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Myeloma: next generation immunotherapy

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The course of multiple myeloma (MM) from initial diagnosis to a relapsed/refractory state is characterized by acquisition of drug resistance as well as progressive immunologic dysfunction. Despite this, however, a number of novel therapies that work in part or solely via immune stimulation are in development for MM, with promising early clinical results. Several new whole-cell or multiepitope vaccine approaches are demonstrating immunologic efficacy in smoldering MM or as posttherapy consolidation, with trials ongoing to see whether this translates into delayed progression or elimination of minimal residual disease. Programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibition in combination with immunomodulatory drugs demonstrated excessive toxicity in randomized trials; however, antibodies targeting PD-1/PD-L1 and other checkpoint molecules continue to be explored in combination with tumor-targeted antibodies and other T cell–directed therapies. B-cell maturation antigen (BCMA) has emerged as the next big antigen target, with multiple BCMA-specific antibody-drug conjugates (ADCs) and T cell–directed bispecific antibodies/bispecific therapeutic engagers (BiTEs) entering the clinic. In initial trials, the ADC GSK2857916 and the BiTE AMG 420 have demonstrated high response rates in relapsed/refractory patients, with depth and durability of responses that may end up rivaling chimeric antigen receptor T-cell therapies. These agents have unique toxicities that require close monitoring, but they are moving forward in larger registration studies and in combination with standard MM agents. Additional ADCs and bispecific antibodies targeting BCMA and other surface antigens (eg, CD38, CD46, CD48, FcRH5, and G protein–coupled receptor, class C group 5 member D) are moving forward in phase 1 trials and may provide even more options for MM patients.

Learning Objectives

- Understand different immunotherapeutic modalities being explored for multiple myeloma, including vaccines, checkpoint inhibitors, antibody-drug conjugates, and bispecific antibodies/bispecific therapeutic engagers (BiTEs)
- Review initial clinical efficacy and toxicity data for B-cell maturation antigen–targeted antibody-drug conjugates and BiTEs in relapsed/refractory myeloma

Clinical case

A 66-year-old woman was diagnosed with immunoglobulin G (IgG) κ multiple myeloma (MM) 7 years ago with diffuse lytic lesions and anemia, revised International Staging System stage 2 with deletion 13q and gain 1q by fluorescence in situ hybridization (FISH). She received VRD (bortezomib, lenalidomide, and dexamethasone) followed by autologous stem cell transplant (autoSCT) and lenalidomide maintenance, achieving a complete response (CR), but she had disease progression after 2.5 years. She then got cyclophosphamide, bortezomib, and dexamethasone followed by another autoSCT, achieving very good partial response (VGPR), followed by bortezomib maintenance, with progression after 1.5 years. Subsequent regimens included daratumumab, lenalidomide, and dexamethasone; carfilzomib, pomalidomide, and dexamethasone; and bortezomib, panobinostat, and dexamethasone, with initial response followed by progressive disease on all of them. Three months ago, she started elotuzumab, pomalidomide, and dexamethasone, with continued biochemical progression. She currently has grade 1 neuropathy, Eastern Cooperative Oncology Group performance status of 1, and preserved blood counts and renal function. Bone marrow biopsy reveals 50% myeloma cells with acquisition of deletion 17p by FISH. She asks what additional treatment options are available to her and is specifically interested in immunotherapy trials.

Introduction

Despite all of the recent advances in MM treatment, resistance eventually develops, and patients become refractory to standard therapies. Several new approaches to MM treatment now entering the clinic seek to overcome this resistance by harnessing surrounding immune effector cells to eliminate the malignant plasma cells rather than directly targeting the MM itself. This has been a challenging task, because progressive MM is associated with multiple immune evasion techniques and induction of significant dysfunction within multiple immune cell compartments, including T, B, natural killer (NK), and myeloid cells (as recently reviewed[1]). Nonetheless, multiple therapeutic modalities have now demonstrated the ability to induce or enhance anti-MM immunity even in advanced patients, leading to promising clinical activity in early trials. In this work, we will review the latest data for several of these modalities, including

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therapeutic vaccines, checkpoint inhibitors, antibody-drug conjugates (ADCs), and bispecific antibodies, focusing on therapies that have entered the clinic. Adoptive cellular therapies, such as marrow-infiltrating lymphocytes and chimeric antigen receptor (CAR) T cells, will be covered in depth elsewhere in this book.

