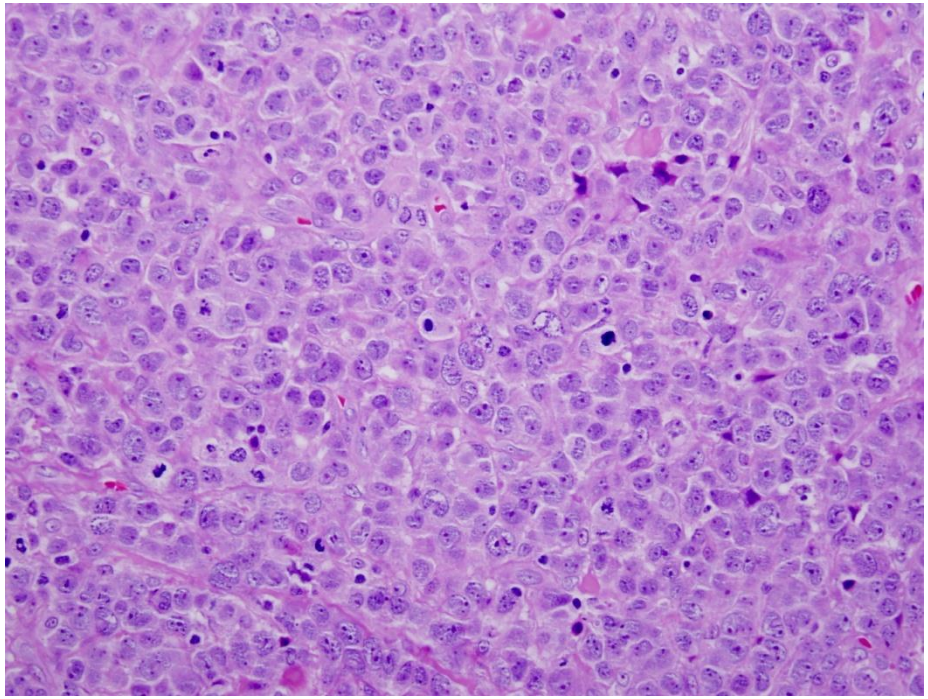
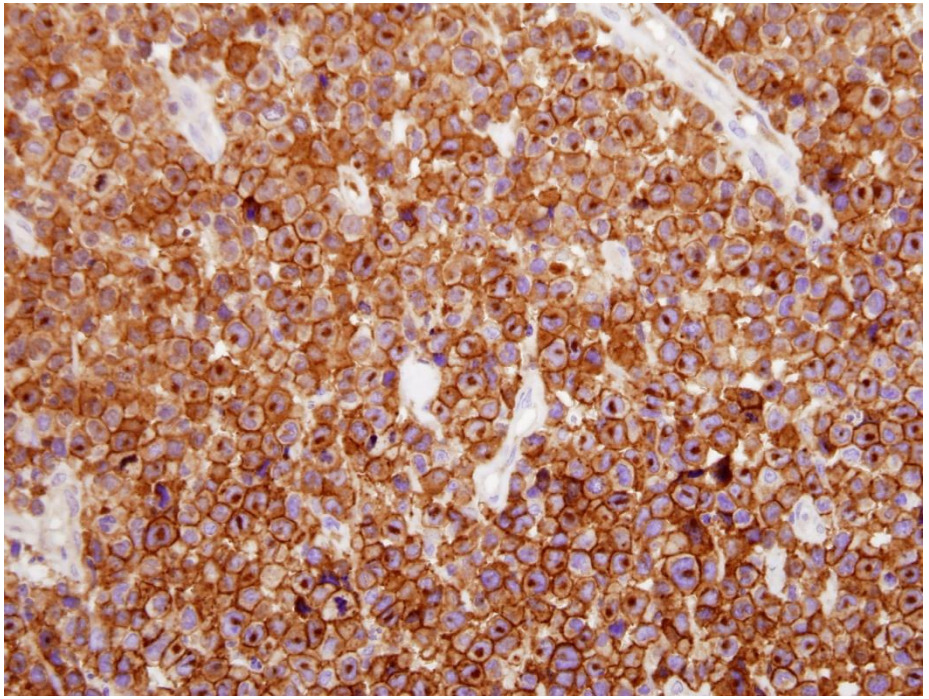
The “CD30+ world”
Brentuximab Vedotin in ALCL

Barbara Pro, MD
Northwestern University

CD30
A (ideal?) Target in ALCL



Systemic ALCL sample H&E staining



Systemic ALCL sample CD30 staining

CD30 selectively expressed in malignant ALCL cells

Targeting CD30

Naked Monoclonal Antibodies

How the Story Began: Unconjugated Anti-CD30 Antibodies

Drug	Patients	Dose	Outcomes	Author(s)
SGN-30 *Chimeric Ab*	24 pts (21 HL & 3 ALCL) Phase I	2 to12 mg/kg x wkly x 6	1 CR in cALCL 6 SD (4/6 in HL)	Bartlett, N et al, *Blood*, 111, 2008
SGN-30	79 pts (38 HL & 41 sALCL) Phase II	6 to 12 mg/kg x wkly x 6	HL RR 0% sALCL RR 17%	Forero, A et al, *ASCO*, 23, 2005 & Leonard, J et al, *ASCO*, 23, 2005
MDX-060 *Fully human Ab*	72 pts (63 HL, 4 ALCL) Phase I/II	1 to 15 mg/kg wkly x 4	RR 8% (CRs in 2 HL + 2 ACLC)	Ansell, S et al, *JCO*, 25:19, 2007

