Critical Reviews in Oncology / Hematology 121 (2018) 74–89

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

A question of class: Treatment options for patients with relapsed and/or refractory multiple myeloma

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ARTICLE INFO

Keywords:
Multiple myeloma
Relapsed
Refractory
Elderly
Cytogenetics

ABSTRACT

Multiple classes of agent with distinct mechanisms of action are now available for the treatment of patients with relapsed and/or refractory multiple myeloma (RRMM), including immunomodulatory agents, proteasome inhibitors, histone deacetylase inhibitors and monoclonal antibodies. Additionally, several different drugs may be available within each agent class, each with their own specific efficacy and safety profile. This expansion of the treatment landscape has dramatically improved outcomes for patients. However, as the treatment options for RRMM become more complex, choosing the class of agent or combination of agents to use in the relapsed setting becomes increasingly challenging. Furthermore, treatment options for specific patient populations such as the elderly, those with high-risk cytogenetic abnormalities and those with refractory disease are yet to be defined in the current treatment landscape. When choosing an appropriate treatment approach, physicians must consider multiple criteria including both patient-related and disease-related factors. The aim should be to provide patient-specific treatment in order to gain a clinical benefit while minimizing toxicity. This review provides an overview of the mechanism of action and efficacy and safety profiles of each class of agent and of treatment regimens that combine different classes of agent, with a special focus on treating specific patient populations.

1. Introduction

Multiple myeloma (MM) is characterized by a relapsing disease course. Despite significant improvements in patient outcomes following the introduction of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) in the first-line setting (Kumar et al., 2008), most patients eventually relapse, and the management of relapsed and/or refractory MM (RRMM) remains a challenge (Laubach et al., 2016). The treatment landscape for patients with RRMM is rapidly changing following the recent approval of three drugs belonging to two novel classes of agent in this setting: a histone deacetylase (HDAC) inhibitor (HDI), panobinostat (Farydak, 2016a; Farydak, 2016b), and two monoclonal antibodies (mAbs), daratumumab and elotuzumab (Squibb, 2015; Squibb, 2016; Darzalex, 2015; Darzalex, 2016). Furthermore, the addition of the second-generation IMiDs lenalidomide and pomalidomide (Celgene Corporation POMALYST, 2016; Celgene Europe Ltd., 2016a; Celgene Corporation Revlimid, 2013; Celgene Europe Ltd., 2016b) and the second-generation PIs carfilzomib and ixazomib (Kyprolis, 2015; Kyprolis, 2016; Millennium Pharmaceuticals Ninlaro, 2015; Takeda Pharma Nilaro, 2016) provides additional within-class treatment options for patients with RRMM. With multiple classes of agent now available, each with differing mechanisms of action and efficacy and safety profiles, it can be difficult for physicians to decide upon the most appropriate agent to use. In the relapsed setting, treatment choice is additionally influenced by a number of patient- and disease-related factors such as age, cytogenetics, pre-existing toxicities, aggressiveness of relapse, previous therapy, response to previous therapy and number of previous therapy lines (Laubach et al., 2016; Cornell and Kassim, 2016; Moreau et al., 2013). Patients should not be defined by one single characteristic: multiple factors should be considered in order to tailor treatment to the individual needs of each patient. Here we provide an overview of the different classes of agent currently approved for the treatment of RRMM and the factors that should guide treatment decisions. We also discuss additional considerations for treating elderly patients, those with high-risk cytogenetic abnormalities and those with refractory disease.

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https://doi.org/10.1016/j.critrevonc.2017.11.016
Received 25 April 2017; Received in revised form 14 November 2017; Accepted 30 November 2017

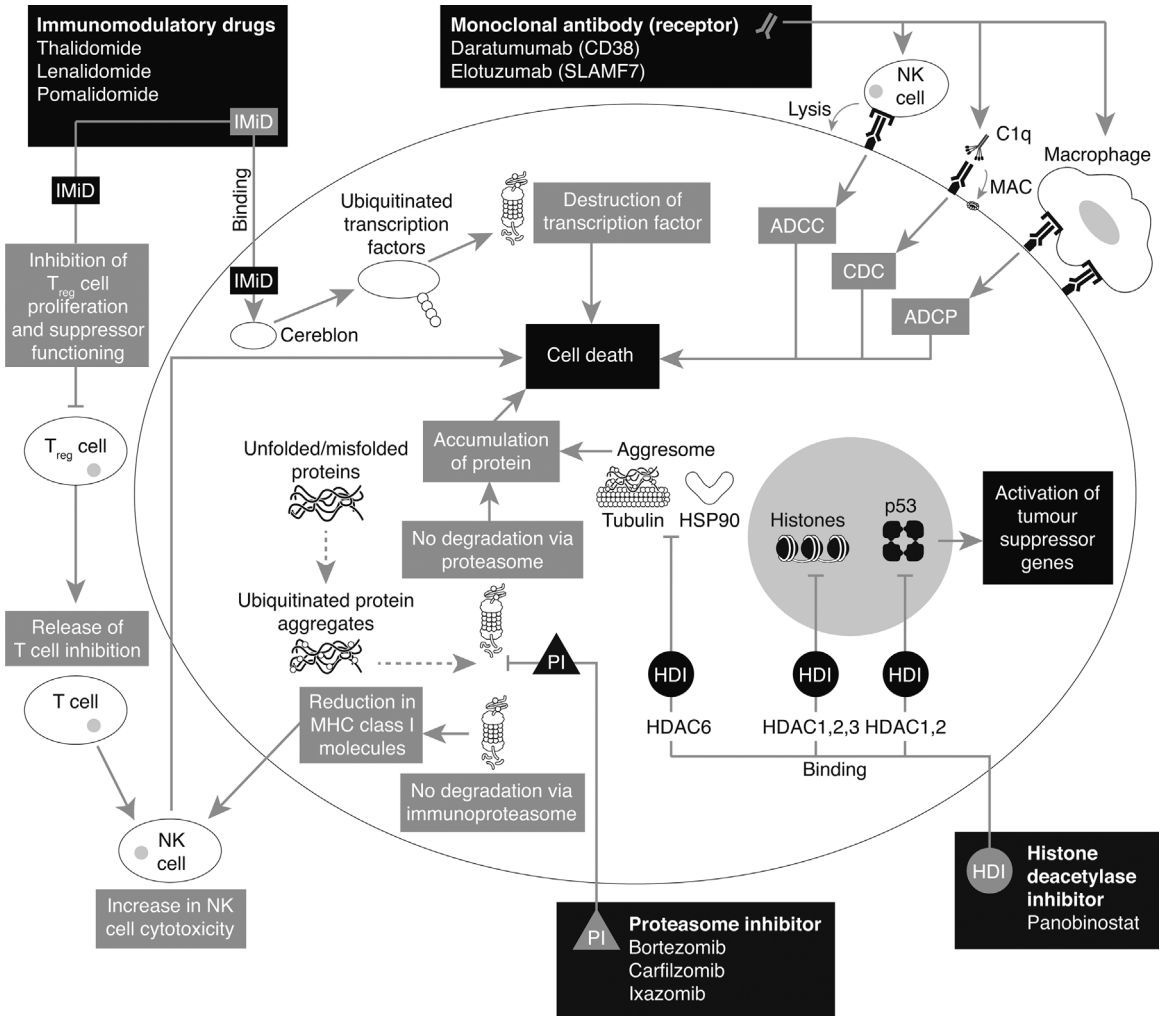

Fig.1. Summary of sub-cellaulr pathway-directed novel agents.

2. Classes of approved agent

2.1. Immunomodulatory drugs

The IMiD thalidomide, a synthetic derivative of glutamic acid, was the first immunomodulatory agent to be used for the treatment of MM (Celgene Corporation Thalomid, 2014; Celgene Europe Ltd., 2016c; Quach et al., 2010). The second-generation IMiDs lenalidomide and pomalidomide are thalidomide analogues (Quach et al., 2010). IMiDs possess multiple anti-myeloma properties that include immune modulation, along with anti-angiogenic, anti-inflammatory and anti-proliferative effects, which are mediated through direct and indirect mechanisms (Quach et al., 2010; Zhu et al., 2013). A direct anti-myeloma mechanism of IMiDs was recently determined with the identification of the IMiD target cereblon, an adaptor subunit of the E3 ubiquitin ligase that is required for their anti-myeloma activity. The binding of an IMiD to cereblon alters its substrate specificity, resulting in aberrant proteasomal degradation of the transcription factors Ikaros and Aiolos; this leads to downregulation of the pro-myeloma interferon regulatory factor 4 (Fig. 1). Lenalidomide, but not thalidomide or pomalidomide, has also been shown to cause cereblon-mediated degradation of casein kinase 1α, which leads to p53 activation (Ito and Handa, 2016). Indirect mechanisms of IMiDs include immunomodulation mediated through enhancement of CD4+ and CD8+ T cell co-stimulation, downregulation of inflammatory cytokines and augmentation of anti-myeloma natural killer cell activity (Zhu et al., 2013). Lenalidomide and pomalidomide additionally inhibit regulatory T cells (Zhu et al., 2013). Lenalidomide and pomalidomide are approved in the USA and Europe for the treatment of patients with RRMM (Table 1).

2.2. Proteasome inhibitors

The PIs bortezomib, carfilzomib and ixazomib target the ubiquitin–proteasome system, which is responsible for the degradation of intracellular proteins and the maintenance of cellular protein homeostasis. Inhibition of this system affects a number of components in cell-signalling pathways, leading to cell-cycle arrest, promotion of apoptosis and disruption of the stress response (Shah and Orlowski, 2009) (Fig. 1). MM cells are particularly sensitive to proteasome inhibition because they produce large quantities of protein in the form of immunoglobulin chains, and are dependent on proteasome-controlled signalling pathways for protein degradation (inhibition of which leads to the toxic accumulation of aggregated proteins) (Shah and Orlowski, 2009). Targeting the immunoproteasome, the proteolytic activity of which generates peptide substrates optimized for presentation on the major histocompatibility complex (MHC) class I molecules, is also relevant in MM because expression of the immunoproteasome is elevated in cells of haematopoietic origin (Kuhn and Orlowski, 2012). Inhibition of the immunoproteasome reduces surface expression of host protein fragments on MHC class I molecules, and thus may enhance natural killer cell-mediated cytotoxicity (Altun et al., 2005). Data suggest that the inhibition of both the constitutive proteasome and the immunoproteasome may be required for MM cell cytotoxicity (Kuhn and Orlowski, 2012).

