Novel treatment Approaches of advanced stage Hodgkin Lymphoma

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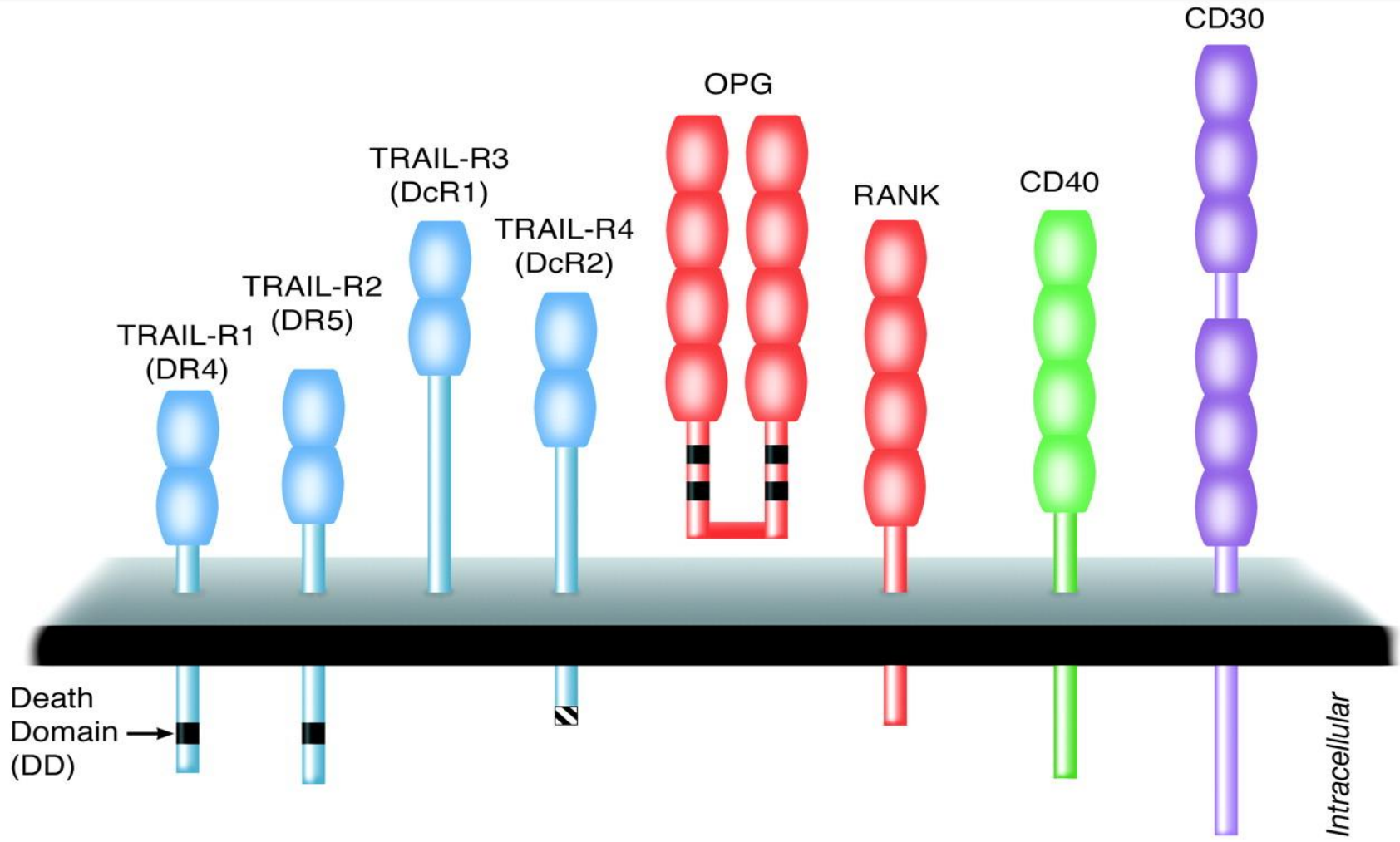
1992 (Cell): Durkop and Stein:

Molecular cloning of CD30 = TNF receptor family member



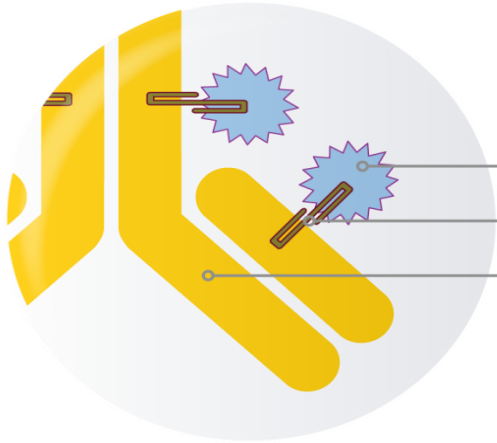
Younes A , Kadin M E JCO 2003;21:3526-3534

