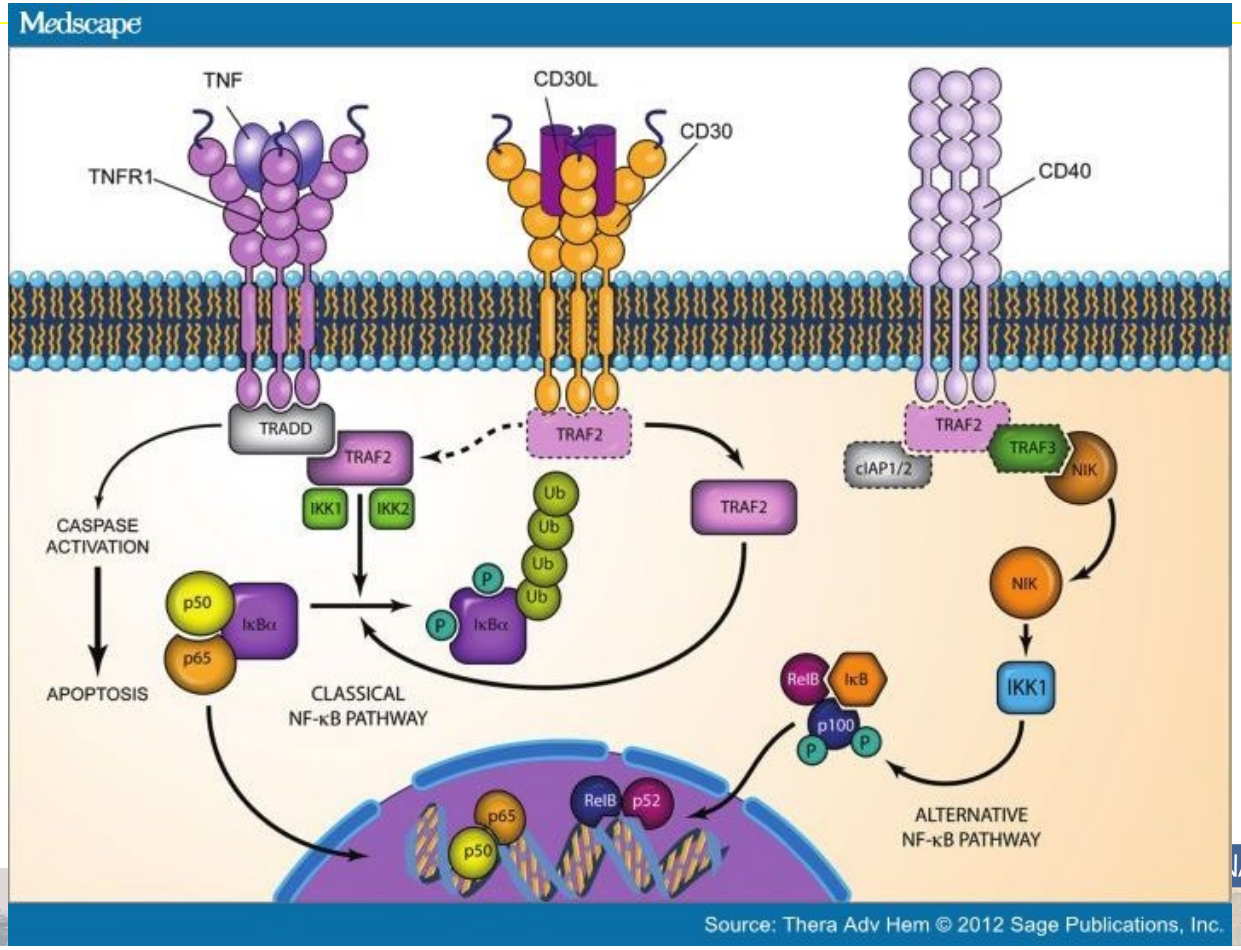
BRENTUXIMAB VEDOTIN

- Pietro Quaglino, Dermatologic Clinic, University of Torino

BRENTUXIMAB VEDOTIN

- CD30 e meccanismo di azione

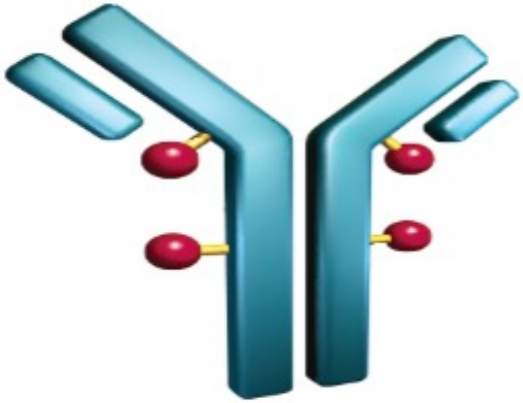
CD30, recettore delle citochine che appartiene alla superfamiglia del tumor necrosis factor receptor (TNFR)



BRENTUXIMAB

Brentuximab has three components:

- **Antibody**: the antibody cAC10 specific for human CD30



- **Cytotoxic agent**: the antimicrotubule agent monomethyl auristatin E (MMAE)
- **Linker**: a protease-cleavable linker that covalently attaches MMAE to Cac10.

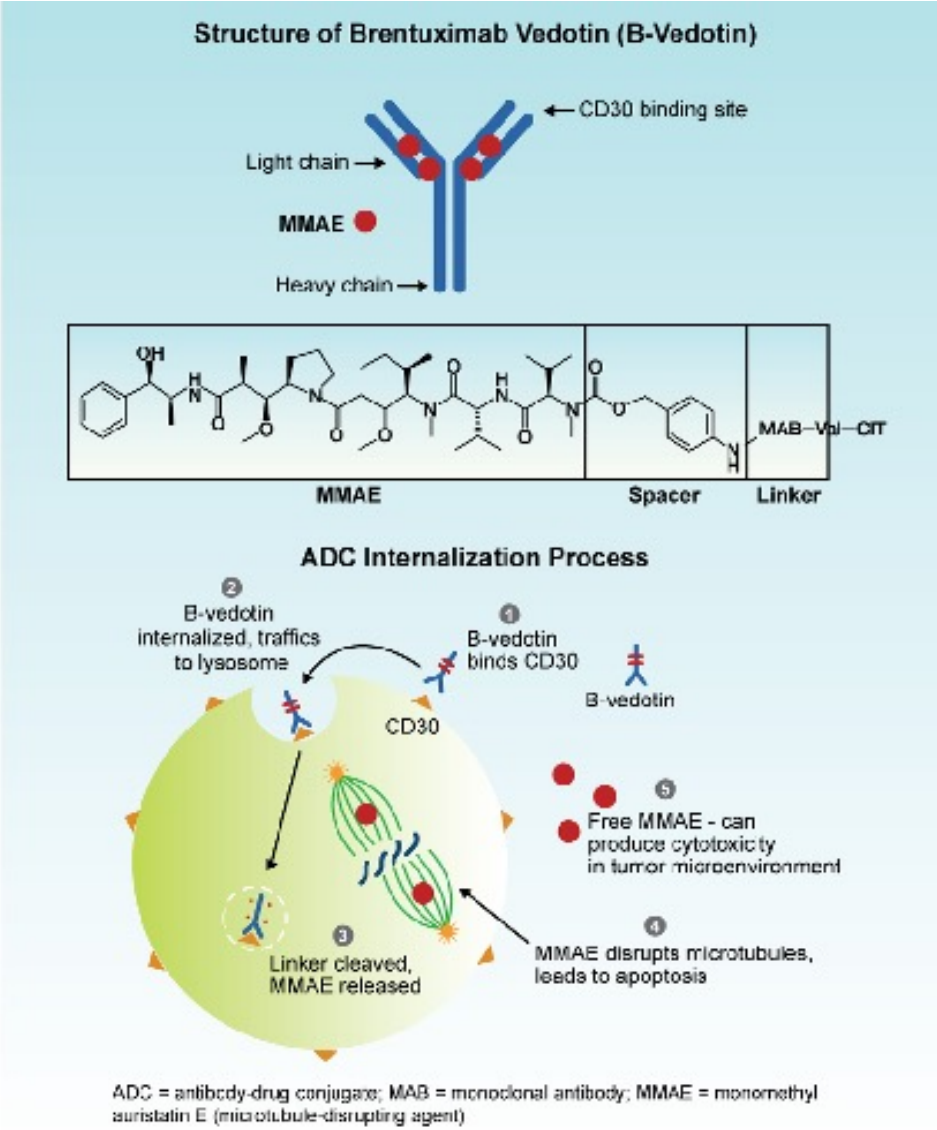


Fig 1. How brentuximab vedotin (BV) works. (1) BV [anti-CD30 monoclonal antibody + monomethyl auristatin E (MMAE)] binds to CD30 receptor; (2) internalization by endocytosis of BV–CD30 receptor complex; (3) fusion with lysosomes; (4) MMAE release through lysosomal cysteine proteases; (5) MMAE disrupts the microtubule network, which leads to cell-cycle arrest and induces apoptosis.

Katz J, Janik JE, Younes A. Brentuximab vedotin (SGN-35). Clin Cancer Res 2011; 17:6428–36.

Mir SS, Richter BW, Duckett CS. Differential effects of CD30 activation in anaplastic large cell lymphoma and Hodgkin disease cells. Blood 2000; 96:4307–12

- diffusion of MMAE into the tumour microenvironment.
- Receptor binding of MMAE itself can trigger an apoptotic signal.

BRENTUXIMAB VEDOTIN

- CD30 e meccanismo di azione
- Risultati degli studi di fase II

VOLUME 33 · NUMBER 32 · NOVEMBER 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

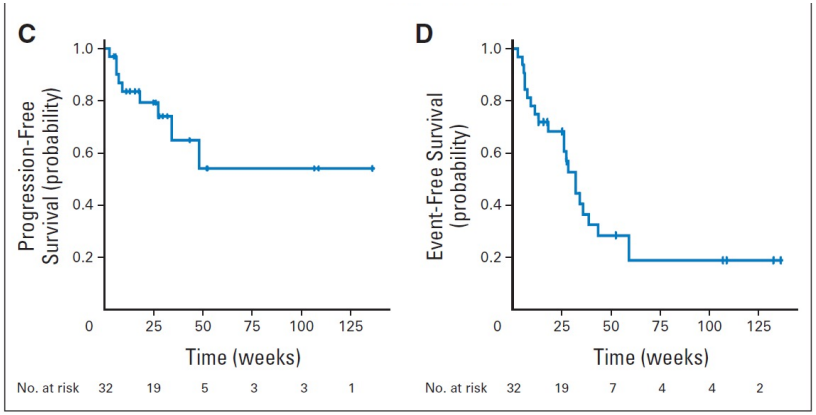
Phase II Investigator-Initiated Study of Brentuximab Vedotin in Mycosis Fungoides and Sézary Syndrome With Variable CD30 Expression Level: A Multi-Institution Collaborative Project

Youn H. Kim, Mahkam Tavallaee, Uma Sundram, Katrin A. Salva, Gary S. Wood, Shufeng Li, Sima Rozati, Seema Nagpal, Michael Krathen, Sunil Reddy, Richard T. Hoppe, Annie Nguyen-Lin, Wen-Kai Weng, Randall Armstrong, Melissa Pulitzer, Ranjana H. Advani, and Steven M. Horwitz

See accompanying articles on pages 3691 and 3759

Youn H. Kim, Mahkam Tavallaee, Uma Sundram, Shufeng Li, Sima Rozati,

A B S T R A C T



ORR:66%

Table 1. Patient Baseline Demographics, Clinical Characteristics, and Clinical Response

Characteristics	All Patients, N = 32, n (%)	Evaluable for Response, n = 30					
		CR	PR	SD	PD	NE	ORR,* n (%)
Sex							
Male	19 (59)	0	13	1	4	1	13 of 18 (72)
Female	13 (41)	1	7	3	1	1	8 of 12 (67)
Age, years, median (range)	62 (20-87)	78	60 (38-87)	60 (20-82)	64 (57-77)	60 (50-70)	
Clinical stage							
All	32 (100)	1	20	4	5	2	21 of 30 (70)
IB	4 (13)	0	3	1	0	0	3 of 4 (75)
IIB	18 (56)	0	14	2	2	0	14 of 18 (78)
IV/SS†	10 (31)	1	3	1	3	2	4 of 8 (50)
Adverse prognostic factors							
LCT or FMF	29 (90)	1	19	3	5	1	20 of 28 (71)
LCT	16 (50)	1	9	2	3	1	10 of 15 (67)
FMF	8 (25)	0	7	1	0	0	7 of 8 (88)
LCT + FMF	5 (16)	0	3	0	2	0	3 of 5 (60)
No. of prior systemic therapies							
< 3	15 (47)	0	8	2	4	1	8 of 14 (57)
≥ 3	17 (53)	1	12	2	1	1	13 of 16 (81)
CD30 grouping at screening							
A (< 10%)	14 (44)	0	7	4	2	1	7 of 13 (54)
B (10% to 50%)	14 (44)	0	11	0	3	0	11 of 14 (79)
C (> 50%)	4 (13)	1	2	0	0	1	3 of 3 (100)

Abbreviations: CR, complete response; FMF, folliculotropic mycosis fungoides; LCT, large-cell transformation; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SS, Sézary syndrome.
*Objective clinical response was observed in 21 (70%) of the 30 efficacy-evaluable patients
†Of 10 stage IV patients, three patients had SS with one CR, one PR, and one PD; one patient was stage IVB who had PR.

