

Monoclonal Antibodies in Multiple Myeloma: A New Wave of the Future

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Abstract

In 2015, 2 monoclonal antibodies were approved for the treatment of relapsed or refractory multiple myeloma (RRMM), elotuzumab and daratumumab. Elotuzumab is a monoclonal IgG- κ antibody directed against SLAMF7 (signaling lymphocytic activation molecule F7), a cell surface receptor involved in natural killer cell activation. Daratumumab is a monoclonal IgG- κ antibody that binds to CD38, a transmembrane protein found on the surface of myeloma cells and responsible for cellular adhesion and ectoenzymatic activity. Both elotuzumab and daratumumab act through recruitment of the immune system to enhance cellular cytotoxicity directed against myeloma cells. Elotuzumab requires lenalidomide and dexamethasone combined to enhance progression-free survival in patients with RRMM, and daratumumab has both single-agent and combination activity with either lenalidomide or the proteasome inhibitor bortezomib in RRMM. The adverse effect profile of both agents mainly consists of allergic-type infusion reactions. Other considerations for monoclonal antibody use in the treatment of MM include the potential for interference in serum protein electrophoresis testing and cross-reactivity of daratumumab with CD38 present on red blood cells. In the present report, we discussed the clinical development of daratumumab and elotuzumab and newer immunologic approaches to the treatment of MM.

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Introduction

Multiple myeloma (MM) is an incurable malignancy of plasma cells and is the second most common hematologic cancer in the United States, with approximately 30,000 new cases annually.¹ Before the arrival of immunomodulatory agents and the proteasome inhibitor class of drugs in the early part of 21st century, the median survival for MM ranged from 2 to 3 years.² Using a combination of these new drugs and focusing on continuous therapy for MM has extended the median survival to > 5 years.³ Inexorably, patients with MM will inevitably develop disease resistant and refractory to the available agents, with a dramatically reduced survival time after previous therapy has failed. One retrospective study noted that the median survival time after disease relapse with previous treatment with lenalidomide (an immunomodulatory agent) and bortezomib (a proteasome inhibitor) was only 9 months.⁴

With more patients with MM eventually developing relapsed or refractory MM (RRMM), a great need exists for further effective therapies. The use of monoclonal antibodies directed against tumor-specific cellular antigens is a treatment modality that has been used for the past 2 decades for B-cell lymphoma. Various antibodies were tried, with limited success, in the treatment of RRMM in previous years. In 2015, 2 new monoclonal antibody therapies were approved for use in RRMM: elotuzumab and daratumumab. Both antibodies have targets that are highly expressed on MM cells, with limited off-target expression. These antibodies have been shown in preclinical and clinical testing to be highly active, with an extended duration of disease control for those for RRMM and, thus, represent a new lifeline for patients in whom previous therapies have failed.

Monoclonal antibody therapy also presents a set of potential challenges for the treating oncologist. Both daratumumab and elotuzumab can be associated with infusion reactions and can interfere with interpretation of the serum protein electrophoresis results. Relapses still occur during and after treatment with both of these agents, necessitating the search for alternative immunologic-based therapies. These include bispecific antibodies, immune checkpoint inhibitors, and antibody–drug conjugates. A full discussion of the targets, the development of elotuzumab and daratumumab, and the alternative immunologic-based therapies is provided.

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Monoclonal Antibodies in Multiple Myeloma

Elotuzumab

Elotuzumab (Empliciti; Bristol-Myers Squibb Co) is a humanized IgG1-K monoclonal antibody directed against signaling lymphocytic activation molecule F7 (SLAMF7; also known as CS1, CD319, or CRACC [CD2-like receptor activating cytotoxic cell]). Elotuzumab combined with lenalidomide received US Food and Drug Administration (FDA) approval for the treatment of MM combined with lenalidomide and dexamethasone (Len/Dex/Elo) after 1 to 3 previous lines of therapy in November 2015. The biologic role of SLAMF7 and the preclinical and clinical results of elotuzumab are discussed in the subsequent sections.

Target SLAMF7

The SLAM immunoglobulin group of cell surface glycoprotein receptors is involved in immune homeostasis, and its members are not expressed on nonimmune cells.⁵ Specific SLAM family members are expressed to different degrees throughout B- and T-cell development.⁶ SLAMF7 is expressed early in B-cell development, is lost as B-cell maturation progresses, and is restored again in mature plasmacytes.⁷ SLAMF7 is also expressed to a lesser degree on natural killer (NK) cells and activated CD8⁺ T cells.⁸ SLAMF7 is absent in hematopoietic progenitor cells, granulocytes, monocytes, and CD4⁺ T cells. SLAMF7 is a self-ligand and activated by binding a copy of itself onto another cell. Further study of the SLAM family members, in particular, SLAMF7, has shown that they play a critical role in NK cell effector function.^{9,10} The cytoplasmic domain of SLAMF7 interacts with the SLAM-associated protein family member EAT-2 (Ewing's sarcoma-activated transcript 2), causing activation of NK cell immune effector function.⁹ The lack of SLAMF7 interaction with EAT-2 produces an inhibitory effect on NK cell function through protein tyrosine phosphatase 1 and Src kinases.¹¹ Thus, depending on the context, SLAMF7 function can lead to either positive or negative immune effects, described mainly for NK cells.

