The changing landscape of relapsed and/or refractory multiple myeloma (MM): fundamentals and controversies

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Abstract

The increase in the number of therapeutic alternatives for both newly diagnosed and relapsed/refractory multiple myeloma (RRMM) patients has widened the clinical scenario, leading to a level of complexity that no algorithm has been able to cover up to date. At present, this complexity increases due to the wide variety of clinical situations found in MM patients before they reach the status of relapsed/refractory disease. These different backgrounds may include primary refractoriness, early relapse after completion of first-line therapy with latest-generation agents, or very late relapse after chemotherapy or autologous transplantation. It is also important to bear in mind that many patient profiles are not fully represented in the main randomized clinical trials (RCT), and this further complicates treatment decision-making. In RRMM patients, the choice of previously unused drugs and the number and duration of previous therapeutic regimens until progression has a greater impact on treatment efficacy than the adverse biological characteristics of MM itself. In addition to proteasome inhibitors, immunomodulatory drugs, anti-CD38 antibodies and corticosteroids, a new generation of drugs such as XPO inhibitors, BCL-2 inhibitors, new alkylators and, above all, immunotherapy based on conjugated anti-BCMA antibodies and CAR-T cells, have been developed to fight RRMM. This comprehensive review addresses the fundamentals and controversies regarding RRMM, and discusses the main aspects of management and treatment. The basis for the clinical management of RRMM (complexity of clinical scenarios, key factors to consider before choosing an appropriate treatment, or when to treat), the arsenal of new drugs with no cross resistance with previously administered standard first line regimens (main phase 3 clinical trials), the future outlook including the usefulness of abandoned resources, together with the controversies surrounding the clinical management of RRMM patients will be reviewed in detail.

Keywords: Multiple myeloma, Monoclonal antibodies, Proteasome inhibitors, Immunomodulatory drugs, New agents, Relapsed, Refractory

Background

Despite the increasing availability of more effective treatments for newly diagnosed multiple myeloma (MM) patients that provide longer disease-free periods, MM progresses in the vast majority of cases. Furthermore, the safety profile of modern drugs means that combinations of 3, 4 or more are now commonly used in the upfront treatment of MM in order to achieve a deeper, more prolonged response. For this reason, treating relapses after regimens that have included a proteasome inhibitor (PI), an immunomodulatory drug (IMID) and, sometimes, an anti-CD38 monoclonal antibody, can be challenging. The recent MM guidelines of the European Hematology Association-European Society of Medical Oncology (EHA-ESMO) include current second-line treatment options for patients who have...
received first-line drugs based on combinations of PI plus IMIDs or daratumumab-based therapies, as well as subsequent relapses [1]. This review provides updated information on novel agents for the treatment of relapsed/refractory MM patients and takes a critical look at the future outlook for clinicians working in this field.

**Basis for the clinical management of patients with relapsed/refractory multiple myeloma**

The development of several generations of new drugs since the first decade of this century has radically improved the prognosis of MM [2]. These advances are the sum of the transfer of new drugs to the front-line setting and the impact of their use as rescue therapies. For patients with relapsed/refractory multiple myeloma (RRMM), this has meant an increase in the number of therapeutic options with no cross resistance with first-line or previous salvage therapies [3]. This scenario differs greatly from previous situations in which the lack of therapeutic options meant that the only alternatives were chemotherapy [4], second autologous stem cells transplantations (ASCT) [5], or even retreatment with bortezomib, thalidomide or lenalidomide previously used in the first line.

**The complexity of the clinical scenarios in RRMM**

The large number of therapeutic alternatives currently available for MM patients gives rise to a wide range of possible clinical settings that cannot easily be covered by a single algorithm [6]. Currently, patients with MM achieve relapsed/refractory status (RR) after a range of therapeutic antecedents, ranging from primary refractoriness or early relapse after first-line treatment with latest-generation drugs, to very late relapse in patients treated with chemotherapy or autologous stem cell transplantation (ASCT) in the first line. Patients with RRMM previously treated with bortezomib (V) plus thalidomide (T) or lenalidomide (R) and dexamethasone (VTd or VRd) with ASCT who achieved median progression-free survival (PFS) of more than 5 years after front line treatments [7, 8] are not represented in the main RCT in RRMM, and are not considered in the algorithms proposed by most authors. This is also applicable to older RRMM patients, in whom first-line treatments with combination bortezomib, melphalan and prednisone, or the most recent monoclonal antibodies (mAbs), achieve a median PFS of more than 3 years [9]. Furthermore, in RRMM the variability of clinical scenarios increases as new lines of treatment are introduced after each episode of RRMM.

In general, the complexity of the contexts in which RRMM occurs is not adequately represented in the inclusion criteria of RCTs, in which the requirements regarding previous treatments are excessively generic, and frequently include euphemisms such as inclusion or exclusion due to prior “exposure” to a drug, without specifying dose, duration and response to treatment, associated drugs, or the interval from exposure to inclusion in the study, all of which are known to impact the efficacy of salvage treatments in MM. An additional confounding factor is the generalized inclusion requirement of “at least a progressive disease status with measurable disease” [10–19], which allows the inclusion of an undetermined percentage of patients in biological progression with a better prognosis than those showing clinical progression [20].

After all these considerations, the choice of treatment for a patient not represented in the main RCTs may be facilitated by resorting to some concepts that are well recognized in RRMM.

**Some keys to the choice of treatment**

In MM, the adverse biological factors present at diagnosis (increased Beta2-microglobulin, hypoalbuminemia, anemia, kidney failure, high-risk genetic abnormalities, high lactate dehydrogenase, extension of active lesions on positron emission tomography/computed tomography (PET/CT), high proliferative index, etc.) are also important in RRMM [21]. However, their relevance in the choice of a rescue treatment is limited. Little information can be gained from RCTs, as patients presenting poor prognostic factors are usually excluded from these clinical studies. Interestingly, real-life data suggest the prognostic significance of performance status or cytogenetics in RRMM patients treated with novel therapies [22, 23].

In RRMM patients, the choice of salvage treatment involves not only an analysis of the response to and toxicity of previous treatments, but also a detailed evaluation of MM-related or unrelated comorbidities. Obviously, primary refractoriness to a drug rules out its use in the management of RRMM. Nevertheless, in MM the rechallenge of a drug previously used with success in the treatment of the disease is still possible, despite a certain loss of efficacy that increases in parallel with the number of previous treatment lines [24–26]. Factors that determine the efficacy of rescue therapies are, i) the use of drugs with proven efficacy in MM other than those previously used, ii) the number of accumulated RRMM episodes and iii) the length of the previous time to progression.

The current arsenal of drugs available for the treatment of RRMM improves the results of drug retreatment [27], which was hitherto the only therapeutic alternative [28, 29]. When choosing a therapeutic alternative it is important to take into consideration the results of RCTs and the possible cross-resistance between drugs from the same therapeutic group, such as
the PIs bortezomib and carfilzomib [11], or the IMiDs lenalidomide and pomalidomide [30, 31].

The occurrence of RRMM episodes with increasingly reduced PFS periods will often exhaust the efficacy of new drug-based treatments. At this point, drug rechallenge [26], use of chemotherapy regimens [32, 33] or second ASCT [5] may halt progression for a limited period of time, though this may be long enough to allow patients to access to a new clinical study. Age, accumulated toxicities, and the anaplastic clonal evolution that is characteristic of very advanced stages of MM limit the efficacy of treatments in these final stages of the disease.

In a large study carried out by the Nordic Myeloma Study Group in patients treated in the 1990s [34], the duration of response to first-line treatment was identified as the prognostic factor with the greatest impact on RRMM. In this analysis, median overall survival (OS) in patients who relapsed after 6, 6 to 12, 12 to 24, and >24 months after ASCT was 3, 17, 28, and 37 months, respectively. Subsequent studies have confirmed that prolongation of the previous response or the length of the therapeutic pause before starting the next treatment favorably affects the prognosis of patients with RRMM after ASCT [35] or allogeneic transplant [36], non-transplanted patients treated with chemotherapy [37] or rescue-based therapies with new drugs [38, 39]. More recent studies confirm the adverse prognosis associated with early relapse [40]. Therefore, the previous time to progression or the duration and depth of the previous response, a prognostic factor systematically ignored in RCTs, is a determining factor in the choice of rescue treatments, and also in the increasingly frequent incidence of very late relapses as a result of the greater efficacy of first-line treatments [7, 8, 41]. RRMM patients previously treated with regimens that achieve long PFS periods could benefit from regimens used in the first-line setting and from new therapeutic opportunities. On the other hand, the time elapsed from the successful use of a drug in an advanced RRMM episode may favor rechallenge with drugs used previously, although obviously with limited results.

When to treat

The established International Multiple Myeloma Working Group (IMWG) criteria for treatment indication in patients with RRMM requires meeting the Progressive Disease or Clinical Relapse criteria of the IMWG [42]. These criteria, maintained since 1998 without major changes, were established at a time when retreatment with chemotherapy or a second autologous transplant were the only available options for RRMM patients [33, 34, 36, 43]. In both cases, the chances of success were conditioned by the length of time before starting treatment, a subclinical waiting time that was considered beneficial for the patient's quality of life. At present, however, patients with RRMM can even be treated with several consecutive lines using drugs that show no cross-resistance with those used in prior lines. At the same time, follow-up techniques based on minimal residual disease (MRD), PET/CT or mass spectrometry have improved, allowing early and accurate prediction of therapeutic failure [44–46]. Importantly, the definition of failure should probably include not only the possibility of predicting progression or recurrence, but also insufficient tumor shrinkage marked by the stagnation of an insufficient response [47]. Although the formal exploration of this approach to RRMM is in its initial phases, data on the superiority of early treatment of RRMM compared to initiating therapy in clinical relapse have already been released, and the influence of tumor burden on treatment efficacy and tolerability in any of the evolutionary phases of MM is well known [48, 49].

