

# Bortezomib, Melphalan, and Dexamethasone for Light-Chain Amyloidosis

Efstathios Kastritis, MD<sup>1</sup>; Xavier Leleu, MD, PhD<sup>2</sup>; Bertrand Arnulf, MD, PhD<sup>3</sup>; Elena Zamagni, MD<sup>4</sup>; María Teresa Cibeira, MD, PhD<sup>5</sup>; Fiona Kwok, MD, MBBS<sup>6</sup>; Peter Mollee, MBBS, MMedSc<sup>7</sup>; Roman Hájek, MD<sup>8</sup>; Philippe Moreau, MD<sup>9</sup>; Arnaud Jaccard, MD, PhD<sup>10</sup>; Stefan O. Schönland, MD<sup>11</sup>; Robin Filshie, MBChB, PhD<sup>12</sup>; Emmanuelle Nicolas-Virelizier, MD<sup>13</sup>; Bradley Augustson, MD<sup>14</sup>; María-Victoria Mateos, MD, PhD<sup>15</sup>; Ashutosh Wechalekar, MD<sup>16</sup>; Eric Hachulla, MD, PhD<sup>2</sup>; Paolo Milani, MD, PhD<sup>17</sup>; Meletios A. Dimopoulos, MD<sup>1</sup>; Jean-Paul Fermand, MD<sup>3</sup>; Andrea Foli, MD<sup>17</sup>; Maria Gavriatopoulou, MD<sup>1</sup>; Catherine Klersy, MD, MScEpid<sup>18</sup>; Antonio Palumbo, MD<sup>19</sup>; Pieter Sonneveld, MD, PhD<sup>20</sup>; Hans Erik Johnsen, MD<sup>21†</sup>; Giampaolo Merlini, MD<sup>17,22</sup>; and Giovanni Palladini, MD, PhD<sup>17,22</sup>

**PURPOSE** Oral melphalan and dexamethasone (MDex) were considered a standard of care in light-chain (AL) amyloidosis. In the past decade, bortezomib has been increasingly used in combination with alkylating agents and dexamethasone. We prospectively compared the efficacy and safety of MDex and MDex with the addition of bortezomib (BMDex).

**METHODS** This was a phase III, multicenter, randomized, open-label trial. Patients were stratified according to cardiac stage. Patients with advanced cardiac stage (stage IIIb) amyloidosis were not eligible. The primary end point was hematologic response rate at 3 months. This trial is registered with ClinicalTrials.gov identifier NCT01277016.

**RESULTS** A total of 109 patients, 53 in the BMDex and 56 in the MDex group, received  $\geq 1$  dose of therapy (from January 2011 to February 2016). Hematologic response rate at 3 months was higher in the BMDex arm (79% v 52%;  $P = .002$ ). Higher rates of very good partial or complete response rates (64% v 39%; hazard ratio [HR], 2.47; 95% CI, 1.30 to 4.71) and improved overall survival, with a 2-fold decrease in mortality rate (HR, 0.50; 95% CI, 0.27 to 0.90), were observed in the BMDex arm. Grade 3 and 4 adverse events (the most common being cytopenia, peripheral neuropathy, and heart failure) were more common in the BMDex arm, occurring in 20% versus 10% of cycles performed.

**CONCLUSION** BMDex improved hematologic response rate and overall survival. To our knowledge, this is the first time a controlled study has demonstrated a survival advantage in AL amyloidosis. BMDex should be considered a new standard of care for AL amyloidosis.

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## ASSOCIATED CONTENT

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[Data Supplement Protocol](#)

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

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## INTRODUCTION

Systemic light-chain (AL) amyloidosis is caused by monoclonal light chains (LCs) misfolding and aggregating into fibrils that deposit in tissue, causing progressive organ dysfunction that is fatal if diagnosis is delayed or treatment is ineffective.<sup>1</sup> Presently, treatment is aimed at reducing the availability of the precursor protein, using chemotherapy to target the plasma cell clone producing the amyloid LC.<sup>2</sup> The regimens derive from those developed for treatment of multiple myeloma and that are attenuated to account for the frailty of patients with AL amyloidosis.<sup>2</sup> The circulating LC exerts a toxic effect on target organs and not only is a marker of clonal disease but is also directly responsible of organ dysfunction.<sup>3</sup> Thus, rapidly achieving a reduction of the LC is key to improve organ dysfunction and extend survival. Assessment

of hematologic response is based on measurement of circulating free LCs (FLCs) and strongly predicts overall survival (OS).<sup>4</sup> Benefit is maximum for patients attaining complete response (CR) and progressively decreases for other response categories.<sup>4</sup> Severity of organ involvement is accurately assessed with biomarkers.<sup>5-7</sup> Changes in biomarker levels are used to assess organ response and are powerful predictors of OS.<sup>4,7</sup> Criteria for hematologic and organ response have been validated on the basis of OS and are used in the treatment of individual patients and as surrogate end points in clinical trials.<sup>4,7</sup> Early assessment of response is necessary to effect a timely shift to rescue treatment in nonresponders.<sup>2,4,8</sup>

With an estimated incidence of 3-13 cases per million person-year, AL amyloidosis is rarer than multiple myeloma.<sup>2,9</sup> Thus, it has been difficult to run large

## CONTEXT

### Key Objective

No controlled studies exist that established a standard of care for newly diagnosed patients with light-chain (AL) amyloidosis who are not eligible for autologous stem cell transplant. Oral melphalan and dexamethasone (MDex) has been used for > 15 years and, more recently, bortezomib combinations have been used off-label. We compared the efficacy and safety of MDex and MDex with the addition of bortezomib (BMDex) in 110 newly diagnosed patients with AL amyloidosis.

### Knowledge Generated

Overall hematologic response rate was higher and hematologic responses were deeper with BMDex. BMDex also resulted in prolonged progression-free and overall survival.