SLAMF7 in MM

The expression of SLAMF7 on myeloma cells is near ubiquitous, regardless of the specific cytogenetic abnormalities, making it an attractive target for monoclonal antibody-directed therapy.¹² The role of SLAMF7 in MM is thus far unknown, because neither the activating nor the inhibitory signals present in NK cells appear to be intact in myeloma cells.¹¹ However, knockdown of SLAMF7 function in a myeloma cell line showed sluggish growth in culture and decreased mortality when implanted into xenograft mice.¹³ Although the function of SLAMF7 in MM is unclear, direct growth inhibition does not appear to be produced by elotuzumab binding.

The primary mechanism of action for elotuzumab against MM appears to be antibody-dependent cell-mediated cytotoxicity (ADCC) through recruitment and activation of NK cells.^{12,14} Elotuzumab binds SLAMF7 present on the myeloma cell surface and engages NK cells via the CD16 receptor (also known as FcγRIII). This binding leads to NK cell activation and ADCC, thereby destroying the myeloma cell in a complement-independent manner (Figure 1). Elotuzumab-mediated myeloma cell death absolutely requires the presence of functional NK cells. Elotuzumab by itself was unable to induce apoptosis in myeloma cells; however, interference with SLAMF7 activity has been shown to inhibit

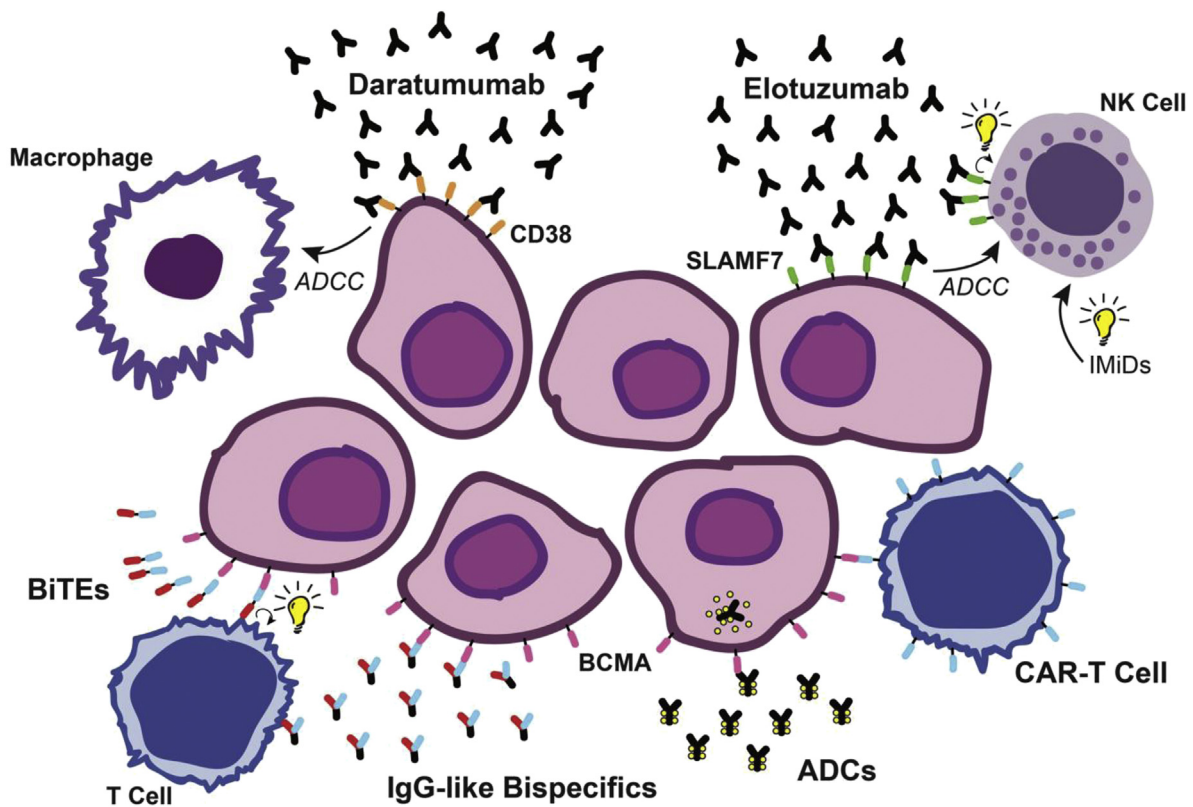
myeloma cell adherence to bone marrow stroma, and elotuzumab had demonstrable single-agent activity in MM mouse xenograft models.¹⁴ In addition to marking myeloma cells to be recognized by NK cells via CD16, elotuzumab also directly binds to the SLAMF7 expressed on the NK cells themselves, thereby causing direct activation of the NK cell via EAT-2 and enhanced cytotoxicity.¹⁵ It has also been postulated that elotuzumab facilitates SLAMF7 self-ligation between NK and myeloma cells, thereby also further enhancing cytotoxicity.¹⁵ In preclinical cell line-based studies, the addition of other anti-MM therapy such as bortezomib or lenalidomide synergized with elotuzumab with amplified antitumor effect.^{16,17}

Clinical Studies of Elotuzumab

With the preclinical data reported in the previous section, elotuzumab entered patient testing (Table 1). The phase I study of elotuzumab (study 1701) tested 0.5 to 20 mg/kg doses of elotuzumab monotherapy in patients with RRMM.¹⁸ Patients in that study had received, on average, 4 previous lines of anti-MM therapy. Using a standard 3 + 3 phase I design, the maximum tolerated dose of elotuzumab was not reached. The side effects from elotuzumab were generally mild (grade 1 or 2) and infusion related; 88.2% of patients experienced a treatment-related adverse event. These included chills, cough, headache, back pain, and fever. At both the 10-mg/kg and 20-mg/kg doses, SLAMF7 was fully saturated on the study participants' bone marrow samples. Overall, the single-agent activity for elotuzumab in that study was modest, with 26.5% of patients achieving stable disease using the European Group for Bone and Marrow Transplantation MM response criteria. This finding prompted further studies of elotuzumab combined with other anti-MM agents.

