ARTICLE

Impact of renal impairment on outcomes with lenalidomide and dexamethasone treatment in the FIRST trial, a randomized, open-label phase 3 trial in transplant-ineligible patients with multiple myeloma

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ABSTRACT

Renal impairment is associated with poor prognosis in myeloma. This analysis of the pivotal phase 3 FIRST trial examined the impact of renally adapted dosing of lenalidomide and dexamethasone on outcomes of patients with different degrees of renal impairment. Transplant-ineligible patients not requiring dialysis were randomized 1:1:1 to receive continuous lenalidomide and dexamethasone until disease progression (n=535) or for 18 cycles (72 weeks; n=541), or melphalan, prednisone, and thalidomide for 12 cycles (72 weeks; n=547). Follow-up is ongoing. Patients were grouped by baseline creatinine clearance into no (≥ 80 mL/min [n=389]), mild (≥ 50 to < 80 mL/min [n=715]), moderate (≥ 30 to < 50 mL/min [n=372]), and severe impairment (< 30 mL/min [n=147]) subgroups. Continuous lenalidomide and dexamethasone therapy reduced the risk of progression or death in no, mild, and moderate renal impairment subgroups *vs.* melphalan, prednisone, and thalidomide therapy (HR = 0.67, 0.70, and 0.65, respectively). Overall survival benefits were observed with continuous lenalidomide and dexamethasone treatment *vs.* melphalan, prednisone, and thalidomide treatment in no or mild renal impairment subgroups. Renal function improved from baseline in 52.6% of lenalidomide and dexamethasone–treated patients. The safety profile of continuous lenalidomide and dexamethasone was consistent across renal subgroups, except for grade 3/4 anemia and rash, which increased with increasing severity of renal impairment. Continuous lenalidomide and dexamethasone treatment, with renally adapted lenalidomide dosing, was effective for most transplant-ineligible patients with myeloma and renal impairment. *Trial registration: ClinicalTrials.gov (NCT00689936); EudraCT (2007-004823-39). Funding: Intergroupe Francophone du Myélome and the Celgene Corporation.*

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Introduction

Renal impairment (RI) is a major disease complicating factor for many patients with multiple myeloma (MM).[1] Twenty percent or more of patients with newly diagnosed MM (NDMM) present with some degree of RI, which is associated with poor outcomes, including poor survival and risk of early death.[1-4] The reversal of RI is associated with prolonged survival.[1,3] Newer agents, including immunomodulatory agents and proteasome inhibitors, are effective in patients with RI, leading to outcomes similar to those in non–renally impaired patients, and often improving renal function.[1,5] Currently bortezomib-based regimens are often used for treating patients with MM and RI.[4,6] However, the evaluation of lenalidomide in patients with RI has been limited by the exclusion of patients with severe RI from clinical trials.[4]

Lenalidomide, a non-nephrotoxic compound, is predominantly excreted renally.[7] However, because it is minimally metabolized, it is recommended that the starting dose be adjusted according to the level of renal function.[7,8] With appropriate dose adjustments, lenalidomide plus dexamethasone has been demonstrated to be effective and tolerable in renally impaired patients with relapsed/refractory MM (RRMM).[8] Improvement in renal function has also been reported in up to 72% of patients with RRMM with lenalidomide plus dexamethasone treatment.[8,9] However, little is known about the efficacy and tolerability of newer therapies in patients with NDMM with RI because many phase 3 clinical trials exclude patients with moderate to severe RI.[10-12]

The Frontline Investigation of Revlimid and Dexamethasone *vs.* Standard Thalidomide (FIRST) study is a phase 3, international, randomized, open-label trial of lenalidomide plus low-dose dexamethasone (Rd) in patients with NDMM who are ineligible for stem cell transplant (SCT).[13] The FIRST trial is notable for enrolling patients with NDMM with any level of RI, excluding only those requiring dialysis. Patients were randomized to Rd until disease progression (Rd continuous); Rd for 72 weeks (18 cycles; Rd18); or melphalan, prednisone, and thalidomide (MPT) for 72 weeks. In the overall study population, Rd continuous resulted in a reduced risk of progression or death *vs.* MPT (hazard ratio [HR], 0.72; $P<0.001$; data cut-off, May 2013). Overall survival (OS) was also improved with Rd continuous *vs.* MPT (HR, 0.78). Both Rd continuous and Rd18 had lower rates of hematologic toxicity than MPT, but slightly higher rates of grade 3-4 infections.

In this study, lenalidomide dosing was adaptable based on renal function and recovery: the starting dose was decreased for patients with moderate to severe RI and could be increased as renal function improved to maintain effective lenalidomide exposure. The goal of this analysis was to assess the effect of lenalidomide treatment, with appropriate dose adjustments for renal function, in combination with low-dose dexamethasone on outcomes in patients with varying degrees of RI in the FIRST study.

Methods

Full study design details were reported previously and are in the *Online Supplementary Methods*.[13] FIRST was a randomized, open-label, phase 3 trial conducted at 246 treatment centers in 18 countries in Europe, North America, and the Asia-Pacific region. Patients were enrolled between August 2008 and March 2011. The trial was approved by the institutional review board of each site and registered with *ClinicalTrials.gov (NCT00689936)* and the *European Clinical Trials Database (2007-004823-39)*.

