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This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1504911> since

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This is an author version of the contribution published on:

Ocio EM, Richardson PG, Rajkumar SV, Palumbo A, Mateos MV, Orlowski R, Kumar S, Usmani S, Roodman D, Niesvizky R, Einsele H, Anderson KC, Dimopoulos MA, Avet-Loiseau H, Mellqvist UH12, Turesson I13, Merlini G14, Schots R15, McCarthy P16, Bergsagel L17, Chim CS18, Lahuerta JJ19, Shah J, Reiman A, Mikhael J, Zweegman S, Lonial S, Comenzo R, Chng WJ, Moreau P, Sonneveld P, Ludwig H, Durie BG, Miguel JF.

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LEUKEMIA (2014)

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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Abstract

Treatment in medical oncology is gradually shifting from the use of non-specific chemotherapeutic agents towards 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, immunomodulatory agents (IMiDs) and alkylators). Then we focus on agents with novel mechanisms of action, such as monoclonal antibodies (MoAb), 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. Also 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, that has produced exciting results in the relapsed/refractory setting.

Keywords: Multiple Myeloma, New Drugs, targeted agents, Phase I clinical trials

Introduction

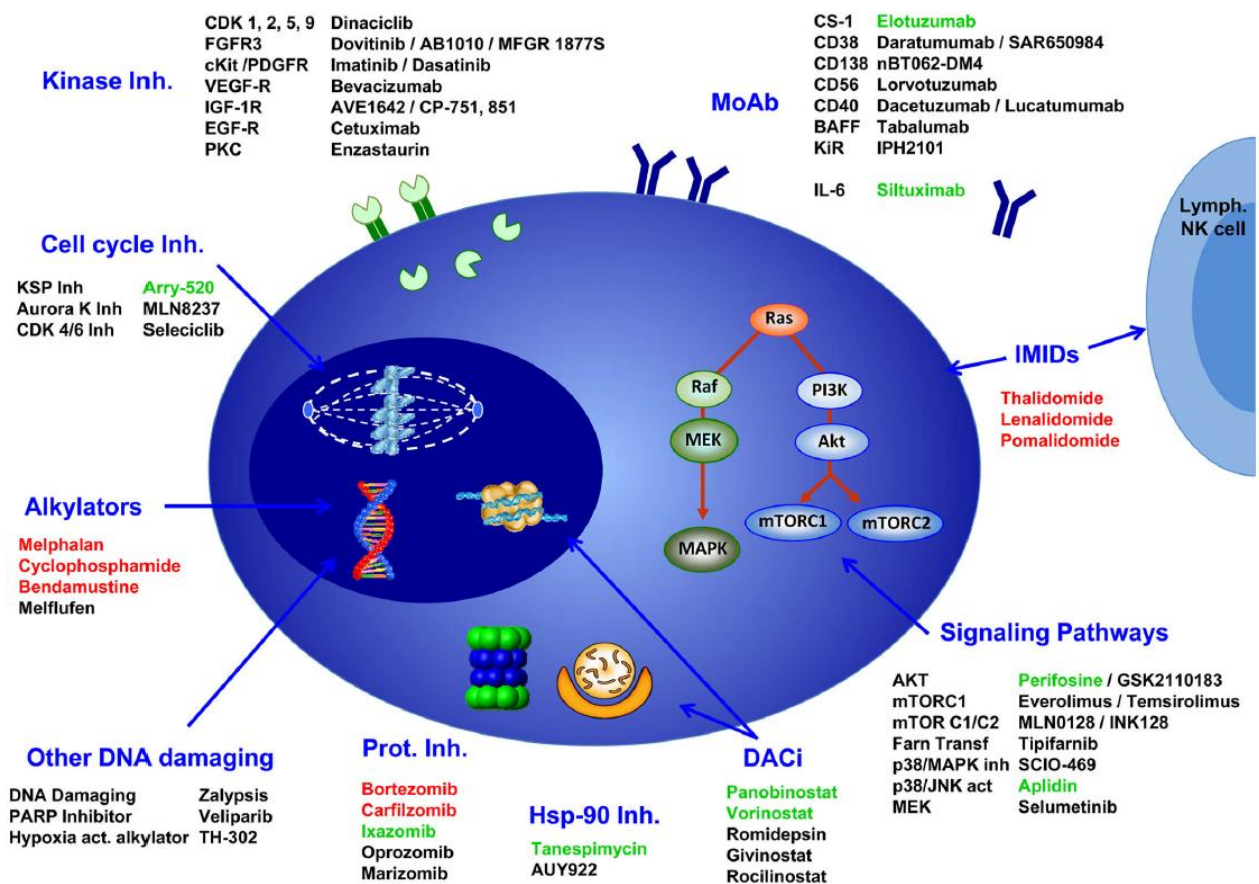
Therapeutics in medical oncology has undergone a marked evolution in recent decades, moving from the chemotherapeutic era in which the drugs were non-specifically directed against highly proliferative cells, towards an era of novel targeted therapy in which drugs and their combinations target specific 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, ponatinib) in chronic myeloid leukemia, anti-CD20 MoAb in non-Hodgkin lymphoma, anti-VEGF-R 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 the standard agents for the care of these patients for over 30 years. However, in the last decade, several agents (proteasome inhibitors and 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 cancer⁶, 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 proteasome inhibitors, immunomodulatory agents and alkylators) and second, (the main focus of this review), drugs with novel mechanisms of action, such as monoclonal antibodies, agents acting on the cell cycle, deacetylase inhibitors, agents acting on the unfolded protein response, 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.

