Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group

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This Policy Review presents the International Myeloma Working Group's clinical practice recommendations for the treatment of relapsed and refractory multiple myeloma. Based on the results of phase 2 and phase 3 trials, these recommendations are proposed for the treatment of patients with relapsed and refractory disease who have received one previous line of therapy, and for patients with relapsed and refractory multiple myeloma who have received two or more previous lines of therapy. These recommendations integrate the issue of drug access in both low-income and middle-income countries and in high-income countries to help guide real-world practice and thus improve patient outcomes.

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Introduction

The treatment of multiple myeloma has changed drastically in the past decade with the incorporation of novel agents into therapeutic strategies. These new drugs, in various combinations, have been added to national and international clinical guidelines and have transformed the approach to the treatment of patients with multiple myeloma, resulting in substantial improvements in overall survival.[1,2]

With the availability of at least seven different classes of approved agents, including alkylators, steroids, proteasome inhibitors, immunomodulatory agents, histone deacetylase inhibitors, monoclonal antibodies, and selective inhibitors of nuclear export, which can be combined in doublet, triplet, or even quadruplet regimens and used with or without high-dose therapy and autologous stem-cell transplantation (ASCT), or in some cases as continuous treatment, the choice of the optimal strategy at diagnosis and at relapse represents a challenge for physicians. Moreover, next-generation immunotherapies or targeted agents will soon improve the therapeutic armamentarium. Also somewhat problematic is the scarcity of trials addressing important questions, such as the integration of the first salvage regimen into the assessment of front-line therapies to define optimal treatment sequencing strategies in homogeneous or at least similar patient populations. Furthermore, few data are available on the efficacy of the different approved regimens in specific patient populations, such as those with refractory disease versus those being treated for relapse after a treatment-free interval, those with biochemical versus symptomatic relapse, those with relapse after one previous line of therapy versus those with more advanced disease, those with high-risk versus standard-risk cytogenetic profiles, and those with extramedullary disease, among others.[3]

Several phase 3 trials have shown improved survival outcomes (progression-free survival, overall survival, or both) with the use of triplet combinations, suggesting that at least two active drugs should be combined with steroids, if patients can safely tolerate this therapeutic regimen. However, combinations of the aforementioned agents are unfortunately associated with a high cost, which raises two important issues: drug access in both low-income and middle-income countries and in high-income countries, and the definition of value versus patient benefit.

At the time of relapse, the treatment choice is affected by many patient-related and disease-related factors, such as patient preference, age, cytogenetic profile, pre-existing toxicities, comorbidities, and aggressiveness of the relapse, but mostly by the type of, and the response to, previous therapies.[4] The aim of this Policy Review is to discuss the currently available data for the treatment of relapsed and refractory multiple myeloma and to propose clear recommendations and guidelines for routine practice, recognising the challenges of clinical trial complications and translating phase 2 and 3 study results to real-world practice.[5]

Treatment of relapsed and refractory disease in patients who have received one previous line of therapy

The most important question for most cases of myeloma relapse, or disease that is resistant to therapy, is whether a patient has lenalidomide-refractory disease or not (figure 1). A second consideration that will be increasingly

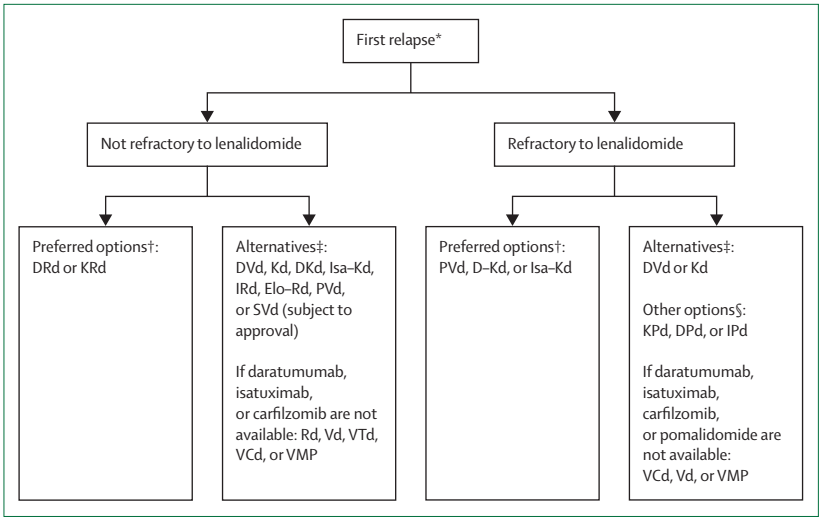

Figure 1: **Recommendations for the first relapse of myeloma in patients with lenalidomide-refractory disease**
DKd=daratumumab plus carfilzomib plus dexamethasone. DPd=daratumumab plus pomalidomide plus dexamethasone. DRd=daratumumab plus lenalidomide plus dexamethasone. DVd=daratumumab plus bortezomib plus dexamethasone. Elo–Rd=elotuzumab plus lenalidomide plus dexamethasone. IPd=ixazomib plus pomalidomide plus dexamethasone. IRd=ixazomib plus lenalidomide plus dexamethasone. Isa–Kd=isatuximab plus carfilzomib plus dexamethasone. Kd=carfilzomib plus dexamethasone. KPd=carfilzomib plus pomalidomide plus dexamethasone. KRd=carfilzomib plus lenalidomide plus dexamethasone. PVd=pomalidomide plus bortezomib plus dexamethasone. Rd=lenalidomide plus dexamethasone. SVd=selinexor plus bortezomib plus dexamethasone. VCd=bortezomib plus cyclophosphamide plus dexamethasone. Vd=bortezomib plus dexamethasone. VMP=bortezomib plus melphalan plus prednisone. VTd=bortezomib plus thalidomide plus dexamethasone. *Consider salvage auto-transplantation in eligible patients. †Grade of recommendation: 1A. ‡Grade of recommendation: 1B. §Grade of recommendation: 1C.

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important is whether the disease is progressing on front-line therapies that include daratumumab.

On the basis of the overall survival benefits seen in randomised trials and meta-analyses, lenalidomide is used as part of the front-line therapy for newly diagnosed multiple myeloma. In patients treated with upfront ASCT, lenalidomide monotherapy at a low dose is approved as a maintenance therapy until disease progression.[6,7] In patients with previously untreated, newly diagnosed multiple myeloma who are not eligible for ASCT, lenalidomide is also approved in combination with low-dose dexamethasone until disease progression, on the basis of the results of the FIRST trial.[8] Additionally, in the prospective SWOG0777 trial, which enrolled patients with newly diagnosed multiple myeloma who were not intended to undergo immediate ASCT, the regimen of bortezomib plus lenalidomide plus dexamethasone followed by lenalidomide plus dexamethasone until progression resulted in significantly improved progression-free survival and overall survival.[9,10] However, ultimately, a high number of patients taking continuous treatment including lenalidomide as front-line therapy have disease progression.

First relapse in patients with lenalidomide-refractory disease

Patients with lenalidomide-refractory disease were rightly excluded from randomised phase 3 trials testing lenalidomide plus dexamethasone versus lenalidomide plus dexamethasone plus a third agent (either a proteasome inhibitor [carfilzomib[11] or ixazomib[12]] or a monoclonal antibody [elotuzumab[13] or daratumumab[14]]). The precise effect of lenalidomide-based triplet combinations in patients with lenalidomide-refractory disease is unknown, but it would most likely lead to suboptimal results, and these regimens are therefore rarely used in this setting. The only known study showing that the addition of a third agent to lenalidomide and steroids might rescue lenalidomide-refractory disease is the phase 1–2 trial (n=67 patients) reported by Nijhof and colleagues,[15] which showed that the addition of continuous low-dose oral cyclophosphamide to lenalidomide and prednisone induced a 67% response rate, with a median progression-free survival of 12·1 months and an overall survival of 29·0 months in lenalidomide-refractory patients.

