ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI MEDICINA SPECIALISTICA, DIAGNOSTICA E SPERIMENTALE

POLICLINICO DI SANT'ORSOLA

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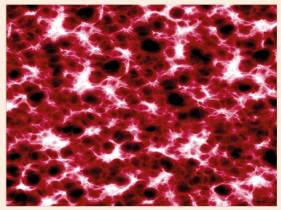
2018... 2022
T-Cell Lymphomas:
Finally vision and
mission!

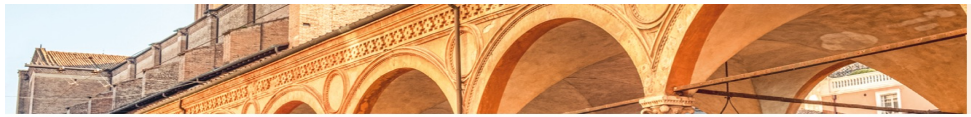


Brentuximab Vedotin in CTCL: Update 2022

H.Miles Prince Peter MacCallum Cancer Centre and Epworth Healthcare, Australia

Bologna
ROYAL HOTEL CARLTON
October 25-26, 2022

President: **Pier Luigi Zinzani**
Co-President: **Michele Cavo**



Disclosures

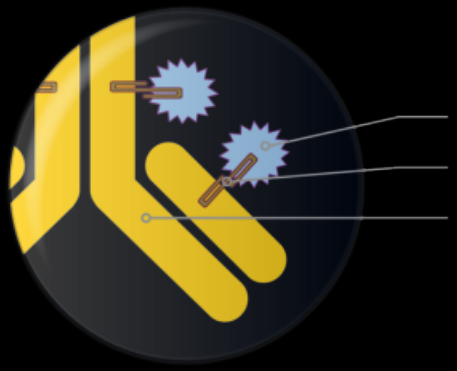
Disclosures of H.Miles Prince

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Celgene/BMS	X					X	
Takeda/Millenium	X					X	
Merck	X					X	
Mundipaharma	X					X	

Brentuximab vedotin – the outstanding issues

- Long term follow up
- Efficacy in extracutaneous disease and LCT
- CD30 positivity
- Re-treatment
- C-ALCL – adding chemotherapy?

Brentuximab vedotin mechanism of action

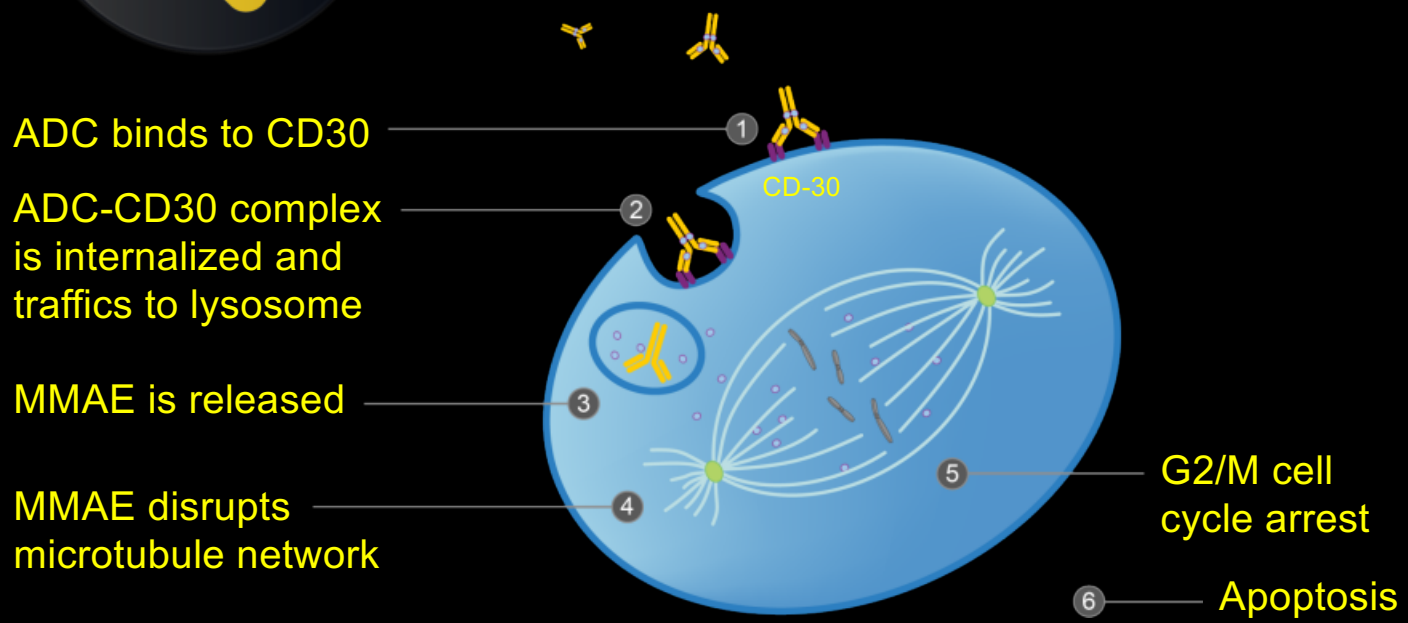


Brentuximab vedotin antibody-drug conjugate (ADC)

Monomethyl auristatin E (MMAE), microtubule-disrupting agent

Protease-cleavable linker

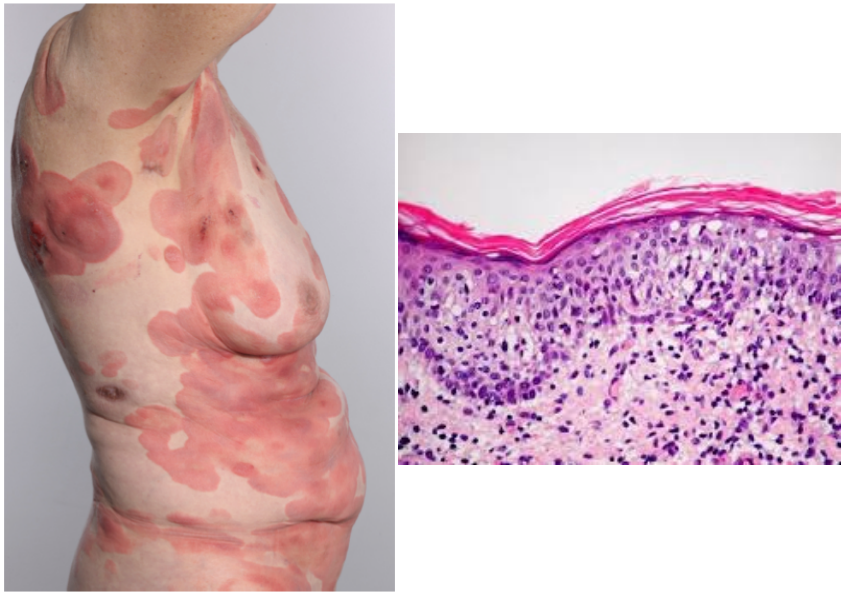
Anti-CD30 monoclonal antibody



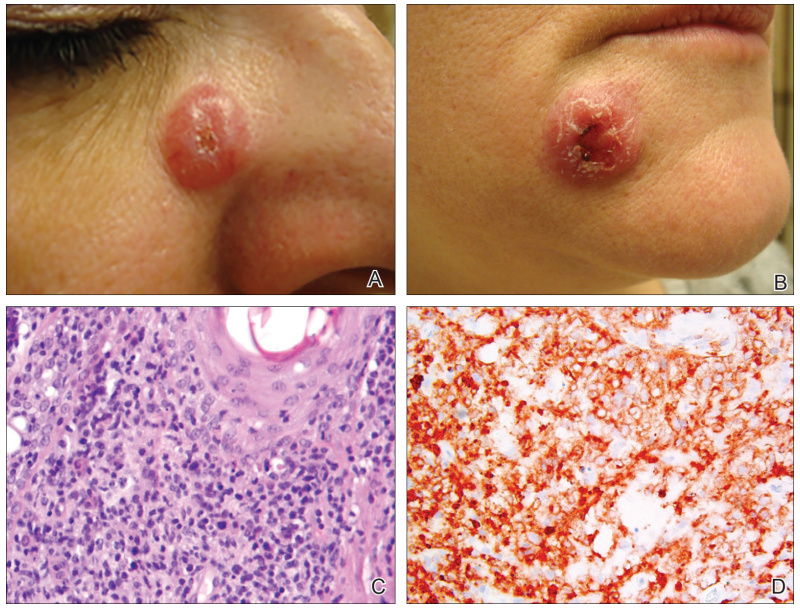
Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial

