Il ruolo del brentuximab vedotin nel linfoma di Hodgkin in prima linea e nel paziente ricaduto/refrattario

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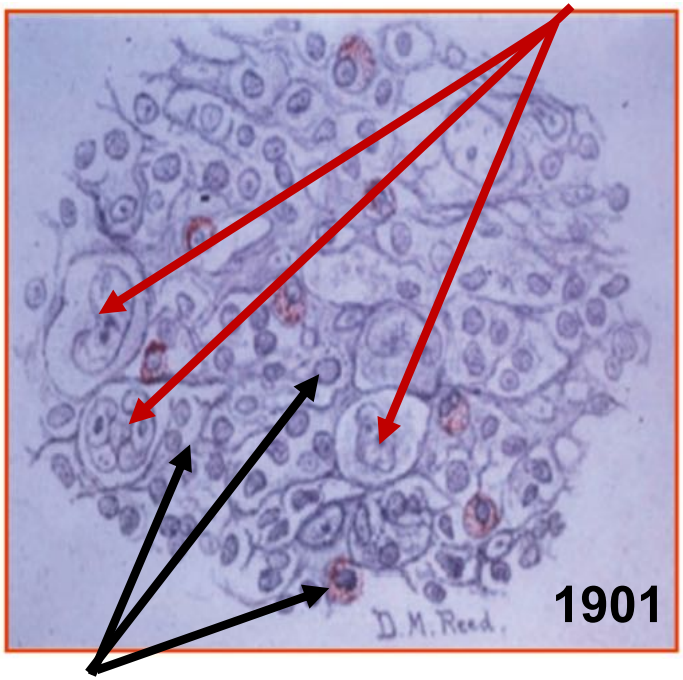
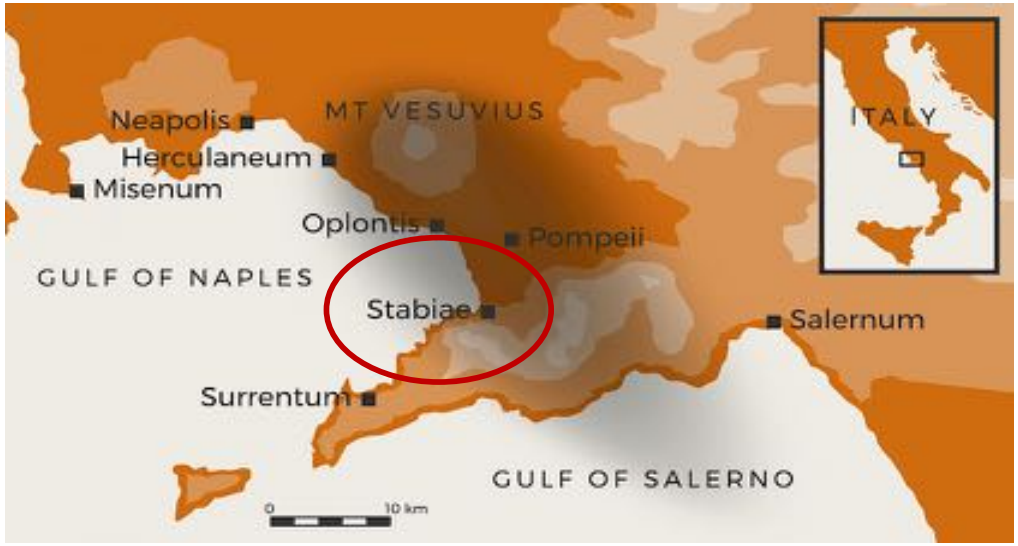
Como 23 DC – C. di Stabia 79 DC



ISTITUTO NAZIONALE TUMORI
IRCCS - Fondazione Pascale

Antibody drug conjugates: …how the story began…

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NATURALIS
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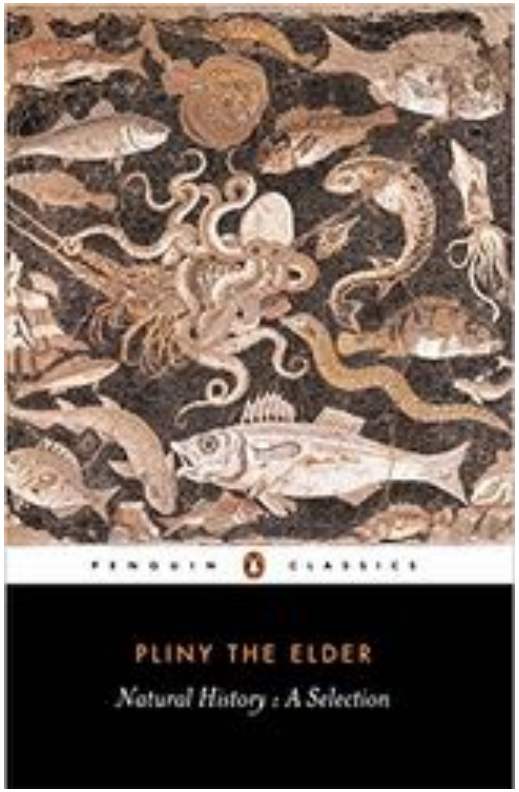

Como 23 DC – C. di Stabia 79 DC

Aquatilium secuntur in medicina beneficia, opifice natura ne in illis quidem cessante et per undas fluctusque…

Seguono i benefici nella medicina degli esseri acquatici, con la natura artefice… e che esercita le instancabili forze attraverso onde e flutti …. …

Brentuximab Vedotin: …CD30…HL…and beyond...

The great Roman natural scientist Gaius Plinius Secundus (Pliny the Elder) in his comprehensive study (4) of about 60 A.D. first described a most potent Indian Ocean sea hare[2] of the genus *Dolabella*. Extracts from this animal and two related *Aplysia* species from the Mediterranean were well known for their toxic properties during the reign of Nero (4, 5). By 150 A.D. Nicander (5) recognized the possibility of using such extracts for treatment of certain diseases. However, the potential of the Indian Ocean *Dolabella* with respect to modern medical problems was not recognized until we uncovered evidence for extremely active anticancer constituents in the Indian Ocean *Dolabella auricularia*[3] (3c).

We have now completed the isolation and preliminary characterization of an exceptionally promising series of cancer chemotherapeutic agents designated dolastatins 1–9 from *D. auricularia*. The dolastatins most probably correspond to the potent *D. auricularia* constituents recognized from ancient to fairly recent (7) times. Since dolastatin 1 has been shown (by the U.S. National Cancer

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[1]The present contribution is part 72 in the series Antineoplastic Agents. For part 71 refer to (1).

[2]The Romans first designated Molluscs of the family Aplysiidae in this fashion due to a similarity between the ears of a hare and the auriculate tentacles of these gastropods, consult (5).

[3]The *D. auricularia* was probably that first described by Pliny and the minor variations recorded in subsequent literature as, e.g., *D. andersoni*, *D. californica*, *D. ecuadoi*, and *D. scapula* are actually one species, namely *D. auricularia*, see (6).

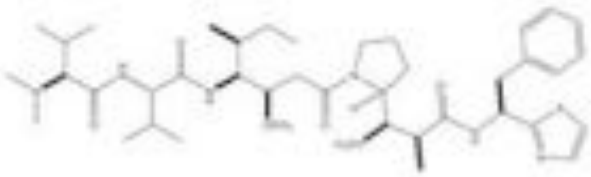
Brentuximab Vedotin: …CD30…HL…and beyond...

Auristatins
(Tubulin polymerase inhibitor)

The Auristatins

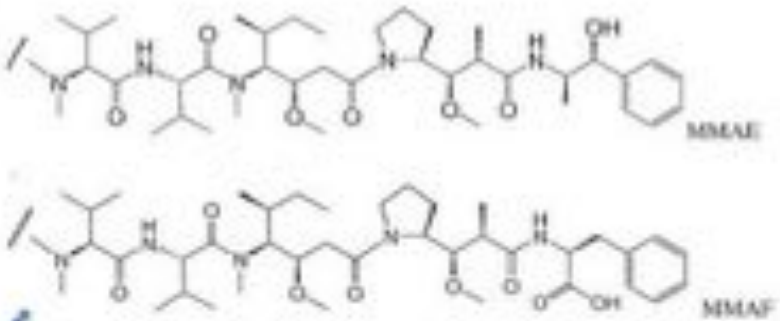
Monomethyl auristatin E (MMAE)
- Warhead of Brentuximab Vedotin
- Up to 1000x more potent than doxorubicin

A.



Dolastatin 10

C.



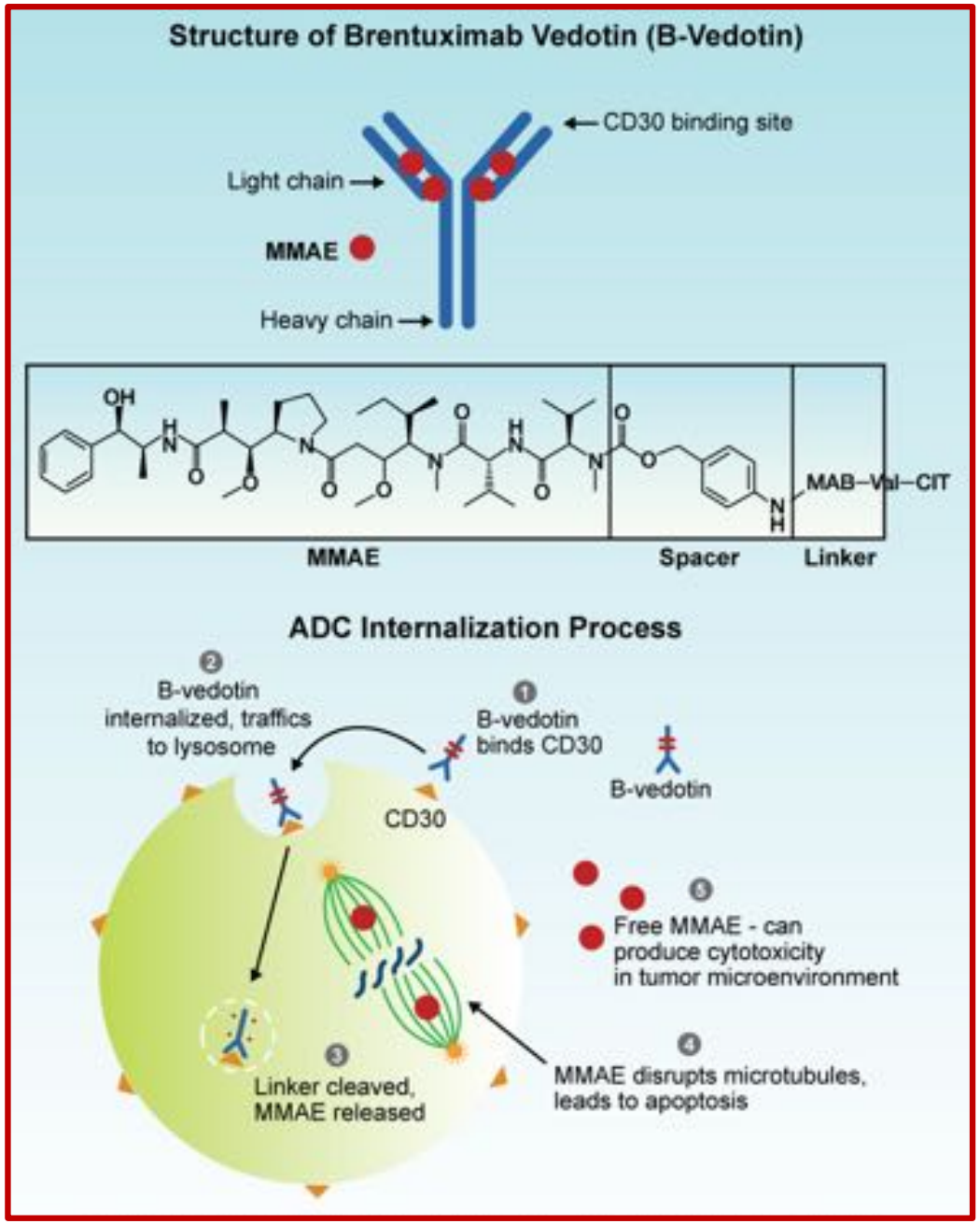
Valine

Tubulin Inhibitors

A. The parent antitubulin agent Dolastatin 10 isolated from the Indian ocean sea hare *Dolabella ariculara* (shown in B)

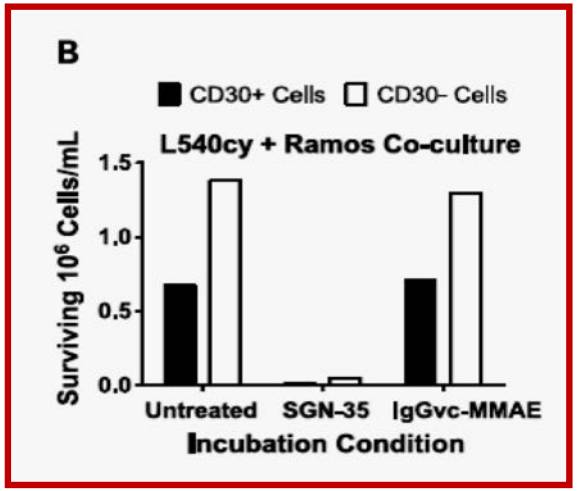
C. The synthetic Dolastatin 10 analogues monomethylauristatin E (MMAE) and monomethylauristatin F (MMAF) are used as payloads for ADCs.

Brentuximab Vedotin: …CD30…HL…and beyond...



In addition to BV's primary MOA non-clinical studies highlight other contributory mechanisms of action, including :

- Antibody dependent phagocytosis (ADCP)
- Bystander effects on nearby cells in the tumor microenvironment due to released MMAE
- Immunogenic cell death (ICD) due to endoplasmic reticulum (ER) stress that drives exposure of immune-activating molecules



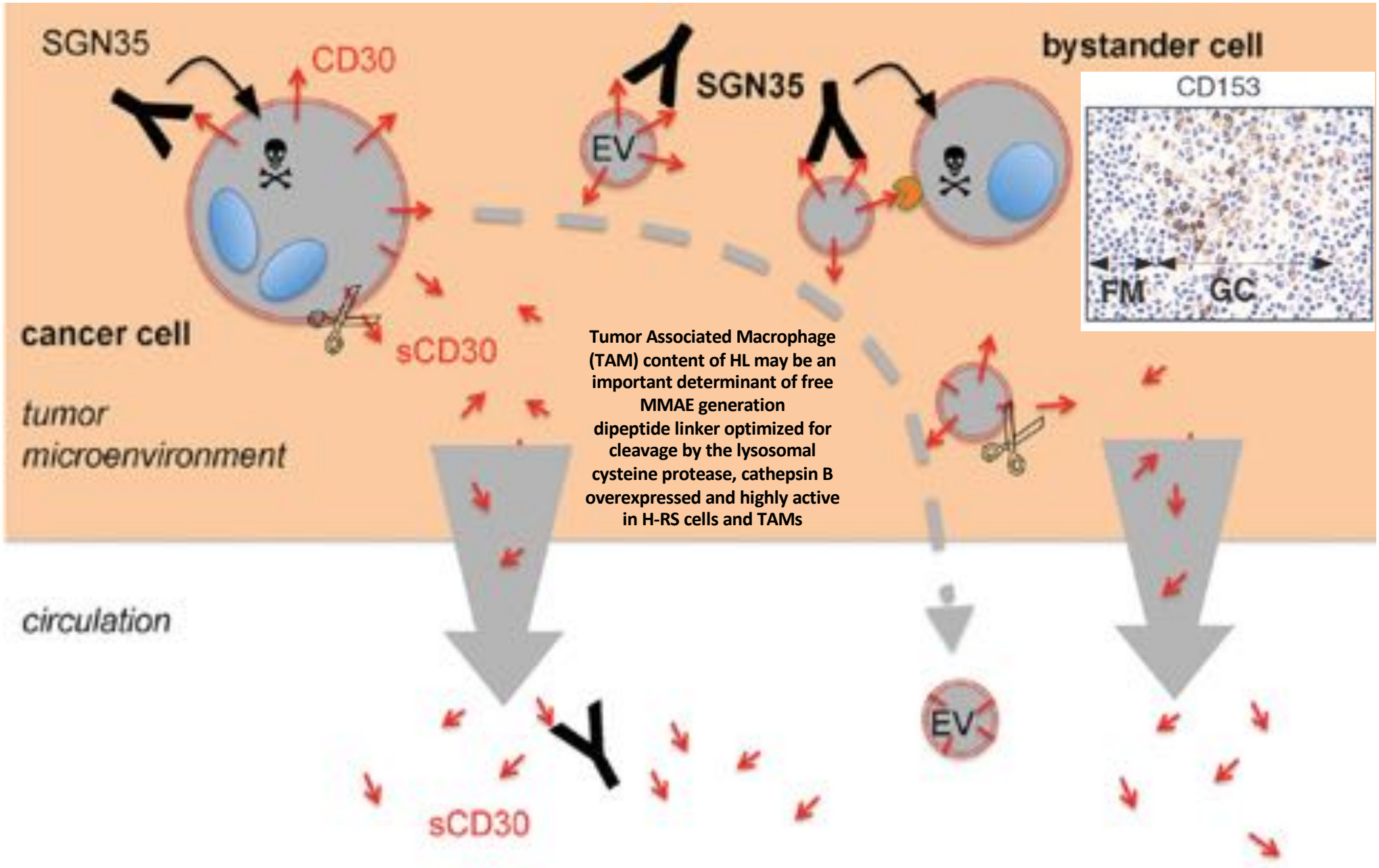
Cancer Therapy: Preclinical

Clinical Cancer Research

Intracellular Activation of SGN-35, a Potent Anti-CD30 Antibody-Drug Conjugate

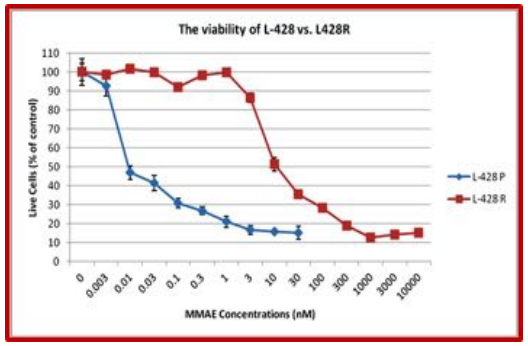
Nicole M. Okeley, Jamie B. Miyamoto, Xinqun Zhang, Russell J. Sanderson, Dennis R. Benjamin, Eric L. Sievers, Peter D. Senter, and Stephen C. Alley

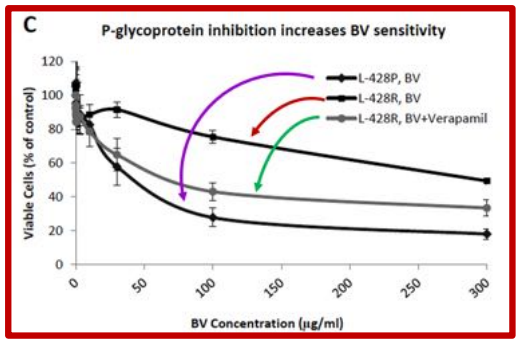
Brentuximab Vedotin: …killing 0f CD30-negative targets

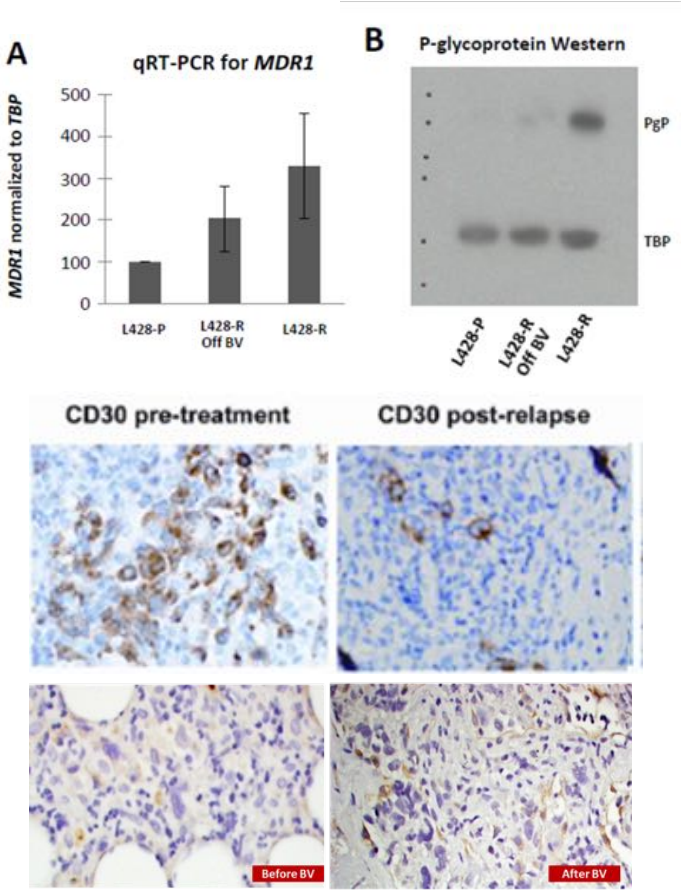


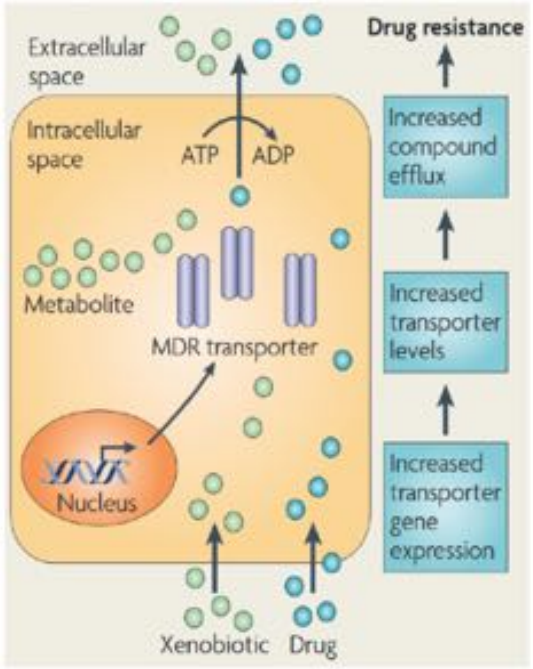
...Novel Agents for cHL: Brentuximab VEDOTIN

The MMAE payload is extruded via MDR proteins









Phase 1 trial of BV+cyclosporine in BV-refractory HL

N = 14
ORR 75%
CR 42%

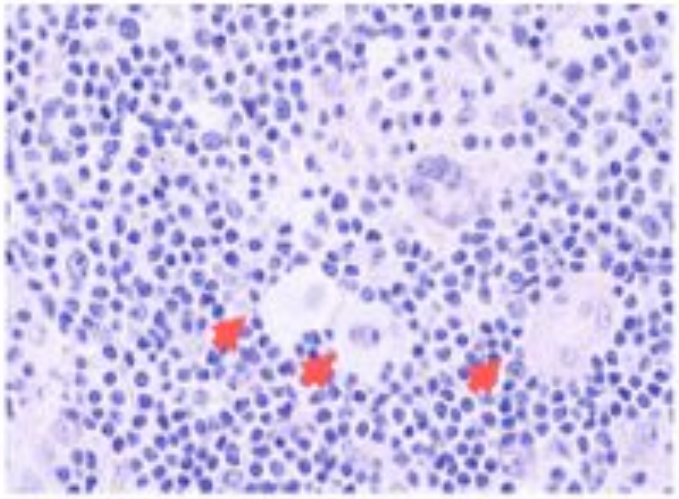
Moderate ↑ in toxicity compared to BV alone

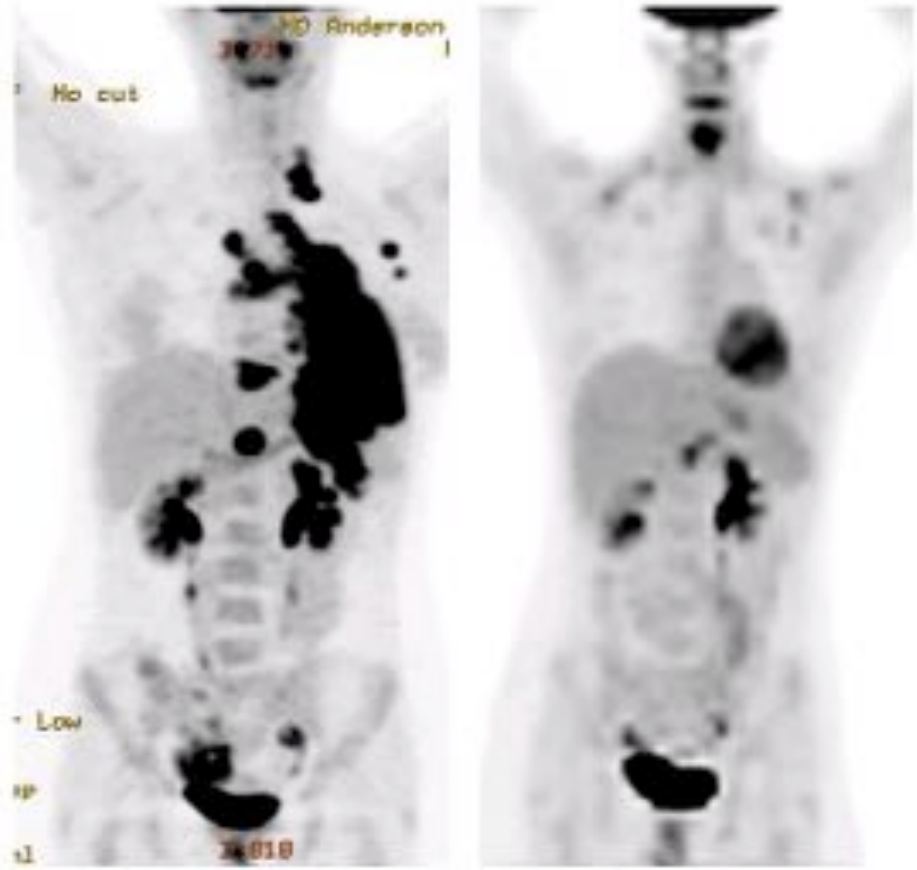
Chen R, et al. ASH 2018

Chen R. et al. Molecular Cancer Therapeutics OnlineFirst on April 3, 2015

Phase I Brentuximab Vedotin in Relapsed HL

- 21-year-old female
- HL diagnosed 2003
  - ABVD + XRT to mediastinum
  - ICE
  - BEAM→ASCT
  - HDAC-inhibitor
- SGN-35 2.7 mg/kg x 8 cycles
  - Best clinical response: CR
  - CT 93% reduction, PET-
  - PET negative



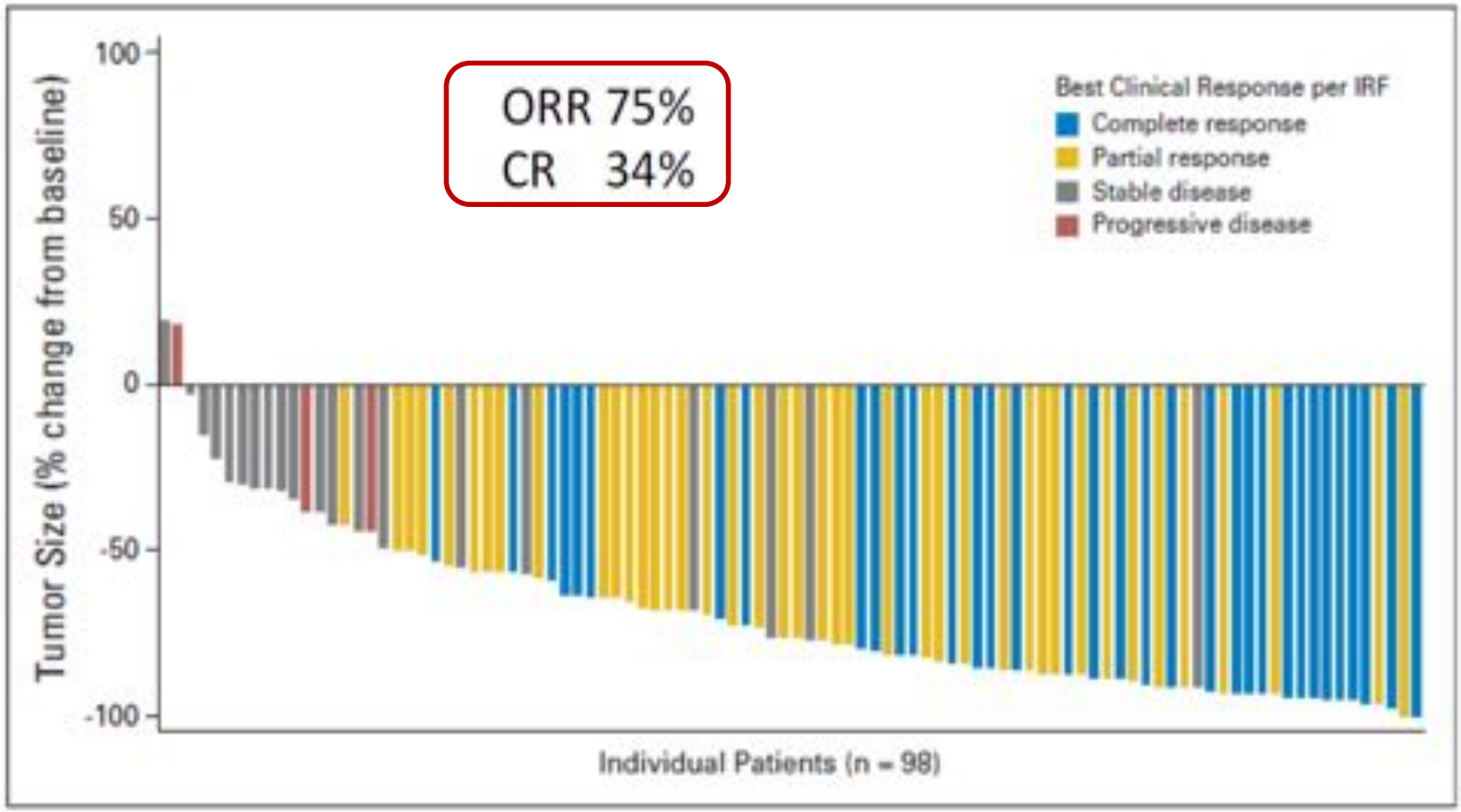


Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand

- **Single agent after ASCT failure**
  - Registration studies
  - Post-Registration (real-life) studies
- **Sequential single agent BV and chemotherapy** (…*on demand strategy*…) ***ASCT-eligible/ineligible***
  - BV alone (about 30-35% of pts. achieve a metabolic CR)
  - BV <mCR: ICE, DICE, IGEV, GVD, GDP
  - BV and Bendamustine or Bendamustine and BV
- **Incorporate BV into salvage**
  - Bendamustine BV (BBV)
  - Gemcitabine BV
  - BV-DHAP (Brave)
  - BV-ESHAP (BrESHAP)
  - BV-ICE
- **BV for *'chemo-free'* salvage**
  - BV+CPIs

Brentuximab Vedotin in the Overall Treatment Strategy for HL

Phase II pivotal study of brentuximab vedotin in relapsed HL post ASCT

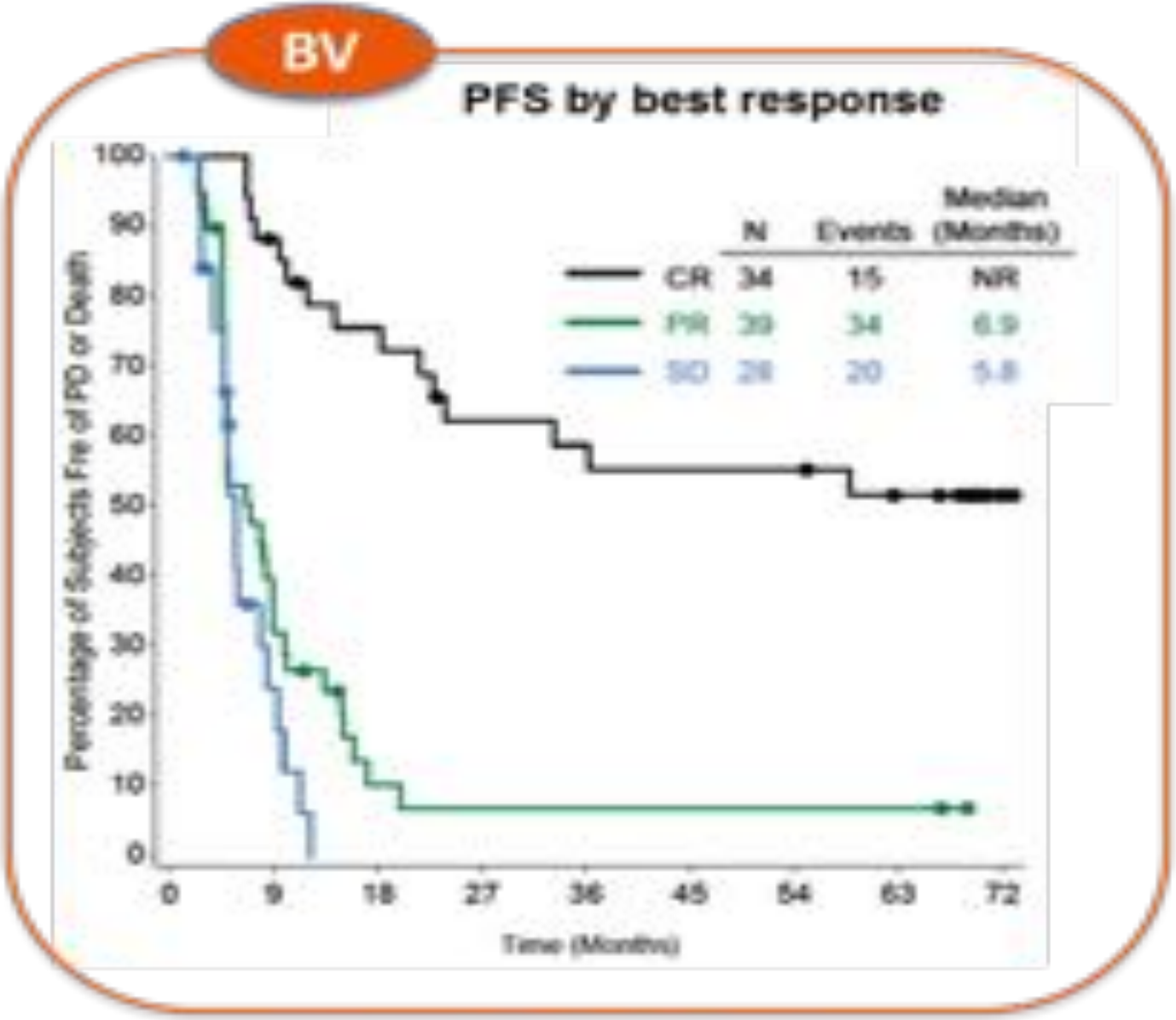


94% patients achieved tumour reduction

IRF – independent review facility

Younes A et al. J Clin Oncol 2012;30: 2183-9.

