original reports abstract

Real-World Outcomes With Generic Pomalidomide in Relapsed Refractory Multiple Myeloma—Experience From a Tertiary Care Cancer Center

Suresh Kumar Bondili, DM[1]; Bhausaheb Bagal, DM[1]; Abhinav Zawar, DM[1]; Pradeep Ventrapati, DM[1]; Jayashree Thorat, MD[1]; Anant Gokarn, DM[1]; Sachin Punatar, DM[1]; Lingaraj Nayak, DM[1]; Avinash Bonda, DM[1]; Hashmukh Jain, DM[1]; Manju Sengar, DM[1]; and Navin Khattry, DM[1]

PURPOSE The prognosis of relapsed and refractory multiple myeloma (RRMM) that is refractory to bortezomib and lenalidomide is very poor wherein the median survival is between 3 and 9 months. We did this retrospective analysis to study the pattern of utilization, tolerance, and outcomes with pomalidomide in these patients having RRMM.

MATERIALS AND METHODS Retrospective analysis of all the patients who were treated with generic pomalidomide at Tata Memorial Centre, Mumbai, during the period of May 2017 to March 2019 was done. Patients with secretory disease and who had completed at least one cycle of pomalidomide were analyzed for response rates, toxicity, and survival outcomes.

RESULTS A total of 81 patients received pomalidomide-based therapy during this study period, out of which 75 were included in the survival analysis. Forty-eight patients (59.3%) were refractory to both lenalidomide and bortezomib. Overall response rate was 58.7%. Five patients (6.7%) achieved complete response, very good partial response was seen in 13 patients (17.3%), and partial response was seen in 26 patients (34.7%). After a median follow-up of 11 months (range 2-27 months), median progression-free survival was 9.1 months (95% CI, 5.4 to 12.9 months). Median progression-free survival for patients who were refractory to both lenalidomide and bortezomib versus nonrefractory was 5.5 and 12.6 months, respectively, which was significant statistically (P = .04, hazard ratio, 0.35, 95% CI, 0.28 to 0.97). The median overall survival was not reached. Important toxicities included anemia (28%), neutropenia (16%), pneumonia (16%), and venous thrombosis (5%).

CONCLUSION Generic pomalidomide-based therapy is an effective option and is well tolerated in patients with RRMM. Higher response rates and longer survival seen in our study are possibly because of heterogeneity of the study population.

JCO Global Oncol 7:361-367. © 2021 by American Society of Clinical Oncology

INTRODUCTION

Patients with multiple myeloma present and respond to therapy in a heterogeneous pattern and invariably relapse. Disease becomes less responsive to therapy and remission duration shortens with subsequent lines of treatment. Relapsed and refractory multiple myeloma (RRMM) is defined as progression of disease in patients who achieve minor response or better, while on therapy or within 60 days of their last treatment.[2] The prognosis of these patients who are refractory to bortezomib and immunomodulatory agents such as lenalidomide is very poor and the median survival is between 3 and 9 months with further therapy.[3] Significant improvements in outcomes have been observed in patients with myeloma majorly because of approval of newer antimyeloma agents.

Pomalidomide is a third-generation immunomodulatory agent wherein exerting its action by binding to cereblon E3 ubiquitin ligase and inhibiting downstream signaling through IRAF and other pathways leading to death of plasma cells.[4] Pomalidomide in combination with low-dose dexamethasone is an effective therapy in patients with relapsed and refractory MM who have received prior therapy with both lenalidomide and bortezomib. The pivotal MM-003[1] and MM-0010 trials[5] showed a significant improvement in overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) with pomalidomide in RRMM in comparison to high-dose dexamethasone. The MM-003 study, which compared pomalidomide and low dose dexamethasone with high dose dexamethasone in patients who progressed on two prior

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on January 5, 2021 and published at ascopubs.org/journal/go on March 10, 2021: DOI https://doi.org/10.1200/GO.20.00228

CONTEXT

Key Objective

Generic pomalidomide is readily available and is an economical option in India and other low middle-income countries; however, its outcomes in the real-world scenario are not well described. Our study evaluated the pattern of use, tolerance, and outcomes with generic pomalidomide.

