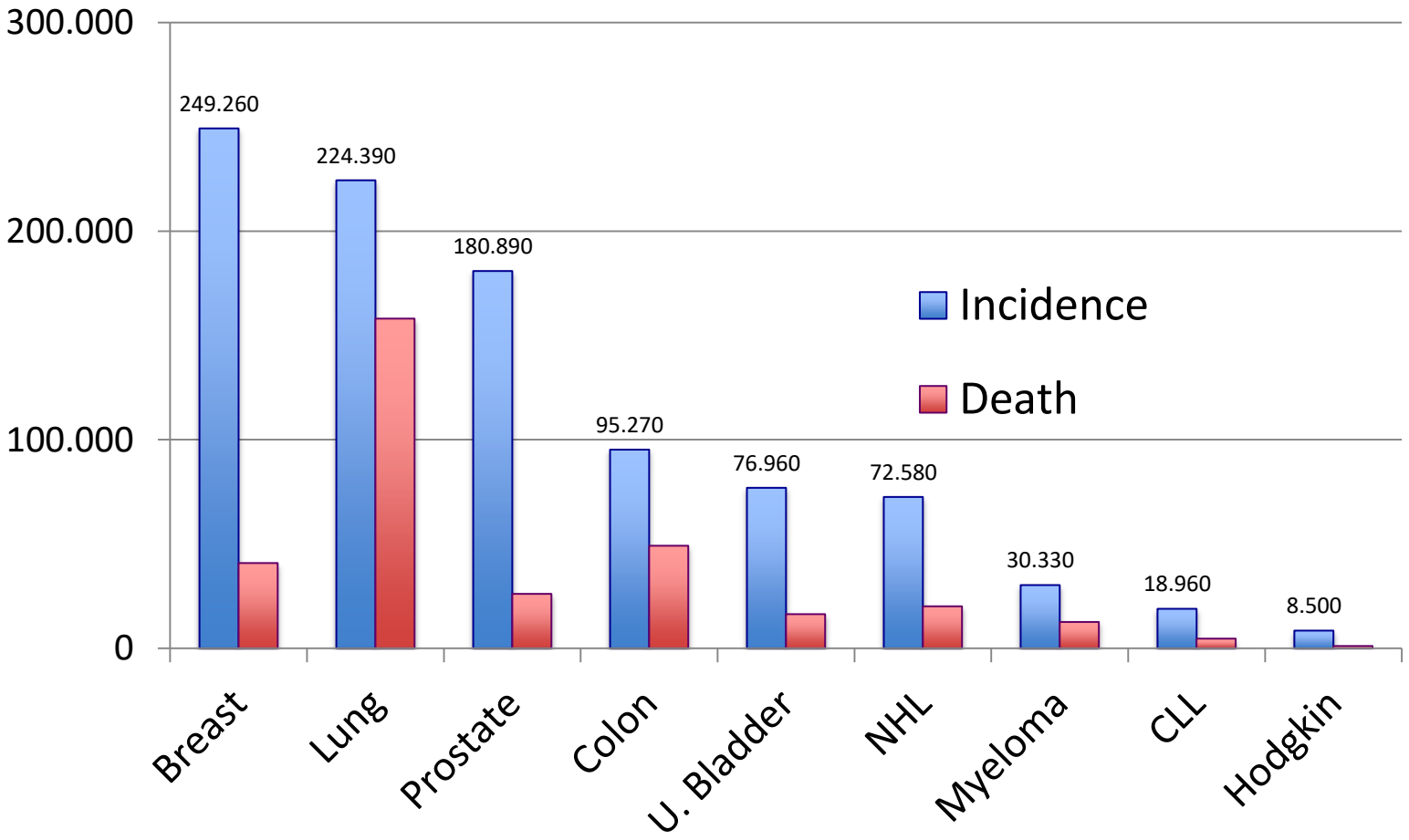
Brentuximab Vedotin

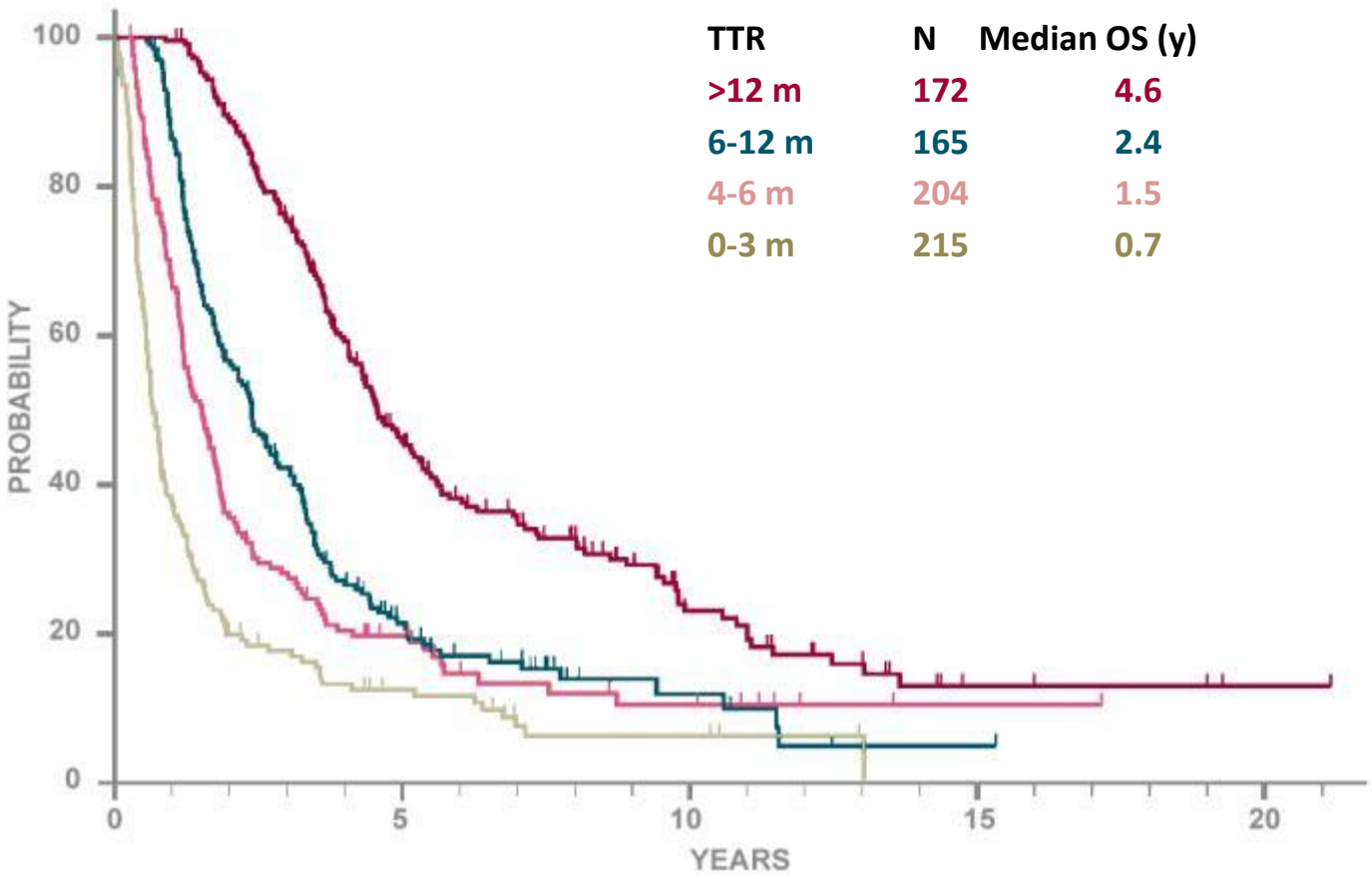
Anas Younes, M.D.
Chief, Lymphoma Service
Memorial Sloan-Kettering Cancer Center

