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ORIGINAL REPORT

Updated Outcomes and Impact of Age With Lenalidomide and Low-Dose Dexamethasone or Melphalan, Prednisone, and Thalidomide in the Randomized, Phase III FIRST Trial

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ABSTRACT

Purpose
This analysis of the FIRST trial in patients with newly diagnosed multiple myeloma (MM) ineligible for stem-cell transplantation examined updated outcomes and impact of patient age.

Patients and Methods
Patients with untreated symptomatic MM were randomly assigned at a one-to-one-to-one ratio to lenalidomide plus low-dose dexamethasone until disease progression (Rd continuous), Rd for 72 weeks (18 cycles; Rd18), or melphalan, prednisone, and thalidomide (MPT; 72 weeks), stratified by age (≤ 75 *v* > 75 years), disease stage (International Staging System stage I/II *v* III), and country. The primary end point was progression-free survival. Rd continuous and MPT were primary comparators.

Results
Between August 21, 2008, and March 7, 2011, 1,623 patients were enrolled (Rd continuous, n = 535; Rd18, n = 541; MPT, n = 547), including 567 (35%) age older than 75 years. Higher rates of advanced-stage disease and renal impairment were observed in patients older than 75 versus 75 years of age or younger. Rd continuous reduced the risk of progression or death compared with MPT by 31% (hazard ratio [HR], 0.69; 95% CI, 0.59 to 0.80; $P < .001$) overall, 36% (HR, 0.64; 95% CI, 0.53 to 0.77; $P < .001$) in patients age 75 years or younger, and 20% (HR, 0.80; 95% CI, 0.62 to 1.03; $P = .084$) in those age older than 75 years. Median overall survival was longer with Rd continuous than with MPT, including a 14-month difference in patients age older than 75 years. Progression-free survival with Rd18 was similar to that with MPT, and overall survival with Rd18 was marginally inferior to that with Rd continuous. Rates of grade 3 to 4 treatment-emergent adverse events were similar for Rd continuous–treated patients age 75 years or older and those age older than 75 years; however, older patients had more frequent lenalidomide dose reductions.

Conclusion
Results support Rd continuous treatment as a new standard of care for stem-cell transplantation–ineligible patients with newly diagnosed MM of all ages.

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INTRODUCTION

Multiple myeloma (MM) is primarily a disease of the elderly,[1] with an annual incidence greater than 30 per 100,000 persons age 75 years or older in the United States and Europe.[2,3] Additionally, the proportion of patients older than 65 years is anticipated to increase by 77% in 2030.[4] Although survival has improved in recent years, there remains a gap between outcomes of younger and older patients.[5-7] Patients with MM age 75 years or older are an understudied population.[8] Because of increased comorbidities and altered pharmacodynamics, older patients are susceptible to adverse events (AEs) that may negatively affect duration of treatment and, consequently, long-term outcomes.[9,10]

Combination therapies including melphalan, prednisone, and thalidomide (MPT); bortezomib,

melphalan, and prednisone; and lenalidomide and low-dose dexamethasone (Rd) are considered standard treatment options in many parts of the world for older patients with newly diagnosed MM who are ineligible for stem-cell transplantation (SCT).[11-14] Both the US and European regulatory authorities recently expanded their approvals of lenalidomide to include newly diagnosed MM (in combination with dexamethasone in the United States and in combination with dexamethasone until disease progression or with melphalan and prednisone followed by lenalidomide monotherapy maintenance for SCT-ineligible patients in Europe).[15,16] Until now, limited data have been available regarding the efficacy and safety of lenalidomide in patients age older than 75 years with newly diagnosed MM.

The FIRST (Frontline Investigation of Revlimid Plus Dexamethasone Versus Standard Thalidomide) trial (MM-020/IFM07-01), a randomized, global, phase III trial, compared the efficacy and safety of continuous Rd until disease progression (Rd continuous), Rd for 72 weeks (18 cycles; Rd18), or MPT for 72 weeks (12 cycles) in patients with newly diagnosed MM ineligible for SCT.[17] Rd continuous treatment led to a 28% reduced risk of progression or death compared with MPT (hazard ratio [HR], 0.72; 95% CI, 0.61 to 0.85; $P < .001$).[17] Rd continuous also extended overall survival (OS) at the time of the interim analysis beyond that seen with MPT (HR, 0.78; 95% CI, 0.64 to 0.96; $P = .02$).[17] Lower rates of grade 3 to 4 neutropenia were associated with Rd continuous than with MPT, but rates of grade 3 to 4 infections were higher than with MPT. A subsequent pooled analysis of the Rd continuous and Rd18 arms found clinically relevant improvements in health-related quality of life (HRQoL) versus MPT.[18]

Here we present an updated analysis of the FIRST trial that assesses outcomes with extended follow-up. Additionally, in a prespecified analysis, we examine the impact of age (≤ 75 *v* > 75 years), a stratification factor in the study, on efficacy and safety of Rd continuous versus MPT and Rd18.