Figure 1

Schematic representation of the main targets in MM plasma cells and the drugs tested against them



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

1. Novel proteasome inhibitors

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 proteasome inhibitor, 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 CDK-inhibitors and tumor suppressor proteins, 2) the inhibition of the clearance of misfolded proteins (inducing endoplasmic reticulum, stress and activation of the unfolded protein response),^{18,19} and 3) the blockade of the NF- κ B transcription factor pathway through the prevention of I κ B (Inhibitor of NF- κ B) degradation after its polyubiquitination by IKK (I κ B kinase).²⁰ After bortezomib, several other proteasome inhibitors 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 since it targets the three catalytic 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 proteasome inhibitors used in monotherapy.

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 (\geq PR)	BR (\geq MR)	PFS (month)	Reference
Carfilzomib (PR-171)	PX-171-001	1	10 MM	-	MTD: 15 mg/m ²	1-5/14d	10%	20%	-	O'Connor, CCR 2009 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, CCR 2012 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, Clin Lymph Myeloma 2012 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, Blood 2012 ¹⁷⁸
Ixazomib (MLN-9708)	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 Blood 2012 ²¹
	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, Leukemia 2013 ²⁵
	C16004	1	60	6 (2-18)	MTD: 2.97 mg/m ²	1, 8, 15/28d	15%	17%	-	Kumar, ASCO 2013 ⁴³
Marizomib (NPI-0052)	C16003	1	57	4 (1-28)	MTD: 2 mg/m ²	1, 4, 8, 11/21d	13%	15%	-	Lonial, ASCO 2012 ⁴⁴
	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, ASH 2011 ⁴⁷

MED: Minimum effective dose

MTD: Maximum tolerated dose

NR: Not reached

Carfilzomib is FDA-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-naïve patients,²¹ and approximately 20% of patients refractory to bortezomib responded to carfilzomib.^{22, 23} Based on 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 (G3) AEs 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 trial²⁷) and in newly diagnosed patients.^{28, 29} Also in newly diagnosed, 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 cyclophosphamide³² and with melphalan.³³ Other innovative combinations are being explored with novel drugs such as histone deacetylase inhibitors,^{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 & CLL).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 (WM) patients already enrolled with a good safety profile and promising preliminary response data.⁴²

