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Lenalidomide in combination with dexamethasone improves survival and time-to-progression in patients ≥ 65 years old with relapsed or refractory multiple myeloma

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Abstract

Two pivotal, phase III, randomised, placebo-controlled, registration trials (MM-009 and MM-010) showed that lenalidomide plus dexamethasone was more effective than placebo plus dexamethasone in the treatment of patients with relapsed or refractory multiple myeloma. This pooled, retrospective subanalysis of MM-009 and MM-010 analysed outcomes according to patient age. A total of 704 patients (390 aged <65 years, 232 aged 65–74 years, and 82 aged 75 years) received lenalidomide or placebo, both in combination with dexamethasone. The overall response rate (ORR) was significantly higher in patients treated with lenalidomide plus dexamethasone versus placebo plus dexamethasone in all age groups ($P < 0.0001$ for all). Median progression-free survival (PFS) and median time-to-progression (TTP) were similar, and both were significantly longer with lenalidomide plus dexamethasone in all age groups ($P < 0.001$ for all). Median overall survival (OS) favoured lenalidomide plus dexamethasone in all age groups,

although the difference was not statistically significant. Adverse events of anaemia, febrile neutropenia, deep-vein thrombosis, neuropathy, and gastrointestinal disorders increased with age. Lenalidomide combined with dexamethasone improved the ORR and prolonged PFS, TTP, and OS compared with placebo plus dexamethasone, irrespective of age. This finding was consistent with the overall MM-009 and MM-010 populations.

Keywords

Lenalidomide; Elderly; Multiple myeloma; Relapsed; Refractory

Introduction

Multiple myeloma (MM) is predominantly a disease of the elderly [1]. According to Surveillance, Epidemiology and End Results (SEER) Program data, the age-adjusted incidence of MM in 2007 was approximately 29 per 100,000 of the population aged ≥ 65 years, compared with 2 per 100,000 of the population aged <65 years. The incidence increased to 33 per 100,000 of the population aged ≥ 75 years [2]. It is likely that clinicians will continue to encounter a growing proportion of elderly patients with MM as life-expectancy lengthens and as diagnosis improves with non-invasive testing for serum monoclonal protein (M-protein) [1].

It is well recognised that advanced age is an important poor prognostic factor among patients with MM [3–5]. Factors contributing to poor survival in elderly patients include multiple comorbidities, poor performance status at diagnosis, decreased physiological reserve, limited social support, referral bias, under-treatment, and low expectations of treatment success (both real and perceived) [1, 6]. Elderly patients with relapsed or refractory MM are vulnerable to increased treatment-emergent adverse effects and poor tolerability, both of which can compromise treatment efficacy and adequate disease control [1]. For this reason, therapeutic options for elderly patients remain limited. Further studies are needed to understand the efficacy and safety of treatments for MM in the elderly, as well as the effect of these therapies on quality of life in this important group of patients [1].

Lenalidomide is an IMiD® (Celgene Corporation, New Jersey, USA) immunomodulatory compound that has tumoricidal and immunomodulatory activity in MM [7]. It is approved for use in >50 countries in combination with dexamethasone in patients with MM who have received at least one prior therapy. Approval was based primarily on the results of two pivotal phase III registration studies in relapsed or refractory MM patients (MM-009 and MM-010), which demonstrated that the addition of lenalidomide to dexamethasone (Len + Dex) significantly improved time-to-progression (TTP), overall survival (OS), and overall response rates (ORR) [8, 9]. In a pooled analysis of data from both studies, the median TTP was 13.4 months with Len + Dex and 4.6 months with placebo plus dexamethasone (Placebo + Dex; $P < 0.001$) [10]. Len + Dex also achieved a significantly higher ORR (60.6 vs. 21.9 %; $P < 0.001$), complete response (CR) rate (15.0 vs. 2.0 %; $P < 0.001$), and duration of response (15.8 vs. 7.0 months; $P < 0.001$). With an extended follow-up period of 48 months, the median OS was 38.0 months with Len + Dex and 31.6 months with Placebo + Dex ($P = 0.045$). This survival benefit was observed despite a crossover of 47.6 % of patients from Placebo + Dex to lenalidomide-based treatment at disease progression or unblinding [10].

