How I treat: New agents in myeloma

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Short title: Novel agents in myeloma

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Abstract

At present, multiple classes of agents with distinct mechanisms of action are available for the treatment of patients with multiple myeloma (MM), including alkylators, steroids, immunomodulatory agents (IMiDs), proteasome inhibitors (PIs), histone deacetylase inhibitors (DACIs) and monoclonal antibodies (mAbs). Over the last 5 years, several new agents, such as the third-generation IMiD pomalidomide, the second generation PIs carfilzomib and ixazomib, the DACI panobinostat and two monoclonal antibodies, elotuzumab and daratumumab, have been approved, incorporated into clinical guidelines and have transformed our approach to the treatment of patients. These agents may be part of doublet or triplet combinations, or incorporated into intensive strategies with autologous stem cell transplantation. In this review, I will discuss the different treatment options available today for the treatment of MM in the frontline and relapse settings.
Introduction

Multiple myeloma (MM) accounts for 1% of all cancers and approximately 10% of all hematologic malignancies. The treatment of this malignancy has changed dramatically in the past decade with the introduction of new drugs into therapeutic strategies both in the frontline and in the relapse settings. This has led to a significant improvement in the median overall survival (OS), which now approaches 6-10 years depending on the age at diagnosis. Over the last 5 years, several new agents, such as the third-generation immunomodulatory agent (IMiDs) pomalidomide, the second generation proteasome inhibitors (PIs) carfilzomib and ixazomib, the histone deacetylase inhibitor (DACIs) panobinostat and two monoclonal antibodies (mAbs), elotuzumab and daratumumab, have been approved. These drugs have been incorporated into clinical guidelines, and have transformed our approach to the treatment of patients. With the availability of at least 6 different classes of agents, i.e., alkylators, steroids, PIs, IMiDs, DACIs and mAbs that can be combined in doublet or triplet regimens, the choice of the optimal strategy at diagnosis and at relapse represents a therapeutic challenge for physicians. There is consensus that treatment should be initiated in all patients with MM according to the updated definition developed by the International Myeloma Working Group (IMWG) in 2014.

In this review, I will provide an overview of possible treatment choices (listed in Table 1) both in the frontline and relapse settings using patient cases, based on my experience with the various classes of agents and based on the latest results from clinical trials.
Case 1: Frontline therapy in a 60-year old patient

Case presentation

A 60-year-old woman was diagnosed with IgG-κ MM in 2014. At that time, she presented with symptomatic myeloma-related bone lesions, and a bone marrow aspirate confirmed the presence of 33% plasma cells. The International Scoring System (ISS) score was low (I) and a fluorescence in situ hybridization (FISH) analysis did not reveal any adverse cytogenetic factors (no t(4;14) translocation, 17p deletion, or t(14;16) translocation). The first line of therapy consisted of 4 cycles of bortezomib – cyclophosphamide – dexamethasone (VCD), followed by high-dose melphalan and autologous stem cell transplantation (ASCT). The patient achieved a complete remission (CR) after ASCT. Lenalidomide maintenance (10 mg/day continuously) was started 2 months following ASCT. In 2017, the patient is still receiving lenalidomide maintenance, with a sustained CR.

Comments on patient 1

For patients in good clinical condition, induction followed by ASCT is the standard treatment. Two recent phase III trials comparing front-line ASCT versus ASCT at the time of first relapse showed that progression-free survival (PFS) was improved in the front-line ASCT arm with the use of triplet novel agent-based induction. Nevertheless, especially in the French trial comparing frontline ASCT versus lenalidomide-bortezomib-dexamethasone (RVD) and delayed ASCT, OS was similar in the two treatment groups, suggesting that delayed transplantation is feasible and does not have a detrimental effect on OS. There is an ongoing “cure versus control” debate on whether patients should receive an aggressive multidrug strategy with the aim of achieving CR, or a sequential disease control approach that emphasizes quality of life (QOL) as well as OS. These objectives are not mutually exclusive. Nevertheless, recent data show that minimal residual disease (MRD) negative status has a favorable prognostic impact, and it is known that frontline ASCT is associated with the higher rate of MRD negativity.

