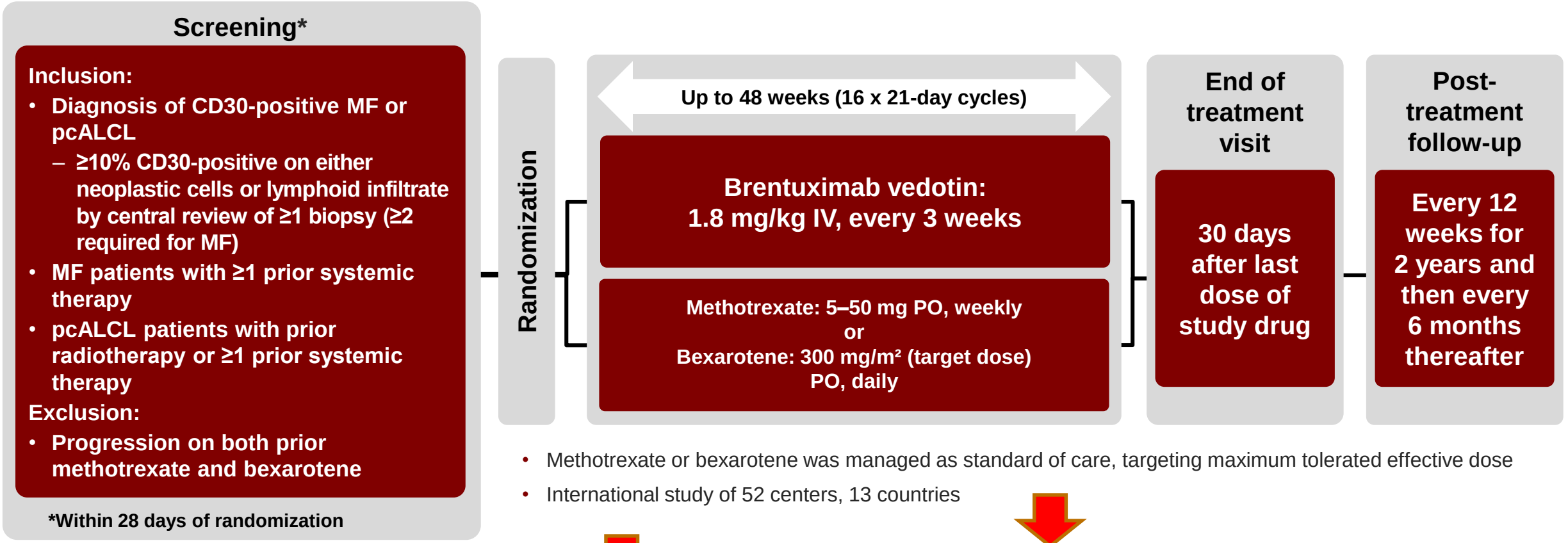
Clinical Activity with Brentuximab Vedotin in Cutaneous T-cell Lymphoma

- Updated analysis -
- Time to next treatment -
- Disease Stages/Compartments -
- CD30 Expression Level -

Disclosures

- Co-funded by Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, and Seattle Genetics, Inc., Bothell, WA, USA
- **H. Miles Prince:** Advisory board member for Millennium/Takeda Pharmaceuticals; has received honoraria for advisory boards and research funding for clinical trials
- Full disclosure information for all authors is available on request

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

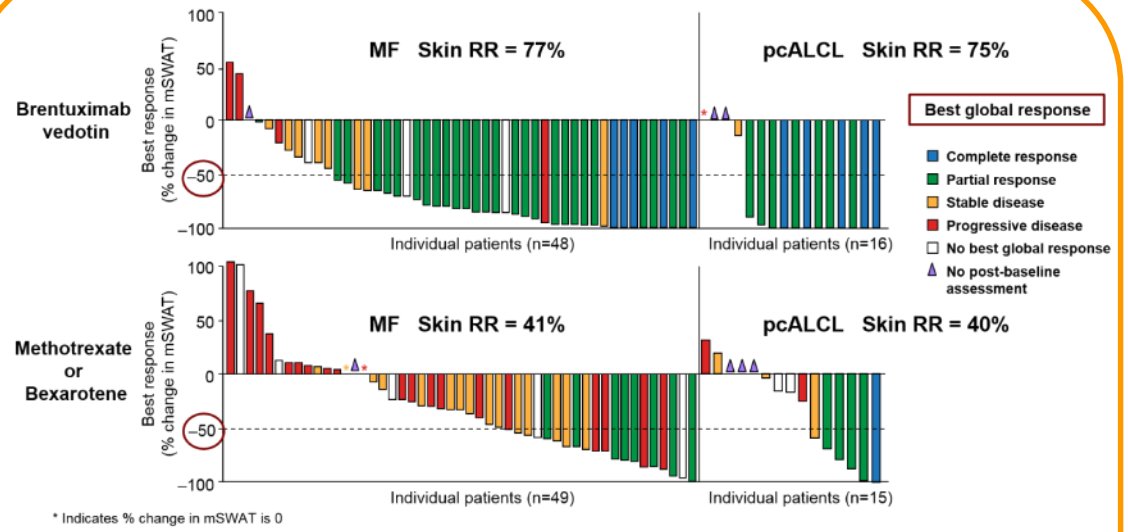
- **Brentuximab vedotin was far superior to physician's choice,** demonstrating **improved ORR4** (56% vs 13%; p<0.0001), **CR rate** (16% vs 2%; adjusted p=0.0046), and **PFS** (16.7 vs 3.5 months; HR=0.270, 95% CI: 0.169, 0.430; adjusted p<0.0001), and **a reduction in patient-reported symptoms** (Skindex-29 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

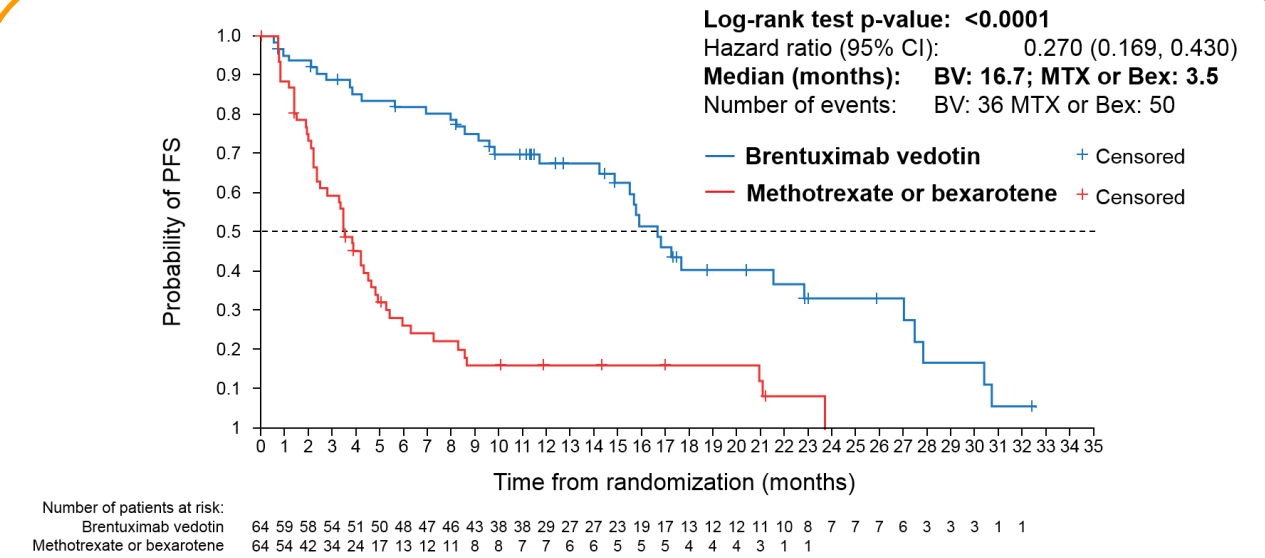
1. Kim YH, et al. Blood 2016;128:182
2. Prince HM, et al. Lancet 2017;390:555–66

ALCANZA: Key efficacy and safety data[1]

