

# Current Antibody-Based Therapies for the Treatment of Multiple Myeloma

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**Abstract:** Despite continued and considerable progress following the introduction of proteasome inhibitors and immunomodulatory agents, multiple myeloma (MM) remains an incurable disease, and new therapeutic strategies are urgently needed. Monoclonal antibodies represent a well-established targeted approach to the treatment of MM, with selective killing properties and limited off-target toxicity. Since their approval, the anti-CD38 agent daratumumab, the anti-SLAMF7 agent elotuzumab, and most recently the anti-CD38 agent isatuximab have led to pivotal improvements in the treatment of double-refractory MM; currently, they are on their way to becoming integral parts in the up-front care of patients who have newly diagnosed MM, with daratumumab already approved in this setting. Several other antibody-based strategies are undergoing clinical assessment in MM. Although the investigation of checkpoint inhibitors in MM has been halted, bispecific T-cell engagers and especially antibody-drug conjugates demonstrate encouraging efficacy and manageable toxicity in triple class-refractory MM. The accelerated approval of belantamab mafodotin represents an important milestone in antibody development; its ability to target B-cell maturation antigen (BCMA) in advanced disease is now established. Here, we present an overview of the currently available monoclonal antibody treatments in MM and discuss the clinical value, significant potential, and possible limitations of these immunotherapeutic approaches to driving deeper responses and achieving longer overall survival among patients with a challenging disease.

## Keywords

Antibody-drug conjugates, bispecific T-cell engager, daratumumab, elotuzumab, isatuximab, monoclonal antibodies, multiple myeloma

## Background

Multiple myeloma (MM) is a plasma cell malignancy. Approximately 32,000 people in the United States will receive a diagnosis of MM in

2020.<sup>1</sup> Over the past 2 decades, the introduction of novel agents such as immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) has significantly improved the prognosis of patients with MM.<sup>2-4</sup> Frontline treatment currently consists of novel agent-based induction therapy followed by transplant-free consolidation or—in eligible patients—autologous stem cell transplant (ASCT) with subsequent maintenance to deepen and sustain disease response. However, outcomes remain poor after relapse, especially among high-risk patients; the estimated overall survival of patients with PI- and IMiD-refractory disease is only 13 months.<sup>5</sup> Long-term drug safety has become increasingly relevant now that patients have a significantly longer life expectancy than formerly. Monoclonal antibodies (mAbs) represent a targeted approach to the treatment of MM, with selective killing properties that include complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP).<sup>6</sup> Because the target antigen is expressed mostly on plasma cells, the tolerability of mAbs is significantly better than that of conventional chemotherapy or ASCT. In the context of IMiD- and PI-refractory disease, mAbs can effectively add anti-MM efficacy without increasing relevant toxicity and can induce deeper and more durable responses. The anti-SLAMF7 mAb elotuzumab (Empliciti, Bristol-Myers Squibb) and the anti-CD38 mAbs daratumumab (Darzalex, Janssen Biotech) and, more recently, isatuximab (Sarclisa, Sanofi Genzyme) are now used in the setting of relapsed/refractory MM (RRMM), with daratumumab becoming a new standard of care in the frontline setting.<sup>7-10</sup> In addition to this first generation of mAbs, several investigational approaches have most recently expanded the immunotherapeutic armamentarium to include antibody-drug conjugates, which selectively convey specific cytotoxic drugs to the target cells of interest; bispecific T-cell engagers (BiTEs), which recruit T cells for the specific targeting of MM cells; and checkpoint inhibitors, which re-stimulate the immune system by targeting the cell surface receptor programmed death 1 (PD-1) and/or its ligand. Here, we present an overview of currently available mAb treatments and discuss the clinical effects, potential, and limitations of immunotherapeutic approaches to the treatment of MM.

### Anti-SLAMF7

SLAM family member 7 (SLAMF7, also known as CS1, CD319, and CRACC) is a glycoprotein expressed on the surface of plasma cells and natural killer (NK) cells. It belongs to the family of signaling lymphocyte-activating molecule-related receptor proteins, promoting cell growth and survival in normal and malignant plasma cells.<sup>11</sup>

SLAMF7 inhibition induces cell death in MM cells<sup>12</sup> and acts by directly activating NK cells and recruiting the SLAM-associated adapter protein EAT-2.<sup>13</sup>

