

Pomalidomide Plus Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma and Renal Impairment: Results From a Phase II Trial

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ABSTRACT

Purpose

Renal impairment (RI) limits treatment options in patients with relapsed/refractory multiple myeloma (RRMM). Here, we prospectively studied pomalidomide plus low-dose dexamethasone (LoDEX) in patients with RRMM and moderate or severe RI, including those receiving hemodialysis.

Patients and Methods

MM-013, a noncomparative, European phase II trial, enrolled three patient cohorts: moderate RI (cohort A; estimated glomerular filtration rate, 30 to < 45 mL/min/1.73 m²); severe RI (cohort B; estimated glomerular filtration rate, < 30 mL/min/1.73 m²); and severe RI that requires hemodialysis (cohort C). Patients received pomalidomide 4 mg/d on days 1 to 21 and LoDEX 20 or 40 mg once per week in 28-day cycles. The primary end point was overall response rate.

Results

Of 81 enrolled patients (33, 34, and 14 patients in cohorts A, B, and C, respectively), 13 were still receiving treatment at data cutoff (January 28, 2017). Overall response rates were 39.4%, 32.4%, and 14.3%, with a median duration of response of 14.7 months, 4.6 months, and not estimable, respectively. Of importance, 100%, 79.4%, and 78.6% of patients, respectively, achieved disease control. With a median follow-up of 8.6 months, median overall survival was 16.4 months, 11.8 months, and 5.2 months, respectively. Complete renal responses were observed only in cohort A (18.2%), and no patients in cohort C became hemodialysis independent. Grade 3 and 4 hematologic treatment-emergent adverse events and pomalidomide discontinuations as a result of treatment-emergent adverse events occurred more frequently in cohort C. Pomalidomide pharmacokinetics were comparable among the three renal cohorts.

Conclusion

Pomalidomide 4 mg/d plus LoDEX is efficacious in patients with RRMM with moderate or severe RI, including those who had more advanced disease and required hemodialysis. The safety profile was acceptable among the three groups, and no new safety signals were observed.

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INTRODUCTION


Renal impairment (RI) is a common comorbidity of multiple myeloma (MM).¹⁻⁴ Approximately 20% to 30% of patients with MM present with RI at diagnosis, with approximately 10% requiring dialysis.¹⁻⁷ Over time, patients with MM may develop RI, which is associated with poor prognosis and short survival (median overall survival [OS], < 2 years).^{1-4,8,9} In addition, RI affects the pharmacokinetics (PK) of drugs that are primarily


excreted by the kidneys, which limits treatment options.¹⁰

Pomalidomide is a potent immunomodulatory agent with direct antimyeloma and immunomodulatory effects on the bone marrow microenvironment, and has demonstrated an OS benefit for patients with relapsed/refractory MM (RRMM). By binding to cereblon, pomalidomide triggers the proteasomal degradation of Ikaros and Aiolos transcription factors, which regulate the expression of *IRF4* and *c-MYC* and repress the transcription of *IL-2*.^{11,12} Pomalidomide is approved

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 Data Supplements
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in combination with low-dose dexamethasone (LoDEX) and is a standard of care for the treatment of patients with RRMM.¹³⁻¹⁵ Clinical trials have demonstrated comparable efficacy and tolerability of this combination in patients with RRMM and moderate RI or normal renal function.^{16,17} Furthermore, patients who achieved disease control had improved long-term survival outcomes.¹⁸ Because patients with severe RI are typically excluded from clinical trials, data on the efficacy and safety of pomalidomide plus LoDEX in this patient population are limited. Moreover, to date, there is no experience with this combination in patients with RRMM who require hemodialysis.

Pomalidomide is extensively metabolized by the liver, with only approximately 2% of active substance eliminated in the urine,^{14,15} which suggests that RI may not affect pomalidomide exposure in a clinically relevant manner. This is in contrast to lenalidomide, which is predominately eliminated unchanged by the kidneys and requires dose adjustment in patients with RI.^{19,20}

In patients with normal renal function, pomalidomide median plasma half-life is approximately 9.5 hours.¹⁴ A recent population PK analysis indicated comparable pomalidomide plasma exposure and clearance between patients with moderate-to-severe RI without hemodialysis and those with normal renal function. In addition, in patients with severe RI who require hemodialysis, pomalidomide should be administered after hemodialysis.²¹

Here, we report the efficacy, renal response, safety, and PK results from the prospective European MM-013 phase II study, which investigated pomalidomide plus LoDEX in patients with RRMM with moderate or severe RI, including those receiving hemodialysis.

older with documented MM diagnosis and had measurable disease by M-protein or serum free light chain (sFLC) levels. Patients must have received one or more prior antimyeloma regimens, including lenalidomide, and documented progression per International Myeloma Working Group criteria during or after their last antimyeloma treatment. In addition, all patients must have had impaired renal function with an estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m² according to the Modification of Diet in Renal Disease equation.²²

Eligible patients were enrolled in three renal cohorts: cohort A: moderate RI (eGFR 30 to < 45 mL/min/1.73 m²); cohort B: severe RI (eGFR < 30 mL/min/1.73 m²); and cohort C: severe RI requiring hemodialysis.

