


# Bendamustine as part of conditioning of autologous stem cell transplantation in patients with aggressive lymphoma: a phase 2 study from the GELTAMO group

Alba M. Redondo,<sup>1</sup> David Valcárcel,<sup>2,3</sup> Ana P. González-Rodríguez,<sup>4</sup> María Suárez-Lledó,<sup>5</sup> José L. Bello,<sup>6</sup> Miguel Canales,<sup>7</sup> Jorge Gayoso,<sup>8</sup> Mercedes Colorado,<sup>9</sup> Isidro Jarque,<sup>10</sup> Raquel del Campo,<sup>11</sup> Reyes Arranz,<sup>12</sup> María J. Terol,<sup>13</sup> José J. Rifón,<sup>14</sup> María J. Rodríguez,<sup>15</sup> María J. Ramírez,<sup>16</sup> Nerea Castro,<sup>17</sup> Andrés Sánchez,<sup>18</sup> Javier López-Jiménez,<sup>19</sup> Santiago Montes-Morero,<sup>20</sup> Javier Briones,<sup>21</sup> Aurelio López,<sup>22</sup> Luis Palomera,<sup>23</sup> Armando López-Guillermo,<sup>5</sup> Dolores Caballero,<sup>1</sup> Alejandro Martín<sup>1</sup>  and on behalf of the Grupo Español de Linfomas y Trasplante Autólogo de Médula Ósea (GELTAMO)

<sup>1</sup>Department of Haematology, Hospital Universitario de Salamanca - IBSAL, CIBERONC, Salamanca, <sup>2</sup>Department of Haematology, Hospital Vall d'Hebron, University Autònoma of Barcelona (UAB), <sup>3</sup>Experimental Haematology Unit, Vall d' Hebron Institute of Oncology (VHIO), Barcelona, <sup>4</sup>Department of Haematology, Hospital Central de Asturias, Oviedo, <sup>5</sup>Department of Haematology, Hospital Clinic, Barcelona, <sup>6</sup>Department of Haematology, Complejo Hospitalario Universitario de Santiago (CHUS), Santiago de Compostela, <sup>7</sup>Department of Haematology, Hospital La Paz, <sup>8</sup>Department of Haematology, Hospital Gregorio Marañón, Madrid, <sup>9</sup>Department of Haematology, Hospital Marqués de Valdecilla, Santander, <sup>10</sup>Department of Haematology, Hospital Universitario La Fe, CIBERONC, Valencia, <sup>11</sup>Department of Haematology, Hospital Son Llàtzer, Palma de Mallorca, <sup>12</sup>Department of Haematology, Hospital de La Princesa, Madrid, <sup>13</sup>Department of Haematology, Hospital Clínico de Valencia, Valencia, <sup>14</sup>Department of Haematology, Clínica Universitaria de Navarra, Pamplona, <sup>15</sup>Department of Haematology, Hospital Universitario de Canarias, Las Palmas de Gran Canaria, <sup>16</sup>Department

## Summary

We conducted a phase 2 trial to evaluate the safety and efficacy of bendamustine instead of BCNU (carmustine) in the BEAM (BCNU, etoposide, cytarabine and melphalan) regimen (BendaEAM) as conditioning for autologous stem-cell transplantation (ASCT) in patients with aggressive lymphomas. The primary endpoint was 3-year progression-free survival (PFS). Sixty patients (median age 55 [28–71] years) were included. All patients (except one who died early) engrafted after a median of 11 (9–72) and 14 (4–53) days to achieve neutrophil and platelet counts of  $>0.5 \times 10^9/l$  and  $>20 \times 10^9/l$ , respectively. Non-relapse mortality at 100 days and 1 year were 3.3% and 6.7%, respectively. With a median follow-up of 67 (40–77) months, the estimated 3-year PFS and overall survival (OS) were 58% and 75%, respectively. Patients in partial response at study entry had significantly worse PFS and OS than patients who underwent ASCT in complete metabolic remission, and this was the only prognostic factor associated with both PFS (Relative risk [RR], 0.27 [95% confidence interval {CI} [0.12–0.56]]) and OS (RR, 0.40 [95% CI 0.17–0.97]) in the multivariate analysis. BendaEAM conditioning is therefore a *feasible* and effective regimen in patients with aggressive lymphomas. However, patients not in complete metabolic remission at the time of transplant had poorer survival and so should be considered for alternative treatment strategies.

**Keywords:** bendamustine, BEAM, autologous stem-cell transplantation, aggressive lymphomas, clinical trial.

of Haematology, Hospital de Jerez, Jerez de la Frontera, <sup>17</sup>Department of Haematology, Hospital 12 de Octubre, Madrid, <sup>18</sup>Department of Haematology, Hospital Virgen de la Arrixaca, Murcia, <sup>19</sup>Department of Haematology, Hospital Universitario Ramón y Cajal, Madrid, <sup>20</sup>Department of Pathology, Hospital Universitario Marqués de Valdecilla, IFIMAV, Santander, <sup>21</sup>Department of Haematology, Hospital Santa Creu i Sant Pau, Barcelona, <sup>22</sup>Department of Haematology, Hospital Arnau de Villanova, Valencia, and <sup>23</sup>Department of Haematology, Hospital Clínico de Zaragoza, Zaragoza, Spain

Received 1 July 2018; accepted for publication 5 November 2018

Correspondence: Alejandro Martín, Haematology Department, Hospital Universitario de Salamanca - IBSAL, Centro de Investigación Biomédica en Red de Cáncer (CIBERONC); Paseo de San Vicente 58-182, Salamanca 37007, Spain.  
E-mail: amartingar@usal.es

High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) is the standard of care for patients with chemosensitive relapsed or primary refractory diffuse large B-cell lymphoma (DLBCL) and other aggressive lymphomas, and is a clinical option for patients with peripheral T-cell lymphomas (PTCL) in first remission (Majhail *et al*, 2015; Sureda *et al*, 2015). Since the 1980s, various conditioning regimens have been used for ASCT in lymphomas, none of which has proved superior in prospective randomized trials. BEAM (carmustine [BCNU], etoposide, cytarabine and melphalan) conditioning is one of the most commonly employed regimens (Chen *et al*, 2015). However, carmustine is currently unavailable or of very limited availability in some countries (Garciaz *et al*, 2016). In addition, it has been associated with late pulmonary complications, non-relapse-related late death and secondary tumours (Bhatia *et al*, 2005; Afessa *et al*, 2012; Chen *et al*, 2015; Isidori *et al*, 2016). Therefore, the substitution of carmustine by other agents could increase efficacy and reduce toxicities associated with the BEAM regimen.

The Benda-EAM (or BeEAM) regimen consists of the standard BEAM regimen but with carmustine being replaced by bendamustine, a nitrogen mustard that combines the alkylating activity of a mustard group with the antimetabolite activity of a purine analogue (Leoni *et al*, 2008). Bendamustine has a high level of activity in alkylating-resistant cell lines (Leoni *et al*, 2008), as well as encouraging high response rates with acceptable toxicity in patients with refractory or relapsed DLBCL (Ohmachi *et al*, 2013) and PTCL (Damaj *et al*, 2013). The Benda-EAM regimen was first

examined by Visani *et al* (2011) in 43 patients with relapsed or refractory lymphoma from various histologies (Hodgkin lymphoma [HL],  $n = 15$ ; DLBCL,  $n = 15$ ; mantle cell lymphoma [MCL],  $n = 5$ ; other aggressive B-cell lymphomas,  $n = 8$ ), and they showed a favourable safety and efficacy profile of this novel HDT regimen. The basis for this regimen arose from preliminary *in vitro* analysis performed at our centre on lymphoma cell lines that demonstrated the greater efficacy of bendamustine in combination with etoposide, cytarabine and melphalan compared to carmustine (Visani *et al*, 2011).