Based on response rates, depth of response and PFS as surrogate markers for outcome, three-drug combinations including bortezomib and dexamethasone are currently the standard of care as induction prior to ASCT, but only limited data from
prospective phase 3 trials are available to demonstrate that one combination is superior to the other. Four to six courses of induction are recommended before proceeding to stem cell collection. The preferred regimens consist of bortezomib-dexamethasone plus cyclophosphamide (VCD), thalidomide (VTD), lenalidomide (RVD) or doxorubicin (PAD). Lenalidomide-bortezomib-dexamethasone is widely used in the US and will probably become standard of care in the EU as soon as it is approved. Carfilzomib-lenalidomide and dexamethasone (KRd) has also been investigated as induction prior to ASCT, and is associated with high response rates and MRD negativity. This triplet regimen, potentially the most active combining a PI and an IMiD, is currently being evaluated in phase 3 trials prior to ASCT. Other ongoing studies are investigating the impact of adding mAbs, either elotuzumab or daratumumab, to a triplet induction combination in order to further increase the MRD negativity rate prior to ASCT.

Patient 1 did not receive any consolidation following ASCT, and this is an issue which remains a matter of debate in 2017. Conflicting data from two recent randomized trials, not yet fully published, are available. The Stamina study, conducted in the US, prospectively compared no consolidation following ASCT, versus tandem ASCT, versus 4 cycles of RVD. Subsequently, patients in all three arms of the trial received maintenance therapy. With a short follow-up, on an intent-to-treat basis, there was no difference regarding PFS or OS. In contrast, the EMN2 European trial evaluated two cycles of RVD versus no consolidation, and in this study, the RVD arm was associated with a better PFS. The latter trial also included a comparison of single versus tandem ASCT prior to RVD consolidation, and PFS was found to be longer in the group of patients who underwent the tandem ASCT procedure, especially among those with high-risk cytogenetics.

This leads to the issue of a risk-adapted strategy in patients eligible for ASCT. Some experts, especially in the US, suggest that patients with standard-risk disease can benefit from ASCT either upfront or at a later stage in the disease course. For the treatment of patients with high-risk disease outside clinical trials, many, especially European experts, recommend tandem stem cell transplantation. For this subgroup of patients, KRd is also frequently proposed in the US. Nevertheless, in 2017, there is no prognostic factor or staging system, such as R-ISS or gene-expression profiling, that is routinely used to define a risk-adapted strategy.
Following ASCT, patient 1 received long-term maintenance therapy with lenalidomide. This drug is approved in this setting and a recent meta-analysis based on individual patient data of more than 1200 cases demonstrated that lenalidomide maintenance following ASCT is associated with an overall OS benefit of more than two years.\textsuperscript{18} We have to recognize that the three individual studies included in the meta-analysis were not planned or powered for OS as the primary endpoint and the OS data were not mature at the time of their initial publications. Nevertheless, lenalidomide maintenance is standard practice, although the optimal duration of maintenance remains to be defined. Bortezomib maintenance has also been evaluated in a two-year study and was associated with a survival benefit over thalidomide maintenance, especially in patients with high-risk disease, but induction therapy was not identical in the two arms of this prospective trial, making a comparison of the two arms difficult.\textsuperscript{16} Ongoing phase 3 trials are evaluating the role of other novel agents in the maintenance setting following ASCT, such as ixazomib, or daratumumab. Combinations of drugs are also undergoing evaluation, for example carfilzomib-lenalidomide versus lenalidomide alone in the FORTE study, lenalidomide-dexamethasone-ixazomib versus lenalidomide-dexamethasone in the GEM14 trial, or elotuzumab-lenalidomide-dexamethasone versus lenalidomide-dexamethasone in the GMMG-HD6 trial. For patient 1, outside a clinical trial, my approach is a triplet induction therapy, followed by ASCT and lenalidomide maintenance.

Case 2: Frontline therapy in a 75-year old patient

Case presentation

A 75-year-old man was diagnosed with IgA-κ myeloma in 2014. The patient presented with myeloma-related anemia and bone lesions. Renal function was normal and the performance status was good and no genetic abnormalities were seen using FISH. The M-spike at the onset of therapy was 3.5 g/dL. The patient was treated with lenalidomide 25mg/day for 21 days out of 28 day-cycles plus low-dose dexamethasone 40 mg/week (Rd). A partial response was achieved following 3 cycles, and a very good partial response (VGPR) following 6 cycles of Rd. However, following cycle 6, neutropenia and fatigue required dose reduction. Therefore, the
lenalidomide dose was reduced to 15 mg/day, while dexamethasone was reduced to 20 mg weekly. Twenty-eight months following the start of therapy the patient is still in VGPR and therapy with Rd is ongoing.

