Brentuximab Vedotin PTCL

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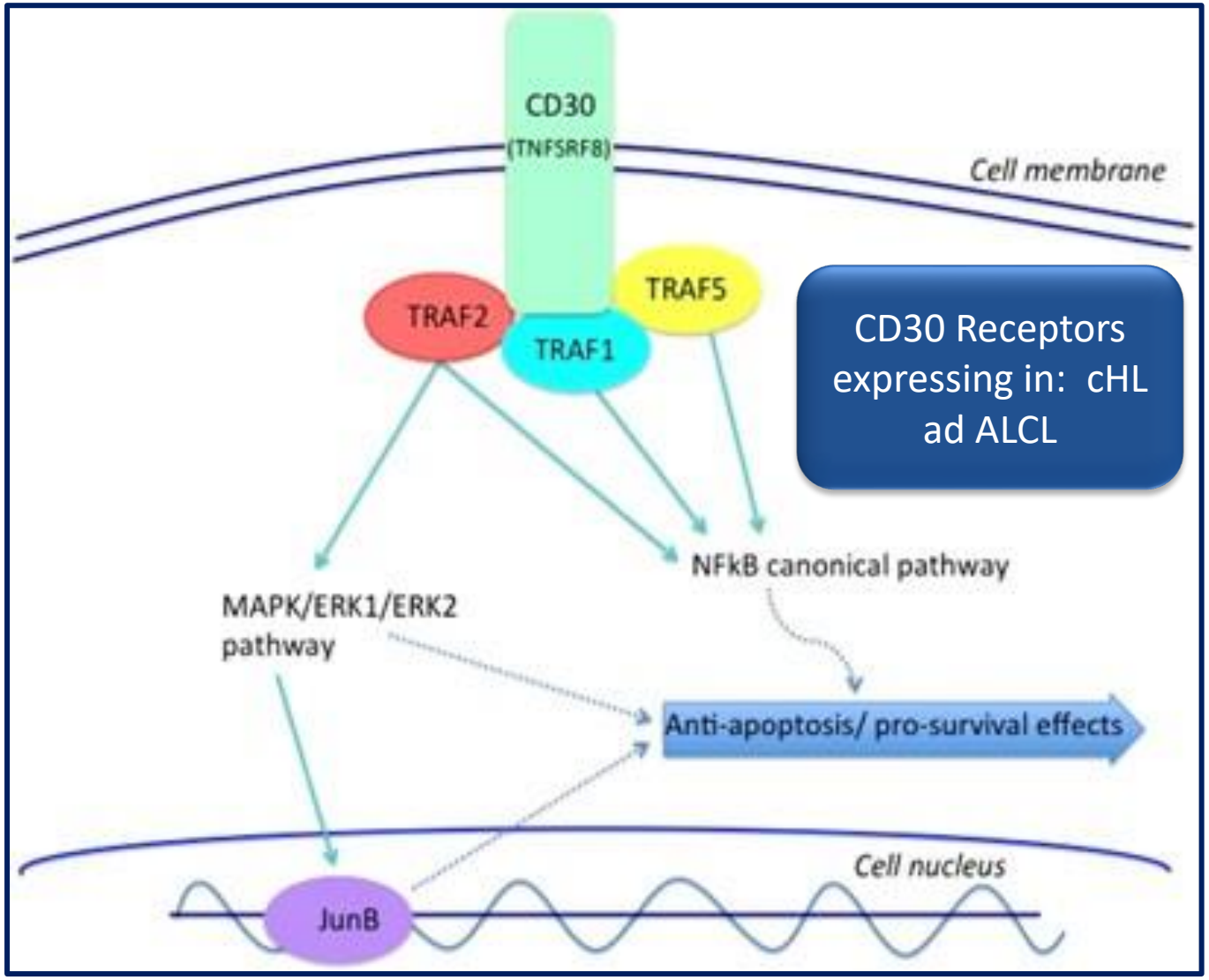
Disclosures for Barbara Pro, MD

I have the following relevant financial relationship to disclose:

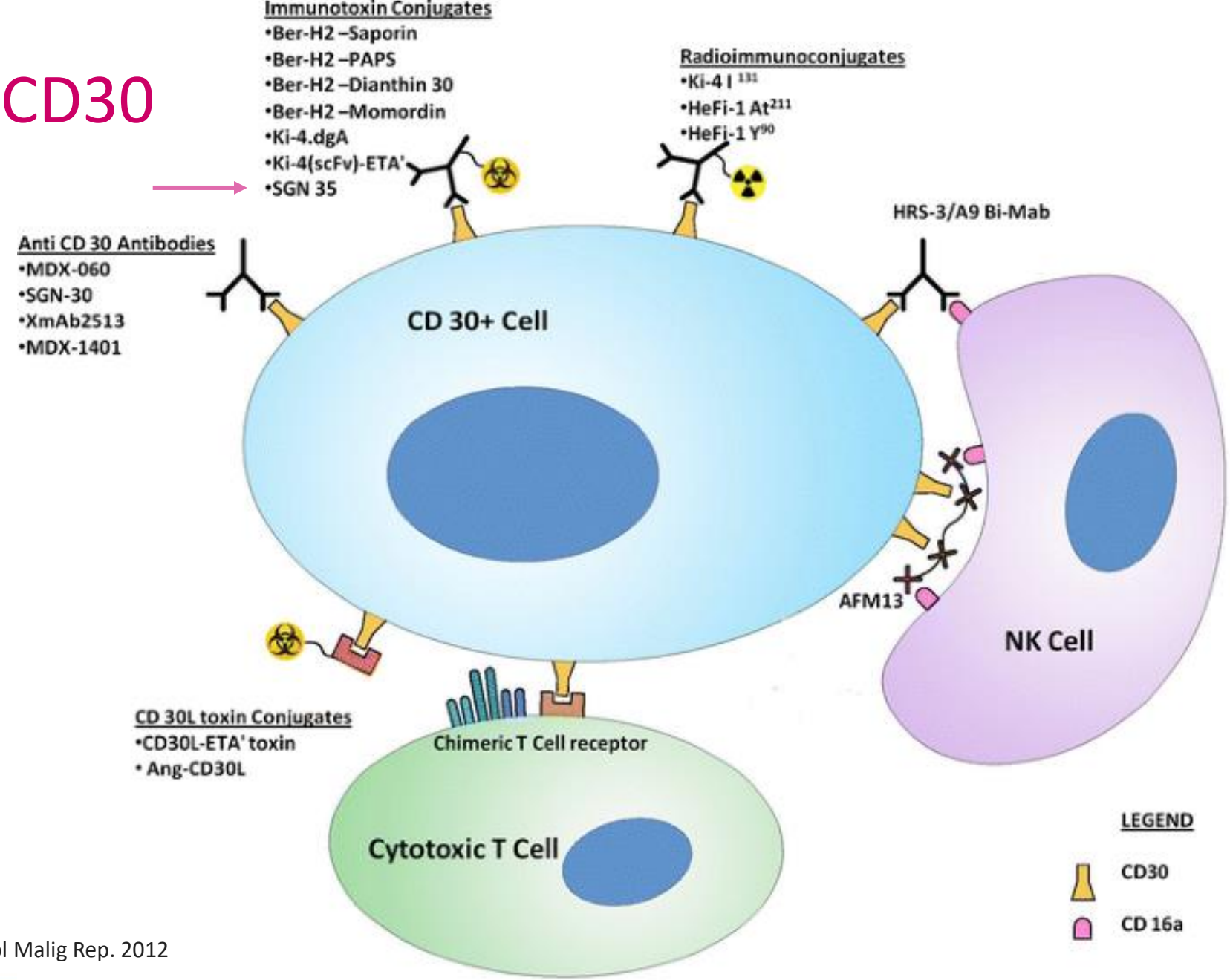
- **Honoraria: Seattle Genetics, Secura Bio**

