Confronto Real world e studi registrativi

V. Pavone
San Giovanni Rotondo
8 Novembre 2018

U.O Ematologia
Az.Osp.Card.G.Panico

MEDICAL NEED IN HL

OUTCOME

IMPROVE
FIRST LINE

IMPROVE
SALVAGE
THERAPY

PREVENT RELAPSE
CONSOLIDATION THERAPY
MAINTENANCE THERAPY

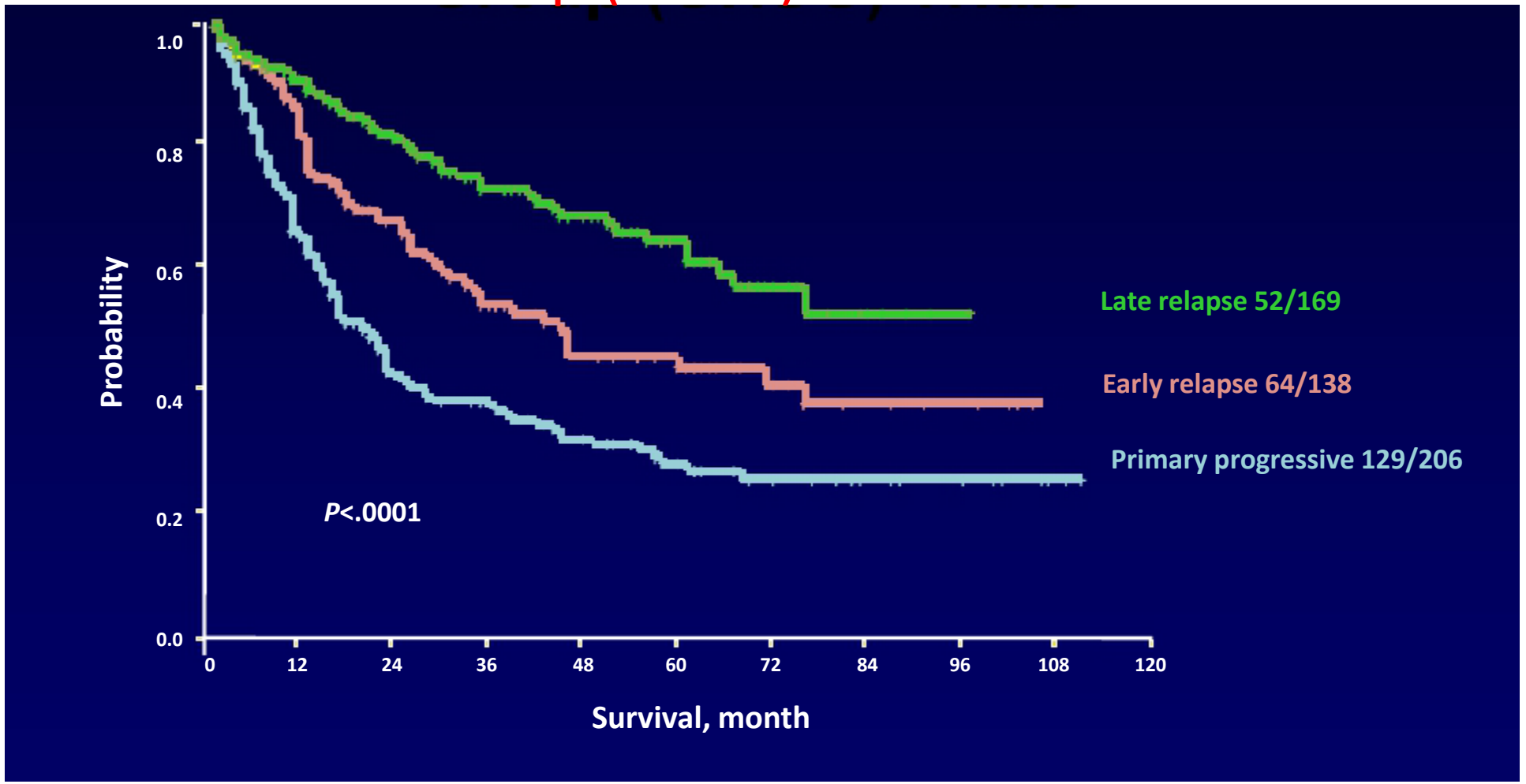
REDUCE TOXICITY

RISK-ADAPTED
STRATEGY

RESPONCE-ADAPTED
STRATEGY

KEY ROLE OF NOVEL
AGENTS

Survival of Relapsed or Refractory HL Patients in German Hodgkin Study Group (GHSG) Trials*

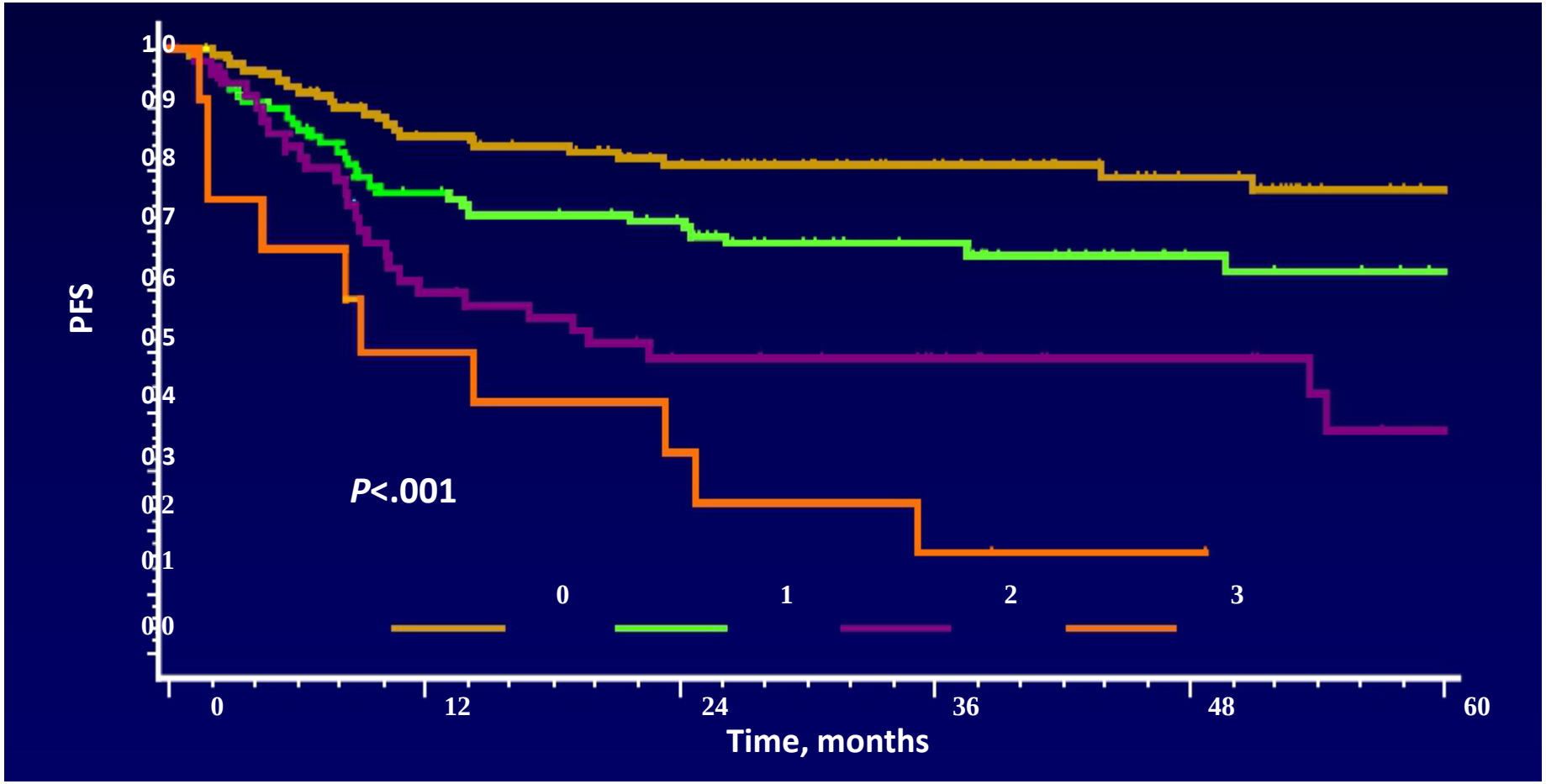


1988-99; n = 513/3809

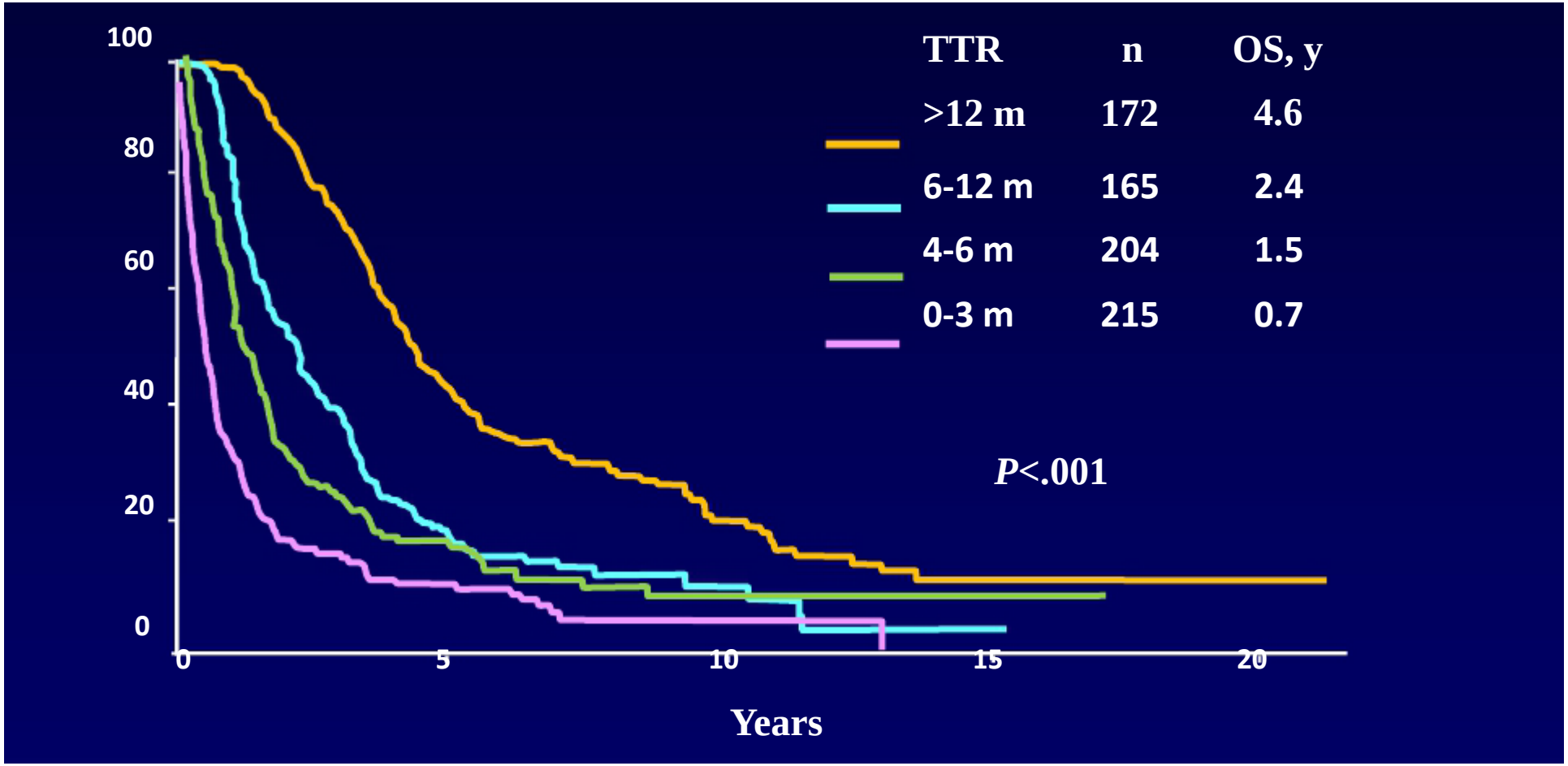
Josting A, et al. *J Clin Oncol.* 2000;18(2):332-339

HDR2 Study for Relapsed HL Prognostic Score

Risk factors: Late and multiple relapses; stage IV; and anemia



Relapse After Auto-TX
OS by Time to Relapse After TX
(n = 756)



Current strategies for salvage treatment for relapsed classical Hodgkin lymphoma

Liana Nikolaenko, Robert Chen and Alex F. Herrera

Ther Adv Hematol

2017, Vol. 8(10) 293–302

DOI: 10.1177/2040620717728000

Abstract: Hodgkin lymphoma (HL) is curable in 70–80% of patients with first-line therapy. However, relapses occur in a minority of patients with favorable early stage disease and are more frequent in patients with advanced HL. Salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant (ASCT) for patients with chemotherapy-sensitive disease is a standard treatment sequence for relapsed or refractory (rel/ref) HL. Patients who achieve complete response prior to ASCT have better survival outcomes. The choice of salvage chemotherapy therapy is becoming increasingly difficult in the era of novel agents, as there are no randomized studies to guide the choice of a second-line regimen. In this article, we will review current salvage therapy options, including combination chemotherapy and novel-agent-based salvage regimens for rel/ref HL.

Prognostic significance of baseline metabolic tumor volume in relapsed and refractory Hodgkin lymphoma

Alison J. Moskowitz,[1] Heiko Schöder,[2] Somali Gavane,[3] Katie L. Thoren,[4] Martin Fleisher,[4] Joachim Yahalom,[1] Susan J. McCall,[1] Briana R. Cadzin,[1] Stephanie Y. Fox,[1] John Gerecitano,[1] Ravinder Grewal,[2] Paul A. Hamlin,[1] Steven M. Horwitz,[1] Anita Kumar,[1] Matthew Matasar,[1] Andy Ni,[5] Ariela Noy,[1] M. Lia Palomba,[1] Miguel-Angel Perales,[1] Carol S. Portlock,[1] Craig Sauter,[1] David Straus,[1] Anas Younes,[1] Andrew D. Zelenetz,[1] and Craig H. Moskowitz[1]

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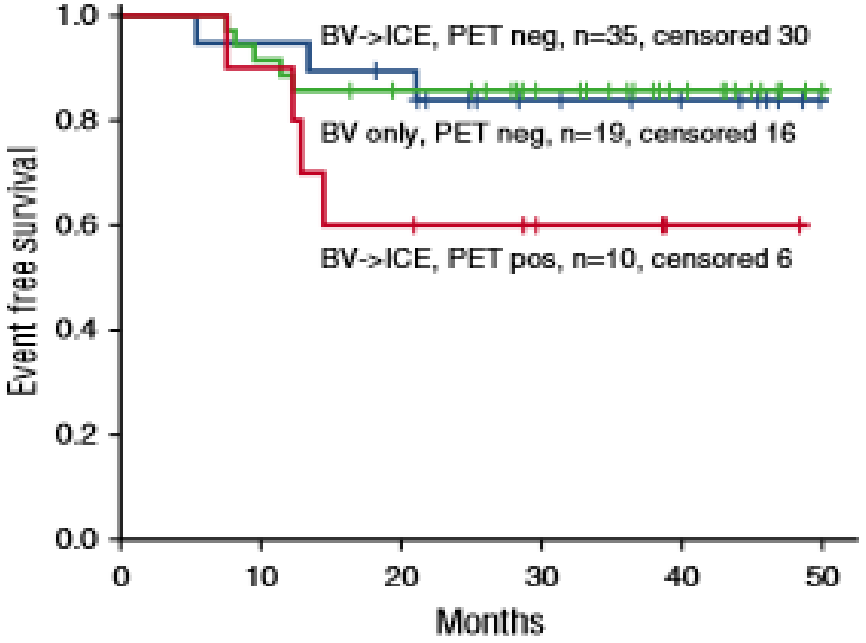
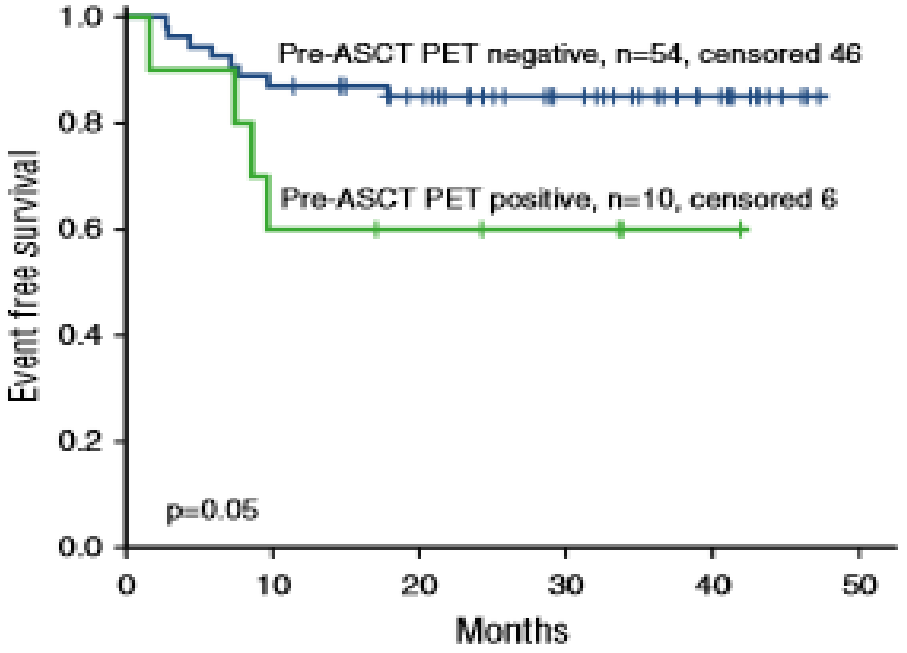
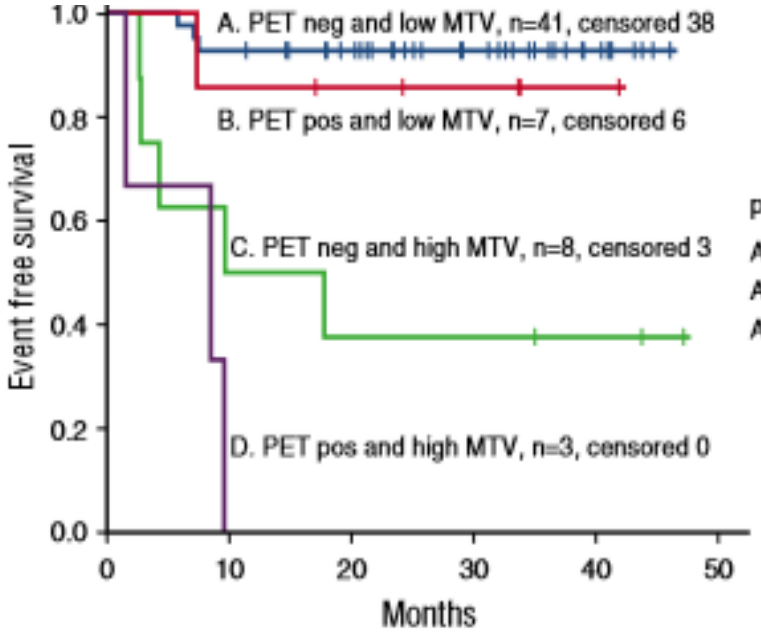
Key Points

- Baseline metabolic tumor volume and the presence of refractory disease predict outcome for patients with relapsed/refractory HL.
- Metabolic tumor volume improves the predictive power of pretransplantation PET in relapsed/refractory HL.

