rete oncologica
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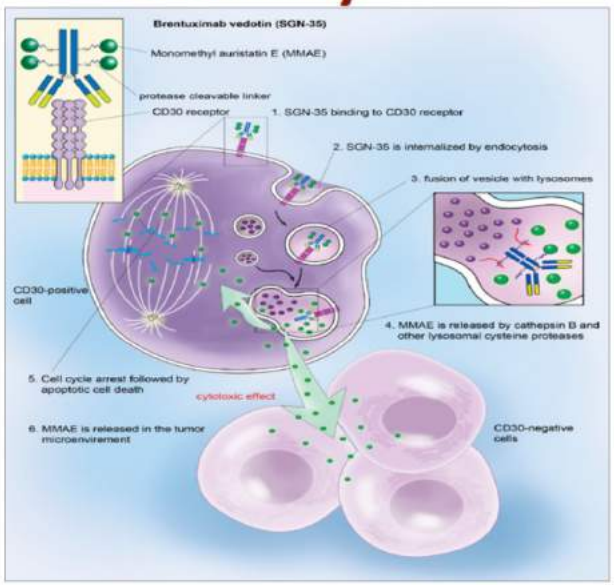
Riunione Rete Oncologica Piemonte

Torino 20 marzo 2019

Linfoma di Hodgkin nel paziente anziano
Nuovi farmaci

Nuovi farmaci HD anziano

Brentuximab Vedotin: Anti-CD30 Monoclonal Antibody



SGN35-015: Brentuximab Vedotin for Older Pts

- Retrospective efficacy/safety analysis of brentuximab vedotin for **relapsed** CD30-positive lymphomas (N = 366)
- Pts ≥ 60 yrs with HL, n = 16
  - ORR: 56% (CR: 38%)
  - Median OS: 12.4 mos
  - Median PFS: 9 mos
- Only number of preexisting AEs predicted grade ≥ 3 treatment-emergent toxicity in pts ≥ 60 yrs

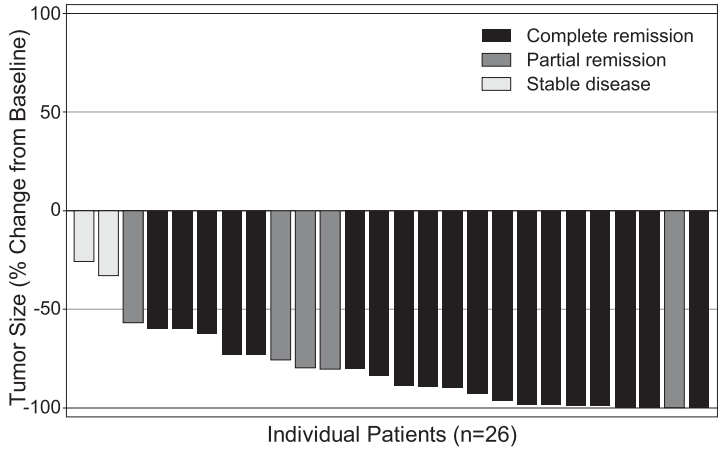
Characteristic*	≥ 60 Yrs (n = 40)	< 60 Yrs (n = 326)
Median age, yrs	66	32
ECOG PS 0/1/2, %	33/63/5	49/49/2
Median CrCl, mL/min/1.73 m^2	80.9	130.5
Median preexisting AEs, n	11.0	6.0
Median concomitant medications prior to study, n	7.5	4.0
Safety outcome, %		
▪Anemia	30	10
▪Peripheral sensory neuropathy	60	46
▪Fatigue	58	43
▪Any grade ≥ 3 TEAE	70	56

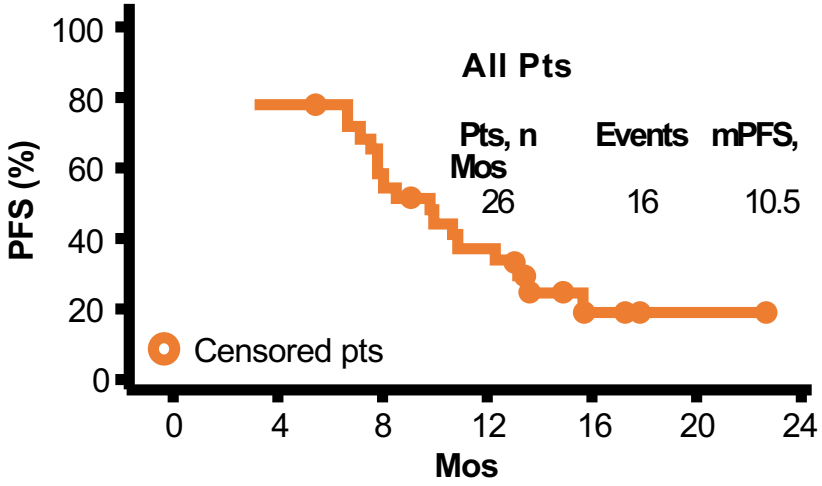
*For pts with ALCL, HL, PTCL-NOS, or gray-zone lymphoma.

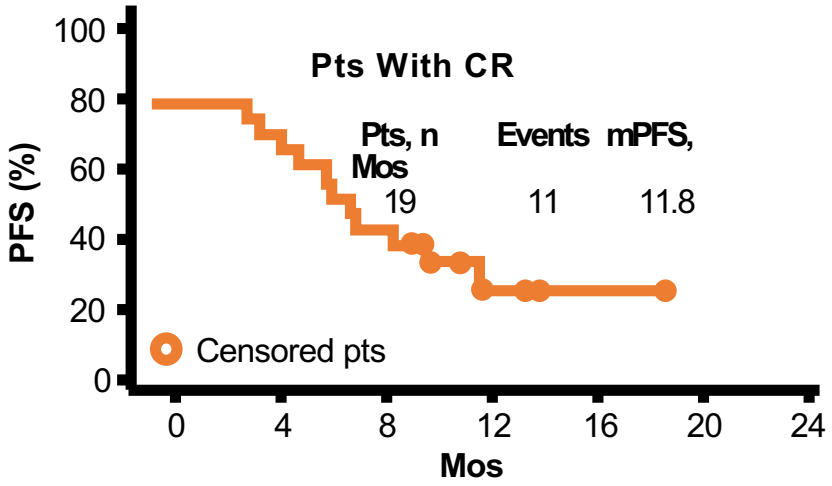
Gopal AK, et al. Leuk Lymphoma. 2014;55:2328-2334.