For a patient who has disease progression while taking lenalidomide as part of their front-line therapy, a reasonable approach would be to switch the class of agent, from an immunomodulatory drug to a proteasome inhibitor. Bortezomib plus dexamethasone was the first combination used in this setting, resulting in progression-free survival ranging from 8 to 10 months.[16] Cyclophosphamide can also be added to bortezomib plus dexamethasone to increase the response rate, but no prospective comparison of bortezomib plus dexamethasone versus bortezomib plus cyclophosphamide plus dexamethasone in relapsed myeloma has been done yet.

Several phase 3 trials have evaluated proteasome inhibitor-based combinations using bortezomib plus dexamethasone as the control regimen in relapsed and refractory multiple myeloma, but few patients with true lenalidomide-refractory disease were included. In the randomised, phase 3 ENDEAVOR trial,[17,18] bortezomib plus dexamethasone was prospectively compared with carfilzomib plus dexamethasone in patients with relapse after one to three previous lines of therapy, until disease progression occurred. This trial, a head-to-head comparison of two proteasome inhibitors, showed that both progression-free survival (median 18·7 months *vs* 9·4 months; hazard ratio [HR] 0·53 [95% CI 0·44–0·65]; p<0·0001)[17] and overall survival (median 47·6 months *vs* 40·0 months; HR 0·79 [95% CI 0·65–0·96]; p=0·01)[18] were superior with carfilzomib plus dexamethasone than with bortezomib plus dexamethasone across the whole group of patients. The number of patients refractory to lenalidomide (regardless of the number of previous lines of therapy) in this trial was 113 in the carfilzomib plus dexamethasone group and 122 in the bortezomib plus dexamethasone group, although the total number of patients who had progressed on front-line lenalidomide was not specified.[19] The median progression-free survival in patients with lenalidomide-refractory disease was rather short: 8·6 months with carfilzomib plus dexamethasone versus 6·6 months

with bortezomib plus dexamethasone.[19] Overall survival was numerically, but not significantly, longer by 7·8 months with carfilzomib plus dexamethasone versus bortezomib plus dexamethasone (median 29·2 months *vs* 21·4 months; HR 0·857 [95% CI 0·623–1·178]; p value not available).[20] These findings suggest that patients with lenalidomide-refractory disease might not benefit as much from carfilzomib plus dexamethasone combination therapy as those with a previous response to lenalidomide.

In the CASTOR trial,[21] bortezomib plus dexamethasone was compared with daratumumab plus bortezomib plus dexamethasone in patients with relapsed multiple myeloma who had received at least one previous line of therapy. The triplet combination was associated with significantly longer progression-free survival in all patients (median not reached *vs* 7·2 months; HR 0·39 [95% CI 0·28–0·53]; p<0·001),[21] as confirmed by an updated analysis in which, after a median follow-up of 47·0 months, the median progression-free survival with bortezomib plus dexamethasone plus daratumumab was longer than with bortezomib plus dexamethasone alone (16·7 months *vs* 7·1 months, HR 0·31 [95% CI 0·25–0·39]; p<0·0001).[22] As in the ENDEAVOR study, the total number of patients whose disease had progressed during front-line lenalidomide treatment was not specified. The only information available is based on a subgroup analysis showing that, in patients with lenalidomide-refractory disease (regardless of the number of previous lines of therapy), progression-free survival was longer with daratumumab plus bortezomib plus dexamethasone (median 7·8 months; n=60) versus bortezomib plus dexamethasone (median 4·9 months; n=81). These results are similar to the data reported in the ENDEAVOR study for a similar subgroup of patients,[23] which suggests that daratumumab plus bortezomib plus dexamethasone is also suboptimal for this patient population. Overall survival data for this subgroup of patients in the CASTOR trial are not yet available. Importantly, the safety profile of the triplet combination seems to be acceptable, and daratumumab was not found to add any substantial toxicity to the bortezomib plus dexamethasone combination.

The phase 3 PANORAMA 1 study,[24] comparing bortezomib plus dexamethasone with bortezomib plus dexamethasone plus panobinostat, enrolled a subgroup of patients progressing on lenalidomide as front-line therapy, but the number of patients in this setting was very small (n not specified) and previous treatment with lenalidomide was not a stratification factor. Overall, the study showed that the combination of bortezomib plus dexamethasone plus panobinostat improved progression-free survival by 4 months compared with the doublet regimen, but did not result in an overall survival benefit.[25] The toxicity observed in the panobinostat group of the trial, especially the high frequency of fatigue, thrombocytopenia, and grade 3 or grade 4 gastrointestinal adverse events, does not support the use of this triplet combination in patients with lenalidomide-refractory disease.

In the phase 3 OPTIMISMM trial,[26] the combination of pomalidomide plus bortezomib plus dexamethasone (n=278) was prospectively compared with bortezomib plus dexamethasone (n=270) in patients with relapsed and refractory multiple myeloma who had received one to three previous lines of therapy that included lenalidomide. More than 70% of the patients had lenalidomide-refractory disease. After a median follow-up of 16 months, pomalidomide plus bortezomib plus dexamethasone resulted in an improved median progression-free survival versus bortezomib plus dexamethasone alone (11·2 months *vs* 7·1 months, HR 0·61 [95% CI 0·49–0·77]; p<0·0001). The median progression-free survival was also longer with pomalidomide plus bortezomib plus dexamethasone than with bortezomib plus dexamethasone alone in patients with lenalidomide-refractory disease (9·5 months *vs* 5·6 months, HR 0·65 [95% CI 0·50–0·84]; p=0·0008), in patients with one previous line of treatment (20·7 months *vs* 11·6 months, HR 0·54 [95% CI 0·36–0·82]; p=0·0027), and, of particular interest, in patients who had received one previous line of treatment and had lenalidomide-refractory disease (17·8 months *vs* 9·5 months, HR 0·55 [0·33–0·94]; p=0·03).[27] Overall survival data are not available due to the relatively short follow-up of this trial (16·4 months).

Combinations of carfilzomib plus dexamethasone plus anti-CD38 antibodies have been evaluated in phase 3 studies. In the CANDOR trial,[28] carfilzomib plus dexamethasone was compared with carfilzomib plus dexamethasone plus daratumumab in patients with relapsed and refractory multiple myeloma who had received one to three previous lines of therapy (446 patients, of whom 147 (33%) had lenalidomide-refractory disease). Median progression-free survival was not reached in the daratumumab plus carfilzomib plus dexamethasone group versus 15·8 months in the carfilzomib plus dexamethasone group (HR 0·63 [95% CI 0·46–0·85]; p=0·0027). Daratumumab plus carfilzomib plus dexamethasone was superior to carfilzomib plus dexamethasone in terms of progression-free survival, both in patients with previous lenalidomide exposure (HR 0·53 [95% CI 0·34–0·82]; p value not available) and in lenalidomide-refractory patients (HR 0·47 [0·29–0·78]; p value not available). Furthermore, both the overall response rate (84% *vs* 75%, p=0·008) and the minimal residual disease negative rate at 12 months (13% *vs* 1%, p<0·0001) were superior with daratumumab plus carfilzomib plus dexamethasone than with carfilzomib plus dexamethasone. In the phase 3 IKEMA trial,[29] 302 patients with relapsed and refractory multiple myeloma and one to three previous lines of therapy were randomly assigned to receive either isatuximab plus carfilzomib plus dexamethasone (n=179) or carfilzomib plus dexamethasone (n=123). After a median follow-up of 20·7 months, median

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progression-free survival was not reached for isatuximab plus carfilzomib plus dexamethasone and was 19·1 months for carfilzomib plus dexamethasone (HR 0·53 [95% CI 0·32–0·89); p=0·0007). Isatuximab plus carfilzomib plus dexamethasone was superior to carfilzomib plus dexamethasone in terms of progression-free survival, both in patients with previous lenalidomide exposure (HR 0·50 [95% CI 0·29–0·87]; p value not available) and in lenalidomide-refractory patients (HR 0·60 [95% CI 0·34–1·06]; p value not available). On Aug 20, 2020, the daratumumab plus carfilzomib plus dexamethasone combination was approved by the US Food and Drug Administration for adult patients with relapsed or refractory multiple myeloma after one to three lines of therapy. Based on progression-free survival data and HRs, daratumumab plus carfilzomib plus and dexamethasone and isatuximab plus carfilzomib plus dexamethasone (approval anticipated soon) might be important treatment options for first relapse in patients with lenalidomide-refractory disease in the near future.