Patients

Eligible patients had previously untreated, symptomatic, and measurable MM.[13] Patients were aged ≥ 65 years or otherwise unable to receive SCT. RI of any degree was allowed, except that requiring hemodialysis or peritoneal dialysis. Full eligibility criteria are in the *Online Supplementary Methods*.

Study design

Patients were randomly assigned 1:1:1 to 3 treatment arms: lenalidomide (25 mg/day, days 1-21) and dexamethasone (40 mg/day, days 1, 8, 15, and 22) in 28-day cycles until disease progression (Rd continuous); lenalidomide and dexamethasone as above in 28-day cycles for 72 weeks (18 cycles; Rd18); or melphalan (0.25 mg/kg/day, days 1-4), prednisone (2 mg/kg/day, days 1-4), and thalidomide (200 mg/day) in twelve 42-day cycles for 72 weeks (MPT). Starting dose adjustments were based on renal function and age (*Online Supplementary Methods*). Randomization was performed using a validated interactive voice response system. Patients were stratified by age (≤ 75 *vs.* > 75 years), International Staging System (ISS) disease stage, and country. Renal function subgroups were defined as the following: no RI, creatinine clearance (CrCl) at baseline ≥ 80 mL/min; mild RI, ≥ 50 to < 80 mL/min; moderate RI, ≥ 30 to < 50 mL/min; and severe RI, < 30 mL/min.

Endpoints and assessments

This analysis was based on an unplanned update at the request of regulatory authorities, with a data cut-off of March 3, 2014 (data cut-off for the primary analysis was May 24, 2013[13]). The objective of this secondary analysis was to evaluate the efficacy and safety of Rd continuous treatment in patients with varying degrees of RI. The primary endpoint was progression-free survival (PFS) for Rd continuous *vs.* MPT. Secondary endpoints included OS, overall response rate (ORR; ≥ partial response [PR]), time to second-line anti-myeloma treatment, improvement in CRAB criteria (calcium, renal, anemia, bone; including improvement of renal function from baseline by observing improvement in CrCl), and safety. Response was investigator-assessed using the International Myeloma Working Group (IMWG) criteria[14] after each treatment cycle and every 28 days during PFS follow-up.

Baseline CrCl was estimated from serum creatinine by a central laboratory at screening using the Cockcroft-Gault formula,[15,16] and reassessed on day 1 (± 3 days) of each treatment cycle. Per-protocol improvement in renal function was defined as an increase of ≥ 1 renal function subgroup (by CrCl as defined above) from baseline at any point during treatment. As an additional retrospective analysis, renal response was assessed according to IMWG criteria[4] (*Online Supplementary Methods*).

Safety was evaluated until 28 days after the last dose of the study drug; adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0.

Results

Patient characteristics

Of the 1623 patients randomized, 389 (24.0%) had no RI, 715 (44.1%) had mild RI, 372 (22.9%) had moderate RI, and 147 (9.1%; the smallest subgroup) had severe RI (excluding patients requiring dialysis). Renal subgroups

were defined using CrCl-based thresholds that correspond to levels at which lenalidomide dose reductions are recommended in patients with RI.[17,18] The median duration of follow-up was 45.5 months with a data cut-off of March 3, 2014 (an update of the previously published final PFS analysis, which had a data cut-off of May 24, 2013[13]). Protocol violations involving incorrect starting dose of lenalidomide or melphalan for level of renal function at randomization, or incorrect dose adjustment due to change in renal function during treatment were rare (< 2%), and only 3 patients were lost to follow-up (*Online Supplementary Figure S1*). Baseline characteristics were well balanced among treatment groups (Table 1). An increasing degree of RI was associated with older age, higher ISS stage, and higher Eastern Cooperative Oncology Group (ECOG) performance status score.

Efficacy

Efficacy results reported here are focused on the Rd continuous and MPT arms (primary comparators in the FIRST trial). A PFS benefit was seen for Rd continuous compared with MPT in all subgroups of patients except those with severe RI (Figure 1). The HR for risk of progression or death for Rd continuous *vs*. MPT was 0.67 in patients with no RI (P=0.015), 0.70 in patients with mild RI (P=0.002), and 0.65 in patients with moderate RI (P=0.005). In patients with severe RI, no clear PFS benefit with Rd continuous *vs*. MPT could be determined (HR, 0.80; P=0.394). Four-year PFS was increased with Rd continuous *vs*. MPT in all renal subgroups: 41.3% *vs*. 18.4% in patients with no RI, 34.3% *vs*. 12.7% in patients with mild RI, 26.9% *vs*. 11.8% in patients with moderate RI, and 22.2% *vs*. 0% in patients with severe RI. Similarly, PFS was extended with Rd continuous *vs*. Rd18 in patients with no RI to moderate RI. Across all treatment arms, a worse level of renal function was associated with a shorter PFS.

