Treatment Approaches in Relapsed/Refractory HL

Brentuximab Vedotin

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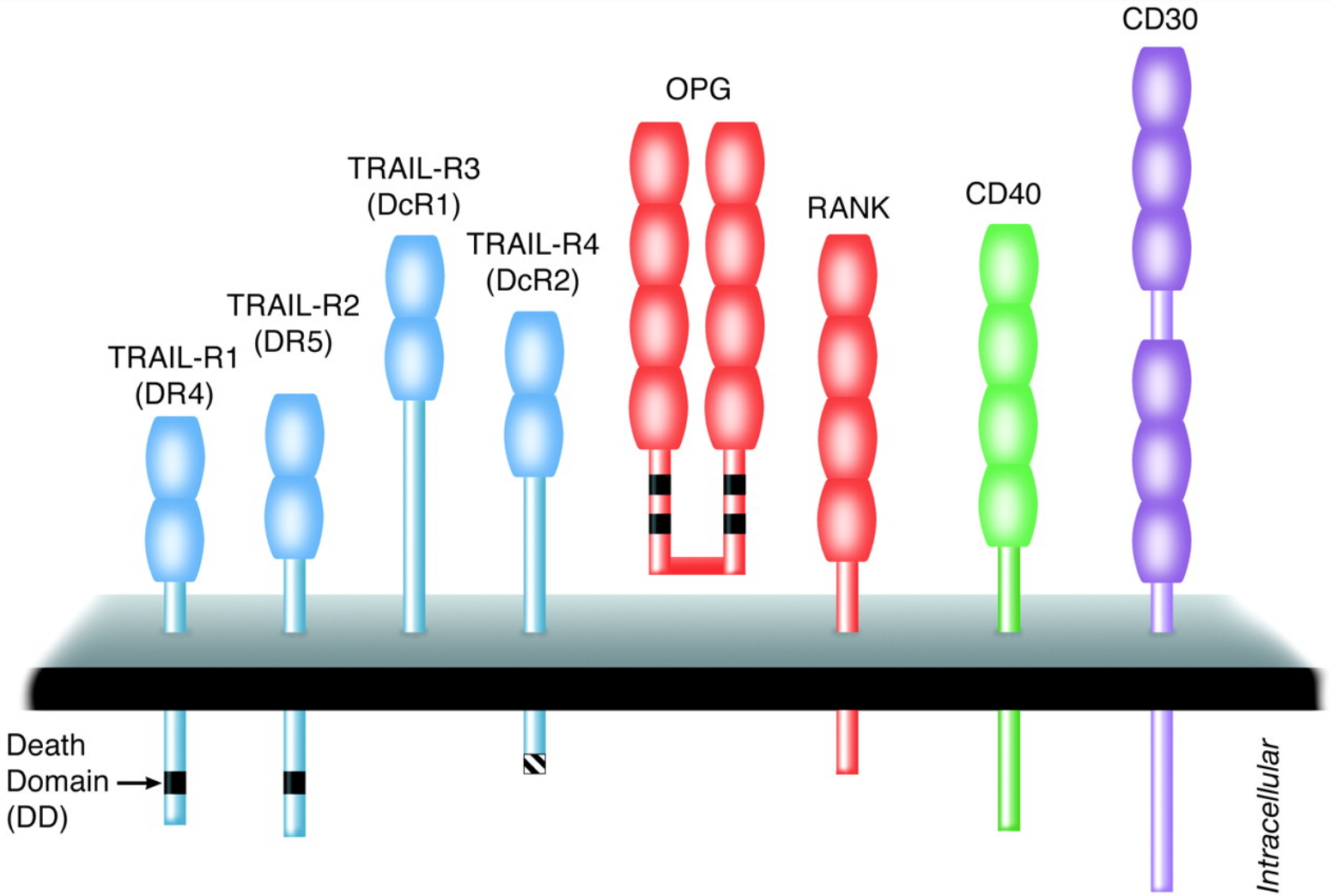
Thursday March 15, 2018: 10:15-10:30 am

1992 (Cell): Durkop and Stein:

Molecular cloning of CD30 = TNF receptor family member



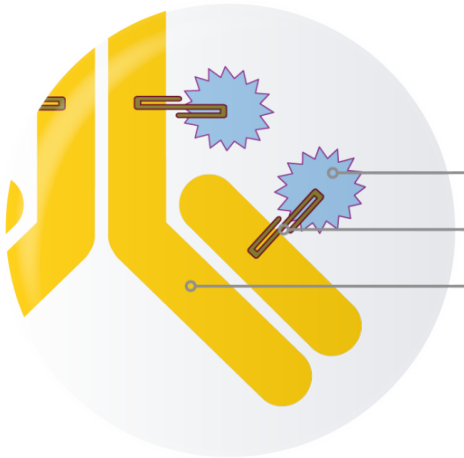
Younes A , Kadin M E JCO 2003;21:3526-3534

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%
131I-Ki4	HL	Murine	I	22	5	1	27%

Younes, A: Curr Opin Oncol. 2011

BRENTUXIMAB VEDOTIN (SGN-35) : MECHANISM OF ACTION

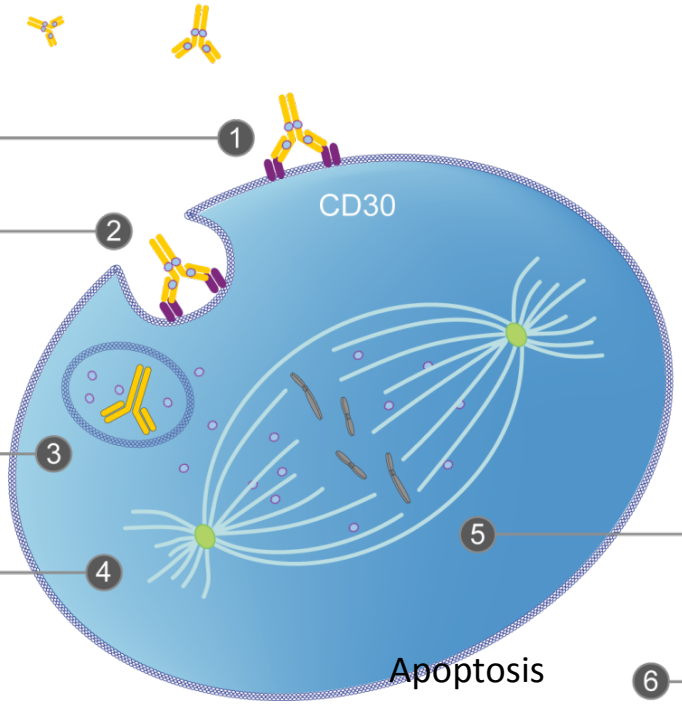


Brentuximab vedotin (SGN-35) ADC

monomethyl auristatin E (MMAE), potent antitubulin agent

protease-cleavable linker

anti-CD30 monoclonal antibody



ADC binds to CD30 (1)

ADC-CD30 complex traffics to lysosome (2)

MMAE is released (3)

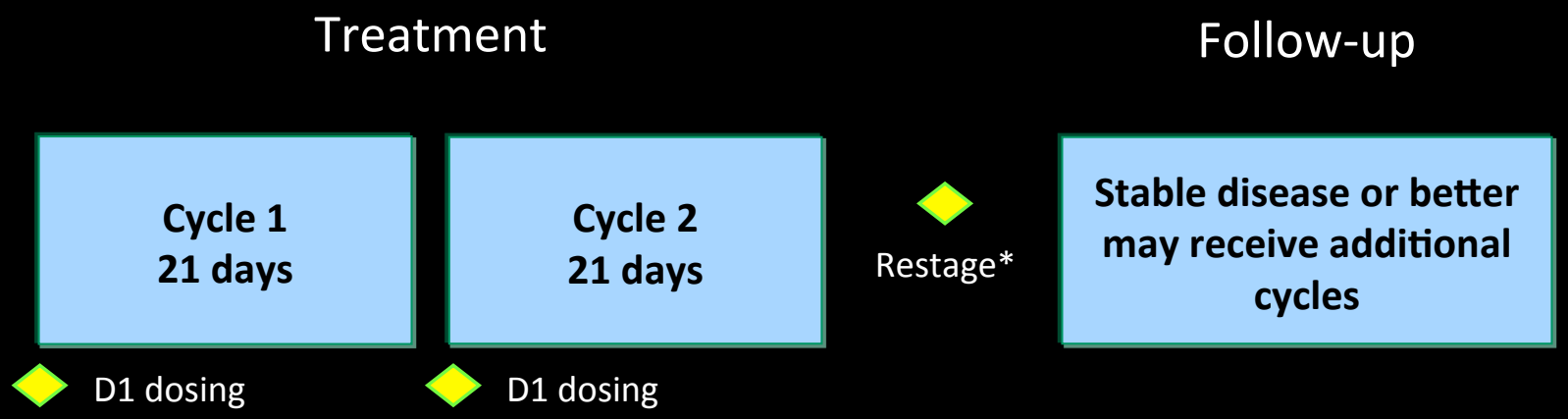
MMAE disrupts Microtubule network (4)

G2/M cell cycle arrest (5)

Apoptosis (6)