Lenalidomide-exposed patients have been studied in a small number of phase 1b/2 trials that evaluated new combinations based on proteasome inhibitors with or without pomalidomide and with or without monoclonal antibodies. Major limitations of these trials are the small number of patients enrolled, the short follow-up, and the absence of overall survival data. Jakubowiak and colleagues[30] did a phase 2 randomised trial comparing bortezomib plus dexamethasone versus elotuzumab plus bortezomib plus dexamethasone in 152 patients with relapsed and refractory multiple myeloma, showing a longer progression-free survival with the triplet combination versus the doublet in the intention-to-treat population (9·7 months *vs* 6·9 months, HR 0·72 [95% CI 0·49–1·06]; p=0.09). Of these patients, 101 (66%) were treated at the time of the first relapse, but the number of patients with disease progression while taking lenalidomide was not reported, and a subgroup analysis of patients previously treated with immunomodulatory agents showed no progression-free survival benefit with the addition of elotuzumab to bortezomib plus dexamethasone (HR 0·87 [95% CI 0·56–1·34]; p value not available). In the phase 1b MMY1001 trial (NCT01998971),[31] the combination of daratumumab plus pomalidomide plus dexamethasone was tested in one treatment group. 92 (90%) of 102 patients enrolled into this group had lenalidomide-refractory disease. The overall response rate in this group of patients overall was 66%, and the median progression-free survival was 10·1 months after a median follow-up of 28·1 months. However, the number of patients with disease progression while taking front-line lenalidomide therapy included in this group was very small (n=3). The same combination, daratumumab plus pomalidomide plus dexamethasone, was investigated in the POM MM 014 phase 2 trial (NCT01946477), which included 112 patients who had disease progression after lenalidomide-based therapy (median two previous lines of treatment), 84 (75%) of which had lenalidomide-refractory disease.[32] With a median follow-up of 8·2 months, the overall response rate (the primary endpoint) was 75% in patients with lenalidomide-refractory disease, and the 9 month progression-free survival was 86·3% (95% CI 76·5–92·2%), whereas the median progression-free survival was not reached.[32] Pomalidomide was also combined with carfilzomib and dexamethasone twice per week, in the prospective EMN011/HO114 trial.[33] This phase 2 trial was designed for patients with refractory disease or first progression after front-line therapy as part of the EMN02 trial, in which patients were randomly assigned to front-line ASCT versus no front-line ASCT, followed by consolidation and lenalidomide maintenance until progression. After four 28 day cycles of reinduction with carfilzomib plus pomalidomide plus dexamethasone, patients were offered either salvage ASCT, if they had not received it as front-line intensive therapy, or four additional cycles of carfilzomib plus pomalidomide plus dexamethasone (a total of eight carfilzomib plus pomalidomide plus dexamethasone cycles). Subsequently, patients with stable disease or better received pomalidomide with or without dexamethasone in 28-day cycles until progression.[33] The analysis of the first 60 patients, 57 (95%) of whom had progressed on lenalidomide maintenance, showed that responses to carfilzomib plus pomalidomide plus dexamethasone were rapid, with a median time to best response of 2 months. The toxicity of carfilzomib plus pomalidomide plus dexamethasone was manageable and, at a median follow-up of 16·3 months, the median progression-free survival was 18 months, with a better outcome in patients with standard-risk cytogenetic profiles (n=40) than in patients with high-risk cytogenetic profile (HR 0·27 [95% CI 0·09–0·83]; p value not available) and in patients who had not received front-line ASCT (n=25; HR 0·49 [95% CI 0·21–1·16]; p value not available). Pomalidomide plus dexamethasone has also been combined with oral weekly ixazomib and tested in a phase 1/2 trial of patients with lenalidomide-refractory disease (n=32), aged up to 84 years, with one to five (median two) previous lines of therapy.[34] The exact number of patients progressing on front-line lenalidomide was unspecified. This triplet all-oral combination was well tolerated and the overall response rate was 48%, with a median progression-free survival of 8·6 months.

A summary of the results of phase 3 trials in patients with lenalidomide-refractory disease, including subgroup analyses, is presented in table 1. The preferred primary options and secondary options (based on the results of phase 3 trials), and alternative options (based on the results of phase 2 trials) for the treatment of patients with lenalidomide-refractory disease are shown in figure 1.

First relapse in patients with disease not refractory to lenalidomide

In patients who have received bortezomib-based front-line therapy (ie, bortezomib plus cyclophosphamide

	Intention-to-treat population			Lenalidomide refractory to any number of previous lines of therapy			Lenalidomide refractory to one previous line of therapy		
	n	Median PFS, months (95% CI)	HR (95% CI);* p value	n	Median PFS, months (95% CI)	HR (95% CI);* p value	n	Median PFS, months (95% CI)	HR (95% CI);* p value
ENDEAVOR[17,18]	..	..	0·53 (0·44–0·65); <0·0001	..	..	NA	NA	NA	NA
Vd group	465	9·4 (8·4–10·4)	..	122	6·6, NA	..	NA	NA	NA
Kd group	464	18·7 (15·6 to NE)	..	113	8·6, NA	..	NA	NA	NA
CASTOR[21,22]	..	..	0·31 (0·25–0·39); <0·0001	..	..	NA	NA	NA	NA
Vd group	247	7·1 (6·2–7·9)	..	81	4·9, NA	..	NA	NA	NA
DVd group	251	16·7 (12·3 to NE)	..	60	7·8, NA	..	NA	NA	NA
OPTIMISMM[26]	..	..	0·61 (0·49–0·77); <0·0001	..	..	0·65 (0·50–0·84); <0·001	..	..	0·55 (0·33–0·94); 0·028
Vd group	278	7·1 (5·9–8·5)	..	118	5·6 (4·4–7·0)	..	65	9·5 (6·3–16·2)	..
PVd group	281	11·2 (9·7–13·7)	..	120	9·5 (8·0–11·3)	..	64	17·8 (12·0 to NE)	..
CANDOR[28]	..	..	0·63 (0·46–0·85); 0·0027 (two-sided)	..	..	0·47 (0·29–0·78); NA	NA	NA	NA
Kd	154	15·8 (12·1 to NE)	..	55	11·1 (7·4–14·9)	..	NA	NA	NA
DKd	312	NR (NE)	..	99	NR (18·5 to NE)	..	NA	NA	NA
IKEMA[29]	..	..	0·53 (0·32–0·89); 0·0007	..	..	0·60 (0·34–1·06); NA	NA	NA	NA
Kd	123	19·1 (15·8 to NE)	..	42	NA	..	NA	NA	NA
Isa-Kd	179	NR (NE)	..	57	NA	..	NA	NA	NA

DKd=daratumumab plus carfilzomib plus dexamethasone. DVd=daratumumab plus bortezomib plus dexamethasone. HR=hazard ratio. Isa–Kd=isatuximab plus carfilzomib plus dexamethasone. Kd=carfilzomib plus dexamethasone. NA=not available. NE=not estimable. NR=not reached. PFS=progression-free survival. PVd=pomalidomide plus bortezomib plus dexamethasone. Vd=bortezomib plus dexamethasone. *HR (95% CI) given for the two treatment groups in each trial.

