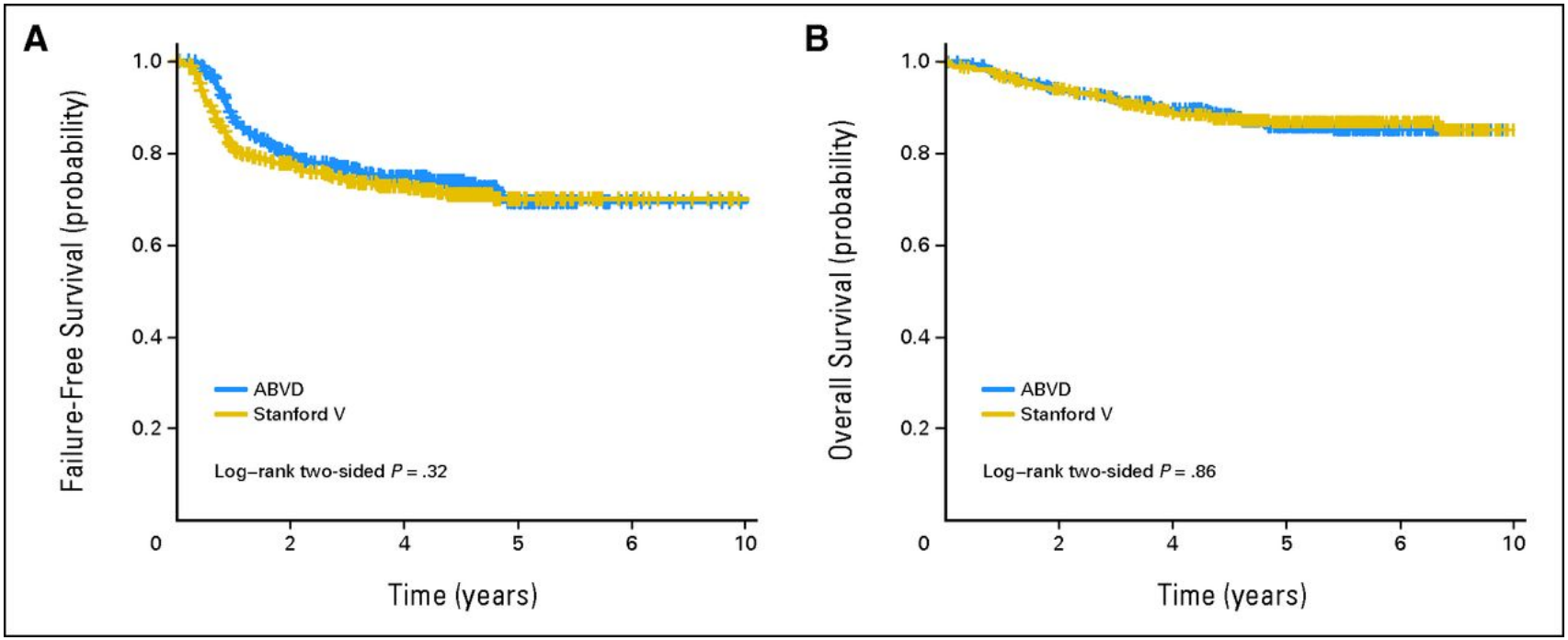
New scenario for frontline advanced stage HL