Against this background, we conducted a phase 2 trial to evaluate the safety and efficacy of the Benda-EAM regimen as conditioning for ASCT in patients with DLBCL or PTCL. Here we report the final results of the trial after a long-term follow-up.

## Methods

### Patients

Eligible patients were aged 18–70 years, with a local histological diagnosis of: (i) DLBCL or grade 3B follicular lymphoma (FL) with refractory or relapsed disease in partial response (PR) or complete remission (CR) after salvage therapy, or (ii) DLBCL transformed from an indolent lymphoma or PTCL (different from anaplastic large cell lymphoma, ALK-positive) in first or subsequent PR or CR. There were no specific recommendations for treatment before study entry. Patients were required to have an Eastern Cooperative Group performance status of 0–2, and adequate cardiac, renal, pulmonary and hepatic functions. All

TABLE I. Patient characteristics.

Characteristic	N	%
Age, years: median (range)	55 (28–71)	
Older than 60 years	20	33.3
Male sex	30	50
Histological diagnosis		
<i>De novo</i> diffuse large B-cell lymphoma	38	63.3
Grade 3B follicular lymphoma	3	5.0
Transformed diffuse large B-cell lymphoma	13	21.7
Peripheral T-cell lymphoma*	6	10.0
First-line treatment		
R-CHOP (14 or 21)	44	73.3
CHOP (14 or 21)	6	10.0
R-EPOCH	3	5.0
Others†	7	11.7
Second and subsequent lines		
R-ESHAP	29	48.3
R-IFE	8	13.3
R-DHAP	5	8.3
ESHAP	3	5.0
R-GEMOX-D	3	5.0
R-CHOP	3	5.0
R-ICE	2	3.3
Rituximab monotherapy	2	3.3
Others‡	6	10
Number of treatment lines prior to study entry		
Median (range)	2 (1–4)	
1	11	18.3
2	41	68.3
3–4	8	13.3
International Prognostic Index at study entry		
0	23	38.3
1	23	38.3
2	13	21.7
3	1	1.7
Disease status at study entry (PET/CT)		
Complete remission after first-line treatment	9	15.0
Complete remission after 2 or more lines of treatment	28	46.7
Partial response after first-line treatment	2	3.3
Partial response after 2 or more lines of treatment	21	35.0
Melphalan dose in conditioning regimen		
140 mg/m <sup>2</sup> (according to protocol)	49	81.7
140 mg (flat dose)	11	18.3

BR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone; CT, computed tomography; FMC, fludarabine, mitoxantrone, cyclophosphamide, PET, positron emission tomography; R-BMD, rituximab, bendamustine, mitoxantrone, dexamethasone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; R-EPOCH, rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin; R-ESHAP, rituximab, etoposide, methyl-prednisolone, cytarabine, cisplatin; R-GEMOX-D, rituximab, gemcitabine, oxaliplatin, dexamethasone; R-GIFOX, gemcitabine, ifosfamide, oxaliplatin, rituximab; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; R-IFE, rituximab, ifosfamide, etoposide; R-miniBEAM, rituximab, carmustine, etoposide, cytarabine, melphalan.

\*Peripheral T-cell lymphoma not otherwise specified ( $n = 3$ ), angioimmunoblastic T-cell lymphoma ( $n = 2$ ), anaplastic large cell lymphoma ALK- ( $n = 1$ ).

†One each: BR-CAP, Burkitt lymphoma protocol, chlorambucil, FMC, ICE, R-CVP, R-ESHAP.

‡One each: Bortezomib, DHAP, GEMOX-D, R-BMD; R-GIFOX, R-miniBEAM.

patients were required to have undertaken apheresis of haematopoietic stem cells, obtaining  $\geq 2 \times 10^6/\text{kg}$  CD34+ cells. All subjects provided written, informed consent before their

inclusion in the study. A retrospective centralized histopathological review was carried out of the 40 patients for whom sufficient material was available.

### Study design and treatment

Our open-label, multicentre phase 2 study was performed in accordance with the declaration of Helsinki and Good Clinical Practice guidelines. It was approved by the national authorities and the institutional ethics committee of each participating centre. The trial was registered at ClinicalTrials.gov (identifier: NCT01296256).

The conditioning regimen consisted of bendamustine (200 mg/m<sup>2</sup>, days -7 and -6), etoposide (200 mg/m<sup>2</sup>, days -5 to -2), cytarabine (400 mg/m<sup>2</sup>, days -5 to -2) and melphalan (140 mg/m<sup>2</sup>, day -1) (BendaEAM regimen), according to the Visani protocol (Visani *et al*, 2011). In the initial protocol, no specific support measures were indicated during the conditioning regimen; each centre followed its institutional protocols. When the first case of renal failure related to the administration of bendamustine was detected, the protocol was amended to recommend minimum hydration of 2000 ml/m<sup>2</sup> intravenously, from the day before the start of the conditioning regimen until day -1. All patients received pegfilgrastim (6 mg on day +6 from autograft) or filgrastim (5 µg/kg/day from day +6 until neutrophil recovery). Patients were nursed in single or double rooms in reverse isolation until haematological recovery. Assessment of symptoms, physical examination and laboratory work-up were performed daily during their hospital stay. Antibiotic prophylaxis and supportive care, including transfusions, were provided at the discretion of the treating physician. Cotrimoxazole and acyclovir after ASCT to prevent *Pneumocystis jirovecii* and viral infections, respectively, were recommended in the protocol.

### Study endpoints and assessments

The primary endpoint of the study was to assess the 3-year progression-free survival (PFS), calculated from the date of stem cell reinfusion until the date of relapse, progression or

death from any cause. Secondary endpoints included assessment of toxicity of BendaEAM regimen, according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 ([https://www.eortc.be/services/doc/ctc/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_5x7.pdf](https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)), evaluation of anti-tumour activity measured by CR and overall response rates (ORR) and overall survival (OS). Response was assessed 3 months after ASCT, using the 2007 revised response criteria for malignant lymphoma (Cheson *et al*, 2007). All patients were evaluated with computed tomography (CT) and positron emission tomography (PET) scans. Bone marrow (BM) biopsy was performed only if the BM was involved by lymphoma at study entry. During the follow-up, CT scans were performed every 3 months for the first year and every 6 months during the following second and third years. PET/CT was performed any time when there was a suspicion of relapse or progression. OS was calculated from the date of stem cell reinfusion to the date of death or of last follow-up. Survival endpoints were assessed on the date of the last patient contact; the most recent follow-up was in November 2017.

