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Efficacy and Tolerability of High- versus Low-dose Lenalidomide Maintenance Therapy of Multiple Myeloma after Autologous Blood Stem Cell Transplantation

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ABSTRACT

Purpose: For multiple myeloma, high-dose chemotherapy and autologous blood stem-cell transplantation (ASCT) followed by lenalidomide maintenance (LenMT) at 10–15 mg/day is considered standard of care. However, dose reductions due to side effects are common and median LenMT doses achieved over time may remain lower. Dose response during LenMT has never been investigated.

Patients and Methods: In a multicenter, randomized, open-label trial, patients with multiple myeloma after ASCT and high-dose lenalidomide consolidation therapy (CT) at 25 mg/day were randomized to receive LenMT at either 25 or 5 mg/day. Primary endpoint was progression-free survival (PFS).

Results: Ninety-four patients (median age, 58 years) were randomized to either arm, with 22% having International Staging System (ISS) stage 3 and 22% being in complete remission (CR). After median follow-up of 46.7 months, median doses of 14.5 and 5 mg/day were achieved in the two arms; 53% of dose reductions occurring during CT. In the high- and the low-dose arm, median PFS was 44.8 and 33.0 months (HR, 0.65; 95% CI, 0.44–0.97; $P = 0.032$), 36% and 23% of patients had stringent CR as best response ($P = 0.08$), and 4-year OS was 79% and 67% ($P = 0.16$), respectively. Hematologic toxicity, grade ≥3 neutropenia, and infections were initially more common with LenMT 25 mg, but decreased after dose adjustments. SPM incidence and quality-of-life (QoL) scores in both arms were similar.

Conclusions: LenMT dose correlated with efficacy and toxicity. High rates of dose reductions during CT argue against a high starting dose. However, continuous up- and down-titration for each patient to the current maximum tolerated dose is prudent.

Introduction

Multiple myeloma remains an incurable disease. However, "operational cure" can be achieved in a reasonable proportion of patients (1), particularly due to the introduction of novel agents and treatment combinations (2). High-dose chemotherapy (HDCT) followed by autologous stem-cell transplantation (ASCT) alongside novel agents for induction and maintenance is the current standard of care for newly diagnosed patients without comorbidities (3). HDCT achieves profound tumor cytoreduction and may induce minimal residual disease negativity, which is essential for long-term disease control (4). Maintenance therapy after ASCT is efficacious in prolonging remissions, but convenience and tolerability are also important because of the continuous treatment (5). Four randomized clinical trials revealed lenalidomide maintenance (LenMT) after ASCT to improve progression-free survival (PFS) in newly treated patients (6–9) and a meta-analysis demonstrated an OS benefit after a long-term follow-up of three of these studies (10). Still, questions concerning the dose and duration of LenMT after ASCT remain: The GMMG-MM5 study demonstrated that LenMT may be continued beyond complete remission (CR; ref. 11). However, whether LenMT should be given until disease progression or for a fixed duration still remains to be answered, once the results of the currently ongoing trials NCT01191060 and NCT01208662 become available (3). Prior to maintenance, studies so far have used short-term consolidation with 25-mg lenalidomide (LenCT; ref. 6), RVD (lenalidomide, bortezomib, dexamethasone; refs. 3, 12), second HDCT with second autologous ASCT (12) or no consolidation at all (7–9). The LenMT dose was either maintained at 10 mg throughout (8, 9, 13) or escalated to 15 mg depending on tolerability (3, 6, 7, 12) and doses were given either intermittently (for 21 days every 4 weeks; refs. 3, 8, 9, 13) or continuously (6, 7, 12). In addition, lenalidomide had to be temporarily halted in case of adverse events (AEs), reduced in dose or even permanently discontinued in a significant proportion of patients. As a result, the actually achieved maintenance doses considerably varied and amounted in the only two studies reporting those to 6.8 mg/day (7, 14) and 10 mg/day (11).

Meanwhile, a starting dose of 10 mg for LenMT is the agreed standard of care, although a dose-finding study for LenMT has actually never been undertaken. Therefore, we investigated a dose response in terms of survival during LenMT in a study population of feasible size, by comparing the efficacy and tolerability of two dose extremes, that is, 25 mg (arm A), commonly used for LenCT, as high dose and 5 mg (arm B), often used as lowest maintenance dose in case of required dose

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Translational Relevance

Although lenalidomide maintenance therapy (LenMT) of multiple myeloma is standard of care, the impact of the actual maintenance dose has never been investigated. By comparison of two extreme LenMT dose regimens, 25 and 5 mg/day, we revealed a dose response regarding efficacy and toxicity, but not quality of life. On the basis of our results, we recommend to start LenMT with standard-of-care 10 mg/day to avoid severe toxicity and to escalate the dose in the absence of toxicity to 15 mg/day or higher, if tolerated. In case of toxicities, the dose should be dropped or suspended, but treatment be resumed and the dose reescalated as soon as possible. Doses lower than tolerated to avoid toxicity beforehand are discouraged, based on inferior outcome. Rather than at any fixed target dose (10 or 15 mg/day), MT should be given at the current, maximum tolerated dose, personalized through continuous up- and down-titration.

reductions, as low dose. To avoid undertreatment in the low-dose arm, all patients received six cycles of 25-mg LenCT prior to LenMT.