OS improvements were observed in patients with no RI or mild RI who were treated with Rd continuous *vs.* MPT (HR, 0.59 and 0.73, respectively; Table 2). No OS benefits were observed in patients with moderate or severe RI with Rd continuous *vs.* MPT. Rates of 4-year survival were higher with Rd continuous compared with MPT for all renal subgroups: 69.7% *vs*. 58.4% in patients with no RI, 63.4% *vs.* 54.4% in those with mild RI, 50.6% *vs*. 45.0% in those with moderate RI, and 41.6% *vs.* 29.5% in those with severe RI. OS was similar with Rd continuous and Rd18, regardless of renal function.

Compared with MPT, Rd continuous extended the time to second-line anti-myeloma treatment in patients with no RI (HR, 0.66), mild RI (HR, 0.66), and moderate RI (HR, 0.55; Table 2). An increase in time to second-line anti-myeloma treatment was not observed in patients with severe RI receiving Rd continuous *vs.* those receiving MPT.

Rd continuous treatment resulted in higher ORRs (≥ PR) *vs.* MPT treatment in patients with mild or moderate RI

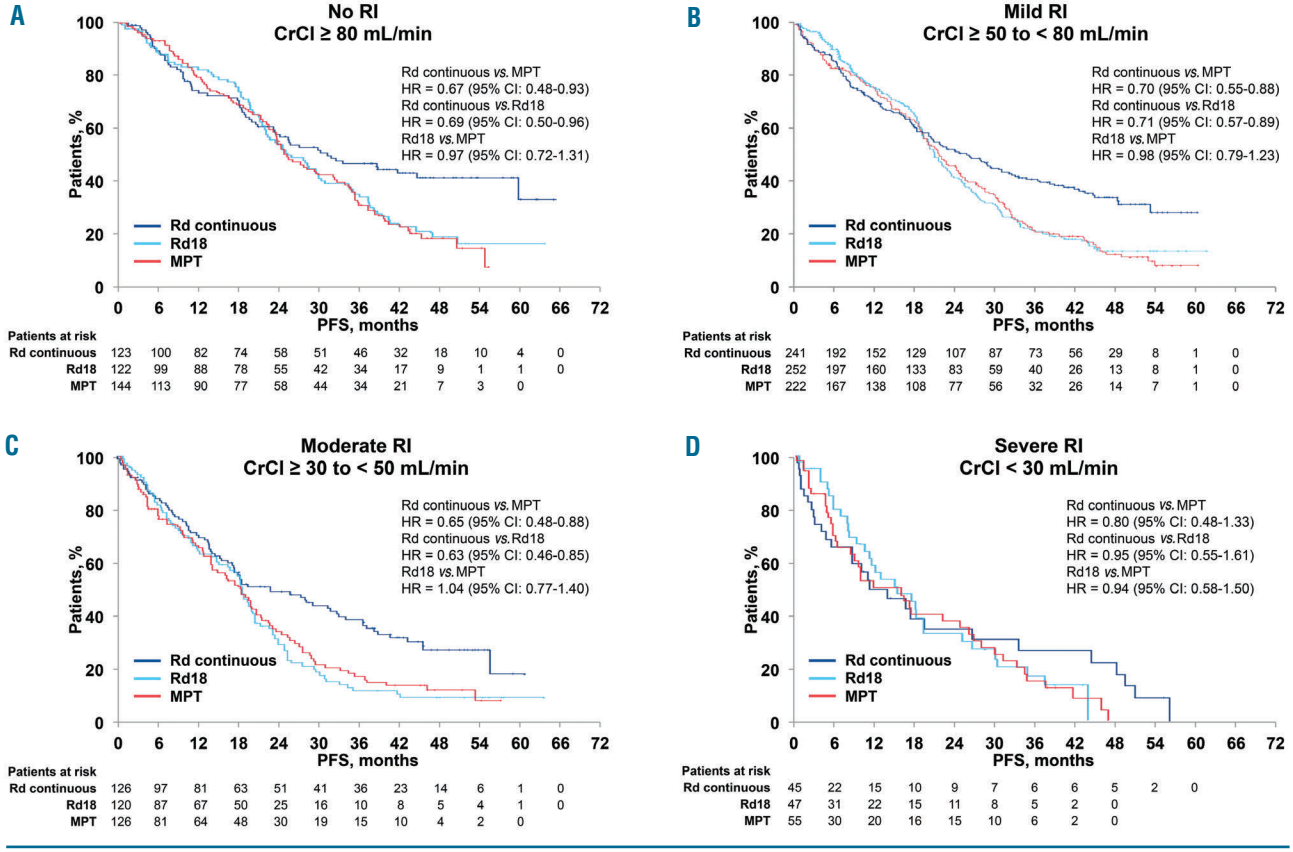

Figure 1. Kaplan-Meier curves of progression-free survival (PFS) in patients with (A) **no renal impairment (RI),** (B) **mild RI,** (C) **moderate RI, and** (D) **severe RI in all renal subgroups.** CrCl: creatinine clearance; HR: hazard ratio; MPT: melphalan, prednisone, and thalidomide; Rd: lenalidomide and low-dose dexamethasone; Rd18: Rd for 18 cycles.

