Nuove Frontiere nella Terapia
delle Malattie Oncologiche ed Oncoematologiche

Treviso, 20 - 21 Novembre 2015

ANTICORPI MONOCLONALI : BRENTUXIMAB VEDOTIN

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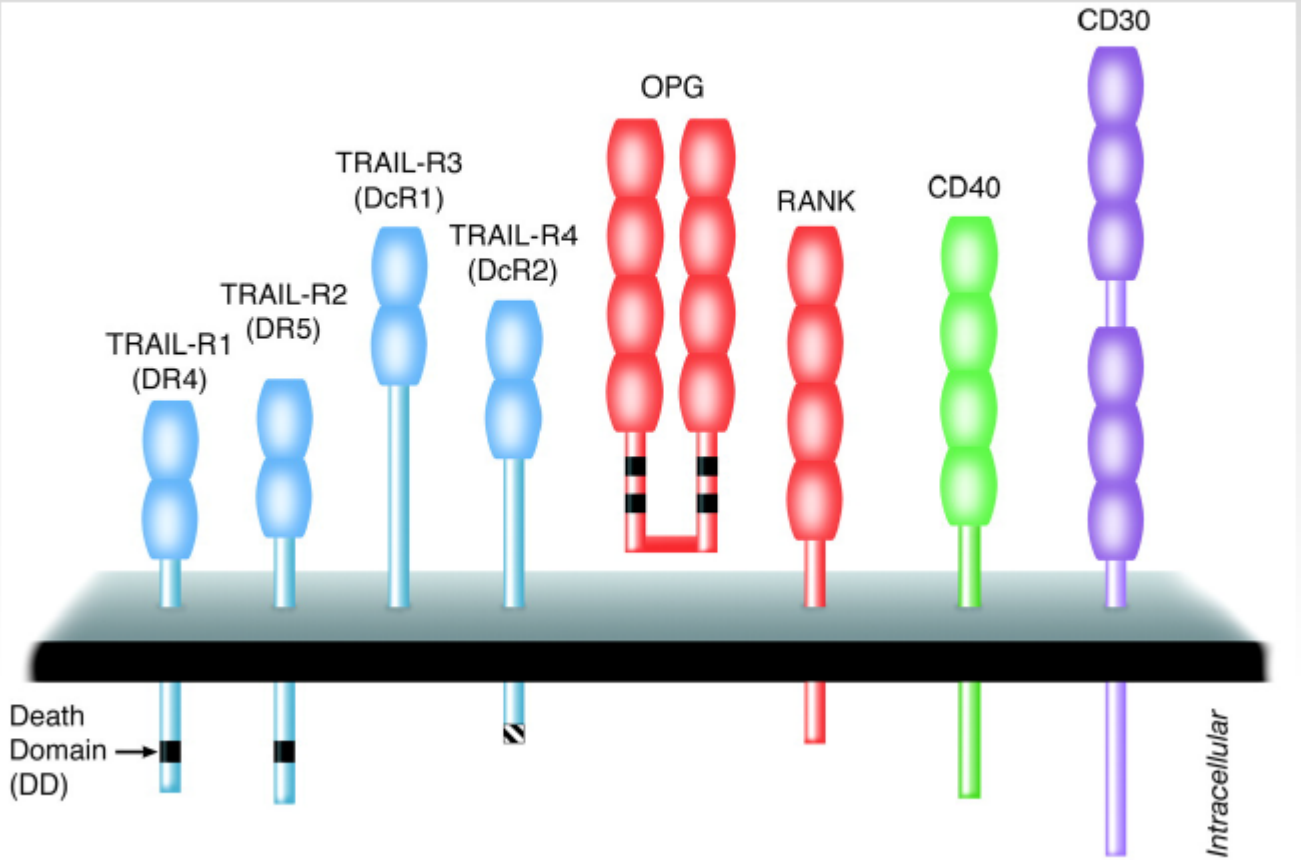
Ospedale "Ca' Foncello" - Treviso

1992 (Cell): Durkop and Stein:
Molecular cloning of CD30 = TNF receptor family member



DR, death receptor; TRAIL, tumor necrosis factor receptor superfamily; OPG, osteoprotegerin; RANK, receptor activator of nuclear factor kappa-B ligand

Younes A, Kadin ME JCO 2003;21:3526-34

ESPRESSIONE DELLA MOLECOLA CD30 SULLA SUPERFICIE CELLULARE

-CD30 esercita molteplici effetti sulla proliferazione e sopravvivenza cellulare, in larga parte dipendenti dall'attivazione dei *pathway* di NF-kB e delle proteine Fas-associated with death domain (FADD).

-È espresso sui linfociti B e T attivati (ma non sui linfociti a riposo), nella mononucleosi infettiva e nelle linfoproliferazioni EBV-correlate, su una piccola quota di eosinofili. E' stata inoltre documentata la sua espressione sulle cellule del pancreas esocrino, sulle cellule deciduali uterine e sull'endometrio durante la gravidanza.

-Il gene codificante per CD30 è localizzato a livello di 1p36

CD30 expression in tumours

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

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

CD30 expression defines a novel subgroup of diffuse large B-cell lymphoma with favorable prognosis and distinct gene expression signature: a report from the International DLBCL Rituximab-CHOP Consortium Program Study

Shimin Hu,[1] Zijun Y. Xu-Monette,[1] Aarthi Balasubramanyam,[2] Ganiraju C. Manyam,[3] Carlo Visco,[4] Alexander Tzankov,[5] Wei-min Liu,[2] Roberto N. Miranda,[1] Li Zhang,[3] Santiago Montes-Moreno,[6] Karen Dybkær,[7] April Chiu,[8] Attilio Orazi,[9] Youli Zu,[10] Govind Bhagat,[11] Kristy L. Richards,[12] Eric D. Hsi,[13] William W. L. Choi,[14] J. Han van Krieken,[15] Qin Huang,[16] Jooryung Huh,[17] Weiyun Ai,[18] Maurilio Ponzoni,[19] Andrés J. M. Ferreri,[19] Xiaoying Zhao,[20] Jane N. Winter,[21] Mingzhi Zhang,[22] Ling Li,[22] Michael B. Møller,[23] Miguel A. Piris,[6] Yong Li,[24] Ronald S. Go,[25] Lin Wu,[2] L. Jeffrey Medeiros,[1] and Ken H. Young[1]

Key Points

- CD30 expression defines a novel and unique subgroup of DLBCL with favorable clinical outcome and distinct gene expression signature.

CD30, originally identified as a cell-surface marker of Reed-Sternberg and Hodgkin cells of classical Hodgkin lymphoma, is also expressed by several types of non-Hodgkin lymphoma, including a subset of diffuse large B-cell lymphoma (DLBCL). However, the prognostic and biological importance of CD30 expression in DLBCL is unknown. Here we report that CD30 expression is a favorable prognostic factor in a cohort of 903 de novo DLBCL patients. CD30 was expressed in ~14% of DLBCL patients. Patients with $CD30^+$ DLBCL had superior 5-year overall survival ($CD30^+$, 79% vs $CD30^-$, 59%; P = .001) and progression-free survival (P = .003). The favorable outcome of CD30 expression was maintained in both the germinal center B-cell and activated B-cell subtypes. Gene expression profiling revealed the upregulation of genes encoding negative regulators of nuclear factor κB activation and lymphocyte survival, and downregulation of genes encoding B-cell receptor signaling and proliferation, as well as prominent cytokine and stromal signatures in $CD30^+$ DLBCL patients, suggesting a distinct molecular basis for its favorable outcome. Given the superior prognostic value, unique gene expression signature, and significant value of CD30 as a therapeutic target for brentuximab vedotin in ongoing successful clinical trials, it seems appropriate to consider $CD30^+$ DLBCL as a distinct subgroup of DLBCL. (*Blood*. 2013;121(14):2715-2724)

CD30 expression in peripheral T-cell lymphoma

by Elena Sabattini, Marco Pizzi, Valentina Tabanelli, Pamela Baldin, Carlo Sagramoso Sacchetti, Claudio Agostinelli, Pier Luigi Zinzani, and Stefano Pileri

Haematologica 2013 [Epub ahead of print]

	CD30 IHC SCORE					
	0	1+	2+	3+	4	Score ≥2+
PTCL, NOS (87 cases)	31 (35.63%)	11 (12.64%)	**18 (20.69%)**	**11 (12.64%)**	**16 (18.39%)**	**45/87 (51.72%)**
AITL (42 cases)	24 (51.14%)	9 (21.42%)	**5 (11.90%)**	**4 (9.52%)**	-	**9/42 (21.42%)**
ENTL (10 cases)	2 (20.00%)	1 (10.00%)	**3 (30.00%)**	**1 (10.00%)**	**3 (30.00%)**	**7/10 (70.00%)**
MF (32 cases)	13* (40.63%)	15** (46.88%)	**2[§] (6.25%)**	-	**2[§§] (6.25%)**	**4/32 (12.50%)**
Transformed MF (9 cases)	-	-	**3 (33.33%)**	**6 (66.67%)**	-	**9/9 100%**
EATL type 1 (9 cases)	-	-	**2 (22.22%)**	-	**7 (77,78%)**	**9/9 (100,00%)**
EATL type 2 (3 cases)	3 (100%)	-	-	-	-	-
All types (192 cases)	73 (38.02%)	36 (18.75%)	**33 (17.18%)**	**17 (8.85%)**	**28 (14.58%)**	**83/192 (43.22%)**

CD30 targeting with brentuximab vedotin: a novel therapeutic approach to primary effusion lymphoma

Shruti Bhatt,[1,2] Brittany M. Ashlock,[3] Yasodha Natkunam,[4] Victoria Sujoy,[5] Jennifer Rose Chapman,[5] Juan Carlos Ramos,[2] Enrique A. Mesri,[3] and Izidore S. Lossos[1,2]

[1]Department of Molecular and Cellular Pharmacology, [2]Department of Medicine, Division of Hematology-Oncology, and [3]Department of Microbiology and Immunology, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL; [4]Department of Pathology, Stanford University School of Medicine, Stanford, CA; and [5]Department of Pathology, University of Miami Miller School of Medicine, Miami, FL

Key Points

- Brentuximab vedotin serves as an effective therapy for PEL.
- Brentuximab vedotin led to cytotoxic effects in PEL cell lines and extended survival of xenograft mice.

Primary effusion lymphoma (PEL) is an aggressive subtype of non-Hodgkin lymphoma characterized by short survival with current therapies, emphasizing the urgent need to develop new therapeutic approaches. Brentuximab vedotin (SGN-35) is an anti-CD30 monoclonal antibody (cAC10) conjugated by a protease-cleavable linker to a microtubule-disrupting agent, monomethyl auristatin E. Brentuximab vedotin is an effective treatment of relapsed CD30-expressing Classical Hodgkin and systemic anaplastic large cell lymphomas. Herein, we demonstrated that PEL cell lines and primary tumors express CD30 and thus may serve as potential targets for brentuximab vedotin therapy. In vitro treatment with brentuximab vedotin decreased cell proliferation, induced cell cycle arrest, and triggered apoptosis of PEL cell lines. Furthermore, in vivo brentuximab vedotin promoted tumor regression and prolonged survival of mice bearing previously reported UM-PEL-1 tumors as well as UM-PEL-3 tumors derived from a newly established and characterized Kaposi's sarcoma-associated herpesvirus- and Epstein-Barr virus-positive PEL cell line. Overall, our results demonstrate for the first time that brentuximab vedotin may serve as an effective therapy for PEL and provide strong preclinical indications for evaluation of brentuximab vedotin in clinical studies of PEL patients. (*Blood*. 2013;122(7):1233-1242)

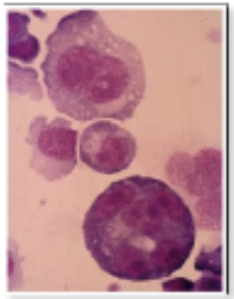
Seminal study: production of a monoclonal antibody specific for HL

Production of a monoclonal antibody specific for Hodgkin and Sternberg–Reed cells of Hodgkin's disease and a subset of normal lymphoid cells

Ulrich Schwab*, Harald Stein*, Johannes Gerdes*, Hilmar Lemke*, Hartmut Kirchner†, Michael Schaadt† & Volker Diehl†

Nature Vol. 299 2 September 1982

Ki-1, one of first 67 clones produced at Kiel



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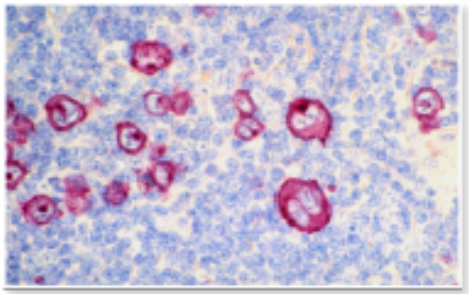
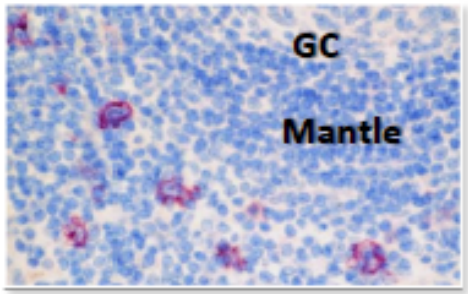


Classical HL



Normal tonsil

Summary results of phase I/II clinical trials targeting CD30

Drug	Disease	Antibody type	Phase	Number of evaluable patients	PR	CR	%PR + CR
MDX-060	HL, ALCL	Humanized	I	HL = 63 ALCL = 9	2 2	2 0	6% 22%
SGN-30	HL, ALCL	Chimeric	I	24	0	0	0
SGN-30	HL, ALCL	Chimeric	II	HL = 38 ALCL = 41	0 5	0 2	0 17%
Xmab2513	HL	Humanized	I	13	1	0	7%
131I-Ki4	HL	Murine	I	22	5	1	27%

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

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

SHORT REPORT

Response of refractory Hodgkin's disease to monoclonal anti-CD30 immunotoxin

B. FALINI A. BOLOGNESI L. FLENGHI
P. L. TAZZARI M. K. BROE H. STEIN
H. DÜRKOP F. AVERSA P. CORNELI
G. PIZZOLO G. BARBABIETOLA
E. SABATTINI S. PILERI M. F. MARTELLI
F. STIRPE

In Hodgkin's disease, Hodgkin and Reed-Sternberg cells consistently express the antigen CD30. We investigated the possible therapeutic role of an immunotoxin prepared by covalent linking of an anti-CD30 monoclonal antibody (Ber-H2) to saporin (SO6), a type-1 ribosome-inactivating protein. The immunotoxin (0·8 mg/kg in one or two doses) was given to four patients with advanced refractory Hodgkin's disease. In three, there was rapid and substantial reduction in tumour mass (50% to >75%). Clinical responses were transient (6–10 weeks). In-vivo binding of the immunotoxin to tumour cells was shown by immunohistology in two patients. Antibodies to both parts of the immunotoxin developed in all patients.