Table 1
Approved indications for agents in relapsed and/or refractory MM (Farydak, 2016a; Farydak, 2016b; Squibb, 2015; Squibb, 2016; Darzalex, 2015; Darzalex, 2016; Celgene Corporation POMALYST, 2016; Celgene Europe Ltd., 2016a; Celgene Corporation Revlimid, 2013; Celgene Europe Ltd., 2016b; Kyprolis, 2015; Kyprolis, 2016; Takeda Pharma Nilaro, 2016; Celgene Corporation Thalomid, 2014; Celgene Europe Ltd., 2016c; Velcade, 2016; Millennium Pharmaceuticals Velcade, 2015).

Class/agent	Region	Year	Therapy setting	Combination	Patient population
Immunomodulatory drugs					
Thalidomide	Europe	2008	First-line[a]	Melphalan and prednisone	Patients with MM aged ≥65 years or who are ineligible for high-dose chemotherapy
	USA	1998	First-line[a]	Dexamethasone	Patient with newly diagnosed MM
Lenalidomide	Europe	2007	Relapsed	Dexamethasone	Patients with MM who have received at least one previous line of therapy
	USA	2005	Relapsed	Dexamethasone	Patients with MM who have received at least one previous line of therapy
Pomalidomide	Europe	2013	Relapsed	Dexamethasone	Patients with MM who have received at least two previous treatment regimens, including lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy
	USA	2013	Relapsed	Dexamethasone	Patients with MM who have received at least two previous therapies, including lenalidomide and a PI, and who have demonstrated disease progression on or within 60 days of completion of the last therapy
Proteasome inhibitors					
Bortezomib	Europe	2004	First-line Relapsed	Melphalan and prednisone	Patients with previously untreated MM who are not eligible for high-dose chemotherapy or a SCT
				Dexamethasone	Patients with progressive MM who have received at least one previous therapy and who have already undergone or are unsuitable for a SCT
				Dexamethasone and thalidomide	
				Monotherapy	
				Pegylated liposomal doxorubicin	
				Dexamethasone	
	USA	2003	First-line and relapsed		Patients with MM
Carfilzomib	Europe	2015	Relapsed	Dexamethasone	Patients with MM who have received at least one previous therapy
				Lenalidomide and dexamethasone	
	USA	2012	Relapsed	Monotherapy	Patients with MM who have received at least two previous therapies, including bortezomib and an IMiD, and who have demonstrated disease progression on or within 60 days of completion of their last therapy
				Lenalidomide and dexamethasone	Patients with MM who have received one to three previous lines of therapy
Ixazomib	Europe	2016	Relapsed	Lenalidomide and dexamethasone	Patients with MM who have received at least one previous therapy
	USA	2015	Relapsed	Lenalidomide and dexamethasone	Patients with MM who have received at least one previous therapy
Histone deacetylase inhibitors					
Panobinostat	Europe	2015	Relapsed	Bortezomib and dexamethasone	Patients with MM who have received at least two previous lines of therapy including bortezomib and an IMiD
	USA	2015	Relapsed	Bortezomib and dexamethasone	Patients with MM who have received at least two previous lines of therapy including bortezomib and an IMiD
Monoclonal antibodies					
Daratumumab	Europe	2016	Relapsed	Monotherapy	Patients with MM whose previous therapy included a PI and an IMiD and who have demonstrated disease progression on the last therapy
	USA	2015	Relapsed	Monotherapy	Patients with MM who have received at least three previous lines of therapy including a PI and an IMiD, or who are double refractory to a PI and an IMiD
				Lenalidomide and dexamethasone OR Bortezomib and dexamethasone	Patients with MM who have received at least one previous line of therapy
Elotuzumab	Europe	2016	Relapsed	Lenalidomide and dexamethasone	Patients with MM who had received at least one previous therapy
	USA	2015	Relapsed	Lenalidomide and dexamethasone	Patients with MM who have received one to three previous lines of therapy

IMiD, immunomodulatory drug; MM, multiple myeloma; PI, proteasome inhibitor; SCT, stem-cell transplantation.

[a] Although thalidomide is approved for first line only, it is an effective treatment that is often used off-label in the relapsed setting (Moreau et al., 2013).

Although the three PIs share a molecular target, they differ in their active moiety and their binding reversibility (Teicher and Tomaszewski, 2015; Offidani et al., 2014). Bortezomib and ixazomib are reversible boronic acid inhibitors of the chymotrypsin-like activity of the proteasome (Teicher and Tomaszewski, 2015; Offidani et al., 2014). Carfilzomib is an irreversible tetrapeptide epoxyketone PI that, compared with bortezomib, is more selective for the chymotrypsin-like activity of the proteasome and shows less reactivity with other proteasome subunits (Teicher and Tomaszewski, 2015; Demo et al., 2007; Yang et al., 2011). In contrast to bortezomib and carfilzomib, ixazomib has good oral bioavailability and thus can be administered in capsule form (Offidani et al., 2014). The European and American approvals for each PI are detailed in Table 1.

2.3. Histone deacetylase inhibitors

HDIs are a novel class of agent in MM. Histone acetyltransferases and HDACs are enzymes that control the acetylation status of proteins and affect a broad array of physiological processes, including cell-cycle regulation, apoptosis and protein folding (Kaufman et al., 2013). In MM, the inhibition of histone deacetylation leads to DNA damage and upregulates proteins that promote apoptosis and cell-cycle arrest (Moore, 2016). Panobinostat is the only HDI approved for the treatment of RRMM; it is indicated in combination with bortezomib and dexamethasone in patients who have received at least two previous lines of therapy including bortezomib and an IMiD (Table 1) (Farydak, 2016a; Farydak, 2016b).

2.4. Monoclonal antibodies

mAbs targeted against antigens expressed on MM cells are an important new class of agent in MM treatment. Such mAbs induce cell death via a number of mechanisms, including Fc-dependent effector mechanisms (antibody-dependent cell-mediated cytotoxicity, [ADCC] complement-dependent cytotoxicity [CDC], and antibody-dependent cellular phagocytosis [ADCP]) (Fig. 1). They may also have direct effects via modulation of the activity of the targeted antigen (van de Donk et al., 2016).

Daratumumab is a fully human immunoglobulin G1 mAb against CD38, a transmembrane glycoprotein that is highly expressed on MM cells (van de Donk et al., 2016). Daratumumab kills MM cells via CDC, ADCC, ADCP, direct induction of apoptosis, and modulation of CD38 ectoenzyme function (van de Donk et al., 2016). Daratumumab is indicated as a single agent (Darzalex, 2015; Darzalex, 2016). In the USA, daratumumab is also indicated in combination with lenalidomide plus dexamethasone and with bortezomib plus dexamethasone (Darzalex, 2015). These combinations have recently received a positive opinion by the European Committee for Medicinal Products for Human Use (European Medicines Agency, 2017).

Elotuzumab is a humanized immunoglobulin G1 mAb against the signalling lymphocytic activation molecule F7 (SLAMF7), a cell-surface glycoprotein expressed on MM cells, natural killer cells and a subgroup of other immune cells (van de Donk et al., 2016). Elotuzumab directly enhances natural killer cell cytotoxicity via SLAMF7 ligation (van de Donk et al., 2016). Elotuzumab is approved for use in combination with lenalidomide and dexamethasone (Table 1) (Squibb, 2015; Squibb, 2016).

An overview of the mechanism of action of each class of agent is presented in Fig. 1.

3. Treatment options for relapsed disease

The choice of therapy at relapse depends on a number of factors, including efficacy of and tolerance to previous therapy, number of previous treatment lines, time since relapse and aggressiveness of relapse, patient age, comorbidities and performance status (Cornell and Kassim, 2016; Moreau et al., 2013). Data suggest that, for patients who relapse following a durable response off treatment of at least 6–9 months, retreatment with the same or similar agents used in the previous line of therapy, or in combination with other agents, may induce a second remission; in two retrospective studies of MM treatment patterns, median time to progression was 9.3–9.7 months following retreatment with bortezomib (Conner et al., 2008; Hrusovsky et al., 2010). However, in those who have experienced a short remission, re-exposure to the same agent in sequential lines of therapy may be associated with increased rates of treatment resistance (Bird et al., 2014).

A second auto stem-cell transplantation (auto-SCT) may be considered in eligible patients who have previously received a transplant; the results of several studies suggest that a minimum interval of 18 months from first auto-SCT to relapse results in a second progression-free survival (PFS) of approximately half the duration of the first remission (Laubach et al., 2016). In a recent study of 297 patients who had relapsed following an auto-SCT, a second salvage auto-SCT resulted in improved PFS compared with the control arm (19 months vs. 11 months) (Cook et al., 2016). The control arm in this study was cyclophosphamide. The efficacy of salvage auto-SCT compared with novel targeted therapies is yet to be determined.

