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REVIEW ARTICLE

Multiple myeloma gammopathies

Relapsed refractory multiple myeloma: a comprehensive overview

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Abstract

Most patients with relapsed/refractory multiple myeloma (RRMM) have been treated with drug combinations including a proteasome inhibitor (PI) and/or an immunomodulatory drug (IMiD). The goal of therapy for such patients is therefore to achieve disease control with acceptable toxicity and patient-defined decent quality of life. Physicians face a difficult task not only deciding who to treat, but also when to treat and how to treat, utilizing knowledge of previously administered therapies, patient comorbidities, potential adverse events, and patient wishes to make such a critical decision. New drugs and combination regimens are continuously underway thus broadening the options for therapy and giving way to a more individualized approach for patients with RRMM. The integration of novel agents into the treatment paradigm has shifted the perception of multiple myeloma (MM) from an incurable, fatal disease to a manageable, chronic one. This comprehensive review addresses the results and challenges posed by many of the newer agents for the treatment of RRMM. It attempts to propose a universal strategy for optimal therapy decision-making thus answering three simple fundamental questions—when to treat, how to treat, and how long to treat for.

Introduction

The treatment of multiple myeloma (MM), the second most common hematological malignancy [1], has advanced significantly over the past decade with the approval of novel agents including proteasome inhibitors (PIs), such as bortezomib (BOR), carfilzomib (CFZ), and ixazomib (IXA); immunomodulatory drugs (IMiDs) such as lenalidomide (LEN) and pomalidomide (POM); monoclonal antibodies (mAbs) namely daratumumab (DARA) and elotuzumab (ELO); and other treatments in development including CAR-T-cell therapy. The therapy of relapsed/refractory MM (RRMM) has thus become more complex posing new challenges for clinicians when deciding on a proper strategy. Standard first line treatment of fit young patients usually includes PI and IMiD-based induction, high-dose melphalan with autologous hematopoietic stem cell transplantation (ASCT) together with posttransplant consolidation and/or long-term LEN maintenance. Despite the improvement in depth and duration of response and prolonged survival, this disease remains incurable for the majority of patients due to the eventual emergence of resistant clones and often imminent relapse. They currently agreed upon definition of cure, or so-called "operational cure", is a relapse-free interval of at least 10–15 years [2, 3]. Long-term outcomes remain dismal with only about 10–15% of transplant patients, and even less transplant-ineligible patients achieving cure [2, 3].

Over the last few years there has been a clear change in the paradigm for the management of RRMM. Patients can now be treated at various relapse phases with the availability of agents or combinations of agents that can be offered at each phase allowing for prolonged survival and sometimes cure [4].

PIs are considered critical components of any regimen used to treat high-risk myeloma whereby they disrupt the cell's ubiquitin proteasome system, thus blocking the breakdown of proteins and increasing proapoptotic stress leading to inevitable cell death [5]. BOR was the first PI to be approved, but this review will also highlight the results of trials of second-generation PIs namely CFZ and the first

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oral PI, IXA. Moreover, other agents such as marizomib, are currently in clinical development.

Another important family of drugs that have contributed to the significant advance in MM treatment are the IMiDs of which the prototype was thalidomide. The second-generation drugs, LEN and POM, are now widely available and extensively used. LEN stands out because of its improved safety profile compared with thalidomide. POM, on the other hand, is more potent, potentially inducing responses in LEN-resistant or refractory patients. Despite their popularity, the mechanism of action of IMiDs is complex and not completely understood. It is suggested that their effect is mediated by cereblon binding, which results in the breakdown of intrinsic proteins such as Ikaros and Aiolos [6]. They are found to act directly on myeloma cells, affecting gene expression by upregulating tumor suppressor genes and inhibiting oncogenes, thus promoting cell cycle arrest and apoptosis. They also act on the microenvironment by inhibiting osteoclast differentiation, growth factor production, and angiogenesis. And last but not least, IMiDs have an immunomodulatory effect, resulting in enhancement of immune function and an increase in natural killer-mediated MM lysis, which could possibly explain their high efficacy in the maintenance setting.

mAbs further built on the foundation paved by PIs and IMiDs, greatly impacting survival both in the upfront and relapse settings. Several classes with different targets were extensively studied, with mainly two making it to the clinic —anti-SLAMF7 and anti-CD38, namely ELO and DARA, respectively—both of which will be extensively discussed.

When to treat

One of the biggest challenges in the relapse setting is the optimal timing to initiate therapy, which can be rather complex. The first step when deciding on therapy initiation should be the identification of clinical versus biochemical relapse. Clinical relapse can be diagnosed using the CRAB criteria (Calcium > 11.5 mg/dl; Cr > 2 mg/dl; Hb < 10 g/dl or >2 points below the lower normal limit; new bone lesions), whereas biochemical relapse occurs with an asymptomatic progressive increase in myeloma monoclonal gammopathy levels [7]. Significant paraprotein relapse on the other hand, is defined by the doubling of the M-component in two consecutive measurements 2 or less months apart, by the increase in the absolute levels of serum M protein by 1 g/dl or more, by the increase in urine M-protein by 500 mg/24 h or more, or by the increase in involved free light chain level by 20 mg/dl or more (plus an abnormal free light chain ratio) in two consecutive measurements 2 or less months apart [7]. Patients with clinical relapse especially with kidney failure, symptomatic hypercalcemia, or medullary compression should be offered immediate treatment. Similarly, significant paraprotein relapse also warrants urgent intervention, whereas asymptomatic biochemical relapse can be carefully followed every 1–2 months and is currently not an indication for therapy.

Regarding patterns of relapse/progression after front-line ASCT, findings suggest that median rescue therapy for asymptomatic patients is around 5.6 months with only 26% of asymptomatic patients never requiring therapy within 2 years [8]. This poses a dilemma since the majority of asymptomatic relapses eventually do require treatment, begging the question whether or not earlier intervention would improve outcome. Subgroup analysis of the phase III randomized ENDEAVOR trial comparing CFZ–DEX with LEN–DEX in RRMM patients demonstrated improved outcomes in the CFZ group regardless of the presence of CRAB symptoms. CFZ–DEX had a more favorable risk-benefit profile in both patients with biochemical and symptomatic relapse, suggesting that perhaps with the incorporation of modern available drugs, patients would benefit from earlier more aggressive interventions [9].

