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REVIEW

New drugs and novel mechanisms of action in multiple myeloma in 2013: a report from the International Myeloma Working Group (IMWG)

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Treatment in medical oncology is gradually shifting from the use of nonspecific chemotherapeutic agents toward an era of novel targeted therapy in which drugs and their combinations target specific aspects of the biology of tumor cells. Multiple myeloma (MM) has become one of the best examples in this regard, reflected in the identification of new pathogenic mechanisms, together with the development of novel drugs that are being explored from the preclinical setting to the early phases of clinical development. We review the biological rationale for the use of the most important new agents for treating MM and summarize their clinical activity in an increasingly busy field. First, we discuss data from already approved and active agents (including second- and third-generation proteasome inhibitors (PIs), immunomodulatory agents and alkylators). Next, we focus on agents with novel mechanisms of action, such as monoclonal antibodies (MoAbs), cell cycle-specific drugs, deacetylase inhibitors, agents acting on the unfolded protein response, signaling transduction pathway inhibitors and kinase inhibitors. Among this plethora of new agents or mechanisms, some are specially promising: anti-CD38 MoAb, such as daratumumab, are the first antibodies with clinical activity as single agents in MM. Moreover, the kinesin spindle protein inhibitor Arry-520 is effective in monotherapy as well as in combination with dexamethasone in heavily pretreated patients. Immunotherapy against MM is also being explored, and probably the most attractive example of this approach is the combination of the anti-CS1 MoAb elotuzumab with lenalidomide and dexamethasone, which has produced exciting results in the relapsed/refractory setting.

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INTRODUCTION

Therapeutics in medical oncology have undergone a marked evolution in recent decades, moving from the chemotherapeutic era in which the drugs were nonspecifically directed against highly proliferative cells toward an era of novel targeted therapy in which drugs and their combinations target specific mechanisms of tumor cell growth and survival.[1] Some targeted agents have changed the treatment paradigm in solid and hematological tumors, such as anti-erb2 monoclonal antibodies (MoAbs) in breast cancer, tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib and ponatinib) in chronic myeloid leukemia, anti-CD20 MoAb in non-Hodgkin lymphoma, anti-vascular endothelial growth factor receptor MoAb in colon cancer and anti-BRAF in melanoma.

Multiple myeloma (MM) has followed a similar pattern in recent years; alkylators such as melphalan along with steroids have been

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the standard agents for the care of these patients for over 30 years. However, in the last decade, several agents (PIs and immunomodulatory drugs (IMIDs)) with singular mechanisms of action have been discovered, developed and approved.[2,3] These advances have resulted in a clear improvement in the outcome of MM patients,[4] but despite this MM remains incurable and patients who become refractory or ineligible to receive bortezomib and IMIDs have a dismal prognosis.[5] This situation along with the pattern of subsequent responses/relapses that characterize the evolution of MM highlights the need for novel drugs. The investigation and discovery of these new drugs and, in particular, their use in combinations should be based on a thorough knowledge and understanding of the pathogenesis of cancer,[6] specifically that of MM.[7–9]

MM is probably one of the malignant diseases for which more active research into novel antitumoral agents has been carried out. However, only a few agents have successfully completed the early phases of clinical development. Moreover, the large number of novel agents under investigation has created some confusion in the clinical arena, whereby there is no consensus about which of them have clinically relevant antitumor activity. The purpose of this manuscript is to review and shed light on the rationale for the use and the clinical results obtained to date for the most promising novel agents currently under investigation. These agents have been divided into two main groups: first, those agents derived from the already approved and active agents (such as second- and third-generation PIs, immunomodulatory agents and alkylators); and second (the main focus of this review), drugs with novel mechanisms of action, such as MoAbs, agents acting on the cell cycle, deacetylase inhibitors (DACis), agents acting on the unfolded protein response (UPR), signaling pathway inhibitors and kinase inhibitors. Figure 1 illustrates a schematic representation of the main drugs that have been tested in MM and the mechanisms they target.

For ease of reading, the mechanism of action is highlighted in italics and the clinical results are detailed in the tables, with only the most relevant aspects discussed in the text. Once the mechanistic and clinical data has been presented, the discussion will analyze the future of this field of novel agents, emphasizing which of them seem more promising and how they should be developed.

AGENTS DERIVED FROM THOSE WITH PROVEN CLINICAL EFFICACY IN MM

Novel PIs

One of the major advances in the treatment of MM patients in recent years has been the discovery of the catalytic activity of proteasomes,[10] along with the synthesis of bortezomib (PS-341),[11] the first-in-class PI, which has demonstrated striking clinical[12–14] efficacy in MM. The anti-MM activity of the inhibition of this pathway is the consequence of several biological effects,[15–17] among which the following are highlighted: (1) the accumulation of cyclin or cyclin-dependent kinase (CDK) inhibitors and tumor suppressor proteins, (2) the inhibition of the clearance of misfolded proteins (inducing endoplasmic reticulum, stress and activation of the UPR),[18,19] and (3) the blockade of the nuclear factor-κB (NF-κB) transcription factor pathway through the prevention of inhibitor of NF-κB) degradation after its polyubiquitination by inhibitor of NF-κB kinase.[20]

After bortezomib, several other PIs have been synthesized and are at different stages of clinical development. Some of them, as is the case of ixazomib (MLN-9708), are also boronate peptides; however, other structural families have been developed: the epoxyketones, including carfilzomib (PR-171) and oprozomib (ONX-0912 or PR-047), and the salinosporamides such as marizomib (NPI-0052). They differ in their biological properties as they target different catalytic subunits of the proteasome. Boronic acid containing PIs (bortezomib and ixazomib) inhibit both the chymotrypsin-like and the caspase-like activities of the proteasome, while carfilzomib and oprozomib are selective of chymotrypsin-like activity. Marizomib, by contrast, has a broader pattern of inhibition, as it targets the three catalytic

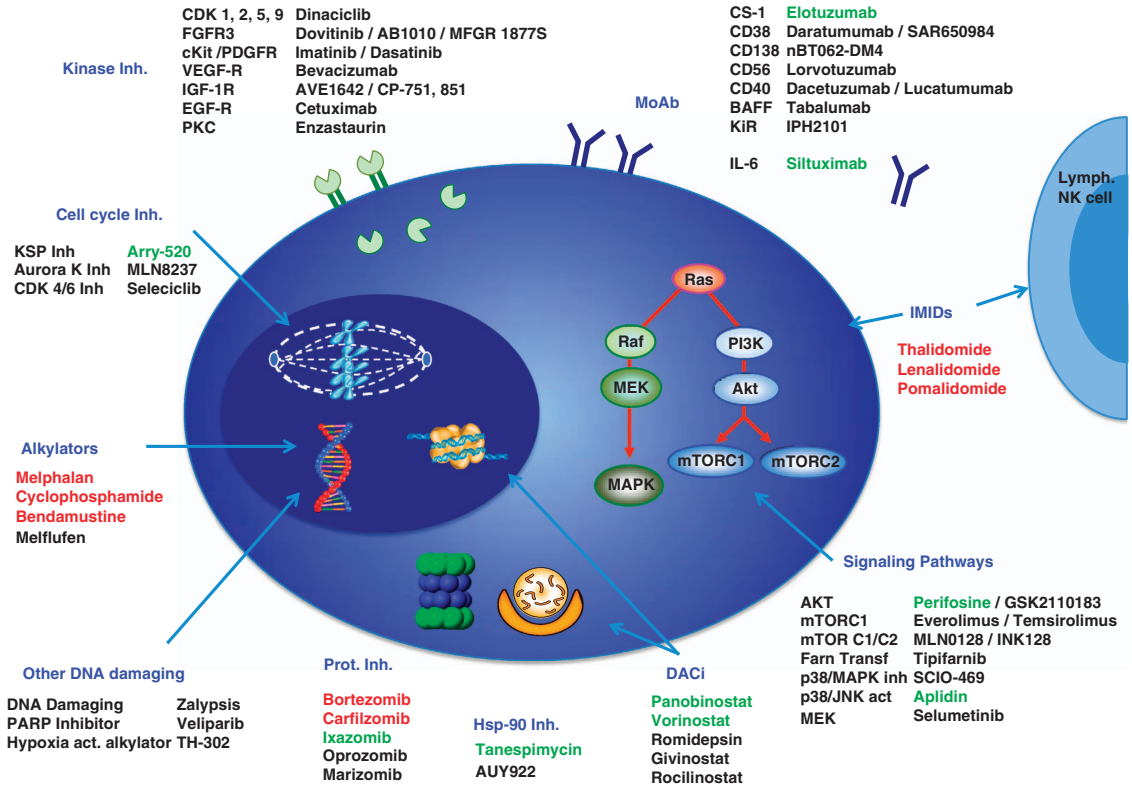

Figure 1. Schematic representation of the main targets in MM plasma cells and the drugs tested against them. Approved drugs are presented in red and drugs that have reached phase III development are presented in green.

