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Novel Agents for Multiple Myeloma to Overcome Resistance in Phase III Clinical Trials

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Abstract

The incorporation of novel agents such as bortezomib and lenalidomide into initial therapy for multiple myeloma has improved the response rate of induction regimens. Also, these drugs are being increasingly used in the peri-transplant setting for transplant-eligible patients, and as part of consolidation and/or maintenance after front-line treatment, including in transplant-ineligible patients. Together, these and other strategies have contributed to a prolongation of progression-free and overall survival in myeloma patients, and an increasing proportion are able to sustain a remission for many years. Despite these improvements, however, the vast majority of patients continue to suffer relapses, which suggests a prominent role for either primary, innate drug resistance, or secondary, acquired drug resistance. As a result, there remains a strong need to develop new proteasome inhibitors and immunomodulatory agents, as well as new drug classes, which would be effective in the relapsed and/or refractory setting, and overcome drug resistance. This review will focus on novel drugs that have reached phase III trials, including carfilzomib and pomalidomide, which have recently garnered regulatory approvals. In addition, agents that are in phase II or III, potentially registration-enabling trials will be described as well, to provide an overview of the possible landscape in the relapsed and/or refractory arena over the next five years.

Introduction

The last decade has in some ways been a golden era for novel therapeutic drug development in multiple myeloma. It started with the approval of the proteasome inhibitor bortezomib for relapsed and refractory myeloma in May, 2003, based on positive findings from a pivotal phase II study (1). This was followed by approvals of bortezomib for relapsed myeloma after at least one prior therapy, first as a single agent in March, 2005 (2), and then in combination with pegylated liposomal doxorubicin in May, 2007 (3). By June, 2008, bortezomib was approved for initial therapy of myeloma based on a randomized study with bortezomib incorporated into a regimen with melphalan and prednisone (4).

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Immunomodulatory drugs (IMiDs) entered the fray against myeloma when thalidomide, which had been used for many years off-label in the relapsed and/or refractory setting (5), was approved with dexamethasone as induction therapy in May, 2006 (6,7). Shortly thereafter, in June, 2006, lenalidomide with high-dose dexamethasone was approved for patients with relapsed disease after at least one prior therapy (8,9). Most recently, the second generation proteasome inhibitor carfilzomib gained regulatory approval for relapsed and refractory disease in July, 2012 (10), and the third-generation immunomodulator pomalidomide was approved for the same population in February, 2013 (11).

Beyond just the approval of these novel agents, two important trends have emerged in the myeloma field, which include moving novel agents first approved in later lines of therapy into the up-front setting, and combining the various drug classes into more effective regimens. Examples of the former include the recent success of regimens such as lenalidomide with low-dose dexamethasone (12), and bortezomib with either dexamethasone (13), or with thalidomide and dexamethasone (14), in outperforming older induction regimens to establish new standards of care. Examples of the latter trend to combine proteasome inhibitors and IMiDs include bortezomib with thalidomide and dexamethasone (14,15), which also may provide superior outcomes in the relapsed setting (16), and regimens such as bortezomib with lenalidomide and dexamethasone (17,18). Moreover, combinations of the most recent generation of agents in each class are being tested as well, as evidenced by studies of carfilzomib with lenalidomide and dexamethasone (19,20), bortezomib with pomalidomide and dexamethasone (21), and carfilzomib with pomalidomide and dexamethasone (22), among others. While some of these have not yet reached the phase III setting, and their full impact on clinical outcomes in myeloma are yet to be determined, it is clear that those that have been part of the first wave of novel drugs have made a very positive impact on prognosis in this disease. Several studies indicate that novel agents have improved outcomes especially in newly-diagnosed (23), but also in relapsed patients (23,24), and have added to the benefits of traditional approaches such as stem cell transplantation (25,26) to the point that survival has been doubled in some settings (23–27). Moreover, an increasing proportion of patients remain in complete remission for prolonged periods of time, prompting some to consider the possibility that at least a fraction of myeloma patients may already be functionally cured of their disease (26,28,29).

Despite these encouraging findings, and the likelihood that the recently approved agents will find their way into earlier lines of therapy, the vast majority of patients with multiple myeloma will still eventually relapse after front-line therapy. As a result, there remains a need to develop new proteasome inhibitors and immunomodulatory agents, and especially new drug classes, which would be effective in the relapsed and/or refractory setting. These agents would be especially useful if they could overcome drug resistance that may have emerged due to prior therapy, and if their use could be guided by biomarkers that identify patients who would be most likely to benefit. This contribution will review some of the current drug classes and agents that could possibly meet some of these criteria, and will update the reader on their progress towards the goal of incorporating them into our armamentarium against multiple myeloma.

Deacetylase Inhibitors

Histone deacetylases (HDAC), along with histone acetyl transferases, regulate acetylation of a wide variety of cellular proteins, including histones. Through these modifications, HDACs influence pathways involved in many key processes in myeloma cells, including gene expression, cell cycle progression, DNA replication and repair, and protein folding through chaperone functions, among others (reviewed recently in (30,31)). Deacetylase inhibitors have shown activity against pre-clinical models of myeloma through a number of important

mechanisms. These include cell cycle arrest through increased expression of $p21^{WAF1}$, decreased expression of the interleukin (IL)-6 receptor, and Retinoblastoma protein dephosphorylation, as well as apoptosis through increased expression of Bax (32,33). Additional mechanisms include cleavage of Bid, as well as of poly(ADP)ribose polymerase (PARP) by calpains, inhibition of stromal cell IL-6 production (33), induction of caspases (34), and suppression of members of the insulin-like growth factor (IGF)/IGF-1 receptor (IGF-1R) pathway, DNA synthesis and repair enzymes, and expression of proteasome subunits and therefore of proteasome activity (35). Deacetylase inhibitors have been validated in a number of combinations with both conventional and novel agents pre-clinically against multiple myeloma (32–35). Perhaps the strongest rationale has been provided for combination regimens with proteasome inhibitors, based in part on the reduction of proteasome subunit expression by HDAC inhibitors (35), which would sensitize cells to agents like bortezomib. In addition, proteasome and deacetylase inhibitors activate apoptosis synergistically by inducing oxidative injury and mitochondrial dysfunction (36). Proteasome inhibition induces formation of aggresomes, aggregates of ubiquitin-conjugated proteins that protect cells from the toxic effects of these proteins, while histone deacetylase inhibitors in general, and HDAC-6 inhibition in particular, disrupt this, thereby enhancing cell killing (37,38). Finally, recent studies identified signaling through the IGF-1/IGF-1R pathway as an important contributor to bortezomib resistance (39), and the ability of HDAC inhibitors to suppress IGF-1/IGF-1R signaling (35) is another rationale for combining them. Taken together, these multiple cooperative mechanisms provided strong support for the possibility that a regimen of a proteasome and deacetylase inhibitor could achieve chemosensitization, and possibly also overcome chemoresistance.