Patients and Methods

Patients

Patients aged 18–75 years with an Eastern Cooperative Oncology Group performance status of 0–2 were eligible, if they had symptomatic and measurable multiple myeloma treated with HDCT (up to six cycles for induction and up to two cycles for mobilization) and ASCT as first-line therapy within 90–120 days from inclusion. Patients with progressive disease after HDCT were excluded; a second HDCT in case of less than very good partial remission (vgPR) or due to conditioning with intermediate-dose melphalan (if age was >65 years) were allowed. Lenalidomide as part of the induction treatment was excluded, not to bias dose response evaluation by potentially lenalidomide refractory patients. All patients provided written informed consent.

Study design and treatment

This was an investigator-initiated, randomized, open-label, phase III trial, conducted in six hospitals throughout Germany (Supplementary Figure 1). Patients were randomized (1:1) at study entry, 90–120 days after last HDT, to receive LenMT at daily doses of either 25 (arm A) or 5 mg/day (arm B). Randomization was stratified by International Staging System (ISS) stage (1 and 2 vs. 3) and age (≤ vs. >65 years) at diagnosis, and remission status at inclusion (CR/vgPR vs. minimal response/stable disease). After randomization, all patients started LenCT at 25 mg/day from day 1–21 every 28 days for 6 months prior to LenMT at the assigned dose, given at the same schedule, that is, for arm A the LenCT regimen was actually continued during LenMT (if not reduced during LenCT). In case of AEs, the dose was reduced in 5-mg steps. The dose in patients with renal insufficiency was adjusted according to their renal function. If the dose had to be adjusted during LenCT, patients in the 25-mg treatment arm continued LenMT with the adjusted dose and patients randomized to the 5-mg arm who discontinued LenCT were not restarted. For initiation of any new cycle, absolute neutrophil and platelet counts had to exceed 1,000 and 75,000/μL, respectively, and all AEs considered lenalidomide-related had to have resolved to grade ≤2. Treatment was administered until disease progression or undue toxicity. All patients received concomitant anticoagulation with aspirin (at 100 mg) or low-molecular-weight heparin. There was no recommendation for prophylactic antibiotic treatment. Erythroid growth factor support was generally excluded and G-CSF was allowed only short-term in case of severe neutropenic infection.

The study was in line with the Declaration of Helsinki and approved by the institutional review board in accordance with all federal and institutional guidelines.

Endpoints and assessments

The primary endpoint was PFS, defined as the time from randomization to progressive disease or death from any cause. Secondary endpoints included overall survival (OS), defined as time from randomization to death from any cause, and OS-2 defined as time from first PD to death from any cause, response rates, incidence of AEs and SPMs, feasibility, and quality-of-life (QoL).

For all patients on LenMT, response was assessed on a monthly basis, based on the criteria of the International Myeloma Working Group (15, 16). Bone marrow testing was only done in patients with at least CR. Patients who had discontinued study drug were followed up every 3 months, for either response or OS, in case of disease progression. AEs were assessed continuously using the NCI CTCAE (version 3.0) and QoL monthly using the EORTC QLQ-C30 questionnaire (version 3.0).

Statistical analysis

The study was supposed to include 194 patients over 39 months and to last for a minimum of 6 years, assuming a drop-out rate of 3%. This sample size had approximately 80% power to detect a superiority in PFS of the high-dose arm of 15% at 3 years from randomization, at a one-sided significance level of 0.05. Interim and final analyses were planned after 48 and 96 patients had developed disease progression with alpha error levels of 0.0031 and 0.049, respectively. As the interim analysis failed to reveal a significant difference for PFS ($P = 0.0053$), the study was continued until final analysis.

The median dose per cycle for LenCT or LenMT was calculated as the cumulative dose from baseline until disease progression/date of analysis divided by the number of cycles (including those with dose 0 mg in case of study drug discontinuation).

For the primary statistical analysis, two-sided log-rank tests were used. Survival functions were estimated using the Kaplan–Meier estimator. HRs were determined using Cox proportional hazard regression. *t* test and Fisher exact test were used to compare continuous and discrete variables, respectively, both two-sided. To assess the occurrence of SPM after randomization a competing risk model was used taking into account death as competing risk. For each patient, the time until either of the two occurred was determined and cumulative incidence curves were compared using the test of Gray. For all statistical analyses, R (version 3.2.4) was used. The statistical analyses were performed by KKS Düsseldorf, Germany and Bresmed, Sheffield, United Kingdom. All authors had access to the primary clinical trial data.