Lancet 1992; **339**: 1195–96.

TREATMENT WITH BER-H2/SO6 AND RESPONSE

Patient	Dose Ber H2/SO6 (mg/kg)	Reduction in tumour size*	Response duration (wk)	Outcome
1	0·3/0·1 (days 1 + 7)†	75–100%	10	Alive 10 mo
2	0·3/0·1 (days 1 + 7)†	⩾25%	6	Alive 5 mo
3	0·6/0·2 (day 1)	50–75%	8	Dead 3 mo
4	0·6/0·2 (day 1)	100% skin, ⩾50% other sites	8	Dead 3 mo

*Measured by computed tomography (CT) scan and expressed as product of two diameters of all measurable lesions.
†Maximum tumour effect seen after first dose.

-Non chiaramente definite la dose e la schedula più appropriate

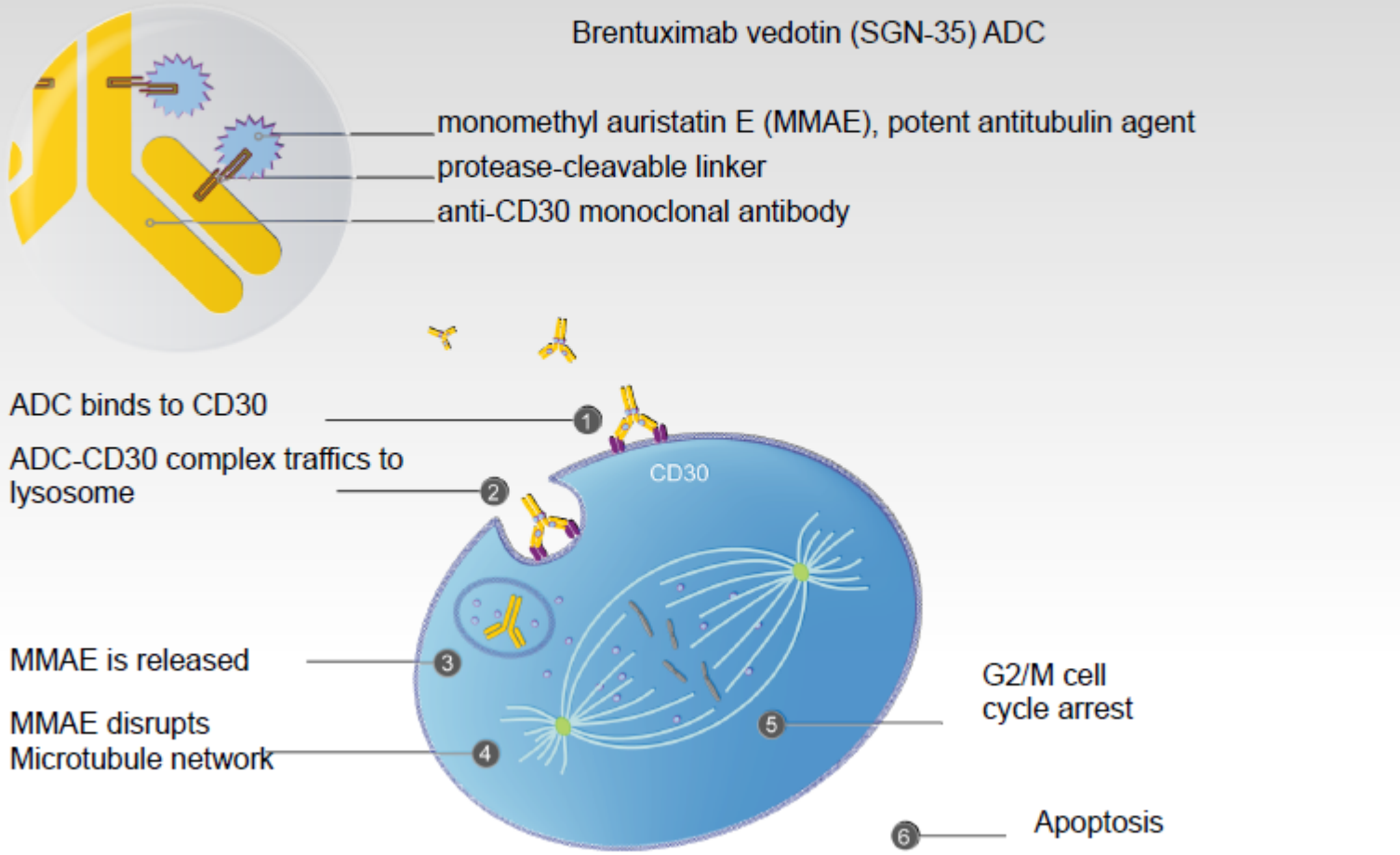
-Risposte molto transitorie

-Tossicità epatica

-Sviluppo di anticorpi anti-BER-H2 e anti-saporina

Falini B, Lancet 1992; 339: 1195-96

Brentuximab vedotin (SGN-35) : Mechanism of action



ADC – antibody drug conjugate

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

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.

From the Department of Lymphoma and Myeloma, University of Texas M.D. Anderson Cancer Center, Houston (A.Y.); Washington University, St. Louis (N.L.B.); Weill Medical College of Cornell University, New York (J.P.L.); Seattle Genetics, Bothell, WA (D.A.K., C.M.L., E.L.S.); and the University of Alabama at Birmingham, Birmingham (A.F.-T.). Address reprint requests to Dr. Younes at the University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or at ayounes@mdanderson.org.

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

BACKGROUND

Hodgkin's lymphoma and anaplastic large-cell lymphoma are the two most common tumors expressing CD30. Previous attempts to target the CD30 antigen with monoclonal-based therapies have shown minimal activity. To enhance the antitumor activity of CD30-directed therapy, the antitubulin agent monomethyl auristatin E (MMAE) was attached to a CD30-specific monoclonal antibody by an enzyme-cleavable linker, producing the antibody–drug conjugate brentuximab vedotin (SGN-35).

METHODS

In this phase 1, open-label, multicenter dose-escalation study, we administered brentuximab vedotin (at a dose of 0.1 to 3.6 mg per kilogram of body weight) every 3 weeks to 45 patients with relapsed or refractory CD30-positive hematologic cancers, primarily Hodgkin's lymphoma and anaplastic large-cell lymphoma. Patients had received a median of three previous chemotherapy regimens (range, one to seven), and 73% had undergone autologous stem-cell transplantation.

RESULTS

The maximum tolerated dose was 1.8 mg per kilogram, administered every 3 weeks. Objective responses, including 11 complete remissions, were observed in 17 patients. Of 12 patients who received the 1.8-mg-per-kilogram dose, 6 (50%) had an objective response. The median duration of response was at least 9.7 months. Tumor regression was observed in 36 of 42 patients who could be evaluated (86%). The most common adverse events were fatigue, pyrexia, diarrhea, nausea, neutropenia, and peripheral neuropathy.

CONCLUSIONS

Brentuximab vedotin induced durable objective responses and resulted in tumor regression for most patients with relapsed or refractory CD30-positive lymphomas in this phase 1 study. Treatment was associated primarily with grade 1 or 2 (mild-to-moderate) toxic effects. (Funded by Seattle Genetics; ClinicalTrials.gov number, NCT00430846.)

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

Processed as a Rapid Communication manuscript. See accompanying editorial on page 2171 and articles on pages 2190 and 2197; listen to the podcast by Dr Soiffer at www.jco.org/podcasts

A B S T R A C T

Purpose
Brentuximab vedotin is an antibody-drug conjugate (ADC) that selectively delivers monomethyl auristatin E, an antimicrotubule agent, into CD30-expressing cells. In phase I studies, brentuximab vedotin demonstrated significant activity with a favorable safety profile in patients with relapsed or refractory CD30-positive lymphomas.

Patients and Methods
In this multinational, open-label, phase II study, the efficacy and safety of brentuximab vedotin were evaluated in patients with relapsed or refractory Hodgkin's lymphoma (HL) after autologous stem-cell transplantation (auto-SCT). Patients had histologically documented CD30-positive HL by central pathology review. A total of 102 patients were treated with brentuximab vedotin 1.8 mg/kg by intravenous infusion every 3 weeks. In the absence of disease progression or prohibitive toxicity, patients received a maximum of 16 cycles. The primary end point was the overall objective response rate (ORR) determined by an independent radiology review facility.

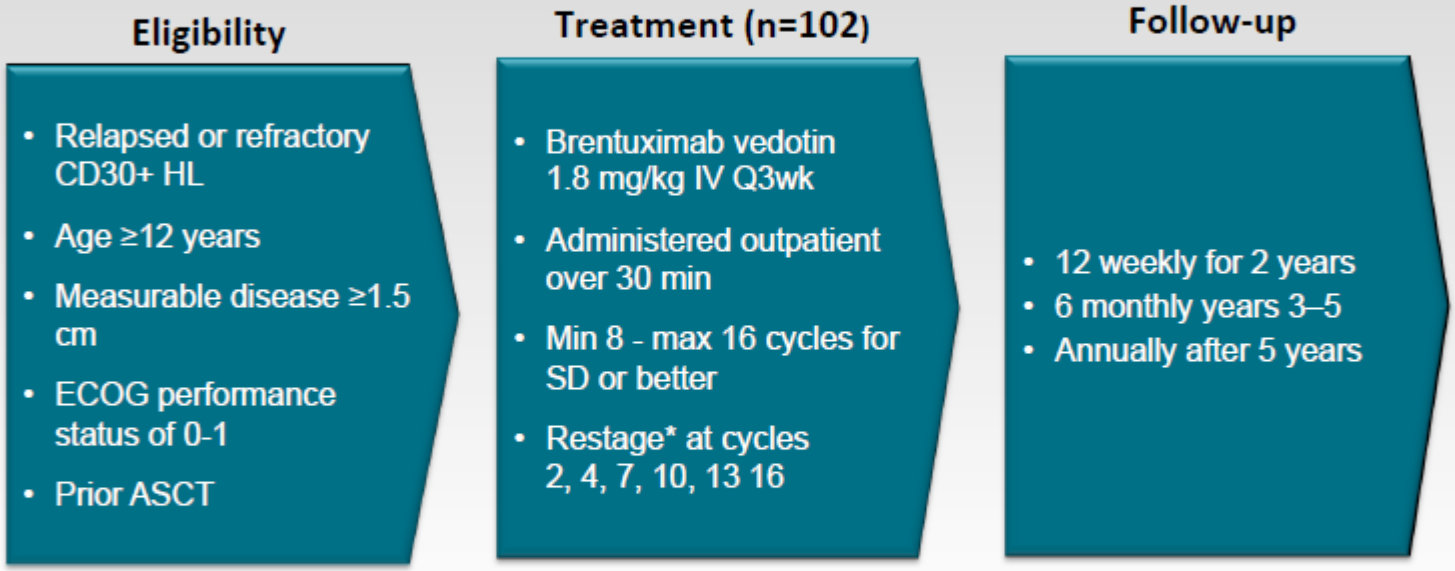
Results
The ORR was 75% with complete remission (CR) in 34% of patients. The median progression-free survival time for all patients was 5.6 months, and the median duration of response for those in CR was 20.5 months. After a median observation time of more than 1.5 years, 31 patients were alive and free of documented progressive disease. The most common treatment-related adverse events were peripheral sensory neuropathy, nausea, fatigue, neutropenia, and diarrhea.

Conclusion
The ADC brentuximab vedotin was associated with manageable toxicity and induced objective responses in 75% of patients with relapsed or refractory HL after auto-SCT. Durable CRs approaching 2 years were observed, supporting study in earlier lines of therapy.

J Clin Oncol 30:2183-2189.

BV = most effective single-agent among old or novel molecules in R/R HL.

