ALCL

Barbara Pro, MD
Kimmel Cancer Center

Thomas Jefferson University

Sidney Kimmel Cancer Center
at Thomas Jefferson University
NCI-designated

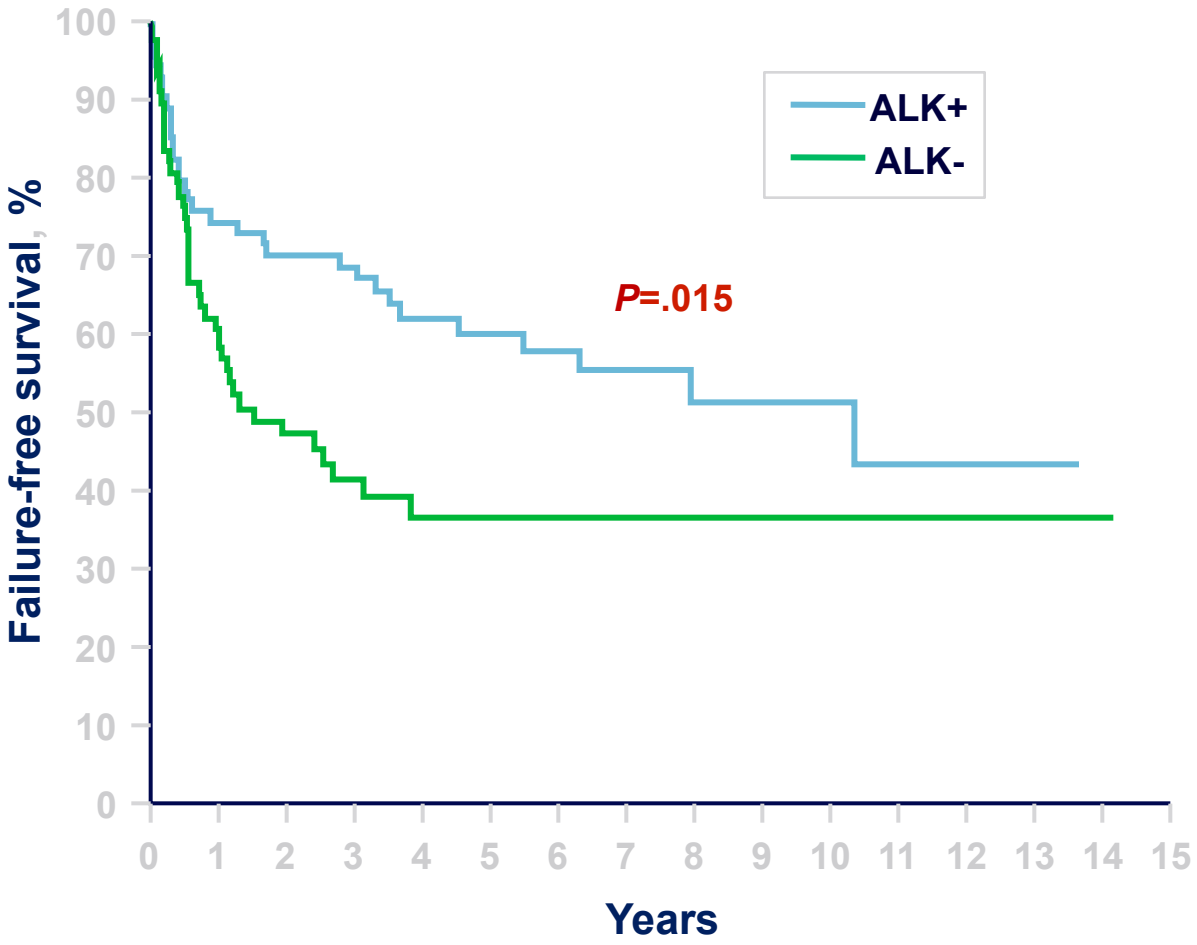
Drexel UNIVERSITY

Systemic Anaplastic Large Cell Lymphoma

- 2013 estimates [1]: ~ 70,000 new cases of non-Hodgkin lymphoma
  - 1394 to 3487 new cases of systemic ALCL[2]
- Broad age distribution at presentation
- More common in males than females
- Majority of patients present with advanced disease and B symptoms[3]
- Skin lesions frequently encountered

1. Siegel R et al. CA Cancer J Clin. 2013;63:11-30. 2. Based on 2% to 5% of all NHL cases being ALCL.
3. Savage KJ, et al. Blood. 2008;111:5496-5504.

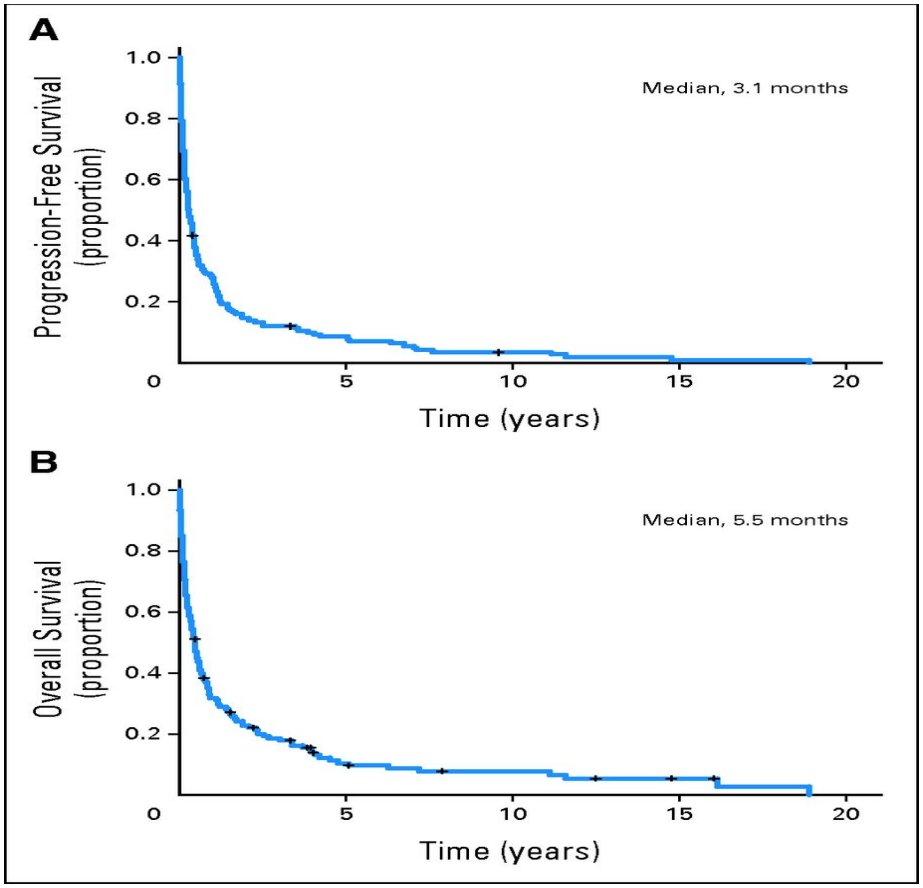
ALK-Negative Patients Have a Worse Outcome Than ALK-Positive Patients

