Il concetto del consolidamento nel linfoma di Hodgkin

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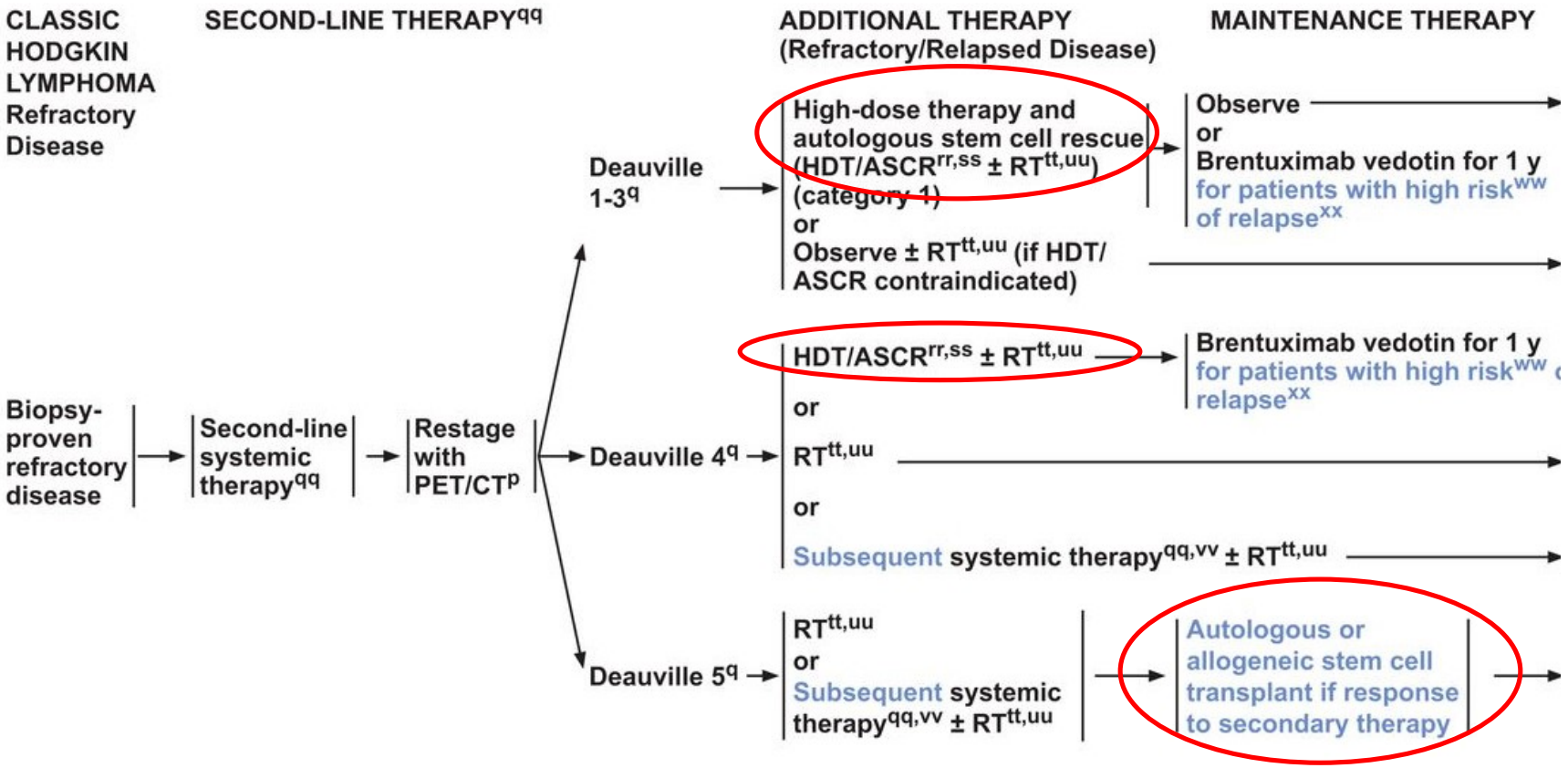
NCCN Guidelines® Insights

Hodgkin Lymphoma, Version 1.2018

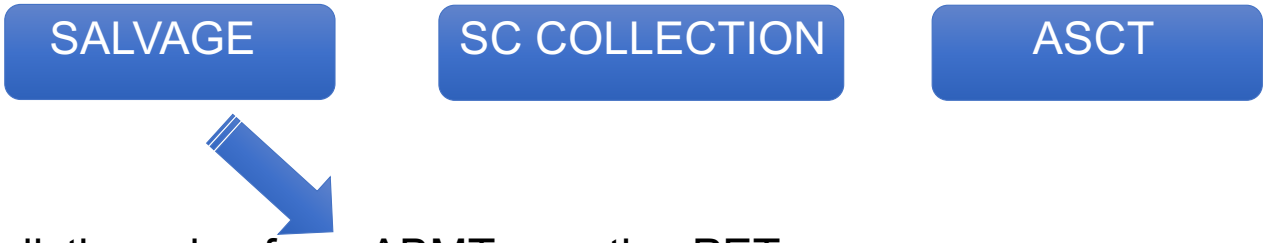
Featured Updates to the NCCN Guidelines

Se in altre forme di linfoma l'avvento di nuovi farmaci ha indebolito il ruolo del trapianto autologo di cellule staminali, nell'Hodgkin conserva un ruolo cardine per il trattamento del paziente recidivato/refrattario



Relapsed /Refractory HL

Salvage strategy:



- Predictive role of pre-ABMT negative PET
- Conventional salvage regimens allows CR (PET-) achievment in 40-70% of Pts

IGEV CR = 53%
(Santoro A et Al. Haematologica. 2007 Jan;92(1):35-41)

IEV CR = 45%
(Zinzani PL et Al. Haematologica. 2002 Aug;87(8):816-21)

DHAP CR = 32%
(Josting et Al. Ann Oncol. 2005; 16 (1):116-123.)

ICE CR = 31%
(Hertzberg MS et Al. Ann Oncol 17 (Supp 4): iv25–iv30, 2006)

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Bendamustine in Combination With Gemcitabine and Vinorelbine Is an Effective Regimen As Induction Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed or Refractory Hodgkin Lymphoma: Final Results of a Multicenter Phase II Study

Armando Santoro, Rita Mazza, Alessandro Pulsoni, Alessandro Re, Maurizio Bonfichi, Vittorio Ruggero Zilioli, Flavia Salvi, Francesco Merli, Antonella Anastasia, Stefano Luminari, Giorgia Annechini, Manuel Gotti, Annalisa Peli, Anna Marina Liberati, Nicola Di Renzo, Luca Castagna, Laura Giordano, and Carmelo Carlo-Stella

Gemcitabine
800 mg/m^2 d 1-4

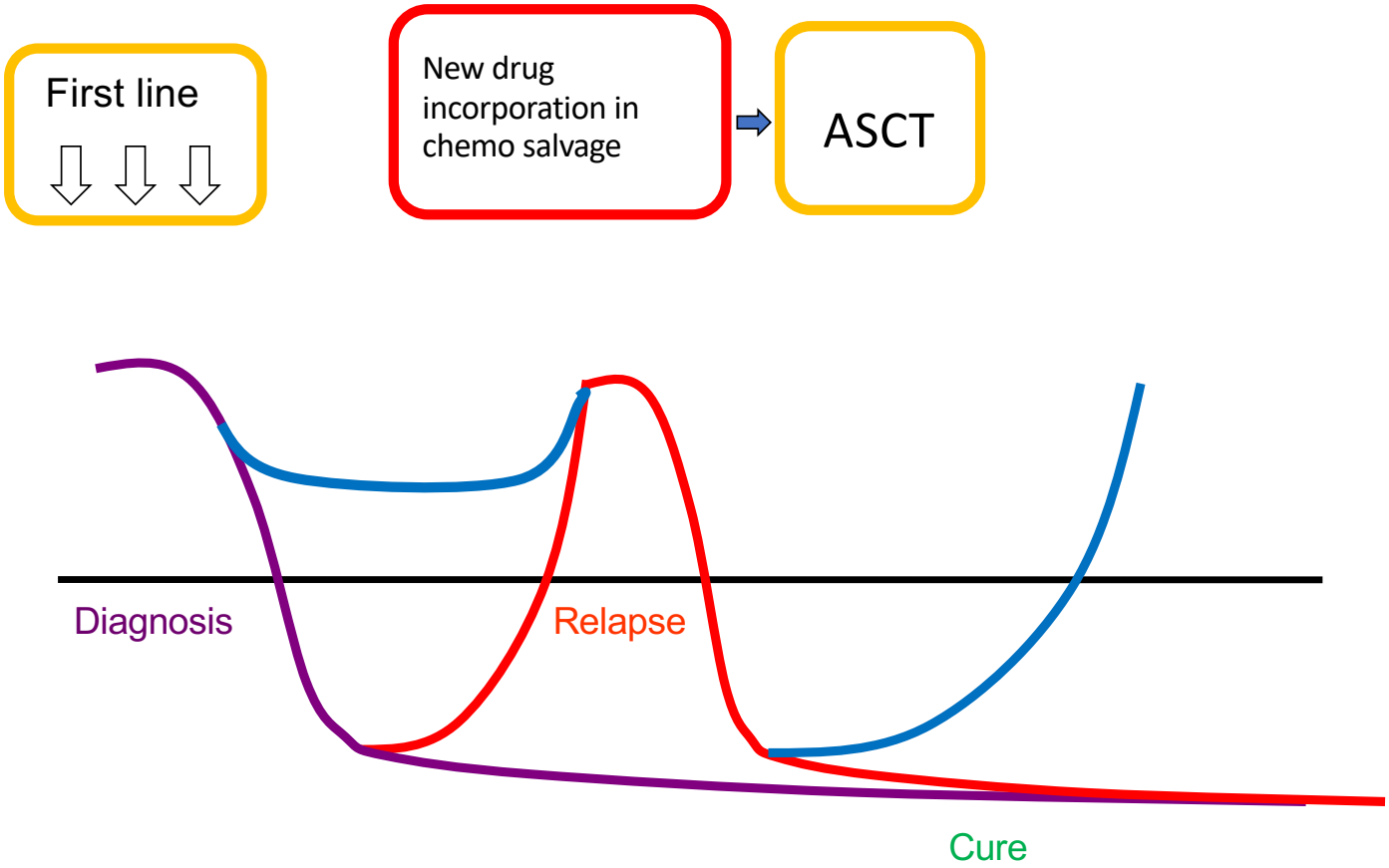
Vinorelbine
20 mg/m^2 d 1

Bendamustine
90 mg/m^2 d 2-3

Table 2. Clinical Responses to BeGEV Regimen According to ITT and Disease Status at Entry

Parameter	No. of Patients	CR		PR		SD		PD		NE	
		No.	%	No.	%	No.	%	No.	%	No.	%
Response by ITT	59	43	73	6	10	1	2	8	14	1	2
Disease status at study entry											
Relapsed	32	27	84*	3	9	1	3	0	0	1	3
Refractory	27	16	59*	3	11	0	0	8	30	0	0

New drug incorporation in traditional salvage



Pre-ASCT strategy incorporating new agents

Brentuximab vedotin plus DHAP as salvage therapy in R/R HL

	All, n=12	DL1, n=3	DL2, n=3	DL3 n=6
Age, years (range)	30.5 (21-56)	32.0 (30-38)	25.0 (24-31)	30.5 (21-56)
Female %	67	67	33	83
ECOG performance status 0 at study entry (%)	100			
Prior therapies (n)				
ABVD	5	1		4
ABVD + RT	4	1	2	1
Escalated BEACOPP	2	1		1
Escalated BEACOPP + RT	1		1	
Diagnosis to 1st BV-DHAP (years)	1.2 (0.7-11.2)	1.2 (1.2-3.3)	1.0 (1.0-1.0)	2.5 (0.7-11.2)
Ann Arbor stage at diagnosis (n)				
I/II	6	1	2	3
III/IV	6	2	1	3
Best response to first-line treatment				
CR	9	3	1	5
PR	2		1	1
Unknown	1*		1	

We observed grade 3-4 adverse events in 7 patients; neutropenia grade 4 (n=2, DL1), neutropenia grade 3 and thrombocytopenia grade 4 (n=1, DL3), thromboembolic event grade 3 (n=1, DL 1), elevated transaminases grade 3 (n=1, DL3, resolved), leukocytosis grade 4 (n=1, DL3) and hypokalemia (n=1, DL3)

- Hagenbeek A et Al. haematologica 2019; 104:e153

Phase I dose-escalation study of brentuximab-vedotin combined with dexamethasone, high-dose cytarabine and cisplatin, as salvage treatment in relapsed/refractory classical Hodgkin lymphoma: The HOVON/LLPC Transplant BRaVE study

haematologica 2019; 104:e151

- DL1: 75% cisplatin, 75% cytarabine (n=3)
- DL2: 75% cisplatin, 100% cytarabine (n=3)
- DL3: Full dose of all agents (n=6)

After three cycles of BV-DHAP, PET CT showed a CMR in 11 out of 12 patients (92%).

All 12 patients underwent subsequent BEAM chemotherapy and ASCT.