H Miles Prince, Youn H Kim*, Steven M Horwitz, Reinhard Dummer, Julia Scarisbrick, Pietro Quaglino, Pier Luigi Zinzani, Pascal Wolter, Jose A Sanches, Pablo L Ortiz-Romero, Oleg E Akilov, Larisa Geskin, Judith Trotman, Kerry Taylor, Stephane Dalle, Michael Weichenthal, Jan Walewski, David Fisher, Brigitte Dréno, Rudolf Stadler, Tatyana Feldman, Timothy M Kuzel, Yinghui Wang, Maria Corinna Palanca-Wessels, Erin Zagadailov, William L Trepicchio, Wenwen Zhang, Hui-Min Lin, Yi Liu, Dirk Huebner, Meredith Little, Sean Whittaker†, Madeleine Duvic†, on behalf of the ALCANZA study group‡*

Mycosis Fungoides

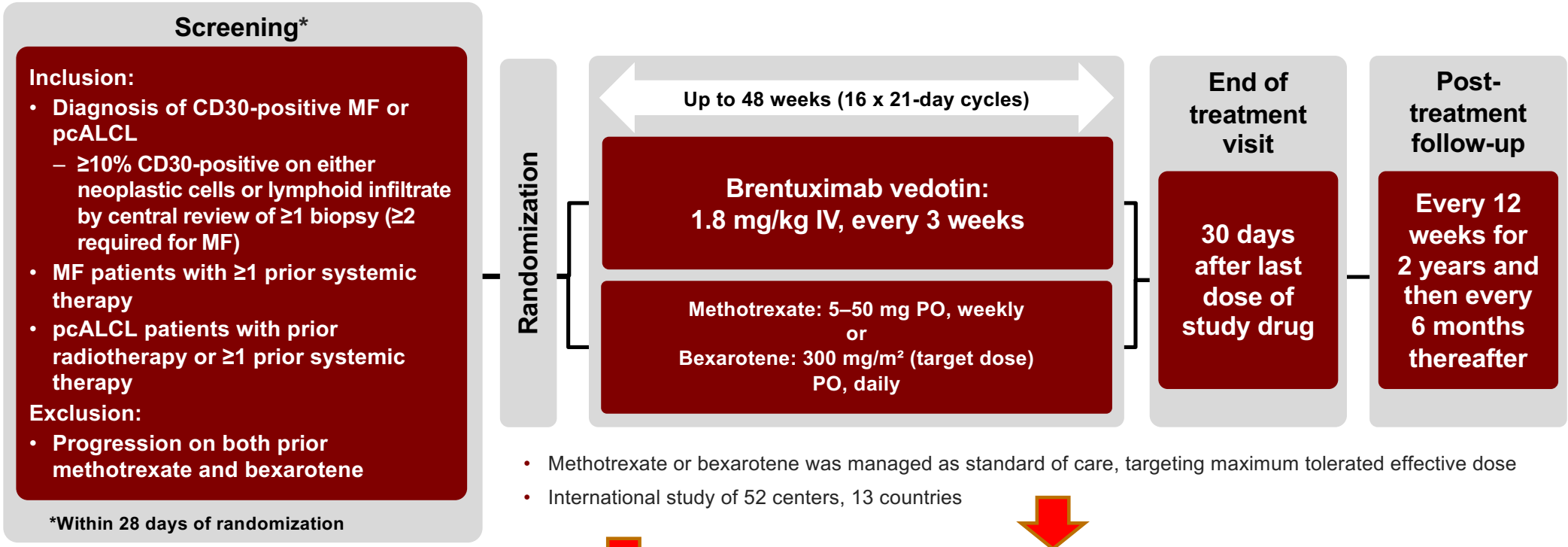


pcALCL



Lancet 2017; 390: 555–66

ALCANZA: A phase 3, randomized study comparing the efficacy and safety of brentuximab vedotin versus physician's choice in CD30-positive MF or pcALCL



- Methotrexate or bexarotene was managed as standard of care, targeting maximum tolerated effective dose
- International study of 52 centers, 13 countries

- **Brentuximab vedotin was far superior to physician's choice,** demonstrating **improved ORR4** (56% vs 13%; p<0.0001), **CR rate** (16% vs 2%; adjusted p=0.0046), and **PFS** (16.7 vs 3.5 months; HR=0.270, 95% CI: 0.169, 0.430; adjusted p<0.0001), and **a reduction in patient-reported symptoms** (Skindex-29 symptom domain; –27.96 vs –8.62; adjusted p<0.0001)[1,2]
- Safety data were consistent with the established tolerability profile[1,2]

CI, confidence interval; CR, complete response; HR, hazard ratio; IV, intravenous; ORR4, overall rate of responses lasting ≥4 months; PFS, progression-free survival; PO, orally

1. Kim YH, et al. Blood 2016;128:182
2. Prince HM, et al. Lancet 2017;390:555–66

Brentuximab vedotin – the outstanding issues

- Long term follow up

OS = median FU = 46months

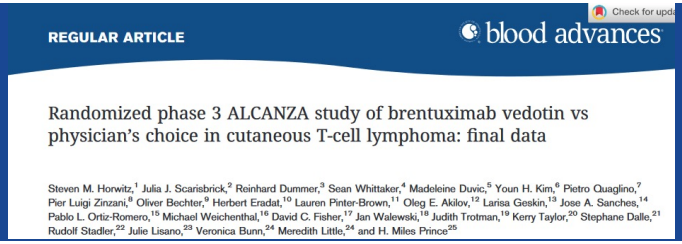

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Table 1. Summary of efficacy in the ITT population

	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-y 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

PD, progressive disease; PR, partial response; SD, stable disease.
*Based on additional information provided to the IRF after the 31 May 2016 data cutoff, the IRF determined that 1 patient had not achieved ORR4 as was originally reported; the change in status was determined through a standard IRF adjudication process.
†Median follow-up for OS in the brentuximab vedotin arm was 48.4 mo.
‡Median follow-up for OS in the physician's choice arm was 42.9 mo.

