haematologica
the hematology journal

Early Release Paper

Brentuximab vedotin in relapsed/refractory Hodgkin's lymphoma: Italian experience and results of the use in the daily clinic outside clinical trials

by Pier Luigi Zinzani, Simonetta Viviani, Antonella Anastasia, Umberto Vitolo, Stefano Luminari, Francesco Zaja, Paolo Corradini, Michele Spina, Ercole Brusamolino, Alessandro Massimo Gianni, Armando Santoro, Barbara Botto, Enrico Derenzini, Cinzia Pellegrini, and Lisa Argnani

Haematologica 2013 [Epub ahead of print]

Citation: Zinzani PL, Viviani S, Anastasia A, Vitolo U, Luminari S, Zaja F, Corradini P, Spina M, Brusamolino E, Gianni AM, Santoro A, Botto B, Derenzini E, Pellegrini C, and Argnani L. Brentuximab vedotin in relapsed/refractory Hodgkin's lymphoma: Italian experience and results of the use in the daily clinic outside clinical trials. Haematologica. 2013; 98:xxx
doi:10.3324/haematol.2012.083048

Haematologica (pISSN: 0390-6078, eISSN: 1592-8721, NLM ID: 0417435, www.haematologica.org) publishes peer-reviewed papers across all areas of experimental and clinical hematology. The journal is owned by the Ferrata Storti Foundation, a non-profit organization, and serves the scientific community with strict adherence to the principles of open access publishing (www.doaj.org). In addition, the journal makes every paper published immediately available in PubMed Central (PMC), the US National Institutes of Health (NIH) free digital archive of biomedical and life sciences journal literature.

DOI: 10.3324/haematol.2012.083048

Original article: Brentuximab vedotin in relapsed/refractory Hodgkin's lymphoma: Italian experience and results of the use in the daily clinic outside clinical trials

Pier Luigi Zinzani[1], Simonetta Viviani[2], Antonella Anastasia[3], Umberto Vitolo[4], Stefano Luminari[5], Francesco Zaja[6], Paolo Corradini[7], Michele Spina[8], Ercole Brusamolino[9], Alessandro M. Gianni[2], Armando Santoro[3], Barbara Botto[4], Enrico Derenzini[1], Cinzia Pellegrini[1] and Lisa Argnani[1].

[1]Institute of Hematology "L. and A. Seràgnoli", S.Orsola-Malpighi Hospital, Bologna, Italy;

[2] Medical Oncology Unit 2, Department of Medical Oncology Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy;

[3]Department of Oncology and Hematology Humanitas Cancer Center, Milano, Italy;

[4]Azienda Ospedaliera Città della Salute e della Scienza di Torino, Torino, Italy;

[5]Department of Oncology, Hematology and Respiratory Disease University of Modena and Reggio Emilia, Modena, Italy;

[6]Clinic of Hematology DISM, AOU SM Misericordia, Udine, Italy;

[7]Division of Hematology, IRCCS Istituto Nazionale dei Tumori, University of Milano, Milano, Italy;

[8]Division of Medical Oncology A, National Cancer Institute, Aviano, Italy;

[9]Clinic of Hematology IRCSS Pol. S.Matteo, Pavia, Italy.

Running Title: Brentuximab vedotin in relapsed Hodgkin's lymphoma

Corresponding author:

Prof. Pier Luigi Zinzani

Institute of Hematology "L. and A. Seràgnoli"

S.Orsola-Malpighi Hospital

Via Massarenti 9 – 40138 Bologna Italy

DOI: 10.3324/haematol.2012.083048

Phone: +39 0516363680;

Fax: +39 0516364037; E-mail: pierluigi.zinzani@unibo.it

Abstract word count: 236

Text word count: 2048

Tables: 3

Figures: 4

Supplemental files: 17 [15 (coi_disclosure for each author) + 1 Author contribution form+1 CTA form]

Authorship and Disclosures

PLZ was the principal investigator and takes primary responsibility for the paper; PLZ and LA gave substantial contributions to conception and design; PLZ, SV, AA, UV, SL, FZ, PC, MS, EB, AMG, AS, BB, ED, CP and LA were responsible for collection of data, interpretation of data, preparation of the text, final approval of the version to be published. PLZ and LA performed data analysis. The authors report no potential conflicts of interest.

