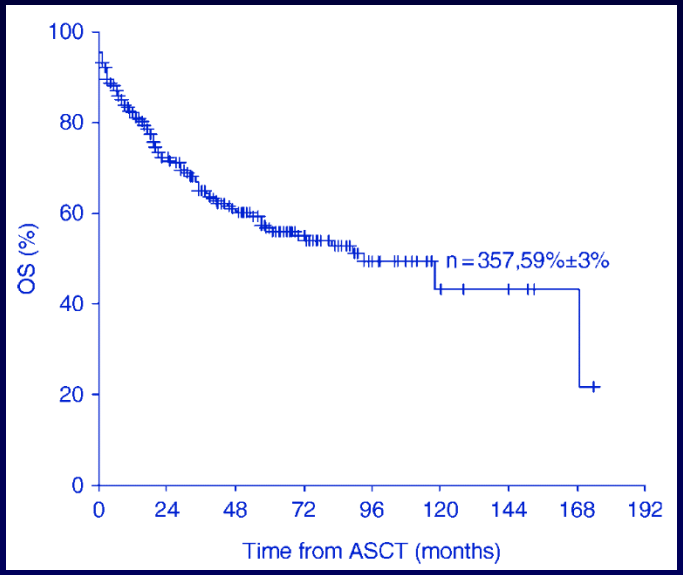
The AETHERA Trial: Results of a Randomized, Double-Blind, Placebo-Controlled Phase III Study of Brentuximab Vedotin in the Treatment of Patients at Risk of Hodgkin Lymphoma Progression Following Autologous Stem Cell Transplant

Abstract #673

Moskowitz CH, Nademanee A, Masszi T, Agura E, Holowiecki J, Abidi MH, Chen AI, Stiff P, Gianni AM, Carella A, Osmanov D, Bachanova V, Sweetenham J, Sureda A, Huebner D, Larsen EK, Hunder NN, and Walewski J

Background

- Autologous stem cell transplant (ASCT) in patients with relapsed or refractory Hodgkin lymphoma (HL) can achieve cure in approximately 50% of patients[a-d]
- Over the past 20 years, no improvement has been shown in efficacy outcomes from randomized trials of ASCT regimens for aggressive lymphomas (HL or diffuse large B-cell lymphoma)
- Brentuximab vedotin (ADCETRIS®; BV) is a CD30-directed therapy that has shown efficacy in patients with HL who relapsed or were refractory after prior ASCT[e]
- We conducted a randomized, placebo-controlled, phase 3 study to assess whether BV consolidation could prevent disease progression post-ASCT in patients at risk for relapse or progression



Prognostic factors affecting long-term outcome after stem cell transplantation in Hodgkin's lymphoma autografted after a first relapse.[a]

a. Sureda A, et al. *Ann Oncol*. 2005 ;16(4):625-633. b. Majhail NS, et al. *Biol Blood Marrow Transplant.* 2006;12: 1065. c. Sirohi B, et al. *Ann Oncol.* 2008;19:1312-1329. d. Hahn T, et al. *Biol Blood Marrow Transplant.* 2013;19:1740-1744. e. Younes A, et al. *J Clin Oncol.* 2012, 30: 2183-2189.

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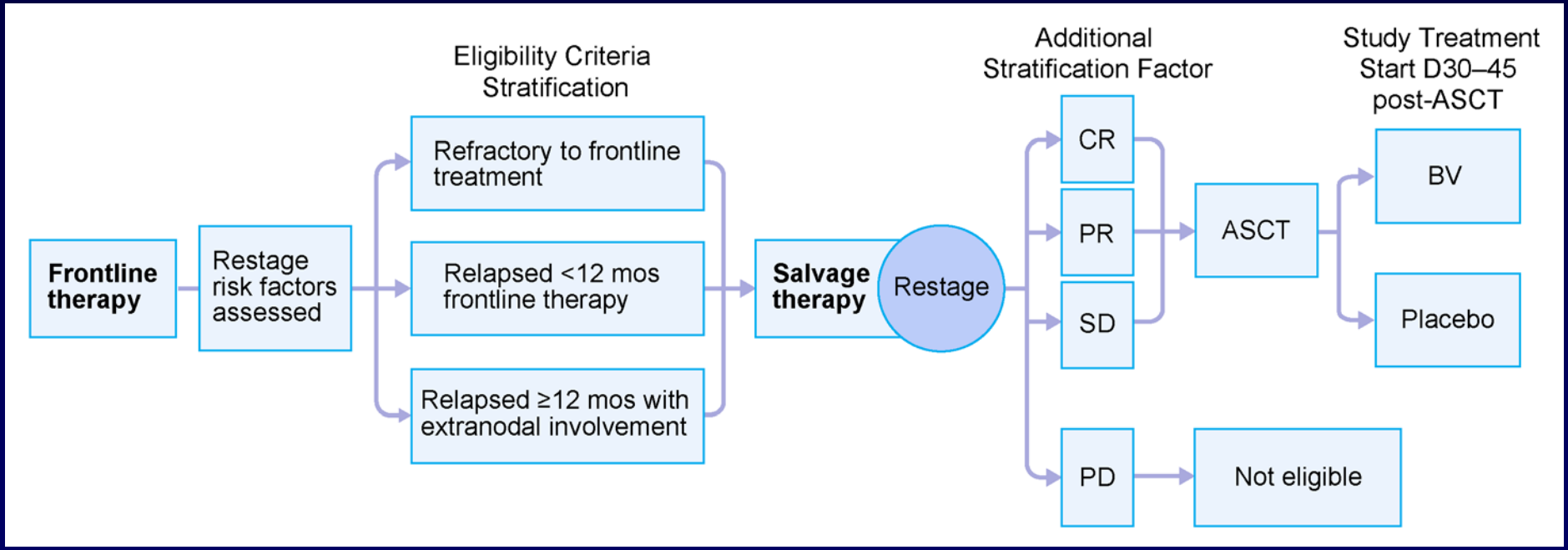
Study Design and Key Eligibility Criteria