How to treat

The old frail and the young fit

Relapse treatment goals cannot be readily generalized and are highly heterogenous, based on both relapse characteristics and patient profile. Older frailer patients have limited options and should most likely receive attenuated-dose therapies, where clinicians must be careful to prevent additional morbidity and preserve a patient-oriented quality of life. Several studies evaluated relapse therapy in elderly patients and demonstrated benefit with treatment when appropriate. BOR–DEX demonstrated not only efficacy but also tolerability in fit elderly patients [10], with its second-generation counterpart CFZ demonstrating even greater response rates. But while CFZ does have better tolerability when it comes to peripheral neuropathy, it can be very cardiotoxic, necessitating assessment by a trained cardiologist with continuous monitoring while ongoing treatment [11, 12]. DARA also proved highly effective and well tolerated in RRMM regardless of patient age, and could therefore be offered to all relapse patients [13]. Finally, long-term LEN maintenance is often withheld in the elderly population in fears of toxicities, and as later discussed the benefits appear to outweigh the risks regardless of patient age, suggesting that LEN maintenance could be offered to everyone [14].

Younger, more fit patients with a first relapse, however, especially after a prolonged response, have a wider selection of options. Apart from reducing the burden of active

Table 1 Factors to consider when deciding on proper RRMM therapy

Patient characteristics	Treatment/disease related
Age	Cytogenetics
Comorbidities	Previous treatments
- Renal function	- Components
- Neuropathy	- Duration
- Bleed	- Response
- Thrombosis	
- etc.	
Bone marrow reserve	Remission
- Prior stem cell transplants	- Duration of remission
- Long-term IMiD therapy	- Relapse under treatment
- Received alkylating agents	
QOL considerations and patient preference	

symptoms, the aim should be to achieve the best disease response possible, namely complete response (CR), MRD < 0 (determined both biologically and through a negative PET-CT scan) and the longest progression free survival (PFS) possible.

High-risk and standard-risk disease

There are two aspects to consider when deciding on proper relapse therapy: patient-related and treatment/disease-related (Table 1).

Bone marrow reserve is an important consideration especially in patients who had prior stem cell transplants, had been on long-term IMiD therapy, or previously received alkylating agents. Decreased renal function, virtually seen in all myeloma patients, peripheral neuropathy (PN), and thromboembolic events, both frequent sequelae in treated patients, are also major sources of morbidity that should be taken into consideration regarding optimal treatment choices.

When looking at treatment and disease-related factors, cytogenetics are very important both at time of diagnosis and in the relapse setting. Very few data are currently available concerning adverse cytogenetics in the relapse settings, with studies mostly aiming to determine optimal upfront therapy for these patients. The Myeloma X trial comparing salvage ASCT to weekly cyclophosphamide (CY) following reinduction in RRMM evaluated the impact of cytogenetics on patient outcomes, namely time to progression (TTP) and OS [15]. High-risk disease was defined as t(4;14), t(14;16) and del(17p). At 76 months median follow-up, ASCT patients had significantly better TTP compared with CY (19 months vs 11 months), with concomitant improvements in OS (67 months vs 55 months). While these results suggest benefit of salvage ASCT in relapsed patients, this benefit is almost lost in the presence of any single high-risk feature.

The more recently published results from the phase III ReLApsE trial comparing salvage ASCT followed by LEN maintenance to LEN maintenance alone suggest similar findings [16]. While an intention to treat analysis did not confer statistical significance between the two groups, subgroup analysis proved salvage ASCT superiority for patients receiving front-line ASCT with low risk features namely having low LDH, no adverse cytogenetics, and R-ISS-1. These results suggest that high-risk cytogenetics patients not only have worse outcomes but respond differently to treatment, highlighting the need for targeted studies in this patient group.

Early versus late relapse

Duration of initial disease response remains one of the strongest prognostic factors in MM, particularly post ASCT. Early relapse (<24 months) after upfront ASCT strongly predicts lower OS, and despite all advancements in the last 2 decades, the natural history of the disease remains grossly unchanged with the proportion of early relapses stable at around 35–38% [17]. These relapses usually present aggressively, with similar dismal outcomes from refractory disease, defined as progression under treatment or within 60 days after treatment cessation. Early relapses also do not allow for proper patient recovery from initial treatments and can severely limit treatment choices. Recently developed Revised International Staging System (R-ISS) combining traditional ISS with genetic markers and lactate dehydrogenase was found to not only accurately prognosticate newly diagnosed MM patients, but also predict early post-ASCT relapse rates and independently affect post-relapse survival [18]. Such tools can be crucial in determining patients at higher risk necessitating earlier more aggressive interventions with closer follow-up post-remission.

Early relapse on LEN maintenance

The rationale behind treatment choice resides on overcoming drug resistance developed by emergent myeloma clones, and hence the use of non-cross-resistant agent combinations, especially with the challenging double refractory (to both PIs and IMiDs) clones [19, 20]. We will briefly mention key studies evaluating LEN-refractory patients, all of which will be discussed in depth in upcoming sections.

Despite being of the same drug class, POM has been shown to be very effective in LEN-refractory patients, with reported improved ORR, PFS, and OS. POM–DEX combinations were evaluated in the NIMBUS [21] and STRATUS [22] studies, while POM–BOR–DEX was evaluated in

the OPTIMISMM trials [23]. All demonstrated positive response and good tolerability.

Monoclonal antibody use is key in the RR setting, especially the promising anti-CD38 DARA. DARA was shown to have single-agent activity in heavily pretreated refractory patients, with even greater responses in triplet combinations [13, 24, 25]. ELO–POM–DEX also demonstrated superiority to POM–DEX alone in the ELOQUENT-3 trial in LEN and BOR refractory patients, suggesting its possible usefulness in these patients [26].

For relapsed patients on LEN maintenance, we therefore recommend treatment as if LEN refractory with reliance on a DARA and PI/IMiD combination (DARA–BOR–DEX, DARA–CFZ–DEX, DARA–POM–DEX). CFZ–DEX is also an option when DARA is not available or not tolerated. Finally, heavily refractory patients can be enrolled in trials evaluating new bispecific or conjugated mAbs among other novel drugs, as well as the use of CAR-T-cell therapy when applicable.

