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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 immunomodulatory 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 β2M (>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-κB, 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-expansion[34] (PX-171–006), and phase 3[35] 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 ($>20/27\,mg/m^2$) 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] ibrutinib 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 Ib 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*)

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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
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	• Overall responses were noted in 31 patients (29.2%) • Median DOR and PFS were 7.4 months and 3.7 months, respectively
Daratumumab, bortezomib, and dexamethasone for multiple myeloma[57]	Phase 3 study (CASTOR)	498	*Daratumumab with bortezomib plus dexamethasone* Bortezomib (1.3 mg/m^2) and dexamethasone (20 mg) alone (control group) or in combination with daratumumab (16 mg/m^2) (daratumumab group)	• 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, lenalidomide, and dexamethasone for multiple myeloma[58]	Randomized, open-label, multicenter, phase 3 study (POLLUX)	569	*Daratumumab with lenalidomide plus dexamethasone* Daratumumab (16 mg/kg IV infusion), lenalidomide (10 mg or 25 mg), and dexamethasone (20 mg) or dexamethasone plus lenalidomide	• 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%, $p < 0.001$)
Elotuzumab				
Elotuzumab therapy for relapsed or refractory multiple myeloma[63]	Phase 3, randomized, open-label trial (ELOQUENT-2	646	*Elotuzumab with lenalidomide plus dexamethasone* 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	*Elotuzumab with pomalidomide plus dexamethasone* 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 ≥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 ½ 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 ¾) 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 lenalidomide[63] or pomalidomide and dexamethasone[64] 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	*Daratumumab plus carfilzomib and dexamethasone* 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 (DPCd) 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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References

1 Kazandjian D. Multiple myeloma epidemiology and survival: a unique malignancy. Semin Oncol 2016;43(06):676–681
2 Cowan AJ, Allen C, Barac A, et al. Global burden of multiple myeloma: a systematic analysis for the global burden of disease study 2016. JAMA Oncol 2018;4(09):1221–1227
3 Multiple Myeloma. Globocan. 2018. Accessed on 29 June, 2020, at: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf
4 Bouée S, Feeron-Chevé D, Trancart M, Gaudin A. Incidence and prevalence of multiple myeloma from 2016 to 2020 according to the treatment line and hematopoietic stem cell transplantation status. Value Health 2016;19:A578–A579
5 India Globocan. 2018. Accessed on 29 June 2020 at: https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf
6 Bora K. Distribution of multiple myeloma in India: heterogeneity in incidence across age, sex and geography. Cancer Epidemiol 2019;59:215–220
7 Mewawalla P, Chilkulwar A. Maintenance therapy in multiple myeloma. Ther Adv Hematol 2017;8(02):71–79
8 San Miguel JF, Schlag R, Khuageva NK, et al; VISTA Trial Investigators. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359(09):906–917
9 Dimopoulos MA, Anagnostopoulos A. Thalidomide in relapsed/refractory multiple myeloma: pivotal trials conducted outside the United States. Semin Hematol 2003;40(4, Suppl 4)8–16
10 Dimopoulos M, Spencer A, Attal M, et al; Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357(21):2123–2132
11 Richardson PG, Larocca A, Lelu X, et al. The burden of relapsed/refractory multiple myeloma: an indirect comparison of health-related quality of life burden across different types of advanced cancers at baseline and after treatment based on HORIZON (OP-106) study of melflufen plus dexamethasone. Blood 2019;134:3487. Doi: 10.1182/blood-2019-124832
12 Kumar SK, Dimopoulos MA, Kastritis E, et al. Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. Leukemia 2017;31(11):2443–2448
13 Anderson KC, Kyle RA, Rajkumar SV, Stewart AK, Weber D, Richardson PASH/FDA Panel on Clinical Endpoints in Multiple Myeloma. Clinically relevant end points and new drug approvals for myeloma. Leukemia 2008;22(02):231–239