Phase II pivotal study of brentuximab vedotin in patients with R/R HL post ASCT



Primary Endpoint: ORR by Independent Review Facility (IRF)

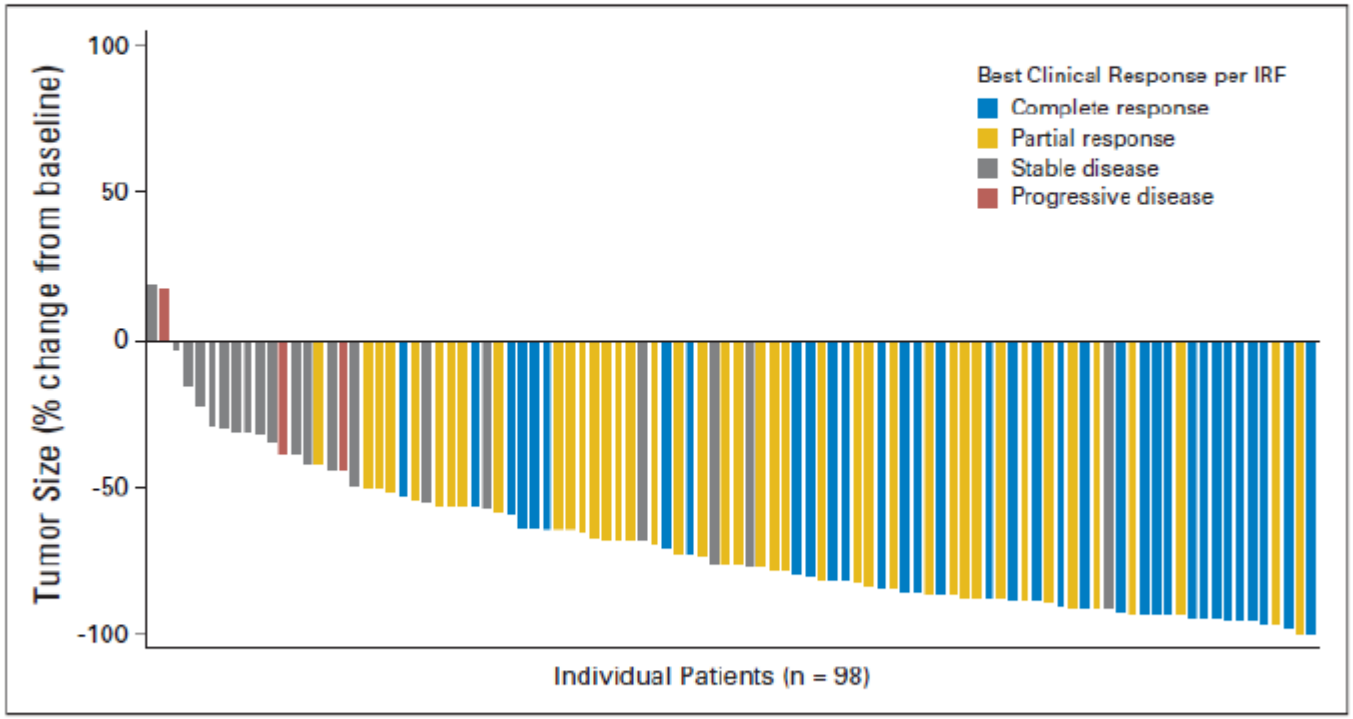
*Revised response criteria for malignant lymphoma (Cheson 2007)

R/R, relapsed / refractory; ASCT, autologous stem cell transplantation;
ECOG, European Cooperative Oncology Group;
SD, stable disease; PD, progressive disease

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

Phase II pivotal study of brentuximab vedotin maximum reduction in target lesions

94% patients achieved tumour reduction



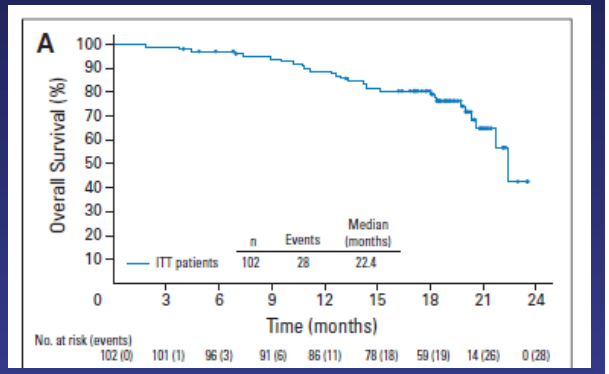
IRF – independent review facility

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

Younes A et al.

Results of a pivotal phase-2 study of Brentuximab Vedotin for patients with relapsed or refractory Hodgkin's lymphoma

J Clin Oncol 2012: 30: 2183-2189



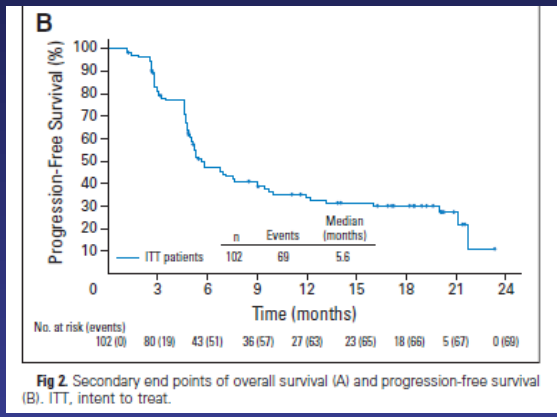


Fig 2. Secondary end points of overall survival (A) and progression-free survival (B). ITT, intent to treat.

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	
Progression-free survival, months		
Median	5.6	
95% CI	5.0 to 9.0	
Overall survival, months		
Median	22.4	
95% CI	21.7 to NE	

Abbreviation: NE, not estimable.

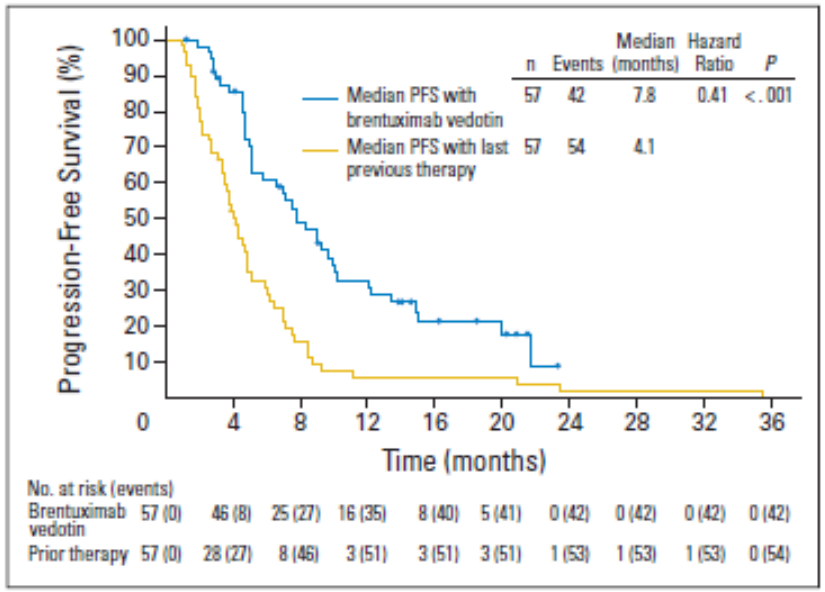


Fig 3. Progression-free survival (PFS) achieved with brentuximab vedotin compared with PFS achieved with the last prior therapy. Data shown are median PFS as assessed by investigator in the subset of patients (n = 57) who received systemic therapy after autologous stem-cell transplantation and before receiving brentuximab vedotin.

Phase II study of brentuximab vedotin treatment related adverse event- 3 year follow-up

- Treatment-related grade ≥3 AEs

Preferred Term	Grade ≥3 AEs
Neutropenia	20%
Peripheral sensory neuropathy	9%
Thrombocytopenia	8%
Anemia	6%
Fatigue	2%
Pyrexia	2%
Diarrhea	1%

- The most common (≥15%) brentuximab vedotin-related adverse events of any grade were peripheral sensory neuropathy, nausea, fatigue, neutropenia, and diarrhea.
- Adverse events of Grade 3 or higher that occurred in ≥5% of patients were neutropenia, peripheral sensory neuropathy, thrombocytopenia, and anemia

AEs, adverse events

Gopal A, et al. ASH 2013, New Orleans, LA, USA (Abstract 4382)

OPEN

Citation: Blood Cancer Journal (2015) 5, e343; doi:10.1038/bcj.2015.72

www.nature.com/bcj

LETTER TO THE EDITOR

Brentuximab vedotin: axonal microtubule's Apollyon

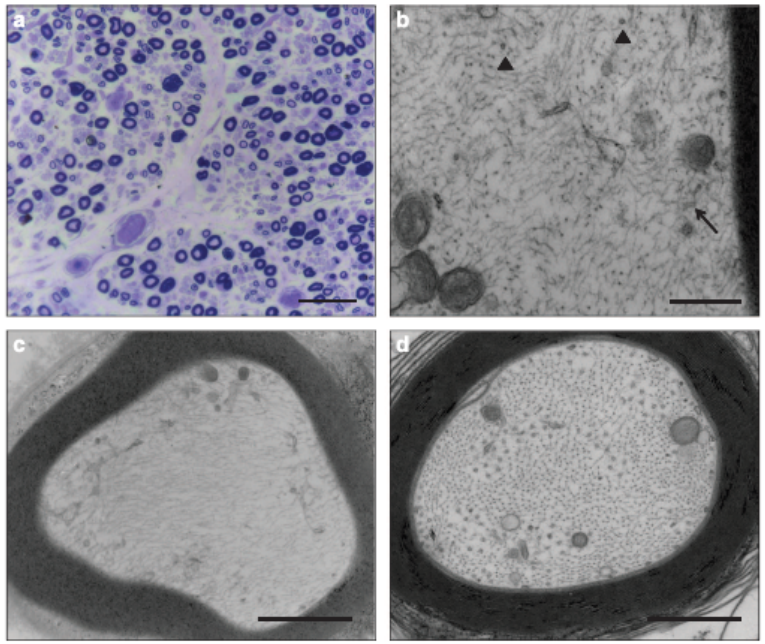


Figure 1. (**a**) A Spurr-embedded section of the sural nerve biopsy specimen shows reduction in density of myelinated fibers, degenerating axons and a few regenerating clusters, findings consistent with ongoing axonal neuropathy (scale bar = 50 μm). (**b**) High magnification electron micrograph of a myelinated axon of the patient's sural nerve shows a few microtubule profiles oriented along the longitudinal axis of the fiber (arrowhead), in addition to tangentially oriented microtubules (arrow; scale bar = 300 nm). (**c**) A myelinated fiber showing severe depletion of microtubules, bundles of misaligned neurofilaments and subaxolemmal segregation of smooth endoplasmic reticulum and membranous organelles (scale bar = 120 nm). (**d**) A control myelinated fiber showing the typical alignment of the axonal cytoskeleton and the distribution of microtubules in distinct microdomains (scale bar = 120 nm).

S Mariotto[1], S Ferrari[1], M Sorio[2], F Benedetti[2], G Tridente[3], T Cavallaro[1], A Gajofatto[1] and S Monaco[1]

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[3]*School of Medicine, University of Verona, Verona, Italy*

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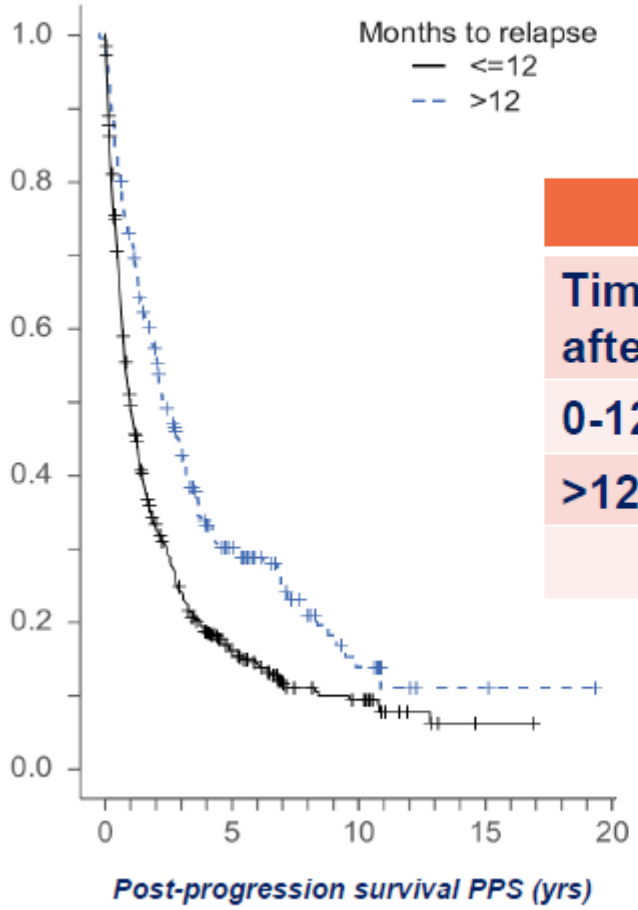
Table 3. Results of the pivotal study and NPP experiences.

Study	N. pts	ORR%	CR%
Pivotal[11]	102	73	32
German NPP[14]	45	60	22
UK NPP[15]	18	72	17
Italian NPP	65	70.7	21.5

NPP: Named Patient Program; pts: patients; ORR, overall response rate; CR: complete response.

Zinzani PL et al. Haematologica 2013; 98(8): 1232

Patients who fail ASCT have a poor prognosis



	All sites	
Time to relapse after ASCT	N	Median PPS (yr)
0-12 months	542	0.98
>12 months	214	2.26
		P<0.0001

Arai S et al. Leukemia & Lymphoma 2013; doi: 10.3109/10428194.2013.798868;

Brentuximab vedotin in refractory CD30+ lymphomas: a bridge to allogeneic transplantation in approximately one quarter of patients treated on a Named Patient Programme at a single UK center

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[1]The Christie NHS Foundation Trust, Manchester; and [2]The University of Manchester, Manchester, UK

ABSTRACT

The CD30-targeted agent brentuximab vedotin has shown impressive activity in relapsed/refractory Hodgkin lymphoma and anaplastic large cell lymphoma in phase II studies. We have treated 24 patients with relapsed/refractory disease enrolled onto a Named Patient Programme during 2010-11 at a single UK center. Overall response rate across all histologies was 67% (Hodgkin 72%; anaplastic large cell 60%), complete response rate 25% (Hodgkin 17%; anaplastic large cell 60%), median progression-free survival 5.1 months, and toxicity mild to moderate in the majority of cases. Six patients proceeded to allogeneic transplantation and one patient awaits this procedure. These results are similar to phase II data and show that brentuximab vedotin provides a bridge to allogeneic transplantation in approximately one quarter of patients refractory to conventional salvage therapies. Best response was seen after four doses, so consideration of allogeneic transplantation should be made early and scheduled following the first assessment indicating response.

 doi:10.3324/haematol.2012.069393
Manuscript received on May 2, 2012. Manuscript accepted on September 18, 2012.
Correspondence: john.radford@manchester.ac.uk

INDICAZIONI UFFICIALI DEL BV NEL LINFOMA DI HODGKIN (SECONDO FDA, EMA e AIFA)

- Pazienti adulti (>18 anni) affetti da linfoma di Hodgkin CD30+ recidivato o refrattario

  a) dopo trapianto autologo di cellule staminali

  b) dopo almeno due precedenti regimi chemioterapici,
  quando lo ASCT non è un'opzione terapeutica

Secondo un recente «Position paper» SIE SIES GITMO ci sono sufficienti evidenze per raccomandare l'impiego di BV nei pazienti con malattia refrattaria alla chemioterapia di salvataggio, candidati a ASCT, e come consolidamento dopo ASCT (Zinzani PL et al. Clin Lymphoma Myeloma Leukemia 2015)

Leukemia & Lymphoma, October 2014; 55(10): 2328–2334

ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2013.876496

informa
healthcare

ORIGINAL ARTICLE: CLINICAL

Brentuximab vedotin in patients aged 60 years or older with relapsed or refractory CD30-positive lymphomas: a retrospective evaluation of safety and efficacy

Ajay K. Gopal[1], Nancy L. Bartlett[2], Andres Forero-Torres[3], Anas Younes[4], Robert Chen[5], Jonathan W. Friedberg[6], Jeffrey V. Matous[7], Andrei R. Shustov[8], Scott E. Smith[9], Jasmine Zain[10], Megan M. O'Meara[11] & Michelle A. Fanale[4]

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Table III. Grade 3 or higher treatment-emergent adverse events occurring in ≥ 10% of patients in either age group.

