Analysis of renal impairment in MM-003, a phase III study of pomalidomide + low–dose dexamethasone *versus* high–dose dexamethasone in refractory or relapsed and refractory multiple myeloma

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ABSTRACT

Pomalidomide + low-dose dexamethasone is effective and well tolerated for refractory or relapsed and refractory multiple myeloma after bortezomib and lenalidomide failure. The phase III trial MM-003 compared pomalidomide + low-dose dexamethasone with high-dose dexamethasone. This subanalysis grouped patients by baseline creatinine clearance ≥ 30 - < 60 mL/min (n=93, pomalidomide + low-dose dexamethasone; n=56, high-dose dexamethasone) or ≥ 60 mL/min (n=205, pomalidomide + low-dose dexamethasone; n=93, high-dose dexamethasone). Median progression-free survival was similar for both subgroups and favored pomalidomide + low-dose dexamethasone *versus* high-dose dexamethasone: 4.0 *versus* 1.9 months in the group with baseline creatinine clearance ≥ 30 - < 60 mL/min (P<0.001) and 4.0 *versus* 2.0 months in the group with baseline creatinine clearance ≥ 60 mL/min (P<0.001). Median overall survival for pomalidomide + low-dose dexamethasone *versus* high-dose dexamethasone was 10.4 *versus* 4.9 months (P=0.030) and 15.5 *versus* 9.2 months (P=0.133), respectively. Improved renal function, defined as an increase in creatinine clearance from < 60 to ≥ 60 mL/min, was similar in pomalidomide + low-dose dexamethasone and high-dose dexamethasone patients (42% and 47%, respectively). Improvement in progression-free and overall survival in these patients was comparable with that in patients without renal impairment. There was no increase in discontinuations of therapy, dose modifications, and adverse events in patients with moderate renal impairment. Pomalidomide at a starting dose of 4 mg + low-dose dexamethasone is well tolerated in patients with refractory or relapsed and refractory multiple myeloma, and of comparable efficacy if moderate renal impairment is present. This trial was registered with *clinicaltrials.gov identifier 01311687* and *EudraCT identifier 2010-019820-30.*

Introduction

Renal impairment is a common presenting feature for patients with multiple myeloma (MM). Approximately 20% to 40% of patients with newly diagnosed MM, who are primarily aged over 65 years, have renal impairment at diagnosis, and this rate increases during the course of disease.[1-4] Renal impairment as a complication of MM often leads to cast nephropathy, potentially resulting in renal tube atrophy and tubulointerstitial fibrosis.[5,6] In addition, impaired renal function may be a result of aging and can also be caused by comorbidities unrelated to MM, such as diabetes, hypertension, vascular disease, or prior non-myeloma therapies.[3] Renal impairment in patients with MM is associated with shortened survival, but recovery of renal function during treatment may improve survival in these patients and even achieve similar outcomes in patients with a history of normal renal function.[3,4,7]

The past several decades have seen advances in the treatment of MM, and outcomes have improved for patients with varying degrees of renal impairment;[3,8] despite this, most patients will ultimately relapse.[9,10] Control of MM *via* effective therapy has been shown to improve renal function in a large proportion of patients.[11,12] However, patients who are refractory to bortezomib and have relapsed following treatment with an immunomodulatory agent, or patients who are refractory to or ineligible to receive an immunomodulatory agent, have a poor prognosis (median survival 9 months).[13] Physicians may perceive that treatment options in these patients may be further limited by the presence of renal impairment, as some novel agents rely on metabolism/excretion by the kidneys.[7]

