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# Is Prolonged Daratumumab Maintenance Useful in Light-Chain Amyloidosis?

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# Abstract

Daratumumab-based therapy is a cornerstone of treatment for light-chain (AL) amyloidosis; however, the optimal treatment duration remains undefined. We retrospectively analyzed 399 newly diagnosed AL amyloidosis patients treated at 2 centers according to center-specific planned daratumumab treatment durations (12 vs ≥ 24 cycles). Overall survival (OS), cumulative incidence of next treatment, and organ responses were compared using an intention-to-treat approach. A separate cohort of 184 relapsed/refractory patients was similarly analyzed. The 12- and ≥ 24-cycle cohorts included 181 and 218 patients, respectively. OS and cumulative incidence of next treatment were comparable between groups (P = 0.639 and P = 0.336, respectively), including among patients aged ≥ 65 years and those with bone marrow plasma cell ≥ 10%. Extended treatment increased the 24-month rate of renal responses ≥very good partial response (42% vs 26%; P = 0.023) but did not improve cardiac responses. Similar findings were observed in relapsed/refractory patients, with better renal responses but no OS or next-treatment benefit. Overall, treatment beyond 12 cycles was not associated with statistically significant improvements in OS or a lower cumulative incidence of next treatment, although clinically meaningful effects cannot be excluded. Prospective studies are needed to clarify the potential benefits of prolonged daratumumab treatment in AL amyloidosis.


# Introduction

Daratumumab has emerged as a cornerstone of first-line therapy for patients with light-chain (AL) amyloidosis, substantially improving hematologic and organ responses when combined with proteasome inhibitor–based regimens.[1] However, the optimal duration of daratumumab therapy remains undefined. Treatment duration is an evolving question across plasma cell disorders, with recent studies in multiple myeloma evaluating continuous versus fixed-duration approaches.[2] In AL amyloidosis, daratumumab therapy has traditionally been administered for a predefined duration, but whether prolonged treatment provides additional clinical benefit remains unknown.

In prospective clinical trials, daratumumab has been administered for variable planned durations. Landmark studies such as ANDROMEDA,[3, 4] EMN22,[5] and AQUARIUS[6] adopted a 24-month treatment strategy, whereas other interventional studies evaluating daratumumab-based regimens limited treatment to approximately 12 months.[7, 8] In routine clinical practice, daratumumab exposure is even more heterogeneous, influenced by patient characteristics, treatment tolerance, physician preference, and healthcare resource constraints. Owing to differences in study populations and designs, available trials do not allow direct inference regarding the optimal duration of therapy.

In the relapsed/refractory setting, the situation is even more complex. Many patients have a relatively low plasma cell burden at the time of daratumumab initiation,[9] although the residual clones may be more treatment-resistant. At the same time, these patients are typically older and may have accumulated toxicities from prior therapies, making treatment safety a critical consideration. Prolonged anti–plasma

cell therapy may increase the risk of infections and further compromise already impaired organ function.[10, 11]

To address this knowledge gap, the EMILIA trial[12] was initiated in 2023 to prospectively compare 6 cycles versus 18 cycles of daratumumab maintenance therapy in newly diagnosed AL amyloidosis, with event-free survival as the primary endpoint. This study aims to determine whether abbreviated maintenance is non-inferior to standard treatment, with the potential to reduce treatment-related toxicity[13] and financial burden; however, results are not yet available.

Since 2021, daratumumab-based therapy has been widely adopted for newly diagnosed AL amyloidosis in both Italy and China, but treatment duration has differed between centers. At the Pavia Amyloidosis Research and Treatment Center, patients generally received prolonged daratumumab-based therapy, with maintenance following multiple myeloma practice and a 24-cycle schedule adopted after the introduction of ANDROMEDA in February 2023.[3] At Peking Union Medical College Hospital (PUMCH), a shorter regimen of 6 induction cycles followed by 6 maintenance cycles was preferentially used to balance efficacy, toxicity, and cost. These approaches broadly parallel the 18- and 6-cycle maintenance arms of the ongoing EMILIA trial, respectively.[12] Similar differences existed in the relapsed/refractory setting, with continuous treatment at Pavia versus a generally 12-cycle limit at PUMCH. These institutional differences provided a real-world framework for evaluating the impact of daratumumab treatment duration.

We therefore conducted a retrospective 2-center study of patients with newly diagnosed and relapsed/refractory AL amyloidosis treated with daratumumab-based regimens to evaluate the association between treatment duration and survival and organ response outcomes.

