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How have evolutions in strategies for the treatment of relapsed/refractory multiple myeloma translated into improved outcomes for patients?

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ABSTRACT

Although multiple myeloma (MM) remains incurable, the introduction of novel agents has improved clinical outcomes dramatically over the past 15 years. Response rates have risen from ~30% with single agents to up to 90% with combination therapies. The immunomodulatory drugs (IMiDs) thalidomide and

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lenalidomide, and the proteasome inhibitor bortezomib, form the foundations for treatment of relapsed and/or refractory MM (RRMM). Newer agents, such as the IMiD pomalidomide, the histone deacetylase inhibitor panobinostat and the proteasome inhibitors carfilzomib and ixazomib, as well as the monoclonal antibodies daratumumab and elotuzumab, have further improved overall response rates in these patients. Importantly, increased response rates have been observed in heavily pretreated patients. The availability of highly effective and tolerable drugs may offer alternative treatment strategies to those who are unsuitable for treatment with thalidomide, lenalidomide or bortezomib. Improving tolerability of treatment regimens and lengthening progression-free intervals has been shown to significantly improve health-related quality of life for patients living with RRMM.

1. Introduction

Multiple myeloma (MM) accounts for approximately 10% of haematological malignancies (Moreau et al., 2013). The course of MM progression is highly variable; however, it is recognised that almost all patients who respond to initial therapy will eventually relapse and require further treatment. For over 20 years, treatment for individuals with MM involved conventional chemotherapy together with high-dose stem cell support (Lonial et al., 2011). The treatment landscape for patients with relapsed and/or refractory MM (RRMM) began to change in 1999 with the introduction of thalidomide (Singhal et al., 1999). Over the past 15 years, novel agents and new combination therapies have continued to dramatically improve outcomes for those with RRMM. Furthermore, developments in the diagnosis and staging of MM may have also contributed to patients receiving improved care and achieving better outcomes.

As most individuals with MM will eventually relapse, the aims of treatment are to control disease and to strive for deep responses (e.g. complete response [CR]), to prolong survival and maximise quality of life (QoL). Several phase 2 and phase 3 trials have demonstrated the efficacy of approved agents in the setting of RRMM, including immunomodulatory drugs (IMiDs), such as lenalidomide, and the proteasome inhibitor, bortezomib. Furthermore, new agents that have been recently approved such as the IMiD pomalidomide, the histone deacetylase inhibitor panobinostat and the proteasome inhibitors carfilzomib and ixazomib, as well as the monoclonal antibodies daratumumab and elotuzumab, and new classes of agents in early-stage development, may add to the treatment strategies available for patients with advanced MM. The evolution of the treatment strategies for patients with RRMM are described herein.

2. History of RRMM treatment strategies

An overview of the evolution of treatment strategies for RRMM over the past 15 years is given in Fig. 1.

2.1. Thalidomide

The immunomodulatory and anti-angiogenic agent thalidomide was one of the first targeted agents to be used for the treatment of MM. Before gaining regulatory approval, thalidomide was used extensively off-label for various haematological disorders, most often for MM (Tucker, 2005) and in 2008, it was approved in Europe as a first-line therapy for MM (Celgene Europe Ltd., 2016a).

Single-agent thalidomide was first shown to have anti-tumour activity in patients with RRMM in 1999 (Singhal et al., 1999). Overall response rates (ORR) of at least 30% were observed in several phase 2 studies (Table 1) (Singhal et al., 1999; Barlogie et al., 2001; Juliusson et al., 2000). However, despite this growing evidence for efficacy of thalidomide in individuals with RRMM, the only phase 3 trial of single-agent thalidomide in patients with relapsed/refractory disease did not meet its primary endpoint (Kropff et al., 2012) and thalidomide is therefore not indicated as a monotherapy (Celgene Europe Ltd., 2016a).

The combination of thalidomide and dexamethasone (Dimopoulos et al., 2001; Palumbo et al., 2001) or thalidomide, dexamethasone and cyclophosphamide (Dimopoulos et al., 2004; Garcia-Sanz et al., 2004; Kropff et al., 2003) in individuals who had received previous lines of therapy has been investigated in several phase 2 studies. The response rates were almost double those observed in the single-agent trials in patients with relapsed/refractory disease who had received more than one previous line of therapy when thalidomide was used together with dexamethasone (Dimopoulos et al., 2001) and were as high as 92% when combined with chemotherapy in those who had received one or more previous lines of chemotherapy (Hussein et al., 2006; Offidani et al., 2006). A randomised, phase 3 trial of the triplet combination bortezomib, thalidomide and dexamethasone in patients who had relapsed showed that this combination was superior to thalidomide and dexamethasone in those who had relapsed following autologous stem cell transplantation (ASCT) (Garderet et al., 2012). In this study, 20% of patients had received previous bortezomib therapy and 8% had received thalidomide. The ORR was 60% in the triplet group and 50% in those who received thalidomide and dexamethasone. CR and near-CR rates were doubled in the triplet group (28% and 17%) compared with thalidomide and dexamethasone treatment (13% and 8%).

Although not approved in patients with RRMM, thalidomide is often used in later lines of treatment (Bird et al., 2014a) and is recommended for use in combination with dexamethasone by several European guidelines (Bird et al., 2011; Bird et al., 2014b; Palumbo et al., 2009). In most of the clinical trials, individuals received treatment until disease progression or adverse events (AEs) requiring discontinuation; therefore, the optimal duration of thalidomide-based therapy has not yet been defined.

Thalidomide is associated with a high incidence of peripheral neuropathy (PN) and thromboembolic and thromboarterial events in patients with RRMM (Barlogie et al., 2001; Cibeira et al., 2006). In phase 2 studies of single-agent thalidomide, up to 9% of participants experienced PN and approximately 2% had deep vein thrombosis (DVT) (Barlogie et al., 2001). Thalidomide in combination with chemotherapy and dexamethasone was also found to be associated with neurotoxicity, and the risk of DVT was higher than with thalidomide monotherapy (Hussein et al., 2006). In the phase 3, single-agent OPTIMUM trial, 37% of patients receiving thalidomide had clinical evidence of neuropathy (Kropff et al., 2012). These individuals were also at a higher risk of cardiac toxicity than those receiving dexamethasone; 8% in the thalidomide group experienced arrhythmia compared with 2% of the dexamethasone group (Kropff et al., 2012). In the triplet combination phase 3 study of