**Comments on patient 2**

Lenalidomide plus low-dose dexamethasone is one of the standard frontline therapies for patients not eligible for ASCT. According to its approval status, it may be administered until progression of the disease. The final OS analysis of the three-arm FIRST/MM020 trial that prospectively compared Rd until progression versus melphalan prednisone thalidomide (MPT) versus Rd for 18 cycles showed that PFS was significantly improved in the treatment arm, in which patients received Rd continuously. In addition, OS was superior with continuous Rd versus MPT, but was identical in the two Rd arms of the study. Therefore, some experts are questioning the role of continuous Rd administration, and instead support a fixed duration (e.g. 18 months) of initial treatment in order to avoid toxicity, save costs, and improve QOL. Patient 2 achieved a VGPR with continuous Rd. The updated analysis of the MM020 trial showed that time-to-next therapy is prolonged in patients who have reached at least VGPR with continuous Rd, and these patients may benefit most from the long-term administration of this combination. Rd is also feasible in frail patients or patients older than 75 years.

In the recently conducted prospective SWOG0777 trial, which enrolled patients with newly diagnosed MM who were not intended to undergo immediate ASCT, Rd was compared to Rd plus bortezomib (VRd). The addition of bortezomib resulted in significantly improved PFS and OS and the combination had an acceptable risk-benefit profile. This triplet combination is recommended as upfront therapy for transplant ineligible patients in several guidelines, but it has to be emphasized that only 43% of the patients enrolled in the SWOG0777 trial were older than 65 years, and that all patients received ongoing maintenance treatment with Rd following the completion of induction therapy.

The triplet combination bortezomib-melphalan-prednisone (VMP) is another standard of care based on data from the randomized phase 3 VISTA trial showing PFS and OS benefit over MP. This regimen is mostly used in Europe. The combination of
bortezomib-cyclophosphamide and dexamethasone (VCD) is also a valuable option.\textsuperscript{1,4}

Patient 2 presented with standard-risk myeloma at diagnosis, and Rd or VRd or VMP or VCD are all feasible options in this setting. For patients with high-risk disease, who are not eligible for ASCT, some experts recommend the use of KRd, however, only few data are available to support this choice.\textsuperscript{3} Rd may be suboptimal for this subgroup of patients.\textsuperscript{19} Very few patients enrolled in the SWOG0777 trials had a cytogenetic evaluation at diagnosis, and while the median PFS was higher with the triplet VRd combination as compared to Rd, this was not statistically significant.\textsuperscript{22}

Patient 2 had an adequate performance status at diagnosis and was able to stay on treatment for a long period of time. Patients not eligible for ASCT represent a very heterogeneous population, and frailty is one of the most important prognostic factors for OS besides ISS and cytogenetics. A geriatric assessment is recommended for all elderly patients at diagnosis and may guide treatment choices.\textsuperscript{24} Dose reduction and/or doublet combinations should be favored for patients considered frail or not fit.

Several important phase 3 trials are ongoing that may change the landscape of frontline therapy in the near future. Rd is currently being compared to Rd + elotuzumab, to Rd + daratumumab, and to Rd + ixazomib in what may become the first all oral triplet regimen combining a PI plus an IMiD for the treatment of patients not eligible for ASCT. The triplet combination VMP is also currently being tested versus VMP + daratumumab.

For patient 2, outside a clinical trial, I would recommend Rd until progression or unacceptable toxicity.

\textbf{Case 3: Relapse treatment in a patient progressing after bortezomib-based induction:}

\textbf{Case presentation}
A 64 year-old male was diagnosed with symptomatic myeloma in 2014. FISH analysis revealed the presence of t(4;14). The patient received four cycles of VCD with the achievement of a VGPR, followed by melphalan 200 and ASCT. No consolidation and no maintenance were given. Twenty months later, the patient presented with disease progression with anemia and bone pain. Renal function and performance status were good at the time of relapse. The patient was treated with the triplet combination KRd according to the schedule of the ASPIRE study. He responded quickly and achieved a VGPR following the first two cycles, and a CR at cycle six. He is currently receiving cycle 15 with a sustained CR, without the occurrence of significant toxicity.