### Relevance

This study showed an overall survival advantage with an effective therapy over another in this rare disease, proving the feasibility of investigator-initiated studies in this challenging context and establishing BMDex as a standard of care and suitable comparator for future trials in AL amyloidosis.

controlled trials. Only a few have been published so far, and none of them evaluated modern agents.<sup>10,11</sup> In 2007, Jaccard et al<sup>12</sup> compared oral melphalan and dexamethasone (MDex) with autologous stem cell transplant (ASCT) in 100 patients. They found OS was superior in the MDex arm but no significant difference was observed when early deaths were excluded.<sup>12</sup> Because of lack of controlled studies, upfront treatment of patients with AL amyloidosis is based on retrospective series or small, uncontrolled trials. Approximately 20% to 25% of patients are eligible for ASCT, whereas MDex has long been considered standard therapy for patients who are not transplant candidates.<sup>2</sup> Hematologic response rate to MDex ranged from 45% to 75%, and median OS > 7 years has been reported.<sup>12-15</sup> However, based on common practice in multiple myeloma and on encouraging results in large retrospective series<sup>16-19</sup> and in a phase II clinical trial in previously treated patients,<sup>19,20</sup> the proteasome inhibitor bortezomib is increasingly used in upfront treatment.

Proteasome inhibition is an appealing treatment approach because amyloidogenic plasma cells use the proteasome to cope with the proteotoxicity exerted by amyloidogenic LCs.<sup>21</sup> Bortezomib is most commonly combined with cyclophosphamide and dexamethasone (CyBorD) or added to MDex (BMDex).<sup>2</sup> In multiple myeloma, the combination of bortezomib, melphalan, and prednisone is standard of care for transplant-ineligible patients and is a backbone of novel combinations.<sup>22-24</sup> Two retrospective, matched case-control studies compared BMDex and CyBorD with MDex and the combination of cyclophosphamide, thalidomide, and dexamethasone, respectively, in patients with AL amyloidosis and found no difference in OS and hematologic response rate.<sup>25,26</sup> Thus, until now, to our knowledge, no controlled study has established bortezomib-based treatment as a standard of care in AL amyloidosis. This is relevant when newer drugs are being tested and established standards of care are needed as comparators. In the

present trial, we compared the safety and efficacy of MDex and BMDex in patients with newly diagnosed AL amyloidosis.

## METHODS

This was an investigator-initiated, multicenter, randomized, controlled, open-label clinical trial aimed to assess the efficacy of BMDex compared with MDex in previously untreated patients with AL amyloidosis who were not candidates for high-dose melphalan with ASCT. The study was approved by the institutional review boards of all participating centers. All patients signed a written informed consent.

### Patients

Eligibility criteria are reported in detail in the Data Supplement (online only). Briefly, patients were required to have a diagnosis of AL-type amyloidosis and adequate blood cell count and renal and liver function. Patients with advanced cardiac amyloidosis were excluded, as were those with overt multiple myeloma. Patients had to have measurable hematologic disease, defined as a difference between involved and uninvolved FLCs (dFLCs) > 50 mg/L with an abnormal ratio and/or a serum monoclonal protein concentration > 10 g/L.

On the basis of the Mayo 2004/European cardiac staging system, which uses *N*-terminal proatriuretic peptide type B (NT-proBNP) and troponin I or T (Data Supplement), patients were stratified as having stage I, II, or IIIa disease.<sup>5,27</sup> Patients with stage IIIb disease, with advanced cardiac involvement, were not eligible. Patients were enrolled and treated in 17 amyloidosis centers in Europe and Australia.

### Interventions

Patients in the MDex arm received oral melphalan 0.22 mg/kg and dexamethasone 40 mg daily for 4 consecutive days every 28 days. Patients in the BMDex arm

received, for cycles 1 and 2, MDex with bortezomib added at 1.3 mg/m<sup>2</sup> on days 1, 4, 8, and 11 of a 28-day cycle; for cycles 3–8, MDex with bortezomib added at 1.3 mg/m<sup>2</sup> was given on days 1, 8, 15, and 22 of a 35-day cycle. Bortezomib administration was shifted from intravenous to subcutaneous in January 2013 after 10 patients had been enrolled in the BMDex arm, once the use of subcutaneous bortezomib was approved. Treatment was continued until completion of maximum allowed number of cycles (9 cycles for MDex; 8 cycles for BMDex), or achievement of a complete hematologic response (CR) after cycle 6, or a partial hematologic response (PR) and organ response after cycle 6 (indicating that hematologic response was profound enough to cause improvement of amyloid organ dysfunction), or achievement of less than PR after cycle 3 or progression of clonal plasma cell disease (to allow starting second-line therapy at local physician's discretion).

### Outcomes

The primary objective was to compare hematologic response after 3 cycles between the 2 arms. CR required negative serum and urine immunofixation and normal FLC ratio, very good partial response (VGPR) achievement of dFLCs < 40 mg/L, and PR, defined as a decrease of dFLC by  $\geq 50\%$ . Organ response was defined by changes in relevant biomarkers: NT-proBNP for the heart, proteinuria for the kidney, and alkaline phosphatase for the liver.<sup>4,28</sup> The primary end point was overall hematologic response rate after 3 cycles. Secondary efficacy end points were:

1. CR and VGPR rate after 3 cycles and after completion of therapy
2. Overall hematologic response rate at completion of therapy
3. Organ response rates at 3, 6, and 9 months
4. Quality of life (QoL) after 3 cycles, assessed with the Quality of Life Questionnaire Core 30 (QLC30 (score for global health status [QL2]) and the physical (PCS) and mental (MCS) component scores on the Short Form 36 health survey, version 2
5. OS and progression-free survival (PFS; defined as death or hematologic and/or organ progression, whichever came first). Safety end points were treatment-related death and toxicity. Response and progression criteria are detailed in the Data Supplement.