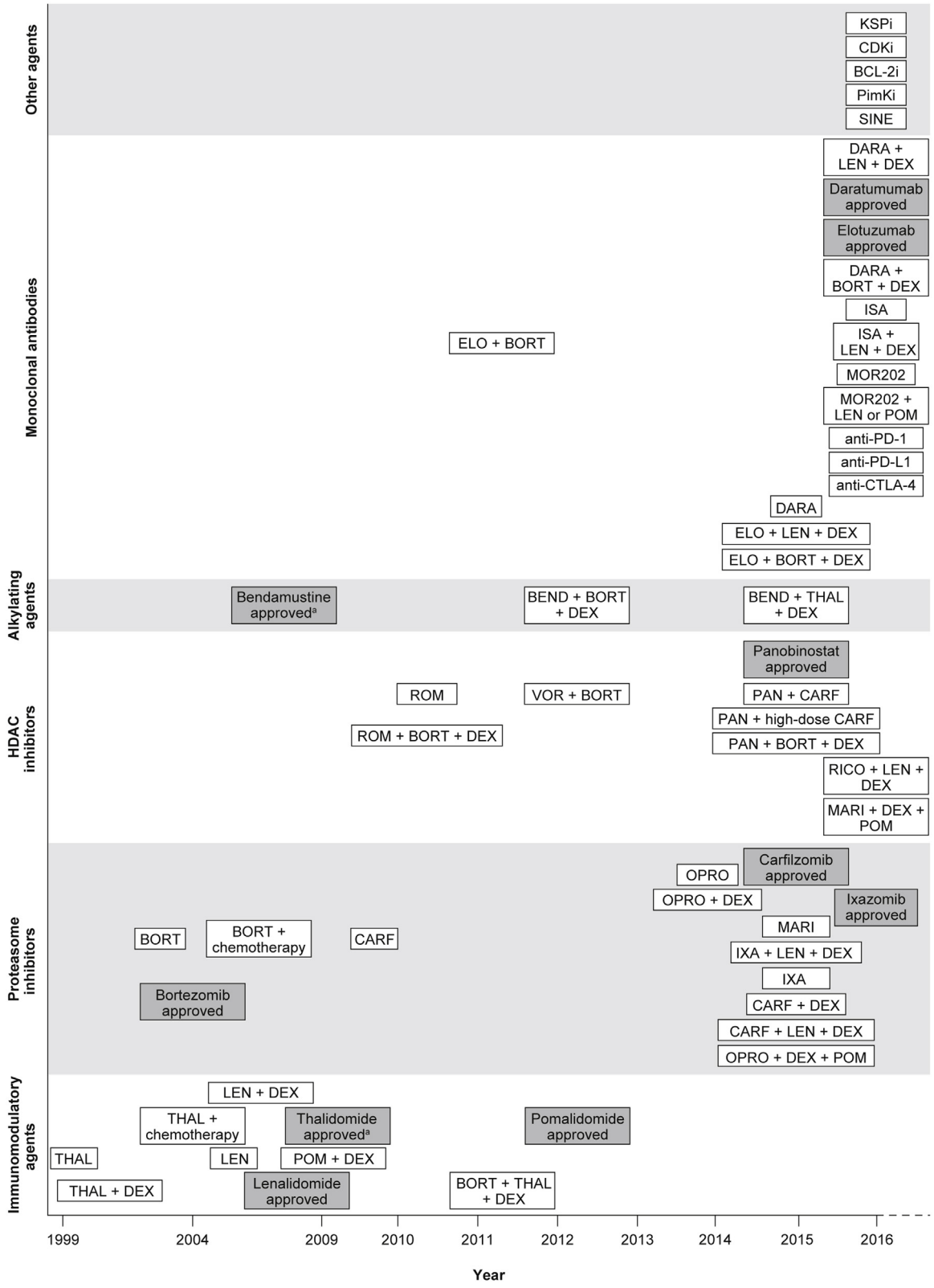

Fig. 1. Evolving treatment strategies for patients with relapsed and/or refractory multiple myeloma.
Figure shows the publication of key clinical trials and European approval of agents for the treatment of relapsed and/or refractory multiple myeloma. [a]Approved for use only as first-line therapy for multiple myeloma. BCL-2i, B-cell lymphoma 2 inhibitor, BEND, bendamustine; BORT, bortezomib; CARF, carfilzomib; CDKi, cyclin-dependent kinase inhibitor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DARA, daratumumab; DEX, dexamethasone; ELO, elotuzumab; HDAC, histone deacetylase; ISA, isatuximab; IXA, ixazomib; KSP-i, kinesin spindle protein inhibitor; LEN, lenalidomide; MARI, marizomib; OPRO, oprozomib; PAN, panobinostat; PD-1, programmed death protein 1; PD-L1, programmed death ligand 1; PIMKi, Pim kinase inhibitor; POM, pomalidomide; RICO, ricolinostat; ROM, romidepsin; SINE, selective inhibitor of nuclear export; THAL, thalidomide; VOR, vorinostat.

Table 1
Summary of key clinical trials of approved agents for the treatment of relapsed and/or refractory multiple myeloma.

Agent Study	Treatment	Phase	Number of patients enrolled	Previous lines of therapy	Outcomes	Selected grade 3–5 adverse events
THAL						
Singhal et al.1999 (Singhal et al., 1999)	THAL	2	84	≥1 cycle of high-dose chemotherapy	ORR: 32% 1-year OS (SE): 58% (±5%) 1-year EFS (SE): 22% (±5%)	Thrombocytopenia: 4% Anaemia: 4%
Barlogie et al. 2001 (Barlogie et al., 2001)	THAL	2	169	≥1 cycle of high-dose chemotherapy	ORR: 54% 2-year OS: 63%	–
OPTIMUM Kropff et al. 2012 (Kropff et al., 2012)	THAL vs DEX	3	499	1–3 (including BOR)	ORR: 18–21% vs 25% OS: 25.6 months–NR vs NR PFS: 6.7–8.1 months vs 6.0 months ($p = 0.051$) DOR: 11.6–13.1 months vs 6.5 months ($p < 0.05$)	Neutropenia: 6% vs 0% Anaemia: 6% vs 4% Pneumonia: 4% vs 4% PN: 0–2% vs 0% Thromboembolic events: 1% vs 2% Arrhythmia: 8% vs 2%
Dimopoulos et al. 2001 (Dimopoulos et al., 2001)	THAL + DEX	2	44	1–≥5	ORR: 55%[a] OS: 12.6 months SD: 18%	NS
Dimopoulos et al. 2004 (Dimopoulos et al., 2004)	THAL + DEX + CYCLO	2	53	≥1 (including THAL)	ORR: 60% OS: 17.5 months	Neutropenia: 26% DVT: 2%
Hussein et al. 2006 (Hussein et al., 2006)	THAL + DEX + PLD + VIN	2	49 (N = 102)[b]	NS	ORR: 90% OS: 39.9 months PFS: 15.5 months	PN: 22%[c] Thromboembolic events: 25%[c] Neutropenia: 14%[c] Pneumonia: 12%[c]
THAL						
Offidani et al. 2006 (Offidani et al., 2006)	THAL + PLD + DEX	2	50	1–> 2	ORR: 92% CR: 26% OS: NR 1-year OS: 79% PFS: 22 months	Neutropenia: 16% DVT: 10% Mucositis, PN, constipation, fatigue, tremors, muscular weakness, constipation, thrombocytopenia, all 2%
MMVAR/IFM 2005-04 Garderet et al. 2012 (Garderet et al., 2012)	THAL + BORT + DEX vs THAL + DEX	3	269	1 (ASCT)	ORR: 88% vs 80% 2-year OS: 71% vs 65% PFS: 18.3 vs 13.6 months ($p = 0.0001$)	PN: 31% vs 14% Thrombocytopenia: 17% vs 7% Neutropenia: 11% vs 16% Infection: 14% vs 17% Cardiac events: 2% vs 1%
BORT						
Richardson et al. 2003 (Richardson et al., 2003)	BORT	2	202	≥2 (THAL. Some patients received only SCT)	ORR: 27% CR or near-CR: 10%	Thrombocytopenia: 31% Neutropenia: 14% PN: 12% Fatigue: 12% Vomiting: 9%
CREST Jagannath et al. 2004, 2008 (Jagannath et al., 2004; Jagannath et al., 2008)	BORT	2	54	≥1 (including THAL)	ORR: 33–50% (Jagannath et al., 2004) OS: 26.8–60.0 months (Jagannath et al., 2008) 1-year OS: 81–82% (Jagannath et al., 2008)	Thrombocytopenia: 23–29% Neutropenia: 11–23% Lymphopenia: 11–12% Limb pain: 11–8% Pneumonia: 0–15% PN: 4–15%

APEX Richardson et al. 2005, 2007 (Richardson et al., 2005; Richardson et al., 2007)	BORT vs DEX	3	669	1–≥4 (including THAL)	ORR: 38% vs 18% ($p < 0.001$) ORR (extended follow-up) (Richardson et al., 2007): 43% vs 9% OS (extended follow-up) (Richardson et al., 2007): 29.8 vs 23.7 months 1-year OS: 80% vs 66% ($p = 0.003$) 1-year OS (extended-follow up) (Richardson et al., 2007): 80% vs 67% ($p = 0.001$)	Thrombocytopenia: 30% vs 6% Neutropenia: 14% vs 1% PN: 8% vs < 1% Fatigue: 5% vs 4%
MMY-3001 Orlowski et al. 2007 (Orlowski et al., 2007)	BORT + PLD vs BORT	3	646	≥1 (including THAL or LEN)	ORR: 44% vs 41% 15-month OS: 76% vs 65% ($p = 0.03$)	Thrombocytopenia: 23% vs 16% Neutropenia: 29% vs 15% Anaemia: 9% each PN: 4% vs 9% Cardiac events: 2% vs 3% Thromboembolic events: 1% each
LEN Richardson et al. 2006 (Richardson et al., 2006)	LEN	2	70	1–≥3 (including THAL or BORT)	ORR: 25% OS: 27–28 months PFS: 4.6 months	Neutropenia: 61–69% Leukopenia: 34–37% Lymphopenia: 37–40% Thrombocytopenia: 31–43% Anaemia: 14–16% Constipation: 25–31% PN: 3% DVT: 3%
MM-009 Weber et al. 2007 (Weber et al., 2007)	LEN + DEX vs placebo + DEX	3	353	≥1 (including THAL or BORT)	ORR: 61% vs 20% ($p < 0.001$) OS: 29.6–20.2 months ($p < 0.001$)	Neutropenia: 41% vs 5% Infection: 22% vs 12% Thrombocytopenia: 15% vs 7% Anaemia: 13% vs 5% Diarrhoea: 3% vs 0% Constipation: 3% vs 0% Venous thromboembolic events: 15% vs 3% PN: 2% vs 1%
MM-010 Dimopoulos et al. 2007 (Dimopoulos et al., 2007)	LEN + DEX vs placebo + DEX	3	351	≥1 (including THAL or BORT)	ORR: 60% vs 24% ($p < 0.001$) OS: NR vs 20.6 months ($p = 0.03$)	Neutropenia: 25% vs 23% Thrombocytopenia: 11% vs 6% PN: < 10% Dyspnoea: 3% vs 2% Death: 3% vs 3% DVT: 4% vs 5% Pulmonary embolism: 5% vs 1%
POM Lacy et al. 2009 (Lacy et al., 2009)	POM + DEX	2	60	1–3 (including THAL, LEN or BORT)	ORR: 63% OS: NR PFS: 11.6 months	Neutropenia: 32% Leukopenia: 17% Fatigue: 17% Pneumonia: 8% Anaemia: 5% PN: 2% Thrombosis: 2%
Baz et al. 2016 (Baz et al., 2016)	POM + CYCLO + DEX vs POM + DEX	2	70	≥2–12 (including BORT, LEN or CARF)	ORR: 65% vs 39% ($p = 0.035$) PFS: 9.5 months vs 4.4 months ($p = 0.106$)	Anaemia: 24% vs 11% Neutropenia: 52% vs 31% Leukopenia: 12% vs 14% Thromboembolic event: 6% vs 0%
MM-003 San Miguel et al. 2013 (San Miguel et al., 2013)	POM + DEX vs DEX	3	455	≥2 (including BORT and LEN)	ORR: 31% vs 10% ($p < 0.0001$) OS: 12.7 vs 8.1 months ($p = 0.0285$) PFS: 4.0 vs 1.9 months ($p < 0.0001$)	Infection: 34% vs 33% Neutropenia: 48% vs 16% Anaemia: 33% vs 37% Thrombocytopenia: 22% vs 26% Pneumonia: 14% vs 10% Dyspnea: 5% each PN: 1% each

Table 1 (*Continued*)

