New Drugs In Hematology

Brentuximab Vedotin in Lymphomas

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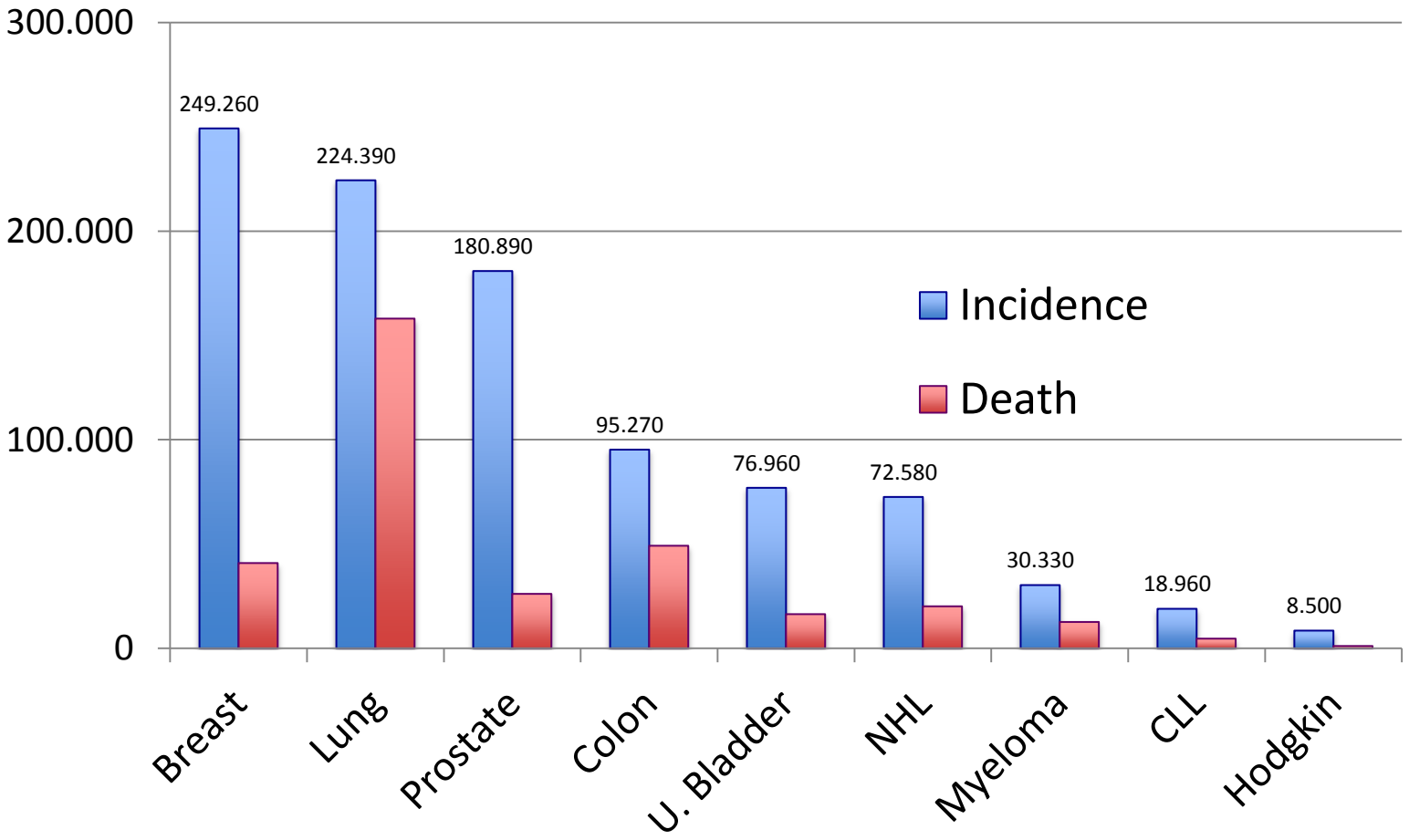
Monday, May 9, 2016
9:15-9:45 a.m

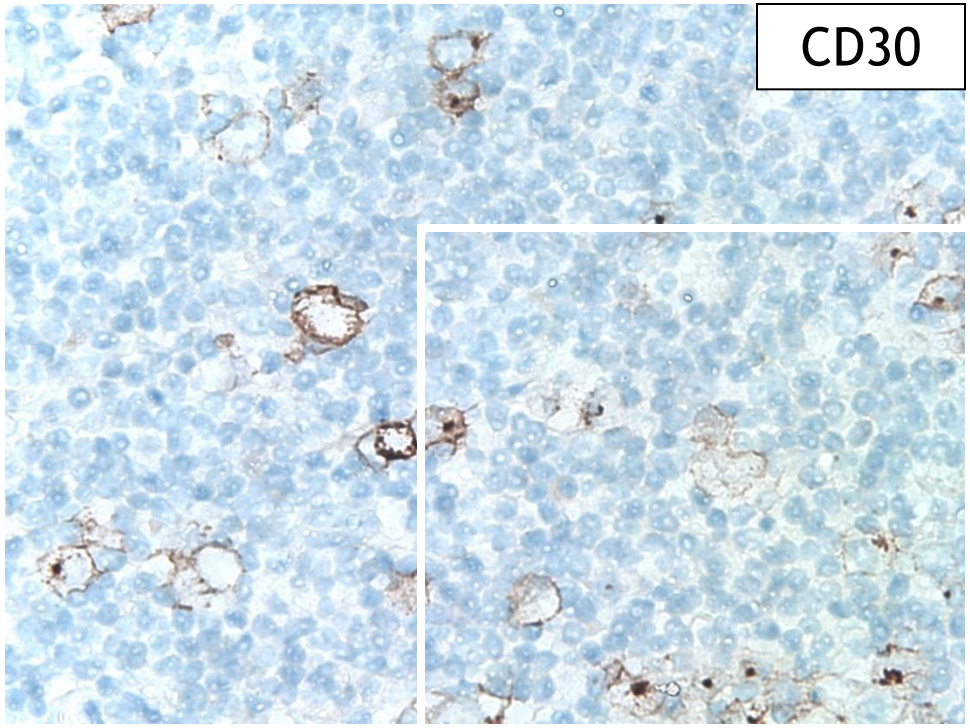
U.S. Cancer Statistics 2016



Siegel R, et al, ACS 2016

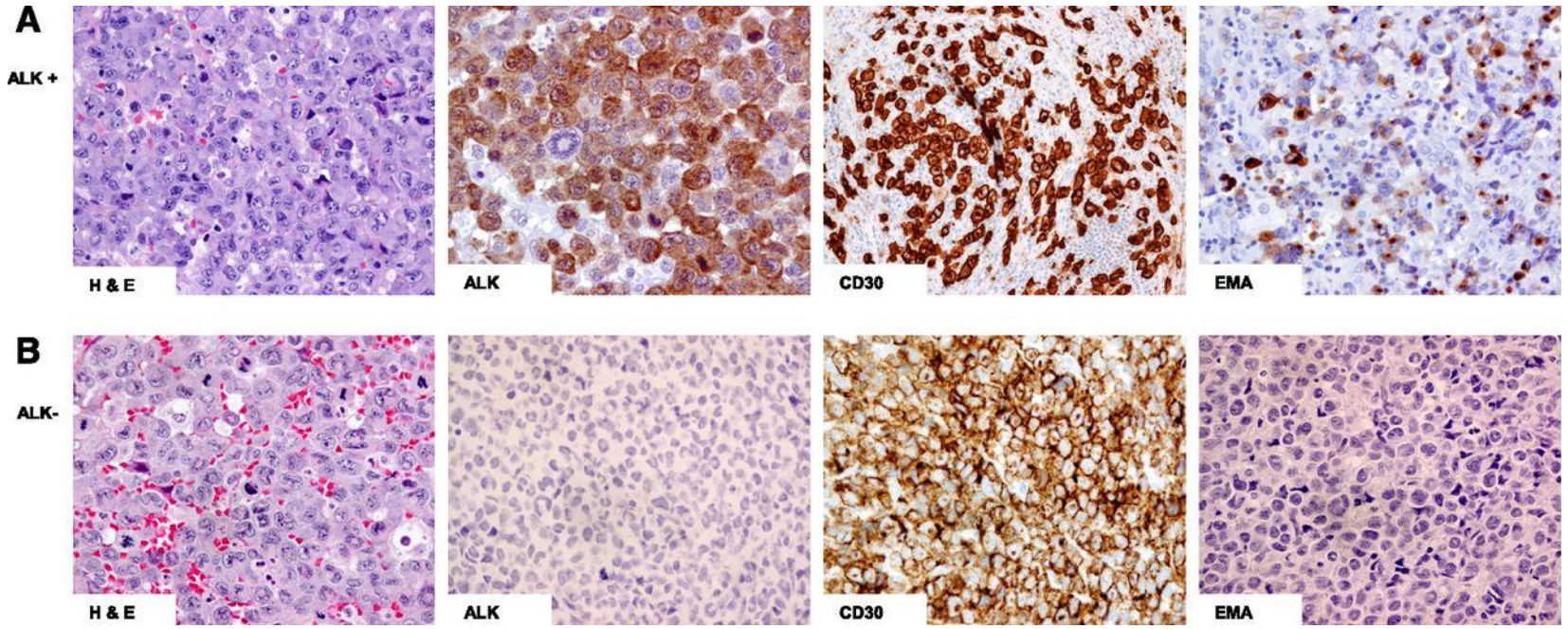
1982, Nature: Schwab, Stein and Diehl:

Production of Ki-1 monoclonal antibody that detects CD30 on HRS cells



CD30 Expression

systemic anaplastic large cell lymphoma



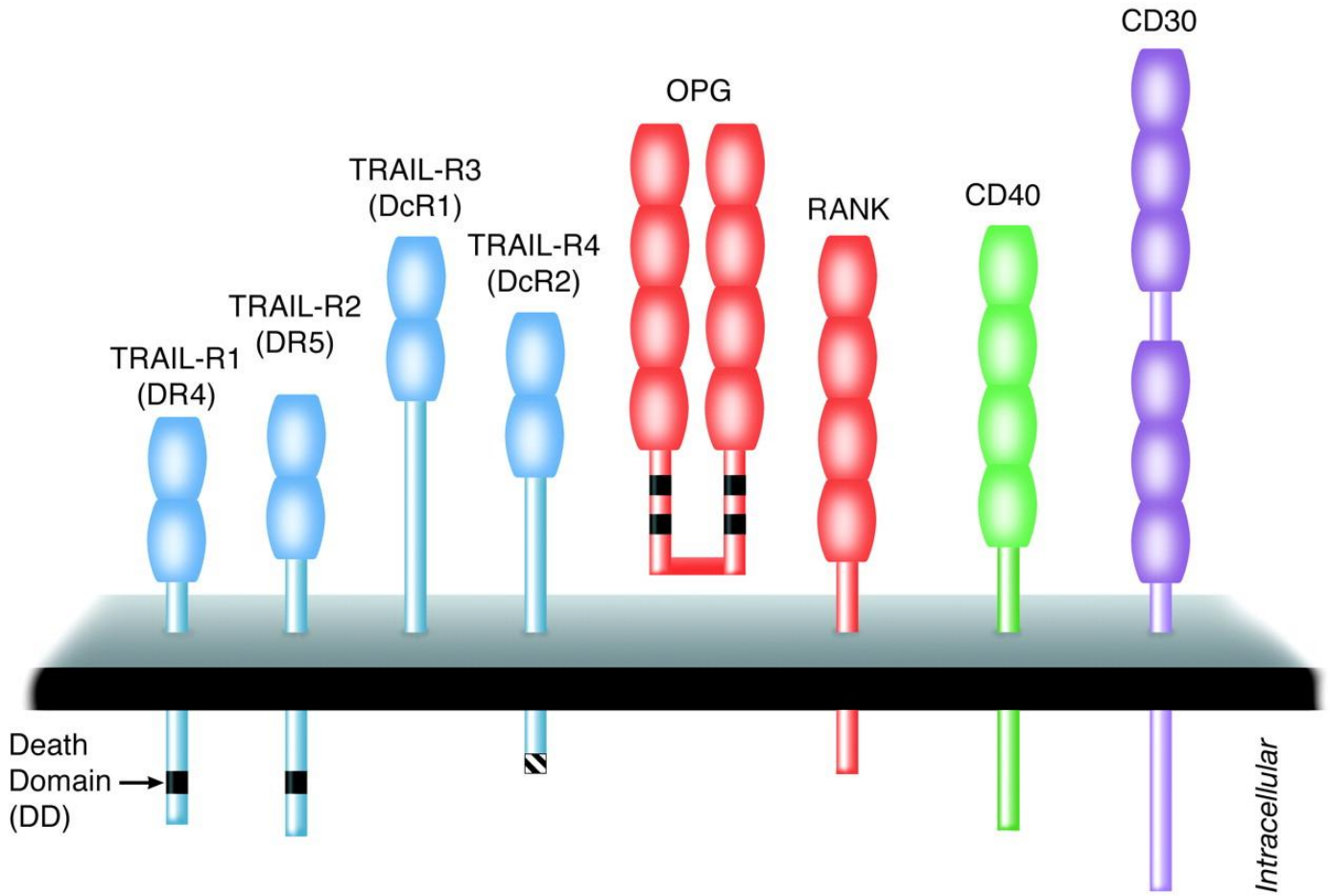
Greg Hapgood, and Kerry J. Savage Blood 2015;126:17-25

1992 (Cell): Durkop and Stein:

Molecular cloning of CD30 = TNF receptor family member

1993 (Cell): Smith et al:

Molecular cloning of CD30L = TNF family member



Younes A , Kadin M E JCO 2003;21:3526-3534

Expression Pattern of CD30 and CD30L

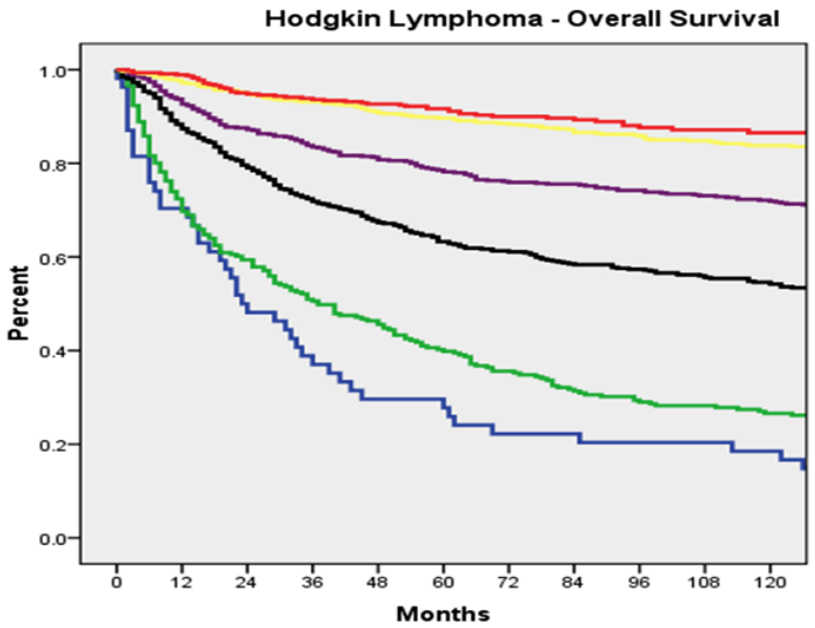
	CD30	CD30L
Gene locus	1p35	9q33
Molecular weight	120 KDa	26 KDa
Soluble form	85 KDa	?
Expression by hematopoitic cells		
Benign	Activated B and T cells Virally infected lymphocytes	Activated T and NK cells Resting B cells
Malignant	HRS cells of HL ALCL subsets of PTCL PMLCL immunoblatc lymphoma	B cell lymphomas
Expression by no-hematopoitic cells	Germ cell tumors Seminoa	

