original reports

# Bortezomib-Dexamethasone, Rituximab, and Cyclophosphamide as First-Line Treatment for Waldenström's Macroglobulinemia: A Prospectively Randomized Trial of the European Consortium for Waldenström's Macroglobulinemia

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abstract

**PURPOSE** Rituximab/chemotherapy is a cornerstone of treatment for Waldenström's macroglobulinemia (WM). In addition, bortezomib has shown significant activity in WM. This study evaluated the efficacy and safety of dexamethasone, rituximab, and cyclophosphamide (DRC) as first-line treatment in WM.

**METHODS** In this European study, treatment-naïve patients were randomly assigned to DRC or bortezomib-DRC B-DRC for six cycles. The primary end point was progression-free survival. Secondary end points included response rates, overall survival, and safety.

**RESULTS** Two hundred four patients were registered. After a median follow-up of 27.5 months, the estimated 24-month progression-free survival was 80.6% (95% CI, 69.5 to 88.0) for B-DRC and 72.8% (95% CI, 61.3 to 81.3) for DRC ($P = .32$). At the end of treatment, B-DRC and DRC induced major responses in 80.6% versus 69.9% and a complete response/very good partial response in 17.2% versus 9.6% of patients, respectively. The median time to first response was shorter for B-DRC with 3.0 (95% CI, 2.8 to 3.2) versus 5.5 (95% CI, 2.9 to 5.8) months for DRC. This resulted in higher major response rates (57.0% *v* 32.5%; $P < .01$) after three cycles of B-DRC compared with DRC. At best response, the complete response/very good partial response increased to 32.6% for B-DRC. Both treatments were well tolerated: grade ≥ 3 adverse events occurred in 49.2% of all patients (B-DRC, 49.5%; DRC, 49.0%). Peripheral sensory neuropathy grade 3 occurred in two patients treated with B-DRC and in none with DRC.

**CONCLUSION** This large randomized study illustrates that B-DRC is highly effective and well tolerated in WM. The data demonstrate that fixed duration immunochemotherapy remains an important pillar in the clinical management of WM.

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ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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## INTRODUCTION

In Waldenström's macroglobulinemia (WM), the treatment goal is to control disease without compromising quality of life by treatment-related toxicity.[1] BTK inhibitors (BTKis) belong to the most efficient drugs for controlling WM.[2-4] However, this class of drugs has limitations: they have to be given as infinite treatment until disease progression and pausing treatment of ibrutinib can induce immunoglobulin M (IgM)–rebound phenomena associated with major constitutive symptoms.[5] In addition, ibrutinib-associated side effects lead to discontinuation of therapy in around one third of patients during the first 4 years.[2,6,7] Immunochemotherapy has the advantage to be a well-established highly efficient fixed duration treatment for patients with WM.[1] On the basis of this, rituximab/chemotherapy is considered to be one of the standards for treatment-naïve or relapsed WM.[1,8] The combination of dexamethasone, rituximab, and cyclophosphamide (DRC) has been shown to be well tolerated with nearly no grade 3/4 hematotoxicity and high antilymphoma activity in WM and, on the basis of this, has become one

## CONTEXT

**Key Objective**

How efficient and safe are dexamethasone, rituximab, and cyclophosphamide (DRC) plus bortezomib and DRC in the first-line treatment of Waldenström's macroglobulinemia (WM)?

**Knowledge Generated**

B-DRC is a highly efficient regimen in the first-line treatment of WM, which induces deep and fast responses in this lymphoma subtype. Because of potential neurotoxicity, individual patient characteristics should be taken into account before adding bortezomib to DRC. The data of this large randomized study demonstrate that fixed duration immunochemotherapy remains an important pillar in the clinical management of WM.

**Relevance *(S. Lentzsch)***

The faster response induction and improved overall response rate achieved by B-DRC is especially beneficial for patients with higher tumor burden requiring a faster response. In contrast to BTK inhibitors, the fixed duration of B-DRC improves tolerability in an elderly patient population. The regimen should be used judiciously in patients with neuropathy.*

*Relevance section written by *JCO* Associate Editor Suzanne Lentzsch, MD, PhD.

of the most widely used regimens in Europe and the United States.[9,10] Besides immunochemotherapy, the proteasome inhibitor bortezomib has shown remarkable activity in WM and minor neurotoxicity when given subcutaneously (SC) and once weekly.[11,12] Thus, addition of bortezomib to DRC might improve outcomes without a significant increase in toxicity, forming a fixed duration combination with high antilymphoma activity in WM. Here, we report the efficacy and safety of DRC in combination with bortezomib in treatment-naïve WM in the large randomized international multicenter European Consortium for Waldenström's Macroglobulinemia (ECWM)-1 study (ClinicalTrials.gov identifier: NCT01788020) initiated by the ECWM.