Agent Study	Treatment	Phase	Number of patients enrolled	Previous lines of therapy	Outcomes	Selected grade 3–5 adverse events
BEND						
Ludwig et al. 2014 (Ludwig et al., 2014a)	BEND + BORT + DEX	2	79	1–6 (including BORT and/or LEN)	ORR: 61% OS: 25.6 months PFS: 9.7 months	Thrombocytopenia: 38% Infection: 20% Anaemia: 18% Leukopenia: 17% Diarrhoea: 8% PN: 6%
Offidani et al. 2013 (Offidani et al., 2013)	BEND + BORT + DEX	2	75	≤ 4 (including BORT, THAL or LEN)	ORR ≥ PR: 72% OS: NR 1-year OS: 78% PFS: 15.5 months	Thrombocytopenia: 31% Neutropenia: 19% Anaemia: 12% Infection: 12% PN: 8%
IFM 2009-01 Rodon et al. 2015 (Rodon et al., 2015)	BEND + BORT + DEX	2	73	1 (including THAL or LEN)	ORR: 67% OS: 23 months PFS: 10.8 months	Infection: 27% PN: 5% Cardiac failure: 4%
CARF						
PX-171-003-A1 Siegel et al. 2012 (Siegel et al., 2012)	CARF	2	266	≥2 (including THAL, LEN or BORT)	ORR: 24% OS: 15.6 months PFS: 3.7 months	Thrombocytopenia: 29% Anaemia: 24% Lymphopenia: 20% Neutropenia: 11% Pneumonia: 9% Fatigue: 8% Dyspnea: 3% PN: 1%
FOCUS Hájek et al. 2016 (Hájek et al., 2016)	CARF vs BSC	3	315	≥3	ORR: 19% vs 11% OS: 10.2 vs 10.0 months PFS: 3.7 vs 3.3 months	Anaemia: 26% vs 31% Thrombocytopenia: 24% vs 22% Acute renal failure: 8% vs 3% Renal failure: 5% vs 1% Pneumonia: 6% vs 12%
ASPIRE Stewart et al. 2015 (Stewart et al., 2015)	CARF + LEN + DEX vs LEN + DEX	3	792	1–3 (including BORT and LEN)	ORR: 87% vs 67% ($p < 0.001$) OS: NR (HR for death, 0.79; 95% CI 0.63–0.99; $p = 0.04$) 2-year OS: 73% vs 65% PFS: 26.3 vs 17.6 months ($p = 0.0001$)	Fatigue: 8% vs 6% Hypokalaemia: 9% vs 5% Hypertension: 4% vs 2% Cardiac failure: 4% vs 2% Acute renal failure: 3% vs 3% Ischaemic heart disease: 3% vs 2%
ENDEAVOR Dimopoulos et al. 2016 (Dimopoulos et al., 2016a)	CARF + DEX VS BORT + DEX	3	929	1–3	ORR: 77% vs 63% ($p < 0.0001$) OS: NR PFS: 18.7 vs 9.4 months ($p < 0.0001$)	Hypertension: 8.9% vs 2.6% Dyspnea: 5.6% vs 2.2% Cardiac failure: 4.8% vs 1.8% Acute renal failure: 4.1% vs 2.6% PN (≥grade 2): 6.3% vs 32.0% ($p < 0.0001$) AE-related death: 3.9% vs 3.4%
IXA						
Kumar et al. 2014 (Kumar et al., 2014a)	IXA	1	60	≥2 (including THAL, LEN, BORT, or CARF)	ORR: 18%[d]	Thrombocytopenia: 33% Neutropenia: 18% Diarrhoea: 17% Anaemia: 7% PN: 2%
Richardson *et al* 2014 (Richardson et al., 2014)	IXA	1	60	≥2 (including THAL, LEN, BORT, or CARF/MARI)	PR or better: 17%	Thrombocytopenia: 37% Neutropenia: 17% Skin disorder: 8% Fatigue: 7%
TOURMALINE-MM1 Moreau et al. 2016 (Moreau et al., 2016)	IXA + LEN + DEX vs placebo + LEN + DEX	3	722	1–3	PFS: 20.6 vs 14.7 months ($p = 0.01$) ORR: 78% vs 72% OS: NR	Neutropenia: 22% vs 24% Thrombocytopenia: 19% vs 8.9% Diarrhoea: 6% vs 3% Acute renal failure: 3% vs 5% Cardiac failure: 3% vs 2% PN: 3% vs 2%

PAN						
PANORAMA-1 San-Miguel et al. 2014, 2016 (San-Miguel et al., 2014; San-Miguel et al., 2016)	PAN + BORT + DEX vs placebo + BORT + DEX	3	768	1–3	ORR: 61% vs 55% OS: 40.3 vs 35.8 months (San-Miguel et al., 2016) PFS: 12.0 vs 8.1 months ($p < 0.0001$)	Thrombocytopenia: 67% vs 31% Lymphopenia: 53% vs 40% Diarrhoea: 26% vs 8% Fatigue: 24% vs 12% PN: 18% vs 15%
Berdeja et al. 2015 (Berdeja et al., 2015a)	PAN + CARF	1/2	42	1–10 (including IMiDs or BORT)	ORR: 67% OS: NR PFS: 7.7 months	Thrombocytopenia: 38% Neutropenia: 21% Fatigue: 11% Anaemia: 9% Hypertension: 9% Dyspnoea: 7% Pneumonia: 5% Death: 2%
Berdeja et al. 2015 (Berdeja et al., 2015b)	PAN + high-dose CARF	1/2	26	≥1 (including a proteasome inhibitor and an IMiD)	ORR: 82%	Thrombocytopenia: 31% Fatigue: 4% Diarrhoea: 4%
ELO						
Jakubowiak et al. 2012 (Jakubowiak et al., 2012b)	ELO + BORT	1	28	1–3 (including LEN or BORT)	ORR: 48%	Lymphopenia: 25% Fatigue: 14% Thrombocytopenia: 11% Hyperglycaemia: 11% Neutropenia: 11% Pneumonia: 11% Acute myocardial infarction: 4%
Jakubowiak et al. 2016 (Jakubowiak et al., 2016)	ELO + BORT + DEX vs BORT + DEX	2	152	1–3	ORR: 66% vs 63% PFS: 9.7 vs 6.9 months	Thrombocytopenia: 9% vs 17% Infection: 21% vs 13% PN: 9% vs 12% Diarrhoea: 8% vs 4%
ELOQUENT-2 Lonial et al. 2015 (Lonial et al., 2015)	ELO + LEN + DEX vs LEN + DEX	3	646	1–3 (including LEN, BORT or THAL)	ORR: 79% vs 66% ($p = 0.0002$) PFS: 19.4 vs 14.9 months ($p = 0.0004$)	Lymphocytopenia: 77% vs 49% Neutropenia: 34% vs 44% Anaemia: 19% vs 21% Thrombocytopenia: 19% vs 20%
DARA						
MMY2002 (Sirius) Lonial et al. 2016 (Lonial et al., 2016)	DARA	2	106 (18 mg/kg group)	≥3 (including a proteasome inhibitor, IMiD, POM or CARF)	ORR: 29% OS: NR PFS: 3.7 months Estimated 1-year OS: 65%	Fatigue: 40% Anaemia: 33%
POLLUX Dimopoulos et al. 2016 (Dimopoulos et al., 2016b)	DARA + LEN + DEX vs LEN + DEX	3	569	≥1	ORR: 93% vs 76% ($p < 0.001$) PFS: NR vs 18.4 months	Neutropenia: 52% vs 37% Anaemia: 12% vs 20% Thrombocytopenia: 13% vs 14%
CASTOR Palumbo et al. 2016 (Palumbo et al., 2016)	DARA + BORT + DEX vs BORT + DEX	3	498	≥1	ORR: 83% vs 63% ($p < 0.001$) PFS: NR vs 7.2 months ($p < 0.001$)	Thrombocytopenia: 45% vs 33% Anaemia: 14% vs 16% Neutropenia: 13% vs 4% PN: 5% vs 7%

ASCT, autologous stem cell transplantation; BEND, bendamustine; BORT, bortezomib; BSC, best supportive care; CARF, carfilzomib; CI, confidence interval; CR, complete response; CYCLO, cyclophosphamide; DARA, daratumumab; DEX, dexamethasone; DOR, duration of response; DVT, deep vein thrombosis; EFS, event-free survival; ELO, elotuzumab; HR, hazard ratio; IMiD, immunomodulatory drug; IXA, ixazomib; LEN, lenalidomide; NR, not reached; NS, not specified; ORR, overall response rate; OS, overall survival; PAN, panobinostat; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PN, peripheral neuropathy; POM, pomalidomide; PR, partial response; SCT, stem cell transplantation; SD, stable disease; SE, standard error; THAL, thalidomide; TTP, time to progression; VIN, vincristine.

[a] ORR = PR (55%) + CR (0%).

[b] Total study population included patients with newly diagnosed multiple myeloma.

[c] Adverse events presented for total study population.

[d] ORR = PR (18%) + CR (0%).

thalidomide, bortezomib and dexamethasone, the incidence of PN was 38% compared with 16% in those receiving thalidomide and dexamethasone. Furthermore, grade 3 PN was significantly more common in the triplet group than in the thalidomide and dexamethasone group (29% vs 12%; $p = 0.01$) (Garderet et al., 2012). In light of these safety data, thalidomide may not be suitable for certain patients, including those with baseline PN. Additionally, thromboprophylaxis should be considered during thalidomide treatment owing to the risk of thromboembolism, particularly in patients with additional thrombotic risk factors (Celgene Corporation Thalomid, 2016).

Thalidomide is a powerful human teratogen, inducing a high frequency of severe and life-threatening birth defects. Therefore, it is contraindicated in women of childbearing potential unless the conditions of the Celgene Pregnancy Prevention Program are met (Celgene Corporation Thalomid, 2016).