PATIENTS AND METHODS

Study Design

The randomized, global, phase III, multicenter, open-label FIRST (MM-020/IFM07-01) study of Rd continuous versus Rd18 and MPT in patients with newly diagnosed MM who were SCT ineligible was conducted at 246 sites in 18 countries (listed in the Data Supplement). It was approved by institutional review boards or ethics committees at all sites before initiation and conducted according to the Declaration of Helsinki and the Harmonisation E6 Guidelines for Good Clinical Practice. This unplanned update was performed after the final analysis of progression-free survival (PFS)[17] at the request of regulatory authorities.

Patients

As previously described,[17] patients recruited were age 18 years or older with previously untreated, symptomatic MM and at least one feature of myeloma-related end-organ dysfunction (CRAB criteria: calcium elevated, renal insufficiency, anemia, or bone lesions). Patients were age 65 years or older or age younger than 65 years and SCT ineligible, with an Eastern Cooperative Oncology Group performance status of 0 to 2. Patients with severe renal impairment (creatinine clearance < 30 mL/min) were allowed; however, those receiving dialysis were ineligible. Additional eligibility details are included in the Data Supplement. All patients provided written informed consent.

Treatment

Patients were randomly assigned at a one-to-one-to-one ratio to treatment arms. Patients were stratified by age (≤ 75 *v* > 75 years), disease stage (International Staging System stage I/II *v* III), and country. Patients assigned to Rd continuous or Rd18 received oral lenalidomide on days 1 to 21 plus oral dexamethasone on days 1, 8, 15, and 22 in 28-day cycles continuously until disease progression or for 18 cycles (72 weeks), respectively. Patients assigned to MPT received oral melphalan on days 1 to 4, oral prednisone on days 1 to 4, and oral thalidomide once per day in twelve 42-day cycles (72 weeks). Starting doses of dexamethasone, melphalan, and thalidomide were reduced for patients age older than 75 years (Data Supplement). All patients received protocol-specified mandatory thromboprophylaxis (details provided in the Data Supplement). Efficacy and safety assessments were performed at baseline, the start of each treatment cycle, and every 28 days during follow-up for PFS. HRQoL assessments are described in the Data Supplement.

Outcomes

The primary objective was to compare the efficacy of Rd continuous versus MPT; comparisons of Rd continuous with Rd18 and Rd18 with MPT were secondary objectives. The primary end point was PFS (International Myeloma Working Group criteria[19]). The key secondary end point was OS; other secondary end points included overall response rate (ORR; $\geq$ partial response [PR]; International Myeloma Working Group criteria[19]), duration of response (DOR), time to first response, time to treatment failure, time to second antimyeloma therapy, response to second antimyeloma therapy, cytogenetics, safety, and HRQoL. Additionally, treatment tolerance was an exploratory end point assessed by examining dose adjustments and discontinuations at 72 weeks. Independent response adjudication ended after the final analysis; therefore, investigator-assessed progression and response data are reported here. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0), and laboratory data were collected by a central laboratory. Treatment-emergent AEs (TEAEs) were those occurring or worsening during or after treatment or within 28 days of the last dose with any study drug.

Statistical Analysis

Efficacy analyses were conducted in the intention-to-treat (ITT) population consisting of all randomly assigned patients. Safety analyses were conducted in all patients who received ≥ 1 dose of study drug. The log-rank test was used for comparisons of time-to-event end points (eg, PFS and OS).[20,21] HRQoL analyses used one-sample *t* tests for changes from baseline and two-sample *t* tests for differences between treatment arms. SAS software (version 9.2; SAS Institute, Cary, NC) was used to perform analyses. Efficacy and safety data were monitored by an independent data monitoring committee until the time of final PFS analysis.

RESULTS

Patients

A total of 1,623 patients were enrolled between August 21, 2008, and March 7, 2011, including 567 (35%) patients age older than 75 years (Fig 1). Five hundred thirty-five patients were randomly assigned to receive Rd continuous, 541 patients to receive Rd18, and 547 patients to receive MPT. With an updated data

