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ORIGINAL ARTICLE

Bortezomib before and after high-dose therapy in myeloma: long-term results from the phase III HOVON-65/GMMG-HD4 trial

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The Dutch-Belgian Cooperative Trial Group for Hematology Oncology Group-65/German-speaking Myeloma Multicenter Group-HD4 (HOVON-65/GMMG-HD4) phase III trial compared bortezomib (BTZ) before and after high-dose melphalan and autologous stem cell transplantation (HDM, PAD arm) compared with classical cytotoxic agents prior and thalidomide after HDM (VAD arm) in multiple myeloma (MM) patients aged 18–65 years. Here, the long-term follow-up and data on second primary malignancies (SPM) are presented. After a median follow-up of 96 months, progression-free survival (censored at allogeneic transplantation, PFS) remained significantly prolonged in the PAD versus VAD arm (hazard ratio (HR) = 0.76, 95% confidence interval (95% CI) of 0.65–0.89, $P = 0.001$). Overall survival (OS) was similar in the PAD versus VAD arm (HR = 0.89, 95% CI: 0.74–1.08, $P = 0.24$). The incidence of SPM were similar between the two arms (7% each, $P = 0.73$). The negative prognostic effects of the cytogenetic aberration deletion 17p13 (clone size $\geqslant 10\%$) and renal impairment at baseline (serum creatinine > 2 mg dl^{-1}) on PFS and OS remained abrogated in the PAD but not VAD arm. OS from first relapse/progression was similar between the study arms (HR = 1.02, $P = 0.85$). In conclusion, the survival benefit with BTZ induction/maintenance compared with classical cytotoxic agents and thalidomide maintenance is maintained without an increased risk of SPM.

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INTRODUCTION

Within the past decade, the available drug classes and agents for multiple myeloma (MM) treatment multiplied, including proteasome inhibitors (PIs),[1,2] immunomodulatory agents (IMiDs)[3–6] and targeted therapies.[7,8] The PI PS341/bortezomib (BTZ)[9,10] changed the upfront treatment paradigm in MM for both transplant-eligibile and -ineligible patients.[11,12]

The Dutch-Belgian Cooperative Trial Group for Hematology Oncology Group-65/German-speaking Myeloma Multicenter Group-HD4 (HOVON-65/GMMG-HD4) phase III trial established BTZ-based induction and maintenance therapy as frontline treatment in patients 18 to 65 years receiving high-dose melphalan followed by autologous stem cell transplantation (HDM).[13] The adverse prognostic effect of renal impairment and the adverse cytogenetic aberration deletion 17p13 were abrogated incorporating BTZ as upfront treatment in comparison to cytotoxic agents in combination with thalidomide maintenance.[13–15]

Long-term observations from large clinical trials are desired to estimate therapeutic effects and are often lacking upon initial presentation of the results. In MM, the broad availability of potent relapse therapies, including PIs and IMiDs, leaves the question, whether survival benefits from firstline treatment are maintained. Therefore long-term data from clinical trials are needed to

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evaluate the sustainability of the intially observed effects and to uncover possible long-term side-effects of the applied treatment, especially second primary malignancies (SPMs).[16–18]

Here we report on the long-term follow-up of the HOVON-65/GMMG-HD4 trial including PFS, OS, incidence of SPMs and the role of prognostic factors.

PATIENTS AND METHODS

The HOVON-65/GMMG-HD4 study is an investigator-sponsored, open-label, randomized, multicenter phase III trial. The trial was registered at www.trialregister.nl as NTR213, at www.isrctn.com as ISRCTN64455289 and at www.clinicaltrialsregister.eu as EudraCT2004-000944-26. The initial results of the primary analysis of the study have been reported previously, including details on the study protocol, inclusion and exclusion criteria, details on the randomization methods and toxicity of the applied treatment.[13] The study was conducted in cooperation with the HOVON and the GMMG at 75 centers in the Netherlands, Germany, and Belgium. The study was approved by the ethics committees of the Erasmus University Medical Center, the University of Heidelberg, and all participating sites. 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).[13]

Eligibility criteria

Briefly, as described previously,[13] major inclusion criteria were: age 18–65 years inclusive, newly-diagnosed MM Salmon and Durie stages II/III,[19] and no previous systemic MM treatment. Exclusion criteria were systemic light chain amyloidosis, non-secretory MM, HIV positivity. Patients with renal impairment (serum creatinine >2 mg dl^{-1}) were not excluded.

Study design and treatment

The study was designed in accordance with the VISTA (Velcade As Initial Standard Therapy in Multiple Myeloma: Assessment With Melphalan and Prednisone) trial[11,20] to evaluate a prolonged treatment with BTZ (64 administrations) versus treatment with classical cytotoxic agents and thalidomide in transplant-eligible patients. Patients were randomly assigned (1:1) to receive either VAD (vincristine, doxorubicin, dexamethason) as induction therapy, followed by HDM and thalidomide maintenance, arm A) or PAD (BTZ, doxorubicin, dexamethason) HDM and bortezomib maintenance, arm B. To balance the random assignment, the hospital, Salmon and Durie stage (II versus III),[19] LDH ($>$upper limit of the normal, yes versus no), and later the hospital and International Staging System (ISS, I versus II versus III)[21] were taken into account.