Comments on patient 3

The choice of therapy in the relapse setting depends on several parameters, such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy, the type of relapse (i.e. clinical versus biochemical relapse) and cytogenetics. In case of progression following bortezomib induction, as for patient 3, who was lenalidomide-naive, Rd is a feasible option. This doublet combination was standard practice until recently, but is currently being used less often. Indeed, Rd has been compared to Rd plus another new agent in four prospective trials. Elotuzumab (Rd-Elo, Eloquent 2 trial), carfilzomib (KRd, Aspire trial), ixazomib (IRd, Tourmaline 1 trial), and daratumumab (DRd, Pollux trial) have all been added to Rd and have shown significant improvements in PFS compared to Rd, leading to the approval of these four regimens. The choice of the optimal combination out of these four for a specific patient is not always straightforward. In terms of efficacy, cross trial comparisons are difficult because of substantial differences in patient populations. However, an evaluation of hazard ratios (HR) is a reliable method to assess PFS data and can be used to compare the four trials (Table 2). For patients previously exposed to bortezomib, as is the case for patient 3, the HR is in favor of each of the new triplet combination versus Rd and ranges from 0.37 (Pollux) to 0.73 (Tourmaline 1), (0.68 in Eloquent 2 and 0.70 in Aspire). Overall survival data are not yet available. Efficacy has to be balanced with safety. The toxicity profile of each regimen is different, with more cardiac and vascular issues with KRd, infusion-related reactions
with mAbs (daratumumab and elotuzumab) and more incidences of rash with IRd. The mAbs are novel drugs in MM that are attractive partners in combination regimens due to their efficacy and excellent tolerability profile. Improvements in QOL, convenience and burden to health-care givers are also of upmost importance (Table 3). The use of triplet combinations in relapse is particularly important for patients with adverse cytogenetics. Patient 3 has t(4;14), and the HR for this specific subgroup of patients is also in favor of the recently approved triplet combinations versus Rd and ranges from 0.44 (Pollux)\textsuperscript{29} to 0.70 (Aspire)\textsuperscript{25}, (0.52 in Eloquent \textsuperscript{27} and 0.64 in Tourmaline \textsuperscript{28}).

For patient 3, outside of a clinical trial, I would recommend DRd.

**Case 4: Relapse treatment in a patient progressing on IMiD therapy**

**Case presentation**

A 71 year-old female patient presented with anemia and bone pain in 2014 and was diagnosed with MM IgG-\textsubscript{\lambda}. FISH did not reveal any adverse cytogenetic abnormalities. In addition, renal function and performance status were adequate. She received Rd as frontline therapy and achieved a partial response following cycle two, which was associated with clinical improvement. During cycle 22, the M-spike increased from 0.5 to 1.1 g/dL with the reappearance of bone pain. A bone marrow aspirate confirmed the relapse, with 28% plasma cells. The results of another cytogenetic analysis did not differ from those of the initial examination. The patient, 73 years old at the time of the relapse, was treated with bortezomib (subcutaneously on days 1-4-8-11 in 21-day cycles) and dexamethasone (20 mg on days 1-2, 4-5, 8-9 and 11-12 of each cycle). She received six cycles of therapy and achieved a VGPR. Treatment was discontinued at the end of cycle six because of the onset of grade 2 peripheral neuropathy (PN). The patient did not receive any further therapy. Response is ongoing, and grade 2 neuropathy is persisting.

**Comments on patient 4**
For a patient progressing on Rd as frontline therapy, the logical approach is a switch in the class of agent, or to try to increase the doses of lenalidomide and dexamethasone (in case of a previous dose reduction) and not to add a third agent to Rd. Bortezomib-dexamethasone (Vd) is commonly used in this setting,26 and cyclophosphamide may also be added (VCd) to increase the response rate. No prospective comparison of Vd versus VCd in relapse is available. The toxicity of Vd is well-known, and despite subcutaneous or weekly administration of bortezomib, peripheral neuropathy remains the most important side-effect of this combination.

The phase 3 randomized ENDEAVOR study prospectively compared Vd versus carfilzomib-dexamethasone (Kd) until progression in the relapse setting.31 This study, a head-to-head comparison of two PIs, demonstrated that both PFS (median 18.7 months vs 9.4) and OS (median 47.6 vs 40 in the updated analysis presented in 2017) were superior with Kd. The results favor Kd for all subgroups of patients, including first relapse (as is the case in patient 4 described above), prior lenalidomide exposure and standard-risk cytogenetics. Based on the results of the ENDEAVOR trial, and following the approval of this doublet combination, Kd could also have been a feasible option for patient 4. The schedule of Kd, however, is more demanding than that of Vd, with IV administration of carfilzomib at the dose of 56 mg/m2 on days 1, 2, 8, 9, 15, and 16 of 28-day cycles until progression. The safety profile is also different from that of Vd, with fewer cases of PN, but instead higher rates of hypertension, dyspnea, cardiac failure and acute renal failure. Nevertheless, the rates of treatment discontinuation due to adverse events were identical in the two arms of the study. Of note, the phase 1 / 2 CHAMPION-1 trial evaluated the more convenient weekly administration of carfilzomib, at a higher dose of 70 mg/m2 in combination with dexamethasone and showed promising response rates and PFS that merits additional evaluation.32