- ALCANZA met its primary endpoint: the proportion of patients achieving an objective global response lasting ≥4 months was 56.3% with brentuximab vedotin versus 12.5% with physician's choice (between-group difference = 43.8% [95% CI, 29.1–58.4; p<0.0001])



Maximum percentage change in skin mSWAT score



PFS (assessed by independent review; ITT)

- Bex, bexarotene; CI, confidence interval; ITT, intention-to-treat; mSWAT, modified Severity-Weighted Assessment Tool; MTX, methotrexate; PFS, progression-free survival; RR, response rate

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

Patient responses per IRF by baseline disease stage/involvement (ITT population)

- Brentuximab vedotin was superior to physician's choice in terms of ORR4, ORR, and CR rate in MF patients across all disease stages and in pcALCL patients with skin-only and extracutaneous disease
- In both the brentuximab vedotin and physician's choice groups, the majority of patients presented with stage IA, IIA or IIB disease and the majority of pcALCL patients presented with skin-only disease

	Treatment group								
	Brentuximab vedotin (N=64)				Physician's choice (N=64)				ORR4 rate difference
n (%)	Total	ORR4	ORR	CR rate	Total	ORR4	ORR	CR rate	(95% CI)
MF	**48 (75)**	**24 (50)**	**31 (65)**	**5 (10)**	**49 (77)**	**5 (10)**	**8 (16)**	**0**	**39.8 (19.9, 56.2)**
Stage*									
IA–IIA	15 (31)	6 (40)	8 (53)	1 (7)	18 (37)	4 (22)	5 (28)	0	17.8 (–16.6, 49.4)
IIB	19 (40)	12 (63)	13 (68)	3 (16)	19 (39)	1 (5)	3 (16)	0	57.9 (25.4, 80.9)
IIIA–IIIB	4 (8)	2 (50)	3 (75)	0	2 (4)	0	0	0	50.0 (–45.2, 98.7)
IVA	2 (4)	2 (100)	2 (100)	1 (50)	9 (18)	0	0	0	100.0 (14.9, 100)
IVB	7 (15)	2 (29)	4 (57)	0	0	NA	NA	NA	NA
pcALCL	**16 (25)**	**12 (75)**	**12 (75)**	**5 (31)**	**15 (23)**	**3 (20)**	**5 (33)**	**1 (7)**	**55.0 (19.7, 80.4)**
Involvement									
Skin only	9 (56)	8 (89)	8 (89)	4 (44)	11 (73)	3 (27)	5 (45)	1 (9)	61.6 (17.9, 88.3)
Extracutaneous	7 (44)	4 (57)	4 (57)	1 (14)	4 (27)	0	0	0	57.1 (–9.0, 93.2)

The percentage shown in the total column describes the proportion of patients from that treatment group and the number of patients demonstrating ORR4, ORR, and CR is presented as a percentage of the figure shown in the total column

*One patient in each arm had incomplete staging data and are not included in the table; one patient in the brentuximab vedotin arm had a PR, and one patient in the physician's choice arm had no response

ITT, intent-to-treat; NA, not applicable

Patient responses per IRF by baseline disease stage/involvement (ITT population)

- Brentuximab vedotin was superior to physician's choice in terms of ORR4, ORR, and CR rate in MF patients across all disease stages and in pcALCL patients with skin-only and extracutaneous disease
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IIB	19 (40)	12 (63)	13 (68)	3 (16)	19 (39)	1 (5)	3 (16)	0	57.9 (25.4, 80.9)
IIIA–IIIB	4 (8)	2 (50)	3 (75)	0	2 (4)	0	0	0	50.0 (–45.2, 98.7)
IVA	2 (4)	2 (100)	2 (100)	1 (50)	9 (18)	0	0	0	100.0 (14.9, 100)
IVB	7 (15)	2 (29)	4 (57)	0	0	NA	NA	NA	NA
pcALCL	**16 (25)**	**12 (75)**	**12 (75)**	**5 (31)**	**15 (23)**	**3 (20)**	**5 (33)**	**1 (7)**	**55.0 (19.7, 80.4)**
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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

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

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	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
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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
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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
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N0	25 (52)	14 (56)	18 (72)	4 (16)	23 (47)	2 (9)	5 (22)	0
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	Brentuximab vedotin (N=64)				Physician's choice (N=64)			
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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
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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
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B0	43 (90)	23 (53)	28 (65)	4 (9)	41 (84)	4 (10)	6 (15)	0
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Patient responses per IRF by baseline TNMB stage per investigator: pcALCL

- For patients with pcALCL, ORR4 and ORR were higher with brentuximab vedotin versus physician's choice in patients with skin involvement, nodal involvement, and visceral involvement

	Treatment group							
	Brentuximab vedotin (N=64)				Physician's choice (N=64)			
n (%)	Total	ORR4	ORR	CR	Total	ORR4	ORR	CR
pcALCL	**16 (25)**	**12 (75)**	**12 (75)**	**5 (31)**	**15 (23)**	**3 (20)**	**5 (33)**	**1 (7)**
Skin								
T1	1 (6)	1 (100)	1 (100)	1 (100)	4 (27)	1 (25)	2 (50)	0
T2	3 (19)	3 (100)	3 (100)	1 (33)	5 (33)	0	1 (20)	0
T3	12 (75)	8 (67)	8 (67)	3 (25)	6 (40)	2 (33)	2 (33)	1 (17)
Node								
N0	10 (63)	8 (80)	8 (80)	4 (40)	11 (73)	3 (27)	5 (45)	1 (9)
N1–NX	6 (38)	4 (67)	4 (67)	1 (17)	4 (27)	0	0	0
Visceral								
M0	12 (75)	9 (75)	9 (75)	5 (42)	14 (93)	3 (21)	5 (36)	1 (7)
M1	4 (25)	3 (75)	3 (75)	0	1 (7)	0	0	0

Updated at 34 month follow up (ITT population)

- updated analyses of treatment response and clinical benefit per investigator assessment after a median follow-up of 33.9 months (data cut-off August 16, 2017)

	Treatment group			
	Brentuximab vedotin (N=64)	Physician's choice (N=64)	Risk difference	
	n (%)	n (%)	(95% CI)	P-value
ORR4	39 (60.9)	5 (7.8)	53.1 (36.5, 67.2)	<0.001
Best response per investigator				
CR	12 (18.8)	0	18.8 (0.7, 35.9)	<0.001
PR	32 (50.0)	14 (21.9)	28.1 (–)	–
ORR	44 (68.8)	14 (21.9)	46.9 (31.7, 62.1)	<0.001
SD	13 (20.3)	29 (45.3)	–25.0 (–)	–
PD	3 (4.7)	13 (20.3)	–15.6 (–)	–

ITT, intent-to-treat; PD, progressive disease; PR, partial response; SD, stable disease