In arm A, VAD was administered for three cycles as follows: vincristine 0.4 mg intravenous (i.v., on days (d) 1–4), doxorubicin 9 mg m^{-2} (i.v., d 1–4), dexamethasone 40 mg per os (p.o., d 1–4, 9–12 and 17–20), repeated every 28 days. In arm B, PAD was administered for three cycles as: BTZ 1.3 mg m^{-2} (i.v., d 1, 4, 8 and 11), doxorubicin 9 mg m^{-2} (i.v., d 1–4), dexamethasone 40 mg per os (p.o., d 1-4, 9–12 and 17–20), repeated every 28 days. Stem cell mobilization and collection were performed according to local procedures applying CAD (cyclophosphamide, doxorubicin and dexamethasone) followed by granulocyte colony-stimulating factor (G-CSF). Thereafter, HDM was performed according to standardized procedures, applying 200 mg m^{-2} melphalan i.v. as described.[22,23] Within the HOVON study group a single HDM was planned, whereas a tandem HDM was scheduled within the GMMG study group.[13] In arm A and B, maintenance treatment consisted of either thalidomide (50 mg p.o. daily) or BTZ (1.3 mg m^{-2} i.v. every two weeks) for 2 years, respectively. Patients with an HLA-identical sibling could proceed to allogeneic stem cell transplantation (alloSCT) after first HDM.

Response assessments and endpoints

As initially reported,[13] the response to MM treatment within the study was assessed according to the European Group for Blood and Marrow Transplantation (EBMT)[24] criteria and expanded for very good partial response (VGPR) according to the International Myeloma Working Group (IMWG) criteria.[25] Response assessment was routinely performed after induction therapy, first and second HDM, and every two months during maintenance and beyond until progressive disease (PD) or relapse.[13] PFS was calculated from randomization until PD, relapse or death, whichever occurred first. For the analysis of the primary endpoint, patients receiving an alloSCT were censored at the date of alloSCT (PFS). If PFS is calculated without cenosring at alloSCT it is denoted PFSa. OS was calculated from randomization until death from any cause. Patients alive were censored at the date of last contact.[13] For the current manuscript, PFS, PFSa and OS were determined from the date of progression/relapse. Cytogenetic analyses were performed from CD138-enriched plasma cell bone marrow aspirates using fluorescence *in situ* hybridization (FISH).[13,15]

Statistical design and analysis

A detailed description of the statistical analysis has been reported earlier.[13] In brief, the trial was designed to detect with 80% power a hazard ratio (HR) of 0.74, which corresponds to an increase of 3-year PFS from 50 to 60% (2-sided significance level $\alpha = 0.049$, because of one planned interim analysis at a significance level $\alpha = 0.001$). The first analysis of the randomization was performed in April 2011, after a median follow-up of 41 months.[13] For the current analysis, the data were used as available of May 2016. The median follow-up of the 400 patients still alive was 96 months (maximum: 128 months). PFS, PFSa and OS were estimated by the Kaplan–Meier method and 95% confidence intervals (95% CIs) were constructed. Survival endpoints were analyzed with Cox regression. HRs and corresponding 95% CIs were determined. Kaplan–Meier curves were generated to illustrate survival. All analyses were performed by intention-to-treat, and as before the primary analysis was done with a multivariate Cox regression including adjustment for ISS stage. Other covariates included in the multivariate Cox regression analyses were age (as continuous variable), sex, WHO performance (0 versus 1 versus 2 versus 3), Salmon & Durie stage (II versus III), IgA (no versus yes), IgG (no versus yes), LDH (normal versus $>$ upper limit of normal (ULN)), ISS (I versus II vs III), FISH del(13q14) and study group (HOVON versus GMMG). In order to include all patients in the multivariate analyses, the MICE method of multiple imputations was used to cope with missing data on these baseline covariates, as described previously.[13] The heterogeneity of the treatment effect in subgroups was explored post-hoc by estimation of the HRs for survival endpoints for each subgroup, together with 95% CIs. All reported *P*-values are two-sided, and have not been adjusted for multiple testing.

RESULTS

Patients and adherence to treatment

From July 2005 to July 2008, 833 patients were equally and randomly assigned to the treatment arms. Six patients were ineligible and excluded from all analyses. In total, 413 and 414 eligible patients were randomized to the VAD and PAD arm, respectively. Baseline characteristics have been reported previously and were evenly distributed.[13] Since July 2011, all patients are in follow-up. The updated consort diagram is displayed in Figure 1. Differences in the applied treatment between the study groups HOVON and GMMG are depicted in the separate consort diagrams for each study group (Supplementary Figure 1). The number of patients proceeding to alloSCT was higher in the HOVON versus GMMG part of the study (HOVON: $n = 20$ [9%] and $n = 27$ [12%] versus GMMG: $n = 1$ [$< 1\%$] and $n = 1$ [$< 1\%$] in the VAD and PAD arms, respectively). Within the GMMG study group, upfront tandem HDM was preplanned and conducted in 69% ($n = 273$) of patients whereas $< 1\%$ ($n = 2$) of patients within the HOVON group received upfront tandem HDM. Maintenance therapy with thalidomide or BTZ according to the study protocol was initiated in 59% ($n = 125$) and 42% ($n = 92$) of HOVON patients compared with 72% ($n = 145$) and 71% ($n = 138$) of GMMG patients, respectively (Supplementary Figure 1). In the VAD and PAD arm, 18% ($n = 76$) and 28% ($n = 115$) of patients completed the study treatment according to protocol.

Progression-free survival and overall survival

The median follow-up of the 400 patients still alive (194 and 206 in the VAD and PAD arm, respectively) was 96 months (maximum 128 months). In the VAD and PAD arm, 328/303 PFS, 354/325 PFSa and 220/207 OS events occured, respectively.

