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Review Article

An Update of the Appropriate Sequencing for Salvage Therapies in Multiple Myeloma

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Abstract. Current treatment strategies have led to unpredictable improvements in the management of multiple myeloma (MM) over time. However, resistance to therapy, particularly regarding lenalidomide refractoriness and, more recently, daratumumab and lenalidomide refractoriness, even in the first-line setting, has become an increasingly significant issue in recent years. This resistance complicates the identification of the optimal treatment algorithm for patients with relapsed/refractory MM, particularly at first relapse. In this review, we focus on current strategies for MM patients progressing on or after lenalidomide-based and daratumumab-lenalidomide-based regimens. The forthcoming availability of next-generation immunotherapies, along with a deeper understanding of resistance mechanisms, is highly anticipated. Meanwhile, based on promising results from recent studies, the approval of novel drugs to expand the current therapeutic armamentarium against MM is bringing us closer to the goal of making a potential cure for the disease much more achievable in the hopefully near future.

Keywords: Multiple myeloma; Refractory Disease; Immunotherapy; Bispecific antibody; CAR-T cells.

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Introduction. Multiple myeloma (MM) remains a challenging malignancy characterized by its recurrent and relapsing nature. Despite significant advances in first-line therapy, a large proportion of patients will experience relapse or refractory disease, requiring the use of salvage therapies. The sequencing of these therapies has become a critical issue in managing relapsed/refractory multiple myeloma (RRMM), as appropriate therapy selection can profoundly impact patient outcomes. In recent years, multiple new drugs have been introduced, and their optimal sequencing for salvage treatment has evolved. This review will discuss the key concepts, recent updates, and challenges related to the appropriate sequencing of salvage therapies in MM. Each agent or combination has distinct mechanisms of action, and the sequencing of these therapies is guided by several factors, including prior treatment exposure, drug resistance profiles, patient performance status, and comorbidities.

Historically, the sequencing of salvage therapies was relatively simple, mainly revolving around the use of a combination of proteasome inhibitors and immunomodulatory agents (IMiDs), mostly lenalidomide, usually combined with corticosteroids.

However, with the advent of monoclonal antibodies, drug conjugate antibodies (ADC), bispecific antibodies (Bs), and CAR-T cell therapies, together with the increasing number of novel agents (Selinexor, Melflufen) and combinations, the approach to treatment relapse and sequencing has become more and more challenging. Overall, recent updates highlight the importance of tailoring therapy based on the following factors:

- *Prior therapy exposure.* A key principle is, when possible, to switch the class of therapeutic agents. At the present time, in Italy, the first-line treatment for the large majority of newly diagnosed transplant-eligible (NDTE) MM patients is represented by the combination of Daratumumab - Bortezomib - Thalidomide - Dexamethasone (D-VTD) followed by autologous stem cell transplantation (ASCT) and lenalidomide maintenance, whereas for most of transplant-ineligible (NTE) patients, the first line therapy is represented by the triplet of Daratumumab-Lenalidomide-Dexamethasone (D-RD).

- *Depth of response to prior therapies*. Some patients may have had prolonged periods of remission with prior therapies, while others experience rapid progressive disease. The prognosis of patients with short-lasting remissions (usually below 18 months) or refractory disease is unfavorable, and these patients may benefit from more aggressive treatments, possibly including new immunotherapy approaches (such as CAR-T or Bispecific antibodies), which offer new avenues of treatment when traditional options have failed.

- *Patients' conditions*. Frailty and associated comorbidities might strongly impact the choice of available therapies.

Sequencing of Myeloma treatment after Lenalidomide refractoriness. Lenalidomide (Len) is nowadays the most used immunomodulatory drug in the treatment of MM, and it plays a pivotal role in the management of both newly diagnosed and relapsed/refractory MM. However, with the widespread use of Len in the first line of treatment both in TE and NTE patients, a significant proportion of patients eventually become refractory to Len at first relapse.[1,2] While still inquiring of whether progression on low dose Len (10 mg used in maintenance) was consistent with progression to full dose (25 mg), retrospective studies indicate the lack of relationship between the outcomes of Len-resistant patients and Len doses during progression, relapse at lower doses (5-15 mg) still being associated with poor outcome.[3] After a patient becomes refractory to Len, the treatment plan should focus on drugs with different mechanisms of action or capable of overcoming the mechanism of resistance. The most common approach in the Len-refractory setting is to use combination therapies, which have been shown to increase response rates compared to single-agent therapy. The most relevant combinations are discussed below (**Figure 1** and **Table 1**).