Brentuximab Vedotin in the Overall Treatment Strategy for HL



Chen et al., Blood 2016

Brentuximab Vedotin in the Overall Treatment Strategy for HL

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 53), pp: 91703-91710

Clinical Research Paper

Italian real life experience with brentuximab vedotin: results of a large observational study on 234 relapsed/refractory Hodgkin's lymphoma

Cinzia Pellegrini[1,*], Alessandro Broccoli[1,*], Alessandro Pulsoni[2], Luigi Rigacci[3], Caterina Patti[4], Guido Gini[5], Donato Mannina[6], Monica Tani[7], Chiara Rusconi[8], Alessandra Romano[9], Anna Vanazzi[10], Barbara Botto[11], Armando Santoro[12], Stefan Hoaus[13], Gian Matteo Rigolin[14], Pellegrino Musto[15], Patrizio Mazza[16], Stefano Molica[17], Paolo Corradini[18], Angelo Fama[19], Francesco Gaudio[20], Michele Merli[21], Fioravante Ronconi[22], Giuseppe Gritti[23], Daniele Vallisa[24], Patrizia Tosi[25], Anna Marina Liberati[26], Antonello Pinto[27], Vincenzo Pavone[28], Filippo Gherlinzoni[29], Maria Paola Bianchi[30], Stefano Volpetti[31], Livio Trentin[32], Maria Cecilia Goldaniga[33], Maurizio Bonfichi[34], Amalia De Renzo[35], Corrado Schiavotto[36], Michele Spina[37], Angelo Michele Carella[38], Vittorio Stefoni[1], Lisa Argnani[1] and Pier Luigi Zinzani[1]

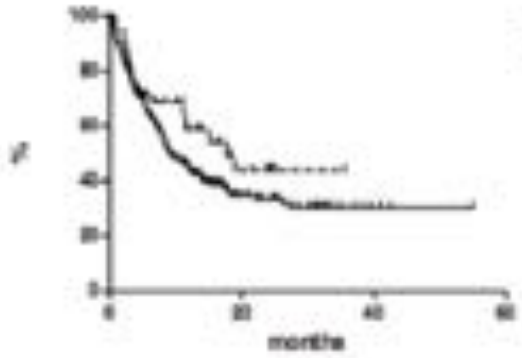


Figure 4: Progression free survival in patients with and without stem cell transplant (SCT) consolidation.

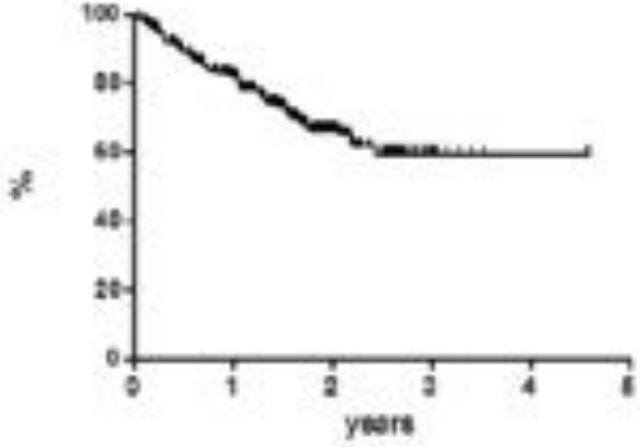
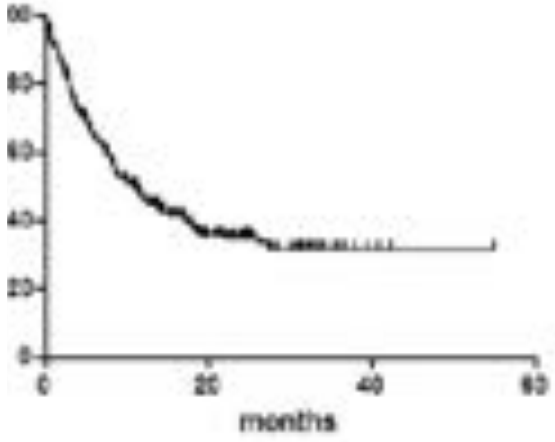


Figure 1: Overall survival.



2: Progression free survival.

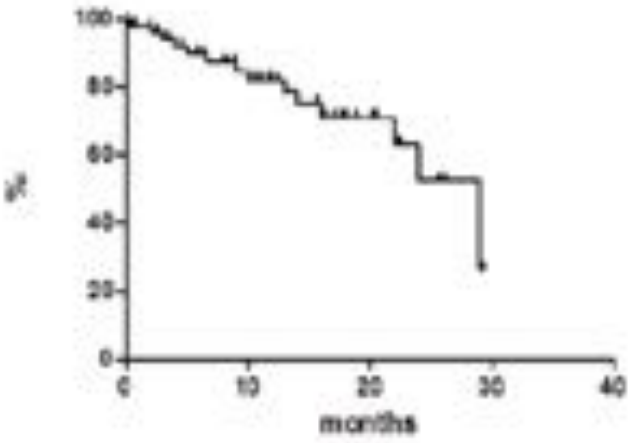
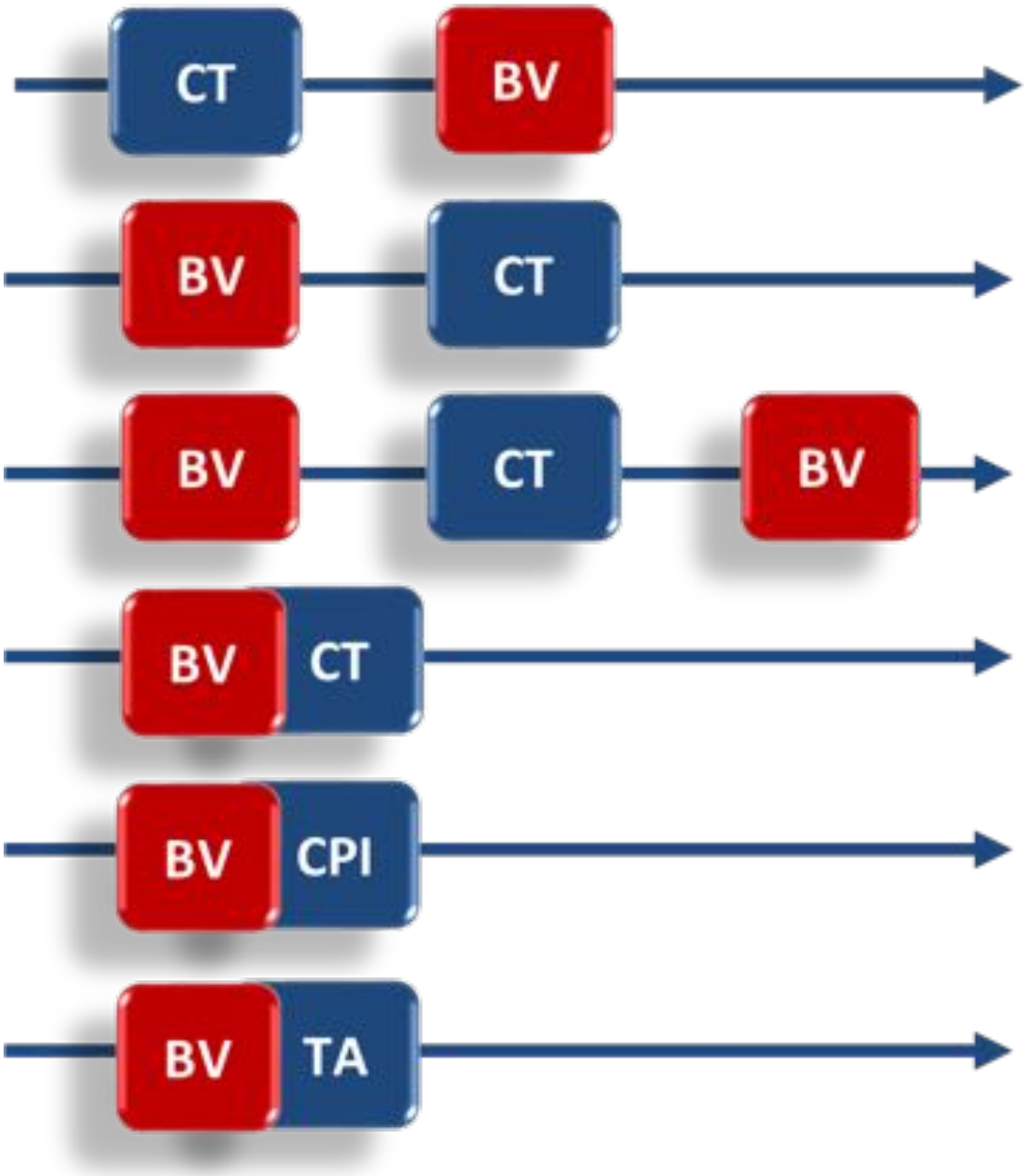


Figure 3: Disease free survival.

...Novel Agents for cHL: Operating Instructions



Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand

Table 1. Patients' demographics and disease characteristics ($n = 30$)

Characteristic	Data
Age, years, mean ± SD, median	30.9 ± 12.8, 27
Sex, male/female, *n*	13/17
Stage, *n* (%)	
II	13 (43.3)
III–IV	17 (56.7)
Primary refractory disease, *n* (%)	21 (70.0)
Regimens prior to BV, median no.	3 (range, 2–11)
First salvage treatment, *n*	
Ifosfamide-containing regimen	17
Cytarabine- and platinum-containing regimen	9
BEACOPP regimen	4
BV cycles, median no.	4 (range, 2–8)

The Oncologist

Brentuximab Vedotin in Transplant-Naïve Relapsed/Refractory Hodgkin Lymphoma: Experience in 30 Patients

Pier Luigi Zinzani,[a] Cinzia Pellegrini,[a] Maria Cantonetti,[a] Alessandro Re,[a] Antonello Pinto,[a] Vincenzo Pavone,[a] Luigi Rigacci,[a] Melania Celli,[a] Alessandro Broccoli,[a] Lisa Argnani,[a] Alessandro Pulsoni[a]

	Outcomes
BV	4 (r 2-8)
ORR	12/30 (40%)
CR @ PET4 (5PDS : ≤ 2)	9 (30%)
PR @ PET4	3 (10%)
ASCT	9 (CR) + 5 (PR/NR)
ASCT outcome @ 18 mo.s	Post-BV CR 8/9 → cCR Post-BV NR 1/5 → cCR

The Oncologist 2015;20:1–4

Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand

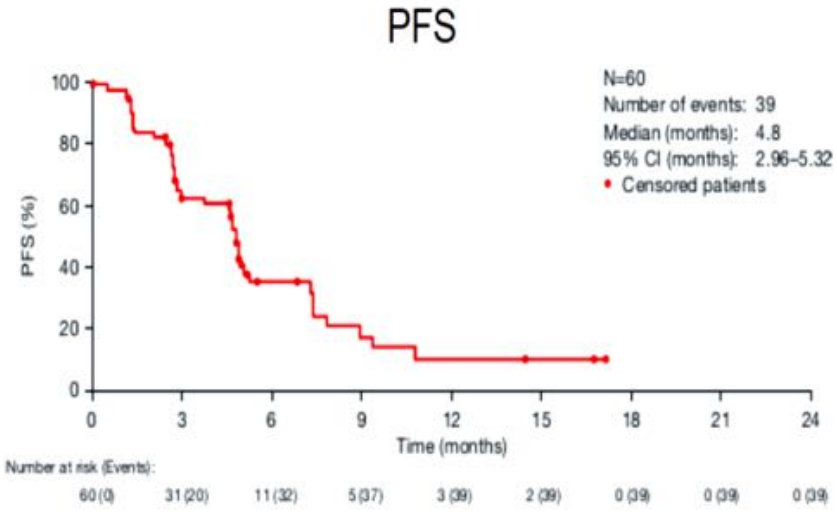
Phase IV study: Brentuximab vedotin in patients with R/R HL ineligible for SCT or multi-agent chemotherapy (NCT01990534)

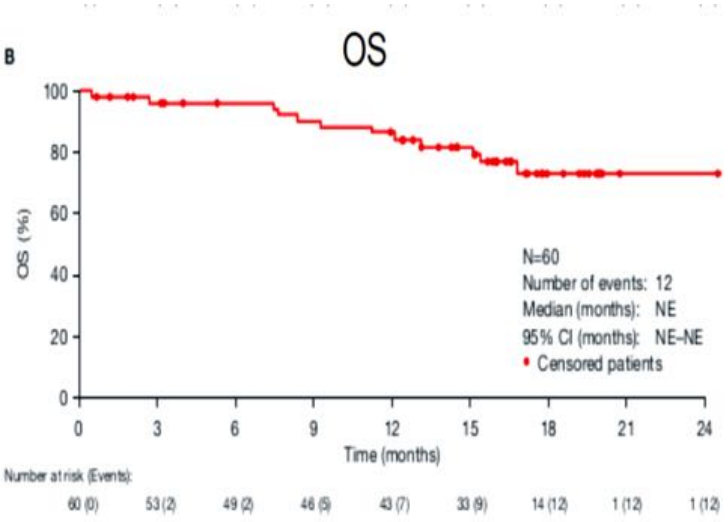
Walewski J, et al. ISHL 2016, Poster presentation #P104

Response:

	ITT population (N=60)	
	Per IRF	Per INV
ORR (CR+PR), n (%) [95% CI]	30 (50) [37–63]	29 (48) [35–62]
Best clinical response, n (%) [95% CI]		
CR	7 (12) [5–23]	9 (15) [7–27]
PR	23 (38) [26–52]	20 (33) [22–47]
Median time to response, weeks (range)		
Time to response (CR+PR)	6.0 (5–39)	6.1 (5–53)
Time to best response	11.2 (5–60)	11.8 (5–53)
Time to CR	12.0 (6–60)	12.1 (11–29)
Time to PR	6.0 (5–39)	9.1 (5–53)

Median PFS (per IRF) 4.8 mos (95% CI: 2.96–5.32); median OS NE





Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand

Brentuximab vedotin in the treatment of elderly Hodgkin lymphoma patients at first relapse or with primary refractory disease: a phase 2 study of FIL ONLUS

Miriam Marangon, Lisa Argnani, Alessandro Re, Arben Lleshi, Maurizio Bonfichi, Antonello Pinto, Nicola Bianchetti, Cinzia Pellegrini, Vittorio Stefoni and Pier Luigi Zinzani

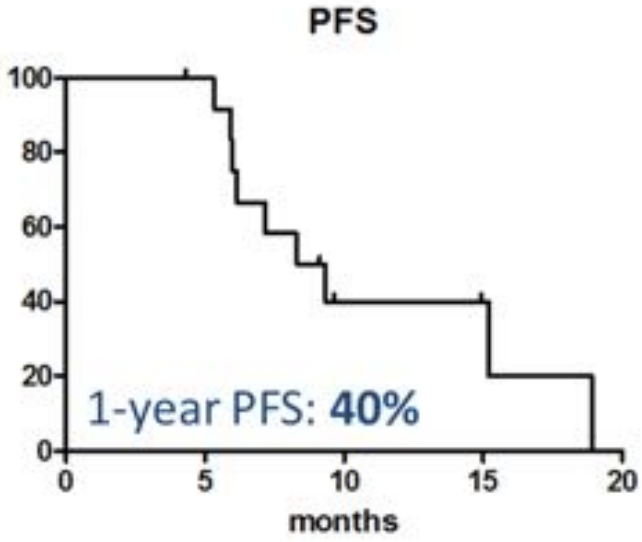
Patients' characteristics (N = 18).

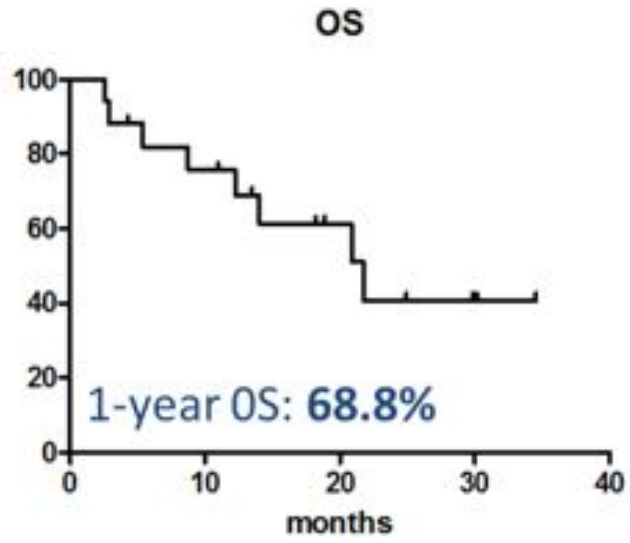
Age	
Median (range), years	73 (61.2-85.7)
Sex, *N*	
Male	9
Female	9
Stage (Ann Arbor), *N*	
At diagnosis:	
I	2
II	0
III	7
IV	9
At time of BV treatment:	
I	1
II	2
III	8
IV	7
Performance status at BV treatment (ECOG), *N*	11
0	7
1	
Time I diagnosis-BV, median (range)	1 year [2 mos-21 yrs]
Time last treatment-BV, **median (range)**	6 mos [1 mo-20 yrs]
Last treatment, *N*	
ABVD/MBVD	13 (2 plus RT)
VBM	2
COPP	2
gemcitabine	1
Outcome, *N*	

Refractory	**6**
Relapsed	**12**

- **ORR: 52.9 %** (9/17)
- **CR: 23.5%** (4/17)
- PR: 9/17
- **Early discontinuation:**
  7 pts. (G2/G3 neuropathy)
  7 pts. (no response/pro)
- **median PFS:** 8.8 mo.s
- **median OS:** 21.7 mo.s

Median DFS: 3.9 mo.s
Time to relapse for CRs:
2.8, 3.4, 4.4, 16.4+ months



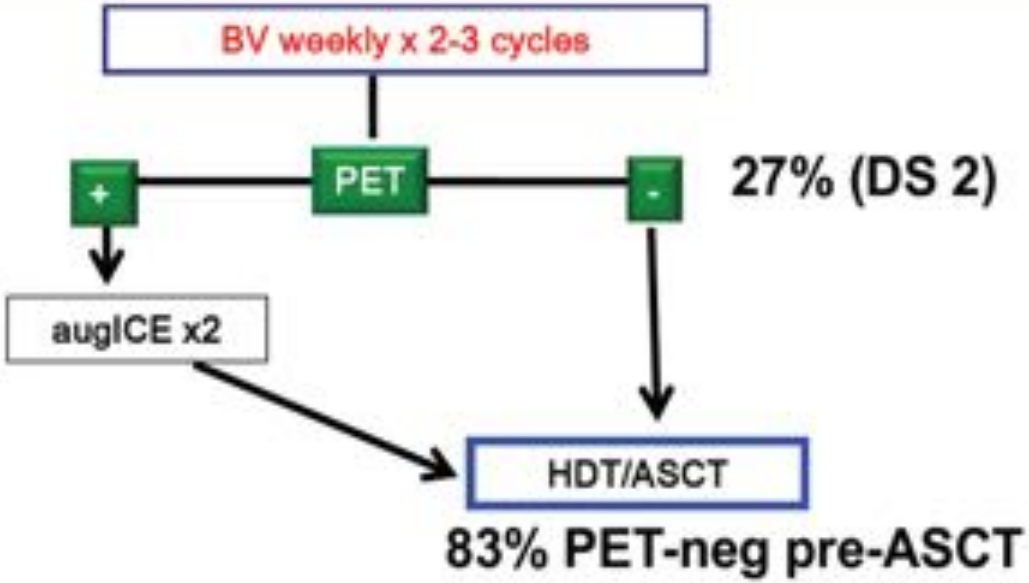


Median FU 24.9 mo.s

Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand

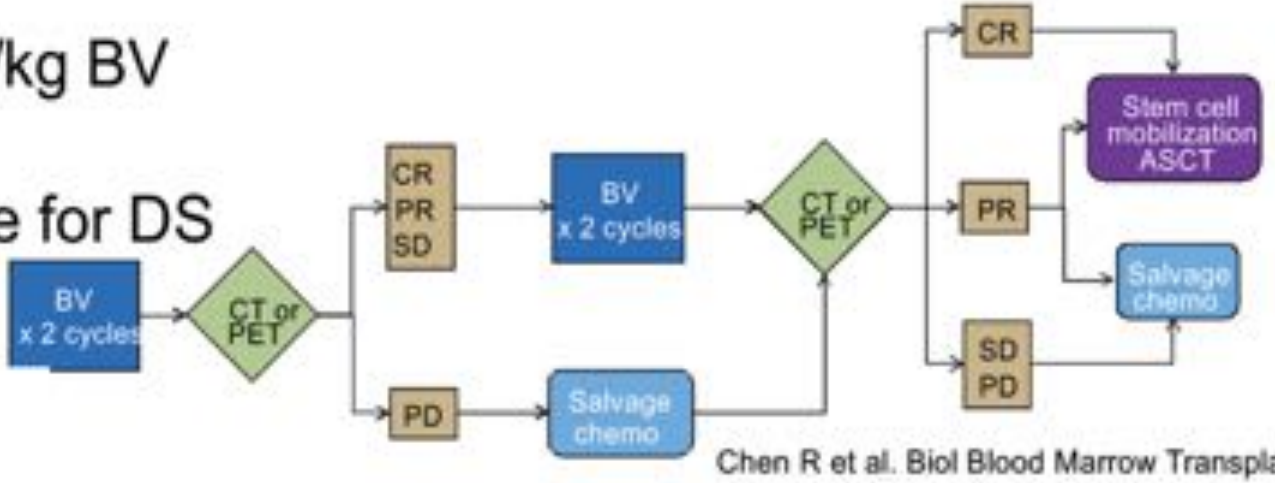
PET-adapted sequential salvage: BV as initial salvage

MSKCC study
- Weekly 1.2mg/kg BV
- D1,8,15 of 28d cycles
- Augmented ICE for DS 3-5



Moskowitz A et al Lancet Oncology 2015

COH study
- Q3W 1.8mg/kg BV
- 21d cycles
- SOC salvage for DS 4-5

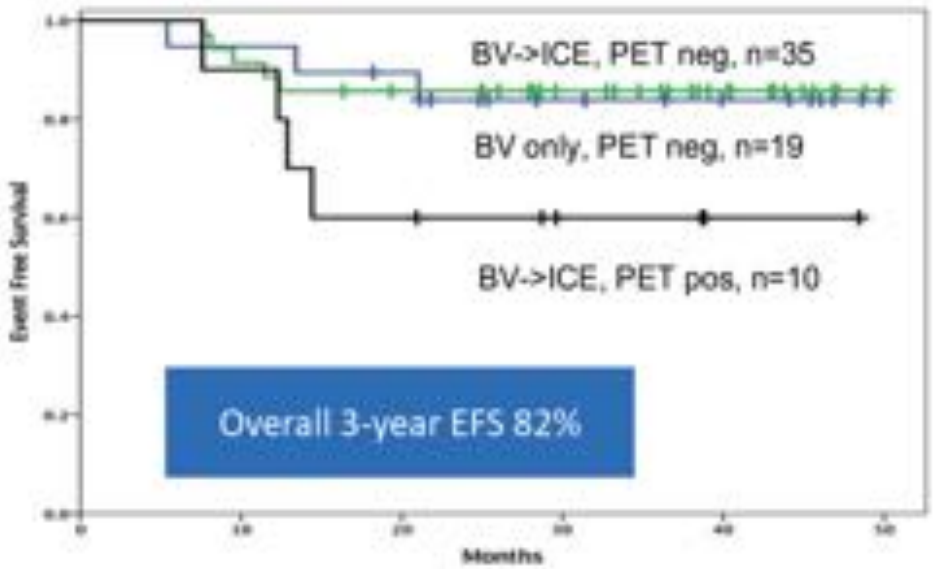


Chen R et al. Biol Blood Marrow Transplant, 2015

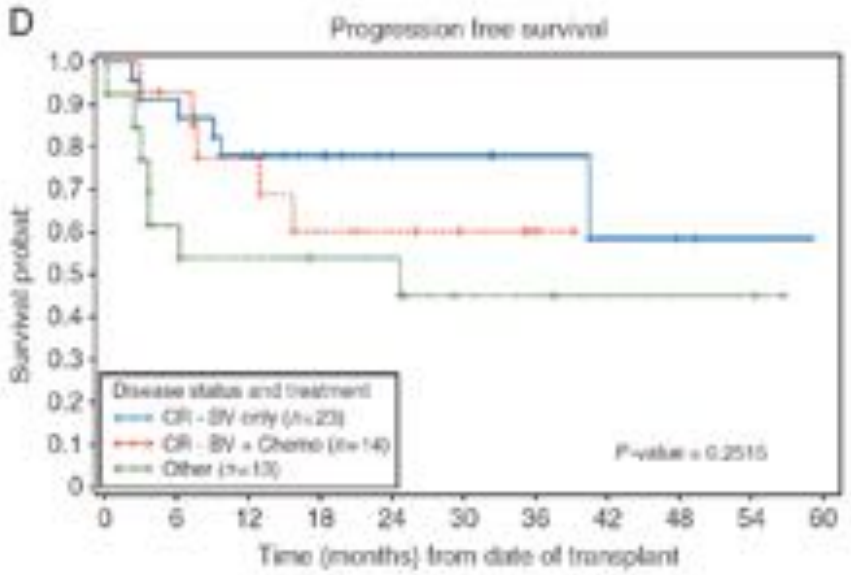
Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand

BV is an effective bridge to ASCT, some pts can avoid chemo

- MSKCC study (n = 65)
  - 28% DS 1-2 direct to ASCT
  - 75% DS 1-2 after BV +/- ICE
  - 64/65 proceeded to ASCT



- COH study (n = 56)
  - 50% direct to ASCT after BV
  - 50/56 proceeded to ASCT
  - 2y PFS 67% overall
  - 2y PFS 77% after BV alone

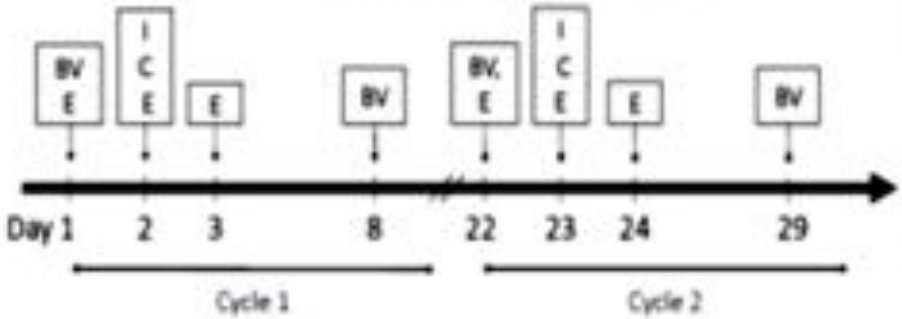


Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand

BV + ICE

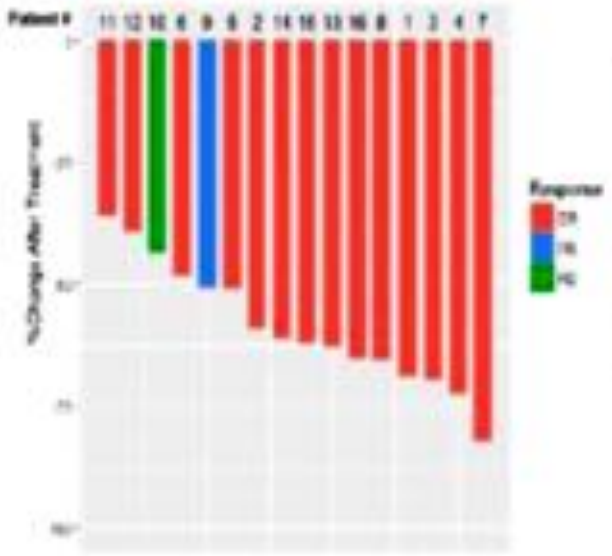
N=16

BV+ ICE chemotherapy Treatment Schema



- Brentuximab vedotin:
  - Dose Level -1: 1.8 mg/m² IV on Day 1 only
  - Dose Level 1: 1.2 mg/m² IV on Days 1 and 8
  - Dose Level 2: 1.5 mg/m² IV on Days 1 and 8
- Ifosfamide (with mesna): 5 g/m² IV over 24 hours starting on Day 2
- Carboplatin: AUC 5 (capped at 800 mg) IV on Day 2
- Etoposide: 100 mg/m² IV on Days 1, 2, and 3

Response Assessment After BV-ICE



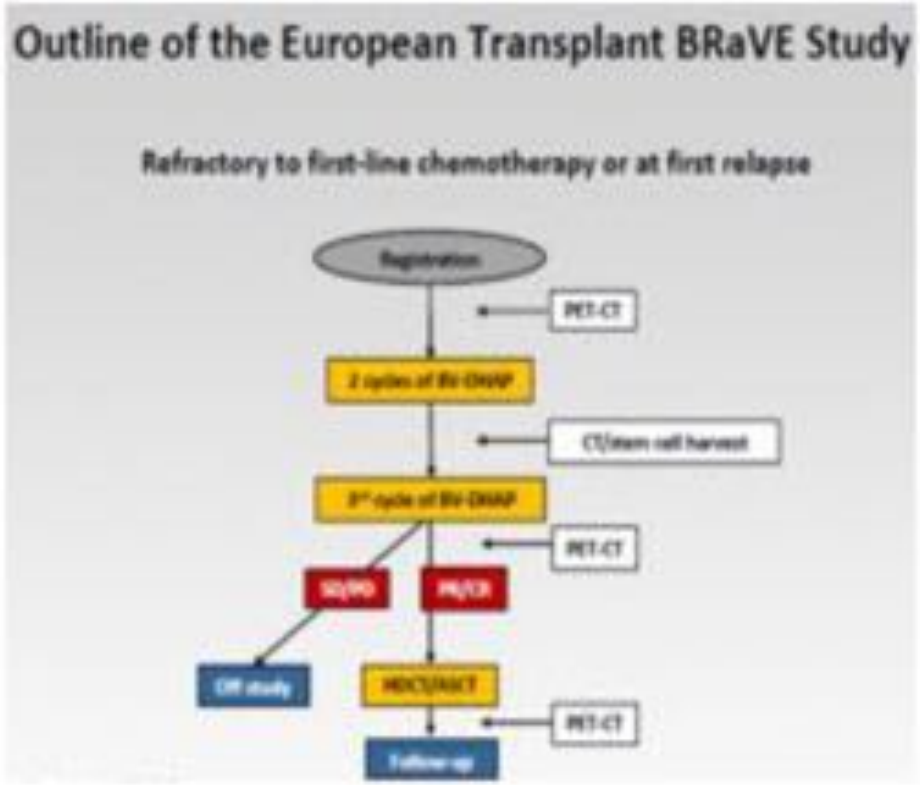
- Investigator-defined response:
  - CR rate = 88%
  - Overall response rate = 94%
- Relapse rate = 19%
- All subjects still alive
- Median follow-up: 10.5 mo

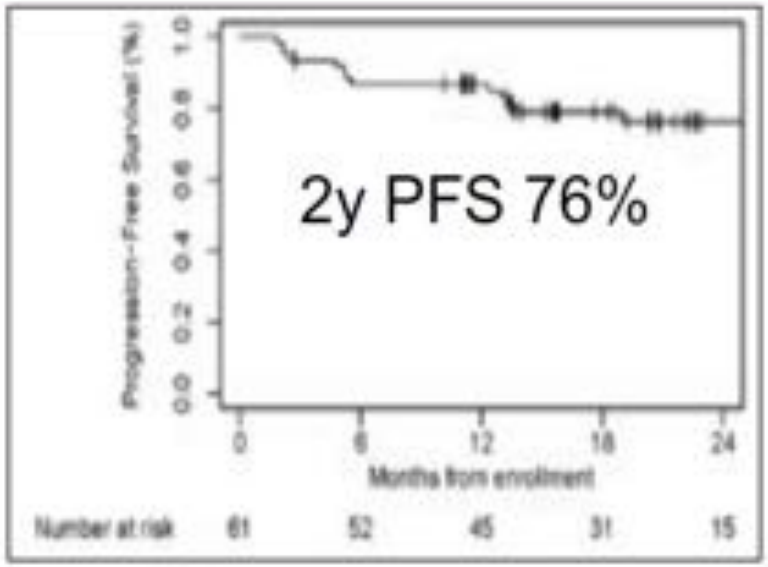
City of Hope.

