UPDATE SUL TRATTAMENTO DEI LINFOMI CD 30+

ANGELO MICHELE CARELLA

GENOVA

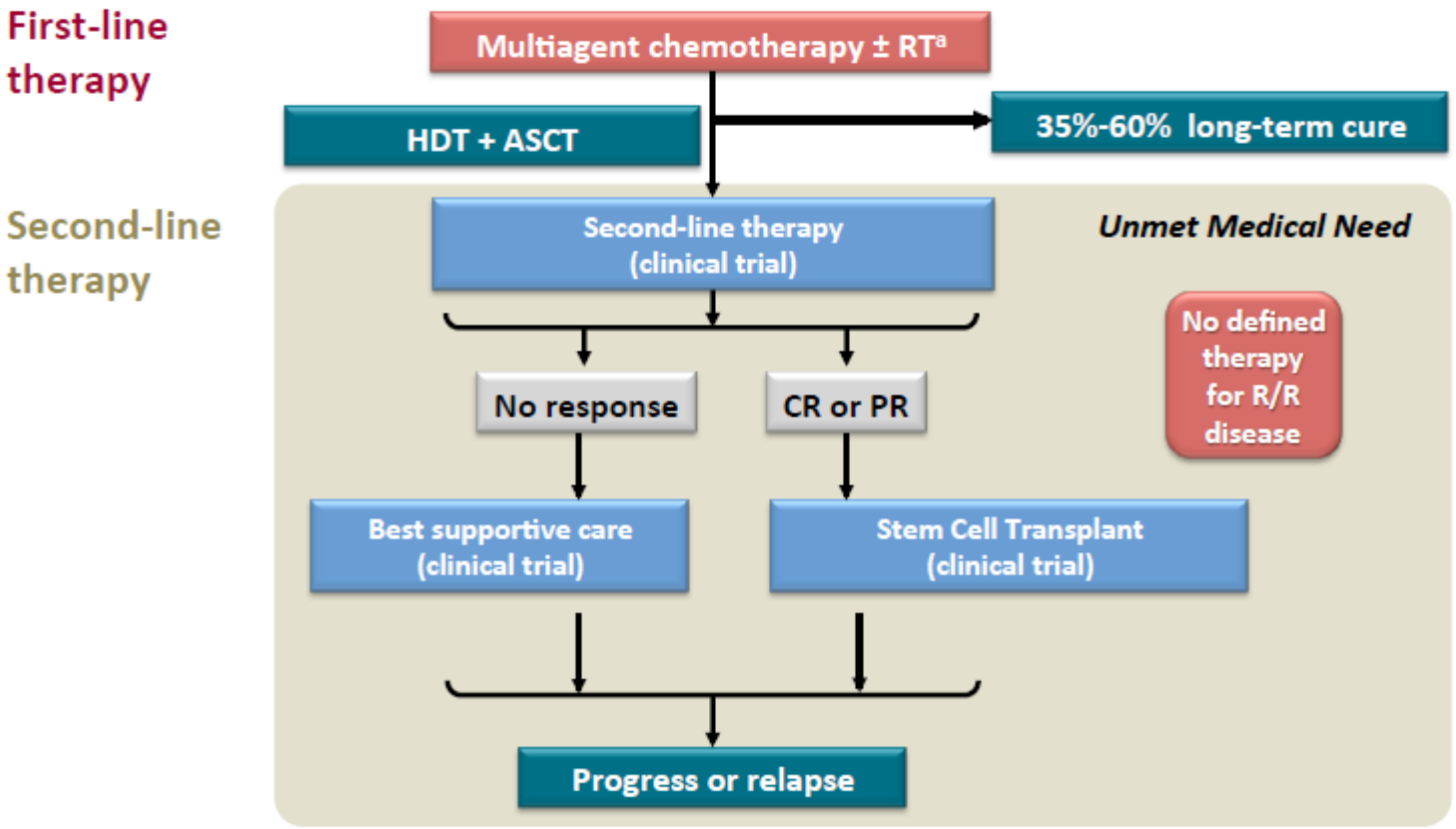
CD30 expression in tumours

- Constitutive:[1]
  - Classical Hodgkin lymphoma (cHL)[2]
  - Primary mediastinal B-cell lymphoma (PMBL)[3]
  - Diffuse large B-cell lymphoma, anaplastic type
  - Anaplastic large cell lymphoma (ALCL), ALK+ & ALK-[2]
  - Aggressive Mastocytosis
  - Embryonic carcinoma[4]

- Variable: several types of tumour, mostly lymphoid

1. Prof Pileri; personal communication; 2. Stein H, *et al.* Blood. 2000;96:3681–95; 3. Pileri SA, *et al.* Am J Pathol. 2003;162:243–53; 4. Falini B, *et al.* Blood. 1995;85:1–14.

Current Treatment Approaches in sALCL



sALCL – systemic anaplastic large cell lymphoma; HDT – high dose therapy; RT – radiation therapy; CR – complete response; PR – partial response; R/R – relapsed/refractory

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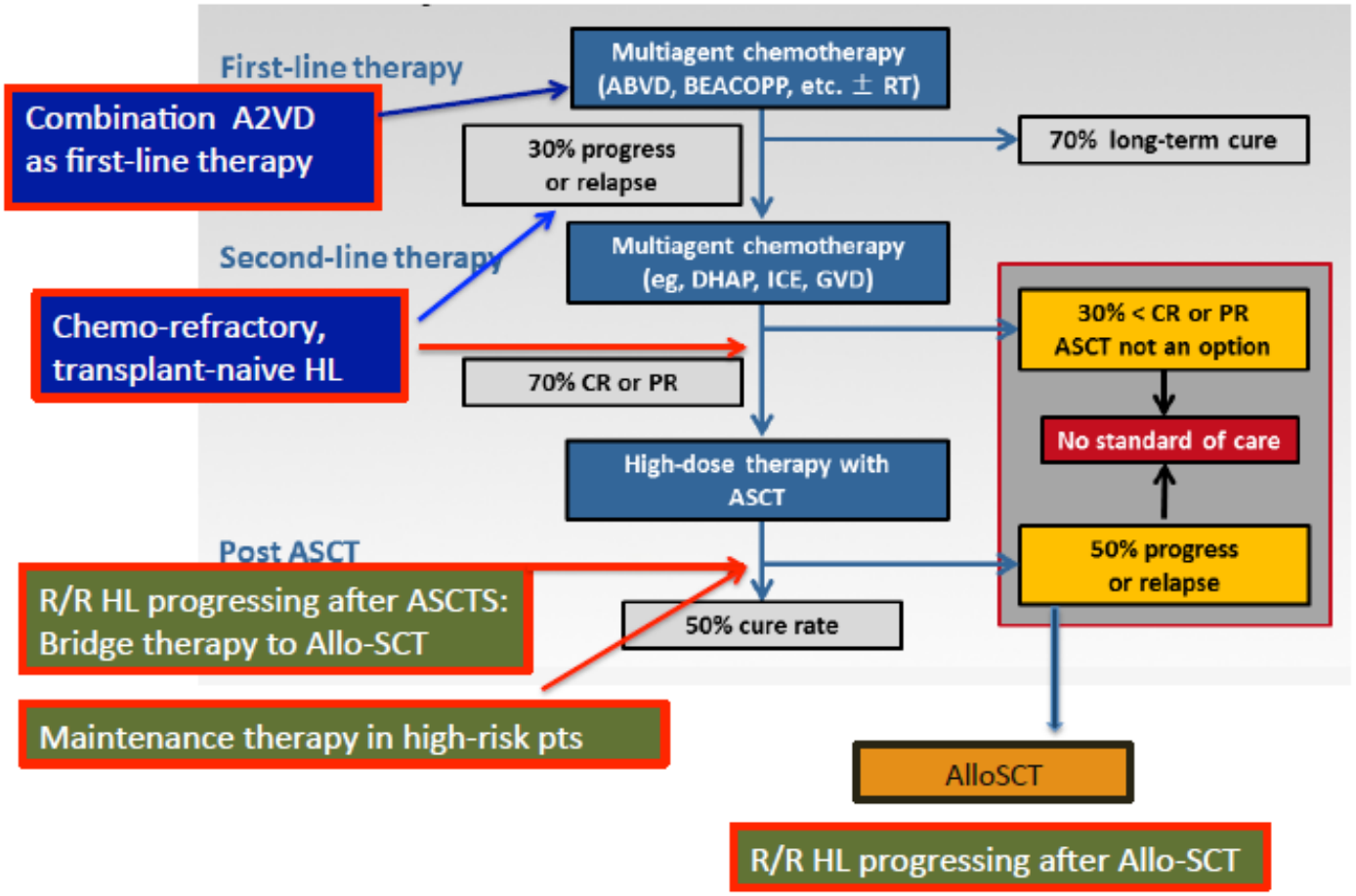
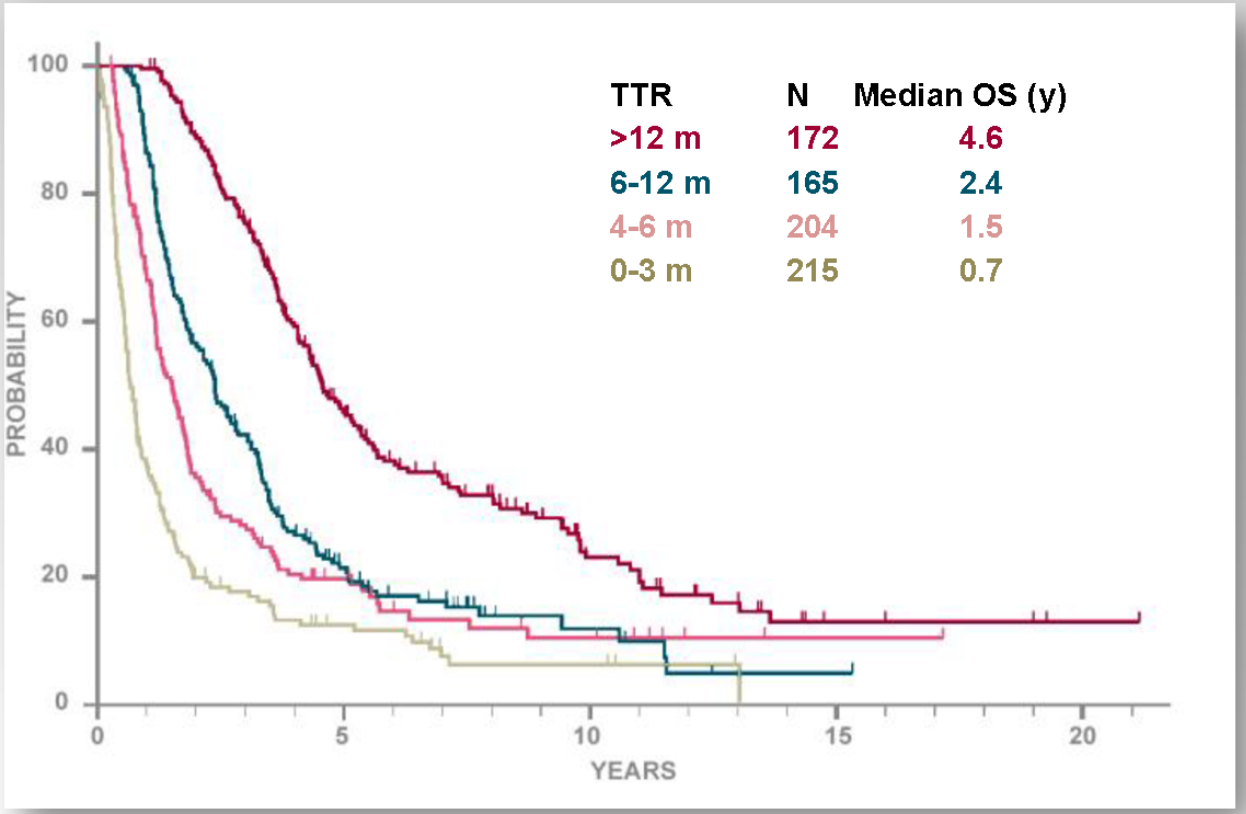
WHAT'S THE FUTURE OF BV IN THE MANAGEMENT STRATEGIES OF HL ?



Overall survival by time to relapse after transplant



OS, overall survival

Horning S et al, Ann Oncol 2008:19 (suppl 4):Abstract 118
Arai S et al. Leukaemia and Lymphoma. 2013. In print

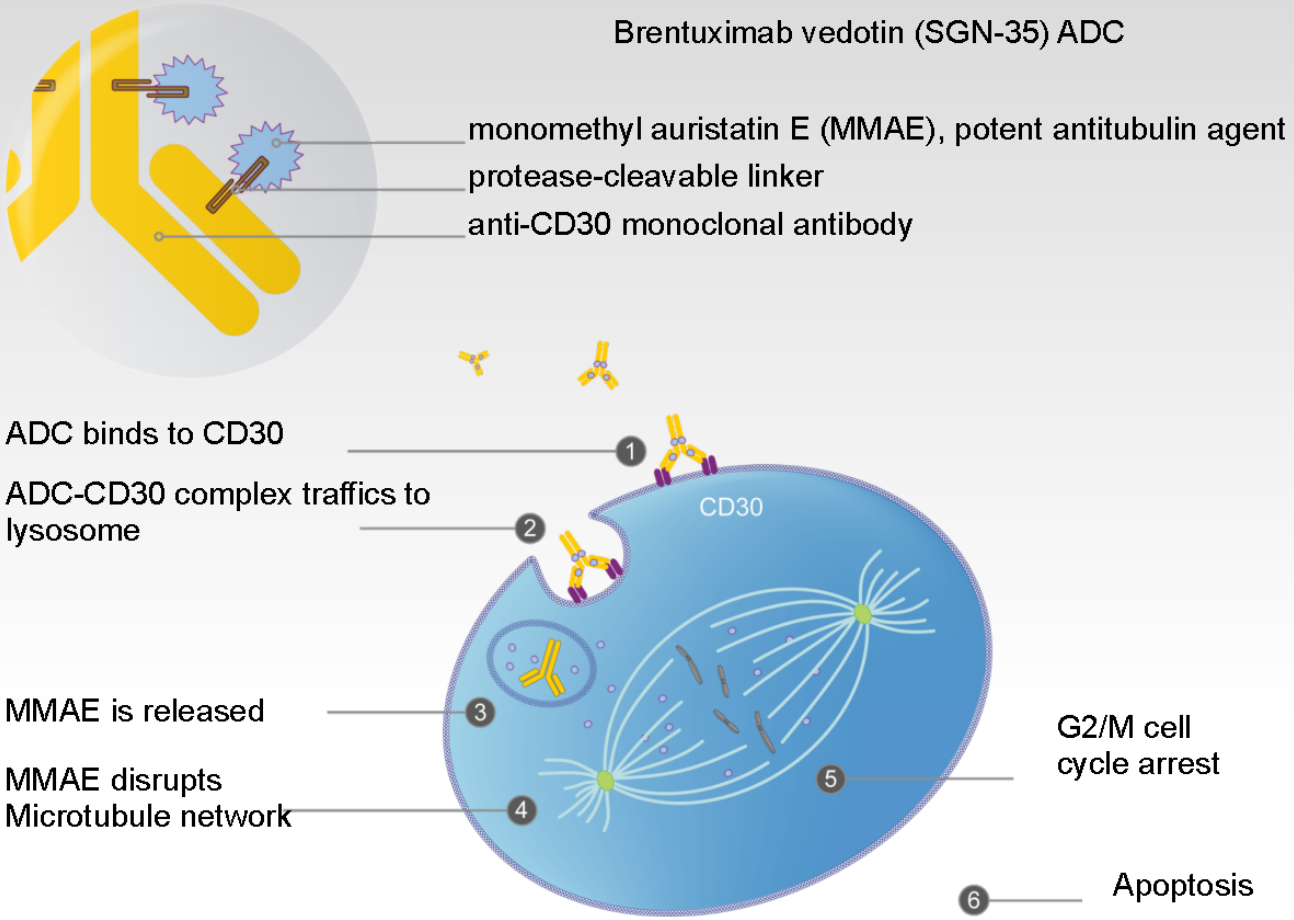
Summary results of phase I/II clinical trials targeting CD30

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%

HL, Hodgkin lymphoma; ALCL, anaplastic large cell lymphoma; PR, partial response; CR, complete response

Younes A Curr Opin Oncol. 2011;23:587-93

Brentuximab vedotin (SGN-35) : Mechanism of action



ADC – antibody drug conjugate

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

Phase 1 Studies in Hodgkin Lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL)

SGN35-002: Phase 1 study of brentuximab vedotin in patients with rel/ref CD30+ hematologic malignancies

- Dose-escalation study (0.4–1.4 mg/kg) of brentuximab vedotin given on days 1, 8, and 15 of 28-day cycles: to assess whether more frequent (weekly) administration could improve anti-tumour activity without increasing toxicity

Patient characteristics

Baseline characteristics	N=44
Median age, years (range)	33 (12–82)
Gender	31 M / 13 F
ECOG performance status, 0/1/2, n (%)	27 (61) / 12 (27) / 5 (11)
Disease diagnosis, n (%)	
HL	38 (86)
sALCL	5 (11)
Peripheral T-cell lymphoma NOS	1 (2)
Prior chemotherapy regimens, median (range)	3 (1–8)
Disease status relative to most recent prior therapy	
Relapsed, n (%)	24 (55)
Refractory, n (%)	20 (45)
Prior ASCT, n (%)	30 (68)

ECOG = Eastern Cooperative Oncology Group;
NOS = not otherwise specified

Fanale MA, et al. Clin Cancer Res 2012;18:248–55.