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

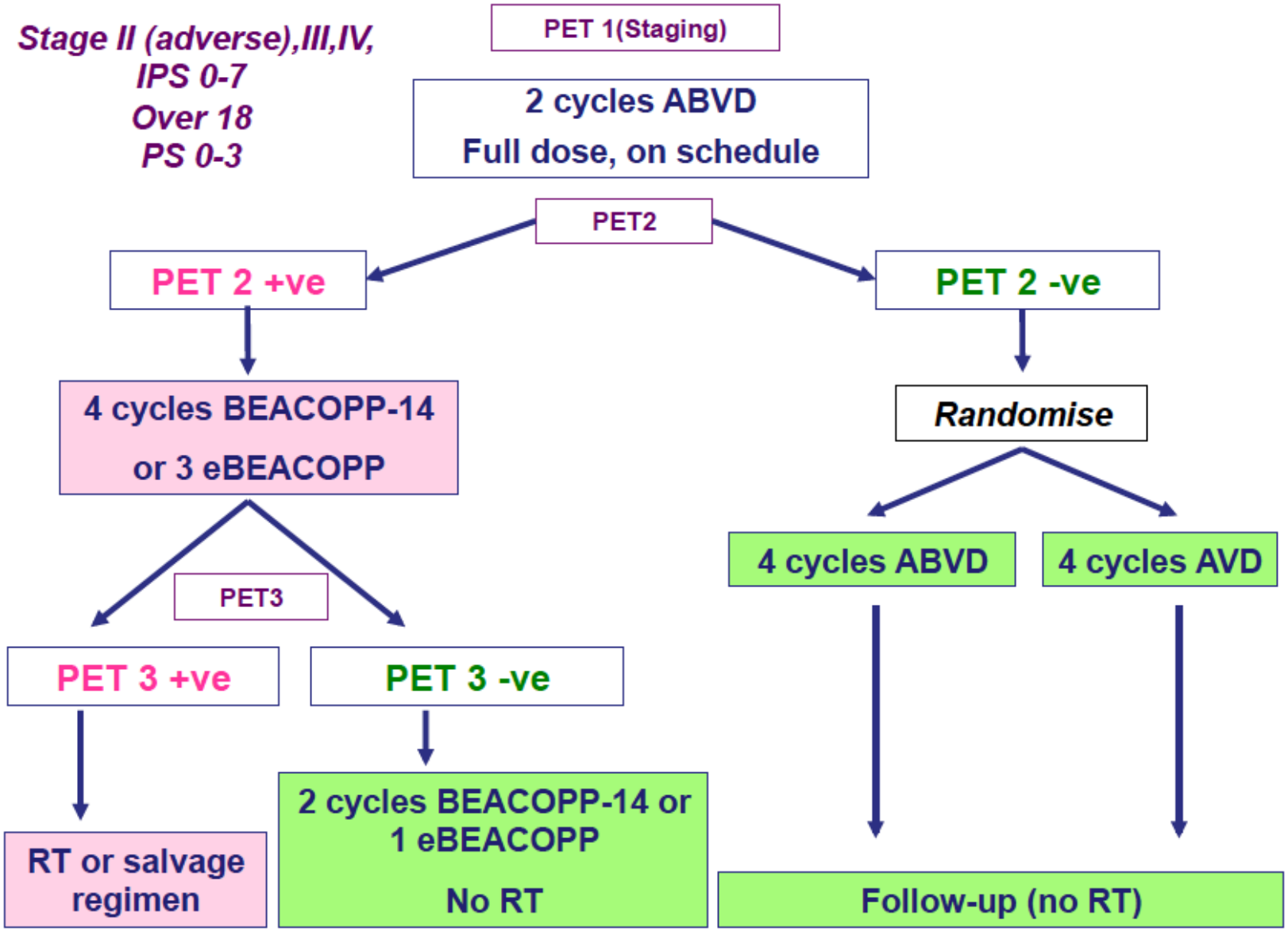
Thursday March 15, 2018: 9:15-9:30 am

ABVD vs Stanford V



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

RATHL Trial



Johnson, P ICML 2015

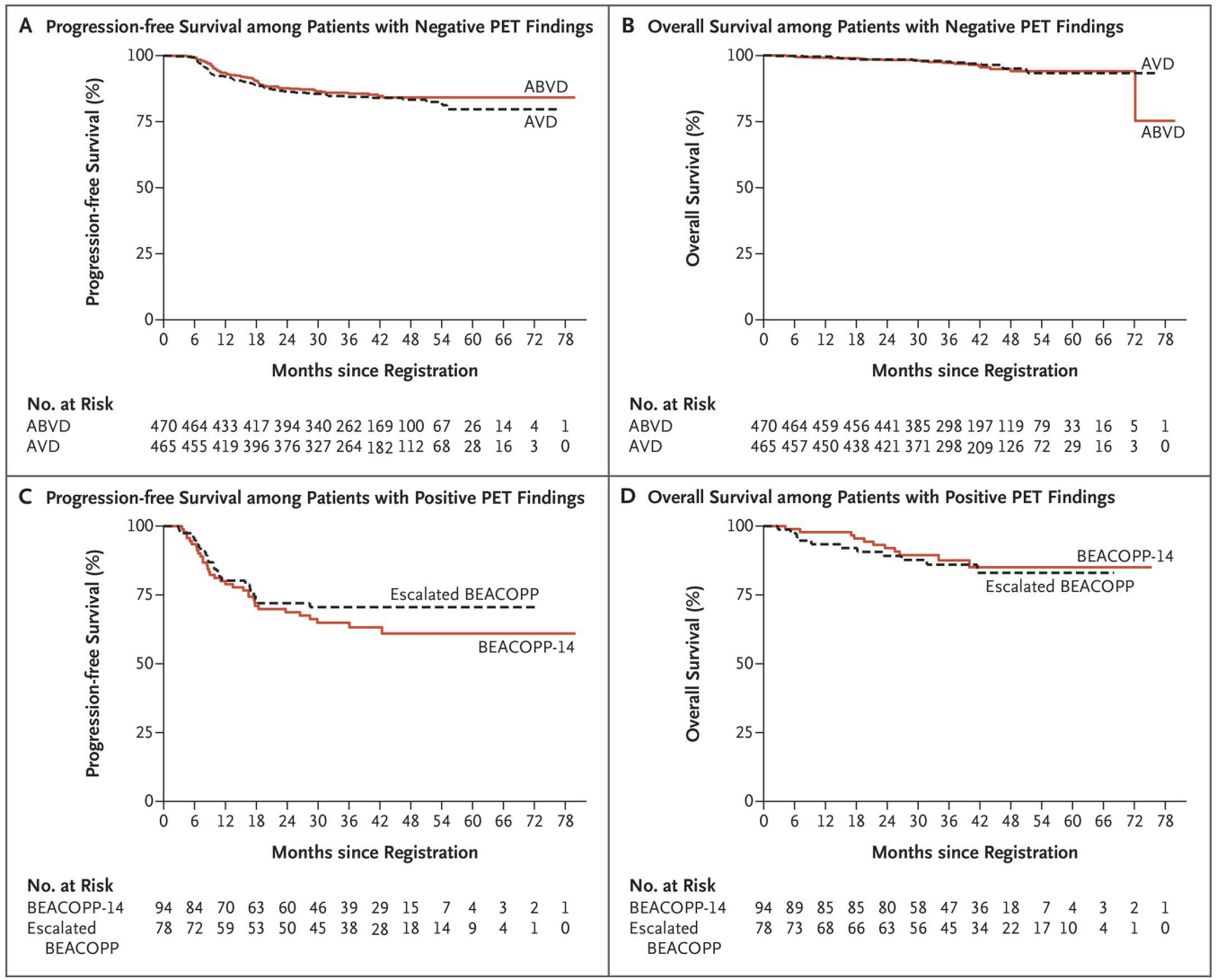
RATHL: PFS and OS

PFS PET2-

OS PET2-

PFS PET2+

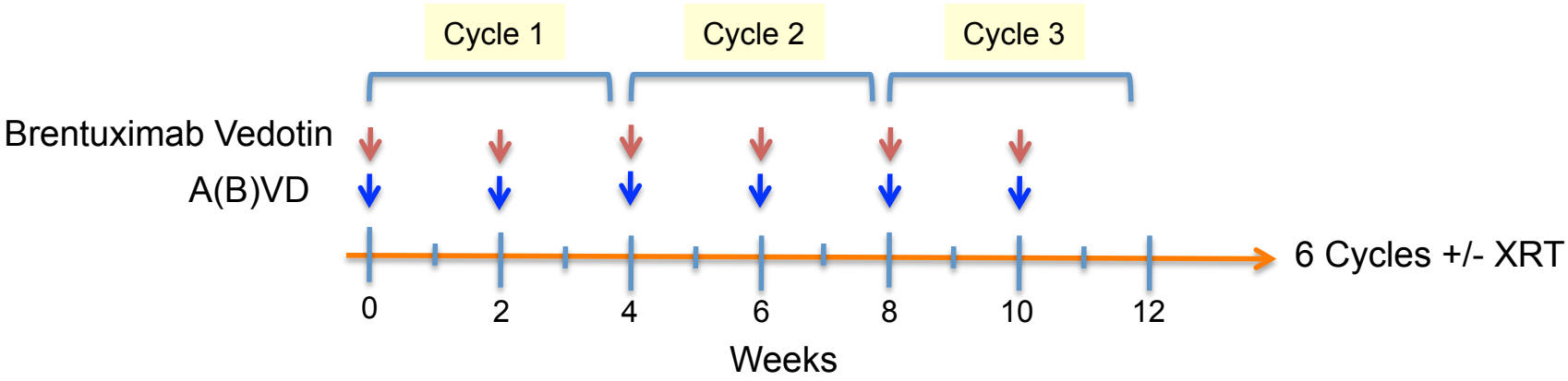