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

Phase I Brentuximab Vedotin in Relapsed HL



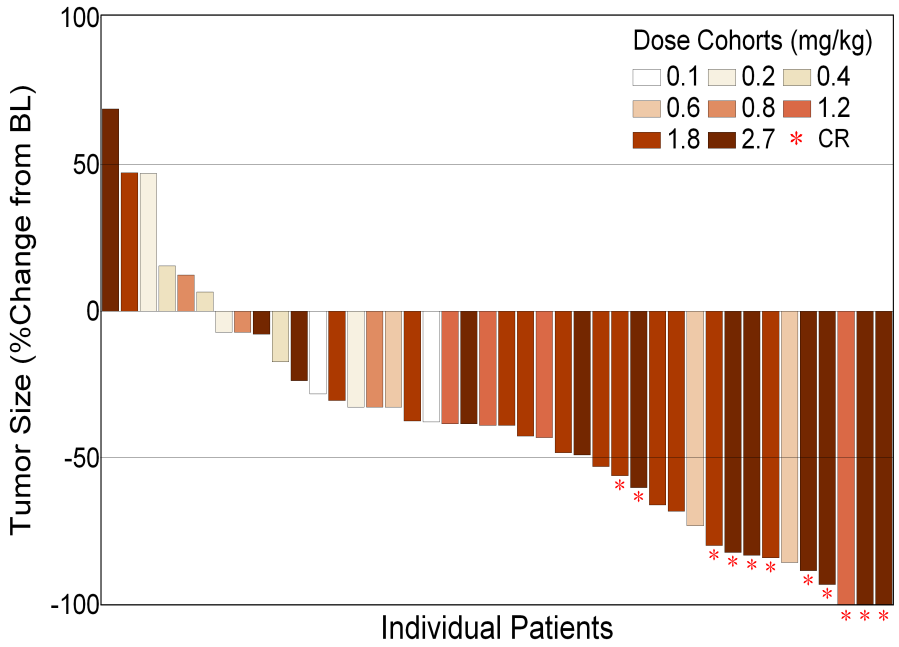
- **SGN-35 administered IV every 21 days**
- **Dose cohorts: 0.1, 0.2, 0.4, 0.6, 0.8, 1.2, 1.8, 2.7, 3.6 mg/kg**

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

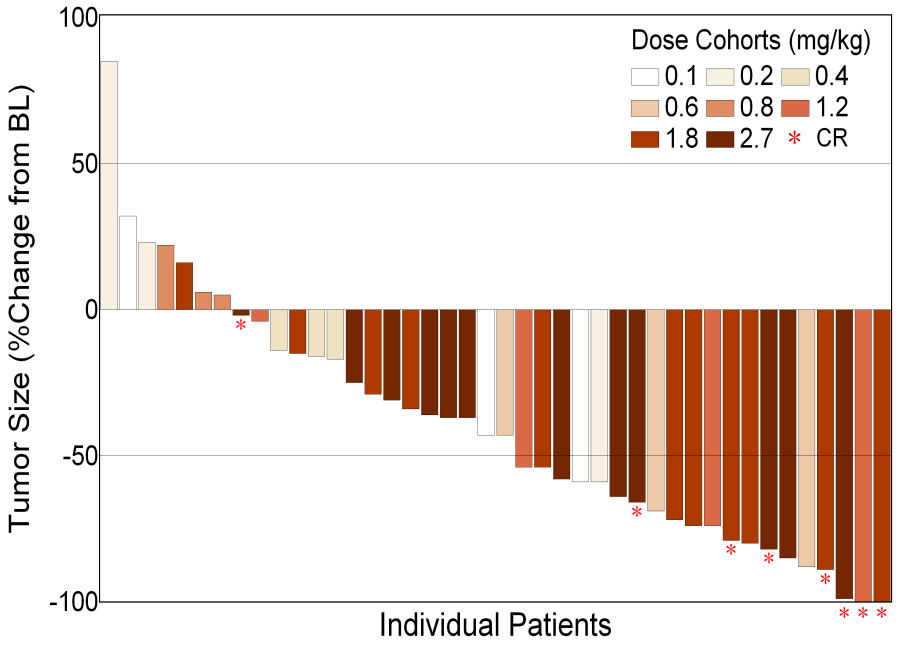
Younes A, et al. N Engl J Med 2010; 363:1812-1821