- 329 patients were randomized at 78 sites in North America and Europe



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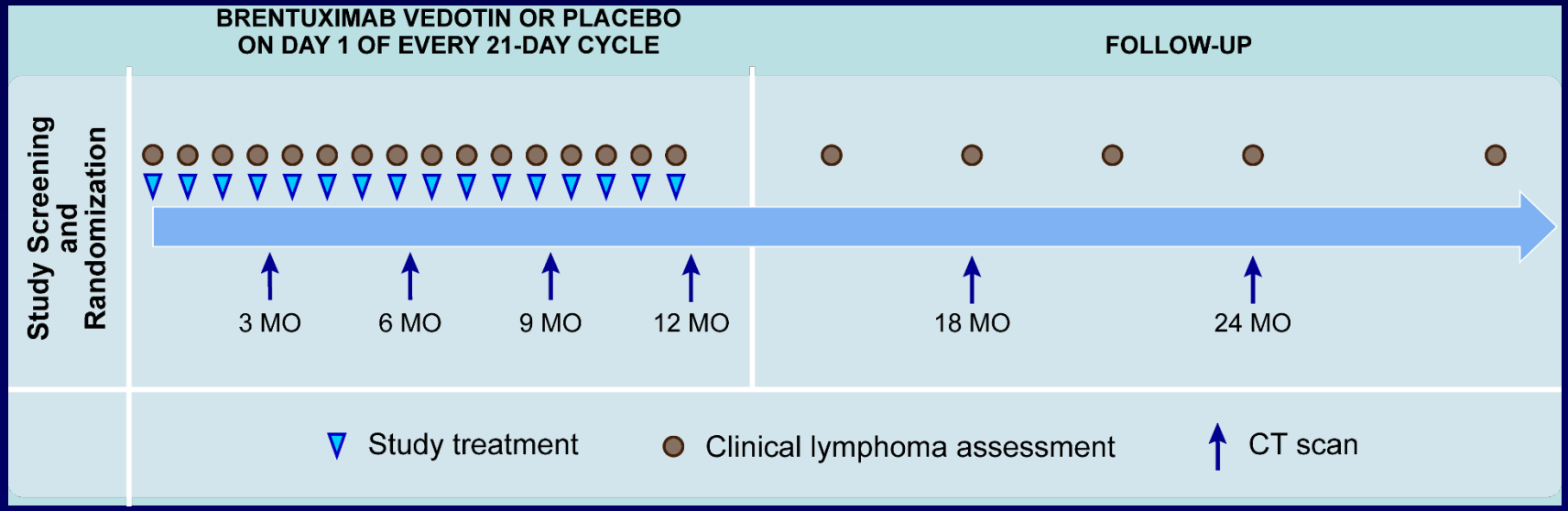
Treatment and Assessment Schedule

- Patients were randomized to receive 16 cycles of BV or placebo
- They were evaluated and treated every 21 days
- Imaging quarterly for first year, then at 18 and 24 months
- **Importantly, patients who progressed on the placebo arm could subsequently receive BV on another trial**



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Main Objectives

- **Primary**
  - **To compare progression-free survival (PFS) per independent review facility (IRF) between the 2 treatment arms**
- **Secondary**
  - **To compare overall survival (OS) between the 2 treatment arms**
  - **To evaluate the safety and tolerability of BV compared to placebo**