Younes, A: Curr Opin Oncol. 2011 Nov;23(6):587-93

Overall survival rates for patients with Hodgkin lymphoma

Initial Therapy

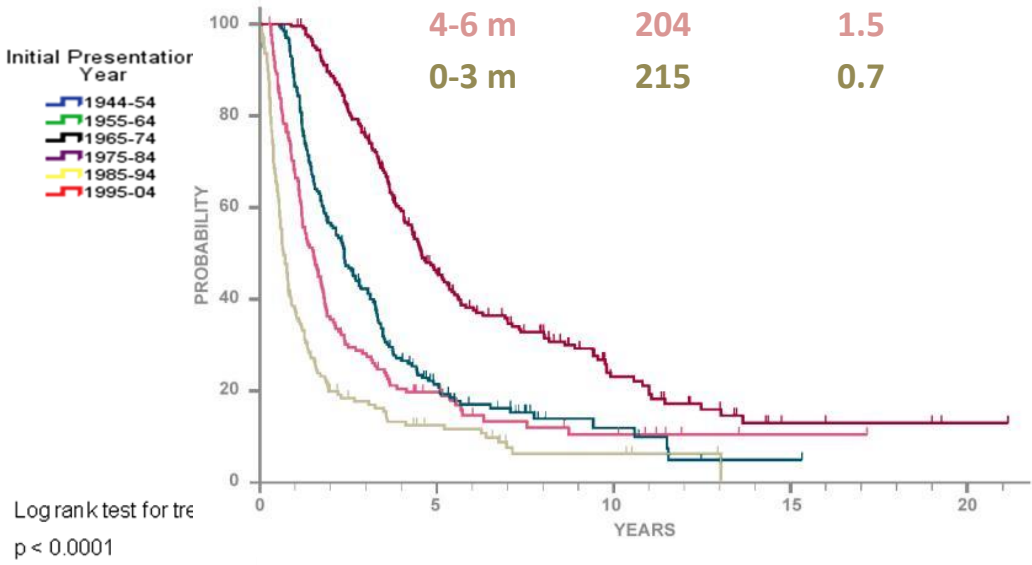
MDACC (1944-2004)
N=2,723



Fanale M and Younes, A et al, 2013

Post ASCT

TTR	N	Median OS (y)
>12 m	172	4.6
6-12 m	165	2.4
4-6 m	204	1.5
0-3 m	215	0.7



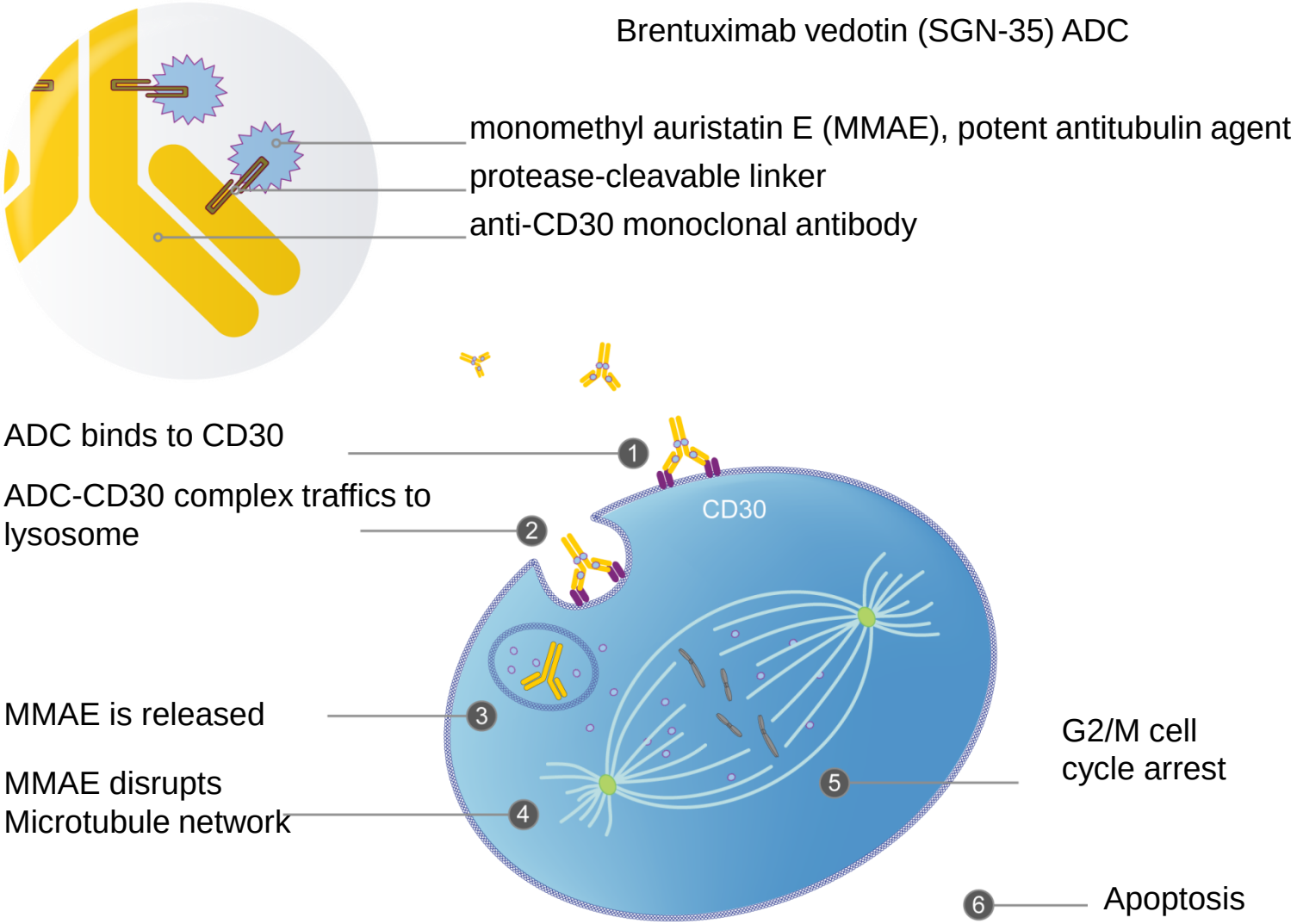
Horning S et al, Ann Oncol 2008:19 (suppl 4):Abstract 118
Arai S et al. Leukaemia and Lymphoma. 2013. In print

Summary results of pahse I/II clinical trials using naked antibodies targeting CD30

Drug	Disease	Antibody type	Phase	Number of evaluable patients	PR	CR	%PR + CR
MDX-060	HL, ALCL	Humanized	I	HL = 63 ALCL = 9	2 2	2 0	6% 22%
SGN-30	HL, ALCL	Chimeric	I	24	0	0	0
SGN-30	HL, ALCL	Chimeric	II	HL = 38 ALCL = 41	0 5	0 2	0 17%
Xmab2513	HL	Humanized	I	13	1	0	7%

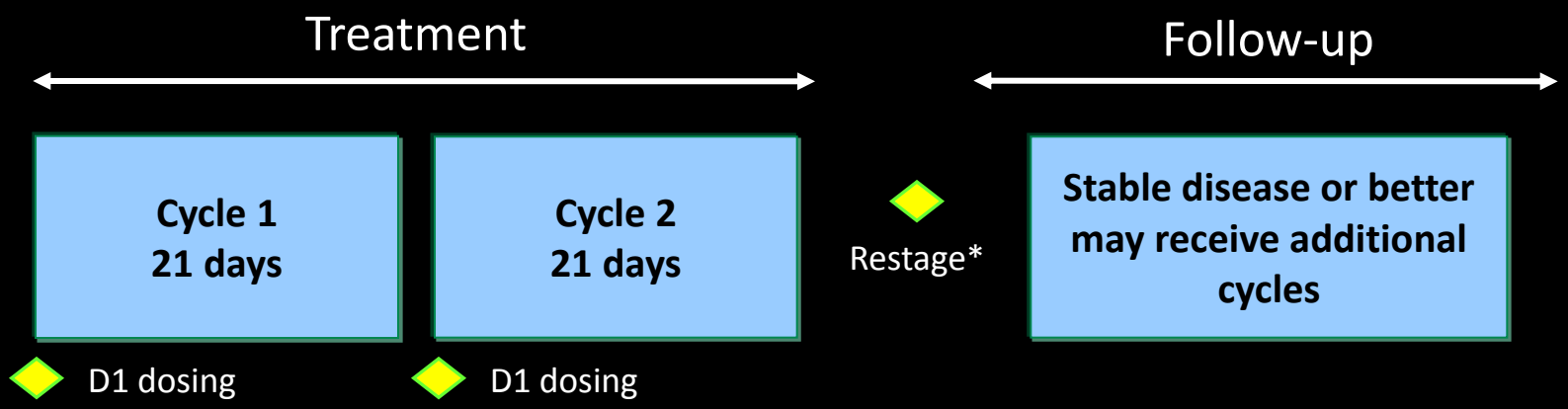
Younes, A: Curr Opin Oncol. 2011

Brentuximab vedotin: mechanism of action



Younes A et al. N Engl J Med 2010; 363:1812-21 (appendix)

Phase I Study of Brentuximab Vedotin (SGN-35) in Relapsed HL and ALCL



- 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

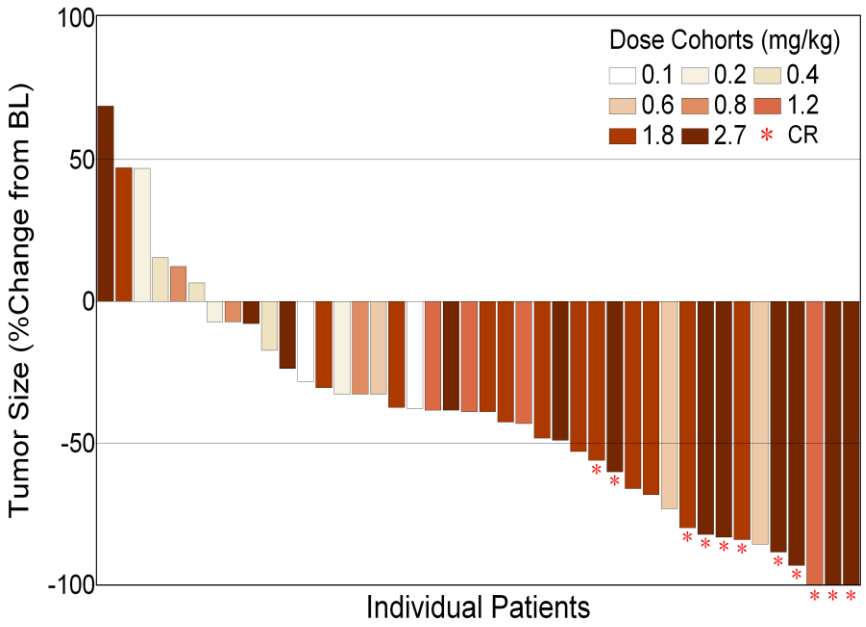
* CT and PET scans were retrospectively reviewed by an independent review facility (IRF)

Younes A, et al. N Engl J Med 2010; 363:1812-1821

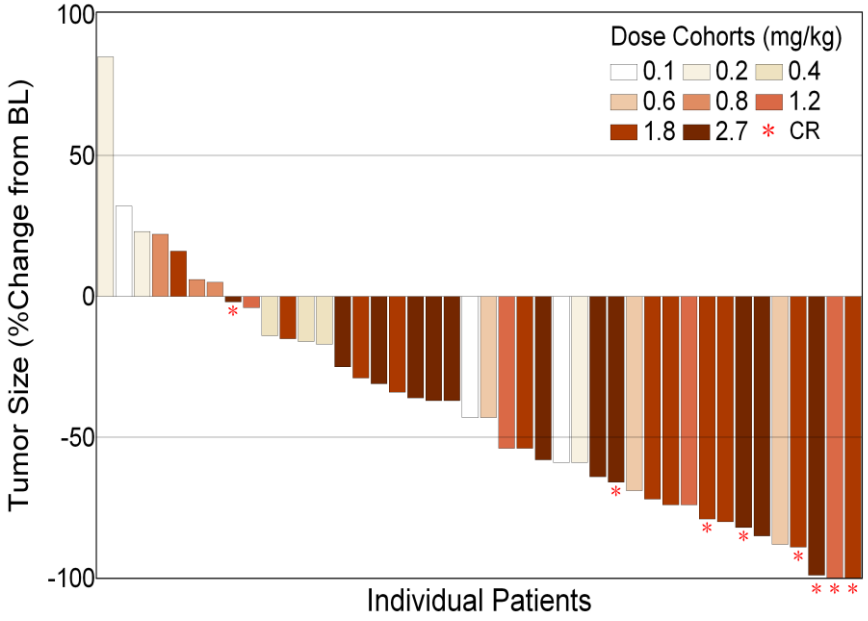
Phase-I brentuximab vedotin in relapsed CD30+ HL and ALCL

Treatment Response

Investigator Assessment



IRF Assessment



Younes A, et al. N Engl J Med 2010; 363:1812-1821

Brentuximab vedotin: Phase I trial

- Phase I dose-escalation study in patients with relapsed or refractory CD30+ lymphoma: best clinical response in 45 patients
- Objective response rate (ORR) (CR+PR) = 38%; CR = 24%; SD = 43%; ORR in patients receiving maximum tolerated dose 1.8 mg/kg = 50%

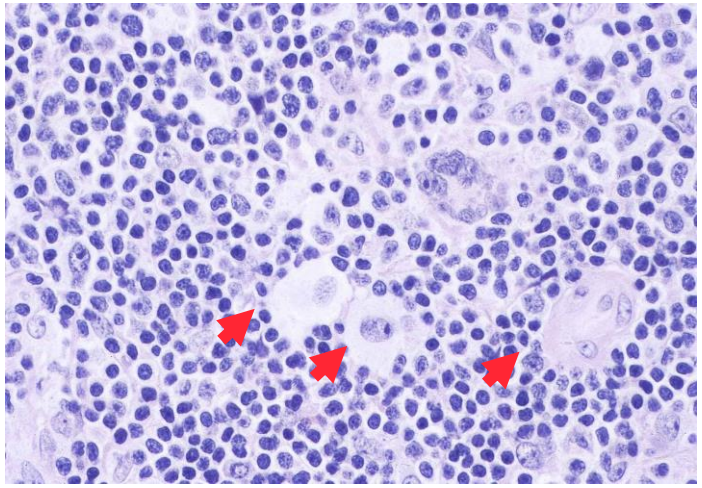
	Dose (mg/kg)								
Response	0.1 (n=3)	0.2 (n=4)	0.4 (n=3)	0.6 (n=3)	0.8 (n=3)	1.2 (n=4)	1.8 (n=12)	2.7 (n=12)	3.6 (n=1)
Complete response (CR)	0	0	0	0	0	1	4	6	0
Partial response (PR)	0	0	0	2	0	1	2	1	0
Stable disease (SD)	2	0	2	1	2	2	5	5	0
Progressive disease (PD)	1	4	1	0	1	0	1	0	0
Could not be evaluated	0	0	0	0	0	0	0	0	1