Phase-I Brentuximab Vedotin in Relapsed HL Treatment Response

Investigator Assessment



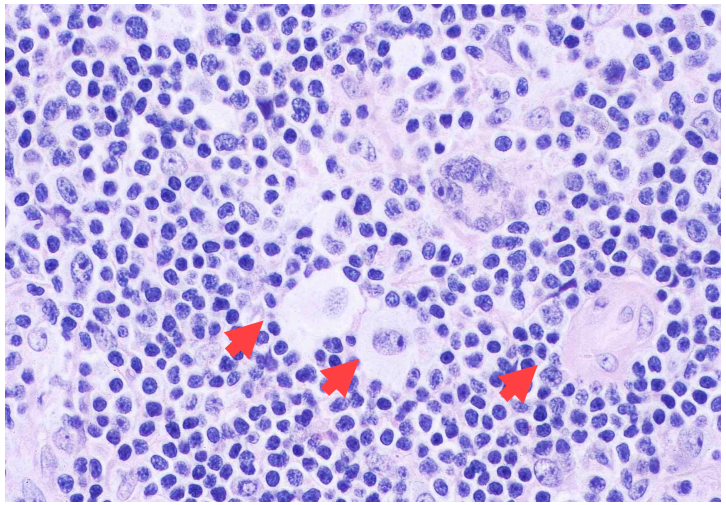
IRF Assessment

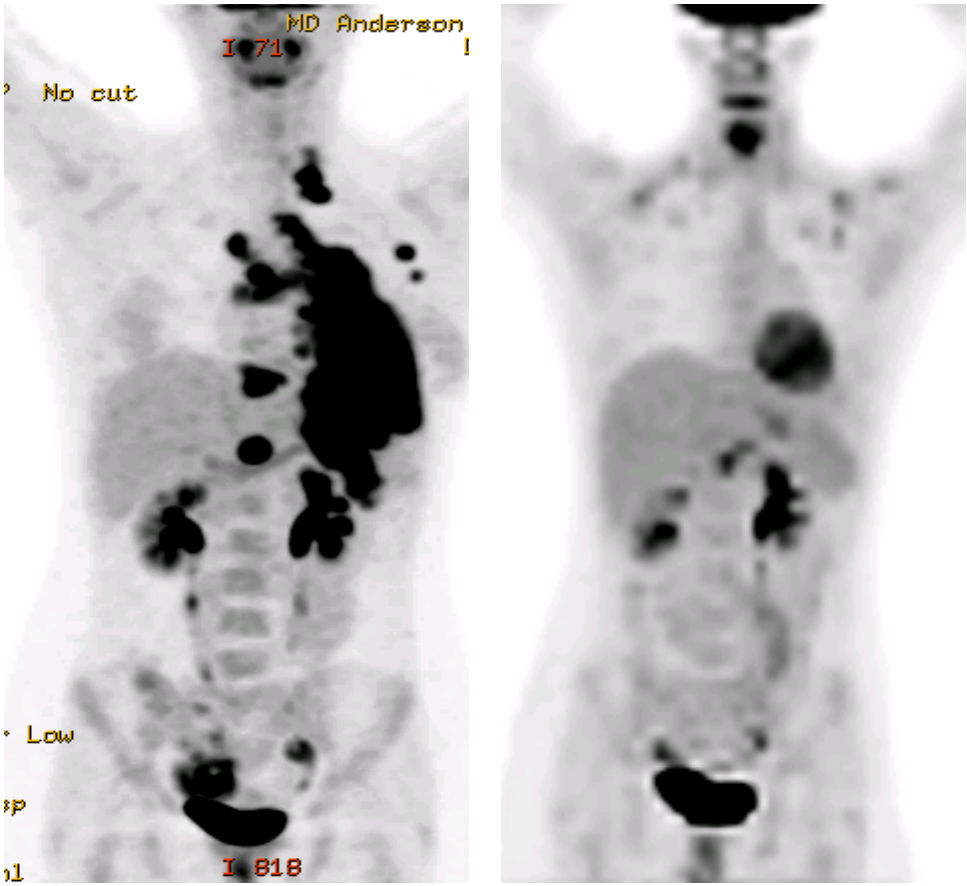


Younes A, et al. N Engl J Med 2010; 363:1812-1821

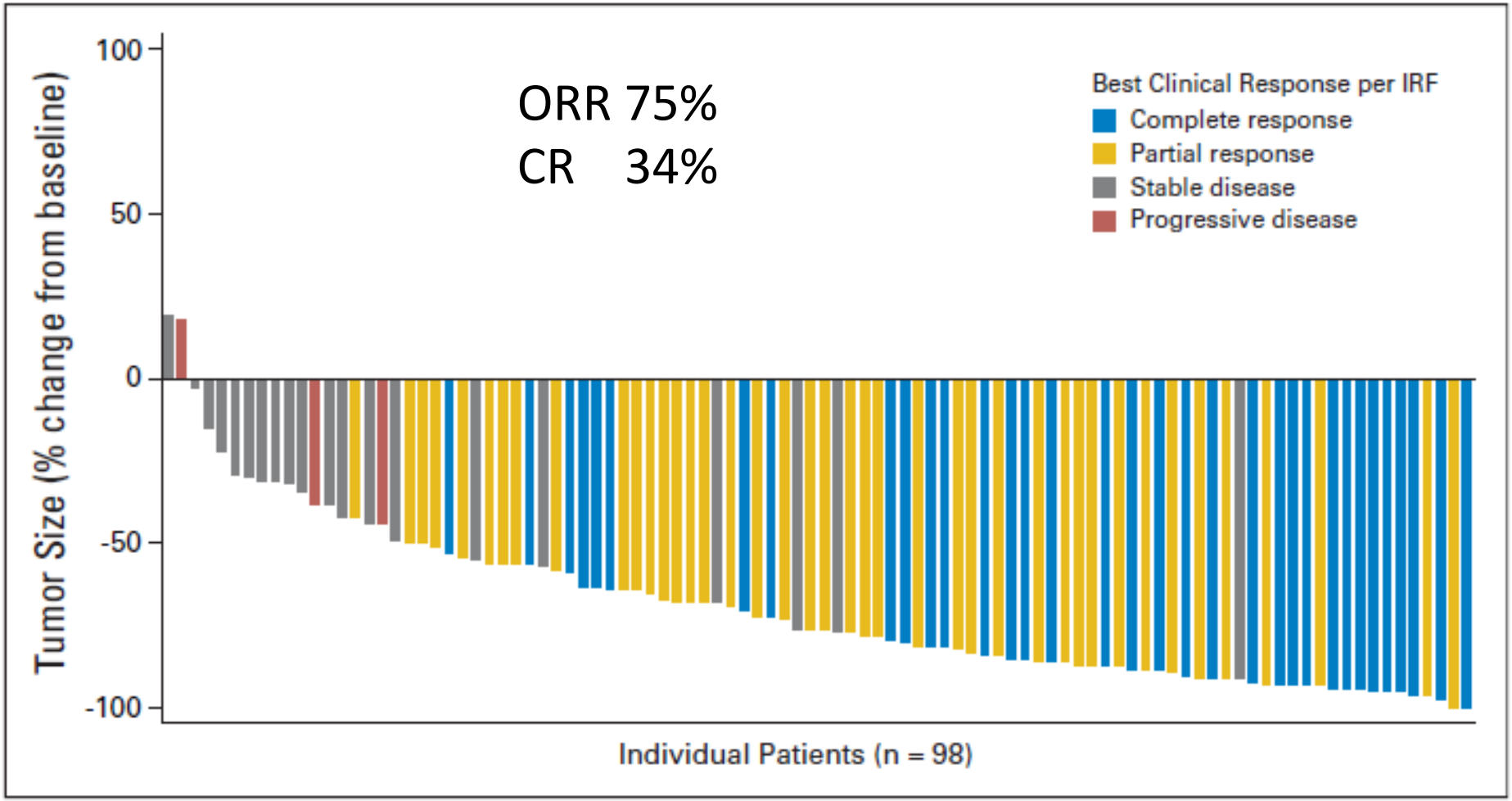
Phase I Brentuximab Vedotin in Relapsed HL

- 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





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



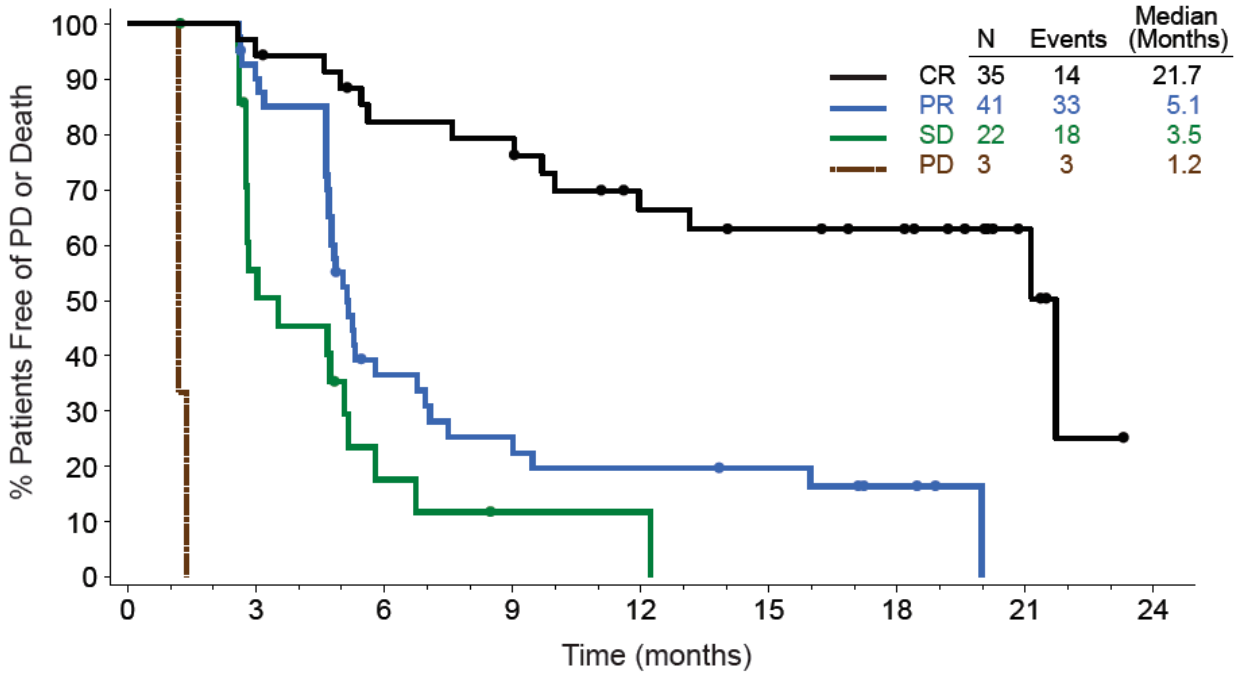
94% patients achieved tumour reduction

IRF – independent review facility

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

Brentuximab vedotin: pivotal Phase II trial PFS results by best response

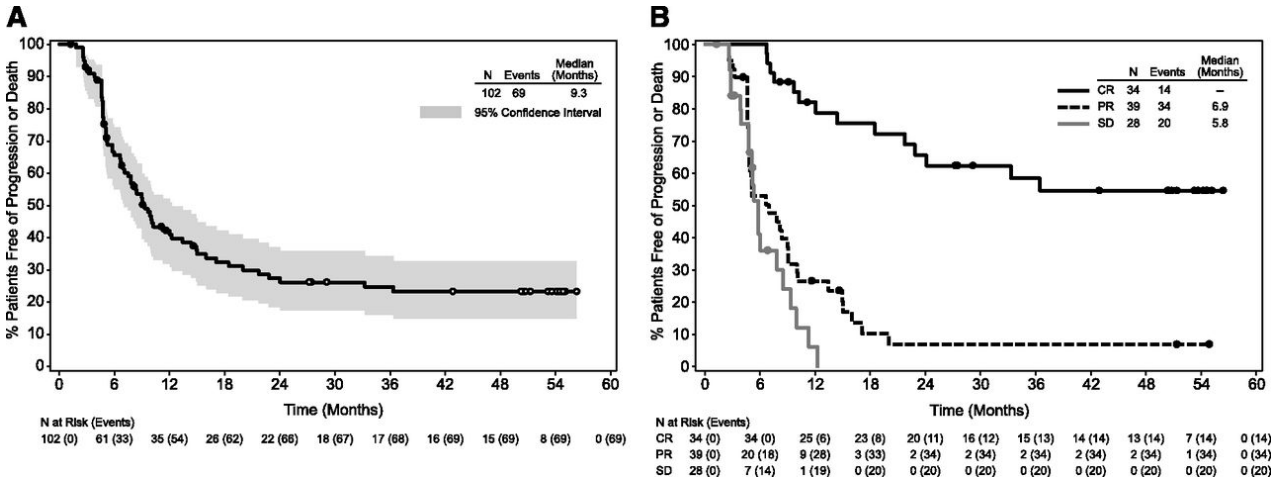
- Phase II pivotal study of brentuximab vedotin in 102 patients with relapsed/refractory HL post ASCT: PFS by best response

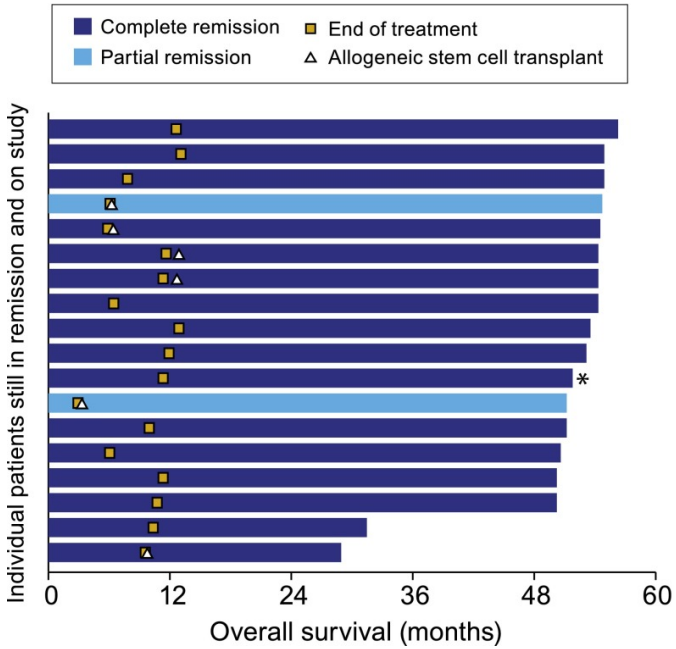


Younes A et al. J Clin Oncol 2012;30: 2183-9.

