

Article

Open Access

Carfilzomib, Pomalidomide, and Dexamethasone As Second-line Therapy for Lenalidomide-refractory Multiple Myeloma

Pieter Sonneveld¹, Sonja Zweegman², Michele Cavo³, Kazem Nasserinejad⁴, Annemiek Broijl¹, Rosella Troia⁵, Ludek Pour⁶, Sandra Croockewit⁷, Paolo Corradini⁸, Francesca Patriarca⁹, Kalung Wu¹⁰, Jolanda Droogendijk¹¹, Gerard Bos¹², Roman Hajek¹³, Maria Teresa Petrucci¹⁴, Paula Ypma¹⁵, Nicholas Zojer¹⁶, Monique C. Minnema¹⁷, Mario Boccadoro^{18,19}

Correspondance: Pieter Sonneveld (p.sonneveld@erasmusmc.nl).

ABSTRACT

This phase 2 trial investigated reinduction with carfilzomib, pomalidomide, and dexamethasone (KPd) and continuous pomalidomide/dexamethasone in patients at first progression during lenalidomide maintenance. The second objective was to evaluate high-dose melphalan with autologous stem cell transplantation (HDM/ASCT) at first progression. Patients were eligible who had progressive disease according to International Myeloma Working Group (IMWG) criteria. Treatment consisted of 8 cycles carfilzomib (20/36 mg/m²), pomalidomide (4 mg) and dexamethasone. Patients without prior transplant received HDM/ASCT. Pomalidomide 4 mg w/o dexamethasone was given until progression. One hundred twelve patients were registered of whom 86 (77%) completed 8 cycles of KPd. Thirty-five (85%) eligible patients received HDM/ASCT. The median time to discontinuation of pomalidomide w/o dexamethasone was 17 months. Best response was 37% ≥ complete response, 75% ≥ very good partial response, 92% ≥ partial response, respectively. At a follow-up of 40 months median PFS was 26 and 32 months for patients who received KPd plus HDM/ASCT and 17 months for patients on KPd (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.37-1.00, $P = 0.051$). PFS was better after longer duration of prior lenalidomide (HR 3.56, 95% CI 1.42-8.96, $P = 0.035$). Median overall survival (OS) was 67 months. KPd-emerging grade 3 and 4 adverse events included hematologic (41%), cardiovascular (6%), respiratory (3%), infections (17%), and neuropathy (2%). KPd followed by continuous pomalidomide is an effective and safe triple drug regimen in second-line for patients previously exposed to bortezomib and/or refractory to lenalidomide.

INTRODUCTION

The treatment outcome of patients with multiple myeloma (MM) significantly improved by introduction of proteasome inhibitors, immunomodulatory agents (IMiDs), and monoclonal antibodies, resulting in higher response rates, longer progression-free survival (PFS) and overall survival (OS). High-dose

melphalan followed by autologous stem cell transplantation (HDM/ASCT), followed by maintenance with lenalidomide is now standard of care. Patients who have progression or relapse during lenalidomide maintenance or shortly after its discontinuation are considered lenalidomide-refractory. In addition, a minor fraction of patients who are exposed to bortezomib and lenalidomide combined with dexamethasone (ie, VRd) as upfront

¹Department of Hematology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

²Department of Hematology, Amsterdam UMC, Vrije Universiteit Amsterdam Cancer Center, The Netherlands

³IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli," Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università degli Studi, Bologna, Italy

⁴Erasmus MC Cancer Institute, Rotterdam, The Netherlands

⁵Hematology, University of Torino, Italy

⁶Hematology, University Hospital, Brno, Czech Republic

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

⁸Hematology Division and Hemato-Oncology Department, University of Milan, Fondazione IRCCS Istituto Nazionale dei Tumori, Italy

⁹Hematology and Bone Marrow Transplant Unit, University of Udine, Italy

¹⁰Hematology, ZNA Stuivenberg, Antwerpen, Belgium

¹¹Hematology, Elisabeth Tweesteden Hospital, Tilburg, The Netherlands

¹²Department of Hematology, University of Maastricht Medical Center, The Netherlands

¹³Department of Hematology, Ostrava Poruba FNO, Czech Republic

¹⁴Department of Hematology, La Sapienza, Rome, Italy

¹⁵Department of Hematology, Haga Hospital, The Hague, The Netherlands

¹⁶Department of Hematology, Wilhelminen Hospital, Vienna, Austria

¹⁷Department of Hematology, University Medical Center Utrecht, Utrecht University, The Netherlands

¹⁸Department of Molecular Biotechnologies and Health Sciences, Hematology Division, University of Torino, Italy

¹⁹Division of Hematology, Città della Salute e della Scienza, Università di Torino, Italy

Supplemental digital content is available for this article.

Copyright © 2022 the Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the European Hematology Association. This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

HemaSphere (2022) 6:10(e786).

<http://dx.doi.org/10.1097/HS9.0000000000000786>.

Received: July 8, 2022 / Accepted: August 31, 2022

therapy may become refractory to both agents. Currently available and approved treatment options for relapsed or refractory patients are anti-CD38 monoclonal antibody combinations or next-generation proteasome inhibition and immunomodulatory agents, as has been recently described in the European Society for Medical Oncology (ESMO) and European Hematology Association (EHA) guidelines.¹ The current treatment options for lenalidomide-refractory patients are bortezomib or carfilzomib-based such as bortezomib with pomalidomide and dexamethasone (OPTIMISM), daratumumab with bortezomib and dexamethasone (Castor), daratumumab with pomalidomide and dexamethasone (Apollo), daratumumab with carfilzomib and dexamethasone (Candor), elotuzumab with pomalidomide and dexamethasone (Eloquent-3) or isatuximab with pomalidomide and dexamethasone (Icaria).²⁻⁷

In the European Myeloma Network trial 02 (EMN02)/HOVON95 collaborative trial, newly diagnosed patients with symptomatic MM were randomized after vincristine, cyclophosphamide, dexamethasone (VCD) induction and PBSC collection to receive HDM/ASCT or bortezomib-based therapy at standard doses (vincristine, melphalan, prednisone [VMP]), followed by a second randomization for consolidation with bortezomib/lenalidomide/dexamethasone (VRd) or no consolidation, followed by lenalidomide maintenance at a standard dose of 10 mg (21/28 d cycles) until progression or toxicity.⁸

Patients with primary refractory or relapsed and refractory disease throughout any treatment phase in EMN02 were asked to participate in a phase 2 trial. The aim of this trial was to evaluate PFS and response with relapse treatment using next-generation proteasome inhibition and IMiD, that is, carfilzomib, pomalidomide, and dexamethasone followed by continuous pomalidomide w/o dexamethasone. Dose and schedule of Carfilzomib and Pomalidomide were based on a phase 1-2 trial in relapsed/refractory myeloma.⁹ The second aim was to evaluate the role of high-dose melphalan with autologous stem cell transplant if patients did not receive this as first-line treatment. This question was based on similar aims in several trials at the time of design.^{8,10,11} This trial was registered at www.trialregister.nl (NTR5349) and with the EU Clinical Trials Register (EudraCT 2013-003265-34).