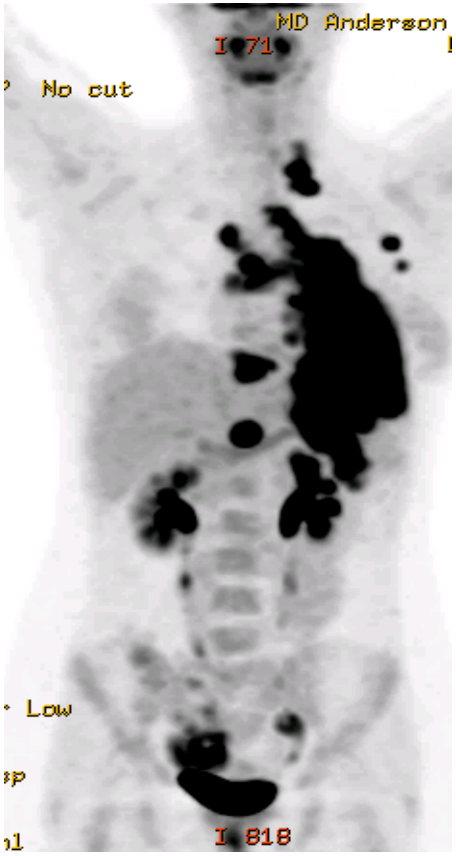
- Tumour regression in 86%, with tumour-related symptoms resolved in 81% of patients
- Median duration of objective response at least 9.7 months

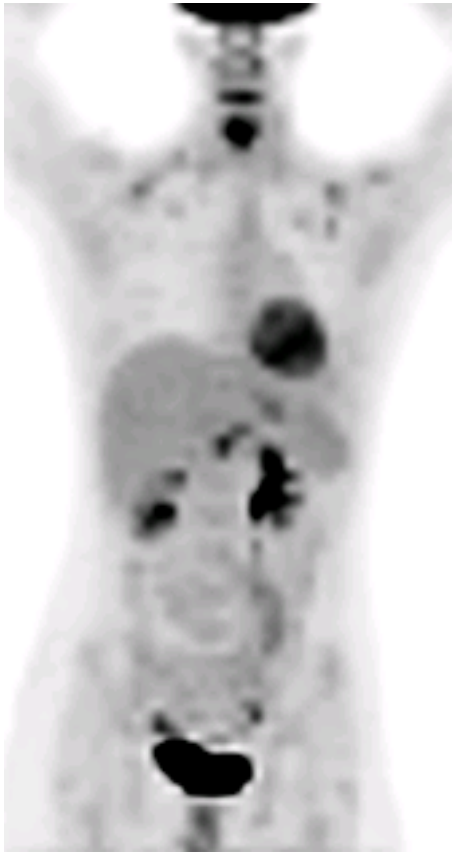
Younes A *et al*. N Engl J Med 2010;363:1812–1821.

Phase I Brentuximab Vedotin in Relapsed HL

- 21-year-old female
- HL diagnosed 2003
  - ABVD + XRT to mediastinum
  - ICE
  - BEAM→ASCT
  - HDAC-inhibitor
- SGN-35 2.7 mg/kg x 8 cycles
  - Best clinical response: CR
  - CT 93% reduction, PET-
  - PET negative

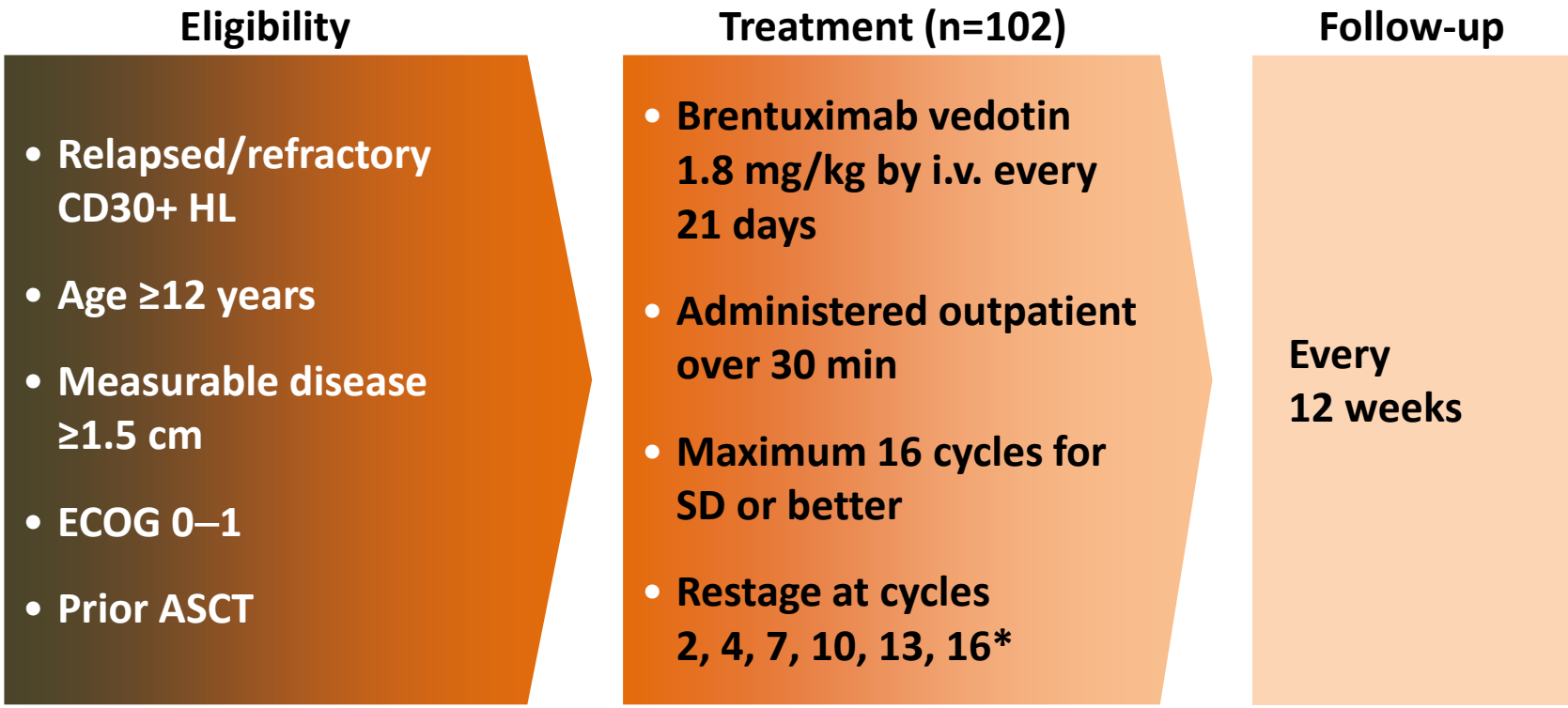






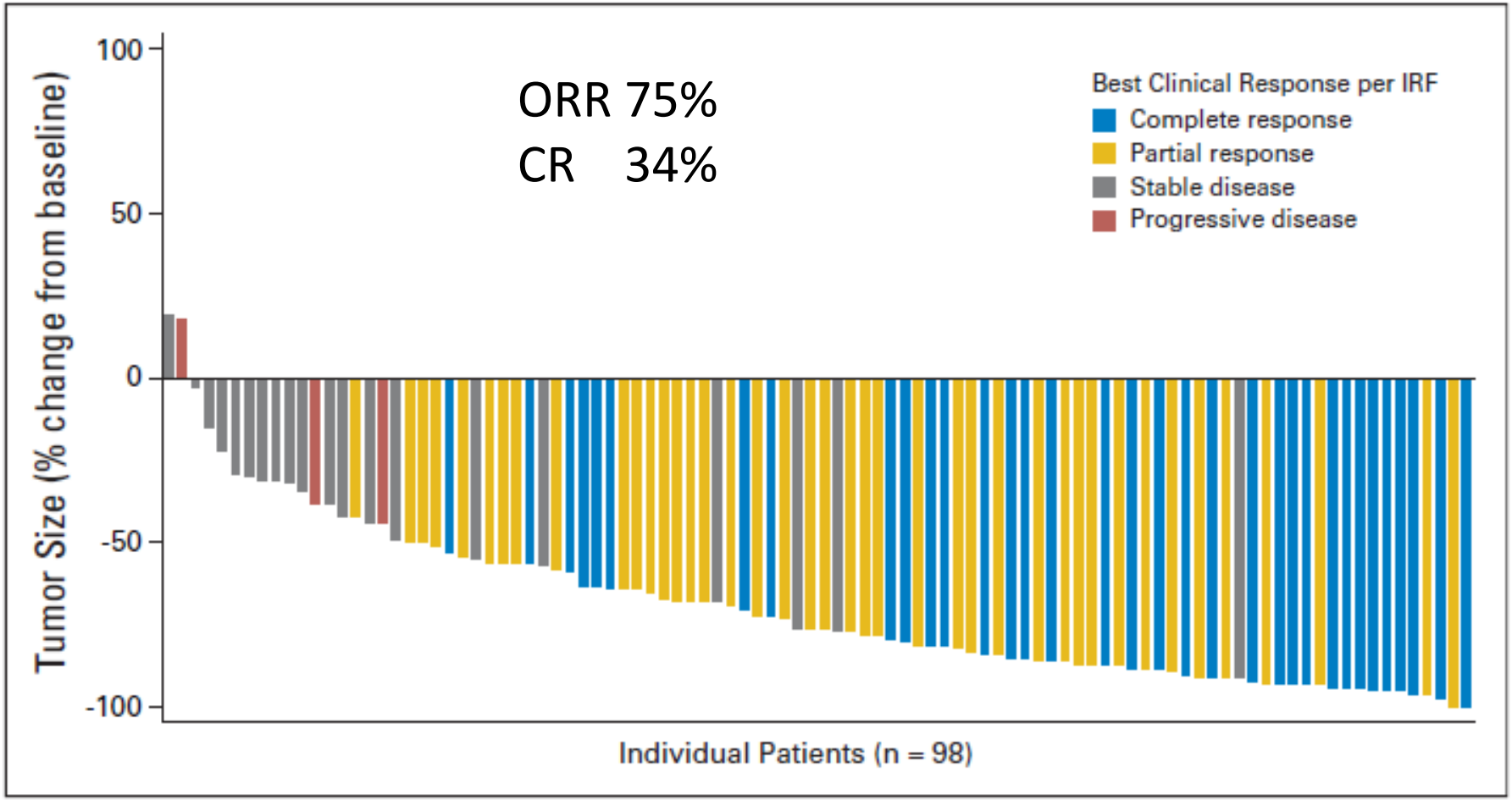
Brentuximab vedotin: pivotal Phase II trial

- 102 patients with relapsed/refractory HL post-autologous stem cell transplantation (ASCT)



Younes A et al. J Clin Oncol 2012;30: 2183-9.

Phase II pivotal study of brentuximab vedotin in relapsed HL post ASCT



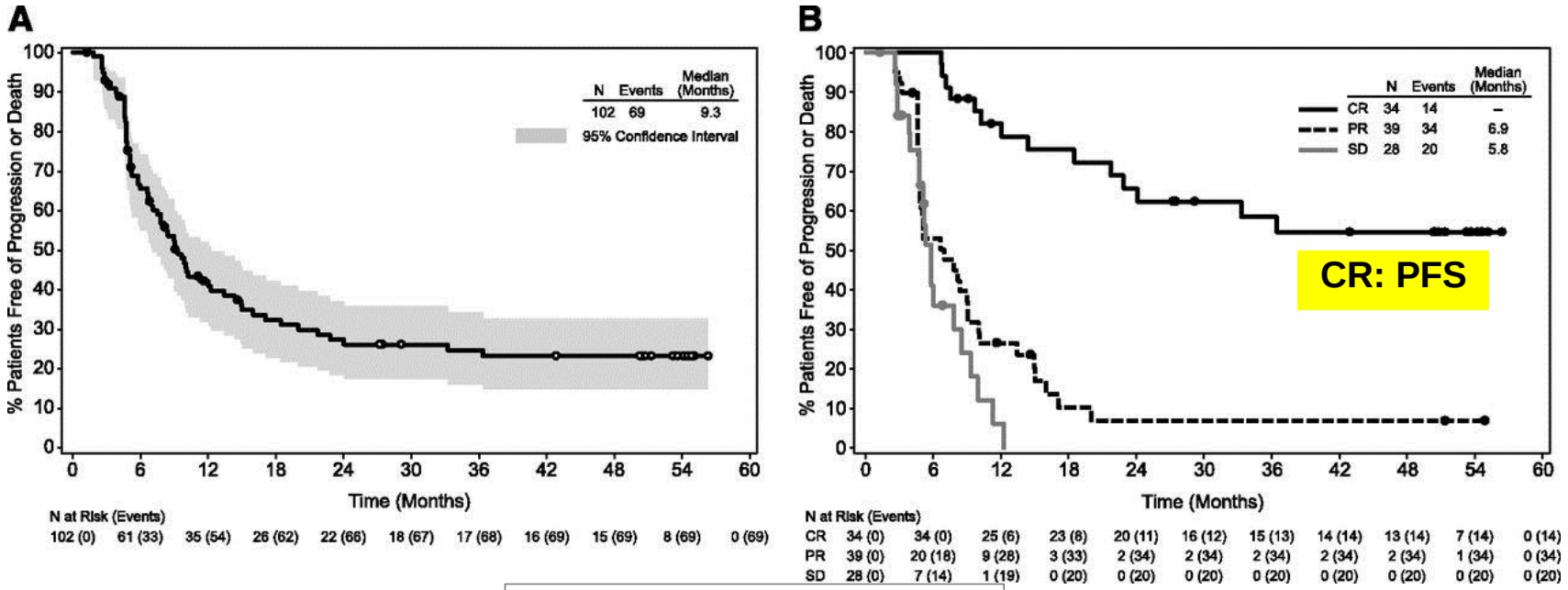
94% patients achieved tumour reduction

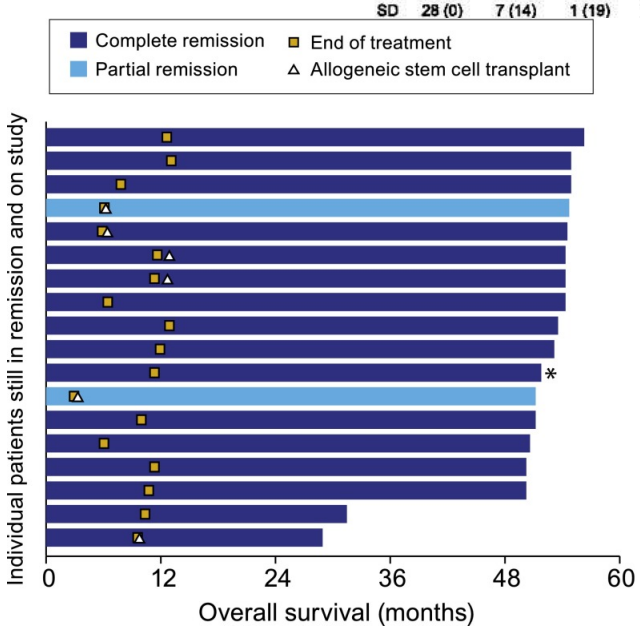
IRF – independent review facility

Younes A et al. J Clin Oncol 2012;30: 2183-9.