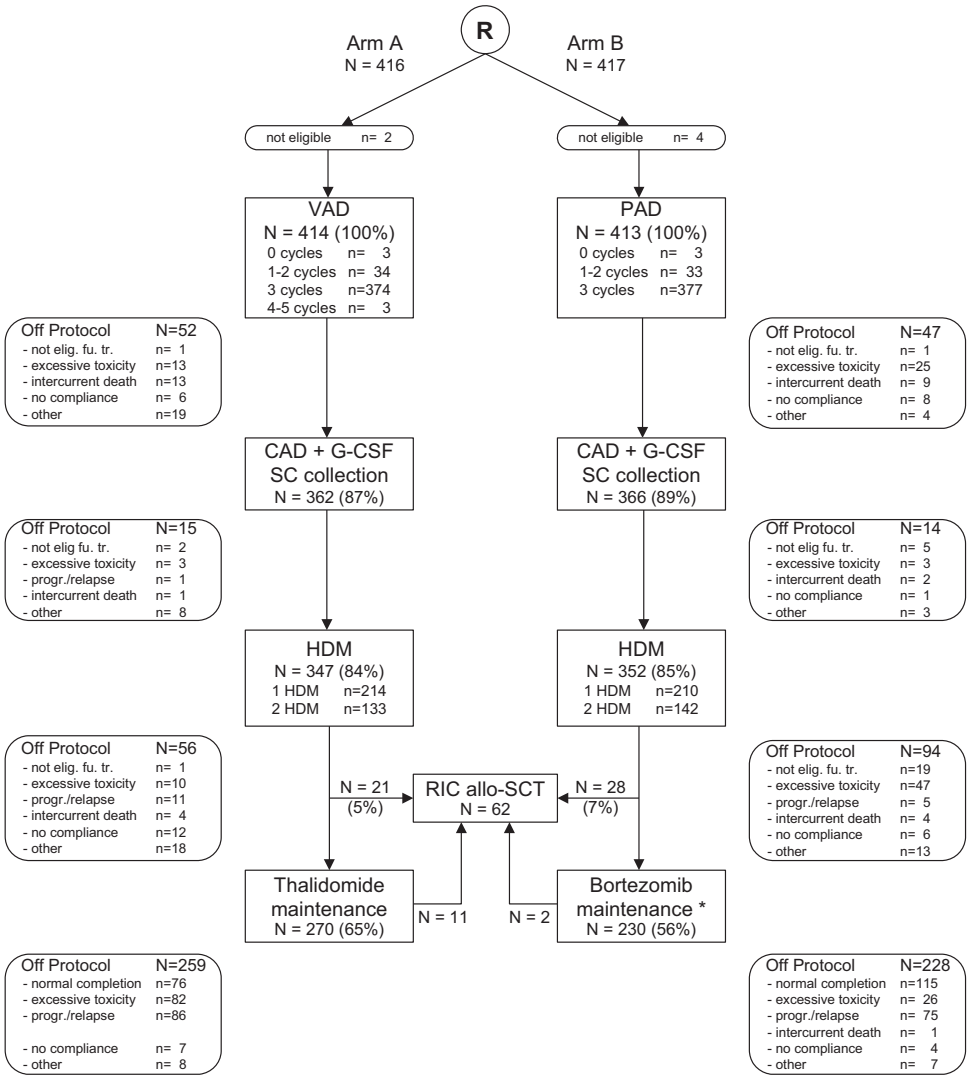

Figure 1. Updated consort diagram of the Dutch-Belgian Cooperative Trial Group for Hematology Oncology-65/German-speaking Myeloma Multicenter Group-HD4 (HOVON-65/GMMG-HD4) trial. alloSCT, allogeneic stem cell transplantation; CAD, cyclophosphamide, adriamycin (doxorubicin), dexamethasone; G-CSF, granulocyte colony-stimulating factor; HDM, high-dose melphalan (and autologous stem cell transplantation); PAD, bortezomib (PS341), adriamycin (doxorubicin), dexamethasone; RIC, reduced-intensity conditioning; SC, stem cell; VAD, vincristine, adriamycin (doxorubicin), dexamethasone. *Including one patient with thalidomide plus bortezomib and one patient with thalidomide only.

The primary endpoint of the study, PFS adjusted for ISS, remained significantly improved in favor of the PAD arm with a hazard ratio (HR) of 0.76 and a 95% CI of 0.65–0.89 ($P < 0.001$, Figure 2a). The median PFS was 28 months (95% CI: 25–32 months) in the VAD arm and 34 months (95% CI: 30–38 months) in the PAD arm, respectively. Similarly, the PFSa was significantly prolonged in the PAD compared with the VAD arm (HR = 0.79, 95% CI 0.68–0.92, $P = 0.003$, Figure 2b). The median PFSa was 29 months (95% CI: 25–32 months) versus 34 months (95% CI: 30–38 months) in the VAD and PAD arm, respectively. The median OS was prolonged in the PAD arm (91 months, 95% CI: 83–108 months) compared with the VAD arm (82 months, 95% CI: 67–96 months). The OS probabilities at 3 and 5 years were 72% (95% CI: 67–76%) vs 79% (95% CI: 74–82%) and 59% (95% CI: 54–64%) vs 65% (95% CI: 60–70%) in the VAD and PAD arm, respectively. However, as long-term OS at 96 months was similar, 45% (95% CI: 40–50%) in the VAD arm versus 48% (95% CI: 43–53%) in the PAD arm, this benefit was not statistically significant (HR = 0.89, 95% CI: 0.74—1.08, log-rank $P = 0.24$, Figure 2c). Because the OS curves of the two arms merged after about 8 years, and the log-rank test is not an optimal statistical method in that case. Therefore, we performed Wilcoxon tests, which give more weight to the early portion of the curve. However, the univariate Wilcoxon test ($P = 0.08$) and Wilcoxon test stratified for ISS ($P = 0.12$) were not statistically significant.