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Results of a Phase II Trial of Brentuximab Vedotin for CD30+ Cutaneous T-Cell Lymphoma and Lymphomatoid Papulosis

Madeleine Duvic, Michael T. Tetzlaff, Pamela Gangar, Audra L. Clos, Dawen Sui, and Rakhshandra Talpur

See accompanying articles on pages 3691 and 3750

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A B S T R A C T

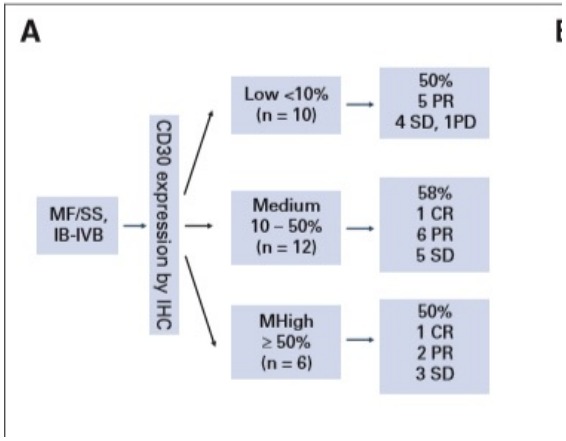
Purpose
Brentuximab vedotin, a monoclonal antibody (cAC10) conjugated to monomethyl auristatin E, targets CD30+ receptors. This phase II open-label trial was conducted to evaluate safety and efficacy in CD30+ cutaneous T-cell lymphomas.

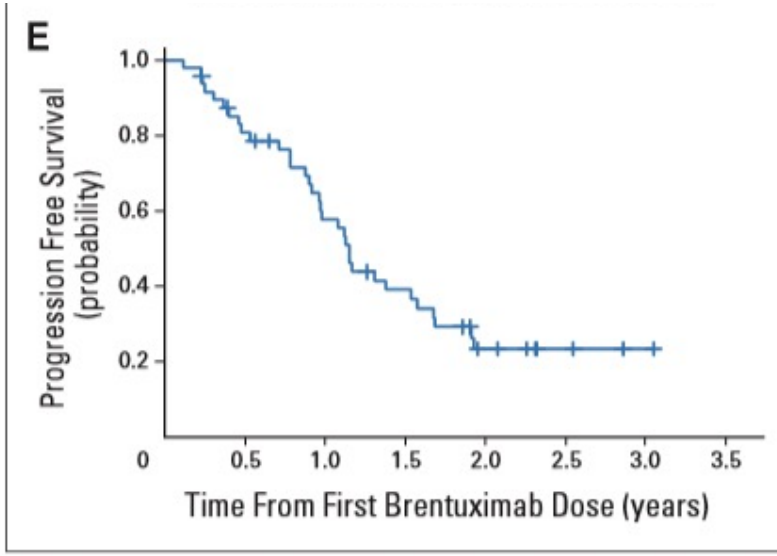
Patients and Methods
Forty-eight patients with CD30+ lymphoproliferative disorders or mycosis fungoides (MF) received an infusion of 1.8 mg/kg every 21 days.

Table 2. Response in Evaluable Patients

Diagnosis	Total No. of Patients (N = 48)	Response		Secondary Response (No.)
		No.	%	
All patients	48	35	73	
MF	28	13 PR, 2 CR	54	
LyP	9	5 CR, 4 PR	100	
pc-ALCL	2	2 CR	100	
LyP/MF	7	6 LyP CR, 1 LyP PR	100	6 MF PR, 1 MF SD
pc-ALCL/LyP	1	CR	100	1 LyP PD
pc-ALCL/MF	1	CR	100	1 MF PR

Abbreviations: ALCL, anaplastic large-cell lymphoma; CR, complete response; LyP, lymphomatoid papulosis; MF, mycosis fungoides; pc, primary cutaneous; PD, progressive disease; PR, partial response; SD, stable disease.





Progression-free survival was 1.1 year (95% CI, 0.9 to 1.4 years;

BRENTUXIMAB VEDOTIN

- CD30 e meccanismo di azione
- Risultati degli studi di fase II
- Lo studio ALCANZA

Brentuximab Vedotin Demonstrates Significantly Superior Clinical Outcomes in Patients With CD30-Expressing Cutaneous T-Cell Lymphoma Versus Physician's Choice (Methotrexate or Bexarotene): the Phase 3 ALCANZA study

Youn H. Kim,[1] Sean Whittaker,[2] Steven Horwitz,[3] Madeleine Duvic,[4] Reinhard Dummer,[5] Julia Scarisbrick,[6] Pietro Quaglino,[7] Pier Luigi Zinzani,[8] Pascal Wolter,[9] Yinghui Wang,[10] Maria Corinna Palanca-Wessels,[10] Erin Zagadailov,[11] William L. Trepicchio,[11] Yi Liu,[11] Meredith Little,[11] H. Miles Prince[12]

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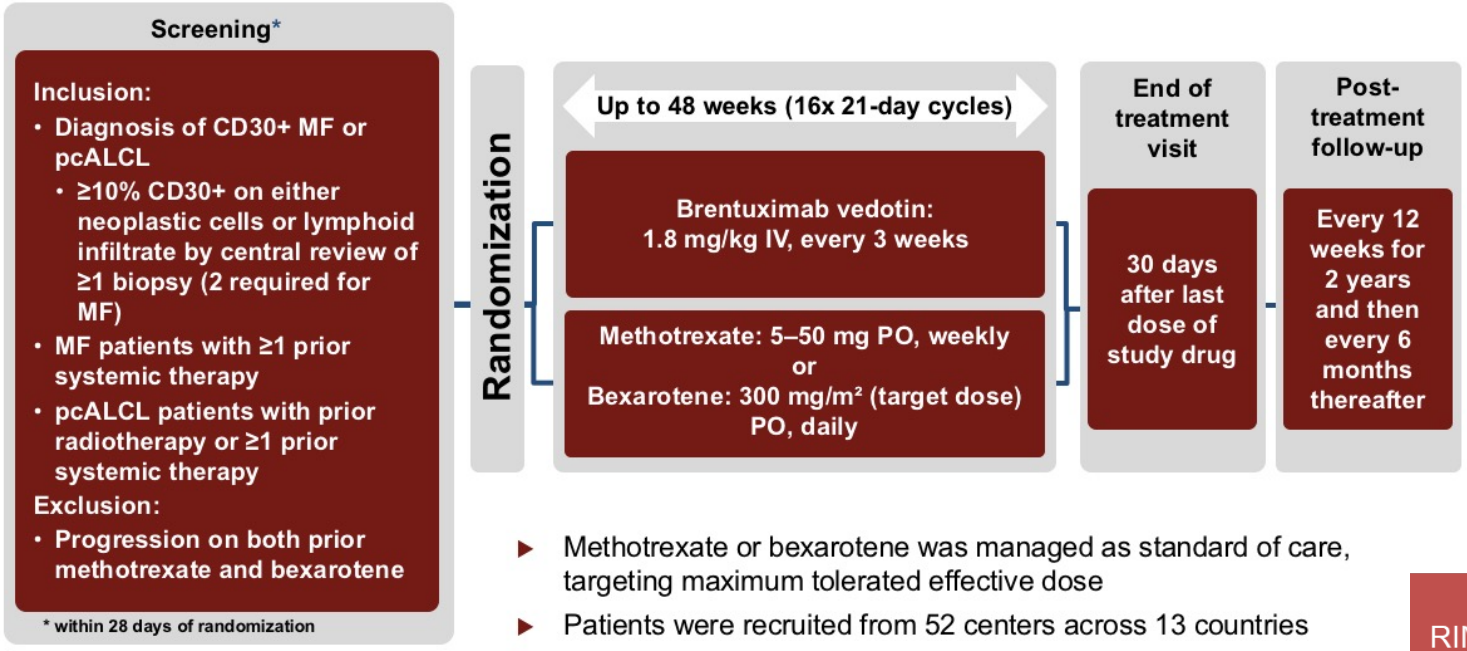
LANCET 2017

ALCANZA: a randomized, open-label, phase 3 trial of brentuximab vedotin vs physician's choice (methotrexate or bexarotene) in patients with CD30+ CTCL



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

IV, intravenously; PO, orally

AIFA RIMBORSABILITA' : CTCL CD30+ SOTTOPOSTI A 1 PREC TERAPIA SISTEMICA

ALCANZA study endpoints

- **Primary endpoint**
  - ORR4 = rate of objective response lasting ≥4 months
  - Independent review of global response of all compartments using consensus criteria (mSWAT for skin evaluation, radiographic assessment, and circulating Sézary cell assessment as appropriate)[1]
  - Sample size calculation: 90% power to detect 30% improvement in ORR4
- **Key secondary endpoints**
  - CR rate
  - PFS
  - Symptom burden/PRO (measure of QoL using Skindex-29[2])

mSWAT, modified severity weighted assessment tool; PRO, patient reported outcome; QoL, quality of life

1. Olsen EA, et al. J Clin Oncol 2011; 29(18):2598–607
2. Chren MM, at al. Arch Dermatol 1997;133:1433-40

Patient baseline characteristics: ITT population, N=128

	Brentuximab vedotin (n=64)	Methotrexate or bexarotene (n=64)
Median age, years (range)	**62 (22–83)**	**59 (22–83)**
Male gender, n (%)	**33 (52)**	**37 (58)**
ECOG performance status 0–1, n (%)	**61 (95)**	**62 (97)**
Median of average CD30 expression from multiple biopsies at baseline, % (range)	**33 (3–100)**	**31 (5–100)**
MF*, n (%)	**48 (75)**	**49 (77)**
Early (IA-IIA)	15 (31)	18 (37)
Advanced (IIB-IVB**)	32 (67)	30 (61)
pcALCL, n (%)	**16 (25)**	**15 (23)**
Skin only	9 (56)	11 (73)
Extracutaneous disease	7 (44)	4 (27)
Total number of prior therapies, median (range)	**4.0 (0–13)**	**3.5 (1–15)**
Number of prior systemic therapies, median (range)	**2.0 (0–11)**	**2.0 (1–8)**

*One patient in each arm had incomplete staging data and are not included
** stage IVB MF, n=7 in brentuximab arm vs. n=0 in methotrexate/bexarotene arm

Disease stage‡§			
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	16 (25%)	15 (23%)	31 (24%)
Disease stage‡			
Skin			
T_1	1/16 (6%)	4/15 (27%)	5/31 (16%)
T_2	3/16 (19%)	5/15(33%)	8/31 (26%)
T_3	12/16 (75%)	6/15 (40%)	18/31 (58%)
Node			
N_0	10/16 (63%)	11/15 (73%)	21/31 (68%)
N_1	2/16 (13%)	1/15 (7%)	3/31 (10%)
N_2	2/16 (13%)	1/15 (7%)	3/31 (10%)
N_3	2/16 (13%)	2/15 (13%)	4/31 (13%)
Visceral			
M_0	12/16 (75%)	14/15 (93%)	26/31 (84%)
M_1	4/16 (25%)	1/15 (7%)	5/31 (16%)