First-line Brentuximab Vedotin in Elderly Pts With HL

- Single-arm phase II study of first-line brentuximab vedotin 1.8 mg/kg Q3W in HL pts 60 yrs of age or older (N = 27)
  - Median age: 78.0 yrs; stage III/IV disease: 63%
  - ORR: 92% (CR: 73%)
  - Grade 3 neuropathy: 30%





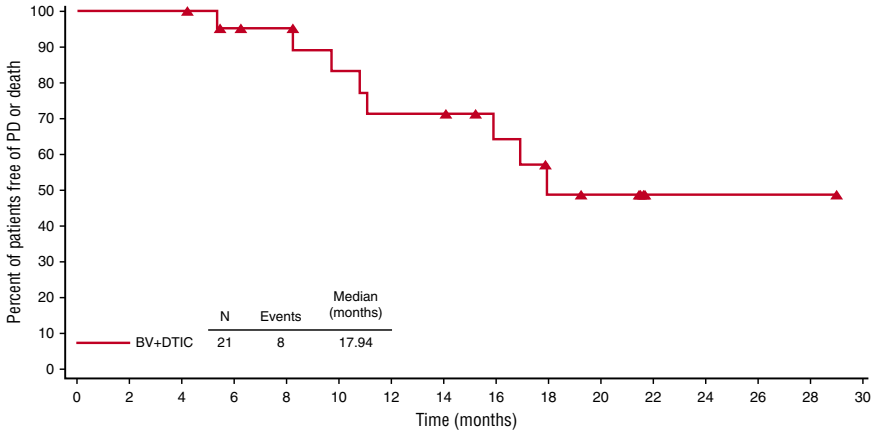


Forero-Torres A, et al. Blood. 2015;126:2798-2804.

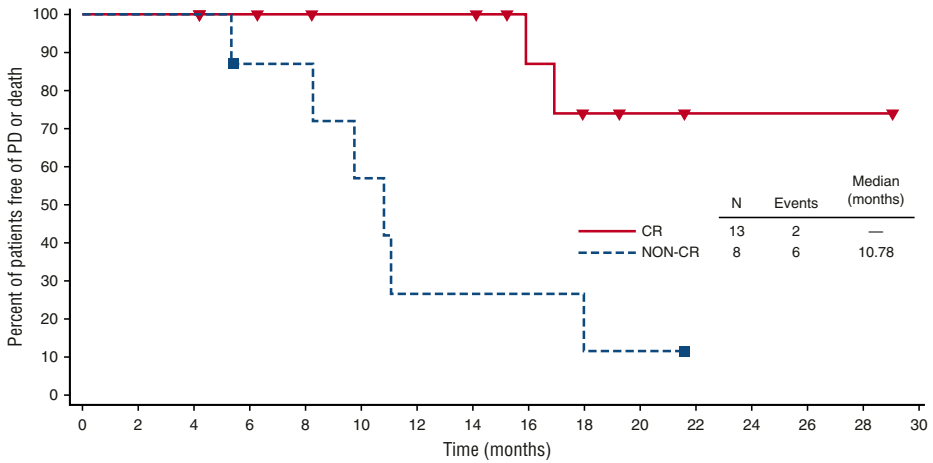
First-line Brentuximab Vedotin With Dacarbazine or With Bendamustine in Older Pts With HL

- Nonrandomized phase II study evaluating BV 1.8 mg/kg + dacarbazine 375 mg/m^2 (n = 22) or BV 1.8 mg/kg + 90/70 mg/m^2 bendamustine (n = 20)
  - **BV + bendamustine discontinued after 65% experienced serious AE (including 2 deaths)**
  - ORR—BV + dacarbazine: 100% (CR: 62%); BV + bendamustine: 100% (CR: 88%)
  - Grade 3 neuropathy—BV + dacarbazine: 27%; BV + bendamustine: 15%

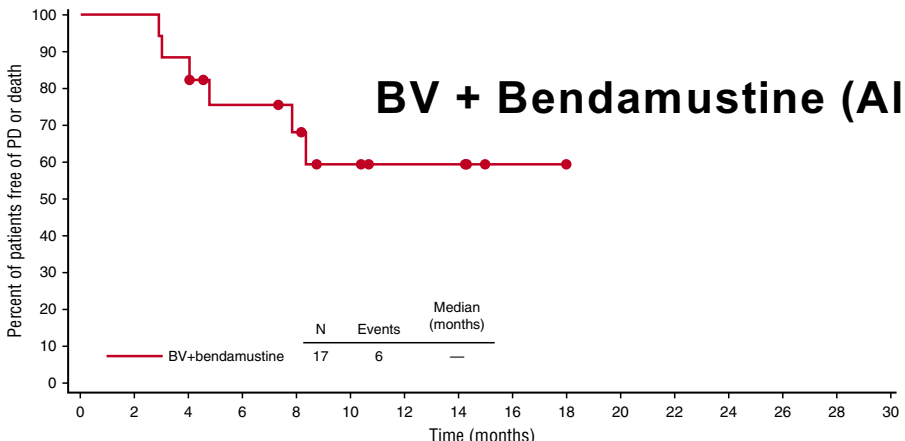
BV + Dacarbazine (All Pts)



BV + Dacarbazine (CR vs Non-CR Pts)



BV + Bendamustine (All Pts)



Friedberg JW, et al. Blood. 2017.