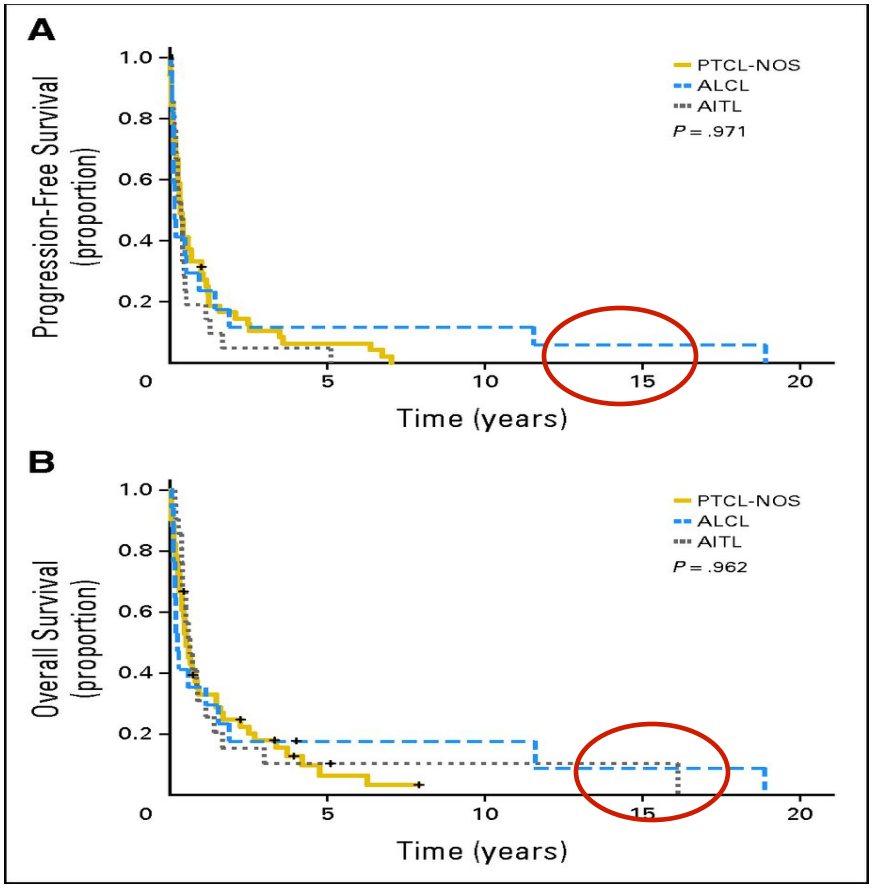


	ALK$^+$	ALK$^-$
IPI score, %	55	45
0, 1	49	41
2	22	20
3	15	24
4, 5	14	15
5-yr FFS by IPI, %	60	36
0, 1	80	62
2	61	44
3	23	16
4, 5	25	13
5-yr OS by IPI, %	70	49
0, 1	90	74
2	68	62
3	23	31
4, 5	33	13

Savage KJ, et al. Blood. 2008;111:5496-5504.

