Monoclonal antibodies in the treatment of multiple myeloma: current status and future perspectives

Sagar Lonial, Emory University
B Durie, Cedars-Sinai Outpatient Cancer Center
A Palumbo, University of Torino
J San-Miguel, Universidad de Navarra

Journal Title: Leukemia
Volume: Volume 30, Number 3
Publisher: Nature Publishing Group | 2016-03-01, Pages 526-535
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1038/leu.2015.223
Permanent URL: https://pid.emory.edu/ark:/25593/rmzhh

Final published version: http://dx.doi.org/10.1038/leu.2015.223

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Accessed November 11, 2018 12:18 PM EST
Monoclonal antibodies in the treatment of multiple myeloma: current status and future perspectives

S Lonial1, B Durie2, A Palumbo3 and J San-Miguel4

The treatment landscape for patients with multiple myeloma (MM) is constantly evolving. Over the past decade, the introduction of novel agents such as proteasome inhibitors and immunomodulatory drugs has led to notable changes in therapeutic strategy, and improvements in survival, yet MM remains incurable in the vast majority of cases. More recently, a targeted approach to MM treatment has emerged, using monoclonal antibodies (mAbs) to target antigens expressed on the surface of MM cells. mAbs tested to date kill MM cells via the host’s immune system and/or by promoting apoptosis, and appear to have generally improved tolerability compared with currently available treatments. Due to their distinct mode of action, mAbs are promising both for patients who have exhausted current regimens, and as part of first-line treatments in newly diagnosed patients. This review examines the recent developments in mAb-based therapy for MM, primarily focused on those agents in ongoing clinical testing.

Leukemia (2016) 30, 526–535; doi:10.1038/leu.2015.223

INTRODUCTION
Multiple myeloma (MM) is a malignancy of antibody-secreting plasma cells.1 Globally, over 80,000 new cases of MM are reported each year, representing ~1% of all new cancer cases and 10% of all hematologic malignancies.2,3 The incidence of MM increases with age, indicative of the accumulation of epigenetic/genetic changes during the typical development of the disease from monoclonal gammapathy of undetermined significance, through smoldering (asymptomatic) myeloma, to symptomatic MM.4 Clinically, symptomatic MM is characterized by end-organ damage, generally involving hypercalcemia, renal failure, anemia and bone marrow lesions (CRAB features).5 Skeletal pain and fatigue are common symptoms of MM, and can severely impact the patient’s quality of life.6
The overall median survival is ~5–6 years from diagnosis of MM,7 yet disease outcomes are strongly influenced by the characteristics of the cancer (for example, high-risk cytogenetics) and/or the patient (for example, age). In younger patients, autologous stem cell transplantation has led to improved progression-free survival (PFS) and overall survival (OS).8,9 Here, patients receive induction therapy, which is typically a combination regimen based on an alkylating agent and/or a proteasome inhibitor (PI; for example, bortezomib [BORT] and carfilzomib [CAR]) and/or an immunomodulatory drug (IMiD; for example, lenalidomide [LEN], thalidomide [THAL] and pomalidomide [POM]), to reduce disease burden before high-dose chemotherapy and stem cell transplantation. As mentioned, however, MM is most prevalent in elderly patients, the majority of whom are ineligible for autologous stem cell transplantation. Induction therapy with novel agents has also improved survival in this population, although management of elderly patients is often complicated by comorbidities.10 Regardless of eligibility for autologous stem cell transplantation, maintenance therapy using novel agents is typically administered with the intention of sustaining disease response.

The development of novel agents over the past decade has improved outcomes in patients with MM,7 although the vast majority of patients will eventually relapse. Outcomes are generally worse for patients who have failed currently available treatments, with a median OS of 9 months estimated for patients who are refractory to PIs and IMiDs.11 As such, there is an unmet need for new therapies to increase survival for patients with MM. The demand is clearly high in patients with relapsed and/or refractory MM (RRMM) who have exhausted current treatment options, yet there is also an opportunity to attain deeper and more sustained response in front-line, or early-line, therapy. Tolerability is also a limitation of current treatments,12–14 particularly in the increasing elderly population with MM who are generally more susceptible to adverse events (AEs). Indeed, careful selection and management of patients with RRMM has been recommended to optimize the benefits of current treatments.15 As such, reduced toxicity would be a key attribute for new agents to facilitate their use in a greater proportion of patients. The corollary of these unmet treatment needs is the extensive pipeline of anti-MM drugs, focused on delivering new agents with novel modes of action.

