REVIEW

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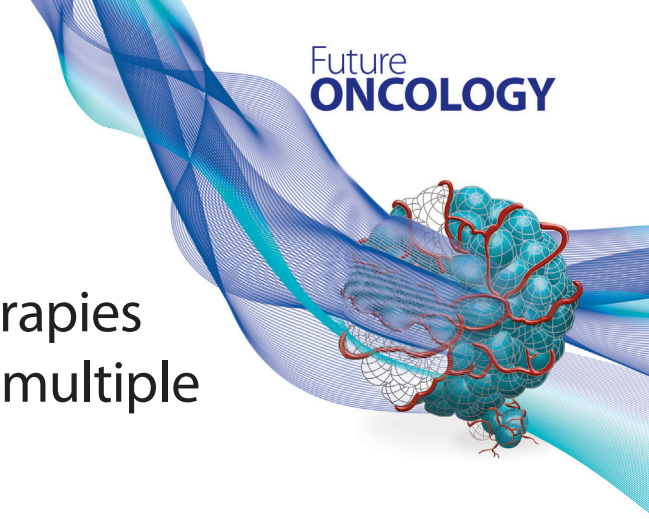

The next generation of novel therapies for the management of relapsed multiple myeloma

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The advent of various novel therapies such as immunomodulators and proteasome inhibitors has transformed the treatment paradigm for patients with multiple myeloma (MM). As a result, the overall survival has improved dramatically over the last decade. Despite these advances, MM remains mostly incurable and most patients experience disease relapse after enjoying a period of disease control or remission. Fortunately, the scientific community continues to make strides in developing 'next-generation' therapies for the management of patients with relapsed MM. This review will summarize the efficacy of some of the newest therapeutic agents available for the treatment of patients with relapsed MM after their upfront treatment with the original novel agents such as thalidomide, lenalidomide and bortezomib.

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KEYWORDS
• multiple myeloma • novel agents • relapse

Background

Multiple myeloma (MM) is a malignant plasma cell disorder that accounts for >10,000 deaths annually in the USA [1]. In the last two decades, high-dose chemotherapy followed by autologous stem cell rescue (ASCT), immunomodulators (IMiDs; thalidomide and lenalidomide) as well as proteasome inhibitors (PIs; bortezomib) have dramatically improved the survival outcomes of patients with MM [2–4]. Unfortunately, these therapeutic advances are not curative and most patients eventually relapse requiring salvage therapies [5]. In patients with relapsed or refractory MM who have failed both IMiDs and PIs, the prognosis is especially poor [6]. The need for salvage therapies for patients with MM who have relapsed after treatment with IMiDs and PIs has led to the development of the next generation of novel therapies. These new salvage therapeutic agents exploit the complex molecular mechanisms within clonal plasma cells (PCs) that are associated with the pathogenesis of MM as well as responsible for the acquired resistance to prior therapies. This review provides a summary of various next-generation agents and key clinical trials leading to their approval for the treatment of patients with relapsed MM **(Table 1)**.

• Proteasome inhibitors

Most normal cells regulate the degradation of cellular proteins involved in their cell function *via* ubiquitination by enzymes such as ubiquitin-activating enzyme E1, ubiquitin-conjugating enzyme E2 and ubiquitin E3 ligases. These proteins subsequently undergo degradation by the 26S proteasome

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Table 1. Summary of next-generation agents and their indications for use in the USA and Europe.

Agent	US FDA approval	EU Commission approval
Carfilzomib	Use as a single agent in the treatment of patients with relapsed MM who had been treated with at least two lines of prior therapy that included a PI and an IMiD Use in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed MM who have received one to three prior lines of therapy	Use in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed MM who have received at least one prior line of therapy
Ixazomib	Use in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed MM who have received at least one prior therapy	Not approved
Pomalidomide	Treatment of patients with MM who have received at least two prior therapies, including lenalidomide and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy	Use in patients with relapsed MM who have received at least two prior therapies, including both lenalidomide and bortezomib, and whose disease progressed after the last treatment
Daratumumab	Used for the treatment of MM patients who have received at least three lines of prior therapy	Use in the treatment of patients with relapsed/refractory MM previously treated with a PI and an IMiD who progressed on their last therapy
Elotuzumab	Use in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received one to three prior therapies	Use in combination with lenalidomide and dexamethasone in MM patients who have had at least one prior therapy
Panobinostat	Use in patients with MM who have received more than or equal to two prior regimens, including bortezomib and an IMiD drug	Use in combination with bortezomib and dexamethasone for adult patients with relapsed/refractory MM following prior treatment with bortezomib and an IMiD

IMiD: Immunomodulator; MM: Multiple myeloma; PI: Proteasome inhibitor.

complex, which consists of a 20S catalytic core and one or two 19S regulatory subunits [7]. Inhibition of this ubiquitin-proteasome system leads to accumulation of ubiquitinated proteins producing endoplasmic reticulum stress leading to apoptosis and cell death [7]. Clonal PCs in MM utilize the ubiquitin-proteasome system to regulate their high rate of protein turnover compared with normal cells. Thus, proteasome inhibition has emerged as a well-established and important therapeutic strategy [8]. Bortezomib, a dipeptide boronic acid derivative and reversible inhibitor of the 20S proteasome subunit, was the first PI to be developed and is currently approved for the upfront treatment of patients with newly diagnosed MM [9]. Two 'second-generation' PIs have since been approved for the management of patients with relapsed MM: carfilzomib and ixazomib.