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Patient Characteristics

	BV (N = 165)	Placebo (N = 164)
Age, years; median (range)	33 (18-71)	32 (18-76)
Gender	46% M / 54% F	59% M / 41% F
No. prior cancer-related systemic salvage therapies		
1	94 (57)	86 (52)
≥2	71 (43)	78 (48)
HL status after frontline therapy		
Refractory	99 (60)	97 (59)
Relapse <12 months	52 (32)	54 (33)
Relapse ≥12 months	13 (8)	13 (8)
Response with salvage therapy pre-ASCT		
Complete remission	61 (37)	62 (38)
Partial remission	57 (35)	56 (34)
Stable disease	47 (28)	46 (28)
Extranodal involvement at pre-ASCT relapse	54 (33)	53 (32)
B symptoms after frontline therapy	47 (28)	40 (24)
Pre-ASCT PET status		
FDG avid	64 (39)	51 (31)
FDG negative	56 (34)	57 (35)
Not available	45 (27)	56 (34)

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Patient Disposition

Reason for treatment discontinuation	BV (N = 165) n (%)	Placebo (N = 164) n (%)
Completed treatment	78 (47)	81 (49)
Progressive disease	24 (15)	69 (42)
Adverse event	54 (33)	10 (6)
Patient decision	9 (5)	4 (2)

*All patients are off treatment

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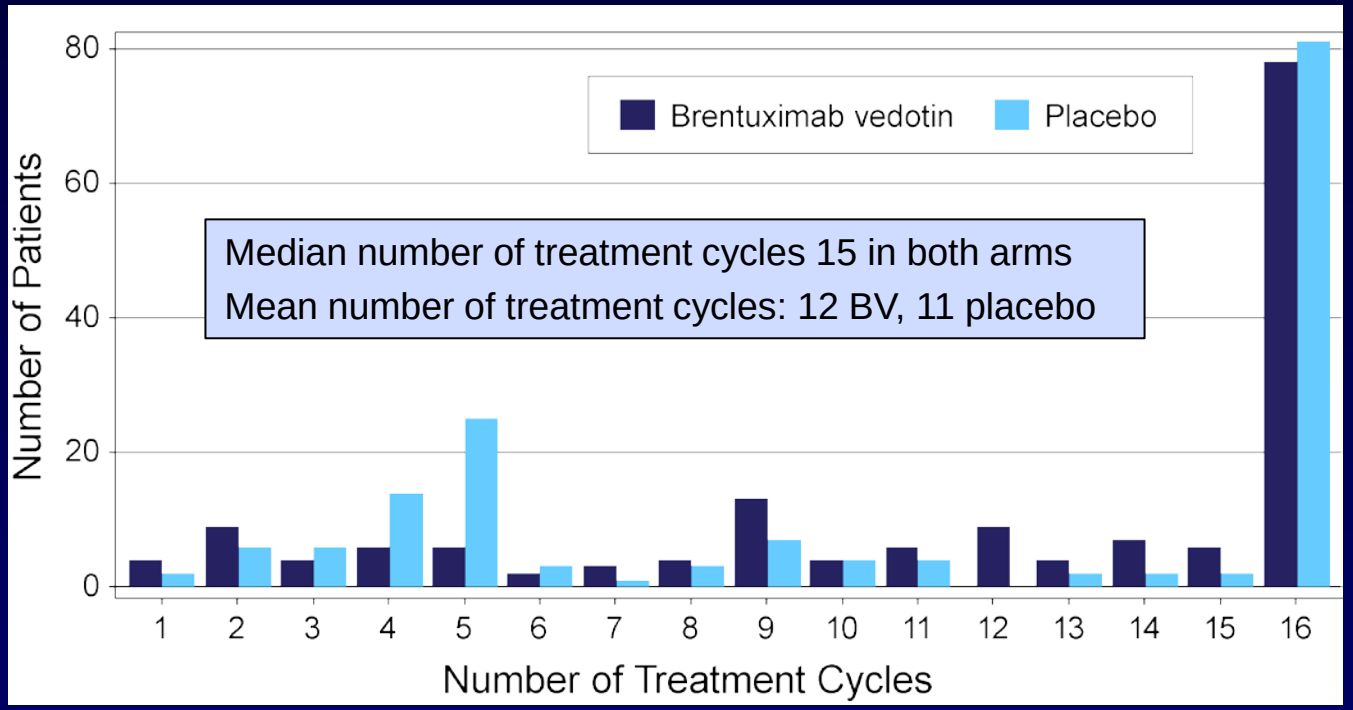
Patient Exposure