Vorinostat

Vorinostat (suberoylanilide hydroxamic acid, SAHA, Zolinza™) was evaluated first as a single agent in multiple myeloma in a phase I study that was abbreviated by the sponsor, and therefore did not identify a maximum tolerated dose (MTD)(40). Common drug-related adverse events (AEs) included fatigue, anorexia, dehydration, diarrhea, and nausea, and one minor response (MR) was seen out of ten evaluable patients. The combination of vorinostat and bortezomib was then studied in two phase I trials, the first of which administered bortezomib at 1.0 or 1.3 mg/m^2 on days 1, 4, 8, and 11 of every 21-day cycle, along with vorinostat at 100–500 mg on days 1–8 of each 21-day cycle (41). Non-hematologic toxicities included diarrhea (seen in 52%), nausea (48%), fatigue (35%), peripheral neuropathy (57%), and increased creatinine (30%), while hematologic toxicities included thrombocytopenia (52%), anemia (30%), and neutropenia (17%). Also, QT interval prolongation was noted in two patients who were treated at one level above what was ultimately defined as the MTD. Out of twenty-one evaluable patients, nine (42%) experienced at least a partial response (PR) and, interestingly, none experienced an improvement with the addition of dexamethasone. In the second phase I study, bortezomib was dosed from 0.7–1.3 mg/m^2, while vorinostat was dosed for fourteen days at 200 mg twice daily, 400 mg daily, or 300 mg twice daily (42). Toxicities of any grade seen in at least one-quarter of patients included nausea (seen in 74%), diarrhea (74%), fatigue (68%), thrombocytopenia (59%), vomiting (59%), peripheral neuropathy (29%), fever (29%), and constipation (27%). Nine out of thirty four patients (27%) achieved a PR, while two patients had MRs (6%), and another twenty had stable disease (SD)(59%). Notably, out of seven patients whose disease was bortezomib-refractory, one experienced a PR while the other six had SD, and the duration of response (DOR) was 120 days among all patients who had SD or better.

The encouraging data obtained from the phase I combination studies led to the design and completion of a phase II trial designed to determine if vorinostat could overcome resistance

to bortezomib. Patients with at least two prior lines of therapy whose disease was refractory to bortezomib, and either refractory or ineligible for thalidomide and/or lenalidomide, received bortezomib and vorinostat, and dexamethasone could be added after 4 cycles if progression or SD was seen (43). An overall response rate (ORR)(PR or better) of 17% was reported, while the clinical benefit response (CBR) rate (MR or better) was 31%, with a DOR of 6.3 months. Progression-free survival was 3.13 months, while the median overall survival (OS) was 11.2 months. Also, a phase III randomized study comparing single-agent bortezomib with placebo to the combination of bortezomib with vorinostat has been completed and reported (44). While the ORR (PR or better) and the CBR rate (MR or better) both were significantly better for the combination regimen (Figure 1), the response duration was not, at 8.5 months for bortezomib and vorinostat, compared to 8.4 months for bortezomib alone. Moreover, progression-free survival (PFS) was 7.63 months for the combination versus 6.83 months for bortezomib alone, and while this represented a statistically significant difference ($P = 0.01$), it translated to a benefit of only 24 days, which was not clinically meaningful. Finally, though not mature, the OS data were comparable for the two arms, while a number of hematologic and non-hematologic toxicities were increased by the addition of vorinostat. These findings do suggest the possibility that a subset of patients may benefit from the regimen of vorinostat and bortezomib, and that if they could be identified prospectively using a molecular signature, this could still be a valuable therapeutic approach. For now, however, further development of vorinostat in the multiple myeloma setting has been put on hold.

Panobinostat

Panobinostat (LBH589), like vorinostat, inhibits a number of the known human deacetylases, including those in classes I, II, and IV, and has activity pre-clinically against myeloma both alone, and in combinations, including with bortezomib, through analogous mechanisms (45–48). A phase II study of single-agent panobinostat given three times weekly for each week of a three week cycle decribed grade 3 or 4 toxicities that occurred in at least 5% of patients as including neutropenia (in 32%), thrombocytopenia (26%), anemia (18%), back pain (8%), hypercalcemia (8%), hypokalemia (8%), fatigue (5%), and pneumonia (5%)(49). Of the thirty-eight patients evaluated, one PR and one MR was seen, demonstrating that, as was the case for vorinostat, single-agent deacetylase inhibitors probably do not have a significant role in relapsed and/or refractory myeloma, despite one case report of a near-CR after panobinostat (50). The combination of panobinostat and bortezomib was studied in a phase Ib trial, which allowed addition of dexamethasone starting with cycle 2 if a suboptimal response was seen (51). Based on this study, the MTD of panobinostat was identified as 20 mg given three times weekly for two weeks, along with the standard dose and schedule of bortezomib. Among forty-seven patients in the dose escalation phase, 36 (76%) achieved at least an MR or better, and 75% of twelve evaluable patients in the dose expansion cohort did as well. Also of note, 11/19 (58%) patients who had previously bortezomib-refractory disease responded to the combination. As a result of these very encouraging data, a phase randomized III trial comparing bortezomib and dexamethasone with or without panobinostat (Table 1) is underway. While data about the primary endpoints have not yet been reported, preliminary presentations of planned interim analyses of up to 525 blinded patients focusing on toxicity have indicated a comparable safety profile to that expected of bortezomib and dexamethasone (52,53).

Proteasome Inhibitors

Bortezomib is the first proteasome inhibitor to reach the clinic, and garnered approvals as a single agent in the relapsed and/or refractory setting based on exciting data from phase I through III trials (1,2,54), and was subsequently approved as part of front-line therapy with

melphalan and prednisone (4). By validating the proteasome as a target for cancer therapy, bortezomib also spurred interest in the possibility that other drugs targeting the proteasome, and indeed the entire ubiquitin-proteasome pathway, could play a role in our armamentarium against multiple myeloma as well. A number of inhibitors of the constitutive and/or immunoproteasomes are under study pre-clinically and clinically (55,56), and carfilzomib and ixazomib have reached the phase III setting for multiple myeloma.

