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Novel Approaches to Treatment of "Double-Refractory" Multiple Myeloma

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Abstract

Multiple myeloma refractory to both proteasome inhibitors and immunomodulatory agents (IMiDs) has a poor prognosis. With the increasing use of these agents as part of initial therapy, and then in the maintenance setting until disease progression, such drug resistance is an emerging problem of great significance. New therapeutic strategies are clearly needed for this patient population, including the development of more potent agents within existing anti-myeloma drug classes, exploration of rational combinations of both novel and conventional drugs, and validation of new myeloma drug targets. Several approaches have shown substantial promise, including use of the second-generation proteasome inhibitor carfilzomib and the third-generation IMiD pomalidomide, which led to the recent regulatory approval of both agents. In addition, the kinesin spindle protein inhibitor ARRY-520 has shown activity as a first-in-class drug in myeloma therapeutics, while the histone deacetylase inhibitors vorinostat and panobinostat have demonstrated efficacy when used in rational combinations. This overview provides a summary of novel agents that have shown activity in double-refractory myeloma in recent phase II and III clinical trials, and a framework for future studies that will help to improve outcomes in this patient population.

Introduction

The introduction of the proteasome inhibitor bortezomib and second-generation immunomodulator (IMiD) lenalidomide to the multiple myeloma (MM) therapeutic armamentarium has led to significant improvements in patient outcomes over the last decade. Both agents now form the backbone of many preferred regimens in the up-front or relapsed settings, and they have contributed to a doubling in the average life expectancy for myeloma patients.[1,2] However, despite these novel therapies, MM remains an incurable disease, and resistance to bortezomib and lenalidomide is being seen with increasing frequency. For these patients with double-refractory disease, prognosis is poor, with a

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Conflicts of Interest

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median overall survival (OS) and progression-free survival (PFS) of 9 months and 5 months, respectively.[3] Improving the outcomes of patients in this setting therefore represents a significant clinical challenge, and is an area of intense research focus. While there is no standard treatment for these patients, several promising agents and strategies are currently under investigation. Notably, this has led to the recent Food and Drug Administration (FDA) approval of the second-generation proteasome inhibitor carfilzomib for patients who have been exposed to bortezomib and an IMiD, and whose disease was refractory to their last therapy. Likewise, the third-generation IMiD pomalidomide has just received regulatory approval for patients with refractory disease who have been previously treated with bortezomib and lenalidomide. Other drugs such as histone deacetylase (HDAC) inhibitors and the kinesin spindle protein inhibitor ARRY-520 have also shown encouraging results in ongoing trials. This overview provides a summary of novel agents in development that have shown clinical activity in double-refractory MM, and may represent potential treatment strategies in this challenging patient subset.

Carfilzomib

Carfilzomib is a novel, highly selective epoxyketone proteasome inhibitor that irreversibly inhibits the chymotrypsin-like activity of the 20S proteasome.[4] Its diminished off-target effects and lower incidence of peripheral neuropathy was demonstrated in early phase clinical trials. The efficacy of single-agent carfilzomib in patients with disease refractory to bortezomib and IMiD therapy was established in the PX-171-003-A1 study, a multicenter single-arm phase II trial.[5] This study enrolled 266 patients who were relapsed or refractory to ≥2 lines of therapy, of whom all but one had received prior bortezomib, and every patient had been treated with an IMiD. Patients received single-agent carfilzomib for up to 12 cycles, and the primary end-point was overall response rate (ORR) using the International Myeloma Working Group (IMWG) criteria. After a median treatment duration of 3 months, ORR (≥partial response (PR)) in 257 response-evaluable was 24%, with 1 (0.4%) complete response (CR), 13 (5%) very good partial responses (VGPRs), and 47 (18%) PRs (Table 1). Among 169 patients who were refractory to both bortezomib and lenalidomide, ORR was 15% with a median duration of response of 7.8 months. Median OS was 15.4 months in the overall population, and 11.9 months in the double-refractory subgroup. Notably, response rates were not affected by unfavorable cytogenetic profiles. Overall, carfilzomib was well tolerated, and the most common grade 3 or 4 adverse events (AEs) were thrombocytopenia (29%) and anemia (24%), while only 12% reported treatment-emergent peripheral neuropathy. The positive results from this study ultimately led to the initial accelerated FDA approval of carfilzomib. A phase III clinical trial, which randomized patients with MM that was relapsed and refractory to all available therapy to carfilzomib or best supportive care, has completed enrollment and will provide additional insight into the role of this agent.[6]