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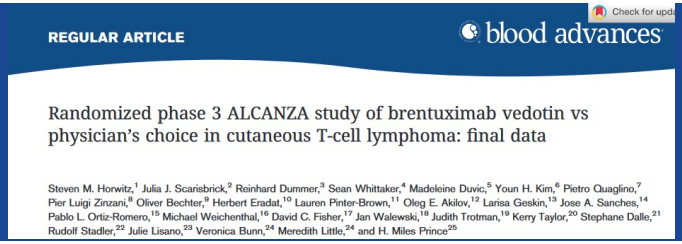
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ALCANZA: PFS results

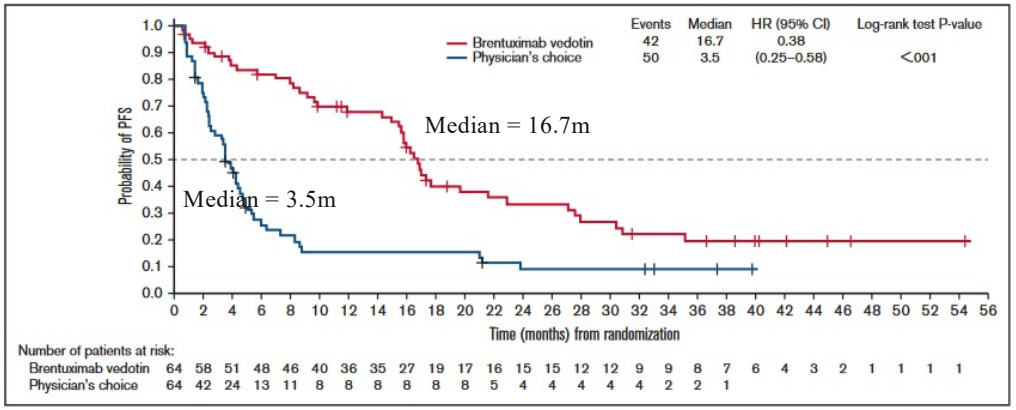

Figure 1. PFS per IRF in the ITT population. PFS was defined as the time from randomization until disease progression per IRF or death of any cause, whichever occurred first. Patients who were lost to follow-up, withdrew consent, or discontinued treatment because of undocumented disease progression after the last adequate disease assessment were censored at the last disease assessment.

ALCANZA: TTNT results

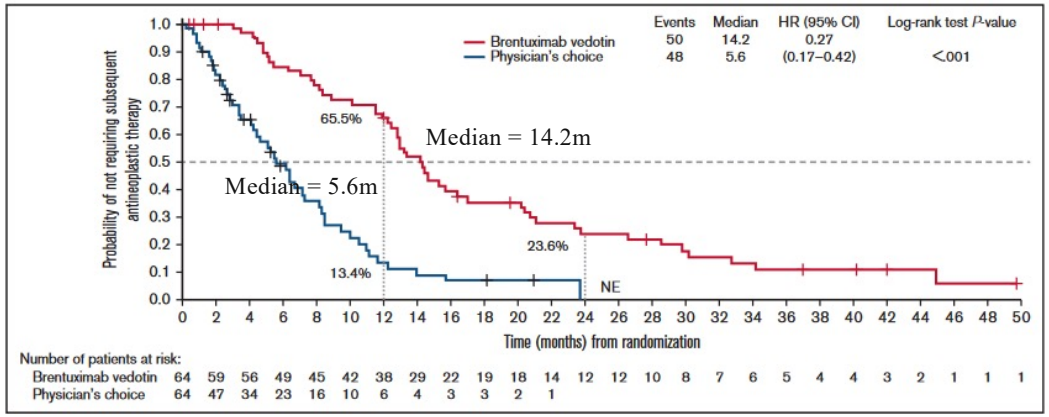

Figure 3. TTNT in the ITT population. Time to next antineoplastic therapy was defined as the time from randomization to the date of the first documentation of antineoplastic therapy or the last contact date for subjects who never received antineoplastic therapy. NE, not evaluable.

PFS

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MF

pcALCL

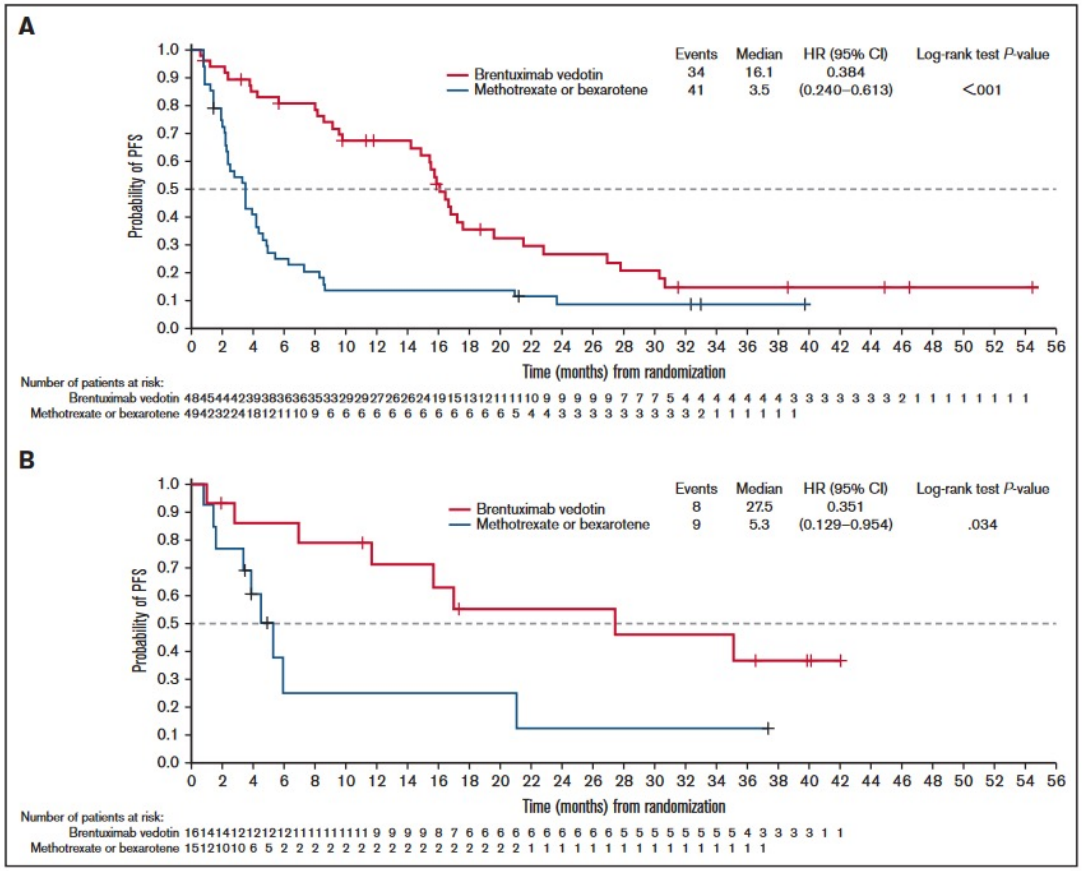

Figure 2. PFS per IRF in the ITT population. (A) PFS for patients with MF. (B) PFS for patients with C-ALCL. PFS is defined in Figure 1. Patients were censored at last disease assessment if they withdrew consent, were lost to follow-up, or discontinued treatment because of undocumented disease progression after the last adequate disease assessment.