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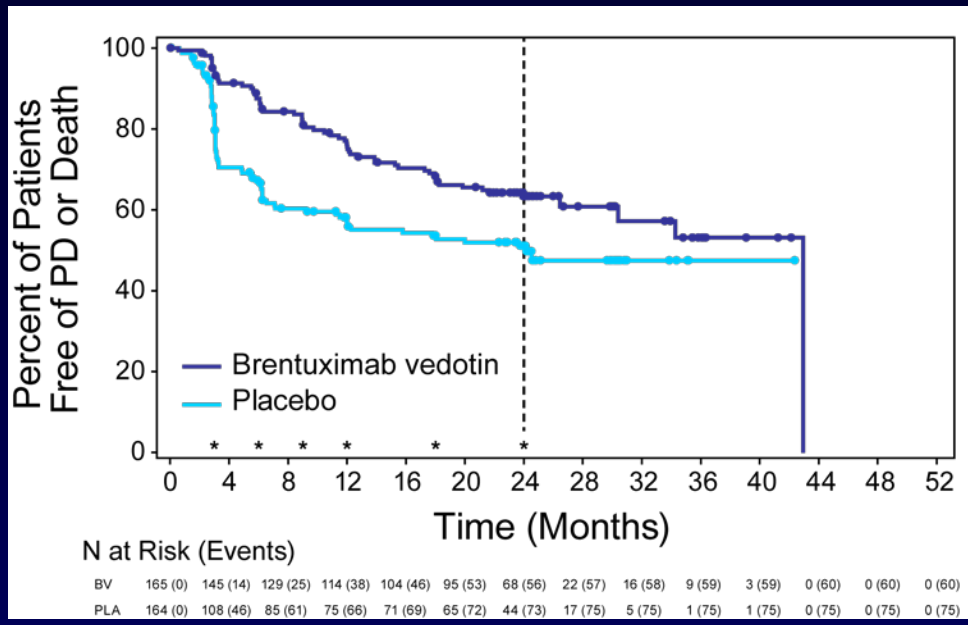
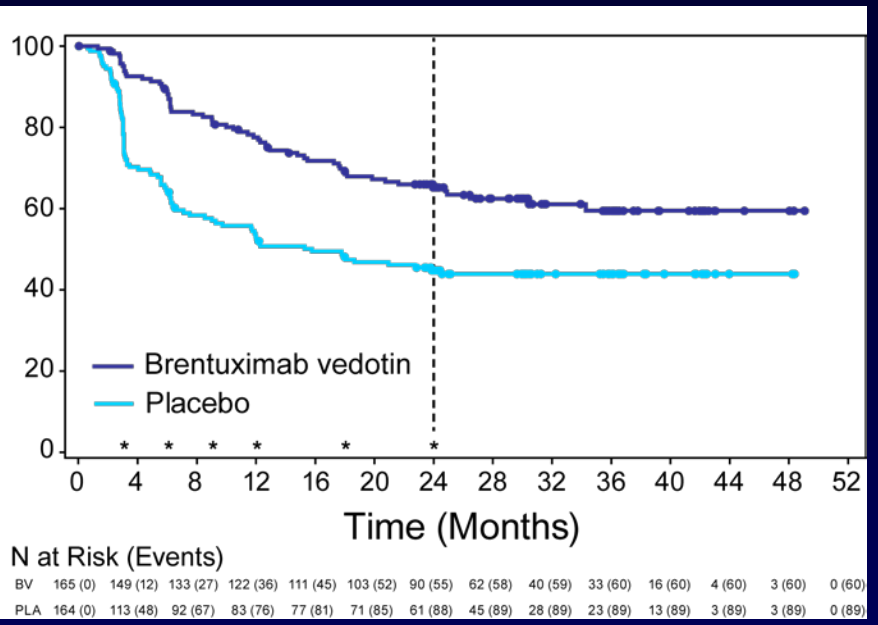
Progression-Free Survival





	BV (N = 165)	Placebo (N = 164)
Hazard Ratio (95% CI)	**0.57 (0.40–0.81, P = .001)**	
Events	**60**	**75**
Median PFS (months)	**43**	**24**
2-year PFS rate	**63%**	**51%**