1.A Overview of Protocol Information:

Organization (local) Protocol No.: 2005-0627

Protocol Title: SHN-30 Monoclonal Antibody and CHOP for the Treatment of CD30+ Anaplastic Large Cell Lymphoma

Name of Lead Organization: M. D. Anderson Cancer Center NCI Institution Code:[1] TX035

(e.g., Group, Consortium, Institution)

Principal Investigator (PI) Name: Barbara Pro NCI Investigator No.:[2] 30988

PI Phone No.: (713) 792-2860 PI Fax No.: (713) 794-5656 PI E-mail Address: bpro@mdanderson.org

PI Mailing Address: 1515 Holcombe Boulevard Box # 429, Houston, TX 77030

Is this a multicenter (Non-Cooperative Group) study? ■ yes ☐ no If yes, refer to the Multicenter Trials guidelines in Section 7.2.15 of the Investigator Handbook or at http://ctep.cancer.gov/monitoring/multicenter.html, for further instructions.

Is CCOP credit requested? ☐ yes ■ no

Projected Start Date of Study: 10/01/05

Format: mm/dd/yyyy

CD30 Targeting Modalities

Naked Anti CD 30 Antibodies
- MDX-060
- SGN-30

Enhanced Anti-CD30 Antibodies
- XmAb2513
- MDX-1401

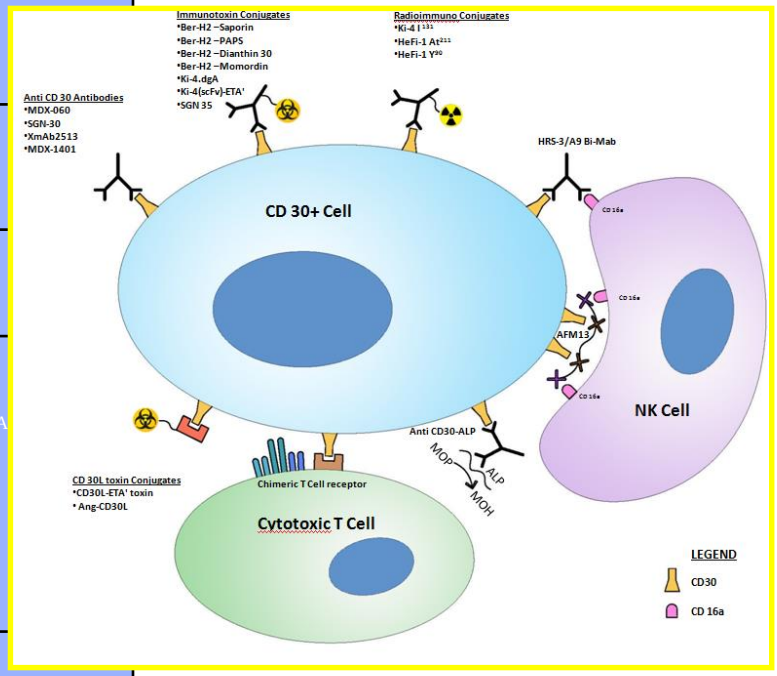
Anti-CD30 Radionuclide Conjugates
- Ki-4 I^{131}
- HeFi-1 At^{211}
- HeFi-1 Y^{90}

Anti CD30 Conjugates
- Ber-H2 linked toxins
  - Ber-H2 –Saporin
  - Ber-H2 – Pokeweed Antiviral Protein from Seeds proteins (PA
  - Ber-H2 –Dianthin 30
  - Ber-H2 –Momordin
- Ki-4 linked toxins
  - Ki-4.dgA
  - Ki-4(scFv)-ETA'
- SGN 35

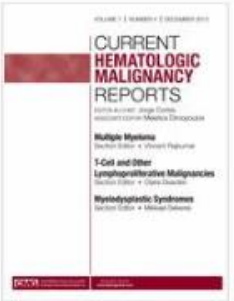
Bispecific Antibodies
- HRS-3/A9 Bi-Mab
- AFM13

CD30 ligand fusion toxins
- Recombinant CD30 ligand -ETA' toxin fusion
- Angiogenin Fused to CD30 Ligand (Ang-CD30L)

T-Cell based immune therapy
- CAR.CD30, with chimeric T cell receptor.
- CAR.CD30 EBV specific-cytotoxic T-lymphocytes, with chimeric T-cell receptor.



Vadakara J, Pro B, 2012

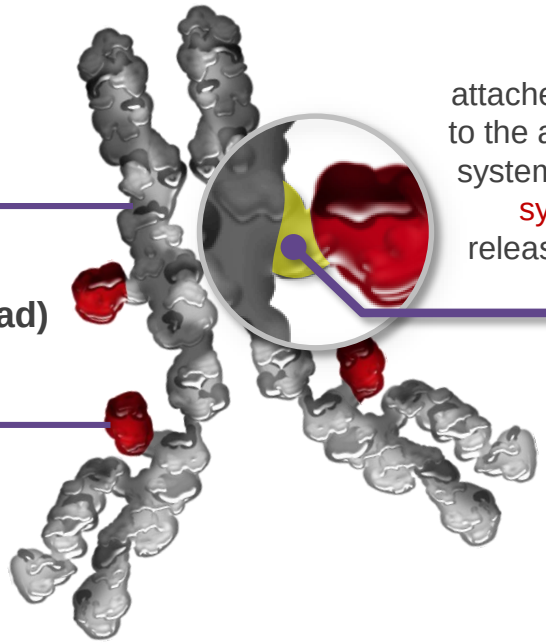


Rationale for ADCs
-Increase the delivery of a potent cytotoxic agent to the tumor
-Decrease toxicity to normal tissue