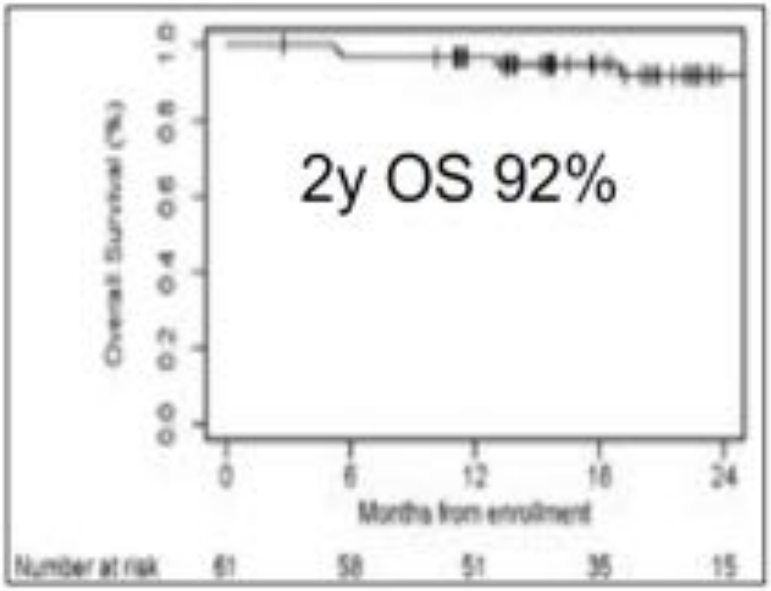
Cassaday et al ASH 2016 #1834

Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand

BV + DHAP (BRaVE study)







N=61, 37% primary refractory
ORR 87%, CR: 79%

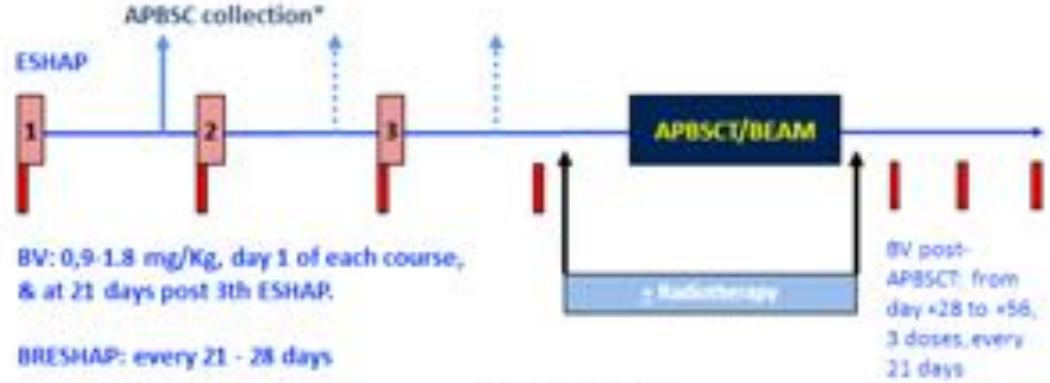
Gr 3-4 Toxicities
63% neutropenia, 30% F&N
81% thrombocytopenia

Hagenbeek A et al. ASH 2018

Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand

Extended follow up from BrESHAP first salvage study demonstrates most patients still in remission at 3 years

- Combination of BV and ESHAP chemotherapy [BRESHAP] as 2nd line therapy for RRHL prior to ASCT
- All but two pts (64/66) underwent stem cell mobilization
- 61 pts were transplanted directly after BRESHAP salvage
- 50 patients received BV consolidation after transplant

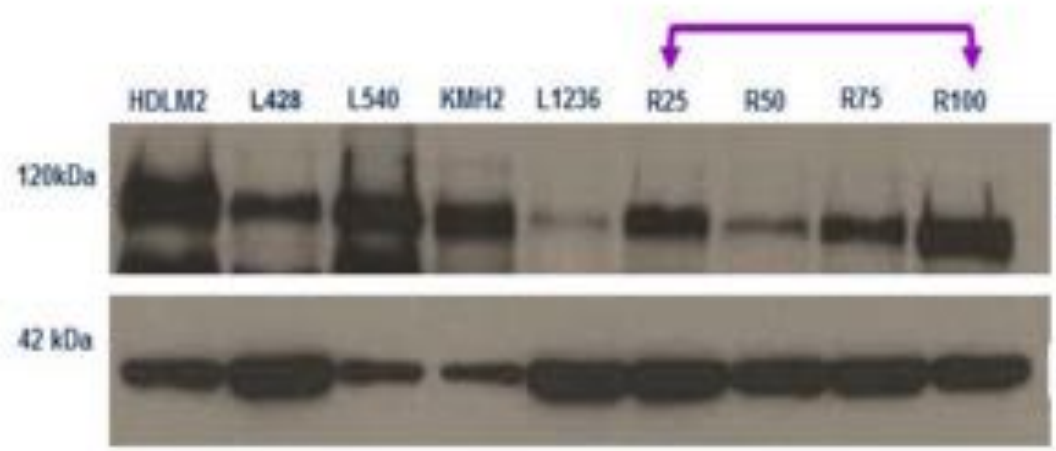


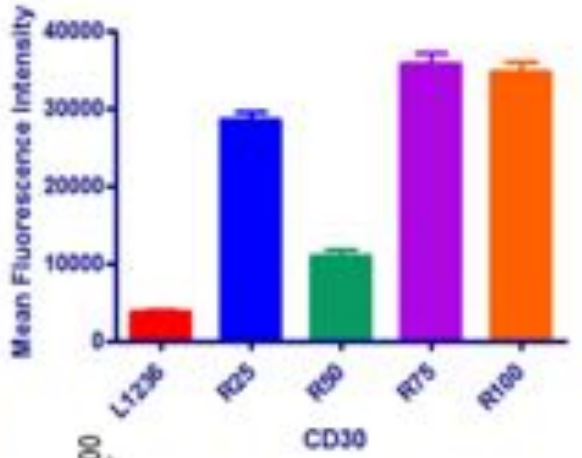
*CD34+ quantification: ≥ x 10^6/kg CD34+ cells
GCSF (+/- Plerixafor) prophylaxis mandatory from day+7

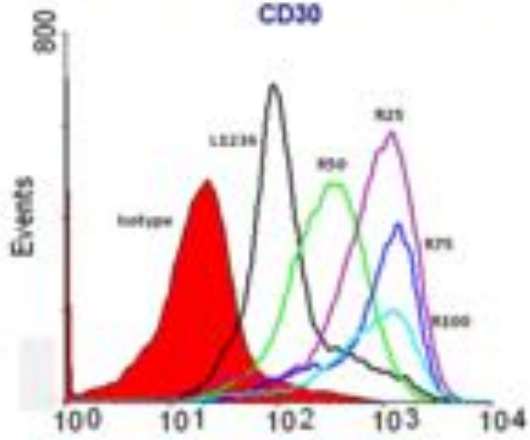
N=65 evaluable pts	BrESHAP
Pre-transplant response	95% (71% CR, 25%PR)
Post-transplant response	92% (82% CR, 10% PR)
3 year time to treatment failure	74%
3 year PFS	71%
3 year OS	91%
AE Summary	N=23 SAEs (22 resolved, 1 death), 2 discontinuations after C3

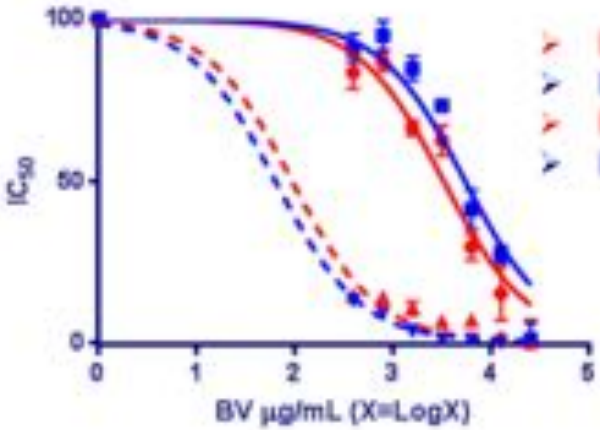
Garcia-Sanz, Abstract #S113 EHA 2018

Immunotherapy for Malignant Lymphoma: 2019









- L1236 48 Hrs IC50 = 3.16
- L1236 72 Hrs IC50 = 3.87
- R100 48 Hrs IC50 = 0.21
- R100 72 Hrs IC50 = 0.19

Extended exposure and resistance to Bendamustine in HL cells is associated to a stable upregulation of CD30 and increased sensitivity to Brentuximab Vedotin

De Filippi *et al.* ASH 2015 ; De Filippi et al. In press 2019

Brentuximab Vedotin in the Overall Treatment Strategy for HL

Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: an international, multicentre, single-arm, phase 1–2 trial

Lancet Oncol 2018; 19: 257–66

Owen A O'Connor, Jennifer K Lue, Ahmed Sawas, Jennifer E Amengual, Changchun Deng, Matko Kalac, Lorenzo Falchi, Enrica Marchi, Ithamar Turenne, Renee Lichtenstein, Celeste Rojas, Mark Francescone, Lawrence Schwartz, Bin Cheng, Kerry J Savage, Diego Villa, Michael Crump, Anca Prica, Vishal Kukreti, Serge Cremers, Joseph M Connors, John Kuruvilla

	Phase 1 (n=28)	Phase 2 (n=37)	Total (n=65)
Overall response	17 (61% [41–79])	29 (78% [62–91])	46 (71% [58–81])
Complete response	5 (18%)	16 (43%)	21 (32%)
Partial response*	12 (43%)	13 (35%)	25 (38%)
Stable disease	4 (14%)	5 (14%)	9 (14%)
Not assessable	1 (4%)	0	1 (2%)
Progression of disease	6 (21%)	3 (8%)	9 (14%)

Data are n (% [95% CI]) or n (%). *The patient with anaplastic large-T-cell lymphoma had a partial response in phase 1.

Table 2: Treatment response by study phase to brentuximab vedotin plus bendamustine

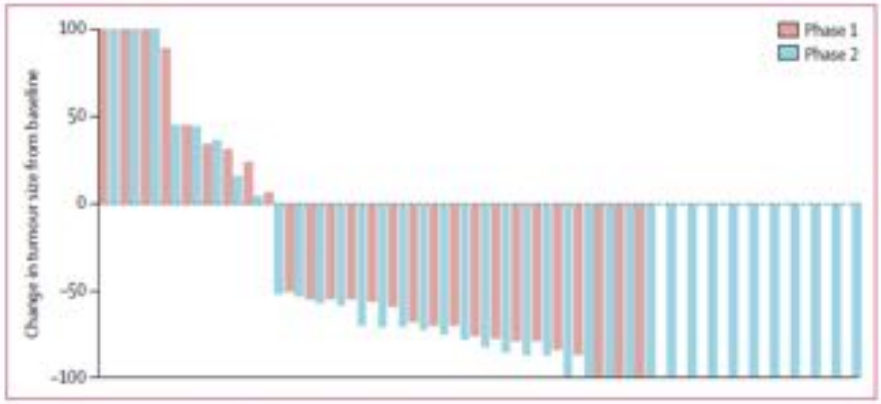
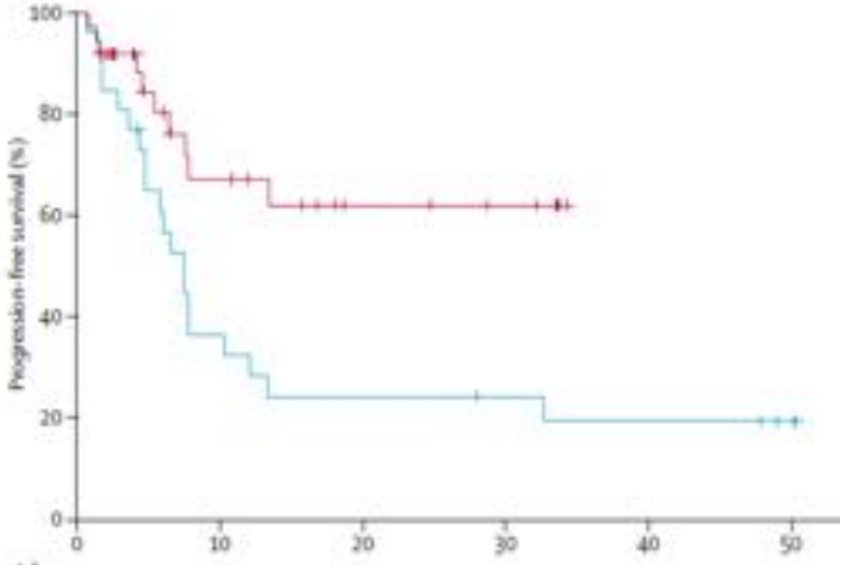


Figure 2: Responses to brentuximab vedotin plus bendamustine by study phase
All complete remissions are defined by functional imaging as PET negative. One patient in phase 1 was not assessed radiologically because of a protocol violation in cycle 1.



Median PFS: 7·5 months (95% CI 4·8–12·1)

Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand

CLINICAL TRIALS AND OBSERVATIONS

Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma

Ann S. LaCasce,[1] R. Gregory Bociek,[2] Ahmed Sawas,[3] Paolo Caimi,[4] Edward Agura,[5] Jeffrey Matous,[6] Stephen M. Ansell,[7] Howland E. Crosswell,[8] Miguel Islas-Ohlmayer,[9] Caroline Behler,[10] Eric Cheung,[11] Andres Forero-Torres,[12] Julie Vose,[2] Owen A. O'Connor,[3] Neil Josephson,[13] Yinghui Wang,[13] and Ranjana Advani[7,14]

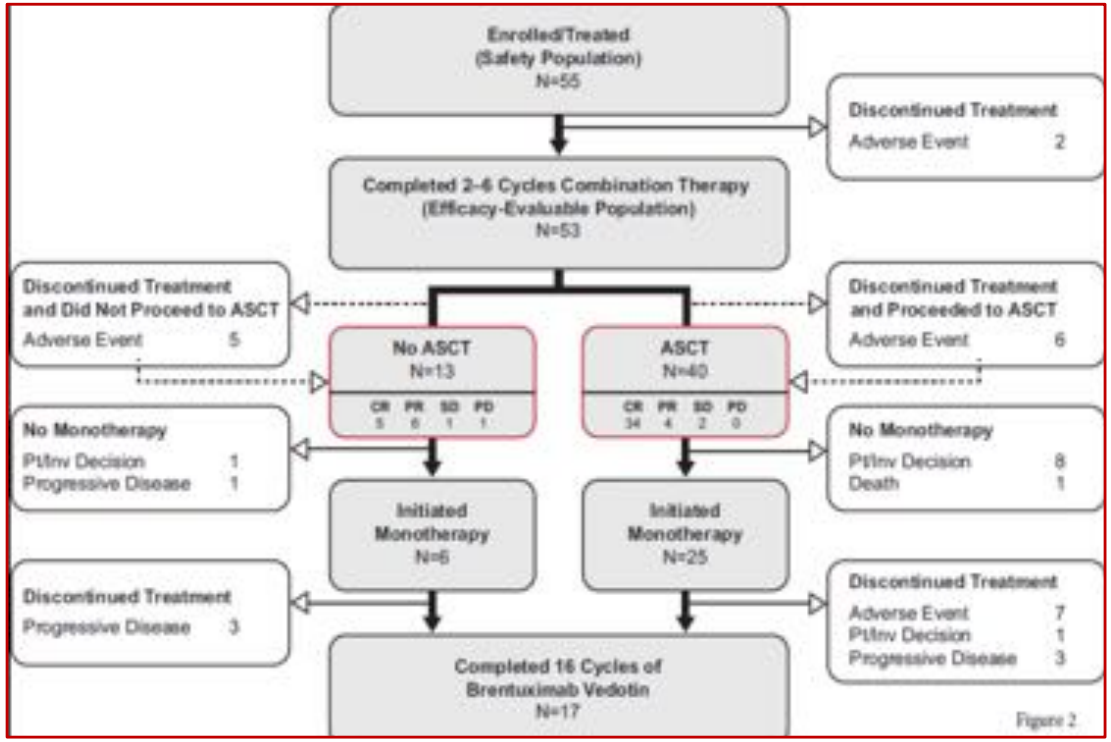
Table 2. Best response on combination therapy

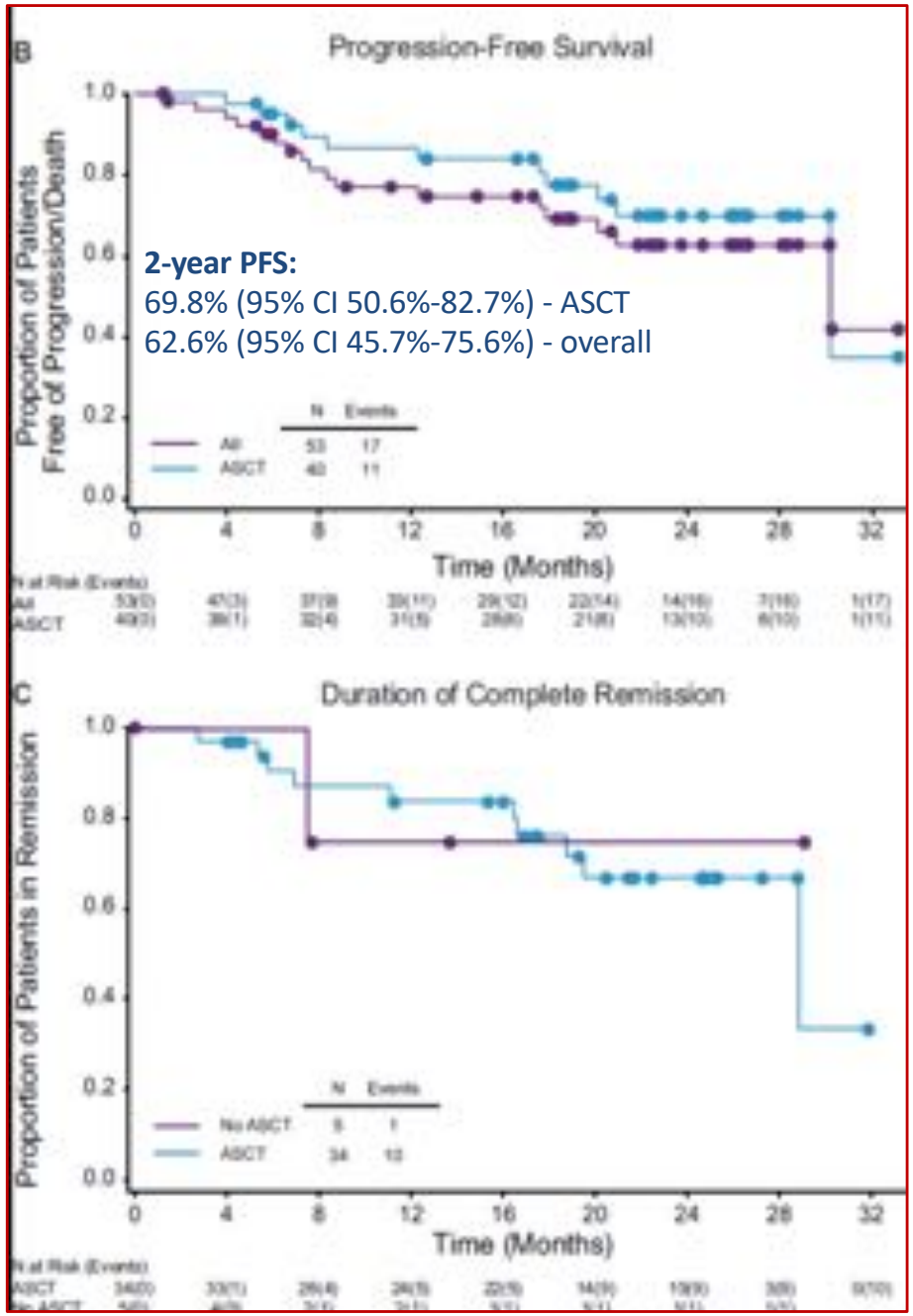
Population	Best clinical response, n (%) [95% CI]				
	CR	PR	SD	PD	ORR*
Overall, N = 53	39 (73.6) [59.7, 84.7]	10 (18.9)	3 (5.7)	1 (1.9)	49 (92.5) [81.8, 97.9]
Response to frontline therapy					
Primary refractory, n = 28	18 (64.3) [44.1, 81.4]	6 (21.4)	3 (10.7)	1 (3.6)	24 (85.7) [67.3, 96.0]
Relapsed, n = 25	21 (84.0) [63.9, 95.5]	4 (16.0)	0 (0.0)	0 (0.0)	25 (100) [86.3, 100]
ASCT					
Yes, n = 40	34 (85.0) [70.2, 94.3]	4 (10.0)	2 (5.0)	0 (0.0)	38 (95.0) [83.1, 99.4]
No, n = 13	5 (38.5) [13.9, 68.4]	6 (46.2)	1 (7.7)	1 (7.7)	11 (84.6) [54.6, 98.1]

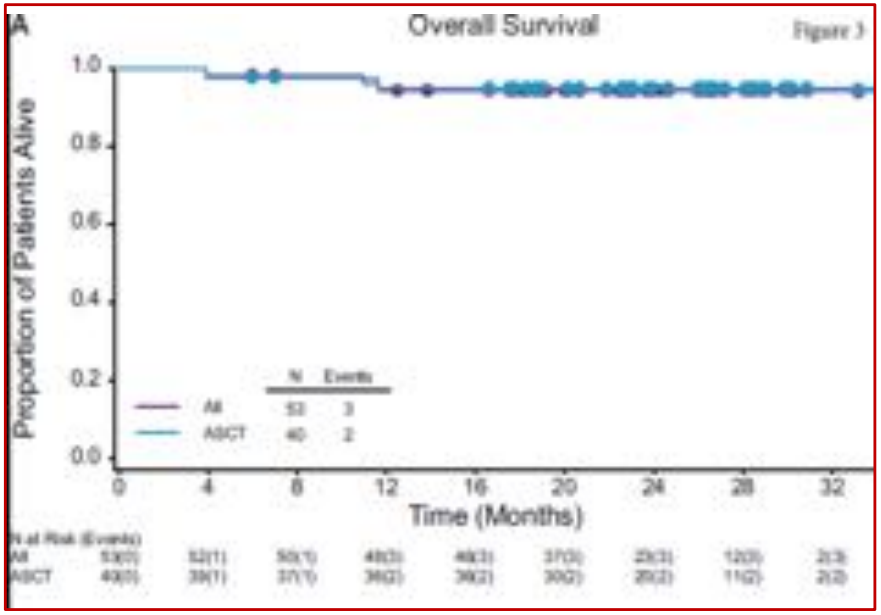
- 97% 1st stem cell mobilization attempt success

blood® 5 JULY 2018 | VOLUME 132, NUMBER 1

Brentuximab Vedotin in the Overall Treatment Strategy for HL





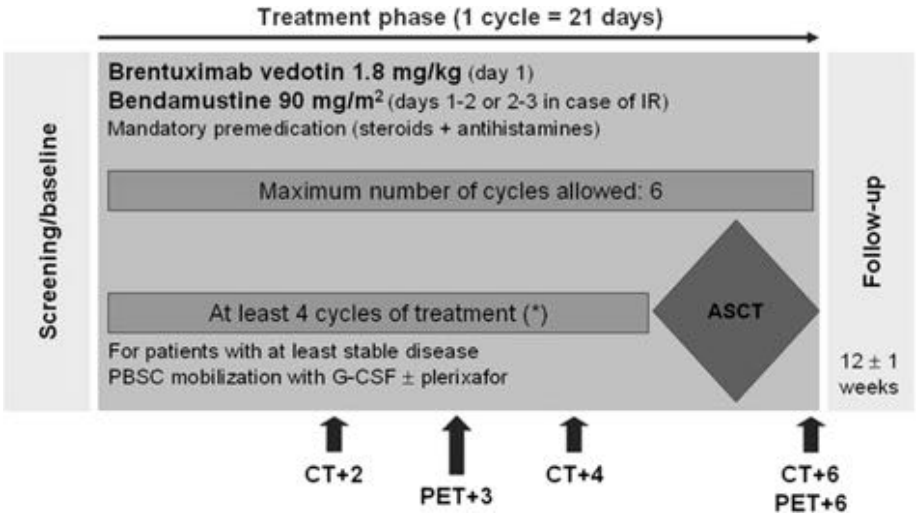


Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand

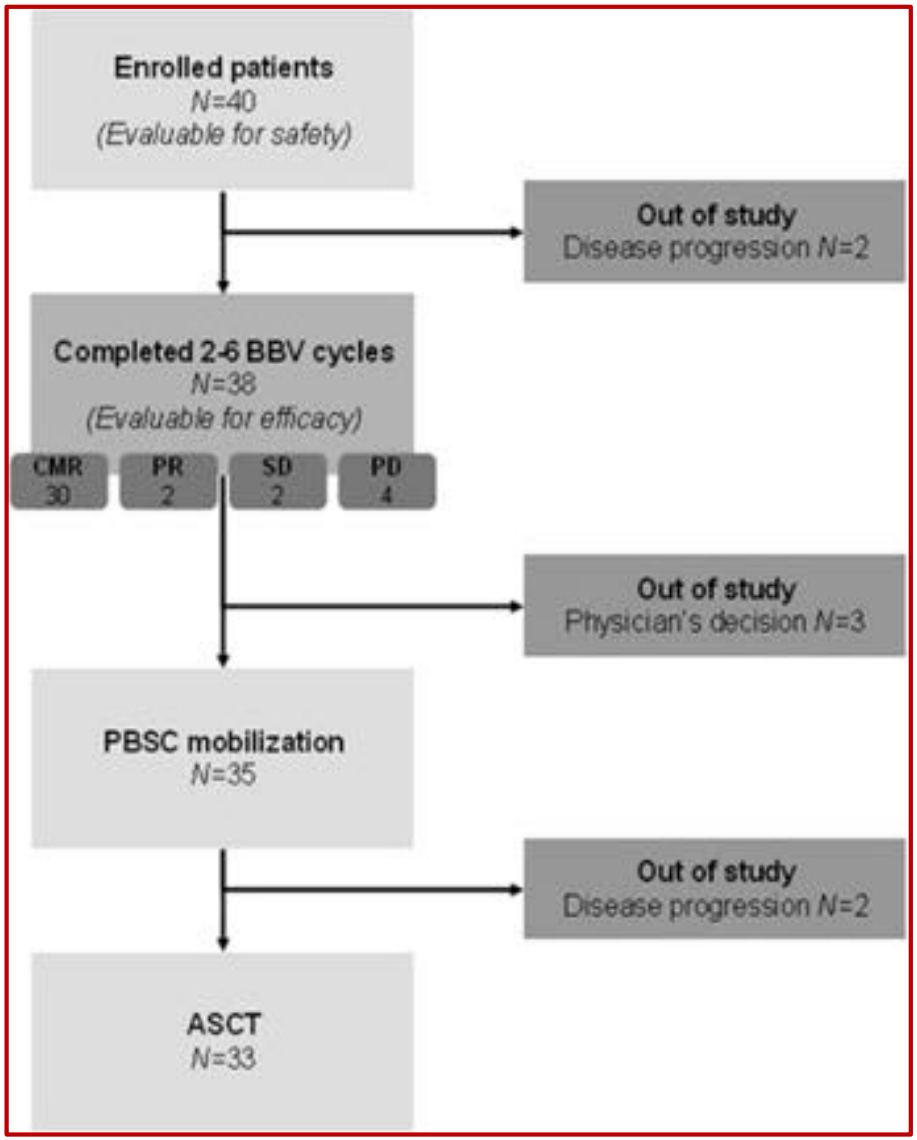
ARTICLE Open Access

First salvage treatment with bendamustine and brentuximab vedotin in Hodgkin lymphoma: a phase 2 study of the Fondazione Italiana Linfomi

A. Broccoli[1], L. Argnani[1], B. Botto[2], P. Corradini[3], A. Pinto[4], A. Re[5], U. Vitolo[2], S. Fanti[6], V. Stefoni[1] and P. L. Zinzani[1], on behalf of Fondazione Italiana Linfomi ONLUS



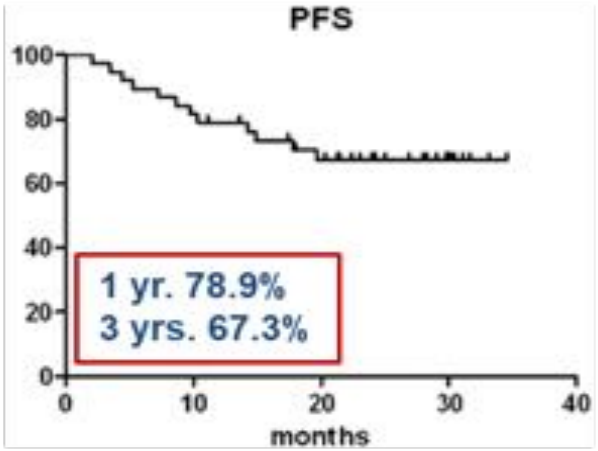
- ORR: 84.2%.
- CMR: 78.9%
- PR: 5.3%
- **Primary refractory**: ORR 75.0%
- **Relapsed:** ORR 94.4%
- 35 pts. successful mobilization
- 33 underwent ASCT

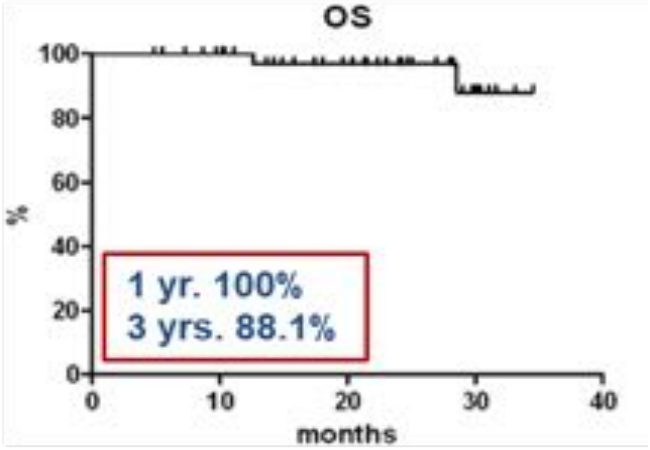


Median FU 23 mo.s

Broccoli et al. *Blood Cancer Journal* (2019)9:100

Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand





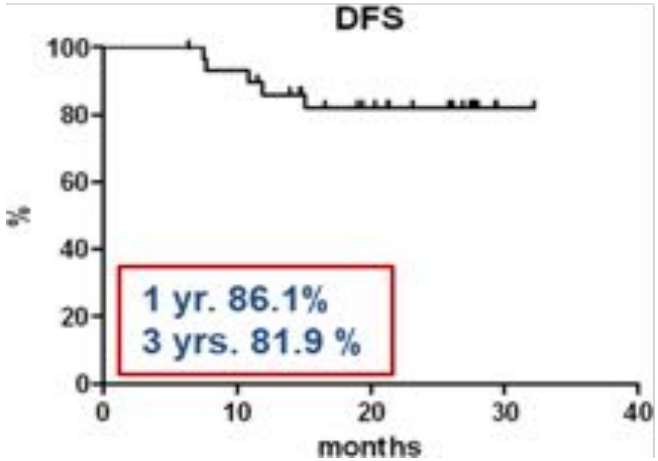
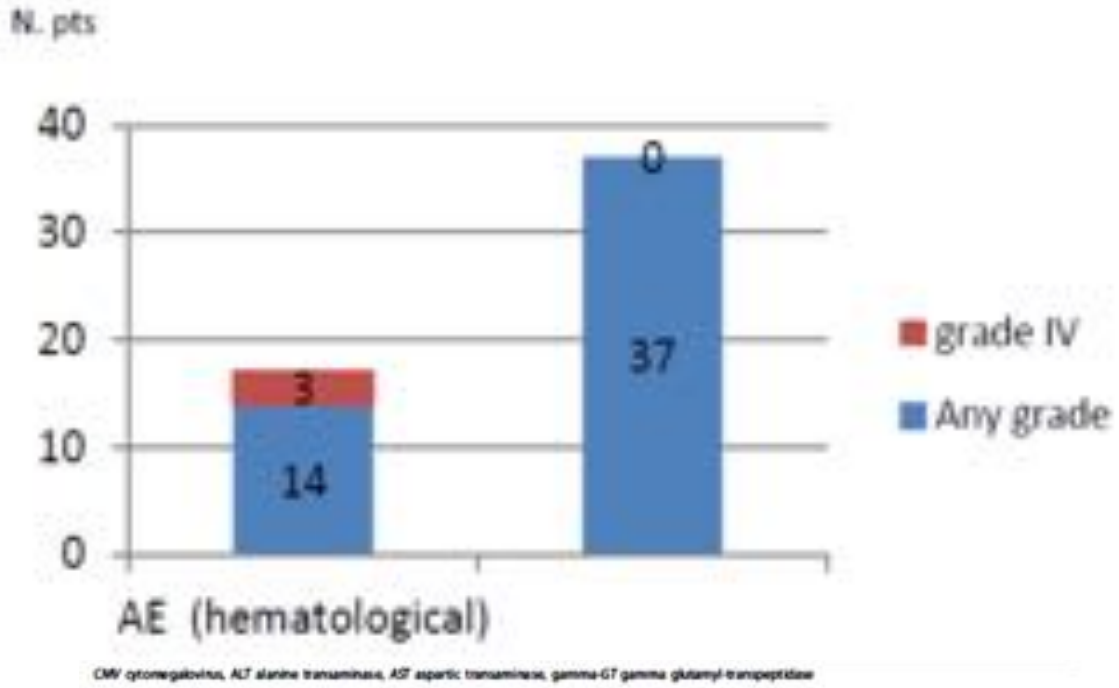


Table 2 AEs of any grade.