OS PET2+



Johnson P et al. N Engl J Med 2016;374:2419-2429

Phase 1 ABVD/AVD + brentuximab vedotin

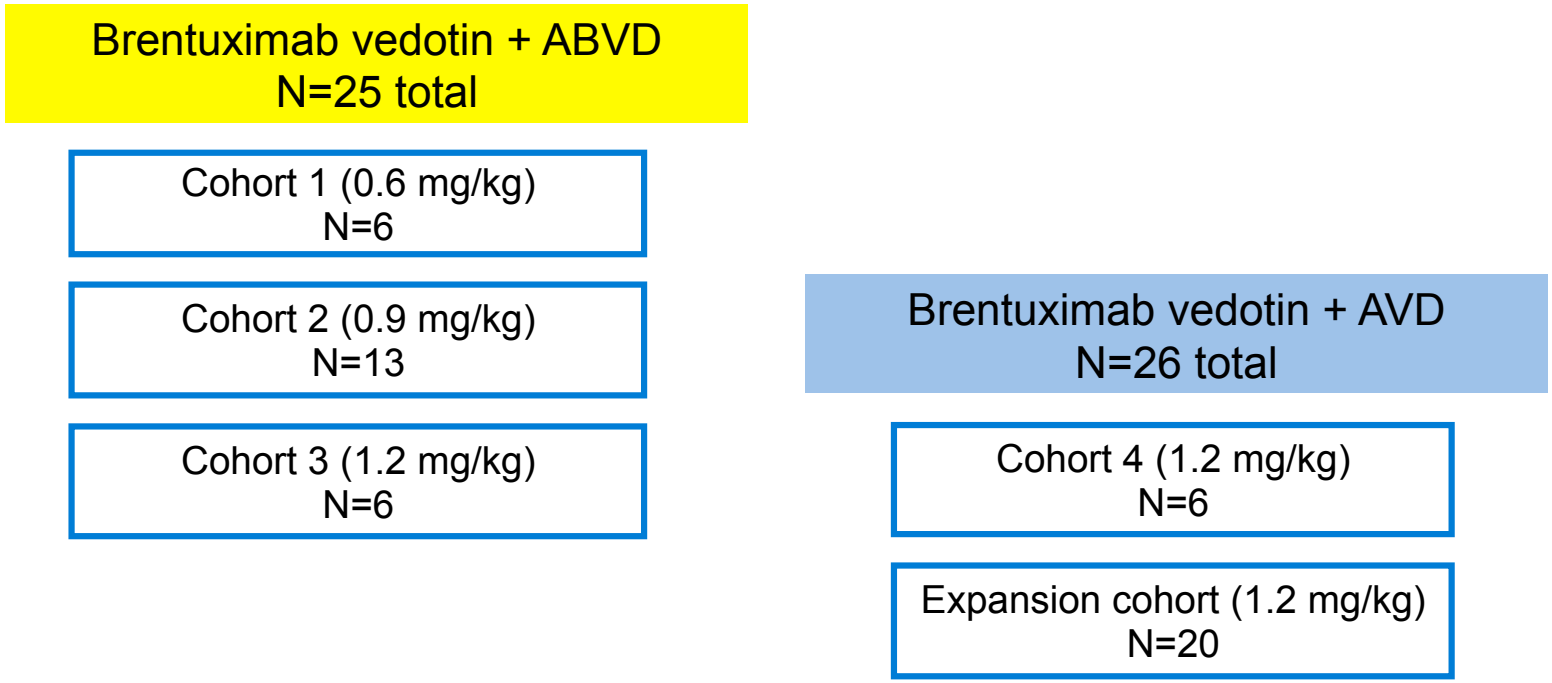
Stage IIa bulky, IIB, III-IV



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

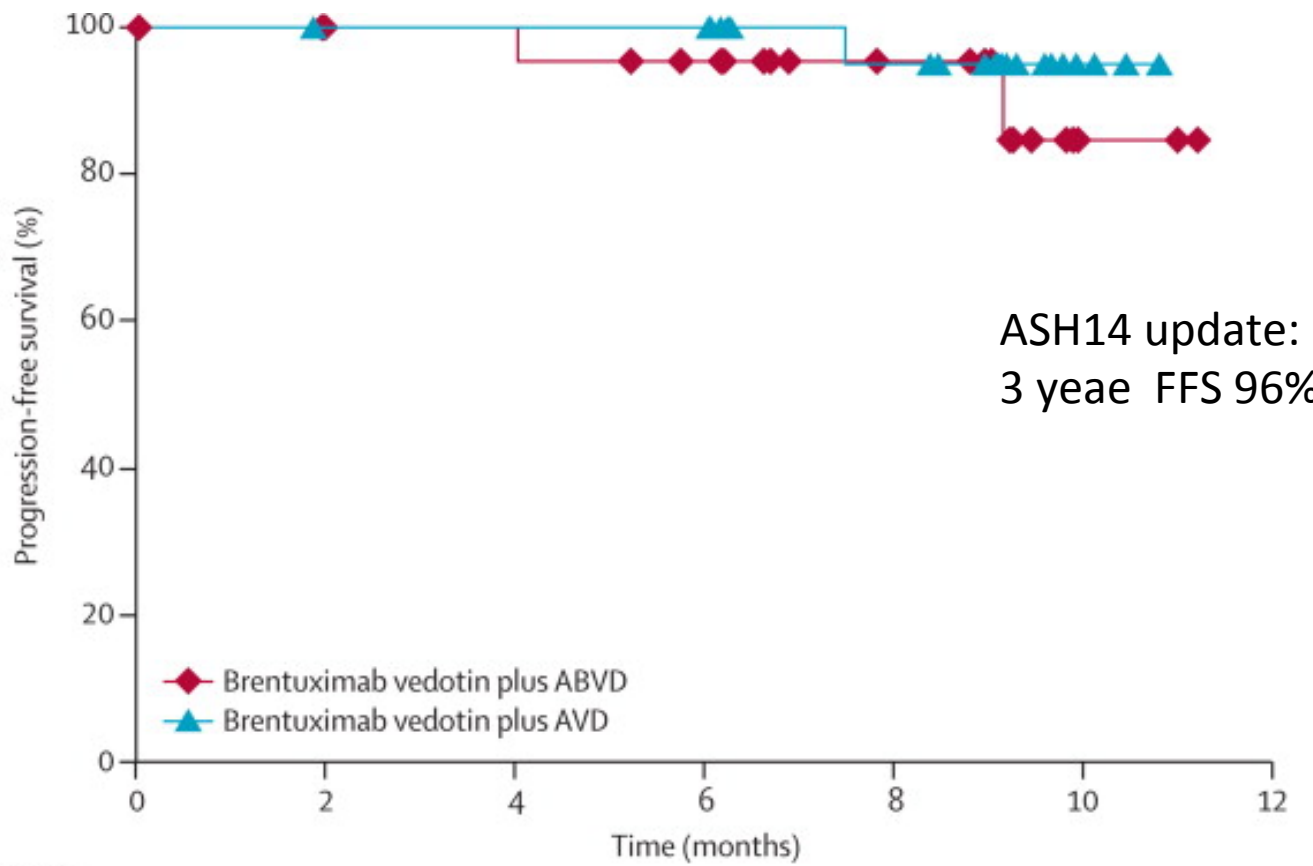
Dose-Escalation Cohorts

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