Here, we report on a pooled analysis of these two trials, which investigated the impact of age (<65, 65–74, or ≥ 75 years) on the efficacy and safety of Len + Dex using an extended follow-up for survival (median 48 months for surviving patients).

Methods

Study design

Data were analysed from 704 patients with relapsed or refractory MM, enrolled in two randomised, double-blind, placebo-controlled, multicentre studies (MM-009 and MM-010) [8, 9]. The design of the two studies was similar and both trials used identical recruitment criteria. MM-009 was conducted in the USA and Canada, and MM-010 was conducted in Europe, Israel, and Australia.

Response rate was assessed according to the international uniform response criteria for multiple myeloma [11]. OS was calculated as time from randomisation until death from any cause. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 [12].

Key eligibility criteria

Patients were eligible if aged >18 years with progressive MM after at least one previous treatment regimen that was sensitive to high dose dexamethasone. All patients had relapsed or refractory MM, with measurable disease (defined as a serum M-protein level of ≥ 0.5 g/dl or a urine Bence-Jones protein level of ≥ 0.2 g/day) and had failed at least one prior therapy for MM. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 , serum aspartate aminotransferase or alanine aminotransferase levels of $\leq 3 \times$ the upper limit of normal (ULN), serum bilirubin levels of $\leq 2 \times$ the ULN, serum creatinine levels of < 2.5 mg/dl, an absolute neutrophil count of ≥ 1000 cells/mm³, and a platelet count of $> 75,000$ /mm³ for patients with < 50 % bone marrow plasma cells or $> 30,000$ /mm³ for patients with ≥ 50 % bone marrow plasma cells.

Treatment

Patients were randomised to receive oral lenalidomide (25 mg per day) or placebo on days 1–21 of each 28-day cycle. Both groups received oral dexamethasone (40 mg per day) on days 1–4, 9–12, and 17–20 of each 28-day cycle; after four cycles, dexamethasone was administered on days 1–4 only [8, 9]. Treatment was continued until disease progression or unacceptable toxicity. At the time of progression, patients assigned to placebo plus dexamethasone were allowed to cross over and receive lenalidomide plus dexamethasone.

Assessment of endpoints

A CR was defined as complete disappearance of serum and urine M-protein by immunofixation (confirmed by 2 measurements) and > 5 % bone marrow plasma cells. Near CR (nCR) was defined as a CR without a confirmed decrease in bone marrow plasma cells to < 5 % and/or without a confirmed disappearance of M-protein in serum and/or urine by repeated immunofixation. Partial response (PR) was defined as a reduction of M-protein by ≥ 50 % in serum and/or ≥ 90 % in urine, confirmed by at least two electro-phoretic measurements. Progressive disease was defined as any of the following: an absolute increase of serum M-protein > 500 mg/dl compared with the nadir, an absolute increase in urine M-protein of > 200 mg/24 h, new bone lesions or plasmacytomas or an increase in size, or development of hypercalcaemia (serum calcium > 11.5 mg/dl).

Response rates, TTP, and progression-free survival (PFS) were based on data obtained at unblinding of the phase III MM-009 and MM-010 trials, which occurred in June 2005 and August 2005, respectively. OS was based on updated pooled data analysis at an extended median follow-up of 48 months in surviving patients at unblinding. The reported incidences of adverse events in the placebo plus dexamethasone group reflect events that occurred

during treatment with placebo plus dexamethasone only (i.e., not after the time of progression and possible crossover to lenalidomide plus dexamethasone).