14 Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;15(12):e538–e548
15 Manier S, Salem KZ, Park J, Landau DA, Getz G, Ghobrial IM. Genomic complexity of multiple myeloma and its clinical implications. Nat Rev Clin Oncol 2017;14(02):100–113
16 Jones JR, Weinhold N, Ashby C, et al; NCRI Haemato-Oncology CSG. Clonal evolution in myeloma: the impact of maintenance lenalidomide and depth of response on the genetics and sub-

clonal structure of relapsed disease in uniformly treated newly diagnosed patients. Haematologica 2019;104(07):1440–1450
17 Zanwar S, Abeykoon JP, Kapoor P. Challenges and strategies in the management of multiple myeloma in the elderly population. Curr Hematol Malig Rep 2019;14(02):70–82
18 Faiman B, Doss D, Colson K, Mangan P, King T, Tariman JD. Renal, GI, and peripheral nerves: evidence-based recommendations for the management of symptoms and care for patients with multiple myeloma. Clin J Oncol Nurs 2017;21(5, Suppl)19–36
19 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 2016;127(24): 2955–2962
20 Podar K, Leleu X. Relapsed/refractory multiple myeloma in 2020/2021 and beyond. Cancers (Basel) 2021;13(20):5154
21 Rajan AM, Rajkumar SV. Interpretation of cytogenetic results in multiple myeloma for clinical practice. Blood Cancer J 2015;5(10): e365
22 Kumar SK, Callander NS, Hillengass J, et al. NCCN guidelines insights: multiple myeloma, version 1.2020. J Natl Compr Canc Netw 2019;17(10):1154–1165
23 Jagannath S, Abonour R, Durie BGM, et al. Heterogeneity of second-line treatment for patients with multiple myeloma in the Connect MM Registry (2010–2016). Clin Lymphoma Myeloma Leuk 2018;18(07):480–485.e3
24 Park JE, Miller Z, Jun Y, Lee W, Kim KB. Next-generation proteasome inhibitors for cancer therapy. Transl Res 2018;198:1–16
25 Botta C, Ciliberto D, Rossi M, et al. Network meta-analysis of randomized trials in multiple myeloma: efficacy and safety in relapsed/refractory patients. Blood Adv 2017;1(07):455–466
26 Kortuem KM, Stewart AK. Carfilzomib. Blood 2013;121(06): 893–897
27 Kyprolis® [package insert]. Thousand Oaks, CA: Amgen; 2016
28 Tzogani K, Camarero Jiménez J, Garcia I, et al. The European Medicines Agency review of carfilzomib for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. Oncologist 2017;22(11):1339–1346
29 Papadopoulos KP, Siegel DS, Vesole DH, et al. Phase I study of 30-minute infusion of carfilzomib as single agent or in combination with low-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma. J Clin Oncol 2015;33(07):732–739
30 Lendvai N, Hilden P, Devlin S, et al. A phase 2 single-center study of carfilzomib 56 mg/m2 with or without low-dose dexamethasone in relapsed multiple myeloma. Blood 2014;124(06):899–906
31 Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. Lancet Oncol 2017;18(10):1327–1337
32 Dimopoulos MA, Moreau P, Palumbo A, et al; ENDEAVOR Investigators. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol 2016;17(01):27–38
33 Niesvizky R, Martin TG III, Bensinger WI, et al. Phase Ib dose-escalation study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma. Clin Cancer Res 2013;19(08):2248–2256
34 Wang M, Martin T, Bensinger W, et al. Phase 2 dose-expansion study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma. Blood 2013;122(18):3122–3128
35 Stewart AK, Rajkumar SV, Dimopoulos MA, et al; ASPIRE Investigators. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015;372(02):142–152
36 Hájek R, Masszi T, Petrucci MT, et al. A randomized phase III study of carfilzomib vs low-dose corticosteroids with optional cyclophosphamide in relapsed and refractory multiple myeloma (FOCUS). Leukemia 2017;31(01):107–114
37 Shah C, Bishnoi R, Wang Y, et al. Efficacy and safety of carfilzomib in relapsed and/or refractory multiple myeloma: systematic review and meta-analysis of 14 trials. Oncotarget 2018;9(34): 23704–23717
38 Chen R, Chen B, Zhang X, Gao C. Efficacy of carfilzomib in the treatment of relapsed and (or) refractory multiple myeloma: a meta-analysis of data from clinical trials. Discov Med 2016;22 (121):189–199
39 Luo XW, Du XQ, Li JL, Liu XP, Meng XY. Treatment options for refractory/relapsed multiple myeloma: an updated evidence synthesis by network meta-analysis. Cancer Manag Res 2018; 10:2817–2823
40 Liu L, Zhao N, Xu W, Sheng Z, Wang L. Pooled analysis of the reports of carfilzomib, panobinostat, and elotuzumab combinations in patients with refractory/relapsed multiple myeloma. J Hematol Oncol 2016;9(01):54