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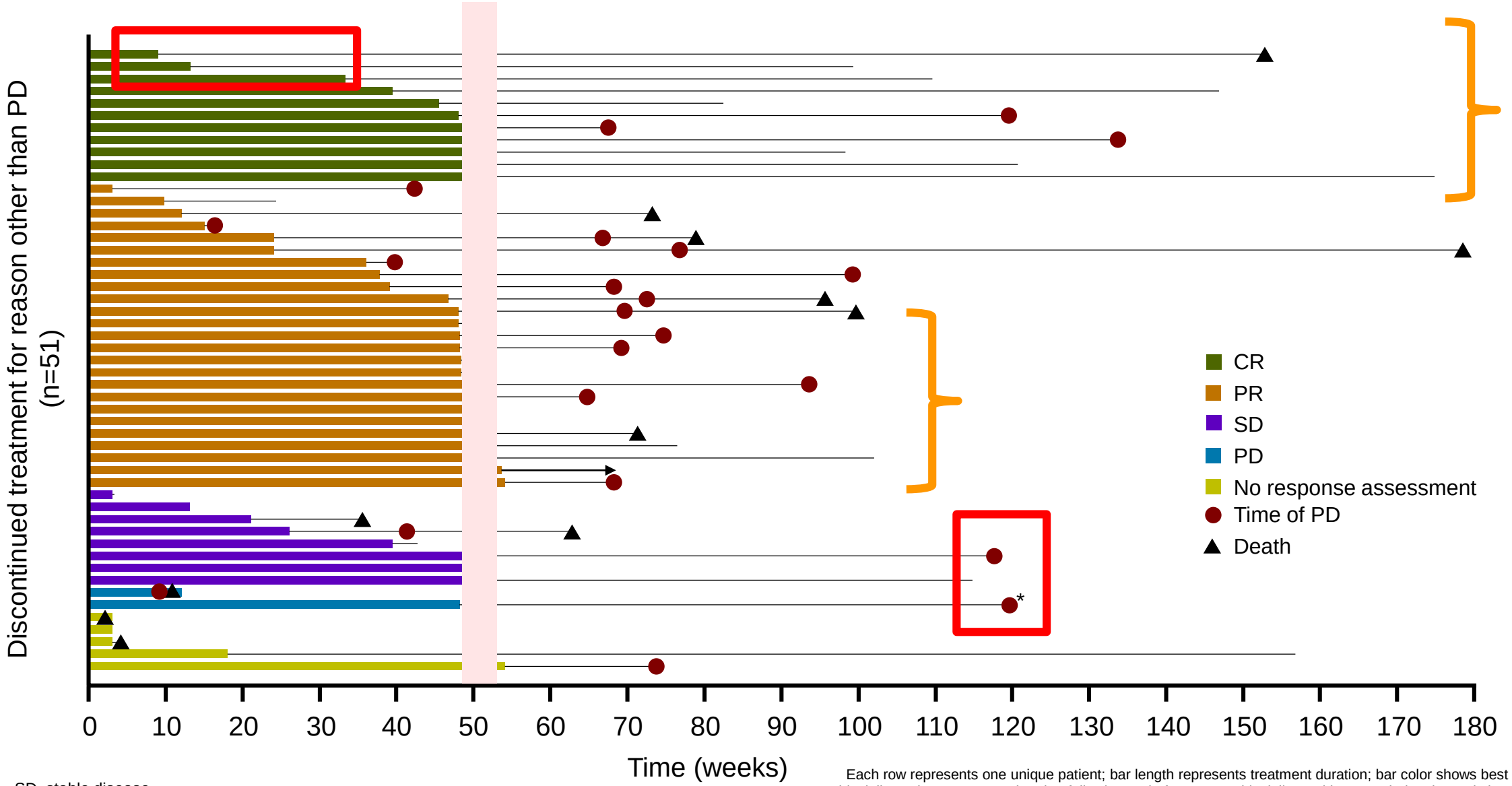
ITT, intent-to-treat; PD, progressive disease; PR, partial response; SD, stable disease

Duration of response by diagnosis

- DoR was much longer for patients with pcALCL receiving brentuximab vedotin (median DoR 25.5 months) than for patients with MF receiving brentuximab vedotin (median DoR 14.4 months)

	Treatment group	
	Brentuximab vedotin (N=64)	Physician's choice (N=64)
MF		
Number of patients, n (%)	48 (75)	49 (77)
Number of responders, n (%)	31 (65)	8 (16)
Median (95% CI) DoR, months	14.4 (8.5, 18.8)	18.3 (2.1, 18.4)
pcALCL		
Number of patients, n (%)	16 (25)	15 (23)
Number of responders, n (%)	12 (75)	5 (33)
Median (95% CI) DoR, months	25.5 (9.5, 25.5)	NE (NE, NE)

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

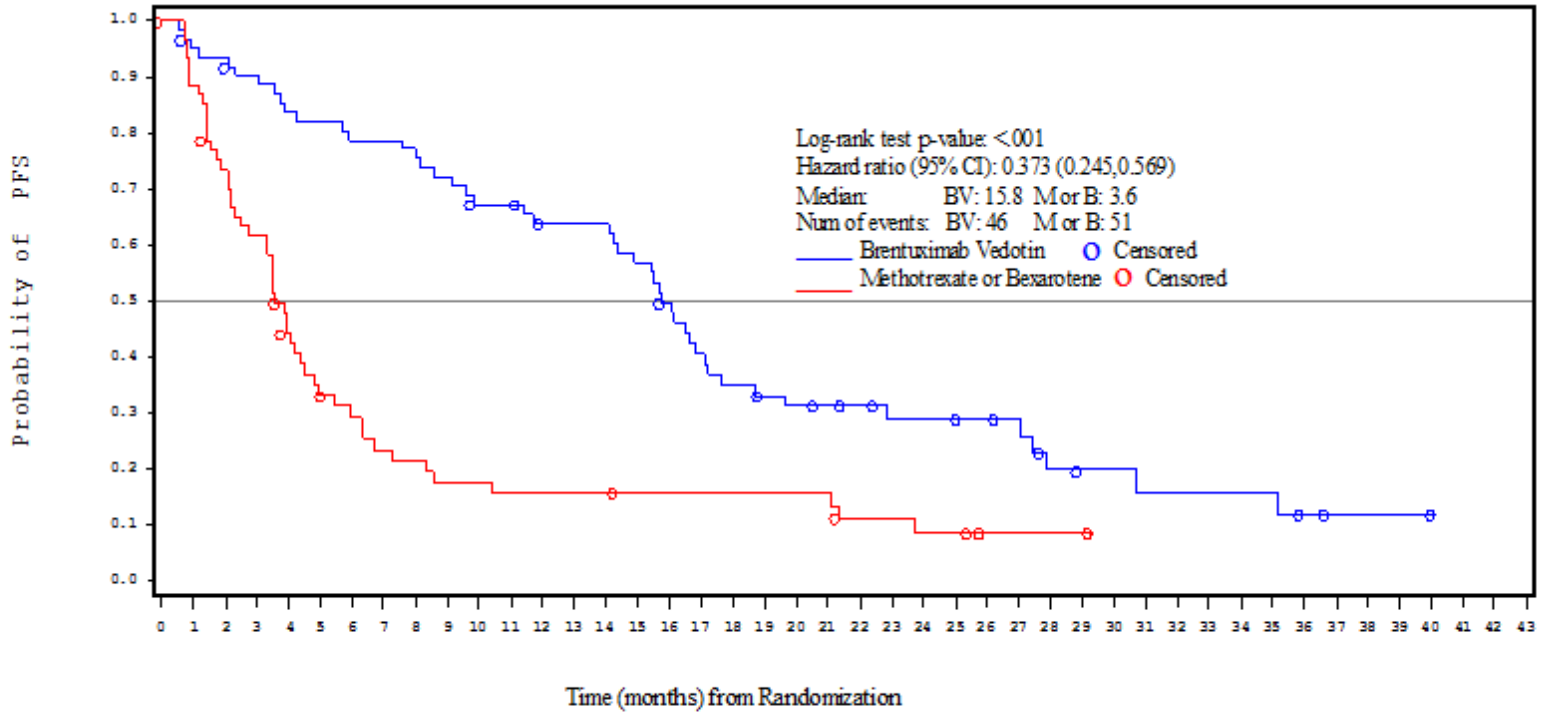


SD, stable disease

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).

