Received: 15 April 2024 | Accepted: 15 April 2024

DOI: 10.1002/jha2.918

eJHaem

British Society for Haematology

SHORT REPORT

HOVON 104, long-term follow-up of bortezomib-dexamethasone induction therapy followed by autologous stem cell transplantation in newly diagnosed AL amyloidosis patients

Monique C. Minnema[1] | Kazem Nasserinejad[2] | Ute Hegenbart[3] | Paula F. Ypma[4] | Ka Lung Wu[5] | Marie Jose Kersten[6] | Sandra Croockewit[7] | Sonja Zweegman[6] | Lidwine Tick[8] | Annemiek Broijl[9] | Harry Koene[10] | Gerard M. J. Bos[11] | Pieter Sonneveld[9] | Stefan O. Schönland[3]

[1]Department of Hematology, UMC Utrecht, University Utrecht, Utrecht, The Netherlands

[2]Department of Hematology, HOVON Data Center, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

[3]Department of Hematology and Oncology, Amyloidosis Center, University Hospital Heidelberg, Heidelberg, The Netherlands

[4]Department of Internal Medicine, Haga Hospital, Den Haag, The Netherlands

[5]Department of Hematology, Ziekenhuis Netwerk Antwerpen Stuivenberg, Antwerp, Belgium

[6]Department of Hematology, Amsterdam University Medical Center, Amsterdam, The Netherlands

[7]Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands

[8]Department of Internal Medicine, Máxima Medical Center, Eindhoven, The Netherlands

[9]Department of Hematology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands

[10]Department of Internal Medicine, Antonius Ziekenhuis, Nieuwegein, The Netherlands

[11]Department of Internal Medicine, Division of Hematology, Maastricht University Medical Center+, Maastricht, The Netherlands

Correspondence
M.C. Minnema, Department of Hematology, UMC Utrecht, Heidelberglaan 100, 3584 CS, Utrecht, The Netherlands.
Email: m.c.minnema@umcutrecht.nl

Funding information
Janssen Research and Development; KWF Kankerbestrijding, Grant/Award Number: UU-2010-4884

Abstract

The HOVON 104 studied bortezomib-dexamethasone induction therapy and autologous stem cell transplantation in 50 patients, of whom 35 received an autologous stem cell transplantation (ASCT). We demonstrate a 5-year overall survival (OS) of 73% and progression-free survival (PFS) of 52% for all 50 patients with a median follow-up of 61.3 months. For the 35 transplanted patients, calculated from the date of ASCT, the 5-year OS and PFS were 91% and 68%, respectively. After ASCT, the rate of organ response improved over time but stabilized around 3 years. A complete cardiac response was seen in around 60% of patients and remained stable from 2 years onward. Reaching complete renal response was slower over time and achieved by 61% of the renal-affected patients at 5 years. We confirm the excellent outcomes after ASCT and demonstrate a 60% complete organ response with longer follow-up.

KEYWORDS
amyloidosis, chemotherapy, SCT

Autologous stem cell transplantation (ASCT) is known for its excellent outcome in a selected group of AL amyloidosis patients [1]. Few data exist on long-term outcomes, especially for organ response, when bortezomib induction therapy is applied before ASCT. The international HOVON 104 study enrolled 50 patients with newly diagnosed AL amyloidosis between 2012 and 2016 [2]. Here, we report the long-term follow-up (LTFU) with a special focus on progression-free survival (PFS), overall survival (OS), and the recently defined graded organ responses, such as complete organ response [3, 4]. PFS was defined as hematological progression or death from any cause, whichever came first.

Treatment consisted of four cycles of bortezomib 1.3 mg/m^2 s.c. on days 1, 4, 8, and 11, and dexamethasone 20 mg p.o. on days 1, 2, 4, 5, 8, 9, 11, and 12, in a 21-day cycle followed by high dose melphalan (200 mg/m^2) and ASCT [2]. Data on medical history, physical examination, NT proBNP, alkaline phosphatase, creatinine, free light chain (FLC) levels, M-protein, and 24-h urine analysis were collected every 3 months until 5 years after registration. Fifty patients were included, median age was 59 years (range 51–63) and 28% had ≥ 10% plasma cell bone marrow infiltration. As published previously, there was no relation between depth of response or survival between patients with less or more than 10% bone marrow infiltration [2]. Mayo classification was 32% class I, 32% II, and 34% IIIa, and renal staging was 40% stage I, 50% II, and 10% III. Two or more organs were involved in 72% of patients and ≥ 3 organs in 38%. Hematological very good partial response (VGPR) and complete response (CR) rates after induction were 38% and 20%, respectively. Thirty-five patients received ASCT and one year thereafter the VGPR rate was 21% and the CR rate was 56% [2]. Fifteen patients were not transplanted mainly due to clinical deterioration during induction therapy.