The arsenal of new drugs and therapies with no cross resistance with the therapeutic standards used in first line to date

PIs, IMiDs, MoAbs and corticosteroids constitute the cornerstone of treatment for patients with RRMM. Data from the main phase 3 RCTs are summarized in Table 1.

Proteasome inhibitors and new combinations

Carfilzomib (K) was approved in 2013 and, in combination with dexamethasone (Kd), has shown benefit compared to bortezomib plus dexamethasone (Vd) [11, 57]. When lenalidomide was added to Kd (KRd), overall response rate (ORR), PFS and OS improved compared to Rd, although the incidence of grade ≥3 adverse events (AEs) was similar [19, 58, 59]. Other combinations, such as the addition of pomalidomide to Kd (KPd), have been evaluated in 3 phase 1/2 RCTs (192 heavily treated patients who had a mean of 3.3 prior lines of therapy), reporting an ORR of 77.1% and a median PFS of 15.3 months [60–63]. Only one study reached an OS of 12 months [64]. So far, no phase 3 RCTs for this combination have been planned. Combinations of targeted therapy with CD38 MoAb, such as the combination of Kd plus daratumumab and Kd plus isatuximab, are a very interesting alternative IMiD-free approach, and have shown clinical benefits in terms of PFS with a favorable benefit-risk profile compared to Kd [50, 51].

The appropriate dosing schedule of K-containing combinations has also been explored in some studies. For example, administration of K once-weekly showed a favorable benefit-risk profile compared to the twice weekly schedule [16]. Other data also support the once-weekly dosing schedule, such as those obtained from triplet regimen with daratumumab in a phase 1 RCT (ORR = 84% and PFS not achieved with a short follow
| Study          | Arms                  | $N$  | Doses and schedule                                                                 | Follow-up (months) | Prior lines | PFS (months) | ORR (%) | ≥CR (%) | OS (months) | >G3 AE (%) |
|---------------|-----------------------|------|-----------------------------------------------------------------------------------|-------------------|-------------|--------------|---------|---------|-------------|------------|
| ASPIRE [19]   | KRd vs. Rd            | 792  | K, 20/27mg/m² BW; R, 25 mg PO, days 1 and 21; 28-days cycle/s.                    | 67.1              | 2 (1-3)     | 20.3 vs. 176 HR 0.690 | 87.1 vs. 66.7 OR 3.472 | 31.8 vs. 9.3 | 48.3 vs. 40.4 HR 0.794 | 87 vs. 833 |
|               |                       |      |                                                                                  |                   |             |              |         |         |             |            |
| ENDEAVOR [11] | Kd vs. Vd             | 929  | K, 20/56 4g/m² IV, BW, 28-days cycle; V, 1.3mg/m² SC/N, BW 21-days cycle/s.     | 12                | 2 (1-3)     | 18.7 vs. 94 HR 0.533 | 76.9 vs. 62.6 OR 2.032 | 13 vs. 6   | 47.6 vs. 40 HR 0.791 | An, 14 vs. 10 |
|               |                       |      |                                                                                  |                   |             |              |         |         |             |            |
| IKEMA [50]    | IsaKd vs. Kd          | 302  | Isa, 10mg/kg QW for 4w, then given Q2W, 28-days cycle/s.                        | 20.7              | 2 (1-3)     | NR vs. 19.15 HR 0.531 | 86.6 vs. 82.9 P 0.19 | 39.7 vs. 27.6 | NA         | 76.8 vs. 67.2 |
|               |                       |      |                                                                                  |                   |             |              |         |         |             |            |
| CANDOR [51]   | DKd vs. Kd            | 466  | D, 8mg/kg, 1’s 1-2 of cycle; 1, 16 mg/kg QW, days 8, 15 and 22 first 2 cycles, then Q2W, cycles 3-6 and every Q4W thereafter; 28-days cycle/s. | 17                | 2 (1-3)     | NR vs. 15.8 HR 0.630 | 84 vs. 75 OR 1.9 | 29 vs. 10 (MRQ, 18 vs. 4) | NA         | 82 vs. 74 |
|               |                       |      |                                                                                  |                   |             |              |         |         |             |            |
| ARROW [16]    | K QW vs. BW           | 478  | K, 20/70mg/m² QW vs. 20/27mg/m² BW; 28-days cycle.                              | 12.6 / 12         | 2 (46% vs 64%) (59% vs 67%) | 11.2 vs. 76 HR 0.690 | 62.9 vs. 40.8 OR 2.68 | 7 vs. 2  | NM         | 68 vs. 62 |
|               |                       |      |                                                                                  |                   |             |              |         |         |             |            |
| ARROW2 (NCT03859427) | KRd QW vs. BIW | 460 | K, 20/56mg/m² QW vs. 20/27mg/m² BW; 28-days cycle/s. | NM | 1-3 | NA² | NM | NM | NM | NM |
|               |                       |      |                                                                                  |                   |             |              |         |         |             |            |
| MM 003 [52]   | Pd vs. d              | 455  | P, 4mg PO, days 1 and 21; 28-days cycle/s.                                     | 10                | >2 (94.5% pts) | 4 vs. 1.9 HR 0.48 | 31 vs. 10 | 1 vs. 0 | 12.7 vs. 8 HR 0.74 | 88.7 vs. 84.7 |
|               |                       |      |                                                                                  |                   |             |              |         |         |             |            |
| ICARIA-MM [10] | IsaPd vs. Pd          | 307  | Isa ± Pd IV 10mg/kg, days 1, 8, 15, and 22 in cycle 1; days 1 and 15 in subsequent cycles; 28-days cycle/s. | 11.6              | ≥2         | 11.53 vs. 647 HR 0.596 | 60.4 vs. 35.3 | 5 vs. 1² | NR | 87 vs. 71 |
|               |                       |      |                                                                                  |                   |             |              |         |         |             |            |
| APOLO EMN14 [53] | DPd vs. Pd           | 304  | Pd ± D 16mg/kg IV or 1.8 g SC QW (8 w), BIW (16 w), Q4W thereafter; 28-days cycle/s. | 16.9              | >1         | 12.4 vs. 69 HR 0.63 | 69 vs. 46 | 25 vs. 4 | NM | 50 vs. 39 |
|               |                       |      |                                                                                  |                   |             |              |         |         |             |            |
| TOURMALINE-MM1 [15] | IRd vs. Rd        | 722  | IRd, 4mg PO, days 1 and 15, each 28-days cycle.                                  | 15                | 2 (1-3)     | 20.6 vs. 147 HR 0.74 | 78.3 vs. 71.5 | 12 vs. 7 | NR | 74 vs. 69 |
|               |                       |      |                                                                                  |                   |             |              |         |         |             |            |
| NCT0314049    | PCd vs. Pd            | 120  | Pd ± Cy 40mg days 1, 8, 15 and 22 each 28-days cycle.                          | NM                | >1         | NM | NM | NM | NM | NM |
|               |                       |      |                                                                                  |                   |             |              |         |         |             |            |
| OPTIMISMM [31] | PVd vs. Vd            | 559  | P, 4mg days 1-14 (each 21-days) +/- SC 1.3mg/m² days 1, 4, 8, and 11 (cycles 1-8) and days 1 and 8 (>cycle 9); | 15.9              | >1         | 11.2 vs. 7.1 HR 0.61 | 82.2 vs. 50 OR 5.02 | 12.5 vs. 3.2 | NR | 57 vs. 42 |

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Table 1 Summary of data from the main phase 3 studies with proteasome inhibitors, immunomodulatory drugs and monoclonal antibodies (Continued)

| Study     | Arms       | N   | Doses and schedule                                                                 | Follow-up | Prior lines | PFS (months) | ORR (%) | ≥CR (%) | OS (months) | >G3 AE (%) |
|-----------|------------|-----|------------------------------------------------------------------------------------|-----------|-------------|--------------|----------|---------|-------------|------------|
| CASTOR [54] | DvD vs. Vd | 498 | D, 16mg/kg IV QW, days 1, 8 and 15 of cycles 1-3; Q3W on day 1 of cycles 4-8, and Q4W thereafter | 40        | 2 (1-10)    | 16.7 vs. 7.1 HR 0.31  (1 prior line, 27.0 vs. 7.9 HR 0.22) | 85 vs. 63 | 30 vs. 10 | NR          | 10         |
| POLLUX [12] | DRd vs. Rd | 569 | D, 16mg/kg IV QW days 1, 8, 15 and 22 of cycles 1-2, 8 w and days 1 and 15 of cycles 3-6, 16 w and Q4W thereafter; 28-days cycle/s. | 44        | 1 (1-11)    | 44.5 vs. 17.5 HR 0.44  (1 prior line, NR vs. 19.6 HR 0.42) | 93 vs. 72 | 57 vs. 23 | NR          | 29 vs. 19  |
| ELOQUENT-2 [14] | EloRd vs. Rd | 646 | Elo 10mg/kg IV, days 1, 8, 15 and 22 of cycles 1-2 and then on days 1 and 15 >cycle 3; 28-days cycle/s. | 48        | 2 (1-4)     | 19.4 vs. 149 HR 0.71  (At 4 y, 21 vs. 14; H-risk, 15 vs. 7) | 79 vs. 66 | 11 vs. 11 | 48 vs. 40   | Inf vs. 33 |
| ELOQUENT-3 [55] | EloPd vs. Pd | 117 | Elo 10mg/kg days 1, 8, 15, and 22, cycles 1-2 and 20mg/kg on day 1 of each cycle thereafter; 28-days cycle/s. | 9         | 3 (2-8)     | 10.3 vs. 4.7 HR 0.54  | 53 vs. 26 | 8 vs. 2   | HR 0.62     | NP vs. 13  |
| KEYNOTE-183 [56] | PembroPd vs. Pd | 249 | Pembro IV 200mg, Q3W; 28-days cycle/s. | 8c        | 4 (2-4)     | 5.6 vs. 84           | 34 vs. 40 | NM       | At 6 m; 82 vs. 90 | NP vs. 14  |