Ixazomib (MLN9708) is the first orally bioavailable proteasome inhibitor 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 proteasome inhibitors still with very preliminary results (table 1).^{43,44} With respect to toxicity, the most remarkable finding was the low rates of significant PN, although treatment related rash has been noted. Ixazomib is also being examined in combination with melphalan and prednisone⁴⁵ and with lenalidomide and low-dose dexamethasone⁴⁶ 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

2. 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 immunomodulatory drugs (IMiDs) due 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 (DDB1) 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 (NK) 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, similarly to lenalidomide and thalidomide, the addition of dexamethasone induces synergy, improving the response rate and the PFS,⁶⁶ and this combination in the initial phase 2 study by Lacy and co-workers induced a 62% response rate with a PFS of 13 months (table 2),⁶⁷ 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.

Table 2

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

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 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} Based on these, although other possibilities may be acceptable, the dose of 4 mg on days 1–21 followed by a one-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 vs 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 (NR vs 7.8 months).⁷² Also 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).

3. Novel alkylators

Bendamustine has a quite unusual mechanism of action, since 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 ASCT and who are not eligible to receive proteasome inhibitors or thalidomide due to preexisting 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 TTP (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% VGPR).^{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 pre clinical testing is melphalan-flufenamide (mel-flufen), 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 melflufen 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 due to their particular mechanism, the clinical data is included in the last chapter of this review.

Agents with novel mechanisms of action

1. Immunotherapy/Monoclonal Antibodies

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 monoclonal antibodies (MoAbs) that are one of the paradigms of targeted therapy since 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 (ADCC) or complement-dependent cytotoxicity (CDC). 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}

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 Blood 2012 ⁸⁸
		+ Len-Dex	1	29	3(1-10)	82%	-	Lonial JCO 2012 ⁸⁹
		+ Len-Dex	2	73	55% ≥2	84%	-	Richardson ASH 2012 ^{90, 91}
		+ Bort-Dex	1	28	2 (1-3)	40%	60%	Jakubowiak JCO 2012 ¹⁸⁸
Daratumumab (HuMax-CD38, Ab005)	CD38	-	1	32	6(2-12)	14% 42% in > 4 mg/kg	28% 66% in > 4 mg/kg	Plesner ASH 2012 ⁹² & ASCO 2013 ⁹³
nBT062-DM4	CD138	-	1	32	-	4%	52%	Jagannath ASH 2011 ⁹⁵
		-	1/2a	29	-	4%	4%	Heffner ASH 2012 ⁹⁶
Lorvotuzumab (IMGN901 – huN901-DM1)	CD56	-	1	37 CD56+ patients	Most of them ≥ 6	7%	18%	Chanani-Khan ASH 2010 ⁹⁴
Dacetuzumab (SGN-40)	CD40	+ Len-Dex	1	44	2 (1-11)	59%	-	Berdeja ASH 2012 ¹⁸⁹
		-	1	44	5(2-14)	0%	0%	Hussein Haemat 2010 ⁹⁸
		+ Len-Dex	1b	36	4(2-14)	39%	81%	Agura ASH 2009 ¹⁹⁰
Lucatumumab	CD40	-	1	28	8(2-17)	4%	4%	Bensinger BJH 2012 ⁹⁷
Tabalumab	BAFF	+ Bort +/- Dex	1	48	3 (1-10)	46%	-	Raje ASH 2012 ⁹⁹
Siltuximab	IL6	+ Dex	2	49	4 (2-9)	19%	28%	Voorhes ASH 2011 ¹⁰⁰
		+ Bort-Dex	2	21 Bort-naïve	2 (1-3)	57%	-	Rossi ASH 2008 ¹⁰¹
IPH2101	KIR	1	1	32	2 (1-7)	0%	0%	Benson Blood 2012 ¹⁰³
		+ Len	1	13	4 (1-8)	31%	46%	Benson ASH 2012 ¹⁰⁴

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 NK 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 more than 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 NK 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.

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 (≥ 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 antiCD38 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 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.