Toxicity	Patients involved, N	Events, N	Overall frequency (%)	Grade 1, N	Grade 2, N	Grade 3, N	Grade 4, N
Hematological toxicity	14	47	100	16	7	15	3
Neutropenia	8	13	31.7		2	8	3
Leukopenia	6	12	29.3	2	4	6	
Anemia	8	8	19.5	7	1		
Thrombocytopenia	5	7	17.1	7			
Febrile neutropenia	1	1	2.4			1	
Extrahematological toxicity	37	166	100	87	69	10	0
Skin reaction	26	46	27.7	19	21	6	
Fever	17	26	15.7	18	7	1	

Hematologic Toxicity Grade	N; type	Non-hematologic Toxicity Grade	N; type
Gr 1-2	21	Gr 1-2	133
Gr 3	15; neutropenia	Gr 3	9; 5 skin reaction, 1 IRR
Gr 4	3; neutropenia	Gr 4	0



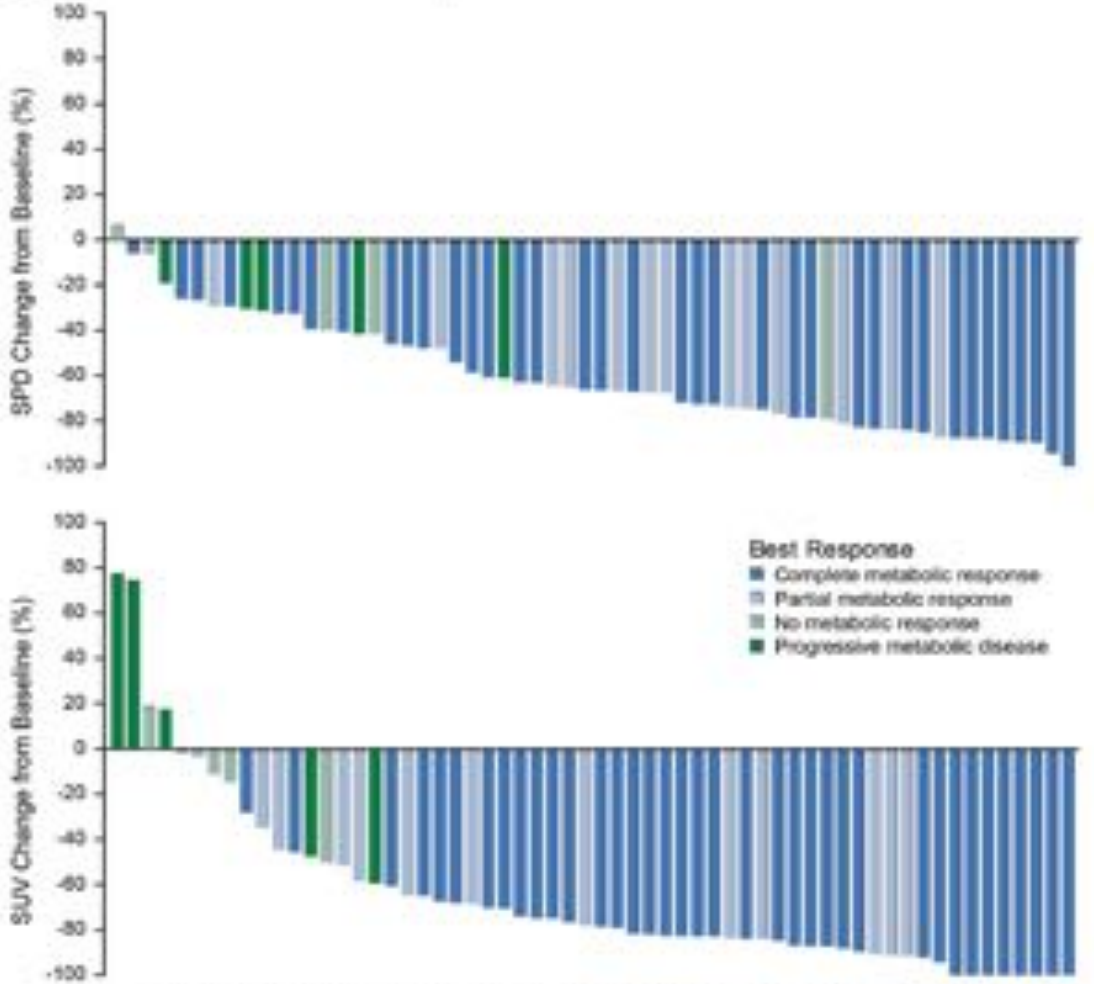
Broccoli et al. *Blood Cancer Journal* (2019)9:100

Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand

BV + Nivolumab is an effective 2nd line therapy and bridge to transplant

87% ORR, 68% CR among efficacy evaluable patients (n=90)

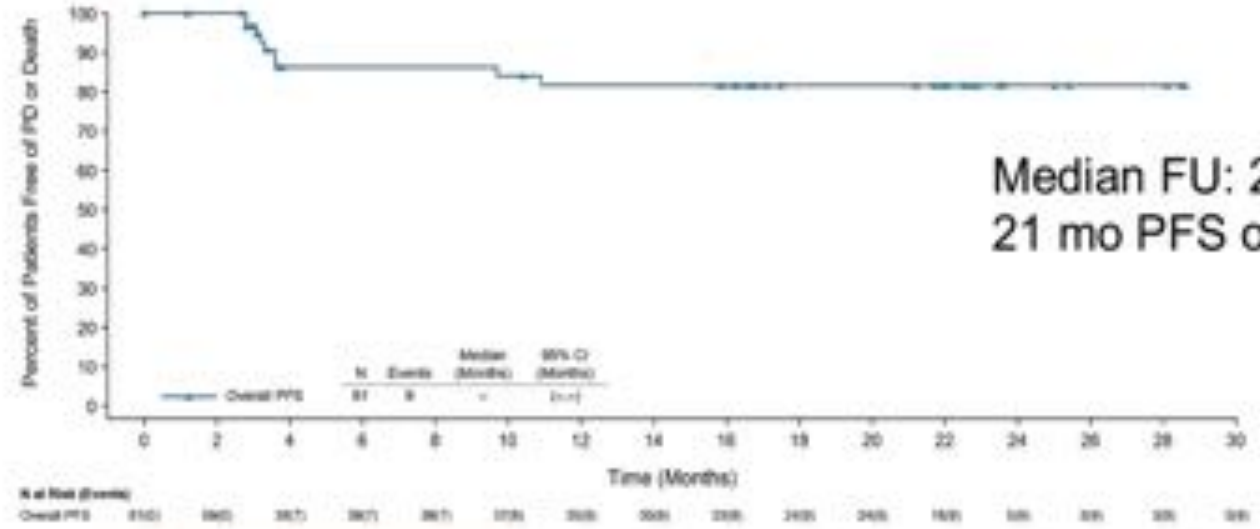
(85% ORR, 66% CR among all treated patients, n=91)



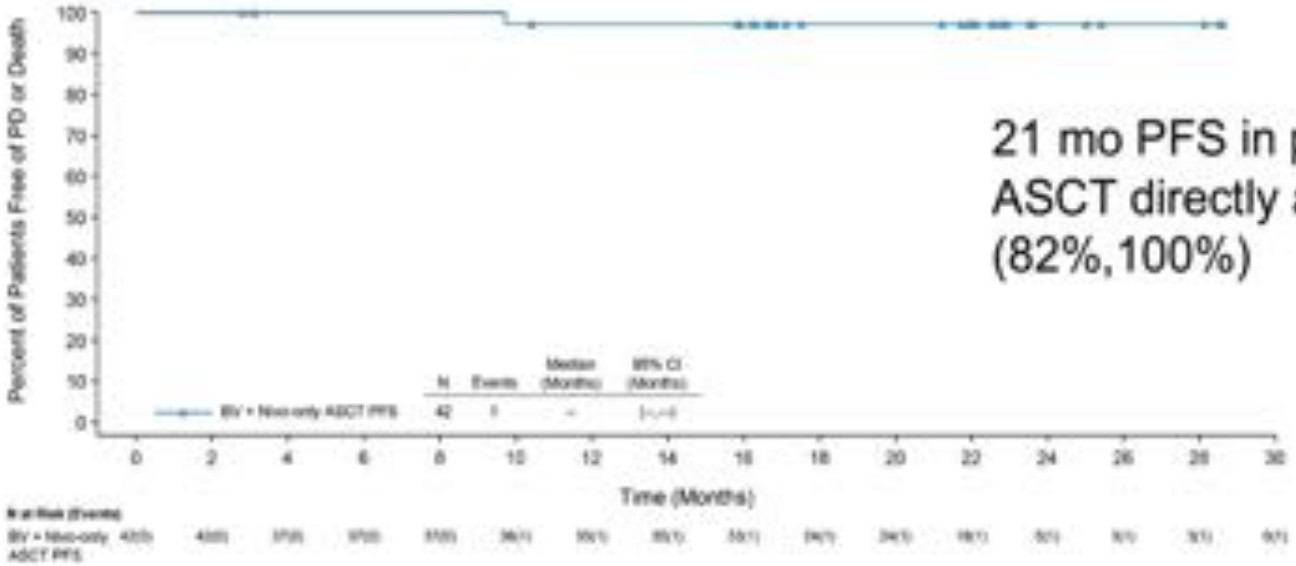
Herrera AF, et al. Blood 2018; Advani R et al. ASH 2018

Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand

PFS after BV+Nivo as 1st salvage therapy for HL



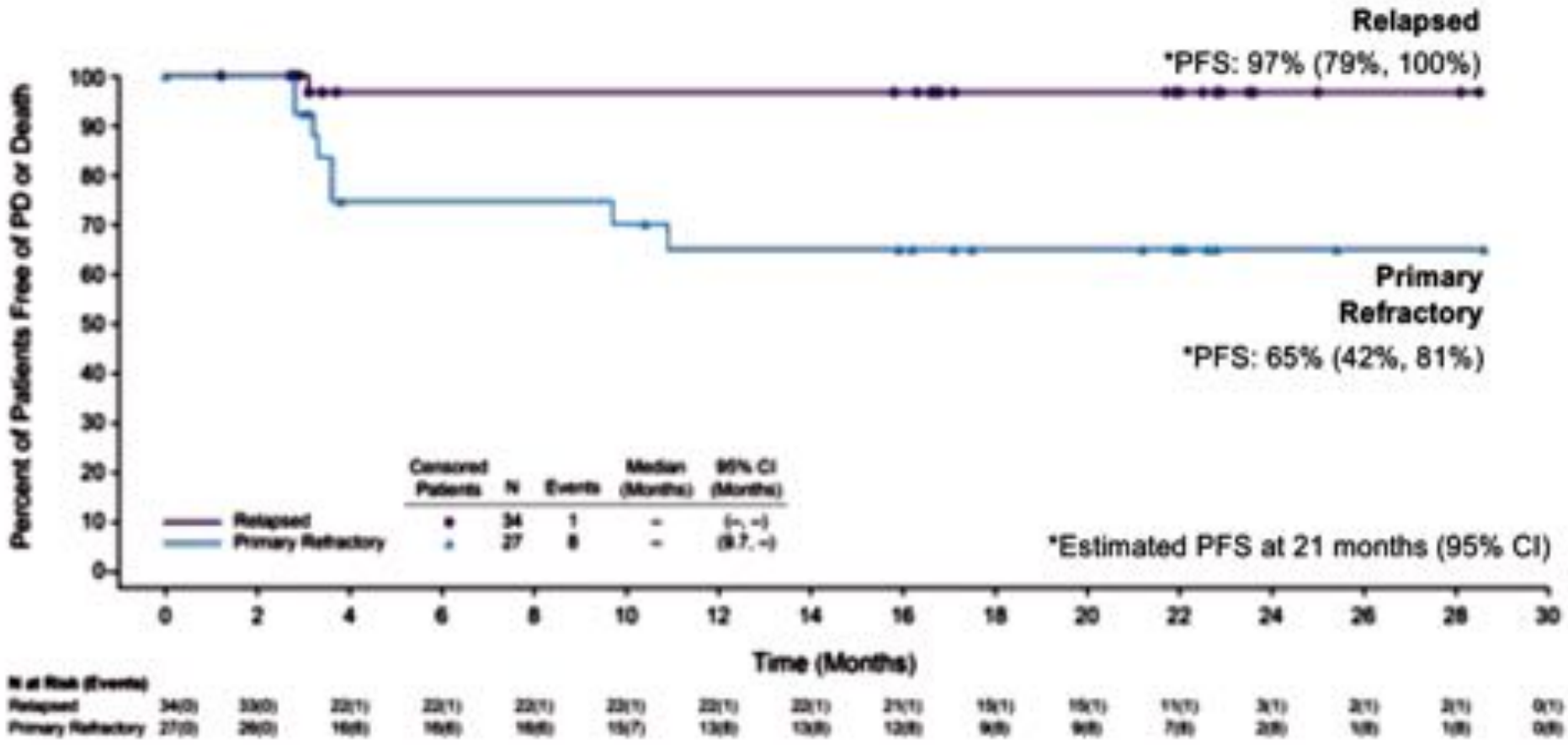
Median FU: 21.8 months
21 mo PFS overall: 82% (67%, 90%)



21 mo PFS in pts who proceeded to ASCT directly after BV+Nivo: 97% (82%,100%)

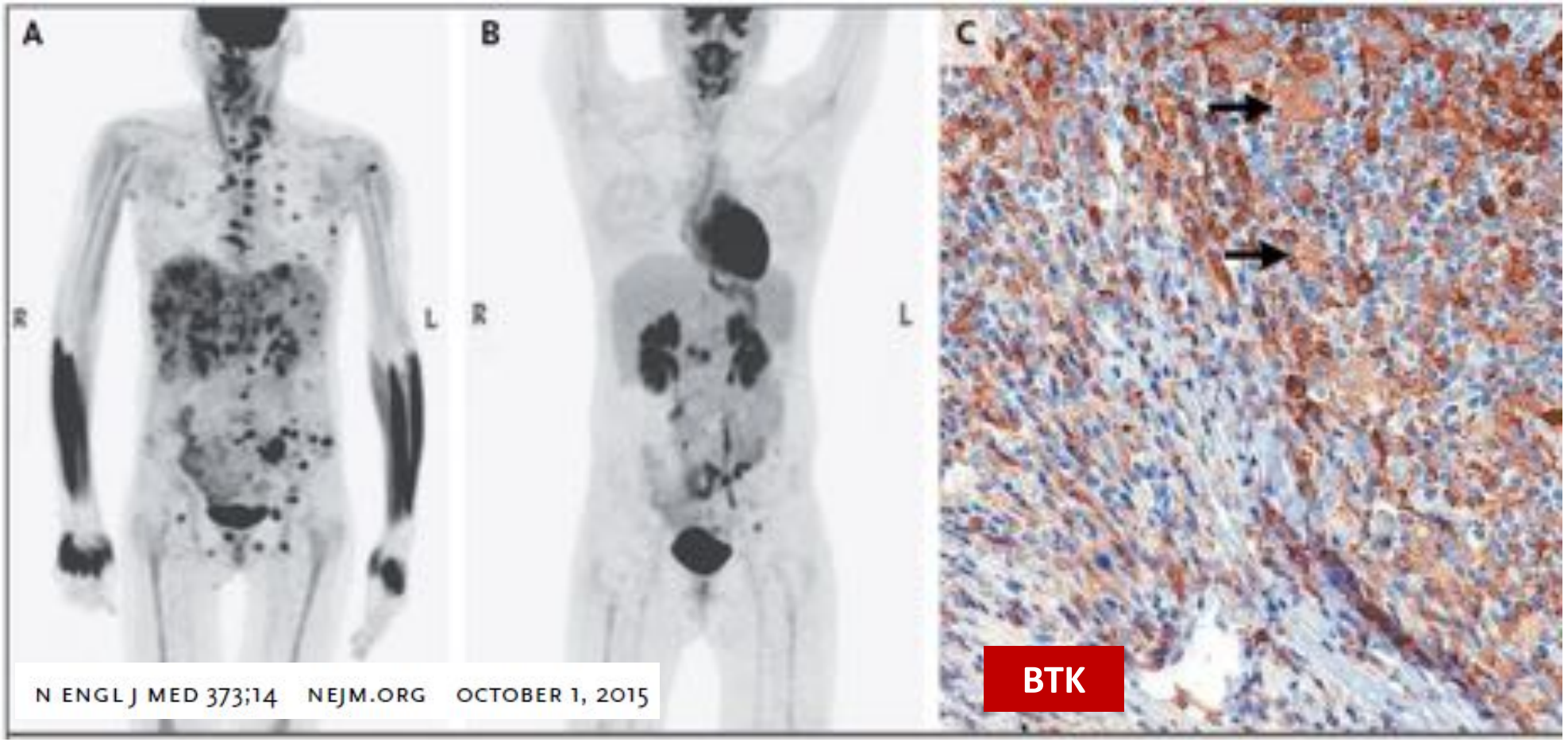
Herrera AF et al. ISHL 2018

Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand



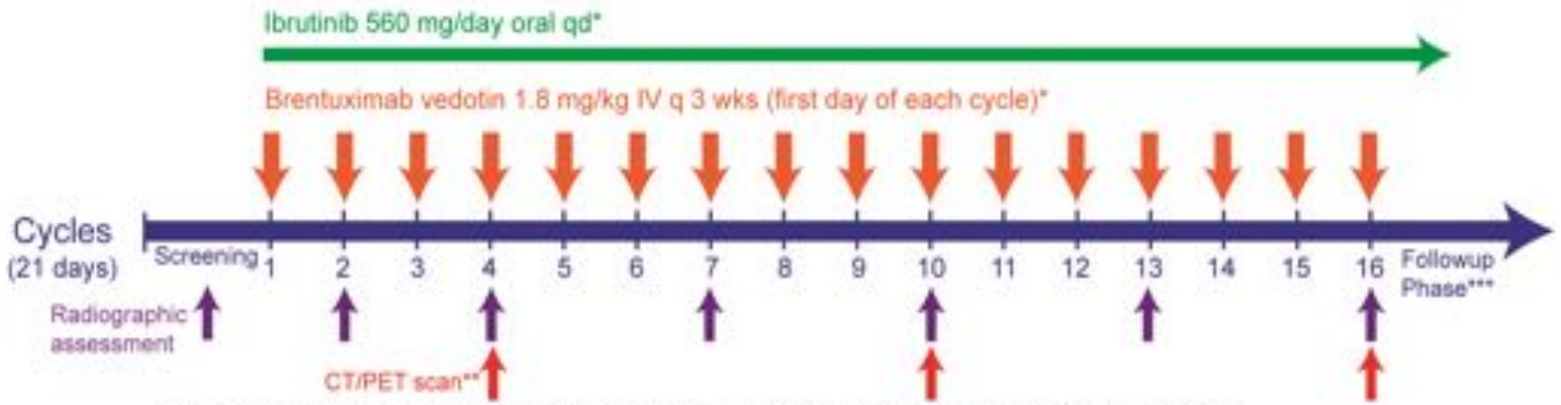
Brentuximab Vedotin in the Overall Treatment Strategy for HL

Ibrutinib in Refractory Classic Hodgkin's Lymphoma



Phase II Study of Brentuximab Vedotin Plus Ibrutinib for Patients With Relapsed/Refractory Hodgkin Lymphoma

Brentuximab Vedotin in the Overall Treatment Strategy for HL



*Patients will be treated until disease progression, unacceptable toxicity, or moving onto auto- or allo-HCT
**Once PET portion is negative, it does not need to be performed again.
***Subjects will be followed for up to two years with q3 month interval visits or telephone calls.

Characteristic, n (%)	Phase II Patients [n = 13] 560 mg Ibrutinib
Gender	
Female	5 (38)
Male	8 (62)
Age	33 (17-69)
Stage at Diagnosis	
I-II	7 (54)
III-IV	6 (46)
B symptoms (at diagnosis)	6 (46)
Prior Therapy	
ABVD	12 (92)
BEACOPP	3 (23)
R-CHOP	1 (8)
IGEV	1 (8)
BV	1 (8)
ICE	0
Clinical Trials	0
PD1 inhibitors	0
Prior Radiation	3 (23)
Status Prior to Treatment	
Progressive Disease	7 (54)
Relapsed Disease	6 (46)
Stable Disease	0
Best Response to Induction	
Refractory	5 (38)
Relapsed	8 (62)

Characteristic, n (%)	Phase II Patients [n = 13] 560 mg Ibrutinib
Median Number of Cycles	5 (2-9)
Best Response	
CR	6 (46)
PR	5 (39)
SD	2 (15)
PD	0
Response Rate (PR/CR)	84.6%

Chen R, et al. *Blood.* 2017;130: Abstract 738.

...Novel Agents for cHL: Operating Instructions

TABLE 1. Newer Salvage Regimens for Relapsed or Refractory Hodgkin Lymphoma

Regimen	n	% PET Negative	ASCT, n (%)	PFS/EFS (ITT)	PFS/EFS (Transplanted Patients)
BV-augICE (PET-adapted, sequential)[17,18]	65	83; 27 (BV alone)	64 (98)	82% at 3 years	NR
BV-ICE and others (PET-adapted, sequential)[19]	56	66; 43 (BV alone)	50 (89)	NR	67% at 2 years
BV plus bendamustine[20]	55	74	40 (72)	62.6% at 2 years	69.8% at 2 years
BeGEV[21]	59	73	43 (73)	62.2% at 2 years	80.8% at 2 years
BV plus gemcitabine[28]	42	67	34 (76)	NR	NR
BV plus ICE[23]	24	87	19 (79)	NR	NR
BV plus DHAP[22]	61	79	53 (87)	76% at 2 years	NR
BV plus ESHAP[24]	66	70	60 (91)	71% at 30 months	NR
BV-nivolumab[27]	62	61	42 (68) after only BV-nivolumab; 14 (23) after additional salvage	82% at 21 months	97% at 21 months for patients transplanted after only BV-nivolumab

Brentuximab vedotin for newly diagnosed advanced HL

- **Elderly**
  - Single agent BV
  - Sequential BV and AVD
  - BV plus DTIC (Bendamustine ?)
  - BV plus Bendamustine (HALO)
  - BV plus Lenalidomide
  - BV plus combination CT (CAP: CTX,Doxo, Pred)
- **Young**
  - A2VD (ECHELON-1)
  - A-A2VD Nonbulky stage I/II HL
  - BrECADD

BV-based combinations for upfront treatment of HL

CLINICAL TRIALS AND OBSERVATIONS

Blood. 2017;130(26):2829-2837

Frontline brentuximab vedotin in combination with dacarbazine or bendamustine in patients aged ≥60 years with HL

Jonathan W. Friedberg,[1] Andres Forero-Torres,[2] Rodolfo E. Bordoni,[3] Vivian J. M. Cline,[4] Dipti Patel Donnelly,[5] Patrick J. Flynn,[6] Gregg Olsen,[7] Robert Chen,[8] Abraham Fong,[9] Yinghui Wang,[9] and Christopher A. Yasenchak[10]

Table 3. Summary of best clinical response

	BV+DTIC (n = 21)	BV+bendamustine (n = 17)
ORR*	21 (100)	17 (100)
95% CI†	83.9, 100	80.5, 100
Best clinical response		
CR	13 (62)	15 (88)
PR	8 (38)	2 (12)
95% CI† for CR rate	38.4, 81.9	63.6, 98.5

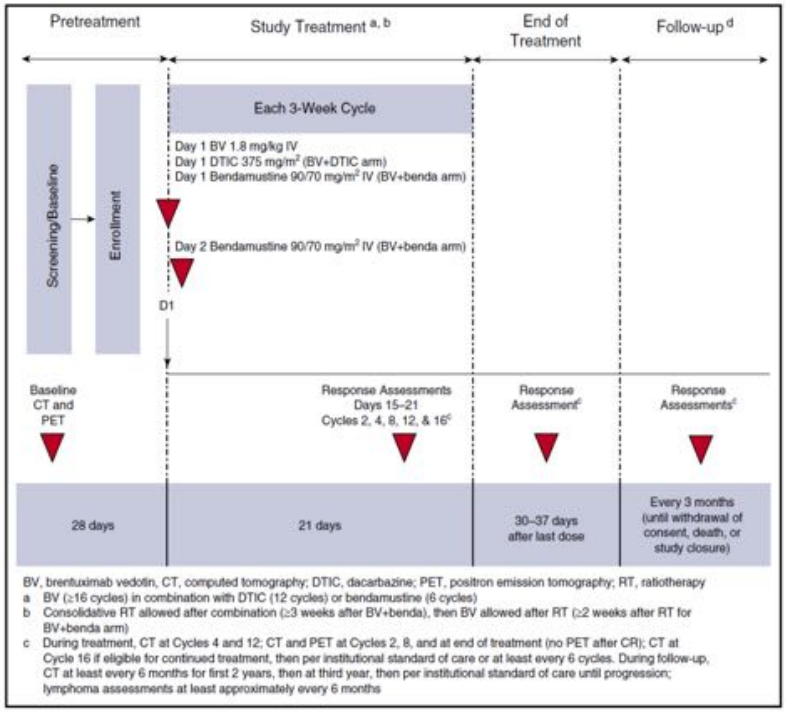
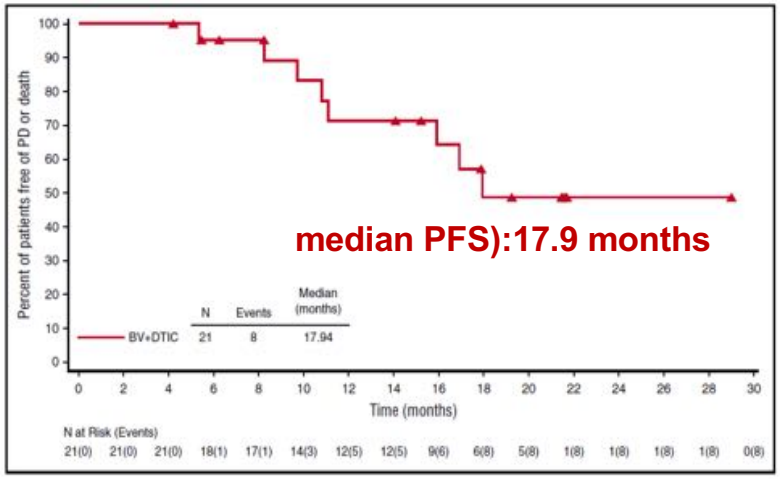


Table 4. Summary of AEs

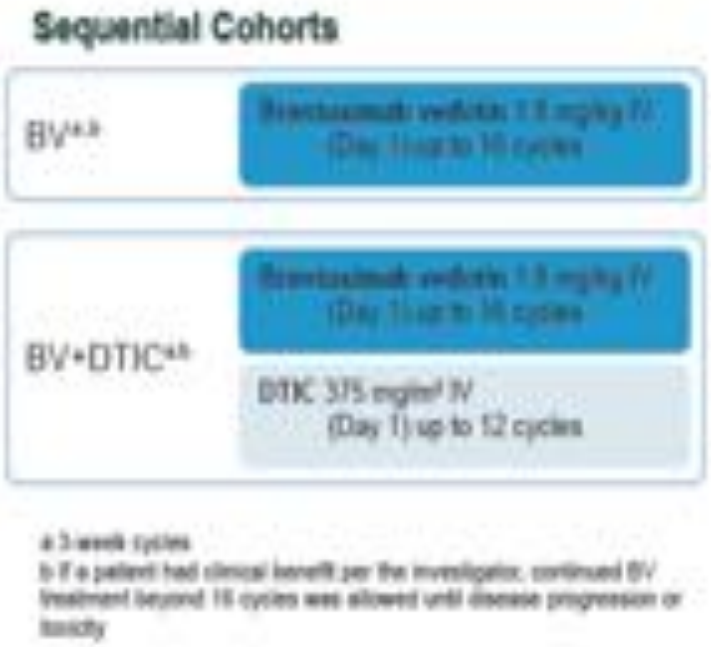
	BV+DTIC (n = 22)	BV+bendamustine (n = 20)
Any TEAE*	22 (100)	20 (100)
Treatment-related AEs	22 (100)	19 (95)
Grade ≥3 AEs	10 (45)	18 (90)
SAEs	4 (18)	13 (65)
AEs leading to treatment discontinuation	12 (55)	12 (60)
Deaths within 30 d of last dose	0	2 (10)†



Brentuximab vedotin for newly diagnosed advanced HL

BV Alone or in Combination (DTIC) for Elderly Patients with untreated HL

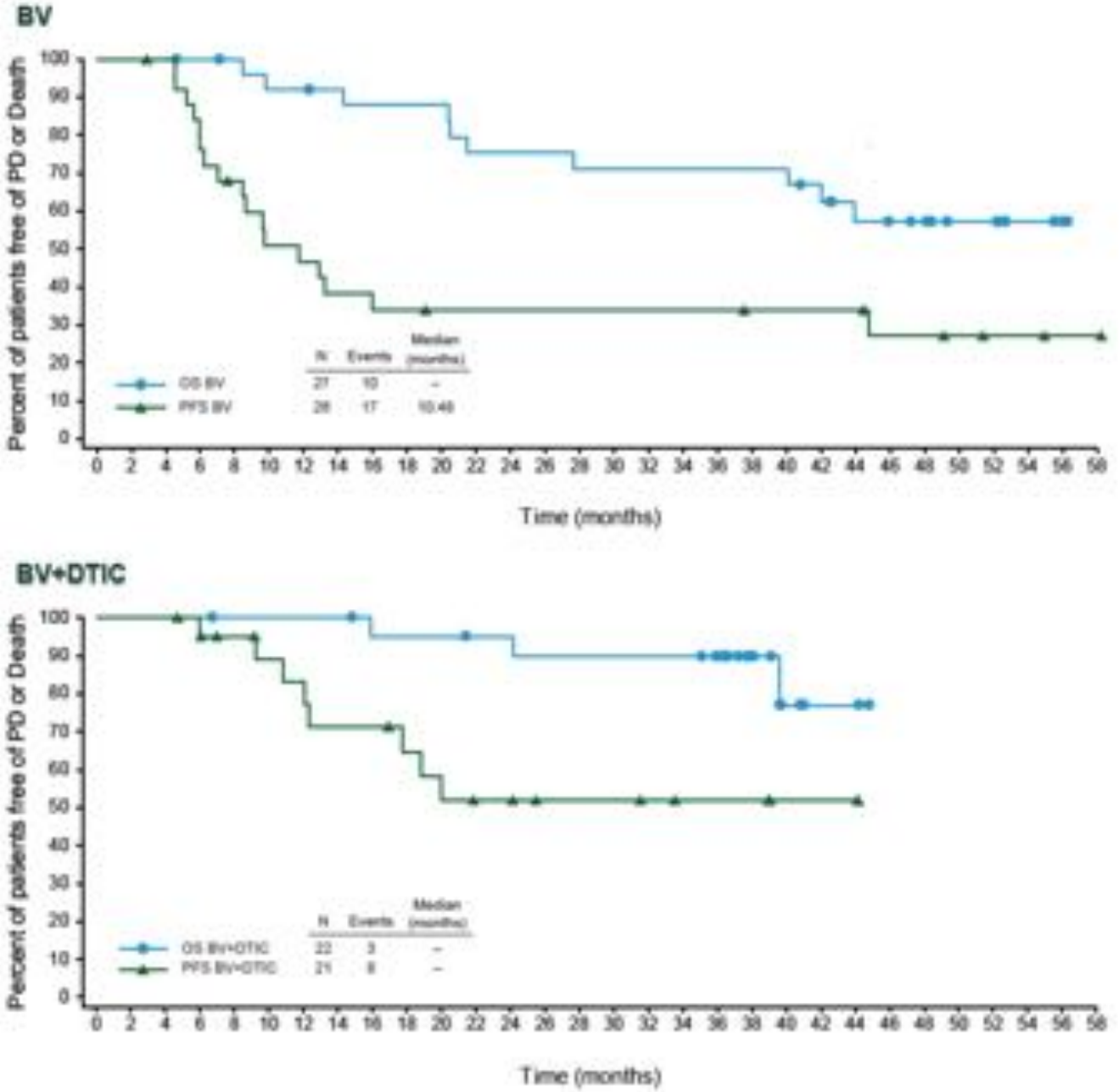
- Long-term follow-up of brentuximab vedotin +/- dacarbazine as first line therapy in elderly patients with HL has shown to induce long-term remissions for a subset of patients
- BV + dacarbazine may be an induction option for frail, elderly patients ineligible for standard treatment with durable responses leading to a 3-year overall survival rate of 90% with combination therapy.
- Median observation time from first dose (time to death or last contact)
  - BV: 42.6 months (range, 4.6–56.3)
  - BV+DTIC: 37.8 months (range, 14.8–44.8)



	BV (N = 27)	BV+DTIC (N = 22)
3-yr PFS rate (95% CI)	34% (16%, 53%)	52% (26%, 73%)
3-yr OS rate (95% CI)	71% (49%, 85%)	90% (65%, 97%)
Tx-emergent PN, n (%)	24 (89%)	19 (86%)
Complete resolution, n/N (%)	9/24 (38%)	5/19 (26%)
Some resolution/improvement, n/N (%)	9/24 (38%)	8/19 (42%)

Friedberg Abstract #7542 ASCO 2018

Brentuximab vedotin for newly diagnosed advanced HL

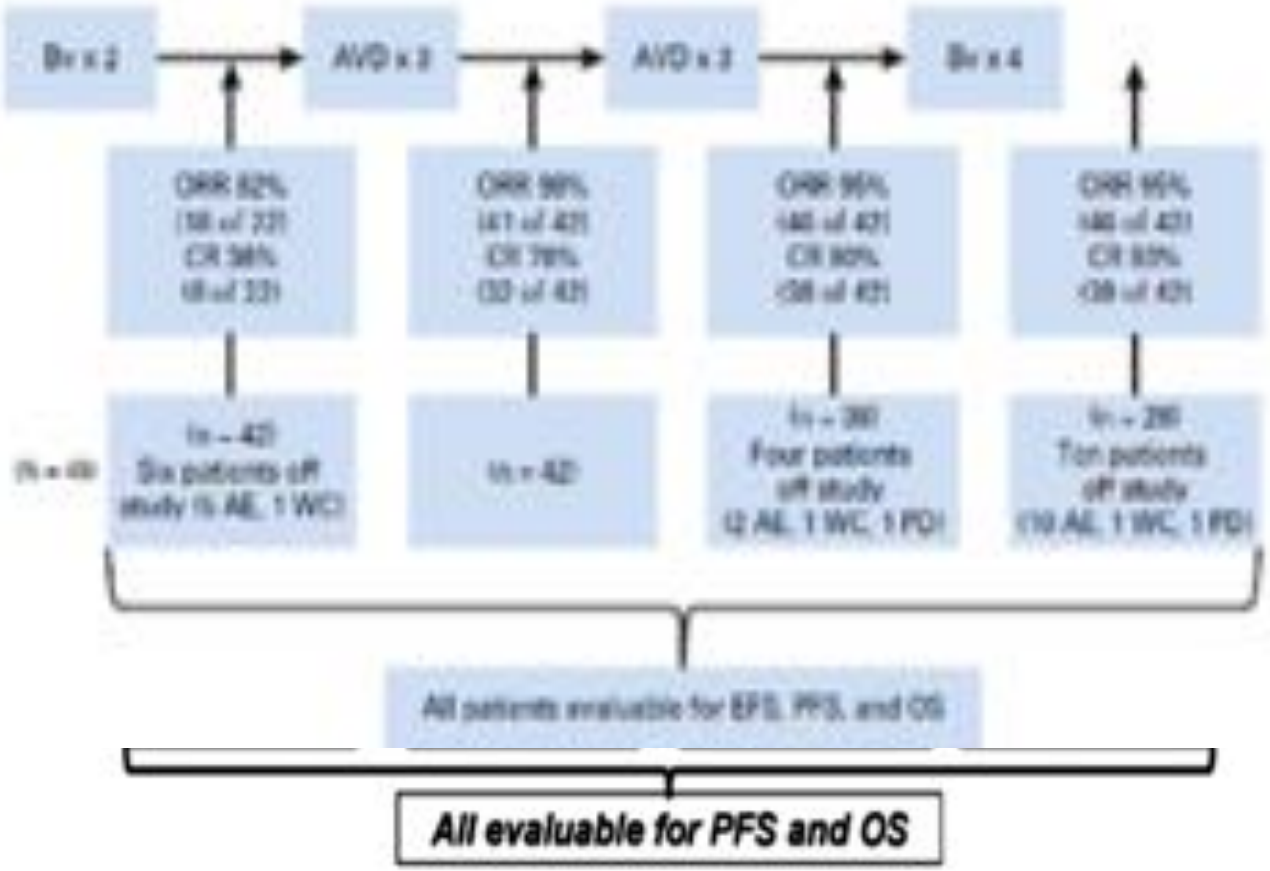


Adding DTIC to BV monotherapy may increase durability of response and survival in the elderly population

Friedberg et al, ASCO 2018, Poster #179, Abstract #7542

Brentuximab vedotin for newly diagnosed advanced HL

- Phase 2 study of untreated older HL patients received 2 doses of BV followed by 6 cycles of AVD: responding pts received 4 BV consolidation doses.