ORR = 16%
PFS = 3.5m

ORR = 33%
PFS = 5.3m

PFS

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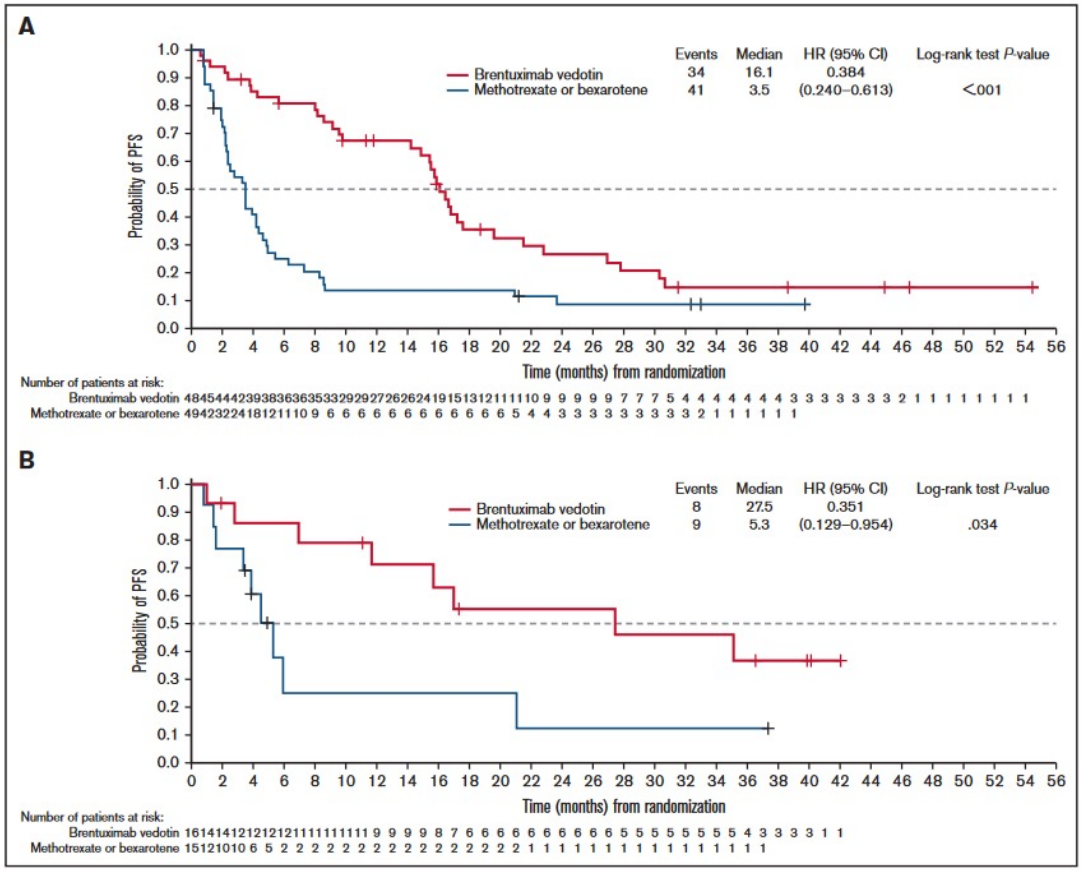
MF

pcALCL



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ORR = 65%
PFS = 16.1m

ORR = 75%
PFS = 27.5m

Neuropathy

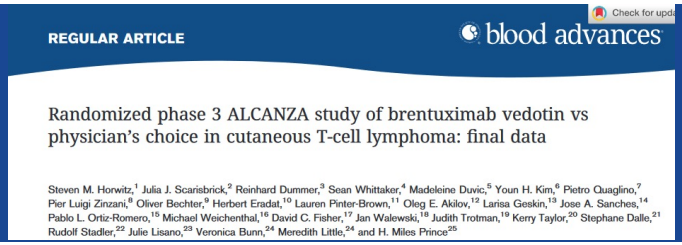
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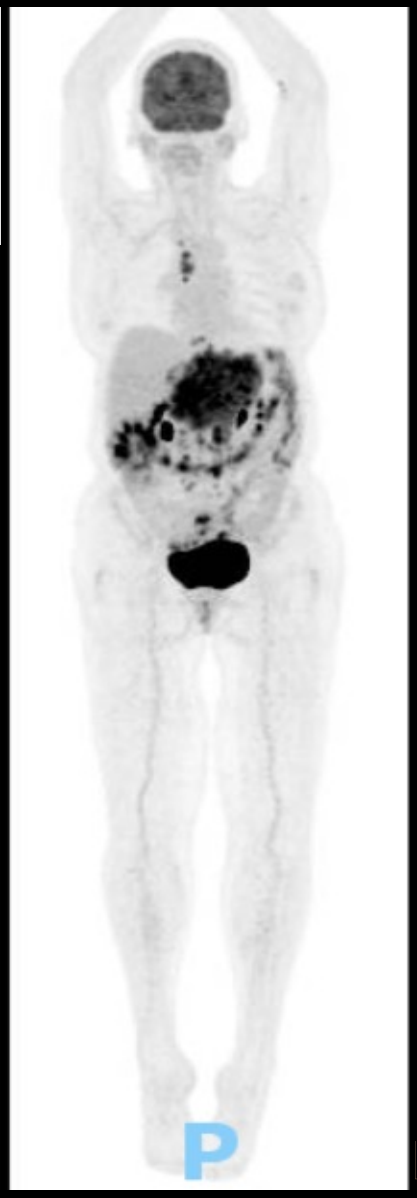
Table 4. Resolution, improvement, and duration of PN (SMQ) in the safety population

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

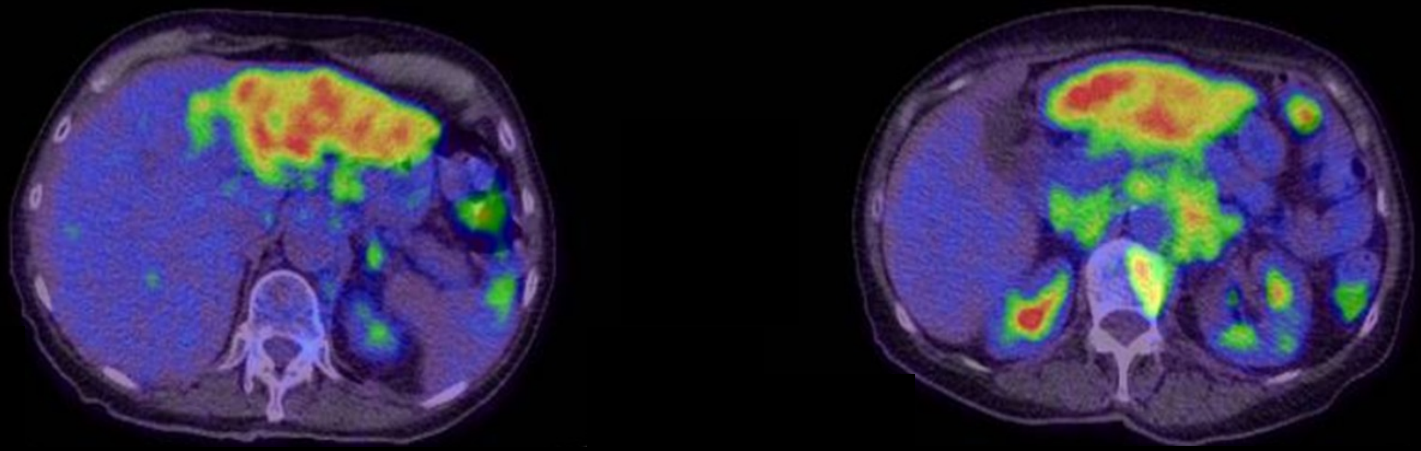
Brentuximab vedotin – the outstanding issues

- Efficacy in extracutaneous disease and LCT

Brentuximab vedotin therapy



Baseline



? Brentuximab vedotin

- How many in Alcanza had Visceral involvement?
- How many in Alcanza had Visceral involvement and LCT?
- How many in Alcanza had Visceral involvement and LCT and low CD30?