Patients in all three cohorts received 28-day cycles of pomalidomide at 4 mg/d on days 1 to 21, and LoDEX at 40 mg/d (if age ≤ 75 years) or 20 mg/d (if age > 75 years) on days 1, 8, 15, and 22. Thromboprophylaxis was mandatory for patients who did not require hemodialysis and used for patients on hemodialysis when appropriate and feasible. Detailed methods for hemodialysis procedures and PK analysis are provided in the Data Supplement.

Study End Points

The primary end point was overall response rate (ORR) per International Myeloma Working Group criteria.²³ Secondary end points included progression-free survival (PFS), time to progression, time to response and duration of response in responders (partial response [PR] or greater), OS, renal response, and time to renal response. Renal response—defined as sustained improvement of baseline eGFR—was assessed according to criteria defined by Dimopoulos et al^{3,24} and Ludwig et al.²⁵ Most laboratory assessments for renal efficacy were performed locally. The safety and occurrence of second primary malignancies were also assessed, as well as the PK of pomalidomide and biomarkers.

Statistical Analysis

MM-013 was a noncomparative study, and the three renal cohorts were evaluated separately. The sample size for cohorts A and B was calculated according to the exact single-stage design and on the basis of the primary end point of ORR (PR or greater). On the basis of an expectation that 15% of patients would have been unevaluable and the need for 27 patients in cohort A and B, 33 patients were planned for enrollment in these cohorts. Target enrollment for cohort C was 14.

PATIENTS AND METHODS

Study Patients

MM-013, a multicenter, open-label, noncomparative, phase II study, was conducted at 18 sites across eight countries in Europe. The study was fully enrolled with 81 patients; 13 remained on the study treatment at the final data cutoff of January 28, 2017 (Fig 1). Patients were age 18 years or

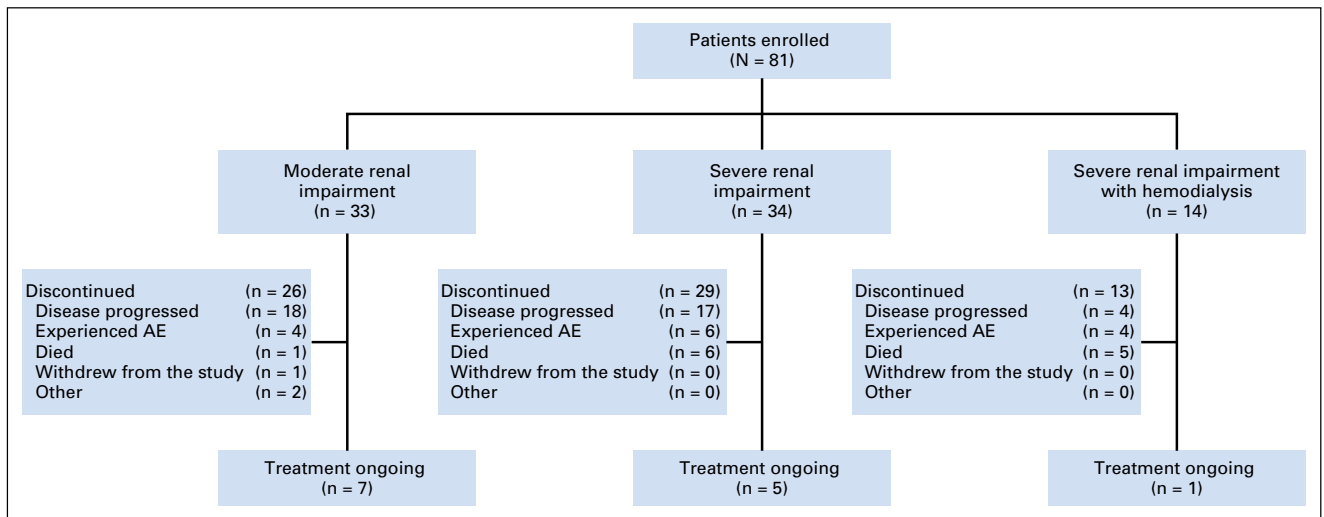


Fig 1. CONSORT diagram. AE, adverse event.

Table 1. Baseline and Disease Characteristics (intent-to-treat population)