(Table 3). ORR was 80.1% with Rd continuous *vs.* 70.7% with MPT (odds ratio [OR], 1.66) in patients with mild RI and 84.9% *vs.* 58.7% (OR, 3.96) in patients with moderate RI. No difference in ORR was shown with Rd continuous *vs.* MPT in the no RI or severe RI subgroups. Patients with moderate RI showed improved ORR with Rd continuous treatment compared with those receiving Rd18 (84.9% *vs.* 70.0%; OR, 2.41). No differences were observed between Rd continuous and Rd18 for ORRs in other renal function subgroups. Patients with severe RI had lower ORRs than those with better renal function across all treatment arms.

Improvement of renal function (per protocol)

Per-protocol improvement of renal function was defined as an increase of ≥ 1 renal function level (defined by the same CrCl thresholds used for the subgroup analysis) from baseline at any point during treatment. For this analysis, results for Rd continuous and Rd18 arms were pooled. Improved renal function was generally observed across all combined Rd and the MPT treatment groups (Figure 2A). All patients with improved renal function in the pooled Rd group ameliorated within the first 18 treatment cycles. Of the patients with severe RI (CrCl < 30

Table 1. Patient baseline characteristics.

	No RI CrCl ≥ 80 mL/min (n = 389)			Mild RI CrCl ≥ 50 to < 80 mL/min (n = 715)			Moderate RI CrCl ≥ 30 to < 50 mL/min (n = 372)			Severe RI CrCl < 30 mL/min (n = 147)		
	Rd Cont (n = 123)	Rd18 (n = 122)	MPT (n = 144)	Rd Cont (n = 241)	Rd18 (n = 252)	MPT (n = 222)	Rd Cont (n = 126)	Rd18 (n = 120)	MPT (n = 126)	Rd Cont (n = 45)	Rd18 (n = 47)	MPT (n = 55)
Median age (range), y	68 (44-84)	69 (40-82)	69 (53-88)	73 (53-86)	73 (54-84)	73 (56-86)	76 (61-91)	77 (59-89)	76 (65-92)	77 (61-87)	75 (56-89)	76 (51-90)
≥ 65 y, n. (%)	105 (85.4)	107 (87.7)	127 (88.2)	231 (95.9)	242 (96.0)	215 (96.8)	124 (98.4)	114 (95.0)	126 (100.0)	44 (97.8)	44 (93.6)	52 (94.5)
> 75 y, n. (%)	14 (11.4)	15 (12.3)	21 (14.6)	75 (31.1)	86 (34.1)	73 (32.9)	72 (57.1)	71 (59.2)	66 (52.4)	25 (55.6)	21 (44.7)	28 (50.9)
Male, n. (%)	77 (62.6)	80 (65.6)	89 (61.8)	122 (50.6)	134 (53.2)	111 (50.0)	74 (58.7)	43 (35.8)	65 (51.6)	21 (46.7)	16 (34.0)	22 (40.0)
ISS stage, n. (%)												
I/II	106 (86.2)	105 (86.1)	120 (83.3)	165 (68.5)	167 (66.3)	155 (69.8)	43 (34.1)	43 (35.8)	42 (33.3)	5 (11.1)	7 (14.9)	6 (10.9)
III	17 (13.8)	17 (13.9)	24 (16.7)	76 (31.5)	85 (33.7)	67 (30.2)	83 (65.9)	77 (64.2)	84 (66.7)	40 (88.9)	40 (85.1)	49 (89.1)
ECOG PS, n. (%)												
0	38 (30.9)	41 (33.6)	45 (31.3)	73 (30.3)	85 (33.7)	72 (32.4)	38 (30.2)	28 (23.3)	30 (23.8)	6 (13.3)	9 (19.1)	9 (16.4)
1	62 (50.4)	62 (50.8)	63 (43.8)	110 (45.6)	117 (46.4)	116 (52.3)	62 (49.2)	63 (52.5)	65 (51.6)	23 (51.1)	21 (44.7)	31 (56.4)
2	22 (17.9)	19 (15.6)	34 (23.6)	58 (24.1)	48 (19.0)	33 (14.9)	24 (19.0)	29 (24.2)	29 (23.0)	15 (33.3)	17 (36.2)	15 (27.3)
3	1 (0.8)	0	0	0	2 (0.8)	0	1 (0.8)	0	2 (1.6)	0	0	0
NA	0	0	2 (1.4)	0	0	1 (0.5)	1 (0.8)	0	0	1 (2.2)	0	0
High-risk cytogenetics,[a] n. (%)	8 (6.5)	6 (4.9)	4 (2.8)	17 (7.1)	16 (6.3)	21 (9.5)	11 (8.7)	8 (6.7)	12 (9.5)	4 (8.9)	4 (8.5)	4 (7.3)

[a]*del(17p) and/or t(4;14). Cont: continuous; CrCl: creatinine clearance; ECOG PS: Eastern Cooperative Oncology Group performance status; ISS: International Staging System; MPT: melphalan, prednisone, and thalidomide; NA: not applicable; Rd: lenalidomide and low-dose dexamethasone; Rd18: Rd for 18 cycles; RI: renal impairment.*

Table 2. OS and time to second anti-myeloma treatment in renal subgroups.