# Methods

The prospectively maintained databases of the Pavia Amyloidosis Research and Treatment Center and PUMCH were systematically searched to identify patients with newly diagnosed AL amyloidosis who received first-line daratumumab-based therapy. Diagnosis was confirmed by tissue biopsy with amyloid subtyping performed using standard methods.[14–16] Patients with concurrent myeloma meeting the SLiM-CRAB criteria were excluded, except when the only criterion met was a free light chain (FLC) ratio ≥ 100. Baseline characteristics prior to daratumumab initiation and longitudinal follow-up data were collected, including number of treatment cycles and reasons for discontinuation. All patients provided written informed consent in accordance with the Declaration of Helsinki and institutional review board requirements.

Hematologic and organ responses were assessed according to validated criteria for AL amyloidosis.[17–20] Hematologic responses included complete response (CR), defined by negative serum and urine immunofixation and normalization of the FLC ratio (unless the involved FLC was lower than the uninvolved FLC); very good partial response (VGPR), defined as a difference between involved and

uninvolved FLCs (dFLC) of < 40 mg/L; and partial response (PR), defined as a ≥ 50% reduction in dFLC from baseline. Hematologic responses were evaluated based on the best response achieved during daratumumab therapy, and patients who died before response assessment without post-baseline evaluation were classified as nonresponders. Cardiac response was defined by reductions in N-terminal pro-B-type natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP),[21] and renal response by changes in proteinuria.[22] Organ responses were assessed at 12 and 24 months.

Demographic and disease characteristics were summarized using counts and percentages for categorical variables and medians with interquartile ranges (IQRs) for continuous variables. Patients were assigned to groups based on the planned daratumumab treatment strategy (12 vs ≥ 24 cycles), and all analyses were performed according to the intention-to-treat (ITT) principle. Categorical and continuous variables were compared using the $\chi^2$ test and Mann–Whitney U test, respectively. Overall survival (OS) was estimated using the Kaplan–Meier method and compared using log-rank tests. The cumulative incidence of next treatment was estimated from treatment initiation using the Fine–Gray subdistribution hazards model, with death as a competing event. We also performed a 12-month landmark sensitivity analysis restricted to patients who had achieved a hematologic response of ≥VGPR, excluding those who initiated next treatment or were lost to follow-up before the landmark. Among patients achieving hematologic CR, the cumulative incidence of CR loss was analyzed similarly, with death treated as a competing event. For organ response analyses, all patients with baseline cardiac or renal involvement were retained in the denominator irrespective of treatment discontinuation. Multivariable time-dependent Cox models were constructed to identify factors associated with OS and time to next treatment (TTNT), incorporating response as a time-dependent variable.

A similar analytical approach was applied to an independent cohort of 184 patients with relapsed/refractory AL amyloidosis treated with daratumumab-based regimens. Statistical analyses were performed using SPSS version 31.0 and R version 4.3.1, with a 2-sided P value < 0.05 considered statistically significant.

## Results

# Characteristics of newly diagnosed patients

A total of 399 patients with newly diagnosed AL amyloidosis who initiated daratumumab-based therapy before December 31, 2023 were included, comprising 181 patients in the planned 12-cycle group and 218 in the planned ≥ 24-cycle group. The median number of treatment cycles was 9 (IQR, 2–12) and 16 (IQR, 5–24), respectively. Baseline clinical characteristics, treatment regimens, and reasons for treatment discontinuation are summarized in Table 1, with detailed descriptions of the specific treatment regimens provided in Supplemental Table 1. The median age was 64 years (IQR, 56–70), and 62% were male. Cardiac and renal involvement were present in 87% and 56% of patients, respectively. According to the modified Mayo 2004 staging system,[23, 24] 9%, 48%, 23%, and 20% of patients had stage I, II, IIIa, and IIIb disease, respectively.

Table 1
Baseline characteristics of patients with newly diagnosed light-chain amyloidosis according to the 2 planned daratumumab treatment durations

| **Variables** | **12-cycle group (n = 181), Median (IQR), N (%)** | **≥ 24-cycle group (n = 218), Median (IQR), N (%)** | **P** |
|---|---|---|---|
| Male, n (%) | 132 (73) | 114 (52) | **< 0.001** |
| Age, years | 60 (54–67) | 67 (58–73) | **< 0.001** |
| λ, n (%) | 141 (78) | 175 (80) | 0.561 |
| cTnI, μg/L | 0.10 (0.03–0.25) | 0.06 (0.02–0.14) | **< 0.001** |
| NT-proBNP, ng/L | 4 547 (1 931 – 10 090) | 2 859 (1 040 – 6 788) | **< 0.001** |
| Renal stage[42] | | | **0.023** |
| Stage I | 51 (64) | 62 (45) | - |
| Stage II | 24 (30) | 62 (45) | - |
| Stage III | 5 (6) | 15 (11) | - |
| Dialysis, n (%) | 0 (0) | 3 (1) | 0.255 |
| dFLC, mg/L | 410 (191–822) | 264 (113–664) | **< 0.001** |
| BMPC, % | 6 (3–9) | 18 (11–25) | **< 0.001** |
| Organ involvement | | | |
| Cardiac | 170 (94) | 177 (81) | **< 0.001** |
| Renal | 80 (44) | 142 (65) | **< 0.001** |
| Hepatic | 30 (17) | 20 (9) | **0.026** |
| Modified Mayo 2004 stage[23,24] | | | **0.004** |
| I | 10 (6) | 26 (12) | - |
| II | 77 (43) | 114 (52) | - |