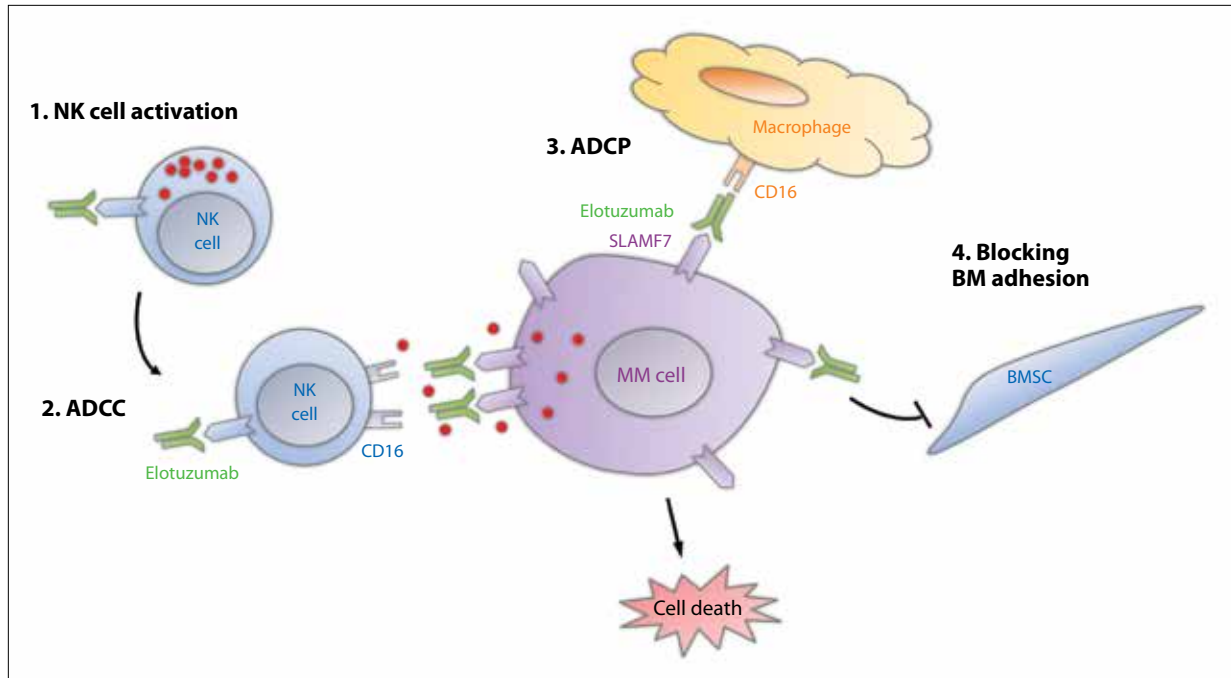
#### *Elotuzumab*

Elotuzumab, formerly HuLuc63, is a humanized immunoglobulin G1 (IgG1) anti-SLAMF7 antibody with a high degree of selectivity and minimal off-target effects. Its activity is delivered primarily by NK cell-mediated ADCC and ADCP (Figure 1).<sup>12,14</sup> Elotuzumab enhances NK cell and macrophage function by Fc interaction with the FcγRIIIa receptor (CD16) on both effector cell types.<sup>12,14</sup> A high-affinity polymorphism for FcγRIIIa has been correlated with favorable outcomes in patients on elotuzumab-containing therapy (NCT01478048) and may serve as a future sensitivity marker to predict elotuzumab response.<sup>15</sup>

**Clinical Studies in Relapsed/Refractory MM.** In a first-in-human phase 1 dose-escalation study, elotuzumab (0.5-20 mg/kg) was associated with modest single-agent activity resulting in disease stabilization in 9 of 35 patients (26%) who had RRMM (NCT00425347).<sup>16</sup>

Preclinical synergism between elotuzumab and bortezomib (Velcade, Millennium/Takeda Oncology) in vitro and in vivo provided the rationale for a phase 1 trial assessing the safety of such a combination in RRMM (N=28; overall response rate [ORR], 48%; NCT00726869).<sup>17,18</sup> In the randomized setting, however, the triplet of elotuzumab plus bortezomib/dexamethasone did not result in a significant clinical benefit compared with bortezomib/dexamethasone (N=152; median progression-free survival [PFS], 9.7 vs 6.9 months; P=.09), with similar response rates reported in the 2 study arms (ORR, 66% vs 63%; NCT01478048).<sup>15</sup>

Enhanced NK cell activity induced by lenalidomide (Revlimid, Celgene) has been reported to demonstrate potential synergism with elotuzumab-driven ADCC in a preclinical study of MM.<sup>19</sup> Promising efficacy was observed for elotuzumab/lenalidomide in a phase 1b-2 trial that randomly assigned patients to weekly elotuzumab at 10 mg/kg (n=36; ORR, 92%) or 20 mg/kg (n=37; ORR, 76%; NCT00742560).<sup>20</sup> Given its favorable efficacy, safety, and target saturation, a dose of 10 mg/kg weekly was selected for the subsequent phase 3 trials. At a median follow-up of 24.5 months, the ELOQUENT-2 study (N=646; NCT01239797) observed a significant survival benefit for elotuzumab in combination with lenalidomide/dexamethasone (elotuzumab-Rd) vs Rd alone (hazard ratio [HR], 0.70; 95% CI, 0.57-0.85; P<.001).<sup>9</sup> Prolonged PFS and improved hematologic responses were noted in the patients in the study arm (ORR, 79%; PFS, 19.4 months) vs those in the control arm (ORR, 66%; PFS, 14.9 months). With these results available, the US



**Figure 1.** Mechanisms of action of elotuzumab.

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; BM, bone marrow; BMSC, bone marrow stroma cell; MM, multiple myeloma; NK cell, natural killer cell; SLAMF7, SLAM family member 7.

Food and Drug Administration (FDA) in 2015 and the European Medicines Agency (EMA) in 2016 approved elotuzumab in combination with Rd for patients with RRMM who had received 1 to 3 prior lines of therapy.

In the phase 2 ELOQUENT-3 study, elotuzumab combined with pomalidomide (Pomalyst, Celgene)/dexamethasone demonstrated significantly improved efficacy in lenalidomide-refractory RRMM vs pomalidomide/dexamethasone alone (N=117; NCT02654132; median PFS, 10.3 vs 4.7 months; ORR, 53% vs 26%).<sup>21</sup> The HR for disease progression or death in the intervention arm vs the control arm was 0.54 (95% CI, 0.34-0.86;  $P=.008$ ). Elotuzumab plus pomalidomide/dexamethasone for the treatment of patients with RRMM and at least 2 previous lines of therapy (including a PI and lenalidomide) received FDA approval in 2018 and EMA approval in 2019. Several clinical trials continue to assess elotuzumab-containing regimens in the context of RRMM. Results from a phase 2 trial testing the first quadruplet protocol of elotuzumab in combination with pomalidomide, bortezomib, and dexamethasone (NCT02718833) showed promising results in a preliminary analysis reported at the 2019 American Society of Hematology (ASH) annual meeting (ORR, 61%; median PFS, 9.8 months).<sup>22</sup>

**Clinical Studies in Newly Diagnosed MM.** The role of elotuzumab in the up-front setting of newly diagnosed

MM (NDMM) remains a field of active investigation, with mixed results to date.

