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ORIGINAL RESEARCH

TRANSFUSION

Autograft cellular composition and outcome in myeloma patients: Results of the prospective multicenter GOA study

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Abstract

Background: Autologous stem cell transplantation (auto-SCT) is a widely used treatment option in multiple myeloma (MM) patients. The optimal graft cellular composition is not known.

Study design and methods: Autograft cellular composition was analyzed after freezing by flow cytometry in 127 MM patients participating in a prospective multicenter study. The impact of graft cellular composition on hematologic recovery and outcome after auto-SCT was evaluated.

Results: A higher graft CD34$^+$ cell content predicted faster platelet recovery after auto-SCT in both the short and long term. In patients with standard-risk

Abbreviations: 7-AAD, 7 - aminoactinomycin; auto-SCT(s), autologous stem cell transplantation(s); B-CD34$^+$, blood CD34$^+$ (count); CY , cyclophosphamide; G-CSF , granulocyte colony-stimulating factor; GOA Study, Graft and Outcome in Autologous Stem Cell Transplantation Study; HDT, high-dose therapy; LD-CY, low-dose cyclophosphamide; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival; PLT, platelet; PLER, plerixafor; ROC, receiver operating characteristic; VRD, bortezomib, lenalidomide and dexamethasone.

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cytogenetics, a higher graft $CD34^+$ count (>2.5 × 10^6/kg) was linked with shorter progression-free survival (PFS; 28 vs. 46 months, $p = 0.04$), but there was no difference in overall survival (OS) ($p = 0.53$). In a multivariate model, a higher graft $CD34^+CD133^+CD38^-$ (>0.065 × 10^6/kg, $p = 0.009$) and NK cell count (>2.5 × 10^6/kg, $p = 0.026$), lenalidomide maintenance and standard-risk cytogenetics predicted better PFS. In contrast, a higher $CD34^+$ count (>2.5 × 10^6/kg, $p = 0.015$) predicted worse PFS. A very low $CD3^+$ cell count (≤20 × 10^6/kg, $p = 0.001$) in the infused graft and high-risk cytogenetics remained predictive of worse OS.

Conclusions: Autograft cellular composition may impact outcome in MM patients after auto-SCT. More studies are needed to define optimal graft composition.

KEYWORDS

autograft cellular composition, autologous stem cell transplantation, $CD34^+$ cells, hematologic recovery, myeloma, NK cells, outcome, T lymphocytes

1 | INTRODUCTION

Multiple myeloma (MM) is the leading indication for autologous stem cell transplantation (auto-SCT) according to the European Group for Blood and Marrow Transplantation registry, which had over 12,000 transplants for MM reported in 2018.[1] High-dose chemotherapy (HDT) followed by auto-SCT after first-line therapy in eligible patients has been proven to prolong progression-free survival (PFS) in newly diagnosed MM patients also in the era of novel drugs.[2-4]

Several factors, including patient characteristics, previous therapy, and the mobilization method used, influence graft cellular composition. The use of lenalidomide prior to graft collection may hamper stem cell mobilization.[5,6] Mobilization with cyclophosphamide (CY) and granulocyte colony-stimulating factor (G-CSF) results in higher $CD34^+$ yields than mobilization with G-CSF alone.[7,8] The addition of CY in the mobilization alters graft cellular composition by decreasing the number of more primitive $CD34^+CD133^+CD38^-$ cells, NK cells, and other lymphocytes.[9] In contrast, the use of plerixafor (PLER) in poorly mobilizing patients seems to increase the B and T lymphocyte, NK cell, and $CD34^+CD133^+CD38^-$ counts in the grafts.[10]

The $CD34^+$ cell count has remained the most important marker of graft quality in the autologous setting. There are also some retrospective data supporting improved PFS and overall survival (OS) in patients with higher graft $CD34^+$ cell doses.[11] A higher number of lymphocytes in the infused blood grafts have been linked with better PFS and OS in MM patients.[12,13] Also a higher graft $CD3^+CD4^+$ count has been associated with better outcome.[14] Data regarding graft NK cells and their role in post-transplant recovery in MM patients are limited. However, faster blood NK cell count recovery has been linked with improved outcome.[15]

The aim of the prospective multicenter Graft and Outcome in Autologous stem cell transplantation (GOA) study is to investigate the effects of different mobilization methods on collected blood graft cellular composition and to evaluate the effects of infused graft composition on hematological and immunological recovery and PFS and OS post-transplant. In this study, we analyzed the influence of graft cellular composition on recovery of blood counts and post-transplant outcome in MM patients.

2 | PATIENTS AND METHODS

2.1 | Patients

Altogether 147 MM patients were included in the prospective non-interventional multicenter GOA study. Graft composition data were available in 127 patients and these patients were included in the present study. The patients received their first auto-SCT between May 2012 and December 2016 at four university hospitals (Kuopio, Oulu, Tampere, and Turku) in Finland. A proportion of the patients ($n = 36$, 28%) participated also in the MM-02 study (NCT01790737) conducted by the Finnish Myeloma Group.[16,17]

The patient characteristics are presented in Table 1. The median time from MM diagnosis to the initiation of stem cell mobilization was 4 months (range 2–65). High-risk cytogenetics were defined by FISH panels according to the revised International Staging System as deletion 17p and/or translocation t(4;14) and/or t(14;16).[18]

TABLE 1 Patient characteristics

Variable	$n = 127$
Sex (male/female)	64/63
Age: median (range)	64 (49–73)
Paraprotein type	
IgG	73 (58%)
IgA	28 (22%)
Light chain	25 (20%)
IgM	1 (1%)
Cytogenetics at diagnosis	
Standard risk	95 (75%)
High risk[a]	22 (17%)
Unknown	10 (8%)
First-line induction therapy[b]	
VCD	44 (35%)
VRD	40 (32%)
VD	38 (30%)
Other[c]	5 (4%)
Mobilization	
Cyclophosphamide + G-CSF	73 (58%)
G-CSF alone	54 (43%)
Use of plerixafor	16 (13%)
Disease status at auto-SCT	
sCR	4 (3%)
CR	21 (17%)
VGPR	58 (46%)
PR	40 (32%)
SD	1 (1%)
PD	3 (2%)
Disease status 3 months after auto-SCT	
sCR	12 (9%)
CR	41 (32%)
VGPR	54 (43%)
PR	14 (11%)
SD	3 (2%)
PD	3 (2%)

Note: VCD, bortezomib–cyclophosphamide–dexamethasone; VD, bortezomib–dexamethasone; VRD, bortezomib–lenalidomide–dexamethasone.
Abbreviations: G-CSF, granulocyte colony-stimulating factor; auto-SCT, autologous stem cell transplantation.
[a]Defined as either any percentage of del(17p) and/or translocation t(4;14) and/or t(14;16).
[b]Twenty-four patients (19%) received > 1 lines of myeloma therapy before stem cell collection.
[c]Bortezomib–melphalan–prednisolone (VMP) in two patients, lenalidomide–dexamethasone (RD) in two patients (2%), and bortezomib–thalidomide–dexamethasone in one patient (1%).