### Statistical considerations

This is a phase 2 study designed according to the Fleming method. The primary endpoint was the 3-year PFS rate. Taking 35% as the lowest acceptable rate, and stipulating 80% power for detecting a significant improvement of ≥20% and a 0.05 alpha significance level for a two-sided exact test of a single proportion, and assuming a 55% target for 3-year PFS and a 15% dropout rate, the minimum necessary sample size was calculated to be 57 patients. The intention-to-treat (ITT) population comprised all patients included in the trial, and this was the population used for the primary efficacy analysis. Survival rates were estimated by the Kaplan–Meier method. A two-tailed log-rank test was used to assess the

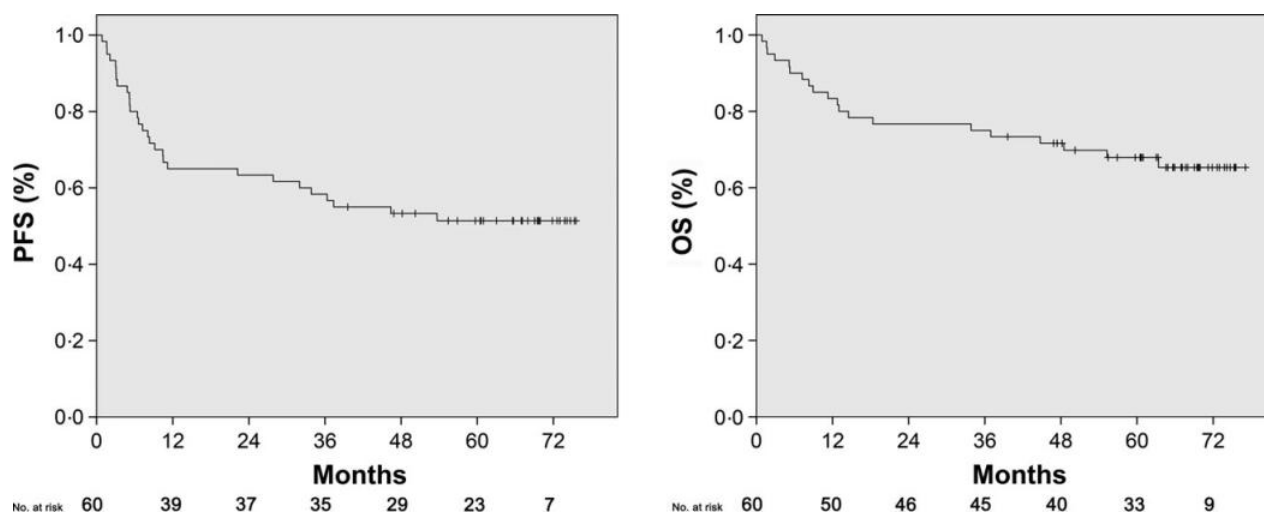


Fig 1. Kaplan–Meier estimates of progression-free survival (PFS) and overall survival (OS).

TABLE II. Univariate analysis of survival.

Prognostic factor	N	5-year PFS (%)	P	5-year OS (%)	P
Age at study entry					
<60 years	40	55	0.526	72	0.440
≥60 years	20	44		58	
Sex					
Male	30	63	0.060	76	0.102
Female	30	40		60	
Diagnosis					
DLBCL or Grade 3B FL	41	53	0.820	68	0.494
Transformed DLBCL	13	54		77	
PTCL	6	25		50	
Time from diagnosis to ASCT					
<1 year	36	55	0.511	63	0.595
≥1 year	24	45		75	
Prior lines of therapy					
1	11	53	0.846	81	0.137
2	41	51		61	
More than 2	8	50		87	
IPI at study entry					
0	23	74	0.023	83	0.064
1	23	34		52	
2–3	14	42		70	
Status at transplant (PET)					
Complete remission	37	67	0.001	75	0.036
Partial response	23	26		56	
Melphalan dose in BendaEAM					
140 mg/m <sup>2</sup>	49	53	0.727	67	0.808
140 mg (flat dose)	11	44		73	

ASCT, autologous stem cell transplantation; Benda EAM, bendamustine, etoposide, cytarabine, melphalan; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IPI, International Prognostic Index; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma.

significance of differences for each prognostic factor in univariate analyses. Covariates with a value of  $P < 0.1$  were entered stepwise into a multivariate Cox proportional hazards model. All statistical analyses were conducted with SPSS version 20.0 (IBM SPSS Inc., Armonk, NY, USA).

## Results

### Patient characteristics

Sixty patients from 22 GELTAMO centres were enrolled between May 2011 and November 2012. Patient characteristics are summarized in Table I. The median age was 55 (range, 28–70) years. Histological diagnosis according to local Pathology was as follows: 38 DLBCLs, 3 grade 3B FLs, 13 transformed DLBCLs and 6 PTCLs. Forty-nine patients (82% of the series) had received two or more lines of treatment prior to ASCT, due to relapsed or refractory disease. Thirty-seven patients (62%) were in metabolic CR (assessed by FDG-PET/CT) at study entry and 23 (38%) were in PR. With respect to the conditioning regimen, 11 patients received a flat dose of 140 mg melphalan, instead of 140 mg/m<sup>2</sup>, due to an internal error at one of the participating centres.

Tissue blocks or unstained slides were available for centralized review of the histopathological diagnosis in 45 patients (75%). Five patients had insufficient material to establish a definitive diagnosis. The other 15 samples were not available because the material had been exhausted or because the patients originated from other centres and it was not possible to obtain the diagnostic sample. Centralized histopathological diagnoses were concordant with local diagnoses in 33 out of the 40 cases (DLBCL,  $n = 31$ , PTCL/not otherwise specified,  $n = 1$ , angioimmunoblastic T-cell lymphoma,  $n = 1$ ). The rate of concordance (82.5%) was similar to those reported in prospective nation-wide analyses (Proctor *et al*, 2011; Laurent *et al*, 2017). Seven patients with a local diagnosis of DLBCL or grade 3B FL were centrally diagnosed with low grade FL (grades 1–2) ( $n = 4$ ), grade 3A FL ( $n = 2$ ) or nodular lymphocyte predominant Hodgkin lymphoma ( $n = 1$ ).

### Efficacy analysis

The CR and PR rates with Benda-EAM were 75% (45 patients) and 10% (6 patients), respectively. Stable disease and progressive disease were observed in one and six patients, respectively, whereas two patients were not

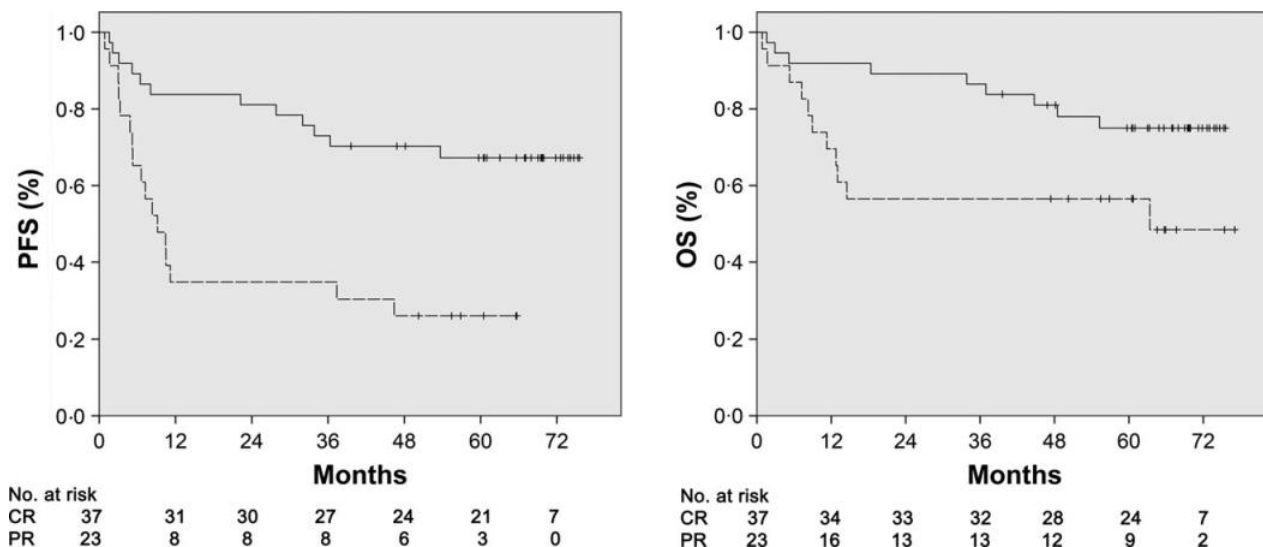


Fig 2. Kaplan–Meier estimates of progression-free survival (PFS) and overall survival (OS) according to status at transplant: complete remission (CR, solid line) and partial response (PR, dotted line).

evaluated due to early death. After a median follow-up of 66.4 months (39.6–77.1), the disease had progressed in 24 patients and 20 patients had died, 16 of them after disease progression. The estimated 3- and 5-year survival rates were 58% and 51%, respectively, for PFS (median not reached), and 75% and 65% for OS (median not reached) (Fig 1).