### Statistical Methods

Planned accrual calculation was based on the primary end point, hematologic response after 3 cycles, which was known to be approximately 60% with MDex.<sup>12,13</sup> The expected hematologic response with BMDex was 85%. With  $\alpha$  (2-sided) equal to 0.05 and power of 0.80, 49 patients were required in each arm (a total 110 patients, accounting for possible dropouts). Details on randomization and blinding are reported in the Data Supplement.

We used STATA 15 (StataCorp, College Station, TX) for computation. All efficacy analyses were performed on the basis of the intent-to-treat (ITT) principle on the modified ITT population including all patients who received  $\geq 1$  dose. The difference in rate and 95% CI in the overall hematologic response were derived from a generalized linear model extended to the binomial family while adjusting for cardiac stage. Secondary end points were analyzed with binomial models when comparing rates, stratified by cardiac stage, with calculation of Huber White robust standard errors to account for intrasubject correlation of measures, when comparing response over time; the test of interaction of time and arm was used to compare the changes in rates of secondary end points between the 2 arms. The log-rank test and Cox regression (stratified for cardiac stage) were used to model time-to-event end points. A linear regression model was fitted for QoL, while adjusting for baseline QoL score and cardiac stage. Rates of grade 3 and 4 adverse events were compared over the number of cycles by Poisson regression. The incidence rate ratios (IRRs) and 95% CIs were computed.

### RESULTS

Recruitment started on January 28, 2011, and was completed in February 15, 2016. Of 178 patients screened, 110 were stratified and subsequently randomly assigned to receive BMDex or MDex (Data Supplementary). One patient in the MDex arm discontinued the study because of renal failure before the first cycle was initiated. A total of 109 patients, 53 in the BMDex and 56 in the MDex group, received  $\geq 1$  dose. Forty-three patients (81%) in the BMDex arm received bortezomib subcutaneously. Baseline characteristics were well balanced (Table 1). The median number of cycles completed was 6 in the BMDex arm (range, 2-9 cycles) and 5 in the MDex arm (range, 1-8 cycles). The median cumulative dose of melphalan was 343 mg/kg (range, 68-739 mg/kg). Forty-three patients (81%) in the MDex arm and 40 (71%) in the BMDex arm stopped treatment before the maximum allowed number of cycles because of achievement of a satisfactory response in 19 (44%) of 43 patients and 31 (77%) of 40 patients in the MDex and BMDex arms, respectively. The remaining patients did not complete the maximum allowed number of cycles, because of toxicity or because hematologic response was not achieved.

### Primary efficacy end point

The primary efficacy end point was overall hematologic response rate after cycle 3 (Table 2). This was significantly higher in the BMDex arm (79% v 52%;  $P = .002$ ). There was no significant difference in response rate between BMDex intravenous and subcutaneous routes (9 patients [90%] v 33 patients [73%]; difference in rate, 17%, 95% CI, -9% to 36%). The distribution of response categories significantly differed between groups, with a higher

**TABLE 1.** Baseline Demographic and Clinical Characteristics of the Patients

| Characteristic                                                                                             | MDex Group<br>(n = 56) | BMDex Group<br>(n = 53) | Total<br>(N = 109) |
|------------------------------------------------------------------------------------------------------------|------------------------|-------------------------|--------------------|
| Median age (25th-75th percentile), years                                                                   | 66 (61-73)             | 65 (59-70)              | 66 (60-71)         |
| Male sex                                                                                                   | 29 (52)                | 32 (60)                 | 61 (56)            |
| Amyloid light-chain type $\lambda$                                                                         | 43 (77)                | 39 (73)                 | 82 (75)            |
| Organ involvement                                                                                          |                        |                         |                    |
| Heart                                                                                                      | 44 (78)                | 41 (77)                 | 85 (78)            |
| Kidney                                                                                                     | 35 (62)                | 36 (68)                 | 71 (65)            |
| Liver                                                                                                      | 7 (12)                 | 7 (13)                  | 14 (13)            |
| Soft tissues                                                                                               | 10 (18)                | 8 (15)                  | 18 (17)            |
| Peripheral nervous system                                                                                  | 4 (7)                  | 4 (7)                   | 8 (7)              |
| Cardiac stage <sup>a</sup>                                                                                 |                        |                         |                    |
| I                                                                                                          | 7 (13)                 | 7 (13)                  | 14 (13)            |
| II                                                                                                         | 39 (70)                | 37 (70)                 | 76 (70)            |
| IIIa                                                                                                       | 10 (17)                | 9 (17)                  | 19 (17)            |
| Renal stage <sup>b</sup>                                                                                   |                        |                         |                    |
| I                                                                                                          | 26 (46)                | 22 (42)                 | 48 (44)            |
| II                                                                                                         | 22 (39)                | 24 (45)                 | 46 (44)            |
| III                                                                                                        | 8 (14)                 | 7 (13)                  | 15 (12)            |
| New York Heart Association class                                                                           |                        |                         |                    |
| No heart involvement                                                                                       | 12 (21)                | 12 (23)                 | 24 (22)            |
| I                                                                                                          | 17 (30)                | 16 (30)                 | 33 (30)            |
| II                                                                                                         | 27 (49)                | 25 (47)                 | 52 (48)            |
| Eastern Cooperative Oncology Group performance status                                                      |                        |                         |                    |
| 0                                                                                                          | 18 (32)                | 16 (30)                 | 34 (31)            |
| 1                                                                                                          | 29 (52)                | 32 (60)                 | 61 (56)            |
| 2                                                                                                          | 9 (19)                 | 5 (10)                  | 14 (13)            |
| Bone marrow plasma-cell infiltrate, median % (25th-75th percentile)                                        | 8 (5-14)               | 8 (5-13)                | 8 (5-13)           |
| Median difference between involved (amyloidogenic) and uninvolved free light chains (25th-75th percentile) | 222 (89-373)           | 172 (98-484)            | 196 (99-379)       |

NOTE. Data reported as No. (%) unless otherwise indicated.