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

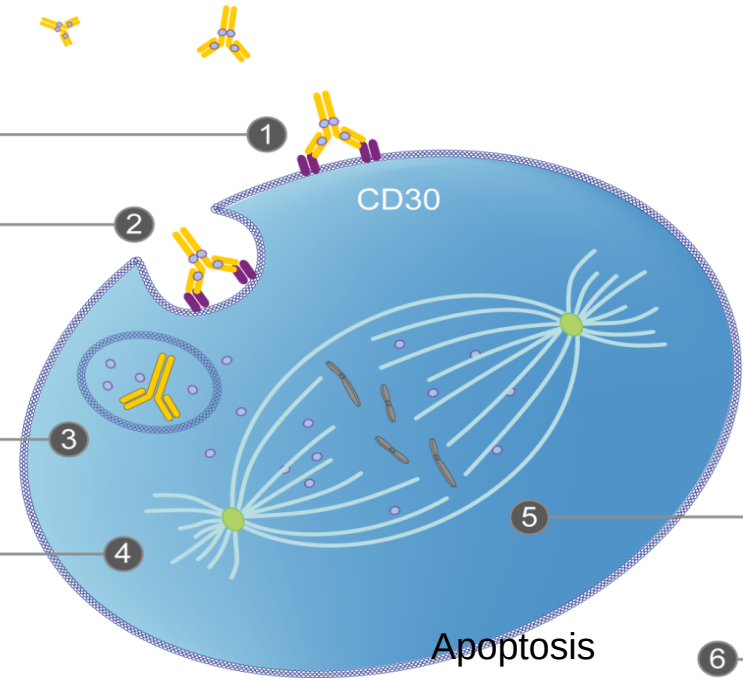


Brentuximab vedotin (SGN-35) ADC

monomethyl auristatin E (MMAE), potent antitubulin agent

protease-cleavable linker

anti-CD30 monoclonal antibody



ADC binds to CD30

ADC-CD30 complex traffics to lysosome

MMAE is released

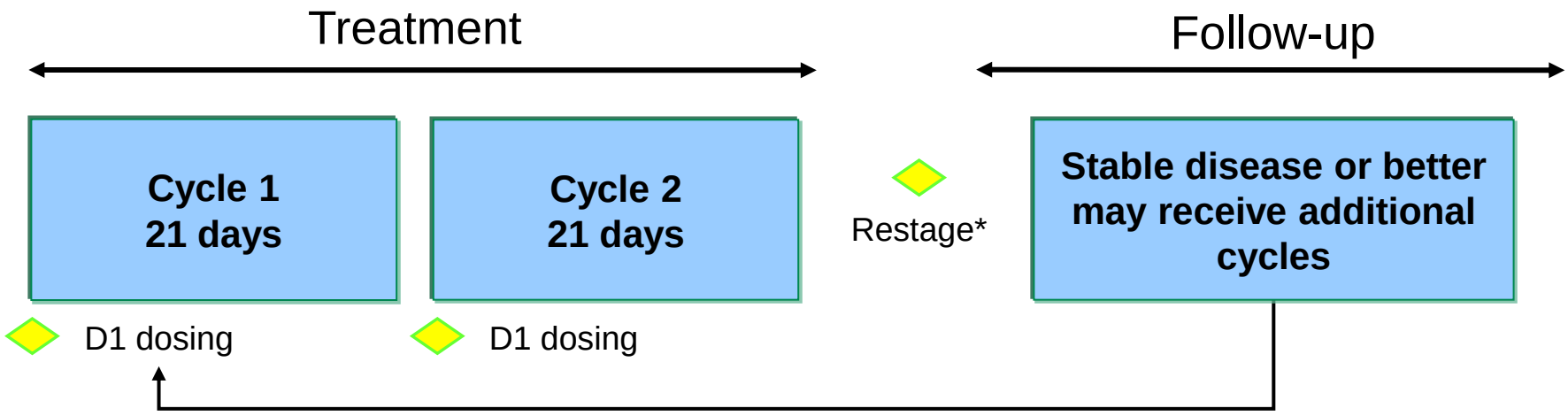
MMAE disrupts Microtubule network

G2/M cell cycle arrest

Apoptosis

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

Phase I Brentuximab Vedotin in Relapsed HL

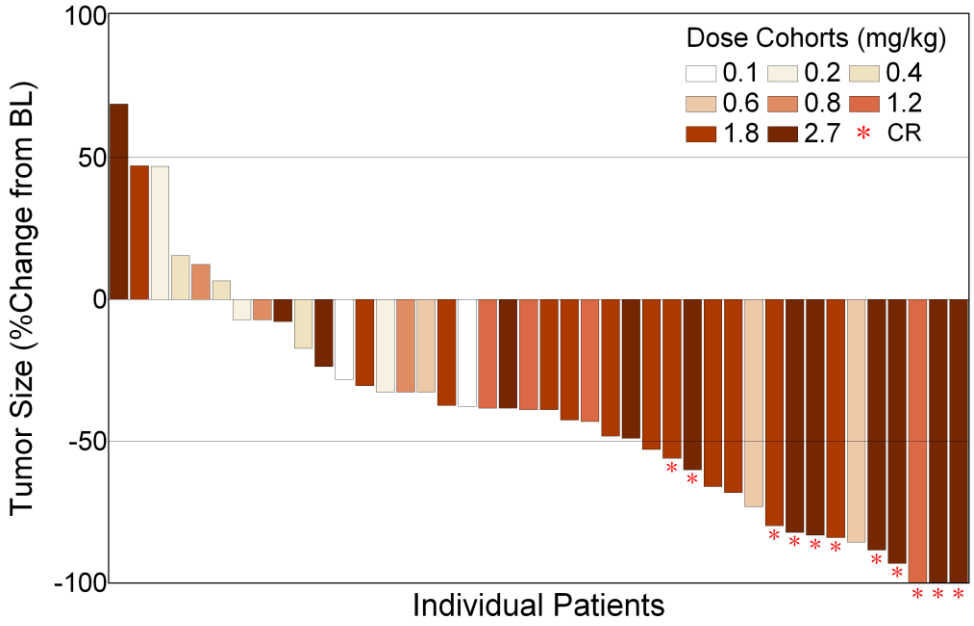


- **SGN-35 administered IV every 21 days**
- **Dose cohorts: 0.1, 0.2, 0.4, 0.6, 0.8, 1.2, 1.8, 2.7, 3.6 mg/kg**

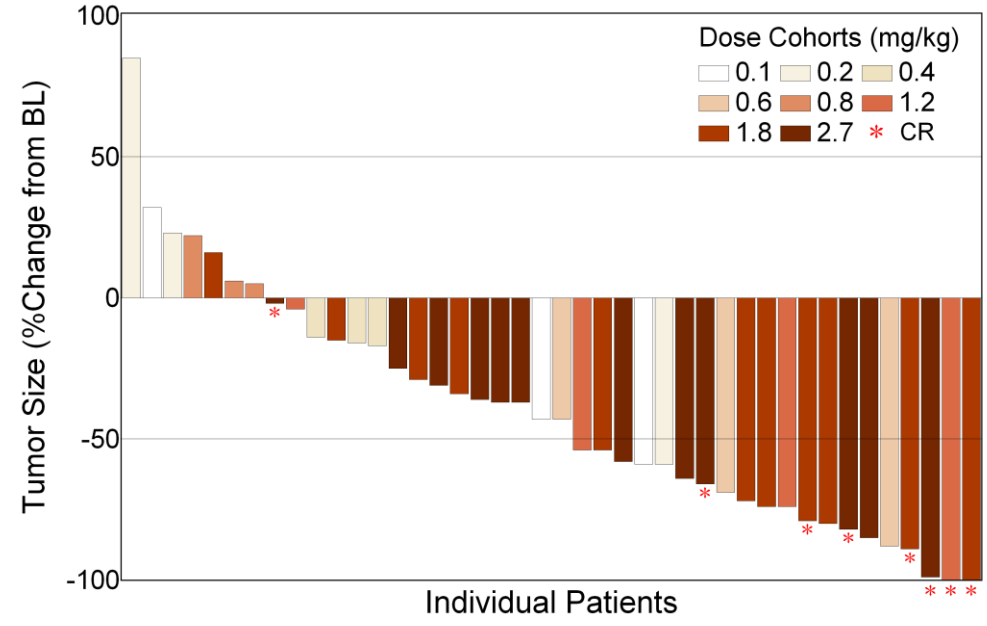
*** CT and PET scans were retrospectively reviewed by an independent review facility (IRF)**