Results of the univariate analyses of survival are shown in Table II. Patients in PR at study entry had significantly worse PFS and OS (Fig 2) than patients who underwent ASCT in CR, and this was the only prognostic factor associated with both PFS (hazard ratio 0.29 [95% CI 0.14–0.60],  $P = 0.001$ ) and OS (hazard ratio 0.40 [95% CI 0.17–0.97],  $P = 0.043$ ) in the multivariate analysis.

### Engraftment

The median number of CD34+ cells infused was  $4.05 \times 10^6$ /kg (range, 1.69–19.80). All patients (except one who died early) engrafted after a median of 11 (9–72) and 14 (4–53) days to achieve neutrophil and platelet counts of  $>0.5 \times 10^9$ /l and  $>20 \times 10^9$ /l, respectively. All patients were required to have undertaken apheresis of haematopoietic stem cells to obtain  $\geq 2 \times 10^6$ /kg CD34+ cells. However, 2 of 60 patients included in the trial received less than this amount. These patients received 1.69 and  $1.93 \times 10^6$ /kg CD34+ cells, respectively, both achieving  $>0.5 \times 10^9$ /l neutrophils after 11 days, and  $>20 \times 10^9$ /l platelets after 43 and 19 days, respectively. Fifty-four of 59 patients reached  $>0.5 \times 10^9$ /l neutrophils between days +9 and +13, and the remaining five patients engrafted by days +14, +15, +19, +22 and +72. The last patient, a 61-year-old male pre-treated with two lines of therapy, had received  $10.09 \times 10^6$ /kg CD34+ cells but had a primary neutrophil graft failure of unknown origin. Regarding platelet engraftment, 49 of 59 patients reached

$>20 \times 10^9$ /l platelets between days +8 and +20, seven patients between days +21 and +30, and the remaining three patients on days +31, +43 and +53. The last patient was a 43-year-old female pretreated with two lines of therapy; she had received  $2.02 \times 10^6$ /kg CD34+ cells and had a delayed platelet engraftment of unknown origin. The median number of days on granulocyte colony-stimulating factor was 6 (range, 1–15 days). Patients received a median of 2 (range, 0–22) red blood cell units. The median time to discharge from hospital was 26 days (range, 15–59 days).

### Serious adverse events and non-haematological toxicity

Thirty-nine serious adverse events (SAEs) were reported before day 100, including 15 infectious episodes (Table III), two of which resulted in respiratory failure and the death of the patient (3.3% of the 100-day transplant-related mortality). Acute renal failure was another major toxicity, which developed in four patients (6.7%) after bendamustine administration (grade 2 in three cases and grade 3 in one). It proved reversible without dialysis in all cases, but was clinically relevant because these patients required the dose of their conditioning regimen to be adjusted. Three of these patients had developed mild renal failure during previous salvage therapy. Other SAEs reported before day 100 were: thrombocytopenia (grade 4, two episodes), anaemia (grade 3, two episodes), neutropenia (grade 4, two episodes), rash (grade 3) and stroke (grade 3). All of these patients recovered after adequate treatment.

The 100-day non-infectious toxicity is reported in Table IV. Twenty-six (43.3%) patients experienced a grade III–IV oral mucositis. The incidence of non-gastrointestinal grade 3–4 toxicities was very low (Table IV). These toxicities were easily managed with supportive care or adequate

TABLE III. Infectious serious adverse events reported by the investigators.

Organ affected	Day of Transplant	SAE criterion	Grade	Documentation	Evolution
Lung infection	+8	Prolongation hospitalization	4	<i>E. cloacae</i>	Recovered
Sepsis				<i>Corynebacterium</i> sp.	
Sepsis	+10	Admission ICU	4	No	Recovered
Lung infection	+13	Death	5	Aspergillosis*	Death
				Influenza A	
Enterocolitis	+16	Hospitalization	2	No	Recovered
Lung infection†	+17	Prolongation hospitalization	4	Aspergillosis*	Recovered
Lung infection	+26	Death	5	No	Death
Enterocolitis	+36	Hospitalization	2	No	Recovered
Enterocolitis	+37	Hospitalization	2	No	Recovered
Sepsis†	+40	Hospitalization	4	No	Recovered
Enterocolitis	+45	Hospitalization	2	<i>C. difficile</i>	Recovered
Joint infection	+49	Hospitalization	3	<i>E. cloacae</i>	Recovered
<i>Herpes zoster</i>	+70	Hospitalization	3	No	Recovered
<i>Herpes zoster</i>	+85	Hospitalization	3	<i>P. aeruginosa</i>	Recovered
Urinary tract infection					
Enterocolitis†	+90	Hospitalization	3	No	Recovered
<i>Herpes zoster</i>	+96	Hospitalization	3	No	Recovered
Sepsis†	+108	Hospitalization	4	<i>S. pneumoniae</i>	Recovered
Lung infection†	+151	Death	5	Aspergillosis*	Death
Sepsis	+186	Hospitalization	4	<i>Candida</i> sp.	Recovered
Sepsis	+338	Hospitalization	4	<i>S. haemolyticus</i>	Recovered
Lung infection‡	+944	Hospitalization	4	No	Recovered
Sepsis‡					
HLH‡	+964	Hospitalization	3	EBV	Recovered
Lung infection‡	+1003	Hospitalization	5	Influenza A	Death after cerebral stroke
				Aspergillosis*	Autopsy revealed progression of lymphoma

EBV, Epstein-Barr virus; HLH, haemophagocytic lymphohistiocytosis, ICU, intensive care unit; SAE, serious adverse event.

\*Probable invasive aspergillosis according to European Organization for Research and Treatment of Cancer criteria (De Pauw *et al*, 2008).

†These episodes correspond to the same patient.

‡These episodes correspond to the same patient.

treatment. No grade III–IV cardiotoxicity was observed. No episodes of veno-occlusive disease were reported.

Non-relapse mortality (NRM) after day 100 was 3.3%: one patient died of Wernicke's encephalopathy on day 154 and another patient died of infectious complications (probable invasive aspergillosis) on day 216, although this last patient had repeated infectious episodes during the early post-transplant period (Table III). No episodes of non-infectious pneumonia were reported. Three patients developed a secondary neoplasm: 2 myelodysplastic syndrome on days 329 and 1434, respectively, and 1 cholangiocarcinoma on day 1232.

## Discussion

For this phase 2 clinical trial, we hypothesized that the replacement of BCNU with bendamustine in the BEAM conditioning regimen (BendaEAM) would improve its efficacy and reduce its toxicity in patients with aggressive lymphoma who are candidates for ASCT. Our clinical trial is the second to use BendaEAM as a conditioning regimen, although the

previous study was performed in patients with various histologies, including HL ( $n = 15$ ), MCL ( $n = 5$ ) and aggressive B-cell lymphomas ( $n = 23$ ) (Visani *et al*, 2011). Our results show that this conditioning regimen is *feasible* and effective.