BAFF (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-BAFF 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 IL-6. 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 melfalan + Prednisone + 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-KIR antibody that aims to block the immunotolerance induced by HLA class I molecules of MM cells when they bind to NK cell inhibitory killer immunoglobulin-like receptors (KIRs). No responses have been observed in monotherapy¹⁰³ and only modest activity (31% \geq PR) has been noted in combination with lenalidomide (table 6).¹⁰⁴

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 BJH 2010 ²⁰⁰
		+ Bort-Dex	1	22	5 (3–11)	9%	15%	Richardson BJH 2010 ¹⁴⁵
		+ Bort-Dex	1/2	72	5 (1–15)	15%	27%	Richardson BJH 2011 ¹⁴⁶
Signaling pathways inhibitors								
AKT inhibitors	Perifosine	+/- Dex [*]	2	64	4 (1–11)	– Dex: 0% + Dex: 13%	– Dex: 2% + Dex: 38%	Richardson ASH 2007 ¹⁴⁷
		+ Bort +/- Dex ^{**}	1/2	84	5 (1–13)	– Dex: 23% + Dex: 32%	– Dex: 41% + Dex: 64%	Richardson JCO 2011 ¹⁴⁸
		+ Len Dex	1	32	2 (1–4)	50%	73% MR	Jakubobiak BJH 2012 ¹⁴⁹
		GSK2110183	1	34	5 (2–8)	9%	19%	Spencer ASH 2011 ¹⁵⁰
mTORC1 inhibitors	Everolimus		1/2	17	-	7%	7%	Guenther ASCO 2010 ¹⁵¹
		+ Len	1	26	4	21%	58%	Mahindra ASH 2010 ¹⁵⁴ & Yee ASH 2011 ¹⁵⁵
	Temsirolimus		2	16	2 (1–5)	6%	38%	Farg Leuk Research 2009 ¹⁵²
		+ Bort	1/2	63	5 (1–14)	28%	42%	Ghobrial Lancet Oncol 2011 ¹⁵³
mTORC1/C2 inhibitors	MLN0128 INK128	+ Len	1	21	3 (1–6)	12%	47%	Hofmeister JCO 2011 ¹⁵⁶
			1	30	2 (1–10)	0%	3%	Ghobrial ASH 2012 ¹⁵⁷
Farnesyl transferase inhibitors	Tipifarnib		2	43	4 (1–6)	0%	-	Alsina Blood 2004 ¹⁵⁸
p38/MAPK inhibitors	SCIO-469	+/- Bort ^{***}	2	62	5	– Bort: 0% + Bort: 26%	– Bort: 0% + Bort: 32%	Siegel ASH 2006 ¹⁶⁰
p38/JNK activators	Plitidepsin (Aplidin)	+/- Dex ^{**}	2	51	4 (1–8)	– Dex: 4% + Dex: 11%	– Dex: 13% + Dex: 22%	Mateos Clin Cancer Res 2010 ¹⁶¹
MEK inhibitors	Selumetinib		2	37	5 (2–11)	8%	8%	Holkova ASH 2011 ¹⁵⁹
Other mechanisms								
TRAIL activators	Circularly permuted TRAIL (CPT)		1b	47	-	19%	33%	Chen ASH 2012 ¹⁶⁴
			2	27	-	33%	-	Chen ASH 2012 ¹⁶⁵

2. DAC inhibitors

Deacetylases (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, Hsp90, HIF-1 α , and Nur77.^{105, 106} DACs are also overexpressed in several tumors, including MM, which has prompted the development of DAC inhibitors (DACis) for antitumoral purposes. There is a particular rationale for using these agents in MM in the search for some specific DACi mechanisms; the inhibition of the epigenetic inactivation of p53 and the blockade of the unfolded protein response, 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 proteasome inhibitors. The basis is the simultaneous targeting of several mechanisms involved in the unfolded protein response: 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 unfolded protein response, 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 since, 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. HR = 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 around 20–30% of these patients could be rescued by the addition of DACi to bortezomib (table 4).

