BV e trapianto nel linfoma di Hodgkin (LH)

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Udine, 22/1/2016

Indicazioni BV

1. In seguito a trapianto autologo di cellule staminali (ASCT)

2. In seguito ad almeno due precedenti regimi terapeutici, quando l'ASCT o la polichemioterapia non è un'opzione terapeutica.

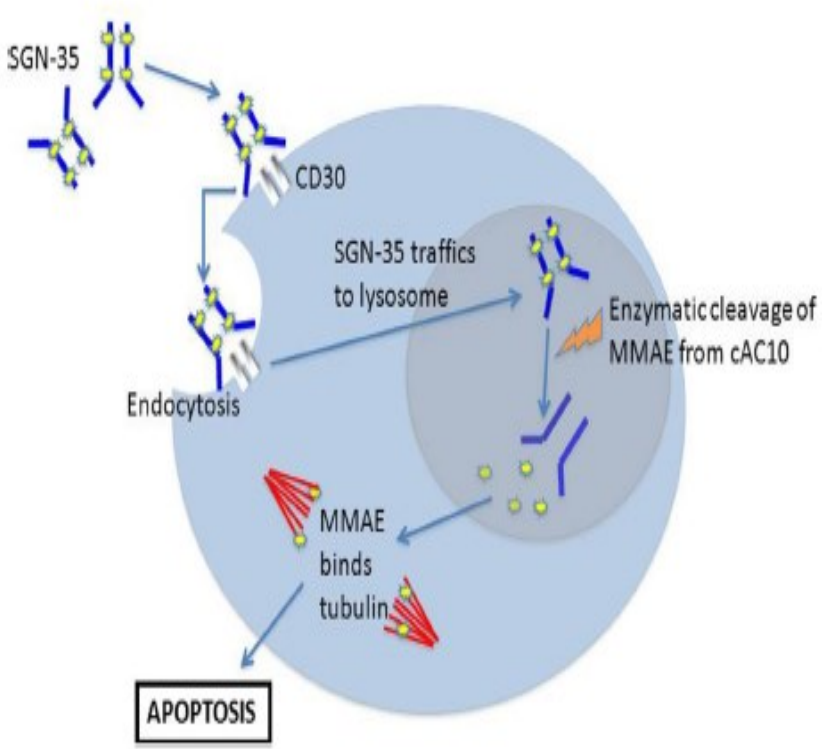
BV e trapianto nel LH

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

Brentuximab Vedotin

- SGN-35 is an ADC containing the antimitotic drug monomethylauristatin E (MMAE) linked to the anti-CD30 monoclonal antibody, cAC10
- Limited expression on normal tissues
  - Activated T cells and B cells; T cells from aGVHD
  - Some activated monocytes and eosinophils
- High level expression in tumors
  - **HL**, ALCL
  - Embryonal carcinoma

Mechanism of Action



- Efficient *intracellular release* of MMAE, with intracellular concentrations of MMAE in the range of 500 nmol/L
  - MMAE has a half-life of retention of 15 to 20 h
- Co-cultures of CD30+ and CD30− cell lines indicate a *bystander activity*
  - MMAE released from CD30+ cells is able to kill CD30− cells

① BV for patients relapsed after AUTO or refractory to CT

Brentuximab Vedotin (SGN-35) for Relapsed CD30-Positive Lymphomas

Anas Younes, M.D., Nancy L. Bartlett, M.D., John P. Leonard, M.D., Dana A. Kennedy, Pharm.D., Carmel M. Lynch, Ph.D., Eric L. Sievers, M.D., and Andres Forero-Torres, M.D.

N Engl J Med 2010;363:1812-21.

Brentuximab Vedotin (SGN-35) for Relapsed CD30-Positive Lymphomas

Table 3. Best Clinical Response in 45 Patients.*

Response	Dose (mg/kg)								
	0.1 (N=3)	0.2 (N=4)	0.4 (N=3)	0.6 (N=3)	0.8 (N=3)	1.2 (N=4)	1.8 (N=12)	2.7 (N=12)	3.6 (N=1)
Complete remission	0	0	0	0	0	1†	4	6†	0
Partial remission	0	0	0	2	0	1	2	1	0
Stable disease	2	0	2	1	2	2	5	5	0
Progressive disease	1	4‡	1	0	1	0	1	0	0
Could not be evaluated	0	0	0	0	0	0	0	0	1§