2.2. Bortezomib

Bortezomib is a reversible proteasome inhibitor that was initially approved in Europe under exceptional circumstances in 2004 for use as a monotherapy to treat patients with MM who have received at least two previous therapies and who have progressed on their last therapy (Janssen-Cilag, 2016a). This approval was supported by data from an open-label, non-randomised clinical trial in which patients with RRMM received 1.3 mg/m^2 of bortezomib twice per week for 2 weeks, followed by 1 week of rest, for up to eight cycles. The ORR was 27%, with 10% of patients achieving a CR or near-CR (Table 1). Most (83%) had received previous thalidomide treatment (Richardson et al., 2003). In order to confirm the clinical benefit of bortezomib two pivotal randomised open-label trials (CREST and APEX) were conducted. In the phase 2 CREST study, bortezomib was administered via intravenous (IV) infusion at two doses (1.0 and 1.3 mg/m^2) to patients who had relapsed or who had become refractory to at least one previous line of treatment. In each dose group, 32% and 27% of patients had received previous thalidomide treatment, respectively. For patients who had progressive or stable disease (SD) after 2 and 4 treatment cycles, respectively, dexamethasone was permitted. The ORR for those who received bortezomib alone or with dexamethasone was 37% and 50% for 1.0 mg/m^2 and 1.3 mg/m^2 doses, respectively. One-year overall survival (OS) was higher than that observed in single-agent thalidomide studies (81–82% vs 58% in a single-agent study (Singhal et al., 1999)) (Table 1) (Jagannath et al., 2004). Furthermore, extended survival analyses reported a median OS of 26.8 months and 60.0 months in the two dose groups, respectively (Jagannath et al., 2008). In the phase 3 APEX trial, bortezomib was found to be superior to high-dose dexamethasone in patients with RRMM who had received one or more lines of previous therapy. The majority of individuals in this study had received two or three previous therapies, and approximately 50% had received thalidomide. The ORRs in the bortezomib and dexamethasone groups were 38% and 18%, respectively (Richardson et al., 2005) (Table 1) and, with extended follow-up of patients who responded to bortezomib, 56% continued to improve upon their initial response, which suggests that there may be a potential benefit of prolonged bortezomib therapy (Richardson et al., 2007). Based on these results the European indication for bortezomib was extended in 2006 to include patients with progressive MM who had received at least one previous therapy (European Medicines Agency, 2015a).

Following the success of bortezomib monotherapy in patients with RRMM, studies began to combine bortezomib with chemotherapy or steroids (Mikhael et al., 2009; Orlowski et al., 2007). A large, international, randomised, phase 3 study (MMY-3001) in patients who had received one or more previous lines of therapy reported that bortezomib and pegylated liposomal doxorubicin was superior to single-agent bortezomib (Table 1) (Orlowski et al., 2007). In this study, 66% of participants had received two or more previous therapies, of which 41% had been treated with lenalidomide or thalidomide. The ORR was 44% in the combination group and 41% in the bortezomib monotherapy group. The 15-month OS was significantly higher in the combination group than in the monotherapy group (76% vs 65%; $p = 0.03$).

Results from a global phase 3b expanded-access study of patients who had received a median of three previous therapies (two-thirds of whom had received previous thalidomide) showed that there was a high response rate to bortezomib with or without dexamethasone (ORR 67%) (Mikhael et al., 2009). Of those who received dexamethasone, 34% had an improved response, suggesting that adding this agent to bortezomib may have clinical benefit in certain patients; however, there is currently a lack of predictive biomarkers to identify such individuals.

As a result of these combination studies, the indication for bortezomib was further extended in 2013 to include use as either a monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone in patients with progressive MM who have received at least one previous therapy and who have undergone or who are unsuitable for haematopoietic stem cell transplantation (European Medicines Agency, 2015c). Positive survival results were reported in a phase 3 randomised trial of bortezomib induction and maintenance therapy in patients with newly diagnosed MM (Sonneveld et al., 2012) and further revisions were made to the bortezomib label; bortezomib is now approved for first-line treatment (Janssen-Cilag, 2016a), but treatment is often repeated in later lines once relapse occurs.

As with thalidomide, the incidence of PN in patients receiving bortezomib is high (Table 1). In the phase 2 CREST trial, 41% of participants experienced PN at any grade, and grade 3–4 PN was reported in 4–15% (Jagannath et al., 2004); similar incidences of PN were also observed in subsequent phase 3 studies (Richardson et al., 2005; Orlowski et al., 2007). Subcutaneous (SC) delivery offers an alternative dosing route with likely fewer AEs as demonstrated in a small randomised phase 3 non-inferiority trial in patients with relapsed MM. Importantly, the incidence of PN was significantly reduced in individuals undergoing SC administration compared with those receiving IV dosing (38% vs 53%; $p = 0.004$) (Moreau et al., 2011). In light of these data, SC administration of bortezomib was approved in Europe in 2012 (European Medicines Agency, 2015b). Regardless of the route of administration, the incidence of PN is high and bortezomib should therefore be used with caution in patients with pre-existing PN (Janssen-Cilag, 2016a; Bringhen et al., 2010). Reducing the frequency of dosing has been shown to reduce toxicity without compromising efficacy. The incidence of grade 3–4 PN was significantly decreased from 28% in those receiving twice-weekly bortezomib to 8% in those in the once-weekly dosing group. Furthermore, there were significantly fewer discontinuations due to PN in the once-weekly dosing group than in the twice-weekly group (Bringhen et al., 2010). Based on data from pivotal clinical trials, a twice-weekly bortezomib dosing schedule is recommended in patients with RRMM (Richardson et al., 2003; Richardson et al., 2005); however, if serious PN becomes apparent, a reduced dosing schedule may be used (Janssen-Cilag, 2016a). This once-weekly dosing regimen may be suitable for those with a history of PN. Cardiac disorders have been reported in 7–15% of those undergoing bortezomib treatment (Richardson et al., 2005; Orlowski et al., 2007) and dyspnoea has also been reported; death caused by respiratory failure was reported in the phase 3 APEX trial (Richardson et al., 2005). Bortezomib is associated with a lower risk of thromboembolic complications than thalidomide and its derivatives, and therefore thromboprophylaxis is not usually required.

2.3. Lenalidomide

In 2006, data were published from a randomised phase 2 clinical trial of the thalidomide analogue, lenalidomide, in patients with RRMM. The ORR was 25% and median OS was 27–28 months in those receiving lenalidomide monotherapy (Table 1) (Richardson et al., 2006). Responses were observed in those who had previously received thalidomide (76% of patients) or bortezomib (18% of patients), indicating that lenalidomide can overcome resistance from drugs in the same class. Following the observed efficacy of single-agent lenalidomide in patients with relapsed or refractory disease, data from two pivotal, randomised, phase 3 trials were published in 2007 (Dimopoulos et al., 2007; Weber et al., 2007). The MM-009 and MM-010 trials had similar designs and compared lenalidomide and high-dose dexamethasone with placebo and dexamethasone in patients with RRMM who had received at least one previous line of therapy, including thalidomide or bortezomib. The ORRs in these trials were significantly higher in the lenalidomide arms (61% and 60%, respectively) than in the placebo arms (20% and 24%, respectively) (Table 1) (Dimopoulos et al., 2007; Weber et al., 2007). Data from these trials led to the approval of lenalidomide in Europe in 2007 for use in combination with dexamethasone in patients who have received at least one previous therapy (Celgene Europe Ltd., 2016b). An open-label, randomised controlled trial of first-line treatment in patients with MM found that low-dose dexamethasone in combination with lenalidomide was non-inferior to, and had lower toxicity than, high-dose dexamethasone plus lenalidomide (Rajkumar et al., 2010). Even though this study was in previously untreated patients, low dose dexamethasone is now often used in later line combination therapies (e.g. carfilzomib plus lenalidomide and dexamethasone) for patients with RRMM (Celgene Europe Ltd., 2016c; Onyx Pharmaceuticals, 2015).

Pooled analyses of the MM-009 and MM-010 trials found that, when patients were stratified according to previous thalidomide exposure, ORR and progression-free survival (PFS) were higher in thalidomide-naïve patients (65% and 13 months, respectively) than in those who had received previous thalidomide treatment (54% and 8 months, respectively) (Wang et al., 2008). Another pooled subgroup analysis reported that patients who had received only one previous therapy had a significant improvement in OS and PFS after first relapse compared with those who had received two or more therapies (Stadtmauer et al., 2009). Evidence from these analyses and others suggests that the greatest benefit from lenalidomide may come from early treatment initiation with continued maintenance therapy (Wang et al., 2008; Stadtmauer et al., 2009; Zago et al., 2014). Indeed, in 2015 lenalidomide was approved in Europe for use in the first-line treatment of MM (Celgene Europe Ltd., 2016b).

The incidence of PN is generally low and PN is less severe in patients receiving lenalidomide than in those receiving bortezomib (Richardson et al., 2006; Dimopoulos et al., 2007; Weber et al., 2007). Cardiovascular events have also been reported in individuals receiving lenalidomide, with one study reporting arrhythmia in 5% and fluid overload in 11% of patients (Baz et al., 2006). In the same study, a small proportion of participants had dyspnea (2%) (Baz et al., 2006). Thrombosis is common in patients receiving lenalidomide or thalidomide (Baz et al., 2006; Knop et al., 2009) and DVT has been reported in 3–6% of those receiving lenalidomide (Richardson et al., 2006; Baz et al., 2006). As a result, the International Myeloma Working Group recommends that patients at a high risk of thromboembolism should receive thromboprophylaxis (Palumbo et al., 2008).

Because lenalidomide is structurally related to thalidomide, a teratogenic effect is also expected with this drug. Therefore, for patients of childbearing potential, the conditions of the Celgene Pregnancy Prevention Program must be fulfilled before treatment can be undertaken (Celgene Europe Ltd., 2016b).