Carfilzomib (Kyprolis®)

Carfilzomib, a tetrapeptide epoxyketone, is a second-generation intravenous PI that irreversibly binds the chymotrypsin-like catalytic site of the 20S proteasome core particle and inhibits its activity [10]. This irreversible binding capacity makes carfilzomib's proteasome inhibition more sustained than bortezomib [10]. Furthermore, carfilzomib has fewer off-target activity and less neurotoxicity compared with bortezomib [10]. **Table 2** summarizes the various clinical trials utilizing carfilzomib as a single agent or in combination with other agents for the management of relapsed MM.

PX-171-003A1 enrolled 266 patients who were mostly refractory or intolerant to both bortezomib and lenalidomide [11]. The overall response rate (ORR) was 23.7% (partial response [PR]: 18%, VGPR: 5% and complete response [CR]: <1%) and the median progression-free survival (PFS) was 3.7 months with a median duration of response of 7.8 months [11]. The median overall survival (OS) for the entire cohort was 15.6 months [11]. Additional studies such as the PX-171–007 evaluated higher doses of carfilzomib in patients with relapsed MM by treating them with carfilzomib dosed at 20 mg/m^2 on days 1 and 2 of cycle 1, followed by escalation to doses up to 70 mg/m^2 at which dose-limiting toxicity was detected. There were 24 patients with relapsed MM who received carfilzomib at a dose of 56 mg/m^2 and the ORR was 60%. Furthermore, these escalated doses of carfilzomib were relatively well tolerated with the majority of adverse events (AEs) related to grade 1 or 2 anemia and thrombocytopenia. It is important to note that many patients with MM have some degree of renal impairment and hence require dose modifications of their therapies [12].

Table 2. Summary of outcomes from various trials evaluating carfilzomib in relapsed myeloma.

Trial	Previous therapy (median number of prior lines)	Regimen schedule	ORR (%)	Median PFS; (95% CI) months	Median OS (95% CI); months
PX-171-003-A1, Phase II, n = 257	Number of prior lines: 5 (1–20) BTZ: 100% LEN: 94%	CFZ 20 mg/m^2 (cycle 1), 27 mg/m^2 (cycle 2+) Days 1, 2, 8, 9, 15, 16 every 4-week cycle	24% CR: 0.4% VGPR: 5.1% PR: 18.3%	3.7 (2.8–4.6)	15.6 (13–19.2)
PX-171-004-A0, Phase II, (BTZ naive) Cohort 1: n = 59 Cohort 2: n = 67	Cohort 1: – Number of prior lines: 2 (1–4) – BTZ: 0% – LEN: 46% Cohort 2: – Number of prior lines: 2 (1–4) – BTZ: 4.3% – LEN: 70%	Cohort 1: – CFZ 20 mg/m^2– Days 1, 2, 8, 9, 15, 16 every 4-week cycle Cohort 2: – CFZ 20 mg/m^2 (cycle 1), 27 mg/m^2 (cycle 2+) – Days 1, 2, 8, 9, 15, 16 every 4-week cycle	42.4% CR: 3.4% VGPR: 13.6% PR: 25.4% 52.2% CR: 1.5% VGPR: 26.9% PR: 23.9%	8.3 (6–12.3) NR (11.3–NR)	– –
PX-171-004-A1, Phase II (BTZ treated), n = 35	Number of prior lines: 3 (1–13) BTZ: 100% LEN: 37%	CFZ 20 mg/m^2 (cycle 1), 27 mg/m^2 (cycle 2+) Days 1, 2, 8, 9, 15, 16 every 4-week cycle	17.1% CR: 3.0% VGPR: 2.9% PR: 11.4%	4.6 (2.1–11.1)	29.9 (NR)
PX-171-005, Phase II (with renal impairment), n = 47	Number of prior lines: 5 (1–15) BTZ: 96% LEN: 88%	CFZ 15 mg/m^2 (cycle 1), 20 mg/m^2 (cycle 2) and 27 mg/m^2 (cycle 3+) Days 1, 2, 8, 9, 15, 16 every 4-week cycle	27.7% CR: 0% VGPR: 0% PR: 25.5%	–	–
ASPIRE Phase III n = 792 Relapsed MM	CFZ/LEN/Dex: – Number of prior lines: 2 (1–3) – BTZ: 65.9% – LEN: 19.9% LEN/Dex: – Number of prior lines: 2 (1–3) – BTZ: 65.7% – LEN: 19.7%	CFZ 20 mg/m^2 (cycle 1, days 1 and 2 only) then 27 mg/m^2 thereafter Days 1, 2, 8, 9, 15, 16 every 4-week (cycle 1–12) Days 1, 2, 15, 16 every 4-week (cycle 13–18) LEN 25 mg (days 1–21) Dex 40 mg (days 1, 8, 15, 22) LEN 25 mg (days 1–21) Dex 40 mg (days 1, 8, 15, 22)	87.1% CR: 31.8% VGPR: 69.9% 66.7% CR: 9.3% VGPR: 40.4%	26.3 (23.2–30.5) 17.6 (15–20.6)	2-year OS: 73.3% 2-year OS: 65%
PX-171-007, Phase Ib/II, n = 33	Number of prior lines: 5 (1–9) BTZ: N/A LEN: N/A	CFZ 20–70 mg/m^2 (extended infusion time) Days 1, 2, 8, 9, 15,16 every 4-week cycle	60% CR: 3% VGPR: 12% PR: 21%	–	–
ENDEAVOUR, Phase III, n = 929, Relapsed MM	CFZ/Dex: – Number of prior lines: 2 (1–2) – BTZ: 54% – LEN: 38% BTZ/Dex: Number of prior lines: 2 (1–2) – BTZ: 54% – LEN: 38%	CFZ 20 mg/m^2 (cycle 1, days 1 & 2 only) then 56 mg/m^2 thereafter Days 1, 2, 8, 9, 15, 16 every 4 weeks Dex 20 mg (days 1, 2, 8, 9, 15, 16, 22, 23) BTZ 1.3 mg/m^2; days 1, 4, 8, 11 every 3 weeks Dex 20 mg (days 1, 2, 4, 5, 8, 9, 11, 12)	77% CR: 13% VGPR: 42% PR: 22% 63% CR: 6% VGPR: 22% PR: 34%	18.7 (15.6–NE) 9.4 (8.4–10.4)	–
CFZ/Pom/Dex, Phase I, n = 32, Relapsed MM	Number of prior lines: 6 (1–15) BTZ: 97% LEN: 100%	CFZ 20 mg/m^2 (cycle 1, days 1 and 2 only) then 27–56 mg/m^2 thereafter Days 1, 2, 8, 9, 15, 16 q4 week (cycle 1–6) Days 1, 2, 15, 16 q4 week (cycle 7 onward) Pom 4 mg (days 1–21) Dex 40 mg (days 1, 8, 15, 22)	50% VGPR: 16% PR: 34%	7.2 (3–9)	20.6 (11.9–28.7)