The combination of elotuzumab with lenalidomide and dexamethasone was tested in the ELOQUENT-1 and -2 studies (ClinicalTrials.gov identifiers, NCT01335399 and NCT01239797, respectively) in patients with newly diagnosed and RRMM, respectively. The ELOQUENT-1 study is ongoing; however, the results from the ELOQUENT-2 study have been reported. ELOQUENT-2 enrolled and randomized 646 patients with MM who had developed relapse and progression after 1 to 3 previous lines of therapy to lenalidomide and dexamethasone with or without elotuzumab (Len/Dex ± Elo).¹⁹ Patients with disease previously refractory to lenalidomide therapy were ineligible for study inclusion. The clinical outcomes for Len/Dex/Elo were superior to Len/Dex, with a partial or greater response rate at 78.5% versus 65.5% and a median progression-free survival (PFS) of 19.4 versus 14.9 months. Intriguingly, 41% of patients were free of disease progression at the 2-year follow-up point in the Len/Dex/Elo arm compared with 27% in the Len/Dex arm, suggesting that a subset of patients experienced prolonged disease control using elotuzumab. The PFS results were recently updated, showing a continued benefit for Len/Dex/Elo at 26% versus 18% of patients alive and without disease progression after 3 years of study follow-up. Subset analyses have shown that the response and PFS continue to be more favorable for the arm containing elotuzumab, independent of cytogenetics, age, MM stage, and previous therapy.²⁵ Adverse reactions attributable to elotuzumab were generally mild and infusion related, similar to the phase I (study 1701) findings.

Figure 1 Diverse Killing Mechanisms for Cell Surface-targeted Immunotherapy in Multiple Myeloma. Clinical Validation Has Now Shown That Multiple Myeloma Cells (Pink) Can Be Successfully Targeted Using Antibody-based Approaches. Monoclonal Antibodies Elotuzumab and Daratumumab Largely Accomplish This Through Antibody-dependent Cellular Cytotoxicity (ADCC). Elotuzumab ADCC Occurs Through Natural Killer (NK) Cells, Whose Effector Function Is Secondarily Activated on Binding to Signaling Lymphocytic Activation Molecule F7 (SLAMF7) Present on Their Surface. Combination With Immunomodulatory Drugs (IMiDs) Potentiates the Activation of NK Cells. In Contrast, Daratumumab-mediated Activity Appears Multifactorial, Including ADCC (eg, Through Macrophages), Complement-dependent Cytotoxicity, and Additional Direct Effects From the Blockade of CD38 on Myeloma Cells (Not Shown). Further Engineering of the Antibodies Has Accessed Other Mechanisms of Myeloma Cell Cytotoxicity. Bispecific Antibodies, Including Both Small Fragment (eg, Bispecific T-cell Engagers [BiTEs]) and More Stable IgG-like Agents, Potently Activate T-cell Immunity by Bridging Target Cells to the CD3 Component of the T-cell Receptor (TCR). Chimeric Antigen Receptor T (CAR-T) Cells Accomplish This Activation Through Engineering the TCR to Recognize Myeloma Cell Antigens Directly. Antibody–drug Conjugates (ADCs) Transform Monoclonal Antibodies Into Chemotherapy Delivery Systems by Targeted Internalization Into Myeloma Cells. Owing to the Highly Specific Expression on Myeloma Cells, B-cell Maturation Antigen (BCMA) Is a Popular Antigen for These More Potent Technologies; However, Other Antigens Are Also Being Evaluated



A randomized phase II study (study CA204-009; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01478048) identifier, NCT01478048) of bortezomib and dexamethasone with or without elotuzumab (Bor/Dex $\pm$ Elo) was similarly performed and reported.²⁰ In the present study, 152 patients with RRMM, with disease not previously refractory to bortezomib, were randomized (77 Bor/Dex/Elo, 75 Bor/Dex). Similar to the ELOQUENT-2 findings, the median PFS was superior with the addition of elotuzumab (9.7 vs. 6.9 months); however, the overall response rate (ORR) was similar between the 2 groups (66% vs. 63%). Patients in the Bor/Dex/Elo arm who tested as homozygous for an allele of Fc γ RIIIa (V158F polymorphism), which has previously been shown to be associated with enhancement of ADCC, had superior PFS at 22.3 months versus only 9.8 months for those without the allele, seeming to validate the critical role that ADCC

plays in the elotuzumab-mediated anti-MM effect.^{20,26-28} In the present study, no clinically significant additional toxicity was seen in the Bor/Dex/Elo arm compared with the Bor/Dex arm. Only 5% of patients experienced infusion-related reactions, which included pyrexia, chills, and flushing, all of which were grade 1 or 2 and further mitigated by premedication.

