Pomalidomide plus low-dose dexamethasone in patients with relapsed/refractory multiple myeloma and moderate renal impairment: a pooled analysis of three clinical trials

David S. Siegel, Katja C. Weisel, Meletios A. Dimopoulos, Rachid Baz, Paul Richardson, Michel Delforge, Kevin W. Song, Jesus F. San Miguel, Philippe Moreau, Hartmut Goldschmidt, Michele Cavo, Sundar Jagannath, Xin Yu, Kevin Hong, Lars Sternas, Mohamed Zaki & Antonio Palumbo

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE: CLINICAL

Pomalidomide plus low-dose dexamethasone in patients with relapsed/refractory multiple myeloma and moderate renal impairment: a pooled analysis of three clinical trials

David S. Siegel[a], Katja C. Weisel[b], Meletios A. Dimopoulos[c], Rachid Baz[d], Paul Richardson[e], Michel Delforge[f], Kevin W. Song[g], Jesus F. San Miguel[h], Philippe Moreau[i], Hartmut Goldschmidt[j], Michele Cavo[k], Sundar Jagannath[l], Xin Yu[m], Kevin Hong[m], Lars Sternas[m], Mohamed Zaki[m] and Antonio Palumbo[n]

[a]Division of Multiple Myeloma, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA; [b]Department of Hematology, Oncology, Immunology, Rheumatology and Pulmonology, University Hospital of Tübingen, Tübingen, Germany; [c]Department of Clinical Therapeutics at the University, National and Kapodistrian University of Athens School of Medicine, Athens, Greece; [d]Department of Malignant Hematology, Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [e]Myeloma Program, Dana-Farber Cancer Institute, Boston, MA, USA; [f]Department of Hematology, University Hospitals Leuven, Leuven, Belgium; [g]Division of Hematology, Vancouver General Hospital, Vancouver, British Columbia, Canada; [h]Director of Clinical and Translational Medicine, Clinica Universidad de Navarra, CIMA, IDISNA, Pamplona, Spain; [i]Hematology Department, CHU Hotel Dieu-CHU de Nantes, France; [j]Department of Medicine V, University of Heidelberg, Heidelberg, Germany; [k]"Seràgnoli" Institute of Hematology, Bologna University School of Medicine, Bologna, Italy; [l]Tisch Cancer Institute, Mount Sinai Hospital, New York City, NY, USA; [m]Celgene Corporation, Summit, NJ, USA; [n]Department of Hematology, University of Turin, Turin, Italy

ABSTRACT

Renal impairment (RI) is a major comorbidity in patients with multiple myeloma (MM). Here we present the pooled safety and efficacy analysis of three clinical trials (MM-002, MM-003, and MM-010) of pomalidomide + low-dose dexamethasone (POM + LoDEX) in patients with moderate RI (creatinine clearance [CrCl] ≥ 30 to <60 mL/min) and without RI (≥ 60 mL/min). Trial protocols were approved by the institutional review board of each site involved. Patients with RI were older than patients without RI, although other baseline characteristics were similar. The dosing and safety profile of POM + LoDEX was similar across RI subgroups. Median overall response rate, progression-free survival, time to progression, and duration of response were not significantly different between RI subgroups. However, patients with vs. without RI had significantly shorter median overall survival (10.5 vs. 14.0 months, respectively; $p = .004$). This analysis demonstrates that POM + LoDEX is a safe and effective treatment for patients with moderate RI. The trials were registered at ClinicalTrials.gov as NCT00833833 (MM-002), NCT01311687 (MM-003), and NCT01712789 (MM-010) and at EudraCT as 2010-019820-30 (MM-003) and 2012-001888-78 (MM-010).