U.S. Cancer Statistics 2016



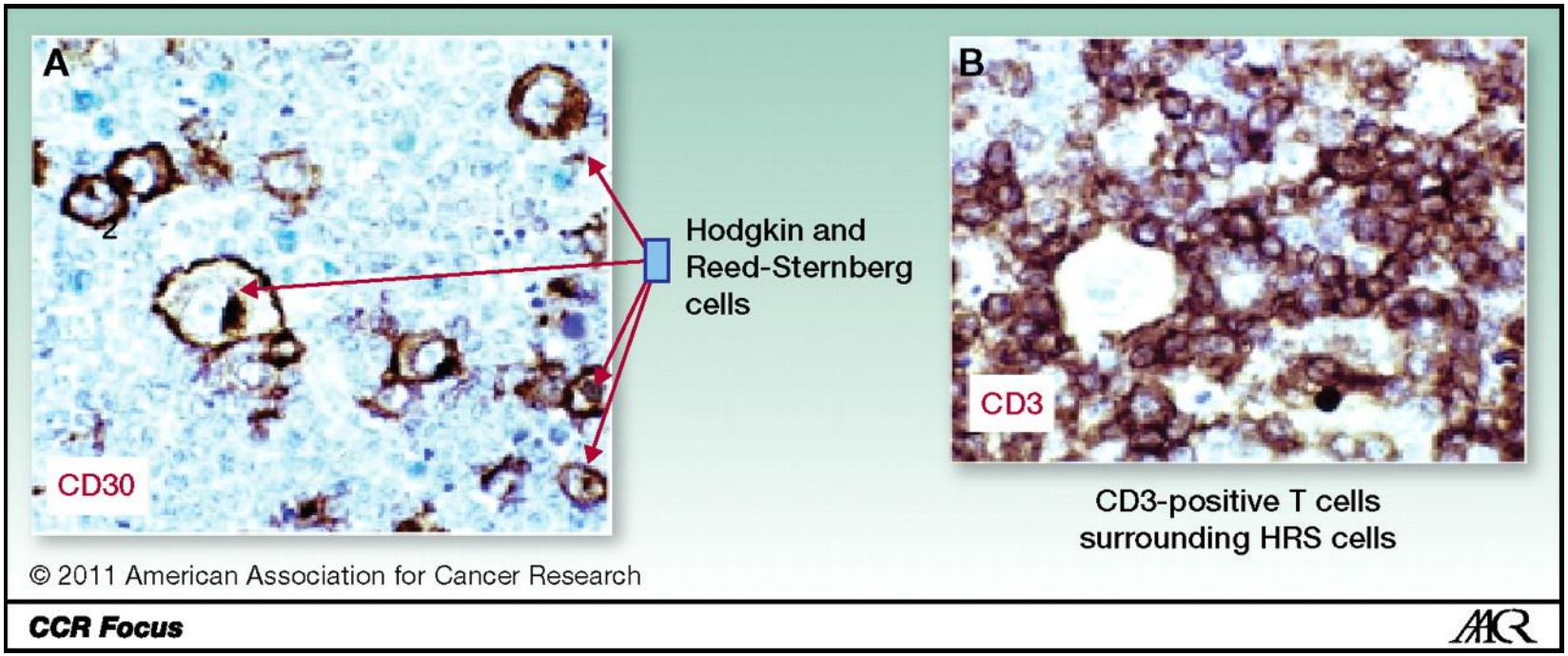
Siegel R, et al, ACS 2016

Overall survival by time to relapse after transplant



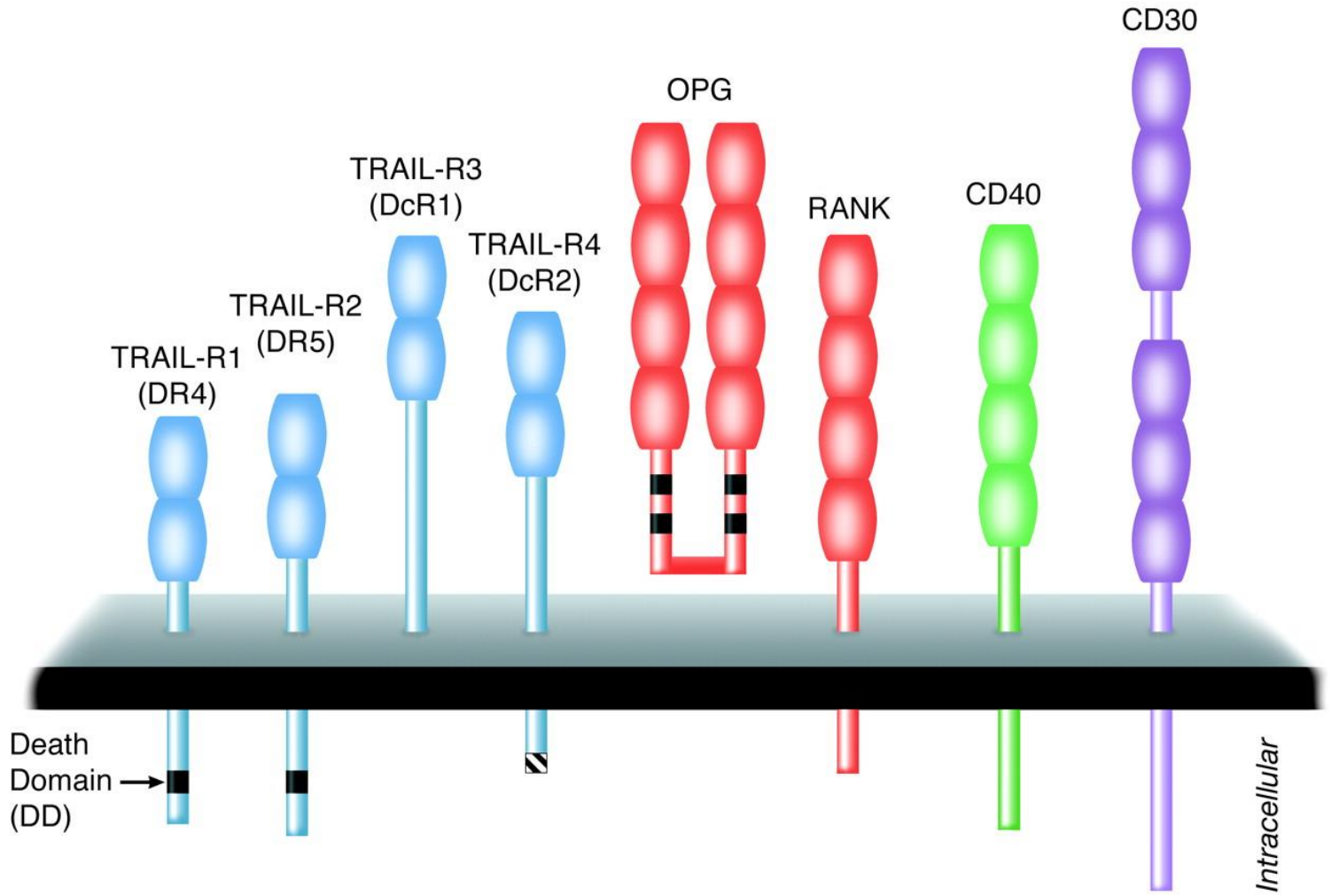
Horning S et al, Ann Oncol 2008:19 (suppl 4):Abstract 118
Arai S et al. Leukaemia and Lymphoma. 2013. In print

A, Hodgkin lymphoma stained for CD30.



Katz J et al. Clin Cancer Res 2011;17:6428-6436

Structure of selected tumor necrosis factor family receptors.



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

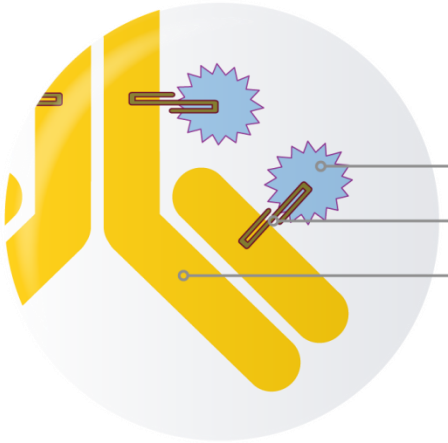
JOURNAL OF CLINICAL ONCOLOGY

Summary results of pahse I/II clinical trials 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

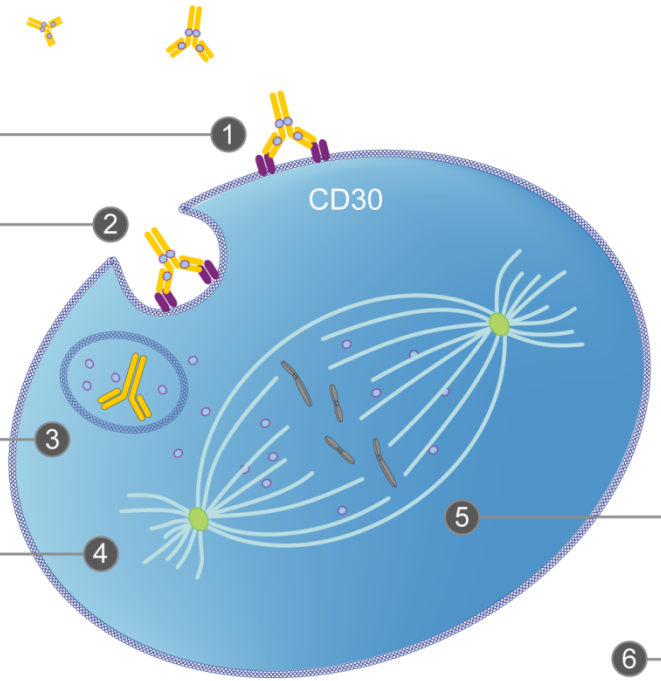


Brentuximab vedotin (SGN-35) ADC

monomethyl auristatin E (MMAE), potent antitubulin agent

protease-cleavable linker

anti-CD30 monoclonal antibody



ADC binds to CD30

ADC-CD30 complex traffics to lysosome

MMAE is released

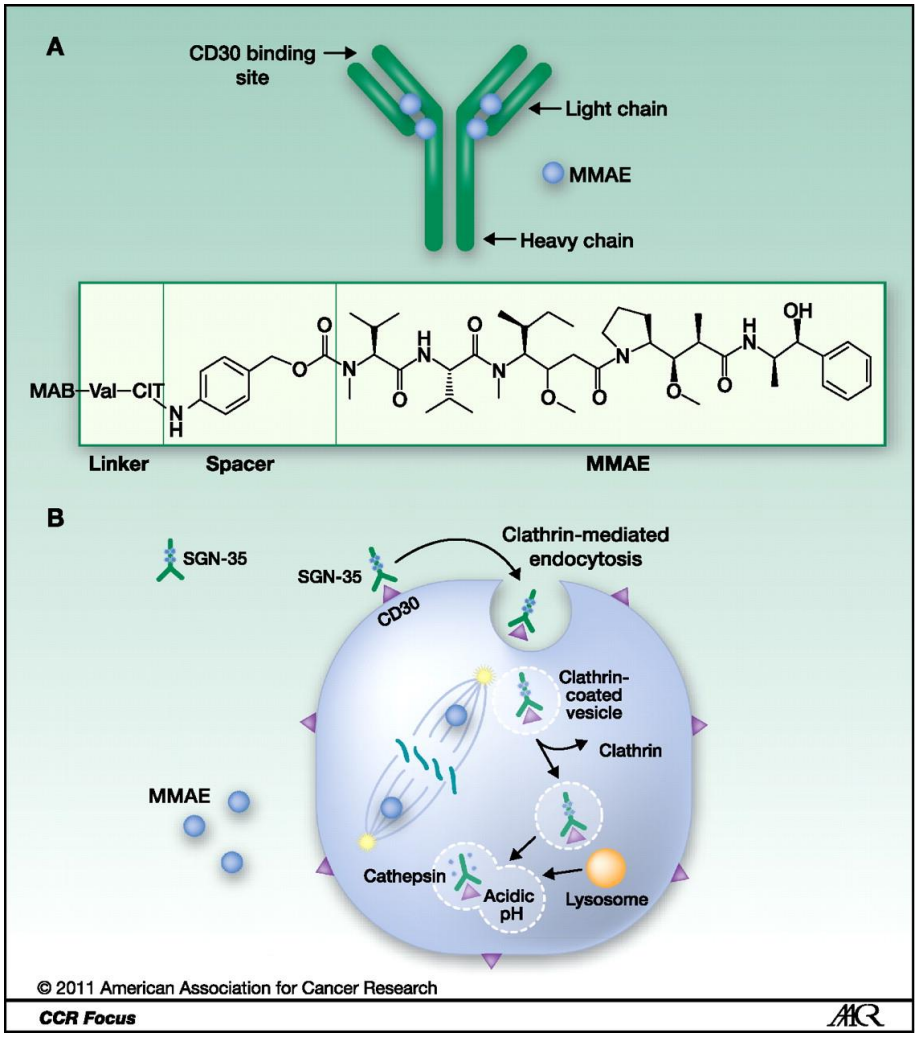
MMAE disrupts Microtubule network

G2/M cell cycle arrest

Apoptosis

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

Brentuximab Vedotin (SGN-35) structure.



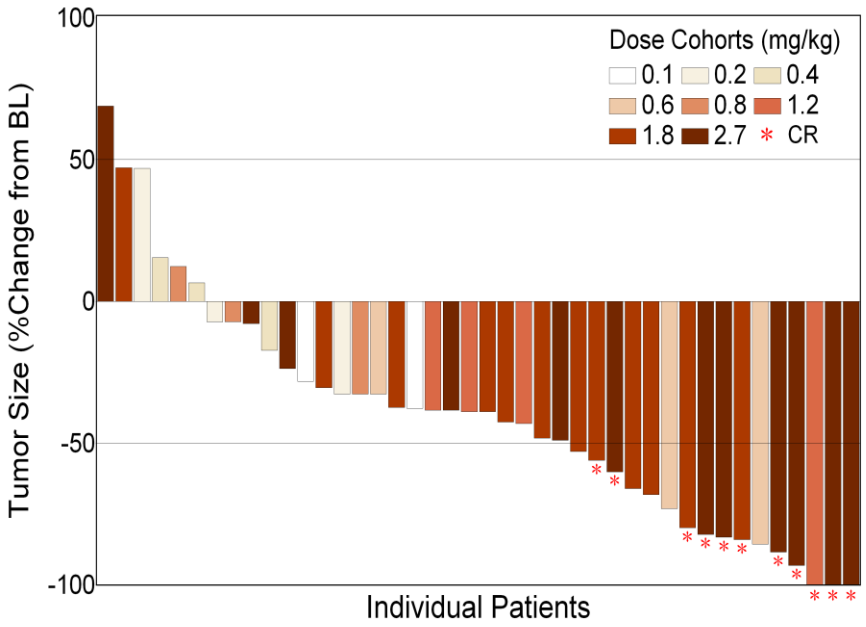
Katz J, JanikJ, and Younes A . Clin Cancer Res 2011;17:6428-6436

Clinical Cancer Research

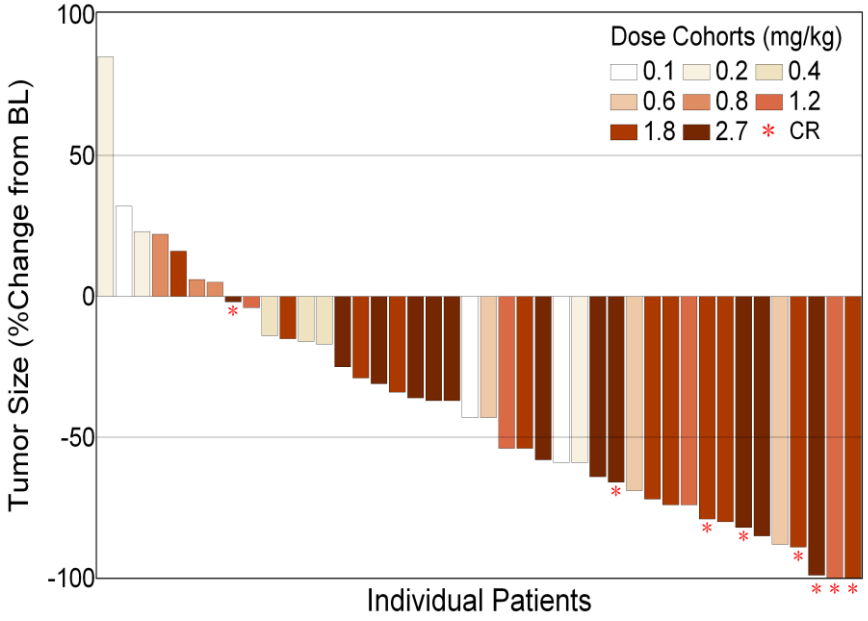
Phase-I brentuximab vedotin in relapsed CD30+ HL and ALCL

