



Management of Relapsed and Refractory Multiple Myeloma: Recent advances

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Abstract

Multiple myeloma (MM) accounts for ~10% of total hematologic malignancies worldwide. In India, the incidence of MM has increased two-fold with marked heterogeneity. Significant improvements in terms of clinical outcomes have been observed in the management of MM in recent years. However, most patients develop a disease relapse with the first or subsequent treatments. A combination of immuno-modulatory drugs (thalidomide and lenalidomide) and proteasome inhibitors (PIs; bortezomib) has been the mainstay for the therapeutic management of relapsed/refractory multiple myeloma (RRMM). This review highlights the management of RRMM with newer agents such as belantamab, carfilzomib, daratumumab, elotuzumab, ixazomib, mafadotin, selinexor, panobinostat, and venetoclax, with more focus on PIs. As a single agent and in combination with other drugs including dexamethasone and carfilzomib has been studied extensively and approved by the United States, European Union, and India. Clinical trials of these newer agents, either alone or in combination, for the treatment of RRMM in Western countries indicate survival, improved outcomes, and overall well-being. However, evidence in Indian patients is evolving from ongoing studies on carfilzomib and daratumumab, which will ascertain their efficacy and safety. Currently, several guidelines recommend carfilzomib-based, daratumumab-based, and panobinostat-based regimens in RRMM patients. Currently, with more accessible generic versions of these drugs, more Indian patients may attain survival benefits and improved quality of life.

Keywords

- relapsed/refractory multiple myeloma
- carfilzomib
- ixazomib
- daratumumab
- elotuzumab
- panobinostat

Introduction

Multiple myeloma (MM) is a chronic and rare cancer affecting plasma cells in the bone marrow. It is the next most prevalent blood cancer after leukemia,¹ affecting ~138,500 individuals worldwide every year.² According to the Globocan 2018 data, the global incidence and mortality of MM are 159,985 and 106,105, respectively,³ and are expected to rise in the future.⁴ Asia has a high incidence, mortality, and 5-year prevalence of MM compared with Europe and North America.³ In India, the estimated incidence in 2018 is 12,923

new cases; mortality is 9,900 cases, and the 5-year prevalence estimate is 24,375 cases. These figures are almost two times higher compared with 2012 data.⁵ Further, there is apparent heterogeneity in the incidence of MM in India across age, sex, and geography.⁶

Despite advancements in induction and maintenance therapies, most patients eventually experience relapse and refractoriness requiring further treatment.⁷ Over the years, novel therapeutic strategies, such as bortezomib,⁸ thalidomide,⁹ and lenalidomide,¹⁰ have been used for MM. However, several studies have highlighted the poor prognosis of

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patients who have been refractory to the currently used drugs.^{11,12} Over the last few years, there has been a visible shift in the treatment of relapsed and/or refractory MM (RRMM). Several newer agents or combinations of agents targeting various relapse phases are currently available with improved patient survival and quality of life. This review focuses on clinical trial results of second-generation proteasome inhibitors (PIs), ixazomib and carfilzomib, and also provides an overview on other novel therapies, including daratumumab, isatuximab, elotuzumab, belantamab mafodotin, and panobinostat, for the management of RRMM.

Definition of RRMM

RRMM is characterized as cancer that becomes progressive within 60 days of receiving the most recent therapy in those who attained a minimal response or improved on previous treatment or cancer that is nonresponsive while on salvage treatment.¹³ While in the nonsecretory subtype, relapse of myeloma is characterized as an absolute rise in the bone marrow plasma cells by $\geq 10\%$.¹⁴

Biology of Resistant MM

Relapsed MM is a biologically and genetically advanced heterogeneous cancer.¹⁵ There are several reasons for relapse in MM cells, including the clonal evolution of MM cells and decreased capacity to adapt to the bone marrow microenvironment changes,¹⁶ old age,¹⁷ comorbidities,¹⁸ and high-risk cytogenetics.¹⁹ The International Myeloma Workshop Group (IMWG) defines the type of relapse based on clinical aggressiveness. In biochemical relapse, the disease progression correlates with an increase in M protein levels in an asymptomatic patient, whereas clinical relapses are accompanied by symptoms with or without organ dysfunction and an increase in M protein levels. A quick onset of symptoms characterizes aggressive relapse, widespread malignancy on laboratory, radiographic, or pathologic findings, and rapid organ dysfunction. The other high-risk features include unfavorable cytogenetic defects, high $\beta 2M$ (>5.5 mg/L) or low albumin (<3.5 g/dL), hypodiploidy, extramedullary disease, International Staging System stage II/III at relapse, and isotype makeover (hyposecretory disease, light chain escape). The presence or re-emergence of one or more CRAB characteristics (calcium, renal impairment, anemia, and destructive bone lesions) or a swift and consistent biochemical relapse is indicated for relapse treatment.¹⁴

The evolution of RRMM is dependent on the modifications in the intrinsic biology of tumor cells, tumor microenvironment, and host-specific factors. The tumor-specific molecular events contributing to RRMM development include accumulating cytogenetic aberrations (chromosomal translocations, gains, and deletions), alterations in signaling pathways (NF- κ B, RAS-MAPK, JAK-STAT3), mutations in genes related to tumor suppression and drug resistance (*TP53*, *RB1*, *CRBN*, *CUL4B*), and epigenetic aberrations (DNA methylation, histone modification).²⁰ Primary cytogenetic abnormalities,

such as trisomies and IgH translocations, occur early when the normal plasma cell transitions to a clonal, premalignant stage. Secondary cytogenetic abnormalities, including Del 17p, Del 1p, t (14:16), and t (14:20), occur during the progression of the malignancy to RRMM.²¹