SGN35-002: Phase 1 study of brentuximab vedotin in patients with rel/ref CD30+ hematologic malignancies

Best clinical response in efficacy-evaluable population (N=41)

Response, n	Dose group, mg/kg						Total (N=41)
	0.4 (n=4)	0.6 (n=4)	0.8 (n=6)	1.0 (n=10)	1.2 (n=12)	1.4 (n=5)	
ORR (CR+PR)	0	2	4	7	7	4	24 (59%)
CR	0	0	4	5	3	2	14 (34%)
PR	0	2	0	2	4	2	10 (24%)
SD	4	1	1	2	4	1	13 (32%)
PD	0	1	1	1	1	0	4 (10%)

- Median follow-up: 45.1 weeks (range 6.0–91.0)
- Median PFS: 28.7 weeks (range 7.3–83.6+); median overall survival (OS) not reached

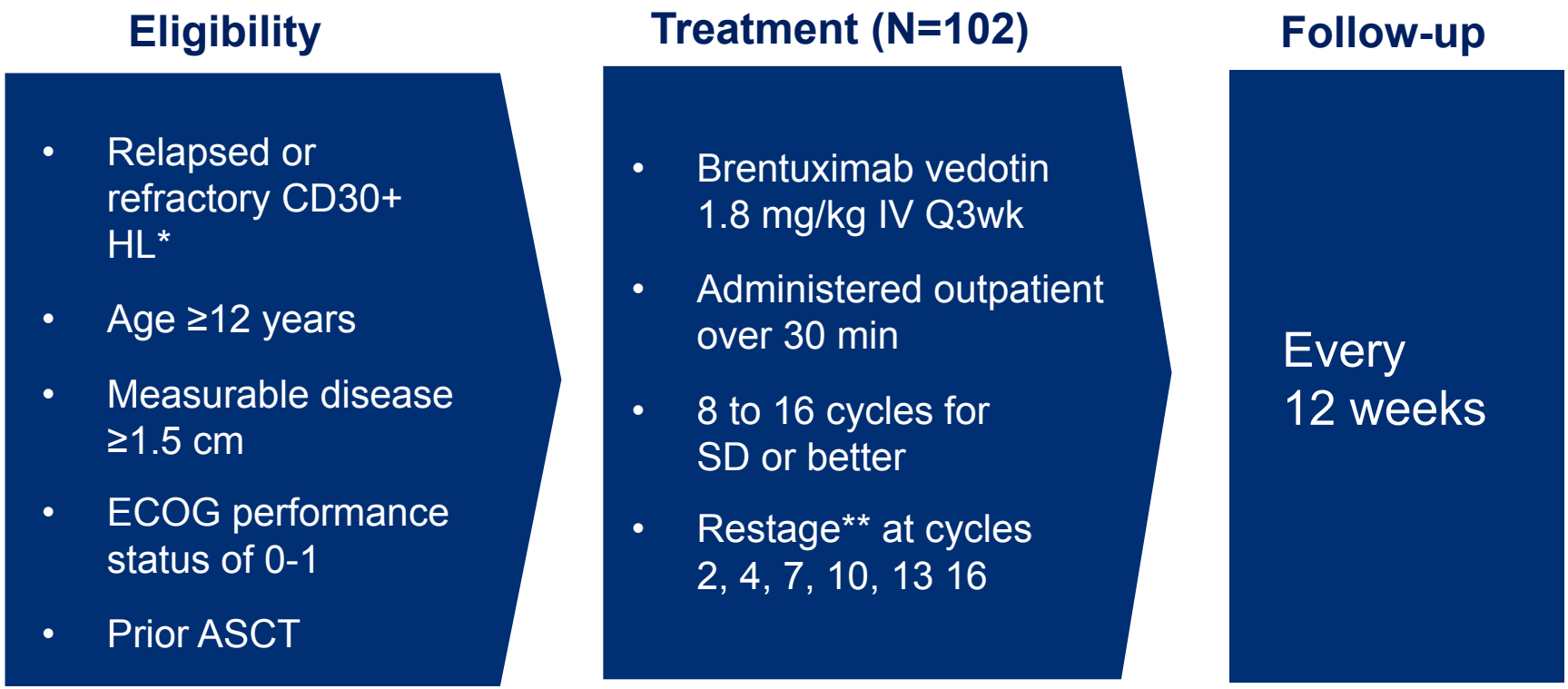
Reprinted from Clinical Cancer Research, 2012;18:248–55. Fanale MA, et al. A Phase I Weekly Dosing Study of Brentuximab Vedotin in Patients with Relapsed/Refractory CD30-Positive Hematologic Malignancies with permission from AACR

Clinical Data in Hodgkin Lymphoma (HL)

Brentuximab vedotin, single agent

- in relapsed/refractory patients post ASCT
- as consolidation therapy post ASCT in patients at increased risk of relapse (AETHERA)
- as salvage therapy prior ASCT

SGN35-003: Phase 2 pivotal study of brentuximab vedotin in patients with rel/ref HL post ASCT: overview (NCT00848926)



Primary Endpoint: ORR by Independent Review Facility

* Histologically documented CD30-positive HL by central pathology review

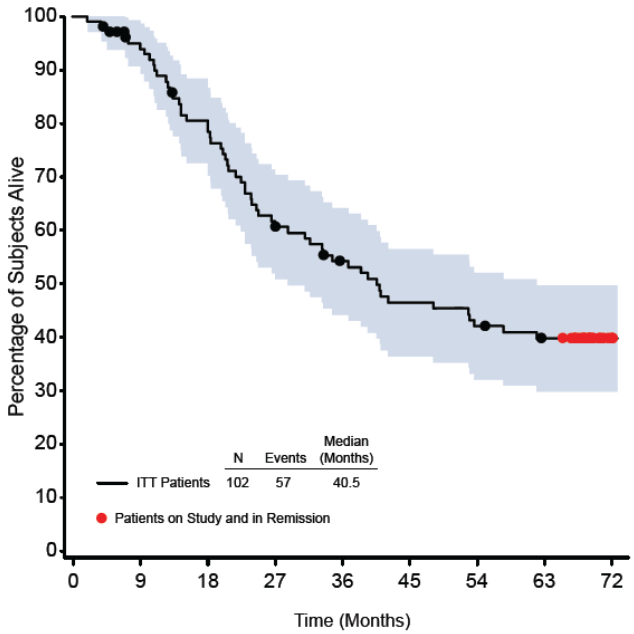
** Revised response criteria for malignant lymphoma (Cheson 2007)

Younes A, et al. J Clin Oncol 2012;30: 2183-2189.
Chen R, et al. ASH 2012, Atlanta, GA, USA (Abstract 3689).

SGN35-003: 5-year follow-up from phase II study of brentuximab vedotin in R/R HL post-ASCT[1] – Update *Blood* 2016(NCT00848926)

Efficacy (cont'd): ORR: 72%; CR rate: 33% (per investigator)

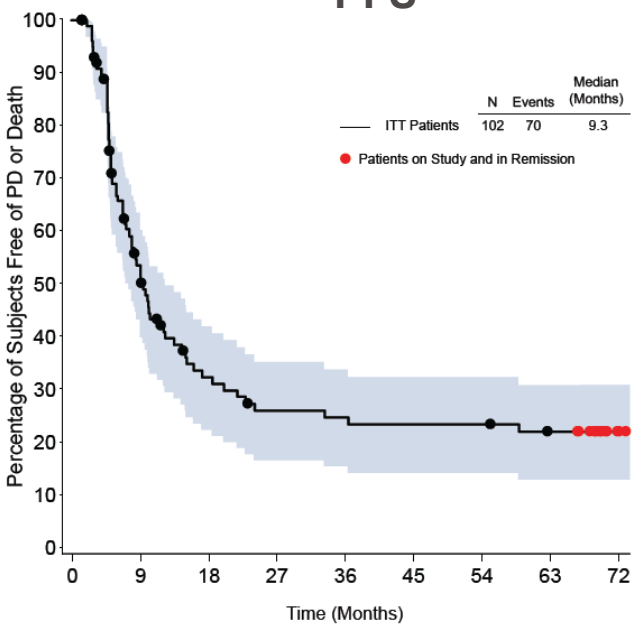
OS



Median OS: 40.5 mos
(95% CI: 28.7, 61.9 [1.8–72.9+])

5-yr OS: 41%
(95% CI: 31%, 51%)

PFS



Median PFS: 9.3 mos
(95% CI: 7.1, 12.2)

5-yr PFS: 22%
(95% CI: 13%, 31%)

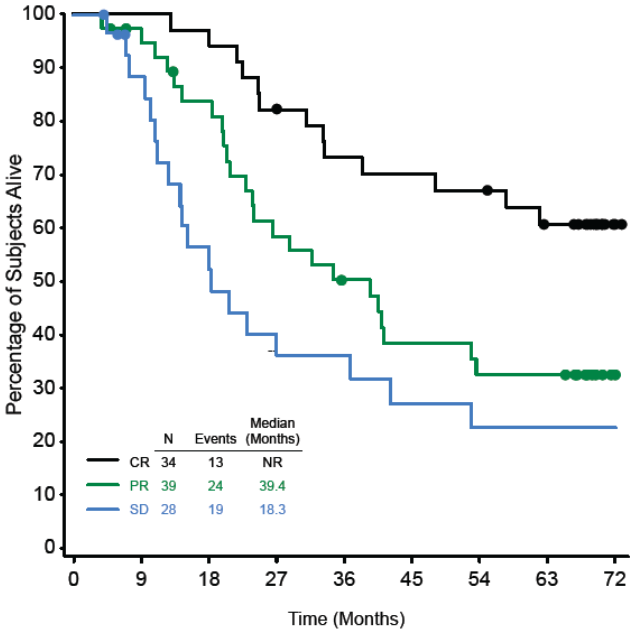
Chen R,, et al. *Blood* 2016

1. Previous publications: Chen R, et al. ASH 2015, Poster presentation from Abstract #2736
Younes A, et al. J Clin Oncol 2012;30:2183-9;
Gopal AK, et al. Blood 2015;125:1236-43

SGN35-003: 5-year follow-up from phase II study of brentuximab vedotin in R/R HL post-ASCT[1] – Update *Blood* 2016(NCT00848926)

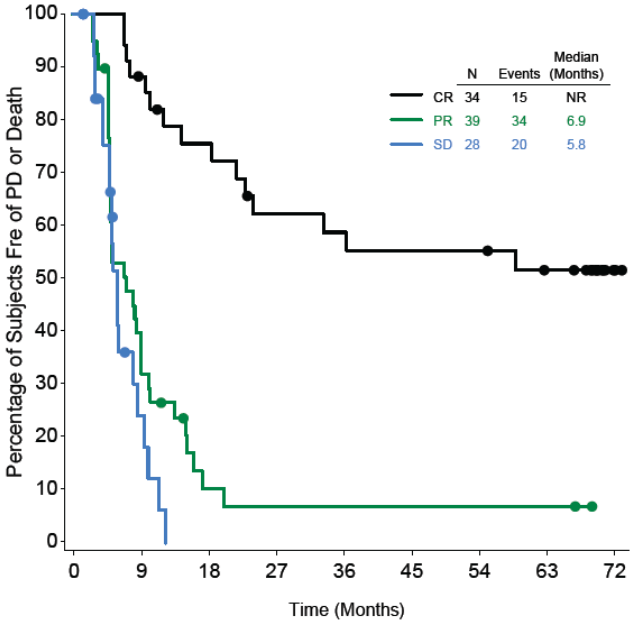
Efficacy (cont'd): Median OS, PFS and DOR were not reached in pts with CR (n=34)

OS by best response



5-yr OS: 64%
(95% CI: 48%, 80%)

PFS by best response



5-yr PFS: 52%
(95% CI: 34%, 69%)

Chen R, et al. *Blood* 2016
Previous publications: Chen R, et al. ASH 2015, Poster presentation from Abstract #2736
Younes A, et al. J Clin Oncol 2012;30:2183-9;
Gopal AK, et al. Blood 2015;125:1236-43

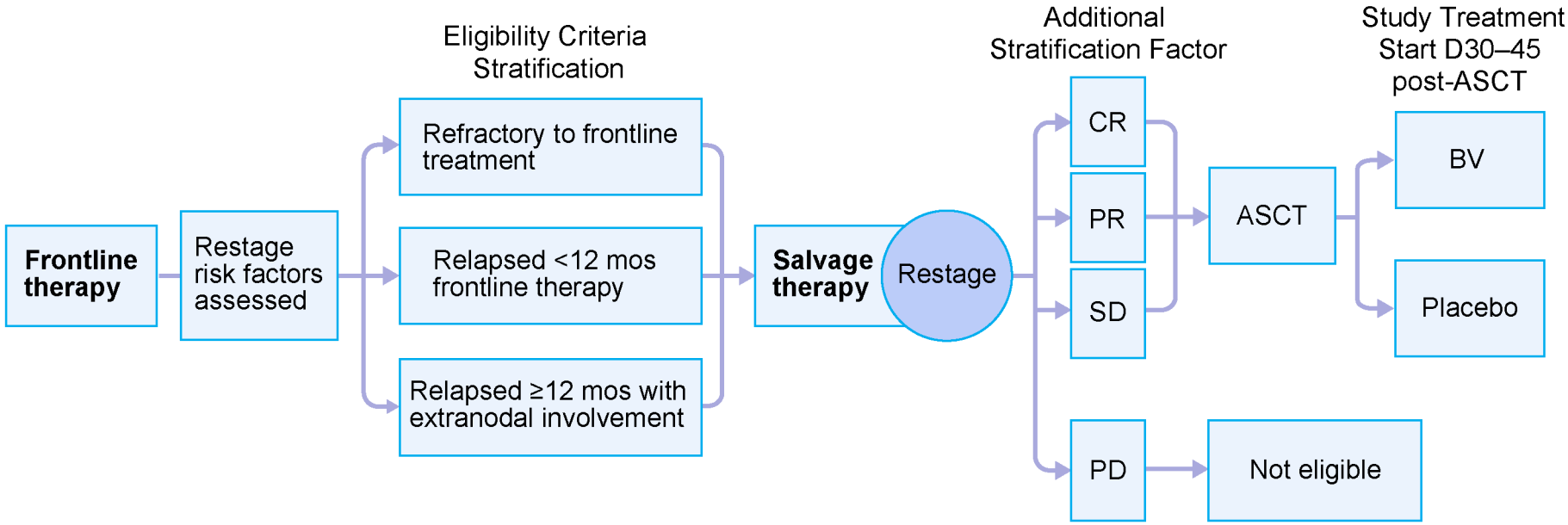
Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial

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

SGN35-005 (AETHERA): phase 3 trial of brentuximab vedotin vs placebo in relapsed or refractory HL pts at risk of relapse post ASCT (NCT01100502)

Design: Phase 3 randomized, double-blind, placebo-controlled, multicenter study of brentuximab vedotin vs placebo in relapsed or refractory HL pts at risk of progression following ASCT

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

- Pts who progressed on placebo could receive brentuximab vedotin in another trial

Moskowitz et al, ASH2014 (Abstract#673)

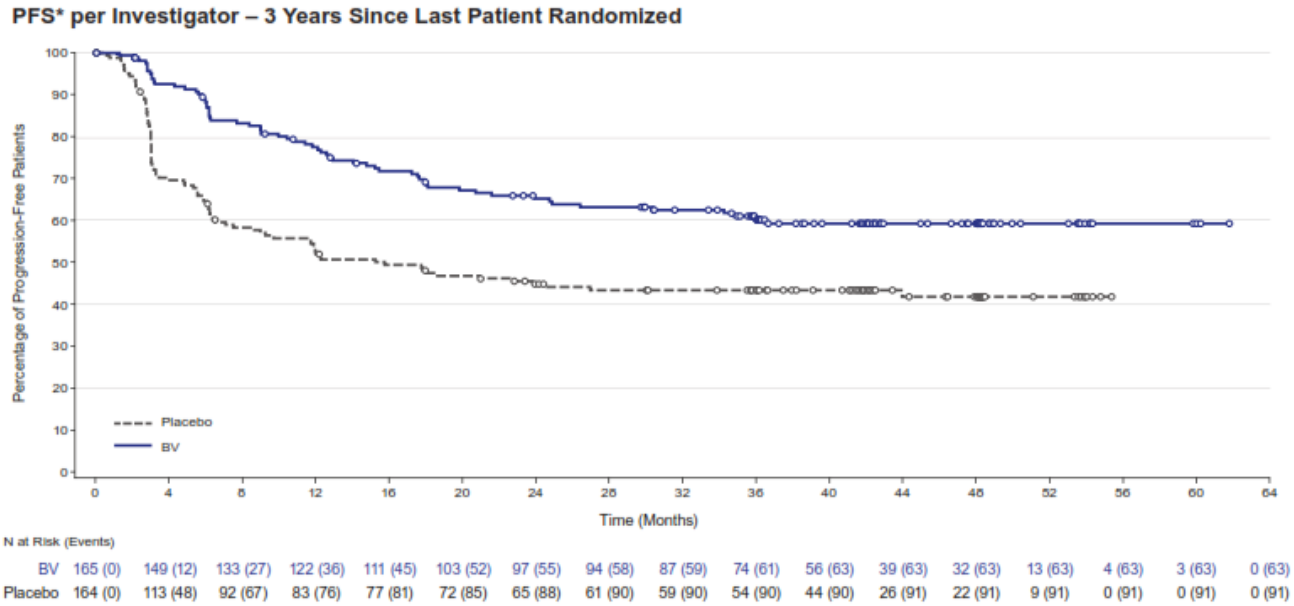
SGN35-005 (AETHERA): phase 3 trial of brentuximab vedotin vs placebo in relapsed or refractory HL pts at risk of relapse post ASCT (NCT01100502)

Pts: 329 refractory or relapsed HL pts at risk of progression following ASCT

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%

Chen et al,ASH2014. San Francisco (Abstract#501)

SGN35-005 (AETHERA): Updated data from phase III trial of brentuximab vedotin vs placebo in R/R HL at risk of relapse post-ASCT[1] (NCT01100502)



PFS rate* by treatment duration in the brentuximab vedotin arm

Mos after first brentuximab vedotin dose	Number of treatment cycles			
	1-4 (n=18)	5-8 (n=7)	9-12 (n=24)	13-16 (n=92)
12	58%	67%	91%	98%
24	58%	67%	69%	82%
36	58%	67%	63%	77%

*Per investigator; excludes pts discontinuing due to PD; not a randomized comparison

Sweetenham J, et al. ASH 2015, Poster presentation from Abstract #3172
1. Previous publication: Moskowitz CH, et al. Lancet 2015;385:1853-62

SGN35-005 (AETHERA): Updated data from phase III trial of brentuximab vedotin vs placebo in R/R HL at risk of relapse post-ASCT[1] (NCT01100502)

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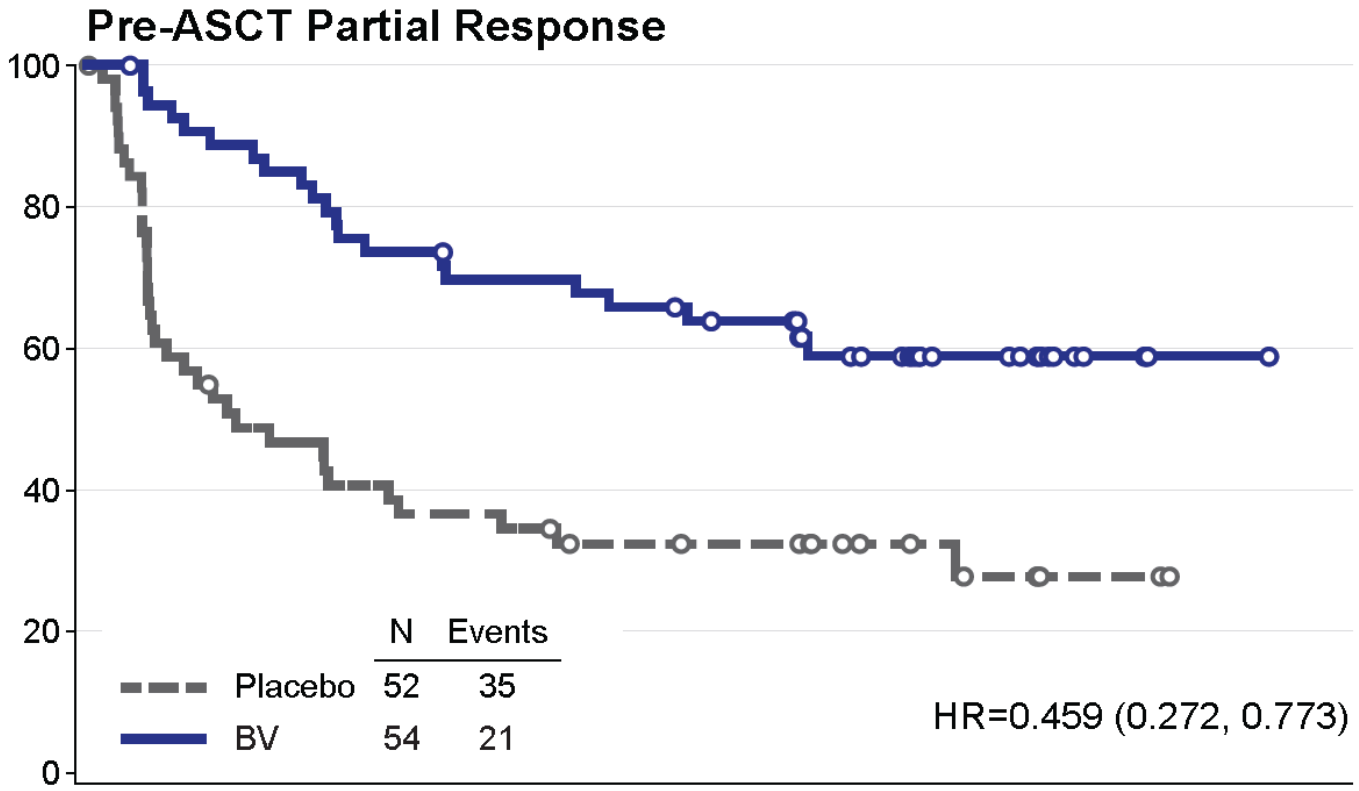