Elements of an antibody-drug conjugate (ADC)

Antibody
specific for a tumor-associated antigen that has restricted expression on normal cells

Cytotoxic agent (payload)
kills target cells when internalized and released



Linker
attaches the cytotoxic agent to the antibody; newer linker systems are designed to be systemically stable and release the cytotoxic agent in targeted cells

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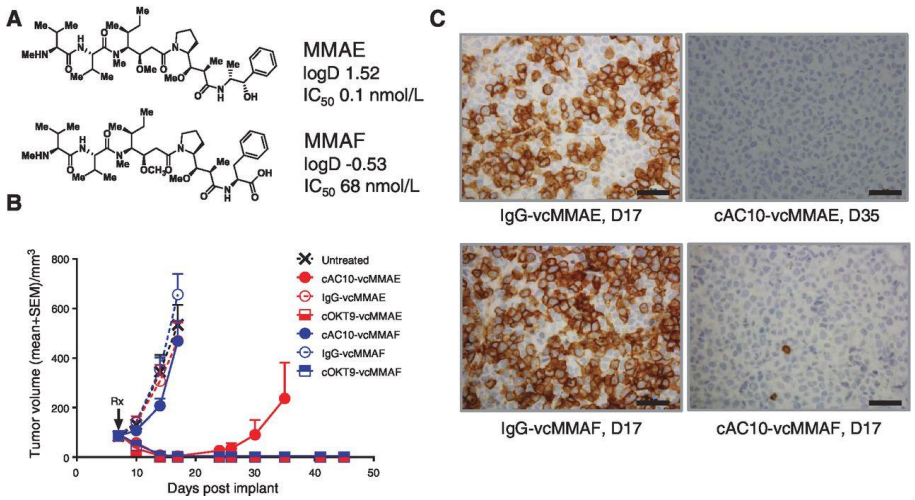
Intracellular Released Payload Influences Potency and Bystander-Killing Effects of Antibody-Drug Conjugates in Preclinical Models

Fu Li, Kim K. Emmerton, Mechthild Jonas, Xinqun Zhang, Jamie B. Miyamoto, Jocelyn R. Setter, Nicole D. Nicholas, Nicole M. Okeley, Robert P. Lyon, Dennis R. Benjamin, and Che-Leung Law

DOI: 10.1158/0008-5472.CAN-15-1795 Published May 2016



-Intracellular concentration of released MMAE correlated with in vitro ADC-mediated cytotoxicity independent of target expression or drug:antibody ratio

-Membrane permeable MMAE demonstrated potent bystander killing of neighboring CD30- cells

-Biophysical properties and amount of release payloads are chief factors determining ADC potency and bystander killing

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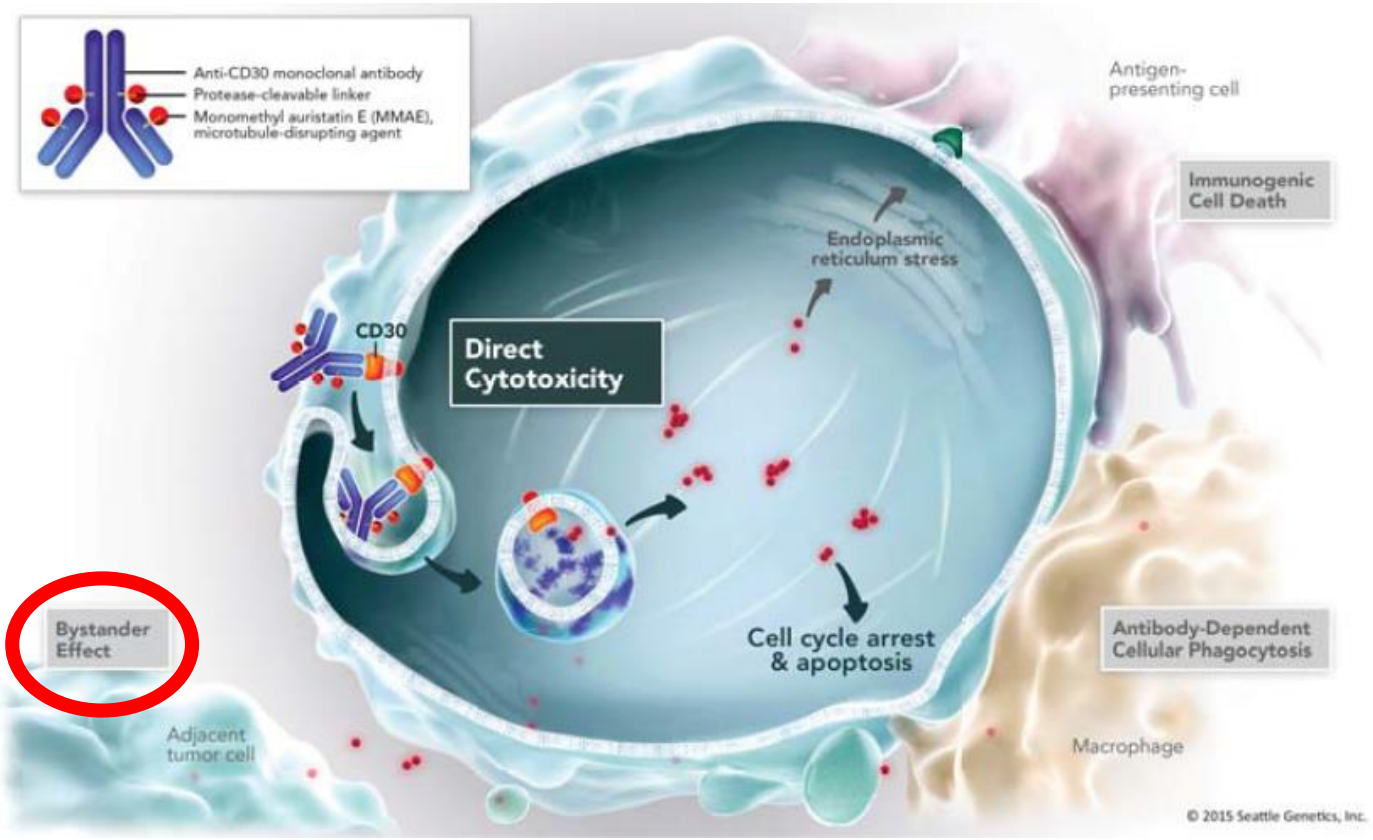
Brentuximab Vedotin