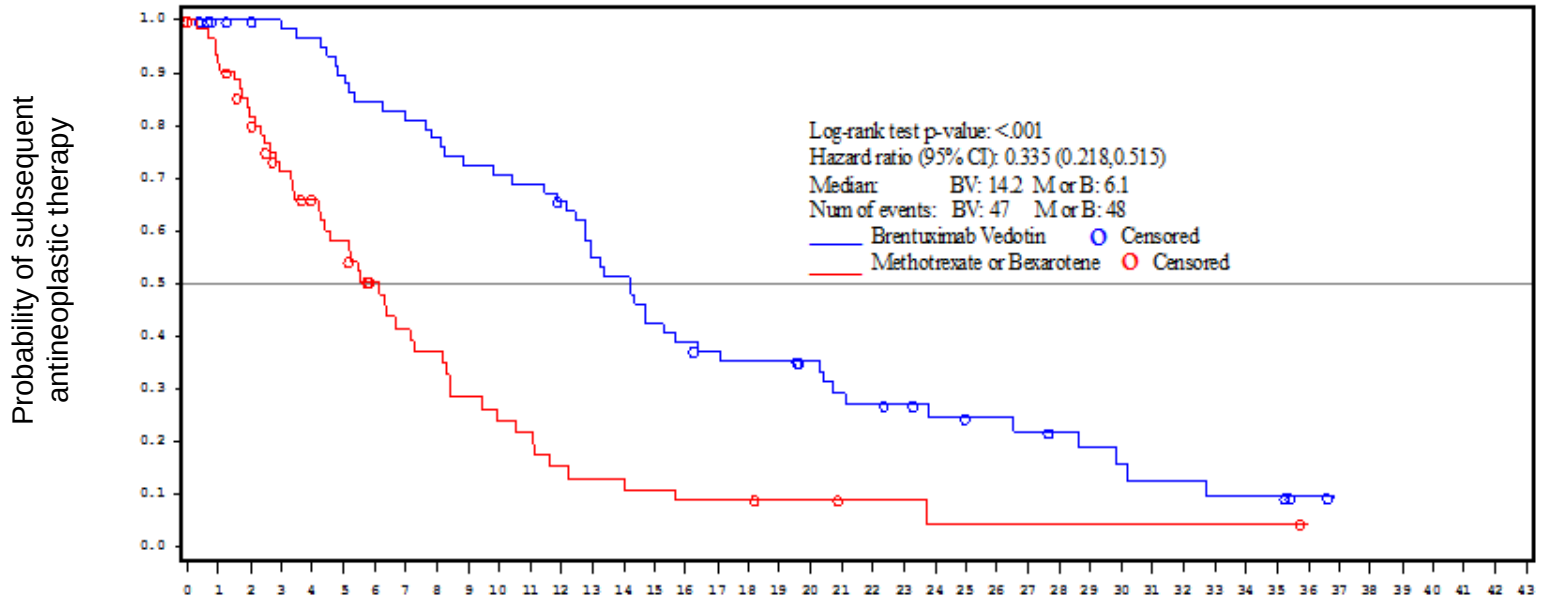
Progression-free survival Updated at 34 month follow up (ITT)

- Median follow-up for PFS was 33.9m
- With 46 and 51 patients having progressed (39 and 46 patients) or died (7 and 5 patients), respectively, median PFS with brentuximab vedotin versus physician's choice was **15.8 versus 3.6 months**
- Kaplan-Meier estimates demonstrated improved PFS rates with brentuximab vedotin versus physician's choice at **1 year (63.9% vs 15.6%)** and **2 years (28.8% vs 8.4%)**



Time to next treatment (TTNT)

- At a median follow-up of 33.9 months, **47 (73%) and 48 (75%) of patients in the brentuximab vedotin and physician's choice arms, respectively, had received ≥1 subsequent antineoplastic therapy**
- Median TTNT was significantly longer with brentuximab vedotin versus physician's choice (**14.2 vs 6.1** months; HR 0.335; 95% CI, 0.218–0.515; p<0.001)
- In the brentuximab vedotin versus physician's choice arms, the probability of patients not requiring subsequent antineoplastic therapy was greater at **1 year (65.5% vs 15.3%)** and **2 years (24.6% vs 4.4%)** post-randomization



PFS vs Time to next treatment (TTNT)

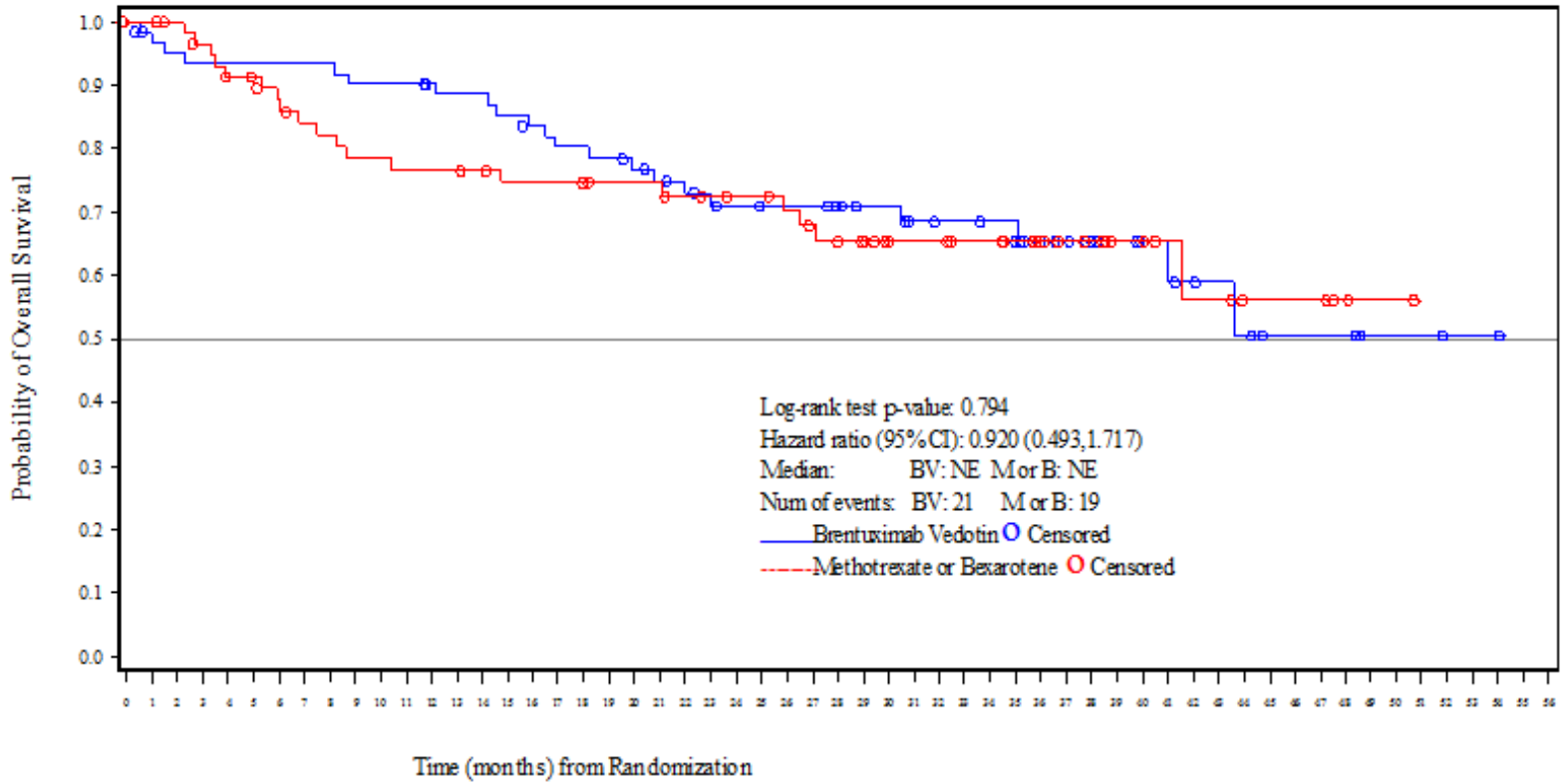
- Median follow-up of approx 34 months
- median PFS with brentuximab vedotin versus physician's choice was **15.8 versus 3.6 months**
- median TTNT with brentuximab vedotin versus physician's choice was **14.2 versus 6.1 months**

- PFS rates with BV versus physician's choice at **1 year (63.9% vs 15.6%)** and **2 years (28.8% vs 8.4%)**
- TTNT rates with BV versus physician's choice at **1 year (65.5% vs 15.3%)** and **2 years (24.6% vs 4.4%)**

- Why a difference
  - PFS does not capture symptoms (itch, pain)
  - PFS does not capture transformation – early treatment before formal PFS*
  - Tempo or severity of relapse can be different – is severity of relapse on BV worse? * - longer TTNT than PFS of 3m for PC
- Do we need to consider these issues in an updated "Response criteria"