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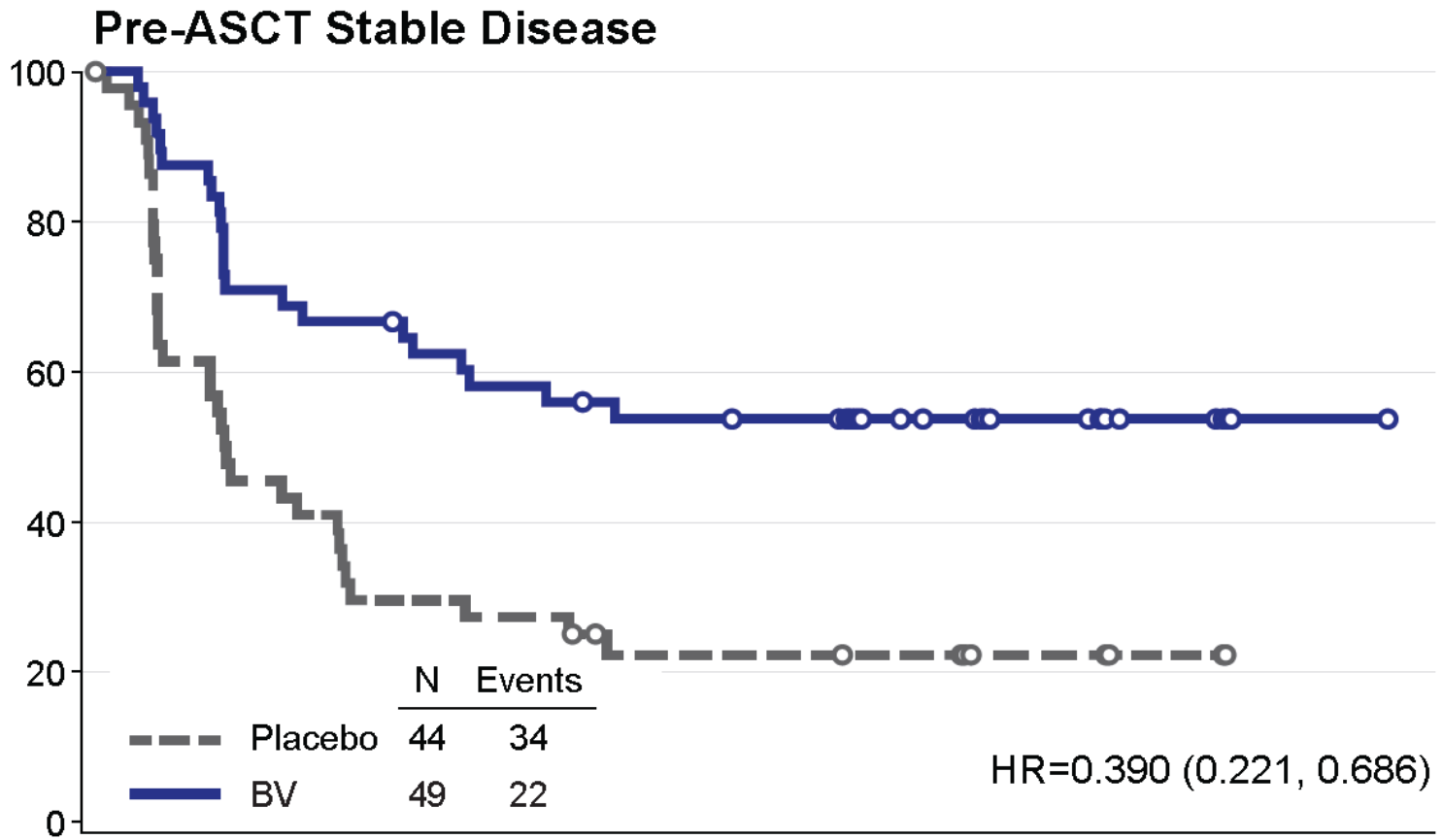

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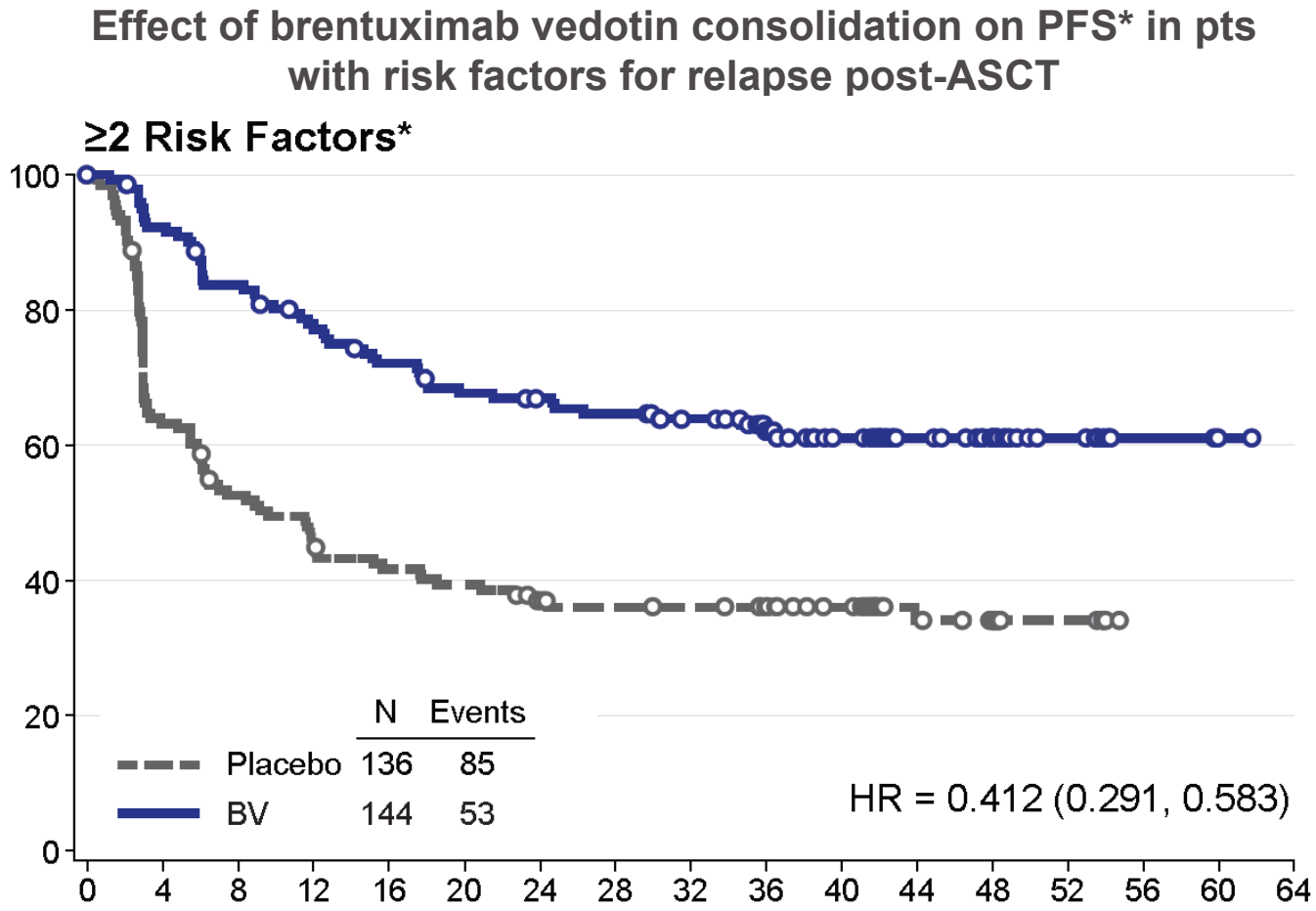

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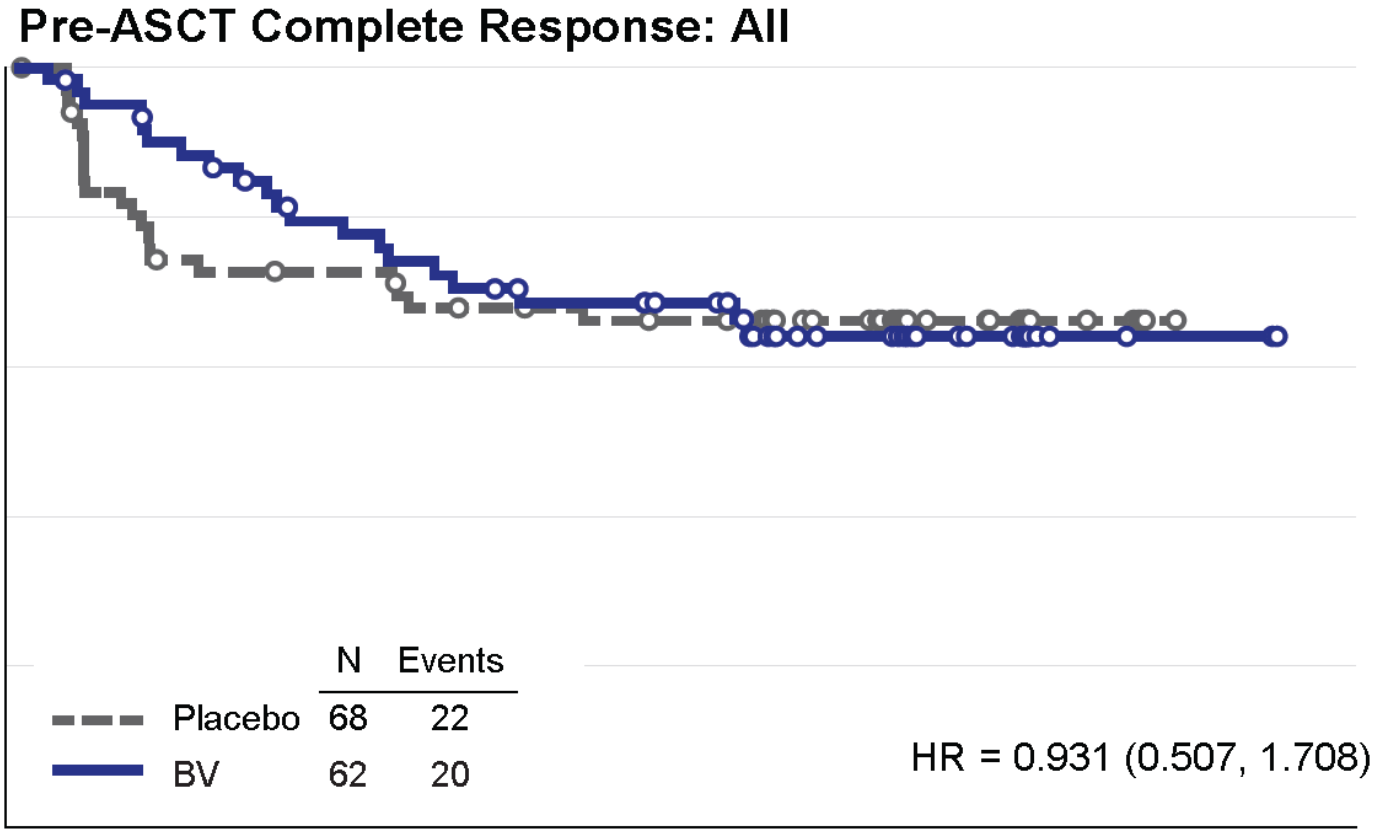

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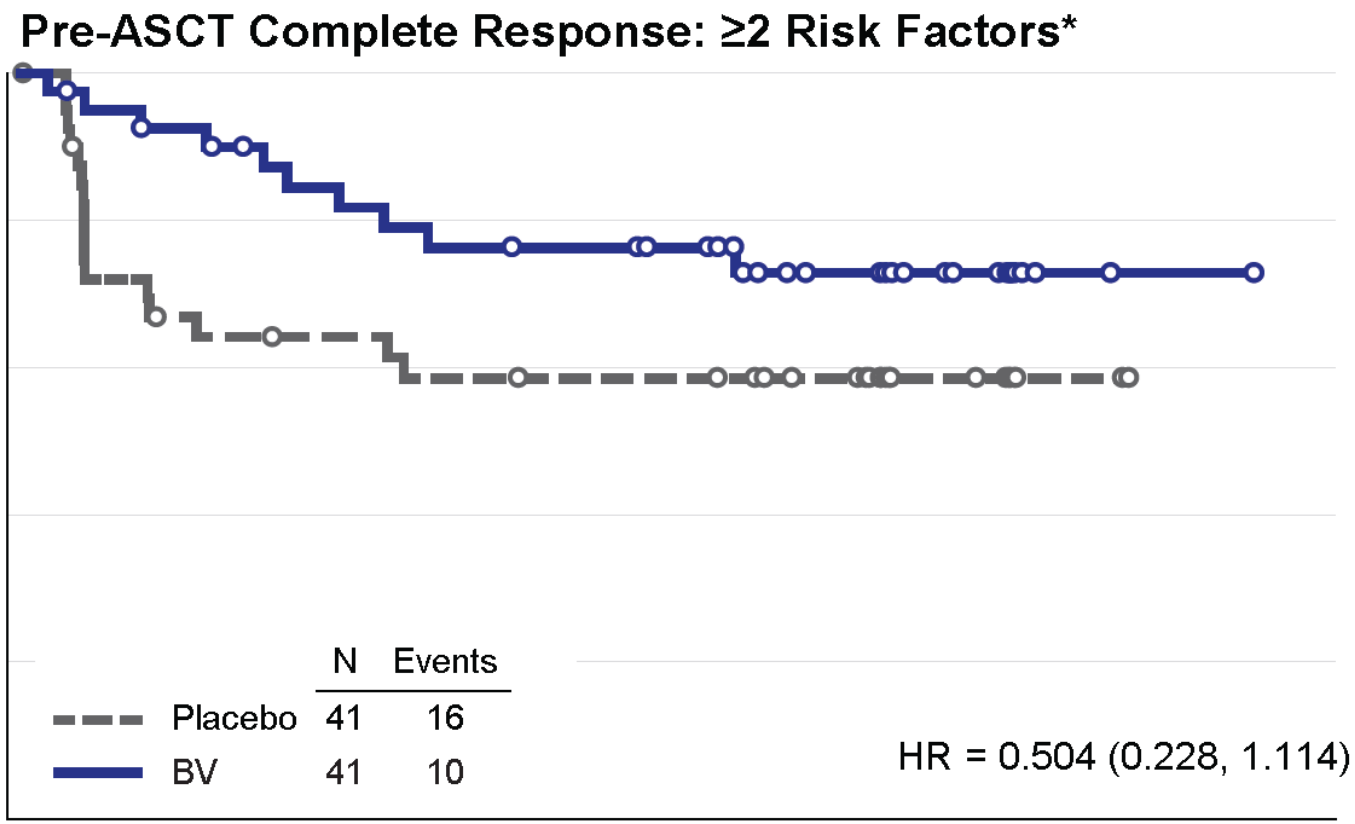

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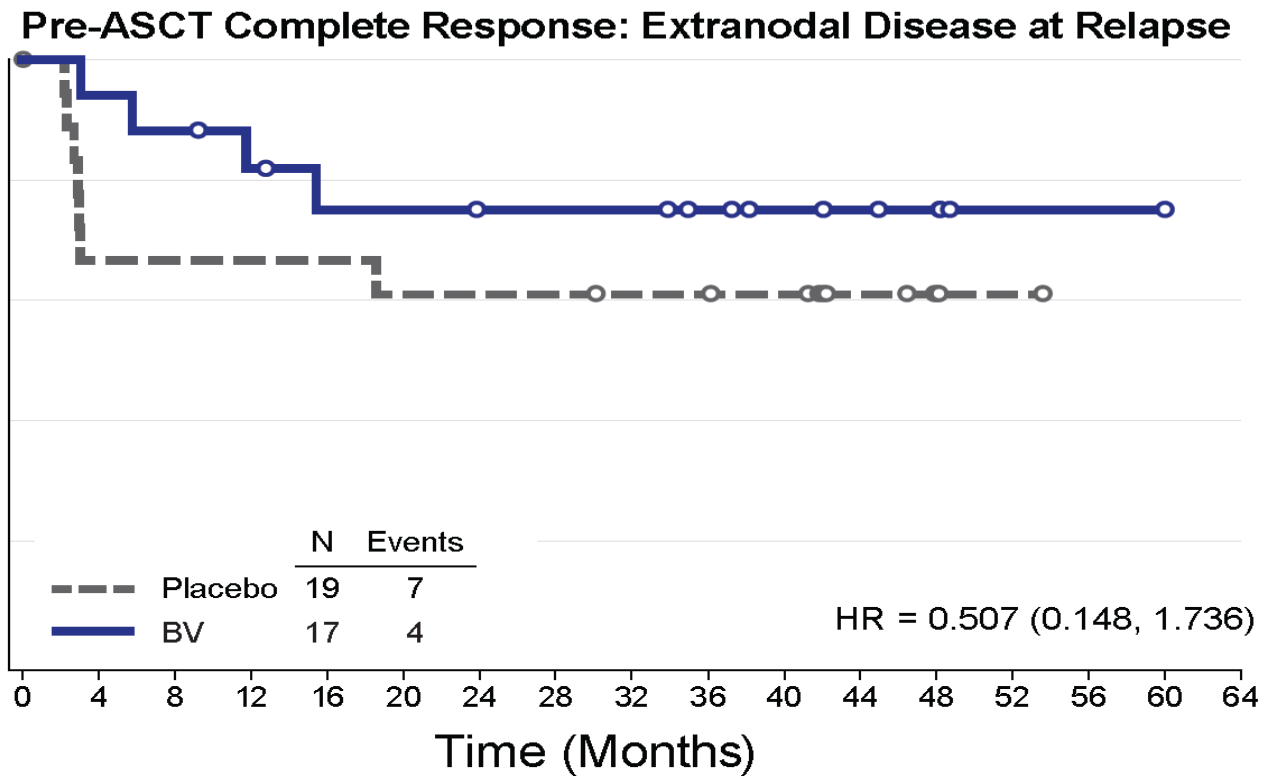

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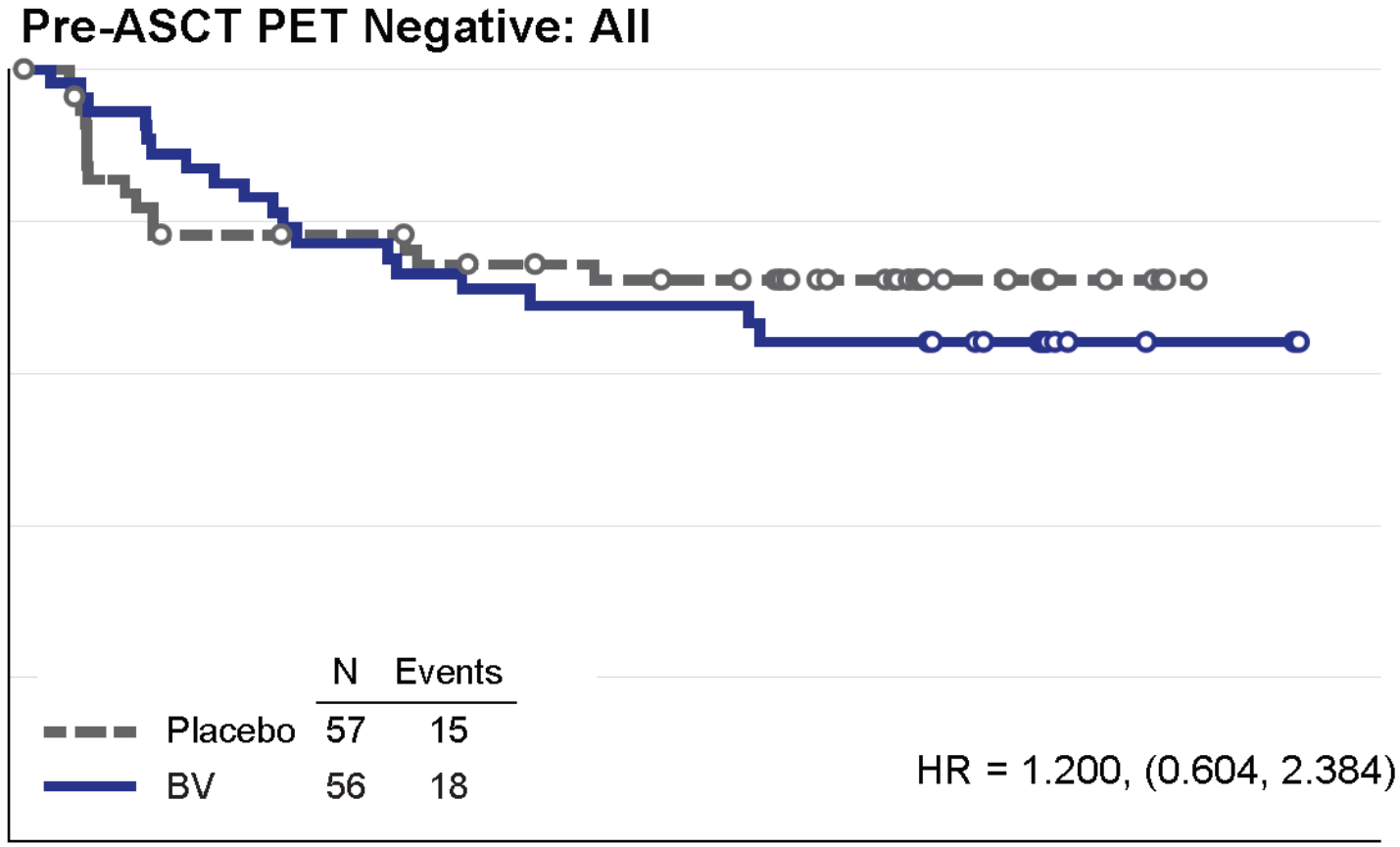