Antibody-drug conjugate SGN-35 in relapsed/refractory CD30+ Lymphomas

SGN-35 administered IV, every 21 days

- Dose cohorts: 0.1,0.2,0.4,0.6,0.8,1.2,1.8, 2.7, 3.6 mg/kg

	N (%)
At doses ≥ 1.2 mg/kg (n=28)	
ORR	15 (54%)
CR	9 (32%)
	2 ALCL
Reduced tumor size	26 (93%)
Median PFS	6 months
Median response duration	22 wks (range 0.1+ to 49+ wks)

Outpatient infusions of SGN-35 were well tolerated

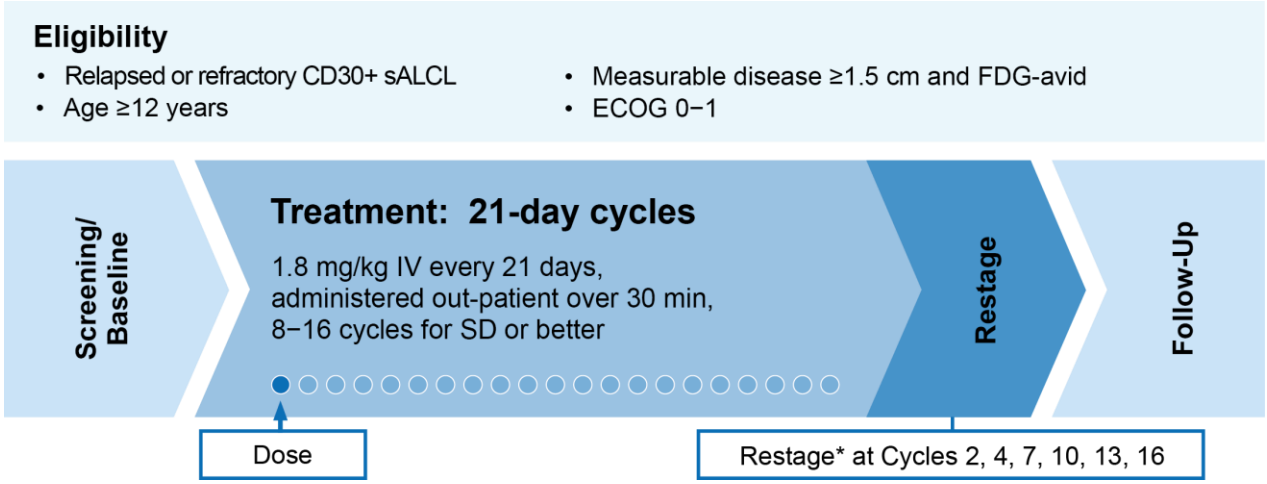
- MTD was defined at 1.8 mg/kg

Weekly dosing study and pivotal systemic ALCL trial ongoing

Younes et al., ASH 2008, Abstract # 1006

Brentuximab Vedotin in ALCL

Endpoints & Design



* Revised Response Criteria for Malignant Lymphoma (Cheson 2007), postbaseline PET scans obtained in Cycles 4 and 7 only

- A phase 2, multicenter, open-label study of brentuximab vedotin in pts with R/R systemic ALCL
- The first pt was enrolled June 2009
- All pts completed treatment June 2011 and were followed for progression and survival until the end of study

Baseline characteristics

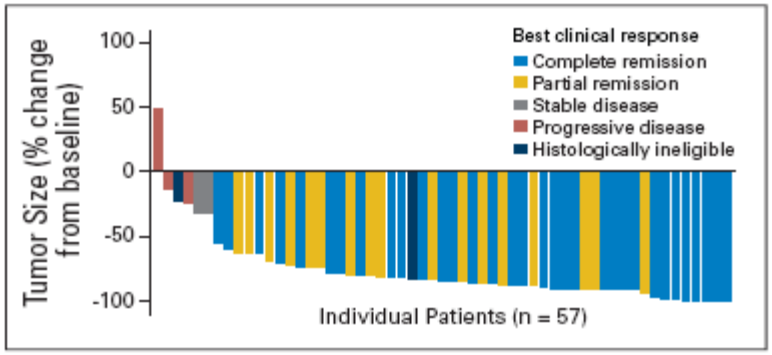
	n=58
Median age, years (range)	52 (14–76)
Gender	33 M / 25 F
ECOG performance status	
0	33%
1	66%
2	2%
ALCL confirmed by central pathology	97%
ALK-negative	72%
Refractory to frontline therapy	62%
Refractory to most recent treatment	50%
No response to any prior treatment	22%
Prior chemotherapy regimens*	2 (1–6)
Prior radiation	45%
Prior ASCT	26%