Recently, Vd was compared to Vd plus daratumumab (DVd) in relapsed MM (CASTOR trial), and the triplet combination was associated with an impressive PFS improvement (HR 0.39).33 The benefit of the addition of daratumumab was observed across all subgroups of patients, including all characteristics of patient 4: first relapse, prior IMiD and above 65 years of age. Importantly, the safety profile of the triplet is acceptable, and daratumumab was not found to add any significant toxicity to the Vd
combination. DVd is now approved and represents another option for patients progressing on Rd.

Other combinations based on Vd are available, but will probably be used less frequently in the future, either because of toxicity (panobinostat-Vd) or paucity of results (elotuzumab-Vd).

For patient 4, outside of a clinical trial, I would propose DVd.

Case 5: Treatment for lenalidomide- and bortezomib-refractory disease

Case presentation

A 67 year-old female patient with standard-risk MM was treated with frontline Rd in 2013. The initial response was good (VGPR), but she progressed on therapy during cycle 26 in 2015. The salvage therapy consisted of VD. Following the achievement of PR after two cycles, which was sustained for three cycles, the patient progressed again with bone pain, anemia, and an M-spike of more than 1.5 g/dL. The patient was then treated with pomalidomide-dexamethasone (pom-dex) in 2016, Response to pom-dex lasted for only 5 months before the disease progressed again. At this point, at the end of 2016, we initiated daratumumab therapy, which induced a PR. The patient is currently still receiving daratumumab single agent, at the dose of 16 mg/kg Q4W, according to the design of the SIRIUS trial, with a sustained response, good tolerance, no bone pain and normal performance status.

Comments on patient 5

Pomalidomide and low-dose dexamethasone is an approved combination regimen for the treatment of patients with refractory disease, who relapse after at least two prior lines of therapy including lenalidomide and bortezomib. Patient 5 was refractory to both Rd and Vd. In the pivotal MM003 study, in which pom-dex was compared to high-dose dexamethasone, the PFS was significantly higher with pom-dex, 4 months vs 1.9 months, translating into an OS benefit (median 12.7 vs 8.1 months). Recently, Baz et al reported the results of a phase 2 trial comparing pom-dex vs pom-dex plus cyclophosphamide (PCD) in an equivalent patient population and showed that the addition of oral cyclophosphamide (400 mg day 1, 8 and 15 of 28-day cycle) to pom-dex was able to increase the PFS from 4.4 to 9.5 months. Patient
5 could have benefitted from the addition of cyclophosphamide, a cheap alkylating agent, to which he had not been exposed previously. In our routine practice, PCD is one of the standard rescue regimen, all oral, effective and manageable, for those patients who progress following lenalidomide and bortezomib exposure. Patient 5 progressed on pom-dex and subsequently received daratumumab. This monoclonal antibody, which targets CD38, was approved by the FDA in 2015 for patients who have received at least three prior treatments, based on the results of two phase II trials, SIRIUS and GEN501. These trials demonstrated significant single-agent activity of daratumumab in patients refractory to all classes of available agents. In the combined analysis of these two trials, the median PFS was 3 months overall, and 15 months for those reaching PR. Furthermore, for responding patients, survival was found to be prolonged (75% at 2 years). Recently, the data of these two trials were used to compare the efficacy of daratumumab monotherapy (148 patients) versus historical controls (658 patients) through an adjusted treatment comparison. This analysis suggests that daratumumab improves OS compared to historical control data in patients with heavily pretreated and highly refractory MM, with an adjusted OS-HR of 0.33. Daratumumab, although rarely used as single-agent in the US, represents a major breakthrough for the treatment of patients with refractory disease. However, the agent will also be used earlier in the course of the disease, in combination with PIs and IMiDs as investigated in the CASTOR and POLLUX trials. The feasibility of retreatment with CD38 monoclonal antibodies remains to be investigated.

For patient 5, who is refractory to bortezomib and lenalidomide, I would recommend PCD or Pomalidomide-dexamethasone and daratumumab, which was recently approved in the US.