Preferred term	Age ≥ 60 ($n = 40$)	Age < 60 ($n = 326$)	p-Value*
Any event, n (%)	28 (70)	181 (56)	0.0917
Neutropenia	10 (25)	53 (16)	0.1831
Anemia	8 (20)	23 (7)	0.0119
Peripheral sensory neuropathy	6 (15)	25 (8)	0.1298
Fatigue	4 (10)	10 (3)	0.0546
Thrombocytopenia	4 (10)	23 (7)	0.5178

*p-Value from Fisher exact test.

Table V. Best clinical response by diagnosis in patients ≥ 60 years of age.

	Diagnosis			
	HL ($n = 16$)	sALCL ($n = 22$)	PTCL-NOS ($n = 2$)	Total ($n = 40$)
Objective response	9 (56)	22 (100)	2 (100)	33 (83)
Complete remission	6 (38)	11 (50)	1 (50)	18 (45)
Partial remission	3 (19)	11 (50)	1 (50)	15 (38)
Stable disease	3 (19)	0	0	3 (8)
Progressive disease	3 (19)	0	0	3 (8)
Not evaluable	1 (6)	0	0	1 (3)

HL, Hodgkin lymphoma; sALCL, systemic anaplastic large cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified.

Gopal AK et al. Leukemia & Lymphoma 2014; 55(10): 2328-2334

PHASE 2 STUDY WITH BRENTUXIMAB VEDOTIN IN MONOTHERAPY AND IN COMBINATION WITH DACARBAZINE IN FRONT-LINE TREATMENT OF HODGKIN LYMPHOMA IN PATIENTS AGED ≥60 YEARS

(Forero-Torres A, Yasenchak CA, Gruppo Cooperatore USA)

CLINICAL TRIALS AND OBSERVATIONS

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]

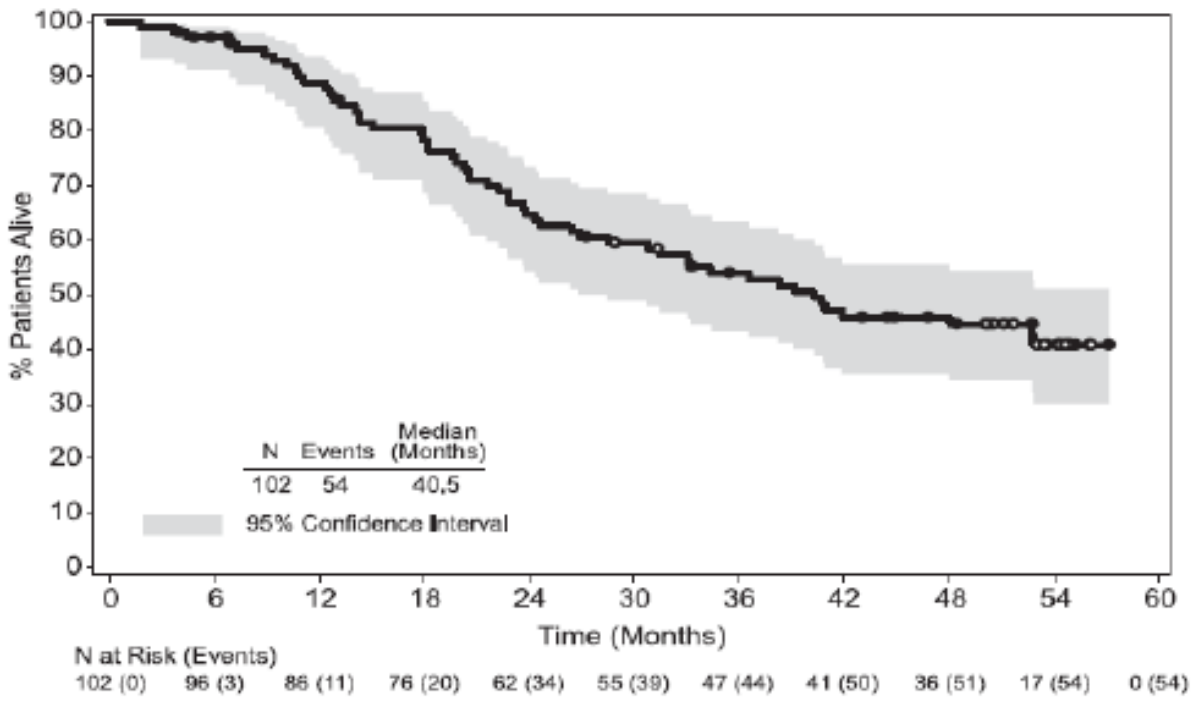
[1]University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA; [2]City of Hope National Medical Center, Duarte, CA; [3]Loyola University Medical Center, Maywood, IL; [4]Mayo Clinic, Rochester, MN; [5]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; [6]British Columbia Cancer Agency Center for Lymphoid Cancer, Vancouver, BC, Canada; [7]University Hospital of Cologne, Cologne, Germany; [8]Seattle Genetics, Inc., Bothell, WA; [9]Takeda Pharmaceuticals International Company, Cambridge, MA; and [10]Memorial Sloan Kettering Cancer Center, New York, NY

Key Points

- A total of 47% of patients who achieved CR on brentuximab vedotin remain progression-free after being followed a median of 53 months.
- Younger age, less functional impairment, and lower disease burden at baseline were associated with CR and prognostic for longer survival.

We present response and survival outcomes of a pivotal phase 2 trial of the antibody-drug conjugate brentuximab vedotin in patients with relapsed/refractory Hodgkin lymphoma following autologous stem cell transplant (N = 102) after a median observation period of approximately 3 years. Median overall survival and progression-free survival were estimated at 40.5 months and 9.3 months, respectively. Improved outcomes were observed in patients who achieved a complete remission (CR) on brentuximab vedotin, with estimated 3-year overall survival and progression-free survival rates of 73% (95% confidence interval [CI]: 57%, 88%) and 58% (95% CI: 41%, 76%), respectively, in this group (medians not reached). Of the 34 patients who obtained CR, 16 (47%) remain progression-free after a median of 53.3 months (range, 29.0 to 56.2 months) of observation; 12 patients remain progression-free without a consolidative allogeneic stem cell transplant. Younger age, good performance status, and lower disease burden at baseline were characteristic of patients who achieved a CR and were favorable prognostic factors for overall survival. These results suggest that a significant proportion of patients who respond to brentuximab vedotin can achieve prolonged disease control. The trial was registered at www.clinicaltrials.gov as #NCT00848926.
(*Blood*. 2015;125(8):1236-1243)

Updated Overall Survival



After a median follow-up period of approximately 3 years for all enrolled patients, 47% of patients (48/102) were alive. The estimated median OS was 40.5 months (95% CI: 28.7, –).

Gopal A, et al. ASH 2013, New Orleans, LA, USA (Abstract 4382)

Updated PFS

- The updated estimated median PFS per the investigator for all patients was 9.3 months (95% CI: 7.1, 12.2) 3 months longer than the median PFS of 6.1 months (95% CI: 4.4, 7.2; Table 1) that was observed on the patients' last systemic therapy prior to Brentuximab Vedotin

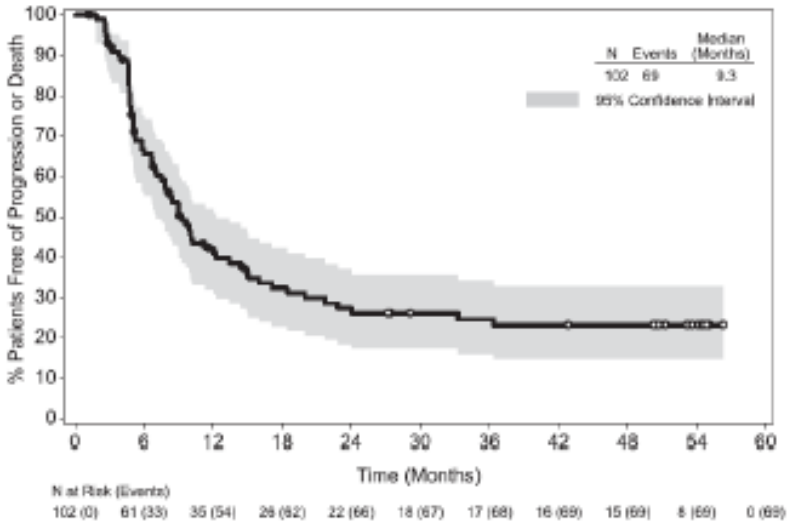
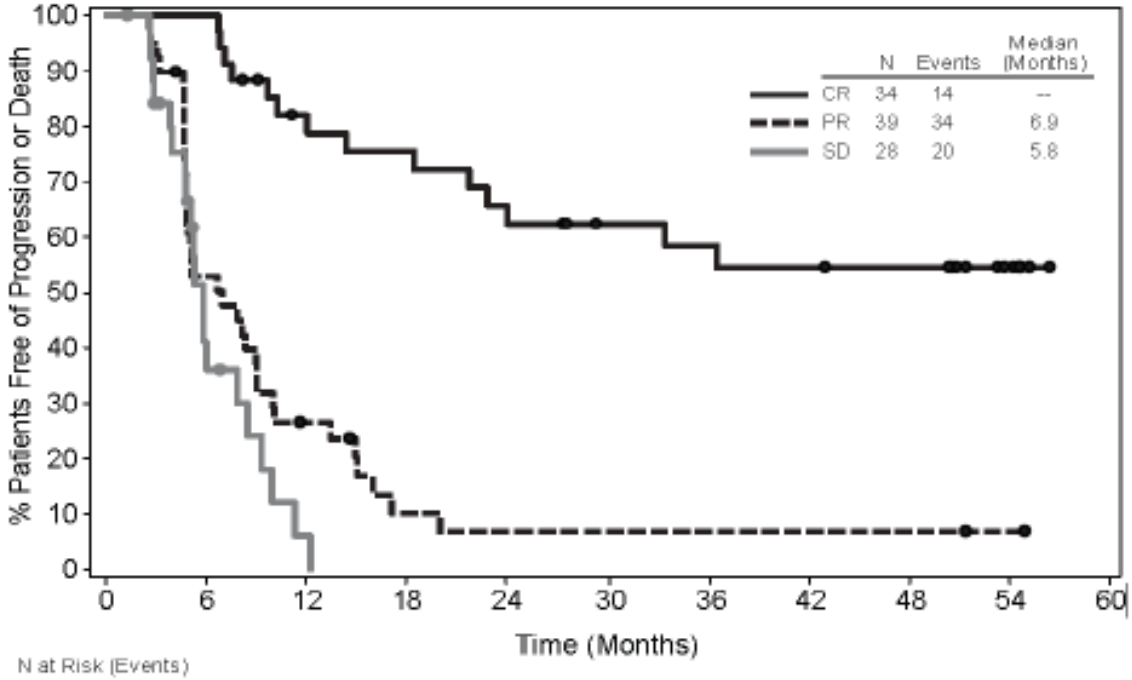


Table 1. Patient demographics and characteristics at enrollment

	All patients (N = 102)
Median time from initial HL diagnosis to first dose in months (range)	38.9 (12-220)
Stage at initial diagnosis, n (%)	
Stage I/II	51 (50)
Stage III	27 (26)
Stage IV	20 (20)
Unknown	4 (4)
ECOG performance status, n (%)	
Grade 0	42 (41)
Grade 1	60 (59)
Patients with primary refractory disease,* n (%)	72 (71)
Disease status relative to most recent prior therapy,† n (%)	
Relapse	59 (58)
Refractory	43 (42)
Median number of prior cancer-related systemic therapy regimens‡ (range)	3.5 (1-13)
Median PFS for most recent regimen in months (95% CI)	6.1 (4.4, 7.2)
Number of prior auto-SCTs, n (%)	
1	91 (89)
2	11 (11)
Median time from most recent auto-SCT to relapse after auto-SCT in months (range)	6.7 (0-131)

Durable Remissions in a Pivotal Phase 2 Study of Brentuximab Vedotin in Relapsed or Refractory Hodgkin Lymphoma

Progression-free survival by best response:



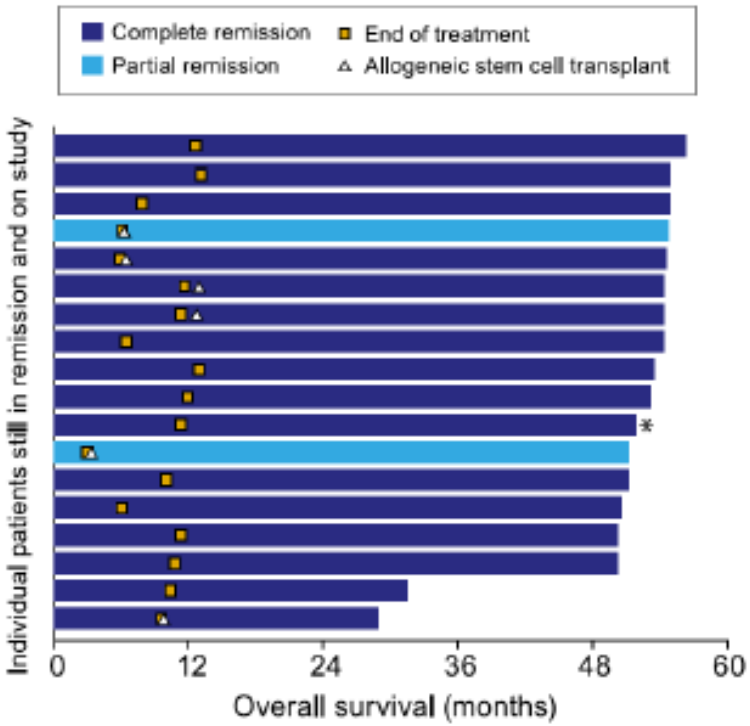
N at Risk (Events)

CR	34 (0)	34 (0)	25 (6)	23 (8)	20 (11)	16 (12)	15 (13)	14 (14)	13 (14)	7 (14)	0 (14)
PR	39 (0)	20 (18)	9 (28)	3 (33)	2 (34)	2 (34)	2 (34)	2 (34)	2 (34)	1 (34)	0 (34)
SD	28 (0)	7 (14)	1 (19)	0 (20)	0 (20)	0 (20)	0 (20)	0 (20)	0 (20)	0 (20)	0 (20)