The SWOG 1211 phase 1/2 trial for NDMM is assessing elotuzumab in combination with lenalidomide, bortezomib, and dexamethasone (elotuzumab-RVd; NCT01668719) in transplant-ineligible patients. Induction with elotuzumab-RVd in this protocol is followed by elotuzumab-RVd maintenance at reduced doses until disease progression or unacceptable toxicities. Safety data released from the phase 1 portion of the trial revealed no major safety signals in comparison with what has previously been reported for RVd, as well as encouraging activity.<sup>3,23</sup> Efficacy data were first released at the 2020 American Society of Clinical Oncology (ASCO) annual meeting; at a median follow-up of 53 months, no difference was noted between median PFS and OS for elotuzumab-RVd vs RVd control.<sup>24</sup>

The GMMG-HD6 trial continues to assess elotuzumab-RVd as induction and consolidation after ASCT, followed by lenalidomide maintenance (NCT02495922). In an interim analysis presented at the 2020 annual meeting of the European Hematology Association (EHA), the addition of elotuzumab did not improve ORR after 4 cycles of induction therapy.<sup>25</sup>

The phase 3 randomized ELOQUENT-1 trial comparing elotuzumab-Rd induction vs Rd alone in

transplant-ineligible patients (NCT01335399) did not reach its primary endpoint because elotuzumab-Rd did not show a statistically significant improvement in PFS vs Rd alone.<sup>26</sup>

A phase 2 trial is evaluating elotuzumab/carfilzomib (Kyprolis, Onyx) in combination with Rd in transplant-ineligible NDMM (NCT02969837) and recently reported a promising ORR of 100%.<sup>27</sup> In the setting of ASCT, an interim analysis reported on elotuzumab-Rd as an induction and post-transplant consolidation and maintenance strategy in a phase 2 study (NCT02843074) that included 52 patients with NDMM.<sup>28</sup> With a median follow-up of 20 months, the median PFS and OS in this study were 20.5 and 22.0 months, respectively, for patients with stage III myeloma by the Revised International Staging System (R-ISS) and high-risk cytogenetic features; they have not yet been reached for patients with standard risk.<sup>28</sup>

To overcome NK cell exhaustion and enhance elotuzumab-mediated ADCC activity, a single-arm phase 1/2 trial has recently been initiated to assess ex vivo expanded NK cell therapy in combination with elotuzumab-Rd as a consolidation strategy after ASCT (UMIN000033128).<sup>29</sup>

**Clinical Studies in Smoldering MM.** Given its favorable safety profile, elotuzumab-Rd has also been investigated for high-risk smoldering multiple myeloma (SMM). In the phase 2 E-PRISM trial (NCT02279394), elotuzumab-Rd was given to 50 patients with SMM for a total of 8 cycles, with the option of stem cell collection and continuation on maintenance therapy. An interim analysis reported an ORR of 84%, with no patients progressing to active MM during the follow-up period of 29 months.<sup>30</sup> Because drug safety is key in SMM, the mild toxicity profile (26% neutropenia) of elotuzumab-Rd in this protocol is encouraging. Similarly, elotuzumab as monotherapy showed excellent tolerability and sustained disease control in a high-risk population in a second multicenter study (N=31; NCT01441973).<sup>31</sup>

**Administration Guidelines.** The safety of elotuzumab compares favorably with that of other immune therapies in MM; common side effects, including grade 1/2 infusion-related reactions (IRRs), are readily manageable. Specifically, premedication with 40 to 60 mg of methylprednisolone, 25 to 50 mg of diphenhydramine, and 650 to 1000 mg of acetaminophen has proven to be highly efficacious as prophylaxis for elotuzumab-related IRRs.<sup>18</sup>

**Diagnostic Challenges.** As a humanized IgGκ mAb, elotuzumab can interfere with serum immunofixation. Thus, it may be challenging to validate complete responses (CRs) in patients with IgGκ MM, and CR rates may generally be underestimated.

## Anti-CD38

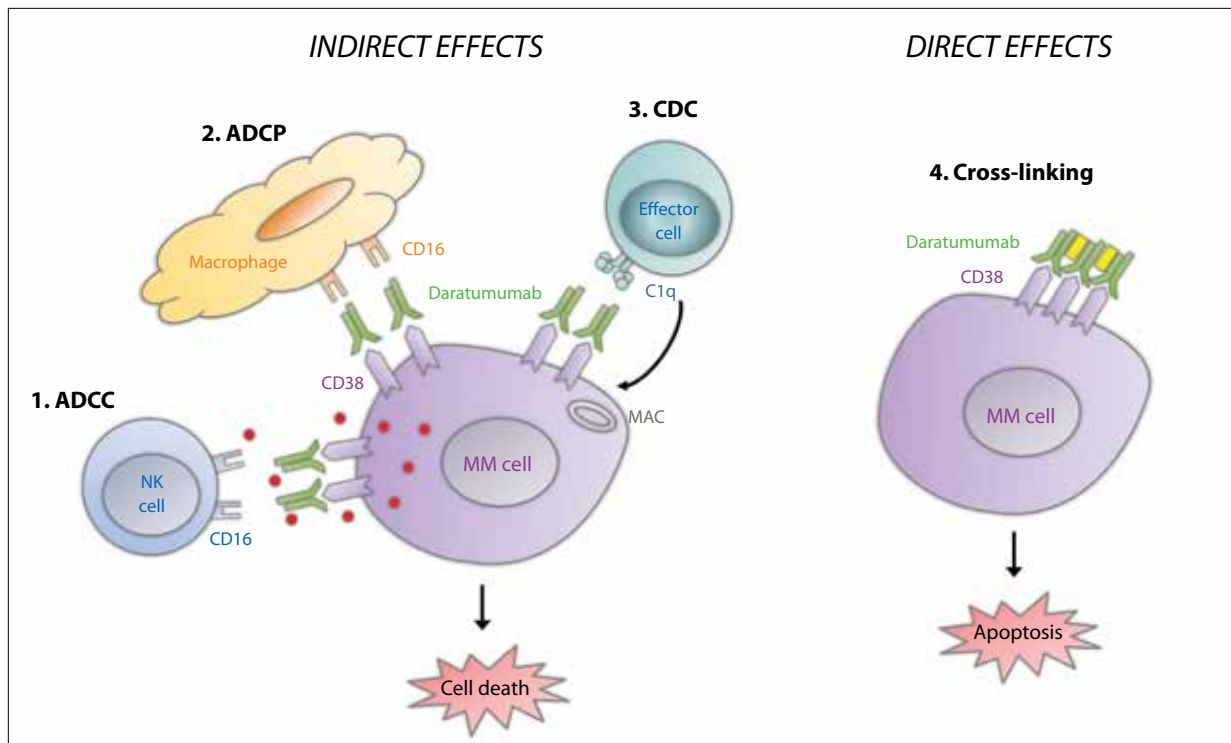
CD38 is a type 2 transmembrane ectoenzyme that is expressed on the surface of various cell types, including myeloid and lymphoid lineage cells, epithelial cells, and smooth muscle cells in the respiratory tract.<sup>32-34</sup> Its relatively high level of expression on plasma cells and its important role in MM biology provide the rationale to employ CD38 as a therapeutic antibody target for the treatment of patients with MM.