Phase-I Brentuximab Vedotin in Relapsed HL: Treatment Response

Investigator Assessment



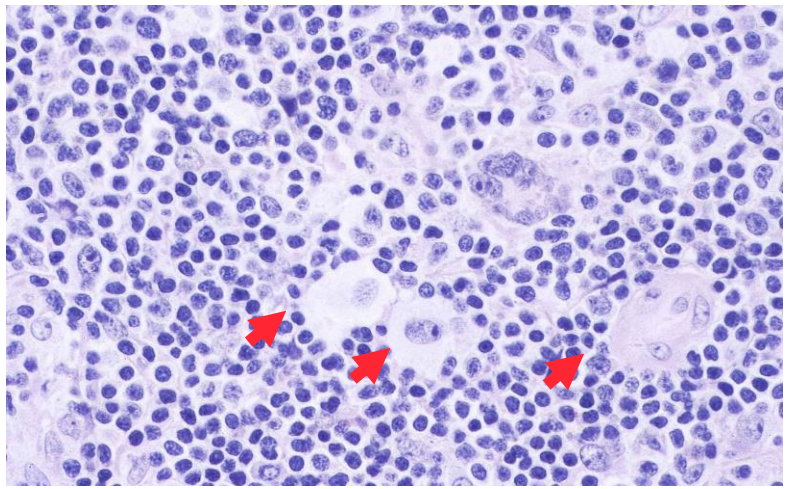
IRF Assessment

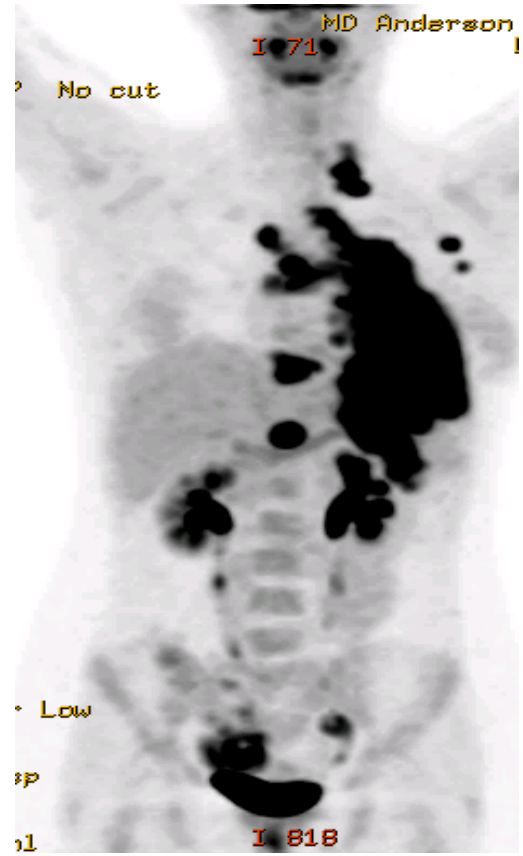


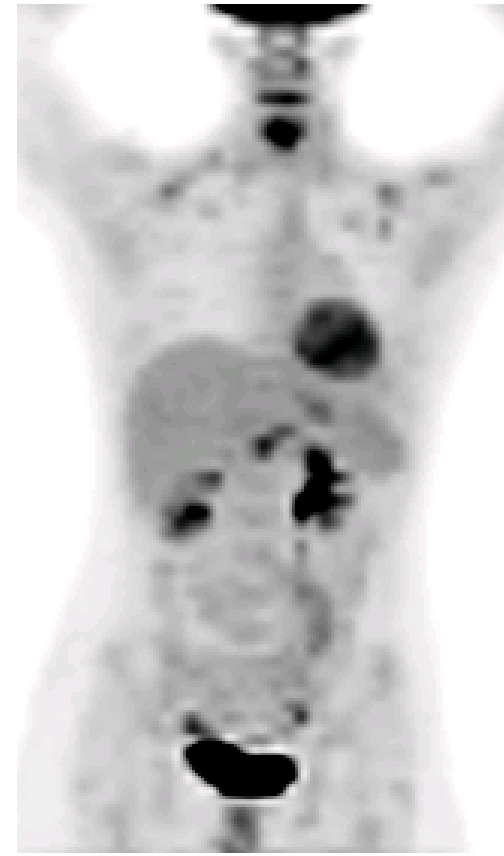
Younes A, et al. N Engl J Med 2010; 363:1812-1821

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

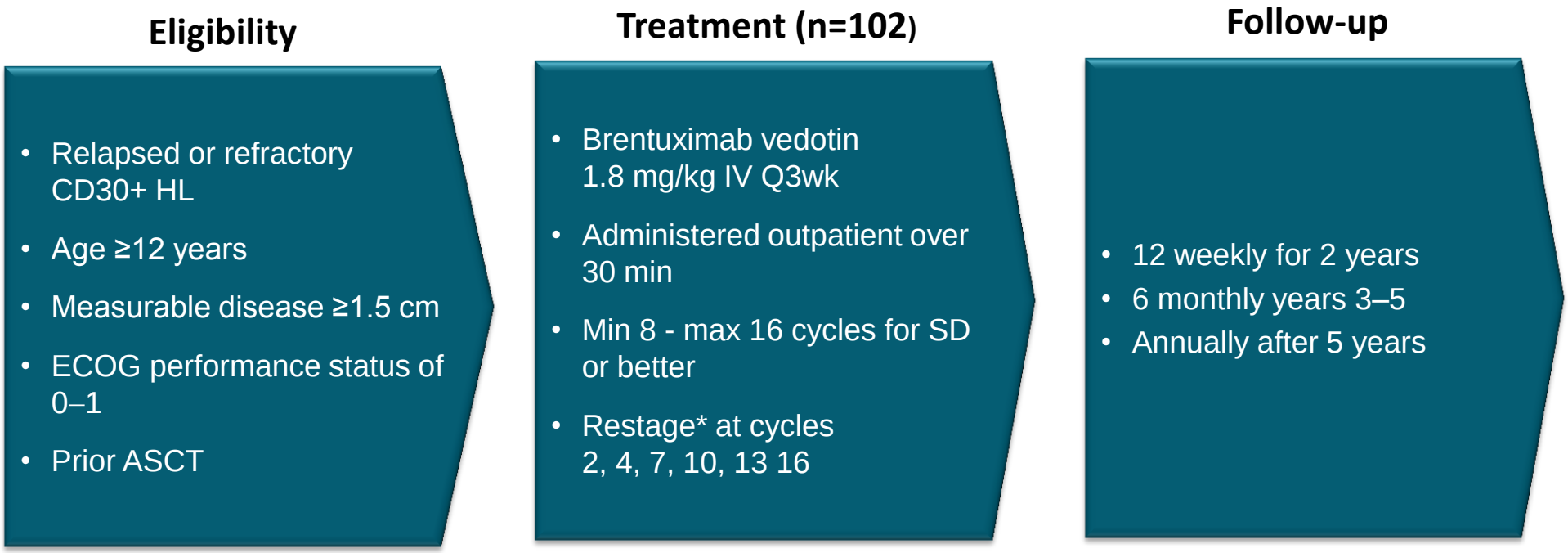






Younes A, et al. N Engl J Med 2010; 363:1812-1821

Phase II Pivotal Study of Brentuximab Vedotin in Patients with R/R HL Post ASCT



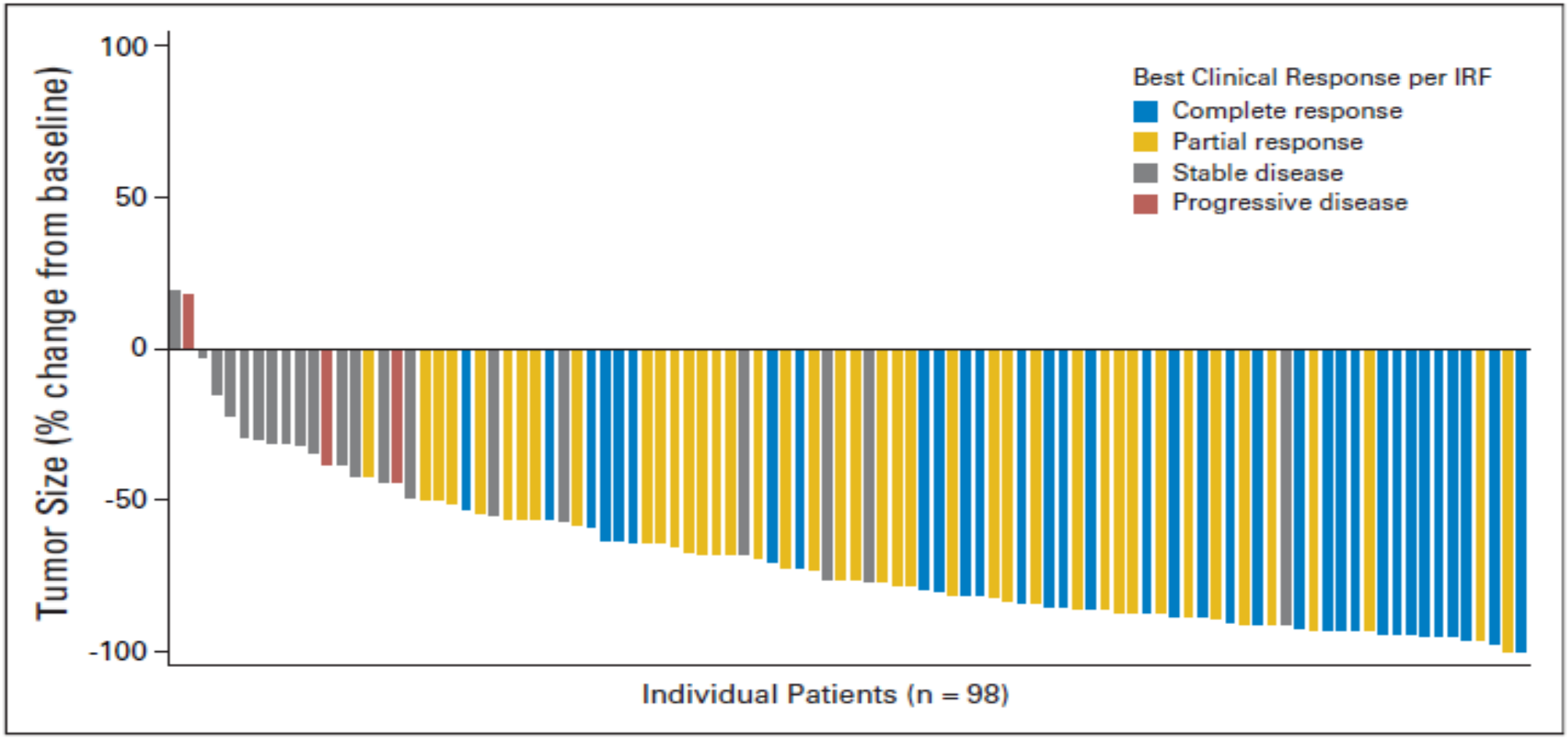
Primary Endpoint: ORR by Independent Review Facility (IRF)