Keywords: brentuximab vedotin, Hodgkin's lymphoma, refractory, relapsed

DOI: 10.3324/haematol.2012.083048

Abstract

Clinical trials results indicate that brentuximab vedotin brings considerable promise for the treatment of patients with relapsed or refractory Hodgkin's lymphoma.

A retrospective multicenter study was conducted on 65 heavily pretreated patients who underwent therapy through a Named Patient Program in Italy (non trial-setting). The primary study endpoint was the objective response rate; secondary endpoints were safety, overall survival and progression free survival.

Best overall response rate (70.7%), including 21.5% complete responses, was observed at the first restaging after the third cycle. After a median follow up of 13.2 months, overall survival at 20 months was 73.8% and progression free survival at 20 months was 24.2%. Globally 9 patients are in continuous complete response with a median follow up of 14 months (range 10-19 months). Four patients proceeded to autotransplant and 9 to allotransplant. The most frequent extra-hematological toxicity was peripheral neuropathy, observed in 21.5% of cases (9 patients with grade 1/2 and 5 patients with grade 3/4); neurological toxicity lead to discontinuation for 3 patients and to dose reduction for 4 ones. In general the treatment was well tolerated and toxicities, both hematological and extra-hematological, were manageable.

This report indicates and confirms that single agent brentuximab vedotin is effective and safe also when used in the standard everyday clinical practice outside a clinical trial. Best overall responses were recorded after 3/4 cycles and showed that brentuximab vedotin provides an effective bridge to further therapeutic interventions.

DOI: 10.3324/haematol.2012.083048

Introduction

Based primarily on clinical advances optimizing systemic cytotoxic chemotherapy over the last several decades, patients with newly diagnosed Hodgkin lymphoma (HL) have an excellent prognosis after frontline therapy, resulting in a 5-year progression-free survival (PFS) rate of 75-80%.[1,2] In addition, the standard approach for relapsed HL patients, salvage chemotherapy followed by autologous stem cell transplantation (ASCT), leads to a long-term disease-free survival for 40-50% of patients.[3-5] However, curing HL patients who have refractory disease after salvage chemotherapy, who relapse after ASCT, or those who are not candidates for ASCT, remains a clinical challenge due to limited effective treatments and with a median overall survival (OS) of 2-3 years. Although there are several promising agents currently under investigations in HL,[6-10] novel therapies that are well tolerated with minimal long-term complications are needed for these patients.

Brentuximab vedotin (BV) is a novel antibody-drug conjugate targeting CD30 linked to a payload comprising a potent synthetic antitubulin chemotherapeutic agent, monomethyl auristatin E. Cell surface expression of CD30 is characteristic of the malignant Hodgkin Reed-Sternberg cells. A multicenter phase II trial of BV in patients with HL recurring after ASCT demonstrated an overall response rate of 75% and a complete response (CR) rate of 34% with a median duration of 20.5 months.[11] After accelerated approval by US FDA, eligible patients in Italy were granted early access through a Named Patient Program (NPP). Herein, we report this Italian multicenter experience with BV in patients with heavily pretreated relapsed and/or refractory HL.

DOI: 10.3324/haematol.2012.083048

Methods

An observational multicenter retrospective study was conducted to analyze outcome and toxicity data of patients managed in a non-trial setting. The study was approved by our institutional board (Azienda Ospedaliera di Bologna, Policlinico S.Orsola-Malpighi, coordinating center) and by all involved Ethical Committees and registered in the Italian Registry of Observational Studies (AIFA, id551). All participants gave written informed consent in accordance with the Declaration of Helsinki.

A shared database was used after the approval of all the authors and variables were strictly defined to avoid bias in reporting data.