METHODS

Trial

This randomized, open-label, phase 3 study was conducted by the European Myeloma Network (EMN) in 7 European countries. Patients were eligible if they were included and received treatment in the EMN02 trial which compared high-dose therapy and standard treatment in TE-NDMM, and who were primary refractory or had progression/relapse during this trial according to the International Myeloma Working Group (IMWG) uniform response criteria.¹² No other treatment except local radiotherapy was allowed. All patients gave written informed consent. The study was approved by independent ethics committees or the institutional review board of participating sites and performed according to the International Conference on Harmonization Guidelines on Good Clinical Practice and the principles of the Declaration of Helsinki. The Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON) sponsored and designed this trial which is registered at www.trialregister.nl as NTR5349 and EudraCT 2013-003265-34.

Treatment

Patients who were included received four 28 days cycles of carfilzomib (20/36 mg/m², days 1, 2, 8, 9, 15, 16) with pomalidomide (4 mg days 1-21) and dexamethasone (20 mg days 1, 2, 8, 9, 15, 16) (KPd). In patients who had not received high-dose therapy as part of the first-line treatment, high-dose melphalan (200 mg/m²) was administered followed by autologous stem cell

transplantation with stem cells which had been harvested and stored as part of the EMN02 trial.⁸ Treatment was continued with 4 additional cycles of KPd, which were identical to the induction cycles. Patients with stable disease or better were randomized to receive pomalidomide 4 mg alone (P) or with weekly dexamethasone (Pd) 40 mg in 21 of 28 days cycles continuously until progression or toxicity. Supportive care with hemopoietic growth factors and prophylactic antibiotics was given when required according to local hospital protocols.

HRQoL questionnaires

Health-related quality of life (HRQoL) was assessed using 2 questionnaires: the cancer specific European Organisation for Research and Treatment of Cancer Quality of Life C30 (EORTC QLQ-C30) and the MM-specific EORTC QLQ-MY20 module. The EORTC QLQ-C30 consists of 15 subscales (global health status, physical functioning, role functioning, cognitive functioning, social functioning, fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties) and EORTC QLQ-MY20 consists of 5 subscales (disease symptoms, side effects of treatment, neuropathy, body image, future perspective). For computing the subscales, the EORTC manual was used to calculate the subscale.

Patients received a paper version of the questionnaires from the local study investigator/nurse and completed the questionnaire at several evaluation times points according to the HRQoL study protocol, namely at baseline (T0), after induction cycle 4 (T1), after induction cycle 8 (T2), after maintenance cycle 2 (T3), after maintenance cycle 4 (T4).

Statistical analysis

The primary study endpoint was progression-free survival (PFS) from randomization to either pomalidomide with dexamethasone or pomalidomide alone. Key secondary endpoint was PFS in the subgroup of patients who received HDM plus ASCT for the first time as part of the KPd regimen. Other secondary endpoints were PFS from registration, response and overall survival. The sample size was calculated based on the PFS estimate from randomization. Assuming a median PFS of 9 months with continuous pomalidomide and 15 months with pomalidomide plus dexamethasone, we estimated that with uniform accrual for 24 months and additional follow-up of 24 months after the last patient was randomized, 146 patients were required to be randomized 1:1 and 126 events of PD or death would be needed to provide 80% power to detect a 40% reduced risk of PD or death (hazard ratio [HR] 0.60), using Cox regression analysis, with an overall two-sided significance level of 0.05. Assuming that 66% of the patients will be randomized, 222 patients had to be registered.

One safety interim analysis was performed in 2017 when 20 patients completed the 4 cycles of induction therapy. An independent data monitoring committee reviewed the results of interim analyses. Efficacy was analyzed in the intention-to-treat population, which includes all randomized patients. PFS and OS were estimated by the Kaplan-Meier method from the date of randomization. Cox regression analysis including only the randomized patients for the primary comparison of PFS between treatment arms and to estimate HRs and 95% CIs. Forest plots were generated to illustrate PFS from randomization within subgroups.

As an exploratory analysis on PFS and OS from registration, we performed a univariable Cox regression analysis to test the impact of prognostic factors in EMN02/HO95, that is, the cytogenetic risk status (high risk versus standard risk, as described later), R-ISS stages, prior response (complete response [CR] versus <CR), patient status (primary refractory versus relapsed and refractory), prior randomization to intensification therapy (VMP versus HDM, and single versus double ASCT), duration of Lenalidomide maintenance, and duration of PFS in EMN02/HO95.

Safety was assessed in all patients who received at least one dose of study drugs. Toxicities were tabulated as adverse events (CTCAE version 4) and second primary malignancies (SPMs).

HRQoL statistical analysis

Change in QoL over time was assessed by a linear mixed-effects model, where time was considered as fixed effect and patient as a random effect in the model. The null hypothesis for analysis was “no change in HRQoL over time” and a P value <0.05 was considered as statistically significant. Clinically meaningful HRQoL change was assessed by minimal important difference (MID). The MID threshold for a clinically relevant change from baseline was based on the standard error of measurement (SEM) for the multi-item subscale, that is, equals the standard deviation (SD) of the baseline QoL score times the square root of $(1 - \text{Cronbach's } \alpha)$.

All analyses were performed using Stata (version 16.1). Data were monitored by an external contract organization and verified for accuracy by a supporting research team at the EMN datacenter. QoL analysis was done according to EORTC scales as described.

The cutoff date for the analysis was June 29, 2021.

This trial is registered with the EU Clinical Trials Register (EudraCT 2013-003265-34) and www.trialregister.nl (NTR5349).