Pomalidomide (POM) acts *via* direct antimyeloma, stromal-support inhibitory, and immunomodulatory effects.[14,15] POM in combination with low-dose dexamethasone (LoDEX) was evaluated for the treatment of relapsed and refractory MM in patients after lenalidomide and bortezomib failure in the MM-002 and MM-003 studies. The phase I component of MM-002 established the maximum tolerated dose for POM at 4 mg daily with or without LoDEX (40 mg weekly).[16] This dose was moved forward into an open-label, randomized, phase II component, which found POM + LoDEX to be more efficacious than POM alone [overall response rate (ORR) 33% *vs.* 18%; median progression-free survival (PFS) 4.2 *vs.* 2.7 months; median overall survival (OS) 16.5 *vs.* 13.6 months]. The pivotal, multicenter, open-label, randomized, phase III study MM-003 verified the safety and efficacy of POM + LoDEX (n=302) compared with high-dose dexamethasone (HiDEX; n=153) in patients with refractory or relapsed and refractory MM previously treated with (and 74% refractory to) lenalidomide and bortezomib.[17] Overall trial results included significant improvements in ORR (31% *vs.* 10%; $P<0.0001$), PFS (4.0 *vs.* 1.9 months; $P<0.0001$), and OS (12.7 *vs.* 8.1 months; $P=0.0285$).[17] Preliminary pharmacokinetic data suggest that renal impairment probably does not impact on POM exposure.[18]

The aim of the current analysis was to examine efficacy and safety of POM + LoDEX *versus* that of HiDEX in patient subgroups enrolled in MM-003 by renal function at baseline [creatinine clearance (CrCl) ≥ 30 - < 60 mL/min *vs.* ≥ 60 mL/min]. In addition, we examined median PFS and OS in patients who had improvement of renal function from CrCl ≥ 30 - < 60 mL/min at baseline to ≥ 60 mL/min at any point during study treatment.

Methods

MM-003 was an open-label, randomized, phase III trial conducted in 93 centers in Europe, Russia, Australia, Canada, and the United States (*clinicaltrials.gov identifier: 01311687; EudraCT 2010-019820-30*). Full details have been described previously.[17] All authors and the study sponsor were involved in data collection and analysis, review and interpretation of results, and the writing of the report.

Patients

Eligible patients were aged 18 years or over with refractory or relapsed and refractory MM, had measurable serum or urine M protein, and were refractory to their last prior treatment [documented progressive disease (PD) during or within 60 days of last therapy]. Prior bortezomib and lenalidomide treatment (≥ 2 consecutive cycles, alone or in combination) must have failed [i.e. refractory (never experienced a response), PD within six months after at least a partial response (PR), or intolerant (to bortezomib only)]. Adequate prior alkylator therapy was required.

Exclusion criteria included: absolute neutrophil count < $1x10^9$/L; platelets < $75x10^9$/L (< $30x10^9$/L if ≥ 50% of bone marrow nucleated cells were plasma cells); CrCl < 45 mL/min; peripheral neuropathy grade ≥ 2; prior exposure to POM; hypersensitivity to thalidomide, lenalidomide, or DEX; or resistance to DEX.

Study design and treatment

Patients were randomized 2:1 to POM + LoDEX (28-day cycles; oral POM: 4 mg/day, days 1-21; LoDEX: 40 mg/day, days 1, 8, 15, and 22) or HiDEX (40 mg/day, days 1-4, 9-12, and 17-20). For patients aged over 75 years, DEX dose was reduced to 20 mg/day in both treatment arms. Patients continued treatment until PD or unacceptable toxicity. Thromboprophylaxis was required for all patients receiving POM and any patient at high risk of developing thrombosis.

Patients provided written informed consent. The study received institutional review board or independent ethics committee approval at all participating centers according to the Declaration of Helsinki and the International Conference on Harmonisation Guidelines on Good Clinical Practice.

Subgroup analyses

In this retrospective analysis, renal impairment cohorts included patients with moderate renal impairment (baseline CrCl ≥ 30 - < 60 mL/min) or without renal impairment (baseline CrCl ≥ 60 mL/min), based on the Cockroft-Gault formula.[19,20] CrCl data were collected prospectively and were estimated at the start of each treatment cycle and upon discontinuation.