	No RI CrCl ≥ 80 mL/min (n = 389)	Mild RI CrCl ≥ 50 to < 80 mL/min (n = 715)	Moderate RI CrCl ≥ 30 to < 50 mL/min (n = 372)	Severe RI CrCl < 30 mL/min (n = 147)
4-year OS, % (SE)				
Rd continuous	69.7 (4.8)	63.4 (3.3)	50.6 (4.8)	41.6 (8.0)
Rd18	70.4 (4.5)	57.9 (3.4)	44.6 (4.9)	46.0 (8.1)
MPT	58.4 (4.5)	54.4 (3.6)	45.0 (4.9)	29.5 (7.5)
HR (95% CI)				
Rd continuous *vs.* MPT	0.59 (0.38-0.91)	0.73 (0.55-0.97)	0.83 (0.58-1.18)	0.92 (0.55-1.53)
Rd continuous *vs.* Rd18	0.78 (0.49-1.24)	0.91 (0.69-1.21)	0.83 (0.58-1.17)	1.27 (0.72-2.21)
Rd18 *vs.* MPT	0.73 (0.49-1.10)	0.80 (0.61-1.05)	1.01 (0.71-1.43)	0.76 (0.45-1.28)
Median time to second-line anti-myeloma treatment, mo				
Rd continuous	43.7	37.0	35.8	17.5
Rd18	31.3	29.9	24.1	23.7
MPT	31.3	27.8	21.8	18.1
HR (95% CI)				
Rd continuous *vs.* MPT	0.66 (0.47-0.92)	0.66 (0.52-0.84)	0.55 (0.39-0.78)	0.74 (0.42-1.29)
Rd continuous *vs.* Rd18	0.80 (0.56-1.12)	0.77 (0.61-0.98)	0.56 (0.40-0.79)	1.02 (0.58-1.80)
Rd18 *vs.* MPT	0.84 (0.61-1.14)	0.85 (0.68-1.06)	0.94 (0.68-1.29)	0.86 (0.51-1.42)

CrCl: creatinine clearance; HR: hazard ratio; MPT: melphalan, prednisone, and thalidomide; OS: overall survival; Rd: lenalidomide and low-dose dexamethasone; Rd18: Rd for 18 cycles; RI: renal impairment; SE: standard error.

mL/min) at baseline who were treated with Rd, 61.4% shifted to a better renal function category (CrCl ≥ 30 mL/min) during treatment, compared with 55.8% of those treated with MPT. For patients with mild (CrCl ≥ 50 to < 80 mL/min) or moderate RI (CrCl ≥ 30 to < 50 mL/min) at baseline, rates of renal function improvement were similar with Rd compared with MPT (mild: 45.5% *vs.* 47.8%, respectively; moderate: 63.8% *vs.* 62.0%, respectively). Normal renal function was achieved by 4.8% of Rd-treated patients and 0% of MPT-treated patients with severe RI at baseline, and by 9.4% and 1.9%, respectively, of patients with moderate RI at baseline. Mild RI was achieved by 18.1% of patients with severe RI who received Rd and 11.6% who received MPT. However,

Table 3. Response to treatment in renal subgroups.

	No RI CrCl ≥ 80 mL/min			Mild RI CrCl ≥ 50 to < 80 mL/min			Moderate RI CrCl ≥ 30 to < 50 mL/min			Severe RI CrCl < 30 mL/min		
	Rd Cont (n = 123)	Rd18 (n = 122)	MPT (n = 144)	Rd Cont (n = 241)	Rd18 (n = 252)	MPT (n = 222)	Rd Cont (n = 126)	Rd18 (n = 120)	MPT (n = 126)	Rd Cont (n = 45)	Rd18 (n = 47)	MPT (n = 55)
ORR (≥ PR), %	83.7	86.1	74.3	80.1	81.3	70.7	84.9	70.0	58.7	64.4	66.0	54.5
CR	20.3	22.1	20.1	24.5	22.6	8.1	18.3	11.7	9.5	15.6	25.5	12.7
VGPR	31.7	32.0	15.3	25.7	24.6	20.3	28.6	28.3	17.5	15.6	21.3	20.0
PR	31.7	32.0	38.9	29.9	34.1	42.3	38.1	30.0	31.7	33.3	19.1	21.8
SD, %	14.6	10.7	20.1	12.4	13.1	19.8	8.7	21.7	20.6	15.6	23.4	32.7
PD, %	1.6	1.6	1.4	2.5	0.8	3.2	1.6	1.7	5.6	0	0	1.8
NE, %	0	1.6	4.2	5.0	4.8	6.3	4.8	6.7	15.1	20.0	10.6	10.9
OR (95% CI)												
Rd Cont *vs.* MPT	1.78 (0.97-3.27)			1.66 (1.08-2.55)			3.96 (2.16-7.23)			1.51 (0.67-3.39)		
Rd Cont *vs.* Rd18	0.83 (0.41-1.68)			0.92 (0.59-1.44)			2.41 (1.29-4.51)			0.94 (0.40-2.21)		
Rd18 *vs.* MPT	2.14 (1.13-4.03)			1.81 (1.18-2.77)			1.64 (0.97-2.78)			1.61 (0.72-3.61)		

Cont: continuous; CR: complete response; CrCl: creatinine clearance; MPT: melphalan, prednisone, and thalidomide; NE: not evaluable; OR: odds ratio; ORR: overall response rate; PD: progressive disease; PR: partial response; Rd: lenalidomide and low-dose dexamethasone; Rd18: Rd for 18 cycles; RI: renal impairment; SD: stable disease; VGPR: very good partial response.