BTZ: Bortezomib; CFZ: Carfilzomib; CR: Complete response; Dex: Dexamethasone; LEN: Lenalidomide; MM: Multiple myeloma; MTD: Maximum tolerated dose; NE: Not evaluable; NR: No response; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; Pom: Pomalidomide; PR: Partial response; VGPR: Very good partial response.

Table 2. Summary of outcomes from various trials evaluating carfilzomib in relapsed myeloma (cont.).

Trial	Previous therapy (median number of prior lines)	Regimen schedule	ORR (%)	Median PFS; (95% CI) months	Median OS (95% CI); months
CHAMPION-1, Phase I/II, Phase I = 27, Phase II = 89	Number of prior lines: 1 (1–3) BTZ: 83% LEN: 50%	Phase I: CFZ 20 mg/m^2 (cycle 1, day 1 only) then subsequent doses started at 45 mg/m^2 and were escalated to 56, 70 or 88 mg/m^2 Phase II: (MTD) of 70 mg/m^2 Dex: 40 mg (days 1, 8, 15 and 22 of cycles 1–8) and omitted on day 22 from cycles ≥9	77% (at MTD) CR: 14% VGPR: 33% PR: 31%	12.6 (9.0–NE)	–

BTZ: Bortezomib; CFZ: Carfilzomib; CR: Complete response; Dex: Dexamethasone; LEN: Lenalidomide; MM: Multiple myeloma; MTD: Maximum tolerated dose; NE: Not evaluable; NR: No response; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; Pom: Pomalidomide; PR: Partial response; VGPR: Very good partial response.

As a result, PX-171-005 enrolled patients with relapsed MM with renal impairment including some patients on hemodialysis, and found no difference in the rates of AEs as well as efficacy **(Table 2)** [13].

Carfilzomib has also been tested in various combination regimens in the relapsed setting. The ASPIRE Phase III trial combined carfilzomib, lenalidomide and dexamethasone (KRd) and compared it with lenalidomide and dexamethasone (Rd) [14]. There was an improvement in PFS from 17.6 months with Rd to 26.3 months with KRd and an improved depth of response (CR rate: 31.8 vs 9.3%) [14]. The median OS was not reached in either group but the 2-year survival was longer with KRd (73.3 vs 65%; p = 0.04) [14]. Carfilzomib, pomalidomide and dexamethasone were also evaluated in a Phase I trial of 32 patients who were heavily pretreated with lenalidomide and bortezomib [15]. The ORR was 50% and the median PFS and OS were 7.2 and 20.6 months, respectively [15].

Biologically, carfilzomib is a more efficacious PI than bortezomib. To this point, the randomized Phase III ENDEAVOUR trial conducted a head-to-head comparison of carfilzomib–dexamethasone versus bortezomib–dexamethasone in 929 patients with relapsed MM [16]. With a median follow-up of 11.5 months, the median PFS and ORR were 18.7 months and 77% in the carfilzomib group versus 9.4 months and 63% in the bortezomib group (p < 0.0001), respectively [16]. No difference in OS was detected at last reported follow-up. The safety and efficacy of weekly carfilzomib with dexamethasone was evaluated in a multicenter, single-arm, Phase I/II study (CHAMPION-1) in patients with relapsed myeloma [17]. Patients received carfilzomib at 20 mg/m^2 on day 1 of cycle 1 while subsequent doses started at 45 mg/m^2 and were escalated until the maximum tolerated dose of 70 mg/m^2 was reached for use in the Phase II part of the trial [17]. The ORR was 72% with a median PFS of 10.6 months. At the maximum tolerated dose (70 mg/m^2), weekly carfilzomib–dexamethasone has acceptable safety and tolerability with promising efficacy [17].

Overall, carfilzomib is very well tolerated but does have some common side effects such as fatigue, hypertension, anemia, nausea and thrombocytopenia. Concerns regarding cardiac toxicity have been raised and have occurred relatively early in the course of treatment especially in patients with cardiovascular comorbidities. This must be taken into account when deciding the use of a carfilzomib-based regimen.

Ixazomib (Ninlaro®)

This is a second-generation PI which is also a boronic acid derivative like bortezomib. However, it is the first and only oral PI currently approved for the treatment of MM. Like bortezomib, it also inhibits the 20S proteasome complex reversibly [18]. However, it has a faster dissociation rate from the proteasome compared with bortezomib, and preclinical studies demonstrate its cytotoxic activity in MM cell lines resistant to bortezomib [19].