Statistical analysis

PFS, TTP, and OS were estimated using Kaplan–Meier methodology. A Cox proportional-hazards regression model of PFS was used to assess the significance of demographic and prognostic variables on relative treatment differences. An unstratified log-rank test was used to compare the time-to-event variables between treatment arms. Differences in response rates were assessed using the Cochran–Mantel–Haenszel test. All *P* values were two-sided with statistical significance evaluated at the 0.05 alpha level and 95 % confidence intervals (95 % CIs) were calculated to assess the precision of the obtained estimates. Analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC, USA) and Stata Version 8.0 (Stata Corporation, College Station, TX, USA).

Results

Patient characteristics

Baseline patient characteristics are listed in Table 1. Of the 704 patients enrolled in MM-009 and MM-010, 390 were aged <65 years, 232 were aged 65–74 years, and 82 were aged ≥75 years. The median time since diagnosis was generally similar in all age groups (median range 2.8–3.7 years). The distribution of disease stages according to Durie-Salmon and International Staging System classification was also comparable among all age groups. The prevalence of unfavourable baseline characteristics, such as poor ECOG performance status, immunoglobulin (Ig)A disease, and increased β_2 -microglobulin level, increased with age. The number of prior antimyeloma therapies was similar in patients aged <65 years and 65–74 years, but was increased in patients aged ≥75 years. The type of prior therapy also differed among age groups: patients aged ≥75 years were more likely to have received prior melphalan, whereas patients aged <65 years were more likely to have undergone prior stem cell transplantation.

Response

Response rates according to age category, risk factors, and treatment group are listed in Table 2. The ORR (CR, nCR, and PR) was significantly higher in patients treated with Len + Dex than in patients treated with Placebo + Dex in both older and younger patients (<65 years, 60.9 vs. 21.7 %; 65–74 years, 54.2 vs. 21.0 %; and ≥75 years, 69.8 vs. 20.5 %; *P* < 0.0001 for all). Analysis of ORR in subsets of patients based on known prognostic factors within each age group demonstrated the benefit of Len + Dex within subgroups by disease stage, performance status, IgA disease, or β_2 -microglobulin level over Placebo + Dex. Patients treated at first relapse appeared to have higher ORRs than those who had received multiple prior lines of therapy, regardless of age. Overall, the type of previous treatment, including prior thalidomide or dexamethasone, did not appear to influence the efficacy advantage of Len + Dex over Placebo + Dex in any age group [13] and this observation continued to be true in this patient population.

Progression-free survival, time-to-progression, and overall survival

Len + Dex was associated with longer median PFS compared with Placebo + Dex in all age groups. In patients aged <65 years the median PFS was 11.1 versus 4.6 months, respectively (hazard ratio [HR] 2.82, 95 % CI 2.16–3.67). In those aged 65–74 years the median PFS was 9.4 versus 4.6 months, respectively (HR 2.67, 95 % CI 1.87–3.81). Finally, in patients aged ≥75 years the median PFS was 14.1 versus 3.8 months, respectively (HR 3.91, 95 % CI 2.08–7.34; *P* < 0.001 for all comparisons) (Fig. 1; Table 3). Len + Dex was also associated

with a significantly longer median TTP compared with Placebo + Dex in all age groups. The median TTP in patients <65 years was 11.3 versus 4.6 months, respectively (HR 3.21, 95 % CI 2.43–4.24). In patients aged 65–74 years, the median TTP was 13.8 versus 4.6 months, respectively (HR 3.25, 95 % CI 2.21–4.80) and in those aged ≥75 years the median TTP was 15.1 versus 4.6 months, respectively (HR 4.13, 95 % CI 2.11–8.10). The comparisons between Len + Dex and Placebo + Dex were highly significant in all age groups ($P < 0.001$) (Table 3).

For OS, the results favoured Len + Dex compared with Placebo + Dex in all age groups, but the difference between treatment groups was not statistically significant in any age group (Table 3).