Durable Remissions in a Pivotal Phase 2 Study of Brentuximab Vedotin in Relapsed or Refractory Hodgkin Lymphoma
Ajay K. Gopal et a l Blood December 22, 2014; DOI 10.1182/blood-2014-08-595801

Duration of response

Patients who remain in remission per the investigator following treatment with brentuximab vedotin



- **18 pts (25% ORR pts) still in remission without the start of a new therapy**
  *(Median FU **53,3 mos -> più di 4 anni**)*
  - **6 with consolidative Allo (4CR /2 PR)**
  - **12 without consolidative Allo**
- 16/34 CR (47%) of patients who achived CR on BV remain progression free after being followed for a median of 53 months
- 12/28 in CR (43%) without Allo (median observation time 52,5 mos)

Durable Remissions in a Pivotal Phase 2 Study of Brentuximab Vedotin in Relapsed or Refractory Hodgkin Lymphoma

Patient Characteristics and Overall Survival (multivariate analysis):

Characteristics	Hazard Ratio	95% CI	P
Age[a]	1.33	1.05, 1.69	0.016
Baseline ECOG performance status	2.05	1.13, 3.73	0.019
Grade 0[b]			
Grade 1			
Baseline SPD per investigator(cm^2)[c]	1.06	1.01, 1.10	0.009
Baseline ECOG performance status			0.004

a- Continuous variable; hazard ratio applies to 10-year increments
b- Reference level for the hazard ratio
c- Continuous variable; hazard ratio applies to 10-cm2 increments

Durable Remissions in a Pivotal Phase 2 Study of Brentuximab Vedotin in Relapsed or Refractory Hodgkin Lymphoma
Ajay K. Gopal et a l Blood December 22, 2014; DOI 10.1182/blood-2014-08-595801

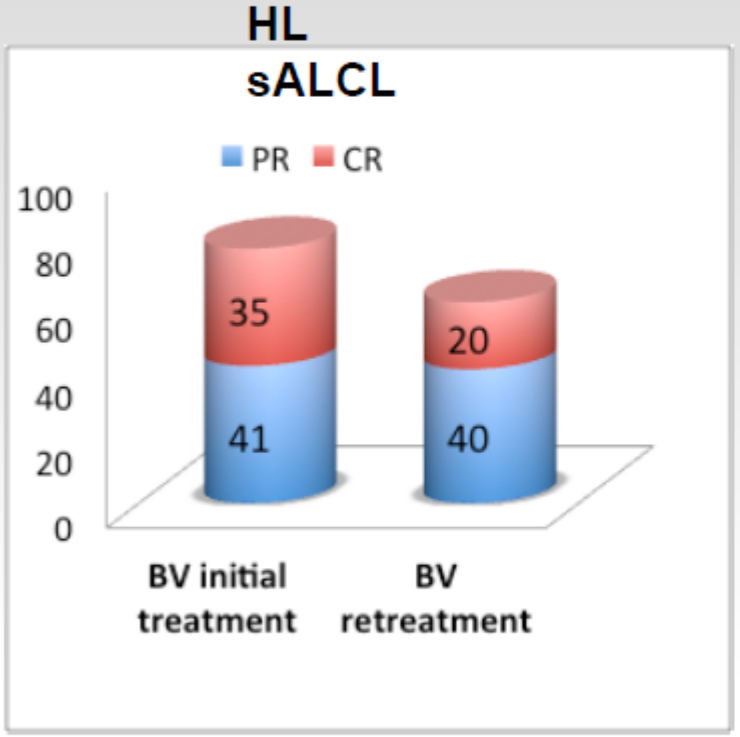
Durable Remissions in a Pivotal Phase 2 Study of Brentuximab Vedotin in Relapsed or Refractory Hodgkin Lymphoma

Conclusion:

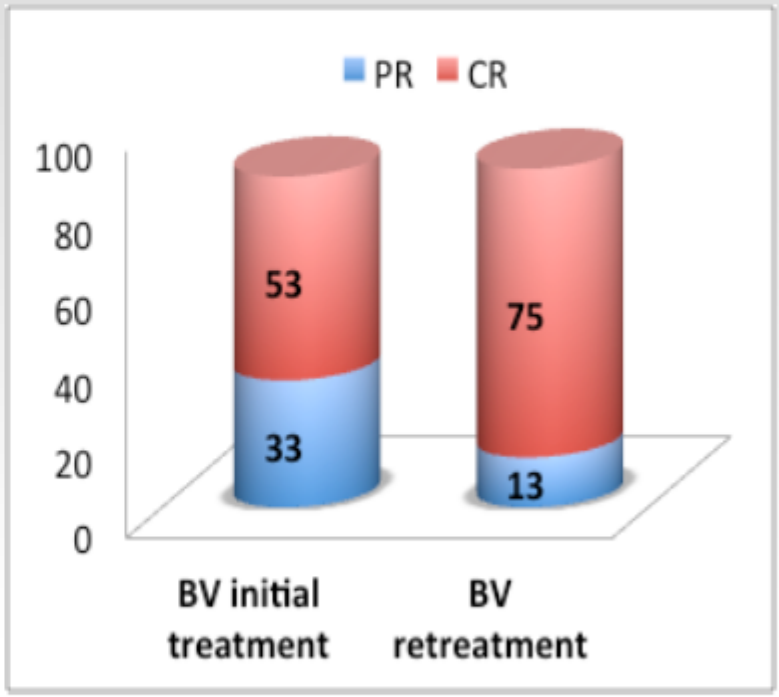
- Patients who achieved a CR had a longer OS compared to those without a CR.
- The estimated 3-year OS for the 34 patients with a CR to Brentuximab Vedotin was 73%.
- The estimated 3-year PFS was 80% for the subgroup of 6 patients with a CR who received a consolidative allo-SCT and 53% for the subgroup of 28 patients with a CR who did not receive a consolidative allo-SCT.
- Three-year PFS was estimated at 58% for the 34 patients with a CR to Brentuximab Vedotin and the median PFS for this patients has not been reached.
- Thirty-one of the 34 patients (91%) with a best response of CR had a longer PFS on Brentuximab Vedotin than their last prior therapy.

Durable Remissions in a Pivotal Phase 2 Study of Brentuximab Vedotin in Relapsed or Refractory Hodgkin Lymphoma
Ajay K. Gopal et a l Blood December 22, 2014; DOI 10.1182/blood-2014-08-595801

Brentuximab vedotin: Initial treatment vs. retreatment



N=102 N=15



N= 58 N=8

HL, Hodgkin lymphoma; sALCL, systemic anaplastic large cell lymphoma; BV, brentuximab vedotin; PR, partial response, CR, complete response

Bartlet N et al , ASCO 2012

Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies

Nancy L Bartlett[1*], Robert Chen[2], Michelle A Fanale[3], Pauline Brice[4], Ajay Gopal[5], Scott E Smith[6], Ranjana Advani[7], Jeffrey V Matous[8], Radhakrishnan Ramchandren[9], Joseph D Rosenblatt[10], Dirk Huebner[11], Pamela Levine[12], Laurie Grove[12] and Andres Forero-Torres[13]

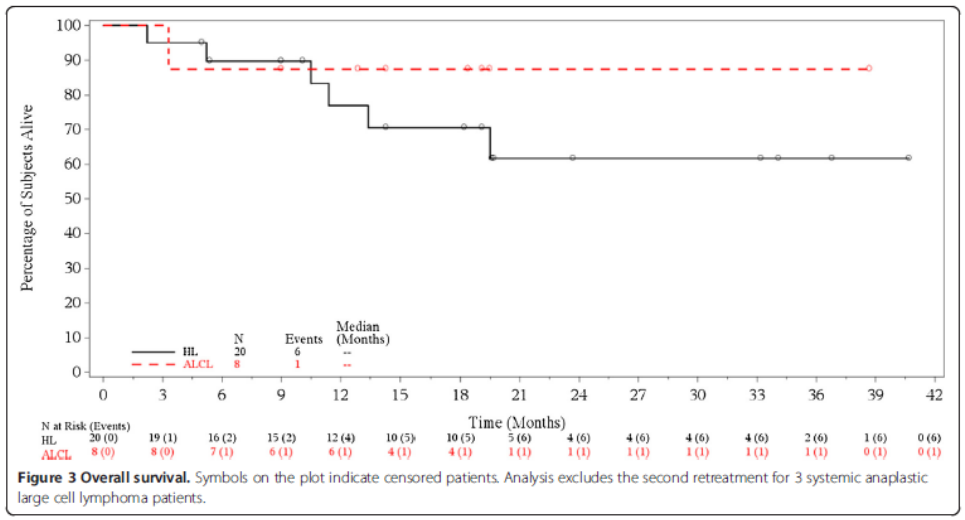


Figure 3 Overall survival. Symbols on the plot indicate censored patients. Analysis excludes the second retreatment for 3 systemic anaplastic large cell lymphoma patients.

Table 3 Treatment-emergent adverse events reported by at least 20% of patients and grade 3 and higher incidence of these events

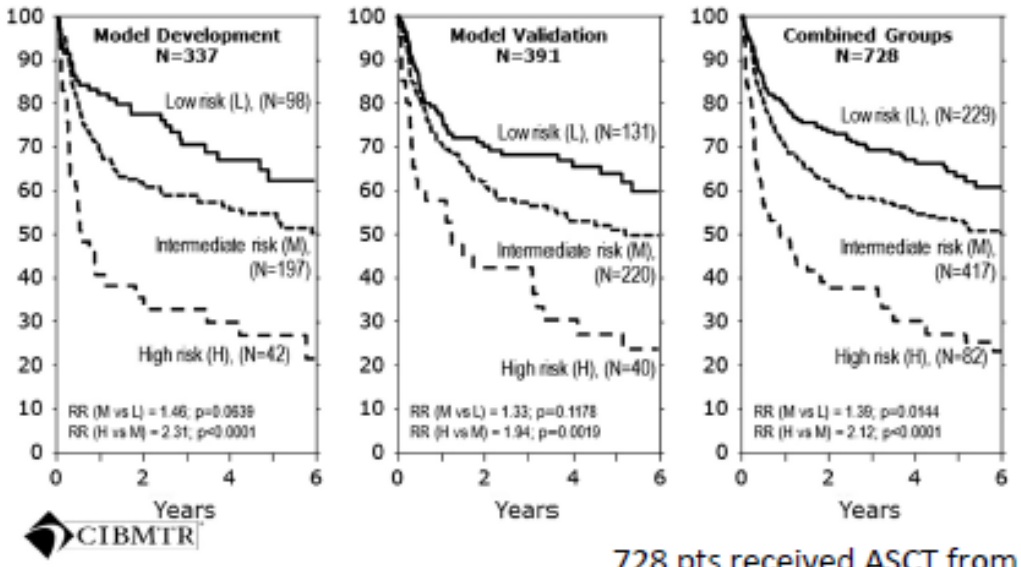
Event term	Treatment-emergent adverse events (any grade)	Any grade 3 events	Any grade 4 events	Any grade 5 events
Any event, n (%)	28 (97)	8 (28)	3 (10)	3 (10)
Peripheral sensory neuropathy	17 (59)	2 (7)	0	0
Fatigue	12 (41)	3 (10)	1 (3)	0
Nausea	12 (41)	1 (3)	0	0
Diarrhea	11 (38)	0	0	0
Arthralgia	8 (28)	2 (7)	0	0
Headache	8 (28)	0	0	0
Peripheral motor neuropathy	8 (28)	2 (7)	0	0
Pyrexia	8 (28)	0	0	0
Anemia	7 (24)	5 (17)	0	0
Dyspnea	7 (24)	1 (3)	1 (3)	0
Back pain	6 (21)	1 (3)	0	0

Bartlett NC et al. J Hematol Oncol 2014; 7:24

BRENTUXIMAB VEDOTIN COME CONSOLIDAMENTO POST-AUTOLOGO NEI PAZIENTI AD ALTO RISCHIO

Prognostic Model for PFS after ASCT

Probability of Progression-free Survival



728 pts received ASCT from 1996-2007

Risk factors	Score
PS < 90	1
Chemoresistant	1
≥ 3 regimens before ASCT	2
Extranodal at relapse/PD	2

Risk groups	Score	4-yr PFS
Low	0	71%
Intermediate	1-3	60%
High	4-6	42%

Hahn t, et al. Biol Blood Marrow Transplant 2013; 19: 1740-44

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 Grou

Summary

Background High-dose therapy followed by autologous stem-cell transplantation is standard of care for patients with relapsed or primary refractory Hodgkin's lymphoma. Roughly 50% of patients might be cured after autologous stem-cell transplantation; however, most patients with unfavourable risk factors progress after transplantation. We aimed to assess whether brentuximab vedotin improves progression-free survival when given as early consolidation after autologous stem-cell transplantation.

Methods We did this randomised, double-blind, placebo-controlled, phase 3 trial at 78 sites in North America and Europe. Patients with unfavourable-risk relapsed or primary refractory classic Hodgkin's lymphoma who had undergone autologous stem-cell transplantation were randomly assigned, by fixed-block randomisation with a computer-generated random number sequence, to receive 16 cycles of 1·8 mg/kg brentuximab vedotin or placebo intravenously every 3 weeks, starting 30–45 days after transplantation. Randomisation was stratified by best clinical response after completion of salvage chemotherapy (complete response *vs* partial response *vs* stable disease) and primary refractory Hodgkin's lymphoma versus relapsed disease less than 12 months after completion of frontline therapy versus relapse 12 months or more after treatment completion. Patients and study investigators were masked to treatment assignment. The primary endpoint was progression-free survival by independent review, defined as the time from randomisation to the first documentation of tumour progression or death. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01100502.

Findings Between April 6, 2010, and Sept 21, 2012, we randomly assigned 329 patients to the brentuximab vedotin group (n=165) or the placebo group (n=164). Progression-free survival by independent review was significantly improved in patients in the brentuximab vedotin group compared with those in the placebo group (hazard ratio [HR] 0·57, 95% CI 0·40–0·81; p=0·0013). Median progression-free survival by independent review was 42·9 months (95% CI 30·4–42·9) for patients in the brentuximab vedotin group compared with 24·1 months (11·5–not estimable) for those in the placebo group. We recorded consistent benefit (HR <1) of brentuximab vedotin consolidation across subgroups. The most frequent adverse events in the brentuximab vedotin group were peripheral sensory neuropathy (94 [56%] of 167 patients *vs* 25 [16%] of 160 patients in the placebo group) and neutropenia (58 [35%] *vs* 19 [12%] patients). At time of analysis, 28 (17%) of 167 patients had died in the brentuximab vedotin group compared with 25 (16%) of 160 patients in the placebo group.