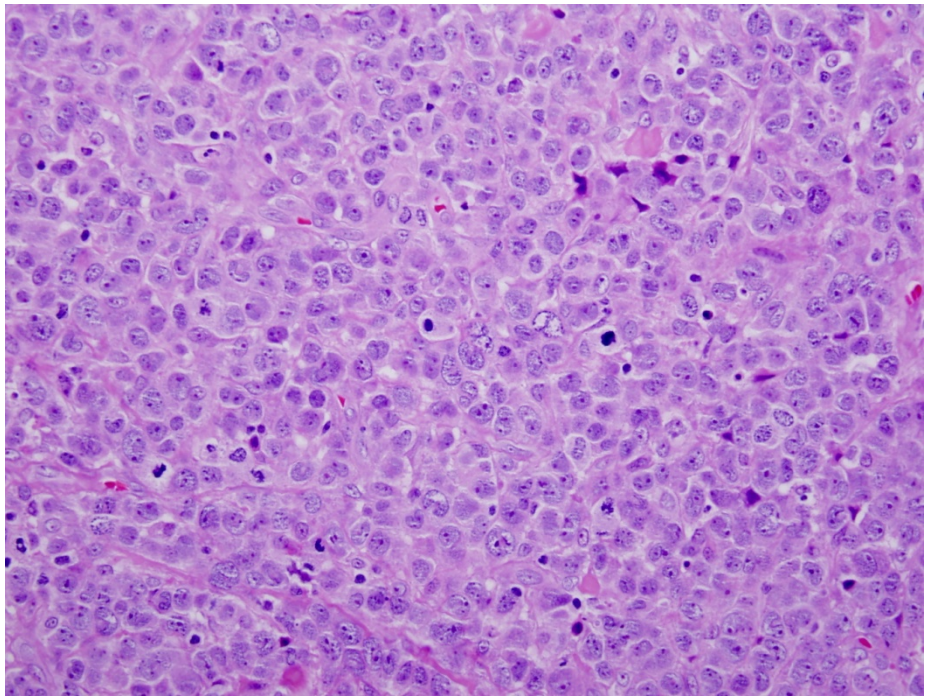
First Relapse or Progression of PTCL



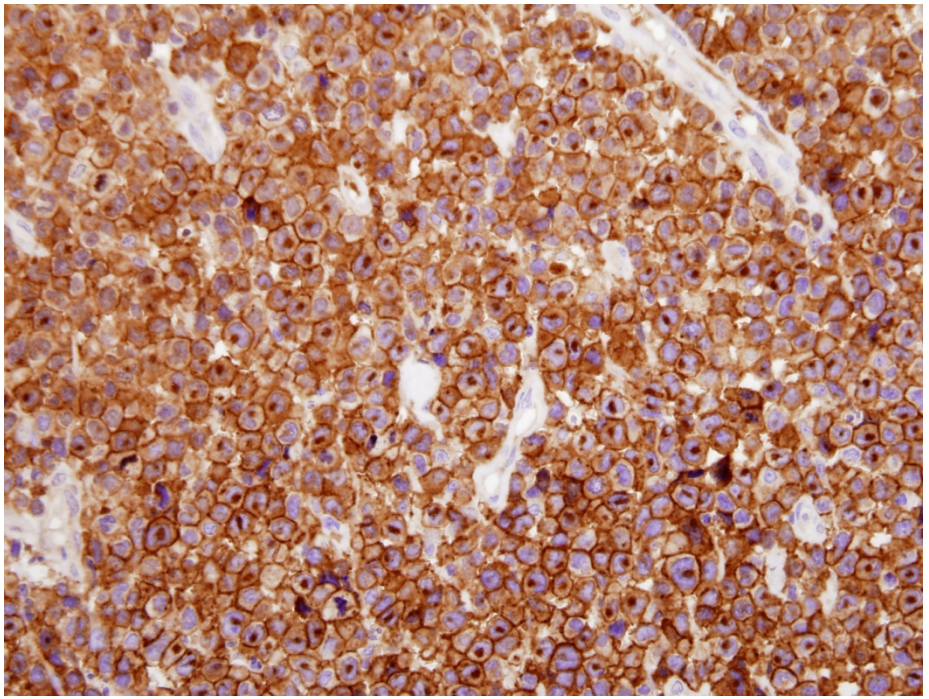


Mak V et al. JCO 2013;31:1970-1976

CD30 Expression in ALCL



Systemic ALCL sample H&E staining



Systemic ALCL sample CD30 staining

Cytokine receptor CD30 selectively expressed in malignant ALCL cells

CD30 Expression in PTCL

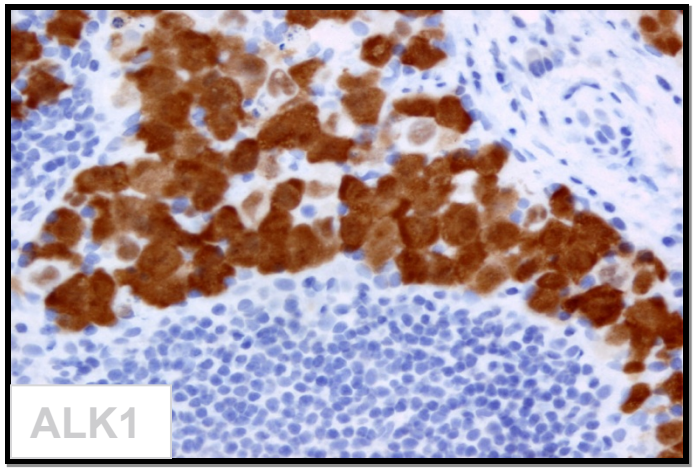
CD30 IHC scores								
% of CD30+ tumor cells	**ALCL ALK+ N=61**	**ALCL ALK- N=19**	**PTCL NOS N=141**	**AITL N=97**	**ENKTL N=28**	**EATL N=14**	**ATLL N=9**	**HSTL N=7**
Score 0 <5%	0	0	59 42%	36 37%	15 53.5%	7 50%	4 44%	7 100%
Score 1 5-24%	0	0	37 26%	46 47%	2 7%	0	1 11%	0
Score 2 25-49%	3 5%	0	13 9%	10 10%	3 11%	0	3 33%	0
Score 3 50-75%	1 2%	0	14 10%	5 5%	4 14%	1 7%	1 11%	0
Score 4 > 75%	57 93%	19 100%	18 13%	0	4 14%	6 43%	0	0
Total positive cases (scores 1-4)	**61 100%**	**19 100%**	**82 58%**	**61 63%**	**13 46%**	**7 50%**	**5 55.5%**	**0**
Strongly positive cases (scores 3-4)	**58 95.1%**	**19 100%**	**32 23%**	**5 5%**	**8 28.5%**	**7 50%**	**1 11%**	**0**

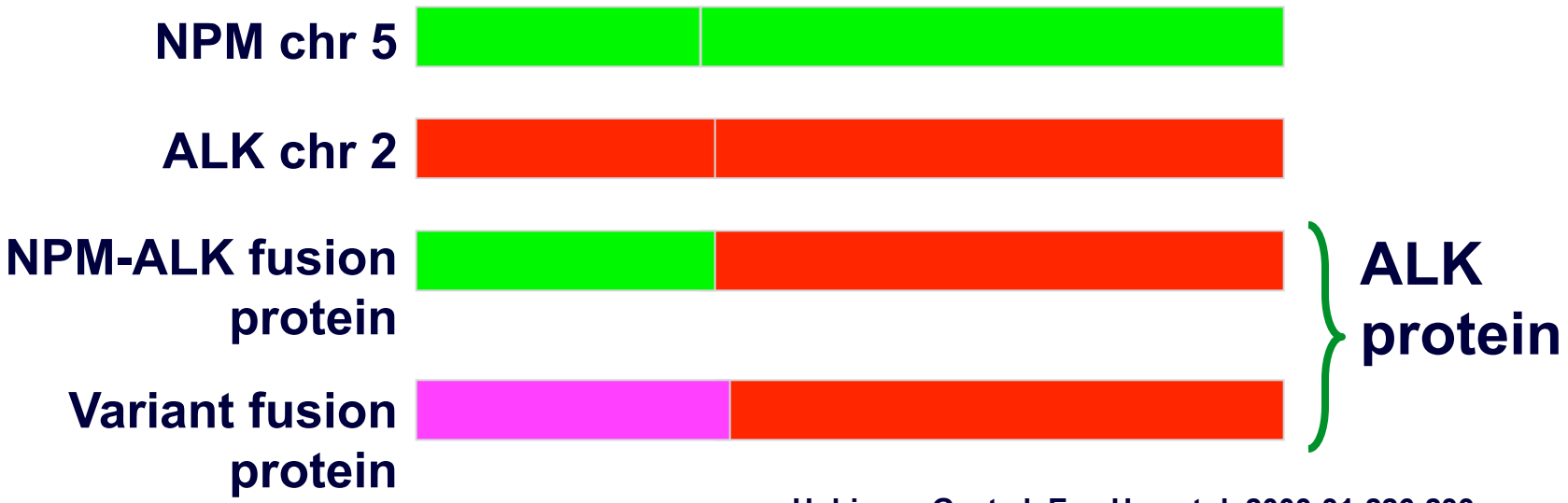
Bossard C et al. Blood 2014

ALK-Positive ALCL

- 60% of ALCL associated with overexpression of the ALK protein = ALK^+

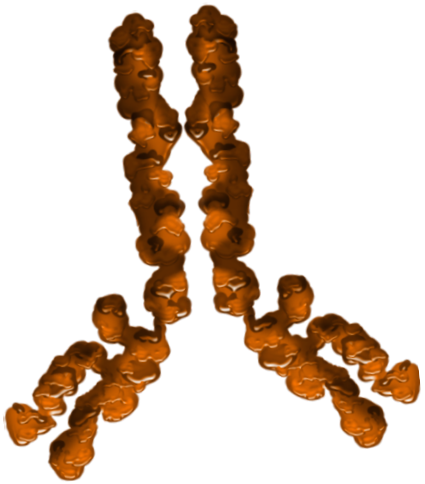
  typical t(2;5) (p23;35)





Hubinger G, et al. Exp Hematol. 2003;31:226-233.