In the current analysis, the median follow-up was 61.3 months (range 55.8–71.6 months). Intention to treat (ITT) analysis demonstrated a 5-year OS of 73% (95% confidence interval [CI] 59%–84%) (Figure 1). In total 13 patients died, with eight additional deaths after the first publication. One patient, with a VGPR as the best response, subsequently progressed and succumbed to plasma cell leukemia. The remaining seven patients died due to complications related to AL amyloidosis and treatment. Five of these patients had a partial response (PR) as the best response during protocol treatment. The 5-year ITT hematological PFS was 52% (95% CI 38%–65%) (Figure 1).

In a landmark analysis, calculated from the date of ASCT, the 5-year OS, and PFS were 91% (95% CI 76%–97%) and 68% (95% CI 50%–81%), respectively (Figure S1). Having a CR after induction therapy and before ASCT was not significantly associated with the duration of OS or PFS, but the 5-year PFS of 88% in the CR patients and 63% in the non-CR patients may suggest a trend. The median OS of the 15 not transplanted patients was 32.7 months (95% CI 5.03 months–NR) (Figure S2). Of the seven patients with flow cytometry performed at 6 months post-ASCT, six were minimal residual disease (MRD) negative, and five of those remained in CR during LTFU.

Cardiac involvement was diagnosed in 33 patients (66%) of whom 23 received an ASCT. Forty-one patients (82%) had renal involvement of whom 29 received an ASCT. After ASCT, the number of patients with the best achieved cardiac response improved slightly from 78% to 91% (21/23 patients), and the best renal response from 69% to 79% (23/29 patients) [5]. Organ responses over time for all patients, at fixed time points, were captured with Sankey plots for the heart (Figure 2A) and kidney (Figure 2B). Total cardiac responses stabilized at 3 years after registration (green bars). In a recent publication, complete cardiac responses were defined as an NT proBNP level ≤ 350 pg/mL [4]. From the 2-year evaluation point onward between 59–65% of the cardiac-responding patients had a complete cardiac response, which did not improve further with longer FU. Total renal responses also stabilized at 3 years, but there was continuous improvement in the complete renal response rate, defined as proteinuria ≤ 200 mg/24 h [3]. At 2 years, four patients (21%) had a complete renal response and this increased to 50%, 56%, and 61% at 3, 4, and 5 years, respectively. Although no data on dialysis was collected, in six of the total of 50 patients creatinine clearance worsened to ≤ 15 ml/min/1.73 m^2.

Sixteen of the 50 patients have received additional treatments with a median time to the next treatment, calculated from the start of the first treatment, of 14 months (range 3–55 months). Second-line treatment was heterogeneous and consisted of a second ASCT (4 pts), lenalidomide based (6 pts), bortezomib re-treatment (4 pts), daratumumab (2 pts), oral cyclophosphamide (1 pt) and pomalidomide-dexamethasone (1 pt). Response to second-line treatment was not captured.

This LTFU analysis confirms the excellent outcome for patients receiving induction therapy followed by ASCT with a 5-year PFS of 68% and OS of 91% after ASCT and for all 50 patients a 5-year PFS of 52% and OS of 73%. Compared to the HOVON 41 study, another community, multi-center, prospective AL amyloidosis study with vincristine-doxorubicin-dexamethasone-based induction therapy, which demonstrated a 5-year OS of 74% after ASCT, our results show that nowadays, with improved induction regimens, relapse treatment options, and better supportive care, the long-term survival after ASCT can still improve [6]. This is in concordance with other contemporary analyses of retrospective datasets such as the CIBMTR analysis of 294 patients receiving bortezomib induction, reporting a 2-year OS calculated from the date of ASCT of 92% (range 88–95%) and a single center Chinese analysis of 124 patients, reporting a 5 year estimated OS of 81% [7, 8]. The Boston study reported an ITT OS analysis with bortezomib induction and ASCT of 80% compared to 73% in our study.[9]