**Final considerations**

In the past decade, the treatment of MM has progressed greatly as a result of the introduction of several new active drugs, which have been approved. Progression-free survival and OS rates have increased markedly, and recent trials incorporating novel agents and ASCT may lead to a statistical cure fraction of approximately 15% of patients. In addition, many other new drugs or immune therapies are in advanced
stages of investigation, including for example isatuximab (CD38 monoclonal antibody), selinexor (nuclear exporter inhibitor), venetoclax (oral Bcl2-inhibitor), ricolinostat (oral HDAC6 inhibitor), check-point inhibitors, bispecific T-cell engager (BITE) antibodies or chimeric antigen receptor (CAR) T-cells which will enrich our therapeutic armamentarium.\textsuperscript{44-45} Some of these agents are first-in-class and may represent true progress, but a recurrent question is how to design a study to demonstrate the true impact of a specific agent on response, PFS or OS. For example, the HR value for PFS achieved with the DRd combination in relapsed MM in the POLLUX trial (0.37) has set the bar so high that it will be difficult to show the superiority of other combinations over DRd in phase 3 trials designed for regulatory approvals.

Moreover, MM is a very heterogeneous disease comprised of different genetic entities that differ from each other in evolution, mode of presentation, response to therapy and prognosis.\textsuperscript{1,3} Clinical trials seldom target specific genetic subtypes that may benefit most from a new drug. In the future, the use of new agents will probably require the identification of biomarkers to predict response to therapy.\textsuperscript{46}

In this manuscript, I have listed numerous possible drug combinations available at diagnosis, in patients with 1-3 prior lines of therapy, or in very advanced disease. Nevertheless, to date the optimal strategy for the frontline therapy of MM, the nature and duration of maintenance, or the ideal sequence of therapy at relapse cannot be defined from the available clinical trials. A list of strategic studies that address important questions have been proposed by some investigators to further optimize the management of patients with MM.\textsuperscript{46} For example, “does modifying therapy based on response or MRD detection improve outcome?” Or, “can limited-duration combination therapy regimens be developed that are as effective as continuous therapy?” Or, “what is the best triplet regimen to use in the most cost-effective way at relapse?” This latter question is of upmost importance since drug access and cost represent the most important challenges for MM patients and physicians worldwide.\textsuperscript{47}

The availability of a host of various classes of agents presents both a great opportunity and a great challenge. On the one hand, we are able to achieve unparalleled results regarding improvements in survival, but on the other hand, many issues surrounding the use of these agents remain to be solved. In this review, I have
discussed practical patient examples and provided the rationale for the various treatment choices based on our experience and recent data from trials to aid the decision-making process for physicians treating patients with myeloma.
Conflict-of-interest disclosures

PM: advisory boards for Takeda, Celgene, Janssen, BMS, Novartis, Amgen.