*The percentages of cytogenetic abnormalities were calculated using the number of patients who underwent the corresponding tests as the denominator.

| Variables | 12-cycle group (n = 181), Median (IQR), N (%) | ≥ 24-cycle group (n = 218), Median (IQR), N (%) | P |
|---|---|---|---|
| IIIa | 47 (26) | 45 (21) | - |
| IIIb | 47 (26) | 33 (15) | - |
| Daratumumab cycle | 9 (2–12) | 16 (5–24) | **< 0.001** |
| Daratumumab regimen | | | **< 0.001** |
| Monotherapy | 6 (3) | 9 (4) | - |
| + PIs | 168 (93) | 159 (73) | - |
| + IMiDs | 5 (3) | 48 (22) | - |
| + others | 2 (1) | 2 (1) | - |
| Early daratumumab discontinuation reason | 97 (54) | 123 (56) | 0.571 |
| ≥very good partial response | 27 (15) | 30 (14) | - |
| Poor tolerance | 2 (1) | 10 (5) | - |
| Unsatisfactory hematologic response | 26 (14) | 32 (15) | - |
| Death | 38 (21) | 46 (21) | - |
| Lost to follow-up | 4 (2) | 5 (2) | - |
| *The percentages of cytogenetic abnormalities were calculated using the number of patients who underwent the corresponding tests as the denominator. | | | |

Table 2
Cardiac and renal responses in patients with newly diagnosed light-chain amyloidosis according to the 2 planned daratumumab treatment durations

| | | 12-cycle group (n = 181) | ≥ 24-cycle group (n = 218) | P |
|---|---|---|---|---|
| Cardiac response at 12 months | ORR | 46 (79/170) | 40 (71/177) | 0.232 |
| | CR+VGPR | 29 (49/170) | 22 (39/177) | 0.146 |
| Cardiac response at 24 months | ORR | 49 (83/170) | 37 (66/177) | **0.030** |
| | CR+VGPR | 35 (59/170) | 26 (46/177) | 0.077 |
| Renal response at 12 months | ORR | 39 (31/80) | 49 (70/142) | 0.130 |
| | CR+VGPR | 24 (19/80) | 33 (47/142) | 0.143 |
| Renal response at 24 months | ORR | 38 (30/80) | 46 (66/142) | 0.195 |
| | CR+VGPR | 26 (21/80) | 42 (59/142) | **0.023** |

Abbreviations: CR, complete response; ORR, overall response rate; VGPR, very good partial response.

Owing to epidemiologic differences between the Pavia and PUMCH cohorts, baseline characteristics differed between treatment groups (Table 1). Compared with the planned 12-cycle group, patients in the ≥ 24-cycle group were older and less frequently male, but had less advanced cardiac disease, as reflected by lower cardiac biomarker levels and a lower prevalence of Mayo 2004 stage IIIb disease (15% vs 26%). Conversely, renal involvement was more frequent (65% vs 44%), whereas baseline dFLC levels were lower (median, 264 vs 410 mg/L). Despite lower dFLC levels, the ≥ 24-cycle group had a higher bone marrow plasma cell (BMPC) burden (18% vs 6%), likely reflecting differences in institutional practice. In Pavia, daratumumab reimbursement was restricted to patients with BMPC ≥ 10% between 2021 and 2023, whereas access in China was independent of BMPC burden. Furthermore, BMPC percentages were primarily assessed by bone marrow biopsy in Pavia but reported from bone marrow smears in China, despite both aspiration and biopsy being performed.