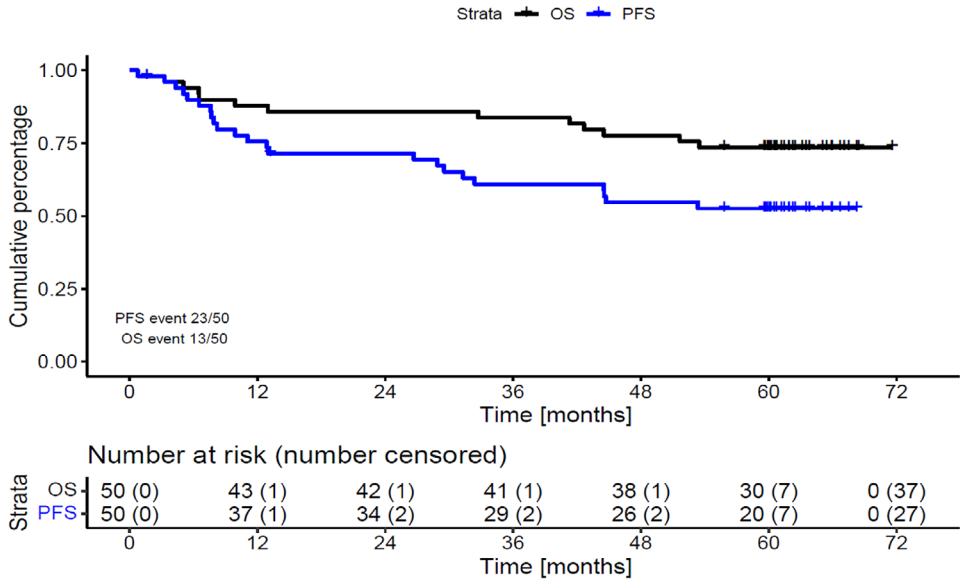

FIGURE 1 Overall survival and progression-free survival of a total cohort of 50 patients. OS: overall survival, PFS: progression-free survival. Median follow-up was 61.3 months (range 55.8–71.6 months).

Best achieved cardiac and renal organ responses were high at 91% and 79%, respectively. These response rates are in line with the Boston study reporting cardiac responses in 88% and renal responses in 65% of patients at 5 years.[9] Organ responses are mostly based upon blood measurements of serum creatinine, NT proBNP, and alkaline phosphatase, which can be volatile and also influenced by non-amyloid-related situations and diseases. Therefore, in most publications best achieved organ response are reported. The pathophysiological reasoning is that organ responses follow deep hematological responses and can improve over time when a patient remains in VGPR/CR. The official organ responses as applied in the trial are binary. However, recently graded organ response criteria were constructed from large retrospective databases [3, 4]. When we apply these to our cohort of patients, we find that complete cardiac responses at 2 years after treatment initiation are achieved in around 60% of patients and thereafter do not improve further. However, complete renal response seems to improve constantly over time up to 5 years and is also seen in 61% of patients at this latest time point.

We tried to evaluate the prognostic value of MRD measurements using flow cytometry at 6 months after ASCT, but only seven patients had samples sent to the central laboratory. All seven were in CR at this time point and six of them were MRD negative with a sensitivity of 10^{-5}. Due to the small number of patients, no further analyses were performed [10].

The role of first-line ASCT in fit patients with AL amyloidosis is challenged by the recent publication of the Andromeda study [11, 12]. In this study, with a median FU of 11.4 months, the best achieved VGPR and CR rates in the patients treated with daratumumab, bortezomib, cyclophosphamide, and dexamethasone were 25.2% and 53.%, respectively. These rates are comparable to the responses reported in the current study, one year after ASCT, with a VGPR rate of 21% and CR rate of 56%. In Andromeda, organ responses were also seen in more than 50% of the patients at a median FU of 18 months [13]. Data on OS with longer FU are currently lacking in the Andromeda trial, and therefore applying ASCT in carefully selected patients can still be considered. The treatment paradigm is shifting towards starting induction treatment in all patients and only proceeding to ASCT when patients do not achieve a CR, sparing patients with a toxic ASCT treatment [14]. However, although caution should be used with small numbers, our data demonstrate that hematological progression seems to occur more frequently in patients who are not in CR before ASCT (Figure S1), implying that ASCT cannot always confer the negative impact of the less than CR status with chemotherapy alone.