brentuximab vedotin in relapsed or refractory HL

Long Term Follow-Up



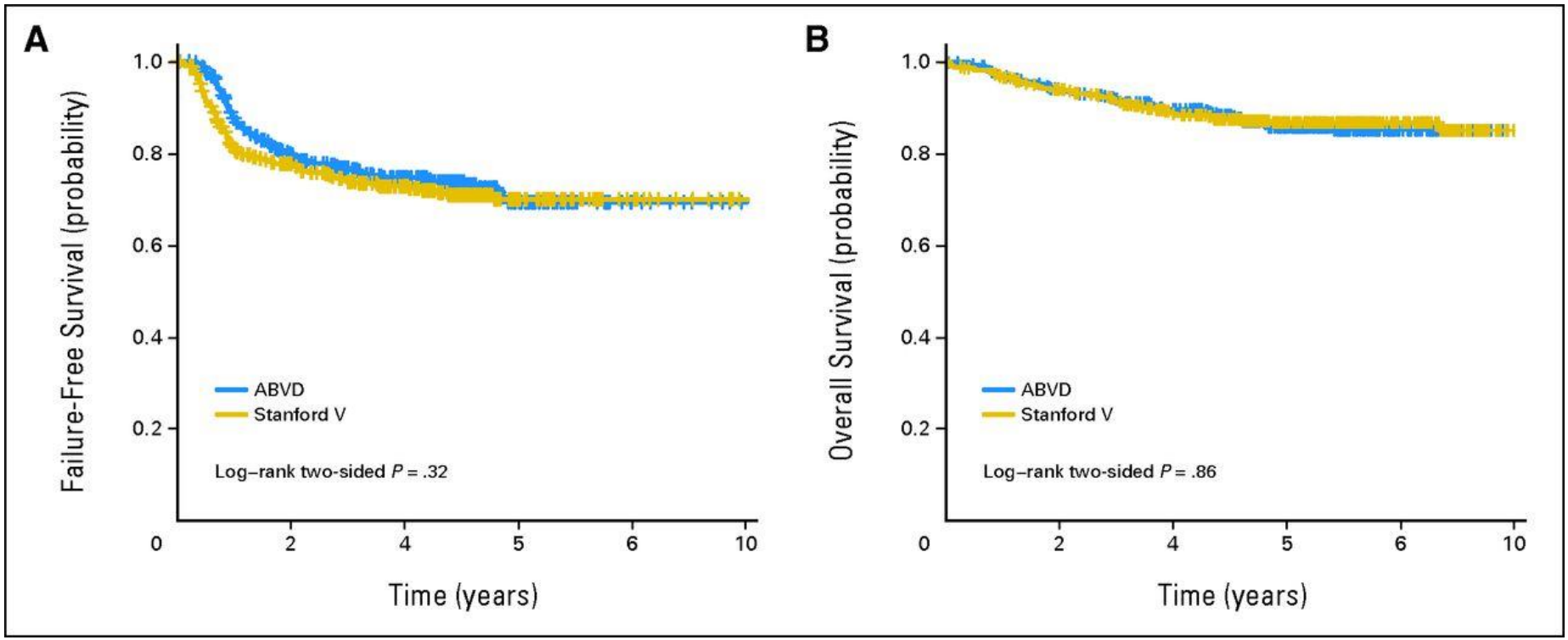


4/16 in CR had Allo SCT

Ajay K. Gopal et al. Blood 2015;125:1236-1243

ABVD vs. Stanford V

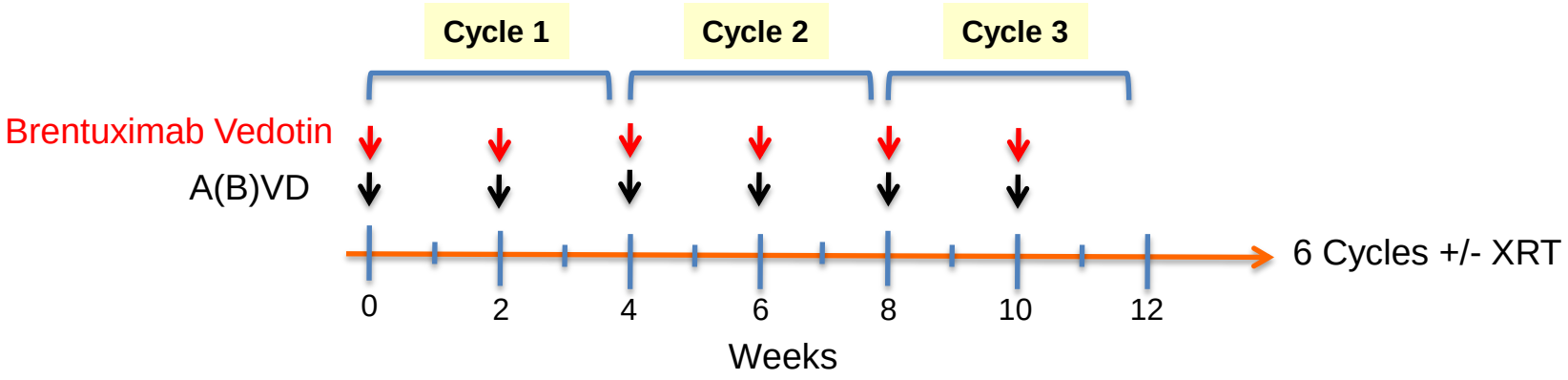
FFS **OS**



Gordon L I et al. JCO 2013;31:684-691

Phase 1 ABVD/AVD + brentuximab vedotin

Stage IIa bulky, IIB, III-IV



Younes A, Ansell S, et al, Lancet Oncology 2013

ABVD or AVD + Brentuximab Vedotin

Brentuximab vedotin + ABVD
N=25 total

- Cohort 1 (0.6 mg/kg) N=6
- Cohort 2 (0.9 mg/kg) N=13
- Cohort 3 (1.2 mg/kg) N=6

Brentuximab vedotin + AVD
N=26 total

- Cohort 4 (1.2 mg/kg) N=6
- Expansion cohort (1.2 mg/kg) N=20

- Dose-limiting toxicities were defined as any Cycle 1 toxicity requiring ≥7-day delay in ABVD or AVD
- Study has completed enrollment
- All patients in the AVD expansion cohort are currently receiving treatment

Brentuximab Vedotin + ABVD or AVD

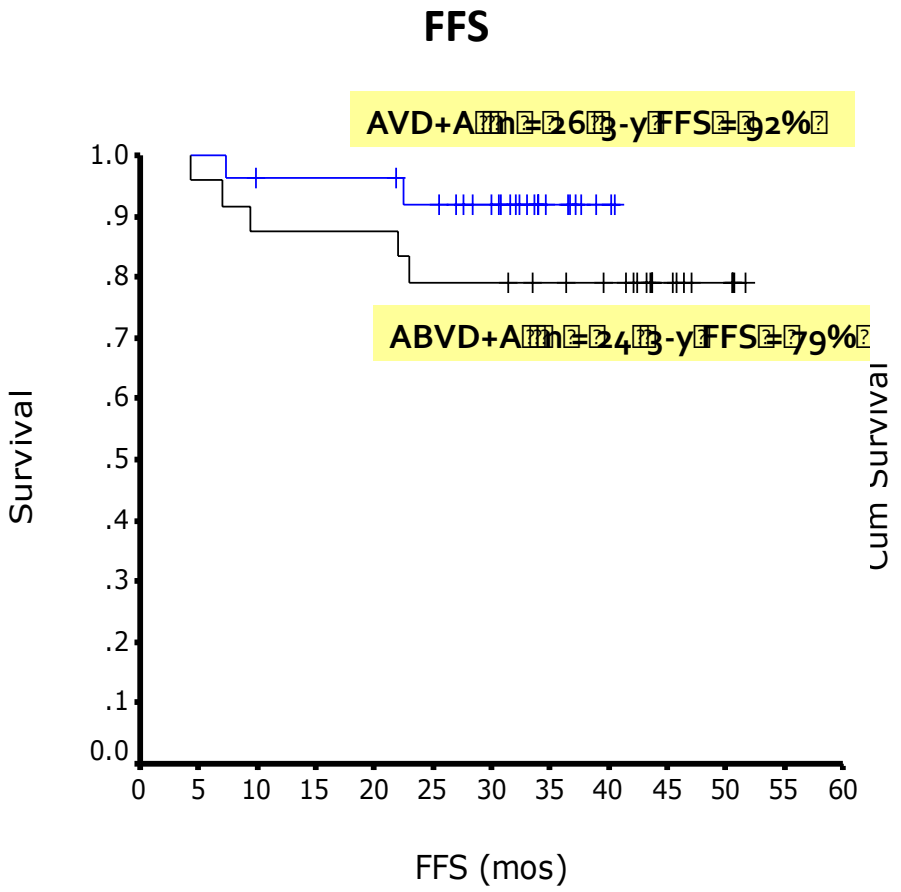
Pulmonary Toxicity and Efficacy

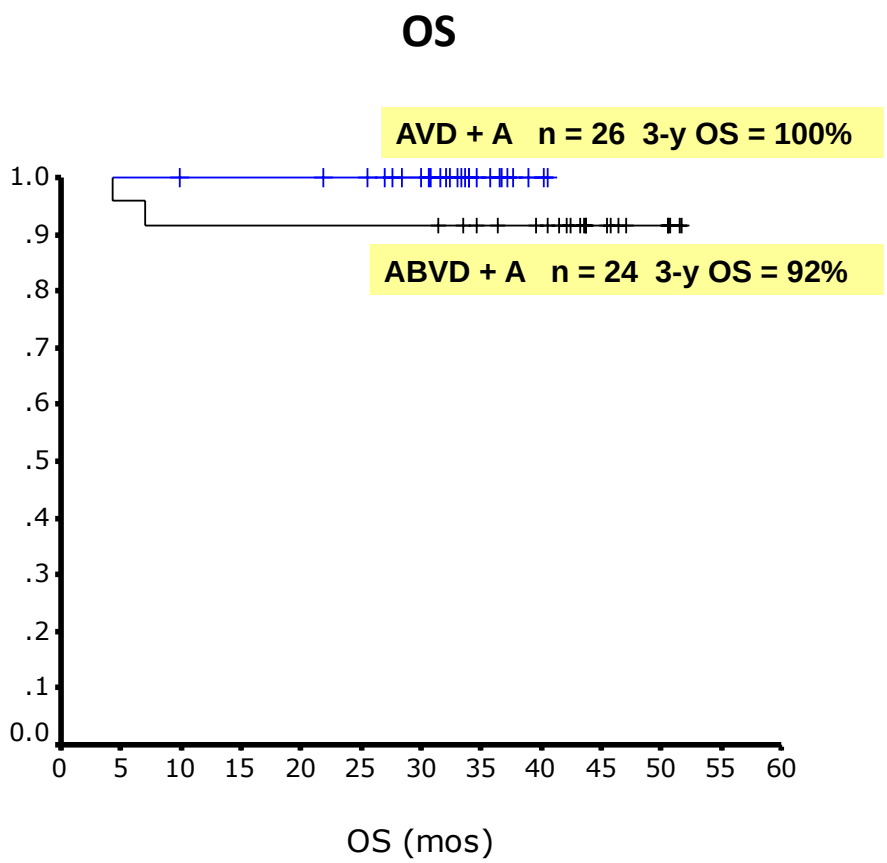
	ABVD with brentuximab vedotin N=25	AVD with brentuximab vedotin N=26
Any event	11 (44)	0
Pulmonary toxicity	9 (36)	0
Interstitial lung disease	1 (4)	0
Pneumonitis	1 (4)	0
PET2 negative results	100%	92%
% CR at end of therapy	95%	96%

Younes A, Ansell S, et al, Lancet Oncology 2013

Phase-I Brentuximab vedotin + AVD Advanced stage HL

3-Year follow up

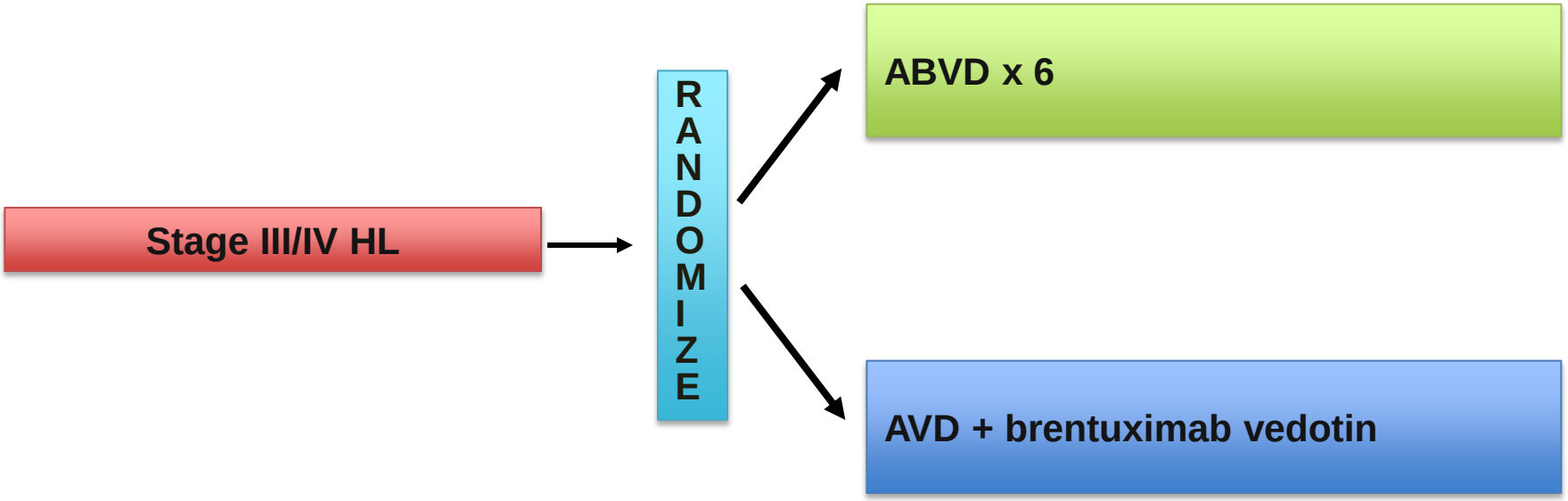




Connors J et al , ASH 2014

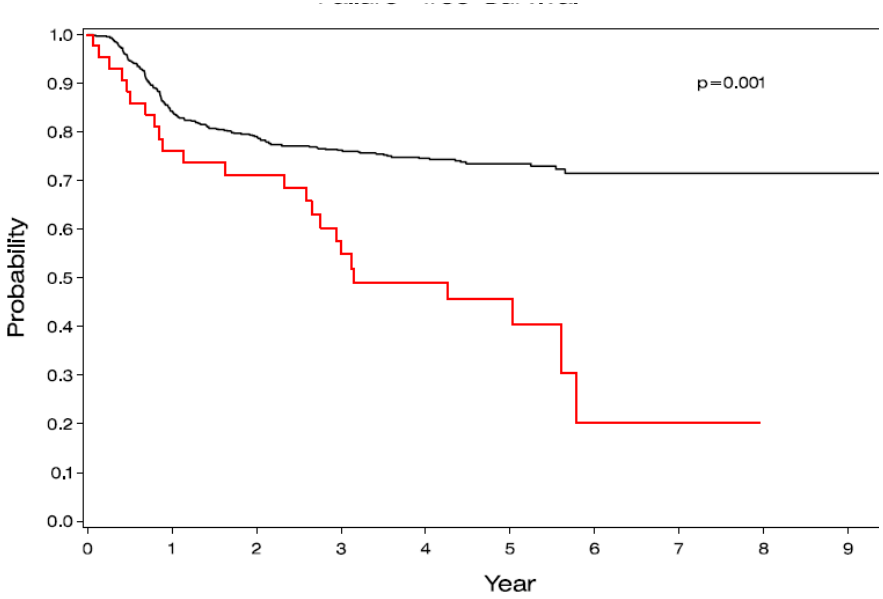
Randomized study in newly diagnosed advanced stage HL