Pomalidomide

Pomalidomide is a third-generation IMiD with immunomodulatory, antiangiogenic, and direct anti-myeloma activity, and greater *in vivo* potency than its predecessors thalidomide and lenalidomide.[7] The safety and promising efficacy of pomalidomide in double-refractory patients was initially reported by Richardson, et al. in a phase 1 study, in which 38 patients were exposed to four different dose levels.[8] A maximum tolerated dose (MTD) was established at 4 mg daily for 21/28 days, and of 24 patients with both bortezomib- and lenalidomide-refractory disease, ORR was 25%, and CR rate was 4% (Table 1).

Pomalidomide has been shown to be active against double-refractory MM in several subsequent phase II and III trials. The Intergroup Francophone du Myélome (IFM) randomized 84 relapsed/refractory patients to pomalidomide given on days 1–21, or days 1–

28 of a 28-day cycle, both with weekly dexamethasone.[9] ORR and ≥VGPR were 35% and 5%, respectively, in the 21/28 arm, and 34% and 7%, respectively, in the continuous dose arm (Table 1). Of 64 double-refractory patients, results were similar, with an ORR of 31%, PFS of 3.8 months, and OS of 13.8 months. Benefit was also seen in patients with adverse cytogenetics, as ORR was 27% in 21 patients with deletion 17p and/or t(4;14). The Mayo group has also investigated the pomalidomide/dexamethasone combination in lenalidomide- and bortezomib-refractory MM as part of six sequential phase II trials comparing different pomalidomide dosing strategies.[10] Two of the cohorts, each containing 35 patients, included only patients refractory to both lenalidomide and bortezomib, and received either pomalidomide 2 mg daily (Cohort 3) or 4 mg daily (Cohort 4). ORR was similar in both groups at 26% (Cohort 3) and 29% (Cohort 4), and PFS was 6.4 months and 3.3 months, respectively.

Additional evidence of the efficacy of pomalidomide and low-dose dexamethasone in double-refractory MM was shown in the MM-002 phase 2 study.[11] 113 patients, all who had received prior bortezomib and lenalidomide therapy, were enrolled in the pomalidomide and low-dose dexamethasone arm of the trial, and ORR was 30%, median PFS was 3.8 months, and median OS was 14.4 months (Table 1). Similar results were seen in the subgroup of 69 bortezomib- and lenalidomide-refractory patients, where ORR was 28%, median PFS was 3.8 months, and median OS was 13.5 months. Recently, the results of the MM-003 phase 3 trial were presented, in which patients were randomized 2:1 to receive pomalidomide and low-dose dexamethasone or single-agent high-dose dexamethasone.[12] Final PFS analysis in 455 patients, all of whom received prior bortezomib and lenalidomide, demonstrated a significant increase in median PFS in the pomalidomide arm at 3.6 months versus 1.8 months in the high-dose dexamethasone arm ($P<.001$). At the interim analysis, median OS was not reached in the pomalidomide arm, while median OS in the high-dose dexamethasone arm was 7.8 months ($P<.001$). In 329 double-refractory patients, median PFS in the pomalidomide arm was 3.2 months versus 1.7 months in the high-dose dexamethasone arm ($P<.001$), and median OS was again not reached in the pomalidomide arm, while median OS in the high-dose dexamethasone arm was 7.4 months ($P<.001$). Based on these results, the Data and Safety Monitoring Board (DSMB) recommended immediate cross-over of patients in Arm B to Arm A. Together, these findings support the use of pomalidomide and low-dose dexamethasone in double-refractory MM, and culminated in the recent FDA approval of pomalidomide for patients refractory to their last therapy, and who had received prior bortezomib and lenalidomide.

Combinations of pomalidomide with other anti-MM agents besides dexamethasone are also being explored. One phase 2 study with pomalidomide, cyclophosphamide, and prednisone (PCP) has been reported by Palumbo et al., in which 16 of 55 response-evaluable subjects were refractory to both bortezomib and lenalidomide.[13] In these double-refractory patients, ORR after one cycle was 50%, with 3 patients achieving a ≥VGPR. Also, results from a recent multi-center phase I study using carfilzomib, pomalidomide, and dexamethasone (Car-Pom-d) were reported by Shah et al.[14] All 32 patients enrolled were lenalidomide-refractory, and all but two were bortezomib-refractory. Of 30 response-evaluable patients, there were 4 VGPRs (13%) and 11 PRs (37%), corresponding to an ORR of 50%. Non-hematologic grade 3 and 4 AEs were rare, including no peripheral neuropathy. These studies highlight the feasibility and potential efficacy of combining pomalidomide with other novel drugs as a treatment strategy in double-refractory patients, and enrollment of a larger phase II cohort in the latter is currently underway.

