

Immunotherapy of Multiple Myeloma: Promise and Challenges

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Abstract: Whereas the treatment of MM was dependent solely on alkylating agents and corticosteroids during the prior three decades, the landscape of therapeutic measures to treat the disease began to expand enormously early in the current century. The introduction of new classes of small-molecule drugs, such as proteasome blockers (bortezomib and carfilzomib), immunomodulators (lenalidomide and pomalidomide), nuclear export inhibitors (selinexor), and histone deacetylase blockers (panobinostat), as well as the application of autologous stem cell transplantation (ASCT), resulted in a seismic shift in how the disease is treated. The picture changed dramatically once again starting with the 2015 FDA approval of two monoclonal antibodies (mAbs) – the anti-CD38 daratumumab and the anti-SLAMF7 elotuzumab. Daratumumab, in particular, has had a great impact on MM therapy and today is often included in various regimens to treat the disease, both in newly diagnosed cases and in the relapse/refractory setting. Recently, other immunotherapies have been added to the arsenal of drugs available to fight this malignancy. These include isatuximab (also anti-CD38) and, in the past year, the antibody-drug conjugate (ADC) belantamab mafodotin and the chimeric antigen receptor (CAR) T-cell product idecabtagene vicleucel (ide-cel). While the accumulated benefits of these newer agents have resulted in a doubling of the disease's five-year survival rate to more than 5 years and improved quality of life, the disease remains incurable. Almost without exception patients experience relapse and/or become refractory to the drugs used, making the search for innovative therapies all the more essential. This review covers the current scope of anti-myeloma immunotherapeutic agents, both those in clinical use and on the horizon, including naked mAbs, ADCs, bi- and multi-targeted mAbs, and CAR T-cells. Emphasis is placed on the benefits of each along with the challenges that need to be overcome if MM is to be considered curable in the future.

Keywords: multiple myeloma, monoclonal antibodies, antibody-drug conjugates, bi-specific antibodies, chimeric antigen receptor T-cells, cytokine release syndrome

Introduction

Multiple myeloma (MM) is characterized by clonal proliferation of plasma cells in the bone marrow accompanied by high levels of monoclonal immunoglobulins in the urine and/or blood. In the United States, the disease ranks second behind non-Hodgkin's Lymphoma (NHL) as a hematological cancer and 14th among all cancers in terms of incidence. According to current estimates, in 2021 MM will be diagnosed in a total of 34,920 individuals (55.3% male) and will be responsible for 12,410 deaths in the U.S.¹ The median age at diagnosis is 69 years, which has been trending lower in recent years. Significant racial disparities have been noted for all stages of MM with the prevalence of the disease in the US being

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substantially greater among African Americans than among Caucasians.² For example, in one analysis of the SEER (Surveillance, Epidemiology, and End Results) data base, maintained by the National Cancer Institute (NCI), it was found that the annual incidence of the disease per 100,000 population among Caucasians is 6.1 for men and 4.0 for women compared to 13.2 and 9.6, respectively, for African Americans.³

The tetrad of symptoms that typically accompanies an active case of MM is known by the acronym CRAB: hypercalcemia, renal insufficiency, anemia, and bone lesions. An active case often is preceded by an asymptomatic state, monoclonal gammopathy of undetermined significance (MGUS), with a risk of progression from MGUS to MM of about 1% per year.⁴ A second asymptomatic phase, smoldering multiple myeloma (SMM), intermediate between MGUS and MM, also has been described.^{5,6} Current guidelines for the diagnosis and treatment of MM have been issued by the National Comprehensive Cancer Network (NCCN).⁷ While the cause of MM remains unknown, cytogenetic anomalies are known to play a role in some MM patients classified as “high risk”. The most frequently encountered of these variances are the chromosomal deletion del(17p) and the transversions t(14;16) and t(4;14).⁸

Remarkable progress has attended the treatment of MM over the past half century. Starting in the mid-1960’s and continuing for nearly three decades, two alkylating agents, melphalan (Alkeran[®])⁹ and cyclophosphamide (Cytoxan[®]), often in regimens that included corticosteroids, were the mainstays of MM therapy. The addition of autologous stem cell transplantation (ASCT) to the MM treatment landscape in the 1990s further improved therapeutic outcomes. However, the picture began to change dramatically by the end of the decade with the discovery of thalidomide’s remarkable immunomodulatory effects that conferred anti-myeloma activity on this once ignominiously regarded drug. Two close chemical derivatives of thalidomide, lenalidomide (Revlimid[®]) (2005) and pomalidomide (Pomalyst[®]) (2013), soon supplanted thalidomide for MM. Meanwhile, the discovery of the potent anti-myeloma actions of proteasome inhibitors led to the introduction of bortezomib (Velcade[®]) (2003), later followed by the mechanistically similar carfilzomib (Kyprolis[®]) and ixazomib (Ninlaro[®]), as important additions to the anti-myeloma arsenal. The list of US Food and Drug Administration (FDA)-approved small molecules that work by additional mechanisms to treat MM has recently expanded to include the pan-histone deacetylase inhibitor

panobinostat (Farydak[®]) (2015) and the nuclear export blocker selinexor (Xpovio[®]) (2019). The cumulative benefits of these therapeutic advances can be seen in the 2.26-fold increase of the MM five-year survival rate over the period from 1975–77 (24.6%) to 2011–17 (55.6%),¹⁰ as well as in the median survival, which has increased from 2.5 years in the mid-1990s to 5.7 years today.¹¹

Treatment options for MM underwent a paradigm shift beginning with the 2015 approval by the FDA of two monoclonal antibodies (mAbs), daratumumab (Darzalex[®]) and elotuzumab (Empliciti[®]), followed by additional immunotherapies, including a third mAb, isatuximab (Sarclisa[®]), an antibody-drug conjugate (belantamab mafodotin; Blenrep[®]), and idecabtagene vicleucel (Abecma[®]), the first chimeric antigen receptor (CAR) T-cell product for the disease. This review is intended to cover the fundamental aspects of these newer agents and the prospects for additional immunotherapeutic agents that now occupy the anti-myeloma pipeline.¹² For recent reviews of the background, history, and current status of the applications of immunotherapy to cancer treatment, the reader is directed to the recent publications of Esfahani,¹³ Waldman,¹⁴ and Tan.¹⁵

CD38 as a Monoclonal Antibody Target

CD38, which has elicited much interest as a target in MM, is a 45 kDa transmembrane glycoprotein, expressed at high levels in both normal and neoplastic plasma cells, as well as at lower levels by a number of other blood cells.¹⁶ This important surface biomarker is known to perform several roles in cells. These functions include, among others, acting as a receptor for CD31 (platelet endothelial cell adhesion molecule; PECAM-1) and as an ectoenzyme with cyclic ADP ribose hydrolase activity, the products of which are important regulators of intracellular calcium levels.^{17,18}

The principal mechanisms by which anti-CD38 antibodies are lethal to myeloma cells are three-fold: antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC). In addition, crosslinks between CD38 on myeloma cells and effector cell Fcγ receptors may be responsible for initiation of apoptosis of myeloma cells.¹⁹ Moreover, anti-CD38 antibodies have demonstrated immunomodulatory actions by blocking myeloid-derived suppressor cells and regulatory T- and B-cells.²⁰

In 2015, daratumumab, a fully human IgG1k mAb directed against CD38, became the first immunotherapeutic agent approved for treatment of MM. Approval was granted based on supporting data from two Phase III trials – CASTOR (NCT02136134) and POLLUX (NCT02076009) – wherein the mAb and dexamethasone were combined with either a proteasome inhibitor (bortezomib)²¹ or an immunomodulator (lenalidomide).²² Initial approval limited daratumumab-dexamethasone use to monotherapy in patients who had relapsed following a minimum of three prior therapies that included either a proteasome inhibitor or an immunomodulator. However, daratumumab-dexamethasone in combination with proteasome inhibitors and/or immunomodulators has since assumed a key role in even earlier courses of anti-myeloma therapy as data from additional phase III trials demonstrated more sustained responses and good tolerability from such combinations, including use in newly diagnosed patients whether ASCT-eligible²³ or -ineligible.²⁴

Current NCCN treatment guidelines for MM, based on most favorable response and safety data, include one triplet protocol (daratumumab-lenalidomide-dexamethasone); and a number of quartet regimens which include, in addition to daratumumab-bortezomib-corticosteroid (dexamethasone or prednisone), either an alkylating agent (cyclophosphamide or melphalan) or an immunomodulator (lenalidomide or thalidomide).⁷ Moreover, combinations with pomalidomide²⁵ and more recently carfilzomib^{26,27} also have received FDA approval for use in relapsed and/or refractory MM (RRMM). Several network meta-analytic studies of random controlled trials provide further evidence of daratumumab's benefits in various myeloma-based settings.²⁸ In addition, recent FDA approval of a subcutaneous (sc) formulation of daratumumab combined with hyaluronidase provides the substantial benefit of enabling markedly shorter administration times – 3–5 minutes vs several hours of intravenous (iv) infusion of the mAb without compromising efficacy or patient safety.^{29–31}

Infusion reactions, which include dyspnea, rash, headache, cough, nausea, vomiting, and nasal congestion represent an adverse, although generally low grade, effect of daratumumab, being noted in up to 50% of patients receiving the drug, especially during the first two infusions. Pre-medication with a glucocorticoid and/or a leukotriene blocker (montelukast) may help mitigate this effect and may be particularly useful in patients with underlying respiratory disease.³² Also, the drug

can interfere with blood typing due to its capacity for binding to CD38 on reagent blood cells, resulting in a positive indirect Coombs test. This can be circumvented by conducting patient blood-typing procedures prior to using daratumumab.³³ The risk of infection, primarily due to the bone marrow suppression, also has been shown to accompany use of the agent and necessitates use of prophylactic antimicrobials, such as cotrimoxazole to prevent *Pneumocystis carinii* pneumonia and antivirals. Table 1 contains a partial list of current clinical trials that include daratumumab.

