

# Updated Perspectives on the Management of Relapsed and Refractory Multiple Myeloma

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## Keywords

Myeloma · Lenalidomide-refractory patients

## Abstract

**Background:** With the availability of T-cell-directed therapy and next-generation compounds of established classes of drugs, the treatment of relapsed/refractory (r/r) myeloma is getting more complex. However, treatment options in practice are limited by availability, approval, and patient comorbidity. The aim of this article is to provide a practical approach toward the choice of treatment for r/r myeloma patients. **Summary:** Regarding market authorization and current guidelines, at least in Germany, most patients nowadays will have received a doublet or triplet combination as first-line therapy containing a proteasome inhibitor and an immunomodulatory drug, mostly lenalidomide. We focus on the treatment options for patients that are ineligible for (another) stem cell transplantation. We will review treatment options for relapse after first- or second-line therapy and beyond third-line. **Key Messages:** There is promising data supporting the efficacy and safety of triplet combinations containing anti-CD38-monoclonal antibodies (anti-CD38 mAbs) at first or second relapse in combination with next-generation compounds. For the treatment beyond third-line, comparative studies are scarce but some promising compounds are available via conditional authorization, and there is more to come in the future. We will present some early phase trials featuring promising results.

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## Introduction

ESMO guidelines offer an abundance of options and differ in various scenarios, but still 9 options listed in the relapsed/refractory (r/r) setting for “bortezomib-sensitive” patients after VRd looks not very helpful for the individual case [1]. We will try to describe existing treatments and stratify or give a certain order to choose from considering comorbidities and availability.

## When to Start Treatment?

The decision whether to start treatment at biochemical disease progression or with the occurrence of symptoms is not always straightforward. By far the most patients eventually develop a clinical relapse. There is some data pointing toward a PFS and OS benefit for early treatment [2, 3]. Presumably, this holds true especially for high-risk myeloma. The situation should be discussed with the patient individually considering cytogenetic risk, aggressiveness of the biochemical relapse, response, and treatment tolerability at earlier lines and comorbidity [4].

## Diagnostic Procedures at the Time of Progression

It is generally recommended to repeat all diagnostic procedures that were abnormal at the initial staging and to add different imaging modalities only when new disease manifestations are clinically suspected, for example,

MRI for extramedullary disease. Whole-body low-dose CT is much more sensitive than conventional X-ray. Therefore, it should be part of the initial staging whenever possible. MRI is most sensitive in the detection of focal intramedullary lesions and extraosseous disease and should be used additionally in patients with a negative CT scan [5]. Its widespread use is limited by availability, high costs, and patient factors (claustrophobia, inability to lie still).

PET-CT scan can replace conventional CT scan as long as it fulfills all criteria for conventional CT skeletal survey. However, in Germany, reimbursement of costs for PET-CT-scanning in myeloma patients is restricted. An advantage of the PET-CT during follow-up is that it may detect focal bone marrow infiltration in cases of sampling error with false-negative bone marrow aspirate and that it may differentiate active disease manifestations from inactive lesions or differential diagnosis such as scars. However, bone marrow enhancement can be false positive during recovery phase and osteolytic activity can be confused with bone healing processes [5].

When progress is suspected it is reasonable to first repeat low-dose CT scanning that can be compared to the initial staging. If this remains negative and there is serological progression or clinical signs of disease activity (e.g., suspected extramedullary manifestation), an MRI or a PET-CT scan can be added. However, in the absence of serological progression, it is recommended to obtain adequate histology of suspected extramedullary lesions, since treatment changes should not be based on imaging alone [5].

Concerning repeat bone marrow aspiration all patients should at least have a baseline sample sent for fluorescence in situ hybridization to detect IgH translocations (i.e.,  $t$  [4; 14] and  $t$  [11; 14]), which are early events, and secondary events that are high-risk features such as del17p and 1q21 gains. Fluorescence in situ hybridization testing should possibly be repeated at relapse (if not high risk in the first place) and include analysis for del17p, ampl/gain 1q and  $t$  (11; 14). Del17p is often acquired during disease course and conveys an unfavorable prognosis. There are not yet specific recommendations for high-risk patients in the relapsed setting. However, the knowledge of high-risk cytogenetics might influence treatment decisions such as when to start treatment, intensity of the treatment regimen, and indication for transplantation [6].

