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LETTER

Bortezomib before and after high-dose therapy in transplant-eligible patients with newly diagnosed multiple myeloma: Long-term overall survival after more than 10 years of follow-up from the phase III HOVON-65/GMMG-HD4 trial

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Life expectancy in patients with multiple myeloma (MM) has increased due to the availability of effective drugs such as proteasome inhibitors (PIs),[1,2] immunomodulatory drugs (IMiDs),[3–5] and more recently, monoclonal antibodies.[6–8]

While the progression-free survival (PFS) rates and the depth of response increase with the use of modern multi-drug combinations, it is not clear whether these effects will translate into an improved long-term overall survival (OS). To draw such conclusions, long-term follow-up analyses from trials are needed as comparators for future trials. Here, we report on the long-term overall survival of the HOVON-65/GMMG-HD4 trial including the OS after more than 10 years, and the role of established prognostic factors.

The investigator-sponsored, open-label, randomized HOVON-65/GMMG-HD4 phase III trial was conducted by the Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON) and the German-speaking Myeloma Multicenter Group (GMMG) in 75 centers in the Netherlands, Belgium, and Germany from May 2005 to May 2008 and included 827 eligible patients. The trial was registered

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at www.trialregister.nl (until June 2022) and https://trialsearch.who.int/ as NTR213, at www.isrctn.com as ISRCTN64455289 and at www.clinicaltrialsregister.eu as EudraCT2004-000944-26. The ethics committees of the Erasmus University Medical Center, the University of Heidelberg, and all participating sites approved this trial. All patients gave written informed consent. The study was conducted in accordance with the European Clinical Trial Directive (2005) and the Declaration of Helsinki (1996).

Initial results of the trial have been published and include a detailed study protocol, inclusion and exclusion criteria, randomization procedures and toxicities,[9] and results after a median follow-up of 96 months.[10] After that, only OS data were collected on which we here report the final long-term survival data.

The aim of the trial was to investigate the use of bortezomib (BTZ) in induction and maintenance compared to treatment with classical cytotoxic agents as induction and thalidomide maintenance in transplant-eligible patients regarding the primary endpoint PFS, while OS was a secondary endpoint. Patients were randomized 1:1 to receive either vincristine, adriamycin, and dexamethasone (VAD) as induction therapy, followed by high-dose chemotherapy with melphalan and autologous stem-cell transplantation (ASCT), followed by maintenance therapy with thalidomide (VAD arm). In the PAD arm, BTZ, adriamycin, and dexamethasone were used in induction, followed by ASCT and maintenance with BTZ. Patients were stratified by center and International Staging System (ISS, I vs. II vs. III). A single ASCT was planned in the HOVON group, whereas in the GMMG, a tandem ASCT was planned. Patients with an HLA-identical sibling could proceed to allogeneic stem cell transplantation (alloSCT) after the first ASCT.

For the current exploratory analysis, the data available at the final database lock were used (as of July 4, 2019). OS was calculated from randomization until death from any cause, censoring patients alive at the date of last contact.[9] OS was estimated by the Kaplan–Meier method, and 95% confidence intervals (CIs) were constructed. The formal test for difference in OS between the two treatment arms was done with a Cox regression analysis with adjustment for the stratification factor ISS. HRs and corresponding 95% CIs were determined. Kaplan–Meier curves were generated to illustrate survival. All analyses were performed on the intention-to-treat population. All reported *p*-values are two-sided and have not been adjusted for multiple testing. A detailed summary of the trial, eligibility criteria, treatment, response assessment, endpoints, and statistical analysis can be found in the Supporting Information Appendix (pages 3–5) and has been published previously.[9,10]

From May 2005 to May 2008, 833 patients were randomly assigned 1:1 to the treatment arms, with 413 and 414 eligible patients being randomized to the VAD and PAD arm, respectively. Six patients were ineligible and excluded from all analyses. Baseline characteristics were reported previously and were evenly distributed.[9]

Since July 2011, all patients are in follow-up. Differences in the applied treatments between the HOVON and GMMG study groups have been described before.[9,10] In short, in the HOVON group, the number of patients receiving an allogeneic stem cell transplantation was higher (HOVON 60 patients vs. GMMG 2 patients), while in the GMMG study group, more patients received an upfront tandem ASCT (GMMG 273 patients; HOVON 2 patients). Maintenance therapy according to the protocol was initiated in 217 patients in the HOVON group and in 283 patients in the GMMG group with a longer duration of study in the GMMG group.[10] A consort diagram for each study group (HOVON and GMMG) and data on documented systemic treatment after the first relapse/progression for MM have been reported previously.[10]