Early relapse NOT on LEN maintenance

Patients who relapse while not on LEN maintenance should not be considered LEN refractory and the paradigm of their treatment should revolve around LEN. Triplet combinations like CFZ–LEN–DEX, DARA–LEN–DEX, or even IXA–LEN–DEX are all standard and can be used, tailored to patient profile, previous responses to prior therapy and availability.

Late relapse

Almost all, if not all, myeloma patients eventually relapse, but while early relapses are usually aggressive and dismal, late relapses (>24 months) generally have a more indolent course. In addition, patients would usually have had time to recover, with little residual toxicity from previous interventions allowing more aggressive approaches. Patients in this setting should be considered as having responded to previous treatment and offered second induction with PI and IMiD-based combinations like BOR–LEN–DEX followed by salvage ASCT. Data from the VISTA and MM-015 studies suggest that the reuse of BOR and LEN, respectively, had response rates around 50–60%, while the RETRIEVE trial also evaluated the role of retreatment with BOR for previous responders and reported ORR around 40% [27–29]. Even in the era of novel agents, salvage ASCT appears to increase PFS and OS in RRMM, especially in late relapses, with its benefits mostly observed after the first relapse as previously alluded by the Myeloma X and ReLApsE trials [16, 30–32]. Outcomes can be further improved using novel reinduction, conditioning and maintenance strategies, but delaying salvage ASCT to third-line treatment or later might not provide the same level of efficacy as providing ASCT immediately after the first relapse. Despite being potential candidates for salvage ASCT, a significant proportion of patients will not make it to transplant in light of their comorbidities, the lack of stem cells collection, or even patient refusal. This pose yet new challenges not easily surmountable.

Late relapses can present aggressively, often observed in those with high-risk disease and those that relapse while on LEN maintenance. Even when presenting beyond the 24 months cutoff, these patients may be considered LEN refractory, and should be treated like their early relapse counterparts with the inclusion of novel agents during induction, namely DARA, CFZ, and POM.

How long to treat

The final challenge in treating RRMM is determining the duration of treatment (DOT) and whether continuous/prolonged therapy versus short duration improves outcomes. The role of LEN maintenance has been well established in not only delaying progression, but also in improving OS in RRMM, with ongoing investigations suggesting possible similar benefits from PIs like BOR and IXA [33–35]. When treating older frailer patients though, physicians tend to be reluctant with indefinite treatment due to toxicity questioning whether treatment would actually improve outcomes. A large multicenter cohort of RRMM patients treated in routine care in the United States was conducted, and results suggest that longer DOT lead to significant improvement of 1-year OS from the initiation of second-line therapy [14]. Comparing DOT and time with next therapy (TTNT), it was found that TTNT is more than two-fold longer than duration of second-line therapy suggesting that treatment was often discontinued for reasons other than disease progression, unlike the clinical trials setting. Most importantly, the observed clinical benefit of continued long-term treatment at relapse was generalizable to all patients irrespective of their heterogeneity. While younger patients (<75 years) did have a more impactful benefit, a positive duration-survival relationship was still observed in the older population. This suggests that regardless of age, maintenance should be offered until disease progression, not a currently routine practice according to this study findings.

Second-generation PIs

The ASPIRE trial is a randomized phase III trial, which compared the combination of the second-generation PI, CFZ (20 mg/m^2 on days 1 and 2 of cycle one; 27 mg/m^2 thereafter), with LEN and dexamethasone (DEX) to the

Table 2 Proteasome inhibitors trials

Study	Median follow-up	*N*	Treatment	Outcome	
				PFS	**OS**
ASPIRE	48.8 months	396	CAR–LEN–DEX	26.1 months	48.3 months
	48 months	396	LEN–DEX	16.6 months	40.4 months
				(HR 0.66; 95% CI 0.55–0.78; $P < 0.0001$)	(HR 0.79; 95% CI 0.67–0.95; $P = 0.0045$)
				OS	
ENDEAVOR	15.9 months	464	CAR–DEX	47.6 months	
		465	BOR–DEX	40 months	
				(HR 0·79; 95% CI 0.648–0.964; $P = 0.010$)	
				PFS	
TOURMALINE-MM1	15 months	360	IXA–LEN–DEX	20.6 months	
		362	Placebo–LEN–DEX	14.7 months	
				(HR 0.74; 95% CI 0.587–0.939)	

standard LEN–DEX [11]. A series of 792 patients with RRMM were randomized to one of the two treatment arms and randomization was stratified by β_2-microglobulin, and prior use of BOR and LEN. The primary end point was PFS, which was significantly improved with CFZ (median 26 months vs 17 months in the control group). At 18 months, the hazard ratio (HR) was 0.55. The median improvement in overall survival (OS) observed in the CFZ group compared with that of the control group was found to be 8 months and was statistically significant (HR 0.79; $P = 0.0045$). In conclusion, the combination of CFZ and LEN demonstrated a statistically significant and clinically meaningful 21% risk reduction of death and should be considered a standard of care in RRMM (Table 2).

ENDEAVOR is a phase III trial directly comparing CFZ (20 mg/m^2 on days 1 and 2 of cycle 1; 56 mg/m^2 thereafter) with BOR–DEX in RRMM [12]. It included 929 patients, 464 assigned to CFZ and 465 to BOR. Median OS was 48 months in the CFZ group versus 40 months in the BOR group, a statistically significant finding. CFZ therefore provided a significant and clinically meaningful risk reduction of death when compared with BOR, a breakthrough in the relapse setting of MM. This study is of significant importance when deciding on a proper PI choice for such patients.

CFZ may be associated with an increased toxicity. In the ASPIRE trial, observed grade ≥3 adverse events (AEs) included acute renal failure (4% vs 3%), cardiac failure (4% vs 2%), ischemic heart disease (4% vs 2%), hypertension (6% vs 2%), and thrombocytopenia (20% vs 15%). ENDEAVOR also suggested increased toxicity with 81% grade ≥3 AEs in the CFZ group compared with 71% in the BOR group (59% vs 40% serious AEs), most frequently anemia (16% vs 10%) and hypertension (15% vs 3%). As such, great care must be taken when selecting patients for infusion with CFZ to ensure they are more likely to benefit from, than be harmed by the drug's toxicities.