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



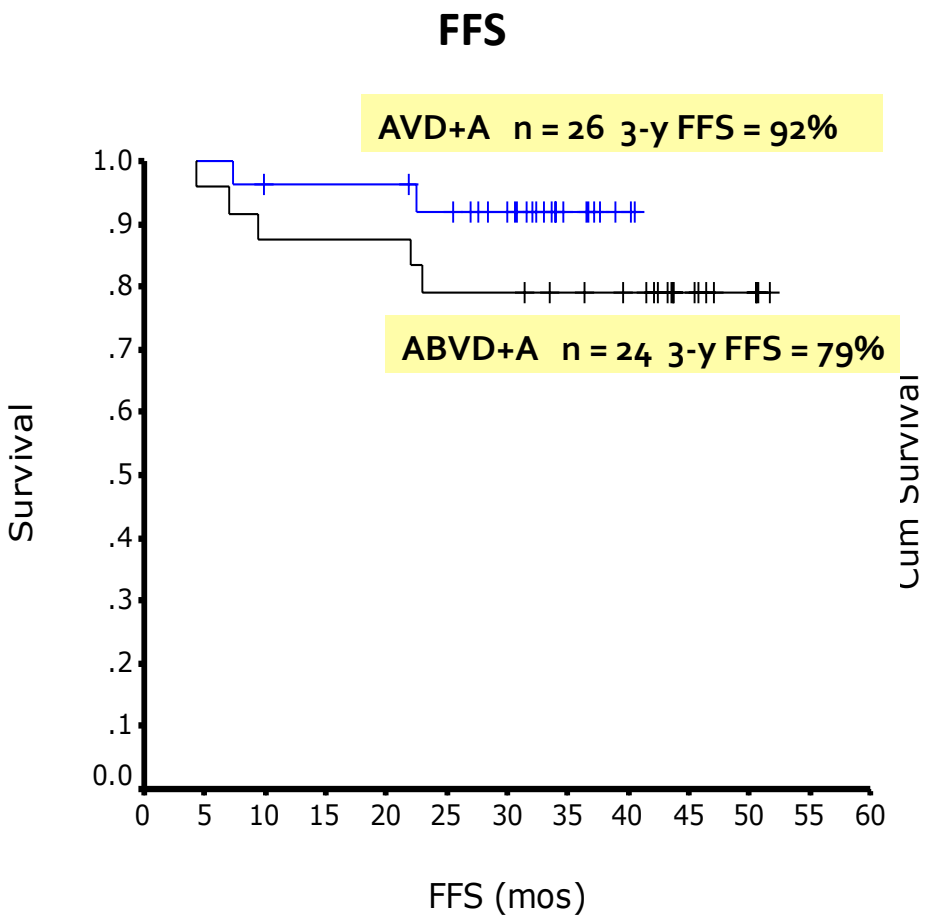
Number at risk							
Brentuximab vedotin plus ABVD	25 (0)	23 (0)	22 (0)	19 (1)	13 (1)	2 (2)	0 (2)
Brentuximab vedotin plus AVD	26 (0)	25 (0)	25 (0)	25 (0)	19 (1)	3 (1)	0 (1)

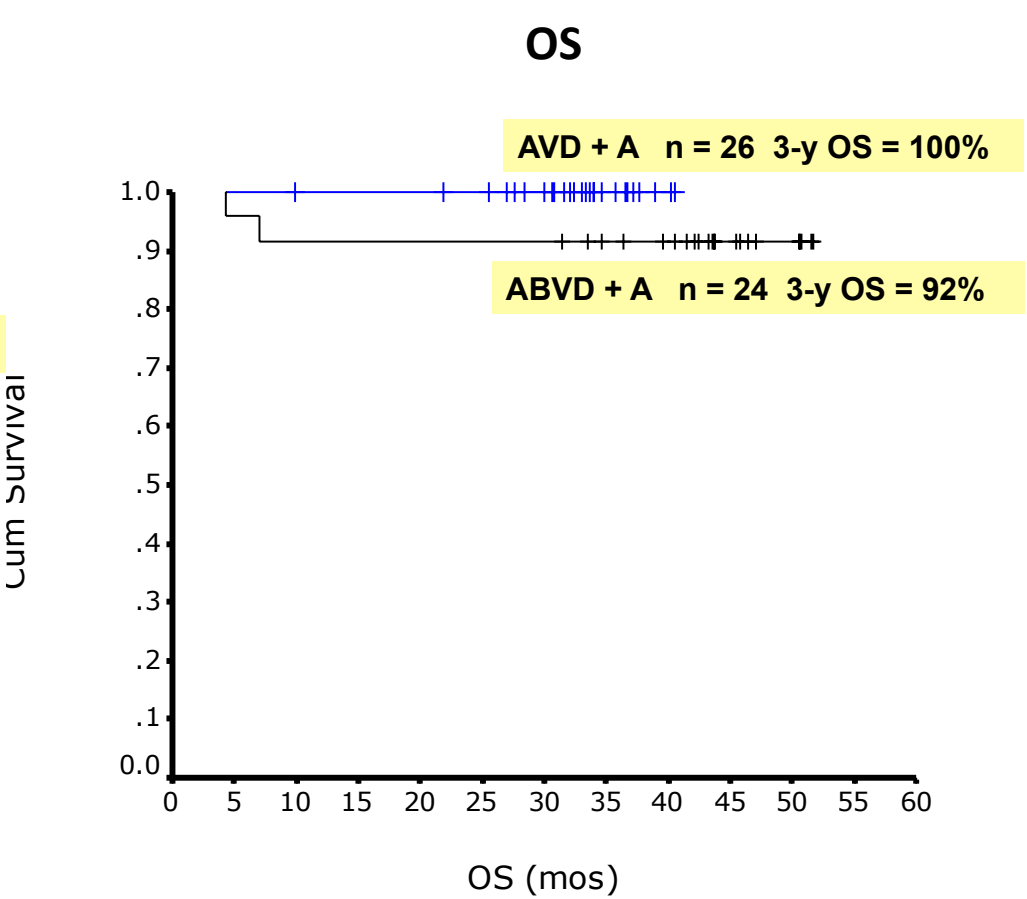
ASH14 update: of A= AVD
3 yeae FFS 96%, OS 100%