The various clinical trials evaluating its efficacy are listed in **Table 3**. However, its approval for clinical use was based on the Phase III, randomized, double-blinded, placebo-controlled study – TOURMALINE-MM1 [20]. In this study, 722 patients with relapsed MM after one to three lines of prior therapy but not refractory to prior lenalidomide or PI-based therapy were enrolled to compare ixazomib in addition to lenalidomide and dexamethasone (IRd) compared with lenalidomide and dexamethasone

(Rd) [20]. The median PFS and ORR were 20.6 months and 78.3% with IRd compared with 14.7 months and 71.5% with Rd (p = 0.012) [20]. Importantly, ixazomib appeared to provide equal therapeutic benefit to patients with relapsed MM who had high-risk cytogenetic features such as deletion 17p, t(4;14) and t(14;16) as they had a similar PFS as the remainder of the standard risk patients [20]. However, the triplet combination of ixazomib, lenalidomide and dexamethasone did not improve OS compared with lenalidomide and dexamethasone alone likely due to short follow-up time and furthermore, it was not superior in PFS when evaluating only patients who received one line of prior therapy. Given its oral formulation, it is especially well suited for use as maintenance therapy post-ASCT and is currently in clinical trial and is being investigated in ongoing clinical trials. The most common AEs for patients receiving ixazomib included gastrointestinal side effects such as nausea, vomiting, diarrhea and constipation as well as other side effects such as thrombocytopenia, peripheral neuropathy and peripheral edema [20].

• Immunomodulators

The IMiDs refer to the various structural analogs of thalidomide that have immunomodulatory properties. The antimyeloma effects of IMiDs arise primarily from its antiangiogenic effect [21], ability to block NF-κB-mediated signaling [22], induce apoptosis via the caspase-8/death receptor pathway [23], down regulate TNF-α, IL-1, IL-6 and IL-12 [24] while augmenting antimyeloma natural killer (NK) cell activity and stimulating cytotoxic T cells [25]. Part of this activity takes place by the ability of IMiDs to bind cereblon resulting in its interaction with the transcription factors Ikaros and Aiolos, leading to their ubiquitination and subsequent proteasomal degradation [26]. Thalidomide and lenalidomide are both US FDA-approved IMiDs that

Table 3. Summary of outcomes from various trials evaluating ixazomib in relapsed myeloma.

Trial	Previous therapy (median number of prior lines)	Regimen schedule	ORR (%)	Median PFS (95% CI); months	Median OS (95% CI); months
Ixazomib, Phase I Dose escalation cohort: n = 32 Expansion cohort: n = 31	Dose escalation cohort: – Number of prior lines: 4 (1–13) – Bortezomib: 97% – LEN: 94% Expansion cohort: – Number of prior lines: 3 (1–12) – Bortezomib: 74% – LEN: 100%	Dose escalation cohort: – Ixazomib (0.24–3.95 mg/m^2) (days 1, 8, 15 on 28-day cycle) Expansion cohort: – Ixazomib (2.97 mg/m^2) (days 1, 8, 15 on 28-day cycle)	5% CR: 0% VGPR: 5% PR: 0% 26% CR: 0% VGPR: 0% PR: 26%	– – 	– –
Ixazomib Phase I Dose escalation cohort: n = 26 Expansion cohort: n = 36	Dose escalation cohort: – Number of prior lines: 4 (2–28) – Bortezomib: 100% – LEN: 85% Expansion cohort: – Number of prior lines: 4 (1–12) – Bortezomib: 81% – LEN: 75%	Dose escalation cohort: – Ixazomib (0.24–2.23 mg/m^2) (days 1, 4, 8, 11 on 21-day cycle) Expansion cohort: – Ixazomib (2.0 mg/m^2) (days 1, 4, 8, 11 on 21-day cycle)	13% (all patients) CR: 2% VGPR: 0% PR: 11%	–	–
TOURMALINE.MM1 Phase III n = 722 Relapsed MM	IXAZ/LEN/Dex: – Number of prior lines: 1 (1–3) – Any PI: 69% – Any IMiD: 54% LEN/Dex: – Number of prior lines: 1 (1–3) – Any PI: 70% – Any IMiD: 56%	IXAZ 4 mg (days 1, 8, 15) LEN 25 mg (days 1–21) Dex 40 mg (days 1, 8, 15, 22) LEN 25 mg (days 1–21) Dex 40 mg (days 1, 8, 15, 22)	78% CR: 14% VGPR: 36% PR: 67% 72% CR: 7% VGPR: 32% PR: 65%	21.4 months 9.7 months 	Median OS NR in either group
Ixaz/Pom/Dex Phase I/II n = 21 Relapsed MM	IXAZ/Pom/Dex: – Number of prior lines: 2 (1–5) – BTZ: 100% – LEN: 100%	IXAZ (dose level 1: 3 mg; dose level 2: 4 mg on days 1, 8, 15) Pom 4 mg (days 1–21) Dex 40 mg (days 1, 8, 15, 22)	44% VGPR: 16% PR: 28%	–	–

CR: Complete response; Dex: Dexamethasone; IXAZ: Ixazomib; IMiD: Immunomodulator; LEN: Lenalidomide; MM: Multiple myeloma; NR: No response; ORR: Overall response rate; OS: Overall survival; PI: Proteasome inhibitor; PFS: Progression-free survival; Pom: Pomalidomide; PR: Partial response; VGPR: Very good partial response.

have been used in the upfront treatment of MM over the last decade. Recent 'second-generation' IMiDs have been approved for the management of patients with relapsed MM.