Survival after first progression/relapse and subsequent treatment

Three-hundred thirteen and 289 patients in the VAD and PAD arm had PD or relapse, of whom 276 (88) and 257 (89%) received a documented systemic treatment after first PD/relapse, respectively. The respective second-line treatments are listed in Table 1 (multiple entries for drugs/treatments were possible). In the VAD arm, 60% of treated patients received a treatment with BTZ compared with 33% in the PAD arm. Lenalidomide was administered in 51% of treated patients in the VAD arm and 71% of patients in the PAD arm. The OS from first PD/relapse was similar in the VAD and PAD arm (HR 1.02, 95% CI 0.83—1.26, $P = 0.85$, Figure 2d), with a median OS of 40 months (95% CI: 34–

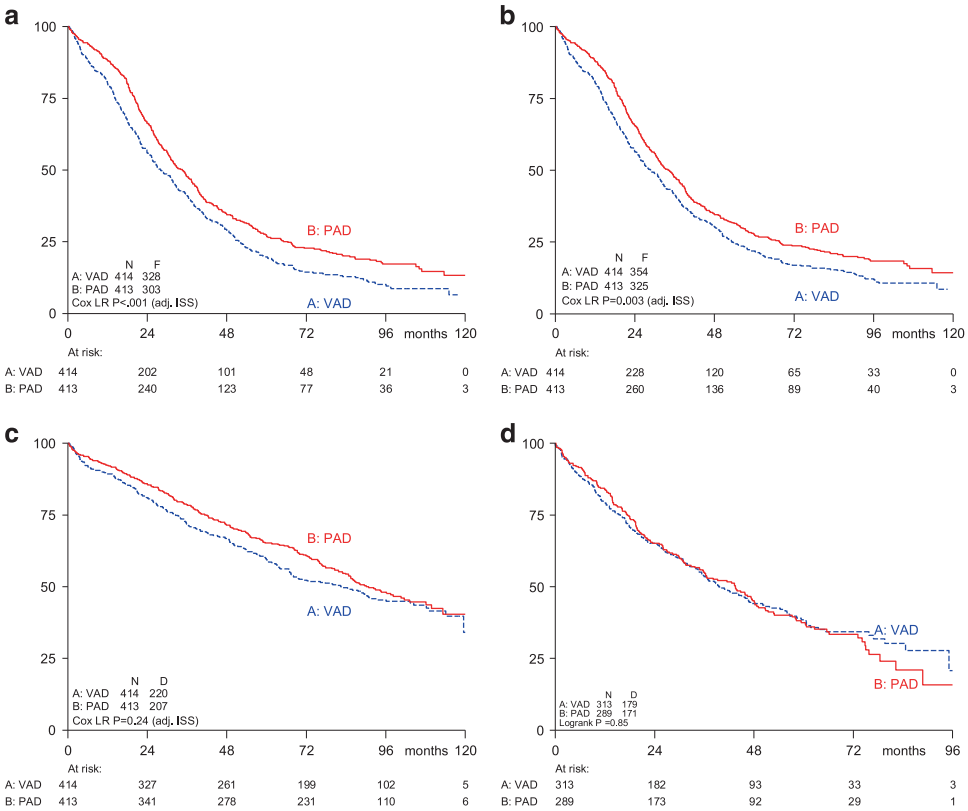

Figure 2. Progression-free survival, overall survival and post-relapse/progression survival. Kaplan–Meier survival curves of (**a**) progression-free survival censored at allogeneic stem cell transplantation (PFS, primary endpoint, adjusted for ISS), (**b**) progression-free survival, not censored at allogeneic stem cell transplantation (PFSa) and (**c**) overall survival (OS) for the two study arms. (**d**) Post-progression/relapse survival for the two study arms. Cox LR, Cox likelihood ratio test; D, number of deaths; F, number of treatment failures; ISS, International Staging System; Log-rank, Log-rank test; PAD, bortezomib, doxorubicin, and dexamethasone plus bortezomib maintenance (arm B); VAD, vincristine, doxorubicin, and dexamethasone plus thalidomide maintenance (arm A).

Table 1. Documented systemic treatment after first relapse/progression

Documented systemic treatment after first relapse/progression	*Arm A* (n = *276*)		*Arm B* (n = *257*)	
	n	%	n	%
Thalidomide	72	26	53	21
Lenalidomide	142	51	183	71
Bortezomib	165	60	86	33
AutoSCT	44	16	46	18
AlloSCT	35	13	28	11

Abbreviations: autoSCT, autologous stem cell transplantation; alloSCT, allogeneic stem cell transplantation. Multiple entries for drugs/combinations were possible. Relative data (in %) are given for all treated patients in each study arm.

47 months) and 43 months (95% CI: 35–48 months) in the VAD and PAD arm, respectively.

Impact of study treatment on adverse cytogenetics

As described previously, cytogenetic aberrations (CA) deletion 17p13 (⩾10%), translocation t(4;14) and gain 1q21 (⩾3 copies) were centrally analyzed within the GMMG part of the study. Therefore, all results on CA are based on GMMG patients only.[13,15] On long-term follow-up, the negative prognostic impact of the deletion 17p13 ($n = 22/17$ patients in the VAD/PAD arm) remains abrogated in the PAD compared with the VAD arm in PFS as well as OS (PFS: VAD $P < 0.001$ and PAD $P = 0.48$; OS: VAD $P < 0.001$ and PAD $P = 0.54$, Figures 3a and b). The OS rates after 96 months in PAD treated patients are similar with or without deletion 17p13 (52% versus 54%).