Results

From June 4, 2009 until February 1, 2015, 194 patients were enrolled and 188 randomized to LenMT with either 25 mg ($n = 94$, arm A) or 5 mg ($n = 94$, arm B) lenalidomide (**Fig. 1**).

Patients in both treatment arms did not show any significant difference at baseline, neither in patient characteristics (including cytogenetic information available for 40% of patients), nor in preceding therapy or remission rates after HDCT (**Table 1**).

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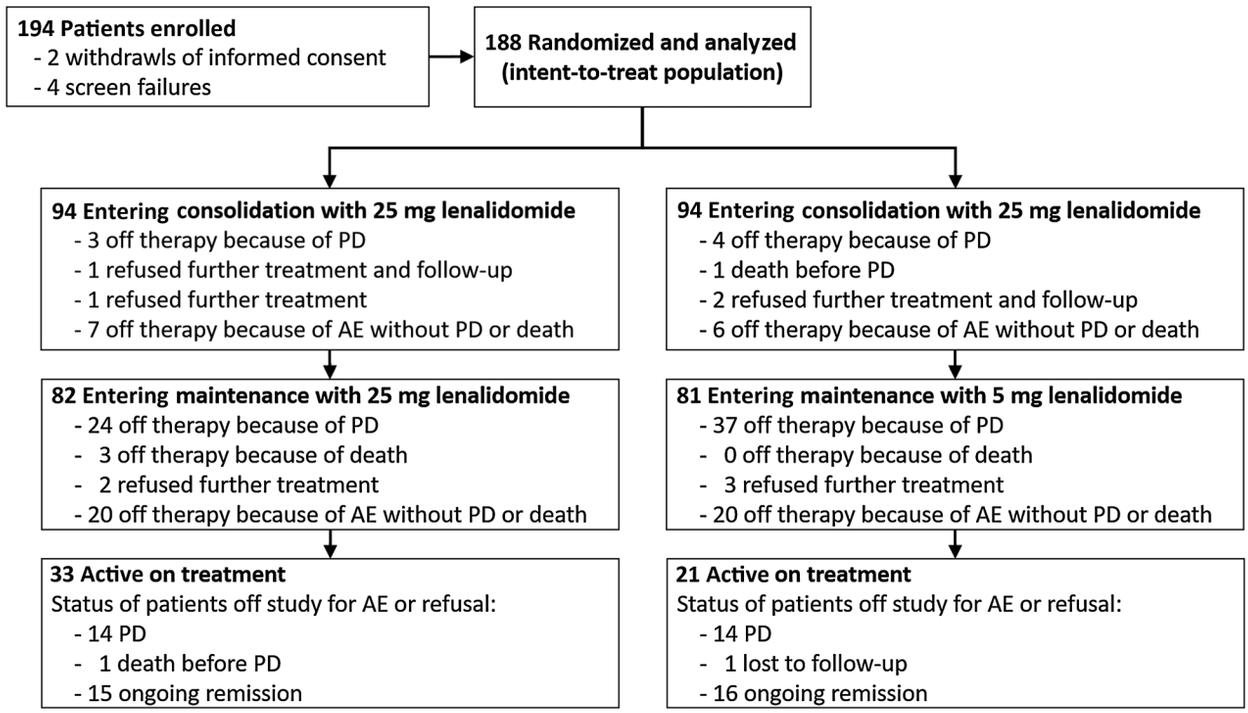

Figure 1.
CONSORT diagram.

Neither induction nor HDCT regimen had an impact on the primary endpoint (PFS) within each randomization arm ($P = 0.99$ and $P = 0.89$ for each arm, respectively; data not shown).

Feasibility of high-dose LenMT

The median follow-up for survival was 46.7 months (95% CI, 42.0–54.3), without significant differences between treatment arms [A: 42.5 (95% CI, 40.6–55.2) vs. B: 47.3 (95% CI, 42.0–56.1) months]. The median treatment duration was significantly longer in the 25-mg arm [26.8 (95% CI, 0.5–87) vs. 22.9 (95% CI, 0.3–69) months; $P = 0.01$; Supplementary Figure 2]. LenCT was completed by 178 patients, of whom 92% were still on study drug at the end of cycle 6, 66% at a dose of 20 to 25 mg (Supplementary Figure 3). After 1, 2, and 3 years of LenMT (i.e., 1.5, 2.5, and 3.5 years after initiation of lenalidomide, LenCT+LenMT), of the 94 patients in either arm, 72%, 44%, and 24% in arm A and 52%, 34%, and 15% in arm B were on lenalidomide, respectively (Supplementary Figure 3). Of all patients, who were still in remission corresponding proportions were 87%, 79%, and 71% in the 25-mg arm and 85%, 78%, and 61% in the 5-mg arm, respectively (Supplementary Figure 3). The median LenMT exposure until disease progression in the 25-mg arm was 14.5 mg/day (range: 0–25, 77% of expected exposure) versus 5 mg/day (range: 0–5) in the 5-mg arm ($P < 0.0001$).