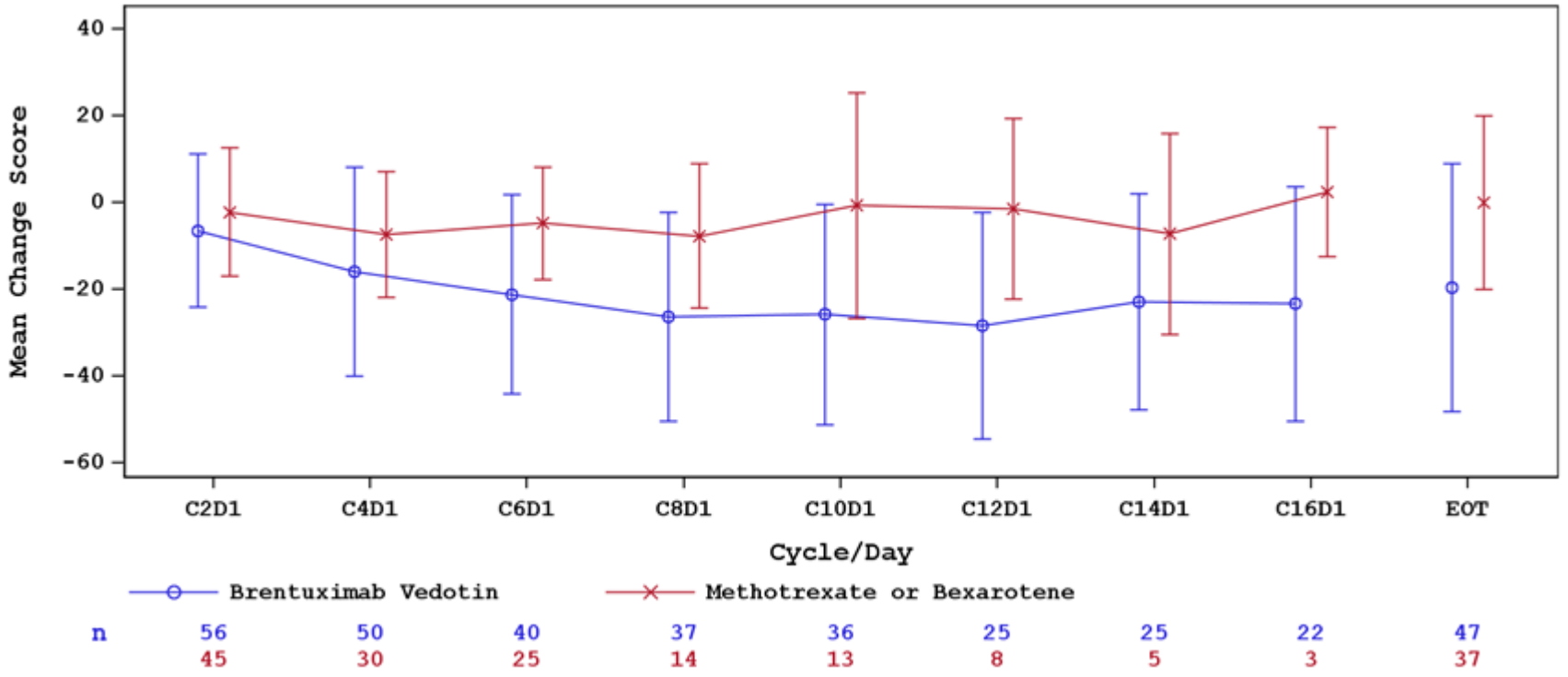
Overall survival

- Median follow-up for OS was 33.9 months, median OS was not reached in either arm; OS was not significantly different between arms (p=0.794)
- Kaplan-Meier estimates demonstrated a higher OS rate with brentuximab vedotin versus physician's choice at 1 year (90.4% vs 76.6%), but not at 2 years (71.1% vs 72.6%)



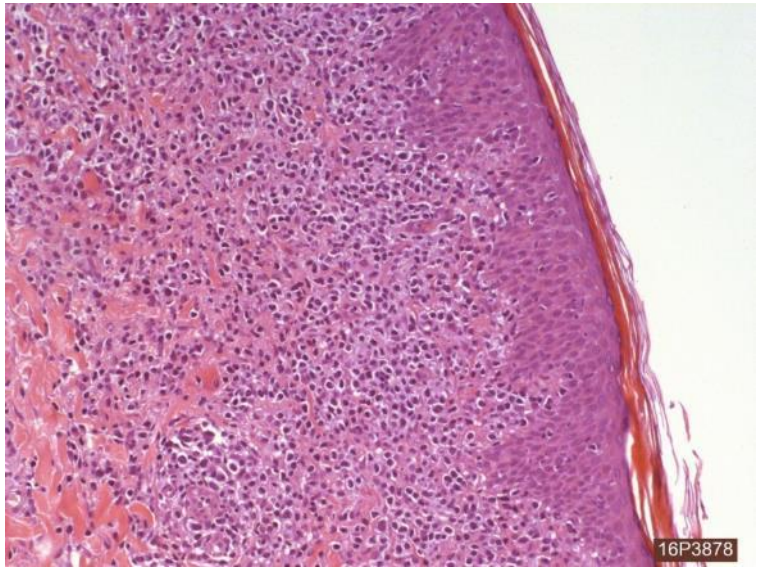
QoL per changes in symptom domain by Skindex-29 questionnaire

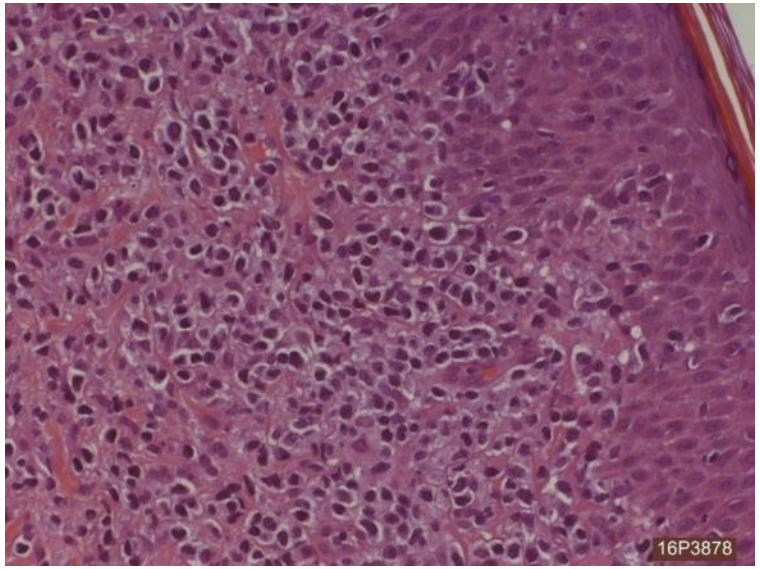
- Patient-reported QoL assessed by Skindex-29 questionnaire showed significantly greater symptom reduction for patients receiving brentuximab vedotin versus physician's choice (mean maximum reduction –28.08% vs –8.62%; p<0.001)

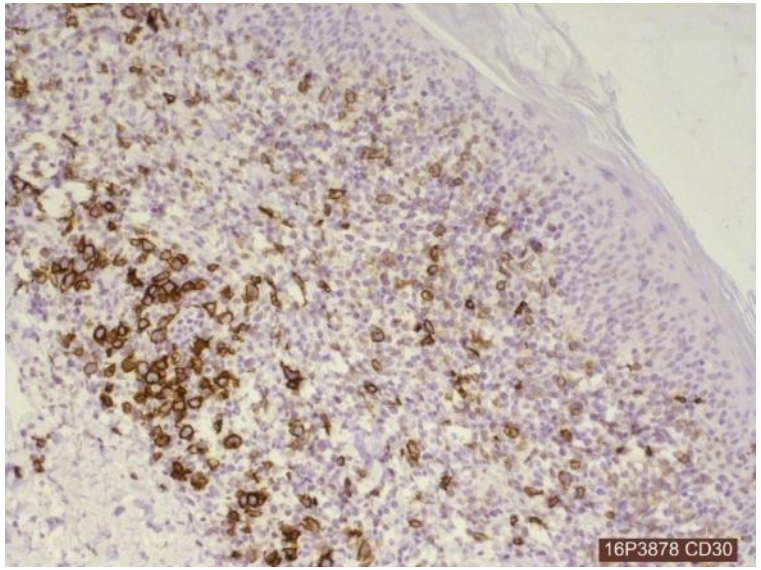


CD30 expression:

Non-transformed mycosis fungoides with some CD30 expression







Challenges in CD30 detection and quantification

How can measurement of CD30 expression be standardised?