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

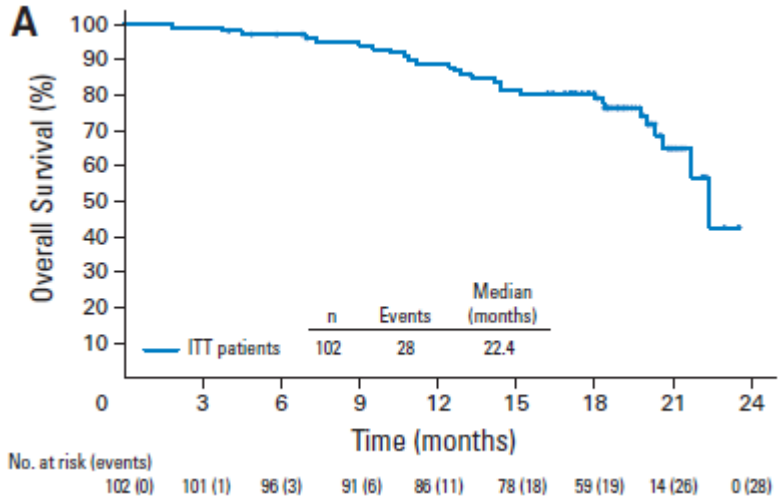
J Clin Oncol 30. © 2012

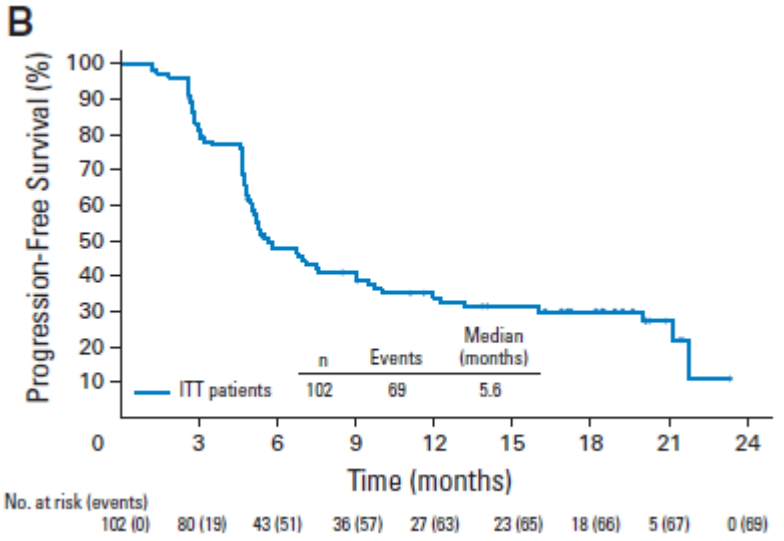
		%
Primary refractory disease†	72	71
Disease status relative to most recent prior therapy‡		
Relapsed	59	58
Refractory	43	42
Best response achieved with most recent systemic regimen		
Complete response	12	12
Partial response	35	34
Stable disease	23	23
Progressive disease	26	25
Unknown/other	6	6
No. of 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	

Results

Table 2. Key Response Results

Parameter	No. of Patients (N = 102)	%
Objective response	76	75
Complete remission	35	34
Partial remission	41	40
Stable disease	22	22
Progressive disease	3	3
Not evaluable	1	1
Duration of objective response, months		
Median	6.7	
95% CI	3.6 to 14.8	
Duration of response for patients with complete remission, months (n = 35)		
Median	20.5	
95% CI	10.8 to NE	

