Novel Targets in Multiple Myeloma

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Abstract

Despite the availability of 6 classes of drugs for the treatment of multiple myeloma (MM), the disease remains incurable in most cases, with patients eventually relapsing on each of these agents. The benchmark for drug approval in heavily pretreated and multidrug-refractory patients is an overall response rate (ORR) of approximately 25% to 30% and progression-free survival (PFS) of approximately 4 months, but more recently in less heavily pretreated patients with relapsed disease after 1 to 3 lines of therapy, based primarily on an improvement in PFS of 3 to 6 months in randomized phase III studies. This article reviews the targets, mechanisms of action (MOA), safety, and efficacy of the recently approved agents in MM that have met one of these benchmarks, including panobinostat, ixazomib, and the monoclonal antibodies (mAbs) elotuzumab and daratumumab. Updated information is provided on the following promising agents including mAbs: isatuximab, a CD38 antibody; indatuximab ravtansine, a CD138 antibody conjugated to maytansinoid; and pembrolizumab, an anti-PD-1 antibody. Non-mAbs discussed include inhibitors of nuclear transport (XPO1), kinesin spindle protein, AKT3, PIM kinase, and cyclin-dependent kinases.

AJHO. 2016;12(10):18-25

Introduction

Although there currently are 6 classes of drugs available for the treatment of multiple myeloma (MM; Table 1), the disease remains incurable in most cases, with patients eventually relapsing on each of these agents. The benchmark for drug approval based on 2 agents approved by the Food & Drug Administration (FDA) prior to 2015 (carfilzomib and pomalidomide) in the relapsed/refractory space was likely to be an overall response rate (ORR) of approximately 25% to 30% and progression-free survival (PFS) of approximately 4 months.[1,2] That said, in less heavily pretreated patients with relapsed disease after 1 to 3 lines of therapy, given a high background rate of responses with already approved agents/regimens shown in **Table 1**, novel agents are also being increasingly approved by the FDA as a part of combination therapy based on PFS extension of 3 to 6 months achieved in randomized phase III studies. The goal of this review is to discuss the targets, mechanisms of action (MOA), safety, and efficacy of the novel agents in MM that are currently have recently met or have the best chance of meeting these benchmarks.

Targets of Immunomodulatory Drugs

Of note, there also have been developments in our understanding of the targets of immunomodulatory drugs (IMiDs). Until recently, it has been unclear how these oral medications achieve antimyeloma benefits without significant toxicity at the site of drug absorption in the gut or other off-target organ toxicities. Recently, cereblon, a member of the E3 ubiquitin ligase family, was identified as the likely mediator of teratogenicity of IMiDs. Cereblon also implicates IMiDs in the dysregulation of the ubiquitination process that targets proteins for proteasomal degradation.[3] Malignant plasma cells, by virtue of being antibody/protein factories, have been demonstrated to be extremely vulnerable to such dysregulation by the proteasome inhibitor (PI) drug class.

Moreover, additional work suggests that the immunologic changes associated with IMiDs may be due to Aiolos and Ikaros, which are not only substrates of cereblon, but also transcription factors involved in interleukin 2–mediated T-cell activation.[4] A better understanding of the MOA of these agents in MM will be essential to overcoming drug resistance and to developing the next generation of IMiDs and PIs. Indeed, CC-122, a so-called pleiotropic pathway modifier that targets cereblon and has antiproliferative, immunomodulatory, and antiangiogeneic activity, has now entered clinical trials.[4]

Monoclonal Antibodies and Other Immune-Mediated Therapies

There are several exciting developments in monoclonal antibody (mAb) use in MM (Table 2). To date, there has been no rituximab—that is, a mAb with single-agent activity—in MM. CD38 is a transmembrane glycoprotein and ectoenzyme with high receptor density on MM cells.[5] The CD38 antibodies daratumumab and isatuximab (SAR650984) are both humanized IgG1 mAbs with multiple MOA, including antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis, complement-dependent cytotoxicity, direct apoptosis induction, inhibition of CD38 enzymatic activity, T-cell clonal expansion, and functional response.[6,7] Other than manageable infusional

TABLE 1. Currently Available Therapies in Multiple Myeloma

Steroid	Conventional Chemotherapy	IMiD	Proteasome Inhibitor	HDAC Inhibitor	mAb
Prednisone Dexamethasone	Melphalan Cyclophosphamide Liposomal doxorubicin DCEP/D-PACE Carmustine (BCNU) Bendamustine	Thalidomide Lenalidomide Pomalidomide	Bortezomib Carfilzomib Ixazomib	Panobinostat	Daratumumab Elotuzumab