- Critical for reliability/reproducibility[1]
- No consensus on what defines CD30 positivity
  – Typically 10–20% of cells, but differs between studies[1–5]
  – >75% in pcALCL and LyP (Type A and C)[6]
- Quantitation methods vary[2–4,7]*
- Issue of staining non-tumour cells; dual staining is not often used

What is the relationship between CD30 expression and treatment efficacy?

- Prognostic value of CD30 expression is unclear: study results are conflicting[5,8–11]
- Prognostic relevance may be subtype specific[5,8,9]
- CD30 expression may impact on efficacy of anti-CD30 therapy,[12] although variability in CD30 expression in patients categorised as CD30+ (≥10%) did not seem to correlate with response[13]

Can CD30 expression change?

- For example, between lesions
  – In patients with MF, CD30 expression can vary from lesion to lesion,[13] and so can change simply because of intrapatient variability

*In IHC, methods and techniques may vary for tissue sampling, fixation, embedding, sectioning and mounting, antigen retrieval, primary antibody, visualisation and interpretation[7]

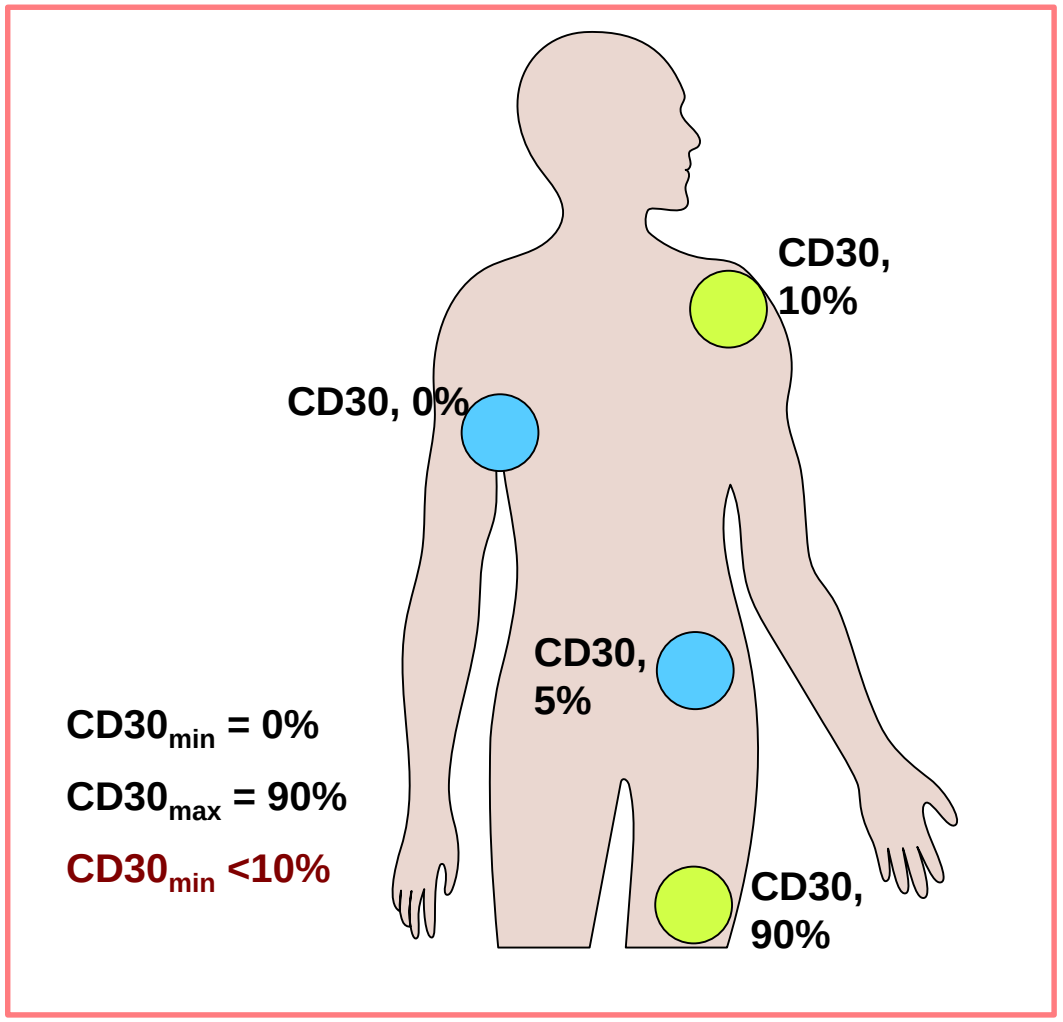
1. Wasik MA, et al. Pathobiology 2013;80:252–8; 2. von Wasielewski R, et al. Am J Pathol 1997;151:1123–30; 3. Weisenburger DD, et al. Blood 2011;117:3402–8; 4. Stacchini A, et al. Am J Clin Pathol 2007;128:854–64; 5. Hu S, et al. Blood 2013;121:2715–24; 6. Willemze R, et al. Blood 2005;105:3768–85; 7. Taylor CR, Rudbeck L (eds). Education guide: Immunohistochemical staining methods, 6th ed. Glostrup: Dako Demark, 2013; 8. Savage KJ, et al. Blood 2008;111:5496–504; 9. Piccaluga PP, et al. J Clin Oncol 2013;31:3019–25; 10. Delabie J, et al. Blood 2011;118:148–55; 11. Kuo T-T, et al. Int J Surg Pathol 2004;12:375–87; 12. Kim YH, et al. J Clin Oncol 2015;33:3750–8; 13. Kim YH, et al. Poster presentation at the American Society of Clinical Oncology Annual Meeting 2017; abstract 7517.

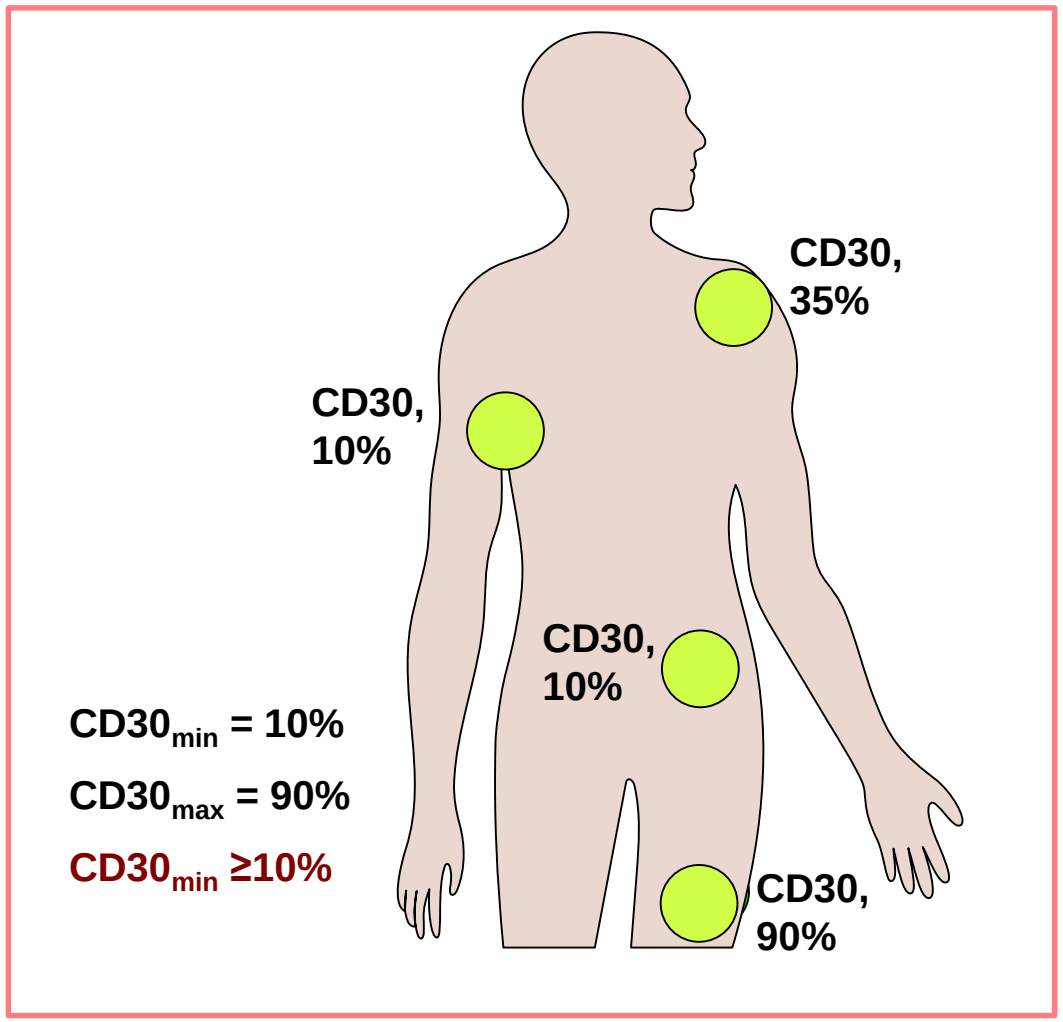
Assessment of CD30 expression and statistical analysis