RRMM Treatment

Treatment selection for RRMM is based usually on previous therapy, duration of disease, transplant status, performance status, cancer-associated factors, such as nature of relapse, disease risk, genomic abnormalities, and overall disease burden, and patient-related factors, such as patient preferences for drug intake, age, and comorbidities, including renal insufficiency.²² With the introduction of immunomodulatory drugs (IMiDs), such as thalidomide, pomalidomide and lenalidomide, second-generation PIs, and more recently monoclonal antibodies targeting CD38, treatment options have been expanded for RRMM management.²³ Currently, new treatment strategies, such as oral HDAC6 inhibitors, bispecific T cell engager antibodies, chimeric antigen receptor T cell (CAR-T) therapy, and cyclin-dependent kinase inhibitors, are being studied in clinical trials. Novel agents, such as second-generation PIs, are generally well-tolerated with a better quality of life (QoL) among adults.²⁴ In a meta-analysis comparing all available agents for RRMM, PIs were the most efficient treatment options with the lowest toxic effects.²⁵ The National Comprehensive Cancer Network guidelines list 8 preferred regimens and more than 20 optional regimens constituting carfilzomib and daratumumab for previously treated MM.²²

However, as the prevalence of MM in elderly patients is expected to increase in the future, optimal care should focus on improving outcomes while preserving the QoL.

In the following section, we will briefly discuss relevant studies and the clinical utility of carfilzomib, ixazomib, daratumumab, isatuximab, elotuzumab, belantamab mafodotin, panobinostat, and selinexor in the management of RRMM exposed to IMiDs and bortezomib.

Carfilzomib

The US Food and Drug Administration (FDA) approved carfilzomib in 2012 as a treatment for individuals with advanced MM, who have used at least one or more prior therapies.²⁶ Unlike bortezomib, carfilzomib selectively and irreversibly inhibits the 20S proteasome's chymotrypsin-like activity and is less susceptible to drug resistance.²⁶ Later, it was approved as a combination with lenalidomide plus dexamethasone or with dexamethasone for the treatment of RRMM, with less than or equal to three lines of prior treatment. In RRMM patients, the FDA recently expanded the prescribing information for carfilzomib to include weekly administration in combination with dexamethasone (Kd70 once weekly).²⁷ Combination of carfilzomib and lenalidomide plus dexamethasone was approved in 2015 by the European Medicines Agency (EMA) for adults with MM who have had at least one previous treatment.²⁸ In 2017, the Drugs Controller General of India approved carfilzomib and dexamethasone combination or carfilzomib and

lenalidomide plus dexamethasone combination for RRMM patients who have received at least one previous treatment.

Carfilzomib and its Combinations

The efficacy and safety of carfilzomib in combination with dexamethasone were determined in clinical studies (►Table 1).^{29–32} Based on these findings, the USA and European countries have approved the combination of low-dose dexamethasone and carfilzomib. Safety and tolerability of carfilzomib in combination with lenalidomide and low-dose dexamethasone were determined in phase 1b dose-escalation,³³ phase 2 dose-expansion³⁴ (PX-171-006), and phase 3³⁵ studies (►Table 1). A randomized phase 3 study investigated the efficacy of carfilzomib versus low-dose corticosteroids with optional cyclophosphamide in RRMM (FOCUS trial) (►Table 1).³⁶

A meta-analysis by Shah et al analyzed carfilzomib-based medicines for the treatment of RRMM (2906 patients); seven trials used carfilzomib plus other agents: dexamethasone (4 studies), lenalidomide plus dexamethasone (2 studies), and panobinostat (1 study).³⁷ The pooled overall response rate (ORR) and clinical benefit rate (CBR) were 45% (95% CI: 29–62) and 56% (95% CI: 41–71), respectively. In a separate analysis of three RCTs (ENDEAVOR, FOCUS, and ASPIRE), ORR and CBR improved significantly in the carfilzomib group compared with the control group. There was no difference between carfilzomib and low-dose corticosteroids alone for overall survival (OR) or progression-free survival (PFS) in patients who had received five previous regimens of low-dose corticosteroids for RRMM; this suggests that carfilzomib needs to be combined with certain drugs and used as first-line chemotherapy (FOCUS trial).³⁷ Compared with a single therapy, combination therapy showed improved ORR and CBR. Further, the treatment response in terms of ORR improved significantly with a more dose of carfilzomib ($>20/27$ mg/m²) compared with the normal dose (65% versus 35%, $p=0.03$). While cardiotoxicity and hypertension were significantly high, peripheral neuropathy events were similar between the two groups.³⁷ In another meta-analysis of eight clinical studies (1,446 patients), Chen et al presented four trials of carfilzomib (monotherapy) for RRMM, two trials of lenalidomide and dexamethasone in combination, and two trials with or without dexamethasone. The pooled ORR and CBR with carfilzomib were 0.44 (95% CI, 0.18–0.69; $p=0.000$) and 0.54 (95% CI, 0.33–0.76, $p=0.000$), respectively.³⁸ In another meta-analysis of 24 studies (10,853 patients), Luo et al identified the time to progression, OS, and PFS of 21 different regimens and recommended triplet therapy of carfilzomib, daratumumab, and elotuzumab or ixazomib, plus dexamethasone and lenalidomide as the preferred choice in patients with RRMM.³⁹ In another meta-analysis of 20 prospective studies (2,220 patients) by Liu et al, the ORR and very good partial response were found to be 61% and 29%, respectively, with the carfilzomib combination regimens in 1,211 RRMM patients.⁴⁰ Several other studies have also determined the safety and efficacy of carfilzomib with dexamethasone and pomalidomide,⁴¹ ibritinib and

dexamethasone,⁴² and daratumumab and dexamethasone.⁴³ In the subgroup analysis of Asian patients, carfilzomib treatment caused increased cardiovascular toxicities (grade 3 or higher) (ARROW and ENDEAVOR trials).⁴⁴