Baseline Characteristic	Cohort A, Moderate RI (n = 33)	Cohort B, Severe RI (n = 34)	Cohort C, Severe RI + Hemodialysis (n = 14)	Overall (N = 81)
Patient				
Age, median (range), years	72.0 (55-86)	72.0 (52-82)	70.0 (55-78)	72.0 (52-86)
≥ 65 years, No. (%)	26 (78.8)	30 (88.2)	10 (71.4)	66 (81.5)
Male, No. (%)	24 (72.7)	16 (47.1)	9 (64.3)	49 (60.5)
Time since MM diagnosis, median (range), years	3.8 (1.1-19.3)	3.7 (0.7-19.4)	3.2 (0.5-7.7)	3.8 (0.5-19.4)
ISS stage, No. (%)				
I	0	0	0	0
II	6 (18.2)	3 (8.8)	0	9 (11.1)
III	27 (81.8)	31 (91.2)	14 (100)	72 (88.9)
ECOG PS, No. (%)				
0 or 1	28 (84.8)	27 (79.4)	7 (50.0)	62 (76.5)
2	5 (15.2)	7 (20.6)	7 (50.0)	19 (23.5)
Disease				
Percent plasma cells in bone marrow, median (range)	50 (3-90)	50 (2-95)	65 (5-90)	50 (2-95)
β ₂ -Microglobulin, median (range), mg/L	6.5 (2.8-17.1)	9.5 (3.5-26.5)	27.5 (12.0-149.0)	9.6 (2.8-149.0)
Measurable serum M-protein, No. (%)				
IgG	11 (33.3)	9 (26.5)	3 (21.4)	23 (24.8)
IgA	4 (12.1)	2 (5.9)	4 (28.6)	10 (12.3)
Involvement sFLCκ, median (range), mg/L*	1,220 (10-15,492)	1,771 (116-40,300)	7,825 (558-25,320)	1,771 (10-40,300)
Involvement sFLCλ, median (range), mg/L†	2,240 (228-3670)	1,966 (19-17,819)	7,289 (280-185,000)	2,365 (19-185,000)
Cytogenetic abnormalities, No. (%)‡				
del(13q)	5 (17.9)	4 (20.0)	8 (61.5)	17 (27.9)
del(17p)	2 (7.1)	0	5 (38.5)	7 (11.5)
t(11;14)	3 (10.7)	1 (5.0)	2 (15.4)	6 (9.8)
t(4;14)	0	2 (10.0)	3 (23.1)	5 (8.2)
Other	12 (42.9)	13 (65.0)	7 (53.8)	32 (52.5)
Renal				
Duration of renal insufficiency, median (range), months	24.7 (0.3-231.2)	40.4 (0.4-189.7)	9.4 (0.1-83.1)	26.0 (0.1-231.2)
Renal insufficiency, No. (%)				
Chronic (> 1 month)	27 (81.8)	31 (91.2)	12 (85.7)	70 (86.4)
Acute (≤ 1 month)	6 (18.2)	3 (8.8)	2 (14.3)	11 (13.6)
Baseline eGFR, median (range), mL/min/1.73 m ² §	38.8 (31.0-47.0)	22.2 (8.0-33.5)	8.9 (4.0-21.0)	27.0 (4.0-47.0)
Cystatin C, median (range), mg/dL	1.8 (1.2-2.4)	2.5 (0.8-4.0)	5.1 (1.1-7.3)	2.2 (0.8-7.3)
NGAL, median (range), μg/L	29.9 (1.0-808.2)	61.9 (8.3-1,867.1)	260.5 (107.5-4,096.0)	58.5 (1.0-4,096.0)
Prior treatment				
Prior treatment regimens, median (range)	3 (2-8)	4 (1-10)	4 (2-5)	4 (1-10)
Prior treatment, No. (%)				
Lenalidomide	33 (100)	34 (100)	14 (100)	81 (100)
Thalidomide	14 (42.4)	15 (44.1)	3 (21.4)	32 (39.5)
Bortezomib	32 (97.0)	33 (97.1)	14 (100)	79 (97.5)
Carfilzomib	4 (12.1)	0	0	4 (4.9)
Ixazomib	1 (3.0)	1 (2.9)	0	2 (2.5)
Cyclophosphamide	24 (72.7)	21 (61.8)	6 (42.9)	51 (63.0)
Melphalan¶	20 (60.6)	15 (44.1)	8 (57.1)	43 (53.1)
Stem cell transplantation	9 (27.3)	8 (23.5)	3 (21.4)	20 (24.7)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; Ig, immunoglobulin; ISS, International Staging System; MM, multiple myeloma; NGAL, neutrophil gelatinase-associated lipocalin; RI, renal impairment; sFLCκ, serum κ free light chain; sFLCλ, serum λ free light chain.

*Patients with involved sFLCκ: n = 23 for moderate RI; n = 16 for severe RI; n = 7 for severe RI + hemodialysis; and n = 46 total.

†Patients with involved sFLCλ: n = 9 for moderate RI; n = 18 for severe RI; n = 7 for severe RI + hemodialysis; and n = 34 total.

‡Patients with cytogenetic abnormalities: n = 15 for moderate RI; n = 12 for severe RI; n = 12 for severe RI + hemodialysis; and n = 39 total.

§Baseline values at day 1 of cycle 1; inclusion into cohort according to screening value.

||Including cyclophosphamide that was administered for stem cell mobilization.

¶Including high-dose melphalan.