- Patients with MF had ≥2 skin biopsies from separate skin lesions obtained at screening (baseline)
- CD30 expression was determined using an investigational IHC diagnostic test (Ventana Medical Systems, Inc., Tucson, AZ, USA)
- Results were assessed centrally by one pathologist; patients were scored CD30-positive and eligible for enrollment if ≥1 biopsy had ≥10% CD30-positive lymphoid cells at any intensity above background
- Of all baseline* biopsies (≥2):
  - **$CD30_{min}$** = minimum CD30 expression score; **$CD30_{max}$** = maximum CD30 expression score
- Efficacy analyses (ORR4 and PFS) were conducted for patients with MF in the brentuximab vedotin versus physician's choice arms by 10% cut-off to assess differences in outcome in those with <u>at least</u>
  1 biopsy <10% CD30-positive ($CD30_{min}$ <10%) versus <u>all</u> biopsies ≥10% CD30-positive ($CD30_{min}$ ≥10%)
- Assessment of outcomes by CD30 expression was carried out in 100/125 eligible MF patients in ALCANZA

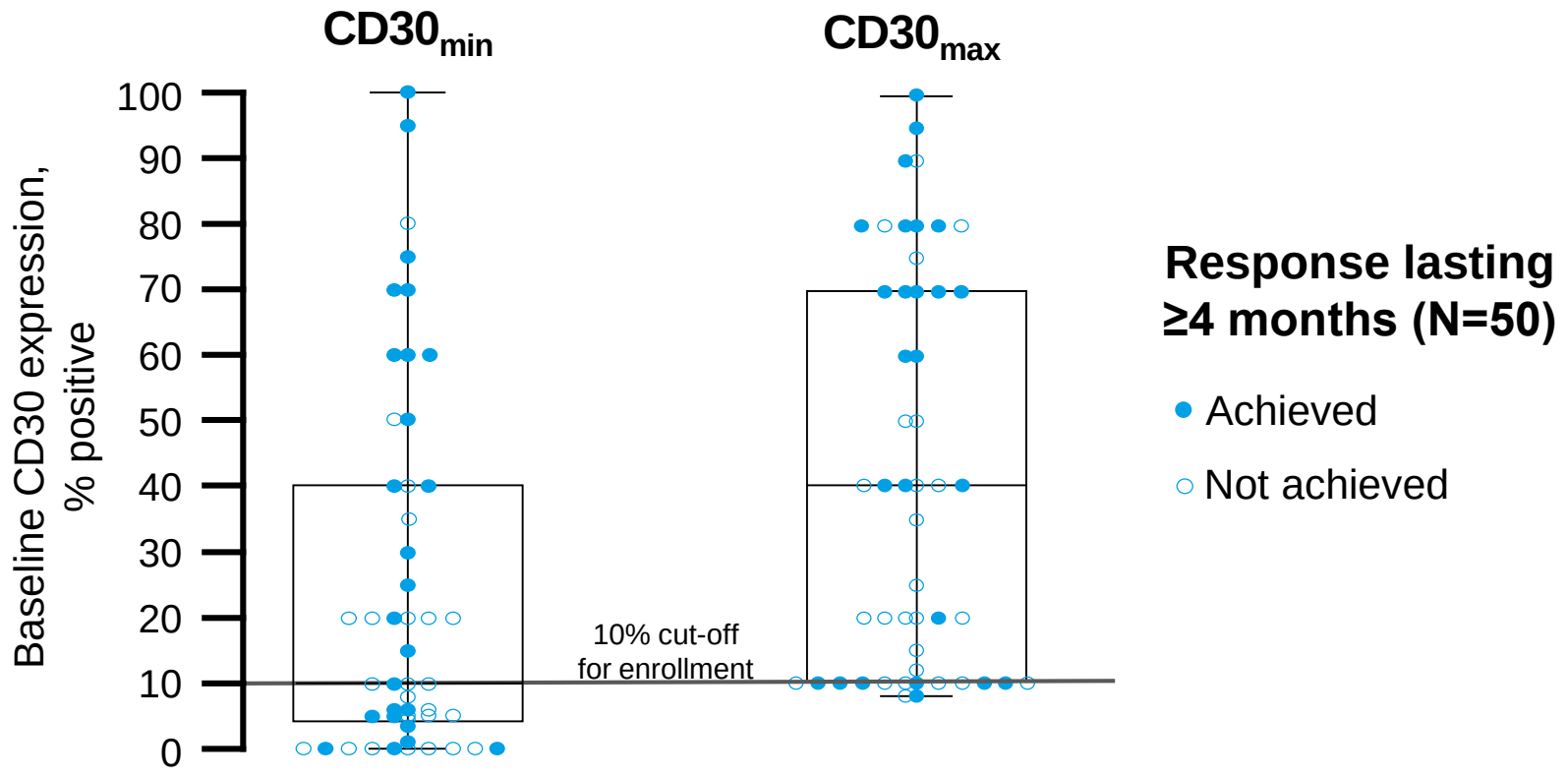
*(screening) visit closest to first dose date