CD30 Structure and Function

- CD30 is a cysteine-rich 120-kDa transmembrane protein that belongs to the family of tumor necrosis factor receptor (TNFR)
- Role of CD30 receptor is not fully elucidated: cell cycle arrest, apoptosis, and NFkB activation
- TRAF-5, TRAF-1, and TRAF-2 → stimulate NFkB



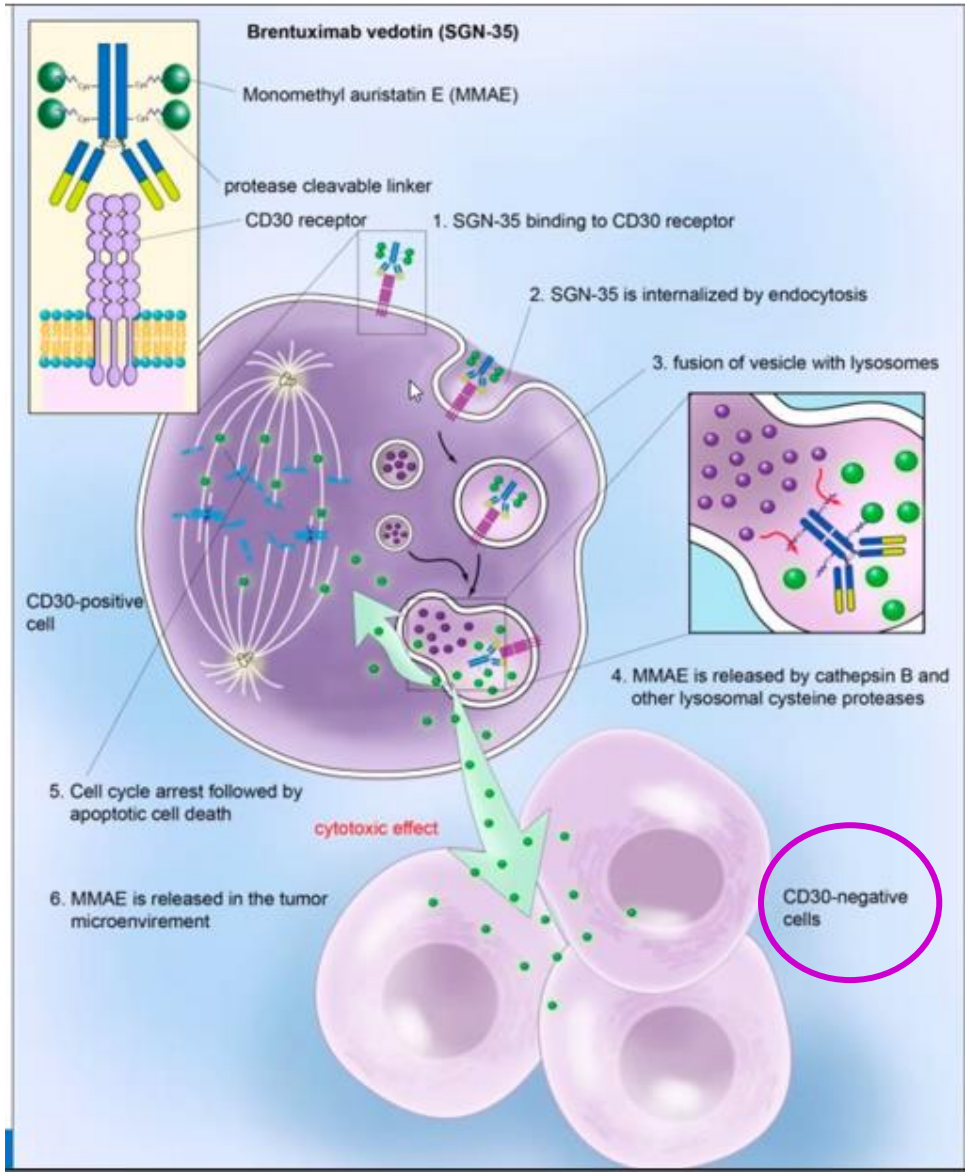
Targeting CD30



Vadakara J, Pro B. Curr Hematol Malig Rep. 2012

Brentuximab Vedotin (**SGN-35**, BV)

- Antibody-drug conjugate
- Potent anti-microtubule cytotoxic
- Chemically conjugated to monomethyl auristatin E by a dipeptide linker
- Stable in physiologic conditions and stable in human plasma, but cleaved selectively by lysosomal enzymes



BV: Phase 1 trial

- Phase 1, open-label, multicenter dose-escalation study,
- BV Dose:0.1 to 3.6 mg/kg every 3 weeks
- 45 patients with relapsed or refractory CD30-positive hematologic cancers
- -2 ALCL/1 AITL
- Patients had received a median of three previous chemotherapy regimens (range, 1-7), and 73% had undergone autologous stem-cell transplantation.

ORIGINAL ARTICLE

Brentuximab Vedotin (SGN-35) for Relapsed CD30-Positive Lymphomas

Anas Younes, M.D., Nancy L. Bartlett, M.D., John P. Leonard, M.D., Dana A. Kennedy, Pharm.D., Carmel M. Lynch, Ph.D., Eric L. Sievers, M.D., and Andres Forero-Torres, M.D.

Table 3. Best Clinical Response in 45 Patients.*

Response	Dose (mg/kg)								
	0.1 (N=3)	0.2 (N=4)	0.4 (N=3)	0.6 (N=3)	0.8 (N=3)	1.2 (N=4)	1.8 (N=12)	2.7 (N=12)	3.6 (N=1)
Complete remission	0	0	0	0	0	1†	4	6†	0
Partial remission	0	0	0	2	0	1	2	1	0
Stable disease	2	0	2	1	2	2	5	5	0
Progressive disease	1	4‡	1	0	1	0	1	0	0
Could not be evaluated	0	0	0	0	0	0	0	0	1§

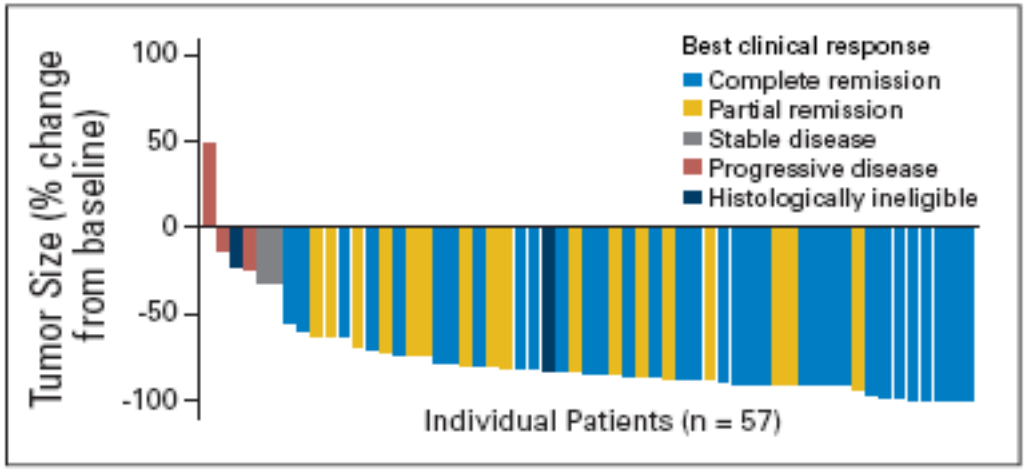
Optimal dosing of BV determined to be 1.8mg/kg IV every 3 weeks
Objective response in 50% of HL patients
Complete remission in 35%
DOR – median 9.7 months