DCEP indicates dexamethasone, cyclophosphamide, etoposide, cisplatin; D-PACE, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide; HDAC, histone deacetylase; IMiD, immunomodulatory drug; mAb, monoclonal antibody.

toxicities expected with mAbs, both agents are well tolerated. In a phase II study of 106 patients with a median of 5 lines of prior therapy, daratumumab monotherapy produced an ORR of 29%, with a median PFS of 3.7 months.[8] Based on these results in a patient, daratumumab received accelerated FDA approval in November 2015 for patients with MM who have received more than 3 lines of therapy or are IMiD- and PI-refractory.

Combination therapy has also been explored with daratumumab. In the CASTOR study, the addition of daratumumab to bortezomib and dexamethasone resulted in an improvement in PFS (not reached [NR] vs 7.16 months; HR, 0.39; 95% CI, 0.28-0.53; $P < .001$); ORR (83 % vs 63%; $P < .001$); and complete response ([CR] 19 % vs 9%; $P < .001$).[9] Similarly, in the POLLUX study, the addition of daratumumab to lenalidomide and dexamethasone led to an improvement in PFS (NR vs 18.4 mo; HR, 0.34; 95% CI, 0.23-0.48; $P < .0001$); ORR (93% vs 76%; $P < .0001$); CR (43% and 19%; $P < .0001$); including VGPR (76% vs 44%; $P < .0001$).[10] On November 21, 2016, based on the above studies, the FDA approved daratumumab in combination with both agents. Daratumumab plus pomalidomide is also being investigated. In an ongoing, multicenter phase Ib trial in 77 patients, the ORR was 59%, including 58% in double-refractory patients. Generally speaking, the addition of daratumumab to the backbone agents in **Table 1** has been with no added toxicity aside from daratumumab-related infusion reactions (**Table 3**).[11]

Isatuximab is a humanized mAb that binds selectively to human CD38 receptor. Isatuximab binds to a different epitope on CD38 than daratumumab and may have more potent inhibition of its function. In a phase II trial in 97 patients with heavily pretreated MM, an ORR of 24% was observed at a dosage of ≥10 mg/kg.[12] In addition, it has been investigated in combination with lenalidomide, with an ORR of 64.5% and a PFS of 5.8 months (**Table 3**).[13] An additional dose-escalation phase of this trial recently reported an ORR of 50% in 10 evaluable patients treated with isatuximab 20 mg/kg in combination with lenalidomide. Of note, 86% of patients treated in this dose-escalation study were lenalidomide-refractory.[14]

Another mAb with activity in MM is elotuzumab, which is a humanized IgG1 mAb that targets cell surface 1 (CS1), a member of the SLAM family, which is uniformly and highly expressed in more than 95% of patients with primary MM, but not on stem cells or other normal tissues. The MOA appears to be ADCC-mediated by natural killer (NK) cells.[15] Although elotuzumab has no significant single-agent activity, it has an excellent safety profile in combination with lenalidomide and dexamethasone. This was demonstrated in the phase III ELOQUENT-2 study, which randomized 646 patients with MM who had 1 to 3 lines of therapy prior to elotuzumab or placebo. All patients received a lenalidomide-and-dexamethasone backbone. The elotuzumab group had an ORR of 79% compared with the placebo group. Progression-free survival was 19.4 months in the elotuzumab group versus 14.9 months in the placebo group. Grades 3 and 4 toxicities were primarily hematologic, which were similar in the 2 groups aside from lymphocytopenia, which was significantly more common in the elotuzumab group. However, there was no significant increase in infections.[16] Elotuzumab received FDA approval in November 2015 for more than 1 line of therapy given with lenalidomide-dexamethasone.

Elotuzumab has also been investigated in combination with bortezomib and dexamethasone. One hundred and fifty-two patients with 1 to 3 prior lines of therapy were randomized to elotuzumab, bortezomib, dexamethasone, or bortezomib and dexamethasone alone. Fifty-one percent in the treatment arm and 53% in the control arm had prior PI exposure. After a median number of 12 treatment cycles, PFS was 9.9 months in the elotuzumab group and 6.8 months in the control arm.[17] Also of note, the CS1 target was now also being targeted by a mAb conjugated to the microtubule inhibitor monomethyl auristatin E (MMAE).[18]