Primary and key secondary endpoint analyses (ITT population)

Endpoint	Brentuximab vedotin N=64	Physician's Choice N=64	Difference Between Arms (95% CI)	Statistical Significance
Primary endpoint				
ORR4, n (%)	36 (56.3%)	8 (12.5%)	43.8% (29.1, 58.4)	p<0.0001
Key secondary endpoints				
CR, n (%)	10 (15.6%)	1 (1.6%)	14.1% (-4.0, 31.5)	p=0.0046 [adj]
Median PFS, months	16.7	3.5		p<0.0001 [adj] HR=0.270 (95% CI: 0.169, 0.430)
Mean maximum reduction in Skindex-29 symptom domain, points	-27.96	-8.62	-18.9 (-26.6, -11.2)	p<0.0001 [adj]

Adj, adjusted p-value calculated from a weighted Holm's procedure; CI, confidence interval; HR, hazard ratio

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

NA, not applicable

Progression-free survival (ITT population)

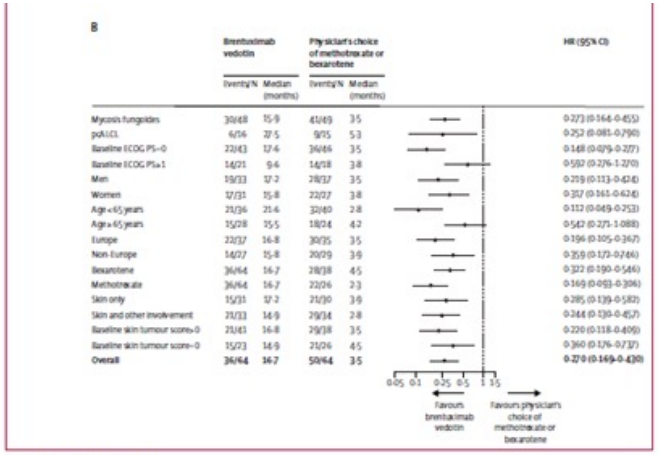
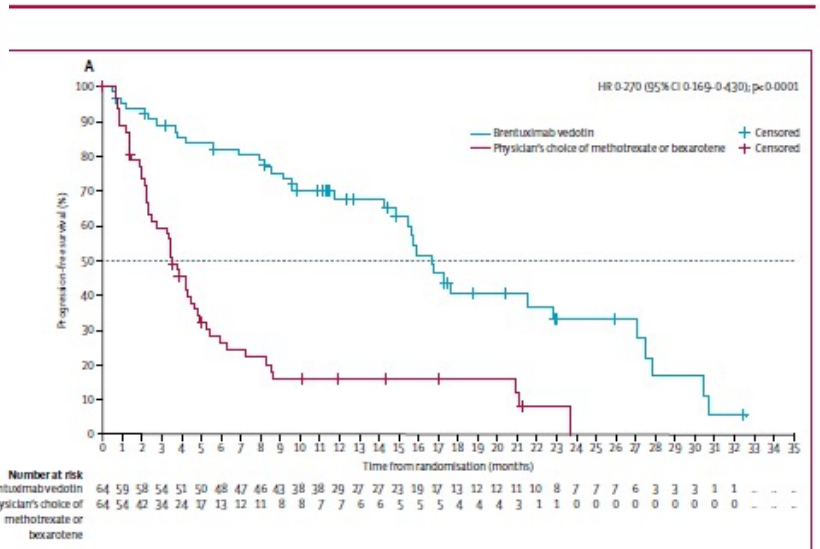


Figure 4: Progression-free survival

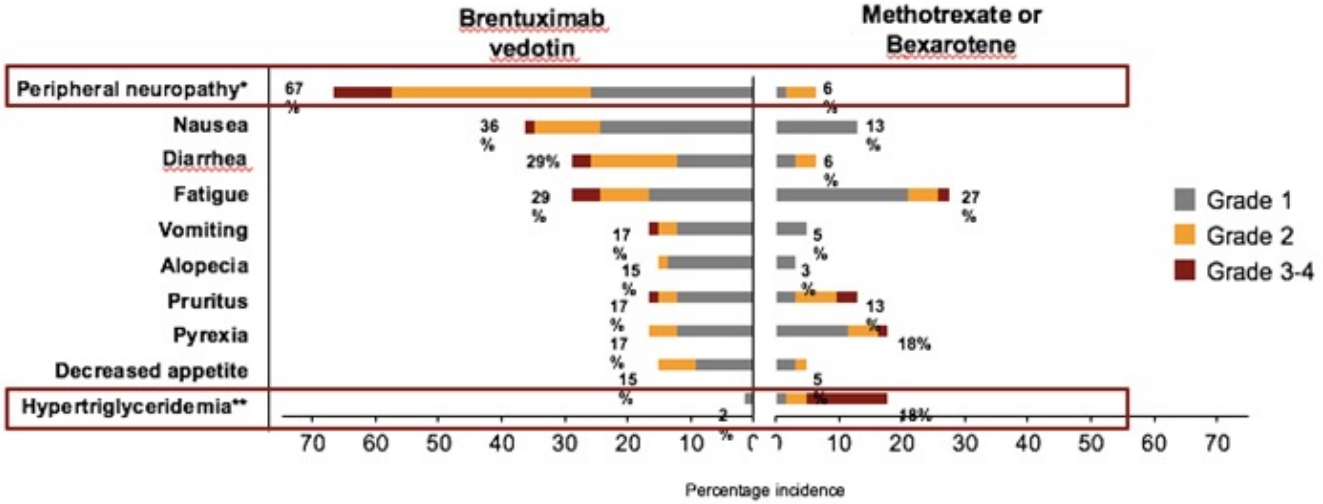
Progression-free survival was assessed in the intention-to-treat population overall (A) and in subgroups (B) by independent review using European Medicines Agency censoring guidelines,[16] which count all events despite missed visits or starting of new anticancer therapies before an event. Assessment using US Food and Drug Administration criteria is presented in the appendix (p 14). pcALCL=primary cutaneous anaplastic large-cell lymphoma. ECOG PS=Eastern Cooperative Oncology Group performance status.



Summary of adverse event (AE) impact - termination, SAEs, deaths

Adverse event (AE), n (%)	Brentuximab vedotin (n=66)	Methotrexate or bexarotene (n=62)
Any AE	63 (95)	56 (90)
Any grade ≥3 AE	27 (41)	29 (47)
Any serious AE	19 (29)	18 (29)
AE resulting in discontinuation of study regimen*	16 (24)	5 (8)
On-study death (death ≤30 days from last dose)**	4 (6)	0

Commonly reported (≥15% of patients) treatment-emergent AEs



Nine patients discontinued assigned treatment due to peripheral neuropathy in the brentuximab vedotin group (none in the physician's choice group). At the last followup (median 22·9 months), 36 (82%) of 44 patients in the brentuximab vedotin group had improvement (≥1 grade) or resolution of peripheral neuropathy.

Final data from the phase 3 ALCANZA study: Brentuximab vedotin versus physician's choice in patients with CD30-positive cutaneous T-cell lymphoma

Poster 232

Steven M. Horwitz,[1]* Julia Scarisbrick,[2] H. Miles Prince,[3] Sean Whittaker,[4] Madeline Duvic,[5] Youn H. Kim,[6] Pietro Quaglino,[7] Pier Luigi Zinzani,[8] Oliver Bechter,[9] Herbert Eradat,[10] Lauren Porter-Brown,[11] Oleg Akilov,[12] Larisa Geskin,[13] Jose Sanches,[14] Pablo Ortiz-Romero,[15] Julie Lisano,[16] Lisa Brown,[16] Maria Corinna Palencia-Wessels,[16] Ashish Gautam,[17] Veronica Dunn,[17] Meredith Little,[17] Reinhard Dummer[11]

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Background

- CTCL represents a heterogeneous group of T-cell lymphomas, primarily involving the skin, that includes MF (the most common type of CTCL) and pcALCL[1]
- CTCLs can have a chronic course, as well as considerable symptom burden and impact on patients' QoL[1,2]
- Early-stage CTCLs are treated using skin-directed therapies. Systemic therapies can be used to treat advanced CTCL, but no regimen has been shown to prolong survival in advanced stages and treatment is focused on reducing disease burden, delaying progression and improving QoL[1-3]
- In pcALCL, by definition, CD30 is expressed by the majority of tumour cells,[2] whereas in MF the proportion of CD30-expressing cells is variable[1,3]
- Brentuximab vedotin is approved in the US for patients with pcALCL or CD30-expressing MF who have received prior systemic therapy* and in the EU for adults with CD30+ CTCL after at least 1 prior systemic therapy.[4] The approval was based on the results of the randomised ALCANZA study.[5]
- ALCANZA is an international, open-label, randomised phase 3 trial of brentuximab vedotin vs physician's choice (PC) of methotrexate or bexarotene in patients with previously treated MF or pcALCL[1,5]
  - With median follow-up of 22.8 months, the original analysis showed that brentuximab vedotin was superior to physician's choice,[1,5] demonstrating:
  - Significantly improved ORR (56% vs 13%; p<0.0001)
  - Significantly higher CR rate (16% vs 2%; adjusted p=0.0046)
  - Significantly longer PFS (median 16.7 vs 3.5 months; HR=0.270, 95% CI: 0.169–0.430; adjusted p<0.0001)
  - Significant reduction in patient-reported symptoms per Skindex-29 symptom domain (–27.96 vs –8.62; adjusted p<0.0001)
- The primary analysis was performed 18 months after the last patient's end of treatment (data cut-off May 31, 2016).
- Here we report final results from the ALCANZA study (data cut-off September 28, 2018).

Objectives of the current analysis

- To report long-term efficacy and safety data from the ALCANZA study in terms of:
  - Primary study endpoint: ORR4 (median follow-up TBC)
  - Other select endpoints: PFS, OS, TTNT, response by disease subtype (MF or pcALCL), and resolution and improvement of PN.

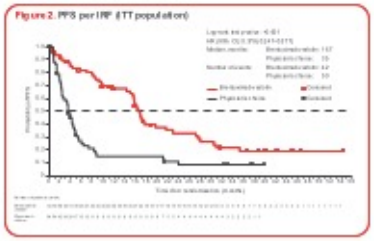
Table 1. Patient baseline characteristics (ITT population)

	Treatment group	
	Brentuximab vedotin (N=64)	Physician's choice (N=64)
Median age, years (range)	62 (22–85)	59 (22–83)
Male, gender, n (%)	33 (52)	37 (58)
ECOG PS 0–1, n (%)	61 (95)	62 (97)
Median CD30 expression, % (range)†	32.5 (0–100)	31.3 (0–100)
MF, † n (%)	48 (75)	49 (77)
Early stage (IA–IIA)	15 (23)	18 (28)
Advanced stage (IIB–IVB)	33 (52)	31 (48)
pcALCL, † (%)	16 (25)	15 (23)
Skin only	5 (8)	11 (17)
Extracutaneous disease	7 (44)	4 (27)
Total number of prior therapies, median (min-max)	4.0 (0–10)	3.5 (1–10)
Months since last prior systemic therapy, median (min-max)	3.0 (0–111)	2.8 (1–9)

Table 2. ORR4, best response to treatment, PFS and OS (ITT population)

	Brentuximab vedotin (N=64)	Physician's choice (N=64)	p-value
ORR4 per IRF, n (%)	36 (56.3)*	9 (14.1)	<0.001
Best response to treatment per IRF, n (%)			
Overall response (CR + PR)	42 (65.6)	13 (20.3)	<0.001
CR	11 (17.2)	1 (1.6)	0.0102
PR	31 (48.4)	12 (18.8)	
SD	16 (25.0)	19 (29.7)	
PD	5 (7.8)	22 (34.4)	
Median PFS, per IRF, mos (95% CI)	16.7 (11.3–NE)	3.5 (2.8–5.6)	<0.0001
3-year OS estimates, % (95% CI)	66.9 (52.7–78.2)†	61.8 (47.3–73.6)†	

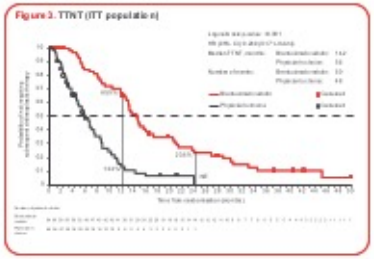
Figure 2. PFS per IRF (ITT population)



TTNT

- With median follow-up for TTNT of 37.3 months, in the brentuximab vedotin and PC arms, 50 (78%) and 48 (75%) of patients had received subsequent antineoplastic therapy, respectively (**Figure 3**).
  - Median TTNT was significantly longer with brentuximab vedotin vs PC (14.2 [95% CI: 12.2–16.4] vs 5.6 months [95% CI: 4.2–7.3]; HR=0.269; 95% CI: 0.171–0.424; p<0.001).
  - In the brentuximab vedotin vs PC arms, the probability of patients not requiring subsequent antineoplastic therapy was greater at 1 year (65.5% [95% CI: 51.8–76.2] vs 13.4% [95% CI: 5.5–24.9]) and 2 years (23.6% [95% CI: 13.3–35.4] vs NE) post-randomisation.