*Primary end point; b Underestimation due to interference with protein studies; c Premature study termination

AE/AEDTH: adverse events/adverse events leading to death; AH: arterial hypertension; An: anemia; BW: twice a week; CF: cardiac failure; CR: complete response; Cy: cyclophosphamide; D: daratumumab; d: dexamethasone; Dsc: discontinuation; Drd: daratumumab/carfilzomib/dexamethasone; Drd/P: daratumumab/pomalidomide/dexamethasone; Drd/Pd: daratumumab/pomalidomide/dexamethasone; Drd/Pd/P: daratumumab/pomalidomide/dexamethasone; Drd/Pd/P/P: daratumumab/pomalidomide/dexamethasone; Drd/Pd/P/P/P: daratumumab/pomalidomide/dexamethasone; Elo: elotuzumab; EloPd: elotuzumab/pomalidomide/dexamethasone; EloRd: elotuzumab/lenalidomide/dexamethasone; F3: grade 3; HR: hazard ratio; H-risk: high risk; I: ixazomib; Inf: infection; IrD: isatuximab/lenalidomide/dexamethasone; IsaKd: isatuximab/carfilzomib/dexamethasone; IsaKd/P: isatuximab/pomalidomide/dexamethasone; IV: intravenous; K: carfilzomib; Kd: carfilzomib/dexamethasone; KRd: carfilzomib/lenalidomide/dexamethasone; LP: lymphocytopenia; MRD: minimal residual disease; NM: not mature; NP: neutropenia; N/P: febrile neutropenia; ORR: overall response rate; OS: overall survival; m: months; P: pomalidomide; PCD: pomalidomide/cyclophosphamide/dexamethasone; PCD/P: pomalidomide/cyclophosphamide/dexamethasone; Pd: pomalidomide/dexamethasone; Pembro: pembrolizumab; PembroPd: pembrolizumab/pomalidomide/dexamethasone; PFS: progression-free survival; PD: pembrolizumab/dexamethasone; Q3W: once weekly; Q4W: once every four weeks; Rd: lenalidomide/dexamethasone; TP: thrombocytopenia; Vd: bortezomib/dexamethasone; w: week; y: years
up of 4.5 months) [65] and with Rd [once-weekly (56 mg/m²) versus twice-weekly (27 mg/m²)], currently being tested in the ARROW2 trial (ClinicalTrials.gov number, NCT03859427).

Regarding other PIs, ixazomib added to Rd (Ixazomib-Rd) showed superior PFS compared to Rd [15, 66]. Furthermore, in a phase 2/3 trial, good tolerability and promising clinical activity has been observed when comparing this regimen with pomalidomide/dexamethasone (Pd) (ClinicalTrials.gov number, NCT03170882) [3].

**Pomalidomide and new combinations**

Pomalidomide has shown favorable results in combination with other agents in clinical studies in which refractoriness and/or at least previous treatment with lenalidomide were the inclusion criteria. With dexamethasone (Pd), an improvement in OS was reported compared to dexamethasone alone [52], and the combination of pomalidomide with cyclophosphamide (PCd) has recently demonstrated better efficacy in phase 2 RCTs (median PFS 9.5 months) [64]. In combination with isatuximab, Pd showed clinical benefits compared to Pd alone in a phase 3 trial, with a higher incidence of some grade 3-4 AEs, but fewer AE-associated discontinuations [10, 67]. The combination with daratumumab (DPd) showed efficacy in a phase 1b study in 103 heavily treated patients (ORR of 60%, median PFS of 8.8 months and median OS of 17.5 months) [68] and the results of the phase 3 RCT that compared daratumumab plus Pd with Pd alone have been published recently [53]. The triplet PVd (pomalidomide, bortezomib and dexamethasone) was effective when compared to Vd in a population of patients of whom 100% had been exposed to lenalidomide and 71% were refractory to the treatment [31]. Finally, 2 ongoing phase 3 RCTs have been designed to evaluate the efficacy of the combination of Pd with nivolumab with or without elotuzumab (Check-Mate-602; ClinicalTrials.gov number, NCT02726581) or with belantamab mafodotin (DREAMM8; ClinicalTrials.gov number, NCT04484623).

**Monoclonal antibodies and combinations**

CD38 has so far been the most widely explored target in RRMM. Isatuximab (Isa) and daratumumab (D) are mAbs against CD38 [69]. Isatuximab has a similar multimodal mechanism of action to daratumumab and elotuzumab, but binds a specific epitope on CD38; additionally, it is able to induce direct apoptosis without cross-linking and shows deeper inhibition of CD38 ectoenzymatic activity [70]. The phase 3 ICARIA-MM study observed that isatuximab combined with Pd in pomalidomide-naïve RRMM patients provided deeper and faster responses than Pd alone (ORR of 60.4% vs. 35.3%) with improved survival outcomes (median PFS 11.5 months), even for lenalidomide refractory patients [10]. Based on these results the European Commission approved the use of isatuximab in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed/refractory multiple myeloma who have received ≥2 prior therapies, including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy [71]. Additionally, the combination of isatuximab with Kd in the IKEMA trial has recently showed promising results, with ORR 86.6%, including 29.6% of MRD-negative (10⁻⁵) patients, and median PFS not reached [hazard ratio (HR) 0.53, p = 0.007] after 20.7 months of follow-up [50]. In fact, isatuximab plus Kd has recently been approved by the European Medicines Agency for patients with RRMM and at least 1 prior therapy.

The combination of daratumumab with Vd [17, 72] or with Rd [12, 73, 74] have clearly demonstrated prolonged PFS, and DRd has achieved higher efficacy compared to Vd or Rd doublets in a network meta-analysis (with a reduction in the risk of death or progression of 81% and 63%, respectively) [75]. The combination of D with Kd is an effective ImiD-free option [51], and combined DPd treatment is currently being tested in the APOLO EMN14 trial (ClinicalTrials.gov number, NCT03180736) [53, 63]. The incidence of grade ≥2 infusion-related reactions (IRRs) was 2%-3% and occurred almost exclusively after the first intravenous infusion. Subcutaneous administration has now received approval based on the results of a phase 3 RCT that showed a similar ORR than that obtained intravenously, but with fewer IRRs [76]. In combination with ImiDs, MOR-202, a novel anti-CD38 MoAb, has demonstrated an ORR ranging from 50%-65 % with lower IRR (7%) than daratumumab and isatuximab [77]. At present, a phase 3 trial comparing MOR-202 plus Rd versus Rd is ongoing.

Elotuzumab is a first-in-class IgG1-kappa that targets SLAMF7, and has already been approved in combination with Rd by the FDA [14, 55] and with Pd by the EMA [78]. The results of its combination with PIs are disappointing, although some RCTs testing elotuzumab plus KPd or elotuzumab plus PVd are currently ongoing. Finally, pembrolizumab, an anti-programmed death 1 (PD-1) checkpoint inhibitor, showed limited efficacy and higher mortality in the KEYNOTE-183 trial, leading to study termination [56].

**New drugs with other mechanisms of action**

A summary of new drugs for RRMM management is included in Table 2. Melflufen, a melphalan prodrug with alkylating properties, induces rapid internalization of MM cells, and in combination with dexamethasone has recently shown promising results in phase 1/2 RCTs (O-
| Trial/NTC Id   | Arms / Phase | N  | New agent                                      | Number of prior lines | PFS (months) | ORR (%) | CBR (%) | Median duration (months) | TTNT (months) | OS (months) | All / (>G3) AEs |
|---------------|--------------|----|------------------------------------------------|-----------------------|--------------|----------|---------|-------------------------|---------------|-------------|------------------|
| O-12-M1 [79]  | Md Phase 1-2 | 81 | Melflufen IV, 15, 25, 40 or 55mg (40mg: maximum tolerated dose) | 4 (3-5)               | 5.7          | 31       | 49      | 8.4                     | NM            | 20.7        | TP, 42           |
|               |              |    |                                                |                       |              |          |         |                         |               |             | NP, 26 Infection, 8 |
| NCT02899052   | Venetoclax + Kd Phase 2 | 42 | Venetoclax PO, 400 or 800mg                     | 2 (1-3)               | 78 (100 % in t(11;14)) | 92       | NP, 14 | NP, 13 | NP, 13 | Venetoclax + Dd Phase 1-2 | 24 | Venetoclax, PO, various doses | 3 (1-8) | 92 | NP, 13 | Arterial hypertension, 12 |
| BOSTON [80]   | Vd ± selinexor Phase 3 | 404 | Selinexor PO, 100mg oral, QW                    | 1-3                   | 13.93 vs. 9.46 HR 0.70 | 76 vs. 62 | 16.1 vs. 10.8 | Venetoclax + Dd Phase 1-2 | 24 | Venetoclax, PO, various doses | 3 (1-8) | 92 | NP, 13 | Arterial hypertension, 8 |
| PANORAMA 1 [18] | Vd ± panobinostat Phase 3 | 768 | Panobinostat PO, 20mg                          | 1-3                   | 11.99 vs. 8.08 HR 0.63 | 61 vs. 54 | 13.1 vs. 10.9 | Vd panobinostat Phase 3 | 768 | Panobinostat PO, 20mg | 1-3 | 92 | NP, 13 | Arterial hypertension, 8 |
| NCT02384083   | Filanesib + Pd Phase 2 | 33  | Filanesib IV, various doses                    | 3 (2-6)               | 7            | 65       | NM      | NM                      | NM            | NM          | NP, 60          |

AEs adverse events; AH arterial hypertension; CBR clinical benefit rate; Dd daratumumab/dexamethasone; G2/G3 grade 2/grade 3; HR hazard ratio; IV intravenous; Kd carfilzomib/dexamethasone; Md melflufen/dexamethasone; NM not mature; NP neutropenia; NR not reached; ORR overall response rate; OS overall survival; PFS progression-free survival; PN pneumonia; PNP peripheral neuropathy; Pd pomalidomide/dexamethasone; PO per orally; QW once weekly; TP thrombocytopenia; TTNT time to next treatment; Vd bortezomib/dexamethasone
12-M1 trial) [79]. A phase 3 study comparing its efficacy with Pd is currently ongoing. Increased ORR (≥80%) has been reported in combination with Vd or daratumumab (ANCHOR trial; ClinicalTrials.gov number, NCT03481556) [81].