*Revised response criteria for malignant lymphoma (Cheson 2007)

R/R – relapsed / refractory; ASCT – autologous stem cell transplantation;
ECOG – European Cooperative Oncology Group;
SD – stable disease; PD – progressive disease

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

Phase II Pivotal Study of Brentuximab Vedotin Maximum Reduction in Target Lesions

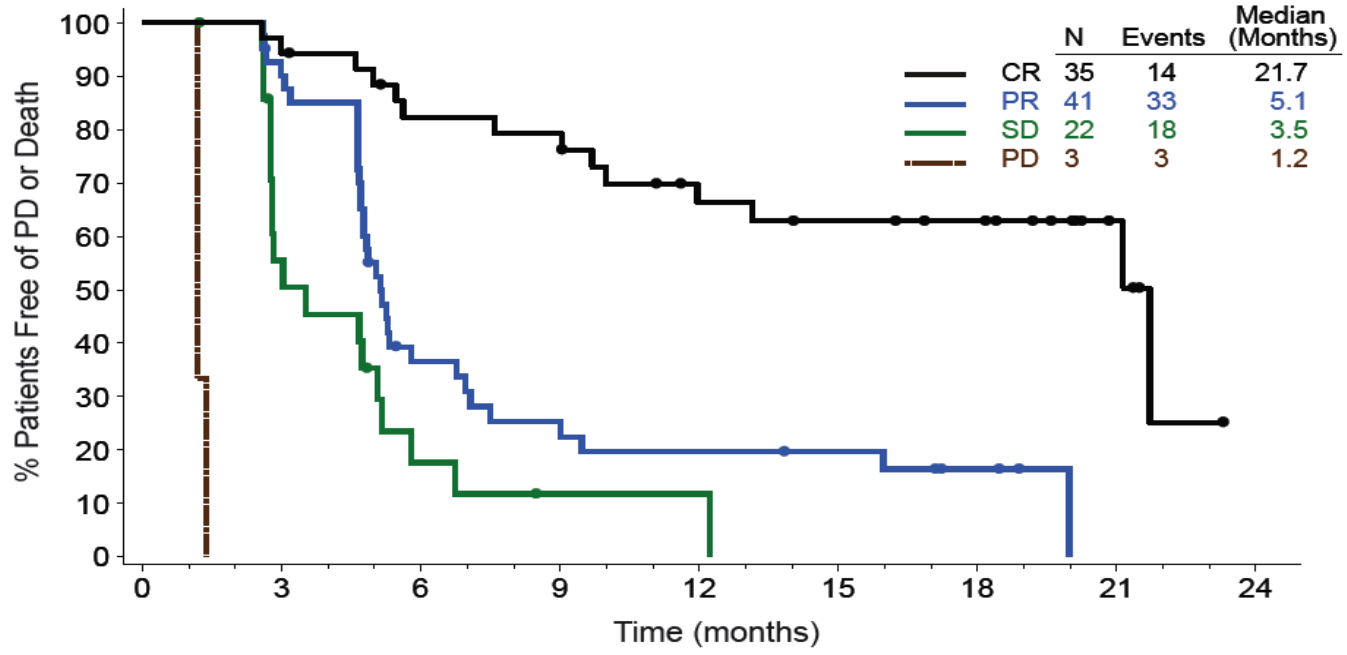


IRF – independent review facility

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

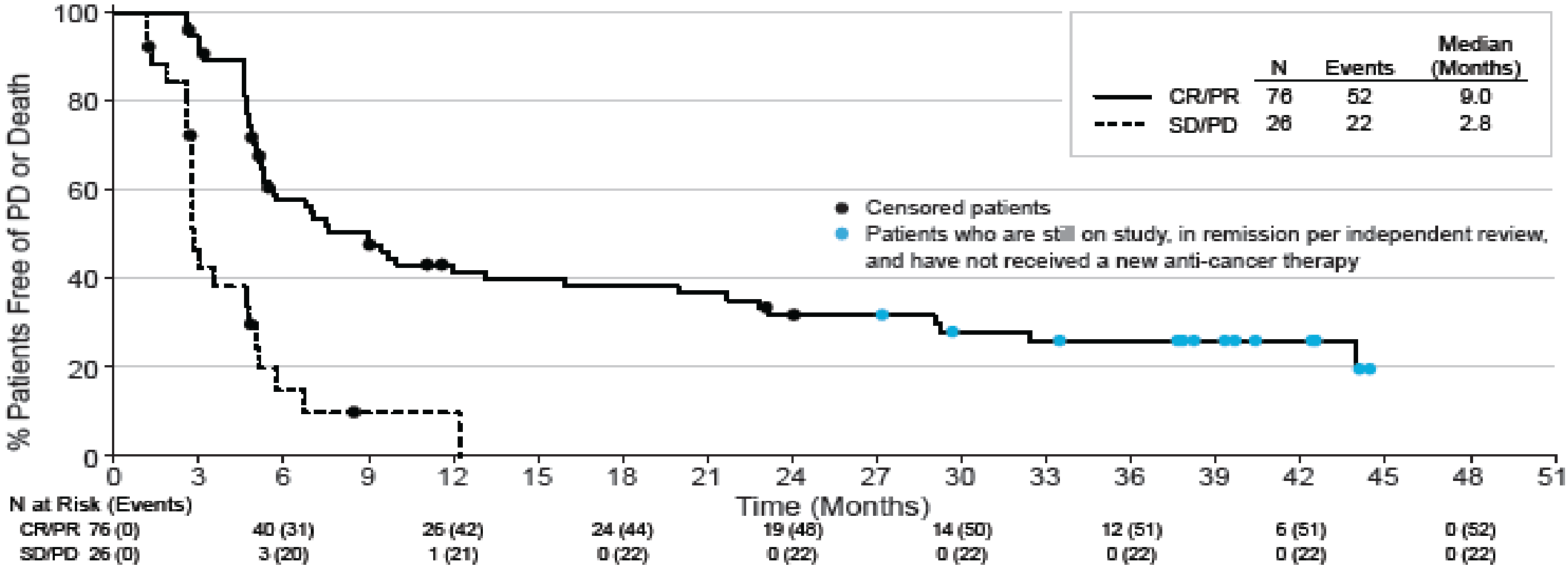
Brentuximab vedotin: pivotal Phase II trial PFS results by best response

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.

Three-year Follow-up Data and Characterization of Long-Term Remissions from an Ongoing Phase 2 Study of Brentuximab Vedotin in Patients with Relapsed or Refractory Hodgkin Lymphoma