Abbreviations: BMDex, bortezomib, melphalan, and dexamethasone; MDex, melphalan and dexamethasone.

<sup>a</sup>Cardiac stage was based on the cTnT or cTnI level and the N-terminal proatriuretic peptide type B (NT-proBNP) level. Thresholds for cTnT, cTnI, hs-cTnT, and NT-proBNP are < 0.035  $\mu$ g/L, < 0.1  $\mu$ g/L, < 77 ng/L, and < 332 ng/L, respectively. Stage III cardiac involvement is defined at cTnT > 0.035 ng/mL or cTnI > 0.1 ng/mL or hs-cTnT > 77 ng/L, and NT-proBNP > 332 ng/L (provided the NT-proBNP is < 8,500 ng/L). Patients with cardiac stage II disease have 1 value of either troponin or NT-proBNP above the thresholds. Patients with stage I disease have troponin and NT-proBNP levels below the thresholds.

<sup>b</sup>Renal stage was based on proteinuria and estimated glomerular filtration rate (eGFR) levels. Threshold for proteinuria was > 5 g/24 h and for eGFR was < 50 mL/min per 1.73 m<sup>2</sup>. For stage I, both proteinuria  $\leq$  5 g/24 h and eGFR  $\geq$  50 mL/min per 1.73 m<sup>2</sup>; for stage II, either proteinuria > 5 g/24 h or eGFR < 50 mL/min per 1.73 m<sup>2</sup>; for stage III, both proteinuria > 5 g/24 h and eGFR < 50 mL/min per 1.73 m<sup>2</sup>.

proportion of VGPR in the BMDex arm (test for trend  $P = .012$ ).

### Secondary efficacy end points

In the BMDex arm, 55% of patients achieved VGPR or CR after cycle 3, compared with 29% in the MDex arm (difference in rate, 26%; 95% CI, 8% to 44%).

At end of treatment, the overall hematologic response rate remained higher in patients receiving bortezomib

(43 patients [81%] v 32 patients [57%]; HR, 2.17; 95% CI, 1.26 to 2.74). CR was achieved in 12 patients (23%) in the BMDex arm and in 11 (20%) in the MDex arm (HR, 1.60; 95% CI, 0.63 to 4.09), whereas VGPR or CR was obtained in 34 patients (64%) in the BMDex arm and in 22 (39%) in the MDex arm (HR, 2.47; 95% CI, 1.30 to 4.71).

Cardiac and renal response rates at 3, 6, and 9 months after treatment initiation are reported in Table 3. No significant differences were observed between arms.

**TABLE 2.** Primary End Point: Hematologic Response After Cycle 3

| Variable                                       | MDex Group<br>(n = 56) | BMDex Group<br>(n = 53) | Δ<br>(95% CI)              | P                 |
|------------------------------------------------|------------------------|-------------------------|----------------------------|-------------------|
| Any hematologic response                       | 29 (52)                | 42 (79)                 | 27 (10 to 44) <sup>a</sup> | .002              |
| Sensitivity analysis by cardiac stage subgroup |                        |                         |                            |                   |
| I (n = 14)                                     | 5 (57)                 | 6 (86)                  | 29 (−16 to 73)             | .212              |
| II (n = 76)                                    | 20 (51)                | 29 (78)                 | 27 (7 to 48)               | .010              |
| IIIa (n = 19)                                  | 5 (50)                 | 7 (78)                  | 28 (−13 to 69)             | .186              |
| Hematologic response category                  |                        |                         | —                          | .012 <sup>b</sup> |
| Complete response (n = 6)                      | 2 (4)                  | 4 (8)                   |                            |                   |
| Very good partial response (n = 39)            | 14 (25)                | 25 (47)                 |                            |                   |
| Partial response (n = 26)                      | 13 (23)                | 13 (24)                 |                            |                   |
| No response (n = 38)                           | 27 (48)                | 11 (21)                 |                            |                   |

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: —, not applicable; Δ, change; BMDex, bortezomib, melphalan, and dexamethasone; MDex, melphalan and dexamethasone.

<sup>a</sup>Stratified by cardiac stage.

<sup>b</sup>Test for trend.

Patient-reported QoL after 3 cycles was not different between the 2 treatment arms. The median QLC30 global health score was 50 (25th-75th percentiles, 37-75) in the MDex arm and 58 (25th-75th percentiles, 33-67) in the BMDex arm (adjusted difference, 4.85; 95% CI, −6.27 to 15.96); median SF36 PCS was 41 (25th-75th percentiles, 33-43) in the MDex arm and 35 (25th-75th percentiles, 32-41) in the BMDex arm (adjusted difference, 3.35; 95% CI, −0.76 to 7.47); median SF36 MCS was 44 (25th-75th percentiles, 36-55) in the MDex arm and 43 (25th-75th percentiles, 38-52) in the BMDex arm (adjusted difference, −0.62; 95% CI, −5.25 to 4.02).

Forty-eight patients died over a median follow-up of 50 months (25th-75th percentiles, 42-61 months), 17 in the BMDex and 31 in the MDex arm, corresponding to a mortality rate of 9.5 (95% CI, 5.9 to 15.3) and 20.4 deaths per 100 person-years (95% CI, 14.3 to 29.0), respectively, and an HR of 0.50 (95% CI, 0.27 to 0.90; Fig 1). Median OS in the MDex arm was 34 months and was not reached in the BMDex arm. For 72 patients, either they died or their disease progressed, 28 in the BMDex and 44 in the MDex arm, corresponding to a rate of 19 progressions per 100 person-months (95% CI, 13 to 28) and 48 (95% CI, 36 to 64), respectively, and an HR of 0.46 (95% CI, 0.28 to 0.74; Fig 2).