Studio di fase I/II di valutazione della sicurezza e dell'efficacia di un nuovo trattamento di prima linea del Linfoma di Hodgkin nel paziente anziano che prevede l'associazione di Adcetris® e Levact®

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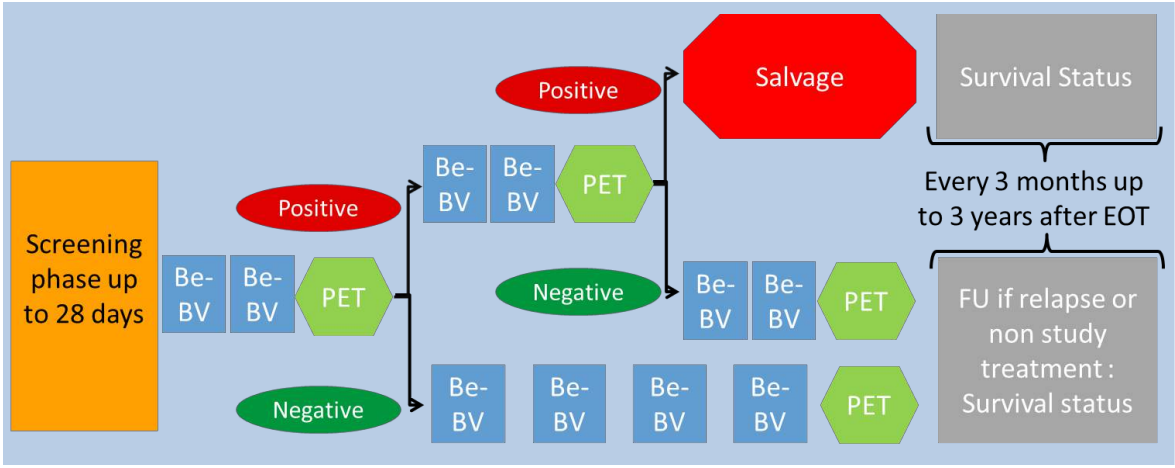
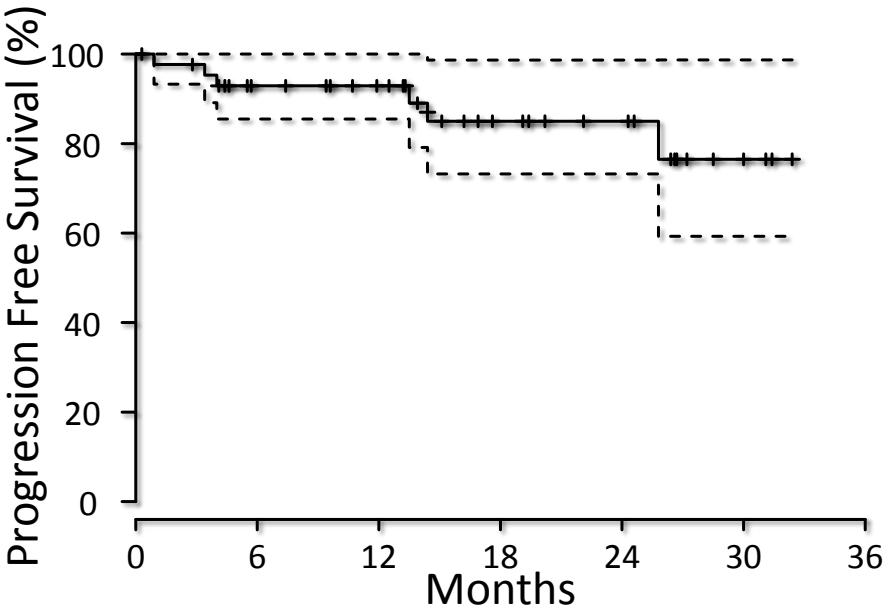


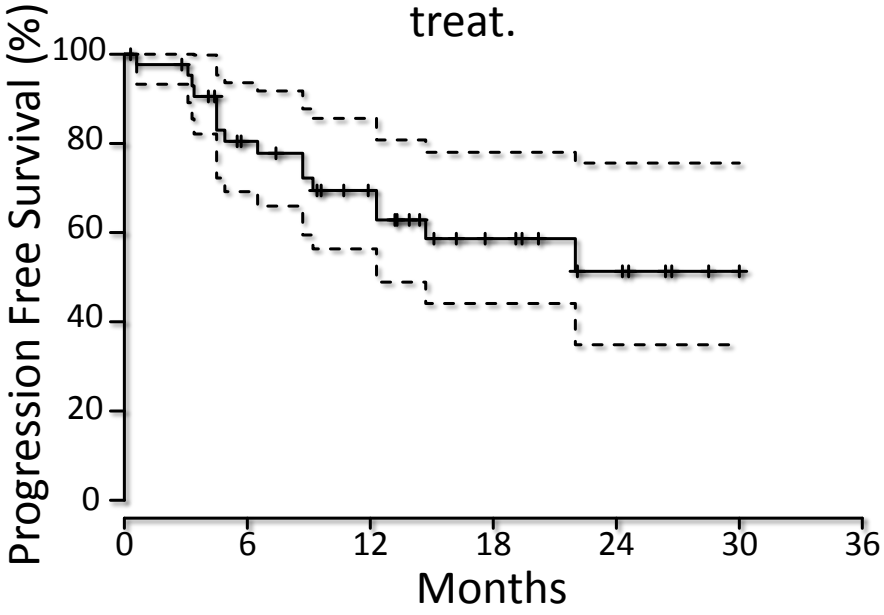
Evaluated treatment cycle			
Deauville score	Cycle 2 (n=44)	**Treatment Response**	End of TRT (n=44)
1-3	35 (85%)	**CR (score 1-3)**	29 (66%)
4	5 (12%)	**PR (score 4)**	2 (5%)
5	1 (3%)	**NR/Pro**	9 (20%)
NE	3* (8%)	**NE**	4**(9%)

Studio di fase I/II di valutazione della sicurezza e dell'efficacia di un nuovo trattamento di prima linea del Linfoma di Hodgkin nel paziente anziano che prevede l'associazione di Adcetris® e Levact®

1) Overall Survival: Intention to treat.