In the planned 12-cycle group, treatment was primarily based on the ANDROMEDA regimen,[3] with cyclophosphamide omitted in most patients. In the planned ≥ 24-cycle group, reimbursement policies contributed to greater treatment heterogeneity, with 17%, 5%, and 22% of patients receiving Dara-VMP, Dara-VTd, and DRd, respectively, based on the ALCYONE,[25] CASSIOPEIA,[26] and MAIA trials (Supplemental Table 1).[27] Although treatment strategies were predefined, early treatment discontinuation before completion of the planned course was common, occurring at similar rates in the planned 12-cycle and planned ≥ 24-cycle groups (54% vs 56%; P = 0.571). The main reasons were achievement of ≥VGPR, unsatisfactory hematologic response (lack of efficacy or subsequent loss of response), death, and poor tolerability (Table 1), with no difference in their distribution between groups (P = 0.409). Only 12 patients discontinued daratumumab because of poor tolerability, most commonly

because of recurrent infections (n = 5) or worsening heart failure (n = 5), with isolated cases of neurotoxicity and diarrhea. Compared with ANDROMEDA (Supplemental Table 2), the higher discontinuation rate in our cohort was partly attributable to more early deaths (21% vs 12%), reflecting the inclusion of patients with Mayo stage IIIb disease. Additionally, although neither center recommended discontinuation upon achieving ≥VGPR, 14% of patients prematurely stopped treatment for personal reasons after achieving satisfactory responses.[4]

## Hematologic and organ responses of newly diagnosed patients

Among the entire cohort, 191 patients (48%) achieved a hematologic CR and 83 (21%) achieved a VGPR, yielding an overall hematologic response rate of 82%. The rates of ≥VGPR and CR were comparable between the planned 12-cycle and ≥ 24-cycle groups (70% vs 67%, P = 0.558; and 52% vs 44%, P = 0.139, respectively).

At 12 months, no significant differences were observed between the 2 treatment groups in either the rate or depth of cardiac and renal responses, further supporting the comparability of the 2 groups and consistent with the similar rates of hematologic ≥VGPR observed between groups. With longer daratumumab exposure, renal outcomes improved. At 24 months, the renal ≥VGPR rate was significantly higher in the planned ≥ 24-cycle group compared with the 12-cycle group (41.5% vs 26.3%; P = 0.023), whereas no corresponding improvement was observed in cardiac ≥VGPR rates.

## Overall Survival of newly diagnosed patients

With a data cutoff of December 31, 2025, the median follow-up was 36 months (95% CI, 34–37) overall, 40 months in the planned 12-cycle group, and 33 months in the planned ≥ 24-cycle group. During follow-up, 114 patients died, and the estimated 3-year OS rate was 71%. In the ITT analysis, planned daratumumab treatment for ≥ 24 cycles did not improve OS compared with the 12-cycle strategy (P = 0.639; Fig. 1A). We further evaluated the impact of prolonged daratumumab treatment in subgroups stratified by age (≥ 65 vs < 65 years; Supplemental Fig. 1), baseline BMPC percentage (≥ 10% vs < 10%; Supplemental Fig. 2), and baseline Mayo 2004 stage (IIIb vs I–IIIa; Supplemental Fig. 3). Prolonged daratumumab treatment was not associated with improved OS in any subgroup.

In multivariable Cox regression analysis, only age ≥ 65 years (HR 5.14, 95% CI 1.32–20.00; P = 0.018) and Mayo 2004 stage IIIb (HR 4.04, 95% CI 1.19–13.71; P = 0.025) were independently associated with inferior OS, whereas the planned 12-cycle treatment duration of daratumumab was not independently associated with worse OS (Supplemental Table 3).

## Cumulative incidence of next treatment in newly diagnosed patients

A total of 72 patients initiated subsequent-line therapy during follow-up, with a median TTNT of 64 months (95% CI, 44–83). Fourteen patients underwent consolidation autologous hematopoietic stem cell transplantation (ASCT) after achieving a hematologic response of ≥VGPR and were not considered to have initiated subsequent-line therapy. Among the 72 patients who received subsequent therapy, the reasons were inadequate daratumumab efficacy (n = 50), hematologic progression (n = 20), and loss of response without meeting progression criteria (n = 2) (Supplemental Table 4). The reasons for initiating subsequent therapy did not differ significantly between the planned 12-cycle and planned ≥ 24-cycle groups (P = 0.477). The most common second-line regimens were venetoclax-based (n = 14), daratumumab-based (n = 13), bortezomib-based (n = 13), and immunomodulatory drug-based therapy (n = 13) (Supplemental Table 4). Although venetoclax was more readily accessible to patients in the planned 12-cycle group, the prevalence of t(11;14) among patients receiving second-line therapy was comparable between groups, suggesting that differential access to venetoclax did not substantially influence the likelihood of initiating subsequent therapy (Supplemental Table 4). Among 65 evaluable patients, hematologic CR and VGPR were achieved in 25 (38%) and 17 (26%), respectively, following second-line therapy.