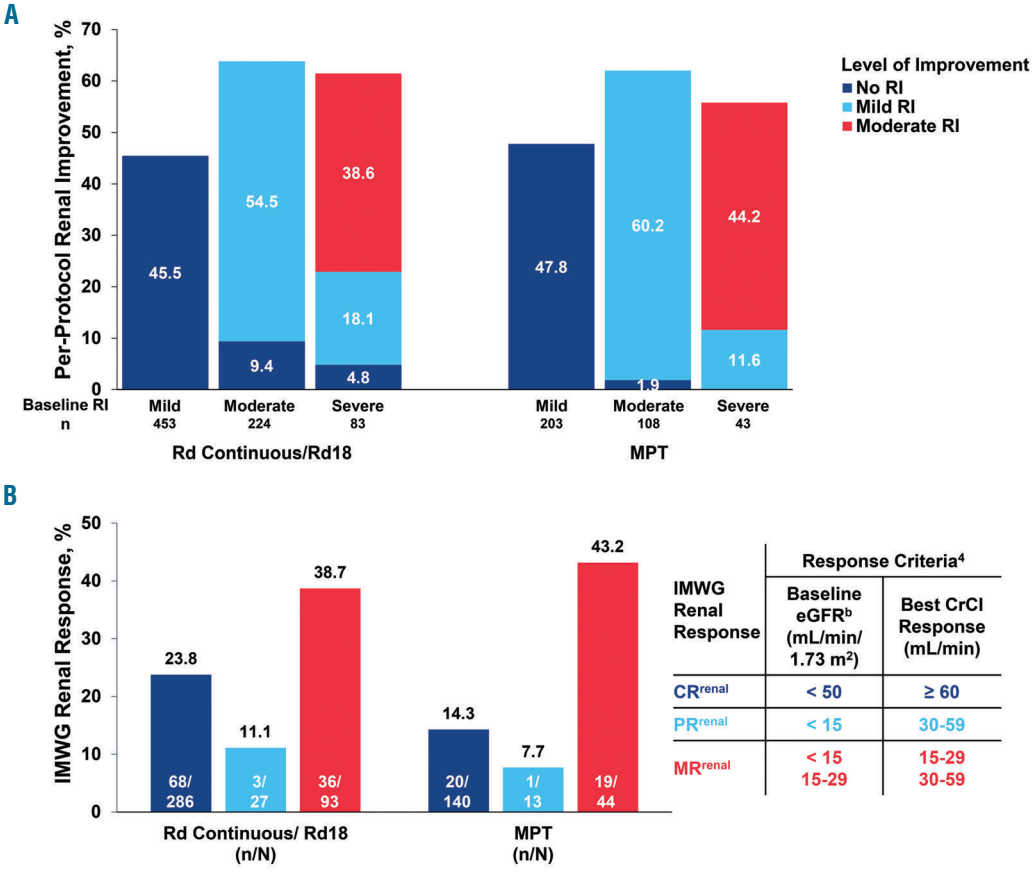

Figure 2. Renal improvement per-protocol (A) **and based on IMWG criteria** (B). [a]Percentages represent patients who improved from baseline to most extreme post-baseline CrCl value, divided by the total number of patients with baseline and post-baseline CrCl data. [b]Based on Modification of Diet in Renal Disease equation. CR: complete response; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; IMWG: International Myeloma Working Group; MPT: melphalan, prednisone, and thalidomide; MR: minor response; PR: partial response; Rd: lenalidomide and low-dose dexamethasone; Rd18: Rd for 18 cycles; RI: renal impairment.

patient numbers within each of these improvement subgroups were small. Overall, < 5% of patients in either treatment group experienced worsening renal function during treatment (Rd, 2.5%; MPT, 2.7%).

Improvement in renal function (IMWG criteria)

IMWG-defined complete renal response (CR^{renal}), a sustained improvement in renal function to near normal levels (CrCl ≥ 60 mL/min), was achieved by 23.8% of patients receiving Rd and 14.3% of patients receiving MPT treatment (Figure 2B). Partial renal response was achieved by 11.1% of patients receiving Rd and 7.7% of patients receiving MPT. Similar rates of minimal renal response were observed across arms.

Of the 68 Rd-treated patients who achieved CR^{renal}, 58 (85.3%) did so within the first 3 cycles of treatment. Eleven of the 68 patients (16.2%) who achieved CR^{renal} received an increased dose of lenalidomide after exhibiting renal improvement; 10 of these 11 patients tolerated the increased dose for the remainder of the study.