Another mAb with an encouraging signal in MM is indatuximab ravtansine (formerly known as BT062), an anti-CD138 chimerized monoclonal IgG4 linked to the microtubule inhibitor maytansinoid (DM4). CD138 is primarily expressed on MM cells and also on epithelial cells, albeit to a lesser extent. Once the mAb binds to CD38, internalization and lysosomal processing of the linker releases the cytotoxic DM4 metabolites that result in apoptosis due to inhibition of tubulin polymerization.[19] In a phase I/IIa trial of patients refractory to lenalidomide, the combination of indatuximab ravtansine plus lenalidomide produced a 78% ORR and 100% clinical benefit rate (CBR), including 73% in lenalidomide-refractory patients.[20]

TABLE 2. Novel Targeted in Multiple Myeloma

Target	Agent
CD138	Indatuximab ravtansine
HDAC-6	Ricolinostat
KSP1	Filanesib
AKT3	Afuresertib
XPO1	Selinexor
PIM kinase	LGH 447
BTK	Ibrutinib
BCL-2	Venetoclax
CDK	Dinaciclib
PD-1	Pembrolizumab

As with other areas of oncology, there is increasing excitement about novel immune modulators in MM. Programmed cell death protein 1 (PD-1) is expressed on activated T-lymphocytes and engages its 2 cognate ligands (PD-L1 and PD-L2), causing inhibition of kinase pathways leading to attenuated T-lymphocyte activation. In healthy individuals, this pathway serves to downregulate unwanted or excessive immune responses.[21] PD-L1 is also expressed on MM cells, allowing for immune evasion. Clinical trials using pembrolizumab, a highly selected anti-PD-1 mAb, is an attractive novel therapeutic for MM. Combination therapy of pembrolizumab with lenalidomide and dexamethasone has been explored in a phase I study of refractory patients produced an ORR of 76% in the 17 evaluable patients. Additionally, there was a 56% ORR in 9 lenalidomide-refractory patients.[22] Pembrolizumab has also been explored in combination with pomalidomide and dexamethasone in a phase II trial of 24 patients, with an observed 50% ORR.[23]

Finally, as with other hematologic malignancies, there is great interest in chimeric antigen receptor (CAR) T-cell therapies. While a discussion of this modality is beyond the scope of this article, the targets being explored for this approach include CD19, CD38, CD40, CD44, CD47, ICAM1, NCAM1, CD74, CD81, CD86, CD200, IGF1R, CD307, CD317, SLAM7, PD-L1, CD138, and B-cell membrane antigen (BCMA).[24] Of note, BCMA is also the target of a novel bispecific antibody manufactured by Janssen that will engage T cells.

Histone Deacetylase Inhibitors

Although MM cells are initially susceptible to PI therapy, the aggresome pathway is also responsible for the destruction of misfolded proteins. Dual-pathway inhibition has demonstrated preclinical synergy, perhaps due to the modulation of acetylation of histones and oncogenesis-related proteins (eg, p53, αtubulin, HIF-1α, hsp90).[25,26] Two oral pan-histone deacetylase inhibitors (HDACs) have completed large phase III studies. The VANTAGE study comparing bortezomib and dexamethasone with either vorinostat or placebo showed only a disappointing 0.8-month improvement in PFS over the control arm.[27]

More recently, the PANORAMA 1 study with bortezomib (intravenous) and dexamethasone with either panobinostat or placebo showed a 3.9-month improvement in PFS and an improvement in CR rates from 15.7% to 27.6%. However, the rates of grade 3 or 4 diarrhea increased from 8% to 26%.[28] Panobinostat was approved by the FDA on February 23, 2015, in combination with bortezomib and dexamethasone in patients who have received at least 2 prior regimens (including bortezomib and an IMiD). Importantly, PANORAMA 2 demonstrated that the addition of panobinostat to bortezomib in bortezomib-refractory patients resulted in a response rate (RR) of 34.5% and PFS of 5.4 months.[29] In addition, when panobinostat is added to lenalidomide and dexamethasone, the ORR was 38% with a median PFS of 6.5 months, and more impressively, in the 22 lenalidomide-refractory patients, the ORR was 28% with a median PFS of 6.5 months.[30]

Ricolinostat (ACY-1215) is an oral selective HDAC6 inhibitor that has shown promising preclinical synergy with lenalidomide and pomalidomide.[31] While tolerated as a monotherapy, it is currently being evaluated in the context of combination therapy. In combination with lenalidomide, it has demonstrated an ORR of 64%.[32] In an ongoing phase I/II study of patients (median 4 lines of prior therapy), combination ricolinostat, pomalidomide, and dexamethasone demonstrated an ORR of 29%, including 3 VGPR.[33] Additionally, ricolinostat combined with bortezomib and dexamethasone produced an ORR of 32% in 48 heavily pretreated patients (5 median lines of therapy).[34] Currently available data on combination therapy with HDAC inhibitors are summarized in **Table 4.**