Authorship

PM wrote the paper.
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## Table 1. Major treatment regimens in multiple myeloma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Usual dosing schedule</th>
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<tbody>
<tr>
<td><strong>Front-line:</strong></td>
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<tr>
<td>Bortezomib/melphalan/prednisone (VMP)</td>
<td>Bortezomib 1.3 mg/m² intravenous days 1, 8, 15, 22; melphalan 9 mg/m² oral days 1 to 4; prednisone 60 mg/m² oral days 1 to 4; repeated every 35 days</td>
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<tr>
<td>Lenalidomide/low-dose dexamethasone (Rd)</td>
<td>Lenalidomide 25 mg oral days 1 to 21 every 28 days; dexamethasone 40 mg oral days 1, 8, 15, 22 every 28 days; repeated every 4 weeks</td>
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<tr>
<td>Melphalan/prednisone/thalidomide (MPT)</td>
<td>Melphalan 0.25 mg/kg oral days 1 to 4 (use 0.20 mg/kg/day oral days 1 to 4 in patients over the age of 75); prednisone 2 mg/kg oral days 1 to 4; thalidomide 100 to 200 mg oral days 1 to 28 (use 100 mg dose in patients &gt;75); repeated every 6 weeks</td>
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<tr>
<td>Bortezomib/cyclophosphamide/dexamethasone (VCD)</td>
<td>Cyclophosphamide 300 mg/m² orally on days 1, 8, 15 and 22; bortezomib 1.3 mg/m² intravenously on days 1, 8, 15, 22; dexamethasone 40 mg orally on days 1, 8, 15, 22; repeated every 4 weeks</td>
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<tr>
<td>Bortezomib/thalidomide/dexamethasone (VTD)</td>
<td>Bortezomib 1.3 mg/m² intravenous days 1, 8, 15, 22; thalidomide 100-200 mg oral days 1 to 21; dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22); repeated every 4 weeks x four cycles as pre-transplant induction therapy</td>
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<tr>
<td>Bortezomib/lenalidomide/dexamethasone (VRD)</td>
<td>Bortezomib 1.3 mg/m² intravenous days 1, 8, 15; Lenalidomide 25 mg oral days 1 to 14; dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22); repeated every 3 weeks</td>
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<td><strong>Relapsed/refractory disease:</strong></td>
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<tr>
<td>Carfilzomib/lenalidomide/dexamethasone (KRD)</td>
<td>Carfilzomib 20 mg/m² (cycle 1) and 27 mg/m² (subsequent cycles) intravenously on days 1, 2, 8, 9, 15, 16; lenalidomide 25 mg oral days 1 to 21; dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22); repeated every 4 weeks</td>
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<tr>
<td>Bortezomib/dexamethasone/panobinostat (VD-Pano)</td>
<td>Bortezomib 1.3 mg/m² intravenous days 1, 8, 15, 22; dexamethasone 20 mg on day of and day after bortezomib; panobinostat 20 mg oral days 1, 3, 5 week 1 and 2; repeated every 3 weeks (cycles 1-8)</td>
</tr>
<tr>
<td>Carfilzomib/dexamethasone (Kd)</td>
<td>Carfilzomib 56 mg/m² i.v. days 1, 2, 8, 9, 15, 16 (20 mg/m² days 1, 2, cycle 1 only); dexamethasone 20</td>
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<tr>
<td>Treatment</td>
<td>Dosage Details</td>
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<td>-------------------------------------------------------------------------------</td>
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<tr>
<td>Lenalidomide/dexamethasone/elotuzumab (Rd-Elo)</td>
<td>Lenalidomide 25 mg oral days 1 to 21; dexamethasone 40 mg weekly; elotuzumab 10 mg/kg i.v. weekly cycle 1 and 2, every other week cycles 3+; repeated every 28 days</td>
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<tr>
<td>Lenalidomide/dexamethasone/ixazomib (IRd)</td>
<td>Lenalidomide 25 mg oral days 1 to 21; dexamethasone 40 mg days 1, 8, 15, 22; ixazomib 4 mg oral days 1, 8, 15; repeated every 28 days</td>
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<tr>
<td>Bortezomib/dexamethasone/daratumumab (DVd)</td>
<td>Bortezomib 1.3 mg/m2 subcutaneous days 1, 4, 8, 11 (cycles 1-8); dexamethasone 20 mg oral days 1, 2, 4, 5, 8, 9, 11, 12 (cycles 1-8); daratumumab 16 mg/kg i.v. every week (cycles 1-3), every 3 weeks (cycles 4-8), every 4 weeks (cycles 9+); cycles 1-8: repeated every 21 days; cycles 9+: repeated every 28 days</td>
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<td>Lenalidomide/dexamethasone/daratumumab (DRd)</td>
<td>Lenalidomide 25 mg oral days 1-21; dexamethasone 40 mg oral weekly; daratumumab 16 mg/kg i.v. weekly (cycles 1-2), every other week (cycles 3-6), q4w cycles 7+; cycles: 28 days</td>
</tr>
</tbody>
</table>
Table 2. Phase 3 trials in RRMM. Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimens</th>
<th>Patients (n)</th>
<th>Median number of prior therapies</th>
<th>ORR (%)</th>
<th>≥ VGPR (%)</th>
<th>PFS (months)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experimental versus placebo arm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ln</td>
<td>Rd ± carfilzomib</td>
<td>792</td>
<td>2 (1-3)</td>
<td>87 versus 67</td>
<td>70 versus 40</td>
<td>26 versus 18</td>
<td>HR 0.69</td>
</tr>
<tr>
<td><strong>TOURMALINE-MM1 [28]</strong></td>
<td>Rd ± ixazomib</td>
<td>722</td>
<td>1 (1-3)</td>
<td>78 versus 72</td>
<td>48 versus 39</td>
<td>20.6 versus 14.7</td>
<td>HR 0.74</td>
</tr>
<tr>
<td><strong>ELOQUENT 2 [27]</strong></td>
<td>Rd ± elotuzumab</td>
<td>646</td>
<td>2 (1-3)</td>
<td>79 versus 66</td>
<td>33 versus 28</td>
<td>19.4 versus 14.9</td>
<td>HR 0.70</td>
</tr>
<tr>
<td><strong>POLLUX [29]</strong></td>
<td>Rd ± daratumumab</td>
<td>569</td>
<td>1 (1-11)</td>
<td>93 versus 76</td>
<td>76 versus 44</td>
<td>Not reached versus 18.4</td>
<td>HR 0.37</td>
</tr>
<tr>
<td><strong>Bortezomib-based regimens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PANORAMA 1 [34]</strong></td>
<td>Vd ± panobinostat</td>
<td>768</td>
<td>1 (1-3)</td>
<td>61 versus 55</td>
<td>Not mentioned</td>
<td>12 versus 8</td>
<td>HR 0.63</td>
</tr>
<tr>
<td><strong>CASTOR [33]</strong></td>
<td>Vd ± daratumumab</td>
<td>498</td>
<td>2 (1-3)</td>
<td>83 versus 63</td>
<td>59 versus 29</td>
<td>Not reached versus 7.16</td>
<td>HR 0.39</td>
</tr>
<tr>
<td><strong>Jakubowiak A et al (randomized phase II study) [35]</strong></td>
<td>Vd ± elotuzumab</td>
<td>150</td>
<td>1 (1-3)</td>
<td>66 versus 63</td>
<td>37 versus 27</td>
<td>9.7 versus 6.9</td>
<td>HR 0.72</td>
</tr>
<tr>
<td><strong>ENDEAVOR [31]</strong></td>
<td>Kd versus Vd</td>
<td>929</td>
<td>1 (1-3)</td>
<td>77 versus 63</td>
<td>54 versus 29</td>
<td>18.7 versus 9.4</td>
<td>HR 0.53</td>
</tr>
</tbody>
</table>