Table 1. Summary of the most relevant clinical trials with novel proteasome inhibitors in monotherapy in relapsed/refractory MM

Drug	Trial	Phase	n	Prior lines	Dose	Schedule	ORR (⩾ PR)	CBR (⩾ MR)	PFS (months)	Reference
Carfilzomib (PR-171)										
	PX-171-001	1	10 MM	—	MTD: 15 mg/m^2	1–5/14d	10%	20%	—	O'Connor *et al.*[175]
	PX-171–002	1	28	—	Recommended dose: 20 mg/m^2 initially 27 mg/m^2 from C1D8	1–2, 8–9, 15–16/28d	19%	27%	—	Alsina *et al.*[176]
	PX-171-003A0	2	46	5 (2–16)	20 mg/m^2	1–2, 8–9, 15–16/28d	17%	24%	3.5	Jagannath *et al.*[177]
	PX-171-003A1	2	266	5 (1–20)	20 mg/m^2 in C1 27 mg/m^2 from C2	1–2, 8–9, 15–16/28d	24%	37%	3.7	Siegel and colleagues[178]
	PX-171-004	2	129 Btz-naïve patients	2 (1–4)	C-1: 20 mg/m^2 C-2: 20 mg/m^2 in C1 27 mg/m^2 from C2	1–2, 8–9, 15–16/28d	C-1: 42% C-2: 52%	C-1: 59% C-2: 64%	C-1: 8.2 C-2: NR	Vij *et al.*[21]
			35 Btz-treated patients	3 (1–13)	20 mg/m^2	1–2, 8–9, 15–16/28d	17%	31%	4.6	Vij *et al.*[23]
	PX-171-005	2	50 (Renal impairment)	5 (1–15)	15 mg/m^2 in C1 20 mg/m^2 in C2 27 mg/m^2 from C3	1–2, 8–9, 15–16/28d	26%	32%	—	Badros *et al.*[25]
Ixazomib (MLN-9708)										
	C16004	1	60	6 (2–18)	MTD: 2.97 mg/m^2	1, 8, 15/28d	15%	17%	—	Kumar *et al.*[43]
	C16003	1	57	4 (1–28)	MTD: 2 mg/m^2	1, 4, 8, 11/21d	13%	15%	—	Lonial *et al.*[44]
Marizomib (NPI-0052)										
	NPI-0052-101 NPI-0052-102	1	34	6	MTD: 0.4 mg/m^2 in 1 h inf. & 0.5 mg/m^2 in 2 h inf	1, 4, 8, 11/21d	14%	14%	—	Richardson *et al.*[47]

Abbreviations: Btz, bortezomib; CBR, clinical benefit rate; MM, multiple myeloma; MR, minimal response; MTD, maximum tolerated dose; NR, not reached; ORR, overall response rate; PFS, progression-free survival.

activities. The other major difference is the reversibility of the inhibition and, in this regard, carfilzomib, oprozomib and marizomib, unlike bortezomib and ixazomib, induce irreversible inhibition. Finally, some of these novel agents (such as ixazomib or oprozomib) are orally bioavailable. Table 1 summarizes the clinical data of these novel PIs used in monotherapy.

Carfilzomib is Food and Drug Administration approved for the treatment of MM patients who have received at least two previous therapies, including bortezomib and an immunomodulatory agent, and are refractory to their last therapy. As a monotherapy, this drug induced an overall response rate (ORR) of 52% in bortezomib-naive patients,[21] and ~20% of patients refractory to bortezomib responded to carfilzomib.[22,23] On the basis of this, a phase 3 randomized trial (Focus) has compared carfilzomib with best supportive care in MM patients for whom no other therapeutic option is available.

With respect to safety, the most frequent grade 3 adverse events were hematological with very mild peripheral neuropathy.[24] However, other non-hematologic toxicities, albeit rare, have emerged, including cardiopulmonary or renal toxicity. Nevertheless, carfilzomib was also safe in patients with renal impairment in a trial specifically designed to evaluate this issue.[25]

Several drug combinations are currently being explored, including that of carfilzomib with lenalidomide and dexamethasone, both in relapsed refractory patients[26] (basis for the phase 3 Aspire trial[27]) and in newly diagnosed patients.[28,29] Also in newly diagnosed patients, carfilzomib + thalidomide + dexamethasone has been tested,[30] even with the addition of cyclophosphamide.[31] Moreover, carfilzomib plus steroids have also been combined in transplant-ineligible newly diagnosed patients, with cyclophosphamide[32] and with melphalan.[33] Other innovative combinations are being explored with novel drugs such as histone DACis,[34–36] pomalidomide[37] and the kinase spindle protein inhibitor Arry-520[38,39] in relapsed and refractory patients.

The second-generation compound oprozomib (ONX-0912; previously PR-047),[40] is a structural analog of carfilzomib that is orally bioavailable. Oprozomib capsules administered in split doses demonstrated clinical activity in a phase 1 trial in patients with hematologic malignancies (MM and chronic lymphocytic leukemia).[41] In order to improve gastrointestinal tolerability, a once-daily administered tablet was introduced in this phase 1b/2 trial with 16 MM and 5 Waldenström's macroglobulinemia patients already enrolled with a good safety profile and promising preliminary response data.[42]

Ixazomib (MLN-9708) is the first orally bioavailable PI evaluated to date in clinical studies for the treatment of MM. Two studies are exploring its activity in monotherapy in relapsed/refractory MM patients previously exposed to PIs still with very preliminary results (Table 1).[43,44] With respect to toxicity, the most remarkable finding was the low rates of significant peripheral neuropathy, although treatment-related rash has been noted. Ixazomib is also being examined in combination with melphalan and prednisone,[45] and with lenalidomide and low-dose dexamethasone,[46] in newly diagnosed patients.