Venetoclax, a selective bcl2-inhibitor, has so far shown the best efficacy results in patients harboring t(11;14) [82]. Vd was tested in 291 patients in combination with venetoclax or placebo, showing improved PFS in the venetoclax arm: updated PFS results are 23.2 vs 11.4 months, [HR 0.60 (0.43, 0.82)] and not reached (NR) vs 9.3 months in patients with t(11;14) [HR 0.09 (0.02, 0.41)], but with a higher death rate [33.5 months vs NR; HR 1.46 (0.91, 2.34)] mainly due to infection [83]. The study was terminated prematurely for this reason. A subgroup analysis showed a tendency toward better PFS and OS with venetoclax-Vd in t(11;14) and high BCL2 expression [83], a result that motivated the performance of the CANOVA study (ClinicalTrials.gov number, NCT03539744) that is currently testing this combination in this setting.

Selinexor, the first-in-class XPO1-inhibitor, has been approved in penta-refractory patients, showing improved efficacy in heavily treated patients (STORM study; ORR 26%, PFS 3.7 months and OS 8.6 months) [65]. Furthermore, increased efficacy was reported when Vd was added (STOMP trial), [84] and recently the results of the phase 3 BOSTON trial (ClinicalTrials.gov number, NCT03110562) has confirmed this benefit in terms of PFS compared to Vd (HR 0.70, 95% CI 0.53–0.93; p= 0.0075) [80]. Other regimens such as selinexor-Pd, selinexor-Kd or selinexor-daratumumab are being tested in phase 2 RCTs.

Panobinostat, a histone deacetylase (HDAC) inhibitor, received approval in 2015, and plus bortezomib plus dexamethasone showed improved benefit in PFS but no improvement in OS compared to Vd [85]. Moreover, toxicity was important, and dose reduction was needed in nearly 50% of patients.

Ibrutinib, a first-in-class covalent inhibitor of Bruton’s tyrosine kinase (BTK), does not have the same activity as in lymphoproliferative neoplasms, while the potent kinesin spindle protein (KSP) inhibitor, filanesib, has shown moderate efficacy when tested with PIs and IMiDs. Finally, JAK inhibitors (ruxolitinib) and cyclin dependent kinases (CDK) inhibitors (dinaciclib) are also being investigated in RRMM patients [86].

Cereblon E3 ligase modulators (CELMoDs) are a new class of agents that stimulate the immune system that have shown enhanced anti-MM activity in preclinical models, and are able to overcome lenalidomide/pomalidomide-resistance [87, 88]. In a phase 1b/2a trial with 66 highly pre-treated RRMM, iberdomide plus dexamethasone achieved ORR of 32.2% (35.3% for IMiD-refractory individuals), with a toxicity profile similar to that of IMiD (grade 3 AEs were mainly hematologic or infections) [89]. These results improved with the addition of bortezomib or daratumumab, achieving an ORR of 60.8% and 42.3%, respectively and maintaining a good safety profile [90]. The combination of CC-92480 plus dexamethasone was tested in a phase 1 trial in RRMM patients with high refractoriness rates [91], in which ORR was 54.5% at 1 mg QD 21/28 days, with 63% of responders being dual-IMiD refractory.

Immunotherapy: Immunoconjugates, CAR-T cells and bispecific antibodies

Outcomes remain poor for triple-class–refractory patients (median OS ≤ 7-9 months), and there is no standard of care [92]. This has led to the need to develop new drugs with novel mechanisms of action to fill this gap.

B cell maturation antigen (BCMA) is an optimal target due to its restriction to B-cell lineage and overexpression in MM cells [93]. The antibody-drug conjugate belantamab mafodotin was the first anti-BCMA therapy approved. In a phase 2 trial in 97 patients, belantamab mafodotin at 2.5 mg/kg achieved an ORR of 32% (58% of responders showed ≥ very good partial response) with a median duration of response of 11 months [94]. Median PFS and OS were 2.8 months and 13 months, respectively, for a highly pre-treated population with a median of 7 prior lines of treatment and a marked refractoriness profile. The most common AE was keratopathy (70%), but this rarely led to discontinuation (1%). The most common grade ≥ 3 AEs were keratopathy (27%), anemia (20%) and thrombocytopenia (20%), with low incidence of grade 3 respiratory infections. IRRs were mostly grade 1-2 (no grade 4-5 and just one discontinuation). Studies evaluating synergies of belantamab mafodotin are ongoing [95, 96].

BCMA is now the most widely explored target for CAR-T cell therapies in MM, with more than 15 constructs being evaluated for RRMM patients (Table 3). Phase 2 trials with anti-BCMA CAR-T therapy [97, 109, 110, 111] confirm the promising results reported in earlier studies, with ORR ranging from 40% to 100% [98–108, 110, 113–116]. Additionally, some phase 1 studies have evaluated multi-antigen CAR-T strategies (targeting simultaneously BCMA and CD19 or CD38) [117, 118] as well as alternative targets (CD138, kLC, APRIL, GPRC5D, NY-ESO-1) with varying results [119–126].

Last but not least, bispecific antibodies in RRMM can be incorporated into the therapeutic arsenal of drugs against RRMM. Recently, results of bispecific CD3/BCMA antibodies as teclistamab and elranatamab, and bispecific CD3/BFCR3450A (talquetamab) and CD3/FcRH5 (cevos-tamab) antibodies have shown a manageable safety profile and encouraging results [21, 127–129].
Table 3  Summary of main trials evaluating anti-BCMA CAR-T cell therapy

| Trials (N) | Construct | Baseline features | CAR-T cell dose | Lymphodepletion | RR | PFS (median) | CRS all/≥G3 (%) | ICANS all/≥G3 (%) |
|------------|-----------|-------------------|-----------------|----------------|----|-------------|----------------|-----------------|
| KarMMa/Ide-cel (N = 128) [97] | Lentivirus Murine scFv 4-1BB/CD3ζ | 6 y since diagnosis 6 prior lines HR cytogenetics: 35% Triple/Penta-refractory: 94/26% | 150-450 x 10^6 cells/kg Cy/Flu | ORR 73%; ≥CR 33% MRD- at 10^-5 79% a | 8.8 m | 84/5 | 18/3 |
| EVOLVE/Ova-cel (N = 62) [98] | Lentivirus Human scFv 4-1BB/CD3ζ EGFRt | 7 y since diagnosis 6 prior lines HR cytogenetics: 41% Triple/Penta-refractory: 94/48% | 300-600 x 10^6 cells Cy/Flu | ORR 92% ≥CR 36% MRD- at 10^-5 84% | NR | 89/3 | 13/3 |
| CARTITUDE-1/Gilda-cel (N = 97) [99] | Lentivirus Llama VH1-24-1BB/CD3ζ | 5.9 y since diagnosis 6 prior lines HR cytogenetics: 23.7% Triple/Penta-refractory: 87.6/42.3% EMD: 13.4% | 0.5-1.0 x 10^6 cells/kg Cy/Flu | ORR 96.9%; ≥CR 67% MRD- at 10^-5 54.6% | At 12-m, 76.6 | 94.8/5 | 16.5/2.1 |
| PRIME/P-BCMA-101 (N = 53) [100] | PiggyBac Human Centyrin 4-1BB/CD3ζ | 4.9 y since diagnosis 8 prior lines Triple-refractory: 60% | 51-1178 x 10^6 cells Q2W cycles or combined with Rix or Lena | Cy/Flu | ORR 56.7% (out of 30 evaluable pts) | NR | 17/0 | 3.8/3.8 |
| LUMMICAR-2/CT053 (N = 20) [101] | Lentivirus Human scFv 4-1BB/CD3ζ | 6 y since diagnosis 5 prior lines HR cytogenetics: 55% Triple/Penta-refractory: 85/50% EMD: 25% | 1.5-3 x 10^6 cells Cy/Flu | ORR 94% ≥CR 27.8% (out of 18 pts with ≥8 w of follow-up) | NR | 78.9/0 | 15.8/5.3 |
| NCI (N = 16) [102] | y-retrovirus Murine scFv CD28/CD3ζ | 9.5 prior lines HR cytogenetics: 40% | 9 x 10^6 cells/kg Cy/Flu | ORR 81% ≥CR 12.5% MRD- at 10^-5 75% | EFS, 31 w | 94/375 | NR/19 |
| CAR-T BCMA/UPenn (N = 25) [103] | Lentivirus Human scFv 4-1BB/CD3ζ | 4.6 y since diagnosis 7 prior lines HR cytogenetics: 96% Penta-refractory: 44% | C1: 1.1-5 x 10^6 cells C2: 1.1-5 x 10^6 cells C3: 1.1-5 x 10^6 cells C1: No C2: Cy C3: Cy | C1: ORR 44%; ≥CR 9% C2: ORR 20%; ≥CR 0% C3: ORR 64%; ≥CR11% | C1: 65 d C2: 73 d C3: 125 d | C1: 89/33 C2: 60/0 C3: 20/0 | C1: 33/22 |
| CRM-402/bb21217 (N = 69) [104] | Lentivirus Murine scFv 4-1BB/CD3ζ, bb007 PI3K inh | 6.7 y since diagnosis 5 prior lines HR cytogenetics: 33% Triple-refractory: 64% | C1: 150 x 10^6 cells C2: 100 x 10^6 cells C3: 250 x 10^6 cells Exp: 450 x 10^6 cells Cy/Flu | C1: ORR 83%; ≥CR 42% C2: ORR 43%; ≥CR 14% C3: ORR 57%; ≥CR 29% Exp: ORR 84%; ≥CR 32% | NR | 70/4 | 16/4 |
| MSKCC/MCARH171 (N = 11) [98] | y-retrovirus Human scFv 4-1BB/CD3ζ EGFRt | 6 y prior lines HR cytogenetics: 82% | 72-818 x 10^6 cells Cy or Cy/Flu | ORR 64% (≥CR 0%) | NR | 60/20 | 10/0 |
| FHRC/FCAHRH143 | Lentivirus | 8 prior lines | 50-800 x 10^6 cells Cy/Flu | ORR 100% (≥CR 36%) | NR | 91/0 | 9/0 |
Table 3 Summary of main trials evaluating anti-BCMA CAR-T cell therapy (Continued)