Tolerability and adverse events

Age did not appear to influence the incidence of haematological adverse events, with the exception of anaemia, which was more common in patients aged ≥75 years, regardless of treatment (Table 4). In all age groups, grade 3 or 4 neutropenia was more common with Len + Dex compared with Placebo + Dex. With Len + Dex, the incidence of febrile neutropenia was <5 % even in the older age category of ≥75 years. With regard to herpes zoster virus infection, there was no clear pattern of incidence related to lenalidomide use or patient age.

For non-haematological adverse events, the incidence of thromboembolism, neuropathy, and gastrointestinal disorders increased with age (Table 4). Grade 3 or 4 thromboembolism and neuropathy were more common with Len + Dex than with Placebo + Dex. A higher proportion of patients aged ≥75 had lenalidomide dose reductions compared with those aged <65 and 65–74 years (30.3, 41.5, and 48.8 % in the <65, 65–74, and ≥75 years age groups, respectively). Patients were evaluated for adverse events at each visit and the NCI CTC was used as a guide for the grading of severity. Dose reductions were mandated for grade 3 or 4 neutropenia, thrombocytopenia (platelet count <30,000/mm³), or other grade 3 or 4 toxicity deemed likely to be related to lenalidomide treatment. Based on these specific protocol-defined reasons for dose reduction, 95 % or more of the dose reductions in each age group were in response to adverse events. Other than to identify which dose reductions were due to an adverse event, the specific adverse event that led to the dose reduction was not coded in the review.

Dose reductions were made earlier in patients aged ≥65 years, with the first reductions occurring after a median of 4.3, 2.6, and 2.6 months in the <65, 65–74, and ≥75 years age groups, respectively. This was reflected by the median lenalidomide dose received by each age group. Those aged <65 years received a median of 23.0 mg lenalidomide, compared with 19.4 and 18.8 mg in those aged 65–74 and ≥75 years, respectively (Table 5).

Discussion

In patients with relapsed or refractory MM, lenalidomide in combination with dexamethasone has shown significantly greater clinical activity than Placebo + Dex [8, 9]. The current analysis demonstrated that the clinical benefit of Len + Dex over Placebo + Dex can be achieved regardless of patient age. A significant increase in ORR, PFS, and TTP was seen with Len + Dex compared with Placebo + Dex, even in patients aged ≥75 years.

In our analysis, the ORR with Len + Dex was similarly high in all age groups (range 54–70 %) and significantly higher than those achieved with Placebo + Dex in respective subgroups (range 21–22 %). The time-to-response and duration of response were not adversely affected by advanced age. These results compare favourably to those achieved in a similar patient

population treated with bortezomib in which the ORRs were 38 and 40 % for patients aged <65 and ≥ 65 years, respectively [14].

PFS was significantly longer with Len + Dex than with Placebo + Dex in all age groups (HRs 2.82, 2.67, and 3.91 for those aged <65, 65–74, and ≥ 75 years, respectively). Similarly, TTP was significantly longer with Len + Dex than Placebo + Dex in all age groups (HRs 3.21, 3.25, and 4.13 for those aged <65, 65–74, and ≥ 75 years, respectively). The similarity between PFS and TTP in the Len + Dex groups highlights the tolerability of this regimen.

These data indicate a trend towards improved OS with Len + Dex in each age group, although the difference between treatment groups did not reach statistical significance, possibly as a result of crossover to lenalidomide-based therapy at the time of progression [10]. Advanced age is generally considered a poor prognostic factor for OS in myeloma patients [3–5]. In a cohort study of unselected newly diagnosed MM patients reported by Kyle et al. [3], the median OS for the whole group was 33 months, but was significantly worse in those aged ≥ 70 years (26.4 months) compared with those aged <70 years (40.5 months; $P < 0.001$).

