haematologica
Journal of the Ferrata Storti Foundation

Impact of maintenance therapy on survival after autologous stem cell transplant for multiple myeloma regardless of response: a global analysis

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Received: May 25, 2026.
Accepted: September 8, 2026.

Citation: Andrew J. Cowan, Luuk Gras, Raffaella Cassano, Yoshiko Atsuta, Laurien Baaij, Francisca Bass, Ali Bazarbachi, Mohamed Amine Bekadja, Katherine Clesham, Peter Dreger, Anita D'Souza, Noel Estrada-Merly, Ai Sim Goh, Minako Iida, Patrick J Hayden, Koji Kawamura, Bor-Sheng Ko, Linda Koster, Christopher Liam, Hira Mian, Arleigh McCurdy, Cristobal Augusto Frutos Ortiz, Nada Hamad, Donal McLornan, Meng Lv, Shohei Mizuno, Aloks Srivastava, Asmaa Quessar, Eloisa Riva, Wael Saber, John Snowden, Hiroyuki Takamatsu, Xavier Cheng-Hong Tsai, Estelle Verburgh, Ho Kim Wah, Daniel Neumann, Anna Sureda, Mahmoud Aljurf, Mickey Boon Chai Koh, Sebastian Galeano, Yoshihisa Kodera, Damiano Rondelli, Dietger W. Niederwieser and Laurent Garderet.
Impact of maintenance therapy on survival after autologous stem cell transplant for multiple myeloma regardless of response: a global analysis.
Haematologica. 2026 Sept 17. doi: 10.3324/haematol.2026.301244 [Epub ahead of print]

Impact of maintenance therapy on survival after autologous stem cell transplant for multiple myeloma regardless of response: a global analysis

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Contributions

Andrew J. Cowan and Luuk Gras designed the research, interpreted the data, and wrote the manuscript. Luuk Gras, Laurien Baaij, Linda Koster, and Daniel Neumann analyzed the data and performed the statistical analyses. Laurent Garderet and Dietger W. Niederwieser conceived and supervised the study, interpreted data, and critically revised the manuscript. Raffaella Cassano, Yoshiko Atsuta, Francisca Bass, Ali Bazarbachi, Mohamed Amine Bekadja, Katherine Clesham, Peter Dreger, Anita D'Souza, Noel Estrada-Merly, Ai Sim Goh, Minako Iida, P.J. Hayden, Koji Kawamura, Bor-Sheng Ko, Christopher Liam, Hira Mian, Arleigh McCurdy, Cristobal Augusto Frutos Ortiz, Nada Hamad, Donal P. McLornan, Meng Lv, Shohei Mizuno, Asmaa Quessar, Eloisia Riva, Wael Saber, John Snowden, Hiroyuki Takamatsu, Xavier Cheng-Hong Tsai, Estelle Verburgh, Ho Kim Wah, Anna Sureda, Mahmoud Aljurf, Mickey Boon Chai Koh, Sebastian Galeano, Yoshihisa Kodera, and Damiano Rondelli contributed vital data and study materials, interpreted the data, and critically reviewed the manuscript. All authors approved the final manuscript and agreed to its submission.

Disclosures

AJC: Research Funding: JNJ, BMS, Sanofi, Regeneron, Merck, Caelum, Opna Bio, Karyopharm; Advisory/Consulting: JNJ, BMS, Sanofi, HopeAI, Abbvie, Kite/Arcellx; Stock ownership: HopeAI
All other co-authors indicate no other relevant COI.

Data-sharing statement

The data of this study are not publicly available. These data are managed in accordance with the WBMT Research Guidelines.

Abstract

The effect of different maintenance therapies on outcome after autologous hematopoietic cell transplantation (AHCT) was analyzed in newly diagnosed multiple myeloma (NDMM) patients using global real-world data.

NDMM patients transplanted between 2013 and 2017 were selected from the Worldwide Network for Blood and Marrow Transplantation (WBMT) registry. Overall survival (OS) was evaluated as primary and progression-free survival (PFS), non-relapse mortality and relapse/progression incidence as secondary endpoints. Multivariable 6-month landmark analyses were performed using Cox proportional hazards models including random effect for country.

Information was available on 8,269 patients with lenalidomide (n=4,148; 50.2%), thalidomide (n=689; 8.3%) or bortezomib (n=726; 8.8%) as maintenance or no maintenance (n=2,706; 32.7%). In the 6-month landmark analysis, OS at 3 years was higher after maintenance with lenalidomide (86%), with thalidomide (80%) and with bortezomib (83%) as compared to no maintenance (79%, $p<0.001$) irrespective of response status at AHCT. In multivariate analyses, maintenance with lenalidomide (HR0.57, 95%CI 0.48-0.68), thalidomide (HR0.76, 95%CI 0.58-1.00) and bortezomib (HR0.65, 95%CI 0.50-0.84) were associated with better OS compared to no maintenance. Compared to no maintenance, all three medications significantly improved PFS early after HCT. The effect was gone by 30, 6, and 12 months for lenalidomide, thalidomide, and bortezomib respectively.

Maintenance with lenalidomide, and to a lesser extend thalidomide and bortezomib resulted in improved OS as compared to no-maintenance in all depths of response prior to AHCT. Weaker and shorter associations were observed for PFS reflecting maintenance type, therapy discontinuation and survivor effects.

Introduction

Multiple myeloma (MM) is a plasma cell malignancy that accounts for 1%-1.8% of all cancers and is the second most common hematological malignancy (1, 2). Although diagnosed more frequently in high-income sociodemographic index (SDI) countries (including Western Europe, North America, and Australia), MM remains a global disease, with an age standardized incidence rate (ASIR) of 1.72/100,000 persons globally (2). MM was responsible for 98,437 deaths worldwide with an age-standardized death rate (ASDR) of 1.5 per 100,000 persons (95% UI, 1.3-1.7) in 2019 [3].

Currently, the state-of-the-art treatment for newly diagnosed MM (NDMM) includes induction with a proteasome inhibitor (PI; most commonly bortezomib), an immunomodulatory agent (most commonly, lenalidomide or thalidomide) and dexamethasone. In some regions of the world, induction will also typically include anti-CD38 monoclonal antibodies, either daratumumab or isatuximab (3, 4). Autologous hematopoietic cell transplantation (AHCT) with melphalan conditioning is standard of care for eligible patients followed by maintenance therapy (3). However, real world global data regarding maintenance agents and the impact in different response categories prior to AHCT has not been published on a global level.

Thalidomide was the first agent explored as maintenance. In the Myeloma IX trial, the use of thalidomide maintenance was associated with potential OS and PFS benefit in patients with favorable, but worse OS in patients with adverse fluorescence in situ hybridization (FISH) findings (5). In the HOVON 50 Trial, thalidomide maintenance was compared to Interferon alpha, confirming the benefit of thalidomide at a median follow-up of 129 months (IQR 123–136), showing significantly longer event free survival in the thalidomide group compared with the control group (6).

Larger randomized trials, and subsequent meta-analyses, have confirmed the beneficial effect of maintenance lenalidomide after AHCT on PFS (7, 8). PFS at 3 years was 59% in the lenalidomide group, as compared with 35% in the placebo group [hazard ratio (HR) 0.50; $p<0.001$]. The benefit was observed across all patient subgroups, even those with different risk profiles based on baseline demographic or disease characteristics, including response at the time of randomization and initial cytogenetic results. Additionally, there was an OS benefit for receipt of

lenalidomide maintenance (8). Furthermore, a meta-analysis including more than 1200 patients revealed a median PFS of 52.8 months for the lenalidomide group and 23.5 months for the placebo or observation group (HR 0.48; 95% CI, 0.41 to 0.55). In this analysis, OS was also improved with lenalidomide; the median OS was not reached for lenalidomide, whereas it was 86.0 months for the control group (HR 0.75; 95% CI, 0.63 to 0.90; p=0.001). Unfortunately, there was no benefit in OS in cohorts of patients with ISS-III disease or high-risk cytogenetics (7). However, a subsequent analysis from the Myeloma XI trial demonstrated a benefit for lenalidomide maintenance even amongst patients harboring high-risk cytogenetic abnormalities (9).

Real world data from the CIBMTR demonstrated that maintenance therapy (including lenalidomide, lenalidomide in combination with bortezomib, or other combinations) yielded significantly improved 3-year PFS vs no post-transplant therapy (55% vs. 39%, p=0.0001). This benefit was most evident in patients not achieving at least complete remission (CR) post-AHCT (10). However, the CIBMTR registry predominantly comprises patients from high-income Socio demographic Index countries.