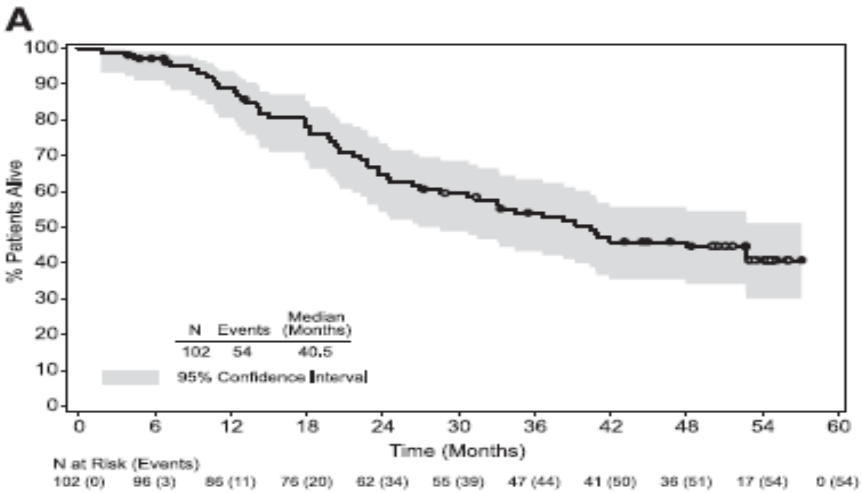


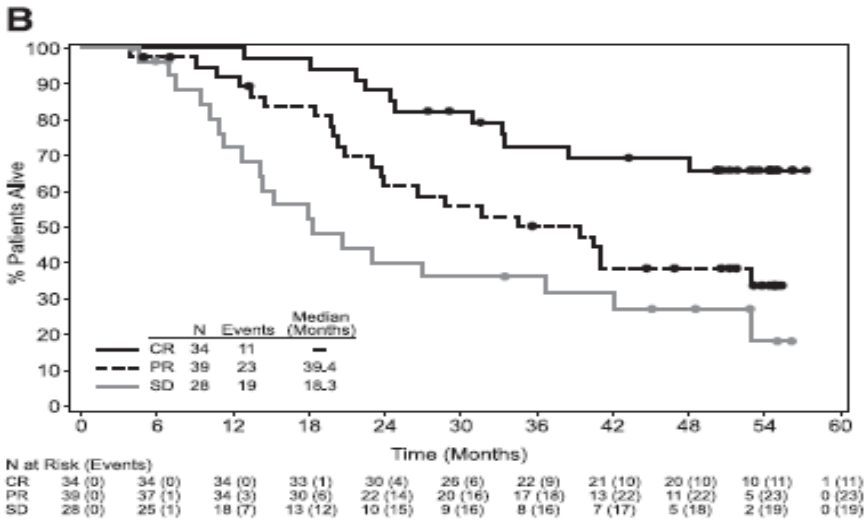


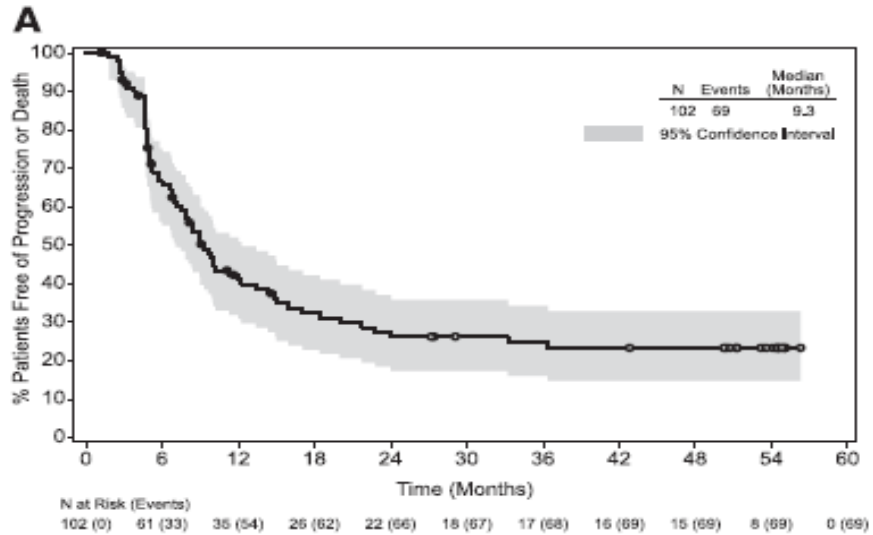
Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma

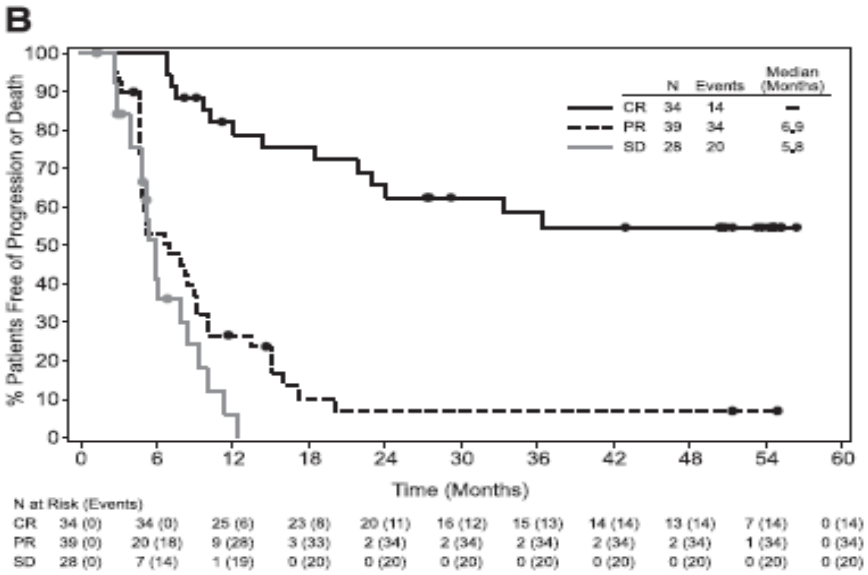
Ajay K. Gopal,[1] Robert Chen,[2] Scott E. Smith,[3] Stephen M. Ansell,[4] Joseph D. Rosenblatt,[5] Kerry J. Savage,[6] Joseph M. Connors,[6] Andreas Engert,[7] Emily K. Larsen,[8] Xuedong Chi,[9] Eric L. Sievers,[8] and Anas Younes[10]

(*Blood*. 2015;125(8):1236-1243)









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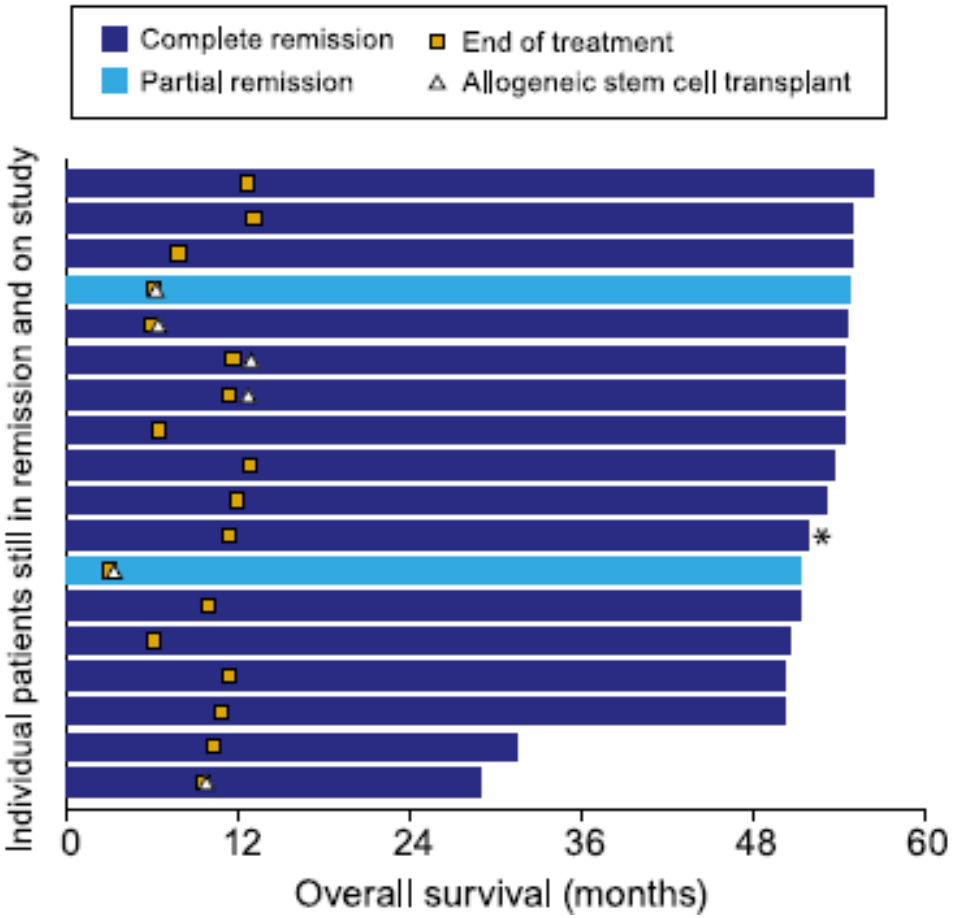