Over the entire study period, 293 dose reductions were required, most commonly due to neutropenia (55.5%), thrombocytopenia (9.2%), and constitutional symptoms (7.1%). Fifty-three percent of dose reductions were during LenCT, 39% during LenMT in the 25-mg arm, and 8% in the 5-mg arm. Despite the higher need for dose reductions in the high-dose arm A, the percentage of patients who discontinued therapy for AE was not significantly different between arms [25 mg: 27 patients (29%) vs. 5 mg: 26 patients (28%); Supplementary Figure 2]. As per protocol, no growth factor support was allowed to avoid dose reductions; short-term G-CSF was used to treat neutropenic infections eight times in arm A and six times in arm B.

Survival

In total, 101 of 188 patients had progressive disease (PD): 45 in the 25-mg and 56 in the 5-mg arm (**Fig. 2A**). Median PFS in the 25-mg arm was 44.8 months versus 33.0 months in the 5-mg arm (HR, 0.65; 95% CI, 0.44–0.97; $P = 0.032$). The significant difference was confirmed by a landmark analysis in only those patients, who did not encounter an event during LenCT and who had received at least one dose of LenMT [median PFS, 25 mg: 44.4 months, $n = 82$ vs. 5 mg: 34.2 months, $n = 81$; HR, 0.63; 95% CI, 0.41–0.99; $P = 0.042$; **Fig. 3**). Subgroups of patients younger than 66 years, R-ISS stage 2+3 at diagnosis, and poor response after ASCT (≤PR) benefited from high-dose LenMT (Supplementary Figure 4).

At the study cutoff, 20 patients had died in the 25-mg arm versus 27 patients in the 5-mg arm (**Fig. 2B**; OS HR, 0.66; 95% CI, 0.37–1.18; $P = 0.16$). Median OS had not been reached in either treatment arm yet. OS-2 was either not significantly different (Supplementary Figure 5; HR, 0.99; 95% CI, 0.55–1.79; $P = 0.98$).

Response rates

After six cycles of LenCT, the overall rate of sCR significantly increased from 8% to 21% ($P = 0.0001$; **Table 2**) and 26% of all patients showed an improvement of response over time entering the next higher response category. During the first year of LenMT, 16% of patients in the 25-mg arm had an improvement of response as compared with 7% in the 5-mg arm ($P = 0.34$); in the second year, there were 5% and 3% of patients with an improved response, respectively ($P = 1.0$); and in the third year, only 1 patient still had

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Table 1. Patient characteristics and treatment at diagnosis (n = 188).

		A: 25 mg n = 94 (100%)	B: 5 mg n = 94 (100%)
Male sex		56 (60)	60 (64)
Age, years	Median (range)	58 (33–71)	58 (30–72)
	≤65	72 (77)	72 (77)
Subtype	IgG	56 (60)	54 (58)
	IgA	18 (20)	16 (17)
	LC	20 (21)	22 (23)
	Other	0 (0)	2 (2)
Durie Salmon stage	I	8 (9)	4 (4)
	II	8 (9)	13 (14)
	III	78 (82)	77 (82)
	A	78 (83)	78 (83)
	B	16 (17)	16 (17)
ISS-Stage	1	50 (54)	53 (57)
	2	25 (27)	19 (20)
	3	18 (19)	22 (23)
FISH cytogenetics	Standard risk	25 (27)	21 (22)
	High risk[a]	15 (16)	14 (15)
	Unknown	54 (57)	59 (63)
R-ISS stage	1	21(22)	17 (18)
	2	38 (41)	31 (33)
	3	3 (3)	9 (10)
	Unknown	32(34)	37 (39)
Chronic kidney disease, stage	1+2	68 (76)	63 (72)
	3	7 (8)	12 (14)
	4	4 (5)	4 (5)
	5, dialysis	10 (11)	8 (9)
Induction therapy containing bortezomib	Yes	76 (81)	80 (85)
	No	18 (19)	14 (15)
Number of induction cycles	Median (range)	3 (1–6)	3 (1–6)
High-dose melphalan regimen [mg/m^2]	200	57 (61)	45 (48)
	200 Tandem	22 (22)	35 (37)
	100 Tandem	15 (16)	14 (15)
Remission after HDCT	CR	14 (16)	24 (28)
	vgPR	45 (49)	38 (37)
	PR	28 (29)	30 (32)
	MR/SD	7 (6)	2 (3)
Diagnosis to baseline, months	Median (range)	10 (7–19)	11 (5–21)
ASCT to baseline (days)	Median (range)	114 (72–195)	117 (61–176)

Abbreviations: LC, Light chain; MR/SD, minimal response/stable disease.
[a]+1q (>3), t(4;14), t(14;16), del17p.

a response improvement. Best response during LenMT was sCR in 36% of patients in the 25-mg arm as compared with 23% in the 5-mg arm (P = 0.08; **Table 2**).