Identification of prognostic factors for patients with relapsed/refractory Hodgkin lymphoma (HL) is essential for optimizing therapy with risk-adapted approaches. In our phase 2 study of positron emission tomography (PET)–adapted salvage therapy with brentuximab vedotin (BV) and augmented ifosfamide, carboplatin, and etoposide (augICE), we assessed clinical factors, quantitative PET assessments, and cytokine and chemokine values. Transplant-eligible patients with relapsed/refractory HL received 2 (cohort 1) or 3 (cohort 2) cycles of weekly BV; PET-negative patients (Deauville score ≤2) proceeded to autologous stem cell transplantation (ASCT) whereas PET-positive patients received augICE before ASCT. Serum cytokine and chemokine levels were measured at baseline and after BV. Metabolic tumor volume (MTV) and total lesion glycolysis were measured at baseline, after BV, and after augICE. Sixty-five patients enrolled (45, cohort 1; 20, cohort 2); 49 (75%) achieved complete response and 64 proceeded to ASCT. Three-year overall survival and event-free survival (EFS) were 95% and 82%, respectively. Factors predictive for EFS by multivariable analysis were baseline MTV (bMTV) ($P < .001$) and refractory disease ($P = .003$). Low bMTV (<109.5 cm^3) and relapsed disease identified a favorable group (3-year EFS, 100%). For patients who received a transplant, bMTV and pre-ASCT PET were independently prognostic; 3-year EFS for pre-ASCT PET-positive patients with low bMTV was 86%. In this phase 2 study of PET-adapted therapy with BV and augICE for relapsed/refractory HL, bMTV and refractory disease were independent prognostic factors for EFS. Furthermore, bMTV improved the predictive power of pre-ASCT PET. Future studies should optimize efficacy and tolerability of salvage therapy by stratifying patients according to risk factors such as bMTV. (*Blood.* 2017;130(20):2196-2203)







p-values

A->B, p=0.551 B->C, p=0.072
A->C, p<0.001 B->D, p=0.012
A->D, p<0.001 C->D, p=0.12

① BV for patients relapsed after AUTO or refractory to CT

BV in relapsed/refractory patients

	Younes 2012	Rothe 2012	Zinzani 2013	Gibb 2013
N	102	45	65	18
Relapse after HDC	100%	87%	92%	33%
ORR	75%	60%	**70%**	72%
CR	34%	22%	21%	17%
PR	41%	38%	8%	55%
DOR all responding	6.7M	8M	6,8M	5M
DOR CR	20 M	13M (CR+PR)	/	/
ALLO (elegible/done)	102/6	39/0	62/9	18/4
OS	73%@3y	83%@1y	74%@20M	/
PFS	58%@3y	43%@1y	23%@20M	20%@1y
Response max	3 cycles	/	3 cycles	4 cycles

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients With Relapsed or Refractory Hodgkin's Lymphoma

Anas Younes, Ajay K. Gopal, Scott E. Smith, Stephen M. Ansell, Joseph D. Rosenblatt, Kerry J. Savage, Radhakrishnan Ramchandren, Nancy L. Bartlett, Bruce D. Cheson, Sven de Vos, Andres Forero-Torres, Craig H. Moskowitz, Joseph M. Connors, Andreas Engert, Emily K. Larsen, Dana A. Kennedy, Eric L. Sievers, and Robert Chen

J Clin Oncol 30. © 2012

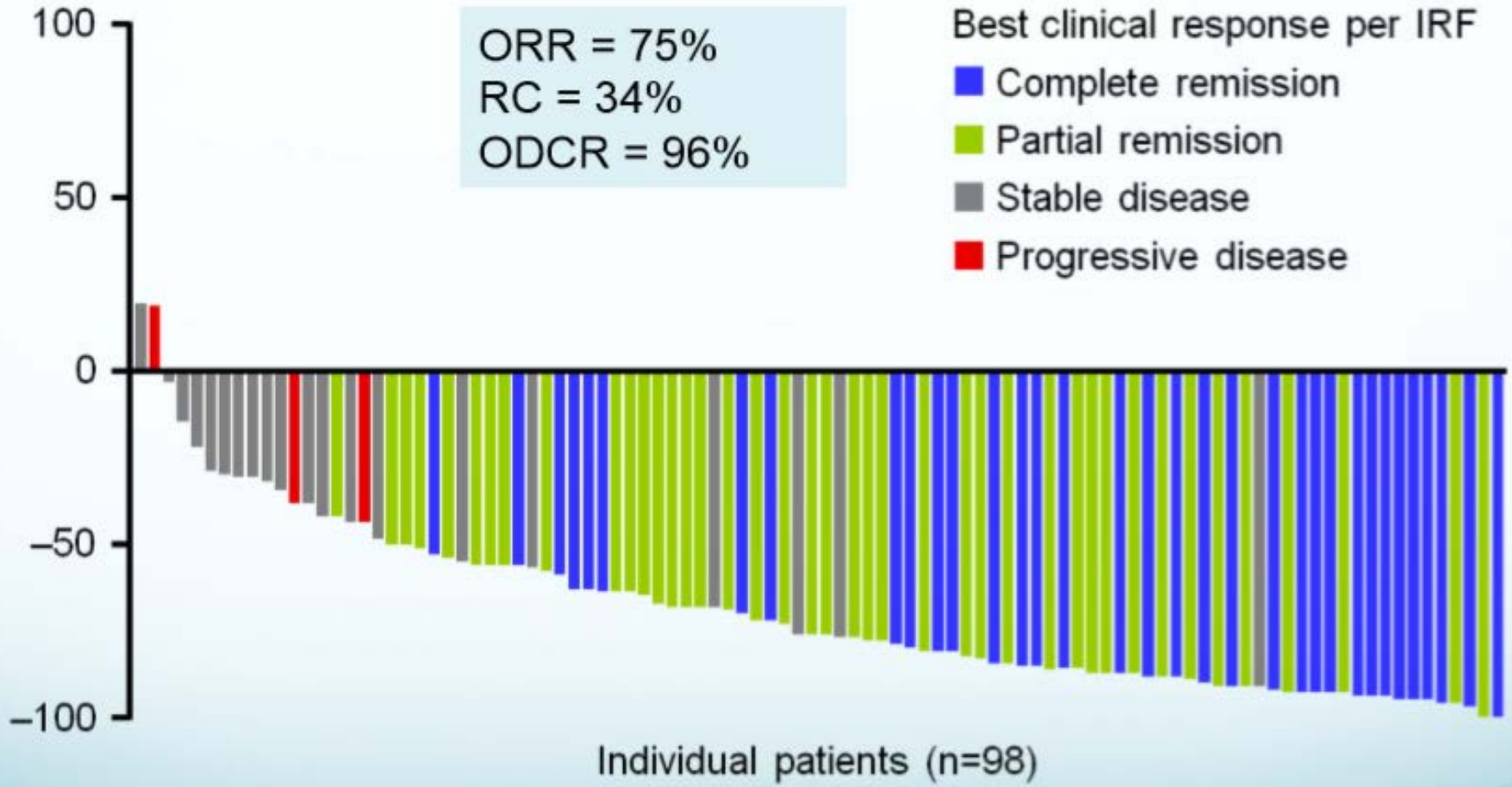
		%
Primary refractory disease†	72	71
Disease status relative to most recent prior therapy‡		
Relapsed	59	58
Refractory	43	42
Best response achieved with most recent systemic regimen		
Complete response	12	12
Partial response	35	34
Stable disease	23	23
Progressive disease	26	25
Unknown/other	6	6
No. of prior auto-SCTs		
1	91	89
2	11	11
Time from auto-SCT to first post-transplantation relapse, months		
Median	6.7	
Range	0-131	
Time from initial diagnosis to first dose of study drug, months		
Median	39.90	
Range	11.8-219.7	

SGN35-003:
Caratteristiche al baseline

	N=102
Età mediana, anni (range)	31 (15-77)
Sesso	48 M / 54 F
ECOG	
0	42 (41%)
1	60 (59%)
Refrattario alla terapia frontline	72 (71%)
Refrattario all'ultima terapia	43 (42%)
Numero di linee precedenti	3.5 (1-13)
Radioterapia precedente	67 (66%)
ABMT precedente	
1	91 (89%)
2	11 (11%)
Tempo tra ABMT e primo relapse	6.7 mesi (0-131)

Younes A, et al. J Clin Oncol 2012;30: 2183-2189.

SGN35-003:
Risposte Ottenute



Younes A, et al. J Clin Oncol 2012;30: 2183-2189.

SGN35-003:
Tossicità

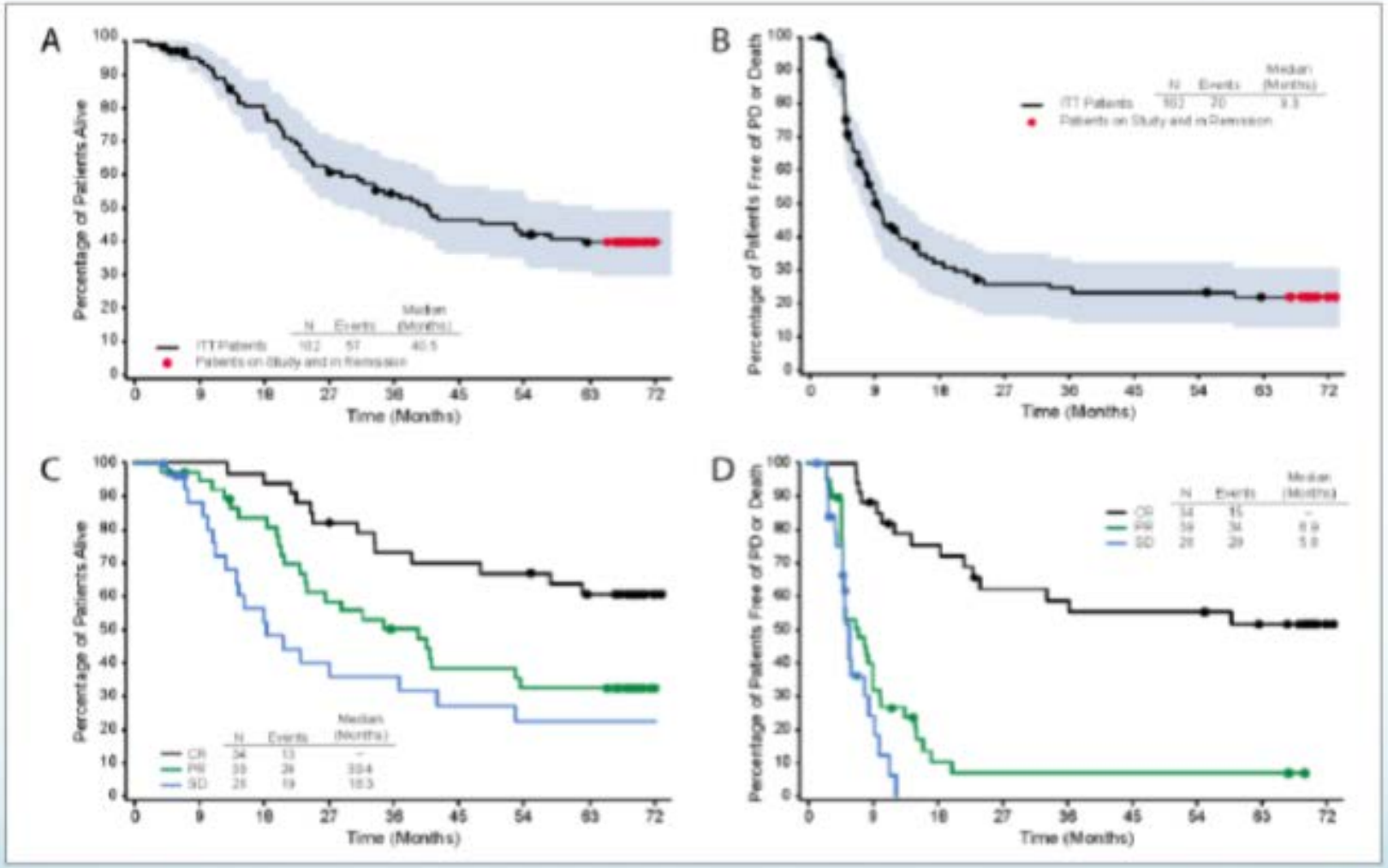
Neuropatia Periferica Sensitiva	42%
Nausea	35%
Fatigue	34%
Neutropenia	19%
Diarrea	18%
Febbre	14%
Vomito	13%
Artralgie	12%
Prurito	12%
Mialgie	11%
Neuropatia Periferica Motoria	11%
Alopecia	10%

- 20% ha dovuto interrompere il trattamento per eventi avversi

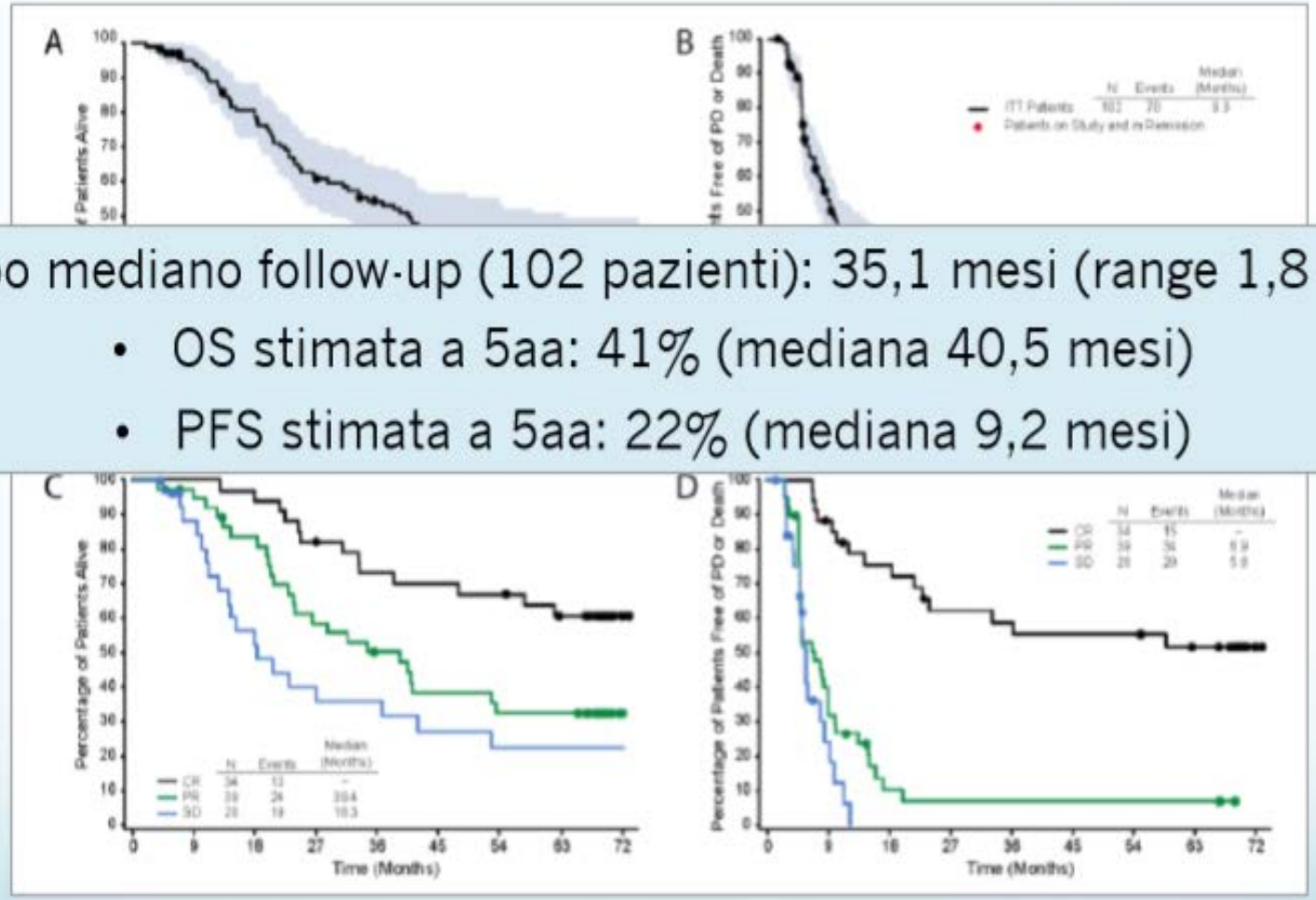
Younes A, et al. J Clin Oncol 2012;30: 2183-2189.

SGN35-003:

Follow-up a cinque anni



SGN35-003:
Follow-up a cinque anni



- Tempo mediano follow-up (102 pazienti): 35,1 mesi (range 1,8 – 72,9)
  - OS stimata a 5aa: 41% (mediana 40,5 mesi)
  - PFS stimata a 5aa: 22% (mediana 9,2 mesi)

ORIGINAL ARTICLE

Brentuximab vedotin as salvage treatment in Hodgkin lymphoma naïve transplant patients or failing ASCT: the real life experience of Rete Ematologica Pugliese (REP)

Vincenzo Pavone[1] · Anna Mele[1] · Daniela Carlino[1] · Giorgina Specchia[2] · Francesco Gaudio[2] · Tommasina Perrone[2] · Patrizio Mazza[3] · Giulia Palazzo[3] · Attilio Guarini[4] · Giacomo Loseto[4] · Prete Eleonora[1] · Nicola Cascavilla[5] · Potito Scalzulli[5] · Angela Melpignano[6] · Giovanni Quintana[6] · Nicola Di Renzo[7] · Giuseppe Tarantini[8] · Silvana Capalbo[9]

Received: 12 June 2017 / Accepted: 21 May 2018

Abstract

Brentuximab vedotin (BV) shows a high overall response rate (ORR) in relapsed/refractory (R/R) Hodgkin lymphoma (HL) after autologous transplant (ASCT). The aim of this multicenter study, conducted in nine Hematology Departments of Rete Ematologica Pugliese, was to retrospectively evaluate the efficacy and safety of BV as salvage therapy and as bridge regimen to ASCT or allogeneic transplant (alloSCT) in R/R HL patients. Seventy patients received BV. Forty-five patients (64%) were treated with BV as bridge to transplant:16 (23%) patients as bridge to ASCT and 29 (41%) as bridge to alloSCT. Twenty-five patients (36%), not eligible for transplant, received BV as salvage treatment. The ORR was 59% (CR 26%). The ORR in transplant naïve patients was 75% (CR 31%). In patients treated with BV as bridge to alloSCT, the ORR was 62% (CR 24%). In a multivariate analysis, the ORR was lower in refractory patients ($p < 0.005$). The 2y-OS was 70%. The median PFS was 17 months. Ten of the 16 (63%) naïve-transplant patients received ASCT, with 50% in CR before ASCT. In the 29 patients treated with BV as bridge to alloSCT, 28 (97%) proceeded to alloSCT with 25% in CR prior to alloSCT. The most common adverse events were peripheral neuropathy (50%), neutropenia (29%) and anemia (12%). These data suggest that BV is well tolerated and very effective in R/R HL, producing a substantial level of CR. BV may also be a key therapeutic agent to achieve good disease control before transplant, improving post- transplant outcomes, also in refractory and heavily pretreated patients, without significant overlapping toxicities with prior therapies.

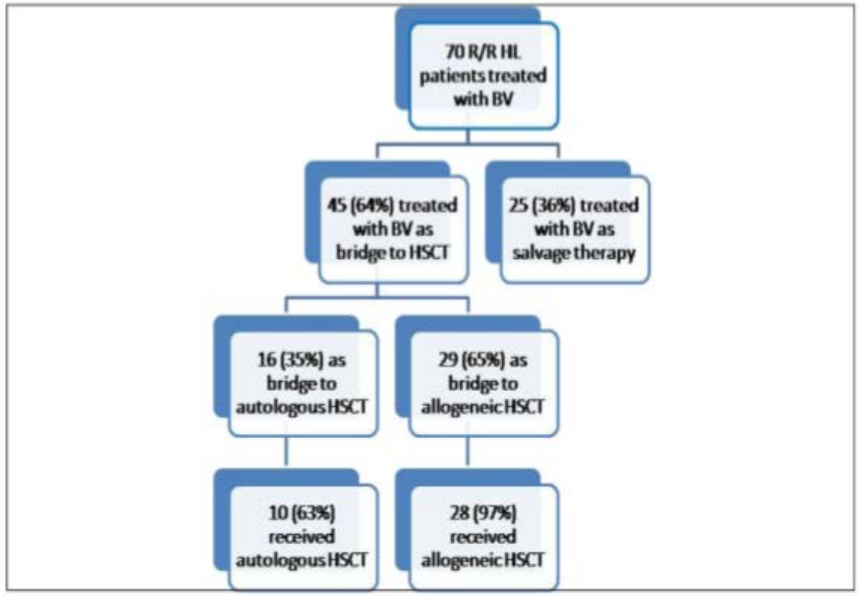


Table 1 Demographics and baseline clinical characteristics at enrollment

	No. of patients (%) ($n = 70$)	Bridge to auto SCT ($n = 16$)	Bridge to allo SCT ($n = 29$)	Salvage therapy ($n = 25$)	p
Median age, yrs. (range)	34 (15–84)	30 (15–65)	32 (22–54)	52 (16–84)	
> 50 yrs	19 (28)	5 (31)	2 (7)	12 (50)	0.001
Disease status at BV					
Refractory	33 (47)	6 (37)	13 (45)	14 (56)	0.48
Relapsed	37 (53)	10 (63)	16 (55)	11 (44)	
ECOG performance status					
0	42 (60)	10 (62)	20 (69)	11 (44)	0.38
1–2	28 (40)	6 (38)	9 (31)	14 (56)	
Baseline B symptoms	39 (57)	12 (75)	14 (48)	13 (56)	0.22
Extranodal disease at diagnosis	29 (44)	7 (47)	10 (37)	12 (59)	0.6
Bulky disease	22 (33)	6 (40)	12 (44)	4 (16)	0.09
III–IV stage	44 (64)	11 (69)	16 (55)	17 (71)	0.68
Median prior chemotherapy regimens, (range)	3 (1–6)	2 (2–3)	3 (2–5)	3 (1–6)	0.001
≥ 3	42 (64)	4 (27)	23 (82)	15 (66)	
First remission < 12 months	41 (68)	12 (80)	17 (68)	12 (60)	0.45
Median time from diagnosis to BV, months (range)	17 (3–111)	14 (5–111)	20 (4–86)	19 (3–104)	0.08
≥ 17	30 (43)	4 (27)	17 (61)	9 (56)	
Prior radiation	16 (23)	2 (12)	8 (28)	6 (26)	0.48
Prior Auto-SCT	40 (57)	NA	28 (97)	12 (48)	0.001
Prior Allo-SCT	6 (9)	NA	NA	6 (100)	0.002
Median time from auto to-relapse, months (range)	5 (1–73)	NA	5 (1–44)	5	0.71
< 6 months	21 (52)		9 (32)	1 (8)	