Knowledge Generated

The overall response rate and median progression-free survival (PFS) of the whole cohort were 58.7% and 9.1 months, respectively. In patients with relapsed refractory multiple myeloma, the median PFS was 5.5 months.

Relevance

Pomalidomide is an effective option in patients with relapsed and refractory multiple myeloma, and outcomes are similar to those described in the literature. Hence, generic pomalidomide may provide a valuable alternative to original pomalidomide, especially in developing countries where affordability is a concern.

lines including bortezomib and lenalidomide, reported an ORR of 32% versus 11%, with a median PFS of 4 months versus 1.9 months and median OS of 13.1 versus 8.1 months, respectively.[1] Pomalidomide does not require dose modification in presence of renal failure and has been reported to have particularly benefitted in patients with p53 deletions and/or t(4:14).[6] Generic pomalidomide has recently become available in India and is inexpensive compared with innovator molecule. Oral administration makes it an attractive candidate to use in relapse setting and thus, pomalidomide-based regimens are commonly used for RRMM in our setup.

Patients in developing countries tend to present late with higher proportion of patients having renal dysfunction and other CRAB (hypercalcemia, anemia, renal insufficiency and bone lesions) features at baseline.[7] They often receive less intense therapy and majority of them do not undergo autologous stem cell transplant (ASCT). This combined with often suboptimal induction leads to inferior responses and shorter PFS and OS in our patients. Given the difference in the prior lines of therapy, outcomes of RRMM in our setup may be different including responses to a particular drug. Given the less intense prior treatment, our patients with RRMM may derive greater benefits than reported in literature.[7] Similarly, given the widespread use of pomalidomide-based regimen in RRMM, it is equally important to understand its tolerance in our patient population. Hence, we planned this retrospective analysis to characterize our patient population receiving pomalidomide and to evaluate the tolerance and outcomes with generic molecule.

MATERIALS AND METHODS

Study Method

Patients receiving pomalidomide for RRMM between May 2017 and March 2019 were included in this analysis. All the patients received the same generic brand of pomalidomide. A total of 81 patients were identified. Patients who have had secretory disease and completed at least one cycle of pomalidomide with follow-up response evaluation were included in the analysis. The baseline characteristics and the prior treatment details of these patients were noted from the electronic medical records. All adverse effects were recorded using CTCAE version 4 grading system. Refractory myeloma has been defined as progression on therapy or within 60 days of stopping bortezomib and/or lenalidomide. Fluorescence in-situ hybridization (FISH) analysis of cytogenetics was available in select patients. High-risk FISH is defined as del(17/17p), t(4,14), t(14,16), t(14,20), gain(1q), or non-hyperdiploid karyotype as per International Myeloma Working Group (IMWG) risk stratification in MM.[8] The study was approved by the institutional ethics committee.

Response Assessment

Response rates including complete response (CR), stringent complete response, very good partial response (VGPR), partial response (PR), minor response, stable disease, and progressive disease were defined as per IMWG 2016 criteria.[9] PFS and OS were calculated from the first day of pomalidomide administration. PFS was defined as the time from the initiation of pomalidomide therapy till disease progression or death. The OS was defined as a period from pomalidomide therapy initiation until all-cause death occurrence.

Statistical Analysis

Statistical analysis was done using the SPSS software (Version 21, IBM Corp., Armonk, NY). Survival analysis was done using the Kaplan-Meier method to estimate the survival, and comparison between the groups was done using the log-rank test. Proportions were compared using chi-square or Fisher exact test.

RESULTS

Demographic Profile

Overall, 81 patients received pomalidomide during the study period as mentioned. Median age of study population was

61.5 years (range 34-78 years); 30 patients (37%) were older than 65 years of age, including 5 patients older than 75 years of age. Fifty-three (65%) were male and 21 patients (25.9%) had an Eastern Cooperative Oncology Group performance status of three or more at the time of treatment. Renal failure (glomerular filtration rate < 40 mL/min by Cockcroft-Gault formula) was seen in 20 (24.7%) patients at the start of pomalidomide-based therapy and 10 patients received dialysis at some point after the start of pomalidomide-based therapy. FISH results were available for 57 patients. High-risk cytogenetics as per IMWG criteria was seen in 27 (33%) with 17p deletion seen in six patients (7.4%).