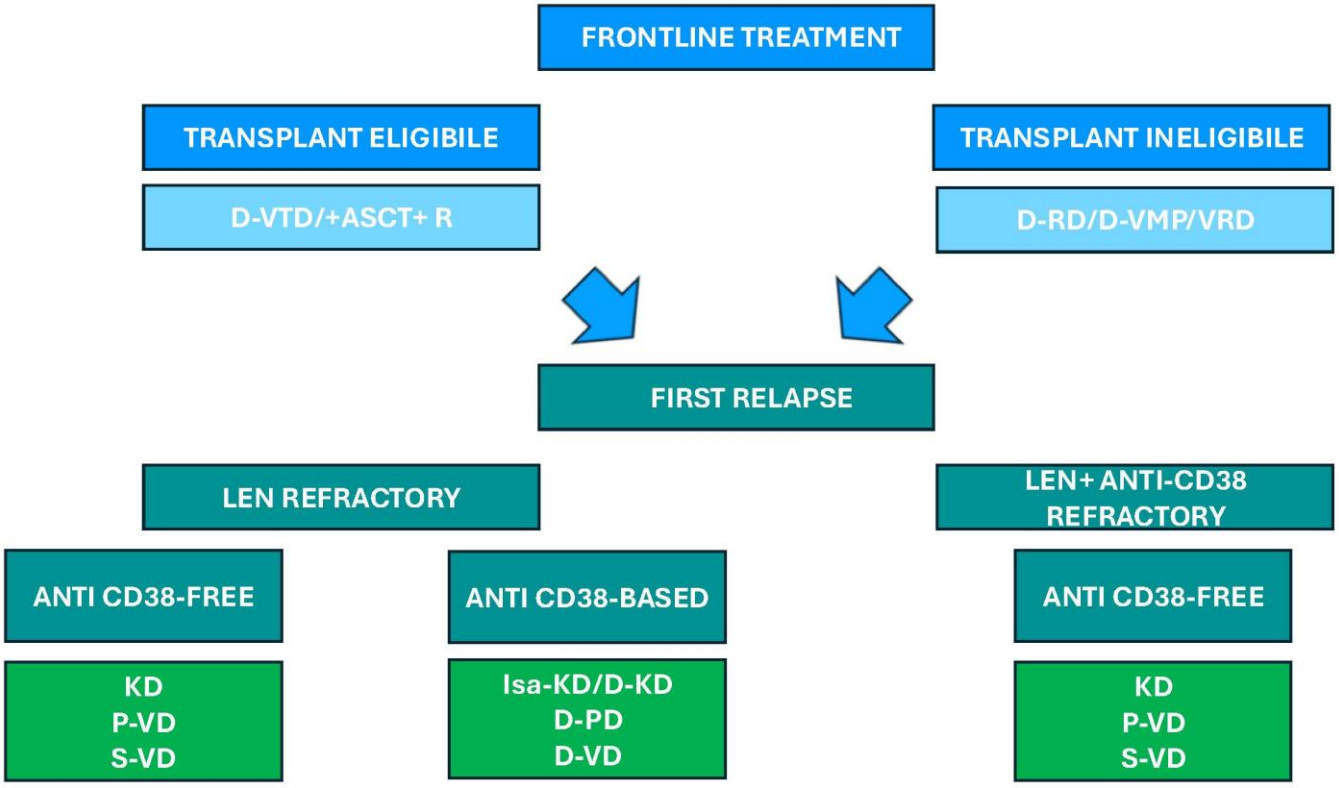

Figure 1. Treatment algorithm at relapse according to the current available treatments.

Table 1. Current pi-based and pom-based regimens approved for the treatment of len refractory patients.

Trial	Regimens	LOT (median)	LEN Exposed (%)	LEN Refractory (%)	ORR %	CR %	MRD – %	mPFS (months)	mPFS In LEN Refractory (months)	mOS (months)
Bortezomib Or Carfilzomib Based Regimens										
Castor	D-VD vs VD	2	36	24	85	30	15.1	16.7	7.8	49.6
Endeavour	KD vs VD	2	38	24	77	13	///	18.7	8.6	47.8
Ikema	Isa-KD-vs KD	2	40	32	86.6	39.7	29.6	35.7	Not reached	59.7% at 48 months
Candor	D-KD vs KD	2	39	32	84	33	27.9	28.4	28.1	50.8
Boston	S-VD	1	39.3	27.2	76.4	17	///	13.9	10.2	36.7
Pomalidomide Based Regimens										
Optimismm	P-VD vs VD	2	100	71	82.2	15.7	///	11.2	9.5	35.6
Apollo	D-PD vs PD	2-3	100	79	69	25	9	12.4	9.9	34.4
Icaria	Isa-PD vs PD	3	100	94	60	5	///	11.5	11.4	24.6

Abbreviations. PI: Proteasome inhibitors. POM: Pomalidomide. LOT: Lines of therapies. LEN: Lenalidomide. ORR: Overall response rate. CR: complete response. PFS: Progression free survival. OS: overall survival.