Introduction

Renal impairment (RI) is a major comorbidity in patients with multiple myeloma (MM),[1] and approximately 20% to 40% of patients present with RI at time of diagnosis.[2–4] Additionally, $\approx 25\%$ to 50% of patients with MM experience some level of RI throughout the course of their disease,[5,6] which is the outcome of disease chronicity and progression that is worsened by age, and of comorbidities that are associated with older age and are unrelated to MM.[3] The presence of RI is of prognostic value;[1] patients with MM and RI experience poorer overall survival (OS),

with a 2- to 4-fold higher risk of death in patients with moderate to severe RI.[3] Although RI can be managed,[7] reversal of RI has been observed in many patients receiving active and novel anti-MM treatment options.[3,6,8–10] However, the majority of patients with MM experience relapse and/or develop refractory disease,[11,12] and higher mortality is still observed, even in patients who achieve normalization of renal function during treatment.[8,13]

The IMiD® immunomodulatory agent pomalidomide (POM) has demonstrated direct anti-myeloma and immunomodulatory effects, including in lenalidomide

---

CONTACT David S. Siegel ✉ DSiegel@HackensackUMC.org 🏢 Myeloma Division, John Theurer Cancer Center, Hackensack University Medical Center, 92 Second Street, Suite 340, Hackensack, NJ 07601, USA

(LEN)-resistant cells.[14] Pivotal trials evaluating POM plus low-dose dexamethasone (LoDEX) demonstrated safety and efficacy in patients with relapsed/refractory multiple myeloma (RRMM; MM-010 trial; [15]) as well as extended survival outcomes vs. POM alone (MM-002 trial; [16]) and vs. high-dose dexamethasone (HiDEX; MM-003 trial; [17]). These results led to the approval of POM + LoDEX in both the United States and European Union for the treatment of RRMM in patients who have experienced failure of treatment with LEN and/or bortezomib (BORT; [18,19]).

Although measuring the glomerular filtration rate (GFR) is a more accurate method to assess renal function, assessment of serum creatinine levels continues to be used when the calculation of GFR is not feasible.[20,21] Creatinine clearance (CrCl), a measure of how rapidly creatinine is renally excreted, is used in clinical practice to estimate GFR with either the Cockcroft-Gault or Modification of Diet in Renal Disease Study (MDRD) mathematical formula.[20,21] The Cockcroft-Gault estimation is routinely used and accounts for serum creatinine (mg/dL), age, weight, and sex. The MDRD method additionally normalizes to a standard body surface area and can add a factor for African American race. Many trials exclude patients with RI, but the MM-002, MM-003, and MM-010 trials included patients with moderate RI,[15–17] although the number of patients with RI enrolled in each trial was limited.

Patients with MM and RI require dose adjustment for LEN as it is predominantly excreted unchanged via the kidneys.[22,23] However, POM is extensively metabolized, with limited renal clearance,[24] and the safety and efficacy in patients with RI is not known. Here we present results of a pooled analysis that allows for a robust examination of the safety and efficacy of POM + LoDEX in patients with moderate RI across the three clinical trials.

Materials and methods

Study design and participants

Detailed descriptions of methods used in the MM-002, MM-003, and MM-010 trials have been previously published.[15–17] Institutional review boards at each enrolling site approved the relevant trial protocol before initiation. The trials were registered at ClinicalTrials.gov as NCT00833833 (MM-002), NCT01311687 (MM-003), and NCT01712789 (MM-010) and at EudraCT as 2010-019820-30 (MM-003) and 2012-001888-78 (MM-010). All patients included in this pooled analysis received POM 4 mg on days 1 to 21 of a 28-day cycle, and dexamethasone 40 mg (if aged ≤75 years) or 20 mg (if aged >75 years) on days 1, 8, 15, and 22 of a 28-day cycle.

The inclusion and exclusion criteria were similar for the MM-002, MM-003, and MM-010 trials.[15–17] Eligible patients with RRMM were aged ≥18 years and had received ≥2 prior therapies, including ≥2 cycles of LEN or BORT, alone or in combination. Refractoriness to LEN and BORT (or intolerance of BORT) was allowed in the MM-002 trial and was required in the MM-003 and MM-010 trials. For all trials, patients must have had documented disease progression during or within 60 days of their last treatment.

The patients with CrCl <45 mL/min (MM-003 and MM-010) or serum creatinine ≥3.0 mg/dL (MM-002) were excluded from the trials. Additional laboratory exclusion criteria included absolute neutrophil count <1000/μL (MM-002, MM-003) or <800/μL (MM-010) and platelet count <75,000/μL (<30,000/μL for patients with ≥50% plasma cells of nucleated bone marrow cells). The patients with peripheral neuropathy grade ≥2 were also ineligible.