Gopal A, et al , BLOOD 2015

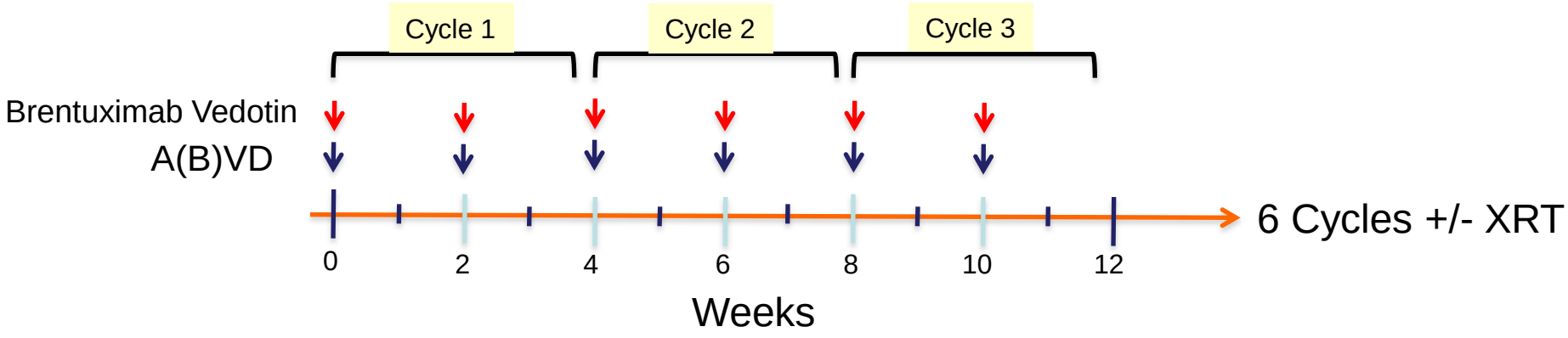
PHASE II STUDY OF BRENTUXIMAB VEDOTIN
TOLERABILITY

Adverse Events in ≥ 20% of Patients

Adverse event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Peripheral sensory neuropathy	47	9	0
Fatigue	46	2	0
Nausea	42	0	0
Upper respiratory tract infection	37	0	0
Diarrhoea	36	1	0
Pyrexia	29	2	0
Neutropenia	22	14	6
Vomiting	22	0	0
Cough	21	0	0

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

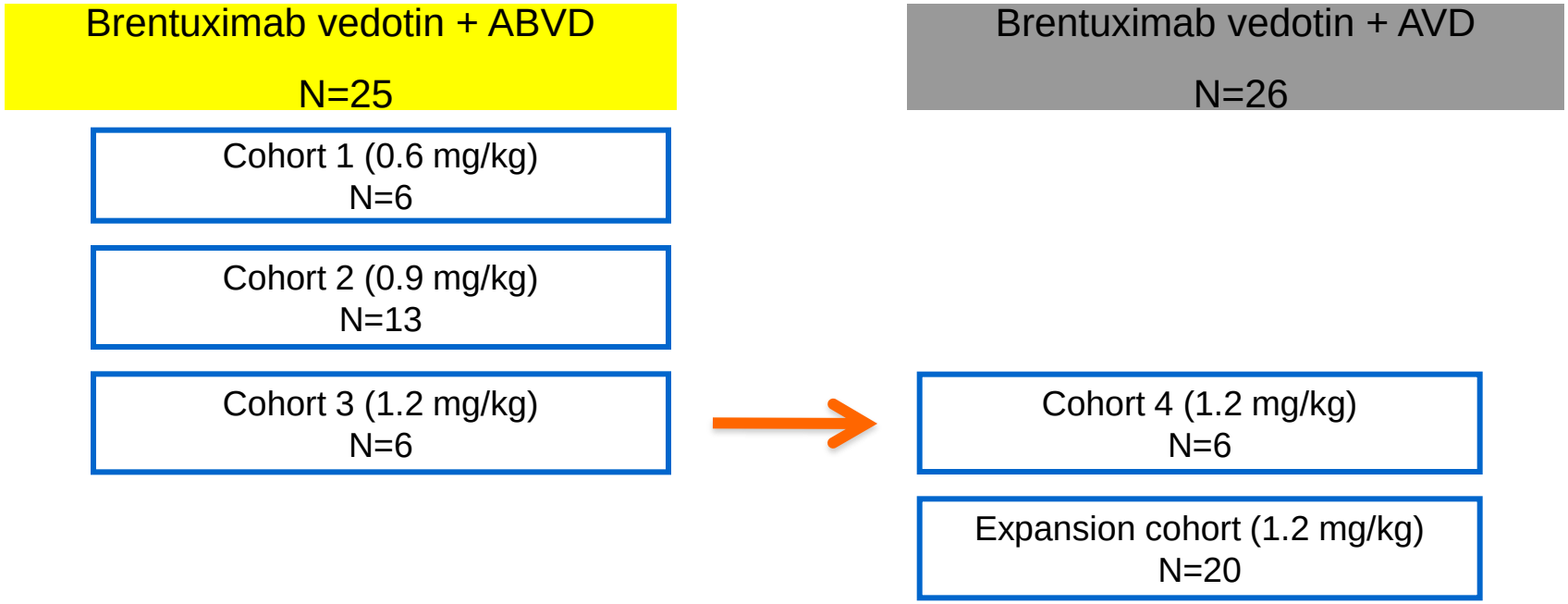
Phase 1 ABVD/AVD + Brentuximab Vedotin



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

Dose-Escalation Cohorts

Patients were enrolled into 1 of 5 cohorts:



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 combined with ABVD vs 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

ABVD/AVD + BV

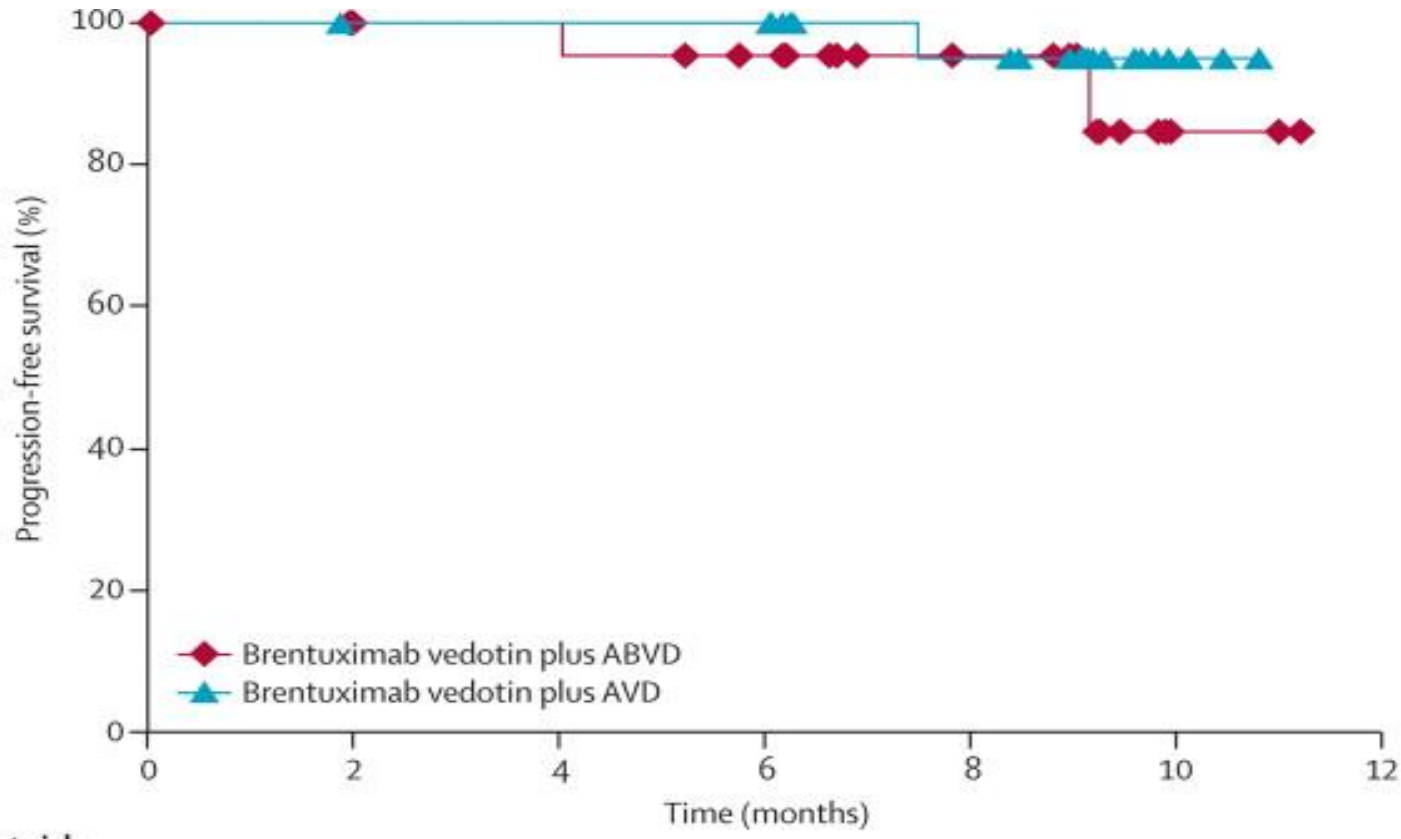
Response Results

FDG-PET Cycle 2	ABVD with brentuximab vedotin N=22[b]	AVD with brentuximab vedotin N=26
PET negative, n (%)	22 (100)	24 (92)
PET positive, n (%)	0	2 (8)