SGN35-003:
Caratteristiche al baseline

	N=102
Età mediana, anni (range)	31 (15-77)
Sesso	48 M / 54 F
ECOG	
0	42 (41%)
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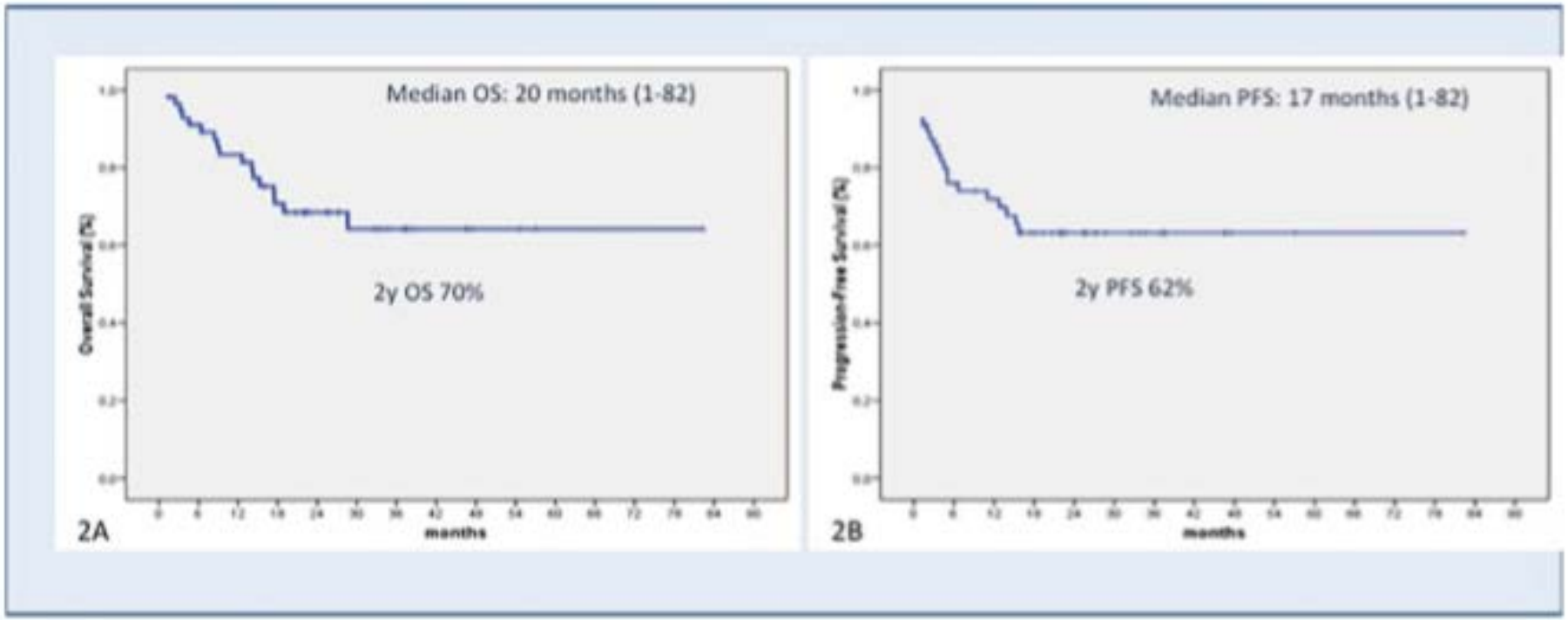
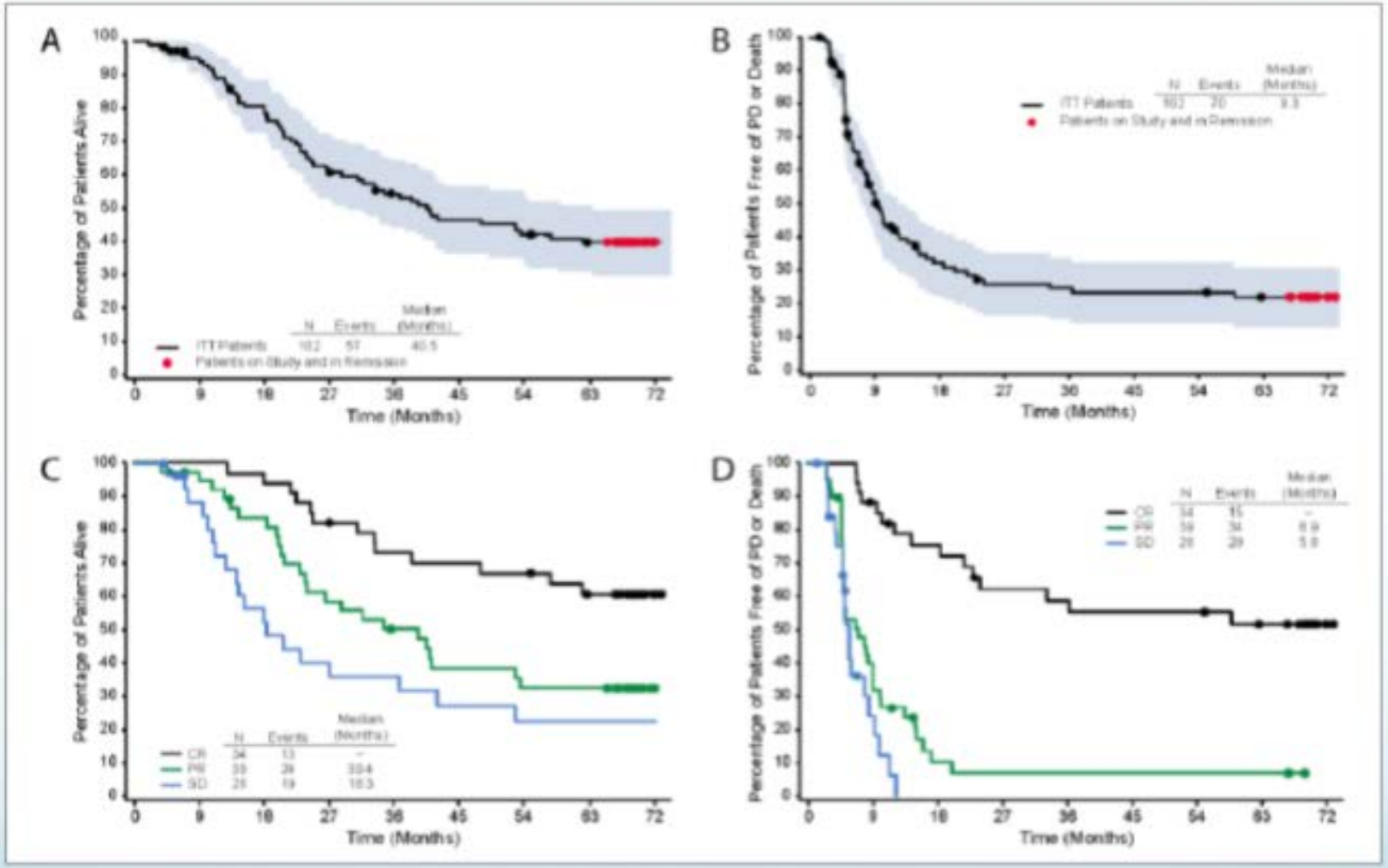


Fig. 2 Kaplan-Meier plots of probabilities of overall survival (OS) (**a**) and progression-free survival (PFS) (**b**) of the whole group

SGN35-003:

Follow-up a cinque anni



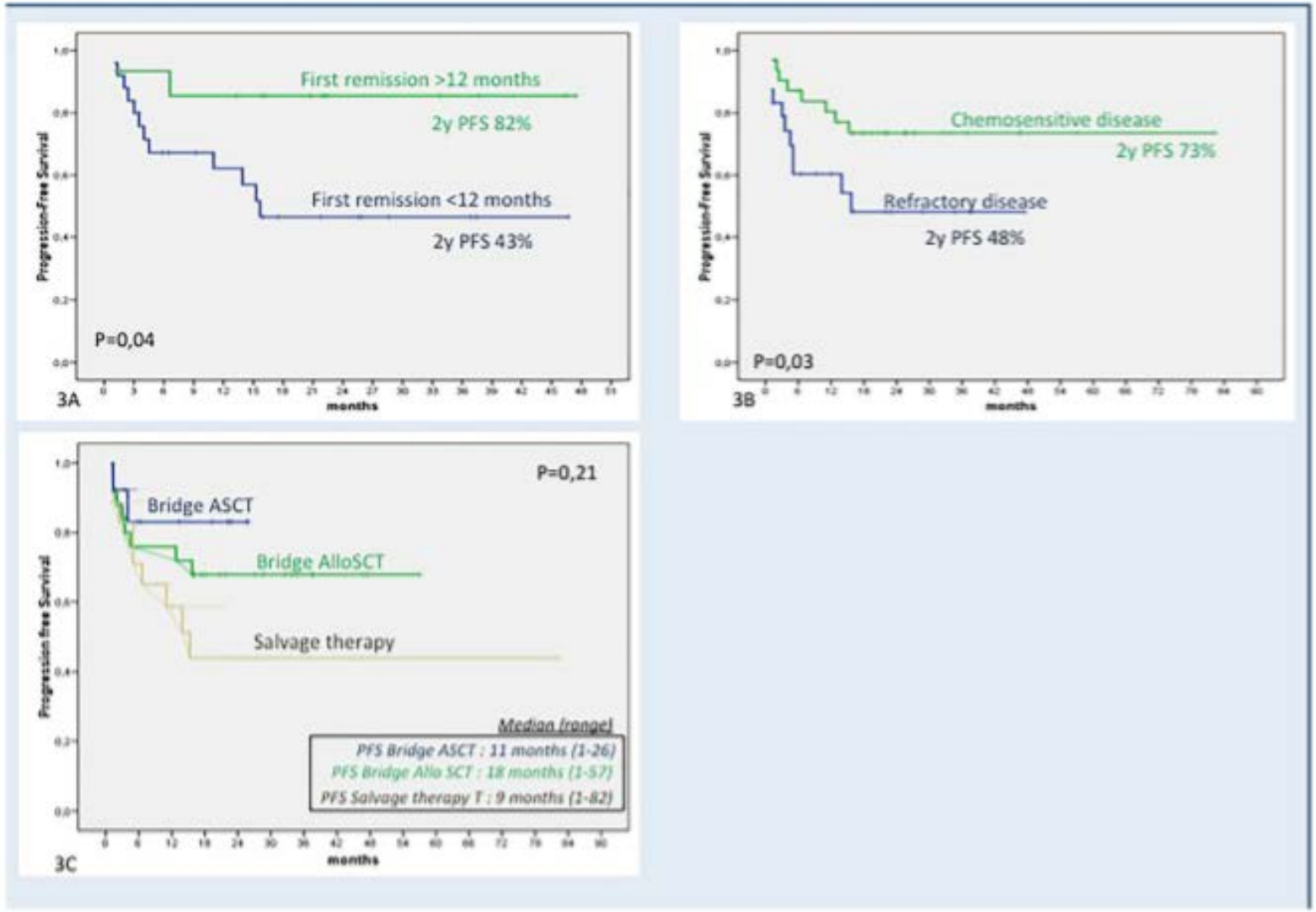
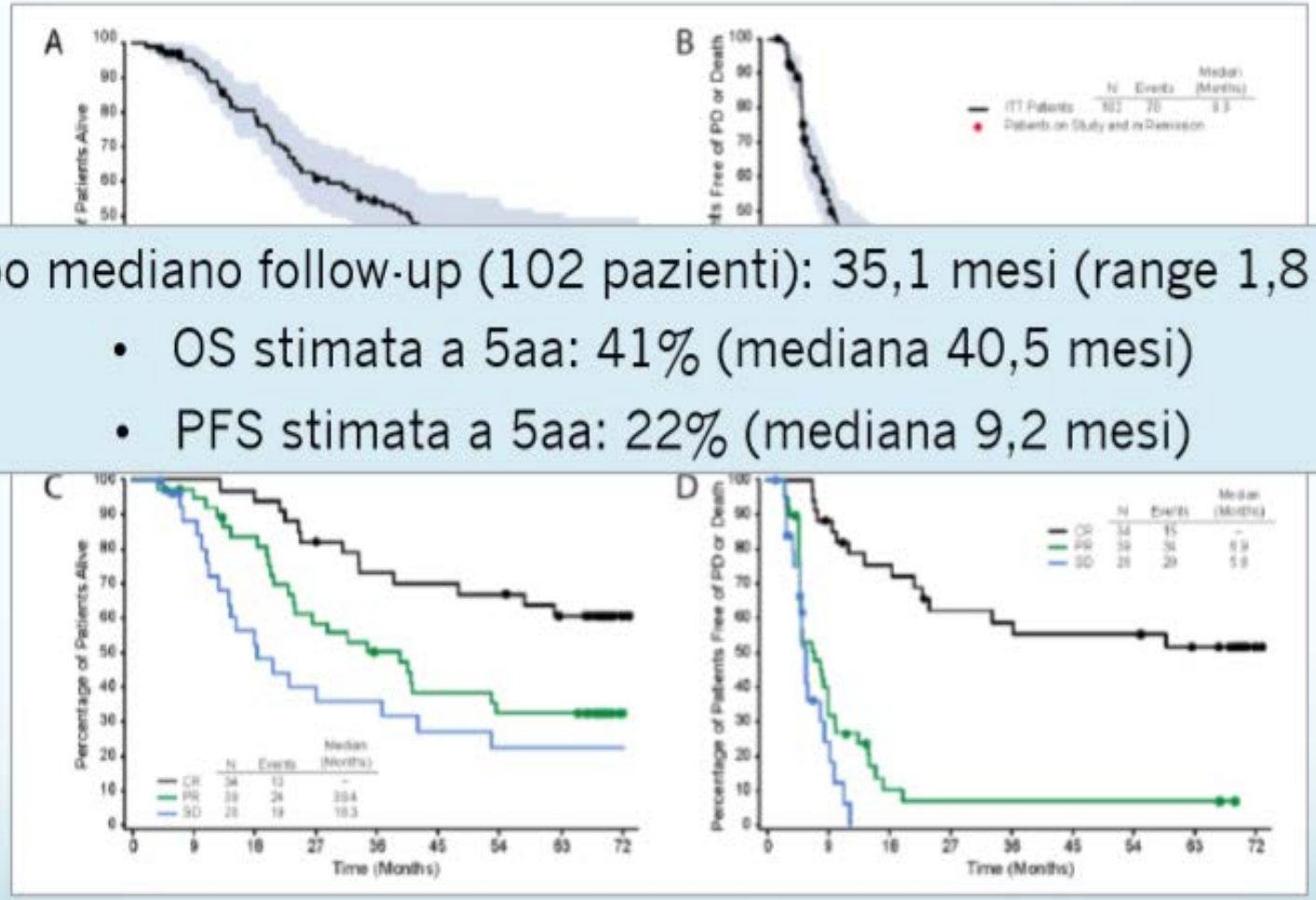


Fig. 3 Progressions free survival (PFS) **a** according to time to relapse, **b** to refractory disease, and **c** to timing of brentuximab vedotin (BV)

SGN35-003:
Follow-up a cinque anni



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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]

ABSTRACT

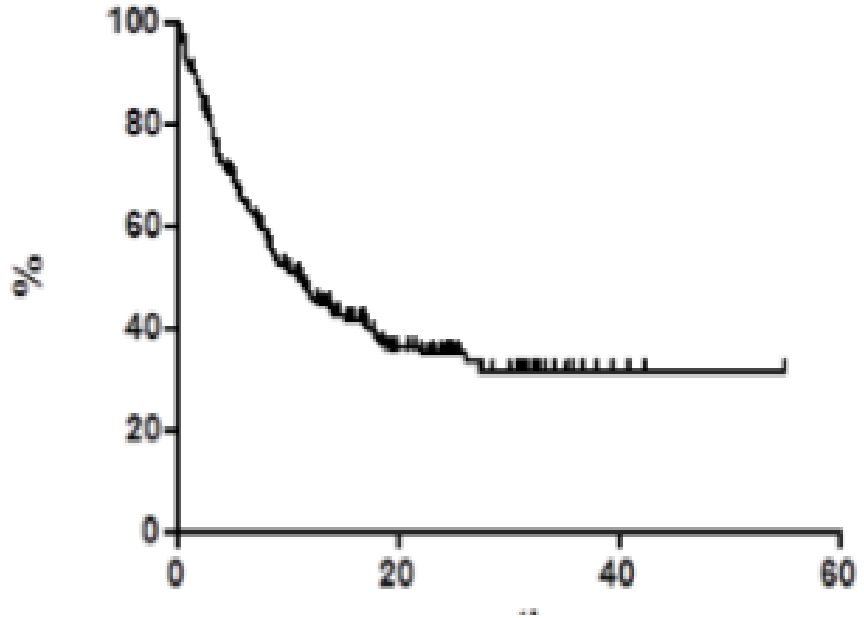
A large Italian multicenter observational retrospective study was conducted on the use of brentuximab vedotin (BV) for patients with relapsed Hodgkin's lymphoma (HL) to check if clinical trial results are confirmed even in a real life context. 234 CD30+ HL patients were enrolled. Best response was observed after a median of 4 cycles in 140 patients (59.8%): 74 (31.6%) patients obtained a complete response (CR) and 66 (28.2%) achieved a partial response (PR); overall response rate at the end of the treatment was 48.3% (62 CR and 51 PR). The best response rate was higher in the elderly subset: 14 (50%) CR and 5 (17.8%) PR. Disease free survival was 26.3% at 3 years and progression free survival 31.9% at 4.5 years. Duration of response did not differ for who achieved at least PR and then either did or did not undergo consolidative transplant. Overall, the treatment was well tolerated and no death has been linked to BV-induced toxicity.

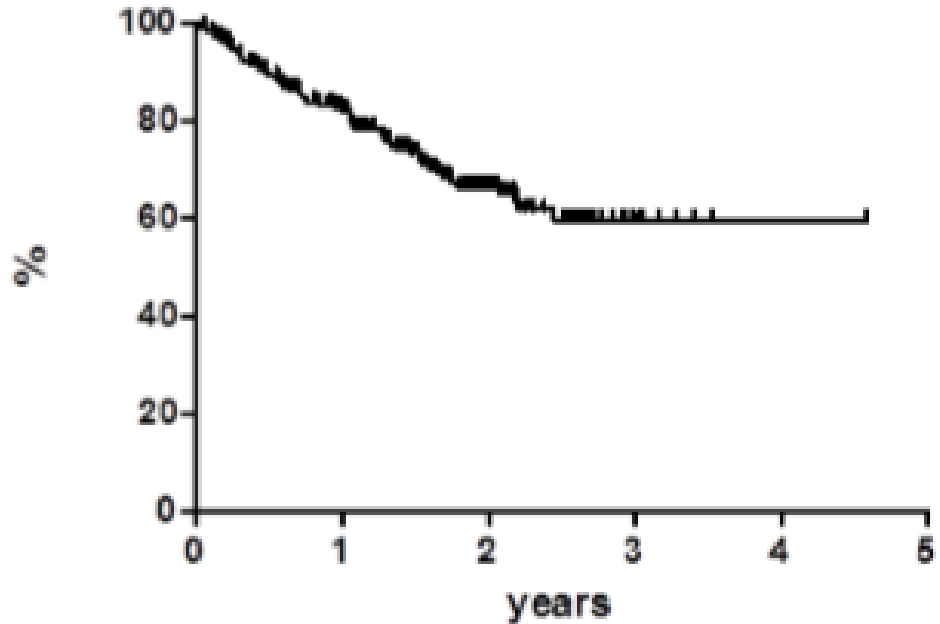
Our report confirms activity in elderly patients, duration of response unrelated to the consolidation with transplant procedure, the relevance of the CR status at first restaging, and the role of BV as a bridge to transplant for chemorefractory patients.

Table 1: Patient demographics and characteristics at baseline

	Total population	Elderly (≥60)
Patients, *N*	234	28
Median age, years (range)	35.4 (18.0-79.0)	66.5 (60.2-78.6)
Median time from diagnosis-BV*, years (range)	2.3 (1.0-33)	2.9 (1.0-19.5)
Male, *N* (%)	129 (55.1)	17 (60.7)
Stage, *N* (%) - I/II - III - IV	 99 (42.3) 48 (20.5) 87 (37.2)	 11 (39.3) 6 (21.4) 11 (39.3)
ECOG† performance status, *N* (%) - 0 - 1 - 2	 26 (60.5) 17 (39.5) -	 7 (25.0) 16 (57.1) 5 (17.8)
Bulky disease, *N* (%)	12 (5.1)	1 (3.5)
Bone marrow involvement, *N* (%)	15 (6.4)	2 (7.1)
Systemic symptoms, *N* (%)	116 (49.6)	10 (35.7)
- Refractory to most recent therapy, *N* (%) - Refractory to first line therapy, *N* (%)	164 (70.1) 119 (50.8)	16 (57.1) 9 (32.1)
Median number of previous therapies (range)	3 (1-6)	2 (1-6)
Prior autologous stem cell transplant, *N* (%)	163 (69.8)	11 (39.3)
Prior radiotherapy, *N* (%)	98 (41.9)	7 (25.0)

*BV: brentuximab vedotin; †ECOG: Eastern Cooperative Oncology Group.