| Trials (N) | Construct | Baseline features | CAR-T cell dose | Lymphodepletion | RR | PFS (median) | CRS all/≥G3 (%) | ICANS all/≥G3 (%) |
|------------|-----------|-------------------|----------------|----------------|----|--------------|----------------|-----------------|
| (N = 7) [105] | Human scFv 4-1BB/CD3ζ, EGFRt | HR cytogenetics: 100% | | | | | | |
| HRAIN Biotechnology (N = 20) [106] | γ-retrovirus Murine scFv 4-1BB/CD3ζ, EGFRt | 5.5 prior lines | 9 x 10⁶ cells/kg | Cy/Flu | ORR 79% (≥CR 45%) | 15 m | 45/5 | NR/7 |
| FH/H-BCMA (N = 12) [107] | γ-retrovirus FHVH33 4-1BB/CD3ζ, EGFRt | 6 prior lines | 0.75-3 x 10⁶ cells/kg | Cy/Flu | ORR 83% (≥CR 17%) | NR | 91.7/83 | 25/83 |
| CT103A (N = 14) [108] | Lentivirus Human scFv 4-1BB/CD3ζ | 4 prior lines | 1-6 x 10⁶ cells/kg | Cy/Flu | ORR 100% (≥CR 71%) | NR | 94.4/28 | 0/0 |
| C-CAR088 (N = 23) [109] | Lentivirus Human scFv 4-1BB/CD3ζ | 4 prior lines | 1-6 x 10⁶ cells/kg | Cy/Flu | ORR 95.7% (≥CR 43.5%) | At 6-m: 65.1% | 91.3/43 | 4.3/0 |
| UNIVERSAL/ALLO-715 (N = 31) [110] | Lentivirus Human scFv Rix-RD 4-1BB/CD3ζ and Allogeneic TC with disrupted TCRα and CD52 | 5.4 y since diagnosis | 40-480 x 10⁶ cells | ALLO-647/ Cy +/- Flu | ORR 62% (≥VGPR 38%) | at 320 x10⁶ cells (n=13) | NR | 45/0 | 0/0 |

aMRD is referred to patients with ≥CR. C cohort; CR complete response; CRS cytokine-release syndrome; Cy cyclophosphamide; d days; EFS event-free survival; EMD extramedullary disease; Exp expansion; FH/VH fully human heavy-chain variable domain; Flu fludarabine; G grade; HR high-risk; ICANS immune-effector cell-associated neurotoxicity syndrome; Lena lenalidomide; m months; MRD minimal residual disease; NR not reported; ORR overall response rate; PFS progression-free survival; Rix rituximab; Rix-RD rituximab recognition domain; RR response rate; scFv single chain variable fragment, TC T-cells; TCR T cell receptor; VGPR very good partial response; VHH variable domain of heavy chain; w weeks; y year
Controversies surrounding the clinical management of patients with RRMM

The clinical value of earlier treatments for RRMM: conventional and high-dose chemotherapy with autologous transplantation, lenalidomide and bortezomib

Conventional chemotherapy (CC) remains a cornerstone in the current therapeutic approach, particularly with new agents. However, CC is gradually being side-lined due to the better risk/benefit ratio of the new combinations [130]. Bridging therapy (when cytoreduction is urgently needed before more definitive therapy is planned) is one of the most common indications for CC, especially in certain circumstances, such as aggressive extramedullary disease or secondary plasma cell leukemia [131].

The role of high-dose chemotherapy and salvage ASCT (sASCT) is currently questioned in today’s RRMM treatment scenario, and must be placed in the context of the re-induction used [132]. The feasibility and efficacy of sASCT is mainly derived from retrospective studies [133–146] (Table 4). So far, two phase 3 trials have demonstrated the benefit of sASCT: the Myeloma X [5, 148] and the ReLApS studies [147], with median PFS of 19 and 20.7 months, respectively.

| Study                | Type of study | N      | ORR (%) | mPFS (months) | mOS (months) |
|----------------------|---------------|--------|---------|---------------|--------------|
| Dhakal B et al. 2020 | Retrospective (no tandem) | 975    | -       | 12            | NR 1-y OS 94% |
| Goldschmidt H et al. 2020 | Phase 3 (ReLApS) | 139    | 82/71   | 20.7/18.8 (ITT) | NR/62.7 (ITT) |
| Manjappa S et al. 2018 | Retrospective (no tandem) | 63     | 92      | 13.8/20.3     | -            |
| Gössi U et al. 2018  | Retrospective  | 86     | 70      | 30.2/13       | 129.6/33.5   |
| Veltri LW et al. 2017 | Retrospective  | 233    | 81      | 17.6          | 48           |
| Nieto Y et al. 2017  | Phase 2       | 74/184 (GBMF vs. MF) | -/70 | 15.1/9.3     | 37.5/23      |
| Zannetti BA et al. 2017 | Retrospective | 66     | 94      | 17            | 43           |
| Singh Abbi KK et al. 2015 | Retrospective | 75     | 82      | 10.1          | 22.7         |
| Cook G et al. 2016  | Phase 3 (Myeloma X) | 89/85 (sASCT vs. CFx12w) | 83/75 | 19/11        | 67/52        |
| Sellner L et al. 2013 | Retrospective | 200    | 80.4    | 15.2          | 42.3         |
| Michaelis LC et al. 2013 | Retrospective (no tandem) | 187    | 68      | 11.2          | 30           |
| Gonsalves WI et al. 2013 | Retrospective | 98     | 86      | 10.3          | 33           |
| Auner HW et al. 2013 | Retrospective | 83     | -       | 15.5          | 31.5         |
| Lemieux E et al. 2013 | Retrospective | 81     | 93      | 18            | 48           |
| Shah N et al. 2012  | Retrospective | 44     | 90      | 12.3          | 31.7         |
| Gertz MA et al. 2000 | Retrospective | 64     | 34 (CR) | 11.4          | 19.6         |

Selecting the best treatment for MM patients previously treated with lenalidomide in their first recurrence/progression

Most patients will have received lenalidomide when relapse occurs as a result of front-line therapy. In this context, at least 3 scenarios are possible: patients treated with upfront ASCT and lenalidomide as maintenance therapy [149]; patients not eligible for ASCT and treated with lenalidomide-containing regimens [41, 150–152] (lenalidomide administered until progression); and a third scenario with a small number of patients treated in first-line with lenalidomide and relapsing after a period without treatment. According to IMWG criteria, patients are defined as refractory to lenalidomide when presenting a non-responsive disease while on a lenalidomide-containing therapy or have progressed within 60 days of the last date of lenalidomide uptake [153]. However, from a clinical point of view there is no consensus on the management of patients with refractoriness to lenalidomide. Most experts recommend lenalidomide-free therapy for clinical progressions, regardless of the duration of response or the dose of lenalidomide [154].

Table 4 Recent studies in salvage autologous stem cell transplantation (sASCT) in relapsed/refractory multiple myeloma

CTna conventional therapy including novel agents; DR double refractory (IPs & IMiDs); GBMF gemcitabine busulfan and melphalan; ITT intention-to-treat-population; M previous maintenance; MF melphalan; mOS median overall survival; mPFS median progression-free survival; NR not reached; PR primary refractory; Rd lenalidomide and dexamethasone, continuous; Re relapse off therapy; RR refractory relapse; sASCT salvage autologous stem cell transplantation; w weeks
patients on low-dose lenalidomide, it is unclear whether response can be achieved with full-dose lenalidomide added to dexamethasone, or even by adding a third drug [154]. This is compounded by the fact that this population has been excluded from phase 3 RCTs evaluating lenalidomide-combinations, so the use of a lenalidomide-free triplet is also a better option in these patients. There is also evidence that a prolonged response to lenalidomide is associated with a better response to subsequent treatments after resistance to lenalidomide [39].