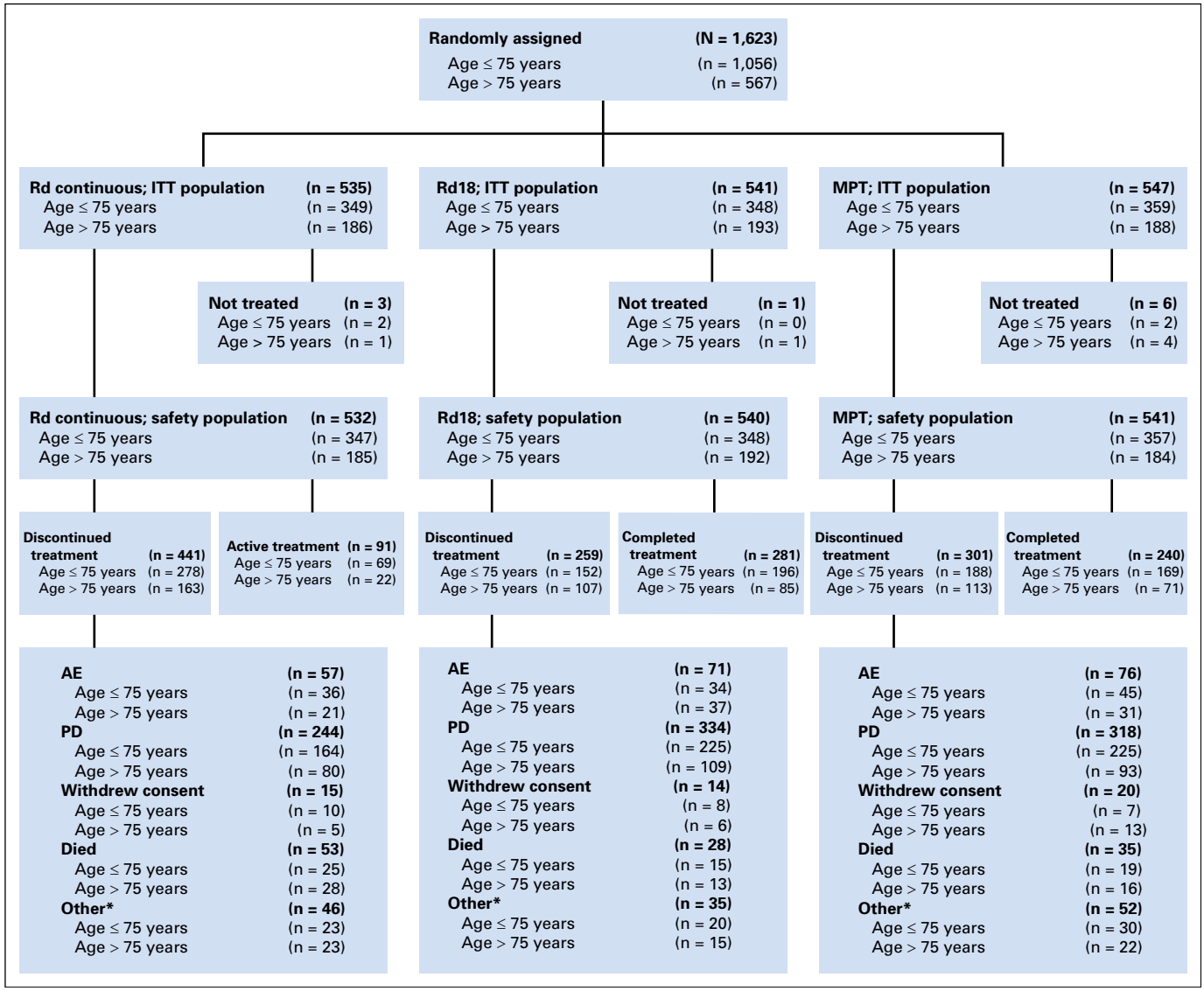

Fig 1. Patient disposition as of data cutoff on March 3, 2014. AE, adverse event; ITT, intention to treat; MPT, melphalan, prednisone, and thalidomide; PD, progressive disease; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles. Bottom boxes represent causes of study discontinuation. *Includes other, lost to follow-up, and protocol violation.

cutoff of March 3, 2014 (final PFS analysis was conducted on May 24, 2013[17]), median follow-up for surviving patients was 45.5 months. In the Rd continuous arm, a higher proportion of patients age 75 years or younger were still receiving treatment (19.8%) compared with those age older than 75 years (11.9%). All patients in the Rd18 and MPT arms had completed or discontinued treatment.

Patient and disease characteristics were well balanced across all treatment arms (Table 1). Age older than 75 years was associated with higher International Staging System stage III disease and more severe renal impairment than age 75 years or younger. There was no increase in the rate of high-risk cytogenetics (del[17p] and/or t[4;14]) in patients age older than 75 years compared with those age 75 years or younger. Both age groups had extensive comorbidities, although rates were higher in the older patient group (Data Supplement).

Efficacy

Longer PFS was achieved by patients treated with Rd continuous versus MPT, independent of age (Figs 2A to 2C). In the ITT population, there was a 31% reduction in the risk of progression or death with Rd continuous versus MPT (HR, 0.69; 95% CI, 0.59 to 0.80; $P < .001$). Patients age 75 years or younger had a 36% risk reduction (HR, 0.64; 95% CI, 0.53 to 0.77; $P < .001$), whereas those age older than 75 years had a 20% risk reduction (HR, 0.80; 95% CI, 0.62 to 1.03; $P = .084$) with Rd continuous versus MPT. Four-year PFS was more than doubled with Rd continuous versus MPT, regardless of age. Results with Rd18 were similar to those with MPT, regardless of age.