In conclusion, this LTFU of the HOVON 104 study demonstrates that patients who received bortezomib induction therapy followed by ASCT had an excellent 5-year median PFS of 68% and OS of 91% after ASCT. The rate of organ responses stabilized around 3 years after treatment with stable complete cardiac responses but complete renal responses continued to improve.

ACKNOWLEDGMENTS

The authors would like to thank all participating patients and study centers. The authors thank the local data managers for study coordination and collecting patient data. MCM performed the research, designed the study, analyzed the data, and wrote the paper. KN analyzed the data, UH and SOS performed the research, designed the study, and analyzed the data. PFY, KLW, MJK, SC, SZ, LT, AB, HK, GMJB, and PS performed the research. This investigator-sponsored trial was financially supported by the Dutch Cancer Society (KWF UU-2010-4884) and Janssen Cilag which provided the drug bortezomib, free of charge.

CONFLICT OF INTEREST STATEMENT

MCM Research Funding: Beigene Consultancy: Janssen Cilag, BMS, GSK, CDR-life, Speakers Bureau: Siemens, Janssen Cilag, all paid to

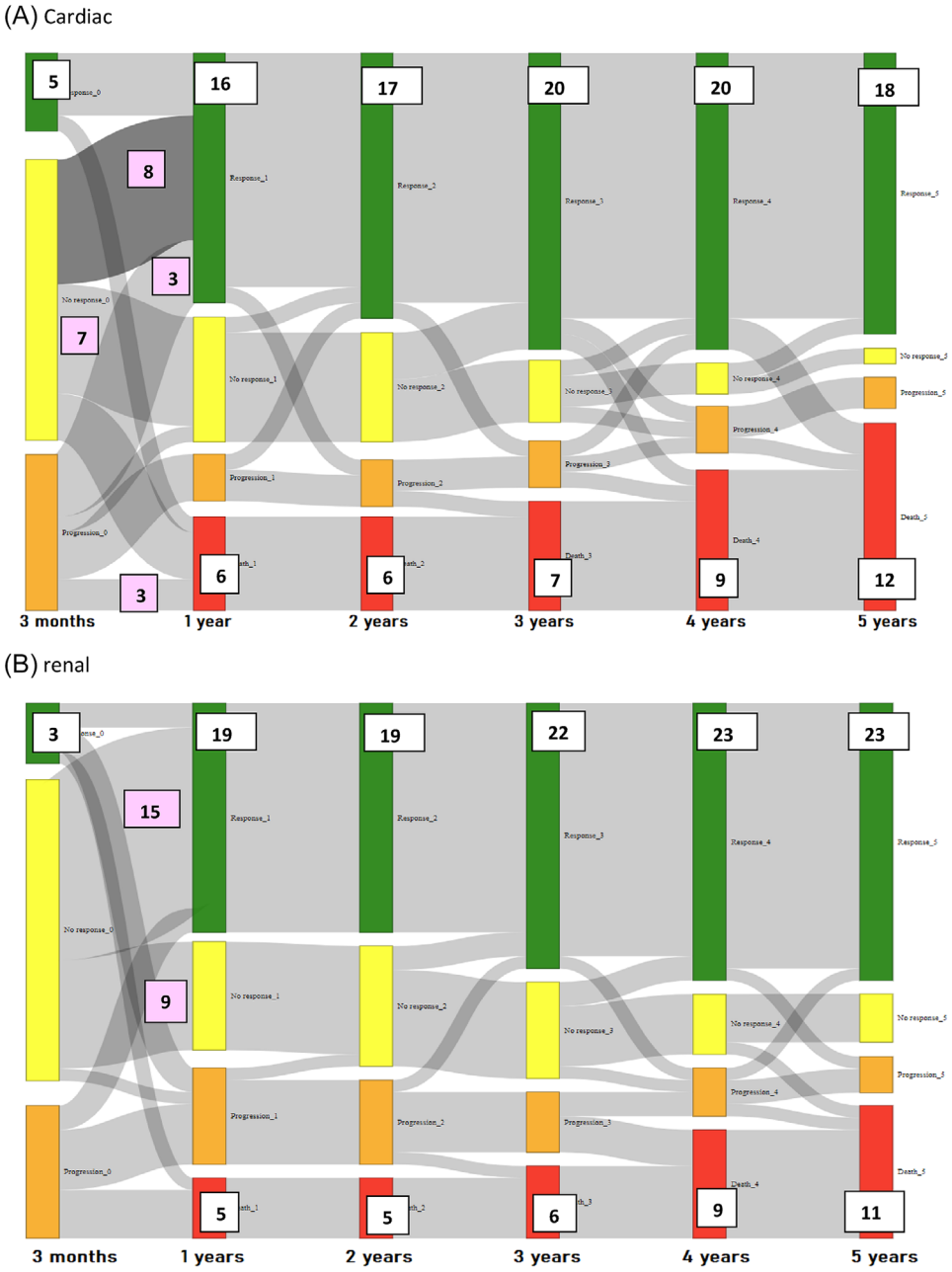

FIGURE 2 Sankey plot with individual organ responses from 3 months to 5 years after treatment initiation in 50 included patients. Response criteria are Response (green), No response (yellow), Progression (orange), and Death (red). (A) Cardiac responses at 3 months, and yearly thereafter for 33 patients with cardiac involvement. (B) Renal responses at 3 months, and yearly thereafter for 41 patients with renal involvement. The numbers in the bars reflect the number of patients in that particular group.