Rd: Lenalidomide/dexamethasone; Vd: bortezomib/dexamethasone; Kd: carfilzomib/dexamethasone; ORR: overall response rate; VGPR: very good partial response; PFS: Progression-free survival; HR: Hazard ratio.
<table>
<thead>
<tr>
<th>Regimens</th>
<th>Route of administration</th>
<th>Dosing schedule</th>
<th>Hospital/clinic visit</th>
<th>Administration time</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRd [25]</td>
<td>IV</td>
<td>Cycle 1-12: Days 1,2,8,9,15 and 16 of 28-day cycle. Cycle 13-18: Days 1,2,15 and 16 of 28-day cycle.</td>
<td>Twice a week (3-week-on/1-week-off)</td>
<td>Overs 30 min + pretreatment hydration</td>
</tr>
<tr>
<td>IRd [28]</td>
<td>PO</td>
<td>Days 1,8,15 of 28-day cycle.</td>
<td>Every 4 weeks</td>
<td>0 hours</td>
</tr>
<tr>
<td>Rd + elotuzumab [27]</td>
<td>IV</td>
<td>Days 1,8,15 and 22 of 28-day cycle 1 and 2 then days 1 and 15 cycle 3+.</td>
<td>Weekly for 8 weeks then twice weekly</td>
<td>5 hours Need premedication</td>
</tr>
<tr>
<td>DRd [29]</td>
<td>IV</td>
<td>Days 1,8,15 and 22 of 28-day cycle 1 and 2, days 1 and 15 for cycle 3 to 6 then every four weeks thereafter.</td>
<td>Weekly for 8 weeks, twice weekly for 16 weeks then every 4 weeks</td>
<td>6.5 hours for the first infusion and 3.5 hours for subsequent infusions. Need premedication</td>
</tr>
<tr>
<td>Vd + panobinostat [34]</td>
<td>PO (+ bortezomib IV)</td>
<td>Panobinostat: days 1, 3, 4, 8, 10, and 12 of 21-day cycle Bortezomib: days 1,4,8 and 11</td>
<td>Twice a week (2-week-on/1-week-off)</td>
<td>About 1 hour for bortezomib</td>
</tr>
<tr>
<td>DVd [33]</td>
<td>IV (+ bortezomib SC)</td>
<td>Daratumumab: days 1, 8 and 15 of 21-day cycle 1 to 3, every three weeks for cycle 4 to 8 then every four weeks Bortezomib: days 1,4,8 and 11</td>
<td>4 to 5 visits by 21-day cycle.</td>
<td>6.5 hours for the first infusion and 3.5 hours for subsequent infusions. Need premedication</td>
</tr>
<tr>
<td>Kd [31]</td>
<td>IV</td>
<td>Daratumumab: Days 1,2,8,9,15 and 16 of 28-day cycle.</td>
<td>Twice a week (3-week-on/1-week-off)</td>
<td>Overs 30 min + pretreatment hydration</td>
</tr>
</tbody>
</table>

How I treat: New agents in myeloma

Philippe Moreau