From December 2010 to August 2011, a total of 9 Italian centers utilized BV according to the NPP in 65 patients with refractory or relapsed HL. All patients had histologically confirmed CD30+ disease; all patients were relapsed after prior ASCT or relapsed after at least two lines of chemotherapy if not ASCT candidates due to insufficient stem cell collection or chemorefractory disease. Participants had an ECOG performance ≤2, and normal organ function including peripheral blood counts within the normal range. All patients underwent baseline assessments including physical examination, routine hematology and biochemistry as well as PET/CT scan prior to therapy.

Patients received a 30-minute infusion of BV at the dose of 1.8 mg/kg of body weight every 3 weeks (for a maximum of 16 cycles) without any routine premedication prior to the first dose. However, patients who experience an infusion-related reaction received subsequent premedication consisting of acetaminophen (500 mg orally) and chlorphenamine (10mg IV) or according to institutional standards.

The primary endpoint of the study was the objective response rate; secondary endpoints were safety, overall survival and progression free survival.

DOI: 10.3324/haematol.2012.083048

In the absence of specific indication, response was assessed by PET/CT scan after cycle 3 and 8 (PET3, PET8) and at discontinuation as the pivotal study reports,[11] using the International Working Group revised response criteria for malignant lymphoma.[12]

Safety and tolerability were evaluated by recording incidence, severity, and type of any adverse event according to NCI CTCAE version 3.0; gastrointestinal side effects were treated according to institutional guidelines and granulocyte colony stimulating factors were utilized as secondary prophylaxis of neutropenia complications. Dose reduction of BV to 1.2 mg/kg was recommended for grade ≥3 toxicity in the subsequent cycles.

OS was defined as the time from initiation of therapy to death from any cause and was censored at the date of last available follow up. PFS was measured from initiation of therapy to progression, relapse, or death from any cause and was censored at the date of last available follow up.

Demographics and patients' characteristics were summarized by descriptive statistics.

Survival functions were estimated by using the Kaplan-Meier[13] method and were compared using log-rank test.

Statistical analyses were performed with Stata 11 (StataCorp LP, TX) and p values were set at 0.05.

Results

Characteristics of the 65 patients are summarized in Table 1. The median age at diagnosis was 27.5 years (range, 12-66 years); thirty-four were males and 31 were females. Fifty patients (77%) had a baseline ECOG performance status of 0 or 1 and fifteen (23%) had an ECOG status of 2. Twenty-nine patients (44.5%) had systemic symptoms at baseline.

DOI: 10.3324/haematol.2012.083048

The median number of prior cancer-related systemic regimens was 4 (range, 2-13) including high dose chemotherapy and ASCT or allogeneic stem cell transplant. Thirty-nine patients (60%) had received prior radiation therapy. For each patient the status after both frontline therapy and most recent therapy was collected. Forty-five patients (69%) had disease that was refractory to frontline therapy and 52 patients (80%) had disease that was refractory to last therapy before BV. Fifty-seven patients (87.6%) had previously failed ASCT and, in addition, 3 (4.6%) of these patients had also failed allogeneic transplant; the remaining 8/65 patients did not previously received ASCT because stem cell collection was not possible.

Safety

All patients received at least three doses of BV and were included in the safety population; patients received a median of eight cycles of BV (range 3-16). In general, the treatment was well tolerated and the toxicity profile was very similar to the previously published data. Dose reduction (to 1.2 mg/kg) because of grade 3-4 toxicity was necessary in only four patients (all for peripheral neuropathy). Globally the neurological toxicity was observed in 14 (21.5%) patients: peripheral sensory neuropathy grade 1/2 was documented in nine patients and grade 3/4 was reported in five patients (in one of these patients there was also a grade 4 peripheral motor neuropathy). Resolution or improvement of peripheral neuropathy was observed in 90% of patients with a median time to resolution or improvement of 12 weeks. Three patients had to stop treatment because of peripheral neuropathy. The other grade 3/4 adverse events were neutropenia (*N*=3), thrombocytopenia (*N*=3), diabetes (*N*=1), and aspergillosis of lung and liver (*N*=1); the relationship of the aspergillosis to BV is therefore unclear.