Of the spectrum of new agents in development for the treatment of MM, monoclonal antibodies (mAbs) have emerged as a potential strategy based on the range of antigens highly expressed on the surface of the malignant cell (Figure 1). In other cancers, mAb-based therapy is already established, with >10 antibodies having received approval from the FDA for solid or hematologic malignancies since 1997.16 Antibodies afford a targeted approach to treatment, with toxicity directed primarily against the malignant cell. Antibodies are also associated with a favorable tolerability profile, as most of the approved agents have different and less severe toxicities compared with standard
Chemotherapeutics. In this review, we evaluate the promise of targeted therapy for MM in light of the key clinical data, focusing on the exciting recent developments in mAb-based therapy for this disease.

**CD38**

CD38 is a multifunctional cell surface glycoprotein that serves as both a receptor for the transduction of activation/proliferation signals and an ectoenzyme that catalyzes the production of nucleotides involved in calcium signaling (Figure 2). As a receptor, CD38 engages the non-substrate ligand CD31, which is also involved in the hydrolysis of cyclic adenosine diphosphate ribose to adenosine diphosphate ribose. In MM, the operation of CD38 with fellow ectoenzymes PC-1 and PC-2 is important in other malignancies, with postulated roles in proliferation and migration in chronic lymphocytic leukemia. CD38 is highly expressed in 80% of cases of MM and serves as a marker for MM cells.

There are presently three anti-CD38 mAbs in clinical development for the treatment of MM: daratumumab (DARA), SAR650984 and MOR202.

Daratumumab

DARA was generated from immunization of human transgenic HuMab-mice with recombinant CD38 protein. In preclinical models, DARAZ shown to elicit cell death through four mechanisms: antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP) and apoptosis via cross-linking (crosslinkage with Fc receptors or anti-human IgG antibody). ADCC was observed in all CD38+ MM cell lines, whereas CDC appeared dependent on CD38 expression level. The anti-tumorigenic potential of DARA has also been explored in combination with other novel and established agents. Here, increased cell lysis was observed when DARA was added to LEN and/or BORT, or to the established triplet regimen of melphalan (MEL)–prednisone (PRED)–BORT.

The clinical data reported for DARA have largely been from the phase I/II trials in patients with RRMM, either as monotherapy (NCT00574288; NCT01985126) or in combination with LEN and dexamethasone (DEX) (NCT01615029). In the expansion phase of the initial monotherapy trial, efficacy appeared dose related: the overall response rate (ORR; at least a partial response (PR)) was 10% for patients who received the 8 mg/kg dose and 35% for patients who received the higher 16 mg/kg dose (Table 1). Median PFS was also longer in these high-dose cohort (23 vs 14.9 weeks), although these data were immature at the time of presentation (May 2014). The apparent dose–response relationship is supported by pharmacokinetic (PK) data, which suggest that target-mediated clearance of this agent is reduced at higher doses, and the 16 mg/kg dose is being advanced in phase III trials. Results at the 16 mg/kg dose have also been recently presented from the second monotherapy trial (SIRIUS), testing daratumumab in 106 patients who had received at least three prior therapies; 95% refractory to last PI and IMID combination. The ORR was 29% in this heavily pre-treated population (median of five prior therapies; 95% refractory to last PI and IMID), with a median duration of response of 7.4 months. An ORR of 20–30% was observed across subgroups (for example, according to age (75 years) or renal function (creatinine clearance ≥ 60 ml/min)), and irrespective of the agent(s) to which patients were previously refractory. The median PFS in this study was 3.7 months, and the estimated 1-year survival rate was 65%.

In the combination study of DARA plus LEN and DEX in a moderately pre-treated population (median of two prior lines of
therapy), the ORR was 91% (39/43) across the dose escalation and expansion phases.\textsuperscript{32} The majority of these patients (n = 30) were assessed in the dose expansion phase at DARA 16 mg/kg, with ORR 87% in this section of the study.\textsuperscript{32} A high proportion of patients assessed in this combination study had received prior IMiD treatment (80%), although it should be noted that only 7% of patients assessed in the dose expansion phase at DARA 16 mg/kg, with ORR 55% in the 11 patients available for efficacy assessment.\textsuperscript{33}