Considering efficacy, our long-term results indicate that BendaEAM is an effective regimen, with median PFS and OS not reached after a median follow-up of 66 (40–77) months, and an estimated 3-year PFS and OS of 58% and 75%, respectively. Although 11 out of 60 patients received a dose of melphalan less than that indicated in the protocol (140 mg flat dose), no significant differences were found in PFS or OS between this group of patients and the others (Table II). In the previous prospective clinical trial (Visani *et al*, 2014), BendaEAM produced a 72% 3-year PFS, although their series also included patients with HL, as stated before. In a single-centre retrospective study, BendaEAM resulted in a 69% and 72% 2-year PFS and OS, respectively, although this series ( $n = 39$ ) was very heterogenous, including patients with HL, DLBCL, PTCL, MCL, FL and other indolent lymphomas (Gilli *et al*, 2017), so the efficacy results

TABLE IV. 100-day non-haematological and non-infectious toxicity.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac disorders	–	5 (8.3)	–	–
Gastrointestinal disorders				
Abdominal pain	–	9 (15)	2 (3.3)	–
Colonic haemorrhage	1 (1.7)	–	–	–
Diarrhoea	28 (46.7)	22 (36.7)	5 (8.3)	–
Oral mucositis	13 (21.7)	20 (33.3)	18 (30)	8 (13.3)
Nausea	17 (28.3)	8 (13.3)	1 (1.7)	–
Vomiting	6 (10)	13 (21.7)	1 (1.7)	–
General disorders				
Fever	26 (43.3)	17 (28.3)	3 (5)	–
Hepatobiliary disorders	2 (3.3)	1 (1.7)	–	–
Metabolism disorders				
Acidosis	–	1 (1.7)	–	–
Hypokalaemia	–	1 (1.7)	1 (1.7)	1 (1.7)
Hypomagnesaemia	–	3 (5)	–	–
Hyponatraemia	–	–	1 (1.7)	–
Hypophosphataemia	–	1 (1.7)	–	–
Nervous system disorders	2 (3.3)	–	–	–
Psychiatric disorders				
Anxiety	–	2 (3.3)	1 (1.7)	–
Depression	1 (1.7)	–	–	–
Renal disorders				
Acute kidney injury	3 (5)	9 (15)	2 (3.3)	–
Noninfective cystitis	2 (3.3)	1 (1.7)	–	–
Respiratory disorders	2 (3.3)	1 (1.7)	–	–
Skin disorders	9 (15)	10 (16.7)	–	–

All values are reported as *n* (% of patients).

of these studies are not comparable with ours. Several recent registry analyses have compared the efficacy of a number of commonly used conditioning regimens in lymphoma patients (Chen *et al*, 2015; Sellner *et al*, 2016). In these retrospective studies, the BEAM regimen or thiotepa-based regimens achieved a 3-year PFS of around 50% in DLBCL patients. However, the lack of randomized trials and the fact that published studies are of several study populations with differing proportions of histologies makes a comparison very difficult (Isidori *et al*, 2016).

In the present trial, patients in CR with a negative FDG-PET at the time of transplant performed better than patients in metabolic PR, as measured by both PFS and OS. This was the single prognostic factor influencing OS in the univariate and multivariate analysis, although, with only 20 events, any multivariable analysis of survival is likely to be unreliable. The prognostic impact of pre-ASCT FDG-PET in patients with relapsed or refractory DLBCL has been shown previously in multiple retrospective studies and uncontrolled prospective series (Schot *et al*, 2007; Derenzini *et al*, 2008; Hoppe *et al*, 2009; Terasawa *et al*, 2010; Armand *et al*, 2013a; Sauter *et al*, 2015; Ulaner *et al*, 2015; Adams & Kwee, 2017). Our results confirm this finding in a prospective and controlled way, and indicate that incorporation of bendamustine into the conditioning regimen does not overcome

the relative chemotherapy insensitivity and poor prognosis of patients undergoing ASCT in metabolic PR.

Another strategy for improving the preparative regimen is to incorporate a targeted agent. One major focus has been the addition of radioimmunotherapy as part of the conditioning regimen for transplantation. Multiple phase 1 and 2 studies using either <sup>131</sup>I-tositumomab or <sup>90</sup>Y-ibritumomab tiuxetan combined with chemotherapy have yielded very promising results (Press *et al*, 2000; Krishnan *et al*, 2008; Winter *et al*, 2009; Decaudin *et al*, 2011; Shimoni *et al*, 2012; Vose *et al*, 2013a; Briones *et al*, 2014). However, a phase 3 study comparing rituximab/BEAM *versus* <sup>131</sup>I-tositumomab/BEAM (Vose *et al*, 2013b) showed no benefit from adding this radioimmunotherapy to BEAM in patients with chemotherapy-sensitive relapsed DLBCL. Once again, the only variable that predicted improved outcome was CR (by either CT or FDG-PET/CT) at the time of transplant. For this reason, future research should be directed towards improving salvage therapy so that a greater proportion of patients achieve metabolic CR, as well as considering post-transplantation consolidation or maintenance therapy, especially for patients receiving their transplant while in metabolic PR. In this setting, PD-1 (also termed PDCD1) blockade after ASCT using pidilizumab has shown promising results in a phase 2 study (Armand *et al*, 2013b), although phase 3 studies are needed. In contrast, the results of the second random assignment from the CORAL study demonstrated no benefit from rituximab maintenance after ASCT (Gisselbrecht *et al*, 2012).

In the present study, given the heterogenous patient population studied and the varying dose of melphalan used, only the feasibility and toxicity profile of BendaEAM can be firmly established. The 100-day and 1-year NRM were 3.3% and 6.7%, respectively. These rates are similar to those reported in prospective clinical trials for rituximab + BEAM (4.1% 100-day treatment-related mortality, TRM) (Vose *et al*, 2013b) and <sup>131</sup>I-tositumomab/BEAM (4.9% 100-day TRM) (Vose *et al*, 2013b), and to those reported in recent registry-based or non-controlled studies of BEAM (4% 1-year NRM) (Chen *et al*, 2015; Sellner *et al*, 2016), thiotepa-based (2% 1-year NRM) (Sellner *et al*, 2016) and fotemustine-based (2.5% 100-day and 5.9% 1-year NRM) (Musso *et al*, 2010, 2016) conditioning regimens. In the previous study by Visani *et al* (2011) of BendaEAM conditioning, the 100-day TRM was 0%. In our series, infections were the main source of toxicity, and TRM was primarily infection-related, as previously described with the BEAM regimen (Damaj *et al*, 2013). The infectious profile in our study (Table III) was similar to that reported by Visani *et al* (2011) but is difficult to compare with those of other series in which infectious episodes were not systematically described, as they are in our trial.

