

## Multiple myeloma - Section 3

# Optimal sequencing in the management of relapsed/refractory myeloma patients

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### Take Home Messages

- Multiple criteria including both patient-related and disease-related factors must be considered when choosing an appropriate treatment for relapsed myeloma
- Drug access and reimbursement of Kd, DVd, DRd, KRd, IRd or EloRd the most active regimens in the relapse setting, are important issues.

### Abstract

Multiple classes of agent with distinct mechanisms of action are now available for the treatment of patients with relapsed and/or refractory multiple myeloma (RRMM), including immunomodulatory agents, proteasome inhibitors, histone deacetylase inhibitors and monoclonal antibodies. Additionally, several different drugs may be available within each agent class, each with their own specific efficacy and safety profile. This expansion of the treatment landscape has dramatically improved outcomes for patients. However, as the treatment options for RRMM become more complex, choosing the class of agent or combination of agents to use in the relapsed setting becomes increasingly challenging. Furthermore, treatment options for specific patient populations such as the elderly, those with high-risk cytogenetic abnormalities and those with refractory disease are yet to be defined in the current treatment landscape. When choosing an appropriate treatment approach, physicians must consider multiple criteria including both patient-related and disease-related factors. The aim should be to provide patient-specific treatment in order to gain a clinical benefit while minimizing toxicity.

### Introduction

Multiple myeloma (MM) is characterized by a relapsing disease course. Despite significant improvements in patient outcomes following the introduction of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) in the first-line setting, most patients eventually relapse, and the management of relapsed and/or refractory MM (RRMM) remains a challenge. The treatment landscape for patients with RRMM is rapidly changing. Multiple classes of agent with distinct mechanisms of action, efficacy and safety profiles are now available, including IMiDs, PIs, histone deacetylase inhibitors and monoclonal antibodies. Until recently, bortezomib plus dexamethasone (Vd) or lenalidomide plus dexamethasone (Rd) were the typical regimens at first or second relapse.<sup>1</sup> In the last 3 to 4 years, several phase 3 randomized trials have shown improvements in progression-free survival (PFS) and/or overall survival (OS) with the use of carfilzomib (K), ixazomib (I), daratumumab (D), elotuzumab

(Elo), or panobinostat (Pano). We have now a long and varied list of options at our disposal, including Vd, Vd-Pano, DVd, Kd, Rd, Rd-Elo, KRd, IRd, DRd, all approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (Figure 1). Each combination has different efficacy and safety profiles, and it can be difficult for physicians to decide upon the most appropriate regimen to use. In the relapsed setting, treatment choice is additionally influenced by many patient- and disease-related factors such as age, cytogenetics, pre-existing toxicities, aggressiveness of relapse, previous therapy, response to previous therapy and number of previous therapy lines. Patients should not be defined by one single characteristic: multiple factors should be considered in order to tailor treatment to the individual needs of each patient.<sup>1</sup>

### Recent important phase 3 trials in RRMM

Among recently approved regimens, 2 have shown an OS benefit vs control therapy in phase 3 trials, and 2 have achieved very good Hazard Ratios (HRs). The ENDEAVOR trial, which prospectively compared Kd (n=464) vs Vd (n=465) in patients with 1-3 prior lines of therapy, showed that patients treated with carfilzomib (56 mg/m<sup>2</sup>) and dexamethasone had a statistically significant improvement in OS over patients treated with Vd (median 47.6 vs 40.0 months; HR, 0.791, p=0.01).<sup>2</sup> The OS benefit was consistent, regardless of prior bortezomib therapy, number of prior regimens, age and cytogenetic risk group. Moreover, the ASPIRE trial, which prospectively compared KRd (n=396) vs Rd (n=396) in patients with 1-3 prior lines of therapy, showed that patients treated with carfilzomib (27 mg/m<sup>2</sup>) plus Rd had a statistically significant improvement in OS compared to patients treated with Rd (median OS 48.3 months for KRd versus 40.4 months for Rd (HR, 0.79, p=0.0045).<sup>3</sup> The advantage in efficacy demonstrated by KRd is most pronounced at first relapse (among those patients, the median OS was 11.4 months longer for KRd versus Rd, while it was 6.5 months longer for KRd vs Rd among patients having received more than two prior lines of therapy). The OS benefit observed for a carfilzomib-containing regimen over current standard therapies represents an important finding. More recently, 2 trials tested dara-