Table 1: **Subgroup analysis of progression-free survival of patients with lenalidomide-refractory disease in phase 3 trials for relapsed and refractory myeloma**

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plus dexamethasone, bortezomib plus thalidomide plus dexamethasone, or bortezomib plus melphalan plus prednisone) without lenalidomide maintenance, or patients treated with a fixed duration of lenalidomide with progression occurring more than 6 months after cessation of therapy, second-line therapy should be based on lenalidomide and dexamethasone regimens, such as carfilzomib plus lenalidomide plus dexamethasone,[11] daratumumab plus lenalidomide plus dexamethasone,[14] ixazomib plus lenalidomide plus dexamethasone,[12] or elotuzumab plus lenalidomide plus dexamethasone.[13] In pivotal phase 3 trials with progression-free survival as the primary endpoint, all of these combinations were found to be superior to lenalidomide plus dexamethasone. Carfilzomib plus lenalidomide plus dexamethasone[35] and elotuzumab plus lenalidomide plus dexamethasone,[36] investigated in the two trials with the longest follow-up (67·1 months for carfilzomib plus lenalidomide plus dexamethasone, 70·6 months for elotuzumab plus lenalidomide plus dexamethasone), also showed an overall survival benefit compared with lenalidomide plus dexamethasone for the intention-to-treat patient population.

The most effective combination available in the setting of first relapse of myeloma not refractory to lenalidomide is daratumumab plus lenalidomide plus dexamethasone.[14] In the POLLUX trial,[37] daratumumab plus lenalidomide plus dexamethasone significantly prolonged progression-free survival in the intention-to-treat population compared with lenalidomide plus dexamethasone (median 45·8 months *vs* 17·5 months; HR 0·43 [95% CI 0·35–0·54]; p<0·0001) after a median of 51·3 months of follow-up. In the subgroup of patients who had received one previous line of therapy, daratumumab plus lenalidomide plus dexamethasone (n=149) also significantly prolonged progression-free survival versus lenalidomide plus dexamethasone (n=146; median 53·3 months *vs* 19·6 months, HR 0·42 [95% CI 0·30–0·57]; p<0·0001). Median second objective disease progression was 53·3 months with daratumumab plus lenalidomide plus dexamethasone versus 31·7 months with lenalidomide plus dexamethasone (HR 0·54 [95% CI 0·43–0·68]; p<0·0001) in the intention-to-treat population.[37] With a longer follow-up, these results are expected to translate into an overall survival benefit. The daratumumab plus lenalidomide plus dexamethasone triplet combination is well tolerated, and the forthcoming availability of a subcutaneous mode of administration of daratumumab will increase convenience.[38] In the ASPIRE trial,[35] the median overall survival was 11·4 months longer with carfilzomib plus lenalidomide plus dexamethasone (n=184) versus lenalidomide plus dexamethasone (n=157) in patients who had received one previous line of therapy (47·3 months *vs* 35·9 months, HR 0·81 [95% CI 0·62–1·06]; p value not available). Elotuzumab plus lenalidomide plus dexamethasone and ixazomib plus

lenalidomide plus dexamethasone are well tolerated, but less effective than daratumumab plus lenalidomide plus dexamethasone, and than carfilzomib plus lenalidomide plus dexamethasone.[35,36] The overall survival benefit observed with elotuzumab plus lenalidomide plus dexamethasone versus lenalidomide plus dexamethasone is restricted to patients who have received two to three previous lines of therapy, and overall survival is similar between the two treatments in patients with one previous line of therapy (median 43·7 months with elotuzumab plus lenalidomide plus dexamethasone *vs* 44·1 months with lenalidomide plus dexamethasone alone, HR 1·00 [95% CI 0·77–1·32]; p value not available).[36]

After front-line therapy based on combinations including a proteasome inhibitor, a retreatment including a proteasome inhibitor can also be considered. Four trials have shown a progression-free survival benefit of other regimens versus bortezomib plus dexamethasone alone: ENDEAVOR[17] (evaluating carfilzomib plus dexamethasone), CASTOR[21] (evaluating daratumumab plus bortezomib plus dexamethasone), BOSTON[39] (evaluating selinexor plus bortezomib plus dexamethasone), and BELLINI[40] (evaluating venetoclax plus bortezomib plus dexamethasone). In ENDEAVOR, patients previously exposed to front-line bortezomib were enrolled if they were not refractory to bortezomib. The median progression-free survival for patients who had received one previous line of therapy was 22·2 months for the 231 patients who received carfilzomib plus dexamethasone versus 10·1 months for the 229 patients who received bortezomib plus dexamethasone (HR 0·45 [95% CI 0·33–0·61]; p<0·0001).[19] For patients who had previously received bortezomib, the median progression-free survival for carfilzomib plus dexamethasone was 15·6 months, versus 8·1 months for bortezomib plus dexamethasone (HR 0·56 [95% CI 0·44–0·73]; p<0·0001). The median overall survival in patients treated after one previous line of therapy was 51·3 months with carfilzomib plus dexamethasone versus 43·7 months with bortezomib plus dexamethasone (HR 0·77 [95% CI 0·58–1·02]; p value not available).[20] In CASTOR, after 19·4 months of median follow-up, daratumumab plus bortezomib plus dexamethasone was found to prolong progression-free survival compared with bortezomib plus dexamethasone alone (median 16·7 months *vs* 7·1 months, HR 0·31 [95% CI 0·24–0·39]; p<0·0001). The progression-free survival benefit of daratumumab plus bortezomib plus dexamethasone was most apparent in patients with one previous line of therapy compared with patients with more than one previous line of therapy (median 27·0 months *vs* 7·9 months, HR 0·22 [95% CI 0·13–0·33]; p<0·0001).[22] The phase 3 BOSTON trial[39] compared bortezomib plus dexamethasone versus selinexor plus bortezomib plus dexamethasone in 402 patients who had received one to three previous lines of therapy. Selinexor plus bortezomib plus dexamethasone significantly prolonged median progression-free survival versus bortezomib plus dexamethasone (13·9 months *vs* 9·4 months, HR 0·70 [95% CI 0·53–0·93]; p=0·0075), but this benefit was less apparent in patients previously exposed to a proteasome inhibitor (HR 0·78 [95% CI 0·58–1·06] in exposed patients *vs* 0·26 [0·11–0·60] in non-exposed patients; p value not available). On Dec 18, 2020, the US Food and Drug Administration approved selinexor in combination with bortezomib plus dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one previous line of therapy. The phase 3 BELLINI trial[40] has compared bortezomib plus dexamethasone versus bortezomib plus dexamethasone plus venetoclax, a selective BCL2 inhibitor, in 291 patients who had received one to three previous lines of therapy. A significant progression-free survival benefit was reported with bortezomib plus dexamethasone plus venetoclax in patients with a t(11;14) translocation (HR 0·11 [95% CI 0·02–0·56]; p=0·0040) and those with high BCL2 expression (HR 0·24 [95% CI 0·12–0·48]; p<0·0001). Bortezomib plus dexamethasone plus venetoclax was also superior to bortezomib plus dexamethasone in terms of progression-free survival (HR 0·21 [95% CI 0·11–0·41]; p<0·0001) and minimal residual disease negativity rate (19% *vs* 0%) for the combined group of patients with t(11;14) or high BCL2 expression. By contrast, in patients without t(11;14) and with low BCL2 expression, median progression-free survival did not differ significantly between the two treatment groups, and increased mortality was seen in the bortezomib plus dexamethasone plus venetoclax group, mostly because of a higher rate of fatal infections (septic shock and pneumonia). Finally, the results of the CANDOR trial,[28] in which carfilzomib plus dexamethasone was compared with daratumumab plus carfilzomib plus dexamethasone, showed no statistically significant difference in progression-free survival between the treatment groups in patients with one previous line of therapy (HR 0·68 [95% CI 0·40–1·14]; p=0·37) or in patients with disease not refractory to lenalidomide (HR 0·74 [95% CI 0·49–1·11]; p=0·15), but an improved progression-free survival with daratumumab plus carfilzomib plus dexamethasone in patients with previous proteasome inhibitor exposure (HR 0·61 [95% CI 0·45–0·84]; p=0·065). The preliminary results of the IKEMA trial, in which carfilzomib plus dexamethasone was compared with isatuximab plus carfilzomib plus dexamethasone, did not show a significant difference in progression-free survival between treatment groups in patients who had received one previous line of therapy (HR 0·59 [95% CI 0·31–1·12]; p value not available), in patients with disease not refractory to lenalidomide (HR 0·45 [95% CI 0·15–1·35]; p value not available), and in patients with previous exposure to a proteasome inhibitor (HR 0·56 [95% CI 0·31–1·04]; p value not available).[29]