The most common AEs associated with DARA treatment were infusion-related reactions, which were generally observed during the first infusion and predominantly Grade 1/2 in intensity.\textsuperscript{31,34} In the monotherapy trials, prophylactic treatment was given, and infusion-related reactions were recorded in 43–50% of patients at the 16 mg/kg dose.\textsuperscript{29,31} The most frequent Grade 3/4 AEs with single-agent daratumumab were thrombocytopenia and pneumonia in the dose expansion part of the original trial, and anemia and thrombocytopenia in the SIRIUS trial.\textsuperscript{29,31} Of note, Grade ≥ 3 thrombocytopenia and anemia occurred more frequently in patients who did not attain an objective response in the SIRIUS study, whereas there was no relationship between neutropenia and response.\textsuperscript{31} In the combination study with LEN–DEX, the majority of Grade ≥ 3 AEs were hematologic, and the maximum tolerated dose (MTD) of DARA was not reached.\textsuperscript{35} DARA was also generally well tolerated in combination with alternate backbone regimens, with no major additional toxicity observed.\textsuperscript{33}

The Phase III studies of LEN–DEX ± DARA (NCT02076009) and BORT–DEX ± DARA (NCT02136134) in patients with RRMM, and BORT–MEL–PRED ± DARA (NCT02195479) and LEN–DEX ± DARA (NCT02252172) in newly diagnosed patients with MM, have been announced.

Table 1. Clinical data from mAb-based treatment in patients with MM

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Combination</th>
<th>n (no. evaluable for response)</th>
<th>Median number of prior therapies</th>
<th>Response rates (%) (evaluable patients)</th>
<th>Reference</th>
</tr>
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<tr>
<td>CD38</td>
<td>DARA</td>
<td>LEN–DEX</td>
<td>4 (2–12)\textsuperscript{a}</td>
<td>35</td>
<td>5, 10</td>
<td>Lokhorst et al.\textsuperscript{29}</td>
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<td>DARA</td>
<td>BORT–DEX</td>
<td>2 (1–4)\textsuperscript{a}</td>
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<td>44, 14</td>
<td>Plesner et al.\textsuperscript{32}</td>
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<td>DARA</td>
<td>BORT–MEL–PRED</td>
<td>0 (newly diagnosed)</td>
<td>100</td>
<td>50, 0</td>
<td>Mateos et al.\textsuperscript{33}</td>
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<tr>
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<td>DARA</td>
<td>BORT–THAL–DEX</td>
<td>0 (newly diagnosed)</td>
<td>100</td>
<td>20, 10</td>
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<tr>
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<td>DARA</td>
<td>POM–DEX</td>
<td>≥ 2 prior lines\textsuperscript{b}</td>
<td>55</td>
<td>9, 18</td>
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<tr>
<td>CD38</td>
<td>DARA</td>
<td>SAR650984 10 mg/kg</td>
<td>6.5 (2–16)\textsuperscript{c}</td>
<td>32</td>
<td>0, 16</td>
<td>Martin et al.\textsuperscript{31}</td>
</tr>
<tr>
<td>CD38</td>
<td>DARA</td>
<td>SAR650984 &gt; 10 mg/kg</td>
<td>7 (2–14)/4 (1–9)\textsuperscript{c}</td>
<td>63</td>
<td>29, 8</td>
<td>Martin et al.\textsuperscript{31}</td>
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<tr>
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<td>DARA</td>
<td>MOR202 ± DEX</td>
<td>4–2 (11)\textsuperscript{d}</td>
<td>4</td>
<td>4, 0</td>
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<td>IL-6</td>
<td>Siltuximab</td>
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<td>79</td>
<td>28, 4</td>
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<td>BAFF</td>
<td>Tabalumab</td>
<td>BORT ± DEX</td>
<td>3 (1–10)</td>
<td>46</td>
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<td>40</td>
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</tr>
<tr>
<td>CD138</td>
<td>Indatuximab ravtansine</td>
<td>LEN–DEX</td>
<td>3 (1–8)</td>
<td>40</td>
<td>10, 8</td>
<td>Mateos et al.\textsuperscript{60}</td>
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<td>CD56</td>
<td>Lorvotuzumab mertansine</td>
<td>LEN–DEX ± DARA</td>
<td>2 (1–4)</td>
<td>32</td>
<td>0, 16</td>
<td>Mateos et al.\textsuperscript{54}</td>
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</tr>
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Abbreviations: BAFF, B-cell activating factor; BORT, bortezomib; CR, complete response; DARA, daratumumab; DEX, dexamethasone; ELO, elotuzumab; IL-6, interleukin-6; LEN, lenalidomide; mAb, monoclonal antibody; MEL, melphalan; MM, multiple myeloma; NR, not reported; POM, pomalidomide; PR, partial response; PRED, prednisolone; THAL, thalidomide; VGPR, very good partial response. *Median number of prior lines of therapy reported. \textsuperscript{11}As defined in inclusion criteria. \textsuperscript{11}Median number of prior therapies across entire study population. Response criteria as defined by International Myeloma Working Group, except in cases where VGPR is not reported for which European Bone Marrow Transplant criteria were used.\textsuperscript{11}
lines tested, whereas the CDC activity was dependent on receptor density. SAR650984 also elicited a direct pro-apoptotic effect, capable of inducing crosslinking-independent apoptosis in addition to the crosslinking-dependent apoptosis observed with DARA. Preclinical investigations also revealed that SAR650984 inhibited CD38 ectoenzyme activity, which has not been reported for DARA or MOR202. SAR650984 has demonstrated synergistic or additive antitumor effects in combination with LEN, BORT, CAR and MEL in mouse xenograft tumor models.