RESULTS

The study was open for inclusion exclusively for patients who had progression or relapse after prior treatment in the EMN02 trial for TE-NDMM. In the EMN02 trial, patients received 3–4 cycles of induction with VCD followed by randomization between HDM/ASCT or bortezomib-based therapy at standard doses (VMP), followed by a second randomization for consolidation with VRD (bortezomib, lenalidomide, dexamethasone) or no consolidation, followed by lenalidomide maintenance at a dose of 10 mg (21/28 d cycles) until progression or toxicity.⁸ The demographics of included patients are shown in Table 1. Due to the completion of EMN02 and the observed decreasing accrual, this trial was closed for inclusion after 112 registered patients. Of these, 86 eligible patients completed 8 cycles of KPd, who were randomized 1:1 to continuous treatment either with pomalidomide (P: 44 patients) or pomalidomide plus dexamethasone (Pd: 42 patients). At the time of the final analysis, 112 patients were registered of whom 1 was ineligible. Fifty-nine patients (53%) had received prior HDM/ASCT (single ASCT, $n = 45$; double ASCT, $n = 14$) and 43 (37%) VMP in EMN02. Eleven patients (10%) had been primary refractory to VCD induction therapy and/or VMP or HDM/ASCT, while 86 patients (77%) were exposed to bortezomib and lenalidomide. All patients had received continuous lenalidomide maintenance therapy. Prior best responses in the EMN02 trial were 44 of 111 (39%) \geq CR, 91 of 111 (81%) \geq very good partial response, and 108 of 111 (97%) \geq partial response. The median duration of maintenance in EMN02 had been 33 months (range 13–88 months), respectively. Median PFS from start of maintenance was 59 months. Adverse risk factors could be assessed in 92 of 111 patients: R-ISS II or III 69 of 92 (75%), del17p 13 of 78 (14%), t(14;16) 1 of 77 (1%), t(4;14) 15 of 88 (17%), amp1q 34/85 (40%). One hundred eight (95%) of patients had progressed during lenalidomide maintenance. The median time from the last dose of lenalidomide and inclusion in this trial was 4.1 months (range 0.5–89 months, interquartile range [IQR] 1–18 months).

Eighty-six (77%) patients completed 8 cycles of KPd, of whom 48 (43%) without any dose reduction of carfilzomib and pomalidomide. These patients received continuous pomalidomide with dexamethasone ($n = 42$; 38%) or without dexamethasone ($n = 44$, 40%). Forty-one of 43 patients randomized to the VMP arm in EMN02 were eligible for HDM/ASCT and 35 of these

Table 1.

Demographics at Registration of Eligible Patients

	N = 111
Median age (y) [range]	62 [39–71]
WHO performance (%)	
0	61 (55)
1	46 (41)
2	4 (4)
ISS disease stage (%)	
I	65 (59)
II	33 (30)
III	13 (12)
Median creatinine clearance (mL/min) [range]	84 [46–194]
Median hemoglobin (mmol/L) [range]	7.6 [4.9–9.7]
Sex (%)	
Male	67 (60)
Female	44 (40)
Cytogenetic risk in EMN02/H095 (%)	
Standard	58 (52)
High	25 (23)
Revised ISS in EMN02/H095	
I	23 (21)
II	61 (55)
III	8 (7)
Best response pre d1 in EMN02/H095	
sCR	26 (23)
CR	18 (16)
VGPR	47 (42)
PR	17 (15)
SD	3 (3)
R1 arm (intensification) in EMN02/H095	
VMP	41 (37)
HDM-1	45 (41)
HDM-2	14 (13)
Earlier off protocol	11 (10)

CR = complete response; EMN02 = European Myeloma Network trial 02; HDM = high-dose melphalan; ISS = International Staging System; PR = partial response; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response; VMP = vincristine, melphalan, prednisone; WHO = World Health Organization.

Table 2.

Best Response According to Prior Treatment (IMWG Criteria)

Response (%)	Prior VMP in EMN02	Prior HDM in EMN02	Lenalidomide Maintenance >6 mo	Lenalidomide Maintenance <6 mo
sCR	24	15	19	14
CR	17	20	20	—
VGPR	37	39	35	71
PR	12	19	18	—
<PR	9	7	8	14
ORR	81	86	84	85

CR = complete response; EMN02 = European Myeloma Network trial 02; HDM = high-dose melphalan; IMWG = International Myeloma Working Group; ORR = overall response rate; <PR = less than partial response; PR = partial response; sCR = stringent complete response; VGPR = very good partial response; VMP = vincristine, melphalan, prednisone.

(85%) received their first HDM plus ASCT after 4 cycles of KPd using cryopreserved stem cells previously collected. Time to first response was 2 months. Best response on protocol was 37% (41/111) \geq CR, 75% (102/111) \geq VGPR, 92% (102/111) \geq PR, respectively (Table 2). At a median follow-up of 40 months (range 9–66 mo), median PFS from registration was 26 months for the intention-to-treat population, that is, 32 months with HDM/ASCT ($n = 35$) and 17 months without ($n = 76$) (HR 0.61, 95% CI 0.37–1.00, $P = 0.051$) (Figures 1 and 2). PFS from