Vol. 8, (No. 53), pp: 91703-91710

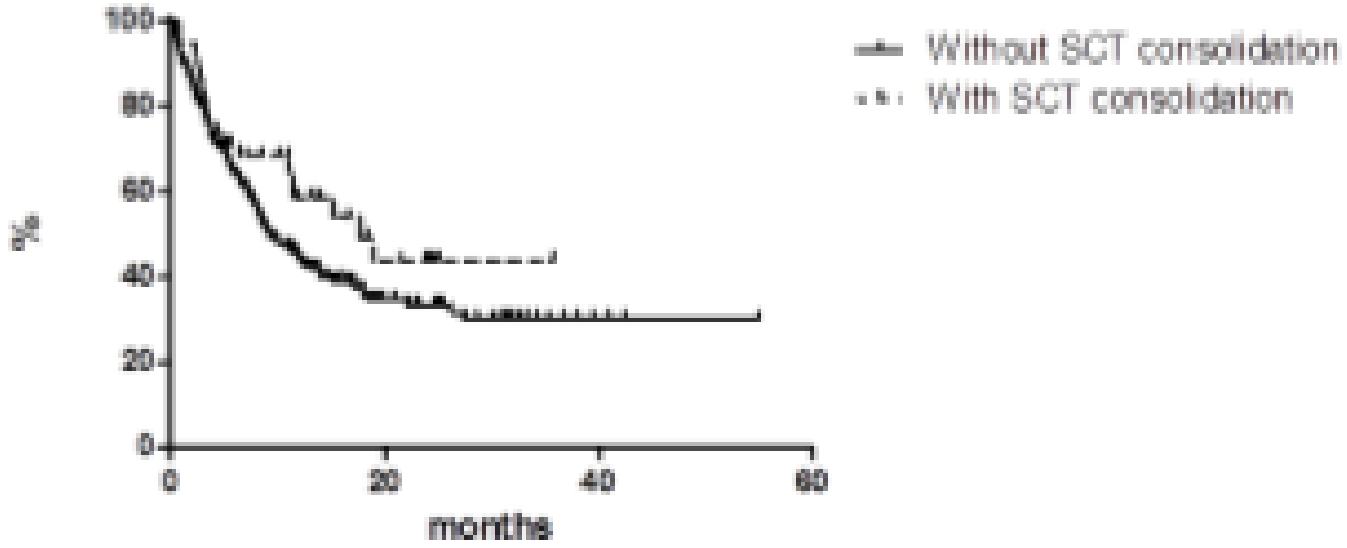


Figure 4: Progression free survival in patients with and without stem cell transplant (SCT) consolidation.

REAL LIFE DATA OF BRENTUXIMAB VEDOTIN USE IN RELAPSED/REFRACTORY HL IN SWEDEN

Background: About 20% of patients with Hodgkin lymphoma (HL) will relapse and only half of them are cured with autologous stem cell transplant (ASCT). Those with a second relapse have poor outcome and historically few treatment alternatives. The antibody-chemotherapy conjugate brentuximab vedotin (BV) has been used in Sweden since 2011.
Methods: This retrospective study aimed to evaluate the response to BV treatment in patients with relapsed/refractory HL in clinical routine. Thirtynine patients, median age 41 (range 17–78) treated with BV in Sweden during 2011–2017 were identified retrospectively from patient files. Not all centers in Sweden have been included in the analysis yet. Median number of previous therapies was two (range 1–9). Seventeen patients had received previous ASCT, three patients had received both ASCT and allo SCT and nineteen patients had no previous stem cell transplant (SCT). The primary endpoints were progression-free survival (PFS), overall survival (OS) and number proceeding to ASCT or allo SCT.
Results: The median number of cycles of BV was five (range 2–19). A majority (n = 24) of patients received BV with a curative intent, usually aiming for transplantation. The objective response rate was 56% (33% CR, 23% PR). 5-year OS and PFS from start of BV treatment were 62% and 33%. Fifteen patients received consolidation with SCT (10 allo, 5 auto), and 80% of them achieved a CR. The median duration of response for these patients was 25.1 months (range 1.7–70.9). Eleven of these patients were still in remission at latest follow-up. Patients (n = 24) who did not proceed to SCT had a median duration of response of 3.8 months (range 0.9–20.2), five still being in remission. The transplanted patients had 1-year PFS of 92% and 5-year PFS of 62%, compared to 1-year PFS of 24% in those not transplanted after BV (Figure 1).
Conclusion: Our study demonstrates that BV can be effective in heavily pre-treated patients with relapsed/refractory HL in real life, here with an objective response in 56%. Few allo SCT were performed in the pivotal trial that led to approval of BV (Younes 2012) and the long term results of those not transplanted seemed equal to those who have been transplanted (Chen 2016). However, in our cohort the outcome of those not transplanted was significantly poorer. Our data also support previous reports that BV can be used as a bridge to allo SCT, with lower treatment-related mortality compared to other strategies.

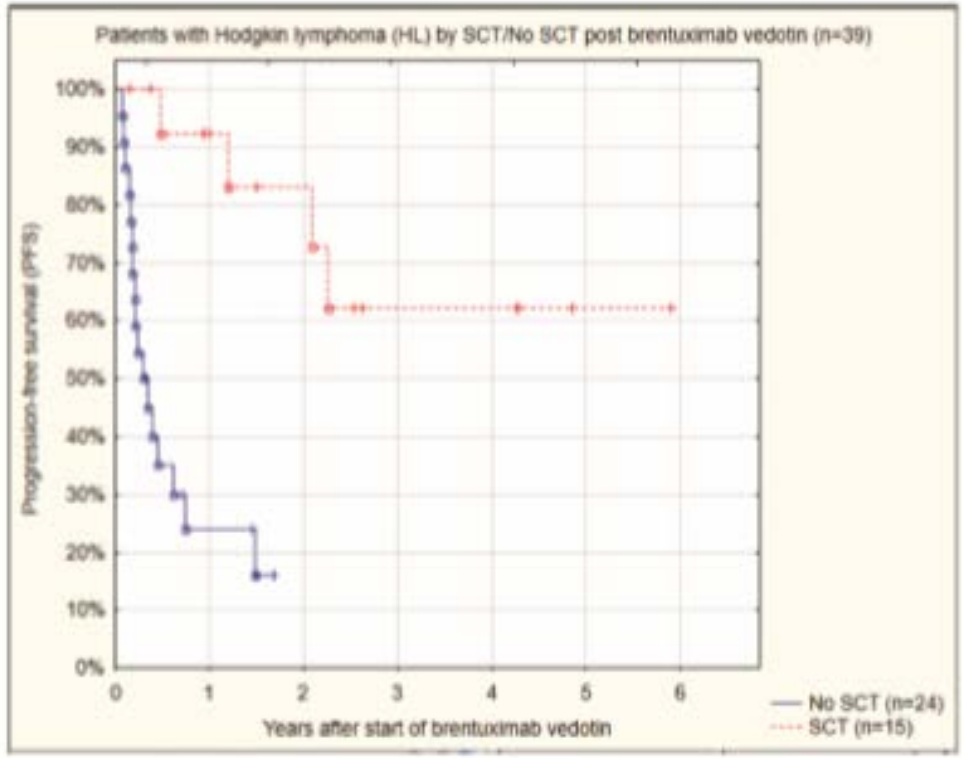


Figure 1. PFS for transplanted and non-transplanted Hodgkin lymphoma patients (Kaplan-Meier, Log Rank) p=0.00018.

Come cambia la strategia del salvataggio

- **BV in monoterapia: in quali pazienti**
- **BV + Chemioterapia: quale?**
- **Sempre ASCT?**
- **Timing ASCT: nuovo**
- **Consolidamento post ASCT**

ALLO RIC

	N	Disease status	Relapse rate	PFS	OS	TRM
Robinson 2002	52	CT S 67%	45%@2y	42%@2y	56%@2y	17%@2y
Peggs 2005	49	CT S 67%	33 %@4y	39%@4y	55%@4y	15%@2y
Alvarez 2006	40	CT S 50%	/	32%@2y	48%@2y	25%@1y
Todisco 2006	14	CT S 57%	/	25%@2y	57%@2y	0
Corradini 2007	32	CT S 62%	81%@3y	/	32%@3y	3%@3y
Anderlini 2008	58	CT S 52%	61%@2y	20%@2y	48%@2y	15%@2y
Devetten 2009	143	CT S 44%	47%@2y	20%@2y	37%@2y	33%@2y
Robinson 2009	285	CT S 59%	53%@3y	29%@4y	25%@4y	19%@1y
Sureda 2012	92	CT S 67%	59%@4y	24%@4y	43%@4y	15%@1y

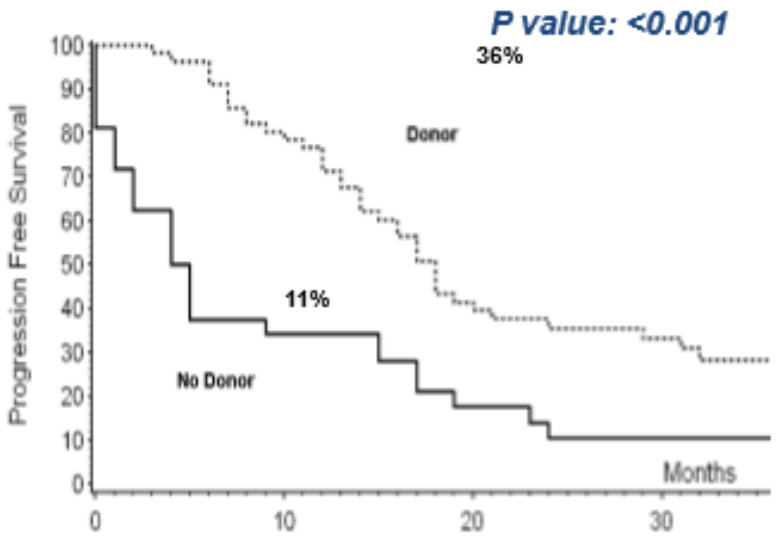
Relapse Rate post-ALLO

	N	Relapse rate	Med time to relapse (months)
Corradini 2007	32	81%@3y	6 (1-42)
Anderlini 2008	58	61%@2y	4 (2-13)
Burroughs 2008	38 id 24 MUD 38 aplo	56%@2y 63%@2y 40%@2y	4 (0-88) 9 (0-28) 6 (0-36)
Robinson 2009	285	53%@3y	6 (1-59)
Sureda 2012	92	59%@4y	6 (3-35)
Castagna 2015*	122	35%@4y	3 (1-21)

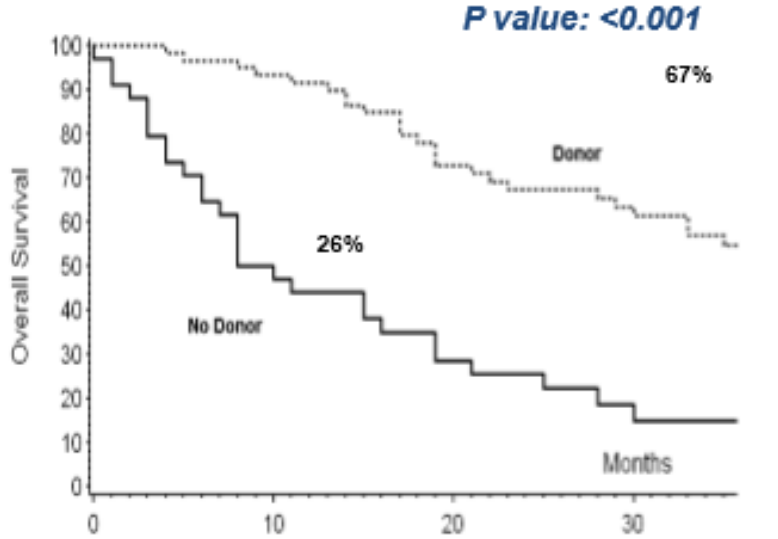
*Submitted

Allogeneic stem cell transplantation after a RIC regimen prolongs the survival in patients with Hodgkin lymphoma (HL) relapsed after high-dose chemotherapy: a retrospective study based on donor availability

Progression free survival$_{2yrs}$



Overall survival$_{2yrs}$



GITMO
GRUPPO ITALIANO TRAPIANTO MIDOLLO OSSEO

B Sarina, Blood 2010

Allogeneic Hematopoietic Stem Cell Transplantation for Hodgkin Lymphomas: A Retrospective Multicenter Experience by the Rete Ematologica Pugliese (REP)

Francesco Gaudio,[1] Patrizio Mazza,[2] Angelo Michele Carella,[3] Anna Mele,[4] Giulia Palazzo,[2] Giovanni Pisapia,[2] Paola Carluccio,[1] Domenico Pastore,[5] Nicola Cascavilla,[3] Giorgina Specchia,[1] Vincenzo Pavone[4]

Abstract

Patients with Hodgkin lymphomas progressing after autologous stem cell transplantation (SCT) have a very poor outcome. Our retrospective analysis confirms that reduced-intensity conditioning allogeneic SCT may be an effective salvage strategy for patients who relapse after an autologous SCT and that outcomes are similar for both sibling and matched-unrelated donor transplants. Patients with active disease at transplantation have poor outcomes.

Background: Hodgkin lymphoma (HL) is a potentially curable disease, and modern therapy is expected to successfully cure more than 80% of the patients. However, patients progressing after intensive treatments, such as autologous stem cell transplantation (SCT), have a very poor outcome. Allogeneic SCT offers the only strategy with a curative potential for these patients. This study reports a retrospective multicenter experience of the Rete Ematologica Pugliese (REP) over the past 17 years, aiming to define the impact of each patient's disease and transplant-related characteristics on outcomes. **Patients and Methods:** We retrospectively studied 72 patients with HL who received allogeneic SCT from 2000 to 2017. At the time of allogeneic SCT, 33 (46%) patients had chemosensitive disease, and 39 (54%) were chemo-refractory. All patients received reduced-intensity conditioning, 50% received grafts from a matched sibling donor, and 50% from a matched-unrelated donor. **Results:** With a median follow-up of 48 months (range, 3-195 months), 30 patients are alive, and 42 have died. The Kaplan-Meier estimates of overall survival and progression-free survival at 5 years were 35% and 34%, respectively. Following transplantation, 12 (17%) patients died of non-relapse mortality at a median of 90 days (range, 1 day-20 months). The causes of death included infection ($n = 7$), graft-versus-host disease ($n = 3$), and multi-organ failure ($n = 2$). **Conclusions:** Allogeneic SCT results extend survival in selected patients with relapsed/refractory HL, showing low treatment-related mortality. Patients with active disease at the time of allogeneic transplantation have poor outcomes. Allogeneic SCT may be an effective salvage strategy for patients who relapse after an autologous SCT.

Allotrapianto
67 pazienti

Median age at diagnosis, years (range)	25 (14-56)
Median age at transplantation, years (range)	34 (16-57)
Diagnosis to transplantation, median months (range)	34 (5-185)
Median number of prior therapies (range)	4 (2-8)
Median time from prior high-dose therapy, months (range)	22 (2-112)
Donor relationship, number (%)	
Matched sibling	29 (43%)
Mismatched related	6 (9%)
Matched unrelated	30 (45%)
Mismatched unrelated	2 (3%)
Stem cell source, number (%)	
PBSC	57 (85%)
BM	10 (15%)
Conditioning Regimen, number (%)	
Fludarabine + Busulphan+ Thiotep	1 (1%)
Cyclophosphamide + Thiotep	4 (6%)
Fludarabine + Cyclophosphamide + Thiotep	62 (93%)

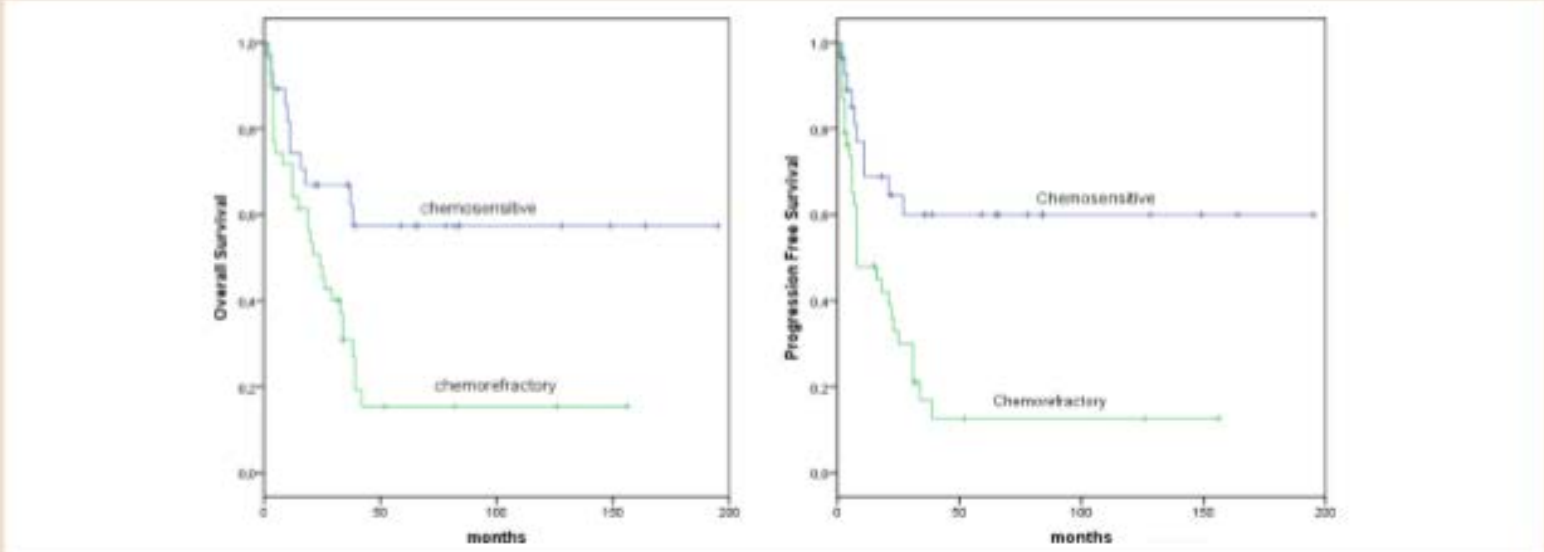
Rete Ematologica Pugliese

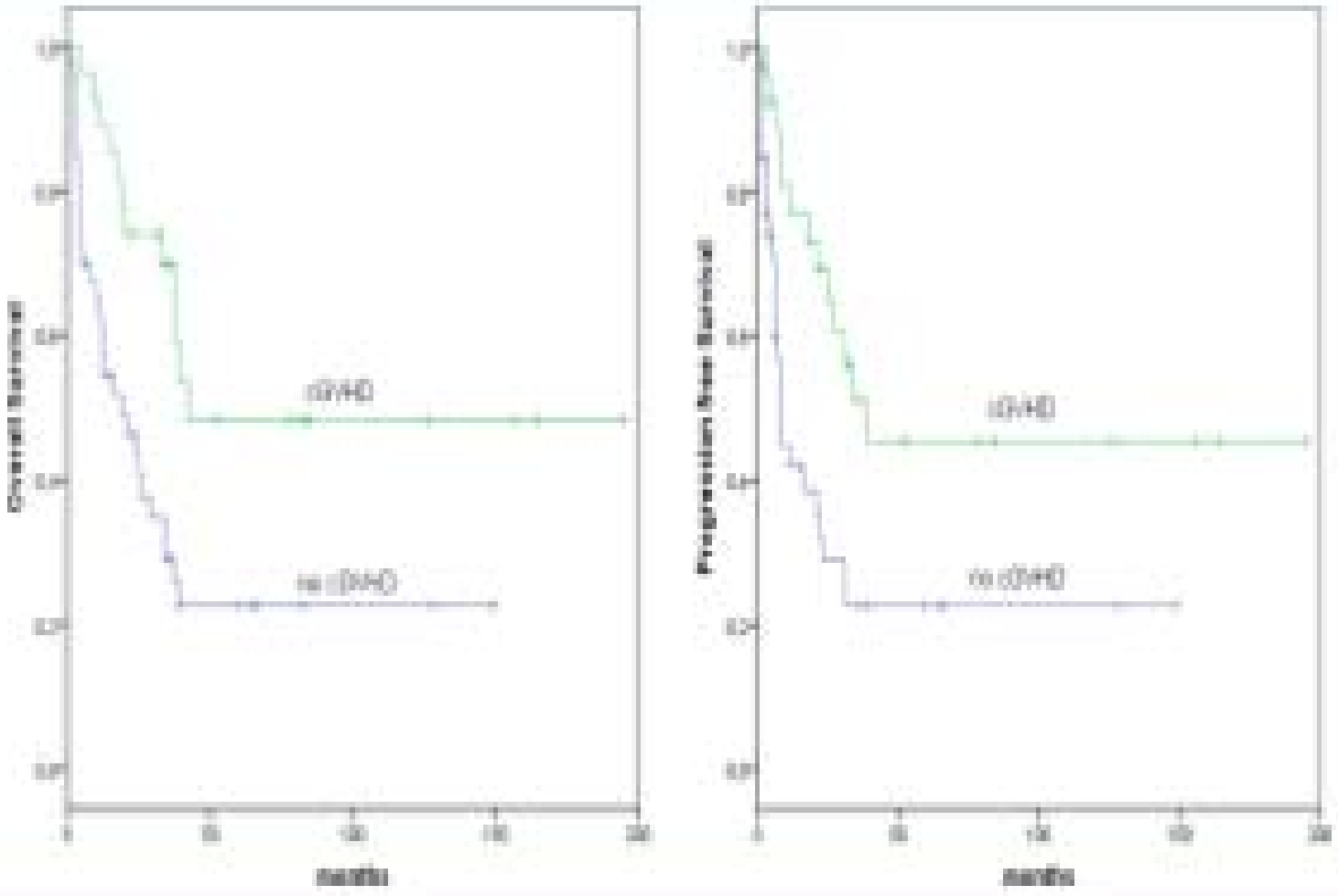
2000-2016

	N	%
Response		
Complete remission	29	43%
Partial remission	19	28%
Stable disease	15	22%
Progressive disease	4	6%
TRM	12	17%
Infections	7	58%
Multi-organ failure	2	17%
GVHD	3	25%

Abbreviations: GVHD = graft versus host disease; TRM = treatment-related mortality.