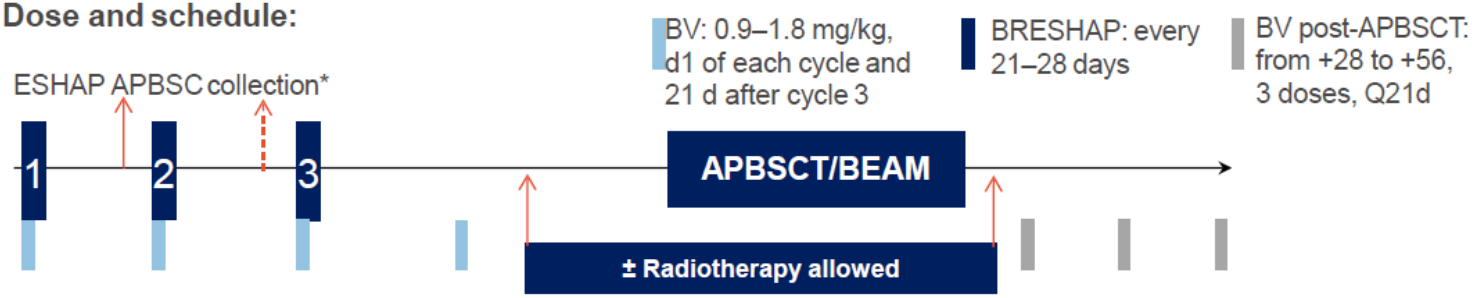
All remained alive in complete response after a median follow up of 2.0 years (range 1.8-3.0 years).

Pre-ASCT strategy incorporating new agents

Brentuximab vedotin and ESHAP is highly effective as second-line therapy for Hodgkin lymphoma patients (long-term results of a trial by the Spanish GELTAMO Group)

R. Garcia-Sanz[1,2*], A. Sureda[3], F. de la Cruz[4], M. Canales[5], A. P. Gonzalez[6], J. L. Pinana[7], A. Rodriguez[8], A. Gutierrez[9], E. Domingo-Domenech[3], B. Sanchez-Gonzalez[10], G. Rodriguez[11], J. Lopez[12], M. Moreno[13], M. J. Rodriguez-Salazar[14], S. Jimenez-Cabrera[15], M. D. Caballero[1,2] & C. Martinez[16]

Dose and schedule:



- Etoposide (40 mg/m²/day IV), metilprednisolone (200 mg/day), cisplatin (25 mg/m²/day IV) on days 1–4; citarabine (2 g/m² IV) on day 5 of 21–28 day cycles
- Phase I: Brentuximab vedotin (0.9, 1.2 or 1.8 mg/kg) on day 1 of each cycle, and day 21 after 3rd ESHAP cycle

- Garcia-Sanz R et Al. Ann Oncol 2019 Apr 1;30(4):612-620

Pre-ASCT strategy incorporating new agents

39 SAE were reported in 22 patients, most frequently fever (n=25, 35% neutropenic), including 3 deaths.

Table 3. Adverse events related to brentuximab vedotin plus ESHAP

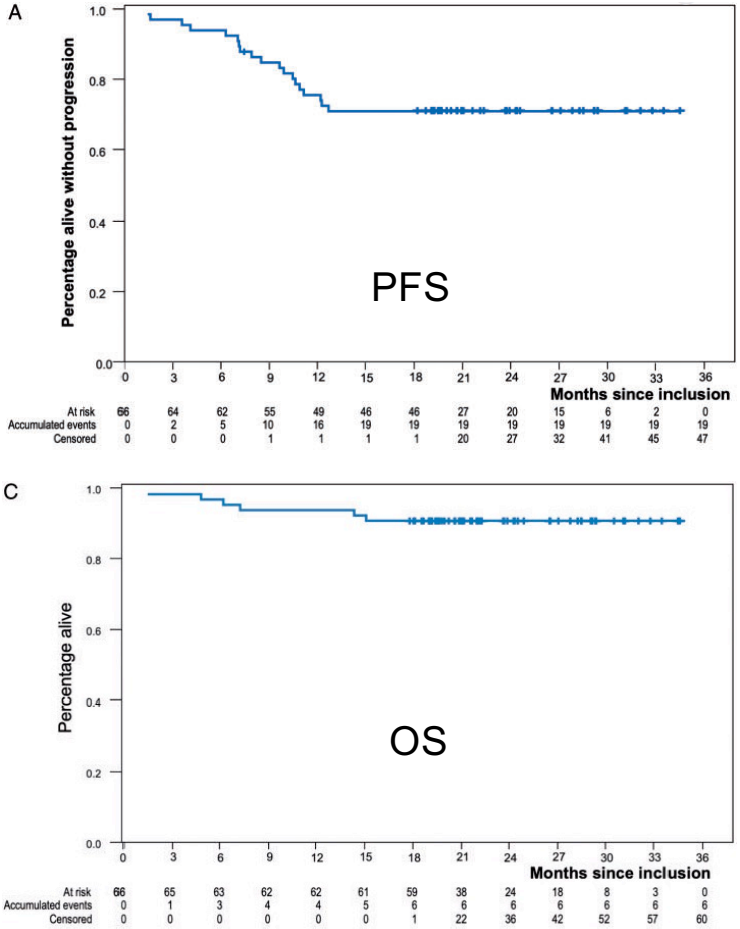
Toxicity		During BRESHAP ($n = 66$)				Post-transplant ($n = 59$)			
Hematologic	Grade any	1	2	3	4	1	2	3	4
Thrombocytopenia	100%	17%	36%	33%	14%	21%	12%	3%	0%
Neutropenia	96%	42%	8%	31%	19%	29%	15%	2%	0%
Anemia	94%	19%	42%	19%	0%	12%	7%	2%	0%
Non-hematologic									
Fever	48%	11%	8%	8%	0%	10%	3%	2%	3%
Mucositis	30%	8%	11%	8%	0%	3%	0%	0%	0%
Pain	29%	19%	6%	0%	0%	4%	0%	0%	0%
Vomiting	28%	14%	6%	0%	0%	8%	0%	0%	0%
Asthenia	23%	11%	6%	3%	0%	4%	0%	0%	0%
Hyporexia	14%	8%	6%	0%	0%	0%	0%	0%	0%
PNP	22%	8%	4%	0%	0%	6%	4%	0%	0%
Constipation	11%	11%	0%	0%	0%	0%	0%	0%	0%
Renal dysfunction	9%	6%	3%	0%	0%	0%	0%	0%	0%
Hypotension	3%	0%	0%	3%	0%	0%	0%	0%	0%
CMV reactivation	3%	0%	3%	0%	0%	0%	0%	0%	0%
Hypomagnesemia	5%	2%	3%	0%	0%	0%	0%	0%	0%

before transplant:

OR = 91%

CR = 70%

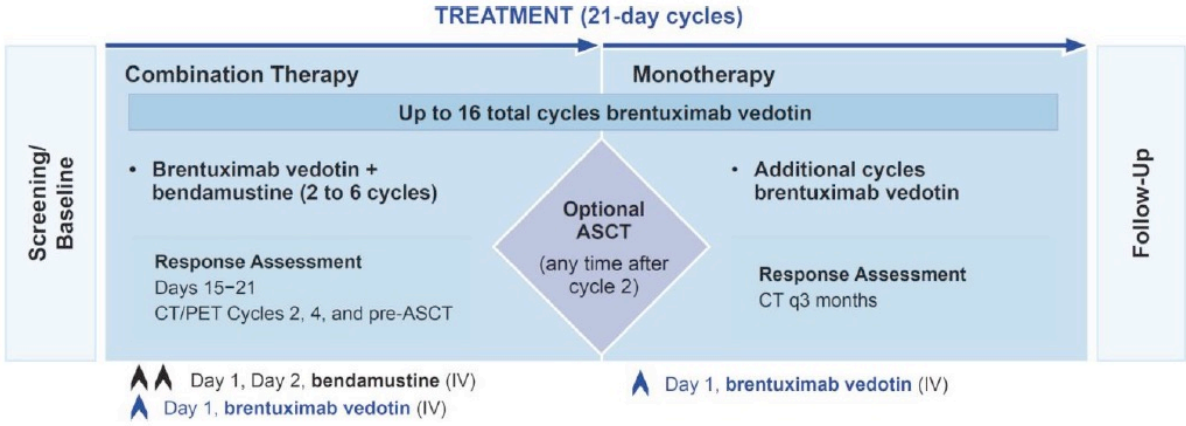
60 patients were transplanted with no failure engraftments. Post-transplant response was CR in 49 patients and PR in 6



- Garcia-Sanz R et Al. Ann Oncol 2019 Apr 1;30(4):612-620

SGN35-016: Phase I/II trial of brentuximab vedotin combined with bendamustine in R/R HL: *updated 2-yr results* (NCT01874054)

Study Design:



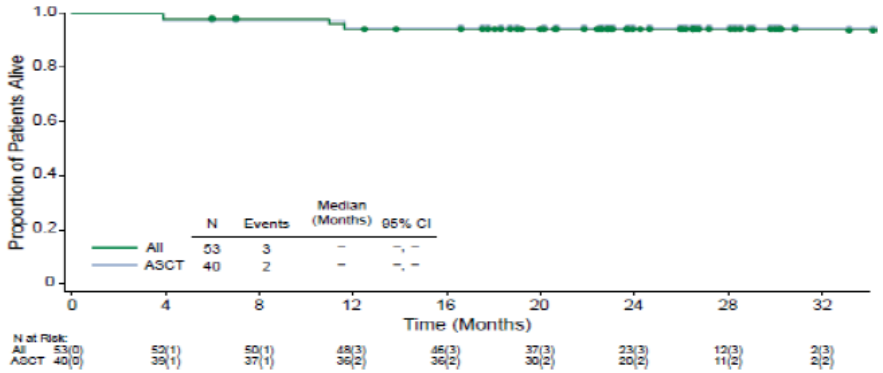
Safety: Median 2 cycles (1–6) of brentuximab vedotin 1.8 mg/kg +bendamustine 90mg/m$_2$, median10 cycles(1–14) of single-agent brentuximab vedotin (n=31;25ASCTpts ,6non-ASCT pts).
3pts died, due to progression of HL (2pts) or septic shock after transplant (1pt)
•IRRs were observed in 58% of pts overall, most common symptoms (≥15%) were pyrexia, chills, dyspnea, flushing, and nausea
•Protocol was amended to require premedication with corticosteroids and antihistamines, the use of which decreased the severity of IRRs.

Best response on combination therapy	N=53	
	n (%)	95% CI
ORR (CR + PR)	49 (93)	81.8, 97.9
CR	39 (74)	59.7, 84.7
PR	10 (19)	-

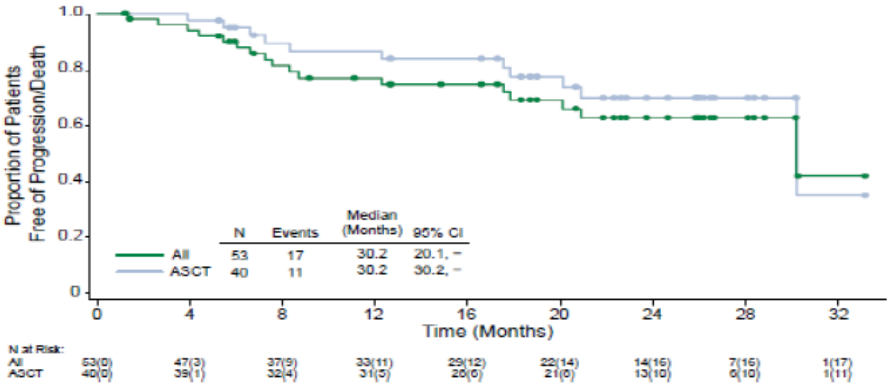
LaCache A et Al. blood-2017-11-815183

Updated 2y results:

OS – all patients and ASCT subset

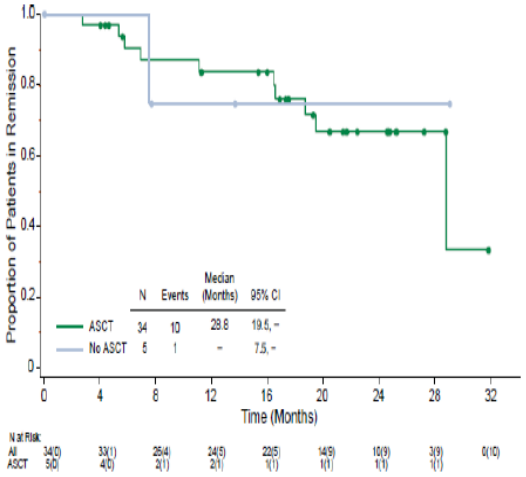


PFS – all patients and ASCT subset

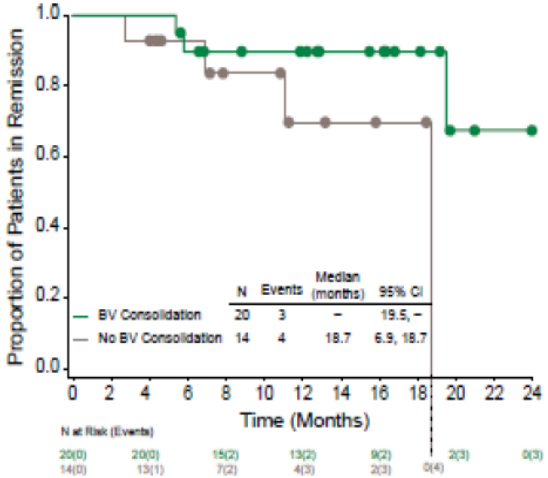


Duration of remission in pts with CR

± ASCT[1]



ASCT ± consolidation[2]



11 of 39 pts in CR experienced an event
10 of 34 pts (29%) who underwent ASCT
1 of 5 pts (20%) without ASCT