Treatment Response

Investigator Assessment



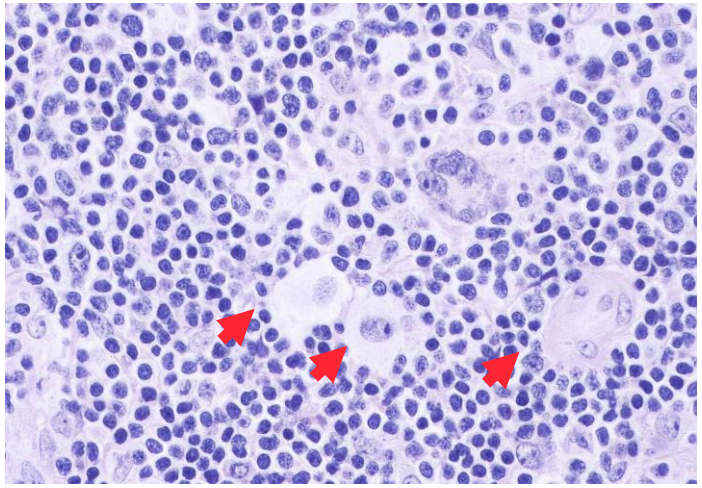
IRF Assessment

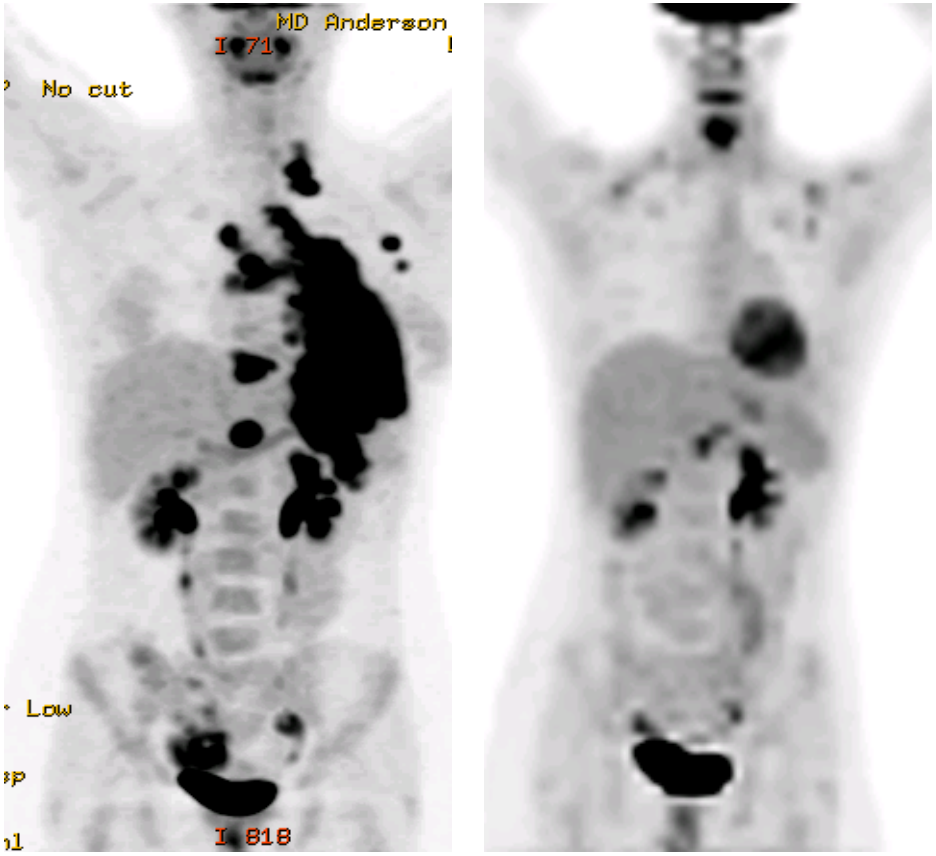


Younes A, et al. N Engl J Med 2010; 363:1812-1821

Phase I Brentuximab Vedotin in Relapsed HL

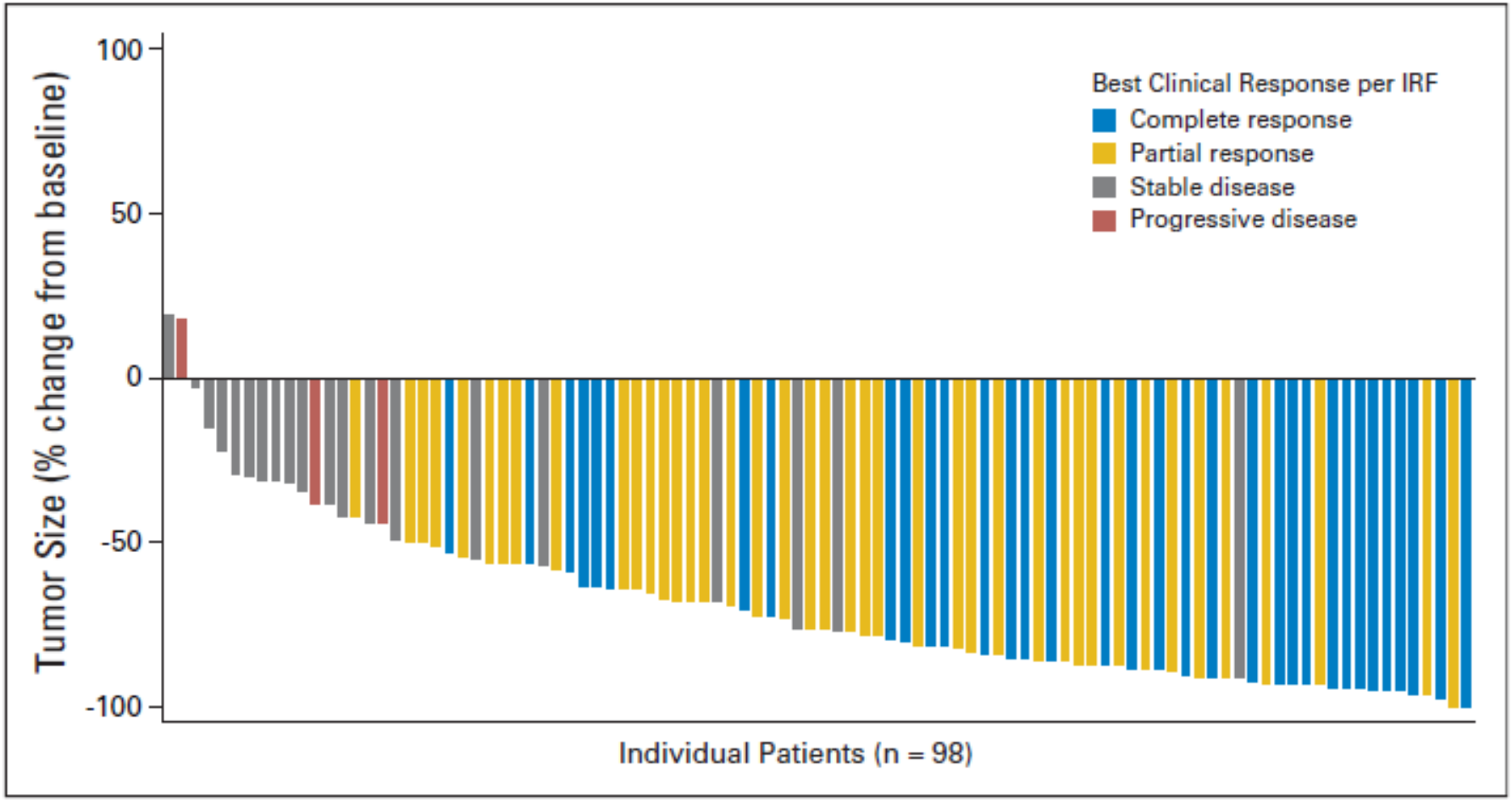
- 21-year-old female
- HL diagnosed 2003
  - ABVD + XRT to mediastinum
  - ICE
  - BEAM→ASCT
  - HDAC-inhibitor
- SGN-35 2.7 mg/kg x 8 cycles
  - Best clinical response: CR
  - CT 93% reduction, PET-
  - PET negative





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

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

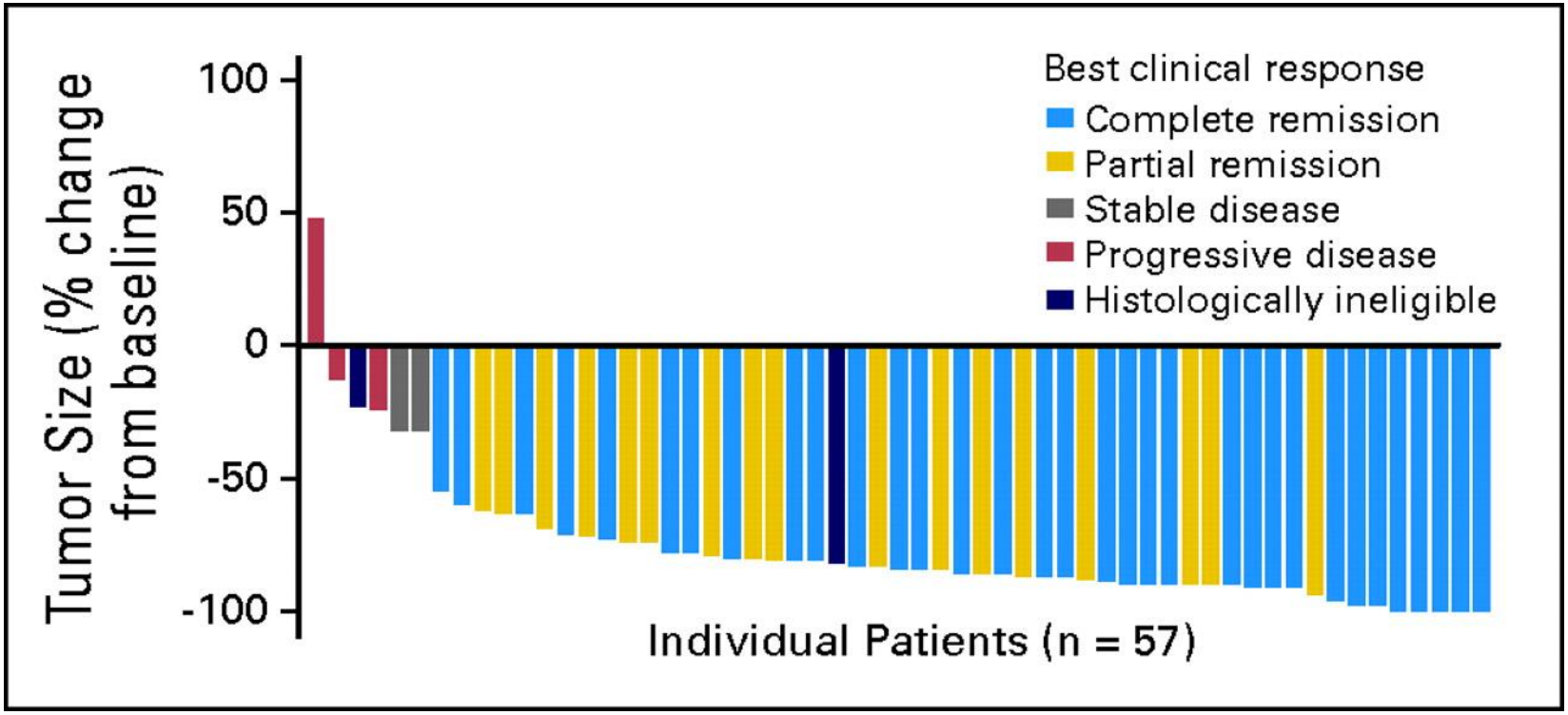


- 94% patients achieved tumour reduction

IRF – independent review facility

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

Brentuximab Vedotin: Relapsed / Refractory ALCL



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

Summary results of pahse I/II clinical trials targeting CD30

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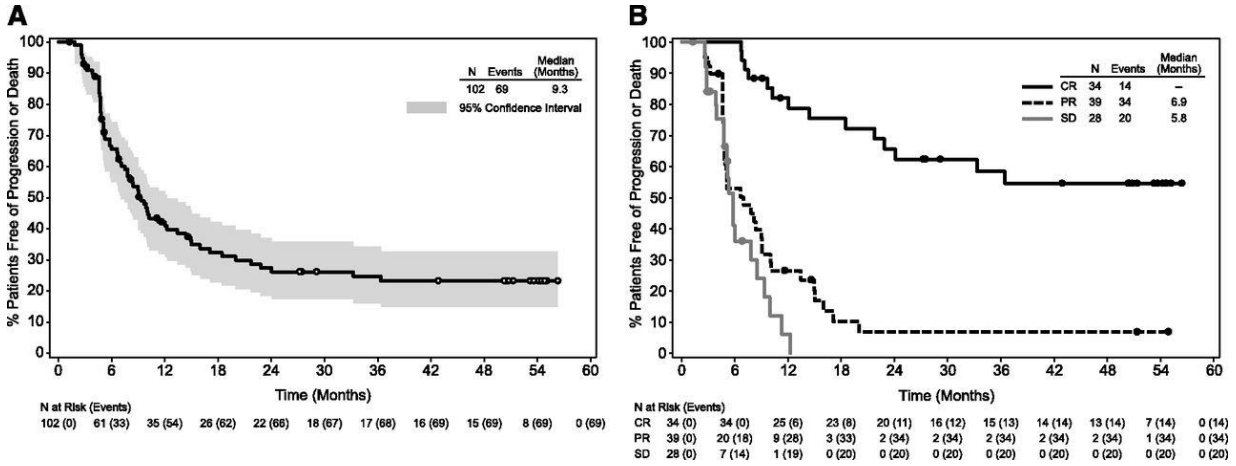
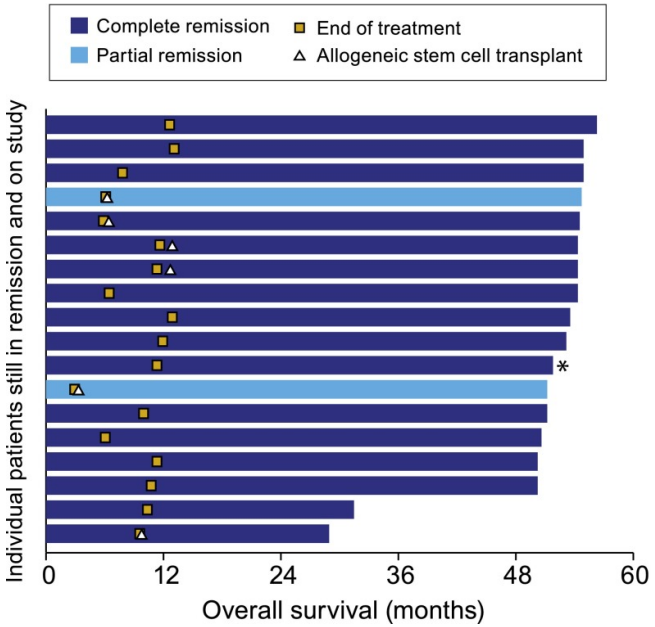
Xmab2513	HL	Humanized	I	13	1	0	7%
131I-Ki4	HL	Murine	I	22	5	1	27%
Brentuximab	HL, ALCL	ADC	I	42	7	10	17 (40%)
Brentuximab (weekly)	HL, ALCL	ADC	I	35	10	6	16 (46%)
Brentuximab	HL	ADC	II	102	41	35	75%
Brentuximab	ALCL	ADC	II	58	19	31	86%

Younes, A: Curr Opin Oncol. 2011

Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma

PFS following treatment with brentuximab vedotin.