Isatuximab, a more recent addition to the anti-CD38 mAb arsenal, differs from daratumumab in that it represents a chimeric mouse-human IgG1k construct. Its mechanism of action is similar to that of daratumumab although cross-linking apparently is not a prerequisite for apoptosis induction.⁴⁹ Initial FDA approval of isatuximab (March 2020) specified its use for the treatment of RRMM in combination with pomalidomide and dexamethasone in patients who have failed at least two prior therapies, including lenalidomide and a proteasome inhibitor.⁵⁰ This was based on the results of the phase III ICARIA trial in which addition of isatuximab to RRMM patients receiving pomalidomide-dexamethasone exhibited significantly longer PFS (11.5 months vs 6.5 months).^{51,52} Subsequently (March 2021), the combination of isatuximab-dexamethasone with carfilzomib was approved for treatment of RRMM patients who had received one to three prior therapies. Approval in this case was predicated on efficacy and safety data from the phase III IKEMA study (NCT03275285) in which the cohort receiving the isatuximab-based regimen exhibited a 45% reduction in the risk of disease progression or death compared to that given carfilzomib-dexamethasone alone.^{53–55} Infusion reactions and upper respiratory infections are the most common adverse reactions noted for isatuximab. An isatuximab formulation intended for subcutaneous use is currently the subject of an ongoing clinical trial (NCT04045795). Several of the current isatuximab-containing clinical trials are shown in Table 2.

Other anti-CD38 mAbs that have been investigated for MM include felzartamab (MOR202), TAK-573, and mezagitamab (TAK-079). The first of these has been dropped by its sponsor from further consideration in MM while the other two, developed by Takeda, remain in early phase clinical trials – NCT03215030 (iv) and NCT03984097 (sc), respectively.

Table I Selected Clinical Trials of Daratumumab in Multiple Myeloma (MM)

| Trial ID (References) | Treatment | Phase | Enrollment (N) | Trial Title |
|---------------------------------|--|-------|----------------|--|
| NCT04656951 | Dara | II | 160 | Daratumumab for first Line treatment of transplant-ineligible myeloma patients followed by daratumumab re-treatment at first relapse (GMMG-DADA) |
| NCT02626481 ³⁴ | Dara + Dex | II | 64 | A multicenter open label Phase II study of daratumumab in combination with dexamethasone in MM resistant or refractory to bortezomib and lenalidomide and pomalidomide |
| NCT02541383 ^{23,35} | Dara alone vs (Bort + Thal + Dex ± Dara) | III | 1085 | Study of daratumumab in combination with bortezomib, thalidomide, and dexamethasone (VTd) in the first line treatment of transplant eligible subjects with newly diagnosed MM (Cassiopeia) |
| NCT03993912 | (Len + Dex) vs (Len + Dex + Dara sc) | III | 294 | A phase III study comparing lenalidomide and subcutaneous daratumumab (R-dara sc) vs lenalidomide and dexamethasone (Rd) in frail subjects with previously untreated MM who are ineligible for high dose therapy |
| NCT02316106 ³⁶ | Dara | II | 123 | A randomized phase II trial to evaluate three daratumumab dose schedules in smoldering MM |
| NCT03158688 ^{26,37,38} | (Carf + Dex) ± Dara | III | 466 | A randomized, open-label, phase III study comparing carfilzomib, dexamethasone, and daratumumab to carfilzomib and dexamethasone for the treatment of patients with RRMM (CANDOR) |
| NCT02136134 ^{21,39} | (Bort + Dex) ± Dara | III | 499 | Phase III study comparing daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in subjects with RRMM (CASTOR) |
| NCT03301220 ⁴⁰ | Dara sc + Hyal | III | 390 | A phase III randomized, multicenter study of subcutaneous daratumumab versus active monitoring in subjects with high-risk smoldering MM (AQUILA) |
| NCT03901963 | Len ± Dara | III | 214 | A randomized study of daratumumab plus lenalidomide versus lenalidomide alone as maintenance treatment in patients with newly diagnosed MM who are minimal residual disease positive after frontline ASCT |
| NCT02076009 ^{22,41,42} | (Len + Dex) ± Dara | III | 569 | Phase III study comparing daratumumab, lenalidomide, and dexamethasone (DRd) vs lenalidomide and dexamethasone (Rd) in subjects with RRMM (POLLUX) |
| NCT03180736 ⁴³ | (Pom + Dex) ± Dara | III | 304 | A phase III study comparing pomalidomide and dexamethasone with or without daratumumab in subjects with RRMM who have received at least one prior line of therapy with both lenalidomide and a proteasome inhibitor (Apollo) |
| NCT04649060 | Dara ± Melf | III | 240 | A randomized, controlled, open-label phase III study of melflufen in combination with daratumumab compared with daratumumab in patients with RRMM (LIGHTHOUSE) |
| NCT02252172 ^{44,45} | (Len + Dex) ± Dara | III | 737 | A phase III study comparing daratumumab, lenalidomide, and dexamethasone (DRd) vs lenalidomide and dexamethasone (Rd) in subjects with previously untreated MM who are ineligible for high dose therapy (MAIA) |

(Continued)

Table 1 (Continued).

| Trial ID (References) | Treatment | Phase | Enrollment (N) | Trial Title |
|------------------------------|------------------------------|-------|----------------|---|
| NCT03652064 | (Bort + Len + Dex) ± Dara | III | 395 | A phase III study comparing daratumumab, bortezomib, lenalidomide, and dexamethasone (D-VRd) with bortezomib, lenalidomide, and dexamethasone (VRd) in subjects with untreated MM and for whom ASCT is not planned as initial therapy |
| NCT03277105 ^{46–48} | Dara (sc vs iv) | III | 522 | A phase III randomized, multicenter study of subcutaneous vs intravenous administration of daratumumab in subjects with RRMM (COLUMBA) |

Abbreviations: Bort, bortezomib; Carf, carfilzomib; Dara, daratumumab; Dex, dexamethasone; Hyal, hyaluronidase; iv, intravenous; Len, lenalidomide; Melf, melflufen; Pom, pomalidomide; sc, subcutaneous; Thal, thalidomide.

Table 2 Selected Clinical Trials of Isatuximab in Multiple Myeloma (MM)

| Trial ID (References) | Treatment | Phase | Enrollment (N) | Trial Title |
|---------------------------------|---------------------------------------|-------|----------------|---|
| NCT04270409 | (Len + Dex) ± Isa | III | 323 | A phase III randomized, open label, multicenter study of isatuximab in combination with lenalidomide and dexamethasone versus lenalidomide and dexamethasone in patients with high-risk smoldering MM |
| NCT02990338 ^{51,56–59} | (Pom + Dex) ± Isa | III | 307 | A phase III randomized, open-label, multicenter study comparing isatuximab in combination with pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with RRMM ICARIA-MM |
| NCT03275285 ^{54,60} | (Isa + Carf + Dex) vs (Carf + Dex) | III | 302 | Randomized, open label, multicenter study assessing the clinical benefit of isatuximab combined with carfilzomib and dexamethasone versus carfilzomib with dexamethasone in patients with RRMM previously treated with 1 to 3 prior lines (IKEMA) |
| NCT02514668 ⁶¹ | Isa | I | 55 | An open-label, dose-escalation and multi-center study to evaluate the safety, pharmacokinetics and efficacy of isatuximab in patients with RRMM |
| NCT02960555 ⁶² | Isa | II | 61 | Phase II single arm trial of isatuximab in patients with high risk smoldering MM |
| NCT02332850 ^{60,63} | Isa + Carf + Dex | I | 89 | A multi-arm phase Ib study of isatuximab in combination with standard carfilzomib, and high-dose weekly carfilzomib and dexamethasone for the treatment of RRMM |
| NCT03319667 ⁶⁴ | (Len + Bort + Dex) ± Isa | III | 475 | A phase III randomized, open-label, multicenter study assessing the clinical benefit of isatuximab in combination with bortezomib, lenalidomide and dexamethasone versus bortezomib, lenalidomide and dexamethasone in patients with newly diagnosed MM not eligible for transplant (IMROZ) |
| NCT01749969 ^{65,66} | Isa + Len + Dex | I | 60 | A phase Ib study of isatuximab in combination with lenalidomide and dexamethasone for the treatment of RRMM |
| NCT02283775 ^{67–70} | Isa + Pom + Dex | I | 89 | A phase Ib study of isatuximab in combination with pomalidomide and dexamethasone for the treatment of RRMM (PomdeSAR) |

Abbreviations: Bort, bortezomib; Carf, carfilzomib; Dex, dexamethasone; Isa, isatuximab; Len, lenalidomide; Pom, pomalidomide.