Another major source of toxicity was acute renal failure, which developed in four patients (6.7%) shortly after bendamustine administration. This was reversible in all cases, but was clinically relevant because these patients required the



dose of their conditioning regimen to be adjusted. It should be noted that three of these patients had developed mild renal failure during previous salvage therapy, so they might have developed renal failure irrespective of any conditioning regimen that had been used. In addition, two of these patients did not receive the hydration recommended in the protocol. No grade III–IV nephrotoxicity was observed in the previous BendaEAM trial (Visani *et al*, 2011). However, a high rate of grade 3–4 renal toxicity associated with BendaEAM (14% at day 0, reversible in all cases) was also described in a small ( $n = 29$ ) single-centre retrospective study (Garciaz *et al*, 2016). The authors concluded that hydration should be increased in patients receiving high doses of bendamustine to avoid the possibility of renal toxicity (Garciaz *et al*, 2016). We agree with this conclusion and with the recommendations of Isidori *et al* (2016) that patients receiving high doses of bendamustine should be hyperhydrated with at least 2.5 l/m<sup>2</sup> liquid per day, starting hydration 1 day prior to bendamustine administration to avoid renal toxicities, and that this should be strictly monitored.

Other common acute toxicities observed in our trial, such as mucositis and gastrointestinal toxicities, were easily managed. No grade III–IV cardiac or hepatic toxicity was reported. Non-infectious pneumonia and late pulmonary complications described with the use of carmustine, such as chronic interstitial fibrosis (Bhatia *et al*, 2005; Isidori *et al*, 2016), were not observed in our study. Regarding haematological toxicity, engraftment data are similar to those previously reported with the BEAM or BEAC (BCNU, etoposide,

cytarabine, cyclophosphamide) regimens (Caballero *et al*, 1997; Jo *et al*, 2008).

In conclusion, our long-term results show that BendaEAM conditioning is a feasible and active regimen for patients with aggressive lymphomas. Infectious and renal toxicities are relatively common and should be carefully monitored. Its efficacy seems to be similar to that previously reported with other commonly used regimens like BEAM, although patients who are not in metabolic CR at the time of transplant tend to have poor outcomes and so are candidates for receiving alternative strategies. Future prospective trials testing novel salvage, preparative and maintenance regimens are needed.

## Acknowledgments

This study was supported in part by research funding from Mundipharma. We are grateful to: Phil Mason and Sergio Guijo for reviewing the English language of the manuscript; Rubén Lesmes for monitoring the study; and to the patients who participated in this study. A.M. and D.C. were responsible for the conduct of the study; A.M. and A.-M.R. performed the data analysis and interpretation; A.M. and A.-M.R. drafted the report, which all co-authors critically revised for significant scientific content; D.V., A.-P.G., M.S.-L., J.-L.B., M.C., J.G., M.C., I.J., R.C., R.A., M.-J.T., J.-J.R., M.-J.R., M.-J.R., N.C., A.S., J.L.-J., J.B., A.L., L.P., A.L.-G. contributed research data to the study; S.M.-M. was responsible for the centralized histopathological review; all co-authors contributed to data analysis and interpretation, and approved the submitted and final versions.

## References

- Adams, H.J. & Kwee, T.C. (2017) Pretransplant FDG-PET in aggressive non-Hodgkin lymphoma: systematic review and meta-analysis. *European Journal of Haematology*, **98**, 337–347.
- Afessa, B., Abdulai, R.M., Kremers, W.K., Hogan, W.J., Litzow, M.R. & Peters, S.G. (2012) Risk factors and outcome of pulmonary complications after autologous hematopoietic stem cell transplant. *Chest*, **141**, 442–450.
- Armand, P., Welch, S., Kim, H.T., LaCasce, A.S., Jacobsen, E.D., Davids, M.S., Jacobson, C., Fisher, D.C., Brown, J.R., Coughlin, E., Freedman, A.S. & Chen, Y.-B. (2013a) Prognostic factors for patients with diffuse large B cell lymphoma and transformed indolent lymphoma undergoing autologous stem cell transplantation in the positron emission tomography era. *British Journal of Haematology*, **160**, 608–617.
- Armand, P., Nagler, A., Weller, E.A., Devine, S.M., Avigan, D.E., Chen, Y.B., Kaminski, M.S., Holland, H.K., Winter, J.N., Mason, J.R., Fay, J.W., Rizzieri, D.A., Hosing, C.M., Ball, E.D., Uberti, J.P., Lazarus, H.M., Mapara, M.Y., Gregory, S.A., Timmerman, J.M., Andorsky, D., Or, R., Waller, E.K., Rotem-Yehudar, R. & Gordon, L.I. (2013b) Disabling immune tolerance by programmed death-1 blockade with pidilizumab after autologous hematopoietic stem-cell transplantation for diffuse large B-cell lymphoma: results of an international phase II trial. *Journal of Clinical Oncology*, **31**, 4199–4206.
- Bhatia, S., Robison, L.L., Francisco, L., Carter, A., Liu, Y., Grant, M., Baker, K.S., Fung, H., Gurney, J.G., McGlave, P.B., Nademanee, A., Ramsay, N.K., Stein, A., Weisdorf, D.J. & Forman, S.J. (2005) Late mortality in survivors of autologous hematopoietic-cell transplantation: report from the Bone Marrow Transplant Survivor Study. *Blood*, **105**, 4215–4222.
- Briones, J., Novelli, S., Garcia-Marco, J.A., Tomas, J.F., Bernal, T., Grande, C., Canales, M.A., Torres, A., Moraleda, J.M., Panizo, C., Jarque, I., Palmero, F., Hernandez, M., Gonzalez-Barca, E., Lopez, D. & Caballero, D. (2014) Autologous stem cell transplantation after conditioning with yttrium-90 ibritumomab tiuxetan BEAM in refractory non-Hodgkin diffuse large B-cell lymphoma: results of a prospective, multicenter, phase II clinical trial. *Haematologica*, **99**, e126.
- Caballero, M.D., Rubio, V., Rifon, J., Heras, I., Garcia-Sanz, R., Vazquez, L., Vidriales, B., del Canizo, M.C., Corral, M., Gonzalez, M., Leon, A., Jean-Paul, E., Rocha, E., Moraleda, J.M. & San Miguel, J.F. (1997) BEAM chemotherapy followed by autologous stem cell support in lymphoma patients: analysis of efficacy, toxicity and prognostic factors. *Bone Marrow Transplantation*, **20**, 451–458.
- Chen, Y.B., Lane, A.A., Logan, B., Zhu, X., Akpek, G., Aljurf, M., Artz, A., Bredeson, C.N., Cooke, K.R., Ho, V.T., Lazarus, H.M., Olsson, R., Saber, W., McCarthy, P. & Pasquini, M.C. (2015) Impact of conditioning regimen on outcomes for patients with lymphoma undergoing high-dose therapy with autologous hematopoietic cell transplantation. *Biology of Blood and Marrow Transplantation*, **21**, 1046–1053.
- Cheson, B.D., Pfistner, B., Juweid, M.E., Gascoyne, R.D., Specht, L., Horning, S.J., Coiffier, B., Fisher, R.I., Hagenbeek, A., Zucca, E., Rosen, S.T., Stroobants, S., Lister, T.A., Hoppe, R.T., Dreyling, M., Tobinai, K., Vose, J.M., Connors, J.M., Federico, M. & Diehl, V. (2007) Revised response criteria for malignant lymphoma. *Journal of Clinical Oncology*, **25**, 579–586.
- Damaj, G., Gressin, R., Bouabdallah, K., Cartron, G., Choufi, B., Gyan, E., Banos, A., Jaccard, A., Park, S., Tournilhac, O., Schiano-de Collela,