10/102

Female,
Younger
Relapsed
ECOG
Limited disease

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%	29/70%	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

Results of a Multicenter Phase II Trial of Brentuximab Vedotin as Second-Line Therapy before Autologous Transplantation in Relapsed/Refractory Hodgkin Lymphoma

Robert Chen [1,*], Joycelynne M. Palmer [2], Peter Martin [3], Nicole Tsai [2], Young Kim [4], Bihong T. Chen [5], Leslie Popplewell [1], Tanya Siddiqi [1], Sandra H. Thomas [1], Michelle Mott [1], Firoozeh Sahebi [6], Saro Armenian [7], John Leonard [3], Auayporn Nademanee [1], Stephen J. Forman [1]

	Best Response to Brentuximab Vedotin (n = 37)	Response to Combination Chemotherapy (ICE/DICE/IGEV/GND) after Brentuximab Vedotin (n = 18)	Disease Status at AHCT (n = 33)
ORR	25/37 (68%)	16/18 (89%)	
CR	13/37 (35%)	11/18 (61%)	24/33 (73%)
PR	12/37 (32%)	5/18 (28%)	9/33 (27%)
SD	10/37 (27%)	1/18 (6%)	1/33 (3%)
PD	2/37 (5%)	1/18 (6%)	

Chen, BBMT 2015

BV in relapsed/refractory after HDC: ICH experience

	N 18
Stage	
I/II	2 (12%)
III/IV	16 (88%)
B symptoms	4 (22%)
Bulky	2 (12%)
Extra-nodal	13 (72%)
Disease at BV	
Refractory	14 (78%)
Relapsed	3 (17%)
UK	1
Best response to BV	14 (78%)
CR	2
PR	12
Final response to BV	
CR/PR	3/5 (44%)
PD	10 (56%)
Therapy post-BV	
ALLO	9 (50%)
CT/Nivolumab	2/3 (28%)
No therapy	4 (22%)

After 2-4 cycles

② BV as consolidation treatment after AUTO

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

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

Lancet 2015; 385: 1853–62

BV as consolidation

Inclusion criteria

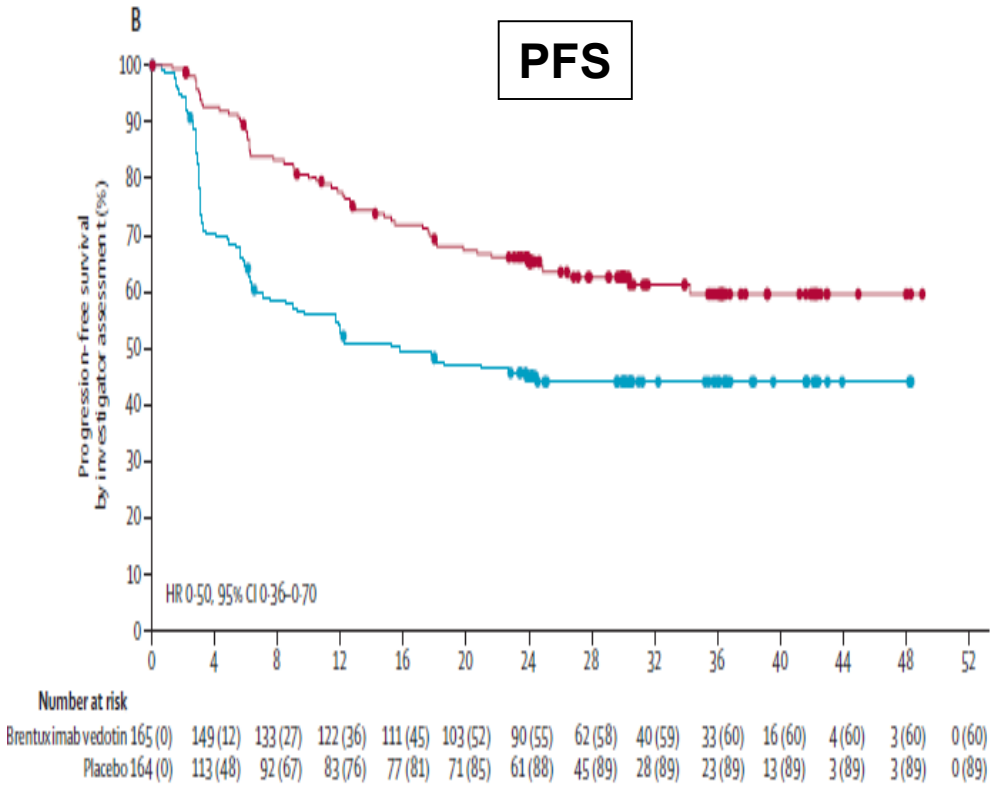
- Failure to achieve CR
- CR < 12M
- Extranodal involvement