In this pooled analysis, baseline CrCl was calculated for all patients using the Cockcroft-Gault formula.[25] Patients were grouped according to RI status, with moderate RI defined as CrCl ≥30 to <60 mL/min and absence of RI defined as CrCl ≥60 mL/min.

Assessments

Overall response rate (ORR) was defined as partial response (PR) or better based on International Myeloma Working Group (IMWG) criteria and calculated as the number of patients with a confirmed response divided by the number of efficacy-evaluable patients. Progression-free survival (PFS) was defined as the time from randomization to the first documentation of disease progression or death from any cause based on investigator assessments. Time-to-response (TTR) was defined as the interval between randomization and achievement of ≥ PR. Duration of response (DOR) was defined as the time from achievement of ≥ PR to first evidence of disease progression or death from any cause. OS was defined as the time from randomization to the time of death from any cause. Adverse event (AE) severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events.[15–17] Statistical comparisons (p values) were calculated using Fisher's exact test for ORR and log-rank test for PFS, OS, TTP, and DOR.

Role of the funding source

Celgene Corporation funded this analysis, and participated in study design, data collection, data analysis,

and data interpretation. Funding for editorial assistance was provided by Celgene Corporation.

Results

Patients

A total of 355 patients with moderate RI and 713 patients without RI were analyzed. Although CrCl <45 mL/min was an exclusion criterion for MM-003 and MM-010, 106 of the 355 patients with moderate RI had CrCl ≥30 to <45 mL/min (often from a post-screening sample obtained predose on cycle 1 day 1). Although the median time since diagnosis was 5.3 years in both patient subgroups, patients with moderate RI were older compared with patients without RI (median age, 70 vs. 63 years, respectively) and had more advanced disease (Table 1).

Safety

Although patients with moderate RI were older than those without RI, the safety profile of POM + LoDEX was similar across RI subgroups. The most common grade 3/4 AEs for patients with moderate RI vs.

without RI were neutropenia (46.7% vs. 49.6%), anemia (36.5% vs. 29.1%), infections (32.2% vs. 34.4%), and thrombocytopenia (23.1% vs. 23.0%; Table 2). The frequency of grade 3/4 deep vein thrombosis/pulmonary embolism was ≤2.5% in both subgroups (2.3% in patients with moderate RI and 1.4% in patients without RI). Grade 3/4 peripheral neuropathy was infrequent (0.9% and 0.8% in the patients with moderate RI and without RI, respectively).

Renal function did not appear to impact POM dosing (Table 3). There were similar frequencies of discontinuations (7.1% vs. 6.3%), dose reductions (25.1% vs. 23.4%), and interruptions (66.4% vs. 66.6%) due to AEs between subgroups of patients with moderate RI vs. without RI. The average daily dose (4.0 mg/day) and median relative dose intensity (0.9) were the same between RI subgroups. The median treatment duration was slightly shorter for patients with moderate RI vs. those without RI (4.0 vs. 5.1 months).

Efficacy

The ORR was not significantly different in patients with moderate RI vs. those without RI (30.4% vs. 33.8%,

Table 1. Baseline characteristics.

	With Moderate RI				Without Moderate RI			
	MM-002 (n = 37)	MM-003 (n = 93)	MM-010 (n = 225)	Overall (n = 355)	MM-002 (n = 68)	MM-003 (n = 205)	MM-010 (n = 440)	Overall (n = 713)
Median age (range), years	66 (34–84)	69 (41–84)	72 (46–88)	70 (34–88)	62 (46–80)	61 (35–80)	63 (37–85)	63 (35–85)
ECOG, %[a]								
0	18.9	38.7	37.8	36.1	35.3	35.6	46.8	42.5
1	70.3	37.6	50.7	49.3	55.9	49.8	43.9	46.7
2	10.8	22.6	11.6	14.4	8.8	14.1	9.1	10.5
ISS stage, %								
I	0	10.8	19.1	14.9	0	34.6	28.2	27.3
II	0	36.6	25.3	25.6	0	39.5	29.3	29.5
III	0	49.5	35.1	35.2	0	21.0	20.7	18.8
Missing	100	3.2	20.4	24.2	100	4.9	21.8	24.4
Median time since diagnosis (range), years	5.8 (1.4–18.1)	5.5 (0.6–30.0)	5.0 (0.7–28.2)	5.3 (0.6–30.0)	5.2 (1.1–17.9)	5.3 (0.8–21.9)	5.3 (0.6–21.4)	5.3 (0.6–21.9)

ECOG: Eastern Cooperative Oncology Group; ISS: International Staging System; RI: renal impairment.
[a]One patient with moderate RI in MM-010 trial and 1 patient without moderate RI in the MM-003 trial had missing ECOG performance status; one patient without moderate RI in the MM-010 trial had ECOG performance status 3.