Non-mAb Novel Agents

There are additional non-mAb novel agents with activity in development (**Table 5**). Filanesib (ARRY-520) is a highly selective allosteric inhibitor of kinesin spindle protein (KSP), which is a microtubule motor protein. KSP inhibition prevents formation of a bipolar spindle, leading to apoptosis particularly in Mcl-1–dependent MM cells.[35] The main toxicity is neutropenia, which is manageable with prophylactic granulocyte-colony stimulating factor (GCSF). As a single agent, the ORR is 16% and the median PFS is 3.7 months (n=32), which is comparable to the 15% and 3.4 months with the addition of dexamethasone to filanesib (n=55), albeit this was in a much more heavily pretreated, IMiD- and PI-refractory population.

Of particular interest, though, is the potential biomarker alpha 1-acid glycoprotein (AAG), an acute-phase protein used to monitor inflammatory conditions. AAG binds to filanesib, such that high AAG concentrations result in increased IC50 for filanesib in vitro. Lower AAG levels seem to correlate with clinical outcomes, as such patients had an ORR without dexamethasone of 24% and a median PFS of 5.1 months. Adverse events (AEs) were primarily hematologic.[36] Although linking drug approval to a novel biomarker is not an easy path forward, to date, there are no biomarkers predictive of response in MM, and KSP inhibition is a novel mechanism of action in MM.

TABLE 3. Summary of Efficacy of Monoclonal Antibodies (at recommended phase II/III dosages)

Treatment	N	Eligibiligy (% Refractory)	Response Rate	PFS (mo)	DOR (mo)	OS (mo)
Daratumumab[8]	106	88% / 90% / 48% / 82% (% Refr: Len / Bor / Car / Bor + Len)	29%	3.7	7.4	17.5
Daratumumab + Len + Dex[10]	286	18% PI Refr, none Len Refr	93%	NE	NE	NE
Daratumumab + Bor + Dex[9]	251	32.9% IMiD Refr	82.9%	NE	NE	NE
Daratumumab + Pom + Dex[11]	77	88% / 65% / 30% / 65% (% Refr: Len / Bor / Car / IMiD + PI)	58.50%	NR	NR	NR
Isatuximab[12]	74	86% / 80% / 57% / 88% (% Refr: Len / Bor / Car / IMiD + PI)	24%	NR	6.6	NR
Isatuximab + Len + Dex[13]	24	85% IMiD Refr	64.50%	5.8	NR	NR
Elotuzumab + Len + Dex[16]	321	22% / 9% (% Refr: Bor / Thal)	79%	19.4	20.7	NR
Elotuzumab + Bor + Dex[17]	77	51% PI Refr	65%	9.9	NR	NR
Indatuximab ravtansine + Len + Dex[20]	45	30% Len Refr	78%	NR	NR	NR
Pembrolizumab + Len + Dex[22]	17	76% Len Refr / 30% IMiD + PI Refr	76%	NR	9.7	NR
Pembrolizumab + Pom + Dex[23]	24	Yes (4), No (3) Missing (1)	50%	NR	NR	NR

Bor indicates bortezomib; Car, carfilzomib; Dex, dexamethasone; DOR, duration of response; IMiD, immunomodulatory drug; mo, months; Len, lenalidomide; NE, not estimable; NR, not reported; PFS, progression-free survival; OS, overall survival; PI, proteasome inhibitor; Pom, pomalidomide; Refr, refractory; Thal, thalidomide.

Filanesib was granted orphan drug approval by the FDA in May 2014.