SLAMF7 as a Monoclonal Antibody Target

Members of the signaling lymphocytic activation molecule family (SLAMF) of proteins are highly expressed on the surface of plasma cells, both normal and from MM patients, as well as natural killer (NK) cells, but not on other blood cells or other body tissues. While mAbs directed against SLAMF3 and SLAMF6 (SGN-CD48A and azintuzumab vedotin/ABBV-838, respectively) have proven unsuccessful in early stages of myeloma-directed clinical trials, SLAMF7 (CS1 or CD319) has emerged as a major target in the fight against MM. The anti-myeloma activity of SLAMF7-targeted antibodies results from their ability to initiate ADCC toward myeloma cells following activation and engagement of NK cells.^{71–74} The foremost anti-SLAMF7 mAb is elotuzumab, a humanized IgG1k antibody.

In 2015, shortly following its action regarding daratumumab, elotuzumab was approved for treatment of MM in the US. Approval was granted for use in combination with lenalidomide and dexamethasone in MM patients who had already received one to three prior therapies.⁷⁵ Unlike daratumumab, elotuzumab lacks single-agent activity.⁷⁶ The FDA's action was prompted by the favorable results of the ELOQUENT-2 trial (NCT01239797) that included 646 RRMM patients, randomly assigned to receive the mAb combined with dexamethasone with or without lenalidomide. A progression-free survival (PFS) of 19.4 months for the elotuzumab group plus an overall response rate (ORR) of 68% after one year and 41% at two years compared very favorably to the 14.9 months and 57% and 27% exhibited by the control cohort.⁷⁷ A four-year follow-up provided further confirmation of the result of this trial.⁷⁸ The ELOQUENT-3 trial (NCT02654132), which investigated the use of elotuzumab-dexamethasone plus pomalidomide in RRMM patients refractory to both lenalidomide and a proteasome blocker, resulted in formal approval of this triplet therapy in patients who had received at least two prior therapies that included these two agents.⁷⁹ Trials with thalidomide, another immunomodulator, have proven inferior in RRMM patients compared to those obtained with lenalidomide or pomalidomide.⁸⁰ Moreover, additional trials combining elotuzumab with proteasome inhibitors – bortezomib^{80–82} or carfilzomib⁸³ – have, thus far, failed to generate the level of favorable outcomes of the scale produced by immunomodulator combinations. A list of selected trials that include elotuzumab is presented in [Table 3](#).

Antibody-Drug Conjugates

Antibody-drug conjugates (ADCs) are drugs designed to kill tumor cells by chemically linking a cytotoxin (or, in some cases a radionuclide) to an antibody which targets either a tumor-specific antigen (TSA) or tumor-associated antigen (TAA). Over the past several years a number of ADCs have been developed to treat an array of malignancies, including breast cancer, acute leukemias, and Hodgkin's lymphoma.

ADC construction is based on three components – a mAb with high specificity for a particular TAA or TSA, a small cytotoxic molecule (the payload), and a linker designed to attach the payload to the mAb. Internalization of the ADC by endocytosis followed by lysosomal processing releases the cytotoxin to initiate apoptosis of the tumor cell. Fully human or humanized IgG1 antibodies often are preferred in these constructs due to their potent ability to activate ADCC and ADCP through FcγRIIIa binding to NK cells.⁹⁷ Removal of fucosyl groups (afucosylation) from the N-linked biantennary complex oligosaccharides in the antibody's Fc region further improves binding to FcγRIIIa receptors on NK cells, resulting in enhanced ADCC.⁹⁸

B-cell maturation antigen (BCMA, CD269, TNFRSF17) is a tumor necrosis factor (TNF) family member that acts as a ligand for BAFF (B-cell activating factor) and APRIL (a proliferation-inducing ligand), two cytokines that play key roles in myeloma cell viability and proliferation.⁹⁹ While inhibitors of BAFF and APRIL have fared poorly in MM trials,^{100,101} BCMA, which was first discovered nearly thirty years ago,^{102–105} has come to the fore in recent years as an attractive target in the search for new drugs to treat MM.^{106–109} As its name implies, expression of this 184-amino acid glycoprotein is a key factor in the normal maturation and differentiation of B-cells into fully functional plasmacytes. Both BCMA and its mRNA, whose presence is almost exclusively confined to plasma cells, are known to be consistently over-expressed during malignant transformation to MM, driving tumor cell growth, survival, and drug resistance as determined in both cell lines and patient samples. Furthermore, much evidence suggests that measurements of membrane bound BCMA may serve not only as a biomarker for MM diagnosis and prognosis, but also as a predictor of treatment response.¹¹⁰

Cleavage of the extracellular domain from membrane-bound BCMA by the action of gamma-secretase results in release of soluble BCMA (sBCMA) into the plasma,¹¹¹ elevation of sBCMA blood levels in MM patients has been

Table 3 Selected Trials of Elotuzumab in Multiple Myeloma (MM)

| Trial ID (References) | Treatment | Phase | Enrollment (N) | Trial Title |
|------------------------------------|--|-------|----------------|--|
| NCT02718833 ⁸⁴ | Elo + Pom + Bort + Dex | II | 52 | A phase II study of elotuzumab in combination with pomalidomide, bortezomib, and dexamethasone in RRMM |
| NCT02159365 ⁸⁵ | Elo + Len + Dex | II | 84 | A phase II single arm study of safety of elotuzumab administered over approximately 60 minutes in combination with lenalidomide and dexamethasone for newly diagnosed or RRMM patients |
| NCT01478048 ⁸⁶ | (Bort + Dex) ± Elo | II | 185 | A Phase II, randomized study of bortezomib/dexamethasone with or without elotuzumab in subjects with RRMM |
| NCT01441973 ^{87,88} | Elo | II | 41 | A phase II biomarker study of elotuzumab monotherapy to assess the association between NK cell status and efficacy in high risk smoldering myeloma |
| NCT02654132 ⁷⁹ | (Pom + Dex) ± Elo | II | 157 | An open label, randomized phase II trial of pomalidomide and dexamethasone with or without elotuzumab in RRMM (ELOQUENT-3) |
| NCT02495922 ⁸⁹ | (Len + Bort + Dex) ± Elo | III | 564 | A randomized phase III trial on the effect of elotuzumab in VRd induction /consolidation and lenalidomide maintenance in patients with newly diagnosed MM |
| NCT01668719 ^{81,90} | (Len + Bort + Dex) ± Elo | I/II | 122 | A randomized phase I/II study of optimal induction therapy of bortezomib, dexamethasone, and lenalidomide with or without elotuzumab for newly diagnosed high risk MM |
| NCT01239797 ^{77,78,91–94} | (Len + Dex) ± Elo | III | 761 | Phase III, randomized, open label trial of lenalidomide and dexamethasone with or without elotuzumab in RRMM (ELOQUENT-2) |
| NCT00742560 ⁹⁵ | Elo + Len + Dex | II | 101 | A phase Ib/II, multicenter, open-label, dose-escalation study of elotuzumab in combination with lenalidomide and dexamethasone in subjects with RRMM |
| NCT02726581 ⁹⁶ | (Pom + Niv + Elo + Dex) vs (Pom + Dex ± Niv) | III | 348 | An open-label, randomized phase III trial of combinations of nivolumab, pomalidomide and dexamethasone in RRMM |

Abbreviations: Bort, bortezomib; Dex, dexamethasone; Elo, elotuzumab; Len, lenalidomide; Niv, nivolumab; Pom, pomalidomide.

correlated with inferior clinical outcomes.¹¹² Moreover, sBCMA not only lowers the density of the target antigen but also provides a soluble decoy having the capacity to reduce the efficacy of new anti-BCMA agents currently under investigation. In an effort to mitigate this potential hurdle, a number of gamma-secretase inhibitors have been developed to enhance effectiveness of BCMA-directed therapies.^{113,114} Crenigacestat (LY3039478, JSMD-194) and nirogacestat are among the orally active γ -secretase inhibitors that have been included in clinical trials of anti-BCMA immunotherapies.