Assessments

The primary end point was investigator-assessed PFS. Survival distribution functions for each treatment group were estimated with the Kaplan-Meier product-limit method and compared with the log-rank test. Key secondary end points included OS, ORR [≥ PR by International Myeloma Working Group (IMWG) criteria], safety [adverse events (AEs) graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v.4.0], and improvement of renal function from CrCl ≥ 30 - < 60 mL/min at baseline to ≥ 60 mL/min at any point during study treatment (only assessed in patients with baseline and post-baseline CrCl data). As an additional retrospective analysis, renal response was assessed according to IMWG criteria.[5] Efficacy was assessed in the intent-to-treat population (all patients randomized to treatment) using IMWG criteria, and tolerability was assessed in the safety population (all patients who received ≥ 1 dose of study drug). PFS

Table 1. Baseline patients' characteristics and prior therapies.

Patients' characteristics	Baseline CrCl ≥ 30 - < 60 mL/min		Baseline CrCl ≥ 60 mL/min	
	POM + LoDEX (n=93)	HiDEX (n=56)	POM + LoDEX (n=205)	HiDEX (n=93)
Median age (range), years	69 (41-84)	69 (36-87)	61 (35-80)	61 (35-80)
Male sex, %	46	45	67	65
Median time from initial diagnosis, years	5.5	5.8	5.3	6.2
ECOG status 0/1/2/3, %[a]	39/38/23/0	16/59/21/4	36/50/14/0	30/56/13/1
ISS stage at study entry I/II/III, %[a]	11/38/51	11/28/61	36/42/22	33/45/22
Median prior treatments (range), n	5 (2-12)	5 (2-17)	5 (2-14)	5 (2-16)
Prior LEN/BORT/DEX, %	100/100/99	100/100/100	100/100/97	100/100/99
Prior SCT, %	60	57	76	79
LEN refractory, %	99	89	93	94
BORT refractory, %	77	84	80	76
LEN and BORT refractory, %	76	79	74	71
Presence of del(17p)/t(4;14), %	30	34	23	17

BORT: bortezomib; CrCl: creatinine clearance; DEX: dexamethasone; ECOG: Eastern Cooperative Oncology Group; HiDEX: high-dose dexamethasone; ISS: International Staging System; LEN: lenalidomide; LoDEX: low-dose dexamethasone; POM: pomalidomide; SCT: stem cell transplant. [a]Percentages based on number of patients with data available.

and OS for patients with renal improvement were calculated according to European Medicines Evaluation Agency criteria. Statistical analyses were performed using SAS software v.9.2.

Results

Patients' characteristics

This analysis was performed using a data cut off of September 1st, 2013, corresponding to a median follow up of 15.4 months. A total of 302 patients received POM + LoDEX, and 153 patients received HiDEX (*Online Supplementary Figure S1*). Patients were heavily pre-treated, with a median of 5 prior lines of treatment in all groups. For patients with baseline CrCl ≥ 30 - < 60 mL/min, data were available for 93 POM + LoDEX and 56 HiDEX patients. For those with baseline CrCl ≥ 60 mL/min, data were available for 205 POM + LoDEX and 93 HiDEX patients. Eight patients were not included in the analysis: 3 patients had missing baseline CrCl values (2 in the POM-LoDEX arm and 1 in the HiDEX arm), and 5 patients had baseline CrCl levels below 30 mL/min (2 in the POM-LoDEX arm and 3 in the HiDEX arm) (*Online Supplementary Figure S1*). Patients with baseline CrCl ≥ 30 - < 60 mL/min were more likely to be older and less likely to have undergone prior SCT compared with patients with baseline CrCl ≥ 60 mL/min (Table 1). The moderate renal impairment cohort also exhibited higher rates of International Staging System stage II-III disease, Eastern Cooperative Oncology Group status of 3, and high-risk cytogenetics.