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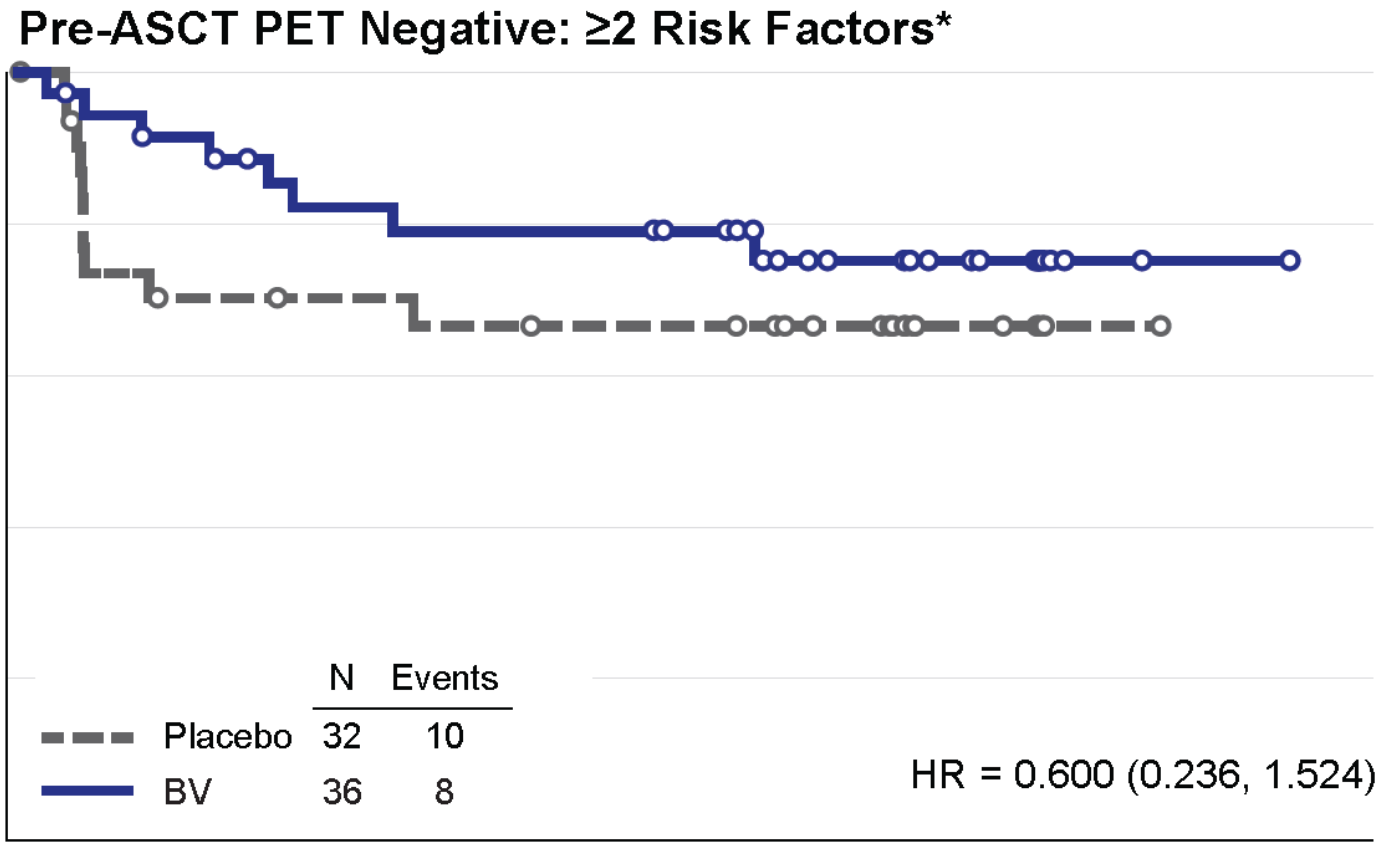

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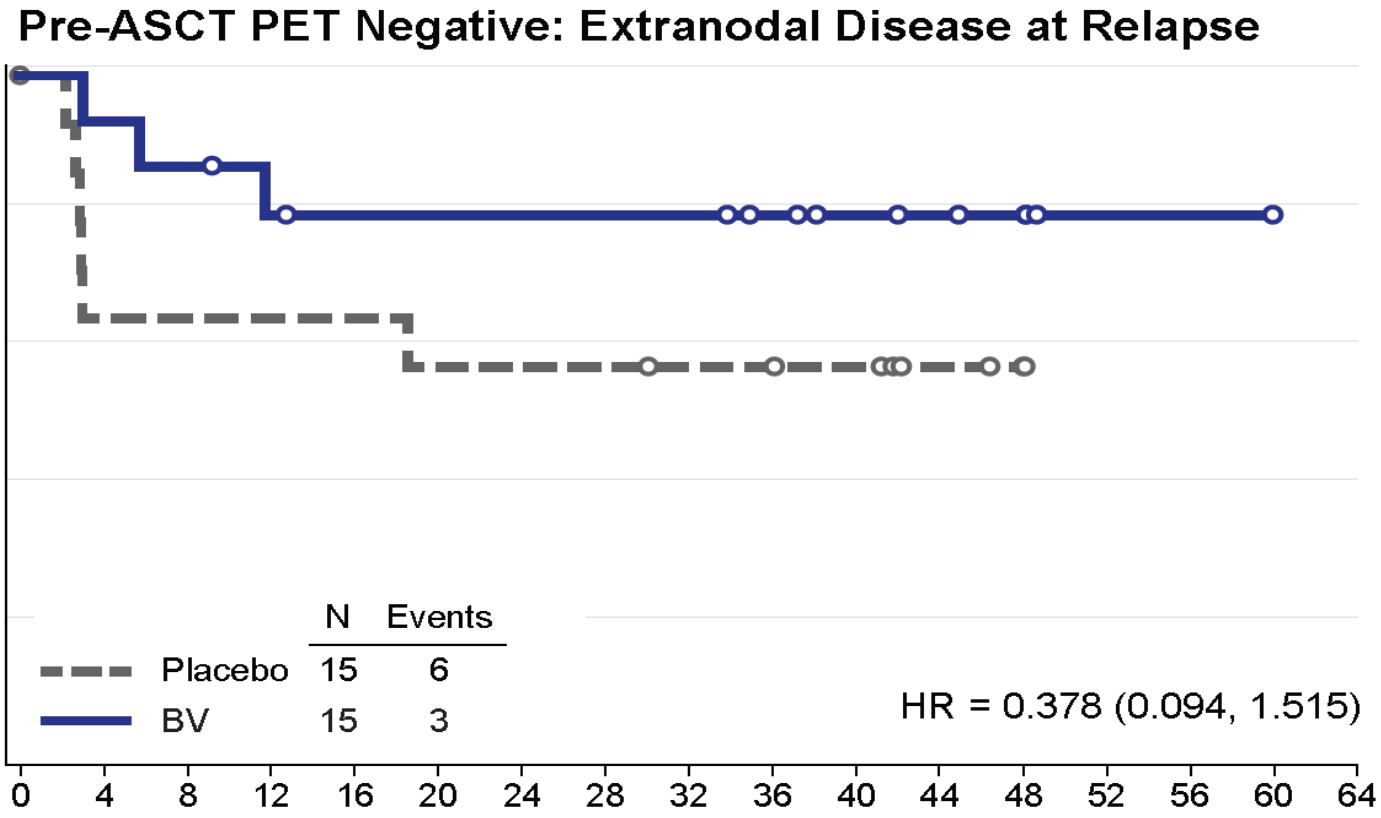

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Sweetenham J, et al. ASH 2015, Poster presentation from Abstract #3172

1. Previous publication: Moskowitz CH, et al. Lancet 2015;385:1853-62

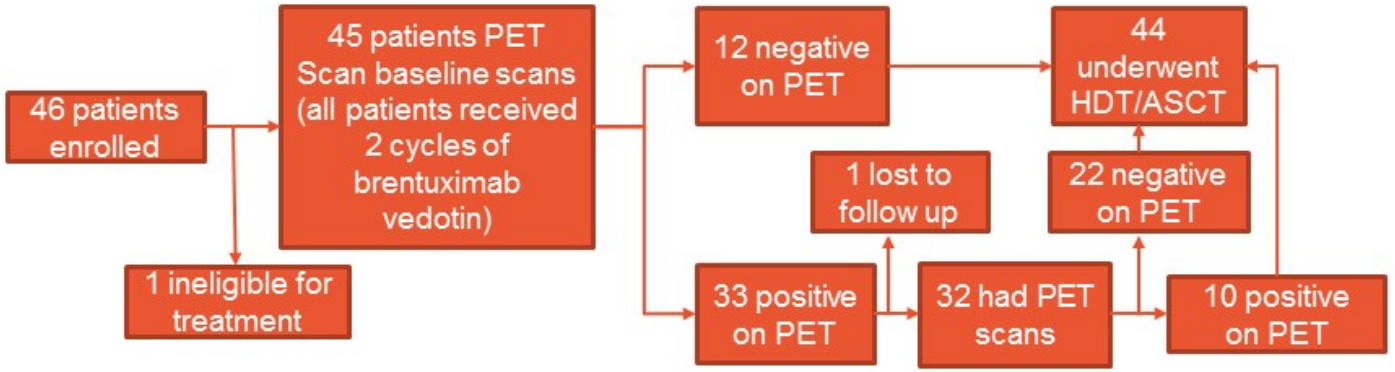
Phase II study: Brentuximab vedotin-based salvage therapy in RR HL pts (NCT01508312)

Design: Phase II, non-randomized, open-label, single-center trial

Objective: Predictive/prognostic utility of quantitative FDG PET/CT-derived parameters

Patients: 45 evaluable RR HL pts with 1 previously failed doxorubicin-containing chemotherapy regimen; median age 31 yrs (13–65); stage II/III/IV: 51%/13%/36%; median baseline MTV 46.6 (9.0–781.5); median baseline TLG 280.1 (34.7–6472.1)

Dose and schedule: Two 28-day cycles of brentuximab vedotin 1.2 mg/kg on days 1, 8 and 15. Pts achieving normalization of PET (Deauville 1–2) proceeded to HDT/ASCT. Pts with persistent PET/CT abnormalities after brentuximab vedotin treatment received 2 cycles of augmented-ICE



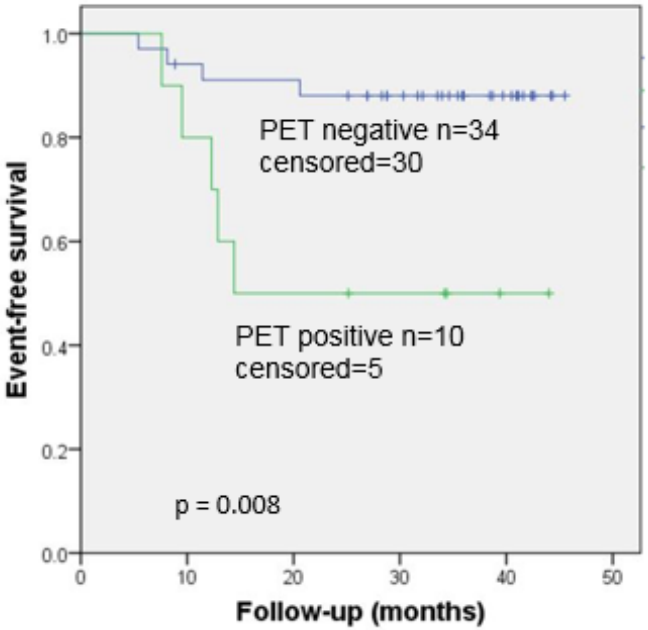
Gavane S, et al. ASCO 2016, Oral presentation from Abstract #11566

Phase II study: Brentuximab vedotin-based salvage therapy in RR HL pts (NCT01508312)

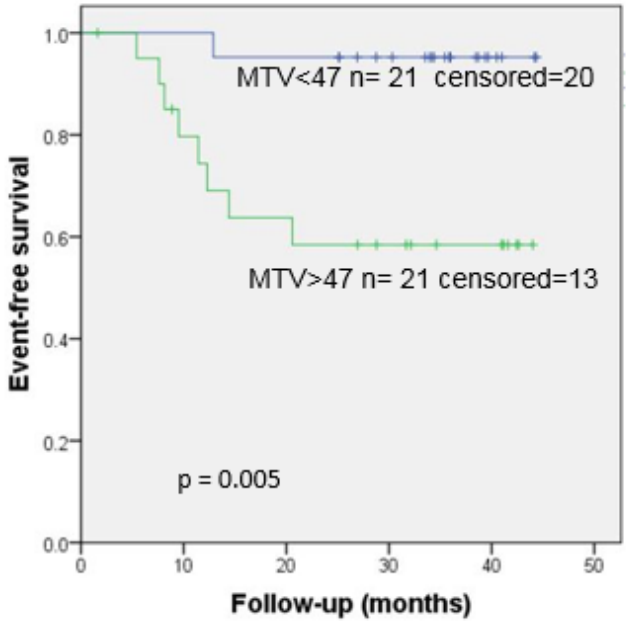
Efficacy (cont'd): Median EFS follow-up was 33.8 mos

- Baseline MTV was an independent predictor of EFS ($p<0.05$)
- Post-brentuximab vedotin and pre-transplant FDG PET imaging parameters (including SUVmax and MTV) did not correlate with EFS

Kaplan Meier curves for EFS according to pre-transplant PET status



Kaplan Meier curves based on median baseline MTV



Gavane S, et al. ASCO 2016, Oral presentation from Abstract #11566

Safety: Not reported

Clinical Data in Hodgkin Lymphoma (HL) Cont'

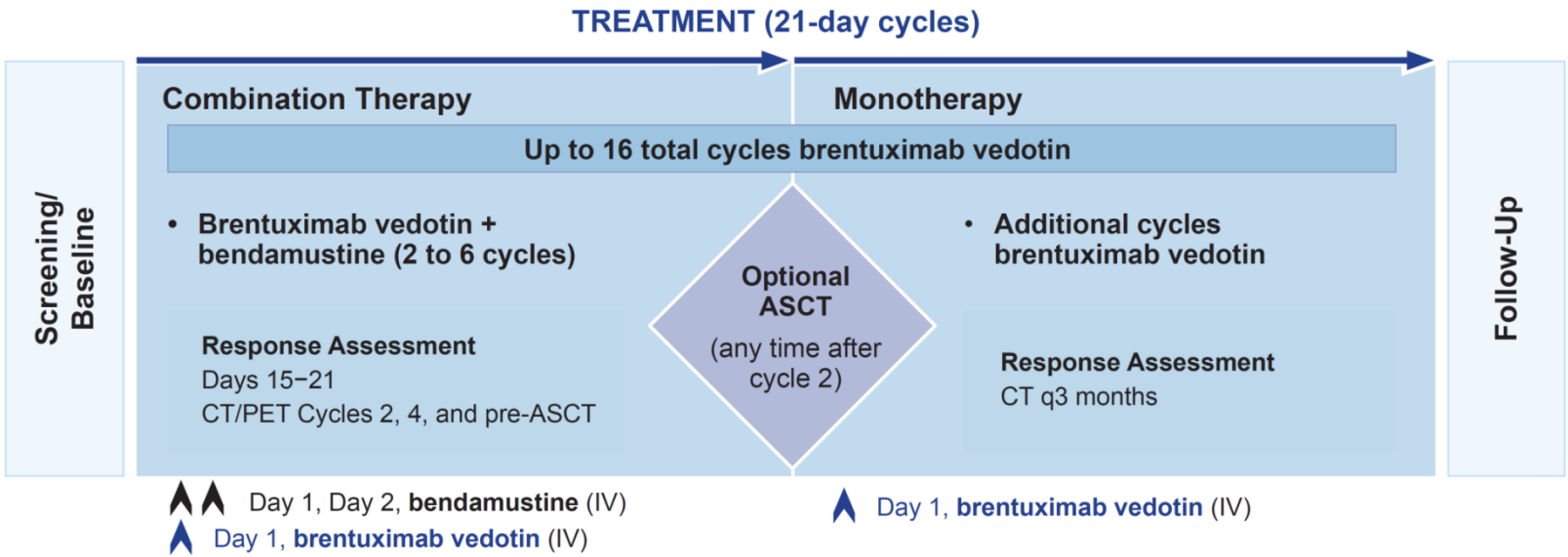
Brentuximab vedotin in combination therapies

- **in relapsed refractory HL patients**

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

Design: Phase I/II, single-arm, two-stage trial of brentuximab vedotin plus bendamustine in R/R HL

- Phase I objectives: dose level of bendamustine, safety/tolerability
- Phase II objectives: best response, DOR, PFS



Dose and schedule: BV 1.8 mg/kg IV day 1 + bendamustine 90 mg/m^2 days 1, 2

LaCasce et al, ASH2014(abstract#293)

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

Update ASH 2015

Endpoints: *Primary*: CR rate; *Secondary:* best response, DOR, PFS, safety; *Exploratory:* stem cell mobilization, OS, subset analyses

Patients: 55 pts with R/R HL after frontline therapy; median age 36 yrs (19–79), 53% stage III-IV at diagnosis, 51%/49% primary refractory/relapsed, 20% remission duration ≤1 yr, 22% B symptoms, 9% bulky disease, 31% extranodal disease, median IPS score of 2 (0–5) at enrollment

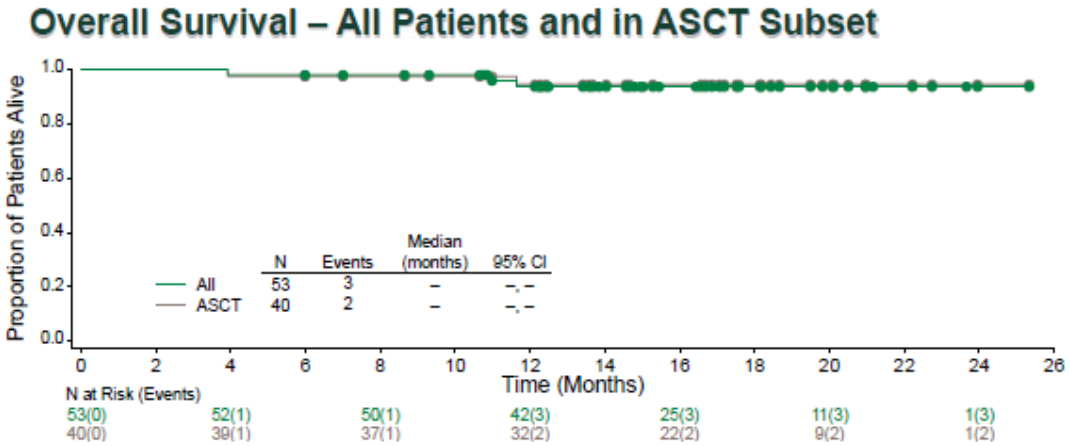
Safety: Median 2 cycles (1–6) of brentuximab vedotin 1.8 mg/kg + bendamustine 90 mg/m^2, median 10 cycles (1–14) of single-agent brentuximab vedotin (n=30; 25 ASCT pts, 5 non-ASCT pts)