In a retrospective study, Gay et al. [15] compared the efficacy and safety of Len + Dex or combination lenalidomide, melphalan, and prednisone (MPR), in elderly patients (aged ≥ 65 years) with newly diagnosed MM. Two-year OS rates were 86.2 and 89.1 % with MPR and Len + Dex, respectively ($P = 0.730$), demonstrating efficacy of both lenalidomide-containing regimens in the treatment of elderly patients [15].

In our study of patients with relapsed or refractory MM, median OS also appeared to decrease slightly with increasing age, regardless of treatment. However, the median OS with Len + Dex was an encouraging 33.3 months in patients aged 65–74 years and 34.3 months in those aged ≥ 75 years.

The primary adverse events associated with Len + Dex are myelosuppression and thromboembolism, both of which can be managed with appropriate intervention, including prophylaxis, careful monitoring, and dose modifications as necessary [8, 9]. The incidence of herpes zoster infection did not appear to be related to lenalidomide use in this population, and advanced age was not associated with an increased risk of infection. Patients with advanced age should be monitored carefully for signs of infection [16], but routine herpes zoster virus prophylaxis does not appear to be warranted with lenalidomide therapy. The increased incidence of anaemia and deep-vein thrombosis in patients aged ≥ 75 years treated with Len + Dex underscores the importance of adequate management of cytopenias and thromboembolism risk in elderly patients with relapsed or refractory MM. Older patients were more likely to require lenalidomide dose modifications and received a lower median dose of lenalidomide, compared with younger patients. Our data provide no indication that the increased need for dose reductions in older patients limited the beneficial effects of lenalidomide therapy. This is consistent with another recent subanalysis of MM-009/010 data that assessed the effects of treatment duration on PFS [17]. Among patients treated with lenalidomide plus dexamethasone for at least 12 months, median PFS was higher in those who required lenalidomide dose reductions after 12 months than in those who required earlier dose reductions or no dose reduction at all. This suggests that lenalidomide dose reductions are not detrimental per se (especially if they allow patients to continue to receive therapy), although efforts should be made to provide full doses for at least the first 12 months of therapy, if possible. Finally, the impact of lenalidomide and dexamethasone on quality of life was not assessed in our study. Maintaining quality of life is an important treatment goal in elderly patients with MM. While the increase in certain adverse events,

particularly anaemia, may have had a negative impact on quality of life in elderly patients, it is unlikely to outweigh the positive effects gained through the significant improvement in TTP (15.1 vs. 4.6 months) and prolongation of OS (34.3 vs. 19.5 months) seen in this age group.

Len + Dex is an established therapy for relapsed or refractory MM. This analysis demonstrates the clinical efficacy and manageable tolerability of Len + Dex regardless of age. Thus, advanced age should not be a factor in preventing treatment with lenalidomide plus dexamethasone.

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Fig. 1. Progression-free survival by age group for all patients treated with combination lenalidomide and dexamethasone (Len + Dex), and placebo plus dexamethasone (Placebo + Dex). **a** Patients aged <65 years, **b** patients aged 65–74 years, and **c** patients aged ≥75 years