2.2 | Mobilization and collection of blood grafts

Seventy-three patients (57%) were mobilized with low-dose (2 g/m^2) cyclophosphamide (LD-CY) + G-CSF, whereas 54 patients (43%) received only daily filgrastim of 10 μg/kg for mobilization (Table S1). The G-CSF used was either filgrastim of 5 μg/kg per day until the completion of graft collection ($n = 53$, 73%) or a single pegfilgrastim of 6 mg injection ($n = 20$, 27%) in chemo-mobilized patients. The G-CSF mobilized patients received filgrastim of 10 μg/kg daily until the completion of cell apheresis. The subgroup of patients participating in the MM02 trial received mobilization with either LD-CY plus filgrastim or filgrastim alone in a randomized fashion after three cycles of induction treatment with bortezomib, lenalidomide and dexamethasone (VRD) followed by a single auto-SCT and lenalidomide maintenance.[16,17] The blood CD34$^+$ (B-CD34$^+$) level was determined daily during the stem cell collection period by flow cytometry using an ISHAGE protocol[19] at the stem cell laboratories of each participating university hospital.

A minimum collection target of 2.0×10^6/kg CD34$^+$ cells was used for a single transplant. The patients participating in the MM-02 study had a higher minimum collection target of 3.0×10^6/kg CD34$^+$ cells for a single transplant and 6.0×10^6/kg if a second transplant was considered feasible. PLER was added to the mobilization in 16 patients (13%). PLER was administered either pre-emptively in case of inadequate mobilization or after failing to reach sufficient CD34$^+$ yields with declining B-CD34$^+$ counts.[20]

Oulu and Tampere University Hospitals used the Spectra Optia Apheresis device (Software 7.2, Terumo BCT) for blood graft collection throughout the study. In Kuopio University Hospital, a COBE Spectra AutoPBSC (Lakewood, CO) apheresis device was used initially, but from April 2013 onwards the Spectra Optia was used. Turku University Hospital used a different apheresis device (COM.TEC Fresenius blood cell separator, Fresenius Hemo Care GmbH). The blood volume circulated per apheresis was 2.3–3.0 times the estimated blood volume of the patient.

2.3 | Graft analysis

Two 0.5 ml tubes were taken from each apheresis product for subsequent graft cellular composition analyses. Dimethyl sulfoxide was added to achieve a concentration of 10% in order to protect the cells. These specimens as

well as the graft bags were cryopreserved in a freezer with controlled-rate freezing in liquid nitrogen. The cryopreserved graft samples were delivered to the Department of Microbiology, University of Eastern Finland, for graft cellular composition analyses, which were performed by a single experienced flow cytometrist (A.R.). After thawing, the graft samples were analyzed using the FACSCanto (Becton Dickinson, San Jose, CA) flow cytometry system.[20]

2.4 | High-dose therapy and post-transplant follow-up

High-dose melphalan of 200 mg/m^2 was given as HDT on day −2. The thawed blood grafts were infused on day 0. Ninety patients (71%) were given G-CSF post-transplant based on institutional preferences, of which 58 patients (64%) received filgrastim of 5 μg/kg daily until neutrophil engraftment, and 32 patients (36%) received a single 6 mg dose of pegfilgrastim.

Neutrophil and platelet (PLT) engraftment were defined as the first of three consecutive days with a blood neutrophil count $>0.5 \times 10^9$/L or a PLT count $>20 \times 10^9$/L without PLT infusions, respectively. The hematologic recovery was assessed by measuring complete blood count on day +15 and at 1, 3, 6, and 12 months after auto-SCT. The follow-up of hematological recovery was discontinued in case of disease progression and re-treatment. Thirty-six patients (28%) received lenalidomide maintenance after auto-SCT as a part of the MM-02 study.

2.5 | Statistical analysis

SPSS Statistics version 25 (IBM Corporation, Armonk, NY) was used for statistical calculations. Continuous variables are presented with medians and ranges. The Mann–Whitney *U*-test and Pearson's chi-square test were used to assess statistical significance. Receiver operating characteristic (ROC) analyses were used to find out optimal cutoff points for graft cellular components correlating with hematological recovery, PFS, and OS,

TABLE 2 Comparison of infused blood graft cellular composition according to the mobilization method in multiple myeloma patients

Blood graft content ($\times 10^6$ cells/kg)	Patients mobilized with CY + G-CSF[a, b], $n = 73$	Patients mobilized with G + CSF alone[a, b], $n = 54$	*p* value
CD34$^+$ cells without 7-AAD	3.5 (1.6–8.7); 73	2.6 (0.6–7.6); 54	<0.001
CD34$^+$ cells with 7-AAD	2.8 (0.7–7.2); 73	1.7 (0.2–4.6); 54	<0.001
CD34$^+$CD133$^+$CD38$^-$ cells	0.07 (0.007–0.6); 73	0.05 (0.005–0.17); 54	0.016
CD3$^+$ cells	41.3 (2.8–354.2); 72	170 (19.6–1576.2); 53	<0.001
CD3$^+$CD4$^+$ cells	25.6 (2.1–290.3); 72	102.2 (14.7–474.7); 53	<0.001
CD3$^+$CD8$^+$ cells	13.8 (0.8–90.7); 72	76.6 (4.7–1213.9); 53	<0.001
CD19$^+$ cells	0.9 (0.0–66.6); 72	5.0 (0.0–61.6); 53	<0.001
NK cells	3.3 (0.2–35.5); 72	25.7 (1.2–748.9); 53	<0.001

[a]Measured by flow cytometry after cryopreservation. Data are reported as median (range); number of observations.
[b]Missing data. One patient from both groups with only CD34$^+$ analysis.