Figure 3. TTNT (ITT population)



Poster presented at the International Co

Median follow-up 45.9 months

Randomized phase 3 ALCANZA study of brentuximab vedotin vs physician's choice in cutaneous T-cell lymphoma: final data

Short title for the running head: Brentuximab vedotin vs physician's choice in CTCL

Steven M. Horwitz,[1] Julia J. Scarisbrick,[2] Reinhard Dummer,[3] Sean Whittaker,[4] Madeleine Duvic,[5] Youn H. Kim,[6] Pietro Quaglino,[7] Pier Luigi Zinzani,[8] Oliver Bechter,[9] Herbert Eradat,[10] Lauren Pinter-Brown,[11] Oleg E. Akilov,[12] Larisa Geskin,[13] Jose A. Sanches,[14] Pablo L. Ortiz-Romero,[15] Michael Weichenthal,[16] David C. Fisher,[17] Jan Walewski,[18] Judith Trotman,[19] Kerry Taylor,[20] Stephane Dalle,[21] Rudolf Stadler,[22] Julie Lisano,[23] Veronica Bunn,[24] Meredith Little,[24] and H. Miles Prince[25]

Table 1. Summary of efficacy (ITT population)

	Brentuximab vedotin (n = 64)	Physician's choice (n = 64)	*P*
ORR4 per IRF, n (%)	35 (54.7)*	8 (12.5)	< .001
Best response per IRF, n (%)			
ORR (CR + PR)	42 (65.6)	13 (20.3)	< .001
CR	11 (17.2)	1 (1.6)	.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)		< .001
3-year OS rate, % (95% CI)	64.4 (50.7-75.2)	61.9 (47.3-73.6)‡	
HR for OS (95% CI)	0.75 (0.42-1.32)		.310

Table 3. Patient response per IRF by baseline disease subtype and stage per investigator (ITT population)

	Patients, n (%)							
	Brentuximab vedotin (n = 64)				Physician's choice (n = 64)			
	Total	ORR4	ORR	CR	Total	ORR4	ORR	CR
MF	48 (75)	24 (50)	31 (65)	5 (10)	49 (77)	5 (10)	8 (16)	0
Stage								
IA-IIA	15 (31)	6 (40)	8 (53)	1 (7)	18 (37)	4 (22)	5 (28)	0
IIB	19 (40)	12 (63)	13 (68)	3 (16)	19 (39)	1 (5)	3 (16)	0
IIIA-IIIB	4 (8)	2 (50)	3 (75)	0	2 (4)	0	0	0
IVA	2 (4)	2 (100)	2 (100)	1 (50)	9 (18)	0	0	0
IVB	7 (15)	2 (29)	4 (57)	0	0	–	–	–
Unknown	1 (2)	0	1 (100)	0	1 (2)	0	0	0
C-ALCL	16 (25)	11 (69)	11 (69)	6 (38)	15 (23)	3 (20)	5 (33)	1 (7)
Involvement								
Skin only	9 (56)	8 (89)	8 (89)	4 (44)	11 (73)	3 (27)	5 (45)	1 (9)
Extracutaneous disease	7 (44)	3 (43)	3 (43)	2 (29)	4 (27)	0	0	0

One patient in each arm had incomplete staging data and are not included in the table: 1 patient in the brentuximab vedotin arm had a PR and 1 patient in the physician's choice arm had no response.
– indicate data were unavailable.
Abbreviations are explained in Table 1.

Table 2. PFS per IRF by number of cycles of brentuximab vedotin received (ITT population)

	Number of 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.

PFS

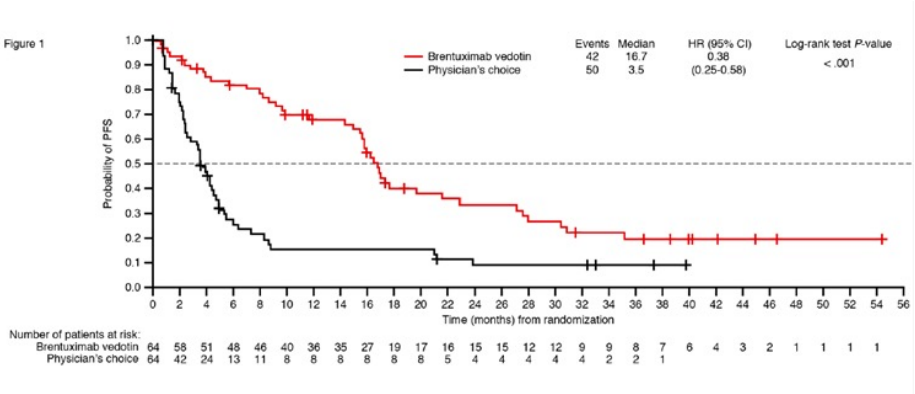


Figure 1
Brentuximab vedotin
Physician's choice
Events Median HR (95% CI) Log-rank test P-value
42 16.7 0.38 < .001
50 3.5 (0.25-0.58)
Probability of PFS
Time (months) from randomization
Number of patients at risk:
Brentuximab vedotin 64 58 51 48 46 40 36 35 27 19 17 16 15 15 12 12 9 9 8 7 6 4 3 2 1 1 1 1
Physician's choice 64 42 24 13 11 8 8 8 8 8 8 5 4 4 4 4 4 2 2 1

TtNT

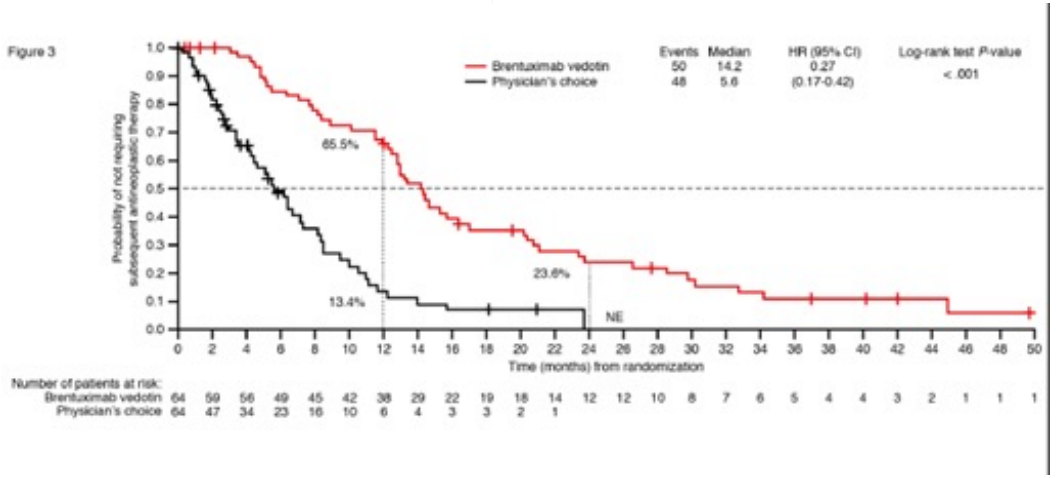


Figure 3
Brentuximab vedotin
Physician's choice
Events Median HR (95% CI) Log-rank test P-value
50 14.2 0.27 < .001
48 5.6 (0.17-0.42)
Probability of not requiring subsequent antineoplastic therapy
65.5%
23.6%
13.4%
NE
Time (months) from randomization
Number of patients at risk:
Brentuximab vedotin 64 59 56 49 45 42 38 29 22 19 18 14 12 12 10 8 7 6 5 4 4 3 2 1 1 1
Physician's choice 64 47 34 23 16 10 6 4 3 3 2 1

Table 4. Resolution, improvement, and duration of PN (SMQ) (safety population)

	Brentuximab vedotin (n = 44)		Physician's choice (n = 4)	
Data cut-off	May 31, 2016	Sep 28, 2018	May 31, 2016	Sep 28, 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, weeks	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, weeks	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)

PN indicates peripheral neuropathy.
— indicate data were unavailable.

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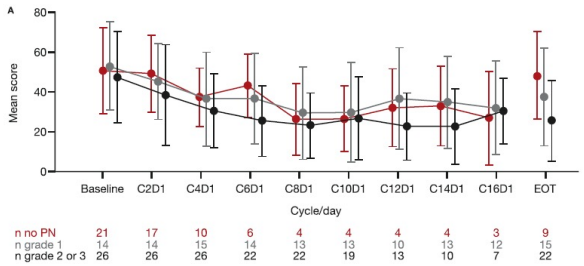
Original Research

Patient-reported quality of life in patients with relapsed/refractory cutaneous T-cell lymphoma: Results from the randomised phase III ALCANZA study

Reinhard Dummer [a,*], Henry M. Prince [b], Sean Whittaker [c], Steven M. Horwitz [d], Youn H. Kim [e], Julia Scarisbrick [f], Pietro Quaglino [g], Pier Luigi Zinzani [h], Pascal Wolter [i], Herbert Eradat [j], Lauren Pinter-Brown [k], Jose A. Sanches [l], Pablo L. Ortiz-Romero [m], Oleg E. Akilov [n], Larisa Geskin [o], Auris Huen [p], Jan Walewski [q], Yinghui Wang [r], Julie Lisano [r], Akshara Richhariya [r], Joseph Feliciano [r], Yanyan Zhu [s], Veronica Bunn [s], Meredith Little [s], Erin Zagadailov [s], Mehul R. Dalal [s], Madeleine Duvic [p]



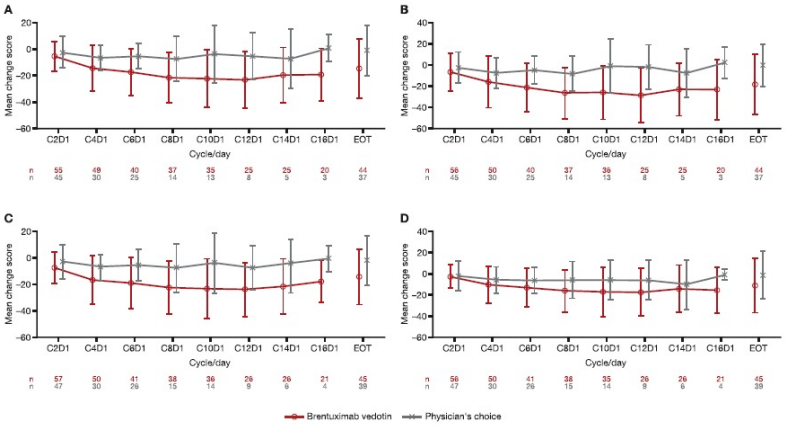


Fig. 1. Mean change from baseline in Skindex-29 total and domain scores in evaluable patients, including the key secondary end-point of Skindex-29 symptom domain score: (A) total score, (B) symptom domain, (C) emotions domain and (D) functioning domain. Bar represents mean ± standard deviation. Higher scores indicate a higher impact of skin disease on quality of life. The psychometric validity of a sum score has not been established. The developer recommends calculating and reporting it largely to simplify the presentation of results. C, cycle; D, day; EOT, end of treatment.