Safety and tolerability

Generally, more grade ≥3 AEs occurred in the 25-mg arm than in the 5-mg arm (87.5% vs. 64.6%; Supplementary Table 6). During LenCT, toxicity was mainly hematologic, with grade ≥3 neutropenia and thrombocytopenia in 39.0% and 8.9% of patients, respectively; grade ≥3 infections occurred in 12.0% of patients. During LenMT, neutropenia and infections were the most relevant clinical AEs, while nonhematologic toxicity occurred in a minority of patients (<6%) only. Grade ≥3 neutropenia was observed in the 25-mg arm in 34.6%, 24.3%, 12.8% during the first, second, and third year, respectively, whereas the incidence remained constant at about 9% of patients in the 5-mg arm. Incidence of grade ≥3 infections over the 3 years also decreased in the 25-mg arm (12.3%, 10.6%, and 7.7% of patients, respectively) and were lower, without any trend over time in the 5-mg arm (5.1%, 2.0%, and 3.1%, respectively).

In the 25-mg arm, three patients died during the study, one from fulminant pulmonary embolism (last dose 5 mg) and two from infections (last dose 15 mg), while in the 5-mg arm, one patient died from sudden death.

Second primary malignancies

After randomization, six new hematologic, seven solid tumor, and 12 nonmelanoma skin cancers were diagnosed among the 188 patients (25 mg: four, three, five vs. five mg: two, four, seven hematologic, solid tumor, and skin cancers, respectively). The cumulative incidence risks for developing SPM and their times to onset (on average 41 and 36 months, respectively) were not significantly different between both arms (Supplementary Figure 7).

QoL

The Global Health Status and Quality of Life (GHS/QoL) score and the utility score were both high at baseline and did not differ between both arms. During LenMT, none of the scores significantly decreased over time in either arm (Supplementary Figure 8).

Discussion

An important treatment goal for patients with newly diagnosed multiple myeloma is to achieve and maintain deep remission to achieve long-term disease control. Maintenance treatment after ASCT plays a key role in delaying time to relapse and prolonging survival (5). Currently, lenalidomide is the standard of care for maintenance treatment (17), based on proven prolongation of remission versus placebo or no maintenance (6–9) and a significant survival benefit (10). A meta-analysis on novel agent–based maintenance over the past 20 years also ascertained lenalidomide to be the best option based on PFS and OS (5). Still, the optimal dosing regimen for LenMT remains open. So far, studies have used a dose of 10 mg/day throughout 21 days every 4 weeks (8, 9, 13) or allowed dose escalation after 3 months to 15 mg/day (3, 6, 7, 12), with the dose being given either intermittently for 21 days every 4 weeks (3, 8, 9, 13) or continuously (6, 7, 12). Prior LenCT was either lacking (7–9) or comprised two cycles of 25-mg lenalidomide (6), two cycles of RVD (3, 12), or a second ASCT (6, 12).

Meanwhile, there is consensus to start LenMT with 10 mg/day and to escalate to 15 mg/day in case of good tolerability as recommended by the drug label. However, there is no real standard lenalidomide regimen and dosing over time has been at the discretion of the treating physician. Our study is the first showing that a high-dose LenMT regimen prolonged PFS on average by 1 year as compared with a low-dose LenMT treatment and was associated with a trend toward prolonged OS. On the downside, patients experienced a higher rate of hematologic AEs, but there was no sign of a higher incidence of SPM, inferior OS-2 or QoL, or higher treatment-related mortality. Thus, we

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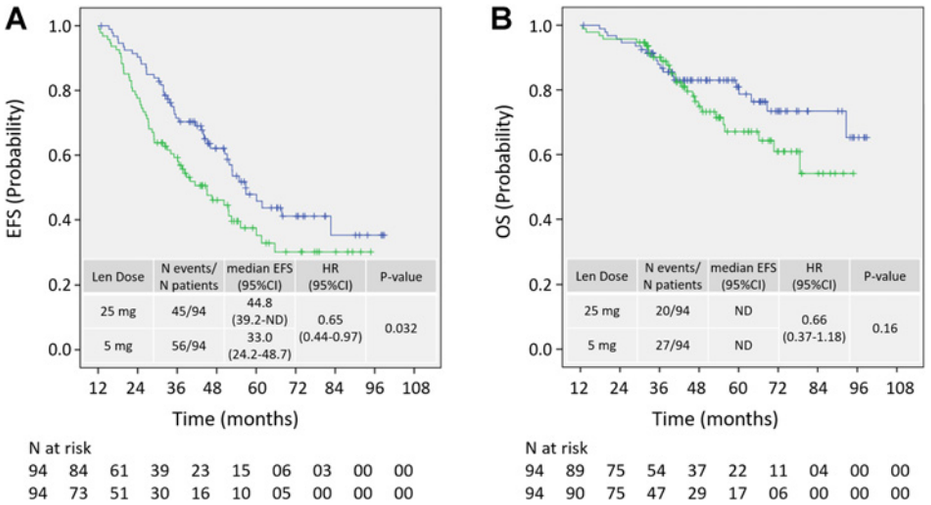

Figure 2.
PFS (**A**) and OS (**B**) from randomization in the 25-mg (blue) and 5-mg arm (green); ITT population, $n = 188$. Len, lenalidomide.

demonstrated that both efficacy in terms of PFS and hematologic toxicity of LenMT are dose-dependent.