Two ongoing phase I/II dose escalation studies are assessing SAR650984 in patients with RRMM: as a monotherapy (NCT01084252) or in combination with LEN and DEX (NCT01749969). In heavily pre-treated patients (median 6.5 prior lines of therapy including BORT, CAR, POM and LEN) who received single-agent SAR650984 0.3–20 mg/kg every other week, ORR was 27% overall, and 32% in patients who received SAR650984 at doses ≥ 10 mg/kg (Table 1). PK data indicated decreased clearance of SAR650984 with increasing dose, suggestive of a dose relationship. The MTD was not reached in this study, and additional dosing regimens are to be tested in the expansion phase of this study.

The combination therapy study, which also included heavily pre-treated patients (median seven prior treatment regimens), reported an ORR of 63% at SAR650984 doses of 10 mg/kg (Table 1). In addition, reductions in paraprotein of >90% were recorded in approximately one-third of patients at this dose. In contrast to the combination trial of DARA with LEN–DEX, the vast majority of patients in this study were relapsed or refractory to LEN, yet the ORR was 48% in this patient subpopulation. Notably, responses were also observed in patients refractory to BORT, CAR or POM. The overall median PFS was 6.2 months, yet in patients who had received only one to two lines of prior therapy (n = 7) median PFS had not been reached at data cut-off. The PK data indicated no significant interaction between LEN and SAR650984.

As a monotherapy, the most common treatment-emergent AEs with SAR650984 were fatigue (53% of patients) and nausea (35%), and the most common drug-related Grade 3/4 event was pneumonia (8%). Infusion reactions (52%) were observed during the first cycle of treatment, and were predominantly Grade 1/2 in severity. Infusion reactions led to treatment disruption in two patients in the combination study, although these events decreased after Cycle 1 when prophylaxis was introduced. In the combination study, the most common Grade 3/4 events were cytopenias, specifically neutropenia and thrombocytopenia.

MOR202
MOR202 is a fully human HuCAL IgG1 antibody, which has been shown to elicit cell death by ADCC and ADCP. Preclinical data published to date have largely focused on MOR202 combination therapy, which has demonstrated that MOR202 antitumor activity is related to CD38 expression level, and is synergistic with POM and LEN and additive with BORT. Of note, both LEN and POM treatment were shown to increase CD38 expression, and thus enhance the cytotoxic effects of MOR202. In addition, treatment with both IMiDs induced activation of immune effector cells, further promoting ADCC and ADCP. These independent activities of LEN and POM suggest that the combination of CD38-targeted agents with IMiDs should provide a potent strategy for MM treatment. In vivo studies using murine MM models have also demonstrated synergistic reductions in bone lysis when MOR202 was combined with LEN, BORT or MEL.

Preliminary clinical data from a phase I/IIa study testing MOR202 with or without DEX in patients with RRMM have recently been reported. Among 23 patients assessed, only one achieved a response better than stable disease (Table 1). With the dosing schedule tested, the most common AEs were anemia, fatigue and nausea; the MTD of MOR202 was not reached in this study. Infusion-related reactions were observed in 31% of patients, yet only in those who received MOR202 alone, and these events occurred mostly during the first infusion. A transient antidrug antibody response to MOR202 was also observed in one patient. As part of the overall MOR202 development program, this mAb will also be evaluated in combination with LEN–DEX and POM–DEX in patients with RRMM.