## METHODS

### Study Design, Sample Size, and Random Assignment

The study was performed as a European multicenter prospective randomized two-armed phase III open-label clinical trial in treatment-naïve patients with WM. Diagnosis of WM had to be confirmed by national reference pathology with the diagnosis of lymphoplasmacytic lymphoma and the presence of a monoclonal serum IgM. Patient inclusion and exclusion criteria are given in detail in the Data Supplement (online only). Patients had to show at least one criterion for initiation of therapy, according to the criteria developed at the second workshop on WM.[13] The protocol was approved by institutional review boards or independent ethics committees at participating institutions. The study was conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines from the International Conference on Harmonization. All patients provided written informed consent before the start of study-specific activities. The study enrolled a total of 204 patients in seven European countries in 53 different sites. Initially, the sample size was planned as a group sequential design according to O'Brien-Fleming with three sequential tests scheduled at 17, 32, and 48 months by a two-sided log-rank test with an overall sample size of 384 patients (corresponding to 106 events and achieving 90% power at a 0.05 significance level to detect a difference of 15% between the progression-free survival in groups 1 and 2, respectively, at the final analysis). This corresponds to a hazard ratio of 0.518. These results were based on the assumption of proportional hazard ratios. The study was conducted as planned in the protocol until September 21, 2018, when the recruitment was terminated early because of the approval of ibrutinib for the treatment of WM and slowing down recruitment. In total, 202 patients were randomly assigned 1:1 to DRC versus bortezomib plus DRC over a period of 4 years and 8 months. Random assignment was performed by the minimization method of Pocock and Simon stratified according to participating countries and three risk groups using the International Scoring System for Waldenström's Macroglobulinemia (ISSWM).[14,15]

### Study Treatment and End Points

Patients received either DRC (dexamethasone 20 mg orally once daily on day 1, rituximab 375 mg/m$^2$ intravenously (IV) once daily on day 1 of cycle 1 and 1,400 mg SC once daily on day 1 of cycles 2-6, and cyclophosphamide 100 mg/m$^2$ $\times$ 2 orally days 1-5) or B-DRC (DRC plus bortezomib given SC at a dose of 1.6 mg/m$^2$ once daily on days 1, 8, and 15) for six cycles (28-day interval). Prophylaxis for Herpes Zoster reactivation was obligatory for all patients treated with bortezomib during the treatment phase. The primary end point of the study was investigator-assessed progression-free survival (PFS). Secondary end points included investigator-assessed response rates (complete response [CR], very good partial response [VGPR], partial response [PR], and minor response) and overall response rate (ORR) 4 weeks after the end of induction therapy, best response, time to best response, time to first response, time to treatment failure, remission duration,

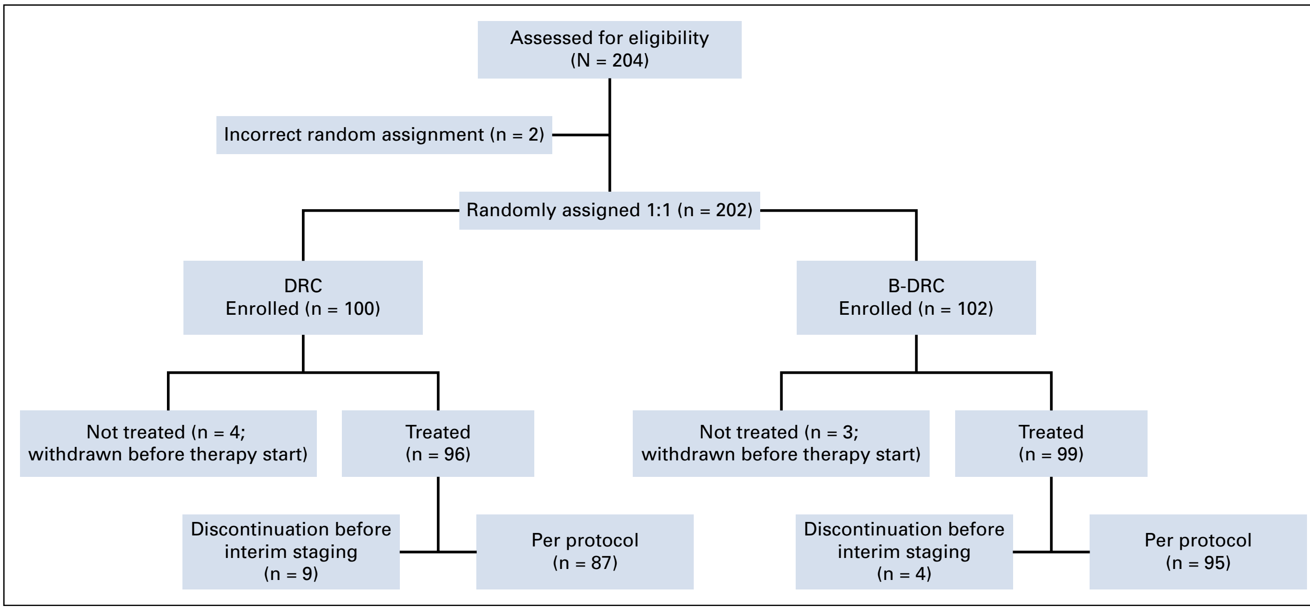


**FIG 1.** CONSORT diagram: patient flow of the study for both treatment arms. B-DRC, bortezomib, dexamethasone, rituximab, and cyclophosphamide; DRC, dexamethasone, rituximab and cyclophosphamide.

and overall survival. All patients who entered the trial were continued to be followed every 3 months for disease progression, subsequent treatment, and survival for 2 years after completion/discontinuation of the induction treatment. Subsequently, patients were monitored every 6 months for three additional years. Responses were assessed using the International Workshop for WM criteria.[16,17] Definitions of CR, VGPR, PR, and minor response; stable disease; and progressive disease followed the modified criteria of the VIth International Workshop (Data Supplement).[16] Toxicity was reported according to the Common Terminology Criteria for Adverse Events version 5.0 .

