

Improved survival with daratumumab-CyBorD compared with CyBorD as frontline therapy for AL amyloidosis

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Key Points

- The addition of daratumumab to CyBorD significantly improves hematological and organ response.
- Dara-CyBorD frontline therapy improves survival and reduces early death in AL amyloidosis.

In the ANDROMEDA phase 3 trial, the addition of daratumumab to cyclophosphamide, bortezomib, and dexamethasone (Dara-CyBorD) as frontline therapy significantly improved hematological and organ responses, and event-free survival (EFS) compared with CyBorD. To validate its results, we performed a retrospective study of 361 consecutive patients with newly diagnosed light chain (AL) amyloidosis treated between 2018 and 2022. Patients who received Dara-CyBorD ($n = 147$) were compared with those treated with CyBorD ($n = 214$) in key outcome endpoints. The 2-month hematological very good partial response or better rate was higher with Dara-CyBorD than with CyBorD (60.8% vs 31.1%; $P < .001$). In addition, 2- and 6-month hematological complete response was also higher with Dara-CyBorD (15.3% vs 3.0% and 39.5% vs 17.8%, respectively; both $P < .001$). Fewer patients treated with Dara-CyBorD required second-line therapy at the 12-month landmark (14.9% vs 42.9%; $P < .001$). The 6- and 12-month cardiac responses were higher and deeper in the Dara-CyBorD group than in the CyBorD group. Dara-CyBorD was associated with a lower 6-month mortality rate (8.8% vs 16.3%; $P = .04$) and superior EFS and overall survival (OS). An OS difference between the treatment groups was statistically significant among patients with stage II cardiac disease, and borderline significant for stage IIIA but not for cardiac stage IIIB. In conclusion, the addition of daratumumab to frontline CyBorD significantly improved hematological and organ response rates, reduced early deaths, and prolonged EFS and OS compared with CyBorD.

Introduction

Immunoglobulin light chain (AL) amyloidosis is a life-threatening, clonal plasma cell disorder characterized by tissue deposition of misfolded amyloid fibrils leading to end-organ failure.¹ Given the heterogeneous and nonspecific clinical presentation, the diagnosis is often delayed, and patients may present with advanced organ failure with dismal outcomes.^{1,2} The heart and kidneys are the most frequently affected organs, and mortality is primarily driven by the degree of cardiac involvement.¹ Achieving a deep and rapid hematological response is crucial for achieving an organ response and improving outcomes.³ Novel plasma cell-directed therapies aimed at eradicating the plasma cell clone have improved the hematological response, translating into improved survival over the last 2 decades.^{4,5}

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Data are available on request from the corresponding author, Eli Muchtar (muchtar.eli@mayo.edu).

The full-text version of this article contains a data supplement.

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The historical standard-of-care treatment for newly diagnosed AL amyloidosis consisted of a bortezomib-based therapy, with the most used regimen being cyclophosphamide in combination with bortezomib and dexamethasone (CyBorD).⁶⁻⁹ A phase 3 study from Europe showed that the addition of bortezomib to melphalan and dexamethasone significantly improved the hematological response and overall survival (OS) compared with melphalan and dexamethasone.¹⁰ However, even in the bortezomib era, survival for patients with AL amyloidosis remained suboptimal, underscoring the need for novel therapies. Daratumumab (Dara) is an immunoglobulin Gκ1 monoclonal antibody targeting CD38 and mediates plasma cell eradication by antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity.^{11,12} Single-agent Dara had demonstrated impressive clinical activity in relapsed/refractory AL amyloidosis.¹³⁻¹⁵ The phase 3 ANDROMEDA study was a practice-changing registrational study that showed that the addition of Dara to CyBorD (Dara-CyBorD) for patients with AL amyloidosis improved the hematological response, organ response, and event-free survival (EFS), leading to the accelerated US Food and Drug Administration approval of Dara in combination with CyBorD for patients with newly diagnosed AL amyloidosis in 2021.¹⁶ We performed this real-world study to investigate the efficacy of a frontline Dara-CyBorD compared with CyBorD in patients with newly diagnosed AL amyloidosis.

Methods

This single-center retrospective study included consecutive patients with AL amyloidosis who were diagnosed and seen at Mayo Clinic, Rochester, MN, between January 2018 and December 2022 and were treated with frontline Dara-CyBorD or CyBorD. We excluded patients who received treatment other than

Dara-CyBorD/CyBorD ($n = 256$, including those receiving upfront modified forms of Dara-CyBorD/CyBorD [ie, omission of bortezomib and/or cyclophosphamide]), unverified treatment with CyBorD/Dara-CyBorD ($n = 15$), and those who received CyBorD/Dara-CyBorD as part of a clinical trial ($n = 9$). A CONSORT diagram highlighting patient selection and treatment groups is provided in Figure 1. The study was approved by the institutional review board. Written consent was obtained from patients to have their medical charts reviewed for medical research.

The primary study objective was to evaluate the efficacy of frontline Dara-CyBorD compared with CyBorD in newly diagnosed AL amyloidosis in routine clinical practice. We compared patients who received Dara-CyBorD with those treated with CyBorD. Dara, bortezomib, and cyclophosphamide were given at standard dosing and schedule for cycles 1 through 6.¹⁶ Dexamethasone was given as a 40 mg weekly dose in cycles 1 through 6 with a dose reduction to 20 mg weekly in patients aged >75 years, in patients with advanced cardiomyopathy, or at the treating physician's discretion. Dara maintenance was typically given to responding patients in those treated with Dara-CyBorD. The hematological and organ response assessments were done on an intention-to-treat analysis, in which responses were assessed based on the assigning treatment group at diagnosis, with response at landmarks was used regardless of whether there was a change in therapy. Hematological responses were assessed at 2 and 6 months from treatment initiation and at best response to first-line therapy and best hematological response ever achieved using the consensus criteria.^{17,18} The low difference between involved and uninvolved free light chain (dFLC) partial response (low dFLC-PR) criterion was used to assess the response in patients with a baseline dFLC between 2 and 5 mg/dL.¹⁹⁻²² Cardiac and renal responses were assessed by the binary¹⁷ and the graded response

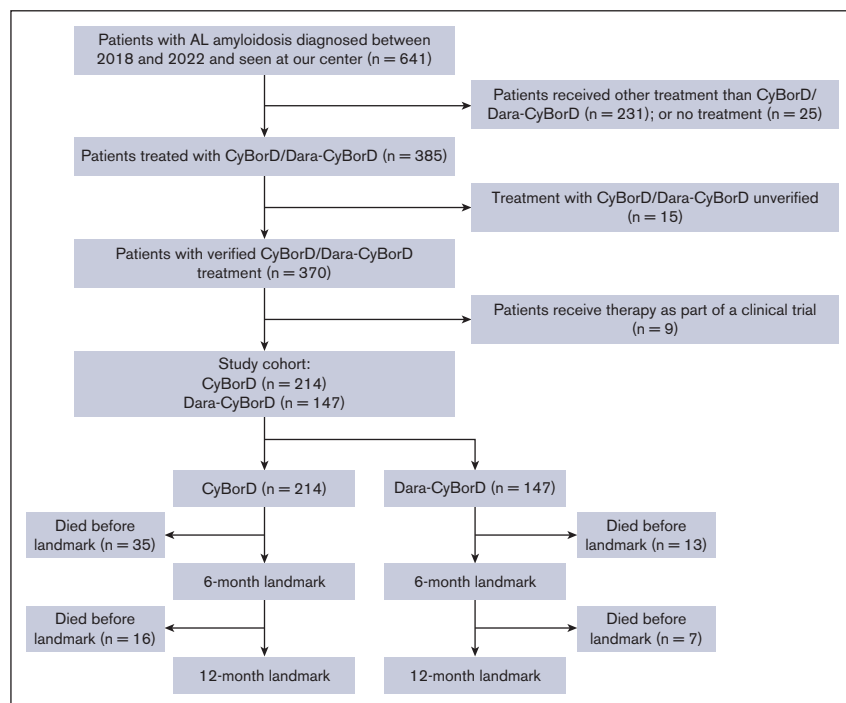


Figure 1. CONSORT diagram of patient selection and treatment groups.