- J.M., Voillat, L., Joly, B., Le Gouill, S., Saad, A., Cony-Makhoul, P., Vilque, J.P., Sanhes, L., Schmidt-Tanguy, A., Bubenheim, M., Houot, R., Diouf, M., Marolleau, J.P., Bene, M.C., Martin, A. & Lamy, T. (2013) Results from a prospective, open-label, phase II trial of bendamustine in refractory or relapsed T-cell lymphomas: the BENTLY trial. *Journal of Clinical Oncology*, **31**, 104–110.
- De Pauw, B., Walsh, T.J., Donnelly, J.P., Stevens, D.A., Edwards, J.E., Calandra, T., Pappas, P.G., Maertens, J., Lortholary, O., Kauffman, C.A., Denning, D.W., Patterson, T.F., Maschmeyer, G., Bille, J., Dismukes, W.E., Herbrecht, R., Hope, W.W., Kibbler, C.C., Kullberg, B.J., Marr, K.A., Munoz, P., Odds, F.C., Perfect, J.R., Restrepo, A., Ruhnke, M., Segal, B.H., Sobel, J.D., Sorrell, T.C., Viscoli, C., Wingard, J.R., Zaoutis, T. & Bennett, J.E. (2008) Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clinical Infectious Diseases*, **46**, 1813–1821.
- Decaudin, D., Mounier, N., Tilly, H., Ribrag, V., Ghesquieres, H., Bouabdallah, K., Morschhauser, F., Coiffier, B., Le Gouill, S., Bologna, S., Delarue, R., Huynh, A., Bosly, A., Briere, J. & Gisselbrecht, C. (2011) 90Y ibritumomab tiuxetan (Zevalin) combined with BEAM (Z -BEAM) conditioning regimen plus autologous stem cell transplantation in relapsed or refractory low-grade CD20-positive B-cell lymphoma. A GELA phase II prospective study. *Clinical Lymphoma, Myeloma and Leukemia*, **11**, 212–218.
- Derenzini, E., Musuraca, G., Fanti, S., Stefoni, V., Tani, M., Alinari, L., Venturini, F., Gandolfi, L., Baccarani, M. & Zinzani, P.L. (2008) Pretransplantation positron emission tomography scan is the main predictor of autologous stem cell transplantation outcome in aggressive B-cell non-Hodgkin lymphoma. *Cancer*, **113**, 2496–2503.
- Garciaz, S., Coso, D., Schiano de Collella, J.M., Broussais, F., Stoppa, A.M., Aurran, T., Chabannon, C., Helvig, A., Xerri, L., Blaise, D. & Bouabdallah, R. (2016) Bendamustine-based conditioning for non-Hodgkin lymphoma autologous transplantation: an increasing risk of renal toxicity. *Bone Marrow Transplantation*, **51**, 319–321.
- Gilli, S., Novak, U., Taleghani, B.M., Baerlocher, G.M., Leibundgut, K., Banz, Y., Zander, T., Betticher, D., Egger, T., Rauch, D. & Pabst, T. (2017) BeEAM conditioning with bendamustine-replacing BCNU before autologous transplantation is safe and effective in lymphoma patients. *Annals of Hematology*, **96**, 421–429.
- Gisselbrecht, C., Schmitz, N., Mounier, N., Singh Gill, D., Linch, D.C., Trneny, M., Bosly, A., Milpied, N.J., Radford, J., Ketterer, N., Shpilberg, O., Duhren, U., Hagberg, H., Ma, D.D., Viardot, A., Lowenthal, R., Briere, J., Salles, G., Moskowitz, C.H. & Glass, B. (2012) Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20 (+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. *Journal of Clinical Oncology*, **30**, 4462–4469.
- Hoppe, B.S., Moskowitz, C.H., Zhang, Z., Maragulia, J.C., Rice, R.D., Reiner, A.S., Hamlin, P.A., Zelenetz, A.D. & Yahalom, J. (2009) The role of FDG-PET imaging and involved field radiotherapy in relapsed or refractory diffuse large B-cell lymphoma. *Bone Marrow Transplantation*, **43**, 941–948.
- Isidori, A., Christofides, A. & Visani, G. (2016) Novel regimens prior to autologous stem cell transplantation for the management of adults with relapsed/refractory non-Hodgkin lymphoma and Hodgkin lymphoma: alternatives to BEAM conditioning. *Leukaemia & Lymphoma*, **57**, 2499–2509.
- Jo, J.C., Kang, B.W., Jang, G., Sym, S.J., Lee, S.S., Koo, J.E., Kim, J.W., Kim, S., Huh, J. & Suh, C. (2008) BEAC or BEAM high-dose chemotherapy followed by autologous stem cell transplantation in non-Hodgkin's lymphoma patients: comparative analysis of efficacy and toxicity. *Annals of Hematology*, **87**, 43–48.
- Krishnan, A., Nademane, A., Fung, H.C., Raubitschek, A.A., Molina, A., Yamauchi, D., Rodriguez, R., Spielberger, R.T., Falk, P., Palmer, J.M. & Forman, S.J. (2008) Phase II trial of a transplantation regimen of yttrium-90 ibritumomab tiuxetan and high-dose chemotherapy in patients with non-Hodgkin's lymphoma. *Journal of Clinical Oncology*, **26**, 90–95.
- Laurent, C., Baron, M., Amara, N., Haioun, C., Dandoit, M., Maynadie, M., Parrens, M., Vergier, B., Copie-Bergman, C., Fabiani, B., Traverse-Glehen, A., Brousse, N., Copin, M.C., Tas, P., Petrella, T., Rousselet, M.C., Briere, J., Charlotte, F., Chassagne-Clement, C., Rousset, T., Xerri, L., Moreau, A., Martin, A., Damotte, D., Dartigues, P., Soubeyran, I., Peoch, M., Dechelette, P., Michiels, J.F., de Mascarel, A., Berger, F., Bossard, C., Arbiou, F., Quintin-Roué, I., Picquenot, J.M., Patey, M., Fabre, B., Sevestre, H., Le Naoures, C., Chenard-Neu, M.P., Bastien, C., Thiebault, S., Martin, L., Delage, M., Filleron, T., Salles, G., Molina, T.J., Delsol, G., Brousset, P. & Gaulard, P. (2017) Impact of expert pathologic review of lymphoma diagnosis: study of patients from the French lymphopath network. *Journal of Clinical Oncology*, **35**, 2008–2017.
- Leoni, L.M., Bailey, B., Reifert, J., Bendall, H.H., Zeller, R.W., Corbeil, J., Elliott, G. & Niemeyer, C.C. (2008) Bendamustine (Treanda) displays a distinct pattern of cytotoxicity and unique mechanistic features compared with other alkylating agents. *Clinical Cancer Research*, **14**, 309–317.
- Majhail, N.S., Farnia, S.H., Carpenter, P.A., Champlin, R.E., Crawford, S., Marks, D.I., Omel, J.L., Orchard, P.J., Palmer, J., Saber, W., Savani, B.N., Veys, P.A., Bredeson, C.N., Giral, S.A. & LeMaistre, C.F. (2015) Indications for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American society for blood and marrow transplantation. *Biology of Blood and Marrow Transplantation*, **21**, 1863–1869.
- Musso, M., Scalone, R., Marcacci, G., Lanza, F., Di Renzo, N., Cascavilla, N., Di Bartolomeo, P., Crescimanno, A., Perrone, T. & Pinto, A. (2010) Fotemustine plus etoposide, cytarabine and melphalan (FEAM) as a new conditioning regimen for lymphoma patients undergoing auto-SCT: a multicenter feasibility study. *Bone Marrow Transplantation*, **45**, 1147–1153.
- Musso, M., Messina, G., Di Renzo, N., Di Carlo, P., Vitolo, U., Scalone, R., Marcacci, G., Scalzulli, P.R., Moscato, T., Matera, R., Crescimanno, A., Santarone, S., Orciuolo, E., Merenda, A., Pavone, V., Pastore, D., Donnarumma, D., Carella, A.M., Ciochetto, C., Cascavilla, N., Mele, A., Lanza, F., Di Nicola, M., Bonizzoni, E. & Pinto, A. (2016) Improved outcome of patients with relapsed/refractory Hodgkin lymphoma with a new fotemustine-based high-dose chemotherapy regimen. *British Journal of Haematology*, **172**, 111–121.
- Ohmachi, K., Niitsu, N., Uchida, T., Kim, S.J., Ando, K., Takahashi, N., Takahashi, N., Uike, N., Eom, H.S., Chae, Y.S., Terauchi, T., Tateishi, U., Tatsumi, M., Kim, W.S., Tobinai, K., Suh, C. & Ogura, M. (2013) Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. *Journal of Clinical Oncology*, **31**, 2103–2109.
- Press, O.W., Eary, J.F., Gooley, T., Gopal, A.K., Liu, S., Rajendran, J.G., Maloney, D.G., Petersdorf, S., Bush, S.A., Durack, L.D., Martin, P.J., Fisher, D.R., Wood, B., Borrow, J.W., Porter, B., Smith, J.P., Matthews, D.C., Appelbaum, F.R. & Bernstein, I.D. (2000) A phase I/II trial of iodine-131-tositumomab (anti-CD20), etoposide, cyclophosphamide, and autologous stem cell transplantation for relapsed B-cell lymphomas. *Blood*, **96**, 2934–2942.
- Proctor, I.E., McNamara, C., Rodriguez-Justo, M., Isaacson, P.G. & Ramsay, A. (2011) Importance of expert central review in the diagnosis of lymphoid malignancies in a regional cancer network. *Journal of Clinical Oncology*, **29**, 1431–1435.
- Sauter, C.S., Matasar, M.J., Meikle, J., Schoder, H., Ulaner, G.A., Migliacci, J.C., Hilden, P., Devlin, S.M., Zelenetz, A.D. & Moskowitz, C.H. (2015) Prognostic value of FDG-PET prior to autologous stem cell transplantation for relapsed and refractory diffuse large B-cell lymphoma. *Blood*, **125**, 2579–2581.
- Schot, B.W., Zijlstra, J.M., Sluiter, W.J., van Imhoff, G.W., Pruim, J., Vaalburg, W. & Vellenga, E. (2007) Early FDG-PET assessment in combination with clinical risk scores determines prognosis in recurring lymphoma. *Blood*, **109**, 486–491.