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

PFS following treatment with brentuximab vedotin.

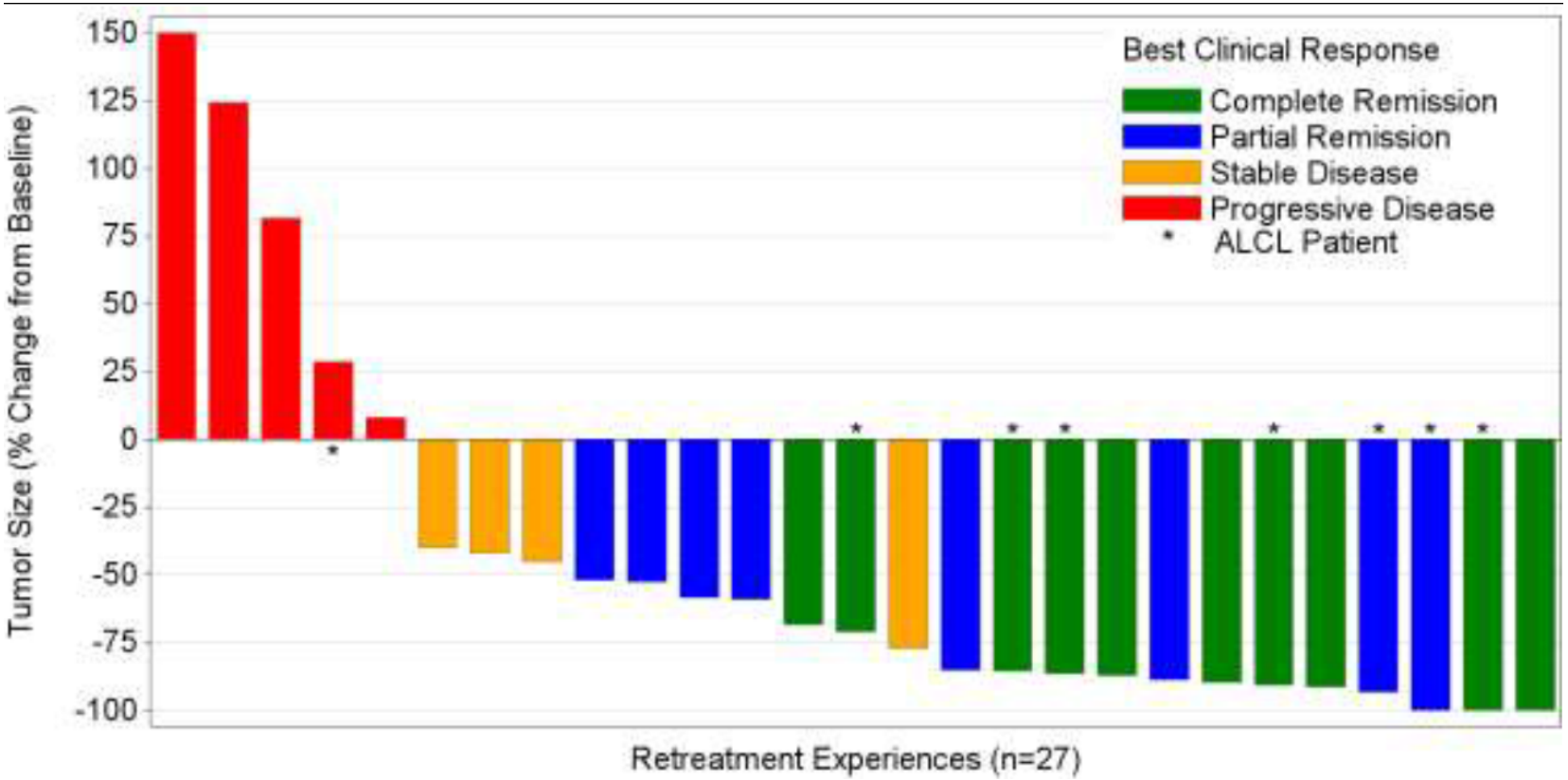




4/16 in CR had all0-SCT

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

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



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

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

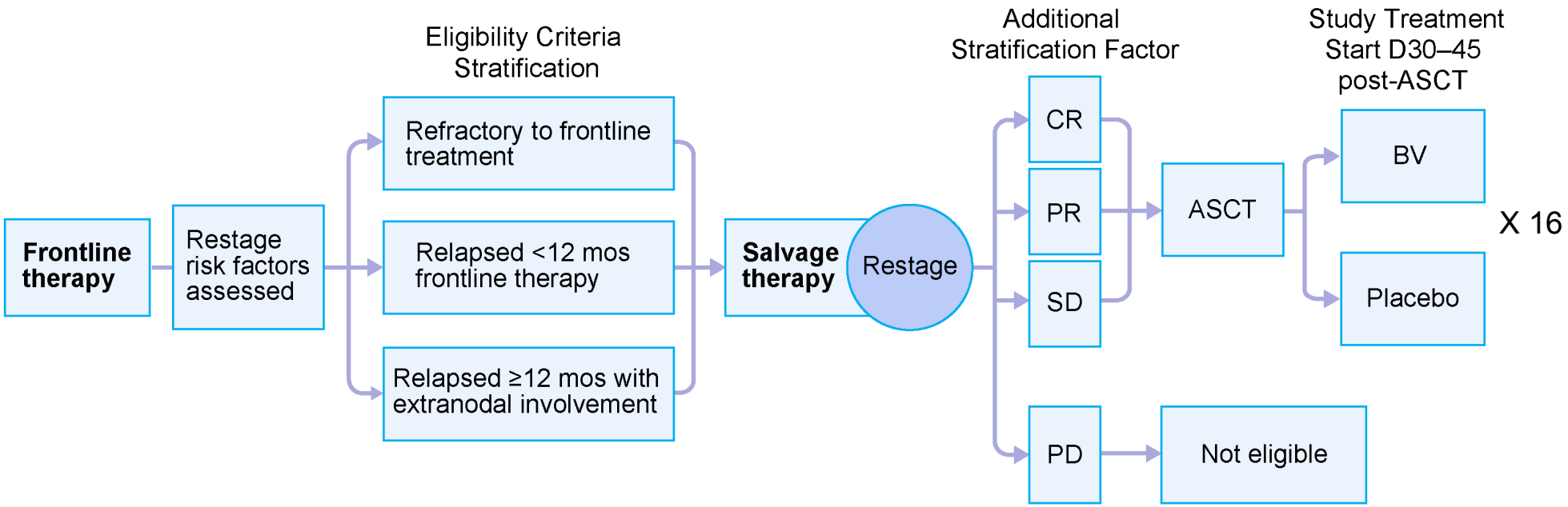
BV combination regimens

	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

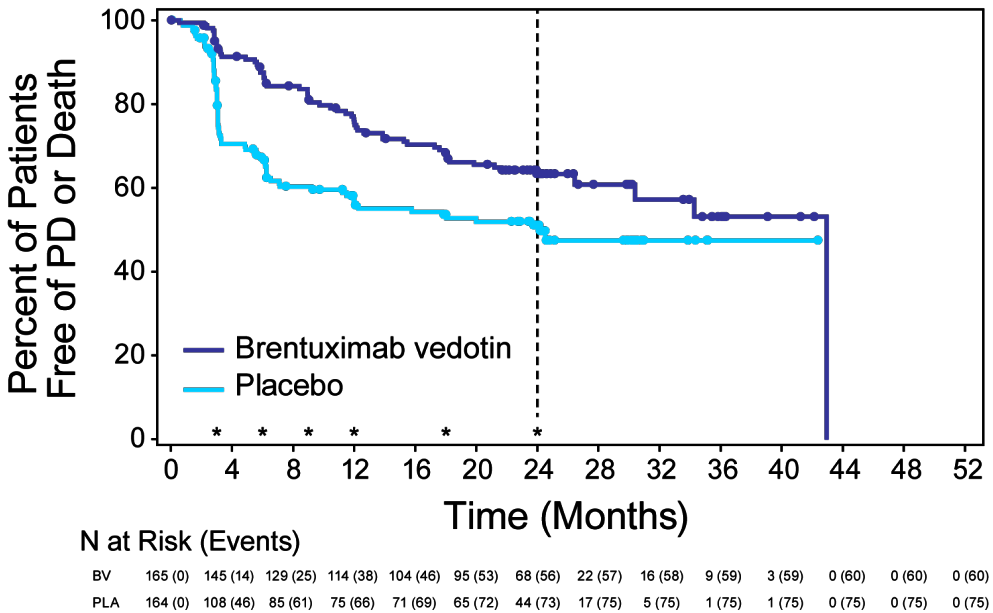
329 patients were randomised at 78 sites in North America and Europe