Echelon-1

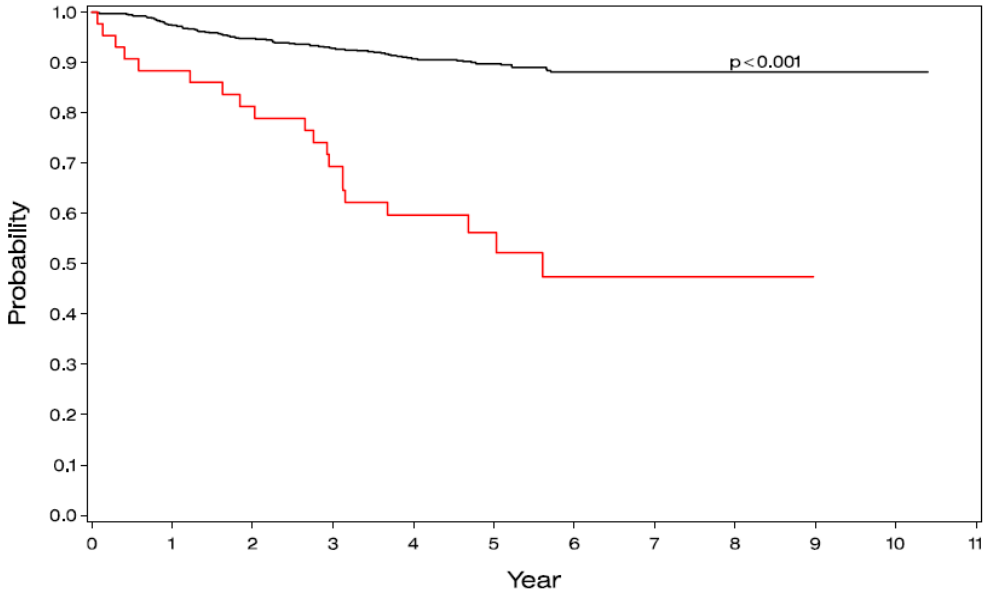


E2496 Advanced Stage HL (ABVD/Stanford V)

Failure-free survival



Overall survival



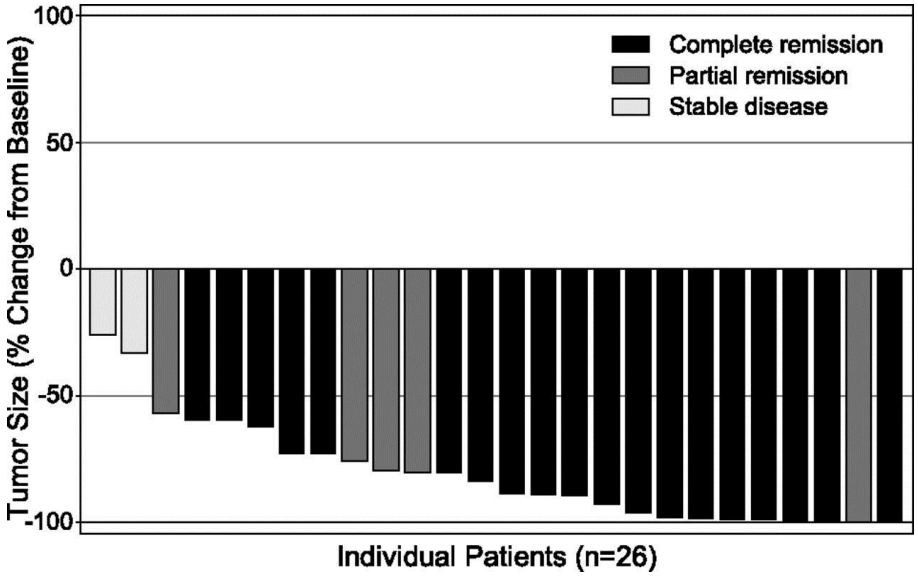
		< 60 years	=/> 60 years	P
FFS	3-year	76%	56%	0.002
	5-year	74%	48%	
OS	3-year	93%	70%	<0.0001
	5-year	90%	58%	

Evens AM et al. Brit J Haem 2013

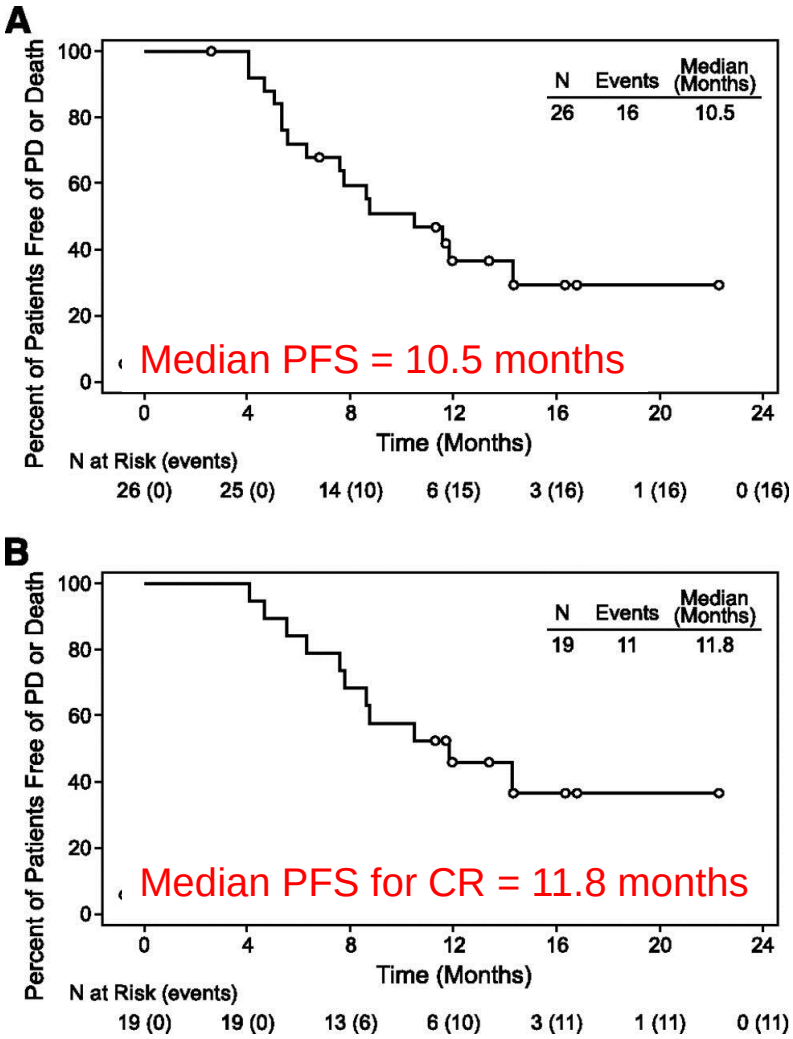
Frontline brentuximab vedotin monotherapy in Hodgkin lymphoma patients aged 60 years and older

ORR = 92% (CR= 73%, PR= 19%)

Patients Characteristics (N=26)	
Median age (yrs), Range	78 (64-92)
Stage 3-4	63%
Bulky disease	22%
Not candidate for combination chemo	52%



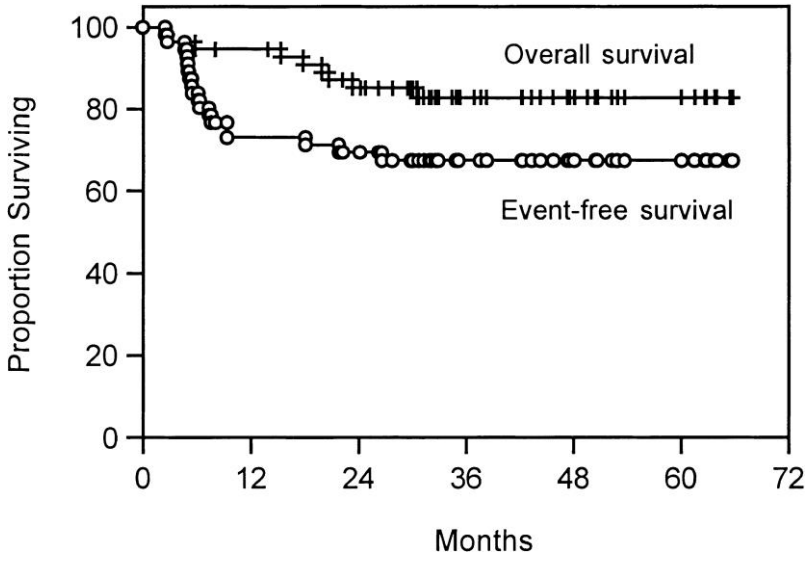
Patients received a median of 8 cycles of brentuximab vedotin (range, 3 to 23 months), with 4 patients completing 16 cycles and 1 patient completing 23 cycles.



Andres Forero-Torres et al. Blood 2015;126:2798-2804

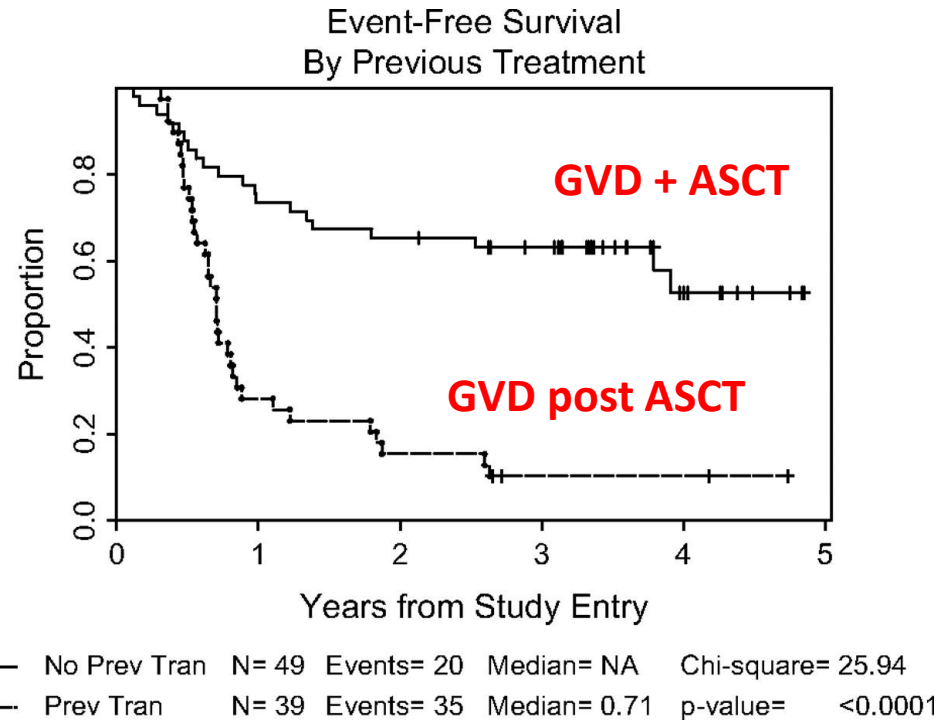
ASCT for relapsed / refractory HL

ICE + ASCT



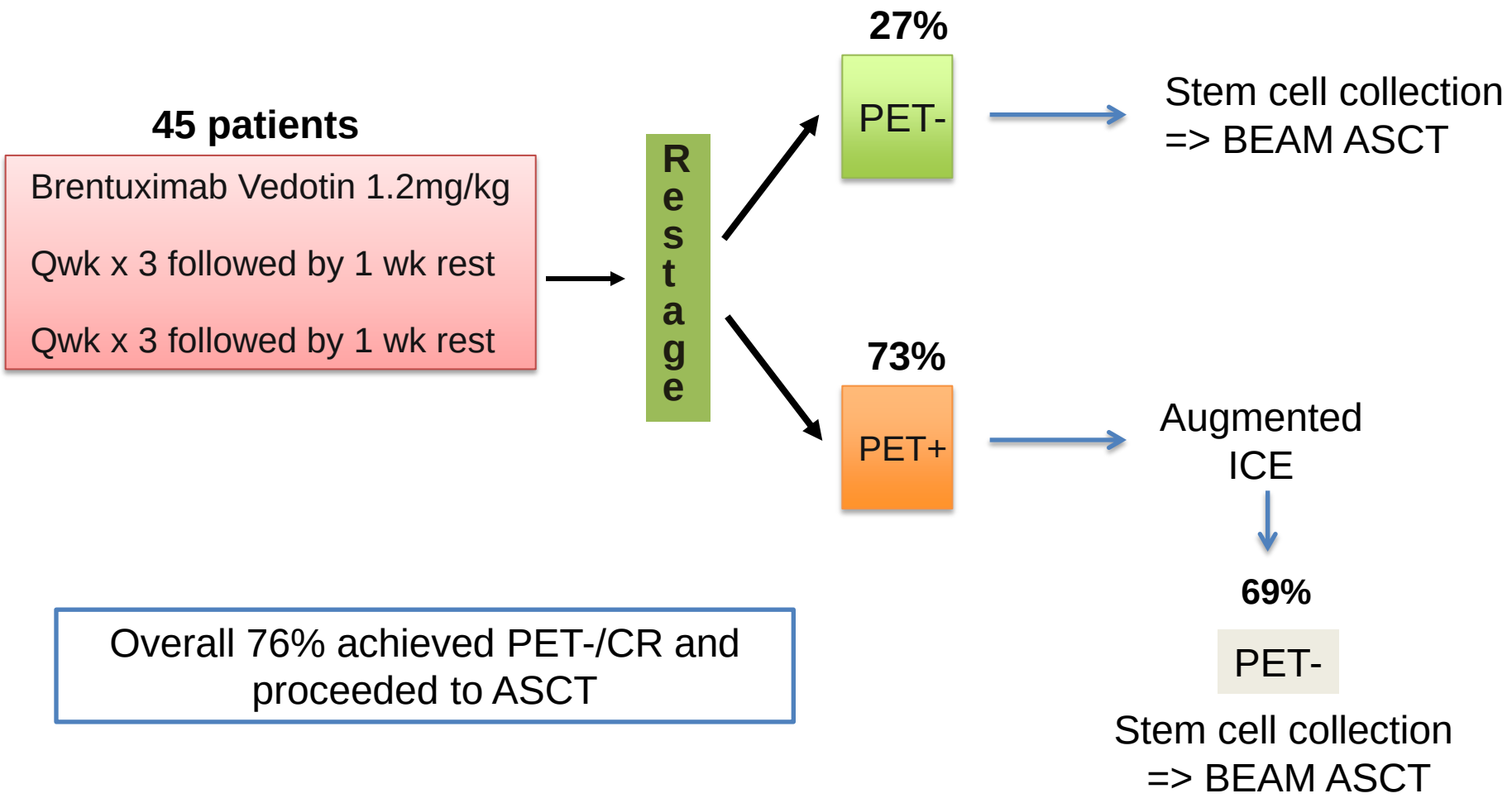
Moskowitz C H et al. Blood 2001;97:616-623