Is there an optimal dose for LenMT?

In our study, dose reductions in the 25-mg arm were frequent and only 38%, 29%, and 15% of patients still in remission at the respective time point and 31%, 29%, and 15% of all patients enrolled in the high-dose arm were actually able to maintain a dose of 20–25 mg over 1.5, 2.5, and 3.5 years (LenCT + LenMT), respectively (Supplementary Figure 3). Percentages may still rise though, as 13% and 25% of all patients were in remission at the time of analysis and had not reached the 2.5 and 3.5 analysis time point yet. Looking at patients on study drug at any dose in the high-dose arm 72%, 44%, and 24% of patients were still treated after 1.5, 2.5, and 3.5 years. Our data are comparable with 70%, 54%, 34%, and 15% of patients after 1, 2, 3, and 4 years of LenMT at 10–15 mg starting dose, reported in a previous study (14). Consistently, none of the studies used growth factor support to avoid dose reductions. LenMT duration with the 25-mg dose in our study was also similar to that reported with 10–15 mg (median 26.8 vs. 28.0 months; ref. 14). In our study, median treatment duration in the high-dose group was significantly longer, most likely due to longer PFS, but discontinuation rates due to AEs were about the same in both arms. Definitely, a higher LenMT dose was not associated with a higher risk for early discontinuation or shorter treatment duration due to higher toxicity. Dose reductions and drug discontinuations are a common phenomenon in the maintenance setting and for many patients effective maintenance treatment is limited to 3–4 years due to decreasing tolerability (5). On the basis of the available data, there might not be one optimal dose, which could be determined in a dose-finding study and would fit all patients. In contrast, each patient may best be titrated specifically to his/her MTD. This titration may be a continuous process and the dose be fluctuating with changes (including both, reductions and reincreases) in the patient situation over the course of many years.

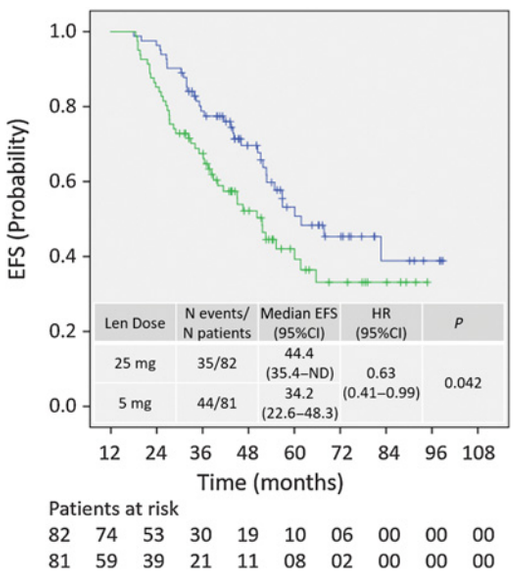

Figure 3.
Landmark analysis for PFS from start of lenalidomide maintenance therapy (25 mg, blue; 5 mg, green) of all patients who completed consolidation and had received at least one dose of LenMT. Len, lenalidomide.

How to achieve the individual LenMT dose?

Currently, the most common LenMT approach is to start with an intermediate dose of 10 mg, which may be increased to 15 mg, if tolerability allows (3, 6, 7, 12). In our study, we tested starting LenMT at 25 mg and keeping the dose high by reduction steps of only 5 mg in case of AEs versus using the lowest dose of 5 mg throughout. Of these two, the high-dose approach proved to be superior by clinically relevant prolongation of PFS. However, due to dose reductions, patients in the 25-mg arm actually achieved a median exposure of 14.5 mg/day only, which appears to comply well with the recommended standard dose of 15 mg/day for LenMT in the routine setting. However, the standard up-titration approach with the goal of achieving 15 mg/day is also subject to dose reductions and discontinuations (14). Detailed exposure data during LenMT in most published studies is lacking or poorly reported (3, 6, 8, 9, 12). In the CALGB 100104 study, which started at 10 mg and recommended escalation to 15 mg after 3 months, the median exposure over the whole duration of LenMT was 6.8 mg/day (7, 14); in the MM5 study targeting also 15 mg/day, it was about 10 mg/day (11). Thus, the down-titration approach applied in the high-dose arm of our study appears to have

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Table 2. Response rates in both treatment arms during the course of the study, number of patients (%).