TABLE 3 Comparison of infused blood graft cellular composition according to use of plerixafor in multiple myeloma patients

Blood graft content ($\times 10^6$ cells/kg)	Patients mobilized without plerixafor[a, b], $n = 111$	Patients mobilized with plerixafor[a, b], $n = 16$	*p* value
CD34$^+$ cells without 7-AAD	3.1 (0.6–8.7); 111	3.0 (1.8–7.6); 16	0.703
CD34$^+$ cells with 7-AAD	2.4 (0.2–7.2); 111	2.2 (1.2–4.6); 16	0.549
CD34$^+$CD133$^+$CD38$^-$ cells	0.06 (0.005–0.6); 111	0.06 (0.013–0.3); 16	0.799
CD3$^+$ cells	65.7 (2.8–1576.2); 110	247.4 (29.2–715.8); 15	0.001
CD3$^+$CD4$^+$ cells	40.9 (2.1–368.4); 110	136.8 (18.8–474.7); 15	<0.001
CD3$^+$CD8$^+$ cells	23.1 (0.8–1213.9); 110	76.6 (10.6–250.1); 15	0.007
CD19$^+$ cells	1.4 (0.0–61.6); 110	12.3 (0.6–66.6); 15	0.001
NK cells	8.9 (0.2–748.9); 110	27.0 (1.2–69.2); 15	0.006

[a]Measured by flow cytometry after cryopreservation. Data are reported as median (range); number of observations.
[b]Missing data. One patient from both groups with only CD34$^+$ analysis.

respectively. ROC curve cutoff points were optimized using Youden's index. The continuous variables were transformed into categorical variables using either median or lower limit of reference values as a cutoff point to perform ROC analyses regarding hematological recovery. PFS was defined as time from auto-SCT to the first documentation of progressive disease or death.

Kaplan–Meier method and log-rank test were used for survival analyses. Cox regression model with categorical variables was applied for multivariate analyses. The results of the Cox regression model are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Two-tailed p values <0.05 were considered statistically significant. No adjustments for multiple comparisons were made.

2.6 | Ethics

The Ethics Committee of North Savo Hospital District provided approval to the GOA study (13/2012). All patients gave their written informed consent to participate in the study.

3 | RESULTS

3.1 | Graft cellular composition

The median graft $CD34^+$ cell count measured before cryopreservation was 3.5×10^6/kg (range 2.0–11.4). The viable $CD34^+$ count (with 7-AAD) after thawing was 2.35×10^6/kg (0.2–7.2). The median loss of $CD34^+$ cells during cryopreservation was 34% (0–93). The infused grafts of LD-CY + G-CSF mobilized patients contained higher amounts of $CD34^+$ and $CD34^+CD133^+CD38^-$ cells than those of G-CSF mobilized patients, but the $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD19^+$, and NK cell counts were significantly lower in the grafts of chemo-mobilized patients (Table 2). The use of PLER also significantly altered graft cellular composition, resulting in higher $CD3^+CD4^+$, $CD3^+CD8^+$, $CD19^+$, and NK cell counts in the grafts (Table 3).

3.2 | Hematologic recovery after auto-SCT

The median time to PLT engraftment was 12 days (0–54) and the neutrophil engraftment was also reached in a median of 12 days (8–30). A higher infused graft $CD34^+$ cell count ($>2.0 \times 10^6$/kg, $n = 70$) was associated with faster PLT engraftment (11 vs. 12 days, $p = 0.019$). In these patients, the PLT counts remained higher from 3 months after auto-SCT (199 vs. 171×10^9/L, $p = 0.017$) until 1 year post-transplant (204 vs. 174×10^9/L, $p = 0.022$). Neutrophil engraftment was not associated with the infused graft $CD34^+$ cell count. More rapid PLT engraftment was linked with a higher graft $CD3^+$ count ($>40 \times 10^6$/kg, $n = 85$; 11 vs. 13 days, $p = 0.031$) and lower NK cell count ($\leq 20 \times 10^6$/kg, $n = 87$; 11 vs. 14 days, $p = 0.009$), which were also associated with slightly faster neutrophil engraftment (12 vs. 12 days, $p = 0.043$).

In multivariate analysis including the graft $CD34^+$ ($>2.0 \times 10^6$/kg), $CD3^+$ ($>40 \times 10^6$/kg) and NK cell ($>20 \times 10^6$/kg) counts, gender, age (>/≤60 years), mobilization method used (LD-CY + G-CSF vs. G-CSF alone), the addition of PLER to the mobilization, and the use of G-CSF post-transplant, none of the abovementioned parameters significantly predicted faster PLT (<12 days) engraftment. NK cell count $\leq 20 \times 10^6$/kg (HR 2.129, CI 1.117–4.055, $p = 0.022$) and the use of G-CSF post-transplant (HR 4.567, CI 1.945–10.723, $p < 0.001$) predicted faster neutrophil (<12 days) engraftment in multivariate model, respectively.

3.3 | Graft cellular composition and post-transplant survival

At the end of the follow-up in May 2020, the median follow-up for patients remaining alive was 68 months (35–89). Ninety patients (71%) had experienced a disease progression and 34 patients (27%) had died. All patients who had died during the follow-up had undergone MM progression. High-risk cytogenetics was associated with inferior PFS (12 vs. 31 months, $p = 0.003$) and OS (43 months vs. not reached, $p < 0.001$) compared to patients with standard risk (SR) cytogenetics. Lenalidomide maintenance had a favorable impact on PFS (median not reached vs. 27 months, $p < 0.001$), but no significant difference in OS was observed at this time point ($p = 0.10$).

In the whole study population, the viable (with 7-AAD) graft $CD34^+$ cell count had no effect on PFS (-Table S2) or OS in univariate analysis. However, in the subpopulation of patients mobilized with G-CSF only ($n = 54$), higher graft viable $CD34^+$ cell count ($>2.5 \times 10^6$/kg, $n = 14$) was associated with inferior PFS (20 vs. 32 months, $p = 0.049$). This did not, however, translate into OS difference ($p = 0.57$). In the standard cytogenetic risk (SR) group ($n = 95$), higher graft $CD34^+$ cell count ($>2.5 \times 10^6$/kg, $n = 43$, Table S3) was also linked with inferior PFS (28 vs. 46 months, $p = 0.04$), but there was no difference in the OS ($p = 0.53$) (Figure 1).