Drug therapies at relapse frequently incorporate an IMiD or a PI in combination with dexamethasone. Results from phase III trials show that, when used in combination with dexamethasone, IMiDs are associated with significant improvements in overall response rate (ORR) and overall survival (OS) compared with dexamethasone alone (Table 2) (Dimopoulos et al., 2007; Weber et al., 2007; San Miguel et al., 2013; Dimopoulos et al., 2004; Dimopoulos et al., 2001; Kropff et al., 2012). IMiDs are associated with a number of adverse events (AEs), notably haematological toxicity (including neutropenia and thrombocytopenia) and venous thromboembolism (Table 2) (Dimopoulos et al., 2007; Weber et al., 2007; San Miguel et al., 2013; Dimopoulos et al., 2009). Thalidomide is additionally associated with an increased risk of peripheral neuropathy (PN) (Rajkumar et al., 2008). The PIs bortezomib and carfilzomib have been shown to improve ORR and PFS when used in combination with dexamethasone (Dimopoulos et al., 2016a; Harrison et al., 2015). Carfilzomib plus dexamethasone has been shown to significantly improve PFS and OS compared with bortezomib plus dexamethasone in the head-to-head phase III ENDEAVOR study (Table 2) (Dimopoulos et al., 2016a; Dimopoulos et al., 2017). Currently there are no phase III study data assessing ixazomib in combination with dexamethasone alone. AEs of special interest that are associated with PIs include neutropenia, thrombocytopenia, PN and cardiovascular events (Kyprolis, 2015; Kyprolis, 2016; Velcade, 2016; Millennium Pharmaceuticals Velcade, 2015). In ENDEAVOR, carfilzomib was associated with a significantly lower incidence of PN of grade ≥ 2 than bortezomib (6% vs. 32%) (Dimopoulos et al., 2016a). Although monotherapy is not commonly used in patients with RRMM, it should be noted that bortezomib monotherapy has shown efficacy in the phase III APEX study (Table II) (Harrison et al., 2015; Richardson et al., 2005). However, carfilzomib monotherapy did not improve OS when compared with low-dose corticosteroid treatment (plus optional cyclophosphamide) in patients who had received ≥ 3 previous lines of therapy (Table 2) (Hajek et al., 2016). Currently there are no phase III trial data assessing the efficacy of ixazomib monotherapy. It should also be highlighted that the recently approved mAb daratumumab has shown efficacy as monotherapy in patients with RRMM who have received a minimum of three previous lines of therapy or who had disease that was double refractory to IMiDs and PIs in the phase II SIRIUS study (Table 2) (Lonial et al., 2016).

Additionally, several studies have demonstrated increased efficacy when different drug classes with distinct mechanisms of action are combined for the treatment of RRMM, and recent guidelines recommend combination therapies in this setting (Laubach et al., 2016). Doublet and triplet regimens often improve response rates compared

Table 2
Pivotal trials in RRMM.

Clinical trial (phase III unless otherwise stated)	Intervention	Patients enrolled	Previous treatments as specified by eligibility criteria	Findings	AEs at grade 3 or above reported by ≥5% of patients treated with the study drug/regimen
Immunomodulatory drugs					
Thalidomide					
(Dimopoulos et al., 2001) (phase II)	THAL + DEX	44	1–5	ORR: 55%[a] OS: 12.6 months	NS
(Dimopoulos et al., 2004) (phase II)	THAL + DEX + CYPH	53	1–5 (including THAL)	ORR: 60% OS: 17.5 months	Neutropenia: 26%
OPTIMUM (Kropff et al., 2012)	THAL vs. DEX	499 (ITT)	1–3	ORR: 18% vs. 25% ($P > 0.05$) PFS: 7.3 vs. 6.0 months OS: 25.6 months vs. NR ($P = 0.904$)	Neutropenia: 6% vs. 0%[b] Anaemia: 6% vs. 4%
Lenalidomide					
MM-009 (Weber et al., 2007)	LEN + DEX vs. placebo + DEX	353	≥1	ORR: 61.0% vs. 19.9% ($P < 0.001$) OS: 29.6 vs. 20.2 months ($P < 0.001$)	Neutropenia: 41.2% vs. 4.6%[b] Infection: 21.5% vs. 12% Thrombocytopenia: 14.7% vs. 6.9% VTE: 14.7% vs. 3.4% Anaemia: 13.0% vs. 5.1%
MM-010 (Dimopoulos et al., 2007)	LEN + DEX vs. placebo + DEX	351	≥1	ORR: 60.2% vs. 24.0% ($P < 0.001$) OS: NR vs. 20.6 months ($P = 0.03$)	Neutropenia: 29.5% vs. 2.3%[b] Thrombocytopenia: 11.4% vs. 5.7% PN: < 10%
Pomalidomide					
MM-003 (San Miguel et al., 2013)	POM + DEX vs. DEX	455	≥2 (including BORT +/− LEN, or adequate alkylator treatment)	ORR: 31% vs. 10% ($P < 0.0001$) OS: 12.7 vs. 8.1 months ($P = 0.0285$) PFS: 4.0 vs. 1.9 months ($P < 0.0001$)	Neutropenia: 48% vs. 16%[c] Infection: 34% vs. 33% Anaemia: 33% vs. 37% Thrombocytopenia: 22% vs. 26% Pneumonia: 14% vs. 10% Dyspnoea: 5% vs. 5%
Proteasome inhibitors					
Bortezomib					
APEX (Richardson et al., 2005)	BORT vs. high-dose DEX	669	1–3 (patients previously exposed to bortezomib and those with DEX-refractory disease were excluded)	ORR: 38% vs. 18% ($P < 0.001$) TTP: 6.22 vs. 3.49 months ($P < 0.001$) 1-year OS rate: 80% vs. 66% ($P = 0.003$)	Thrombocytopenia: 30% vs. 6%[b] Anaemia: 10% vs. 11% Neutropenia: 14% vs. 1% Dyspnoea: 5% vs. 4% PN: 8% vs. 1% Diarrhoea: 7% v 2% Fatigue: 6% vs. 4%
Carfilzomib					
FOCUS (Hajek et al., 2016)	CFZ vs. CS + optional CYPH	315	≥3 (including BORT, LEN or THAL or alkylating agent CS and an anthracycline)	ORR: 19.1% vs. 11.4% ($P = 0.031$) OS: 10.2 vs. 10.0 ($P = 0.417$) PFS: 3.7 vs. 3.3 months ($P = 0.248$)	Anaemia: 25% vs. 31%[c] Thrombocytopenia: 24% vs. 22% Neutropenia: 8% vs. 12% Acute renal failure: 8% vs. 3% Pneumonia: 6% vs. 12% Renal failure: 5% vs. 1%
ASPIRE (Stewart et al., 2015)	CFZ + LEN + DEX vs. LEN + DEX	792	1–3 (including BORT and LEN + DEX)	ORR: 87.1% vs. 66.7% ($P < 0.001$) OS: NR (HR for death, 0.79; $P = 0.04$) 2-year OS: 73.3% vs. 65.0% PFS: 26.3 vs. 17.6 months	Hypokalaemia: 9.4% vs. 4.9%[c] Fatigue: 7.7% vs. 6.4%

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Table 2 (*continued*)

Clinical trial (phase III unless otherwise stated)	Intervention	Patients enrolled	Previous treatments as specified by eligibility criteria	Findings	AEs at grade 3 or above reported by ≥5% of patients treated with the study drug/regimen
				($P = 0.0001$)	
ENDEAVOR (Dimopoulos et al., 2016a; Dimopoulos et al., 2017)	CFZ + DEX vs. BORT + DEX	929	1–3 (including BORT + CFZ)	ORR: 76.9% vs. 62.6% ($P < 0.0001$) OS: 47.6 vs. 40.0 months (HR for death, 0.79; $P = 0.01$) PFS: 18.7 vs. 9.4 months ($P < 0.0001$)	Anaemia: 14% vs. 10%[c] Hypertension: 9% vs. 3% Thrombocytopenia: 9% vs. 9% Fatigue: 5% vs. 7% Dyspnoea: 5% vs. 2%
Ixazomib					
TOURMALINE-MM1 (Moreau et al., 2016a; Food and Drug Administration, 2015)	IXA + LEN + DEX vs. placebo + LEN + DEX	722	1–3 (patients refractory to LEN or PI were not included; patients with primary refractory disease were included)	First interim analysis: ORR: 78% vs. 72% ($P = 0.04$) OS: NR PFS: 20.6 vs. 14.7 months ($P = 0.01$) Second interim analysis: ORR: 78% vs. 72% OS: NR PFS: 20.0 vs. 15.9 months ($P = 0.0548$)	Neutropenia: 23% vs. 24% Thrombocytopenia: 19% vs. 9% Anaemia: 9% vs. 13% Diarrhoea: 6% vs. 3% Rash: 5% vs. 2% Arrhythmias: 6% vs. 3%
Histone deacetylase inhibitors					
Panobinostat					
PANORAMA 1 (San-Miguel et al., 2014)	PANO + BORT + DEX vs. placebo + BORT + DEX	768	1–3 (patients with primary refractory or BORT-refractory disease were excluded)	ORR: 60.7% vs. 54.6% ($P = 0.09$) PFS: 12.0 vs. 8.1 months ($P < 0.0001$) OS: data not mature (at the time of analysis 33.6 vs. 30.4 months; $P = 0.26$)	Lymphocytopenia: 54% vs. 40% Neutropenia: 35% vs. 11% Diarrhoea: 26% vs. 8% Asthenia of fatigue: 24% vs. 12% Anaemia: 18% vs. 19% PN: 18% vs. 15% Pneumonia: 13% vs. 11% Nausea: 6% vs. 1% Vomiting: 7% vs. 1%
Monoclonal antibodies					
Elotuzumab					
ELOQUENT-2 (Lonial et al., 2015a)	ELO + LEN + DEX vs. LEN + DEX	646	1–3	ORR: 79% vs. 66% ($P = 0.001$) OS: not mature PFS: 19.4 vs. 14.9 months (HR for progression or death in ELO + LEN + DEX group, 0.70; $P < 0.001$)	Lymphocytopenia: 77% vs. 49% Neutropenia: 34% vs. 44% Thrombocytopenia: 19% vs. 20% Anaemia: 19% vs. 21% Fatigue: 8% vs. 8% Diarrhoea: 5% vs. 4% Back pain: 5% vs. 4%
Daratumumab					
SIRIUS (Lonial et al., 2016) (phase 2)	DARA	106	≥3 (including PI and IMiDs or patients with PI- and ImiD-refractory disease)	ORR: 29.2% PFS: 3.7 months OS: 17.5 months	Anaemia: 24% Thrombocytopenia: 19% Neutropenia: 12%
CASTOR (Palumbo et al., 2016)	DARA + BORT + DEX vs. BORT + DEX	498	≥1 (patients with PI-refractory disease were excluded)	OS: not mature PFS: NR vs. 7.2 months ($P < 0.001$)	Thrombocytopenia: 45.3% vs. 32.9% Anaemia: 14.4% vs. 16% Neutropenia: 12.8%vs. 4.2%