Marizomib (NPI-0052) is still in the early stages of development, showing minimal peripheral neuropathy with 15–20% ORR in heavily pretreated patients (Table 1).[47]

Novel IMIDs

Since the discovery of the anti-MM activity of thalidomide,[48,49] several thalidomide analogs (lenalidomide-CC-5013 or pomalidomide-CC-4047) have been developed. Drugs in this group are called IMIDs, owing to their action on the immune system. Recent studies suggest that IMIDs exert their function by binding to cereblon, a molecule that forms an E3 ubiquitin ligase complex with damaged DNA-binding protein 1 and Cul4A.[50] In fact, the absence of cereblon is associated with resistance to IMIDs,[51,52] and the teratogenic

potential of this family of drugs has also been linked to the binding to this protein.[50] *Although their precise mode of action is not well established, three mechanisms have been implicated in their antimyeloma activity: tumoricidal, immunomodulatory and antiangiogenic. The tumoricidal activity of lenalidomide may be mediated by several mechanisms: (1) down regulation of IRF4 levels*[53,54] *that lead to an initial G1 cell cycle arrest, decreased cell proliferation and cell death associated with a decrease in MYC levels and the induction of several CDK inhibitors (p15, p16, p21 and p27);*[55,56] *(2) induction of p21 WAF-1 expression through an LSD1-mediated epigenetic mechanism;*[57] *and (3) disruption of the interaction between tumor cells and their microenvironment.*[55,58] *The immunomodulatory effect is mediated through the augmentation of natural killer cytotoxicity,*[59,60] *the inhibition of regulatory T cells*[61] *or the restoration of the immune synapse formation.*[62]

Thalidomide[48,49] and lenalidomide[63–65] were approved in the last decade for the treatment of MM patients. However, pomalidomide has recently emerged as a very potent IMID, both alone and in several combinations (Table 2). In this regard, similar to lenalidomide and thalidomide the addition of dexamethasone induces synergy, improving the response rate and the progression-free survival (PFS),[66] and this combination in the initial phase 2 study by Lacy *et al.*[67] induced a 62% response rate with a PFS of 13 months (Table 2), similar to that previously obtained with lenalidomide + dexamethasone.[63–65] This is relevant considering that in this trial, 62% of the patients had been previously exposed to IMIDs.

Several trials have explored the activity of pomalidomide + dexamethasone in lenalidomide-refractory patients[68,69] or in lenalidomide- and bortezomib-refractory patients.[69–71] In these trials, approximately one-third of patients achieved at least partial response (PR) and the PFS ranged from 3.3 to 7.7 months (Table 2).

Regarding the optimal dose and schedule of administration (2 vs 4 mg or 21/28 vs 28/28 days), several schedules have been used and compared (see Table 2).[69–71] On the basis of these, although other possibilities may be acceptable, the

Table 2. Summary of the most relevant clinical trials with pomalidomide in relapsed MM patients

Phase	*± Dex or other comb.*	n	*Prior lines*	*Dose*	*Schedule*	*ORR ⩾PR*	*CBR ⩾MR*	*PFS months*	*OS months*	*Reference*
1	No	24	3 (1–6)	MTD: 2 mg	1–28 (daily)	54%	71%	9.7	22.5	Schey *et al.*[179]
1	No	20	4 (1–7)	MTD: 5 mg	1–28 (Every other day)	50%	55%	10.5	33	Streetly *et al.*[180]
1b	Dex[a]	38[b]	6 (2–17)	MTD: 4 mg	1–21	Pom: 13% + Dex: 21%	± Dex: 42%	4.6	18.3	Richardson *et al.*[66]
2	No	108[b]	5 (1–13)	4 mg	1–21	15%	31%	2.6	13.6	Richardson *et al.*[181] and Siegel *et al.*[182]
	Dex	113[b]		4 mg	1–21	34%	45%	4.6	16.5	
2	Dex	60	2 (All ⩽3)	2 mg	1–28	65%	—	13	40	Lacy *et al.*[67,69]
2	Dex	34[c]	4 (1–7 +)	2 mg	1–28	32%	47%	5	33	Lacy *et al.*[68,69]
2	Dex	60[c]	2 (All ⩽3)	4 mg	1–28	38%	—	7.7	92%[d]	Lacy *et al.*[69]
2	Dex	120[c]	—	4 mg	1–21	21%	—	4.3	74%[d]	Lacy *et al.*[69]
2	Dex	35[e]	6 (3–9)	2 mg	1–28	26%	49%	6.4	16	Lacy *et al.*[69,70]
	Dex	35[e]	6 (2–11)	4 mg	1–28	29%	43%	3.3	9.2	
2	Dex	43[e]	5 (1–13)	4 mg	1–21	35%	—	5.4	14.9	Leleu *et al.*[71]
	Dex	41[e]		4 mg	1–28	34%	—	3.7	14.8	
3	Dex	302[c]	5 (1–17)	4 mg	1–21	31%	—	4	NR	San Miguel *et al.*[72]
2	Clarithromycin/Dex	100	5 (3–15)	4 mg	1–21	54%	59%	8.2	NR	Mark *et al.*[183]
1/2	Carfilzomib/Dex	32[c]	6 (2–15)[f]	4 mg	1–21	33%	56%	70%[d,f]	—	Shah *et al.*[37]
2	PLD/Dex	27	5 (1–18)	MTD: 3 mg	1–21	22%	39%	—	—	Hilger *et al.*[184]
1	Bortezomib/Dex	21[c]	1–4	MTD: 4 mg	1–21	72%	—	—	—	Richardson *et al.*[185]
1	Cyclophosphamide/ Dex	10[c]	5 (3–10)	4 mg	1–21	40%	50%	—	—	Baz *et al.*[186]
1/2	Cyclophosphamide/ prednisone	55	3 (1–3)	MTD: 2.5 mg	—	51%	—	10.4	—	Larocca *et al.*[187]

Abbreviations: CBR, clinical benefit rate; Dex, low-dose dexamethasone (40 mg weekly) except for the trial with cyclophosphamide + dexamethasone that are high doses; MM, multiple myeloma; MR, minimal response; MTD, maximum tolerated dose; NR, not reached; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PR, partial response. [a]Dex added in 22 non-responding patients. [b]Previous lenalidomide and bortezomib. [c]Lenalidomide-refractory patients. [d]OS/PFS at 6 months. [e]Lenalidomide and bortezomib refractory. [f]Corresponds to the 12 patients enrolled in the phase 1.

dose of 4 mg on days 1–21 followed by a 1-week rest period has been chosen as the standard for the subsequent randomized trials.

All these studies were the bases for the phase 3 trial (MM-003) in which MM patients that had failed both lenalidomide and bortezomib, and were refractory to their last therapy, were randomized to receive pomalidomide + low-dose dexamethasone versus high-dose dexamethasone. There was a significant advantage for the pomalidomide arm over dexamethasone in terms of ORR (31% vs 10%), PFS (4 vs 1.9 months) and OS (not reached vs 7.8 months).[72] Moreover, pomalidomide has been tested in genomically defined high-risk relapsed MM patients with some activity in this setting.[73]

The safety profile of this agent is quite similar to that of lenalidomide, with hematological side effects being the main source of toxicity, with low rates of deep venous thrombosis, especially when using prophylactic measures.

As with carfilzomib, several trials in relapsed/refractory patients are already testing the activity of pomalidomide and dexamethasone in combination with several agents (Table 2).

Novel alkylators

Bendamustine has a quite unusual mechanism of action, as it combines an alkylator structure with a purine analog ring. In combination with prednisone, it has already been approved in Europe for the treatment of newly diagnosed MM patients who are not candidates for autologous stem cell transplantation and who are not eligible to receive PIs or thalidomide due to pre-existing neuropathy. This was based on a phase III trial that compared bendamustine + prednisone with melphalan + prednisone in newly diagnosed patients, and showed a benefit especially in terms of time to progression (14 vs 10 months).[74]

Several pilot phase II studies have evaluated the activity of this agent in different combinations in relapsed refractory MM: with bortezomib (50–75% ORR in combination with dexamethasone),[75–79] thalidomide (26–86% ORR)[80–82] or, more recently, lenalidomide (52–76% ORR with 24–33% very good PR).[83,84] Results are quite variable, reflecting the heterogeneity of the patient population included in the different trials (mainly with regard to previous lines of therapy). Another novel alkylator undergoing with promising preclinical testing is melphalan–flufenamide, a novel dipeptide prodrug of melphalan. *It consists of melphalan conjugated to an amino acid, phenylalanine, creating a dipeptide with higher antimyeloma potency than the parental drug based on a preferential delivery of melphalan to tumor cells due to the intracellular cleavage of melphalan–flufenamide by some peptidases overexpressed in malignant cells.*[85] *Another alkylator with the peculiarity of being activated when in an hypoxic niche, TH-302, has been developed and tested but owing to their particular mechanism, the clinical data is included in the last chapter of this review.*