Vaccines

Several studies over the past decade have demonstrated the feasibility of breaking immune tolerance in MM patients through active vaccination, generating both antibody and T-cell responses against self/MM tumor antigens, such as hTERT, survivin, MAGE-A3, and idiotype.[2-5] All of these studies used either peptide or whole-protein vaccines targeting a single antigen given in conjunction with autoSCT as well as vaccine-primed autologous lymphocyte infusion, trying to take advantage of post-SCT immune reconstitution to induce a more robust anti-MM response. Despite demonstrating immunologic efficacy, however, the progression-free survival (PFS) in these studies was not appreciably different than that expected from autoSCT alone, suggesting limited clinical impact from targeting these particular antigens or with these specific vaccines.

Rather than targeting a single-tumor antigen, Avigan and colleagues[6] have developed a novel personalized vaccine approach in which each patient's MM cells are fused ex vivo with autologous dendritic cells (DCs). The resulting DC-MM fusion vaccine allows for presentation of the full repertoire of MM antigens for each patient, including unique mutation-induced neoantigens that may be particularly immunogenic. A phase 2 study of this vaccine given in conjunction with autoSCT in 24 patients demonstrated no significant safety issues and expansion of MM-specific T cells in most patients, with upgrading of response postvaccination in 24%.[6] This vaccine strategy in conjunction with autoSCT is currently being tested in a randomized trial (Bone Marrow Transplantation–Clinical Trials Network 1401; NCT02728102), which will allow for evaluation of the feasibility of this approach in a multicenter setting as well as the magnitude of clinical benefit, if any, over autoSCT alone.

Other vaccine approaches currently being evaluated in clinical trials include an allogeneic cellular vaccine product (GVAX) consisting of 2 MM cell lines plus K562 cells modified to express granulocyte-macrophage colony-stimulating factor, which serves as an adjuvant to attract antigen-presenting cells[7] (NCT03376477), and a multipeptide vaccine (PVX-010) targeting XBP1, CD138, and CS1/SLAMF7 being evaluated in smoldering MM with and without lenalidomide[8] and/or a histone deacetylase inhibitor (NCT02886065). A common theme among these current approaches is an attempt to induce immunity against multiple targets to limit the ability of the MM cells to escape via loss of a single antigen and to vaccinate in a minimal disease or smoldering setting when tumor burden and/or aggressiveness are low and immune dysfunction may be less profound.

Checkpoint inhibition

The programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) axis is an important mediator of peripheral tolerance that limits tumor immunity. PD-L1 can be expressed on MM cells as well as surrounding cells within the marrow microenvironment, and antibodies that block the PD-1/PD-L1 axis can augment T cell–mediated anti-MM activity in preclinical models.[9-11] A phase 1 study of the anti–PD-1 antibody nivolumab included 27 MM patients, with no objective responses observed.[12] However, 2 phase 1/2 studies combining the anti–PD-1 antibody pembrolizumab with either lenalidomide and dexamethasone[13] or pomalidomide and dexamethasone[14] showed promising response rates of 76% and 60%, respectively, in relapsed/refractory MM patients. Autoimmune toxicities, including pneumonitis, were observed, but primarily, they were grade 1/2. Based on these studies, multiple trials combining various anti–PD-1 or anti–PD-L1 antibodies with immunomodulatory drugs (IMiDs) were opened for both newly diagnosed and relapsed/refractory MM. In July 2017, the Food and Drug Administration (FDA) halted all of these trials owing to increased death rates on interim analysis of 2 of these studies. In the phase 3 KEYNOTE-183 trial, relapsed/refractory patients randomized to pembrolizumab, pomalidomide, and dexamethasone had a hazard ratio for death of 1.61 (95% confidence interval [95% CI]: 0.91, 2.85) compared with those randomized to pomalidomide and dexamethasone. In the phase 3 KEYNOTE-185 trial, newly diagnosed patients randomized to pembrolizumab, lenalidomide, and dexamethasone had a hazard ratio for death of 2.06 (95% CI: 0.93, 4.55) compared with those randomized to lenalidomide and dexamethasone. In both studies, the overall response rates and time to progression were no different between the arms.[15] Most common causes of death were infections and cardiopulmonary toxicities, including autoimmune toxicities, such as myocarditis.