Targeting CD30



Naked Monoclonal Antibodies

SGN-30

- Chimeric anti-CD30 antibody

Phase I

- 2-12 mg/kg weekly X 6
  - **24 patients**
  - **21 HL, 3 ALCL**
- 1 CR in ALCL

Phase II

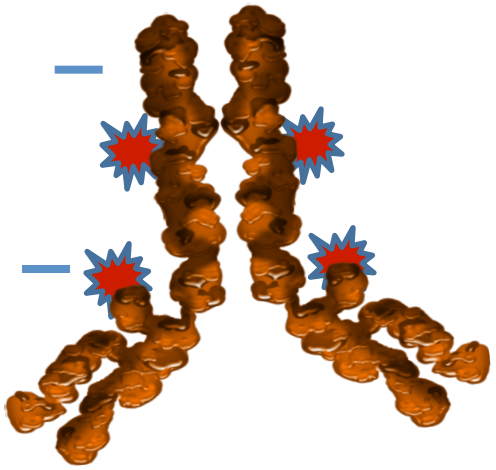
- 79 patients
- 6-12 mg/kg weekly X 6
- ORR 9%

Bartlett et al, *Blood*, 111, 2008
Forero-Torres et al,Br J Haematol 146, 2009

Elements of an Antibody-Drug Conjugate

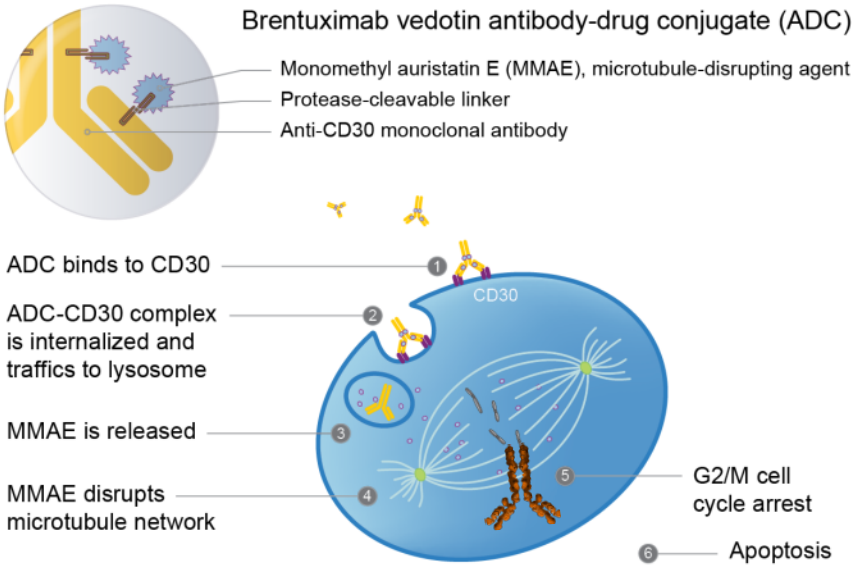
Antibody
Specific for a tumor-associated antigen

Cytotoxic agent



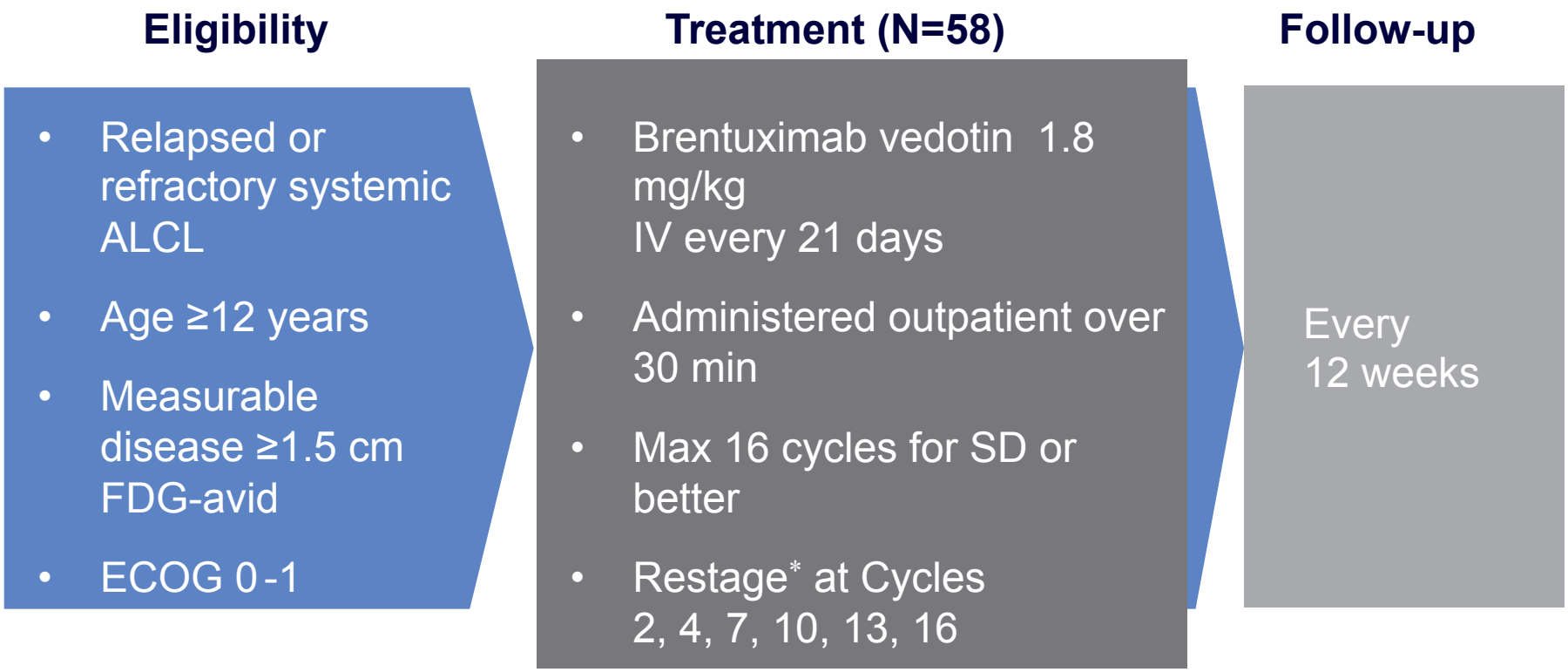
Linker
Newer linker systems are designed to be systemically stable

Brentuximab Vedotin



Pivotal Study Endpoints & Design

- Primary Endpoint: ORR by independent review facility (IRF)
- Secondary Endpoints: CR, Duration of response, PFS, OS



Demographics and Baseline Characteristics

	N=58
Age*	52 yr (14-76)
Gender	33 M / 25 F
ECOG 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%
* Median (range)	