	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

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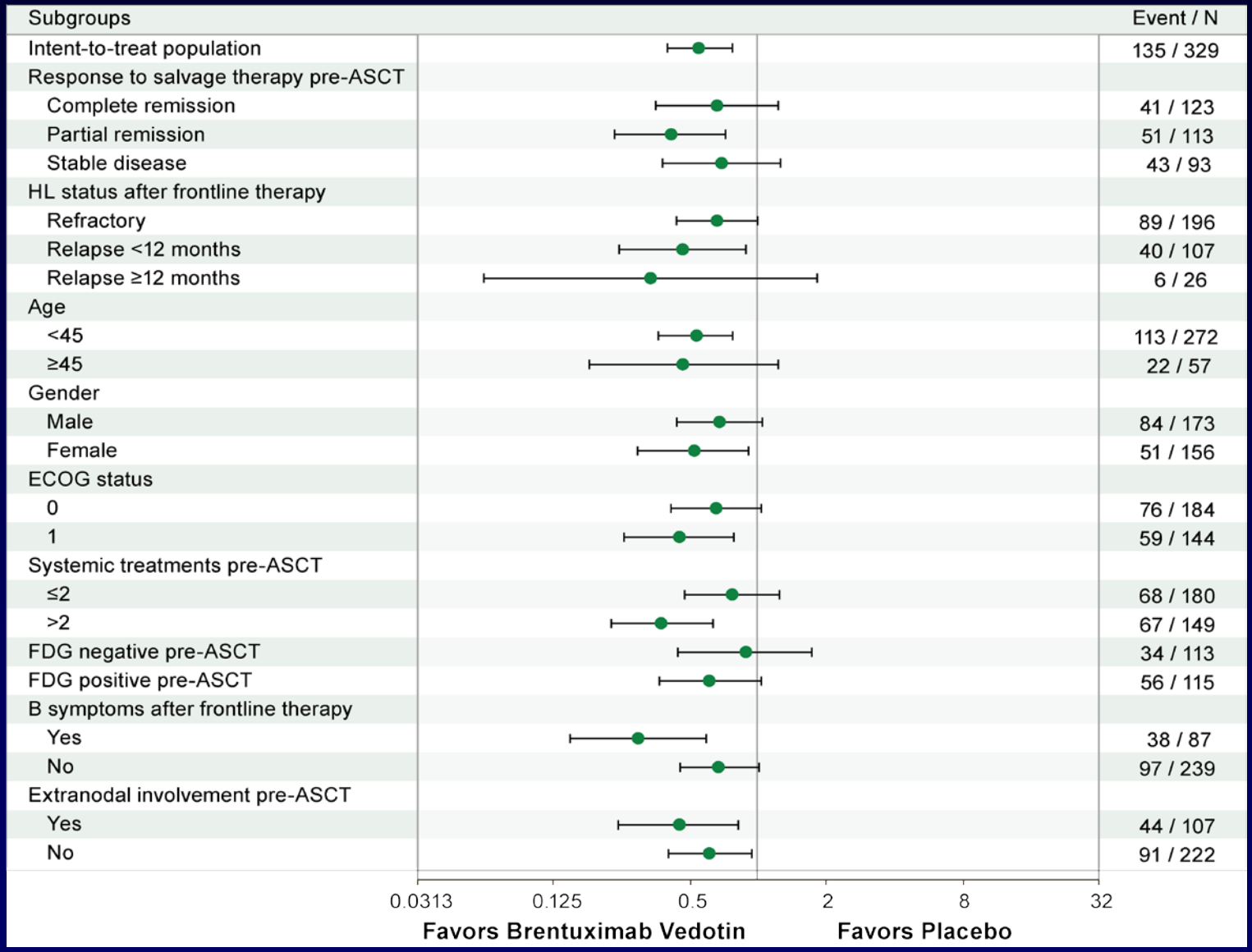
Subgroup Analysis of PFS per IRF