### Mutational Analysis

As the study was designed before the relevance of MYD88 and CXCR4 mutations in WM was established, mutational analysis was not part of the protocol and occurred only in a part of patients according to local standards ranging from allele-specific oligonucleotide polymerase chain reaction for MYD88 assessment in CD19-selected cells from bone marrow (BM) aspirates to Sanger sequencing or Next-Generation Sequencing (NGS) from nonselected BM material for MYD88 and from Sanger sequencing to NGS in CD19+-selected or nonselected BM cells for CXCR4.

### Statistical Analysis

Summary statistics are provided for all relevant efficacy end points by treatment group. The primary efficacy analyses are based on the intent-to-treat population, which includes all randomly assigned patients. PFS, the primary end point of this study, was defined as the interval between time from random assignment to the first documented progression or death because of any cause. Patients in ongoing remission at the time of analysis are censored on the date of their last follow-up. Secondary end points are analyzed to further assess treatment efficacy. Data from all patients who received at least one dose of study drug are included in the safety analyses. Life-threatening adverse events or events resulting in death or inpatient hospitalization or significant disability/incapacity, as well as cancers, which occurred during induction to 28 days after last dose of treatment, were considered as serious adverse events (SAE).

Continuous data are described using mean and standard deviation or median and quartiles as appropriate. In addition, minimum and maximum are provided. Categorical data are presented as frequencies and percentages. For survival analysis, the Kaplan-Meier method and the log-rank test were used. For analysis of response rates (part of the secondary end points), the chi square test or Fisher's exact test was used as appropriate to compare treatment groups. For analysis of continuous data, the Wilcoxon rank-sum test was used. In addition, to estimate the effect of prognostic factors, the hazard ratio with 95% CI was calculated using the Cox proportional hazard regression model. All statistical tests were performed at a two-sided significance level of $\alpha = 0.05$ and have—with exception of the primary analysis—to be interpreted as hypothesis-generating. Adjustment for multiple testing was not made. For statistical analyses, SAS version 9.4 (SAS Institute, Cary, NC) was used.

## RESULTS

### Patients

Two patients of 204 registered patients were excluded because of incorrect random assignment. One hundred two patients were randomly assigned into B-DRC, and 100

**TABLE 1.** Patient Characteristics

| Characteristic | DRC (n = 100) | B-DRC (n = 102) |
|---|---|---|
| Age, years, median (range) | 68.3 (39.1-83.1) | 68.0 (34.5-89.3) |
| > 65 years, No. (%) | 61 (61) | 63 (62) |
| > 75 years, No. (%) | 19 (19) | 27 (26) |
| Sex, No. (%) | | |
| Male | 67 (67) | 68 (67) |
| Female | 33 (33) | 34 (33) |
| ISSWM, No. (%) | | |
| Low | 12 (13) | 10 (10) |
| Intermediate | 31 (34) | 44 (44) |
| High | 49 (53) | 46 (46) |
| Evaluable patients | n = 92 | n = 100 |
| ECOG, No. (%) | | |
| 0 | 57 (59.4) | 51 (51) |
| 1 | 34 (35.4) | 44 (44) |
| 2 | 5 (5.2) | 4 (4) |
| Evaluable patients | n = 96 | n = 99 |
| Lymphadenopathy, No. (%) | 40 (43) | 51 (53) |
| Evaluable patients | n = 93 | n = 96 |
| Splenomegaly (≥ 13 cm), No. (%) | 31 (33) | 22 (23) |
| Evaluable patients | n = 94 | n = 95 |
| BM infiltration, % median (range) | 60 (7-97) | 60 (2-100) |
| Evaluable patients | n = 78 | n = 81 |
| Laboratory values | | |
| IgM g/L median (range) | 31.9 (1.0-112.0) | 31.7 (1.1-105.0) |
| Evaluable patients | n = 95 | n = 100 |
| Hb g/dL median (range) | 9.8 (7.1-15.4) | 10.0 (5.7-16.3) |
| Evaluable patients | n = 97 | n = 101 |
| Serum IgM > 70 g/L, % | 11.6 | 4.0 |
| Hemoglobin 10-11.5 g/dL, % | 25.8 | 30.7 |
| Hemoglobin < 10 g/dL, % | 54.6 | 48.5 |
| Platelets < 100 × $10^9$/L, % | 14.4 | 17.8 |
| ß2-Microglobulin > 3 mg/L, % | 74.4 | 75.5 |
| Genotype, No. (%) | | |
| $MYD88^{L265P}/CXCR4^{WT}$ | 19 (52.8) | 26 (65.0) |
| $MYD88^{L265P}/CXCR4^{MUT}$ | 12 (33.3) | 9 (22.5) |
| $MYD88^{WT}/CXCR4^{WT}$ | 5 (13.9) | 5 (12.5) |
| Evaluable patients | n = 36 | n= 40 |