Pro B, et al. J Clin Oncol. 2012;30:2190-2196

Key Response Results

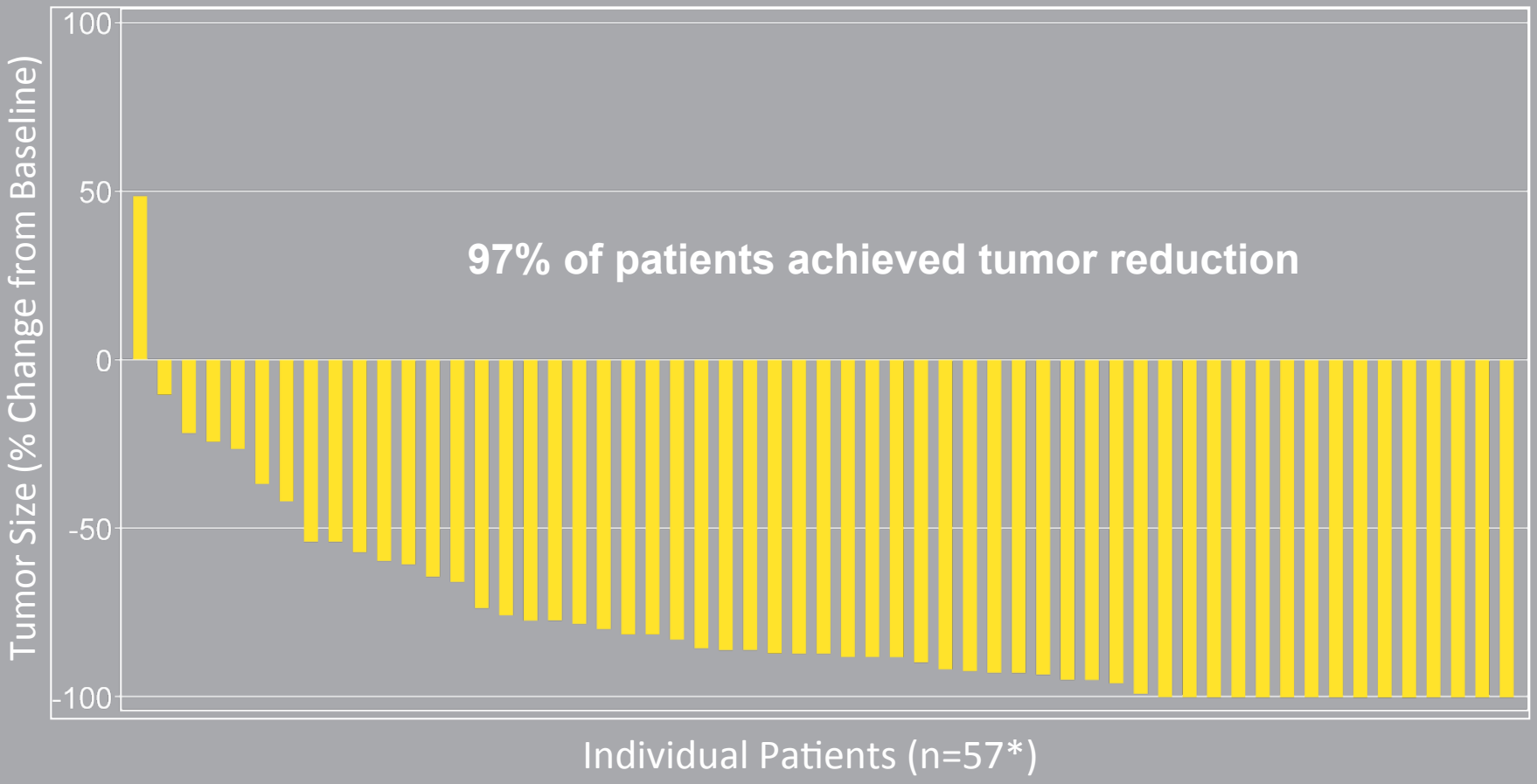
Clinical Response	N=58
Objective response rate (95% CI)	86% (75, 94)
Complete remission (CR) rate (95% CI)	59% (45, 71)

Median Duration	Months
Objective response (95% CI)	13.2 (5.7, NE)
Response in patients with CR (95% CI)	Not reached (13, NE)

NE=not estimable

Pro B, et al. J Clin Oncol. 2012;30:2190-2196

Maximum Tumor Reduction per IRF



* 57 of 58 patients with post-baseline CT assessments

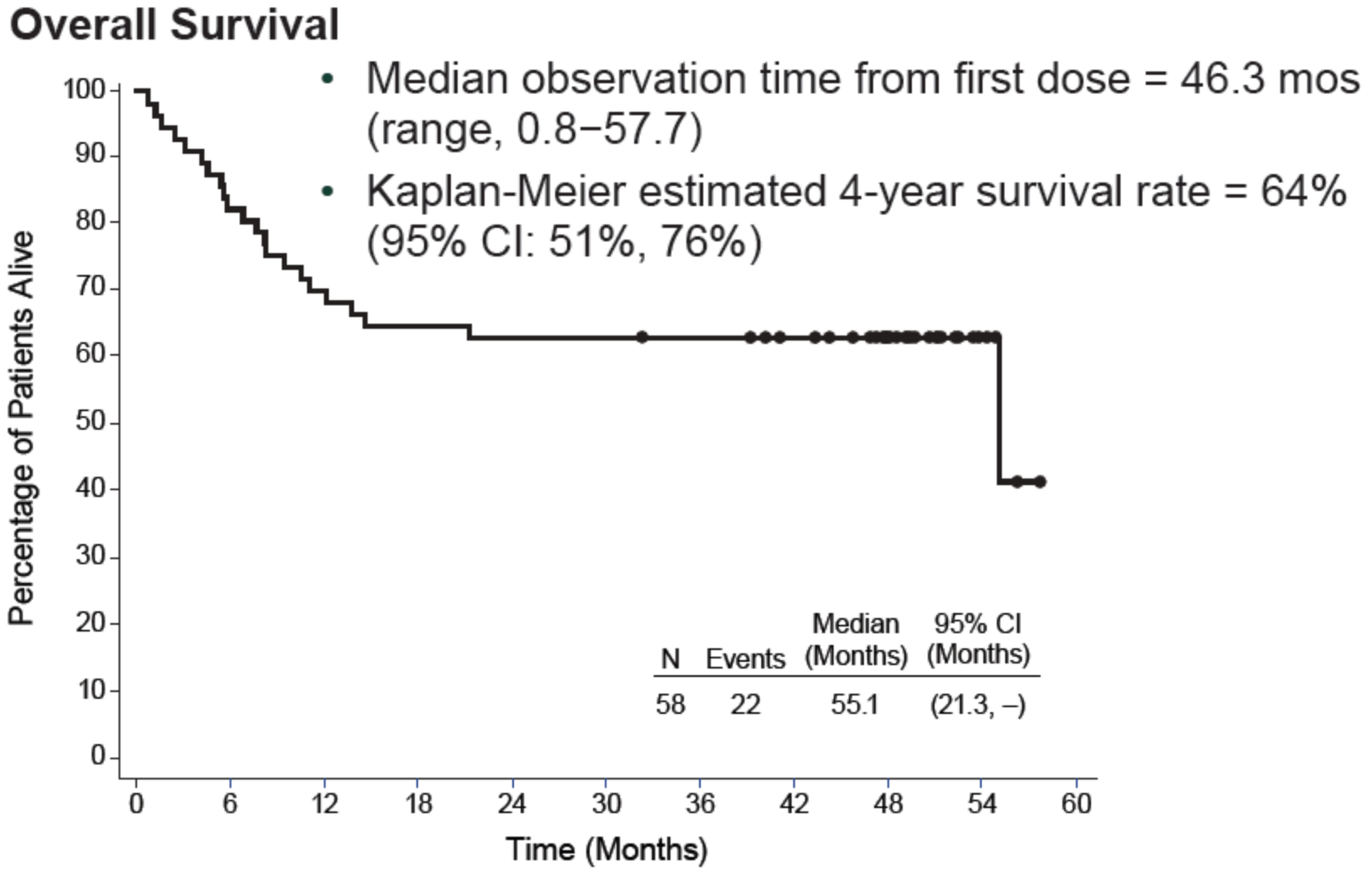
Pro B, et al. J Clin Oncol. 2012;30:2190-2196