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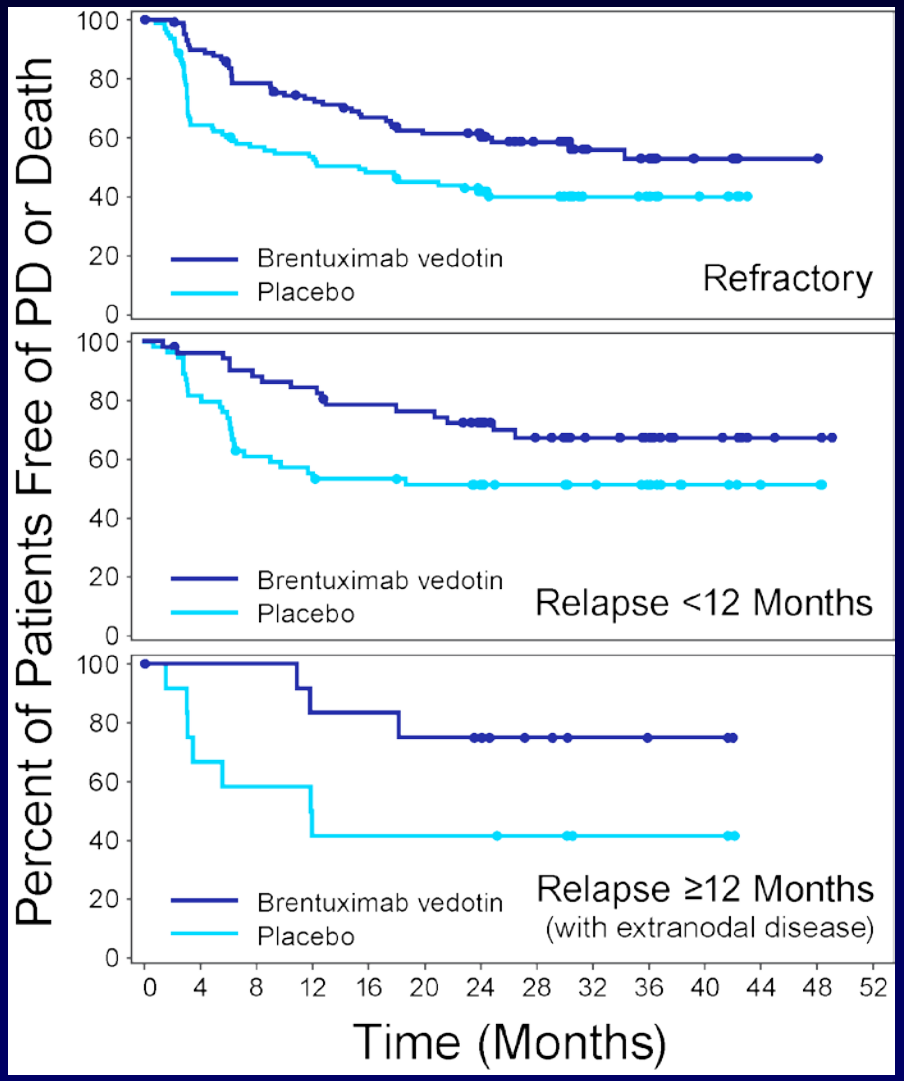
PFS* by Eligibility Criteria



N = 196

N = 107

N = 26

*Per investigator analysis

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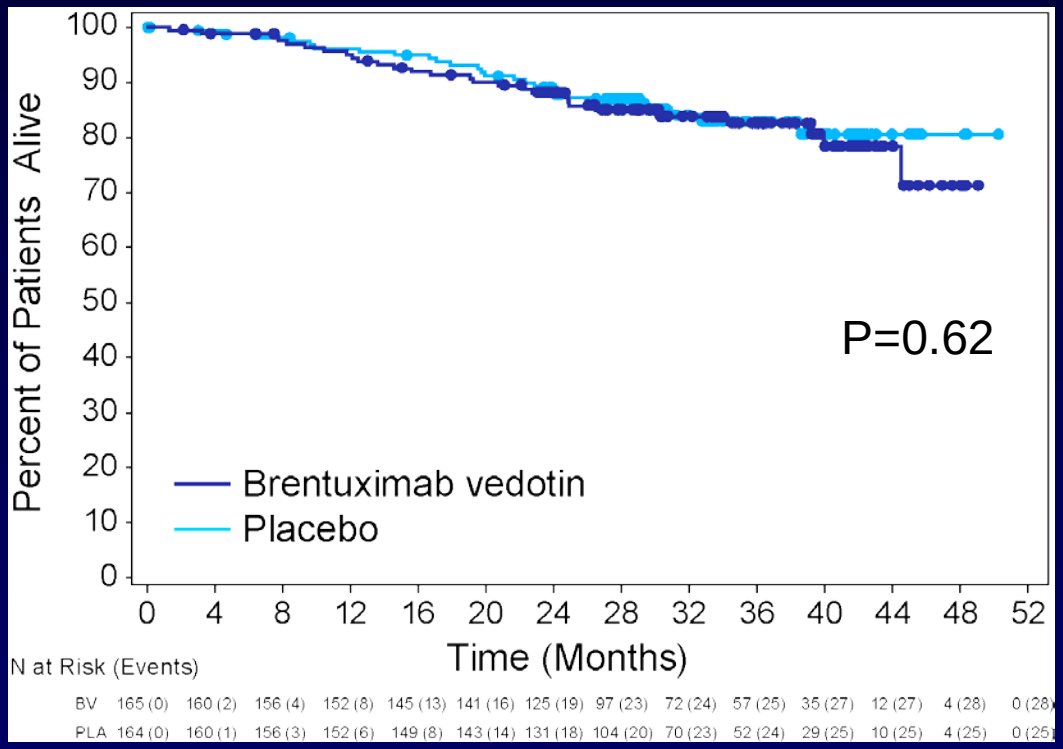
Overall Survival



Risk Factors

- **Relapsed <12 months or refractory to frontline therapy**
- **Best response of PR or SD to most recent salvage therapy**
- **Extranodal disease at pre-ASCT relapse**
- **B symptoms at pre-ASCT relapse**
- **Two or more prior salvage therapies**