Filanesib has also been explored in combination therapy. A phase I study with bortezomib, filanesib, and dexamethasone in 55 patients (median 3 prior lines of therapy) produced an ORR of 20%, and was 29% for 14 PI-refractory patients receiving therapeutic doses of filanesib at ≥1.25 mg/m^2.[36] The responses ranged from 3.8 months to more than 24.6 months.[37] In a phase II study, carfilzomib combined with filanesib or placebo (randomized in 2:1 fashion) demonstrated a 30% ORR in the combination arm versus 10% with carfilzomib alone.[38]

Another promising target is the phosphatidylinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) signaling pathway, which is activated in MM. In preclinical models, inhibition of this pathway leads to apoptosis.[39] The oral, reversible, pan-AKT3 inhibitor afuresertib has been examined as a single agent in MM, demonstrating a favorable safety and pharmacokinetic profile, but on producing a RR of only 9%. The main toxicities were gastrointestinal (GI).[40] Combination therapy with afuresertib, bortezomib, and dexamethasone may be more efficacious. This was demonstrated by a trial of 67 patients with relapsed MM where this combination produced an ORR of 61%.[41] The pan-PIM kinase inhibitor LGH 447 has demonstrated an ORR of 10.5% in a phase I trial of heavily pretreated patients. While the single-agent responses for afuresertib and LGH 447 are modest, their use in combination therapy may be promising.[42]

Signal transduction inhibitors have been valuable therapeutic targets in other B-cell malignancies, but none have been approved for MM to date. Ibrutinib, an oral inhibitor of Bruton's tyrosine kinase (BTK), is FDA-approved for treatment of chronic lymphocytic leukemia (CLL), mantle cell lymphoma, and Waldenström's macroglobulinemia. In patients with MM, it produces a modest single-agent activity. In a phase II trial of ibrutinib, a cohort receiving ibrutinib 840 mg daily and dexamethasone experienced an ORR of 5% but a CBR of 25%.[43] However, when combined with carfilzomib in a phase I trial of 40 patients, an ORR of 58% was achieved.[44]

Another related target is BCL-2, an antiapoptosis protein. Venetoclax is a potent, selective inhibitor of BCL-2 with efficacy in CLL and has been investigated as a single agent in MM. In a phase I study of 43 heavily pretreated patients (median 5 prior therapies), an ORR of 12% was observed. However, in patients with t(11;14) translocation, the ORR was 24%.[45]

TABLE 4. Summary of Combination Therapy with Histone Deacetylase Inhibitors

Regimen	Phase	N	Outcome
Panobinostat vs Placebo + Bor + Dex[28]	3	768	ORR: 60.7% vs 54.6% (*P* = .09) OS: 33.6 vs 30.4 mo (*P* = .26) PFS: 12.0 vs 8.1 mo (*P* < .0001)
Panobinostat + Len + Dex[30]	2	27	ORR:41 %; CBR: 74% Len Refr: ORR: 36%, CBR: 64% (n = 22)
Panobinostat + Car[52]	1/2	45	ORR: 67%; CBR: 79% Bor Refr: ORR: 67% (n = 15) IMiD Refr: 75% (n= 12)
Vorinostat vs Placebo + Bor[27]	3	637	ORR: 54% vs 41% (*P* < .0001) PFS: 7.6 vs 6.8 mo (*P* < .01) OS: no difference
Ricolinostat + Bor[34]	1	16	ORR: 25%; CBR: 60%
Ricolinostat + Len + Dex[32]	1	16	ORR: 64%; CBR: 100%
Ricolinostat + Pom + Dex[33]	1/2	22	ORR: 29%; CBR 50%

Bor indicates bortezomib; CBR, clinical benefit rate; Dex, dexamethasone; DOR, duration of response; IMiD, immunomodulatory drug; Len, lenalidomide; mo, months; ORR, overall response rate; OS, overall survival; PI, proteasome inhibitor; Pom, pomalidomide; PFS, progression-free survival; Refr, refractory.

Another novel target is cyclin-dependent kinases (CDKs), which regulate cell cycle progression. In MM, (Ig)H translocation can cause dysregulation of CDKs.[46] Dinaciclib, a small molecular inhibitor of CDKs, has shown promise as a therapeutic agent in CLL and some solid tumors. It has been investigated as a single agent in a phase I/II trial of 27 patients, producing an ORR of 11% and CBR of 19%.[46] The most common AEs were hematologic (leukopenia and thrombocytopenia), GI-related, and fatigue.[47]

The nuclear protein exportin 1 (XP01) is a promising target in oncology. Preclinically, inhibition of XPO1 induced MM cytotoxicity and impaired osteoclastogenesis. Additionally, it may resensitize cells to bortezomib via blockade of NF-kB.[48] Selinexor, a reversible XPO1 inhibitor, has been investigated in a phase I dose-escalation trial that included 29 patients with MM. A dosage of >65 mg produced 1 CR (3%), 6 partial responses (21%), and 6 minor responses (21%), giving an ORR of 24%. Selinexor was generally well tolerated, with primarily GI AEs reported.[49] The addition of dexamethasone to selinexor was investigated in a phase I study of 28 patients with refractory MM with a median of 6 prior regimens. In 10 patients receiving selinexor 45 mg/m^2 and dexamethasone 20 mg, ORR was 60% (including 1 stringent CR and a CBR of 80%.[50] This agent also has potential in heavily pretreated patients. An early press release of an ongoing phase IIb trial of selinexor reported an encouraging ORR of 20.8% in 48 quad-refractory patients and an ORR of 20% in 30 penta-refractory patients.[51]