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Table 2 (*continued*)

Clinical trial (phase III unless otherwise stated)	Intervention	Patients enrolled	Previous treatments as specified by eligibility criteria	Findings	AEs at grade 3 or above reported by ≥5% of patients treated with the study drug/regimen
				ORR: 82.9% vs. 63.2% ($P < 0.001$)	Lymphocytopenia: 9.5% vs. 2.5% Hypertension: 6.6% vs. 0.8% Pneumonia: 8.2% vs. 9.7%
POLLUX (Dimopoulos et al., 2016b)	DARA + LEN + DEX vs. LEN + DEX	569	≥1 (patients with LEN-refractory disease were excluded)	ORR: 92.9% vs. 76.4% ($P < 0.001$) PFS: NR vs. 18.4 months ($P < 0.001$) OS data not mature	Lymphocytopenia: 5.3% vs. 3.6% Thrombocytopenia: 12.7% vs. 13.5% Neutropenia: 51.9% vs. 37.0% Anaemia: 12.4% vs. 19.6% Febrile neutropenia: 5.7% vs. 2.5% Diarrhoea: 5.3% vs. 3.2% Fatigue: 6.4 vs. 2.5% Pneumonia: 7.8% vs. 8.2%

AE, adverse events; BORT, bortezomib; CFZ, carfilzomib; CYPH, cyclophosphamide; CS, corticosteroid; DARA, daratumumab; DEX, dexamethasone; ELO, elotuzumab; HR, hazard ratio; IMiD, immunomodulatory drug; IXA, ixazomib; LEN, lenalidomide; NR, not reached; NS, not stated; ORR, overall response rate; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; PI, proteasome inhibitor; POM, pomalidomide; PN, peripheral neuropathy; RRMM, relapsed and/or refractory multiple myeloma; THAL, thalidomide; TTP, time to progression; VTE, venous thromboembolism.

[a] Reported results are for the approved dose of thalidomide, 200 mg/day. [b]AE grade 3–4. [c]AE grade ≥3.

with single-agent therapy, but they can be associated with increased toxicity; therefore, single-agent or doublet therapy, rather than triplet therapy, may be preferable in patients with a poor performance status (Bird et al., 2014). With multiple classes of agent available, and now often several drug options within each class, it can be a challenge for the physician to determine which agent or combination of agents to use at relapse (Fig. 2).

3.1. Combining IMiDs and PIs

Preclinical and clinical data in patients with RRMM provide strong evidence for combining IMiDs and PIs. By targeting the immunoproteasome, PIs reduce expression of host protein fragments on MHC class I molecules, enhancing natural killer cell-mediated cytotoxicity (Altun et al., 2005). Given the ability of IMiDs to stimulate natural killer cells, a synergistic effect is observed when these two classes of agent are combined (Anderson, 2012). IMiDs and PIs may, theoretically, work antagonistically because PIs could prevent degradation of cereblon protein targets required for IMiD anti-myeloma activity (Shi et al., 2015). However, in a phase III study in which patients received thalidomide and dexamethasone with or without bortezomib, median PFS was significantly longer for patients who received bortezomib than those who did not (18.3 months vs. 13.6 months; hazard ratio [HR], 0.59; $P < 0.001$) (Garderet et al., 2012). Grade 3 PN was, however, more frequent with the three-drug than with the two-drug regimen (29% vs. 12%; $P < 0.001$) (Garderet et al., 2012). This is perhaps unsurprising given that both thalidomide and bortezomib are independently associated with an increased risk of PN (Rajkumar et al., 2008; Richardson et al., 2005). In this study bortezomib was administered intravenously on a twice-weekly dosing schedule (Garderet et al., 2012). Subcutaneous administration of bortezomib on a weekly dosing schedule rather than intravenous administration has been shown to reduce the incidence of PN (Moreau et al., 2011; Mateos and San Miguel, 2012). There was no difference in the incidence of cardiac AEs between patients who received bortezomib and those who did not (15% vs. 13%) (Richardson et al., 2005). However, bortezomib treatment has been associated with cases of congestive heart failure or new-onset left ventricular ejection fraction (Velcade, 2016).

In the phase III ASPIRE study, the addition of carfilzomib to lenalidomide and dexamethasone significantly improved median PFS compared with lenalidomide and dexamethasone (26.3 months vs. 17.6 months; $P = 0.0001$) in patients who had received one to three previous lines of therapy and whose disease had not progressed during treatment with bortezomib or lenalidomide plus dexamethasone if it was their most recent treatment (Table 2) (Stewart et al., 2015). Interestingly, patients in the carfilzomib group reported superior health-related quality of life than those in the control group (Stewart et al., 2015). Grade ≥3 AEs were reported in 83.7% of patients in the carfilzomib group and 80.7% of patients receiving lenalidomide and dexamethasone only (Stewart et al., 2015). Cardiac AEs of grade ≥3 were more common in the carfilzomib group than in the control group (hypertension 4.3% vs. 1.8%; cardiac failure 3.8% vs. 1.8%; ischaemic heart failure 3.3% vs. 2.1%, respectively). In contrast to the data presented above on combining bortezomib and IMiDs, adding carfilzomib to lenalidomide and dexamethasone did not increase the incidence of PN (17.1% vs. 17.0%, respectively) (Stewart et al., 2015).

The phase III TOURMALINE-MM1 study comparing ixazomib plus lenalidomide and dexamethasone vs. lenalidomide and dexamethasone provided further support for the combination of IMiDs and PIs in patients with RRMM (Table 2). The study enrolled patients who had received one to three previous lines of therapy and who were not refractory to previous therapy with lenalidomide or a PI. Median PFS was significantly longer for patients in the ixazomib group than for patients receiving lenalidomide and dexamethasone only (20.6 months vs. 14.7 months; HR, 0.74; $P = 0.01$) (Moreau et al., 2016a). However, an updated analysis conducted by the U.S. Food and Drug Administration

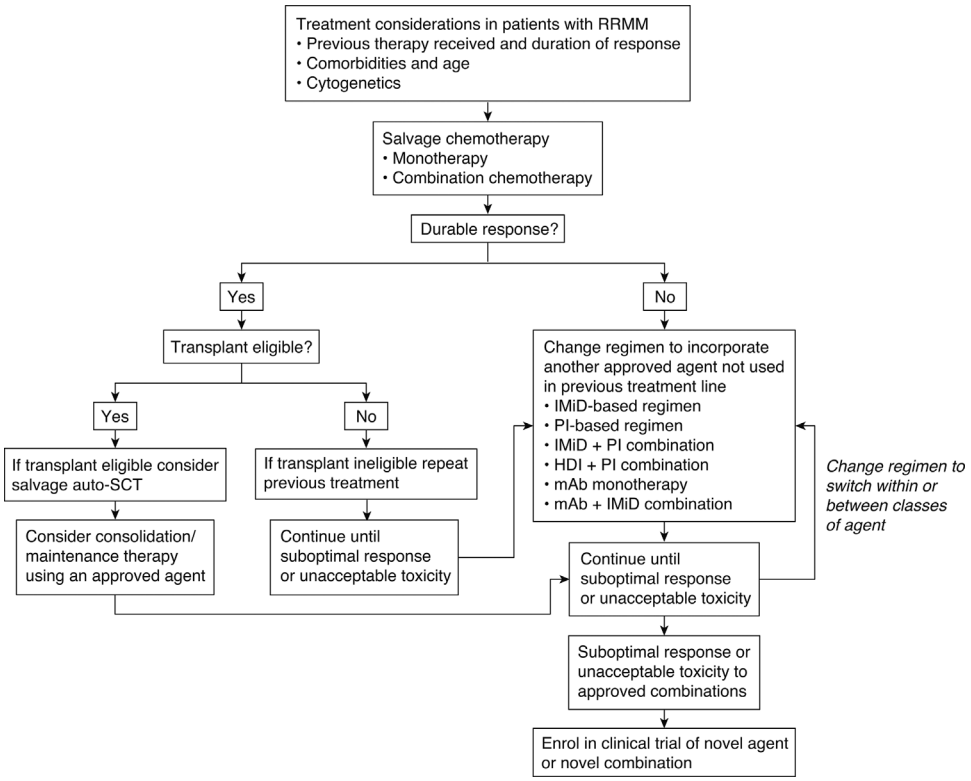

Fig. 2. Proposed treatment pathway for the management of RRMM.

found that ixazomib did not significantly improve PFS compared with control treatment (20.0 months vs. 15.9 months; HR, 0.82; $P = 0.0548$) (Food and Drug Administration, 2015). Median OS has not been reached in either group and the study is ongoing. The incidence of grade 3 PN was 2% in both groups (Moreau et al., 2016a). Thrombocytopenia of grade 3–4 occurred more frequently in the ixazomib group (19%) than in the control group (9%). Additionally, compared with control treatment, ixazomib was associated with an increased frequency of low grade gastrointestinal AEs including diarrhoea (6% vs. 3%). This is most likely because of its oral route of administration (Moreau et al., 2016a).