In our retrospective study of real-world data, we aimed to explore the worldwide use of maintenance type and outcome. This is of considerable importance in view of diverse access to maintenance drugs worldwide. In the light of results published so far on effect of disease response status prior to AHCT, we conducted an analysis of the interaction between response status and maintenance treatment on outcomes after AHCT.

Methods

Study Design, Data Sources

This is a retrospective analysis of registry data, conducted through the Worldwide Network for Blood and Marrow Transplantation (WBMT) utilizing data from its member societies, or international/regional registries. A full description of the registry has been published previously (11). Data obtained from patients with NDMM, aged ≥18 years at time of AHCT between 2013 and 2017 and data available on maintenance (lenalidomide, bortezomib, thalidomide or no maintenance/unknown) was selected. As no individual patient data were used, no ethics committee approval was mandated. The need for additional informed consent from patients was waived because

the study was performed by the secondary use of registry data, and no personal information was transferred. The primary endpoint was OS and the secondary endpoint PFS, non-relapse mortality (NRM) and relapse/progression incidence (RPI). Outcome data were acquired through regional registries (see supplement Table S1)

Statistical Analysis

Baseline clinical, demographic, and transplantation-related characteristics were grouped according to the maintenance groups (lenalidomide, thalidomide, bortezomib, and no maintenance), and were reported as median, range, and interquartile ranges for continuous variables. Maintenance was started according to general agreement during the first months after AHCT and given for a duration of 2 to 3 years or until progression (Prog) or toxicity. Differences between groups were assessed using p-values obtained with the $\chi 2$ test for categorical variables and the Kruskal-Wallis test for continuous data.

To account for the variable timing of maintenance initiation and data on start and stop of maintenance not being available, we performed a 6-month landmark analysis. For those who had survived beyond 6 months without relapse, OS was calculated as the time from the 6-month landmark to death from any cause and PFS as the time from the 6-months landmark to death or disease Prog. NRM was defined as death without progression or relapse (Rel). In analyses of OS, PFS, Rel/Prog and NRM events occurring more than three years after the 6-month landmark were artificially censored. Median follow-up after the 6-month landmark and 95% confidence intervals (CI) were calculated using the reverse Kaplan-Meier method. The probability of OS and PFS was estimated based on the Kaplan-Meier method and differences were analyzed using the log-rank test. The crude cumulative incidence estimator and Gray's test were used for competing events (Rel/Prog together with NRM). Multivariable analyses (MVA) were performed using Cox (cause-specific) proportional hazards models including a random effect for country. Variables included in MVA, apart from maintenance and response status at AHCT according to IMWP [12] are listed in the Supplement.

We included interaction terms between maintenance treatment and disease stage at AHCT in OS and PFS models to check whether the association of maintenance and outcome was similar across all disease stage. We analyzed whether the association between the maintenance and outcome was constant over time (for proportional hazards

assumption, see details in supplement). Missing values were modeled using a separate missing category. All statistical tests were 2-sided, and significance was defined as $p < 0.05$. All analyses were performed in R version 4.4.2 (12) using 'survival', 'cmprsk,', 'prodlim' packages. No adjustment for multiple comparisons were made.

Results

From 2013 to 2017, 61,802 patients were reported to the WBMT registry. Of these, 8,269 (13.4%) had information available on maintenance, which included lenalidomide in 4,148 (50.2%), thalidomide in 689 (8.3%), bortezomib in 726 (8.8%) and no maintenance in 2,706 (32.7%) patients. In addition, 746 patients were reported to have received no further defined maintenance, 536 an IMiD + proteasome inhibitor combination, and 66 carfilzomib as maintenance. These latter groups were excluded from this evaluation due to low numbers or incomplete clinical information. Demographics of the 8,269 patients treated with lenalidomide, thalidomide, bortezomib or without maintenance are shown in Table 1. Of those, 7,645 were alive at 6 months post-AHCT and included in the landmark analysis (51.8% with lenalidomide, 7.6% thalidomide, 8.7% bortezomib and 31.9% without maintenance; Table 1).

Data obtained from patients were entered by the following registries: Japan (34.7%), EBMT (32.6%), CIBMTR (22.3%), LABMT (3.2%), Canada (2.0%), Malaysia (2.0%), Taiwan (1.9%), China (0.7%) and EMBMT (0.7%) (Table S1). Maintenance differed across world regions. While in Europe, North America, Japan and EMBMT lenalidomide was the most frequently used drug, thalidomide was the most utilized drug in Taiwan, Latin America and China. The majority were ISS I (36.2%), were male (56.8%) and IgG myeloma (57.2%). The median time from diagnosis to AHCT was 7.1 months (Interquartile range [IQR], 5.6 – 10.0), and the median age at AHCT was 60.0 years (range 20.2-82.4 years). Response status at AHCT was CR in 19.8%, VGPR in 36.2%, PR in 37.8%, SD/MR in 4.4% and Rel/Prog in 1.7%. The majority had melphalan 200 mg/m^2 conditioning (74.2%) and a single AHCT (91.2%). The cytogenetic risk score was high in 22.2%, KPS ≤90% in 65.9% and high HCT-CI in 17.2% of patients, as with the response status at HCT, were unevenly distributed between the four maintenance groups. Except for sex, patient characteristics were not equally distributed between the groups, with a higher percentage of lenalidomide patients with AHCT in more recent years. Thalidomide patients were at a younger age at AHCT, a

higher percentage were in CR, had a KPS of 100, a low HCT-CI and had standard cytogenetic risk compared to lenalidomide.

Univariable analysis

The OS and PFS of the whole population with maintenance information (n=8266) starting from AHCT is shown in Supplemental Figure S1. At 6 months OS was 99.0% (95% CI 98.7-99.2%) and PFS was 95.3% (95% CI 94.8-95.9%). All following analyses include only those patients who were alive and relapse-free at 6 months post AHCT (n=7,645). Median follow-up (IQR) after the 6-month landmark was 45.0 months (29.0-61.2 months).

A deeper response prior to AHCT and type of maintenance were associated with better OS and PFS after the 6-month landmark analysis (Figure1, all $p<0.001$). OS at 3 years was 87% (95% CI 85-89) for patients in CR, 84% (95% CI 83-86) in VGPR, 82% (95% CI 80-83) in PR and 74% (95% CI 69-78) in SD/MR/Prog (Figure 1a and Table S2). OS at 3 years of the patients who received maintenance lenalidomide was 86% (95% CI 85-87), thalidomide 80% (95% CI 76-84), bortezomib 83% (95% CI 80-86) and no maintenance 79% (95% CI 77-80) ($p<0.001$; Figure 1b). PFS resembled the patterns of OS with respect to response status (Figure 1c and Table S2). PFS at 3 years was 63% (95% CI 61-65%) with lenalidomide, 53% (95% CI 48-57%) with thalidomide and 52% (95% CI 47-56%) with bortezomib maintenance as compared to 60% (95%CI 58-63%) without maintenance ($p<0.001$ Figure 1d and Table S2).

We then investigated whether the type of maintenance affected outcomes equally in the different response categories. In univariate analysis, patients with lenalidomide maintenance had the highest OS at all response categories prior AHCT (CR, VGPR, PR and SD/MR/Progr) and 3-year OS was 91% (95% CI 88-93%), 86% (95% CI 84-88%), 85% (95% CI 83-87%) and 81% (95% CI 75-87%), respectively. Patients with thalidomide maintenance had lower and decreasing OS at 3 years according to response status at AHCT reaching 78% (95% CI 70-85%), 84% (95% CI 78-90%), 81% (95% CI 74-88%), and 72% (95% CI 56-87%), respectively. Patients with bortezomib maintenance, although inferior to thalidomide, had response dependent OS at 3 years of 89% (95% CI 84-95%), 85% (95% CI 80-90%), 77% (95% CI 70-83%) and 86% (95% CI 73-99%), respectively. The lowest OS was observed in those patients who did not receive maintenance amounting to 84% (95% CI 81-88%), 80% (95%

CI 76-83%), 78% (75-81%) and 63% (95% CI 55-71%) respectively (Table S2 and supplemental Figure S2). Similarly, patients treated with lenalidomide and to a lesser extend with thalidomide and bortezomib, had improved 3-years PFS across all response categories in comparison to no maintenance (Table S2). The differences in OS and PFS were mainly due to a reduced incidence of Rel/Prog incidence. Although NRM was very low (2-5%), differences between the maintenance groups were detected. NRM was highest in the no maintenance group (Table S2).