OS was also extended in patients treated with Rd continuous versus MPT (Figs 2D to 2F). Overall median OS differed by more than 10 months with Rd continuous versus MPT (median, 58.9 *v* 48.5 months; HR, 0.75; 95% CI, 0.62 to 0.90),

Table 1. Baseline Patient Demographic and Clinical Characteristics

Characteristic	No. (%)					
	Age ≤ 75 Years			Age > 75 Years		
	Rd Continuous (n = 349)	Rd18 (n = 348)	MPT (n = 359)	Rd Continuous (n = 186)	Rd18 (n = 193)	MPT (n = 188)
Age, years						
Median	70	70	70	79	79	79
Range	44-75	40-75	51-75	76-91	76-89	76-92
Male sex	188 (54)	184 (53)	193 (54)	106 (57)	89 (46)	94 (50)
ECOG PS*						
0	107 (31)	104 (30)	116 (32)	48 (26)	59 (31)	40 (21)
1	167 (48)	174 (50)	174 (48)	90 (48)	89 (46)	101 (54)
2	73 (21)	68 (20)	66 (18)	46 (25)	45 (23)	45 (24)
≥ 3	1 (< 1)	2 (1)	1 (< 1)	1 (1)	0 (0)	1 (1)
Missing	1 (< 1)	0 (0)	2 (1)	1 (1)	0 (0)	1 (1)
ISS stage						
I/II	221 (63)	220 (63)	229 (64)	98 (53)	102 (53)	94 (50)
III	128 (37)	128 (37)	130 (36)	88 (47)	91 (47)	94 (50)
CrCl, mL/min						
< 30	20 (6)	26 (7)	27 (8)	25 (13)	21 (11)	28 (15)
≥ 30 and < 50	54 (16)	49 (14)	60 (17)	72 (39)	71 (37)	66 (35)
≥ 50	275 (79)	273 (78)	272 (76)	89 (48)	101 (52)	94 (50)
High-risk cytogenetics†	28 (8)	26 (7)	29 (8)	12 (6)	8 (4)	12 (6)

Abbreviations: CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; MPT, melphalan, prednisone, and thalidomide; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.
*Six patients across the three study groups experienced worsening ECOG PS from 2 to 3 during the screening period.
†del(17p) and/or t(4;14).

including a more than 14-month median OS difference observed in patients age older than 75 years with Rd continuous versus MPT (median, 52.3 *v* 37.8 months; HR, 0.72; 95% CI, 0.54 to 0.96). For patients age 75 years or younger, median OS was 60.9 months with Rd continuous versus 55.3 months with MPT (HR, 0.76; 95% CI, 0.60 to 0.96). OS rate with Rd18 was marginally lower than with Rd continuous (3% and 4% lower at 4 years in patients age 75 years or younger and age older than 75 years, respectively).

Rd continuous resulted in higher ORR (≥ PR), including high-quality responses (≥ very good partial response [VGPR]), and prolonged DOR in the ITT population and both age groups compared with MPT (Table 2). ORR was 81% with Rd continuous compared with 67% with MPT (odds ratio [OR], 2.04; 95% CI, 1.54 to 2.70). Median DOR of 32 months with Rd continuous was extended compared with DOR of 22 months with MPT (HR, 0.60; 95% CI, 0.51 to 0.72). Rd continuous similarly resulted in higher ORR versus MPT in patients age 75 years or younger (82% *v* 71%; OR, 1.91; 95% CI, 1.34 to 2.73) and age older than 75 years (78% *v* 61%; OR, 2.30; 95% CI, 1.46 to 3.61). Median DOR was also prolonged in both age groups: 37 versus 22 months in patients age 75 years or younger (HR, 0.55; 95% CI, 0.44 to 0.69) and 27 versus 22 months in patients age older than 75 years (HR, 0.73; 95% CI, 0.54 to 1.00). Rates of VGPR or better were higher with Rd continuous versus MPT overall and in both age groups. Median time to response was shorter at 2 months with Rd continuous versus 3 months with MPT. In both age groups, Rd18 resulted in responses similar to those with Rd continuous and DORs similar to those with MPT. Rd continuous extended the time to second antimyeloma therapy compared with either Rd18 or MPT (Data Supplement).

Dosing and Safety

Mean treatment duration of Rd continuous was 24 months for patients age 75 years or younger, 4 months longer than the 20 months for patients age older than 75 years (Table 3). This was approximately twice the mean treatment duration with MPT, which was 12 months for patients age 75 years or younger and 11 months for those age older than 75 years. A substantial proportion of patients received long-term treatment (≥ 2 years) with Rd continuous, including 41% of patients age 75 years or younger and 35% of those age older than 75 years.

Patients who continued Rd treatment beyond 18 cycles (ie, those in the Rd continuous arm) had a limited need for additional dose reductions of lenalidomide as a result of AEs. Lenalidomide dose reductions were not considerably more frequent among patients treated with Rd continuous than with Rd18: 37% versus 27%, respectively, in those age 75 years or younger and 44% versus 32%, respectively, in those age older than 75 years (Table 3). Rates of dose reduction were slightly higher overall in patients age older than 75 years compared with those age 75 years or younger for both Rd continuous and Rd18. Thalidomide dose reductions for patients treated with MPT were more frequent in patients age 75 years or younger than in those age older than 75 years (52% *v* 36%), likely because younger patients received a higher starting dose.