Abbreviations: B-DRC, bortezomib, dexamethasone, rituximab, and cyclophosphamide; BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; DRC, dexamethasone, rituximab and cyclophosphamide; Hb, hemoglobin; IgM, immunoglobulin M; ISSWM, International Scoring System for Waldenström's Macroglobulinemia.

patients into the DRC arm, with 99 and 96 patients treated, respectively (Fig 1). The median follow-up was 27.5 (interquartile range, 17.2-36.1) months at the time of the data cutoff, and 53 events were recorded. The median age was 68 (range, 34-89) years in both arms. According to the ISSWM prognostic score, 11% of patients were at low, 39% at intermediate, and 50% at high risk in both treatment arms. The median baseline hemoglobin level for B-DRC and DRC was 10.0 and 9.8 g/dL, and the median baseline IgM level was 31.7 and 31.9 g/L, respectively. Mutational status was available for 76 patients (Table 1 and Data Supplement). Eighty-seven percent of treated patients in the DRC arm and 92% in the B-DRC arm received six cycles of induction, and only 7% in DRC and 4% in B-DRC received two or fewer cycles of treatment (Data Supplement). The mean dose density for bortezomib was 95% (range, 61%-100%) for all patients who received bortezomib. In 40% of the patients, bortezomib was reduced, receiving a mean dose of 86% (range, 61-97) of the full dose (Data Supplement). Addition of bortezomib did not result in any major dose reduction of the DRC regimen compared with DRC alone (data not shown).

## Responses

At the end of treatment, B-DRC induced major responses (at least PR) in 80.6% (75 of 93) of patients (*v* 69.9% for DRC; 58 of 83; *P* = .10) and a CR/VGPR in 17.2% of patients (16 of 93; *v* 9.6% for DRC; 8 of 83; *P* = .14) with an overall response of 94.6 (88 of 93) compared with 86.7% (72 of 83; *P* = .07) for DRC (Fig 2A). One patient in the B-DRC arm achieved a CR, confirmed by BM biopsy. The median time to first response was shorter for B-DRC with 3.0 (95% CI, 2.8 to 3.2) months versus 5.5 (95% CI, 2.9 to 5.8) months for DRC. This resulted in higher response rates after three cycles of treatment for B-DRC compared with DRC with an ORR and major response of 78.5% and 57.0% versus 65.0% and 32.5% (*P* < .01 for major response), respectively (*P* = .05 for ORR; Fig 2B). At best response, major response rates increased to 85.3% for B-DRC and 82.4% for DRC with 32.7% and 20.9% CR/VGPR, respectively (Fig 2C; *P* = .60 for major response and *P* = .07 for CR/VGPR). Responses at the end of induction were largely independent of the mutational status of MYD88 and CXCR4 although patient numbers were limited (Data Supplement). B-DRC and DRC induced a robust decline of IgM and an increase in hemoglobin (Hb): compared with baseline, the median IgM level decreased by 79% and 72% (*P* = .15, Wilcoxon rank-sum test) and the median Hb level increased by 28% and 32% (*P* = .51, Wilcoxon rank-sum test) in the B-DRC and DRC arm, respectively, at the end of induction (Fig 3). In line with a more rapid response after three cycles for B-DRC, the median IgM level dropped to 10.8 g/L (0.3-67.9) and 17.3 g/L (0.4-88.0) in the B-DRC and DRC arm, respectively (*P* = .01, Wilcoxon rank-sum test; Fig 3).

## Survival

The estimated 24-month PFS was 80.6% (95% CI, 69.5 to 88.0) for B-DRC and 72.8% (95% CI, 61.3 to 81.3) for DRC (*P* = .32; Fig 4A). PFS was dependent on the risk group according to the ISSWM with a 24-month PFS in the DRC arm