2.4. Pomalidomide

Pomalidomide is another thalidomide derivative and was first investigated in a phase 2 trial in patients with RRMM in 2009. The ORR was 63% in patients who received pomalidomide in combination with low-dose dexamethasone (Table 1) (Lacy et al., 2009). Importantly, this high response rate was observed consistently regardless of whether or not patients had received previous treatment, including thalidomide, lenalidomide, or bortezomib. The pivotal, randomised, phase 3 MM-003 trial compared pomalidomide plus low-dose dexamethasone with high-dose dexamethasone monotherapy in patients with RRMM who had progressed following at least two previous lines of treatment with bortezomib and lenalidomide (San Miguel et al., 2013). The ORR was 31% in the pomalidomide group and 10% in the pomalidomide and dexamethasone group ($p < 0.0001$). Patients in the pomalidomide group had a significantly prolonged median PFS compared with those in the high-dose dexamethasone group (4.0 months vs 1.9 months; $p < 0.0001$) (Table 1). Data from this trial led to the European approval of pomalidomide in combination with low-dose dexamethasone in 2013 for patients with RRMM who have received at least two previous therapies, including bortezomib and lenalidomide, and who have demonstrated disease progression (Celgene Europe Ltd., 2016c).

In the phase 2 study of pomalidomide in combination with low-dose dexamethasone, the incidence of PN was 23% and thromboembolism was reported in 1.6% of patients (Lacy et al., 2009).

Recently, a European expert panel suggested that pomalidomide plus low-dose dexamethasone may be an important new treatment option for patients with relapsed MM who are refractory to bortezomib and lenalidomide (Dimopoulos et al., 2014). The combination of pomalidomide, bortezomib and low-dose dexamethasone is being investigated in a large, multicentre, randomised phase 3 trial in patients who have received one to three previous therapies (MM-007). The primary endpoint is PFS and secondary endpoints include OS and ORR (Richardson et al., 2015). Patients with lenalidomide-refractory MM may benefit from pomalidomide combined with low-dose dexamethasone and cyclophosphamide. In a phase 2 trial, a statistically superior ORR was observed in patients who received pomalidomide, low-dose dexamethasone, and cyclophosphamide (65%) compared with those who received pomalidomide and low-dose dexamethasone alone (39%; $p = 0.035$) (Baz et al., 2016). Median PFS was longer when cyclophosphamide was added to pomalidomide plus dexamethasone (9.5 months vs 4.4 months; $p = 0.106$) (Baz et al., 2016). PN (grade 1/2) was reported in 12% and 17% of patients in the triple combination and control arms, respectively (Baz et al., 2016).

Because pomalidomide is a thalidomide derivative, a teratogenic effect is expected with this drug. Therefore, as with thalidomide and lenalidomide, the conditions of the Celgene Pregnancy Prevention Program must be fulfilled before treatment can be initiated in patients of childbearing potential (Celgene Europe Ltd., 2016c).

2.5. Bendamustine

Bendamustine is an alkylating agent that gained regulatory approval in Europe in 2010 for the first-line treatment of MM in combination with prednisone for patients older than 65 years who are not eligible for ASCT and who have clinical neuropathy at the time of diagnosis, precluding use of thalidomide- or bortezomib-containing treatment (Napp Pharmaceuticals Ltd., 2015). This approval was granted following a randomised phase 3 study that reported that the combination of bendamustine and

prednisone was superior to melphalan and prednisone in patients with previously untreated MM (Ponisch et al., 2006).

Bendamustine is currently under investigation in clinical trials for the treatment of patients in later lines of therapy. A phase 2 study of bendamustine in combination with bortezomib and dexamethasone in individuals with relapsed or refractory disease reported an ORR of 60.9% (Table 1) (Ludwig et al., 2014a). These patients had been exposed to a median of two previous treatment regimens, including bortezomib or lenalidomide. An ORR of 72% was reported in another phase 2 study in patients who had received one to four previous lines of treatment. At the time of analysis, median OS had not been reached, and the 1-year OS was 78% (Offidani et al., 2013). The same bendamustine combination has been investigated in elderly patients with RRMM and an ORR of 67% was reported. The median PFS was 10.8 months and the median OS was 23 months (Rodon et al., 2015). In 2015, a retrospective analysis of relapsed patients who were refractory to lenalidomide and bortezomib and who were given bendamustine in combination with thalidomide and dexamethasone found that most patients (87%) achieved SD or better (Lau et al., 2015). In this study, median PFS was 4.0 months and median OS was 7.2 month, illustrating that this treatment regimen may be a viable option for patients in later lines of therapy. Although not approved for individuals with RRMM, bendamustine has been used off-label in this patient group in various European countries (Damaj et al., 2012; Grey-Davies et al., 2012) and is recommended by the UK Myeloma Forum for use in this setting (Pratt et al., 2013).

The incidence of PN following bendamustine treatment is high; in the phase 2 study combining bendamustine with bortezomib and dexamethasone, 57% of patients experienced PN (Ludwig et al., 2014a). Furthermore, there appeared to be a cumulative effect of treatment and the incidence of PN rose with increasing duration of treatment: at baseline, the incidence of grade 1 or 2 PN was 19%, rising to 52% by cycle 8 (Ludwig et al., 2014a).

2.6. Carfilzomib

Carfilzomib is a next-generation irreversible proteasome inhibitor that received accelerated approved in the USA in 2012 for use in patients with progressive MM who have received at least two previous therapies, including bortezomib and an IMiD (Onyx Pharmaceuticals, 2015). This approval was based on the pivotal, phase 2, open-label, single-arm study (PX-171-003-A1) in patients who had received at least two previous treatment regimens. In this study, single-agent carfilzomib treatment led to an ORR of 23.7% and a median duration of response (DOR) of 7.8 months (Table 1) (Siegel et al., 2012).

Data from the randomised, phase 3, open-label FOCUS trial of single-agent carfilzomib versus best supportive care (BSC) were released in 2014 (Ludwig et al., 2014b). In this study, participants had received three or more previous therapies and most (95%) in the control group received both corticosteroids and cyclophosphamide (Hájek et al., 2016). The ORR was 19% in the carfilzomib group and 11% in the BSC group (Table 1) but the study did not meet its primary endpoint of OS (Hájek et al., 2016).

As with other agents for the treatment of RRMM, combination studies have yielded exceptional results. The phase 3 ASPIRE trial reported that the addition of carfilzomib to lenalidomide and low-dose dexamethasone significantly improved PFS (26.3 months vs 17.6 months; $p = 0.0001$) and ORR (stringent CR + CR + very good partial response [PR] + PR; 87.1% vs 66.7%; $p < 0.001$) when compared with lenalidomide and dexamethasone combination therapy. Furthermore, the PFS benefit was observed regardless of patients' cytogenetic risk. Median OS was not reached in either group at the interim analysis. Twenty-four-month OS rates were 73% and 65% in the carfilzomib and control groups, respectively (hazard ratio for death, 0.79; 95% confidence interval [CI], 0.63–0.99; $p = 0.04$). These results, however, did not cross the prespecified stopping boundary for OS at the interim analysis (Stewart et al., 2015). Nonetheless, data from this trial supported the European approval of this combination in 2015 for the treatment of patients with MM who have received at least one previous line of therapy (Amgen, 2016). The randomised, phase 3, open-label ENDEAVOR trial, compared carfilzomib (20/56 mg/m^2, 30 min IV infusion) and dexamethasone with bortezomib and dexamethasone in patients with relapsed MM who have received between one and three previous lines of therapy. Data from the interim analyses showed that patients receiving carfilzomib had significantly prolonged median PFS compared with those receiving bortezomib (18.7 months vs 9.4 months; $p < 0.0001$). The ORR was also significantly higher in the carfilzomib group than in the bortezomib group (77% vs 63%; $p < 0.0001$) (Dimopoulos et al., 2016a). These data supported the extension of the carfilzomib indication in 2016 to include this doublet combination (Amgen, 2016). Novel combinations of carfilzomib with other agents and trials of alternate dosing schedules (e.g. the phase 1/2 CHAMPION-1 trial; NCT01677858) are underway.

A combined safety analysis of four phase 2 trials of single-agent carfilzomib reported that overall, 22% of patients experienced cardiac-related AEs of any grade, and 9.5% of patients had grade 3 or higher cardiac AEs (Siegel et al., 2013). However, the majority of individuals had a history of cardiovascular events (74%) or had baseline cardiac risk factors (70%). Dyspnea was reported in 42% of patients receiving carfilzomib; however, this later resolved in a large proportion (68%) without the need for dose adjustment. In the ASPIRE trial, grade 3 or higher cardiac AEs were slightly more common in the carfilzomib arm than in the lenalidomide and dexamethasone arm (cardiac failure: 3.8% vs 1.8%; ischaemic heart disease: 3.3% vs 2.1%) (Stewart et al., 2015), and in the ENDEAVOR trial, grade 3 or higher cardiac failure affected 4.8% of patients receiving carfilzomib compared with 1.8% of those receiving bortezomib (Dimopoulos et al., 2016a). Grade 3 or higher dyspnoea was reported in 2.8% and 5.4% of patients receiving carfilzomib in the ASPIRE and ENDEAVOR trials, respectively (Stewart et al., 2015; Dimopoulos et al., 2016a). Two cases of DVT were deemed possibly related to carfilzomib infusion in a phase 1/2 trial of 53 patients receiving carfilzomib in combination with lenalidomide and low-dose dexamethasone (Jakubowiak et al., 2012a). Nonetheless, low rates of grade 3 or higher DVT were reported in both arms of the ASPIRE trial (1.8% in the carfilzomib arm, 1.0% in the lenalidomide and dexamethasone arm) (Stewart et al., 2015). Grade 3 or higher hypertension occurred in 4.3% and 1.8% of the two ASPIRE groups, respectively (Stewart et al., 2015). In ENDEAVOR, grade 3 or higher hypertension was reported in 9% of the carfilzomib group and 3% of the bortezomib group (Dimopoulos et al., 2016a). Carfilzomib has demonstrated a good renal safety profile; in phase 3 trials, grade 3 or higher acute renal failure was uncommon (3–8%)(Hájek et al., 2016; Stewart et al., 2015; Dimopoulos et al., 2016a).