criteria.^{23,24} Patients were eligible for cardiac response assessment if they had a baseline N-terminal prohormone of brain natriuretic peptide (NT-pro BNP) value of ≥ 650 pg/mL or BNP of ≥ 150 pg/mL with at least 1 postbaseline NT-pro BNP/BNP measurement. Patients were eligible for renal response assessment if they had a baseline urinary protein excretion of >500 mg per 24 hours with at least 1 postbaseline 24-hour urine protein measurement. The cardiac and renal responses were analyzed at the 6- and 12-month landmarks, best response to first-line therapy, and best response ever achieved. When evaluating the best hematological and organ response to first-line therapy, the best response before autologous stem cell transplant (ASCT) or switching to a second-line therapy was used.

In patients with missing hematological and organ response at landmarks, the best response observed before the landmark was imputed, if possible. If no prior response was available, a nonresponse was imputed. This imputation method was applied specifically to missing hematological response data at the 2- and 6-month landmark and missing organ response data at the 6- and 12-month landmark. Patients who died before response assessment or those lost to follow-up were counted as nonresponders. Hematological response was imputed for 11 (3.0%) and 19 (5.2%) patients at 2 and 6 months, respectively. Cardiac response was imputed for 7 (3.4%) and 10 (4.8%) patients at 6 and 12 months, respectively. Imputation of renal response was done for 22 (13.4%) and 20 (12.2%) patients at 6 and 12 months, respectively. If patients achieved hematological and organ response before death, this was counted toward their best response but was not included in landmark analysis if they were not alive at the landmark. Cardiac staging was done using the Mayo 2004 model with the European modification.⁹ The 2014 renal staging was used for determining the renal stage.²⁵ In patients who received an ASCT, it was considered a consolidation if they achieved at least a partial response to first-line therapy. In contrast, ASCT was considered a salvage therapy if it was performed for no response to first-line therapy. All patients who received at least 1 dose of plasma cell-directed therapy were included in statistical analyses.

Statistical analysis

The patient characteristics were summarized using descriptive statistics. The Mann-Witney *U* test was used to compare the continuous variables in the 2 groups. For continuous variables, the median and interquartile range were reported. The Fisher exact test was used to compare the hematological and organ responses in the 2 treatment groups. Time-to-event data variables were assessed using the Kaplan-Meier method and comparisons were done using the log-rank test. For EFS analysis, an event was defined as death, hematological progression, end-stage cardiac or renal failure, or need for subsequent anti-plasma cell therapy in the absence of hematological progression. Hematological progression was defined as abnormal free light chain ratio (light chain must double) or any detectable monoclonal protein from complete response (CR), or a 50% increase in serum M protein to >0.5 g/dL or a 50% increase in urine M protein to >200 mg/d from any response or increase in free light chain of 50% to >100 mg/L.²⁶ OS was calculated from the date of initiation of treatment to death or the last date of follow-up. Proportional hazards Cox regression analysis was done to identify independent predictive factors for EFS and OS. The statistical analysis was done using

GraphPad Prism 9.0 (GraphPad Software Inc, La Jolla, CA) with $P < .05$ set as statistically significant.

Results

Baseline characteristics

A total of 361 consecutive patients with newly diagnosed AL amyloidosis diagnosed between 2018 and 2022 were included (CyBorD, $n = 214$; Dara-CyBorD, $n = 147$). Table 1 summarizes the baseline clinical and demographic characteristics of the study population. In the whole study population, cardiac and renal involvement was seen in 68.1% ($n = 246$) and 55.6% ($n = 201$) of patients, respectively, with no significant difference between the treatment groups. The 2 treatment groups also showed no difference in age, sex, bone marrow plasma cells (BMPCs) percentage, and baseline dFLC, NT-pro BNP, and 24-h proteinuria. However, a higher proportion of patients in the Dara-CyBorD group had cardiac stage I and renal stage I disease compared with those in the CyBorD group (25.1% vs 13.5% [$P = .005$] and 38.1% vs 23.9% [$P = .04$], respectively). The median time from the diagnosis to treatment initiation was 28 days (interquartile range, 15-56).

The median follow-up was significantly shorter in the Dara-CyBorD group at 30.0 months (range, 0.2-66.5) compared with 59.4 months (range, 0.1-75.6) in the CyBorD group ($P < .001$).

Hematological response

In the ITT analysis, the overall hematological response and hematological CR at 2 months were higher with Dara-CyBorD than with CyBorD (91.6% vs 68.3% and 15.3% vs 3.0%, respectively; both $P < .001$). Similarly, a higher proportion of patients achieved a very good partial response or better at 2 months in the Dara-CyBorD group compared with the CyBorD group (60.8% vs 31.1%; $P < .001$). At 6 months, a higher overall hematological response, hematological VGPR or better, and hematological CR was observed with Dara-CyBorD than with CyBorD (97.7% vs 87.7%, 78.3% vs 60.3%, and 39.5% vs 17.8%, respectively; $P < .001$ for all comparisons). The proportion of patients who achieved hematological CR and VGPR or better as the best response to first-line therapy was higher with Dara-CyBorD than with CyBorD group (42.8% vs 12.1% and 76.1% vs 42.0%, respectively; $P < .001$ for both comparisons). While evaluating the best hematological response ever achieved irrespective of the treatment line, hematological CR and VGPR or better were more frequently seen with Dara-CyBorD compared with in the CyBorD group (53.7% vs 39.2% [$P = .007$] and 86.3% vs 73.3% [$P = .003$], respectively; Figure 2A).

An involved free light chain level of ≤ 2 mg/dL at best hematological response was more frequently observed in the Dara-CyBorD group (42.8% vs 15.1%; $P < .001$). Furthermore, the proportion of patients who achieved a dFLC of <1 mg/dL at best hematological response was higher in the Dara-CyBorD group than in the CyBorD group (45.5% vs 13.2%; $P < .001$). A summary comparison of the hematological response between the 2 treatment groups is provided in supplemental Table 1. A subgroup analysis of patients with hematological CR showed a consistent benefit with Dara-CyBorD across various subgroups (supplemental Table 2). Among patients with t(11;14) mutation ($n = 129$; Dara-CyBorD, $n = 55$; CyBorD, $n = 74$), the best overall hematological