Efficacy

Median PFS with POM + LoDEX *versus* HiDEX was consistent in patients with baseline CrCl ≥ 30 - < 60 mL/min (4.0 *vs.* 1.9 months; $P<0.001$) (Figure 1A) and ≥ 60 mL/min (4.0 *vs.* 2.0 months; $P<0.001$) (Figure 1B). POM + LoDEX also improved median OS compared with HiDEX in patients with baseline CrCl ≥ 30 - < 60 mL/min (10.4 *vs.* 4.9 months; $P=0.030$) (Figure 2A) and ≥ 60 mL/min (15.5 *vs.* 9.2 months; $P=0.133$) (Figure 2B). The OS advantage of POM + LoDEX over HiDEX was achieved despite a substantial proportion of HiDEX patients receiving subsequent POM (50% of HiDEX patients with baseline CrCl ≥ 30 - < 60 mL/min and 60% of HiDEX patients with baseline CrCl ≥ 60 mL/min crossed over to POM + LoDEX). POM + LoDEX significantly improved ORR *versus* HiDEX regardless of baseline renal function (Table 2). Duration of response (for patients achieving ≥ PR) was consistently longer for POM + LoDEX *versus* HiDEX in both groups.

Improvement in renal function

A total of 273 patients in the POM + LoDEX arm and 128 patients in the HiDEX arm had CrCl data for baseline and ≥ 1 post-baseline assessment and were thus evaluable for change in renal function (for patients with > 1 post-baseline assessment, the best value during the first 6 cycles was used). Renal improvement to CrCl ≥ 60 mL/min was noted in 42% of patients (33 of 79) treated with POM + LoDEX who had renal impairment (CrCl < 60 mL/min) at baseline (Table 3). Renal improvement was seen in 47% (20 of 43) of HiDEX-treated patients. The median time to improvement was similar for each treatment arm (POM + LoDEX: 1.0 month; HiDEX: 0.9 months). In these POM + LoDEX and HiDEX-treated patients with renal improvement, median PFS was 6.5 (95%CI: 4.6, 8.4) and 3.2 (95%CI: 2.1, 5.5) months, respectively; median OS was 12.6 (95%CI: 7.6, 25.7) and 10.1 (95%CI: 5.7, 17.7) months, respectively.

According to IMWG criteria for renal response,[5] 32% (14 of 44) of POM + LoDEX-treated patients with estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73 m^2 achieved complete response of CrCl ≥ 60 mL/min (Table 3). In a similar analysis of the HiDEX-treated patients, 43% (9 of 21) achieved a complete response. Few or no patients in either treatment arm were eligible for partial or minimal response by having baseline eGFR < 30 mL/min/1.73 m^2.

Safety

The AE profiles for POM + LoDEX and HiDEX were similar across both renal function subgroups (Table 4). The most common grade 3/4 AEs for the POM + LoDEX treatment arm were neutropenia (48% for baseline CrCl ≥ 30 -

< 60 mL/min and 49% for baseline CrCl ≥ 60 mL/min), anemia (40% and 30%, respectively), and infections (31% and 34%, respectively). With mandatory thromboprophylaxis, incidence of grade 3/4 deep vein thrombosis/pulmonary embolism was low (≤ 2% in both groups).

POM discontinuations and dose modifications due to AEs were similar regardless of moderate renal impairment (Table 5). Median duration of POM treatment was similar in patients with baseline CrCl ≥ 30 - < 60 mL/min (3.7 months) and ≥ 60 mL/min (4.6 months). Renal function did not affect frequency of dose reductions and interruptions. Median relative dose intensity was consistent at 90% for both renal function subgroups.

Discussion

POM + LoDEX was efficacious and well tolerated in patients with refractory or relapsed and refractory MM and moderate renal impairment. POM + LoDEX significantly extended PFS *versus* HiDEX for all patients regardless of renal impairment (baseline CrCl ≥ 30 - < 60 mL/min, 4.0 *vs.* 1.9 months; baseline CrCl > 60 mL/min, 4.0 *vs.* 2.0 months; $P<0.001$ for both groups), similar to the benefits observed in the general study population (4.0 *vs.* 1.9 months; $P<0.001$).[17] OS results showed a similar 5- to 6-month benefit for POM + LoDEX in both renal function subgroups (baseline CrCl ≥ 30 - < 60 mL/min, 10.4 *vs.* 4.9