ITT median follow-up 23 mos

- **2 yr PFS 84%**
- **2yr OS 95%**

In this elderly population, the following prognostic factors were associated with significantly inferior PFS

- High Cumulative Illness Rating Scale-Geriatric (CIRS-G)co-morbidity score ($p<0.0001$)
- loss of instrumental activities of daily living (iADL) ($p<0.0001$)

Evens Abstract #7540 ASCO 2018

Brentuximab vedotin for newly diagnosed advanced HL

HALO STUDY: Phase 1/2 Trial of BV + Bendamustine in Elderly Pts. (n= 51) With Advanced HL

Objective: *Phase I:* Tolerability and toxicity (n=12); *Phase II:* Response rate after completion of treatment (n=48)

Patients: elderly pts with advanced classical HL

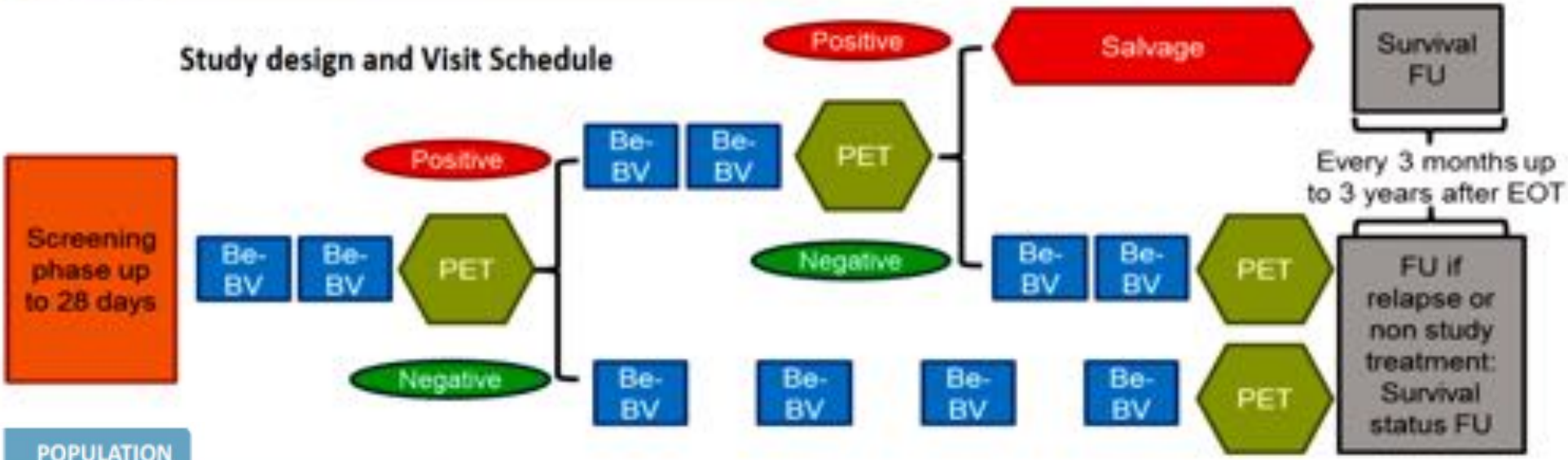
Dose and schedule: Brentuximab vedotin 1.2 mg/kg IV over 30 minutes on days 1 plus bendamustine 90 mg/m² IV over 30–60 minutes on days 1 and 2, Q3wk

1) Adcetris® (BV) : 1.2 mg/kg intravenously
- Infusion over 30 min

2) Levact® (Be): 90 mg/m²/day IV at D1 and D2
- 30 min after Adcetris infusion, infusion over 30-60 min

Schedule of the BV-Be regimen

Study design and Visit Schedule



POPULATION	
Study population (n=51)	
Age mean (range)	70.4 (62-79)

Gallamini ICML 2019, Lugano, CH

Brentuximab vedotin for newly diagnosed advanced HL

HALO STUDY: Phase 1/2 Trial of BV + Bendamustine in Elderly Pts. With Advanced HL

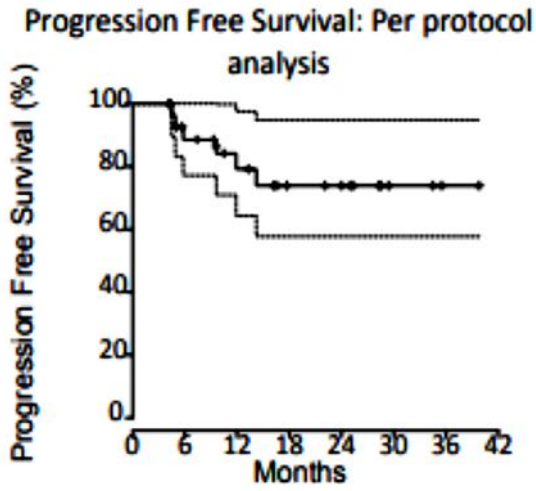
RESPONSES

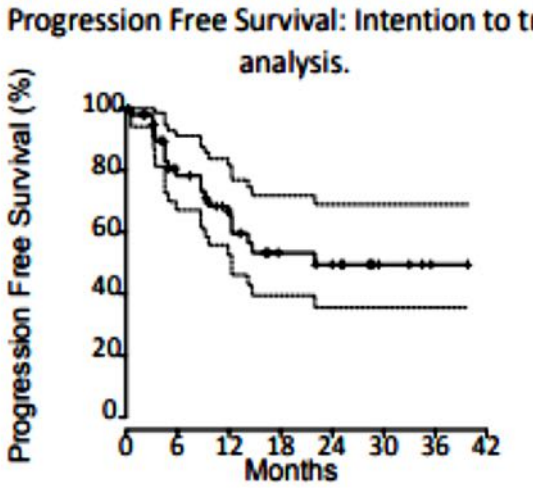
Evaluated treatment cycle			
Deauville score	Cycle 2 (n=51)	Treatment Response	End of TRT (n=51)
1-3	40 (78%)	CR (score 1-3)	32 (63%)
4	6 (12%)	PR (score 4)	2 (4%)
5	2 (4%)	NR/Pro	10 (19%)
NE	3* (6%)	NE	7**(14%)

Toxicities grade > 3 (n=208)	
Lymphocytopenia	91 (58.5%)
WBC decreased	33 (21%)
Rash/Infusion reaction/Device infection	5 (3%)
CMV reactivation	5 (3%)
Febrile neutropenia	3 (2%)
Stomatitis	2(1.5%)
Thrombocytopenia	1 (0.5%)
Other(ALAT increased, GGT increased, Hypersensitivity, Pyrexia, Rash maculo-papular	16 (10.5%)

Safety :

- Toxicities grade 3-4 : No platelet or erythrocyte cells transfusion were required during treatment
- No neuropathy recorded ≥ grade 3





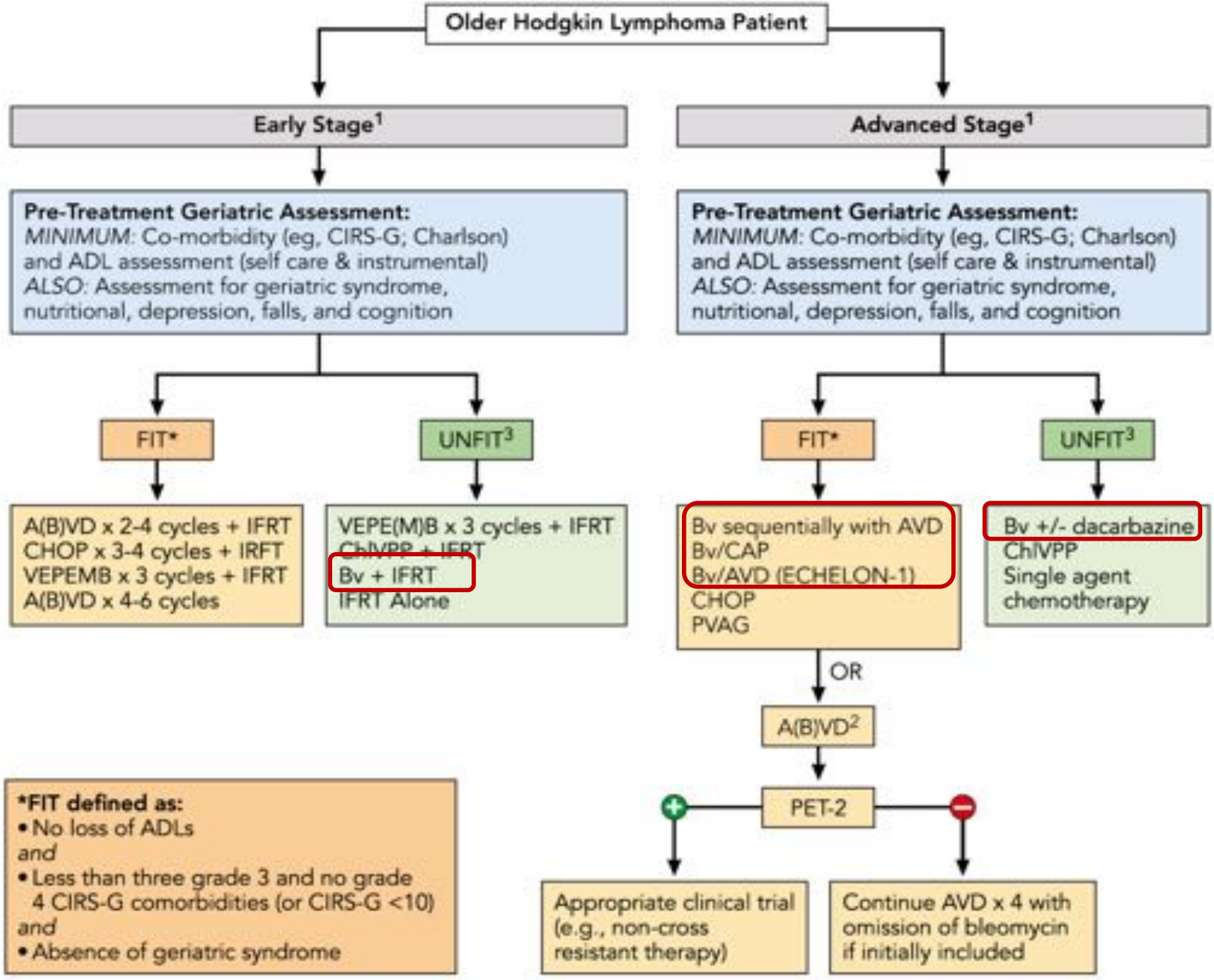
- 6/51 (10%) pts died: recurrent HL (3), CMV reactivation (2), 2nd neoplasm (1)
- Median follow-up of 22 (0-30) months: 31/51 (63%) pts in continuous CR in PP analysis

Conclusions

The present analysis, though conducted in 85% of enrolled patients, showed that Be-BV is an effective regimen in the real life of elderly HL, when delivered according to the schedule.

The toxicity of this treatment could be improved by a more strict prophylaxis of CMV infections,

Brentuximab vedotin for newly diagnosed advanced HL



Brentuximab vedotin for newly diagnosed advanced HL

CLINICAL TRIALS AND OBSERVATIONS

Brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine for nonbulky limited-stage classical Hodgkin lymphoma

Jeremy S. Abramson,[1] Jon E. Arnason,[2] Ann S. LaCasce,[3] Robert Redd,[3] Jeffrey A. Barnes,[1] Lubomir Sokol,[4] Robin Joyce,[2] David Avigan,[3] Donna Neuberg,[3] Ronald W. Takvorian,[1] Ephraim P. Hochberg,[1] and Celeste M. Bello[4]

Table 1. Patient characteristics (N = 34)

Characteristic	n
Age, median (range), y	36 (20-75)
Female/male	17/17
Stage	
IA	6 (18%)
IIA	24 (71%)
IIB	4 (12%)
Size of largest lesion, median (range), cm	3.34 (1.51-8.33)
Risk	
Early favorable	21 (62%)
Early unfavorable	13 (38%)
Histology	
Nodular sclerosis	18 (53%)
Mixed cellularity	4 (12%)
Lymphocyte-rich	4 (12%)
Classical not otherwise specified	8 (24%)

- Dose reductions: 38% of pts. (periph. sens. neuropathy)
- All grade neuropathy: 79%
- Grade 3/4 toxicities:
  - Neutropenia (62%)
  - Febr. neutropenia (35%)
  - Neuropathy (24%)
- 1 Neutropenic death (1° course)

KEY POINTS

- **Brentuximab vedotin plus AVD without consolidative radiation is an effective therapy for nonbulky limited-stage HL.**
- **Peripheral neuropathy and neutropenic fever appear increased with brentuximab-AVD compared with the expected toxicities of ABVD alone.**

Table 2. Response (N = 34)

Time point	Overall response	CR	Partial response	Progressive disease	Not evaluable*
Monotherapy lead-in	34 (100; 89.7-100)	18 (52.9; 35.1-70.2)	16 (47.1; 29.8-64.9)	0 (0; 0-10.3)	0 (0; 0-10.3)
Cycle 2	33 (97.1; 84.7-99.9)	33 (97.1; 84.7-99.9)	0 (0; 0-10.3)	0 (0; 0-10.3)	1 (2.9; 0.1-15.3)
End of treatment	31 (91.2; 76.3-98.1)	31 (91.2; 76.3-98.1)	0 (0; 0-10.3)	1 (2.9; 0.1-15.3)	2 (5.9; 0.7-19.7)

Blood. 2019;134(7):606-613

Brentuximab Vedotin: upfront treatment of HL

Five-year follow-up of brentuximab vedotin combined with ABVD or AVD for advanced-stage classical Hodgkin lymphoma

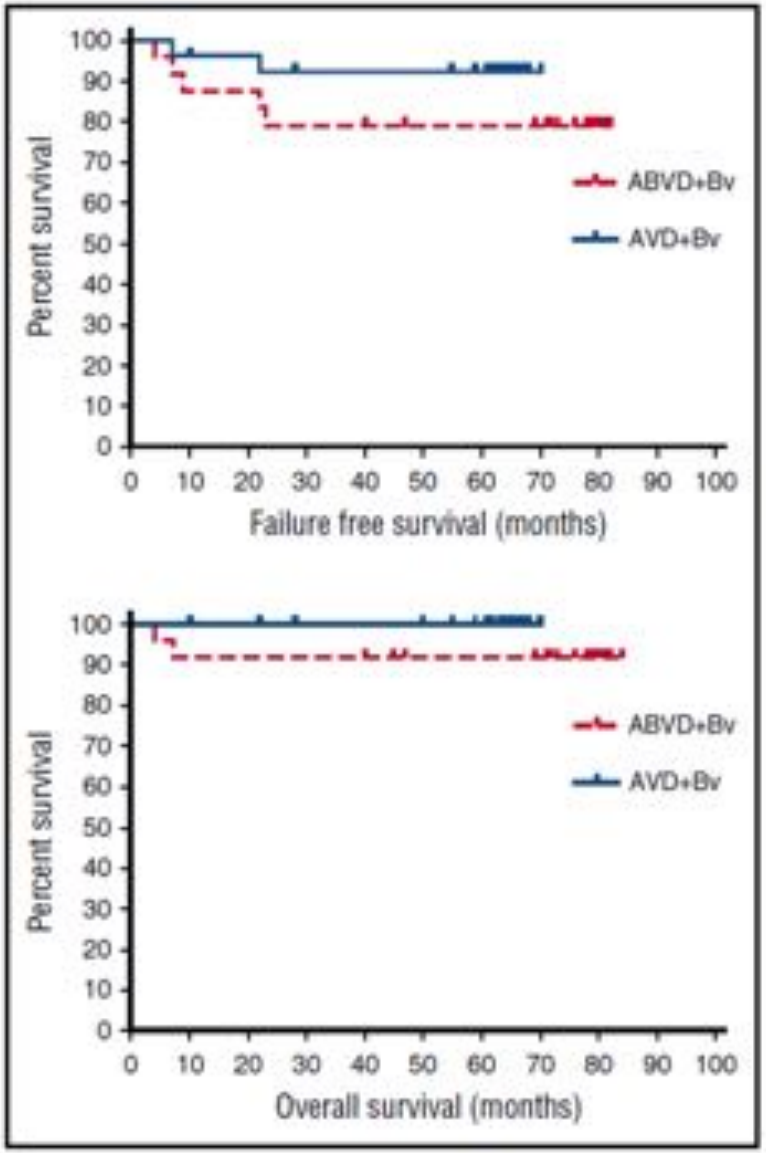
Joseph M. Connors,[1] Stephen M. Ansell,[2] Michelle Fanale,[3] Steven I. Park,[4] and Anas Younes[5]

Table 1. Patient characteristics

	ABVD + brentuximab vedotin	AVD + brentuximab vedotin
n	25	26
Age, y, median (range)	35 (19-59)	33 (18-58)
Male sex, n (%)	20 (80)	17 (65)
Performance status,* n (%)		
0	13 (52)	11 (42)
1	12 (48)	15 (58)
Stage, n (%)		
IIA bulky†	0	3 (12)
IIB	4 (16)	4 (15)
IIIA	5 (20)	3 (12)
IVA	4 (16)	5 (19)
IVB	12 (48)	11 (42)
International Prognostic Score, n (%)		
0-3	5 (20)	12 (46)
4-7	20 (80)	14 (54)

*Eastern Cooperative Oncology Group scale.
†Bulky = any mass ≥10 cm.

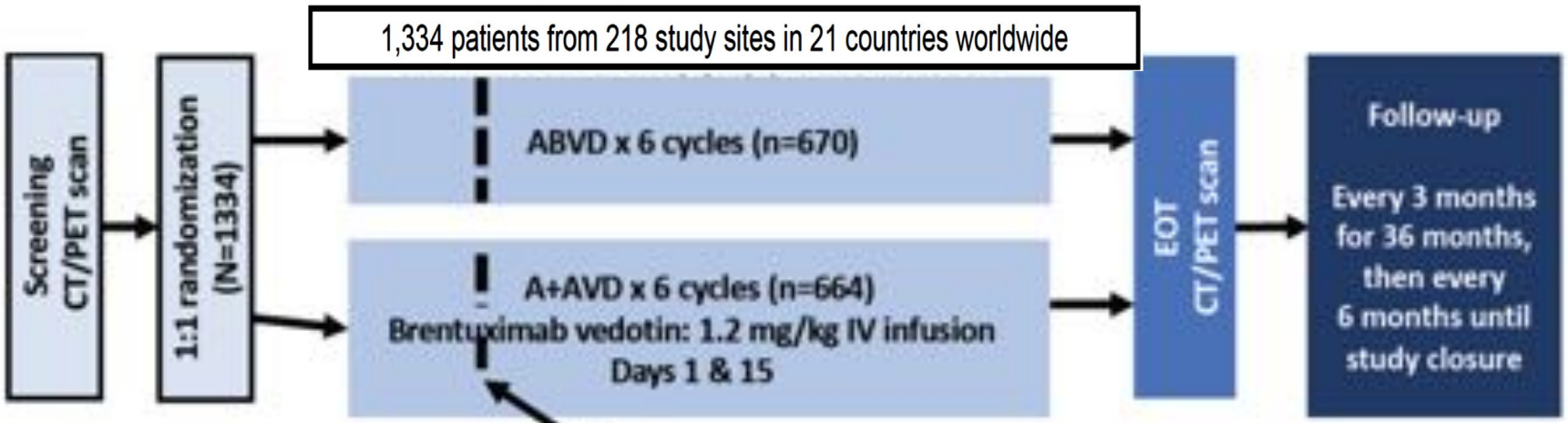
CR: 96%
5-year FFS: 92%
5-year OS: 100%



BLOOD, 14 SEPTEMBER 2017 • VOLUME 130, NUMBER 11

Brentuximab vedotin for newly diagnosed advanced HL

ECHELON-1: A+AVD versus ABVD in advanced stage HL



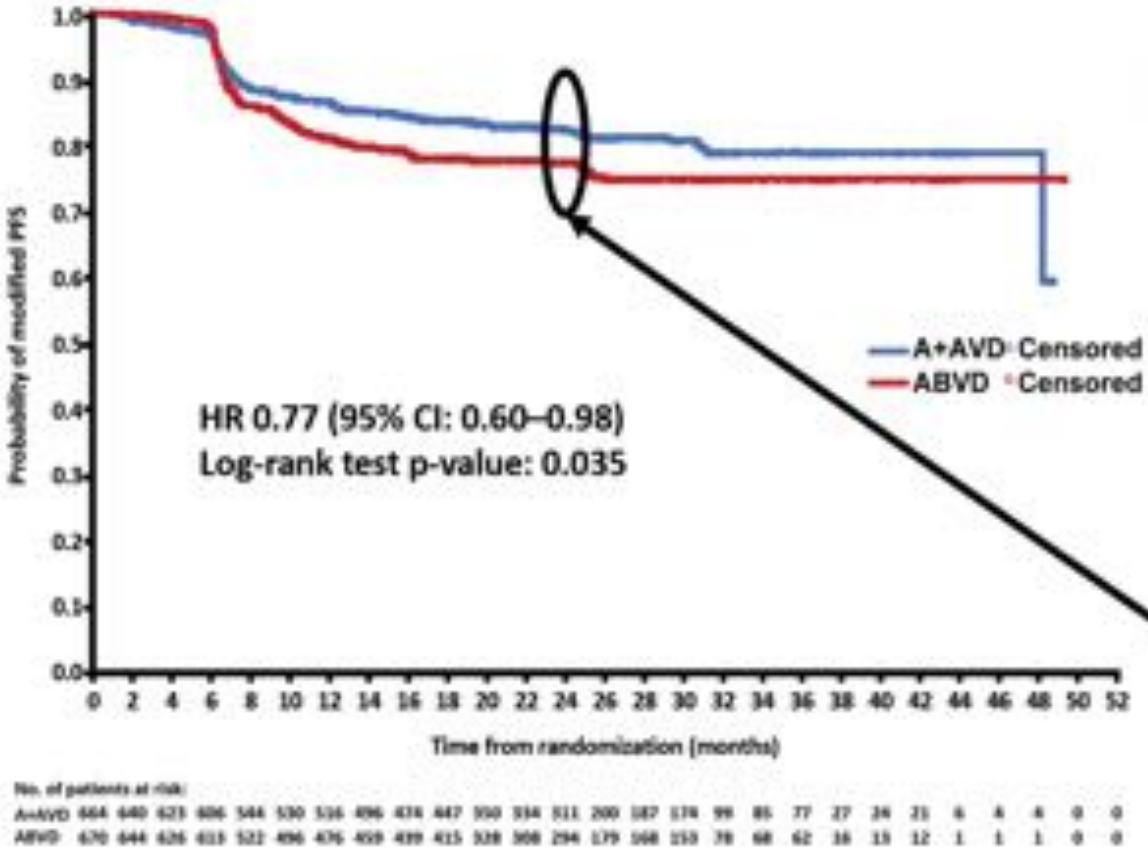
- Inclusion criteria
  - cHL stage III or IV
  - ECOG PS 0, 1 or 2
  - Age ≥18 years
  - Measurable disease
  - Adequate liver and renal function

Primary endpoint: modified PFS per IRF, with an event defined by the first evidence of:

- Disease progression, or
- Death, or
- Evidence of non-complete response (PET scan Deauville score 3–5) after completion of frontline therapy, followed by subsequent anticancer therapy.

. Connors JM, et al. N Engl J Med 2018;378:331–44.

Echelon-1: BV improves modified PFS



Number of events

Category	A+AVD N=117	ABVD N=146
Progression	90	102
Death	18	22
Modified progression	9	22
Chemotherapy	7	15
Radiotherapy	2	7

Modified PFS estimates

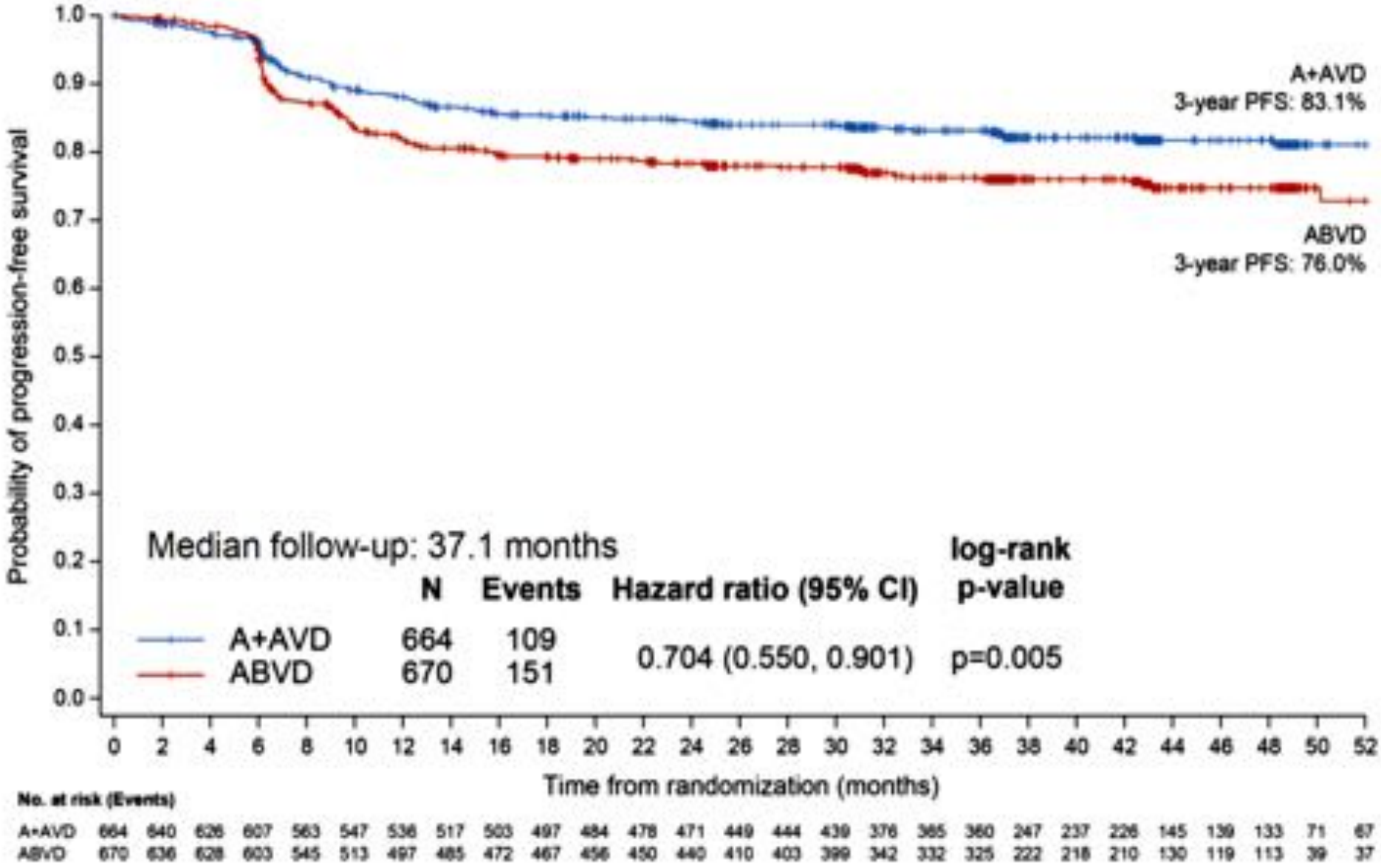
Time	A+AVD (95% CI)	ABVD (95% CI)
2-year	82.1 (78.7–85.0)	77.2 (73.7–80.4)

Median follow-up (range): 24.9 months (0.0–49.3)

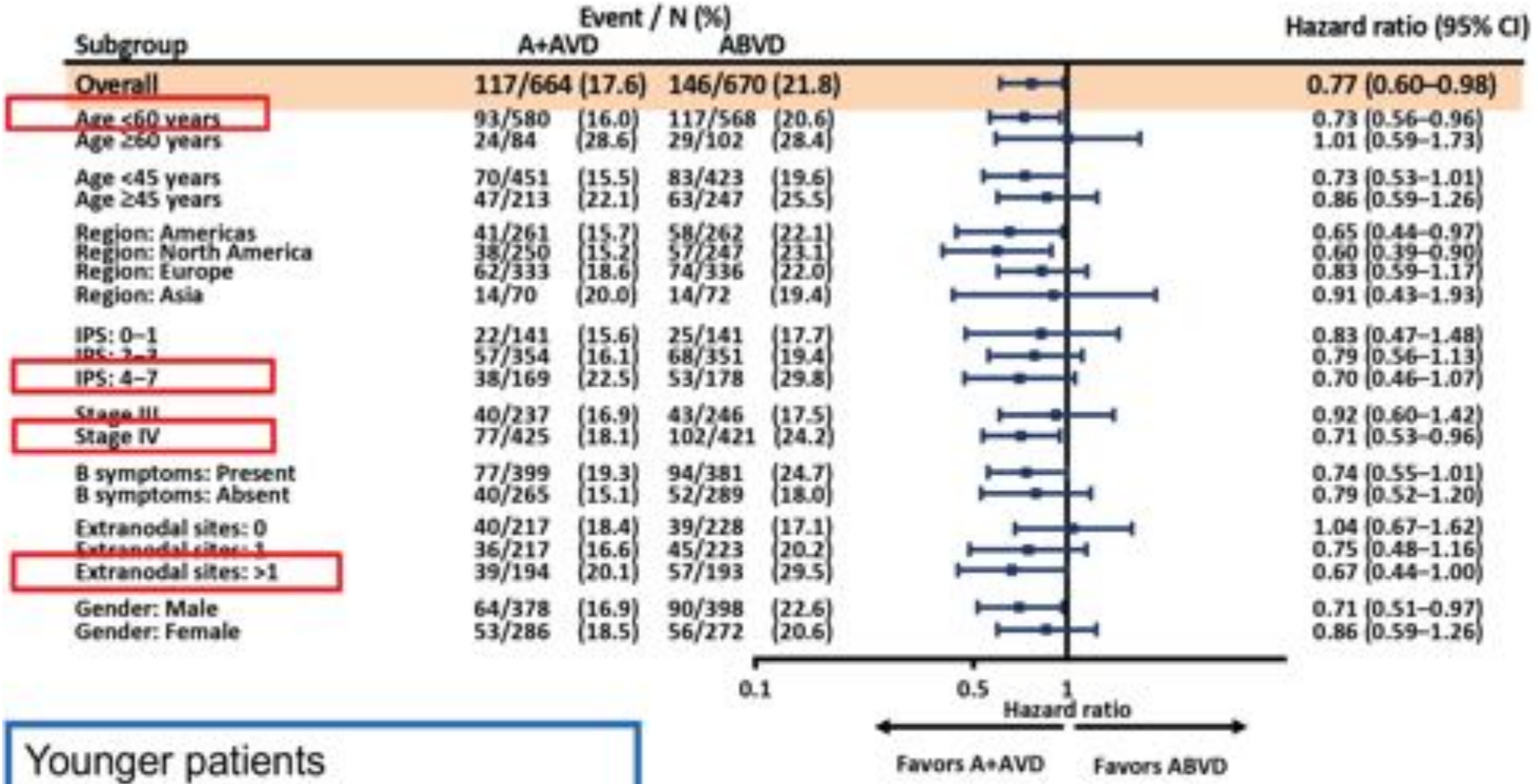
Connors et al. *NEJM* online 2017

Brentuximab vedotin for newly diagnosed advanced HL

- A+AVD vs ABVD resulted in a 30% reduction in the risk of progression or death at 3 years



Echelon-1: Who benefits from addition of BV?