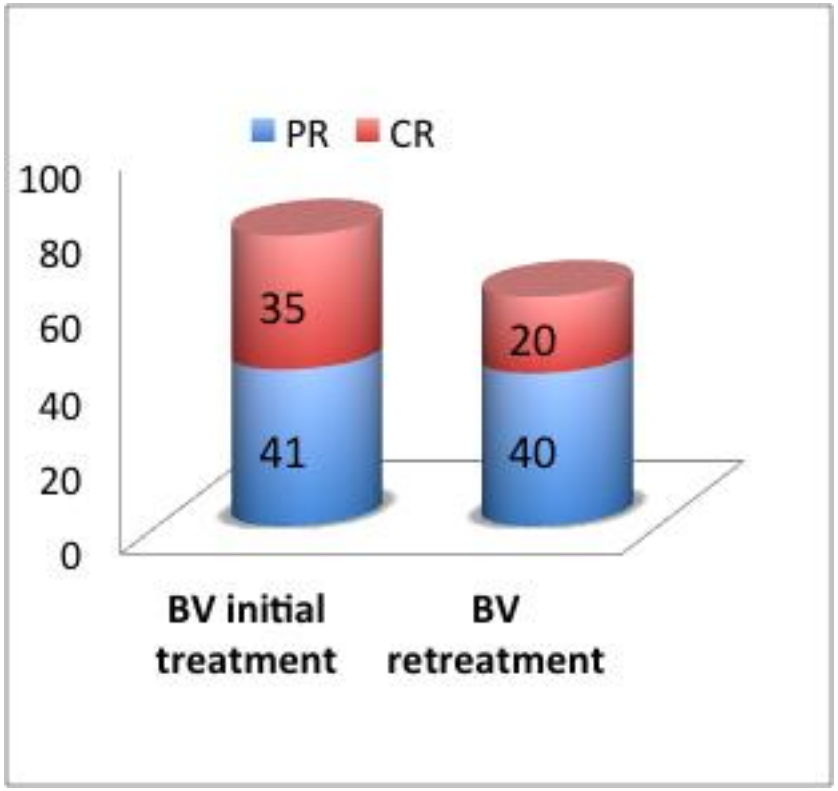
4/16 in CR had all0-SCT

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

Brentuximab Vedotin

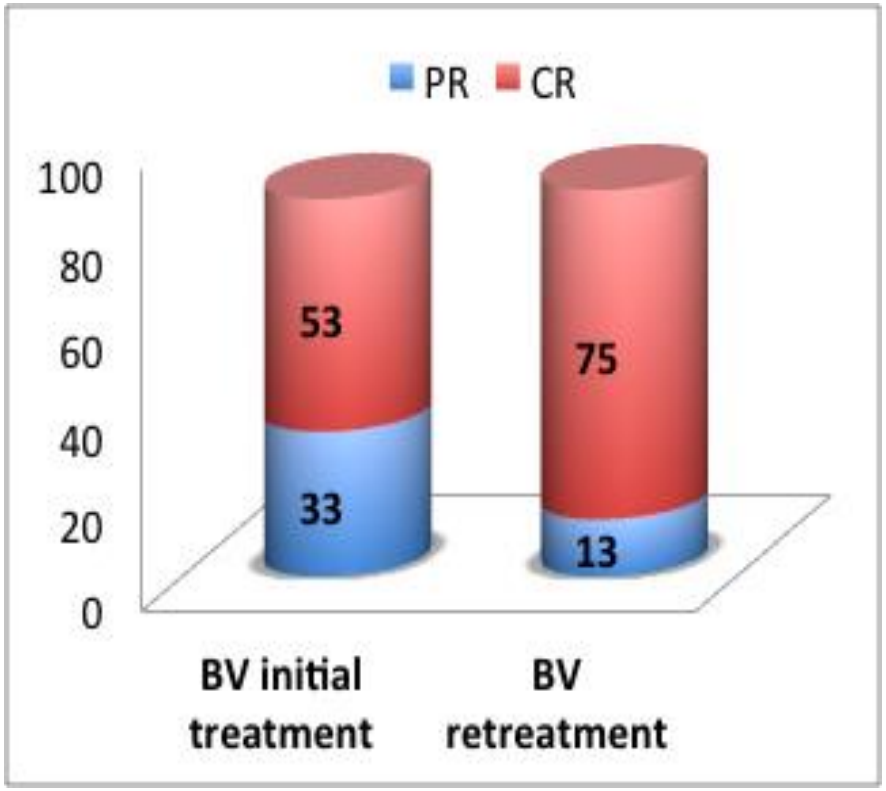
Initial treatment vs retreatment

HL



N=102 N=15

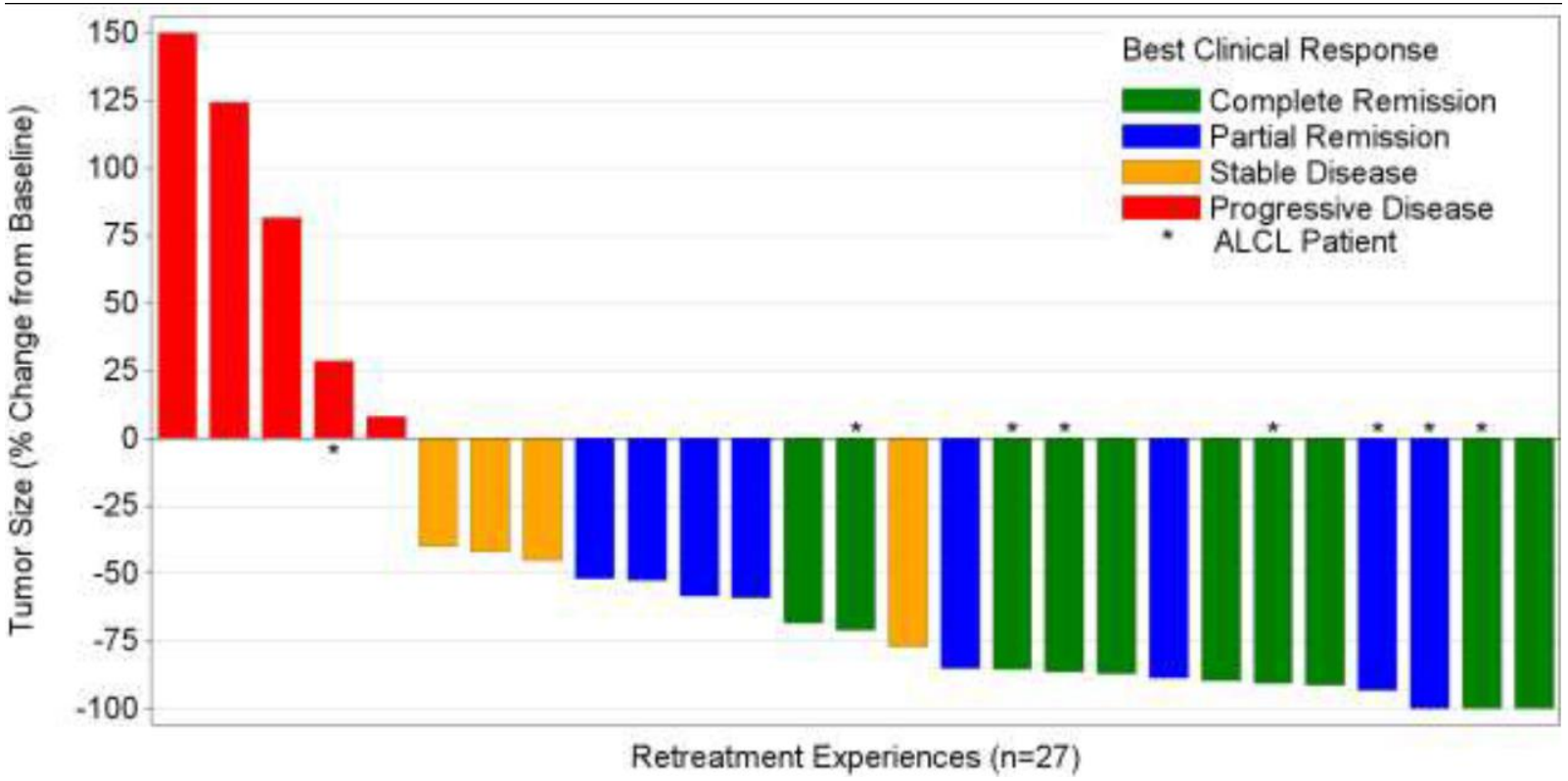
sALCL



N= 58 N=8

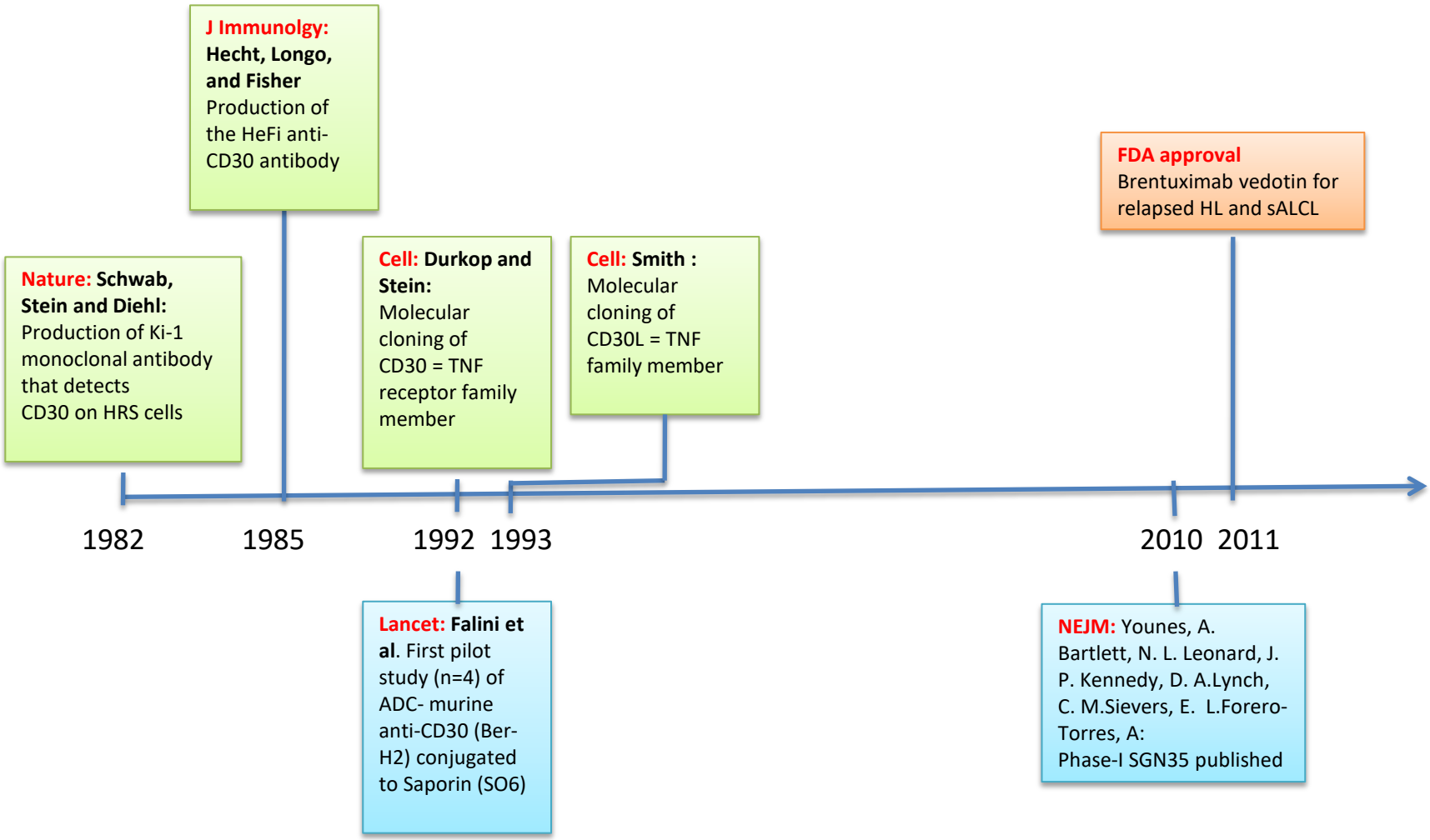
Bartlet et al , ASCO 2012

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



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

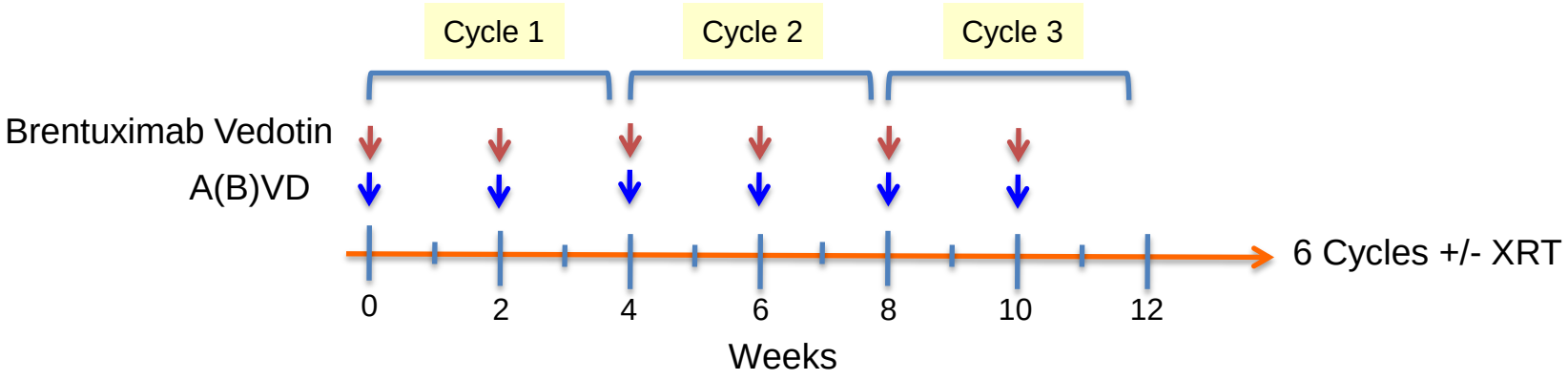
Timelines for development of the first FDA-approved targeted therapy for patients with relapsed HL and ALCL.



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

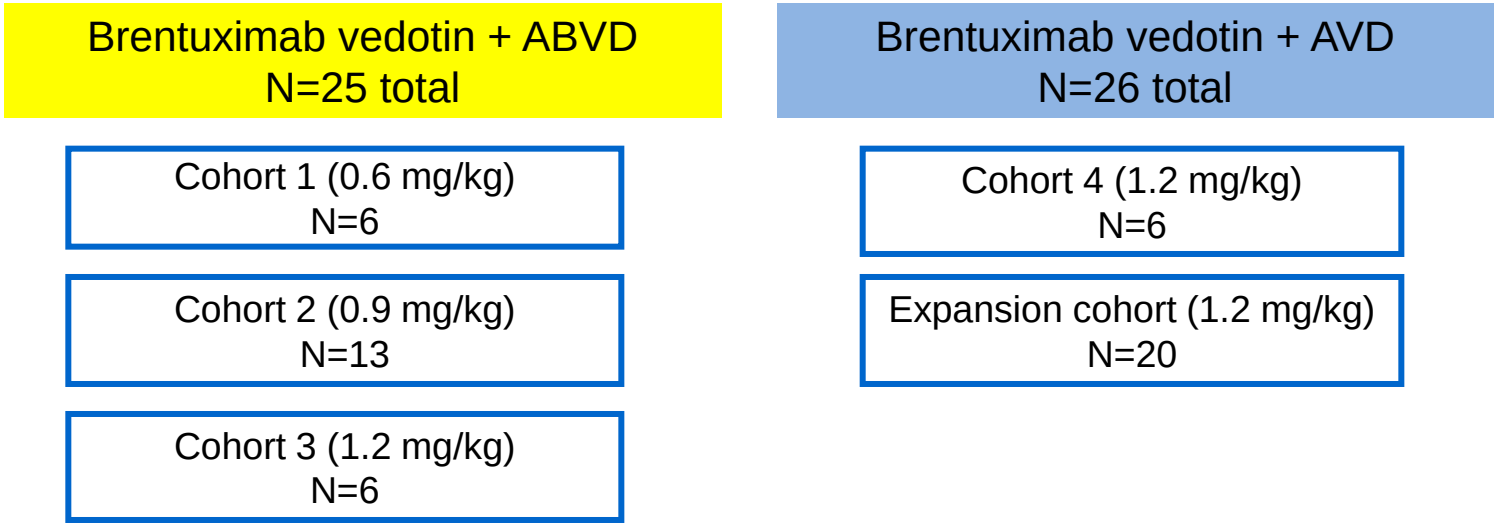
Phase 1 ABVD/AVD + brentuximab vedotin