Patient responses per IRF by baseline TNMB stage per investigator: MF

- For patients with MF, ORR4 and ORR were superior with brentuximab vedotin versus physician's choice across subgroups defined by TNMB stage

	Treatment group							
	Brentuximab vedotin (N=64)				Physician's choice (N=64)			
n (%)	Total	ORR4	ORR	CR	Total	ORR4	ORR	CR
MF	**48 (75)**	**24 (50)**	**31 (65)**	**5 (10)**	**49 (77)**	**5 (10)**	**8 (16)**	**0**
Skin*								
T1	5 (10)	1 (20)	1 (20)	0	1 (2)	0	1 (100)	0
T2	13 (27)	7 (54)	10 (77)	1 (8)	20 (41)	4 (20)	4 (20)	0
T3	25 (52)	13 (52)	16 (64)	4 (16)	24 (49)	1 (4)	3 (13)	0
T4	5 (10)	3 (60)	4 (80)	0	4 (8)	0	0	0
Node								
N0	25 (52)	14 (56)	18 (72)	4 (16)	23 (47)	2 (9)	5 (22)	0
N1–NX	23 (48)	10 (43)	13 (57)	1 (4)	26 (53)	3 (12)	3 (12)	0
Visceral*								
M0	41 (85)	22 (54)	27 (66)	5 (12)	48 (98)	5 (10)	8 (17)	0
M1	7 (15)	2 (29)	4 (57)	0	0	NA	NA	NA
Blood†								
B0	43 (90)	23 (53)	28 (65)	4 (9)	41 (84)	4 (10)	6 (15)	0
B1	4 (8)	1 (25)	2 (50)	1 (25)	7 (14)	1 (14)	2 (29)	0
B2‡	0	NA	NA	NA	1 (2)	0	0	0

*One patient in the physician's choice arm had no biopsy performed to confirm visceral staging, and had no response; †One patient in the brentuximab vedotin arm had incomplete staging data, and had a PR; ‡One patient in the physician's choice arm had confirmed blood stage B1 at screening and B2 at baseline

ALCANZA: LCT status in patients with MF by patient demographics

- 35% of patients had LCT in both study arms

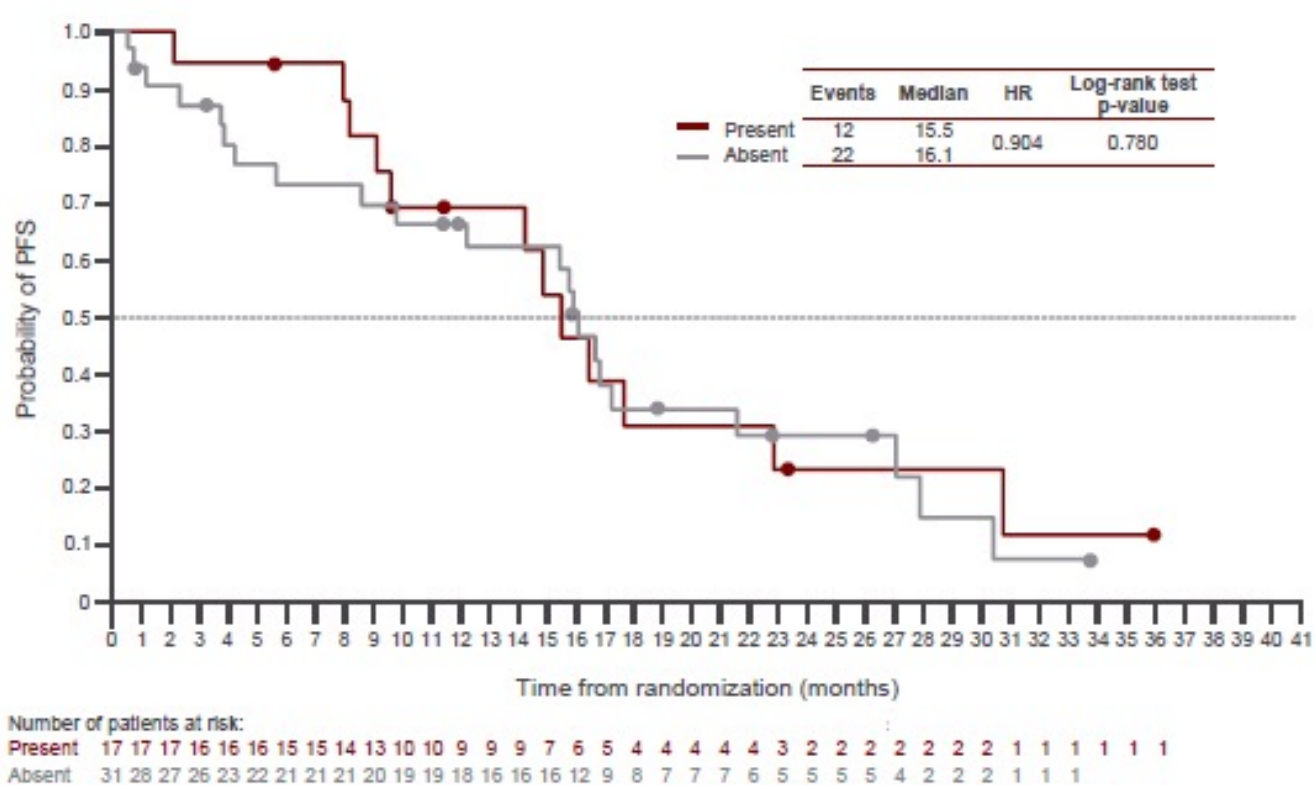
Table 1. Baseline demographics, disease characteristics, and LCT status in patients with MF in ALCANZA

LCT	Brentuximab vedotin (n=48)		Physician's choice (n=48)	
	Present (n=17)	Absent (n=31)	Present (n=17)	Absent (n=31)
Male, n (%)	11 (65)	16 (52)	8 (47)	18 (58)
Median age, years (range)	56.0 (37–81)	60.0 (22–83)	49.0 (27–74)	60.0 (22–81)
Median number of prior systemic therapies, n (range)	2.0 (1–11)	2.0 (1–11)	2.0 (1–6)	2.0 (1–6)
Overall staging, n (%)				
IA	0 (0)	4 (13)	0 (0)	1 (3)
IB/IIA	1 (6)	10 (32)	6 (35)	12 (39)
IIB	10 (59)	9 (29)	7 (41)	11 (35)
IIIA/IIIB	2 (12)	2 (6)	0 (0)	2 (6)
IVA_1	0 (0)	0 (0)	0 (0)	1 (3)
IVA_2	1 (6)	1 (3)	4 (24)	4 (13)
IVB	3 (18)	4 (13)*	0 (0)	0 (0)

*One additional patient had an unknown staging.

ALCANZA: Efficacy of brentuximab vedotin by LCT status

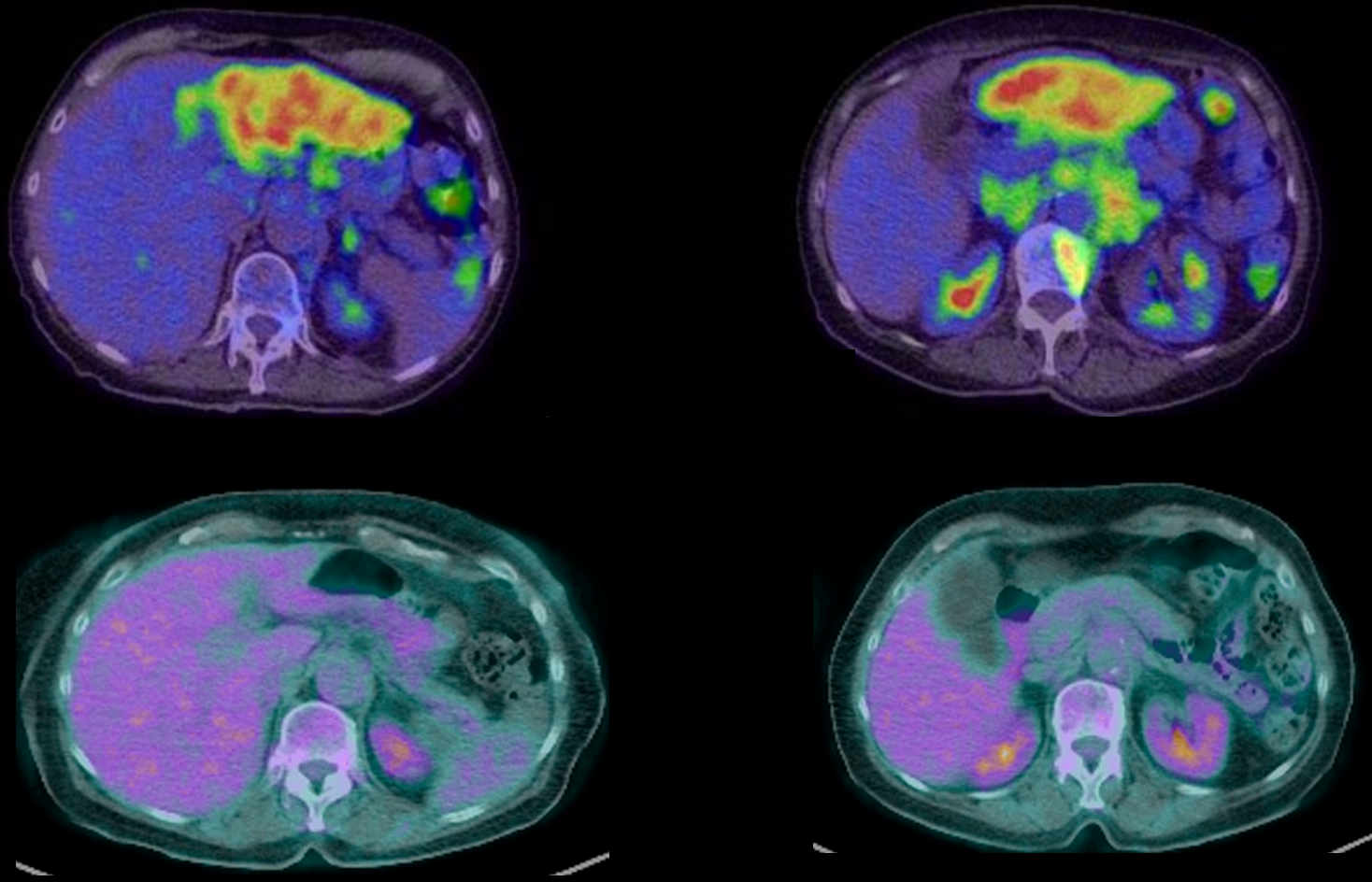
- Proportions of patients who achieved an ORR4 were higher in LCT-positive patients versus LCT-negative patients in the brentuximab vedotin arm (65% vs 39%) and the PC arm (18% vs 6%)
- Median PFS improved with brentuximab vedotin versus PC in patients with LCT (15.5 vs 2.8 months) and without LCT (16.1 vs 3.5 months)