AGENTS WITH NOVEL MECHANISMS OF ACTION

Immunotherapy/MoAbs

Activating the immune system against MM is one of the areas in which a more extensive investigation is being made. One of the agents included in this family are MoAbs that are one of the paradigms of targeted therapy, as they are specifically directed against antigens present in tumor cells. Once bound, they induce their antitumoral effect through several mechanisms:[86,87] *(1) direct cytotoxicity, which can be due to the direct induction of apoptosis or to the conjugation with radioisotopes or toxins; (2) to the enhancement of the immune function through antigen-dependent cellular cytotoxicity or complement-dependent*

Table 3. Summary of the most relevant clinical trials with monoclonal antibodies, alone and in combination with other agents in relapsed MM

Drug	*Target*	*Comb*	*Phase*	n	*Prior lines*	*ORR (⩾PR)*	*CBR (⩾MR)*	*Reference*
Elotuzumab	CS1	—	1	35	4 (2–10)	0%	0%	Zonder *et al.*[88]
		+ Len–Dex	1	29	3 (1–10)	82%	—	Lonial *et al.*[89]
		+ Len–Dex	2	73	55% ⩾2	84%	—	Richardson *et al.*[90,91]
		+ Bort–Dex	1	28	2 (1–3)	40%	60%	Jakubowiak *et al.*[188]
Daratumumab (HuMax-CD38, Ab005)	CD38	—	1	32	6 (2–12)	14% 42% in > 4 mg/kg	28% 66% in > 4 mg/kg	Plesner *et al.*[92,93]
nBT062-DM4	CD138	—	1	32	—	4%	52%	Jagannath *et al.*[95]
		—	1/2a	29	—	4%	4%	Heffner *et al.*[96]
Lorvotuzumab (IMGN901–huN901-DM1)	CD56	—	1	37 CD56+ patients	Most of them ⩾6	7%	18%	Chanan-Khan *et al.*[94]
		+ Len–Dex	1	44	2 (1–11)	59%	—	Berdeja *et al.*[189]
Dacetuzumab(SGN-40)	CD40	—	1	44	5 (2–14)	0%	0%	Hussein *et al.*[98]
		+ Len–Dex	1b	36	4 (2–14)	39%	81%	Agura *et al.*[190]
Lucatumumab	CD40	—	1	28	8 (2–17)	4%	4%	Bensinger *et al.*[97]
Tabalumab	BAFF	+ Bort ± Dex	1	48	3 (1–10)	46%	—	Raje *et al.*[99]
Siltuximab	IL6	+ Dex	2	49	4 (2–9)	19%	28%	Voorhes *et al.*[100]
		+ Bort–Dex	2	21Bort naive	2 (1–3)	57%	—	Rossi *et al.*[101]
IPH2101	KIR	—	1	32	2 (1–7)	0%	0%	Benson *et al.*[103]
		+ Len	1	13	4 (1–8)	31%	46%	Benson *et al.*[104]

Abbreviations: BAFF, B-cell activating factor; Bort, bortezomib; CBR, clinical benefit rate; Dex, dexamethasone; KIR, killer cell immunoglobulin-like receptor; Len, lenalidomide; MM, multiple myeloma; MR, minimal response; ORR, overall response rate; PR, partial response.

cytotoxicity. Rituximab (anti-CD20) was the first of these agents to be tested in MM, with discouraging results, as it was used as a debulking drug, whereas it might be more effective against immature CD20+ cells. Since then, several other MoAbs have been tested in MM (Table 3).[78,79]

Elotuzumab is the best evaluated of these agents in MM. It is directed against CS1, a glycoprotein that is highly specific to plasma cells, although it may also be expressed in natural killer and CD8+ T cells. Although the results in monotherapy were modest (with stable disease as best response),[88] the combination with lenalidomide and dexamethasone has given excellent results with >80% PR in relapsed patients and, what is more important, prolonged PFS (33 months in the last update).[89–91] *The proposed mechanism of action of the synergy is an immune-mediated mechanism: lenalidomide would prepare the natural killer and lymphoid cells by, among other mechanisms, changing the conformation of their cytoskeleton, to favor the immune recognition, and elotuzumab would modify the plasma cells to be more prone to be targeted by the immune cells.* A phase III registration-enabling trial in relapsed myeloma comparing lenalidomide + dexamethasone with lenalidomide + dexamethasone + elotuzumab has just been completed.

Table 4. Summary of the most relevant clinical trials with deacetylase inhibitors in MM

Drugs	*Phase*	n	*Previous lines*	*ORR (⩾PR)*	*CBR (⩾MR)*	*Response in refractory patients*[a]		*Reference*
						ORR (⩾ PR)	*CBR (⩾ MR)*	
Monotherapy								
Vorinostat	1	13		0%	10%	—	—	Richardson *et al.*[116]
Panobinostat	2	38	5	3%	5%	—	—	Wolf *et al.*[117]
Romidepsin	2	13	3 (2–4)	0%	0%	—	—	Niesvizky *et al.*[115]
Givinostat ± Dex	2	19	3 (1–8)	0%	0%	—	—	Galli *et al.*[114]
Rocilinostat	1/2	13	88%⩾3	0%	0%	—	—	Raje *et al.*[126]
+ Bort ± Dex								
Vorinostat + Bort ± Dex	1	23	7 (3–13)	43%	90%	38%	88%	Badros *et al.*[118]
Vorinostat + Bort ± Dex	1	34	4 (1–14)	27%	32%	14%	14%	Weber *et al.*[121]
Vorinostat + Bortezomib[b]	3	317	2 (1–3)	56%	71%	—	—	Dimopoulos *et al.*[123]
Panobinostat + Bort + Dex	1b	62	2 (1–10)	68%	82%	43%	71%	San Miguel *et al.*[120]
Romidepsin + Bort + Dex	1/2	25	2 (1–3)	60%	72%	—	—	Harrison *et al.*[119]
Quisinostat + Bort + Dex	1b	18	2 (1–3)	88%	—	—	—	Leleu *et al.*[122]
Vorinostat + Bort[b,c]	2	143 Bort refractory	4 (2–17)	18%	33%	18%	33%	Siegel *et al.*[124]
Panobinostat + Bort + Dex[b]	2	55 Bort refractory	4 (2–11)	35%	53%	35%	53%	Richardson *et al.*[125]
+ Len + Dex								
Vorinostat + Len + Dex	1	31	4 (1–10)	53%	70%	20%	30%	Richardson *et al.*[191]
Vorinostat + Len + Dex[d]	2	29 LD refractory	4 (2–13)	24%	51%	24%	51%	Richter *et al.*[192]
Panobinostat + Len + Dex	1b	46	2 (1–8)	57%	—	—	—	Mateos *et al.*[193]
Other combinations								
Vorinostat + PLD + Bort	1	32	2 (1–9)	65%	74%	45% In Bort refractory	64% In Bort refractory	Voorhees *et al.*[194]
Vorinostat + Len + Bort + Dex in RR	2	9 RVD refractory	5 (2–10)	44%	89%	44%	89%	Siegel *et al.*[195]
Vorinostat + Len + Bort + Dex in ND	1	30 New diagnosis	0	100%	100%	—	—	Kaufman *et al.*[196]
Panobinostat + Melphalan	1/2	25	4 (–17)	16%	60%	—	—	Berenson *et al.*[197]
Panobinostat + MPT	1/2	24	21% ⩾2	50%	—	—	—	Offidani *et al.*[198]
Panobinostat + Carfilzomib	1/1b	17	5 (2–15)	35%	41%	—	—	Shah *et al.*[35]
Panobinostat + Carfilzomib	1/2	10	3 (1–7)	60%	70%	—	—	Berdeja *et al.*[34]

Abbreviations: Bort, bortezomib; CBR, clinical benefit rate; DAC, deacetylase; Dex, dexamethasone; Len, lenalidomide; LD, lenalidomide and dexamethasone; MM, multiple myeloma; MPT, melphalan, thalidomide and prednisone; MR, minimal response; ND, newly diagnosed; ORR, overall response rate; PLD, pegylated liposomal doxorubicin; PR, partial response; RR, response rate; RVD, lenalidomide, bortezomib and dexamethasone. [a]Response in patients previously refractory to the drugs administered in combination with the DAC inhibitors (bortezomib or lenalidomide in their respective combinations). [b]Data obtained from the presentation at the ASH 2011 meeting. [c]Bort-refractory patients. [d]Lenalidomide- and dexamethasone-refractory patients.