Figure 1 Overall Survival and Progression-Free Survival According to Clinical Status (Log Rank Test $P < .05$)




Overall Survival
cGVHD
no cGVHD
months
Progression free Survival
cGVHD
no cGVHD
months

BRENTUXIMAB VEDOTIN PRIOR TO ALLOGENEIC TRANSPLANTATION IN HODGKIN'S LYMPHOMAS REDUCES CHRONIC GVHD WITHOUT WORSENING THE OUTCOME

Francesco Gaudio [1], Patrizio Mazza [2], Angelo Michele Carella [3], Anna Mele[4], Giulia Palazzo [2], Giovanni Pisapia [2], Paola Carluccio [1], Domenico Pastore [5], Nicola Cascavilla [3], Giorgina Specchia [1], Vincenzo Pavone [4]

[1] Haematology, Policlinico Hospital, Bari, Italy, [2] Haematology, "G.Moscati" Hospital, Taranto, Italy [3] Haematology, "Casa Sollievo della sofferenza" Hospital, San Giovanni Rotondo (FG), Italy [4] Haematology, "G.Panico" Hospital, Tricase (LE), Italy [5] Haematology, "A.Perrino" Hospital, Brindisi, Italy

Patients with classic Hodgkin's lymphoma (cHL) progressing after autologous stem cell transplantation (SCT) have a very poor outcome. Brentuximab vedotin (BV), an anti-CD30 targeting antibody-drug conjugate has been studied in this patients setting. This study reports a retrospective multicenter experience of the Rete Ematologica Pugliese (REP) over the past 16 years, aiming to compare the patients characteristics and outcomes of 21 BV pre-treated patients to 51 patients who received reduced intensity conditioning (RIC) allogeneic SCT without prior BV, in the time period before the drug became available.

Table 1: Patients' characteristics

Median age at diagnosis, years (range)	25 (14-56)
Female	35(49%)
Male	37(51%)
Median age at SCT, years (range)	34 (16-57)
Diagnosis to SCT time, median months (range)	34 (5-185)
Median number of prior therapies (range)	4 (2-8)
Prior treatment with brentuximab vedotin	26 (36%)
Prior autologous SCT	61 (89%)
Median time from prior high-dose therapy, months (range)	22 (2-112)
Donor relationship, number (%)	
MRD	36 (50%)
MUD	36 (50%)
Stem cell source, number (%)	
PBSC	62 (86%)
BM	10 (14%)
Status at transplant	
Chemosensitive disease	33 (46%)
Chemorefractory disease	39 (54%)

72 patients with cHL who received allogeneic SCT from 2000 to 2017 were retrospectively studied. Median age was 34 years (range 16-57 years) and 36 (54%) were male. At the time of allogeneic SCT, 33 (46%) patients had chemosensitive disease and 39 (54%) were chemorefractory.

Following transplantation, 40 patients relapsed or progressed at a median time of 6.3 months (range 1- 59 months) post-transplant.

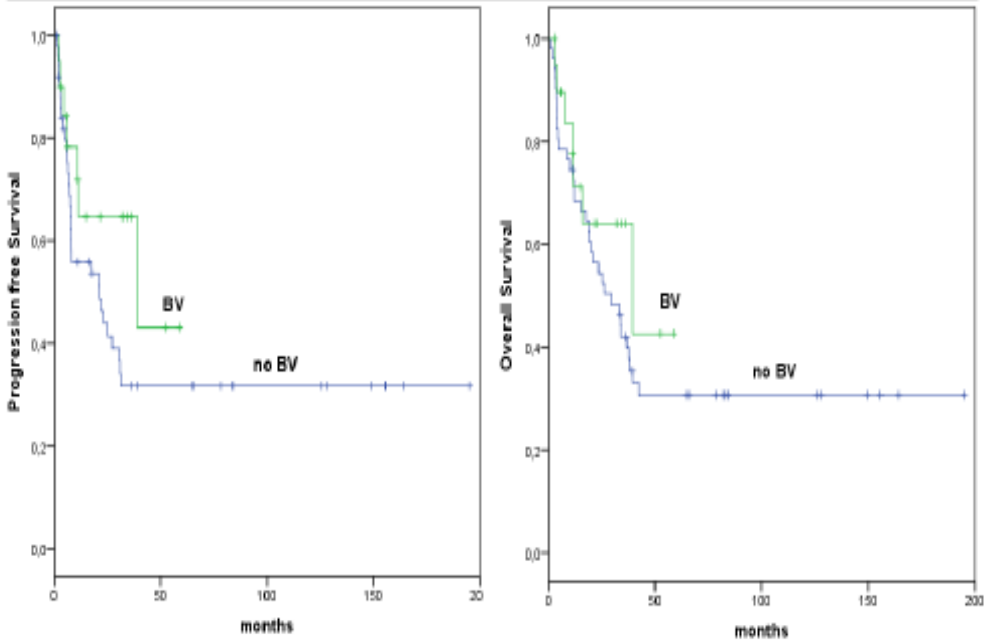
After a median follow-up of 38 months (range 3-195 months) 41 patients remain alive and 26 have died. At univariate analysis, prior use of BV had no effect on either engraftment or the incidence and severity of acute graft versus host disease (GVHD). There was a lower incidence of chronic GVHD in the BV group, with a 41% cumulative incidence at 3 years versus 48% in the no BV group, but this was not statistically significant.

Despite the low incidence of chronic GVHD, we did not observe a worse survival in the BV treated group: 3-year progression free survival (PFS) was 64%, 3-year overall survival (OS) was 64%, 3-year non relapse mortality (NRM) was 19%. In the no-BV group the 3-year PFS was 32%, 3-year OS was 42%, 3-year NRM was 16%.

Table 2: Response to transplant and complications

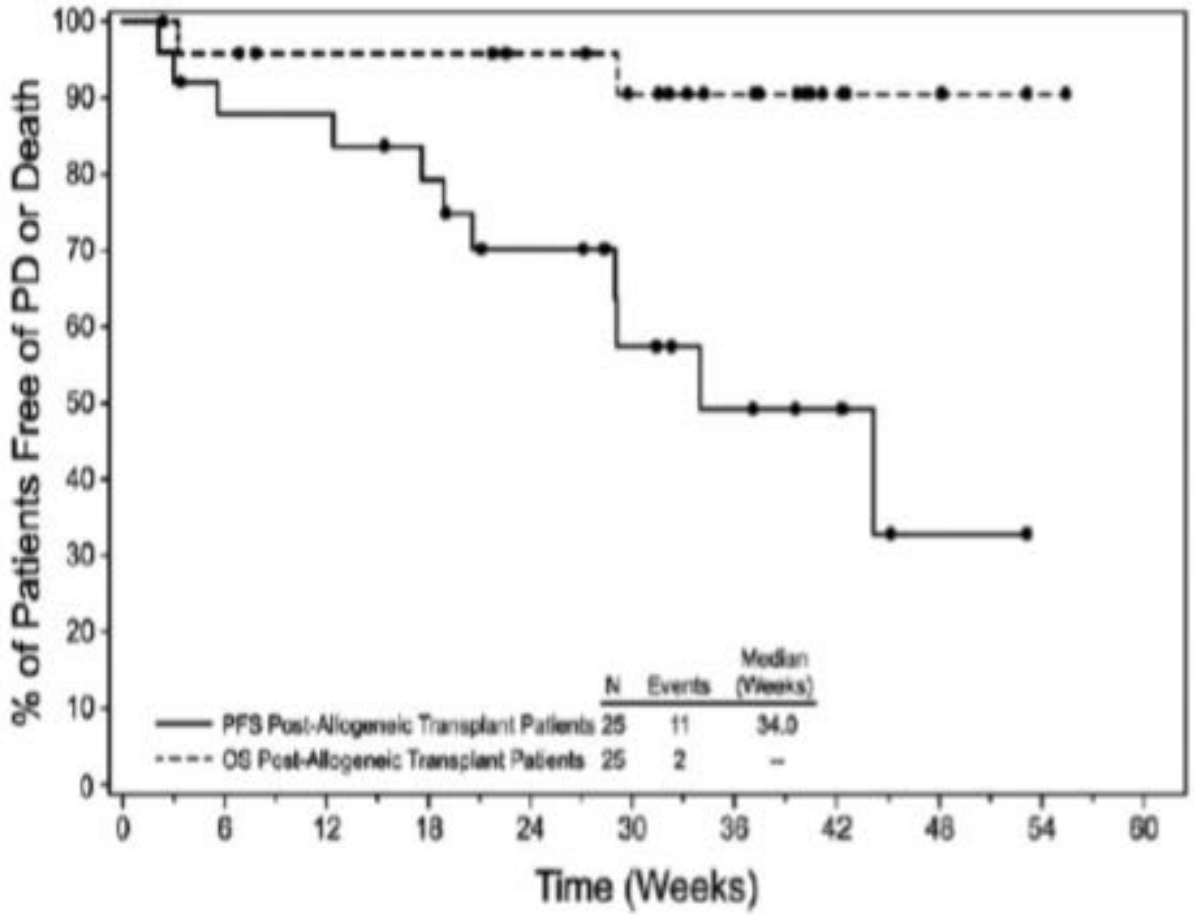
Response	*n*	%
Complete remission	29	43%
Partial remission	19	28%
Stable disease	15	22%
Progression disease	4	6%
TRM	12	17%
Infections	7	58%
multi-organ failure	2	17%
GVHD	3	25%

Fig.1 Progression-free survival and overall survival according to prior BV treatment (Log-Rank test-p=n.s.)



CONCLUSIONS: Allogeneic SCT may be an effective salvage strategy for patients who relapse after autologous SCT. Use of BV salvage treatment yields improved responses over conventional multi-agent chemotherapy with less toxicity, thereby providing better candidates for allogeneic SCT

Brentuximab post ALLO



Gopal, Blood 2012

BV and relapse after ALLO

	Gopal 2012	Carlo-Stella 2015
N	25	16
ORR	75%	68%
CR	34%	31%
PR	41%	37%
DOR all responding	6.7M	5M
DOR CR	20 M	11M
OS	73%@3y	61%@2y
PFS	58%@3y	20%@2y

POST-ALLOSCT IMMUNOMODULATION → **DLI in CR/PR/SD**

	N	Relapse rate	N paz DLI	ORR
Anderlini 2008	58	61%@2y	14	43%
Peggs 2011	76	33%@4y	24/31	79%
Sureda 2012	92	59%@4y	20/40	50%

NEW DRUGS TARGET THERAPY →

- Brentuximab V.
- Panobinostat
- PI3K inhibitor
- Anti PD1/PDL1

Brentuximab could replace Chemotherapy salvage and increase Pet negativity and ASCT frequency and outcome??

And

Reserve ice or Igev or Dhap if Pet + after BV

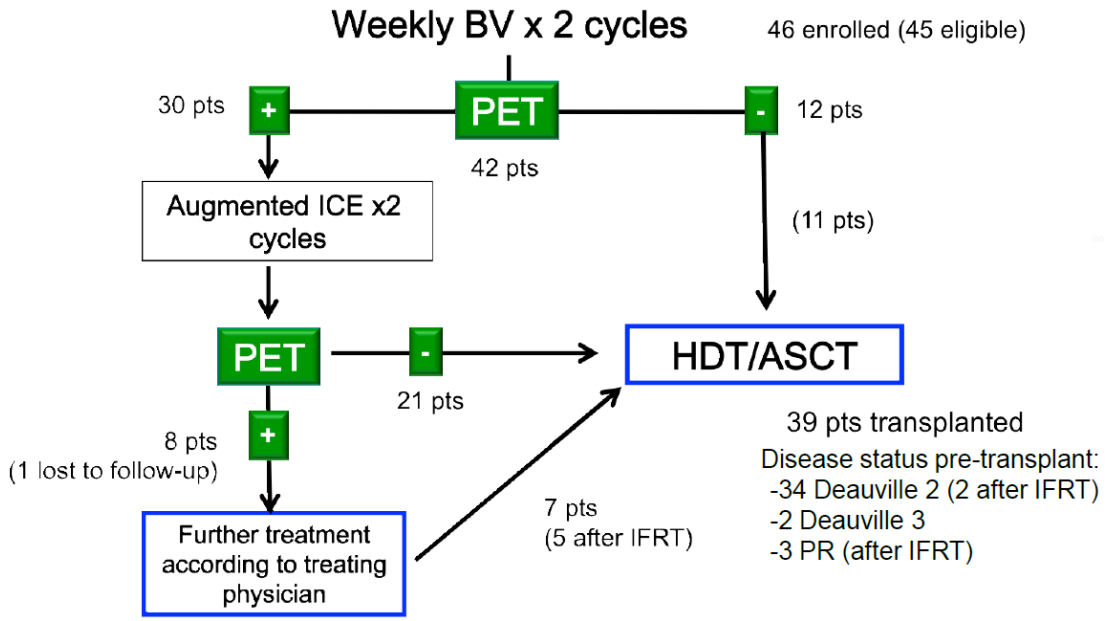
IISR Study: Phase 2 brentuximab vedotin with augmented ICE in rel/ref Hodgkin lymphoma

Moskowitz A et al. ASH 2013, New Orleans, LA, USA (Abstract 2099)

IISR Study: Phase 2 brentuximab vedotin with augmented ICE in rel/ref Hodgkin lymphoma

Study aims were to determine whether brentuximab vedotin can replace ICE salvage therapy, increase rate of PET normalization, and enhance referral to ASCT patients who fail frontline therapy

Study Design:



ICE ifosfamide, carboplatin, etoposide

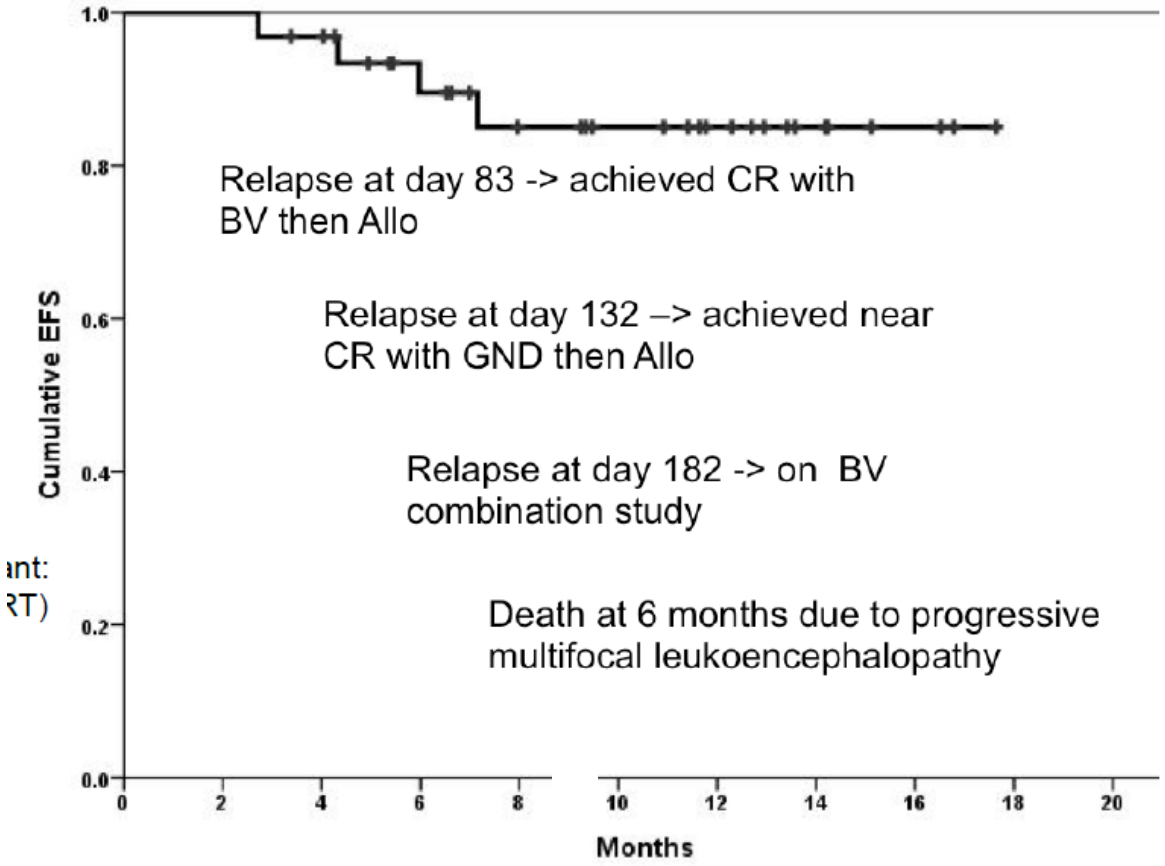
Patients:

Characteristic	N=42
Male	25 (59%)
Median age (range)	31 (13-65)
Initial stage	I: 1 (2%) II: 20 (48%) III: 9 (21%) IV: 12 (29%)
Stage at enrollment	II: 19 (45%) III: 6 (14%) IV: 17 (40%)
Prior radiation	8 (19%)
Relapse > 1 year from initial Rx	7 (17%)
Relapse within 1 year of initial Rx	14 (33%)
Primary refractory	21 (50%)
Extranodal disease	18 (43%)
B symptoms	13 (31%)

Moskowitz A et al. ASH 2013, New Orleans, LA, USA (Abstract 2099)

IISR Study: Phase 2 brentuximab vedotin with augmented ICE in rel/ref Hodgkin lymphoma

- EFS:



Median follow-up from transplant: 10 months

ICE ifosfamide, carboplatin, etoposide

Moskowitz A et al. ASH 2013, New Orleans, LA, USA (Abstract 2099)

Phase 2 trial of brentuximab vedotin as first salvage prior to ASCT in RR HL

Design:

Phase 2, multicenter trial of brentuximab vedotin as first-line salvage therapy prior to ASCT in RR HL

- Primary objective: ORR (CR + PR)
- Secondary objectives: toxicity, stem cell mobilization rate, engraftment, biomarkers

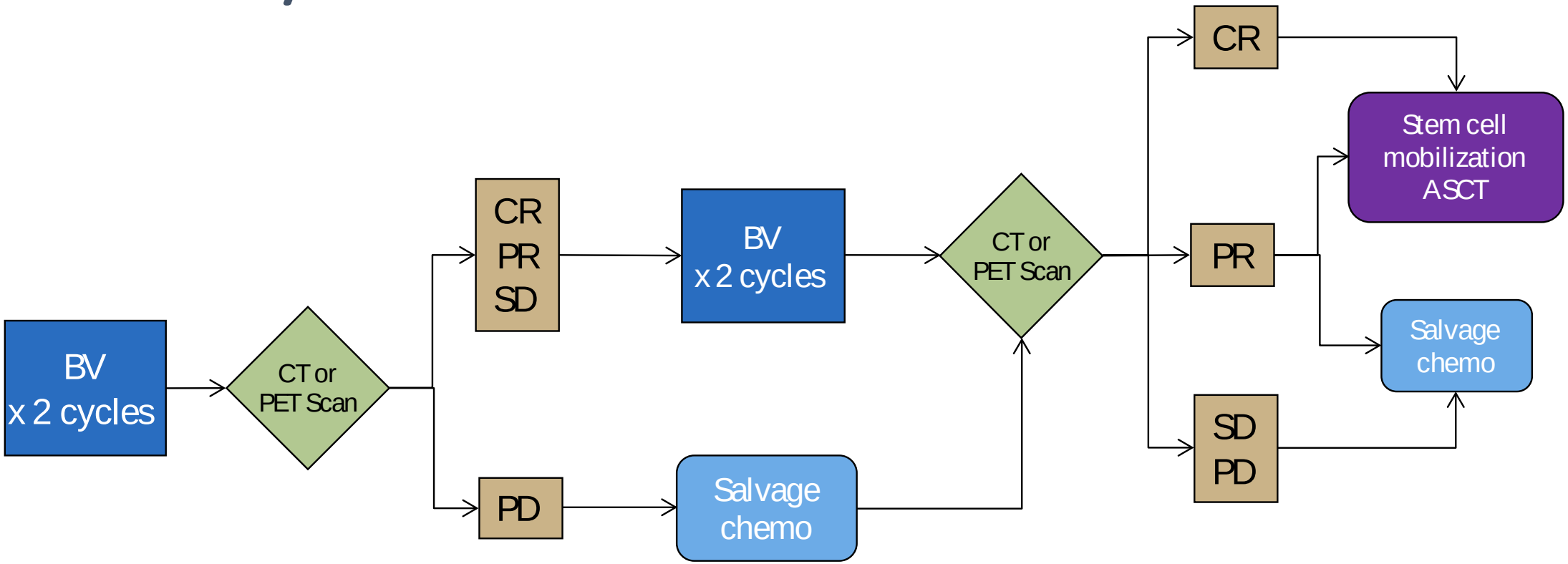
Pts:

37 pts with RR CD30+ HL after induction with ABVD (n=34), ABVD/BEACOPP (n=2), or ABVE-PC (n=1)

•Median age 34 (11–67) yrs, best response to induction: 65% primary refractory, 35% relapsed (within 7 mos), 51%/49% stage I-II/III-IV, 24% prior XRT, 62% B symptoms, 86% bulky disease

Chen 501, Mon Dec 8

Study Schema



Dose and schedule:
Brentuximab vedotin 1.8 mg/kg IV every 3 wks for up to 4 cycles

Protocol amendment:
Brentuximab vedotin dose increased to **2.4 mg/kg** after 2 cycles for pts with PR or SD

Chen 501, Mon Dec 8

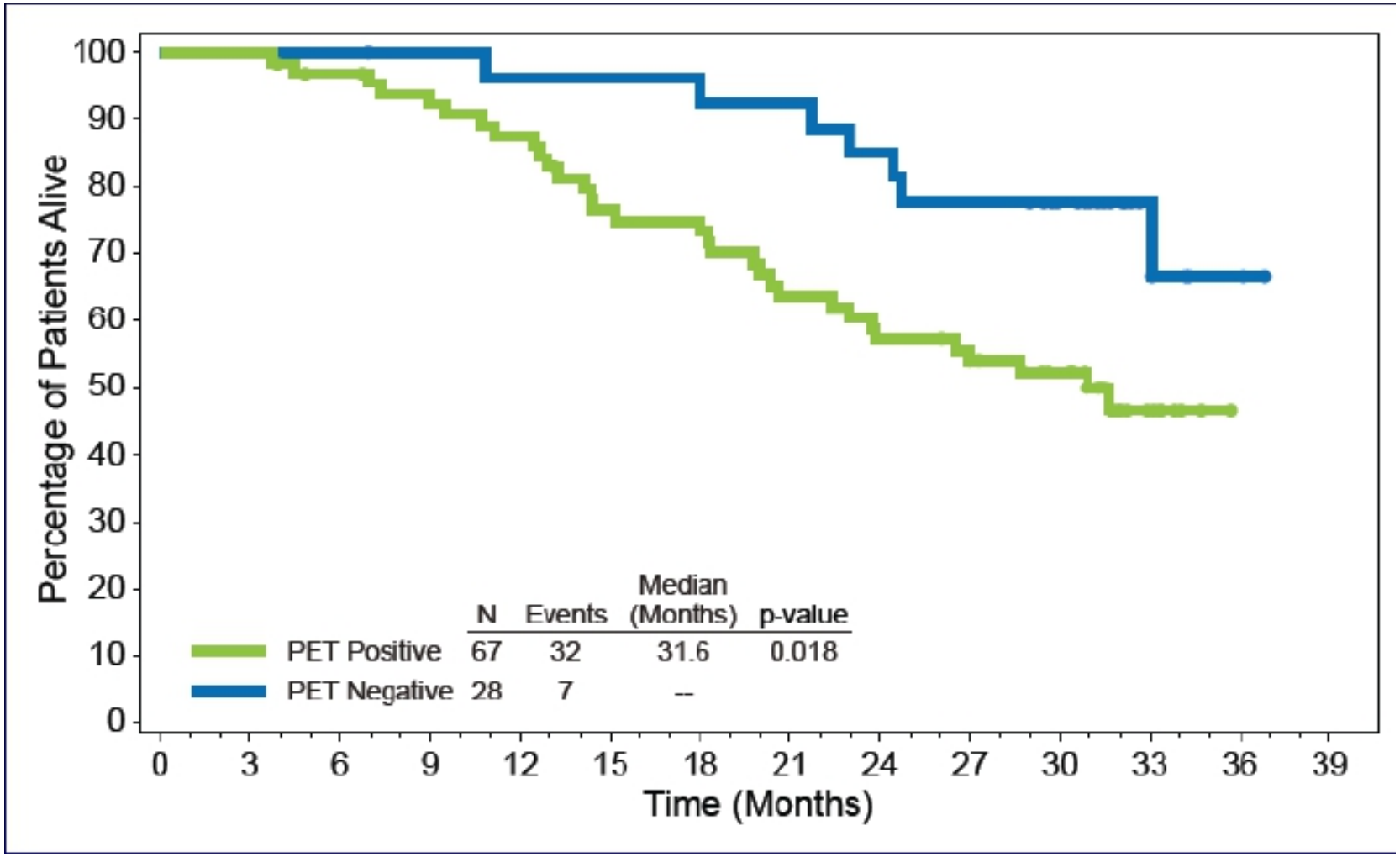
Phase 2 trial of brentuximab vedotin as first salvage prior to ASCT in RR HL: results

Brentuximab vedotin Mobilization and transplant outcomes	
Proceeded to ASCT (n=37)	33 (89%)*
Proceeded to ASCT without further salvage chemotherapy (n=33) CR pts (n=13) PR pts (n=12)	17 (52%) 13 4
Proceeded to ASCT with salvage chemotherapy (n=33)	16 (48%)†
Response status at time of ASCT (n=33) CR PR SD	 24 (73%) 8 (26%) 1 (3%)
Median CD34+ cells collected (range)	5.97×10^6 ($2.64–34.45 \times 10^6$)
Median time for stem cell collection (range)	2 days (1–6)
Median time to neutrophil engraftment (range)	11 days (10–12)
Median time to platelet engraftment (range)	13 days (9–23)

* 1 pt proceeded to allo-SCT and 3 could not be salvaged; †ICE, DICE, IGEV, or GVD

Chen 501, Mon Dec 8

Ongoing Phase II Study of Brentuximab Vedotin
Overall Survival by PET Status at Cycle 4



BV IN COMBINATION AS SALVAGE

Brentuximab Vedotin in Combination with Bendamustine for Patients with Hodgkin Lymphoma who are Relapsed or Refractory after Frontline Therapy

Ann LaCasce[1], R. Gregory Bociek[2], Jeffrey Matous[3], Ahmed Sawas[4], Paolo Caimi[5], Stephen Ansell[6], Miguel Islas-Ohlmayer[7], Eric Cheung[8], Edward Agura[9], Caroline Behler[10], Howland Crosswell[11], Julie Vose[2], Neil Josephson[12], Ranjana Advani[13]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]University of Nebraska Medical Center, Omaha, NE, USA; [3]Colorado Blood Cancer Institute, Denver, CO, USA; [4]Columbia University Medical Center, New York, NY, USA; [5]University Hospitals Case Medical Center, Cleveland, OH, USA; [6]Mayo Clinic, Rochester, MN, USA; [7]The Jewish Hospital-Mercy Health, Cincinnati, OH, USA; [8]The Oncology Institute of Hope & Innovation, Whittier, CA, USA; [9]Charles A. Sammons Cancer Center, Dallas, TX, USA; [10]Pacific Hematology Oncology Associates, San Francisco, CA, USA; [11]St. Francis Hospital, Greenville, SC, USA; [12]Seattle Genetics, Inc., Bothell, WA, USA; [13]Stanford Cancer Center, Stanford, CA, USA

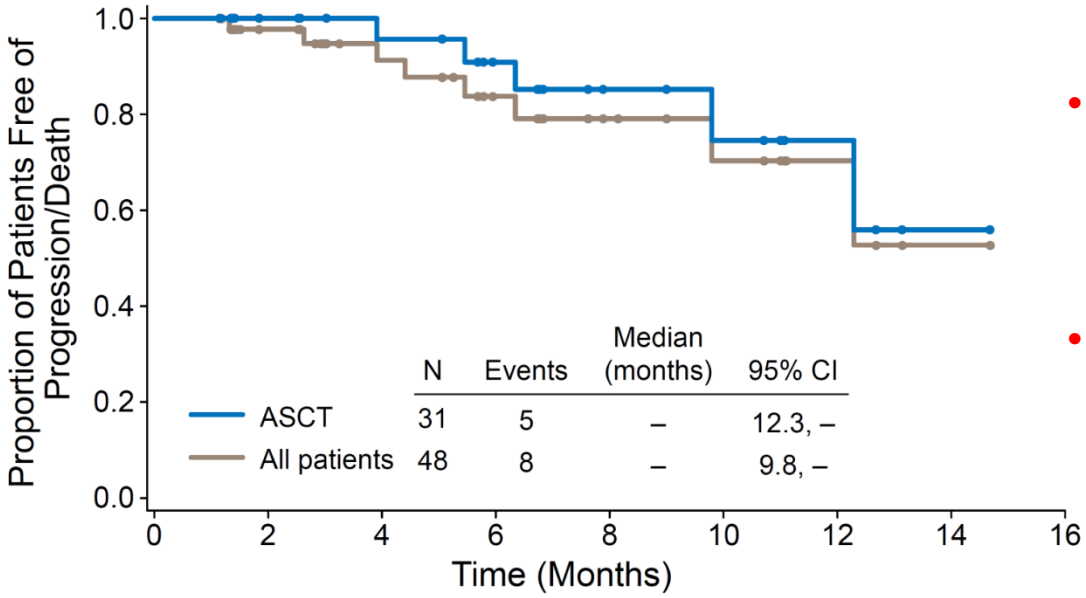
56th ASH Annual Meeting
December 6–9, 2014
San Francisco, CA

Abstract No. 293

SGN35-016: Phase 1/2 trial of brentuximab vedotin combined with bendamustine in RR HL: results

Best clinical response	N=48
ORR, n (%; [95% CI])	46 (96; [86, 100])
CR rate, n (%; [95% CI])*	40 (83; [70, 93])
PR rate, n (%)	6 (13%)

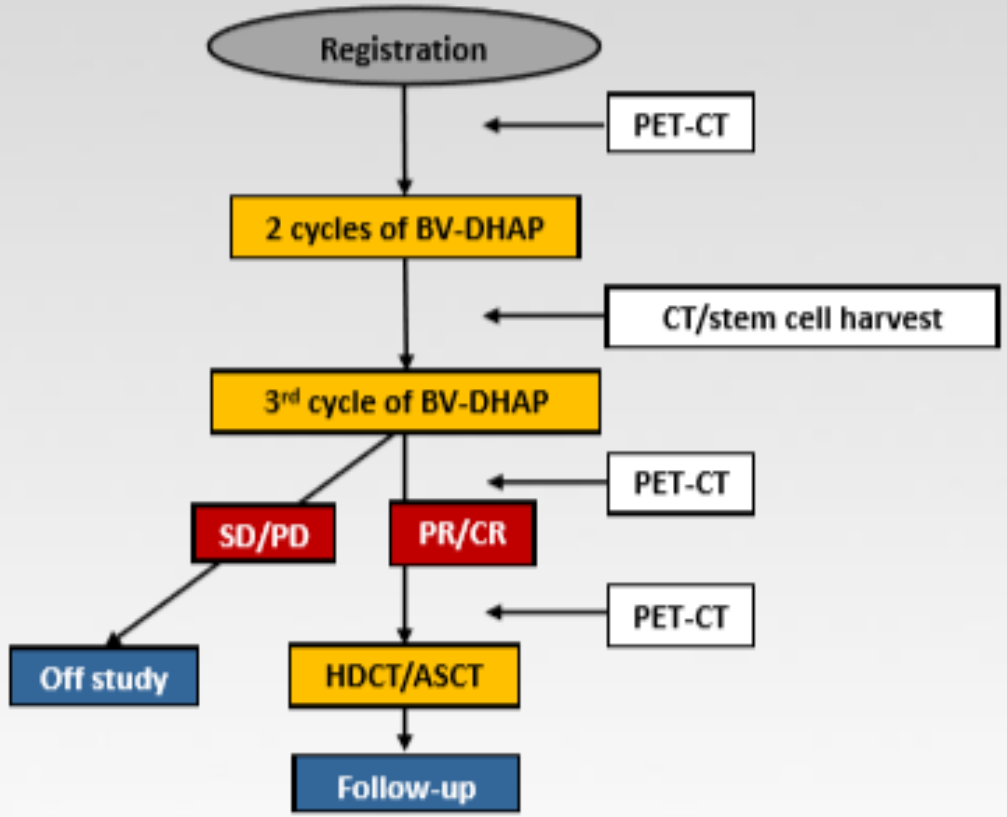
*34/40 CR achieved at cycle 2 restage



- Median PFS: NR
  - 4 progressions and 1 death subsequent to ASCT (8 events overall)
- Median DOR and OS: NR

LaCasce 293, Mon Dec 8

Outline of the European Transplant BRaVE Study



Courtesy of Anton Hagenbeek, MD, PhD.

BV e trapianto nel LH

- BV for patients relapsed after AUTO or refractory to CT
- BV as consolidation treatment after AUTO
- BV as treatment of relapse after ALLO

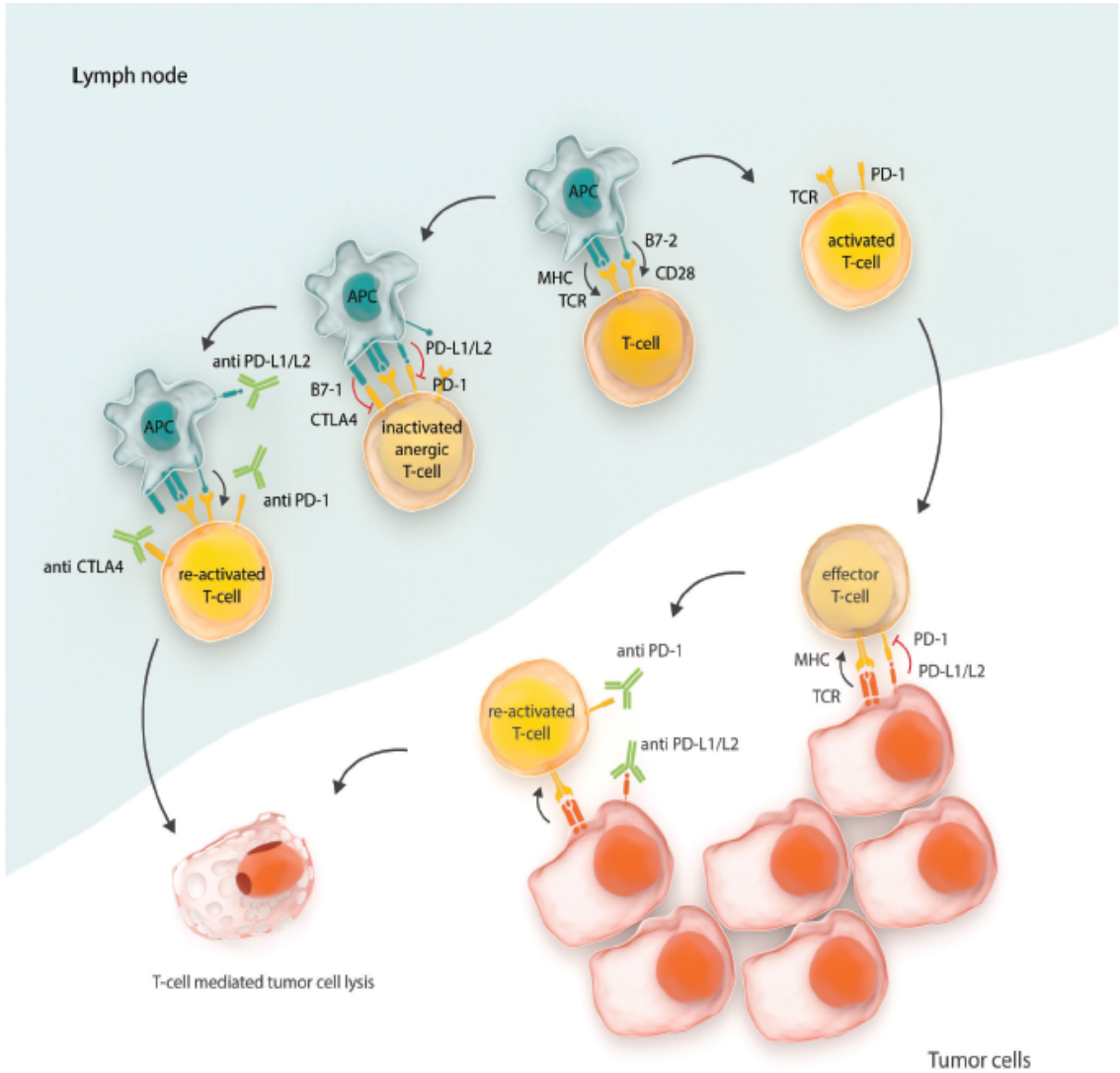


Figure 1. Inhibition of the immune checkpoints PD-1 and CTLA4 to restore T-cell activation. Antigen-presenting cells (APC) present an antigen (e.g., tumor-associated antigen – TAA) to naïve T cells via interaction of T-cell receptor (TCR) and major histocompatibility 1 (MHC-I) molecule, followed by a co-stimulatory signal by CD28/B7-2 interaction, which leads to T-cell activation. The activation is followed by expression of inhibitory checkpoint molecules such as PD-1 and CTLA-4 on T cells. In an immunosuppressive lymph node microenvironment, APC express corresponding inhibitory ligands, bringing T cells to an inactivated or anergic state (via the CTLA4/B7-1 and/or PD-1/PD-L1/L2 interaction). If co-stimulatory signals overpower the co-inhibitory ones, activated effector T cells are released into the blood stream, where they encounter TAA presented on MHC-I molecules on tumor cells. Co-expression of PD-L1 on tumor cells induces inactivation of tumor-specific effector T cells, disabling adequate T-cell-mediated immune responses. Treatment with immune checkpoint inhibitors (ICI) affects both the priming phase of T-cell activation in lymph nodes and the effector phase in the tumor microenvironment (TME), by blocking the inhibitory checkpoint interaction between activated T cells and APC and/or tumor cells, restoring T-cell activity and leading to T-cell-mediated tumor cell lysis. TCR: T-cell receptor; MHC-I: major histocompatibility complex; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; PD-L2: programmed death-ligand 2; CTLA-4: cytotoxic T-lymphocyte-associated protein 4.

Table 1. Early phase clinical trial data for ICI according to lymphoma type.