Pomalidomide is indicated in patients who have received at least two previous therapies including bortezomib and lenalidomide (Table 1) (Celgene Corporation POMALYST, 2016; Celgene Europe Ltd., 2016a) and is thus a treatment option at second or later relapse. New triplet combinations based on the addition of a PI to pomalidomide plus dexamethasone have shown promising efficacy in phase I/II studies (Hofmeister et al., 2013; Shah et al., 2015; Voorhees et al., 2015); however, to date, no phase III trial data are available for these combinations.

3.2. Combining IMiDs and mAbs

Preclinical evidence shows that lenalidomide enhances the anti-myeloma activity of elotuzumab and daratumumab via activation of the effector cells of ADCC (van de Donk et al., 2016). Recent clinical studies support the use of this combination in patients with RRMM. In the phase III ELOQUENT-2 trial, the addition of elotuzumab to lenalidomide and dexamethasone significantly increased PFS compared with lenalidomide and dexamethasone alone (19.4 months vs. 14.9 months; $P = 0.001$) (Lonial et al., 2015a). Grade 3–4 lymphocytopenia occurred more frequently in patients receiving elotuzumab than in the control group (77% vs. 49%) (Table 2). Infusion reactions occurred in 10% of patients in the elotuzumab group: most were grade 1 or 2 (Lonial et al., 2015a). Elotuzumab has also been associated with secondary primary malignancies (SPMs); 6.9% of patients receiving elotuzumab plus lenalidomide and dexamethasone developed invasive SPMs compared with 4.1% of patients receiving lenalidomide and dexamethasone (Squibb, 2016). It must be noted that lenalidomide has also been associated with an increased risk of SPM. Overall, the incidence of SPMs is low and should be considered in the context of the benefits and risks of treatment with other options (Musto et al., 2016).

In the phase III POLLUX study, the addition of daratumumab to lenalidomide and dexamethasone significantly increased PFS (not reached [NR] vs. 18.4 months; HR, 0.37; $P < 0.001$) (Dimopoulos et al., 2016b). Grade 3–4 AEs in the daratumumab and control groups included neutropenia, thrombocytopenia and anaemia (Table 2). Infusion reactions occurred in 48% of patients in the daratumumab group and were mostly grade 1 or 2 (Dimopoulos et al., 2016b). Infusion reactions are a key safety signal for both elotuzumab and daratumumab, with most AEs of this type occurring during the first infusion (Squibb, 2016; Darzalex, 2016). The incidence and severity of infusion reactions can be reduced by the pre-infusion prophylactic administration of dexamethasone, antihistamines and acetaminophen (van de Donk et al., 2016).

Although mature phase III study data are available only for lenalidomide and mAbs, preclinical and clinical synergy has also been demonstrated between mAbs and the IMiDs thalidomide and pomalidomide; phase II and III studies assessing these combinations are ongoing (Chari et al., 2015; Mateos et al., 2016a; San Miguel et al., 2016).

3.3. Combining PIs and mAbs

Preclinical data show enhanced ADCC in MM cells when bortezomib and daratumumab are used together. The synergistic efficacy of these two classes of agent has been confirmed in the phase III CASTOR study comparing daratumumab plus bortezomib and dexamethasone vs. bortezomib and dexamethasone. In a pre-specified interim analysis, treatment with daratumumab led to a significant increase in median PFS compared with bortezomib and dexamethasone treatment alone (NR vs. 7.2 months; HR, 0.39; $P < 0.001$) (Palumbo et al., 2016). Grade 3–4 AEs in the daratumumab group and the bortezomib and

dexamethasone only group included thrombocytopenia, anaemia and neutropenia (Table 1). Infusion-related reactions were reported in 45.3% of the patients in the daratumumab group; these reactions were mostly grade 1–2 (Palumbo et al., 2016). As noted above, most infusion reactions associated with mAbs occur during the first dose (Darzalex, 2016). It should also be noted that daratumumab treatment has been shown to interfere with blood compatibility testing, which may complicate blood transfusions (Dimopoulos et al., 2016b).

No phase III study data are available on the combination of mAbs with carfilzomib or ixazomib, but it is possible that similar synergy would be seen with these PIs.

3.4. Combining PIs and HDIs

By inhibiting the proteasome, PIs lead to accumulation of protein aggregates that can be removed from the cell by autophagy. HDAC6 is thought to promote MM cell survival by facilitating autophagy, and HDIs prevent HDAC6 from performing this function. Therefore, a synergistic effect is seen when combining PIs and HDIs (Kaufman et al., 2013). In the phase III PANORAMA 1 study, addition of panobinostat to bortezomib and dexamethasone significantly improved PFS compared with bortezomib and dexamethasone alone (12.0 months vs. 8.1 months; HR, 0.63: $P < 0.0001$). There was no significant difference in median OS between the panobinostat and control groups; however, OS data are not mature and the study is ongoing (San-Miguel et al., 2014). Grade 3–4 AEs that occurred more frequently in the panobinostat plus bortezomib and dexamethasone group than in the bortezomib and dexamethasone group were diarrhoea (25.5% vs. 8.0%), nausea (5.5% vs. < 1.0%) and vomiting (7.3% vs. 1.3%) (Table 2) (San-Miguel et al., 2014).

4. Special patient subgroups

With the expanding treatment options now available in RRMM, the individualization of treatment is becoming increasingly important to optimize patient outcomes. Better understanding of treatment effects in patient subgroups can, therefore, help to inform physicians. Despite many studies not being powered to analyse differential treatment outcomes between patient subgroups, they can provide helpful information to aid treatment pathway decisions. However, it is important to note that although subgroup data are useful, patients may have multiple subgroup characteristics and thus treatment selection should be guided by multiple patient and disease factors. Subgroup analyses from pivotal studies in RRMM are presented in Table 3.

4.1. Elderly patients

Management of RRMM in elderly patients (those aged ≥65 years) and very elderly patients (those aged ≥75 years) is particularly challenging owing to an increased burden of patient comorbidities and a reduced resilience to treatment-related toxicities (Larocca and Palumbo, 2015). A meta-analysis of 1435 patients aged ≥65 years who were enrolled in four phase III studies confirmed that an age of ≥75 years is an independent negative risk factor for death (Bringhen et al., 2013). The survival benefits seen in younger patients following the availability of novel agents have not been observed to the same extent in elderly patients (Schaapveld et al., 2010). In very elderly frail patients, the aim of treatment may not be to achieve a deep response but rather to maintain the disease in an asymptomatic state in order to preserve quality of life while avoiding excessive toxicity (Larocca and Palumbo, 2015).

Elderly patients comprise a heterogeneous population of variable fitness, so the decision regarding when and how intensely to treat depends upon the characteristics of the patient (Kastritis et al., 2015). When making treatment decisions in this patient population, there is clear benefit in the use of geriatric assessment scores that combine multiple patient factors including age, comorbidity burden and functional status (Palumbo et al., 2015a; Hamaker et al., 2012). Indeed, in a recent pooled analysis of 869 elderly patients, scoring individuals for fitness according to age, comorbidities and cognitive and physical condition predicted mortality and risk of toxicity (Palumbo et al., 2015a). Several studies of novel classes of agent in RRMM, including IMiDs, PIs and mAbs, have reported similar efficacy in elderly patients compared with younger patients (San Miguel et al., 2013; Lonial et al., 2016; Lonial et al., 2015a; Castelli et al., 2015; Palumbo et al., 2014; Palumbo et al., 2015c). However, currently, no data are available on the efficacy of different treatment regimens according to the geriatric score, and subgroup analyses according to age have been conducted by chronological age only. Additionally, frailty scores are time consuming to calculate and thus are rarely used in routine clinical practice; the development of computer-based applications to calculate frailty scores may help to increase their use (Palumbo et al., 2015a).

Clinical data show that the IMiDs and PIs have efficacy in elderly patients (San Miguel et al., 2013; Palumbo et al., 2014; Richardson et al., 2007; Touzeau et al., 2012). In the MM-003 pomalidomide study, the HR for death or disease progression with pomalidomide plus dexamethasone vs. dexamethasone alone was 0.50 for patients aged ≤75 years and 0.36 for patients aged > 75 years (San Miguel et al., 2013). In the ENDEAVOR study carfilzomib showed improved PFS compared with bortezomib, when both PIs were used in combination with dexamethasone (Dimopoulos et al., 2016a). Median PFS was improved in each age subgroup receiving carfilzomib compared with bortezomib (< 65 years: NR vs. 9.5 months; 65–74 years: 15.6 months vs. 9.5 months; ≥75 years: 18.7 months vs. 8.9 months) (Palumbo et al., 2015c). Carfilzomib also improved OS for each age subgroup compared with bortezomib (HR for death, < 65 years: 0.85; 65–74 years: 0.71; ≥75 years: 0.84) (Dimopoulos et al., 2017). However, improvements in PFS and OS reported for patients aged ≥75 should be interpreted carefully owing to relatively small patient numbers in these analyses; 77 and 66 patients were aged ≥75 years in the carfilzomib and bortezomib groups, respectively.

Combination therapy with IMiDs and PIs have also shown efficacy in elderly patients. In the ASPIRE study, addition of carfilzomib to lenalidomide and dexamethasone resulted in improved outcomes for elderly patients compared with control treatment; however, the clinical benefit was not as great as that seen for younger patients (HR for disease progression with carfilzomib, ≥65 years: 0.85; 18–64 years, 0.60) (Stewart et al., 2015). Interim analysis of the TOURMALINE-MM1 study showed that addition of ixazomib to lenalidomide and dexamethasone improved median PFS for patients aged ≤65 years and for those aged ≥75 years, but not for patients aged > 65–75 years (≤65 years: 20.6 months vs. 14.1 months; > 65–75 years: 17.5 months vs. 17.6 months; ≥75 years: 18.5 months vs. 13.1 months) (Moreau et al., 2016a). However, owing to relatively small patient numbers in these subgroup analyses (47 and 61 patients were aged > 75 years in the ixazomib and placebo groups, respectively), further studies will be needed to clarify the role of ixazomib in patients aged 65–75 years. Ixazomib may be a good option for very elderly patients because of its weekly oral administration and its tolerable safety profile (discussed above and presented in Table 2) (Larocca and Palumbo, 2015).