### *Daratumumab*

Daratumumab is a potent human anti-CD38 IgG1κ mAb. Its activity is mediated by FcγR-mediated cross-linking and indirect effector mechanisms, including CDC, ADCC, and ADCP (Figure 2).<sup>35-37</sup> Additional immunomodulation occurs through daratumumab-inducible depletion of CD38+ regulatory B- and T-cell populations and reciprocal expansion of CD4+ helper and CD8+ effector T cells.<sup>33</sup> Because CD38 acts as a cyclic ADP-ribose hydrolase, inhibition of its enzymatic activity can also lead to the preservation of nicotinamide adenine dinucleotide levels in T cells to overcome T-cell exhaustion and increase anti-MM immunity.<sup>38</sup>

**Clinical Studies in Relapsed/Refractory MM.** In 2015, the GEN501 phase 1/2 study (NCT00574288) reported pivotal safety and tolerability data on daratumumab monotherapy in RRMM.<sup>39</sup> Toxicity was generally mild, with grade 1/2 IRRs the most common side effect. No maximum tolerated dose was reached in the dose-escalation phase, up to 24 mg/kg. The highest level of activity was reported for daratumumab at a dose of 16 mg/kg (ORR, 36%). In a combined analysis of the GEN501 phase 1/2 trial and the SIRIUS phase 2 trial (NCT01985126) comprising 148 patients with RRMM (median of 5 prior lines of therapy; 87% with double-refractory disease), single-agent daratumumab at 16 mg/kg resulted in an impressive ORR of 31%, a median PFS of 4.0 months, and a median OS of 20.1 months,<sup>40,41</sup> leading to FDA and EMA approval in 2015 for patients with RRMM who had received at least 3 prior lines of therapy, including both a PI and an IMiD.

On the basis of preclinical findings suggesting synergism between daratumumab and IMiDs via NK cell stimulation and enhancement of ADCC, the GEN503 phase 1/2 trial (NCT01615029) tested the activity of daratumumab when combined with Rd (Dara-Rd) in a cohort of 32 patients who had RRMM (ORR, 81%; 2-year PFS rate, 69%, 2-year OS rate, 78%).<sup>42,43</sup> These findings were validated by the results of the randomized phase 3 POLLUX trial (MMY3003; NCT02076009).<sup>8</sup> In this study, 569 patients with RRMM were randomly assigned to Rd with or without daratumumab. The HR



**Figure 2.** Mechanisms of action of daratumumab.

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cell-mediated phagocytosis; CDC, complement-dependent cytotoxicity; C1q, complement component 1q; MAC, membrane-attacking complex; MM, multiple myeloma; NK cell, natural killer cell.

for disease progression or death in the Dara-Rd group vs the control group was 0.37 ( $P < .001$ ). At a median follow-up of 44.3 months, PFS was 44.5 months in the Dara-Rd arm (ORR, 93%) vs 17.5 months in the control arm (ORR, 76%).<sup>44</sup> Dara-Rd is currently approved by the FDA and EMA for patients with RRMM and at least 1 prior therapy.

In the EQUULEUS trial (N=103; NCT01998971), daratumumab was next assessed for its efficacy in combination with pomalidomide and dexamethasone (Dara-Pd).<sup>45</sup> Dara-Pd resulted in a promising ORR of 60%. These findings are currently being confirmed in the randomized phase 3 APOLLO trial (Dara-Pd vs Pd; NCT03180736); Dara-Pd received accelerated approval from the FDA in 2017 for patients with RRMM and at least 2 prior lines of therapy.

Daratumumab has also been combined with PIs, most notably bortezomib. In the phase 3 CASTOR study (N=498; NCT02136134), patients were randomly assigned to receive daratumumab in combination with bortezomib/dexamethasone (Dara-Vd) vs Vd alone.<sup>7</sup> The HR for progression or death with Dara-Vd vs Vd was 0.39 ( $P < .001$ ). The triplet produced a significantly higher ORR (83% for daratumumab plus bortezomib

and dexamethasone vs 63% for bortezomib and dexamethasone in relapsed or refractory multiple myeloma in the updated analysis of CASTOR;  $P < .001$ ) and very good partial response rates or better (59% vs 29%;  $P < .0001$ ) than the doublet. At a median follow-up of 19.4 months, the median PFS was 16.7 months in the Dara-Vd group vs 7.1 months in the control group (HR, 0.31;  $P < .0001$ ),<sup>46</sup> with Dara-Vd showing superiority across cytogenetic risk groups. Given these findings, the FDA granted fast-track approval to Dara-Vd for the treatment of patients with RRMM who had received at least 1 prior line of therapy.

Daratumumab was assessed for its safety and efficacy in combination with carfilzomib and dexamethasone (Dara-Kd; N=85; NCT01998971).<sup>47</sup> The ORR in this phase 1b study was 84% among patients with RRMM and was particularly promising in the subgroup of patients with lenalidomide-refractory disease (ORR, 79%); toxicity was manageable, with no unexpected side effects seen. Further investigation of Dara-Kd in the phase 3 CANDOR trial (NCT03158688) achieved its primary endpoint, showing a 37% reduction in the risk for progression or death (HR, 0.63;  $P = .0014$ ) with Dara-Kd (PFS not reached) vs Kd (PFS 15.8 months).<sup>48</sup> FDA approval for this combination was granted in August 2020.