Response evaluation

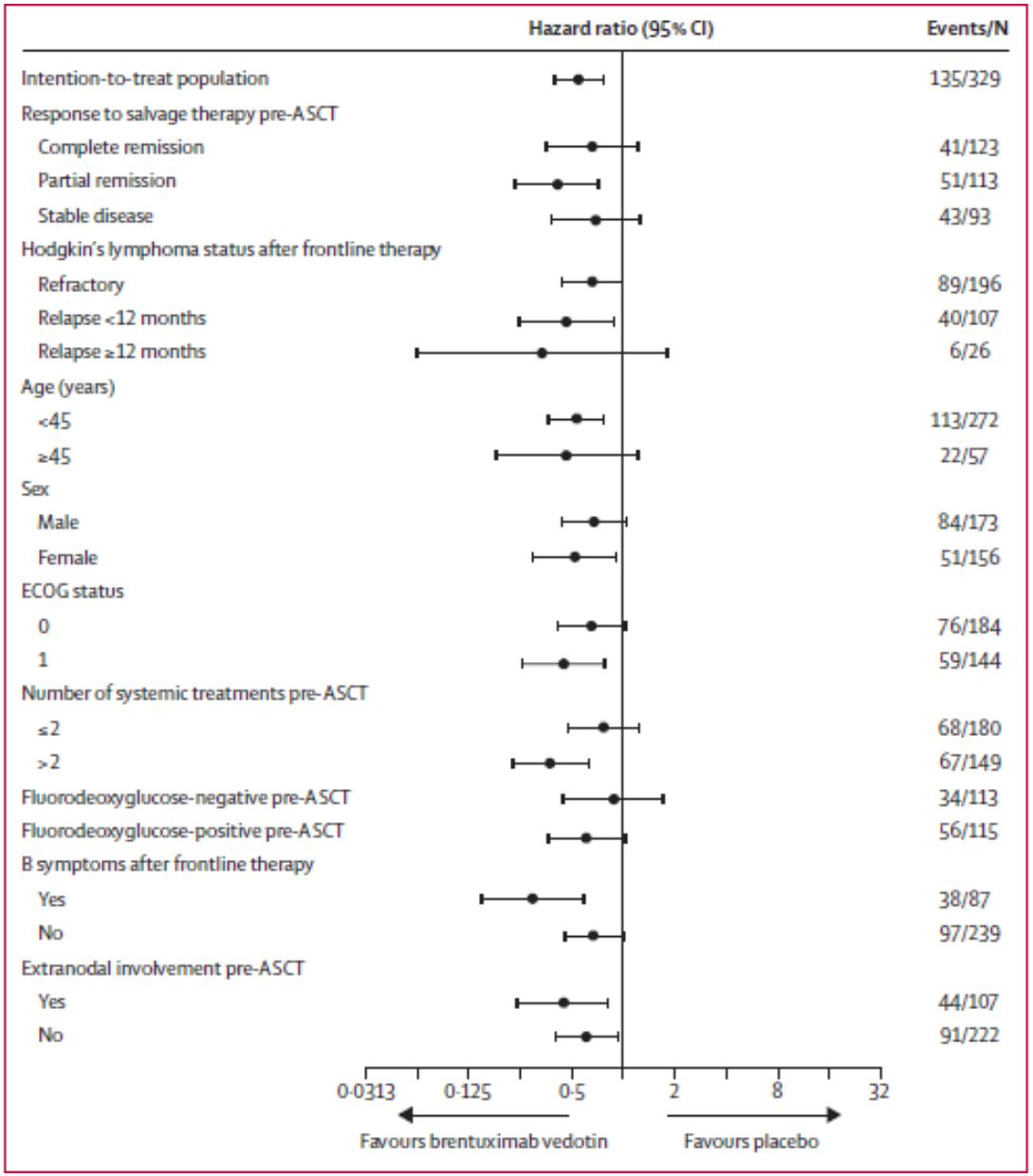
- CT scan

Primary end-point

- PFS



BV as consolidation



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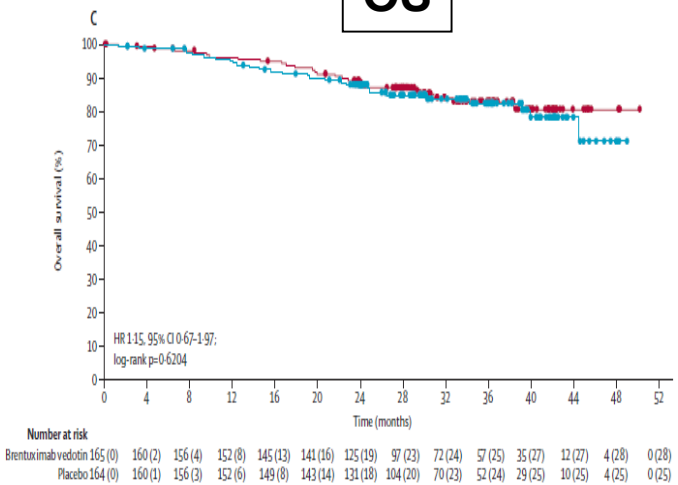