GVD + ASCT



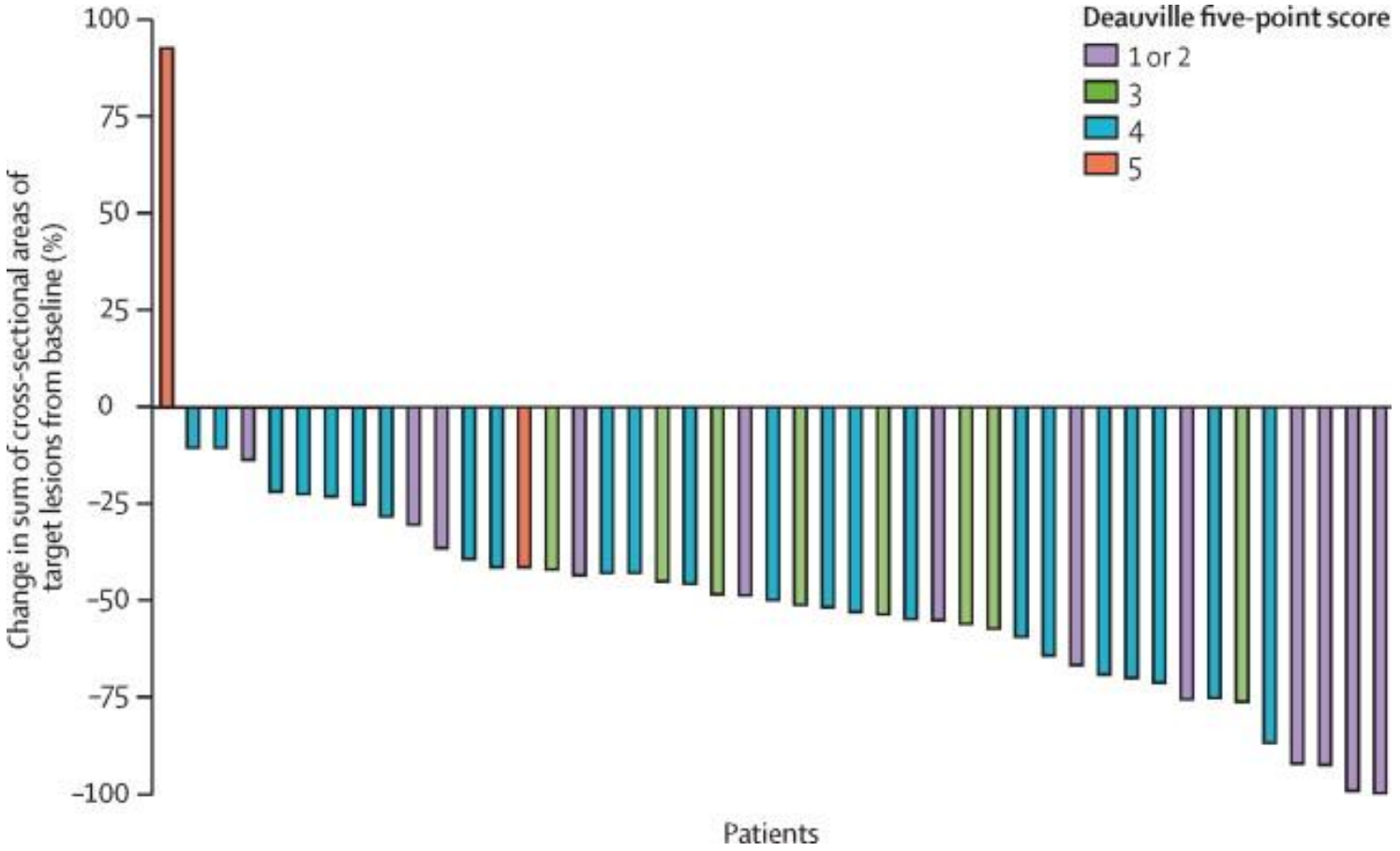
Bartlett N et al. Ann Oncol 2007;18:1071-1079

Response adapted salvage therapy for transplant eligible HL



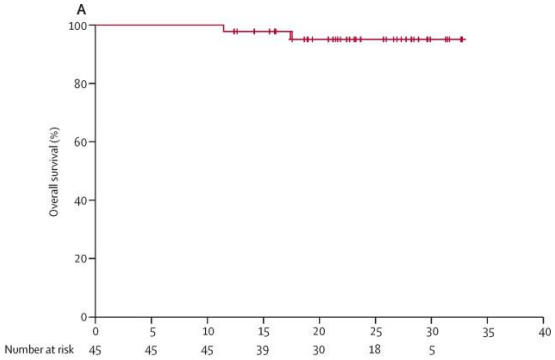
Alison J Moskowitz , et al The Lancet Oncology, , 2015, 284 - 292

Tumour reduction after brentuximab vedotin Data shows PET status according to the Deauville scores of 1–5

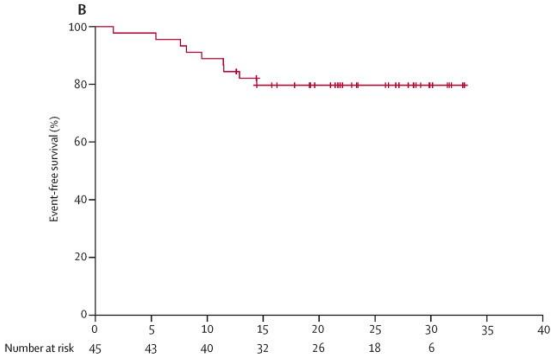


Alison J Moskowitz , et al The Lancet Oncology, , 2015, 284 - 292

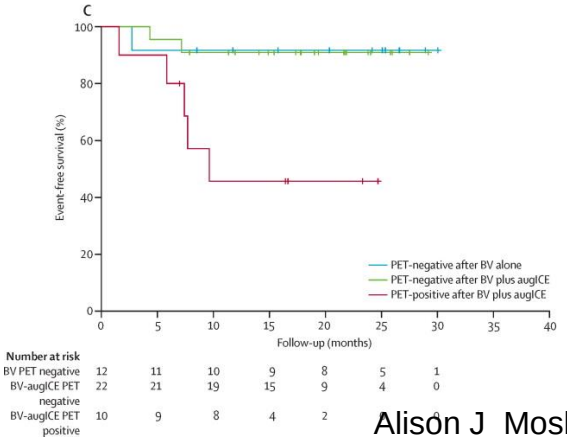
Brentuximab vedotin +/- AugICE for relapsed HL



OS



EFS



EFS by PET and treatment groups

Alison J Moskowitz , et al The Lancet Oncology, , 2015, 284 - 292

Brentuximab Vedotin as Second-Line Therapy before Autologous Transplantation in Relapsed/Refractory Hodgkin Lymphoma

	Best response to BV (N=37)	Response to chemotherapy after BV (ICE/IGEV/GND) (N=18)	Best response at the time of ASCT (n=33)
N	37	18	33
ORR	68%	89%	
CR	35%	61%	73%
PR	32%	28%	27%
SD	27%	6%	3%
PD	5%	6%	

Robert Chen, et al: Biology of Blood and Marrow Transplantation 2015

Brentuximab vedotin in pre-ASCT therapy

	N	% CR	% CR with BV	Reference
ICE	97	60%	N/A	Mockowitz C, BLOOD 2012
BV->ICE	46	73%	27%	Moskowitz A, Lancet Oncol 2015
BV -> chemo	36		35%	Chen R, ASH 2014
BV+Benda	34	82%	N/A	LaCasce A, ASH 2014

Brentuximab Vedotin Plus Bendamustine: A Highly Active Salvage Treatment Regimen for Patients with Relapsed or Refractory Hodgkin Lymphoma

Ann S. LaCasce, MD1, Gregory Bociek2, Ahmed Sawas3, Paolo F. Caimi, MD4, Edward Agura5, Jeffrey Matous6, Stephen Ansell, MD, PhD7, Howland Crosswell, MD8, Miguel Islas-Ohlmayer9*, Caroline Behler10, Eric Cheung11*, Andres Forero-Torres12, Julie Vose2, Owen A. O'Connor, MD, PhD3*, Neil Josephson13 and Ranjana Advani14

Benda + BV x up to 6 → ASCT → BV x 16 doses

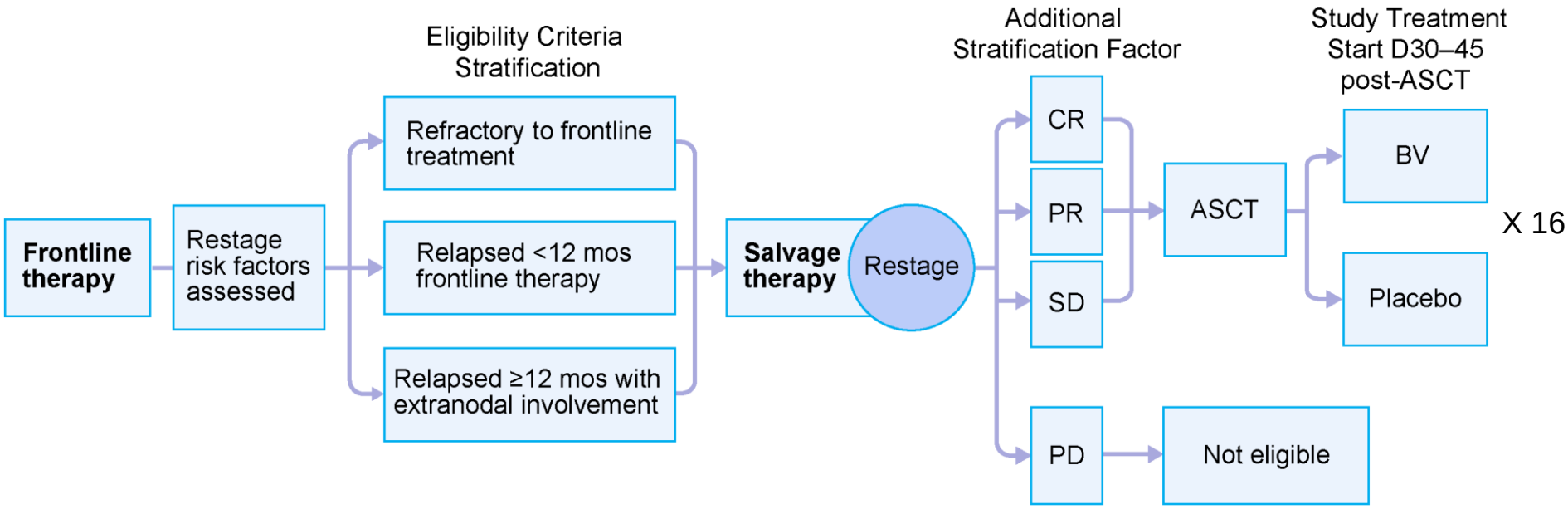
N=55 pts
ORR = 93%
CR = 74%

1-year PFS = 80%

ASH 2015

The AETHERA study

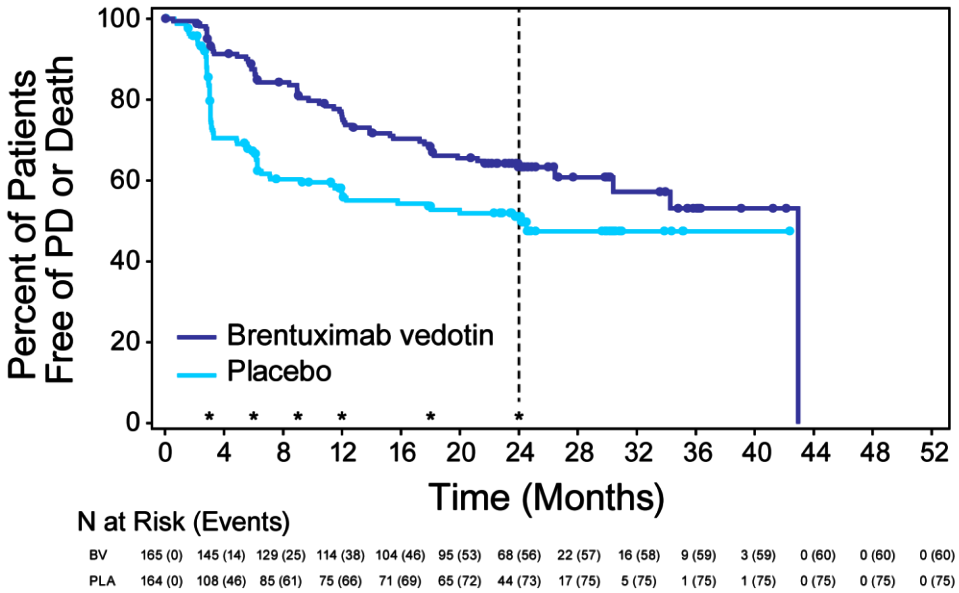
329 patients were randomised at 78 sites in North America and Europe



Moskowitz C, et al The Lancet 2015

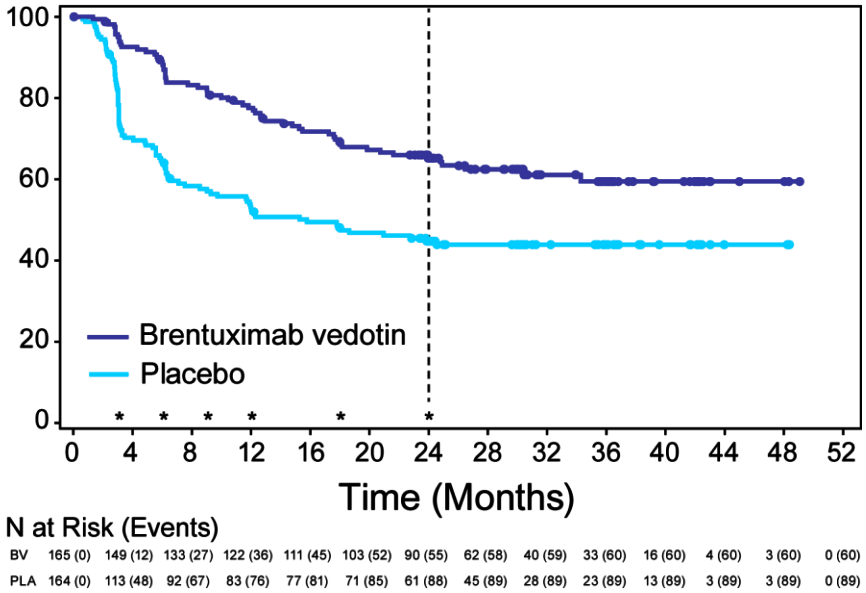
Progression-free survival

PFS per IRF



	BV (N=165)	Placebo (N=164)
Hazard Ratio (95% CI)	**0.57 (0.40–0.81, P=0.001)**	
Events	60	75
Median PFS (months)	43	24
2-year PFS rate	63%	51%

PFS per Investigator†



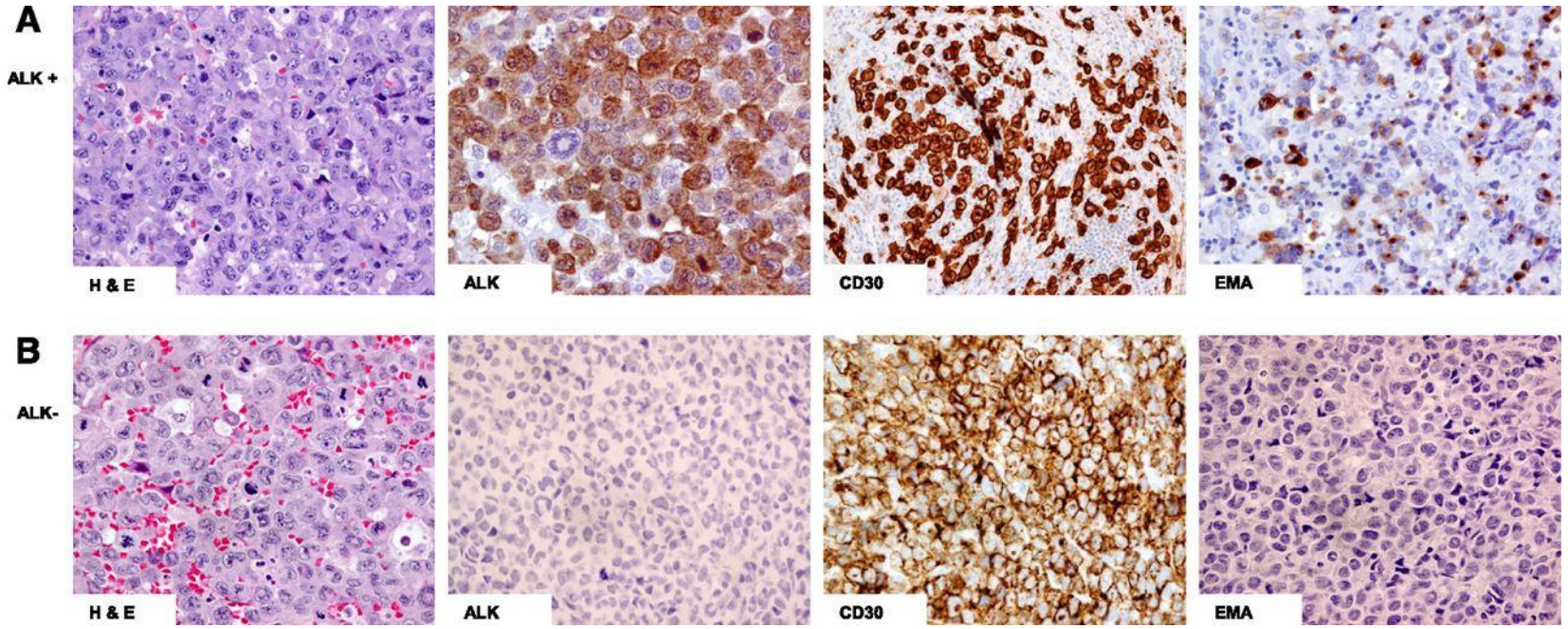
	BV (N=165)	Placebo (N=164)
Hazard Ratio (95% CI)	**0.50 (0.36–0.70)**	
Events	60	89
Median PFS (months)	--	16
2-year PFS rate	65%	45%