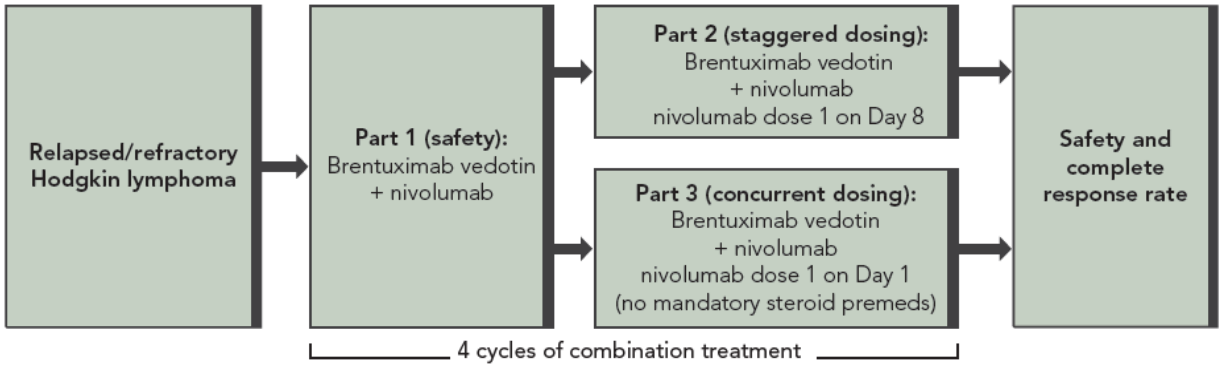
Overall estimated 24-month PFS:

- All pts: 63% (95% CI: 46,76)
- ASCT: 70% (95% CI: 51,83)

Pre-ASCT strategy CHEMO-FREE

Phase 1/2 Study of Brentuximab Vedotin in Combination with Nivolumab in Patients with Relapsed or Refractory Classic Hodgkin Lymphoma: Part 3 (Concurrent Dosing) Results and Updated Progression-Free Survival Results from Parts 1 and 2 (Staggered Dosing)

Ranjana H. Advani, MD[1], Alison J. Moskowitz, MD[2], Nancy L. Bartlett, MD[3], Julie M. Vose, MD, MBA[4], Radhakrishnan Ramchandren, MD[5], Tatyana A. Feldman, MD[6], Ann S. LaCasce, MD[7], Beth A. Christian, MD[8], Stephen M. Ansell, MD, PhD[9], Craig H. Moskowitz, MD[10], Keenan Fenton[11], Carol Anne Ogden, PhD[11], David Taft[11], Daniel E. Zak, PhD[11], Mariana Sacchi, MD[12], Faith Gallerani, DO[13], and Alex F. Herrera, MD[13]



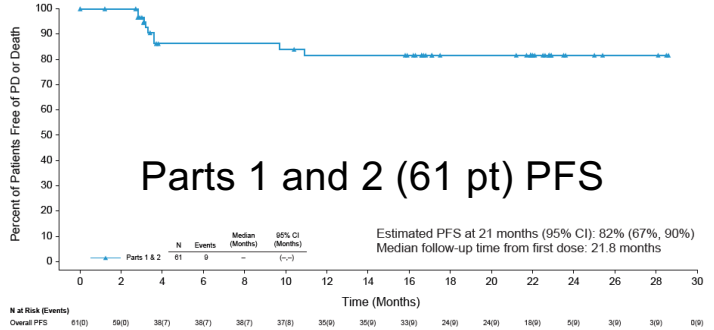
Serious adverse events (17%):
- Guillain-Barre syndrome (G3),
- pancreatitis (G4),
- pneumonia (G2),
- pneumonitis (G4),
- cellulitis (G3)

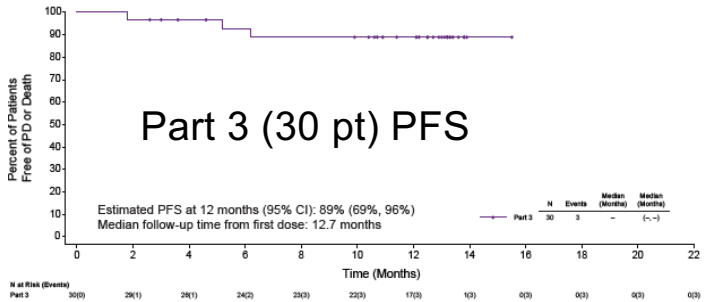
Immune-Related Adverse Events (IRAE) Requiring Systemic Corticosteroids:
2 patients (7%):
- pneumonitis (G4),
- GBS (G3)

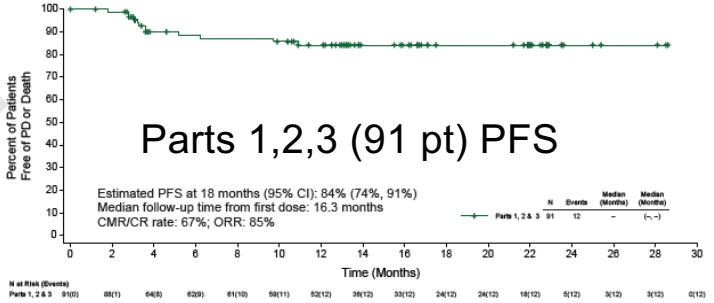
No treatment discontinuations

CMR/CR rate: 67%; ORR: 85%
Estimated PFS at 18 months (95% CI): 84% (74%, 91%)
Median follow-up time from first dose: 16.3 months

Part 3 results, along with the durable remissions noted in Parts 1 and 2, support BV+Nivo combination as an encouraging first salvage therapy prior to ASCT in patients with R/R cHL







- Advani RH et Al. ASH 2018

Response adapted stategies

Cohort 1: 45 R/R HL pts received 2 cycles of brentuximab vedotin (1.2 mg/kg weekly, 6 doses over 8 weeks);

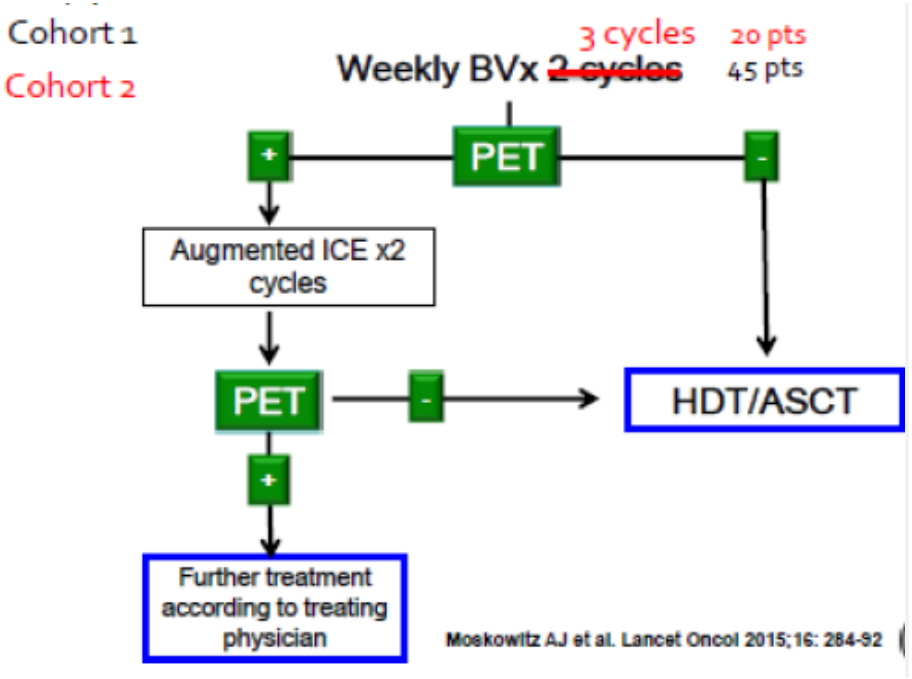
Cohort 2: 20 R/R HL pts received 3 cycles of brentuximab vedotin (1.2 mg/kg weekly, 9 doses over 12 weeks).

In both cohorts, pts with residual PET-positivity received 2 cycles of augmented ICE

Characteristics, n (%)	Cohort 1 (n=45) 2 cycles	Cohort 2 (n=20) 3 cycles
Median age (range)	31 (13–65)	35 (19–59)
Early / advanced stage	23 (51) / 22 (49)	13 (65) / 7 (35)
Refractory	25 (56)	9 (45)
B symptoms	9 (20)	1 (5)
Extranodal disease	19 (42)	5 (25)
Bulk (>5 cm)	12 (27)	4 (20)

PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study

Alison J Moskowitz, Heiko Schöder, Joachim Yahalom, Susan J McCall, Stephanie Y Fox, John Gerecitano, Ravinder Grewal, Paul A Hamlin, Steven Horwitz, Rachel Kobos, Anita Kumar, Matthew Matasar, Ariela Noy, M Lia Palomba, Miguel-Angel Perales, Carol S Portlock, Craig Sauter, Neerav Shukla, Peter Steinherz, David Straus, Tanya Trippett, Anas Younes, Andrew Zelenetz, Craig H Moskowitz

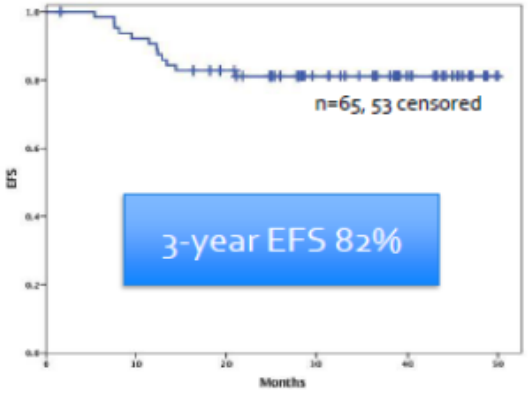


1.Moskowitz AJ, et al ISHL 2016, Poster presentation #P088 and update ICML 2017 #18
Update from 2. Gavane S, et al. ASCO 2016, Oral presentation from Abstract #11566
3 Moskowitz AJ et al. The Lancet oncology 2015;16:284-92

Dopo BV

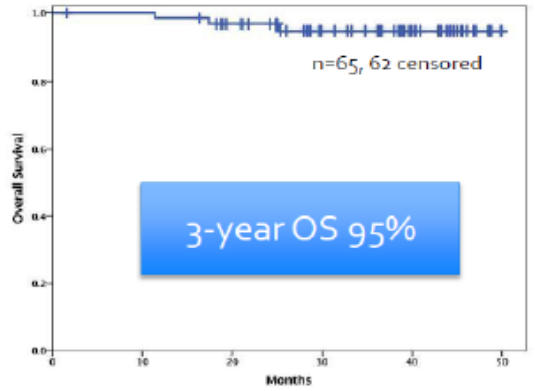
Response: 18/65 (28%) pts PET-negative (Deauville 2) and 27/65 (42%) PET-negative (Deauville 3) after single-agent brentuximab vedotin

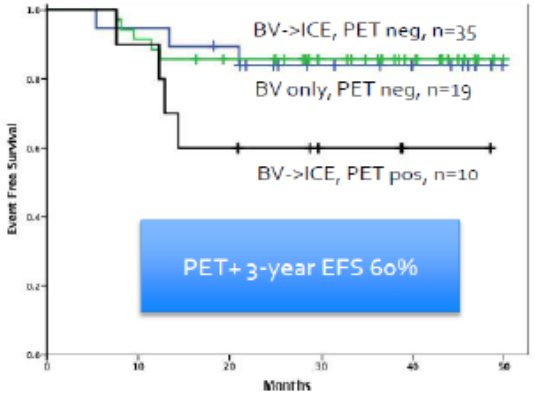
- Cohort 1: 12/45 (27%) CR
- Cohort 2: 6/20 (30%) CR



Dopo BV+ICE

- Overall, 49/65 pts (75%) achieved a CR (Deauville 2) and 54/65 (83%) achieved PET-negative (Deauville 3) after PET-adapted therapy
- 64 pts proceeded to ASCT (1 pt lost to follow-up after brentuximab vedotin)
- median follow-up for survivors is 40 mos and 20 mos for cohorts 1 and 2 respectively