Treatment arm	A: 25 mg						B: 5 mg					
After	RAND	LenCT	LenMT				RAND	LenCT	LenMT			
Time (years)	0	0.5	1	2	3	Best	0	0.5	1	2	3	Best
sCR	6 (6)	22 (23)	28 (30)	20 (21)	14 (15)	34 (36)	8 (9)	18 (19)	17 (18)	14 (15)	12 (13)	22 (23)
CR	9 (10)	11 (12)	12 (13)	7 (7)	4 (4)	13 (14)	18 (19)	20 (21)	16 (17)	12 (13)	6 (6)	23 (24)
vgPR	46 (49)	33 (35)	20 (21)	12 (13)	6 (6)	29 (31)	35 (37)	25 (27)	11 (12)	7 (7)	3 (3)	26 (28)
PR	27 (29)	20 (21)	13 (14)	10 (11)	5 (5)	15 (16)	30 (32)	23 (24)	13 (14)	7 (7)	2 (2)	22 (23)
MR or SD	6 (6)	4 (4)	4 (4)	3 (3)	2 (2)	3 (3)	3 (3)	2 (2)	1 (1)	1 (1)	0 (0)	1 (1)
Off study[a]	0 (0)	4 (4)	17 (17)	30 (32)	37 (39)	-	0 (0)	6 (6)	34 (35)	43 (46)	52 (56)	-
Active patients[b]	0 (0)	0 (0)	0 (0)	12 (13)	26 (28)	-	0 (0)	(0)	2 (2)	10 (10)	19 (20)	-

Abbreviations: (s)CR, (stringent) complete response; MR, minimal response; RAND, randomization; SD, stable disease.
[a]Off study because of progressive disease, death, or lost to follow up.
[b]Active patients in remission, who have not completed this time point at the time of analysis.

indeed resulted in the highest LenMT exposure reported so far. In this context, it is noteworthy, that in the two randomized studies reporting the longest duration of remissions, CALGB 100104 (7) and Myeloma XI (9), overall lenalidomide exposure is also likely to have exceeded that in other trials: in CALGB 100104, because reescalation in case of resolving toxicities was allowed, and in Myeloma XI, because the first 442 patients were also treated with 25-mg lenalidomide, before the dose was reduced per amendment. Altogether, there is evidence of a relationship between the LenMT dose and the duration of remission. Therefore, we recommend to attempt applying the highest tolerable dose per cycle.

Is the benefit–risk ratio in favor of high-dose LenMT?

The toxicity in our study was generally manageable and there was no need for routine growth factor support or prophylactic antibiotic treatment. More frequent grade ≥3 neutropenia during maintenance decreased over time, as did infections. The observed toxicity matched with incidences of grade ≥3 neutropenia (23%–55%) and infections (6%–13%) reported in other randomized trials (6–9, 12, 14). There was no sign of a dose-dependent increase in SPMs, although longer-term data are lacking. Therefore, with close patient monitoring and alertness especially of neutropenia, the benefit–risk ratio for a higher dose of LenMT should be positive as also supported by our QoL data, with high baseline scores for global health and utility being maintained throughout and without differences between treatment arms.

Limitations of study design

In this study, lenalidomide was excluded during induction therapy, which has meanwhile become current practice (mostly in combination with a proteasome inhibitor). In the CALGB 100104 study, patients benefited from LenMT, regardless of whether induction therapy included lenalidomide or not (7). However, a meta-analysis of LenMT trials revealed for patients with lenalidomide induction a better OS as compared with those without (10). Actually, the lacking lenalidomide induction in our study might have been outweighed by the consolidation therapy: one phase III trial with lenalidomide-based induction did not observe any benefit from subsequent consolidation with bortezomib, lenalidomide, and dexamethasone (12), while another phase III trial not using lenalidomide for induction did show a significant PFS benefit from lenalidomide-containing consolidation therapy (18). Notably, the difference in PFS between arms in our study was persistent, regardless of whether the analysis referred to the start of LenCT (**Fig. 2**) or of LenMT (**Fig. 3**). Even if the impact of neither the lacking lenalidomide induction nor the used consolidation regimen on survival outcome can be conclusively evaluated on the basis of our data, both appear unlikely to have affected the demonstrated dose response.

Subgroup analyses indicated that elderly patients (>65 years) with low-risk prognostic factors and good response after ASCT may not benefit from high-dose LenMT, that is, a frail patient subgroup may be exposed to high doses without need. Indeed, the trend for all three prognostic factors, that is, ISS, FISH cytogenetics, and R-ISS, was consistent and their association with the response after ASCT plausible. However, our study was not at all powered for such subgroup analyses and results for age were not robust. In addition, the rates of dose reductions and the incidence of AEs in the elderly were not considerably different (data not shown) and thus tolerability and feasibility of the high-dose regimen were comparable. Therefore, further studies are warranted to justify specific treatment recommendations for patient subgroups.