RESULTS

Patients

Between February 2014 and July 2016, 81 patients with RRMM and RI were enrolled—33 patients in cohort A, 34 in cohort B, and 14 in cohort C. Median age of the overall population

was 72 years (range, 52 to 86 years), and the majority of patients were age 65 years or older (81.5%) and male (60.5%; Table 1). Median time from MM diagnosis to enrollment was 3.8 years (range, 0.5 to 19.4 years). Most patients had chronic—defined as > 1 month—renal insufficiency, with a median duration of renal insufficiency before study enrollment of 24.7, 40.4, and 9.4 months

in cohorts A, B, and C, respectively. Patients in cohort C had higher involved sFLC levels than did patients in cohorts A and B (Table 1). Overall, patients received a median of four prior antimyeloma regimens, and all patients had received prior lenalidomide treatment and 97.5% had received prior bortezomib. Approximately 25% of patients underwent prior stem cell transplantation. Kidney biopsy results, which confirmed MM-related renal disease, were available in 23.5% of patients. Cytogenetic abnormalities at baseline were reported in 45.5%, 35.3%, and 85.7% of patients in cohorts A, B, and C, respectively (Table 1).

As of January 28, 2017, 13 patients (16.0%) were still on treatment—seven in cohort A, five in cohort B, and one patient in cohort C (Fig 1). A total of 68 patients discontinued treatment, mostly because of progressive disease (39 patients; 48.1%).

Efficacy

ORRs (PR or greater) were 39.4%, 32.4%, and 14.3% in cohorts A, B, and C, respectively (Table 2). Clinical benefit (minimal response or greater) was achieved in 51.5%, 41.2%, and 21.4% of patients, respectively. Of 14 patients in cohort C, 10 had their response assessed by M-protein (serum or urine) levels and three by sFLC levels—one patient was not evaluable. Among patients in cohort C, 57.1% had stable disease and 78.6% had disease control (stable disease or greater). In patients who achieved PR or greater, median time to response was 0.99, 0.95, and 1.91 months, and median duration of response was 14.7 months, 4.6 months, and not estimable in cohorts A, B, and C, respectively.

Cystatin C was measured at baseline and postbaseline in all patients as a marker of renal function. In a subanalysis of patients with myeloma (PR or greater) in cohorts A and B, cystatin C values declined over time (Data Supplement).

In a univariable analysis for myeloma response, three variables—baseline eGFR, prior therapy, and time since diagnosis—met a threshold of $P < .2$ and were entered into a multivariable analysis. Prior therapy (odds ratio, 3.25; 95% CI, 1.03 to 10.25; $P = .0438$) and time since diagnosis (odds ratio, 3.65; 95%

CI, 1.17 to 11.43; $P = .0260$) were identified as significant predictors of myeloma response in multivariable analysis.

With a median follow-up duration of 4.6 months, patients in cohort A had a median PFS of 6.5 months. Patients in cohorts B and C had a median PFS of 4.2 months and 2.4 months, respectively (Fig 2A and 2B). Median time to progression was 6.2 months overall, and 8.3 months, 5.5 months, and 4.0 months in cohorts A, B, and C, respectively. With a median follow-up duration of 8.6 months, median OS was 16.4 months, 11.8 months, and 5.2 months in cohorts A, B, and C, respectively (Fig 2C and 2D). Similar efficacy results were noted in patients who were treated with both bortezomib and lenalidomide as prior therapies (Data Supplement).

Renal response with pomalidomide and LoDEX treatment was achieved by six (18.2%), 12 (35.3%), and one (7.1%) patients in cohorts A, B, and C, respectively (Table 3). Complete renal response was achieved in 18.2% of patients in cohort A. Stable renal responses were noted in all cohorts: 75.8% in cohort A, 47.1% in cohort B, and 85.7% in cohort C. Six patients experienced worsening of renal function—two in cohort A and four in cohort B. No patient became hemodialysis independent. Median time to renal response was 0.95 months overall—0.95 and 0.95 in cohorts A and B, respectively. Baseline sFLC level was the only variable that met the threshold of $P < .2$ in a univariable analysis for renal response (odds ratio, 2.08; 95% CI, 0.72 to 6.00; $P = .1744$), and a multivariable analysis was therefore not performed.

Safety

The median duration of treatment was 5.5 months—6.7 months, 4.9 months, and 2.4 months in cohorts A, B, and C, respectively (Table 4). Median number of treatment cycles was 6.0 (range, one to 21 cycles)—7.0 cycles (range, one to 21), 5.5 cycles (range, one to 20), and 3.0 cycles (range, one to 11) in cohorts A, B, and C, respectively. Median average daily pomalidomide dose was 4 mg/d in all cohorts, and the median relative dose intensity was 0.94 to 0.99 across the three cohorts.