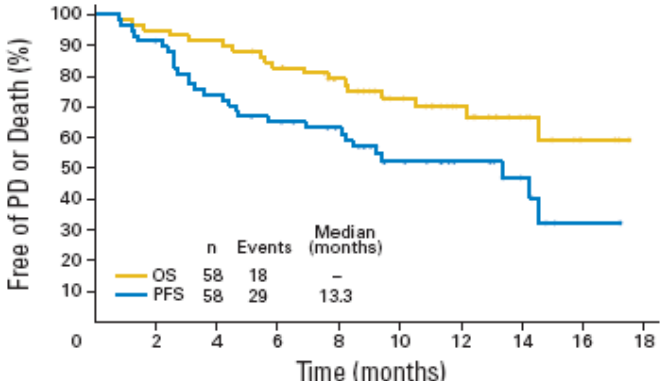
Pro B et al. J Clin Oncol 2012;30:2190–6;
Pro et al. ASH Dec 2014, Abstract 3095.

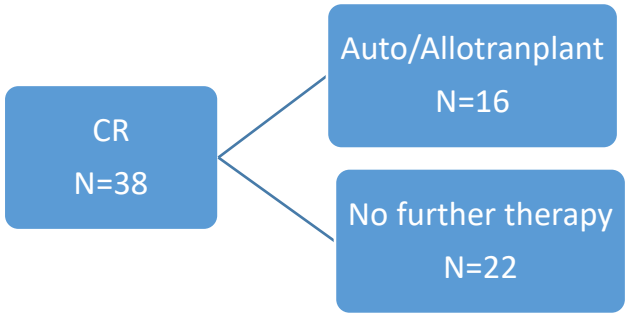
Brentuximab vedotin in R/R sALCL

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







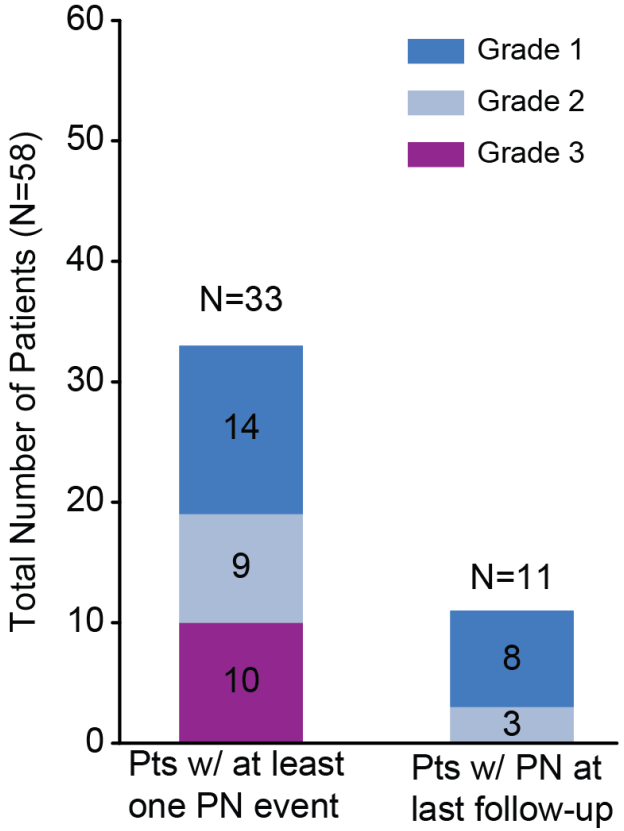
Pro et al. *J Clin Oncol* 2012 ; Pro et al. ASH meeting 2016

Safety

- The most common (≥20%) treatment-emergent adverse events were peripheral neuropathy (PN), nausea, fatigue, pyrexia, diarrhea, rash, constipation, and neutropenia
- Adverse events of Grade 3 or higher that occurred in ≥5% of pts were neutropenia (21%), PN (17%), thrombocytopenia (14%), anemia (7%), fatigue (5%), and recurrent ALCL (5%)

Resolution of Peripheral Neuropathy

- 33 of 58 pts (57%) experienced PN[a], the majority of whom had symptoms ≤ Grade 2
  - 30/33 pts (91%) experienced complete resolution or some improvement of PN symptoms at last follow-up
    - 22/33 pts (67%) had complete resolution[b]
    - No Grade 3 PN events were observed at last follow-up
- The majority of pts with ongoing PN (8/11) had a maximum severity of Grade 1 at last follow-up
- For those PN events that resolved, the median time from onset to resolution was 14 weeks



[a] Standardized MedDRA query (SMQ) analysis
[b] Resolution is defined as event status of resolved/recovered or resolved/recovered with sequelae; or return to baseline or lower severity as of the last follow-up

