The Role of Panobinostat Plus Bortezomib and Dexamethasone in Treating Relapsed or Relapsed and Refractory Multiple Myeloma: A European Perspective

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ABSTRACT

Panobinostat is an oral pan-histone deacetylase inhibitor developed by Novartis. Panobinostat acts via epigenetic modification and inhibition of the aggresome pathway. In August 2015, the European Commission authorized panobinostat for use in combination with bortezomib and dexamethasone for the treatment of relapsed or relapsed and refractory multiple myeloma (MM) in patients who have received ≥2 prior regimens including bortezomib and an immunomodulatory drug. In January 2016, the National Institute for Health and Care Excellence recommended panobinostat for use in the same combination and patient population. The authorization and recommendation were based on results from the pivotal phase 3 PANORAMA 1 (NCT01023308) clinical trial, which demonstrated an improvement in median progression-free survival of 7.8 months for the three-drug combination compared with placebo plus bortezomib and dexamethasone in this patient population. This review will discuss the current treatment landscape for relapsed/refractory MM, the mechanism of action of panobinostat, clinical data supporting the European authorization, concerns about safety and strategies for mitigating toxicity, and how panobinostat fits into the current MM landscape in Europe.

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Keywords: Multiple myeloma; Oncology; Panobinostat; Relapsed; Relapsed and refractory

INTRODUCTION

Multiple myeloma (MM) is a hematologic disorder characterized by clonal proliferation of malignant plasma cells in the bone marrow.
that overproduce abnormal monoclonal proteins [1]. It can be classified as asymptomatic or active, based on the presence of MM biomarkers (clonal bone marrow plasma cells, serum free light chain ratio, and focal lesions) or CRAB criteria (disease-associated organ damage that includes hypercalcemia, renal insufficiency, anemia, and bone disease) [2]. MM tends to present in older patients, with the median age at diagnosis being $\approx 70$ years [1]. Therefore, the incidence of MM is expected to increase as the population ages, as seen in a recent European survey [3]. In this survey, there were $\approx 39,000$ cases of newly diagnosed MM in 2012 [4], with the incidence expected to rise by 30% by 2035 [3].

MM remains an incurable disease. Over the past decade, breakthroughs in myeloma therapy, particularly the introduction of proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) and the use of autologous stem cell transplantation, have vastly improved patient outcomes [5, 6]. However, due to the clonal nature of the disease, the majority of patients will relapse after currently available therapies, and with each successive relapse, the prognosis worsens [7, 8]. Therefore, an unmet need exists for agents with new mechanisms of action that can overcome disease resistance to current therapeutic regimens.

Panobinostat, a first-in-class pan-deacetylase inhibitor (DACi), was recently authorized by the European Commission (EC) and recommended by the National Institute for Health and Care Excellence (NICE) in combination with bortezomib and dexamethasone for the treatment of patients with MM who have received $\geq 2$ prior therapeutic regimens including bortezomib and an IMiD. This review will discuss the current treatment landscape for relapsed/refractory MM (RRMM), the unique mechanism of action of panobinostat, clinical data supporting the EC authorization of panobinostat in patients with relapsed or RRMM who have received $\geq 2$ prior therapeutic regimens, concerns about safety and strategies for mitigating toxicity, and how this novel therapeutic fits into the current MM treatment landscape in Europe.

Compliance with Ethics Guidelines

This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

TREATMENT OF RRMM IN EUROPE: THE CURRENT THERAPEUTIC LANDSCAPE

Although, as mentioned, major advances have been made in the treatment of patients with MM [5, 8], the majority of patients will eventually relapse after or become refractory to the available therapies [7, 8]. However, the majority of agents currently authorized by the EC for the treatment of MM are derived from just two drug classes, PIs and IMiDs (Table 1). The two approved PIs are bortezomib (authorized April 26, 2004) and carfilzomib (authorized November 19, 2015). Authorized IMiDs include lenalidomide (June 14, 2007), thalidomide (April 16, 2008), and pomalidomide (August 5, 2013); however, thalidomide is authorized only in patients with untreated myeloma [9]. Other agents include classical chemotherapeutics, such as doxorubicin, cyclophosphamide, and bendamustine—as possible salvage therapies or in combination with novel agents—as well as...
| Agent         | Trade name | MOA                         | European Commission indication                                                                                                                                                                                                                                                                                                                                 | Date of authorization |
|--------------|------------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Doxorubicin  | Caelyx®    | Anthracycline               | Treatment of patients with progressive MM who have received ≥1 previous therapeutic regimen and have undergone or are unsuitable for bone marrow transplant                                                                                                                                                                                                                                                                  | 21 June 1996          |
| Interferon α-2b | IntronA®   | Recombinant cytokine        | As maintenance therapy in patients with MM who have achieved an objective response (>50% reduction in M-protein) following induction chemotherapy                                                                                                                                                                                                                                                                         | 09 March 2000         |
| Bortezomib   | Velcade®   | Proteasome inhibitor        | Treatment of patients with MM Who are previously untreated and not eligible for high-dose chemotherapy and ASCT; in combination with melphalan and prednisone Who are previously untreated and are going to receive high-dose chemotherapy and ASCT; in combination with dexamethasone or thalidomide and dexamethasone Who have progressed following ≥1 prior therapeutic regimen and have received or are ineligible to receive ASCT; either as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone | 26 April 2004         |
| Lenalidomide | Revlimid®  | IMiD                        | Treatment of patients with MM Who are previously untreated and are not eligible for ASCT Who have received ≥1 prior antimyeloma therapy; in combination with dexamethasone                                                                                                                                                                                                                                                              | 14 June 2007          |
| Thalidomide  | Thalomid®  | IMiD                        | Treatment of patients with MM who are previously untreated and aged ≥65 years or ineligible for high-dose chemotherapy; in combination with melphalan and prednisone                                                                                                                                                                                                                                                                                                     | 16 April 2008         |
| Pomalidomide | Innovid®   | IMiD                        | Treatment of patients with relapsed and refractory MM who have received ≥2 prior regimens including bortezomib and lenalidomide and have demonstrated disease progression on the last therapy; in combination with dexamethasone                                                                                                                                                                                                                                                       | 05 August 2013        |
| Panobinostat | Farydak®   | Pan-deacetylase inhibitor   | Treatment of patients with relapsed or relapsed and refractory MM who have received ≥2 prior regimens including bortezomib and an IMiD; in combination with bortezomib and dexamethasone                                                                                                                                                                                                                                                         | 28 August 2015        |
the recently approved monoclonal antibodies elotuzumab and daratumumab.