The lenalidomide-free options available so far were Kd and daratumumab plus VD (DVd) [11, 72]; however, these were less effective in patients previously treated with lenalidomide, and their efficacy following first relapse remains unknown due to the small number of patients included in clinical studies [11, 72, 155]. More effective carfilzomib- and pomalidomide-containing regimens are being incorporated in this setting. These have been assessed in studies in which a more representative population of patients already exposed to lenalidomide were included, especially in regimens containing pomalidomide, in which previous exposure to lenalidomide and even refractoriness was mandatory for recruitment (Table 5). Therapy with anti-CD38 plus Kd or Pd should be considered [159]. Daratumumab plus Kd (DKd) [51, 160], isatuximab plus Kd (Isa-Kd) [50], Isa-Pd [10] and DPd [53] have recently shown efficacy in exposed and refractory patients to lenalidomide in phase 3 RCTs. On first relapse after lenalidomide, there are only available data with DPd in a phase 2 study [156] and with anti-CD38-free therapy; in this context, pomalidomide plus PI (KPd) [157] or Vd (PVd) [31, 158] have shown efficacy. In conclusion, based on the current evidence, pomalidomide could be the key salvage combination in patients refractory to lenalidomide, and adding antiCD38 or carfilzomib will probably improve efficacy.

Finally, in the third scenario (patients who relapse after a long lenalidomide-free period), the treatment with lenalidomide triplets [DRd, KRd, VRd, Isa-Rd or elotuzumab-Rd] could be an option. Although no head-to-head comparison studies are available, DRd is probably the best treatment option in terms of PFS [3]; however, as mentioned above, the number of patients already exposed to lenalidomide included in these RCTs was small, so lenalidomide triplets were optimal when the only alternative was DVd or Kd. Nevertheless, in the context of the next available alternative, even in the third scenario, a lenalidomide-free combination could be a better choice.

First-line of rescue vs. more advanced phases and double refractory patients in the main phase 3 trials for RRMM patients

A gradual decrease has been observed in the number of patients with improved clinical outcomes after each subsequent line of therapy, and the likelihood of obtaining a deep response is progressively slimmer. Therefore, an in-depth analysis of the results of the aforementioned main phase 3 trials in specific subpopulations according to prior lines of therapy will show what to expect from each drug-combination and how to maximize their performance. Overall, as expected, most treatments performed better at first relapse. Since slightly different inclusion criteria are used in these studies, direct comparisons are not always possible (Table 6). Furthermore, since subanalysis based on the number of prior lines were not performed in many studies, no information on the major prognostic factors that characterize each cohort is available. A cursory analysis would lead to a hypothetically longer PFS in patients with 2-3 prior lines of treatment that were rescued with Rd compared to those treated with Pd. Nevertheless, the latter was considered in early relapse after treatment with lenalidomide and bortezomib. Another important aspect is the difference in dosing schedules for the same control arms across different clinical trials. Thus, treatment with Vd was limited to 8 cycles in CASTOR [17, 54] and 12 cycles in PANORAMA-1 [18] and maintained until progression or intolerance in ENDEAVOR [11, 161, 162] and OPTIMISMM, [31] which limits comparisons based on HR. Similarly, Vd-based therapies provide shorter PFS than Rd-based regimens after first and second/third relapses, even though the latter was maintained as part of triplet therapy indefinitely [55, 58, 66, 72]. Treatment was discontinued at some point in both the CASTOR and PANORAMA-1 trials [17, 18, 54]. In contrast, PVd was maintained in the OPTIMISMM trial, with PFS outcomes at first relapse in the range of Rd-based therapies [31]. New triplets including MoAbs have not achieved median PFS, but considering their long follow-up (≥17 months), outcomes are expected to be promising [50, 51, 156].

Patients refractory to PIs and IMiDs have shown limited survival (median OS of 5-10 months), but no recent data on the benefit obtained with new therapies are available [165, 166], and there is no clear consensus on the meaning of double refractoriness. While double refractoriness was originally defined as refractoriness to bortezomib and lenalidomide, alternative drugs (carfilzomib, pomalidomide) are sometimes used in the first line setting. Thus, several studies define double-refractory patients as those who are refractory to any PI plus lenalidomide or to any PI plus any IMiD. Nevertheless, these double-refractory patients are not the same, and their outcomes could be different. Additionally, the front-line use of anti-CD38 MoAbs is becoming more frequent, and it is not uncommon to find patients who are refractory to anti-CD38 MoAbs following an earlier relapse. Thus, the traditional definition of double-refractoriness is fast
| Study         | Regimen | Phase | V-ex (%) | V-ref (%) | R-ex (%) | R-ref (%) | R-ref in 1L n (%) | ORR/CR (%) | ORR/CR R-ref (%) | PFS (months) | PFS R-ex (months) | PFS R-ref (months) | PFS R-ref in 1L (months) |
|--------------|---------|-------|----------|-----------|----------|-----------|-------------------|-------------|-----------------|--------------|-------------------|------------------------|------------------------|
| ENDEAVOR [11]| Kd      | 3     | 54       | 4         | 38       | 25        | 32 a              | 77/13       | ---             | 18.7         | 12.9              | 86                     | 15.6 ^c                |
| CASTOR [72]  | DVd     | 3     | 65       | 0         | 36       | 24        | ---               | 85/30       | ---             | 16.7         | 9.5               | 78 vs 4.9 HR 044       | ---                    |
| OPTIMISMM [31]| PVd     | 3     | 72       | 9         | 100      | 71        | 129 (23) b       | 82.2/15.7   | ---             | 11.2         | 11.2              | 95                     | 17.8 ^b                |
| CANDOR [51]  | DKd     | 3     | 92       | 29        | 42       | 33        | ---               | 84/31.8     | ---             | 11.2         | 11.2              | 95                     | 17.8 ^b                |
| MM-014 [156] | DPd     | 2     | 78       | ---       | 100      | 75        | 70 (62.5)         | ---         | ---             | 11.2         | 11.2              | 95                     | 17.8 ^b                |
| APOLLO EMN14 [53] c | DPd | 3     | 100     | 47        | 100      | 79        | 16 (11)          | 69/25       | ---             | 12.4 vs 69 HR 0.63 | 87/65             | 18                     | 18                     |
| IKEMA [50]   | IsaKd   | 3     | 93       | 31        | ---      | 32        | ---               | 86.6/39.7   | ---             | NR           | NR vs. 11.1 HR 0.45 | ---                    | ---                    |
| EMN011 [157] d | Kpd     | 2     | 100     | 100       | 100      | 100       | 100               | 87/65       | 87/65           | 18           | 18 vs. 65 HR 066   | 18                     | 18                     |
| ICARIA-MM [10] | IsaPd | 3     | 100     | 77        | 100      | 94        | ---               | 60.4        | ---             | 11.53        | 11.53 HR 0.59       | ---                    | 18                     |

Data from ENDEAVOR and Champion-1 [155]; Dimopoulos et al. (2018) [158]; Only 11% after 1L in APOLLO; ^a Prior first line treatment in EMN02/H095 trial; CR: complete response; DKd: daratumumab/carfilzomib/dexamethasone; DPd: daratumumab/pomalidomide/dexamethasone; DVd: daratumumab/bortezomib/dexamethasone; ex: exposed; HR: hazard ratio; IsaPd: isatuximab/pomalidomide/dexamethasone; Kd: carfilzomib/bortezomib; Kpd: carfilzomib/pomalidomide/dexamethasone; 1L: first line; NR: not reached; ORR: overall response rate; PFS: progression-free survival; R: refractory; V: bortezomib; y: years
| Regimen – Trial | Median PFS, months | Key Inclusion Criteria |
|-----------------|--------------------|------------------------|
| **Vd** | | |
| Vd – CASTOR [54, 72] | 7.9 (n = 113) 6.3 (n = 106) 5.4 (n = 28) | -PR to ≥1 prior line -No refractoriness to PI -No prior anti-CD38 |
| Vd - PANORAMA-1 [18, 85] | 8.5 (n = 174) 7.6 (n = 207) - | -No refractoriness to PI -No prior HDAC inhibitor |
| Vd – OPTIMISM [31] | 11.63 (n = 115) 7.10* (n = 163) - | -No refractoriness to V at 1.3 mg/m2 BIW -Prior R, no prior P |
| Vd – ENDEAVOR [161, 162] | 10.1 (n = 232) 8.4 (n = 233) - | -PR to ≥1 prior line -Prior PI allowed if ≥PR and ≥6 m since last dose |
| **Rd** | | |
| Rd – ASPIRE [58] | 17.6 (n = 157) 16.7 (n = 239) - | -PR to ≥1 prior line -No refractoriness to V, no prior K -No prior PD during 3 first m of Rd or any PD if Rd was the last therapy -No refractoriness to PI -No prior anti-CD38 |
| Rd – POLLUX [73, 74] | 19.6 (n = 146) 15.7 (n = 118) 17.1 (n = 19) - | -PR to ≥1 prior line -No prior anti-CD38 -No refractoriness to R |
| Rd - TOURMALINE-1 [66] | 16.6 (n = 213) 12.9 (n = 149) - | -No refractoriness to R or PI (refractoriness to thali is allowed) |
| Rd - ELOQUENT-2 [55] | 12.1 (n = 97) 13.1 (n = 65) - | -Prior R is allowed if no refractoriness, ≥PR, no more than 9 prior cycles and at least 9 m before progression |
| Rd - ELOQUENT-2 [55] | 19.4 (n = 62) 14.9 (n = 101) - | -Prior R is allowed if no refractoriness, ≥PR, no more than 9 prior cycles and at least 9 m before progression |
| **Pd** | | |
| Pd – MM-010 [13] | 3.9 (n = NR) 4.6 (n = NR) - | -≥2 prior lines including V and R -At least 4 cycles of alkylator or PD after at least 2 cycles or ASCT -PD within 6 m of discontinuation after PR with V and R -No prior P |
| Pd – ICARIA-MM [10, 163] | 7.8 (n = 101) 4.3 (n = 52) | -At least prior ≥MR -At least 2 prior lines including 2 cycles of a PI and R and PD within 6 m of discontinuation after PR -No prior P, no refractoriness to anti-CD38 |
| Pd – APOLLO EMN14 [53] | 12.6 (n = 18) 6.5 (n = 113) 6.6 (n = 22) - | -At least 1 prior line including lena and a PI -PR to ≥1 prior line -No prior P, no prior anti-CD38 |
| Pd – ELOQUENT-3 [78] | 4.8 (n = 36) 4.3 (n = 21) - | -At least 2 prior lines including 2 cycles of a PI and R and PD within 6 m of discontinuation after PR -Refractory to PI and R -No prior P |
| **Kd** | | |
| Kd – ENDEAVOR [161, 162] | 22.2 (n = 232) 14.9 (n = 232) - | -PR to ≥1 prior line -Prior PI allowed if ≥PR and ≥6 m since last dose |
| Kd – CANDOR [51, 164] | 21.3 (n = 67) 12.5 (n = 87) - | -PR to ≥1 prior line -Prior K and/or anti-CD38 allowed if ≥PR, no refractoriness and ≥6 m since last dose |
| Kd – IKEMA [50] | NA (n = 55) 16.2 (n = 68) - | -No prior K -No refractoriness to prior anti-CD38 |
| **Vd** | | |
| Dv – CASTOR [54, 72] | 27 (n = 122) 9.8 (n = 107) 8.1 (n = 22) - | -PR to ≥1 prior line -No refractoriness to PI -No prior anti-CD38 |
| PanoVd – PANORAMA-1 [18, 85] | 12.3 (n = 178) 12 (n = 209) - | -No refractoriness to PI -No prior HDAC inhibitor |
| Pvd – OPTIMISM [31] | 20.73 (n = 111) 11.2* (n = 170) - | -No refractoriness to V at 1.3 mg/m2 BIW -Prior lena, no prior poma |
| VeneVd – BELLINI [83] | 22.4 (n = 135) NA (n = 156) - | -At least PR to any prior PI -No refractoriness or intolerance to prior PI |
becoming triple-refractoriness. This scenario is not included in many studies, particularly earlier ones, and the heterogeneity makes it difficult to obtain precise information about outcomes in double-refractory patients.