	Intention-to-treat population			One previous line of therapy		
	n	Median PFS, months (95% CI)	HR (95% CI);* p value	n	Median PFS, months (95% CI)	HR (95% CI);* p value
ASPIRE[11]	..	..	0·69 (0·57–0·83); <0·0001	..	..	0·69 (0·52–0·94); 0·012
Rd group	396	17·6 (15·0–20·6)	..	157	17·6 (15·0–22·2)	..
KRd group	396	26·3 (23·3–30·0)	..	184	29·6 (23·2–33·5)	..
TOURMALINE[12]	..	..	0·74 (0·59–0·94); 0·012	..	..	0·83 (0·63–1·20); NA
Rd group	362	14·7, NA	..	217	NA	..
IRd group	360	20·6, NA	..	224	NA	..
POLLUX[14,38]	..	..	0·44 (0·35–0·54); <0·0001	..	..	0·42 (0·30–0·57); <0·0001
Rd group	283	17·5 (13·9–20·8)	..	146	19·6, NA	..
DRd group	286	44·5 (34·1–NE)	..	149	53·3, NA	..
ELOQUENT-2[13]	..	..	0·70 (0·57–0·85); 0·0004	..	..	0·75 (0·56–1·00); NA
Rd group	325	14·9 (12·1–17·2)	..	159	NA	..
Elo–Rd group	321	19·4 (16·6–22·2)	..	151	NA	..
ENDEAVOR[17,19]	..	..	0·53 (0·44–0·65); <0·0001	..	..	0·45 (0·33–0·61); <0·0001
Vd group	465	9·4 (8·4–10·4)	..	229	10·1, NA	..
Kd group	464	18·7 (15·6–NE)	..	231	22·2, NA	..
CASTOR[21,22]	..	..	0·31 (0·25–0·39); <0·0001	..	..	0·22 (0·15–0·31); <0·0001
Vd group	247	7·1 (6·2–7·9)	..	113	7·9, NA	..
DVd group	251	16·7 (12·3 to NE)	..	122	27·0, NA	..
OPTIMISMM[26]	..	..	0·61 (0·49–0·77); <0·0001	..	..	0·54 (0·36–0·82); 0·0027
Vd group	278	7·1 (5·9–8·5)	..	115	11·6 (7·5–15·7)	..
PVd group	281	11·2 (9·7–13·7)	..	111	20·7 (15·1–28·0)	..
BOSTON[39]	..	..	0·70 (0·53–0·93); 0·0075	..	..	0·63 (0·41–0·96); NA
Vd group	207	9·4 (8·1–10·8)	..	99	NA	..
SVd group	195	13·9 (11·7–NE)	..	99	NA	..
CANDOR[28]	..	..	0·63 (0·46–0·85); 0·0027	..	..	0·68 (0·40–1·14); 0·1479
Kd group	154	15·8 (12·1–NE)	..	67	NA	..
DKd group	312	NR (NE)	..	133	NA	..
IKEMA[29]	..	..	0·53 (0·32–0·89); 0·0007	..	..	0·59 (0·31–1·12); NA
Kd group	123	19·1 (15·8–NE)	..	55	NA	..
Isa–Kd group†	179	NR (NE)	..	79	NA	..
BELLINI[40]	..	..	0·63 (0·44–0·90); 0·010	..	..	0·75 (0·45–1·26); NA
Vd group	97	11·5 (9·6–15·0)	..	44	11·4 (9·0 –NE)	..
Vd plus venetoclax group	194	22·4 (15·3–NE)	..	91	22·4 (12·2–NE)	..

DKd=daratumumab plus carfilzomib plus dexamethasone. DRd=daratumumab plus lenalidomide plus dexamethasone. DVd=daratumumab plus bortezomib plus dexamethasone. Elo–Rd=elotuzumab plus lenalidomide plus dexamethasone. HR=hazard ratio. IRd=ixazomib plus lenalidomide plus dexamethasone. Isa–Kd=isatuximab plus carfilzomib plus dexamethasone. Kd=carfilzomib plus dexamethasone. KRd=carfilzomib plus lenalidomide plus dexamethasone. NA=not available. NE=not estimable. NR=not reached. PFS=progression-free survival. PVd=pomalidomide plus bortezomib plus dexamethasone. Rd=lenalidomide plus dexamethasone. SVd=selinexor plus bortezomib plus dexamethasone. Vd=bortezomib plus dexamethasone. *HR (95% CI) given for the two treatment groups in each trial. †One patient in the isatuximab plus carfilzomib plus dexamethasone group was previously exposed to daratumumab but was not refractory to this antibody.

Table 2: **Subgroup analysis of progression-free survival of patients with one previous line of therapy in phase 3 trials for relapsed and refractory myeloma**

A summary of the progression-free survival results of phase 3 trials in patients with multiple myeloma not refractory to lenalidomide, including subgroup analysis in patients with one previous line of therapy, is presented in table 2. Recommendations for first relapse in patients with disease not refractory to lenalidomide are shown in figure 1.

First relapse in patients progressing on front-line daratumumab-based combinations

The approval of daratumumab-based regimens (daratumumab plus bortezomib plus melphalan plus prednisone [ALCYONE trial][41,42] and daratumumab plus lenalidomide plus dexamethasone [MAIA trial][43]) as the front-line therapy for myeloma is making treatment decisions challenging. So far, no data exist to support daratumumab retreatment at second line, and salvage therapy with isatuximab in patients progressing on daratumumab is unlikely to be a suitable option because both antibodies target the same antigen (CD38).