Table 1. Basic clinical characteristics in each treatment group

	Dara-CyBorD (n = 147)	CyBorD (n = 214)	P value
Age, median (range), y	65 (23-82)	64.5 (35-89)	.64
Sex, male, n (%)	95 (64.6)	134 (62.6)	.73
Light chain isotype, n (%)			.07
λ	119 (81.0)	155 (72.4)	
κ	28 (19.0)	58 (27.1)	
Baseline dFLC			
Median (IQR), mg/dL	24.7 (10.1-55.9)	27.5 (9.9-69.9)	.74
<5 mg/dL, n (%)	18 (12.2)	23 (10.7)	
<2 mg/dL, n (%)	9 (6.1)	10 (4.6)	
BMPC infiltration, median (IQR), %	10.5 (7.0-20.0)	10 (5.7-20.0)	.26
Baseline NT-pro BNP, median (IQR), pg/mL	1326 (261.0-4670)	2084 (611.8-4841)	.23
Baseline proteinuria, median (IQR), mg/24 h	1926 (241.0-5090)	1948 (335.0-5684)	.64
Involved organs, n (%)			
Heart	94 (63.9)	152 (71.0)	.16
Kidney	84 (57.1)	117 (54.6)	.66
Liver	13 (8.8)	35 (16.3)	.04
Gastrointestinal tract	23 (15.6)	35 (16.3)	.88
Peripheral nerve	8 (5.4)	16 (7.4)	.52
Autonomic nervous system	13 (8.8)	24 (11.2)	.48
Others	21 (14.2)	23 (10.7)	.32
Mayo 2004 cardiac stage with European modification, n (%)			
I	37 (25.1)	29 (13.5)	.005
II	43 (29.2)	77 (35.9)	.21
IIIA	39 (26.5)	64 (29.9)	.55
IIIB	16 (10.8)	32 (14.9)	.27
Missing	12 (8.1)	12 (5.6)	
Renal stage, n (%)			
I	32 (38.1)	28 (23.9)	.04
II	29 (34.5)	52 (44.4)	.18
III	20 (23.8)	30 (25.6)	.86
Missing	3 (3.6)	7 (5.9)	

IQR, interquartile range. Bold indicates statistical significance at $p < 0.05$.

response, VGPR or better, and CR were higher with Dara-CyBorD than with CyBorD (96.3% vs 71.6%, 74.5% vs 39.1%, and 43.6% vs 8.1%, respectively; $P < .001$ for all comparisons).

Cardiac and renal responses

A total of 205 patients were eligible for cardiac response assessment (Dara-CyBorD, $n = 78$; CyBorD, $n = 127$). The overall cardiac response at 6-month and 12-month landmarks was higher in the Dara-CyBorD group than with CyBorD (46.2% vs 21.2% and 76.6% vs 43.6%, respectively; both $P < .001$). In the Dara-CyBorD group, a higher proportion of patients achieved a cardiac VGPR or better at the 6-month and 12-month landmarks when compared with CyBorD (22.3 % vs 8.3% [$P = .01$] and 38.3 % vs 18.0% [$P = .007$], respectively). The proportion of patients who achieved a cardiac CR and VGPR or better as best response to first-line therapy was significantly higher in the Dara-CyBorD group than

in the CyBorD group (16.6% vs 3.1% [$P = .001$] and 44.8% vs 12.5% [$P < .001$], respectively). Similarly, cardiac CR and VGPR or better as best response ever (regardless of the number of treatment lines) were more frequently seen in the Dara-CyBorD group compared with the CyBorD group (17.9% vs 9.4% [$P = .08$] and 50.0% vs 35.4% [$P = .04$], respectively; [Figure 2B](#)). Patients who achieved cardiac VGPR or better at the 6-month and 12-month landmarks had a superior 2-year OS compared with those with cardiac response of less than VGPR (90.6% vs 65.3% [$P = .03$] and 95.6% vs 54.5% [$P < .001$], respectively). A summary of the cardiac responses by treatment groups is provided in supplemental Table 3.

Among 163 patients (Dara-CyBorD, $n = 66$; CyBorD, $n = 97$) who were eligible for renal response assessment, there was no statistically significant difference in renal responses at the 6-month and 12-month landmarks between the Dara-CyBorD and CyBorD

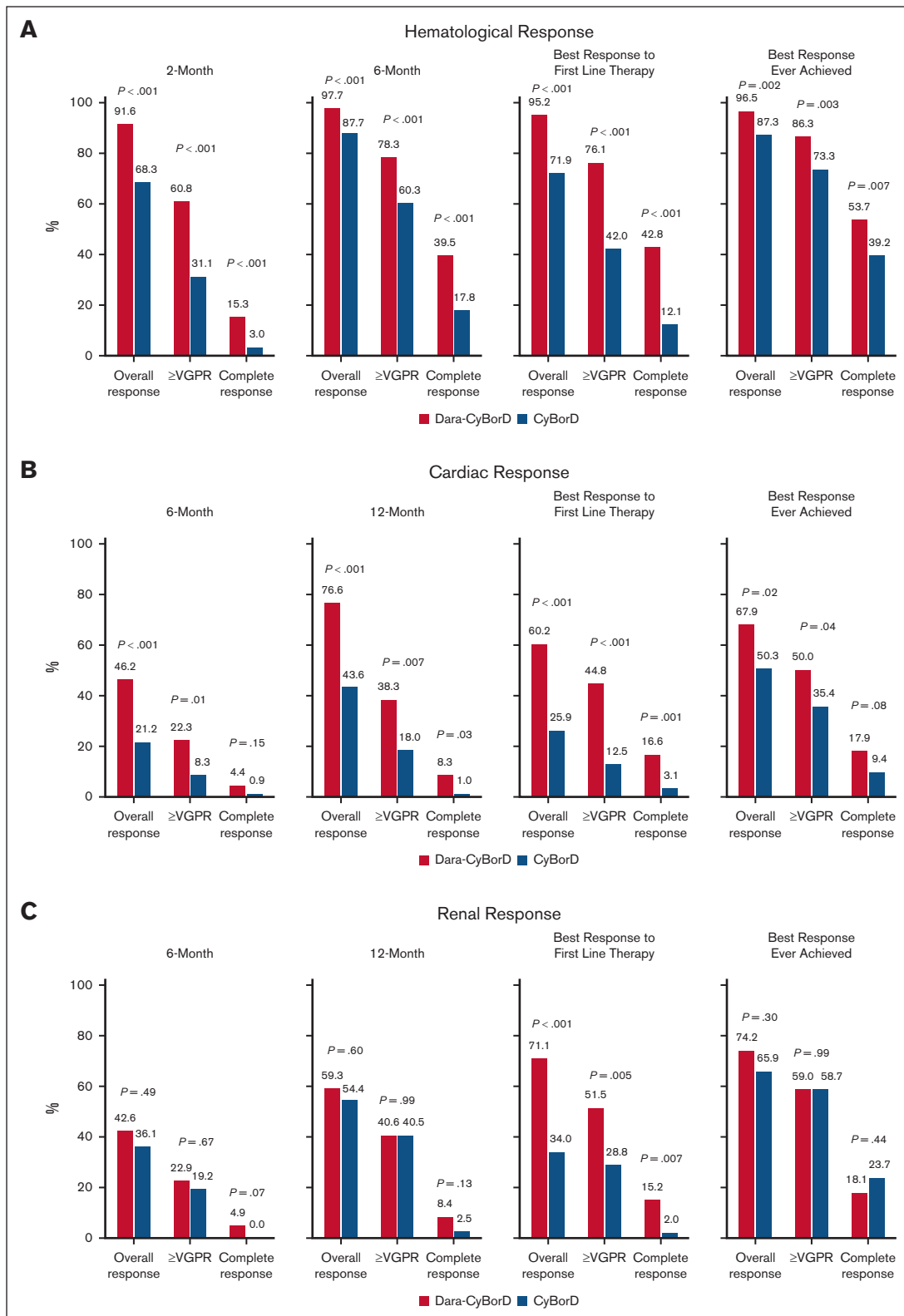


Figure 2. Hematological and organ responses at designated landmarks. (A) Hematological response. (B) Cardiac response. (C) Renal response.

groups (42.6% vs 36.1% [$P = .49$] and 59.3% vs 54.4% [$P = .60$], respectively; [Figure 2C](#)). At the 6-month and 12-month landmarks, the proportion of patients who achieved a renal VGPR or better was similar between the Dara-CyBorD and CyBorD groups (22.9% vs 19.2% [$P = .67$] and 40.6% vs 40.5% [$P = .99$], respectively). However, the proportion of patients with an overall renal response, renal VGPR or better, and renal CR, at best response to first-line therapy was significantly higher in the Dara-CyBorD group than in the CyBorD group (71.1% vs 34.0% [$P < .001$], 51.5% vs 28.8% [$P = .005$], and 15.2% vs 2.0% [$P = .007$], respectively; [Figure 2C](#)). A higher proportion of patients in the CyBorD group progressed to end-stage renal disease (ESRD) than those treated with Dara-CyBorD (16.4% vs 9.0%; $P = .24$), even when the analysis was restricted to the 24-month landmark (12.3% vs 6.0%; $P = .28$), but statistical significance was not reached. A summary of renal response is provided in supplemental Table 3.