**PIs**

It is believed that MM cells are much more sensitive to proteasome inhibition than normal cells due to the aberrant production of abnormal and mutant proteins [10]. Blockade of the proteasome leads not only to an unfolded protein stress response within the cell [11], but can also directly influence expression of proteins normally degraded through active proteasomes, including those involved in apoptosis, cell cycle progression, and activation of the transcriptional factor NFκB. Therefore, inhibiting the proteasome can lead to apoptosis and inhibition of proliferation [12, 13].

**Bortezomib**

Bortezomib was the first PI to be authorized for the treatment of MM by the EC (Table 1). Bortezomib is a boronic acid analog that reversibly binds and inhibits the chymotryptic activity of the 20S proteasome subunit [14]. In the phase 3 APEX trial (NCT00048230), bortezomib was superior to dexamethasone for the treatment of MM that had relapsed after 1–3 previous therapies (Table 2) [15]. Patients treated with bortezomib had a significant increase in overall response rate (ORR; 38% vs 18%; \( P < 0.001 \)), a significantly prolonged time to progression (TTP; 6.2 vs 3.5 months; \( P < 0.001 \)), and a significant overall survival (OS) benefit (80% vs 66% at 1 year; \( P = 0.003 \)) (Table 2).

**Carfilzomib**

Carfilzomib, a second-generation PI, is a tetrapeptide epoxyketone analog of epoxomicin that primarily inhibits the chymotrypsin site of the 20S subunit of the proteasome but may also act upon the trypsin-like and caspase-like sites at high concentrations [12, 16]. Carfilzomib binds

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**Table 1 continued**

| Agent     | Trade name | MOA                  | European Commission indication                                                                 | Date of authorization |
|-----------|------------|----------------------|--------------------------------------------------------------------------------------------------|-----------------------|
| Carfilzomib | Kyprolis® | Proteasome inhibitor | Treatment of patients with MM who have received ≥1 prior therapy; in combination with lenalidomide and dexamethasone | 19 November 2015       |
| Elotuzumab | Empliciti™ | Anti-SLAMF7 monoclonal antibody | Treatment of patients with MM who have received ≥1 prior therapy; in combination with lenalidomide and dexamethasone | 11 May 2016           |
| Daratumumab | Darzalex™ | Anti-CD38 monoclonal antibody | Treatment of patients with RRMM whose prior therapy included a PI and an IMiD and who have demonstrated disease progression on the last therapy; monotherapy | 20 May 2016           |

ASCT autologous stem cell transplant, IMiD immunomodulatory drug, MOA mechanism of action, MM multiple myeloma, RRMM relapsed/refractory multiple myeloma, SLAMF7 signaling lymphocytic activation molecule F7, PI proteasome inhibitors
Table 2  Key trials for novel agents authorized for the treatment of patients with relapsed/refractory multiple myeloma

| Regimen          | Trial                      | Phase | N     | Population                                      | Median no. of prior therapies | ORR, %   | PFS/TTP, mo | OS, mo |
|------------------|---------------------------|-------|-------|-------------------------------------------------|-------------------------------|----------|-------------|--------|
| BTZ vs Dex       | APEX [15]                 | 3     | 669   | Relapsed MM with 1–3 prior lines                 | 2                             | 38 vs 18 | TTP:        | 1-year OS: |
|                  |                           |       |       |                                                  |                               | P < 0.001| 6.2 vs 3.5 | 80% vs 66% |
|                  |                           |       |       |                                                  |                               | P < 0.001| P = 0.003  |        |
| CFZ-Dex vs BTZ-Dex| ENDEAVOR [19]             | 3     | 929   | Relapsed or refractory MM with 1–3 prior lines   | 2                             | 77 vs 63 | PFS:        | NA     |
|                  |                           |       |       |                                                  |                               | P < 0.0001| 18.7 vs 9.4| P < 0.001|        |
| CFZ-LEN-Dex vs LEN-Dex | ASPIRE [18] | 3     | 792   | Relapsed MM with 1–3 prior lines                 | 2                             | 87 vs 67 | PFS:        | 2-year OS: |
|                  |                           |       |       |                                                  |                               | P < 0.001| 26.3 vs 17.6| 73% vs 65% |
|                  |                           |       |       |                                                  |                               | P = 0.0001| P = 0.04   |        |
| LEN-Dex vs DEX  | MM-009 [26]               | 3     | 353   | At least 1 prior therapy                         | NA                            | 61 vs 20 | TTP:        | 29.6 vs 20.2 |
|                  |                           |       |       |                                                  |                               | P < 0.001| 11.1 vs 4.7| P < 0.001|        |
|                  |                           |       |       |                                                  |                               | P < 0.001|            |        |
| LEN-Dex vs DEX  | MM-010 [27]               | 3     | 351   | At least 1 prior therapy                         | 2                             | 60 vs 24 | TTP:        | NR vs 20.6 |
|                  |                           |       |       |                                                  |                               | P < 0.001| 11.3 vs 4.7| P = 0.03  |        |
|                  |                           |       |       |                                                  |                               | P < 0.001|            |        |
| POM-Dex vs DEX  | MM-003 [31]               | 3     | 302   | Relapsed or relapsed and refractory MM with ≥2 prior treatments including BTZ and LEN | 5                             | 31 vs 10 | PFS:        | 12.7 vs 8.1 |
|                  |                           |       |       |                                                  |                               | P < 0.0001| 4.0 vs 1.9 | P = 0.0285|        |
|                  |                           |       |       |                                                  |                               | P < 0.0001|            |        |
| PAN-BTZ-Dex vs BTZ-Dex | EU-authorized subpopulation of PANORAMA 1 [80] | 3     | 149   | Relapsed or relapsed and refractory MM with ≥2 prior regimens including BTZ and LEN | 3                             | 59 vs 39 | PFS:        | 25.5 vs 19.5 |
|                  |                           |       |       |                                                  |                               | P = 0.01703| 12.5 vs 4.7| HR, 1.01 (0.68–150) |
|                  |                           |       |       |                                                  |                               | HR, 0.47 |            |        |
| Regimen                | Trial                  | Phase | N   | Population                                                                 | Median no. of prior therapies | ORR, % | PFS/TTP, mo | OS, mo |
|------------------------|------------------------|-------|-----|----------------------------------------------------------------------------|-------------------------------|--------|-------------|--------|
| ELO-LEN-Dex vs LEN-Dex | ELOQUENT-2 [40]        | 3     | 646 | Relapsed or refractory MM with 1–3 prior therapies                         | 2                             | 79 vs 66 | PFS:         | NA     |
|                        |                        |       |     |                                                                             |                               | P < 0.001 | 19.4 vs 14.9 | P < 0.001|
| ELO-BTZ-Dex vs BTZ-Dex | NCT01478048 [41]       | 2     | 152 | Relapsed/refractory MM with 1–3 prior lines                                | 1                             | 66 vs 63 | PFS:         | NA     |
|                        |                        |       |     |                                                                             |                               | 9.7 vs 6.9 | PFS:         | HR, 0.61|
|                        |                        |       |     |                                                                             |                               | P = 0.09 | HR (0.43–0.85)|        |
| DARA                   | SIRIUS [46]            | 2     | 106 | Relapsed or relapsed and refractory MM with ≥3 prior regimens, including a PI and IMiD, or refractory to both PI and IMiD | 5                             | 29      | PFS: 3.7     | 17.5   |
|                        |                        |       |     |                                                                             |                               | (2.8–4.6) | (13.7–NR)    |        |
| DARA-LEN-Dex vs LEN-Dex| POLLUX [51]            | 3     | 569 | Relapsed MM with ≥1 prior line                                              | 1                             | 93 vs 76 | TTP:         | NA     |
|                        |                        |       |     |                                                                             |                               | P < 0.0001 | NR vs 18.4 | P < 0.0001|
| DARA-BTZ-Dex vs BTZ-Dex| CASTOR [52]            | 3     | 498 | Relapsed or refractory MM with ≥1 prior line                                | 2                             | 83 vs 63 | TTP:         | NA     |
|                        |                        |       |     |                                                                             |                               | P < 0.0001 | NR vs 7.3  | P < 0.0001|