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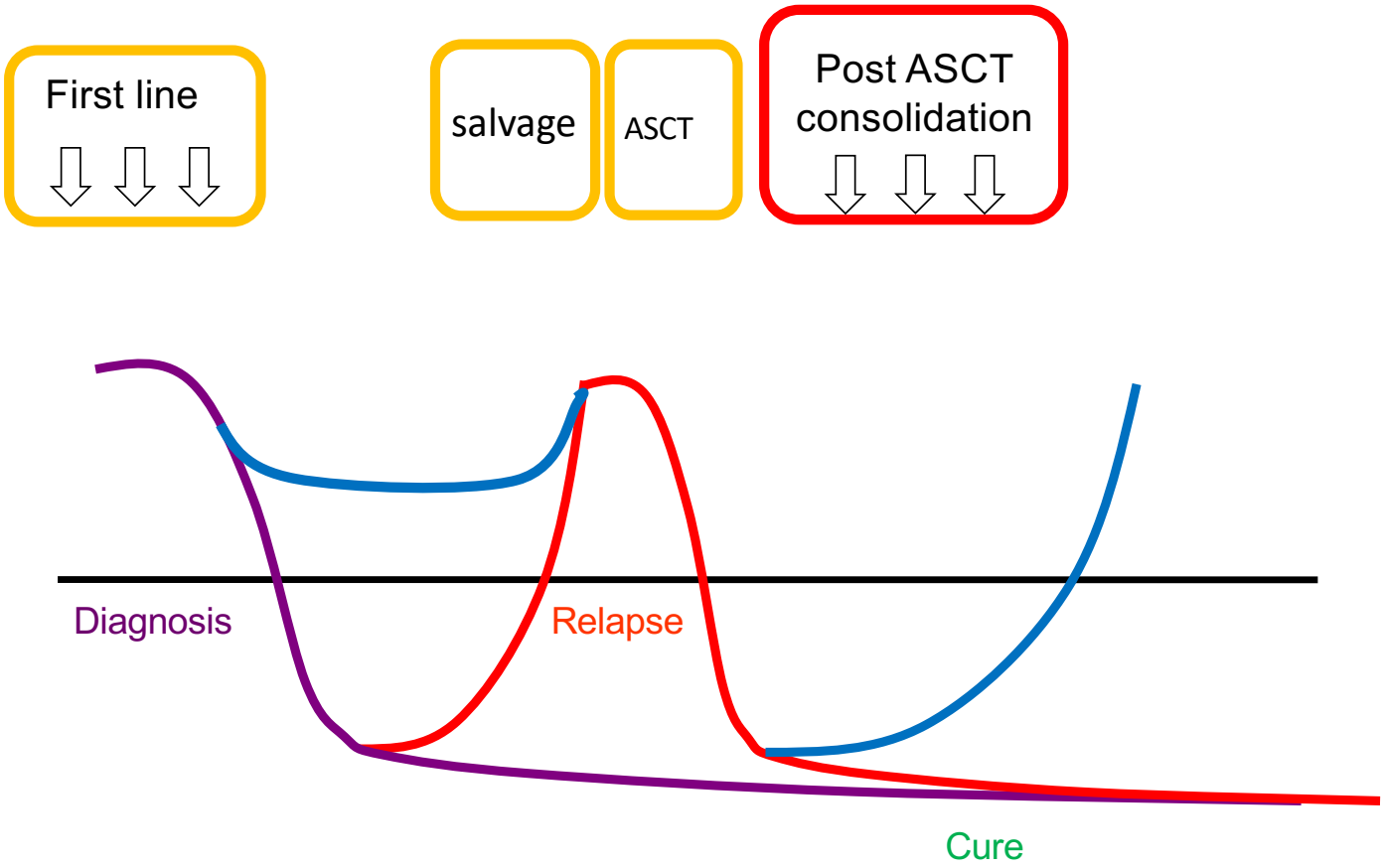
Post ASCT consolidation



Ulteriore terapia dopo ASCT:
Strategia consolidata anche in altre malattie linfoproliferative (Mieloma, linfoma follicolare, mantellare..)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma

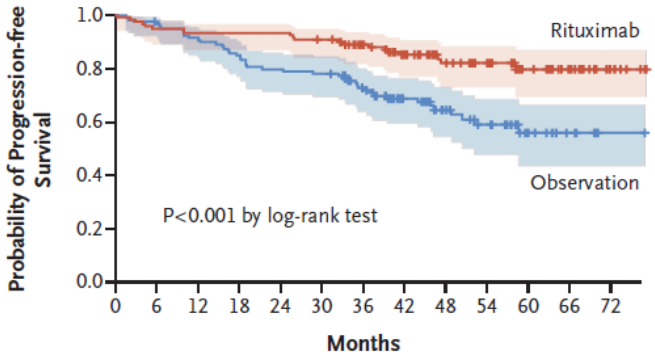
S. Le Gouill, C. Thieblemont, L. Oberic, A. Moreau, K. Bouabdallah, C. Dartigeas, G. Damaj, T. Gastinne, V. Ribrag, P. Feugier, O. Casasnovas, H. Zerazhi, C. Haioun, H. Maisonneuve, R. Houot, F. Jardin, E. Van Den Neste, O. Tournilhac, K. Le Dû, F. Morschhauser, G. Cartron, L.-M. Fornecker, D. Canioni, M. Callanan, M.C. Béné, G. Salles, H. Tilly, T. Lamy, R. Gressin, and O. Hermine, for the LYSA Group*

Rituximab maintenance therapy after transplantation prolonged event-free survival, progression-free survival, and overall survival among patients with mantle cell lymphoma

N ENGL J MED 377;13 NEJM.ORG SEPTEMBER 28, 2017

B Progression-free Survival

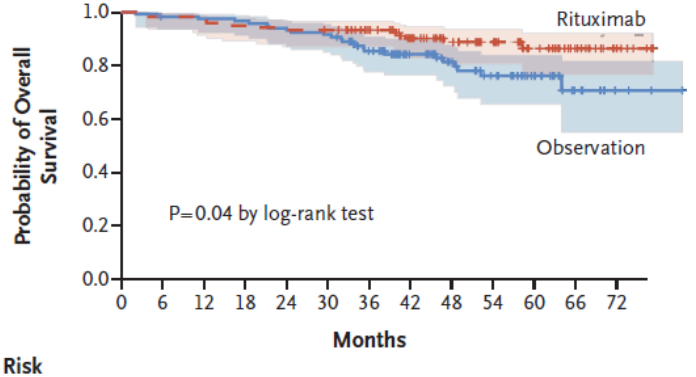
	No. of Patients	Patients with Event	Patients with Censored Data	Median Survival
		no. (%)		
Rituximab	120	20 (17)	100 (83)	Not reached
Observation	120	43 (36)	77 (64)	Not reached



No. at Risk													
Rituximab	120	114	112	112	112	108	96	75	55	44	29	20	7
Observation	120	116	109	101	95	93	77	57	37	29	13	6	1

C Overall Survival

	No. of Patients	Patients with Event	Patients with Censored Data	Median Survival
		no. (%)		
Rituximab	120	13 (11)	107 (89)	Not reached
Observation	120	24 (20)	96 (80)	Not reached



No. at Risk													
Rituximab	120	118	116	114	112	111	100	79	60	48	32	20	7
Observation	120	117	116	115	111	109	90	71	50	39	23	10	3

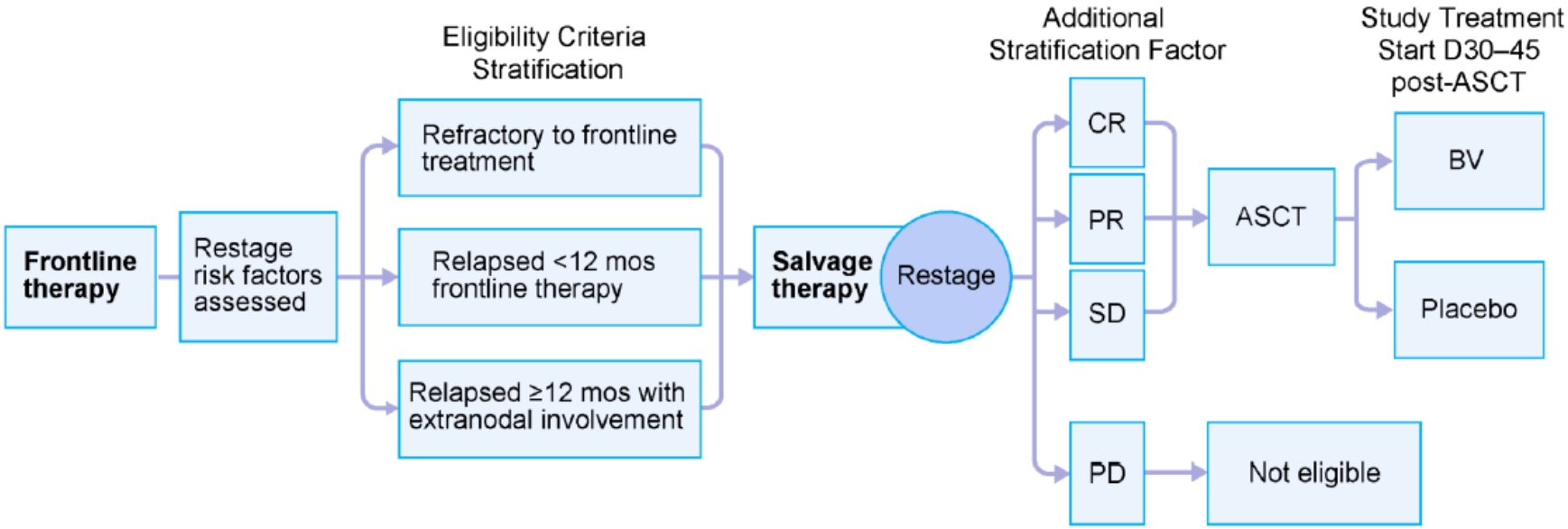
Post ASCT consolidation

Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial

Lancet 2015; 385: 1853–62

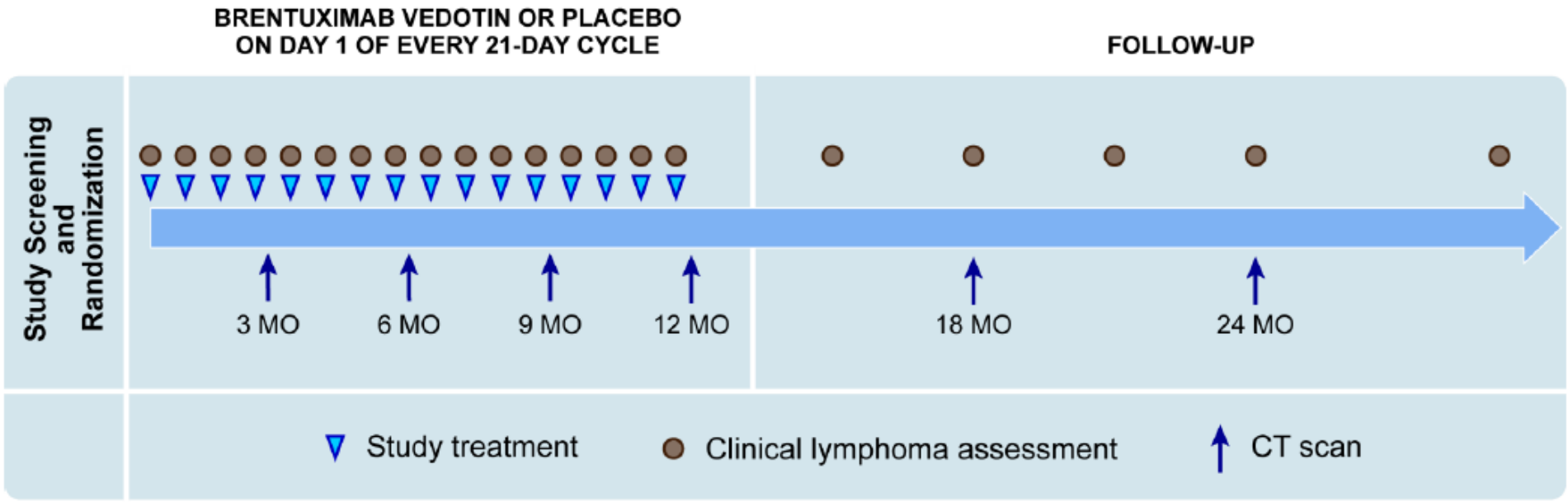
Craig H Moskowitz, Auayporn Nademanee, Tamas Masszi, Edward Agura, Jerzy Holowiecki, Muneer H Abidi, Andy I Chen, Patrick Stiff, Alessandro M Gianni, Angelo Carella, Dzhelil Osmanov, Veronika Bachanova, John Sweetenham, Anna Sureda, Dirk Huebner, Eric L Sievers, Andy Chi, Emily K Larsen, Naomi N Hunder, Jan Walewski, for the AETHERA Study Group

Objectives: *Primary:* PFS per IRF; *Secondary:* OS, safety/tolerability

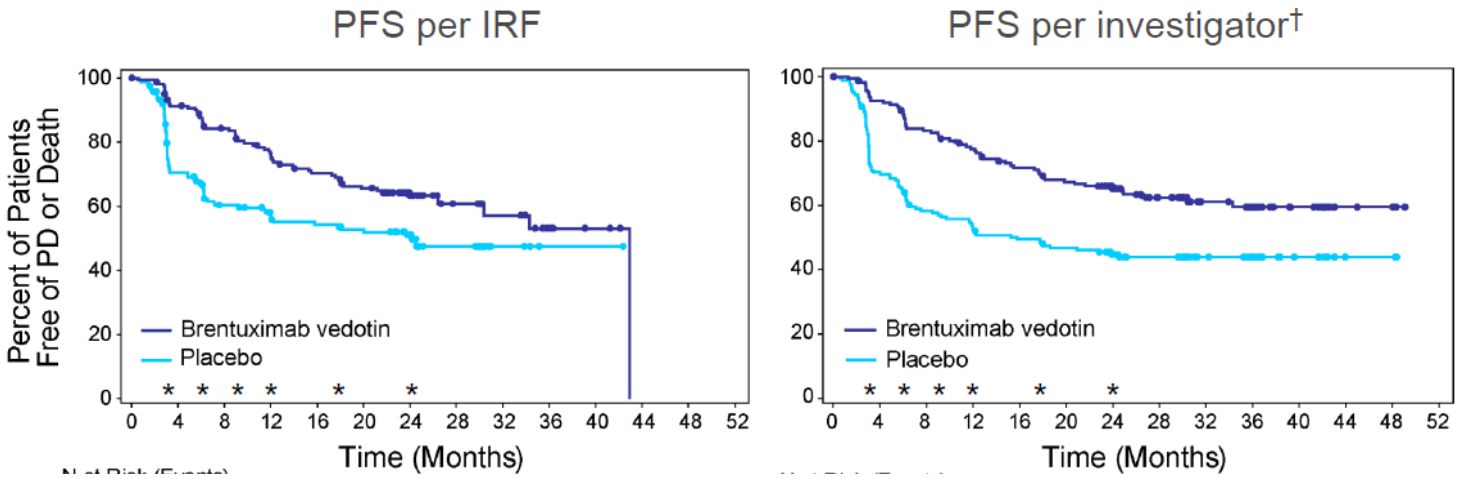


Dose and schedule: Pts were randomized 1:1 to receive 16 21-day cycles of brentuximab vedotin 1.8 mg/kg IV day 1 or placebo