Anti-CD38 plus Carfilzomib and Dexamethasone combinations. The IKEMA and CANDOR trials both demonstrated that the addition of the anti-CD38 monoclonal antibody (Isatuximab or Daratumumab, respectively) to Carfilzomib and Dexamethasone significantly improved overall response rate (ORR), minimal residual disease (MRD) negativity rates and progression-free survival (PFS 35.7 and 28.4 months, ORR 87% and 84%, > VGPR 73% and 69%, MRD negativity rates 33.5% and 18%, respectively), with an improvement in overall survival (OS) compared to Carfilzomib and Dexamethasone alone.[4-9] Although not pre-specified in the protocols, the same results were also reported for Len refractory patients, accounting for roughly 30% of enrolled patients in both trials. Concerning safety, more patients in the anti-CD38 arms complain of hematological toxicities (mostly neutropenia and thrombocytopenia) and nonhematological (mostly upper respiratory tract infections), although treatment discontinuations were consistent with the control group. Interestingly a recently published paper, 103 real-life patients treated with IsaKD showed consistent results with respect to the original trial; interestingly, nearly all patients were len-exposed (19%) and Len-refractory (71%), thus reinforcing the data of IKEMA.[10]

Anti-CD38 plus Pomalidomide and Dexamethasone combinations. The APOLLO study demonstrated that the combination of Daratumumab-Pomalidomide-Dexamethasone (D-PD) significantly improves PFS (12.4 months) and ORR (69%) in patients with RR MM, compared to Pomalidomide and Dexamethasone alone. In this phase 3 trial, 89% of patients were Len refractory, with a median number of previous lines of two. This combination also granted deeper responses (≥ VGPR 51%), with a 9% rate of MRD negativity, and showed a manageable safety profile.[11,12] Additionally, the phase 2 MM014 trial evaluated the D-PD regimen in 112 patients after 1 or 2 previous lines of therapy and prior Len exposition, with 75% of cases Len refractory. With a median follow-up of 28.4 months, Len refractory patients showed an ORR of 76.2%, with 47.6% achieving a VGPR or better and PFS of 23.7 months, with no new safety signals observed.[13]

Interestingly, a real-life experience of D-PD recently published reported a mPFS of 18.9 months in patients progressing on Len and receiving second-line D-PD, thus reinforcing the MM014 results.[14]

The EMA approved the combinations of Pomalidomide and Dexamethasone with Isatuximab (Isa-PD) in the context of RRMM patients with 2 previous lines of therapy (LOT). Specifically, 307 patients, almost all patients (94%) were refractory to Len, who had received at least two previous LOTs, were randomized to receive Isa-Pd (154) or Pd (153) in the ICARIA trial.[15] With a median follow-up of 35.3 months, PFS was 11.1 vs 5.9 months in the control arm ($p<0{\cdot}0001$), and higher ORR and depth of response were reported.[16,17] Though treatment discontinuation was infrequent, dose reductions were more frequent in the Isa-Pd arm, with pneumonia being the most frequent serious AE (all grades, both groups: 23% for Isa-Pd and 21% in controls).[18] Of note, with a follow-up to approximately 52 months, Isa-Pd maintained a significant advantage with a benefit of 6.9-month improvement in OS (24.6 vs 17.7 months), proving Isa-Pd to be an option for patients who are refractory to other treatments, such as Len.[18,19]

Pomalidomide Bortezomib and Dexamethasone (P-VD). This combination was evaluated in the phase 3 OPTIMISMM trial, which was designed to assess the efficacy and safety of P-VD compared to VD in patients

with RRMM who had received one to three prior lines of therapy. The results of this study showed that the median PFS was longer with P-VD (11.2 months), with a 39% reduction in the risk of disease progression or death compared to Vd. At first relapse, Len refractory patients showed a PFS of 17.8 months, with an advantage in ORR (85.9%), quality of response (≥VGPR 56.3%), and MRD negativity rates. Concerning safety, neutropenia (35.9% vs. 12.9%) and thrombocytopenia (17.2% vs. 22.6%), peripheral sensory neuropathy (9.4% vs. 3.2%) and infections (29.7% vs 21.0%) were the most common grade 3/4 hematologic and nonhematologic TEAEs (P-VD vs VD), respectively.[20-22]

Daratumumab Bortezomib and Dexamethasone (D-VD) and Carfilzomib Dexamethasone (KD). In the CASTOR and the ENDEAVOUR trials, which evaluated the D-VD and KD, respectively, a clear PFS advantage was obtained with respect to the VD control arm, particularly at the first relapse (D-VD 27 months and KD 22.2 months); however, considering Len refractory patients (accounting for 24% of the study population in each trial), median PFS was 7.8 and 8.6 months, respectively. Consistently, both D-VD and KD yielded better PFS when used at first relapse; however, the advantage over VD in len refractory patients is markedly less pronounced.[23-28]