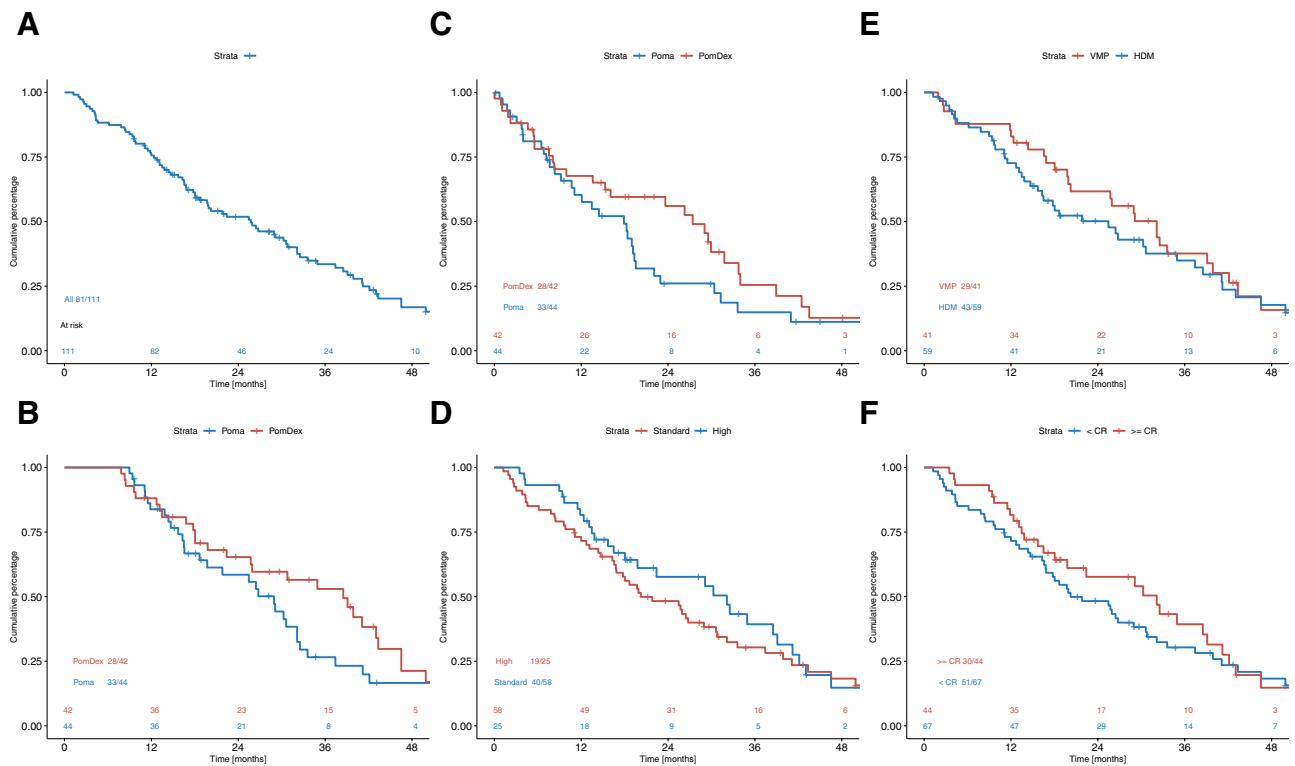


Figure 1. Progression-free survival. (A) All patients. (B) From registration by arm. (C) From randomization by arm. (D) By high risk versus standard risk cytogenetics. (E) By prior treatment in EMN02. (F) By best response on prior treatment in EMN02. EMN02 = European Myeloma Network trial 02.

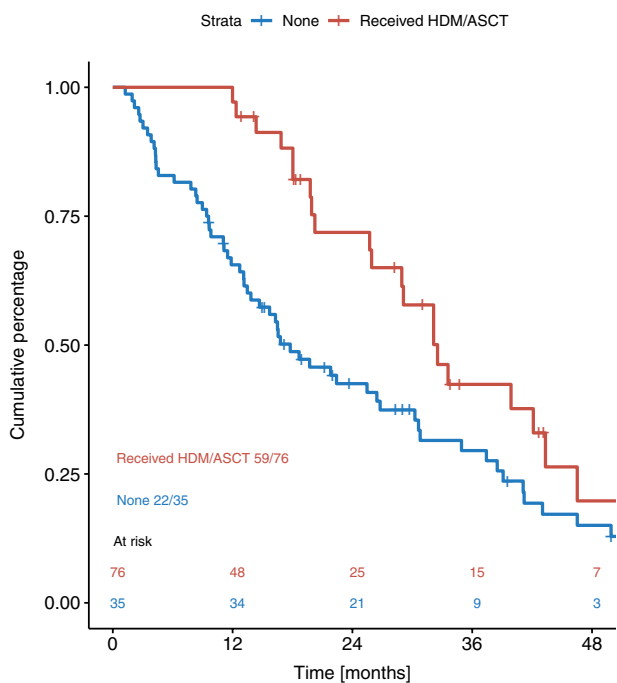


Figure 2. Progression-free survival in patients who received HDM/ASCT versus none. HDM/ASCT = high-dose melphalan followed by autologous stem cell transplantation

randomization was 27 months with pomalidomide plus dexamethasone versus 18 months with pomalidomide monotherapy, respectively (HR 0.68, 95% CI 0.41-1.13, $P = 0.14$) (Table 3). Time to discontinuation from start of pomalidomide with dexamethasone or pomalidomide was 18 and 15 months, respectively.

Table 3.

Progression-free Survival and Overall Survival (Months)

PFS, OS (mo, CI of median)	Pomalidomide/ Dexamethasone, N = 42		
	All	N = 44	N = 42
Median PFS from randomization (mo); n = 86	19.1 (13.5–27.4)	17.9 (9.2–29.3)	27.4 (13.6–33.7)
Median PFS from registration (mo); n = 111	25.7 (18.0–30.8)	28.9 (18.7–32.1)	38.5 (22.4–43.3)
Median OS from randomization (mo); n = 86	57.0 (38.7–NR)	43.3 (24.4–NR)	57.0 (57.0–NR)
Median OS from registration (mo); n = 111	66.7 (41.9–NR)	50.7 (36.5–NR)	66.7 (88.7–NR)

OS = overall survival; NR = not reached; PFS = progression-free survival.

Sixty-five (76%) went of treatment of whom 53 (61%) because of progressive disease (Figure 3). Seventy (63%) of patients are alive and in follow-up. With Cox regression analysis predefined risk factors for PFS or OS including high-risk cytogenetics (HR 1.36, 95% CI 0.80-2.41) or prior HDM/ASCT (HR 1.25, 95% CI 0.78-2.01) were not significant (Figure 4 and Suppl. Table S1). Duration of prior Lenalidomide maintenance longer than 36 months negatively affected PFS in this trial (HR 3.56, 95% CI 1.42-8.96, $P = 0.035$). Median overall survival (OS) was 67 months in both arms (Figure 5). As an exploratory endpoint OS was compared for patients receiving HDM plus ASCT or not, showing a favorable outcome with HDM plus ASCT. When OS was compared for patients receiving HDM plus ASCT or not, a favorable outcome was observed with KPd plus HDM/ASCT (HR and 95% CI 0.35 [0.14-0.84], $P = 0.019$).

KPd was well tolerated with 86 of 111 patients completing 8 cycles. Twenty-five patients did not complete KPd for reasons of disease progression (n = 10), adverse events (n = 7), or others. The number of patients receiving full-dose