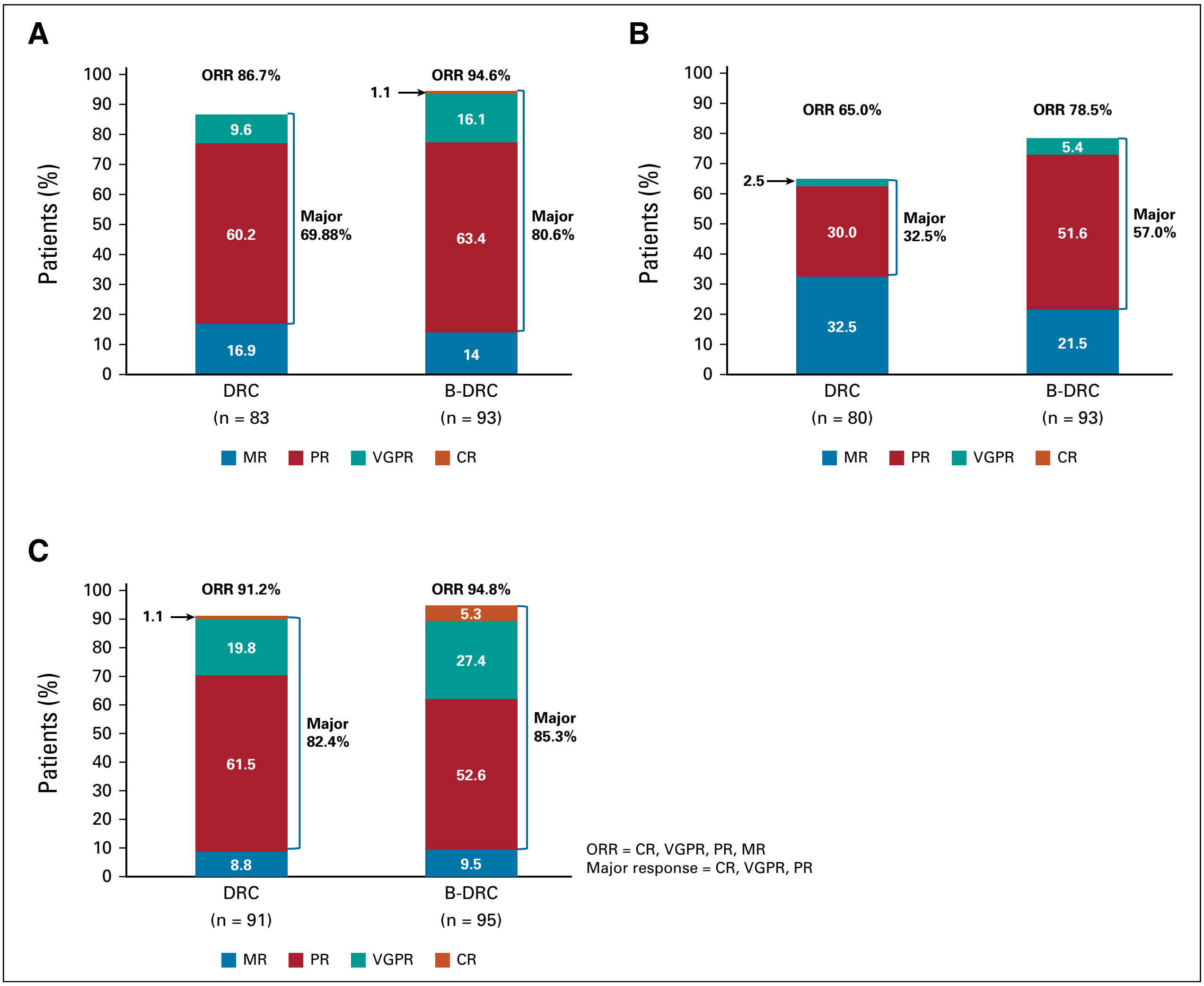


**FIG 2.** Response rates: (A) ORR at the end of induction, (B) ORR at the end of cycle 3, and (C) best response. B-DRC, bortezomib, dexamethasone, rituximab, and cyclophosphamide; CR, complete response; DRC, dexamethasone, rituximab, and cyclophosphamide; MR, minor response; ORR, overall response rate; PR, partial response; VGPR, very good partial response.

of 100.0% in the low- versus 68.3% and 69.8% in the intermediate- and high-risk group, respectively. In the B-DRC arm, the 24-month PFS was 100.0% for the low- versus 77.7% for the intermediate- and 77.5% for the high-risk group (Fig 4B). DRC and B-DRC induced comparable PFS in the MYD88-mutated patients with or without CXCR4 mutation, but follow-up and patient number were limited (Data Supplement). Median OS has not been reached in either treatment arm with five deaths in the B-DRC and six in the DRC arm (Fig 4C). Causes of death were classified as lymphoma-related in four patients (three patients in the DRC and one patient in the B-DRC arm), and two patients developed secondary neoplasia (one in each arm; Data Supplement).

## Safety

B-DRC and DRC were well tolerated: grade ≥ 3 AEs occurred in 49.2% of all patients (B-DRC 49.5%, DRC 49%). In the total patient group, most common grade ≥ 3 AEs included neutropenia (25.6%), anemia (6.2%), and thrombocytopenia (5.1%). A total of 46 patients developed infections with a trend toward more infections including upper respiratory infections in the B-DRC arm compared with DRC alone. SAEs occurred in 40 patients (20.5%; DRC, 26 [27.1%]; B-DRC, 14 [14.1%]). Peripheral sensory neuropathy occurred in 18 patients treated with B-DRC (two patients with grade 3 and 16 patients grade 1-2) and in three patients treated with DRC (all grade 1 and 2; Table 2). In total, in 13 of 21 patients, neuropathy had been resolved at the end of induction; eight patients had ongoing neuropathy (one patient with grade 1, six patients with grade 2, and one patient with grade 3, all in the B-DRC arm).