- Sellner, L., Boumendil, A., Finel, H., Choquet, S., de Rosa, G., Falzetti, F., Scime, R., Kobbe, G., Ferrara, F., Delmer, A., Sayer, H., Amorim, S., Bouabdallah, R., Finke, J., Salles, G., Yakoub-Agha, I., Faber, E., Nicolas-Virelizier, E., Facchini, L., Vallisa, D., Zuffa, E., Sureda, A. & Dreger, P. (2016) Thiotepa-based high-dose therapy for autologous stem cell transplantation in lymphoma: a retrospective study from the EBMT. *Bone Marrow Transplantation*, **51**, 212–218.
- Shimoni, A., Avivi, I., Rowe, J.M., Yeshurun, M., Levi, I., Or, R., Patachenko, P., Avigdor, A., Zwas, T. & Nagler, A. (2012) A randomized study comparing yttrium-90 ibritumomab tiuxetan (Zevalin) and high-dose BEAM chemotherapy versus BEAM alone as the conditioning regimen before autologous stem cell transplantation in patients with aggressive lymphoma. *Cancer*, **118**, 4706–4714.
- Sureda, A., Bader, P., Cesaro, S., Dreger, P., Duarte, R.F., Dufour, C., Falkenburg, J.H., Farge-Bancel, D., Gennery, A., Kroger, N., Lanza, F., Marsh, J.C., Nagler, A., Peters, C., Velardi, A., Mohty, M. & Madrigal, A. (2015) Indications for allo- and auto-SCT for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2015. *Bone Marrow Transplantation*, **50**, 1037–1056.
- Terasawa, T., Dahabreh, I.J. & Nihashi, T. (2010) Fluorine-18-fluorodeoxyglucose positron emission tomography in response assessment before high-dose chemotherapy for lymphoma: a systematic review and meta-analysis. *Oncologist*, **15**, 750–759.
- Ulaner, G.A., Goldman, D.A., Sauter, C.S., Migliacci, J., Lilienstein, J., Gonen, M., Schoder, H., Moskowitz, C.H. & Zelenetz, A.D. (2015) Prognostic Value of FDG PET/CT before Allogeneic and Autologous Stem Cell Transplantation for Aggressive Lymphoma. *Radiology*, **277**, 518–526.
- Visani, G., Malerba, L., Stefani, P.M., Capria, S., Galièni, P., Gaudio, F., Specchia, G., Meloni, G., Gherlinzoni, F., Giardini, C., Falcioni, S., Cuberli, F., Gobbi, M., Sarina, B., Santoro, A., Ferrara, F., Rocchi, M., Ocio, E.M., Caballero, M.D. & Isidori, A. (2011) BeEAM (bendamustine, etoposide, cytarabine, melphalan) before autologous stem cell transplantation is safe and effective for resistant/relapsed lymphoma patients. *Blood*, **118**, 3419–3425.
- Visani, G., Stefani, P.M., Capria, S., Malerba, L., Galièni, P., Gaudio, F., Specchia, G., Meloni, G., Gherlinzoni, F., Gonella, R., Gobbi, M., Santoro, A., Ferrara, F., Rocchi, M., Ocio, E.M., Caballero, M.D., Loscocco, F. & Isidori, A. (2014) Bendamustine, etoposide, cytarabine, melphalan, and autologous stem cell rescue produce a 72% 3-year PFS in resistant lymphoma. *Blood*, **124**, 3029–3031.
- Vose, J.M., Bierman, P.J., Loberiza, F.R., Enke, C., Hankins, J., Bociek, R.G., Chan, W.C., Weisenburger, D.D. & Armitage, J.O. (2013a) Phase II trial of 131-Iodine tositumomab with high-dose chemotherapy and autologous stem cell transplantation for relapsed diffuse large B cell lymphoma. *Biology of Blood and Marrow Transplantation*, **19**, 123–128.
- Vose, J.M., Carter, S., Burns, L.J., Ayala, E., Press, O.W., Moskowitz, C.H., Stadtmauer, E.A., Mineshi, S., Ambinder, R., Fenske, T., Horowitz, M., Fisher, R. & Tomblyn, M. (2013b) Phase III randomized study of rituximab/carmustine, etoposide, cytarabine, and melphalan (BEAM) compared with iodine-131 tositumomab/BEAM with autologous hematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: results from the BMT CTN 0401 trial. *Journal of Clinical Oncology*, **31**, 1662–1668.
- Winter, J.N., Inwards, D.J., Spies, S., Wiseman, G., Patton, D., Erwin, W., Rademaker, A.W., Weitner, B.B., Williams, S.F., Tallman, M.S., Micallef, I., Mehta, J., Singhal, S., Evens, A.M., Zimmer, M., Molina, A., White, C.A. & Gordon, L.I. (2009) Yttrium-90 ibritumomab tiuxetan doses calculated to deliver up to 15 Gy to critical organs may be safely combined with high-dose BEAM and autologous transplantation in relapsed or refractory B-cell non-Hodgkin's lymphoma. *Journal of Clinical Oncology*, **27**, 1653–1659.