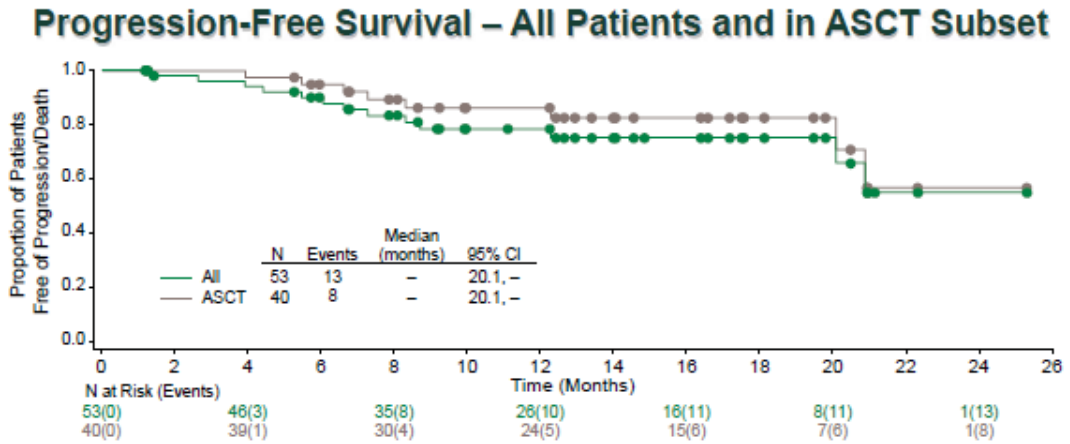
- Rate of Gr ≥3 AE was 32% (n=25) before protocol amendment to premedicate with corticosteroids and antihistamines to reduce IRR, and 17% post-amendment (n=30)
- Discontinuation of treatment and SAE were 24% each pre-amendment and 7% and 10% post-amendment, respectively

LaCasce AS, et al. ASH 2015, Poster presentation from Abstract #3982

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

Efficacy (Cont'd): Median follow-up: ~15 mos from first dose (N=53), 13 mos from ASCT (n=40)





18-month PFS:

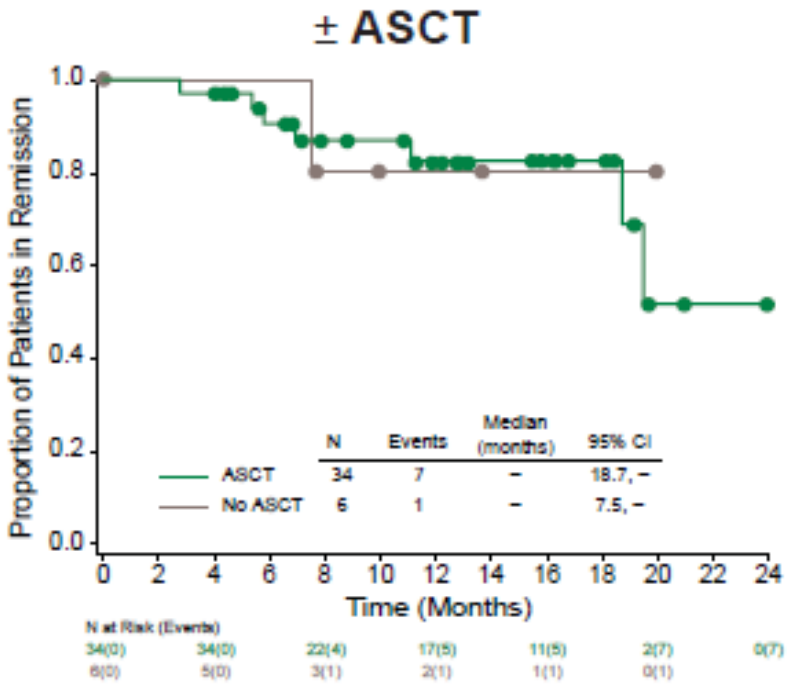
- All pts: 75%
- ASCT subset: 83%

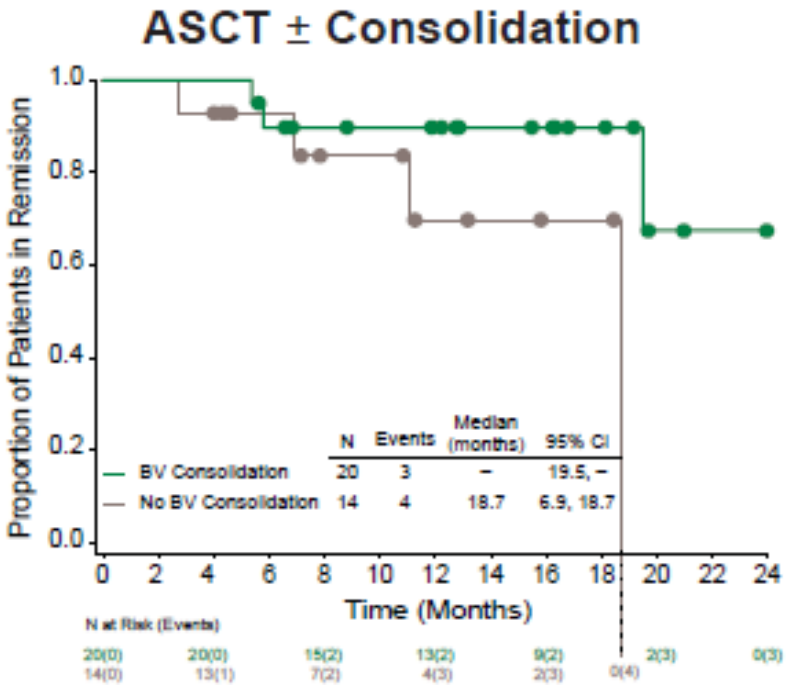
LaCasce AS, et al. ASH 2015, Poster presentation from Abstract #3982

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

Efficacy (Cont'd):

Duration of remission in pts with CR





LaCasce AS, et al. ASH 2015, Poster presentation from Abstract #3982

Phase II study: Brentuximab vedotin and bendamustine alone and in combination in R/R HL

Objectives: Efficacy and safety

Patients: 24 pts with RR HL; median age 32.5 yrs (16–73)

Patient baseline characteristics	Arm A (n=10)	Arm B (n=6)	Arm C (n=8)
Median age, yrs	31.5	25.3	35.3
Median number of prior therapies (range)	3 (2–6)	4 (2–7)	6 (2–8)

Dose and schedule: Pts were assigned by chance to one of 3 arms:

Arm A Bendamustine 90 mg/m^2 on days 1 and 2 plus DHAP every 28 days for 3 cycles

Arm B Brentuximab vedotin 1.8 mg/kg every 3 wks for 4–8 cycles

Arm C Bendamustine 120 mg/m^2 on days 1 and 2 plus brentuximab vedotin 1.8 mg/kg on day 3 every 28 days for 4–6 cycles. Growth factor support was systemically administered with antimicrobial prophylaxis

Cerchione C, et al. EHA 2016, Poster from Abstract #LB2258

Phase II study: Brentuximab vedotin and bendamustine alone and in combination in R/R HL

Efficacy: Median follow-up not reported

Response and survival	Arm A (n=10)	Arm B (n=6)	Arm C (n=8)
ORR, %	40	66	100
CR	40	50	100
PR	–	17	–
Median OS, mos (range)	22 (18–28)	28 (24–35)	32 (27–44)
Median PFS, mos (range)	10 (8–19)	13 (9–21)	15 (9–18)
Treatment following salvage regimen, n			
ASCT	2	–	4
Haploidentical-SCT	1	2	4

Safety: Median cycles not reported

- Grade 3 thrombocytopenia reported in 4 pts (40%) in arm A and 2 pts (33%) in Arm C
- Grade 3 neuropathy reported in 1 pt (17%) in Arm B

Cerchione C, et al. EHA 2016, Poster from Abstract #LB2258

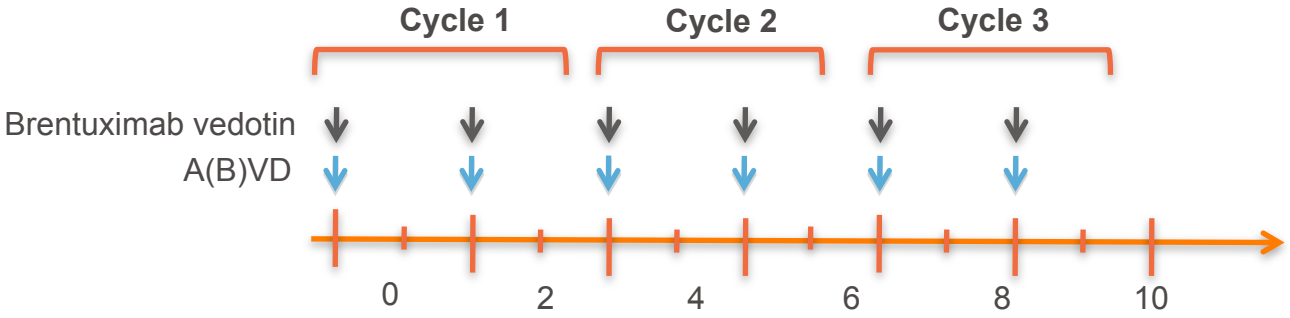
Clinical Data in Previously Untreated Hodgkin Lymphoma

Combinations with ABVD, prior ABVD and following ABVD
Combinations with BEACOPP
Combinations with AVD in elderly, unfavorable risk, HIV associated HL

SGN35-009: Phase 1 multicenter dose-escalation study of brentuximab vedotin + ABVD or AVD in patients with previously untreated advanced HL – Overview (NCT01060904)

Design: Phase 1, multicenter, dose-escalation study in previously untreated, stage IIA-IV HL

- Long-term objectives: durability of response, time distribution of any relapses



Dose and schedule:
Six 28-day cycles +/- XRT
(dosing on days 1, 15)

Brentuximab vedotin IV + ABVD (n=25)
Cohort 1 (0.6 mg/kg) n=6
Cohort 2 (0.9 mg/kg) n=13
Cohort 3 (1.2 mg/kg) n=6

Brentuximab vedotin IV+ AVD (n=26)
Cohort 4 (1.2 mg/kg) n=6
Expansion cohort (1.2 mg/kg) n=20

Pts: 50 pts with previously untreated, stage IIA-IV HL

- Median age 33 yrs (18–59), 23% IPS ≥4, 6%/16%/14%/18%/46% stage IIA bulky/IIB/IIIA/IIIB/IV

Younes A et. al . Lancet Oncol. 2013 Dec;14(13):1348-56.

SGN35-009: Phase 1 multicenter dose-escalation study of brentuximab vedotin + ABVD or AVD in patients with previously untreated advanced HL – Pulmonary Toxicity (NCT01060904)

- **Safety: Pulmonary Toxicity**

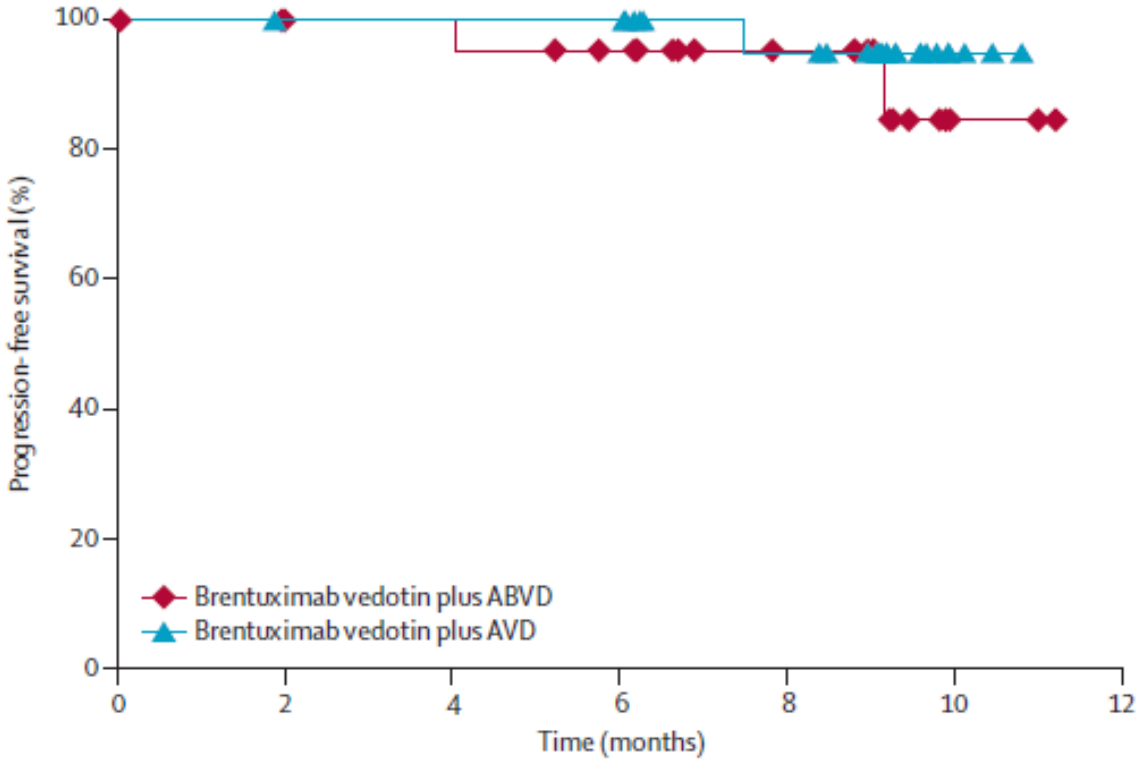
Preferred term, n (%)	ABVD with brentuximab vedotin (n=25)	AVD with brentuximab vedotin (n=26)
Any event	11 (44)	0
Pulmonary toxicity	9 (36)	0
Interstitial lung disease	1 (4)	0
Pneumonitis	1 (4)	0

  - Two patient deaths were associated with pulmonary toxicity
  - Events resolved in 9 of 11 patients (82%)
  - 6 of 11 patients with events discontinued bleomycin and were able to complete treatment with AVD combined with brentuximab vedotin
  - Concomitant administration of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity

Younes A et. al . Lancet Oncol. 2013 Dec;14(13):1348-56.

SGN35-009: Phase 1 multicenter dose-escalation study of brentuximab vedotin + ABVD or AVD in patients with previously untreated advanced HL – Response (NCT01060904)

Progression free survival per investigator assessment



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 . Lancet Oncol. 2013 Dec;14(13):1348-56

SGN35-009: Phase 1 multicenter dose-escalation study of brentuximab vedotin + ABVD or AVD in patients with previously untreated advanced HL – Antitumor Activity (NCT01060904)

- **DLT:** No protocol-defined DLTs observed with either ABVD or AVD in combination with brentuximab vedotin (up to the maximum planned dose of 1.2 mg/kg)
- **Antitumor activity:**

Response at end of frontline therapy, n (%)*	ABVD with brentuximab vedotin (n=22)	AVD with brentuximab vedotin (n=25)
Complete remission	21 (95)	24 (96)
Progressive disease	0	1 (4)
Not evaluable due to AE	1 (5)**	0

  - 1 patient withdrew consent and 3 patients were lost to follow-up prior to completion of frontline therapy
- Phase 3 study ongoing to assess treatment with brentuximab vedotin in combination with AVD compared to ABVD alone in treatment-naive patients

* Per Investigator

** Patient had Grade 5 pulmonary toxicity prior to end of frontline therapy

Younes A et. al . Lancet Oncol. 2013 Dec;14(13):1348-56.

SGN35-009 long-term follow-up: phase 1 trial of brentuximab vedotin + ABVD or AVD in previously untreated stage IIA-IV HL: safety (NCT01060904)

- Pulmonary toxicity observed in
  - 44% of brentuximab vedotin + ABVD pts
  - 0% of brentuximab vedotin + AVD pts
- Pulmonary toxicity resolved in 9/11 brentuximab vedotin + ABVD pts
  - Fatal in 2 pts
  - Median time to resolution: 2.6 wks (1.6–5)
- 8 pts discontinued bleomycin and completed treatment with brentuximab vedotin + AVD
- No other safety data reported
- No deaths from HL

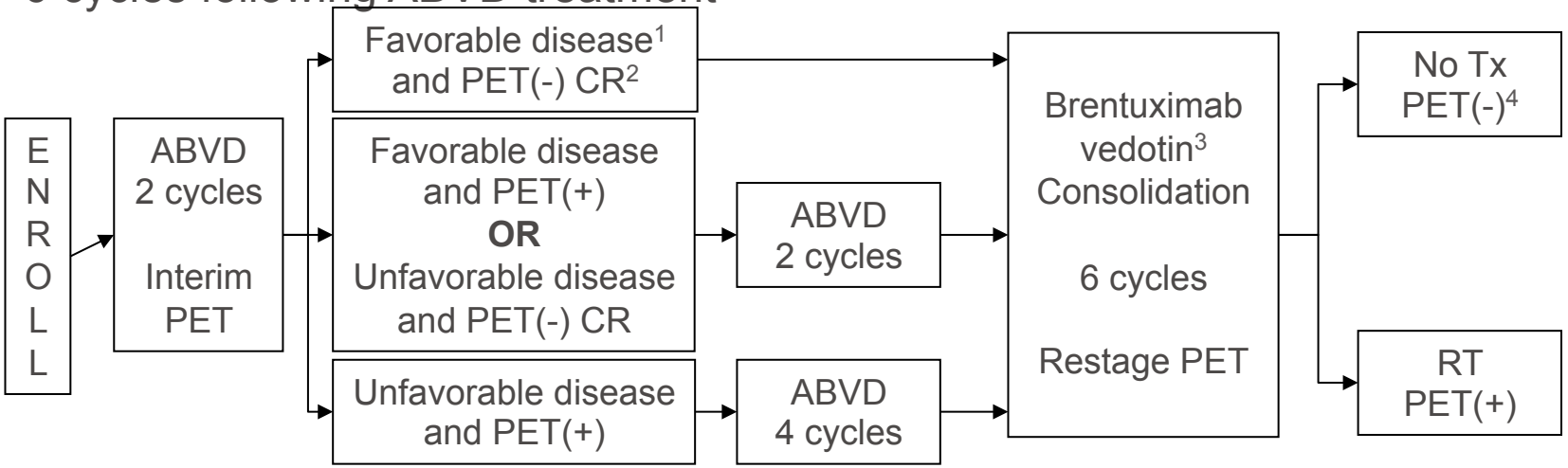
Connors et al, ASH2014 (Abstract# 292)

LCCC 1115 phase II trial: ABVD followed by brentuximab vedotin consolidation therapy in limited stage non-bulky HL (NCT01578967)

Design: Phase II multicenter study conducted at six sites

Objectives: *Primary;* proportion of pts who are PET(-); *Secondary;* CR, ORR, conversion rate to CR after brentuximab vedotin from PR at end of ABVD, 5-yr PFS, toxicity, tolerability, cytokine levels and correlation with clinical outcome

Dose and schedule: 21-day cycles of brentuximab vedotin 1.8 mg/kg for 6 cycles following ABVD treatment



[1]Unfavorable disease defined by presence of B symptoms, ESR >50, or >3 sites of disease; [2]Deauville score of ≤3 indicates CR; [3]Brentuximab vedotin (1.8 mg/kg every 3 wks) consolidation for 6 cycles; [4]Deauville score of ≤2 indicates CR. If PET-positive at EOT, radiation therapy recommended

Park S, et al. ASCO 2016, Oral presentation from Abstract #7508

LCCC 1115 phase II trial: ABVD followed by brentuximab vedotin consolidation therapy in limited stage non-bulky HL (NCT01578967)

Patients: 40 evaluable pts with previously untreated limited (I/II) stage non-bulky HL; median age 29 yrs (19–67); Stage I/IIA/IIB: 5%/70%/25%; 45%/55% favorable/unfavorable risk