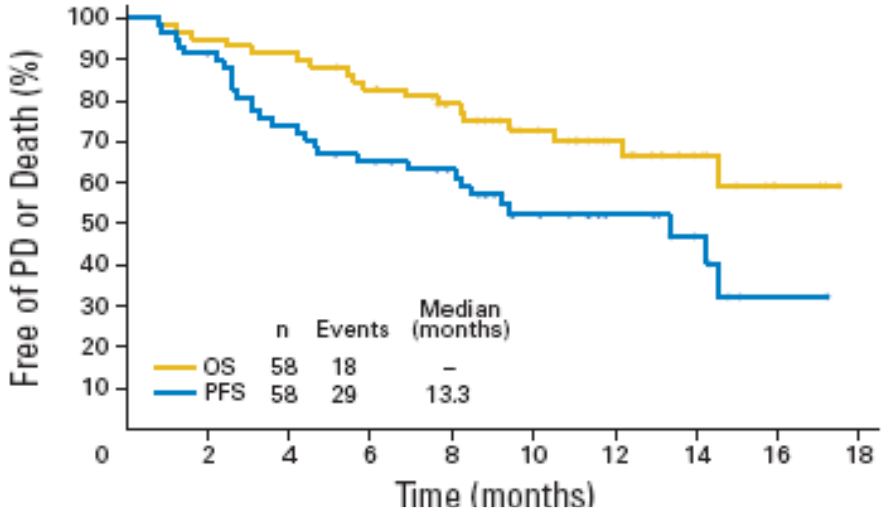
Younes et al NEJM 2010
Abid et al Annals of Hem 2016

Brentuximab vedotin in R/R sALCL

Table 2. Key Response Results per Independent Review

Measure	Response (N = 58)	95% CI
Objective response rate, %	86	74.6 to 93.9
CR rate*	57	43.2 to 69.8
Partial remission rate	29	
Stable disease, %	3	
Progressive disease, %	5	
Histologically ineligible, %†	3	
Not evaluable, %	2	
Median duration of objective response, months	12.6	5.7 to NE
Median duration of response in patients with CR, months	13.2	10.8 to NE





CR N=38

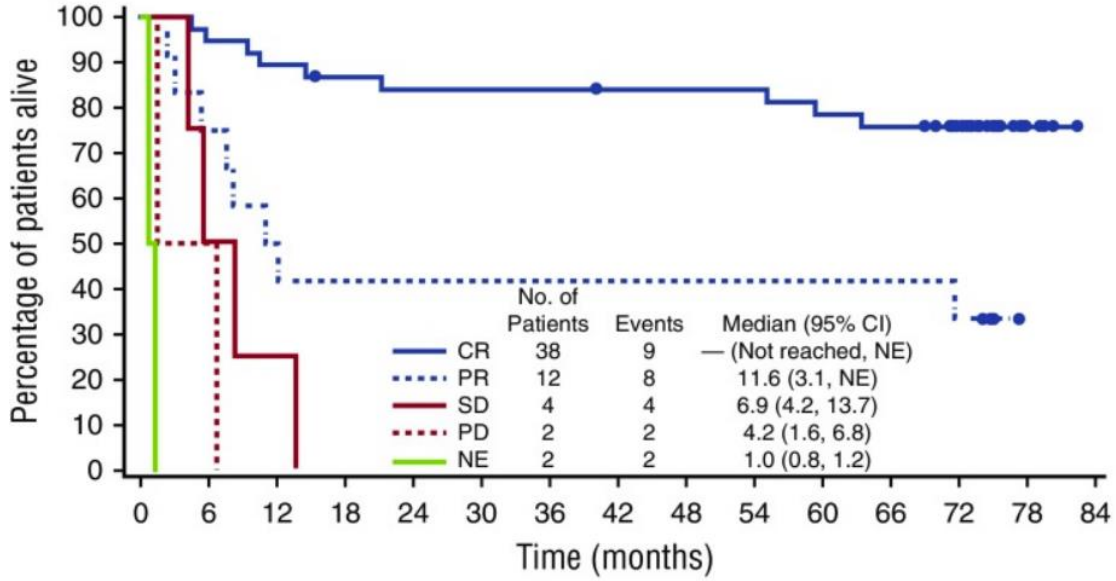
- Auto/Allotranplant N=16
- No further therapy N=22

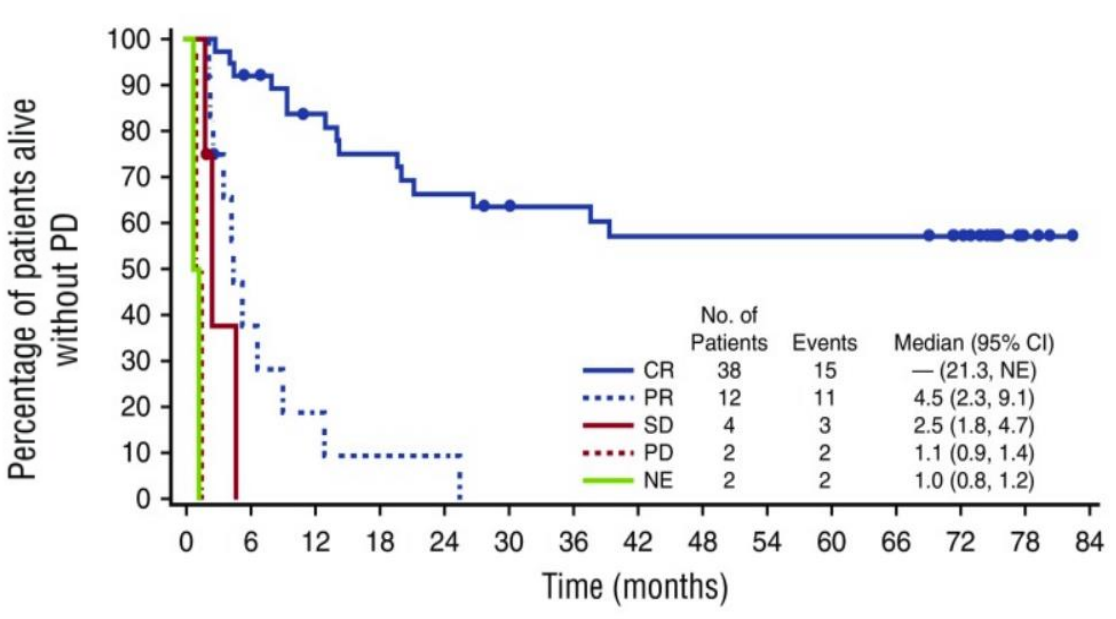
Pro B, et al. *J Clin Oncol* 2012

Brentuximab Vedotin Activity in a Phase 2 Study of R/R sALCL

CR N=38

- Autologous/allogeneic transplant (n=16)
- No further treatment (n=22)