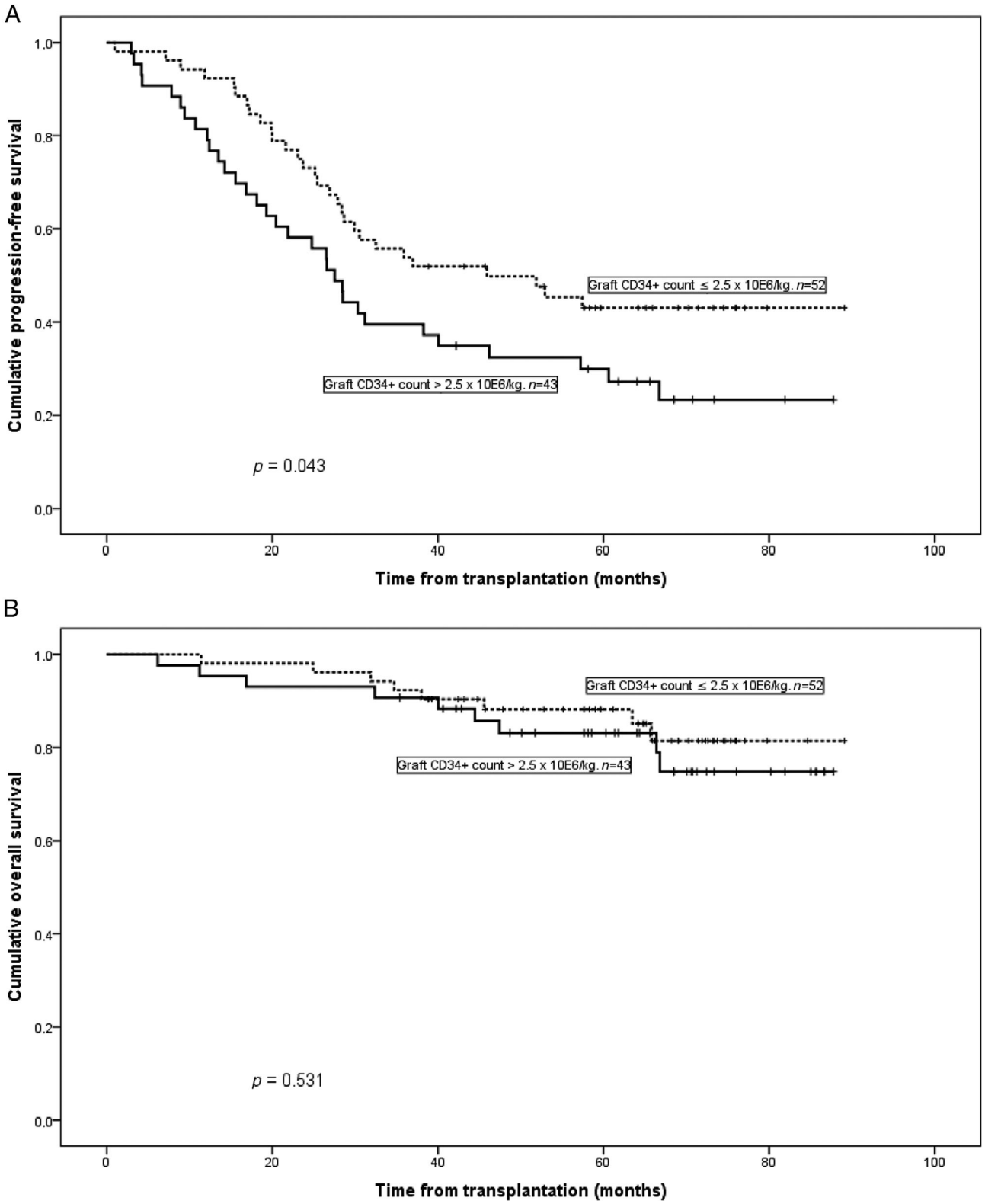

FIGURE 1 Progression-free survival (A) and overall survival (B) of the standard cytogenetic risk myeloma patients according to the graft $CD34^+$ count

Higher graft $CD34^+CD133^+CD38^-$ cell count (>0.065 $\times 10^6$/kg, $n = 59$, Table S4) did not significantly improve PFS (40 vs. 27 months, $p = 0.066$) or OS ($p = 0.081$) in the whole patient cohort. In the subgroup of chemo-mobilized patients ($n = 73$), however, $CD34^+CD133^+$ $CD38^-$ cell count >0.065 $\times 10^6$/kg ($n = 40$) was

associated with a clearly better PFS (42 vs. 22 months, $p = 0.021$) and an OS benefit ($p = 0.025$) was also observed (Figure 2).

The graft $CD3^+$ cell count had no impact on PFS. Very low $CD3^+$ count ($<20 \times 10^6$/kg, $n = 16$, Table S5) was associated with inferior OS in the whole study population

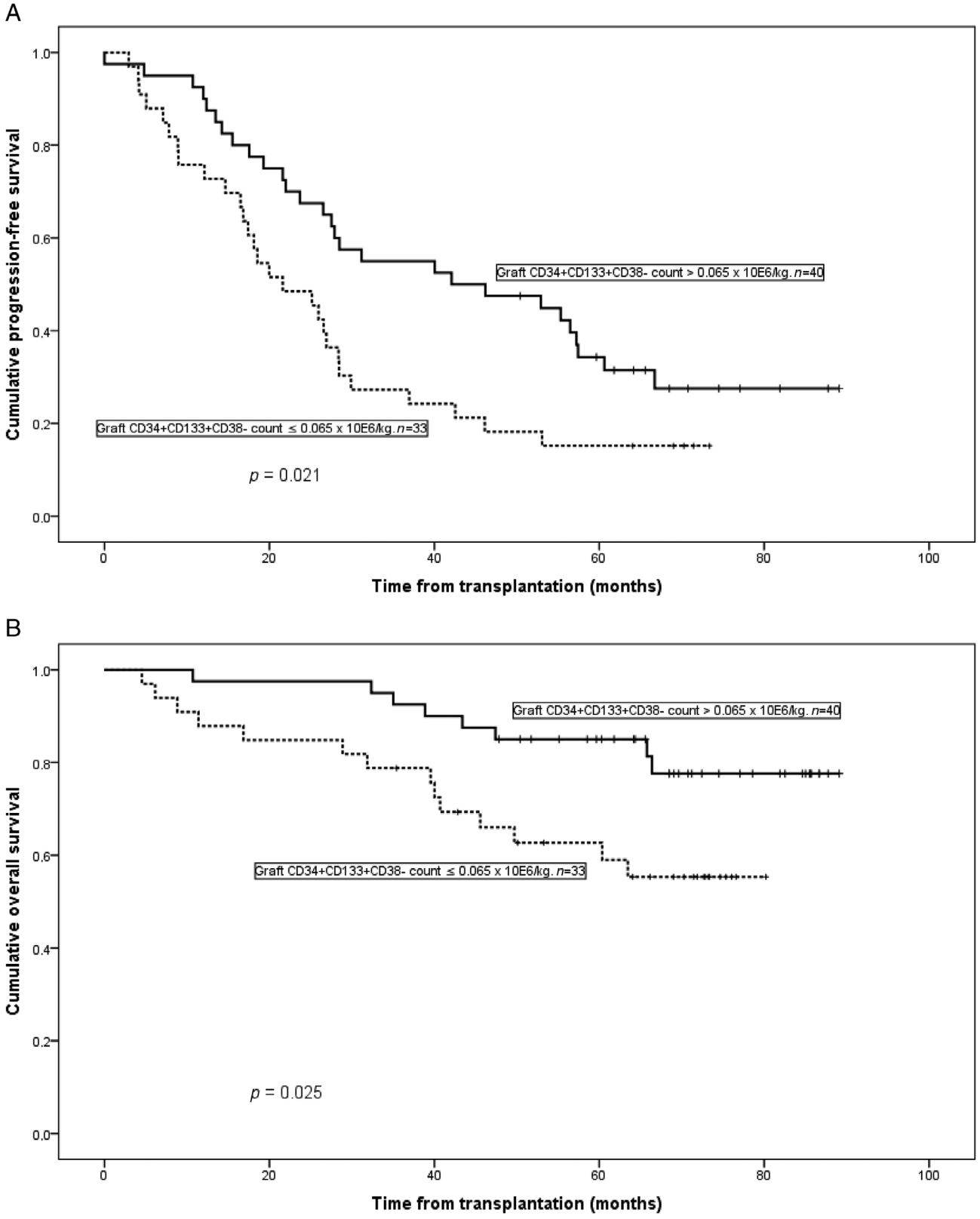

FIGURE 2 Progression-free survival (A) and overall survival (B) of myeloma patients mobilized with cyclophosphamide + G-CSF according to the graft $CD34^+CD133^+CD38^-$ count. G-CSF, granulocyte colony-stimulating factor