The HDI panobinostat in combination with the PI bortezomib and dexamethasone provided improved outcomes in elderly patients compared with bortezomib and dexamethasone alone, although the impact was not as great as that seen in younger patients (HR, ≥65 years: 0.72; < 65 years: 0.59) (San-Miguel et al., 2014).

Newly approved mAbs, in combination with either an IMiD or a PI, have been shown to give striking improvements in outcomes for elderly patients with RRMM. Elotuzumab in combination with lenalidomide and dexamethasone improved PFS in older patients compared with lenalidomide and dexamethasone alone (HR, ≥65 years: 0.65; < 65 years: 0.75) (Lonial et al., 2015a). Similarly, daratumumab in combination with bortezomib and dexamethasone significantly

Table 3
Subgroup analyses of pivotal RRMM trials.

	Endpoint	MM-003 (San Miguel et al., 2013) pomalidomide	ASPIRE (Stewart et al., 2015) carfilzomib	ENDEAVOR (Dimopoulos et al., 2016a)carfilzomib	TOURMALINE–MM1 (Moreau et al., 2016a) ixazomib	PANORAMA 1 (San-Miguel et al., 2014) panobinostat	ELOQUENT-2 (Lonial et al., 2015a) elotuzumab	SIRIUS (Lonial et al., 2016) daratumumab	CASTOR (Palumbo et al., 2016) daratumumab	POLLUX (Dimopoulos et al., 2016b) daratumumab
		HR for PFS (95% CI)	HR for PFS (95% CI)	HR for PFS (95% CI)	HR for PFS (95% CI)	HR for PFS (95% CI)	HR for PFS (95% CI)	HR for PFS (95% CI)	HR for PFS (95% CI)	HR for PFS (95% CI)
Patient subgroup										
Age, years	18–64	–	0.60 (0.46–0.79)	0.58 (0.44–0.78)	0.68	0.59 (0.46–0.76)	0.75 (0.55–1.02)	31.0 (19.5–44.5)	0.44 (0.28–0.68)	0.40 (0.24–0.65)
	≥65	–	0.85 (0.65–1.11)	NR	–	0.72 (0.53–0.96)	0.65 (0.50–0.85)	–	0.35 (0.22–0.57)	–
	65–74	–	–	0.53 (0.38–0.73)	0.83	–	–	25.0 (12.1–42.2)	–	0.40 (0.24–0.67)
	< 75	0.50 (0.40–0.63)	–	–	–	–	–		–	–
	≥75	0.36 (0.16–0.83)	–	0.38 (0.23–0.65)	0.87	–	–	33.3 (9.9–65.1)	–	0.11 (0.02–0.51)
Cytogenetic risk	High-risk	–	0.70 (0.43–1.16)	0.65 (0.45–0.92)	0.54	0.47 (0.18–1.25)	–	20.0 (5.7–43.7)	–	–
	Standard-risk	–	0.66 (0.48–0.90)	0.44 (0.33–0.58)	0.64	0.88 (0.60–1.29)	–	29.4 (19.0–41.7)	–	–
	del(17p)	–	–	–	–	–	0.65 (0.45–0.94)	–	–	–
	1q21	–	–	–	–	–	0.75 (0.56–0.99)	–	–	–
	t(4:14)	–	–	–	–	–	0.53 (0.29–0.95)	–	–	–
ISS stage	I	–	–	0.45 (0.32–0.63)	–	0.62 (0.46–0.85)	0.63 (0.46–0.87)	38.5 (20.2–59.4)	0.25 (0.13–0.48)	0.40 (0.23–0.72
	II	–	–	–	–	–	0.86 (0.61–1.22)	30.0 (16.6–46.5)	0.37 (0.23–0.61)	0.29 (0.17–0.50)
	I/II	–	–	–	0.75	–	–	–		
	III	–	–	–	0.72	–	0.70 (0.47–1.04)	22.5 (10.8–38.5)	0.55 (0.31–1.41)	0.40 (0.21–0.76)
	II/III	–	–	0.57 (0.45–0.72)	–	0.61 (0.47–0.80)	–	–	–	–
Previous treatment	THAL	–	–	0.54 (0.41–0.71)	–	–	0.64 (0.48–0.85)	–	–	–
	BORT	0.52 (0.37–0.73)	0.70 (0.56–0.88)	0.56 (0.44–0.73)	–	0.58 (0.44–0.77)	0.68 (0.54–0.86)	–	0.46 (0.32–0.66)	
	LEN	0.38 (0.26–0.58)	0.80 (0.52–1.22)	0.69 (0.52–0.92)	–	–	0.59 (0.25–1.40)	28.0 (19.1–38.2)	–	0.42 (0.19–0.90)
	PI	–	–	–	0.74	–	–	–	–	0.37 (0.26–0.52)
	IMiD	–	–	0.60 (0.48–0.75)	0.74	0.54 (0.43–0.68)	–	–	0.38 (0.27–0.55)	–
Previous treatment lines	1	–	–	0.45 (0.33–0.61)	0.83	0.66 (0.50–0.86)	0.75 (0.56–1.00)	–	0.31 (0.18–0.52)	0.41 (0.26–0.66)
	> 1	–	–	–	–	–	–	–	–	
	2	0.47 (0.18–1.25)	–	–	0.75	–	–	–	0.50 (0.28–0.89)	0.29 (0.16–0.53)
	> 2	0.48 (0.39–0.61)	–	–	–	–	–	–	–	
	≤3	–	–	–	–	–	–	26.3 (9.1–51.2)	–	
	3	–	–	–	0.37	–	–	–	0.66 (0.31–1.41)	0.36 (0.13–1.03)
	2/3	–	–	0.60 (0.47–0.68)	–	0.64 (0.50–0.83)	0.65 (0.49–0.87)	–		
	> 3	–	–	–	–	–	–	29.9 (20.5–40.6)	0.48 (0.20–1.16)	0.53 (0.10–2.87)
Refractory status	LEN	0.50 (0.40–0.62)	–	0.80 (0.57–1.11)	–	–	–	–	–	–
	BORT	–	0.80 (0.49–1.30)	0.37 (0.13–1.08)	–	–	–	–	–	–
	IMiD	–	0.64 (0.44–0.91)	–	–	–	–	29.4 (20.8–39.3)	0.50 (0.31–0.80)	–
	PI	–	–	–	–		–	28.8 (20.4–38.6)	–	0.50 (0.27–0.93)
Renal function: creatinine clearance, mL/min	< 30	–	–	0.99 (0.46–2.16)	–	–	–	–	–	–
	30–50	–	–	0.35 (0.20–0.60)	–	–	–	–	–	–
	50–80	–	–	0.48 (0.35–0.65)	–	–	–	–	–	–
	≤60	–	–	–	–	–	0.56 (0.39–0.82)	–	0.55 (0.30–1.02)	–
	> 60	–	–	–	–	–	0.74 (0.58–0.94)	–	0.30 (0.20–0.44)	–
	≥80	–	–	0.60 (0.43–0.83)	–	–	–	–	–	–

BORT, bortezomib; CI, confidence interval; HR, hazard ratio for comparison between investigational agent/regimen and control agent/regimen; IMiD, immunomodulatory drug; ISS, International Staging System; LEN, lenalidomide; NR, not reached; ORR, overall response rate; PFS, progression-free survival; PI, proteasome inhibitor; THAL, thalidomide; –, data not reported.

Table 4
Safety considerations for elderly patients (Farydak, 2016b; Squibb, 2016; Darzalex, 2016; Celgene Europe Ltd., 2016a; Celgene Europe Ltd., 2016b; Kyprolis, 2016; Millennium Pharmaceuticals Ninlaro, 2015; Celgene Europe Ltd., 2016c; Velcade, 2016).

Agent	Special considerations for elderly patients	Dose reductions
Immunomodulatory drugs		
Thalidomide	No overall difference in safety was observed between patients aged > 75 years and younger patients; however, patients aged > 75 years are potentially at risk of a higher frequency of serious AEs	No specific dose adjustments are recommended for patients aged ≤75 years For patients aged > 75 years, the recommended starting dose is 100 mg/day
Lenalidomide	No overall difference in safety was observed between elderly and younger patients, but a greater predisposition of older individuals to AEs cannot be ruled out Myelosuppression is a concern in elderly patients Elderly patients are more likely to have decreased renal function; therefore, care should be taken in dose selection and renal function should be monitored	Initial dose: 25 mg/day First reduction: 15 mg/day Second reduction: 10 mg/day Third reduction: 5 mg/day
Pomalidomide		No dose adjustment is required for patients aged ≥65 years
Proteasome inhibitors		
Bortezomib	Thrombocytopenia is a particular concern for elderly patients	No dose adjustment is required for patients aged ≥65 years
Carfilzomib	The subject incidence of AEs (including cardiac failure) was higher for patients aged ≥75 years compared with patients aged < 75 years	Carfilzomib, lenalidomide and dexamethasone Initial dose: 27 mg/m^2 First reduction: 20 mg/m^2 Second reduction: 15 mg/m^2 Carfilzomib and dexamethasone Initial dose: 56 mg/m^2 First reduction: 45 mg/m^2 Second reduction: 36 mg/m^2 Third reduction: 27 mg/m^2
Ixazomib	No overall differences in safety were observed between elderly patients and younger patients, but greater sensitivity of some older individuals cannot be excluded	
Histone deacetylase inhibitors		
Panobinostat	It is recommended to monitor patients aged ≥65 years more frequently, especially for thrombocytopenia and gastrointestinal toxicity For patients aged > 75 years, dose adjustments may be considered	Panobinostat treatment may be started at a dose of 15 mg, and if tolerated in the first cycle, escalated to 20 mg in the second cycle
Monoclonal antibodies		
Daratumumab		No dose adjustment is required for patients aged ≥65 years
Elotuzumab		No dose adjustment is required for patients aged ≥65 years

AE, adverse event.

increased PFS for elderly patients compared with bortezomib and dexamethasone alone (HR, ≥65 years: 0.35; < 65 years: 0.44) (Palumbo et al., 2016). Daratumumab monotherapy may also be a good treatment option for elderly patients with RRMM; in the SIRIUS study, the ORR with daratumumab was 31.0% in patients aged 18–64 years, 25.0% in those aged 65–74 years and 33.3% for those aged ≥75 years (Lonial et al., 2016).