Table 2. Grade 3/4 AEs.

	With moderate RI				Without moderate RI			
	MM-002 (n = 37)	MM-003 (n = 93)	MM-010 (n = 221)	Overall (n = 351)	MM-002 (n = 68)	MM-003 (n = 203)	MM-010 (n = 438)	Overall (n = 709)
Most frequent grade 3/4 AEs (> 5%), %								
Neutropenia	40.5	48.4	47.1	46.7	39.7	48.8	51.6	49.6
Febrile neutropenia	2.7	5.4	4.1	4.3	2.9	11.3	6.2	7.3
Thrombocytopenia	16.2	20.4	25.3	23.1	19.1	22.7	23.7	23.0
Anemia	24.3	39.8	37.1	36.5	19.1	29.6	30.4	29.1
Infections	43.2	30.1	31.2	32.2	45.6	30.0	34.7	34.4
Pneumonia	24.3	18.3	12.2	15.1	23.5	9.9	12.8	13.0
Grade 3/4 AEs of interest, %								
DVT/PE	2.7	1.1	2.7	2.3	2.9	1.5	1.1	1.4
PN	0	1.1	0.9	0.9	0	1.5	0.7	0.8

AE: adverse event; DVT: deep vein thrombosis; PE: pulmonary embolism; PN: peripheral neuropathy; RI: renal impairment.

Table 3. POM dose intensity and dose modifications due to AEs.

	With moderate RI				Without moderate RI			
	MM-002 (n = 37)	MM-003 (n = 93)	MM-010 (n = 221)	Overall (n = 351)	MM-002 (n = 68)	MM-003 (n = 203)	MM-010 (n = 438)	Overall (n = 709)
Median average daily dose (range), mg/day	4.0 (2.1–4.0)	4.0 (2.6–4.0)	4.0 (1.6–4.0)	4.0 (1.6–4.0)	4.0 (1.6–4.2)	4.0 (2.1–4.0)	4.0 (2.2–4.0)	4.0 (1.6–4.2)
Median relative dose intensity (range)	0.9 (0.5–1.2)	0.9 (0.4–1.3)	0.9 (0.2–1.3)	0.9 (0.2–1.3)	0.9 (0.2–1.2)	0.9 (0.3–1.2)	0.9 (0.2–1.2)	0.9 (0.2–1.2)
Median Tx duration (range), mo	4.2 (0.5–47.8)	3.6 (0.1–21.4)	4.6 (0.1–25.1)	4.0 (0.1–47.8)	5.7 (0.1–47.6)	4.6 (0.1–20.1)	5.5 (0.2–28.3)	5.1 (0.1–47.6)
Discontinuations due to AE, %	5.4	10.8	5.9	7.1	10.3	6.9	5.5	6.3
Reduction due to AE, %	32.4	28.0	22.6	25.1	25.0	26.6	21.7	23.4
Interruption due to AE, %	73.0	66.7	65.2	66.4	63.2	66.0	67.4	66.6

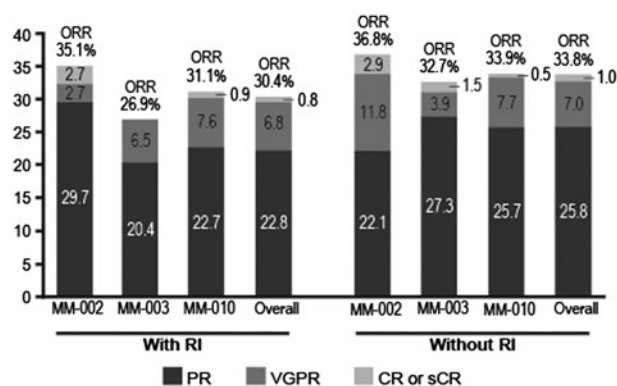AE: adverse event; RI: renal impairment; Tx: treatment.