Response End of Therapy	ABVD with brentuximab vedotin N=22	AVD with brentuximab vedotin N=25
Response at end of frontline therapy, n (%)		
Complete remission	21 (95)	24 (96)
Progressive disease	0	1 (4)
Not evaluable due to AEs	1[b] (5)	0

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

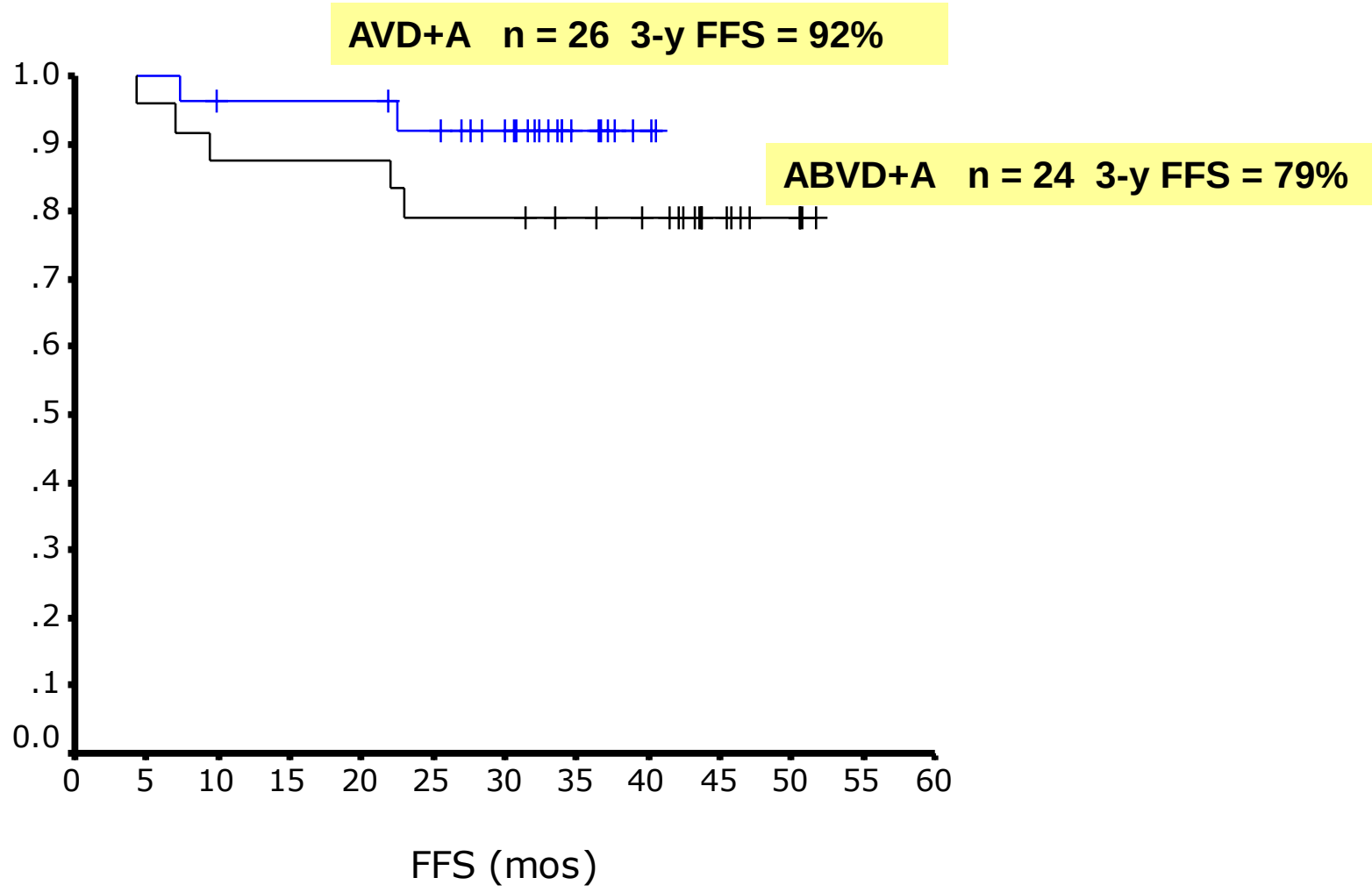
Phase-I Study of Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin lymphoma: PFS



Number at risk							
Brentuximab vedotin plus ABVD	25 (0)	23 (0)	22 (0)	19 (1)	13 (1)	2 (2)	0 (2)
Brentuximab vedotin plus AVD	26 (0)	25 (0)	25 (0)	25 (0)	19 (1)	3 (1)	0 (1)