## DISCUSSION

Rituximab/chemotherapy combinations such as DRC or rituximab-bendamustine are still one of the pillars in the

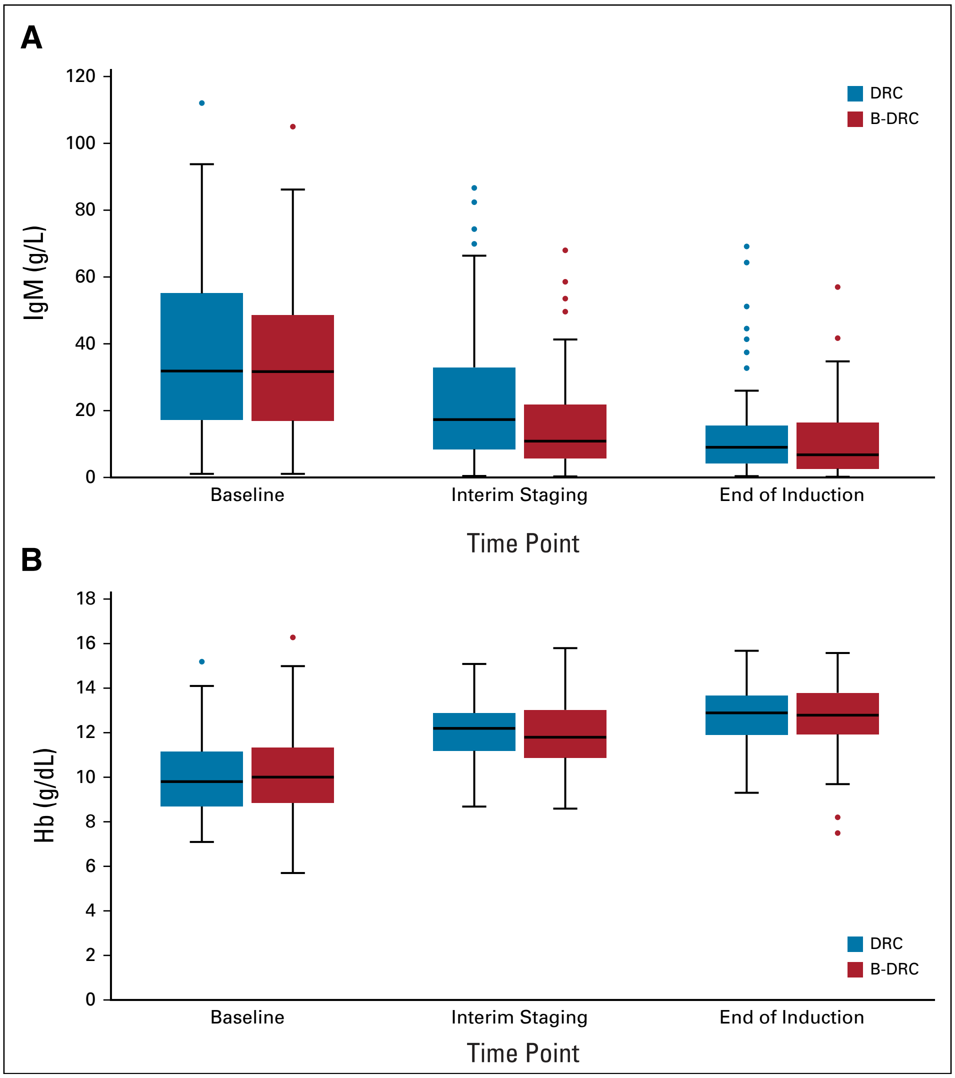


**FIG 3.** IgM and hemoglobin: changes in (A) IgM and (B) hemoglobin levels at interim staging and the end of induction. B-DRC, bortezomib, dexamethasone, rituximab, and cyclophosphamide; DRC, dexamethasone, rituximab and cyclophosphamide; IgM, immunoglobulin M.

treatment landscape of WM, on the basis of their potential to control WM over years despite their timely fixed duration of treatment.[1,18] The ECWM embarked on a prospective international randomized trial, which aimed at testing the efficacy of added SC bortezomib to DRC in comparison with DRC. This trial that enrolled more than 200 patients is one of the largest of its kind in the rare lymphoma subtype of WM. The data demonstrate that adding bortezomib to DRC shortened median time to first response and increased the number of patients achieving a CR/VGPR. This resulted in an improved ORR and a significant increase in the major response rate after three cycles of treatment for the bortezomib arm. The high activity of B-DRC was confirmed at best response with nearly every third patient achieving a CR/VGPR compared with 20.9% for DRC. This high activity of B-DRC did not translate into an improved PFS or OS compared with the DRC regimen, with few events for both PFS and OS at the data cutoff. Longer follow-up is needed to evaluate the impact of adding bortezomib to DRC on PFS. There were around 10% more patients with intermediate-/high-risk ISSWM progression-free at 2 years in the B-DRC arm compared with DRC alone, but longer follow-up will clarify whether B-DRC is able to improve PFS compared with DRC in the different risk groups.

Neuropathy is a concern for bortezomib, and patients with pre-existing ≥ grade 2 neuropathy were excluded from the study. We applied bortezomib SC at a dose of 1.6 mg/m$^2$ once weekly in this trial, on the basis of data in relapsed and treatment-naïve patients with WM and favorable toxicity data of weekly versus twice weekly application of bortezomib in multiple myeloma.[11,19,20] Development of peripheral neuropathy clustered in the B-DRC arm, with 18 patients versus three patients developing neuropathy in the DRC arm. Most of the neuropathies were grade 1-2;