Preliminary results with pomalidomide and daratumumab in patients relapsing after bortezomib and lenalidomide [13, 52, 167–169] improved when they were combined in triplets [51, 68, 78, 164, 170, 171]. Recent clinical studies with novel drugs have included triple-refractory patients, and aimed to improve outcomes in this population (Table 7) [94, 171]. Nevertheless, some questions remain, such as whether a single definition for double-refractoriness exists and whether this definition is applicable when new drugs shift to upfront use, and whether it is advisable to reuse in a new combination certain drugs to which the patient has developed refractoriness.

Table 6 Progression-free survival outcomes in the main advanced-phase clinical trials for RRMM patients according to number of prior lines of therapy (Continued)

| Regimen – Trial | Median PFS, months | Key Inclusion Criteria |
|-----------------|--------------------|------------------------|
|                 | 1 prior line | 2-3 prior lines | >3 prior lines |
| XVd – BOSTON [80] | 16.6 (n = 99) | 11.8 (n = 96) | - |
| Prolonged if ≤3.5 years from diagnosis; at least 60 days PI-treatment-free interval; prior PI intolerability not allowed | |
| Rd based | 29.6 (n = 184) | 25.8 (n = 212) | - |
| Kd – ASPIRE [58] | 20.6 (n = 212) | NA (FU 14.8 m) | - |
| Carfilzomib/dexamethasone; prior PI to R or PI (refractoriness to thalidomide is allowed) | |
| DRd – POLLUX [73, 74] | 53.3 (n = 149) | 28.9 (n = 123) | 38.8 (n = 14) |
| Prior R is allowed if no refractoriness, no more than 9 prior cycles and at least 9 m before progression | |
| IRd – TOURMALINE-1 [66] | 15.8 (n = 103) | 13.1 (n = 58) | - |
| Prior R is allowed if no refractoriness, 2PR, no more than 9 prior cycles and at least 9 m before progression | |
| EloRd – ELOQUENT-2 [55] | 30.6 (n = 48) | 25 (n = 112) | - |
| Prior R is allowed if no refractoriness, 2PR, no more than 9 prior cycles and at least 9 m before progression | |
| Pd based | 14.1 (n = 16) | 10.7 (n = 114) | 19.3 (n = 21) |
| IsaPd – ICARIA-MM [10, 163] | NA (FU 17.2 m) | - | - |
| - No prior P, no prior anti-CD38 | |
| DPd – MM-014 [156] | 1y-PFS 78.8% (FU 17.2 m) | 1y-PFS 69.0% (FU 17.2 m) | - |
| - 1-2 prior lines with at least 2 cycles of R | |
| DPd – APOLLO [53] | 10.3 (n = 36) | 10.3 (n = 24) | - |
| EloPd – ELOQUENT-3 [78] | - | - | - |
| - No prior P, no prior anti-CD38 | |
| Kd based | 24.2 (n = 179) | - | - |
| Dk – CANDOR [51, 164] | NA (FU 17.2 m) | - | - |
| - PR to ≥1 prior line | |
| IsaKd – IKEMA [50] | NA (FU 20.7 m) | - | - |
| - No prior K | |

*Result for ITT population; a ≤3.5 years from diagnosis; b >3.5 years from diagnosis; c Just 2 prior lines of therapy; ASCT autologous stem cell transplantation; BIW twice in a week; D daratumumab; EloPd elotuzumab/pomalidomide/dexamethasone; EloRd elotuzumab/panobinostat/dexamethasone FU follow-up; HDAC histone deacetylase; IRd ixazomib/lenalidomide/dexamethasone; Isa isatuximab; IV intravenous; K carfilzomib; Kd carfilzomib/dexamethasone; m months; MR minimal response; NA not achieved; NR not reported; P pomalidomide; PanOVo panobinostat/bortezomib/dexamethasone; PD progressive disease; Pd pomalidomide/dexamethasone; PFS progression-free survival; PI proteasome inhibitor; PR partial remission; R lenalidomide; Rd lenalidomide/dexamethasone; Thal thalidomide; V bortezomib; Vd bortezomib/dexamethasone; VeneVd venetoclax/bortezomib/dexamethasone; XVd selinexor/bortezomib/dexamethasone
Pros and cons of using the characteristics of MM as inclusion criteria in recent finalist phase 3 clinical trials for RRMM

Intense research into new agents for MM management has led to a wide range of possible drug combinations [173]. One of the goals at present, especially in the context of first relapse, is to obtain bone marrow and PET&MRD negativity, which are associated with better PFS and OS outcomes [174]. Another interesting positive aspect is the incorporation of immunotherapy, including CAR-T cells, as a new therapeutic approach to improve survival [175]. Finally, there is growing evidence that previous use of lenalidomide is unlikely to have an impact on response or survival if pomalidomide is used in subsequent therapies [39].

Some uncertainties in the management of RRMM patients should be also considered. Firstly, the proportion of upfront lenalidomide-treated patients is higher in the real-world (RW) than in the clinical trial setting [39]. This makes it difficult to transfer the results of RCTs to clinical practice, because a growing number of patients are currently receiving lenalidomide as part of their first-line treatment, and this differs greatly from the results of the main RRMM studies. Inclusion criteria is often vague, and efforts should be made to define these more clearly in upcoming phase 3 trials. There is also a need for a more accurate definition of the concept of progressive disease, a criterion that currently allows the inclusion of an unspecified percentage of patients in biological progression in most clinical studies, and of the duration of previous therapy as a prognostic and predictive factor of survival. It is also necessary to ensure the homogeneity of patient populations in RCTs as far as possible by defining, for example, the number of previous lines of therapy. Multi-refractoriness to multiple drugs used in MM is of particular concern. In this context, it is important to remember that survival to triple or higher refractoriness is probably shorter in the pre-scrub setting compared to stage I. In addition, little has been done to evaluate the transferability of clinical trial efficacy and safety results to the RW, and some results suggest the existence of a trial efficacy/RW effectiveness gap that limits the generalizability of clinical trial conclusions [176]. Finally, it is important to bear in mind that most RCTs do not include special populations (renal failure, extramedullary disease, etc.) that are frequently found in RRMM patients.