Safety of Carfilzomib

Polyneuropathy

In a pooled analysis of four phase 2 studies, 71.9% of 84.8% of patients at baseline experienced polyneuropathy (PNP) of grade 1 or 2. PNP grade 3 occurs in ~1.3% of patients.⁴⁵ However, the ENDEAVOR trial has reported a lower incidence of PNP with carfilzomib versus bortezomib,³¹ whereas the ASPIRE trial observed a similar incidence of PNP between the lenalidomide and dexamethasone (Rd) and carfilzomib, lenalidomide, and dexamethasone (KRd) groups.³⁵

Cardiotoxicity

Carfilzomib can cause chest pain, myocardial infarction, cardiac failure, hypertension, and peripheral edema. In a meta-analysis of 24 prospective studies ($N=2594$), adverse cardiovascular events of any grade were seen in 18.1% of patients and of high degree (≥ 3) in 8.2% of patients. The incidence of these events was two times higher than the control group.⁴⁶ In another meta-analysis of 29 studies (4,164 patients), incidences of high-grade and any-grade cardiotoxicity were found to be 4.92% and 8.68%, respectively. The carfilzomib group had significantly higher odds of developing cardiotoxicity than the control group (OR, 2.03; 95% CI, 1.19–3.46; $p=0.010$ for any grade and OR, 2.04; 95% CI, 1.31–3.17, $p=0.002$ for high grade). The incidence of cardiotoxicity was similar in recently diagnosed compared with RRMM and in a high dose compared with a standard dose of carfilzomib.⁴⁷ However, the risk seems to be high with the addition of IMiDs compared with without addition (6.54% vs. 4.35%, $p=0.033$). Clinicians need to be aware of these adverse events, and more research is required to develop risk mitigation strategies.⁴⁶

Renal Toxicity

Acute kidney injury is another crucial adverse event of carfilzomib, especially in individuals with RRMM. In a recent meta-analysis of four RCTs (2,954 patients), renal toxicities were reported to be 21.3% for any grade and 8.3% for high grade in the carfilzomib group. The risk of renal toxicity was significantly high in the carfilzomib group compared with the control group ($p<0.001$) (pooled relative risk [RR], 1.79; 95% CI, 1.43–2.23 for any grade and RR, 2.29; 95% CI, 1.59–3.30 for high grade). The incidence of renal toxicities did not differ based on carfilzomib dose, infusion duration, and treatment setting.⁴⁸

Ixazomib

The safety and tolerability of oral ixazomib and its maximum tolerated dose were determined in a phase 1 trial.⁴⁹ The efficacy and safety of ixazomib in combination with lenalidomide and dexamethasone,⁵⁰ as well as pomalidomide and dexamethasone,^{51,52} were investigated in different clinical studies. (►Table 1).

Table 1 Clinical evidence on advancements in relapsing and refractory multiple myeloma treatment

Study title	Study type	No. of patients	Intervention	Outcomes
Carfilzomib				
Phase 1 study of 30-minute infusion of carfilzomib as a single agent or in combination with low-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma ²⁹	Phase 1 study	33	Carfilzomib and dexamethasone carfilzomib (initial dose of 20 mg/m ² and gradually raised to 70 mg/m ²) in combination with dexamethasone (40 mg per week)	• CBR and ORR for carfilzomib monotherapy were both 48% and 52%, respectively • The addition of dexamethasone increased the CBR and ORR to 64% and 55%, respectively, with acceptable tolerability
A phase 2 single-center study of carfilzomib 56 mg/m ² with or without low-dose dexamethasone in relapsed multiple myeloma ³⁰	Investigator-initiated, phase 2, single-arm, single-center, open-label study	44	Carfilzomib and dexamethasone carfilzomib was administered for the first two cycles (20 mg/m ²) and 56 mg/m ² thereafter. Dexamethasone (20 mg) was administered in six patients who progressed with carfilzomib monotherapy	• Partial response was achieved in 55% (23/42) of patients with carfilzomib for the first two cycles • Median DOR was 11.7 months and median OS and PFS were 20.3 and 4.1 months, respectively • In patients with dexamethasone added, 67% (4/6) achieved a partial response
Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomized, phase 3 trial ³¹	Phase 3, open-label, randomized controlled trial (ENDEAVOR trial)	929	Carfilzomib or bortezomib and dexamethasone The initial dose of carfilzomib was 20 mg/m ² for the first two days of cycle one and was increased to 56 mg/m ² in further cycles and bortezomib 2 mg SC or IV was administered weekly twice. Dexamethasone (20 mg oral or intravenous infusion) was given on different days after the first two days in the carfilzomib group and bortezomib group.	• Median OS was 47.6 months in the carfilzomib group versus 40.0 months in the bortezomib group ($p = 0.010$)
Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomized, phase 3, open-label, multicenter study ³²	Randomized, phase 3, open-label, multicenter study		Carfilzomib or bortezomib and dexamethasone Carfilzomib (20 mg/m ² on days 1 and 2 of cycle 1; 56 mg/m ² thereafter; 30-minute intravenous infusion) and dexamethasone (20 mg oral or intravenous infusion) or bortezomib (1.3 mg/m ² ; intravenous bolus or subcutaneous injection) and dexamethasone (20 mg oral or intravenous infusion)	• Median PFS was 18.7 months in the carfilzomib group versus 9.4 months in the bortezomib group at a preplanned interim analysis ($p < 0.0001$)
Phase 1b dose-escalation study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma ³³	Phase 1b dose-escalation study (PX-171-006)	40	Carfilzomib in combination with lenalidomide and low-dose dexamethasone (CRd) CRd was administered on 28-day dosing cycles: carfilzomib 15–27 mg/m ² on days 1, 2, 8, 9, 15, and 16; lenalidomide 10–25 mg on days 1–21; and dexamethasone 40 mg weekly.	• ORR was 62.5%, and clinical benefit response rate was 75.0% • Median DOR and PFS were 11.8 and 10.2 months, respectively
Phase 2 dose-expansion study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma ³⁴	Phase 2 dose-expansion study (PX-171-006)	52	Carfilzomib, dexamethasone plus lenalidomide Carfilzomib was given initially at a dose of 15 mg/m ² and slowly increased to 27 mg/m ² combined with lenalidomide (10 mg/day to 25 mg per day for 21 days in a 1-month cycle) and low-dose dexamethasone in a dosage of 40 mg/week	• Median ORR and PFS of 76.9% and 15.4 months, respectively, with a median DOR of 22.1 months • Patients who were resistant to lenalidomide had a median PFS of 7.9 months and a mean ORR of 70% with a median DOR of 10.8 months