* Regularly scheduled CT scans

† Includes information from both radiographic assessments and clinical lymphoma assessments

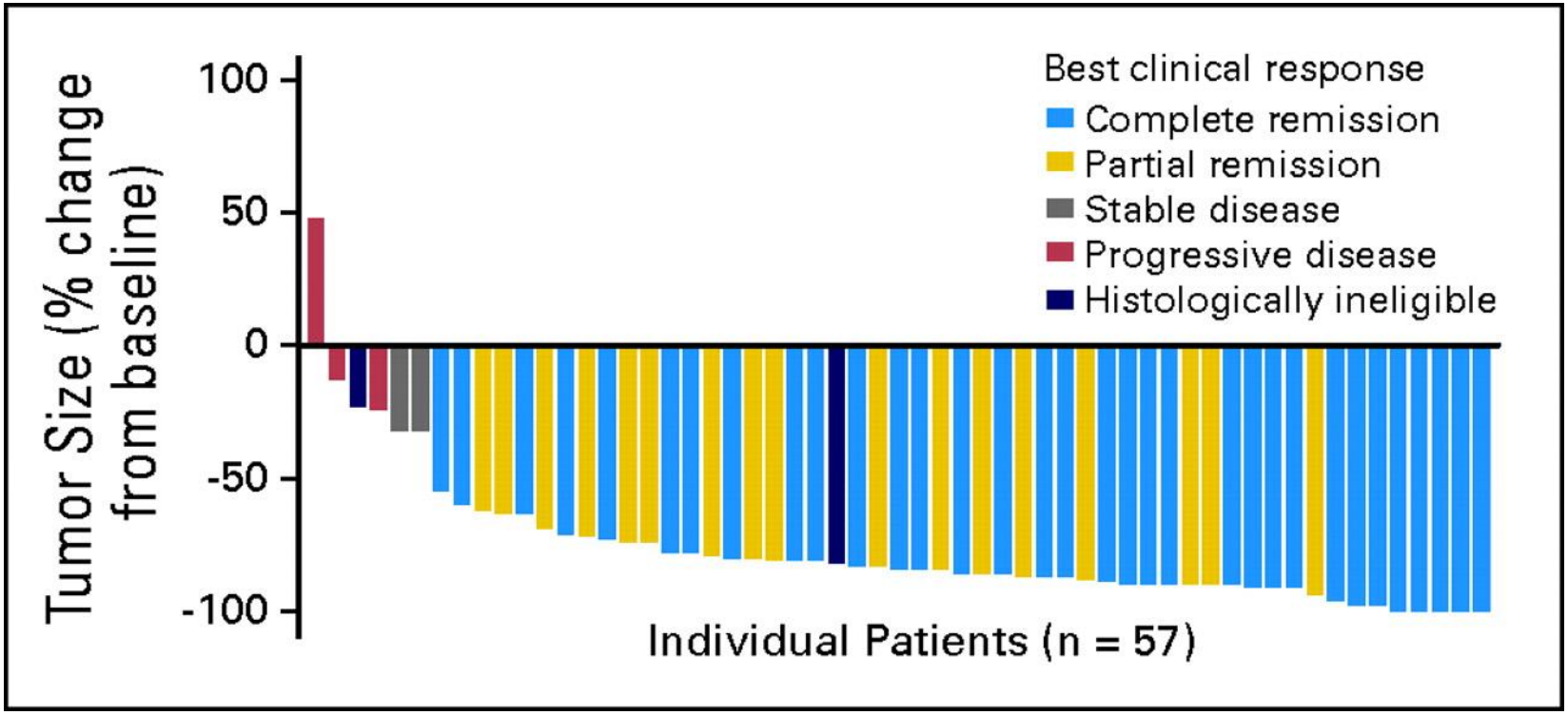
Moskowitz C, et al The Lancet 2015

systemic anaplastic large cell lymphoma



Greg Hapgood, and Kerry J. Savage Blood 2015;126:17-25

Brentuximab Vedotin: Relapsed / Refractory ALCL



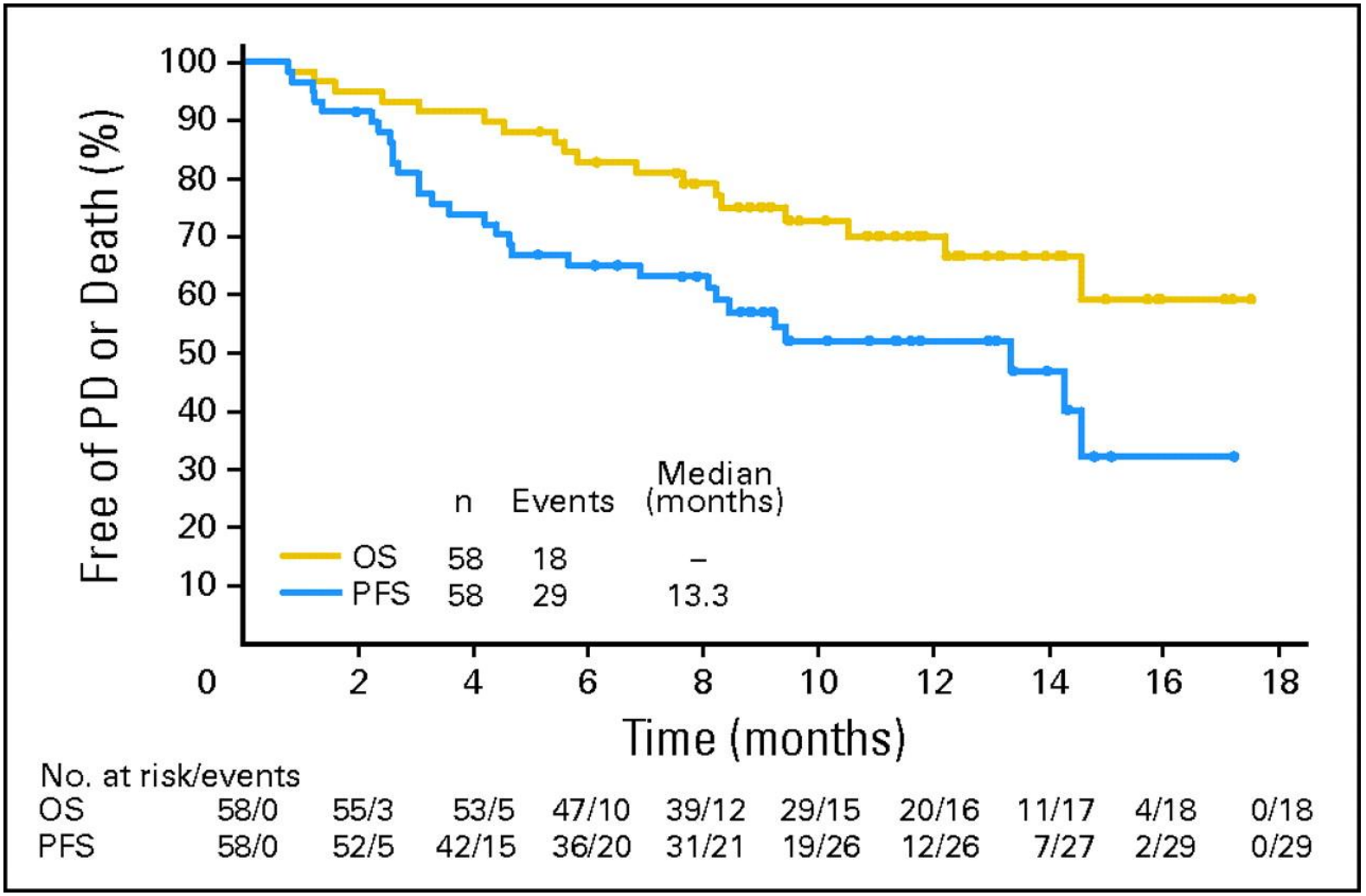
Barbara Pro et al. JCO 2012;30:2190-2196

Brentuximab Vedotin: Relapsed / Refractory ALCL

Response / Outcome	
ORR	86%
CR	59%
Median DOR	13.2 months
Median DOR (for patients who obtained CR)	26.3 months
Median PFS	14.6 months
Median OS	Not yet reached
Median OS (for patients who obtained CR)	7.7 months
Estimated 3-year survival	63%

Pro B, et al. ASH Meeting 2013. Abstract 1809.

Brentuximab Vedotin: Relapsed / Refractory ALCL



Barbara Pro et al. JCO 2012;30:2190-2196

Brentuximab vedotin plus CHOP/CHP for CD30+ PTCL – phase I

Treatment schema	Patients	ORR	CR
Sequential treatment: BV x2 -> CHOPx6 -> BV x8	13 ALCL	85%	62%
Combination treatment BV plus CHP x6 -> BV x 10	19 ALCL 7 non-ALCL	100%	88%

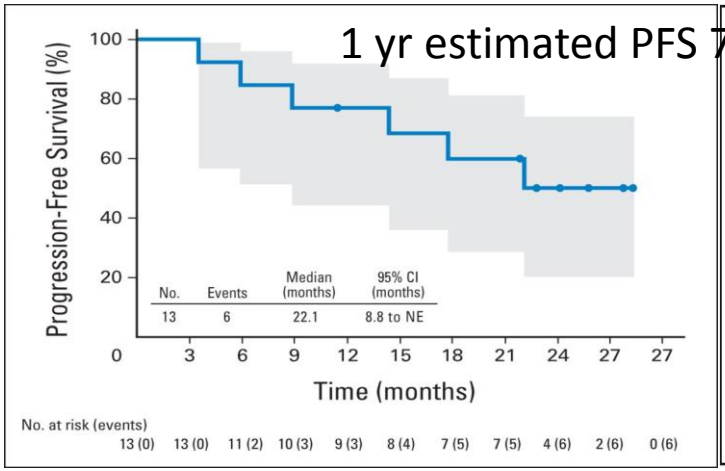
Notable grade ≥3 adverse events in combination arm:

- Febrile neutropenia 31%
- Peripheral sensory neuropathy 8%
- Cardiac failure 8%

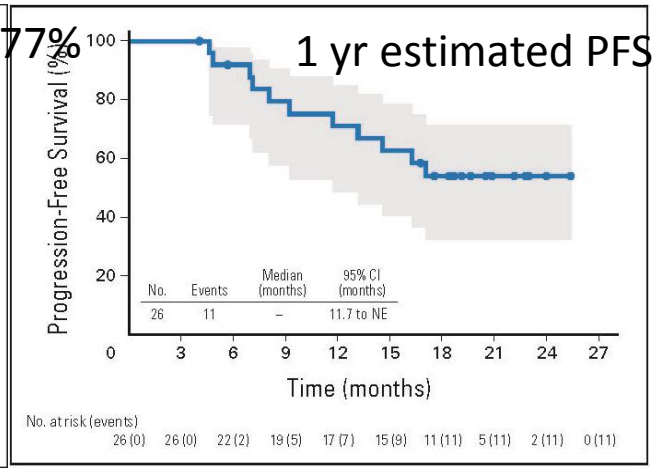
Michelle A. Fanale et al. JCO 2014;32:3137-3143

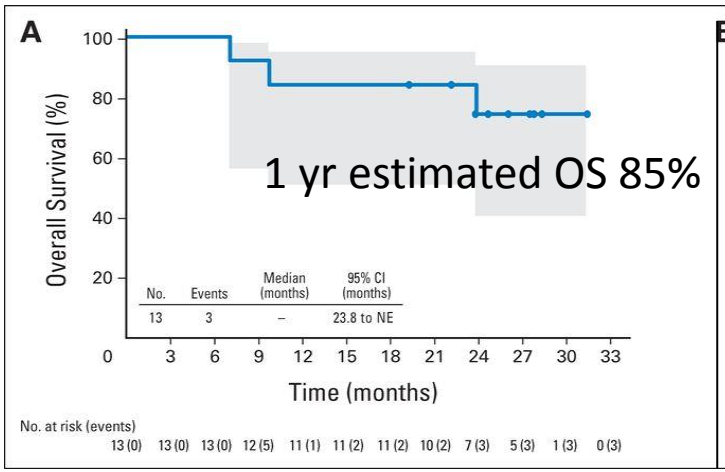
Phase 1 Trial Brentuximab Vedotin + CHP

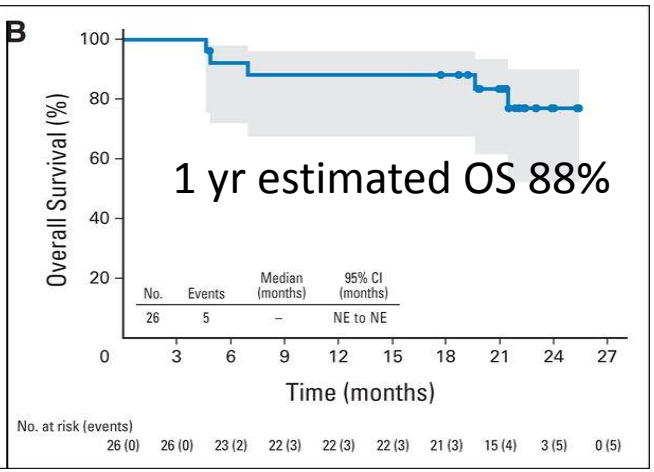
Sequential Treatment (med f/u 23.8 mo)



Combination Treatment (med f/u 21.4 mo)