BTZ bortezomib, CFZ carfilzomib, DARA daratumumab, Dex dexamethasone, ELO elotuzumab, LEN lenalidomide, MM multiple myeloma, NA not available, NR not reached, ORR overall response rate, OS overall survival, PAN panobinostat, PFS progression-free survival, POM pomalidomide, TTP time to treatment progression, IMiDs immunomodulatory drugs, PI proteasome inhibitors, MO month, HR hazard ratio
irreversibly to the proteasome and, compared with bortezomib, appears to be a more specific PI, leading to diminished off-target effects [12, 16, 17]. In the phase 3 ASPIRE trial (NCT01080391) of patients with relapsed RRMM who received 1–3 prior regimens, carfilzomib plus lenalidomide and dexamethasone led to significant improvements in ORR (87% vs 67%; \( P < 0.001 \)) and median progression-free survival (PFS; 26.3 vs 17.6 months; hazard ratio [HR] 0.69 [95% confidence interval [CI] 0.57–0.83]; \( P = 0.0001 \)) vs lenalidomide plus dexamethasone (Table 2) [18]. These results led to the EC authorization of carfilzomib plus lenalidomide and dexamethasone for the treatment of patients who had received ≥1 prior MM therapy.

Carfilzomib has also shown greater efficacy than bortezomib in patients with MM. In the phase 3 ENDEAVOR trial (NCT01568866) of patients with RRMM who had received 1–3 prior therapies, carfilzomib plus dexamethasone demonstrated superiority over bortezomib plus dexamethasone with a significantly prolonged median PFS of 18.7 months (95% CI, 15.6–NE) in patients in the carfilzomib–dexamethasone group vs 9.4 months [95% CI, 8.4–10.4; HR, 0.53 (95% CI, 0.44–0.65); \( P < 0.0001 \)] in those in the bortezomib–dexamethasone group [19].

Interestingly, the open-label, phase 3 FOCUS trial (NCT01302392) comparing single-agent carfilzomib with low-dose dexamethasone in patients who had received ≥3 prior therapies failed to meet its primary endpoint of improved OS (HR, 0.975; 95% CI, 0.760–1.249; \( P = 0.4172 \)) [20]. These findings suggested that carfilzomib must be used in combination with additional agents in the RRMM setting. Of note, most control group patients (>90%) received cyclophosphamide–dexamethasone.

**IMiDs**

The class of agents known as IMiDs appears to promote antitumor activity through binding to cereblon, a key component of the E3 ubiquitin ligase complex [21]. This binding promotes the ubiquitination and degradation of Ikaros and Aiolos, 2 distinct zinc-finger transcription factors that are essential to B cell development and are linked to IMiD-mediated myeloma cell death [22, 23]. Currently, lenalidomide and pomalidomide are the two IMiDs authorized for the treatment of patients with RRMM.

**Lenalidomide**

Lenalidomide is a thalidomide derivative that showed clinical activity in patients with refractory MM in phase 1 and 2 trials [24, 25]. Based on these promising findings, two large randomized phase 3 studies were initiated, one in North America (MM-009; NCT00056160) [26] and one in Europe, Australia, and Israel (MM-010; NCT00424047) [27]. These studies assessed the combination of lenalidomide plus dexamethasone vs placebo plus dexamethasone in patients with RRMM who had received ≥1 prior therapy (Table 2). Both MM-009 and MM-010 demonstrated the superiority of lenalidomide plus dexamethasone vs dexamethasone alone, with very similar results. Significant improvements were observed in ORR (MM-009, 61% vs 20%; MM-010, 60% vs 24%; \( P < 0.001 \)), TTP (MM-009, 11.1 vs 4.7 months; MM-010, 11.3 vs 4.7 months; \( P < 0.001 \)), and median OS (MM-009, 29.6 vs 20.2 months [\( P < 0.001 \]); MM-010, not reached vs 20.6 months [\( P = 0.03 \)]). These findings led to the authorization of lenalidomide plus dexamethasone for the treatment of patients with MM who have received ≥1 prior therapy [28]. A pooled update of the MM-009 and
MM-010 studies showed that responses were durable and that the OS benefit was retained [29].

**Pomalidomide**
Pomalidomide is a third-generation IMiD agent that was recently approved by the EC for the treatment of patients with RRMM who have had ≥2 prior treatments, including bortezomib and lenalidomide, and have progressive disease on treatment [30]. This approval was based on the findings from the phase 3 MM-003 study (NCT01311687), which compared pomalidomide plus low-dose dexamethasone vs high-dose dexamethasone in patients with RRMM (Table 2) [31]. ORR was higher in the pomalidomide plus dexamethasone group than in the high-dose dexamethasone group (31% vs 10%; \( P < 0.0001 \)) and median PFS was longer [4.0 vs 1.9 months; HR, 0.48 (95% CI, 0.39–0.60); \( P < 0.0001 \)]. Similarly, an increase in OS was observed in the pomalidomide plus low-dose dexamethasone group [12.7 vs 8.1 months; HR, 0.74 (95% CI, 0.56–0.97); \( P = 0.0285 \)].