Stage IIa bulky, IIB, III-IV



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

ABVD or AVD + brentuximab vedotin



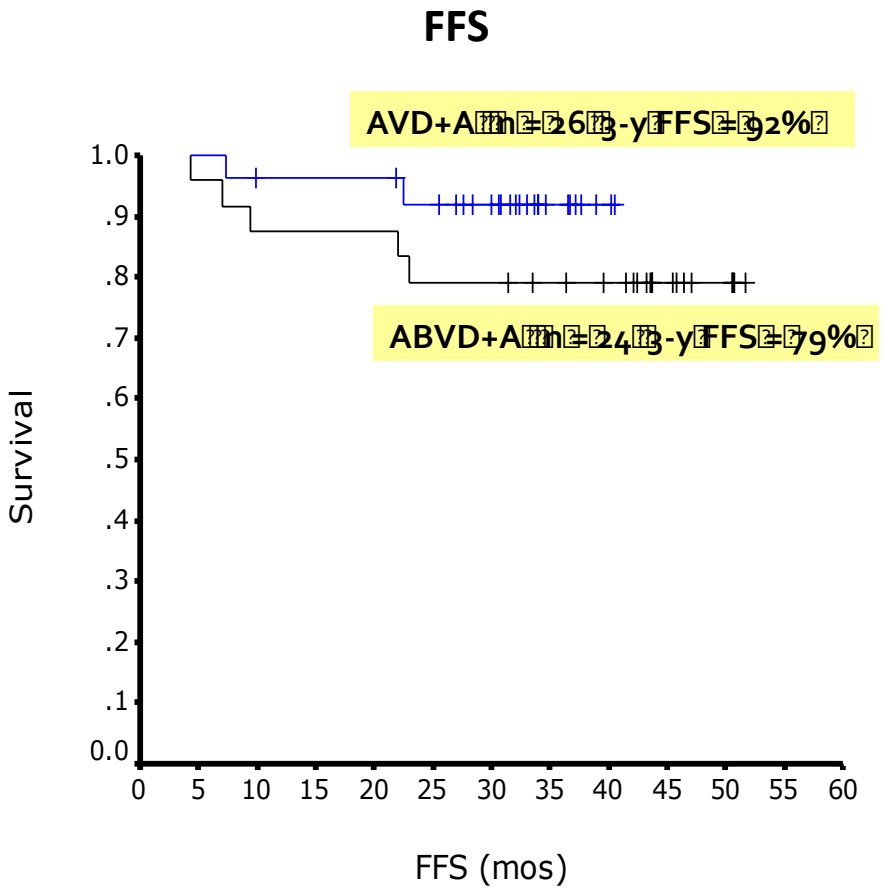
- Dose-limiting toxicities were defined as any Cycle 1 toxicity requiring ≥7-day delay in ABVD or AVD
- Study has completed enrollment
- All patients in the AVD expansion cohort are currently receiving treatment

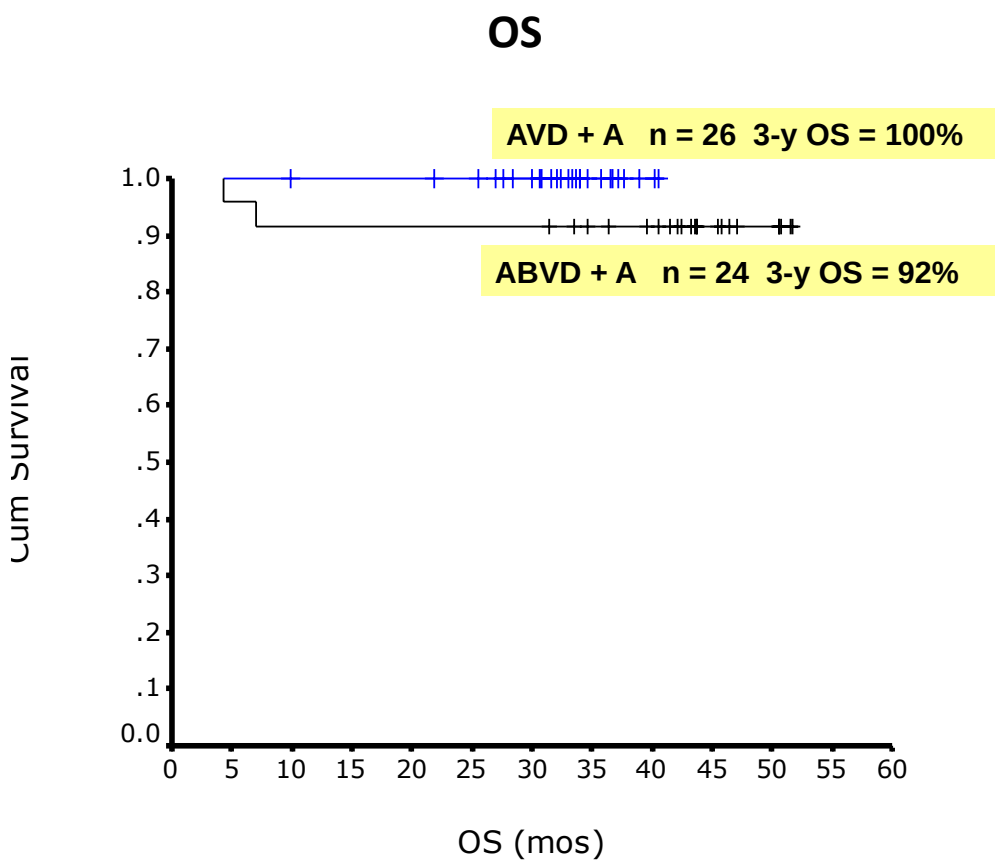
ABVD or AVD + brentuximab vedotin

	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
PET negative results	100%	92%
% CR at end of therapy	95%	96%

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

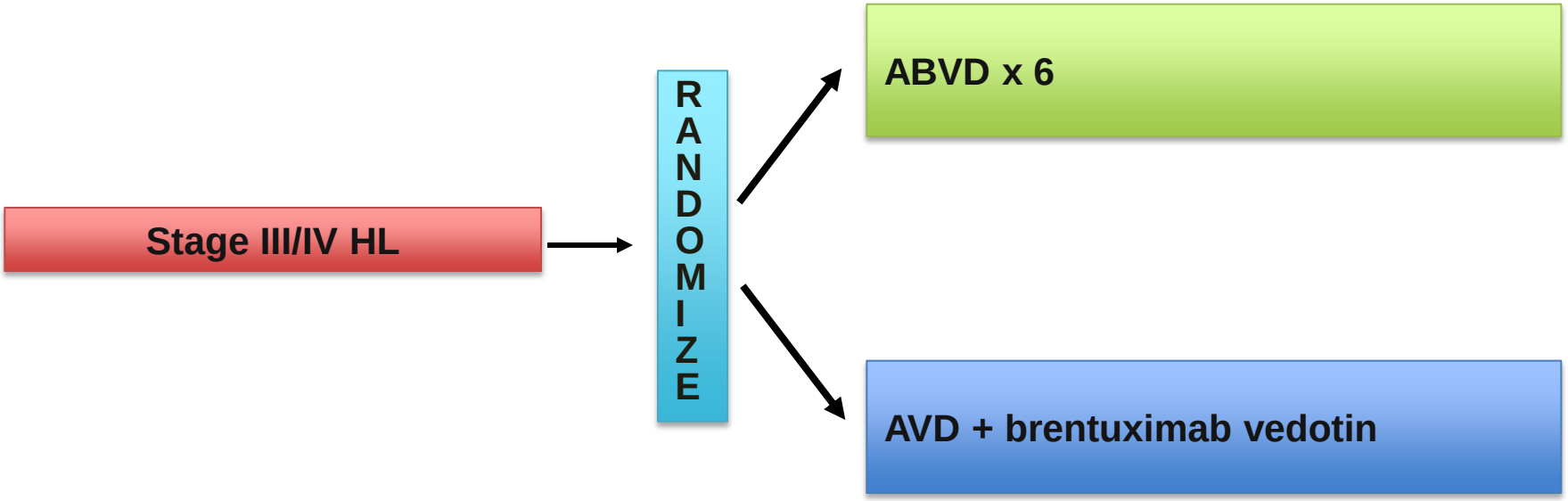
Long term follow up
Brentuximab vedotin + AVD
Advanced stage HL