Safety

The median duration of treatment in the Rd continuous arm was 22.4 months (range, 0.9-66.2 months) for patients with no RI, 18.9 months (range, 0.3-61.7 months) for those with mild RI, and 18.9 months (0.2-60.0 months) for those with moderate RI (*Online Supplementary Table S1*). Patients with severe RI had the shortest median duration of treatment of only 6.8 months (0.3-56.2 months). Actual lenalidomide dosing on the Rd continuous treatment arm was close to planned dosing for patients with no, mild, or moderate RI, with a median relative dose intensity of ≥ 0.9. Patients with severe RI had a median relative dose intensity of only 0.7 with Rd continuous. The discontinuation rate due to AEs was similar across renal subgroups (Table 4). The most frequent hematologic grade 3/4 AEs across renal subgroups were anemia (15%-27% with Rd continuous and 15%-35% with MPT) and neutropenia (22%-32% for Rd continuous and 29%-53% for MPT; Table 4). In all treatment arms, the incidence of anemia increased with the degree of RI. Rash also occurred at a higher rate in patients with severe RI treated with Rd continuous or Rd18. The most frequent nonhematologic AE was infection (28%-31% with Rd continuous and 14%-24% with MPT). Rates of deep vein thrombosis and pulmonary embolism were not impacted by renal function.

Discussion

RI is present in a substantial number of patients with NDMM, is often related to comorbidities such as hypertension and diabetes in addition to the MM insult, and is associated with increased morbidity and mortality.[1-3,19]

Table 4. Discontinuations due to AEs and grade 3/4 AEs.

Variable, n (%)	No RI CrCl ≥ 80 mL/min (n = 389)			Mild RI CrCl ≥ 50 to < 80 mL/min (n = 715)			Moderate RI CrCl ≥ 30 to < 50 mL/min (n = 363)			Severe RI CrCl < 30 mL/min (n = 147)		
	Rd Cont (n = 123)	Rd18 (n = 122)	MPT (n = 144)	Rd Cont (n = 240)	Rd18 (n = 252)	MPT (n = 222)	Rd Cont (n = 124)	Rd18 (n = 119)	MPT (n = 120)	Rd Cont (n = 45)	Rd 18 (n = 47)	MPT (n = 55)
Discontinuation of any study drug due to AEs	40 (33)	13 (11)	36 (25)	69 (29)	56 (22)	63 (28)	44 (36)	23 (19)	38 (32)	14 (31)	17 (36)	16 (29)
Any grade 3/4 AE	108 (88)	90 (74)	130 (90)	195 (81)	206 (82)	199 (90)	112 (90)	96 (81)	98 (82)	39 (87)	41 (87)	53 (96)
Hematologic AEs (≥ 10% in any renal subgroup of any treatment arm)												
Neutropenia	27 (22)	25 (21)	76 (53)	76 (32)	72 (29)	112 (51)	37 (30)	35 (29)	39 (33)	11 (24)	11 (23)	16 (29)
Anemia	18 (15)	11 (9)	22 (15)	42 (18)	33 (13)	34 (15)	27 (22)	29 (24)	27 (23)	12 (27)	12 (26)	19 (35)
Thrombocytopenia	7 (6)	6 (5)	20 (14)	24 (10)	22 (9)	26 (12)	10 (8)	10 (8)	11 (9)	4 (9)	5 (11)	3 (6)
Leukopenia	4 (3)	6 (5)	17 (12)	12 (5)	12 (5)	22 (10)	8 (7)	8 (7)	10 (8)	0	4 (9)	4 (7)
Nonhematologic AEs (≥ 10% in any renal subgroup of any treatment arm)												
Infections	38 (31)	23 (19)	20 (14)	68 (28)	53 (21)	36 (16)	39 (31)	30 (25)	24 (20)	14 (31)	12 (26)	13 (24)
Pneumonia	11 (9)	9 (7)	7 (5)	25 (10)	23 (9)	12 (5)	5 (4)	10 (8)	9 (8)	4 (9)	3 (6)	3 (6)
Back pain	8 (7)	14 (12)	7 (5)	19 (8)	13 (5)	12 (5)	8 (7)	6 (5)	7 (6)	4 (9)	1 (2)	2 (4)
Fatigue	7 (6)	8 (7)	8 (6)	20 (8)	23 (9)	10 (5)	11 (9)	8 (7)	5 (4)	2 (4)	7 (15)	8 (15)
Rash	5 (4)	2 (2)	6 (4)	11 (5)	13 (5)	8 (4)	8 (7)	8 (7)	11 (9)	9 (20)	5 (11)	3 (6)
Renal failure	2 (2)	3 (3)	1 (1)	7 (3)	3 (1)	3 (1)	3 (2)	4 (3)	5 (4)	1 (2)	8 (17)	7 (13)
Renal failure, acute	1 (1)	1 (1)	2 (1)	2 (1)	6 (2)	2 (1)	10 (8)	6 (5)	7 (6)	5 (11)	3 (6)	2 (4)
PSN	1 (1)	0	16 (11)	3 (1)	1 (< 1)	22 (10)	1 (1)	1 (1)	9 (8)	1 (2)	0	4 (7)
General physical health deterioration	1 (1)	0	3 (2)	6 (3)	11 (4)	5 (2)	4 (3)	4 (3)	2 (2)	5 (11)	1 (2)	2 (4)
Hypocalcemia	0	2 (2)	1 (1)	8 (3)	4 (2)	2 (1)	12 (10)	8 (7)	3 (3)	3 (7)	5 (11)	2 (4)
Blood creatinine increased	0	0	1 (1)	1 (< 1)	1 (< 1)	0	4 (3)	1 (1)	2 (2)	5 (11)	3 (6)	3 (6)

AE: adverse event; Cont: continuous; CrCl: creatinine clearance; MPT: melphalan, prednisone, and thalidomide; PSN: peripheral sensory neuropathy; Rd: lenalidomide and low-dose dexamethasone; Rd18: Rd for 18 cycles; RI: renal impairment.