We next evaluated the impact of planned daratumumab treatment duration on the cumulative incidence of next treatment, treating death as a competing event. Planned daratumumab treatment for ≥ 24 cycles was not associated with a lower cumulative incidence of next treatment than the 12-cycle strategy (subdistribution hazard ratio [SHR] 1.29, 95% CI 0.82–2.05; Gray's test P = 0.336; Fig. 1B). Subgroup analyses stratified by age (≥ 65 vs < 65 years; Supplemental Fig. 4), sex (Supplemental Fig. 5), baseline BMPC percentage (≥ 10% vs < 10%; Supplemental Fig. 6), and baseline dFLC (≥ 180 vs < 180 mg/L; Supplemental Fig. 7) consistently showed no reduction in the cumulative incidence of next treatment with prolonged daratumumab duration. In a sensitivity analysis using a 12-month landmark and restricted to patients who had achieved a hematologic response of ≥VGPR, treatment for ≥ 24 cycles was likewise not associated with a lower cumulative incidence of next treatment (SHR 1.20, 95% CI 0.52–2.76; Gray’s test P = 0.712; Supplemental Fig. 8).

In multivariable Cox regression analysis of TTNT, male sex (HR 1.73, 95% CI 1.01–2.96; P = 0.047), baseline BMPC ≥ 10% (HR 1.90, 95% CI 1.02–3.54; P = 0.044), and baseline dFLC ≥ 180 mg/L (HR 2.34, 95% CI 1.24–4.43; P = 0.009) were independently associated with shorter TTNT, whereas the planned 12-cycle treatment duration of daratumumab was not independently associated with inferior TTNT (Supplemental Table 5).

# Cumulative incidence of loss of hematologic CR in newly diagnosed patients

Among the 191 patients who achieved a best hematologic response of CR, 20 (10%) lost CR by last follow-up, including 1 patient with baseline IgGκ monoclonal protein in whom the daratumumab-related band was excluded at the time of CR loss; 11 of these patients initiated subsequent-line therapy. The median duration of CR was not reached. Extending daratumumab treatment beyond 12 cycles did not

reduce the cumulative incidence of CR loss (SHR 1.81, 95% CI 0.70–4.68; Gray's test P = 0.238; Supplemental Fig. 9A). Similar findings were observed among patients with BMPC ≥ 10% (SHR 2.25, 95% CI 0.56–9.07; Gray's test P = 0.268; Supplemental Fig. 9B).

## Impact of planned daratumumab duration in relapsed/refractory patients

We further evaluated the impact of planned daratumumab treatment duration in relapsed/refractory AL amyloidosis. A total of 184 patients were stratified into planned 12-cycle (n = 82) and planned ≥ 24-cycle (n = 102) groups (Supplemental Tables 6 and 7). Baseline characteristics were generally balanced between the 2 groups with respect to sex, age, organ involvement, modified Mayo 2004 stage, and number of prior lines of therapy. Patients in planned ≥ 24-cycle group had a higher prevalence of prior ASCT and a greater BMPC burden. The proportions of patients discontinuing treatment before completing the planned course were similar between the planned 12-cycle and planned ≥ 24-cycle groups (66% vs 61%; P = 0.479).

Hematologic ≥VGPR rates were comparable between the 12-cycle and ≥ 24-cycle groups (74% vs 73%; P = 0.779). Prolonged daratumumab treatment was associated with higher renal overall and ≥VGPR response rates at 12 months, as well as a higher renal ≥VGPR rate at 24 months, but did not improve cardiac response (Supplemental Table 8).

From the start of daratumumab therapy, the median follow-up was 59 months (95% CI, 53–65), during which 59 patients died. The median OS was not reached, and the 5-year OS rate was 65%. OS did not differ between the 12-cycle and ≥ 24-cycle groups (P = 0.776; Fig. 2A), including among patients with BMPC ≥ 10% (P = 0.853) or age ≥ 65 years (P = 0.219).

A total of 71 patients initiated subsequent-line therapy, with a median TTNT of 66 months (95% CI, 45–87). Of these, 31 switched therapy because of suboptimal response to daratumumab and 39 because of hematologic progression or loss of response. Only 1 patient transitioned while remaining in hematologic VGPR in an attempt to deepen the response to CR, which was unsuccessful. Among the 62 patients evaluable for hematologic response to subsequent therapy, 28 (45%) achieved ≥VGPR. The cumulative incidence of next treatment was similar between the 12-cycle and ≥ 24-cycle groups (SHR 0.78, 95% CI 0.48–1.26; Gray's test P = 0.452; Fig. 2B), with consistent findings among patients with BMPC ≥ 10% (SHR 1.75, 95% CI 0.85–3.62; Gray's test P = 0.139) or dFLC ≥ 180 mg/L (SHR 0.76, 95% CI 0.33–1.72; Gray's test P = 0.619). Similarly, in the landmark sensitivity analysis restricted to patients who achieved a hematologic response of ≥VGPR, treatment for ≥ 24 cycles was not associated with a lower cumulative incidence of next treatment (SHR 1.35, 95% CI 0.69–2.64; Gray's test P = 0.377).