At this time, the future of checkpoint inhibition in MM remains unclear. Although the risks of PD-1/PD-L1 inhibition in combination with IMiDs seem to outweigh any potential benefits, there remains preclinical rationale to combine these drugs with other immune-mediated therapies, including vaccines, monoclonal antibodies, and cellular therapies.[9,16,17] Initial data reported at an American Society of Hematology Annual Meeting in 2018 demonstrated responses in 4 of 6 evaluable patients (1-3 prior therapies) receiving the anti–PD-L1 antibody atezolizumab + daratumumab, with 5 remaining progression free for >15 months.[18] This study as well as other trials exploring these combinations (eg, nivolumab + daratumumab, NCT01592370) remain open. In addition, other inhibitory receptors, such as T-cell immunoglobulin and mucin protein-3 (Tim-3), lymphocyte activation gene-3 (LAG-3), and T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT), have been implicated in MM-associated T-cell dysfunction,[19,20] and antibodies blocking these checkpoints are soon to enter clinical trials in relapsed/refractory MM based on promising preclinical activity.[20-22] Time will tell if there is a subset of patients or a particular combination or clinical setting (eg, post-autoSCT or post-CAR T-cell therapy) where checkpoint inhibition can still play a role in MM.

MM-targeted antibodies and ADCs

Two monoclonal antibodies are currently FDA approved for MM: elotuzumab, which targets SLAMF7 (also called CS1), and daratumumab, which targets CD38. Clinical safety and efficacy data for these agents have been extensively reviewed[23] and will not be discussed here. Additional CD38-targeted naked antibodies in clinical development include isatuximab, MOR202, and TAK-579 (Table 1). The primary mechanism of action of these agents is thought to be Fc mediated via binding to Fc receptors on effector cells, such as NK cells, monocytes, and macrophages, to induce antibody-dependent cellular cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP) and/or binding to complement to induce complement-mediated cytotoxicity.[24] Interestingly, however, both elotuzumab and anti-CD38 antibodies have additional immunomodulatory effects independent of their binding to MM cells. SLAMF7 is also expressed on NK cells, and elotuzumab binding to SLAMF7 can send a direct activating signal to these cells, further augmenting their killing ability.[25] Daratumumab and other anti-CD38 antibodies can inhibit the ectoenzyme activity of CD38 and also deplete CD38-expressing regulatory B and

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Table 1. Monoclonal antibodies and antibody-drug conjugates in development for MM

Target	Agent	Type (toxin)	Comments	Clinical trials no.*
SLAMF7	Elotuzumab	Naked	FDA approved	Multiple
CD38	Daratumumab	Naked	FDA approved	Multiple
CD38	Isatuximab	Naked	Phase 3 combo with pom/dex under FDA review	NCT02990338
CD38	MOR202	Naked	Combinations with dex, len/dex, and pom/dex	NCT01421186
CD38	TAK-079	Naked	Subcutaneous administration, phase 1 single agent	NCT03439280
CD38	TAK-573	ADC (IFNα)	Phase 1 single agent	NCT03215030
CD38	TAK-169	ADC (shiga-like toxin A subunit)		Preclinical
BCMA	SEA-BCMA	Naked	Phase 1 single agent	NCT03582033
BCMA	GSK2857916 (belantamab mafodotin)	ADC (MMAF)	21 of 35 (60%) ORR in phase 1 expansion; ongoing trials alone and with len/dex, pom/dex, bort/dex, pembrolizumab	NCT02064387, NCT03525678, NCT03544281, NCT03848845, NCT03715478
BCMA	MEDI2228	ADC (PBD)	Phase 1 single agent	NCT03489525
BCMA	HDP-101	ADC (Amanitin)		Preclinical
CD48	SGN48A	ADC (MMAE)	Phase 1 single agent	NCT03379584
CD46	FOR46	ADC (MMAF)	Phase 1 single agent	NCT03650491
CD56	IMGN901 (lorvotuzumab mertansine)	ADC (DM1)	2 of 37 (6%) ORR in phase 1	NCT00346255
CD74	STRO-001	ADC (SC236)	Phase 1 single agent	NCT03424603

ADC, antibody-drug conjugate; bort, bortezomib; dex, dexamethasone; DM1, maytansinoid; IFNα, interferon-α; len, lenalidomide; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; ORR, overall response rate (partial response or better); PBD, pyrrolobenzodiazepine; pom, pomalidomide; SC236, noncleavable maytansinoid-linker warhead.
*Search conducted on www.clinicaltials.gov on May 15, 2019.