According to neuropathy: no worsening in Skindex-29

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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 [y], Julie Lisano [z], Matthew Onsum [z], Veronica Bunn [z], Meredith Little [z], William L. Trepicchio [z], Reinhard Dummer [r]

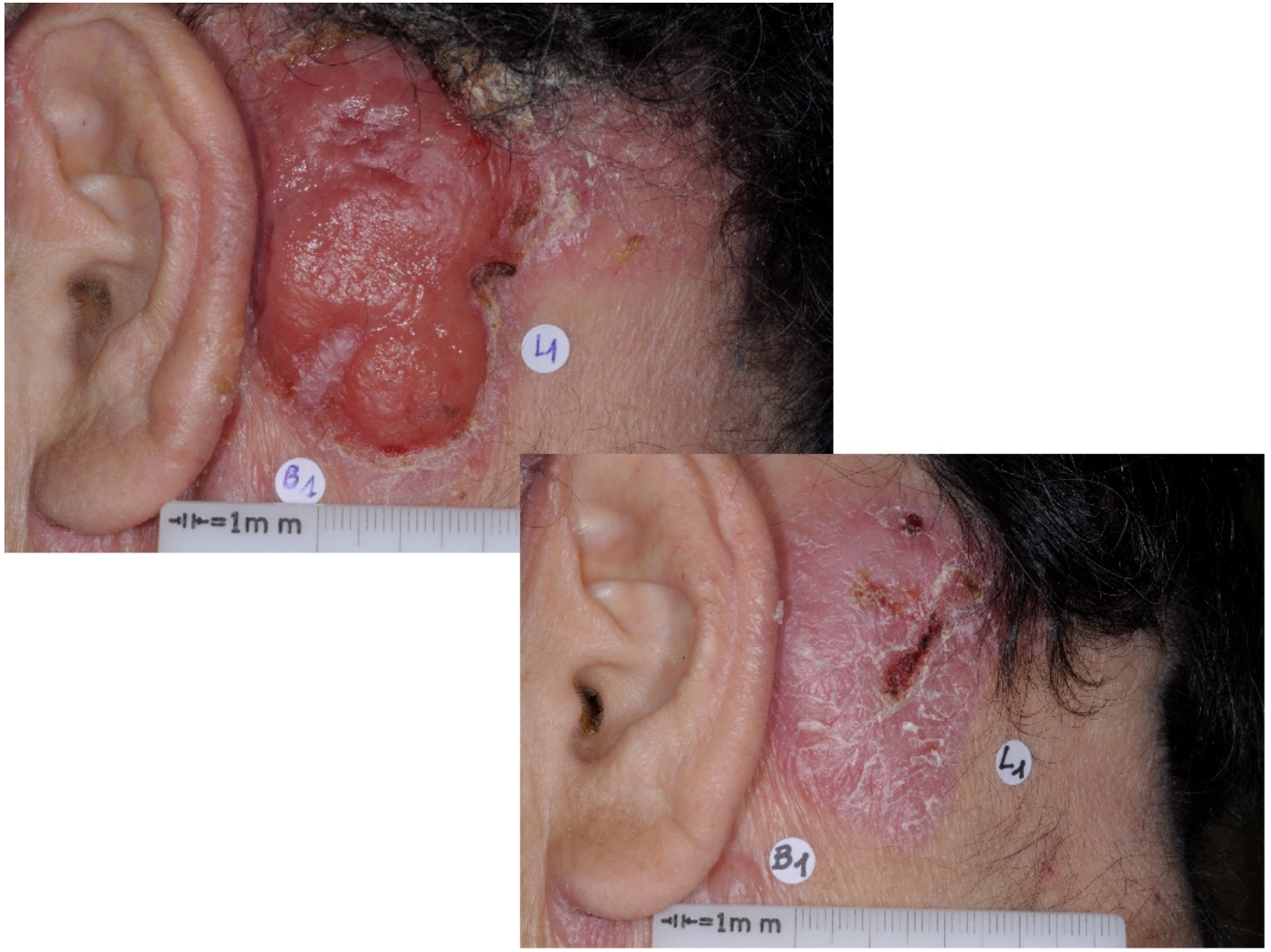
Table 2
Efficacy of brentuximab vedotin and PC by CD30 expression and LCT status.

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.

BRENTUXIMAB VEDOTIN

- CD30 e meccanismo di azione
- Risultati degli studi di fase II
- Lo studio ALCANZA
- Real-life data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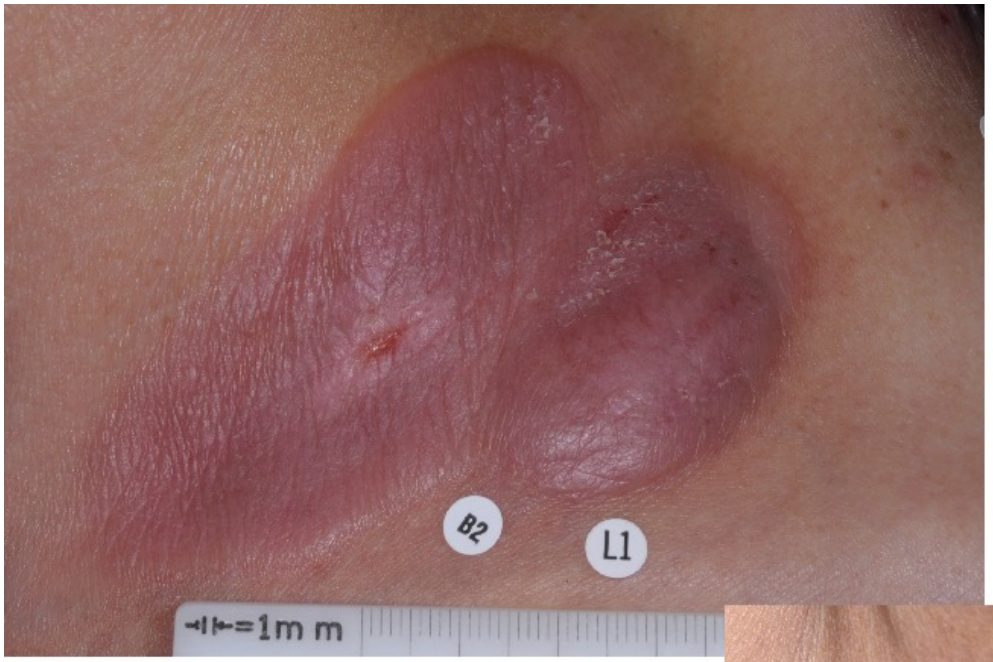
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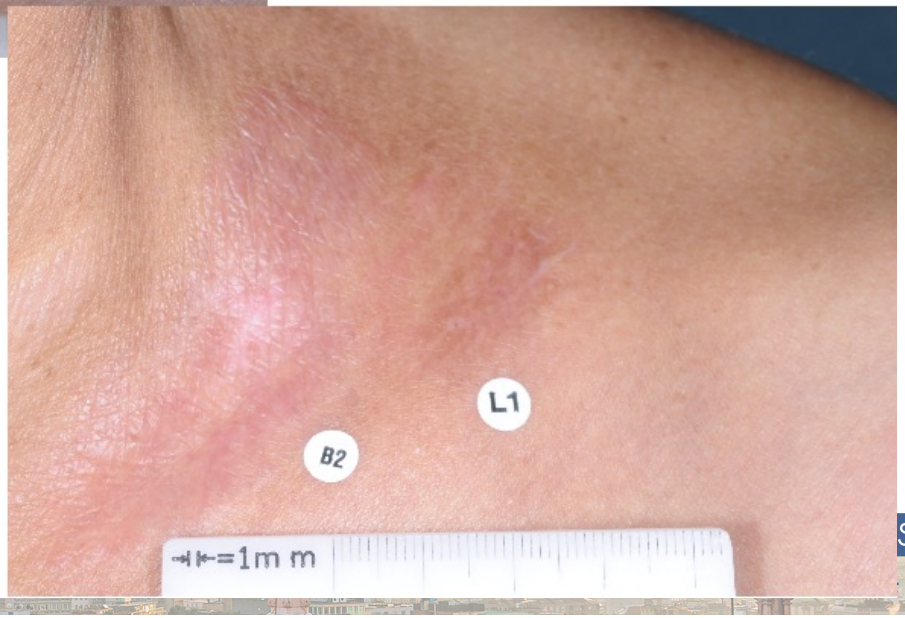
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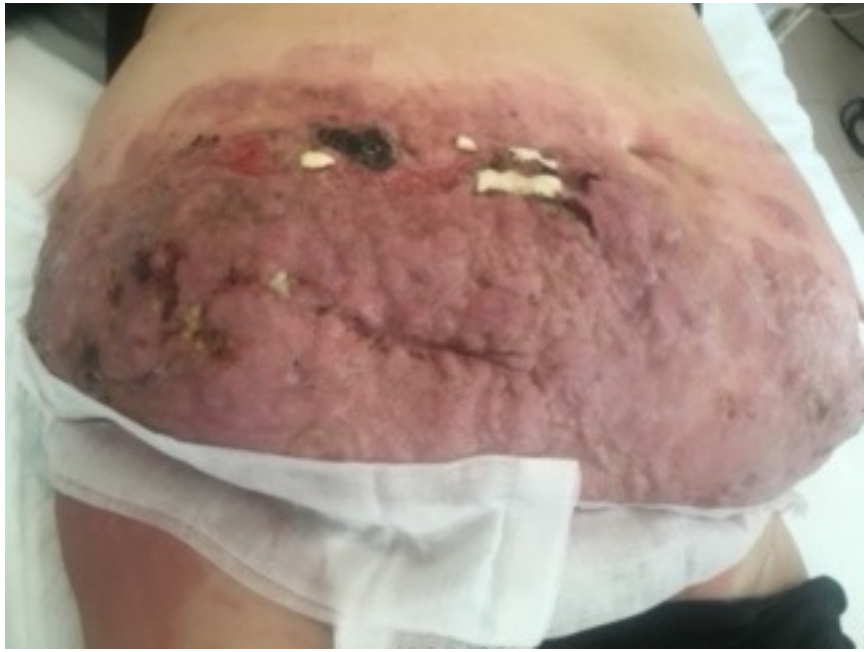