Figure 1. Overall response rate (ORR) in patients with baseline renal impairment (RI; creatinine clearance [CrCl] ≥ 30 and <60 mL/min) and without baseline RI (≥ 60 mL/min). CR: complete response; PR: partial response; sCR: stringent complete response; VGPR: very good partial response.

respectively; $p = .299$; Figure 1). For patients with vs. without moderate RI, median PFS was 3.8 months (95% CI: 2.9, 4.6 months) vs. 4.6 months (95% CI: 4.4, 5.5 months; $p = .070$), respectively (Table 4). The median TTP was 4.6 months (95% CI: 3.8, 4.9 months) vs. 5.3 months (95% CI: 4.6, 5.8 months; $p = .302$), respectively, in patients with moderate RI vs. those without RI. Patients with moderate RI experienced a median DOR of 6.9 months (95% CI: 5.8, 8.8 months) vs. 7.6 months (95% CI: 6.5, 8.8 months; $p = .435$) for patients without RI. Median OS was significantly shorter for patients with moderate RI, 10.5 months (95% CI: 8.9, 11.5 months) vs. those without RI, 14.0 months (95% CI: 12.4, 15.2 months; $p = .004$).

Discussion

RI is a common comorbidity and cause of end-organ damage in patients with MM in whom it is associated with poorer clinical outcomes.[1,3] In an effort to better understand the impact of RI on safety and efficacy of POM + LoDEX, we analyzed the patients with moderate RI in the MM-002, MM-003, and MM-010 trials. Our analysis demonstrates that POM + LoDEX is a

well-tolerated and effective treatment option in patients with moderate RI.

Efficacy of POM + LoDEX appeared to be independent of RI status, with similar median PFS, median TTP, and median DOR observed for patients with and without moderate RI. Although considerable overlap was observed in the individual trials, in the pooled analysis median OS was shorter in patients with moderate RI vs. patients without RI. This result is consistent with the shorter OS previously reported in a retrospective analysis of patients with MM and moderate to severe RI.[3] In the controlled study MM-003, POM + LoDEX still showed an OS benefit in RI patients compared with HiDEX.[26]

As expected, the most common grade 3/4 AEs were hematologic (neutropenia, anemia, and thrombocytopenia) and infections. The frequency of these AEs was generally similar between the 2 RI subgroups analyzed, suggesting that moderate RI did not have a significant impact on tolerability of POM + LoDEX.

Dose modifications and the need for dose reductions due to RI are a concern of treating physicians. However, unlike LEN, POM is extensively metabolized, and only approximately 2% of the parent drug is eliminated via the renal route.[24] Therefore, the pharmacokinetic profile of POM [24] as well as previous clinical studies [27–30] provide substantial evidence for the approved dosing of POM. Importantly, recently published consensus recommendations also support the use of the approved dosing of POM for treatment of patients with mild to moderate RI.[31]

Previous subanalyses of patients with RI from MM-002 and MM-003 demonstrated safety and efficacy similar to that observed in the overall patient populations,[29,30] although there were comparatively few patients in these intratrial analyses. This pooled analysis provided the opportunity to more comprehensively assess the safety and efficacy of POM + LoDEX in a larger population of patients with MM and RI. One limitation is that the exclusion of patients with severe RI from MM-002, MM-003, and MM-010 prevents an analysis of this subgroup here. Additionally, we did not

Table 4. Efficacy outcomes in patients with vs. without moderate RI.

	With Moderate RI				Without Moderate RI			
	MM-002 (n = 37)	MM-003 (n = 93)	MM-010 (n = 225)	Overall (n = 355)	MM-002 (n = 68)	MM-003 (n = 205)	MM-010 (n = 440)	Overall (n = 713)
Median PFS (95% CI), months	3.8 (2.8, 7.9)	4.0 (2.8, 4.8)	3.7 (2.8, 4.6)	3.8 (2.9, 4.6)	5.4 (3.7, 6.8)	4.2 (3.7, 5.6)	4.8 (4.1, 5.5)	4.6 (4.1, 5.5)
Median TTP (95% CI), months	4.7 (3.1, 9.3)	4.4 (2.9, 6.5)	4.6 (3.7, 5.4)	4.6 (3.8, 4.9)	5.5 (3.7, 7.2)	4.9 (3.9, 6.7)	5.3 (4.6, 6.0)	5.3 (4.6, 5.8)
Median DOR (95% CI), months	8.3 (5.8, 14.1)	6.6 (3.9, 9.7)	6.8 (4.6, 9.5)	6.9 (5.8, 8.8)	7.7 (3.7, 12.5)	7.0 (5.6, 12.4)	7.9 (6.5, 9.2)	7.6 (6.5, 8.8)
Median OS (95% CI), months	13.4 (8.7, 23.8)	10.4 (6.6, 12.4)	9.8 (8.1, 12.0)	10.5 (8.9, 11.5)	16.9 (13.4, 21.7)	14.6 (11.8, 16.6)	12.9 (11.4, 14.7)	14.0 (12.4, 15.2)