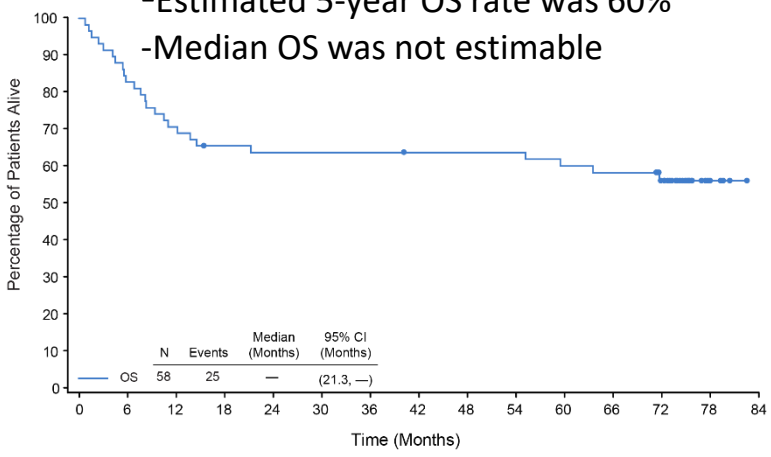
Pro et al., Blood 2017; 30: 2709-2717

Long-Term Survival and Durability

- At study closure, which occurred approximately 5 years after the last pt's end-of-treatment visit, the median observation time for all enrolled pts was 71.4 months from first dose (range, 0.8 to 82.4)