Table 2. Myeloma Response

Response	Cohort A, Moderate RI (n = 33)	Cohort B, Severe RI (n = 34)	Cohort C, Severe RI + Hemodialysis (n = 14)	Overall (N = 81)
ORR (\geq PR), No. (%); 95% CI	13 (39.4); 22.9 to 57.9	11 (32.4); 17.4 to 50.5	2 (14.3); 1.8 to 42.8	26 (32.1); 22.2 to 43.4
CBR (\geq MR), No. (%); 95% CI	17 (51.5); 33.5 to 69.2	14 (41.2); 24.7 to 59.3	3 (21.4); 4.7 to 50.8	34 (42.0); 31.1 to 53.5
sCR	0	0	0	0
CR	0	0	0	0
VGPR	6 (18.2)	3 (8.8)	1 (7.1)	10 (12.3)
PR	7 (21.2)	8 (23.5)	1 (7.1)	16 (19.8)
MR	4 (12.1)	3 (8.8)	1 (7.1)	8 (9.9)
SD	16 (48.5)	13 (38.2)	8 (57.1)	37 (45.7)
PD	0	3 (8.8)	2 (14.3)	5 (6.2)
Not evaluable	0	4 (11.8)	1 (7.1)	5 (6.2)
DCR*	33 (100)	27 (79.4)	11 (78.6)	71 (87.7)
TTR, median (range), months	0.99 (0.9-6.6)	0.95 (0.9-5.8)	1.91 (1.0-2.9)	0.97 (0.9-6.6)
DOR, median (95% CI), months	14.7 (4.6 to NE)	4.6 (2.8 to 12.5)	NE (1.5 to NE)	5.8 (4.6 to 14.7)

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; DOR, duration of response; MR, minimal response; NE, not estimable; ORR, overall response rate; PD, progressive disease; PR, partial response; RI, renal impairment; sCR, stringent complete response; SD, stable disease; TTR, time to response; VGPR, very good partial response.

*DCR = sCR + CR + VGPR + PR + MR + SD.

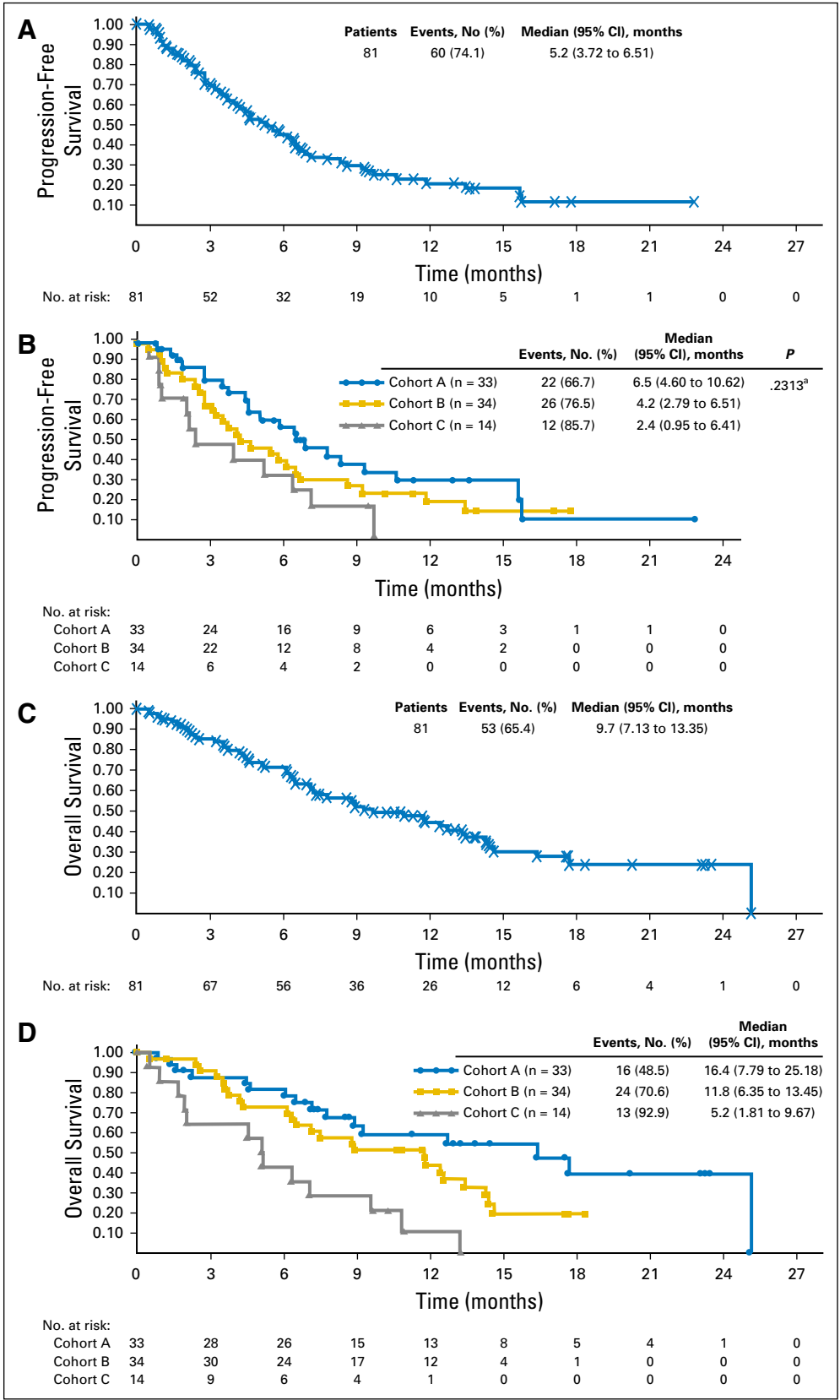


Fig 2. Survival outcomes. (A) Progression-free survival in the overall population. (B) Progression-free survival by renal impairment. (C) Overall survival in the overall population. (D) Overall survival by renal impairment. ^aPvalue is for the exploratory comparison between cohorts A and B.