Of the 827 patients, 508 (61%) have died and 78 (9%) patients were lost to follow-up. The median follow-up of the 319 patients still alive including the patients lost to follow-up is 11.4 years (inter-quartile range: 10.2–12.3). The 12-year OS in the VAD arm was 32% (95% CI: 27%–37%) versus 36% (95% CI: 31%–41%) in the PAD arm (Figure 1A and Supporting Information Appendix page 6). The difference in OS was not statistically significant, neither in the Cox regression analysis (HR = 0.87, 95% CI: 0.73–1.04, $p = 0.12$, adjusted for ISS) nor with the stratified log-rank test ($p = 0.15$). Univariable analyses are shown as forest plots in Figure 1B. As in the previous reports,[9,10] patient subgroups with ISS stage 3 (HR = 0.66, 95% CI: 0.45–0.97), del(13q14) (HR = 0.68, 95% CI: 0.51–0.90), and renal impairment (HR = 0.31, 95% CI: 0.16–0.57) showed a promising benefit from PAD versus VAD treatment. To further assess the prognostic value of selected baseline characteristics on OS, multivariable Cox regression analysis was performed (Table 1). This analysis revealed a statistically significant OS benefit in favor of the PAD versus VAD arm (HR = 0.84, 95% CI: 0.70–1.00, $p = 0.048$).

OS on patients with renal impairment, adverse cytogenetics (GMMG patients only[10]), and according to response status as previously analyzed are shown in Supporting Information S1: Figures 1–3 and remained unchanged with regard to the previous long-term follow-up of the trial.[10] In this trial, the use of single versus tandem ASCT was not determined as per the study protocol. However, the procedures between the study groups differed especially regarding upfront allogeneic transplantation, the use of tandem ASCT, and the duration of maintenance therapy.[10] A post hoc analysis of OS from the date of the last ASCT showed a 10-year OS for 41% (95% CI: 36%–45%) of patients after single, and 41% (95% CI: 34%–47%) of patients after tandem ASCT (HR = 0.99, 95% CI: 0.81–1.21, $p = 0.93$).

In this final long-term follow-up of the multicenter, phase III trial HOVON-65/GMMG-HD4 with a median follow-up of 11.4 years, more than 35% of patients are alive, and 10-year OS of the overall intention-to-treat population is 40% (95% CI: 36%–43%). OS did not differ significantly between the study arms in univariable analyses but showed a significant OS advantage for the PAD arm in a multivariable analysis. Treatment in the PAD arm led to improved PFS as was already shown in the previous analyses.[9,10] In patients with renal impairment, OS improved significantly with PAD compared to VAD, resulting in a similar OS as compared to patients without renal impairment. Similarly, the negative prognostic impact of del(17p13) was overcome in the PAD arm with a remarkable 37% OS at 10 years compared to 43% in patients without del(17p13).

Whether the use of a tandem ASCT improves the outcome was extensively elaborated and discussed in an earlier analysis of this study.[10] Because of the described confounders it is not possible to draw a definite conclusion about the efficacy of a tandem ASCT compared to a single ASCT from this trial.

Despite comparing chemotherapy plus thalidomide-based to a bortezomib-based strategy, the difference regarding OS is rather small. Likely, a less effective therapy during the first line might be partially overcome by the use of novel therapies in relapsed MM. Bortezomib was indeed used in a higher number of patients at first relapse in the VAD as compared to the PAD arm (60% vs. 33%).[10] Several novel agents have been developed for MM treatment after the completion of this trial.[2,6,7] Therefore, patients with a longer PFS after first-line treatment may have been more likely to be treated with these novel agents after relapse than patients with an early relapse. Since patients with early relapse are usually patients with high-risk features, and the fact that at the time of relapse these novel, more effective agents may not have been available yet, this may in part explain our OS results, particularly in high-risk MM, and support risk-adapted strategies with more intense induction therapies for