Histone Deacetylase Inhibitors

While proteasome inhibitors and IMiDs have garnered much of the recent attention in MM therapeutics, histone deacetylase (HDAC) inhibitors represent another novel drug class that may have potential activity in the double-refractory setting. HDAC inhibitors promote the acetylation of histone proteins, which decondenses chromatin to its active form and reverses the epigenetic silencing of transcription factors and tumor suppressor genes that regulate cell growth. Numerous non-histone proteins such as p21, p53, and NF- κB have also been implicated as targets of HDAC inhibitors whose modulation promotes cell cycle arrest and apoptosis.[15] Although HDAC inhibitors have demonstrated only modest activity as single-agents[16], more potent clinical activity has been observed when HDAC inhibitors are combined with other MM drugs. Perhaps the most promising combination is with bortezomib, as disruption of aggresome formation by HDAC inhibition, together with proteasome inhibition, leads to greater interference with protein turnover and induction of the misfolded protein response.[17,18] Based on this rationale, the pan-deacetylase inhibitor vorinostat was studied in combination with bortezomib in the VANTAGE 095 trial.[19] All 143 patients enrolled in this multicenter single-arm phase IIB study were bortezomib-refractory, and 87% were refractory to ≥1 IMiD. After a median treatment duration of 4 cycles, ORR was 17%, including 12% PR, 4% VGPR, and 1% CR. In patients achieving a major response or better, median response duration was 6.3 months, PFS was 3.1 months, and median OS was 11.2 months. Common grade 3 or 4 AEs included thrombocytopenia (68%), anemia (38%), neutropenia (32%), and diarrhea (17%).

The synergistic activity of HDAC inhibitors with bortezomib in bortezomib-refractory patients is also being investigated with the pan-deacetylase inhibitor panobinostat in the PANORAMA 2 study.[20] In this single-arm phase 2 trial, 55 bortezomib-refractory patients who had also been exposed to prior IMiD therapy were treated with bortezomib, panobinostat, and dexamethasone.

Each cycle was repeated every 21 days for 8 cycles, and patients achieving clinical benefit (≥stable disease) could continue with 6-week cycles using a modified bortezomib schedule. At analysis following the first treatment phase, ORR was 31% with three patients (5%) achieving a VGPR. Notably, only one-third of patients completed all 8 cycles of therapy, and most frequent grade 3 or 4 AEs were thrombocytopenia (62%) and diarrhea (20%). A final analysis, including those patients who continued onto the second treatment phase, is still pending.

Several other phase I and II trials studying the tolerability and efficacy of treatment regimens containing HDAC inhibitors are ongoing, and will provide additional insight into the optimal use of these agents in rational combinations with other conventional and novel drugs. The development of more selective HDAC inhibitors that minimize off-target toxicities is also likely needed for the potential of this therapeutic approach to be fully appreciated. The selective HDAC-6 inhibitor rocilinostat is one such promising example, and final results from an ongoing phase I/II study with monotherapy, and in combination with bortezomib/dexamethasone, are awaited.[21]

Kinesin Spindle Protein Inhibitor

Anti-mitotic agents have long been recognized and successfully utilized in cancer therapy across a variety of tumor subtypes. Many of these drugs target microtubule assembly and function, although lack of specificity in disrupting cellular transport processes often leads to dose-limiting toxicities, including peripheral neuropathy. Kinesin spindle protein (KSP), part of a larger subfamily of kinesin-5 motor proteins, represents a novel anti-mitotic target with greater specificity towards actively dividing cells. These proteins are essential

components of the early stages of mitosis as they move apart overlapping microtubules, which ultimately leads to centromere separation and bipolar spindle formation.[22,23]