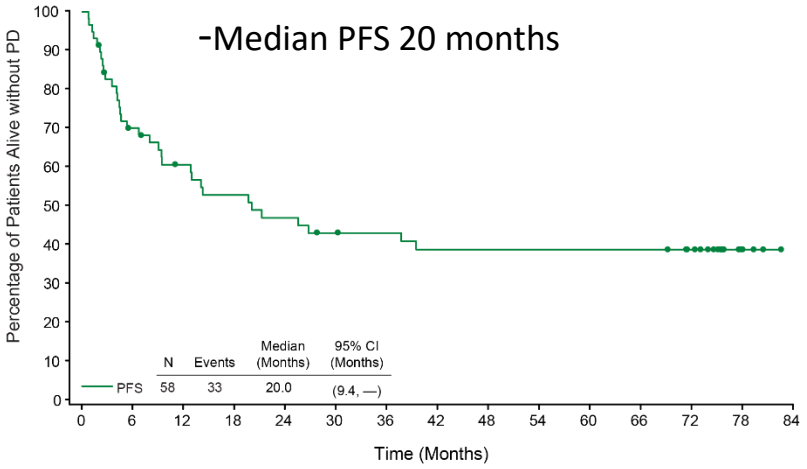
OS

-Estimated 5-year OS rate was 60%
-Median OS was not estimable



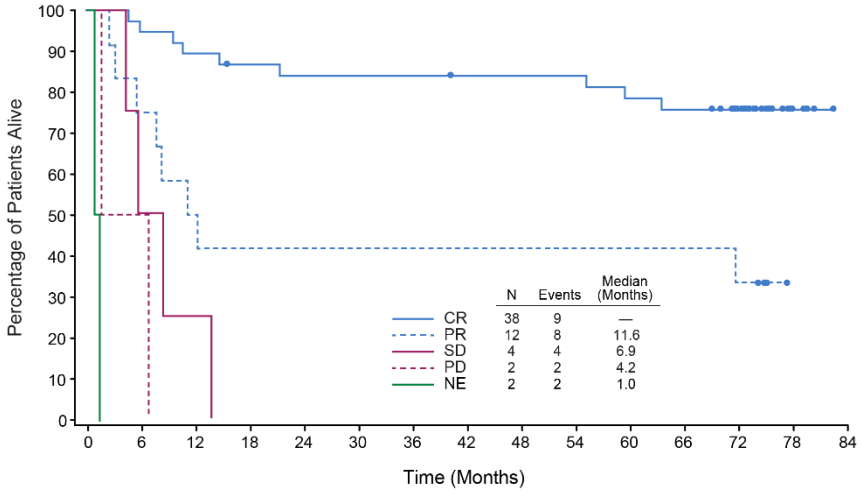
PFS

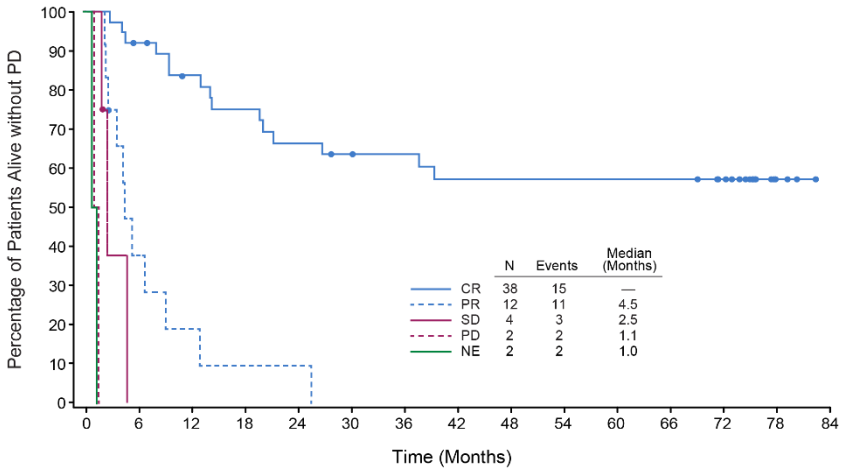
-Median PFS 20 months



Pro et al., Blood 2017; 30: 2709-2717

OS and PFS by Best Response per Investigator

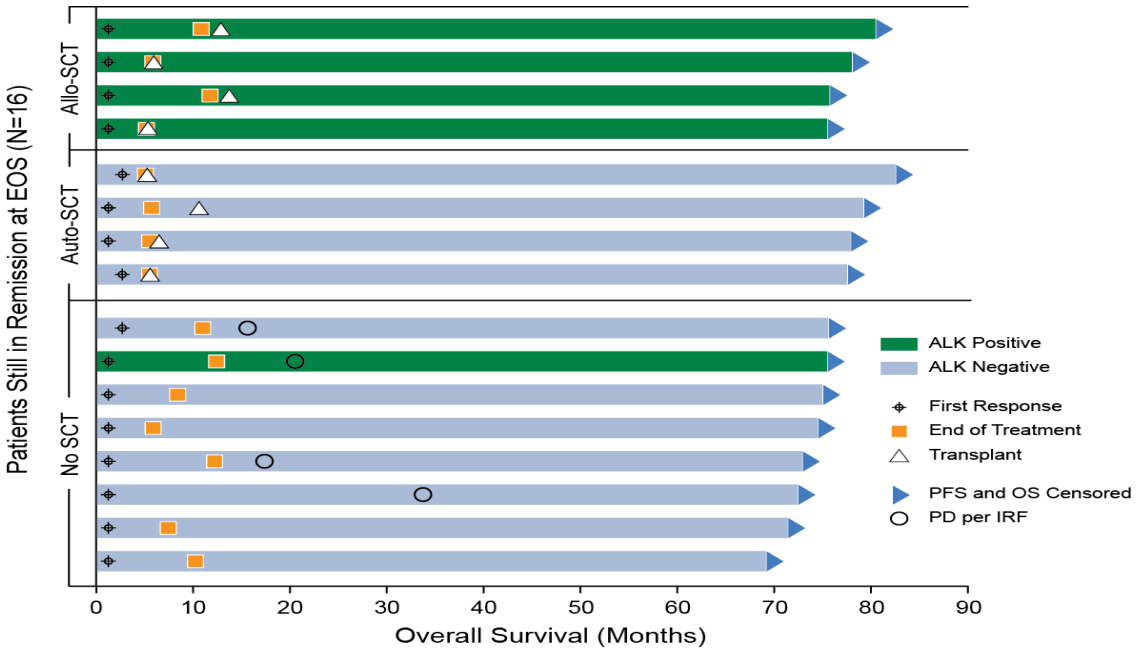




Pro et al., Blood 2017; 30: 2709-2717

Patients in Remission at End of Study (N=16)

- Of the 38 pts who achieved CR, 16 pts (42%) were still on study and in remission at study closure without the start of new anticancer therapy, other than SCT
- The median observation time for the 16 pts still on study and in remission was 75.4 months (range, 69 to 82.4)



Pro et al., Blood 2017; 30: 2709-2717

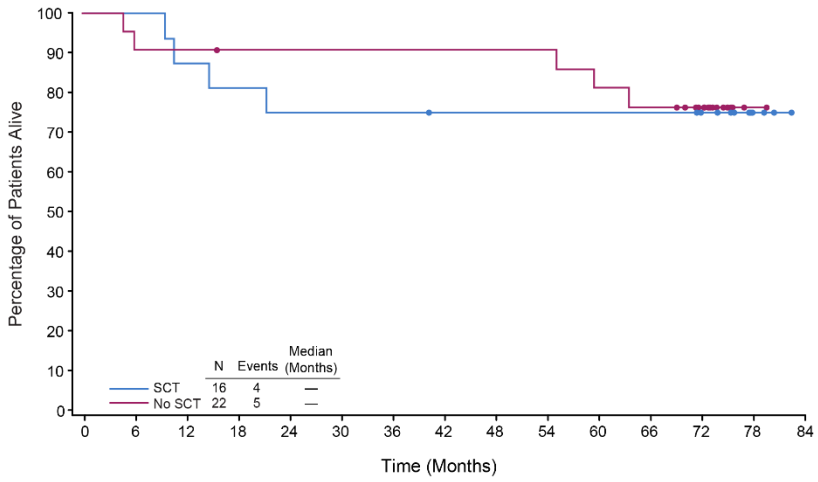
Baseline Characteristics of Patients with Best Response of CR