In the ALCYONE trial,[41] patients in the daratumumab plus bortezomib plus melphalan plus prednisone group received nine 6-week cycles of subcutaneous bortezomib,

oral melphalan, and oral prednisone, plus intravenous daratumumab until disease progression or unacceptable toxicity. At a median follow-up of 40·1 months, the Kaplan-Meier estimate of 36 month overall survival was significantly longer in this group than in the bortezomib plus melphalan plus prednisone group (HR 0·60 [95% CI 0·46–0·80]; p=0·0003). The Kaplan-Meier estimate of 36 month overall survival was 78·0% (95% CI 73·2–82·0) in the daratumumab plus bortezomib plus melphalan plus prednisone group and 67·9% (95% CI 62·6–72·6) in the bortezomib plus melphalan plus prednisone group. No data are yet available regarding subsequent therapies after disease progression on daratumumab plus bortezomib plus melphalan plus prednisone. Nevertheless, at the time of relapse, the logical approach is to use a lenalidomide-based combination without daratumumab. ALCYONE enrolled patients aged 65 years or older not eligible for ASCT. A suitable option would be carfilzomib plus lenalidomide plus dexamethasone for fit patients above the age of 65 years in this setting, but for frail patients or those older than 75 years of age, dexamethasone in combination with ixazomib or elotuzumab might be the best approaches after progression on daratumumab plus bortezomib plus melphalan plus prednisone.

In the MAIA trial,[43] patients received front-line daratumumab plus lenalidomide plus dexamethasone until disease progression. This combination is now approved by the US Food and Drug Administration and by the European Medicines Agency, and the impressive progression-free survival results will probably lead to a widespread use of this triplet combination, even in patients older than 75 years. No data on salvage regimens at the time of progression in the MAIA trial are available. A proteasome inhibitor-based combination without daratumumab is the logical approach. In this setting, carfilzomib plus dexamethasone, bortezomib plus cyclophosphamide plus dexamethasone, pomalidomide plus bortezomib plus dexamethasone, bortezomib plus melphalan plus prednisone, or carfilzomib plus pomalidomide plus dexamethasone are reasonable options. Alternatively, elotuzumab plus bortezomib plus dexamethasone, selinexor plus bortezomib plus dexamethasone, or ixazomib plus pomalidomide plus dexamethasone could be considered.

Salvage ASCT

Front-line ASCT is the standard of care for fit patients younger than 70 years of age in many countries.[1,2] Nevertheless, given the absence of an overall survival benefit of front-line ASCT in patients with standard-risk disease, compared with bortezomib plus lenalidomide plus dexamethasone followed by lenalidomide maintenance, for example,[44] some investigators and patients prefer to delay ASCT to the time of the first relapse, after harvesting and storing stem cells during induction. In this setting, salvage ASCT should be systematically considered in patients who have never previously received a transplant.[2] One issue is the selection of the optimal reinduction regimen before salvage ASCT, especially for patients progressing on front-line, long-term lenalidomide therapy. Few data are available regarding reinduction regimens. Carfilzomib plus pomalidomide plus dexamethasone was found to be active in this setting in the phase EMN011 2 trial.[33]

Salvage ASCT can also be considered in patients progressing after front-line ASCT. The only randomised, controlled trial to show the role of salvage ASCT in patients with myeloma at first relapse or progression at least 12 months after ASCT was the UK Myeloma X study.[45,46] In this trial, patients with relapsed multiple myeloma who had at least stable disease after reinduction with bortezomib plus doxorubicin plus dexamethasone had a longer time to disease progression (19 months *vs* 11 months; HR 0·45 [95% CI 0·25–0·53]; p<0·0001)[45] and overall survival (67 months *vs* 52 months; HR 0·56 [95% CI 0·35–0·90]; p=0·022)[46] with salvage ASCT (n=89) versus weekly oral cyclophosphamide (n=85) as consolidation (probably a suboptimal scheme because oral cyclophosphamide is not normally used as consolidation therapy). Another prospective phase 3 study compared continuous lenalidomide plus dexamethasone versus continuous lenalidomide plus dexamethasone reinduction followed by ASCT and maintenance with lenalidomide in 277 patients with first to third relapse, of which 260 (94%) had one previous line of therapy at the time of study entry, and 259 (94%) received front-line ASCT.[47] Median progression-free survival was 20·7 months in the ASCT group and 18·8 months in the continuous dexamethasone arm (HR 0·87 [95% CI 0·65–1·16]; p=0·34). Median overall survival was not reached in the ASCT group and was 62·7 months in the control group (HR 0·81 [95% CI 0·52–1·28]; p=0·37).

The most important prognostic factor for progression-free survival after salvage ASCT is the duration of remission after the first ASCT procedure. Because front-line ASCT followed by lenalidomide maintenance is associated with a median duration of response of 50 months,[44] salvage ASCT should not be recommended for patients with a response duration of less than 3 years after the first ASCT, but this cutoff is arbitrary and could be reduced to 2 years if the patient has not received maintenance therapy (grade 2A recommendation).

Treatment of relapsed and refractory disease after two or more previous lines of therapy

The treatment of patients with relapsed and refractory multiple myeloma who have received two or more previous lines of therapy is becoming particularly challenging. Lenalidomide and bortezomib are often used as part of front-line therapy or at first relapse. Monoclonal antibodies (eg, daratumumab and elotuzumab) and carfilzomib are also being increasingly used during the first two lines of treatment. Therefore, at the time of the second relapse, all

agents considered but not used for first relapse can be considered again. Enrolling the patient in a clinical trial, when available, should always be considered.

Few phase 3 trials have focused on patients who have received two or more previous lines of therapy. In patients whose disease has progressed after treatment with bortezomib and lenalidomide, pomalidomide plus dexamethasone has been considered as standard of care, on the basis of the results of the MM-003 randomised study.[48] This combination (pomalidomide plus dexamethasone) has been compared with isatuximab plus pomalidomide plus dexamethasone in the ICARIA trial[49] in patients previously treated with two or more lines of therapy including lenalidomide and a proteasome inhibitor. Notably, 284 (92%) of 307 patients had lenalidomide-refractory disease, and 301 (98%) of 307 were refractory to their last line of therapy. At a median follow-up of 11·6 months, the median progression-free survival (the primary endpoint) was 11·5 months in the 154 patients in the isatuximab plus pomalidomide plus dexamethasone group versus 6·5 months in the 153 patients in the pomalidomide plus dexamethasone group (HR 0·59 [95% CI 0·44–0·81]; p=0·0010).[49] Isatuximab plus pomalidomide plus dexamethasone was approved by the US Food and Drug Administration on March 2, 2020, and by the European Medicines Agency on June 2, 2020, for adult patients with relapsed and refractory multiple myeloma who received at least two previous lines of therapies including lenalidomide and a proteasome inhibitor and demonstrated disease progression on the last therapy. The CANDOR study,[28] in which carfilzomib plus dexamethasone was compared with daratumumab plus carfilzomib plus dexamethasone, also included a prespecified analysis of the outcome of 266 patients who had received two or more previous lines of therapy; this analysis showed a progression-free survival benefit with the triplet combination (HR 0·61 [95% CI 0·45–0·84]; p value not available). Similarly, the IKEMA trial,[29] in which carfilzomib plus dexamethasone was compared with isatuximab plus carfilzomib plus dexamethasone, analysed the outcome of 167 patients who had received two or more previous lines of therapy, and found a progression-free survival benefit of isatuximab plus carfilzomib plus dexamethasone (HR 0·48 [95% CI 0·29–0·78]; p value not available).