Table 1

Baseline characteristics

Characteristic	Age<65 years		Age 65–74 years		Age ≥ 75 years	
	Len + Dex (N = 192)	Placebo + Dex (N = 198)	Len + Dex (N = 118)	Placebo + Dex (N = 114)	Len + Dex (N = 43)	Placebo + Dex (N = 39)
Median age, years (25, 75 %)	57 (52, 61)	57 (52, 61)	69 (67, 71)	69 (67, 72)	78 (76, 81)	77 (76, 79)
Median time since diagnosis, years (25, 75 %)	3.2 (2.1, 5.3)	3.4 (2.2, 5.5)	3.4 (2.1, 5.2)	3.7 (2.3, 6.0)	2.8 (1.6, 4.4)	3.3 (2.0, 5.1)
Male sex, <i>n</i> (%)	114 (59.4)	125 (63.1)	69 (58.5)	63 (55.3)	27 (62.8)	19 (48.7)
Durie-Salmon stage, <i>n</i> (%)						
I or II	71 (37.0)	74 (37.4)	39 (33.3) ^b	36 (31.6)	13 (30.2)	15 (38.5)
III	121 (63.0)	124 (62.6)	78 (66.7) ^b	78 (68.4)	30 (69.8)	24 (61.5)
ISS stage, <i>n</i> (%)						
I or II	151 (80.8) ^b	160 (81.6) ^b	86 (76.1) ^b	87 (77.7) ^b	29 (67.4)	29 (76.3) ^b
III	36 (19.2) ^b	36 (18.4) ^b	27 (23.9) ^b	25 (22.3) ^b	14 (32.6)	9 (23.7) ^b
ECOG performance status, <i>n</i> (%) ^a						
0	101 (54.3)	90 (46.2)	41 (35.3)	44 (39.3)	10 (23.8)	16 (41.0)
1	85 (45.7)	105 (53.8)	75 (64.7)	68 (60.7)	32 (76.2)	23 (59.0)
IgA disease, <i>n</i> (%)	33 (17.3) ^b	43 (21.7)	30 (25.4)	29 (25.4)	12 (27.9)	11 (29.0) ^b
β ₂ -Microglobulin ≥ 2.5 mg/l, <i>n</i> (%)	125 (66.5) ^b	130 (66.3) ^b	94 (83.2) ^b	97 (86.6) ^b	41 (95.4) ^b	33 (86.8) ^b
No. of prior SCTs, <i>n</i> (%)						
0	43 (22.4)	44 (22.2)	63 (53.4)	69 (60.5)	40 (93.0)	38 (97.4)
1	122 (63.5)	120 (60.6)	46 (39.0)	36 (31.6)	3 (7.0)	0
2	27 (14.1)	34 (17.2)	9 (7.6)	9 (7.9)	0	1 (2.6)
No. of prior antimyeloma therapies, <i>n</i> (%)						
1	80 (41.7)	92 (46.5)	49 (41.5)	47 (41.2)	13 (30.2)	8 (20.5)
2	112 (58.3)	106 (53.5)	69 (58.5)	67 (58.8)	30 (69.8)	31 (79.5)
Type of prior treatment, <i>n</i> (%)						
Thalidomide	75 (39.1)	90 (45.5)	37 (31.4)	41 (36.0)	15 (34.9)	16 (41.0)
Dexamethasone	147 (76.6)	151 (76.3)	87 (73.7)	71 (62.3)	25 (58.1)	22 (56.4)
Bortezomib	15 (7.8)	14 (7.1)	9 (7.6)	7 (6.1)	3 (7.0)	6 (15.4)
Doxorubicin	123 (64.1)	122 (61.6)	59 (50.0)	56 (49.1)	13 (30.2)	11 (28.2)
Melphalan	69 (35.9)	50 (25.3)	57 (48.3)	62 (54.4)	32 (74.4)	33 (84.6)

Dex dexamethasone, ECOG Eastern Cooperative Oncology Group, IgA immunoglobulin A, ISS International Staging System, Len lenalidomide, SCT stem cell transplantation

^aData were unavailable for 6, 3, 2, 2, 1, and 0 patient(s) in each subcategory, respectively

^bMissing patients removed from the denominator

Table 2

Overall response rate according to age category, risk factors, and treatment group