DOR: duration of response; OS: overall survival; PFS: progression-free survival; RI: renal impairment; TTP: time to progression.

perform pharmacokinetic analyses in the pooled patient population. However, pharmacokinetics is being assessed in 2 ongoing trials, MM-008 and MM-013, which are investigating POM + LoDEX for the treatment of RRMM in patients with severe RI.[32,33] Investigators are evaluating POM 2 vs. 4 mg in the dose-escalation component of MM-008, and preliminary analysis shows that the pharmacokinetics of POM in patients with severe RI and no or mild RI are similar with both doses.[32] Although additional patients and follow-up are required to more conclusively demonstrate the impact of 2 vs. 4 mg POM in patients with RRMM and severe RI, preliminary data from the MM-008 trial also indicate that POM dose reduction is not required, even in patients with severe RI,[32] supporting 4 mg as the appropriate dose in these patients.

In this larger analysis, dose reductions and modifications were similar between the 2 RI subgroups. Although comparison between POM + LoDEX and a comparator arm was not feasible because each trial had different or no comparators, this more robust analysis provides support for POM 4 mg as a safe, effective, and overall appropriate dose, even in patients with moderate RI.

Acknowledgements

References

[1] Korbet SM, Schwartz MM. Multiple myeloma. J Am Soc Nephrol. 2006;17:2533–2545.

[2] Kastritis E, Anagnostopoulos A, Roussou M, et al. Reversibility of renal failure in newly diagnosed multiple myeloma patients treated with high dose dexamethasone-containing regimens and the impact of novel agents. Haematologica. 2007;92:546–549.

[3] Dimopoulos MA, Delimpasi S, Katodritou E, et al. Significant improvement in the survival of patients with multiple myeloma presenting with severe renal impairment after the introduction of novel agents. Ann Oncol. 2014;25:195–200.

[4] Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78:21–33.

[5] Dimopoulos MA, Terpos E, Chanan-Khan A, et al. Renal impairment in patients with multiple myeloma: a consensus statement on behalf of the International Myeloma Working Group. J Clin Oncol. 2010;28:4976–4984.

[6] Chanan-Khan AA, San Miguel JF, Jagannath S, et al. Novel therapeutic agents for the management of patients with multiple myeloma and renal impairment. Clin Cancer Res. 2012;18:2145–2163.

[7] Goldschmidt H, Lannert H, Bommer J, et al. Multiple myeloma and renal failure. Nephrol Dial Transplant. 2000;15:301–304.

[8] Knudsen LM, Hjorth M, Hippe E. Renal failure in multiple myeloma: reversibility and impact on the prognosis. Nordic Myeloma Study Group. Eur J Haematol. 2000;65:175–181.

[9] Dimopoulos MA, Rossou M, Gkotzmanidou M, et al. The role of novel agents on the reversibility of renal impairment in newly diagnosed symptomatic patients with multiple myeloma. Leukemia. 2013;27:423–429.

[10] Uttervall K, Duru AD, Lund J, et al. The use of novel drugs can effectively improve response, delay relapse and enhance overall survival in multiple myeloma patients with renal impairment. PLoS One. 2014;9:e101819.

[11] Attal M, Harousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood. 2006;108:3289–3294.

[12] Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111:2516–2520.

[13] Gonsalves WI, Leung N, Rajkumar SV, et al. Improvement in renal function and its impact on survival in patients with newly diagnosed multiple myeloma. Blood Cancer J. 2015;5:e296.