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

Phase-I Brentuximab vedotin + AVD Advanced stage HL

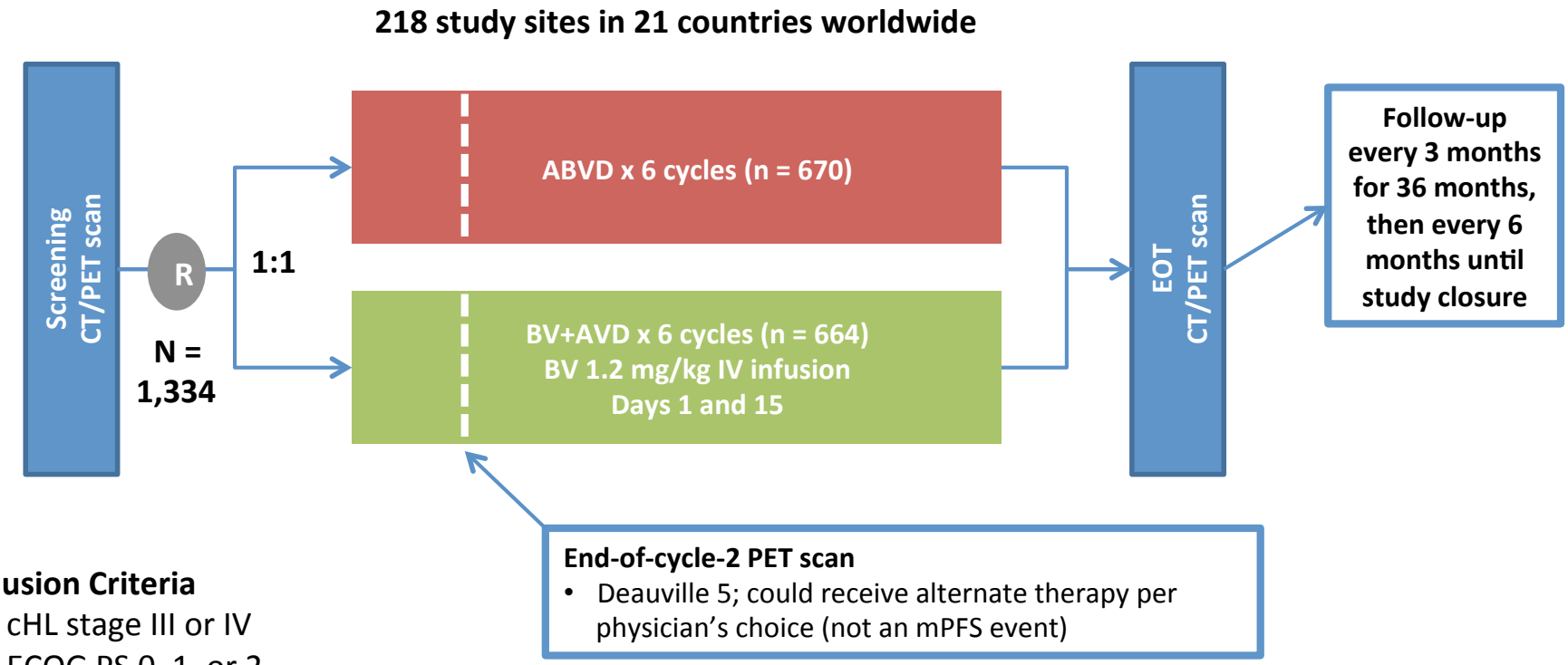
3-Year follow up





Connors J et al , ASH 2014

ECHELON-1: Phase 3 Study of BV+AVD Versus ABVD in Newly Diagnosed, Advanced cHL[1]



Inclusion Criteria

- cHL stage III or IV
- ECOG PS 0, 1, or 2
- Age ≥18 years
- Measurable disease
- Adequate liver and renal function

1. Connors JM et al. (ASH 2017) and NEJM 2017.

Disease Characteristics Comparable Between BV+AVD and ABVD

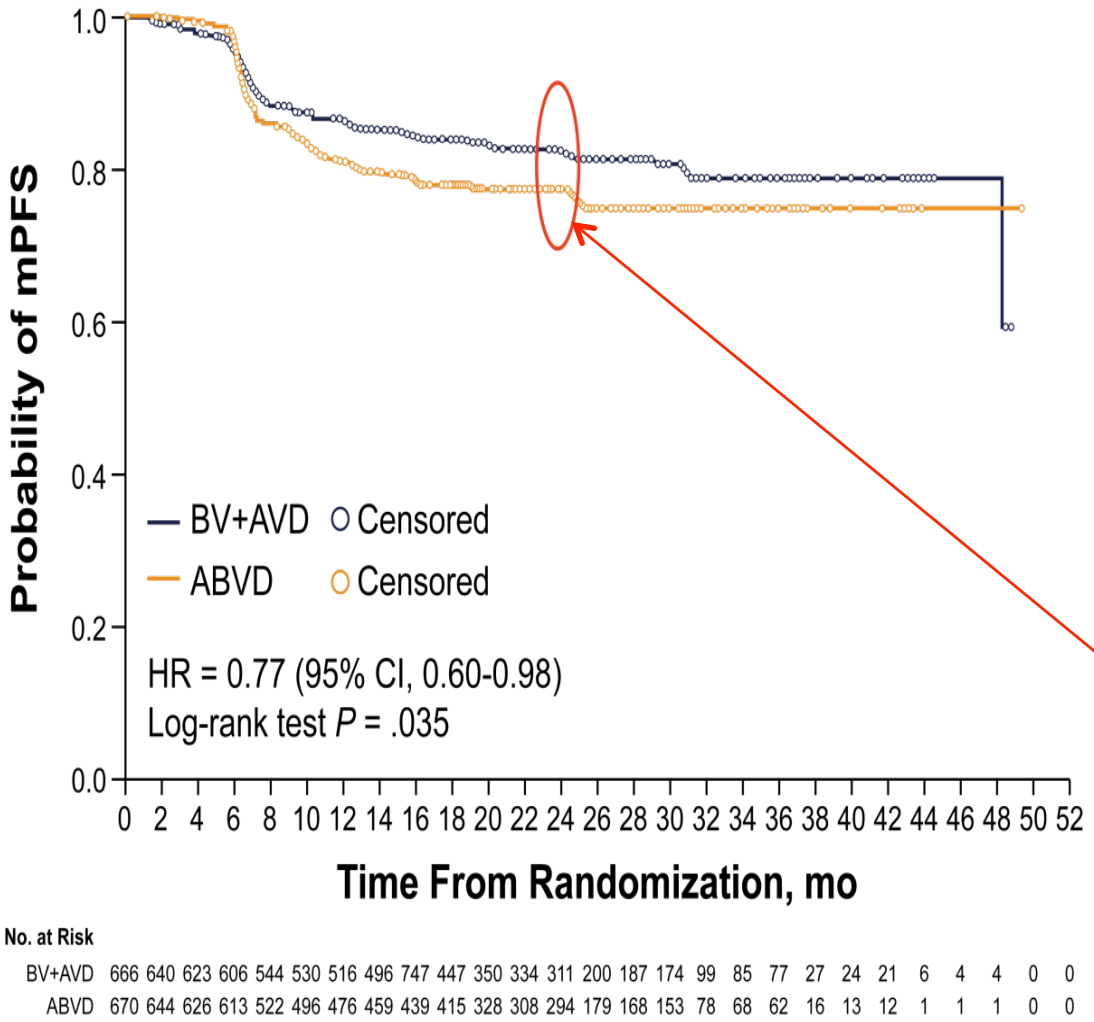
Characteristic	BV+AVD (n = 664)	ABVD (n = 670)
Male, %	57	59
Not Hispanic/Latino, %	86	86
White, %	84	83
Median age, y (range)	35 (18-82)	37 (18-83)
Age, %		
• <45 y	68	63
• 45-59 y	19	22
• 60-64 y	4	6
• ≥65 y	9	9
Median time from initial dx, mo	0.92	0.89
Region, %		
• Americas	39	39
• Europe	50	50
• Asia	11	11

Characteristic	BV+AVD (n = 664)	ABVD (n = 670)
Ann Arbor stage III/IV, %	36/64	37/63
IPS risk factors, %[a]		
• 0-1	21	21
• 2-3	53	52
• 4-7	25	27
ECOG PS, %		
• 0	57	57
• 1	39	39
• 2	4	4
B symptoms, %	60	57
BM involvement, %	22	23
Extranodal sites, %		
• 0	33	34
• 1	33	33
• >1	29	29
• Unknown/missing	5	4

[a] Percentages do not total 100% due to rounding.