Selinexor - Bortezomib - Dexamethasone (S-VD). Selinexor is an oral, selective inhibitor of nuclear export (SINE) that blocks XPO1 (exportin 1), a protein responsible for transporting various tumor suppressor proteins and other important proteins out of the nucleus. The Selinexor-Bortezomib-Dexamethasone combination (S-VD) has been evaluated in the BOSTON trial, where S-VD demonstrated a significant PFS advantage with respect to VD.[29] However, the number of patients previously exposed to Dara was low (6%) and only 37% of patients were previously exposed to Len.[29] Interestingly, post hoc analysis from the BOSTON trial with 28 months follow-up further supported the role of S-VD in patients with Len-refractory disease (26% of total, n=106) at first relapse, particularly if PI naïve, showing a significant improvement in OS (OS 26.7 vs 18.6 months, respectively; HR 0.53; $p = 0.015$) compared with VD. The median PFS was longer in all subgroups (Len refractory: 10.2 vs. 7.1 months, PI-naïve: 29.5 vs. 9.7; bortezomib-naïve: 29.5 vs. 9.7; 1LOT: 21.0 vs. 10.7; $p < .05$), highlighting the importance of a double class switch in these patients.[30] One of the major concerns with Selinexor is represented by its toxicity profile, which includes hematologic toxicities (e.g., thrombocytopenia, neutropenia) and nonhematologic toxicities (e.g., fatigue, nausea, anorexia, and gastrointestinal effects), often leading to discontinuation (median time to discontinuation in Len-refractory patients: 6.1 vs 4.7 months for S-VD and VD arms, respectively), raising questions about tolerability of this combination. These effects were mitigated by dose modification of combination therapies, frequent monitoring of blood counts, and supportive care. Pre-medication with anti-nausea agents and adjusting the dose of dexamethasone may also help manage some side effects. These adverse events (AE) were also the most represented in a recently published real-world analysis.[31] Of notice, the once-weekly bortezomib administration significantly reduced the peripheral neuropathy rates with respect to bi-weekly administration scheduled in other regimens (i.e. D-VD or P-VD).

Novel Belantamab-based combinations. Belantamab mafodotin (Bela) is a BCMA-targeted antibody-drug conjugate (ADC) that has emerged as a promising treatment option in RRMM, particularly in patients who have become refractory to Len and Dara. Bela is composed of an anti-BCMA monoclonal antibody conjugated to a cytotoxic drug, monomethyl auristatin F (MMAF), which is delivered directly to the BCMA-expressing plasma cells. Once bound to BCMA, the ADC is internalized, and the cytotoxic drug MMAF induces cell death, making it an effective therapeutic agent in the treatment of multiple myeloma. The presence of BCMA on malignant plasma cells and its critical role in the survival of these cells makes BCMA-targeted therapies a central focus in the treatment of MM, especially for patients who have already undergone multiple lines of therapy.

In the DREAMM-2 study, single-agent belantamab mafodotin showed a response rate of about 31% in heavily pretreated patients, including those who were triple and penta-class refractory, and the treatment was associated with durable responses. In this setting, corneal toxicity (keratopathy) remains a significant dose-limiting side effect that has led to the investigation of combination therapies to optimize outcomes and minimize adverse effects.[32,33] Clinical trials investigating this combination have shown very encouraging results, with bortezomib potentially mitigating some of the immune suppression that can occur with daratumumab and lenalidomide resistance.

In the DREAMM-7 trial, Bela in combination with VD (Bela-VD) has been evaluated in 494 RRMM patients after at least one prior line of therapy, 34% of whom were Len-refractory (53% Len-exposed). In this study, after a median follow-up of 28.2 months, although the ORR was not clearly different from the control arm Dara-VD (82.7% vs. 71.3%, respectively), the PFS (36.6 vs. 13.4 months, respectively), the percentage of MRD negativity (MRD negativity 38.7% vs 17.1%) and DOR (35.6 vs 17.8 months) were significantly improved.[34] Notably, though OS was not reached in either arm at first interim analysis, OS at 18 months was 84% in the Bela-

VD group and 73% in the Dara-VD group, with a strong benefit in favor of Bela-VD (HR:0.57).[34] Interestingly, the advantage observed with Bela was extended to all subgroups, including Len refractory patients, that achieved an mPFS of 25 months and CR plus MRD of 25% compared to 6% with Dara-VD).

At the same time, Bela, in combination with Pomalidomide and Dexamethasone (Bela-PD), was tested in the DREAMM-8 trial. This study included 100% of Len-exposed patients with ¼ of previously anti-CD38 mAb exposure. At a median follow-up of 21.8 months, the results are extremely interesting, with a 48% reduction of risk of progression or death and a superior PFS compared to the control arm P-VD (12.7 months in the P-VD group), with a 12-month estimated PFS of 71% with Bela-Pd and 51% with P-VD. ORR was 77% (40% ≥CR, 24% MRD negative) vs 72% (16% ≥CR, 5% MRD negative), while follow-up for OS is ongoing.[35] Of note, among patients treated in the second line (n=82 in the Bela-arm, n=77 in the P-VD arm), PFS was not reached with Bela-Pd and 18.5 months with P-VD (12-month PFS rate: 78% vs. 64%; ≥CR: 46% vs. 23%, with MRD negativity of 27% vs 4%; median DOR: not reached vs 18.0 months, respectively). Specifically, results from Len-refractory patients receiving 2-line treatment (66 and 53 patients in the two arms, respectively) mPFS was not reached with Bela-Pd and 13.1 months with P-VD (12-month PFS rate: 74% vs. 53%; ≥CR: 44% vs. 21%, with MRD negativity of 22% vs 3%; median DOR: not reached vs 13.8 months; respectively).[36] AE is, as expected, mostly ocular (43% grade 3 or 4) but was effectively managed by protocol-recommended dose modification of Bela and was characterized by high rates of resolution, low treatment discontinuation rates, and the absence of a negative effect on patient-assessed QoL.