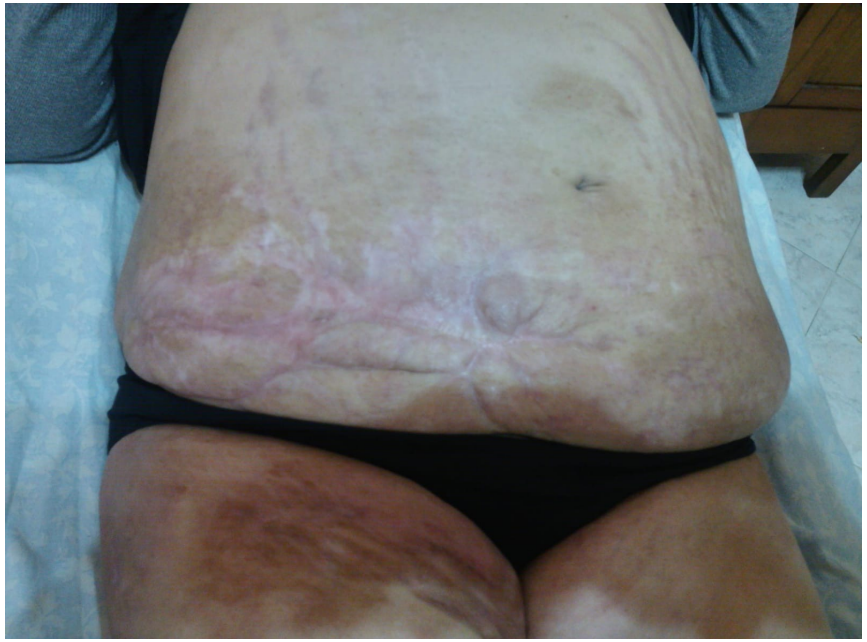

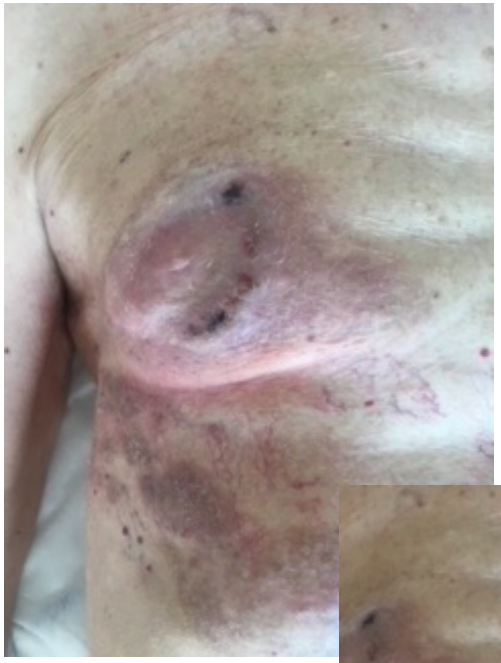

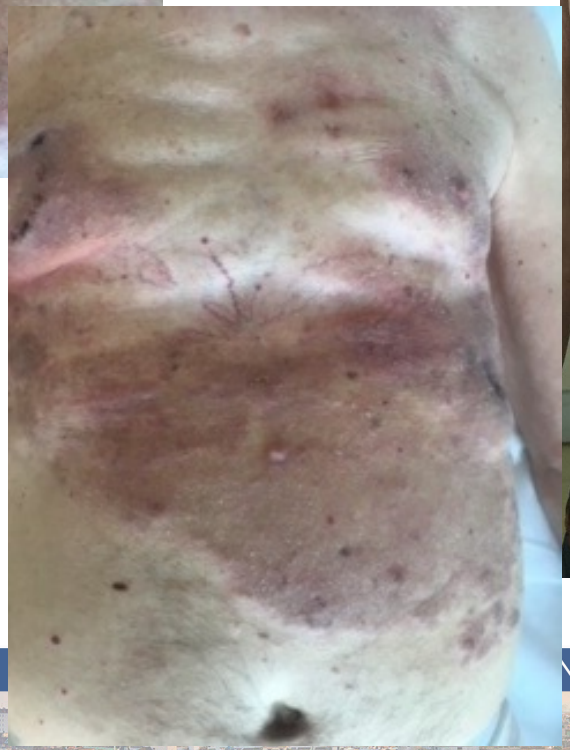

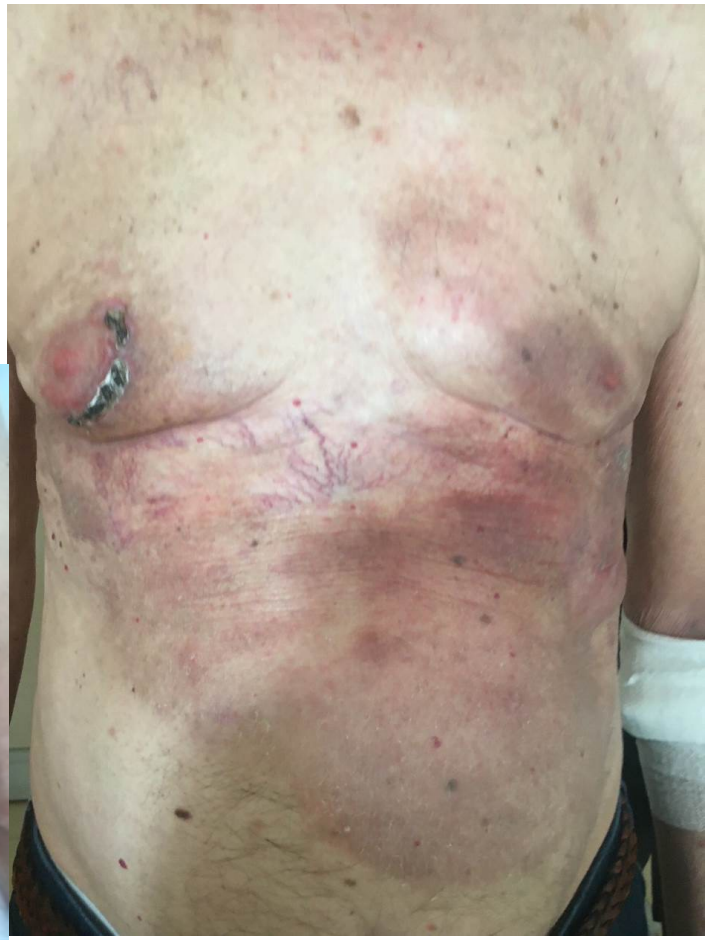

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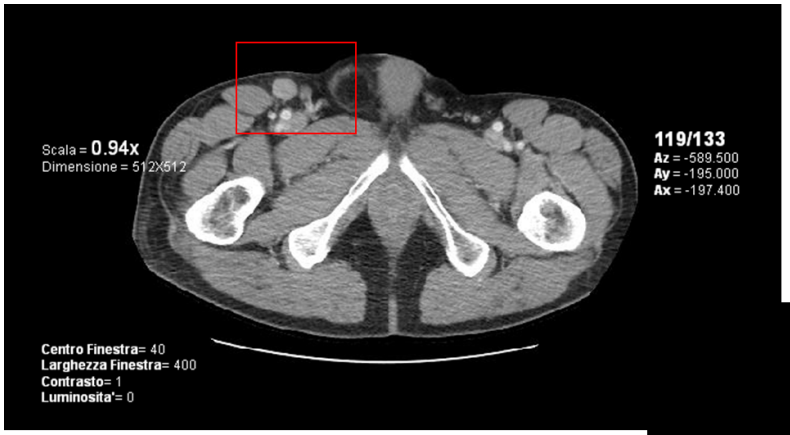
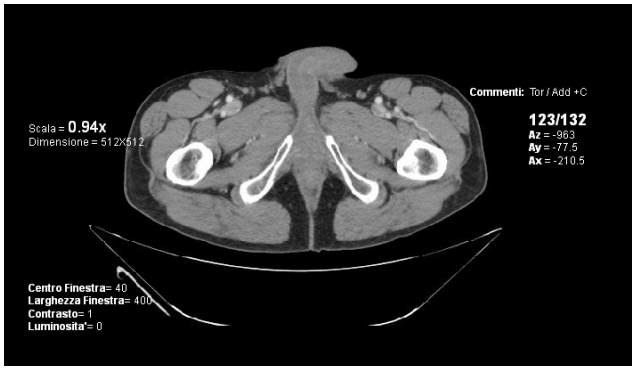
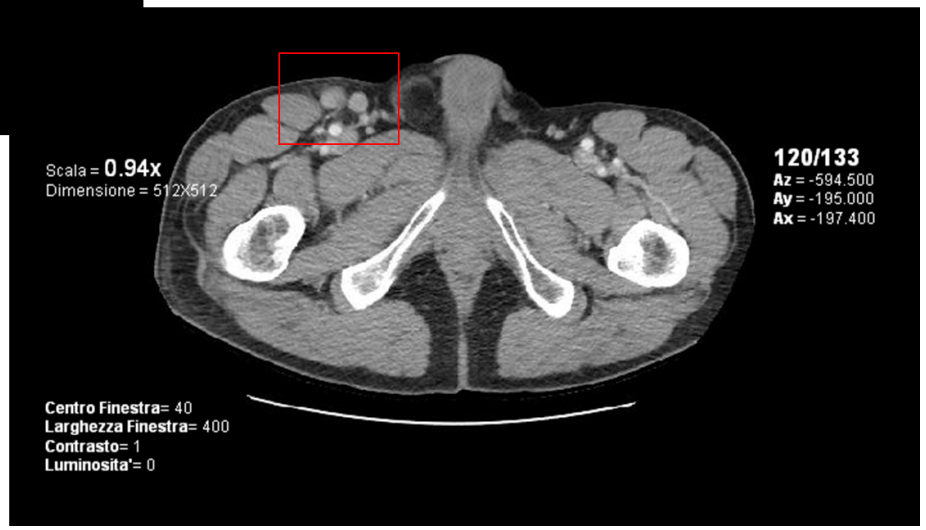
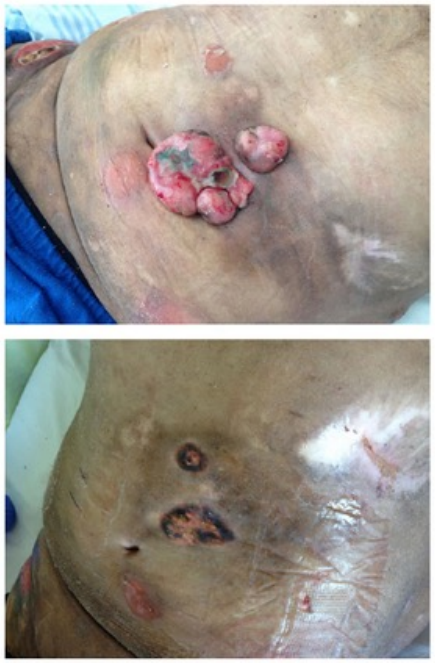






bjh images in haematology

Rapid response of nodular CD30-positive mycosis fungoides to brentuximab vedotin



A patient diagnosed with mycosis fungoides presented with erythrodermic and scaly patches and plaques covering almost his entire body surface, with nodular lesions (up to 10 × 10 cm) fungating from the abdominal wall. Immunohistochemical analysis of the skin biopsy specimen showed CD30 expression in 50% of CD3/CD4-positive lymphoid cells. We treated the patient with four courses lesions had completely disappeared and the other skin lesions had improved (bottom). CD30 positivity (defined as >10% of the lymphoid infiltrate) has varied from 10% to 63% in two reported series of patients at all stages of the disease (Duvic, 2011; Krathen *et al*, 2012) indicating that brentuximab vedotin is a potential new therapy for mycosis fungoides.

MEDICAL DERMATOLOGY

BJD
British Journal of Dermatology

Multicentric EORTC retrospective study shows efficacy of brentuximab vedotin in patients who have mycosis fungoides and Sézary syndrome with variable CD30 positivity

E. Papadavid,[1] E. Kapniari [1] V. Pappa,[2] V. Nikolaou [1] T. Iliakis,[2] M. Dalamaga [3] C. Jonak,[4] S. Porkert,[4] S. Engelina,[5] P. Quaglino [5] P.L. Ortiz-Romero [6] C. Vico [7] A. Cozzio,[8,9] F. Dimitriou [8,9] R. Guiron,[10] E. Guenova [11,12] E. Hodak,[5] M. Bagot [13,14] and J. Scarisbrick [15]

Table 1. Patients' demographics and clinical characteristics

Age (years)	
Mean ± SD	61.3 ± 12.4
Sex (N, %)	
Male	43/72 (59.7 %)
Female	29/72 (40.3 %)
Country (N, %)	
Switzerland	16/72 (22.2%)
UK	15/72 (20.8%)
Greece	10/72 (13.9%)
France	10/72 (13.9%)
Austria	6/72 (8.3%)
Spain	5/72 (6.9%)
Italy	4/72 (5.6 %)
Israel	6/72 (8.3 %)
Disease Characteristics	
Disease Duration (Years)	
Median (IQR)	4 (2-8)
CTCL type(N, %)	
SS	15/72 (20.8%)
MF	57/72 (79.2%)
CTCL stage at BV initiation(N, %)	
IB	1/72 (1,4%)
IIB	32/72 (44,4%)
IIIA	1/72 (1,4%)
IIIB	4/72 (5,6%)
IVA1	5/72 (7%)
IVA2	17/72 (23,6%)
IVB	12/72 (16,6%)
B involvement (N, %)	
B0	54/72 (75%)
B1	3/72 (4.2 %)
B2	15/72 (20,8%)
N involvement (N, %)	
N0	34/72 (47.2%)
N1	4/72 (5.6%)
N2	4/72 (5.6%)
N3	23/72 (31.9%)
NX	7/72 (9.7%)
M Metastases (N, %)	
M0	62/72 (86.2%)
M1	10/72 (13.8%)
CD30 presence(N, %)	
≤5	14/72 (19.4%)
5-10	14/72 (19.4%)
>10	44/72 (61.2%)
LCT (N, %)	49/68* (72.1%)
No of systemic previous treatments (N, %)	
<3	46/72 (63.9%)
≥3	26/72 (36.1%)
No of previous treatment	
Median (IQR)	2 (1-3)