Although cross-study comparisons have inherent limitations, it does appear from the cited studies that the combination of Len/Dex/Elo might be more active than Bor/Dex/Elo. This might in part be because of the mechanism of action of both lenalidomide and bortezomib. Lenalidomide is an immunomodulatory drug (IMiD) that has been shown to enhance T- and NK-cell effector function.^{29,30} Given that the primary anti-MM effect of elotuzumab is through ADCC, it follows that lenalidomide, and other drugs of

Monoclonal Antibodies in Multiple Myeloma

Table 1 Summary of Clinical Trials With Elotuzumab and Daratumumab in Multiple Myeloma

Trial	Design	Regimen	Previous Lines (n)	ORR (%)	PFS (mo)	MoAb Dose	Ref
Elotuzumab							
Study 1701	DE phase I	Monotherapy	Mean 4	0	NA	0.5-20 mg/kg/2 wk	18
ELOQUENT-2	Phase III RCT	Len/Dex ± Elo	Median 2	79	19	10 mg/kg/wk ^a	19
CA204-009	Phase II RCT	Bor/Dex ± Elo	1-3 (1 for 65%)	66	10	10 mg/kg/wk ^a	20
Daratumumab							
Initial study	DE phase I-II	Monotherapy	Median 4 ^b	36 ^b	6 ^b	0.005-24 mg/kg/wk ^a	21
SIRIUS	RCT phase II	Monotherapy	Median 5 ^b	29	4 ^b	8 or 16 mg/kg/wk ^a	22
CASTOR	RCT phase III	Bor/Dex ± Dara	Median 2	82	NR	16 mg/kg/wk ^a	23
POLLUX	RCT phase III	Len/Dex ± Dara	Median 1	93	NR	16 mg/kg/wk ^a	24

Abbreviations: Bor = bortezomib; Dara = daratumumab; DE = dose-escalation (3 + 3 design); Dex = dexamethasone; Elo = elotuzumab; Len = lenalidomide; MoAb = monoclonal antibody; NA = not available; NR = not reached; ORR = overall response rate; RCT = randomized clinical trial; Ref = reference.

^aInitial dosing shown; subsequent schedules varied.

^bDose cohort, 16 mg/kg.

the same class such as thalidomide and pomalidomide, might synergize with elotuzumab by enhancing the NK response when FcγRIIIa is engaged. Bortezomib is a proteasome inhibitor (PI), which leads directly to MM apoptosis through cell cycle interruption. It has also been shown to sensitize cells to NK cell-mediated killing via TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) and Fas ligand-mediated lysis.^{31,32} However, bortezomib itself has also been shown to decrease TRAIL expression in activated human NK cells and also to inhibit NK cell-mediated myeloma cell line death.³³ This implies that bortezomib treatment might, in fact, decrease NK cell activity against tumors. Given the contradictory results seen, more work is needed to elucidate the nature of elotuzumab activity against MM when used concurrent with bortezomib.

Other combinations of elotuzumab with chemotherapy and with other immunologic agents are currently being testing in both upfront and RRMM settings. In RRMM, these include elotuzumab plus pomalidomide and dexamethasone (study CA2014-125; [ClinicalTrials.gov](https://clinicaltrials.gov) identifier, NCT02654132 [ELOQUENT-3]) and elotuzumab with nivolumab, pomalidomide, and dexamethasone ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier, NCT02726581). In the upfront setting, elotuzumab is being evaluated in combination with bortezomib, lenalidomide, and dexamethasone ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier, NCT01668719).

Daratumumab

Daratumumab (Darzalex; Janssen Biotech, Inc) is an IgG1-K human antibody directed against CD38. Daratumumab was approved by the US FDA in November 2015 for use as a single agent in the treatment of patients with MM who had received ≥ 3 previous lines of therapy, including a PI and an IMiD or with disease double refractory to a PI and an IMiD. The label was expanded November 21, 2016, with FDA approval of the use of daratumumab combined with lenalidomide and dexamethasone (Len/Dex/Dara) or bortezomib and dexamethasone (Bor/Dex/Dara) for the treatment of patients with MM who had received ≥ 1 previous therapy. The target of daratumumab, its mechanism of action, and the clinical trial results are discussed in the subsequent sections.

Target CD38 and Daratumumab Development

CD38 is a 46-kDa type II transmembrane glycoprotein with varied, setting-dependent, functional properties, including roles in cellular adhesion and as a bifunctional ectoenzyme.³⁴⁻³⁹ Although it was initially identified on B and T cells in a differentiation state and activation-specific fashion, CD38 expression was later identified in a broad variety of tissues, including epithelial cells of the gut, lung, and prostate and on certain neurons, osteoclasts, retinal cells, and smooth and striated muscle.^{35,40} Within the hematologic compartment, CD38 is additionally expressed on committed hematopoietic progenitor cells, erythrocytes, platelets, basophils, and NK cell and monocyte subsets. CD38 is commonly expressed on plasma cells, with MM cells, in particular, having strong and uniform expression of CD38. Therefore, CD38 is a standard marker used for immunophenotypic identification of MM.⁴¹