Second-line therapy usage

A total of 149 patients (Dara-CyBorD, $n = 29$; CyBorD, $n = 120$) proceeded to second-line therapy (supplemental Table 4) with a median of 5.1 months from first-line therapy. Among the 128 patients in the CyBorD group who received a second-line therapy or higher, 86.7% received Dara-based therapy. To adjust for the difference in follow-up time between the 2 treatment groups, we analyzed the second-line therapy use at the 12-month landmark, which was statistically higher with CyBorD than with Dara-CyBorD (42.9% vs 14.9%; $P < .001$). Also, at 12 months, a higher proportion of patients treated with CyBorD received ASCT than with Dara-CyBorD (24.3% vs 13.6%; $P = .01$). Among 85 patients who received ASCT, 72 patients (Dara-CyBorD, $n = 20$; CyBorD, $n = 52$) received ASCT as a consolidation whereas 13 patients (Dara-CyBorD, $n = 2$; CyBorD, $n = 11$) underwent ASCT as a salvage therapy.

Early death

A total of 112 patients (31% of the study population) died (Dara-CyBorD, $n = 27$; CyBorD, $n = 85$), of whom 12 patients (Dara-CyBorD, $n = 2$; CyBorD, $n = 10$; $P = .13$) died within 30 days of treatment initiation. Patients in the Dara-CyBorD group had a significantly lower 3- and 6-month early death rate than those in the CyBorD group (4.1% vs 8.8% [$P = .09$] and 8.8% vs 16.3% [$P = .04$], respectively). The 2-year OS was superior in the Dara-CyBorD group than in the CyBorD group (82.0% vs 69.6%; hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.36-0.79; $P = .003$; [Figure 3B](#)).

Hematological progression, EFS, and OS

Hematological progression was more frequently seen with CyBorD compared with Dara-CyBorD (12.6% vs 5.4%; $P = .02$), even at the 12-month landmark (6.0% vs 1.3%; $P = .03$). The 2-year EFS was superior in the Dara-CyBorD group than in the CyBorD group (2-year EFS, 65.2% vs 25.9; HR, 0.36; 95% CI, 0.27-0.47; $P < .001$; [Figure 3A](#)). In a univariate analysis, λ light chain isotype, a baseline dFLC of ≥ 18 mg/dL, t(11;14), and cardiac stage IIIA/IIIB were associated with worse EFS, whereas treatment with Dara-CyBorD was associated with better EFS. In a multivariate regression analysis, t(11;14), dFLC of ≥ 18 mg/dL, cardiac stage IIIA/IIIB, and treatment group remained as independent prognostic factors for EFS ([Table 2](#)). We compared the OS difference between the treatment groups based on baseline cardiac biomarkers, dFLC, fluorescence in situ hybridization cytogenetics, and percentage of

BMPCs. We observed a significant improvement in OS with the addition of Dara to CyBorD compared with CyBorD in patients with low cardiac biomarkers at diagnosis (NT-pro BNP of <1800 pg/mL, high sensitivity cardiac troponin T of <50 ng/L, or troponin T of <0.035 ng/L; supplemental Figures 1 and 3) but not among patients with adverse cardiac biomarkers levels at diagnosis (supplemental Figures 2 and 4). In addition, patients with dFLC of ≥ 18 mg/dL (supplemental Figure 6), and t(11;14) (supplemental Figure 7) had longer OS with Dara-CyBorD than with CyBorD. We did not observe OS difference between the treatment groups in those with dFLC of <18 mg/dL at baseline (supplemental Figure 5). Patients with BMPCs of $<20\%$ or $\geq 20\%$ derived survival benefits from the addition of Dara to CyBorD backbone with a greater benefit seen in the $\geq 20\%$ BMPCs subgroup (supplemental Figures 8 and 9). In a multivariate regression analysis accounting for sex, baseline dFLC, and cardiac stage, treatment with Dara-CyBorD was associated with a better OS compared with CyBorD ([Table 2](#)).

We plotted OS based on treatment groups, with the CyBorD group further subclassified based on Dara usage in subsequent line(s) of therapy ([Figure 3C](#)). This analysis shows that there was no significant difference in OS between patients treated with frontline Dara-CyBorD and those who received frontline CyBorD with subsequent Dara usage (HR, 0.99; 95% CI, 0.59-1.64; $P = .96$), whereas no use of Dara at any line was associated with inferior survival (Dara-CyBorD vs CyBorD without subsequent use of Dara [HR, 0.31; 95% CI, 0.20-0.49; $P < .001$]; frontline CyBorD with subsequent use of Dara vs CyBorD without subsequent Dara [HR, 0.41; 95% CI, 0.27-0.64; $P < .001$]).

Outcomes by baseline cardiac stage

The EFS was significantly better in the Dara-CyBorD group than in the CyBorD group across cardiac stages I, II, and IIIA ([Figure 4A-C](#)). A statistically significant OS benefit for Dara-CyBorD compared with CyBorD was seen only in patients with cardiac stage II ([Figure 5B](#)) and borderline survival benefit for cardiac stage IIIA ([Figure 5C](#)). Cardiac stage I (no cardiac involvement) had excellent survival regardless of the treatment group. In patients with cardiac stage IIIB ($n = 48$; Dara-CyBorD, $n = 16$; CyBorD, $n = 32$), 7 patients (43.7%) in the Dara-CyBorD group and 15 patients (46.8%) in the CyBorD group had died within 6 months of treatment initiation ($P = .99$) and there was no statistical difference in EFS or OS between the 2 treatment groups over time, with 2-year EFS and OS dismal at 12.5% vs 9.3% and 15.6% vs 40.6% for Dara-CyBorD and CyBorD, respectively ([Figures 4D and 5D](#)).