The median time from diagnosis to initiation of pomalidomide therapy was 56 months (range 9-160 months). Median number of previous lines was three (range 1-6), with 63% patients having received three or more prior lines of therapies. Seventy-eight patients (96.3%) received prior bortezomib, 67 patients (82.7%) received lenalidomide, and 32 patients had received thalidomide. Overall, 80.2% and 76.5% were refractory to bortezomib and lenalidomide, respectively, whereas 48 (59.3%) of patients were double-refractory, ie, to both bortezomib and lenalidomide. Eleven patients (13.6%) had undergone prior ASCT. Majority of patients (n = 49) received pomalidomide in combination with low-dose dexamethasone. Few patients received triplet

TABLE 1. Demographic Characteristics

Characteristic	Number of Patients (N = 81)
Median age, years	61.5 (range 34-78)
< 65	51 (63%)
> 65	30 (37%)
Sex	
Male	53 (65%)
Female	28 (35%)
ECOG performance status	
0-2	60 (74.1%)
3-4	21 (25.9%)
International staging system	N = 81
1	11 (13.6%)
2	29 (35.8%)
3	41 (50.6%)
FISH available	N = 57 (70%)
High-risk cytogenetics[a]	27 (33%)
17p deletion	6 (7.4%)
Median time from diagnosis to start of pomalidomide	56 months (range 9-160)
Median no. of prior antimyeloma therapies	3 (range 1-6)
Prior lenalidomide	67 (82.7%)
Lenalidomide refractory	62 (76.5%)
Prior bortezomib	78 (96.3%)
Bortezomib refractory	65 (80.2%)
Lenalidomide and bortezomib refractory	48 (59.3%)
Prior autologous HSCT	11 (13.6%)
Combination therapy	
Pomalidomide plus dexamethasone	49 (60.5%)
Pomalidomide plus dexamethasone plus bortezomib	22 (27.2%)
Pomalidomide plus dexamethasone plus carfilzomib	8 (9.9%)
Pomalidomide plus dexamethasone plus daratumumab	1 (1.2%)
Pomalidomide plus dexamethasone plus cyclophosphamide	1 (1.2%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in-situ hybridization; HSCT, hematopoietic stem-cell transplantation.

[a]High-risk FISH is defined as del(17/17p), t(4,14), t(14,16), t(14,20), gain(1q), or non-hyperdiploid karyotype as per International Myeloma Working Group risk stratification in MM.[8]

therapy—with the third drug being bortezomib in 22 patients, carfilzomib in eight patients, daratumumab in one patient, and cyclophosphamide in one patient. Median number of pomalidomide cycles administered was six, with range from one cycle to 28 cycles. Starting dose of pomalidomide was 2 mg in 39 patients (52%), 3 mg in 22 patients (29.3%), and 4 mg in 14 patients (18.7%) (Table 1).

Disease Response

Response rates are summarized in Table 2. Follow-up data were available for 75 patients and were analyzed. Among the six excluded patients, four patients died within one month of starting pomalidomide and follow-up details were not available for two patients.

The ORR was 58.7% with CR in 6.7%, VGPR in 17.3%, and PR in 34.7% of the patients. Among patients who received the doublet of pomalidomide and dexamethasone (n = 46), the ORR was 65.2%. The median time to best response was 3 months. There was no significant difference in the response rates according to ISS staging or high-risk cytogenetics.

Survival Outcomes

The median follow-up duration was 11 months. The median PFS of the whole group of patients who were included for analysis was 9.1 months (95% CI, 5.4 to 12.9) as given in Figure 1. The median OS was not reached.