From the phase 3 carfilzomib trials, the incidence of PN (any grade) was lower than that observed with lenalidomide or bortezomib (5–17%% (Hájek et al., 2016; Stewart et al., 2015; Dimopoulos et al., 2016a) vs 23–39% (Baz et al., 2006; Knop et al., 2009; San Miguel et al., 2013)). Data from the ENDEAVOR trial reported that the incidence of grade 3 or higher PN was lower in the carfilzomib group than in the bortezomib group (2% vs 8%), even though the majority of patients received SC bortezomib (Dimopoulos et al., 2016a). Importantly, in the FOCUS trial, although 52% of participants had PN at baseline, only 4.5% of patients receiving carfilzomib experienced treatment-emergent PN (Hájek et al., 2016). This is in agreement with data from the ASPIRE trial, in which the incidence of PN was similar in both treatment arms (~17% each) (Stewart

et al., 2015). Data from these phase 2 and phase 3 trials suggest that carfilzomib may not exacerbate pre-existing PN.

2.7. Panobinostat

Panobinostat is a histone deacetylase (HDAC) inhibitor that was granted European approval in 2015 for use in combination with bortezomib and dexamethasone for the treatment of patients with RRMM who have received at least two previous treatment regimens, including bortezomib and an IMiD (Novartis, 2016). This approval was based upon results from the randomised, phase 3 PANORAMA-1 trial in which the combination of panobinostat, bortezomib and dexamethasone was compared with placebo, bortezomib and dexamethasone in patients who had received between one and three previous lines of therapy. The ORRs were similar in both groups (61% and 55%, respectively); however, the proportion of patients achieving a CR or near-CR was significantly higher in the panobinostat group than in the placebo group (28% vs 16%; $p = 0.00006$). Furthermore, patients receiving panobinostat had a significantly longer median PFS than those in the placebo group (12.0 months vs 8.1 months, respectively; $p < 0.0001$) (Table 1) (San-Miguel et al., 2014). The OS benefit in the panobinostat group versus the placebo group was modest (median OS 40.3 vs 35.8 months, $p = 0.54$) (San-Miguel et al., 2016).

The combination of panobinostat and carfilzomib has been investigated in a phase 1/2 trial in patients who had received at least one previous line of therapy (Berdeja et al., 2015a). In this study, participants had received a median of five previous therapies, and most had received a proteasome inhibitor or an IMiD. At the time of the interim analysis, the ORR was 67% (Table 1). Furthermore, 75% of patients who were refractory to IMiDs and 67% of those who were refractory to proteasome inhibitors responded to this combination. As the maximum tolerated dose of carfilzomib was not reached, the study was extended and the carfilzomib dose was escalated from 20/45 mg/m^2 to 20/56 mg/m^2. The ORR in patients receiving this higher dose of carfilzomib was 82% and the clinical benefit rate was 91% (Berdeja et al., 2015b). Owing to the promising results observed in these studies, longer studies in larger cohorts are warranted.

In the clinical studies of panobinostat completed so far, the incidence of PN has been low, affecting up to 18% of patients (San-Miguel et al., 2014; Berdeja et al., 2015a). In the phase 1/2 dose escalation study of patients receiving panobinostat in combination with carfilzomib, the most common grade 3 or higher AEs were thrombocytopenia (38%), neutropenia (21%), anaemia, and hypertension (both 9%). One (2%) treatment-related death was reported due to heart failure (Berdeja et al., 2015a). Further studies are required to assess fully the safety profile of this agent and its combinations.

2.8. Daratumumab

Daratumumab binds to CD38, a cell-surface molecule that is expressed by malignant plasma cells. It was the first monoclonal antibody to be approved for use in MM, and was granted marketing authorisation in Europe in 2016 (Janssen-Cilag, 2016b). The approval is based on use of the drug as a monotherapy in heavily pretreated patients, with prior therapy including a proteasome inhibitor and an IMiD (Lonial et al., 2016). The efficacy of daratumumab monotherapy has been demonstrated in study MMY2002 (SIRIUS). In heavily pretreated patients (≥3 previous lines of therapy), the ORR was 29% and the estimated 1-year OS was 65% (Table 1) (Lonial et al., 2016).

Two randomised phase 3 clinical trials in patients with RRMM are underway investigating daratumumab in combination with either lenalidomide and dexamethasone (MMY3003; POLLUX) or bortezomib and dexamethasone (MMY3004; CASTOR); interim data have been published for both studies. After a median follow-up of 13.5 months in MMY3003, the addition of daratumumab to lenalidomide and dexamethasone significantly improved median PFS (63% reduction in the risk of progression/death) compared with lenalidomide and dexamethasone alone. ORR was also higher in patients receiving daratumumab than in the control group (93% vs 76%; $p < 0.001$) (Dimopoulos et al., 2016b). The most common grade 3–4 AEs (in the daratumumab and control groups, respectively) were neutropenia (52% vs 37%), anaemia (12% vs 20%) and thrombocytopenia (13% vs 14%) (Dimopoulos et al., 2016b). In CASTOR, after a median follow-up of 7.4 months, PFS was significantly improved for patients receiving daratumumab, bortezomib and dexamethasone versus those receiving bortezomib and dexamethasone alone (hazard ratio for progression or death, 0.39; $p < 0.001$) (Palumbo et al., 2016). ORRs were higher in the daratumumab arm than in the control arm (83% vs 63%; $p < 0.001$). The most common grade 3–4 AEs were thrombocytopenia (45% vs 33%), anaemia (14% vs 16%) and neutropenia (13% vs 4%) (Palumbo et al., 2016).

2.9. Elotuzumab

Elotuzumab is a humanised monoclonal antibody directed against signalling lymphocytic activation molecule family member 7 (SLAMF7), a cell-surface glycoprotein highly expressed in MM cells. Like daratumumab, it was approved in 2016 by the European Medicines Agency; this agent, however, is licensed for use in combination with lenalidomide and dexamethasone for the treatment of MM in adult patients who have received at least one prior therapy (one to three in the USA) (Bristol-Myers Squibb, 2016).

Interim analyses have been reported from the phase 3 ELOQUENT-2 trial in which patients with RRMM who had received one to three previous therapies received lenalidomide and dexamethasone with or without elotuzumab. The addition of elotuzumab to lenalidomide and dexamethasone significantly prolonged PFS compared with not receiving elotuzumab (19.4 vs 14.9 months; $p < 0.001$). Furthermore, the ORR in the elotuzumab arm was significantly higher than in the lenalidomide plus dexamethasone arm (79% vs 66%; $p < 0.001$) (Lonial et al., 2015). The most common grade 3–4 AEs were lymphocytopenia (77% vs 49%) and neutropenia (34% vs 44%).

A recent phase 2 study investigated the effect of adding elotuzumab to bortezomib and dexamethasone. It met its primary endpoint: PFS was prolonged in the elotuzumab group compared with the bortezomib and dexamethasone group (9.7 months vs 6.9 months; $p = 0.09$). The ORR was 66% and 63% in the two treatment arms, respectively (Jakubowiak et al., 2016).

2.10. Ixazomib

The reversible, oral proteasome inhibitor ixazomib was approved in 2016 in Europe for use in combination with lenalidomide and dexamethasone to treat patients with MM who have received at least one prior therapy (Takeda, 2016). The approval was based on the randomised, phase 3, double-blind, placebo-controlled TOURMALINE MM-1 trial, in which patients received ixazomib or placebo on a background of lenalidomide and dexamethasone (Moreau et al., 2016). At a median follow-up of 14.7 months, median PFS was signficantly longer in patients who received ixazomib than those who received placebo(20.6 months vs 14.7 months; Table 1). At a median follow-up of approximately 23 months,median OS had not been reached in either study group. With regards to safety, AEs of grade 3 or higher occurred in 74% of patients in the ixazomib group and 69% of the patients in the placebo group. Thrombocytopenia (any grade) occurred more frequently in the ixazomib group than the placebo group (31% vs 16%,

respectively) as did rash (36% vs 23%). The incidence of PN was 27% in the ixazomib group compared with 22% in the placebo group.

The first phase 1 study of once-weekly dosing with ixazomib included individuals who had received a median of six previous treatment regimens; most had received bortezomib and lenalidomide, 53% had received thalidomide and 15% had received carfilzomib. An ORR (all PRs) of 18% was recorded (Kumar et al., 2014a). PN was experienced by 12% of patients in the once-weekly study and this did not increase with more frequent dosing of ixazomib monotherapy (Richardson et al., 2014).

3. New agents in development for RRMM

3.1. Proteasome inhibitors

3.1.1. Marizomib

Marizomib is a second-generation proteasome inhibitor that targets all three proteolytic activities of the proteasome (Rajan and Kumar, 2016). Clinical activity has been demonstrated in phase 1 trials of marizomib in patients with RRMM, as a single agent (Harrison et al., 2015a) and in combination with dexamethasone and pomalidomide (Spencer et al., 2015).

3.1.2. Oprozomib

Oprozomib is a new oral, irreversible proteasome inhibitor. Its potential for use in RRMM is currently supported by phase 1b/2 data as a single agent (Vij et al., 2014), in combination with dexamethasone (Hari et al., 2014), and in combination with pomalidomide and dexamethasone (Shah et al., 2015).