(Continued)

Table 1 (Continued)

Study title	Study type	No. of patients	Intervention	Outcomes
Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma ³⁵	Phase 3, multicenter trial (ASPIRE trial)	792	Carfilzomib, dexamethasone plus lenalidomide in patients receiving carfilzomib with lenalidomide and dexamethasone (carfilzomib group) or lenalidomide and dexamethasone alone (control group). Carfilzomib was administered as a 10-minute infusion (starting dose, 20 mg/m ² on days 1 and 2 of cycle 1; target dose, 27 mg/m ² thereafter), lenalidomide and dexamethasone were given at 25 mg and 40 mg, respectively	- The median PFS was significantly higher in the carfilzomib group than in the control group (26.3 months compared with 17.3 months; $p < 0.001$) - The OS and ORR at 2 years were significantly high in the carfilzomib group compared with the control group (73.3% versus 65.0% and 87.1% versus 66.7%, respectively, $p < 0.0001$) - The median DOR was also high with the carfilzomib versus control group (28.6 months versus 21.2 months)
A randomized phase 3 study of carfilzomib versus low-dose corticosteroids with optional cyclophosphamide in relapsed and refractory multiple myeloma (FOCUS) ³⁶	Randomized, phase 3, open-label, multicenter study (FOCUS)	315	Carfilzomib monotherapy versus low-dose corticosteroids and optional cyclophosphamide: Carfilzomib (10-minute intravenous infusion; 20 mg/m ² on days 1 and 2 of cycle 1; 27 mg/m ² thereafter) or a control regimen of low-dose corticosteroids (84 mg of dexamethasone or equivalent corticosteroid) with optional cyclophosphamide (1400 mg) for 28-day cycles	- Median OS was 10.2 (95% CI, 8.4–14.4) versus 10.0 months (95% CI, 7.7–12.0) with carfilzomib versus control (HR = 0.975; 95% CI, 0.760–1.249; $p = 0.4172$). - PFS was similar between groups • ORR was higher with carfilzomib (19.1% versus 11.4%)
Ixazomib				
Phase 1 study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed or refractory multiple myeloma ⁴⁹	Open-label, dose-escalation phase 1 study	60	Ixazomib was administered orally on 3 days of a 28-day cycle for up to 12 cycles or until disease progression or unacceptable toxicity	Among 30 response-evaluable patients treated at the MTD, 8 achieved a PR for an ORR of 27%
Final overall survival analysis of the TOURMALINE-MM1 phase 3 trial of ixazomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma ⁵⁰	Double-blind, placebo-controlled, phase 3 study (TOURMALINE-MM1)	722	Ixazomib (4 mg) plus lenalidomide (25 mg) and dexamethasone (40 mg) (ixazomib-Rd) or matching placebo (placebo-Rd)	Median OS was 53.6 months in the ixazomib-Rd arm and 51.6 months in the placebo-Rd arm (HR, 0.939; $p = 0.495$)
A phase 1/2 study of ixazomib, pomalidomide, and dexamethasone for lenalidomide and proteasome inhibitor refractory multiple myeloma ⁵¹	Phase 1/2 study (Alliance A061202)	29	Ixazomib/pomalidomide/dexamethasone 4 mg dose of pomalidomide and ixazomib and 20/40 mg dose of dexamethasone	- ORR (partial response or better) was 51.7% with a median DOR of 16.8 months - Median PFS and OS were 4.4 months and 34.3 months, respectively
A phase 1/2 study of ixazomib (Ix) pomalidomide (POM) dexamethasone (DEX) in relapsed or refractory multiple myeloma: initial results ⁵²	Phase 1/2 study	21	Ixazomib/pomalidomide/dexamethasone Ixazomib 3 mg, pomalidomide 4 mg, dexamethasone 40 mg, or ixazomib 4 mg with identical pomalidomide/dexamethasone for 28-day treatment cycles	CBR was 67% and ORR was 40%

Table 1 (Continued)