Moskowitz C, et al The Lancet 2015

Progression-free survival

PFS per IRF

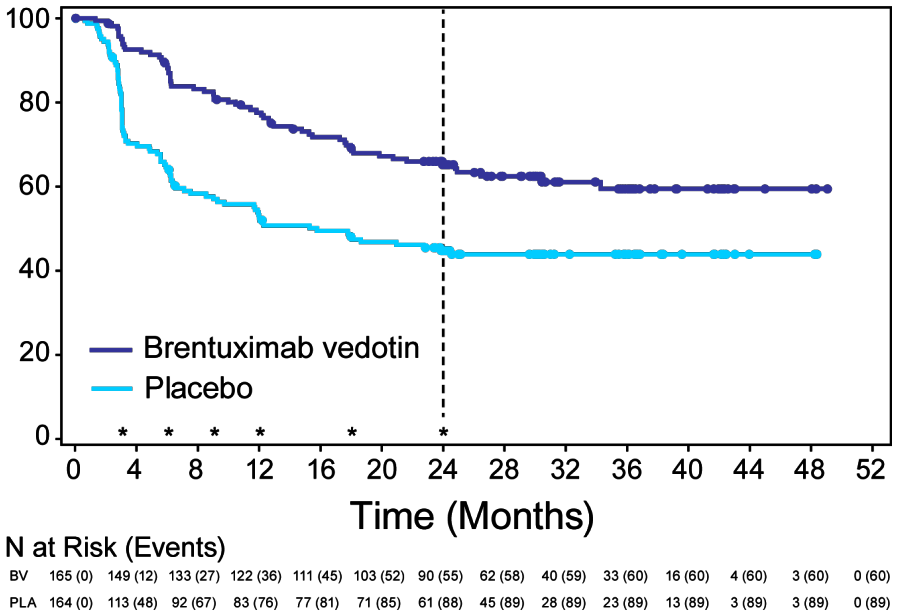


N at Risk (Events)

BV	165 (0)	145 (14)	129 (25)	114 (38)	104 (46)	95 (53)	68 (56)	22 (57)	16 (58)	9 (59)	3 (59)	0 (60)	0 (60)	0 (60)
PLA	164 (0)	108 (46)	85 (61)	75 (66)	71 (69)	65 (72)	44 (73)	17 (75)	5 (75)	1 (75)	1 (75)	0 (75)	0 (75)	0 (75)

	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†



N at Risk (Events)

BV	165 (0)	149 (12)	133 (27)	122 (36)	111 (45)	103 (52)	90 (55)	62 (58)	40 (59)	33 (60)	16 (60)	4 (60)	3 (60)	0 (60)
PLA	164 (0)	113 (48)	92 (67)	83 (76)	77 (81)	71 (85)	61 (88)	45 (89)	28 (89)	23 (89)	13 (89)	3 (89)	3 (89)	0 (89)

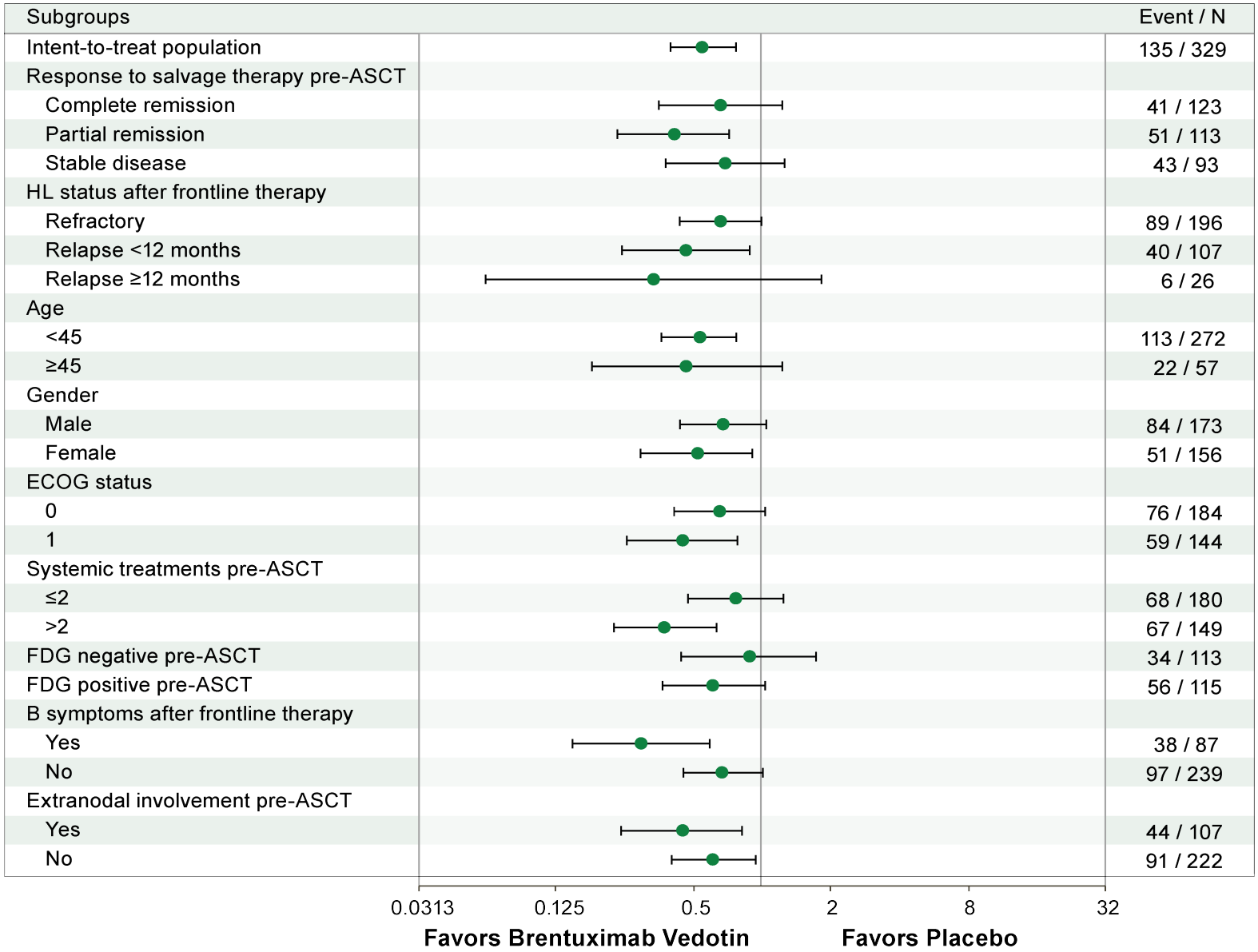
	BV (N=165)	Placebo (N=164)
Hazard Ratio (95% CI)	**0.50 (0.36–0.70)**	
Events	60	89
Median PFS (months)	--	16
2-year PFS rate	65%	45%

* 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



Treatment Approaches in Relapsed/Refractory HL

The Combo News

Anas Younes, M.D.
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Thursday March 15, 2018: 11:00-11:15 am

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%	Chen, R & C. Moskowitz JCO 2017
Nivolumab (Fully human IgG4)	3 mg/kg IV Q 2 wks	80	66%	9%	Younes, A/Lancet Oncology 2016

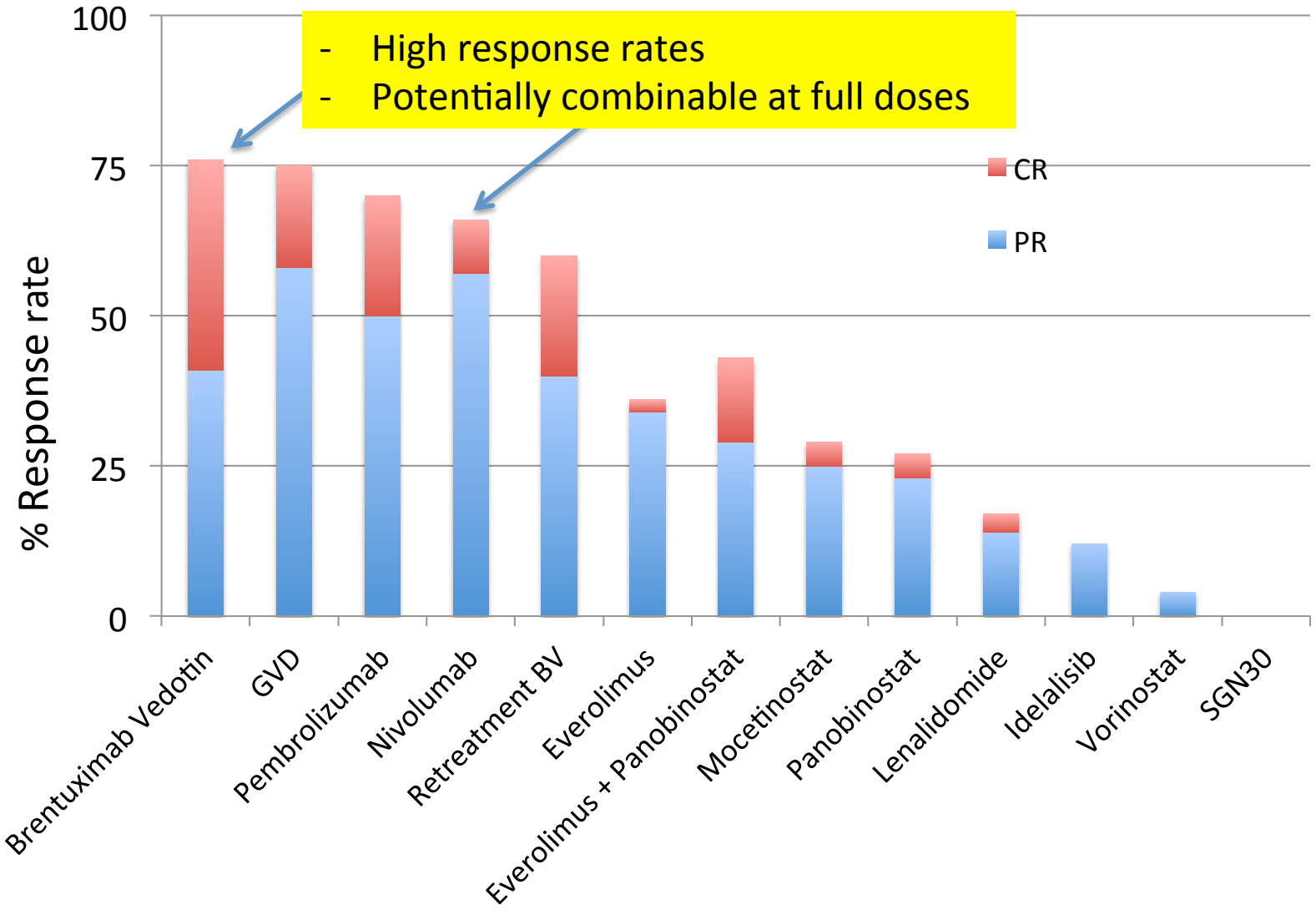
Results of PD1 Blocking Antibodies in Relapsed HL