Summary and Future Directions

For many decades, the treatment of MM was dependent upon only 2 classes of drugs: corticosteroids and conventional cytotoxics. In the past 10 years, the approval of PIs and IMiDs have made substantial contributions towards improving the outcomes of patients with MM, as evidenced by the fact that deletion of 13q and t(4;14) are no longer considered high risk. The approval of 4 new drugs in 2015, including 3 agents in novel classes (ie, HDAC and mAb), is truly remarkable for any cancer, let alone a relatively uncommon one such as MM. Although the single-agent activity (ie, ORR and PFS) of these agents is modest, rational combination therapies based on synergy and lack of overlapping toxicity is very encouraging. The true impact of these agents in groups of patients that remain at increased risk of death (eg, high molecular risk, frail/elderly, renal failure) is yet to be fully determined.

From a biologic perspective, improving upon this remarkable progress will require a better understanding of myelomagenesis, the mechanisms of resistance to current agents, and exploration of potential anti-MM targets. Similarly, future clinical trials will need to focus on biologically guided/risk-adapted therapy, continue to rapidly transition from the bench to bedside those agents with novel targets, and finally, use minimal residual disease to identify promising agents/combinations to help accelerate drug approval. As outlined in this article, many promising targets hold the potential to build upon the already impressive progress made in the last decade.

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Author disclosures: Dr. Tremblay has no disclosures. Dr. Chari

has served as a consultant or is on a paid advisory board for Array Biopharma, Celgene, Millennium/Takeda, and Novartis, and has received grants from Array Biopharma, Celgene, Millennium/Takeda, Novartis, Onyx, GlaxoSmithKline, and Pharmacyclics.
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TABLE 5. Summary of Non-Monoclonal Antibody Studies in Development

Regimen	N	Eligibiligy	ORR	PFS (mo)	DOR (mo)	OS (mo)
Single Agent						
Filanesib	32	75% IMiD Refr,	16%	3.7	8.6	19
in low AAG[36]	21	53% PI Refr	24%	5.3	8.6	23.3
Filanesib + Dex	55	100% IMiD Refr,	15%	3.4	5.1	10.5
in low AAG[36]	36	98% PI Refr	19%	5.1	5.1	10.8
Afuresertib[40]	34	97% IMiD Exp, 88% PI Exp	9%	NR	NR	NR
LGH 447[42]	59	NR	11%	NR	5.8	NR
Ibrutinib + Dex[43]	20	44% IMiD + PI Refr	5%	NR	NR	NR
Venetoclax[45]	48	77% Len Refr, 67% Bor Refr	12%	NR	NR	NR
Dinaciclib[47]	27	70% Len Exp, 89% Bor Exp	11%	3.5	7.7	18.8
Selinexor[49]	29	NR	24%	NR	NR	NR
Selinexor + Dex[50]	10	All PI and IMiD Exp	60%	NR	29	NR
Selinexor + Dex[51*]	30	All Len, Pom, Bor, Car, Dara Refr	20%	NR	NR	NR
Combination						
Filanesib + Bor + Dex[53]	55	All PI and IMiD Exp	20%	NR	NR	NR
Filanesib + Car + Dex[38]	30	67% IMiD and Bor Refr	30%	NR	NR	NR
Afuresertib + Bor + Dex[41]	23	96% IMiD Exp, 88% PI Exp	61%	NR	NR	NR
Ibrutinib + Car + Dex[44]	36	73% / 73% / 58%, Bor / Len / IMiD + PI Refr	58%	NR	NR	NR
Selinexor + Car + Dex[54]	8	50% Car Refr	75%	NR	NR	NR

*Based on press release of preliminary results.
AAG indicates alpha 1-acid glycoprotein; Bor, bortezomib; Car, carfilzomib; Dara, daratumumab; Dex, dexamethasone; DOR, duration of response; Exp, exposed; IMiD, immunomodulatory drug; Len, lenalidomide; mo, months; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; Pom, pomalidomide; Refr, refractory; Sens, sensitive.

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