Lastly, the DARA/ATRA study (NCT02751255) is evaluating the efficacy of daratumumab combined with all-trans retinoic acid (ATRA) on the basis of preclinical data showing ATRA-mediated upregulation of CD38 expression on plasma cells.<sup>49</sup> An interim analysis of 42 patients with RRMM reported that patients with a prior partial response or better on daratumumab monotherapy appeared to benefit from the addition of ATRA, with PFS prolonged by a median of 7.8 months, although these results remain preliminary.<sup>50</sup>

**Clinical Studies in Newly Diagnosed MM.** Various clinical trials continue to assess daratumumab in the up-front setting. Because CD38 expression is greater in untreated MM, and given that daratumumab efficacy depends on a functional immune system, the integration of daratumumab into up-front regimens will likely further improve PFS and OS rates as well as depth of response, including minimal residual disease (MRD).

Final results from the phase 3 ALCYONE study (NCT02195479) reported on melphalan/bortezomib/prednisone with vs without daratumumab (Dara-VMP vs VMP) for transplant-ineligible patients with NDMM (N=706)<sup>51</sup>; the HR for disease progression or death was 0.6 for Dara-VMP vs control ( $P=.0003$ ). CR rates nearly doubled with Dara-VMP vs control (46% vs 25%), and median PFS was 36.4 vs 19.3 months, respectively. MRD negativity was reported in 28% of patients in the Dara-VMP arm vs 7% in the VMP arm. Except for a higher frequency of grade 3/4 infections (22% vs 15%), the overall rate of treatment discontinuation with Dara-VMP was low, and the combination is currently approved by the FDA for the first-line treatment of transplant-ineligible patients with NDMM.

In the MAIA phase 3 trial (N=737; NCT02252172), Dara-Rd vs Rd resulted in a significantly reduced risk for progression or death (HR, 0.56;  $P<.001$ ),<sup>52</sup> with MRD occurring in 24% of patients in the Dara-Rd arm vs only 7% of patients in the Rd arm ( $10^{-5}$  sensitivity threshold,  $P<.001$ ).

In the setting of ASCT, Dara-RVd vs RVd has been evaluated as an induction and post-transplant consolidation and maintenance regimen in transplant-eligible patients with NDMM (GRIFFIN trial; NCT02874742). In an updated analysis of this randomized phase 2 study with a total of 207 patients, Dara-RVd showed improved responses and MRD negativity.<sup>53</sup> Responses deepened over time, with rates of CR or better of 52% for Dara-RVd vs 42% for RVd by the end of consolidation. The MRD negativity rate was also significantly higher in the Dara-RVd arm (59% vs 24%), together with remarkable PFS and OS to date.<sup>54</sup>

The randomized phase 3 CASSIOPEIA trial (NCT02541383), which compared daratumumab in

combination with bortezomib, thalidomide, and dexamethasone (Dara-VTd) vs VTd alone in a cohort of 1085 transplant-eligible patients with NDMM,<sup>55</sup> demonstrated rates of CR or better after consolidation in 39% of patients in the Dara-VTd arm vs 26% of those in the VTd group. In addition, the rate of MRD negativity was higher (64% vs 44%;  $10^{-5}$  sensitivity threshold), and the risk for progression or death was significantly reduced with Dara-VTd (HR, 0.47;  $P<.0001$ ). Although the rates of engraftment did not differ significantly between CASSIOPEIA and GRIFFIN, a lower number of cells was collected with Dara-VTd than with VTd alone, and a more frequent use of plerixafor (Mozobil, Sanofi-Aventis) was required with Dara-VTd than with VTd alone (22% vs 8% in the CASSIOPEIA trial). On the basis of these results, the FDA approved Dara-VTd in 2019 as an induction regimen for patients with transplant-eligible NDMM. Several other phase 2/3 trials are ongoing to evaluate frontline daratumumab in transplant-eligible patients. This includes the phase 3 PERSEUS trial (NCT03710603; Dara-RVd vs RVd) and the phase 2 EMN18 study (NCT03896737; induction phase with daratumumab plus cyclophosphamide, bortezomib, and dexamethasone [Dara-VCd] vs VTd).

**Clinical Studies in Smoldering MM.** In smoldering MM, 3 daratumumab dose schedules have been evaluated as part of the randomized phase 2 CENTAURUS study (NCT02316106); at the prespecified primary analysis after 15.8 months of median follow-up, none of the dose schedules had met the co-primary endpoint of a CR rate greater than 15%.<sup>56</sup> The DETER-SMM study is a phase 3 trial that compares Rd with vs without daratumumab in patients with high-risk SMM (NCT03937635). Subcutaneous (SC) daratumumab vs active monitoring is being evaluated in the AQUILA phase 3 trial for high-risk SMM (NCT03301220).

Single-agent daratumumab is also being assessed in a phase 2 trial for patients with low-risk SMM or high-risk monoclonal gammopathy of unknown significance (MGUS; NCT03236428). The results of these studies are awaited with interest.

**Administration Guidelines.** The most commonly reported toxicities associated with daratumumab are IRRs.<sup>7,8,39,41,45,51</sup> Consequently, pre-medications should be administered to all patients 1 hour before daratumumab infusion. These medications include intravenous (IV) methylprednisolone at 100 mg for the first 2 infusions and at 60 mg for subsequent infusions; acetaminophen at 650 to 1000 mg, and diphenhydramine at 25 to 50 mg. Corticosteroid therapy should also be given on the 2 days following daratumumab. In the context of Dara-Kd, montelukast as a premedication has been shown to reduce IRR frequency from 59% to 38%.<sup>57</sup> Split dosing also has

been used effectively to reduce IRRs.<sup>58</sup> The infusion time for daratumumab at first IV administration is approximately 7 hours. In an attempt to achieve better tolerability and faster administration, daratumumab is now available as a SC co-formulation with recombinant human hyaluronidase PH20 enzyme (rHuPH20). In the phase 1b PAVO (NCT02519452) study, SC daratumumab at a flat dose of 1800 mg demonstrated a low frequency of IRRs (24%) and a response rate (ORR, 42%) similar to that seen with IV daratumumab.<sup>59</sup> Noninferior efficacy of SC vs IV daratumumab has recently been confirmed in an updated analysis of the phase 3 COLUMBA trial (NCT03277105).<sup>60</sup> The phase 2 LXNX trial is currently exploring the efficacy of SC daratumumab in patients with RRMM previously exposed to IV daratumumab (NCT03871829).