As initially reported,[13,15] the negative prognostic impact of the CA translocation t(4;14) ($n = 26/24$ patients in the VAD/PAD arm) was not overcome by VAD nor PAD (PFS: VAD $P = 0.005$ and PAD $P = 0.04$; OS: VAD $P = 0.004$ and PAD $P = 0.01$, Figures 3c and d). The OS at 96 months was inferior in both VAD and PAD treated patients harboring a translocation t(4;14) (VAD: 23 versus 48%; PAD: 33 versus 57%).

Similar results on PFS and OS were observed for gain 1q21 in VAD and PAD treated patients ($n = 56/57$).[15] In the current, updated analysis, both VAD and PAD did not overcome the negative prognostic effect of this CA (PFS: VAD $P < 0.001$ and PAD $P = 0.006$; OS: VAD $P < 0.001$ and PAD $P < 0.001$, Figures 3e and f). The OS at 96 months was significantly shorter in patients with the CA gain 1q21 of either study arm (VAD: 28 versus 55%; PAD: 36 versus 62%).

Impact of study treatment on renal impairment

For patients with renal impairment at baseline treated in the PAD (36/412 patients) arm, PFS and OS remained similar as reported earlier[13,14] (PFS $P = 0.56$ and OS $P = 0.74$, Figures 3g and h), whereas VAD treatment did not abrogate the adverse prognostic impact of renal impairment (45/413 patients, PFS $P < 0.001$ and

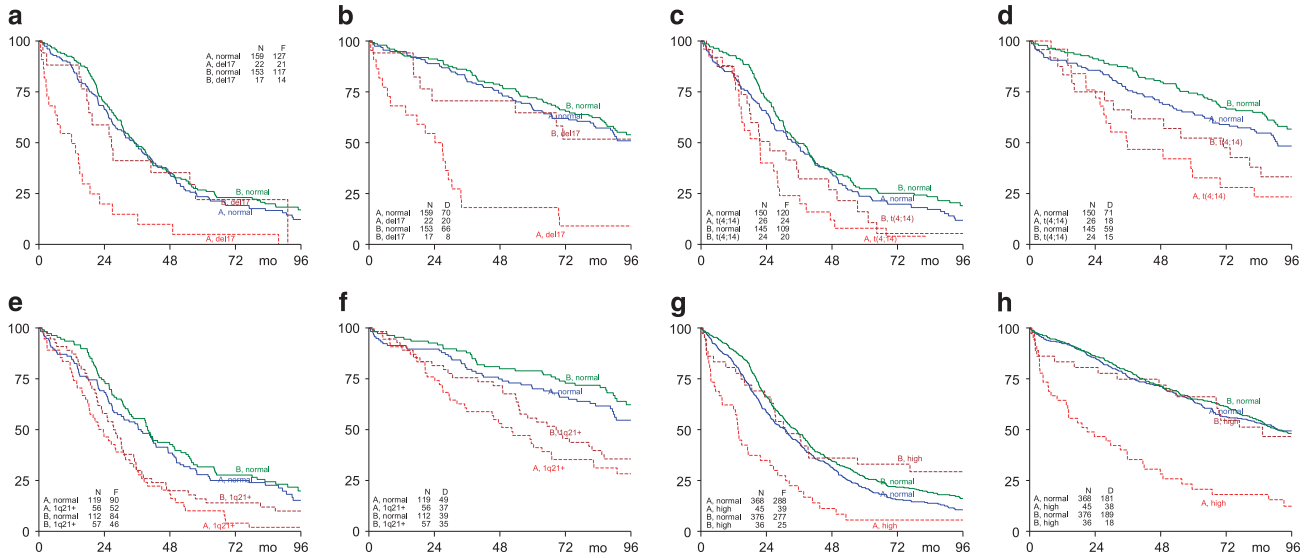

Figure 3. Progression-free survival and overall survival for adverse cytogenetic aberrations and renal impairment. Kaplan–Meier survival curves of progression-free survival censored at allogeneic stem cell transplantation (PFS) and overall survival (OS) for patients harboring the cytogenetic aberration (CA) deletion 17p13 (**a**, **b**), translocation t(4;14) (**c**, **d**) and gain 1q21 (⩾3 copies) (**e**, **f**) in the study arms A and B. Data on cytogenetic aberrations were only centrally evaluated for GMMG patients as previously reported.[15] Therefore, all results on CA are based on GMMG patients only. Kaplan–Meier survival curves of PFS and OS (**g**, **h**) for patients with renal impairment at baseline (serum creatinine >2 mg dl^{-1}) in the two study arms. D, number of deaths; F, number of treatment failures; PAD, bortezomib, doxorubicin, and dexamethasone plus bortezomib maintenance (arm B); VAD, vincristine, doxorubicin, and dexamethasone plus thalidomide maintenance (arm A). Arm A (blue and red colored), arm B (green and brown colored).