Carfilzomib

Carfilzomib (Kyprolis™) is a peptide epoxy-ketone that binds the N-terminal threonine active site of the β5 subunit of the proteasome in an irreversible manner, possibly providing a more durable inhibition of the proteasome than reversible agents such as bortezomib (57,58). In models of multiple myeloma, carfilzomib induced apoptosis in part through the c-Jun-N-terminal kinase (JNK), and activated both the intrinsic and extrinsic caspase pathways (59). Notably, carfilzomib was effective against cell lines and primary samples that were resistant to conventional and novel drugs, including bortezomib, acted synergistically with other agents such as dexamethasone (59), and showed *in vivo* anti-tumor activity (60). In addition to its anti-myeloma effects, carfilzomib may also have the benefit of suppressing bone resorption and promoting bone anabolic activities (61), and may be more specific than bortezomib for the proteasome (62), possibly contributing to a more favorable toxicity profile.

Phase I studies of carfilzomib evaluated the safety and toxicity of this drug on two schedules, including dosing five days in a row followed by nine days off (63), or two consecutive days for three weeks on and one week off, which translated to dosing on days 1, 2, 8, 9, 15, and 16 of every 28-day cycle (64). On the more intensive schedule, the MTD was 15 mg/m^2, with dose limiting toxicities (DLTs) including febrile neutropenia and thrombocytopenia (63). Activity was seen against mantle cell lymphoma, Waldenström's macroglobulinemia, and multiple myeloma, with the latter including a response in a patient whose disease had previously been refractory to bortezomib. With twice weekly concecutive day dosing, an MTD was not identified, and the highest dose level tested administered carfilzomib at 20 mg/m^2 on days 1 and 2 of cycle 1, and then 27 mg/m^2 on subsequent days of that cycle, and on all later dosing days (64). As was the case for the earlier phase I trial, the latter also showed evidence of activity against multiple myeloma and non-Hodgkin lymphoma, and this schedule was selected for further evaluation in the phase II setting.

One combination regimen incorporating carfilzomib that has garnered particular attention is that with lenalidomide and dexamethasone. For patients with relapsed or progressive myeloma (20), no MTD was defined, and the highest level was recommended for further study. This consisted of carfilzomib at 20 mg/m^2 on days 1 and 2 of cycle 1, followed by 27 mg/m^2 on all subsequent days of cycle 1 and later cycles, along with lenalidomide at 25 mg on days 1–21, and dexamethasone at 40 mg on days 1, 8, 15, and 22. Treatment-emergent AEs that occurred in at least 10% of patients, and that reached grade 3 or 4 severity, included neutropenia (seen in 40%), thrombocytopenia (33%), anemia (18%), lymphopenia (18%), hyperglycemia (15%), hyponatremia (15%), and hypophosphatemia (15%), with no grade 3 or 4 neuropathic events. The ORR including patients with at least PR was 63%, and clinical benefit with at least an MR was seen in 75%, while response duration and PFS were 11.8 and 10.2 months, respectively. A similar regimen has also been studied in the front-line setting (19), where carfilzomib was escalated to the highest planned dose level of 36 mg/m^2 with standard dose lenalidomide and low-dose dexamethasone. Addition of a proteasome inhibitor to an immunomodulatory agent could have the ability to overcome lenalidomide resistance through a number of mechanisms. Cereblon expression has been found to be important for the effects of lenalidomide and other immunomodulatory drugs, and low

expression may be associated with resistance (65,66). Since the abundance of most cellular proteins is regulated in part through the ubiquitin-proteasome pathway, inhibition of the proteasome should increase Cereblon levels, which could enhance the activity of lenalidomide. Also, Cereblon may itself inhibit the proteasome by binding to the β4 subunit (67), which is a distinct target from the β5 subunit to which carfilzomib predominantly binds, possibly providing a mechanism for synergistic proteasome inhibition. Finally, resistance to lenalidomide has also been associated with activation of signaling through the Wnt/β-catenin pathway (68), possibly through up-regulation of CD44 and adhesion-mediated drug resistance (69). β-catenin is also a target for the ubiquitin-proteasome pathway (70), but may be cleared in part through aggresomes (71). Thus, it is possible that proteasome inhibition directs β-catenin to the aggresome/lysosome pathway, leading to decreased signaling throught the Wnt/β-catenin pathway, thereby overcoming lenalidomide resistance.

Due to the encouraging data with carfilzomib in the phase I setting, phase II studies were initiated targeting patients with relapsed and refractory disease. Regulatory approval of carfilzomib was based on the outcomes from the PX-171-003-A1 trial, in which patients received dosing at 20 mg/m^2 during cycle 1, and then 27 mg/m^2 starting in cycle 2. Among 257 patients who were evaluable for efficacy, of whom 95% had disease that was refractory to their most recent line of therapy, and 80% were either refractory or intolerant to lenalidomide and bortezomib, an ORR of 24% was reported. Responses were also sustained, with a DOR of 7.8 months, and a median OS of 15.6 months (10). Common AEs that reached grade 3 or 4 severity, and were seen in at least 5% of patients, included thrombocytopenia (in 29%), anemia (24%), lymphopenia (20%), neutropenia (11%), pneumonia (9%), hyponatremia (8%), fatigue (8%), leukopenia (7%), hypophosphatemia (6%), and upper respiratory tract infection (5%). Peripheral neuropathy of any grade was seen in only 33 patients (12%), including only three events at grade 3 (1%), and none at grade 4. A second study of carfilzomib, PX-171-004, evaluated patients with relapsed and/or refractory myeloma who were bortezomib-naive, and included two cohorts, the first of which received dosing at 20 mg/m^2 throughout, while the second used stepped up dosing in cycle 2 at 27 mg/m^2 (72), as had been the case for PX-171-003-A1. The toxicity profile was comparable to the prior phase II study, with again a low rate of peripheral neuropathy. Notably, there was a trend towards a better response rate in the latter cohort (42% vs 52%), response durability (median DOR of 13.1 months vs. not reached), and TTP (median of 8.3 months vs. not reached) with the latter approach. An additional phase II study of note focused on patients with relapsed and/or refractory disease who had been exposed to bortezomib (73), and reported a response rate of 17.1%, indicating the presence of some cross-resistance between bortezomib and carfilzomib, while DOR was >10.6 months, and TTP was 4.6 months. Additional information about phase II studies with carfilzomib can be found in the article by Drs. Mateos, Ocio, and San Miguel.