DOI: 10.3324/haematol.2012.083048

Effectiveness

The best responses were seen at PET3 evaluation with 14 (21.5%) CRs, 32 (49.2%) PRs, 11 SDs and 8 PDs reaching at this time-point the best ORR of 70.7%.

Immediately after PET3 evaluation, 6 patients discontinued the BV treatment: 2 patients died (one patient due to PD and 1 CR patient due to second neoplasia: an acute myeloid leukemia), 2 SD patients underwent allogeneic transplant, 1 PD patient was shifted to bendamustine therapy, and 1 PD patient was lost to follow-up.

Before the second interim evaluation scheduled after 8 cycles (PET8), other 15 patients discontinued the BV treatment: nine patients due to PD, two patients due to adverse events (one for diabetes and one for infection, respectively), two patients proceeded to ASCT and two patients proceeded to allogeneic transplant.

Thus, forty-four patients completed eight cycles of BV and underwent PET8 evaluation: ten (22.7%) patients were in CR and ten (22.7) in PR, with an ORR of 45.4%.

Figure 1 summarizes the outcome of the whole study population at PET3 and PET8 evaluations.

From this point only 15 patients have continued the BV treatment and only two patients have completed the scheduled 16 cycles.

All in all, 14 patients obtained a CR within the first three cycles of BV therapy. Table 2 provides a summary of patient demographics, disease characteristics, and prior treatments for these 14 patients who obtained a CR. All patients underwent ABVD therapy in frontline treatment. In terms of the number of BV cycles, the median number was six and, in particular, three patients received three cycles, two patients five cycles, four patients six cycles, one patient eight cycles, two patients nine cycles, one patient ten cycles, and one patient 16 cycles. Two out of 14 patients were not pretreated with ASCT and one patients received both ASCT and allogeneic transplant before BV. Among these 14 patients, four died: one for second neoplasia (acute myeloid leukemia after four months), one for post-

DOI: 10.3324/haematol.2012.083048

transplant lymphoproliferative disease, two for lymphoma progression (one after ASCT and one after allogeneic transplant). The outcome of remaining ten CR patients is reported in Figure 2.

Four out of ten patients proceeded to allotransplant and all of them are in continuous CR (CCR) after 10, 15, 16, and 20 months, respectively. Three patients received ASCT and they are in CCR after 11, 14, and 14 months, respectively. One patient had a relapse after 11 months (he had a further treatment with bendamustine obtaining a PR and then underwent allogeneic transplant). The last two patients are in CCR after 10 and 13 months without any transplant consolidation. The specific characteristics of these last two patients were: the former was refractory to the last prior treatment (ASCT) and globally he had 5 prior chemotherapy regimens; the latter had a relapse at the last treatment prior to BV (allogeneic transplant) and he received 11 prior chemotherapy regimens. In particular, these two patients received 9 and 16 cycles, respectively; both reported peripheral sensory neuropathy probably related to drug (grade 2/3 and grade 3, respectively) leading to dose reduction of BV.

The final response of the whole sample was as follows: 14 CRs (21.5%), 5 partial responses (PRs, 7.7%), 6 stable diseases (SDs) and 40 PDs.

Globally, with a median follow up of 13.2 months a total of 49 out of 65 patients were alive at the last available follow up: OS at 20 months was 73.8% and the median OS has not been reached yet (Figure 3 A). Global PFS at 19.4 months was 24.2%, the median was achieved at 6.8 months (Figure 3 B). Estimated PFS as a function of the achieved response did not show statistically significant differences (p=0.087) between CR (62.5%), PR (80.0%) and SD patients (83.3%) (Figure 4).

Subset of patients without prior ASCT. Among these eight patients, three are in CCR after consolidation with ASCT after 11, 14, and 14 months, respectively.

DOI: 10.3324/haematol.2012.083048

Subset of patients with prior allogeneic transplant. Among these three patients, one is in CCR after 13 months.