Pomalidomide (Pomalyst®)

Pomalidomide is a potent IMiD that is about a 100-times more potent than thalidomide and ten-times more potent than lenalidomide *in vitro* [27]. The various clinical trials evaluating its efficacy are listed in **Table 4**. A large multicenter randomized Phase III trial (MM-003) compared 4 mg daily for 21 of 28 days and dexamethasone 40 mg weekly versus dexamethasone 40 mg alone in 455 patients with MM refractory to lenalidomide and bortezomib [28]. The median PFS was 15.7 weeks in the pomalidomide–dexamethasone arm versus 8.0 weeks with dexamethasone alone; furthermore, the median OS was not reached in the pomalidomide–dexamethasone arm but was 34 weeks with dexamethasone alone. Recent updates demonstrated that the difference in median OS between patients in the pomalidomide–dexamethasone and dexamethasone alone arms due to the crossover effect was 7.0 months (12.7 vs 5.7 months, respectively). Prior Phase II studies demonstrated responses even in patients with relapsed MM at a dose of 2 mg daily with dexamethasone 40 mg weekly in a 28-day cycle as well as those with high-risk cytogenetic or molecular markers defined as a PC-labeling index ≥3%, deletion 17p, t(4;14) or t(14;16) by FISH, or deletion 13 on conventional cytogenetics [29]. Long-term follow-up data reported by the Mayo Clinic revealed no difference in outcomes based on two different dose levels of pomalidomide (2 and 4 mg) and low-dose dexamethasone [30], although earlier Phase I data had conflicting results suggestive of a dose response [31].

Pomalidomide has been evaluated in combination with other agents. The Phase II ClaPD trial evaluated pomalidomide in combination with clarithromycin and dexamethasone. In 100 highly refractory patients with MM [32], the ORR was 54% and the median PFS was 8.2 months [32]. Similarly, pomalidomide and dexamethasone were combined with cyclophosphamide and compared with pomalidomide and dexamethasone in a randomized Phase II trial for patients with relapsed and refractory MM [33]. The ORR was 69% in the cyclophosphamide-containing arm compared with 39% in the comparator arm ($p = 0.03$). Furthermore, the PFS was superior in the former (9.2 vs 4.4 months; $p = 0.04$) [33].

• Monoclonal antibodies

Recently, monoclonal antibodies specific for antigens present on clonal PCs are being used in clinical practice for the treatment of patients with relapsed MM with many more being investigated in ongoing clinical trials. These antibody therapies provide a targeted approach to treatment with favorable toxicity and tolerability profiles compared with conventional chemotherapy agents.

The two targets on clonal PCs of particular interest include: CD38 and SLAMF7 or formerly known as CS1. CD38 is a cell surface glycoprotein, highly expressed on PCs in the bone marrow and is involved in activating signal transduction and calcium-based signaling [34]. Similarly, SLAMF7 is a glycoprotein expressed on most clonal PCs in MM and NK cells but not on normal tissues that enables selective killing of myeloma cells with minimal effects on healthy tissue [35]. The various clinical trials evaluating the efficacy of both monoclonal antibodies are listed in **Table 5**.

Daratumumab (Darzalex™)

Daratumumab (HuMax-CD38, Genmab, Copenhagen, Denmark) is a humanized IgG1κ monoclonal antibody that targets the CD38 on clonal PCs with single agent activity in patients with relapsed MM. Its main mechanism of action is by inducing target cell killing of CD38-expressing cells by means of complement-mediated, antibody-dependent cell-mediated cytotoxicity [36,37].

In a Phase I–II trial, the ORR was 36% in the cohort that received it at a dose of 16 mg/kg (15 patients had a ≥PR, including two with a CR and two with a VGPR) and 10% in the cohort that received 8 mg/kg (three had a PR) [38]. The median PFS was 5.6 months in the 16 mg/kg cohort, and 65% of the patients who had a response did not have progression at 12 months [38].

An open-label, international multicenter, Phase II trial enrolled patients with MM who were previously treated with at least three lines of therapy (including PI and IMiDs), or were refractory to both PI and IMiDs [39]. A total of 106 patients received daratumumab 16 mg/kg in parts 1 and 2. Overall responses were noted in 31 patients (29.2%, 95% CI: 20.8–38.9). The

Table 4. Summary of outcomes from various trials evaluating pomalidomide in relapsed myeloma.