41 Shah JJ, Stadtmauer EA, Abonour R, et al. Carfilzomib, pomalidomide, and dexamethasone for relapsed or refractory myeloma. Blood 2015;126(20):2284–2290
42 Chari A, Larson S, Holkova B, et al. Phase 1 trial of ibrutinib and carfilzomib combination therapy for relapsed or relapsed and refractory multiple myeloma. Leuk Lymphoma 2018;59(11): 2588–2594
43 Chari A, Martinez-Lopez J, Mateos MV, et al. Daratumumab plus carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma. Blood 2019;134(05):421–431
44 Dimopoulos MA, Moreau P, Iida S, et al. Outcomes for Asian patients with multiple myeloma receiving once- or twice-weekly carfilzomib-based therapy: a subgroup analysis of the randomized phase 3 ENDEAVOR and A.R.R.O.W. Trials. Int J Hematol 2019; 110(04):466–473
45 Siegel D, Martin T, Nooka A, et al. Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies. Haematologica 2013;98(11): 1753–1761
46 Waxman AJ, Clasen S, Hwang WT, et al. Carfilzomib-associated cardiovascular adverse events: a systematic review and meta-analysis. JAMA Oncol 2018;4(03):e174519
47 Shah C, Bishnoi R, Jain A, et al. Cardiotoxicity associated with carfilzomib: systematic review and meta-analysis. Leuk Lymphoma 2018;59(11):2557–2569
48 Ball S, Behera TR, Anwer F, Chakraborty R. Risk of kidney toxicity with carfilzomib in multiple myeloma: a meta-analysis of randomized controlled trials. Ann Hematol 2020;99(06):1265–1271
49 Kumar SK, Bensinger WI, Zimmerman TM, et al. Phase 1 study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma. Blood 2014; 124(07):1047–1055
50 Richardson PG, Kumar SK, Masszi T, et al. Final overall survival analysis of the TOURMALINE-MM1 phase III trial of ixazomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. J Clin Oncol 2021;39(22):2430–2442
51 Voorhees PM, Mulkey F, Hassoun H, et al. Alliance A061202. A phase I/II study of pomalidomide, dexamethasone and ixazomib versus pomalidomide and dexamethasone for patients with multiple myeloma refractory to lenalidomide and proteasome inhibitor based therapy: phase I results. Blood 2015;126(23):375
52 Krishnan AY, Kapoor P, Palmer J, et al. A phase I/II study of ixazomib (Ix) pomalidomide (POM) dexamethasone (DEX) in relapsed refractory (R/R) multiple myeloma: Initial results. J Clin Oncol 2016;34(15):8008
53 DARZALEX® [Package Insert]. Horsham, PA: Janssen; 2015
54 DARZALEX® [Package Insert]. Einsteinweg, Leiden: Janssen; 2015
55 Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Engl J Med 2015;373(13):1207–1219
56 Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma

(SIRIUS): an open-label, randomised, phase 2 trial. Lancet 2016; 387(10027):1551–1560
57 Palumbo A, Chanan-Khan A, Weisel K, et al; CASTOR Investigators. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 2016;375(08):754–766
58 Dimopoulos MA, Oriol A, Nahi H, et al; POLLUX Investigators. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016;375(14):1319–1331
59 van Beurden-Tan CHY, Franken MG, Blommestein HM, Uyl-de Groot CA, Sonneveld P. Systematic literature review and network meta-analysis of treatment outcomes in relapsed and/or refractory multiple myeloma. J Clin Oncol 2017;35(12): 1312–1319
60 Maiese EM, Ainsworth C, Le Moine JG, Ahdesmäki O, Bell J, Hawe E. Comparative efficacy of treatments for previously treated multiple myeloma: a systematic literature review and network meta-analysis. Clin Ther 2018;40(03):480–494.e23
61 Weisel K. Spotlight on elotuzumab in the treatment of multiple myeloma: the evidence to date. OncoTargets Ther 2016; 9:6037–6048
62 Gormley NJ, Ko CW, Deisseroth A, et al. FDA drug approval: elotuzumab in combination with lenalidomide and dexamethasone for the treatment of relapsed or refractory multiple myeloma. Clin Cancer Res 2017;23(22):6759–6763
63 Lonial S, Dimopoulos M, Palumbo A, et al; ELOQUENT-2 Investigators. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med 2015;373(07):621–631
64 Dimopoulos MA, Dytfeld D, Grosicki S, et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. N Engl J Med 2018;379(19):1811–1822
65 Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol 2020; 21(02):207–221
66 San-Miguel JF, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15(11):1195–1206
67 Gao X, Shen L, Li X, Liu J. Efficacy and toxicity of histone deacetylase inhibitors in relapsed/refractory multiple myeloma: systematic review and meta-analysis of clinical trials. Exp Ther Med 2019;18(02):1057–1068
68 FARYDAK®[Package Inset]. Roonstrasse, Nuremberg: Novartis; 2015