Belantamab mafodotin (Blenrep[®], belamaf, GSK2857916) is an ADC in which the BCMA-targeted

humanized afucosylated IgG1 antibody is coupled to the microtubule inhibitor monomethyl auristatin F (mafodotin, MMAF) through a non-cleavable maleimidocaproyl linker.^{115,116} ADCC is induced by the antibody following its binding to the BCMA receptor on the myeloma cell surface while the cytotoxic component causes cell cycle arrest at the G2/M checkpoint.¹¹⁷ In August 2020, belantamab mafodotin became the first ADC to receive FDA approval for MM. The endorsement was provided on an accelerated basis for use in RRMM patients who had received at least four earlier regimens, including a proteasome inhibitor, an anti-CD38 mAb, and an immunomodulator.¹¹⁸ Approval was predicated on data

from the DREAMM-2 trial (NCT03525678), which included a total of 196 RRMM patients, divided into two dosage cohorts: 2.5 mg/kg (N = 97) and 3.4 mg/kg (N = 99). ORR and PFS data recorded for the two groups was 31% and 2.9 months and 34% and 4.9 months,

respectively.¹¹⁹ Table 4 lists a number of clinical trials that include belantamab mafodotin, which are currently active or in the initial planning stages. Thrombocytopenia and anemia were among the commonly reported adverse events noted with the drug in the DREAMM-2 trial, as well as in

Table 4 Selected Trials of Belantamab Mafodotin in Multiple Myeloma (MM)

| Trial ID (References) | Treatment | Phase | Enrollment (N) | Trial Title |
|--------------------------------|-------------------------------|-------|----------------|---|
| NCT02064387 ¹²⁸ | BelMaf | I | 79 | A phase I open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamics, immunogenicity and clinical activity of the antibody drug conjugate GSK2857916 in subjects with RRMM and other advanced hematologic malignancies expressing BCMA (DREAMM-1) |
| NCT03525678 ^{129,130} | BelMaf | II | 221 | A phase II, open label, randomized, two-arm study to investigate the efficacy and safety of two doses of the antibody drug conjugate GSK2857916 in participants with MM who had 3 or more prior lines of treatment, are refractory to a proteasome inhibitor and an immunomodulatory agent and have failed an anti-CD38 antibody (DREAMM 2) |
| NCT04162210 ¹³¹ | BelMaf vs (Pom + Dex) | III | 380 | A phase III, open-label, randomized study to evaluate the efficacy and safety of single agent belantamab mafodotin compared to pomalidomide plus low dose dexamethasone in participants with RRMM (DREAMM 3) |
| NCT03848845 ¹³² | BelMaf + Pembro | I/II | 41 | A phase I/II single arm open-label study to explore safety and clinical activity of GSK2857916 administered in combination with pembrolizumab in subjects with RRMM (DREAMM 4) |
| NCT03544281 ^{133,134} | BelMaf + Dex + (Len or Bort) | I/II | 152 | A phase I/II, open-label, dose escalation and expansion study to evaluate safety, tolerability, and clinical activity of GSK2857916 administered in combination with lenalidomide plus dexamethasone, or bortezomib plus dexamethasone in participants with RRMM (DREAMM-6) |
| NCT04246047 ¹³⁵ | Bort + Dex + (BelMaf or Dara) | III | 478 | DREAMM 7: a multicenter, open-label, randomized phase III study to evaluate the efficacy and safety of the combination of belantamab mafodotin, bortezomib, and dexamethasone compared with the combination of daratumumab, bortezomib, and dexamethasone in participants with RRMM |
| NCT04484623 ¹³⁶ | Pom + Dex + (BelMaf or Bort) | III | 450 | A phase III, multicenter, open-label, randomized study to evaluate the efficacy and safety of belantamab mafodotin in combination with pomalidomide and dexamethasone versus pomalidomide plus bortezomib and dexamethasone in participants with RRMM (DREAMM 8) |
| NCT04091126 ¹³⁷ | Bort + Len + Dex (± BelMaf) | I | 144 | A Phase I, randomized, dose and schedule evaluation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of belantamab mafodotin administered in combination with standard of care in participants with newly diagnosed MM (DREAMM 9) |
| NCT04398745 | BelMaf | I | 36 | A phase I study to evaluate the pharmacokinetics and safety of belantamab mafodotin monotherapy in participants with RRMM who have normal and varying degrees of impaired renal function (DREAMM 12) |
| NCT04398680 | BelMaf | I | 28 | A phase I study to evaluate the pharmacokinetics and safety of belantamab mafodotin monotherapy in participants with RRMM who have normal and varying degrees of impaired hepatic function (DREAMM 13) |

Abbreviations: BelMaf, belantamab mafodotin; Bort, bortezomib; Dara, daratumumab; Dex, dexamethasone; Len, lenalidomide; Pembro, pembrolizumab; Pom, pomalidomide.

the earlier Phase I study. However, the toxic effect of greatest concern has been the corneal microcyst-like epithelial changes (MECs) that were observed with belantamab mafodotin as a single agent in 72% (68/95) of patients.¹²⁰ Neither corticosteroid eye drops nor artificial tears appeared to mitigate this toxic reaction, whose mechanism is unknown. MECs also have been a commonly reported issue in studies of patients receiving other ADCs that employ MMAF as the cytotoxic component.¹²¹ For this reason, FDA approval was accompanied by a Boxed Warning requirement indicating that changes in the corneal epithelium may result in vision loss, blurred vision, corneal ulcers, and dry eyes. Consequently, the drug is available only under a restricted Risk Evaluation and Mitigation Strategy (REMS) program.

Another BCMA-targeted ADC that has been in a phase I trial (NCT03489525) for RRMM is MEDI2228. Although this agent had shown some early promise in terms of efficacy and toxicity, it was recently announced that the drug has been dropped by its sponsor (AstraZeneca) from further consideration for MM. AMG 224, an IgG1 mAb, conjugated to the microtubule inhibitor mertansine via a maleimidocaproyl-derived non-cleavable linker, has shown some encouraging results in a phase I trial (NCT02561962) in which an ORR of 23% was reported in an initial study of 40 heavily pretreated RRMM patients.¹²²

Amanitin, an extremely potent inhibitor of RNA polymerase II that is produced by the deadly *Amanita phalloides* (“death cap”) mushroom, has come to the fore recently as a cytotoxin exhibiting a novel mode of action among ADCs. One such ADC is HDP-101, comprised of an amanitin analog coupled to a BCMA-targeted antibody via a cathepsin B-cleavable linker.^{123–125} Based on the highly favorable results of a pre-clinical study,¹²⁶ HDP-101 recently (May 2021) was advanced to a phase I safety-assessment trial (NCT04879043) in RRMM patients.¹²⁷

T-Cell-Engaging Bi-Specific Antibodies

T-cell-based immunotherapies have assumed major importance as viable approaches to cancer treatment, especially during the past decade. The field has been dominated particularly by two areas of research: chimeric antigen receptor (CAR) T-cell therapies and T-cell-engaging bi-specific antibodies (T-BsAbs). The latter will be described

in this section first while discussion of the former will be reserved for the following segment.

Based on a concept originally proposed sixty years ago by Nisonoff,¹³⁸ T-BsAbs are predicated on the construction of a dual-targeting antibody whereby one arm first binds to the T-cell CD3 co-receptor while the other arm subsequently is recruited to a TAA or TSA on the targeted cancer cell. Although there are numerous variations on this concept, the basic strategy results in tethering of cytotoxic T-cells to tumor cells in order to cause cytolysis of the latter.^{139–141} The destructive effects are due to the combined actions of two cytolytic-initiating proteins released by cytotoxic T-cells: perforin, which generates transmembrane pores in the tumor cells and granzyme B, which navigates through the formed pores to initiate apoptotic death of the tumor cell.^{142,143} The bi-specific antibody approach affords certain advantages by obviating the need for antibody-presenting cells, co-stimulatory molecules, or interaction between an antigen and a major histocompatibility complex (MHC) molecule. In addition, the persistent T-cell activation enables polyclonal expansion of T memory cells. Furthermore, such constructs remove any requirement for ex vivo T-cell manipulation, thus making “off the shelf” products feasible. Modification of each arm’s relative binding affinity for its respective target permits fine-tuning of each construct’s therapeutically relevant properties to optimize activity and biopharmaceutical parameters.^{144–147}

The first, and thus far only, successful application of the bi-specific antibody concept to cancer immunotherapy has been the result of a collaboration between Amgen and Micromet that developed the BiTE[®] (Bi-specific T-cell Engager) platform in which the crosslink between T-cell CD3 co-receptor and tumor cell lymphocyte antigen CD19, is provided by tandem single-chain variable fragments (scFvs). The resulting product, blinatumomab (Blinicyto[®]), was granted accelerated FDA approval in 2014 for use in B-cell precursor acute lymphocytic leukemia (B-cell ALL).^{148,149} However, extension of the blinatumomab success to RRMM has not been as favorable in terms of employing CD19 as a bi-specific binding partner. This may be related to the observation that CD19 expression by B-cells is known to progressively decrease throughout their development from the pre-B-cell stage to differentiation into plasma cells and even further during transformation into myeloma cells.^{150,151} This increasing loss of CD19 has been proposed as a contributing factor in

myeloma cell proliferation, which would appear to preclude realization of benefits of anti-CD19 therapy in MM. However, the recent finding of CD19 at very low levels on MM cells by super-resolution microscopy,¹⁵² although undetectable by conventional flow cytometry, may yet make CD19 an intriguing target for immunotherapy of MM. A single phase I RRMM-based trial (NCT03173430) of blinatumomab, combined with ASCT, unfortunately had to be terminated at an early stage because of “slow patient accrual”.