③ BV as treatment of relapse after ALLO

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

BV and relapse after ALLO

	N	Relapse rate	Med time to relapse (months)
Corradini 2007	32	81%@3y	6 (1-42) CR/PR 11 Refractory 4
Anderlini 2008	58	61%@2y	4 (2-13)
Sureda 2008	89	57%@3y	6 (1-50)
Burroughs 2008	38 id 24 UD 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 2012 unp	53	31%@1y	4 (1-13)

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

BV and relapse after ALLO

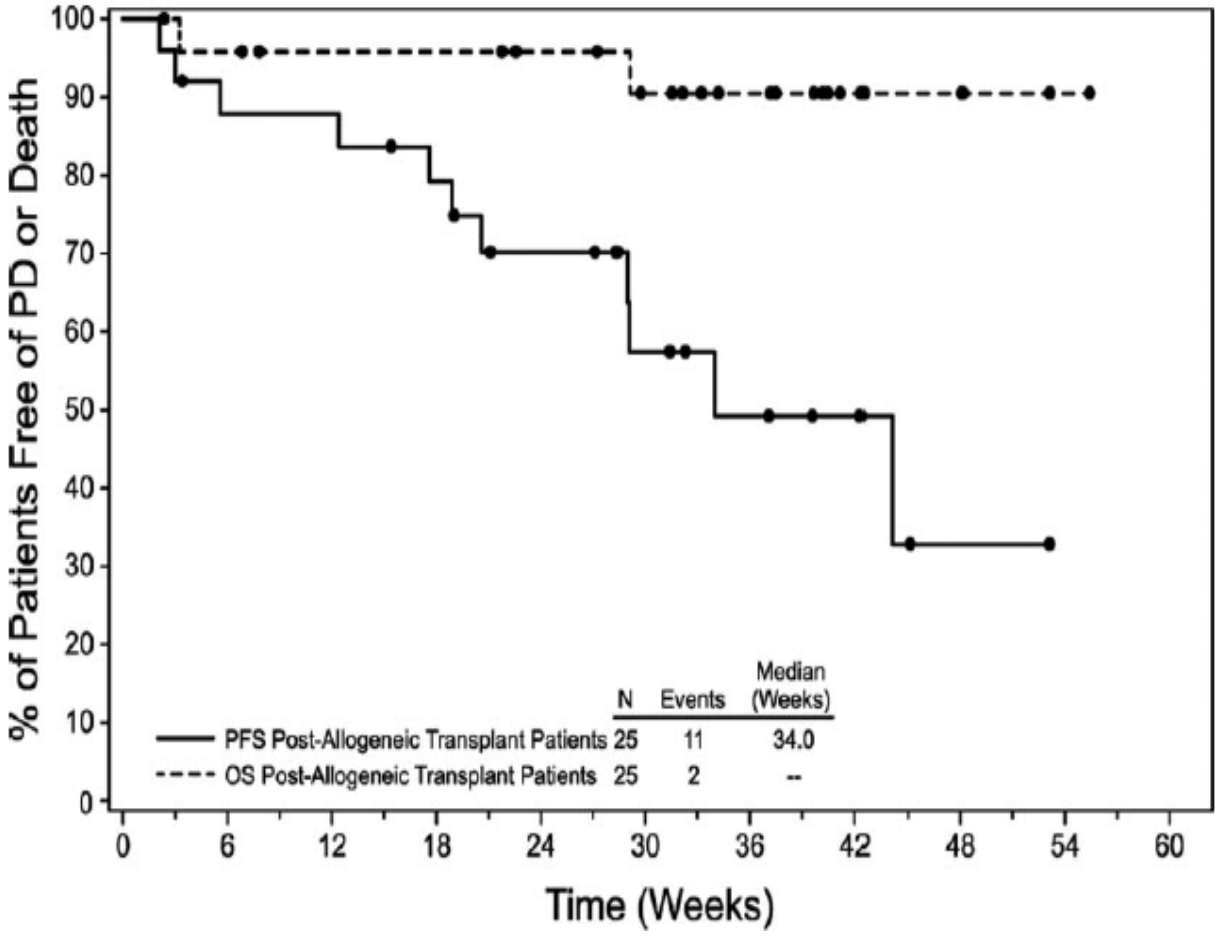
	N = 25
Median age, y (range)	32 (20-56)
Male sex, n (%)	13 (52)
ECOG performance status, n (%)	
0	9 (36)
1	16 (64)
Median time from HL diagnosis to first dose of brentuximab vedotin, mo (range)	72 (19-159)
Total number of prior regimens, median (range)*	9 (5-19)
Prior systemic chemotherapy, n (%)	25 (100)
Median no. (range)	5 (2-12)
Prior external beam radiation, n (%)	22 (88)
Prior autoSCT, n (%)	19 (76)
Prior alloSCT, n (%)	25 (100)
Prior DLI, n (%)	6 (24)

Median time from ALLO to SGN35: 42 months (6-116)

Median time from ALLO to SGN35: 30 months (9-87)