Discussion

This real-world large study confirms the superiority of Dara-CyBorD over CyBorD in newly diagnosed AL amyloidosis in achieving a rapid and deep hematological response, higher and deeper rates of cardiac response, and lower early mortality. As a result, patients treated with frontline Dara-CyBorD had superior EFS and OS than with CyBorD owing to the higher response rates with Dara-CyBorD. This real-world analysis showed an OS benefit with Dara-CyBorD compared with CyBorD in patients with newly diagnosed AL amyloidosis who were assessed and treated at a large referral center for AL amyloidosis, which was also recently reported by the ANDROMEDA study investigators.²⁷

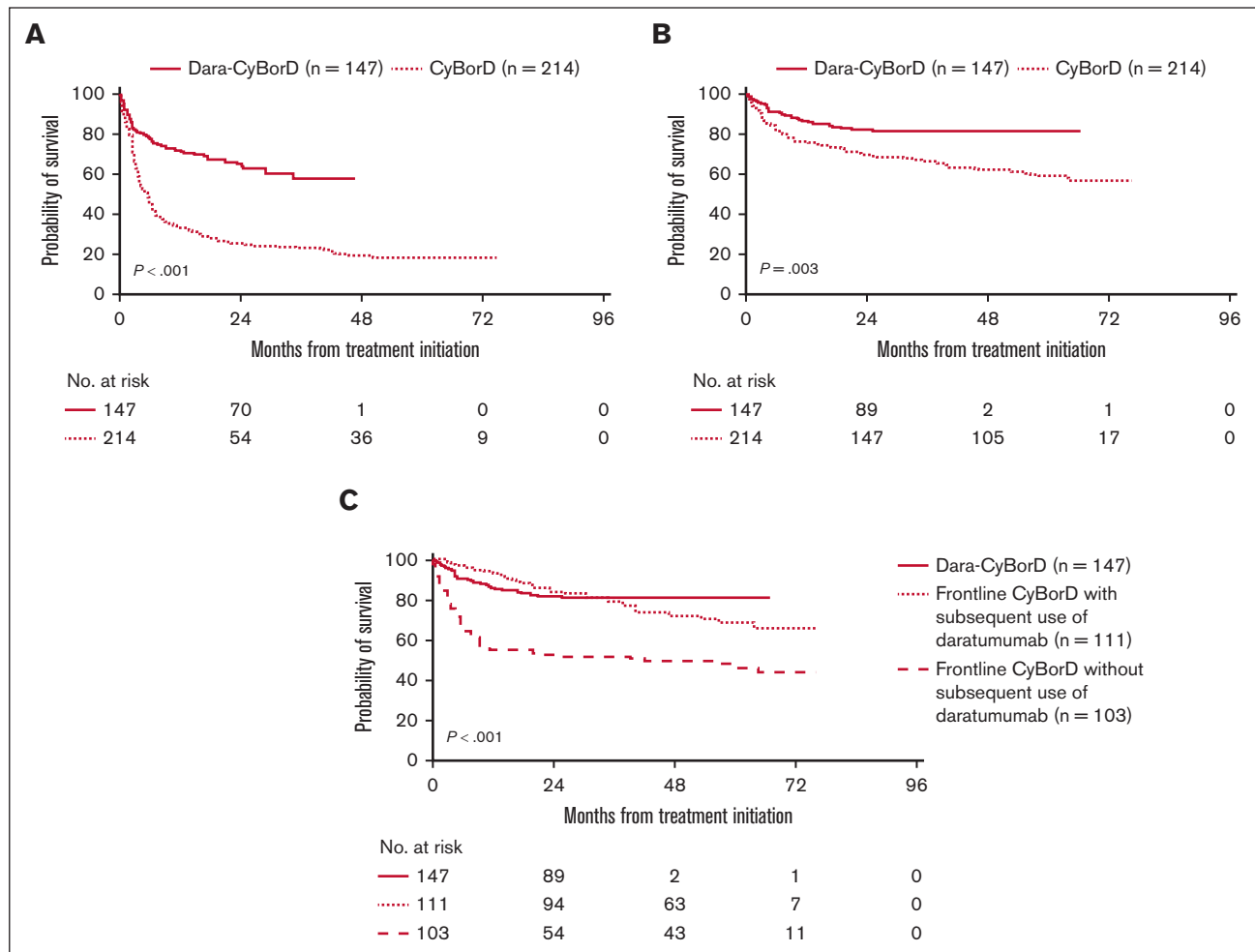


Figure 3. Survival outcomes by treatment group. (A) EFS comparing Dara-CyBorD vs CyBorD (2-year EFS, 65.2% vs 25.9%; HR, 0.36; 95% CI, 0.27-0.47; $P < .001$). (B) OS comparing Dara-CyBorD vs CyBorD (2-year OS, 82.0% vs 69.6%; HR, 0.53; 95% CI, 0.36-0.79; $P = .003$). (C) OS comparing Dara-CyBorD vs frontline CyBorD with subsequent use of Dara vs frontline CyBorD without subsequent Dara use (2-year OS, 82.0% vs 84.6% vs 53.4% [$P < .001$]; Dara-CyBorD vs CyBorD with subsequent Dara use [$P = .96$]; Dara-CyBorD vs frontline CyBorD without subsequent Dara use [$P < .001$]; frontline CyBorD with subsequent use of Dara vs frontline CyBorD without subsequent Dara use [$P < .001$]).

Table 2. Univariate and multivariate regression analysis, EFS and OS

	EFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age, ≥ 65 y	0.99 (0.65-1.5)	.97	Not included		1.32 (0.84-2.07)	.22	Not included	
Male	1.1 (0.73-1.8)	.55	Not included		1.48 (0.93-2.41)	.08	1.35 (0.91-2.06)	.13
Light chain isotype λ (reference κ)	1.86 (1.11-3.21)	.02	1.30 (0.64-2.68)	.46	0.80 (0.46-1.36)	.42	Not included	
BMPCs of $>20\%$	1.03 (0.62-1.73)	.88	Not included		1.27 (0.74-2.12)	.36	Not included	
dFLC ≥ 18 mg/dL	2.58 (1.67-4.01)	<.001	2.15 (1.18-3.96)	.01	1.35 (0.85-2.15)	.19	1.11 (0.75-1.67)	.59
t(11;14)	1.69 (1.03-2.77)	.03	1.94 (1.08-3.54)	.02	0.83 (0.48-1.42)	.50	Not included	
Proteinuria ≥ 5 g/24 h	0.94 (0.58-1.54)	.81	Not included		0.78 (0.45-1.31)	.35	Not included	
Mayo 2004 with European modification stage IIIA/IIIB	3.17 (2.05-5.09)	<.001	3.29 (1.81-6.16)	<.001	5.71 (3.45-9.67)	<.001	4.29 (2.78-6.79)	<.001
Dara-CyBorD (vs CyBorD)	0.15 (0.08-0.27)	<.001	0.37 (0.2-0.53)	<.001	0.33 (0.20-0.54)	<.001	0.55 (0.33-0.86)	.01

P values <0.05 in bold indicate statistical significance.