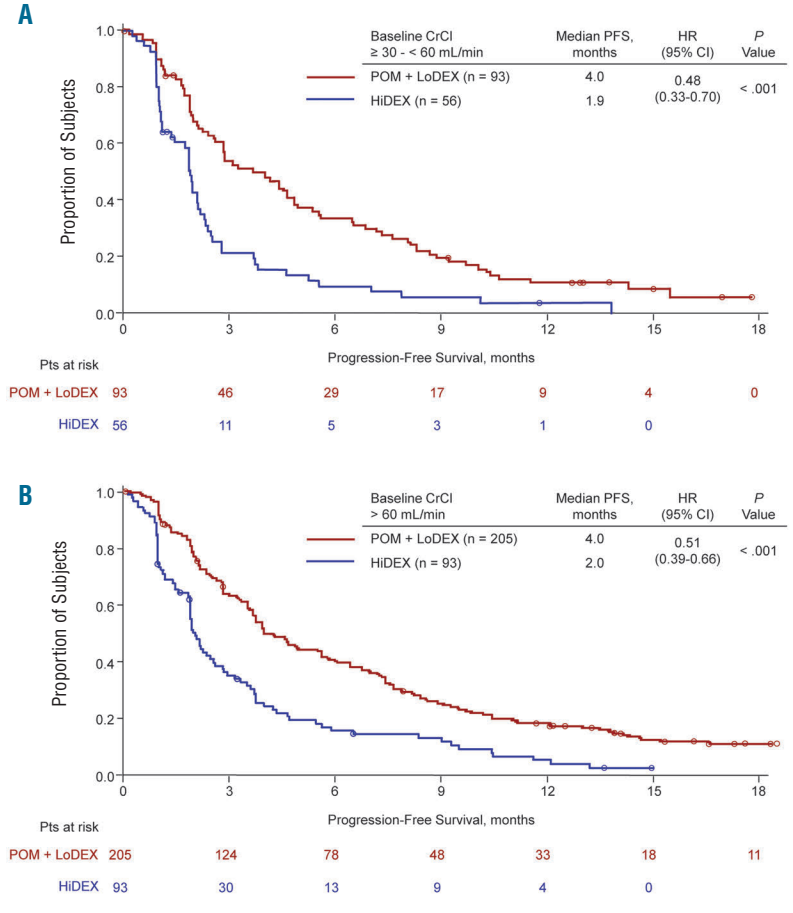

Figure 1. Progression-free survival for patients with baseline creatinine clearance ≥ 30 - < 60 mL/min (A) or ≥60 mL/min (B).

Table 2. Response to treatment (IMWG criteria).

Variable	Baseline CrCl ≥ 30 - < 60 mL/min		Baseline CrCl ≥ 60 mL/min	
	POM + LoDEX (n=93)	HiDEX (n=56)	POM + LoDEX (n=205)	HiDEX (n=93)
ORR (≥ PR), %	28	11	34	12
sCR	0	0	1	0
CR	0	0	2	0
VGPR	7	0	5	1
PR	22	11	26	11
SD, %	52	48	50	50
Median DOR, months[a]	6.6	4.4	7.5	5.1

CR: complete response; CrCl: creatinine clearance; DOR: duration of response; HiDEX: high-dose dexamethasone; IMWG: International Myeloma Working Group; LoDEX: low-dose dexamethasone; ORR: overall response rate; POM: pomalidomide; PR: partial response; sCR: stringent complete response; SD: stable disease; VGPR: very good partial response. [a]For patients with ≥ PR.

months; baseline CrCl > 60 mL/min, 15.5 *vs.* 9.2 months) compared with those of the overall patient population (13.1 *vs.* 8.2 months),[17] although these results were only statistically significant for patients with reduced renal function (baseline CrCl ≥ 30 - < 60 mL/min, *P*=0.030; baseline CrCl > 60 mL/min, *P*=0.133). This finding is likely to be confounded by the high number (56% overall) of HiDEX patients crossing over to receive POM after progression, as *per* protocol.