Adverse Events (AEs) ≥ 20% from Pivotal sALCL Trial

Preferred Term	All Grades	Grade 3	Grade 4
Peripheral Neuropathy	57%	17%	-
Nausea	40%	2%	2%
Fatigue	38%	3%	-
Pyrexia	34%	2%	-
Diarrhea	29%	3%	-
Rash	24%	-	-
Constipation	22%	2%	-
Neutropenia	21%	12%	9%

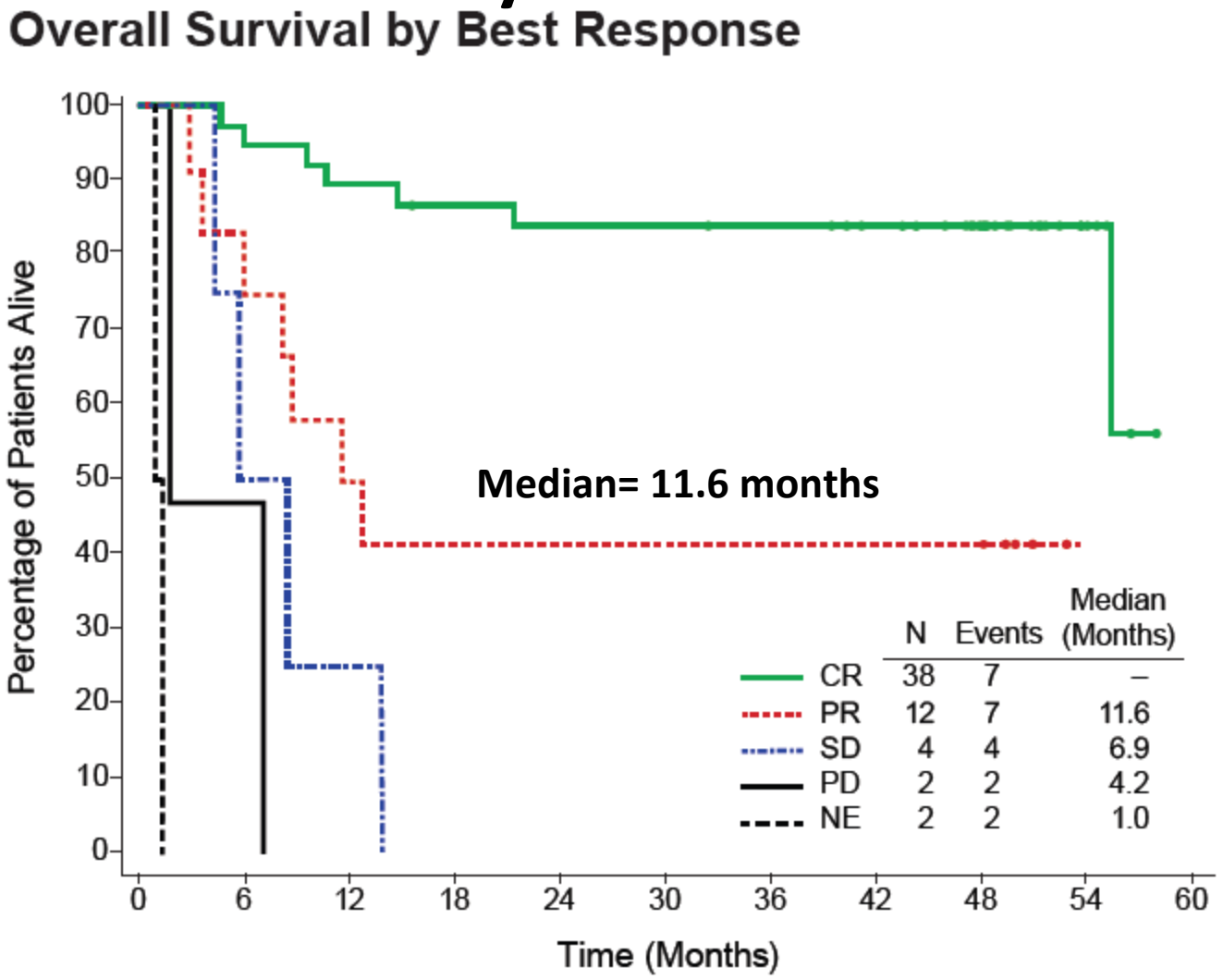
Pro, B et al, *JCO*, 2012;30:2190-2196;
Pro, B et al, *ASH*, 2013;1809