Several phase III trials that will provide further insights into the role of carfilzomib are currently underway (Table 1). The ASPIRE study comparing lenalidomide and low-dose dexamethasone with or without carfilzomib for patients with relapsed myeloma who have received one to three prior lines of therapy has already completed enrollment. Positive data from this trial would lead to full approval of carfilzomib for patients in the relapsed setting, supporting the earlier approval of single-agent carfilzomib in relapsed and refractory myeloma. In addition, the FOCUS study is comparing carfilzomib to best supportive care in patients with relapsed and refactory myeloma who have undergone at least three prior lines of treatment (74). FOCUS has also completed enrollment, and encouraging findings could support the approval of carfilzomib in Europe. Finally, the ongoing ENDEAVOR study for patients with one to three prior lines of therapy and relapsed myeloma is comparing bortezomib and dexamethasone as a salvage regimen to carfilzomib and dexamethasone.

Notably, in this study, carfilzomib is being administered at 20 mg/m^2 on days 1 and 2 of cycle 1, and then 56 mg/m^2 for all later doses. This dosing is based on results from a phase Ib study indicating that carfilzomib can be safely administered at doses up to 56 mg/m^2 as an infusion over 30 minutes (75), as opposed to the standard 2–10 minutes. Adverse events with this approach were similar to those in other carfilzomib studies, including fatigue (seen in 36%), headache (36%), thrombocytopenia (36%), anemia (32%), cough (32%), dyspnea (32%), insomnia (27%), upper respiratory tract infection (27%), nausea (23%), and hypertension (18%). Responses were seen in patients with relapsed and/or refractory myeloma, including two very good PRs. Moreover, a recent phase II study using this approach in patients with relapsed or refractory multiple myeloma corroborated the encouraging safety signal (76), and noted a response rate of 58% among patients who received at least four cycles of therapy, or who progressed during their first four cycles. ENDEAVOR will therefore determine if this higher dose carfilzomib regimen has a role to play in therapy of relapsed myeloma.

Ixazomib

Both of the currently approved proteasome inhibitors are administered as injections, with bortezomib available either through an intravenous or subcutaneous route (77), while carfilzomib is delivered intravenously. Ixazomib, on the other hand, also known as MLN9708, is the first orally available proteasome inhibitor to reach the clinic. This drug, which is rapidly metabolized *in vivo* to the active agent, MLN2238, is characterized by a shortened proteasome dissociation half-life, which may allow it to more rapidly redistribute from off-target tissues to tumor cell proteasomes, and induce greater anti-tumor activity (78). In models of multiple myeloma, ixazomib activated apoptosis through both caspase 8 and caspase 9, induced the endoplasmic reticulum stress response while inhibiting nuclear factor kappa B, and showed synergistic anti-tumor activity in combination with dexamethasone and lenalidomide (79). Recent studies also suggest a role for modulation of micro RNA 33b by ixazomib in its mechanism of action (80).

As a single agent in the relapsed and/or refractory setting, the MTD of ixazomib given on the bortezomib schedule of day 1, 4, 8, and 11 every 21-days was 2.0 mg/m^2 (81). Drug-related AEs included fatigue (in 45%), thrombocytopenia (30%), nausea (26%), diarrhea (25%), vomiting (23%), and rash (23%), while neuropathy (8%) was rare. Among 36 response-evaluable patients, six had at least an MR (17%), while 22 patients had SD (61%). A second study has been evaluating ixazomib given once weekly, and has reported similar drug-related AEs, though with a lesser incidence of rash, and no DLTs as of yet (82). Finally, a phase I/II study is being conducted with ixaomib in combination with lenalidomide and dexamethasone for patients with previously untreated multiple myeloma (83). An ORR of 88% has been seen to date, including 18% in CR and 40% with very good PR, while tolerability has been comparable to what would be expected of single-agent ixazomib, as well as lenalidomide with low-dose dexamethasone (12). Based on the latter data, a phase III study in the relapsed and/or refractiory setting is ongoing comparing lenalidomide and low dose dexamethasone with or without the addition of ixazomib on days 1, 8, and 15 of every 28-day cycle. Successful completion of this study with supportive data could lead to the regulatory approval of this oral proteasome inhibitor.

Immunomodulatory agents

Thalidomide and lenalidomide are the first two members of the immunomodulatory (IMiD) drug family to obtain regulatory approvals for treatment of multiple myeloma, and they have contributed significantly to the improvements seen recently in patient outcomes (84–86). Other IMiDs are also under development, with pomalidomide being the agent that has

advanced furthest, having been approved on an accelerated basis in February, 2013, for patients with relapsed and refractory myeloma who have had at least two prior lines of therapy which included bortezomib and lenalidomide.

Pomalidomide

Pomalidomide is a third-generation IMiD which was previously known as CC-4047, and while Actimid™ was its trade name in the past, the current name is Pomalyst™. Like other agents in this class of drugs, pomalidomide has multiple mechanisms of action, including modulating and stimulating the host immune system, inhibiting angiogenesis and production of stromal cell cytokines that would normally make the microenvironment more permissive for myeloma cells, and also directly suppressing tumor cell proliferation and activating programmed cell death (84–86). While structurally similar to thalidomide and lenalidomide, pomalidomide has been shown in a number of assays to be more potent than its predecessors (87,88), which in part prompted hopes that it could help to overcome resistance that had emerged after therapy with either thalidomide or lenalidomide.

The first phase I study of pomalidomide in patients with relapsed or refractory multiple myeloma found it to be well tolerated from the standpoint of serious non-hematologic AEs, but did report neutropenia and deep vein thrombosis (89). An MTD of 2 mg per day was identified, and MR or better was seen in 67% of patients, while 54% experienced at least a PR. Correlative studies showed an associated increase in serum levels of the IL-2 receptor and of IL-12, supporting the possibility of T-cell costimulation as a mechanism of action. Pomalidomide at 2 mg daily was then combined with low dose dexamethasone, and this regimen was found to be well tolerated and active against relapsed myeloma (90), with a similar ORR of 63%, including CR in three patients (5%), and very good PR in seventeen (28%). Response durability was also documented, with a PFS of 11.6 months, which was not significantly reduced in patients with high-risk cytogenetic features. This approach was also shown to be effective against myeloma that was relapsed and refractory (91), though, as would be expected, the response rates were lower in this group that had more resistant disease, with 32% of patients having a PR or better.