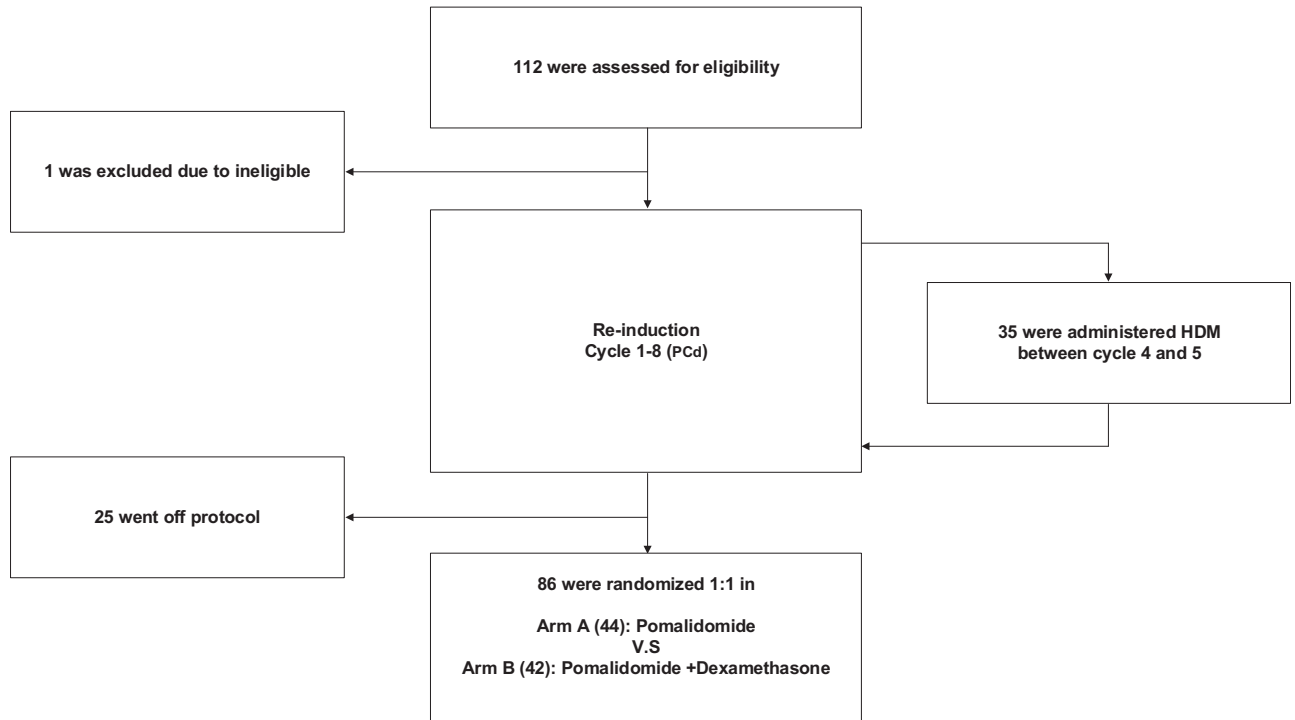


Figure 3. Consort diagram of the EMN011/HOVON114 trial.

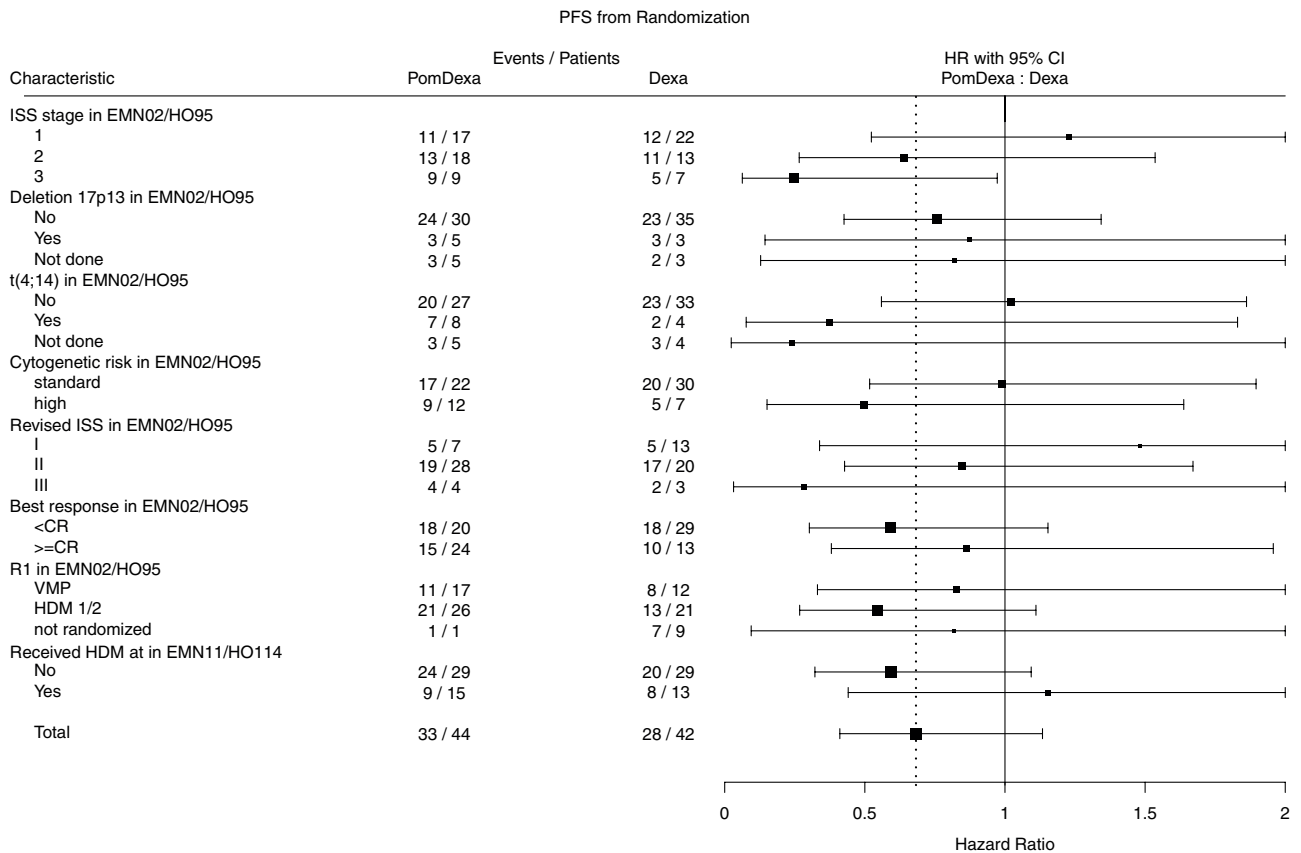


Figure 4. Forest plot of risk factors for progression-free survival.