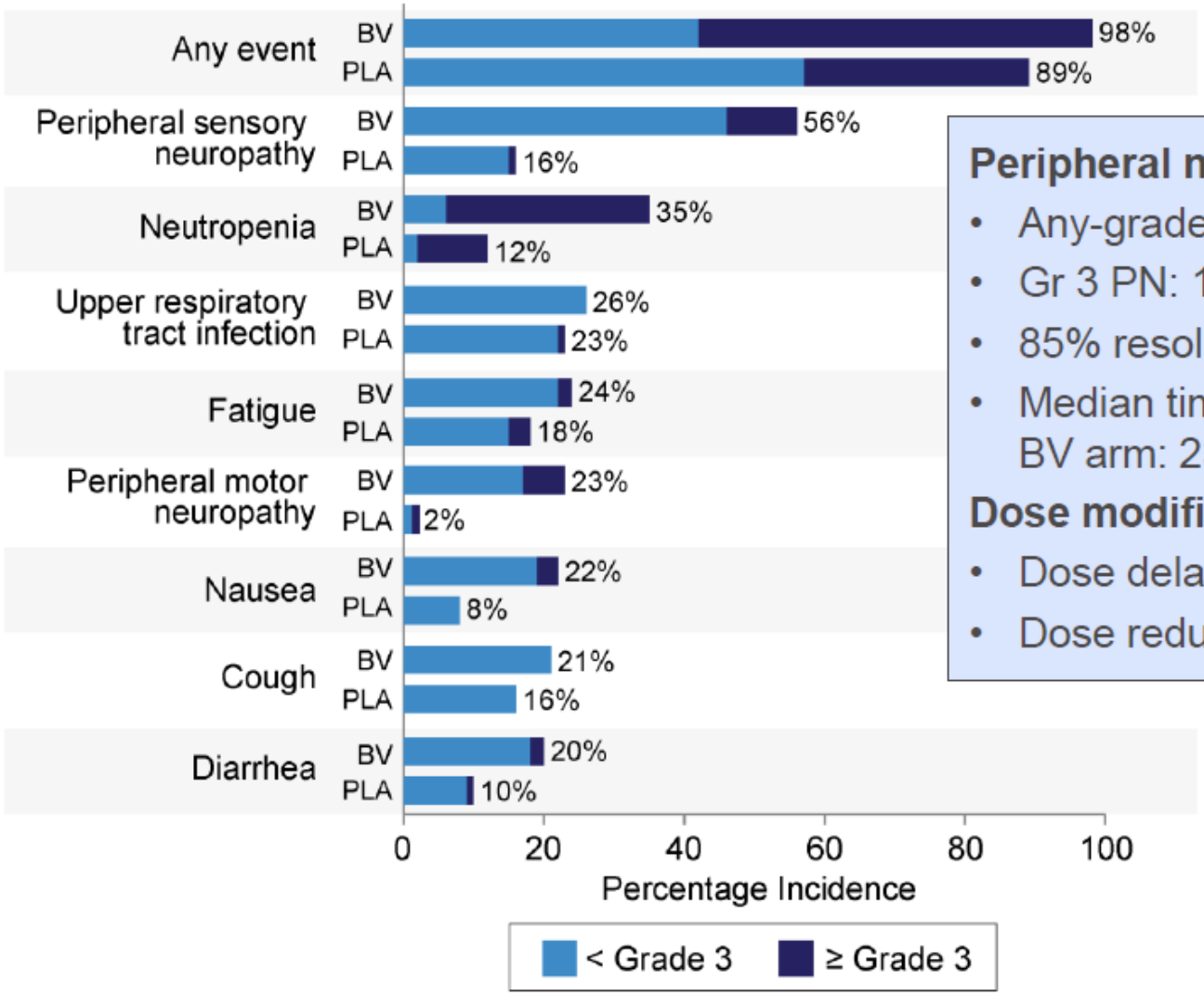
- Patients were randomized to receive 16 cycles of BV or placebo
- They were evaluated and treated every 21 days
- Imaging quarterly for first year, then at 18 and 24 months
- Importantly, patients who progressed on the placebo arm could subsequently receive BV on another trial



Characteristic	Brentuximab vedotin (n=165)	Placebo (n=164)
Median age, yrs (range)	33 (18–71)	32 (18–76)
No. of prior systemic salvage therapies		
1	57%	52%
≥2	43%	48%
HL status after frontline therapy		
Refractory	60%	59%
Relapse <12 mos	32%	33%
Relapse ≥12 mos	8%	8%
Response to salvage therapy pre-ASCT		
CR	37%	38%
PR	35%	34%
SD	28%	28%
Extranodal involvement at pre-ASCT relapse	33%	32%
B symptoms after frontline therapy	28%	24%
Pre-ASCT PET status		
FDG avid	39%	31%
FDG negative	34%	35%
Not available	27%	34%



AE in ≥20% of pts in the brentuximab vedotin arm



Peripheral neuropathy (SMQ analysis)

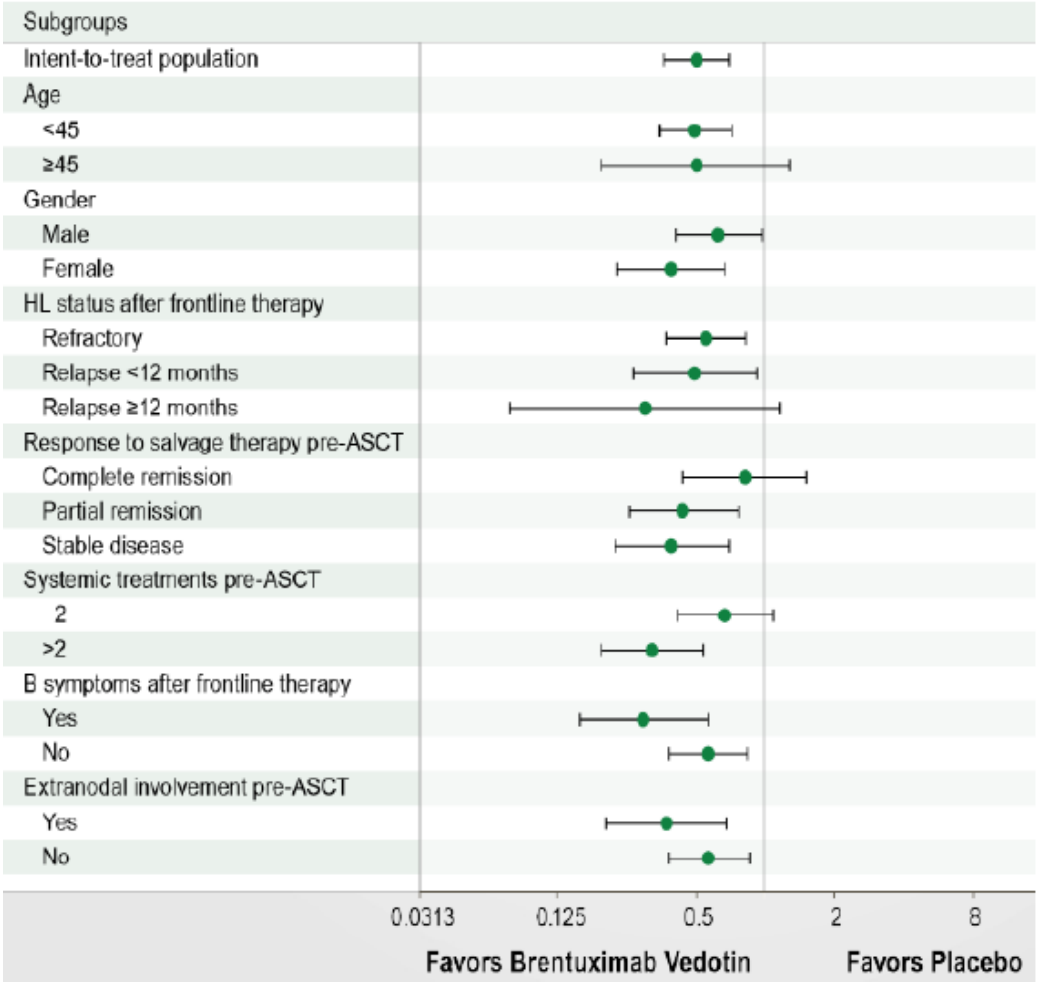
- Any-grade PN: 67% BV, 19% placebo
- Gr 3 PN: 13% BV, 1% placebo (no Gr 4)
- 85% resolution/improvement in BV arm
- Median time to resolution or improvement in BV arm: 23.4 wks

Dose modifications due to AE

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

Moskowitz ASH2014 (Abstract#673)
Sureda et al. EBMT 2015. Oral presentation 0112

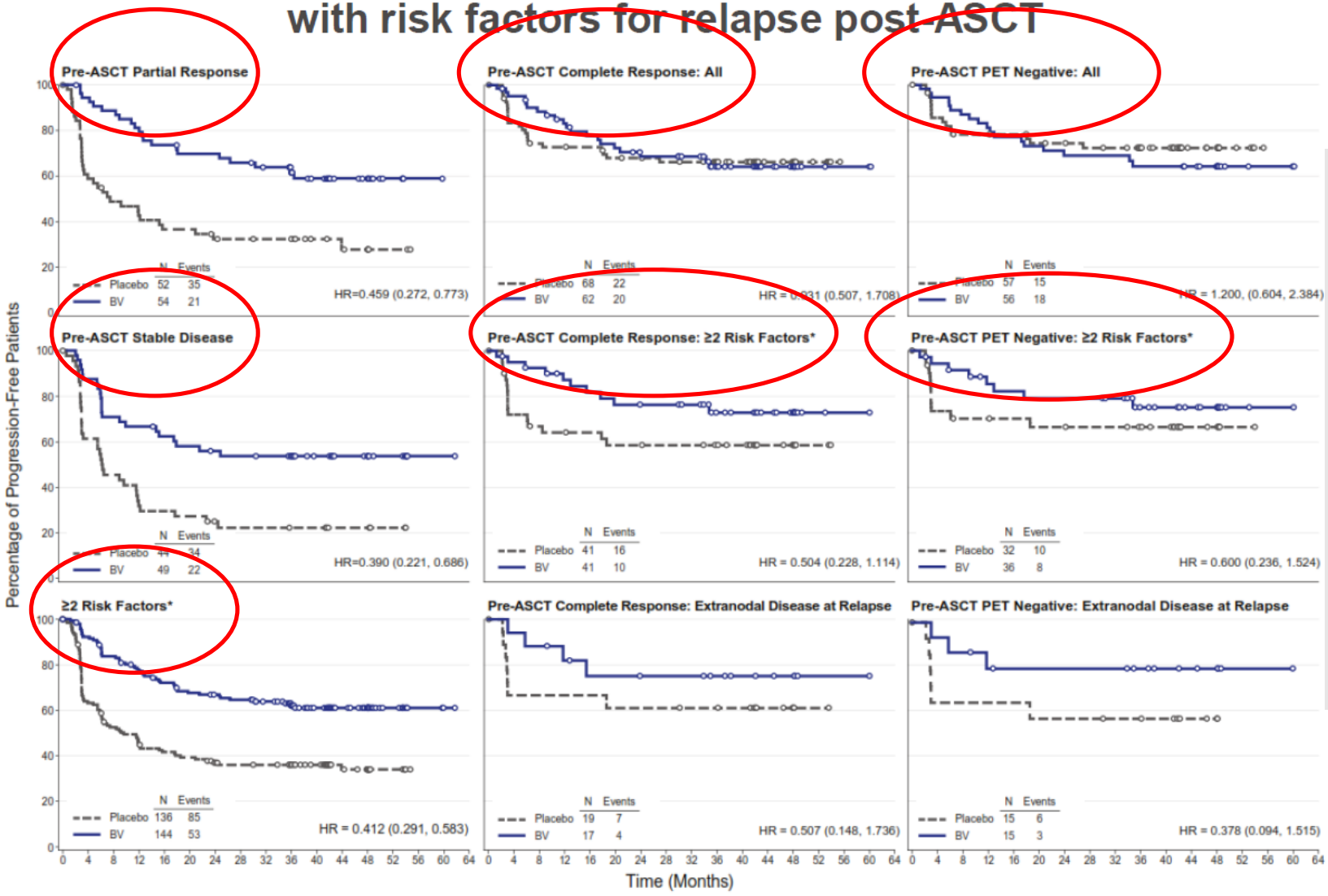
Hazard Ratios from Subgroup Analyses*



- Una parte rilevante dei pazienti trattati con ASCT in seconda linea ottiene la eradicazione della malattia, per questi non è necessaria una terapia di consolidamento.