(not reached vs. 47 months, $p = 0.017$). In the non-HR subpopulation ($n = 103$), graft $CD3^+$ count >60 × 10^6/kg, however, was linked with better OS ($p = 0.042$). A higher graft $CD3^+CD8^+$ cell count (> 15 × 10^6/kg, $n = 83$, Table S6) was not linked with statistically significant difference in PFS (32 vs. 22 months, $p = 0.082$), but an OS

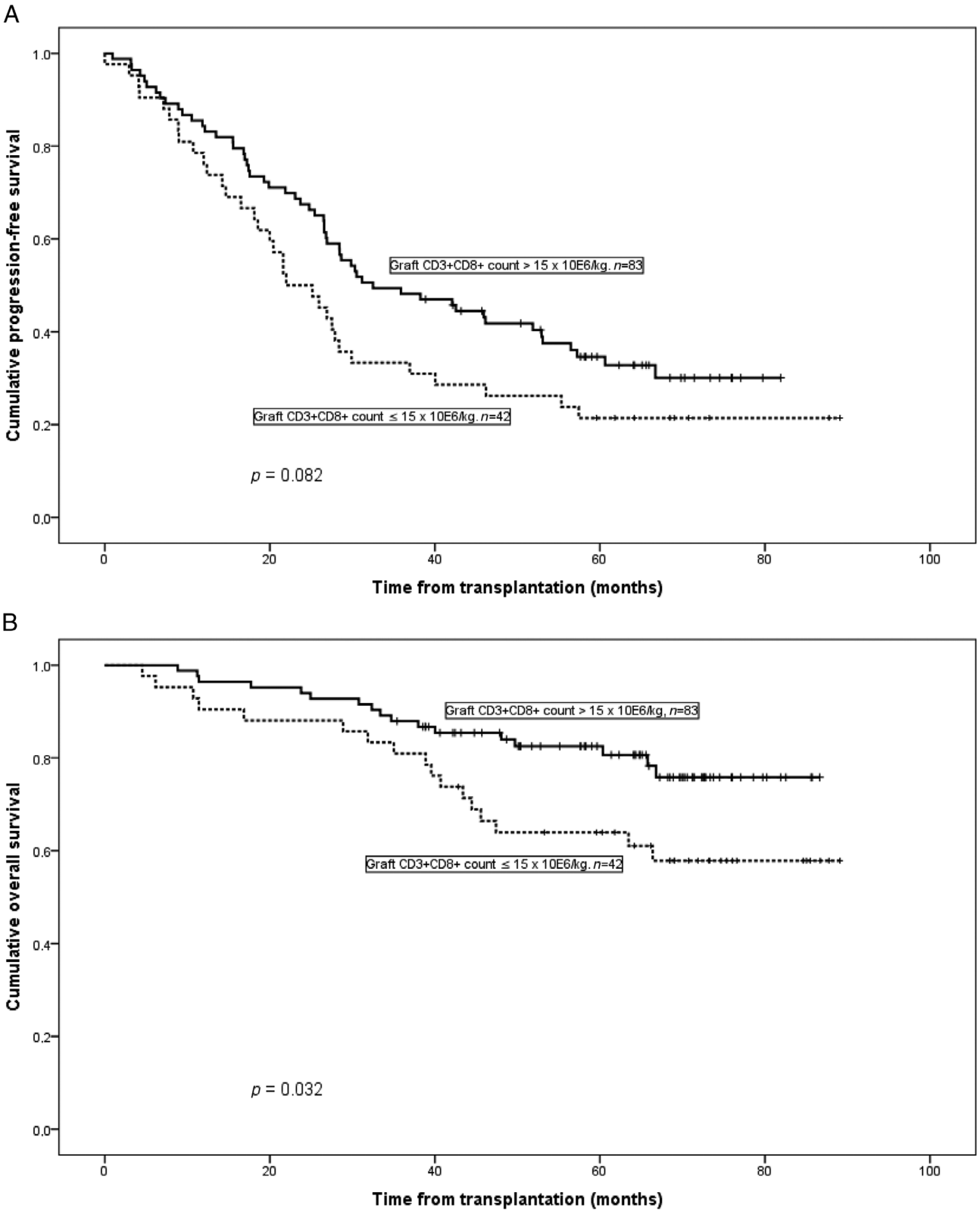

FIGURE 3 Progression-free (A) and overall survival (B) of the myeloma patients according to the graft $CD3^+CD8^+$ count

advantage was observed ($p = 0.032$, Figure 3). Graft $CD3^+CD4^+/CD3^+CD8^+$ ratio had no effect on PFS or OS (data not shown).

In the whole study cohort, a low graft NK cell count ($<2.5 \times 10^6$/kg, $n = 34$, Table S7) did not significantly impact PFS (25 vs. 30 months, $p = 0.155$) or OS