Sequencing of Multiple Myeloma Therapy After anti-CD38 mAb and Lenalidomide Refractoriness. The daratumumab-lenalidomide-dexamethasone (D-RD) regimen represents the first choice for NTE NDMM patients, significantly improving their survival outcomes.[37] However, a substantial proportion of patients are becoming both Dara and Len refractory, posing a complex challenge for clinicians. In line with this data, although at the time of this review, the number of Dara and Len refractory/relapsed patients is relatively low (the combination was introduced at relapse in Italy in 2018 and for the first line in 2021), it is expected that the number of double refractory patients will increase. Roughly 3,000 RRMM patients will become Dara and Len refractory in the period 2024-2028. Thus, refractoriness to these agents represents a critical point in disease progression. According to guidelines, actual treatment strategies at first relapse following Dara Len include PI-based and/or Pomalidomide-based combination, to which has been recently added the combination of S-VD (**Figure 2** and **Table 2**). The potential utility of anti-CD38 mAb retreatment does not represent an appealing opportunity since preliminary results showed no significant benefit.[38]

The use of KD and P-VD has already been discussed in previous paragraphs. In CD38 and Len refractory patients, the combination of Elotuzumab with Pomalidomide and Dexamethasone (Elo-PD) after at

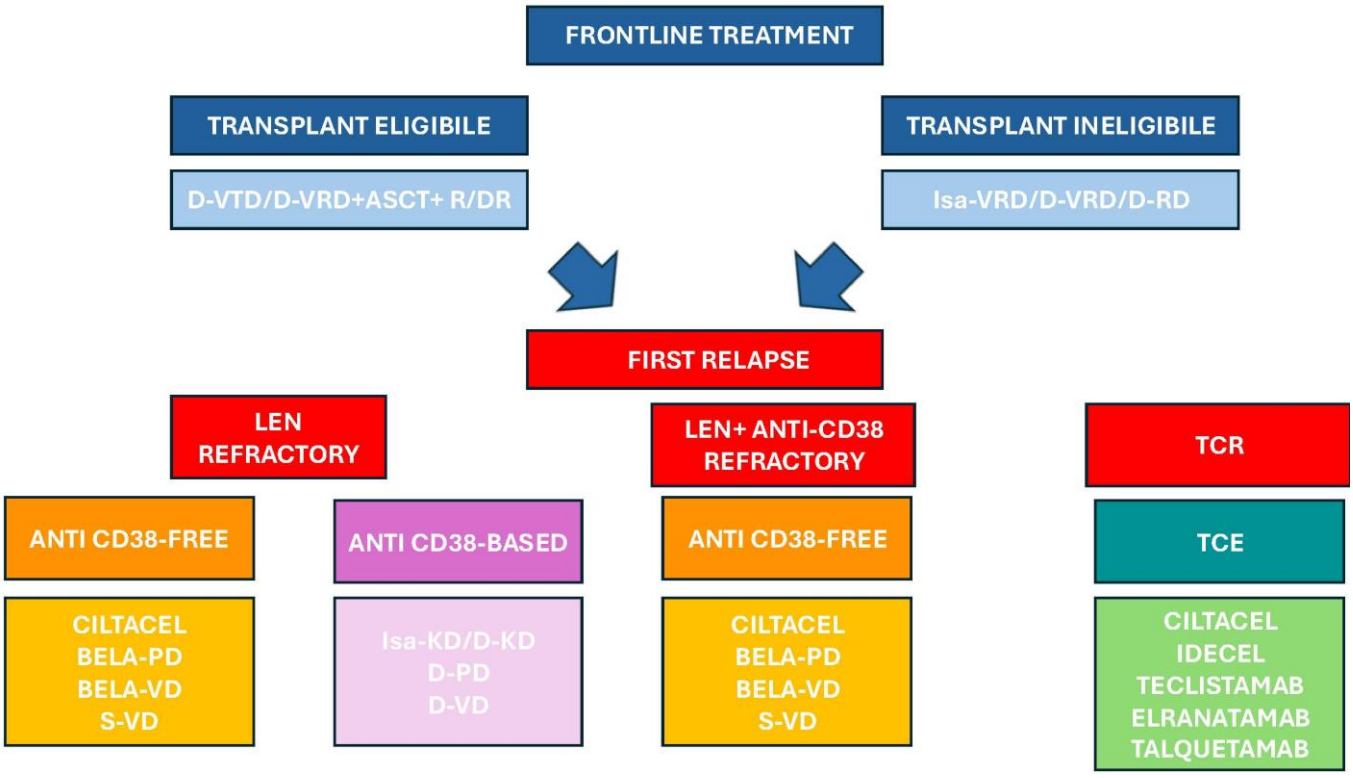

Figure 2. Treatment algorithm at relapse according to the future available treatments.