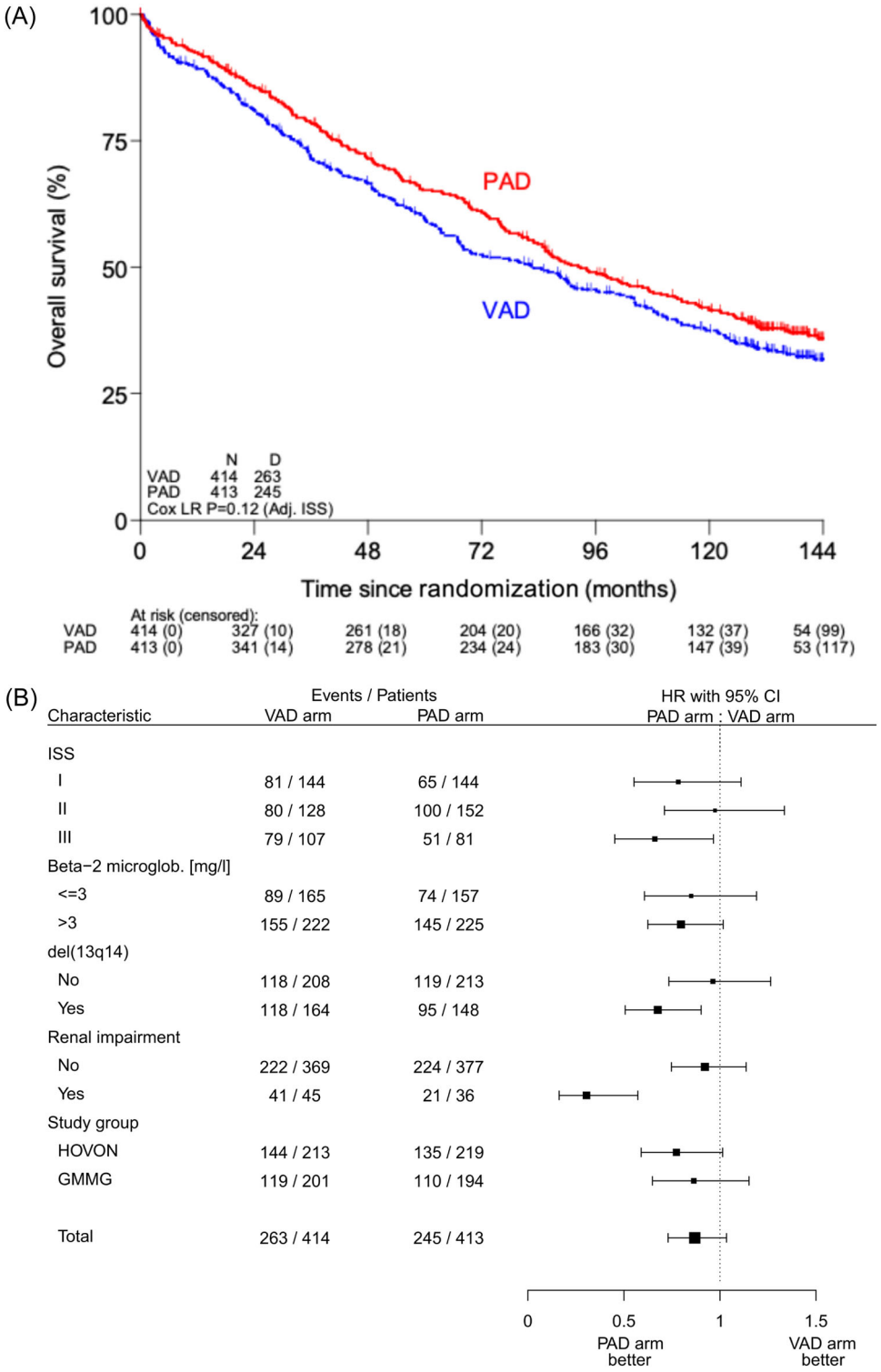

FIGURE 1 **Final overall survival analysis of the HOVON-65/GMMG-HD4 trial. (A)** Overall survival. Kaplan–Meier survival curves of overall survival (OS) for the two study arms. Cox LR, Cox likelihood ratio test; D, number of deaths; ISS, International Staging System; PAD, bortezomib, adriamycin, and dexamethasone plus bortezomib maintenance (PAD arm); VAD, vincristine, adriamycin, and dexamethasone plus thalidomide maintenance (VAD arm). **(B)** Forest plot of OS on relevant subgroups with PAD versus VAD treatment. HR, hazard ratio; CI, confidence interval; ISS, International Staging System; HOVON, Dutch-Belgian Cooperative Trial Group for Hematology Oncology; GMMG, German-speaking Myeloma Multicenter Group; PAD, bortezomib, adriamycin, and dexamethasone plus bortezomib maintenance (PAD arm); VAD, vincristine, adriamycin, and dexamethasone plus thalidomide maintenance (VAD arm).