Should 25 mg/day become the recommended starting dose for LenMT?

Principally, the maximum tolerated individual dose might be achieved by up- or down-titration. In our study, consolidation with six cycles of 25-mg lenalidomide was feasible, no unexpected toxicity occurred, and 26% of patients improved their remission category. Starting with a high lenalidomide dose is more like a continuation of primary therapy than a mere MT. Bearing in mind that the depth of response is mostly a surrogate parameter for treatment outcome (4) further improving disease response within the first months after HDCT certainly argues for a higher starting dose. On the other hand, more than half of the dose reductions occurred during high-dose LenCT and the probability for infections remained higher during the following 3 months. Not all patients tolerated the high lenalidomide dose as evidenced by cytopenias during the initial treatment period. So as starting with a high lenalidomide dose does not seem to be practicable in all patients, our study results do not argue against the current state-of-the-art starting dose of 10 mg (9, 10, 12, 13, 19). However, our comparison of a toxicity-minimizing versus an efficacy-maximizing approach provides data supporting the notion that modulation of the starting dose in both directions is prudent. Additional studies may help to adapt our strategies to the changing nature of the therapeutic landscape, for example, in the context of two-drug maintenance regimen or to corroborate results for subgroups benefiting most.

Conclusion

Our study showed a dose dependence of both efficacy and toxicity of LenMT and that a higher dose regimen is feasible. However, the MTD varied among patients and therefore needs to be up- or down-titrated

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on an individual basis. Of note, for the time being, OS only showed a trend in favor of the high-dose treatment, but long-term follow-up may further endorse using high-dose LenMT from the outset.

Disclosure of Potential Conflicts of Interest

R. Fenk reports grants, personal fees, and non-financial support from Celgene and grants and personal fees from Amgen during the conduct of the study, as well as grants, personal fees, and non-financial support from Celgene, personal fees and non-financial support from Janssen and Bristol-Meyers, and personal fees from Amgen outside the submitted work. A. Giagounidis reports personal fees from Celgene Corp outside the submitted work. H. Goldschmidt reports grants, personal fees, non-financial support, and other from Amgen (advisory board paid to institution), BMS/Celgene (advisory board paid to institution), Chugai, Janssen (advisory board paid to institution), Sanofi (advisory board paid to institution); grants from Incyte and Molecular Partners; non-financial support from Merck, Sharp and Dohme (MSD), Mundipharma; non-financial support and other from Takeda (advisory board paid to institution), Novartis (advisory board paid to institution); other from Adaptive Biotechnology (advisory board paid to institution); and personal fees from GlaxoSmithKline (GSK) outside the submitted work. N. Kroger reports grants from Celgene outside the submitted work. A. Boquoi reports other from Amgen (travel, accommodation, expenses), Celgene (travel, accommodation, expenses), BMS (travel, accommodation, expenses), Janssen (travel, accommodation, expenses), and BMS (travel, accommodation, expenses) outside the submitted work. D. Lopez reports non-financial support from Celgene and personal fees from BMS outside the submitted work. E.K. Mai reports personal fees, non-financial support, and other from Janssen (travel grant), Takeda (travel grant), Celgene (travel grant); non-financial support and other from BMS (travel grant) and Mundipharma (travel grant) outside the submitted work. G. Kobbe reports grants and non-financial support from Celgene and grants from Amgen during the conduct of the study, as well as grants and personal fees from Celgene and personal fees from Amgen, Abbvie, Pfizer, Medac, Roche, BMS, MSD, Jazz, Novartis, and Biotest outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

R. Fenk: Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing-original draft, project administration, writing-review and editing. **A. Giagounidis:** Resources, investigation, writing-review and editing. **H. Goldschmidt:** Resources, investigation, writing-review and editing. **M. Heinsch:** Resources, investigation, writing-review and editing. **M. Rummel:** Resources, investigation, writing-review and editing. **N. Kroger:** Resources, investigation, writing-review and editing. **A. Boquoi:** Resources, investigation, writing-review and editing. **D. Lopez:** Resources, investigation, writing-review and editing. **C. Gerrlich:** Resources, investigation, writing-review and editing. **J. Baier:** Resources, investigation, writing-review and editing. **S. Liesenjohann:** Resources, investigation, writing-review and editing. **K. Hauck:** Resources, investigation, writing-review and editing. **I. Savickaite:** Resources, investigation, writing-review and editing. **E.K. Mai:** Resources, investigation, writing-review and editing. **C. Aul:** Resources, investigation, writing-review and editing. **J. Strapatsas:** Resources, investigation, writing-review and editing. **A. Dienst:** Resources, investigation, writing-review and editing. **M. Kondakci:** Resources, investigation, writing-review and editing. **R. Haas:** Resources, investigation, writing-review and editing. **G. Kobbe:** Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing-original draft, project administration, writing-review and editing.

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