Multivariable Analysis

In the OS multivariate analysis of 7,547 patients (Table 2), lenalidomide (HR 0.57, 95% CI 0.48-0.68; p<0.0001), bortezomib (HR 0.65, 95% CI, 0.50-0.84, p=0.001), and thalidomide (HR 0.76, 95% CI, 0.58-1.00; p=0.05) were associated with a lower risk of death compared to no maintenance. There was a trend towards a lower risk of death in the lenalidomide group compared to thalidomide (HR 0.79, 95% CI 0.61-1.02, p=0.07), and no significant difference between lenalidomide and bortezomib (HR 0.88, 95% CI 0.69-1.11, p=0.27).

In the PFS analysis of 7,008 patients there was a significant difference in the association with lenalidomide (HR 0.65, 95% CI 0.57-0.73, p<0.0001), but not overall with thalidomide (HR 0.90, 95% CI 0.75-1.09, p=0.29) or bortezomib (HR 0.93, 95% CI 0.78-1.09, p=0.36). Lenalidomide was associated with better PFS than thalidomide (HR 0.72, 95% CI 0.60-0.85, p<0.0001) and bortezomib (HR 0.68, 95% CI 0.59-0.79, p<0.0001).

We then tested whether these HR were constant during the entire follow-up period. Indeed, HR´s were not constant during the follow-up period (Figure 2) and a trend of HR's closer to 1 with longer time after the 6 month landmark were noted (Table S3). The association of better OS with lenalidomide was strongest at the 6-month landmark (HR 0.25) and diminished with longer time after follow-up. HR's were significantly lower for lenalidomide vs. no maintenance comparison in OS up to 42 months after AHCT. A similar pattern was observed for thalidomide and for Bortezomib compared to no maintenance up to 16 months and 30 months after AHCT for OS, respectively. In the PFS comparison between lenalidomide vs. no maintenance we also observed diminishing HR´s with longer time during follow-up, but a significant improved PFS (significant the first 30 months after HCT). There was evidence

for a significant better PFS for thalidomide maintenance the first 6 months and for Bortezomib maintenance the first 12 months post-transplant (Figure 2 and Table S3)

Other significant risk factors for poorer OS resembled the results published previously on 61,797 patients [10]: more advance disease stage prior to AHCT, older age, earlier calendar year of AHCT, lower KPS, higher ISS stage and cytogenetic high-risk, but not gender and HCT-CI (Table 2). Response status prior to AHCT, female, ISS II and III, high-risk cytogenetics, but not age, year of AHCT and HCT-CI were significant prognostic factors for PFS (Table 2). There was no evidence for an interaction between the type of maintenance and the response status prior to AHCT in either the analysis of OS (p=0.06) and PFS (p=0.10) suggesting a similar beneficial effect of maintenance across all disease stages.

Predicted OS and PFS probabilities during the first 3 years after the 6-month landmark for a reference patient according to response status at AHCT and receiving either lenalidomide, bortezomib, thalidomide or no maintenance is given in Figure 3. Predictions were calculated using the results from the models presented in Table 2 and Figure 2. Differences were more pronounced with higher risk of death in SD/MR/Prog disease stages at AHCT. For maintenance therapies there was a predicted PFS benefit up to 36 months, but at 36 months after the 6-month landmark predicted PFS was similar for bortezomib, thalidomide and no maintenance.

Discussion

In our analysis of a global multiple myeloma registry of AHCT recipients, we analyzed the impact of response depth prior to AHCT and the interaction with maintenance on long-term outcomes. As we demonstrated previously, better response status at the time of AHCT was significantly associated with better PFS and OS (11). In this analysis, we demonstrated that lenalidomide maintenance improved OS and PFS irrespective of the response at the time of AHCT. Bortezomib and thalidomide were superior to no maintenance with respect to OS, however, they were inferior to lenalidomide maintenance, and they did demonstrate a significant lower risk of death/Rel, but only early after HCT.

Our results have some important messages. Despite randomized trials demonstrating the survival advantage (7), maintenance is still not used consistently globally, and when utilized, lenalidomide, bortezomib, and thalidomide are all being used in different world regions. According to our global registry, lenalidomide was used most frequently in Europe, USA, EMBMT region and Japan (in 73.2%, 66.2%, 68.5% and 25.7%, respectively; Table S1). In contrast, China, Malaysia, the LABMT, and Taiwan more frequently utilize thalidomide. Despite these differences, we have found that all agents deliver some benefit, though lenalidomide appeared to be the best. Interestingly, high percentages of patients in many regions still receive no maintenance at all (see Table S1).

Our results showed the beneficial effect of lenalidomide in all patients, even in those with SD/MR or worse. The association became smaller with longer follow up (HR lenalidomide vs. no maintenance became closer to 1), and after 36 months there was no significant difference. The reasons for this effect may include disease progression, survivor effects, and therapy discontinuation due to cumulative toxicities such as second primary malignancies (SPM) or cytopenias (8). Unfortunately, we do not have data on start and stop dates of maintenance treatment. Efforts to determine the ideal length of maintenance should be undertaken.

Our findings align with recent real world registry data; however, our analysis utilizes a global registry including some lower middle-income countries (LMIC). In a recently published analysis of 1109 MM patients from a large US-based academic center, the outcomes of patients who achieved a suboptimal response prior to AHCT, defined as less than a VGPR, were reported (13). A median PFS of 38.6 months was reported, and in a multivariate analysis, the use of post-transplant maintenance was associated with a superior PFS HR when compared to no maintenance of 0.60 ($p<0.001$). However, in this cohort, only 30% of patients did not receive maintenance, and the majority who received maintenance had lenalidomide (73%). Only 22% received a non-lenalidomide maintenance regimen. In an older study from the CIMBTR, investigators examined the impact of additional therapy prior to AHCT for patients who achieved a PR or less to induction therapy (14). While additional therapy deepened response in 68% of patients, there was no impact on PFS or OS. In our analysis, we only assessed response at the time of AHCT, and included a global cohort of patients, which is different from the patient populations in the prior analyses.

Given the findings of our analysis and prior meta-analyses and large randomized phase 3 trials demonstrating a PFS and OS benefit of maintenance our findings from a real-world global registry argue strongly for routine use of maintenance (7, 8). Although lenalidomide demonstrated the strongest HR in favor of PFS and OS at all response levels, both thalidomide and bortezomib were also utilized globally and demonstrated a favorable impact on OS and PFS – notably, prior phase 3 studies have shown that bortezomib demonstrates superior outcomes over thalidomide (15). In summary, access to maintenance therapy is critical, regardless of whether lenalidomide or bortezomib/thalidomide are used, even in cases where the response prior to AHCT was suboptimal.

Our results are strengthened by including cohorts from large registries across the globe with international representation. Multiple myeloma is a global disease (1, 2), and it is critical to understand the impact of therapies across all persons diagnosed with this cancer to deepen understanding and report outcomes equitably. We also describe the impact of non-lenalidomide maintenance therapy at a global perspective.

However, there are some weaknesses to our analysis. Our analysis covered the years 2013-2017, and maintenance agents utilized during this era have been supplanted by newer, sometimes expensive maintenance treatment strategies, and thus, may not reflect current best practices. For example, daratumumab is increasingly being incorporated into maintenance therapy, with improved outcomes – based on the results of the PERSEUS and CASSIOPEIA trials - and we do not have data on this agent in the WAUSTIM dataset at this time (4, 16). We did not have detailed toxicity or secondary primary malignancy data which is critical to understanding the long-term toxicities of lenalidomide. Indeed, SPM detection may have an impact on early compared to late OS benefit; as has been shown in previous trials, wherein the OS benefit for lenalidomide maintenance outweighed any impact related to SPM incidence over time (7, 8). Our dataset also suffered from missing data (for instance, the EBMT registry did not have data on no maintenance), on timing of maintenance, duration of therapy, and treatment adherence, which are also relevant when assessing a therapy that is given over a long duration. Although our cohort attempted to include a broader spectrum of global regions, most of our data is from Japanese, North American, and European regions, highlighting the need to create inclusive global disease-based registries and treatment outcomes. China, one of the most populous regions globally, contributed only a small proportion of patients to our registry. Improving registry participation and more inclusive international collaborations are needed with support from health

authorities and policymakers. Finally, we lack data on induction regimens; as has been demonstrated in recent large trials, such as CASSIOPEIA, agents included in induction and in maintenance may have an impact on PFS (17).

Taken together, our analysis of a global MM transplant registry sheds important light on the significance of maintenance therapy after AHCT, and the ability of maintenance to improve outcomes even in the setting of a less-than-optimal response prior to AHCT. Furthermore, although lenalidomide in our analysis resulted in superior outcomes for PFS and OS in all response categories, both bortezomib and thalidomide, which in some regions may be more broadly available (11), also provided an OS benefit over no receipt of maintenance therapy in multivariate analysis. Our findings also support pragmatic trials in low resource settings to assess the feasibility and outcomes of different maintenance strategies.