Table 2. Current and novel treatments for len and len+anti-cd38 refractory patients.

Trial	Regimens	LOT (median)	LEN Refractory (%)	Anti-CD38 mAB Refractory (%)	ORR %	CR %	MRD – %	mPFS (months)	mOS (months)
Eloquent-3	Elo-PD vs PD	2-3	90	1	53	5	///	10.3	29.8
Horizon	Melflufen-Dexa	5	97	80	26*	0*	///	3.9*	11.2*
Belantamab-Based Combinations									
Dreamm-7	BELA-VD vs D-VD	1	33	0	82.7	34.6	39	36.3	Not reached
Dreamm-8	BELA-PD VS P-VD	1	81	23	77	24	50	Not reached	Not reached
Car-T Cells									
Karmma-1	IDECEL	6	98	94	73	33	26	8.8	19.4
Karmma-3	IDECEL vs SOC	3	79	94	71	39	35	13.3	41.1
Cartitude-1	CILTACEL	6	81	97	97	67	34	34.9	Not reached
Cartitude-4	CILTACEL vs D-PD/P-VD	2	100	24	84.6	73.1	60.6	59.4% at 30 months	76.4% at 30 months
Bispecifics Antibodies									
Majestec-1	TECLISTAMAB	5	92.1	89.7	63	39.4	85.7%**	11.3	21.9
Magnetismm-3	ELRANATAMAB	5	96.7*	96.7*	61	35	89.7%°	17.2	24.6
Monumental-1	TALQUETAMAB	6	71	92	69§	40§	///	11.2§	77% at 12 months

*Triple class refractory; **In evaluable patients; ° in patients with ≥CR; § 0.8 mg/Kg every 2 weeks.
Abbreviations. LOT: Lines of therapies. LEN: Lenalidomide. ORR: Overall response rate. CR: complete response. PFS: Progression free survival. OS: overall survival.

least two lines of therapy has demonstrated efficacy (PFS 10.3 months and OS 29.8 months) with a low-level of toxicity in a phase 2 trial.[39,40] However, this study did not include patients with anti-CD38 mAb treatment, and an Italian real-life experience has reported a significantly lower response to this combination in Dara-refractory patients.[41,42]

Melphalan sulfenamide (*Melflufen*) is a recently approved chemotherapy drug in the treatment of MM, according to data from the Ocean trial, namely in patients with relapsed/refractory multiple myeloma who have not received an ASCT or progressed >36 months after receiving an ASCT.[43,44] It is a hybrid molecule that combines the alkylating agent melphalan with a peptide linker, allowing for more targeted delivery of the drug to myeloma cells. Melflufen is an alkylating agent that works by binding to the DNA of cancer cells, leading to cross-linking of DNA strands, preventing replication, and triggering cell death. Ongoing trials and studies have shown that melflufen when used with dexamethasone, provides promising results (PFS 5.6 months and OS 23.4 months) for patients who are heavily pretreated (i.e., who have undergone at least three previous lines of prior therapy). Side effects and toxicity concerns have been raised. One of the most common adverse effects is hematologic toxicity, particularly thrombocytopenia and neutropenia.[43,44]

As previously reported, the combinations of Bela-VD and Bela-PD represent an interesting option for these patients. In particular, Bela-PD represents a promising combination in this setting since in the DREAMM-8 study, the percentages of Len and anti-CD38 mAb refractory patients were 81% and 23%, respectively. Although these therapies will represent a relevant improvement in the RRMM setting, novel immunotherapies have favored the more relevant progress in the therapy of RRMM. These approaches include CAR-T cells and Bispecific Antibodies.