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%	Chen, R & C. Moskowitz JCO 2017
Nivolumab (Fully human IgG4)	3 mg/kg IV Q 2 wks	63	68%	22%	Fanale, M/ ICML2017

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)

1105 Preliminary Results from a Phase 1/2 Study of Brentuximab Vedotin in Combination with Nivolumab in Patients with Relapsed or Refractory Hodgkin Lymphoma

Alex F Herrera, MD[1], Nancy L Bartlett, MD[2], Radhakrishnan Ramchandren, MD[3*], Julie M Vose, MD[4], Alison J Moskowitz, MD[5], Tatyana A Feldman, MD[6], Ann S LaCasce, MD[7], Stephen M Ansell, MD, PhD[8*], Craig H. Moskowitz, MD[5], Keenan Fenton[9*], Kazunobu Kato, MD[10], Abraham Fong, MD, PhD[9] and Ranjana H Advani, MD[11]

Nivolumab + Brentuximab Salavage Therapy for HL

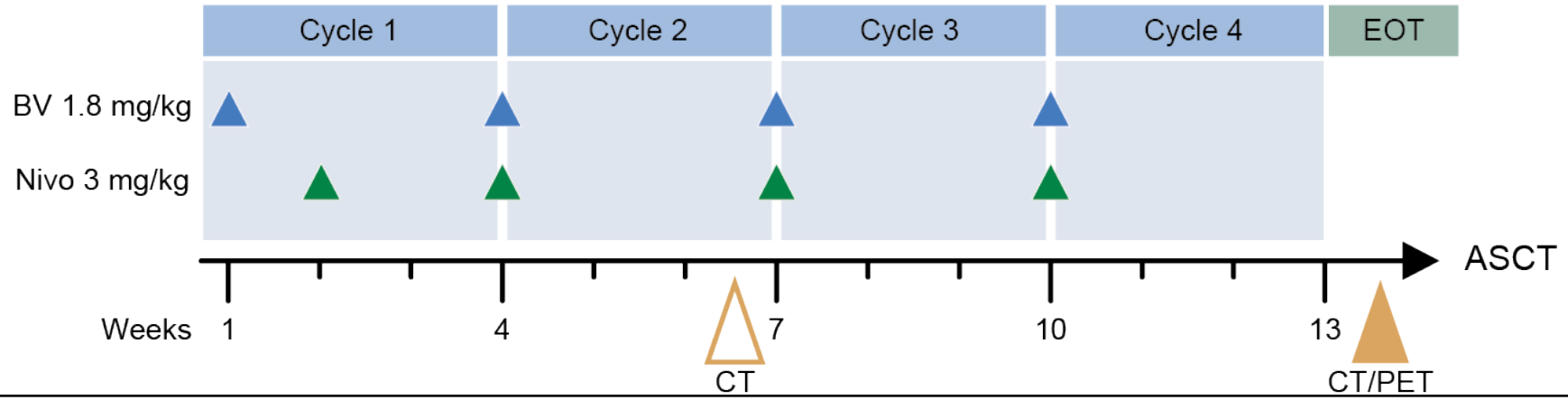
Brentuximab Vedotin 1.8mg/kg

Nivolumab 240 mg

Q 3wks x 4

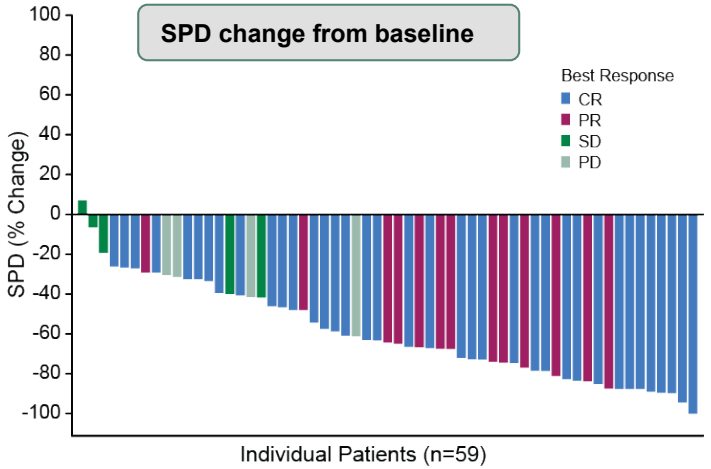
→ Restage

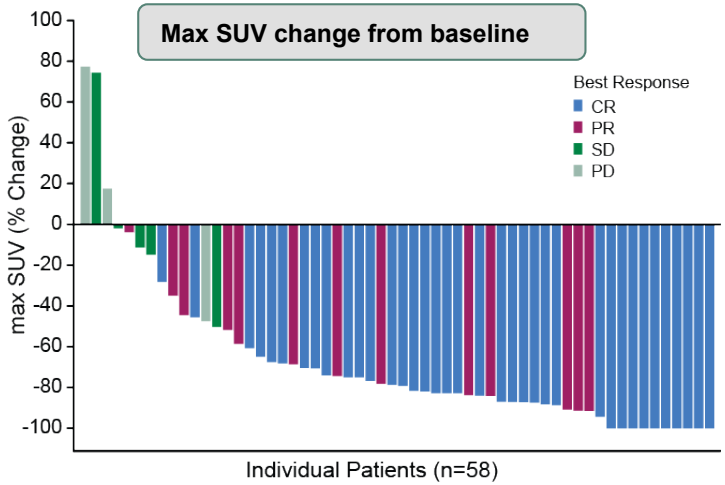
- PR/CR → Stem cell collection => BEAM ASCT
- < PR → Chemo salvage → Stem cell collection => BEAM ASCT



Tumor Response (N=59)