At 72 weeks (the end of Rd18 or MPT treatment), a greater proportion of patients treated with Rd continuous and Rd18 maintained their full starting dose of lenalidomide than had patients treated with MPT maintained their full starting dose of thalidomide: 40% and 44% versus 16%, respectively, in patients age 75 years or younger and 30% and 27% versus 19%, respectively,

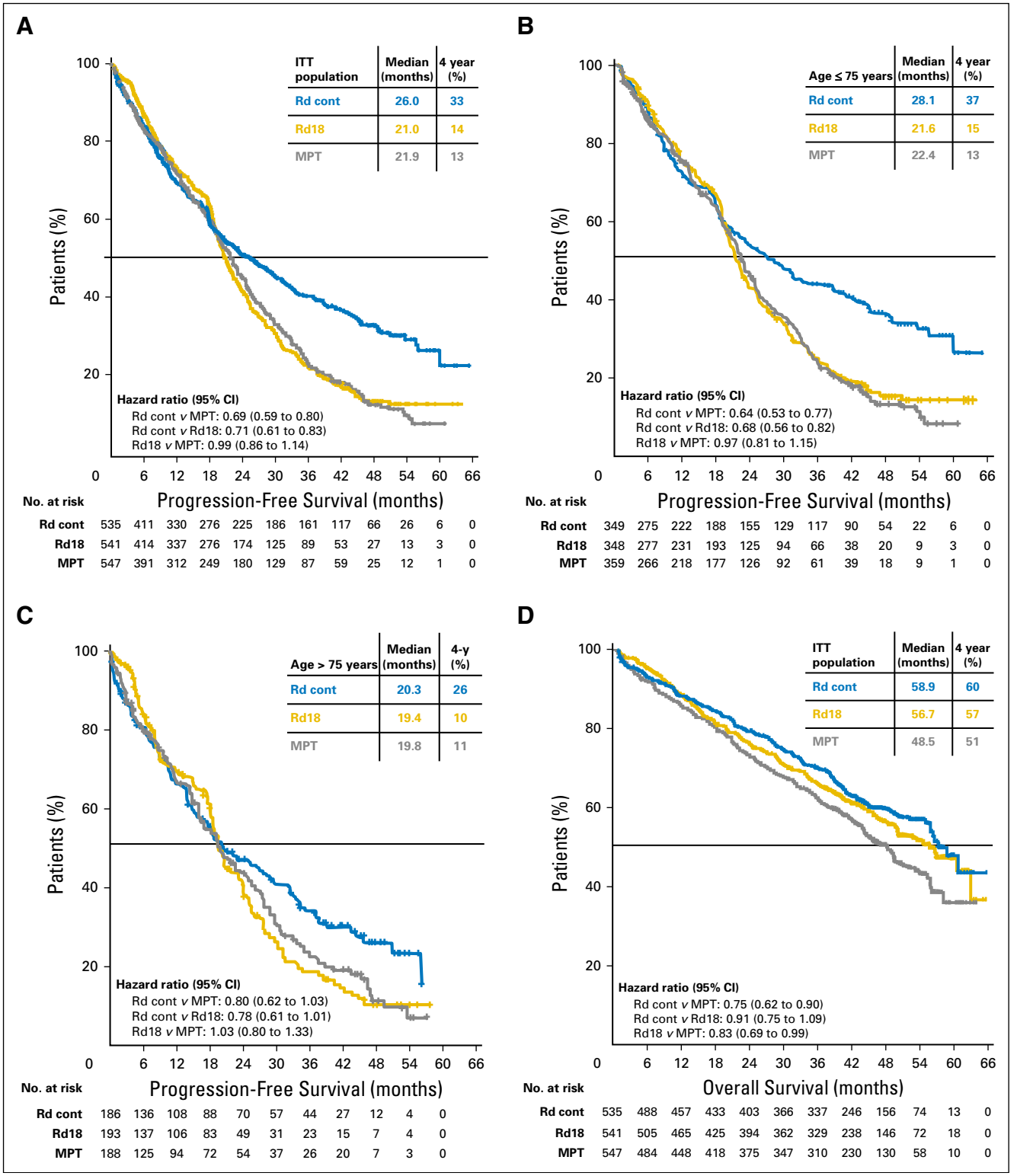

Fig 2. (A to C) Progression-free and (D to F) overall survival for (A, D) overall intention-to-treat (ITT) population, (B, E) patients age 75 years or younger, and (C, F) patients age older than 75 years. MPT, melphalan, prednisone, and thalidomide; Rd cont, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

in patients age older than 75 years. Lower discontinuation rates at 72 weeks were observed with Rd18 versus MPT for both age groups: 14% versus 26% for patients age younger than 75 years and 23% versus 29% for patients age older than 75 years. Rates of discontinuation were slightly lower with Rd continuous than with MPT in both age groups, despite the longer mean treatment