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 ^{**}		Reference
						ORR (≥ PR)	CBR (≥ MR)	
Vorinostat + Len + Bort + Dex in RR	2	9 RVD- refractory	5 (2–10)	44%	89%	44%	89%	Siegel IMW 2011 ¹⁹⁵
Vorinostat + Len + Bort + Dex in ND	1	30 new diagnosis	0	100%	100%	-	-	Kaufman ASH 2012 ¹⁹⁶
Panobinostat + Melphalan	1/2	25	4 (-17)	16%	60%	-	-	Berenson IMW 2011 ¹⁹⁷
Panobinostat + MPT	1/2	24	21% ≥ 2	50%	-	-	-	Offidani IMW 2011 ¹⁹⁸
Panobinostat + Carfilzomib	1/1b	17	5 (2–15)	35%	41%	-	-	Shah ASH 2012 ³⁵
Panobinostat + Carfilzomib	1/2	10	3 (1–7)	60%	70%	-	-	Berdeja ASH 2012 ³⁴

* Data obtained from the presentation at the ASH 2011 meeting

** Indicates the response in patients previously refractory to the drugs administered in combination with the DAC inhibitors (bortezomib or lenalidomide in their respective combinations)

§ Bortezomib-refractory patients

§§ Lenalidomide- and dexamethasone-refractory patients

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 (≥ PR)	CBR (≥ MR)	Reference
Agents acting on the cell cycle								
CDK 4/6 inhibitors	Selelclib PD0332991	+ Bort-Dex	2	30	2 (1-8)	18%	24%	Niesvitzky ASH 2010 ¹⁹⁹
Aurora kinase A inhibitors	MLN8237	+ Bort	1	19	-	26%	52%	Stewart ASH 2012 ¹²⁹
KSP inhibitors	ARRY-520		1	31	6 (1-16)	10%	13%	Shah ASH 2011 ¹³⁰
			2	32	6 (2-19)	16%	19%	Shah ASH 2012 ¹³¹
		+ Dex	2	18	10 (5-13)	22%	28%	
Kinase inhibitors								
CDK 1, 2, 5, 9 inhibitors	Dinaciclilb		1/2	29	4 (1-5)	11%	18%	Kumar ASH 2012 ¹³³
FGFR3 inhibitors	Dovitinib (TKI-258)		2	43	86% ≥ 3	0%	0%	Scheid ASH 2012 ¹³⁴
	AB1010	+ Dex*	-	24 t(4:14)+	-	- Dex: 0% + Dex: 18%	- Dex: 0% + Dex: 36%	Amulf ASH 2007 ¹³⁶
	MFGR1877S		1	14	5 (1-10)	0%	0%	Trudel ASH 2012 ¹³⁵
cKIT/PDGFR inhibitors	Imatinib		2	23 c-kit +	-	0%	0%	Dispenzieri Leuk Lymph 2006 ¹³⁷
	Dasatinib		2	21	3 (1-14)	5%	5%	Wildes Leuk Lymph 2009 ¹³⁸
		+ Len-Dex	1	16	3 (1-6)	57%	93%	Facon ASH 2009 ¹³⁹
VEGF-R inhibitors	Bevacizumab	+ LD	2	31	3 (1-7)	71%	-	Callander ASH 2009 ¹⁴⁰
IGF1R inhibitors	AVE1642		1	15	4	0%	7%	Moreau Leukemia 2011 ¹⁴²
		+ Bort	1	11	4	18%	45%	
		+/- Dex**	1	47	4 (0-8)	- Dex: 0% + Dex: 22%	- Dex: 0% + Dex: 33%	Lacy JCO 2008 ¹⁴¹
EGF-R inhibitors	Cetuximab	+/- Dex***	2	15	-	- Dex: 0% + Dex: 7%	- Dex: 0% + Dex: 27%	Von Tresckow ASH 2011 ¹⁴³
PKC inhibitors	Enzastaurin	+ Bort	1	23	70% ≥ 3	17%	26%	Ghobrial Am J Haem 2011 ¹⁴⁴