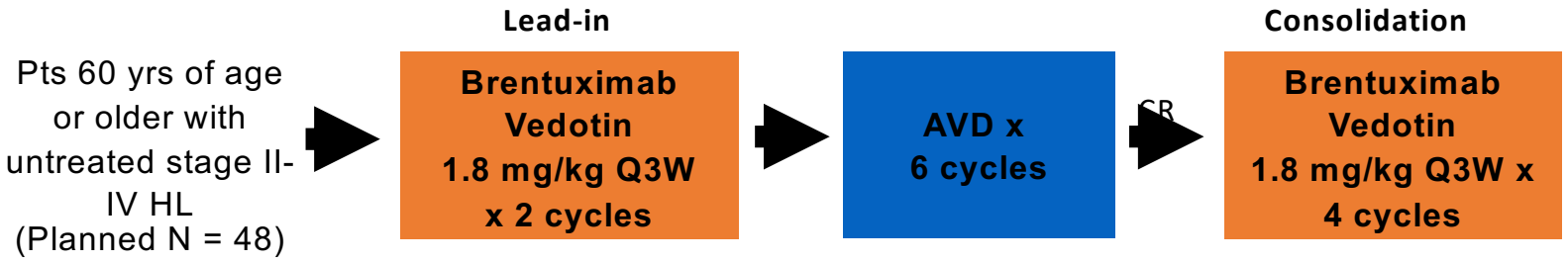
2) Progression Free Survival: Intention to treat.



- **Toxicities grade 3,4 : No platelet or erythrocyte cells transfusion were required during treatment.**
- **No neuropathy occurred during treatment**

Efficacy and Safety Outcomes With Sequential Brentuximab Vedotin/AVD

- Single-arm, multicenter, open-label phase II trial



- Primary endpoint: CR rate by FDG-PET after AVD, prior to consolidation
- Tissue-based studies, CGA (CIRS-G), and HRQoL assessments

Evens AM, et al. ISHL 2016.

Efficacy and Safety Outcomes With Sequential Brentuximab Vedotin/AVD

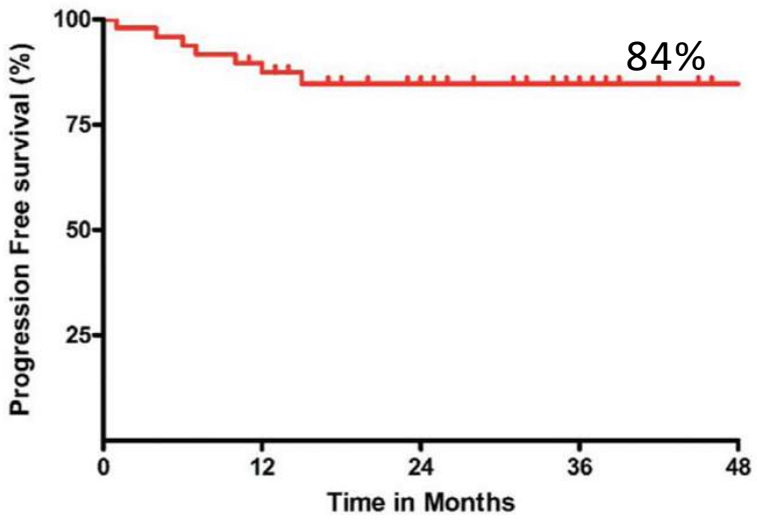
- Evaluable pts (n =48):
  - Median age: 69 (60-88)
  - Stage III-IV 60%
  - Median CIRS-G 7
  - 77% completed 6 AVD and 73% at least 1 BV consolidation

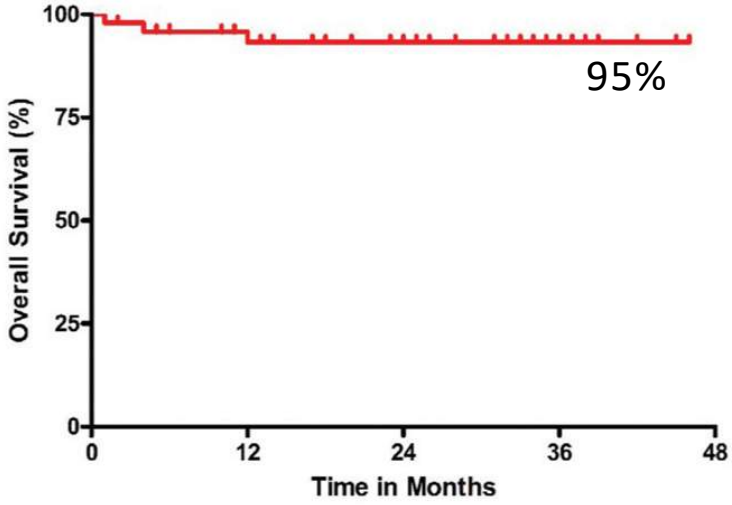
- After 2 “lead-in” cycles of BV—ORR: 82% (CR: 36%)
- After 6 cycles of AVD—ORR: 95% (CR: 90%)

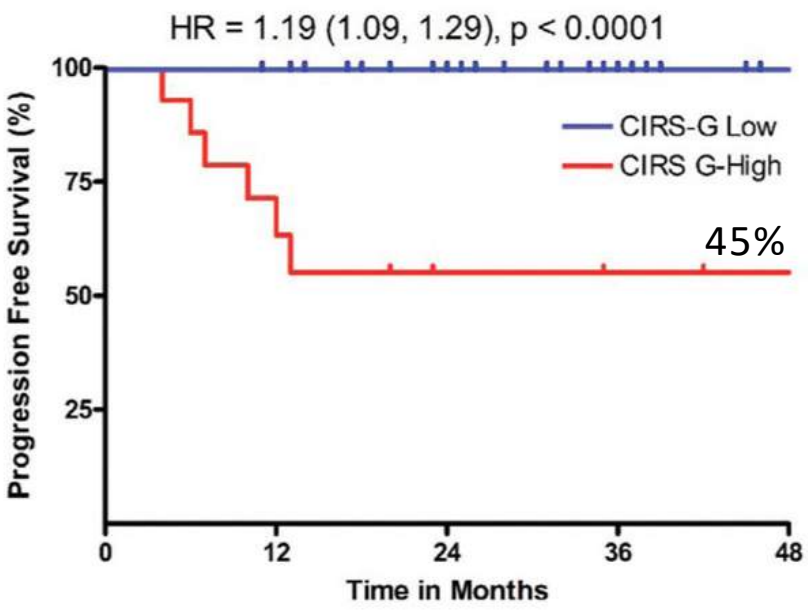
- Grade 3/4 AEs occurring in 20/48 pts (42%):
  - Neutropenia 44%
  - Pneumonia 8%
  - Neuropathy 4%