Twice weekly CFZ at 27 mg/m^2 is currently approved and standard for the treatment of RRMM. Optimal dosing strategies however have been investigated, with an established maximum tolerated dose of 70 mg/m^2 in the phase 1/2 CHAMPION-1 study [36]. The ARROW trial is a phase III randomized open-label trial comparing PFS in patients with RRMM given once weekly CFZ (20 mg/m^2 day 1 of cycle 1; 70 mg/m^2 thereafter) versus twice weekly CFZ (20 mg/m^2 days 1 and 2 of cycle 1; 27 mg/m^2 thereafter) [37]. Four hundred and seventy-eight patients were included (240 once weekly; 238 twice weekly). Median PFS was significantly higher in the once weekly group (11 months vs 7·6), with a slight increase in grade 3 or worse AEs incidence (68% vs 62%). Once weekly CFZ at 70 mg/m^2 significantly prolonged PFS compared with the twice weekly administration with comparable overall safety between the groups. It appears safe and more effective with a convenient dosing schedule.

The TOURMALINE-MM1 study results led to the approval of the other second-generation PI, IXA, a reversible PI and the only orally administered one [38]. This randomized, double-blind, placebo-controlled phase III trial comprised 722 RRMM patients with measurable disease, who were not refractory to PIs or LEN and satisfied several clinical and laboratory criteria including a creatinine

Table 3 Pomalidomide trials

Study	Median follow-up	*N*	Treatment	Outcome	
				PFS	
NIMBUS	10 months	302	POM–Ld–DEX	4.0 months	
		153	Hd–DEX	1.9 months	
				(HR 0.48; 95% CI 0.39–0.60; $P < 0.0001$)	
				PFS	**OS**
STRATUS	16.8 months	682	POM–Ld–DEX	4.6 months	11.9 months
				(95% CI 3.9–4.9)	(95% CI 10.6–13.4)
				PFS	
OPTIMISMM	16 months	281	POM–Ld–DEX	11.2 months	
		278	BOR–Ld–DEX	7.1 months	
				(HR 0.61; 95% CI 0.49–0.77; $P < 0.0001$)	

Ld low dose, *Hd* high dose

clearance of ≥30 mL/min. The trial compared the triple combination of IXA–LEN–DEX with placebo–LEN–DEX. The primary endpoint was PFS [7], and secondary endpoints included OS, as well as OS in high-risk patients carrying deletion of chromosome 17. The study completion date however is estimated to be around December 2020, and hence median OS is yet to reached in both groups. All patients received treatment in 28-day cycles until disease progression or unacceptable toxicity. An intention to treat analysis showed that median PFS with the addition of IXA was significantly better than the standard of care group (21 months vs 15 months; $P = 0.012$). The HR for disease progression or death was 0.74 [38]. The rates of both serious AEs and death were similar in the two study groups. AEs of at least grade 3 severity occurred in 74% and 69% in the IXA and control groups, respectively. In terms of all grade nonhematologic AEs, upper respiratory tract infections, peripheral neuropathy, and gastrointestinal AEs including diarrhea, constipation, nausea, and vomiting were more frequently observed in the IXA group. These side effects however are all relatively easily manageable with symptomatic therapy. Due to this, IXA use as an oral agent proved feasible and especially convenient in older and frailer patients.

Immunomodulatory drugs (IMiDs)

NIMBUS is a multicenter, open-label, randomized phase III trial where RRMM patients who failed at least two previous treatments of BOR and LEN were randomized to either POM plus low-dose DEX, or high-dose DEX [21]. The primary endpoint was PFS. Three hundred and two patients received POM plus low-dose DEX and 153 high-dose DEX. After a median follow-up of 10 months, median PFS with POM was 4 months versus 2 months with high-dose DEX (HR 0.48; $P < 0.0001$). The most common grade 3/4 hematological AEs in the POM versus high-dose DEX groups were neutropenia (48% vs 16%), anemia (33% vs 37%), and thrombocytopenia (22% vs 26%); and grade 3/4 non-hematological AEs included pneumonia (13% vs 8%), bone pain (7% vs 5%), and fatigue (5% vs 6%). Treatment-related AEs leading to death were 4% in the POM group and 5% in the high-dose DEX group (Table 3).

The STRATUS study also assessed safety and efficacy of POM plus low-dose DEX in RRMM [22]. A total of 682 patients who failed treatment with BOR and LEN (80% to both) with adequate prior alkylator therapy were enrolled, with safety as the primary end point and secondary end points including overall response rate (ORR), duration of response (DOR), PFS, and OS. Median number of prior regimens was 5. Median follow-up was 17 months, and median DOT was 5 months. Most frequent grade 3/4 hematologic AEs included neutropenia (50%), anemia (33%), and thrombocytopenia (24%), and nonhematologic were pneumonia (11%) and fatigue (6%). The ORR was 33%, and the median DOR was 7 months. Median PFS and OS were 5 months and 12 months, respectively. This study further supports that POM plus low-dose DEX in RRMM patients offers both clinically meaningful benefit and is generally well tolerated.

Another randomized, multicenter, open-label phase III trial called OPTIMISMM, tested the efficacy of the combination therapy comprising POM–BOR–DEX [23]. The control group received BOR–DEX only, currently approved although not as popular as LEN–DEX in some countries. A total of 559 patients with RRMM were randomized with the primary endpoint being PFS. ITT analysis proved