Median PFS for patient with double-refractory (refractory to both bortezomib and lenalidomide) myeloma was 5.5 months versus 12.6 months in others ($P = .039$, hazard ratio [HR]. 0.53, 95% CI, 0.29 to 0.97, Fig 2). There was significant difference in 18-month survival for double-refractory myeloma versus nonrefractory, which was 55% and 80%, respectively ($P = .025$, HR 0.31, 95 CI, 0.11 to 0.90).

The median PFS for patients who were lenalidomide refractory was 7.3 months, for high-risk cytogenetics 6.1 months, and among patients with age < 65 years and > 65 years—9 months and 6 months, respectively. The median PFS in patients treated with doublet (Pom dexa) was 10.3 months and in those treated with triplet combination was 5.3 months. However, since the cohort is small, accurate comparisons could not be made among the subgroups.

The median PFS was not reached in patients who achieved CR and VGPR, whereas it was 14 months (95% CI, 7.9 to 20 mg, $P = .001$) in patients with PR. The median PFS was 6.0 months in patients receiving 2 mg/3mg of pomalidomide and 24.8 months in those who received 4 mg daily-dose pomalidomide ($P = .001$, HR, 0.19, 95% CI, 0.07 to 0.50).

Toxicity and Tolerability

Toxicities seen with pomalidomide have been summarized in Table 3. Grade 3 or more hematologic toxicity was seen in around 30% of the patients, the most common being anemia in 23 patients. Thirteen patients (16%) had grade 3 or more neutropenia, and 15 (18.5%) had grade 3 or more thrombocytopenia. Among nonhematologic toxicities, fatigue of any grade (most common) was seen in 22 patients (27.2%), followed by pneumonia in 13 patients (16%). Peripheral neuropathy (any grade) was seen in nine patients (11%). Significant venous thromboembolism occurred in four patients—one of whom had coexisting diabetes, hypertension, and chronic kidney disease. Pomalidomide therapy was discontinued in six patients. The causes for discontinuation include pulmonary embolism (n = 4), grade 3 anemia (n = 1), and worsening peripheral neuropathy (n = 1). Dose reduction was done in three patients because of myelosuppression. Notably, no patient died because of toxicity. But, three patients died within one month of starting pomalidomide because of disease progression.

DISCUSSION

RRMM represents an unmet medical need and this is particularly challenging in our setup because of cost constraints. Here, we report outcomes in a large cohort of patients treated with pomalidomide-based regimen and demonstrate the utility and safety in our setting.

Generic pomalidomide has been available in India since mid-2017. This is a huge benefit for developing countries such as India, where affordability of the innovator brand (which costs around $900 for 21 capsules of 4 mg when compared with around $170 for generic) is low. With a huge cost difference and likely prolonged use of pomalidomide with more effective regimens such as Daratumumab-pom-

TABLE 2. Response Rates

Best Response	Response Rate—Entire Cohort (n = 75)	Response Rate—Doublet Cohort (n = 46)
Complete response	5 (6.7%)	3 (6.5%)
VGPR	13 (17.3%)	9 (19.6%)
PR	26 (34.7%)	18 (39.1%)
Minimal response	4 (5.3%)	3 (6.5%)
Stable disease	4 (5.3%)	1 (2.2 %)
Progressive disease	23 (30.7%)	12 (26.1%)

Abbreviations: PR, partial response; VGPR, very good partial response.