To further evaluate the safety and efficacy of pomalidomide plus low-dose dexamethasone in this patient population, the phase 3b multicenter European study STRATUS (NCT01712789) was initiated [32]. This is the largest study of pomalidomide plus low-dose dexamethasone to date, with 682 patients enrolled at the last analysis [33]. Findings were consistent with what was observed in the MM-003 study; the ORR was 33% (median duration of response, 7.4 months) and the median PFS and OS were 4.6 and 11.9 months, respectively.

Triple-drug combinations with pomalidomide are also being assessed, given that recent studies have shown the addition of a third agent to treatment regimens leads to deeper responses in patients with RRMM. The addition of cyclophosphamide to pomalidomide plus dexamethasone was recently evaluated in a phase 2 multicenter study in patients with RRMM (\( N = 80 \)) [34]. Patients were randomized (1:1) to receive pomalidomide–dexamethasone or pomalidomide–dexamethasone with cyclophosphamide. The triple combination of pomalidomide–cyclophosphamide–dexamethasone resulted in a higher ORR (65% vs 39%; \( P = 0.035 \)) and PFS (9.5 vs 4.4 months; \( P = 0.106 \)) than pomalidomide–dexamethasone in patients with lenalidomide-refractory MM. A new study evaluating the combination of pomalidomide and dexamethasone with low-dose, twice-daily cyclophosphamide is currently enrolling (NCT02176213).

Pomalidomide is also being evaluated in combination with low-dose dexamethasone and bortezomib. This combination showed promising activity (ORR, 71%) and good tolerability in a phase 1 dose-escalation study in patients with RRMM [35] and is now being assessed in the global, randomized, phase 3 MM-007 study (OPTIMISMM; NCT01734928) [36]. MM-007 is designed to compare pomalidomide plus bortezomib plus low-dose dexamethasone vs bortezomib plus dexamethasone in patients with RRMM who have received 1–3 prior lines of therapy, including lenalidomide (target enrollment 782). The primary endpoint will be PFS.

**Monoclonal Antibodies**

Monoclonal antibodies have shown antitumor activity in a variety of cancers. These agents selectively target markers found exclusively or predominantly on myeloma cells. In addition to targeting myeloma cells for death, they may exert immunologic control of minimal residual
disease by acting against immunosuppressive cells such as regulatory T cells, regulatory B cells, and/or myeloid-derived suppressor cells. The two monoclonal antibodies that have received authorization from the EC are elotuzumab and daratumumab.

**Elotuzumab**

Elotuzumab is a monoclonal antibody directed against signaling lymphocytic activation molecule F7, a cell-surface glycoprotein expressed on natural killer cells and myeloma cells but not on normal cells, enabling selective targeting [37]. Elotuzumab can exert antimyeloma activity through activation of natural killer cells and through antibody-dependent cell-mediated cytotoxicity [38] but has no activity as a single agent [39]. However, in the phase 3 ELOQUENT-2 trial (NCT01239797), the addition of elotuzumab to the backbone of lenalidomide and dexamethasone in patients with 1–3 prior therapies led to a prolonged median PFS [19.4 vs 14.9 months; HR, 0.70 (95% CI, 0.57–0.85); \( P < 0.001 \)] and increased ORR (79% vs 66%; \( P < 0.001 \)) compared with lenalidomide and dexamethasone alone (Table 2) [40]. Elotuzumab, in combination with lenalidomide and dexamethasone, received authorization on May 11, 2016, for the treatment of patients with MM who have received ≥1 prior therapy.

Elotuzumab has also shown clinical efficacy when combined with bortezomib and dexamethasone. In an open-label phase 2 study (NCT01478048), patients with RRMM were randomized to receive elotuzumab–bortezomib–dexamethasone \( (n = 77) \) or bortezomib–dexamethasone \( (n = 75) \) [41]. The triple-agent combination resulted in a greater PFS than did the bortezomib–dexamethasone combination (9.7 vs 6.9 months). ORR was also higher in patients treated with elotuzumab–bortezomib–dexamethasone than with bortezomib–dexamethasone (66% vs 63%), and early OS results indicated an HR of 0.61 (70% CI, 0.43–0.85).

**Daratumumab**

Daratumumab is a monoclonal antibody that targets CD38, a marker that is highly expressed on myeloma cells with only minimal expression on normal lymphoid and myeloid cells [42]. Daratumumab is unique in that it can exert antimyeloma cell activity through a number of different pathways, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and apoptosis [43–45]. In contrast to elotuzumab, daratumumab has demonstrated clinical efficacy as a single agent in heavily treated patients with RRMM. In the phase 2 SIRIUS trial (NCT01985126), patients who had received ≥3 prior regimens, including a PI and an IMiD, were treated with daratumumab monotherapy. In this very heavily pretreated and highly refractory population, daratumumab demonstrated an ORR of 29% with a median PFS of 3.7 months and a median OS of 17.5 months (Table 2) [46]. In the dose-escalation phase 1/2 study GEN 501 (NCT00574288), daratumumab demonstrated clinical efficacy in patients with RRMM who were refractory to ≥2 prior lines of therapy. In the dose-expansion part of the study, patients received 8 mg/kg \( (n = 30) \) or 16 mg/kg \( (n = 42) \) of daratumumab. The ORR was 36% in the cohort that received 16 mg/kg and 10% in the cohort that received 8 mg/kg. The estimated median PFS was 5.6 and 2.4 months in patients who received 16 and 8 mg/kg, respectively. The OS rate at 12 months was 77% in both cohorts.
An updated pooled analysis of 148 patients treated with daratumumab 16 mg/kg monotherapy has recently been published. Data were combined from part 2 of a first-in-human phase 1/2 study and from a phase 2 study; 86.5% of patients were refractory to both a PI and an IMiD. The ORR was 31%, which included 13 very good partial responses, 4 complete responses, and 3 stringent complete responses. The median duration of response was 7.6 months; median PFS and OS were 4.0 and 20.1 months, respectively [48]. Based on these findings, daratumumab was authorized by the EC on May 20, 2016, as a monotherapy for the treatment of patients with RRMM previously treated with a PI and an IMiD.

Daratumumab also showed synergistic antimyeloma activity in combination with lenalidomide in preclinical studies. Based on these findings, a phase 1/2 study (GEN 503; NCT01615029) of daratumumab in combination with lenalidomide and low-dose dexamethasone in patients with RRMM who had ≥1 prior line of therapy was initiated [49]. Daratumumab at a dose of 16 mg/kg plus lenalidomide and low-dose dexamethasone had a favorable benefit:risk profile and was associated with durable responses [50]. The ORR was 88%, and the median duration of response was not reached; responses deepened over time in 61% of responders.