T cells and myeloid-derived suppressor cells, altering the immunosuppressive milieu and potentially augmenting effector T-cell activity within the marrow.[24,26] This provides rationale for combining these agents with other immunotherapies, such as checkpoint inhibitors and other T cell–directed therapies (eg, bispecific antibodies), and adoptive NK- and T-cell therapies.

A new promising target for antibody-based therapy in MM is B-cell maturation antigen (BCMA). BCMA is a cell surface receptor expressed primarily by plasma cells, and it normally functions to maintain long-lived plasma cell homeostasis.[27] BCMA is expressed consistently on MM cell lines and primary patient samples, although intensity of expression is variable from patient to patient.[28-30] Signaling through BCMA by its ligands APRIL and BAFF promotes MM cell proliferation, survival, and drug resistance.[31,32] BCMA is also shed from the cell surface, leading to a soluble form (soluble BCMA) that is detectable in circulation, with higher levels associated with poorer clinical outcomes.[33] Thus, BCMA is a rational target for anti-MM therapy. The BCMA-targeted antibody farthest along in clinical development is GSK2857916 (belantamab mafodotin), a novel ADC. This is a humanized IgG1 anti-BCMA antibody linked to monomethyl auristatin F (MMAF), a potent tubulin polymerization inhibitor. This agent had significant in vitro and in vivo activity in preclinical testing, and it may work via several potential mechanisms of action, including direct apoptosis induced by intracellular release of MMAF after internalization of the ADC, induction of ADCC and ADCP via binding of the afucosylated Fc portion to Fc receptors on immune effector cells, blockade of BCMA signaling, and induction of immunogenic cell death that may augment/broaden endogenous anti-MM immunity.[29,34]

A phase 1 study of GSK2857916 in relapsed/refractory MM initially enrolled 38 patients at doses ranging from 0.03 to 4.6 mg/kg given intravenously every 3 weeks as a 1-hour infusion for up to 16 cycles. An additional 35 patients were enrolled at the recommended phase 2 dose of 3.4 mg/kg in an expansion cohort. No dose-limiting toxicities were identified during dose escalation. The most common toxicities at the 3.4-mg/kg dose were thrombocytopenia (58%, grade 3-4 in 35%) and corneal toxicity (63%, grade 3-4 in 9%). The only other grade 3 to 4 event seen at this dose in >2 patients was anemia (14%). Corneal events were an expected toxicity from the MMAF toxin, and symptoms included dry eye, blurred vision, foreign body sensation, and/or photophobia, with keratitis and corneal microcystic changes noted on eye exam, all of which were reversible. Median time to onset was 23 days (range 1-84). Management included dose reductions and/or delays, artificial tears, and steroid eye drops, with median time to resolution of 30 days (range 5-224). Corneal events led to treatment discontinuation in 2 patients during dose escalation and 0 patients during dose expansion. Infusion reactions were seen in 23% of patients, all grade 1 or 2 and occurring during the first dose when premedications were not permitted, and they did not recur when premedications were added.[35]

In the 35-patient expansion cohort, 57% had 5 or more prior lines of therapy; 89% were dual refractory to a proteasome inhibitor (PI) and IMiD, and 34% were refractory to a PI, IMiD, and daratumumab. A partial response (PR) or better was seen in 21 (60%), including 43% with VGPR and 9% with CR. In an updated analysis with median 14 months of follow-up, median PFS for this cohort was 12 months, with median duration of response (DOR) of 14.3 months. Median overall survival was not reported. Six of 14 (43%) patients refractory to daratumumab responded, with median PFS of 6.8 months.[36] This study demonstrated proof of concept that targeting BCMA with an antibody-based therapy has clinical activity, with impressive single-agent activity and response durability in a heavily pretreated population.