LW – July 2019 to Jan 2020 – PET scans = CR

Baseline

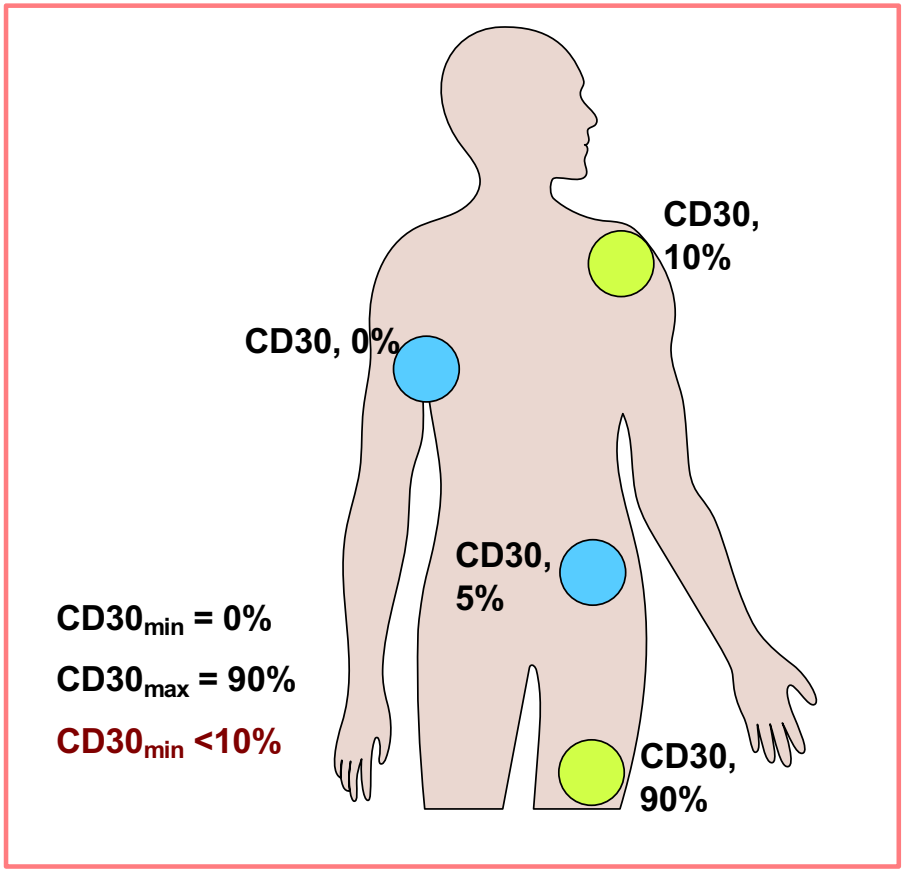
End cycle 9

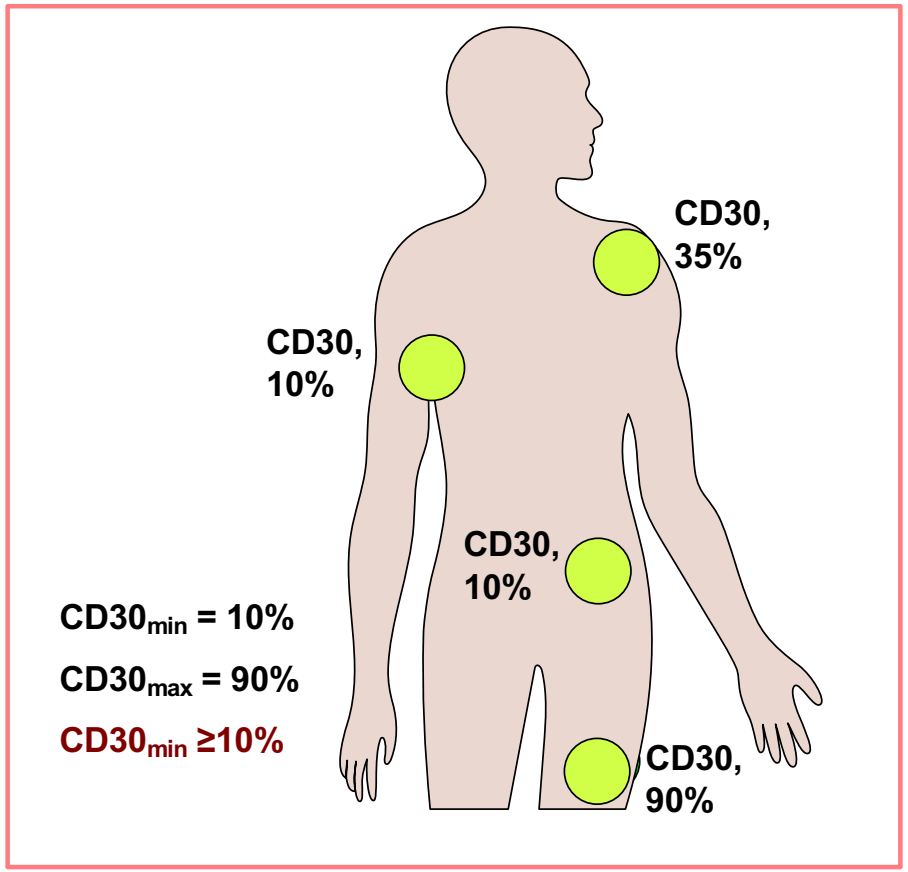


Brentuximab vedotin – the outstanding issues

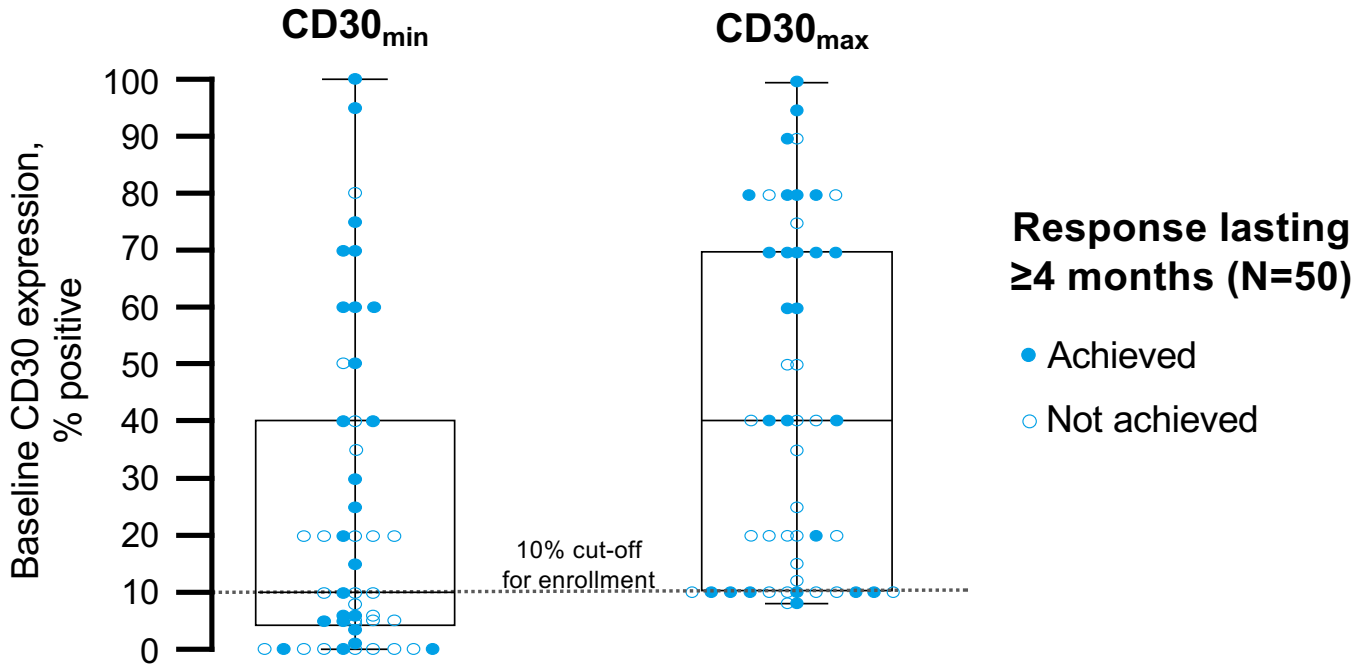
- CD30 positivity

Assessment of CD30 expression and statistical analysis





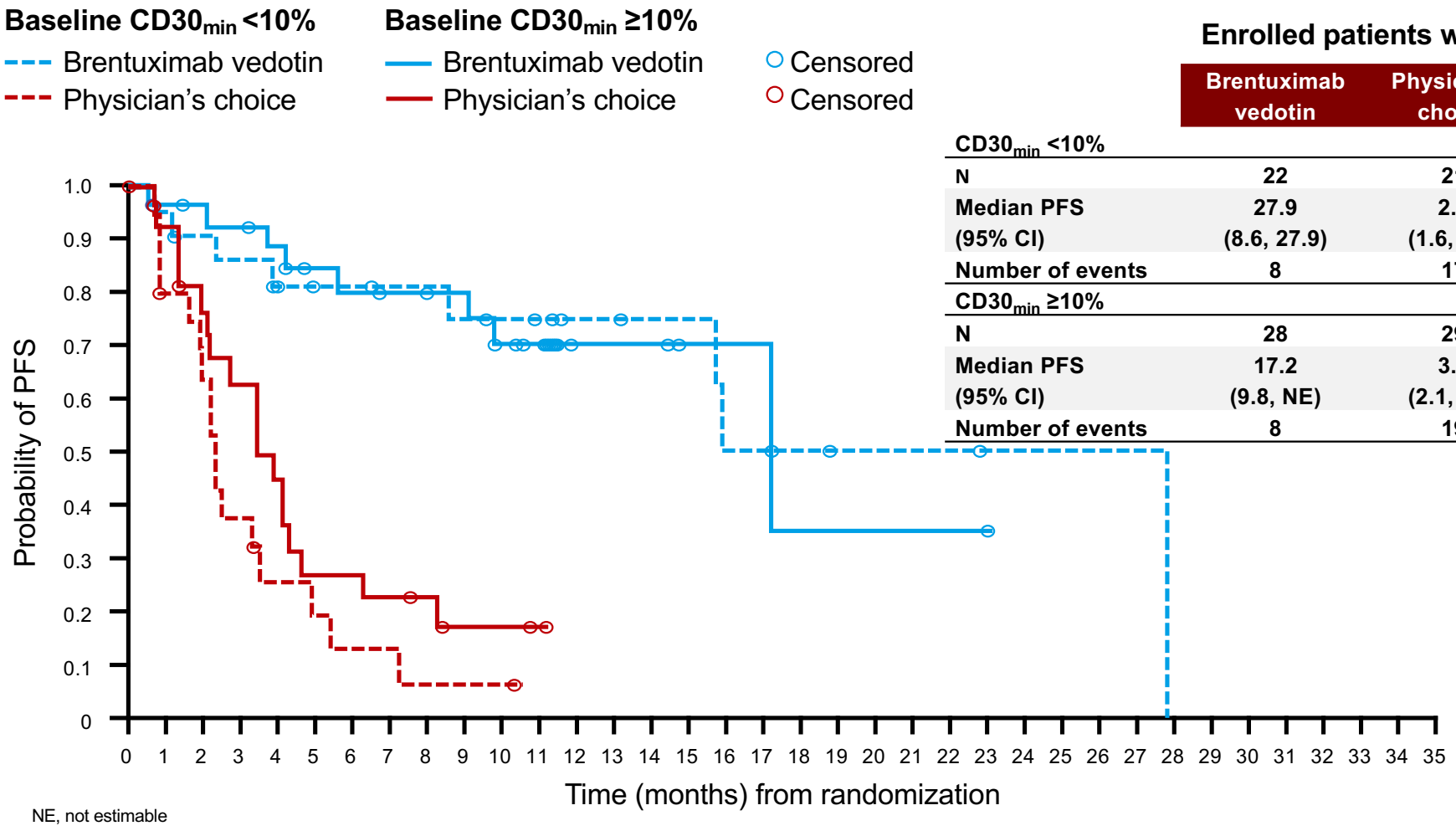
ORR4 with brentuximab vedotin across a broad range of baseline CD30 expression scores



MF patients who achieved ORR4

$CD30_{min}$ per patient	Brentuximab vedotin n/N (%)	Physician's choice n/N (%)	Difference % (95% CI)
$CD30_{min}$ <10%	9/22 (40.9)	2/21 (9.5)	31.4 (2.8, 58.1)
$CD30_{min}$ ≥10%	16/28 (57.1)	3/29 (10.3)	46.8 (20.6, 67.0)

Superior PFS with brentuximab vedotin versus physician's choice regardless of baseline CD30 expression