Pivotal Phase II Study
4-Year Survival Data



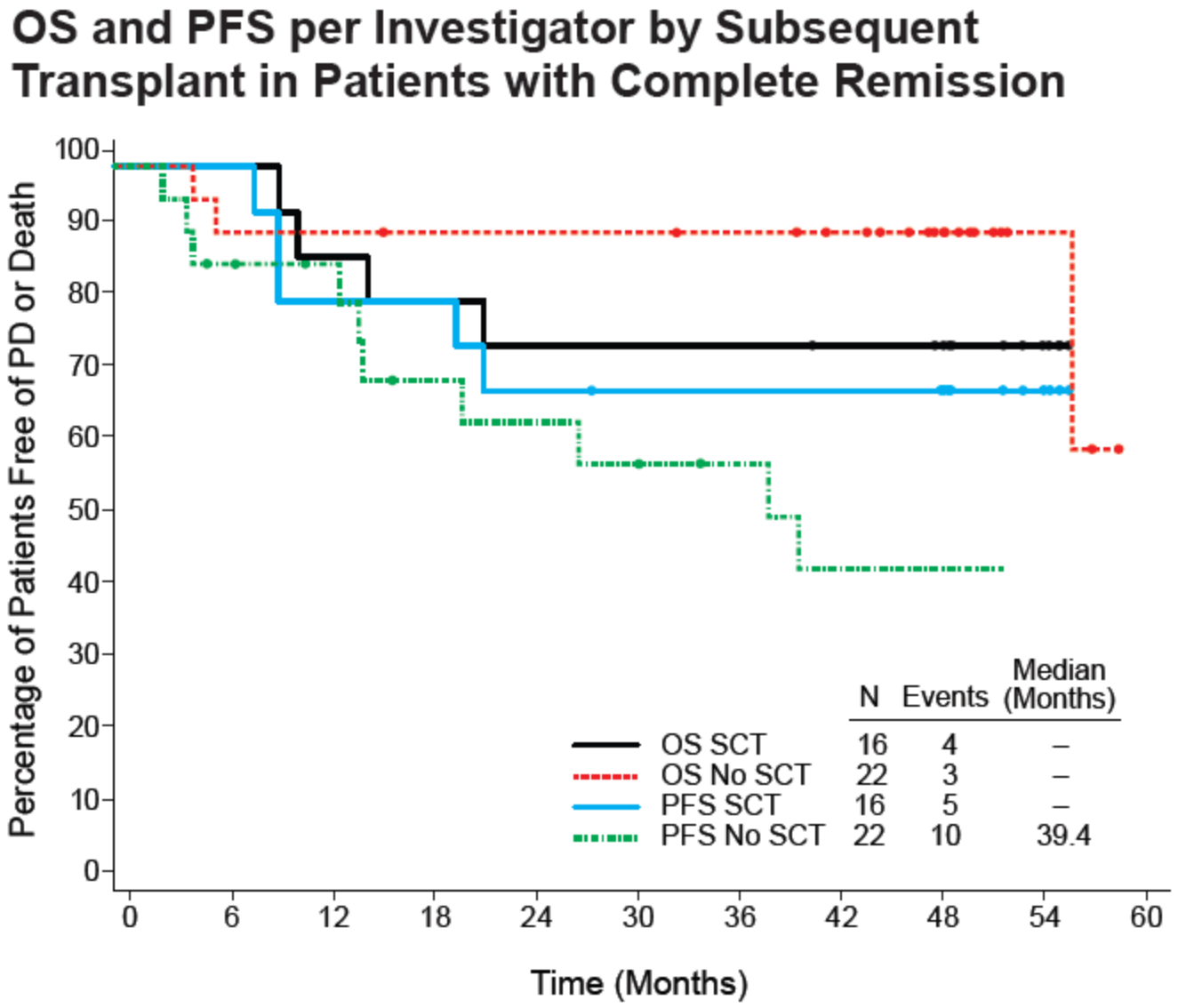
Pro B et al. ASH 2014 Abstract 3095

Pivotal Phase II Study



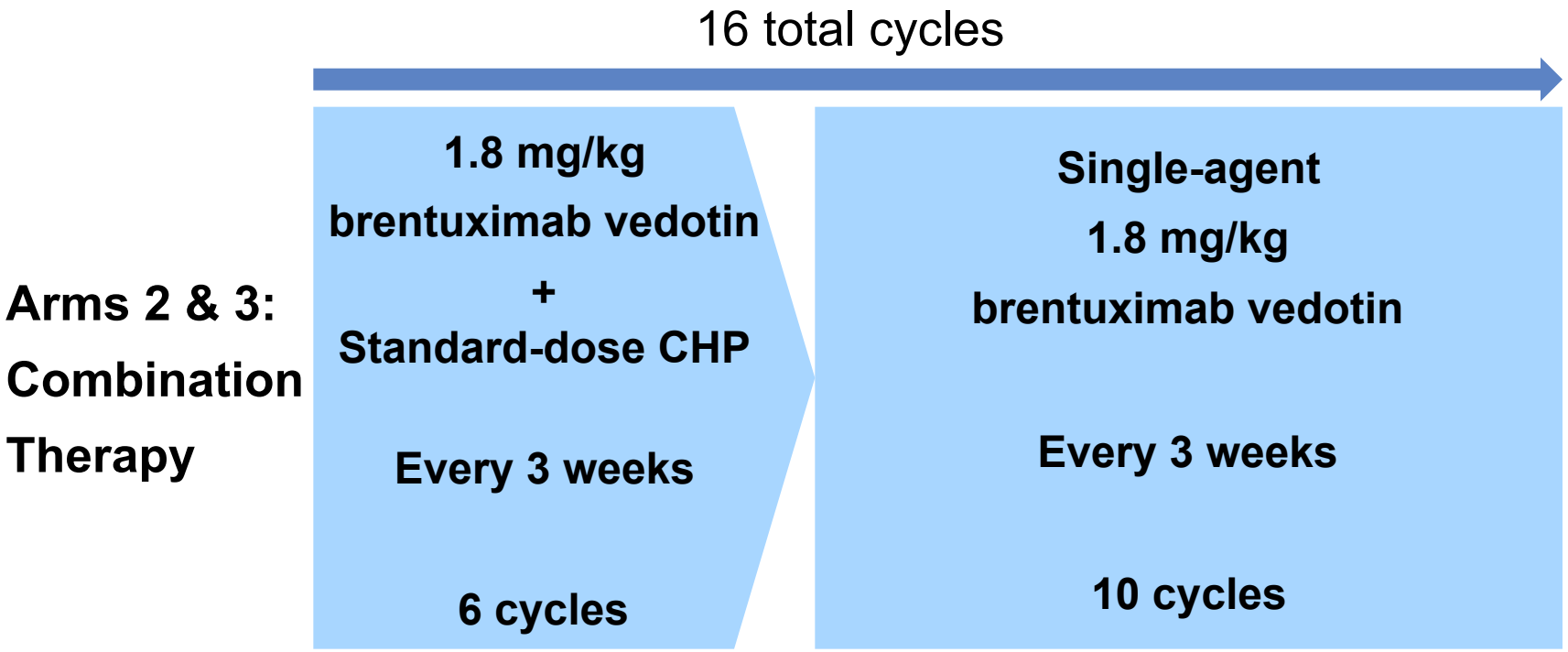
Pro B et al. ASH 2014 Abstract 3095

Pivotal Phase II Study



Pro B et al. ASH 2014 Abstract 3095

Phase I Frontline Combination Study
Combination therapy arms*



- Phase 1, open-label, multicenter study
- Arm 2 designed to determine recommended dose of brentuximab vedotin in combination with CHP (CHOP without vincristine) to be further evaluated in Arm 3
  - **The maximum-tolerated dose was not exceeded at 1.8 mg/kg q3wk**

*Arm 1 investigated sequential brentuximab vedotin and CHOP

Fanale, M et al, *JCO*, 2014;32:3137-3143

Best Response by Disease Diagnosis[a]

	sALCL (N=19)	Other diagnoses (N=7)	Total (N=26)
Objective response rate, n (%)	19 (100)	7 (100)	26 (100)
CR	16 (84)	7 (100)	23 (88)
PR	3 (16)	--	3 (12)
Median PFS (95% CI)	--	--	-- (4+, 13+)
Median OS (95% CI)	--	--	-- (4+, 13+)

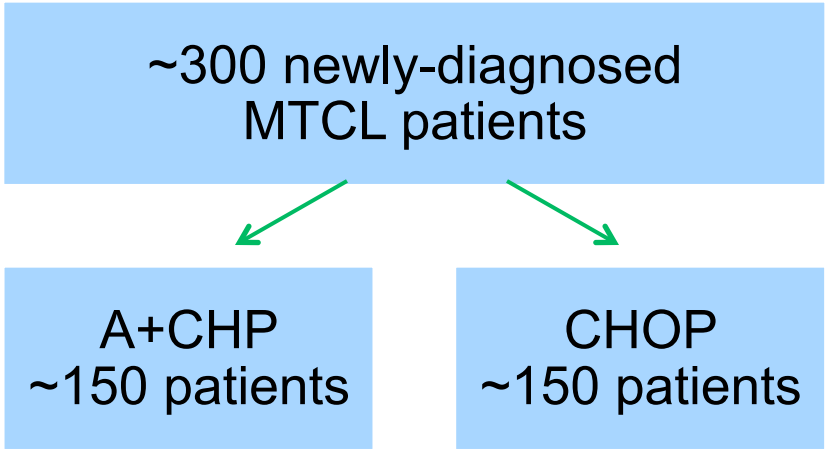
a. Response per investigator (Cheson 2007) at end of Cycle 6 or at latest assessment for 3 patients who discontinued prior to Cycle 6