Given these promising results, the combination of daratumumab plus lenalidomide and dexamethasone was evaluated in the POLLUX study (NCT02076009), a phase 3, multicenter, open-label, randomized study (Table 2) [51]. In this study, 569 patients who had received ≥1 prior line of therapy were randomized (1:1) to daratumumab–lenalidomide–dexamethasone or to lenalidomide–dexamethasone. The primary endpoint was PFS. Daratumumab led to a significant improvement in median PFS (63% reduction in the risk of progression or death) and a delayed TTP compared with lenalidomide–dexamethasone alone (not reached vs 18.4 months; \( P < 0.0001 \)). ORR was also significantly higher in patients treated with daratumumab (93% vs 76%; \( P < 0.0001 \)). Neutropenia, thrombocytopenia, and anemia were the most common grade 3/4 adverse events (AEs).

Daratumumab is also being evaluated in combination with bortezomib in a second randomized phase 3 study (CASTOR; NCT02136134), and findings from an interim analysis were recently reported (Table 2) [52]. Patients who had received ≥1 prior line of therapy were randomized 1:1 to receive either daratumumab–bortezomib–dexamethasone \((n = 251)\) or bortezomib–dexamethasone \((n = 247)\). Daratumumab plus bortezomib significantly improved median PFS, the primary endpoint, leading to a 61% reduction in the risk of progression or death vs bortezomib alone \((P < 0.0001)\). In addition, daratumumab increased the TTP (not reached vs 7.3 months; \( P < 0.0001 \)) as well as the ORR (83% vs 63%; \( P < 0.0001 \)). The safety profile of the combination therapy was consistent with that of daratumumab and bortezomib, with thrombocytopenia, anemia, and neutropenia being the most common grade 3/4 AEs.

**Novel Agents**

As MM therapy continues to evolve at a rapid pace, a number of new agents are in clinical development. These agents include the first oral proteasome inhibitor (ixazomib) and a novel monoclonal antibody targeting CD38 (isatuximab).
**Ixazomib**

Ixazomib, like bortezomib, is a boronic acid-based proteasome inhibitor, although its chemical structure and pharmacology are distinct from those of its predecessor [53, 54]. Results from the phase 3 TOURMALINE-MM1 trial (NCT01564537) demonstrated that the addition of oral ixazomib to lenalidomide and dexamethasone led to significant improvement in median PFS vs placebo plus lenalidomide and dexamethasone [20.6 vs 14.7 months; HR, 0.74 (95% CI, 0.59–0.94); \(P = 0.012\)] [55]. Ixazomib was recently approved by the US Food and Drug Administration but received a negative opinion from the Committee for Medicinal Products for Human Use on May 27, 2016.

**Isatuximab**

Isatuximab (formerly SAR650984) is a humanized anti-CD38 antibody that, like daratumumab, has shown clinical efficacy both as a single agent and in combination with other therapies [56]. Preliminary findings from a phase 1 study (NCT01084252) that included 35 patients with RRMM showed that isatuximab was well tolerated and induced an ORR of 24% [57]. Preliminary reports from a second phase 1 study (NCT01749969; \(n = 12\)) found that the efficacy of isatuximab was enhanced when given in combination with lenalidomide and dexamethasone (ORR 58%) [58]. Additionally, a preclinical study showed that pomalidomide increased isatuximab-induced MM cell killing, and that it did so more potently than lenalidomide [59]. Furthermore, enhanced antitumor activity has been demonstrated with isatuximab plus bortezomib in preclinical models [60]. Currently, isatuximab is being evaluated in patients with RRMM as combination therapy with carfilzomib (NCT02332850) and with pomalidomide and dexamethasone (NCT02283775) in patients with RRMM. There is also an ongoing study of isatuximab plus bortezomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed MM (NCT02513186).

**DACi for the Treatment of MM**

**Epigenetics as a Target in MM**

DACi prevents deacetylation, a process involved in epigenetic regulation. Several studies have suggested that targeting the epigenome may be a viable strategy in treating MM. Epigenetic modifications such as histone methylation and acetylation have been shown to affect myeloma cell biology and are important for the pathogenesis of MM [61–63]. For instance, hypermethylation of histone H3K27 by the Polycomb group proteins results in an underexpressed gene expression profile common to patients with MM [64]. Additionally, a recent study found that patients with MM had reduced expression of tumor suppressor genes due to hypermethylation of these genes, a modification that was also prognostic for reduced OS in these patients [65]. Furthermore, dysregulation of histone deacetylase (HDAC) expression has also been observed in MM cells, with overexpression correlating with shorter survival [66].

Several preclinical studies have shown that DACi are active in MM. One study showed that a DACi (panobinostat) reactivated genes repressed by the hypermethylation of H3K27 by the Polycomb group proteins and reduced proliferation and increased apoptosis in human MM cell lines [64]. Additionally, panobinostat led to gene upregulation, reduction of tumor load, and increased OS in preclinical models [64]. Likewise, upregulation of genes following treatment of MM cell lines with DACi correlated...
with increased OS [67]. Interestingly, the antimyeloma activity of DACi was found to occur largely through inhibition of HDAC1, an event necessary for maximal MM cell death [68].

Based on these and other preclinical findings, several DACi are being evaluated in clinical studies as therapeutic options in MM. Vorinostat, a panDACi, has shown clinical efficacy in combination with bortezomib in patients with RRMM in the VANTAGE-088 phase 3 randomized study (NCT00773747) [69]. However, although vorinostat plus bortezomib significantly prolonged PFS compared with placebo, investigators did not think the difference in PFS between the two treatment groups was of clinical relevance.

Ricolinostat is a selective HDAC6 inhibitor that has demonstrated promising efficacy in patients with RRMM. Several phase 1/2 studies are underway, and preliminary analyses have shown that ricolinostat has clinical activity in patients with RRMM when combined with bortezomib and low-dose dexamethasone [70], lenalidomide and dexamethasone [71], and pomalidomide and dexamethasone [72]. Additionally, its selective HDAC6 inhibition is expected to result in increased tolerability.

Panobinostat, in combination with bortezomib and dexamethasone, is the only approved DACi for the treatment of RRMM, specifically in patients who have received ≥2 prior regimens including bortezomib and an IMiD. The following sections will further describe the mechanism of action of panobinostat and the efficacy and safety of this agent in this patient subpopulation.