Interpretation Early consolidation with brentuximab vedotin after autologous stem-cell transplantation improved progression-free survival in patients with Hodgkin's lymphoma with risk factors for relapse or progression after transplantation. This treatment provides an important therapeutic option for patients undergoing autologous stem-cell transplantation.

Moskowitz CH et al.
Lancet Oncol 2015

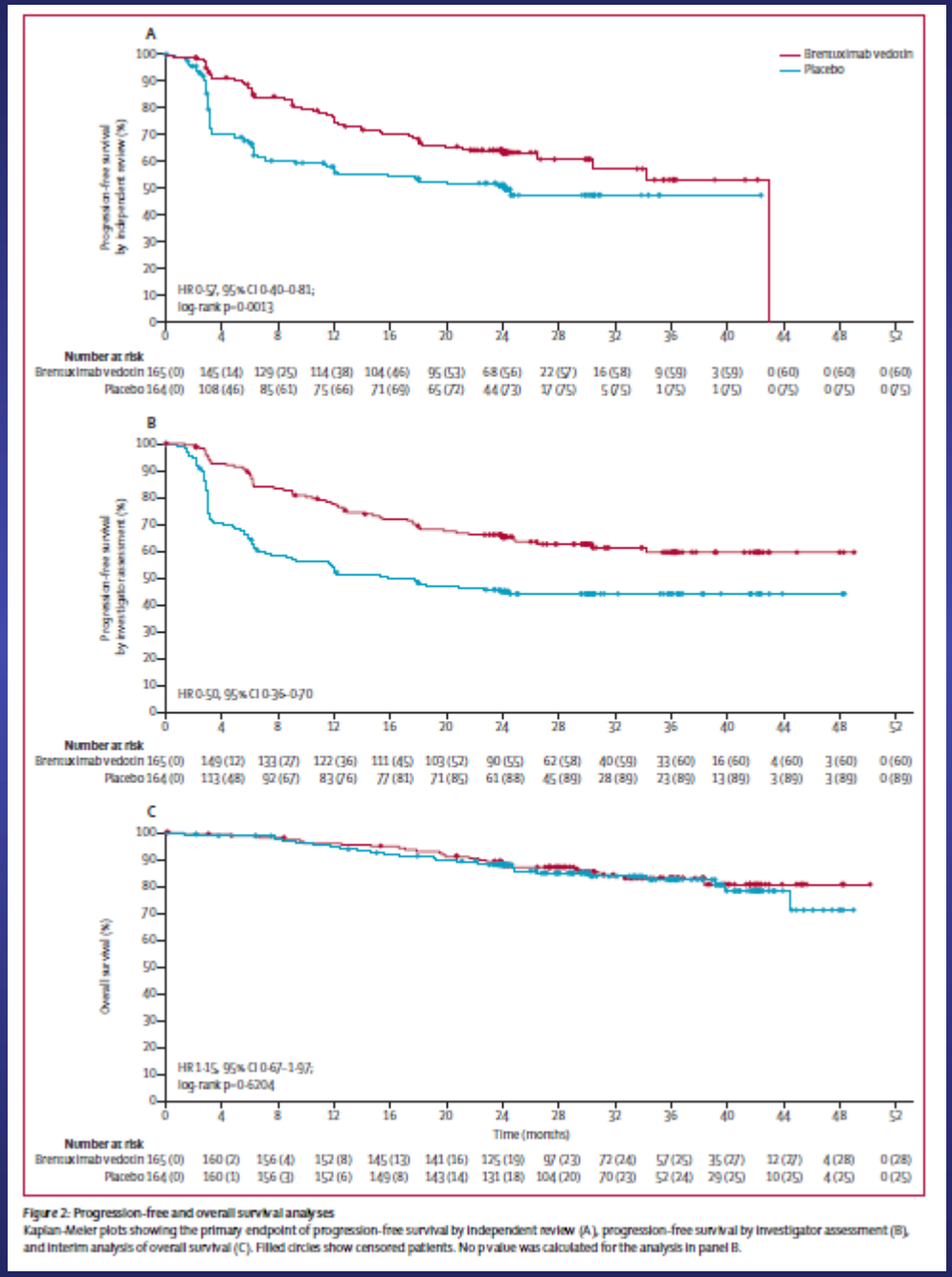


Figure 2: Progression-free and overall survival analyses
Kaplan-Meier plots showing the primary endpoint of progression-free survival by independent review (A), progression-free survival by investigator assessment (B), and interim analysis of overall survival (C). Filled circles show censored patients. No p value was calculated for the analysis in panel B.

Moskowitz CH et al.
Lancet Oncol 2015

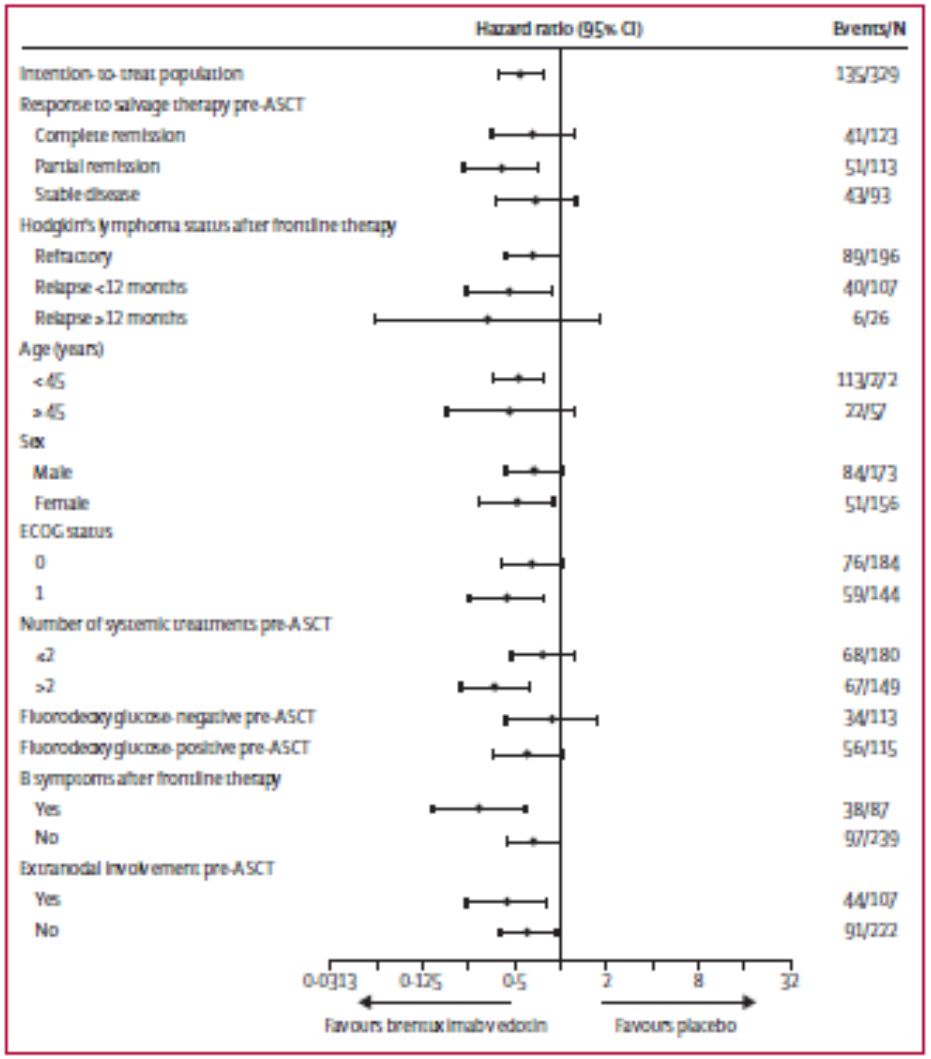
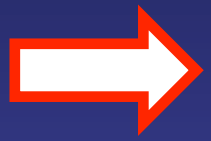


Figure 3: Subgroup analysis of progression-free survival by independent review
ASCT=autologous stem-cell transplantation. ECOG=Eastern Cooperative Oncology Group.

Moskowitz CH et al.
Lancet Oncol 2015



	Brentuximab vedotin group (n=167)		Placebo group (n=160)	
	Any grade	≥Grade 3*	Any grade	≥Grade 3
Any event	163 (98%)	93 (56%)	142 (89%)	51 (32%)
Peripheral sensory neuropathy	94 (56%)	17 (10%)	25 (16%)	2 (1%)
Neutropenia	58 (35%)	49 (29%)	19 (12%)	16 (10%)
Upper respiratory tract infection	44 (26%)	0	37 (23%)	2 (1%)
Fatigue	40 (24%)	3 (2%)	29 (18%)	4 (3%)
Peripheral motor neuropathy	38 (23%)	10 (6%)	3 (2%)	1 (1%)
Nausea	36 (22%)	5 (3%)	12 (8%)	0
Cough	35 (21%)	0	26 (16%)	0
Diarrhoea	33 (20%)	3 (2%)	16 (10%)	1 (1%)
Pyrexia	31 (19%)	3 (2%)	25 (16%)	0
Weight decreased	32 (19%)	1 (1%)	9 (6%)	0
Arthralgia	30 (18%)	1 (1%)	15 (9%)	0
Vomiting	27 (16%)	4 (2%)	11 (7%)	0
Abdominal pain	23 (14%)	3 (2%)	5 (3%)	0
Constipation	21 (13%)	4 (2%)	5 (3%)	0
Dyspnoea	21 (13%)	0	10 (6%)	1 (1%)
Decreased appetite	20 (12%)	1 (1%)	9 (6%)	0
Pruritus	20 (12%)	1 (1%)	12 (8%)	0
Headache	19 (11%)	3 (2%)	13 (8%)	1 (1%)
Muscle spasms	18 (11%)	0 (0%)	9 (6%)	0
Myalgia	18 (11%)	1 (1%)	6 (4%)	0
Chills	17 (10%)	0	8 (5%)	0
Paraesthesia	16 (10%)	3 (2%)	2 (1%)	0

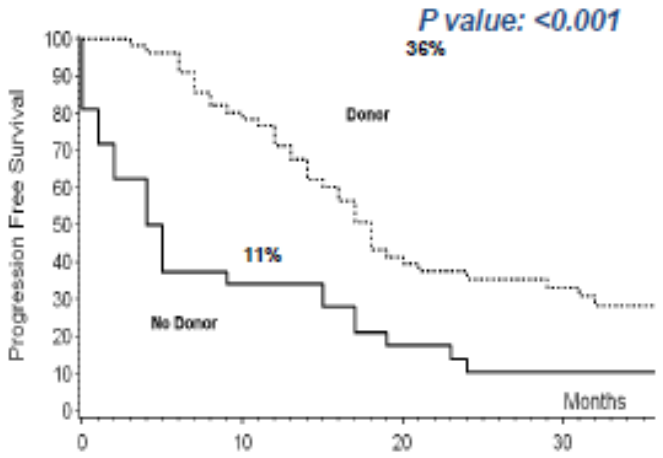
Data are n (%). *Inclusive of all treatment-emergent adverse events of grade 3 or higher severity with an incidence of 5% or more in the brentuximab vedotin group.

Table 3: Treatment-emergent adverse events with an incidence of 10% or more in the brentuximab vedotin group, in the safety analysis set

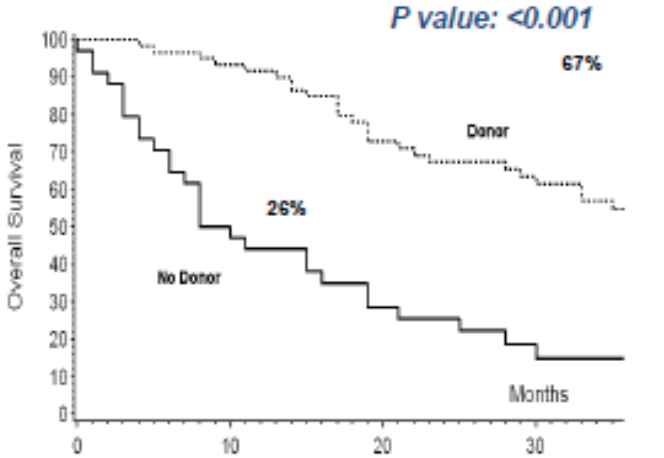
Moskowitz CH et al.
Lancet Oncol 2015

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

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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

Courtesy: A. Santoro

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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 363;19 NEJM.ORG NOVEMBER 4, 2010

BV POST ALLO-SCT, Gopal Blood 2012

- Relapsed CD30+ HL
- At least 100 days post allo-SCT
- No GvHD
- No anti-GvHD treatment or prophylaxis

→

- Brentuximab vedotin 1.2 or 1.8 mg/kg IV Q3wk†
- Best response assessed by investigator; based on Cheson 2007