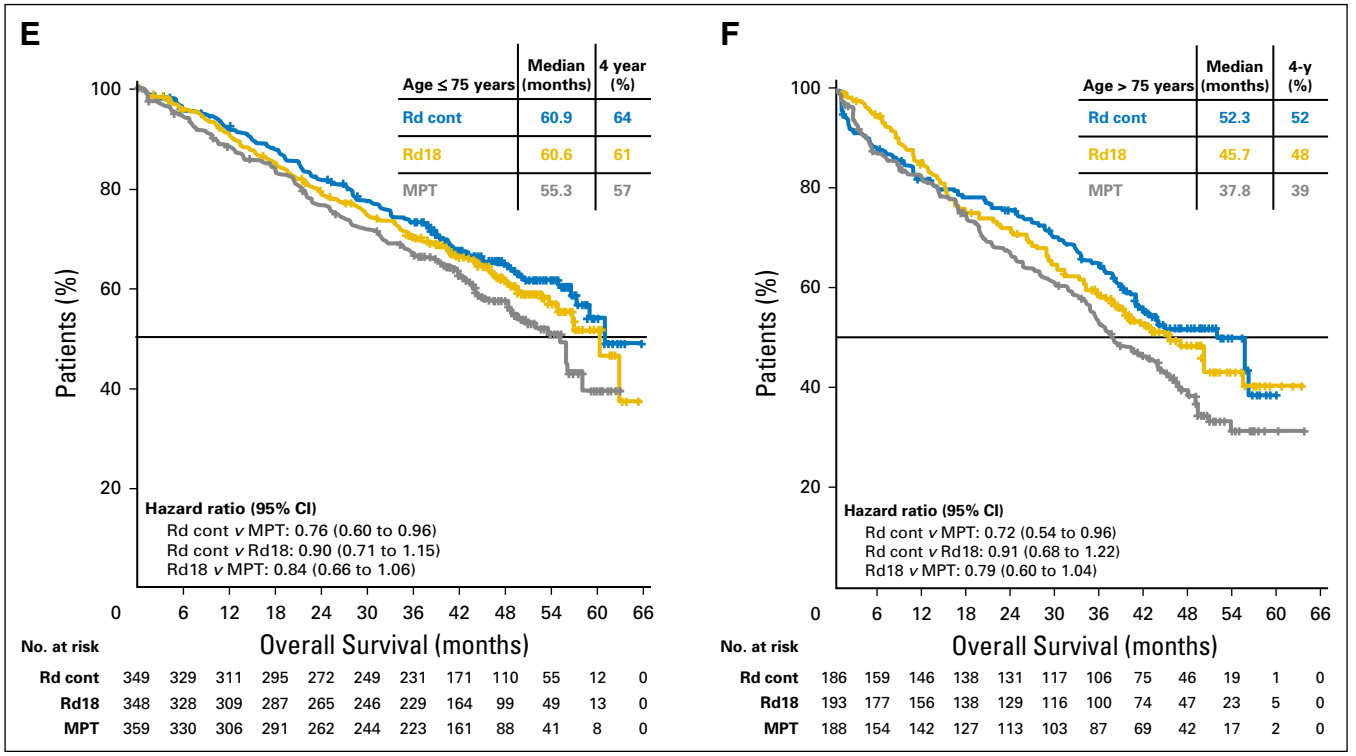

Fig 2. (Continued).

duration with Rd continuous (age ≤ 75 years: 21% *v* 26%; age > 75 years: 26% *v* 30%).

Rates of grade 3 to 4 TEAEs (hematologic and nonhematologic) were similar across age groups (Table 4). The most frequent grade 3 to 4 hematologic TEAEs were neutropenia and anemia. Rate of grade 3 to 4 neutropenia was higher among patients treated with MPT than among those treated with Rd continuous or Rd18, regardless of age. Infections were the most common grade 3 to 4 nonhematologic TEAEs and were more frequently reported in the Rd arms in both age groups. Grade 3 to 4 peripheral sensory neuropathy was less frequent, whereas rates of deep vein thrombosis and pulmonary embolism were generally slightly higher in patients treated with Rd continuous and Rd18 than with MPT. Overall incidence rates of invasive second primary malignancy were 4% in the Rd continuous arm, 6% in the Rd18 arm, and 6% in the MPT arm and did not vary notably by age (Table 4).