Study title	Study type	No. of patients	Intervention	Outcomes
Daratumumab				
Targeting CD38 with daratumumab monotherapy in multiple myeloma ⁵⁵	Open-label, multicenter, phase 1/2, dose-escalation and expansion study (GEN 501)	104	In the dose-escalation period, daratumumab was administered at 0.005 to 24 mg/kg, and in the dose-expansion period, the starting dose of daratumumab is 8 or 16 mg/kg	- The ORRs of patients receiving 16 mg/kg and 8 mg/kg of daratumumab were 36% and 10%, respectively - Median PFS was 5.6 months for 8 mg/kg - Overall responses were noted in 31 patients (29.2%) - Median DOR and PFS were 7.4 months and 3.7 months, respectively
Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomized, phase 2 trial ⁵⁶	Open-label, multicenter, phase 2 study (SIRIUS)	106	Intravenous daratumumab 8 mg/kg or 16 mg/kg in part 1 of the study. In part 2, patients received 8 mg/kg or 16 mg/kg	- Median PFS was not reached in the daratumumab group and was 7.2 months in the control group ($p < 0.001$) - ORR was higher in the daratumumab group than in the control group (82.9% vs. 63.2%, $p < 0.001$)
Daratumumab, bortezomib, and dexamethasone for multiple myeloma ⁵⁷	Phase 3 study (CASTOR)	498	<i>Daratumumab with bortezomib plus dexamethasone</i> Bortezomib (1.3 mg/m ²) and dexamethasone (20 mg) alone (control group) or in combination with daratumumab (16 mg/m ²) (daratumumab group)	- Kaplan–Meier PFS rate at 12 months was higher in the daratumumab group compared with control group (83.2% versus 60.1%) - ORR in the daratumumab group was higher than that in the control group (92.9% versus 76.4%, $p < 0.001$)
Daratumumab, lenalidomide, and dexamethasone for multiple myeloma ⁵⁸	Randomized, open-label, multicenter, phase 3 study (POLLUX)	569	<i>Daratumumab with lenalidomide plus dexamethasone</i> Daratumumab (16 mg/kg IV infusion), lenalidomide (10 mg or 25 mg), and dexamethasone (20 mg) or dexamethasone plus lenalidomide	- Median PFS in the lenalidomide group was 19.4 months versus 14.9 months in the control group ($p < 0.001$) - ORR in the lenalidomide group was 79% versus 66% in the control group ($p < 0.001$)
Elotuzumab				
Elotuzumab therapy for relapsed or refractory multiple myeloma ⁶³	Phase 3, randomized, open-label trial (ELOQUENT-2)	646	<i>Elotuzumab with lenalidomide plus dexamethasone</i> Elotuzumab (IV; 10 mg/kg) plus lenalidomide (oral; 25 mg/day) and dexamethasone (elotuzumab group) or lenalidomide and dexamethasone alone (control group). Dexamethasone was administered orally at 40 mg during the week without elotuzumab and 8 mg IV plus 28 mg oral on the day of elotuzumab administration	- Median PFS in the elotuzumab group was 19.4 months versus 14.9 months in the control group ($p < 0.001$) - ORR in the elotuzumab group was 79% versus 66% in the control group ($p < 0.001$)
Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma ⁶⁴	Multicenter, randomized, open-label, phase 2 trial (ELOQUENT-3)	117	<i>Elotuzumab with pomalidomide plus dexamethasone</i> Elotuzumab (IV; 10 mg/kg) plus pomalidomide (oral; 4 mg/day) and dexamethasone (elotuzumab group) or pomalidomide and dexamethasone alone (control group). Dexamethasone was administered orally at 40 or 20 mg during the week without elotuzumab and 8 mg IV plus 28 or 8 mg oral on the day of elotuzumab	- Median PFS was 10.3 months in the elotuzumab group and 4.7 months in the control group - ORR was 53% in the elotuzumab group as compared with 26% in the control group

(Continued)

Table 1 (Continued)

Study title	Study type	No. of patients	Intervention	Outcomes
Belantamab mafodotin				
Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomized, open-label, phase 2 study ⁶⁵	Open-label, two-arm, randomized, phase 2 study (DREAMM-2)	196	2.5 mg/kg or 3.4 mg/kg belantamab mafodotin via IV infusion	31% of patients in the 2.5 mg/kg cohort and 34% in the 3.4 mg/kg cohort achieved an overall response
Panobinostat				
Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicenter, randomized, double-blind, phase 3 trial ⁶⁶	Multicenter, randomized, placebo-controlled, double-blind, phase 3 trial (PANOROMA I)	768	Panobinostat with bortezomib plus dexamethasone Panobinostat (20 mg) plus bortezomib (IV; 1.3 mg/m ²) and dexamethasone (oral; 20 mg) or placebo plus bortezomib and dexamethasone	- Median PFS was significantly longer in the panobinostat group than in the placebo group (11.99 months versus 8.08 months; $p < 0.0001$) - Median OS was 33.64 months for the panobinostat group and 30.39 months for the placebo group
Selinexor				
Oral selinexor/dexamethasone for triple-class refractory multiple myeloma ⁶⁹	Phase 2b trial (STORM)	122	Selinexor and dexamethasone Oral selinexor (80 mg) plus dexamethasone (20 mg)	- Partial response or better was observed in 26% of patients - Median DOR was 4.4 months, and median PFS and OS were 3.7 months and 8.6 months, respectively
Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomized, open-label, phase 3 trial ⁷⁰	Randomized, open-label, phase 3 trial (BOSTON)	402	Selinexor with bortezomib and dexamethasone Once per week selinexor (100 mg), bortezomib (1.3 mg/m ²), and dexamethasone (20 mg) or twice per week bortezomib and dexamethasone	Median PFS was 13.93 months with selinexor, bortezomib, and dexamethasone and 9.46 months with bortezomib and dexamethasone ($p = 0.0075$)
Venetoclax				
Efficacy of venetoclax as targeted therapy for relapsed/refractory t (11; 14) multiple myeloma ⁷¹	Phase 1 study	66	Venetoclax was given daily from 300 mg up to 1200 mg	- ORR was 21%, and 15% achieved $\geq$VGPR 86% of responses were reported in patients with t(11;14), and ORR was 40% in this group
Real-world data on safety and efficacy of venetoclax-based regimens in relapsed/refractory t (11; 14) multiple myeloma ⁷²	Real-world data	10	Venetoclax was initiated at 400 mg for 1 week and then titrated to 800 mg	- ORR was 78% - Kaplan–Meier 6-month OS and PFS were 77% and 28%, respectively
Phase 1 study of venetoclax plus daratumumab and dexamethasone, with or without bortezomib, in patients with relapsed or refractory multiple myeloma with and without t (11; 14) ⁷³	Multicenter, dose-escalation and dose-expansion, phase 1 study	48	Venetoclax with daratumumab and dexamethasone with or without bortezomib Venetoclax (800 mg) with daratumumab (1800 mg SC) and dexamethasone (40 mg) (VenDd) and VenDd with bortezomib (1.3 mg/m ²) (VenDVd)	- ORR was 96% with VenDd and 92% with VenDVd - The 18-month PFS rate was 90.5% with VenDd and 66.7% with VenDVd