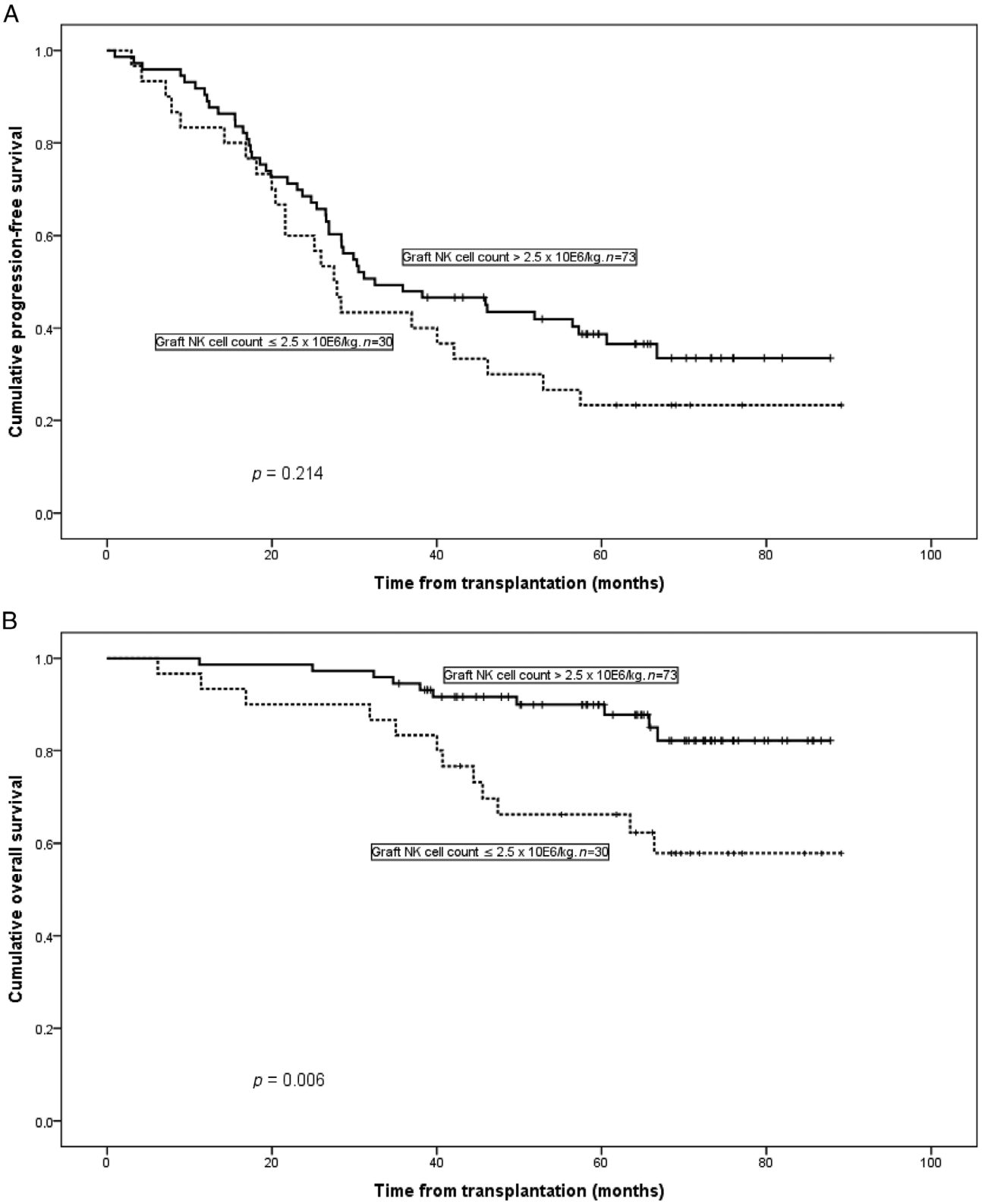

FIGURE 4 Progression-free (A) and overall survival (B) of the non-high-risk cytogenetics myeloma patients according to the graft NK cell content

TABLE 4 Associations between graft cellular components and progression-free survival and overall survival in univariate and multivariate cox regression analyses

	Progression-free survival				Overall survival			
	Univariate		Multivariate[a]		Univariate		Multivariate[a]	
Graft cellular component ($\times 10^6$/kg)	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
$CD34^+$ cells with 7-AAD >2.5	1.480 (0.979–2.239)	0.063	**1.899 (1.162–3.102)**	**0.010**	0.808 (0.412–1.583)	0.534		
$CD34^+CD133^+CD38^-$ cells >0.0065	0.676 (0.444–1.029)	0.068	**0.501 (0.301–0.835)**	**0.008**	0.540 (0.267–1.091)	0.086		
$CD3^+$ cells <20	1.544 (0.856–2.784)	0.149			**2.545 (1.152–5.624)**	**0.021**	**4.160 (1.758–9.842)**	**0.001**
$CD3^+CD4^+$ cells >35	0.804 (0.527–1.226)	0.310			0.525 (0.267–1.034)	0.062		
$CD3^+CD8^+$ cells >15	0.683 (0.443–1.053)	0.084			**0.486 (0.248–0.953)**	**0.036**		
NK cells <2.5	1.388 (0.882–2.184)	0.157	**1.799 (1.099–2.947)**	**0.020**	1.916 (0.968–3.7 95)	0.062		
Len maintenance	**0.254 (0.139–0.462)**	**<0.001**	**0.315 (0.158–0.625)**	**0.001**	0.459 (0.190–1.109)	0.084		
Mobilization method								
CY + G-CSF	1				1			
G-CSF alone	0.807 (0.527–1.236)	0.323			0.804 (0.397–1.628)	0.545		
Use of plerixafor	1.013 (0.539–1.905)	0.967			0.918 (0.323–2.608)	0.873		
Cytogenetic risk		**0.004**		**0.045**		**<0.001**		**<0.001**
SR	1		1		1		1	
HR	**2.214 (1.319–3.714)**	**0.003**	**2.000 (1.154–3.466)**	**0.013**	**4.163 (1.985–8.731)**	**<0.001**	**5.645 (2.528–12.609)**	**<0.001**
Unknown	1.943 (0.985–3.797)	0.055	1.275 (0.632–2.573)	0.498	**2.958 (1.090–8.023)**	**0.033**	**3.311 (1.209–9.064)**	**0.020**
Disease status 3 months after transplantation		**0.011**		**0.011**		0.493		
sCR	1		1		1			
CR	3.487 (1.057–11.499)	0.040	1.803 (0.371–8.773)	0.465	1.262 (0.268–5.952)	0.769		
VGPR	**5.090 (1.573–16-470)**	**0.007**	2.698 (0.570–12.760)	0.211	2.177 (0.505–9.390)	0.297		
PR or worse	**6.299 (1.839–21.569)**	**0.003**	4.667 (0.982–22.180)	0.053	1.983 (0.400–9.843)	0.402		
Gender								
Male	1				1			
Female	0.980 (0.648–1.482)	0.924			1.284 (0.652–2.527)	0.469		
Age >60	1.380 (0.839–2.270)	0.205			1.135 (0.514–2.506)	0.755		

Note: The *p* values marked with bold are statistically significant (<0.05).

Abbreviations: CI, confidence interval; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; SR, standard risk.

[a]Only variables significant in the final step of backward Cox regression are shown.

($p = 0.058$). In the non-HR group, a low graft NK cell count was associated with worse OS ($p = 0.006$, Figure 4).