85% objective response rate with 63% complete responses



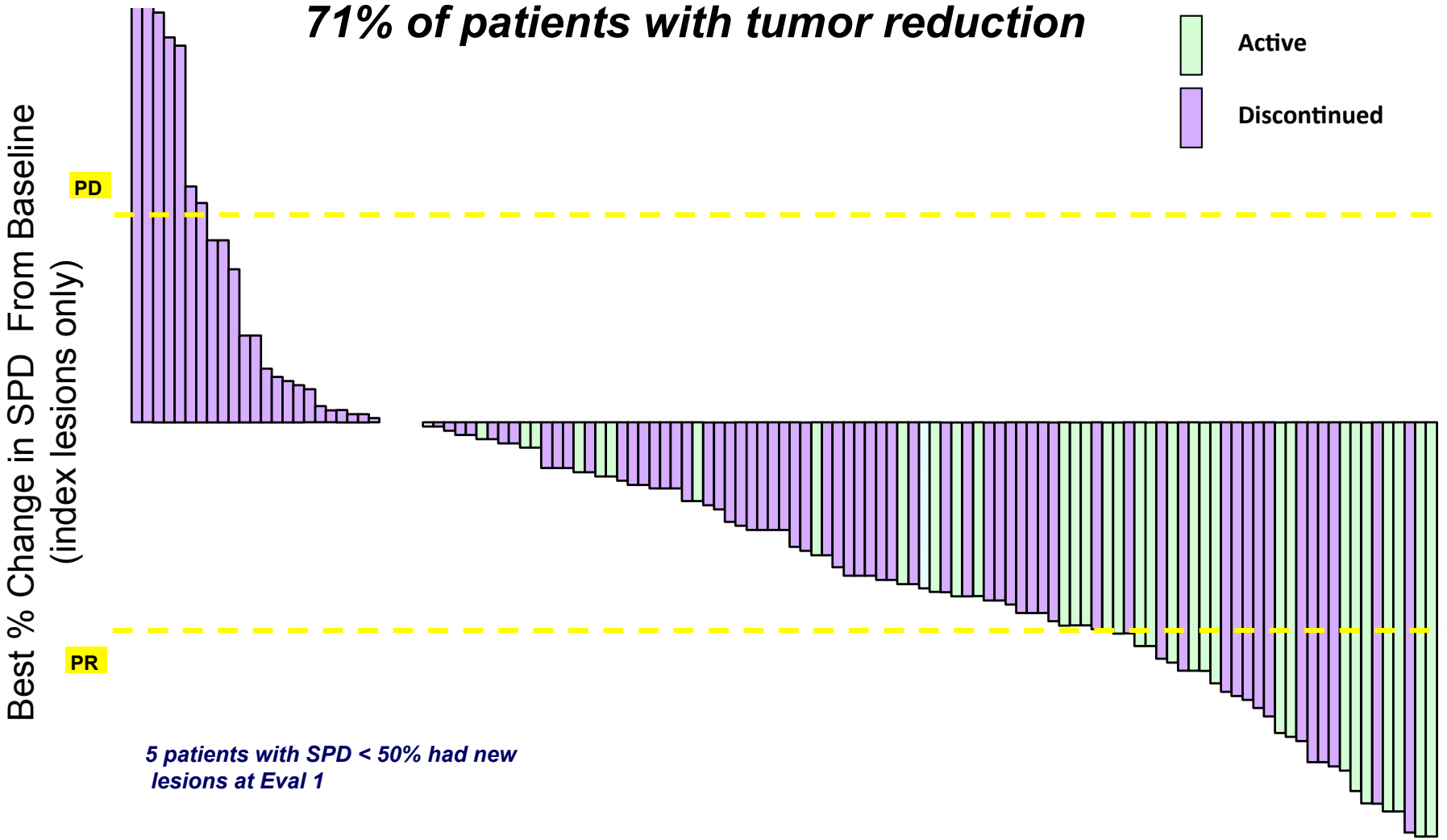


	N = 59 n (%)
Complete response (CR)	**37 (63)**
Deauville ≤ 2	29 (49)
Deauville 3	7 (12)
Deauville 5[a]	1 (2)
Partial response (PR)	**13 (22)**
Deauville 4	7 (12)
Deauville 5	6 (10)
No metabolic response (SD)	**5 (8)**
Deauville 5	5 (8)
Progressive disease (PD)	**3 (5)**
Deauville 5	2 (3)
Missing	1 (2)
Clinical Progression (CP)	**1 (2)**

a. 1 pt had uptake in lymph node, but no evidence of disease was found on biopsy

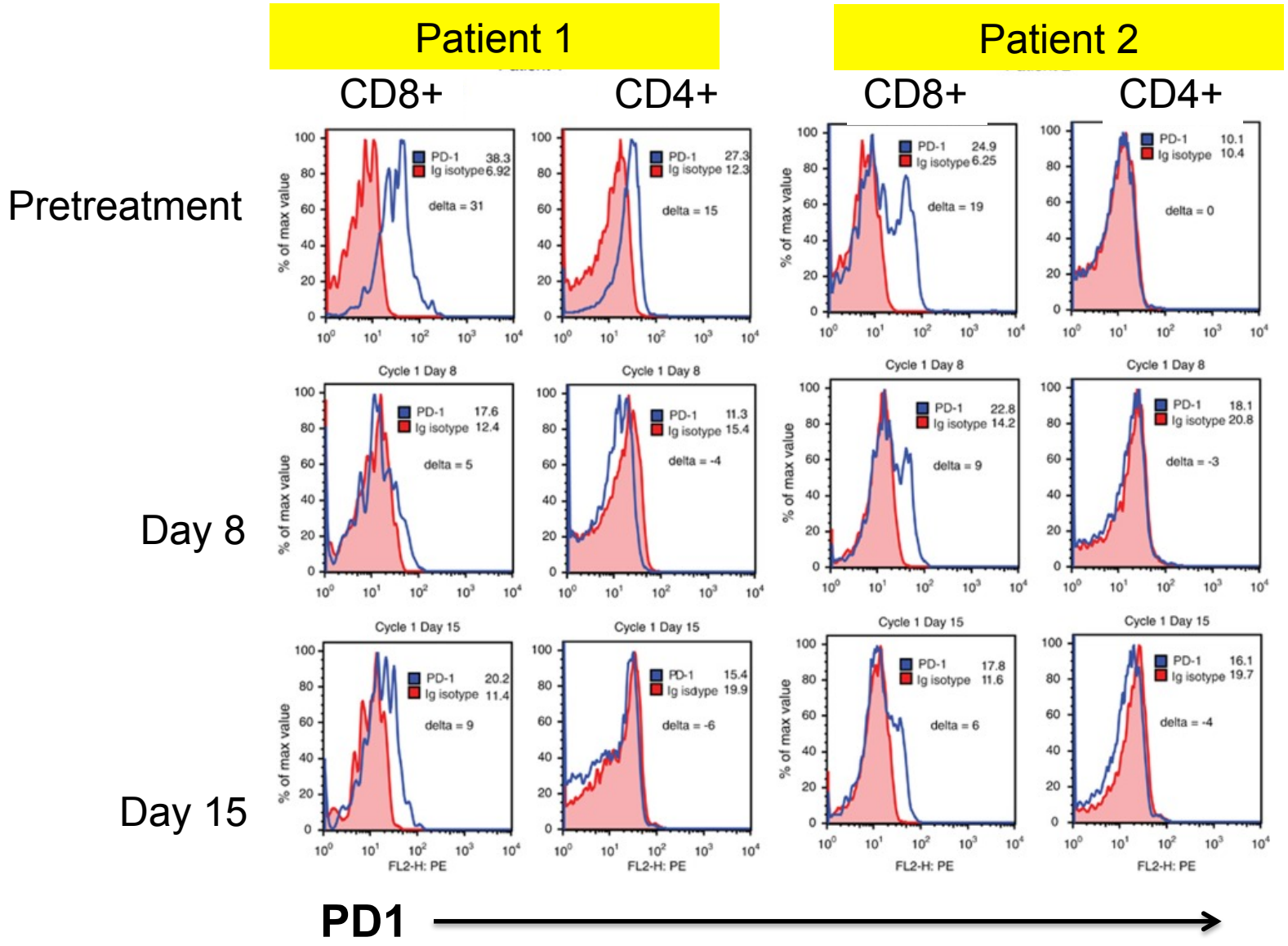
SPD, sum of the product of the diameters; SUV, standard uptake value

Panobinostat Phase II Study in Relapsed HL



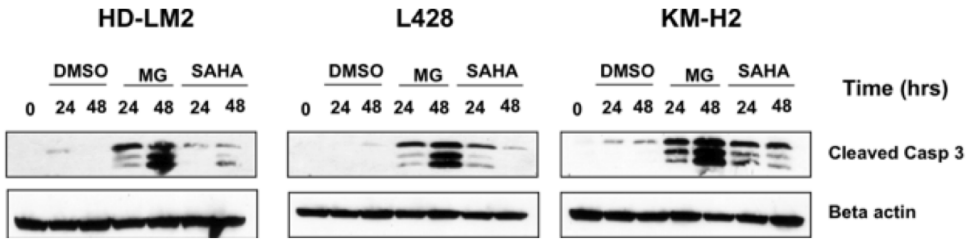
Younes A,,Soreda A,, et al. JCO 2012

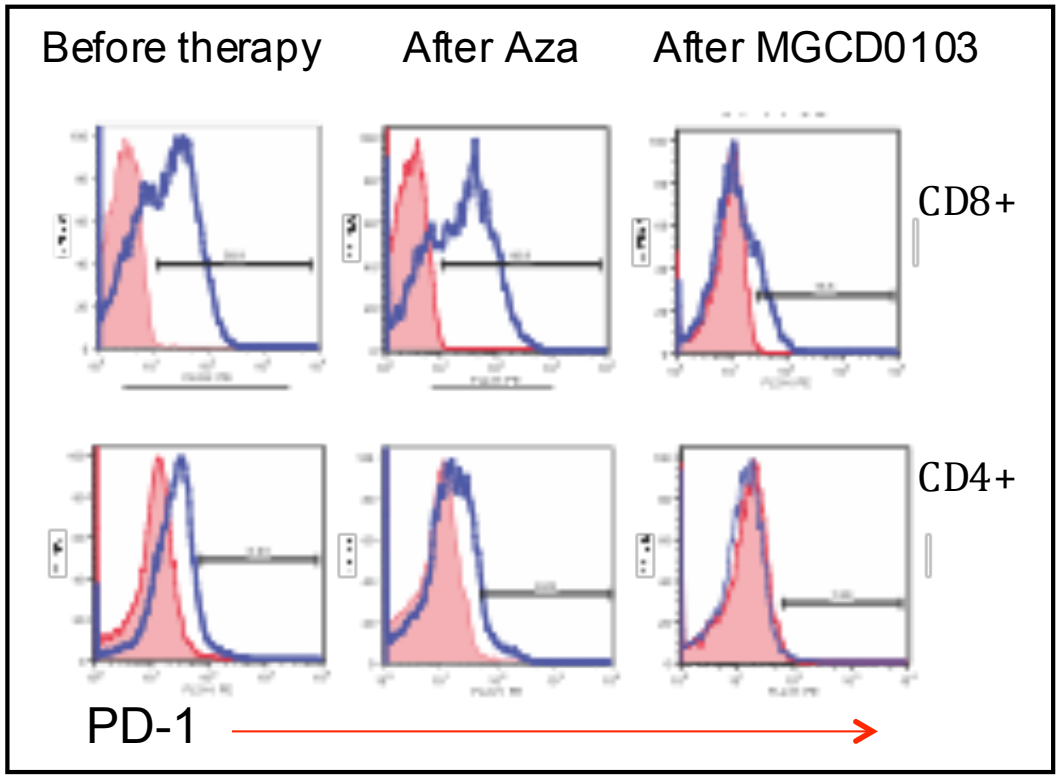
Panobinostat Downregulates PD-1 on T cells of Patients with Relapsed HL in Vivo



Oki Y and Younes A - Blood Cancer J. 2014 Aug; 4(8): e236.