Table 4 Monoclonal antibodies trials

Study	Median follow-up	*N*	Treatment	Outcome	
				PFS	**OS**
ELOQUENT-2	48 months	321	ELO–LEN–DEX	19.4 months	48.3 months
		325	LEN–DEX	14.9 months	39.6 months
				(HR 0.71; 95% CI 0.59–0.86)	(HR 0.78; 95% CI 0.63–0.96)
				PFS	
ELOQUENT-3	9.1 months	60	ELO–POM–DEX	10.3 months	
		57	POM–DEX	4.7 months	
				(HR 0.54; 95% CI 0.34–0.86; $P = 0.008$)	
				PFS	**PFS2**
POLLUX	32.9 months	286	DARA–LEN–DEX	Not reached	Not reached
		283	LEN–DEX	17.5 months	32.3 months
				(HR 0.44; 95% CI 0.34–0.55; $P < 0.0001$)	(HR 0.52; 95% CI 0.38–0.67; $P < 0.0001$)
				PFS	**PFS2**
CASTOR	26.9 months	251	DARA–BOR–DEX	16.7 months	Not reached
		247	BOR–DEX	7.1 months	20.7 months
				(HR 0.32; 95% CI 0.25–0.4; $P < 0.0001$)	(HR 0.47; 95% CI 0.36–0.63; $P < 0.0001$)
				PFS	**12-month PFS**
NCT01998971	4.5 months	85	DAR–CFZ–DEX	Not reached	74% (65% in lenalidomide refractory)
				PFS	**OS**
NCT01998971	13.1 months	103	DARA–POM–DEX	8.8 months	17.5 months
				(95% CI 4.6–15.4)	(95% CI 13.3–Not estimable)

superiority of POM therapy over the control group with a 39% risk reduction of disease progression or death. At a median follow-up of 16 months, median PFS was 11 months in the POM group versus 7 months in the control group (HR 0.61; $P < 0.0001$). Although follow-up is rather short, these results are indeed promising. In addition, patients who received 1 prior treatment line were more likely to benefit from the addition of POM whereby risk of disease progression/death was reduced by a significant 46%. The median PFS was 21 months versus 12 months with POM versus control, respectively (HR 0.54; $P = 0.0027$). These results are in concordance with those of other combination therapies mentioned above. In terms of side effects, the most frequent grade 3/4 AEs were neutropenia (although not necessarily significant when uncomplicated), infections, and thrombocytopenia.

POM has therefore proven to be very effective in the RR setting, with significant results in very advanced relapses including LEN-refractory patients and high-risk cytogenetic diseases. However, these responses remained short-lived urging the necessity of earlier POM usage, whether with classical agents such as CY or BOR, or even more recent drugs including CFZ and DARA. POM–CY–DEX combinations are currently being evaluated, with the addition of CY yielding greater response rates compared with POM–DEX alone, and proving high tolerability, easy administration, and cost effectiveness. This suggests that alkylating agents could still have a role in the relapse setting, and that they can be used when appropriate [39–41].

Monoclonal antibodies (mAbs)

mAbs have paved the way for modern treatments of hematological malignancies and MM is no exception. This family of novel agents has been found to have a great impact not only in the relapse setting, but also as part of front-line therapy. Historically, several mAbs were extensively tested and yet failed in RRMM, such as rituximab (anti-CD20), lucatamumab (anti-CD40), lorvotozumab (anti-CD56 + maytansine), AVE1642 (anti-IGF1-R), BT062 (anti-CD138 + maytansine), and siltuximab (anti-Il6) among many others (Table 4).

ELO however was the first mAb to be approved in RRMM, following the ELOQUENT-2 study, a randomized, multicenter, phase III trial. In this study, ELO was combined with LEN and DEX and compared with LEN–DEX [42]. ELO has no single-agent activity and acts by targeting

CS1 (also known as SLAMF7) on plasma cells. Only RRMM patients that had already received 1–3 prior lines of treatment and were nonrefractory to LEN were included. At the extended 4-year follow-up, there was a 29% risk reduction of progression/death (HR 0.71) when using ELO [43]. OS was also improved in the ELO arm (50% vs 43%) with similar long-term safety profiles between the two arms. While results were positive, and ELO use is indeed safe, its action remains relatively slow with modest improvements compared with other drugs. Great care must therefore be taken when selecting appropriate patients who would benefit from ELO treatment combinations.

More recently published results of the phase II ELOQUENT-3 trial have shown that in MM patients refractory to LEN and a PI, the risk of progression/death was significantly lower among those who received ELO–POM–DEX compared with POM–DEX alone [26]. Median PFS was 10 months in the ELO group versus 5 months in the control group with a HR for disease progression/death of 0.54 ($P = 0.008$). The most common grade 3/4 AEs in both groups were neutropenia, anemia, and hyperglycemia and infusion reactions occurred in only three patients (5%) in the ELO group.

Currently, the most promising mAbs in MM are those directed against CD38 such as DARA, isatuximab and MOR202. Isatuximab (formerly known as SAR650984), a chimeric mAb, is currently under investigation in phase III trials [44]. MOR202, a humanized IgG1 CD38 mAb, has shown single-agent activity in preclinical models of MM and synergy in combination with the IMiDs LEN and POM, displaying promising preliminary efficacy and long-lasting tumor control [45].

The humanized IgG1 mAb DARA, was the first anti-CD38 to be approved and is currently the most widely available and used, both in the relapse and front-line setting. DARA has multiple mechanisms of action [46–50]. By targeting the highly expressed CD38 antigen on myeloma plasma cells, DARA directly induces tumor cell death. In addition, it has an immunomodulatory effect by activating potent cytotoxic immune effector functions. DARA also has an immune-mediated effect with data suggesting that apart from direct plasma cell targeting, it also allows for the expansion and skewing of T-cells shifting the immune response away from regulatory and suppressive cells. DARA has a single-agent activity and is currently approved in many countries as monotherapy for patients with heavily treated RRMM.

Two phase III trials investigating DARA in combination with standard of care regimens LEN–DEX and BOR–DEX, have demonstrated a significant benefit in PFS upon the addition of DARA in patients who previously received ≥ 1 treatment.