Subset of patients who underwent allogeneic transplant after BV. Nine patients had allogeneic transplant after a median of 6 BV cycles (range, 3-11); five of them were in CR, one in PR, two in SD, and one in PD. After the transplant, five patients are in CR (four patients maintained the CR previously obtained with BV, one patient converted from PR to CR and another patient died after 7 months for transplant related toxicity, namely post-transplant lymphoproliferative disorder), two patients are in PR and one patient has to be evaluated after the transplant.

Discussion

These data on BV for patients treated within the NPP indicate that this drug is highly effective and very well tolerated also in the standard everyday clinical practice, i.e. outside the clinical trial setting, in relapsed/refractory HL.[14-16] In particular, regarding the toxicity, the peripheral neuropathy is the most common side effect with a reduced rate compared to the pivotal phase II study.[11] In terms of effectiveness, this report confirms the trend of CR and ORR rates. In fact, comparing our study with the pivotal study, the German and UK NPP experiences the ORR and CR rates are the same (Table 3).[11,14,15]

in addition, there is a further demonstration of the real role of BV as a therapeutic “bridge”, inducing a rapid response, to ASCT or allogeneic transplant and, on the other hand, of the potential role of this drug to induce a long-lasting continuous CR without any consolidation although in a small subset of refractory HL patients. The major result of our study indicates that best responses were observed after 3/4 cycles leading to consider consolidation early and scheduled after the first evaluation indicating response.

DOI: 10.3324/haematol.2012.083048

In conclusion, our data represent the largest NPP report on BV as single agent in the real life experience of the treatment of relapsed/refractory HL patients; further investigation could be designed to achieve a larger sample (for example a global European NPP report) and a necessary longer follow up to assess long term survival and unknown side effects.

DOI: 10.3324/haematol.2012.083048

References

1.Canellos GP, Anderson JR, Propert KJ, Nissen N, Cooper MR, Henderson ES, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med. 1992;327(21):1478-84.

2.Diehl V, Franklin J, Pfreundschuh M Lathan B, Paulus U, Hasenclever D, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP_ABVD for advanced Hodgkin's disease. N Engl J Med. 2003;348(7):2386-95.

3.Linch DC, Winfield D, Goldstone AH, Moir D, Hancock B, McMillan A, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: Results of a BNLI randomised trial. Lancet. 1993;341(8852):1051-4.

4.Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haematopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: A randomised trial. Lancet. 2002;359(9323):2065-71.

5.Andre M, Henry-Amar M, Pico JL, Brice P, Blaise D, Kuentz M, et al. Comparison of high-dose therapy and autologous stem-cell transplantation with conventional therapy for Hodgkin's disease induction failure: A case-control study. J Clin Oncol. 1999;17(1):222-9.

6.Fehniger TA, Larson S, Trinkaus K, Siegel MJ, Cashen AF, Blum KA, et al. A phase 2 multicenter study of lenalidomide in relapsed or refractory classical Hodgkin lymphoma. Blood. 2011;118(19):5119-25.

7.Johnston PB, Inwards DJ, Colgan JP, Laplant BR, Kabat BF, Habermann TM, et al. A phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma. Am J Hematol. 2010;85(5):320-4.

8.Younes A, Sureda A, Ben-Yehuda D, Zinzani PL, Ong TC, Prince HM, et al. Panobinostat in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem-cell transplantation: results of a phase II study. J Clin Oncol 2012;30(18):2197-03.

9.Younes A, Bartlett NL, Leonard JP, Kennedy DA, Lynch CM, Sievers EL, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med. 2010;363(19):1812-21.

10.Fanale MA, Forero-Torres A, Rosenblatt JD, Advani RH, Franklin AR, Kennedy DA, et al. A phase I weekly dosing study of brentuximab vedotin in patients with relapsed/refractory CD30-positive hematologic malignancies. Clin Cancer Res. 2012;18(1):248-55.

11.Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol. 2012;30:2183-9.

12.Cheson BD, Pfistner B, Juwed ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25:579-86.

13.Kaplan ES, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc. 1958;58:457-81.