69 Chari A, Vogl DT, Gavriatopoulou M, et al. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. N Engl J Med 2019;381(08):727–738
70 Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet 2020; 396(10262):1563–1573
71 Kumar S, Kaufman JL, Gasparetto C, et al. Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma. Blood 2017;130(22):2401–2409
72 Basali D, Chakraborty R, Rybicki L, et al. Real-world data on safety and efficacy of venetoclax-based regimens in relapsed/refractory t(11;14) multiple myeloma. Br J Haematol 2020;189(06): 1136–1140
73 Bahlis NJ, Baz R, Harrison SJ, et al. Phase I 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). J Clin Oncol 2021;39(32):3602–3612
74 Kumar SK, Harrison SJ, Cavo M, et al. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 2020;21(12):1630–1642
75 Nooka A, Moreau P, Usmani SZ, et al. Teclistamab, a B-cell maturation antigen (BCMA) x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM): Updated efficacy and safety results from MajesTEC-1. 2022 ASCO Annual Meeting – American Society of Clinical Oncology. 2022; 40(16): 8007–8007
76 Updated Data for Janssen's Bispecific Teclistamab Suggest Continued Deep and Durable Responses in the Treatment of Patients with Relapsed or Refractory Multiple Myeloma. Accessed on August 01, 2022, at: https://www.jnj.com/updated-data-for-janssens-bispecific-teclistamab-suggest-continued-deep-and-durable-responses-in-the-treatment-of-patients-with-relapsed-or-refractory-multiple-myeloma
77 Usmani SZ, Garfall AL, van de Donk NWCJ, et al. Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. Lancet 2021;398 (10301):665–674
78 Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. N Engl J Med 2022;387 (06):495–505
79 Consensus document for management of multiple myeloma: prepared as an outcome of ICMR subcommittee on multiple myeloma. Published in 2017 by the Division of Publication and Information on behalf of the Secretary DHR & DG, ICMR, New Delhi. https://main.icmr.nic.in/sites/default/files/guidelines/Multiple%20Myeloma_0.pdf
80 Garg A, Morgunskyy M, Belagali Y, Gupta N, Akku SPIndia and Ukraine Haemato-oncology Group. Management of multiple myeloma and usage of bortezomib: perspective from India and Ukraine. Front Oncol 2016;6:243
81 Bondili SK, Bagal B, Zawar A, et al. Real-world outcomes with generic pomalidomide in relapsed refractory multiple myeloma-experience from a tertiary care cancer center. JCO Glob Oncol 2021;7:361–367
82 Jandial A, Mishra K, Lad D, Prakash G, Khadwal A, Malhotra P. Real world experience with "generic" pomalidomide in relapsed refractory multiple myeloma. Leuk Lymphoma 2019;60(04): 1102–1104
83 Mehta P, Yadav N, Folbs B, et al. Retrospective study of carfilzomib-pomalidomide-dexamethasone in relapsed/refractory multiple myeloma patients in a tertiary care hospital in India. Indian J Hematol Blood Transfus 2022;38(02):264–273
84 ClinicalTrials.gov Identifier: NCT03934684. Study to Evaluate Safety Tolerability & Efficacy of Kyprolis (Carfilzomib) in Relapsed or Refractory Multiple Myeloma. Accessed October 18, 2022, at: https://clinicaltrials.gov/ct2/show/NCT03934684
85 ClinicalTrials.gov Identifier: NCT03768960. 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. Accessed October 18, 2022, at: https://clinicaltrials.gov/ct2/show/NCT03768960
86 Dubey AP, Khatri S, Maggo S, Singh NK, Sharma D. Daratumumab plus carfilzomib: an optimistic approach in relapsed/refractory multiple myeloma. Indian J Med Paediatr Oncol 2020;41:846–849
87 Pragnya C, Linga VG, Thota NK, Gundeti S, Digumarti R. Bortezomib in newly diagnosed patients with multiple myeloma: a retrospective analysis from a tertiary care center in India. Indian J Cancer 2015;52(04):537–540
88 DBT. Department of Biotechnology supported First CAR-T cell therapy conducted at ACTREC, Tata Memorial Hospital in Mumbai; DBT/BIRAC-NBM Supported Phase I/II Clinical Trial. Ministry of Science & Technology. Accessed October 18, 2022: https://pib.gov.in/PressReleasePage.aspx?PRID=1725254

89 Laubach J, Garderet L, Mahindra A, et al. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. Leukemia 2016;30(05):1005–1017
90 Moreau P, San Miguel J, Ludwig H, et al; ESMO Guidelines Working Group. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(Suppl 6): vi133–vi137
91 Dingli D, Ailawadhi S, Bergsagel PL, et al. Therapy for relapsed multiple myeloma: guidelines from the mayo stratification for myeloma and risk-adapted therapy. Mayo Clin Proc 2017;92(04): 578–598
92 XPOVIO [Package Insert]. Newton, MA. Karyopharm Therapeutics Inc. 2019