When addressed in a timely manner, myeloma-associated RI tends to improve or normalize.[1,3] This secondary cohort analysis of the FIRST trial assessed the activity and tolerability of continuous Rd therapy, with renally adapted dosing of lenalidomide, in patients with NDMM and RI who were ineligible for SCT. Rd continuous treatment reduced the risk of progression or death by 33%, 30%, and 35% in patients with no, mild, or moderate RI, respectively, compared with MPT. Rd continuous also improved ORR and extended time to second-line anti-myeloma treatment compared with MPT in patients with mild and moderate RI, and provided OS benefits for patients with mild RI. These data are consistent with efficacy results in patients with normal renal function and the overall study population from the FIRST trial.[13]

In patients with severe RI, the efficacy benefits of Rd continuous compared with MPT could not be clearly demonstrated due to wide confidence intervals, which limited a definitive interpretation of the results. Analysis was further limited by the low number of patients with severe RI (only 9.1% of the overall trial population) and their short duration of treatment (median, 6.8 months, compared with 18.9 months for other patients with RI). Severe RI has been shown to be an adverse prognostic factor for outcomes with regimens containing novel agents, including bortezomib-based combinations.[20] This was shown even for patients whose renal function improved with therapy, suggesting that the poor prognostic impact of severe RI may be related to myeloma biology.[20] Indeed, in the current study, severe RI was associated with worse baseline disease characteristics, including higher disease stage and ECOG performance status score. The shorter duration of lenalidomide treatment in patients with severe RI, compared with those with better renal function, was likely not due to decreased tolerability of lenalidomide given that the treatment discontinuation rate due to AEs was similar across renal subgroups. Instead, patients with severe RI likely progressed more rapidly despite treatment, as evidenced by lower rates of ORR and shorter PFS across all treatment arms.

Previous analyses have demonstrated the efficacy of lenalidomide plus dexamethasone treatment in patients with RRMM and mild to moderate RI.[9] However, in these studies, standard lenalidomide dosing was associated with increased toxicity and more frequent use of subsequent dose reductions and interruptions due to AEs in patients with moderate to severe RI *vs.* patients with mild or no RI.[9] Recommendations have since been made for lenalidomide starting dose adjustments for moderate to severe RI based on pharmacokinetic data.[7,17] Lenalidomide is not nephrotoxic,[18] but is primarily renally excreted,[7] such that RI greatly affects its pharmacokinetics. Therefore, doses are adjusted in patients with RI to match exposure levels achieved by standard dosing in patients with normal renal function.[7] In a series of 50 patients with RRMM, lenalidomide plus dexamethasone, with starting dose adjustments of lenalidomide based on renal function, was shown to be active with similar rates of AEs in patients with and without RI.[8]

This analysis demonstrated that applying dose adjustments of lenalidomide, adapted to the level of renal function, results in a similar safety profile across all levels of RI in patients with NDMM. An exception was anemia, which increased with the degree of RI in all treatment arms even with dose adjustments, suggesting that anemia may be a consequence of RI, independent of treatment. Physicians should be vigilant about monitoring for and managing anemia in RI patients. Rd continuous was well tolerated across renal function groups, with similar rates of discontinuation due to AEs for patients with and without RI. Patients with mild to moderate RI also tolerated sustained treatment with lenalidomide for durations similar to those tolerated by patients without RI.

Reversibility of RI is an important treatment goal and is associated with improved survival outcomes.[3] Although severe RI was only a small subset of the FIRST trial and patients requiring dialysis were excluded, Rd continuous or Rd18 treatment improved renal function using the per-protocol assessment in most patients (52.6%), including 61.4% of those with severe RI. Additionally, the rate of IMWG-defined CR^{renal} was 23.8% in Rd-treated patients. Compared with MPT, Rd treatment resulted in a greater degree of renal improvement, although patient numbers were small. Results were consistent with previous observations of improvement in renal function in both NDMM and RRMM with lenalidomide-based treatment.[6,8,9] Overall, lenalidomide represents an active treatment option for patients with NDMM and RI, especially those who may have contraindications for bortezomib such as preexisting peripheral neuropathy.

Challenges remain in assessing renal function in patients with MM.[1,4,21] There is a lack of consensus regarding the most appropriate assessment method, and there are additional difficulties in assessing renal function in the elderly, including lower production of serum creatinine.[1,9,21] Despite these limitations, continuous therapy with Rd until disease progression improved renal function and provided PFS benefits in a large proportion of patients with mild to moderate RI with a manageable safety profile. With renally adapted dosing of lenalidomide, Rd continuous represents an effective and tolerable treatment option for many patients with NDMM with RI who are ineligible for SCT.

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