Table 2. Response to Treatment as Assessed by IMWG Criteria

	No. (%)								
	ITT Population			Age ≤ 75 Years			Age > 75 Years		
Response	Rd Continuous (n = 535)	Rd18 (n = 541)	MPT (n = 547)	Rd Continuous (n = 349)	Rd18 (n = 348)	MPT (n = 359)	Rd Continuous (n = 186)	Rd18 (n = 193)	MPT (n = 188)
ORR	432 (81)	425 (79)	368 (67)	287 (82)	286 (82)	254 (71)	145 (78)	139 (72)	114 (61)
CR	114 (21)	110 (20)	66 (12)	75 (22)	82 (24)	48 (13)	39 (21)	28 (15)	18 (10)
VGPR	144 (27)	145 (27)	100 (18)	99 (28)	92 (26)	60 (17)	45 (24)	53 (27)	40 (21)
PR	174 (33)	170 (31)	202 (37)	113 (32)	112 (32)	146 (41)	61 (33)	58 (30)	56 (30)
SD	66 (12)	83 (15)	117 (21)	45 (13)	42 (12)	72 (20)	21 (11)	41 (21)	45 (24)
PD	10 (2)	6 (1)	17 (3)	6 (2)	4 (1)	12 (3)	4 (2)	2 (1)	5 (3)
NE	27 (5)	27 (5)	45 (8)	11 (3)	16 (5)	21 (6)	16 (9)	11 (6)	24 (13)
DOR, months*									
Median	32	22	22	37	22	22	27	21	22
95% CI	26 to 37	19 to 23	20 to 25	27 to 42	19 to 24	20 to 25	20 to 33	17 to 23	17 to 27
TTR, months*									
Median	2	2	3	2	2	3	2	2	3
Range	1-22	1-35	1-50	1-22	1-35	1-50	1-18	1-11	1-34

Abbreviations: CR, complete response; DOR, duration of response; IMWG, International Myeloma Working Group; ITT, intention to treat; MPT, melphalan, prednisone, and thalidomide; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles; SD, stable disease; TTR, time to first response; VGPR, very good partial response.
*For patients achieving PR or better.

Table 3. Treatment Exposure and Tolerability (safety population)

Treatment Characteristic	No. (%)					
	Age ≤ 75 Years			Age > 75 Years		
	Rd Continuous (n = 347)	Rd18 (n = 348)	MPT (n = 357)	Rd Continuous (n = 185)	Rd18 (n = 192)	MPT (n = 184)
Overall treatment duration						
Mean, months	24	13	12	20	12	11
Standard deviation	18	6	6	16	6	6
Treatment exposure ≥ 2 years	143 (41)	0	1 (< 1)*	65 (35)	0	1 (1)*
Lenalidomide or thalidomide						
Dose reduction	129 (37)	93 (27)	187 (52)	81 (44)	62 (32)	67 (36)
Discontinuation	72 (21)	49 (14)	92 (26)	48 (26)	44 (23)	54 (29)
At full planned dose at 72 weeks, %†	40	44	16	30	27	19

Abbreviations: MPT, melphalan, prednisone, and thalidomide; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.
*Two patients in the MPT arm (one patient per age group) were receiving treatment ≥ 2 years because of treatment delays.
†For patients with a starting dose of lenalidomide 25 mg or thalidomide 200 mg if they were age ≤ 75 years and 100 mg if they were age > 75 years.

HRQoL assessments, collected during the first 18 months of treatment, showed clinically meaningful improvements in several measures for both age groups of Rd-treated patients (Rd continuous and Rd18 combined; Data Supplement). However, disease progression was associated with a decline in HRQoL across relevant key domains: physical function, fatigue, pain, global QoL, disease symptoms, and health utility ($P < .05$ for all domains; data not shown). This was observed in the whole trial population and for both Rd continuous and MPT arms.

DISCUSSION

Elderly patients with MM, although historically under-represented in clinical trials, are a heterogeneous population in which treatment strategies are influenced by many factors beyond age, such as comorbidities, general physical fitness, and cognitive function.[22-24] The FIRST trial compared the efficacy and safety of Rd administered until disease progression or for 18 cycles versus fixed-duration MPT in patients with newly diagnosed MM who were

Table 4. Incidence of TEAEs and SPM (safety population)

TEAE or SPM	No. (%)					
	Age ≤ 75 Years			Age > 75 Years		
	Rd Continuous (n = 347)	Rd18 (n = 348)	MPT (n = 357)	Rd Continuous (n = 185)	Rd18 (n = 192)	MPT (n = 184)
Grade 3 to 4 hematologic TEAEs*						
Neutropenia	98 (28)	87 (25)	169 (47)	53 (29)	56 (29)	74 (40)
Anemia	63 (18)	41 (12)	70 (20)	36 (19)	44 (23)	32 (17)
Thrombocytopenia	28 (8)	30 (9)	47 (13)	17 (9)	13 (7)	13 (7)
Leukopenia	17 (5)	21 (6)	39 (11)	7 (4)	9 (5)	14 (8)
Grade 3 to 4 nonhematologic TEAEs*						
Infection	105 (30)	73 (21)	57 (16)	54 (29)	45 (23)	36 (20)
Cardiac disorder	41 (12)	22 (6)	22 (6)	22 (12)	17 (9)	24 (13)
Fatigue	23 (7)	27 (8)	17 (5)	17 (9)	19 (10)	14 (8)
Back pain	21 (6)	26 (7)	18 (5)	18 (10)	8 (4)	10 (5)
Peripheral sensory neuropathy	5 (1)	2 (1)	36 (10)	1 (1)	0 (0)	15 (8)
TEAEs of special interest						
Cataract	27 (8)	11 (3)	1 (< 1)	6 (3)	3 (2)	2 (1)
DVT	23 (7)	11 (3)	10 (3)	6 (3)	9 (5)	4 (2)
PE	13 (4)	10 (3)	17 (5)	7 (4)	6 (3)	3 (2)
SPM						
Invasive SPM	13 (4)	19 (6)	22 (6)	8 (4)	14 (7)	8 (4)
Hematologic malignancy	2 (1)	2 (1)	9 (3)	1 (1)	0	3 (2)
Solid tumor	11 (3)	18 (5)	13 (4)	7 (4)	14 (7)	5 (3)
Noninvasive SPM (NMSC)	17 (5)	13 (4)	15 (4)	10 (5)	7 (4)	11 (6)