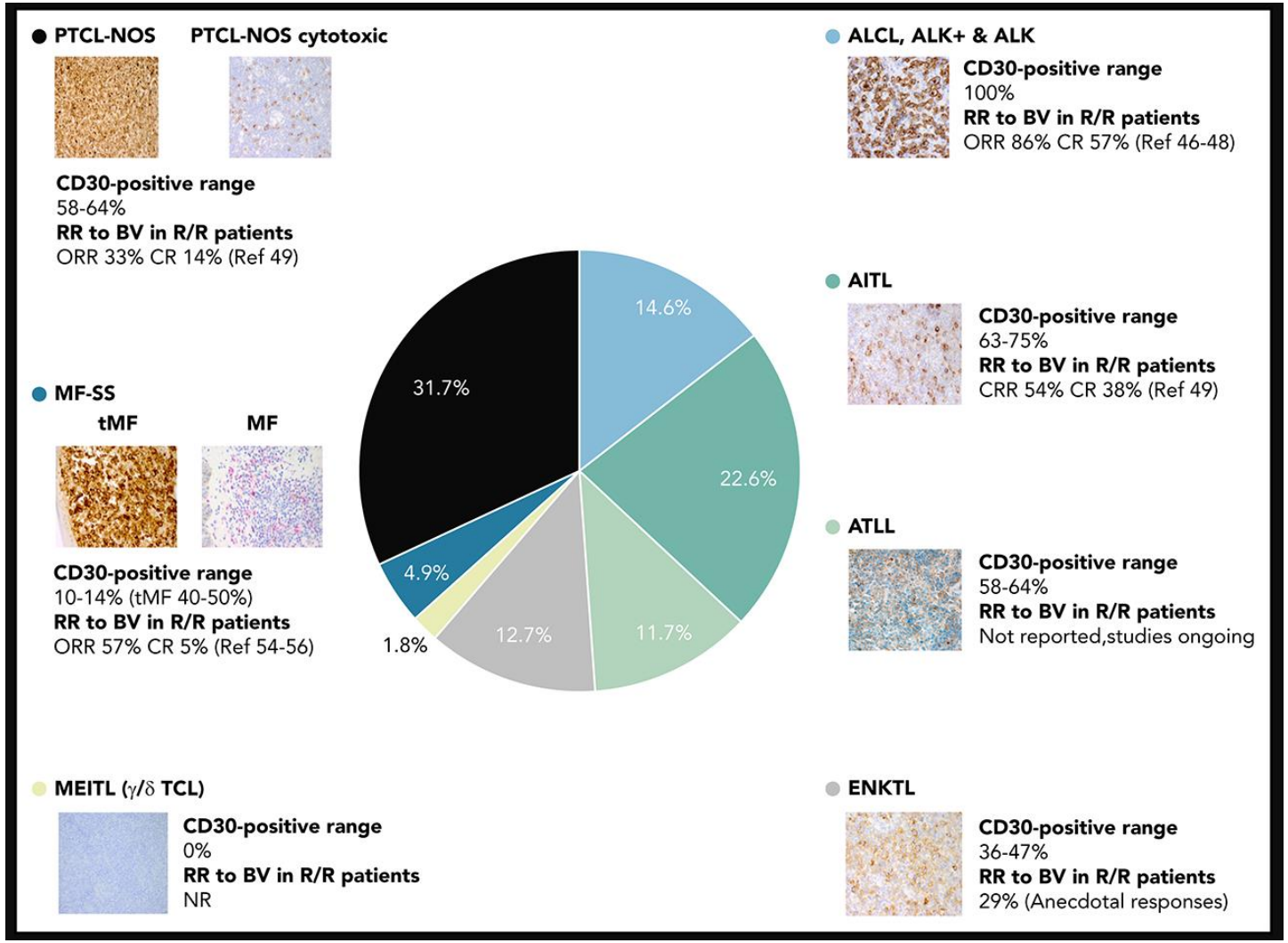




- Patients with R/R ALCL who achieved CR with brentuximab vedotin had 79% OS and 57% PFS at 5 years, with median response duration not reached.

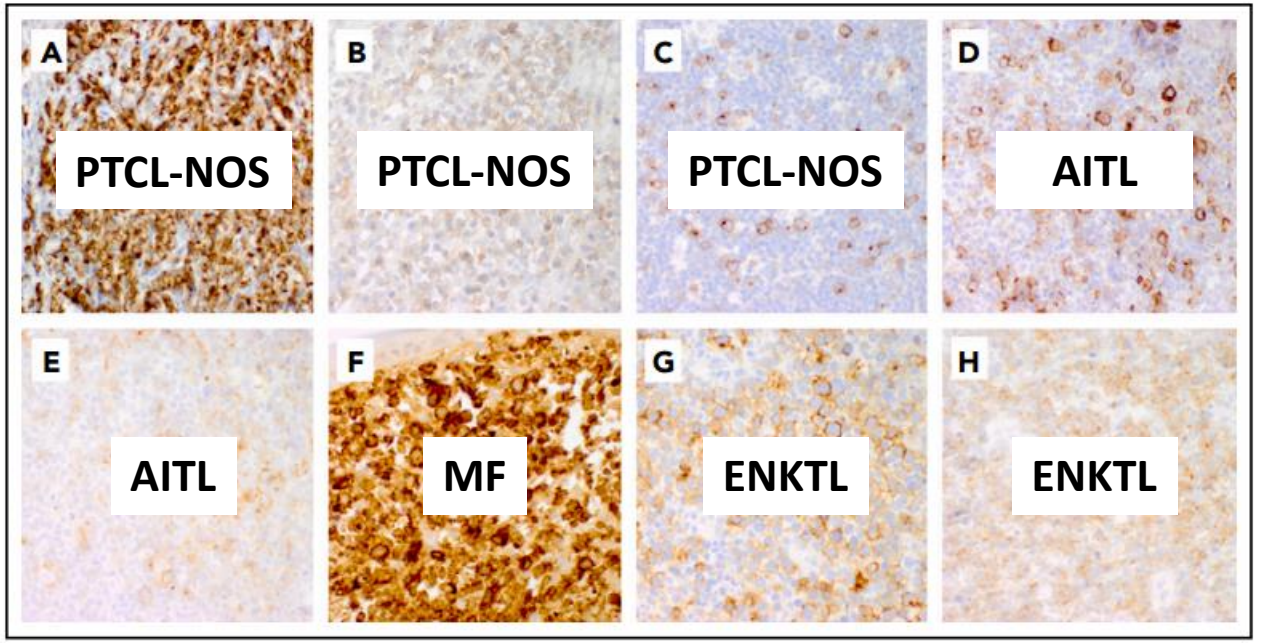
Pro B, et al. *Blood* 2017

CD30 Positivity in Different Subtypes



Barta S, et al. Blood 2019

Pattern of CD30 expression in non-ALCL PTCLs

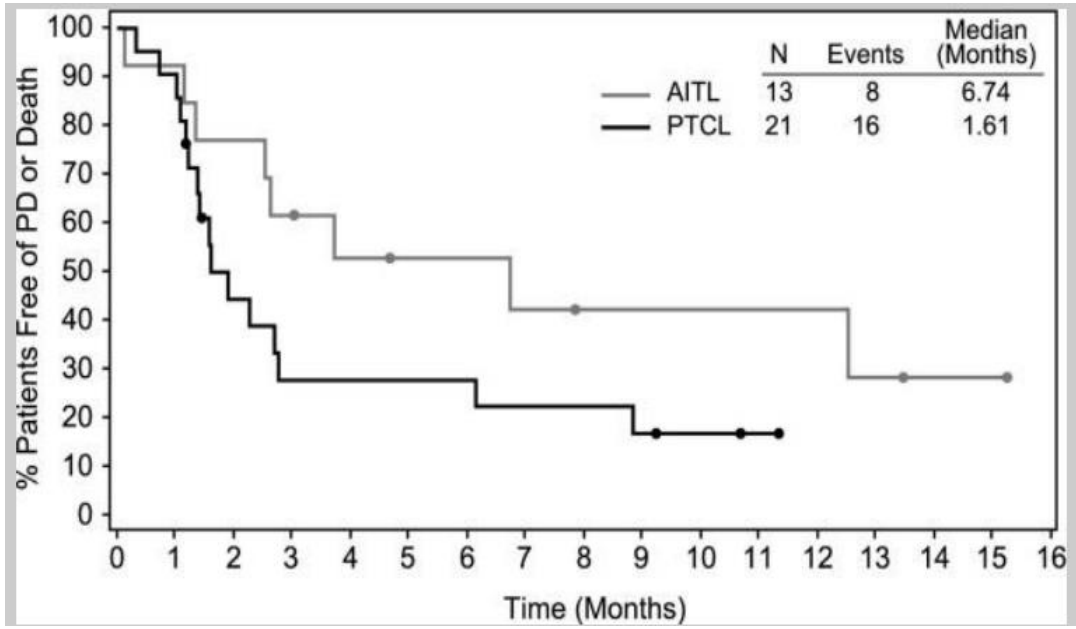


Barta S, et al. Blood 2019

Brentuximab Vedotin in non-ALCL

- In a follow-up study of *non-ALCL*, CD30+ PTCL, patient were treated with BV at the same dosing regimen
- The ORR in this population had an ORR of 41%, including 24% CR with a median DOR of 6.4 months