Elderly patients are more susceptible to AEs than younger patients (Larocca and Palumbo, 2015), and bortezomib-induced thrombocytopenia and lenalidomide-induced myelosuppression are a concern in these patients (Mehta et al., 2010; Tosi et al., 2013). Platelet transfusion should be considered for the treatment of thrombocytopenia (Velcade, 2016), and antibacterial prophylaxis may be warranted in severe cases of myelosuppression (Larocca and Palumbo, 2015). Subgroup analyses of the ENDEAVOR study showed that cardiac AEs associated with carfilzomib occurred most frequently in very elderly patients (Palumbo et al., 2015c). Elderly patients should be monitored for AEs more frequently than younger patients to ensure that AEs, where possible, are treated and/or doses reduced to ensure treatment can be continued (Table 4). However, in the ENDEAVOR study, the greatly improved efficacy of carfilzomib compared with bortezomib in very elderly patients may relate to better overall tolerability of carfilzomib. Rates of discontinuation owing to AEs between the two treatment arms were similar in patients aged < 65 years and those aged 65–74 years; however, in patients aged ≥75 years, discontinuations were higher in the bortezomib arm than in the carfilzomib arm (35% vs. 26%) (Palumbo et al., 2015c). Carfilzomib may, therefore, be an attractive option for elderly patients who could benefit from treatment with a PI. Reduction in bortezomib treatment frequency is efficacious and may help to reduce the AEs associated with this therapy (Ozaki et al., 2016; Fukushima et al., 2011).

4.2. Patients with high-risk cytogenetic abnormalities

MM is a highly heterogeneous disease both phenotypically and genotypically (Chng et al., 2014). A number of genetic abnormalities have been associated with poor prognosis, including del(17p), t(4;14), t(14;16) and gain in 1q (Moreau et al., 2014; Mikhael et al., 2013). Until recently, risk classification did not impact on treatment decisions. However, data show that, compared with two-drug combinations, three-drug combinations improve outcomes for patients with high-risk cytogenetic abnormalities (CAs) (Stewart et al., 2015; Moreau et al., 2016a; Lonial et al., 2015a; Dimopoulos et al., 2010). For patients with high-risk CAs, aggressive therapy should be used to prevent the emergence of resistant clones. This approach may require treatment gaps or shorter treatment durations compared with less aggressive therapy (Lonial et al., 2015b).

When considering data on treatment efficacy in patients with high-risk CAs, it is important to note that definitions of high-risk CAs may differ between studies. A consensus on the standardization of analytical techniques and the proportion of abnormal cells that determine high-risk disease is needed (Sonneveld et al., 2016). Despite this, the identification of patients who have high-risk CAs is now a crucial first step in managing their disease. CAs may differ between first and later

relapses because of clonal evolution, which may influence the effect of treatment (Sonneveld et al., 2016). Currently, however, many patients are not tested for CAs and, furthermore, retesting at relapse is not routinely performed. Owing to the impact of high-risk CAs on treatment decisions, it is recommended that patients with a normal cytogenetic profile at diagnosis should be retested at relapse.

Data are conflicting on the use of IMiDs in patients with high-risk CAs: efficacy appears to be affected by the specific genetic mutation present. Thalidomide is not recommended for patients with high-risk CAs (Lonial et al., 2015b); the role of other IMiDs in high-risk disease is unclear. A subgroup analysis of the MM016 trial compared lenalidomide plus dexamethasone with dexamethasone alone in 130 patients with del(13q), t(4;14) or del(17p13) (Reece et al., 2009). Compared with patients without high-risk CAs, median OS was similar for patients with del(13q) (24.5 months vs. 14.7 months; $P = 0.15$) or t(4;14) (18.1 months vs. 23.7 months; $P = 0.91$) (Reece et al., 2009). However, compared with patients without high-risk CAs, those with del(17p13) had a significantly worse outcome (median OS, 23.7 months vs. 4.7 months; $P = 0.001$) (Reece et al., 2009). Pomalidomide, in combination with dexamethasone, has shown efficacy in the treatment of patients with high-risk CAs (San Miguel et al., 2013). Results from the Intergroupe Francophone Myélome (IFM) 2010–02 trial showed that patients with del(17p) gained benefit from treatment with pomalidomide and dexamethasone, whereas patients with t(4;14) did not gain benefit from this combination (Leleu et al., 2015).

PIs have also shown some efficacy in the treatment of patients with high-risk CAs. A prospective study assessing the impact of cytogenetics on treatment outcome with bortezomib in combination with lenalidomide and dexamethasone found that for patients receiving bortezomib, there was no difference in ORR between those with high-risk CAs and those with standard-risk cytogenetics ($P = 0.219$) (Dimopoulos et al., 2010). However, in the control group (lenalidomide plus dexamethasone), the ORR was significantly lower for patients with high-risk CAs than for those with standard-risk cytogenetics ($P = 0.01$) (Dimopoulos et al., 2010).

Carfilzomib may be a more potent PI option than bortezomib for patients with high-risk CAs. In pre-planned subgroup analyses of ENDEAVOR, carfilzomib improved outcomes compared with bortezomib regardless of cytogenetic risk category. Carfilzomib prolonged PFS compared with bortezomib in patients with high-risk CAs (8.8 months vs. 6.0 months; HR, 0.65; $P = 0.0075$) and in those with standard-risk cytogenetics (not estimable vs. 10.2 months; HR, 0.44; $P < 0.0001$); however, it must be noted that outcomes for patients with high-risk CAs were worse than for those with standard-risk CAs (Chng et al., 2017). Carfilzomib has also shown efficacy in this patient population in combination with lenalidomide and dexamethasone. In ASPIRE, a significant increase in PFS was observed with carfilzomib regardless of patients' cytogenetic risk, where a 60% cut-off was used to define high-risk patients for t(4;14), t(14;16) and del(17p). In patients with high-risk CAs, there was a trend for increased PFS with carfilzomib compared with lenalidomide and dexamethasone alone by 9 months ($P = 0.083$) (vs. an increased PFS of 10 months for patients with standard-risk cytogenetics; $P = 0.003$) (Avet-Loiseau et al., 2016). However, it must be noted that in both ENDEAVOR and ASPIRE carfilzomib treatment did not completely overcome the poor prognosis associated with high-risk CAs (Stewart et al., 2015; Chng et al., 2017; Avet-Loiseau et al., 2016).

In TOURMALINE-MM1, ixazomib in combination with lenalidomide and dexamethasone has also been shown to improve outcomes for patients with high-risk CAs compared with lenalidomide and dexamethasone alone: in the primary analysis, median PFS among patients with high-risk CAs was 21.4 months and 9.7 months, respectively. This improvement in PFS was greater than that seen in patients with standard-risk cytogenetics (HR, 0.54 vs. 0.64) (Moreau et al., 2016a). However, the false positive cut-offs used to define patients with high-risk CAs were 5%, 3% and 3% for del(17p), t(4;14) and t(14;16), respectively, which differed from cut-offs used in similar trials of novel agents (Stewart et al., 2015; Lonial et al., 2015a). *Post hoc* analyses were conducted using more stringent cut-offs for del(17p) (20% and 60%) and t(4;14) (10%), which showed that the beneficial effect of ixazomib in patients with high-risk CAs was maintained regardless of the false-positive cut-off used to define high-risk patients (Richardson et al., 2016). It must be noted that the most appropriate cut-off for each mutation type is not known. Serial analysis of bone marrow aspirates from 936 patients by the IFM group showed that in relation to outcome the most powerful cut-offs were 74% for del(13) and 60% for del(17p) (Avet-Loiseau et al., 2007). For interpretation of all of the above trials, it must be noted that PFS is poor in patients with high-risk CAs treated with lenalidomide and dexamethasone only, and this two-drug combination is not recommended in this patient population.

The mAbs daratumumab and elotuzumab are also good treatment options for patients with high-risk CAs. In the ELOQUENT-2 study, elotuzumab exhibited similar efficacy across all patient subgroups, including those with high-risk CAs: HRs for disease progression ranged from 0.53 to 0.75 for patients with del(17p), 1q21 and t(4;14) compared with 0.70 for the overall population. However, for del(17p) no cut-off was used and patients were considered positive if one or more cells had the del(17)p mutation; therefore, the results must be considered with caution (Lonial et al., 2015a). Similar results were found for daratumumab monotherapy in the single-arm SIRIUS study: the ORR was 20% in patients with high-risk CAs compared with 29.4% in those with standard-risk cytogenetics (Lonial et al., 2016). The efficacy of daratumumab in patients with high-risk CAs was confirmed in recent subgroup analyses of the POLLUX and CASTOR trials. In patients who had received one to three previous lines of therapy and had high-risk CAs, the addition of daratumumab to lenalidomide and dexamethasone significantly improved PFS (NR vs. 8.3 months; HR, 0.30; $P = 0.0019$) and ORR (91% vs. 69%; $P = 0.0267$) compared with lenalidomide and dexamethasone treatment (Usmani et al., 2016a). In CASTOR, in patients who had received one to three previous lines of therapy and who had high-risk CAs, the addition of daratumumab to bortezomib and dexamethasone significantly improved PFS (HR, 0.46; $P = 0.0367$) and 12-month PFS rates (63% vs. 27%) compared with bortezomib and dexamethasone treatment (Mateos et al., 2016b). For comparison, the 12-month PFS rates for patients without high-risk CAs in this subgroup analysis were 58% for daratumumab plus bortezomib and dexamethasone and 27% for bortezomib and dexamethasone (Mateos et al., 2016b).