**Diagnostic Challenges.** Daratumumab is an IgGκ mAb and can interfere with the detection of M protein on serum protein electrophoresis and immunofixation. The daratumumab interference reflex assay (DIRA) is a murine anti-daratumumab antibody that has been developed to overcome such interference and assess the true hematologic response.<sup>61</sup> Alternatively, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) can be applied to distinguish daratumumab from disease-related IgGκ monoclonal protein.<sup>62</sup>

Daratumumab, as well as other anti-CD38 mAbs, may also interfere with the detection of allo-antibodies in blood compatibility testing by CD38 binding on the surface of donor red blood cells. Different mitigation strategies have been proposed, including the use of a neutralizing agent (anti-idiotypic antibody, recombinant soluble CD38, or DaraEx), chemical CD38 denaturation via dithiothreitol (DTT), or genotyping with phenotyping before anti-CD38 mAb treatment.<sup>63-66</sup>

### **Isatuximab**

**Clinical Studies in Relapsed/Refractory MM.** The IgGκ anti-CD38 antibody isatuximab (formerly SAR650984) has shown clinical efficacy in the context of RRMM. Its mechanisms of action are similar to those of daratumumab but also include direct pro-apoptotic effects independent of Fc cross-linking and pronounced effects on the immune milieu, in part driven by its binding to a different epitope.<sup>67,68</sup>

Isatuximab (10 mg/kg weekly) in combination with Rd resulted in a promising ORR of 56% in a phase 1b clinical trial in patients with heavily pretreated RRMM and a median of 5 prior lines of therapy (median PFS, 8.5 months; 82% of patients with lenalidomide-refractory disease; NCT01749969).<sup>69</sup> IRRs were seen in 56% of patients. Similar efficacy was reported for isatuximab in combination with Pd (ORR, 62%; NCT02283775)

and Kd (ORR, 66%; NCT02332850).<sup>70,71</sup> At a median follow-up of 11.6 months, the ICARIA-MM phase 3 trial (N=307; NCT02990338) showed significantly improved PFS for isatuximab-Pd (median PFS, 11.5 months; ORR, 60%) vs Pd alone (PFS, 6.5 months; ORR, 35%;  $P < .0001$ ).<sup>10</sup> Isatuximab-Kd is currently being investigated in the randomized IKEMA phase 3 trial (NCT03275285). In a first analysis presented at EHA 2020, the addition of isatuximab to Kd resulted in strikingly superior PFS (not reached) vs Kd control (19.2 months; median follow-up, 20.7 months).<sup>72</sup> MRD negativity was reported in 30% of patients in the isatuximab-Kd arm vs 13% in the control arm ( $P = .0004$ ). Although limited data exist on the use of isatuximab after daratumumab failure, this is an important question because daratumumab is increasingly being used earlier in treatment. It will be critical to understand the effect of combination approaches as salvage, given the strength of the ICARIA and IKEMA data.

**Clinical Studies in Newly Diagnosed MM.** In the up-front setting, isatuximab in combination with RVd as an induction regimen followed by isatuximab-Rd maintenance has been shown to result in an ORR of 93% and an MRD negativity rate of 39% (NCT02513186).<sup>73</sup> Similarly, isatuximab-VCd induction followed by single-agent isatuximab maintenance leads to high response rates (ORR, 87%; NCT02513186).<sup>74</sup>

Results have yet to be reported for the phase 3 IMROZ trial, in which transplant-ineligible patients are randomly assigned to isatuximab-RVd or RVd as first-line treatment (NCT03319667).<sup>75</sup> The GMMG-CONCEPT phase 2 study continues to assess isatuximab with KRd in patients with NDMM and high-risk cytogenetic features (NCT03104842). A recent interim analysis (N=50) presented at the ASCO annual meeting in 2020 reported a promising ORR of 100% and a CR rate of 46%.<sup>76</sup>

**Clinical Studies in Smoldering MM.** Preliminary data from a phase 2 study have reported promising activity of single-agent isatuximab (20 mg/kg) in high-risk SMM (ORR, 62.5%; NCT02960555); data for isatuximab compared favorably with data for daratumumab in the same setting.<sup>77</sup>

### **MOR202 and TAK-079**

On the basis of preliminary data presented in late 2019, TAK-079, a fully human, non-agonistic anti-CD38 IgG1 antibody with SC administration, is safe and has promising single-agent activity in RRMM (N=28; ORR, 43%; NCT03439280).<sup>78</sup> TAK-079 is currently undergoing further assessment in RRMM with Rd or RVd (NCT03984097).

The human HuCAL (human combinatorial antibody libraries) anti-CD38 antibody MOR202 showed activity signals in combination with Rd (ORR, 65%)

and Pd (ORR, 48%) in a prior phase 1/2a trial in RRMM (NCT01421186).<sup>79</sup> Despite these findings, further development has been discontinued in the United States, although clinical trials are ongoing in China (NCT03860038, NCT03952091).

## Other Antigens

Immunophenotyping has led to the discovery of numerous antigens with potential targetability. These can be either direct targets expressed on the surface of MM cells (eg, CD40, CD56, CD138, intercellular adhesion molecule 1 [ICAM-1], and C-X-C chemokine receptor 4 [CXCR4]) or indirect targets on the surface of effector cells (killer cell immunoglobulin-like receptor [KIR], programmed death 1 [PD-1], and programmed death ligand 1 [PD-L1]). A detailed overview of selected mAbs currently in clinical development and/or reported previously appears in the Table.