Assessment of CD30 expression and statistical analysis





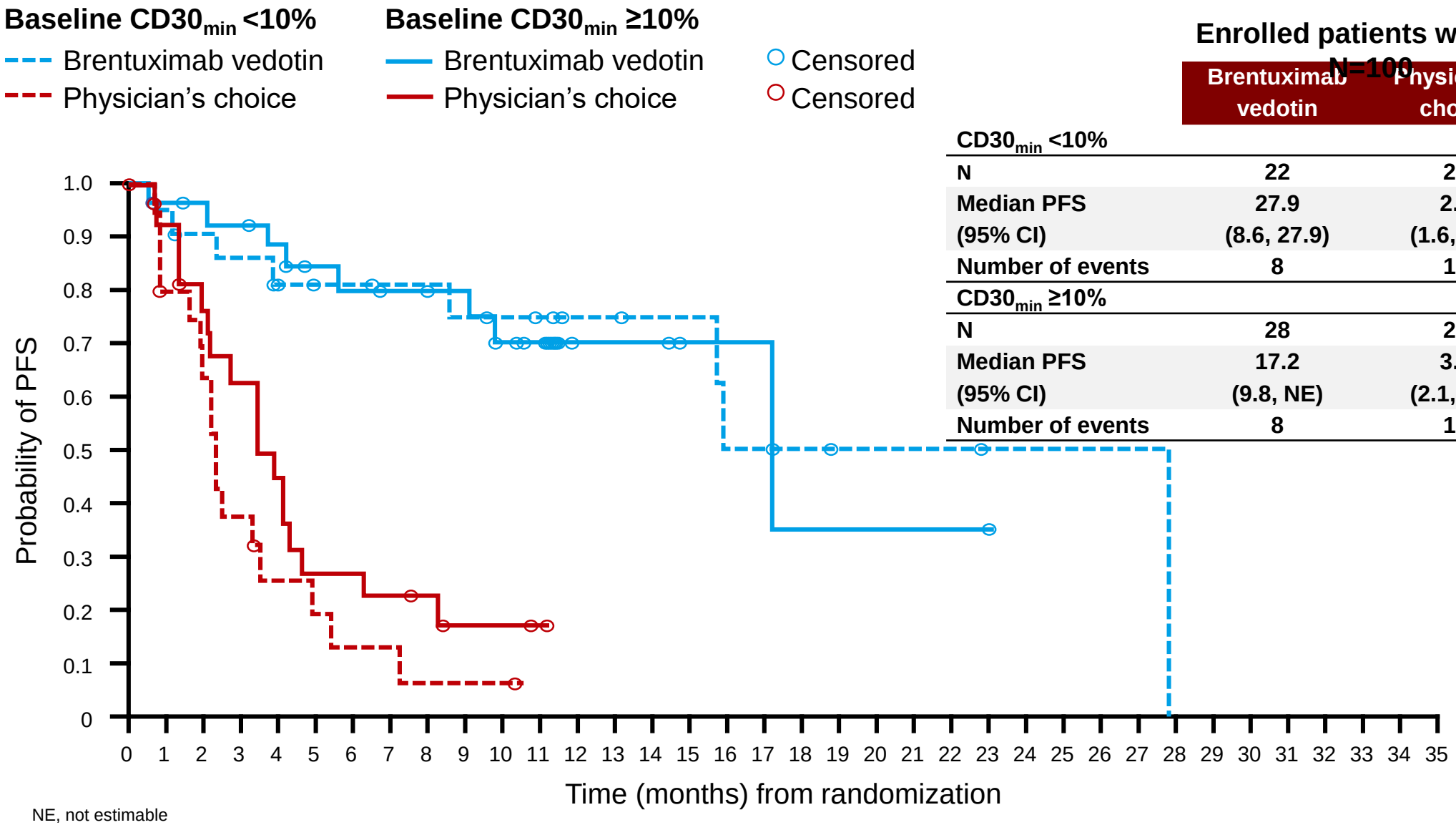
ORR4 with brentuximab vedotin across a broad range of baseline CD30 expression scores



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	–

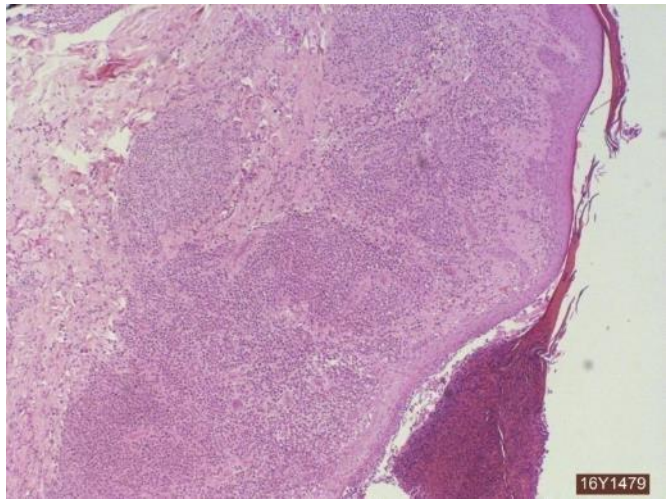
NE, not estimable

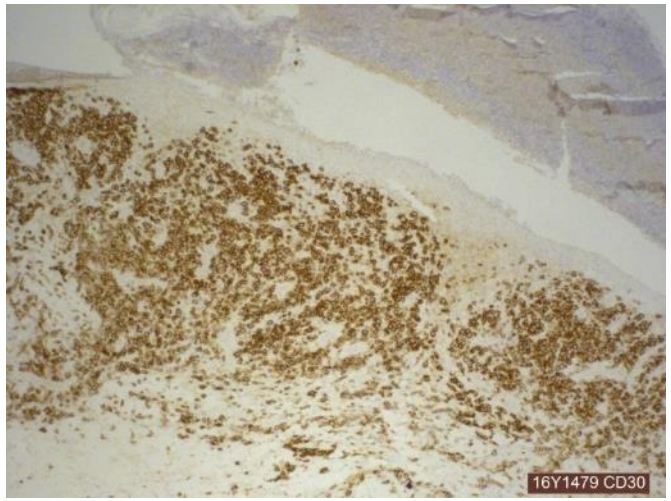
Safety profile of brentuximab vedotin unaffected by baseline CD30 expression

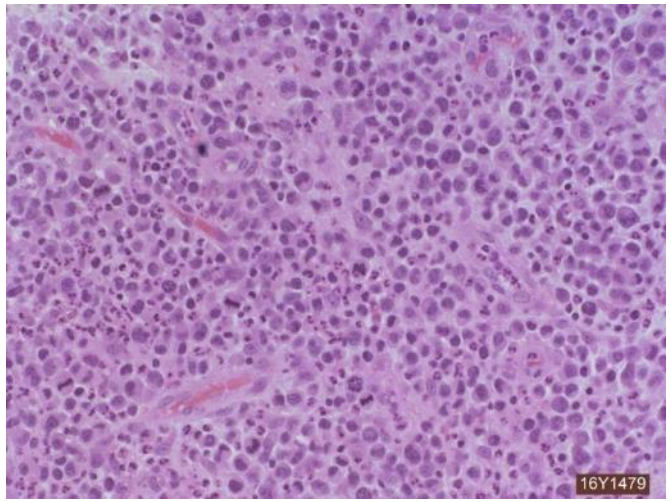
Enrolled patients with MF (safety population), N=99

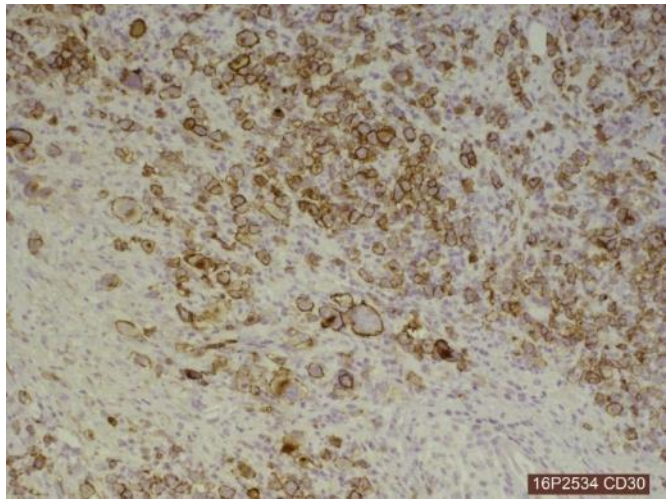
AEs, n/N (%)	Brentuximab vedotin (N=50)	Physician's choice (N=49)
Any AE		
$CD30_{min}$ <10%	22/22 (100)	20/21 (95)
$CD30_{min}$ ≥10%	28/28 (100)	23/28 (82)
Grade ≥3		
$CD30_{min}$ <10%	11/22 (50)	12/21 (57)
$CD30_{min}$ ≥10%	10/28 (36)	9/28 (32)
Serious AE		
$CD30_{min}$ <10%	7/22 (32)	9/21 (43)
$CD30_{min}$ ≥10%	8/28 (29)	5/28 (18)
Peripheral neuropathy		
$CD30_{min}$ <10%	15/22 (68)	0/21 (0)
$CD30_{min}$ ≥10%	19/28 (68)	2/28 (7)

CD30+ transformed mycosis fungoides? Results being analyzed









IHC images provided by HM Prince

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1. Battisti WP, et al. Ann Intern Med 2015;163:461–4