A substantial number of renally impaired patients treated with POM + LoDEX had improved renal function (42% *per* protocol criteria and 32% *per* IMWG criteria), which

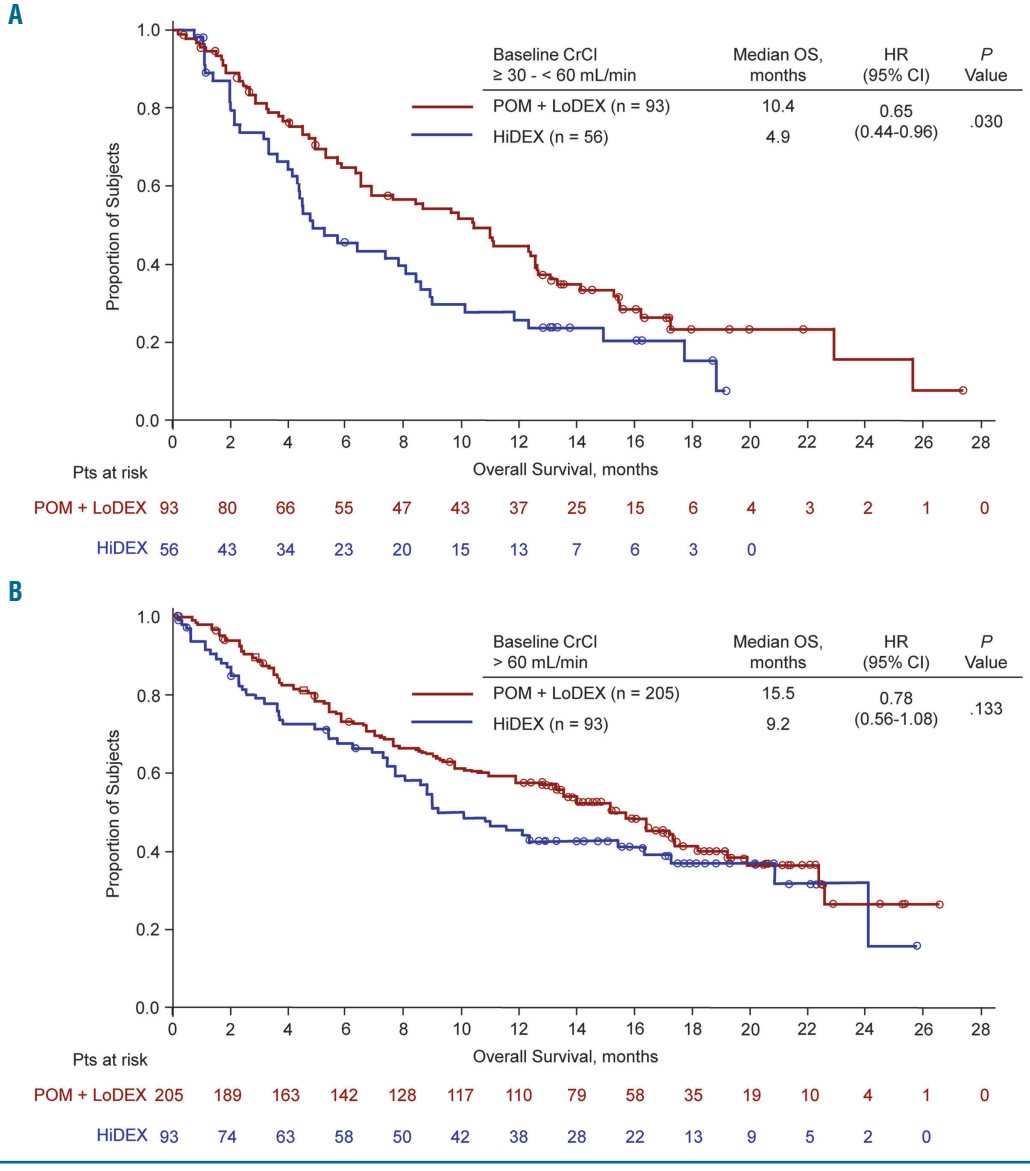

Figure 2. Overall survival for patients with baseline creatinine clearance ≥ 30 - < 60 mL/min (A) or ≥ 60 mL/min (B).