- Il consolidamento con Brentuximab vedotin va quindi impiegato nei pazienti a rischio di recidiva o progressione dopo ASCT. ***Come identificarli?***

Effect of brentuximab vedotin consolidation on PFS* in pts with risk factors for relapse post-ASCT



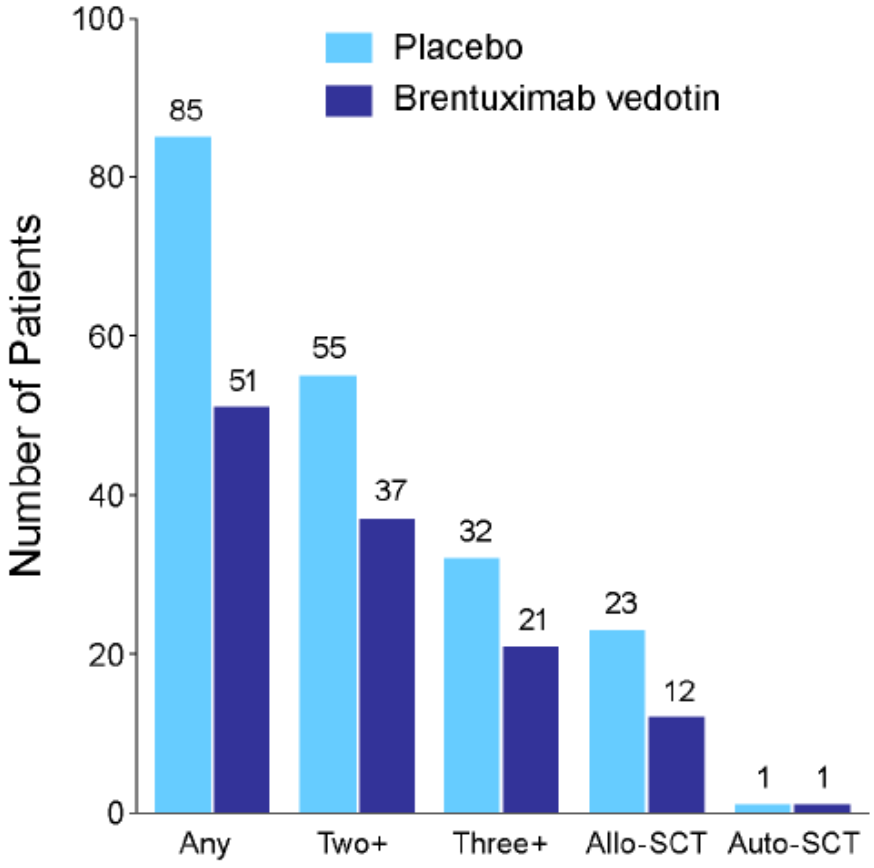
Risk Factors:

- Relapse <12 months or refractoriness to frontline therapy;
- Partial response or stable disease to most recent salvage therapy;
- Extranodal disease at pre–auto-HSCT relapse;
- B symptoms at pretransplantation relapse;
- ≥2 prior salvage therapies.

Subsequent antitumor therapies

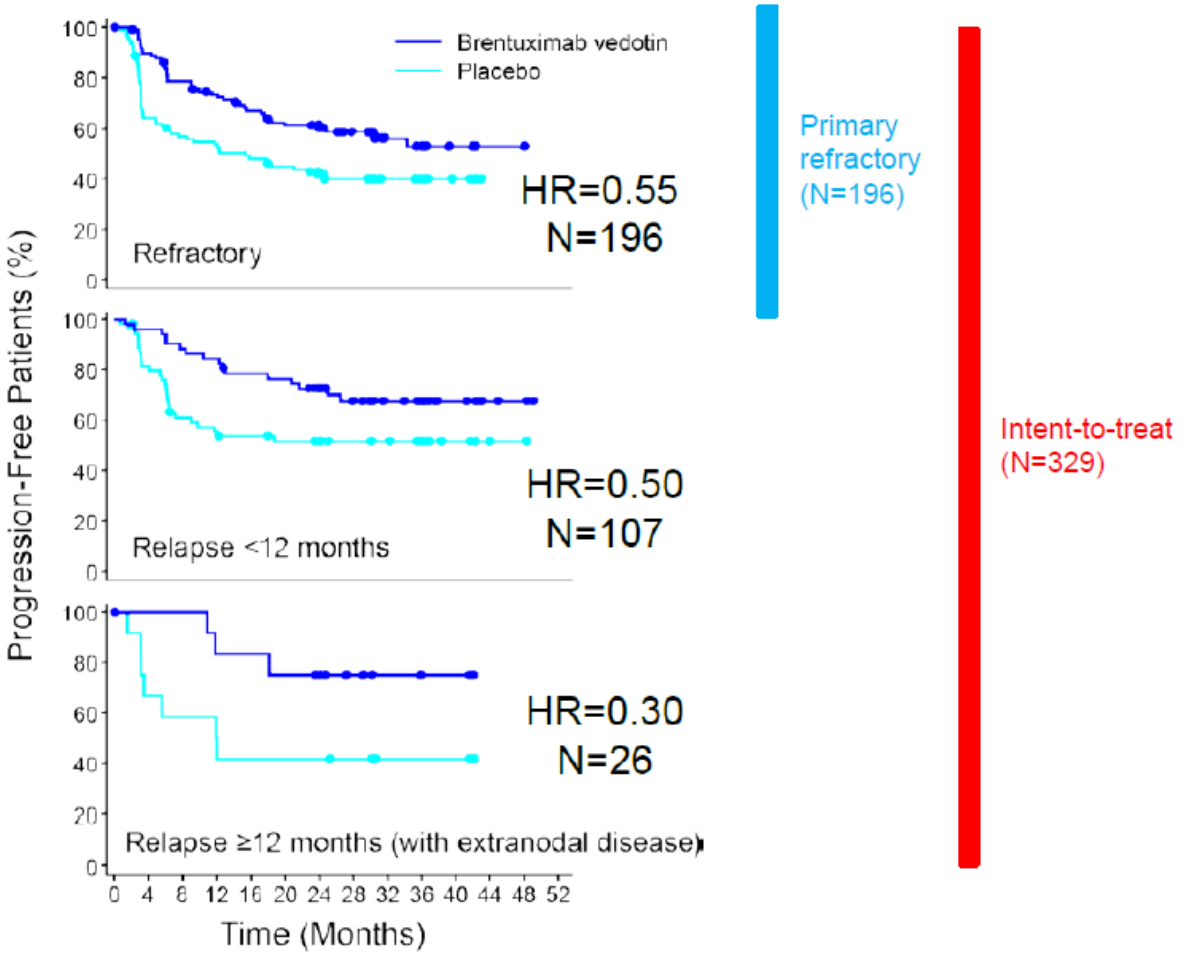
Pts with subsequent antitumor therapy, n (%)	Brentuximab vedotin (n=51)	Placebo (n=85)
Single-agent BV	8 (16)	72 (85)
Multi-agent regimen including BV	1 (2)	1 (1)
SCT*	13 (25)	24 (28)
Multi-agent chemotherapy	35 (69)	34 (40)
Radiation	22 (43)	23 (27)
Single-agent chemotherapy	22 (43)	22 (26)
Donor lymphocyte infusion	2 (4)	1 (1)
Other treatment	1 (2)	2 (2)

* Allo-SCT in 12 BV and 23 placebo pts



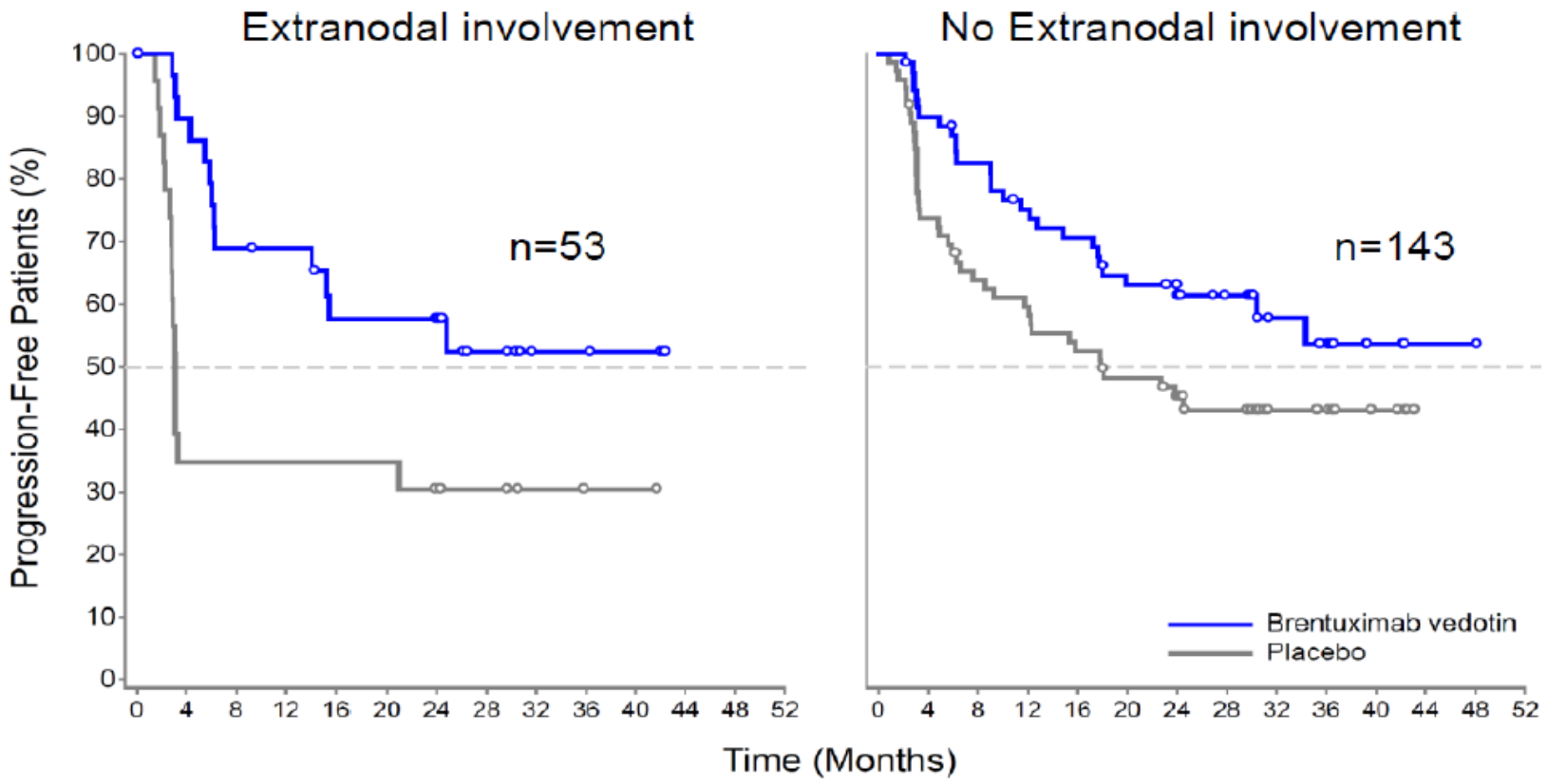
AETHERA : Post hoc analysis of primary-refractory HL pts following brentuximab vedotin consolidation after ASCT

PFS by response to front-line therapy:



AETHERA : Post hoc analysis of primary-refractory HL pts following brentuximab vedotin consolidation after ASCT

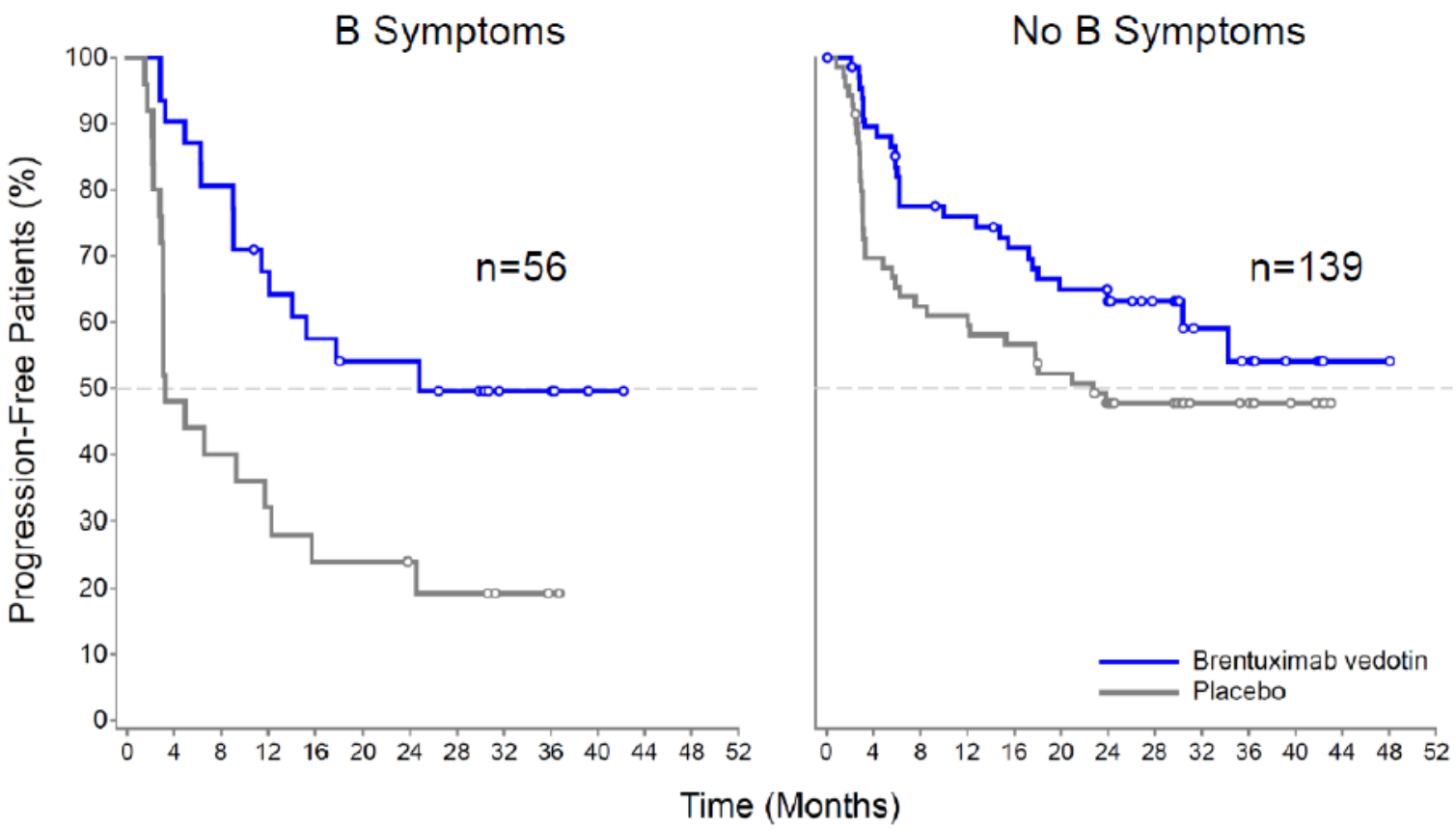
PFS by extranodal involvement:



Includes primary-refractory pts with or without extranodal involvement at pre-ASCT relapse

AETHERA : Post hoc analysis of primary-refractory HL pts following brentuximab vedotin consolidation after ASCT

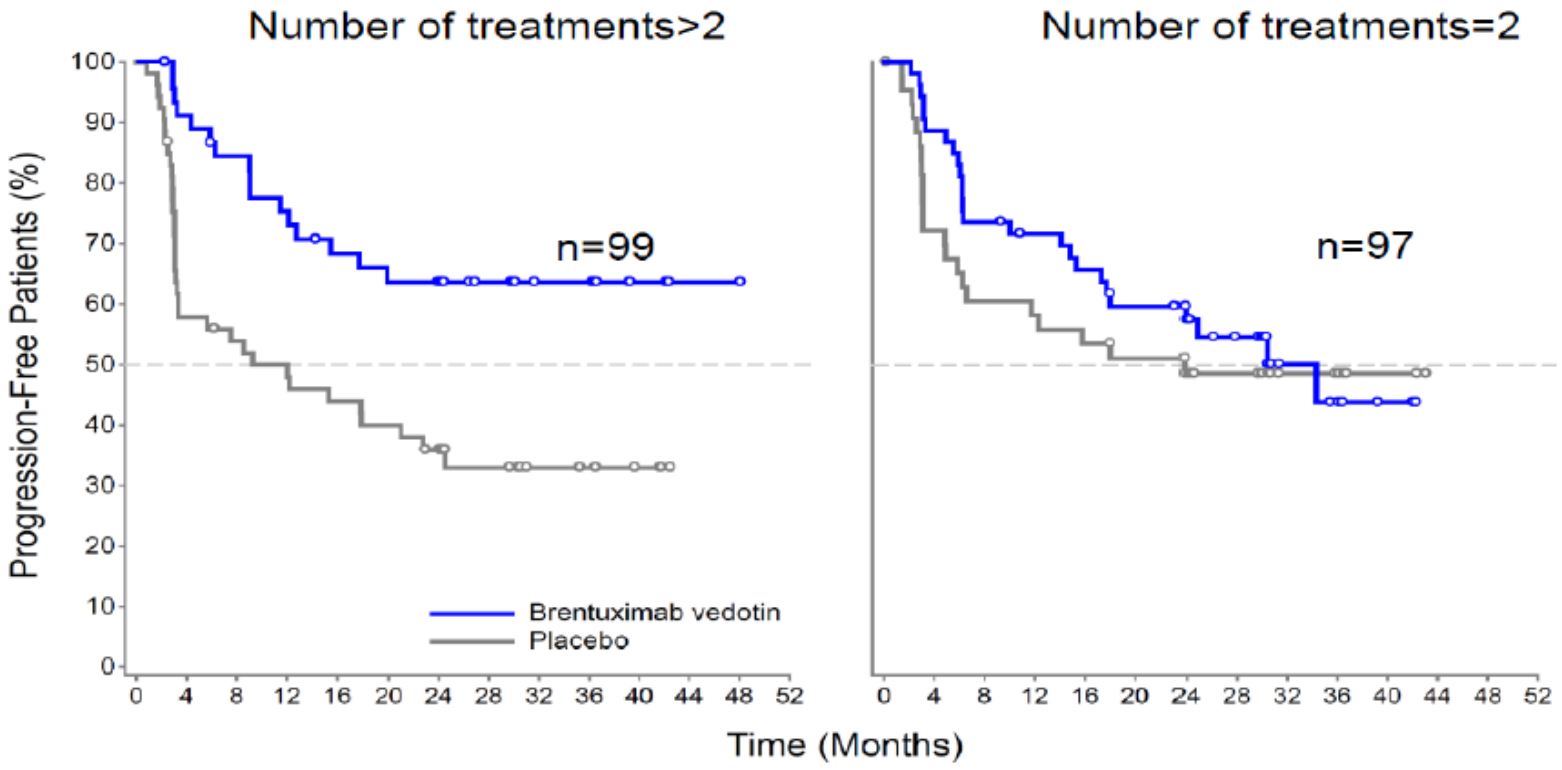
PFS by B symptoms:



Includes primary-refractory pts with or without B symptoms after failure of frontline therapy

AETHERA : Post hoc analysis of primary-refractory HL pts following brentuximab vedotin consolidation after ASCT

PFS by number of prior treatments:



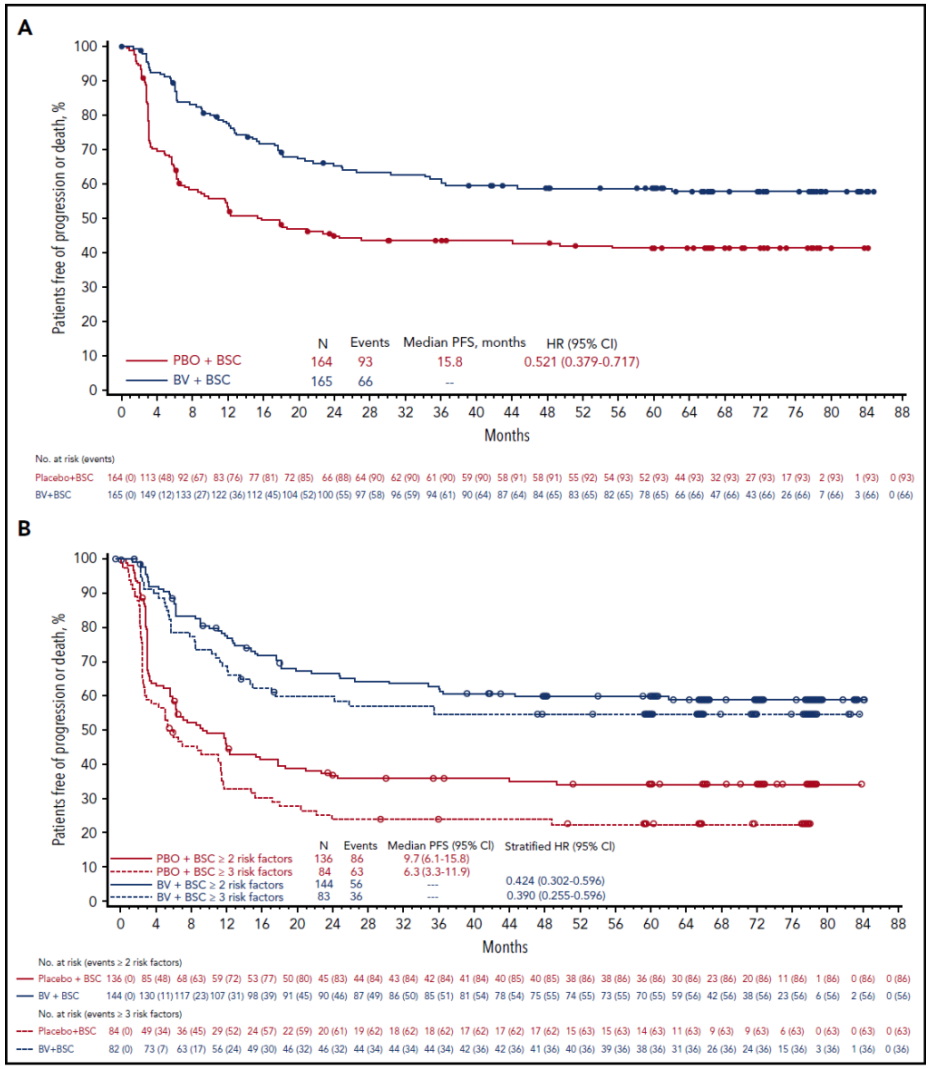


Figure 1. Five-year PFS. PFS at 5 years per investigator (A) and in patients with ≥2 or ≥3 risk factors (B). BSC, best supportive care; PBO, placebo.

- Moskowitz CH et Al. BLOOD 20 DECEMBER 2018 | VOLUME 132, NUMBER 25

CLINICAL TRIALS AND OBSERVATIONS

Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse

Craig H. Moskowitz,[1] Jan Walewski,[2] Auayporn Nademanee,[3] Tamas Masszi,[4] Edward Agura,[5] Jerzy Holowiecki,[6] Muneer H. Abidi,[7] Andy I. Chen,[8] Patrick Stiff,[9] Simonetta Viviani,[10] Veronika Bachanova,[11] Anna Sureda,[12] Teresa McClendon,[13] Connie Lee,[14] Julie Lisano,[13] and John Sweetenham[15]

Risk factors

- Relapse <12 months or refractoriness to frontline therapy;
- Partial response or stable disease to most recent salvage therapy;
- Extranodal disease at pre–auto-HSCT relapse;
- B symptoms at pretransplantation relapse;
- ≥2 prior salvage therapies.

5-year PFS HR:

≤1 risk factors: no difference

≥2 risk factors: 0.424 (95% CI, 0.302-0.596)

≥3 risk factors: 0.390 (95% CI, 0.255-0.596)

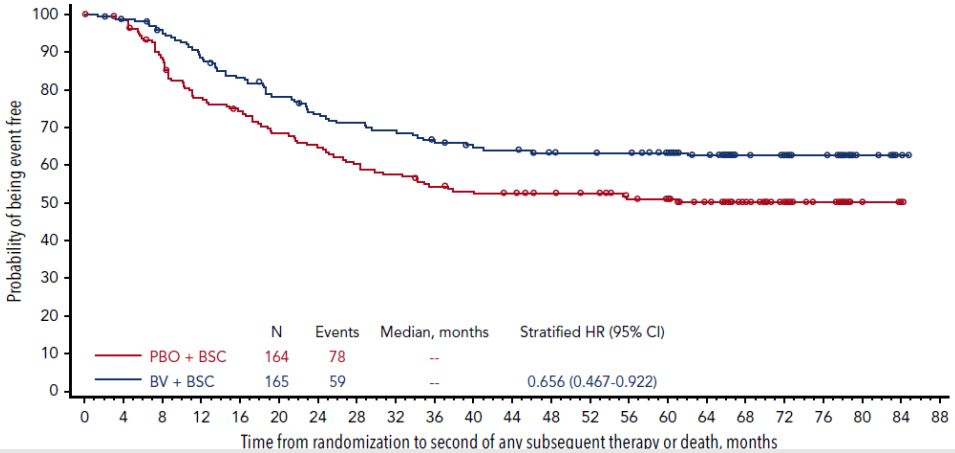
Peripheral neuropathy continued to improve and/or resolve in 90% of patients

At 5-year follow-up, BV continued to provide patients with sustained PFS benefit; ***5-year PFS was 59% with BV vs 41% with placebo*** *(hazard ratio [HR], 0.521; 95% CI, 0.379- 0.717)*

A

Regimen type	Placebo (n = 164) n (%)	BV (n = 165) n (%)
Any subsequent therapy	89 (54)	53 (32)
Single-agent BV*	77 (47)	10 (6)
Multi-agent regimen†	46 (28)	38 (23)
Single-agent therapy (non-BV)	33 (20)	24 (15)
Radiation	29 (18)	25 (15)
Stem cell transplant	35 (21)	19 (12)
Other‡	4 (2)	3 (2)

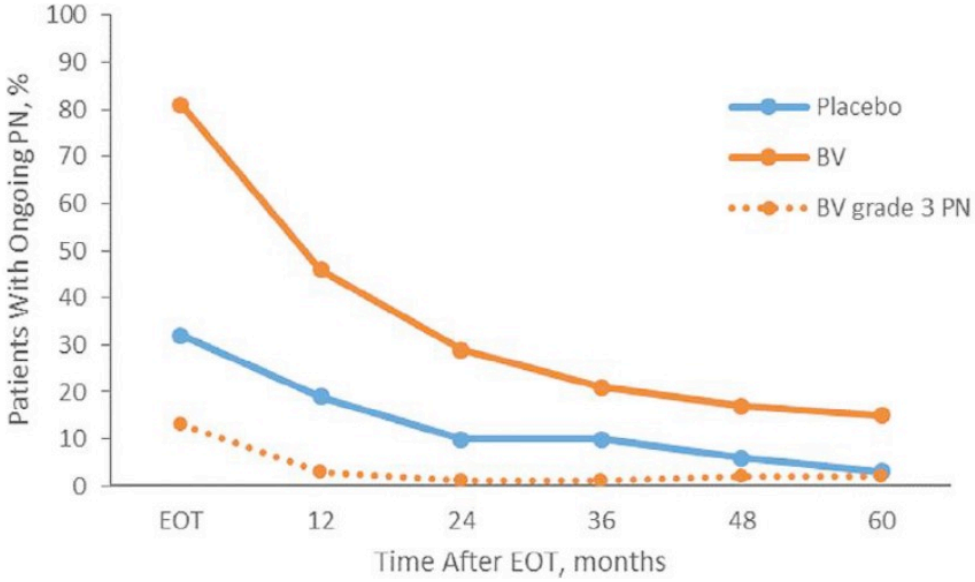
B



Significantly fewer patients treated with BV received subsequent anticancer therapy (32%, n = 53) compared with patients treated with placebo (54%, n = 89)

Physicians should consider each patient's HL risk factor profile when making treatment decisions.