CD38 had been identified as a potential focus for immunotherapeutic targeting in MM since the early 1990s, although initial attempts to develop this were ultimately unsuccessful.^{42,43} Daratumumab is a human CD38-directed monoclonal antibody generated by immunization of HuMAb mice with purified HA-CD38 recombinant protein. It is an IgG1-K subclass molecule and was selected from a panel of potential antibodies for its ability to potently induce complement-dependent cytotoxicity (CDC) in experimental models.⁴⁴ In addition to inducing CDC, laboratory studies have demonstrated that daratumumab appears to have anti-MM activity through several other mechanisms, including ADCC, macrophage-mediated phagocytosis, the induction of programmed cell death, and blocking the enzymatic function of CD38 itself.⁴⁴⁻⁴⁷ Daratumumab has shown in vitro synergy with various other anti-MM therapies, in particular, lenalidomide, which increased ADCC in cell line- and patient-derived models during coexposure by augmenting the anti-MM capacity of effector NK and T cells.^{48,49}

Clinical Studies of Daratumumab

The clinical studies with daratumumab are summarized in Table 1. Initial phase I/II testing of daratumumab as a single agent in a heavily pretreated cohort of patients with RRMM demonstrated that the drug was very well tolerated, with no maximum tolerated dose identified during dose escalation.²¹ Impressively,

daratumumab demonstrated hitherto unprecedented single-agent activity in patients who had received a median of 4 previous therapies, with an ORR of 36% in the 16-mg/kg dose cohort. Additionally, 65% of patients who achieved a response maintained it for > 12 months. These results were corroborated by the larger scale phase I SIRIUS trial (daratumumab monotherapy in patients with treatment-refractory multiple myeloma), which also evaluated daratumumab monotherapy.²² In the 106 patients treated at the target 16-mg/kg dose, the overall response was 29%. Both of these studies indicated a benign safety profile for daratumumab, with the most common adverse events observed being infusion related, similar to the experience with elotuzumab. Daratumumab received initial FDA approval on the strength of these early phase results for patients who had received ≥ 3 previous lines of therapy, including a previous PI and an IMiD.⁵⁰ The initial encouraging results demonstrating the safety and potential efficacy of daratumumab combined with lenalidomide or bortezomib and dexamethasone in patients with RRMM in phase I-II studies led to the development of the landmark CASTOR (addition of daratumumab to combination of bortezomib and dexamethasone in participants with relapsed or refractory multiple myeloma) and POLLUX (a study comparing daratumumab, lenalidomide, and dexamethasone with lenalidomide and dexamethasone in relapsed or refractory multiple myeloma) trials.^{51,52}

The CASTOR trial randomized 498 patients with RRMM to receive either daratumumab combined with bortezomib and dexamethasone or bortezomib and dexamethasone alone.²³ The study was stopped after the prespecified interim analysis showed the median PFS was not reached for the Bor/Dex/Dara group versus 7.2 months for the Bor/Dex group, with a hazard ratio of progression or death of 0.39 (95% confidence interval, 0.28-0.53; $P < .001$). The response rates at all levels were significantly greater for the Bor/Dex/Dara group than for the control group, including partial responses or better (82.9% vs. 63.2%; $P < .001$), very good partial responses or better (59.2% vs. 29.1%; $P < .001$), and complete responses or better (19.2% vs. 9.0%; $P < .001$). Patients in the Bor/Dex/Dara group experienced greater rates of any grade and grade 3-4 thrombocytopenia, neutropenia, and lymphopenia and a greater rate of any grade peripheral neuropathy. Also, 45% of patients experienced an infusion reaction, and 98% of the infusion reactions occurred with the first infusion. Only 8.6% experienced a grade 3 infusion-related reaction, and no grade 4 events were reported.

The POLLUX trial randomized 569 patients to Len/Dex/Dara or Len/Dex alone.²⁴ Again, the study was stopped after the prespecified interim analysis showed a hazard ratio for progression or death in the Len/Dex/Dara compared with Len/Dex of 0.37 (95% confidence interval, 0.27-0.52; $P < .001$). The study also showed significant improvements in the responses at all levels, including the ORR (92.9% vs. 76.4%; $P < .001$) and complete response or better (43.1% vs. 19.2%; $P < .001$). The adverse events that occurred more frequently in the daratumumab group than in the control included neutropenia, diarrhea, upper respiratory tract infection, and cough, some of which might have been related to the increased duration of therapy compared with that of the control arm, which had a greater attrition rate owing to disease progression. The rates, timing, and severity of the reported infusion-related reactions were very similar to those reported in the CASTOR trial. The results of

the CASTOR and POLLUX trials led to an expansion of the FDA approval of daratumumab for use in the RRMM setting after 1 previous line of therapy combined with either lenalidomide or bortezomib.

Management and Monitoring Issues With Daratumumab

Daratumumab use does present some unique clinical challenges in patient monitoring and management. Infusion-related reactions remain quite common during the initial treatments. In addition to the recommended premedication with steroids, acetaminophen, and antihistamines, a recently completed study demonstrated the benefit of montelukast (Singulair) in decreasing the frequency and severity of infusion reactions.⁵³ The use of montelukast reduced the frequency of any grade of infusion reaction during the initial infusion from 58% to 38% and also reduced the average infusion time by almost 1 hour. Currently, work is ongoing to evaluate the equivalence of split dosing for the first daratumumab infusion and to develop alternative administrative approaches, including a subcutaneous delivery method.⁵⁴

Owing to its reactivity with CD38 on reagent red blood cells, patients treated with daratumumab have demonstrated panagglutination during indirect Coombs testing, complicating appropriate cross-matching of blood for transfusion.⁵⁵ This positivity can persist for ≤ 6 months after the last daratumumab exposure. Currently, the American Association of Blood Banking has recommended that providers setup procedures to inform their transfusion service when patients are starting daratumumab to perform type and screening, including baseline antigen phenotyping or genotyping, before the initiation of daratumumab. Treating red blood cell samples used for antibody screening with dithiothreitol can negate interference by daratumumab, although this can also affect some red blood cell antigens.^{56,57}