	AITL, n = 13	PTCL-NOS, n = 21	Total, N = 34
Best clinical response, n (%)[*]			
CR	5 (38)	3 (14)	8 (24)
PR	2 (15)	4 (19)	6 (18)
SD	3 (23)	3 (14)	6 (18)
PD	3 (23)	11 (52)	14 (41)
Objective response rate, n (%)	7 (54)	7 (33)	14 (41)
95% CI for objective response rate[†]	25.1, 80.8	14.6, 57	24.6, 59.3
Disease control rate, n (%)[‡]	10 (77)	10 (48)	20 (59)



- FIL Phase II study: ORR 30.4%, median DOR 3.4 months

Horwitz S, et al. *Blood*. 2014; Stefoni et al. ASH 2020

Phase 1 Study of BV in **Frontline** ALCL

VOLUME 32 · NUMBER 28 · OCTOBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY

Brentuximab Vedotin in the Front-Line Treatment of Patients With CD30$^+$ Peripheral T-Cell Lymphomas: Results of a Phase I Study

Michelle A. Fanale, Steven M. Horwitz, Andres Forero-Torres, Nancy L. Bartlett, Ranjana H. Advani, Barbara Pro, Robert W. Chen, Andrew Davies, Tim Illidge, Dirk Huebner, Dana A. Kennedy, and Andrei R. Shustov

Table 5. Best Response After Sequential or Combination Treatment

	Sequential ALCL (n = 13)		Combination					
			ALCL (n = 19)		Non-ALCL (n = 7)		Total (n = 26)	
Response	No.	%	No.	%	No.	%	No.	%
Objective response	11	85	19	100	7	100	26	100
Complete remission	8	62	16	84	7	100	23	88
Partial remission	3	23	3	16	0		3	12
Stable disease	0		0		0		0	
Progressive disease	2	15	0		0		0	

Phase 1: study. 39 patients with newly diagnosed PTCLs, 32 of which with systemic ALCL (6 ALK positive, 26 ALK negative)

Sequential treatment: BV for 2 cycles → 6 cycles of CHOP

- **Combination** treatment: BV + CHP x 6 cycles
- All patient who responded to treatment received single agent BV for 8-10 additional cycles
- ORR 85% (11/13) for sequential
  - CR 62% (8/13)
- **ORR 100% (19/19) for combination**
  - 84% CR (16/19)
  - PFS 21.4 months (95%, CI 11.7 to not reached)

ECHELON-2: Brentuximab Vedotin + CHP vs CHOP in Previously Untreated CD30+ PTCL

Multicenter, randomized, double-blind, double dummy, active-controlled phase III trial

Stratification for IPI score (0-1 vs 2-3 vs 4-5), histologic subtype (ALK+ sALCL vs other subtypes)

Adult patients with previously untreated CD30+ (≥ 10% expression) PTCL* (N = 452)

BV+CHP
Brentuximab Vedotin† +
CHP‡ Q3W for 6-8 cycles +
Placebo for Vincristine
(n = 226)

CHOP‡
Q3W for 6-8 cycles +
Placebo for Brentuximab Vedotin
(n = 226)

End-of-treatment PET

*PTCL includes sALCL (including ALK+ sALCL with IPI ≥ 2 and ALK- sALCL), PTCL-NOS, AITL, ATLL, EATL, HSTCL. Study targeted 75% (± 5%) ALCL in line with European regulatory commitment. †Brentuximab vedotin: 1.8 mg/kg. ‡Cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (CHOP only), prednisone 100 mg on Days 1-5. G-CSF primary prophylaxis, consolidative RT, SCT per investigator discretion.

- Primary endpoint: PFS per BICR (SCT or RT consolidation not considered events)
- Secondary endpoints: OS, PFS per BICR in sALCL patients, CR, ORR, safety

Horwitz, Lancet 2019;393:229.

ECHELON-2: Baseline Characteristics

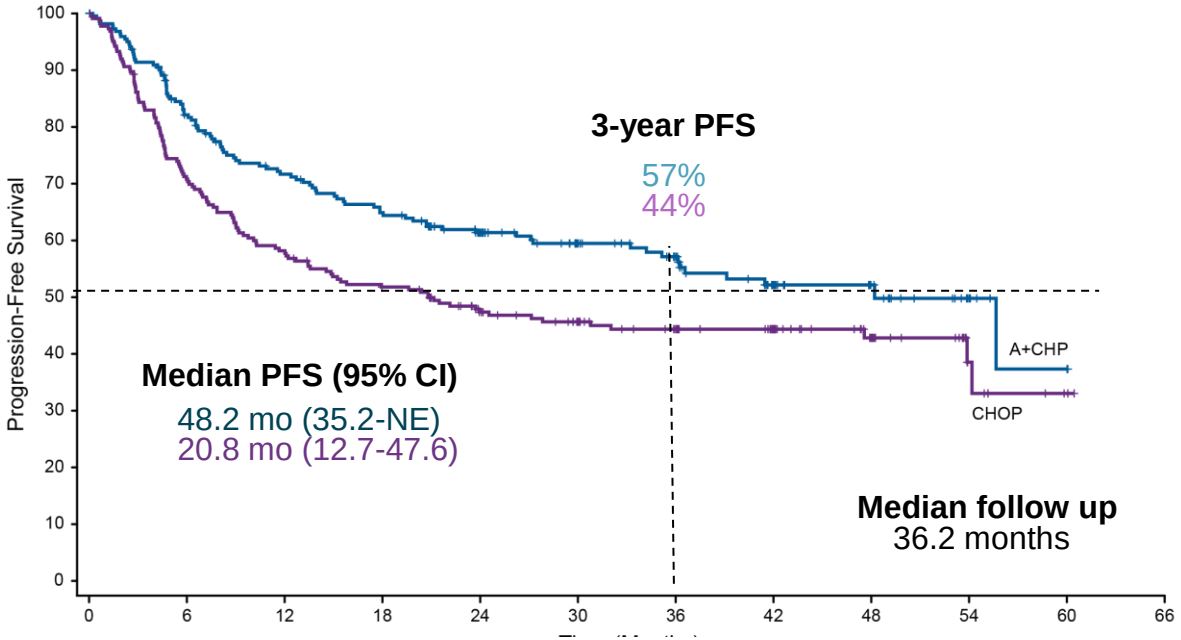
Patient Characteristic	BV+CHP (n = 226)	CHOP (n = 226)
Male, n (%)	133 (59)	151 (67)
Median age, yrs (IQR)	58 (45–67)	58 (44–67)
IPI score, n (%)		
0-1	53 (23)	48 (21)
2-3	140 (62)	144 (64)
4-5	33 (15)	34 (15)
Stage III/IV, n (%)	184 (81)	180 (80)

Patient Characteristic	BV+CHP (n = 226)	CHOP (n = 226)
Disease diagnosis, n (%)		
sALCL	162 (72)	154 (68)
ALK+	49 (22)	49 (22)
ALK-	113 (50)	105 (46)
PTCL-NOS	29 (13)	43 (19)
AITL	30 (13)	24 (11)
ATLL	4 (2)	3 (1)
EATL	1 (0)	2 (1)