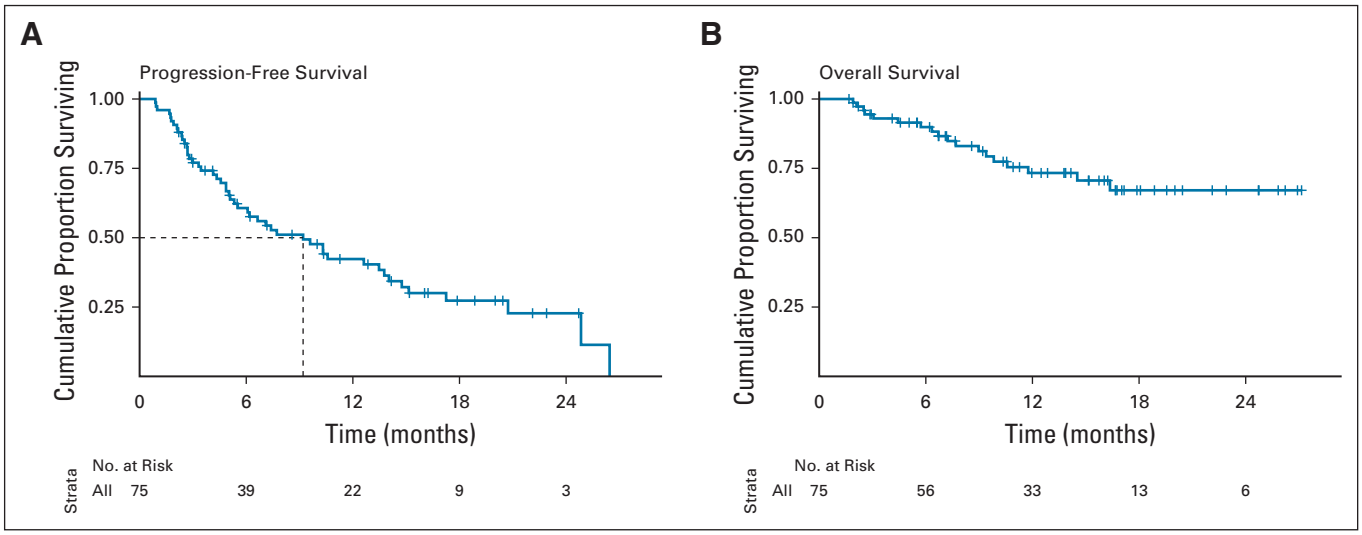

FIG 1. Overall progression-free survival and overall survival.

dexa,[10] the financial implications of use of generic molecule are likely to be important for Western patient populations or healthcare system as well.

ORR in our study was 65.2% among patients who received the doublet (pom dexa), which is higher than that observed in pivotal pomalidomide trials (31% in MM-003 and 32.6% in MM-010 trial) and other real-world studies from Australia, United Kingdom, and Poland. Median PFS in our study is 10.3 months (doublet cohort) in contrast with 4.0 and 4.6 months seen in MM-003 and MM-010 trials, respectively. Similarly, median OS is not reached in our study, whereas it was 13.1 months in the MM-003 trial and 11.9 months (doublet cohort) in the MM-010 trial.[5] Real-world experience of pomalidomide from Australia showed a median PFS of 3.4 months and a median OS of 7.5 months, which was similar to the MM-003 and MM-010 trials.[11] Similarly, a multicenter analysis from United Kingdom, which retrospectively studied about 70 patients, reported a PFS of 5.2 months and an OS of 13.7 months.[12] The Polish myeloma group, which retrospectively analyzed 50 patients on pomalidomide, revealed a PFS and OS of 10 months and 14 months, respectively, which closely resembles our study results.[13]

The higher response rates and survival seen in our study when compared with the pivotal trials of pomalidomide therapy can be explained by the background difference in the study population and the treatment administered. The MM-003 study included patients only who failed treatment with both bortezomib and lenalidomide, have received prior alkylator therapy, and Eastern Cooperative Oncology Group performance status 0, 1, or 2; patients with creatinine clearance ≤ 45 mL/min were excluded from the MM-003