There are some examples that molecularly targeted treatments may be particularly useful, such as Venetoclax in patients with  $t$  (11; 14). Venetoclax as a late-line therapeutic option will be discussed at the end of this review. About 4% of myeloma patients carry an activating BRAF-mutation at diagnosis, the proportion doubles (app. 8%) at relapse [7]. It has no prognostic impact so far. How-

ever, results from the BIRMA trial indicate that the combination of the BRAF-inhibitor encorafenib and the MEK-inhibitor binimetinib might be effective in the treatment of BRAF-mutated myeloma, with an ORR of 82% in a small patient collective. There is some experience with the combination of a BRAF-inhibitor and a MEK-inhibitor in the treatment of solid tumors and the side effects observed in myeloma patients did not differ from those reported in solid tumors [7]. Thus, targeted mutational analysis at the time of progression might become even more important in the future.

Bone marrow aspiration is not required prior to immune-therapies, neither for anti-CD38 nor for BCMA-directed therapies. When anti-CD38 antibody-retreatment is considered, it may be useful to reassure that there is still CD38+-expression on plasma cells, since there are case reports of CD38-loss at relapse [8, 9].

### Can “Next Generation Compounds” Overcome Resistance?

Since lenalidomide is commonly used in first-line therapy and often combined with bortezomib, a high number of patients are pretreated with both substances early in their treatment course. Is lenalidomide retreatment feasible? Patients that progressed are usually excluded from further trials using the same compound, whereas in real-world retreatment or treatment beyond progression is not exceptional especially as part of a combination therapy. Treatment tolerability as well as aggressiveness of the progression should be taken into consideration [10].

### Is Pomalidomide an Option for Lenalidomide-Refractory Patients?

While all IMiDs (Immunomodulatory Drugs) exert their effects by targeting cereblon, pomalidomide has a distinct pharmacology compared to lenalidomide and, despite having a comparable binding affinity, results in higher efficacy by faster degradation of its substrates [11, 12]. It can induce responses in lenalidomide-refractory patients in combination with low-dose dexamethasone (ORR 32–33% [11, 13]), even directly after failure of lenalidomide and especially in patients who received only low-dose lenalidomide (15 mg or less) [12]. Pomalidomide is approved in Europe for second-line therapy in combination with bortezomib and dexamethasone (Vd) as well as in third-line therapy in combination with dexamethasone or Vd in patients pretreated with lenalidomide [14].

## Is Carfilzomib an Option for Bortezomib-Refractory Patients?

Proteasome inhibitors induce plasma cell apoptosis by blocking protein degradation. Carfilzomib is an irreversible proteasome inhibitor in contrast to bortezomib and ixazomib, which are reversible proteasome inhibitors [15]. The ENDEAVOR trial compared carfilzomib/dexamethasone to bortezomib/dexamethasone and included patients who were pretreated with bortezomib. In direct comparison, carfilzomib showed higher response rates (ORR 77% vs. 63%) and an overall survival benefit of 7 months than bortezomib (47 months vs. 40 months) [16]. One important toxicity of bortezomib is peripheral neuropathy. This side effect occurs infrequently following carfilzomib and patients with preexisting neuropathy can be treated with carfilzomib without worsening of neuro-pathic symptoms [17]. Carfilzomib can cause hypertension and cardiac failure as well as renal failure. Thus, it should be used with caution in patients with preexisting cardiac constraint and patients with preexisting hypertension [18]. Ixazomib was not effective in a small number of bortezomib-refractory patients (ORR/CBR = 0% for 3 mg and 18.7% for 4 mg). Adverse events were mostly hematotoxic [19].