In multivariate analysis taking into account different graft cellular components, gender, age, risk group by cytogenetics, mobilization method, use of PLER,

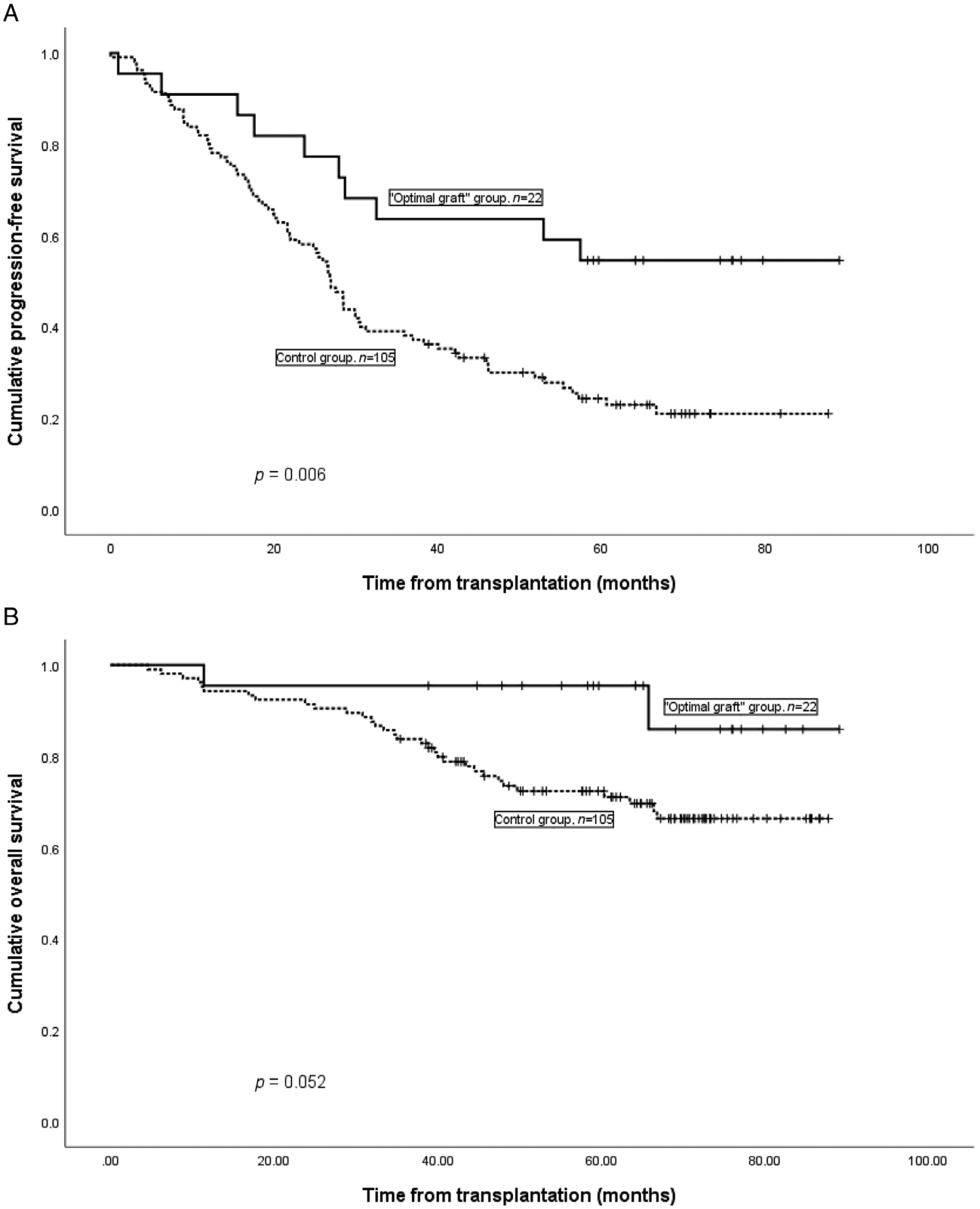

FIGURE 5 Progression-free (A) and overall (B) survival of the myeloma patients according to the graft composition. "Optimal graft" group comprises patients with a graft $CD34^+$ cell count $\leq 2.5 \times 10^6$/kg and $CD34^+CD133^+CD38^-$ cell count $>0.065 \times 10^6$/kg. The rest of the study population form the control group

lenalidomide maintenance and disease status 3 months after auto-SCT, higher graft $CD34^+CD133^+CD38^-$ count ($>0.065 \times 10^6$/kg) and lenalidomide maintenance remained predictive of better PFS. In contrast, a high graft $CD34^+$ count ($>2.5 \times 10^6$/kg), low graft NK cell count ($<2.5 \times 10^6$/kg), and high-risk cytogenetics predicted worse PFS. A very low graft $CD3^+$ lymphocyte count ($<20 \times 10^6$/kg) and non-SR cytogenetics were associated with worse OS in the multivariate model (Table 4).

In a subgroup of 22 patients (17%, Table S8), the infused graft contained $\leq 2.5 \times 10^6$/kg $CD34^+$ cells and $>0.065 \times 10^6$/kg $CD34^+CD133^+CD38^-$ cells. These graft components were linked with improved survival and could therefore be hypothesized to represent "optimal graft" in MM patients. The PFS of this subgroup was superior (NR vs. 27 months, $p = 0.006$) compared to the rest of the patient cohort but no statistically significant difference in OS was observed at this time point ($p = 0.052$) (Figure 5).

4 | DISCUSSION

This prospective multicenter study evaluated the impact of autograft cellular composition on post-transplant hematologic recovery, PFS, and OS in MM patients. A higher graft $CD34^+$ cell count was associated with better PLT recovery. Surprisingly, higher $CD34^+$ cell count predicted shorter PFS in the multivariate model. Of the other graft components, higher graft $CD34^+CD133^+CD38^-$ and $CD3^+CD8^+$ cell counts were beneficial, whereas a very low graft $CD3^+$ cell count and low NK cell count correlated with an adverse outcome. These observations are of interest as, until now, scarce data are available regarding graft composition in MM patients.

The correlation of a higher infused graft $CD34^+$ dose with faster PLT recovery and higher long-term PLT levels after auto-SCT have been described before.[21-24] Klaus et al.[25] have also shown a higher infused $CD34^+$ count to correlate with faster leukocyte recovery. However, there are also previous studies suggesting that the infused $CD34^+$ dose has no role in neutrophil recovery post-transplant.[23,24,26] In our study, graft $CD34^+$ counts had no effect on neutrophil engraftment or long-term neutrophil counts, but the use of G-CSF post-transplant predicted faster neutrophil engraftment in multivariate analysis.