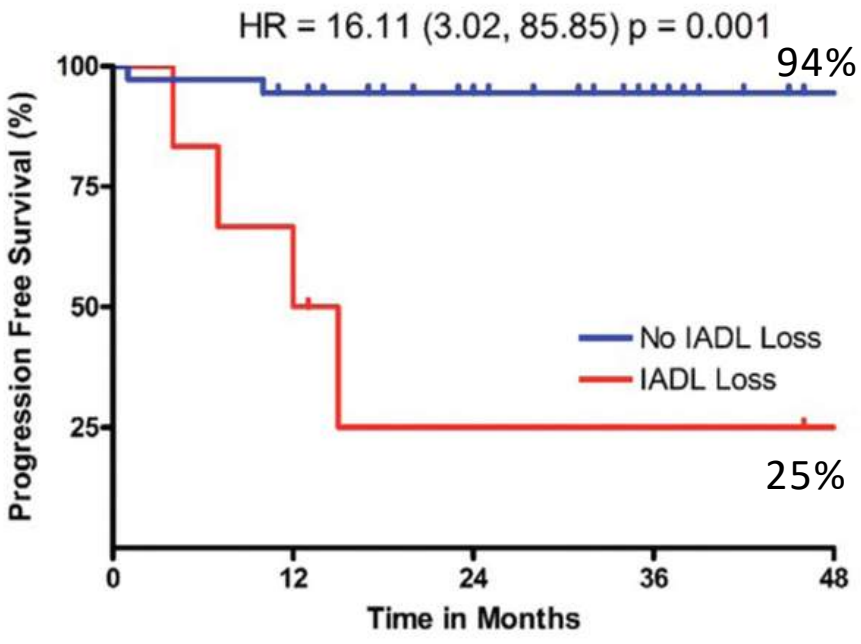
Evens AM, et al. ISHL 2018. Abstract P001.

Efficacy and Safety Outcomes With Sequential Brentuximab Vedotin/AVD





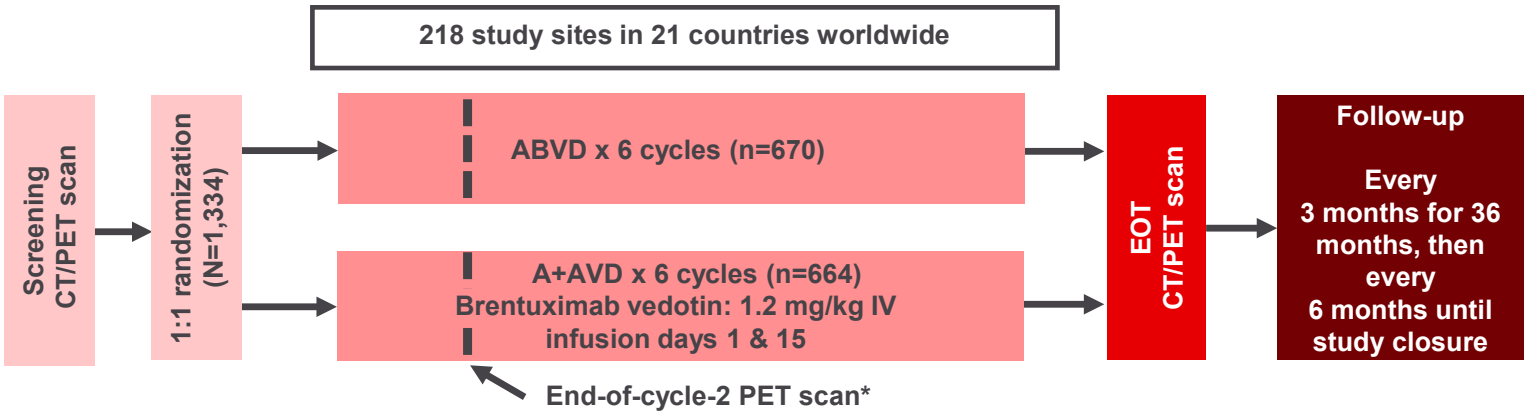




Evens AM, et al. ISHL 2018. Abstract P001.

Older patients with previously untreated classical Hodgkin lymphoma: A detailed analysis from the phase 3 ECHELON-1 study

Figure 1. ECHELON-1 study design



*Patients with Deauville 5 per IRF at PET2 were permitted to switch to an alternative frontline therapy at physician's discretion (this switch was not counted as a modified PFS event).

Older patient (≥60 years) sub-analyses

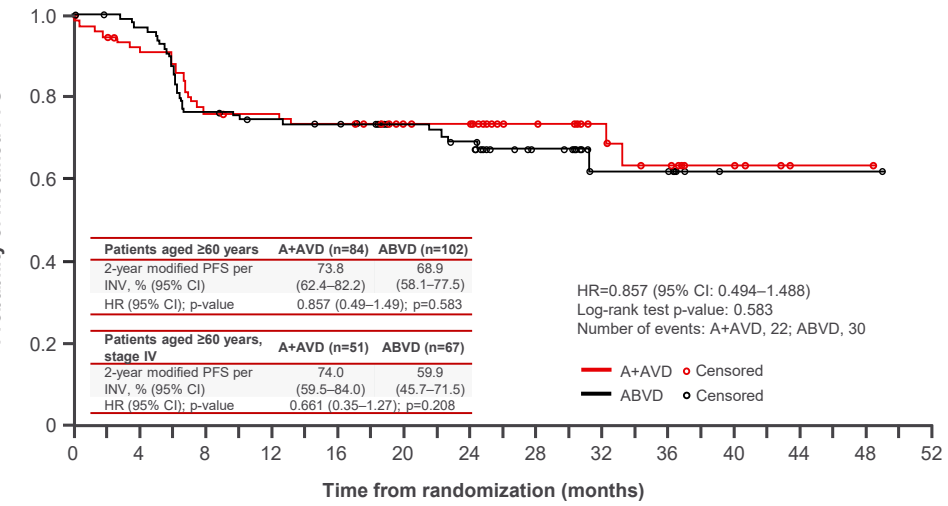
- Key secondary endpoint: overall survival (OS).
- Prespecified subgroup analysis: modified PFS per IRF for patients aged ≥60 years; modified PFS was defined as time to progression, death, or modified event (defined as evidence of non-CR [Deauville score ≥3] after completion of frontline therapy, followed by subsequent anticancer therapy [chemotherapy and/or radiotherapy]).[15]
  - ECHELON-1 was not powered for age-based subgroup analyses; p values are descriptive, without multiplicity adjustment.
- Exploratory analyses included PFS per investigator assessment for patients aged ≥60 years and safety in treated patients ≥60 years.