→

- Evaluable

25 patients

Courtesy: A. Santoro

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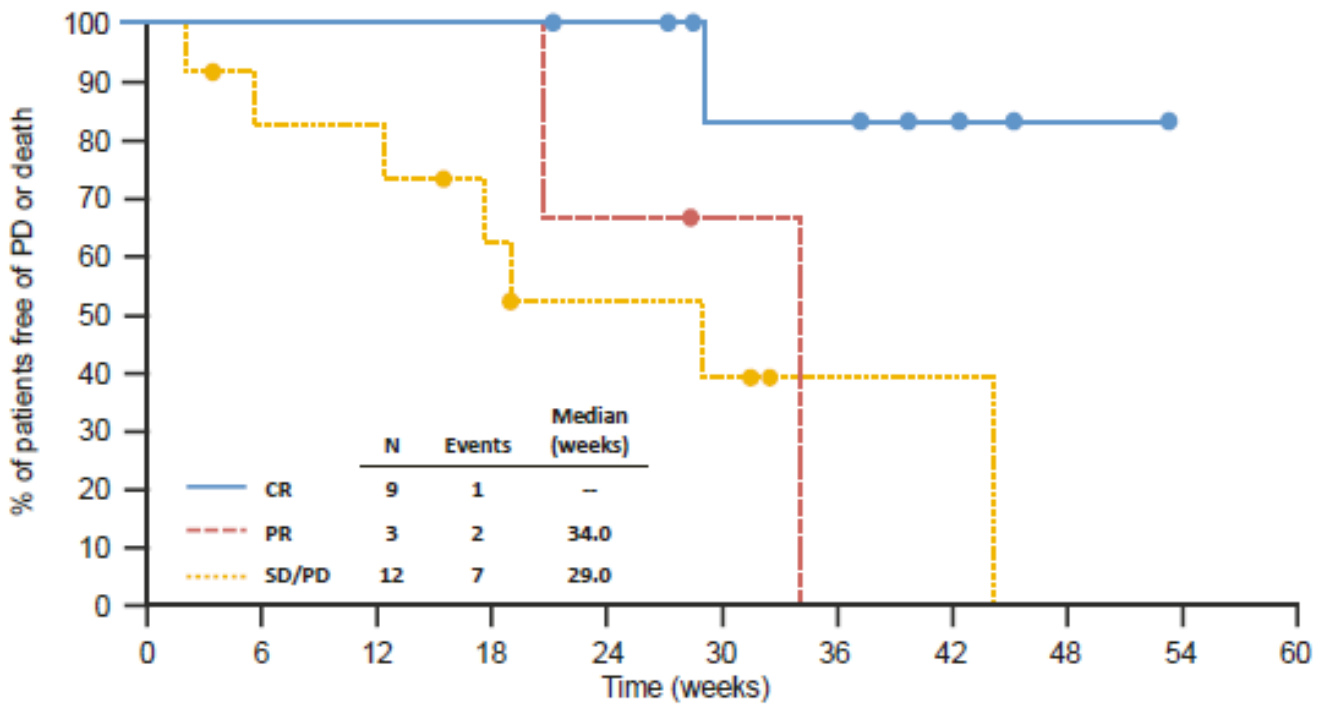
TREATMENT WITH BV POST ALLO-SCT

	N=25
Disease state prior to allo-SCT, n (%)	
Relapsed/refractory disease	13 (52)
Remission	7 (28)
Unknown	5 (20)
Median interval between allo-SCT and:	
Next subsequent treatment, months	12.5 (2–36)
First dose of brentuximab vedotin, months	42 (6–116)

Gopal A, et al. Blood 2012

Courtesy: A. Santoro

BV: PFS POST ALLO-SCT



Gopal A, et al. Blood 2012

Courtesy: A. Santoro

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BV IN HL PATIENTS POST ALLO-SCT COMPARED WITH HL PATIENTS IN SG035-0003

	Post allo-SCT patients N=25	SG035-0003[a] N=102
OR, %	50	75
CR, %	38	34
Disease control (CR + PR + SD), %	92	96
Median PFS, weeks (range)	7.8 (0.5–12.2+)	5.6 (NA)
95% CI	NA	(5.0, 9.0)
Median time to OR, weeks (range)	8.1 (5.3–32)	5.7 (5.1–56)
Patients with CR, n (%)	9 (38)	35 (34)
Median time to CR, weeks (range)	10.7 (6.3–32.0)	12 (5.1–56)

[a]Patients who had previously received allo-SCT were excluded

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Safety of BV in HL post allo-SCT vs HL patients in SG035-0003

	Post allo-SCT N=25	SG035-0003[b] N=102
Grade ≥3 AEs, %	72	55
AE leading to treatment discontinuation, %	36	20
Most common treatment-related grade ≥3 AEs, %		
Peripheral Sensory Neuropathy	48	42
Nausea	28	35
Alopecia	24	10
Neutropenia	24	19
Fatigue	20	34
Vomiting	20	13

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BRENTUXIMAB VEDOTIN IN COMBINAZIONE ALLA DIAGNOSI

Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study

Anas Younes, Joseph M Connors, Steven I Park, Michelle Fanale, Megan M O'Meara, Naomi N Hunder, Dirk Huebner, Stephen M Ansell

-51 pazienti alla diagnosi, stadio II A bulky o II B – IV

-ECOG PS $\leq$2

-BV alle dosi di 0.6-0.9-1.2 mg/Kg ogni 2 settimane + ABVD o AVD x 6 cicli

-Obiettivo primario: profilo di tossicità e individuazione della maximum tolerated dose (MTD)

Younes A et al. Lancet Oncol 2013

	Brentuximab vedotin and ABVD group (N=25)	Brentuximab vedotin and AVD group (N=26)
Median age (years), range	35, 19–59	33, 18–58
Sex		
Male	20 (80%)	17 (65%)
Female	5 (20%)	9 (35%)
Ethnic origin		
Asian	3 (12%)	1 (4%)
Black or African American	3 (12%)	1 (4%)
White	19 (76%)	24 (92%)
ECOG performance status		
0	13 (52%)	11 (42%)
1	12 (48%)	15 (58%)
Stage at initial diagnosis		
Stage IIA bulky	0	3 (12%)
Stage IIB	4 (16%)	4 (15%)
Stage IIIA	5 (20%)	3 (12%)
Stage IIIB	4 (16%)	5 (19%)
Stage IV	12 (48%)	11 (42%)
Bulky disease		
Yes	5 (20%)	12 (46%)
No	20 (80%)	14 (54%)
International Prognostic Score		
0–3	18 (72%)	20 (77%)
≥4	7 (28%)	6 (23%)

Data are n (%) unless otherwise indicated.

Table 1: **Baseline characteristics**

Younes A et al. Lancet Oncol 2013

	Brentuximab vedotin and AVD group (n=25)				Brentuximab vedotin and AVD group (n=26)			
	Adverse events, any grade	Any grade 3 events	Any grade 4 events	Any grade 5 events	Adverse events, any grade	Any grade 3 events	Any grade 4 events	Any grade 5 events
Neutropenia	20 (80%)	4 (16%)	16 (64%)	0	20 (77%)	1 (4%)	19 (73%)	0
Nausea	18 (72%)	0	0	0	22 (85%)	0	0	0
Peripheral sensory neuropathy	18 (72%)	0	0	0	19 (73%)	1 (4%)	0	0
Vomiting	15 (60%)	0	0	0	12 (46%)	0	0	0
Pyrexia	14 (56%)	1 (4%)	0	0	3 (12%)	0	0	0
Fatigue	11 (44%)	1 (4%)	0	0	13 (50%)	1 (4%)	0	0
Constipation	12 (48%)	0	0	0	9 (35%)	0	0	0
Chills	11 (44%)	0	0	0	2 (8%)	0	0	0
Diarrhoea	6 (24%)	0	0	0	11 (42%)	0	0	0
Insomnia	7 (28%)	0	0	0	10 (38%)	0	0	0
Bone pain	5 (20%)	0	0	0	10 (38%)	0	0	0
Alopecia	9 (36%)	0	0	0	9 (35%)	0	0	0
Cough	9 (36%)	1 (4%)	0	0	3 (12%)	0	0	0
Headache	9 (36%)	0	0	0	4 (15%)	0	0	0
Pulmonary toxic effects	9 (36%)	3 (12%)	2 (8%)*	1 (4%)	0	0	0	0
Decreased weight	8 (32%)	0	0	0	5 (19%)	0	0	0
Dyspnoea	8 (32%)	2 (8%)	1 (4%)	0	6 (23%)	1 (4%)	0	0
Decreased appetite	7 (28%)	0	0	0	7 (27%)	1 (4%)	0	0
Rhinorrhoea	7 (28%)	0	0	0	3 (12%)	0	0	0
Myalgia	3 (12%)	0	0	0	6 (23%)	0	0	0
Rash	3 (12%)	1 (4%)	0	0	6 (23%)	0	0	0
Arthralgia	4 (16%)	0	0	0	6 (23%)	0	0	0
Pain in extremity	0	0	0	0	6 (23%)	0	0	0
Dyspepsia	3 (12%)	0	0	0	6 (23%)	0	0	0
Anaemia	5 (20%)	5 (20%)	0	0	4 (15%)	2 (8%)	1 (4%)	0
Anxiety	5 (20%)	0	0	0	2 (8%)	0	0	0
Febrile neutropenia	5 (20%)	4 (16%)	1 (4%)	0	2 (8%)	2 (8%)	0	0
Hyperuricaemia	5 (20%)	0	0	0	0	0	0	0
Abdominal pain	1 (4%)	0	0	0	4 (15%)	0	0	0
Stomatitis	4 (16%)	0	0	0	4 (15%)	0	0	0
Back pain	3 (12%)	0	0	0	2 (8%)	0	0	0
Mucosal inflammation	3 (12%)	0	0	0	3 (12%)	0	0	0
Peripheral motor neuropathy	3 (12%)	0	0	0	3 (12%)	1 (4%)	0	0
Syncope	3 (12%)	3 (12%)	0	0	2 (8%)	2 (8%)	0	0

Events reported by at least 10% of all patients, and grade 3 and worse incidence of these events irrespective of relation to brentuximab vedotin. *While admitted to hospital for a grade 4 pulmonary toxic effect event, one patient experienced additional complications that led to a cerebral haemorrhage and brain death. One patient had a grade 5 event recorded during the study; the other patient was only discovered to have died after the reporting period so the event of pulmonary toxicity was ongoing at the time of study completion.

Table 2: Treatment-emergent adverse events

Younes A et al. Lancet Oncol 2013

	Brentuximab vedotin and ABVD group (n=25)	Brentuximab vedotin and AVD group (n=26)
Any event	11 (44%)	0
Pulmonary toxic effects	9 (36%)	0
Interstitial lung disease	1 (4%)	0
Pneumonitis	1 (4%)	0

Table 3: Patient incidence of pulmonary toxic effects

	Brentuximab vedotin and ABVD group (n=25)	Brentuximab vedotin and AVD group (n=26)
Cycle 2 PET scan per IRF*	22†	26
Negative	22 (100%)	24 (92%)
Positive	0	2 (8%)
Best response at end of front-line treatment per investigator	22‡	25§
Complete response	21 (95%)	24 (96%)
Progressive disease	0	1 (4%)
Not evaluable¶	1 (5%)	0
95% CI for complete response‖	77·2–99·9	79·7–99·9

IRF=independent review facility. *Using the Deauville criteria with uptake above liver background judged positive. †Denominator includes all patients with a response assessment at cycle 2; two patients did not have evaluable CT/PET scans at cycle 2 and one patient withdrew consent before cycle 2 and no post-baseline assessments captured. ‡Denominator includes all patients with a response assessment at end of first-line treatment; two patients withdrew from the study because of financial or immigration issues and did not have any assessments captured after cycle 2; one patient withdrew consent before cycle 2 and so has no post-baseline assessments were captured. §Denominator includes all patients with a response assessment at end of first-line treatment; one patient was lost to follow-up and did not have any assessments captured after cycle 2. ¶Patient had a grade 5 pulmonary toxic effect event before the end of front-line therapy. ‖A two-sided 95% exact CI was computed using the Clopper-Pearson method.

Table 4: Key response results for evaluable patients

Younes A et al. Lancet Oncol 2013

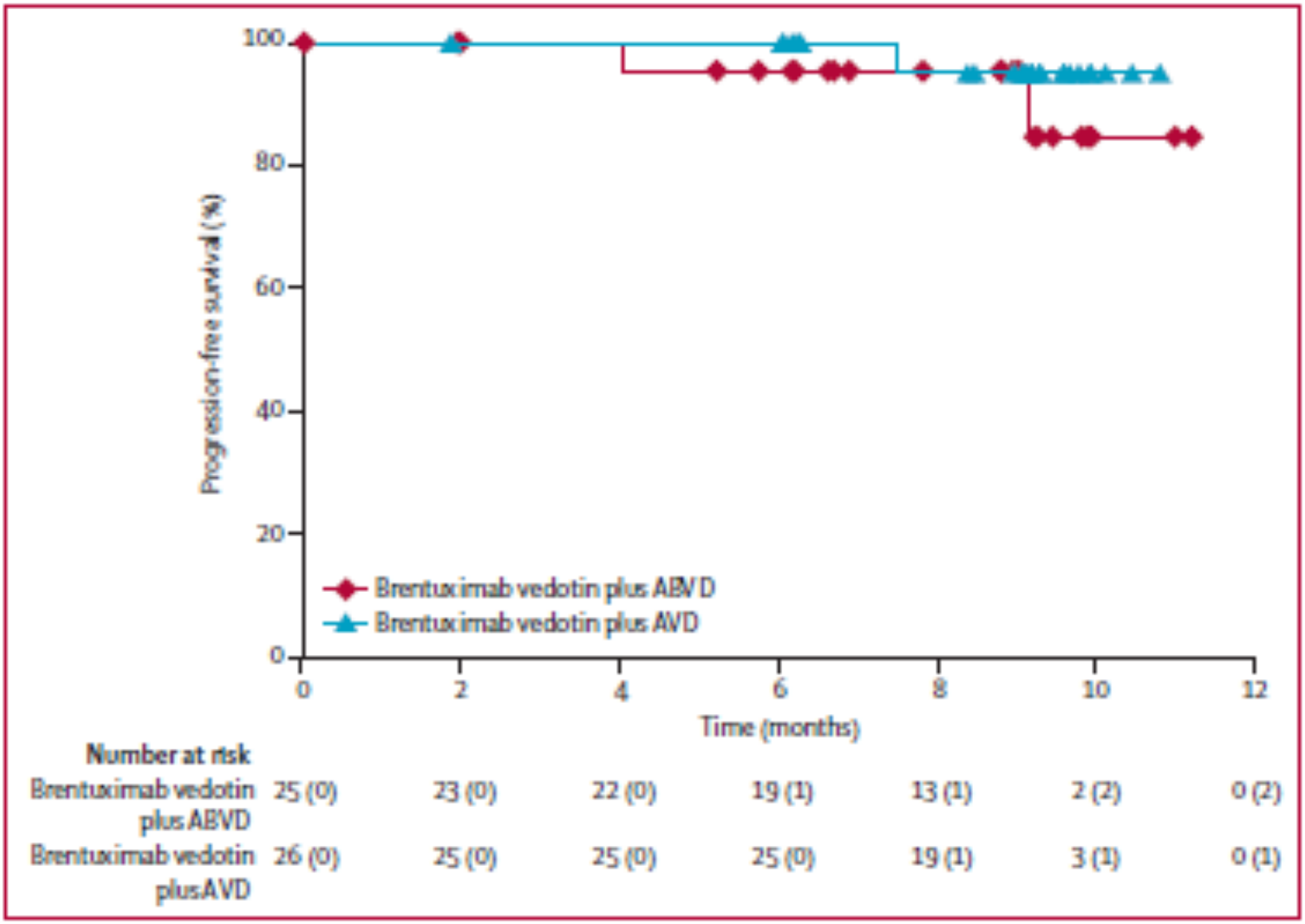


Figure 2: Progression-free survival per investigator assessment

Younes A et al. Lancet Oncol 2013

CONCLUSIONI

-La MTD di BV, quando associato alla chemioterapia, è pari a 1.2 mg/Kg ogni 2 settimane

-L'associazione di BV + Bleomicina può indurre una severa tossicità a livello polmonare (quindi MAI BV + ABVD !!)