## Checkpoint Inhibitors

Immune tolerance is regulated by balanced signaling of agonistic and inhibitory immune checkpoints including the transmembrane receptor PD-1 and its ligand PD-L1. In MM, high-level PD-L1 expression on malignant plasma cells leads to PD-1-mediated diminution of NK cell and T-cell activity, thereby driving the immune escape of MM cells.<sup>80</sup> Initial results with the PD-1 mAb pembrolizumab (Keytruda, Merck) showed its efficacy in combination with Rd (N=62; ORR, 44%; KEYNOTE-023; NCT02036502) and Pd (N=48; ORR, 60%; NCT02289222) in the context of RRMM.<sup>81,82</sup> Two subsequent phase 3 trials, KEYNOTE-185 (N=301; pembrolizumab-Rd vs Rd for NDMM; NCT02579863) and KEYNOTE-183 (N=249; pembrolizumab-Pd vs Pd for RRMM; NCT02576977), were put on clinical hold by the FDA following immune-mediated fatalities (myocarditis, pneumonitis, and Stevens-Johnson syndrome) attributed to pembrolizumab.<sup>81,83,84</sup> These concerns also led to the discontinuation of several trials examining nivolumab (Opdivo, Bristol-Myers Squibb), although this human IgG1 anti-PD-1 mAb had shown favorable safety and clinical efficacy in a prior phase 1b trial (NCT02726581).<sup>85</sup> Following protocol amendments, the FDA decided to lift the clinical hold on nivolumab-containing trial protocols in 2017. For the time being, the CheckMate 602 phase 3 trial (NCT01592370; NIVO-elo-Pd vs NIVO-Pd vs Pd), the CheckMate 039 phase 1 study (NCT01592370; nivolumab/ipilimumab [Yervoy, Bristol-Myers Squibb]/lirilumab) and the phase 2 CA204-142 trial (NCT02612779; NIVO-elo vs elo-Pd) continue to assess PD-1 inhibition in RRMM. Along with nivolumab,

the anti-PD-1 agent cemiplimab (REGN2810; Libtayo, Regeneron/Sanofi-Aventis), the anti-PD-L1 agent atezolizumab (Tecentriq, Genentech), and the anti-PD-L1 agent durvalumab (Imfinzi, AstraZeneca) continue to undergo clinical evaluation in RRMM (NCT03194867, NCT03000452, NCT02431208).

## Bispecific T-Cell Engagers

BiTE molecules are antibodies that combine the variable fragments of 2 mAbs on one polypeptide chain. This allows immune effector cells to be redirected, resulting in potent T-cell/NK-cell-mediated lysis of tumor cells. In a first-in-human phase 1 study for RRMM, the anti-CD3/anti-BCMA (B-cell maturation antigen)-specific BiTE AMG420, given at its maximum tolerated dose of 400 mg/d, led to an ORR of 70%, including 1 patient with an MRD-negative CR (N=10; NCT02514239).<sup>86</sup> The ORR across all dose levels was 31% (13 of 42 patients), with only 1 patient (2%) affected by cytokine-release syndrome requiring tocilizumab (Actemra, Genentech) treatment. However, tolerability and feasibility with this particular platform have been a challenge. Another anti-BCMA/anti-CD3 IgG2a BiTE, PF-3135, is currently being assessed in an ongoing phase 1 trial for RRMM (NCT03269136). Preliminary findings have recently been reported from the dose-escalation portion of this trial (n=17; clinical benefit rate, 41%).<sup>87</sup> Further BiTEs are undergoing clinical assessment in RRMM, all of which employ an anti-CD3 domain for T-cell engagement. These include anti-BCMA BiTEs, such as the half-life extended AMG701 (NCT03287908), as well as CC-93269 (NCT03486067), JNJ-64007957 (NCT03145181), and REGN5458 (NCT03761108); the anti-CD38 BiTE GBR-1342 (NCT03309111); and lastly, JNJ-64407564, a BiTE against the G-protein-coupled receptor C family 5D unit (GPRC5D; NCT03399799).

## Antibody-Drug Conjugates

Antibody-drug conjugates (ADCs) link mAbs to a highly potent cytotoxic reagent to limit off-target toxicity and deliver maximum therapeutic efficacy to tumor cells.<sup>88</sup> The safety of ADCs is highly dependent on the specificity of the respective target antigen; encouraging activity overall among heavily pretreated patients has been seen to date in a number of studies.

BT062 is an ADC in which the CD138 (syndecan) IgG4 antibody indatuximab is conjugated to the microtubule inhibitor maytansinoid DM4.<sup>89</sup> The combined results of a phase 1/2a trial of BT062 single-agent activity in a total of 67 patients with RRMM (NCT00723359, NCT01001442)<sup>90</sup> reported disease stabilization in 77%



**Table 1.** Selected Monoclonal Antibodies Currently in Clinical Development and/or Reported Beyond Anti-CD38 and Anti-SLAMF7

Target	Drug	Aliases	Formulation	Design	Combina- tion	Patients, No.	Response	Indica- tion	Reference
<i>Direct (target is on MM cells)</i>									
CD40	Dacetuzumab	SGN-40	Humanized IgG1	Phase 1	-	44	CBR 20%	RRMM	Hussein et al (2010) <sup>101</sup>
CD40	Dacetuzumab	SGN-40	Humanized IgG1	Phase 1b	LEN-DEX	36	ORR 39%	RRMM	Agura et al (2009) <sup>102</sup>
CD40	Lucatumumab	HCD122	Human IgG1	Phase 1	-	28	CBR 46%	RRMM	Bensinger et al (2012) <sup>103</sup>
ICAM-1	BI-505	-	Human IgG1	Phase 1	-	35	CBR 24%	RRMM	Hansson et al (2015) <sup>104</sup>
BAFF	Tabalumab	LY2127399	Human IgG4	Phase 1	BORT +/- DEX	48	ORR 42%	RRMM	Raje et al (2016) <sup>105</sup>
BAFF	Tabalumab	LY2127399	Human IgG4	Phase 2	+/- BORT-DEX	220	ORR 59% (same as placebo arm)	RRMM	Raje et al (2017) <sup>106</sup>
GRP78	PAT-SM6	-	Human IgM	Phase 1	-	12	CBR 33%	RRMM	Rasche et al (2015) <sup>107</sup>
CD74	Milatuzumab	hLL1	Humanized IgG1κ	Phase 1	-	25	CBR 26%	RRMM	Kaufman et al (2013) <sup>108</sup>
IL-6	Siltuximab	CNTO-328	Chimeric IgG1κ	Phase 2	-	14	CBR 0%	RRMM	Voorhees et al (2013) <sup>109</sup>
IL-6	Siltuximab	CNTO-328	Chimeric IgG1κ	Phase 2	DEX	39	CBR 28%	RRMM	Voorhees et al (2013) <sup>109</sup>
IL-6	Siltuximab	CNTO-328	Chimeric IgG1κ	Phase 2	BORT	142	ORR 55%	RRMM	Orlowski et al (2015) <sup>110</sup>
IL-6	Siltuximab	CNTO-328	Chimeric IgG1κ	Phase 2	BORT-MEL-PRED	52	ORR 88% vs 80%	NDMM	San Miguel et al (2014) <sup>111</sup>
CXCR4	Ulocuplumab	BMS-936564	Human IgG4	Phase 1	LEN-DEX	29	CBR 72%	RRMM	Ghobrial et al (2020) <sup>112</sup>
CXCR4	Ulocuplumab	BMS-936564	Human IgG4	Phase 1	BORT-DEX	16	CBR 50%	RRMM	Ghobrial et al (2020) <sup>112</sup>
<i>Indirect (target is on effector cells)</i>									
KIR (on NK cells)	IPH 2101	-	Human IgG4	Phase 1	-	32	CBR 34%	RRMM	Benson et al (2012) <sup>113</sup>
KIR (on NK cells)	IPH 2101	-	Human IgG4	Phase 1	LEN	15	CBR 40%	RRMM	Benson et al (2015) <sup>114</sup>