Overall response rate, <i>n</i> (%)	Age <65 years		Age 65–74 years		Age ≥75 years	
	Len + Dex (<i>N</i> = 192)	Placebo + Dex (<i>N</i> = 198)	Len + Dex (<i>N</i> = 118)	Placebo + Dex (<i>N</i> = 114)	Len + Dex (<i>N</i> = 43)	Placebo + Dex (<i>N</i> = 39)
Total	117 (60.9)	43 (21.7)	64 (54.2)	24 (21.0) ^a	30 (69.8)	8 (20.5)
Male sex	65 (57.0)	31 (24.8)	44 (63.8)	14 (22.2)	18 (66.7)	6 (31.6)
Durie-Salmon stage						
I or II	47 (66.2)	14 (18.9)	18 (46.2)	7 (19.4)	9 (69.2)	3 (20.0)
III	70 (57.9)	29 (23.4)	45 (57.7)	17 (21.8)	21 (70.0)	5 (20.8)
ISS stage						
I or II	97 (64.2)	42 (26.2) ^a	54 (62.8)	19 (21.8)	21 (72.4)	7 (24.1)
III	17 (47.2)	1 (2.3) ^a	8 (29.6)	5 (20.0)	9 (64.3)	1 (11.1)
ECOG performance status						
0	59 (58.4)	19 (21.1)	21 (51.2)	12 (27.3)	7 (70.0)	2 (12.5)
1	52 (61.2)	24 (22.9)	42 (56.0)	11 (16.2)	22 (68.8)	6 (26.1)
IgA disease	21 (63.6)	5 (11.6)	19 (63.3)	8 (27.6)	12 (100)	1 (9.1)
β ₂ -Microglobulin ≥2.5 mg/l	69 (55.2)	18 (13.9)	48 (51.1)	18 (18.6)	29 (70.7)	6 (18.2)
No. of prior SCTs						
0	25 (58.1)	5 (11.4)	28 (44.4)	14 (20.3)	29 (72.5)	8 (21.1)
1	77 (63.1)	30 (25.0)	31 (67.4)	4 (11.1)	1 (33.3)	0
2	15 (55.6)	8 (23.5)	5 (55.6)	6 (66.7)	0	0
No. of prior antimyeloma therapies						
1	51 (63.8)	23 (25.0)	30 (61.2)	14 (29.8)	8 (61.5)	2 (25.0)
2	66 (58.9)	20 (18.9)	34 (49.3)	10 (14.9)	22 (73.3)	6 (19.4)
Type of prior treatment						
Thalidomide	41 (54.7)	15 (16.7)	18 (48.7) ^a	5 (12.2)	9 (60.0)	1 (6.3)
Dexamethasone	89 (60.5)	28 (18.5)	48 (55.2)	11 (15.5)	16 (64.0)	5 (22.7)
Bortezomib	10 (66.7)	1 (7.1)	4 (44.4)	1 (14.3)	3 (100)	0
Doxorubicin	70 (56.9)	25 (20.5)	32 (54.2)	8 (14.3)	8 (61.5)	4 (36.4)
Melphalan	40 (58.0)	7 (14.0)	29 (50.9)	12 (19.4)	24 (75.0)	7 (21.2)

Dex dexamethasone, ECOG Eastern Cooperative Oncology Group, IgA immunoglobulin A, ISS International Staging System, Len lenalidomide, SCT stem cell transplantation

^aMissing patients removed from the denominator

Table 3

Progression-free survival (PFS), time-to-progression (TTP), and overall survival (OS) according to age category and treatment group

Age (years)	Median PFS (months)			Median TTP (months)			Median OS (months)		
	Len + Dex	Placebo + Dex	HR (95 % CI) P value	Len + Dex	Placebo + Dex	HR (95 % CI) P value	Len + Dex	Placebo + Dex	HR (95 % CI) P value
<65	11.1	4.6	2.82 (2.16–3.67) <0.001	11.3	4.6	3.21 (2.43–4.24) <0.001	43.9	36.2	1.13 (0.87–1.47) 0.367
65–74	9.4	4.6	2.67 (1.87–3.81) <0.001	13.8	4.6	3.25 (2.21–4.80) <0.001	33.3	23.3	1.31 (0.95–1.82) 0.104
75	14.1	3.8	3.91 (2.08–7.34) <0.001	15.1	4.6	4.13 (2.11–8.10) <0.001	34.3	19.5	1.36 (0.77–2.37) 0.287

CI confidence interval, Dex dexamethasone, HR hazard ratio, Len lenalidomide

Table 4

Haematological and non-haematological grade 3 or 4 adverse events by age category and treatment group