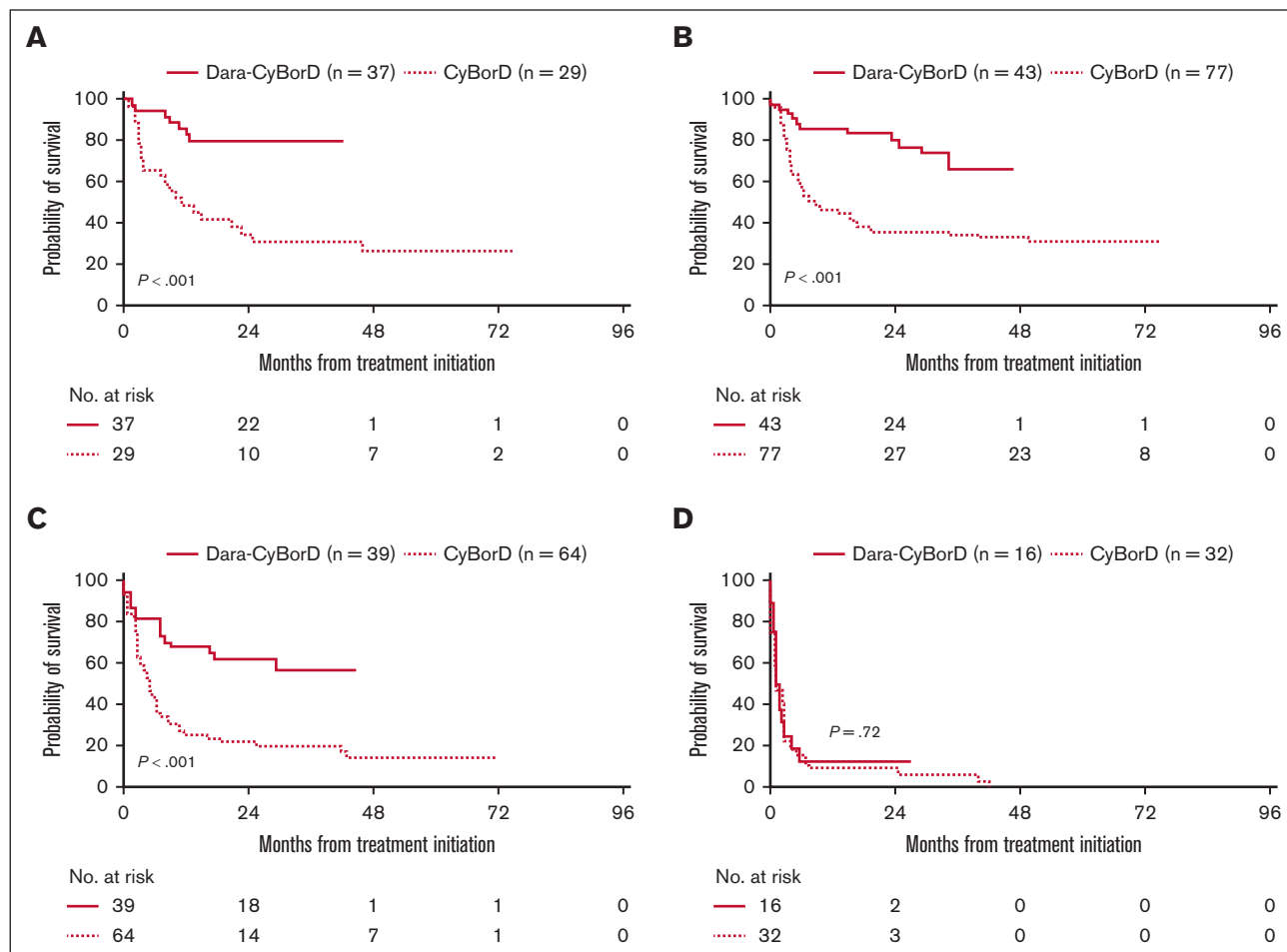


Figure 4. EFS based on cardiac stage stratified by treatment group. (A) Cardiac stage I (2-year EFS, 80% vs 30%; HR, 0.22; 95% CI, 0.10-0.46; $P < .001$). (B) Cardiac stage II (2-year EFS, 77.1% vs 37.1%; HR, 0.29; 95% CI, 0.17-0.48; $P < .001$). (C) Cardiac stage IIIA (2-year EFS, 62.2% vs 22.2%; HR, 0.34; 95% CI, 0.21-0.56; $P < .001$). (D) Cardiac stage IIIB (2-year EFS, 12.5% vs 9.3%; HR, 0.89; 95% CI, 0.48-1.66; $P = .72$).

The overall hematological response to a frontline bortezomib-based regimen is ~60% to 65%, with ~20% achieving a hematological CR.⁶⁻⁸ In the ANDROMEDA trial, with the addition of Dara to CyBorD, the hematological CR improved to 53%.¹⁶ We have identified a similar finding, with a 6-month hematological CR rate of 39.5%, with 53.7% in the Dara-CyBorD group achieving hematological CR as best response. The deeper hematological responses with Dara-CyBorD compared with CyBorD led to a higher likelihood of achieving a stringent FLC response (dFLC of <1 mg/dL and involved free light chain of <2 mg/dL), which are associated with a superior organ response and OS, independent of the traditional hematological response criteria.^{8,28,29} Our lower hematological CR rates compared with the results reported in the ANDROMEDA study may be a result of the use of a mass spectrometry-based immunofixation assay in our study compared with the traditional immunofixation assay in the ANDROMEDA study, with the former being more sensitive in detecting low levels of monoclonal protein, thus less likely to achieve a hematological CR.³⁰

We have demonstrated an improved cardiac response with the use of Dara-CyBorD at similar rates to what has been reported in the ANDROMEDA study. In addition, we report that this improved

cardiac response rate extends into the 12-month landmark. Deeper cardiac responses (ie, cardiac VGPR or better), an important factor for survival,²³ were noted with Dara-CyBorD. However, unlike the ANDROMEDA study, we could not demonstrate a difference in renal response between the 2 treatment groups at the 6- and 12-month landmarks, albeit at best renal response, higher renal response rates were noted in the Dara-CyBorD arm compared with the CyBorD arm. This may be explained by the higher ASCT and/or second-line therapy use in the CyBorD group in this study than in the ANDROMEDA trial (66.6% vs 13.4%, respectively). In addition, we have found that more patients in the Dara-CyBorD arm achieved renal CR, and renal VGPR or better at best response to first-line therapy compared with CyBorD and the risk of progression to ESRD was also lower in the Dara-CyBorD group. A recent study has shown that among patients with renal AL amyloidosis, those who achieve a renal VGPR or better have a lower cumulative incidence of progression to dialysis.²⁴ Therefore, we anticipate fewer patients in the current era may eventually develop ESRD.

We confirm the post-hoc analysis from the ANDROMEDA trial that demonstrated that patients with cardiac stage I, II, and IIIA had better EFS from the addition of Dara.³¹ However, we did not find an