*N of patients with available data

MEDICAL DERMATOLOGY

BJD
British Journal of Dermatology

Multicentric EORTC retrospective study shows efficacy of brentuximab vedotin in patients who have mycosis fungoides and Sézary syndrome with variable CD30 positivity

E. Papadavid,[1] E. Kapniari [1] V. Pappa,[2] V. Nikolaou [1] T. Iliakis,[2] M. Dalamaga [3] C. Jonak,[4] S. Porkert,[4] S. Engelina,[5] P. Quaglino [5] P.L. Ortiz-Romero [6] C. Vico [7] A. Cozzio,[8,9] F. Dimitriou [8,9] R. Guiron,[10] E. Guenova [11,12] E. Hodak,[5] M. Bagot [13,14] and J. Scarisbrick [15]

Table 2 Response rates, durability results and overall survival of brentuximab vedotin in patients with mycosis fungoides/Sézary syndrome

Variable	Value
Overall response lasting at least 4 months	28/67 (42)
Overall response rate	45/67 (67)
Complete response	18/67 (27)
Partial response	27/67 (40)
Stable disease	9/67 (13)
Progression of disease	13/67 (19)
Skin overall response rate	47/65[a] (72)
Blood overall response rate	4/10[a] (40)
Time to response (weeks)	
Median (IQR)	8 (5·5–14)
Mean (SD)	10·8 (7·9)
Response duration (months)	
Median (IQR)	9 (3·4–14)
Mean (SD)	10·05 (7)
Response duration in patients with complete response (months)	
Median (IQR)	13·5 (6·4–21·8)
Mean (SD)	14·3 (8·6)
Response duration in patients with partial response (months)	
Median (IQR)	9 (3·2–12·5)
Mean (SD)	8·6 (5·2)
Progression-free survival	
Median (IQR)	7 (2–12)
Mean (SD)	8·02 (6·9)
Time to next treatment (days)	
Median (IQR)	30 (6–157·5)
Mean (SD)	127·6 (204·7)

Data are n/N(%) unless otherwise indicated. [a]n of patients with available data.

JAMA Dermatology | Brief Report

Brentuximab Vedotin for Relapsed or Refractory Sézary Syndrome

Daniel J. Lewis, MD; Paul L. Haun, MD; Sara S. Samimi, MD; Carmela C. Vittorio, MD; Jennifer Villasenor-Park, MD, PhD; Stefan K. Barta, MD; Daniel J. Landsburg, MD; Jakub Svoboda, MD; Sunita D. Nasta, MD; Stephen J. Schuster, MD; Alain H. Rook, MD; Ellen J. Kim, MD

IMPORTANCE Treatment options for Sézary syndrome (SS) are limited and associated with low response rates. Brentuximab vedotin is a CD30-directed antibody-drug conjugate approved for refractory CD30-positive cutaneous T-cell lymphoma. However, limited data exist on its efficacy in SS, including in the pivotal phase 3 ALCANZA (A Phase 3 Trial of Brentuximab Vedotin (SGN-35) Versus Physician's Choice [Methotrexate or Bexarotene] in Participants With CD30-Positive Cutaneous T-Cell Lymphoma) trial.

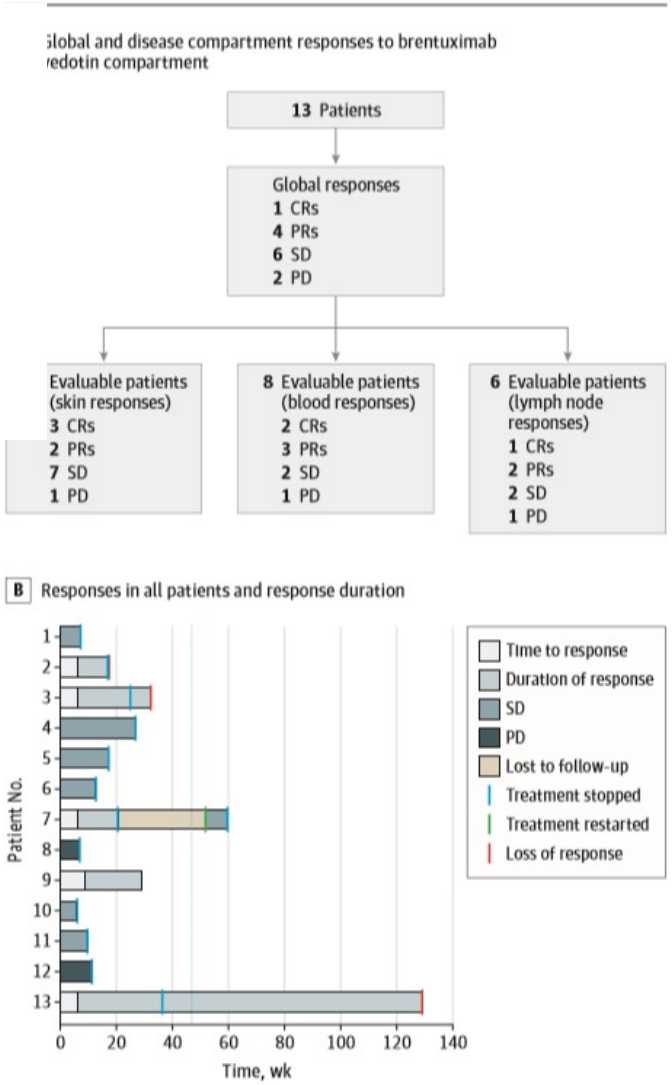
OBJECTIVE To assess the preliminary efficacy and tolerability of brentuximab vedotin for SS.

Key Points

Questions What is the global response rate of brentuximab vedotin in Sézary syndrome (SS), and how does it compare with other therapies used for SS?

Findings In this case series, 5 of 13 patients with SS (38%) achieved a global response, including 1 complete response. Response rates by disease compartment were 38% in the skin, 63% in the blood, and 50% in the lymph nodes.

Meaning Brentuximab vedotin is associated with some efficacy in SS.



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Article type : Research Letter

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Brentuximab a novel antibody therapy: Real-World Use Confirms Efficacy and Tolerability for CD30 positive cutaneous lymphoma

S. Engelina, M. Saggu, J. Yoo, F. Shah, A. Stevens, C Irwin, S. Chaganti and J. J. Scarisbrick.
University Hospital Birmingham (UHB), Birmingham, UK.

Patient	Gender	Diagnosis	Age at diagnosis	Stage prior to BV	No. of BV cycles	No. of weeks	CD30%	Response	No. of previous systemics
1	F	MF	57	IIB	4	12	10	SD	3
2	M	MF	60	IIB	9	27	30	CR	3
3	M	MF	60	IIB	13	39	27	PR	3
4	F	MF	57	IIIB	7	21	10	CR	4
5	M	MF	76	IIIB	16	48	100	CR	3
6	M	MF	47	IVA2	5	15	5	PR	4
7	M	MF	43	IVA2	9	27	10	PD	4
8	M	MF	48	IVA2	10	30	100	CR	2
9	F	MF	50	IVA2	16	48	1.5	PR	1
10	M	pcALCL	59	T3N0M1	4	12	100	PD	2
11	M	pcALCL	39	T2CN1M0	6	18	100	CR	1
12	M	pcALCL	41	T3AN2M0	8	24	100	CR	2

pcALCL: primary anaplastic large-cell lymphoma.MF: mycosis fungoides. CR: complete response. PR: partial response. SD: stable disease. PD: disease progression.

International Journal of Dermatology

Correspondence

Complete remission with brentuximab vedotin in a case of primary cutaneous gamma-delta T-cell lymphoma relapsed after allogeneic stem cell transplantation

Dear Editor,

Primary cutaneous gamma-delta T-cell lymphoma (GD-TCL) is a rare and aggressive entity. Clinically, it has a variable presentation more frequently as rapidly growing erythematous, ulcerated plaques, and nodules; less frequently, yet typically, with initial subcutaneous involvement, resembling subcutaneous panniculitis, such as T-cell lymphoma (SPLTCL), progressing

CD30 immunotoxin) was started while considering a new allo-transplantation procedure. BV was administered (1.8 mg/kg i.v. q21) for 16 cycles. A clinical CR was obtained already after eight cycles, with non-remarkable side effects, and chimerism assay showed 100% of donor cells. The patient is currently still disease-free.

At last clinical follow-up, after 36 months from last BV cycle, the patient is still in complete remission.

The 2016 update of the WHO classification for myeloid and lymphoid neoplasms recognizes primary cutaneous GD-

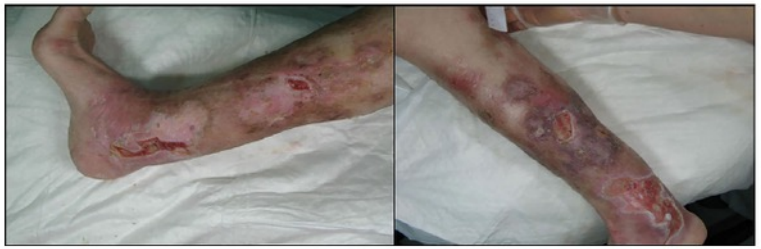

Figure 1 Clinical photos showing details of lesions on both legs at the time of relapse. Active lesions presented as multiple, painful subcutaneous plaques and nodules with tendency to ulceration

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Complete remission with brentuximab vedotin in a case of primary cutaneous gamma-delta T-cell lymphoma relapsed after allogeneic stem cell transplantation.
Lastrucci I, Grandi V, Gozzini A, Vannucchi M, Kovalchuk S, Santucci M, Pimpinelli N. Int J Dermatol. 2021 Jun;60(6):778-780.

REVIEW ARTICLE

BJD
British Journal of Dermatology

Brentuximab vedotin in CD30$^+$ cutaneous lymphoma: How do we treat, how shall we treat? A review of the literature

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[2]Department of Dermatology, Klinikum Ludwigshafen, Skin Cancer Centre Rheinpfalz, Ludwigshafen, Germany
[3]Department of Dermatology and Venereology, University of Cologne, Cologne, Germany

Linked Comment: Scarisbrick. *Br J Dermatol* 2017; **177**:1474–1475.

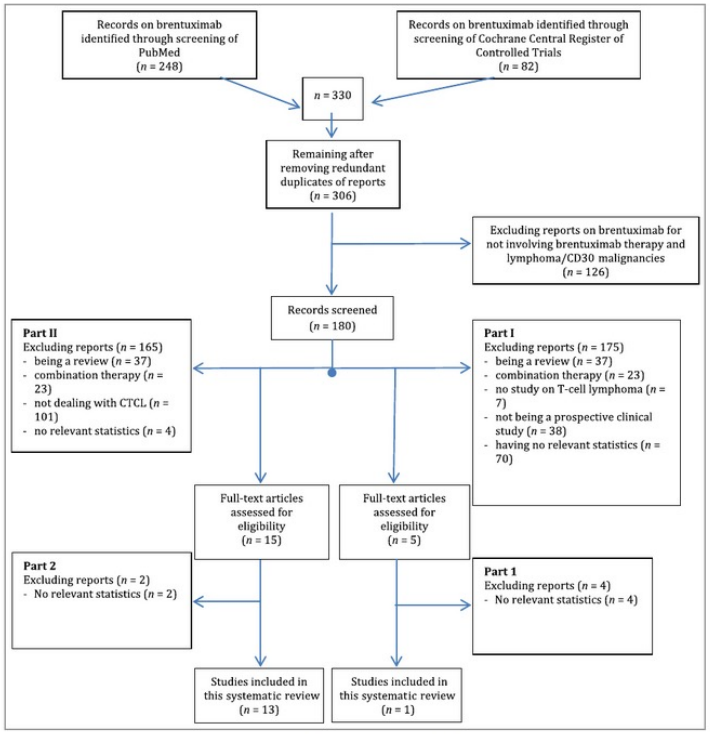
Table 2 Overview of the pooled data

Number of studies	13
Number of patients	149
CR	37
PR	75
ORR (%)	75

CR, complete response; PR, partial response; ORR, overall response rate.