- Approximately 70% of patients had sALCL

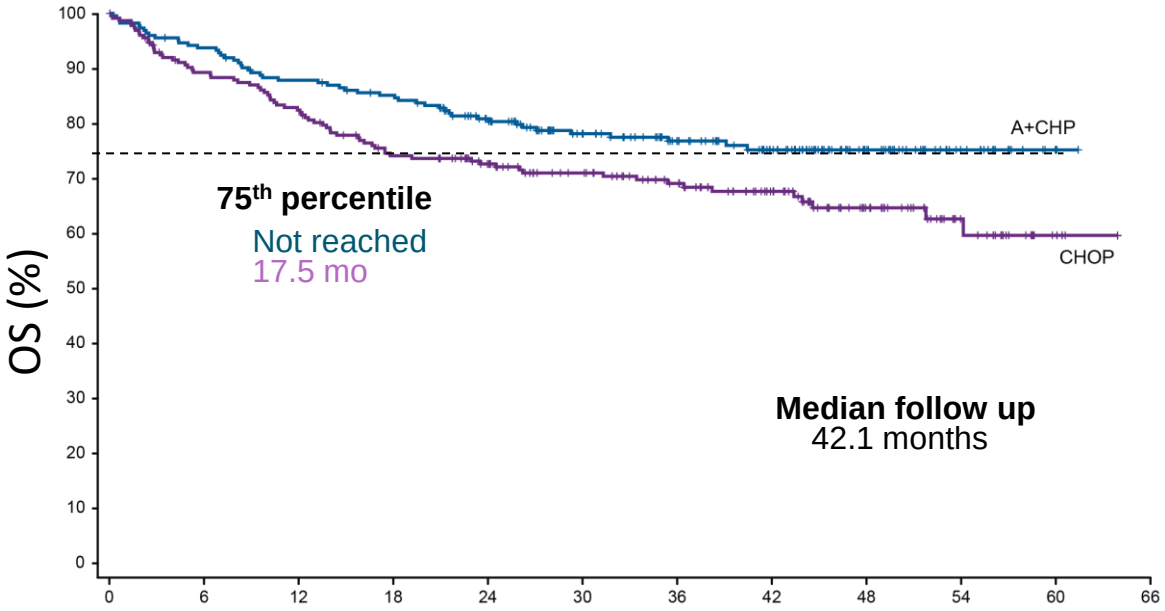
Horwitz S, et al. Lancet. 2019

ECHELON-2: PFS and OS with BV + CHOP vs CHOP Alone in ALCL



Mos

Treatment	Events, n (%)	HR (95% CI)	*P* Value
BV+CHP	95 (42)	0.71 (0.54-0.93)	.011
CHOP	124 (55)		



Mos

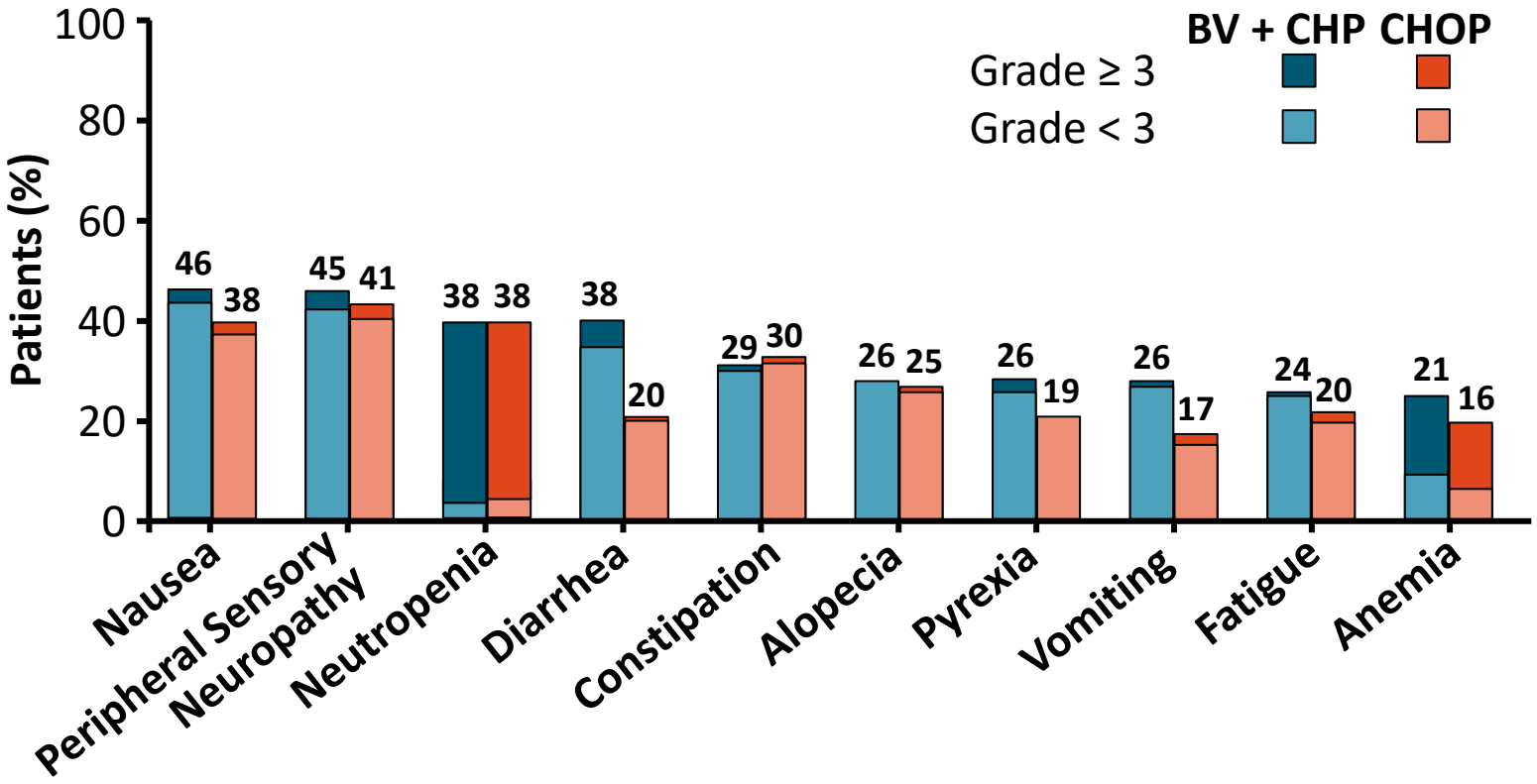
Treatment	Deaths, n (%)	HR (95% CI)	*P Value*
BV+CHP	51 (23)	0.66 (0.46-0.95)	.0244
CHOP	73 (32)		

Horwitz S, et al. Lancet. 2019

ECHELON-2: AEs

AE, n (%)	BV+CHP (n = 223)	CHOP (n = 226)
Any AE	221 (99)	221 (98)
Grade ≥ 3 AEs	147 (66)	146 (65)
Serious AEs	87 (39)	87 (38)
Death due to AEs	7 (3)	9 (4)

Subjects, n (%)	BV+CHP (n=223)	CHOP (n=226)
Treatment-emergent PN	117 (52)	124 (55)
Resolution of all PN events	58 (50)	79 (64)
Ongoing PN at last follow up	61 (52)	45 (36)
Grade 1	44 (72)	32 (71)
Grade 2	15 (25)	12 (27)
Grade 3	2 (1)	1 (1)



Horwitz S, et al. Lancet 2019. Horwitz S, et al. ASH 2018. Abstract 997.