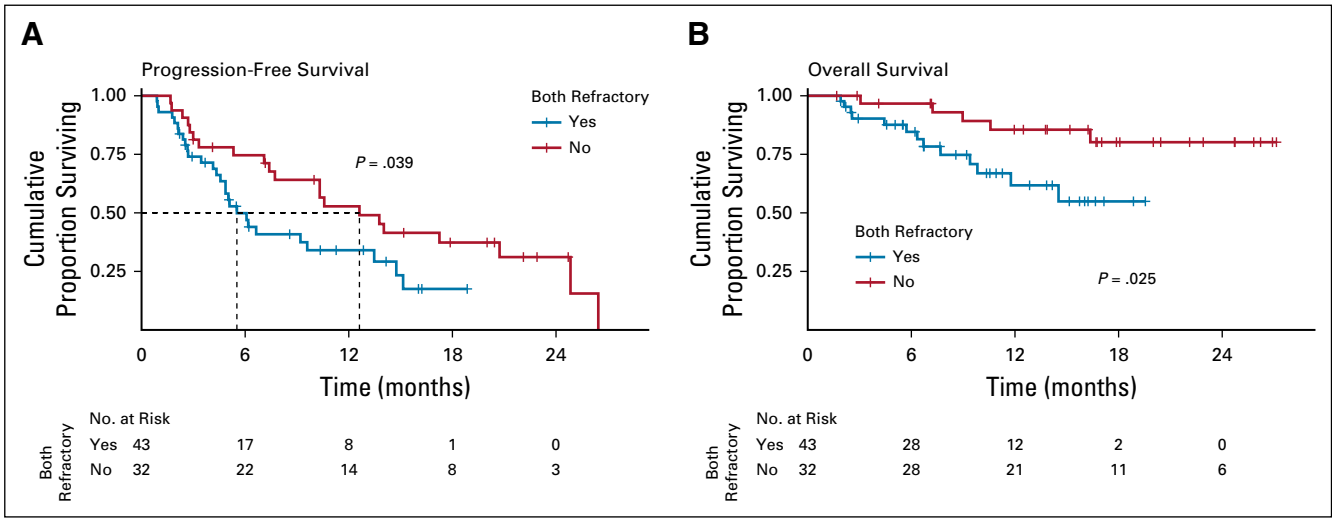

FIG 2. Progression-free survival and overall survival in patients with relapsed and refractory multiple myeloma.

TABLE 3. Toxicity

Toxicity	Number of patients (N = 81)
Anemia grade 3 or 4	23 (28.3%)
Fatigue, any grade	22 (27.2%)
Thrombocytopenia, grade 3 or 4	15 (18.5%)
Neutropenia, grade 3 or 4	13 (16%)
Pneumonia	13 (16%)
Peripheral neuropathy, any grade	9 (11.1%)
Venous thromboembolism	4 (4.9%)
Febrile neutropenia G3 or G4	3 (3.9%)
Diarrhea G3 or G4	3 (3.7%)
Renal failure	3 (3.7%)
Atrial fibrillation	2 (2.6%)

trial. However, in our study, around 13 patients (17.3%) never received lenalidomide because of renal failure (glomerular filtration rate $<$ 30 mL/min), who would have been excluded in the MM 003 study, and median lines of prior therapy were three in the current study compared with five in MM-003. This could account for a higher response rates with pomalidomide in our study. Also, studies have shown that there is no significant difference in response rates in patients with or without poor renal function. Smaller number of double-refractory patients (60%) and lower number of prior ASCT (13.6% *v* 71% in MM-003) study are other possible explanations for the higher rates and PFS. Other differences with the MM-003 study include a lesser percentage of patients older than 65 years of age (37% *v* 45%).

Pomalidomide was relatively well tolerated in our study population. Grade 3 or 4 hematologic or nonhematologic toxicities were seen in about 30% of cases as opposed to 60% in the MM-003 trial. This may be because of differences in patient selection. However, it may be more likely because of the use of 2 mg dose in more than half of our patients. The dosage of 4 mg has been criticized because of higher toxicity and reports of similar efficacy between 2 and 4 mg doses.[14] In a study by Sehgal et al,[15] which compared 2 mg versus 4 mg of pomalidomide, comparable response rates were observed between both the cohorts with higher toxicity (venous thromboembolism or myelosuppression) reported using 4 mg dosage in that cohort study.

The limitations of our study include its retrospective design and heterogeneous nature of treatment regimens, besides variation in the pomalidomide dose used. This is common in real-world studies and would predict outcomes in settings like ours than the registered studies on pomalidomide with strict eligibility criteria.

In conclusion, generic pomalidomide-based therapy is an effective option and is well tolerated in patients with RRMM. Higher response rates and longer survival seen in our study are possibly because of heterogeneity of the study population.