the institution, UH Speakers Bureau: Janssen Cilag, Pfizer, Alnylam, Akcea, Prothena, Astra Zeneca, Hospitality: Janssen, Prothena, Pfizer. Advisory Boards: Pfizer, Prothena, Janssen, Alexion. MJK Honoraria: BMS/Celgene, Kite/Gilead, Novartis, Roche; Consulting or Advisory Role: BMS/Celgene, Kite/Gilead, Miltenyi, Biotech, Novartis, Takeda, Adicet Bio and Miltenyi Biomedicine; Research Funding: Kite/Gilead, all paid to the institution. SZ Research funding: Janssen Cilag, Advisory board: Janssen Cilag, BMS, Sanofi, Oncopeptides, Amgen, all paid to the institution. AB Advisory board: Janssen Pharmaceuticals, Amgen, Celgene, BMS, Takeda. PS Research funding: Janssen Pharmaceuticals, Amgen, Celgene, Karyopharm. Advisory board: Janssen Pharmaceuticals, Pfizer, BMS. SOS Research support: Janssen, Prothena, Sanofi, Neurimmune Advisory boards: Janssen, Telix and Prothena Honoraria: AstraZeneca, Alexion, Sobi, Janssen, Takeda, Pfizer, Prothena. KN, PFY, SC, LT, KLW, GMJB, and HK declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

All procedures were conducted in compliance with the Declaration of Helsinki. Written informed consent to participate in the study was provided by all patients (EudraCT number 2010-021445-42).

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION

Dutch Trial Register identifier NTR3220.

ORCID

Monique C. Minnema https://orcid.org/0000-0002-3139-8379
Kazem Nasserinejad https://orcid.org/0000-0002-5666-5015
Ute Hegenbart https://orcid.org/0000-0003-1917-6746
Paula F. Ypma https://orcid.org/0000-0003-1250-7979
Ka Lung Wu https://orcid.org/0000-0001-6042-978X
Marie Jose Kersten https://orcid.org/0000-0002-8904-3802
Sandra Croockewit https://orcid.org/0000-0003-3101-1194
Sonja Zweegman https://orcid.org/0000-0002-5011-1820
Lidwine Tick https://orcid.org/0000-0002-0771-5231
Annemiek Broijl https://orcid.org/0000-0002-0554-8003
Pieter Sonneveld https://orcid.org/0000-0002-0808-2237
Stefan O. Schönland https://orcid.org/0000-0002-4853-5579