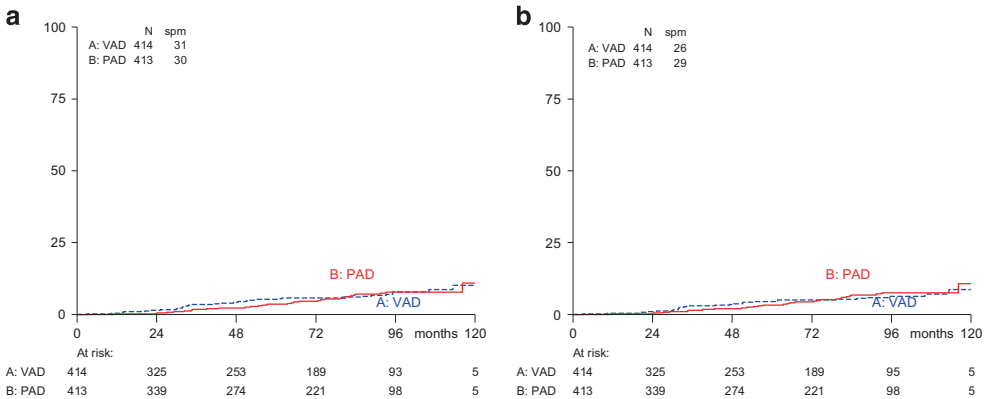

Figure 4. Incidence of second primary malignancies. Incidence of second primary malignancies (SPM) within the HOVON-65/GMMG-HD4 trial (**a**) including (**b**) excluding secondary plasma cell leucemia (secondary PCL). Abbreviations: N, number of patients; PAD, bortezomib, doxorubicin, and dexamethasone plus bortezomib maintenance (arm B); SPM, second primary malignancy; VAD, vincristine, doxorubicin, and dexamethasone plus thalidomide maintenance (arm A).

OS $P < 0.001$). The 96 months OS rates for patients with or without renal impairment were 12% versus 49% in the VAD arm and 47% versus 48% in the PAD arm, respectively.

Second primary malignancies

At least one SPM was reported in 31/414 (7%) and 30/413 (7%) patients in the VAD and PAD arm, respectively. Hematological, solid (non skin) and skin cancers occured in 49% ($n = 16$) versus 19% ($n = 6$), 30% ($n = 10$) versus 56% ($n = 18$) and 21% ($n = 7$) versus 25% ($n = 8$) of patients with a SPM in the VAD and PAD arm, respectively. The SPMs are listed in Supplementary Table 1. The incidence of SPM, including and excluding secondary plasma cell leukemia (sPCL) were similar between the study arms (SPM including sPCL, HR = 0.91, 95% CI: 0.55—1.51, $P = 0.73$; and SPM excluding sPCL, HR = 1.05, 95% CI: 0.62–1.79, $P = 0.85$, Figures 4a and b).

Response rates

The response rates were initially reported.[13] Updated response rates, including overall response (defined as partial response or better, ⩾PR), very good partial response or better (⩾VGPR) and complete response (CR) after induction therapy, first and second HDM as well as best response on study are displayed in Supplementary Table 2. The rates of ⩾VGPR and CR increased marginally from first to second HDM in the PAD arm (⩾VGPR: first HDM: 61% to second HDM: 63%, and CR: first HDM: 21% to second HDM: 23%).

Multivariate analyses on prognostic factors

Multivariate Cox regression analyses were performed to assess the prognostic value of selected baseline characteristic on PFS and OS (Table 2). For PFS, known MM prognostic factors such as higher ISS stages (HR = 1.18, $P = 0.005$), poor WHO performance status (HR = 1.22, $P = 0.001$), IgA subtype (HR = 1.60, $P < 0.001$) were confirmed as well as treatment within the PAD arm (HR = 0.74, $P < 0.001$). For OS, again higher ISS (HR = 1.21, $P = 0.009$), increased serum LDH levels (HR = 1.56, $P < 0.001$), renal impairment (HR = 1.54, $P = 0.01$) and the study group (HR = 0.81, $P = 0.04$) were significant predictors.

DISCUSSION

The current long-term follow-up from our multicenter, phase III trial HOVON-65/GMMG-HD4 supports the initially drawn conclusion: the upfront treatment incorporating BTZ as induction and maintenance therapy in transplant-eligible MM patients significantly prolongs PFS (HR = 0.76, $P < 0.001$) and is the standard of care for MM patients up to 65–70 years.[12,26,27] Expectedly, as multiple, potent therapies and novel drug classes are available for progressive/relapsed MM[2,6–8] and MM remains incurable in the majority of patients, no statistically significant OS advantage with upfront BTZ treatment compared with classical cytotoxic agents plus thalidomide maintenance was yielded (median OS plus 9 months for PAD vs VAD, HR = 0.89, $P = 0.24$). Nonetheless, median OS was prolonged by 9 months in the PAD arm. BTZ treatment was administered in more than half (60%) of the patients treated within the VAD arm at first relapse/progression and more than 90% of patients from both arms were treated with novel agents at first relapse/progression. OS from first relapse/progression was similar between the two study arms (HR 1.02, $P = 0.85$).

SPMs are of emerging importance in MM, as prolonged exposure to therapies and improved survival lead to higher cumulative incidences of SPM in MM patients.[16,28] Alkylating agents, such as melphalan, are well-described risk factors for the development of SPM, especially acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).[16,18,28,29] Recently, a meta-analysis identified the combination of IMiDs and melphalan p.o. as compared with melphalan alone or i.v. in combination with IMiDs as risk factor for the development of SPMs.[18] In our study, the incidence of SPM was similar in the two study arms (7% each, $P = 0.73$), in line with the VISTA trial.[20] BTZ in combination with either p.o. or i.v. melphalan appears not to increase the rates of SPM compared with the combination of cytotoxic agents with thalidomide. The early detection and treatment of SPM will be of upcoming importance in the evolving field of long-term MM survivorship and should be emphasized in clinical practice. However, the current probability of death from MM or MM-related diseases, such as severe infections or renal failure, by far exceeds the risk of death from a SPM.[28]