Table 3 Alternative treatment regimens

Dose (mg kg^{-1})	Interval
1·2	Every 3 weeks
1·2	Start every 3 weeks Extension of the intervals depending on the response
1·8 followed by reduction to 1·2	Start every 3 weeks Extension of the intervals depending on response



BRENTUXIMAB VEDOTIN

- CD30 e meccanismo di azione
- Risultati degli studi di fase II
- Lo studio ALCANZA
- Real-life data
- Positioning del farmaco

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*

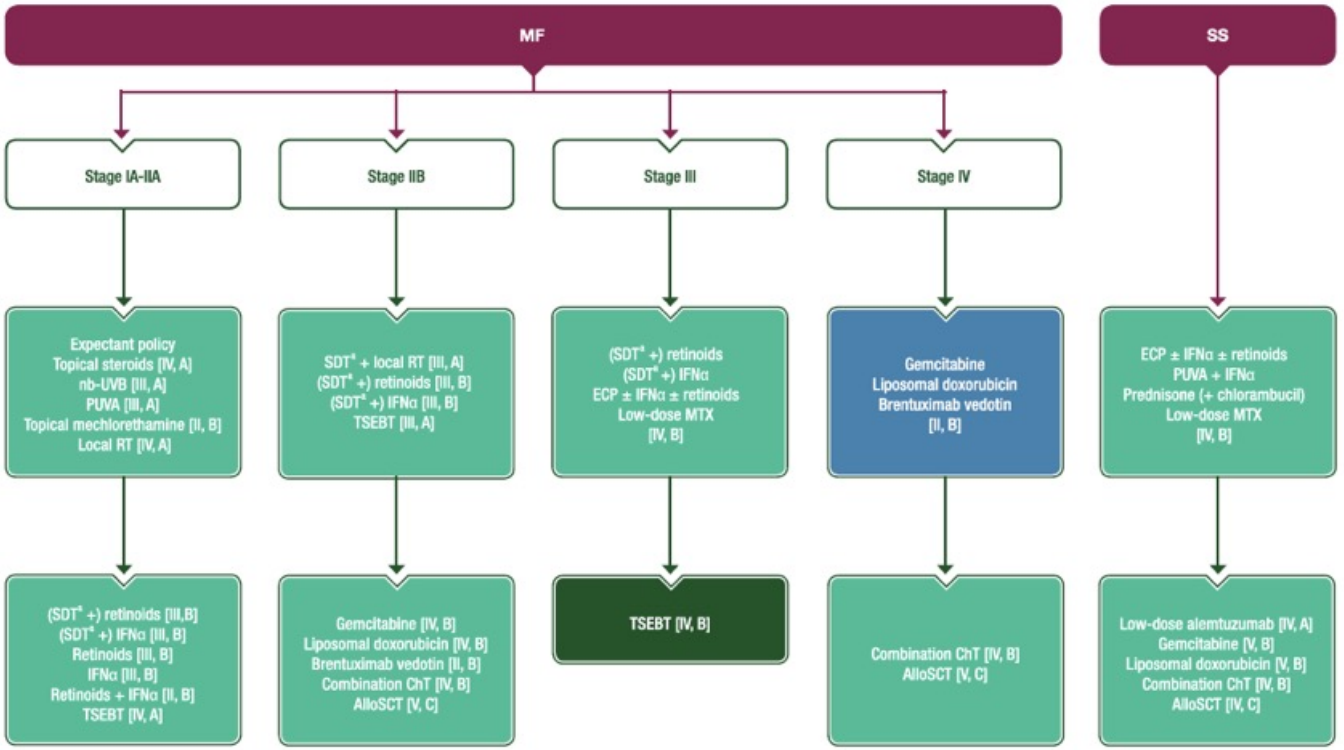
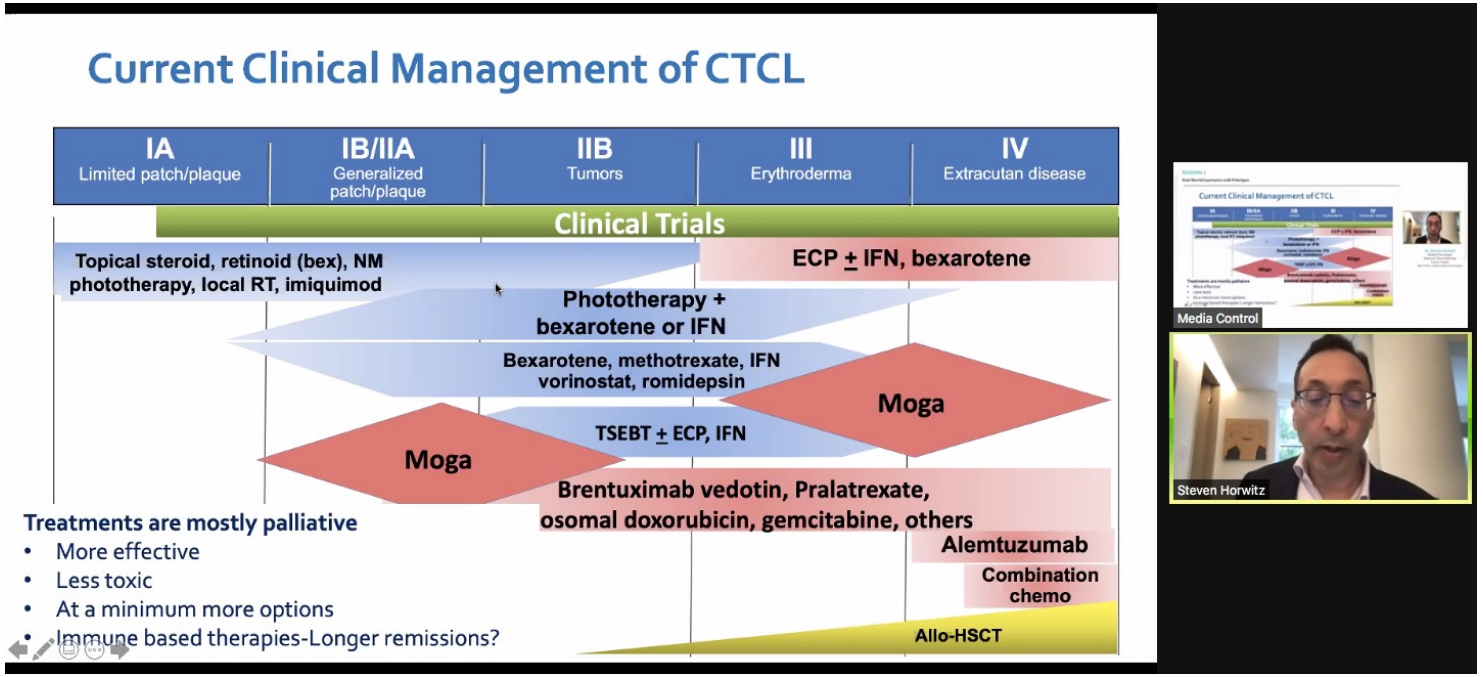


Figure 1. Recommendations for the treatment of MF/SS.
[a]Most commonly PUVA.
AlloSCT, allogeneic stem cell transplantation; ChT, chemotherapy; ECP, extracorporeal photopheresis; IFNα, interferon alpha; MF, mycosis fungoides; MTX, methotrexate; nb-UVB, narrow-band ultraviolet B; PUVA, psoralens plus ultraviolet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

Annals of Oncology
Clinical Practice


Current Clinical Management of CTCL
IA
Limited patch/plaque
IB/IIA
Generalized patch/plaque
IIB
Tumors
III
Erythroderma
IV
Extracutan disease
Clinical Trials
Topical steroid, retinoid (bex), NM phototherapy, local RT, imiquimod
ECP ± IFN, bexarotene
Phototherapy + bexarotene or IFN
Bexarotene, methotrexate, IFN vorinostat, romidepsin
Moga
TSEBT ± ECP, IFN
Moga
Brentuximab vedotin, Pralatrexate, osomal doxorubicin, gemcitabine, others
Alemtuzumab
Combination chemo
Allo-HSCT
Treatments are mostly palliative
More effective
Less toxic
At a minimum more options
Immune based therapies-Longer remissions?
Media Control
Steven Horwitz

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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]

BV should be considered in cases with multifocal skin lesions CD30+, preferentially plaques and/or nodules, refractory to conventional therapies and in patients developing extracutaneous disease.

According to the available data, the Panel stated that MOGA has become a part of the "2nd line" setting of the therapeutic armamentarium, for patients with SS or highly-symptomatic erythrodermic MF. B.

Both drugs BV and MOGA represent compelling strategies as potential bridge to alloHSCT in transplant-eligible patients.


1 L'Italia L'Italia
2 'a Criatura La bambina
3 'a Jatta La gatta
4 'o Puorco Il maiale
5 'a Mano La mano
11 'e surice I topi
12 'e Surdate I soldati
13 Sant'Antonio Sant'Antonio
14 'o Mbriaco L'ubriaco
15 'o Guaglione Il ragazzo
21 'a Femmena annura La donna nuda
22 'o Pazzo Il pazzo
23 'o Scemo Lo sciocco
24 'e Gguardie Le guardie
25 Natale Natale
31 'o patrone 'e casa Il padrone di casa
32 'o Capitone Il capitone
33 'll'anne 'e Cristo Gli anni di Cristo
34 'a Capa La testa
35 l'Aucelluzz L'uccello
41 'o Curtiello Il coltello
42 'o Ccafè Il caffè
43 'a Donna 'o Barcone La donna al balcone
44 'e Ccancelle La prigione
45 'o Vino Il vino
51 'o Ciardino Il giardino
52 'a Mamma La mamma
53 'o Viecchio Il vecchio
54 'o Cappiello Il cappello
55 'a Museca La musica
61 'o Cacciatore Il cacciatore
62 'o Muorto acciso Il morto ammazzato
63 'a Sposa La sposa
64 'a Sciammeria La marsina
65 'o Chianto Il pianto
71 l'ommo 'e merda Uomo di merda
72 'a Meraviglia Lo stupore
73 'o Spitale L'ospedale
74 'a Rotta La grotta
75 Pullecenella Pulcinella
81 'e Sciure I fiori
82 'a Tavula mbandita La tavola imbandita
83 'o Maletiempo Il cattivo tempo
84 'a Cchiesa La chiesa
85 Ll'aneme o priatorio L'anima del purgatorio
6 chella ca guarda 'Nterra Quella che guarda a terra
7 'o Vasetto Il vaso da notte
8 'a Maronna La Madonna
9 'a figliata La figliolanza
10 'e fasule I fagioli
16 'o culo Il deretano
17 'a disgrazia La disgrazia
18 'o Sanghe Il sangue
19 'a resata Una risata
20 'a Festa La festa
26 Nannenella Piccola Anna
27 'o Cantero Il pitale
28 'e ZZizze Le tette
29 'o Pate d'e criature Il padre dei bambini
30 'e palle d''o tenente Le palle del tenente
36 'e CCastagnelle Le nacchere
37 'o Monaco Il monaco
38 'e Mmazzate Le botte
39 'a funa n'ganna La corda al collo
40 'a paposcia La noia
46 è denare Il denaro
47 'o Muorto Il morto
48 'o Muorto che parla Il morto che parla
49
50
56 A caruta La caduta
57 'o Scartellato Il gobbo
58 'o Paccotto Il regalo
66 E ddoie zetelle Le due zitelle
67 'o totaro int'a chitarra Il totano
68 'a zuppa cotta La zuppa cotta
76 'a Funtana La fontana
77 'e Riavule I diavoli
78 'a bella figliola La bella figliola
86 'a puteca La bottega
87 'e Perucchie I pidocchi
88 'e Casecavalle I caciocavalli
30 'e palle d''o tenente Le palle del tenente