Table 3. Improvement in renal function.

Category	Baseline renal function	Best renal function	POM + LoDEX, n/N (%)[a]	HiDEX, n/N (%)[a]
Per-protocol improvement	CrCl < 60 mL/min	CrCl ≥ 60 mL/min	33/79 (42)	20/43 (47)
IMWG CR^{renal}	eGFR < 50 mL/min/1.73 m^2	CrCl ≥ 60 mL/min	14/44 (32)	9/21 (43)
IMWG PR^{renal}	eGFR < 15 mL/min/1.73 m^2	CrCl 30-59 mL/min	0/3	0/1
IMWG MR^{renal}	eGFR < 15 mL/min/1.73 m^2 eGFR 15-29 mL/min/1.73 m^2	CrCl 15-29 mL/min CrCl 30-59 mL/min	0/0	0/0

CrCl: creatinine clearance; CR^{renal}: complete renal response; eGFR: estimated glomerular filtration rate; HiDEX: high-dose dexamethasone; IMWG: International Myeloma Working Group; LoDEX: low-dose dexamethasone; MR^{renal}: minimal renal response; POM: pomalidomide; PR^{renal}: partial renal response. [a]Percentages represent patients who improved from baseline to most extreme post-baseline value, divided by the total number of patients with evaluable baseline and post-baseline data.

was similar to the improvement rate noted in the HiDEX arm. HiDEX treatment can rapidly suppress M-protein and light-chain excretion leading to recovery of renal function and can be used for acute myeloma treatment.[12,21,22] In the present study, however, response rates in renally impaired patients greatly favored the POM+LoDEX arm compared with the HiDEX arm: 28% *versus* 11%, respectively. In patients treated with POM + LoDEX whose kidney function improved from moderate impairment to normal, PFS reached 6.5 months, which exceeded the results of patients with normal baseline kidney function (4.0 months). Despite a similar proportion of patients with renal improvement noted in the HiDEX arm, their PFS was only 3.2 months. The OS improvement observed in these patients was in the same range as that in patients with normal renal function.

Tolerability profiles were consistent regardless of baseline renal function. Rates of discontinuation due to AEs were similar in both subgroups, indicating that patients with moderate renal impairment did not experience increased toxicity. Slightly increased incidences of pneumonia were observed in patients with baseline CrCl ≥ 30 - < 60 mL/min. Duration of treatment and dose intensity were not affected by baseline renal function. These findings demonstrate that up-front dose modification is not required in patients with moderate renal impairment, and that 4 mg is a safe and appropriate starting dose of POM in combination with LoDEX for these patients.

The efficacy results of POM + LoDEX in renal function subgroups of MM-003 confirm those found previously. In the phase II component of MM-002, patients without renal impairment (baseline CrCl > 60 mL/min) had an ORR of 34%, median PFS of 5.4 months, and median OS of 16.9 months, and patients with moderate renal impairment (baseline CrCl ≥ 45 to ≤ 60 mL/min) had an ORR of 43%, median PFS of 4.7 months, and median OS of 19.5 months. It should be noted, however, that there were only 14 patients in this subgroup in that study.[23] Safety profiles and relative dose intensities for these subgroups were consistent between the phase II study and the one presented here.[23] This cumulative body of evidence regarding POM + LoDEX further supports use of a 4-mg starting dose for patients with mild or moderate renal impairment without up-front dose reduction.