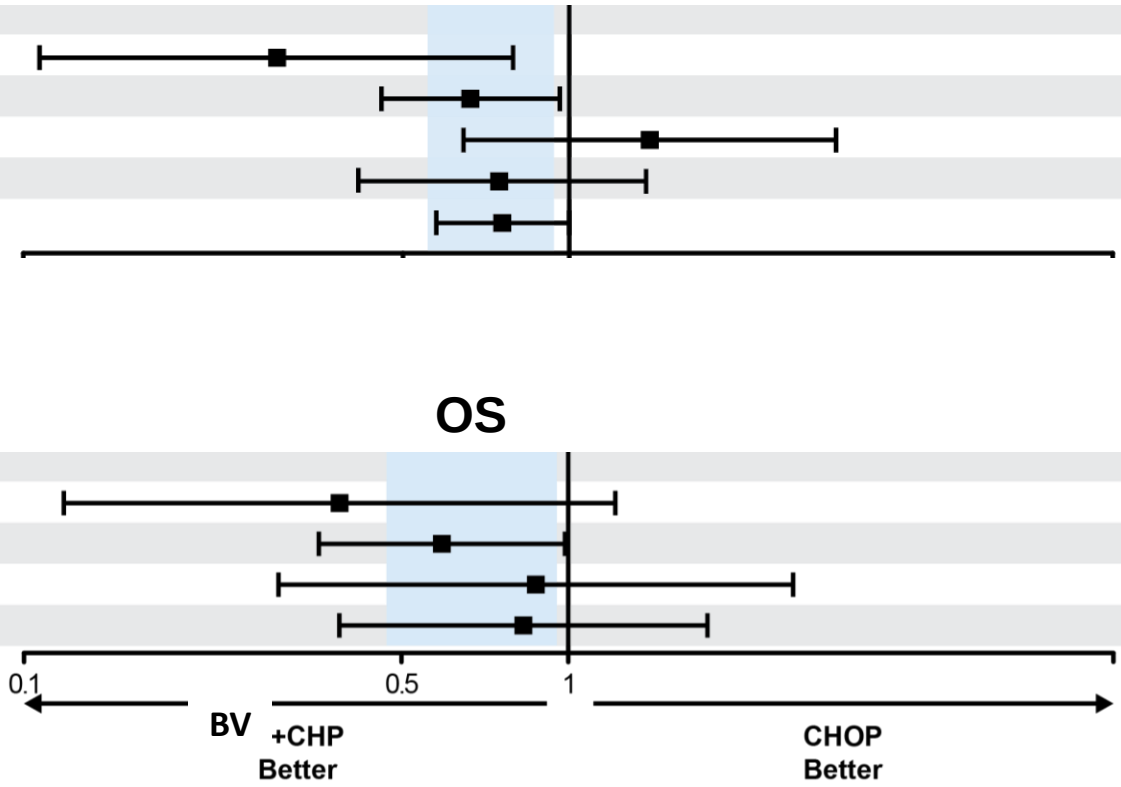
ECHELON-2: PFS and OS by PTCL Subtypes

PFS

	Event/N		HR (95% CI)
	BV +CHP	CHOP	
Disease Indication			
ALK-positive sALCL	5/49	16/49	0.29 (0.11, 0.79)
ALK-negative sALCL	50/113	60/105	0.65 (0.44, 0.95)
AITL	18/30	13/24	1.40 (0.64, 3.07)
PTCL-NOS	19/29	31/43	0.75 (0.41, 1.37)
PFS (PD, Death)	84/226	103/226	0.75 (0.56, 1.00)

OS

Disease Indication			
ALK-positive sALCL	4/49	10/49	0.38 (0.12, 1.22)
ALK-negative sALCL	25/113	34/105	0.58 (0.35, 0.98)
AITL	8/30	6/24	0.87 (0.29, 2.58)
PTCL-NOS	11/29	20/43	0.83 (0.38, 1.80)



- PFS and OS benefits greatest in patients with sALCL

Horwitz S, et al. Lancet 2019.

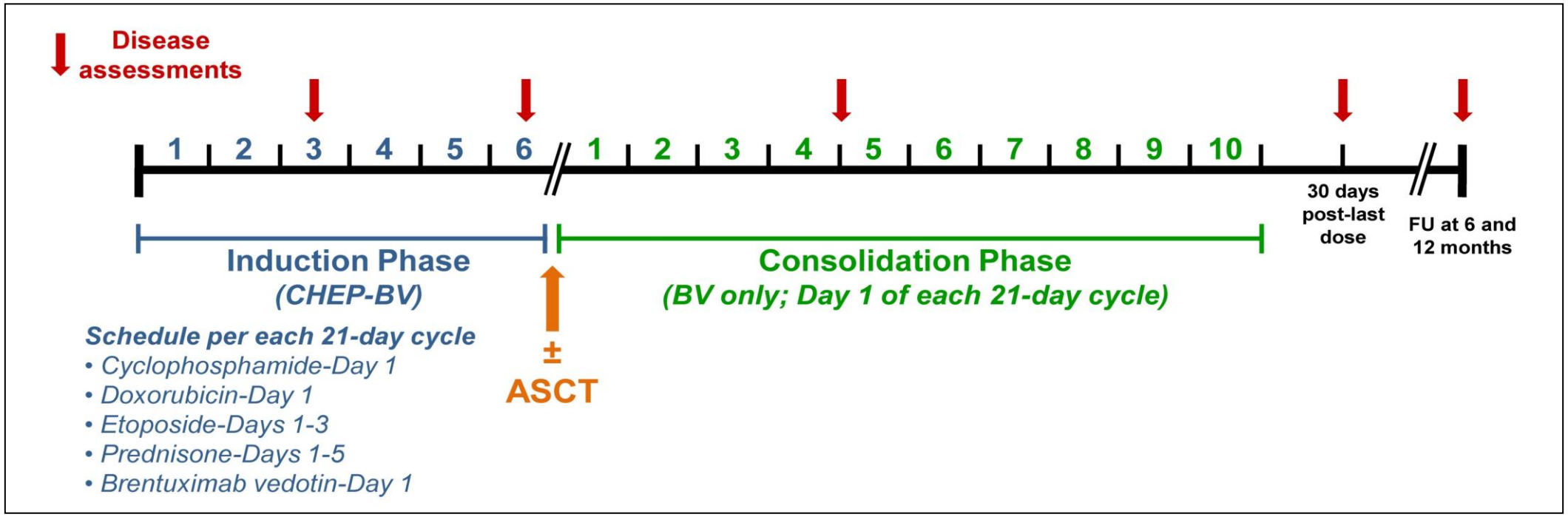
Echelon-2 -Analysis by Subtypes: Estimated 5-year PFS and OS rates in prespecified subgroups

Subgroup	Estimated 5-year PFS rate		HR (95% CI)	P-value	Estimated 5-year OS rate		HR (95% CI)	P-value
	A+CHP	CHOP			A+CHP	CHOP		
PTCL subtype								
PTCL-NOS, % (n)	26.5 (29)	25.7 (43)	0.79 (0.43, 1.43)	0.4	46.2 (29)	35.9 (43)	0.75 (0.37, 1.48)	0.4003
AITL, % (n)	26.6 (30)	48.1 (24)	1.41 (0.64, 3.11)	0.3958	67.8 (30)	62.5 (24)	1.01 (0.40, 2.55)	0.9855
sALCL								
Overall, % (n)	60.6 (162)	48.4 (154)	0.55 (0.39, 0.79)	0.0009	75.8 (162)	68.7 (154)	0.66 (0.43, 1.01)	0.0529
ALK+ % (n)	87 (49)	67 (49)	0.40 (0.17, 0.98)	0.0372	91.5 (26)	79.6 (27)	0.48 (0.16, 1.40)	0.1688
ALK– % (n)	49 (113)	39 (105)	0.58 (0.40, 0.86)	0.0054	68.7 (50)	63.3 (41)	0.71 (0.44, 1.12)	0.1373
sALCL, IPI Score								
0–1, % (n)	59.5 (41)	47.6 (32)	0.42 (0.18, 0.94)	0.0301	87.0 (41)	86.2 (32)	0.73 (0.20, 2.73)	0.6411
2–3, % (n)	68.5 (95)	50.9 (100)	0.57 (0.35, 0.90)	0.0158	80.6 (95)	68.7 (100)	0.57 (0.32, 1.01)	0.0496
4–5, % (n)	27.2 (26)	36.4 (22)	0.73 (0.35, 1.50)	0.3839	38.0 (26)	43.2 (22)	0.89 (0.42, 1.89)	0.7606

ITT, intent-to-treat; IPI, International Prognostic Index

Horwitz S, et al. ASH 2021

Frontline Therapy with BV-CHEP + BV Maintenance (n=46)