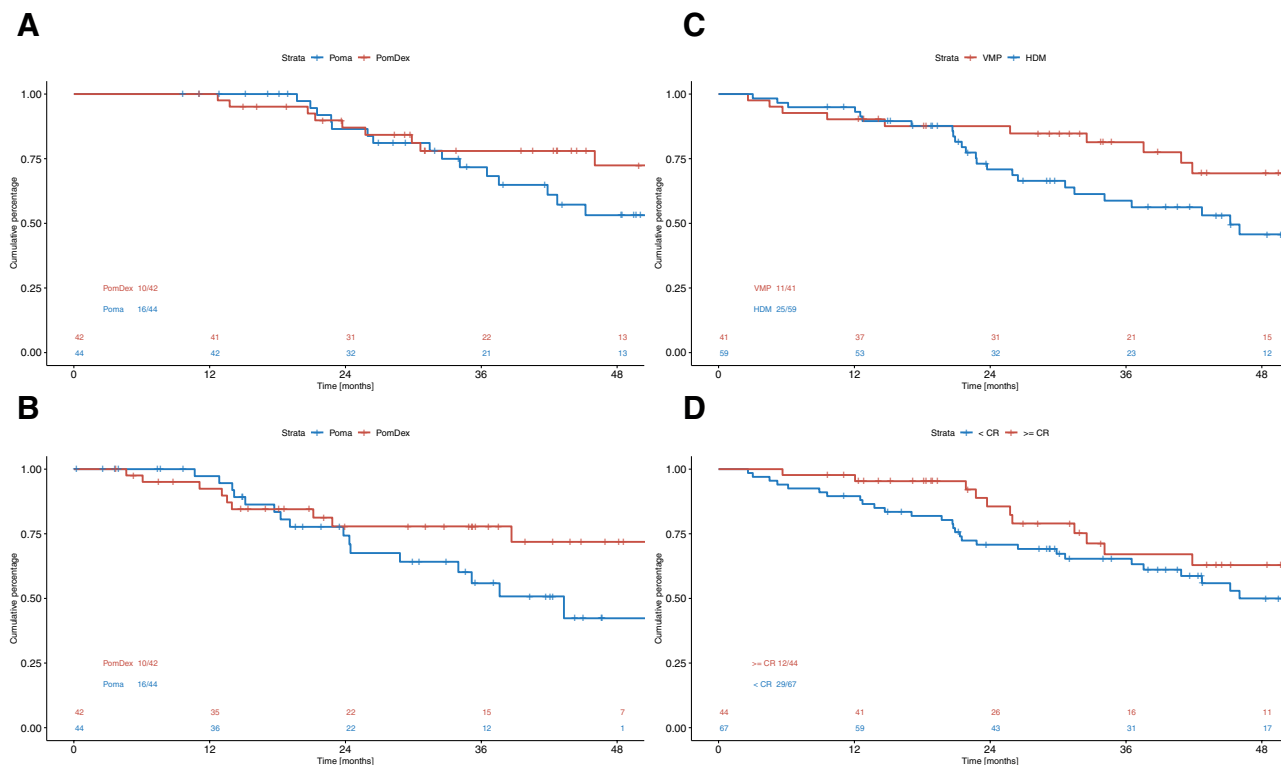


Figure 5. Overall survival. (A) From registration by arm. (B) From randomization by arm. (C) By prior treatment in EMN02. (D) By best response on prior treatment in EMN02. EMN02 = European Myeloma Network trial 02.

Table 4.
Adverse Events During Reinduction (KPd) and During Continuous Treatment (PD/D)

Adverse Event CTC Grades 3+4 (%)	Pomalidomide/ Dexamethasone		
	KPd	Pomalidomide/ Dexamethasone	Pomalidomide
All	58	41	54
Hematologic	25	19	33
Infections	16	10	14
Cardiovascular	5	0	0
Gastrointestinal	4	2	0
Neurologic	4	5	2
Metabolic	13	7	7

CTC = common terminology criteria; KPd = carfilzomib, pomalidomide, and dexamethasone.

carfilzomib was 72%, for pomalidomide 68% and for dexamethasone 81%, respectively. KPd-emergent grade 3 and 4 adverse events included hematologic (41%), cardiovascular (6%), respiratory (3%), infections (17%), and neuropathy (2%) (Table 4). Pomalidomide w/o dexamethasone was well tolerated.

The median [range] duration of follow-up from randomization for patients who are still alive was 30.23 [12.27–41.89], 35.02 [18.35–44.34] months for pomalidomide and pomalidomide + dexamethasone arms, respectively. The study proved underpowered (power = 50%) for the comparison of pomalidomide/dexamethasone versus pomalidomide alone.

During this part of the protocol grade 3 or 4, adverse events occurred in 36% and 12% of patients, respectively, the majority being hematologic (26%) and infections (12%) equally in both arms. During protocolary treatment 6 fatal SAEs were observed not related to progression (1 patient cardiovascular).

The results of EORTC QLQ-C30 (for 15 subscales) and EORTC QLQ-MY20 (for 5 subscales) over the 5 time points were analyzed and shown in Figure 6. The *P* value in each panel

indicates the *P* value of mixed-effects model for the pertinent subscale. The dashed-blue lines show the MID threshold and the solid-yellow line show the average changes from baseline over time. From EORTC QLQ-C30, the changes of cognitive functioning, pain, and constipation subscales were statistically significant and from QLQ-MY20 the disease symptom and future perspective were statistically significant.

DISCUSSION

The prognosis of patients with MM who progress during lenalidomide maintenance treatment and who were exposed to prior bortezomib is poor and represents a clinical challenge.¹³ With the introduction of anti-CD38 monoclonal antibodies, combinations of daratumumab plus bortezomib and dexamethasone or lenalidomide and dexamethasone have shown significant efficacy, although high-risk patients such as refractory and/or frail patients were underrepresented in these trials.^{3,14} Carfilzomib combined with dexamethasone is an alternative option which is superior to bortezomib plus dexamethasone.¹⁵ Alternatively, pomalidomide plus dexamethasone (Pd) has been approved for patients who progress after lenalidomide.¹⁶

In the present study, we merged these regimens by adding carfilzomib to pomalidomide and dexamethasone in transplant-eligible NDMM patients with one prior line of therapy who were either primary refractory or progressed during lenalidomide maintenance. Eleven patients (10%) had been primary refractory to VCD induction therapy and subsequently received VMP or HDM/ASCT and lenalidomide maintenance. One hundred patients (90%) had been exposed to standard VCD induction, high-dose therapy (53%) or VMP (47%) and a median lenalidomide exposure of 33 months during maintenance. Hence, this trial represents a typical group of patients in the current treatment landscape of TE-NDMM. KPd was limited to 8 cycles for reasons of feasibility, safety, cost because it was followed by continuous pomalidomide w/o dexamethasone resulting in a