Finally, during monoclonal antibody therapy, interference on serum protein electrophoresis and immunofixation testing frequently occurs, because a band will appear for IgG- κ , indicating the presence of the monoclonal antibody therapy. The interference band can comigrate with a patient's monoclonal protein and make the demonstration of a complete response difficult, especially in cases of IgG- κ MM.⁵⁸ A daratumumab-specific immunofixation reflex assay using a mouse anti-daratumumab has been developed for use in disease assessment and monitoring.⁵⁹ The need and utility for this might be greater in the clinical trial setting, with reported efficacy determined using strict International Myeloma Working Group guidelines, than in routine clinical management, in which the presence of the antibody can be anticipated.

Building on the Success of Daratumumab and Elotuzumab

With FDA approval of daratumumab and elotuzumab, it can become easy to forget that they constitute only a small fraction of the monoclonal antibodies that have entered MM clinical trials. Of the dozens of antibody-target antigen pairs tested, only anti-CD38 antibodies exhibited notable single-agent activity in patients.⁶⁰ However, MM remains an appealing disease for antibody therapies owing to the easy access of these large molecule drugs through sinusoidal endothelium to malignant cells in the bone marrow.^{61,62} The clinical success of anti-CD38- and anti-SLAMF7-targeted

Monoclonal Antibodies in Multiple Myeloma

naked antibodies has now validated that myeloma cells can be effectively targeted in patients using antibody-based approaches.^{19,21} With advances in antibody technology and protein engineering, multiple modalities have emerged, with varying mechanisms of action, to improve further on the success of daratumumab and elotuzumab (Figure 1). Monoclonal antibody spinoff approaches now in clinical development include checkpoint blockade, antibody–drug conjugates, bispecific antibodies, and chimeric antigen T cells (Table 2).

Checkpoint Blockade

Blockade of the programmed cell death-1 (PD1) interaction with programmed cell death ligand-1 has emerged as revolutionary strategy against solid tumors. This approach allows antibodies to activate T-cell anticancer immunity. The expression of programmed cell death ligand-1, which calms innate T-cell cytotoxicity and allows cancer cells to evade immune surveillance, is upregulated on myeloma cells (Figure 2).^{77–82} Antibody blockade of the PD1 axis has led to FDA approval for several other malignancies and great interest in pursuing this in MM.^{84,85} Initial single-agent studies with PD1 inhibitors in hematologic malignancies did not indicate any clear activity in MM.⁸⁶ However, preclinical evidence emerged that IMiDs enhance the anti-MM immune activity mediated by PD1 inhibition.⁸³ This led to combination trials first with pembrolizumab with either lenalidomide or pomalidomide, which showed early phase efficacy and safety.^{63–65} Checkpoint inhibition studies have now advanced to phase III trials (ClinicalTrials.gov identifiers, NCT02576977, NCT02579863, and NCT02903381). Another interesting group of trials is underway, combining monoclonal antibodies with checkpoint inhibitors, in search of activation of

multiple concurrent mechanisms of anti-MM immunity (ClinicalTrials.gov identifiers, NCT01592370, NCT02726581, NCT01592370, and NCT03000452).

Antibody–Drug Conjugates

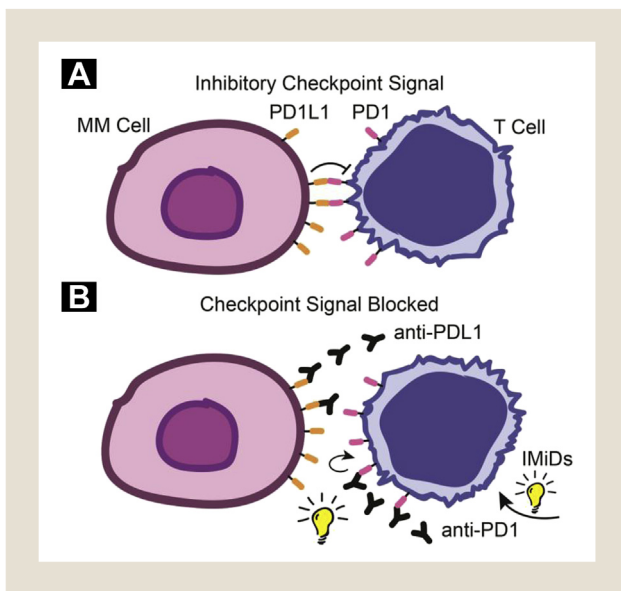
Antibody–drug conjugates (ADCs) are another promising new class of targeted therapeutic agents against MM. ADCs have recently seen proof-of-concept clinical success against Hodgkin lymphoma (brentuximab vedotin) and HER2⁺ breast cancer (ado-trastuzumab emtansine).^{87,88} ADCs have the potential to further improve on the efficacy of naked antibodies via targeted delivery of highly cytotoxic chemotherapy directly to malignant cells.^{89,90} In contrast to the other antibody offshoot approaches, ADCs do not depend on immune function, which is relatively compromised in MM patients. In light of this potential for benefit, new ADCs should be tested in MM; however, thus far, trials have been limited. Currently, CD138 and B-cell maturation antigen (BCMA) are the most activity pursued agents for ADC development in MM after promising preclinical studies for both.^{91,92} Anti-CD138 ADC indatuximab ravtansine completed a single-agent phase I-IIa study of MM with the preliminary report showing an ORR of 11%.⁶⁷ Indatuximab ravtansine is also being studied in steroid/IMiD combinations.^{93,68} The preliminary findings of the anti-BCMA ADC GSK2857916 has also been reported, showing an ORR of 25% (minor response or better) in patients with RRMM, all at doses of ≥ 0.24 mg/kg (ClinicalTrials.gov identifier, NCT02064387).⁶⁶ Other notable ADCs recently demonstrated to have promising preclinical activity target the CD46 and FcRL5 antigens.^{94,95} Thus far, all ADC trials have been single-agent, dose-escalation trials; thus, it is yet to be seen whether ADCs

