS PER COUNTRY (status: 01-Feb-2019)



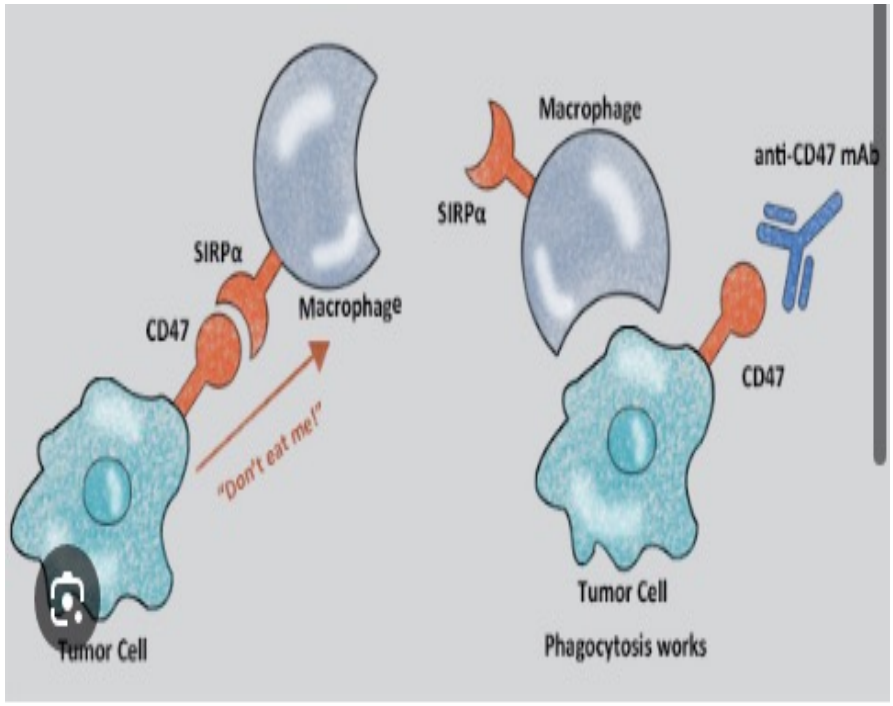
We thank you for your continued efforts and dedication.

If you have any questions or concerns or feel that 4SC or ICON may be able to provide assistance with your site's recruitment efforts, please contact your local monitor or 4SC at RESMAIN@4sc.com.

Best Regards
The RESMAIN team at 4SC and ICON

ANTI-CD47 “DO NOT EAT ME” signals

- CD47 is a potent ‘do not eat me’ signal that enables cancer cells to evade detection by the innate immune system, thereby avoiding destruction by first responder cells, such as macrophages.
- CD47 overexpression is common in solid and hematological tumors including acute leukemia, non-Hodgkin’s lymphoma (NHL), colorectal, and ovarian cancers.
- In many malignancies, its expression correlates with an aggressive phenotype and an overall poor clinical prognosis.
- Inhibition of CD47 signaling enhances macrophage phagocytic activity, and in preclinical models, leads to impaired tumor growth, inhibition of metastatic spread, and tumor regression.



A Phase IB/II Study of Hu5F9-G4 (Magrolimab) in Combination with Mogamulizumab to Treat Recurrent or Persistent T-Cell LymphomaShareFull TitleA Phase 1b/2 Study of Hu5F9-G4 (Magrolimab) in Combination with Mogamulizumab in Relapsed/Refractory Treated T-Cell Lymphoma (NCI 10384) (CIRB)

Mo-Abs anti-CD70

- CD70 is a member of the tumor necrosis factor receptor superfamily.
- Emerging data indicate that CD70 may be a suitable target for various malignancies.
- We investigated the expression of CD70 in cutaneous and systemic T-cell lymphomas and conducted preclinical studies of SGN-CD70A, a CD70-directed antibody-drug conjugate (ADC), using patient-derived xenograft cutaneous T-cell lymphoma (CTCL PDX) models.

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Targeting CD70 in cutaneous T-cell lymphoma using an antibody-drug conjugate in patient-derived xenograft models

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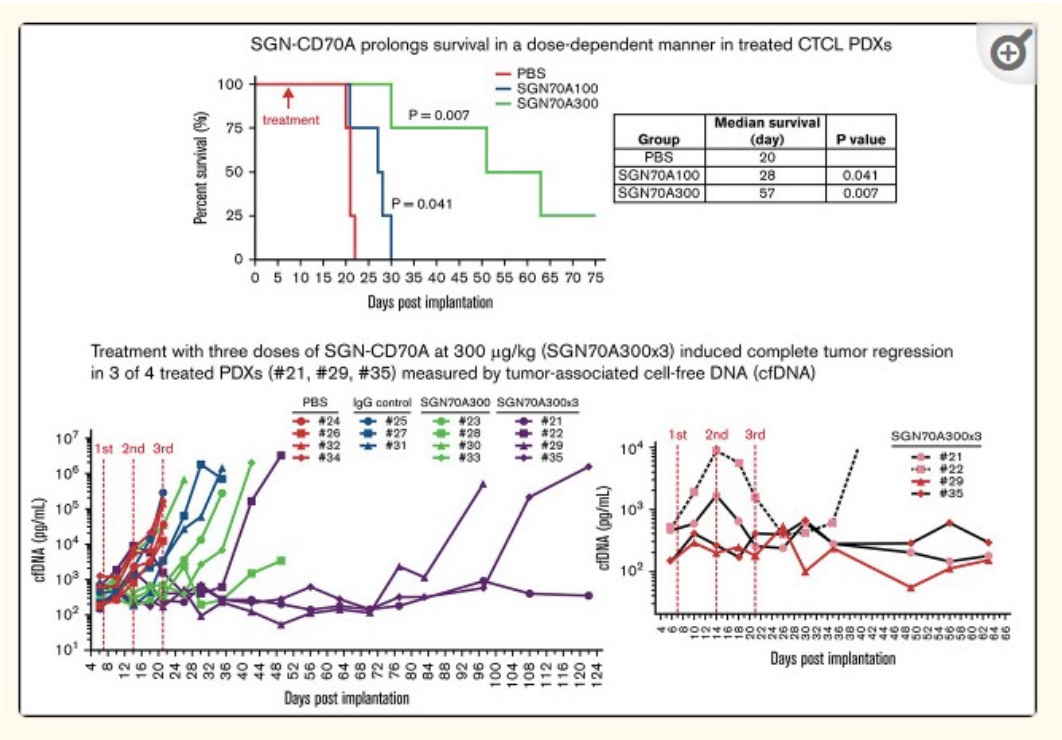


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