Response assessment by investigators: 2014 Lugano classification

Herrera A, et al. ASH 2021

Response to CHEP-BV

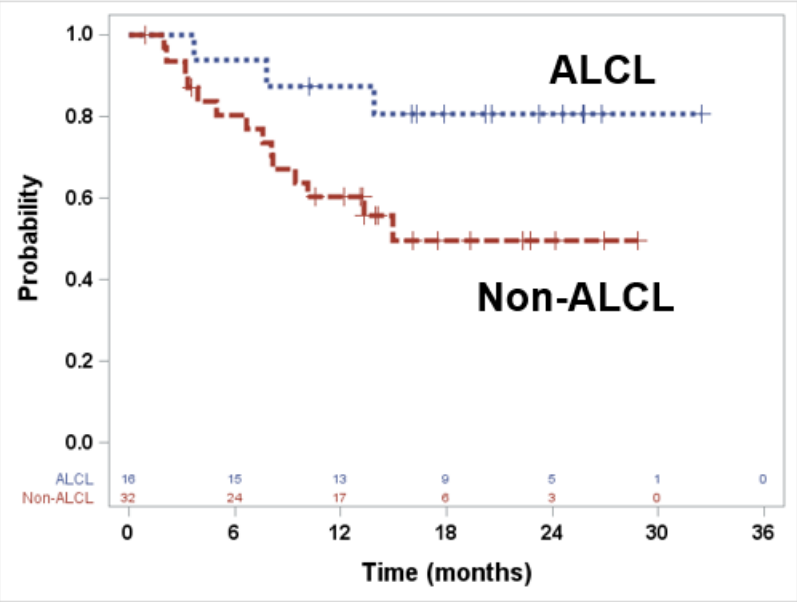
	All Patients (n=46)	
Response	**Interim**	**End of CHEP-BV**
Overall response (ORR)	**44 (96%)**	**42 (91%)**
Complete response (CR)	**27 (59%)**	**37 (80%)**
Partial response (PR)	17	5
Stable disease (SD)	1	0
Progressive disease (PD)	1	4

Response	ALCL (n=16)	Non-ALCL (n=30)	AITL (n=17)	PTCL NOS (n=11)	PTCL TFH (n=2)
ORR	15 (94%)	27 (90%)	16 (94%)	9 (82%)	2 (100%)
CR	15 (94%)	22 (73%)	14 (82%)	6 (55%)	2 (100%)
PR	0	5	2	3	0
SD	0	0	0	0	0
PD	1	3	1	2	0

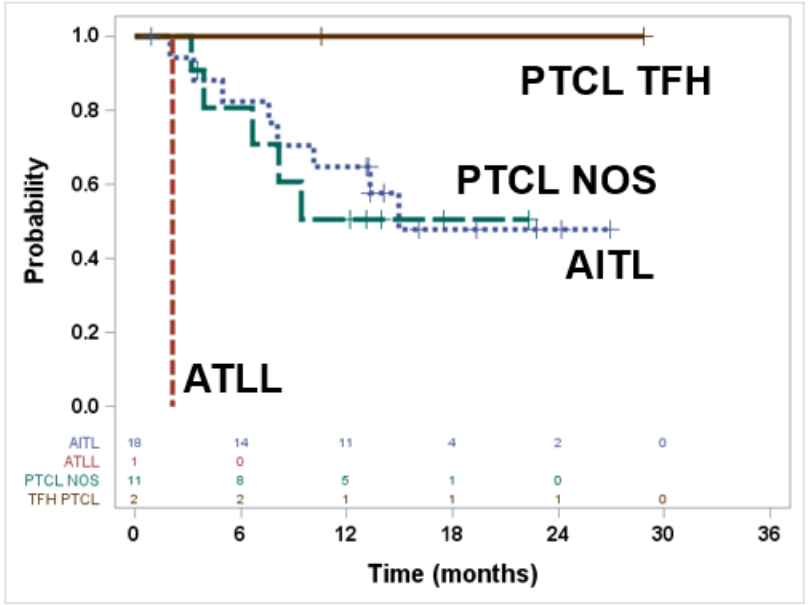
Herrera A, et al. ASH 2021

PFS from treatment start in subgroups

- **18mo PFS: ALCL 81% vs non-ALCL 49%**
  - ALCL (n=16): ASCT 7 vs no 9
  - Non-ALCL (n=32): ASCT 17 vs no 15



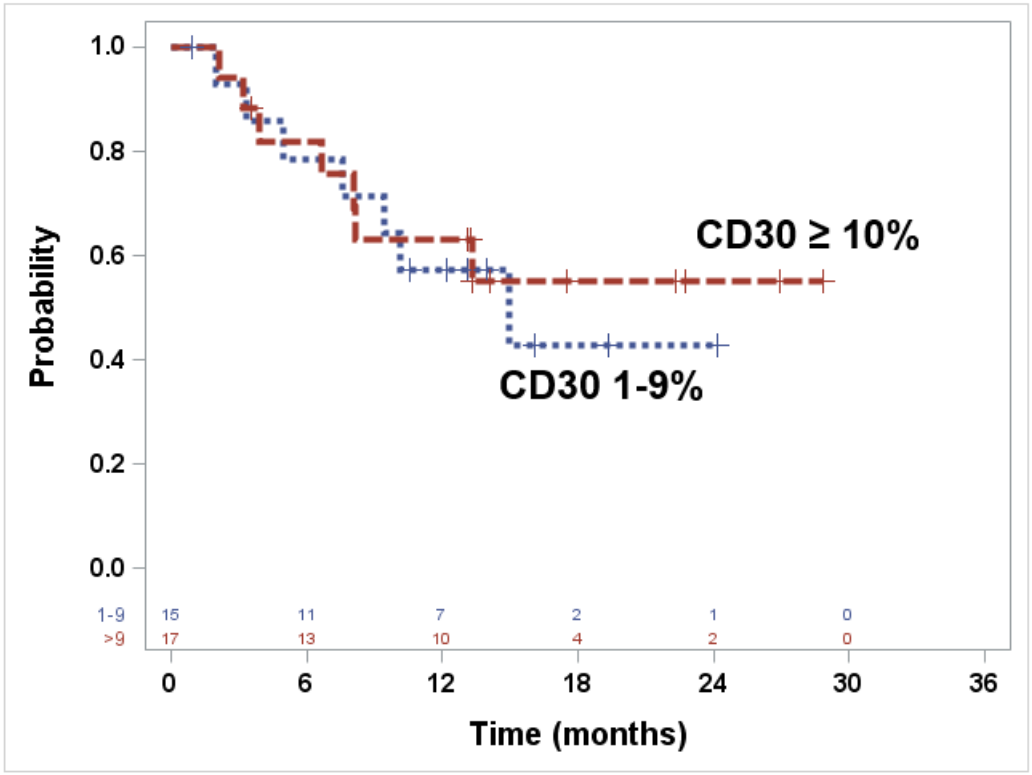
- **18mo PFS: AITL 48%, PTCL NOS 51%**
  - AITL (n=18): ASCT 12 vs no 6
  - PTCL NOS (n=11): ASCT 4 vs no 7



Herrera A, et al. ASH 2021

PFS from treatment start by CD30%

- **18mo PFS by CD30% (non-ALCL)**
  - **CD30 1-9% (n=15): 43%**
  - **CD30 ≥ 10% (n=17): 55%**



Herrera A, et al. ASH 2021

Conclusions

- R/R : BV→ high CR rate, improved PFS/OS in sALCL
  - Role in non-ALCL
  - Retreatment vs prolonged treatment/ maintenance
- 1L : BV-CHP improves PFS /OS→ new SOC
  - Difference most pronounced in ALCL
  - Less pronounced with AITL or PTCL

    -Role of CD30 positivity/Need alternative strategies
  - Consolidation with ASCT

CHEP-BV tolerable and high CR rate

- CHEP-BV + ASCT + BV consolidation associated with excellent PFS→ merits further study

Thank you!
Grazie