No. risk factors	N	PFS per IRF HR (95% CI)	OS HR (95% CI)
≥1	329	0.57 (0.40-0.81)	1.15 (0.67-1.97)
≥2*	280	0.49 (0.34-0.71)	0.94 (0.53-1.67)
≥3*	166	0.43 (0.27-0.68)	0.92 (0.45-1.88)

* Ad hoc analysis

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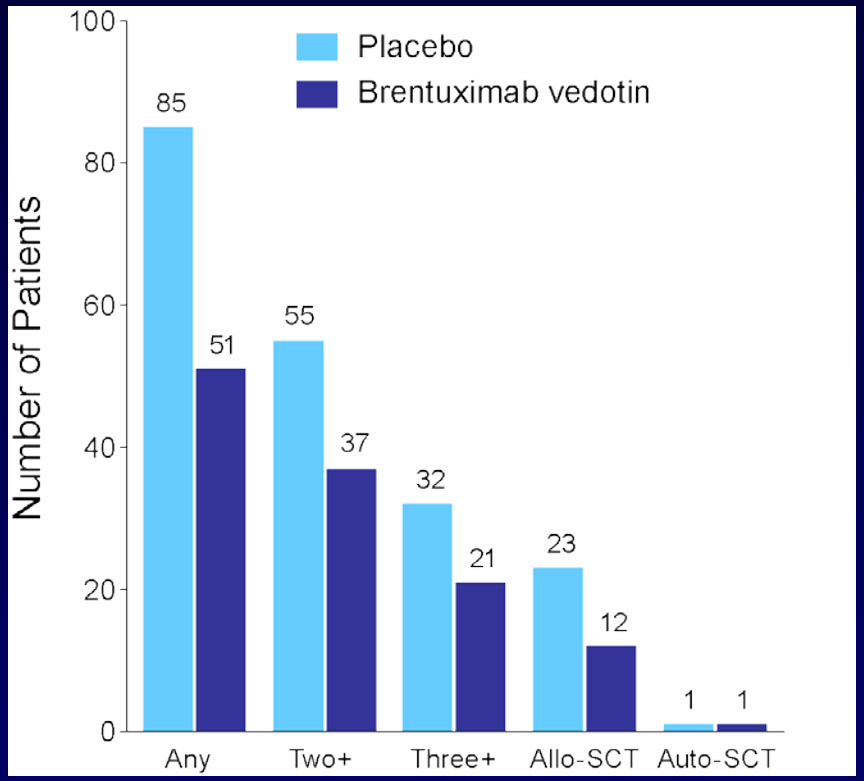
Subsequent Anti-tumor Therapies

Patients who received subsequent anti-tumor therapy

	BV (N = 51) n (%)	Placebo (N = 85) n (%)
Single-agent BV	8 (16)	72 (85)
Multi-agent regimen including BV	1 (2)	1 (1)
Stem cell transplant*	13 (25)	24 (28)
Multi-agent chemotherapy	35 (69)	34 (40)
Radiation	22 (43)	23 (27)
Single-agent chemotherapy	22 (43)	22 (26)
Donor lymphocyte infusion	2 (4)	1 (1)
Other treatment	1 (2)	2 (2)

* Most were allogeneic (12 BV, 23 placebo)