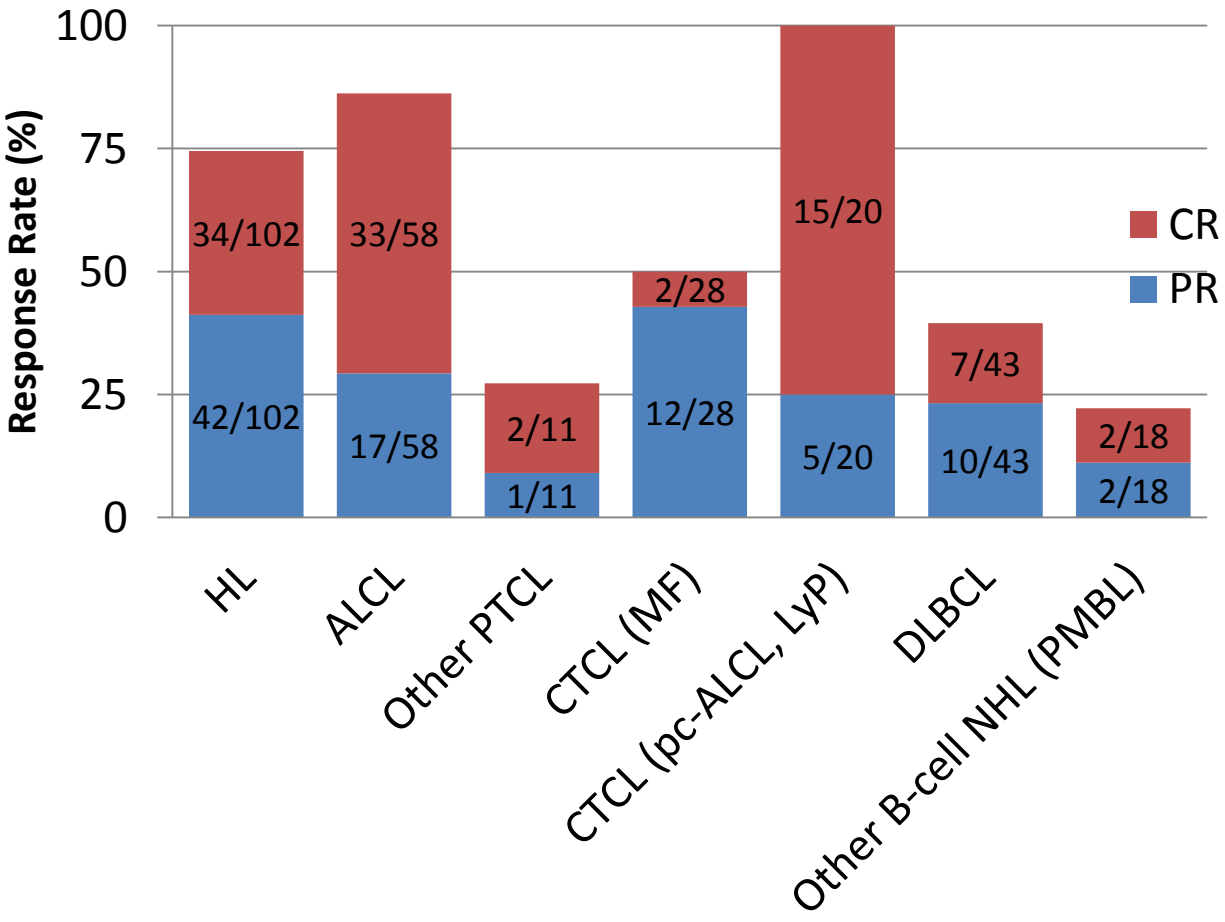




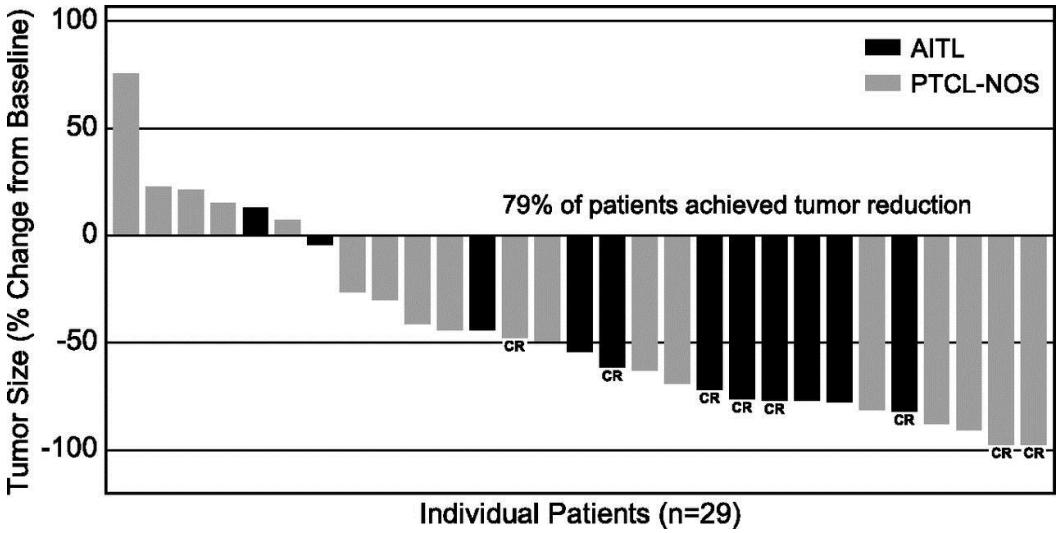


Fanale M A et al. JCO 2014

Activity of Brentuximab Vedotin in Relapsed CD30+ Lymphoma

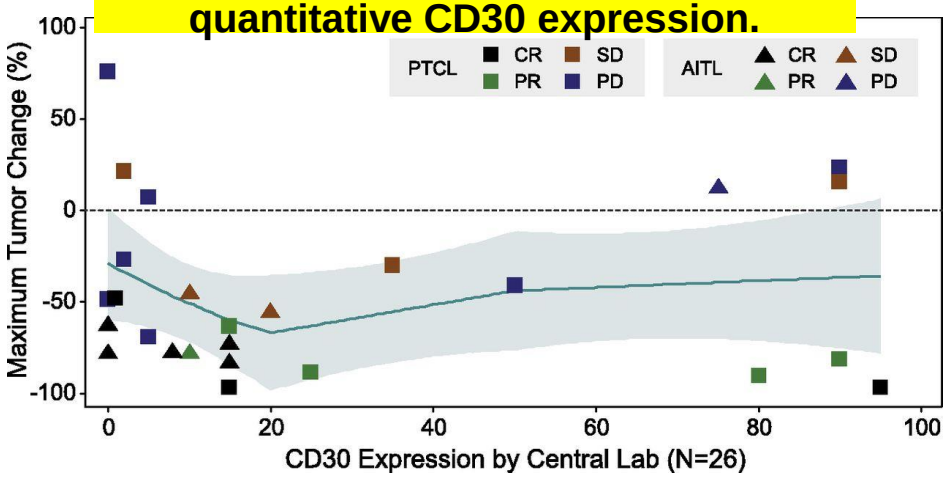


Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin

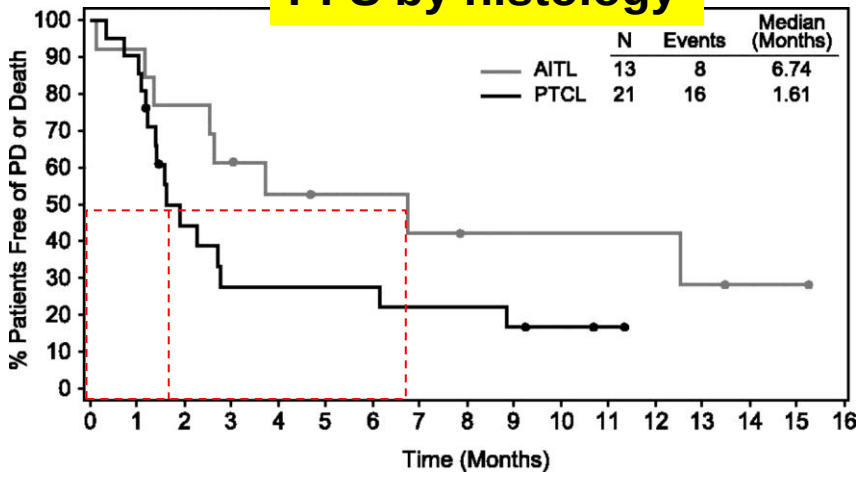


	%ORR	%CR
All (n=34)	41%	23%
AITL (N=13)	54%	38%
PTCL (N=21)	33%	14%

Maximum tumor size decrease by quantitative CD30 expression.

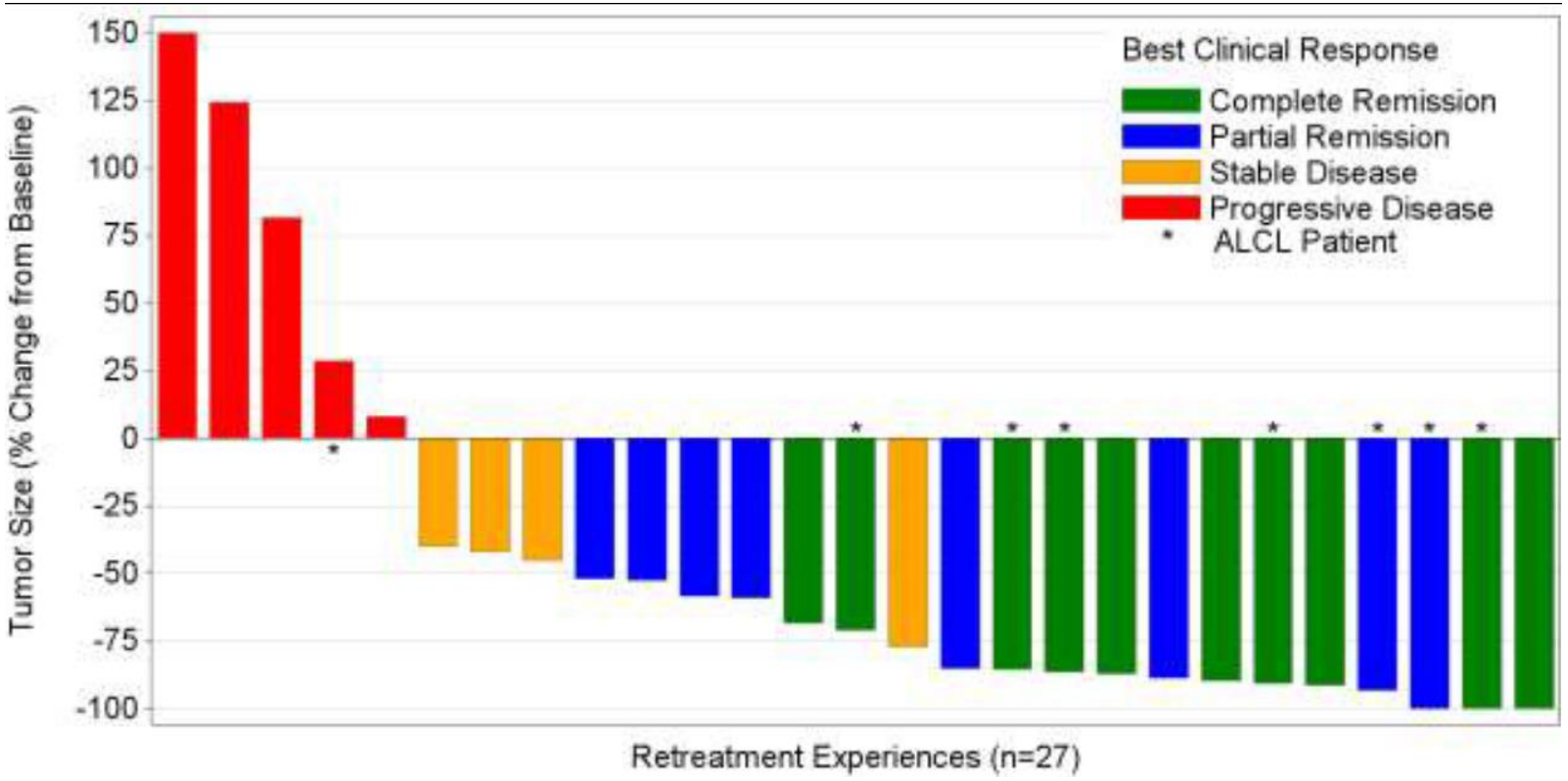


PFS by histology



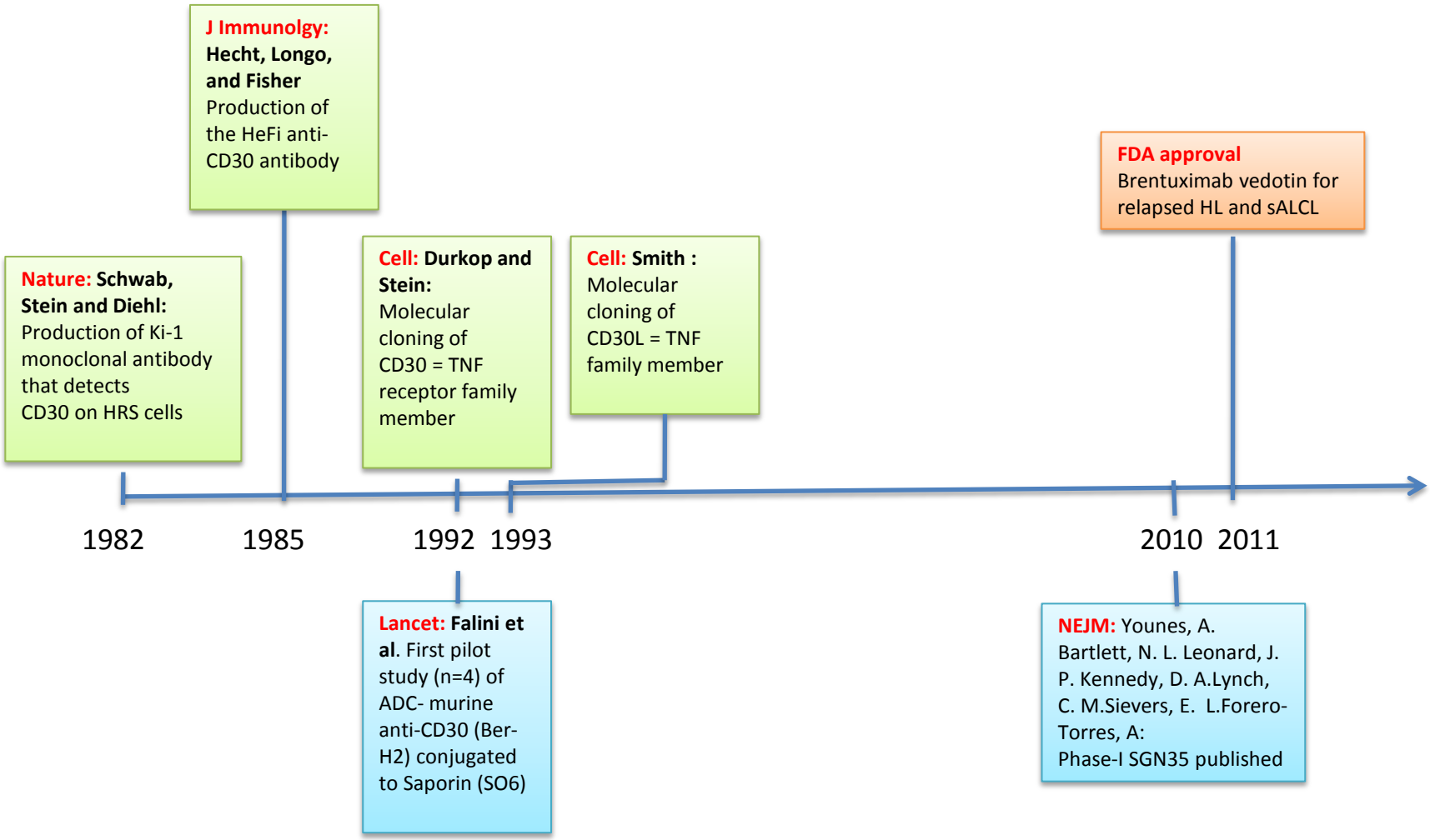
Steven M. Horwitz et al. Blood 2014;123:3095-3100

Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies



Bartlett, N et al: Journal of Hematology & Oncology 2014, **7**:24

CD30 : From a Biomarker to Therapeutic Target



Younes, A: Curr Opin Oncol. 2011 Nov;23(6):587-93