CAR-T cell therapy. Idecabtagene vicleucel (Ide-cel) is the first class anti-BCMA CAR-T cell therapy approved due to the results of the KarMMa-1 trial, which enrolled patients with six previous lines of therapy, some patients being still in remission after 3 years follow up.[45] Real-life results were consistent with those of the clinical trial, although more than 70% of patients treated in real life did not meet the criteria for the KarMMA-1 study.[46] More recently, in the KarMMa-3 trial enrolling Triple Class–Exposed (TCE) RRMM patients who have received at least two prior therapies, ide-cel compared to P-VD, obtained an extended PFS (PFS: 13.3 vs. 4.4 months, P <0.001), ORR (71% vs. 42%, p<0.0001) including ≥CR (44% vs 6%) and ≥CR plus MRD-negativity (35% vs 2%, at 10^{-5} sensitivity) and OS (41.4 vs 37.9 months), with an overall manageable toxicity profile.[47,48] Of great interest, Ide-cel has demonstrated a favorable risk-to-benefit ratio in the KarMMa-2 cohorts 2a and 2c in early relapse of the disease with high rate, deep and sustained responses in patients with RRMM progressing within 18 months after treatment initiation, with a manageable safety profile.[49,50]

More appealing results originate from the second

approved anti-BCMA CAR-T cell, Ciltacabtagene autoleucel (Cilta-cel). The CARTITUDE 1 study enrolled patients with more than six previous lines of therapy, 87% of whom were triple-class refractory and 40% penta-refractory. The ORR was nearly 98%, with an MRD negativity rate of 90% (for valuable patients), the PFS was 34.7 months, and the median OS was not reached.[51,52]

The CARTITUDE-4 is a phase 3 clinical study designed to assess the efficacy and safety of Cilta-cel in Len refractory patients with 1-3 prior lines of treatment. The CARTITUDE-4 study has shown enthusiastic results, with ORR of 85% and many patients achieving stringent complete responses (CR >73%) and a median PFS that has not been reached and is significantly higher with respect to the control arm (either D-PD or P-VD, PFS 11 months). At the last updated at 30 months follow up, PFS in the Cilta-cel and control arms was 59.4% and 25.7%, respectively (HR (95% CI): 0.29 (0.22–0.39); P<0.0001), while 30-month OS was 76.4% vs 63.8% in the groups, respectively (HR, 0.55; 95% CI 0.39-0.79; P = 0.0009).[53,54]

While CAR-T cells showed promising efficacy in Len and Dara refractory patients, there are notable safety concerns associated with these therapies that require careful management. Both Ide-cel and Cilta-cel have been associated with cytokine-release syndrome (CRS), though generally manageable with supportive care and the use of IL-6 inhibitors like tocilizumab. Interestingly, in the CARTITUDE-4 trial, CRS was reported to have a lower incidence with respect to the registration study, likely due to a better bridging therapy, and, in most cases, it was mild to moderate. Immune effector cell–associated neurotoxicity syndrome (ICANS) is another known side effect of CAR-T therapies; fortunately, neurotoxicity with Cilta-cel in the CARTITUDE-4 trial appears to be manageable, and most cases are reversible. CAR-T cells are also associated with hematologic toxicities, such as cytopenias (e.g., neutropenia, thrombocytopenia, and anemia), which are common after the infusion due to the impact on the bone marrow. Prolonged cytopenias can occur, and patients may require growth factors and transfusions to support blood counts during recovery. Due to the immunosuppressive effects of CAR-T therapy and the pre-conditioning chemotherapy, infections are a concern. Prophylactic measures for bacterial, viral, and fungal infections are typically recommended during the initial months following CAR-T cell infusion.

Bispecific Antibodies in Refractory Multiple Myeloma. Another promising approach to treat RRMM is the use of bispecific antibodies (BsAbs). These are engineered antibodies that can bind simultaneously to two different antigens. In the context of multiple myeloma, bispecific antibodies are designed to engage both the CD3 receptor on T cells and tumor-associated antigens (such as BCMA, GPRC5D, or FCRH5) on the surface of myeloma cells. This dual targeting facilitates T-cell activation and directs them to kill the myeloma cells, leading to improved anti-tumor activity. Up to now, the anti-BCMA BsAbs Teclistamab and Elranatamab and the anti-GPRC5D BsAb Talquetamab are available for the treatment of RRMM.

Teclistamab activity was investigated in the Majestec-1 trial. In this study, Cohort A included patients with a median of 5 previous lines of therapies (LOT), nearly 60% of triple class refractory (TCR), and 30% of penta refractory (PCR). At 30 months of follow-up, the ORR is 63% (≥ VGPR 59.4%), the median PFS is 11.3 months, and the median OS is 21.9 months. Major toxicities were represented by neutropenia and infection (the latter 50% of grade 3-4), whereas CRS and ICANS incidence was very low and mostly of grade 1-2.[55] Real-life data on Teclistamab were recently published by American and European groups, with consistent results. In these studies, the large majority of patients would have been excluded from the Majestec-1 trial, mostly for previous exposition to anti-BCMA agents, either CAR-T cells or Belantamab Mafodotin. However, efficacy data were consistent with the pivotal trial.[56]

Elranatamab efficacy and toxicities were evaluated in the MagnetisMM-3 trial. In this study, patients included presented a median LOT of 5, and half of them were PCR. The recently updated results reported an ORR of 61% (≥ VGPR nearly 60%) and median PFS and OS of 17.2 months and 24.6 months, respectively. As for Teclistamab, major toxicities were represented by neutropenia and infections, while CRS, although reported in 71% of cases, were mostly of grades 1-2. Finally, ICANS was less than 4%. Overall, the observed safety profile with Elranatamab is consistent with that of Teclistamab as well as other BCMA-targeted bispecific antibodies.[57,58]