1. Connors JM et al. ASH 2017. Abstract 6.

mPFS Per Independent Review



Number of Events

	BV+AVD (n = 117)	ABVD (n = 146)
Progression	90	102
Death	18	22
Modified progression	9	22
• Chemotherapy	7	15
• Radiotherapy	2	7

mPFS Estimates

	BV+AVD (95% CI)	ABVD (95% CI)
2-year	82.1 (78.7-85.0)	77.2 (73.7-80.4)

Median follow-up (range): 24.9 mo (0.0-49.3)

1. Connors JM et al. ASH 2017. Abstract 6.

OS, CR, ORR, and PET Negativity by IRF

Endpoint, n (%)	BV+AVD (n = 664)	ABVD (n = 670)
CR[a] rate at end of randomized regimen	488 (73)	472 (70)
ORR[a] at end of randomized regimen	569 (86)	553 (83)
PET Deauville score 1-2 after completing first-line tx	563 (85)[b]	537 (80)[b]
PET Deauville score after completing cycle 2 • 1-3 • 4 • 5 • Unavailable	 588 (89) 26 (4) 21 (3) 29 (4)	 577 (86) 28 (4) 30 (4) 35 (5)

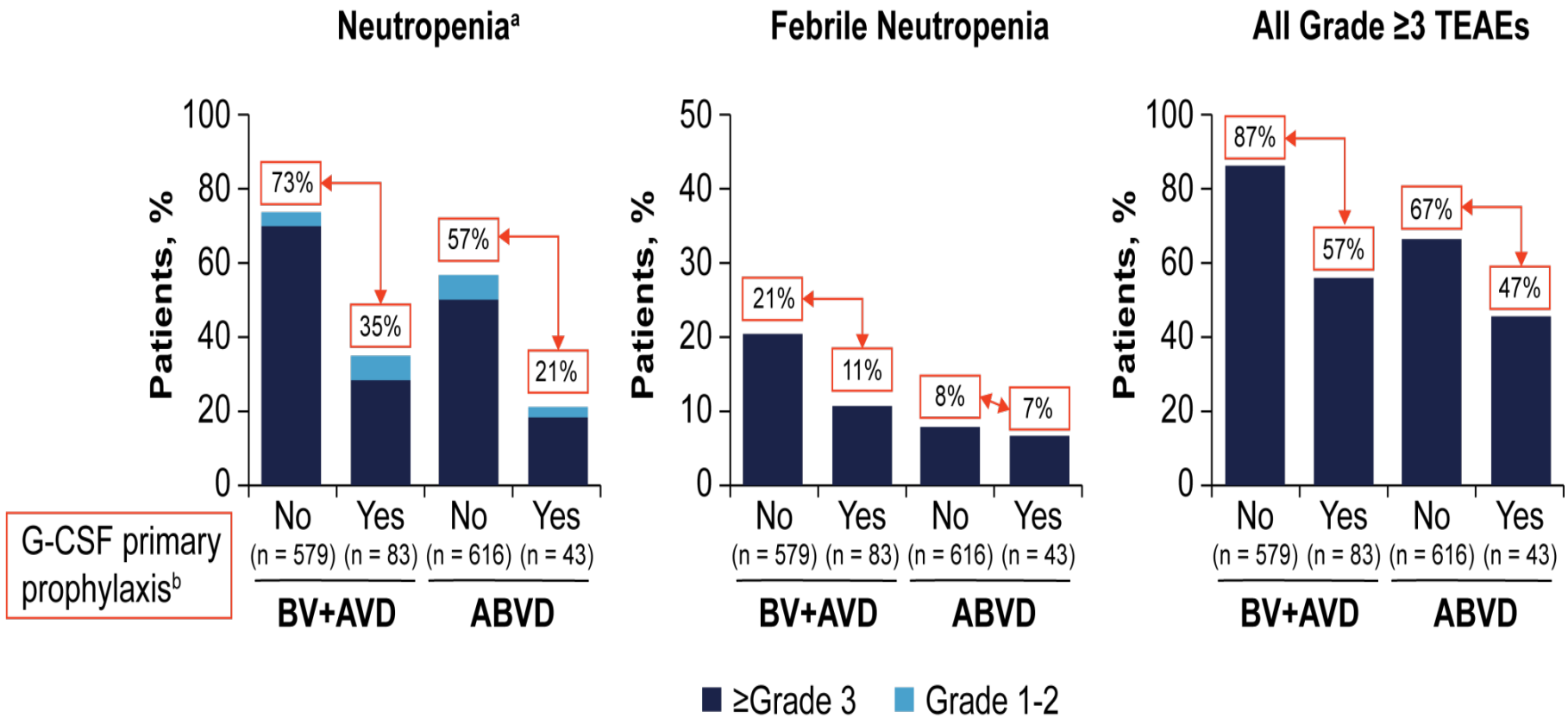
Incidence (Any Grade) ≥20% + Febrile Neutropenia

TEAEs in ≥20% of Patients and/or Febrile Neutropenia[a]	BV+AVD (n = 662)		ABVD (n = 659)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Neutropenia	58	54	45	39
Constipation	42	2	37	<1
Vomiting	33	3	28	1
Fatigue	32	3	32	1
Peripheral sensory neuropathy	29	5	17	<1
Diarrhea	27	3	18	<1
Pyrexia	27	3	22	2
Peripheral neuropathy	26	4	13	<1
Abdominal pain	21	3	10	<1
Stomatitis	21	2	16	<1
Febrile neutropenia	19	19	8	8

Partial list focuses on most clinically important AEs; other AEs in ≥20% of patients: alopecia, anemia, decreased weight, nausea.

1. Connors JM et al. ASH 2017. Abstract 6.

Summary of Treatment-Emergent Febrile Neutropenia and AEs by Primary Prophylaxis With G-CSF



- G-CSF primary prophylaxis for BV+AVD resulted in an overall safety profile comparable to ABVD
- G-CSF primary prophylaxis is recommended for all BV+AVD patients

[a] Includes preferred terms: neutropenia, neutrophil count decreased.
[b] Defined as G-CSF use by day 5 of study treatment.

1. Connors JM et al. ASH 2017. Abstract 6.

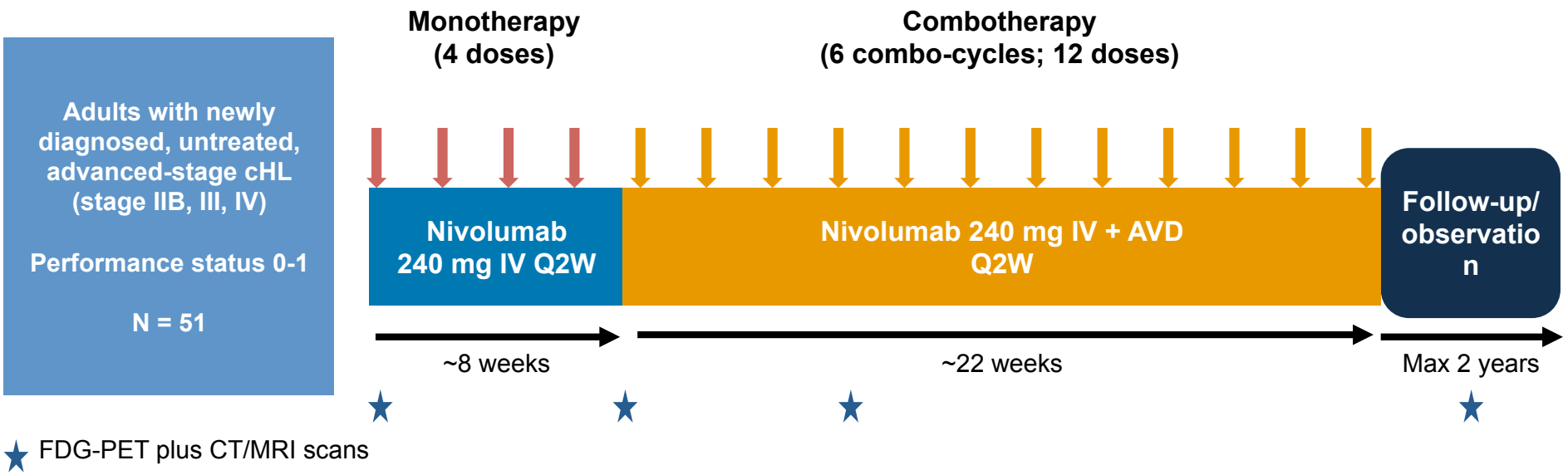
Nivolumab for Newly Diagnosed Advanced-Stage Classical Hodgkin Lymphoma: Results From the Phase 2 CheckMate 205 Study