Although utilization of CD19 as a suitable binding partner for bi-specific antibodies in MM appears to be stymied at this point, BCMA, as in the ADC arena, has assumed a major role in BiTE[®] research.^{153–156} One such agent, AMG 420 (BI-836909) demonstrated favorable results in a phase I dose-escalation trial (NCT02514239), achieving a 31% ORR in 42 RRMM patients, including 70% (7/10) in those who received the maximum tolerated dose (400 mg/day). Infections and polyneuropathy were the most serious adverse events related to treatment. Cytokine release syndrome (CRS) (see below), primarily grade 1, was reported in 38% of patients in the study.¹⁵⁷ Pavurutamab (AMG 701), another BiTE[®] product from Amgen, with an extended serum half-life compared to AMG 420, is the subject of a phase I study (NCT03287908), both as monotherapy and in combination with pomalidomide; inclusion of the latter was suggested by the results of an earlier preclinical study.¹⁵⁸ Initial results from 75 heavily pretreated RRMM patients indicated that monotherapy with pavurutamab demonstrated encouraging activity and a manageable safety profile.¹⁵⁹ A recent press release revealed that this study has been paused in order to “discuss protocol modifications to optimize safety monitoring and mitigation with the FDA”.¹⁶⁰

Additional BCMAxCD3 bi-specific and related constructs that currently are in phase I trials for RRMM include the following:^{154,161}

- REGN5458 (NCT03761108) and REGN5459 (NCT04083534), under development by a Regeneron/Sanofi partnership. Thus far, both pre-clinical and preliminary patient data have been reported only for the former.^{162,163}
- Teclistamab (JNJ-64007957), which has been shown to be well tolerated in a monkey model¹⁶⁴ and has demonstrated other favorable characteristics in vitro,¹⁶⁵ has been included in a dose-escalation study (NCT03145181) in which an ORR of 78% (7/9) was

reported for patients receiving the highest dose while exhibiting a manageable safety profile.^{166–168}

- Elranatamab (PF-06863135; PF-3135), derived from hinge-mutation engineering of an IgG2a backbone,¹⁶⁹ has been the subject of a safety and efficacy investigation (NCT03269136) for which preliminary results have been reported.^{170–173} The drug’s advancement to a phase II trial recently was announced.¹⁷⁴
- CC-93269, a trivalent T-cell engager in which one arm binds to CD3ε while the other two arms attach bivalently to BCMA, exhibited promise in one cohort of heavily pretreated RRMM patients who attained an ORR of 83% (10/12) at the highest dose level (6 mg.) (NCT03486067).¹⁷⁵
- TNB-383B, a collaborative effort between AbbVie and Tenebio, is comprised of a single light chain domain and two variable heavy chains in a BCMAxCD3 format. Its strong T-cell activation kinetics and low-affinity anti-CD3ε arm are said to be responsible for the reduced level of cytokine release without diminishing cytotoxicity associated with the product.^{176–178} An ORR of 52% (12/23) at well-tolerated doses recently was reported in a preliminary study (NCT03933735) of TNB-383B, which received FDA designation as an Orphan Drug in 2019.^{179,180}
- HPN217, developed by Harpoon Therapeutics, is another example of a tri-specific engager. In this case, the molecule consists of three binding domains in a single chain: a BCMA-binding component at the N-terminus, a CD3ε T-cell receptor (TCR) binding domain at the C-terminus, and a central human serum albumin-binding portion. This product’s smaller size and flexibility are thought to account for its prolonged half-life.¹⁸¹ A recent report outlined the design of a phase I/II investigation of HPN217 in RRMM patients.¹⁸²

Targeting TAA or TSA receptors on NK cells represents an alternative strategy for development of BCMA-targeted bi-specifics. As with cytotoxic T-cells, NK cells release granzyme and perforin while they also express certain apoptosis-inducing ligands.^{183,184} A tri-specific engager that binds BCMA and CD200 on myeloma cells and CD16A on NK cells is one such example.^{106,185} Another is RO7297089 (AFM26), a bi-specific designed to engage myeloma cell BCMA and NK CD16A, which

exhibited an acceptable safety profile in preclinical work.¹⁸⁶ An additional example is Compass Therapeutics' bi-specific CTX-4419 in which the binding partners are myeloma cell BCMA and NK cell p30, demonstrating that although NK CD16A binding may enhance cytotoxicity, it may not be a requirement for anti-myeloma activity. Some promise has been shown in pre-clinical work on CTX-4419.¹⁸⁷ Similar properties have been noted for CTX-8573, another Compass entry into the anti-myeloma multi-specific antibody arena.¹⁸⁸

Myeloma surface antigens other than BCMA also have served as targets for bi-specific antibody development. A major candidate in this area is cevostamab (BFCR4350A; RO7187797), designed to bind T-cell CD3 with FcRH5,¹⁸⁹

expressed on virtually all myeloma cells and now the subject of two clinical trials for RRMM (NCT04910568 and NCT03275103).^{190,191} Among the other non-BCMA directed constructs also under investigation are the CD3xCD38 mAb found in GBR 1342 (NCT03309111),¹⁹² a CD3xCD20 bi-specific,^{193,194} and talquetamab (JNJ-64407564), a bi-specific construct designed to link CD3 to G-protein-coupled receptor class C group 5 member D (GPCR5D), a TAA expressed at high levels in malignant plasma cells but limited to hair follicles and lung tissue in healthy individuals.^{168,195–197} An initial phase I evaluation (NCT03399799) of talquetamab monotherapy reported ORRs of 78% (14/18) when given iv and 67% (8/12) when used sc.¹⁹⁶ Also under study are combinations of subcutaneous daratumumab (with or without pomalidomide)

Table 5 Selected Trials of T-Cell Engaging Bi-Specific Antibodies in Multiple Myeloma (MM)

| Trial ID (References) | Treatment | Phase | Enrollment (N) | Trial Title |
|--------------------------------|--|-------|----------------|---|
| NCT02514239 ¹⁹⁸ | AMG 420 | I | 43 | An open label, phase I, dose escalation study to characterize the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous doses of AMG 420 in RRMM patients |
| NCT03287908 ^{159,199} | AMG 701 alone vs (AMG 701 + Pom ± Dex) | I/II | 408 | A phase I/II open-label study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of pavurutamab (AMG 701) monotherapy, or in combination with pomalidomide, with and without dexamethasone in subjects with RRMM (ParadigmMM-1B) |
| NCT03761108 ^{162,200} | REGN5458 | I/II | 200 | Phase I/II FIH study of REGN5458 in patients with RRMM |
| NCT03145181 ¹⁶⁷ | Tecl | I | 204 | A phase I, first-in-human, open-label, dose escalation study of teclistamab in subjects with RRMM |
| NCT04649359 | Elra | II | 150 | MAGNETISMM-3 an open-label, multicenter, non-randomized phase II study of elranatamab (PF-06863135) monotherapy in participants with MM who are refractory to at least one proteasome inhibitor, one immunomodulatory drug and one anti-CD38 antibody |
| NCT03486067 | CC-93269 | I | 175 | A phase I, open-label, dose finding study of CC-93269, a BCMA X CD3 T cell engaging antibody, in subjects with RRMM |
| NCT03933735 ¹⁸⁰ | TNB-383B | I | 133 | A multicenter, phase I, open-label, dose-escalation and expansion study of TNB-383B, a bi-specific antibody targeting BCMA in subjects with RRMM |
| NCT04184050 | HPN217 | I/II | 70 | A phase I/II open-label, multicenter, dose escalation and dose expansion study of the safety, tolerability, and pharmacokinetics of HPN217 in patients with RRMM |
| NCT04434469 | RO7297089 | I | 80 | An open-label, multicenter, phase I trial evaluating the safety and pharmacokinetics of escalating doses of RO7297089 in patients with RRMM |
| NCT03399799 ¹⁹⁶ | Talq | I | 245 | A phase I, first-in-human, open-label, dose escalation study of talquetamab in subjects with RRMM |

Abbreviations: Dex, dexamethasone; Elra, elranatamab; Len, lenalidomide; Pom, pomalidomide; Talq, talquetamab; Tecl, teclistamab.

plus either talquetamab or the above-noted teclistamab (NCT04108195).

A list of selected clinical trials that include T-cell engaging bi-specific antibodies is shown in [Table 5](#).

Chimeric Antigen Receptor (CAR) T-Cells

Over the past decade, chimeric antigen receptor (CAR) T-cell therapy has risen to a place of prominence as a viable immunotherapeutic approach to cancer treatment.^{201,202} As a form of adoptive cell transfer (ACT), this strategy endeavors to genetically modify a patient's own cytotoxic T-cells to enable them to attack and kill a specific type of malignant cell. By employing recombinant DNA technology a viral vector is constructed so as to enable eventual expression of a chimeric receptor designed to attach to a TAA or TSA found on the targeted cancer cell. Reinfusion of the engineered T-cells back into the patient results in T-cell engagement with the targeted malignant cells leading to their death. The technique has been most successfully applied to the treatment of hematological cancers, particularly B-cell malignancies, targeting CD19 although such has not been the case when applied to MM for reasons described earlier. For example, a trial of the anti-CD19 CAR tisagenlecleucel combined with ASCT only resulted in a poor clinical benefit in a cohort of ten MM subjects (NCT02135406).²⁰³

The attainment of durable remissions with anti-CD19 CAR T-cells initially proved difficult even though ORRs in excess of 80% were seen in some early studies.^{204–207} The solution to this conundrum eventually was revealed when the value of adding lymphodepletion to the pre-ACT regimen became clear. The benefits of lymphodepletion, usually consisting of combined cyclophosphamide and fludarabine, were demonstrated in several CAR T-cell-based trials by reports of enhanced T-cell persistence and expansion, as well as clinical outcomes.²⁰⁸ Although the mechanism underlying the improved efficacy associated with lymphodepletion remains obscure, several possibilities have been proposed, including elimination of homeostatic cytokine sinks for interleukins-2, -7, and -15,²⁰⁹ greater levels of monocyte chemoattract protein-1 (MCP-1),²¹⁰ and downregulation of tumor cell indoleamine 2,3-dioxygenase (IDO)²¹¹ to block formation of tryptophan-derived metabolites known to inhibit T-cell activity and induce tolerance to tumor antigens.²¹² Parenthetically, it is noteworthy that linrodostat (BMS-986205),²¹³ an oral

irreversible inhibitor of IDO1, has been included in a CAR T-cell-based MM trial (NCT04855136) that was started in April 2021.