One area of controversy that arose early in the development of pomalidomide was with respect to its most appropriate dose and schedule. Pomalidomide was given at either 2 mg or 4 mg continuously with low-dose dexamethasone in patients with myeloma that was refractory to both bortezomib and lenalidomide in a non-randomized study (92). Myelsuppression was the most commonly seen toxicity, while MRs or better were seen in 49% of patients who received 2 mg dosing, and 43% who received 4 mg dosing. Interestingly, the OS at 6 months for these two groups was 78% and 67%, suggesting that there was no advantage for the 4 mg dose over the 2 mg dose. Also, two different schedules of pomalidomide with low-dose dexamethasone have been studied in such patients with so-called “double-refractory” myeloma, comparing pomalidomide at 4 mg given for twenty-one days of each twenty-eight day cycle, or pomalidomide with continuous dosing throughout the cycle (93). This randomized study suggested that the median time to the first response could be longer with dosing for only twenty-one days, but the response rates were comparable (Table 2), and most of the measures of response durability were either similar, or favored twenty-one day dosing followed by one week off. Finally, the appropriate dose was likely settled by a phase I study of patients who had refractory myeloma after prior therapy with both lenalidomide and bortezomib (94). After DLTs of grade 4 neutropenia were seen at a dose of 5 mg, the MTD was established as 4 mg on the twenty-one day dosing schedule. Minor response or better was seen in 42% of thirty-eight patients, twenty-two of whom had addition of dexamethasone, and median OS was an encouraging 18.3 months. Thus, while a formal randomized study has not been performed comparing all of the

doses and schedules, the dose that was taken forward into registration studies was 4 mg for three consecutive weeks of each 28-day cycle.

Accelerated approval of pomalidomide was recently granted based on the findings of the MM-002 phase II study, which randomized patients to either pomalidomide alone, or to pomalidomide with low-dose dexamethasone (95). Grade 3 and 4 AEs for the two arms were predominantly hematologic, including neutropenia, thrombocytopenia, anemia, or leukopenia, while non-hematologic events included pneumonia, fatigue, back pain, and dyspnea. The response rate for pomalidomide alone was 9%, while PR or better was seen in 30% of patients who received the combination. Median DOR was 7.4 months for pomalidomide with dexamethasone, while it had not yet been reached with pomalidomide alone, suggesting that while dexamethasone was improving the response rate, it was in patients with biologically more aggressive disease that was not likely to remain in remission. Other durability measures tended to favor the combination, however, including PFS, which was 3.8 months for both agents compared to 2.5 for pomalidomide alone, while OS was 14.4 and 13.6 months, respectively. Most recently, initial results of the phase III NIMBUS trial (Table 1) were reported, which compared pomalidomide with low dose dexamethasone to high dose dexamethasone (96). Response durability as measured by the median PFS and OS was significantly superior for the combination (Table 3), and these data may support the approval of this treatment regimen in Europe.

A confirmatory phase III study of pomalidomide is underway, which is comparing pomalidomide with bortezomib and dexamethasone to bortezomib and dexamethasone in patients with one to three prior lines of therapy (Table 1). This is based in part on data from a phase I study of the three-drug regimen, which did not detect DLTs within the planned dosing cohorts (21), and noted a PR or better rate of 73%. Encouraging findings from the international phase III study would support full approval of pomalidomide. Other interesting combinations based on pomalidomide that are being studied include carfilzomib with pomalidomide and dexamethasone, which has reported a 50% ORR in patients with lenalidomide-refractory disease (22), and pomalidomide with clarithromycin and dexamethasone, which induced a PR or better in 54% of patients with relapsed or refractory myeloma. The interested reader is referrred to the accompanying contribution by Drs. Mateos, Ocio, and San Miguel for additional data on pomalidomide.

Monoclonal antibodies

No monoclonal antibodies have yet been approved for the treatment of multiple myeloma, though this is likely to change in the near future, since a number of such agents are in clinical trials and showing encouraging signs of activity. Several of these antibodies have been raised against cell surface proteins, such as elotuzumab, which recognizes CS1, daratumumab, which is directed against CD38, and lorvotuzumab mertansine, which targets CD138. Other antibodies target cytokines that are important to the plasma cell in its microenvironment, such as siltuximab, which neutralizes IL-6, and tabalumab, which recognizes B-cell activating factor. A number of excellent reviews have recently been published which detail the properties and pre-clinical as well as known clinical activity of these antibodies (31,97–99). Two of these, including siltuximab and elotuzumab, have reached potential registration-enabling studies, and greater detail about these agents is provided below.

Siltuximab

Signaling through the IL-6 pathway has been shown to play a key role in myeloma pathobiology, including in processes such as plasma cell proliferation, survival, and chemotherapy resistance, as well as osteoclast activation, providing a strong rationale to

target IL-6 with monoclonal antibodies (100,101). Pre-clinical studies with siltuximab revealed activity as a single agent against both IL-6-dependent and –independent cell lines and primary samples, and it enhanced the cytotoxicity of bortezomib in an additive to synergistic manner (102). This occurred in part through inhibition of bortezomib-mediated induction of anti-apoptotic heat shock protein 70, and myeloid cell leukemia 1. Additional studies showed that siltuximab sensitized models of myeloma to corticosteroid-induced cell death (103), as well as to alkylating agents such as melphalan (104).

Based in part on the strong rationale outlined above, siltuximab was studied in a phase I dose escalating trial for patients with relapsed and refractory myeloma (105). Treatment was well tolerated, and decreases were seen in the IL-6 surrogate marker C-reactive protein, but no responses were seen among the twelve patients treated. The excellent safety profile of single-agent siltuximab was then confirmed in a subsequent phase I study in patients with a variety of hematologic malignancies, including B-cell non-Hodgkin lymphoma, myeloma, as well as Castleman's disease, in which DLTs were not seen (106). Notably, activity was seen against multiple myeloma, with five patients treated for at least one year showing benefit, including two CRs (106), and the possibility to achieve CR with single-agent siltuximab has also been reported from another study (107). These findings prompted a phase II study of siltuximab in patients with myeloma, which included one cohort in which siltuximab was used first and dexamethasone could be added later if an inadequate response was seen, while a second cohort gave the two agents together (108). Siltuximab alone showed no activity in this heavily pre-treated population, among whom 83% were relapsed and refractory to their last line of therapy. However, when combination therapy with siltuximab and dexamethasone was given, 23% of patients achieved at least an MR, including in patients whose disease was previously refractory to a corticosteroid-containing regimen. Response durations were reasonable as well, with a median PFS of 3.7 months, median TTP of 4.4 months, and a median OS of 20.4 months. Finally, the results of a randomized phase II study were recently reported, which compared the efficacy of bortezomib with placebo to bortezomib with siltuximab in relapsed myeloma patients with up to three prior lines of therapy who were bortezomib-naïve (109). While the ORR was superior for the combination compared to bortezomib alone (55% achieved at least a PR vs. 47%), as was the CR rate (11% vs. 7%), significant differences in long-term outcomes were not seen. Progression-free survival, for example, which was the primary endpoint, was 245 days for the combination in 142 patients, while for bortezomib with placebo it was 232 days in 144 patients. Also, OS slightly favored patients in the bortezomib + placebo arm, at 1121 days, compared with 1068 days for the bortezomib/siltuximab arm. A number of factors likely contributed to the negative outcome of this study, including the use of what was later identified as a suboptimal dose and schedule for siltuximab, a greater rate of discontinuations due to AEs on the siltuximab arm, and the influence of subsequent therapies on outcome. Due to these disappointing findings, however, further development of siltuximab in multiple myeloma has been halted.