[14] Quach H, Ritchie D, Stewart AK, et al. Mechanism of action of immunomodulatory drugs (IMiDs) in multiple myeloma. Leukemia. 2010;24:22–32.

[15] Dimopoulos MA, Palumbo A, Corradini P, et al. The STRATUS (MM-010) trial: a single-arm, phase 3B study evaluating safety and efficacy of pomalidomide + low-dose dexamethasone in patients with refractory or relapsed and refractory multiple myeloma. Haematologica. 2015;100:(Supplement). Abstract 273.

[16] Richardson PG, Siegel DS, Vij R, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood. 2014;123:1826–1832.

[17] San Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14:1055–1066.

[18] Pomalyst (pomalidomide) [package insert]. Summit, NJ: Celgene Corporation; 2015.

[19] Imnovid (pomalidomide) [summary of product characteristics]. Uxbridge, UK: Celgene Europe; 2015.

[20] Botev R, Mallie JP, Wetzels JF, et al. The clinician and estimation of glomerular filtration rate by creatinine-based formulas: current limitations and quo vadis. Clin J Am Soc Nephrol. 2011;6:937–950.

[21] National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:S1–S266.

[22] Chen N, Lau H, Kong L, et al. Pharmacokinetics of lenalidomide in subjects with various degrees of renal impairment and in subjects on hemodialysis. J Clin Pharmacol. 2007;47:1466–1475.

[23] Dimopoulos MA, Christoulas D, Roussou M, et al. Lenalidomide and dexamethasone for the treatment of refractory/relapsed multiple myeloma: dosing of lenalidomide according to renal function and effect on renal impairment. Eur J Haematol. 2010;85:1–5.

[24] Hoffmann M, Kasserra C, Reyes J, et al. Absorption, metabolism and excretion of [14C]pomalidomide in humans following oral administration. Cancer Chemother Pharmacol. 2013;71:489–501.

[25] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41.

[26] Weisel KC, Dimopoulos MA, Moreau P, et al. Analysis of MM-003 patients with moderate renal impairment using pomalidomide + low-dose dexamethasone (POM + LoDEX) vs. high-dose dexamethasone (HiDEX) in relapsed/refractory multiple myeloma (RRMM). Haematologica. 2013;98:(Supplement). Abstract 244.

[27] Leleu X, Attal M, Arnulf B, et al. Pomalidomide plus low dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: Intergroupe Francophone du Myélome 2009-02. Blood. 2013;121:1968–1975.

[28] Richardson PG, Siegel D, Baz R, et al. Phase 1 study of pomalidomide MTD, safety, and efficacy in patients with refractory multiple myeloma who have received lenalidomide and bortezomib. Blood. 2013;121:1961–1967.

[29] Weisel K, Dimopoulos M, Moreau P, et al. Pomalidomide plus low-dose dexamethasone (POM + LoDEX) versus high-dose dexamethasone (HiDEX) in relapsed/refractory multiple myeloma (RRMM): MM-003 analysis of patients (pts) with moderate renal impairment (RI). J Clin Oncol. 2013;31:(Supplement). Abstract 8527.

[30] Siegel DS, Richardson PG, Baz R, et al. Pomalidomide (POM) with low-dose dexamethasone (LoDEX) in patients with relapsed and refractory multiple myeloma (RRMM): impact of renal function on patient outcomes. Blood. 2012;120:(Supplement). Abstract 4072.

[31] Dimopoulos MA, Leleu X, Palumbo A, et al. Expert panel consensus statement on the optimal use of pomalidomide in relapsed and refractory multiple myeloma. Leukemia. 2014;28:1573–1585.

[32] Matous J, Siegel D, Lonial S, et al. MM-008: a phase 1 trial evaluating pharmacokinetics and tolerability of pomalidomide + low-dose dexamethasone in patients with relapsed or refractory and refractory multiple myeloma and renal impairment. Blood. 2014;124:(Supplement). Abstract 4730.

[33] Sonneveld P, Heyne N, Kueenburg E, et al. MM-013: an ongoing phase 2 trial of pomalidomide and low-dose dexamethasone (POM + LoDEX) in relapsed/refractory multiple myeloma (RRMM) with moderate or severe renal impairment (RI), including patients (pts) undergoing hemodialysis. J Clin Oncol. 2014;32:TPS8626.