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A follow-up randomized phase 2 trial exploring 2 different doses (2.5 and 3.4 mg/kg) of GSK2857916 in relapsed/refractory MM has recently completed accrual, and studies exploring combinations with PIs, IMiDs, and pembrolizumab are ongoing (Table 1). These should help to further delineate the activity and toxicity of this agent and where it might fit into the MM treatment landscape.

Several additional antibodies and ADCs are currently in clinical development (Table 1), including naked antibodies against BCMA (SEA-BCMA) and its ligand APRIL (BION-1301)[32] and novel ADCs against BCMA (MEDI2228[37] and HDP-101[38]), which use different toxic payloads (pyrrolobenzodiazepine and amanitin, respectively) than GSK2857916 and thus, would not be expected to have the corneal toxicity. Despite the attractiveness of BCMA as a target, resistance is still likely to develop, potentially from antigen loss (which has been described after BCMA-specific CAR T-cell therapy[39]) or other mechanisms; thus, ADCs against several additional targets expressed by MM, including CD56, CD74, CD48, CD46, and CD38, are also moving forward in development. Some of these use traditional cytotoxins, such as maytansinoids, MMAF, and monomethyl auristatin E in lorvotuzumab mertansine (targeting CD56)[40] and STRO-001 (targeting CD74),[41] FOR46 (targeting CD46),[42] and SGN-CD48A (targeting CD48),[43] respectively. Lorvotuzumab mertansine, an anti–CD56-DM1 ADC given intravenously on days 1 and 8 every 21 days, had modest activity in a phase 1 trial in 37 relapsed/refractory MM patients, with 2 PR (6%) and 4 minimal response (MR) (11%), although responses were durable in the 6 patients with MR or PR, with median DOR of 62 weeks. The maximum tolerated dose (MTD) was 112 mg/m^2, and most common toxicities were headache, fatigue, neuropathy, and transaminitis.[40] Other ADCs exploring more novel payloads include TAK-573, an anti-CD38 antibody bound to an attenuated form of the immunomodulatory agent interferon-α, and TAK-169, an anti-CD38 antibody fragment bound to the Shiga-like toxin A subunit, which irreversibly inhibits protein synthesis.[44] All of these ADCs have entered or are soon to enter phase 1 trials.

Bispecific antibodies and bispecific therapeutic engagers

Another novel immunotherapy approach showing promising clinical activity in MM and other hematologic malignancies is that of bispecific antibodies and bispecific therapeutic engagers (BiTEs). These are agents engineered to have 2 binding domains: one typically of high affinity to an antigen on the tumor cell surface and the other of lower affinity to an activating receptor on immune effector cells, typically CD3 for T cells or CD16 for NK cells. These agents force an immunologic synapse within the tumor microenvironment, activating the endogenous effector T or NK cells and promoting tumor killing. The term BiTE refers to a construct specifically composed of 2 single-chain variable fragments with a short linker. The resulting protein has a low molecular weight and very short half-life in circulation, requiring a continuous infusion pump to maintain therapeutic concentrations. The most successful example to date of a BiTE is the CD3 × CD19–bispecific agent blinatumomab, which redirects T cells to CD19+ B-cell malignancies and was FDA approved for relapsed/refractory acute lymphoblastic leukemia in 2014.[45] Toxicities include cytokine release syndrome (CRS) and neurotoxicity, such as confusion and aphasia, similar to that seen with CAR T cells, which usually improve rapidly with stopping the infusion and if needed, administering steroids and/or tocilizumab.