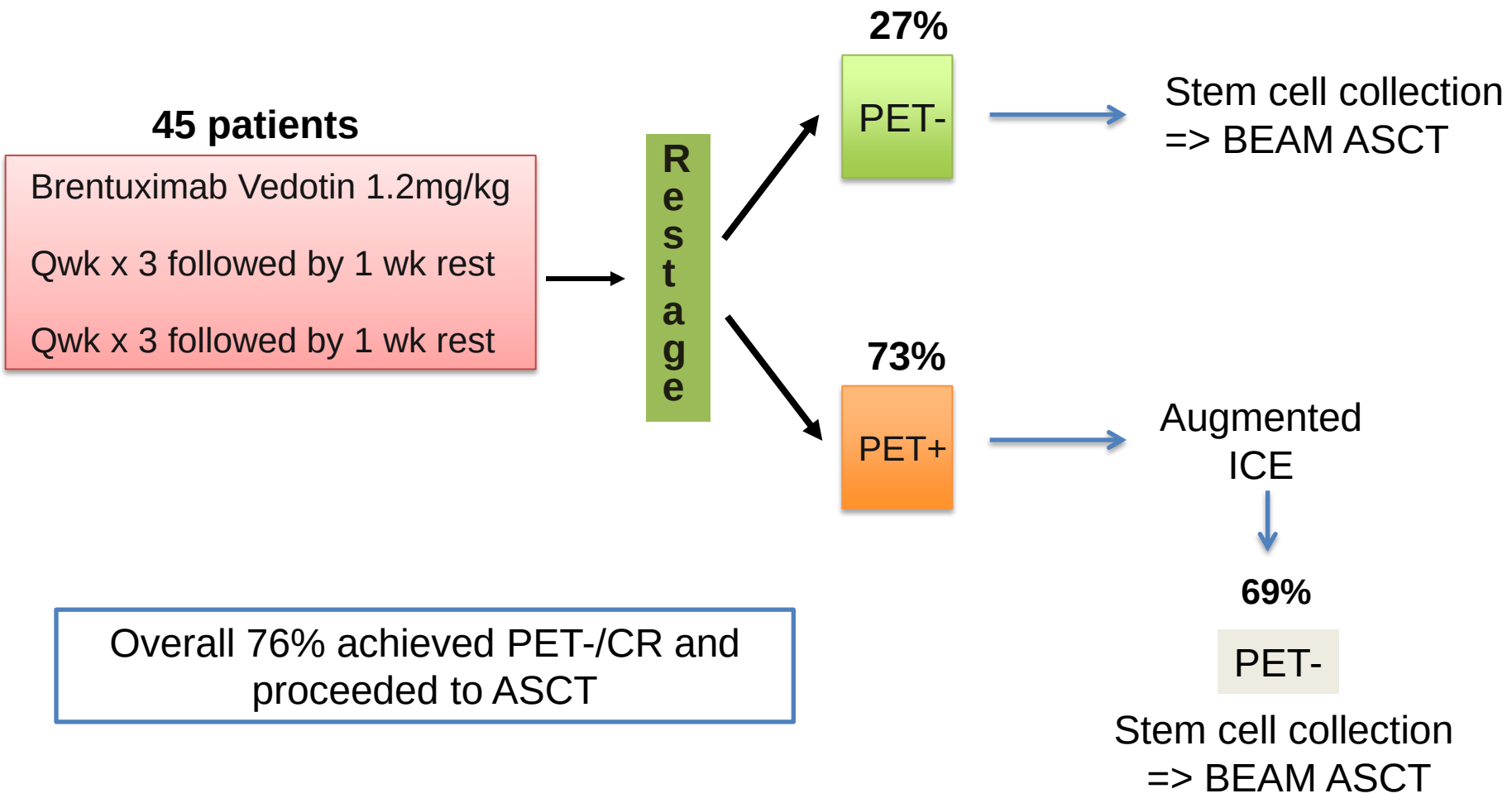


Connors J et al , ASH 2014

Randomized study in newly diagnosed advanced stage HL

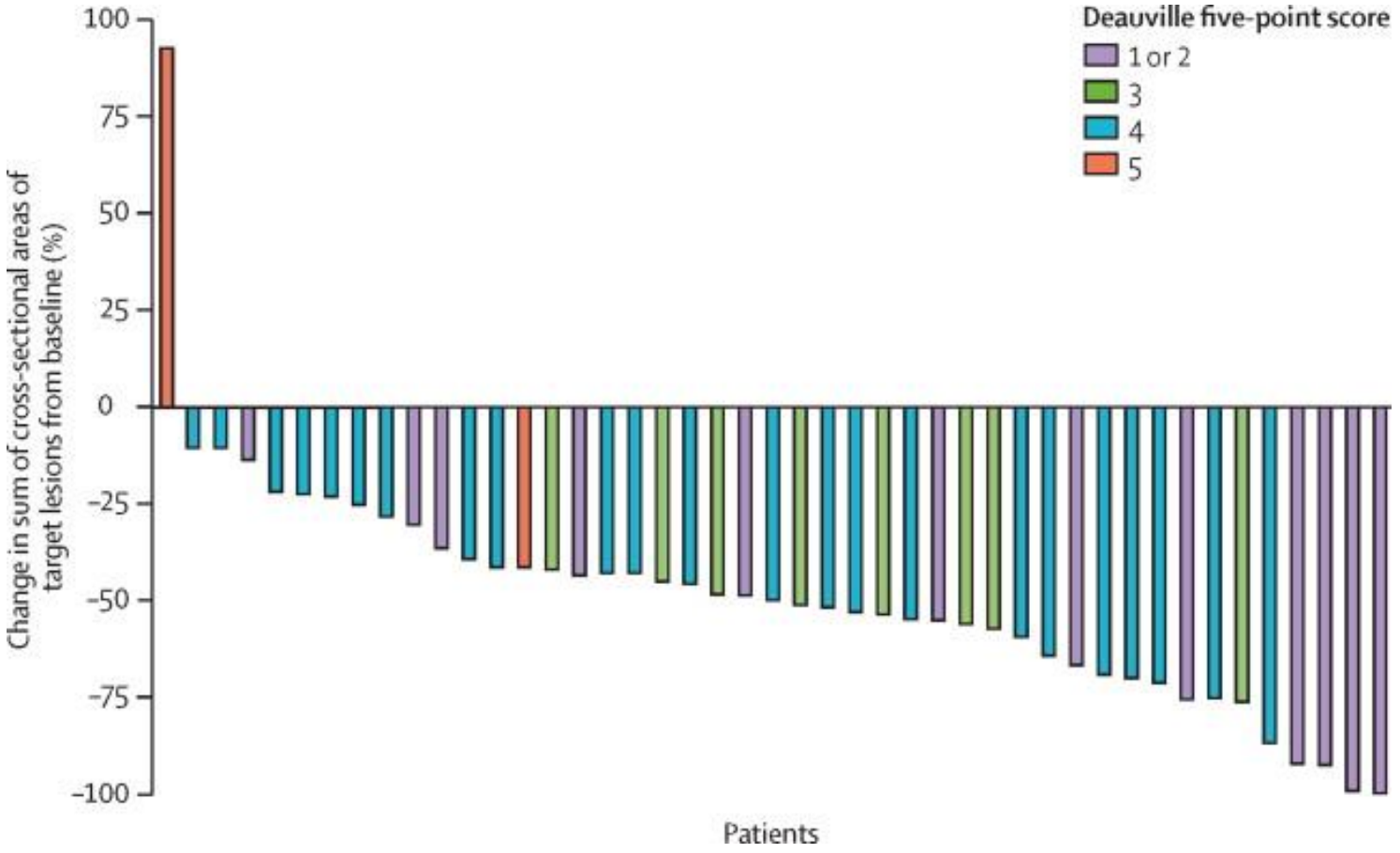


Response adapted salvage therapy for transplant eligible HL



Alison Moskowitz et al, Lancet Oncology 2015

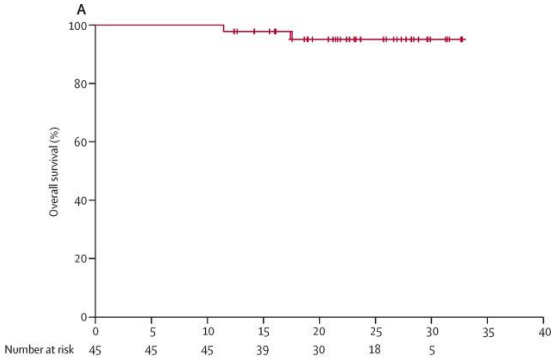
Tumour reduction after brentuximab vedotin Data shows PET status according to the Deauville scores of 1–5



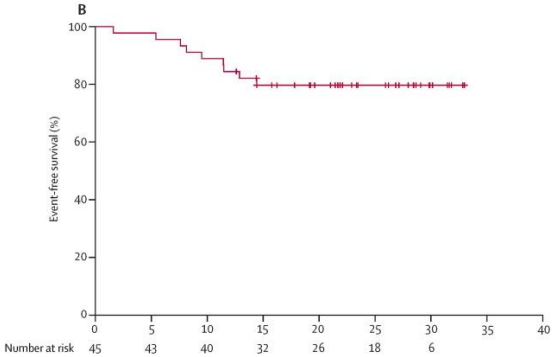
Alison J Moskowitz , et al The Lancet Oncology, Volume 16, Issue 3, 2015, 284 - 292

http://dx.doi.org/10.1016/S1470-2045(15)70013-6

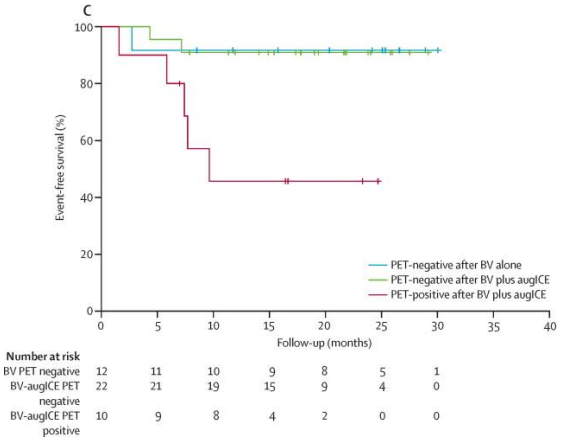
Brentuximab vedotin +/- AugICE for relapsed HL



OS



EFS



EFS by PET and treatment groups

http://dx.doi.org/10.1016/S1470-2045(15)70013-6

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		33%	Chen R, ASH 2014
BV+Benda	34	82%	N/A	LaCasce A, ASH 2014

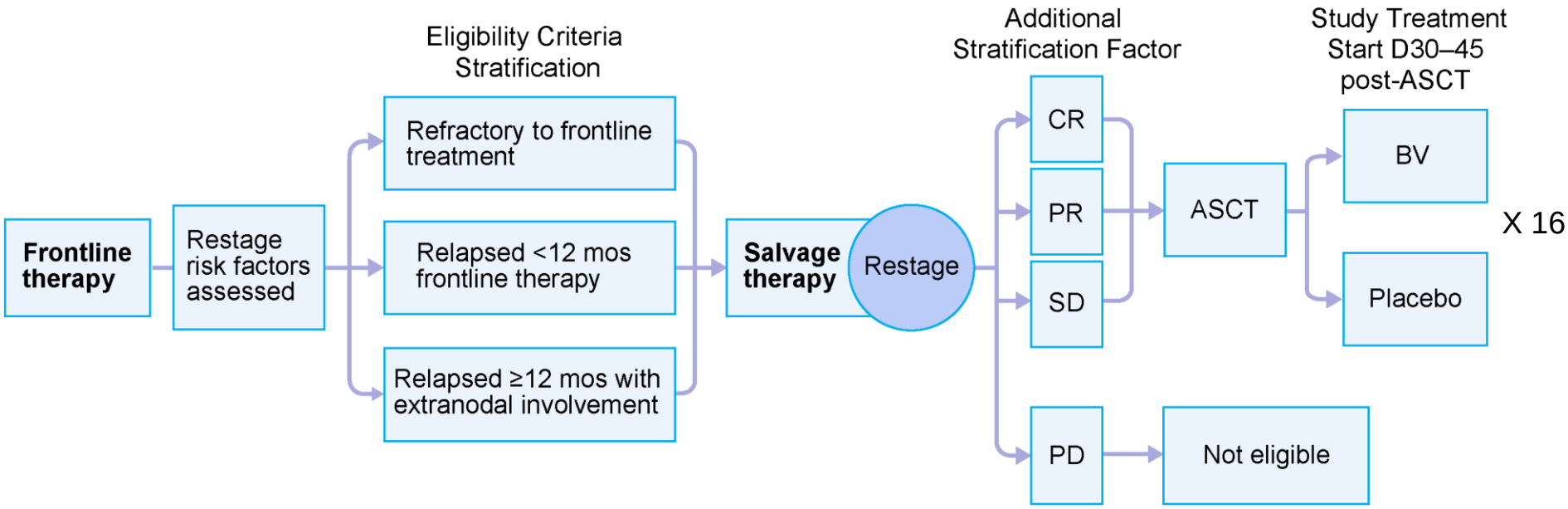
BV combination regimens

	BV + bendamustine	BV + ESHAP	BV + ICE
N	55	66	16
Dose	-1.8 mg/kg BV on D1 -Bendamustine D1 and D2	-1.8 mg/kg BV on D1 -ESHAP days 1-4	-1.5 mg/kg BV on D1 and 8 -ICE days 2-4
Response Rates	93% ORR 74% CR	94% ORR 70% CR	94% ORR 88% CR 69% CR (IR)
Toxicity	56% infusion reaction	Myelosuppression, infections	Myelosuppression, Peripheral neuropathy
PFS/OS	12 months PFS 80%	18 months TTF 74%	N/A