Among the 73 patients who achieved a hematologic CR as their best response, 71 had an identifiable time point of CR achievement. By last follow-up, 19 patients had lost CR, including 15 who subsequently initiated next-line therapy. The median duration of maintained CR was 78 months (95% CI, 44–112).

Extending daratumumab treatment to ≥ 24 cycles did not reduce the cumulative incidence of CR loss (SHR 1.29, 95% CI 0.49–3.39; Gray's test P = 0.599; Supplemental Fig. 10).

## Discussion

In this study, we compared 2 planned durations of daratumumab treatment (12 vs ≥ 24 cycles) and evaluated their associations with organ responses and clinical outcomes in patients with AL amyloidosis. We also characterized treatment discontinuation patterns and tolerability in a real-world setting. To our knowledge, this is the first study to systematically investigate the optimal duration of daratumumab therapy in both newly diagnosed and relapsed/refractory AL amyloidosis. A planned treatment duration of ≥ 24 cycles was not associated with statistically significant improvements in OS or a lower cumulative incidence of next treatment. Nor was prolonged treatment associated with longer hematologic CR duration. Even among patients with BMPC infiltration ≥ 10%, a subgroup with a more myeloma-like phenotype,[28] prolonged treatment conferred no survival advantage. In contrast, extended treatment was associated with a greater depth of renal response at 24 months in both newly diagnosed and relapsed/refractory disease.

The controversy surrounding prolonged daratumumab maintenance in AL amyloidosis reflects the relatively low plasma-cell burden and limited clonal evolution compared with multiple myeloma.[29–31] Cost considerations and potential cumulative toxicities further reduce enthusiasm for indefinite treatment. Notably, even in the ANDROMEDA trial, daratumumab maintenance was limited to 18 cycles.[3] A previous study from Boston reported superior major organ deterioration–free survival and OS among patients receiving > 12 cycles of daratumumab, although the reasons for treatment discontinuation were not described.[32] In contrast, we consistently observed no survival benefit with treatment beyond 12 cycles in either the newly diagnosed or relapsed/refractory setting.

Several observations support the robustness of our findings. First, despite a higher prevalence of Mayo 2004 stage IIIb disease in the planned 12-cycle group, which is associated with higher early mortality and poorer long-term survival,[7, 33] OS remained comparable between groups. Second, although patients in the ≥ 24-cycle group were older, age-stratified analyses (< 65 vs ≥ 65 years) showed no survival advantage with extended treatment. Third, OS was also comparable between treatment groups in the relapsed/refractory cohort, where age and Mayo stage were well balanced. The expanding availability of effective salvage therapies and clinical trials may have attenuated the impact of frontline treatment duration on long-term survival, potentially explaining the discrepancy between our findings and previous reports.[32, 34, 35]

To minimize bias from response-driven treatment extension or discontinuation, we used an ITT approach to evaluate the cumulative incidence of next treatment. Similar rates and reasons for premature discontinuation, together with comparable hematologic ≥VGPR and 12-month organ response rates, supported this approach. Prolonged treatment did not reduce the cumulative incidence of next treatment in the overall population or among patients with BMPC ≥ 10%, a subgroup with a more myeloma-like

phenotype[36] that might theoretically benefit from maintenance therapy. No benefit was observed in the relapsed/refractory cohort either. These patients had lower baseline dFLC levels (median, 115 vs 321 mg/L) and potentially more treatment-resistant clones. Notably, 31% of patients in the ≥ 24-cycle group discontinued prematurely because of inadequate or lost response, suggesting limited benefit from continued treatment in this setting. Landmark sensitivity analysis yielded consistent results. Overall, our findings do not establish a benefit of prolonged daratumumab treatment in delaying subsequent therapy, although clinically meaningful effects cannot be excluded. Prospective validation from ongoing studies such as EMILIA is awaited.[12]

With respect to organ responses, prolonged treatment improved renal responses at 24 months but did not enhance cardiac responses. Notably, in the relapsed/refractory cohort, the benefit extended to 12-month renal responses, possibly because premature treatment discontinuation was more common in the 12-cycle group than in the frontline cohort, thereby further limiting renal recovery. The discordance between cardiac and renal responses may reflect organ-specific mechanisms of light-chain toxicity, [37, 38] differences in histologic injury,[39] and variable capacity for repair.[40] We speculate that rapid involved FLC reduction is critical for cardiac response, while renal improvement may depend more on sustained and stable involved FLC suppression. Interestingly, despite the lack of cardiac benefit from prolonged treatment, the planned 12-cycle group had significantly higher overall cardiac response rates at 24 months, potentially reflecting their younger age. Given that maximal renal responses typically occur within approximately 2 years,[21, 22, 41] discontinuation of therapy after renal responses have plateaued appears to be a reasonable strategy.