In MM, the first BiTE to demonstrate clinical activity was AMG 420 (previously BI 836909). This agent targets CD3 and BCMA and induced potent T cell–directed lysis of primary MM cells ex vivo at nanomolar concentrations, with activity in MM xenograft murine models.[46] A phase 1 study explored AMG 420 as a continuous intravenous infusion in 42 relapsed/refractory MM patients at doses from 0.2 to 800 μg/d given for 4 weeks on and 2 weeks off for up to 10 cycles. Hospitalization to observe for toxicities was required at the start of cycle 1 (4 days) and cycle 2 (1 day). Patients had a median of 4 prior lines of therapy, with 31% dual PI/IMiD refractory and 21% daratumumab refractory. There were 2 dose-limiting toxicities at 800 μg/d of grade 3 polyneuropathy and grade 3 CRS, and 400 μg/d was chosen to explore in a small expansion cohort. A second patient also developed grade 3 polyneuropathy; both cases involved progressive peripheral motor and sensory nerve dysfunction, and both returned to baseline in 1 to 2 months after holding study drug and treatment with steroids and intravenous immune globulin. There were 2 deaths from adverse events: 1 from respiratory failure from influenza and aspergillosis and 1 from hepatic failure from adenovirus; neither was felt to be treatment related. Other common toxicities included infections in 29% (including 5 line infections) and CRS in 38% (most grade 1). In updated data presented at the 2019 American Society of Clinical Oncology Annual Meeting, responses were seen in 13 of 42 (31%), including 7 of 10 (70%) patients treated at the MTD of 400 μg/d, with 5 achieving a minimal residual disease–negative stringent CR. Median time to response was 1 month, and response duration is 5.6 to 10.4 months to date, with several ongoing.[47] A phase 2 multicenter study for potential registration has recently opened (Table 2).

Because of the inconvenience and infection risk associated with a continuous infusion pump, the majority of bispecific antibodies now going forward in trials for MM (Table 2) have been engineered with an Fc portion to create an "IgG-like" molecule with more favorable pharmacokinetics, resembling that of typical monoclonal antibodies. The advantages are a longer half-life allowing for dosing weekly, every 2 weeks, or even every 3 weeks as well as potential for subcutaneous administration. The potential disadvantages are more prolonged toxicity, because there is no continuous infusion to just shut off as with the short half-life BITEs, and perhaps, decreased tissue penetration compared with the smaller BiTEs, which could be an issue with bulky extramedullary disease.[45] The majority of these longer half-life bispecifics are targeting BCMA. Each has differences in the way that they are constructed, the binding sites and affinities for BCMA, and the functional activity (or lack thereof) of the Fc portion, which may impact their pharmacokinetics, cytokine release/toxicity profile, and efficacy. Most (eg, AMG701, PF-06863135, JNJ-64007957, EM801, CC-93269/EM901, REGN5458, HPN217, and TNB-383B) target CD3 and are T-cell redirecting, although at least 1 (AFM26) targets CD16 and NK cells. All have demonstrated the requisite preclinical activity in vitro and in xenograft models,[30,48-54] although no clinical data are yet available. Over the next year, we will have a sense of their initial safety and efficacy data and whether these more convenient approaches provide similar clinical activity without additional toxicity to the canonical BiTEs.

As with ADCs, BCMA is not the only target being explored for bispecific antibody therapy. Several CD3 × CD38 bispecifics have entered early-phase trials, including GBR1342[55] and AMG424,[56] and it will be interesting to see how the safety and efficacy profiles of these agents differ from the CD38 antibodies and ADCs, particularly if the redirected T cells can be engaged at lower antigen densities, which may enhance both efficacy (eg, by recognizing MM cells that have downregulated CD38 expression, a potential resistance mechanism to daratumumab[57]) as well as toxicity (by potentially recognizing

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Table 2. Bispecific antibodies/BiTEs in development for MM

Target	Agent	Type	Comments	Clinical trials no.*
BCMA	AMG 420 (BI 836909)	BiTE	7 of 10 (70%) ORR in phase 1 expansion at MTD; single-agent phase 1b/2 ongoing	NCT02514239, NCT03836053
BCMA	PF-06863135	Bispecific	Single-agent phase 1	NCT03269136
BCMA	JNJ-64007957	Bispecific	Single-agent phase 1	NCT03145181
BCMA	TNB-383B	Bispecific	Single-agent phase 1	NCT03933735
BCMA	REGN5458	Bispecific	Single-agent phase 1	NCT03761108
BCMA	CC-93269 (EM901)	Bispecific	Single-agent phase 1	NCT03486067
BCMA	AMG 701	Bispecific	Single-agent phase 1	NCT03287908
BCMA	AFM26	Bispecific	CD16 × BCMA, targets NK cells, preclinical	
BCMA	HPN217	Bispecific	Preclinical	
BCMA	EM801	Bispecific	Preclinical	
CD38	AMG 424	Bispecific	Single-agent phase 1	NCT03445663
CD38	GBR 1342	Bispecific	Single-agent phase 1	NCT03309111
FcRH5	BFCR4350A	Bispecific	Single-agent phase 1	NCT03275103
GPRC5D	JNJ-64407564	Bispecific	Single-agent phase 1	NCT03399799