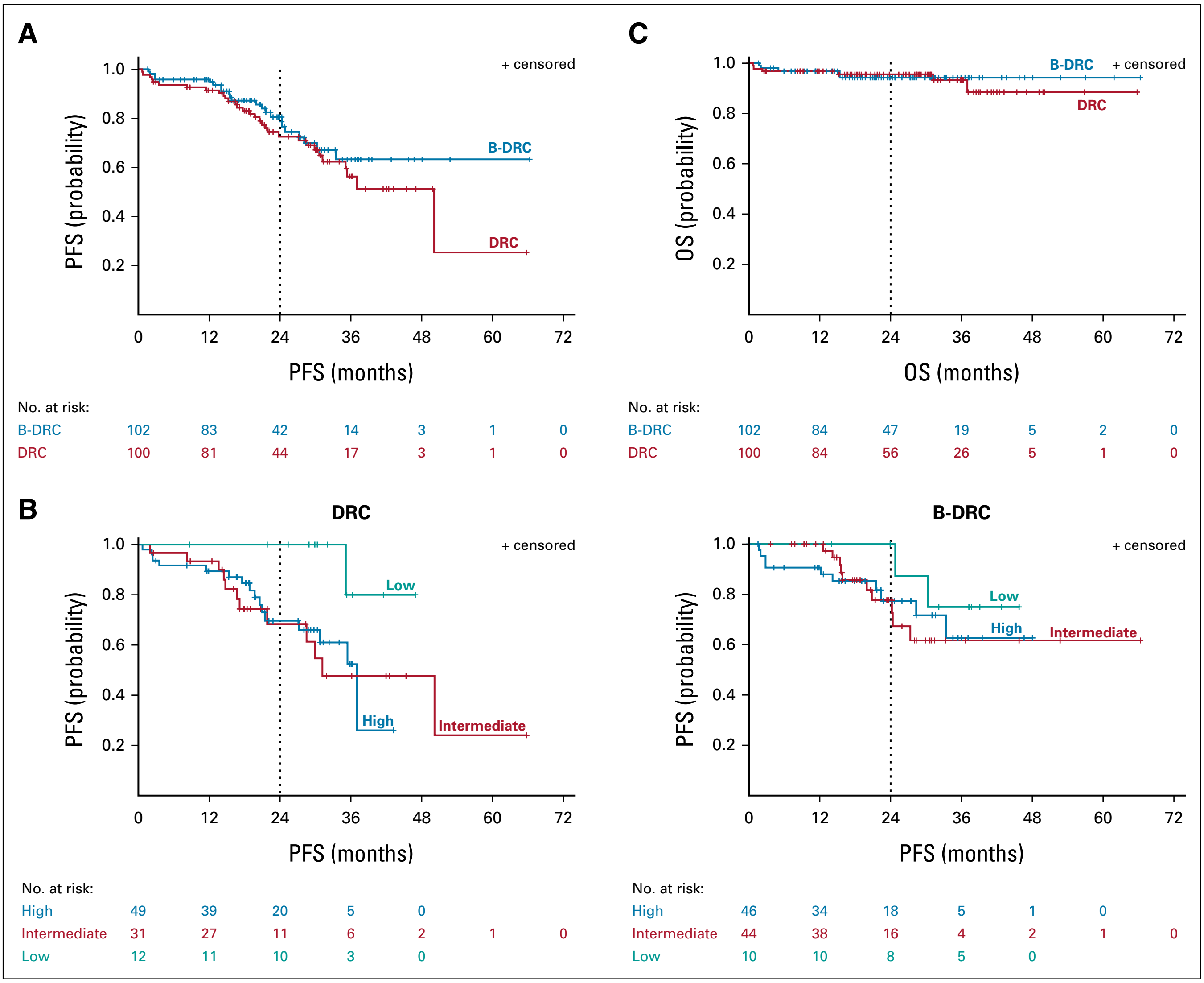


**FIG 4.** PFS for (A) the total cohort and (B) according to the treatment arm and ISSWM score and (C) OS for the total cohort. B-DRC, bortezomib, dexamethasone, rituximab, and cyclophosphamide; DRC, dexamethasone, rituximab, and cyclophosphamide; ISSWM, International Scoring System for Waldenström's Macroglobulinemia; OS, overall survival; PFS, progression-free survival.

however, even lower-grade neurotoxicity can be clinically challenging and compromise the patient's quality of life. However, in 10 of 18 patients treated with B-DRC, neuropathy resolved at the end of treatment. In a previous phase II study, 54% of patients with WM developed neuropathy after treatment with bortezomib IV weekly at 1.6 mg/m$^2$ once daily on days 1, 8, 15, every 28 days $\times$ 6 cycles, and rituximab weekly at 375 mg/m$^2$ once daily on cycles 1 and 4.[19] Thus, bortezomib given once weekly and via SC injection was associated with low neurotoxicity, but individual patient characteristics should be taken into account before adding bortezomib to DRC.

The study also underlines that DRC is a highly active and very safe first-line treatment option for patients with WM, also when de-escalated by applying 4-week intervals in contrast to the original schedule as a 3-week interval regimen.[19] At the end of induction, DRC induced a major response of nearly 70% with an overall response of 86.7% in treatment-naïve patients with WM, comparable with data reported for DRC given in 3-week intervals.[9,21] This illustrates that on the basis of a robust and large data set, 4-weekly applications of DRC are feasible and do not compromise the antilymphoma activity of the regimen. Of note, DRC given every 4 weeks over six cycles had an excellent safety profile: grade 3 or higher hematotoxicity was very low with 4% of the patients developing leukopenia or thrombocytopenia and 3% of the patients suffering from infections grade $\geq$ 3.