Enrolled patients with MF, N=100

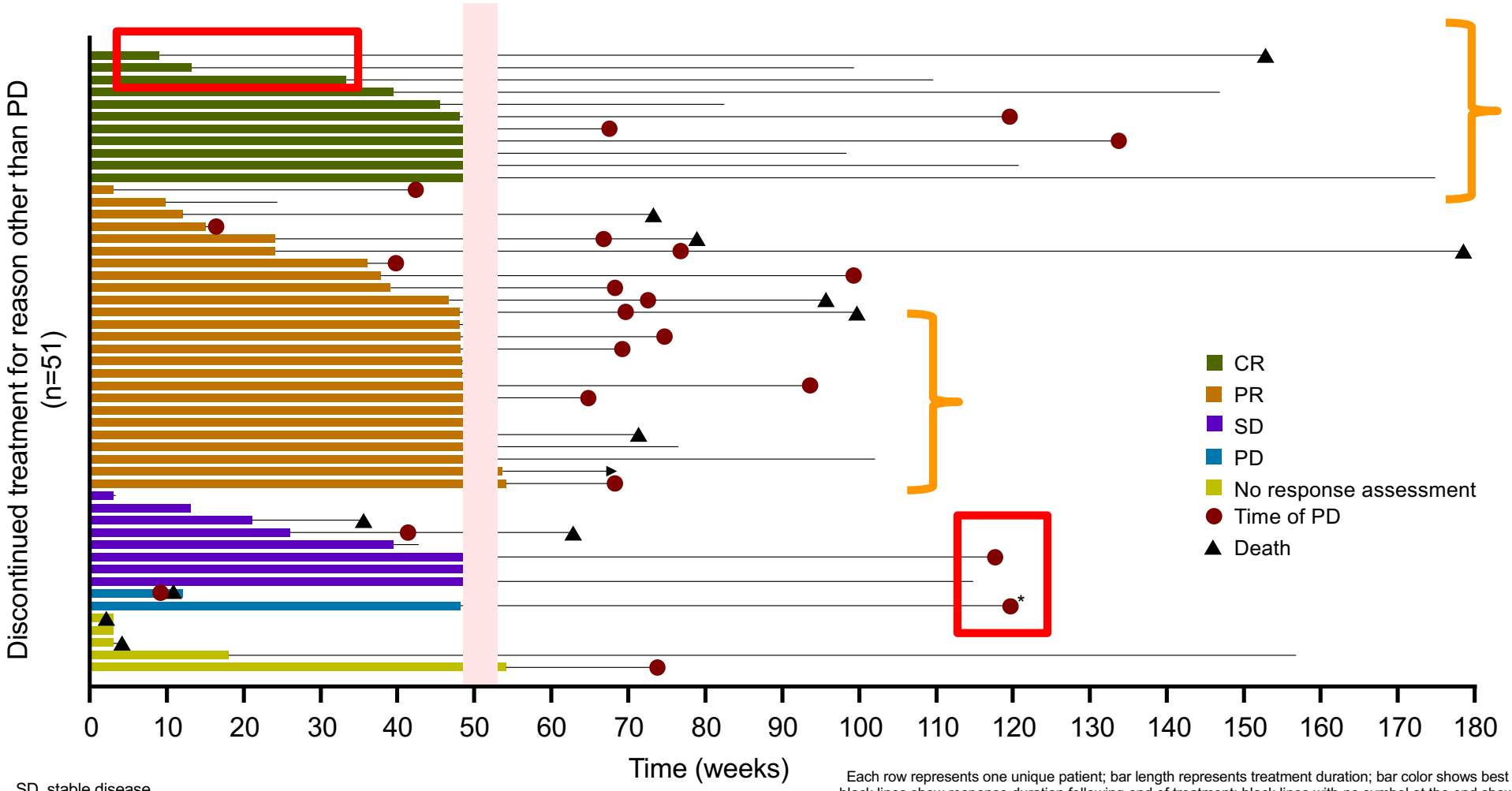
	Brentuximab vedotin	Physician's choice	HR (95% CI)
$CD30_{min}$ <10%			
N	**22**	**21**	**–**
Median PFS (95% CI)	**27.9 (8.6, 27.9)**	**2.3 (1.6, 3.5)**	**0.125 (0.044, 0.355)**
Number of events	**8**	**17**	**–**
$CD30_{min}$ ≥10%			
N	**28**	**29**	**–**
Median PFS (95% CI)	**17.2 (9.8, NE)**	**3.5 (2.1, 4.6)**	**0.176 (0.072, 0.432)**
Number of events	**8**	**19**	**–**

NE, not estimable

Brentuximab vedotin – the outstanding issues

- Re-treatment

Treatment duration and follow-up status of patients receiving brentuximab vedotin (MF and pcALCL)



SD, stable disease

Each row represents one unique patient; bar length represents treatment duration; bar color shows best overall response; black lines show response duration following end of treatment; black lines with no symbol at the end shows no PD/death at last assessment;*Patient response was not evaluable until 120 weeks (response assessment at 120 weeks showed PD).

Brentuximab vedotin – the outstanding issues

- C-ALCL – adding chemotherapy in extracutaneous disease?

How I treat primary cutaneous CD30+ lymphoproliferative disorders

Michi M. Shinohara[1,*] and Andrei Shustov[2,*]

[1]Division of Dermatology and [2]Division of Hematology, Department of Medicine, University of Washington, Seattle, WA

T: skin
- T1: solitary skin involvement
- T1a: solitary lesion <5-cm diameter
- T1b: solitary >5-cm diameter
- T2: regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions*
- T2a: all-disease-encompassing in a <15-cm diameter circular area
- T2b: all-disease-encompassing in a >15- and <30-cm diameter circular area
- T2c: all-disease-encompassing in a >30-cm diameter circular area
- T3: generalized skin involvement
- T3a: multiple lesions involving 2 noncontiguous body regions
- T3b: Multiple lesions involving ≥3 body regions

N: node
- N0: no clinical or pathologic lymph node involvement
- N1: involvement of 1 peripheral lymph node region† that drains an area of current or prior skin involvement
- N2: involvement of ≥2 peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement
- N3: involvement of central lymph nodes

M: visceral
- M0: no evidence of extracutaneous non–lymph node disease
- M1: extracutaneous non–lymph node disease present

Table 3. Most frequently used treatment modalities for pcALCL

	Skin directed	Systemic
Localized (T1, T2)	Radiotherapy,[56-58] surgical excision[3]	Low-dose methotrexate[59]
Widespread localized (T2) or generalized (T3) with no regional node involvement		BV (preferred),[23,73] low-dose methotrexate,[59] retinoids,[61,62] pralatrexate[70]
pcALCL with regional node involvement		BV (preferred),[23,73] low-dose methotrexate,[55,59] retinoids,[61,62] pralatrexate,[70] CHOP,[8,53] RT[55]

Outcomes of rare patients with a primary cutaneous CD30$^+$ lymphoproliferative disorder developing extracutaneous disease

Rutger C. Melchers,[1] Rein Willemze,[1] Joost S. P. Vermaat,[2] Patty M. Jansen,[3] Laurien A. Daniëls,[4] Hein Putter,[5] Marcel W. Bekkenk,[6] Ellen R. M. de Haas,[7] Barbara Horvath,[8] Michelle M. van Rossum,[9] Cornelus J. G. Sanders,[10] Joep C. J. M. Veraart,[11] Maarten H. Vermeer,[1] and Koen D. Quint[1]

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C-ALCL – adding chemotherapy to BV

- Melchers et al, reported that 12% of patients with C-ALCL developed extracutaneous manifestations:
  - CR 61% to front-line therapy with CHOP.
  - TTP = 27 months.
- ECHELON-2 (PTCL): 50% were ALK negative systemic ALCL
  - CR 56% with CHOP therapy.
  - PFS = 20.8 months.
- ALCANZA: extracutaneous C-ALCL (n =7)
  - RR = 57%
  - CR only 14%.
  - PFS = 27.5 months but only 14.9 m for extracutaneous disease.

Given ECHELON-2 which demonstrated the value of adding BV to CHOP-based Rx in sALCL . Suggest BV+CHP be the preferred therapy for extracutaneous C-ALCL over BV-alone or systemic chemotherapy-alone.

Brentuximab vedotin – the outstanding issues

- Long term follow up
- Efficacy in extracutaneous disease and LCT
- CD30 positivity
- Re-treatment
- C-ALCL – adding chemotherapy?