## Anti-CD38-Monoclonal Antibodies

Daratumumab is a monoclonal antibody targeting CD38 (anti-CD38 mAb). It exerts its cytotoxic effects by recruitment and activation of immune cells and the complement system. It is effective as monotherapy in r/r myeloma and has a favorable toxicity profile. An ORR of 29% in heavily pretreated patients was observed in the SIRIUS trial [20]. Isatuximab is an anti-CD38 mAb that can additionally induce apoptosis in CD38<sup>+</sup>-cells directly independent of other immune cells. To the best of our knowledge, isatuximab has not been directly compared to daratumumab yet. The data for isatuximab used in subjects with daratumumab pretreatment is scarce and limited to heavily pretreated patients. It suggests that a longer interval after daratumumab without anti-CD38 treatment increases the likelihood of response to isatuximab [21].

Regarding the current standard in Europe, most patients receive at least lenalidomide or bortezomib in first-line therapy and many patients receive both substances upfront. Treatment options to consider at first relapse after VRD are daratumumab/pomalidomide/dexamethasone (DPd), anti-CD38 mAb/carfilzomib/dexamethasone (DKd or IsaKd) or, for patients that are unable to tolerate a more intensive regime, daratumumab monotherapy. For patients who are not bortezomib-

refractory, DVd and PVD are additional options. Elotuzumab (Elo)/pomalidomide/dexamethasone has received EMA approval from third-line therapy and onward in 2019 [1].

For patients considered lenalidomide-sensitive, KRd, DaraRd and Elotuzumab/lenalidomide/dexamethasone or IxaRd would be additional options. Here, we will focus on lenalidomide-refractory patients [1].

In the OPTIMISMM trial, PVD was compared to Vd in r/r myeloma. All patients had pretreatment with lenalidomide, and a large subgroup was lenalidomide-refractory (60%). There was a mPFS benefit of about 4 months (11.2 vs. 7.1 months; HR 0.61) for all patients including the subgroup of lenalidomide-refractory patients (9.5 vs. 5.6 months). It must be pointed out that 59% of the patients with only 1 prior line of therapy had pretreatment with bortezomib [22]. Thus, even if bortezomib-refractory patients were excluded from the trial, in a real-world situation Vd would not be considered an optimal treatment option for the patients in the control arm.

Daratumumab-Pd (DPd) was compared to Pd in the APOLLO trial. All patients had at least 1 prior line of therapy including pretreatment with lenalidomide and 80% of patients were lenalidomide-refractory. DPd resulted in a mPFS improvement of 5.5 months (12.4 vs. 6.9 months; HR 0.63) [23].

The ICARIA trial-tested isatuximab-Pd versus Pd in patients that were pretreated with a medium of 3 prior lines and were nonresponsive or refractory or could not tolerate lenalidomide, with a high proportion of patients being both refractory to lenalidomide and a proteasome inhibitor (71%). Isatuximab-Pd resulted in an mPFS benefit of 5 months (11.5 vs. 6.5 months; HR 0.6) and was adequately tolerated [24]. Of note, in these 2 latter studies, patients randomized to Pd apparently fared better (in terms of a cross-trial PFS comparison) in contrast to the pivotal study [25].

Kd seems to be an option as a doublet in lenalidomide-refractory patients with modest PFS of about 8 months [16, 26]. In the CANDOR trial, daratumumab-Kd (DKd) was tested against Kd in r/r myeloma patients with a median of 2 prior therapy lines and lenalidomide refractoriness in 33% of patients. Treatment with DKd resulted in an increase in mPFS. MPFS was not reached for DKd versus 15.8 months for Kd (HR 0.63) [27], an update was presented at ASH2020 with an mPFS of 28.6 months in the DKd-arm versus 15.6 months in the Kd arm (HR 0.59) [28]. The mPFS benefit was maintained in the group of lenalidomide-refractory patients (HR 0.45). The proportion of patients who discontinued treatment due to adverse events was approximately the same in both treatment arms (22% vs. 25%). Bronchial infection was more common in the daratumumab arm [27].