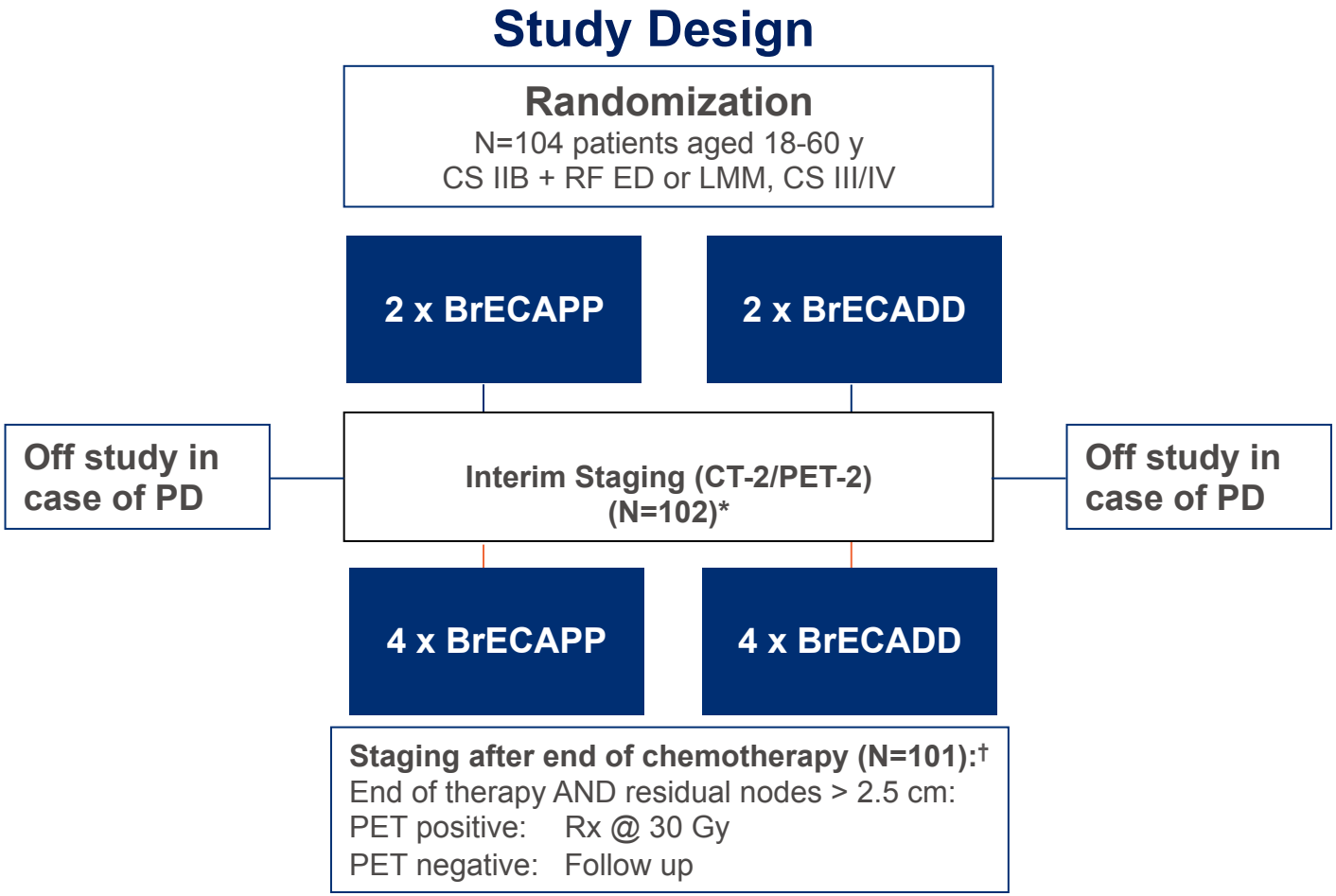
Efficacy:

- 2/4/>4 cycles ABVD received by 28%/65%/8% pts
- 73% pts achieved Deauville ≤2 post 2 ABVD cycles; 88% pts achieved Deauville ≤2 post ABVD; 94% pts achieved Deauville ≤2 post brentuximab vedotin
- Median follow-up 17 mos; estimated 1-yr PFS 91% (CI, 75–97%); 1-yr OS 97% (CI, 81–100%)

Deauville, %	Interim PET (post ABVD2)	Post ABVD	End of therapy (post-brentuximab vedotin)
1	28	35	47
2	45	53	47
3	20	10	3
4	8	0	0
5	0	3	3

Park S, et al. ASCO 2016, Oral presentation from Abstract #7508

Phase II study: brentuximab vedotin as part of targeted BEACOPP in frontline HL (NCT01569204)



*Withdrawal before therapy, n=2 (1 pt: consent withdrawn; 1 pt: acute infection with fever plus inclusion criteria violation [no advanced-stage HL]); †Early treatment termination, n=1

BEACOPP: bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; BrECAPP: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, procarbazine, prednisone

Borchmann P, et al. ASH 2015, Oral presentation from Abstract #580
Update of Borchmann P, et al. EHA 2014, Oral presentation

Phase II study: brentuximab vedotin as part of targeted BEACOPP in frontline HL (NCT01569204)

Dose: BrECAPP (n=49) and BrECADD (n=52) regimens were administered every 21 days for 6 cycles. Brentuximab vedotin dose was 1.8 mg/kg IV

Drug	Day	BEACOPP escalated X6 Cycles	BrECADD x6 Cycles	BrECAPPx6 Cycles
Bleomycin (mg/m²)	8	10	–	–
Etoposide (mg/m²)	1–3	200	150	200
Doxorubicin (mg/m²)	1	35	40	35
Cyclophosphamide (mg/m²)	1	1250	1250	1250
Vincristine (mg/m²)	8	1.4	–	–
Brentuximab vedotin (mg/kg)	1	–	1.8	1.8
Procarbazine (mg/m²)	1–7	100	–	100
Dacarbazine (mg/m²)	2–3	–	250	–
Prednisone (mg)	1–14	40	–	40
Dexamethasone (mg)	1–4	–	40	–

Borchmann P, et al. ASH 2015, Oral presentation from Abstract #580
Update of Borchmann P, et al. EHA 2014, Oral presentation

Phase II study: brentuximab vedotin as part of targeted BEACOPP in frontline HL (NCT01569204)

Safety:

NCIC-CTC Grade	Regimen	Grade III n (%)	Grade IV n (%)	Grade III/IV %
Hematologic	BrECAPP	6 (12)	40 (80)	80
	BrECADD	4 (8)	41 (79)	83
	BEACOPPesc*	–	–	93
Organ	BrECAPP	3 (6)	1 (2)	8
	BrECADD	1 (2)	–	2
	BEACOPPesc*	–	–	15

- Gr 3 sensory PN was reported in 1 (1%) patient receiving tBEACOPP (n=102) and no Gr 4 sensory PN was observed; 1 pt developed Gr 3 motor PN which resolved completely
- All treatment-related PN events resolved completely
- No severe neurotoxicity reported with BrECADD
- Brentuximab vedotin was reduced/stopped in cycle 5 and/or cycle 6 in 8/102 pts (8%) vs 20% for VCR with BEACOPPesc

*HD18, N=675, pts scheduled to receive 6x BEACOPPesc, weighted estimate

Borchmann P, et al. ASH 2015, Oral presentation from Abstract #580
Update of Borchmann P, et al. EHA 2014, Oral presentation

Phase II study: brentuximab vedotin as part of targeted BEACOPP in frontline HL (NCT01569204)

AE of special interest: Gr 4 hematological toxicities

Gr 4 AE	BrECAPP (n=50) n (%)	BrECADD (n=52) n (%)	HD18* (n=630) %
Anemia	3 (6)	–	10
Thrombocytopenia	20 (40)	15 (29)	47
Infection	1 (2)	1 (2)	2
Total (pts with AE Gr 4)	20 (40)	15 (29)	50

*HD18, pts scheduled to receive 6x BEACOPP

Borchmann P, et al. ASH 2015, Oral presentation from Abstract #580
Update of Borchmann P, et al. EHA 2014, Oral presentation

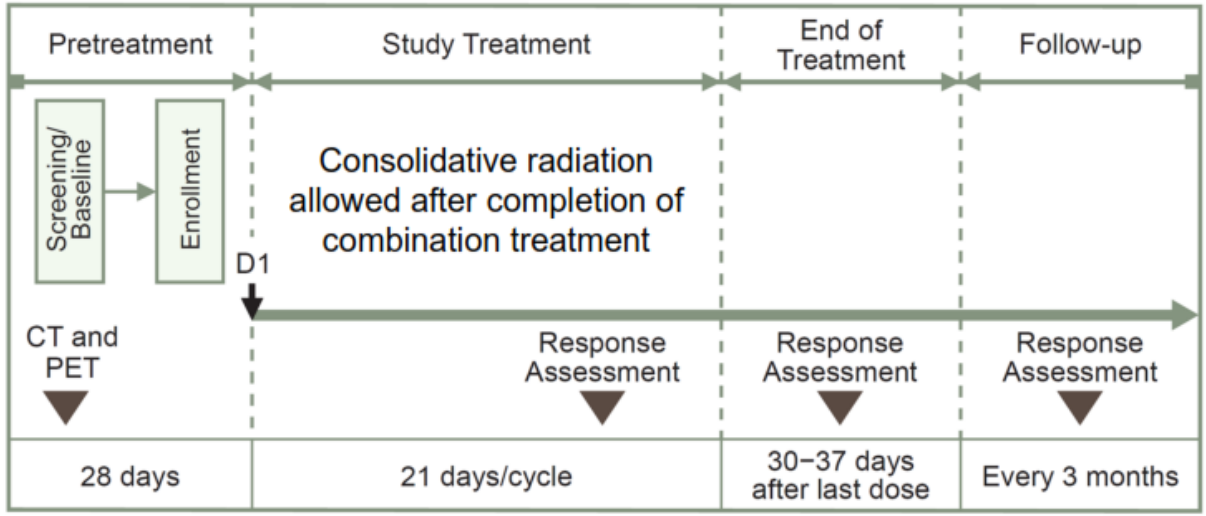
SGN35-015: Phase II trial of brentuximab vedotin alone and in combination in previously untreated HL pts aged ≥60 yrs (NCT01716806): Interim results

Dose and schedule:

Part A Brentuximab vedotin 1.8 mg/kg IV day 1

Part B Brentuximab vedotin 1.8 mg/kg + dacarbazine 375 mg/m^2 IV day 1

Part C Brentuximab vedotin 1.8 mg/kg IV day 1 + bendamustine 90 mg/m^2 days 1, 2 (Protocol amended to reduce bendamustine starting dose from 90 to 70 mg/m^2 IV Days 1 and 2 for up to 6 cycles)



CT: cycles 2, 4, 8, 16
CT + PET: cycles 2, 8
Max. 16 21-day cycles

1.Forero-Torres et al. *Blood* Dec 2015; 126(26):2798-804.
2. Yasenchak CA, et al. ASH 2015, Poster presentation from Abstract #587
3. Ferero-Tores A, et al. ASH 2014, Abstract #294
4. Forero-Tores A, et al. Blood, 2015; Sep 16 [Epub ahead of print]

SGN35-015: Phase II trial of brentuximab vedotin alone and in combination in previously untreated HL pts aged ≥60 yrs (NCT01716806): Interim results

Efficacy (n=63): Median observation time: brentuximab vedotin, 23.1 months[2]; brentuximab vedotin + dacarbazine, 13.4 months; brentuximab vedotin + bendamustine, 4.6 months (insufficient for reliable estimates of PFS)[1]

	Brentuximab vedotin (n=26)*[2,4]	Brentuximab vedotin + dacarbazine (n=21)*[2]	Brentuximab vedotin + bendamustine (n=16)*[2]
ORR, n (%)†	24 (92)	21 (100)	16 (100)
CR, n (%)	19 (73)	14 (67)	13 (81)
PR, n (%)	5 (19)	7 (33)	3 (19)
6-month PFS, %	72	95	NR
9-month PFS, %	51	89	NR
1-year PFS, %	38	66	NR

*Efficacy-evaluable patients; †Cheson 2007 criteria

1.Forero-Torres et al. *Blood* Dec 2015; 126(26):2798-804.
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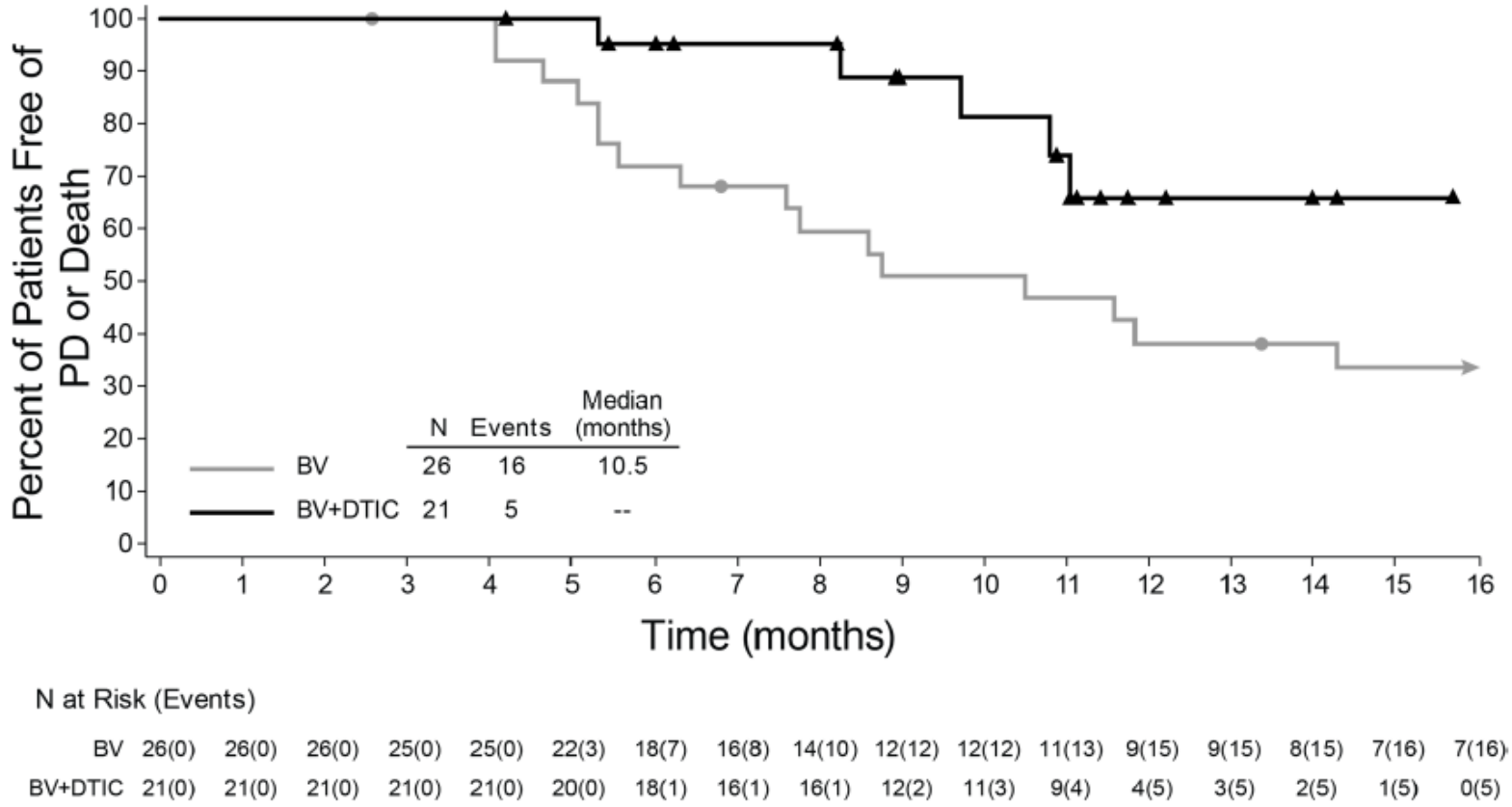
SGN35-015: Phase II trial of brentuximab vedotin alone and in combination in previously untreated HL pts aged ≥60 yrs (NCT01716806): Interim results

PFS:



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4. Forero-Tores A, et al. Blood, 2015; Sep 16 [Epub ahead of print]

SGN35-015: Phase II trial of brentuximab vedotin alone and in combination in previously untreated HL pts aged ≥60 yrs (NCT01716806): Interim results

Safety (n=69): Pts remaining on treatment (at October 8, 2015): brentuximab vedotin, 0; brentuximab vedotin + dacarbazine, 2 (9%); brentuximab vedotin + bendamustine, 11 (55%)[1]

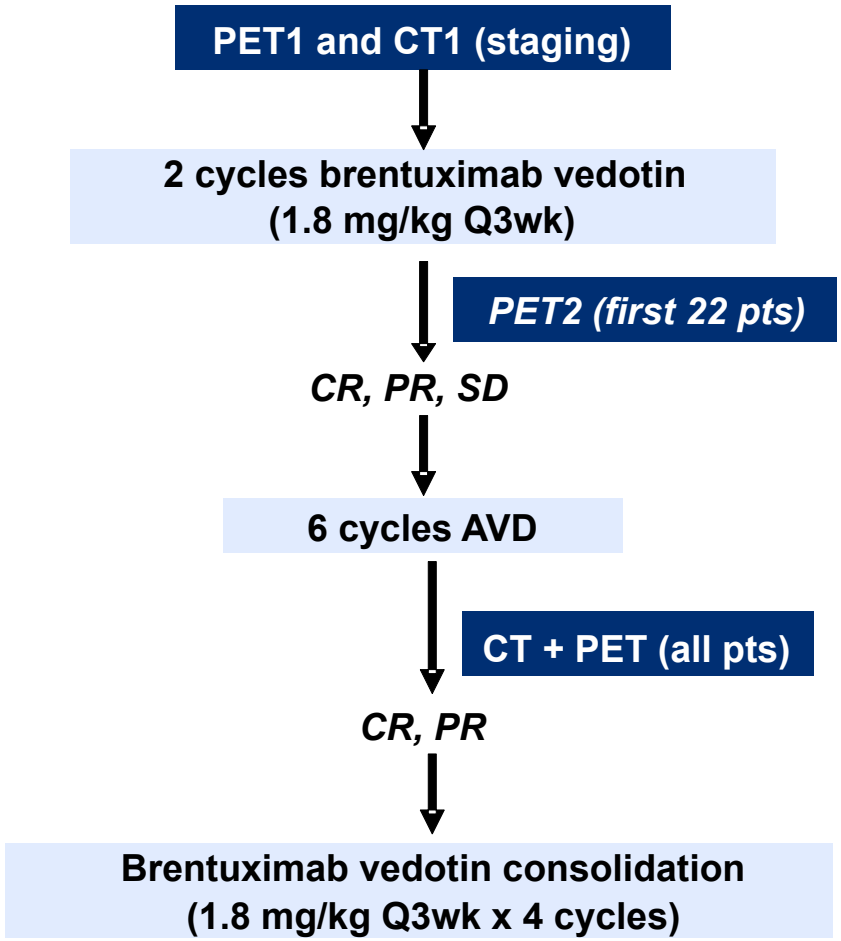
	Brentuximab vedotin (n=27)[1,3]	Brentuximab vedotin + dacarbazine (n=22)[1]	Brentuximab vedotin + bendamustine (n=20)[1]
Median cycles, n (range) Brentuximab vedotin Dacarbazine or bendamustine	 8 (3–23) –	 12.5* (2–20) 12 (1–12)	 3.5* (1–12) 3.5 (1–6)
AE leading to treatment discontinuation, n (%)	11 (41)	9 (41)	5 (25)
Death within 30-day safety period, n (%)	0	0	2† (10)
Any SAE, n (%)	6 (22)	2 (9)	12 (60)
Gr ≥3 treatment-related AE, n (%)	13 (48)	8 (36)	13 (65)
Most common Gr ≥3 AE	Sensory PN	Sensory PN	Fatigue, hypokalemia, sensory PN, UTI

*Ongoing single-agent brentuximab vedotin therapy
†Sudden death (unrelated to study treatment); Hodgkin's disease (unrelated to study treatment)