Younger patients
North American pts
Extranodal sites > 1
Stage IV

Connors et al. *NEJM* online 2017

Brentuximab vedotin for newly diagnosed advanced HL

Echelon-1: 1+ extranodal sites or stage IV disease

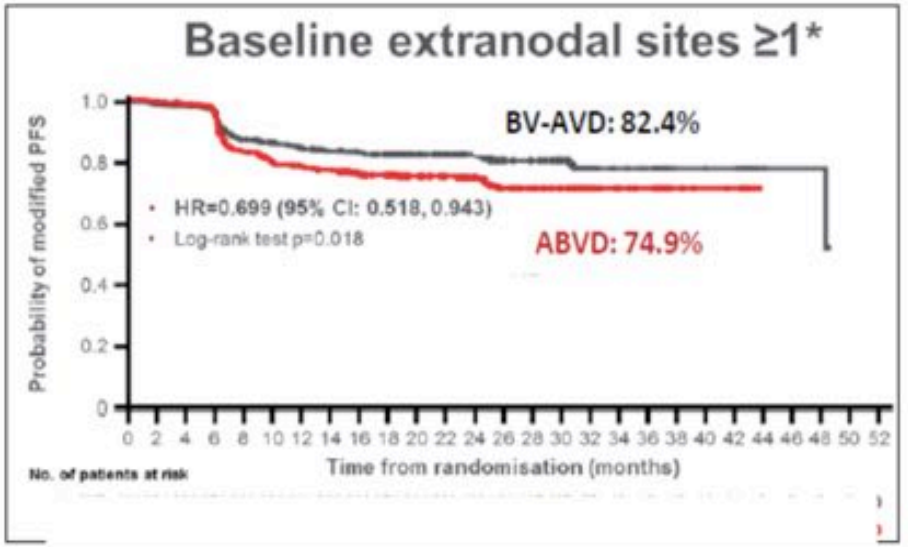
Summary of mPFS per IRF: High-risk sub-groups

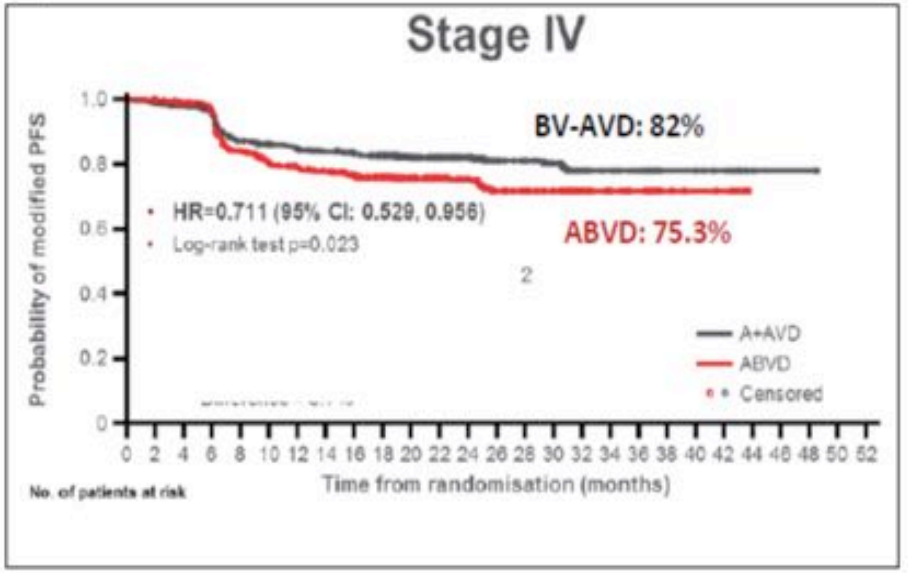
Sub-group	BV-AVD no. of events/total no. (%)	ABVD no. of events/total no. (%)	HR (95% CI)
Overall	**117/664 (17.6)**	**146/670 (21.8)**	**0.77 (0.60–0.98) p=0.04**
Baseline Ann Arbor stage			
Stage III	40/237 (16.9)	43/246 (17.5)	0.92 (0.60–1.42) p=0.712
Stage IV	77/425 (18.1)	102/421 (24.2)	0.71 (0.53–0.96) p=0.023
Baseline extranodal sites			
0	40/217 (18.4)	39/228 (17.1)	1.04 (0.67–1.62) p=0.856
1	36/217 (16.6)	45/223 (20.2)	0.75 (0.48–1.16) p=0.191
>1	39/194 (20.1)	57/193 (29.5)	0.67 (0.44–1.00) p=0.049
≥1*	75/411 (18.2)	102/416 (24.5)	0.70 (0.53–0.94) p=0.018

0.1 0.5 1.0

Favours BV-AVD ⟵ ⟶ Favours ABVD

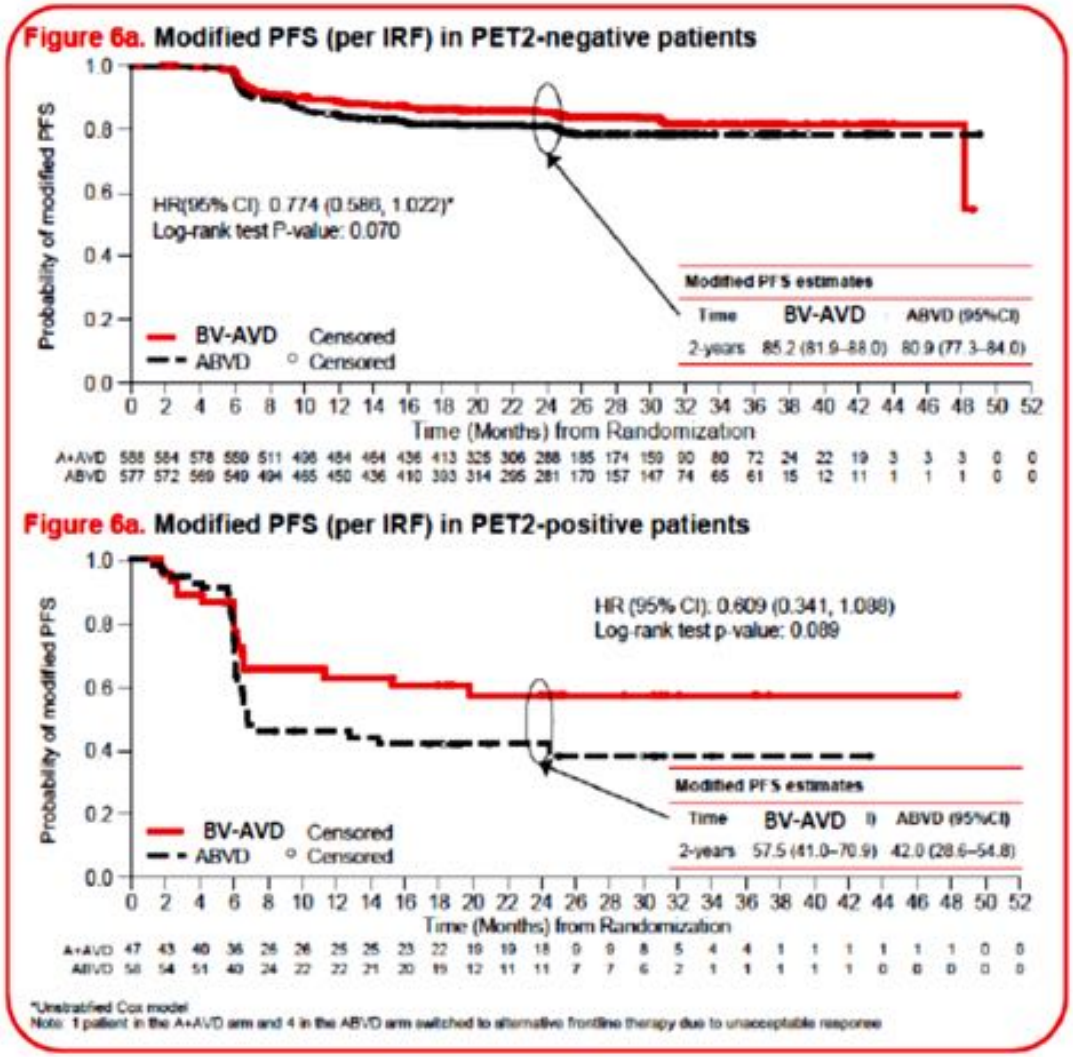
*Ad hoc analysis.
HR, hazard ratio; IRF, independent review facility





Courtesy Dr Hutchins EHA 2018

Echelon-1: Favorable outcomes after PET2+ with BV-AVD



Courtesy Chen et al ASCO 2018 # 7539

	PET2 neg 2-y mPFS
BV-AVD	85 %
ABVD	82 %

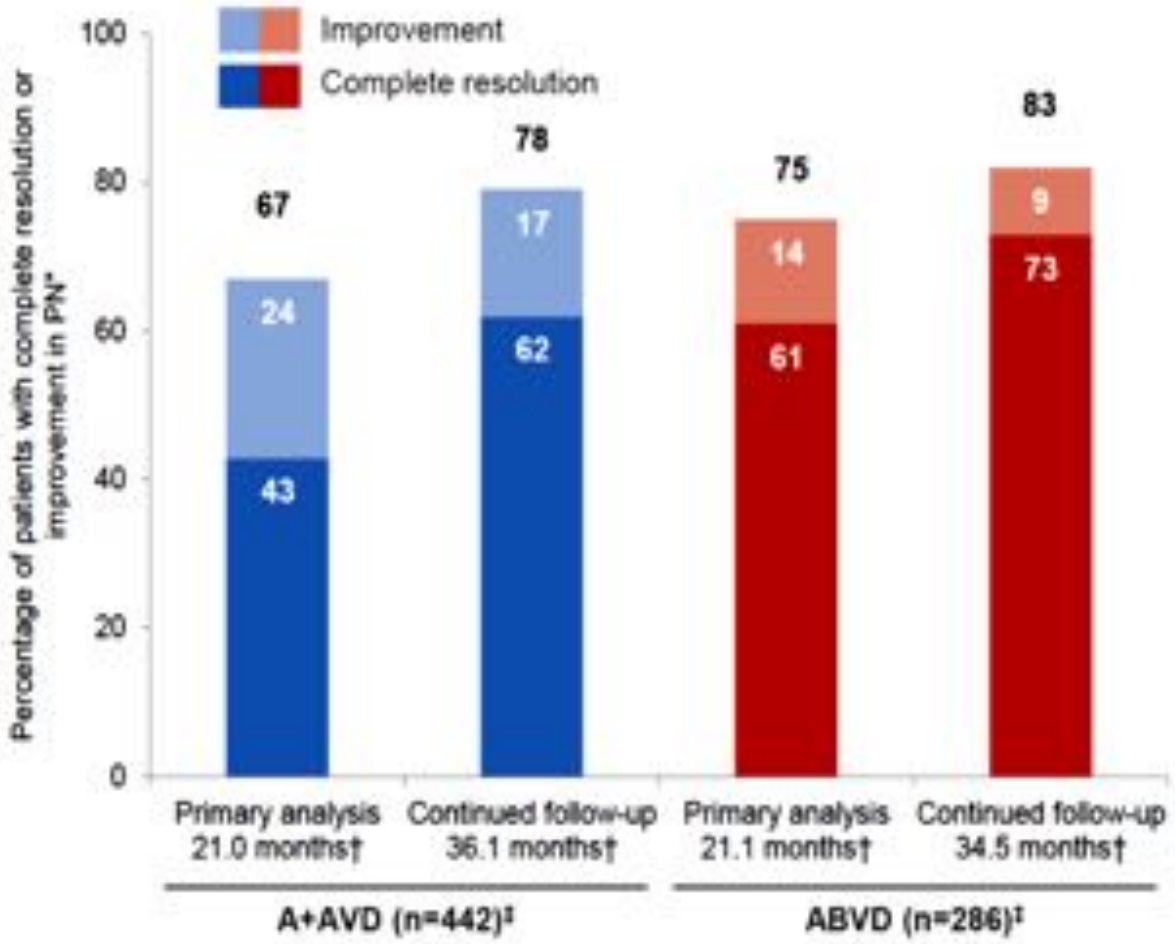
Impact of BV-AVD most notable in PET2+ pts

	PET2 pos 2-y mPFS
BV-AVD	58 %
ABVD	42 %

A2VD is more toxic than ABVD and requires G-CSF support

	BV+AVD	ABVD
Grade ≥3 AE	549 (83%)	343 (66%)
SAE	284 (43%)	178 (27%)
PN all grades	55%	30%
PN grade ≥ 3	9%	1%
SAE of febrile neutropenia, sepsis, infection, neutropenia	33% no G-CSF ppx 24% G-CSF ppx	17% no G-CSF ppx 9% G-CSF ppx

Brentuximab vedotin for newly diagnosed advanced HL

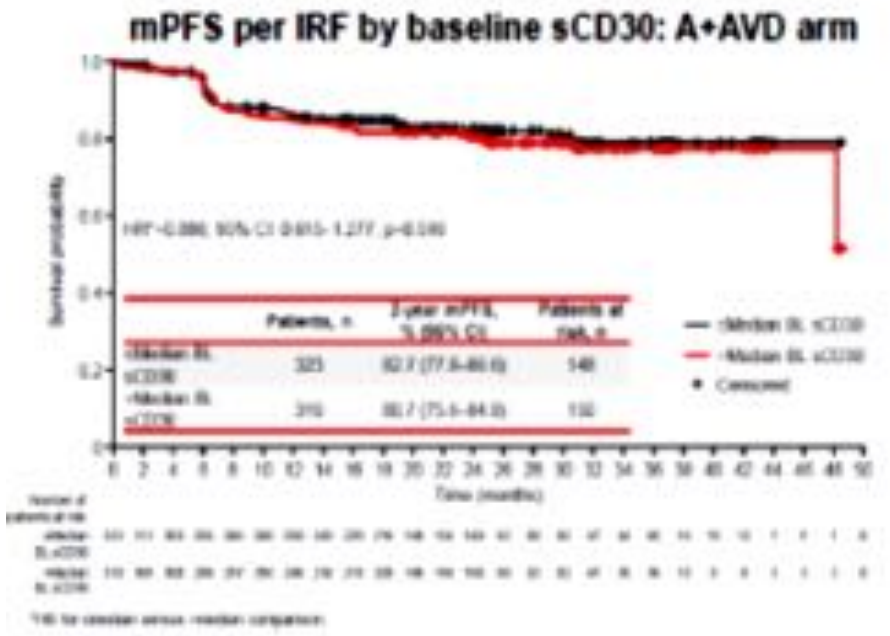


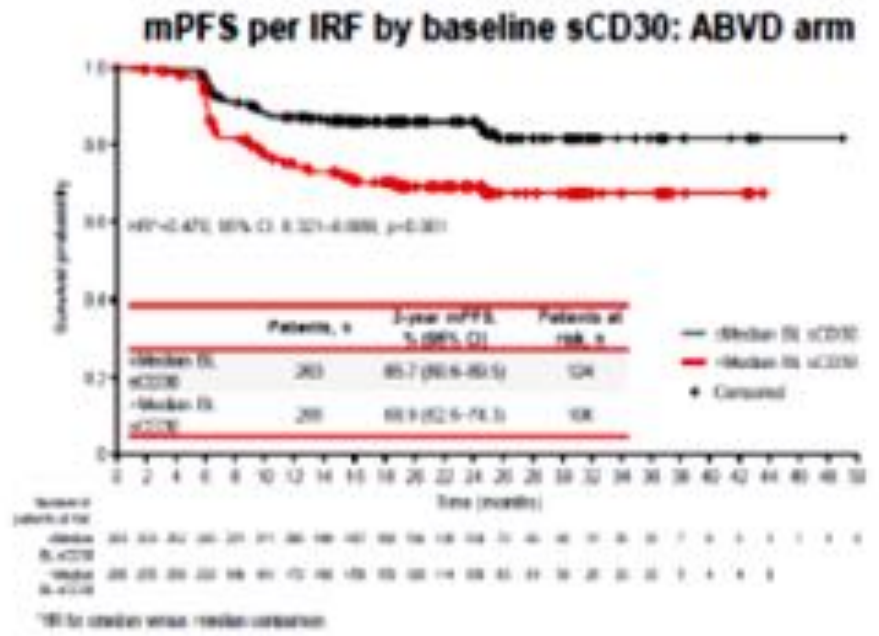
	A+AVD (n=442)	ABVD (n=286)
Ongoing PN, n(%)	170 (38)	77 (27)
Grade 1/2, n(%)	159 (36)	73 (26)
Median time to complete resolution,* weeks (range)	28 (0–167)	14 (0–188)
Median time to improvement,* weeks (range)	40 (8–129)	32 (2–70)

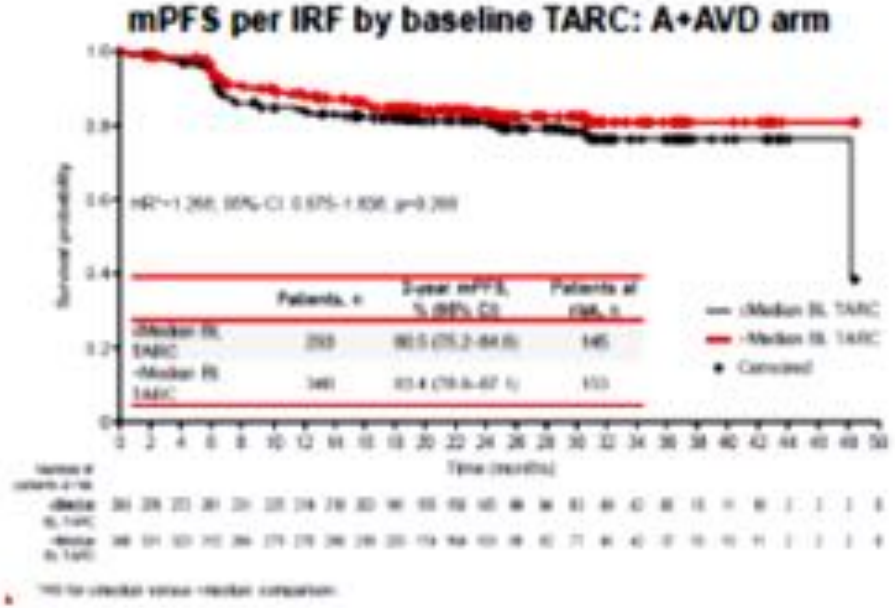
- PN continues to resolve and improve over time, with the majority of patients experiencing complete resolution

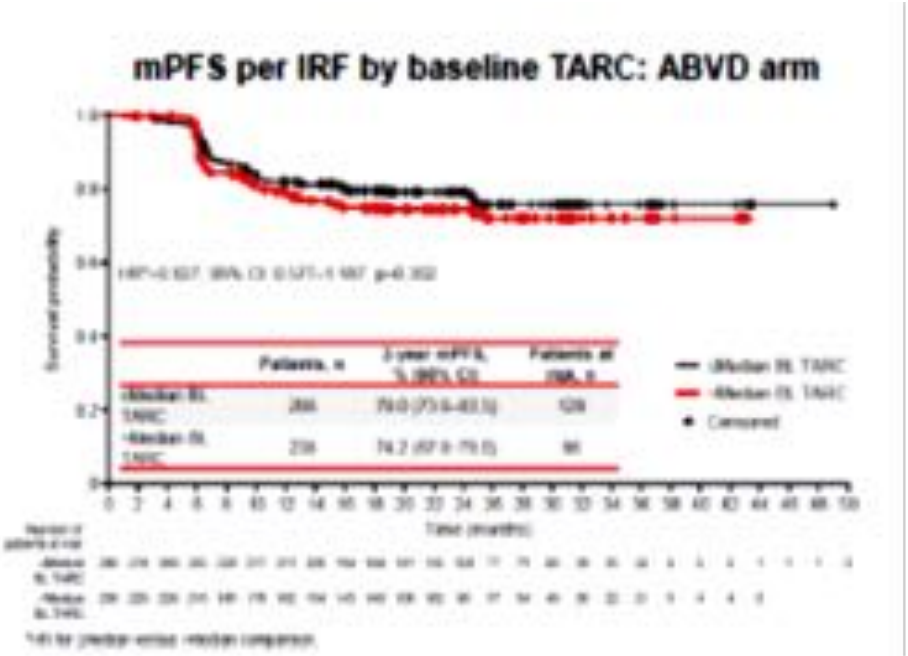
Straus D et al. Abstract #7532. Poster presented at the American Society of Clinical Oncology 2019, Chicago, IL, USA.

Brentuximab vedotin for newly diagnosed advanced HL









Radford J, et al. ICML 2019, Poster presentation from Abstract #235

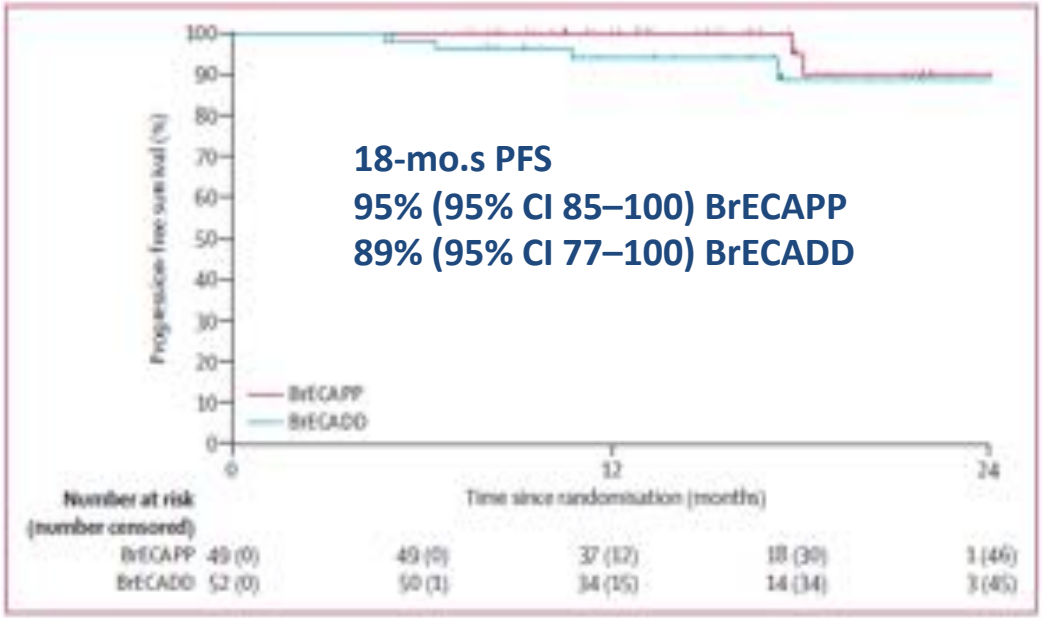
Brentuximab Vedotin in the Overall Treatment Strategy for HL

	BrECAPP	BrECADD
Restaging after two cycles*		
CR	2/50 (4%)	0/52
CRu	4/50 (8%)	6/52 (12%)
PR	40/50 (80%)	45/52 (87%)
NC	4/50 (8%)	1/52 (2%)
PET after two cycles (Deauville score)		
1	13/49 (27%)	9/52 (17%)
2	7/49 (14%)	14/52 (27%)
3	18/49 (37%)	18/52 (35%)
4–5	11/49 (22%)	11/52 (21%)
Restaging after six cycles†		
CR	4/48 (8%)	3/52 (6%)
CRu	3/48 (6%)	7/52 (13%)
PR	1/48 (2%)	2/52 (4%)
PR (residual ≥2·5 cm)	40/48 (83%)	39/52 (75%)
PD (residual ≥2·5cm)	0/48	1/52 (2%)
PET after chemotherapy (Deauville score)‡		
1	10/40 (25%)	13/40 (33%)
2	9/40 (23%)	13/40 (33%)
3	14/40 (35%)	8/40 (20%)
4–5	7/40 (18%)	6/40 (15%)
Complete response to chemotherapy		
No (further treatment recommended by CREP)	7/49 (14%)	6/52 (12%)
Yes (CR or PR <2·5 cm [local investigator] or no indication for further treatment [CREP])	42/49 (86%)	46/52 (88%)

Lancet Oncol 2017; 18: 1680–87

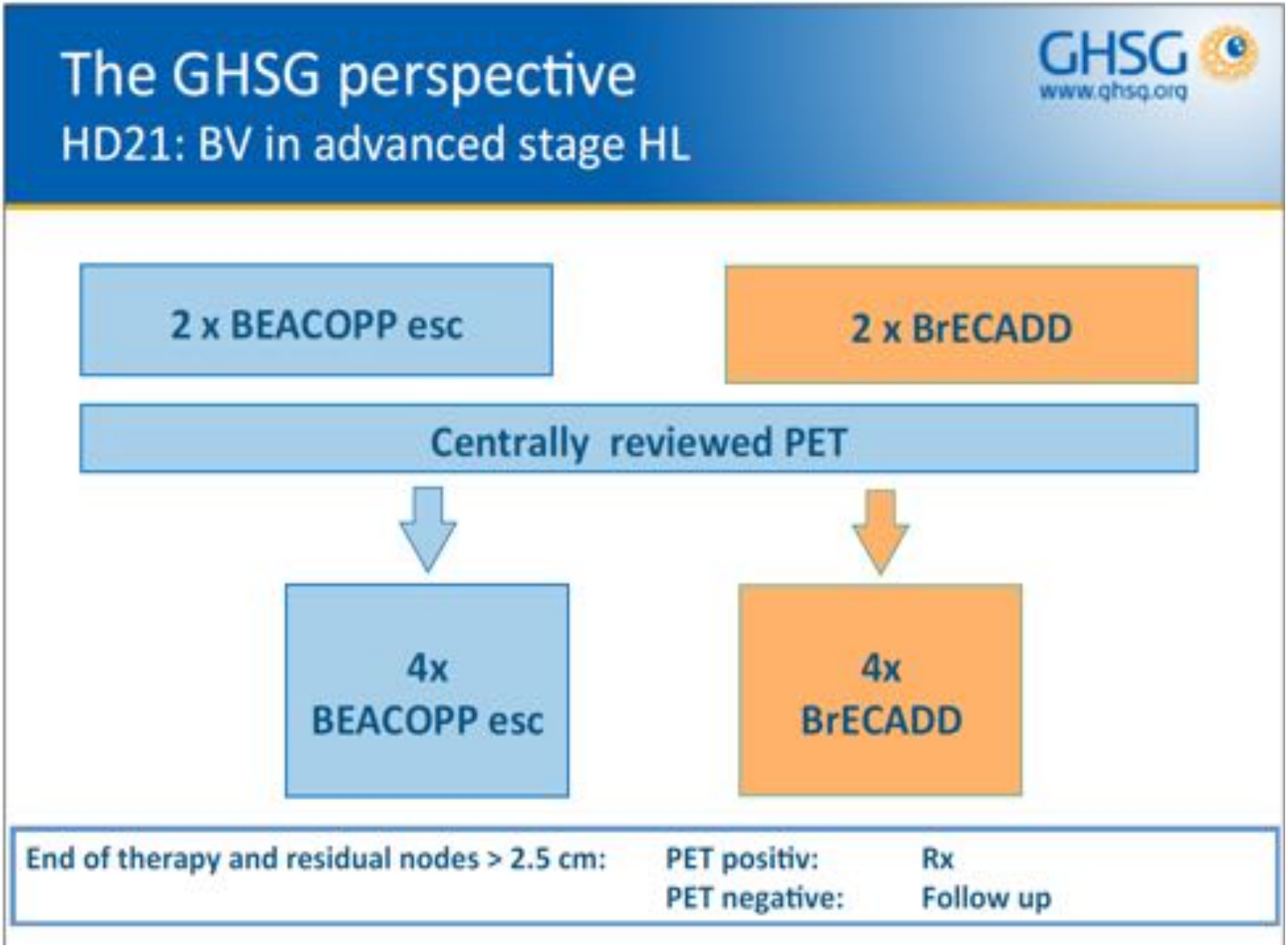
Remodeling BEACOPPesc with Brentuximab Vedotin

Drug	Day	6x BEACOPP	6x BrECADD	6x BrECAPP
Bleomycin	8	10		
Etoposide	1-3	200	150	200
[redacted]	1	35	40	35
Cyclophosphamide	2	1250	1250	1250
Vincristine	8	1.4		
Brentuximab vedotin	1		1.8	1.8
Procarbazine	1-7	100		100
Prednisone	1-14	40		40
Dacarbazine	2-3		250	
Dexamethasone	1-4		40	