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Table 1. Demographic, Disease and Patient Characteristics.

Maintenance	All n (%)	Lenalidomide n (%);	Thalidomide n (%)	Bortezomib n (%)	No maintenance n (%)
Total patients	8269 (100.0)	4148 (50.2)	689 (8.3)	726 (8.8)	2706 (32.7)
Patients alive at 6 months landmark	7645(100.0)	3960 (51.8)	583 (7.6)	664 (8.7)	2438 (31.9)
ISS at diagnosis					
I	2310 (36.2)	1150 (39.0)	154 (28.6)	171 (35.0)	835 (34.6)
II	2348 (36.8)	1065 (36.1)	187 (34.7)	176 (36.0)	920 (38.2)
III	1729 (27.1)	734 (24.9)	198 (36.7)	142 (29.0)	655 (27.2)
missing	*1882 (22.8)*	*1199 (28.9)*	*150 (21.8)*	*237 (32.6)*	*96 (10.9)*
Sex					
Male	4696 (56.8)	2405 (58.0)	390 (56.6)	394 (54.3)	1507 (55.7)
Female	3570 (43.2)	1741 (42.0)	299 (43.4)	332 (45.7)	1198 (44.3)
MM classification					
IgG	4658 (57.2)	2418 (59.0)	360 (53.7)	377 (53.1)	1503 (56.2)
IgA	1556 (19.1)	729 (17.8)	137 (20.4)	141 (19.9)	549 (20.5)
Light chain	1656 (20.3)	832 (20.3)	143 (21.3)	166 (23.4)	515 (19.3)
Other Ig	162 (2.0)	64 (1.6)	19 (2.8)	8 (1.1)	71 (2.7)
Non-secretory	117 (1.4)	53 (1.3)	12 (1.8)	18 (2.5)	34 (1.3)
missing	*120 (1.5)*	*52 (1.3)*	*18 (2.6)*	*16 (2.2)*	*34 (1.3)*
Diagnosis-AHCT Interval median (IQR) months	7.1 (5.6-10.0)	6.7 (5.3-9.2)	8.3 (6.2-12.0)	6.9 (5.4-9.6)	7.7 (5.9-10.8)
Year of AHCT					
2013	1298 (15.7)	541 (13.0)	90 (13.1)	87 (12.0)	580 (21.4)
2014	1378 (16.7)	565 (13.6)	122 (17.7)	119 (16.4)	572 (21.1)
2015	1562 (18.9)	706 (17.0)	151 (21.9)	179 (24.7)	526 (19.4)
2016	1830 (22.1)	977 (23.6)	170 (24.7)	178 (24.5)	505 (18.7)
2017	2198 (26.6)	1357 (32.7)	156 (22.6)	163 (22.5)	522 (19.3)
Age at AHCT median	60.0	60.6	58.6	60.5	60.0
(IQR) years	(53.9-65.0)	(54.2-65.6)	(51.5-63.4)	(52.5-65.4)	(54.0-65.0)
(range) years	(20.2-82.4)	(20.2-82.4)	(21-75.3)	(30.3-79.3)	(25-77.8)
Disease status at AHCT					
CR	1620 (19.8)	671 (16.4)	228 (33.5)	165 (22.9)	556 (20.7)
VGPR	2961 (36.2)	1600 (39.2)	237 (34.9)	273 (37.9)	851 (31.6)
PR	3087 (37.8)	1602 (39.2)	170 (25.0)	247 (34.3)	1068 (39.7)
SD/MR	357 (4.4)	164 (4.0)	22 (3.2)	28 (3.9)	143 (5.3)
Rel/Prog/Prim. Refr.	135 (1.7)	44 (1.1)	23 (3.4)	6 (0.8)	62 (2.3)
Untreated	17 (0.2)	5 (0.1)		1 (0.1)	11 (0.4)
missing	*92 (1.1)*	*62 (1.5)*	*9 (1.3)*	*6 (0.8)*	*15 (0.6)*
Cytogenetics risk score at diagnosis					
Standard	4636 (77.8)	2108 (73.2)	255 (81.0)	290 (63.3)	1983 (85.8)
High	1325 (22.2)	770 (26.8)	60 (19.0)	168 (36.7)	327 (14.2)
missing	*2308 (27.9)*	*1270 (30.6)*	*374 (54.3)*	*268 (36.7)*	*396 (14.6)*
Karnofsky PS at AHCT					
100	2690 (34.1)	1237 (31.4)	257 (41.1)	199 (29.1)	997 (37.7)
≤90	5207 (65.9)	2708 (68.6)	368 (58.9)	485 (70.9)	1646 (62.3)
missing	*372 (4.5)*	*203 (4.9)*	*64 (9.3)*	*42 (5.8)*	*63 (2.3)*
HCT-CI risk group					
Low (0)	4535 (59.7)	2068 (54.9)	395 (68.1)	373 (56.9)	1699 (65.6)
Intermediate (1-2)	1753 (23.1)	900 (23.9)	136 (23.4)	168 (25.6)	549 (21.2)
High (≥ 3)	1309 (17.2)	802 (21.3)	49 (8.4)	115 (17.5)	343 (13.2)
missing	*672 (8.1)*	*378 (9.1)*	*109 (15.8)*	*70 (9.6)*	*115 (4.2)*
Conditioning					
Mel200	6119 (74.2)	3114 (75.3)	470 (68.2)	398 (55.0)	2137 (79.1)
Mel140	1132 (13.7)	591 (14.3)	98 (14.2)	134 (18.5)	309 (11.4)
Mel unknown dose	754 (9.1)	362 (8.8)	45 (6.5)	157 (21.7)	190 (7.0)
Other conditioning	243 (2.9)	68 (1.6)	76 (11.0)	34 (4.7)	65 (2.4)
Tandem protocol					
No	7535 (91.2)	3793 (91.5)	558 (81.0)	652 (89.8)	2532 (93.6)
es	731 (8.8)	353 (8.5)	131 (19.0)	74 (10.2)	173 (6.4)

Abbreviations: CR, complete response; VGPR, Very good partial response; PR, partial response; SD/MR, Stable disease/minimal response; Rel/Prog/Prim. Refr., Relapse/Progression/Primary Refractory; Mel200, Melphalan 200 mg/m^2; Mel140, melphalan 140 mg/m^2.

Table 2. Multivariable analysis of OS and PFS according to maintenance and disease stage at auto-HCT adjusted for other baseline variables included in the model. The hazard ratio's of maintenance therapy compared no maintenance are shown in Figure 2.

	OS (n=7,547)		PFS (n=7,008)	
	HR (95% CI)	**(Overall) p-value**	**HR (95% CI)**	**(Overall) p-value**
Maintenance		(<0.0001)		(<0.0001)
No maintenance	1.00		1.00	
Lenalidomide	0.57 (0.48-0.68)	<0.0001	0.65 (0.57-0.73)	<0.0001
Thalidomide	0.76 (0.58-1.00)	0.05	0.90 (0.75-1.09)	0.29
Bortezomib	0.65 (0.50-0.84)	0.001	0.93 (0.78-1.09)	0.36
Lenalidomide vs. thalidomide	*0.79 (0.61-1.02)*	*0.07*	*0.72 (0.60-0.85)*	*<0.0001*
Lenalidomide vs. bortezomib	*0.88 (0.69-1.11)*	*0.27*	*0.68 (0.59-0.79)*	*<0.0001*
Disease stage at AHCT		(<0.0001)		(<0.0001)
CR	1.00		1.00	
VGPR	1.32 (1.09-1.60)	0.004	1.23 (1.09-1.40)	0.0008
PR	1.63 (1.35-1.97)	<0.0001	1.59 (1.41-1.80)	<0.0001
SD/MR/Relapse/Progression	2.72 (2.10-3.50)	<0.0001	1.81 (1.50-2.19)	<0.0001
Age at AHCT (per 10 years older)	1.09 (1.01-1.17)	0.04	1.06 (1.01-1.11)	0.02
Year of AHCT (per year later)	1.01 (0.96-1.06)	0.71	0.97 (0.94-1.00)	0.08
Sex				
Male	1.00		1.00	
Female	0.88 (0.78-1.00)	0.05	0.91 (0.84-0.99)	0.02
Karnofsky PS at AHCT				
100	1.00		1.00	
≤90	1.23 (1.07-1.42)	0.004	1.01 (0.92-1.11)	0.79
MM classification		(<0.0001)		(0.007)
IgG	1.00		1.00	
IgA	1.33 (1.14-1.56)	0.0003	1.19 (1.07-1.33)	0.001
Light chain	1.00 (0.85-1.19)	0.96	1.14 (1.03-1.27)	0.02
Other Ig	2.23 (1.60-3.10)	<0.0001	1.41 (1.05-1.89)	0.02
Non-secretory	1.54 (0.92-2.59)	0.10	1.07 (0.74-1.54)	0.73
Conditioning dosage		(0.44)		(0.89)
Mel 200	1.00		1.00	
Mel 140	0.99 (0.83-1.18)	0.89	0.99 (0.88-1.12)	0.92
Other conditioning	0.77 (0.48-1.23)	0.50	0.99 (0.75-1.31)	0.95
ISS at diagnosis		(<0.0001)		(<0.0001)
I	1.00		1.00	
II	1.41 (1.18-1.70)	0.0002	1.28 (1.14-1.44)	<0.0001
III	2.38 (1.99-2.85)	<0.0001	1.80 (1.60-2.02)	<0.0001
Cytogenetics				
Normal risk	1.00		1.00	
High risk	2.17 (1.86-2.54)	<0.0001	1.63 (1.46-1.82)	<0.0001
HCT-CI at AHCT		(0.08)		(0.53)
Low risk (0)	1.00		1.00	
Intermediate risk (1-2)	1.01 (0.87-1.19)	0.87	1.06 (0.96-1.18)	0.23
High risk (≥3)	1.23 (1.01-1.46)	0.02	1.09 (0.97-1.23)	0.15