The first of these, the POLLUX trial, is a multicenter, randomized, open-label, active-controlled phase III trial in RRMM patients who had been exposed to but are not refractory to LEN, received ≥1 prior lines of therapy and who had a creatinine clearance of ≥30 ml/min [51–53]. Stratified randomization (1:1) was by number of prior lines of therapy, ISS stage at study entry and prior LEN use. At a median follow-up of 33 months, DARA dramatically improved PFS (median not reached vs 17.5 months; HR 0.44; $P < 0.0001$) and was associated with a 56% risk reduction of progression/death [53]. The 30-month PFS rates were 58% versus 35%, respectively. DARA also significantly improved the ORR (93% vs 76%; $P < 0.0001$) with 51% versus 21% achieving a CR [51]. The DARA combination also allowed for impressive unique levels of MRD-negativity in such relapse settings, with rates of 27% versus 5% at 10^{-5} sensitivity ($P < 0.0001$), an important finding especially in light of the increasing evidence linking MRD-negativity to survival [51]. The OS benefit cannot yet be evaluated, but PFS2 can be considered a good surrogate marker for OS [51]. PFS2 is defined as the time from randomization to disease progression after the next line of subsequent salvage therapy or death [51]. In the POLLUX trial, the 30-month PFS2 was also significantly better with DARA compared with control, (median not reached vs 32 months; HR 0.51; $P < 0.0001$), with rates of 73% and 58%, respectively; suggesting that DARA does not appear to negatively impact subsequent therapy [51]. AEs were mainly associated with infusion-related reactions, and most common grade 3/4 AEs were neutropenia, thrombocytopenia, and anaemia [53].

The CASTOR trial is another multicenter, randomized, open-label, active-controlled phase III trial that included 498 RRMM patients who had been exposed to but were not refractory to BOR [54–56]. Patients were randomized to either DARA–BOR–DEX or BOR–DEX alone. Of note is that the control group received only eight cycles of treatment repeated every 21 days while the DARA arm received the combination continuously (cycles 9+, repeated every 28 days). The primary end-point of the study was PFS, which after a median follow-up of almost 27 months, was significantly prolonged in the DARA group, with a median of 17 months versus 7 months in the ITT population (HR 0.32; $P < 0.0001$) and 24-month PFS rates of 37% versus 5%, respectively [57, 58]. In patients who previously received one line of therapy, PFS was also significantly prolonged in the DARA arm with a median of 26 months versus 8 months (HR 0.23; $P < 0.0001$). The 24-month PFS rates were 55% versus 8%, respectively [59]. It must be stressed however, that the control arm therapy of BOR–DEX is not ideal and not widely used, and that PFS rates of 5% and 8% are relatively low even for a control

Table 5 Other novel treatments

Study	*N*	Treatment	Outcome		
			PFS	**OS**	**ORR**
STORM	122	Selinexor–DEX	3.7 months	8.6 months	26%
			PFS	**ORR**	
STOMP	42	Selinexor–BOR–DEX	9 months	63%	
			PFS	**ORR**	
NCT02343042	34	Selinexor–POM–DEX	10.3 months	55%	
			PFS	**OS**	**ORR**
PANORAMA	387	Panobinostat–BOR–DEX	12 months	34 months	61%
	381	BOR–DEX	8 months	30 months	55%
			PFS	**OS**	**ORR**
NCT01549431	32	Panobinostat–CFZ	8 months	23 months	63%
				ORR	
NCT01794507	66	Venetoclax–BOR–DEX		67%	
			PFS	**OS**	**ORR**
NTC02188537	34	Nelfinavir–BOR–DEX	12 months	12 months	65%

regimen. Nevertheless, these results are still encouraging, and many patients may benefit from similar DARA combinations. The CASTOR trial also looked at PFS2 as a surrogate marker for OS, with a median PFS2 in the ITT DARA group "never reached" versus 21 months in the control group (HR 0.47; $P < 0.0001$). The 24-month PFS2 rates were 68% versus 42%, respectively. Again, it is evident that salvage treatment is possible with the continuously increasing availability of novel agents. The safety profile of DARA also remained consistent with earlier reports after longer follow-up [56, 59].

Triple combinations with DARA were consistently superior to the standard double combinations in all prognostic subgroups including patients with high-risk cytogenetics and regardless of age or the number of prior lines of therapy. However, the benefit was still most evident in the first relapse setting encouraging a non-delaying strategy when using DARA in RR patients [13].

DARA was also evaluated with the second-generation PI CFZ as DARA–CFZ–DEX in a phase 1b study including 60% LEN-refractory RRMM patients [25]. Eighty five patients were included, and received CFZ weekly on days 1, 8, and 15 of each 28-day cycle (20 mg/m^2 initial dose, 70 mg/m^2 thereafter), DEX 40 mg/week, and DARA as per approved schedule. Toxicities were similar to other combinations with most common grade 3/4 AEs being thrombocytopenia (31%), lymphopenia (24%), anemia (21%), and neutropenia (21%) with almost half of patients developing infusion-related reactions. ORR was 84% (79% in LEN refractory), median PFS was not reached and 12-month PFS rates were 74% for all-treated patients (65% for LEN refractory). DARA–CFZ combinations appear promising, pending phase III results to fully understand their contributions to RR setting.

Another non-randomized trial of a DARA combination therapy (DARA–POM–DEX) was evaluated in RRMM patients treated with ≥2 prior lines of therapy who were refractory to their last treatment [24]. The primary endpoint of the study was safety while secondary endpoints were ORR and MRD-negativity. A total of 103 patients were included with a median of four prior therapies. The safety profile of the DARA–POM–DEX group was found to be very similar to that of the historically observed POM–DEX group, except for some increased DARA-specific infusion-related reactions (50%) and a higher incidence of neutropenia with no increased infection rate. The ORR was 60%, and among patients with CR, 29% were MRD-negative at a threshold of 10^{-5}. At a median follow-up of 13 months, the median PFS was 9 months and median OS was 17.5 months, with an estimated 1-year survival rate of 66%. Deep, durable responses with a tolerable safety profile were therefore observed in heavily treated patients given DARA, which is consistent with the previously presented results.

Other novel agents

With novel therapies always on the rise, it is exciting to witness the emergence of entirely new families of novel agents being developed and eventually being added to the already existing available arsenal (Table 5).

Selinexor, a first-in-class oral selective inhibitor of nuclear export (SINE), works by blocking the action of a protein called XPO1 found within the nucleus of MM cells resulting in the accumulation of tumor suppressors, inhibition of NF-KB and suppression of several oncoproteins. It proved to be most effective when combined with other

currently available treatments such as BOR and DEX, with early stage clinical trials showing effective responses in myeloma patients who are relapsed and/or refractory to several prior treatments [60].