Younes, A et al: The Lancet Oncology, Volume 14, Issue 13, 2013, 1348 - 1356

Failure Free Survival

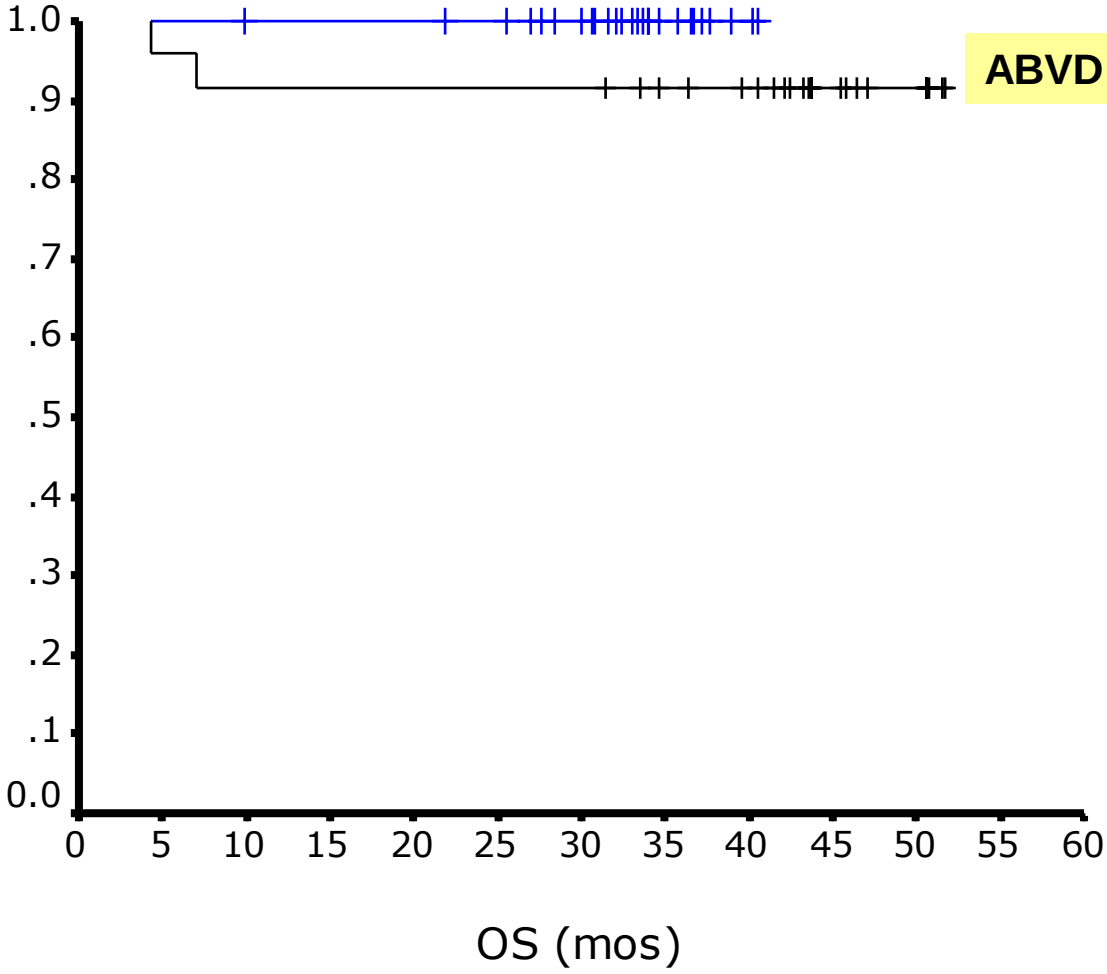


Connors J et al , ASH 2014

Overall Survival

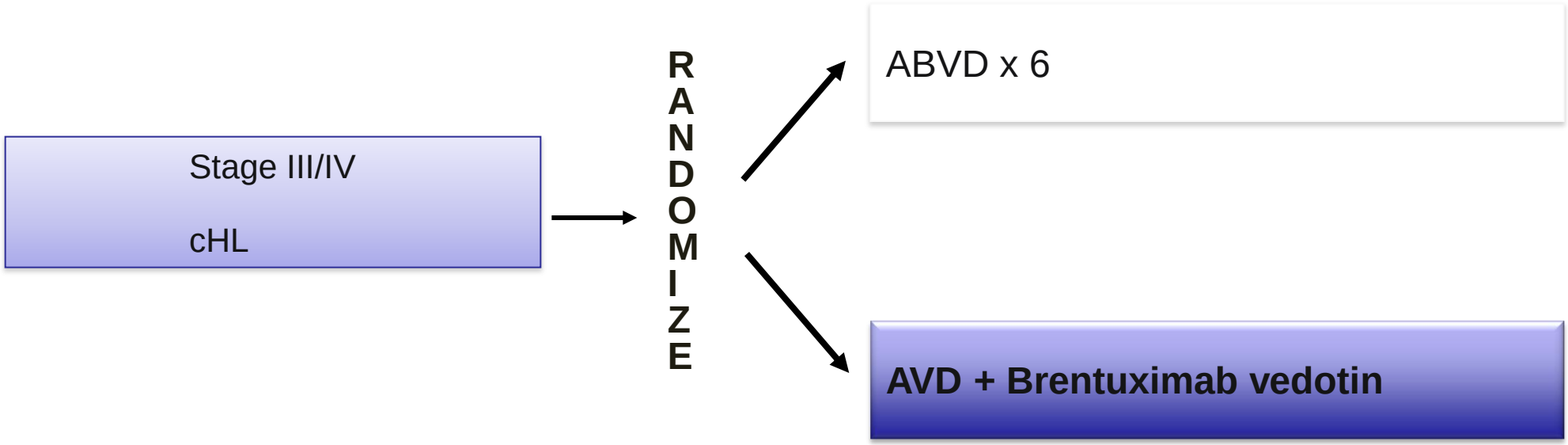
AVD + A n = 26 3-y OS = 100%

ABVD + A n = 24 3-y OS = 92%



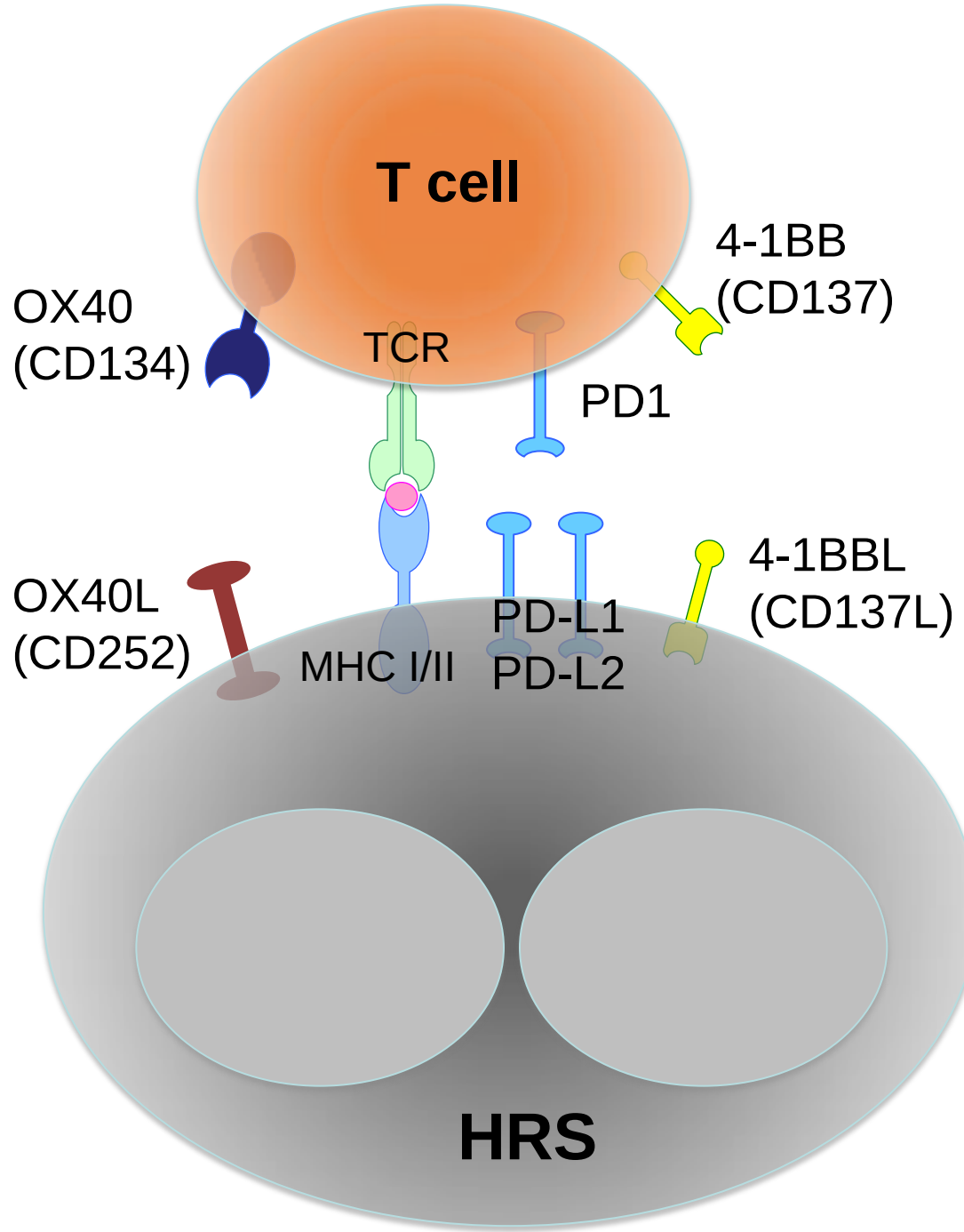
Connors J et al , ASH 2014

Randomized Study in Newly Diagnosed Advanced Stage HL

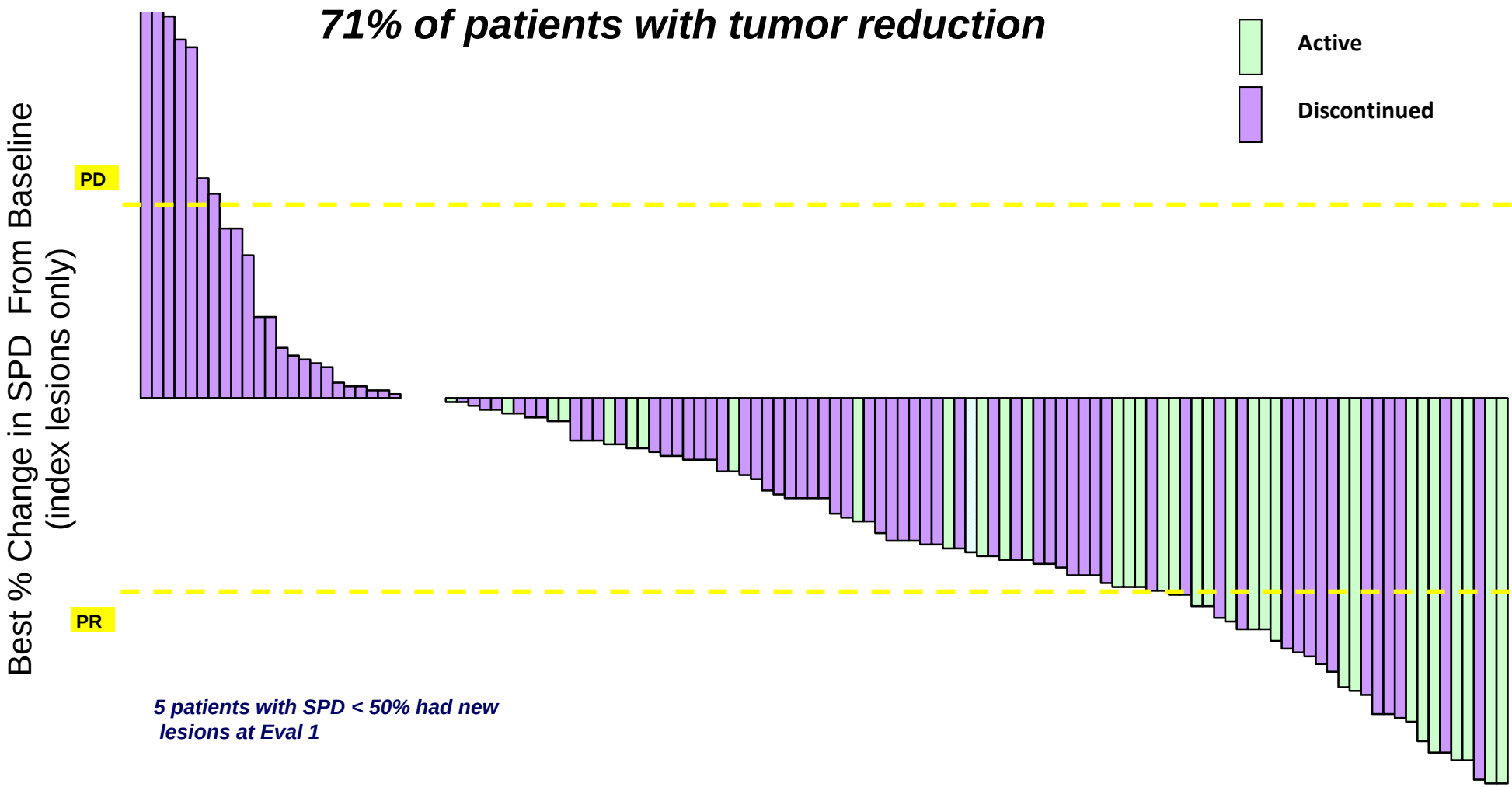


BrECADD Regimen

Drug	Day	esBEACOPP	BrECADD
Bleomycin [mg/m²]	8	10	
Etoposide [mg/m²]	1-3(2-4)	200	150
Doxorubicin [mg/m²]	1 (2)	35	40
Cyclophosphamide [mg/m²]	1 (2)	1250	1250