* Dexamethasone added if PD

** Dexamethasone added if PD at cycle 2 or if < PR at cycle 4

*** Dexamethasone added if PD at week 5 or < PR at week 9

All these DACs 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 tolerability¹²⁶ and is currently being combined with bortezomib and lenalidomide, with good preliminary results mainly in the combination with the IMiD, with 5 out of 6 evaluable patients achieving PR or better.¹²⁷

3. 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 (cyclin-dependent kinases), which are the proteins that phosphorylate and activate these cyclins, in particular CDK 4/6, which is responsible for cyclin-D phosphorylation. Seliciclib (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 proteasome inhibitor. 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: 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

KSP (kinesin spindle protein) is a member of the kinesin superfamily of microtubule-based motors; it plays a critical role in mitosis as it mediates centrosome separation and bipolar spindle assembly and maintenance.ARRY-520 is a KSP 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 dexamethasone¹³¹ in very refractory patients with a median of six and ten previous lines of therapy respectively (table 5). It is already being combined with proteasome inhibitors such as bortezomib and carfilzomib and is one of the most promising agents currently under exploration.

4. 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% \geq MR and 11% \geq 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 FGFR3 inhibitors in patients with t(4;14). Two small molecules^{134, 135} and one MoAb¹³⁶ have been explored in patients with this translocation, with disappointing results (table 5).

Inhibitors of cKit/PDGFR have also been tested: imatinib did not induce any response¹³⁷ 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-VEGF-R MoAb bevacizumab, which, in combination with lenalidomide, induced 71% of PR or better,¹⁴⁰ and IGF1-R,^{141, 142} EGF-R¹⁴³ and PKC¹⁴⁴ inhibitors that did not respond in monotherapy, but may have some role in combination with other agents such as bortezomib (table 5).

5. Agents acting on the unfolded protein response (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 unfolded protein response. Heat-shock 90 proteins (Hsp-90) are amongst the main members of this system, and represent a potential target for use in myeloma treatment. Similarly to DACis, there is a good rationale for combining Hsp-90 inhibitors with proteasome inhibitors in order to achieve synergistic activation of the unfolded protein response. 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 HSP90 inhibitors or the IRE1alpha inhibitors, but they are still in preclinical phases of development.

6. Signal transduction pathway inhibitors

Myeloma cells, like 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 NFkB 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 proteasome inhibitors, which interfere with the NFkB pathway by hampering the degradation of the inhibition of NFkB (IkB) 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 perifosine¹⁴⁷ 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 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 bortezomib¹⁵³ or lenalidomide^{154–156} in more heavily pretreated patients (table 6). Recently, MLN1018, a new mTOR inhibitor targeting the mTOR-C1 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/MAPK inhibitor SCIO-469, which has been combined with bortezomib.¹⁶⁰ Another interesting drug, is the p38/JNK 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, since, 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

7. Drugs with different mechanisms of action

The search for ligands of death receptors (FAS or TRAIL-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 TRAIL (CPT) 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 PARP 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, makes the future optimistic in the aim of transforming MM into a chronic disease. Although none of the agents with novel mechanisms of action (after proteasome inhibitors 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 proteasome inhibitors and IMiDs, but its use will be soon expanded to other settings and used in different combinations. Particularly valuable may be for newly diagnosed patients, where 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, since, 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 proteasome inhibitors, 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 is still pending (Panorama 1 trial); moreover, it could be that the use of more specific DACi such as the HDAC6 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, but 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 that 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 BCMA chimeric antigen receptors,¹⁷¹ dendritic cell/myeloma fusion cellular vaccine¹⁷² or the incorporation of the PD-1/PDL-1 axis antagonists^{173, 174} may harness the body's own immune system, generating an anti-tumor response 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, ADCC and CDC have raised quite 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 KSP 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 CDK5 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. Also among these signaling pathways-specific agents we can emphasize aplidin, a p38, JNK activator with efficacy in the phase 2 trial, and that 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 eligibility. 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 CRBN to stratify patients sensitive or resistant to IMiDs or the measurement of serum AAG to also detect patients that will not respond to Argy-520.

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