Trial	Previous therapy (median number of prior lines)	Regimen schedule	ORR%	Median PFS (95% CI); months	Median OS (95% CI); months
IFM 2009-02 Phase II Cohort 1: n = 43 Cohort 2: n = 41	Cohort 1: – Number of prior lines: 5 (1–13) – Bortezomib: 79% – Lenalidomide: 84% Cohort 2: – Number of prior lines: 5 (2–10) – Bortezomib: 83% – Lenalidomide: 95%	Cohort 1: – Pom 4 mg (21/28 days) Cohort 2: – Pom 4 mg (28/28 days)	35% CR: 2% VGPR: 2% PR: 30% 34% CR: 5% VGPR: 2% PR: 27%	5.4 (3–9) 3.7 (2–7)	14.9 (9–NR) 4.8 (9–20)
Pom/Dex Phase II Cohort 1: n = 35 Cohort 2: n = 35	Cohort 1: – Number of prior lines: 6 (3–9) – Bortezomib: 100% – Lenalidomide: 100% Cohort 2: – Number of prior lines: 6 (2–11) – Bortezomib: 100% – Lenalidomide: 100%	Cohort 1: – Pom 2 mg (28/28 days) Cohort 2: – Pom 4 mg (28/28 days)	26% CR: 0% VGPR:14% PR: 11% 28% CR: 3% VGPR: 9% PR: 17%	6.5 (3.9–8.9) 3.2 (1.9–8.6)	– –
Pom/Dex, Phase II, n = 60	Number of prior lines: 2 (1–3) Bortezomib: 33% Lenalidomide: 35%	Pom 2 mg (28/28 days)	63% CR: 5% VGPR: 28% PR: 30%	11.6 (9.2–NR)	NR
Pom/Dex, Phase II, n = 34	Number of prior lines: 4 (1–8) Bortezomib: 59% Lenalidomide: 100%	Pom 2 mg (28/28 days)	32% CR: 0% VGPR: 6% PR: 26%	4.8 (2.7–10.1)	13.9 (NA)
MM-002, Phase II, Pom/Dex: n = 113 Pom: n = 108	Pom/Dex: – Number of prior lines: 5 (2–13) – Bortezomib: 100% – Lenalidomide: 100% Pom: – Number of prior lines: 5 (1–12) – Bortezomib: 100% – Lenalidomide: 100%	Pom 4 mg (21/28 days) + Dex 40 mg (1, 8, 15, 22 days) Pom 4 mg (21/28 days)	34% CR: 3% VGPR: 0% PR: 31% 15% CR: 1% VGPR: 0% PR: 14%	4.6 2.5	16.5 13.6
MM-003, Phase III, Pom/Dex: n = 302 Dex: n = 153	Pom/dex: – Number of prior lines: 5 (2–14) – Bortezomib: 100% – Lenalidomide: 100% Dex: – Number of prior lines: 5 (2–17) – Bortezomib: 100% – Lenalidomide: 100%	Pom 4 mg (21/28 days) + Dex 40 mg (1, 8, 15, 22 days) Dex (1–4, 9–12, 17–20)	31% CR: 1% VGPR: 5% PR: 25% 10% CR: 0% VGPR: 1% PR: 9%	4.0 1.9	NR 7.8 (5.4–9.2)
ClaPD, Phase II, n = 98	Number of prior lines: 5 (3–15) Bortezomib: 84% Lenalidomide: 85%	Clarithromycin 500 mg b.i.d. Pom 4 mg (21/28 days) Dex 40 mg (1, 8, 15, 22 days)	57% CR: 6% VGPR:17% PR: 34%	8.67	NR
Pom/Cytox/Dex, Phase II, n = 70	Pom/Cytox/Dex: – Number of prior lines: 4 (2–9) – Bortezomib: 71% – Carfilzomib: 38% Pom/Dex: – Number of prior lines: 4 (2–12) – Bortezomib: 78% – Carfilzomib: 44%	Pom 4 mg (21/28 days) Cyclophosphamide 400 mg (days 1, 8, 15) Dex 40 mg (1,8,15,22 days) Pom 4 mg (21/28 days) Dex 40 mg (1, 8, 15, 22 days)	65% CR: 3% VGPR: 9% PR: 53% 39% CR: 3% VGPR: 11% PR: 25%	9.5 (4.6–14) 4.4 (2.3–5.7)	NR (13.1–NR) 16.8 (9.3–NR)

b.i.d.: Two-times a day; CR: Complete response; NR: No response; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; Pom: Pomalidomide; PR: Partial response; VGPR: Very good partial response.

Table 5. Summary of outcomes from various trials evaluating histone deacetylase inhibitors and monoclonal antibodies in relapsed myeloma.

Trial	Previous therapy (median number of prior lines)	Regimen schedule	ORR (%)	Median PFS (95% CI); months	Median OS (95% CI); months
PANOMARAMA-II, Phase II, n = 55	Number of prior lines: 4 (2–14) Bortezomib: 100% Any IMiDs: 100%	Phase I (cycle 1–8) every 3 weeks: – Panobinostat 20 mg (days 1, 3, 5, 8, 10, 12) – Bortezomib 1.3 mg/m^2 intravenous (days 1, 4, 8, 11) – Dex 20 mg (days 1, 2, 4, 5, 8, 9, 11, 12) Phase II (cycle 9+) every 3 weeks: – Panobinostat 20 mg (days 1, 3, 5, 8, 10, 12) – Bortezomib 1.3 mg/m^2 intravenous (days 1 and 8) – Dex 20 mg (days 1, 2, 8, 9)	29% CR: 0% VGPR: 4% PR: 25%	–	–
PANORAMA-I, Phase III, n = 768	Number of prior lines: 1 (1–3) Bortezomib: 43% Lenalidomide: 20%	Panobinostat 20 mg (days 1, 3, 5, 8, 10, 12) Bortezomib 1.3 mg/m^2 intravenous (days 1, 4, 8, 11) Dex 20 mg (days 1, 2, 4, 5, 8, 9, 11, 12)	61% CR: 11% VGPR: 17% PR: 33%	12 (10.3–13)	33.6 (31.3–NE)
		Bortezomib 1.3 mg/m^2 intravenous (days 1, 4, 8, 11) Dex 20 mg (days 1, 2, 4, 5, 8, 9, 11, 12)	55% CR: 6% VGPR: 10% PR: 39%	8.1 (7.6–9.2)	30.4 (26.9–NE)
Elotuzumab: Phase II Cohort 1: n = 39 Cohort 2: n = 37	Cohort 1: – More than or equal to two prior lines: – Bortezomib: 62% – Thalidomide: 62%	Cohort 1: – Elotuzumab 10 mg/kg (days 1, 8, 15, 22) – Lenalidomide 25 mg (days 1–21) – Dex 40 mg (days 1, 8, 15, 22)	92% CR: 14% VGPR: 50% PR: 28%	33 (15–NR)	–
	Cohort 2: – More than or equal to two prior lines: – Bortezomib: 64% – Thalidomide: 59%	Cohort 2: – Elotuzumab 20 mg/kg (days 1, 8, 15, 22) – Lenalidomide 25 mg (days 1–21) – Dex 40 mg (days 1, 8, 15, 22)	76% CR: 11% VGPR: 38% PR: 27%	18.6 (13–32)	–
Elotuzumab, ELOQUENT-2, Phase III	Number of prior lines: 2 (1–4) Bortezomib: 70% IMiD: 54%	Elotuzumab 20 mg/kg (days 1, 8, 15, 22) Lenalidomide 25 mg (days 1–21) Dex 40 mg (days 1, 8, 15, 22) Lenalidomide 25 mg (days 1–21) Dex 40 mg (days 1, 8, 15, 22)	79% CR: 4% VGPR: 28% PR: 46%	19.4 (16.6–22.2)	–
			66% CR: 7% VGPR: 21% PR: 38%	14.9 (12.1–17.2)	–
Daratumomab, Phase I/II Dose escalation: n = 32	Relapsed/refractory	Daratumomab weekly intravenous infusion (0.005–24 mg/kg)	15.5% CR: 0% VGPR: 0% PR: 15.5%	–	–
Daratumumab: – Part 1: n = 32 – Part 2: n = 72	8 mg/kg: – Number of prior lines: 4 (3–10) – Bortezomib: 83% – Lenalidomide: 100%	8 mg/kg: eight once weekly infusions and then in twice monthly infusions for 16 weeks	10% CR: 3% VGPR: 3% PR: 15%	2.4 (1.4–3.5)	1-year OS: 77%
	16 mg/kg: – Number of prior lines: 4 (2–12) – Bortezomib: 71% – Lenalidomide: 74%	16 mg/kg: treated weekly for 8 weeks and then twice monthly for 14 weeks	36% CR: 0% VGPR: 0% PR: 3%	5.6 (4.2–8.1)	1-year OS: 77%