14.Rothe A, Sasse S, Goergen H, Eichenauer DA, Lohri A, Jäger U, et al. Brentuximab vedotin for relapsed or refractory $CD30^+$ hematologic malignancies: the German Hodgkin Study Group experience. Blood. 2012;120:1470-2.

15.Gibb A, Jones C, Bloor A, Kulkarni S, Illidge T, Linton K, et al. 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 Centre. Haematologica. 2012. Published on October 12, 2012. doi:10.3324/haematol.2012.069393

16. Chen R, Palmer JM, Thomas SH, Tsai NC, Farol L, Nademanee A, et al. Brentuximab vedotin enables successful reduced-intensity allogeneic hematopoietic cell transplantation in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2012;119:6379-81.

DOI: 10.3324/haematol.2012.083048

Figure Legends

Figure 1. Algorithm of the responses at PET3 and at PET8 evaluations [CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, overall response rate].

Figure 2. Duration of complete response in alive patients [Black circle, allogeneic transplant; grey circle, autologous stem cell transplant].

Figure 3. Survival: Overall (A) and Progression Free (B).

Figure 4. Progression Free Survival for the three categories [CR, complete response; PR, partial response; SD, stable disease; pts, patients].

DOI: 10.3324/haematol.2012.083048

Table 1. Demographics and baseline of patients (*N*=65).

Median Age at diagnosis, years (range)	27.5 (12-66)
Sex, M/F, *N*	34/31
ECOG, *N* (%) 0 1 2	 24 (36.9) 26 (40.0) 15 (23.1)
Systemic symptoms at baseline, *N* (%)	29 (44.6)
Prior radiation therapy, *N* (%)	39 (60.0)
Prior autologous stem cell transplant, *N* (%)	57 (87.7)
Prior allogeneic transplant, *N* (%)	3 (4.6)
Median prior chemotherapy regimens, *N* (range)	4 (2-13)
Refractory to first line therapy, *N* (%)	45 (69.2)
Refractory to most recent therapy, *N* (%)	52 (80.0)

DOI: 10.3324/haematol.2012.083048

Table 2. Characteristics of all 14 patients who obtained a complete response.

Median Age at diagnosis, years (range)	30.3 (16.7-52.8)
Sex, M/F, *N*	9/5
Prior radiation therapy, *N* (%)	7 (50)
Prior autologous stem cell transplant, *N* (%)	11 (78.6)
Prior allogeneic transplant, *N* (%)	1 (7.1)
Median prior chemotherapy regimens, *N* (range)	4 (2-11)
Refractory to first line therapy, *N* (%)	12 (85.7)
Refractory to most recent therapy, *N* (%)	7 (50)