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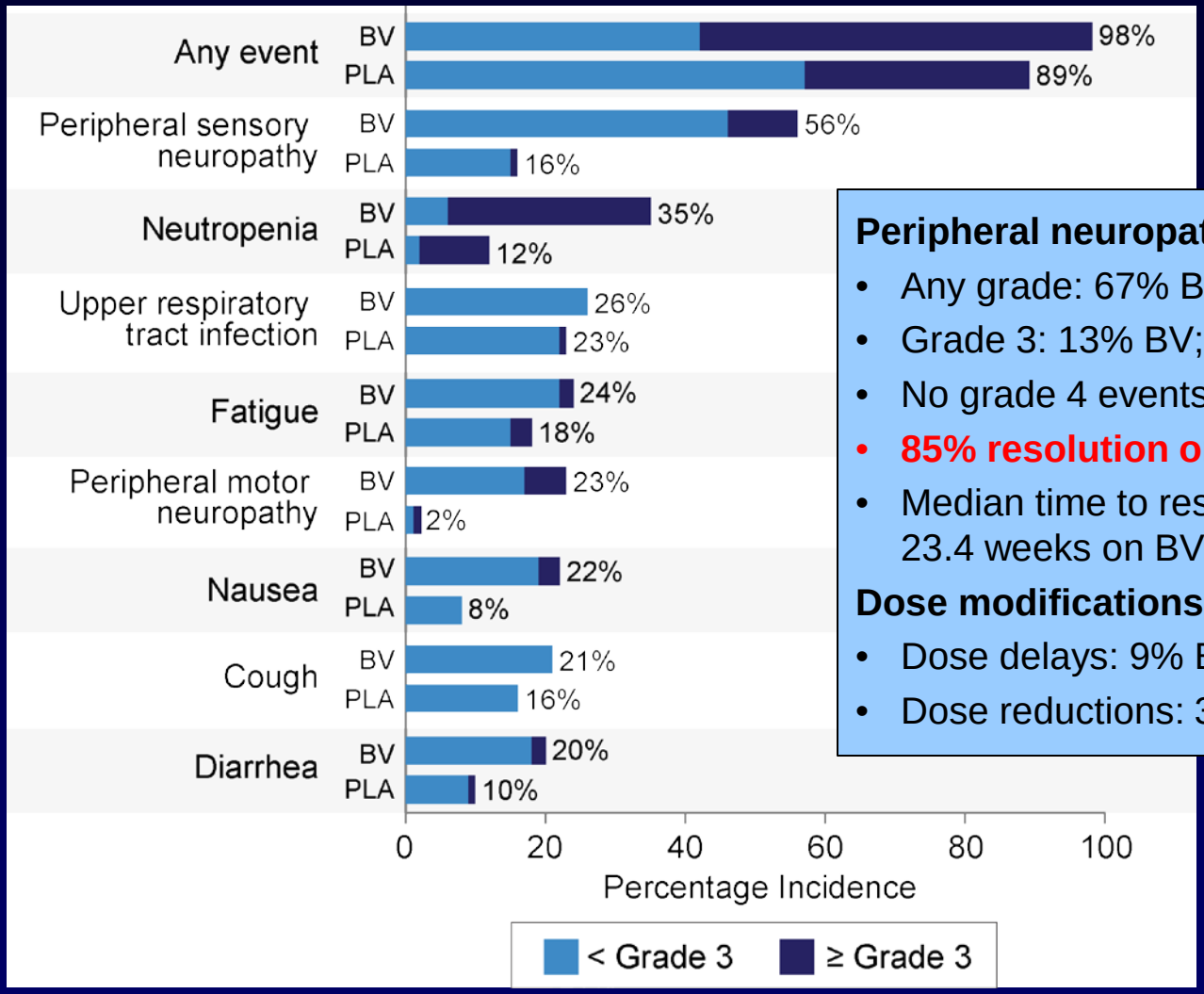
Adverse Events*



Peripheral neuropathy (SMQ analysis)

- Any grade: 67% BV; 19% placebo
- Grade 3: 13% BV; 1% placebo
- No grade 4 events
- **85% resolution or improvement on BV arm**
- Median time to resolution or improvement 23.4 weeks on BV arm

Dose modifications due to adverse events

- Dose delays: 9% BV, 3% placebo (by dose)
- Dose reductions: 32% BV, 3% placebo (by pt)

* Treatment-emergent adverse events regardless of relationship to therapy; incidence ≥20% on BV arm

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Deaths

	BV N = 167 n (%)	Placebo N = 160 n (%)
Total	28 (17)	25 (16)
Related to disease	18 (11)	17 (11)
Not related to disease	9 (5)	7 (4)
Disease relationship unknown	1 (1)	1 (1)
Prior to PD per investigator	5 (3)	3 (2)

- One death within 30 days of BV treatment:
  - Treatment-related acute respiratory distress syndrome (ARDS) associated with pneumonitis
- One death at study day 40 (BV treatment arm):
  - ARDS following an episode of treatment-related acute pancreatitis, which had resolved at the time of death

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Conclusions

- Early consolidation post-ASCT with BV demonstrated improved PFS per IRF in HL patients with risk factors for relapse or progression (HR = 0.57, *P* = .001)
  - PFS benefit was sustained, with 2-year PFS rates per investigator of 65% and 45% on the BV and placebo arms, respectively
  - Consistent benefit was observed across subgroups
- Interim analysis of overall survival did not show a significant difference between treatment arms (*P* =.62)
  - Analysis limited by small number of events and the large number of patients on the placebo arm crossing over to BV after progression
  - More patients on the placebo arm received subsequent anti-tumor therapy and/or allogeneic stem cell transplant
- Consolidation therapy was generally well tolerated
  - Peripheral sensory neuropathy and neutropenia were common, and were manageable with dose reductions or delays
  - Two deaths occurred within 40 days of dosing with BV
- BV consolidation therapy is an important therapeutic option for HL patients undergoing ASCT to reduce the risk of relapse or progression

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