Table 3. Renal Response

Renal Response	Cohort A, Moderate RI (n = 33)	Cohort B, Severe RI (n = 34)	Cohort C, Severe RI + Hemodialysis (n = 14)	Overall (N = 81)
Renal response, No. (%); 95% CI	6 (18.2); 7.0 to 35.5	12 (35.3); 19.7 to 53.5	1 (7.1); 0.2 to 33.9	19 (23.5); 14.8 to 34.2
RCR*	6 (18.2)	0	0	6 (7.4)
RPR†	NA	2 (5.9)	0	2 (2.5)
RMR‡	NA	10 (29.4)	1 (7.1)	11 (13.6)
Stable§	25 (75.8)	16 (47.1)	12 (85.7)	53 (65.4)
Worsening	2 (6.1)	4 (11.8)	0	6 (7.4)
TTRR, median (range), months	0.95 (1.0-4.6)	0.95 (0.9-6.0)	3.06 (3.1-3.1)	0.95 (0.9-6.0)

NOTE. Data presented as No. (%) unless otherwise indicated.
Abbreviations: eGFR, estimated glomerular filtration rate; NA, not applicable; RCR, renal complete response; RI, renal impairment; RMR, renal minimal response; RPR, renal partial response; TTRR, time to renal response.
*Sustained improvement (≥ 2 months) of baseline eGFR from < 50 mL/min/1.73 m² to ≥ 60 mL/min/1.73 m².
†Sustained improvement of baseline eGFR from < 15 mL/min/1.73 m² to 30-59 mL/min/1.73 m².
‡Sustained improvement of baseline eGFR from < 15 mL/min/1.73 m² to 15-29 mL/min/1.73 m². If baseline eGFR was 15-29 mL/min/1.73 m², improvement was to 30-59 mL/min/1.73 m².
§Stable renal response in cohort C indicates patients remained on hemodialysis.

Pomalidomide dose reductions as a result of adverse events (AEs) occurred in 13 patients (16.0%)—six (18.2%) in cohort A, five (14.7%) in cohort B, and two patients (14.3%) in cohort C. Dose interruptions as a result of AEs were noted in 49 patients (60.5%)—19 (57.6%), 22 (64.7%), and eight patients (57.1%) in cohorts A, B, and C, respectively.

The most prevalent grade 3 and 4 hematologic treatment-emergent AEs (TEAEs) across all three cohorts were neutropenia (53.1%), anemia (35.8%), and thrombocytopenia (27.2%; Table 5). Infections, mainly pneumonia, were the most commonly reported grade 3 and 4 nonhematologic TEAEs—26 (32.1%) overall and 13 (39.4%), nine (26.5%), and four (28.6%) in cohorts A, B, and C, respectively. Other grade 3 and 4 nonhematologic TEAEs included hypocalcemia, hyperkalemia, renal failure, pyrexia, fatigue, and peripheral edema. A total of 51 patients (63.0%) presented with one or more serious TEAEs, reported in 18 (54.5%), 21 (61.8%), and 12 patients (85.7%) in cohorts A, B, and C, respectively. Second primary malignancies were reported in three patients (3.7%)—one each of squamous cell lung cancer, pancreatic cancer, and skin carcinoma). No new safety signals were observed with pomalidomide and LoDEX treatment in any of the three cohorts.

Antibiotic and antiviral prophylaxis for infectious disease was used during the treatment period in 77.8% of patients overall—81.8%, 73.5%, and 78.6% of patients in cohorts A, B, and C, respectively. Granulocyte colony-stimulating factor therapy or

equivalent was administered to 51.9% of patients—54.5%, 52.9%, and 42.9% of patients in cohorts A, B, and C, respectively.

A total of 23 patients (28.4%) died during treatment, which was defined as death on or after the date of first study drug dose and within 28 days of the last study drug dose—six (18.2%) in cohort A, 10 (29.4%) in cohort B, and seven patients (50.0%) in cohort C. Myeloma progression was the most common cause of death, with plasma cell myeloma reported in five patients overall—one patient in cohort A, three patients in cohort B, and one patient in cohort C—and plasma cell leukemia in one patient in cohort B. Death as a result of septic shock and cardiac failure occurred in two patients each. Other causes of death that occurred in one patient each included pancreatic carcinoma, pneumonia, infectious colitis, cardiac arrest, traffic accident, traumatic intracranial hemorrhage, thrombocytopenia, intestinal ischemia, hyperkalemia, brain hemorrhage, renal failure, and acute respiratory distress syndrome.