Lymphoma	Agent	Ref.	Phase	Disease setting	No of Pts	Treatment plan	Outcome	Safety	Most common AE
HL	ipilimumab	(30)	I	r/r HL after allogeneic SCT	14	dose esc. trial: 0.1 mg/kg - 0.33 mg/kg - 0.66 mg/kg - 1.0 mg/kg - 3.0 mg/kg	ORR: 14% CR: 14%	no Gr 3/4 GvHD 1 pt Gr 4 pneumonitis no TRD	fatigue chills/ fever abdominal pain
	ipilimumab + BV	(31)	I/II	r/r HL	23	dose esc. trial: IPI 1 mg/kg - 3 mg/kg Q21d x 4 doses BV: 1.8 mg/kg Q21d x 16 doses	ORR: 72% CR: 50% median PPS: 1.02y	100% any AE 1 pt Gr 4 AE (thrombocytopenia) no TRD	neuropathy nausea/ vomiting fatigue pruritus/rash
	nivolumab	(18, 32)	I	r/r HL	23	3 mg/kg NIVO at week 1 and 4, Q2w thereafter until 2y	ORR: 87% CR: 22% median OS and PFS not reached after 101m FU 1.5y OS 83%	1 pt Gr 3 pneumonitis 1 pt Gr 3 colitis	rash/pruritus hypothyroidism diarrhea
	nivolumab	(33)	II	r/r HL	80[1]	3 mg/kg Q2w	ORR: 66% CR: 8,8% PR: 57,5% ORR (no BV response)*: 72%	90% any AE 1 TRD 25% Gr 3/4 AE	hypothyroidism/ thyreoiditis rash hypersensitivity
	pembrolizumab	(36)	Ib	r/r HL (failing BV)	31	10 mg/kg Q2w/2y	ORR: 65% CR: 16% PR: 48% 24w PPS 69%	no Gr 4 AE 5 pt Gr 3 AE	hypothyroidism diarrhea nausea/vomiting pneumonitis
	pembrolizumab	(37)	II	r/r HL	90[2]	200 mg Q3w	cohort 1: ORR 73%, CR 27%, PR 47% cohort 2: ORR 83%, CR 30%, PR 53% cohort 3: ORR 73%, CR 30%, PR 43%	4% Gr 4 AE no TRD 7 pt Gr AE	pyrexia diarrhea
DLBCL + PMBCL	ipilimumab	(46)	I	r/r B-NHL	3 DLBCL	dose level 1: 3 mg/kg once + 1 mg/kg Q1m x3 dose level 2: 3 mg/kg Q1m x4	1 CR DOR > 31 months	5 pt Gr 3 AE (diarrhea) no Gr 4 or TRD	fatigue diarrhea abdominal pain thrombocytopenia
	nivolumab	(47)	I	r/r lymphoid malignancies	11 DLBCL + 2 PMBCL	dose level 1: 1 mg/kg at w 1 and 4, thereafter Q2w/2y dose level 2: 3 mg/kg at w 1 and 4, thereafter Q2w/2y	DLBCL: CR 18%, PR 18%, SD 27%, Median PFS 7w PMBCL: SD 100%	all AE 71%[3] Gr 3-5 AE: pneumonitis, ARDS, dermatitis, diplopia, enteritis, eosinophilia, mucosal inflammation, pyrexia, vomiting	fatigue pneumonitis pruritus/rash
	pembrolizumab	(48)	Ib	PMBCL	16	10 mg/kg Q2W or 200 mg Q3W/2y	ORR: 37,5% CR: 6,25% PR: 31,25%	62% TR AE 1 pt Gr 3 AE (neutropenia) no Gr 4 AE, no TRD	decreased apetite, nausea fatigue diarrhea hypothyroidism
FL	nivolumab	(47)	I	r/r lymphoid malignancies	10 FL	dose level 1: 1 mg/kg Q2w/2y dose level 2: 3 mg/kg Q2w/2y	ORR: 40% CR: 10% PR: 30% Median PPS not reached	any AE 72% of pt[3] Gr 3-5 AE: pneumonitis, ARDS, dermatitis, diplopia, enteritis, eosinophilia, mucosal inflammation, pyrexia, vomiting	fatigue pneumonitis pruritus/rash
CLL	pembrolizumab	(67)	II	r/r CLL (including RS)	16, 7 evaluable	200 mg Q3w	ORR: 57% CR: 14% PR: 14% 2 responses before PD	2 pt Gr 3 AE no Gr 4, no TRD	dyspnea anemia

Nivolumab for Relapsed/Refractory Classic Hodgkin Lymphoma After Failure of Autologous Hematopoietic Cell Transplantation: Extended Follow-Up of the Multicohort Single-Arm Phase II CheckMate 205 Trial

Philippe Armand, Andreas Engert, Anas Younes, Michelle Fanale, Armando Santoro, Pier Luigi Zinzani, John M. Timmerman, Graham P. Collins, Radhakrishnan Ramchandren, Jonathon B. Cohen, Jan Paul De Boer, John Kuruvilla, Kerry J. Savage, Marek Trneny, Margaret A. Shipp, Kazunobu Kato, Anne Sumbul, Benedetto Farsaci, and Stephen M. Ansell

ABSTRACT

Purpose

Genetic alterations causing overexpression of programmed death-1 ligands are near universal in classic Hodgkin lymphoma (cHL). Nivolumab, a programmed death-1 checkpoint inhibitor, demonstrated efficacy in relapsed/refractory cHL after autologous hematopoietic cell transplantation (auto-HCT) in initial analyses of one of three cohorts from the CheckMate 205 study of nivolumab for cHL. Here, we assess safety and efficacy after extended follow-up of all three cohorts.

Methods

This multicenter, single-arm, phase II study enrolled patients with relapsed/refractory cHL after auto-HCT treatment failure into cohorts by treatment history: brentuximab vedotin (BV)–naïve (cohort A), BV received after auto-HCT (cohort B), and BV received before and/or after auto-HCT (cohort C). All patients received nivolumab 3 mg/kg every 2 weeks until disease progression/unacceptable toxicity. The primary end point was objective response rate per independent radiology review committee.

Results

Overall, 243 patients were treated; 63 in cohort A, 80 in cohort B, and 100 in cohort C. After a median follow-up of 18 months, 40% continued to receive treatment. The objective response rate was 69% (95% CI, 63% to 75%) overall and 65% to 73% in each cohort. Overall, the median duration of response was 16.6 months (95% CI, 13.2 to 20.3 months), and median progression-free survival was 14.7 months (95% CI, 11.3 to 18.5 months). Of 70 patients treated past conventional disease progression, 61% of those evaluable had stable or further reduced target tumor burdens. The most common grade 3 to 4 drug-related adverse events were lipase increases (5%), neutropenia (3%), and ALT increases (3%). Twenty-nine deaths occurred; none were considered treatment related.

Conclusion

With extended follow-up, responses to nivolumab were frequent and durable. Nivolumab seems to be associated with a favorable safety profile and long-term benefits across a broad spectrum of patients with relapsed/refractory cHL.

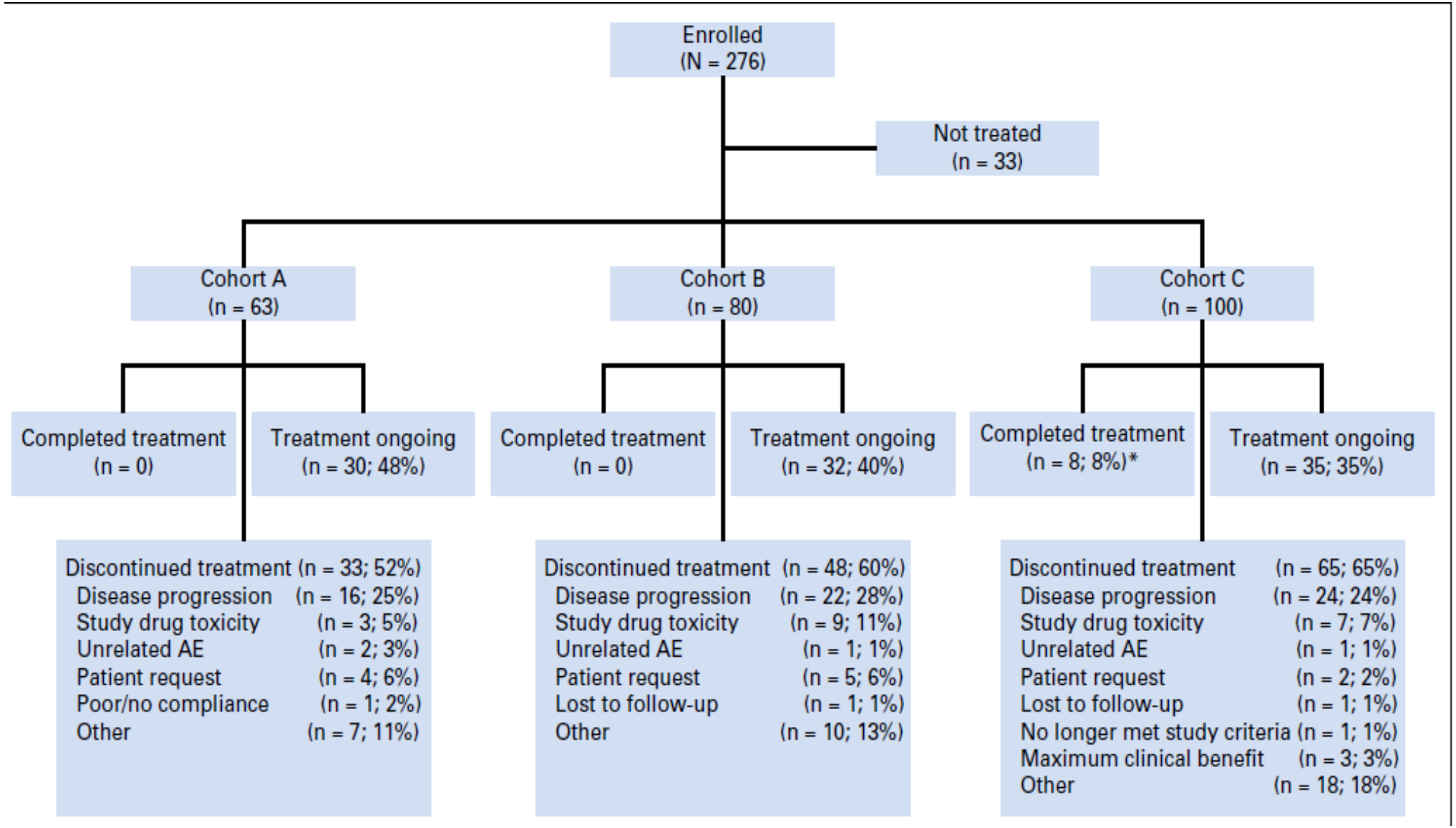

Enrolled
(N = 276)
Not treated
(n = 33)
Cohort A
(n = 63)
Cohort B
(n = 80)
Cohort C
(n = 100)
Completed treatment
(n = 0)
Treatment ongoing
(n = 30; 48%)
Completed treatment
(n = 0)
Treatment ongoing
(n = 32; 40%)
Completed treatment
(n = 8; 8%)*
Treatment ongoing
(n = 35; 35%)
Discontinued treatment (n = 33; 52%)
Disease progression (n = 16; 25%)
Study drug toxicity (n = 3; 5%)
Unrelated AE (n = 2; 3%)
Patient request (n = 4; 6%)
Poor/no compliance (n = 1; 2%)
Other (n = 7; 11%)
Discontinued treatment (n = 48; 60%)
Disease progression (n = 22; 28%)
Study drug toxicity (n = 9; 11%)
Unrelated AE (n = 1; 1%)
Patient request (n = 5; 6%)
Lost to follow-up (n = 1; 1%)
Other (n = 10; 13%)
Discontinued treatment (n = 65; 65%)
Disease progression (n = 24; 24%)
Study drug toxicity (n = 7; 7%)
Unrelated AE (n = 1; 1%)
Patient request (n = 2; 2%)
Lost to follow-up (n = 1; 1%)
No longer met study criteria (n = 1; 1%)
Maximum clinical benefit (n = 3; 3%)
Other (n = 18; 18%)

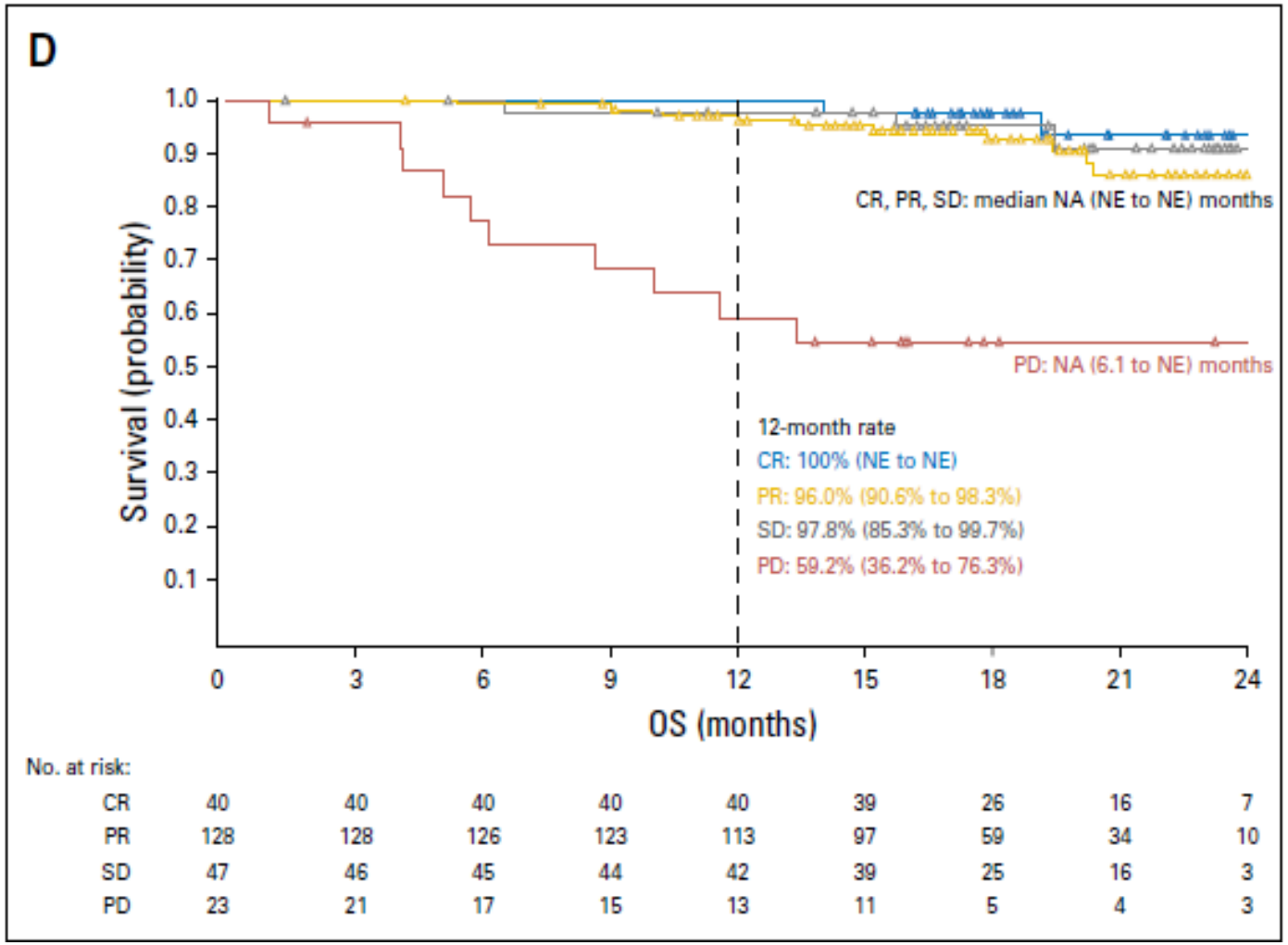
Table 2. Objective and Best Overall Response per IRC

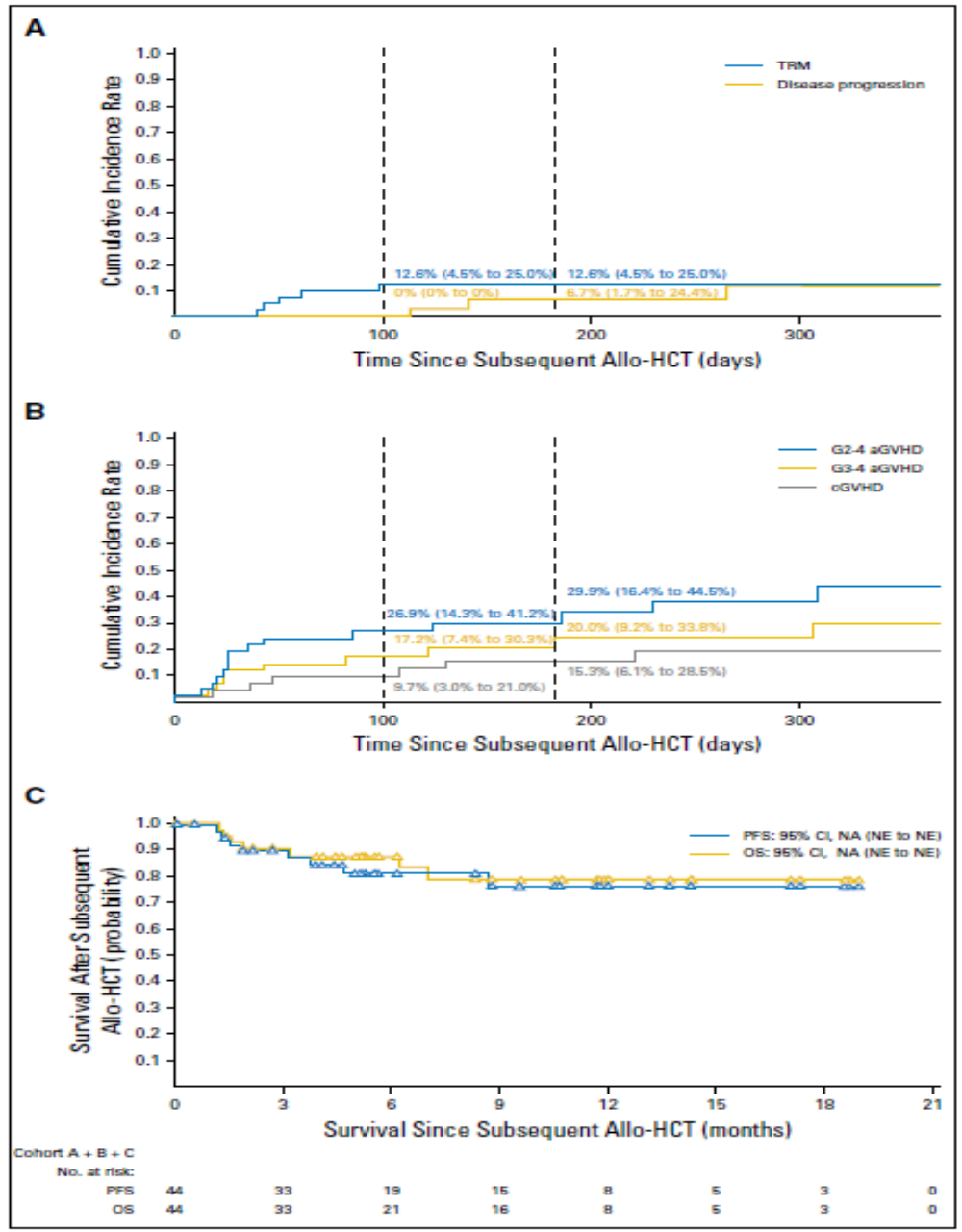
Response	Protocol-Specified Analysis by Cohort: BV Naïve: Cohort A (n = 63)	BV After Auto-HCT: Cohort B (n = 80)	BV Before and/or After Auto-HCT: Cohort C (n = 100)	All patients (N = 243)
ORR, % (95% CI)	65 (52-77)	68 (56-78)	73 (63-81)	69 (63-75)
Best overall response				
Complete remission	18 (29)	10 (13)	12 (12)	40 (16)
Partial remission	23 (37)	44 (55)	61 (61)	128 (53)
Stable disease	15 (24)	17 (21)	15 (15)	47 (19)
Progressive disease	7 (11)	6 (8)	10 (10)	23 (9)
Unable to determine	0	3 (4)	2 (2)	5 (2)

	Exploratory Analyses by Refractory Status (all patients): To First Line (n = 142)	To Last Line (n = 114)	To BV After Auto-HCT (n = 75)
ORR	73	68	68
Best overall response			
Complete remission	25 (18)	15 (13)	5 (7)
Partial remission	78 (55)	62 (54)	46 (61)
Stable disease	25 (18)	22 (19)	13 (17)
Progressive disease	12 (8)	12 (11)	8 (11)
Unable to determine	2 (1)	3 (3)	3 (4)

NOTE. Data presented as No. (%) unless otherwise indicated. Best overall response was unable to be determined for five patients, all because of missing or unknown postbaseline tumor assessments.

Abbreviations: auto-HCT, autologous hematopoietic cell transplantation; BV, brentuximab vedotin; IRC, independent radiology review committee; ORR, objective response rate.


D
Survival (probability)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
CR, PR, SD: median NA (NE to NE) months
PD: NA (6.1 to NE) months
12-month rate
CR: 100% (NE to NE)
PR: 96.0% (90.6% to 98.3%)
SD: 97.8% (85.3% to 99.7%)
PD: 59.2% (36.2% to 76.3%)
0
3
6
9
12
15
18
21
24
OS (months)
No. at risk:
CR 40 40 40 40 40 39 26 16 7
PR 128 128 126 123 113 97 59 34 10
SD 47 46 45 44 42 39 25 16 3
PD 23 21 17 15 13 11 5 4 3


A
Cumulative Incidence Rate
TRM
Disease progression
12.6% (4.5% to 25.0%)
12.6% (4.5% to 25.0%)
0% (0% to 0%)
6.7% (1.7% to 24.4%)
Time Since Subsequent Allo-HCT (days)
B
Cumulative Incidence Rate
G2-4 aGVHD
G3-4 aGVHD
cGVHD
29.9% (16.4% to 44.5%)
26.9% (14.3% to 41.2%)
20.0% (9.2% to 33.8%)
17.2% (7.4% to 30.3%)
15.3% (6.1% to 28.5%)
9.7% (3.0% to 21.0%)
Time Since Subsequent Allo-HCT (days)
C
Survival After Subsequent Allo-HCT (probability)
PFS: 95% CI, NA (NE to NE)
OS: 95% CI, NA (NE to NE)
Survival Since Subsequent Allo-HCT (months)
Cohort A + B + C
No. at risk:
PFS 44 33 19 15 8 5 3 0
OS 44 33 21 16 8 5 3 0

NIVOLUMAB IN RELAPSED/REFRACTORY CLASSIC HODGKIN LYMPHOMA: EXPERIENCE WITH TEN PATIENTS

Reyad Dada1,2, Yazeed Zabani3

Objectives: One of the newly discovered mechanisms to escape the immune response in classic Hodgkin lymphoma (cHL) is to induce immune tolerance through interaction of program cell death 1 (PD-1) on activated T cells and PD ligand-1 (PD-L1) on tumor cells. Tissue of patients with cHL was recently found to overexpress PD-L1. Nivolumab is a novel checkpoint inhibitor designed to block PD-1 and inhibits interaction between PD-1 and PD-L1. Unlike many available antibodies and chemotherapies, nivolumab itself is not cytotoxic but rather inhibits the tolerance of tumor cells through activation of the immune system.