Anti-CD38 mAb summary
The anti-CD38 mAbs have shown potent activity in preclinical MM models both as single agents and in combination with other agents, with all three demonstrating ADCC and ADCP. ADCC may be particularly pertinent for treatment of MM, as high numbers of macrophages are present in the bone marrow. However, despite their similarities, there are also distinct differences between DARA, SAR650984 and MOR202. Each antibody targets a distinct epitope on CD38, and there are differences in their modes of action. For example, DARA induces crosslinking-dependent apoptosis, whereas SAR650984 can promote apoptosis with or without crosslinking. Furthermore, SAR650984 is a much more potent inhibitor of CD38 ectoenzyme function than DARA or MOR202.

This activity may provide another mechanism to suppress MM growth, based on the proposed role of CD38 ectoenzyme signaling in protecting MM cells in the bone marrow niche, although the clinical significance of such an activity is not clear. Combination therapy to date has focused on the addition of these mAbs to other novel agents, such as LEN which can enhance the activity of effector cells (for example, natural killer cells), and upregulate CD38 expression on MM cells. As receptor density impacts CDC for SAR650984 and DARA, and ADCC and ADCP for MOR202, LEN appears a natural partner for the anti-CD38 mAbs. Owing to their non-overlapping modes of action and distinct CD38-binding sites, the therapeutic combination of anti-CD38 mAbs is also conceivable.

The assessment of monoclonal immunoglobulin protein (M-protein) reduction by immunofixation electrophoresis is used to define the depth of response according to the International Myeloma Working Group criteria. Therapeutic mAbs may interfere with this assay and thereby influence clinical interpretation of response to therapy. Data were recently presented for a DARA immunofixation electrophoresis reflex assay (DIRA), in which the binding of an anti-idiotypic antibody to DARA altered its electrophoretic migration and thus distinguished this mAb from the disease-associated M-protein in patient samples. The use of such an assay may be necessary to confirm the reduction, and most specifically the absence (necessary for complete response (CR)) of M-protein in future mAb trials.

CS1/SLAMF7
CS1 is a member of the signaling lymphocyte activating-molecule-related family and is highly expressed on the surface of normal plasma cells and MM cells. This molecule is also expressed on other lymphocytes, for example natural killer cells, although at lower levels. CS1 is normally involved in regulating the immune response, but appears to have a role in survival pathways in MM.

Elotuzumab (ELO) is a humanized IgG1 mAb directed against human CS1. Preclinical models, ELO was shown to mediate cell death via ADCC and inhibit CS1-mediated MM cell adhesion to bone marrow stem cells, in a dose-dependent manner. In addition, ELO may act beyond ADCC by enhancing the cytotoxic activity of natural killer cells.

Despite the promising preclinical data, a phase I clinical trial of ELO in patients with RRMM demonstrated that this agent was not...
effective as a monotherapy.\textsuperscript{57} Indeed, no objective responses were observed during the study and \textasciitilde 75\% of patients had progressive disease.\textsuperscript{57} However, ELO at doses up to 20 mg/kg every other week was generally well tolerated,\textsuperscript{37} supporting its investigation as a part of a combination regimen.

In a phase I study of ELO plus BORT in patients with RRMM, the ORR was 48\% (Table 1), including responses in two of three patients previously refractory to BORT.\textsuperscript{60} This level of response was also attained in 7 of 10 patients with high-risk cytogenetics.\textsuperscript{58} ELO–BORT–DEX was compared with BORT–DEX alone in a phase II trial, which demonstrated that, despite a similar ORR (65 vs 63\%), the triplet regimen improved median PFS (9.7 months vs 6.9 months) over BORT–DEX alone in patients with RRMM.\textsuperscript{59} ELO has also been tested in a phase II trial with THAL and DEX in patients with RRMM, with an ORR of 40\% reported.\textsuperscript{60}