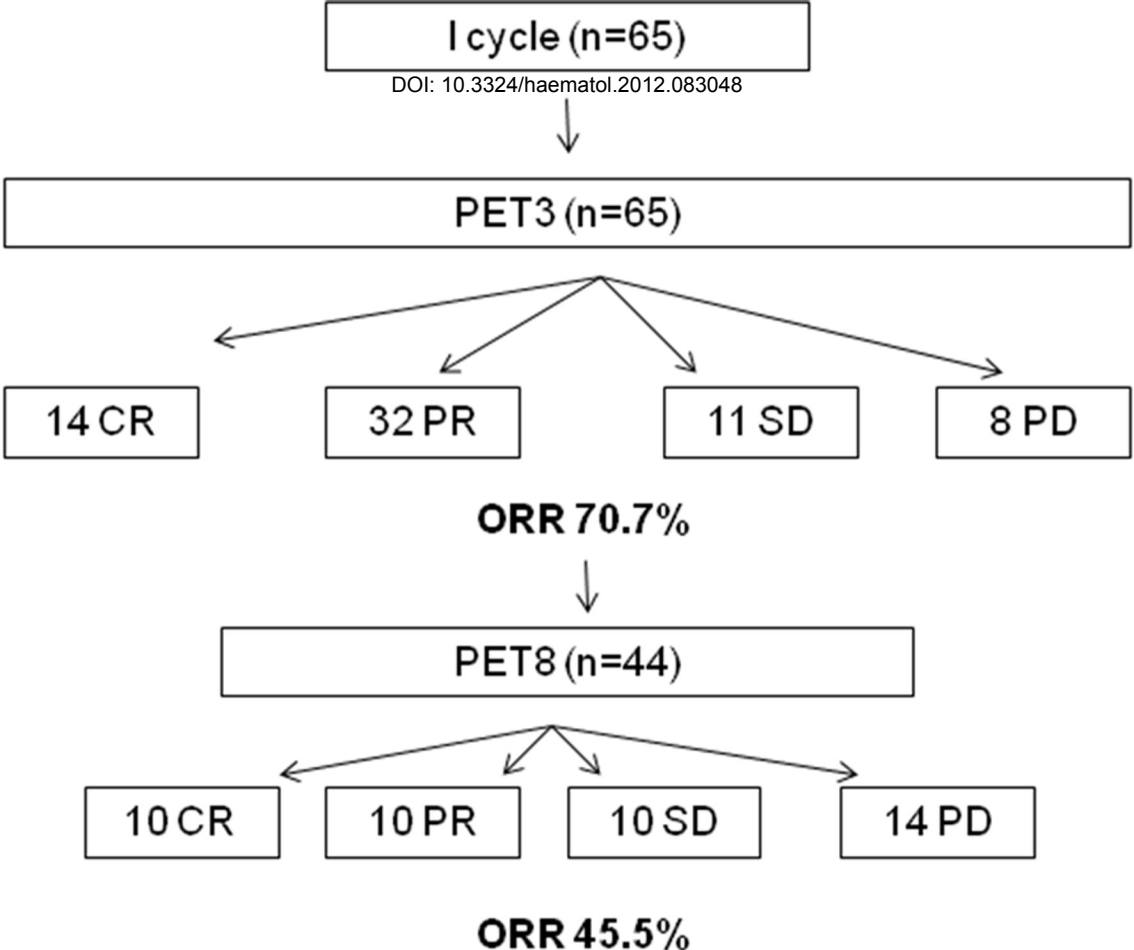
DOI: 10.3324/haematol.2012.083048

Table 3. Comparison of pivotal study versus NPP experiences

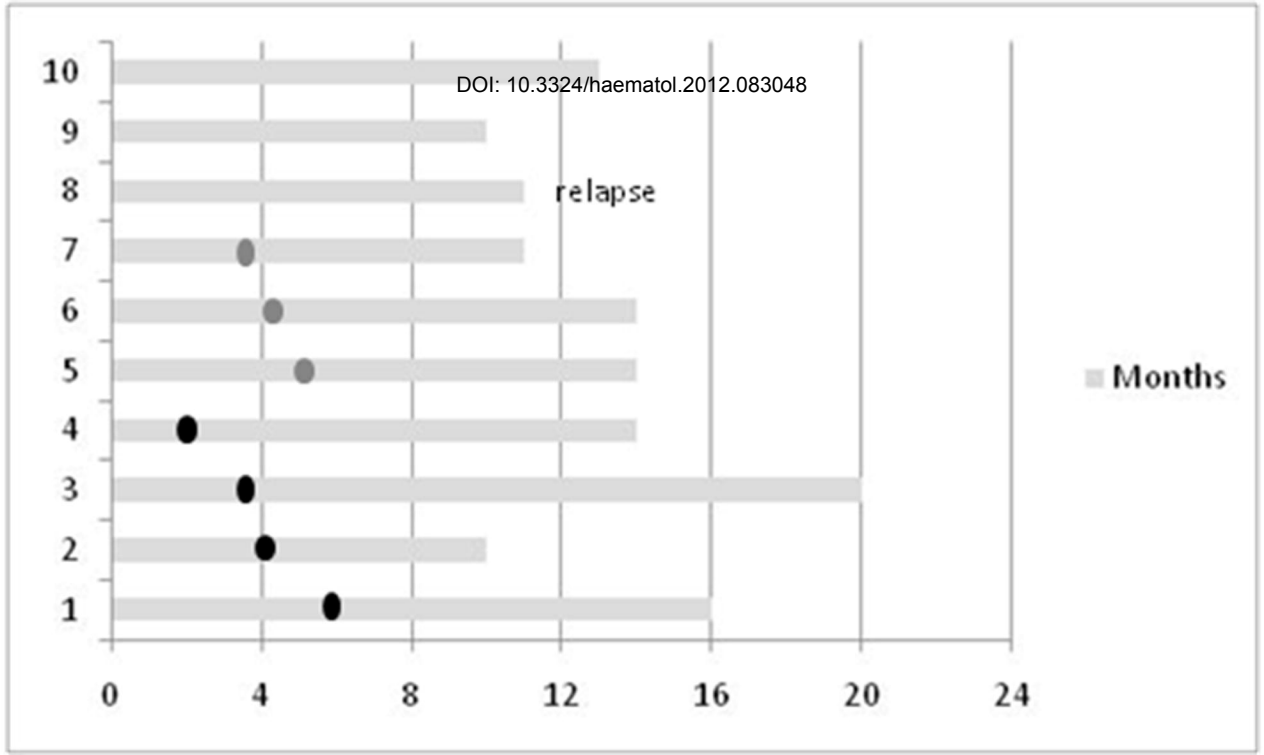
Study	N. pts	ORR%	CR%
Pivotal[11]	102	73	32
German NPP[14]	45	60	22
UK NPP[15]	18	72	17
Italy NPP	65	70.7	21.5