Patients and methods: We report on ten patients with relapsed/refractory cHL who were treated between 05/2016 and 03/2018 with single agent nivolumab in a tertiary care hospital. Follow-up was performed after 4 cycles with positron emission tomography (PET). Patients' files were retrospectively analyzed.

Results: Mean age was 26.2 year (range 15–40). Prior to nivolumab 3/10 and 5/10 patients failed ASCT and brentuximab vedotin respectively. Mean follow-up time was 12.3 months (range 5–32). Average of prior lines was 6.3. After 4 cycles of nivolumab response rate was 80% with complete metabolic (CR) and partial remission rates of 70% and 10% respectively. In one case PET showed stable disease and another patient experienced progressive disease. Three deaths occurred after 32, 9 and 5 months of nivolumab's initiation.

One patients experienced pneumonitis grade 2 and was manageable by oral steroids. Another patient had an asymptomatic TSH elevation. Two patients had grade 2 neutropenia. No serious adverse events (grade ≥3) were observed. All patients experienced a remarkable improvement of quality of life. On treatment start, two patients had performance status ECOG 3 and 4 which were attributed to refractory Hodgkin lymphoma. They recovered dramatically each to ECOG 2 within 7 days and 10 days after nivolumab start respectively.

Conclusion: The CR rate seen in our cohort supports the high sensitivity of relapsed/refractory cHL to checkpoint inhibition. Nivolumab induces impressive clinical and radiological responses with excellent tolerance. The drug enriches our treatments armamentarium in treating cHL. Further controlled studies are needed to determine the effectiveness on a large patients' cohort.

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]

[1]City of Hope National Medical Center, Duarte, CA; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Division of Hematology and Oncology, Washington University School of Medicine, St. Louis, MO; [4]University of Nebraska Medical Center, Omaha, NE; [5]Karmanos Cancer Institute, Detroit, MI; [6]Hackensack University Medical Center, Hackensack, NJ; [7]Dana-Farber Cancer Institute, Boston, MA; [8]Mayo Clinic, Rochester, MN; [9]Seattle Genetics, Inc, Bothell, WA; [10]Bristol-Myers Squibb, Princeton, NJ; and [11]Stanford University Medical Center, Palo Alto, CA

KEY POINTS

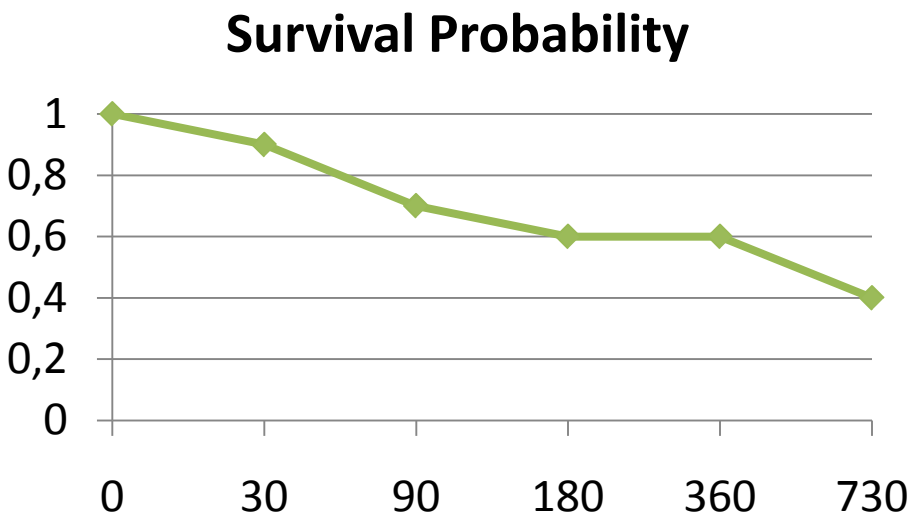
- **BV and Nivo were well-tolerated in patients with R/R HL, with less than 10% of patients treated with systemic steroids for immune-related AEs.**
- **The complete response rate was 61% (82% objective response rate), and patients were able to undergo stem cell transplant without adverse impact.**

In this phase 1/2 study, brentuximab vedotin (BV) and nivolumab (Nivo) administered in combination were evaluated as initial salvage therapy in patients with relapsed or refractory (R/R) classical Hodgkin lymphoma (HL). Patients received up to 4 cycles of combination treatment, with BV administered on day 1 and Nivo on day 8 of the first cycle. For cycles 2 to 4, BV and Nivo were both administered on day 1. After study treatment, responses were evaluated by investigators per the 2014 Lugano classification, and patients could proceed to autologous stem cell transplantation (ASCT). Sixty-two patients were enrolled; the complete response rate among all treated patients (n = 61) was 61%, with an objective response rate of 82%. Before ASCT, adverse events (AEs) occurred in 98% of patients, mostly grades 1 and 2. Infusion-related reactions (IRRs) occurred in 44% of patients overall, with 41% of patients experiencing an IRR during at least 1 infusion of BV. Five patients (8%) were treated with systemic steroids for immune-related AEs. A reduction of peripheral T-cell subsets including regulatory T cells was observed after the first dose of BV, and reduced serum levels of thymus- and activation-regulated chemokine concurrent with an increase in proinflammatory cytokines and chemokines were seen after the first BV plus Nivo infusions. The combination of BV plus Nivo was an active and well-tolerated first salvage regimen, potentially providing patients with R/R HL an alternative to traditional chemotherapy. This trial was registered at www.clinicaltrials.gov as #NCT02572167. (*Blood*. 2018;131(11):1183-1194)

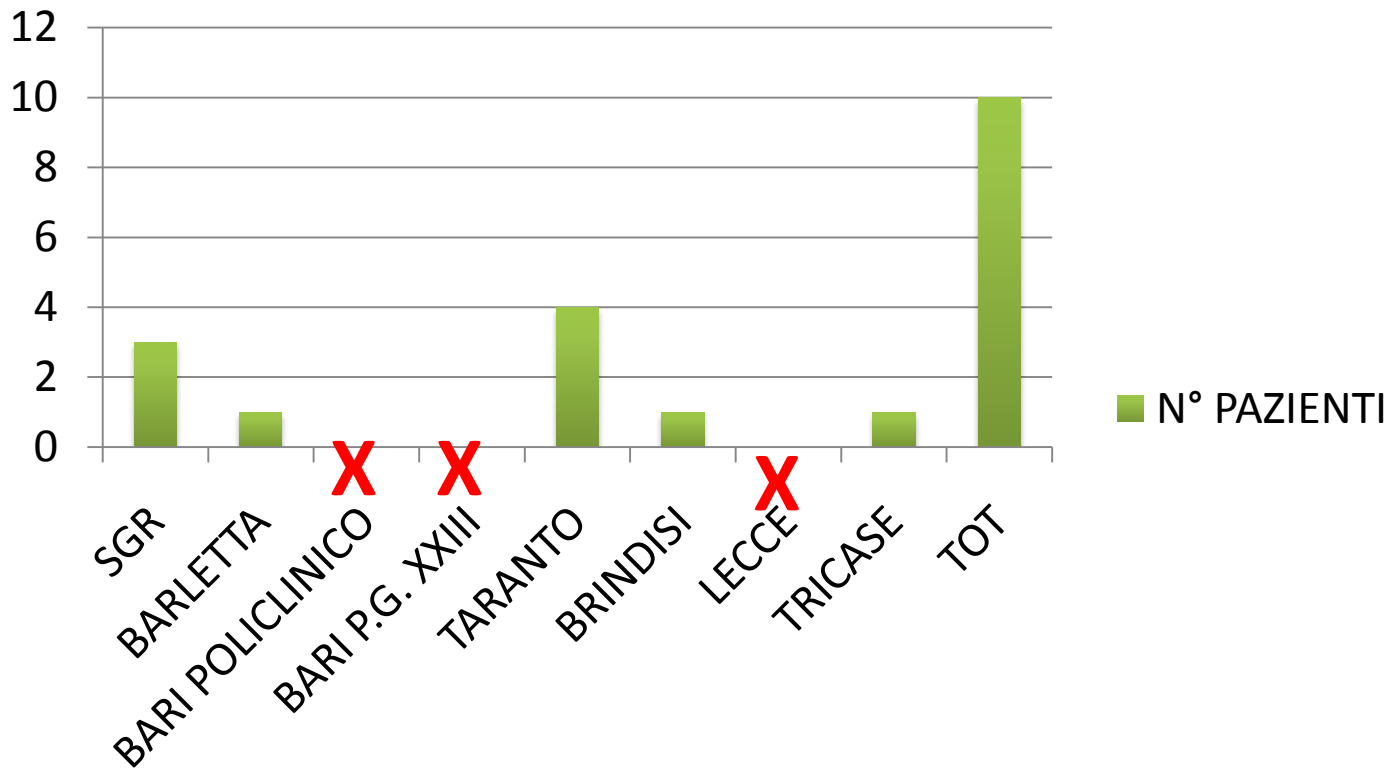
NIVOLUMAB
OUTCOME AND SAFETY

	%	Mediana mo(range)
Responce		
RC	1	
RP	2	
SD	2	
PD	3	
NA	2	
ORR	37,5%	
CR	12,5%	
F-UP		7,8 (1-27,7)

Toxicity G3-4	10%
Exitus	10%



NIVOLUMAB
REP'S REAL LIFE EXPERIENCE



- Ma «real life»: solo raccolta dati ,studi retrospettivi o anche proposte di studi prospettici multicentrici in grado poi di cambiare la vita reale ??

BV and relapse after ALLO

	Gopal 2012	Carlo-Stella 2015
N	25	16
ORR	75%	68%
CR	34%	31%
PR	41%	37%
DOR all responding	6.7M	5M
DOR CR	20 M	11M
OS	73%@3y	61%@2y
PFS	58%@3y	20%@2y

Investigator Studies Program Review Committee (MISP-RC) IIS Clinical Concept Form

All fields are required, an incomplete form will be returned to the submitter. If a field is not completed, please note the reason.

Proposed Study Title	
Study Title:	Pembrolizumab and BeEAM high dose chemotherapy before autologous stem cell transplant (ASCT) for high risk Hodgkin Lymphoma (PET+ after salvage): Safety and Efficacy
Request Date:	16 February 2018
Principal Investigator Contact Information	
Name:	VINCENZO PAVONE
Title:	DIRECTOR OF HEMATOLOGY – CARD.G.PANICO HOSPITAL
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Address 2	
City, ST, Zip	TRICASE - LECCE-73039-ITALY
Phone/Fax:	+39 0833773111 / +39 0833773461
E-mail:	enzopavone@libero.it

TREATMENT PLAN

Pembrolizumab :
200mg/day every 3 weeks for 3 cycles before

Pembrolizumab :
200mg i.v. on day on day -8

TREATMENT PLAN

Be EAM:

Bendamustine i.v. once daily -7 and -6 at 200mg/mq/day
Cytarabine (ARA-C) 200 mg/mq i.v. every 12 h from day -5 to day -2
Etoposide 100mg/mq i.v. every 12 h from day -5 to day -2
Melphalan 140mg/mq/day i.v. once on day -1,

Followed by reinfusion of autologous stem cells at day 0

Ages

- 18 to 65 years OR
- 16 to 65 years

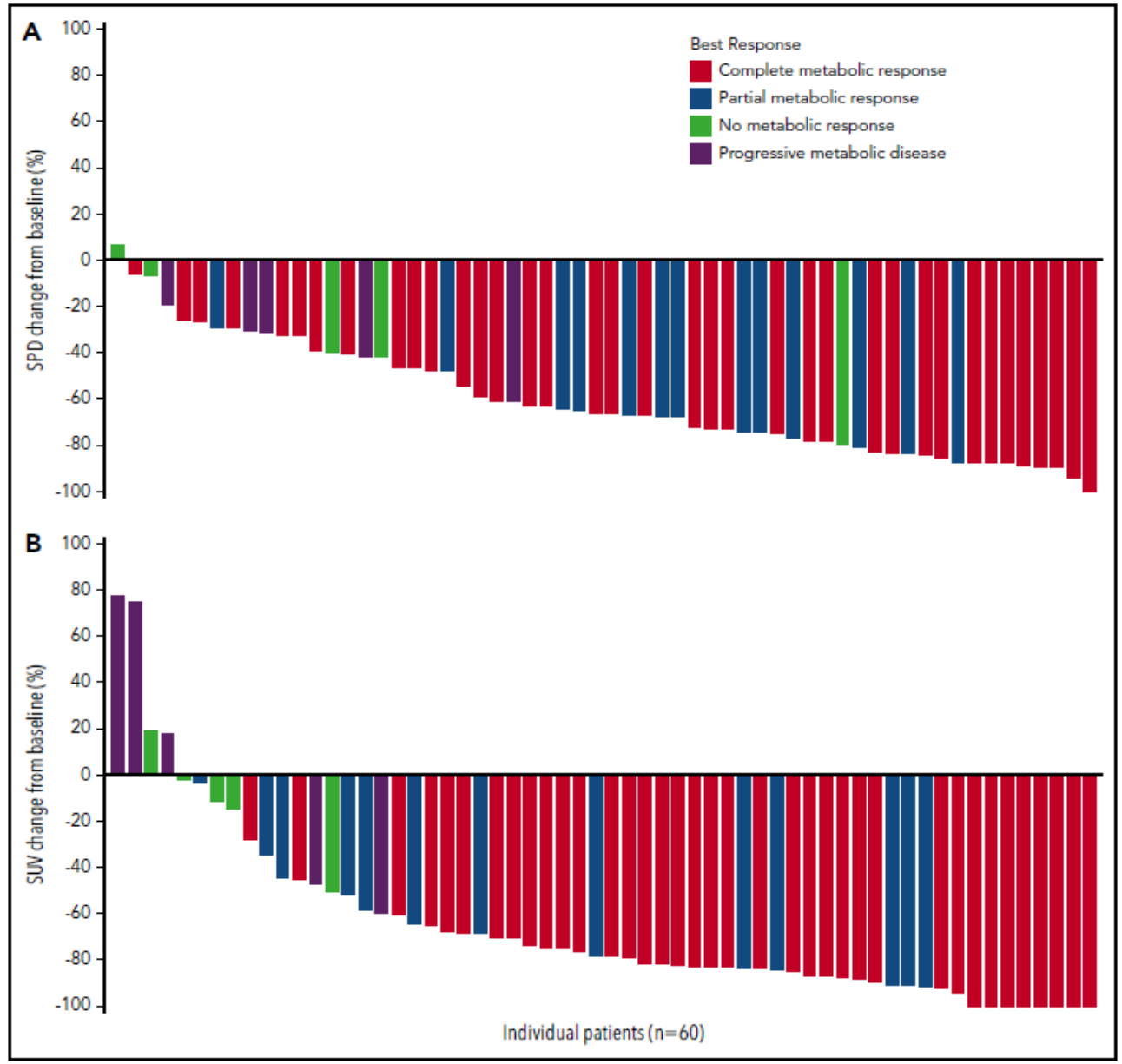
The emerging role of immune checkpoint inhibition in malignant lymphoma

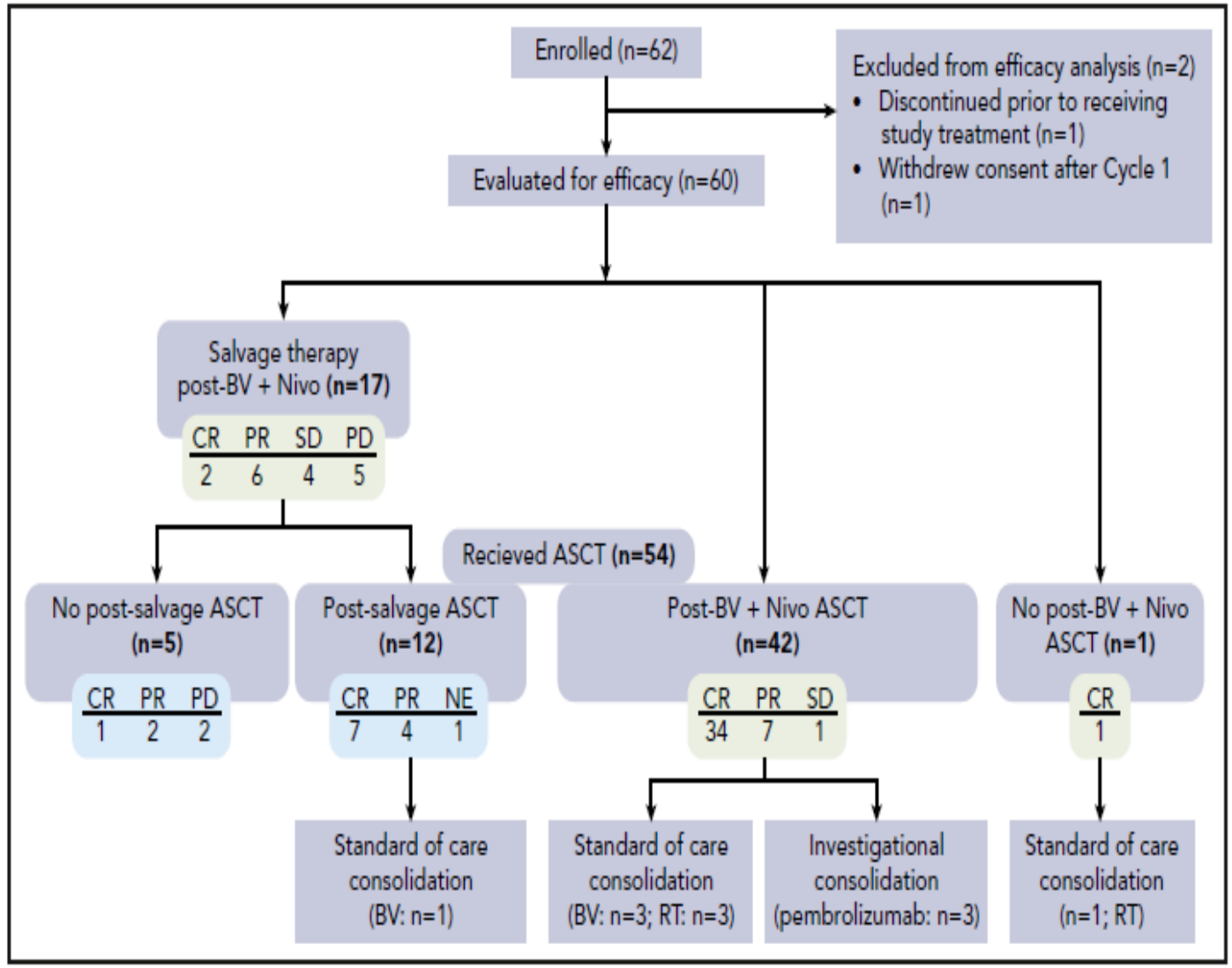
Ida Hude,[1] Stephanie Sasse,[2] Andreas Engert[2] and Paul J. Bröckelmann[2]

[1]Department of Internal Medicine, Division of Hematology, University Hospital Center Zagreb, Croatia and [2]Department I of Internal Medicine and German Hodgkin Study Group (GHSG), University Hospital of Cologne, Germany

ABSTRACT

To evade elimination by the host immune system, tumor cells commonly exploit physiological immune checkpoint pathways, restraining efficient anti-tumor immune cell function. Growing understanding of the complex dialog between tumor cells and their microenvironment contributed to the development of immune checkpoint inhibitors. This innovative strategy has demonstrated paradigm-shifting clinical activity in various malignancies. Antibodies targeting programmed death 1 and cytotoxic T-lymphocyte-associated protein-4 are also being investigated in lymphoid malignancies with varying levels of activity and a favorable toxicity profile. To date, evaluated only in the setting of relapsed or refractory disease, anti-programmed death 1 antibodies such as nivolumab and pembrolizumab show encouraging response rates particularly in classical Hodgkin lymphoma but also in follicular lymphoma and diffuse-large B-cell lymphoma. As the first immune checkpoint inhibitor in lymphoma, nivolumab was approved for the treatment of relapsed or refractory classical Hodgkin lymphoma by the Food and Drug Administration in May 2016. In this review, we assess the role of the pathways involved and potential rationale of checkpoint inhibition in various lymphoid malignancies. In addition to data from current clinical trials, immune-related side effects, potential limitations and future perspectives including promising combinatory approaches with immune checkpoint inhibition are discussed.


A
B
Best Response
Complete metabolic response
Partial metabolic response
No metabolic response
Progressive metabolic disease
SPD change from baseline (%)
SUV change from baseline (%)
100
80
60
40
20
0
-20
-40
-60
-80
-100
Individual patients (n=60)


Enrolled (n=62)
Excluded from efficacy analysis (n=2)
• Discontinued prior to receiving study treatment (n=1)
• Withdrew consent after Cycle 1 (n=1)
Evaluated for efficacy (n=60)
Salvage therapy post-BV + Nivo (n=17)
CR PR SD PD
2 6 4 5
Recieved ASCT (n=54)
No post-salvage ASCT (n=5)
CR PR PD
1 2 2
Post-salvage ASCT (n=12)
CR PR NE
7 4 1
Post-BV + Nivo ASCT (n=42)
CR PR SD
34 7 1
No post-BV + Nivo ASCT (n=1)
CR
1
Standard of care consolidation (BV: n=1)
Standard of care consolidation (BV: n=3; RT: n=3)
Investigational consolidation (pembrolizumab: n=3)
Standard of care consolidation (n=1; RT)