STORM is a phase IB/II trial evaluating selinexor in combination with low-dose DEX in both quad-refractory (BOR, CFZ, LEN, and POM) and penta-refractory (BOR, CFZ, LEN, POM, and DARA) MM patients [61]. Recently presented results show an ORR of 26% along with rapid and deep responses, with two patients even achieving stringent complete remission [62]. These results are very impressive considering how heavily pretreated these patients were (median 7 prior regimens, 53% high risk) especially with no severe AEs or organ toxicities reported. Selinexor has been granted Orphan Drug Designation and Fast Track designation in penta-refractory MM patients in light of these results.

Selinexor has also been evaluated in triplet regimens including BOR–DEX in the phase IB/II Selinexor and Backbone Treatments of Multiple Myeloma Patients (STOMP) study with similarly encouraging results. ORR for both PI-refractory and nonrefractory patients was 63% (43% for PI-refractory and 84% for PI-nonrefractory). Median PFS for all patients was 9 months (6 months for PI-refractory and 18 months for PI-nonrefractory) [63].

Selinexor is also being evaluated in other combinations in the relapse setting with POM–DEX as an all oral combination with similarly promising results (ORR up to 55% and PFS of 10 months), albeit the rates of toxicities and especially dose limiting toxicities were significantly higher [64].

Panobinostat (PAN) is a pan-histone deacetylase inhibitor (HDACi) exerting activity on class I, II, and IV HDACs, regulating cell cycle, apoptosis, and intracellular protein homeostasis [65, 66]. While PAN monotherapy only showed modest single-agent activity among RRMM patients in a phase II study [67], its mechanism of action and preclinical data suggest possible synergy with PIs. In fact, HDACis and PIs both regulate misfolded proteins metabolism leading to their intracellular accumulation by respective inhibition of proteasome and aggresome [68].

PAN–BOR–DEX combination was evaluated in RRMM patients in the placebo-controlled, phase III PANORAMA-1 study. The combination proved effective, with reported median PFS of 12 months with PAN versus 8 months with BOR–DEX alone, which led to the drug's FDA approval for RR patients who have received at least two prior therapies, including BOR and an IMiD [69]. But despite its effectiveness, the combination was burdened by significant rates of grade 3/4 AEs mainly thrombocytopenia (67%) and gastrointestinal (GI) toxicity (25%), due to their overlapping toxicity profiles [69, 70].

A phase I study on 32 patients was therefore conducted, evaluating the combination of PAN with the second-generation PI CFZ administered until progression. Maximum tolerated doses for CFZ and PAN were found to be 36 mg/m2 (on days 1, 2, 8, 9, 15, and 16) and 20 mg (3 times per week, 3 weeks on/1 week off, every 28 days), respectively. Most common grade 3/4 AEs were thrombocytopenia (41%), fatigue (17%), and nausea/vomiting (12%). The ORR and clinical benefit rate were 63% and 68%, respectively. Median PFS and OS were 8 and 23 months, respectively. Interestingly, no differences in terms of ORR, PFS, or OS were observed between BOR-sensitive and -refractory patients. PAN–CFZ proved a safe and effective steroid-sparing regimen for heavily pretreated RRMM patients [71].

Venetoclax is a selective, orally bioavailable BCL-2 inhibitor that induces cell apoptosis in MM cells, particularly in those harboring t(11;14) which is associated with higher ratios of BCL-2/BCL-2 L1, a positive predictor of Venetoclax response [72]. Venetoclax monotherapy has an acceptable safety profile, and could be an excellent targeted therapy for MM, especially t (11,14)+. The triple combination of venetoclax–BOR–DEX was also tested in a phase IB trial in patients with RRMM [73]. The triplet appeared to be safe and efficacious even in patients without t(11,14).

The oral anti-HIV drug nelfinavir has shown interesting in vitro results when combined with PIs, allowing an induced response in otherwise PI-resistant MM cells. An unprecedented ORR of 65% in BOR, LEN, and POM triple-refractory patients has been reported after receiving a nelfinavir–BOR–DEX combination, which warrants further investigation to explore its potential synergistic benefit in well-established PI combinations [74].

New immunotherapy strategies for RRMM

Chimeric antigen receptor (CAR) T-cell therapy is another therapy on the rise for cancer treatment and is being tested in a number of different hematological malignancies. T-cells are harvested either from the patient himself (autologous), or from another donor (allogeneic); genetically engineered to express a specific CAR, programming them to target a specific antigen only (or preferentially) expressed on the surface of malignant cells; and then reinfused into the patient. This reengineering allows the cells to overcome the HLA barriers by forcefully redirecting the T-cell receptor toward the tumor antigen inducing proliferation of high affinity T-cells and killing of tumor cells.

CAR-T-cell therapy (especially autologous) is a complex multistep procedure, which necessitates the identification of a disease specific tumor antigen with the production of a high-affinity antibody. Efficacy must hence be assessed both in vitro and in vivo with murine models, for safety is

Table 6 CAR-T-cells trials

Study	Median follow-up	*N*	Treatment	Outcome	
				PFS	**ORR**
CRB-401	35 weeks	21	bb2121	Not reached	94%
				PFS	**OS**
NCT03090659	8 months	57	LCAR-B38M	15 months (95% CI 11—Not estimable)	Not reached

paramount in avoiding cross reactions with essential normal tissues.

CAR-T-cell therapy: potential antigens in myeloma

Selecting the correct antigen for a given tumor is perhaps the most challenging step when it comes to CAR-T-cell therapy, especially in multiple myeloma due to its diverse potential targetable antigens. The most currently used targets in MM are CD138 (also known as Syndecan-1), Kappa-light chain and CD19 although infrequently expressed on myeloma cells. The first proof of concept case report was published in 2015 and was of a CAR-T-cell therapy directed against CD19 [75]. SLAMF7, targeted by ELO, is also an attractive antigen for MM CAR-T cells. Currently though, the most appealing and widely tested target is the B-cell maturation antigen (BCMA). BCMA is a member of the tumor necrosis factor receptor superfamily and is expressed by both plasma cells and some mature B cells. BCMA is universally expressed in MM, and even in a subset of lymphomas, and hence in terms of safety and efficacy, one would expect BCMA CAR-T cells to be both highly sensitive and specific. When studying BCMA knockout mice, the animals were found to be healthy, of normal physical appearance and had normal B cell counts [76]. Only the long-term survival of plasma cells seemed to be impaired suggesting indeed a good safety profile for patients receiving BCMA CAR-T cells as there does not appear to be any cross reactivity with other healthy tissues [76].