Although daratumumab is associated with hypogammaglobulinemia and an increased risk of infection,[13] treatment discontinuation because of intolerance occurred in only 3% of newly diagnosed patients. This favorable tolerability may reflect the limited cumulative exposure to prior immunosuppressive therapies in the frontline setting. Given the manageable safety profile of daratumumab, a 24-cycle treatment duration, consistent with the ANDROMEDA regimen,[3] appears to represent a reasonable strategy for newly diagnosed patients with prominent renal involvement and heavy proteinuria. In contrast, 6.5% of patients in the relapsed/refractory cohort discontinued treatment because of intolerance. As these patients had accumulated toxicities from previous therapies, shortening daratumumab treatment after achieving an initial hematologic response may represent a more appropriate strategy.

This study has several limitations. First, combining data from 2 referral centers introduced between-center heterogeneity in patient characteristics, BMPC assessment, and treatment regimens. Although we addressed this using stratified and multivariable analyses, residual confounding cannot be excluded. Heterogeneity in treatment regimens also resulted in variable induction durations, precluding the identification of a uniform time point for maintenance initiation from which to assess subsequent outcomes. Instead, we assessed total daratumumab exposure, with outcomes inevitably influenced by the types and durations of concomitant agents. Second, cytogenetic data were unavailable for many patients, precluding analyses of genetic risk factors such as 1q21 amplification. Furthermore, early

discontinuation for personal reasons despite satisfactory hematologic responses in 14% of patients may have further attenuated differences in actual treatment exposure between groups, complicating the assessment of treatment duration effects. Finally, follow-up in the newly diagnosed cohort was relatively short; however, the largely overlapping survival curves make a substantial late divergence in OS less likely, although longer follow-up is warranted.

In summary, prolonged daratumumab treatment beyond 12 cycles was not associated with statistically significant improvements in OS or a lower cumulative incidence of next treatment, although the interpretation of these findings is limited by the retrospective study design and potential residual confounding. Extended treatment was associated with a greater depth of renal response. Prospective studies are warranted to clarify the clinical significance of the observed renal response benefit and to define the optimal duration of daratumumab treatment in AL amyloidosis.

## Declarations

# Authorship Contributions

KS, PM and YX designed the study, evaluated patients, collected data, analyzed data, wrote the manuscript and gave final approval. GP and JL designed the study, evaluated patients, critically reviewed the manuscript, and gave final approval. MB, AG, CB, CX and MN evaluated patients, collected data, critically reviewed the manuscript, and gave final approval.

# Competing Interests

GP received honoraria from Pfizer, Sebia, and Siemens and served on advisory boards Alexion, Argobio, GSK, Janssen, and Prothena. PM has received honoraria from Janssen, Prothena, Pfizer (also research grant), Bayer (also served on advisory board) and Siemens (also served on advisory board). MN has received honoraria from Janssen, Prothena, Pfizer (also research grant), and Argobio and has served on advisory board and received research grant from Gate Bioscience.

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# Data Availability Statement

Original data can be obtained upon reasonable request by contacting giovanni.palladini@unipv.it.