Elotuzumab

Elotuzumab targets CS1, which was noted to be highly expressed on more than 97% of primary patient plasma cells (110), though it also has been found on natural killer (NK) cells, NK-like T cells, and $CD8^+$ T cells (111). Consistent with the possibility that this protein plays a role in cellular adhesion, eloutuzmab inhibited binding of myeloma cells to stromal cells (110). It exerted an antibody-dependent cytotoxic effect both alone (110), and in the presence with effector NK cells (111). Also, elotuzumab exerted enhanced activity when it was added to a variety of conventional and novel agents, including bortezomib (110,112) and lenalidomide (110), and showed anti-tumor activity *in vivo* (110,111).

As a single agent, with elotuzumab adminstered intravenously every two weeks from 0.5 to 20 mg/kg, no maximum tolerated dose was identified in the phase I study, while common adverse events included cough, headache, back pain, fever, and chills (113). CS1 on marrow plasma cells was found to be saturated at 10 and 20 mg/kg, but stable disease was the best response, and was seen in nine patients (27%). In combination with bortezomib, elotuzumab again was well tolerated without an MTD within the tested range, while frequent grade 3 and 4 AEs were lymphopenia and fatigue (114). Partial response or better was seen in 48% of 27 evaluable patients and, interestingly, though only three patients had bortezomib-refractory disease, two responded, and the overall median TTP was an encouraging 9.5 months. The most impressive clinical activity in a phase I setting were obtained when elotuzumab was combined with lenalidomide and low-dose dexamethasone, which lilkewise found no DLTs or MTD (115). Some myelosuppression was seen, with neutropenia in 36% of patients and thrombocytopenia in 21%, and two patients did have serious infusion-related toxicities during the first treatment cycle only. A PR or better was seen in 82% of patients, including 21/22 (95%) who were lenalidomide-naïve, 15/16 (94%) who had been exposed to thalidomide, and 10/12 (83%) of those whose disease was refractory to their most recent therapy. To obtain additional information to guide a phase III trial, a randomized phase II study was then started comparing lenalidomide and dexamethasone with elotuzumab at either 10 or 20 mg/kg (116). Common toxicities in this larger study were lymphopenia (in 19%), neutropenia (18%), thrombocytopenia (16%), anemia (12%), leukopenia (10%), hyperglycemia (10%), pneumonia (7%), diarrhea (7%), fatigue (7%), and hypokalemia (6%), while infusion reactions occurred in 12% of patients. Notably, while the ORR and PFS were excellent in both arms (Table 4), there was a trend towards better results in both of these endpoints with the 10 mg/kg group. As a result, the ongoing phase III study comparing lenalidomide/low dose dexamethasone with or without elotuzumab (Table 1) is utilizing this lower dose, and has already reached its accrual goal.

Signal transduction inhibitors

The major drug classes being tested in myeloma remain within the catgories of deacetylase inhibitors, proteasome inhibitors, immunomodulatogry agents, and monoclonal antibodies. However, a number of other agents with activity as inhibitors of signal transduction pathways important to the pathobiology of multiple myeloma are also being evaluated in radomized phase III trials that could lead to new drug approvals.

Masitinib

Masitinib, also known as AB1010 (and KINAVET-CA1™ for canine use), is a novel phenylaminothiazole-type tyrosine kinase inhibitor that targets the stem cell factor receptor c-Kit, as well as the platelet-derived growth factor receptor (PDGFR), the intracellular Lyn kinase, and fibroblast growth factor receptor (FGFR) 3 (117). It was first reported to delay TTP of recurrent or non-resectable grade II or III mast cell tumors in canines (118). A later phase I human study determined that 12 mg/kg/day was safe for human dosing, and also reported stable disease in 29% of patients with imatinib-resistant gastrointestinal stromal tumors (GIST)(119). Activity in this disease was later confirmed in the first-line for patients with GIST, who experienced a median PFS of 41.3 months (120). Among other human malignancies, masitinib is active against systemic and cutaneous mastocytosis (121), and mast cell leukemia (122). Pre-clinical studies documenting the activity of masitinib either alone, or in combination with other agents, have not yet appeared in the peer-reviewed literature. However, c-Kit is expressed in myeloma and may play a role in plasma cell proliferation (123), and FGFR-3, especially in the setting of the 4;14 translocation, is known to contribute to high-risk features of this disease (124). Also, since signaling through Lyn kinase (125,126) and PDGFR (127) may play roles in myeloma proliferation and

angiogenesis, it is certainly possible that masitinib may have activity against this disease. To determine if this could be the case, a phase III trial comparing bortezomib and dexamethasone to masitinib with bortezomib and dexamethasone is currently underway (Table 1).

Plitidespin

Plitidepsin (Aplidin™) is a marine-derived cyclodepsipeptide that has shown activity against myeloma in both the syngeneic 5T33MM murine mouse model (128), and in human myeloma cell lines and primary samples (129). In the latter, plitidepsin activated the p38 and JNK kinases, and also induced Fas/CD95 translocation to lipid rafts, as well as caspase activation. A phase II clinical trial of plitidepsin has been completed targeting patients with relapsed and refractory multiple myeloma, which administered this drug at 5 mg/m^2 as a 3-hour infusion every two weeks, with the possibility to later add oral dexamethasone if a suboptimal response was seen. Common hematologic toxicities included grade 3 and 4 anemia (in 29% of patients), thrombocytopenia (18%), and neutropenia (18%). Non-hematologic toxicities included elevations of laboratory studies such as the alanine (28%) or aspartate (10%) aminotransferases, creatinine (4%) or creatine kinase (6%), and alkaline phosphatase or total bilirubin (2% each), as well as fatigue (16%), myalgia (4%), or either nausea, muscle weakness, anorexia, vomiting, or dyspnea (2% each)(130). The ORR (including at least MRs) was reported as 13% with plitidepsin alone, which rose to 22% in the 19 patients who also received dexamethasone. Time to progression and PFS for plitidepsin alone was 2.3 months, which rose to 4.2 and 3.8 months, respectively, in the subgroup who received added dexamethasone. In the ongoing phase III study (Table 1), plitidepsin with dexamethasone is being compared to dexamethasone alone for patients with relapsed or relapsed and refractory disease that has been treated with at least three but not more than six prior regimens.