The majority of clinical data for ELO, however, has been attained in combination with LEN and DEX, with this triplet regimen tested in moderately pre-treated patients with RRMM in phase I, II and III trials. The phase I study demonstrated the tolerability and activity (ORR, 82\%) of ELO–LEN–DEX\textsuperscript{61} with the 10 and 20 mg/kg ELO doses advanced to phase II. In a LEN-naïve patient population, an overall ORR of 84\% (61/73) was reported in the phase II study.\textsuperscript{62} However, efficacy appeared better in the 10 mg/kg cohort compared with the 20 mg/kg cohort, both in terms of ORR (92 vs 76\%) and PFS (33 months vs 18.6 months).\textsuperscript{62} As expected, ORR and median PFS were reduced in patients with \textasciitilde 2 previous therapies compared with those who had received only one prior therapy (ORR, 78 vs 91\%; PFS, 21.3 months vs 25.0 months),\textsuperscript{63} although these were the first data from a mAb study to demonstrate the impact of pre-treatment level on response. Comparison of response rates between different agents should thus take account of the number of lines of prior therapy. With the improved efficacy data at 10 mg/kg compared with 20 mg/kg, this lower dose was tested in 646 patients with RRMM in the recently reported phase III ELOQUENT-2 study. In a population who had received a median of two prior therapies (6\% had received LEN), ELO–LEN–DEX significantly extended median PFS (co-primary end point) compared with LEN–DEX alone (19.4 months vs 14.9 months; hazard ratio, 0.57–0.85; P < 0.0001).\textsuperscript{64} The benefit of ELO–LEN–DEX with respect to PFS was maintained in patients < 65 and \textasciitilde 65 years, and in patients with the del(17p) and t(4;14) abnormalities.\textsuperscript{64} The 1-year PFS rate was higher in the ELO–LEN–DEX arm (68 vs 57\%), and this difference was slightly greater at 2 years (41 vs 27\%).\textsuperscript{64} ELO–LEN–DEX also improved ORR (co-primary end point) compared with LEN–DEX (79 vs 66\%; P < 0.0001)\textsuperscript{64} (Table 1); PFS was longer in patients who achieved at least PR with ELO–LEN–DEX than with LEN–DEX alone.\textsuperscript{64} The OS data were immature at the time of presentation.

As a single agent, the most common treatment-emergent AEs reported with ELO were chills and pyrexia, which were mostly reported with ELO.\textsuperscript{67} However, ELO at doses up to 20 mg/kg every other week was generally well tolerated,\textsuperscript{37} supporting its investigation as a part of a combination regimen.

In a phase I study of ELO plus BORT in patients with RRMM, the ORR was 48\% (Table 1), including responses in two of three patients previously refractory to BORT.\textsuperscript{60} This level of response was also attained in 7 of 10 patients with high-risk cytogenetics.\textsuperscript{58} ELO–BORT–DEX was compared with BORT–DEX alone in a phase II trial, which demonstrated that, despite a similar ORR (65 vs 63\%), the triplet regimen improved median PFS (9.7 months vs 6.9 months) over BORT–DEX alone in patients with RRMM.\textsuperscript{59} ELO has also been tested in a phase II trial with THAL and DEX in patients with RRMM, with an ORR of 40\% reported.\textsuperscript{60}

INTERLEUKIN-6

IL-6 is involved in the survival and proliferation of MM cells with a key role proposed during the early stages of disease development.\textsuperscript{70,71} Siltuximab, a chimeric mAb against IL-6, has been shown to sensitize MM cells to DEX-mediated apoptosis\textsuperscript{72} and to enhance the activity of BORT and MEL, in preclinical models.\textsuperscript{73,74} In combination with DEX, siltuximab was well tolerated but demonstrated only modest efficacy in patients with RRMM (ORR, 11\%); as a single agent, siltuximab did not induce any objective responses.\textsuperscript{75} The benefit of adding siltuximab to BORT was also tested in BORT-naïve patients with RRMM, but although ORR increased with the combination regimen (ORR, 55 vs 47\%), there was no improvement in PFS or OS compared with BORT–placebo.\textsuperscript{76}

As patients with RRMM may have residual MM cells that are less dependent on IL-6, siltuximab was tested in patients with newly diagnosed MM in a phase II study: siltuximab–BORT–MEL–PRED vs BORT–MEL–PRED. An EBMT ORR (PR+CR) of 88\% was reported in patients who received siltuximab–BORT–MEL–PRED compared with 80\% in the comparator arm, but the study did not meet its primary end point as the difference in CR rate between the study arms was < 10\%.\textsuperscript{77} The very good PR rate was significantly increased in the siltuximab arm, although this did not translate to differences in OS or PFS, raising questions over the association between this level of response and outcomes.\textsuperscript{77} The incidence of Grade \textasciitilde 3 events was slightly higher in the siltuximab arm (92 vs 81\%), with an increased rate of hematologic events and infections.\textsuperscript{77}

The possibility that IL-6 is involved during early MM development has also led to initial testing of siltuximab in patients with monoclonal gammapathy of undetermined significance or smoldering myeloma. Here, single-agent siltuximab reduced paraprotein in a subset of patients and did not yield any new safety signals.\textsuperscript{78} As such, siltuximab is being tested against placebo in a phase II trial in patients with high-risk smoldering myeloma (bone marrow plasma cells \textasciitilde 10\% and either serum monoclonal protein \textasciitilde 3 g/dl, or abnormal free light chain ratio < 0.126 or > 8, and serum M-protein < 3 g/dl but \textasciitilde 1 g/dl) (NCT01484275).