CR: Complete response; IMiD: Immunomodulator; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; q: Every.

Table 5. Summary of outcomes from various trials evaluating histone deacetylase inhibitors and monoclonal antibodies in relapsed myeloma (cont.).

Trial	Previous therapy (median number of prior lines)	Regimen schedule	ORR (%)	Median PFS (95% CI); months	Median OS (95% CI); months
Dara/Rev/Dex: n = 32	Number of prior lines: 2 (1–3) Lenalidomide: 34%	Dara: 16 mg/kg q week for two cycles, then every 2 weeks for four cycles, and every 4 weeks Len: 25 mg (days 1–21) Dex: 40 mg q week	88% CR: 25% VGPR: 28% PR: 34%	–	–
Dara/Pom/Dex: n = 77	Number of prior lines: 4 (2–10) Bortezomib: 65% Lenalidomide: 88%	Dara: 16 mg/kg q week for two cycles, then every 2 weeks for four cycles and every 4 weeks Pom: 4 mg (days 1–21) Dex: 40 mg every week	58.5% CR: 5% VGPR: 16% PR: 20%	–	–

CR: Complete response; IMiD: Immunomodulator; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; q: Every.

median PFS was 3.7 months (95% CI: 2.8–4.6) and the median OS was 17.5 months (95% CI: 13.7–not estimable) [39]. Daratumumab was well tolerated; infusion reactions during the first cycle, fatigue and anemia of any grade were the most common AEs [39].

Recently, an open-label Phase I/II study of daratumumab in combination with lenalidomide and dexamethasone was reported in 32 patients. The ORR was 88%, and the median duration of response was not reached [40]. The most common AEs included neutropenia, muscle spasms, cough, diarrhea, fatigue and hypertension. Eighteen (56%) patients had infusion-related reactions and these were generally mild to moderate and occurred mostly during the first cycle [40]. Similarly, another study also evaluated the combination of daratumumab, pomalidomide and dexamethasone [41]. Most patients had infusion-related reactions consisting of chills, cough and dyspnea. The ORR was 59% with many responses deepening over time and among the patients refractory to PIs and IMiDs the ORR of 58% [41].

Elotuzumab (Emplicity™)

Elotuzumab is a humanized IgG1 monoclonal antibody targeted against SLAMF7. It is believed to directly activate NK cells through both the SLAMF7 pathway and Fc receptors as well as target SLAMF7 on PCs, thereby facilitating the interaction of PCs with the NK cells to mediate the killing of PCs through antibody-dependent cell-mediated cytotoxicity. In preclinical *in vitro* and *in vivo* models, the combination of elotuzumab and lenalidomide resulted in enhanced activation of NK cells that was greater than the effects of either agent alone and increased antitumor activity.

This approval was based on the randomized controlled Phase III ELOQUENT-2 trial that compared elotuzumab (10 mg/kg on days 1, 8, 15 and 22 during the first two cycles and then on days 1 and 15 of a 28-day cycle thereafter) in combination with lenalidomide (25 mg/day on days 1–21) and low-dose dexamethasone (40 mg weekly) versus just lenalidomide and low-dose dexamethasone alone [42]. At 1 year, the PFS in the elotuzumab group was 68 versus 57% in the control group [42]. The median PFS in the elotuzumab group was 19.4 versus 14.9 months in the control group ($p < 0.001$), indicating a relative reduction of 30% in the risk of disease progression or death [42]. This PFS benefit was seen in patients with typically poor outcomes (older age, International Staging System stage III, renal impairment or deletion 17p by molecular cytogenetic studies such as FISH) and irrespective of prior exposure to therapies such as bortezomib, IMiDs or ASCT [42]. The most common AEs were the infusion reactions (10%) noted with the elotuzumab infusions, which included pyrexia, chills and hypertension. Most of these infusion reactions were grade 1 or 2 and occurred mainly with the first dose of study therapy [42]. It is important to note that elotuzumab had virtually no single agent activity.