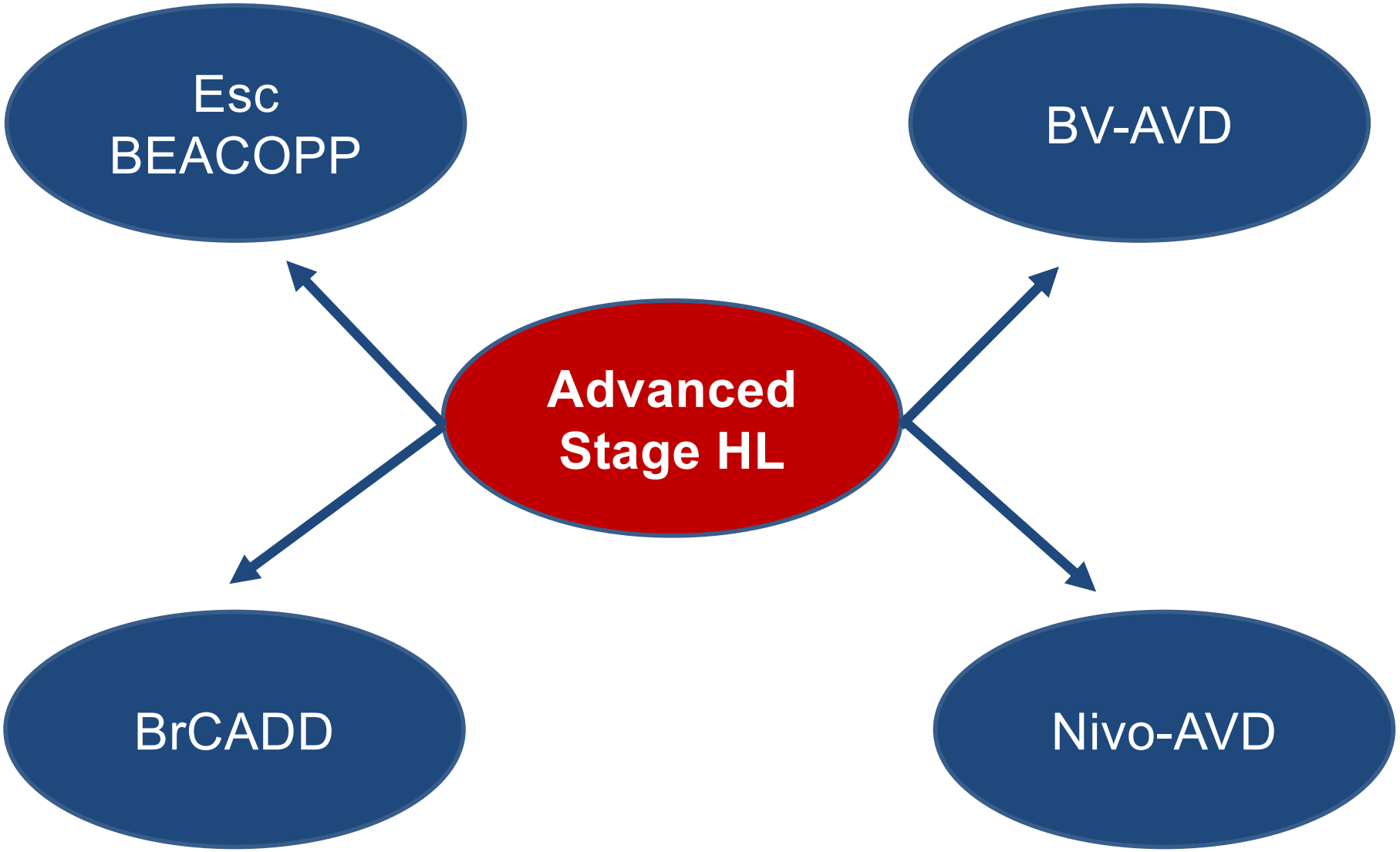


18-mo.s PFS
95% (95% CI 85–100) BrECAPP
89% (95% CI 77–100) BrECADD

Brentuximab Vedotin in the Overall Treatment Strategy for HL

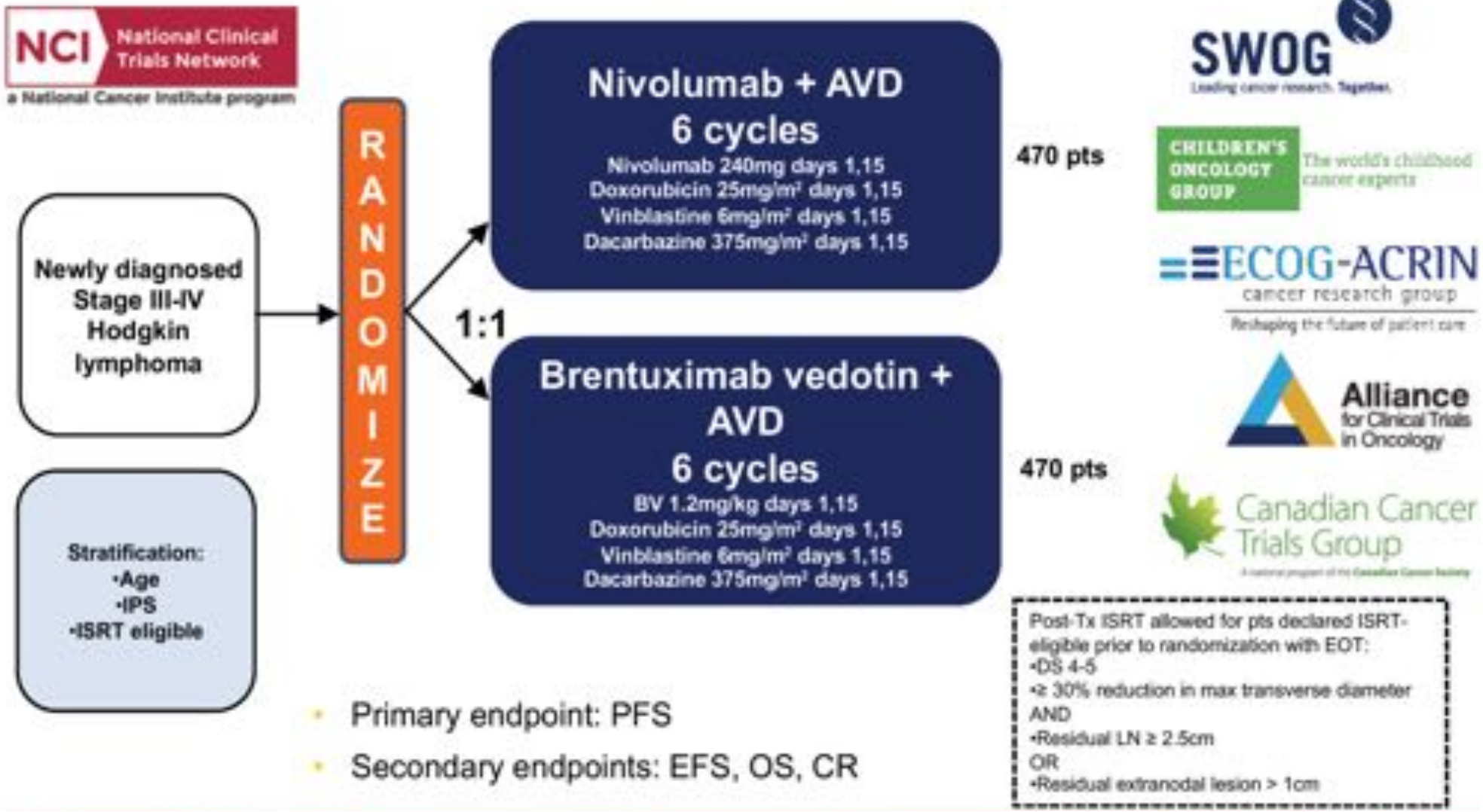


Brentuximab vedotin for newly diagnosed advanced HL

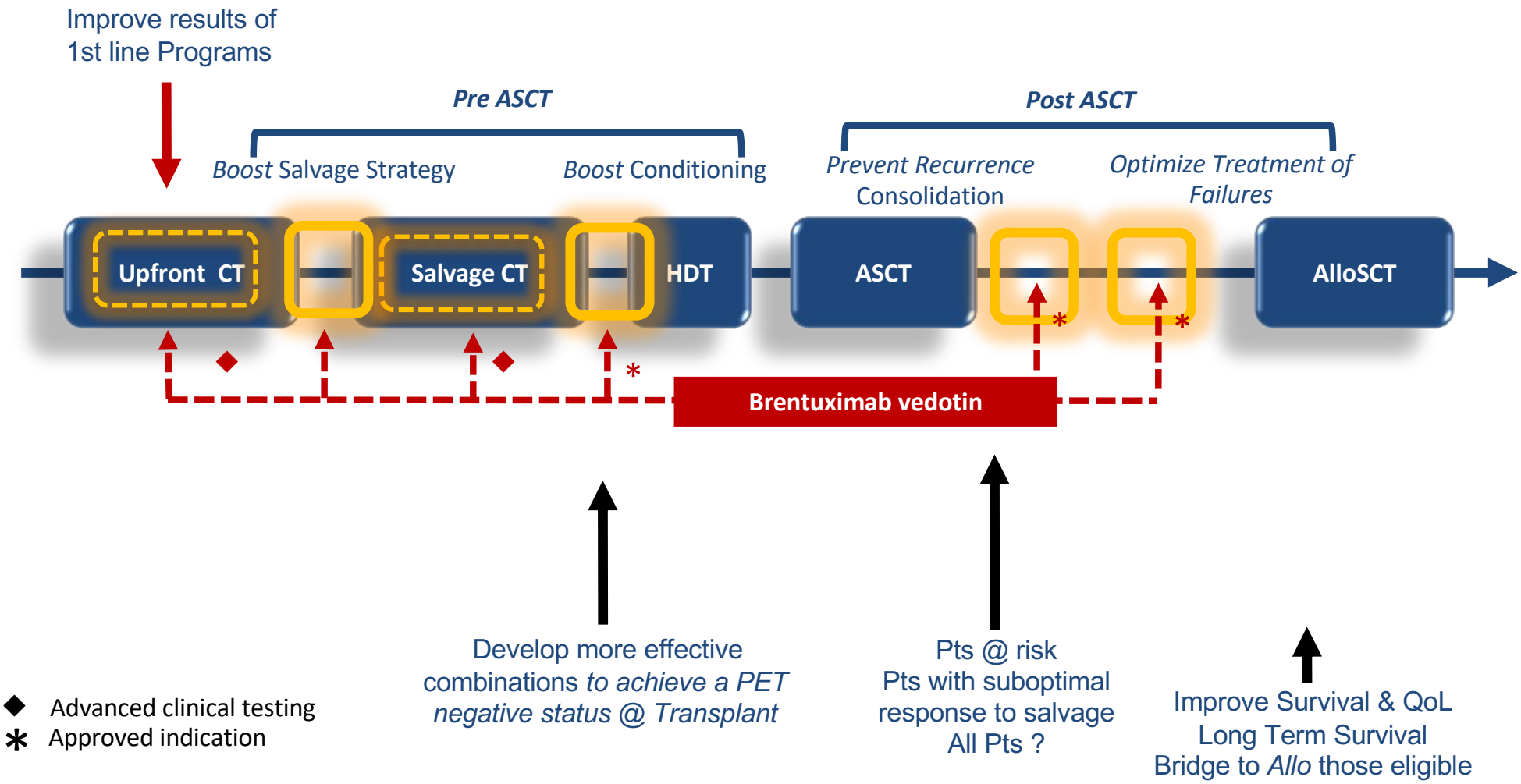


...Novel Agents for cHL: Operating Instructions

S1826: A Phase III Randomized Trial of Nivolumab [redacted] Plus AVD or Brentuximab Vedotin [redacted] Plus AVD in Patients (Age ≥ 12 Years) With Newly Diagnosed Advanced Stage Classical Hodgkin Lymphoma



Brentuximab Vedotin in the Overall Treatment Strategy for HL



...Novel Agents for cHL: Checkpoint Inhibitors

3. CPIs are effective (ORR) regardless of disease chemorefractoriness

- **CheckMate 205: Response According to Refractory Status**

	Primary refractory n = 142	Refractory to last line n = 114	Refractory to BV after auto-HSCT n = 70
Objective response, %	**73**	**68**	**69**
Best overall response, %			
Complete remission	18	13	6
Partial remission	55	54	63
Median DOR in patients with PR, months (95% CI)	13 (9, 18)	17 (9, NE)	17 (8, NE)[a]

ORR to Pembrolizumab by Blinded C Review: Subgroup Analyses

	Primary Refractory Disease (n = 73)		Relapsed After ≥3 Lines of Therapy (n = 146)	
	n (%)	95% CI[‡]	n (%)	95% CI[‡]
ORR	58 (79.5)	68.4-88.0	99 (67.8)	59.6-75.3
Complete remission	17 (23.3)	14.2-34.6	31 (21.2)	14.9-28.8
Partial remission	41 (56.2)	44.1-67.8	68 (46.6)	38.3-55.0
Stable disease	4 (5.5)	1.5-13.4	24 (16.4)	10.8-23.5
Progressive disease	8 (11.0)	4.9-20.5	20 (13.7)	8.6-20.4
Unable to determine	3 (4.1)	0.9-11.5	3 (2.1)	0.4-5.9

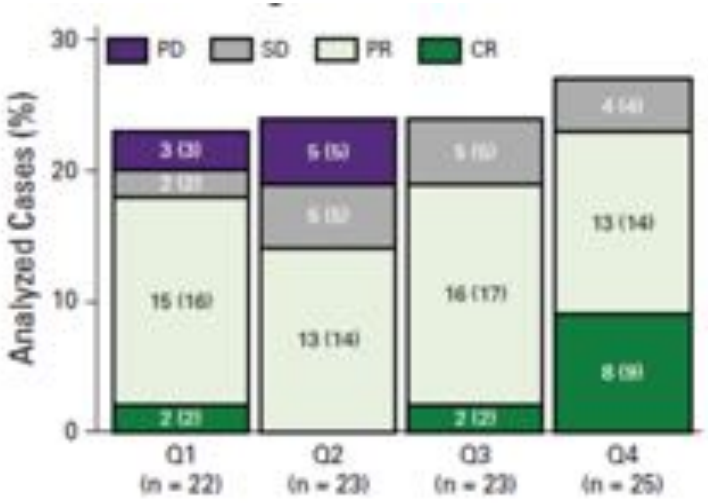
[†]These subgroups are not mutually exclusive
[‡]Based on binomial exact confidence interval method

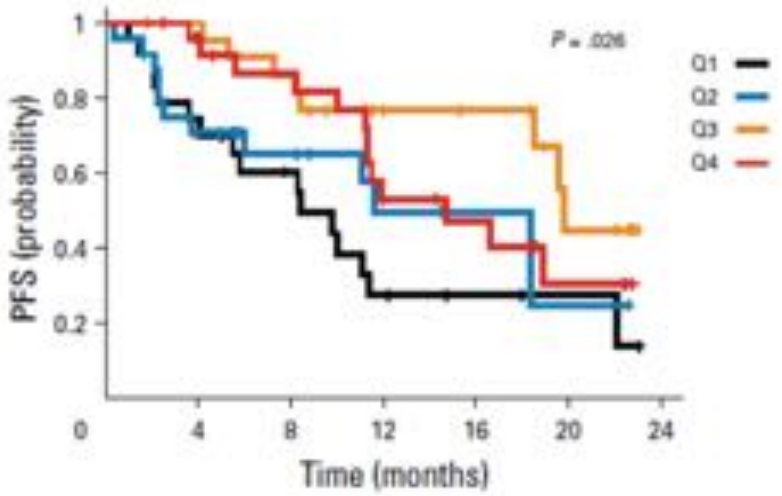
Zinzani, 14-ICML

...Novel Agents for cHL: Checkpoint Inhibitors

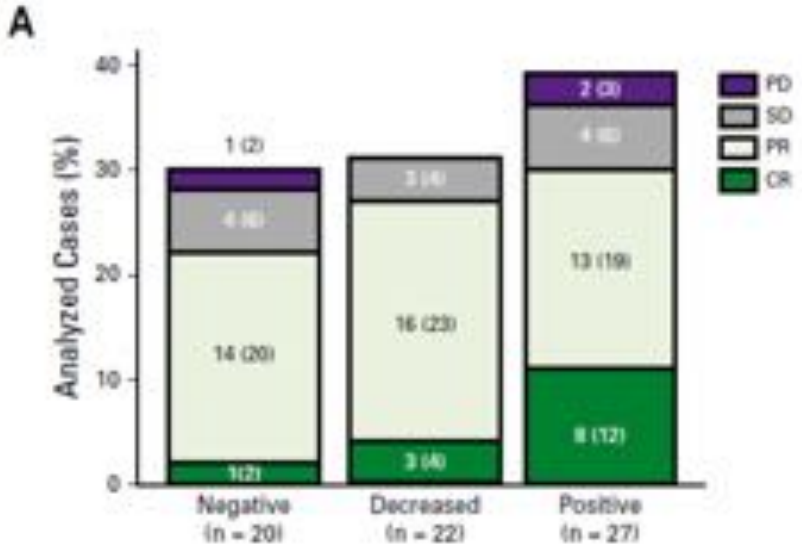
Putative Mechanism of Resistance: not known

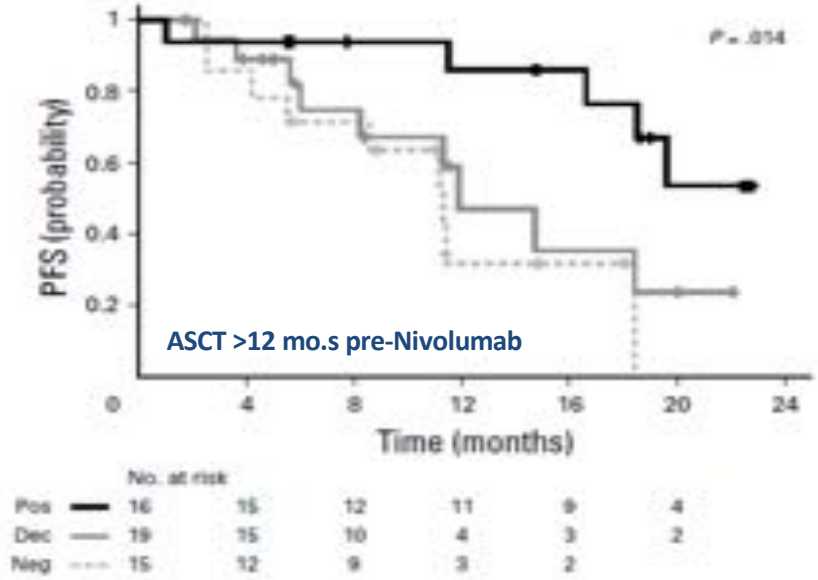
1. More CR and longer PFS observed with higher degrees of PD-L1 expression



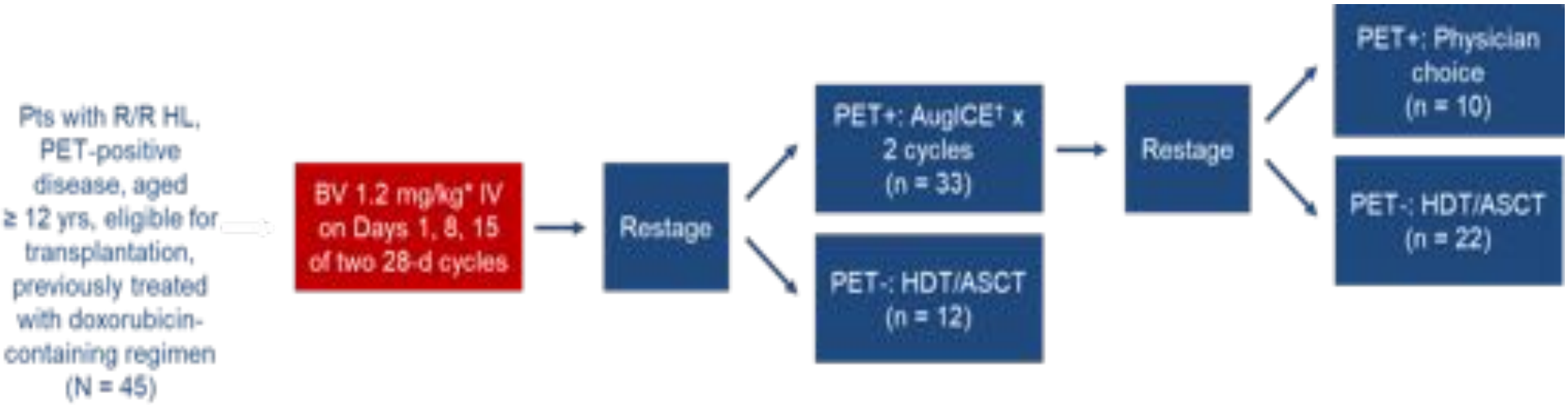


2. More CR and longer PFS observed with higher degrees of HLA-DR expression





BV ± PET-Adapted Sequential AugICE Prior to ASCT for R/R HL



*For pts with weight > 100 kg, dosing calculated with upper limit of 100 kg. In pts with grade 2 neuropathy, BV dose reduced to 0.8 mg/kg; with grade 3 neuropathy, BV discontinued. †AugICE consisted of 2 doses ifosfamide 5000 mg/m^2 + unprotective agent mesna 5000 mg/m^2 IV on Days 1-2; 3 doses of etoposide 200 mg/m^2 IV Q12H beginning on Day 1; carboplatin at AUC of 5 (max. 800 mg) on Day 3.

- Overall 76% achieved PET- status and proceeded to HDT/ASCT

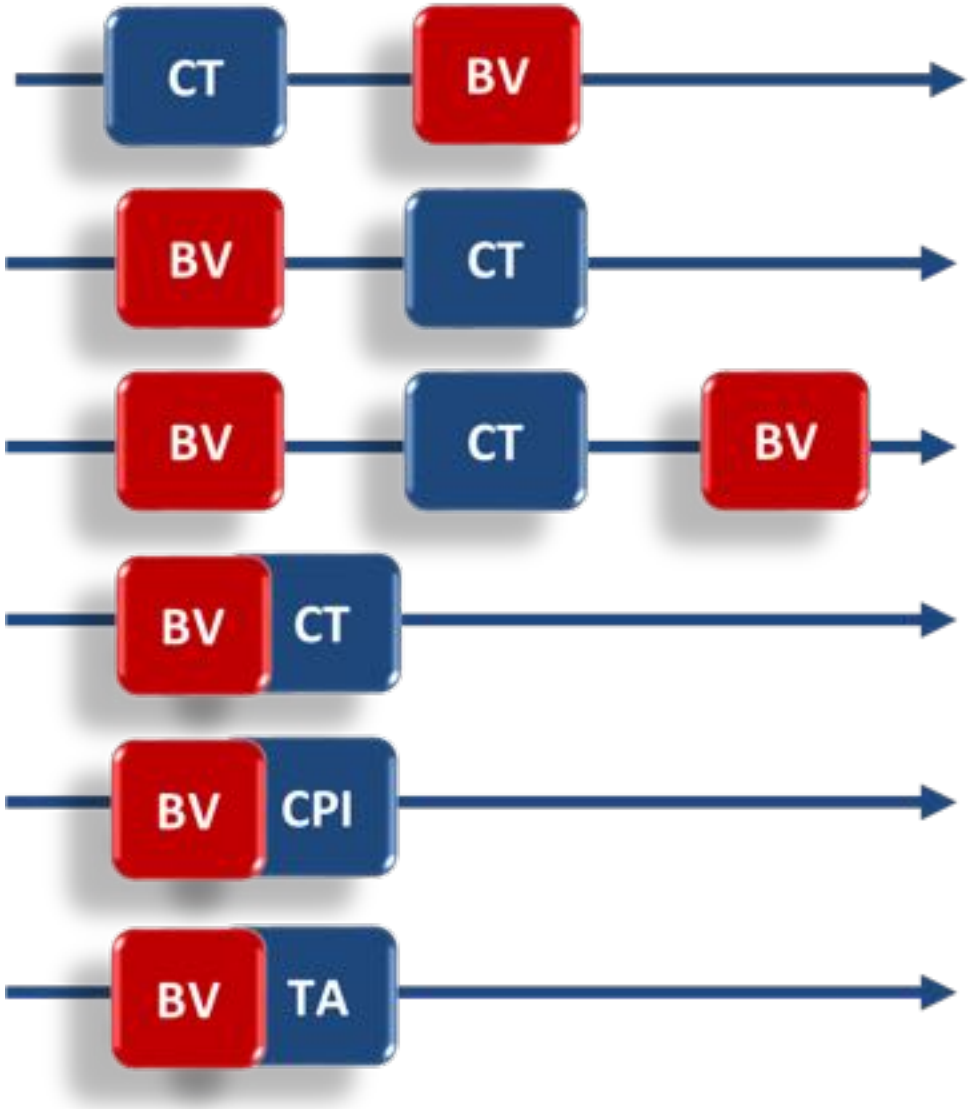
Moskowitz AJ, et al. Lancet Oncol. 2015;16:284-292.

RR-HL: Effect of Pre-Transplant (ASCT) PET assessment

Strategies to achieve a PET neg.ve status @ transplant:

- **Sequential single agent BV and chemotherapy**
  (…*on demand*…)
  - BV alone (about 30-35% of pts. achieve a metabolic CR)
  - BV <mCR: ICE, DICE, IGEV, GVD, GDP
  - BV and Bendamustine or Bendamustine and BV
- **Incorporate BV into salvage**
  - Bendamustine BV (BBV)
  - BV-DHAP (Brave)
  - BV-ESHAP (BrESHAP)
  - BV-ICE
- **Change 'conventional' salvage platform**
  - BeGEV
  - Test a 'chemo-free' strategy (BV+CPI)

...Novel Agents for cHL: Operating Instructions

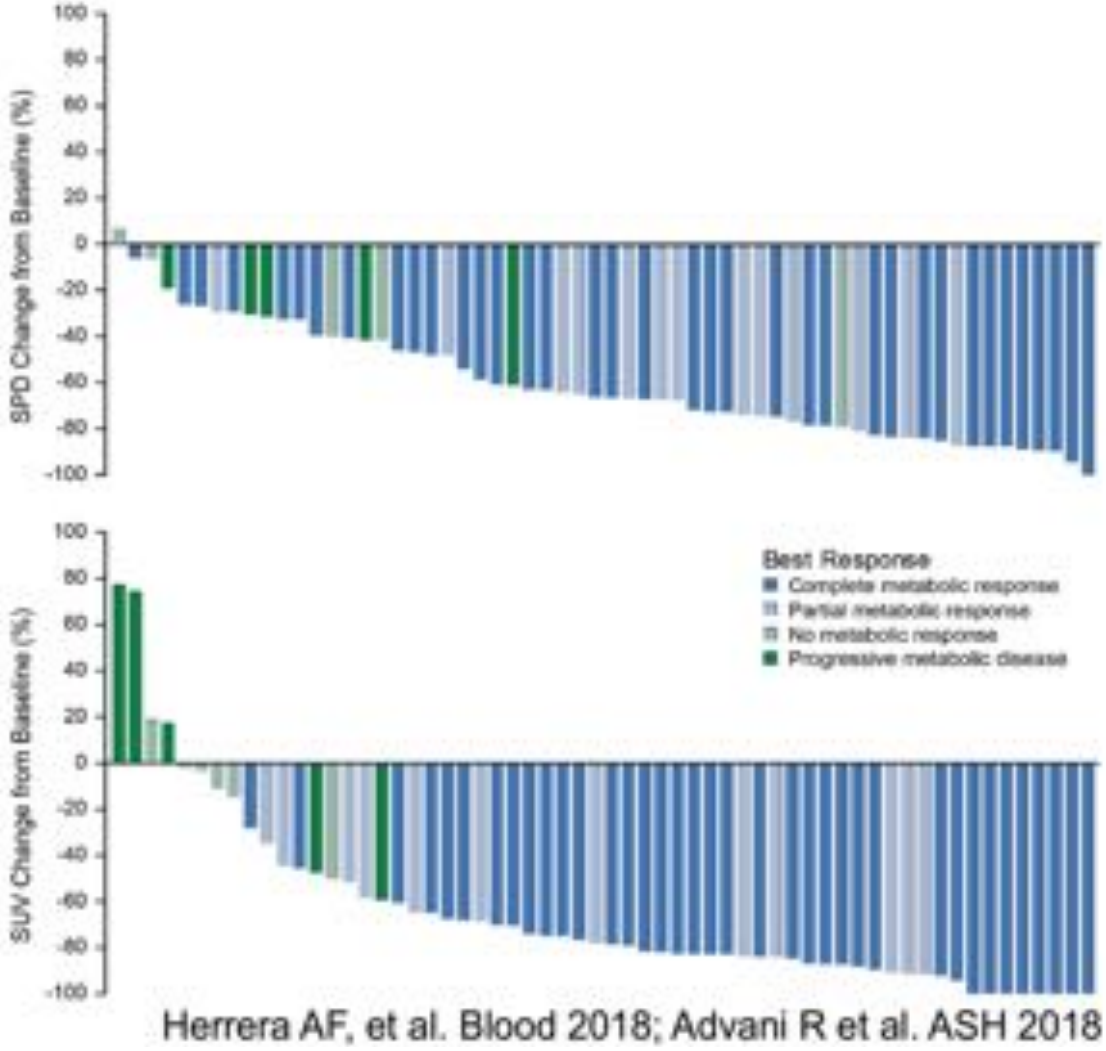


...Novel Agents for cHL: Operating Instructions

BV + Nivolumab is an effective 2nd line therapy and bridge to transplant

87% ORR, 68% CR among efficacy evaluable patients (n=90)

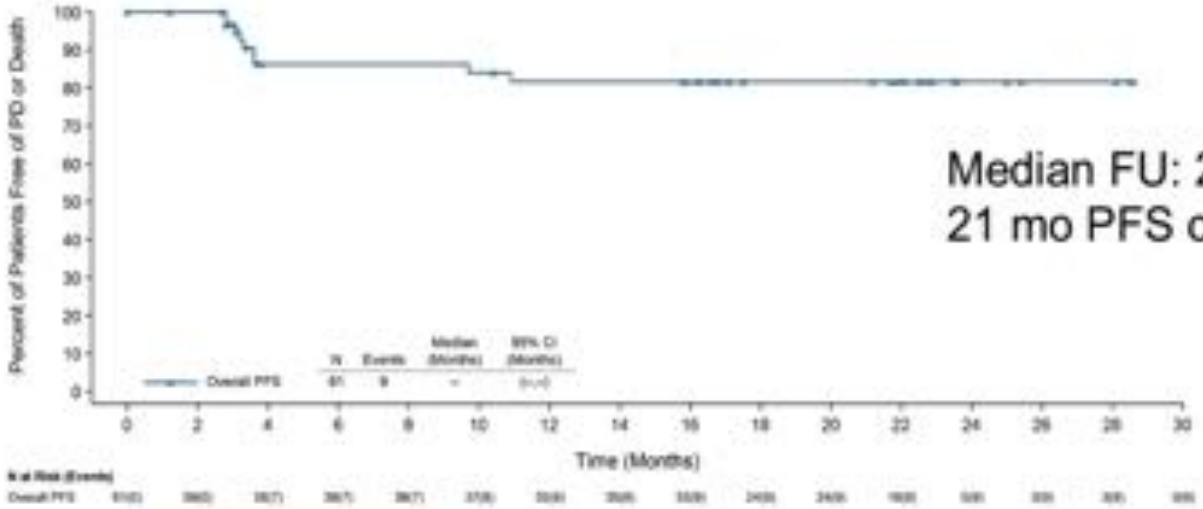
(85% ORR, 66% CR among all treated patients, n=91)



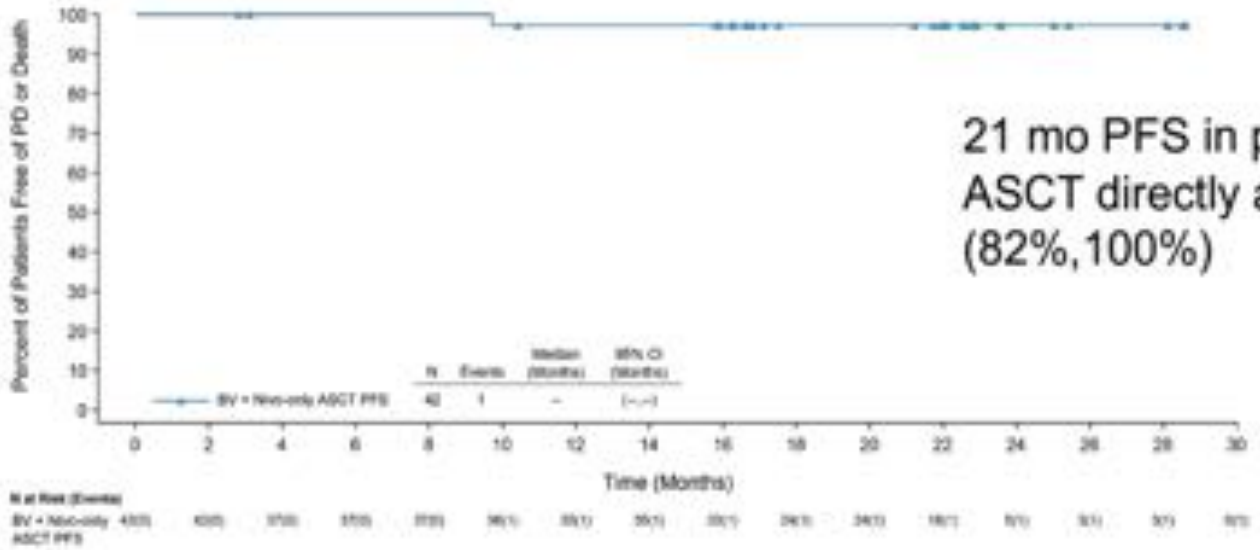
Herrera AF, et al. Blood 2018; Advani R et al. ASH 2018

...Novel Agents for cHL: Operating Instructions

PFS after BV+Nivo as 1st salvage therapy for HL



Median FU: 21.8 months
21 mo PFS overall: 82% (67%, 90%)



21 mo PFS in pts who proceeded to ASCT directly after BV+Nivo: 97% (82%,100%)

Herrera AF et al. ISHL 2018

Immunotherapy Lymphoma 2019

Dolabella auricularia,la miglior soluzione contro qualsiasi tipo di alga,anche quelle più ostili come l'alga briopsis.
Instancabile divoratrice di qualsiasi alga infestante possiate trovarvi in acquario.