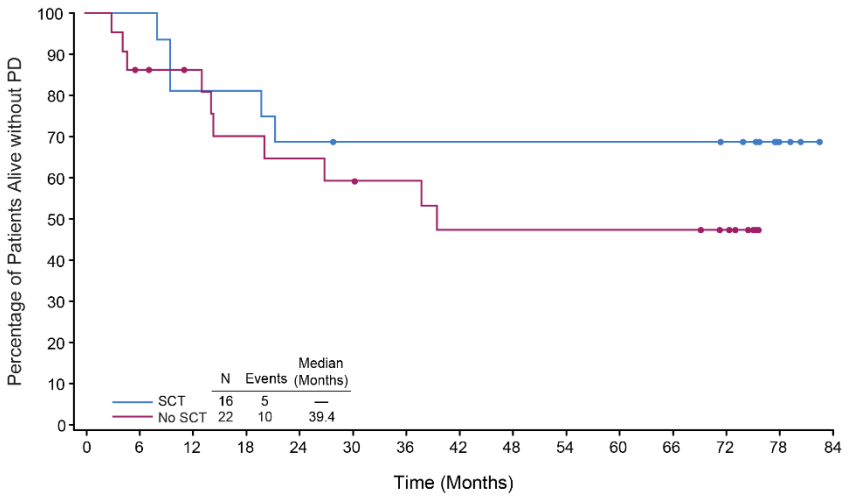
	CR and in remission at EOS (N=16)	All other CR (N=22)
Median age in years (range)	56 (14, 76)	50 (17, 74)
Female, n (%)	4 (25)	13 (59)
ECOG status, n (%)		
0	4 (25)	11 (50)
1	12 (75)	11 (50)
ALK negative, n (%)	11 (69)	17 (77)
Median time from initial diagnosis, months (range)	22 (6.2, 113.2)	20 (4.4, 186.5)
Stage III/IV at initial diagnosis, n (%)	6 (37)	10 (46)
Refractory to frontline therapy, n (%)	7 (44)	16 (73)
Refractory to most recent treatment, n (%)	5 (31)	11 (50)
Median baseline SPD, cm^2 (range)	14 (3.2, 76.8)	12 (2.0, 51.3)
Baseline bone marrow involvement, n (%)	0	2 (9)

SPD = sum of the product of diameters

Pro et al., Blood 2017; 30: 2709-2717

OS and PFS by Consolidative Transplant (N=38)

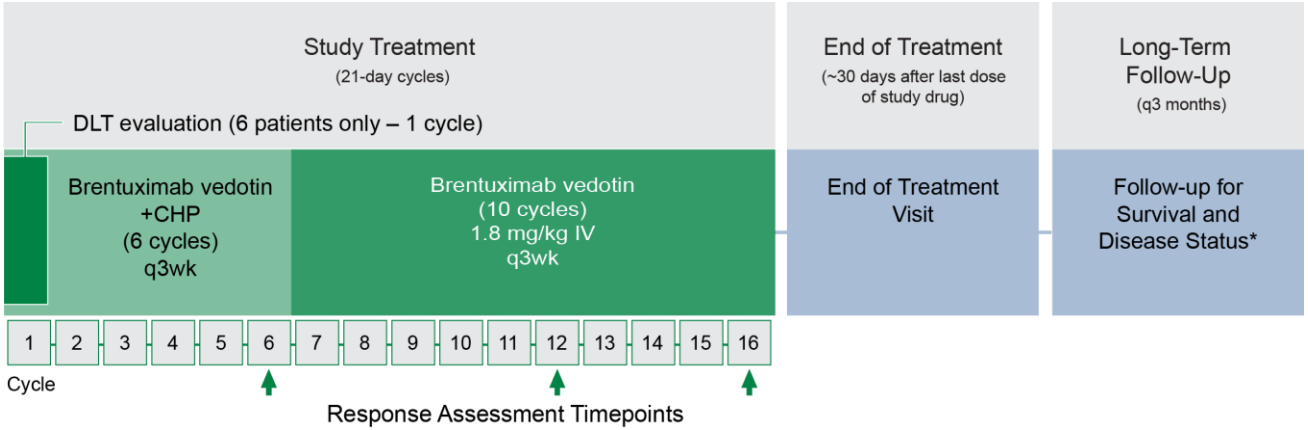




- Of the 38 CR pts, 16 underwent consolidative
- Median OS and PFS were not reached in these pts who underwent subsequent SCT
- In the 22 pts with CR who did not receive SCT as consolidation, the median OS was not reached, and the median PFS was 39.4 months

Pro et al., Blood 2017; 30: 2709-2717

Brentuximab Vedotin + CHP Methods – Study Design



* Pts who discontinue study treatment for reasons other than PD or initiation of new therapy have CT/PET q3 months for the first year of follow-up, then follow-up for survival and disease status thereafter

- Pts who achieved at least a partial response (PR) following 6 cycles of brentuximab vedotin + CHP could receive up to 10 additional cycles of single-agent brentuximab vedotin (1.8 mg/kg q3wk)
- Pts followed for survival and disease status every 3 months after the end of treatment
- All response assessments were performed by the investigator

Summary of Clinical Response at the End of Combination Therapy

- All 26 pts achieved an objective response (100% objective response rate, 88% CR rate) with brentuximab vedotin + CHP
- 1 pt with PR converted to CR during brentuximab vedotin monotherapy

	ALCL (N=19)	Non-ALCL[a] (N=7)	Total (N=26)
Clinical Response[b, c], n (%)			
Complete Response (CR)	16 (84)	7 (100)	23 (88)
Partial Response (PR)	3 (16)	0	3 (12)

Fanale et al., J Clin Oncol 32:3137-3143; 2014

Summary and Conclusions

- The end-of-study results of the pivotal trial, presenting over 5 years of follow-up data, demonstrate that among pts with R/R systemic ALCL, the majority of pts have achieved clinically significant durable remissions, and a subset may have been potentially ***cured*** with single-agent brentuximab vedotin

- Associated toxicities are manageable, with high rates of improvement or resolution for peripheral neuropathy

- A randomized phase 3 trial (ECHELON-2) evaluating the combination of brentuximab vedotin with cyclophosphamide, doxorubicin, and prednisone for frontline treatment of CD30-expressing peripheral T-cell lymphomas, including systemic ALCL (NCT01777152) is now complete!

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Grazie!

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