Older patients with previously untreated classical Hodgkin lymphoma: A detailed analysis from the phase 3 ECHELON-1 study

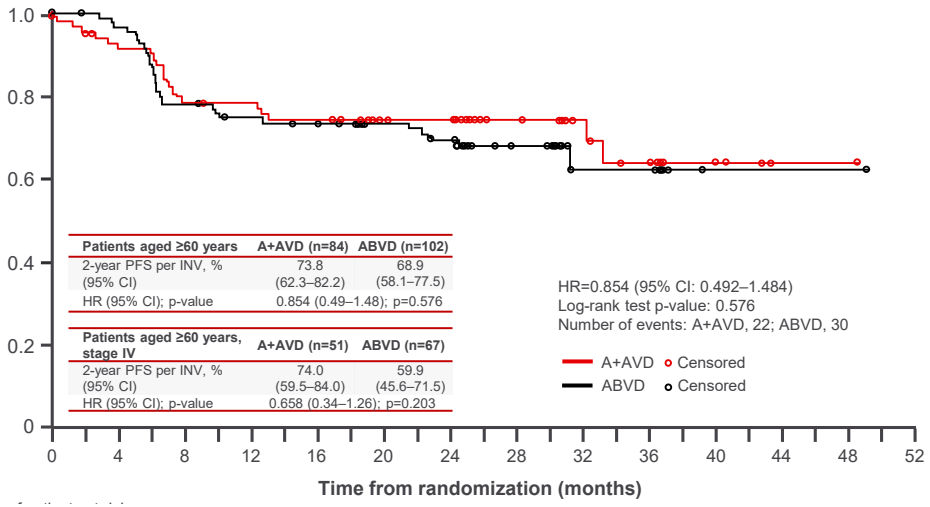
Table 1. Baseline characteristics of older patients

	Patients aged ≥60 years		ITT population (all ages)	
	A+AVD (n=84)	ABVD (n=102)	A+AVD (n=664)	ABVD (n=670)
Median age, (range)	68 (60–82)	66 (60–83)	35 (18–82)	37 (18–83)
Male, %	65	63	57	59
White, %	90	90	84	83
Ann Arbor stage, %				
III	37	34	36	37
IV	61	66	64	63
ECOG PS score, %				
0	36	36	57	57
1	52	54	39	39
2	12	10	4	4

mPFS per investigator in patients aged ≥60 years



PFS per investigator in patients aged ≥60 years



Older patients with previously untreated classical Hodgkin lymphoma: A detailed analysis from the phase 3 ECHELON-1 study

	Patients aged ≥60 years evaluable for safety* (n=181)		Patients aged <60 years evaluable for safety* (n=1,140)	
	A+AVD (n=83)	ABVD (n=98)	A+AVD (n=579)	ABVD (n=561)
Grade ≥3 AEs, n (%)	73 (88)	78 (80)	476 (82)	356 (63)
Fatal AEs, n (%)	3 (4)	5 (5)	6 (1)	8 (1)
Grade ≥3 neutropenia, n (%)	58 (70)	58 (59)	372 (64)	259 (46)
Any-grade FN on study, n (%)	31 (37)	17 (17)	97 (17)	35 (6)
Any-grade pulmonary AEs, n (%)	2 (2)	13 (13)	10 (2)	31 (6)

•Among older patients (≥60 years) in ECHELON-1, modified PFS and PFS findings were comparable between treatment groups.

•Overall, older patients in the ECHELON-1 study exhibited a higher incidence of treatment-emergent AEs than the younger patient group.
– Theincidence of pulmonary toxicities was lower in the A+AVD arm compared with the ABVD arm.

- The use of G-CSF primary prophylaxis was not mandated on study.
- The high incidence of FN in older A+AVD patients points to the need for administration of G-CSF primary prophylaxis.
- Within each arm,the rates of any-grade PN were similar between older and younger patients; however, the incidence of grade 3/4 PN was higher in older patients treated with A+AVD.

B-CAP (brentuximab vedotin, cyclophosphamide, doxorubicin and predniso(lo)ne) in Older Patients with Advanced Stage Hodgkin Lymphoma: Results of a Phase II Intergroup Trial By the German Hodgkin Study Group (GHSG) and the Nordic Lymphoma Group (NLG)

Abs 926

Boris Böll, Alexander Fosså, Helen Görgen, Peter Kamper, Sirpa Leppä, Daniel Molin, Julia Meissner, Ellen Ritter, Jacob Haaber, Martin Hutchings, Michael Fuchs, Andreas Engert, Carsten Kobe, and Peter Borchmann on behalf of the German Hodgkin Study Group and the Nordic Lymphoma Group

GHSG

German Hodgkin Study Group

NORDIC LYMPHOMA GROUP

DEDICATED TO PROMOTING RESEARCH IN TREATMENT, BIOLOGY AND EPIDEMIOLOGY OF MALIGNANT LYMPHOMAS IN THE NORDIC COUNTRIES

Dose level 3 (full dose):

Brentuximab vedotin	1.8 mg/kg	IV	day 1	
Cyclophosphamide	750 mg/m²	IV	day 1	Repeat on day 22
Doxorubicin.	50 mg/m²	IV	day 1	
Predniso(lo)ne	100 mg	PO	days 2-6	Growth factor support mandatory