### Safety

Adverse events are listed in Table 4 and the Data Supplement. A total of 292 and 300 treatment cycles were administered in the BMDex and MDex arm, respectively. Grade 3 and 4 adverse events occurred significantly more frequently in the BMDex arm (n = 60) than in the MDex arm (n = 29), occurring in 20% versus 10% of cycles (IRR 2.13; 95% CI, 1.34 to 3.43). Treatment was discontinued because of adverse events in 8 patients (15%) in the BMDex arm (neuropathy [n = 7], thrombocytopenia

[n = 1]). Four patients (8%) in the MDex arm discontinued because of adverse events (fluid retention [n = 2], renal failure [n = 1], and thrombocytopenia [n = 1]). Six patients died while receiving treatment, 4 in the BMDex arm and 2 in the MDex arm. No death was deemed to be treatment related.

### DISCUSSION

To our knowledge, this was the first randomized trial in patients with AL amyloidosis that prospectively compared a contemporary, bortezomib-based regimen with the combination of MDex, which has been used as standard care for at least a decade, and the first study to show a clear benefit in terms of hematologic response, progression, and OS.

The trial met its primary end point, showing a significantly higher overall hematologic response rate when bortezomib was added to MDex. After a median of 6 cycles, the hematologic response rate to BMDex was high (81%) and, importantly, responses were deep, with 23% of patients attaining a CR, and 41% obtaining a VGPR. Cardiac and renal response rates were also high and were reached in 38% and 44%, respectively, of patients treated with BMDex. This was not significantly higher compared with MDex (cardiac and renal response in 28% and 43% of patients, respectively) up to 9 months after treatment initiation. In AL amyloidosis, late organ responses are possible, and longer follow-up could have revealed differences in organ response rate. However, the trial was not powered to detect the effect of superior hematologic response on organ response. Patient-reported QoL was not adversely affected by the addition of bortezomib.

Treatment was associated with low hematologic toxicity. The cumulative dose of melphalan administered was low, and no secondary myelodysplasia or acute leukemia was

**TABLE 3.** Cardiac and Renal Response Rates

| Response                                    | 3 Months    |            |                       |      | 6 Months    |            |                       |      | 9 Months    |            |                       |      |
|---------------------------------------------|-------------|------------|-----------------------|------|-------------|------------|-----------------------|------|-------------|------------|-----------------------|------|
|                                             | BMDex Group | MDex Group | $\Delta$ (%) (95% CI) | P    | BMDex Group | MDex Group | $\Delta$ (%) (95% CI) | P    | BMDex Group | MDex Group | $\Delta$ (%) (95% CI) | P    |
| Cardiac response <sup>a</sup>               | 8/26 (31)   | 8/36 (22)  | 2 (-18 to 22)         | .834 | 10/26 (38)  | 8/36 (22)  | 15 (-8 to 37)         | .207 | 10/26 (38)  | 10/36 (28) | 9 (-14 to 32)         | .195 |
| Renal response (2005 criteria) <sup>b</sup> | 8/36 (22)   | 5/35 (14)  | 8 (-10 to 26)         | .383 | 10/35 (29)  | 9/35 (26)  | 2 (-22 to 19)         | .863 | 12/36 (33)  | 9/35 (26)  | 2 (-19 to 24)         | .827 |
| Renal response (2014 criteria) <sup>c</sup> | 13/36 (36)  | 13/35 (37) | 0 (-22 to 23)         | .969 | 14/36 (39)  | 15/35 (43) | 4 (-27 to 20)         | .768 | 16/36 (44)  | 15/35 (43) | 3 (-20 to 27)         | .776 |

NOTE. Data presented as No. of No. (%) unless otherwise indicated. Change values are adjusted for cardiac stage. Test for interaction of time and treatment of cardiac and renal response  $P = .223$  and  $1.000$ , respectively.

Abbreviations:  $\Delta$ , change; BMDex, bortezomib, melphalan, and dexamethasone; MDex, melphalan and dexamethasone.

<sup>a</sup>Cardiac response: decrease of *N*-terminal proatriuretic peptide type B (NT-proBNP)  $> 30\%$  and  $> 300$  ng/L in patients who had baseline NT-proBNP  $> 650$  ng/L.

<sup>b</sup>Renal response (2005 criteria):  $> 50\%$  decrease in proteinuria in the absence of a  $> 25\%$  decrease in estimated glomerular filtration rate (eGFR).

<sup>c</sup>Renal response (2014 criteria): Renal response is defined as a decrease in proteinuria  $\geq 30\%$  or a drop of proteinuria below  $0.5$  g/24 h in the absence of renal progression (ie, renal progression is defined as a decrease in eGFR  $\geq 25\%$ ).

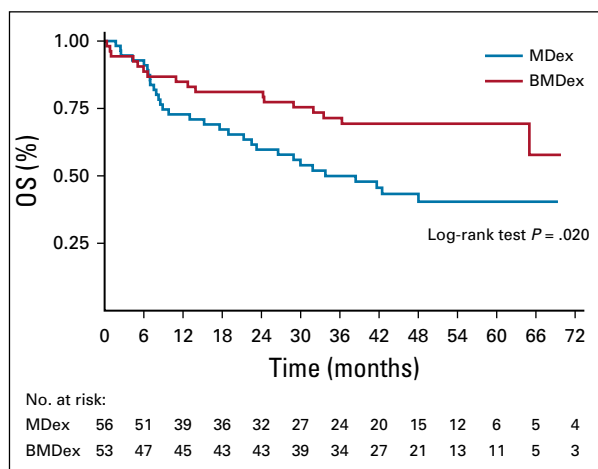
observed during the 50-month follow-up. This confirms that treatment with oral melphalan is practical and well tolerated in AL amyloidosis and allows the concurrent use of bortezomib. However, the addition of bortezomib was associated with a 2-fold increase in grade 3 and 4 adverse events.