ARRY-520 is a potent, highly selective KSP inhibitor that has demonstrated single agent activity in preclinical MM xenograft models, and phase I clinical studies in the relapsed and refractory setting.[24,25] Based on these results, a phase II study with ARRY-520 was conducted as both a single agent (Cohort 1) and in combination with low-dose dexamethasone (Cohort 2)[26] as preclinical studies have suggested that ARRY-520 downregulates Mcl-1, a known dexamethasone resistance mechanism.[27] Notably, all 18 patients enrolled in cohort 2 had disease that was refractory to bortezomib and lenalidomide, and all but one was refractory to dexamethasone. After a median treatment time of 3.9 months, ORR rate was 22%, with 4 patients (22%) achieving a PR, and median duration of response was 5.4 months. Most frequent grade 3 or 4 AEs included neutropenia (62%) and thrombocytopenia (57%), although these were generally reversible and not cumulative. Importantly, there was no association of peripheral neuropathy with ARRY-520 therapy. Cohort 1 contained a more modest number of bortezomib (53%) and lenalidomide-refractory (75%) patients, and of 32 response-evaluable patients, ORR was 16% with 5 PRs (16%). These data support further investigation of ARRY-520 in the double-refractory setting, and phase 1 studies evaluating the tolerability and efficacy of ARRY-520 in combination with other novel MM drugs such as bortezomib and carfilzomib are also ongoing.

Conclusions

While the prognosis of MM refractory to lenalidomide and bortezomib therapy is poor, recent studies have highlighted several potential effective strategies in this challenging subset of patients. These have included the use of more potent analogues of existing myeloma drug classes, the development of rational combinations to overcome drug resistance, and the discovery of novel drug targets. Future work remains in establishing predictive biomarkers to help individualize therapy based on an improved understanding of disease biology and emerging mechanisms of drug resistance, such as Cereblon depletion and Wnt/β-catenin-mediated CD44 overexpression in lenalidomide resistance, or insulin-like growth factor-1 (IGF-1) upregulation in bortezomib resistance.[28–30] Together, these approaches will hopefully continue to build on the improvement in outcomes seen in MM over the last decade, and result in longer intervals of disease control and even disease eradication.

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References

1. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008; 111:2516–20. [PubMed: 17975015]
2. Anderson KC. The 39th David A. Karnofsky Lecture: bench-to-bedside translation of targeted therapies in multiple myeloma. J Clin Oncol. 2012; 30:445–52. [PubMed: 22215754]
3. Kumar SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leukemia. 2012; 26:149–57. [PubMed: 21799510]
4. Kuhn DJ, Orlowski RZ, Bjorklund CC. Second generation proteasome inhibitors: carfilzomib and immunoproteasome-specific inhibitors (IPSIs). Curr Cancer Drug Targets. 2011; 11:285–95. [PubMed: 21247387]