The effect of the two different study groups, HOVON and GMMG, on OS (HR = 0.81, $P = 0.04$) is based on several factors. The rates of alloSCT (higher in the HOVON part), the HDM policy (single in the HOVON versus tandem in the GMMG part) and the rate of initiation of maintenance therapy (PAD arm: HOVON 42 versus GMMG 71%) differ between the two study groups. However, reponse assessments after first and second HDM indicate, that the rate of $\geqslant$VGPR only marginally increased in the PAD arm ($\geqslant$VGPR: first HDM 61% and second HDM 63%), reflecting the yet high efficacy of the applied BTZ-based therapy in our trial. Therefore, conclusions regarding the effects of single versus tandem HDM cannot be drawn from this trial. Prospective trials, such as the European Myeloma Network (EMN) 02/HOVON--95 (EMN02/HO95, NCT01208766) trial, the Blood and Marrow Clinical Trials Network study (BMT CTN 0702; NCT01109004) and large meta-analyses[30] are needed to answer the question, whether tandem HDM should be performed in the era of novel agents. In addition, the majority of phase III trials investigating upfront single versus tandem HDM did not observe an OS benefit,[31–34] except for the earliest trial from the French study group (IFM94),[35] which was initiated before the launch of the novel agents in MM therapy and did not apply the current standard of care HDM.

Advances in the efficacy and tolerability in induction therapies lead to even higher response rates or improved toxicity profiles compared with PAD as applied in our study: VD (bortezomib and dexamethasone) with either cyclophosphamide (VCD),[36] thalidomide (VTD)[37–39] or lenalidomide (VRD)[40,41] generate higher rates of $\geqslant$VGPR and the administration of BTZ subcutaneously (s.c.) reduced rates of peripheral neuropathy (PN).[42,43] Therefore, these regimens should nowadays be preferred over PAD as induction therapy.

In patients with the deletion 17p13 by FISH, BTZ as applied in the PAD arm of this study abrogates the negative prognostic

Table 2. Multivariate Cox model on prognostic factors for progression-free survival censored at allogeneic transplantation and overall survival

Parameter	*PFS*			*OS*		
	HR	*95%-CI*	P-*value*	*HR*	*95%-CI*	P-*value*
Study arm (*B* vs *A*)	0.74	0.63–0.87	< **0.001**	0.86	0.71–1.04	0.13
Age *(per year)*	1.01	1.00–1.02	0.15	1.02	1.00–1.03	**0.03**
Sex *(female* vs *male)*	0.82	0.70–0.97	**0.02**	0.84	0.69–1.03	0.10
ISS (I, II, III)	1.18	1.05–1.33	**0.005**	1.21	1.05–1.40	**0.009**
WHO PS *(0, 1, 2, 3)*	1.22	1.09–1.37	**0.001**	1.29	1.13–1.47	< **0.001**
IgA subtype *(yes* vs *no)*	1.60	1.24–2.06	< **0.001**	1.69	1.25–2.29	**0.001**
IgG subtype *(yes* vs *no)*	1.36	1.09–1.70	**0.006**	1.27	0.97–1.67	0.09
Salmon and Durie stage *(II, III)*	1.01	0.81–1.26	0.92	1.14	0.86–1.51	0.37
LDH *(> ULN)*	1.24	1.00–1.54	0.05	1.56	1.22–2.00	< **0.001**
Deletion 13q14 *(yes* vs *no)*	1.27	1.07–1.50	**0.006**	1.48	1.19–1.82	< **0.001**
Study group *(GMMG* vs *HOVON)*	0.92	0.78–1.07	0.28	0.81	0.67–0.99	**0.04**
Renal impairment *(yes* vs *no)*	1.09	0.81–1.46	0.58	1.54	1.11–2.14	**0.01**

Abbreviations: GMMG, German-speaking Myeloma Multicenter Group; HOVON, Dutch-Belgian Cooperative Trial Group for Hematology Oncology; ISS, International Staging System; Ig, Immunoglobuline; LDH, lactate dehydrogenase; WHO PS, World Health Organization Performance Status. Renal impairment was defined as serum creatinine >2 mg dl^{-1} at baseline. Deletion 13q14 was assessed using FISH analysis. Salmon and Durie stage was assessed according to Durie and Salmon.[19] Bold entries depict significant *P* values. Italic entries depict groups that were compared.

impact of this CA (96 months OS with/without deletion 17p13: 52 versus 54%, $P = 0.54$). However, the IFM 2005-01 trial found no improvement in event-free survival (EFS) and OS for this subgroup, when treated with BTZ and dexamethason or VAD before HDM.[44] These results prompt the hypothesis, that patients harboring a deletion 17p13 benefit from prolonged BTZ treatment after HDM and/or the addition of a third agent to induction therapy. Further, the clone size by FISH is differentially defined between these study groups (GMMG $\geqslant$10 vs IFM $\geqslant$60%). This influences the PFS but not OS as demonstrated by a recent retrospective analysis (10–60 vs $>$60% deletion 17p13-positive plasma cells, PFS:19 vs 26 months, ($P = 0.03$); OS: 30 vs 54 months, ($P = 0.09$)).[45] Therefore the present study might underestimate the negative prognostic effect of the deletion 17p13, however a subgroup analysis applying a threshold of $>$60% clone size is not reasonable due to the small number of patients. The impact of single vs tandem HDM cannot be determined in this subgroup, since the rates of tandem HDM were comparable between the two study arms in the GMMG part of the study (VAD: 75 vs PAD: 83%).