3.2. HDAC inhibitors

3.2.1. Romidepsin

Romidepsin has been investigated as a single agent in patients with RRMM, though it did not produce an objective response in a phase 2 study in pretreated, refractory individuals who had received a median of three previous treatment lines (Niesvizky et al., 2011). Despite this, romidepsin is under investigation in combination with other agents, including bortezomib and dexamethasone. In a phase 1/2 dose-escalation study in patients with RRMM who had received at least one previous therapy, 72% of participants achieved a minor response or better when treated with romidepsin, bortezomib and dexamethasone. However, the incidence of PN was high (76%) and 8% of individuals experienced grade 3 PN (Harrison et al., 2011). Further studies are required to evaluate fully the efficacy and safety of romidepsin in patients with relapsed or refractory disease.

3.2.2. Vorinostat

Vorinostat, another HDAC inhibitor, has been developed, but has shown limited activity in combination with other agents. In the phase 3 randomised, double-blind, placebo-controlled VANTAGE 088 trial, vorinostat or placebo, both in combination with bortezomib, were administered to patients who had received between one and three previous regimens, but who were not yet refractory to treatment (Dimopoulos et al., 2013). The ORR was 56.2% and 40.6% in the vorinostat and placebo groups, respectively and median PFS was significantly prolonged in the vorinostat group compared with the placebo group (7.6 months vs 6.8 months, respectively; $p = 0.01$). The clinical relevance of this difference in PFS is unclear, however.

A phase 1 study of vorinostat in combination with lenalidomide and dexamethasone in patients with RRMM who had received between one and ten previous treatments, including lenalidomide, thalidomide or proteasome inhibitors, reported an ORR of 47% (Siegel et al., 2014).

In both trials, the incidence of AEs was high, with almost all individuals experiencing toxicity (Dimopoulos et al., 2013; Siegel et al., 2014). Indeed, almost half of patients receiving vorinostat in combination with lenalidomide and dexamethasone experienced at least one serious AE (Siegel et al., 2014). The most common grade 3–4 AEs in patients receiving vorinostat in the VANTAGE 088 trial were thrombocytopenia (45%) and neutropenia (28%) (Dimopoulos et al., 2013).

3.2.3. Ricolinostat

Ricolinostat is an oral selective HDAC6 inhibitor with phase 1b data that support further investigation of its use in combination with lenalidomide and dexamethasone. A dose-finding study of this combination in patients with previously treated RRMM provided preliminary evidence of an overall response in 55% of the 38 participants (Yee et al., 2016). The structurally similar compound ACY-241, which is administered orally, has entered phase 1 development in RRMM, in combination with pomalidomide and dexamethasone (the trial is currently recruiting; NCT02400242)

3.3. Monoclonal antibodies

3.3.1. Anti-CD38

Further to the approval of daratumumab, other anti-CD38 monoclonal antibodies are in development for RRMM. Isatuximab, for example, has demonstrated encouraging activity as a single agent in a phase 2 trial of patients with heavily pretreated RRMM. Patients treated with isatuximab had a median PFS of 3.7 months and a median OS of 18.6 months. The ORR – including among those with high-risk cytogenetics – was 24.3% (Richter et al., 2016). Interim phase 1b data have also demonstrated efficacy of isatuximab in combination with lenalidomide and dexamethasone in patients with heavily pretreated RRMM (Vij et al., 2016). MOR202 is an anti-CD38 monoclonal antibody that, unlike others in its class, does not induce complement-dependent cytotoxicity and may therefore have potential for a reduced rate of infusion-related reactions. Data from an ongoing phase 1/2a trial of MOR202 alone or in combination with lenalidomide or pomalidomide have been suggestive of promising efficacy and long-lasting tumour control (Raab et al., 2016).

3.3.2. Anti-PD-1

A number of monoclonal antibodies that inhibit the programmed death protein 1 (PD-1) receptor in the immune checkpoint pathway are in development as potential agents for RRMM. Nivolumab, for example, is being investigated in a phase 3 trial in combination regimens including elotuzumab, pomalidomide and dexamethasone (NCT02726581). Nivolumab is also being investigated in combination with a number of other checkpoint inhibitor agents in a phase 1 study which includes patients with RRMM (NCT01592370). Patients are being enrolled into a phase 3 trial investigating the effect of adding the anti-PD1 antibody pembrolizumab to pomalidomide and low-dose dexamethasone (NCT02576977). Patients are currently being recruited for the first trials evaluating the efficacy of the anti-programmed death ligand-1 (PD-L1) agent durvalumab, as a monotherapy or in combination with pomalidomide with or without dexamethasone (NCT02616640). A phase 1/2 study of the new anti-PD-1 agent pidilizumab is also recruiting patients, for investigation in combination with lenalidomide (NCT02077959).

3.3.3. Anti-CTLA-4

The anti-cytotoxic T-lymphocyte-assocaited protein 4 (anti-CTLA-4) monoclonal antibody ipilimumab is one of a number of checkpoint inhibitor agents being investigated in the phase 1 study

with nivolumab, mentioned above (NCT01592370). Combinations of anti-CTLA-4/anti-PD-1/anti-PD-L1 agents in development (ipilimumab/nivolumab and tremelimumab/durvalumab) are also entering early stages of clinical development for patients with pretreated MM considered to be at high risk of relapse (NCT02716805; NCT02681302).

3.4. Other agents

A range of additional novel agents are in development for RRMM. Filanesib is a kinesin spindle protein inhibitor which is supported by phase 1 data in combination with bortezomib and dexamethasone (Chari et al., 2016). Dinaciclib is a novel potent small molecule cyclin-dependent kinase inhibitor, and has demonstrated activity as a single agent in relapsed MM in a phase 1/2 trial (Kumar et al., 2015). Venetoclax is an oral selective inhibitor of the pro-survival protein B cell lymphoma 2 (BCL-2), with potential to restore the apoptotic ability of malignant cells. Its first indication is in selected patients with chronic lymphocytic leukaemia, but it is in phase 1 development for MM (Deeks, 2016). LGH447 is a novel, specific pan-Pim kinase inhibitor that has demonstrated phase 1-level evidence of durable single-agent efficacy in patients with heavily pretreated RRMM (Raab et al., 2014). Finally, selinexor is a novel selective inhibitor of nuclear export (SINE) that has generated promising data as a single agent in a phase 1 dose-escalation study (Chen et al., 2013), and is under investigation in combinations with dexamethasone (NCT02336815), carfilzomib and dexamethasone (NCT02199665), liposomal doxorubicin (NCT02186834), and dexamethasone with either pomalidomide, bortezomib or lenalidomide (NCT02343042).

4. How and when to treat patients with RRMM?

The treatment options for patients with RRMM have dramatically increased over the past 15 years; however, because of the heterogeneity amongst patients with MM, there is currently no standardised approach for treating patients with relapsed or refractory disease. Multiple factors should be considered when determining an individual's treatment regimen, including treatment goal, age, timing of relapse, efficacy of and tolerance to prior therapy, comorbidities and patient preference (Moreau et al., 2013; Bird et al., 2011; Bird et al., 2014b).

Early guidelines for the management of RRMM recommended that patients should receive retreatment with chemotherapy following the first relapse (Smith et al., 2006). More recently, guidelines suggest that patients should be treated with thalidomide, bortezomib, or lenalidomide, and that maximum benefit may be achieved by using these agents in combination with dexamethasone, pegylated doxorubicin, or chemotherapy (Moreau et al., 2013; Bird et al., 2011; Bird et al., 2014b; Palumbo et al., 2009; Smith et al., 2006; Harousseau and Dreyling, 2010). Additionally, for patients who relapse following a durable response, retreatment (usually after a 6-month period off-treatment) with the same regimen used in the previous line of therapy may induce a second remission (Palumbo et al., 2009; Harousseau and Dreyling, 2010). However, in those who have experienced a short remission, re-exposure to the same treatments in sequential lines of therapy may be associated with increased rates of treatment resistance (Bird et al., 2011; Bird et al., 2014b). For young patients ($\leq$ 65 years) whose MM has relapsed following a previous good response (with PFS of more than 24 months) to ASCT, a second ASCT may be considered. Allogenic stem cell transplantation may be an option but only in a clinical trial setting (Moreau et al., 2013).Understanding when to initiate treatment, with which regimen and for how long, is challenging owing to individual patient characteristics and a complicated treatment landscape. There is emerging evidence to suggest that treatment can be delayed in certain patients who experience asymptomatic relapse, but for those with symptomatic relapse or with advanced disease at diagnosis, prompt treatment is required (Blade et al., 2015). Once treatment has been initiated, the role of maintenance therapy in patients with RRMM is unclear. There is evidence to suggest that continuous treatment until relapse may be beneficial in reducing symptoms and prolonging PFS in certain patients (Blade et al., 2015; Guglielmelli and Palumbo, 2015). For example, lenalidomide maintenance therapy provided durable disease control in patients with relapsed or refractory MM (Lazaryan et al., 2014). Another study, however, found that ongoing lenalidomide and bortezomib maintenance in patients with RRMM had no clinical benefit (Harrison et al., 2015b). Further studies on the effect of maintenance therapy in the relapsed or refractory setting are warranted.

5. Improving outcomes and HRQoL

Health-related QoL (HRQoL) in patients with RRMM is influenced by disease-related symptoms, treatment-related toxicity and treatment response. Long-term survivors of advanced MM report that the cumulative impact of intensive treatment can significantly impact HRQoL, mainly linked to the burden of disease-related and treatment-related symptoms (Boland et al., 2013). Indeed, a European, multi-centre cohort study found that MM disease symptoms were associated with significant reductions in QoL scores. Receiving any type of MM treatment was linked to significant reductions in QoL scores, likely due to treatment-related side-effects (Jordan et al., 2014). Therefore, the improvements in toxicity profiles and PFS seen with new agents and combinations are likely to be associated with improved HRQoL. For example, patients receiving pomalidomide and dexamethasone in the MM-003 trial not only had improved clinical outcomes but also had significantly better HRQoL than those receiving high-dose dexamethasone (Song et al., 2015). Furthermore, patients receiving carfilzomib in combination with lenalidomide and dexamethasone in the phase 3 ASPIRE trial not only had improved outcomes but also reported superior HRQoL compared with those receiving lenalidomide and dexamethasone without carfilzomib (Stewart et al., 2015). A systematic literature review has also identified the link between positive clinical outcomes and improved HRQoL (Sonneveld et al., 2013); therefore, the improved clinical responses achieved with novel agents and their combinations may translate into improved QoL for patients living with RRMM.