Abbreviations: DVT, deep vein thrombosis; MPT, melphalan, prednisone, and thalidomide; NMSC, nonmelanoma skin cancer; PE, pulmonary embolism; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles; SPM, second primary malignancy; TEAE, treatment-emergent adverse event.
*Occurring in ≥ 10% of patients in either age group.

SCT ineligible.[17] To the best of our knowledge, this is the largest cohort of patients age older than 75 years with newly diagnosed MM (n = 567) enrolled in a registration study. Regardless of patient age, Rd continuous was more effective than MPT in this updated analysis after a median follow-up of 45.5 months. Rd continuous extended PFS versus MPT in patients age both 75 years or younger and older than 75 years. However, in patients age older than 75 years, this benefit was not reflected by medians, which were similar across treatment arms, even though the risk of progression or death with Rd continuous was reduced by 22% and 20% versus Rd18 and MPT, respectively, and 4-year PFS with Rd continuous was more than double that with Rd18 and MPT.

In addition to PFS benefits, a median OS advantage of 10 months was observed in the ITT population receiving Rd continuous versus MPT. This advantage was seen regardless of age, including a 14-month OS advantage in patients age older than 75 years. ORR, including rate of high-quality responses (≥ VGPR), was consistently higher with Rd continuous than MPT in both age groups. In line with PFS results, Rd continuous treatment also extended DOR and time to second-line antimyeloma therapy for older and younger patients. ORR with fixed-duration Rd18 was comparable to that with Rd continuous and greater than that with MPT, but PFS with Rd18 was similar to that seen with MPT, suggesting that the major benefits of Rd continuous treatment are derived from the prolonged duration of first-line therapy. However, OS for patients receiving Rd18 was only slightly shorter than OS for patients receiving Rd continuous, which may be affected by subsequent treatments, including lenalidomide-based second-line regimens.

Rd was generally well tolerated in the Rd continuous and Rd18 arms, with similar safety profiles in patients age 75 years or younger and older than 75 years and in the ITT population. Age-based dexamethasone dose adjustments likely contributed to a consistent toxicity profile between younger and older patients. Melphalan and thalidomide were also adjusted on the basis of age, contributing to an acceptable safety profile for MPT, in line with previous results.[25-27] There was an overall greater tolerance of Rd versus MPT in both age groups. Importantly, 35% of patients age older than 75 years who received Rd continuous continued to receive therapy for more than 2 years. Rates of grade 3 to 4 AEs in patients treated with Rd continuous were consistent across age groups.

It is crucial to evaluate novel agents in the elderly population, either through dedicated clinical trials[3] or by ensuring adequate representation in global trials. The FIRST patient population was generally elderly (median age, 73 years), with 35% of patients age older than 75 years,[17] a statistic consistent with recent epidemiologic results for MM.[3] To better approximate a real-world older population, age-related comorbidities such as history of cardiac events, diabetes, and renal impairment (not requiring dialysis) were not exclusion criteria and were present in a large proportion of patients in the FIRST trial.

Older age and comorbidities can negatively affect patient outcomes. An analysis of 869 patients with newly diagnosed MM from three clinical trials divided elderly patients with MM in three groups (fit, intermediate fitness, and frail) on the basis of age, comorbidities, and cognitive and physical statuses that were predictive of risk of mortality and toxicity.[24] Results suggested that patient fitness should be considered when making treatment decisions because this factor may affect the optimal balance between efficacy and safety.[24] Although chronologic age is not necessarily an indicator of frailty, FIRST trial results did show greater PFS and OS benefits with Rd continuous versus MPT therapy, regardless of age.

Efficacy results by patient age were consistent with those of the ITT population and may support additional improvements in the survival of elderly patients with MM that have been observed with advances in treatment.[28] This extended follow-up and subanalysis of the FIRST trial establishes continuous treatment with Rd until disease progression as a new standard of care for patients with newly diagnosed MM who are ineligible for SCT, regardless of age. With proper monitoring and dose adjustment, Rd continuous is an effective and tolerable treatment option for even the most elderly patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Updated Outcomes and Impact of Age With Lenalidomide and Low-Dose Dexamethasone or Melphalan, Prednisone, and Thalidomide in the Randomized, Phase III FIRST Trial

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