5. Siegel DS, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PX-171–003-A1) in patients with relapsed and refractory multiple myeloma. Blood. 2012; 120:2817–25. [PubMed: 22833546]
6. Hajek R, Bryce R, Ro S, et al. Design and rationale of FOCUS (PX-171–011): A randomized, open-label, phase 3 study of carfilzomib versus best supportive care regimen in patients with relapsed and refractory multiple myeloma (R/R MM). BMC Cancer. 2012; 12:415. [PubMed: 22992303]
7. Schey S, Ramasamy K. Pomalidomide therapy for myeloma. Expert Opin Investig Drugs. 2011; 20:691–700.
8. Richardson PG, Siegel D, Baz R, et al. Phase I study of pomalidomide MTD, safety and efficacy in patients with refractory multiple myeloma who have received lenalidomide and bortezomib. Blood. 2012
9. Leleu X, Attal M, Arnulf B, et al. Pomalidomide plus low dose dexamethasone is active and well tolerated in bortezomib and lenalidomide refractory multiple myeloma: IFM 2009–02. Blood. 2013
10. Lacy MQ, Kumar SK, LaPlant BR, et al. Pomalidomide Plus Low-Dose Dexamethasone (Pom/Dex) in Relapsed Myeloma: Long Term Follow up and Factors Predicing Outcome in 345 Patients. ASH Annual Meeting Abstracts. 2012; 120:201.
11. Vij R, Richardson PG, Jagannath S, et al. Pomalidomide (POM) with or without low-dose dexamethasone (LoDEX) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Outcomes in pts refractory to lenalidomide (LEN) and/or bortezomib (BORT). J Clin Oncol. 2012; 30(suppl):abstr 8016.
12. Dimopoulos MA, Lacy MQ, Moreau P, et al. Pomalidomide in Combination with Low-Dose Dexamethasone: Demonstrates a Significant Progression Free Survival and Overall Survival Advantage, in Relapsed/Refractory MM: A Phase 3, Multicenter, Randomized, Open-Label Study. ASH Annual Meeting Abstracts. 2012; 120:LBA-6.
13. Palumbo A, Larocca A, Montefusco V, et al. Pomalidomide Cyclophosphamide and Prednisone (PCP) Treatment for Relapsed/Refractory Multiple Myeloma. ASH Annual Meeting Abstracts. 2012; 120:446.
14. Shah JJ, Stadtmauer EA, Abonour R, et al. A Multi-Center Phase I/II Trial of Carfilzomib and Pomalidomide with Dexamethasone (Car-Pom-d) in Patients with Relapsed/Refractory Multiple Myeloma. ASH Annual Meeting Abstracts. 2012; 120:74.
15. Cea M, Cagnetta A, Gobbi M, et al. New insights into the treatment of multiple myeloma with histone deacetylase inhibitors. Curr Pharm Des. 2013; 19:734–44. [PubMed: 23016853]
16. Wolf JL, Siegel D, Goldschmidt H, et al. Phase II trial of the pan-deacetylase inhibitor panobinostat as a single agent in advanced relapsed/refractory multiple myeloma. Leuk Lymphoma. 2012; 53:1820–3. [PubMed: 22288662]
17. Catley L, Weisberg E, Kiziltepe T, et al. Aggresome induction by proteasome inhibitor bortezomib and alpha-tubulin hyperacetylation by tubulin deacetylase (TDAC) inhibitor LBH589 are synergistic in myeloma cells. Blood. 2006; 108:3441–9. [PubMed: 16728695]
18. Hideshima T, Bradner JE, Wong J, et al. Small-molecule inhibition of proteasome and aggresome function induces synergistic antitumor activity in multiple myeloma. Proc Natl Acad Sci U S A. 2005; 102:8567–72. [PubMed: 15937109]
19. Siegel DS, Dimopoulos MA, Yoon S-S, et al. Vantage 095: Vorinostat in Combination with Bortezomib in Salvage Multiple Myeloma Patients: Final Study Results of a Global Phase 2b Trial. ASH Annual Meeting Abstracts. 2011; 118:480.
20. Alsina M, Schlossman R, Weber DM, et al. PANORAMA 2: A phase II study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory multiple myeloma. J Clin Oncol. 2012; 30(suppl):abstr 8012.
21. Raje N, Hari PN, Vogl DT, et al. Rocilinostat (ACY-1215), a Selective HDAC6 Inhibitor, Alone and in Combination with Bortezomib in Multiple Myeloma: Preliminary Results From the First-in-Humans Phase I/II Study. ASH Annual Meeting Abstracts. 2012; 120:4061.
22. Kapoor TM, Mayer TU, Coughlin ML, et al. Probing spindle assembly mechanisms with monastrol, a small molecule inhibitor of the mitotic kinesin, Eg5. J Cell Biol. 2000; 150:975–88. [PubMed: 10973989]

23. Sawin KE, LeGuellec K, Philippe M, et al. Mitotic spindle organization by a plus-end-directed microtubule motor. Nature. 1992; 359:540–3. [PubMed: 1406972]
24. Shah JJ, Zonder J, Cohen A, et al. ARRY-520 Shows Durable Responses in Patients with Relapsed/Refractory Multiple Myeloma in a Phase 1 Dose-Escalation Study. ASH Annual Meeting Abstracts. 2011; 118:1860.
25. Woessner R, Tunquist B, Cox A, et al. Combination of the KSP Inhibitor ARRY-520 with Bortezomib or Revlimid Causes Sustained Tumor Regressions and Significantly Increased Time to Regrowth in Models of Multiple Myeloma. ASH Annual Meeting Abstracts. 2009; 114:2858.
26. Shah JJ, Zonder JA, Cohen A, et al. The Novel KSP Inhibitor ARRY-520 Is Active Both with and without Low-Dose Dexamethasone in Patients with Multiple Myeloma Refractory to Bortezomib and Lenalidomide: Results From a Phase 2 Study. ASH Annual Meeting Abstracts. 2012; 120:449.
27. Tunquist BJ, Woessner RD, Walker DH. Mcl-1 stability determines mitotic cell fate of human multiple myeloma tumor cells treated with the kinesin spindle protein inhibitor ARRY-520. Mol Cancer Ther. 2010; 9:2046–56. [PubMed: 20571074]
28. Bjorklund CC, Ma W, Wang ZQ, et al. Evidence of a role for activation of Wnt/beta-catenin signaling in the resistance of plasma cells to lenalidomide. J Biol Chem. 2011; 286:11009–20. [PubMed: 21189262]
29. Kuhn DJ, Berkova Z, Jones RJ, et al. Targeting the insulin-like growth factor-1 receptor to overcome bortezomib resistance in preclinical models of multiple myeloma. Blood. 2012; 120:3260–70. [PubMed: 22932796]
30. Zhu YX, Braggio E, Shi CX, et al. Cereblon expression is required for the antimyeloma activity of lenalidomide and pomalidomide. Blood. 2011; 118:4771–9. [PubMed: 21860026]