Table 1 (Continued)

Study title	Study type	No. of patients	Intervention	Outcomes
Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomized, double-blind, multicenter, phase 3 trial ⁷⁴	Randomized, double-blind, multicenter, phase 3 trial (BELLINI)	291	Venetoclax with bortezomib and dexamethasone Venetoclax (800 mg) or placebo with bortezomib (1.3 mg/m ²) and dexamethasone (20 mg)	- Median PFS was 22.4 months with venetoclax and 11.5 months with placebo ($p = 0.010$) - ORR was 82% with venetoclax and 68% with placebo ($p = 0.0081$)
Teclistamab				
Teclistamab, a B cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicenter, open-label, single-arm, phase 1 study ⁷⁷	Open-label, single-arm, phase 1 study (MajesTEC-1)	157	Teclistamab was given injected as IV (range, 0.3–19.2 µg/kg [once every 2 weeks] or 19.2–720 µg/kg [once per week]) or as SC (range, 80–3000 µg/kg [once per week]) in different cohorts, with step-up dosing for 38.4 µg/kg or higher doses	- Recommended phase 2 dose (RP2D) was identified as once per week subcutaneous administration of teclistamab at 1500 µg/kg after 60 µg/kg and 300 µg/kg step-up doses - ORR at RP2D was 65% (95% CI, 48–79) - Median DOR was not reached at RP2D
Teclistamab in relapsed or refractory multiple myeloma ⁷⁸	Phase 1/2 study (MajesTEC-1)	165	Teclistamab was given subcutaneously (1.5 mg/kg body weight) every week after receiving step-up doses of 0.06 mg and 0.3 mg/kg	- ORR was 63%, with complete response in 39.4% of patients - Median DOR was 18.4 months (95% CI, 14.9 to not estimable) - Median duration of PFS was 11.3 months (95% CI, 8.8–17.1)

Abbreviations: CBR: Clinical benefit rate; DOR: Duration of response; IV: Intravenous; MTD: Maximum tolerated dose; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; SC: Subcutaneous; VGPR: Very good partial response.

Daratumumab

The FDA in 2015 approved daratumumab, a first-in-class human IgG1j monoclonal antibody against CD38, in patients treated before for MM. In 2016, it was authorized in the combination of dexamethasone and bortezomib or dexamethasone and lenalidomide. In 2017, the combination with dexamethasone and pomalidomide was approved for RRMM.⁵³ The EMA has approved a combination of dexamethasone and daratumumab plus either lenalidomide or bortezomib with a minimum of one previous treatment in MM patients or as monotherapy with previous treatment of a PI and an immunomodulatory agent, and who had disease progression on previous therapy in adult RRMM patients.⁵⁴

Daratumumab Monotherapy and Other Combinations

The efficacy and safety of daratumumab monotherapy^{55,56} or its combination with bortezomib and dexamethasone,⁵⁷ as well as lenalidomide plus dexamethasone,⁵⁸ were investigated in different clinical trials (►Table 1).

In one of the meta-analyses, out of 18 therapy choices, daratumumab/lenalidomide/dexamethasone combination was found better in PFS (HR, 0.13; 95% CI, 0.09–0.19) and likely to be the very best option (99% of the simulations).⁵⁹ In comparison to dexamethasone/bortezomib/dexamethasone, and lenalidomide/dexamethasone, this combination reduced progression or death by 87%, 81%, and 63%, respectively.⁵⁹ In another meta-analysis of 27 RCTs, both daratumumab/lenalidomide/dexamethasone and daratumumab/bortezomib/dexamethasone were found likely of being the best treatment options and were associated with the minimum chance of progression or mortality versus other FDA-authorized therapy of MM.⁶⁰

Safety of Daratumumab

Daratumumab is generally well tolerated. In a pooled analysis (GEN501 part 2 and SIRIUS), anemia, cough, fatigue, nausea, back pain, neutropenia, upper respiratory tract infection, and thrombocytopenia were commonly reported adverse events.⁵⁶ The most frequent adverse events (grade 3/4) listed in the CASTOR and POLLUX trials were thrombocytopenia, neutropenia, and anemia. In both trials, neutropenia events (grade 3/4) were higher in the daratumumab than in the control group (13% vs. 4% in CASTOR and 52% vs. 37% in the POLLUX trial). CASTOR trial participants with daratumumab experienced more thrombocytopenia events (grade 3/4) than those with control medication (45 vs. 33%).^{57,58}

Elotuzumab-Based Combinations in RRMM

It is a humanized immunostimulatory monoclonal antibody against signaling lymphocytic activating molecule family member 7. The FDA has approved it in combination with either lenalidomide or bortezomib and dexamethasone after a minimum of one line of failed therapy in the appropriate setting.^{61,62} Its combination with dexamethasone and lenalidomide⁶³ or pomalidomide and dexamethasone⁶⁴ showed a significant relative reduction in the risk of disease progression or death in patients with RRMM (►Table 1).

Belantamab Mafadotin

It is an anti-B-cell antigen bound to monomethyl auristatin, a microtubule inhibitor that, in the phase 2 DREAMM-2 study, produced an overall response in 31% and 34% of patients, respectively, in the 2.5 mg/kg and 3.4 mg/kg cohorts of highly pre-treated patients with RRMM. Thrombocytopenia, anemia, and rarely keratopathy were common adverse events (►Table 1).⁶⁵ The FDA has approved it for RRMM after four lines of failure (including an IMiD, PI, and anti-CD38 monoclonal antibody).