Treatment with BMDex resulted in prolonged PFS and, most importantly, OS, with a 50% decrease in mortality rate. The longer duration of response can be relevant in younger patients, carefully balancing exposure to melphalan in patients who may become eligible for ASCT at relapse. After a median follow-up of 50 months, median OS was not reached in the BMDex arm. To our knowledge, this is the

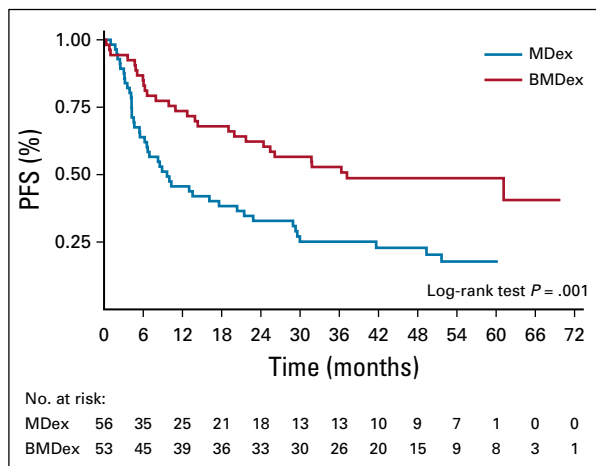
first time a controlled study has demonstrated such a clinically important improvement.

This study establishes BMDex as a standard of care in AL amyloidosis. Comparison with other studies reporting the outcome of patients with AL amyloidosis receiving bortezomib-based therapy are prone to misinterpretations due to different populations and study design. The overall hematologic response rate to BMDex (81%) compares favorably with that reported with CyBorD in patients with stage I, II, and IIIa disease (68%) in a European retrospective study.<sup>17</sup> In the largest study (N = 819 patients) published so far, the overall hematologic response rate to CyBorD was 65%. However, previous smaller series reported higher response rates (range, 81%-94%) with this regimen.<sup>29,30</sup> Moreover, these retrospective series of patients treated with CyBorD did not exclude patients with relevant ventricular arrhythmias and/or syncope and/or profound hypotension; such patients did not meet inclusion criteria for the present trial. In the present study, we also excluded patients with severe chronic kidney disease, who represent 15%-17% of patients with AL amyloidosis and renal involvement.<sup>7</sup> In these patients, melphalan can be less manageable and cyclophosphamide may be preferred.<sup>2</sup> Melphalan-containing regimens are usually avoided in patients with potentially reversible contraindications to ASCT, because they can jeopardize subsequent stem cell harvest.<sup>2</sup> However, melphalan-containing regimens may have the advantage of overcoming the effect of t(11;14) that reduces response rates and survival in patients treated with CyBorD.<sup>31,32</sup> Unfortunately cytogenetics data were not available in the current study.

The BMDex combination could be considered a backbone of associations with newer drugs to be evaluated in future



**FIG 1.** Kaplan-Meier graph of overall survival (OS) by study arm. BMDex, bortezomib, melphalan, and dexamethasone; MDex, melphalan and dexamethasone.



**FIG 2.** Kaplan-Meier graph of progression-free survival (PFS) by study arm. BMDex, bortezomib, melphalan, and dexamethasone; MDex, melphalan and dexamethasone.

trials. Similarly to multiple myeloma,<sup>24</sup> the addition of daratumumab to BMDex should be considered as primary choice and could further improve the response rate and deepen responses, resulting in even longer survival. A phase III study comparing CyBorD and CyBorD plus daratumumab has completed enrollment.

The present trial also confirmed the efficacy of MDex, with a 57% overall hematologic response rate and a good toxicity profile. Oral MDex remains a viable option for patients who are not candidates for ASCT and have contraindications to bortezomib, such as severe peripheral or autonomic neuropathy.

This was an academic, investigator-initiated study. We were free to select relevant surrogate end points (biomarker-based hematologic response in this study) that were highly innovative. Remarkably, reaching this end point was associated with improved OS. We set up an infrastructure and trained dedicated clinical research assistants who remain available to the network for ongoing and future studies. Until now, in AL amyloidosis, novel agents were introduced in clinical practice on the basis of findings from small phase II trials or retrospective series. This practice hampered recruitment. Indeed, a parallel clinical trial planned in the United States was closed due to insufficient recruitment. Enrollment also was slower than expected in the present trial. Nevertheless, we were able to complete the study and the long follow-up allowed us to demonstrate a significant difference in OS. Our study paved the way to the more recent clinical trials in this rare disease, and it is now generally recognized that in AL amyloidosis, solid evidence