tumumab in combination with either Vd or Rd in a randomized fashion, and showed very good HRs for PFS. The CASTOR study prospectively compared Vd (n=247) versus DVd (n=251).<sup>4</sup> The 12-month PFS rate was 60.7% in the daratumumab group versus 26.9% in the control group. After a median follow-up period of 7.4 months, the median PFS was not reached in the daratumumab group and was 7.2 months in the control group (HR, 0.39; p<0.001). The study was recently updated with a median follow-up of 27 months, and the median PFS was 16.7 months in the daratumumab arm vs 7.1 in the control arm (HR, 0.32; p<0.0001).<sup>5</sup> Overall survival data are not yet mature, but DVd is already approved by the FDA and EMA, and this triplet combination is becoming a standard in the relapse setting. Furthermore, the POLLUX study prospectively compared Rd (n=283) versus DRd (n=286).<sup>6</sup> PFS at 12 months was 83.2% in the daratumumab group, as compared to 60.1% in the control group (HR, 0.37; p<0.001). Updated results were presented at ASH 2017, with a median follow-up of 33 months, confirming the PFS benefit in the daratumumab arm (HR, 0.44).<sup>7</sup> In the daratumumab group, 22.4% of the patients had results below the threshold for the detection of MRD (1 tumor cell x 10<sup>5</sup> white cells) vs 4.6% of those in the control group (p<0.001). Of note, results below the threshold for the detection of MRD were associated with improved outcomes. DRd is also approved by the FDA and EMA and is playing a key role in relapsed MM.

**Open issues and challenges in the management of relapsed MM**

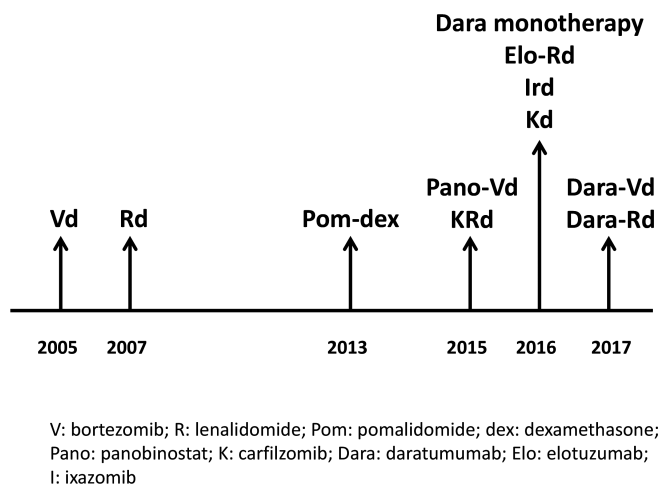
Drug access and reimbursement of Kd, DVd, DRd, or KRd, the most active regimens in the relapse setting, will be important issues. The same is true for IRd or EloRd. One way to reduce cost could be the use of a fixed duration of therapy, instead of the application of treatment until progression. All recent phase 3 trials have followed the same design: PFS as a primary endpoint and treatment until progression. We should recommend trials asking strategic questions, such as: can combination regimens be developed that are given for a fixed duration and that are as effective as continuous therapy? Or, what is the most cost-effective triplet regimen to be used at relapse?<sup>8</sup> Treatment at relapse is selected according to the first line treatment, and the duration of the first response, among other crite-

ria. Following the recent approval of Rd until progression (in elderly patients), and lenalidomide maintenance after autologous stem cell transplantation until progression, many patients will progress while receiving lenalidomide. In this situation, the switch to a PI-based combination as salvage therapy will be a logical approach. We need to develop trials integrating the first salvage regimen into the assessment of front-line therapies in order to define the optimal sequencing strategies and evaluating PFS2 as an important end-point.

The very good HRs of POLLUX<sup>6</sup> and CASTOR<sup>4</sup> present a challenge for the development of new agents in relapsed MM. Despite the promising activity of Venetoclax,<sup>9</sup> or Selinexor,<sup>10</sup> for example, one cannot anticipate that an experimental arm including these 2 agents will be superior to DRd or DVd in a phase 3 trial. New agents are typically initially examined in patients with end-stage, refractory disease. Their evaluation earlier in the disease course in patients who progress after 1 line of therapy will require innovative study designs, or the restriction to specific genetic subtypes or to a patient population selected via a specific biomarker predicting efficacy and response to therapy.

**References**

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**Figure 1. Combinations approved by European Medicines Agency.**