PK

The PK-evaluable population included 18 patients overall (Data Supplement). Pomalidomide was absorbed with a maximum plasma concentration of 75.6 $\mu\text{g/L}$, 111.0 $\mu\text{g/L}$, and 75.6 $\mu\text{g/L}$, and with an area under the plasma concentration-time curve from time 0 to the last measured time point (plasma exposure) of 899.8 $\text{h} \times \mu\text{g/L}$, 944.9 $\text{h} \times \mu\text{g/L}$, and 665.4 $\text{h} \times \mu\text{g/L}$ in cohorts A, B, and C (on nonhemodialysis days), respectively. Comparable

Table 4. Pomalidomide Dosing Information

Pomalidomide Dosing	Cohort A, Moderate RI (n = 33)	Cohort B, Severe RI (n = 34)	Cohort C, Severe RI + Hemodialysis (n = 14)	Overall (N = 81)
Median duration of treatment (range), months	6.7 (0.9-23.7)	4.9 (0.5-18.6)	2.4 (0.5-10.3)	5.5 (0.5-23.7)
Median No. of treatment cycles (range)	7.0 (1-21)	5.5 (1-20)	3.0 (1-11)	6.0 (1-21)
Median average daily dose (range), mg/d	4.0 (2.4-4.0)	4.0 (2.9-4.0)	4.0 (3.3-4.0)	4.0 (2.4-4.0)
Median relative dose intensity (range)	0.95 (0.57-1.00)	0.94 (0.29-1.02)	0.99 (0.62-1.04)	0.95 (0.29-1.04)
Dose reductions as a result of AEs, No. (%)*	6 (18.2)	5 (14.7)	2 (14.3)	13 (16.0)
Dose interruptions as a result of AEs, No. (%)†	19 (57.6)	22 (64.7)	8 (57.1)	49 (60.5)

Abbreviations: AE, adverse event; RI, renal impairment.
*Patients with ≥ 1 dose reduction due to AEs.
†Patients with ≥ 1 dose interruption due to AEs.

Table 5. Selected TEAEs and Pomalidomide Dose Modifications

Parameter	Cohort A, Moderate RI (n = 33)	Cohort B, Severe RI (n = 34)	Cohort C, Severe RI + Hemodialysis (n = 14)	Overall (N = 81)
≥ 1 serious TEAE, No. (%)	18 (54.5)	21 (61.8)	12 (85.7)	51 (63.0)
Grade 3 and 4 hematologic TEAEs, No. (%)				
Neutropenia	20 (60.6)	15 (44.1)	8 (57.1)	43 (53.1)
Anemia	9 (27.3)	12 (35.3)	8 (57.1)	29 (35.8)
Thrombocytopenia	9 (27.3)	6 (17.6)	7 (50.0)	22 (27.2)
Leukopenia	4 (12.1)	4 (11.8)	5 (35.7)	13 (16.0)
Febrile neutropenia	1 (3.0)	1 (2.9)	0	2 (2.5)
Grade 3 and 4 nonhematologic TEAEs, No. (%)				
Infections	13 (39.4)	9 (26.5)	4 (28.6)	26 (32.1)
Pneumonia	4 (12.1)	2 (5.9)	1 (7.1)	7 (8.6)
Hypocalcemia	1 (3.0)	3 (8.8)	0	4 (4.9)
Hyperkalemia	0	3 (8.8)	2 (14.3)	5 (6.2)
Renal failure	3 (9.1)	2 (5.9)	0	5 (6.2)
Pyrexia	1 (3.0)	1 (2.9)	0	2 (2.5)
Peripheral edema	0	1 (2.9)	0	1 (1.2)
Fatigue	1 (3.0)	3 (8.8)	1 (7.1)	5 (6.2)
Dose modifications as a result of TEAEs, No. (%)				
POM discontinuation	4 (12.1)	6 (17.6)	4 (28.6)	14 (17.3)
POM reduction	6 (18.2)	6 (17.6)	2 (14.3)	14 (17.3)
POM interruption	19 (57.6)	21 (61.8)	7 (50.0)	47 (58.0)

Abbreviations: POM, pomalidomide; RI, renal impairment; TEAE, treatment-emergent adverse event.

outcomes were noted across the three cohorts for time to maximum plasma concentration (3.6 hours, 3.0 hours, and 3.0 hours) and mean apparent terminal half-life (11.8 hours, 8.3 hours, and 9.0 hours). Mean apparent clearance values were also similar among the cohorts (2.5 L/h, 2.6 L/h, and 3.8 L/h, respectively). Mean pomalidomide plasma concentration-time profiles indicated similar trends in all three cohorts (Data Supplement). Peak concentrations were detected at approximately 4 hours postdose in cohorts A and B and approximately 1 hour later in cohort C.

PK Analysis With High Cutoff Membranes

PK parameters were also assessed during hemodialysis with high cutoff membranes. In cohort C, during hemodialysis, visual examination of pomalidomide concentration-time profiles suggested that concentrations from the arterial side (withdrawal) were higher than those from the venous side (returning) of the dialyzer (Data Supplement). Pomalidomide hemodialysis clearance ranges—3.0 to 5.9 L/h using standard membranes, and 4.5 to 7.4 L/h with high cutoff membranes—were higher than pomalidomide total plasma clearance, which suggests that the hemodialysis procedure significantly removed pomalidomide from the blood (Data Supplement).