6. Discussion

The advent of novel treatment regimens for RRMM has translated into improvements in outcomes over the past 15 years (Table 1). In particular, response rates have dramatically increased, even in patients who have received multiple lines of previous therapy (Fig. 2). Furthermore, the 2-year OS rates have increased from 48% in individuals receiving single-agent thalidomide (Barlogie et al., 2001) to 73% in those receiving carfilzomib in combination with lenalidomide and dexamethasone (Stewart et al., 2015). Such indirect comparisons should be considered in the context of the patient populations involved in the trials. While head-to-head studies are needed to determine definitively which agents are superior, it is interesting to note that patients in the trials of pomalidomide and carfilzomib had often received several lines of targeted treatment, whereas they had received only one or two previous lines of therapy in earlier trials of thalidomide, lenalidomide, and bortezomib.

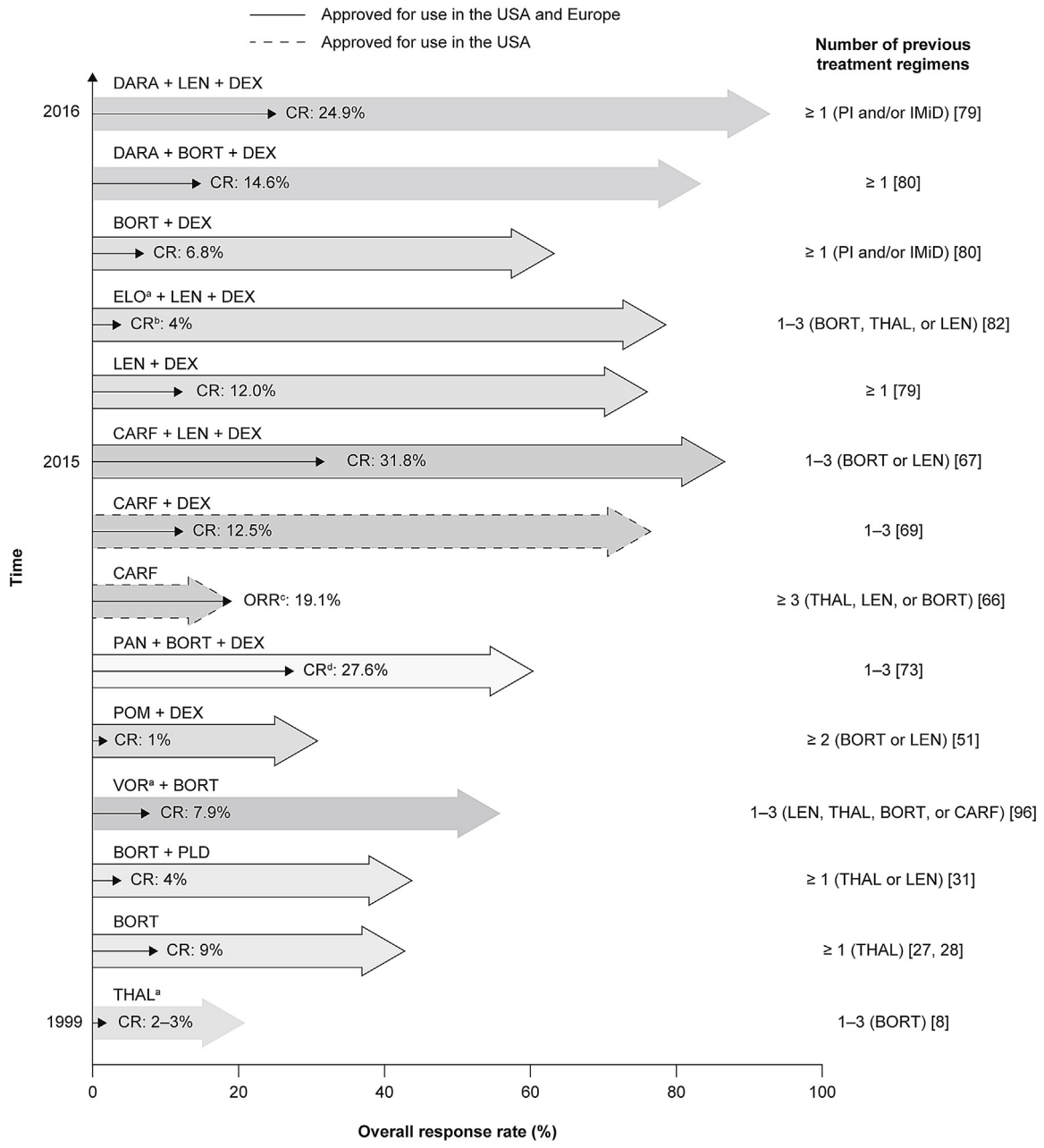

Fig. 2. Overall response rates in key phase 3 studies in patients with relapsed and/or refractory multiple myeloma.
—Approved for use in the USA and in Europe in patients with relapsed and/or refractory multiple myeloma. - - - Approved for use in the USA in patients with relapsed and/or refractory multiple myeloma. [a]CR not available (ORR: sCR + CR + VGPR + PR); [b]CR + near CR; [c]Not yet approved for use in patients with RRMM; [d]sCR + CR. BORT, bortezomib; CARF, carfilzomib; CR, complete response; DARA, daratumumab; DEX, dexamethasone; ELO, elotuzumab; IMiD, immunomodulatory drug; LEN, lenalidomide; ORR, overall response rate; PAN, panobinostat; PI, proteasome inhibitor; PLD, pegylated liposomal doxorubicin; POM, pomalidomide; PR, partial response; sCR, stringent complete response; THAL, thalidomide; VGPR, very good partial response; VOR, vorinostat.

The high response rates and improvements in outcomes observed in clinical trials of these new agents in patients who had previously received multiple lines of therapy and who have more advanced disease are encouraging. However, it should also be noted that over the past decade, in addition to introducing new therapeutic agents, advances in diagnosis, early intervention and better supportive care may also have contributed towards the improvements in patient outcomes. Indeed, a study of 1038 patients diagnosed with MM between 2001 and 2010 reported significant improvements in OS from 2001 to 2005 to 2006–2010 (4.6 years vs 6.1 years; $p = 0.002$). The 6-year OS increased significantly from 40% between 2001 and 2005 to 51% in the second half of the decade ($p < 0.001$) (Kumar et al., 2014b).

Bortezomib, thalidomide and lenalidomide form the foundations of current MM treatment regimens but it must be noted that such treatments are associated with toxicity affecting the peripheral nervous system. PN is the degeneration of peripheral nerves and can result in numbness, loss of motor function, and neuropathic pain (Delforge et al., 2010). The disease characteristics of MM and comorbidities may pre-dispose certain patients to experiencing PN (Dispenzieri and Kyle, 2005; Morawska et al., 2014). Treatment with bortezomib, thalidomide, or lenalidomide can also exacerbate PN; indeed, treatment-induced PN occurs in 25–75% of individuals (Morawska et al., 2014). Therefore, regular clinical monitoring is recommended before and during treatment with agents known to cause PN (Delforge et al., 2010; Mohty et al., 2010; Richardson et al.,

2012). Furthermore, patients who have received multiple lines of therapy may be more likely to have baseline at PN. Carfilzomib and pomalidomide have been shown to be effective in individuals with baseline PN and the incidence of treatment-emergent PN remained low (Lacy et al., 2009; Siegel et al., 2012; Stewart et al., 2015), therefore these agents may be useful in such patient populations.

With the availability of many new agents for the treatment of patients with RRMM in recent years, understanding who will benefit from specific agents and classes of treatment, and the optimal treatment sequence of these, is important for optimal patient outcomes. These questions are beginning to be addressed in clinical trials (Mohty et al., 2012) and theoretical disease models (Heeg et al., 2010). Emerging evidence from exploratory analyses of subpopulations of patients with MM from clinical trials, such as elderly individuals and those with high risk cytogenetic abnormalities, suggest that certain treatments may be beneficial to such groups and these are the first steps towards individualised therapy (Chng et al., 2014; Sonneveld et al., 2016).

7. Conclusions

Continuing improvements in outcomes for patients with RRMM are being observed with the introduction of new agents, including proteasome inhibitors and HDAC inhibitors. These drugs, together with novel classes of agents, such as monoclonal antibodies, may lead to new treatment strategies for this disease. For the past 15 years, treatment for patients with RRMM has centred on multiple lines of thalidomide, lenalidomide, and bortezomib; however, new agents may offer an alternative to retreatment with the same agents in consecutive lines. Promising clinical responses have even been seen in heavily pretreated patients, suggesting that the new therapeutic options have the potential to benefit those who appear to have exhausted all traditional lines of therapy. Furthermore, improvements in tolerability and disease-free intervals will positively impact HRQoL in patients undergoing multiple lines of therapy. With the introduction of several novel treatment strategies, determining the optimal sequence, combination and timing of each agent will be necessary.

Conflict of interest statement

Pieter Sonneveld has participated in advisory board meetings for, and has recevied research funding from, Amgen, Janssen, Celgene, Karyopharm, and Takeda-Millennium. Philippe Moreau has participated in advisory board meetings for Janssen, Amgen, Celgene, Takeda, and Novartis. Edwin De Wit is a former employee of Amgen and holds stock.

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