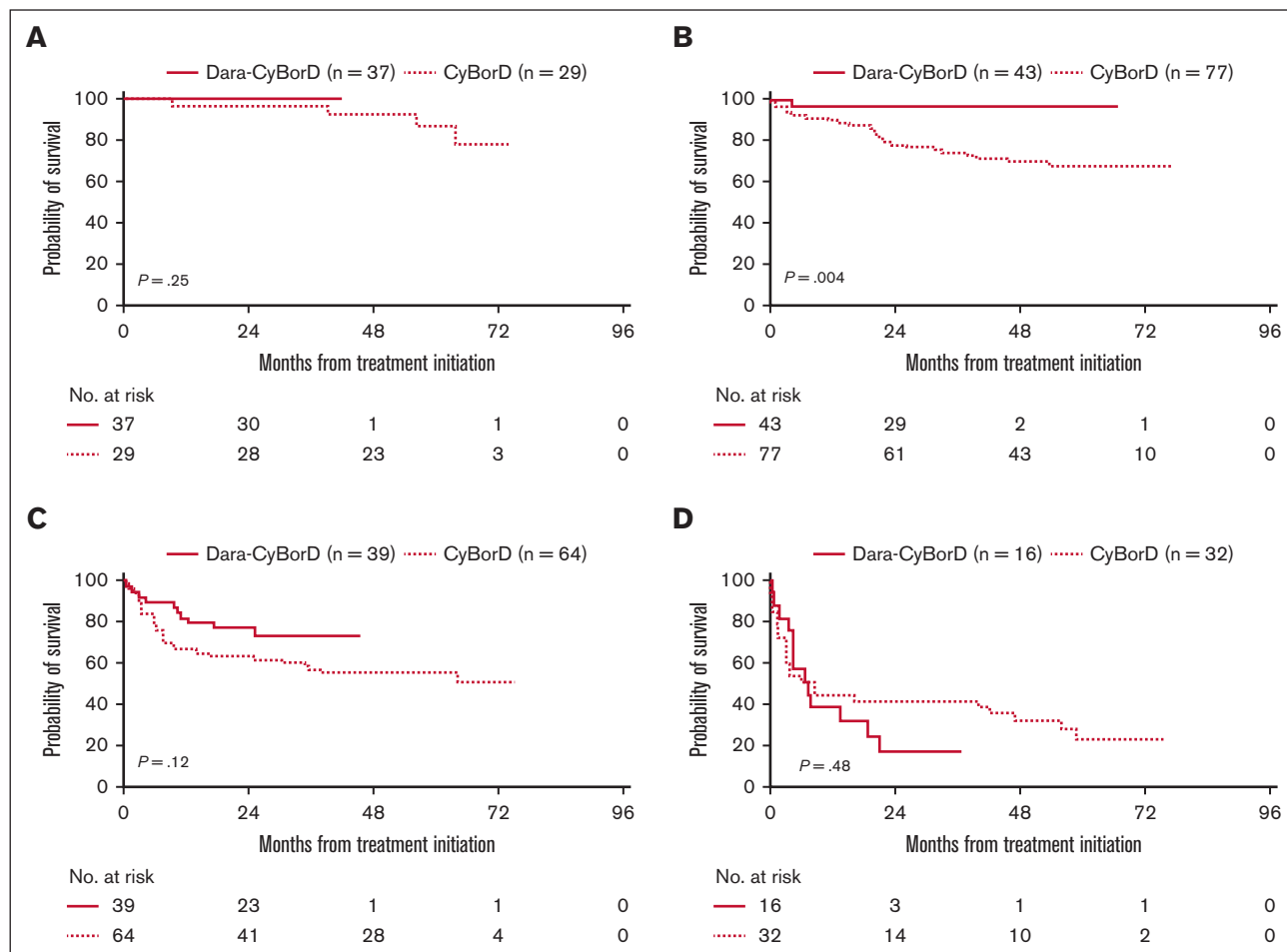


Figure 5. OS based on cardiac stage stratified by treatment group. (A) Cardiac stage I (2-year OS, 100% vs 96.5%; HR, 0.14; 95% CI, 0.004-4.11; $P = .25$). (B) Cardiac stage II (2-year OS, 97.6% vs 78.9%; HR, 0.10; 95% CI, 0.04-0.24; $P = .004$). (C) Cardiac stage IIIA (2-year OS, 76.9% vs 61.9%; HR, 0.57; 95% CI, 0.30-1.10; $P = .12$). (D) Cardiac stage IIIB (2-year OS, 15.6% vs 40.6%; HR, 1.25; 95% CI, 0.62-2.53; $P = .48$).

EFS benefit in the Dara-CyBorD group over CyBorD in patients in stage IIIB, a patient population that was excluded from the ANDROMEDA trial. Despite EFS benefit with Dara-CyBorD across cardiac stages I to IIIA, this study shows that the patients who mostly benefited from Dara-CyBorD over CyBorD in terms of OS were mostly patients at earlier cardiac stage (but not cardiac stage I who have exceptionally low mortality rate, given lack of cardiac involvement). Thus, the patients who mostly benefited from Dara-CyBorD were patients with cardiac stage II, with a marginal benefit for patients with cardiac stage IIIA disease. Patients with stage IIIB did not seem to gain any benefit from the addition of Dara to CyBorD. This stands in contrast to few other studies showing that Dara improved the outcome of these very high-risk patients. Oubari et al reported a multicenter study of patients with stage IIIB cardiac amyloidosis ($n = 119$) from Europe and outcomes were superior for patients treated with a frontline Dara-based regimen than other regimens.³² Similarly, Chakraborty et al reported a multicenter study ($n = 19$) from the United States showing a 1-year OS of 68% in patients with stage IIIB cardiac amyloidosis.³³ Shen et al reported encouraging results with Dara, bortezomib, and dexamethasone in stage IIIB cardiac amyloidosis, achieving a 50% cardiac response at 6 months and a 2-year OS of 65%.³⁴ Similarly,

a European Myeloma Network phase 2 study demonstrated the safety and meaningful clinical activity of this combination, with a VGPR or better of 55% and a median OS of 10.3 months.³⁵ However, that study initially treated patients with Dara and dexamethasone alone to mitigate potential cardiac toxicity associated with the full Dara-CyBorD regimen. Our study excluded patients treated with modified Dara-CyBorD regimens, precluding analysis of this strategy's impact on survival in the stage IIIB group. Further research is needed to optimize treatment for this fragile population.

Lenalidomide, an immunomodulatory drug, may enhance hematological response when combined with Dara, bortezomib, and dexamethasone. This combination is increasingly used in multiple myeloma with excellent efficacy.³⁶ However, its use in advanced cardiac AL amyloidosis is limited by poor tolerability. Kastiris et al reported deep hematological responses with a bortezomib, low-dose lenalidomide, and dexamethasone regimen in newly diagnosed AL amyloidosis but also observed increased toxicity.³⁷ Larger studies are needed to further evaluate this approach.

Early deaths driven by advanced cardiac and/or multiorgan involvement have remained a major challenge, with up to 40% of patients dying within 6 months in historical cohorts.^{38,39} In the era

of novel plasma cell–directed therapies, early deaths have declined over the last 4 decades. A study from our institution of unselected patients with AL diagnosed between 2000 and 2014 highlighted a significant reduction in early mortality from 37% in the 2000-2004 period to 25% and 24% in the years 2005-2009 and 2010-2014, respectively.⁵ Although the current study has a specific patient population, it is nonetheless encouraging to note the early death rate in this study was lower than the above figures and reached 8.8% in the Dara-CyBorD group.

Novel therapies are urgently needed for relapsed and refractory AL amyloidosis. Given disease rarity and heterogeneity, multidomain composite end points are essential for evaluating new treatments in clinical trials. Composite progression end points, such as major organ dysfunction–progression free survival used in the ANDROMEDA trial, can facilitate early efficacy detection and have regulatory approval. Identifying such clinically meaningful endpoints is crucial for accelerating the development and approval of new therapies.

The strengths of this study include the large sample size of consecutive patients with AL amyloidosis. This study reflects the strength of collaboration between community physicians and a large academic center in treating patients with rare and challenging diseases such as AL amyloidosis. There are several limitations to our study. Given its retrospective design and resultant selection bias, results need to be interpreted with caution. Because of missing data at the landmark, we imputed responses for ~3% to 5% of patients for cardiac response and 11% to 14% of patients for renal response. The follow-up in patients treated with Dara-CyBorD was significantly short compared with the CyBorD group. Hence, some of the analyses are premature and we provided landmark analyses when appropriate.

In conclusion, Dara-CyBorD is an effective regimen that can achieve a rapid and deep hematological response, deep organ responses, and provides an OS benefit in AL amyloidosis when compared with CyBorD. This study provides important insight into the real-world experience with this regimen and supports the current benchmark of a contemporary Dara-based induction regimen in AL amyloidosis, with a high likelihood of successful translation to real-world practice and potential survival advantage, reflecting other experiences derived from clinical trials in a similar context.⁴⁰

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Authorship

Contribution: B.Y. and E.M. conceptualized and designed the study; B.Y., M.R., and E.M. collected and assembled the data; B.Y. and E.M. analyzed the data and drafted the manuscript; and all authors provided study material or recruited patients, interpreted and revised data, and gave final approval of the manuscript.