LaCase A et al, ASH 2015
Garcia-Sanz R et al. ASH 2016
Cassaday R et al, ASH 2016

The AETHERA study

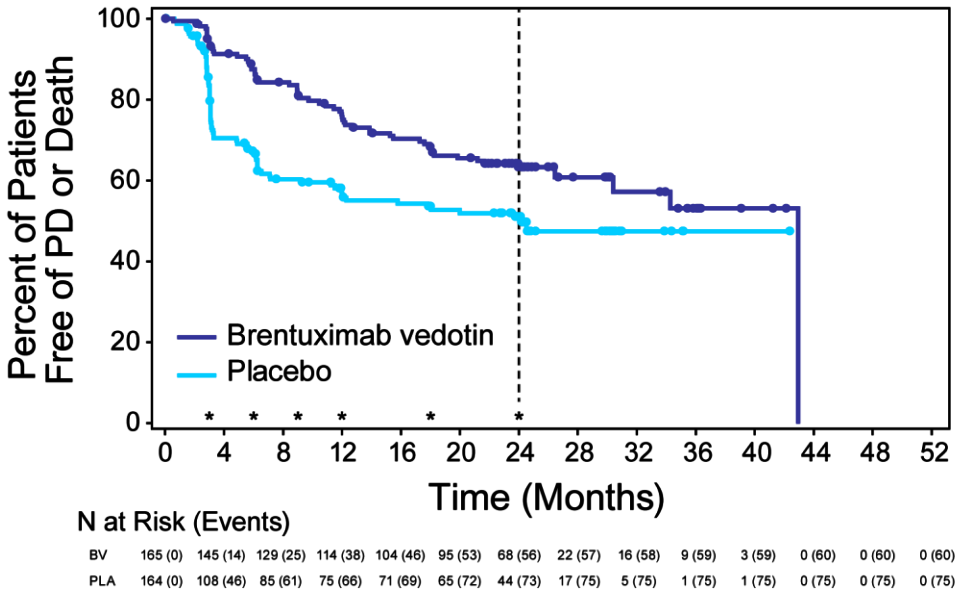
329 patients were randomised at 78 sites in North America and Europe



Moskowitz C, et al The Lancet 2015

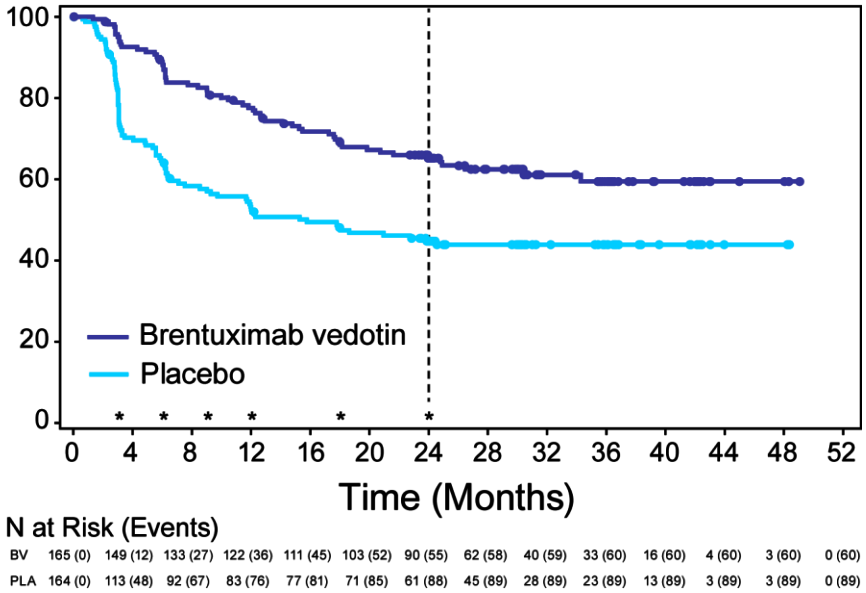
Progression-free survival

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†



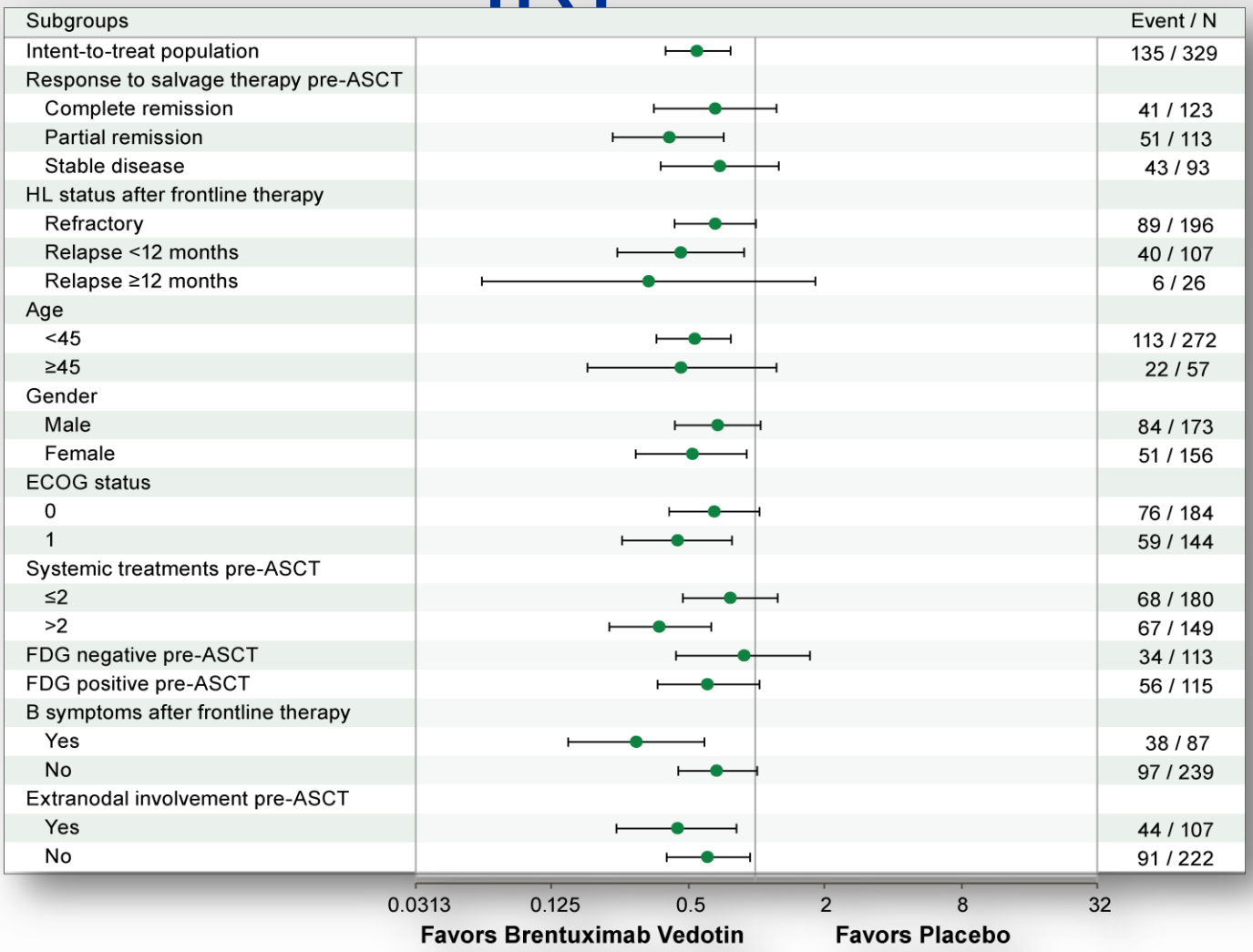
	BV (N=165)	Placebo (N=164)
Hazard Ratio (95% CI)	**0.50 (0.36–0.70)**	
Events	60	89
Median PFS (months)	--	16
2-year PFS rate	65%	45%

* Regularly scheduled CT scans

† Includes information from both radiographic assessments and clinical lymphoma assessments

Moskowitz C, et al The Lancet 2015

Subgroup Analysis of PFS per IRF



Moskowitz C, et al. *The Lancet.* 2015.

Results of PD1 Blocking Antibodies in Relapsed HL

Results of Phase-II Studies

Post ASCT and Brentuximab Vedotin

Drug	Dose/Schedule	N	% ORR	% CR	1st Author/Ref
Pembrolizumab (humanized IgG4)	200 mg IV Q 3wks	69	72%	21%	Moskowitz, C/ ASH 2016
Nivolumab (Fully human IgG4)	3 mg/kg IV Q 2 wks	80	66%	9%	Younes, A/Lancet Oncology 2016

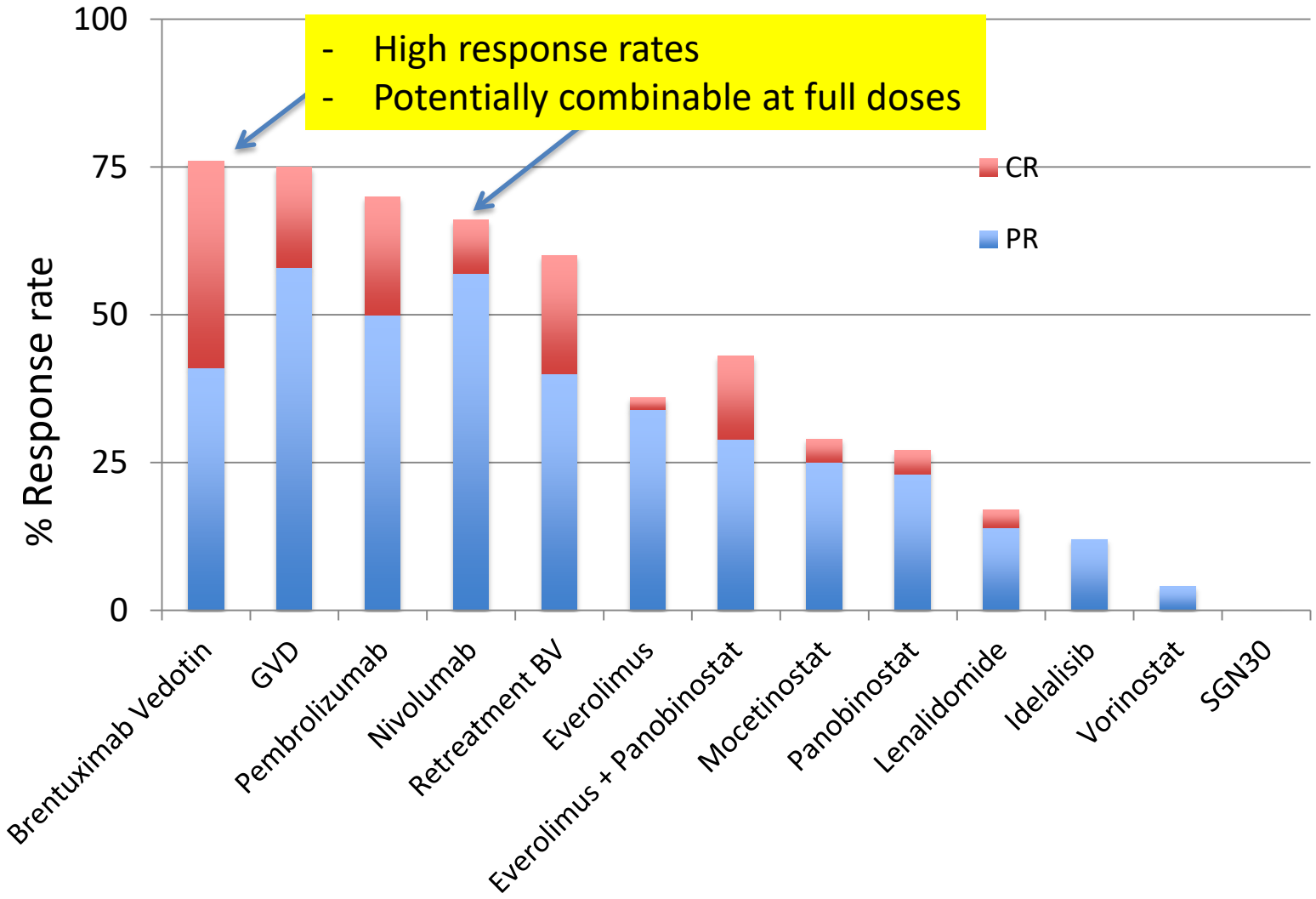
Results of PD1 Blocking Antibodies in Relapsed HL