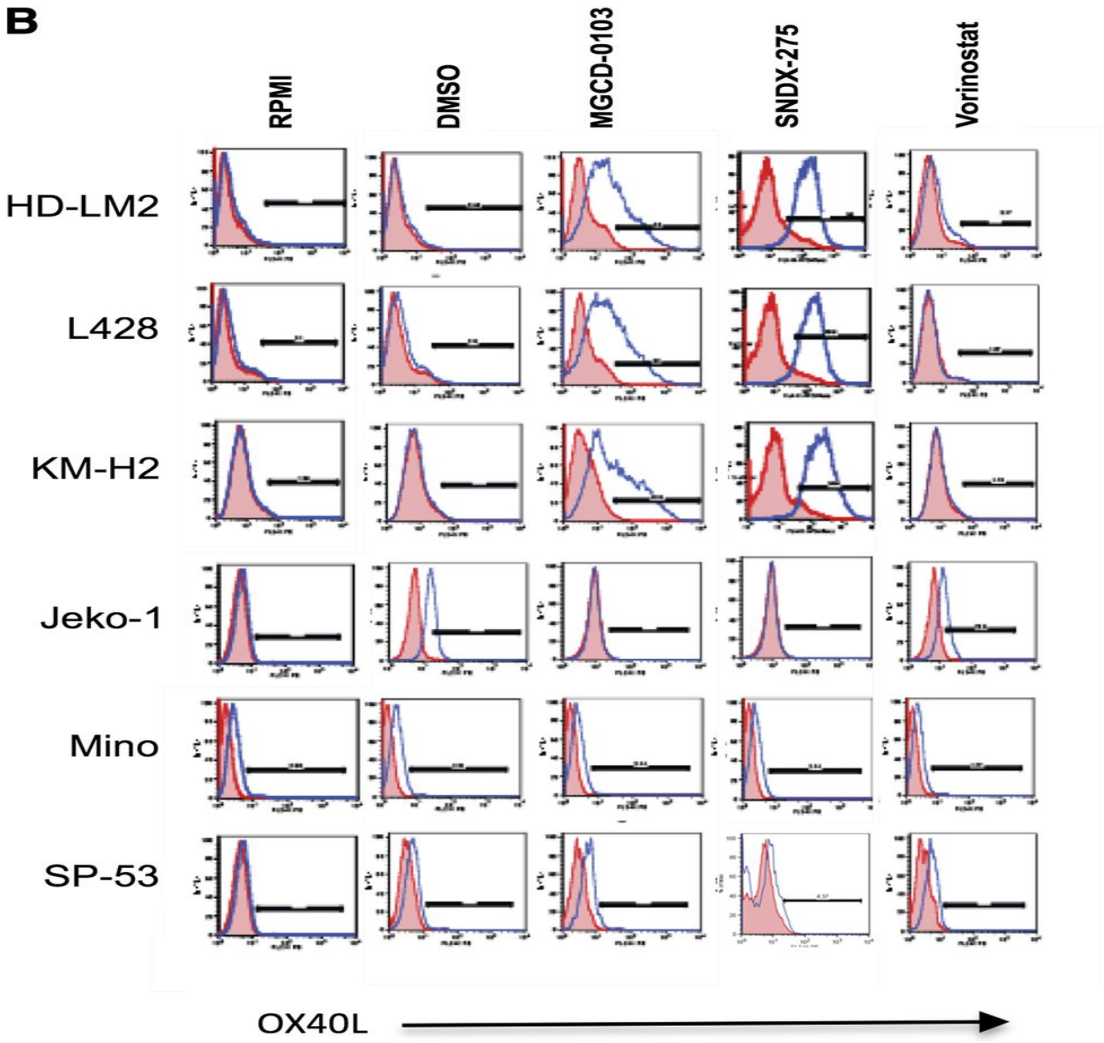
DAC Inhibitors in HL: Regulation of Cell Survival and Immunity





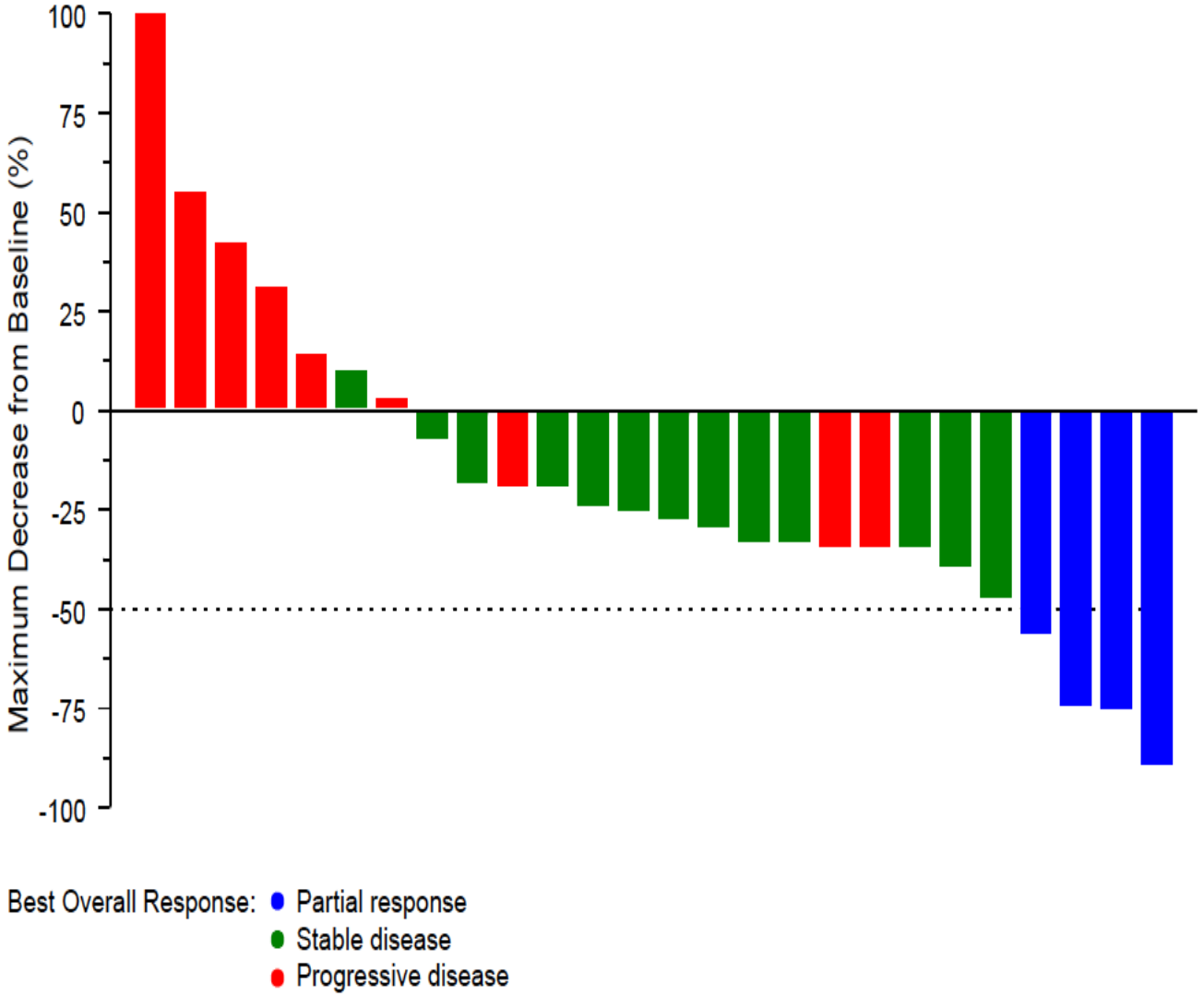
HDACi Upregulate OX40L on HRS Cells

Inhibition of T-reg function



Buglio D, et al BLOOD 2011

Entinostat in Relapsed HL



Batlevi et al, Haematologica 2017

Phase I/II Study of Entinostat (HDACi) + Pembrolizumab (anti-PD1)

- Relapsed HL
- Relapsed FL