Panobinostat

The PANOROMA I trial evaluated the outcomes of a combination of panobinostat (a pan-histone deacetylase [HDAC] inhibitor) and bortezomib/dexamethasone and suggested that panobinostat could be beneficial for patients with RRMM who had a minimum of one previous treatment.⁶⁶

In a recent meta-analysis of 19 trials (2,193 patients), the pooled ORR for panobinostat-treated patients was 0.64, whereas, for HDAC inhibitor-treated bortezomib- or lenalidomide-refractory patients, ORRs were 0.36 and 0.46, respectively.⁶⁷ The US FDA and EMA authorized the combination of panobinostat and bortezomib/dexamethasone in patients who had a minimum of two previous treatments, containing IMiD and bortezomib.⁶⁸ The same combination was approved in India in 2016. The FDA has approved panobinostat for RRMM patients with failed response to lenalidomide and bortezomib.

Safety of Panobinostat

The commonly found hematologic adverse events (grade 3/4) were neutropenia, thrombocytopenia, and anemia.⁶⁶ The most frequent nonhematologic adverse events with panobinostat were gastric-related.⁶⁸

Selinexor

The safety and efficacy of selinexor, a nuclear export inhibitor inducing apoptosis, were evaluated in a phase 2b trial (STORM),⁶⁹ which led to its approval by the FDA for use with dexamethasone in RRMM following four lines of therapy failing IMiDs, PIs, and two monoclonal antibodies. A phase 3 trial (BOSTON) revealed significant improvement in PFS with the addition of selinexor to bortezomib and dexamethasone in patients who had previously received treatment for MM (►Table 1).⁷⁰

Venetoclax

A phase 1 study revealed an acceptable safety profile and effectiveness of venetoclax (a BCL-2 inhibitor) monotherapy in patients with RRMM harboring t(11;14).⁷¹ Real-world

data on the safety and efficacy of venetoclax-based regimens in RRMM patients harboring t(11;14) showed an overall response rate of 78%.⁷² The efficacy and safety of venetoclax plus daratumumab and dexamethasone, with or without bortezomib, were evaluated in patients with RRMM with and without t(11;14)⁷³ and those of venetoclax plus bortezomib and dexamethasone were evaluated in patients with RRMM (BELLINI trial)⁷⁴ as shown in ►Table 1.

Teclistamab

Teclistamab is an under-investigation fully humanized IgG4 bispecific antibody that targets both the T cell receptor CD3 and the B cell maturation antigen (BCMA). It works by rerouting CD3+ T lymphocytes to promote T cell activation and lysis of myeloma cells that express BCMA.⁷⁵ The safety and efficacy of teclistamab in patients with RRMM who have received at least three other lines of therapy are being studied in ongoing clinical studies (►Table 1). Additionally, two trials are investigating its effectiveness and safety in combination with other agents for the treatment of patients with RRMM.⁷⁶ Common adverse events include cytokine release syndrome, neutropenia, and thrombocytopenia.^{77,78}

Treatment of Patients with RRMM in India

In India, most of the patients receive bortezomib, lenalidomide, or thalidomide-based medications as treatment for RRMM.⁷⁹ The market for generic medications is growing in India. The cost of these medications is relatively lower because of the stiff competition among many generic drug manufacturers in the country. Thus, the development of generic versions of medications, such as pomalidomide and carfilzomib, makes them more accessible and affordable for cancer patients.⁸⁰ Since 2017, generic pomalidomide has been available in India. The results are comparable to those reported in the literature for the original molecule. Hence, it is considered an effective treatment choice for those with RRMM, as well as a less expensive alternative to original pomalidomide in India and other developing countries where affordability is an issue.^{81,82} ►Table 2 shows data from clinical studies that investigated the efficacy and safety of drugs or their combinations for the treatment of RRMM patients in the Indian setting.^{82–87}

The CAR-T therapy is a novel and emerging therapy for MM. Global clinical trials have demonstrated that CAR-T treatment is beneficial in RRMM patients. Although this technology has a great deal of therapeutic potential for cancer patients, it is still not available in India because of the exorbitant cost. In this regard, researchers at the Department of Bioscience and Bioengineering, IIT, Mumbai, designed and manufactured the country's first CAR T cells using lentiviral technology.⁸⁸ In June 2021, India's first CAR-T therapy was done at the bone marrow transplant unit at Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Hospital, Mumbai.⁸⁸ Furthermore, the first CAR-T product HCAR19 showed favorable efficacy and less toxicity with no relapse in 10 lymphoma

Table 2 Clinical evidence of relapsed and refractory multiple myeloma treatment in India

Study title	Study type	No. of patients	Intervention	Outcomes
Retrospective study of carfilzomib/pomalidomide/dexamethasone in relapsed or refractory multiple myeloma patients in a tertiary care hospital in India ⁸³	Retrospective study	69	Carfilzomib/pomalidomide/dexamethasone Carfilzomib was given intravenously at 20 mg/m ² on days 1–2 and thereafter at 27 mg/m ² from week 2 (cycle 1) and from cycle 2 onward (biweekly regimen) IV carfilzomib was given at 20 mg/m ² on day 1 and day 2 followed by 36 mg/m ² in weekly doses (once weekly) Pomalidomide (4 mg) was given on days 1–21 and dexamethasone (IV; 20 mg weekly) was given in 28-day treatment cycles	• ORR was 65.2% • Relapse was observed in 24 patients (34.8%) • Estimated median PFS and median OS were 11.3 months (95% CI, 8.3–14.2) and 28 months (95% CI, 20.4–35.5)
Study to evaluate safety, tolerability, and efficacy of Kyprolis (carfilzomib) in relapsed or refractory multiple myeloma ⁸⁴	Prospective, open-label, noncomparative, multicenter, phase 4 study	100	Carfilzomib plus dexamethasone and carfilzomib plus lenalidomide with dexamethasone Carfilzomib 20 mg/m ² on days 1 and 2, and if tolerated, escalated to a target dose of 56 mg/m ² or 27 mg/m ² starting on day 8 of cycle 1 and thereafter Dexamethasone 20 or 40 mg taken by mouth or intravenously Lenalidomide 25 mg is taken orally on days 1–21	• Ongoing trial, so results are awaited