Perifosine

Perifosine ([octadecyl-(1,1-dimethyl-piperidinio-4-yl)-phosphate]; KRX-0401) is an alkylphospholipid which was found to induce cytotoxicity in myeloma cell lines and patient samples, overcome drug resistance, and enhance the activity of other anti-myeloma agents (131). This occurred in part through activation of the JNK pathway, and in association with inhibition of activation of anti-apoptotic Akt (131). Since activation of Akt by bortezomib is a proposed mechansim of resistance to this proteasome inhibitor (131,132), perifosine could be a directed strategy to enhance proteasome inhibitor sensitivity, and possibly overcome drug resistance. Additional mechanisms of action for perifosine may include down-regulation of Survivin (133), while recruitment of death receptors and associated signaling molecules into lipid rafts may play a role as well (134,135). Two combination approaches to myeloma therapy incorporating perifosine have been reported, including one study with lenalidomide and dexamethasone (136), and another with bortezomib, which allowed later addition of dexamethasone (137). The latter has formed the basis for an ongoing phase III study comparing bortezomib/dexamethasone to the same regimen with added perifosine (Table 1). Eligible patients include those who have had one to four prior lines of therapy, and are relapsed and/or refractory, providing that their disease was not refractory to a bortezomib-containing regimen. Selection of the latter strategy was based in part on the findings from the phase I trial, which recommended a perifosine dose of 50 mg daily for further study in combination with bortezomib. Toxicities seen in at least 25% of patients included nausea (63%), diarrhea (57%), fatigue (43%), musculoskeletal pain (42%), upper respiratory tract infection (33%), anorexia (33%), peripheral neuropathy (29%), vomiting (29%), and coughing (25%). More significant, grade 3 or 4 events in at least 10% of patients included thrombocytopenia (23%), neutropenia (15%), anemia (14%), pneumonia (12%),

musculoskeletal pain (11%), and bleeding (10%). Responses, including at least an MR, were seen in 41% of patients overall, including in 13/20 (65%) who were bortezomib relapsed, and 17/53 (32%) who were bortezomib refractory. These encouraging findings formed the rationale for the randomized study, the results of which are eagerly awaited.

Conclusions

The recent approvals of carfilzomib and pomalidomide for patients with relapsed and refractory myeloma after at least two prior lines of therapy are likely harbingers of their future adoption into the relapsed setting for patients with one or more prior therapies. Moreover, other new agents that represent new drug classes, such as panobinostat and elotuzumab, may be on the cusp of approval, since registration-enabling studies have already been fully enrolled, and hopefully positive data will be reported soon. Further in the future, even more novel drugs are showing promise, including other monoclonal antibodies such as daratumumab (138), and new drug classes such as kinesin spindle protein inhibitors (139,140). If they continue to demonstrate encouraging activity in the refractory setting, they too may soon become incorporated into the treatment algorithm for relapsed disease. These will give patients and caregivers facing decisions on treatment of relapsed myeloma an ever wider and better array of treatment options, which will likely induce a greater response rate and deeper response quality than our currently available agents and, most importantly, improve quality of life and overall survival.

Despite this encouraging picture, many challenges remain for development of drugs in the relapsed setting. With the increasing efficacy of front-line therapy (23–27), and the greater tendency to use maintenance after either stem cell transplant (141,142) or standard dose approaches (143,144), fewer patients will have relapsed disease. Patients will tend to either stay in remission, which will certainly be welcome, or will develop disease that is refractory and more chemotherapy resistant, which will slow drug development. The latter may prove to be an argument that will allow continued use of the accelerated approval pathway for myeloma, without which all new drug applications would likely need to come from large, randomized phase III studies that slow the time to wide availability of new drugs. Another matter is that of the economics of therapy, since while current analyses have suggested that agents such as bortezomib, thalidomide, and lenalidomide alone, and in combination, are likely cost-effective (145,146), there is agreement that more studies are needed in this area (147).

All of these arguments support the need for a greater understanding of the molecular mechanisms that support the pathobiology of multiple myeloma in the relapsed setting. It is likely that drug resistance is mediated by a finite set of pathways whose relative contributions will vary in individual patients in a manner that could be determined through the use of validated biomarkers. If so, this would allow genomic and proteomic analyses to be performed on primary samples from patients with relapsed myeloma to determine which targets need to be suppressed or activated to restore sensitivity to drugs that were used successfully in a prior line of therapy, or to maximize the benefits of the available new drug options. For example, if lenalidomide resistance emerged due to decreased expression of Cereblon (65,66), current data argue that pomalidomide alone may be less successful for such patients, while pomalidomide with a proteasome inhibitor to increase Cereblon levels could be of value. In contrast, if lenalidomide resistance were instead mediated by induction of the Wnt/β-catenin pathway (68), pomalidomide could be more successful, or lenalidomide could be reused with approaches that suppress Wnt/β-catenin, such as antibodies that target CD44, or all-*trans*-retinoic acid, which reduces CD44 expression (69). By so personalizing therapy, we would optimize patient outcomes by targeting the vulnerabilities of each person’s myeloma, minimize toxicities by limiting exposure of

patients to agents to which their disease would be unlikely to respond, save valuable healthcare resources, and speed new drug development.

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Abbreviations

AEs	adverse events
CBR	clinical benefit response
DLTs	dose-limiting toxicities
DOR	duration of response
FGFR	fibroblast growth factor receptor
GIST	gastrointestinal stromal tumor
HDAC	histone deacetylases
IGF	insulin-like growth factor
IGF-1R	insulin-like growth factor-1 receptor
IL	interleukin
IMiDs	immunomodulatory drugs
JNK	c-Jun-N-terminal kinase
MR	minor response
MTD	maximum tolerated dose
NK	natural killer
ORR	overall response rate
OS	overall survival
PARP	poly(ADP)ribose polymerase
PFS	progression-free survival
PGFR	platelet-derived growth factor receptor
PR	partial response
SD	stable disease

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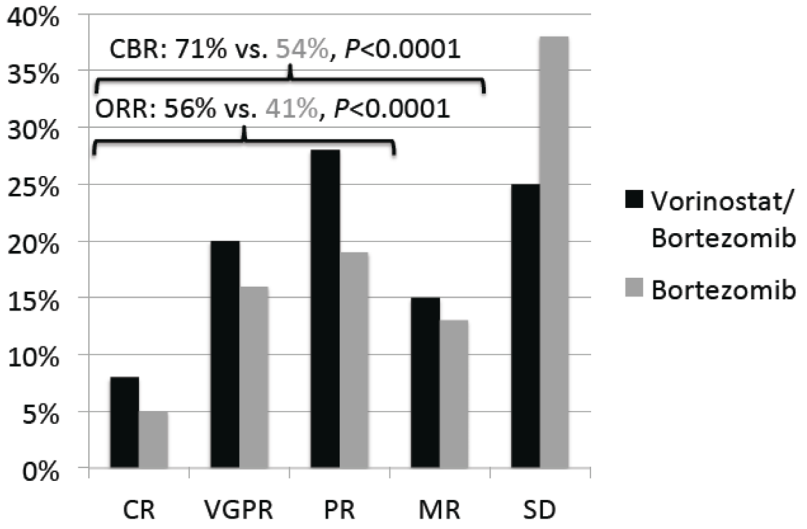

Figure 1.