• Histone deacetylase inhibitors

Histone deacetylase (HDAC) inhibitors are enzymes specialized in the removal of acetyl groups from proteins. They play a role in oncogenesis through their epigenetic activity of targeting histones as well as by regulating

nonhistone proteins relevant to tumor progression [43]. Epigenetic changes, such as acetylation of histone or nonhistone proteins, are important in the pathogenesis of MM [44].

Panobinostat (Farydak®)

Panobinostat is an oral deacetylase inhibitor of all class I (HDACs 1, 2, 3 and 8), class II (HDACs 4, 5, 6, 7, 9 and 10) and class IV (HDAC 11) HDACs. It has been shown to overcome PI resistance in PCs by inhibiting HDAC6 leading to disruption of the aggresome pathway, which is an alternative mechanism for protein degradation in PCs when the proteasome pathway is disrupted. Thus, combining bortezomib with panobinostat simultaneously inhibits the proteasome and aggresome pathways resulting in synergistic cytotoxicity [45]. In the Phase III PANORAMA-1 trial consisting of 768 patients with relapsed myeloma, panobinostat in combination with bortezomib and dexamethasone improved the median PFS to 12 months compared with 8.1 months with placebo plus bortezomib and dexamethasone ($p < 0.0001$) [46]. This improvement in PFS was more striking in patients who had received more than or equal to two prior regimens, including bortezomib and an IMiD drug (12.5 vs 4.7 months) [47]. The most common grade 3 and 4 AEs among patients who received panobinostat were thrombocytopenia, lymphopenia, diarrhea and fatigue/asthenia [47].

Practical considerations

Though the overall outcome of patients with relapsed myeloma after therapy with previous IMiDs and bortezomib is poor, the emergence of newer approved therapies as single agents or in combinations with other therapies is encouraging. Nevertheless, when choosing the next appropriate therapy in these challenging clinical situations, one should take into account both disease- and patient-related factors at the time of disease relapse. Disease-related factors include the tumor burden, type of relapse (i.e., aggressive symptomatic relapse versus indolent asymptomatic serologic relapse only) as well as the aggressiveness of the disease, such as the presence or absence of high-risk biology. Patient-related factors include the presence of peripheral neuropathy, age, performance status and renal function. Thus, in patients with relapsed MM who are either experiencing aggressive relapses or are physiologically fit, triplet combination regimens are likely to provide more benefit compared with sequential doublet regimens. However, if in the setting of an indolent paraprotein only relapse, an elderly patient may benefit from a doublet just as well while limiting the toxicities associated with triplet therapies. Similarly, toxicity profiles of the agents being used must be taken into consideration when deciding on a therapy (i.e., risk of cardiac or renal toxicity or peripheral neuropathy). Finally, mode of delivery such as intravenous infusions versus oral formulations can greatly affect the treated patient and hence, the patient's preference must also be taken in to account. Various combinations of therapies for MM in the relapsed setting are present and can be viewed online at the mSMART website [48].

Conclusion

The introduction of novel agents such as IMiDs and PIs more than a decade ago changed the natural history and improved the survival outcomes for patients with MM. Likewise, these new therapeutic agents reviewed in this manuscript hold promise in continuing to improve the outcomes of patients with MM.

Continual use of these novel agents in clinical practice will help identify the most effective sequence and dosing modifications required to continue to improve outcomes of patients with MM.

Future perspective

As the clinical trial pipeline for novel therapeutic agents continues to deliver effective treatments for patients with relapsed MM, one can anticipate eventual and continuous improvements in the OS for patients with newly diagnosed MM. New immunotherapies such as chimeric antigen T-cell therapy and anti-PD-1 antibody therapies as well as dendritic vaccine therapy will likely enter the clinical practice space upon further evaluation. Such novel agents will continue to provide an opportunity for the design and implementation of new combination regimens capable of providing deeper and more durable responses for patients with MM. Given the complex nature of MM, it will likely take such combinations of novel therapies to be used in the upfront setting in order to allow for the realization of the ultimate goal: a cure.

Disclaimer

The contents of this work are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Authors' contribution

WI Gonsalves, P Milani, D Derudas and FK Buadi reviewed the literature, wrote and edited the manuscript.

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EXECUTIVE SUMMARY

Proteasome inhibitors

- Carfilzomib in combination with dexamethasone or in combination with lenalidomide and dexamethasone is a well tolerated, efficacious regimen for patients with relapsed multiple myeloma (MM).
- Ixazomib in combination with lenalidomide and dexamethasone is an oral regimen useful for the treatment of patients with relapsed MM with efficacy even in those patients with high-risk features.

Immunomodulators

- Pomalidomide in combination with dexamethasone alone or in addition to cyclophosphamide is a potent oral regimen for the treatment of patients with relapsed MM.

Monoclonal antibodies

- Daratumumab is a monoclonal antibody directed against CD38 and has significant single agent activity in the treatment of patients with relapsed MM. It appears to have synergistic efficacy in combination with immunomodulators and dexamethasone.
- Elotuzumab is a monoclonal antibody directed against the SLAMF7 antigen but has no single agent activity. However, in combination with lenalidomide and dexamethasone, it has improved synergistic efficacy.

Histone deacetylase inhibitor

- Panobinostat is the first pan-histone deacetylase inhibitor approved for the treatment of relapsed MM in combination with bortezomib and dexamethasone.

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