AFFILIATION

[1]Department of Medical Oncology, Tata Memorial Hospital, Parel, and Homi Bhabha National Institute, Mumbai, Maharashtra, India

CORRESPONDING AUTHOR

Bhausaheb Bagal, DM, Department of Medical Oncology, Adult Hemotolymphoid Disease Management Group,Tata Memorial Hospital, Main Building, Room No 81, Parel, Mumbai, India 400012; e-mail: bagalbp@gmail.com.

AUTHOR CONTRIBUTIONS

Conception and design: Suresh Kumar Bondili, Bhausaheb Bagal, Lingaraj Nayak, Hashmukh Jain, Navin Khattry
Financial support: Lingaraj Nayak
Administrative support: Lingaraj Nayak, Navin Khattry
Provision of study materials or patients: Bhausaheb Bagal, Pradeep Ventrapati, Anant Gokarn, Lingaraj Nayak, Hashmukh Jain, Manju Sengar, Navin Khattry
Collection and assembly of data: Suresh Kumar Bondili, Bhausaheb Bagal, Abhinav Zawar, Pradeep Ventrapati, Jayashree Thorat, Anant Gokarn, Sachin Punatar, Lingaraj Nayak, Hashmukh Jain, Navin Khattry
Data analysis and interpretation: Suresh Kumar Bondili, Bhausaheb Bagal, Abhinav Zawar, Pradeep Ventrapati, Avinash Bonda, Hashmukh Jain, Manju Sengar, Navin Khattry
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

No potential conflicts of interest were reported.

REFERENCES

1. Miguel JS, 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 14:1055-1066, 2013
2. Nooka AK, Kastritis E, Dimopoulos MA, et al: Treatment options for relapsed and refractory multiple myeloma. Blood 125:3085-3099, 2015

3. Kumar SK, Lee JH, Lahuerta JJ, et al: Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: A multicenter international myeloma working group study. Leukemia 26:149-157, 2012
4. Pomalidomide in the treatment of multiple myeloma: Design, development and place in therapy. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5574598/
5. Dimopoulos MA, Palumbo A, Corradini P, et al: Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS (MM-010): A phase 3b study in refractory multiple myeloma. Blood 128:497-503, 2016
6. Dimopoulos MA, Weisel KC, Song KW, et al: Cytogenetics and long-term survival of pomalidomide and low-dose dexamethasone in refractory or relapsed and refractory multiple myeloma. Haematologica 100:1327-1333, 2015
7. Chanana R, Sengar M, Jain H, et al: A retrospective cohort study to evaluate the outcomes of multiple myeloma treated in a tertiary care centre from India. Clin Lymphoma Myeloma Leuk 17:e92, 2017
8. Sonneveld P, Avet-Loiseau H, Lonial S, et al: Treatment of multiple myeloma with high-risk cytogenetics: A consensus of the International Myeloma Working Group. Blood 127:2955-2962, 2016
9. Kumar S, Paiva B, Anderson KC, et al: International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 17:e328-e346, 2016
10. Chari A, Suvannasankha A, Fay JW, et al: Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood 130:974-981, 2017
11. Scott A, Weber N, Tiley C, et al: "Real-world" Australian experience of pomalidomide for relapsed and refractory myeloma. Leuk Lymphoma 59:1514-1516, 2018
12. Maciocia N, Melville A, Cheesman S, et al: Real-world use of pomalidomide and dexamethasone in double refractory multiple myeloma suggests benefit in renal impairment and adverse genetics: A multi-centre UK experience. Br J Haematol 176:908-917, 2017
13. Charlinski G, Grzasko N, Jurczyszyn A, et al: The efficacy and safety of pomalidomide in relapsed/refractory multiple myeloma in a "real-world" study: Polish Myeloma Group experience. Eur J Haematol 101:354-361, 2018
14. Zander T, Aebi S, Pabst T, et al: Spotlight on pomalidomide: Could less be more? Leukemia 31:1987-1989, 2017
15. Sehgal K, Das R, Zhang L, et al: Clinical and pharmacodynamic analysis of pomalidomide dosing strategies in myeloma: Impact of immune activation and cereblon targets. Blood 125:4042-4051, 2015