Key Points

- Multiple myeloma patients with disease that is refractory to lenalidomide and bortezomib have a poor prognosis, and new therapeutic strategies are needed in this challenging patient population.
- Potent analogues of existing myeloma drugs, such as the second-generation proteasome inhibitor carfilzomib and third-generation immunomodulator pomalidomide have demonstrated clinical efficacy in the double-refractory setting, resulting in recent regulatory approval of both drugs.
- While HDAC inhibitors have shown modest activity when used as single agents, clinical activity has been seen when they were combined with other novel myeloma drugs, highlighting the development of rational drug combinations as an important therapeutic approach.
- One novel strategy against double-refractory myeloma may be to target kinesin-spindle protein (KSP) with the first-in-class inhibitor ARRY-520, which has shown promising activity.
- Future studies should focus on establishing biomarkers to help predict response to therapy, with the goal of individualizing treatment based on an improved understanding of disease biology and resistance mechanisms.

Table 1

Phase 2/3 trials reported to-date with novel agents active in double-refractory multiple myeloma

Study	Phase	Drug/Dosing Regimen	N (DR N)	ORR[a] (DR ORR)
Siegel, et al.[5]	II	Carfilzomib 20/27 mg/m^2 D1-2, 8–9, 15–16 (28-day cycle)[b]	257 (169)	24% (15%)
Leleu, et al.[9]	II	Arm A: Pomalidomide 4 mg D1-21, dexamethasone 40 mg/week Arm B: Pomalidomide 4 mg D1-28, dexamethasone 40 mg/week (28-day cycle)	84 (64)	Arm A: 35% Arm B: 34% (31% both arms)
Lacy, et al.[10]	II	Cohort 3: Pomalidomide 2 mg D1-28, dexamethasone 40 mg/week Cohort 4: Pomalidomide 4 mg D1-28, dexamethasone 40 mg/week (28-day cycle)	70 (70)	Cohort 3: 26% (26%) Cohort 4: 29% (29%)
Vij, et al.[11]	II	Pomalidomide 4 mg on D1-21, dexamethasone 40 mg/week (28-day cycle)	113 (69)	30% (28%)
Dimopoulos, et al.[12]	III	Arm A: Pomalidomide 4 mg D1-21, dexamethasone 40 mg/week Arm B: Dexamethasone 40 mg D1-4, 9–12, 17–20 (28-day cycle)	455 (329)	Arm A: 21% (N/A) Arm B: 3% (N/A)
Palumbo, et al.[13]	II	Pomalidomide 2.5 mg D1-28, cyclophosphamide 50 mg QOD, prednisone 50 mg QOD (28-day cycle)	55 (16)	51% (50%)
Siegel, et al.[19]	II	Vorinostat 400 mg on D1-14, bortezomib 1.3 mg/m^2 D1, 4, 8, 11 (21-day cycle)	143 (N/A)[c]	17% (N/A)
Alsina, et al.[20]	II	Panobinostat 20 mg TIW, bortezomib 1.3 mg/m^2 D1, 4, 8, 11, dexamethasone 20 mg D1-2, 4–5, 8–9, 11–12 (21-day cycle)	55 (N/A)	31% (N/A)
Shah, et al.[26]	II	ARRY-520 1.5 mg/m^2 D1-2, dexamethasone 40 mg/week, G-CSF D3-7 (14-day cycle)	18 (18)	22% (22%)

Abbreviations: D, day; DR, double-refractory; G-CSF, granulocyte colony stimulating factor; N, number of patients; N/A, not available; ORR, overall response rate; QOD, every other day; TIW, three times weekly

[a] ORR defined as ≥PR.

[b] Dose-escalated to 27 mg/m^2 with cycle 2, provided that 20 mg/m^2 dose with cycle 1 was well tolerated

[c] All bortezomib-refractory and 87% refractory to ≥ 1 IMiD