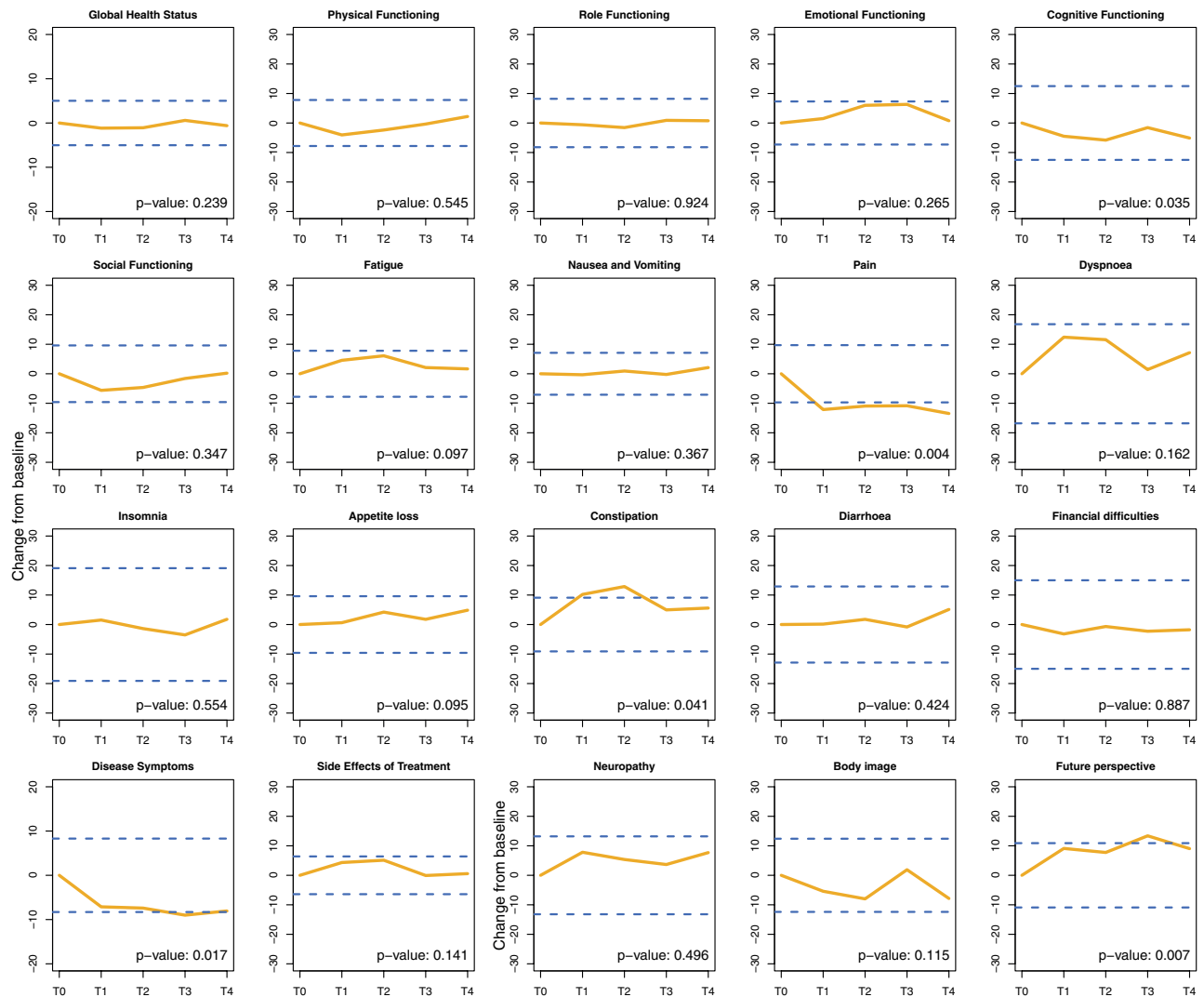


Figure 6. Profile of EORTC QLQ-C30 and EORTC QLQ-MY20 items over time. EORTC QLQ-C3 = European Organisation for Research and Treatment of Cancer Quality of Life C30.

clinically meaningful response rate of more than 90% including 35% CR or better, with a significant number of CR in the cytogenetic high-risk group. The regimen is well tolerated and no new safety signals were observed. A median PFS of 26 months with autologous transplant and 17 months without indicates that disease stabilization is achieved in the majority of patients and that this regimen is active in patients who progress from prolonged exposure to maintenance dose lenalidomide. While the definition of lenalidomide-refractoriness is still a matter of discussion, in routine clinical care the majority of NDMM patients are treated with lenalidomide maintenance at a daily dose of 10 to 15 mg for a fixed duration or until progression. Hence, a second-line regimen must be active against lenalidomide-exposed and/or refractory myeloma. Carfilzomib and pomalidomide based combinations may be the cornerstone of treatment, while alternatively combinations with anti-CD38 antibodies are effective but not always accessible.^{3,4,14,17} Because of the high response rate and durability of responses, combined with good tolerability, KPd may also be considered as a bridging regimen toward cellular therapy. The number of dose reductions for the 2 highly effective compounds was 32 and 28%, respectively, which seems acceptable for this situation. Since the KPd regimen was merged from other protocols, a formal dose-finding part was not included. A limitation of the study is

the slow accrual due to few relapses from EMN02. Hence, the study proved underpowered for the comparison of pomalidomide/dexamethasone versus pomalidomide alone. While this is a restriction, it does not undermine the observations made with KPd followed by pomalidomide w/o dexamethasone.

An important observation in this trial is that the administration of high-dose melphalan in patients who had not received this during initial therapy after diagnosis is feasible and well tolerated. In this trial, 85% of eligible patients received their first HDM and ASCT, which is comparable with the number observed in the French IFM trial.¹⁸ Moreover, HDM contributed to a longer PFS compared to patients who did not receive this intensification. While this intervention was included as an exploratory analysis only, these data indicate that intensification is feasible and that it improves the prognosis of these lenalidomide-refractory patients.