Two other antibody-based combinations that can be considered for patients with advanced disease have been approved on the basis of the results from phase 2 trials. In the randomised phase 2 ELOQUENT-3 trial,[50] patients who had received at least two previous lines of therapy were randomly assigned to receive either elotuzumab plus pomalidomide plus dexamethasone (n=60) or pomalidomide plus dexamethasone (n=57).[50] After 9 months of follow-up, the median progression-free survival was 10·3 months in the elotuzumab plus pomalidomide plus dexamethasone group versus 4·7 months in the pomalidomide plus dexamethasone group (HR 0·54 [95% CI 0·34–0·86]; p=0·0080). On June 16, 2017, the combination of daratumumab plus pomalidomide plus dexamethasone was also licensed by the US Food and Drug Administration for patients whose disease has not responded to at least two previous lines of therapy, including lenalidomide and a proteasome inhibitor. This approval was granted on the basis of the results of a phase 2 non-randomised study, the EQUULEUS trial,[31] in which daratumumab plus pomalidomide plus dexamethasone was given to 103 patients with relapsed and refractory multiple myeloma. At a median follow-up of 13 months, the median progression-free survival was 8·8 months and the median overall survival was 17·5 months.[31] The phase 3 APOLLO study (NCT03180736; EMN14) enrolled 304 patients and was designed to compare pomalidomide plus dexamethasone (n=153) versus daratumumab plus pomalidomide plus dexamethasone (n=151; randomly assigned) in patients refractory to lenalidomide and proteasome inhibitors. 33 (11%) patients had received at least one previous line of therapy (median 2, range 1–5), and 242 (80%) patients were refractory to lenalidomide. The results, presented for the first time at the American Society of Hematology 2020 meeting, showed a median progression-free survival benefit with daratumumab plus pomalidomide plus dexamethasone versus pomalidomide plus dexamethasone (12·4 months *vs* 6·9 months; HR 0·63 [95% CI 0·47–0·85]; p=0·0018).[51]

A simple and inexpensive option to improve the results of pomalidomide plus dexamethasone when other agents are not available is the addition of cyclophosphamide to this treatment combination. Although no direct com-

	n	Median PFS, months (95% CI)	HR (95% CI);* p value
ICARIA[49]	..	..	0·59 (0·44–0·81); 0·001
Pd group	153	6·5 (4·5–8·3)	..
Isa-Pd group†	154	11·5 (8·9–13·9)	..
ELOQUENT-3[50]	..	..	0·54 (0·34–0·86); 0·0078
Pd group	57	4·7 (2·8–7·2)	..
Elo-Pd group	60	10·3 (5·6 to NE)	..
EQUULEUS[31]	..	..	..
DPD group	103	8·8 (95% CI 4·6–15·4)	..
STORM[54]	..	..	..
Sd group	122	3·7 (95% CI 3·0–5·3)	..
DREAMM-2[59]	..	..	NA
Belantamab 2·5 mg/kg group	97	2·9 (95% CI 2·1–3·7)	..
Belantamab 3·4 mg/kg group	99	4·9 (95% CI 2·3–6·2)	..
KarMMa[62]	..	..	..
Ide-cel group	128	8·8 (95% CI 5·6–11·6)	..

Elo–Pd=elotuzumab plus pomalidomide plus dexamethasone. HR=hazard ratio. Ide-cel=Idecabtagene vicleucel. Isa–Pd=isatuximab plus pomalidomide plus dexamethasone. NA=not available. NE=not estimable. Pd=pomalidomide plus dexamethasone. PFS=progression-free survival. Sd=selinexor plus dexamethasone. *HR (95% CI) given for the two treatment groups in each trial. †One patient in the isatuximab plus pomalidomide plus dexamethasone group was previously exposed to daratumumab but was not refractory to this antibody.

Table 3: **Clinical trials in patients with relapsed and refractory myeloma who have received two or more previous lines of therapy**

parisons are available from phase 3 studies, several phase 2 trials have shown that the median progression-free survival of pomalidomide plus cyclophosphamide plus dexamethasone is approximately 7–9 months, compared with 4–6 months for the same subgroup of patients treated with pomalidomide plus dexamethasone alone (table 3).[52]

Additional options for patients with relapsed and refractory disease after two or more previous lines of therapy

The outcome is very poor for patients whose multiple myeloma has become refractory to proteasome inhibitors, immunomodulatory agents, and anti-CD38 antibodies, with one study showing that these patients have a median overall survival of only 5·6 months.[53] In this setting, intensive chemotherapeutic combinations, such as bortezomib plus dexamethasone plus thalidomide plus cisplatin plus doxorubicin plus cyclophosphamide plus etoposide, can be used,[54] although prospective data are not available for these combinations.

Selinexor, a selective inhibitor of nuclear export compound that blocks exportin 1 and forces nuclear accumulation and activation of tumour suppressor proteins, has been evaluated in combination with dexamethasone in patients previously exposed to (individually or in combination) bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, or an alkylating agent and had disease refractory to at least one proteasome inhibitor, one immunomodulatory agent, and daratumumab (triple-class refractory) in the phase 2 STORM study.[55] A total of 122 patients were included, 65 (53%) of which had high-risk cytogenetic abnormalities, such as del(17p)/p53, t(4;14), t(14;16), and gain(1q). A partial response or better was observed in 32 (26%) of 122 patients, the median progression-free survival was 3·7 months, and the median overall survival was 8·6 months.[55] A prespecified subgroup analysis of 83 patients whose disease was refractory to (individually or in combination) bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab showed an overall response rate of 25·3%, with a median response duration of 3·8 months. Based on these results, the US Food and Drug Administration granted accelerated approval to selinexor for the treatment of this subgroup of patients in July, 2019. One problem with selinexor is its safety profile: about 25% of the patients experienced grade 3 fatigue, gastrointestinal toxicity, and thrombocytopenia, but these side-effects are more manageable with less frequent doses and supportive care.[55]

As discussed previously, the oral pan-deacetylase inhibitor panobinostat was approved in combination with bortezomib plus dexamethasone on the basis of the results of the phase 3 PANORAMA 1 trial,[24,25] but is less commonly used due to a previously challenging tolerability profile, and little evidence of clinical benefit. Nevertheless, the phase 2 PANORAMA 2 trial showed that panobinostat was able to revert bortezomib resistance in about 25% of the cases progressing on bortezomib plus dexamethasone.[56] Therefore, when patients are progressing on proteasome inhibitors and few therapeutic options are available, the addition of panobinostat in combination can be tested, with careful dose adaptation.

Melflufen (melphalan flufenamide) is a first-in-class anti-cancer peptide-drug conjugate that rapidly delivers an alkylating payload into tumour cells. This agent has been tested in combination with dexamethasone in the phase 1/2 O-12-M1 trial[57] in patients with relapsed and refractory multiple myeloma who had received two or more previous lines of therapy (including lenalidomide and bortezomib) and were refractory to their last line of therapy. In the phase 2 part of the study, 31% of patients treated with melflufen plus dexamethasone achieved an overall response. The most common grade 3 or 4 adverse events were thrombocytopenia (in 62% of patients) and neutropenia (in 58% of patients), and non-haematological toxicity was infrequent. Melflufen is not yet approved, but the HORIZON trial,[58] testing melflufen plus dexamethasone in patients refractory to pomalidomide, daratumumab, or both, has been recently completed. Of 157 patients (with a median of five previous lines of therapy) enrolled and treated, 119 patients (76%) had triple-class refractory disease, 55 (35%) had extramedullary disease, and 92 (59%) were refractory to previous alkylator therapy. The overall response rate was 29% in the all-treated population, with 26% in the triple-class refractory population. In the all-treated population, median duration of response was 5·5 months, median progression-free survival was 4·2 months, and median overall survival was 11·6 months at a median follow-up of 14 months.