**RW patients vs. patients included in phase 3 trials for MM. Exclusion criteria bias**

A growing body of evidence shows the gap between RRMM patients in RCTs and RW studies. Patients

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### Table 7 Outcomes of double-refractory RRMM patients included in the main clinical trials

| Study | Phase | Refractoriness | N | ORR (%) | ≥VGPR/CRR/MRD (%) | Median PFS (months) | Median OS (months) | Median DoR (months) |
|-------|-------|----------------|---|---------|-------------------|---------------------|-------------------|-------------------|
| Dk – GEN-501 + SIRIUS [169] | 2 | PI + IMID | 148* | 30.4 | 14/5/- | 4.0 | 20.5 | 8.0 |
| Dp – ICARIA-MM [170] | 3 | PI + R | 111 | 59 | 29.7/- | 11.2 | - | - |
| Dp – APOLLO [53] | 3 | PI + IMID | 64 | - | - | 7.7 | - | - |
| Dp – MMY-1001 [68] | 3 | PI + IMID | 73 | 57.5 | - | - | - | - |
| Dk – CANDOR [51, 164] | 3 | - | RR: 99 | RR: 79.8 | RR: -/-/13.1 | RR: NA | - | - |
| Dk – MMY-1001 [171] | 3 | PI + IMID | 25 | 83 | -/-/6.9 | 25.7 | NA | 1y-OS 75% |
| Ik – IKEMA [50] | 3 | - | RR: 57 | RR: 66.7/38.6/24.6 | RR: 55.8/28.8/17.3 | RR: NA | - | - |
| Eolp – ELOQUENT-3 [78] | 2 | PI + R | 41 | - | - | 10.2 | - | - |
| Kp – EMN07 [172] | 1/2 | V + R | 21 | 71 | 24/5/- | 10.3 | - | - |
| Sd – STORM [65] | 2b | PI + IMID + D | 122 | 26 | 6.56/1.64/- | 3.7 | 8.6 | 4.4 |
| Belanaf – DREAMM-2 [94] | 2 | PI + IMID + D | 97 | 32 | 18/7/- | 2.8 | 13.7 | 11 |

* Patients from GEN-501 and SIRIUS trials who received daratumumab at 16 mg/kg are presented together. Not all are double refractory, but 87% are refractory to lenalidomide.

Belanaf belantamab mafodotin; CRR complete response rate; D daratumumab; DKd: daratumumab/carfilzomib/dexamethasone; Dkt: daratumumab/pomalidomide/dexamethasone; DPd: daratumumab/pomalidomide/dexamethasone; ElopEloplatumab/pomalidomide/dexamethasone; Ikd: ixazomib/carfilzomib/dexamethasone; IMID: immunomodulatory drug; IPd: isatuximab/pomalidomide/dexamethasone; Kd: carfilzomib/dexamethasone; KPd: carfilzomib/pomalidomide/dexamethasone; L: lenalidomide; LR: lenalidomide-refractory; MRD: minimal residual disease; NA not achieved; NR not reached; ORR overall response rate; OS overall survival; Pd: pomalidomide/dexamethasone; PFS: progression-free survival; PI: proteasome.
included in RCTs represent a select group of MM patients. Multiple confounding factors influence the interpretation of efficacy (RCTs) or effectiveness (RW), making these impossible to compare, and potentially affecting the external validity of the study. There are also differences in safety in RW settings versus RCTs, highlighting the importance of post marketing pharmacovigilance studies.

Older patients and patients with a high comorbidity burden are frequently underrepresented in RCTs. Renal impairment is a well-known prognostic factor and a commonly applied exclusion criterion in RCTs. As a result, PFS is generally shorter in RW studies compared to RCTs, and duration of therapy is reduced in RW due to poorer tolerability.

A recent RW study has shown that up to 75% of RRMM patients receiving routine care do not meet the eligibility criteria of hallmark RCTs in approved or recommended regimens in the RW setting. Moreover, OS was significantly worse (50% increased risk of mortality) in patients unable to meet study’s eligibility criteria. The most common reasons for RCT ineligibility were renal insufficiency and other malignancies [177]. In a retrospective study including 1601 RRMM patients, 40% received more than 2 lines of therapy. Substantial variation in RW PFS and OS was observed, ranging from 3.5-12.0 and 5.8-48.2 months, respectively. Overall, these values are lower than those observed in recent RCTs for the same agents in third and higher lines of therapy [178].

Translating RCTs findings to the RW setting is challenging. The stricter the RCT inclusion/exclusion criteria, the greater difference in results in RW studies. However, little or no gap is observed when all-oral regimens or bortezomib-based regimens are used. The discrepancy between RW and RCT’s data is also minimized in later versus earlier lines of therapy [179].

Both RCTs and RW studies provide complementary information of paramount importance in clinical decision-making. RW effectiveness is increasingly emphasized when determining the effectiveness of new approved regimens in the heterogeneous and complex population of RRMM patients. In this regard, it is essential to have access to high quality RW data provided by consolidated population-based cancer registries (PBCRs). In coming years, therefore, RCTs and PBCRs will need to work closely together at the local, regional and national level.

**Final considerations: key points in the orientation of RRMM treatment**

The therapeutic strategy for RRMM must follow a comprehensive, standardized, personalized approach that includes patient, disease, biology and previous therapy (response characteristics and toxicity). The treatment of RRMM is a rapidly changing field, and it is highly recommended to encourage patients to participate in a clinical study, if available. The best regimen should be chosen, taking into consideration all clinically relevant variables, as well as patient preference, the cost-benefit ratio, and local availability.

Achieving the deepest possible response must always be weighed up against achieving the best quality of life, particularly in the elderly, frail population. The importance of supportive care throughout RRMM management must be emphasized. Several phase 3 RCTs have shown, in most cases, the superiority of triplets over the doublet Vd and Rd, and later, Kd and Pd. Determining patient refractoriness to these agents at the time of relapse is a key factor in the choice of the optimal regimen.

Approaches to the treatment of triple-class (PIs, IMiDs and monoclonal antibodies) RRMM patients, including CC, sASCT and retreatment, are currently limited. CC is still a therapeutic option (almost always associated with new agents), and is usually used as a bridge to more definitive treatment, or in certain circumstances such as bulky disease or neurological complications that require rapid cytoreduction. High dose therapy followed by sASCT remains a safe and probably cost-effective approach for a selected subgroup of RRMM patients. However, continuous approval of new agents and the emergence of safer and more effective combinations have now called the role of sASCT into question. All in all, more evidence is needed before a paradigm shift occurs.

Retreatment has been used with limited results when no other choice is available, but new drugs should now be used instead whenever possible. New combinations based on second generation PIs and IMiDs, new monoclonal antibodies, histone deacetylase inhibitors, new class drugs such as venetoclax in the presence of t(11; 14) or selinexor, and drugs with new mechanisms of action such as melflufen can be suggested after approval.

Research should prioritize triple-class refractory patients, and they should be encouraged to participate in clinical trials. BCMA-directed CAR-T-cell therapy, bispecific antibodies and belantamab mafodotin are new immunotherapeutic approaches that have shown promising results. Non-myeloablative reduced-intensity conditioning allogeneic stem cell transplantation (RIC Allo) could be considered in certain young patients with high-risk cytogenetics, particularly in the context of a clinical study.

Translating the efficacy results of RCTs into RW effectiveness is challenging, mainly due to differences in clinical characteristics in both populations and different levels of tolerability, particularly for non-oral drugs. Comparison between most recent phase 3 RCTs and RW studies confirm the existence of an important gap,
with the exception of studies using all-oral regimens and V-based regimens. Currently, about half of all patients cannot be included in RCTs due to comorbidities (mainly renal failure) or special features (non-secretory myeloma, plasma cell leukemia, extramedullary disease, etc.).

Conclusions
The dramatic advances made in biology, prognosis and therapy for RRMM patients in recent years has created new challenges:

- How to order the sequence of lines of treatment of RRMM after the incorporation of IMiDs and AntiCD38 MoAbs into the first-line approach?
- Is there still a role for chemotherapy in the treatment of RRMM patients?
- Should ASCT be abandoned following the emergence of new biological and cellular therapies? In this regard, more evidence on the optimal timing of CAR-T cell therapy is needed.
- In this new COVID-19 era, which is the best approach for the treatment of patients with MM? [180].
- Is maintenance therapy until progression or intolerance still the most appropriate strategy for improving survival?

Despite the exciting therapeutic development of many new generation agents and combination regimens (including IMiDs or immunotherapy agents, as anti-CD38 monoclonal antibodies, conjugated antibodies, bispecific antibodies, and CAR-T) that are providing considerable improved progression-free survival and overall survival, there is still room left to further increase the rates of response and survival. RRMM management will soon be improved by the introduction of new biomarkers that will improve patient stratification and prognosis. This along with the definition of newer treatment algorithms that allow clinicians to design personalized therapeutic regimens (which balance the clinical and biological characteristics of MM, and patients’ comorbidities and preferences) will likely result in a safer and more effective precision medicine [181].

Abbreviations
ASCT/ASCT: Autologous stem cells transplants/ salvage autologous stem cells transplants; CC: Conventional chemotherapy; Dkd: Daratumumab plus carfilzomib plus dexamethasone; Dpd: Daratumumab plus pomalidomide plus dexamethasone; DRd: Daratumumab plus lenalidomide plus dexamethasone; DVd: Daratumumab plus bortezomib plus dexamethasone; HR: Hazard ratio; IMiDs: Immunomodulatory drugs; IRRs: Infusion-related reactions; Isa-Kd: Isatuximab plus carfilzomib plus dexamethasone; Isa-Pd: Isatuximab plus lenalidomide plus dexamethasone; Isa-Rd: Isatuximab plus lenalidomide plus dexamethasone; Kd: Carfilzomib plus dexamethasone; Kd: Carfilzomib plus lenalidomide plus dexamethasone; MoAbs: Monoclonal antibodies; MM: Multiple myeloma; OS: Overall survival; ORR: Overall response rate; PFS: Progression-free survival; Pd: Pomalidomide plus dexamethasone; PIs: Proteasome inhibitors; Pvd: Pomalidomide plus bortezomib plus dexamethasone; RCTs: Randomized clinical trials; Rd: Lenalidomide plus dexamethasone; RR: Relapsed/refractory; RW: Real world; Vd: Bortezomib plus dexamethasone; VaD: Bortezomib plus lenalidomide plus dexamethasone; VTd: Bortezomib plus thalidomide plus dexamethasone; XPO inhibitor: inhibitor of nuclear exportin

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