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References

1. Merlini G, Dispenzieri A, Sanchirawala V, et al. Systemic immunoglobulin light chain amyloidosis. *Nat Rev Dis Primers*. 2018;4(1):38.
2. Weiss BM, Hebreo J, Cordaro DV, et al. Increased serum free light chains precede the presentation of immunoglobulin light chain amyloidosis. *J Clin Oncol*. 2014;32(25):2699-2704.
3. Kastritis E, Fotiou D, Theodorakakou F, et al. Timing and impact of a deep response in the outcome of patients with systemic light chain (AL) amyloidosis. *Amyloid*. 2021;28(1):3-11.
4. Staron A, Zheng L, Doros G, et al. Marked progress in AL amyloidosis survival: a 40-year longitudinal natural history study. *Blood Cancer J*. 2021;11(8):139.
5. Muchtar E, Gertz MA, Kumar SK, et al. Improved outcomes for newly diagnosed AL amyloidosis between 2000 and 2014: cracking the glass ceiling of early death. *Blood*. 2017;129(15):2111-2119.
6. Venner CP, Lane T, Foard D, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. *Blood*. 2012;119(19):4387-4390.
7. Mikhael JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. *Blood*. 2012;119(19):4391-4394.
8. Manwani R, Cohen O, Sharpley F, et al. A prospective observational study of 915 patients with systemic AL amyloidosis treated with upfront bortezomib. *Blood*. 2019;134(25):2271-2280.
9. Palladini G, Sachchithanatham S, Milani P, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. *Blood*. 2015;126(5):612-615.
10. Kastritis E, Leleu X, Arnulf B, et al. Bortezomib, melphalan, and dexamethasone for light-chain amyloidosis. *J Clin Oncol*. 2020;38(28):3252-3260.
11. Overdijk MB, Verploegen S, Bögels M, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. *MAbs*. 2015;7(2):311-321.
12. de Weers M, Tai Y-T, van der Veer MS, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol*. 2011;186(3):1840-1848.
13. Sher T, Fenton B, Akhtar A, Gertz MA. First report of safety and efficacy of daratumumab in 2 cases of advanced immunoglobulin light chain amyloidosis. *Blood*. 2016;128(15):1987-1989.
14. Kaufman GP, Schrier SL, Lafayette RA, et al. Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. *Blood*. 2017;130(7):900-902.
15. Abeykoon JP, Zanwar S, Dispenzieri A, et al. Daratumumab-based therapy in patients with heavily-pretreated AL amyloidosis. *Leukemia*. 2019;33(2):531-536.
16. Kastritis E, Palladini G, Minnema MC, et al. Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. *New England Journal of Medicine*. 2021;385(1):46-58.
17. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. *J Clin Oncol*. 2012;30(36):4541-4549.
18. Palladini G, Schönland SO, Sanchirawala V, et al. Clarification on the definition of complete haematologic response in light-chain (AL) amyloidosis. *Amyloid*. 2021;28(1):1-2.
19. Dittich T, Bochtler T, Kimmich C, et al. AL amyloidosis patients with low amyloidogenic free light chain levels at first diagnosis have an excellent prognosis. *Blood*. 2017;130(5):632-642.
20. Milani P, Basset M, Russo F, et al. Patients with light-chain amyloidosis and low free light-chain burden have distinct clinical features and outcome. *Blood*. 2017;130(5):625-631.
21. Nguyen VP, Rosenberg A, Mendelson LM, et al. Outcomes of patients with AL amyloidosis and low serum free light chain levels at diagnosis. *Amyloid*. 2018;25(3):156-159.
22. Sidana S, Tandon N, Dispenzieri A, et al. Clinical presentation and outcomes in light chain amyloidosis patients with non-evaluable serum free light chains. *Leukemia*. 2018;32(3):729-735.
23. Muchtar E, Dispenzieri A, Wisniewski B, et al. Graded cardiac response criteria for patients with systemic light chain amyloidosis. *J Clin Oncol*. 2023;41(7):1393-1403.
24. Muchtar E, Wisniewski B, Geyer S, et al. Graded organ response and progression criteria for kidney immunoglobulin light chain amyloidosis. *JAMA Oncol*. 2024;10(10):1362-1369.
25. Palladini G, Hegenbart U, Milani P, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. *Blood*. 2014;124(15):2325-2332.

26. Comenzo RL, Reece D, Palladini G, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. *Leukemia*. 2012;26(11):2317-2325.
27. Kastritis E, Palladini GO, Minnema MC, et al. Subcutaneous daratumumab (DARA) + bortezomib, cyclophosphamide, and dexamethasone (VCd) in patients with newly diagnosed light chain (AL) amyloidosis: overall survival and final major organ deterioration progression-free survival results from the phase 3 andromeda study. *Blood*. 2024;144(suppl 1):891.
28. Muchtar E, Dispenzieri A, Leung N, et al. Optimizing deep response assessment for AL amyloidosis using involved free light chain level at end of therapy: failure of the serum free light chain ratio. *Leukemia*. 2019;33(2):527-531.
29. Milani P, Basset M, Nuvolone M, et al. Indicators of profound hematologic response in AL amyloidosis: complete response remains the goal of therapy. *Blood Cancer J*. 2020;10(8):90.
30. Mills JR, Barnidge DR, Dispenzieri A, Murray DL. High sensitivity blood-based M-protein detection in sCR patients with multiple myeloma. *Blood Cancer J*. 2017;7(8):e590.
31. Minnema MC, Dispenzieri A, Merlini G, et al. Outcomes by cardiac stage in patients with newly diagnosed AL amyloidosis: phase 3 ANDROMEDA trial. *JACC CardioOncol*. 2022;4(4):474-487.
32. Oubari S, Hegenbart U, Schoder R, et al. Daratumumab in first-line treatment of patients with light chain amyloidosis and Mayo stage IIIb improves treatment response and overall survival. *Haematologica*. 2024;109(1):220-230.
33. Chakraborty R, Rosenbaum C, Kaur G, et al. First report of outcomes in patients with stage IIIb AL amyloidosis treated with Dara-VCD front-line therapy. *Br J Haematol*. 2023;201(5):913-916.
34. Shen K, Gao Y, Chang L, et al. Efficacy and safety of daratumumab plus bortezomib and dexamethasone in newly diagnosed Mayo 2004 stage IIIA or IIIB light-chain amyloidosis: a prospective phase II study. *Haematologica*. 2024.
35. Kastritis E, Minnema MC, Dimopoulos M-A, et al. Efficacy and safety of daratumumab monotherapy in newly diagnosed patients with stage 3B light chain amyloidosis: a phase 2 study by the European Myeloma Network. *Blood*. 2024;144(suppl 1):1979.
36. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *New England Journal of Medicine*. 2024;390(4):301-313.
37. Kastritis E, Dialoupi I, Gavriatopoulou M, et al. Primary treatment of light-chain amyloidosis with bortezomib, lenalidomide, and dexamethasone. *Blood Adv*. 2019;3(20):3002-3009.
38. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. *Lancet*. 2016;387(10038):2641-2654.
39. Kumar SK, Gertz MA, Lacy MQ, et al. Recent improvements in survival in primary systemic amyloidosis and the importance of an early mortality risk score. *Mayo Clin Proc*. 2011;86(1):12-18.
40. Richardson PG, San Miguel JF, Moreau P, et al. Interpreting clinical trial data in multiple myeloma: translating findings to the real-world setting. *Blood Cancer J*. 2018;8(11):109.