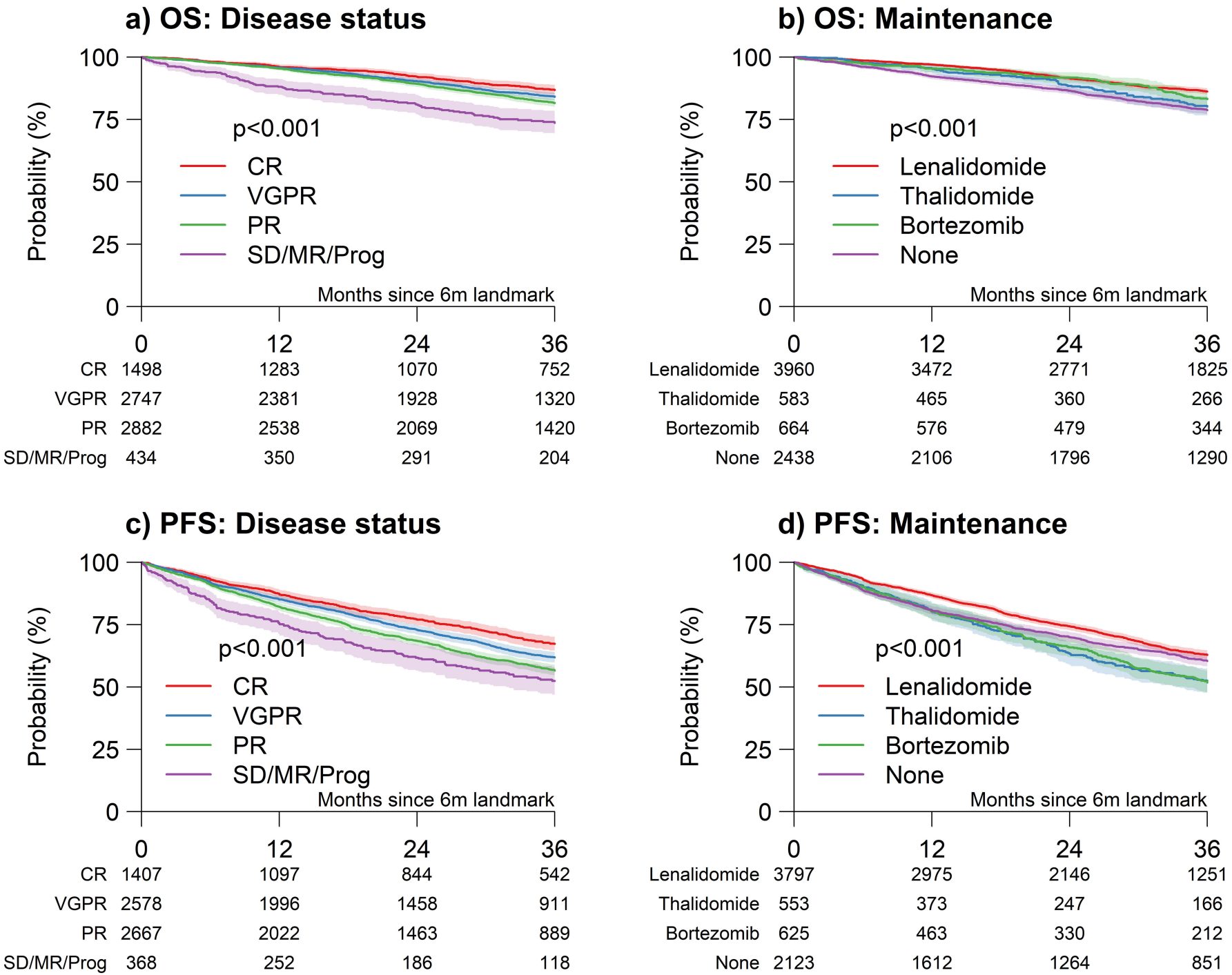
Models included a country specific random effect. Overall p-values were obtained using the likelihood ratio test and test whether in multicategorical variables associations between categories and the outcome in question are all the same. Missing values were modeled using a missing category (not shown in this table). Abbreviations: OS, Overall survival; PFS, progression-free survival; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; MR, minor response; Prog, progression; CI, confidence interval; PS, performance score; AHCT, autologous hematopoietic stem cell transplantation; HCT-CI, hematopoietic stem cell transplantation comorbidity index; ISS, International staging system; Ig, Immunoglobulin

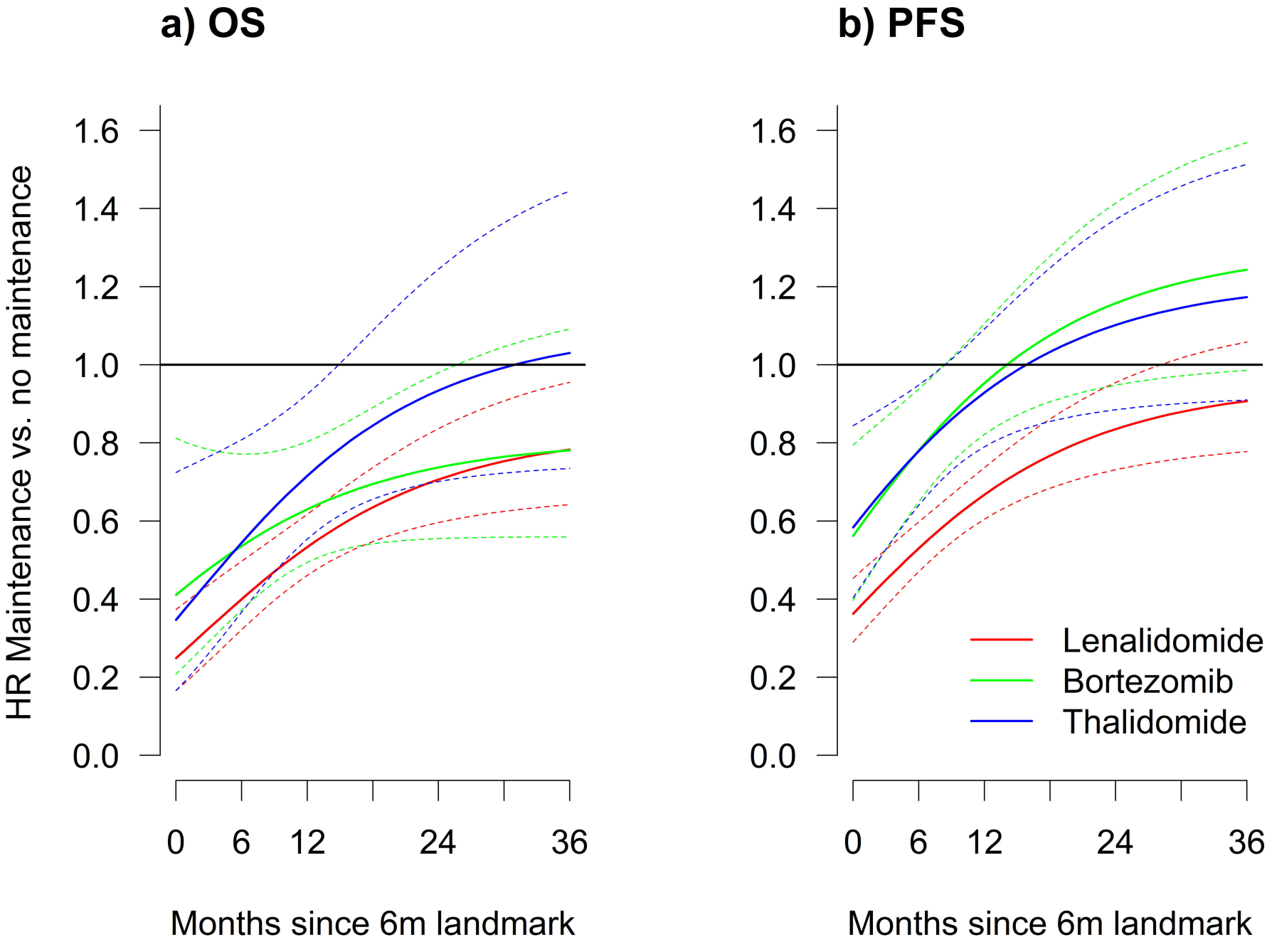
Legend to Figures.