Dose level 2: reduce BV, cyclophosphamide and doxorubicin **to 75%**

Dose level 1: reduce BV, cyclophosphamide and doxorubicin **to 50%**

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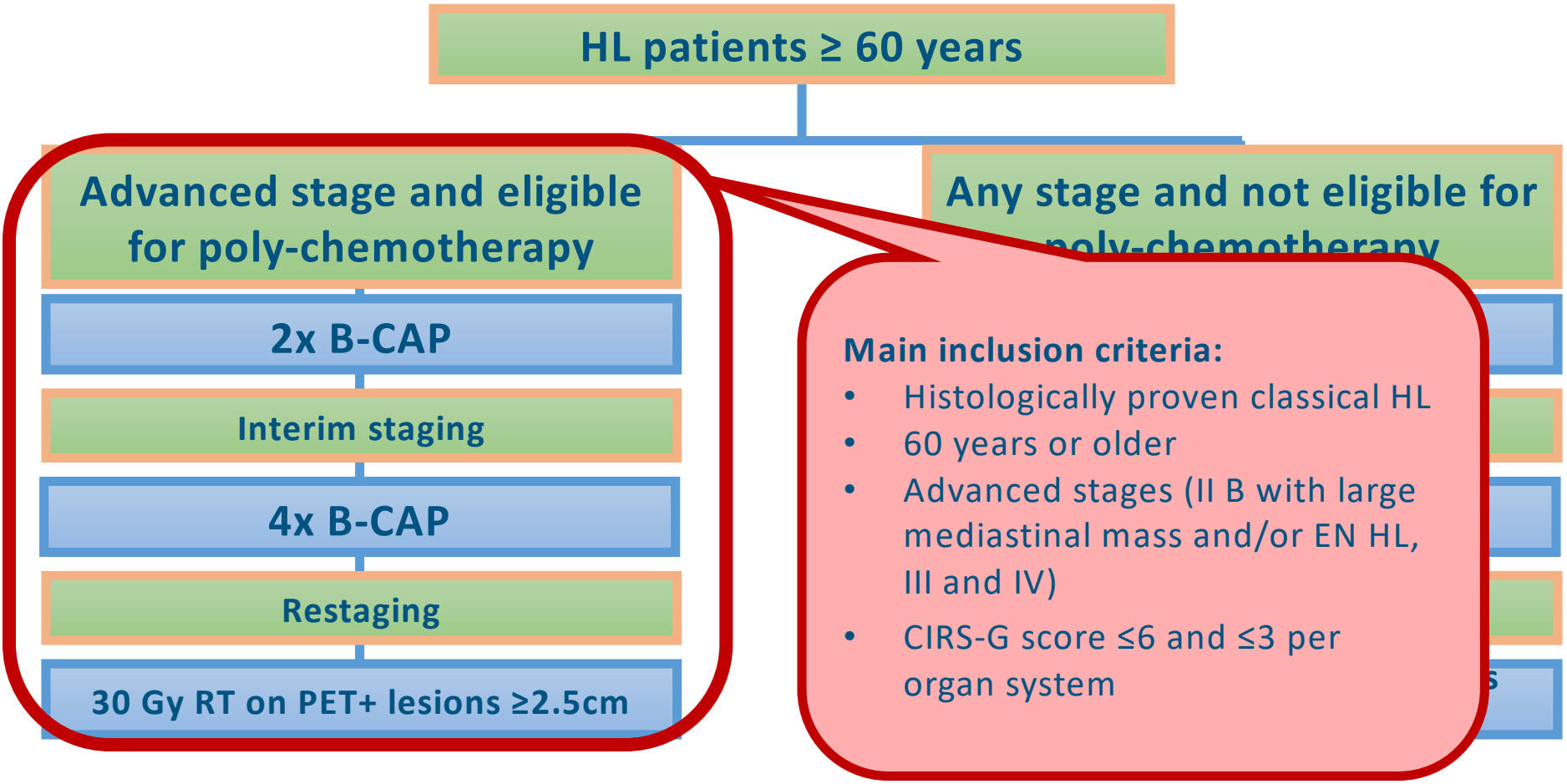

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Patient characteristics (ITT population, N=49)

Age	median **66 years** (range 60 to 84 years)
Sex	23 (47%) female, 26 (53%) male
Ann Arbor stage	2 (4%) IIB, 7 (14%) IIIA, 8 (16%) IIIB, 7 (14%) IVA, **25 (51%) IVB**
GHSG risk factors	5 (10%) large mediastinal mass 7 (14%) extranodal involvement 38 (78%) three or more nodal areas 32 (65%) elevated ESR
IPS (N=48)	3 (6%) IPS=1, 21 (44%) IPS=2-3, **24 (50%) IPS=4-7**
ECOG performance status	13 (27%) ECOG=0, 30 (61%) ECOG=1, 4 (8%) ECOG=2, 2 (4%) ECOG=3
Histologic subtype (N=35)	18 (51%) NS, 12 (34%) MC, 1 (3%) LR, 4 (11%) cHL (nos)

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	Grade 3	Grade 4	Grade 5	Any grade
Any hematological toxicity	8%	53%	0	92%
Thrombocytopenia	4%	6%	0	51%
Neutropenia	12%	41%	0	59%
Anemia	18%	0	0	80%
Febrile neutropenia				27%
Infection	29%	2%	2%	61%
Gastrointestinal tract	10%	0	0	53%
Respiratory tract	6%	0	0	29%
Heart	4%	0	0	10%
Neuropathy	0	0	0	67%

# of cycles	6 cycles	46%
Lowest dose level	3 (100%)	84%
	2 (75%)	16%
Relative dose intensity	mean	92.9%

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		ITT N=48		
		N	%	95% LCL
CT-based response	CR/CRu	21	44%	
	PR	26	54%	
	PD	1	2%	
		47	**98%**	**90.5%**

Metabolic CR rate:
31/48=65%

			PR	PD	Total
				N=1	N=48*
PET-based remission status					
	DS1	13	2		15 (31%)
	DS2	7	6		13 (27%)
	DS3	1	2		3 (6%)
	DS4		10		10 (21%)
	DS5		6	1	7 (15%)