Beside immunochemotherapy, BTKis are widely used for the treatment of WM. In a phase II study in treatment-naïve patients with WM, best responses for ibrutinib were reported to be 83%, with 20% VGPR and none of the patients

**TABLE 2.** Safety

| | DRC (n = 96) | B-DRC (n = 99) |
|---|---|---|
| **Event** | **No. (%)** | **No. (%)** |
| Patients with any AE | 87 (90.6) | 91 (91.9) |
| Most common AEs (all grades) | | |
| Anemia | 22 (23) | 21 (21.2) |
| Nausea | 36 (38) | 40 (40.4) |
| Neutropenia | 27 (28) | 27 (27.3) |
| Patients with ≥ 3 grade AE | 47 (49.0) | 49 (49.5) |
| Most common AEs (≥ 3 grade) | | |
| Anemia | 6 (6.3) | 6 (6.1) |
| Leukopenia | 4 (4.2) | 3 (3.0) |
| Thrombocytopenia | 4 (4.2) | 6 (6.1) |
| Neutropenia | 24 (25.0) | 26 (26.3) |
| Infections (all grades) | 14 (14.6) | 32 (32.3) |
| Upper respiratory infection | 2 (2.1) | 15 (15.2) |
| Infections (≥3 grade) | 3 (3.1) | 4 (4.0) |
| Upper respiratory infection | — | 3 (3.0) |
| Peripheral sensory neuropathy | | |
| Grade 1 | 1 (1.0) | 10 (10.1) |
| Grade 2 | 2 (2.1) | 6 (6.1) |
| Grade 3 | | 2 (2.0) |
| Patients with SAEs | 26 (27.1) | 14 (14.1) |
| Most common SAEs | | |
| Dyspnea | 2 (2.1) | 1 (1.0) |
| Neoplasm (various) | 1 (1.0) | 2 (2.0) |
| Pneumonitis | 2 (2.1) | 2 (2.0) |
| Fever | 5 (5.2) | 1 (1.0) |
| SUSAR | — | — |

Abbreviations: AE, adverse event; B-DRC, bortezomib, dexamethasone, rituximab, and cyclophosphamide; DRC, dexamethasone, rituximab, and cyclophosphamide; SAEs, serious adverse events; SUSAR, suspected unexpected serious adverse reaction.

achieving a CR after a median treatment duration of 13.4 months.[22] In the ASPEN trial comparing zanubrutinib with ibrutinib in MYD88-mutated WM, zanubrutinib achieved a VGPR rate of 26% compared with 17% for ibrutinib, with no CRs in both treatment arms for treatment-naïve patients.[3] After a median treatment of 47 months with ibrutinib, the major response rate increased to 78%, including 27% of patients with VGPR.[23] In light of these data, the proportion of patients with 32.6% achieving a VGPR/CR with B-DRC is remarkable after just 6 months of treatment. In the same line, the estimated 24-month PFS of 80.6% after B-DRC treatment confirms its high efficacy in WM and underlines that with regard to efficacy and safety, B-DRC is a highly attractive regimen for treatment-naïve patients with WM also in the era of BTKi. In this trial, DRC and B-DRC acted largely independent of the MYD88 mutational status with regard to response. The methods used for determining the mutational status were approximately balanced between both arms although not for all patients, this information was available. These data, however, have to be taken with caution as the patient number was limited and there was no central methodologically harmonized mutational analysis performed in this study. Furthermore, there were too few events to evaluate the impact of the genotype on PFS in the limited number of patients available for analysis in this trial. However, the observation that in contrast to BTKis, immunochemotherapies and bortezomib act independent of the mutational status in WM is in line with previous reports.[3,4,24,25]

One of the key questions will be how chemotherapy-free approaches of fixed duration will compare with immunochemotherapy. Thus, randomized trials comparing head-to-head immunochemotherapies with BTKi or BCL2 inhibitors given for a limited time period are urgently needed.[26] In an upcoming trial coordinated by the ECWM, six cycles of 4-weekly DRC will be compared with venetoclax/rituximab limited to 12-month treatment (ClinicalTrials.gov identifier: NCT05099471).

Taken together, DRC remains an important treatment option in WM. In patients with a need of rapid response not suffering from WM-associated neuropathy, addition of bortezomib to DRC might be an attractive therapy, always weighing the more rapid and deeper responses achieved by this regimen against potential neurotoxicity. B-DRC has the advantage over R-bendamustine to avoid long-lasting and deep T-cell depletion. This might be particularly important in the era of emerging novel therapies such as bispecific antibodies or CAR-T cells, which are compromised by T-cell exhaustion. In addition, B-DRC is a timely fixed duration treatment in contrast to BTKis, improving tolerability by shortening the treatment duration in an elderly patient population. Finally, the data demonstrate that immunochemotherapy remains an important pillar in the clinical management of WM in the era of targeted therapies.

## AFFILIATIONS

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Bortezomib-Dexamethasone, Rituximab, and Cyclophosphamide as First-Line Treatment for Waldenström's Macroglobulinemia: A Prospectively Randomized Trial of the European Consortium for Waldenström's Macroglobulinemia**

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