The IFM 2005-01 study demonstrated an improvement in EFS and OS for patients with translocation t(4;14), though the negative prognostic effect of this CA was not abrogated. Similar results were observed in our trial: patients in the PAD arm showed an improved OS in comparison to the VAD arm (33 versus 23% at 96 months). Nonetheless, the negative prognostic effect of the translocation t(4;14) was not fully abrogated. A promising strategy for the treatment of this high-risk collective might be consolidation and maintenance with lenalidomide and BTZ, which achieved excellent $\geqslant$VGPR rates of 96% and a median PFS of 28 months for patients with a deletion 17p13.[46] In patients with renal impairment at initial diagnosis another study using PAD[47] and our current study demonstrated the benefit of upfront BTZ treatment. In our trial the long-term OS rates after 96 months in the PAD arm were even similar between patients with or without renal impairment (47 versus 48%) and PAD treatment resulted in improved renal responses as compared with VAD (81 versus 63% overall renal response rate, $P = 0.31$).[14]

Ongoing studies such as the CASSIOPEIA trial (NCT02541383) or the GMMG-HD6 trial (NCT02495922) need to answer whether upfront IMiDs and PIs combined with targeted therapies (such as the monoclonal antibodies daratumumab or elotuzumab) further improve the prognosis of MM and perhaps yield functional cure for a growing subset of patients.

In summary, our trial, applying BTZ as induction and maintenance in transplant-eligible MM, demonstrated a sustained improvement in PFS and PFSa compared with classical cytotoxic agents in combination with thalidomide. Median OS was prolonged by 9 months in favor of the PAD arm. However, because MM ultimately relapses in the majority of patients and due to multiple potent relapse therapies, the OS difference was not statistically significant on long-term follow-up. Overall SPM incidences were similar between the two study arms. Therefore, BTZ in combination with HDM is a standard of care for transplant-eligible MM patients.

CONFLICT OF INTEREST

EKM: Honoraria: Janssen-Cilag, Takeda; Advisory boards: Takeda; Other support (travel grants): Janssen-Cilag, Takeda, Celgene, Onyx and Mundipharma; PS: Research support from Janssen, Celgene, Amgen, Takeda, Karyopharm Honoraria and advisory boards: Janssen, Celgene, Amgen, Takeda, Karyopharm; MSR: Research Support from Novartis, Amgen, Morphosys; Consulting for Novartis, Amgen, Celgene, Janssen; JH: Advisory boards: Celgene, Janssen, Novartis; Speakers honoraria: Celgene, Janssen, BMS, Amgen; Consultancy: Amgen; Travel support: Amgen, BMS, Takeda; Research Support: Novartis, Sanofi; HJS: Honoraria: Janssen, Celgene; Travel support: Janssen, Celgene; KCW: Consultancy: Amgen, Bristol Myers Squibb, Celgene, Novartis, Janssen, Takeda; Honoraria: Amgen, Bristol Myers Squibb, Celgene, Novartis, Janssen, Takeda; Research funding: Celgene, Janssen; IWB: Research grant: Celgene and Janssen; Advisory boards: Janssen, Celgene, Amgen, Takeda, Novartis, BMS; PS: SkylineDx: Membership on an entity's Board of Directors or advisory committees; Karyopharm: Research Funding; Amgen: Honoraria, Research Funding; Celgene: Honoraria, Research Funding; Janssen: Honoraria, Research Funding; SZ: Celgene: Honoraria, Research Funding; Takeda Millennium: Honoraria, Research Funding; Onyx: Honoraria; Annemiek Broijl: Amgen: Membership on an entity's Board of Directors or advisory committees; Celgene: Membership on an entity's Board of Directors or advisory committees; Christ of Scheid: Janssen: Honoraria; Celgene: Honoraria; AP: Janssen: Employment; Dirk Hose: Takeda: Other: Travel grant; EngMab AG: Research Funding; M-JK: Takeda Millennium: Research Funding; Janssen: Honoraria, Research Funding; Roche: Honoraria, Research Funding; UD: Alexion: Honoraria; Janssen: Honoraria; HML: Janssen: Honoraria, Research Funding; Genmab: Honoraria, Research Funding; Amgen: Honoraria; Goldschmidt: Celgene: Honoraria, Research Funding; Janssen: Honoraria, Research Funding; Novartis: Honoraria, Research Funding; Chugai: Honoraria, Research Funding; Onyx: Honoraria, Research Funding; Millennium: Honoraria, Research Funding; BMS: Honoraria, Research Funding. The remaining authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conception and design: PS, PB, SZ, EV, GMJB, DH, MvM-K, PWW, HML and HG. Financial support: AP. Administrative support: BvdH, LeJ, UB, HML and HG. Provision of study materials or patients: PS, IGHS-W, HS, SZ, EV, IWB, KCW, SC, GMJB, MS-K, CS, MP, DH, JH, MSR, RR, RMS, M-JK, MvM-K, UD, WL, PWW, HML and HG. Collection and assembly of data: PS, PB, LeJ, UB, HS, SZ, EV, AB, IWB, KCW, JH, MSR, EKM, SC, GMJB, MS-K, CS, MP, AJ, TH, RR, RMS, M-JK, MvM-K, UD, HWL, PY, HML and HG. Data analysis and interpretation: PS, BvdH, LeJ, SZ, MS-K, CS, PY, HML, TH, EKM and HG. Writing of the first manuscript draft: EKM and BvdH. Manuscript editing and writing: all authors. Final approval of manuscript: all authors.

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Supplementary Information accompanies this paper on the Leukemia website (http://www.nature.com/leu)