**Panobinostat: First-in-Class DACi for the Treatment of MM**

**Mechanism of Action** Panobinostat is a potent panDACi with activity in the nanomolar range [73] that has shown potent antitumor activity, especially when combined with other agents, such as PIs [74]. Interestingly, MM cells are particularly reliant on protein degradation due to the high production of antibodies and abnormal or mutant proteins in these cells [13, 75]. Therefore, this synergistic anti-MM activity may be due to the complementary inhibition of protein degradation pathways, the proteasome and the aggresome. The proteasome is the main mechanism for degradation of intracellular proteins [75]. The aggresome is an alternative protein degradation pathway that appears to rely on HDAC6 for binding of the polyubiquitinated misfolded protein to dynein to facilitate transport to the lysosome [76]. Simultaneous blockade of the proteasome and the aggresome by PIs and DACi may lead to the synergistic antimyeloma activity observed with panobinostat plus bortezomib (Fig. 1a) [77]. However, there is also evidence that suggests a complementary role between PIs and DACi in epigenetic regulation as well. A study investigating the mechanism of bortezomib-induced cytotoxicity found that bortezomib downregulates the expression of class I HDAC and induces histone hyperacetylation in MM cells [78]. Additionally, HDAC1 activity negatively correlates with the antimyeloma activity of bortezomib, suggesting that bortezomib targets HDACs through a different mechanism compared with DACi [78]. Therefore, the synergy of panobinostat with bortezomib appears to occur through two distinct mechanisms, epigenetic alteration and protein metabolism (Fig. 1b).

**Dosing and Administration** The recommended starting dose is 20 mg taken orally once every other day for three doses per week in week 1 and 2 of a 3-week cycle for eight
cycles. Treatment should be continued for an additional eight cycles if the patient shows clinical benefit and no severe AEs. If clinically necessary, dose reductions of panobinostat should proceed in 5-mg intervals, but panobinostat should be discontinued if a dose reduction below 10 mg three times per week is required. Similarly, bortezomib dose reductions (in 25% decrements) are advised if clinically necessary.

Fig. 1 Panobinostat mechanism of action: synergy with bortezomib. a Dual blockade of proteasomes and aggresome pathway. b Synergistic impact on epigenetics. HDAC histone deacetylase, SP1 Simian virus 40 promotor factor 1
**Panobinostat Efficacy and Safety: A Focus on the EU-Indicated Subpopulation**

Panobinostat, in combination with bortezomib and dexamethasone, was well tolerated and significantly improved PFS in patients with relapsed or RRMM in the pivotal phase 3 PANORAMA 1 study (NCT01023308; N = 768) [79]. In this study, patients with relapsed or RRMM (excluding those with bortezomib-refractory or primary-refractory MM) who had received 1 to 3 prior regimens were randomized 1:1 to receive 21-day cycles of placebo or panobinostat (20 mg orally on days 1, 3, 5, 8, 10, and 12), both in combination with bortezomib (1.3 mg/m² intravenously on days 1, 4, 8, and 11) and dexamethasone (20 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12). The study met its primary endpoint of PFS [79].

A subgroup analysis of PANORAMA 1 patients who had received ≥2 prior regimens, including bortezomib and an IMiD, demonstrated that panobinostat (n = 75) provided this patient population with a PFS benefit of 7.8 months vs placebo (n = 74) (Tables 2, 3) [80]; median PFS was 12.5 months (95% CI, 7.3–14.0) in the panobinostat group and 4.7 months (95% CI, 3.7–6.1) in the placebo group [HR, 0.47 (95% CI, 0.31–0.72)] (Fig. 2). Similarly, patients who had received ≥2 prior regimens including bortezomib and an IMiD had a higher ORR with panobinostat than with placebo (59% vs 39%; P = 0.01703) (Table 3) [80]. Likewise, panobinostat led to more high-quality responses than did placebo (complete or near-complete response rate, 22% vs 8%; P = 0.02296). Median duration of response was also higher in the panobinostat group [12.0 months (95% CI, 9.7–13.4)] vs the placebo group [7.0 months (95% CI, 4.9–13.4)]. Notably, in patients treated with panobinostat, median PFS was similar between this patient subgroup and the overall PANORAMA 1 patient population (12.5 vs 12.0 months, respectively), whereas heavily pretreated patients who received bortezomib–dexamethasone alone had a substantially reduced PFS (4.7 vs 8.1 months, respectively). This suggests that the efficacy of the panobinostat–bortezomib–dexamethasone combination is somewhat resistant to the negative impacts of prior treatment. Analysis of the treatment-free interval (TFI), defined as the mean PFS less the mean duration of treatment, demonstrated that TFI was more than double in the panobinostat group vs the placebo group (4.7 vs 1.9 months) among patients with ≥2 prior regimens including bortezomib and an IMiD, implying the potential for enhanced off-treatment benefit in the panobinostat group [80]. In this subgroup, the recent final OS analysis of PANORAMA 1 presented at the 2015 American Society of Hematology annual meeting demonstrated a 6.0-month OS benefit favoring the panobinostat group, although the HR did not favor either treatment group [median OS: panobinostat group, 25.5 months; placebo group, 19.5 months; HR, 1.01 (95% CI, 0.68–1.50)] [81].

Overall, the safety profile in this subgroup was similar to that in the overall PANORAMA 1 population (Table 4) [79, 80]. The most common hematologic AEs in patients who had received ≥2 prior regimens including bortezomib and an IMiD were thrombocytopenia [panobinostat, 97% (grade 3/4, 68%); placebo, 90% (grade 3/4, 44%)] and neutropenia [panobinostat, 83% (grade 3/4, 40%); placebo, 45% (grade 3/4, 16%)]. These rates were comparable to those of thrombocytopenia and neutropenia in the overall population. The most common nonhematologic AEs in this patient subgroup were diarrhea [panobinostat, 76% (grade 3/4, 33%); placebo, 47% (grade 3/4, 15%)] and
fatigue or asthenia [panobinostat, 60% (grade 3/4, 26%); placebo, 49% (grade 3/4, 14%)], with rates comparable to those seen in the overall population.

The proportion of on-treatment deaths was similar between the two treatment groups among patients who received ≥2 prior regimens including bortezomib and an IMiD [panobinostat, 6.9%; placebo, 6.8%] [80]. Deaths due to progressive disease among patients in this group were slightly higher in the placebo group (panobinostat, 0%; placebo, 2.7%). The proportion of on-treatment deaths was slightly higher in the panobinostat group of the overall PANORAMA 1 population than in the placebo group or the subgroup of patients who received ≥2 prior regimens including bortezomib and an IMiD [79, 80]. The proportion of deaths due to progressive disease in the overall population was similar to that observed in the heavily pretreated subgroup.