CD38, CD138, CD56 and CD40 are other antigens of the plasma cells that have been targeted by MoAbs. Daratumumab is an anti-CD38 antibody designed to induce the killing of myeloma cells by the three proposed mechanisms. In the dose-escalation study with daratumumab monotherapy, in a very heavily pretreated population, 42% of them achieved at least PR at doses considered to reach therapeutic levels ($\geqslant$4 mg/kg; Table 3).[92,93] These results are highly promising for a drug used in monotherapy in patients with a median of six previous treatments. This has prompted the development of other anti-CD38 MoAbs, such as SAR650984, which has a similar profile and is already being tested in phase I clinical trials. *Lorvotuzumab and nBT062 are two antibodies directed against CD56 and CD138, respectively. They have in common that they are conjugated with a cytotoxic agent (DM1 and DM4, respectively) that is released inside the plasma cell once bound to it.* The results of the phase 1 trials in monotherapy showed some minimal responses (MRs) and even PRs in very heavily pretreated patients (Table 3).[94–96] Two MoAbs against CD40, dacetuzumab and lucatumumab, have been designed, both of which have shown modest responses as monotherapy (Table 3).[97,98] Some of these antibodies are currently being combined with other agents, several of them with lenalidomide and dexamethasone (Table 3), in the search for a potential immune synergy.

B-cell activating factor is a member of the tumor necrosis factor superfamily that promotes the survival of malignant B cells, including those in MM. An anti-B-cell activating factor MoAb, tabalumab, has been combined with bortezomib with or without dexamethasone with 46% achieving PR or better (Table 3).[99]

Siltuximab has a different mechanism as it is not directed against surface antigens, but it targets soluble IL6. Its purpose is to sequester this cytokine and prevent its binding to IL6-R. Two phase 2 trials in combination with dexamethasone or with bortezomib and dexamethasone have been carried out, yielding ORRs of 19% and 57%, respectively (Table 3).[100,101] However, the results of the randomized trial that compared melphalan + prednisone

Table 5. Summary of the most relevant clinical trials with inhibitors of proteins acting in cell cycle and other kinase inhibitors in MM

Mechanism	*Name*	*Combinations*	*Phase*	n	*Previous lines*	*ORR ($\geqslant$PR)*	*CBR ($\geqslant$MR)*	*Reference*
Agents acting on the cell cycle								
CDK 4/6 inhibitors	Seleciclib PD0332991	+ Bort–Dex	2	30	2 (1–8)	18%	24%	Niesvitzky *et al.*[199]
Aurora kinase A inhibitors	MLN8237	+ Bort	1	19	—	26%	52%	Stewart *et al.*[129]
KSP inhibitors	ARRY-520		1	31	6 (1–16)	10%	13%	Shah *et al.*[130]
			2	32	6 (2–19)	16%	19%	Shah *et al.*[131]
		+ Dex	2	18	10 (5–13)	22%	28%	
Kinase inhibitors								
CDK 1, 2, 5, 9 inhibitors	Dinaciclib		1/2	29	4 (1–5)	11%	18%	Kumar *et al.*[133]
FGFR3 inhibitors	Dovitinib (TKI-258)		2	43	86% $\geqslant$3	0%	0%	Scheid *et al.*[134]
	AB1010	+ Dex[a]	—	24 t(4:14) +	—	− Dex: 0% + Dex: 18%	− Dex: 0% + Dex: 36%	Arnulf *et al.*[136]
	MFGR1877S		1	14	5 (1–10)	0%	0%	Trudel *et al.*[135]
cKIT/PDGFR inhibitors	Imatinib		2	23 c-kit +	—	0%	0%	Dispenzieri *et al.*[137]
	Dasatinib		2	21	3 (1–14)	5%	5%	Wildes *et al.*[138]
		+ Len–Dex	1	16	3 (1–6)	57%	93%	Facon *et al.*[139]
VEGF-R inhibitors	Bevacizumab	+ LD	2	31	3 (1–7)	71%	—	Callander *et al.*[140]
IGF1-R inhibitors	AVE1642		1	15	4	0%	7%	Moreau *et al.*[142]
		+ Bort	1	11	4	18%	45%	
	CP-751,851	± Dex[b]	1	47	4 (0–8)	− Dex: 0% + Dex: 22%	− Dex: 0% + Dex: 33%	Lacy *et al.*[141]
EGF-R inhibitors	Cetuximab	± Dex[c]	2	15	—	− Dex: 0% + Dex: 7%	− Dex: 0% + Dex: 27%	Von Tresckow *et al.*[143]
PKC inhibitors	Enzastaurin	+ Bort	1	23	70% $\geqslant$3	17%	26%	Ghobrial *et al.*[144]

Abbreviations: Bort, bortezomib; CBR, clinical benefit rate; Dex, dexamethasone; EGF-R, epidermal growth factor receptor; FGFR3, fibroblast growth factor receptor 3; IGF1-R, insulin-like growth factor I receptor; KSP, kinesin spindle protein; Len, lenalidomide; MM, multiple myeloma; MR, minimal response; ORR, overall response rate; PDGFR, platelet-derived growth factor receptor; PKC, protein kinase C; PR, partial response; VEGF-R, vascular endothelial growth factor receptor. [a]Dex added if progression. [b]Dex added if progression at cycle 2 or if $<$PR at cycle 4. [c]Dex added if progression at week 5 or $<$PR at week 9.

+bortezomib with or without siltuximab in newly diagnosed MM patients were not positive, as there were no significant differences in terms of responses, PFS or OS.[102]

IPH2101 is an anti-killer immunoglobulin-like receptor antibody that aims to block the immunotolerance induced by HLA class I molecules of MM cells when they bind to natural killer cell inhibitory killer immunoglobulin-like receptors. No responses have been observed in monotherapy[103] and only modest activity (31%⩾PR) has been noted in combination with lenalidomide (Table 6).[104]

Deacetylase inhibitors

DACs are enzymes specialized in the removal of acetyl groups from several proteins. They have a role in oncogenesis through their epigenetic activity of targeting histones, but also through their regulation of non-histone proteins relevant to tumor progression, such as p53, E2F family members, Bcl-6, heat-shock 90 protein (Hsp-90), HIF-1α and Nur77.[105,106] *DACs are also overexpressed in several tumors, including MM, which has prompted the development of DACis for antitumoral purposes. There is a particular rationale for using these agents in MM in the search for some specific DACi*

Table 6. Summary of the most relevant clinical trials with Hsp-90 inhibitors, agents interfering with signaling pathways and agents with other mechanisms of action in MM