ORR, overall response rate (partial response or better).
*Search conducted on www.clinicaltials.gov on May 15, 2019.

normal hematopoietic cells with low CD38 expression). FcRH5 (also called FcLH5 or CD307) is an immunoglobulin superfamily receptor overexpressed in normal and malignant plasma cells, particularly in MM samples with gain of chromosome 1q21, with lower expression in normal B cells and no other normal tissue expression. Its ligand and function are unknown.[58] The CD3 × FcRH5 bispecific antibody BFCR4350A had significant anti-MM activity against primary patient samples and in xenograft models, and a phase 1 study in relapsed/refractory MM is ongoing (Table 2). G protein–coupled receptor, class C group 5 member D (GPRC5D) is a protein originally described in the hair follicle but later found to be overexpressed in MM cells without other normal tissue expression. CAR T cells targeting GPRC5D had significant preclinical anti-MM activity, including against BCMA-negative cells.[59] The CD3 × GPRC5D bispecific antibody JNJ-64407564 is currently being explored in a phase 1 study.

Final thoughts

The next generation of MM immunotherapies is rapidly approaching and will likely provide a plethora of new treatment options to choose from. BCMA-targeted ADCs, BiTEs, and CAR T cells (discussed elsewhere in this book) have all demonstrated the ability to induce deep and durable remissions in highly refractory patients, such as the one described at the beginning of this chapter. This patient had received 2 prior stem cell transplants and was refractory to almost all available MM therapies, with a likely expected survival of only a few months. Enrolling her in a trial of any of the BCMA-targeted modalities would be a reasonable next option, with a relatively high chance of clinical benefit given such a refractory setting. It is possible that all 3 of these modalities will gain regulatory approval in the next year or 2, making choosing between them challenging, because each has its pros and cons as summarized in Table 3. In the absence of direct comparative data, the choice may come down to what best fits with the biology of disease/pace of progression, patient comorbidities and prior toxicities, logistical issues (eg, cost and proximity to a center with CAR T-cell capability), and patient preference. Of note, there are anecdotal reports that patients who have progressed on one BCMA-targeted therapy can subsequently respond to a different BCMA-targeted modality,[60] and therefore, these may not be mutually exclusive; exploring the optimal sequencing of these therapies and incorporating them into our current treatment algorithms for less refractory patients will be key challenges for the field in the near future as will be understanding the dynamics of BCMA expression and mechanisms of resistance. For those patients who do become refractory to these therapies, we will soon learn if switching to an

Table 3. Comparison of BCMA-targeted modalities in MM

	ADCs	Bispecific antibodies/BiTEs	CAR T cells
Off the shelf	Yes	Yes	No*
Logistics/ease of administration	Easiest, outpatient dosing†	More difficult, requires hospitalization for initial dosing, familiarity with CRS/neurotoxicity management	Most difficult, requires leukapheresis, specialty center with CAR T expertise, delays owing to manufacturing, hospitalization, familiarity with CRS/neurotoxicity management
Repeated dosing required	Yes	Yes	No
Dependent on patient T-cell "fitness"	No	Yes	Yes
Unique toxicities	Infusion reactions, toxin dependent	CRS, neurotoxicity	CRS, neurotoxicity
Toxicity duration	Ongoing	Ongoing	Usually 7-21 d
Durable clinical activity seen	Yes	Yes	Yes

*Allogeneic "off-the-shelf" CAR T cells are in development for MM, but no clinical data are available yet.
†The anti-BCMA ADC GSK2857916 does require close monitoring with an ophthalmologist owing to corneal toxicity; other non–MMAF-containing ADCs should not have this issue.

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immunotherapy targeting one of the alternative antigens described above can provide additional clinical benefit. It is still very early in the development of novel immunotherapies for MM, but the future looks bright.

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