Just as seen above with bi- and multi-specific antibodies, BCMA has taken its place as the major TSA of interest in anti-myeloma CAR T-cell research.^{155,214} Several of the anti-BCMA constructs of consequence are described below, and [Table 6](#) lists several of the currently active myeloma-based anti-BCMA CAR T-cell trials.

The first clinical trial (NCT02215967) of an anti-BCMA CAR T-cell construct utilized a lentivirus engineered paradigm in which the anti-BCMA scFv was linked in series to a CD8 hinge, a transmembrane region, a CD28 co-stimulatory domain, and CD3 ζ as the T-cell activator.²¹⁵ Data reported for 16 RRMM patients in the study (median of 9.5 lines of prior therapy) showed a median PFS of 31 weeks and an ORR of 81% at the highest dose used (9×10^6 T-cells per kg).²¹⁶ This encouraging result led to a phased series of KarMAa trials of Bluebirdbio's idecabtagene vicleucel (Abecma[®]; bb2121; ide-cel), whose structure included an anti-BCMA scFv linked to CD137 (4-1BB) co-stimulatory and CD3 ζ signaling domains.²¹⁷ The product was approved by the FDA in March 2021 for RRMM²¹⁸ based on the results of a pivotal phase II trial (NCT03361748; KarMAa-1) that incorporated 128 RRMM patients who had failed at least three previous regimens, including a proteasome inhibitor, an immunomodulator, and an anti-CD38 mAb. An ORR of 73% (94/128) was attained and one-third (42/128) experienced complete responses or better. The median PFS was 13.3 months. CRS was the most common non-hematologic adverse effect, being found in 84% of treated subjects with 5% experiencing grade 3 or 4. Neurotoxicity developed in 23 (18%) patients – four in grade 3 and none in grade 4.²¹⁹ Bluebirdbio's next generation entry into the field, bb21217, employs the same lentiviral design as its predecessor with the addition during ex vivo culture of an extra phosphoinositide-3-kinase (PI3K) inhibitor domain (bb007). This modification significantly enhances CAR T-cell-based immunotherapy by enriching the product's population of memory-like T-cells to enhance T-cell durability and potency.²²⁰ The drug was the subject of two recent reports of an ongoing dose-escalation study (NCT03274219) of 44 RRMM patients. Confirmed responses were noted in 24 (55%) patients with CRS and neurotoxicity observed in 67% and 10%, respectively. Preliminary data indicated a positive correlation between

Table 6 Selected Trials of CAR T-Cells in Multiple Myeloma (MM)

| Trial ID (References) | Treatment | Phase | Enrollment (N) | Trial Title |
|------------------------------------|--|-------|----------------|---|
| NCT03361748 ^{219,271} | Ide-cel | II | 149 | A phase II, multicenter study to determine the efficacy and safety of ide-cel in subjects with RRMM (KarMMa) |
| NCT03601078 | Ide-cel | II | 181 | A phase II, multicohort, open-label, multicenter study to evaluate the efficacy and safety of ide-cel in subjects with RRMM and in subjects with clinical high-risk MM (KarMMa-2) |
| NCT03651128 | Ide-cel vs 5 different standard of care regimens | III | 381 | A phase III, multicenter, randomized, open-label study to compare the efficacy and safety of ide-cel vs standard regimens in subjects with RRMM (KarMMa-3) |
| NCT03274219 ^{221,222,272} | bb21217 | I | 72 | A phase I study of bb21217 in RRMM |
| NCT03090659 ^{223–225} | Cilta-cel | I/II | 100 | A clinical study of cilta-cel in treating RRMM |
| NCT03548207 ^{226,273} | Cilta-cel | I/II | 126 | A phase Ib-II, open-label study of cilta-cel, a CAR-T therapy directed against BCMA, in subjects with RRMM (CARTITUDE-1) |
| NCT04133636 ²²⁸ | Cilta-cel | II | 160 | A phase II, multicohort open-label study of cilta-cel, a CAR-T therapy directed against BCMA in subjects with MM (CARTITUDE-2) |
| NCT03288493 ²³² | P-BCMA-101 + Rimiducid | I/II | 220 | Open-label, multicenter, phase I study to assess the safety of P-BCMA-101 in subjects with RRMM followed by a Phase 2 assessment of response and safety (PRIME) |
| NCT03915184 ²³⁸ | Zevo-cel | I | 70 | Open label, multi-center, phase Ib/II clinical trial to evaluate the safety and efficacy of autologous zevo-cel in patients with RRMM (LUMMICAR 2) |

Abbreviations: Cilta-cel, ciltacabtagene autoleucl; Ide-cel, idecabtagene vicleucl; Zevo-cel, zevorcabtagene autoleucl.

the presence of memory-associated T-cell markers and peak expansion and duration of response, providing some tentative support for the mechanistic hypothesis underlying the product's design.^{221,222}

Johnson and Johnson's contribution to this arena is ciltacabtagene autoleucl (JNJ-68284528; JNJ-4528; LCAR-B38M; cilta-cel), which differs from other BCMA-targeted T-cell therapies by being directed against two BCMA epitopes (VH1 and VH2), a feature which improves affinity for BCMA-expressing cells. The phase I LEGEND-2 study (NCT03090659) of this product was conducted on 57 patients who showed an ORR of 88% and PFS of 15 months. There was evidence of CRS, primarily grades 1 or 2 in 83% of trial subjects.^{223–225} Reported results from 97 RRMM patients (median of 6 prior lines of therapy) in the CARTITUDE-1 phase Ib/II trial (NCT03548207) were similar (97% ORR, CRS 95%) to those seen in the LEGEND-2 study.²²⁶ As a result of data from the LEGEND-2 and CARTITUDE-1 studies, in 2019 this drug was accorded PRIME status by the European Medicines Agency (EMA) and was designated

a Breakthrough Therapy and subsequently granted priority review by the FDA.²²⁷ Two additional studies of the efficacy of ciltacabtagene autoleucl in RRMM currently are in progress: CARTITUDE-2 (NCT04133636) and CARTITUDE-4 (NCT04181827). Recently reported data from the former trial (phase II) indicated deep and early responses with a single infusion.²²⁸ The latter is a phase III comparison with two standard myeloma triplet therapies; no results have been reported as yet from this trial.

P-BCMA-101, a fully humanized anti-BCMA CAR T-cell product from Poseida Therapeutics, contains a CD3 ζ /4-1BB signaling domain fused to a non-immunoglobulin Centyrin[®] scaffold. Such constructs generally are smaller than those patterned after immunoglobulins and offer advantages of higher binding affinities, improved stability, reduced immunogenicity, and lower production costs. Instead of using a viral vector in the manufacturing process, P-BCMA-101 employs proprietary transposon-based technology (piggy-BAC[®]).²²⁹ The process has been shown in preclinical work to yield a preponderance of T stem cell

memory cells (Tscm), offering the potential for improved therapeutic longevity.²³⁰ The product also is noteworthy for the inclusion in its design of a truncated caspase 9 domain as a safety switch. Rimiducid, a caspase 9 dimerizing agent, can be administered to initiate apoptosis if patient safety is threatened.²³¹ P-BCMA-101 has been the subject of a phase I trial (NCT03288493; PRIME) in heavily pretreated RRMM patients. An ORR of 57% after a single administration recently was reported for a cohort of 34 evaluated subjects in the study. CRS, one in grade 3, was observed in 17% of the patients. A possible case of neurotoxicity also was reported.²³² A long-term (15 years) follow-up study (NCT03741127) has been initiated to explore in-depth issues of this product's efficacy and toxicity.