Mechanism	*Name*	*Combinations*	*Phase*	n	*Previous lines*	*ORR (⩾PR)*	*CBR (⩾MR)*	*Reference*
			Hsp-90 inhibitors					
Hsp-90 inhibitors	Tanespimycin		1	29	4 (2–19)	0%	3%	Richardson *et al.*[200]
		+Bort–Dex	1	22	5 (3–11)	9%	15%	Richardson *et al.*[145]
		+Bort–Dex	1/2	72	5 (1–15)	15%	27%	Richardson *et al.*[146]
			Signaling pathways inhibitors					
AKT inhibitors	Perifosine	±Dex[a]	2	64	4 (1–11)	−Dex: 0% +Dex: 13%	−Dex: 2% +Dex: 38%	Richardson *et al.*[147]
		+Bort±Dex[b]	1/2	84	5 (1–13)	−Dex: 23% +Dex: 32%	−Dex: 41% +Dex: 64%	Richardson *et al.*[148]
		+Len–Dex	1	32	2 (1–4)	50%	73% MR	Jakubobiak *et al.*[149]
	GSK2110183		1	34	5 (2–8)	9%	19%	Spencer *et al.*[150]
mTORC1 inhibitors	Everolimus		1/2	17	—	7%	7%	Guenther *et al.*[151]
		+Len	1	26	4	21%	58%	Mahindra *et al.*[154, 155]
	Temsirolimus		2	16	2 (1–5)	6%	38%	Farag *et al.*[152]
		+Bort	1/2	63	5 (1–14)	28%	42%	Ghobrial *et al.*[153]
		+Len	1	21	3 (1–6)	12%	47%	Hofmeister *et al.*[156]
mTORC1/C2 inhibitors	MLN0128 INK128		1	30	2 (1–10)	0%	3%	Ghobrial *et al.*[157]
Farnesyl-transferase inhibitors	Tipifarnib		2	43	4 (1–6)	0%	—	Alsina *et al.*[158]
p38/MAPK inhibitors	SCIO-469	±Bort[c]	2	62	5	−Bort: 0% +Bort: 26%	−Bort: 0% +Bort: 32%	Siegel *et al.*[160]
p38/JNK activators	Plitidepsin (Aplidin)	±Dex[b]	2	51	4 (1–8)	−Dex: 4% +Dex: 11%	−Dex: 13% +Dex: 22%	Mateos *et al.*[161]
MEK inhibitors	Selumetinib		2	37	5 (2–11)	8%	8%	Holkova *et al.*[159]
			Other mechanisms					
TRAIL activators	Circularly permuted TRAIL (CPT)		1b	47	—	19%	33%	Chen *et al.*[164]
			2	27	—	33%	—	Chen *et al.*[165]
		+Thal	2	43 Thal-refractory	—	22%	34%	Chen *et al.*[166]
DNA-damaging agents	Zalypsis		1/2	22	3 (2–5)	6%	31%	Ocio *et al.*[167]
PARP 1/2 inhibitors	Veliparib	+Bort	1	—	3 (1–9)	50%	87%	Neri *et al.*[168]
Hypoxia-activated alkylator	TH-302	+Dex	1	11	6 (3–10)	22%	44%	Ghobrial *et al.*[170]

Abbreviations: Bort, bortezomib; CBR, clinical benefit rate; Dex, dexamethasone; Hsp-90, heat-shock protein 90; JNK, c-Jun N-terminal kinase; Len, lenalidomide; MAPK, mitogen-activated protein kinase; MM, multiple myeloma; MR, minimal response; PARP, poly (ADP-ribose) polymerase; PR, partial response; ORR, overall response rate; TRAIL, tumor necrosis factor-related apoptosis inducing ligand. [a]Dex added if progression. [b]Dex added if <MR at cycle 4. [c]Bort added if <MR.

mechanisms: the inhibition of the epigenetic inactivation of p53 and the blockade of the UPR through the inhibition of the aggresome formation and autophagy (by targeting DAC6), and the inactivation of the chaperone system (by acetylating HSP-90).

Four classes of DACs have been described. Class I, II and IV DACs are known as classical DACs and are the ones that have been implicated in oncogenesis and are targets of DACis.[105,107] *Class III DACs are called sirtuins, due to their homology with yeast Sir2, and display characteristic features.*

Several DACis have been tested in MM. Despite their promising preclinical activity,[108–113] their clinical efficacy in monotherapy in relapsed/refractory MM patients was very modest (Table 5).[114–117] *This prompted the development of several combinations among which the one with the strongest scientific rationale is probably that of DACis and PIs. The basis is the simultaneous targeting of several mechanisms involved in the UPR: the inhibition of the proteasome blocks the degradation of the ubiquitinated misfolded proteins and the use of DACis interferes with the activity of heat-shock proteins, which are necessary for the correct folding of proteins, and with aggresome formation and autophagy (through inhibition of DAC6), which is also important for the elimination of toxic misfolded proteins. Overall, this induces the accumulation of toxic misfolded proteins in the myelomatous cells with ineffective UPR, leading to apoptosis.* The phase 1 trials with several of these DACis in combination with bortezomib have produced promising results (Table 4),[118–122] but the phase 3 randomized trial (Vantage 088) that compared bortezomib with bortezomib + vorinostat did not confirm them,[123] as, although it showed an improved response rate (ORR 56% vs 41%, $P<0.0001$), this translated into only a minimal advantage in PFS (7.6 vs 6.8 months; hazard ratio = 0.774 (0.64–0.94); $P=0.010$) and no differences in OS (Table 4). Another phase 3 randomized trial (Panorama 1) with the same rationale but with panobinostat instead of vorinostat and with the addition of dexamethasone in both arms has been recently completed, although results are not available yet. A question that remains unanswered is whether the addition of a DACi could revert bortezomib resistance. To address this, two trials, one with vorinostat and the other with panobinostat, are analyzing the activity of their combination with bortezomib (± dexamethasone) in bortezomib-refractory patients.[124,125] Results indicate that ~20–30% of these patients could be rescued by the addition of DACi to bortezomib (Table 4).

All these DACis have a broad spectrum of inhibition of DACs, as they are either pan-DACi (inhibition of the classes of DAC) or class 1 inhibitors, and this has been associated with significant toxicity, which is mainly manifested as general or gastrointestinal symptoms. With the purpose of overcoming this, while maintaining efficacy, a novel HDAC-6-specific inhibitor (rocilinostat) has been developed. Although no responses were obtained as monotherapy, it showed good tolerability[126] and is currently being combined with bortezomib and lenalidomide, with good preliminary results mainly in the combination with the IMID, with five out of six evaluable patients achieving PR or better.[127]

Agents acting on proteins and enzymes involved in the cell cycle

The only common oncogenic event found in MM patients to date is cyclin D deregulation.[128] *Therefore, efforts have been made to develop agents that can target the cell cycle abnormalities present in MM cells (Table 5). The main focus has been the CDKs, which are the proteins that phosphorylate and activate these cyclins, in particular CDK 4/6, which is responsible for cyclin-D phosphorylation. Seleciclib (PD0332991) is a CDK 4/6 inhibitor that was combined with bortezomib using an attractive sequential approach that attempts to synchronize cells with the CDK inhibitor and make them more susceptible to the cytotoxic effect of the PI.* Nevertheless, results were discouraging, and the development of this compound in MM was stopped. Other compounds evaluated in cell cycle have been those involved in the spindle formation and function, for example, aurora kinase A inhibitors, such as the novel MLN8237, whose combination with bortezomib has been recently reported, with 52% of patients achieving at least MR and 26% PR or better (Table 5).[129]

kinesin spindle protein is a member of the kinesin superfamily of microtubule-based motors; it has a critical role in mitosis as it mediates centrosome separation and bipolar spindle assembly and maintenance. Arry-520 is a kinesin spindle protein inhibitor that, by blocking this protein, arrests cells in mitosis and subsequently induces apoptosis through the degradation of survival signals. The drug on its own has already shown up to 16% PR or better[130,131] and 22% in combination with dexamethasone[131] in very refractory patients with a median of 6 and 10 previous lines of therapy, respectively (Table 5). It is already being combined with PIs such as bortezomib and carfilzomib, and is one of the most promising agents currently under exploration.