B-CELL ACTIVATING FACTOR

B-cell activating factor (BAFF) is a member of the tumor necrosis factor superfamily that is produced in the bone marrow, and is overexpressed in MM cells compared with normal plasma cells at the transcript level.\textsuperscript{79} BAFF appears to promote survival of MM cells.\textsuperscript{80} Tabalumab (LY2127399) is a human mAb against BAFF that neutralizes the membrane-bound and soluble forms of this factor.\textsuperscript{81} In a phase I study in patients with RRMM (patients were not refractory to BORT), the combination of tabalumab with BORT–DEX achieved an ORR of 46\%.\textsuperscript{82} Treatment discontinuation was reported owing to neuropathy, neuralgia, fatigue and thrombocytopenia.\textsuperscript{82} A phase II trial of tabalumab (100 or 300 mg) – BORT–DEX vs placebo–BORT–
T cell

CD138

patients with RRMM (NCT01101594).

trial of milatuzumab conjugated with doxorubicin is ongoing in

agent, which was otherwise generally well tolerated.86 A phase I/II

pre-treated patients with RRMM (median of three prior therapies).90 This trial is ongoing, although

therapy was stable disease.86 Modifi-

DEX, an ORR of 78% was attained and acceptable tolerability

preclinical models.85 In a phase I dose escalation study in heavily

no future trials of indatuximab ravtansine have been announced.

lucatumumab have been reported in the MM setting.

therapies.102,103 Dose-related neuropathy was observed in both

56% was achieved in patients with CD56+ RRMM, although this

modest ORR (39%) was attained when dacetuzumab was

weak ef-

factor superfamily member CD40, had good tolerability but only

Dacetuzumab and lucatumumab, mAbs to the tumor necrosis

other target antigens (Figure 1), and to date, mAbs to CD40, CD56,

ICAM-1, demonstrated that this agent can stabilize disease,

clinical data, the anti-CD38 mAbs DARA and SAR650984 have

remains for newer agents with novel modes of action. Inspiration

mAb-based therapies. Of those agents which have reported

CD74 is a major histocompatibility complex class II chaperone

involves antigen presentation. It is also frequently expressed in

CD74

CD74

CD138/syndecan-1 is expressed during B-cell development, and is

specifically located on plasma cells and MM cells in the bone

Indatuximab ravtansine (BT062) comprises a mAb against CD138 conjugated to the cytotoxic maytansinoid DM4.88

As a monotherapy, indatuximab ravtansine treatment achieved at

least PR in only 4% (1/27) of patients with RRMM, but was
generally well tolerated.89 As a combination therapy with LEN–

DEX, an ORR of 78% was attained and acceptable tolerability

maintained in a moderately pre-treated RRMM population

(median of three prior therapies).90 This trial is ongoing, although

no future trials of indatuximab ravtansine have been announced.

Elsewhere, a [211Bi] radiolabelled antibody against CD138 is in

preclinical development.91

PD-1/PD-L1

PD-1 is expressed on the surface of T and B cells, and inhibits T-cell

activation and proliferation through its interaction with the PD-L1

ligand expressed on antigen-presenting cells.72,93 PD-1/PD-L1

signaling is dysregulated in patients with MM, with PD-L1

expressed on MM cells, and PD-1 expressed on natural killer cells

and upregulated on T cells.94 Thus, the PD-1/PD-L1 signaling axis

provides a mechanism through which MM cells can interfere with

the immune response and avoid death (Figure 3). The use of mAbs

targeting PD-1/PD-L1 has been tested in the preclinical setting, with

anti-myeloma activity demonstrated using an anti-PD-L1–

based treatment protocol.95 The anti-PD-1 mAb most advanced in

the clinic is nivolumab, although monotherapy with this agent has

thus far achieved only disease stabilization (no objective responses reported) in patients with RRMM.96 However, nivolu-
mab was shown to be tolerable, and its combination with the

CTLA-4 mAb ipilimumab (activation of CTLA-4 dampens the host

T-cell response97) or lirilumab is under assessment as part of the

same phase I trial (NCT01592370). In addition, early-stage clinical

trials of the anti-PD-1 antibodies pembrolizumab (MK-3475) and

pidilizumab, typically in combination with IMiDs, are ongoing in

patients with RRMM.