Vincristine [mg/m²][1]	8	1.4	
Brentuximab vedotin [mg/kg body weight][2]			1
1.8			
Procarbazine [mg/m²]	1-7 (2-8)	100	
Dacarbazine [mg/m²]	2-3		2x 250
Prednisone [mg/m²]	1-14 (2-15)	40	
Dexamethasone [mg]	2-5		40

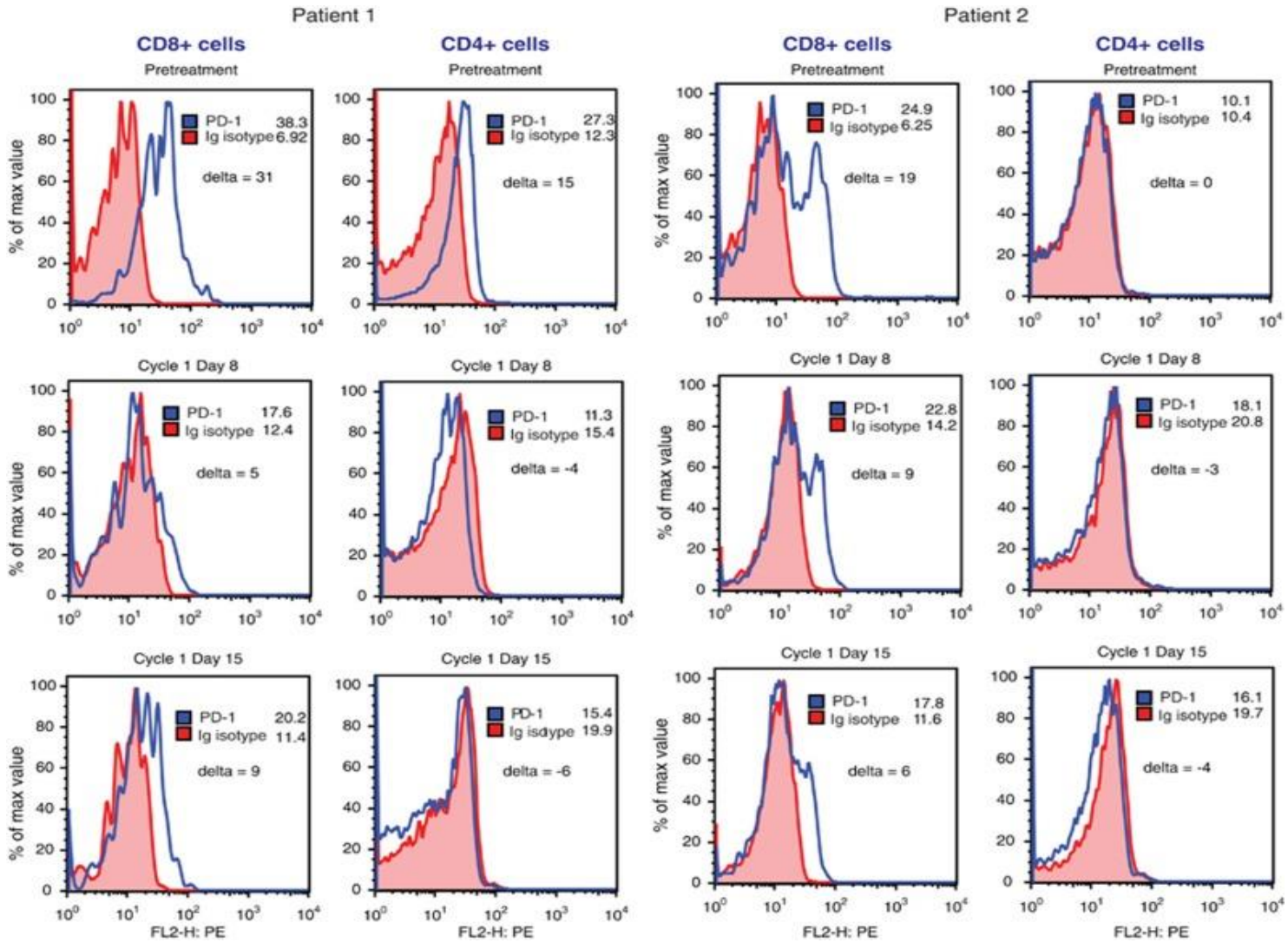

T cell
4-1BB
(CD137)
OX40
(CD134)
TCR
PD1
OX40L
(CD252)
MHC I/II
PD-L1
PD-L2
4-1BBL
(CD137L)
HRS

International Panobinostat Phase II Study in Relapsed HL



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

PD1 expression levels decreased after treatment with panobinostat in both CD4- and CD8-positive cells



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

Hodgkin Lymphoma : Future Directions