Table 2 Monoclonal Antibody Derivative Approaches in Clinical Development for Multiple Myeloma

Agent	Target	Company	Features	Clinical Study	Reference
Checkpoint inhibitors					
Pembrolizumab	PD1	Merck	IMiD combinations	Phase III	63–65
Nivolumab	PD1	BMS	IMiD, MoAb combinations	Phase I-II	NA
Durvalumab	PDL1	Celgene	IMiD, MoAb combinations	Phase I-II	NA
Antibody–drug conjugates					
GSK2857916	BCMA	GSK	J6M0-mcMMAF	Phase I	66
Indatuximab ravtansine	CD138	Biotest	nBT062-SPDB-DM4	Phase I-IIa	67,68
Bispecific antibodies					
BCMA bispecific	BCMA	Pfizer	CD3, IgG-like	Preclinical	69
EM801	BCMA	Celgene	CD3, IgG-like	Preclinical	70,71
AMG420	BCMA	Amgen	CD3, BiTE	Preclinical	NA
FcRH5/CD3 TDB	FcRH5	Genentech	CD3, IgG-like	Preclinical	72
BiTE-hlgFc (STL001)	CD138	Unknown	BiTE-Fc fusion	Preclinical	73
Chimeric antigen T cells					
CAR-BCMA T cells	BCMA	NCI	CD3 ζ , CD28 domains	Phase I	74
CART-BCMA	BCMA	Novartis	CD3 ζ , 4-1BB domains	Phase I	75
bb2121	BCMA	Bluebird	CD3 ζ , 4-1BB domains	Phase I	NA
KITE-585	BCMA	Kite	Unknown	Preclinical	NA
CTL019 cells	CD19	Novartis	CD3 ζ , 4-1BB domains	Phase I	76

Abbreviations: BiTE = bispecific T-cell engager; BCMA = B-cell maturation antigen; CART = chimeric antigen T (cells); GSK = GlaxoSmithKline; IMiD = immunomodulatory drug; MoAb = monoclonal antibody; NA = not available; NCI = National Cancer Institute; TDB = T cell-dependent bispecific antibody.

Figure 2 Checkpoint Signal Blockade and T-cell Activation Against Multiple Myeloma (MM). (A) MM Cells Upregulate Checkpoint Ligand Programmed Cell Death Ligand-1 (PDL-1) and T Cells Upregulate Programmed Death-1 (PD1). PDL1 Interacts With PD1 and Prevents Activation of T Cells Through Inhibitory Signaling.⁷⁷⁻⁸² PDL1 on Other Bone Marrow Cells in the Tumor Microenvironment Is Also Upregulated (Data Not Shown).⁸³ (B) Blockade of Checkpoint Interactions With Monoclonal Antibodies Directed Against PD1 or PDL1 Result in Activation of T Cells. T-cell Activation Against MM Cells Is Potentiated by the Immunomodulatory Drug (IMiD) Lenalidomide, Which Downregulates PD1 on T Cells and Also Downregulates PDL1 on MM Cells and Other Bone Marrow Cells.⁸³ Thus, Both PD1 and PDL1 Antibodies Are Currently in Clinical Testing in Combinations With Both IMiDs and Antibody-dependent Cellular Cytotoxicity (ADCC)-evoking Monoclonal Antibodies



emerge as tolerable single agents or enhance efficacy in combination strategies.

Bispecific Antibodies

Bispecific antibodies have been diversely engineered to accomplish recognition of 2 separate target antigens simultaneously. The prototype of this class are the bispecific T-cell engagers (BiTEs) in which antibody single-chain variable fragments binding to an antigen expressed on a malignant cell are connected to a second single-chain variable fragments recognizing the common T-cell antigen CD3. These serve to effectively bridge the malignant cells to T cells and evoke cytotoxicity via the close proximity. The first-in-class FDA-approved agent for this drug class is the CD19-targeted BiTE blinatumomab.⁹⁶ Although clearly efficacious, the drawback of the small fragment BiTE format is the rapid renal clearance, necessitating logistically difficult continuous infusions. More IgG-like bispecifics that have pharmacokinetics similar to monoclonal antibodies will likely facilitate broader applicability to this modality in the near future.^{97,98} For MM, BCMA-, CD138-, and FcRL5 (aka FcRH5)-targeted bispecifics in both BiTE and IgG-like formats

have been developed and will soon enter clinical trials.^{70,71,69,73,72} A BCMA-targeted bispecific composed of 2 chemically linked antibody fragment antigen binding had more potent cytotoxicity in vitro than one targeted to SLAMF7.⁹⁹ An attractive feature of anti-MM bispecifics is the high (picomolar) potency in vitro, which might prove ideal with targets that have high specificity but relatively low-level expression such as BCMA.