Kinase inhibitors

Several tyrosine or serine threonine kinase inhibitors have been grouped within this section of the review. They have been clinically investigated in MM, yielding different outcomes (Table 5). One of the most recent is the CDK inhibitor dinaciclib. It inhibits CDK 1, 2, 5 and 9, and is included in this rather than the previous section, because it was selected on the basis of its CDK-5 inhibitory activity, which is not related to the cell cycle. CDK-5 inhibition was identified as one of the top bortezomib-sensitizing mechanisms in high-throughput RNAi screening.[132] This inhibitor shows some activity as a single agent (18 ⩾ MR and 11% ⩾ PR; Table 5)[133] and may synergize with bortezomib. Among the tyrosine kinase inhibitors, those with the best rationale for use in MM are probably the fibroblast growth factor receptor 3 inhibitors in patients with t(4;14). Two small molecules[134,135] and one MoAb[136] have been explored in patients with this translocation, with disappointing results (Table 5).

Inhibitors of cKit/platelet-derived growth factor receptor have also been tested: imatinib did not induce any response[137] and dasatinib, demonstrating 5% response in monotherapy,[138] has been tested with bortezomib and lenalidomide (Table 5).[139] This gave some responses but it was difficult to assess whether dasatinib added anything to the combination of agents. Other inhibitors are the anti-vascular endothelial growth factor receptor MoAb bevacizumab, which, in combination with lenalidomide, induced 71% of PR or better,[140] and insulin-like growth factor I receptor,[141,142] epidermal growth factor receptor[143] and protein kinase C[144] inhibitors that did not respond in monotherapy, but may have some role in combination with other agents such as bortezomib (Table 5).

Agents acting on the UPR pathway

The chaperone system is responsible for the correct folding of proteins. Its malfunctioning therefore induces the accumulation of misfolded proteins and activates the UPR. Hsp-90 are among the main members of this system and represent a potential target for use in myeloma treatment. Similar to DACis, there is a good rationale for combining Hsp-90 inhibitors with PIs in order to achieve synergistic activation of the UPR. In fact, one of these Hsp-90 inhibitors, tanespimycin, has been combined with bortezomib and dexamethasone in two phase 1 trials, giving an ORR of up to 15% in patients who had received five previous lines of therapy (Table 6).[145,146] AUY922, another drug of this family, has also been combined with bortezomib ± dexamethasone in relapsed/refractory patients, without reported clinical results yet.

Other agents that could have a role in this important pathway are the purine scaffold HSP-90 inhibitors or the IRE1α inhibitors, but they are still in preclinical phases of development.

Signal transduction pathway inhibitors

Myeloma cells, similar to other tumor cells, are characterized by an abnormal activation of several of the most important signaling pathways, such as the PI3K/AKT/mTOR, RAF/MEK/ERK, JAK/STAT and NF-κB pathways. This has prompted the development of several drugs aimed at blocking these routes at different levels. One of the main types is the group of PIs, which interfere with the NF-kB pathway by hampering the degradation of the inhibition of NF-kB by the proteasome. Other more selective inhibitors of different components of these pathways are summarized in Table 6.

The PI3K/AKT/mTOR pathway has been extensively studied and targeted, as it is probably one of the most important in MM pathogenesis. AKT inhibitors such as perifosine[147] have been combined with bortezomib (in the search for the synergistic inhibition of AKT with perifosine and ERK with bortezomib)[148] or with lenalidomide,[149] with up to 32% and 50% with at least PR, respectively (Table 6). GSK211083 is another novel AKT inhibitor that is active in monotherapy (9% ⩾ PR, Table 6).[150] The mTOR (mammalian target of rapamycin) complexes lie downstream of this pathway. Two compounds targeting mTORC1, everolimus and temsirolimus have been tested, with 6% and 7% PR in monotherapy, respectively.[151,152] These values improved when the compounds were combined with bortezomib[153] or lenalidomide[154–156] in more heavily pretreated patients (Table 6). Recently, MLN1018, a new mTOR inhibitor targeting the mTORC1 and mTOR-C2 complexes, has been tested but no responses were observed in monotherapy (Table 6).[157]

The RAS/RAF/MEK/ERK pathway was the second to be investigated, addressing not only the blockade of top upstream molecules of the pathway by the farnesyl-transferase inhibitor tipifarnib,[158] *which impedes the activation of RAS, to MEK inhibitors such as selumetinib (ARRY-6244),*[159] *but also the p38/mitogen-activated protein kinase inhibitor SCIO-469, which has been combined with bortezomib.*[160] Another interesting drug is the p38/c-Jun N-terminal kinase activator Plitidepsin, which, after showing activity in heavily pretreated patients in the phase II trial (Table 6), is currently in phase 3 evaluation.[161] Of these, selumetinib is probably the most promising, because, as a single agent, it has given an 8% PR in patients with five previous lines of therapy (Table 6). Recently, whole-genome sequencing revealed activating mutations of the kinase BRAF in 4% MM patients.[162] Vemurafenib, a small molecule inhibitor specifically targeting V600E-mutated BRAF, has been reported to induce a PR in a patient relapsing after several lines of therapy and harboring this mutation.[163]

Drugs with different mechanisms of action

The search for ligands of death receptors (FAS or tumor necrosis factor-related apoptosis inducing ligand-R) that directly activate the extrinsic pathway of apoptosis has always been an area of interest in the field of novel antitumoral agents, although, to date, they have not shown significant efficacy and have been quite toxic. However, recent promising preliminary results from two trials in monotherapy with a circularly permuted tumor necrosis factor-related apoptosis inducing ligand have registered 19 and 33% PR or better.[164,165] This agent has also been combined with thalidomide, with 22% with at least PR and 34% with at least MR in thalidomide-refractory patients (Table 6).[166]

Two novel agents share a common mechanism of DNA-damage induction or DNA-repair inhibition. Zalypsis is a marine-derived compound that binds to the minor groove of DNA and induces DNA double-strand breaks. As a single agent in patients with a median of three previous lines of therapy, it has given 31% MR or better, including 6% PR. (Table 6).[167] *The other agent is the poly (ADP-ribose) polymerase 1/2 inhibitor, velaparib, which has been combined with bortezomib in the search for a synergistic combination of DNA-damage induction and DNA-repair inhibition*, and has resulted in 50% PR (Table 6).[168]

The presence of a hypoxic niche in the bone marrow has been associated with MM pathogenesis.[169] *In this regard, TH-302, an alkylator designed to be activated by hypoxia has been developed* and clinically tested in combination with dexamethasone, with some responses (22% PR and 22% MR) in heavily pretreated patients.[170]

DISCUSSION

The incurable nature of MM makes it necessary to increase the treatment armamentarium against this disease. As it is shown in this review, the ongoing extensive research and the already-positive clinical results with several agents make the future optimistic in the aim of transforming MM into a chronic disease. Although none of the agents with novel mechanisms of action (after PIs or IMIDs) are still approved, it is reasonable to think that several of them will be in the near future. The initial approval for most of them will be for patients refractory to PIs and IMIDs, but its use will be soon expanded to other settings and used in different combinations. This may be particularly valuable for newly diagnosed patients, in whom the disease is more sensitive, and probably the use of optimized multitargeted combinations in these patients could derive in the curability of some of them.

Nevertheless, this optimism should be balanced with the reality of the clinical results, as many of the novel agents, despite having a good scientific rationale and promising activity in preclinical models of MM, have not demonstrated clinical activity. This discordance may be due to several reasons, one of them being the limitations of the preclinical models of MM to accurately reflect the patient's setting. The other obvious issue is the heterogenetic and multigenetic nature of MM, and the pathogenesis of a complex malignancy, which seems to rely not only on one unique hit but on many of them. An example of this is that although cyclin-D is deregulated in the vast majority of MM patients, agents targeting this mechanism have not produced the expected clinical results.