**Table 1.** Overview: treatment options for lenalidomide-refractory patients at first or second relapse

Treatment	Landmark study	Median prior lines of therapy	% Lenalidomide-refractory patients	mPFS	EMA approval
DKd versus Kd	CANDOR <i>n</i> = 466 [27, 28]	2	33	28.6 versus 15.6 months (HR 0.59)	Approved (second line and beyond)
IsaKd versus Kd	IKEMA <i>n</i> = 302 [29]	2	33	Not reached versus 19.1 months (HR 0.53)	Approved (second line and beyond)
DPd versus Pd	APOLLO <i>n</i> = 304 [23]	2	80	12.4 versus 6.9 months (HR 0.63)	Approved (len-refractory, third line and beyond)
IsaPd versus Pd	ICARIA <i>n</i> = 308 [24]	3	93	11.5 versus 6.5 months	Approved (third line and beyond)
EloPd versus Pd	ELOQUENT 3	3	87	10.3 versus 4.7 months	Approved (third line and beyond)
DVd versus Vd	CASTOR [30]	2	21	16.7 versus 7.1 months (HR 0.31)	Approved (second line and beyond)
PVd versus Vd	OPTIMISMM <i>n</i> = 559 [22]	2	60	11.2 versus 7.1 months (HR 0.61)	Approved (second line and beyond)

Dpd, daratumumab/pomalidomide/dexamethasone; EloPd, Elotuzumab (Elo)/pomalidomide/dexamethasone; DKd, daratumumab-Kd; IsaKd, isatuximab-Kd; IsaPd, isatuximab-Pd.

The combination isatuximab-Kd (IsaKd) was compared to Kd in r/r myeloma in the IKEMA trial. Patients had a median of 2 prior therapy lines and approximately 33% of patients were refractory to lenalidomide. An mPFS benefit was observed favoring IsaKd (mPFS not reached at 20.7 months' follow-up for IsaKd vs. 19.1 months for Kd; HR 0.53). The proportion of patients who discontinued treatment due to adverse events was lower in the IsaKd arm (8.5% vs. 13.9%). Pneumonia and dyspnea were more frequently reported in the isatuximab arm [29]. Study characteristics and outcomes are displayed in Table 1.

In conclusion, after failing first-line therapy, a triplet combination should be preferred over a doublet. Anti-CD38 mAbs obviously add benefit to next-generation Imids or PIs with good tolerability. We need more data concerning daratumumab-refractory patients.

The mPFS rates reported in the anti-CD38 mAb-Pd trials [23, 24], appear to be shorter than mPFS in the anti-CD38 mAb-Kd trials [28, 29], but those cannot be compared due to the differences in trial design and patient populations. The proportion of lenalidomide-refractory patients was higher in the APOLLO trial and especially high in the ICARIA trial where patients were more advanced in their disease course [23, 24]. Treatment selection should be based on comorbidity and prior therapy. We need more studies to compare the triplets with each other. Of note, carfilzomib-based mAb combinations are intended to be “continuous” rather than “fixed duration” treatments as a major discrepancy between carfilzomib/dex and bortezomib/dex “backbones” [28, 30]. This might, at least in part account for their excellent efficacy.

### Beyond Third-Line Therapy

Patients that are refractory to 2 IMiDs, 2 proteasome inhibitors and daratumumab, are called “penta-refractory” [31]. They pose a challenge to their treating physicians and should preferably be treated in clinical trials if available. Fortunately, some new treatment options have come up for this patient population. It goes beyond the scope of this review to list all of them. We chose to mention some of them in more detail. We will conclude with an outlook to promising treatment options that are currently in early clinical trial phase.