Chimeric Antigen T Cells

A key question in the future of treatment of MM is whether chimeric antigen T (CAR-T) cells can be as successful as they have been found to be in B-cell acute lymphoblastic leukemia (B-ALL). CAR-T cells incorporate an antibody's variable region into a chimeric receptor, including a T-cell receptor and costimulatory domains, to reprogram engineered immune effector T cells to eliminate malignant cells. In selecting an antigen for CAR-T cells, a critical consideration is its specificity for the target cell population. In B-ALL, CD19 has shown to be suitable owing to the restricted expression on B cells. A side effect of anti-CD19 CAR-T cells is aplasia of normal B cells, although surprisingly humoral immunity appears to remain intact.¹⁰⁰ MM can be targeted with CAR-T cells via differentiation antigens only present on plasma cells, best exemplified by BCMA. Thus, BCMA has emerged as another promising antigen for CAR-T cells in MM, with deep remissions produced in patients with treatment-refractory disease, although cytokine release syndrome, prolonged cytopenias, and hypogammaglobulinemia have occurred.^{74,75} The CAR-T cell dose needed for clinical activity was notably greater than that in the previous CD19 CAR-T trials of B-ALL.⁷⁴ The durability of response to BCMA CAR-T cells has not yet been determined, and multiple versions of this approach are in clinical trials in the United States and China (ClinicalTrials.gov identifiers, NCT02215967, NCT02658929, NCT02546167, and NCT02954445). An early report of CD19 CAR-T cells tested in MM also produced deep responses in conjunction with melphalan and autologous stem cell transplantation.⁷⁶ Clinical studies of CD19 CAR-T cells in MM are ongoing at the University of Pennsylvania (ClinicalTrials.gov identifiers, NCT02794246 and NCT02135406). Other potential CAR-T cell targets under investigation for MM are CD138 and CD38 (ClinicalTrials.gov identifier, NCT01886976).^{101,102} Our expectation is that more clinical data for CAR-T cells in MM will be forthcoming soon and that trials will become more broadly available.

Future Directions

MM has long been postulated as an ideal disease for monoclonal antibody therapy. After initially disappointing results with other agents, persistence resulted in the useful additions of daratumumab and elotuzumab to the anti-MM pharmacy. We can conclude from the current data that the CD38 and SLAMF7 proved to be ideal targets owing to high and ubiquitous expression on myeloma cells (especially for CD38), along with the strong NK cell ADCC elicited by elotuzumab and potent multifactorial effects of daratumumab. Clear efficacy and favorable side effect profiles have made these drugs very attractive for both physicians and patients. From the current clinical trial results, elotuzumab combined with lenalidomide appears most suited for early relapses, where it produced a

Monoclonal Antibodies in Multiple Myeloma

high response rate in the ELOQUENT-2 trial. The potential role of elotuzumab with bortezomib is currently less clear. Daratumumab-based therapy with either bortezomib or lenalidomide in the CASTOR and POLLUX trials, respectively, has shown the greatest response rates and most durable effect in relapsed disease to date. In addition, daratumumab monotherapy, for which it was first FDA approved, remains an important option for RRMM patients who are resistant or intolerant to PIs and IMiDs.

Studies considering the expansion of the applicability of daratumumab and elotuzumab are well underway. These include studying their addition to 3-drug upfront combinations and combinations with new agents for RRMM. Maximizing the benefit of daratumumab is of particular interest. CD38 expression correlates with the response, and treatment with daratumumab has been shown to downregulate its expression.¹⁰³ At approximately 6 months after daratumumab discontinuation, patients' myeloma cells had recovered their CD38 expression. This raises the question of whether daratumumab use in later lines of therapy can likewise recover its efficacy.¹⁰³ For example, one might foresee eventual integration of daratumumab into front-line therapy, for both fit and unfit patients, and also into their treatment regimen at relapse years later. It is also possible that establishing a biomarker assay of CD38 levels could be useful to further refine when best to use it.

Conclusion

Breakthrough clinical studies with daratumumab and elotuzumab have established monoclonal antibodies as the next revolution in the treatment of MM, a decade after the last revolution with PIs and IMiDs. Now, state-of-the art protein engineering, CAR-T cell therapy, and new methods for using antibodies are poised to transform treatment again. Checkpoint inhibitors combined with IMiDs have shown early phase potential, and phase III studies are ongoing in attempt to confirm their efficacy. ADCs have shown intriguing single-agent activity in phase I clinical trials. CAR-T cells have promising salvage potential if the approach can be scaled up and becomes more widely available. Bispecific antibody platforms have rapidly evolved and diversified since their first-in-class FDA approval in leukemia. Several BiTEs are being developed for MM and will start entering trials in 2017. A great need remains to develop treatment that will be effective for patients with advanced, high-risk (eg, deletion of chromosome 17p) and treatment-refractory disease. Although the improvements we have discussed are greatly encouraging, patients continue to experience progressively shorter cycles of remission, followed by relapse, with their disease eventually becoming resistant to all PIs, IMiDs, and monoclonal antibodies. Incorporating daratumumab, elotuzumab, and new immunotherapy approaches, while simultaneously exploring new treatment modalities, will be paramount in addressing this great remaining clinical need.

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