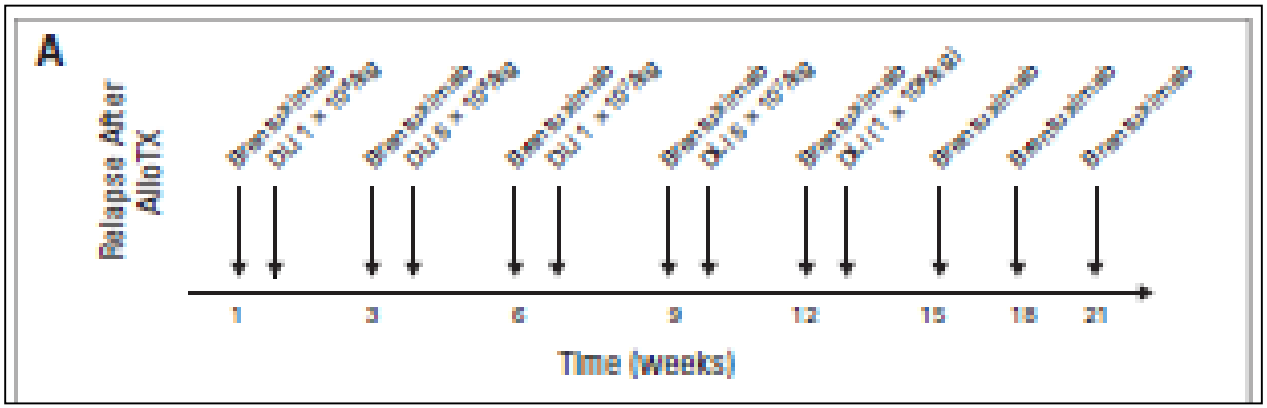
Gopal, Blood 2012

Brentuximab post ALLO



Gopal, Blood 2012

Brentuximab post ALLO



- 4 patients have been treated
- All pts showed a metabolic response
- Demonstrating an immunological effect on HL cell lines, by a heterogenous lymphocytes population, CD161+ CD4+ cells ,corresponding to Th17 T cells.

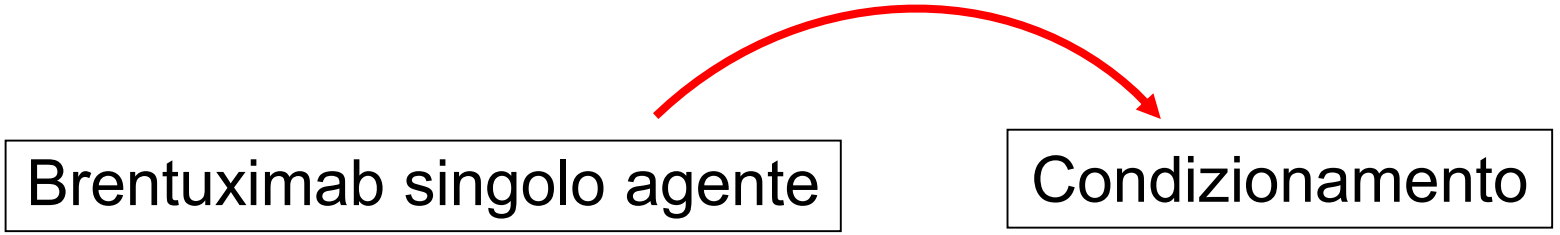
Theurich, JCO 2012

Quali scenari ALLO-SGN35

Brentuximab singolo agente → Condizionamento

Brentuximab + DLI
Brentuximab + DLI + CT →
- Profilassi
- Pre-emptive
- Recidiva/progressione

Quali scenari ALLO-SGN35



- **Warning**
  - Associazione SGN35 con alcuni farmaci può associarsi a complicanze (bleomicina, gemcitabina)
  - Associazione “proibita” con busulfano?

Quali scenari ALLO-SGN35

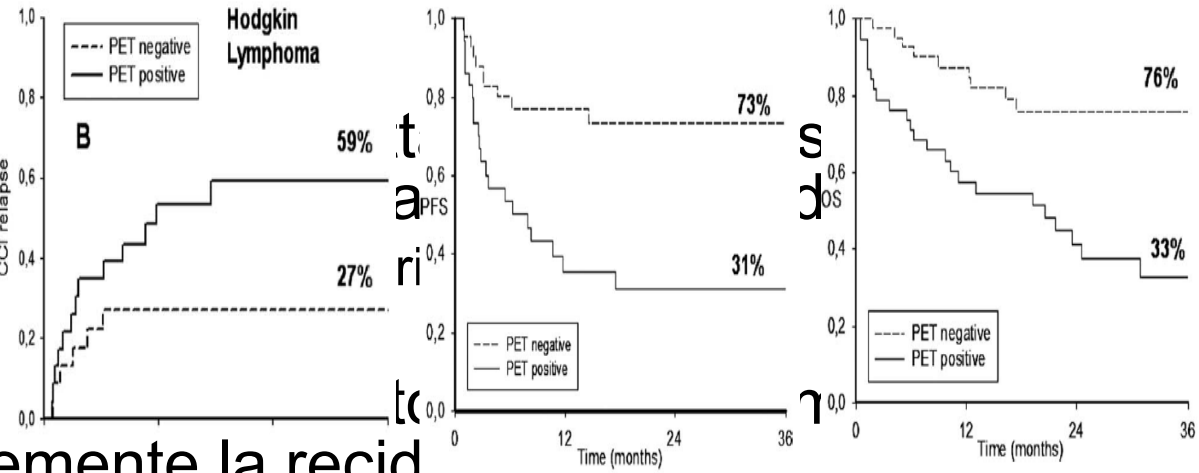
Brentuximab + DLI

Brentuximab + CT + DLI

- Profilassi
- Pre-emptive
- Recidiva/progressione

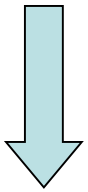
(Gopal 2012)

- **Profilassi**: tutti paz… t… s… recidiva è elevato i… a… d…
  - Esistono pazienti p… ri…
- **Pre-emptive**: si ba… t… n… individuare precocemente la recid…va.
  - PET post-allo?