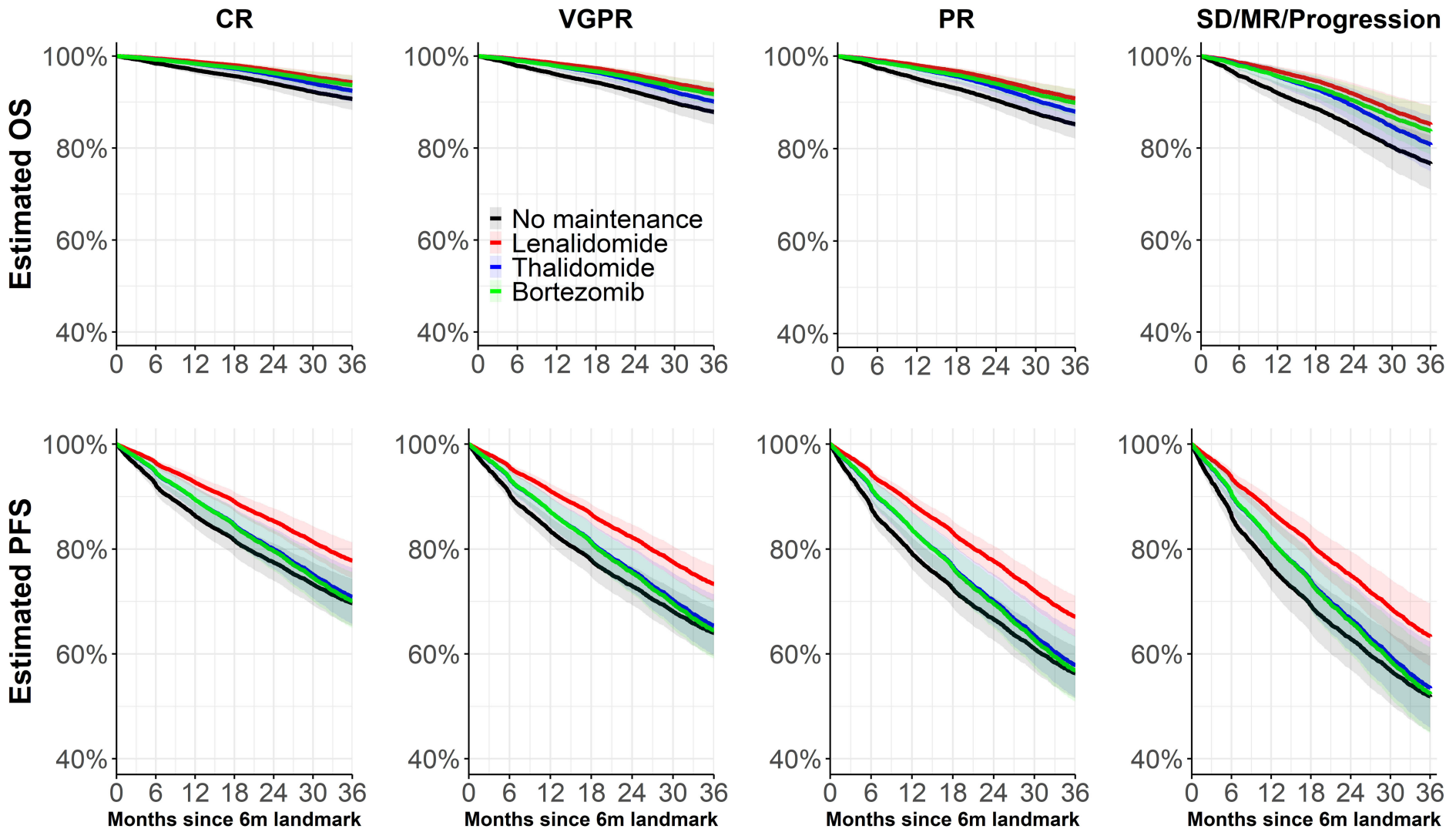
Figure 1. **Kaplan Meier-plots for overall survival (OS) and progression free survival (PFS): a) OS by Response/disease status at AHCT, b) OS by maintenance, c) PFS by Response/disease status at AHCT, and d) PFS by maintenance.** Shaded areas show the 95% confidence intervals. Numbers below the graphs show the number of patients still at risk. Abbreviations: AHCT, autologous hematopoietic stem cell transplantation, CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; MR, minor response; Prog, progression

Figure 2. **Time dependent hazard ratios of a) OS and b) PFS of maintenance therapies compared to no maintenance modelled over the follow-up period.** Dashed lines show the 95% confidence intervals.

Figure 3. **Predicted OS and PFS probabilities for reference patients receiving either lenalidomide, bortezomib, thalidomide or no maintenance according to disease stage at AHCT.** The predictions were made using the results presented in Table 2. We assumed the patient was a male MM patient, with standard cytogenetic risk score and an age of 60 years at AHCT (in 2017), KPS ≤90 at AHCT, IgG classification, conditioning with Mel 200, ISS I, a low risk HCT-CI and a country random effect of 0.


a) OS: Disease status
Probability (%)
100
75
50
25
0
p<0.001
CR
VGPR
PR
SD/MR/Prog
Months since 6m landmark
0
12
24
36
CR 1498 1283 1070 752
VGPR 2747 2381 1928 1320
PR 2882 2538 2069 1420
SD/MR/Prog 434 350 291 204
b) OS: Maintenance
Probability (%)
100
75
50
25
0
p<0.001
Lenalidomide
Thalidomide
Bortezomib
None
Months since 6m landmark
0
12
24
36
Lenalidomide 3960 3472 2771 1825
Thalidomide 583 465 360 266
Bortezomib 664 576 479 344
None 2438 2106 1796 1290
c) PFS: Disease status
Probability (%)
100
75
50
25
0
p<0.001
CR
VGPR
PR
SD/MR/Prog
Months since 6m landmark
0
12
24
36
CR 1407 1097 844 542
VGPR 2578 1996 1458 911
PR 2667 2022 1463 889
SD/MR/Prog 368 252 186 118
d) PFS: Maintenance
Probability (%)
100
75
50
25
0
p<0.001
Lenalidomide
Thalidomide
Bortezomib
None
Months since 6m landmark
0
12
24
36
Lenalidomide 3797 2975 2146 1251
Thalidomide 553 373 247 166
Bortezomib 625 463 330 212
None 2123 1612 1264 851


a) OS
b) PFS
HR Maintenance vs. no maintenance
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
6
12
24
36
Months since 6m landmark
Lenalidomide
Bortezomib
Thalidomide


CR
VGPR
PR
SD/MR/Progression
Estimated OS
Estimated PFS
100%
80%
60%
40%
0 6 12 18 24 30 36
No maintenance
Lenalidomide
Thalidomide
Bortezomib
Months since 6m landmark

Supplement:

Global Participating Registries

1. The European Society for Blood and Marrow Transplantation (EBMT; www.ebmt.org). Information on maintenance in this group did not distinguish between missing or no maintenance given, therefore none of the EBMT patients were included in the no maintenance category.

2. The Center for International Blood and Marrow Transplantation (CIBMTR; www.cibmtr.org), the United States of America (USA),

3. The Canada registry using the Ottawa Blood Disease Center MM Database (OBDCMMD),

4. Latin American Blood and Marrow Transplantation group (LABMT).

5. The Asian Pacific Blood and Marrow Transplant Group (APBMT; www.apbmt.org) with reporting registries

    a. Myeloma Transplant Registry, Ministry of Health, Malaysia (MTRMOHM)

    b. Japan Society for Transplantation and Cellular Therapy/ Japanese Data Center for Hematopoietic Cell Transplantation (JSTCT/JDCHCT)

    c. Taiwan Society of Blood and Marrow Transplantation (TBMT)

    d. Beijing Bone Marrow Transplant registry

6. Eastern Mediterranean Blood and Marrow Transplant Group (EMBMT).

Supplement to Methods

Variables included in multivariable analyses and their definitions

Apart from maintenance and disease stage at AHCT models included patient sex, International Staging System (ISS) at diagnosis, high-risk cytogenetic (t(4;14) and/or del 17p and/or t(14;16) and in Europe t(4;14) and/or del 17p and/or t(14;16) t(14;20) and/or hypodiploid and/or 1q gain and/or deletion 1p), myeloma sub-classification, year of AHCT, time from diagnosis to AHCT, Karnofsky performance status (KPS), HCT-specific comorbidity index (HCT-CI) and melphalan conditioning dose.