Abstract 651

Ramchandren R, Fanale MA, Rueda A, Armand P, Trneny M, Feldman TA, Ansell SM, Provencio M, Jaeger U, Cohen JB, Savage KJ, Willenbacher W, Sacchi M, Sumbul A, Domenech ED

PeerView Live

Phase 2 CheckMate 205 Study Design: Nivolumab in Newly Diagnosed cHL[1]



Primary Endpoint
- Safety and tolerability (Grade 3-5 TRAEs)

Additional Endpoints
- Discontinuation rate
- CR and ORR by IRC
- CR and ORR by investigator
- mPFS
- OS

Responses were assessed using the IWG 2007 criteria.
At database lock (October 2017), median duration of follow-up was 11.1 months.
Bleomycin excluded due to potential overlapping pulmonary toxicity.

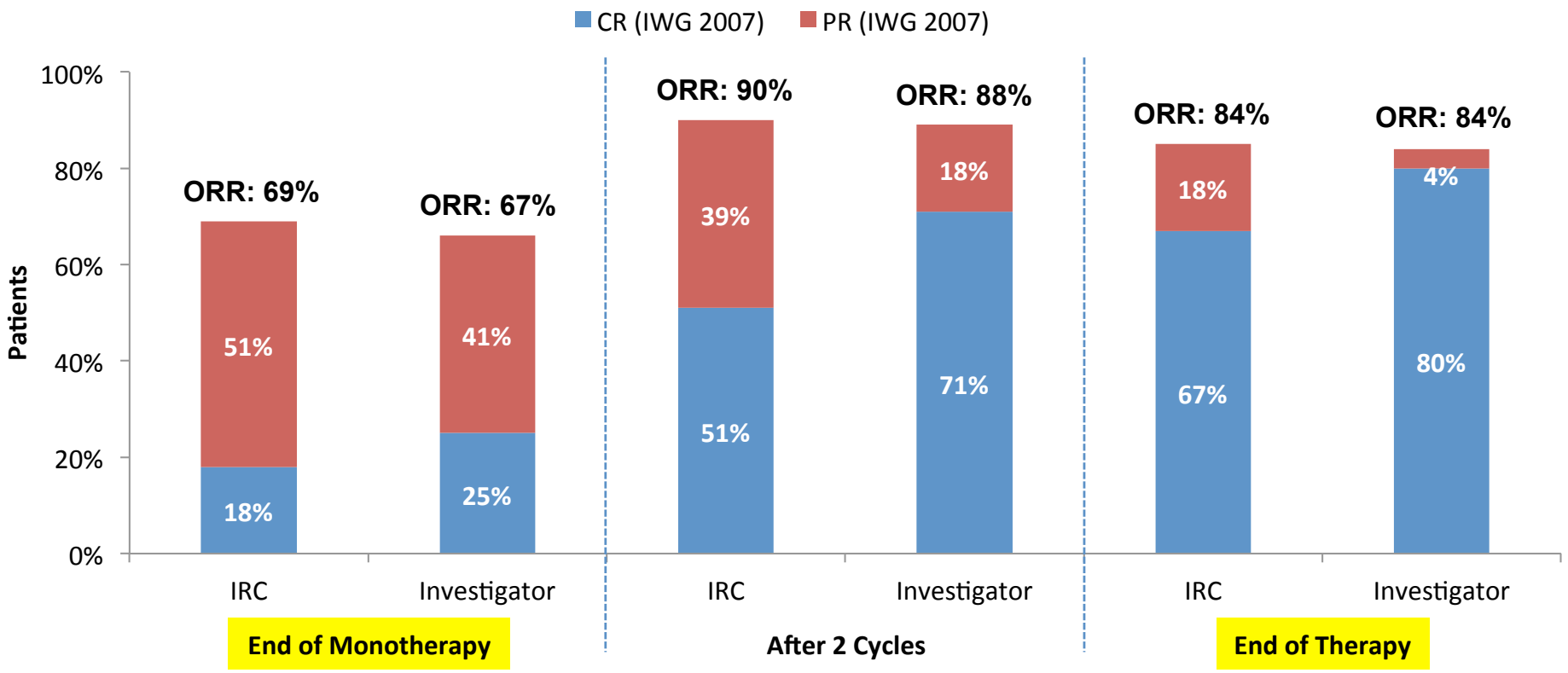
1. Ramchandren R et al. *Blood*. 2017;130:Abstract 651.

Baseline Demographics and Clinical Characteristics[1]

	Cohort D (N = 51)
Age, median (min-max) years	37 (18-87)
Male	32 (63%)
IPS at diagnosis • 0-2 • ≥3 • Not reported	 21 (41%) 25 (49%) 5 (10%)
disease stage at diagnosis • II • III • IV	 10 (20%) 12 (24%) 29 (57%)
B symptoms at diagnosis	41 (80%)
Bulky disease (10 cm)	16 (31%)
Extranodal involvement	25 (49%)

1. Ramchandren R et al. *Blood*. 2017;130:Abstract 651.

Response per IRC and Investigator: ITT Population[1]