The finding that POM does not require dose adjustment in patients with moderate renal impairment *versus* patients with normal renal function is related to its metabolism and excretion. In contrast to lenalidomide, which is excreted primarily *via* the kidneys,[24] POM is extensively metabolized (with only 2.2% excreted as the parent drug in urine) and, therefore, does not require dose reductions in patients with impaired renal function;[18,25] the same obser-

Table 4. Safety profile.

Event	Baseline CrCl ≥ 30 - < 60 mL/min		Baseline CrCl ≥ 60 mL/min	
	POM + LoDEX (n=93)	HiDEX[a] (n=56)	POM + LoDEX (n=203)	HiDEX[a] (n=90)
Grade 3/4 hematologic AEs in ≥ 10% of pts, %				
Neutropenia	48	21	49	16
Anemia	40	46	30	34
Thrombocytopenia	22	38	23	20
Febrile neutropenia	5	0	11	0
Grade 3/4 non-hematologic AEs in ≥ 10% of pts, %				
Infections	31	27	34	24
Pneumonia	19	9	11	8
Grade 3/4 AEs of interest, %				
DVT/PE	1	0	2	0
Peripheral neuropathy[b]	1	2	2	1
Discontinuation due to AEs, %	13	11	8	10

AE: adverse event; CrCl: creatinine clearance; DVT: deep vein thrombosis; HiDEX: high-dose dexamethasone; LoDEX: low-dose dexamethasone; PE: pulmonary embolism; POM: pomalidomide; pt: patient. [a]Patients may have received POM + LoDEX after crossover. [b]Peripheral neuropathy includes the preferred terms "hyperesthesia," "neuropathy peripheral," "peripheral sensory neuropathy," "paresthesia," "hypoesthesia," and "polyneuropathy."

Table 5. Pomalidomide dose modification due to adverse events and dose intensity.

Variable	Baseline CrCl ≥ 30 - < 60 mL/min (n=93)	Baseline CrCl ≥ 60 mL/min (n=203)
POM dose modifications due to AEs, %		
Interruption	69	67
Reduction	28	28
Discontinuation	12	7
POM dose intensity		
Planned POM dose/day, mg	4	4
Median relative dose intensity (range)[a]	0.9 (0.4-1.3)	0.9 (0.3-1.2)
Median duration of treatment (range), months	3.7 (0.1-21.4)	4.6 (0.1-25.6)

AEs: adverse event; CrCl: creatinine clearance; POM: pomalidomide. [a]Relative dose intensity = dose intensity/planned dose intensity. May be more than 1 due to patient discontinuation prior to end of 28-day cycle.

vation applies to thalidomide.[26,27] The safety profile of POM + LoDEX as assessed in the study presented here demonstrated no difference in frequency of dose reductions in patients with moderate renal impairment and only slightly higher rates of anemia and pneumonia.

However, this analysis was limited by the fact that it concerns only patients with normal or moderately impaired renal function, as the study excluded patients with CrCl < 45 mL/min at the time of screening [although 28 (9%) POM + LoDEX and 15 (10%) HiDEX patients had baseline CrCl below this cut off due to the time that had elapsed between screening and the first treatment cycle]. To address this, 2 trials are in progress to assess the use of POM + LoDEX in patients with severe renal impairment, including those requiring dialysis: MM-008 in the United States (*clinicaltrials.gov identifier 01575925*) and MM-013 in the European Union (*clinicaltrials.gov identifier 02045017*).

Newer treatment options, including lenalidomide, thalidomide, and bortezomib, have improved outcomes and survival for many patients with MM in recent years.[28,29] In addition, although newer agents can improve outcomes, including renal function, for many patients with MM with renal impairment,[5,7] it remains a significant risk factor for early death in MM.[3,30] Thus, the efficacy of POM + LoDEX in renally impaired relapsed/refractory MM populations is of particular importance. This analysis has demonstrated that a starting dose of POM 4 mg may be used safely regardless of moderate renal impairment, with no unexpected toxicities observed and no additional dose modifications or discontinuations required when compared with the overall trial population. PFS and OS benefits achieved by patients with moderate renal impairment were also consistent with the overall MM-003 trial population.

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