Orvacabtagene autoleucel (orva-cel; JCARH125) and FCARH143 are two similar fully human svFv bicistronic CARs that incorporate a 4–1BB co-stimulatory domain and use a lentiviral vector although they differ in the method of production.^{233,234} Initial results of a trial (NCT03430011) of orva-cel in 51 RRMM patients reported an ORR of 91% while exhibiting a manageable safety profile.^{234,235}

Zevorcabtagene autoleucel (zevo-cel; CT053) and CT103A are two BCMA-targeted CAR T-cell products under development by CARsGen Therapeutics. Both are fully human scFv constructs, containing a CD8 α hinge, 4–1BB co-stimulatory and CD3 ζ activation domains, in addition to a transmembrane component. In 2019, the FDA granted CT053 the Regenerative Medicine Advanced Therapy (RMAT) designation, based on the initial results of two trials (NCT03975907, LUMMICAR-1; and NCT03915184, LUMMICAR-2) in RRMM patients who previously had been treated with a median of four prior regimens.^{236,237} Updated results on 10 evaluable patients in the LUMMICAR-2 trial were presented recently and showed an ORR of 100% at a dose of 1.5–3.0 $\times 10^8$ CAR T-cells.²³⁸ Notable early results also have been reported for the related construct CT103A, which recently has been under study in the RRMM setting in China (ChiCTR1800018137): ORR of 100% in the first 18 patients in this phase I trial.^{239,240} Numerous other strategic approaches to BCMA-based autologous CAR T-cell product development are represented in the array of currently active clinical trials extant in the NCI data base for MM. Included among these products are CART-ddBCMA,²⁴¹ C-CAR088,²⁴² and FHVH-BCMA-T.^{243,244}

Both CD19- and BCMA-targeted CAR T-cells have been used in combination in some trials in order to

enhance efficacy, improve patient safety, and deepen clinical response. Simultaneous targeting of BCMA and SLAMF7 also is being studied.²⁴⁵ The dual-targeting strategy may involve co-infusion of two different pools of T-cells each expressing a different CAR or a single T-cell pool in which each T-cell expresses two different CARs (arranged either bicistronic or in tandem).^{246–249} For example, dual targeting has been explored in trials in newly diagnosed high-risk MM (NCT03455972) and in RRMM patients (NCT03196414). A recent review detailed the various combinations of dual-targeting strategies.²⁵⁰ However, meaningful patient data from trials of these dual-targeted combinations in MM have thus far been very limited.^{249,251–253} Future work needs to focus on the relevance of the various combinatorial approaches to the different stages of MM from newly diagnosed patients to those who fail established regimens.

Finally, preclinical data have informed trials of CAR T-cells that are directed against TSAs or TAAs other than BCMA. These targets include SLAMF7 (NCT03958656; NCT03710421),^{254,255} CD38 (NCT03464916),²⁵⁶ and CD138.²⁵⁷ However, only limited patient data are available on these studies. Alternatives to T-cells also have been explored in efforts to expand available options to treat RRMM. The primary contemporary candidates here are anti-BCMA-engineered NK cells;^{256,258–260} although SLAMF7 and CD138 also have been considered as NK cell targets in the past.^{261,262} Nevertheless, only a single trial (NCT03940833), involving a product from Asclepius Technology in China, is now in progress to explore the potential role of BCMA-directed NK-engineered CARs in RRMM.

Although the autologously administered CAR T-cells described above have thus far produced highly promising results, their use is not without drawbacks, such as the short-lived responses they elicit and the high risk of CRS and other dose-limiting adverse events. As a result, some CAR T-cell originators have initiated innovative programs to develop “off-the shelf” allogeneic anti-BCMA products that use T-cells from healthy donors. The pipeline of agents in this category currently is headed by two major players: ALLO-715 from Allogene Therapeutics and Precision Bioscience's PCAR269A.

ALLO-715 is manufactured using the proprietary Transcription Activator-like Effector Nuclease (TALEN[®]) system, a site-specific BCMA gene-editing technique that is hypothesized to limit the product's potential T-cell receptor-mediated immune responses,

such as graft versus host disease (GvHD) and rapid rejection.^{263,264} Recently (April 2021), ALLO-715 received the FDA's RMAT designation,²⁶⁵ which was based on the initial findings of the dose-escalation phase I UNIVERSAL trial (NCT04093596) of 15 heavily pre-treated RRMM patients in whom were reported an acceptable safety profile and an ORR of 33% at the dose levels tested.²⁶⁶ Significantly, ALLO-715 is the first anti-BCMA CAR T-cell product whose design strategy incorporates a CD20-based mimotope capable of activation by rituximab. Moreover, the UNIVERSAL trial also is noteworthy for its use of an anti-CD52 antibody, ALLO-647, as a selective lymphodepletion agent.²⁶⁷

PBCAR269A was developed using Arcus Bioscience's patented nuclease gene-editing platform, which is based on the homing endonuclease I-CreI scaffold.^{268,269} In 2020, this product received Fast-Track status from the FDA²⁷⁰ and was advanced to a phase I trial for RRMM (NCT04171843).

Cytokine Release Syndrome (CRS) and Neurotoxicity

Issues related to toxicity constitute important challenges that effect immunotherapy of hematologic cancers, including the bi- and multi-specific engaging antibodies and CAR T-cell platforms described in this review. These potentially lethal toxicities, whose inability to be easily reversed may require multidisciplinary management and intensive care, often are divided into two different types: 1) a general toxicity caused by T-cell recognition and activation against the targeted malignant cells and subsequent uncontrolled cytokine release at high levels (on-target, on-tumor toxicity) and 2) toxicity caused by cytokine release when CAR T-cells bind to the target antigen located on normal cells (on-target, off-tumor toxicity). BCMA-targeted anti-multiple myeloma products carry a low-risk of on-target, off-tumor type reactions given the virtually exclusive confinement of the antigen to plasma cells. The discussion that follows is devoted to the on-target, on-tumor types of adverse events.

The most important adverse effects that accompany on-target, on-tumor toxicity are the cytokine release syndrome (cytokine storm; CRS) and neurotoxicity. Two terms often are used in the literature to describe the neurotoxic reactions: CAR T-cell-related encephalopathy syndrome (CRES) and immune effector cell-associated neurotoxicity syndrome (ICANS). Almost without exception, CRS and neurotoxicity are seen in varying degrees of severity in

a percentage of participants in every trial of the immunotherapeutic agents described in this paper.^{274,275} For instance, in the CAR T-cell therapy setting meta-analysis of 15 trials (N=977) of anti-CD19 or anti-BCMA constructs, 62.3% (range: 11% to 100%) experienced some degree of CRS with 18.4% (range 0.8% to 46%) in grades 3 or 4.²⁷⁶ Also, attempts to assess relative safety risks between different immunotherapeutic modalities may present complex problems. For example, meta-analysis of 8 clinical trials of anti-CD19 blinatumomab in relapsed/refractory ALL and NHL patients (N=729) found that the pooled occurrence rate of CRS of grades 3 or 4 was 3.5% and that of neurotoxicity was 12%.²⁷⁷ These data compare with the 19% and 18% respective rates of grades 3 or higher found in a recent meta-analysis of 15 trials (N=448) of RR B-cell ALL patients who received C-19-specific CAR T-cell therapy.²⁷⁸ Although tending to indicate that CRS and neurotoxicity may occur with greater frequency and severity in patients receiving CAR T-cell therapy as opposed to bi-specific antibody therapy, at least in terms of treatments targeting CD16, a number of factors, including type of malignancy under study, structure and target of the immunotherapeutic product involved, the grading scales used, and routes and timing of administration, as well as other variables may account for observed differences.

The symptoms of CRS, which generally occur in the first two weeks of therapy and resemble those of a severe inflammatory reaction, are attributed to marked increased expression and release of certain cytokines, including IL-6, IL-2R, IL-10, IFN- γ , and TNF- α .^{279,280} Furthermore, CRS has been effectively implicated as a major contributor to the deadly effects associated with COVID-19 infections during the current global pandemic.^{281–284} The IL-6 blocker tocilizumab (Actemra[®]) is the treatment of choice for cases of CRS associated with CAR T-cell therapy, FDA approval for this indication having been granted in 2017.²⁸⁵ However, optimal timing of tocilizumab intervention in patients at-risk for CRS remains an open question.^{286,287} In addition, the agent usually is administered with corticosteroid infusions although the efficacy of combining corticosteroids with tocilizumab in the management of CRS has not been tested through randomized controlled studies.

ICANS/CRES symptoms, which typically begin around 4–5 days after initiation of CART-cell therapy and usually follow the peak of CRS severity, are related to impairment of blood–brain barrier (BBB) integrity enabling CSF cytokine and lymphocyte infiltration.

Tocilizumab is not effective in the management of neurotoxicity. Rather, glucocorticoids play the major role in its treatment although their efficacy remains undocumented.^{288–290}

In efforts to gain better control over toxicity of CAR T-cell therapy some formats have been designed to incorporate a safety switch to enable activity curtailment through administration of a pharmacologic antagonist.²⁹¹ Inclusion in the construct of a transduced CD20 receptor that can be switched “off” by administration of the CD20 blocker rituximab is one illustration of this strategy.²⁹² Another is the incorporation of a non-functional truncated epidermal growth factor receptor (tEGFR) that can be antagonized by cetuximab.^{293,294} Dimerization of caspase-9 to activate apoptosis by use of the dimerizing agent rimiducid represents yet another example.^{295–297} The strengths and weaknesses of the various molecular safety switches employed in CAR T-cell design have been described in a recent comprehensive review of the subject.²⁹⁸

Checkpoint Inhibitors

Over the course of the past decade, immune checkpoint blockade has become a major strategy for immunotherapeutic drug development in the anticancer field. The approach is predicated on the interaction of specific cell surface biomarkers and their cognate ligands that enable the immune system to overcome the ability of malignant cells to evade immune surveillance and elimination. This tactic has resulted in the introduction of several antitumor mAbs designed to block these biomarker/ligand interactions. In particular, two of these biomarkers cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and the programmed death (PD) receptor thus far have been successfully applied as targets in this innovative line of attack on a variety of cancers.¹³ However, their utility as targets in MM has yet to be conclusively demonstrated.²⁹⁹ Two myeloma-based trials (NCT01592370 and NCT02681302) of the anti-CTLA-4 mAb ipilimumab combined with another checkpoint inhibitor, nivolumab, are currently ongoing. An initial report in the latter trial concluded that the combined checkpoint inhibitor therapy is safe and has potential to increase the “depth of response in patients with high-risk disease”.³⁰⁰ Encouraging results were seen in early phase studies of PD-1 blocker pembrolizumab in MM, especially when used together with immunomodulators.³⁰¹ However, major safety issues arose concerning these pairings in phase III trials, resulting

in suspension of these studies although it is noteworthy that additional combinations of pembrolizumab and other PD-1/PD-L1 blockers continue to be studied in MM as shown in Table 7. In addition to those studies shown in the table is a myeloma-based trial (NCT03111992; N=26) in which the PD-1 blocker spartalizumab was combined with an anti-IL17A mAb (CJM112) and a SMAC (second mitochondrial-derived activator of caspases) mimetic (LCL161); no results have yet appeared for this recently completed study.