OTHER ANTIGENS

Immunophenotyping of MM cells has also revealed a number of

other target antigens (Figure 1), and to date, mAbs to CD40, CD56,

ICAM-1 and CXCR4 have been tested in clinical studies. Dace-
tuzumab and lucatumumab, mAbs to the tumor necrosis factor superfamily member CD40, had good tolerability but only

weak efficacy as single agents96,99 (Table 1). In addition, only

modest ORR (39%) was attained when dacetuzumab was

combined with LEN–DEX in patients with RRMM.100 Development

of dacetuzumab has been discontinued, and no upcoming trials of

lucatumumab have been reported in the MM setting.

Lorvotuzumab mertansine, a humanized mAb to CD56 conjugated to the cytotoxic maytansinoid derivative DM1, also
displayed low activity as a monotherapy in patients with RRMM

(ORR, 7%; Table 1).101 In combination with LEN–DEX, an ORR of

56% was achieved in patients with CD56+ RRMM, although this

population had received only a median of two prior anti-myeloma

therapies.102,103 Dose-related neuropathy was observed in both

the monotherapy and combination therapy studies,101,102 and no

new trials have been announced for lorvotuzumab mertansine.

Clinical data from a phase I trial of BI-505, a human mAb against

ICAM-1, demonstrated that this agent can stabilize disease,

although no objective responses were observed following

2 months’ treatment of patients with RRMM (Bioinvest press

release). However, this agent was generally well tolerated and a

phase II study of single-agent BI-505 in patients with smoldering

myeloma is now recruiting (NCT01838369).

Similar to the above agents, the anti-CXCR4 mAb ulocuplumab is also under investigation in patients with RRMM, in combination

with either LEN–DEX or BORT–DEX (NCT01359657). The ORR was

55% and 40% for the LEN–DEX and BORT–DEX groups,

respectively, and an increase in circulating lymphocytes was

observed after each ulocuplumab infusion at the two highest
doses tested.104 Both combination regimens were generally well
	tolerated, with the MTD not reached during the dose escalation

phase of this study.104

CONCLUSIONS

The introduction of PIIs and IMiDs has improved outcomes for

patients with MM, although these agents do not cure the disease

and most patients will eventually relapse. As such, the need

remains for newer agents with novel modes of action. Inspiration

has been derived from knowledge of molecules expressed on the

surface of myeloma cells, with a number of targets identified for

mAb-based therapies. Of those agents which have reported

clinical data, the anti-CD38 mAbs DARA and SAR650984 have

shown robust single-agent activity, which has been enhanced

through the addition of LEN–DEX, whereas the activity of other

agents (for example, ELO) appears restricted to combination

regimens.
The antibodies discussed here are generally well tolerated, and importantly most appear to have a safety profile that is distinct from current treatments. Combination therapy is thus a viable strategy, and in this regard LEN may have an inherent advantage due to its demonstrated positive effects on the immune responses through which a number of the mAbs operate. However, other combinations are under clinical testing, and the potential remains for combining the antibodies themselves providing that the modes of action are distinct. High response rates have been achieved in patients with RRMM with combination therapy, in some cases even in heavily pre-treated patients. However, these agents may also have a role in early-line therapy, with data from other novel agents suggesting increased ORR and deeper responses can be achieved in front-line therapy compared with treatment of RRMM.105,106 As treatment paradigms shift, mAb therapy may also be utilized for patients with monoclonal gamopathy of undetermined significance or smoldering MM; toxicities associated with current regimens for symptomatic MM may deter their use in these patients, although a tolerable, efficacious mAb monotherapy would not face the same issues. Here, it is notable that single-agent clinical studies of both DARA and ELO in patients with smoldering MM have been announced. The development of mAbs thus represents an exciting new chapter in the battle against MM. Future data from larger studies will reveal how much of an impact these agents will make on long-term survival and the quality of life in patients with MM.

CONFLICT OF INTEREST
SL has acted as a consultant for Millennium, Celgene, Novartis, Bristol-Myers Squibb, Onyx and Sanofi. AP has acted as a consultant and received honoraria from Amgen, Bristol-Myers Squibb, Genmab A/S, Celgene, Janssen-Cilag, Millennium and Onyx. He has also received honoraria from Novartis and Sanofi. JSM has served on advisory committees for Millennium, Celgene, Novartis, Onyx, Janssen, Bristol-Myers Squibb, Merck Sharpe & Dohme and Sanofi. The remaining author declares no conflict of interest.

ACKNOWLEDGEMENTS
The authors received editorial assistance from Neil Harrison of Adelphi Communications Ltd, funded by Sanofi.

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