Regarding response status prior to AHCT, CR, very good partial response (VGPR), partial response (PR), minor response (MR)/stable disease (SD), and Rel / Prog were defined according to the International Myeloma Working Group criteria [11]. Conditioning was categorized as either melphalan 140 mg/m^2, 200 mg/m^2, and "others" if melphalan was used in combination with additional drugs. We included interaction terms between maintenance treatment and disease stage at AHCT in OS and PFS models to check whether the association of maintenance and outcome was similar across all disease stage. We analyzed whether the association between the maintenance and outcome was constant over time (the proportional hazards assumption) by including an interaction term between maintenance and follow-up time in the models using the tt function part of the coxph function in R. In these models the country random effect was first estimated without the time-dependent coefficients and subsequently included in models with time dependent coefficients as a fixed variable using the offset statement.

Supplemental Table S1

Registry Contribution

Maintenance	**All** n (%)	**Lenalidomide** n (%);	**Thalidomide** n (%)	**Bortezomib** n (%)	**No maintenance** n (%)
Total patients	8269 (100.0)	4148 (50.2)	689 (8.3)	726 (8.8)	2706 (32.7)
Patients alive at 6 months landmark	7645(100.0)	3960 (51.8)	583 (7.6)	664 (8.7)	2438 (31.9)
Japan	2866 (34.7)	756 (18.2)	17 (2.5)	96 (13.2)	1997 (73.8)
% of registry	*100.0*	*26.9*	*0.6*	*3.3*	*69.7*
EBMT	2691 (32.6)	1969 (47.5)	335 (48.6)	387 (53.3)	
% of registry	*100.0*	*(73.2)**	*(12.4)**	*(14.4)**	
CIBMTR	1841 (22.3)	1218 (29.4)	4 (0.6)	180 (24.8)	439 (16.2)
% of registry	*100.0*	*66.2*	*0.2*	*9.8*	*23.8*
EMBMT	54 (0.7)	37 (0.9)	9 (1.3)	8 (1.1)	
% of registry	*100.0*	68.5	16.7	14.8	
Taiwan	158 (1.9)	6 (0.1)	152 (22.1)		
% of registry	*100.0*	*3.8*	*96.2*		
LABMT	261 (3.2)	67 (1.6)	105 (15.2)	43 (5.9)	46 (1.7)
% of registry	*100.0*	*25.7*	*40.2*	*16.5*	*17.6*
Canada	168 (2.0)	75 (1.8)			93 (3.4)
% of registry	*100.0*	*44.6*			*55.4*
Malaysia	166 (2.0)	7 (0.2)	36 (5.2)	10 (1.4)	113 (4.2)
% of registry	*100.0*	*4.2*	*21.7*	*6.0*	*68.1*
China	61 (0.7)	11 (0.3)	31 (4.5)	2 (0.3)	17 (0.6)
% of registry	*100.0*	*18.0*	*50.8*	*3.3*	*27.9*

Abbreviations: AHCT, autologous hematopoietic cell transplantation; EBMT, European Bone Marrow Transplant; CIBMTR, Center for International Blood and Marrow Transplant; EMBMT, Eastern Mediterranean Blood and Marrow Transplantation; LABMT, Latin American Bone Marrow Transplantation;

Supplemental Table S2. Estimated OS, PFS and cumulative incidence of relapse and NRM at 3 year after 6 month landmark, according to maintenance groups and disease stage at auto-HCT. Log-rank p-values (OS and PFS) and Gray's test p-values (relapse and NRM) apply to the whole length of the curves, not just to the 3-year estimate.

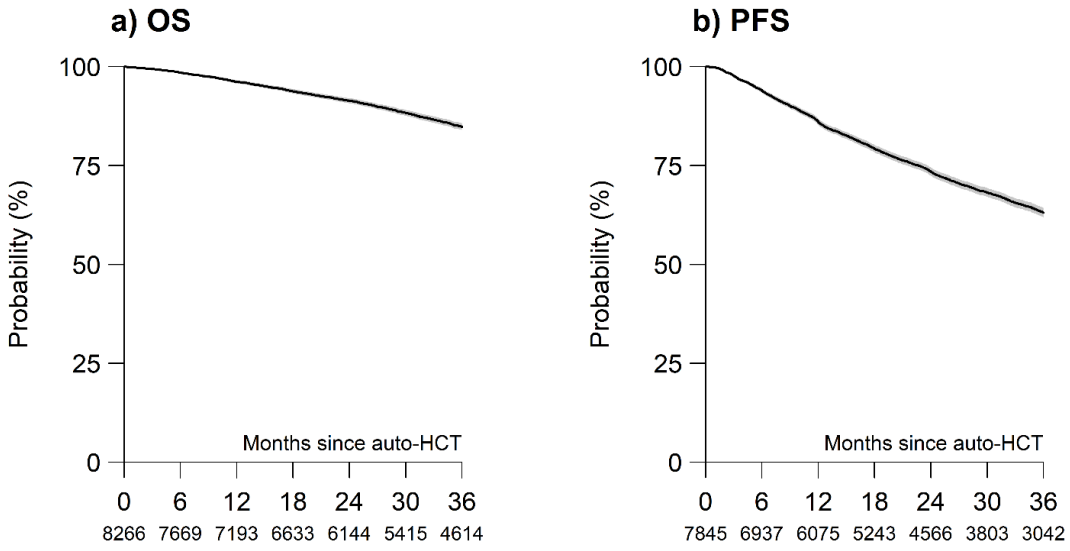
	Overall		CR		VGPR		PR		SD/MR/Prog	
	n	**% (95% CI)**	**n**	**% (95% CI)**	**n**	**% (95% CI)**	**n**	**% (95% CI)**	**n**	**% (95% CI)**
OS at 3 years										
Total	7645	83 (82-84)	1498	87 (85-89)	2747	84 (83-86)	2882	82 (80-83)	434	74 (69-78)
Lenalidomide	3960	86 (85-87)	634	91 (88-93)	1533	86 (84-88)	1539	85 (83-87)	196	81 (75-87)
Thalidomide	583	80 (76-84)	188	78 (70-85)	188	84 (78-90)	155	81 (74-88)	44	72 (56-87)
Bortezomib	664	83 (80-86)	154	89 (84-95)	245	85 (80-90)	229	77 (70-83)	32	86 (73-99)
None	2438	79 (77-80)	522	84 (81-88)	781	80 (76-83)	959	78 (75-81)	162	63 (55-71)
p-value		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**0.05**
PFS at 3 years										
Total	7098	60 (59-62)	1407	67 (64-70)	2578	62 (60-64)	2667	57 (54-59)	368	52 (47-58)
Lenalidomide	3797	63 (61-65)	612	70 (66-74)	1477	65 (62-68)	1467	59 (56-62)	186	57 (49-65)
Thalidomide	553	53 (48-57)	179	53 (44-62)	181	54 (45-62)	145	50 (42-59)	40	45 (28-63)
Bortezomib	625	52 (47-56)	150	71 (63-79)	233	50 (43-57)	209	41 (34-49)	30	48 (29-67)
None	2123	60 (58-63)	466	67 (63-72)	687	61 (57-65)	846	57 (54-61)	112	49 (39-59)
p-value		**<0.001**		**0.002**		**<0.001**		**<0.001**		0.30
Relapse cumulative incidence at 3 years										
Total	7098	36 (34-37)	1407	29 (26-32)	2578	35 (33-37)	2667	39 (37-41)	368	43 (38-49)
Lenalidomide	3797	34 (33-36)	612	28 (24-32)	1477	33 (30-36)	1467	38 (35-40)	186	44 (36-53)
Thalidomide	553	45 (40-49)	179	41 (32-49)	181	43 (35-52)	145	50 (41-58)	40	52 (34-70)
Bortezomib	625	45 (41-49)	150	27 (20-35)	233	45 (38-52)	209	56 (48-63)	30	57 (37-76)
None	2123	33 (31-35)	466	27 (22-31)	687	33 (29-37)	846	36 (32-39)	112	59 (45-74)
p-value		**<0.001**		**0.04**		**<0.001**		**<0.001**		0.30
NRM cumulative incidence at 3 years										
Total	7098	4 (3-5)	1407	4 (3-5)	2578	3 (3-4)	2667	5 (4-5)	368	4 (2-6)
Lenalidomide	3797	3 (2-3)	612	2 (1-4)	1477	2 (1-3)	1467	4 (3-5)	186	2 (0-5)
Thalidomide	553	3 (1-4)	179	7 (2-11)	181	3 (0-5)	145	0 (0-0)	40	0 (0-0)
Bortezomib	625	3 (2-5)	150	2 (0-4)	233	5 (2-7)	209	3 (0-6)	30	4 (0-11)
None	2123	6 (5-8)	466	6 (3-8)	687	6 (4-8)	846	7 (5-9)	112	9 (3-14)
p-value		**<0.001**		**0.01**		**<0.001**		**0.04**		**0.030**

Abbreviations: CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; MR, minor response; Prog, progression; CI, confidence interval; OS, overall survival; PFS, progression-free survival; NRM, non-relapse mortality.