BAFF, B-cell activating factor; BORT, bortezomib; CBR, clinical benefit rate; CXCR4, C-X-C chemokine receptor 4; DEX, dexamethasone; GRP78, glucose-regulated protein 78; Ig, immunoglobulin; ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin 6; KIR, killer cell immunoglobulin-like receptor; LEN, lenalidomide; MEL, melphalan; NDMM, newly diagnosed multiple myeloma; NK cell, natural killer cell; ORR, overall response rate; PRED, prednisolone; RRMM, relapsed/refractory multiple myeloma.

of patients and a median PFS of 3 months. In addition, evaluations of BT062 in combination with Rd or Pd have shown ORR rates of 77% and 79% for BT062-Rd (n=47) and BT062-Pd (n=17), respectively (NCT01638936).<sup>91</sup> However, no future trials of BT062 have been announced.

Belantamab mafodotin (Blenrep, GlaxoSmithKline), previously known as GSK2857916, is an afucosylated, humanized anti-BCMA mAb conjugated by a protease-resistant cysteine linker to the microtubule-disrupting agent monomethyl auristatin F (MMAF).<sup>92</sup> Given as single agent every 3 weeks in a phase 2 cohort of 35 patients with RRMM, belantamab mafodotin resulted in an ORR of 60%, with a median time to response of 1.2 months and a median response duration of 14.3 months (DREAMM-1 trial; NCT02064387).<sup>93</sup> Most notably, these results also included durable responses in 37% of patients with double-class–refractory disease and prior daratumumab treatment (median PFS, 6.2 months). Grade 1/2 ocular toxicity occurred in 69% of all patients but resolved after a median of 35 days. The subsequent DREAMM-2 trial in triple-class–refractory RRMM demonstrated an ORR of 34% in patients who received 3.4 mg/kg every 3 weeks (n=99) and 31% in the 2.5-mg/kg cohort (n=97).<sup>94</sup> Median duration of response for the 2.5-mg/kg cohort was 11 months, and this dose is being taken forward as it was also associated with less toxicity.<sup>95</sup> In August 2020, accelerated FDA approval was granted to belantamab mafodotin for patients with triple-class–refractory RRMM and at least 4 prior lines of therapy.

A phase 1/2 multicenter study is evaluating the safety and efficacy of belantamab mafodotin in combination with Pd in patients who have RRMM. Interim findings presented at the 2020 EHA annual meeting reported a favorable toxicity profile and promising efficacy, with an encouraging ORR of 86% (N=14), which is similar to results in other combination studies, such as DREAMM-6 (NCT03544281), which incorporates bortezomib.<sup>96</sup>

Belantamab mafodotin is also being evaluated in the DREAMM-5 platform trial, a phase 1/2 study that incorporates multiple belantamab mafodotin–containing combinations in separate sub-studies for RRMM (NCT04126200).<sup>97</sup> At the same time, a randomized phase 3 study (DREAMM-3) has started recruitment to evaluate belantamab mafodotin monotherapy vs Pd in patients with RRMM (NCT04162210).

Single-agent activity in RRMM has also been reported for IMG901, an anti-CD56 antibody (lorvotuzumab) conjugated to the microtubule inhibitor maytansinoid DM1 (N=37, ORR, 6%; stable disease or better, 43%; NCT00346255).<sup>98</sup> In hLL1-DOX, the anthracycline doxorubicin is conjugated to the humanized anti-CD74 antibody milatuzumab. This ADC is currently being tested in a phase 1 clinical trial for RRMM (NCT01101594).

Lastly, TAK-169, a dimeric anti-CD38 fusion protein coupled to a modified Shiga-like toxin-A subunit, is being assessed in a first-in-human phase 1 trial for RRMM (NCT04017130).<sup>99</sup>

## Future Perspectives

MM continues to elude cure, despite significant progress. Novel therapeutic strategies with highly selective mechanisms of action as well as manageable toxicity are needed, especially for patients with disease that is refractory to multiple lines of therapy. The FDA approvals of daratumumab, elotuzumab, and isatuximab have been pivotal in the treatment of double-refractory RRMM, and daratumumab has become integral in the up-front care of NDMM, reflecting the successful application of phase 2/3 studies in real-world practice.<sup>100</sup> Although the investigation of checkpoint inhibitors in MM has been suspended, BiTEs, and in particular ADCs, demonstrate encouraging efficacy and relative safety in triple-class–refractory RRMM. The approval of belantamab mafodotin is another important milestone in expanding the role of mAbs in the treatment of MM. Future combination studies will increase our understanding of how best to bring these agents into clinical use and further improve patient outcomes.

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