(Continued)

Table 2 (Continued)

Study title	Study type	No. of patients	Intervention	Outcomes
Real-world outcomes with generic pomalidomide in relapsed/refractory multiple myeloma—experience from a tertiary care cancer center ⁸¹	Retrospective analysis	81	Generic pomalidomide (2 mg/3 mg/4 mg daily dose) Generic pomalidomide and dexamethasone (doublet)	• ORR was 58.7% and 65.2% in those who received doublet • Five patients (6.7%) achieved CR; VGPR was seen in 13 patients (17.3%), and PR in 26 patients (34.7%) • Median PFS was 5.5 months and the median OS was not reached
A study of DARZALEX (daratumumab) in Indian participants with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent ⁸⁵	Prospective, single-arm, multicenter, pragmatic phase 4 trial (NCT03768960)	150	Daratumumab is given intravenously (16 mg/kg) every week in cycles 1 and 2 (days 1, 8, 15, and 22) and every 2 weeks in cycles 3–6 (days 1 and 15) in 28-day treatment cycles	• Ongoing trial, so results are awaited
Daratumumab plus carfilzomib: an optimistic approach in relapsed/refractory multiple myeloma ⁸⁶	Prospective analysis	19	<i>Daratumumab plus carfilzomib and dexamethasone</i> Daratumumab (16 mg/kg IV) was administered weekly during cycles 1 and 2, every 2 weeks during cycles 3–6, and every 4 weeks thereafter Carfilzomib was administered as a 30-minute infusion weekly on days 1, 8, and 15 of each 28-day cycle Patients received an initial carfilzomib dose of 20 mg/m ² on days 1 and 2; 27 mg/m ² on days 8, 9, 15, and 16 of cycle 1, which increased to 70 mg/m ² on days 1, 8, and 15 from cycle 2 onward if found tolerable Dexamethasone was given at a fixed dose of 40 mg weekly	• PFS was 95%, and median PFS was not reached
Real-world experience with “generic” pomalidomide in relapsed/refractory multiple myeloma ⁸²	Real-world study	24	Most of the patients (17/24) received generic pomalidomide plus dexamethasone (doublet therapy) and the remaining seven patients received a third drug (carfilzomib, bortezomib, or melphalan) additionally (triplet therapy). Furthermore, many (16/24) received generic pomalidomide at a starting dose of 4 mg daily for 21–28 days	• ORR was 50% • Median PFS was 6 months (95% CI, 0.2–15.3 months)
Bortezomib in newly diagnosed patients with multiple myeloma: a retrospective analysis from a tertiary care center in India ⁸⁷	Retrospective analysis	41	Patients who received bortezomib (1.3 mg/m ² of the body surface area as an intravenous bolus twice weekly for 2 weeks, on days 1, 4, 8, and 11 in a 21-day cycle or weekly in a 28-day cycle) as first-line therapy were enrolled into the study All patients received dexamethasone (40 mg with bortezomib)	• ORR to bortezomib was 88.5% with CR at 31.4%, VGPR at 34.2%, and PR at 22.8% • At a median follow-up of 9 months, the median PFS was not reached

Abbreviations: DOR, Duration of response; ORR, Overall response rate; OS, Overall survival; PFS, Progression-free survival; PR, Partial response; VGPR, Very good partial response.

patients in a phase 1 clinical trial conducted at ACTREC, Mumbai. A phase 2 trial involving 40 patients is currently underway.⁸⁸ The researchers were able to significantly reduce the cost through this innovation, making it affordable and accessible to patients.

Guideline and Cancer Group Recommendations for RRMM

Patients with relapsed myeloma who have failed to respond to bortezomib and lenalidomide should be treated with pomalidomide or carfilzomib (IMWG). Carfilzomib must be taken along with low-dose dexamethasone and lenalidomide. The working group also recommends a combination of panobinostat, bortezomib, and dexamethasone for those with a few treatment options and who have a positive performance status.⁸⁹ According to the ESMO guidelines on the clinical management of MM, treatment options at second or subsequent relapse include daratumumab monotherapy or a combination of pomalidomide with dexamethasone plus daratumumab.⁹⁰ According to the Mayo Stratification for Myeloma and Risk-Adapted Therapy guidelines, daratumumab, bortezomib, and dexamethasone (DvD) for IMiD refractory; daratumumab, lenalidomide, and dexamethasone (DRd) for PI refractory; carfilzomib, lenalidomide, and dexamethasone (KRd) or carfilzomib, pomalidomide, and dexamethasone (KpD) for dual refractory to bortezomib/ixazomib and lenalidomide; daratumumab, pomalidomide, and dexamethasone (DPd) or daratumumab, pomalidomide, cyclophosphamide, and dexamethasone (DPdC) for triple refractory to carfilzomib, lenalidomide, and bortezomib/ixazomib; daratumumab based or PI and panobinostat for triple refractory to lenalidomide, bortezomib/ixazomib, and pomalidomide have been recommended.⁹¹ The FDA had authorized selinexor in association with dexamethasone for adult RRMM patients who had a minimum of four previous treatments and whose disease is refractory to a minimum of two PIs, two IMiDs, and an anti-CD38 monoclonal antibody.⁹²

Conclusion

The approval of PIs, IMiDs, and mAbs in patients with RRMM has considerably modified the treatment options of RRMM in the last few years. Several randomized clinical trials have demonstrated favorable outcomes of these novel drugs in combination therapies. Further studies evaluating the long-term safety and efficacy of combination therapies are warranted. The availability of less expensive generic versions of carfilzomib, daratumumab, and panobinostat in India should pave way for a change in the outlook of patients with improved outcomes, survival, and QoL.

Authors' Contributions

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Conflict of Interest

None declared.

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