Belantamab mafodotin is the first-in-class antibody-drug conjugate directed against BCMA. It has been granted conditional authorization in the EU based on the DREAMM-2 study [32] that compared 2 different dose levels of belantamab mafodotin (2.5 mg/kg vs. 3.4 mg/kg) with each other but did not compare the substance to standard of care anti-myeloma treatment. The trial was conducted in heavily pretreated (at least triple-refractory) patients with a median of 6–7 prior lines of therapy and resulted in an ORR of 31% (2.5 mg/kg) versus 34% (3.4 mg/kg) and a mPFS of 2.8 months (2.5 mg/kg) versus 3.9 months (3.4 mg/kg). However, all patients experienced adverse events [33]. Even at the lower dose level of 2.5 mg/kg, grade 3/4 adverse events occurred in 83% of the patients [32]. The most frequently observed grade 3/4 adverse events were keratopathy (27%) and hematotoxicity (thrombocytopenia 20% and anemia 20%). Eight percent of the patients treated with 2.5 mg/kg discontinued treatment because of side effects, mostly due to keratopathy [33]. Comparative trials to established myeloma treatment regimes, such as Pd, are already underway

**Table 2.** Selected treatment options beyond third-line therapy

Treatment	Landmark study	Median prior lines of therapy	ORR, %	mPFS	EMA approval
Belamaf 2.5 mg/kg vs. 3.4 mg/kg	DREAMM 2 <i>n</i> = 196 [33]	6–7	31 vs. 34	2.8 vs. 3.9 months	Conditional authorization
Selinexor	STORM <i>N</i> = 122 [34]	7	26	3.7 months	Conditional authorization
VenetoclaxVd vs. PlaceboVd	BELLINI <i>n</i> = 291 [36]	1–3	82	22.4 vs. 11.5 months	Orphan designation
Melflufen	HORIZON <i>n</i> = 157 [38]	5	30	4.2 months	Not yet approved
Idecabtagene vicleucel	KarMMa <i>n</i> = 128 [42]	6	73	8.6 months	Positive EMA CHMP opinion (Jun 2021)

Belamaf, belantamab mafodotin; Melflufen, Melphalan flufenamide.

(DREAMM 3) [32]. Patients should be carefully selected with regard to the hematotoxic side effects.

Selinexor is an inhibitor of exportin 1 thereby blocking nuclear export. It has been evaluated in the STORM trial in combination with dexamethasone in patients that were pretreated with a median of 7 prior therapy lines. The investigators observed an ORR of 26% and a mPFS of 3.7 months. Severe thrombocytopenia was the most common grade 3/4 toxicity and occurred in 59% of patients. Eighteen percentage of the patients discontinued treatment because of side effects [34]. Again, the EMA granted conditional authorization because of a favorable risk-to-benefit ratio [35].

Venetoclax is the first example of personalized therapy based on molecular cytogenetic testing in myeloma. In the BELLINI trial, it was shown that venetoclax in combination with bortezomib/dexamethasone improves progression-free survival by about 9 months compared to Vd. However, there were more treatment-related fatal infections so that venetoclax in combination with bortezomib/dexamethasone had an unfavorable risk-to-benefit ratio except for patients with chromosomal aberration *t* (11; 14) and high *bcl2*-expression for whom PFS benefit was more pronounced but failed to demonstrate an OS advantage. In fact, regarding the increased risk of neutropenia and infection [36] patients should be carefully selected for venetoclax treatment. Other molecularly targeted therapies are under development.

Iberdomide is a modulator of cereblon-E-ligase that targets cereblon in a different way compared to the other IMiDs. So far, only very few results were reported. It is tested in 2 triplet combinations, iberdomide/daratumumab/dexamethasone (IberDd) versus iberdomide/bortezomib/dexamethasone (IberVd) in a small group of heavily pretreated patients (19 patients with a median number of 4 lines of therapy, ranging from 1 to 12 lines, vs. 21 patients with a median number of 6 prior lines of therapy, ranging from 1 to 14 lines). As far as the results are comparable in such small groups of patients, an ORR of 35% (IberDd) versus 50% (IberVd) was observed. This would be in line with the treatment options mentioned

earlier. The proportion of patients experiencing grade 3/4 events was 78% (IberDd) versus 65% (IberVd). Toxicity was mostly hematotoxic [37]. So far, there is no comparison of iberdomide combinations to established triplets, but we expect to learn more about this substance and its therapeutic potential in the future.