**TABLE 4.** List of Adverse Events

| Adverse Event                    | MDex Group |              | BMDex Group <sup>a</sup> |              | Overall   |              |
|----------------------------------|------------|--------------|--------------------------|--------------|-----------|--------------|
|                                  | Any Grade  | Grade 3 or 4 | Any grade                | Grade 3 or 4 | Any Grade | Grade 3 or 4 |
| Hematologic                      |            |              |                          |              |           |              |
| Thrombocytopenia                 | 12         | 5            | 27                       | 10           | 39        | 15           |
| Neutropenia                      | 8          | 4            | 4                        | 8            | 12        | 12           |
| Anemia                           | 36         | 2            | 45                       | 4            | 81        | 6            |
| Nonhematologic                   |            |              |                          |              |           |              |
| Fluid retention                  | 42         | 4            | 21                       | 10           | 63        | 9            |
| Peripheral sensory neuropathy    | 10         | 1            | 52                       | 7            | 62        | 8            |
| Fatigue                          | 36         | 3            | 21                       | 4            | 57        | 7            |
| Fever                            | 10         | 1            | 20                       | 5            | 30        | 6            |
| GI disorders <sup>b</sup>        | 40         | 3            | 40                       | 1            | 80        | 4            |
| Metabolic disorders <sup>c</sup> | 15         | 1            | 12                       | 3            | 27        | 4            |
| Creatinine increase              | 12         | 1            | 9                        | 2            | 21        | 3            |
| Dyspnea                          | 20         | 2            | 13                       | 1            | 33        | 3            |
| Skin rash                        | 12         | 1            | 4                        | 1            | 16        | 2            |
| Vascular/hypotension             | 8          | 1            | 5                        | 1            | 13        | 2            |
| Insomnia                         | 2          | —            | 2                        | 3            | 4         | 2            |
| Total                            | 263        | 29           | 275                      | 60           | 538       | 89           |

Abbreviations: BMDex, bortezomib, melphalan, and dexamethasone; MDex, melphalan and dexamethasone.

<sup>a</sup>Grade 3 and 4 adverse events occurred significantly more frequently in the BMDex arm than in the MDex arm, occurring in 20% versus 10% of cycles performed (IRR, 2.13; 95% CI, 1.34 to 3.43,  $P < .001$ ).

<sup>b</sup>Nausea, gastric pain, vomiting, constipation, diarrhea, anorexia.

<sup>c</sup>Hypokalemia, hyperkalemia, hyperglycemia,  $\gamma$ -GT increase.

can and should be obtained before introducing novel agents in clinical practice.

In conclusion, we have demonstrated that investigator-initiated trials are feasible in a rare disease such as AL amyloidosis. This trial showed that BMDex is well tolerated in AL amyloidosis and provides more frequent and more profound hematologic responses than the previous

standard-of-care MDex, which translates to a significant improvement in PFS and OS. The results of this study provide precious information for the design of future trials, validating early overall hematologic response as a surrogate end point and establishing bortezomib-based regimens as standard of care and suitable comparators for future trials.

## AFFILIATIONS

<sup>1</sup>Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

<sup>2</sup>Hopital Huriez Centre Hospitalier Régional Universitaire, Lille, France

<sup>3</sup>Immunohematology Unit, Hospital Saint-Louis, Assistance Publique – Hôpitaux de Paris, Paris, France

<sup>4</sup>Bologna University School of Medicine, Bologna, Italy

<sup>5</sup>Amyloidosis and Myeloma Unit, Hospital Clinic of Barcelona, August Pi Sunyer Biomedical Research Institute, Barcelona, Spain

<sup>6</sup>Westmead Hospital, Sydney, New South Wales, Australia

<sup>7</sup>Princess Alexandra Hospital and University of Queensland, Brisbane, Queensland, Australia

<sup>8</sup>Department of Hemato-oncology, University Hospital, Ostrava and Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic

<sup>9</sup>Centre Hospitalier Universitaire Hotel Dieu, Nantes, France

<sup>10</sup>Centre Hospitalier Universitaire, Limoges, France

<sup>11</sup>Medical Department V, Amyloidosis Centre, University Hospital, Heidelberg, Germany

<sup>12</sup>St Vincent's Hospital, Melbourne, Victoria, Australia

<sup>13</sup>Centre Leon Berard, Lyon, France

<sup>14</sup>Sir Charles Gairdner Hospital, Perth, Western Australia, Australia

<sup>15</sup>University Hospital of Salamanca, Instituto de Investigación Biosanitaria de Salamanca, Institute of Cancer Molecular and Cellular Biology, Salamanca, Spain

<sup>16</sup>University College London Medical School, Royal Free Hospital Campus, London, United Kingdom

<sup>17</sup>Amyloidosis Research and Treatment Center “Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo,” Pavia, Italy

<sup>18</sup>Clinical Epidemiology and Biometry Service, “Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo,” Pavia, Italy

<sup>19</sup>University of Torino, Torino, Italy

<sup>20</sup>Erasmus MC Cancer Institute, Rotterdam, the Netherlands

<sup>21</sup>Aalborg University Hospital, Aalborg, Denmark

<sup>22</sup>Department of Molecular Medicine, University of Pavia, Pavia, Italy

†Deceased.

## CORRESPONDING AUTHOR

Giovanni Palladini, MD, PhD, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Viale Golgi, 19, 27100 Pavia, Italy; e-mail: giovanni.palladini@unipv.it.

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## AUTHOR CONTRIBUTIONS

**Conception and design:** Efstathios Kastritis, Xavier Leleu, Peter Mollee, Arnaud Jaccard, Stefan O. Schönland, Ashutosh Wechaleka, Meletios A. Dimopoulos, Jean-Paul Fermand, Catherine Klersy, Antonio Palumbo, Pieter Sonneveld, Hans Erik Johnsen, Giampaolo Merlini, Giovanni Palladini

**Provision of study material or patients:** Efstathios Kastritis, Xavier Leleu, Elena Zamagni, Maria Teresa Cibeira, Peter Mollee, Arnaud Jaccard, Stefan O. Schönland, Robin Filshie, Maria-Victoria Mateos, Andrea Foli, Ashutosh Wechalekar, Eric Hachulla, Paolo Milani, Meletios A. Dimopoulos, Jean-Paul Fermand, Giampaolo Merlini, Giovanni Palladini