In addition to CTLA-4 and PD-1/PD-L1, other checkpoints have been proposed as potential targets for immunotherapy in general or MM specifically although only limited preclinical or clinical data are available at present.³⁰² These include killer-cell immunoglobulin-like receptors (KIR),^{259,303} CD47,^{304,305} LAG3,³⁰⁶ TIGIT,^{307–309} and TIM-3.³¹⁰ In this connection, note should be made of an ongoing phase I/II trial (NCT04150965; N=104) in which RRMM patients receiving the anti-LAG3 relatlimab (BMS-986016) or anti-TIGIT BMS-986207 are compared to a control arm receiving a standard care regimen of elotuzumab-pomalidomide-dexamethasone.

Summary and Conclusions

The therapeutic landscape of MM has shifted dramatically in the past two decades as the number of treatment options has expanded enormously and five-year survival rates, progression-free survival data, and quality of life studies continue to evidence major advances.³¹³ The disease itself has become redefined over the years, moving away from the traditional CRAB symptoms to a risk stratification approach that aims to identify factors that can be determinant before signs and symptoms of the disease emerge, such as the progression from asymptomatic MGUS to SMM to MM. These criteria, encompassing bone marrow evaluation, immunoglobulin and free light chain analyses, cytogenetic studies, and imaging technologies, have become pillars of contemporary diagnostic evaluation, prognostication of disease course, and determination of intervention strategies.⁷ This optimism has been invigorated further in recent years by the advent of immunologic-based approaches to cancer treatment in general and MM in particular. Once considered an idealistic fantasy, cancer immunotherapy has now emerged as a validated fixture in medicine, grounded in decades of work aimed at deciphering the fundamental complex relationships between the immune system and cancer initiation, proliferation, and metastasis. This bright picture is tempered,

Table 7 Selected Trials of Checkpoint Inhibitors in Multiple Myeloma (MM)

| Trial ID (References) | Treatment | Phase | Enrollment (N) | Trial Title |
|----------------------------|--|-------|----------------|--|
| PD-I Inhibitors | | | | |
| NCT03848845 ¹³² | Pembro + BelMaf | I/II | 41 | A phase I/II single arm open-label study to explore safety and clinical activity of GSK2857916 administered in combination with pembrolizumab in subjects with RRMM (DREAMM 4) |
| NCT04361851 ³¹¹ | Pembro + Dara | II | 33 | Phase II Study of daratumumab-pembrolizumab for MM patients with \geq three prior lines of therapy |
| NCT03267888 | Pembro + Radiation | I | 24 | Pilot study of pembrolizumab and single-fraction, low-dose, radiation therapy in patients with RRMM |
| NCT03292263 | Niv + ASCT | I | 30 | Autologous stem cell transplantation with nivolumab in patients with MM |
| NCT04205409 | Niv | II | 20 | Nivolumab for relapsed or refractory disease post CAR T-cell treatment in patients with hematologic malignancies, including MM |
| NCT04119336 | Niv + Ixazo + Ctx + Dex | II | 50 | A phase II study of nivolumab in combination with ixazomib, cyclophosphamide, and dexamethasone in RRMM |
| NCT03194867 | Isa + Cem | I/II | 109 | A phase I/II study to evaluate safety, pharmacokinetics and efficacy of isatuximab in combination with cemiplimab in patients with RRMM |
| PD-L1 Inhibitors | | | | |
| NCT02431208 ³¹² | [Atz \pm Len] or [(Atz + Dara) \pm (Len or Pom)] | I | 85 | A phase Ib study of the safety and pharmacokinetics of atezolizumab alone or in combination with an immunomodulatory drug and/or daratumumab in patients with MM |
| CD47 Inhibitors | | | | |
| NCT03530683 ³⁰⁵ | TTI-622 | I | 156 | A phase Ia/Ib dose escalation and expansion trial of TTI-622 in patients with advanced relapsed or refractory lymphoma or myeloma |

Abbreviations: Atz, atezolizumab; BelMaf, belantamab mafodotin; Cem, cemiplimab; Ctx, cyclophosphamide; Dara, daratumumab; Dex, dexamethasone; Isa, isatuximab; Ixazo, ixazomib; Len, lenalidomide; Niv, nivolumab; Pembro, pembrolizumab; Pom, pomalidomide.

however, by the knowledge that MM is still considered incurable regardless of the treatment measures used. The vast majority of patients who experience initial therapeutic benefits eventually become refractory to treatment modalities and experience relapse. Thus, although much progress has been made to date, the obstacles that remain must be overcome if MM is ever to be considered curable.

Fundamental to MM immunotherapy is the challenge to identify potential cancer-driving biomarkers that can serve as targets for therapy. At the forefront of this search are CD38, SLAMF7, and BCMA, which serve as the basis for the immunotherapies in use today. CAR T-cell-based therapies targeting BCMA have demonstrated remarkable clinical efficacy in MM with ORRs of at least 80% recorded in several clinical studies; however, response durations are short. It is now recognized that BCMA

expression by myeloma cells is not as homogeneous as once thought. For example, one study found that a substantial proportion (33/85) of MM patients was BCMA-negative.²¹⁵ Moreover, downregulated tumor-cell BCMA expression (antigen escape) has been reported during CAR T-cell therapy, as well as instances in which a significant fraction of initially responding patients experienced relapse despite continuing to express BCMA.^{216,246,314–317} Furthermore, a genome-wide gene-editing CRISPR study failed to identify BCMA as being among 90 different genes essential for MM.³¹⁸ Thus, combinatorial strategies using BCMA and other established targets, such as CD19, CD38, and SLAMF7 or emerging viable targets, for instance GPRC5D³¹⁹ and FcRH5,¹⁹⁰ may be of value in overcoming this issue.²⁵⁰ The orphan receptor GPRC5D has special appeal as

a target in immunotherapy constructs since its expression is associated with poor prognosis in MM.³²⁰ Moreover, as a seven-pass transmembrane protein it, unlike BCMA, does not shed into the serum. In addition, expression of GPRC5D is independent of BCMA, offering the possibility of a suitable alternative target in instances of anti-BCMA therapy relapse. The encouraging results, noted earlier, from myeloma-based studies of the CD3xGPRC5D bi-specific talquetamab should inform future clinical exploration of the potential of GPRC5D-targeted CARs. Indeed, this prospect was bolstered by the finding that anti-GPRC5D CAR T-cells produced long-term survival, accompanied by disease eradication, in a myeloma mouse model resistant to BCMA-targeted therapy.³¹⁹

As CAR T-cell and T-BsAb-based immunotherapies become more widespread in the future, the role of ASCT in MM patients who are considered transplant-ineligible, generally defined as elderly (over 75 years) and/or exhibiting frailty and possible comorbidities, will need to be more clearly defined. Current treatment protocols tend to favor the combination of daratumumab, lenalidomide, and dexamethasone for newly diagnosed and RRMM patients who are ASCT ineligible.²⁴ However, much more work lies ahead, including the need to conduct head-to-head comparison trials, in order to adequately serve this patient population.³²¹

Going forward, much better insight into the mechanisms that drive resistance to MM therapy needs to be gained. A key to deepening our knowledge in this area is the bone marrow microenvironment and the role it plays in enabling malignant cells to escape immune detection. Better understanding of the mechanisms at play here will contribute to future advances that will translate into further improving immunotherapeutic outcomes for MM, including the ability to reverse bone loss.³²² In addition to PFS, OS, ORR, and other measures, the ability to detect minimal residual disease (MRD) is now emerging as a key element in directing anti-myeloma therapy. Achievement of MRD negativity is increasingly viewed as a reliable prognostication marker of PFS and potential relapse.³²³ As technological advances enable malignant cell detection at extremely low levels, MRD measurements need to be more consistently and uniformly employed in clinical trials in order to drive therapeutic decision-making in the future.

The upsurge in knowledge gained about MM and its treatment over the past twenty years has been most impressive. The deeper understanding of the mechanisms that underlie the disease and the identification of an array

of druggable biomarkers have been translated into more efficacious treatments that enable positive outcomes with greater frequency, elevating the disease to its current status as a reasonably manageable chronic condition, at least in the short-term. However, the road to a true cure for MM remains fraught with challenges which, although not insurmountable, will need to be overcome for that dream to become a future reality.

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Disclosure

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