Finally, it is important to place the KPd regimen and continuous pomalidomide against the other regimens for these patients. As mentioned above, combinations of pomalidomide and carfilzomib with either Isatuximab (ICARIA and IKEMA) or daratumumab (APOLLO and CANDOR) in RRMM show a PFS benefit of the triplet combination.^{4,6,7,19} Several triplet combinations of Pd were recently investigated in relapsed/refractory patients with one to three prior lines of therapy, demonstrating

clinically relevant PFS, such as elotuzumab-Pd (median PFS 10.3 mo), daratumumab-Pd (median PFS 12.4 mo), cyclophosphamide-Pd (median PFS 24 mo), isatuximab-Pd (median PFS 11.5 mo), and bortezomib-Pd (median PFS 11.2 mo). While these trials included patients with 1–3 prior lines of therapy and lenalidomide-exposed patients, many of those were not lenalidomide-refractory. Only in OptimisMM, Icaria, and Eloquent-3, the percentage of lenalidomide-refractory patients was higher than 70%.^{2,5,6,18,20,21} Median PFS from registration in the current trial of patients who mostly (90%) were refractory to first-line lenalidomide maintenance was 26 or 17 months for those patients who did not receive HDM/ASCT. PVd (OptimisMM) as second-line therapy in lenalidomide-refractory patients led to median PFS value of 18 months, which seems comparable to KPd. PFS with DKd (Candor) was 25 months, a difference that probably must be attributed to the use of anti-CD38 treatment. Hence, careful consideration in individual patients should be based on tolerance, prior treatments and state of the disease. Within this plethora of regimens, KPd represents a unique combination of next-generation proteasome inhibition and immunomodulation. It is an alternative for anti-CD38 based combinations and may be well implemented in the routine clinical setting.

CONCLUSIONS

This phase 2 trial demonstrates that KPd followed by continuous pomalidomide is an effective and safe triple drug regimen in second-line for patients who have been previously treated and are refractory to lenalidomide. A 92% overall response and 18–27 months PFS is clinically relevant in this population, especially when other novel treatments are not available. HDM followed by ACT is feasible and effective in eligible patients in the context of this regimen.

ACKNOWLEDGMENTS

This trial was conducted as an investigator sponsored trial by HOVON and the European Myeloma Network EMN and supported by a grant from the Dutch Cancer Foundation and by independent grants and drug supply from Amgen and BMS/Celgene.

AUTHOR CONTRIBUTIONS

Study design: PS, MC, MB, KN; Statistics: KN; Generation and contribution of data: All authors; Data management: RT; Analysis of data: PS, SZ, MC, MB, KN; Manuscript writing: PS, SZ, MC, MB, KN; Reading, interpretation, comments and approval of manuscript: All authors.

DISCLOSURES

PS has a membership on an entity's Board of Directors or advisory committees: Amgen, Janssen, BMS/Celgene, Karyopharm, Oncopeptides, Sanofi. Research Funding: Amgen, BMS/Celgene, Janssen, SkylineDx. SZ has a Membership on an entity's Board of Directors or advisory committees: Celgene, Janssen, Takeda, Oncopeptides, Sanofi. Research Funding: Janssen, Takeda. MC has received an honoraria from AbbVie, Adaptive Biotechnologies, Amgen, BMS, Celgene, GSK, Janssen, Takeda; has a membership on an entity's Board of Directors or advisory committees: AbbVie, Amgen, BMS, Celgene, GSK, Janssen. Research Funding: Celgene, Janssen. AB: BMS, Amgen, Janssen, Celgene. PC has received an honoraria from Abbvie, Celgene, Roche, Sandoz, Gilead, Takeda; and an Advisory Board and Lecturer: Abbvie, Celgene, Roche, Sandoc, Gilead, Novartis, Takeda, Sanofi, Gilead; and is an editor: HemaSphere. FP has an advisory role in Celgene, Janssen, Jazz, MSD Italy, Medac. GB: employment, has received an honoraria, Stock Ownership: CiMaas. NZ has an advisory role in Celgene, Janssen, Amgen, Takeda. RH has a consultancy/advisory role in Amgen, AbbVie, Celgene/BMS, Janssen, Novartis, Takeda; Research Funding: Amgen, BMS/Celgene, Novartis, Takeda. MTP has received an honoraria and advisory board: BMS-Celgene, Janssen, Sanofi, Takeda, GSK, Amgen, Karyopharm, Roche. MCM: Hospitality; Celgene. Consultancy: Jansen Cilag, Gilead, Alnylam. MB has received an honoraria from Amgen, Celgene, Janssen, Sanofi. Research Funding: Amgen, Celgene, Janssen, Sanofi. All the other authors have no conflicts of interest to disclose.

REFERENCES

- Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *HemaSphere*. 2021;5:e528.
- Richardson PG, Oriol A, Beksac M, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:781–794.
- Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375:754–766.
- Dimopoulos M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. *Lancet*. 2020;396:186–197.
- Dimopoulos MA, Dytfield D, Grosicki S, et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. *N Engl J Med*. 2018;379:1811–1822.
- Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet*. 2019;394:2096–2107.
- Dimopoulos MA, Terpos E, Boccadoro M, et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22:801–812.
- Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. *Lancet Haematol*. 2020;7:e456–e468.
- Shah JJ, Stadtmauer EA, Abonour R, et al. Carfilzomib, pomalidomide, and dexamethasone for relapsed or refractory myeloma. *Blood*. 2015;126:2284–2290.
- Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med*. 2017;376:1311–1320.
- Stadtmauer EA, Pasquini MC, Blackwell B, et al. Autologous transplantation, consolidation, and maintenance therapy in multiple myeloma: results of the BMT CTN 0702 trial. *J Clin Oncol*. 2019;37:589–597.
- Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20:1467–1473.
- Kumar SK, Dimopoulos MA, Kastritis E, et al. Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. *Leukemia*. 2017;31:2443–2448.
- Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375:1319–1331.
- Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol*. 2016;17:27–38.
- San Miguel JF, Weisel KC, Song KW, et al. Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma. *Haematologica*. 2015;100:1334–1339.
- Mateos MV, Spencer A, Nooka AK, et al. Daratumumab-based regimens are highly effective and well tolerated in relapsed or refractory multiple myeloma regardless of patient age: subgroup analysis of the phase 3 CASTOR and POLLUX studies. *Haematologica*. 2020;105:468–477.
- Garderet L, Kuhnowski F, Berge B, et al. Pomalidomide, cyclophosphamide, and dexamethasone for relapsed multiple myeloma. *Blood*. 2018;132:2555–2563.
- Moreau P, Dimopoulos MA, Yong K, et al. Isatuximab plus carfilzomib/dexamethasone versus carfilzomib/dexamethasone in patients with relapsed/refractory multiple myeloma: IKEMA Phase III study design. *Future Oncol*. 2020;16:4347–4358.
- Dimopoulos M, Weisel K, Moreau P, et al. Pomalidomide, bortezomib, and dexamethasone for multiple myeloma previously treated with lenalidomide (OPTIMISMM): outcomes by prior treatment at first relapse. *Leukemia*. 2021;35:1722–1731.
- Dimopoulos MA, Sonneveld P, Siegel D, et al. Carfilzomib and pomalidomide in patients with relapsed and/or refractory multiple myeloma with baseline risk factors. *Ann Oncol*. 2015;26:2247–2256.