Results of Phase-II Studies

Post ASCT but No PRIOR Brentuximab Vedotin

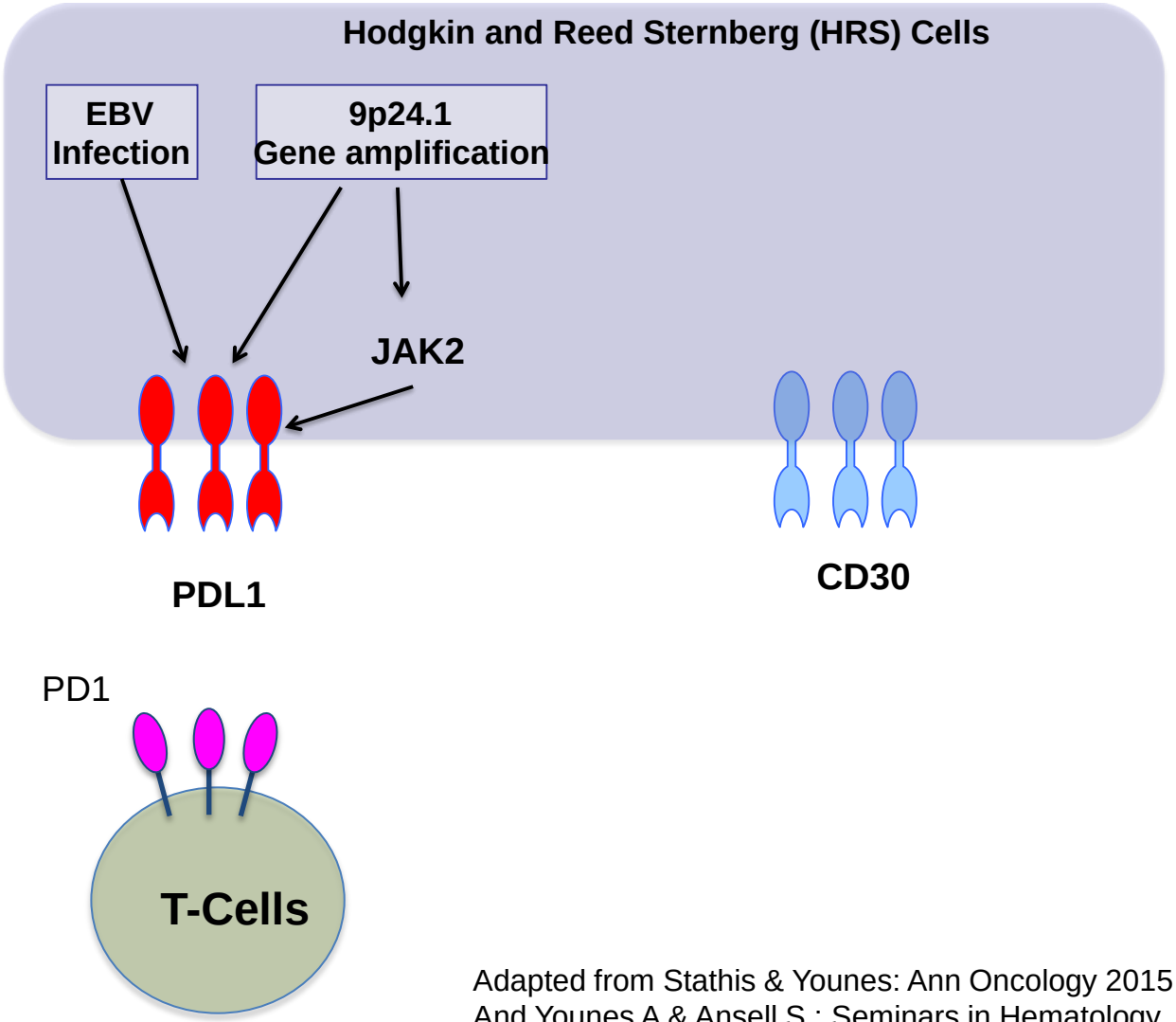
Drug	Dose/Schedule	N	% ORR	% CR	1st Author/Ref
Pembrolizumab (humanized IgG4)	200 mg IV Q 3wks	60	67%	21%	Moskowitz, C/ ASH 2016
Nivolumab (Fully human IgG4)	3 mg/kg IV Q 2 wks	63	68%	22%	Timmerman, J/ ASH 2016

Single agent activity of novel agents in relapsed cHL



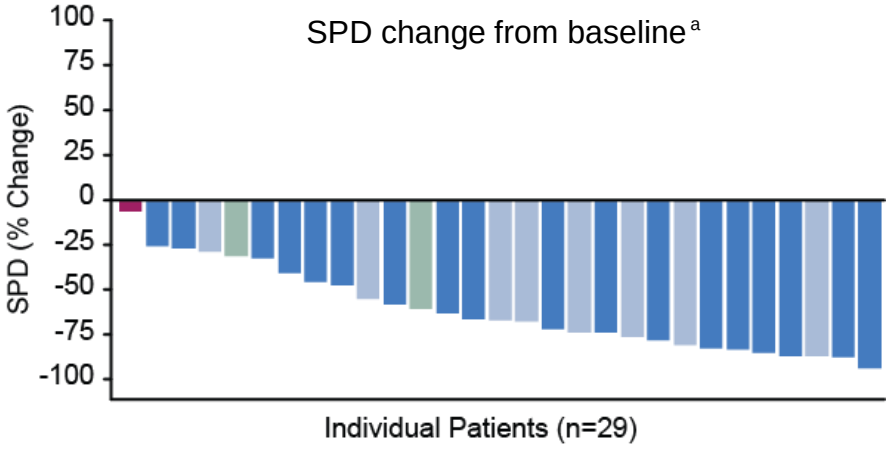
Updated from Betlevi and Younes, Hematology Am Soc Hematol Educ Program. 2013
Smith, K et al : Hodgkin Lymphoma, Hoffan Textbook of Hematology 2015 (In Press)

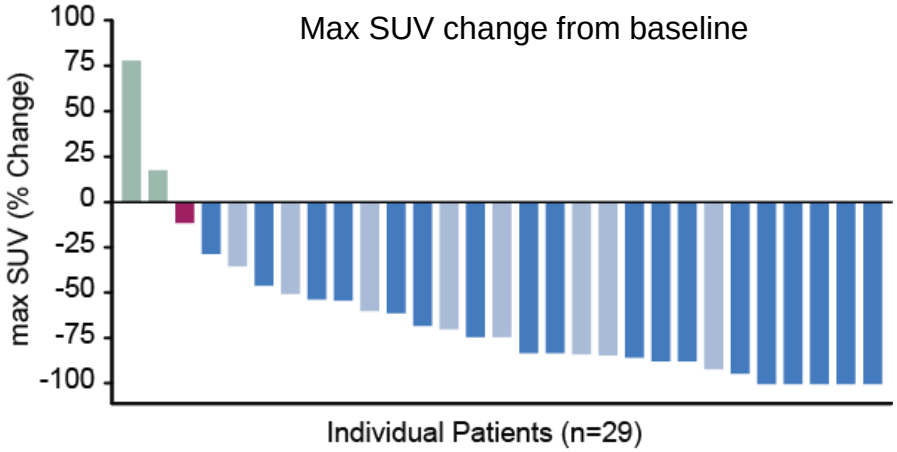
Targeting CD30 and PD1/PDL in Combination Strategies



Adapted from Stathis & Younes: Ann Oncology 2015
And Younes A & Ansell S : Seminars in Hematology, 2016, 186–189

Tumor Response per Investigator





ORR (26/29) = 90%

95% CI: 72.6, 97.8

CR (18/29) = 62%

95% CI: 42.3, 79.3

Deauville score (N=29)

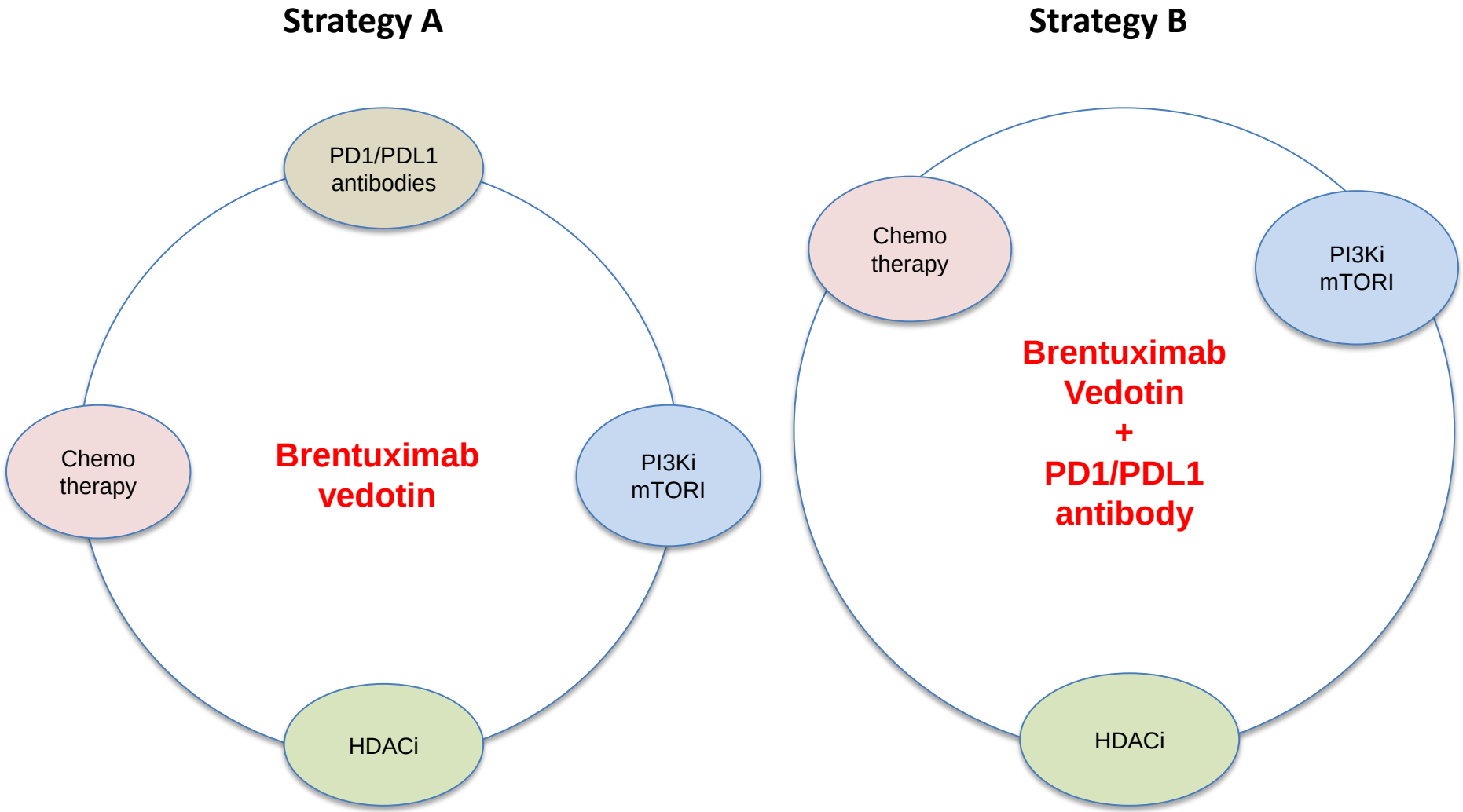
5-Point Score	Best Metabolic Response	n (%)	Total n (%)
1	CR	8 (28)	18 (62)
2		6 (21)	
3		3 (10)	
Missing		1 (3)	
4	PR	6 (21)	8 (28)
5		2 (7)	
5	SD	1 (3)	1 (3)
5	PD	2 (7)	2 (7)

Best Metabolic Response:

Complete response (CR) Partial response (PR) Stable disease (SD) Progressive disease (PD)

[a] Cycle 2 SPD reported for 1 patient

Hodgkin Lymphoma : Future Directions



Conclusions

- Brentuximab Vedotin is a highly active single agent in relapsed HL
- Combination strategies are ongoing in front-line, second line, and post transplant setting
- In the era of highly active new agents, the role of ASCT in second line treatments needs to be re-examined
- Immune checkpoint inhibitors are active agents in BV failures
- BV + PD-1 antibodies seems to be safe and effective, and may provide a new backbone for future drug development in HL
- Standard of care therapy is likely to change in the next few years

SAVE THE DATE

MSK SYMPOSIUM ON LYMPHOMA

STATE-OF-THE-ART IN BIOLOGY, THERAPY AND PATIENT CARE

May 5-6, 2017

Memorial Sloan Kettering Cancer Center
Zuckerman Research Center
417 East 68th Street
New York, NY 10065

Course Director
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