There are some retrospective studies suggesting that the infused graft $CD34^+$ cell dose has no effect on survival in MM patients.[25,27] In contrast, Toor et al.[11] have demonstrated higher amount of infused $CD34^+$ cells to predict better PFS and OS after auto-SCT. Also, O'Shea et al.[28] have shown that graft $CD34^+$ count $>3.5 \times 10^6$/kg $CD34^+$ cells correlates with better OS. In addition, poor mobilization has predicted shorter PFS and OS in some studies.[29,30] In our study, a higher graft $CD34^+$ cell count was associated with shorter PFS with no effect on OS. A potential explanation to this PFS difference might be mobilization of malignant plasma cells into the graft, which has previously been linked with shortened PFS and OS,[31-34] although in some studies this connection has not been detected.[35] $CD34^+$ cell selection has been able to decrease the amount of tumor cells in the grafts but, however, not impacted PFS or OS in previous studies.[36,37] We did not measure clonal plasma cells in the grafts in the GOA study, but the majority of the patients had achieved at least a very good partial response at the time of mobilization of blood grafts.

A higher $CD34^+CD133^+CD38^-$ cell count ($>0.065 \times 10^6$/kg) in the graft predicted better PFS in multivariate analysis in this study, and in the subgroup of chemo-mobilized patients this cell compartment was associated with better PFS and also OS. This association has not been described previously in MM patients. Henon et al. have suggested a minimum graft content of 0.05×10^6/kg $CD34^+CD133^+CD38^-$ cells to ensure timely and durable trilineage hematopoietic reconstitution.[38] A higher graft $CD34^+CD133^+CD38^-$ cell count has been shown to correlate with more rapid immune recovery after auto-SCT in NHL patients.[39] Respectively, also in MM patients, more rapid immune recovery has been linked with better outcome.[13,15,40,41] This might also be an explanation for our finding although immune recovery was unfortunately not studied in GOA study in detail.

Porrata et al.[12] have previously demonstrated that an infused graft total lymphocyte count $>500 \times 10^6$/kg was linked with better PFS and OS in MM patients. In addition, Hiwase et al.[13] have shown infused total lymphocyte dose $>200 \times 10^6$/kg to be associated with improved lymphocyte recovery at day +30 after graft infusion, which, in turn, predicted better PFS and OS. Also, conflicting results have been published in this topic.[42] In our study, a very low graft $CD3^+$ count ($<20 \times 10^6$/kg, $n = 16$) was linked with worse OS. In the non-HR patient subgroup, an OS advantage was observed also with graft $CD3^+$ $>60 \times 10^6$/kg. A higher infused graft lymphocyte count is known to correlate with more rapid immune recovery after auto-SCT.[12,13] The possible explanation to the observed survival benefit might be the complex anti-tumor effects mediated by these immune cells.[43,44]

Schmidmeier et al. have previously demonstrated a higher autograft $CD3^+CD4^+/CD3^+CD8^+$ ratio and higher graft $CD4^+$ count to correlate with prolonged event-free survival in MM patients.[14] In this study, no such correlation was observed. However, a higher graft $CD8^+$ cell count seemed to be beneficial in terms of

OS. The immune reconstitution after auto-SCT, although not addressed in this study, has been shown to be important for disease control in MM patients.[44]

The graft NK cell compartment is of special interest because in MM patients faster NK cell recovery has been linked with improved outcome after auto-SCT,[15] dysfunction of NK cells has been associated with disease progression,[45] and a lower NK cell count post-transplant has correlated with disease relapse after auto-SCT.[44] In this study, graft NK cell count $>2.5 \times 10^6$/kg predicted better PFS in a multivariate model. There are no previous publications linking graft NK cell count with improved outcome in MM patients. NK cells may vary in terms of immunophenotype and function.[46] In the future, more precise immunophenotyping of the graft NK cells in regard to outcome after auto-SCT should be performed. The NK cell compartment might well be a critical factor in addition to disease biology in the efficacy of post-transplant strategies including lenalidomide maintenance.

These results should be interpreted with caution, as there are some limitations in this study. First, the differences in the mobilization method used lead to significant variation in graft cellular composition. Second, pre- and post-transplant treatment regimens used differed to some extent and this is likely to affect the outcome of the patients. Third, the categorization of continuous variables leads to inevitable loss of information. Although subgroup analyses were performed and a multivariate model was used to determine the significant graft cellular components and cutoffs in regard to outcome, some information is likely to be lost. Finally, although some graft components remained significant in terms of PFS and OS in the multivariate model, causality cannot be evaluated with this study design. On the other hand, the prospective multicenter setting, a reasonable number of patients, centralized graft analysis and a long follow-up are among the obvious strengths of this study.

To conclude, in this prospective multicenter study, we observed survival differences in MM patients according to graft cellular composition. The associations between higher graft $CD34^+CD133^+CD38^-$ and NK cell counts and improved outcome after auto-SCT have not been described earlier. The negative correlation between graft $CD34^+$ count and PFS is a quite provocative finding, which raises questions about the optimal graft $CD34^+$ dose in terms of outcome. Validation of these findings in an independent patient cohort or in a randomized study setting aiming for desired graft composition in the future is essential. This study suggests that the autograft cellular composition beyond the $CD34^+$ cell count might be of importance.

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CONFLICT OF INTEREST

Dr RS has received Celgene Research Funding for FMG-MM02 study, Amgen, BMS, and Takeda Research funding, compensation as a member of the Scientific Advisory Boards of Celgene, Amgen, Janssen-Cilag, Takeda and consultancy fees from Amgen, Celgene, Jansen-Cilag, and Sanofi. Dr AP reports honoraria from Behring and Abbvie and has participated in Scientific Advisory Board meetings organized by Abbvie and Takeda. Dr JV has participated in Scientific Advisory Boards organized by Amgen and Janssen-Cilag and has also received consultancy fees from Amgen, Sanofi, and Janssen-Cilag. Dr TS has participated in the Scientific Advisory Boards of Roche, Amgen, Novartis, and Pfizer and received consultancy fees from Amgen. Dr MP has received consultancy fees from Janssen-Cilag, Amgen, Takeda, Celgene, and Sanofi and has participated in the Scientific Advisory Boards organized by Amgen, Janssen-Cilag, Takeda, Celgene, and Sanofi. Dr TK has received consultancy fees from Sanofi-Genzyme, BMS, Sanofi, Celgene, Roche, Amgen, Janssen-Cilag, Pfizer, Leo-Pharma, Sobi, MSD, Takeda, Bayer, Novo Nordisk, and Boehringer-Ingelheim, has received grants from Novartis and Astra Zeneca and has participated in the Scientific Advisory Board organized by Celgene. Dr MP has received honoraria from Amgen, Novartis, and Pfizer and participated in Scientific Advisory Boards organized by Pfizer. Dr EJ has participated in the Scientific Advisory Boards of Amgen, Takeda, TEVA, and Sanofi. Dr VV reports consultancy fees from Abbvie, Amgen, Celgene, Janssen-Cilag, Roche, and Sanofi. AT, MS, KP, AS, ERS, PM, and PJ have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

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