Response rates seen in patients treated on the VANTAGE 088 trial for relapsed myeloma with either bortezomib, or the combination of vorinostat and bortezomib. Abbreviations: CR, complete response; CBR, clinical benefit response; MR, minor response; ORR, overall response rate; PR, partial response; SD, stable disease; VGPR, very good partial remission

Table 1

Phase III Trials of Novel Agents in Relapsed/Refractory Multiple Myeloma*

Trial Name	Clinicaltrials.gov Identifier	Regimens Control vs. Experimental	Projected Accrual	Estimated Completion
Novel proteasome inhibitors				
ASPIRE	NCT01080391	Lenalidomide/dexamethasone vs. Carfilzomib/Lenalidomide/dexamethasone	780	12/2013
FOCUS	NCT01302392	Best supportive care vs. Carfilzomib	302	6/2014
ENDEAVOR	NCT01568866	Bortezomib/dexamethasone vs. Carfilzomib/dexamethasone	888	1/2015
TOURMALINE-MM1	NCT01564537	Lenalidomide/dexamethasone vs. MLN9708/Lenalidomide/dexamethasone	703	2/2019
Novel immunomodulatory agents				
NIMBUS	NCT01311687	High dose dexamethasone vs. Pomalidomode/dexamethasone	426	5/2013
OPTIMISMM	NCT01734928	Bortezomib/dexamethasone vs. Pomalidomide/Bortezomib/dexamethasone	782	1/2015
Novel deacetylase inhibitors				
VANTAGE 088		Bortezomib vs. Vorinostat/Bortezomib	637	12/2011
PANORAMA-1	NCT01023308	Bortezomib/dexamethasone vs. Panobinostat/Bortezomib/dexamethasone	762	6/2013
Novel monoclonal antibodies				
ELOQUENT-2	NCT01239797	Lenalidomide/dexamethasone vs. Elotuzumab/Lenalidomide/dexamethasone	640	3/2014
Novel signal transduction inhibitors				
AB06002	NCT01470131	Bortezomib/dexamethasone vs. Masitinib/Bortezomib/dexamethasone	300	4/2013
ADMYRE	NCT01102426	Dexamethasone vs. Plitidepsin/dexamethasone	250	6/2014
PERIFOSINE 339	NCT01002248	Bortezomib/dexamethasone vs. Perifosine/Bortezomib/dexamethasone	450	9/2014

*Data are based on a search of clinicaltrials.gov performed on February 23, 2013, using the terms “multiple myeloma” and “relapse” and “phase 3.” The “estimated completion” column provides the date when data about the primary endpoint will be mature, as provided by the study sponsors. Studies within each drug category are arranged based on when they may be expected to report their primary endpoint data. Phase III single-center trials, studies of non-therapeutic interventions, and those that did not incorporate a novel agent were excluded.

Table 2

Outcomes Data from the IFM 2009–02 of Pomalidomide with Low-dose Dexamethasone in Relapsed/Refractory Multiple Myeloma

Outcome Measure, n (%)	Pomalidomide 21/28 Days (n = 43)	Pomalidomide 28/28 Days (n = 41)	Total Population (N = 84)
Overall response rate (at least partial response)	15 (35%)	14 (34%)	29 (35%)
Complete response rate	1 (2%)	2 (5%)	3 (4%)
Very good partial response rate	1 (2%)	1 (2%)	2 (2%)
Partial response rate	13 (30%)	11 (27%)	24 (27%)
Stable disease	19 (44%)	21 (51%)	40 (48%)
Progressive disease	5 (12%)	3 (7%)	8 (10%)
Not evaluable	4 (9%)	3 (7%)	7 (8%)
Median time to first response (months)	2.7	1.1	1.8
Median response duration (months)	6.4	8.3	7.3
One-year relapse-free survival (%)	42%	47%	44%
Median time to progression (months)	5.5	4.6	5.4
Median progression-free survival (months)	5.4	4.4	4.6
Median overall survival (months)	14.9	14.8	14.9

*Data are from reference (93).

Table 3

Progression-free and Overall Survival Data from the NIMBUS Study in Relapsed/Refractory Multiple Myeloma*

Outcomes by Group	Pomalidomide + Low Dose Dexamethasone (n = 302)	High Dose Dexamethasone (n = 153)	Hazard Ratio	P Value
Median Progression-free Survival				
Intent to treat population	3.6 months	1.8 months	0.45	<0.001
Refractory to bortezomib	3.6 months	1.8 months	0.47	<0.001
Refractory to lenalidomide	3.7 months	1.8 months	0.38	<0.001
Refractory to bortezomib & lenalidomide	3.2 months	1.7 months	0.48	<0.001
Median Overall Survival				
Intent to treat population	Not reached	7.8 months	0.53	<0.001
Refractory to bortezomib	Not reached	8.1 months	0.56	0.037
Refractory to lenalidomide	Not reached	8.6 months	0.39	0.003
Refractory to bortezomib & lenalidomide	Not reached	7.4 months	0.56	0.003

* Data are from reference (96).

Table 4

Response Rate and Response Durability Data from a Phase II Trial of Elotuzumab with Lenalidomide and Low-dose Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma*

	Elotuzumab10 mg/kg (n = 36)	Elotuzumab 20 mg/kg (n = 36)	Overall (N = 73)
Median progression-free survival (PFS; months)	26.9	18.6	25.0
Overall response rate, n (%)	33 (92%)	28 (76%)	61 (84%)
Selected subgroup analyses			
ORR and PFS in patients with one prior line of Therapy	NR	NR	91% 25.0 months
ORR and PFS in patients with two or more prior lines of therapy	NR	NR	78% 21.3 months
ORR and PFS in patients with prior treatment with thalidomide	NR	NR	82% 26.9 months

Abbreviations: NR, not reported; ORR, overall response rate; PFS, progression-free survival

*Data are from reference (116).