Talquetamab, the first-in-class BsAb targeting GPRC5D, was explored in the MonumeTAL-1 study, which included heavily pretreated patients (median LOT=6, TCR=75%, PCR=25%). Despite a different target, the results were almost superimposable with the other BsAb, with ORR of 60-70% and a median PFS of 7.5 and 11.9 months in the once-weekly and every-two-week dosing cohorts, respectively.[59]

Current present and future directions in Salvage Therapy Sequencing. Although the sequencing of therapy in RRMM is evolving rapidly, the current standard for Len refractory patients at first relapse typically involves IsaKD or D-PD in patients who are naïve to or still sensitive to anti-CD38 monoclonal antibodies. For others, combinations like S-VD, P-VD, or KD can offer viable alternatives. The choice between these options is often influenced by factors such as the patient's overall fitness, cardiovascular health, and the

need for biweekly intravenous administration of carfilzomib. On the other hand, Dara-PD, which benefits from the subcutaneous administration of daratumumab, may influence the decision for third-line therapy. In patients who are double-refractory to Daratumumab and Lenalidomide, S-VD and, in the coming years, Bela-VD are considered the most appropriate options.

Additionally, CAR-T therapies and BsAbs are poised to play an increasingly crucial role. Cilta-cel, in particular, has shown promising results in Len refractory patients at first relapse, as demonstrated in the CARTITUDE-4 trial, offering significant benefits over current standard therapies. However, concerns remain regarding the real-world feasibility of these therapies, especially as potential second-line options. One of the major issues is the optimal sequencing between CAR-T and BsAb. Real-world evidence suggests that anti-BCMA CAR-T should be offered before anti-BCMA BsAb, while Talquetamab could be an appropriate bridging therapy to Idecel or Ciltacel.[60,61] The high number of patients in need of CAR-T therapy and the limited number of Centers capable of administering these treatments pose substantial challenges. Moreover, the requirement for dedicated hospital beds at each Center represents a logistical barrier. Bispecific antibodies, which are off-the-shelf treatments, may soon offer a more feasible alternative to CAR-T, yet robust data on the optimal sequencing to maximize their efficacy is still needed. The lower risk of severe infections compared to anti-BCMA BsAb, along with the efficacy demonstrated even after previous anti-BCMA therapy, could be key factors in the choice of Talquetamab in patients with reduced performance status or with a high risk of infectious complications. Finally, the management of ongoing therapy and treatment-related toxicities remains critical when using these agents.

Although not likely available soon, another interesting class of drugs, i.e., the cereblon E3 ligase modulator (Celmod) compounds, characterized by increased potency, selectivity for cereblon, and enhanced immune stimulation compared to IMiDs, would contribute to improving the possibility of limiting the neoplastic plasm cell growth. Iberdomide and Mezigdomide were specifically designed to achieve rapid, potent, and deep degradation of Ikaros and Aiolos, key transcription factors in hematopoietic cell development and differentiation, and initial promising data have been recently published with the use of these drugs in heavily pretreated MM patients.

Furthermore, the sequencing of salvage therapies will likely be influenced by several key factors.[64] Biomarker-driven therapies, particularly as mechanisms of resistance to treatment become better understood, will play an increasingly important role. As the molecular profiling of multiple myeloma advances, it will become clearer which patients would benefit most from specific therapies, such as BCL-2 inhibitors or BCMA-targeted therapies. The challenge of optimizing treatment combinations will also intensify in the near future. The most effective ways to combine newer drug classes (e.g., CAR-T, BsAbs) with traditional agents (e.g., proteasome inhibitors, IMiDs, Celmod) are still being explored in clinical trials, with the goal of improving response rates and overall survival. Another promising avenue is the combination of different BsAbs (e.g., Talquetamab and Teclistamab), which have shown encouraging results in difficult-to-treat conditions like extramedullary disease, even if careful attention must be given to severe adverse events related to these drugs. Finally, ongoing trials of new therapies—such as novel monoclonal antibodies targeting alternative immune checkpoints, small molecule inhibitors, and next-generation CAR-T therapies—are set to expand the therapeutic options available for salvage treatments. These developments will provide additional sequencing choices for patients with relapsed/refractory disease.

Conclusions. The sequencing of salvage therapies in multiple myeloma is a dynamic and evolving process influenced by the increasing number of available therapeutic agents. Personalization based on the patient's disease characteristics, prior treatment history, and individual preferences is central to optimizing outcomes. As new drugs and strategies emerge, clinicians must continuously update their treatment algorithms to ensure that patients with RRMM receive the most effective and appropriate therapies at each stage of disease progression. The future of salvage therapy sequencing in multiple myeloma holds promise, with the potential for even more tailored and efficacious treatments.

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