Quali scenari ALLO-SGN35

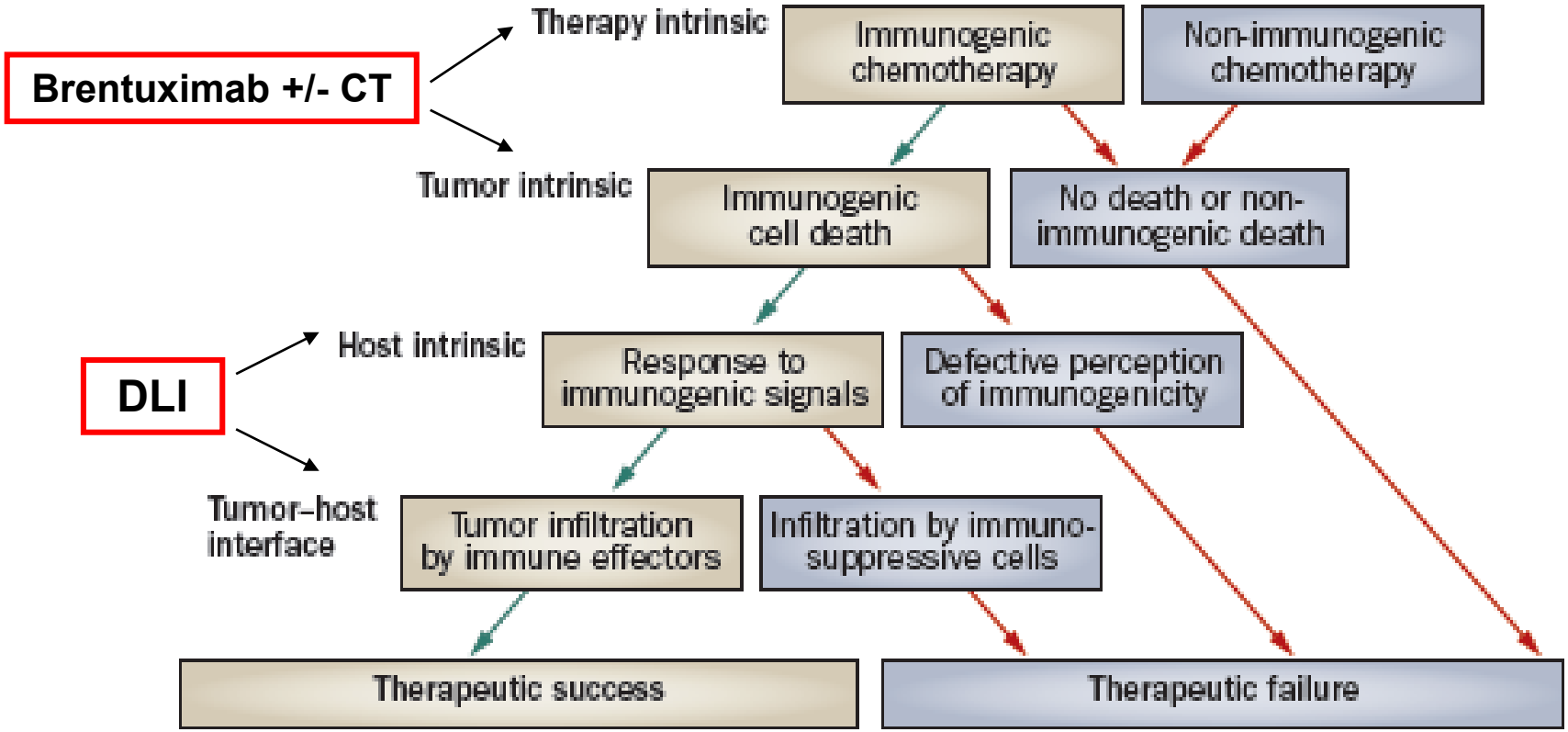
- In profilassi o pre-emptive
  - Brentuximab singolo farmaco o in associazione?
  - Tossicità eccessiva
  - Aumento del rischio di complicanze immunologiche



- Brentuximab +/- CT + DLI è probabilmente la scelta più idonea
- Inizio < 6 mesi

Quali scenari ALLO-SGN35

- La sequenza Brentuximab +/- CT + DLI è probabilmente la più idonea



Zitvogel, Nat Rev 2011

Brentuximab Vedotin in CD30-Positive Lymphomas: A SIE, SIES, and GITMO Position Paper

Pier Luigi Zinzani,[1] Paolo Corradini,[2] Alessandro M. Gianni,[3,4] Massimo Federico,[5] Armando Santoro,[6] Umberto Vitolo,[7] Giovanni Barosi,[8] Sante Tura[9]

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