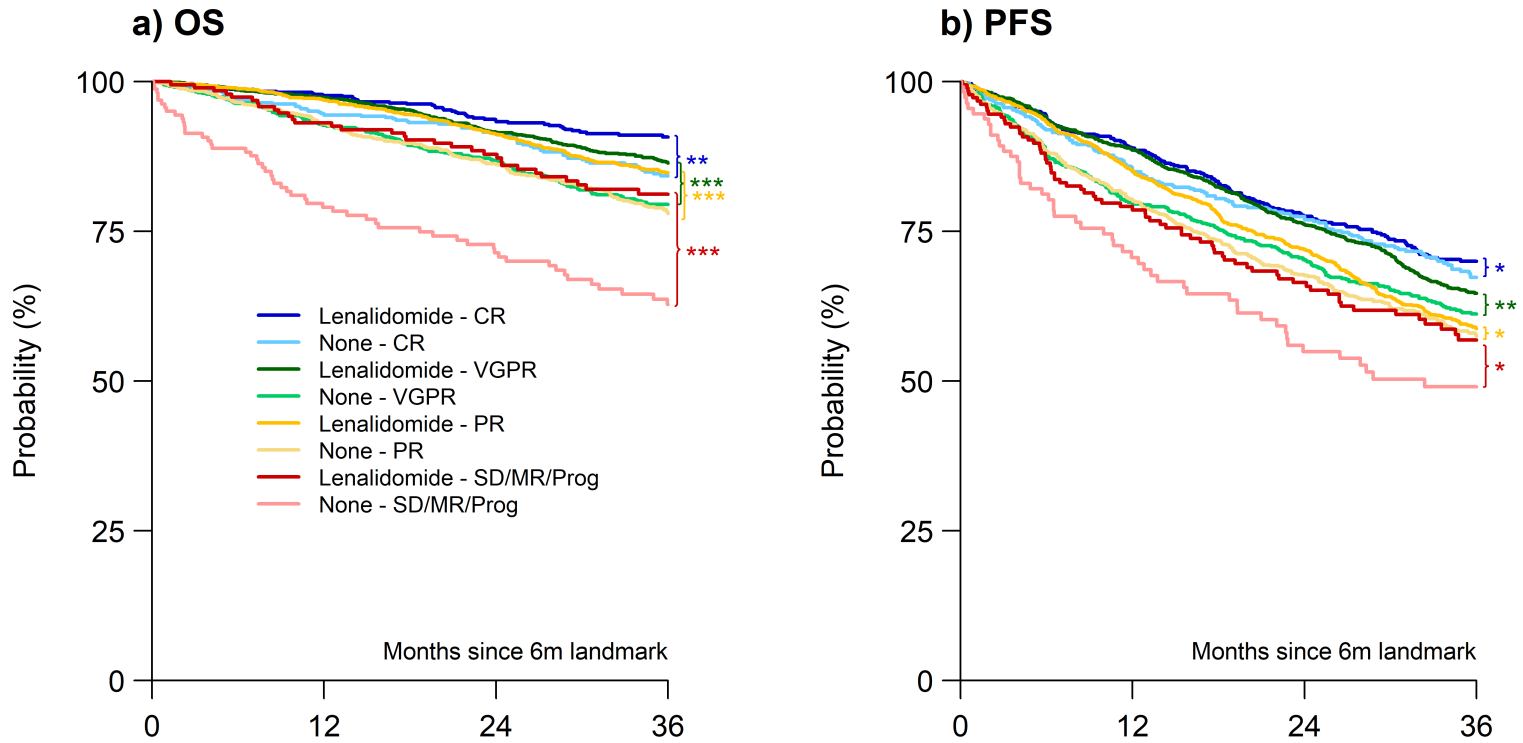
Supplemental Table S3. Time dependent hazard ratio's (HR) of maintenance therapies vs. no maintenance and 95% CI's after the 6-month landmark.

	Lenalidomide vs. no maintenance				Thalidomide vs. no maintenance				Bortezomib vs. no maintenance			
Time point after 6-month landmark	**OS HR (95% CI)**	**p-value* (<0.001)**	**PFS HR (95% CI)**	**p-value* (0.02)**	**OS HR (95% CI)**	**p-value* (0.04)**	**PFS HR (95% CI)**	**p-value* (0.01)**	**OS HR (95% CI)**	**p-value* (0.02)**	**PFS HR (95% CI)**	**p-value* (0.002)**
0 months	0.25 (0.17-0.37)	<0.001	0.36 (0.29-0.45)	<0.001	0.35 (0.17-0.72)	0.005	0.58 (0.40-0.84)	0.004	0.41 (0.21-0.81)	0.01	0.56 (0.40-0.79)	0.001
6 months	0.40 (0.32-0.50)	<0.001	0.53 (0.47-0.60)	<0.001	0.54 (0.37-0.81)	0.003	0.78 (0.64-0.95)	0.01	0.54 (0.37-0.77)	<0.001	0.78 (0.65-0.94)	0.009
12 months	0.53 (0.46-0.62)	<0.001	0.67 (0.60-0.74)	<0.001	0.72 (0.55-0.93)	0.01	0.93 (0.79-1.09)	0.37	0.63 (0.49-0.80)	<0.001	0.95 (0.82-1.11)	0.52
18 months	0.63 (0.55-0.74)	<0.001	0.77 (0.68-0.86)	<0.001	0.84 (0.66-1.09)	0.19	1.03 (0.85-1.25)	0.74	0.69 (0.54-0.89)	0.004	1.08 (0.91-1.28)	0.41
24 months	0.70 (0.60-0.84)	<0.001	0.84 (0.73-0.95)	0.008	0.93 (0.70-1.24)	0.64	1.10 (0.88-1.37)	0.39	0.74 (0.55-0.98)	0.04	1.16 (0.95-1.41)	0.15
30 months	0.75 (0.62-0.91)	0.003	0.88 (0.76-1.02)	0.08	0.99 (0.72-1.36)	0.96	1.15 (0.90-1.46)	0.27	0.76 (0.56-1.05)	0.09	1.21 (0.97-1.51)	0.09
36 months	0.78 (0.64-0.96)	0.02	0.91 (0.78-1.06)	0.22	1.03 (0.73-1.45)	0.86	1.17 (0.91-1.51)	0.22	0.78 (0.56-1.09)	0.15	1.24 (0.99-1.57)	0.07

Supplemental Figure S1. Overall survival (OS) and progression-free survival (PFS) after autologous hematopoietic stem cell transplantation. Numbers below the graph indicate the number at risk. Shaded areas the 95% confidence intervals.



Supplemental Figure S2. Landmark analysis of OS (a) and PFS (b) for maintenance lenalidomide vs no maintenance by IMWG response (***, p<0.001; **, p<0.05; *, p≥0.05). P-values apply to the whole length of the curve 0-36 months not just at 36 months. Numbers below the graphs show the number of patients still at risk.



	0	12	24	36
Lenalidomide - CR	634	561	467	317
None - CR	522	454	397	270
Lenalidomide - VGPR	1533	1343	1059	685
None - VGPR	781	683	578	431
Lenalidomide - PR	1539	1359	1075	712
None - PR	959	839	709	509
Lenalidomide - SD/MR/Prog	196	166	141	95
None - SD/MR/Prog	162	118	101	73

	0	12	24	36
Lenalidomide - CR	612	492	370	224
None - CR	466	367	300	195
Lenalidomide - VGPR	1477	1179	846	495
None - VGPR	687	522	412	293
Lenalidomide - PR	1467	1135	804	459
None - PR	846	642	493	322
Lenalidomide - SD/MR/Prog	186	133	102	61
None - SD/MR/Prog	112	71	51	37