Melphalan flufenamide (Melflufen) is a peptide-conjugated lipophilic alkylating agent for intravenous injection. It was tested in the HORIZON trial in combination with dexamethasone in pretreated patients (medium number of 5 prior lines) with a relatively high proportion of extramedullary disease (35% of the patients included). An ORR of 30% with a mPFS of 4.2 months was reported. However, 96% of patients experienced grade 3/4 adverse events that were mostly hematotoxic. Seventy-nine percentage of patients developed grade 3/4 neutropenia, 76% grade 3/4 thrombocytopenia, and 43% grade 3/4 anemia. It deserves special mentioning that 24% of the patients with extramedullary disease had at least a partial remission [38], what seems promising in this difficult-to-treat patient population [39]. An overview of recent study results is displayed in Table 2.

Numerous studies tested anti-BCMA CAR-T-cell therapy in very small subsets of heavily pretreated r/r myeloma patients with impressive response rates over short observational periods [40]. One of the larger studies utilizing the second-generation compound idecabtagene vicleucel was reported by Raje et al. [41] with an ORR of 85% in 33 patients with a median number of 7 prior lines of therapy. Thirty-six patients were enrolled in the study, but 3 patients (8%) did not make it to CAR-T-cell reinfusion because of progression after leukapheresis. Ninety-seven percentage of patients experienced grade 3/4 adverse events that were mostly hematotoxic (85% of patients developed grade 3/4 neutropenia, 45% of patients developed grade 3/4 thrombocytopenia) and attributable to the lymphodepleting chemotherapy. The incidence of grade 3 CRS was low (6%), and there was no grade 4 CRS. One grade 4 neurologic event was observed [41]. The KarMMa trials are about to test BCMA-directed CAR-T-cells in larger patient cohorts. First results from the

KarMMA trial were presented at the ASCO 2020. In 128 patients, pretreated with a medium number of 6 prior lines of therapy, ORR was 73%. The toxicity observed was again mostly hematotoxicity. Grade 3 CRS was observed in 5% of patients and grade 3/4 neurologic events were observed in 3% of patients [42]. It remains to be seen how durable responses are.

One difficulty about CAR-T-cell therapy is to get the patient through the time between apheresis and CAR-T-cell infusion. In contrast, bispecific antibodies are off-the-shelf products. Early clinical data about the bispecific antibody talquetamab, CD3 × GPCR5, look very promising. The ORR was 63% in heavily pretreated patients (median prior lines of therapy: 5.5). The most important grade 3/4 events reported were neutropenia (45%), anemia (29%), and CRS (4%). No grade 3/4 neurotoxicity occurred. Most frequent low-grade AEs (75%, no grade 3/4) were skin related [43]. Teclistamab is another bispecific antibody, CD3 × BCMA. It resulted in an ORR of 63.8% in heavily pretreated patients (median number of 6 prior lines of therapy). Grade 3/4 events, observed in 39% of the patients, were mostly neutropenia (23%), infection-related AEs (15%), and anemia (9%). No grade 3/4 CRS occurred. Grade 3/4 neurotoxicity occurred in 2% of the patients [44]. The results for the bispecific antibodies, with some of them even administered via subcutaneous injection [43, 44], seem very promising and leave us excited about further clinical data.

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## Conclusion

In conclusion, there are several new treatment options for patients with r/r myeloma. The anti-CD38 mAb-triplets with carfilzomib or pomalidomide are effective and safe options at first or second relapse including in lenalidomide-refractory patients. Beyond third-line therapy, several new treatment options have emerged and are currently further investigated. Some of them are already available via conditional authorization. Since we might miss patients with each line of therapy, we need more comparative trials and real-world data to make the treatment choices based on an individual risk-to-benefit assessment.

## Conflict of Interest Statement

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## Author Contributions

Both authors have contributed equally.

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