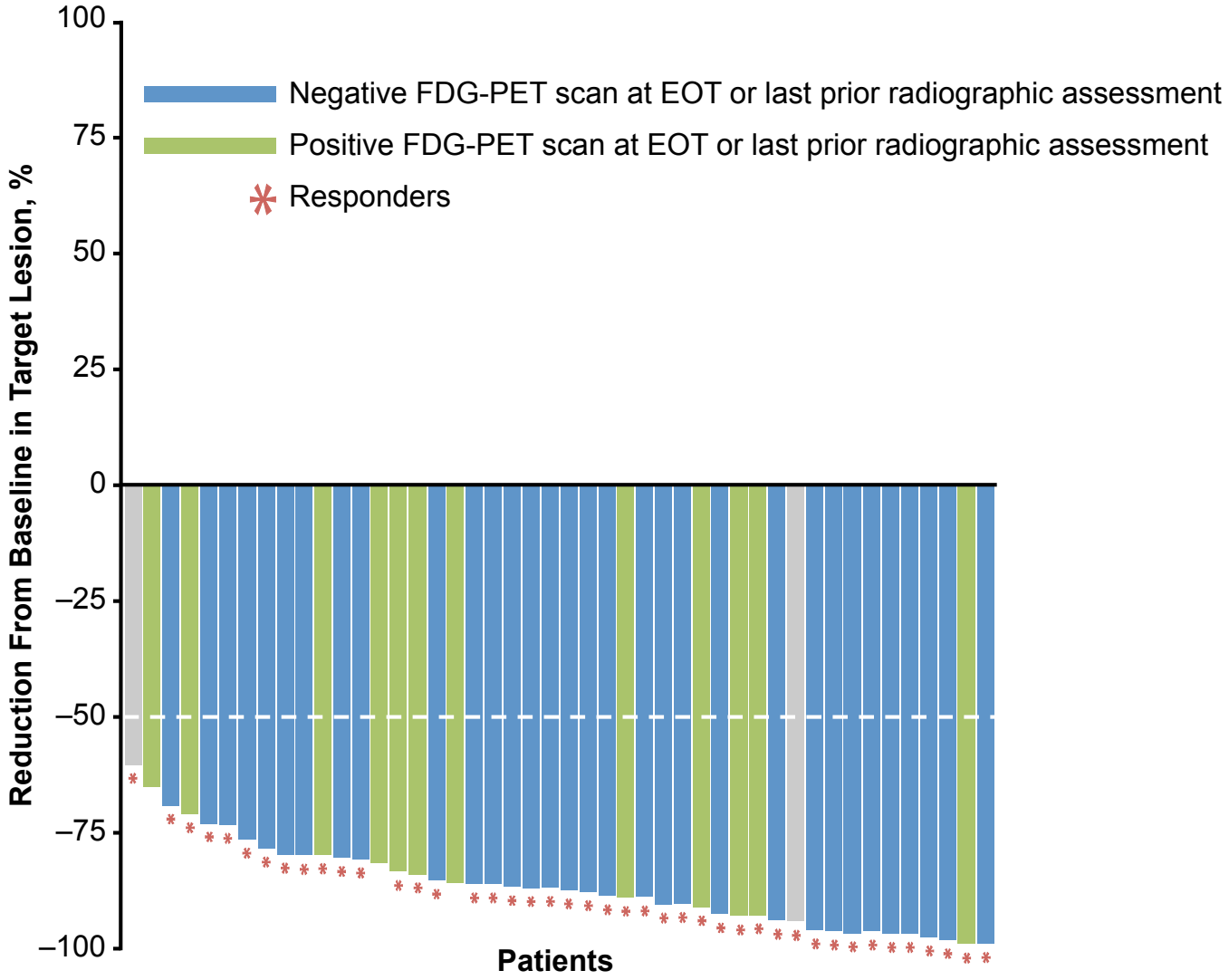


- At end of therapy, ORR per investigator for the ITT population was 84%, with 80% of patients achieving CR
- Five patients were nonevaluable at end of therapy[a]

[a] No evaluable scan in at least one on-study time point.
Biopsies were not required for patients to be considered to have progressive disease.
Values may not add together due to rounding.

1. Ramchandren R et al. *Blood*. 2017;130:Abstract 651.

Best Change in Target Lesion Per IRC at End of Chemoimmunotherapy[1]

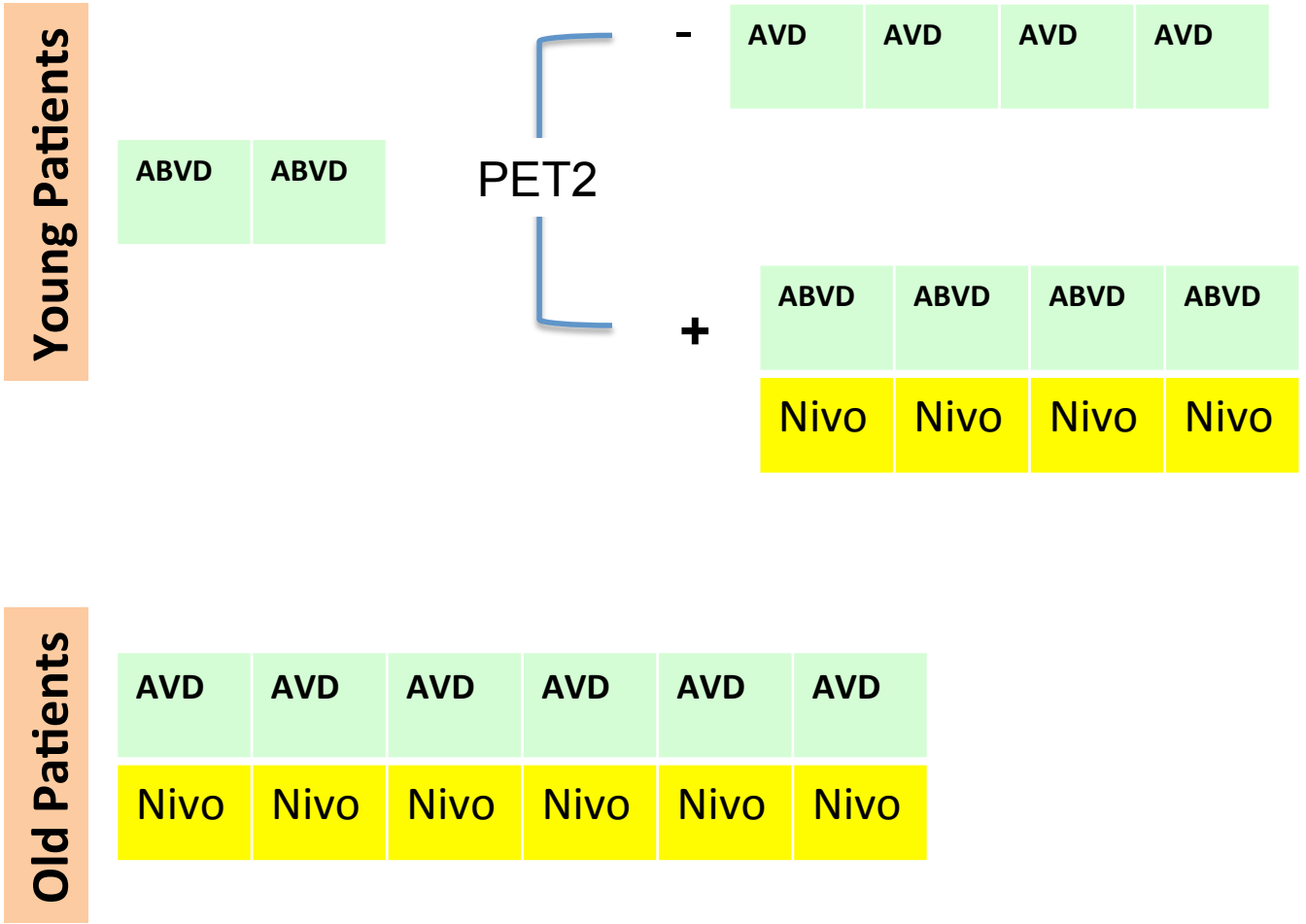


46/51 patients had available response data.

1. Ramchandren R et al. *Blood*. 2017;130:Abstract 651.

MSKCC Phase I/II ABVD + Nivolumab in Advanced Stage HL

PI: A. Moskowitz



Conclusions

- ABVD remains the most widely used regimen for the treatment of advanced stage HL
  - PET2 negative scans : Continue with AVD
  - PET2 positive scans: No standard of care. eBEACOPP is an option

- BV + AVD: marginally (5% -but statistically significant) improved mPFS/EFS
  - EOT ORR 86%, CR 73%
  - Difference was higher in North America
  - A new option.
  - Room for improvement

- Nivo + AVD
  - EOT ORR 84%, CR 67%
  - Unlikely to be superior to BV + AVD
  - Role in PET2+ to be determined