NPP, named patient program; pts, patients; ORR, overall response rate; CR, complete response.

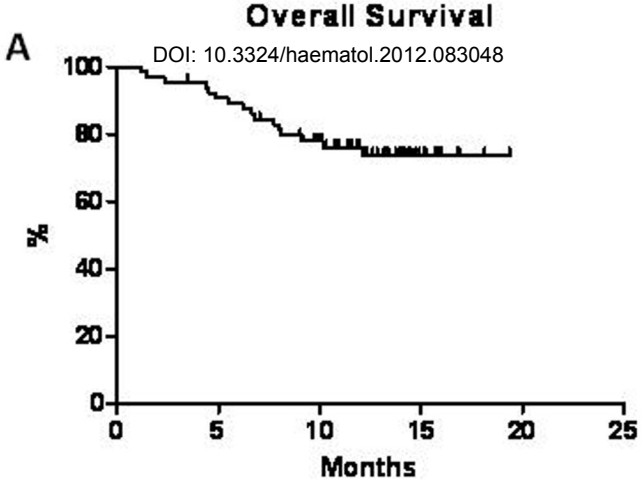
DOI: 10.3324/haematol.2012.083048

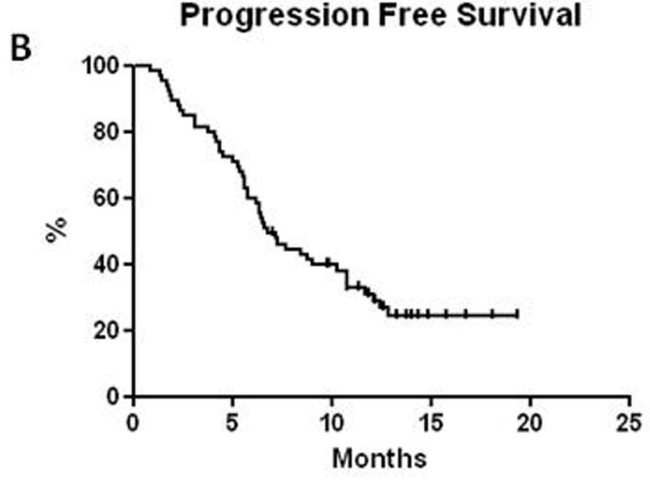


DOI: 10.3324/haematol.2012.083048



DOI: 10.3324/haematol.2012.083048





DOI: 10.3324/haematol.2012.083048