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# Figures

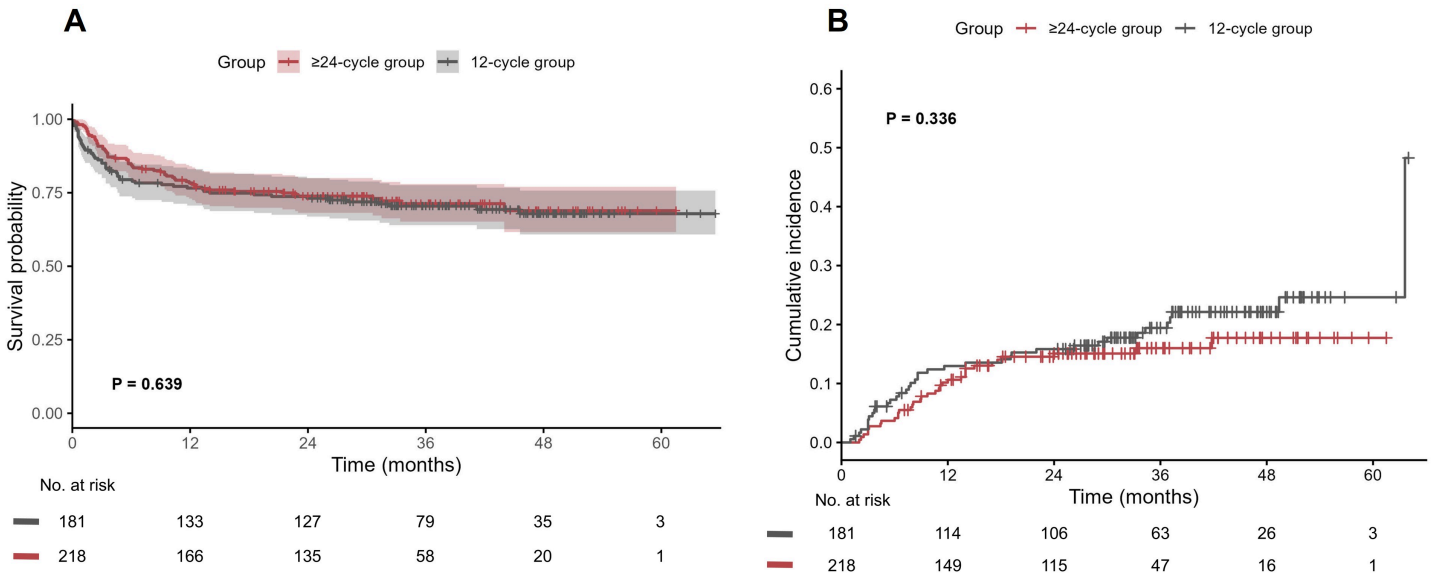


**Figure 1**

**Impact of planned daratumumab treatment duration on overall survival and cumulative incidence of next treatment in newly diagnosed light-chain amyloidosis patients.** (A) Overall survival; (B) Cumulative incidence of next treatment.

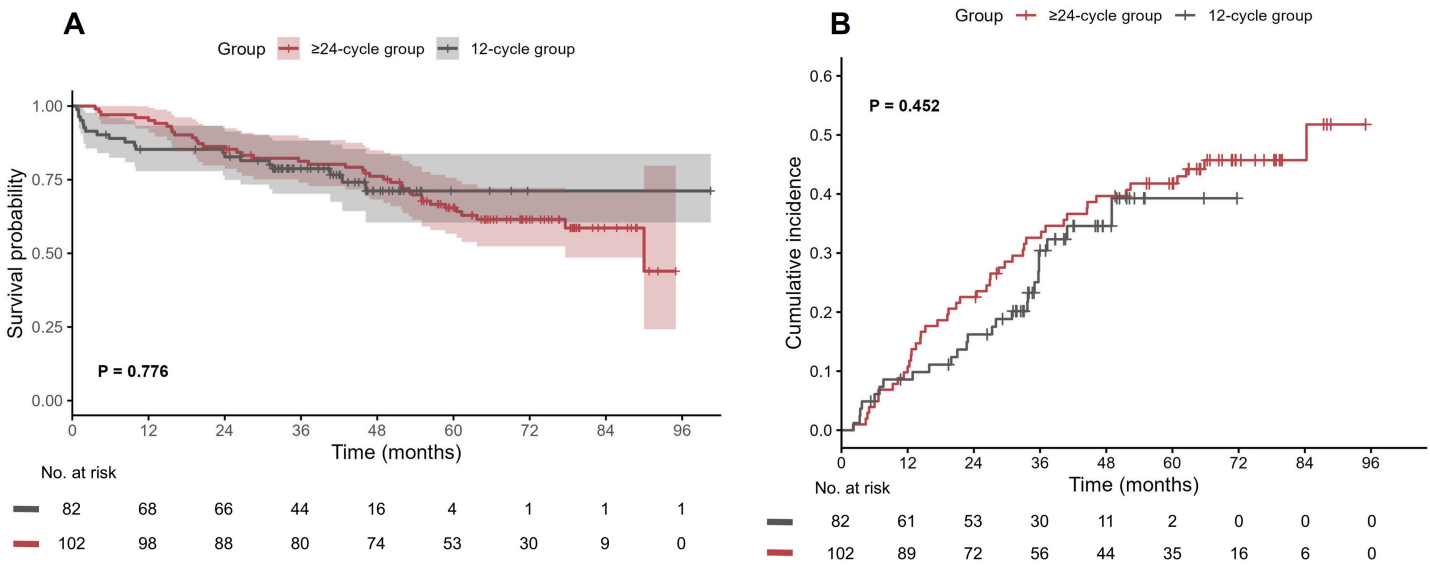


**Figure 2**

**Impact of planned daratumumab treatment duration on overall survival and cumulative incidence of next treatment in relapsed/refractory light-chain amyloidosis patients.** (A) Overall survival; (B) Cumulative incidence of next treatment.

# Supplementary Files

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