€22.90

...Novel Agents for cHL: Operating Instructions

Brief Report

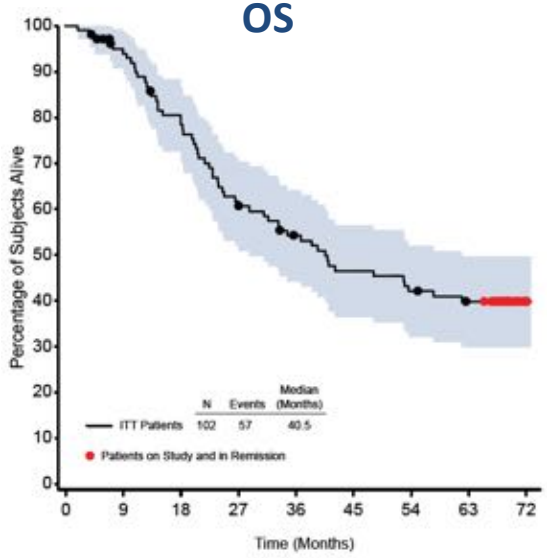
blood

CLINICAL TRIALS AND OBSERVATIONS

Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma

Robert Chen,[1,*] Ajay K. Gopal,[2,*] Scott E. Smith,[3] Stephen M. Ansell,[4] Joseph D. Rosenblatt,[5] Kerry J. Savage,[6] Joseph M. Connors,[6] Andreas Engert,[7] Emily K. Larsen,[8] Dirk Huebner,[9] Abraham Fong,[8] and Anas Younes[10]

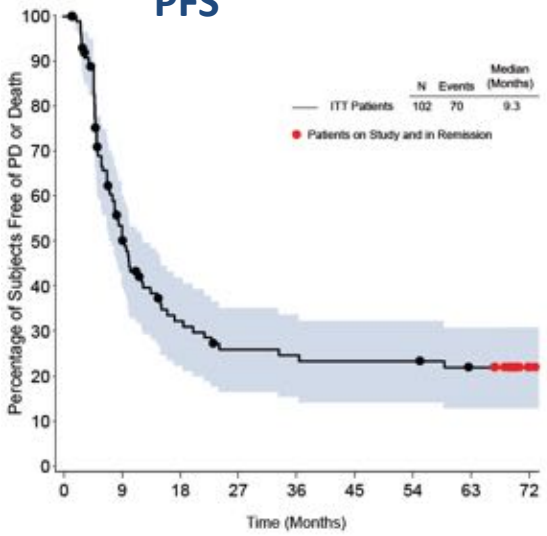
OS



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

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

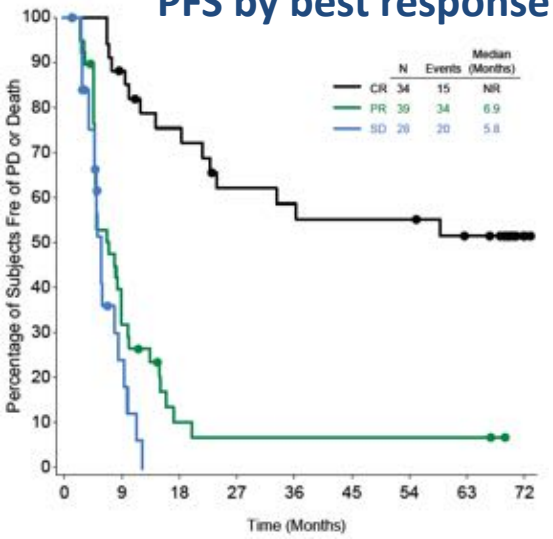
PFS



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

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

PFS by best response

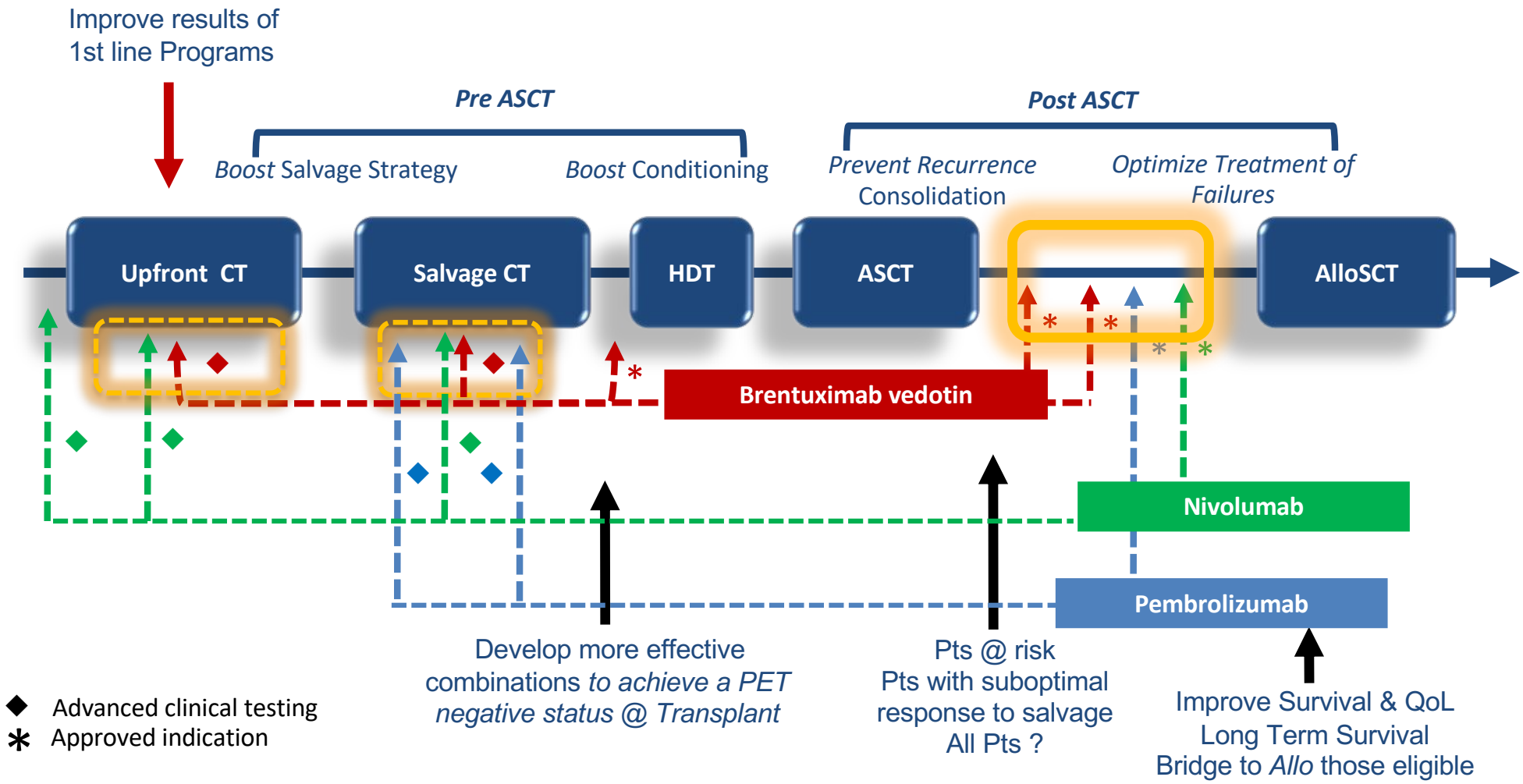


Median OS & PFS
not reached in pts with CR

For patients in CR, the estimated 5-years OS rate was 64% and PFS was 52%

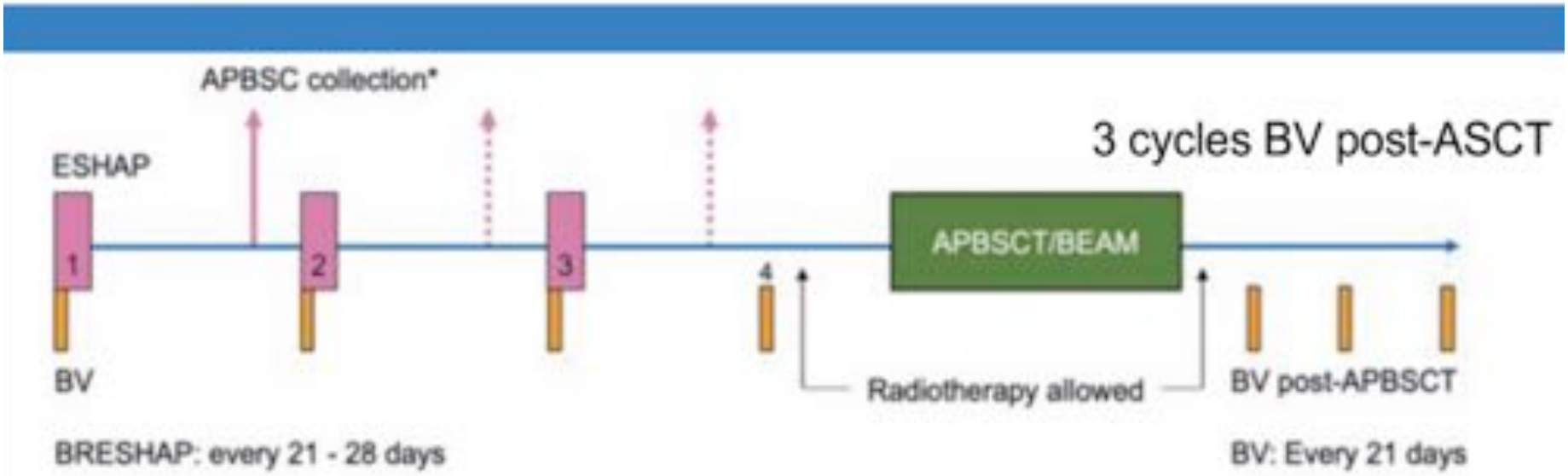
Blood , 22 September 2016

Overall Treatment Strategy for (adv. HL): a moving target



Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand

BV + ESHAP (BRESHAP)



N = 66, 61% 1º refractory

Pre-ASCT responses

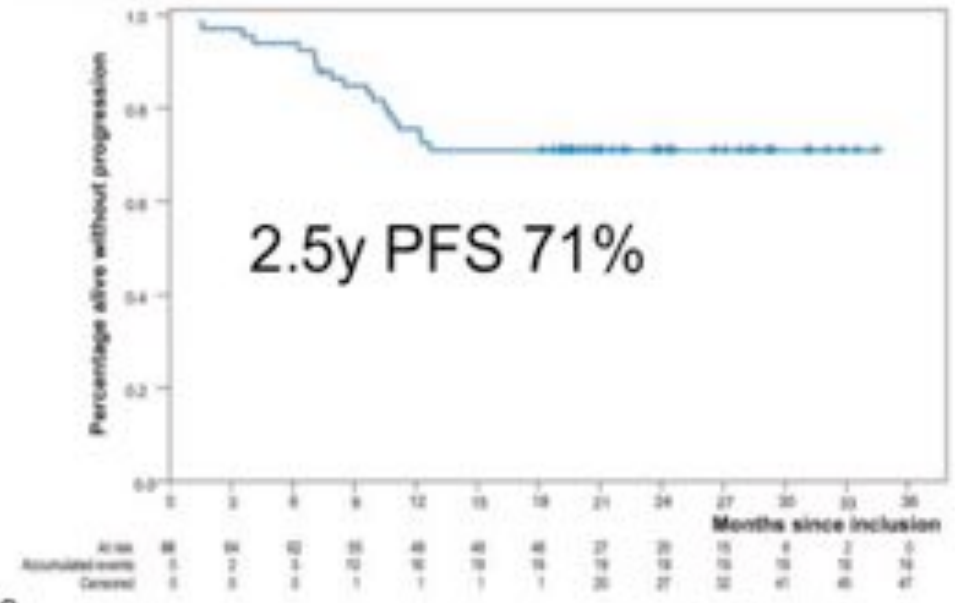
Overall response 91%

Complete response 70%

Gr 3-4 toxicities

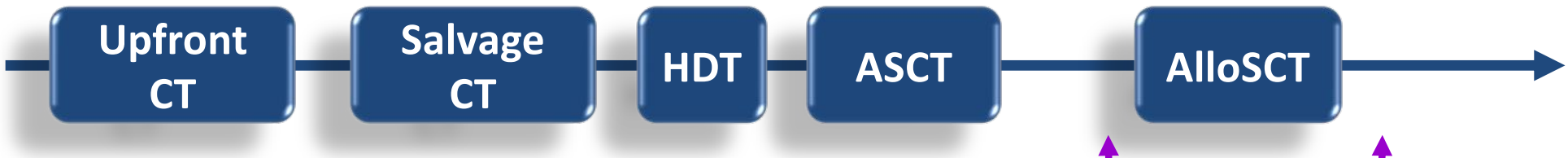
47% thrombocytopenia

50% neutropenia



Garcia-Sanz et al. Ann Oncol 2019

Hodgkin Lymphoma: defining Hi-Risk Patients



Primary refractory
progression at any time during upfront CT± RT or ***early relapse***
≤3 months after EOT

Nonresponse to 1st salvage
pts. not *achieving a PET negative status @ Transplant*

Early failures
post ASCT
(< 12 mo.s)

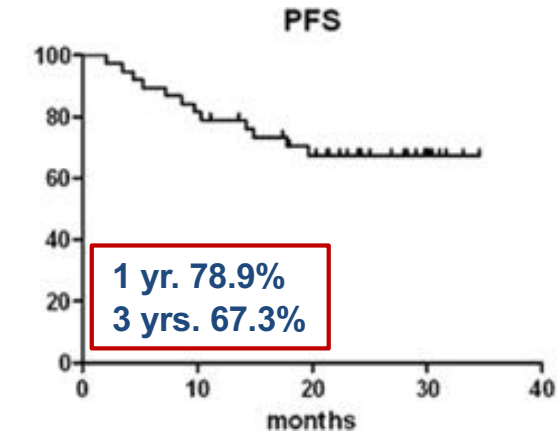
Allo-SCT
failures

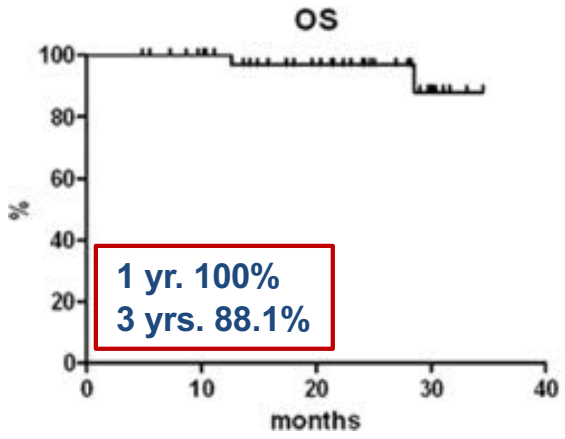
Failures from PET-adapted strategies
PET2 negative EOT-PET positive
PET2 positive failing early escalation
(EscBEACOPP, early ASCT)

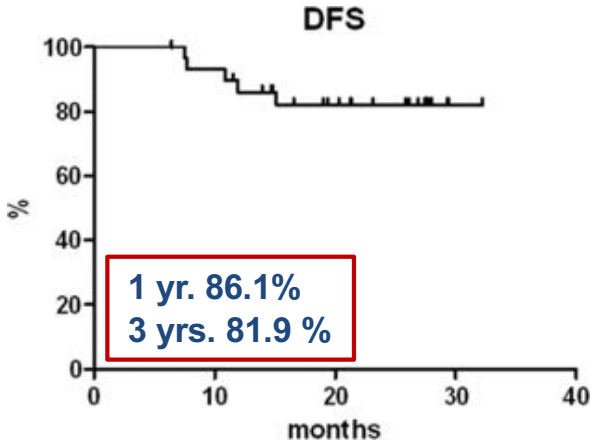
Failures (?) after novel agents
PD1-blockade (BV & PD1)

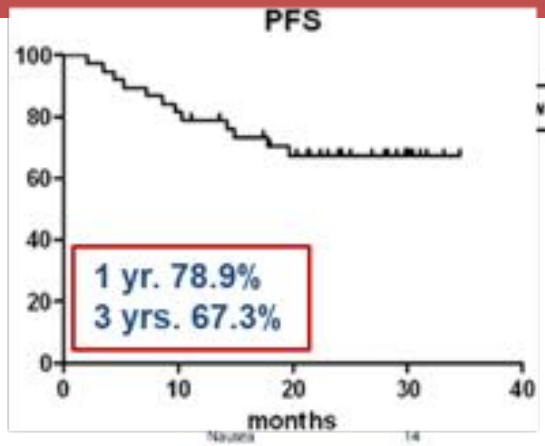
Pinto A., 2018

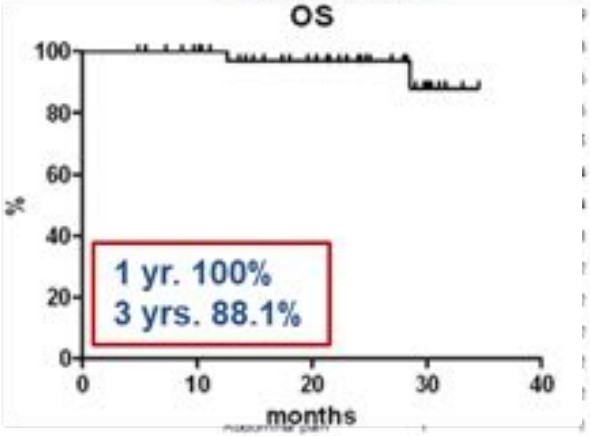
Brentuximab vedotin for RR-HL: one, no one, one-hundred-thousand

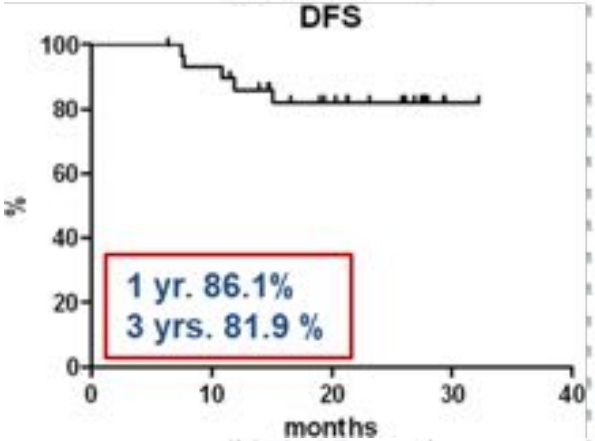










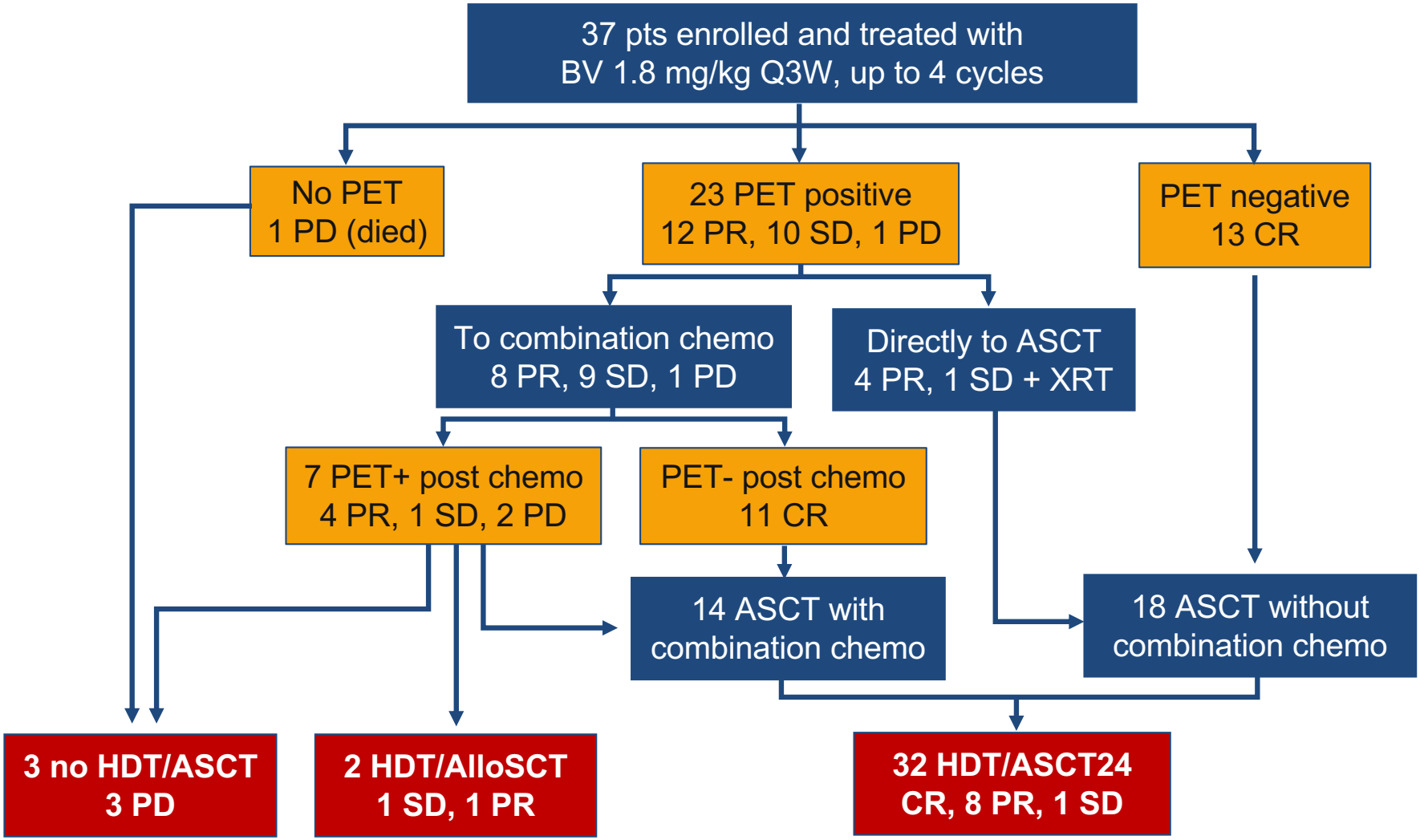


	Events, N	Overall frequency (%)	Grade	Grade 2, N	Grade 3	Grade 4, N
	47	330	16	7	13	3
	13	31.7		2	8	3
	12	29.3	2	4	6	
	8	19.5	7	1		
	7	17.1	7			
	1	2.4			1	
	166	100	87	69	10	0
	46	27.7	19	21	6	
	26	15.7	18	7	1	
	24	14.5	16	8		
	9	5.4	1	8		
	8	4.8	4	4		
	6	3.6	1	5		
	6	3.6	4	2		
	5	3.0	4	1		
	4	2.4	1	3		
	4	2.4	4			
	3	1.8	3			
	2	1.2	2			
	2	1.2	1	1		
	2	1.2	2			
	2	1.2		1	1	
	2	1.2	1	1		
	1	0.6	1			
	1	0.6		1		
	1	0.6		1		
	1	0.6			1	
	1	0.6		1		
	1	0.6	1			
	1	0.6	1			
	1	0.6		1		
	1	0.6		1		
	1	0.6	1			
	1	0.6			1	
	1	0.6	1			
	1	0.6		1		
Viral gastroenteritis	1	0.6	1			

CMV cytomegalovirus, ALT alanine transaminase, AST aspartic transaminase, gamma-GT gamma glutar

Broccoli et al. *Blood Cancer Journal* (2019)9:100

Salvage BV ± PET-Adapted Physician's Choice of CT Prior to ASCT



Chen R, et al. Biol Blood Marrow Transplant. 2015;21:2136-2140.

RR-HL: Effect of Pre-Transplant (ASCT) PET assessment

1. Works

Parameter	No.	CR (%)	PR (%)	ORR (%)
Response (all pts)	36	12(33)	7 (19)	19 (53)
Response to last Rx				
Sensitive	16	9 (56)	2 (13)	11 (69)
Resistant	18	3 (17)	5 (28)	8 (45)

Reference	n	Dose	ORR	CR	Prior Rx
Corazzelli	41	90-120 mg/m2, days 1 &2, every 3-4 wks	58%	31%	
Ghesquieres	28	90-120 mg/m2, days 1 &2, every 4 wks	50%	29%	
Anastasia	67	90-120 mg/m2, days 1 &2, every 4 wks	57%	25%	67% failed auto SCT 33% failed allo SCT
Zinzani	27	90 mg/m2, days 1 &2, every 4 wks	56%	37%	All received prior BV 56% refractory to BV

Moskowitz AJ, Hamlin PA, Perales MA, et al. Phase II Study of Bendamustine in Relapsed and Refractory Hodgkin Lymphoma. J Clin Oncol. 2013 Feb 1;31(4):456-6c

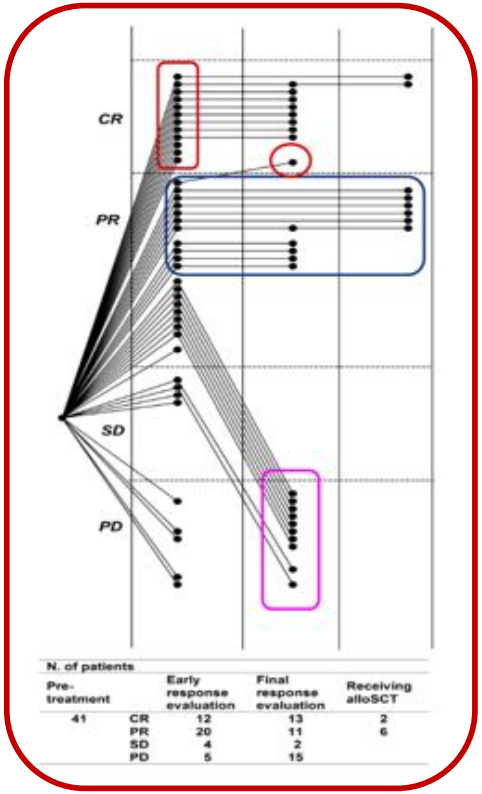
Corazzelli, et al. British Journal of Haematology, 2013;160:207-215

Ghesquieres, et al. Leukemia & Lymphoma, 2013;54(11):2399-2404

Anastasia, et al. British Journal of Haematology, 2014;166:140-153

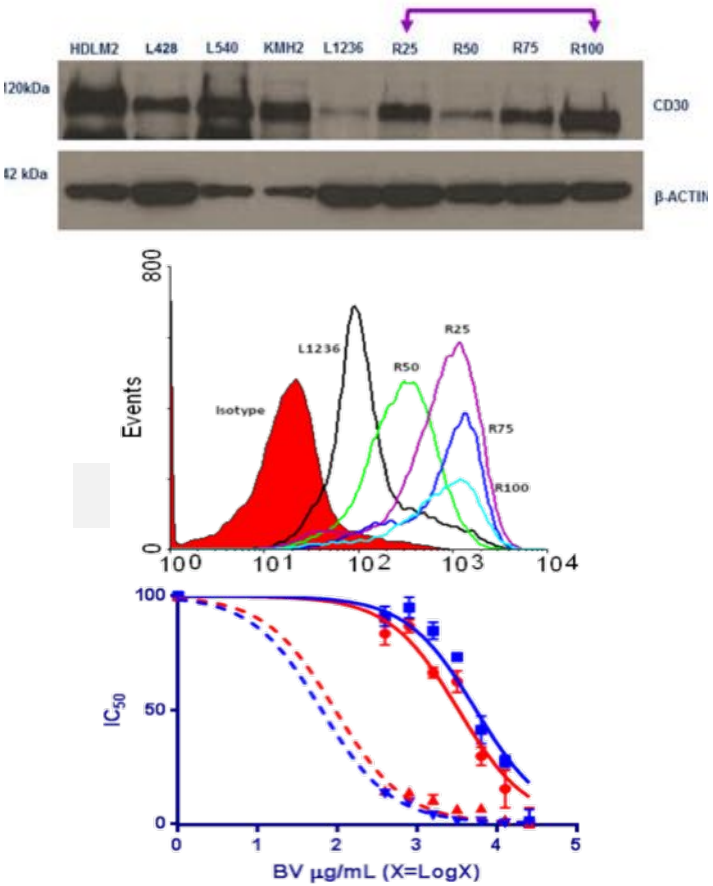
Zinzani, et al. Clinical Lymphoma, Myeloma & Leukemia, 2015;15(7):404-408

2. Works rapidly



2-4 courses to best resp.

3. Synergizes with BV



De Filippi *et al.* ASH 2015 Leoni *et al*. ASH 2003

Brentuximab Vedotin-based combinations for RR-HL

CLINICAL TRIALS AND OBSERVATIONS

Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma

Alex F. Herrera,[1] Alison J. Moskowitz,[2] Nancy L. Bartlett,[3] Julie M. Vose,[4] Radhakrishnan Ramchandren,[5] Tatyana A. Feldman,[6] Ann S. LaCasce,[7] Stephen M. Ansell,[8] Craig H. Moskowitz,[2] Keenan Fenton,[9] Carol Anne Ogden,[9] David Taft,[9] Qu Zhang,[9] Kazunobu Kato,[10] Mary Campbell,[9] and Ranjana H. Advani[11]

Methods

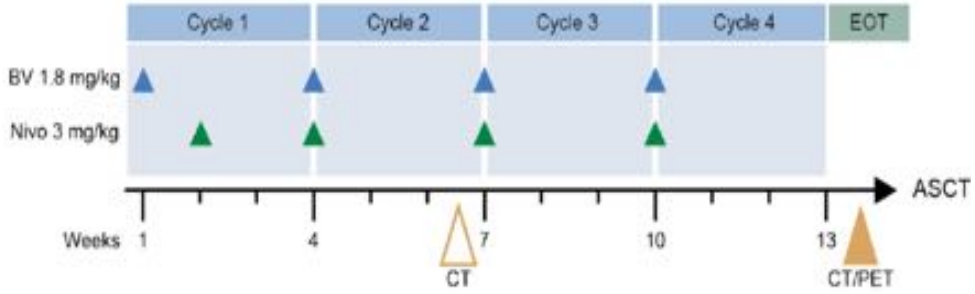
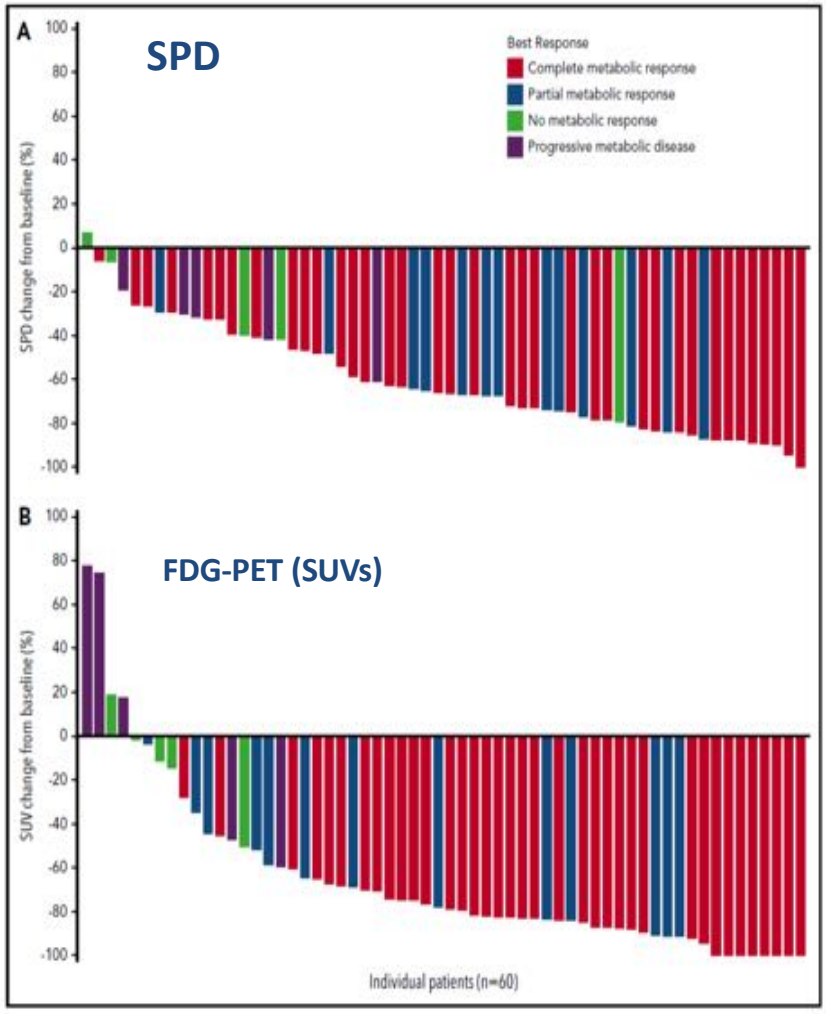


Table 1. Baseline demographics and disease characteristics

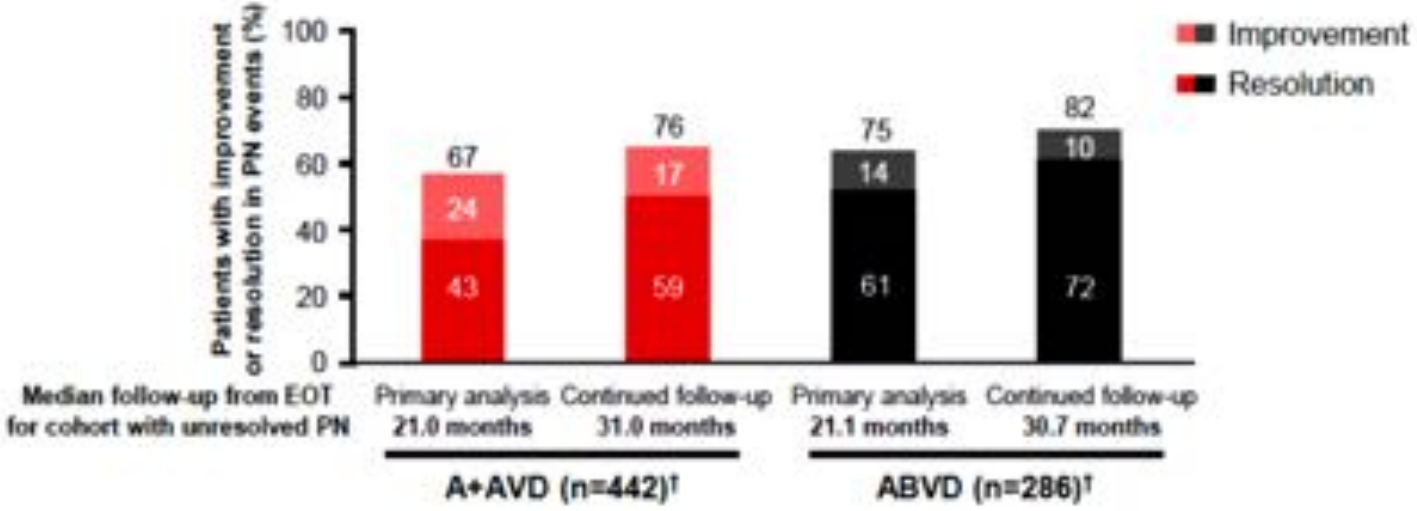
	n = 62
Age (y), median (range)	36 (18–69)
Sex, n (%)	
Male	30 (48)
Female	32 (52)
Disease stage at initial diagnosis, n (%)	
I/II	37 (60)
III/IV	24 (39)
Unknown	1 (2)



CR rate: 61%,
ORR: 82%
6-mo.s PFS: 86%

Brentuximab vedotin for newly diagnosed advanced HL

Resolution or improvement* in PN events with continued follow-up



*Resolution is defined as event outcome of 'resolved' or 'resolved with sequelae'. Improvement was defined as 'improved by ≥1 grade from worst grade as of the latest assessment'.
†Total patients with PN.

Ongoing PN events at primary analysis and after 10 months additional follow-up*

	A+AVD		ABVD	
	Primary analysis	Continued follow-up	Primary analysis	Continued follow-up
Patients with ongoing PN, n	251	182	112	81
Maximum severity grade 1, n (%)	160 (64)	106 (58)	80 (71)	53 (65)
Maximum severity grade 2, n (%)	72 (29)	58 (32)	28 (25)	24 (30)
Maximum severity grade 3, n (%)	18 (7)	17 (9)	4 (4)	4 (5)
Maximum severity grade 4, n (%)	1 (<1)	1 (<1)	0	0

*Beyond 36 months follow-up was every 6 months.

Radford J, et al. ASH 2018, Poster presentation from Abstract #2921