- Patients followed for a median of 9 months (range, 4–13)
- Following these assessments, 10 of 26 patients continued therapy with single-agent brentuximab vedotin
  - At the end of Cycle 12, ORR=12/13 (92%), CR rate=11/13 (85%)
  - At the end of Cycle 16, ORR=4/4 (100%), CR rate=4/4 (100%)
- No patients went on to receive autologous or allogeneic stem cell transplants

Fanale, M et al, *JCO*, 2014;32:3137-3143

ECHELON-2 Phase 3 Study

- Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of brentuximab vedotin and CHP (A+CHP) vs CHOP for the frontline treatment of CD30+ MTCL*
- Enrolling approximately 300 patients at 130 sites in 14 countries (ClinicalTrials.gov #NCT01777152)



Stratified by:

- **MTCL histology: ALK-positive sALCL, all others**
- **IPI score: 0–1, 2–3, 4–5**

Retreatment With Brentuximab Vedotin: Patient and Disease Characteristics

- Pt population (N = 24)
  - sALCL (n = 8), ALK negative (n = 5)
  - HL (n = 16)
- Median number of previous systemic therapies: 4 (2-12)
- Previous transplant
  - Autologous (n = 16)
  - Auto/allo- (n = 4)

Best Response to Previous Brentuximab Vedotin, n	sALCL (n = 8)	HL (n = 16)
CR	5	6
PR	3	9
SD		1

- Median duration of most recent response to brentuximab vedotin: 9.6 mos (range: 0-14.2)

Bartlett NL, et al. ASCO 2012. Abstract 8027.

Retreatment With Brentuximab Vedotin
Best Clinical Responses

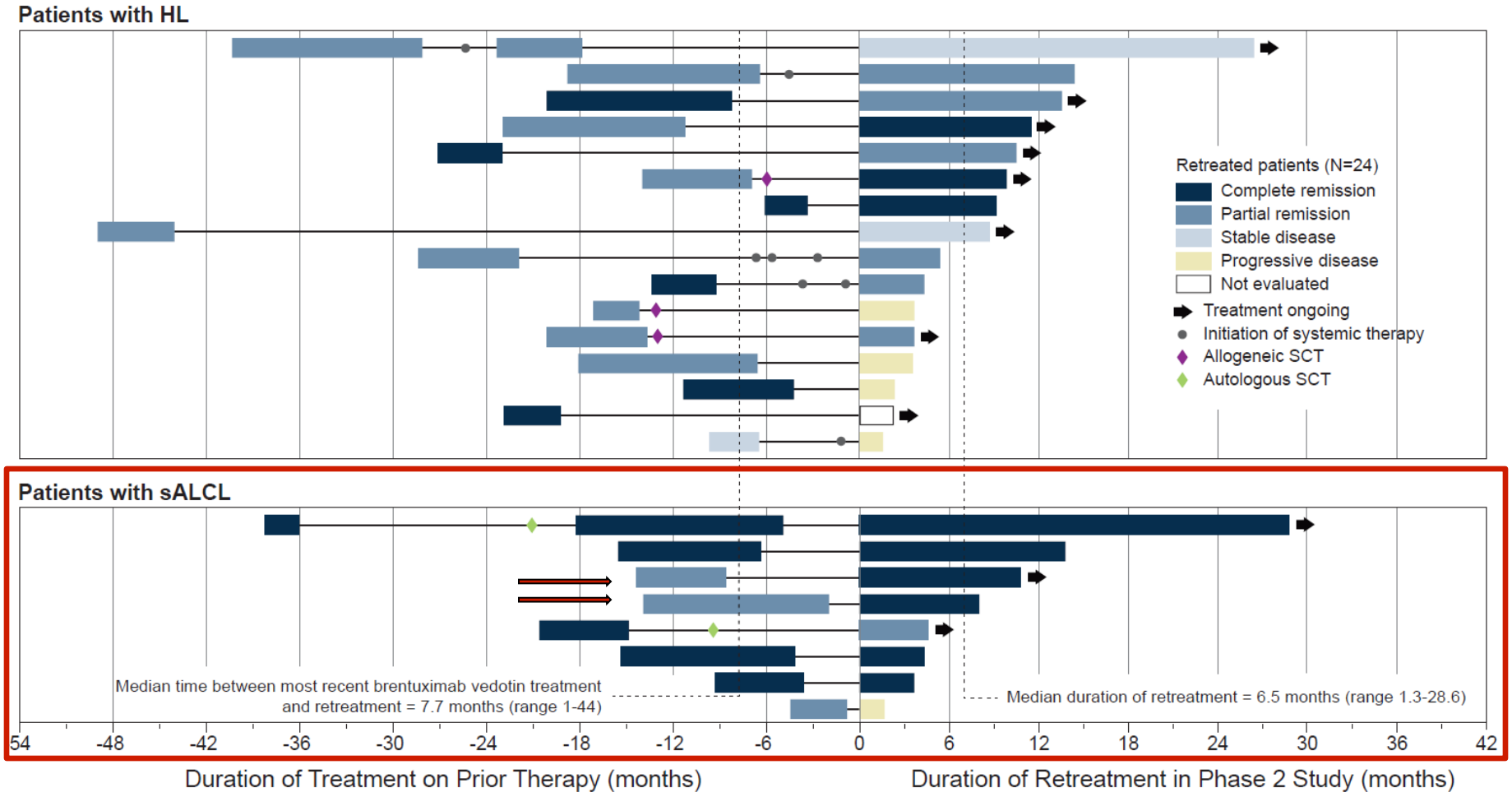
Best Response in Retreatment	Disease Diagnosis, n (%)		
	HL (n = 15*)	sALCL (n = 8)	Total (N = 23)
CR	3 (20)	6 (75)	9 (39)
PR	6 (40)	1 (13)	7 (30)
SD	2 (13)	0	2 (9)
PD	4 (27)	1 (13)	5 (22)

Median DOR: 9.5 months

*1 additional patient not yet evaluated for response.

Bartlett NL, et al. ASCO 2012. Abstract 8027.
Bartlett NL, et al. J Hematol Oncol. 2014

Duration of Brentuximab Vedotin Treatment



Bartlett NL, et al. ASCO 2012. Abstract 8027.

Summary

- **CD30 is an ideal target , owing to its dense expression by malignant cells and limited expression in normal tissue**
- **ADCs can overcome limitations of previous constructs**
- **Brentuximab vedotin is an anti-CD30 ADC with significant activity in R/R ALCL and others CD30+ lymphoma**
- **Retreatment is possible and associated with significant activity**

Perhaps a brighter future for ALCL and PTCL?

Grazie !

Barbara.Pro@Jefferson.edu