5. Patients with refractory disease: switching within and between classes of agent

Owing to the relapsing disease course of MM, patients will often receive multiple lines of therapy. Refractory disease is, therefore, a major challenge in the treatment of relapsed MM. With most patients receiving a backbone therapy of an IMiD and dexamethasone or a PI and dexamethasone, the development of disease that is refractory to one or both of these classes is a concern in RRMM. A key question following the development of refractory disease is whether to switch the class of agent from the previous line or to switch to another treatment option within the same class of agent (Ludwig et al., 2014).

5.1. IMiD-refractory disease

Evidence suggests that switching to other agents within the IMiD class can be effective in IMiD-refractory disease. Pomalidomide has shown efficacy in patients who are refractory to lenalidomide. In the MM-003 trial, pomalidomide improved outcomes compared with high-dose dexamethasone regardless of lenalidomide-refractory status; median PFS was significantly longer with pomalidomide in patients who were refractory to lenalidomide (3.9 months vs. 1.9 months; $P < 0.0001$) (San Miguel et al., 2013). Additionally, in the single-arm

phase IIIb STRATUS study of pomalidomide with low-dose dexamethasone, most enrolled patients were refractory to lenalidomide (96%), bortezomib (84%) or both (80%). Subgroup analyses showed that the efficacy (ORR, OS and PFS) of pomalidomide in combination with dexamethasone was independent of treatment history: ORRs were generally similar regardless of previous thalidomide therapy, number of previous regimens and resistance to lenalidomide or bortezomib (Moreau et al., 2015).

Combining agents with synergistic activity may also overcome drug resistance. In a recent phase I/II study in patients who had received multiple previous lines of therapy, the addition of prednisone and low-dose cyclophosphamide to lenalidomide led to an ORR of 67%, a median PFS of 12.1 months and a median OS of 29.0 months. Interestingly, similar results were achieved in the subset of patients with lenalidomide-refractory disease, and in those with bortezomib-refractory disease (Nijhof et al., 2016).

Switching to another class of agent may also overcome resistance to IMiDs. In CASTOR, for patients with IMiD-refractory disease (32.3% of the total patient population), median PFS was 9.2 months in those receiving daratumumab compared with 5.4 months in the control group (Palumbo et al., 2016). Subgroup analysis showed that among patients who were refractory to lenalidomide at the last previous treatment line, PFS was significantly longer with daratumumab than in the control group (10.3 months vs. 4.4 months; HR, 0.37; $P = 0.0004$) (Chanan-Khan et al., 2016). It must be noted, however, that efficacy was greater in patients without refractory disease than in those with refractory disease (PFS with daratumumab was NR in the total population) (Palumbo et al., 2016).

PIs have also shown efficacy in patients with lenalidomide-refractory disease. In ASPIRE, carfilzomib improved PFS compared with lenalidomide and dexamethasone alone in patients who were refractory to an immunomodulatory agent and in those who were not (HR, 0.64 and 0.72). These results should, however, be interpreted with caution owing to the relatively small number of patients in this study who had disease refractory to an immunomodulatory agent (85 patients receiving carfilzomib and 88 patients in the control group had immunomodulatory agent refractory disease). (Stewart et al., 2015). In subgroup analyses of ENDEAVOR, for patients receiving carfilzomib plus dexamethasone, median PFS was 8.6 months for patients with lenalidomide-refractory disease and not estimable in those who were not refractory to lenalidomide. In individuals receiving bortezomib plus dexamethasone, median PFS was 6.6 months for patients with lenalidomide-refractory disease and 11.2 months for those who were not refractory to lenalidomide (Moreau et al., 2016c). It must be noted that for both PIs efficacy was greater in patients who were not refractory to lenalidomide than in those with refractory disease.

5.2. PI-refractory disease

The second-generation PI carfilzomib has shown efficacy in patients who are refractory to bortezomib. In a phase I/II trial, bortezomib was replaced with carfilzomib in patients who had progressed while receiving or within 12 weeks of receiving a bortezomib-containing regimen. The study found that the use of carfilzomib in patients who were refractory to bortezomib was both effective and had a good tolerability profile; median PFS was 8.3 months and median duration of response was 9.9 months for patients who experienced a partial response or better (Berenson et al., 2014). Very few patients who were refractory to bortezomib were included in the ENDEAVOR study because patients could be randomised to the bortezomib arm, making it difficult to analyse outcomes in this subgroup.

Adding a novel class of agent can also elicit a response in patients with PI-refractory disease. Data from the PANORAMA 2 study found that the addition of panobinostat elicited responses in patients with RRMM who were previously refractory to bortezomib: the ORR was 34.5% and the median duration of response was 6.0 months (Richardson et al., 2013).

Switching between agents is also an option for PI-refractory disease, and the mAb daratumumab has shown efficacy in this setting. In POLLUX, 28% of patients receiving daratumumab and 27% of those receiving lenalidomide plus dexamethasone alone were refractory to the last line of previous therapy; 20% of patients receiving daratumumab and 16% of those in the control group were PI refractory; patients refractory to lenalidomide were excluded from the study. In the total patient population, the ORR was 93% for patients receiving daratumumab plus lenalidomide and dexamethasone compared with 76% for patients receiving lenalidomide and dexamethasone alone. Treatment with daratumumab resulted in a HR of 0.37 for the total population and 0.50 for those refractory to a proteasome inhibitor for PFS (Dimopoulos et al., 2016b). Subgroup analyses showed that among patients who were refractory to bortezomib, PFS was significantly longer with daratumumab than in the control group (NR vs. 10.3 months; HR, 0.46; $P = 0.0117$) (Moreau et al., 2016b).

5.3. Double refractory disease

Patients with double refractory disease (those resistant to both IMiDs and PIs) have very poor prognosis (median PFS and OS of 5 months and 9 months, respectively) (Kumar et al., 2012). Pomalidomide in combination with dexamethasone has shown limited efficacy in these patients. In individuals with disease refractory to lenalidomide and bortezomib, treatment with pomalidomide led to an ORR of 31%, median PFS of 3.8 months and median OS of 13.8 months (Leleu et al., 2013). The novel combination of pomalidomide plus carfilzomib and dexamethasone has also shown efficacy in heavily pretreated patients. The phase I dose-escalation study of this combination, in which all patients were refractory to lenalidomide and most (91%) were also refractory to bortezomib, reported an ORR of 50% and median OS of 20.6 months (Shah et al., 2015).

Mechanisms of resistance towards previous therapies do not appear to affect response to the mAbs, making these good treatment options for patients with double refractory disease. In the SIRIUS study of 106 heavily pretreated patients (median of five previous lines), daratumumab monotherapy resulted in a 29.2% ORR and an estimated 1-year OS of 65% (Lonial et al., 2016). A partial response or better was reported in 29.7% of patients who were refractory to an IMiD and a PI (Lonial et al., 2016). The efficacy of daratumumab in heavily pretreated patients is additionally supported by a recent pooled analysis of 148 patients who took part in two phase II trials of daratumumab monotherapy (Usmani et al., 2016b). Among the pooled population, patients had received a median of five previous lines of therapy, and 87% were double refractory to an IMiD and a PI: the ORR was 31.1% and median PFS and OS were 4.0 months and 20.1 months, respectively (Usmani et al., 2016b). In the ELOQUENT-2 study, assessing the efficacy of combining elotuzumab with lenalidomide and dexamethasone, most patients had previously received an IMiD (thalidomide or lenalidomide) or a PI (bortezomib), and 35% of patients were resistant to their previous therapy (Lonial et al., 2015a). Compared with the control group, the HR for disease progression with elotuzumab was 0.56 for patients who were resistant to their previous therapy and 0.77 for those who relapsed following response to their previous therapy (Lonial et al., 2015a).

Overall, current data show that, for patients with single or double refractory disease, switching agents within a class as well as between classes can lead to clinical response in the relapsed setting.

6. Conclusions

The treatment options for patients with RRMM have expanded dramatically in recent years, and now there are multiple new classes of agent available. It is important that survival improvements afforded by the availability of new agents are extended to all patients including the

elderly and those with high-risk CAs. There is a need for improved differentiation of patients with RRMM, which should not be considered a single disease but rather a mix of different disease entities that further interact with individual patient characteristics (Palumbo et al., 2015b). Better understanding of the mechanism of action of each agent and its clinical efficacy in different patient subgroups, and in patients with characteristics that fit within multiple subgroups, will enable physicians to navigate the treatment landscape, leading to individualized treatment and better patient outcomes.

Author contributions

All authors were involved with drafting and critically reviewing the manuscript. All authors approved the final version of the manuscript.

Funding sources

Medical writing support for this manuscript was funded by Amgen (Europe) GmbH.

Conflicts of interest

Gordon Cook has received research funding and honoraria from Celgene, Janssen-Cilag and Takeda and had received honoraria from Amgen, Bristol-Myers Squibb, GlycoMimetics and Sanofi.

Sonja Zweegman has participated in advisory board meetings for Amgen, Celgene, Janssen and Takeda and receives research funding from Celgene, Janssen and Takeda.

María-Victoria Mateos has received honoraria from and participated in advisory boards for Amgen, Bristol-Myers Squibb, Celgene, Janssen, Novartis and Takeda.

Florence Suzan is an employee of Amgen and holds stocks.

Philippe Moreau has participated in advisory board meetings for Amgen, Celgene, Janssen, Novartis and Takeda.

Acknowledgements

Medical writing support, funded by Amgen (Europe) GmbH, was provided by Kelly Soady PhD from Oxford PharmaGenesis, Oxford, UK.

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