1.Forero-Torres et al. *Blood* Dec 2015; 126(26):2798-804.
2. Yasenchak CA, et al. ASH 2015, Poster presentation from Abstract #587
3. Ferero-Tores A, et al. ASH 2014, Abstract #294
4. Forero-Tores A, et al. Blood, 2015; Sep 16 [Epub ahead of print]

Phase II: multicenter study with brentuximab vedotin + AVD in older patients with untreated HL (NCT01476410)

Incorporation of brentuximab vedotin into frontline therapy



CGA, comprehensive geriatric assessment; CIRS-G, cumulative illness rating scale-geriatric; CT, computed tomography; FDG-PET, flurodeoxyglucose positron emission tomography; HRQL, health-related quality of life; IADL, Instrumental activities of daily living scale

Endpoints: *Primary:* CR rate after AVD

Patients: 26 elderly pts (≥60 yrs) with untreated advanced-stage HL

- Median 69 yrs (60–88); 15% ECOG PS 2; 92% stage III/IV; IPS median 4 (2–7); functional status: CIRS median 5 (52% grade 3–4), 8% geriatric syndrome, 8% loss IADLs

Study design:

- Window (lead in) study with brentuximab vedotin
- Tissue based studies
- CGA (CIRS-G) and HRQL assessments
- Study of "early" FDG-PET

Evens A et al. ICML 2015, Oral presentation from Abstract #89

Phase II: multicenter study with brentuximab vedotin + AVD in older patients with untreated HL (NCT01476410)

Efficacy: Efficacy population: 20 of 26 pts

Response, %	Post-brentuximab vedotin (x2 cycles)*	Post-AVD (x3 cycles)	Post-AVD (x3 cycles)
ORR	85	95	95
CR	30	70	95
ITT ORR		81	81
ITT CR		62	81

Safety:

- Median follow-up 14 mos; 92% pts alive; 95% of evaluable pts were disease free
- 6 pts were not evaluable for efficacy
  - 4 pts due to toxicity
    - 1 pt: treatment-related mortality due to pancreatitis
    - 3 pts: pneumonitis/diarrhea (brentuximab vedotin); hepatic (brentuximab vedotin); wound infection (cycle 1 AVD)
  - 1 pt withdrew consent
  - 1 pt refused therapy after 1 cycle ABVD (toxicity)
- Mean CIRS scores: 15 (11–19) vs 5 (0–14) for pts with vs without toxicity, respectively

CIRS, cumulative illness rating scale; ITT, intent-to-treat

Evens A et al. ICML 2015, Oral presentation from Abstract #89

Clinical Data in systemic anaplastic large cell lymphoma (sALCL)

Brentuximab vedotin, single agent

- in relapsed/refractory sALCL

SGN35-004: Phase 2 study of brentuximab vedotin in patients with rel/ref sALCL (NCT00866047)

Demographics and baseline characteristics

	N=58
Median age, years (range)	52 (14–76)
Gender	33 M / 25 F
ECOG performance status	
0	33%
1	66%
2	2%
ALCL confirmed by central pathology	97%
ALK-negative	72%
Refractory to frontline therapy	62%
Refractory to most recent treatment	50%
No response to any prior treatment	22%
Prior chemotherapy regimens*	2 (1–6)
Prior radiation	45%
Prior ASCT	26%

* Median (range)

Pro B, et al. J Clin Oncol 2012; 30:2190–6.

SGN35-004: Phase 2 study of brentuximab vedotin in patients with rel/ref sALCL (NCT00866047)

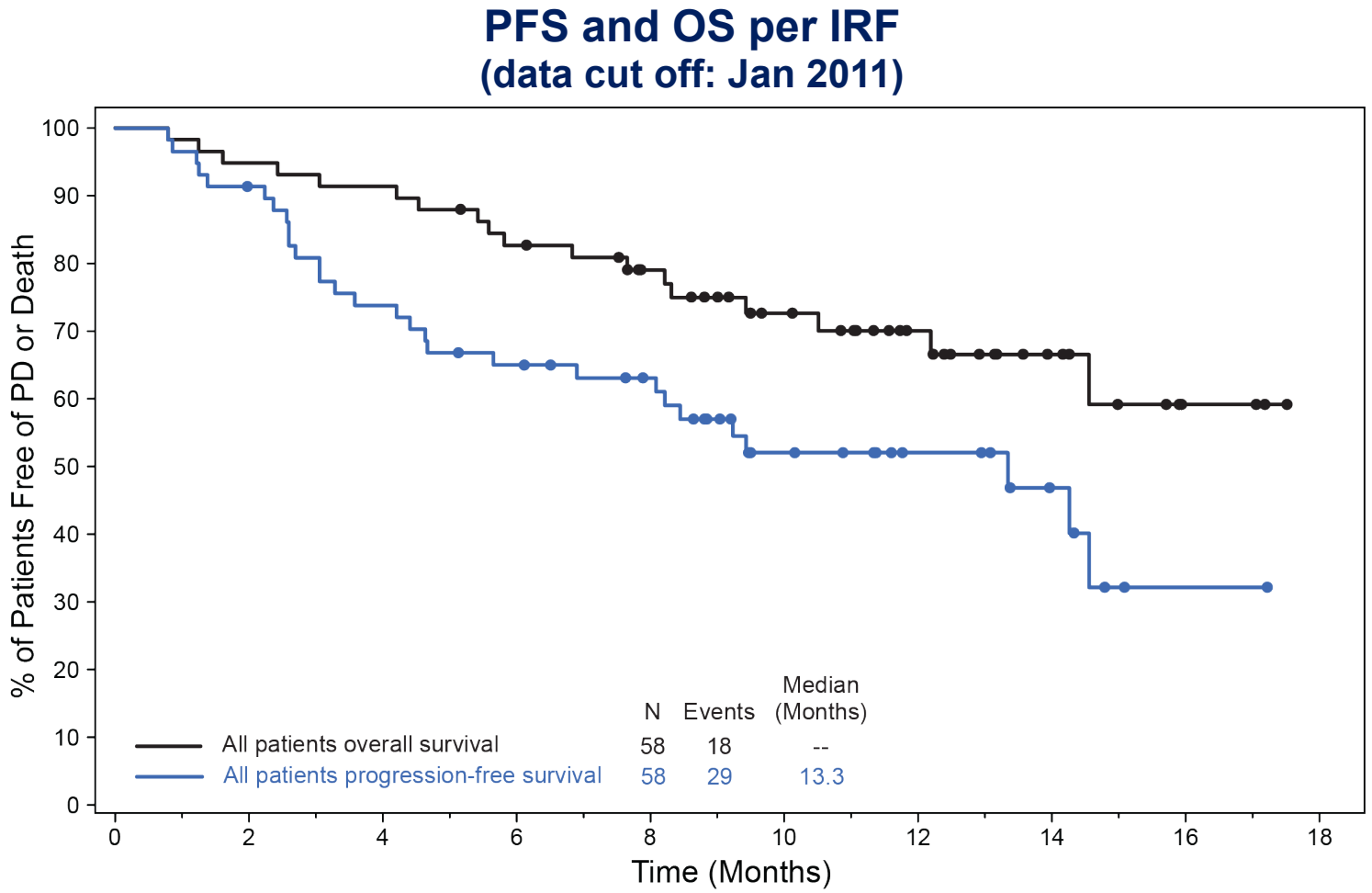
Response and outcomes
(data cut off: Jan 2011)

	IRF (N=58)
ORR, % (95% CI)	86 (74.6, 93.9)
CR, % (95% CI)	57 (43.2, 69.8)
PR, %	29
SD, %	3
PD, %	5
Histologically ineligible, %	3
NE, %	2
Median duration of OR, months (95% CI)	12.6 (5.7, NE)
Median duration of response in patients with CR, months (95% CI)	13.2 (10.8, NE)
Median PFS, months (95% CI)	13.3 (6.9, NE)
Median OS, months (95% CI)	NR (14.6, NE)
12-mo OS, %	70

NR = not estimable

Pro B, et al. J Clin Oncol 2012; 30:2190–6.

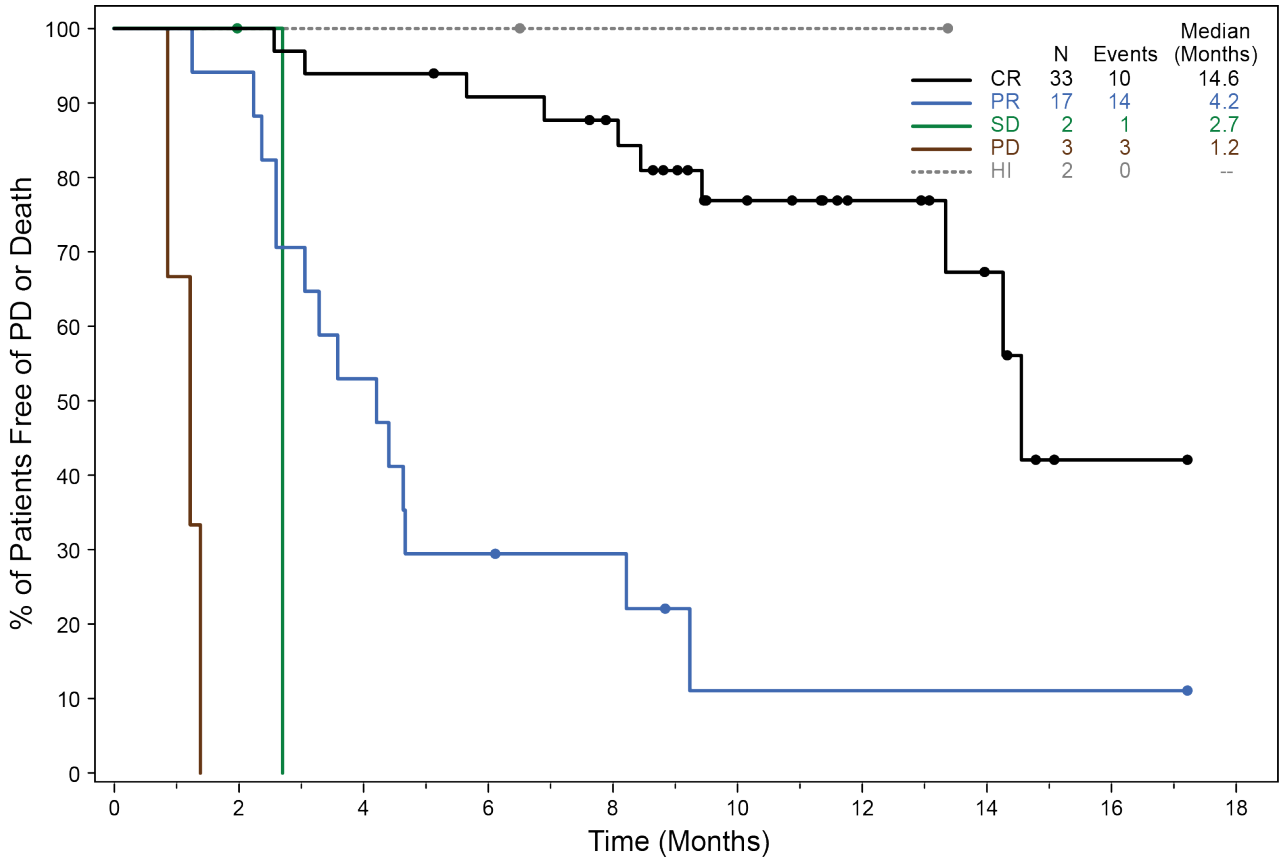
SGN35-004: Phase 2 study of brentuximab vedotin in patients with rel/ref sALCL (NCT00866047)



Pro B, et al. J Clin Oncol 2012; 30:2190–6.

SGN35-004: Phase 2 study of brentuximab vedotin in patients with rel/ref sALCL (NCT00866047)

PFS by best response, per IRF
(data cut off: Jan 2011)

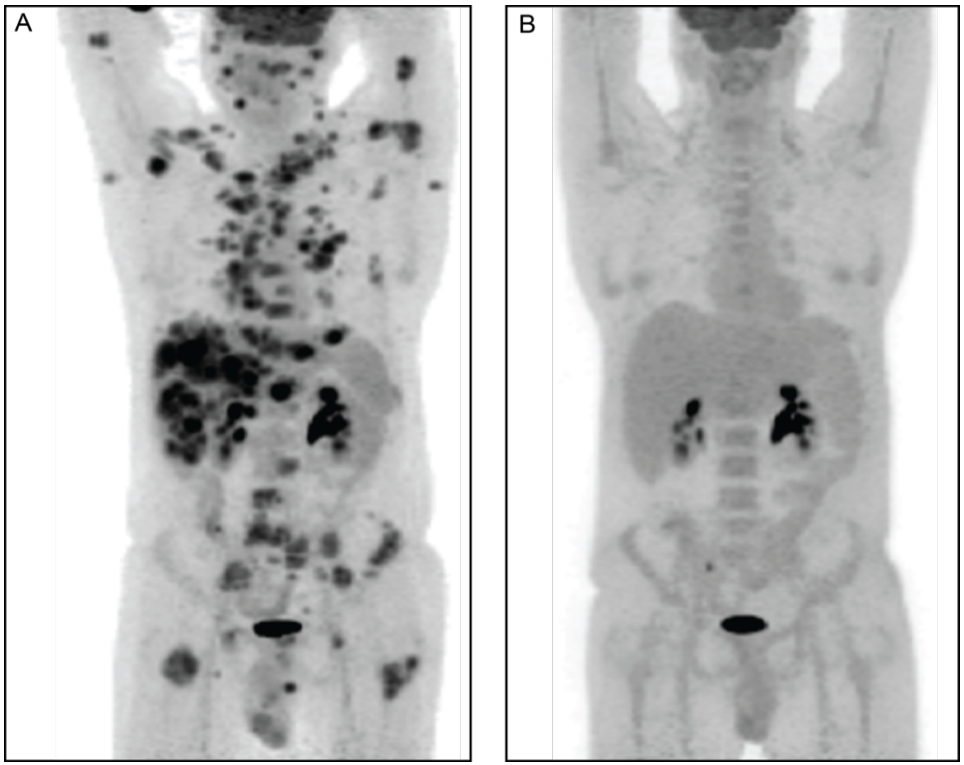


Pro B, et al. J Clin Oncol 2012; 30:2190–6.

SGN35-004: Phase 2 study of brentuximab vedotin in 58 patients with relapsed or refractory sALCL (NCT00866047)

Case study

Baseline **After 4 cycles**

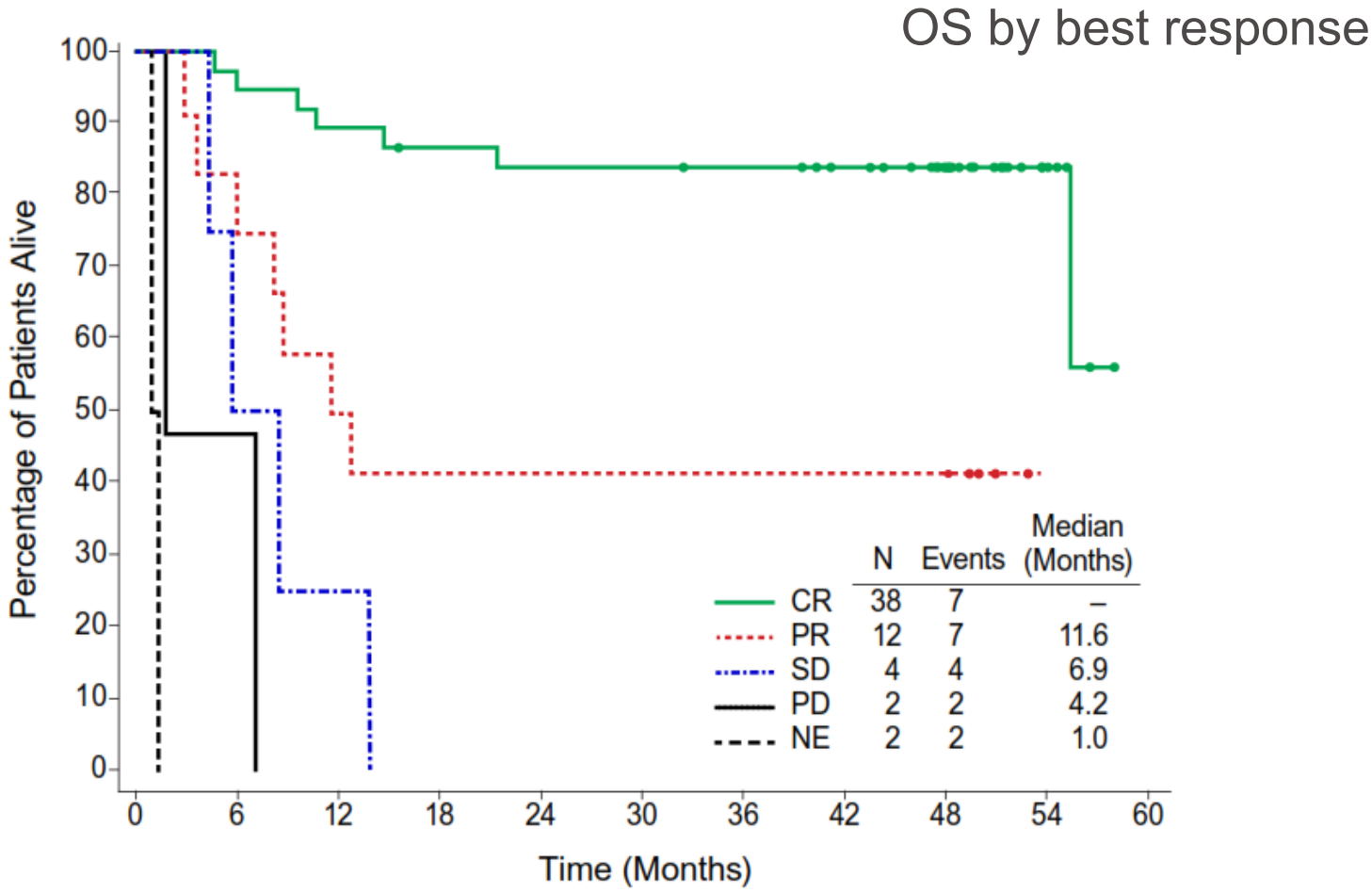


CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone
VAPEC B = doxorubicin, cyclophosphamide, etoposide, vincristine, and bleomycin

- 48-year-old male, ALK+ sALCL
- Prior treatment:
  - CHOP
  - VAPEC B
  - ASCT
- Cycle 4 restaging: CR
- Patient experienced tumor lysis syndrome after first dose, recovered
- Patient received 8 cycles in total

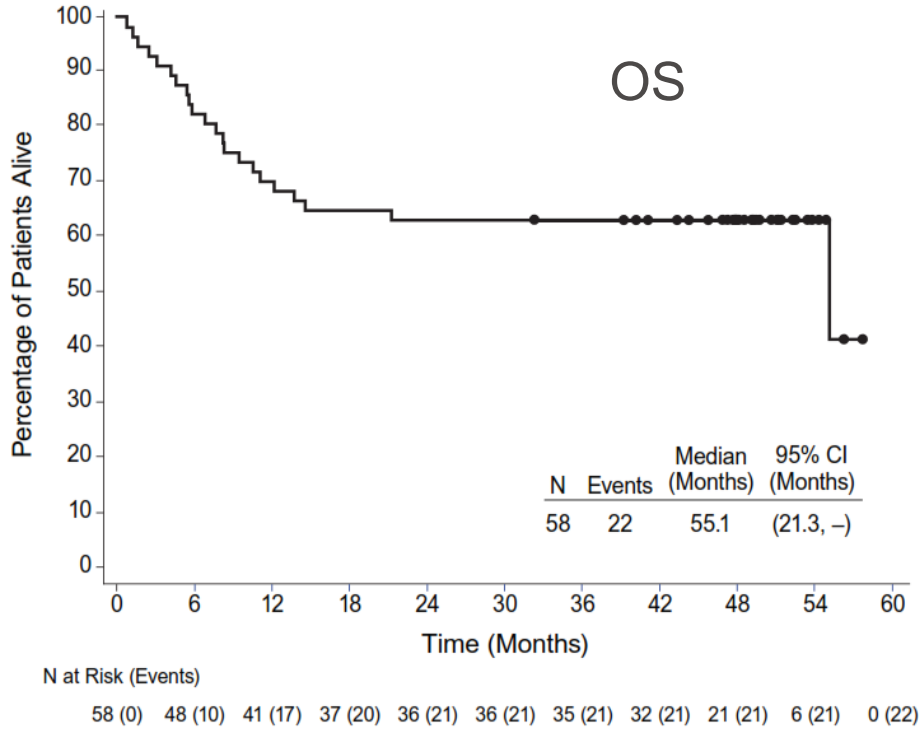
Pro B, et al. J Clin Oncol 2012; 30:2190–6.