-I più frequenti eventi avversi sono neutropenia, nausea e neuropatia sensitiva periferica, per lo più di grado 1-2 e facilmente gestibili

-Non incremento della neurotossicità periferica attesa nonostante l'associazione con un alcaloide della vinca

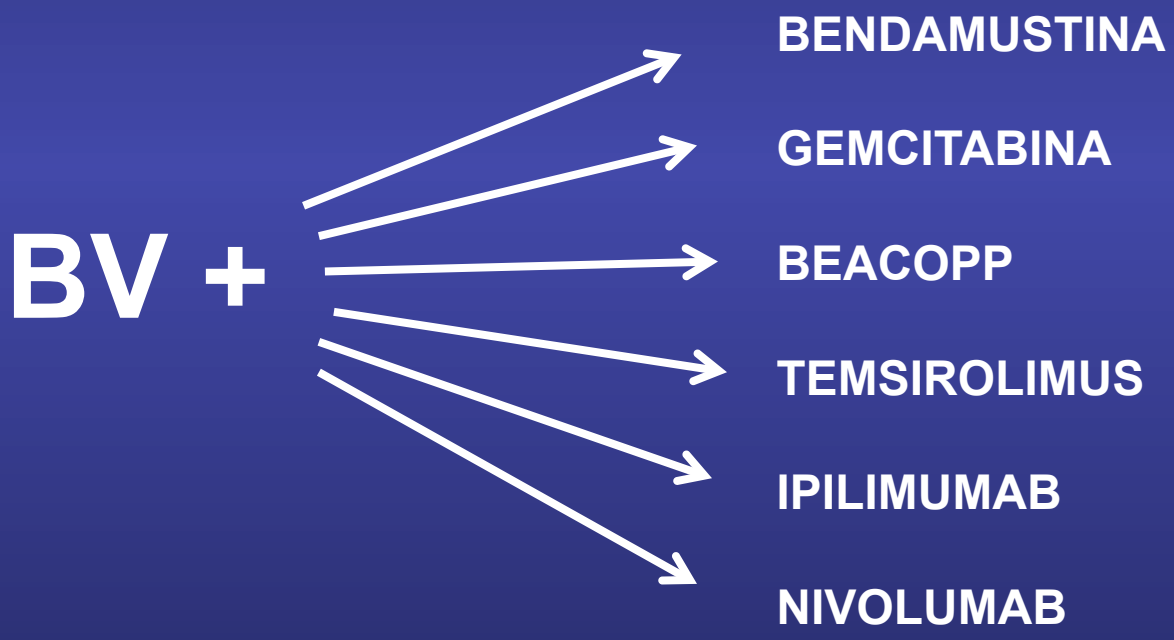
-La percentuale di RC (95-96%) appare più elevata rispetto a quanto riportato con ABVD da sola negli stadi avanzati (intorno all'80%)

ECHELON-1 STUDY

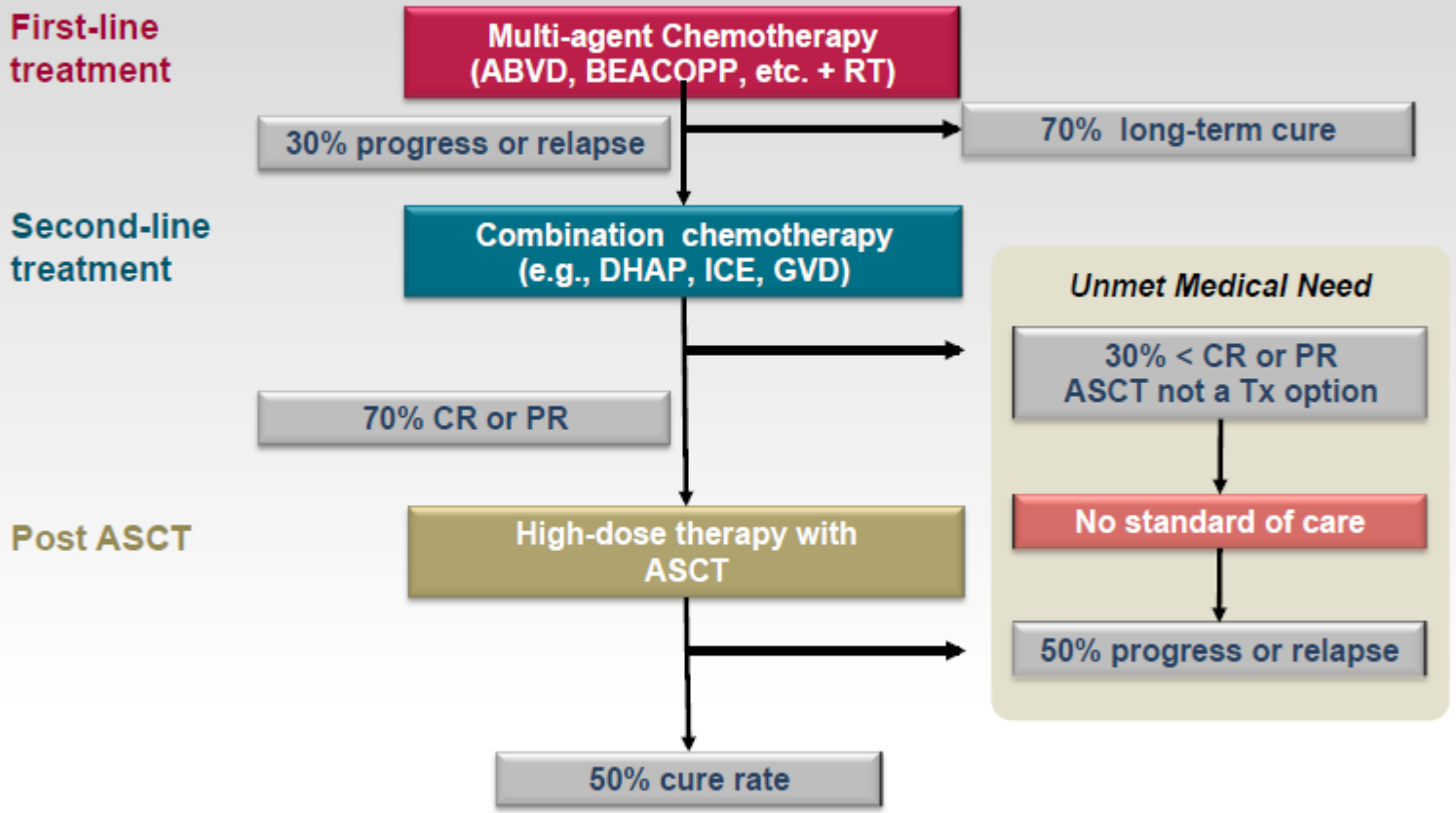
A randomized open-label phase 3 trial of BV + AVD versus ABVD as frontline therapy in patients with advanced Hodgkin lymphoma

(Clinicaltrials.gov, Number NCT 01712490)

BRENTUXIMAB VEDOTIN IN COMBINAZIONE



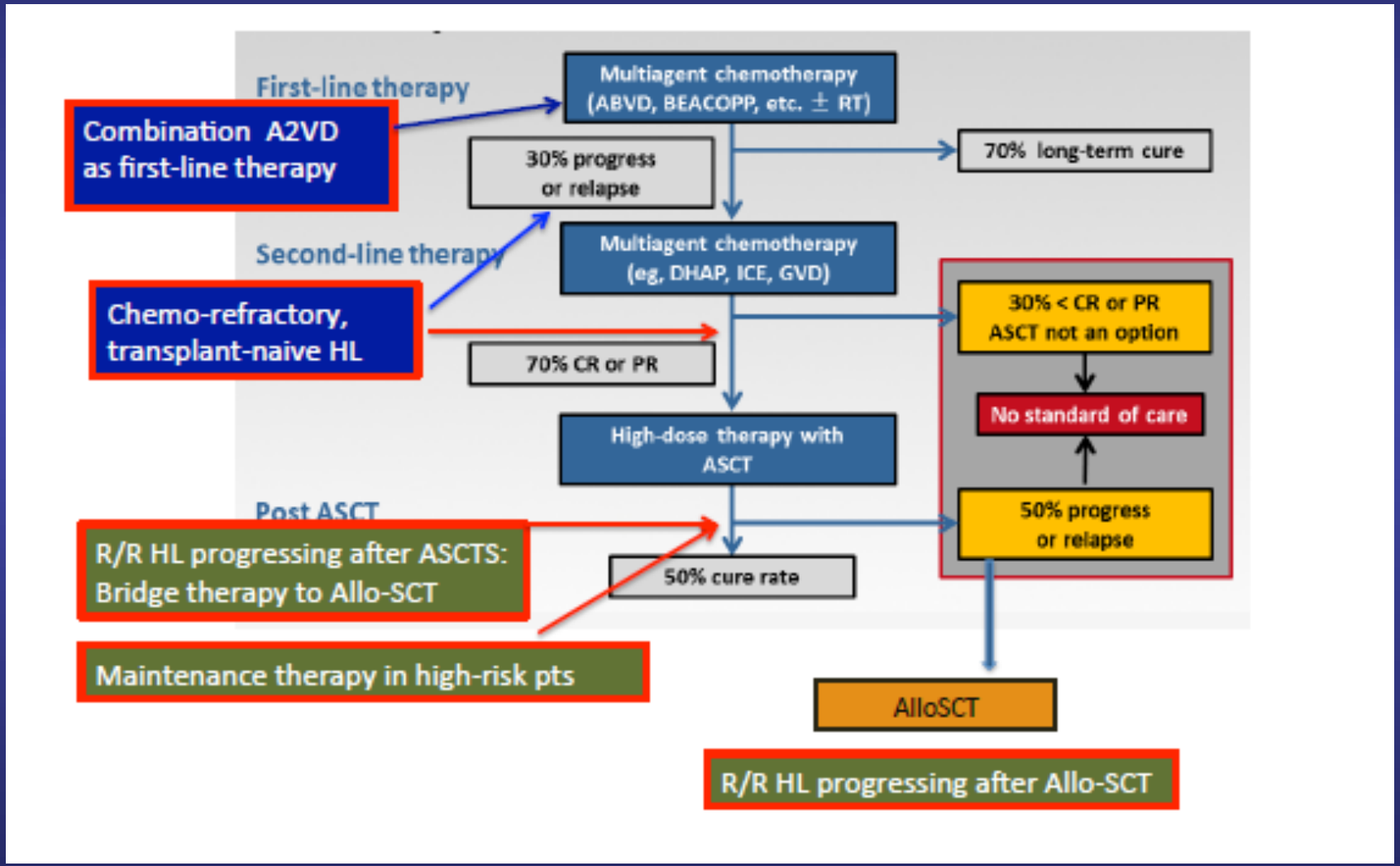
Defining the unmet medical need in HL



ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; RT, radiotherapy; DHAP, dexamethasone, high-dose cytarabine, cisplatin; ICE, carboplatin, etoposide, isofamide; GVD, gemcitabine, vinorelbine, pegylated liposomal doxorubicin; CR, complete response; PR, partial response; ASCT, autologous stem cell transplantation

CHMP Oral Presentation 22nd May 2012

What's the future of BRENTUXIMAB VEDOTIN in the management strategies of HL ?



Priority Paper Evaluation

Immunotherapy

Could bystander killing contribute significantly to the antitumor activity of brentuximab vedotin given with standard first-line chemotherapy for Hodgkin lymphoma?

Evaluation of: Younes A, Connors JM, Park SI *et al.* Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a Phase 1, open-label, dose-escalation study. *Lancet Oncol.* 14(13), 1348–1356 (2013). With exceptionally high response rates, the CD30-directed antibody–drug conjugate brentuximab vedotin (BV) was US FDA approved for treatment of patients with relapsed/refractory Hodgkin lymphoma (HL). Now in Phase I clinical trial, it has been shown that combining BV with multiagent chemotherapy (excluding bleomycin) as first-line treatment in HL patients with high-risk disease is feasible. Complete response rates were over 90% and toxicity was manageable. Given that the malignant cell population comprises a minority of HL lesions, and that BV releases a diffusible cytotoxin via a cathepsin B-cleavable linker, we argue that a significant proportion of the antitumor activity of BV can be attributed to bystander cytotoxicity in addition to direct killing of CD30-expressing malignant cells.

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Keywords: antibody–drug conjugate • bystander effect • cathepsin

EFFETTO BYSTANDER DEL BV

-l'incubazione del BV in una co-coltura di cellule di linfoma CD30+ e CD30- induce un effetto proapoptotico anche sulle cellule CD30- poiché il clivaggio del linker del BV nelle cellule CD30+ determina il rilascio di MMAE libera nel mezzo di coltura

-studi in vitro con anticorpi farmaco-coniugati dimostrano una significativa attività antitumorale da parte del farmaco libero in sede extracellulare

-Catepsina B e catepsina S sono secrete dalle cellule di R-S e si possono ritrovare nel plasma dei pazienti con LH a livelli significativamente più elevati rispetto ai controlli

-Catepsina B e catepsina S sono altamente espresse nei macrofagi tumore-associati nel LH, il cui contenuto nel linfonodo si associa ad una prognosi più favorevole

ELEMENTI DI DISCUSSIONE

-meccanismo d'azione del BV ancora da definire in tutti i suoi aspetti (target anche del microambiente?)

-non evidente correlazione tra livello di espressione del CD30 ed efficacia della molecola

-è possibile predire quali siano i pazienti che più possono beneficiare dall'impiego del BV ?

-meccanismi di resistenza al BV

-segnalazione di eventi avversi molto rari, ma molto severi (pancreatite, leucoencefalopatia multifocale progressiva)