Trials of CAR-T-cell therapy

Promising early results have recently been reported from the CRB-401 trial, a phase I multicenter study with a second-generation CAR-T-cell therapy called bb2121 [77]. This trial of 43 patients included a dose-escalation phase ($n = 21$) and a dose-expansion phase ($n = 22$). Patients received a single infusion of bb2121 following a 3-day lymphodepletion with fludarabine/cyclophosphamide (Table 6). This trial has shown that in the dose-escalation phase, patients receiving an active dose achieved a median PFS of 12 months. In the 16 responding patients achieving MRD-negativity, the median PFS was 18 months. These results are quite significant since these patients were all highly refractory with very advanced disease whereby half of them had already been exposed to more than seven lines of therapy. Several AEs were encountered however. Cytokine release syndrome (CRS), a well-documented potentially fatal complication of CAR-T therapy, occurred in 67% of patients, with tocilizumab (anti-IL6R) remaining its only approved treatment. Furthermore, 33% of patients experienced neurotoxicity, another important side effect for which the exact pathophysiology remains unknown. Other AEs observed were neutropenia (81%), thrombocytopenia (61%), anemia (56%), and infection (61%). Other trials evaluating bb2121 including the phase II KarMMa trial are currently ongoing [78].

Another CAR-T being evaluated in MM is LCAR-B38M, a dual epitope-binding CAR-T-cell therapy directed against 2 distinct BCMA epitopes [79]. An ongoing phase I, single-arm, open-label, multicenter study enrolled patients with RRMM who received LCAR-B38M CAR-T cells in three separate infusions. The primary objective was to evaluate the safety of LCAR-B38M CAR-T cells and the secondary was to evaluate the antimyeloma response to the treatment based on the guidelines of the International Myeloma Working Group. Fifty-seven patients received LCAR-B38M CAR-T cells, all of whom experienced at least one AE. Indeed, 65% of the patients reported grade ≥ 3 AEs including leukopenia (30%), thrombocytopenia (23%), and increased liver enzymes (21%). Importantly, CRS occurred in 90% of patients with 7% experiencing an advanced grade (≥3). The ORR was reported to be 88% with 68% of patients achieving CR and 63% reaching MRD-negativity. Median PFS was 15 months, and OS was never reached. As such, LCAR-B38M CAR-T-cell therapy demonstrated safety and deep, durable responses in patients with RRMM.

Other immunotherapies targeting BCMA

Antibody-drug conjugate is a growing class of cancer therapeutics composed of recombinant mAbs covalently bound to cytotoxic chemicals (payload) via synthetic chemical linkers. The mAbs bind to their specific tumor antigen and are then internalized together with the attached cytotoxic payload.

GSK285791 is a humanized IgG1 mAb with high affinity to BCMA and uses non-cleavable linker (maleimidocaproyl) with a new class of antimitotic agents (monomethyl auristatin F) as payload [80]. GSK2857916 was evaluated in a phase I study on heavily pretreated RRMM patients, with dose-escalating and expansion parts [81]. GSK2857916 monotherapy demonstrated a 60% response rate and a median PFS of 8 months with an acceptable toxicity profile; and has recently been awarded Breakthrough Therapy designation from the FDA and received PRIME designation from the European Medicines Agency.

Other antibody-drug conjugates such as HDP-101 and MEDI2228 have also demonstrated potent in vitro cytotoxicity against BCMA-expressing MM cell lines with early ongoing clinical trials [82, 83].

Bispecific T-cell engager (BiTE) is a single-chain variable fragment (scFv) composed of two linked mAbs (bispecific antibodies) that mainly target CD3 on the surface of T-cells and tumor-associated antigens. This unique structure allows BiTE to engage T-cells with tumor cells promoting antitumor cytotoxicity and cytokine production [84].

AMG 420 is a bispecific T-cell engager targeting BCMA. Recent phase I trial results showed that the drug elicited a response in 31% of patients and was associated with relatively manageable side effects [85]. BI836909 is another bispecific T-cell engager that binds to BCMA-expressing MM cells, ultimately leading to T-cell activation and lysis of BCMA + MM cells [86]. Mouse and monkey models have shown that BI836909 leads to tumor shrinkage and bone marrow plasma cell depletion along with prolonged survival [86].

BiTE technology may be a safe and effective treatment for patients with RRMM, with more clinical data required to fully understand its treatment role and potential.

Conclusion

Up until today, treatment of RRMM remains very challenging. While the integration of novel agents into treatment regimens offers the possibility of long-term survival and improved quality of life, the constantly emerging combination therapies for front-line use challenges our choice of optimal therapy. For instance, DARA that had been reserved for relapsed disease is currently approved for use in the front-line setting, thus leaving clinicians at a dilemma when encountering relapsed patients already exposed to the drug. Another major challenge is the constantly evolving control group with which randomized trials cannot keep up. Many trials were designed before LEN had changed the maintenance landscape and by not including patients treated with LEN in the control arms, results must be analyzed with caution.

Many factors influence clinicians' decision-making regarding therapy in the RR setting. Patient symptomatology, accumulated toxicity and morbidity are widely heterogenous making treatment generalizability difficult. Patient age, although a factor, should not deprive patients from established beneficial treatments like DARA and LEN maintenance in fear of intolerance. The number and nature of prior therapy lines need to be taken into account to determine sensitivity to previously administered drugs that could be potential candidates for reuse. Time to relapse is prognostic, with early relapses being more aggressive requiring more novel agent incorporation like DARA, CFZ, and POM, whereas late relapses can be managed with reinduction and salvage ASCT. Finally, patient expectations and wishes are to be prioritized, especially since they can vary during the course of the disease. It is also important to mention that access to and affordability of novel drugs can pose serious challenges with widely heterogenous geographic availability. Therapy choice must therefore be based on availability and pharmaco-economics, with a need to address the expensive cost of next-generation combinations to maximize their worldwide access [87].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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