Importantly, despite toxicities being observed with the panobinostat–bortezomib–dexamethasone regimen, analysis of health-related quality of life showed no appreciable difference in patient-reported outcomes between treatment groups in the subgroup of patients who had received ≥2 prior regimens including bortezomib and an IMiD [82]. At week 24, similar scores were reported for the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (panobinostat group vs placebo group, 31.75 vs 33.57), European Organisation for Research and Treatment (EORTC) 20-item disease symptom (23.84 vs 16.55), and EORTC 30-item core quality-of-life global health status (53.82 vs 58.05) questionnaires. Overall, these results suggested that the addition of panobinostat to the established bortezomib–dexamethasone regimen did not profoundly impact health-related quality of life.

### Table 3 Efficacy of panobinostat in patients with relapsed or relapsed and refractory multiple myeloma who have received ≥2 prior regimens, including bortezomib (BTZ) and an immunomodulatory drug [80]

|                               | PAN-BTZ-Dex | Pbo-BTZ-Dex |
|--------------------------------|-------------|-------------|
| Overall response rate (95% CI), % | 59 (47–70) | 39 (28–51) |
| P value                        | P = 0.01703 |             |
| Complete or near-complete response rate (95% CI), % | 22 (13–33) | 8 (3–17) |
| P value                        | P = 0.02296 |             |
| Duration of response, median (95% CI), mo | 12.0 (9.7–13.4) | 7.0 (4.9–13.4) |
| Time to response, median (95% CI), mo | 1.5 (1.4–2.6) | NE (2.1–NE) |
| Time to progression, relapse, or death, median (95% CI), mo | 12.7 (8.3–14.2) | 5.0 (3.8–6.8) |
| Progression-free survival, median (95% CI), mo | 12.5 (7.3–14.0) | 4.7 (3.7–6.1) |
| Hazard ratio (95% CI)          | 0.47 (0.31–0.72) |            |
| Treatment-free interval (mean progression-free survival — mean duration of response), mo | 4.7 | 1.9 |

*Dex* dexamethasone, *NE* not evaluable, *PAN* panobinostat, *Pbo* placebo, *BTZ* bortezomib, *MO* month, *CI* confidence interval
Based on these results and the enhanced benefit:risk profile of the panobinostat–bortezomib–dexamethasone regimen in this subpopulation with few treatment options, on August 28, 2015, the EC authorized panobinostat in combination with bortezomib and dexamethasone for the treatment of relapsed or RRMM in patients who received ≥2 prior regimens, including bortezomib and an IMiD (Fig. 3). Concerns were raised during the authorization process about the safety and tolerability of the panobinostat–bortezomib–dexamethasone regimen, and thus a risk management plan was devised to ensure that the regimen was provided as safely as possible and included guidance for management of key AEs [83]. On January 27, 2016, NICE also recommended panobinostat in combination with bortezomib and dexamethasone for adult patients with RRMM who have received ≥2 prior regimens including bortezomib and an IMiD [84]. The Appraisal Committee thoroughly reviewed the efficacy and safety of the panobinostat plus bortezomib and dexamethasone combination and concluded that the AEs associated with the treatment were manageable in clinical practice. The Committee also compared the cost-effectiveness of panobinostat–bortezomib–dexamethasone with that of lenalidomide–dexamethasone and determined that the cost per quality-adjusted life year for the panobinostat combination was within the range considered to be cost-effective. Therefore, the drug was launched in the United Kingdom in February.

**Management of Key AEs Associated with Panobinostat–Bortezomib–Dexamethasone Therapy**

**Thrombocytopenia** A decrease in platelet count is an AE associated with both bortezomib and panobinostat due to the inhibition of megakaryocyte maturation and

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**Fig. 2** Progression-free survival among patients in the PANORAMA 1 study who received ≥2 prior regimens, including bortezomib and an immunomodulatory agent [80]. BTZ bortezomib, Dex dexamethasone, PAN panobinostat, Pbo placebo, PFS progression-free survival, CI confidence interval. This research was originally published in Blood. Richardson [80]. © The American Society of Hematology
the reduced release of proplatelets [85, 86]. Although platelets typically rebound during the off-treatment week [79], the risk of severe bleeding events remains in some patients. Identifying patients at increased risk of severe bleeding prior to starting panobinostat–bortezomib–dexamethasone and monitoring of platelet levels regularly during the course of therapy are recommended. Platelet counts should be monitored at least weekly in patients with ≥grade 3 thrombocytopenia (platelet count <50 × 10⁹/L) [87].

In general, dose adjustment (delay or reduction) is typically sufficient for proper management of patients who develop on-treatment thrombocytopenia. Grade 3 thrombocytopenia with bleeding or grade 4 thrombocytopenia (platelet count <25 × 10⁹/L) should be managed with interruption of panobinostat and bortezomib dosing [87]. Once thrombocytopenia recovers to ≤grade 2 (platelet count ≥50 × 10⁹/L), panobinostat and bortezomib dosing should be resumed. Panobinostat should be restarted at a reduced dose. Bortezomib should be restarted at the same dose if only 1 dose was omitted or a reduced dose if ≥2 doses were omitted. Physicians should consider platelet transfusions for patients who experience
severe thrombocytopenia. If thrombocytopenia does not resolve or the patient requires multiple platelet transfusions, treatment should be discontinued.

**Diarrhea** Frequent loose or watery stool was common with panobinostat–bortezomib–dexamethasone treatment and can be associated with dehydration and electrolyte imbalances. Patients should be advised to initiate antidiarrheal medication and contact their physician at the first sign of abdominal cramping, loose stool, or diarrhea. Patients should also contact their physician if signs of dehydration are present. Prophylactic antiemetic therapy could be considered, but avoidance of those that cause electrocardiographic changes is warranted. Periodic monitoring of salt levels and fluid balance is advised [87].