DISCUSSION

The results of this prospective study indicate that patients with RRMM and moderate or severe RI, including those who require hemodialysis, benefit from pomalidomide plus LoDEX treatment, with ORRs of 39.4%, 32.4%, and 14.3% in cohorts A, B, and C, respectively. Of note, 78.6% of patients in cohort C achieved disease control, despite receiving a short duration of treatment—median of three cycles—and having advanced disease. In a post hoc analysis of

the phase III MM-003 registration trial, disease stabilization with pomalidomide plus LoDEX treatment was associated with a survival benefit in patients with RRMM and normal or moderately impaired renal function.¹⁸ Of importance, this study demonstrated that the recommended dose of pomalidomide 4 mg/d can be safely administered to patients with RI, including those receiving hemodialysis.

Compared with other trials of patients with RRMM and RI, this phase II study included a patient population that had more advanced disease (median of four prior antimyeloma regimens), was older (81.5% age ≥ 65 years), and was more frail (only one in four patients received prior stem cell transplantation).²⁶⁻²⁸ Despite these differences in the trial population, clinical outcomes observed in cohort A align with the outcomes of a subanalysis of the pivotal phase III study, which demonstrated an ORR, PFS, and OS of 28%, 4.0 months, and 10.4 months, respectively, in patients with RRMM and moderate RI (creatinine clearance, ≥ 30 to < 60 mL/min).¹⁷ Indeed, results across all cohorts were encouraging because patients with MM and end-stage renal disease who were evaluated in a European Renal Association registry had a median OS of 10.9 months.²⁹ The current study is the first prospective trial to demonstrate that pomalidomide plus LoDEX can lead to disease stabilization, a clinically relevant outcome in patients with severe RI and high disease burden.

A retrospective study demonstrated the clinical benefit of pomalidomide treatment in patients with RRMM with RI (eGFR, < 45 mL/min) who were treated at five centers in the United Kingdom. Among the 12 evaluable patients with RI, ORR was 50%, median PFS was 3.2 months, and median OS was 7.4 months.³⁰

Despite RI and advanced disease, most patients in this study received the full, standard 4-mg dose of pomalidomide. Median relative dose intensity was 0.94 to 0.99, which is similar to that previously reported in patients with RRMM and normal renal function in a phase III study.²⁶ The percentages of AEs leading to

dose reductions were also similar, which confirmed that pomalidomide 4 mg is tolerable in patients with all levels of RI.

These findings are also supported by the comparable values of PK parameters across the three cohorts after the oral administration of multiple doses of pomalidomide 4 mg, and by the population PK analysis that demonstrated that impaired renal function had a limited effect on pomalidomide exposure in patients with moderate or severe RI who did not require hemodialysis.²¹ On the basis of the results from the hemodialysis clearance in the current study and those from the population PK analysis, it is recommended that pomalidomide be administered after patients undergo hemodialysis, because the procedure effectively removed pomalidomide from the blood.

The safety profile of pomalidomide plus LoDEX was acceptable and generally similar to what was previously reported in patients with RRMM and normal or moderately impaired renal function.^{27,28} No new toxicity signals were observed. Neutropenia, anemia, thrombocytopenia, leukopenia, and infections were the most common grade 3 and 4 TEAEs. In general, AEs were managed appropriately with pomalidomide dose modifications, prophylactic anti-infectives, and concomitant supportive care, including granulocyte colony-stimulating factor.

Normalization of renal function is an important prognostic factor in patients with newly diagnosed MM who present with RI³¹; however, stabilization of renal function represents a more achievable goal in a heavily pretreated population, such as that studied here. Complete renal responses were observed only in cohort A (18.2%), whereas patients in cohort B experienced partial (5.9%) and minimal (29.4%) renal responses, which suggests that the normalization of renal function during treatment with pomalidomide plus LoDEX is more likely to occur in patients with moderate RI. Furthermore, these findings are clinically relevant because most patients presented with chronic renal insufficiency before starting treatment with pomalidomide plus LoDEX.

Patients with RRMM and RI are frequently seen in clinical practice; however, to date, a limited number of reports have addressed the treatment of patients with RRMM and moderate-to-severe RI, and few included patients who underwent hemodialysis. The MM-013 trial is the first study to provide evidence that these patients can benefit from treatment with pomalidomide plus LoDEX, and supports the use of this regimen in patients with RRMM and severe RI, including those receiving hemodialysis.¹⁵ Achieving disease control and stabilization has meaningful clinical benefits, particularly for patients who require hemodialysis. Results presented here add to the limited body of evidence of treatment options for patients with advanced stages of MM and RI and will help health care providers make appropriate treatment choices for this patient population.

In conclusion, pomalidomide 4 mg/d plus LoDEX can be safely administered and is efficacious in patients with moderate or severe RI, including those receiving hemodialysis.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Pomalidomide Plus Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma and Renal Impairment: Results From a Phase II Trial

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