Peripheral neuropathy (PN; 67%), infections (60%), and neutropenia (35%) were the most common BV-associated treatment-emergent AEs.



After the end of treatment, PN continued to resolve: 60 months after the end of treatment, 85% of patients who experienced treatment-emergent PN with BV had PN resolution.

PD-1 blockade with pembrolizumab for classical Hodgkin lymphoma after autologous stem cell transplantation

Philippe Armand,[1] Yi-Bin Chen,[2] Robert A. Redd,[3] Robin M. Joyce,[4] Jad Bsat,[1] Erin Jeter,[1] Reid W. Merryman,[1] Kimberly C. Coleman,[1] Parastoo B. Dahi,[5] Yago Nieto,[6] Ann S. LaCasce,[1] David C. Fisher,[1] Samuel Y. Ng,[1] Oreofe O. Odejide,[1] Arnold S. Freedman,[1] Austin I. Kim,[1] Jennifer L. Crombie,[1] Caron A. Jacobson,[1] Eric D. Jacobsen,[1] Jeffrey L. Wong,[1] Sanjay S. Patel,[7] Jerome Ritz,[1] Scott J. Rodig,[7] Margaret A. Shipp,[1] and Alex F. Herrera[8]

AE	Grade 1	Grade 2	Grade 3	Grade 4
Total no. of AEs	308 (93)	96 (77)	21 (30)	7 (10)
Grade 2-4 TRAE				
Leukopenia		4 (7)	5 (13)	1 (3)
Neutropenia		3 (7)		4 (10)
Transaminitis		3 (10)	3 (7)	
Diarrhea/colitis		1 (3)	3 (7)	
Pneumonitis/ dyspnea		3 (7)	1 (3)	
Hypothyroidism		4 (7)		
Rash		3 (7)		
Lymphopenia		1 (3)	1 (3)	
Thrombocytopenia		2 (7)		
Febrile neutropenia				1 (3)
Pulmonary hemorrhage*			1 (3)	
Hyperthyroidism		1 (3)		
Arthritis		1 (3)		
Fatigue		1 (3)		
Neck pain		1 (3)		
Creatinine increase		1 (3)		
Blurred vision		1 (3)		
Total no. of TRAEs	82 (67)	30 (47)	14 (27)	6 (10)
Grade 2-4 irAEs				
Transaminitis		2 (7)	3 (7)	
Pneumonitis/ dyspnea/cough		4 (10)	1 (3)	
Diarrhea/colitis		1 (3)	2 (7)	
Rash		3 (7)		
Hypothyroidism		3 (3)		
Pulmonary hemorrhage*			1 (3)	
Hyperthyroidism		1 (3)		
Arthritis		1 (3)		
Creatinine increase		1 (3)		
Total no. of irAEs	16 (33)	16 (33)	7 (20)	0 (0)

Pembrolizumab: 200 mg IV every 3 weeks for up to 8 cycles
Primary end point: to improve the progression-free survival (PFS) at 18 months after ASCT from 60% to 80%.

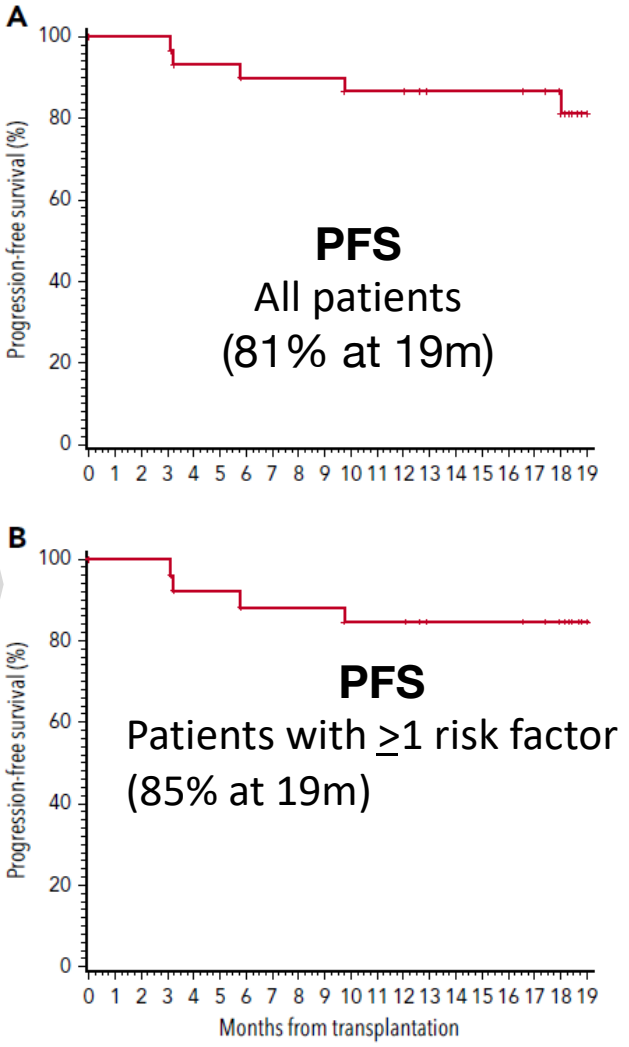
Risk factors:
- primary refractory or relapse within 1 year
- residual FDG-avid disease at ASCT
- >1 salvage regimen
- extranodal disease
- B symptoms at relapse

Among patients who would have been eligible for the AETHERA study the 19-month PFS was 85% (95CI, 64% to 94%).

The 19-month PFS of 85% in this subgroup compares favorably to that of patients treated with placebo (45%) and that of patients treated with BV (70%) on AETHERA.

Blood. 2019;134(1):22-29

Post ASCT consolidation



Post ASCT consolidation

JAMA Oncology | Special Communication

Maintenance Therapies for Hodgkin and Non-Hodgkin Lymphomas After Autologous Transplantation

A Consensus Project of ASBMT, CIBMTR, and the Lymphoma Working Party of EBMT

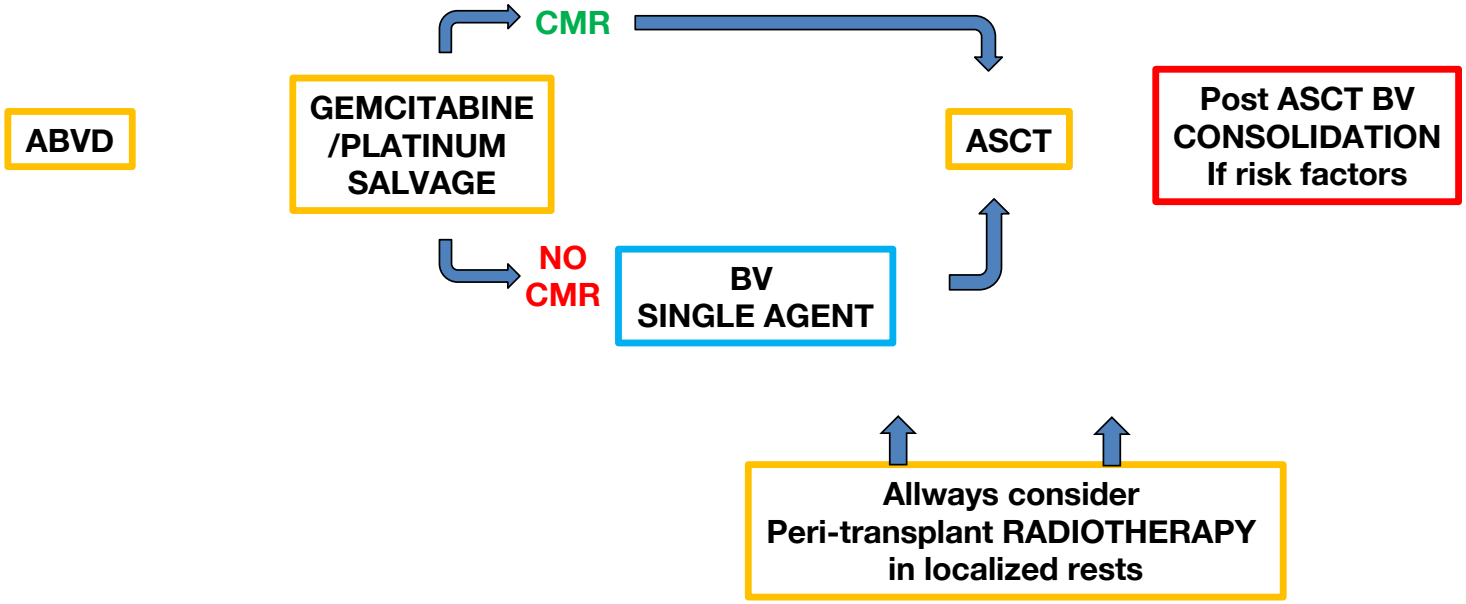
Abraham S. Kanate, MBBS; Ambuj Kumar, MD, MPH; Peter Dreger, MD; Martin Dreyling, MD; Steven Le Gouill, MD; Paolo Corradini, MD; Chris Bredeson, MD, MSc, FRCPC; Timothy S. Fenske, MD; Sonali M. Smith, MD; Anna Sureda, MD; Alison Moskowitz, MD; Jonathan W. Friedberg, MD; David J. Inwards, MD; Alex F. Herrera, MD; Mohamed A. Kharfan-Dabaja, MD; Nishitha Reddy, MBBS; Silvia Montoto, MD; Stephen P. Robinson, MD; Syed A. Abutalib, MBBS; Christian Gisselbrecht, MD; Julie Vose, MD; Ajay Gopal, MD; Mazyar Shadman, MD; Miguel-Angel Perales, MD; Paul Carpenter, MD; Bipin N. Savani, MD; Mehdi Hamadani, MD

JAMA Oncol. 2019;5(5):715-722.

Table 1. Final Clinical Practice Guidelines Consensus Statements on Maintenance Therapy After High Dose Therapy and Autologous Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Consensus Statements: Hodgkin Lymphoma	Grading of Recommendations[a]	Panelists in Agreement, % (n=26)
1. The panel recommends post-autologous HCT consolidation/ maintenance with BV for 16 cycles in BV-naïve classic Hodgkin lymphoma (HL) with at least 1 or more high-risk features as defined by the AETHERA study[b]	A	92
2. The panel does not recommend postautologous HCT consolidation/ maintenance with BV for HL with prior evidence of disease refractory to BV	C	96
3. The recommended duration of post-auto-HCT BV consolidation/ maintenance therapy is for a maximum of 16 cycles every 3 weeks as described in AETHERA trial, or until unacceptable toxicity or disease relapse/progression (whichever occurs first)[b]	A	100
4. The panel recommends post-autologous HCT consolidation/ maintenance with BV in HL with one or more high-risk features as defined by the AETHERA trial and limited prior exposure to BV (approximately 4-6 cycles) preceding the autologous HCT, but without any evidence of BV refractory disease	C	100
5. Sufficient data do not exist to use the preautologous-HCT PET (or PET/CT) scan status to guide the use of post-autologous HCT consolidation/ maintenance therapy with BV for HL with one or more high-risk features as defined by AETHERA Trial	C	84

Today options:



Next future scenario:

ABVD → New drug + chemo SALVAGE → ASCT → Post ASCT BV CONSOLIDATION If risk factors

or

ABVD → Chemo-free SALVAGE → ASCT → Post ASCT BV CONSOLIDATION If risk factors

or

ABVD → Response-adapted SALVAGE → ASCT → Post ASCT BV CONSOLIDATION If risk factors

Next future scenario:

or

BV-AVD

SALVAGE:
- **Gemcytabine/platinum**
- **BV+CPI**
- **Response adapted**
- **BV+chemo**

ASCT

Post ASCT BV/CPI CONSOLIDATION If risk factors

Allways consider Peri-transplant RADIOTHERAPY in localized rests

Take home message:

- In HL the introduction of new drugs allows optimization of the ASCT, without reducing the central role of the procedure;

- Central role of new drugs in increasing efficacy (CMR) / reducing toxicity of pre-ASCT salvage;

- ***Post ASCT BV consolidation:***
  - not necessary in patients going to be cured by ASCT alone
  - high efficacy in patients with risk factor(s):
  (**R/R <12 months, PR/SD to salvage, Extranodal disease, B symptoms, >2 salvage therapies)**
- Prevents a relevant proportion of relapses occurring early after ASCT;

- The sustained PFS advantage is stable over time, an updated OS estimation is programmed in 2020.

- Updated results also show a reduction of neuropathy over time.

- CPI post ASCT consolidation: promising (in pt. coming from BV in first line?)