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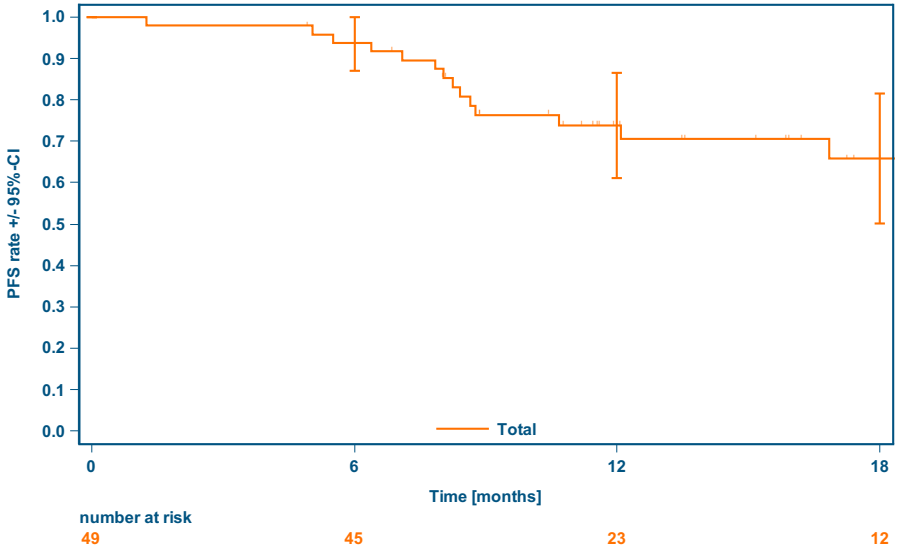
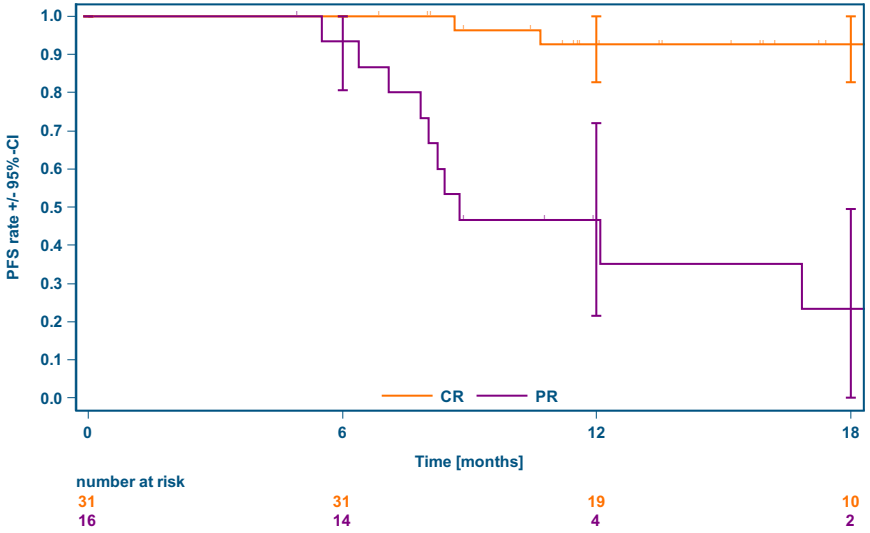


One-year estimate: 73.9% [61.1% to 86.6%]

Median observation time 15 months



One-year estimate

Metabolic CR 92.6% [82.7% to 100%]

Metabolic PR 46.7% [21.4% to 71.9%]

Median observation time 15 months

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- B-CAP regimen is feasible in older patients with acceptable toxicity
- Primary endpoint, i.e. exclusion of an objective response rate ≤ 60%, was met
- Patients with PET-positive residuals after 6 cycles of B-CAP are at high risk for progression or early relapse
- Longer follow-up is needed to draw conclusions on long-term safety and efficacy

Hodgkin Lymphoma in Older Pts: Clinicaltrials.gov

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Brentuximab Vedotin or B-CAP in the Treatment of **Older** Patients With Newly Diagnosed Classical **Hodgkin** Lymphoma	• **Hodgkin** Lymphoma	• Drug: B-CAP • Drug: Brentuximab Vedotin	• 1st Dept. of Medicine, Cologne University Hospital Cologne, Germany
2	☐	Recruiting	Study Of Nivolumab Alone, Or In Combination With Vinblastin In Patients With Classical **Hodgkin** Lymphoma	• **Hodgkin** Lymphoma • Coexisting Medical Conditions	• Drug: Nivolumab • Drug: Vinblastin	• ZNA Stuivenberg Antwerpen, Belgium • Az Sint Jan Bruges, Belgium • Clinique Universitaire Saint LUC Brussels, Belgium • (and 48 more...)
3	☐	Recruiting	Nivolumab and Brentuximab Vedotin in Treating **Older** Patients With Untreated **Hodgkin** Lymphoma	• Ann Arbor Stage IB **Hodgkin** Lymphoma • Ann Arbor Stage II **Hodgkin** Lymphoma • Ann Arbor Stage IIA **Hodgkin** Lymphoma • (and 8 more...)	• Drug: Brentuximab Vedotin • Other: Laboratory Biomarker Analysis • Biological: Nivolumab	• Stanford Cancer Institute Palo Alto Palo Alto, California, United States • MedStar Georgetown University Hospital Washington, District of Columbia, United States • Emory University/Winship Cancer Institute Atlanta, Georgia, United States • (and 7 more...)

Hodgkin Lymphoma in Older Pts: Summary

	pts	ORR	CR	PFS	
BV single agent	27	92%	73%	10 months	Forero Torres 2015
BV + DTIC	22	100%	62%	17 months	Friedberg 2017
BBV	44	71%	66%	22 months	Gallamini 2018
Sequential BV AVD	48	95%	90%	84%	Evens 2018
A/AVD (echelon 1)	84	-	-	74%	Evens 2018
B-CAP	49	98%	65%	74%	Fossa 2018

- Combination of BV with chemo is necessary to prolong PFS
- BV in combination not feasible for unfit or frail patients
- No advantages with A/AVD in elderly
- More hematologic and infectious toxicity
- Primary GCSF mandatory
- No prospective trials available in R/R elderly
- Clinical trial if possible