REFERENCES

1. Gustine JN, Staron A, Szalat RE, Mendelson LM, Joshi T, Ruberg FL, et al. Predictors of hematologic response and survival with stem cell transplantation in AL amyloidosis: A 25-year longitudinal study. Am J Hematol. 2022;97(9):1189–99.
2. Minnema MC, Nasserinejad K, Hazenberg B, Hegenbart U, Vlummens P, Ypma PF, et al. Bortezomib-based induction followed by stem cell transplantation in light chain amyloidosis: results of the multicenter HOVON 104 trial. Haematologica. 2019;104(11):2274–82.
3. Muchtar E, Dispenzieri A, Leung N, Lacy MQ, Buadi FK, Dingli D, et al. Depth of organ response in AL amyloidosis is associated with improved survival: grading the organ response criteria. Leukemia. 2018;32(10):2240–49.
4. Muchtar E, Dispenzieri A, Wisniowski B, Palladini G, Milani P, Merlini G, et al. Graded cardiac response criteria for patients with systemic light chain amyloidosis. J Clin Oncol. 2023;41(7):1393–403.
5. Comenzo RL, Reece D, Palladini G, Seldin D, Sanchorawala V, Landau H, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. Leukemia. 2012;26(11):2317–25.
6. Hazenberg BP, Croockewit A, van der Holt B, Zweegman S, Bos GM, Delforge M, et al. Extended follow up of high-dose melphalan and autologous stem cell transplantation after vincristine, doxorubicin, dexamethasone induction in amyloid light chain amyloidosis of the prospective phase II HOVON-41 study by the Dutch-Belgian Co-operative Trial Group for Hematology Oncology. Haematologica. 2015;100(5):677–82.
7. Cornell RF, Fraser R, Costa L, Goodman S, Estrada-Merly N, Lee C, et al. Bortezomib-based induction is associated with superior outcomes in light chain amyloidosis patients treated with autologous hematopoietic cell transplantation regardless of plasma cell burden. Transplant Cell Ther. 2021;27(3):264.e1–264.e7.
8. Huang X, Ren G, Chen W, Guo J, Zhao L, Zeng C, et al. The role of induction therapy before autologous stem cell transplantation in low disease burden AL amyloidosis patients. Amyloid. 2021;28(2):75–83.
9. Gupta VK, Brauneis D, Shelton AC, Quillen K, Sarosiek S, Sloan JM, et al. Induction therapy with bortezomib and dexamethasone and conditioning with high-dose melphalan and bortezomib followed by autologous stem cell transplantation for immunoglobulin light chain amyloidosis: long-term follow-up analysis. Biol Blood Marrow Transplant. 2019;25(5):e169–73.
10. Sidana S, Muchtar E, Sidiqi MH, Jevremovic D, Dispenzieri A, Gonsalves W, et al. Impact of minimal residual negativity using next generation flow cytometry on outcomes in light chain amyloidosis. Am J Hematol. 2020;95(5):497–502.
11. Kastritis E, Palladini G, Minnema MC, Wechalekar AD, Jaccard A, Lee HC, et al. Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. N Engl J Med. 2021;385(1):46–58.
12. Sanchorawala V, Boccadoro M, Gertz M, Hegenbart U, Kastritis E, Landau H, et al. Guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis: EHA-ISA working group guidelines. Amyloid. 2022;29(1):1–7.
13. Comenzo R, Palladini G, Kastritis E, Minnema MC, Wechalekar AD, Jaccard A, et al. Subcutaneous daratumumab with bortezomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed light chain (AL) amyloidosis: 18-month analysis of the Phase 3 Andromeda Study. Blood. 2021;138(159):159–159.
14. Chakraborty R, Milani P, Palladini G, Gertz M. Role of autologous haematopoietic cell transplantation in the treatment of systemic light chain amyloidosis in the era of anti-CD38 monoclonal antibodies. Lancet Haematol. 2023;10(11):e936–40.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Minnema MC, Nasserinejad K, Hegenbart U, Ypma PF, Wu KL, Kersten MJ, et al. HOVON 104, long-term follow-up of bortezomib-dexamethasone induction therapy followed by autologous stem cell transplantation in newly diagnosed AL amyloidosis patients. eJHaem. 2024;5:815–19. https://doi.org/10.1002/jha2.918