SGN35-004: updated data from ASH2014



Pro et al, ASH014 (Abstract # 3095)

SGN35-004: updated data from ASH2014



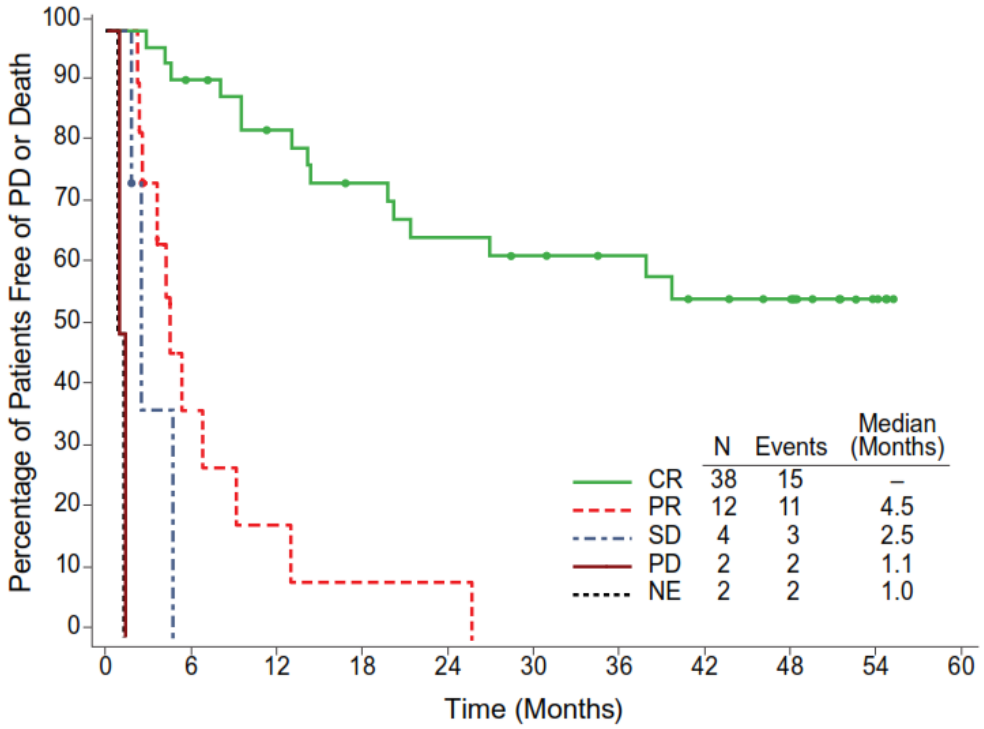
- 4-year OS: 64% (95% CI: 51%, 76%)

Pro et al, ASH014 (Abstract # 3095)

SGN35-004: updated data from ASH2014

- Median PFS by investigator: 20 mos (95% CI: 9.4, NE)
- 19/38 pts (50%) with CR per investigator remain progression-free
  - 11 pts received consolidative SCT
  - 8 pts received no further therapy

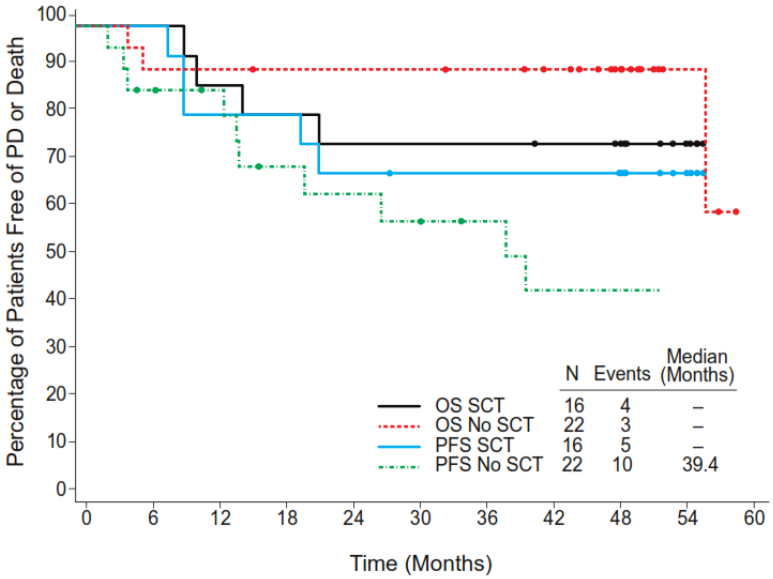
PFS by best response



Pro et al, ASH014 (Abstract # 3095)

SGN35-004: updated data from ASH2014

OS/PFS* by subsequent SCT in pts with CR



OS/PFS* by PET4 and ALK status

Status	4-yr PFS (95% CI)	4-yr OS (95% CI)
PET4 status		
PET+ (n=20)	16% (0%, 32%)	50% (28%, 72%)
PET- (n=28)	63% (44%, 83%)	86% (72%, 99%)
ALK status		
ALK+ (n=16)	37% (11%, 62%)	56% (32%, 81%)
ALK- (n=42)	38% (22%, 54%)	67% (52%, 81%)

- There were no differences in OS or PFS between pts undergoing allo-SCT (n=8) or ASCT (n=8)

* PFS by investigator

Pro et al, ASH014 (Abstract # 3095)

Summary

- CD30 is an ideal target, owing to its dense expression by malignant cells and limited expression in normal tissue
- ADCs can overcome limitations of previous constructs
- Brentuximab vedotin is an anti-CD30 ADC with significant activity in R/R ALCL and others CD30+ lymphoma
- Retreatment is possible and associated with significant activity

ADC – antibody drug conjugate; R/R – relapsed/refractory; ALCL – anaplastic large cell lymphoma

Bartlett NL, et al. ASCO 2012. Abstract 8027.

Re-Treatment

SGN35-006: Phase 2 study of brentuximab vedotin retreatment in patients with CD30+ hematologic malignancies with a prior response (NCT00947856)

Eligibility

- Relapsed CD30+ hematologic malignancy
- Achieved CR or PR with brentuximab vedotin in a prior study
- Discontinued prior study with brentuximab vedotin when in remission
- Subsequent disease progression/relapse

Treatment (N=24)*

- Brentuximab vedotin 1.2 or 1.8 mg/kg IV Q3wk
- No maximum number of cycles
- Frequency of restage per institutional SOC
- Best response assessed by investigator; based on Cheson 2007

Objectives

To investigate whether patients who previously responded to brentuximab vedotin could achieve another remission with retreatment

*Study ongoing
SOC = standard of care

Forero-Torres A, et al. Poster presentation at EHA 2012, Amsterdam, Netherlands (Abstract #1166);

SGN35-006: Phase 2 study of brentuximab vedotin retreatment in patients with CD30+ hematologic malignancies with a prior response (NCT00947856)

Baseline characteristics N=29

	HL patients (n = 21)	ALCL patients (n= 8)*
Median age at retreatment, y (range)	30 (16, 65)	51.5 (24, 72)
ECOG performance status at retreatment baseline, n (%)		
0/1	8 (38)/ 12 (57)	3 (38)/ 4 (50)
2	1 (5)	1 (13)
Median number of systemic therapies prior to retreatment,[e] n (range)	4 (2–12)	3 (2, 6)
Time between last brentuximab vedotin dose on prior study and first dose of retreatment (months, range)	11.4 (4, 45)	4.7 (2, 15)
Number of patients with intervening systemic therapies, n (%)	6 (21)	0
Best response to prior brentuximab vedotin treatment,% SD/PD/ unknown	1 (17)/ 4 (67)/ 1 (17)	-/-/-
Disease status relative to most recent prior therapy, n (%)		
Refractory	5 (24)	0
Relapse after response	16 (76)	8 (100)

*(5/8 ALK-negative, ECOG=Eastern Cooperative Oncology Group, PR=partial remission, SD=stable disease

Bartlett et al, JhemOnc2014c

SGN35-006: Phase 2 study of brentuximab vedotin retreatment in patients with CD30+ hematologic malignancies with a prior response (NCT00947856)

Response

Parameters	HL patients (n = 20)	ALCL patients (n= 8)
Objective response rate (CR+PR), % (95% CI)	12 (60)	7 (88)
Best Clinical Responses [a] n (%)		
CR	6 (30)	5 (63)
PR	6 (30)	2 (25)
SD/PD	4 (20)/ 4 (20)	0/1 (13)
95% CI for ORR[b]	36.1, 80.9	47.3, 99.7
95% CI for CR rate[b]	11.9, 54.3	24.5, 91.5
Duration of objective response in patients (months) [c]	12 (60)	7 (88)
Median duration of objective response months[c] (median 95%CI)	9.2 (2.1, −)	12.3 (6.6, −)
Duration of response for patient with CR, (months) [c]	6 (30)	5 (63)
Median duration of response for patient with CR, (median 95%CI)	9.4 (1.7, 14.2)	12.9 (7.4,-)
PFS months e (median 95%CI)[d]	9.9 (3.4, 13.4)	12.9 (1.4, 18.5)
OS months e (median 95%CI) [d]	- (11.4, −)	- (3.3, −)

Analysis excludes the second retreatment for 3 systemic anaplastic large cell lymphoma patients.[a]Best response (according to Cheson 2007) prior to the start of any new antitumor treatment, exclusive of stem cell transplant. [b]Two-sided 95% exact confidence interval (CI), computed using the Clopper-Pearson method (1934). [c]Duration of response is calculated from the earliest occurrence of either complete or partial remission. [d]Computed using the log-log transformation method of Collett (1994). [e] As estimated using Kaplan-Meier methods

Bartlett et al, JhemOnc2014

SGN35-006: Phase 2 study of brentuximab vedotin retreatment in patients with CD30+ hematologic malignancies with a prior response (NCT00947856)

Safety: The median number of brentuximab vedotin cycles was 7 (range, 2-37). The median duration of retreatment was 5 months (range, 1- 38).

Most Common (≥20%)Treatment-Emergent AE

AE (n, %)	Grade 3	Grade 4
Any events	8 (28)	3 (10)
Peripheral sensory neuropathy	2 (7)	0
Peripheral motor neuropathy	2 (7)	0
Nausea	1 (3)	0
Fatigue	3 (10)	1 (3)
Anemia	5 (17)	0
Arthralgia	2 (7)	0
Back pain	1 (3)	0
Dyspnea	1 (3)	1 (3)

Bartlett et al, JhemOnc2014c

Clinical data in Graft versus Host Disease (GVHD)

Patients with R/R HL have received brentuximab vedotin pre and post allogeneic transplant

Retrospective analysis: Patients with R/R HL who received reduced intensity Allo-SCT post brentuximab vedotin

- Clinical outcomes

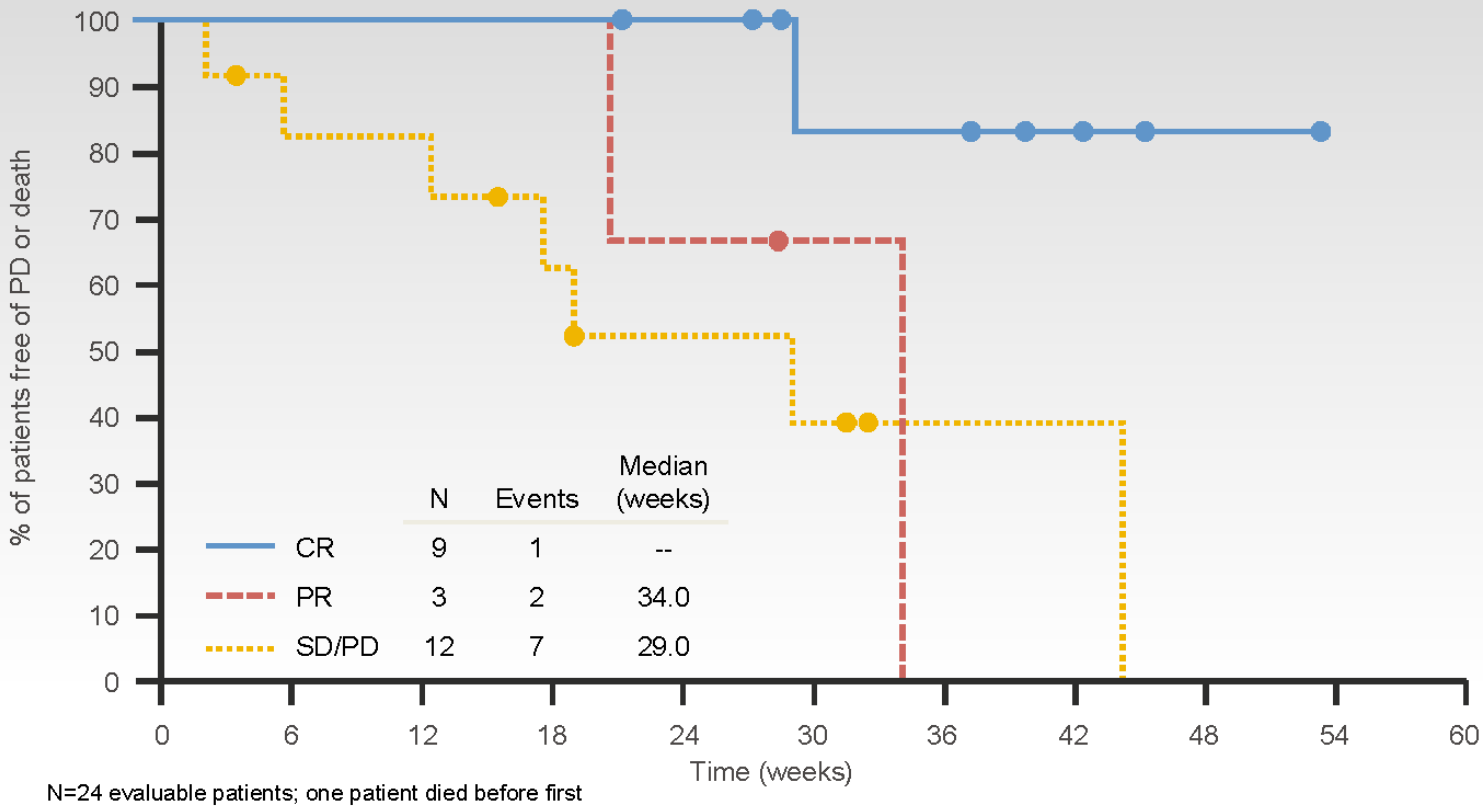
	N=19
Median follow-up, months	25.6
2 - year OS, %	79.3 (CI: 56.0, 91.1)
2 - year PFS, %	59.3 (CI: 43.9, 71.7)
2 – year PFS in CR patients, %	71.4 (CI: 40.3, 88.3)
2 - year PFS in non-CR patients, %	54.6 (CI: 37.5, 68.9)

R/R, relapsed/refractory; HL, Hodgkin lymphoma; Allo-SCT, allogeneic stem cell transplantation; OS, overall survival; PFS, progression free survival; CR, complete response

Chen R et al. Oral presentation at ICML 2013, Lugano, Switzerland (Abstract #140).

Treatment with brentuximab vedotin post allo-SCT

- PFS by response to brentuximab vedotin



N=24 evaluable patients; one patient died before first response assessment.

PFS, progression free survival; allo-SCT, allogeneic stem cell transplantation; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

Gopal AK et al. Blood. 2012;120:560–68

Phase I multicenter trial: brentuximab vedotin for steroid refractory acute graft vs host disease (GVHD)

Objectives: *Primary:* MTD of brentuximab vedotin treatment for steroid refractory GVHD

Patients: 24 pts treated (progressive acute GVHD on corticosteroid therapy, n=18; flare of symptoms upon tapering of steroids, n=6). Median age was 55 years (range, 33–72); donor types included: 17 MUD/MRD, 5 MMUD and 2 UCB; conditioning was 16 RIC and 8 MAC

Dose and schedule: 3+3 cohort design with 3 doses of brentuximab vedotin administered (initially 0.6 mg/kg, n=3, then 0.9 mg/kg, n=3) weekly followed by maintenance dosing with a 4 week DLT period. Revised to escalating cohorts of 5 pts treated with 4 doses of brentuximab vedotin administered every 2 weeks with a DLT period of 8 weeks; 18 pts were treated with revised regimen (0.6 mg/kg, n=10; 0.8 mg/kg, n=8)

MTD: 0.8 mg/kg IV every two weeks

DLT: Neutropenia (n=1; 0.8 mg/kg)

Safety: AE Gr ≥3 included thrombocytopenia (n=1), fatigue (n=1) and ileus (n=1). 2/6 developed neutropenia and died

Efficacy: ORR at day 28 was 37.5% (12.5% CR, 25% VGPR). Of 4 pts with SD at day 28, 2 pts achieved CR and VGPR (n=1 each) after day 28.

•At median follow-up of 12.9 months, 9/24 pts were alive

Chen YB, et al. ASH 2015, Poster presentation from Abstract #1930

Conclusions

- The addition of brentuximab vedotin prior to allogeneic transplantation does not appear to adversely affect engraftment, GVHD, or mortality
- Brentuximab vedotin may provide sufficient disease control for selected patients to proceed to allo SCT
- Brentuximab vedotin is active in HL patients who relapse after allo SCT
- Treatment with brentuximab vedotin was associated with manageable AEs similar to those in the pivotal trial

GvHD, graft verses host disease; SCT, stem cell transplantation; HL, Hodgkin lymphoma; AE, adverse events

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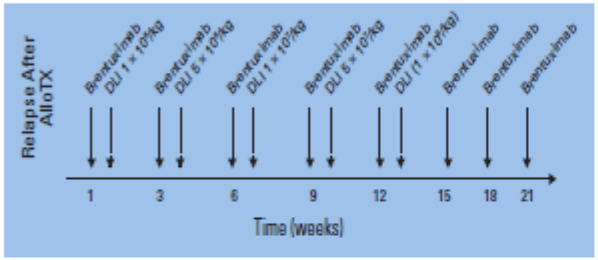
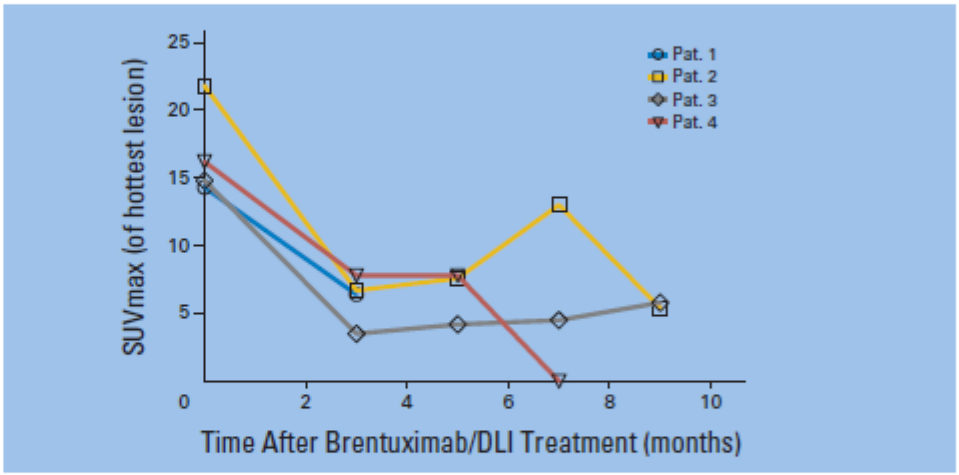
BV PLUS DLI FOR RELAPSE AFTER ALLOSCT



Theurich, JCO 2013



CONCLUSION

BV/DLI is effective in HL pts not cured by allo-transplant

Preclinical data imply that targeting CD30 on T cells may abrogate GVHD