In fact, agents with a quite pleiotropic mechanism of action, such as PIs, immunomodulatory agents or alkylators, are those that have demonstrated to be effective in MM and, therefore, along with steroids, have become the backbone of the treatment of MM patients. Nevertheless, not all agents with a broad spectrum of mechanisms have been effective in MM. As previously shown, DACi, which target several different proteins and mechanisms in the tumor cell, have not confirmed the expectations in the dual combination, based on the results of the phase 3 Vantage trial recently reported. However, data on a triple combination with corticosteroids are still pending (Panorama 1 trial); moreover, it could be that the use of more specific DACi such as the HDAC-6-specific rocilinostat may result in higher efficacy due to a more favorable toxicity profile that would translate into a prolonged drug exposure.

The results of the so-called targeted agents that display quite specific mechanisms of action when used in monotherapy are usually not very optimistic, but we also have to consider that most of these trials have been performed in quite heavily pretreated patients. Accordingly, the lack of activity as single agents should probably not preclude the future investigation of these drugs in MM in scientifically based combinations. A good example of this situation is the combination of the anti-CS1 MoAb elotuzumab with lenalidomide and dexamethasone; despite the lack of efficacy of elotuzumab as single agent, it has yielded remarkable results in terms of response rate, but particularly in terms of PFS (33 months) in the relapsed/refractory setting, based on the potentiation of an anti-MM immune response. This leads to an important point, as most of these novel agents in monotherapy does not induce long PFS, probably reflecting again the bad

prognosis of the patients included in these trials, and also the fact that cells are able to rather quickly overcome the effects of these targeted drugs and develop mechanisms of resistance. Probably, the use of rationally based combinations as the one just mentioned could avoid the development of this resistance and increase the durability of the responses.

One of the most promising strategies in the current arena is immunotherapy. This approach has been traditionally used in several cancers, and specifically in MM. In this regard, we cannot forget the use of interferon, whose use was stopped due to the low tolerability but which showed benefit in the maintenance setting. Several decades later, a novel family of agents, IMIDs, appeared in the treatment armamentarium of MM, cooperating in the revolution of MM therapy and outcome. In this same line, immunotherapy with B-cell maturation antigen chimeric antigen receptors,[171] dendritic cell/myeloma fusion cellular vaccine[172] or the incorporation of the PD-1/PDL-1 axis antagonists[173,174] may harness the body's own immune system, generating an antitumor response that have been preclinically explored. Quite recently, several drugs and combinations that are based on immunological mechanisms have appeared and are currently being tested in the clinics. This is the case of different MoAb that target surface molecules of the malignant plasma cell. In addition to the already mentioned elotuzumab, there are several other MoAb that, by inducing direct cytotoxicity and, mainly, antigen-dependent cellular cytotoxicity and complement-dependent cytotoxicity, have raised quite an interest. Probably the most exciting target is CD38, against which several antibodies have been developed. The most advanced of these antibodies, daratumumab, has demonstrated clear activity as monotherapy in heavily pretreated patients with 42% responses at therapeutic doses.

Several other of the currently tested agents have also already shown some activity in monotherapy. One of the most promising is the kinesin spindle protein inhibitor Arry-520, which alone or in combination with dexamethasone in very refractory patients, has produced 10–16% responses. This agent is now being investigated in several combinations with novel and conventional agents. The CDK-5 inhibitor, identified in an RNAi screening of druggable targets, induced responses in 11% of cases, but, probably, the combination with bortezomib is expected to be more potent, based on the preclinical rationale. Other agents with some responses as single agents, although in more preliminary stages of development are agents targeting different signaling pathways such as PI3K/AKT/mTOR inhibitors and the novel MEK inhibitor selumetinib, all of which produce 5–10% PR. Moreover, among these signaling pathway-specific agents, we can emphasize aplidin, a p38, c-Jun N-terminal kinase activator with efficacy in the phase 2 trial, which is being evaluated in a phase 3 trial in combination with dexamethasone.

Before the availability of the recently approved drugs, the limited availability of agents did not allow the selection of a particular therapy for a particular patient, and treatment was standard for all patients, with the only differentiation being based on age and transplant elegibility. The development of the novel agents has prompted the initiation of more personalized of therapy, in order to investigate the activity of new drugs/combinations in selected cohorts of patients, based on cytogenetic, molecular or clinical (extramedullary disease). Moreover, biomarkers for sensitivity/resistance to particular drugs are under way. Examples of this situation is the use of cereblon to stratify patients sensitive or resistant to IMIDs, or the measurement of serum α1-acid glycoprotein to also detect patients that will not respond to Arry-520.

CONFLICT OF INTEREST

EMO—consultancy: Onyx, Bristol Myers Squibb, Array Pharmaceuticals; research funding: Celgene, Onyx, Pharmamar, Array Pharmaceuticals. PGR—consultancy: Celgene, Millennium Takeda, Johnson & Johnson, Novartis, Bristol Myer Squibb; research funding: Celgene and Millenium. SVR—no conflicts to disclose. AP—consultancy and honoraria: Amgen, Bristol Myers Squibb, Celgene, Janssen-Cilag, Millennium, ONYX. MVM—consultancy: Janssen-Cilag, Celgene, Millennium. RO—consultancy: Abbott Laboratories, Centocor Ortho Biotech, Cephalon, Millennium, Novartis, Onyx; research funding: Celgene, Johnson & Johnson, Millennium, Onyx. SK—consultancy: Millennium, Celgene, Onyx; research funding: Celgene, Millennium, Novartis, Celphalon, Sanofi, Onyx. SU—consultancy: Celgene; honoraria: Celgene, Onyx; research funding: Celgene, Onyx, Millennium. DR—honoraria: Amgen; research funding: Eli Lilly. RN—consultancy: Onyx, Millennium, Celgene; honoraria: Onyx, Millennium, Celgene; research funding: Onyx, Millennium, Celgene. HE—consultancy: Celgene, Janssen; honoraria: Celgene, Janssen; research funding: Celgene, Janssen. KCA—consultancy: Gilead, Sanofi-Aventis, Onyx, Celgene; stock ownership: Acetylon, Oncoprep. MAD—consultancy: Celgene, Ortho Biotech; honoraria: Celgene, Ortho Biotech; research funding: Celgene. HA—honoraria: Celgene, Janssen, Onyx. UHM—honoraria: Celgene, Janssen-Cilag. IT—No conflicts to disclose. GM—consultancy: Millennium Takeda, Neotype; honoraria: Millennium Takeda, Pfizer. RS—No conflicts to disclose. PM—consultancy: Celgene, Janssen; honoraria: Celgene, Janssen. PLB—honoraria: Onyx. CSC—No conflicts to disclose. JJL—honoraria: Celgene; research funding: Celgene, Janssen-Cilag. JS—research funding: Janssen-Cilag, Celgene, Onyx. AR—consultancy: Celgene; research funding: Celgene, Bristol Myers Squibb, Millennium, Astra Zeneca, Onyx. JM—research funding: Celgene, Onyx, Sanofi. SZ—research funding: Celgene, Janssen-Cilag, Millennium. SL—consultancy: Celgene, Millennium, Novartis, Bristol Myers Squibb, Onyx, Janssen-Cilag. RC—consultancy: Millennium; research funding: Millennium, Prothena Biotech. WJC—honoraria: Janssen, Celgene, Novartis; research funding: Celgene, Roche. PM—consultancy: Celgene, Janssen, Millennium; honoraria: Celgene, Janssen. PS—research funding: Janssen-Cilag, Celgene, Onyx. HL—honoraria: Celgene, Mundi Pharma, Janssen-Cilag; research funding: Celgene, Mundi Pharma, Janssen-Cilag. BD—honoraria: Celgene Corporation, Onyx Pharmaceutical, Millennium Pharmaceutical, The Takeda Company. JFSM—consultancy and honoraria: Janssen-Cilag, Millennium, Celgene, Onyx, Novartis, Bristol Myers Squibb.

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APPENDIX

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