TABLE 1 Multivariable Cox model on prognostic factors for overall survival.

Risk factor	HR	95% CI	*p* value
Treatment arm (PAD)	0.84	0.70–1.00	**0.048**
Age (per year)	1.02	1.01–1.03	**0.002**
Sex (female)	0.83	0.69–0.99	**0.044**
ISS stage (I, II, III)	1.19	1.04–1.35	**0.010**
WHO PS (0, 1, 2, 3)	1.32	1.17–1.48	**<0.001**
IgA (yes)	1.56	1.18–2.06	**0.002**
IgG (yes)	1.18	0.92–1.51	0.19
Salmon and Durie stage (III)	1.14	0.88–1.47	0.34
LDH (>ULN)	1.44	1.14–1.82	**0.002**
del13/13q14 (yes)	1.42	1.17–1.73	**<0.001**
Study group (GMMG)	0.90	0.76–1.08	0.27
Renal impairment (yes)	1.42	1.04–1.95	**0.026**

Note: Bold font denotes statistically significant *p* values.

Abbreviations: CI, confidence interval; GMMG, German-speaking Myeloma Multicenter Group; HR, hazard ratio; Ig, immunoglobulin; ISS, International Staging System; LDH, lactate dehydrogenase; PAD, bortezomib, adriamycin, and dexamethasone; ULN, upper limit of Normal; WHO PS, World Health Organization Performance Status.

patients with high-risk features.[11] Yet, long-term OS as an outcome measure remains important to elucidate differences in therapeutic strategies.

In summary, in this final long-term follow-up analysis, the primary analysis did not show a statistically significant improvement in OS. However, improvement of OS in subgroups of patients with a del(17p13) or renal impairment was observed. Furthermore, the survival of a substantial fraction of patients for 12 years and longer indicates the effectiveness of current treatment strategies for MM and underlines the importance of long-term follow-up analysis in future trials.

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AUTHOR CONTRIBUTIONS

Pieter Sonneveld, Peter Brossart, Sonja Zweegman, Gerard M. J. Bos, Henk M. Lokhorst, and Hartmut Goldschmidt were involved in conception and design. Bronno van der Holt, Uta Bertsch, Henk M. Lokhorst, and Hartmut Goldschmidt were involved in administrative support. Pieter Sonneveld, Hans J. Salwender, Sonja Zweegman, Katja C. Weisel, Sandra Croockewit, Gerard M. J. Bos, Marian Stevens-Kroef, Christoph Scheid, Jens Hillengass, Marc S. Raab, Christine Hanoun, Henk M. Lokhorst, and Hartmut Goldschmidt were involved in provision of study materials or patients. Pieter Sonneveld, Peter Brossart, Uta Bertsch, Hans J. Salwender, Sonja Zweegman, Annemiek Broijl, Axel Nogai, Katja C. Weisel, Jens Hillengass, Marc S. Raab, Elias K. Mai, Sandra Croockewit, Gerard M. J. Bos, Marian Stevens-Kroef, Christoph Scheid, Anna Jauch, Thomas Hielscher, Christine Hanoun, Paula Ypma, Henk M. Lokhorst, and Hartmut Goldschmidt were involved in collection and assembly of data. Elias K. Mai, Axel Nogai, Bronno van der Holt, Sonja Zweegman, Marian Stevens-Kroef, Christoph Scheid, Paula Ypma, Thomas Hielscher, Hartmut Goldschmidt, and Pieter Sonneveld were involved in data analysis and interpretation. Elias K. Mai, Axel Nogai, and Bronno van der Holt were involved in writing of the first manuscript draft. All authors involved in manuscript editing and writing, final approval of manuscript.