Grade 3 or 4 adverse event, n (%)	Age <65 years		Age 65–74 years		Age ≥75 years	
	Len + Dex (N = 192)	Placebo + Dex (N = 198)	Len + Dex (N = 118)	Placebo + Dex (N = 114)	Len + Dex (N = 43)	Placebo + Dex (N = 39)
Haematological						
Neutropenia	65 (33.9)	9 (4.6)	43 (36.4)	2 (1.8)	13 (30.2)	1 (2.6)
Thrombocytopenia	17 (8.9)	13 (6.6)	21 (17.8)	7 (6.1)	5 (11.6)	2 (5.1)
Anaemia	16 (8.3)	5 (2.5)	10 (8.5)	10 (8.8)	9 (20.9)	5 (12.8)
Febrile neutropenia	3 (1.6)	0	3 (2.5)	0	2 (4.7)	0
Non-haematological						
Deep-vein thrombosis	13 (6.8)	2 (1.0)	10 (8.5)	8 (7.0)	6 (14.0)	2 (5.1)
Pulmonary embolism	5 (2.6)	1 (0.5)	7 (5.9)	1 (0.9)	2 (4.7)	1 (2.6)
Neuropathy	6 (3.1)	5 (2.5)	5 (4.2)	1 (0.9)	3 (7.0)	0
Peripheral neuropathy	2 (1.0)	1 (0.5)	1 (0.8)	1 (0.9)	2 (4.7)	0
Fatigue	8 (4.2)	10 (5.0)	12 (10.2)	5 (4.4)	3 (7.0)	2 (5.1)
Gastrointestinal disorders	19 (9.9)	15 (7.6)	13 (11.0)	10 (8.8)	6 (14.0)	5 (12.8)
Herpes zoster infection	4 (2)	0	0	2 (2)	0	0

Dex dexamethasone, *Len* lenalidomide

Table 5

Dose and dose reductions

	<u>Age < 65 years</u>		<u>Age 65–74 years</u>		<u>Age ≥ 75 years</u>	
	Len + Dex (N = 192)	Placebo + Dex (N = 198)	Len + Dex (N = 118)	Placebo + Dex (N = 114)	Len + Dex (N = 43)	Placebo + Dex (N = 39)
Dose of Len (mg)						
Median (25, 75 %)	23.0 (18.3, 24.5)	23.9 (20.8, 24.7) ^a	19.4 (14.5, 23.2)	23.1 (19.3, 24.5) ^a	18.8 (12.9, 22.2)	22.5 (14.9, 24.3) ^a
Dose of Dex (mg)						
Median (25, 75 %)	8.4 (7.4, 11.0)	11.2 (8.8, 14.7)	8.2 (6.8, 12.4)	12.3 (9.1, 15.0)	7.6 (6.5, 9.6)	11.4 (8.2, 15.2)
Patients with Len dose reduction, n (%)	58 (30.2)	21 (10.6) ^a	49 (41.5)	11 (9.7) ^a	21 (48.8)	6 (15.4) ^a
Time to first Len dose reduction (months)						
Median (25, 75 %)	4.3 (2.3, 9.2)	2.4 (1.0, 4.0) ^a	2.6 (1.9, 7.6)	2.3 (1.3, 2.8) ^a	2.6 (1.4, 3.7)	1.4 (1.4, 2.4) ^a
Patients with Dex dose reduction, n (%)	44 (22.9)	30 (15.2)	34 (28.8)	16 (14.0)	14 (32.6)	6 (15.4)
Time to first Dex dose reduction (months)						
Median (25, 75 %)	5.5 (2.0, 8.7)	4.4 (3.7, 6.5)	3.7 (1.0, 7.4)	3.6 (2.3, 6.2)	7.2 (1.4, 10.8)	1.9 (1.6, 3.7)

^aPlacebo dose and reduction