B-cell maturation antigen (BCMA; also known as TNFSRS17) promotes multiple myeloma pathogenesis in the bone marrow microenvironment and is a very specific multiple myeloma target antigen. Immunologically based therapies targeting BCMA show promise independent of genetic heterogeneity and genetic risk, even in patients with multiple myeloma with no other treatment options.[59] These agents include antibody–drug conjugates, autologous chimeric antigen receptor engineered T cells (CAR T cells), and bispecific T cell or NK engagers. Little data are yet available for bispecific agents, and early clinical trials are ongoing.[59]

Belantamab mafodotin is an anti-BCMA antibody–drug conjugate containing monomethyl auristatin F. In the phase 2 DREAMM-2 trial,[60] 196 patients with triple-class-refractory multiple myeloma received two different doses of belantamab mafodotin (2·5 mg/kg [n=97] or 3·4 mg/kg [n=99]). Overall response rates were 31% for the 2·5 mg/kg dose and 34% for the 3·4 mg/kg dose. The median progression-free survival was 2·9 months in the 2·5 mg/kg group, and 4·9 months in the 3·4 mg/kg group, but overall survival data were not available at the time of publication in December, 2019.[60] The most common grade 3 or 4 adverse events included

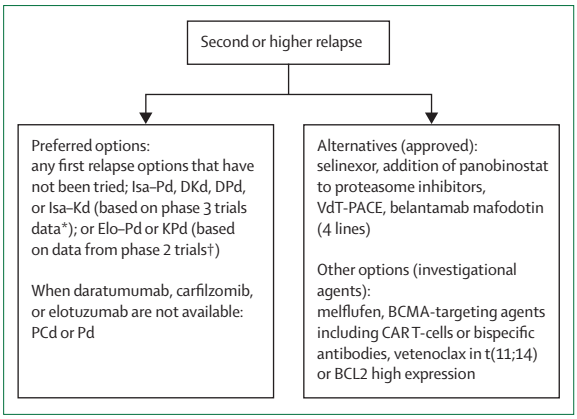

Figure 2: **Recommendations for second or higher relapse**
BCMA=B-cell maturation antigen. CAR=chimeric antigen receptor. DKd=daratumumab plus carfilzomib plus dexamethasone. DPd=daratumumab plus pomalidomide plus dexamethasone. Elo-Pd=elotuzumab plus pomalidomide plus dexamethasone. Isa-Kd=isatuximab plus carfilzomib plus dexamethasone. Isa-Pd=isatuximab plus pomalidomide plus dexamethasone. KPd=carfilzomib plus pomalidomide plus dexamethasone. PCd=pomalidomide plus cyclophosphamide plus dexamethasone. Pd=pomalidomide plus dexamethasone. VdT-PACE=bortezomib plus dexamethasone plus thalidomide plus cisplatin plus doxorubicin plus cyclophosphamide plus etoposide. *Grade of recommendation: 1A. †Grade of recommendation: 1B.

Search strategy and selection criteria

A PubMed search was done using the terms "myeloma", "relapsed", and "trial" to identify clinical trials on relapsed myeloma published in English (exclusively) between Jan 1, 2013, and Sept 30, 2020. Published data were analysed by an interdisciplinary panel of experts representing all cooperative groups worldwide on behalf of the International Myeloma Working Group. Levels of evidence and grades of recommendations were assigned using established criteria in line with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system. The initial draft was circulated to each panel member for critical evaluation and to provide feedback on the levels of evidence and grading of recommendations. The manuscript subsequently underwent two rounds of revision between the panel members and final consensus between all authors was reached. The guidelines were developed for worldwide applicability, and therefore needed to accommodate the substantial disparity in drug availability in different parts of the world.

keratopathy, thrombocytopenia, and anaemia.[60] Of note, in the phase 1 study (DREAMM-1), at the dose of 3·4 mg/kg, the median progression-free survival was longer (12 months, compared with 4·9 months in the phase 2 study), and the overall response rate was 60%, but fewer patients had disease refractory to anti-CD38 antibodies than in the phase 2 study.[61] Belantamab mafodotin was approved by the US Food and Drug Administration (on Aug 6, 2020) and by the European Medicines Agency (on Aug 26, 2020) as a monotherapy treatment for patients with relapsed and refractory multiple myeloma who have received at least four previous lines of therapy including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Early clinical trials of CAR T-cell therapy have shown encouraging results in multiple myeloma. In a phase 1 study of idecaptagene cicleucel (previously known as bb2121), a BCMA-targeting CAR T-cell construct, 33 of the 36 enrolled patients received CAR T cells after lymphodepleting chemotherapy.[62] Three patients progressed during CAR T-cell manufacturing, which was successful in all patients. A total of 26 (79%) patients receiving CAR T-cell therapy were refractory to both a proteasome inhibitor and an immunomodulatory agent; six (18%) patients were refractory to (individually or in combination) bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab. The overall response rate was 85%, including a complete response rate of 45%. Of the 16 patients with a haematological response and who were evaluated for minimal residual disease, 15 had no minimal residual disease. For patients who received at least 150×10^6 CAR T cells, the median progression-free survival was 11·8 months.[62] Cytokine release syndrome occurred in 25 (76%) of 33 patients, and grade 3 or grade 4 neurotoxicity in 1 (3%) of 33 patients. The initial results of the phase 2 trial study of idecabtagene vicleucel (KarMMa) were reported at the American Society of Clinical Oncology Annual 2020 meeting.[63] 140 patients were enrolled, of whom 128 (91%) were treated with idecabtagene vicleucel across the target dose levels of $150–450\times10^6$ CAR T cells. All treated patients had been exposed to at least three previous lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and all were refractory to their last regimen. 107 (84%) of 128 patients were triple-refractory (refractory to an immunomodulatory agent, proteasome inhibitor, and an anti-CD38 antibody). With a median follow-up of 13·3 months and across the target dose levels (150, 300, and 450×10^6 CAR T cells), the overall response rate was 73·4% (including 33% complete response) and the median progression-free survival was 8·8 months.[63] These promising results have not yet been fully published, and idecabtagene vicleucel is not yet approved by regulatory authorities. In the results from a phase 1 study of LCAR-B38M CAR T cells (LEGEND-2, n=57),[64] 88% of less heavily pretreated patients (with a median of three previous lines of therapy) achieved an overall response, and the median progression-free survival was 15 months. LCAR-B38M is a dual epitope-binding CAR T-cell therapy directed against two distinct BCMA epitopes. The biepitope BCMA-binding moieties confer high-avidity binding and distinguish LCAR-B38M from other BCMA CAR constructs.[64] Ongoing trials in Europe and the USA are using LCAR-B38M; an example is the

phase 1b/2 CARTITUDE1 trial,[65] reported at the American Society of Clinical Oncology Annual 2020 meeting, in which 25 of 29 patients were triple-class refractory. The overall response rate was 100%, including 86% stringent complete response, with a 9 month progression-free survival of 86%. Cytokine release syndrome occurred in 27 (93%) of 29 patients (7% with grade ≥3), and grade 3 or grade 4 neurotoxicity occurred in 1 (4%) of 29 patients. Albeit promising, these results require confirmation in a larger number of patients, and LCAR-B38M/JNJ-4528 is not yet approved by regulatory authorities. Many other CAR T-cell therapies targeting BCMA or other molecules such as SLAMF7, CD38, NKG2D (KLRK1) ligands, or CD138 (SYND1), are under evaluation.[66] The use of CAR T cells raises several issues, especially in patients with very advanced disease: progression of the disease during product manufacturing, mechanisms of resistance (no plateau of progression-free survival curves) related to antigen escape or absence of long-term persistence of CAR T cells, and the safety profile of this therapy (eg, risk of cytokine release syndrome and neurotoxicity).[66]

Treatment recommendations for patients with relapsed and refractory disease who have received two or more previous lines of therapy are shown in figure 2.

Contributors

PM, SKK, JSM, M-VM, SVR, MAD, and PGR researched the topic, reviewed the literature, and wrote the paper. All authors reviewed and approved the final version of the manuscript.

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