CONFLICT OF INTEREST STATEMENT

Elias K. Mai reports consulting or advisory role with Amgen, BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Pfizer, Sanofi, Stemline, and Takeda; honoraria from Amgen, BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Pfizer, Sanofi, Stemline, and Takeda; research funding from BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Sanofi, and Takeda; and travel accommodations and expenses from BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Sanofi, Stemline, and Takeda. Axel Nogai reports consulting or advisory role with Celgene, Roche, Takeda, Alexion, Janssen, BMS, Sanofi and GSK; honoraria from Celgene, Roche, Takeda, Alexion, Janssen, BMS, Sanofi, and GSK; research support from BMS, Janssen, and Celgene; and travel accommodations and expenses from Takeda, Janssen, Alexion, and Amgen. Bronno van der Holt reports honoraria for data safety monitoring board membership from IFM. Sonja Zweegman reports consulting or advisory role with Janssen, BMS, Sanofi, Oncopeptides, and GSK; and research funding from Takeda and Janssen. Katja C. Weisel reports consulting or advisory role with Abbvie, Amgen, Adaptive Biotech, Bristol Myers Squibb/Celgene, BeiGene, Janssen, GlaxoSmithKline, Karyopharm, Oncopeptides, Pfizer, Regeneron, Roche Pharma, Sanofi, Takeda, and Menarini; honoraria from Abbvie, Amgen, Adaptive Biotech, Astra Zeneca, Bristol Myers Squibb/Celgene, BeiGene, Janssen, GlaxoSmithKline, Karyopharm, Novartis, Oncopeptides, Pfizer, Roche Pharma, Sanofi, Stemline, Takeda, and Menarini; and research funding from Abbvie, Amgen, Bristol Myers Squibb/Celgene, Janssen, GlaxoSmithKline, Pfizer, Sanofi, and Takeda. Jens Hillengass reports advisory role with Prothena, Sebia, and Regeneron; honoraria from Targeted Oncology; and member of data safety monitoring boards with Janssen. Marc S. Raab reports consulting or advisory role with BMS, Amgen, GSK, Janssen, Sanofi, Pfizer, AbbVie, and Takeda; research funding from BMS, Janssen, Sanofi, and Heidelberg Pharma; travel accommodation and expenses from BMS, Amgen, and Janssen; and honoraria from BMS, Janssen, AbbVie, and Sanofi. Annemiek Broijl reports honoraria from Amgen, Sanofi, Janssen, and BMS. Peter Brossart reports consulting or advisory role from Astra-Zeneca, BMS, MSD, BeiGene, and Gilead; research funding from BMS; and honoraria from Gilead, MSD, BMS, and Astra-Zeneca. Christoph Scheid reports consulting or advisory role from Bristol Myers Squibb, GlaxoSmithKline, Janssen, Pfizer, Roche, and Takeda; honoraria from Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen, MSD, Novartis, Roche, Sanofi, and Takeda; research funding from Janssen, and Takeda; and travel accommodation and expenses from Bristol Myers Squibb, Janssen, Sanofi Aventis, and Takeda. Hans J. Salwender reports consulting or advisory role with Amgen, AstraZeneca, Bristol Myers Squibb/Celgene, Genzyme, GSK, Janssen Cilag, Oncopeptides, Pfizer, Sanofi, and Stemline; honoraria from Abbvie, Amgen, AstraZeneca, Bristol Myers SquibbMS/Celgene, Genzyme, GSK, Janssen Cilag, Oncopeptides, Pfizer, Roche, Sanofi, Stemline, and Takeda; and travel accommodation and expenses from Amgen, Bristol Myers Squibb/Celgene, Janssen Cilag, and Sanofi. Hartmut Goldschmidt reports consulting or advisory role with Amgen, BMS, Janssen, Sanofi, and Adaptive Biotechnology; honoraria from Amgen, BMS, Chugai, GlaxoSmithKline,

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data from published parts of the HOVON-65/GMMG-HD4 trial can be made available upon request to and decision of the principal investigators (Pieter Sonneveld; p.sonneveld@erasmusmc.nl and Hartmut Goldschmidt; hartmut.goldschmidt@med.uni-heidelberg.de).

ETHICS STATEMENT

The ethics committees of the Erasmus University Medical Center, the University of Heidelberg, and all participating sites approved this trial. All patients gave written informed consent. The study was conducted in accordance with the European Clinical Trial Directive (2005) and the Declaration of Helsinki (1996).

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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