Physicians should manage grade 2 diarrhea (4–6 stools/day above baseline) with

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### Table 4 Safety summary of panobinostat in patients with relapsed or relapsed and refractory multiple myeloma who have received ≥2 prior regimens, including bortezomib (BTZ) and an immunomodulatory drug [80]

| Hematologic laboratory abnormality, n (%) | PAN-BTZ-Dex (n = 72) | Pbo-BTZ-Dex (n = 73) |
|------------------------------------------|----------------------|----------------------|
|                                          | All grade | Grade 3/4 | All grade | Grade 3/4 |
| Thrombocytopenia                          | 70 (97)   | 49 (68)   | 65 (90)   | 32 (44)   |
| Leukopenia                                | 60 (83)   | 15 (21)   | 40 (55)   | 8 (11)    |
| Lymphopenia                               | 60 (83)   | 35 (49)   | 56 (77)   | 36 (49)   |
| Neutropenia                               | 60 (83)   | 29 (40)   | 33 (45)   | 12 (16)   |
| Anemia                                    | 42 (58)   | 15 (21)   | 42 (58)   | 15 (21)   |

| Nonhematologic adverse events, n (%)     |           |           |           |           |
|                                          | All grade | Grade 3/4 | All grade | Grade 3/4 |
| Diarrhea                                 | 55 (76)   | 24 (33)   | 34 (47)   | 11 (15)   |
| Fatigue or asthenia                      | 43 (60)   | 19 (26)   | 36 (49)   | 10 (14)   |
| Peripheral neuropathy                    | 42 (58)   | 12 (17)   | 39 (53)   | 5 (7)     |
| Nausea                                   | 27 (38)   | 8 (11)    | 16 (22)   | 1 (1)     |
| Peripheral edema                         | 16 (22)   | 2 (3)     | 11 (15)   | 0         |
| Vomiting                                 | 18 (25)   | 4 (6)     | 7 (10)    | 2 (3)     |
| Hypokalemia                              | 18 (25)   | 15 (21)   | 12 (16)   | 5 (7)     |
| Decreased appetite                       | 16 (22)   | 1 (1)     | 10 (14)   | 0         |
| Upper respiratory tract infection        | 21 (29)   | 4 (6)     | 12 (16)   | 0         |
| Pyrexia                                  | 10 (14)   | 0         | 10 (14)   | 3 (4)     |
| Constipation                             | 19 (26)   | 2 (3)     | 20 (27)   | 2 (3)     |
| Cough                                    | 19 (26)   | 0         | 15 (21)   | 0         |
| Abdominal pain                           | 17 (24)   | 1 (1)     | 8 (11)    | 2 (3)     |

Dex dexamethasone, PAN panobinostat, Pbo placebo, BTZ bortezomib
interruption of panobinostat and bortezomib dosing until resolution to \leq grade 1 diarrhea [87]. Panobinostat should be restarted at the same dose, while bortezomib should be restarted at a reduced dose or changed to once-weekly dosing. Grade 3 diarrhea (\geq 7 stools/day above baseline) should be managed with interruption of panobinostat and bortezomib dosing until resolution to \leq grade 1 diarrhea. Panobinostat should be restarted at a reduced dose, and bortezomib should also be restarted at a reduced dose or changed to once-weekly dosing. For patients who experienced grade 4 diarrhea (life-threatening consequences), treatment should be discontinued.

**Other Notable AEs** Patients at risk of infection should be treated prior to receiving the regimen [87]. White blood cell counts should be monitored regularly, and any developing infection should be treated promptly [87]. Panobinostat therapy should be avoided in patients at risk for QTc prolongation or receiving concomitant medications known to prolong the QT interval that cannot be stopped [87]. Electrocardiographic monitoring should be conducted regularly, along with fluid balance and salt monitoring. If QT prolongation occurs, panobinostat should be stopped until QT prolongation resolves. AEs may be more severe in patients over 65 years of age, and thus more frequent monitoring, particularly of blood cell counts and gastrointestinal toxicity, may be warranted, and dose reductions should be used as needed. Further research into optimization of the dose, schedule, and route of administration of panobinostat and bortezomib is important and may improve AEs, including fatigue and peripheral neuropathy.

**The Role of Panobinostat in the Current MM Treatment Armamentarium**

There are a number of factors that help guide treatment decisions in patients with RRMM, including patient age, comorbidities, performance status, prior treatment received, toxicities developed during prior treatment, and response to prior therapy [88]. However, following a short response on a therapy, a change to an agent with a new mechanism of action is often advised. Recent evidence also suggests that the addition of a third agent to backbone regimens can provide additional benefit over two-drug combinations in patients with RRMM [89]. As outlined previously, the current MM treatment landscape in the European Union comprises two main backbone regimens, PIs and IMiDs. However, as most patients will eventually relapse after or become refractory to the currently available agents, there is a substantial unmet need for agents with novel mechanisms of action in these patients.

Panobinostat, in combination with bortezomib and dexamethasone, is authorized for patients with relapsed or RRMM who have received \geq 2 prior treatment regimens including bortezomib and an IMiD, and it is one of the first agents with a new mechanism of action to be authorized for MM in over a decade. The addition of panobinostat to bortezomib and dexamethasone in the label subpopulation led to a significant increase in the rate of high-quality responses (complete or near-complete response) compared with placebo–bortezomib–dexamethasone (22% vs 8%; \( P = 0.02296 \)) [80]. The median PFS in patients treated with panobinostat was similar between the label subpopulation and the overall PANORAMA 1 patient population, suggesting that patients derive benefit from panobinostat.
regardless of prior treatment [79, 80]. Additionally, panobinostat has demonstrated the potential to recapture responses in patients who are refractory to bortezomib [90]. In the single-arm, phase 2 PANORAMA 2 study (NCT01083602), adding panobinostat to a bortezomib–dexamethasone regimen resulted in an ORR of 34.5% and a clinical benefit rate of 52.7% in 55 heavily pretreated patients who had received ≥2 prior lines of therapy, including an IMiD, and who were refractory to bortezomib-based therapy. Median PFS was 5.4 months, and median OS was 17.5 months [91]. A previous study by the International Myeloma Working Group found that among patients who are refractory to bortezomib and have relapsed following, have MM refractory to, or are ineligible to receive an IMiD, median OS and event-free survival were 9 months and 5 months, respectively [7]. Thus, the findings from the PANORAMA 2 study suggest that panobinostat may have a role in the management of bortezomib–refractory patients.

Panobinostat is also being investigated in the relapsed and refractory setting in other novel combinations with PIs (carfilzomib and ixazomib) and IMiDs (lenalidomide and thalidomide). In addition, panobinostat is being studied in the newly diagnosed setting in combination with lenalidomide, bortezomib or carfilzomib, and dexamethasone. Use of these panobinostat-based combinations is not yet approved in Europe.

CONCLUSION

Overall, panobinostat is likely to be an important new option for patients who have aggressive disease previously treated with PIs and IMiDs. Findings from the PANORAMA clinical program show that panobinostat can recapture responses, increase response quality, and overcome the negative impact of prior treatment on patient outcomes. Improvement in the quality of response has been recently linked to better patient outcomes [92] and may represent an important goal in the treatment of patients with RRMM. Targeted therapies, such as a DACi like panobinostat, will allow patients to achieve maximal responses and prolonged survival, therefore proving to be instrumental therapeutic options in the MM treatment armamentarium.

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