**Collection and assembly of data:** Efstathios Kastritis, Xavier Leleu, Bertrand Arnulf, Maria Teresa Cibeira, Fiona Kwok, Peter Mollee, Roman Hájek, Philippe Moreau, Arnaud Jaccard, Stefan O. Schönland, Eric Hachulla, Paolo Milani, Meletios A. Dimopoulos, Andrea Foli, Pieter Sonneveld, Giampaolo Merlini, Giovanni Palladini

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

**Accountable for all aspects of the work:** All authors

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST****Bortezomib, Melphalan, and Dexamethasone for Light-Chain Amyloidosis**

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**Efstathios Kastritis**

**Honoraria:** Amgen, Genesis Pharma, Janssen Oncology, Takeda, Prothena, Pfizer

**Consulting or Advisory Role:** Amgen, Janssen Oncology, Takeda, Genesis Pharma, Prothena, Pfizer

**Research Funding:** Janssen Oncology (Inst), Amgen (Inst)

**Travel, Accommodations, Expenses:** Janssen Oncology, Genesis Pharma, Takeda, Pfizer

**Xavier Leleu**

**Honoraria:** Janssen-Cilag, Celgene, Amgen, Novartis, Bristol Myers Squibb, Takeda, Sanofi, AbbVie, Merck, Roche, Karyopharm Therapeutics, Carsgen Therapeutics, Oncopeptides, GlaxoSmithKline

**Consulting or Advisory Role:** Janssen-Cilag, Celgene, Amgen, Takeda, Bristol Myers Squibb, Novartis, Merck, Gilead Sciences, AbbVie, Roche, Karyopharm Therapeutics, Oncopeptides, Carsgen Therapeutics, GlaxoSmithKline

**Travel, Accommodations, Expenses:** Takeda

**Bertrand Arnulf**

**Honoraria:** Celgene, Janssen-Cilag, Sanofi, Takeda

**Consulting or Advisory Role:** Janssen-Cilag, Celgene, Amgen

**Research Funding:** Janssen-Cilag

**Travel, Accommodations, Expenses:** Celgene, Janssen-Cilag, Takeda, Amgen

**Elena Zamagni**

**Honoraria:** Janssen-Cilag, Celgene, Amgen, Bristol Myers Squibb, Takeda

**Consulting or Advisory Role:** Celgene, Janssen-Cilag, Amgen, Sanofi

**Travel, Accommodations, Expenses:** Janssen-Cilag, Celgene, Amgen

**María Teresa Cibeira**

**Honoraria:** Janssen, Amgen, Celgene

**Consulting or Advisory Role:** Janssen, Akcea Therapeutics

**Peter Mollee**

**Consulting or Advisory Role:** Janssen-Cilag (Inst), Celgene (Inst), Amgen (Inst), Pfizer (Inst), Takeda (Inst), Caelum (Inst)

**Research Funding:** Janssen-Cilag (Inst)

**Travel, Accommodations, Expenses:** Amgen

**Roman Hájek**

**Consulting or Advisory Role:** Takeda, Amgen, Celgene, AbbVie, Bristol Myers Squibb, PharmaMar, Janssen-Cilag, Novartis

**Speakers' Bureau:** Takeda, Amgen

**Research Funding:** Novartis (Inst), Bristol Myers Squibb (Inst), Amgen (Inst), Celgene (Inst), Takeda (Inst)

**Philippe Moreau**

**Honoraria:** Celgene, Takeda, Novartis, Janssen-Cilag, Amgen, GlaxoSmithKline

**Consulting or Advisory Role:** Celgene, Takeda, Janssen, Amgen, GlaxoSmithKline

**Arnaud Jaccard**

**Honoraria:** Janssen, Pfizer, Prothena, Sanofi

**Research Funding:** Janssen (Inst), Celgene (Inst)

**Travel, Accommodations, Expenses:** Janssen, AbbVie, Celgene

**Stefan O. Schönland**

**Research Funding:** Janssen-Cilag (Inst), Sanofi (Inst), Prothena (Inst), Medac

**Travel, Accommodations, Expenses:** Janssen-Cilag, Prothena, Sanofi

**María-Victoria Mateos**

**Honoraria:** Janssen-Cilag, Celgene, Amgen, Takeda, GlaxoSmithKline, AbbVie/Genentech, Adaptive

**Consulting or Advisory Role:** Takeda, Janssen-Cilag, Celgene, Amgen, AbbVie, GlaxoSmithKline, Pharmamar-zeltia

**Paolo Milani**

**Honoraria:** Pfizer, Janssen-Cilag

**Travel, Accommodations, Expenses:** Celgene

**Meletios A. Dimopoulos**

**Honoraria:** Amgen, Celgene, Takeda, Janssen-Cilag, Bristol Myers Squibb

**Consulting or Advisory Role:** Amgen, Janssen-Cilag, Takeda, Celgene, Bristol-Myers Squibb

**Andrea Foli**

**Honoraria:** Health Publishing & Services

**Maria Gavriatopoulou**

**Honoraria:** Amgen, Janssen, Celgene, Takeda

**Consulting or Advisory Role:** Amgen, Karyopharm Therapeutics

**Research Funding:** Novartis

**Travel, Accommodations, Expenses:** Takeda, Genesis Pharma, Janssen

**Antonio Palumbo**

**Employment:** Takeda

**Stock and Other Ownership Interests:** Takeda

**Honoraria:** Takeda

**Consulting or Advisory Role:** Takeda

**Research Funding:** Takeda (Inst)

**Travel, Accommodations, Expenses:** Takeda

**Pieter Sonneveld**

**Consulting or Advisory Role:** Celgene Janssen, Amgen, Karyopharm, Carsgen Therapeutics

**Research Funding:** Janssen (Inst), Amgen (Inst), Skyline Diagnostics (Inst)

**Giovanni Palladini**

**Honoraria:** Janssen-Cilag

**Consulting or Advisory Role:** Janssen-Cilag, Celgene

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