Emerging immunotherapies in multiple myeloma

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ABSTRACT

Despite considerable advances in treatment approaches in the past two decades, multiple myeloma remains an incurable disease. Treatments for myeloma continue to evolve with many emerging immunotherapies. The first immunotherapy used to treat hematologic cancers, including multiple myeloma, was an allogeneic stem cell transplant. In the mid-2000s, immunomodulatory drugs thalidomide, lenalidomide, and subsequently pomalidomide were proven to be effective in multiple myeloma and substantially improved survival. The next wave of immunotherapies for multiple myeloma included the monoclonal antibodies daratumumab and elotuzumab, which were approved by the Food and Drug Administration in 2015. Subsequently, a variety of immunotherapies have been developed for multiple myeloma, including chimeric antigen receptor T cells, bispecific antibodies, antibody drug conjugates, and checkpoint inhibitors. Many of these emerging treatments target the B cell maturation antigen, which is expressed on plasma cells, although several other novel receptors are also being studied. This review summarizes the evidence of these various immunotherapies, their mechanism of action, and data from clinical trials regarding the treatments’ safety and efficacy.

Introduction

Multiple myeloma, a malignancy of unregulated plasma cell growth, is the second most common hematologic cancer among adults.1 Multiple myeloma is characterized by progressive immune dysfunction (innate and adaptive), and over the past two decades we have seen substantial progress in treatment, including immunotherapies.2 These newer treatments have improved outcomes with deeper responses and longer survival. Despite these advances, most patients eventually relapse, and multiple myeloma is therefore still considered an incurable disease. This review focuses on immunotherapies approved by the Food and Drug Administration, as well as several emerging treatments that have shown promising results and will likely be part of standard treatment for patients soon.

Incidence and prevalence

Multiple myeloma accounts for about 1% of all cancers and 10% of all hematologic malignancies.3 The age standardized incidence rate of the disease worldwide in 2016 was 2.1 per 100,000 people, and about 160,000 patients had newly diagnosed multiple myeloma in 2018.4 5 In the US, the age standardized incidence rate was higher than the global rate at 7.1 per 100,000 people in 2016,6 and incident rates have gradually increased, which is consistent with the global trend.7 The prevalence of this cancer has also increased, given that the median overall survival for patients has doubled in the past decade.8 9

Sources and selection criteria

We identified references for this review by doing a PubMed and Medline search for years 2000-19. We used keywords and combinations of keywords such as multiple myeloma, immunotherapy, CAR T cell, therapy, immune, antibody. We included articles based on the quality of study design and size, favoring randomized controlled trials, reports from large registries, and guidelines. We excluded case reports and papers in non-peer reviewed journals. We screened about 1000 articles of evidence classes I-IV. Studies were prioritized by design, and by patient numbers, quality, and publication date. However, given the breadth of this review and the lack of large studies in some aspects of immunotherapy in multiple myeloma, we included observational and preclinical studies as well as ongoing trials where preliminary results are available as meeting abstracts. We highlighted the limitations of these studies where relevant.

Current immunotherapies

Allogeneic stem cell transplantation

One of the earliest immunotherapies used to treat hematologic cancers is allogeneic hematopoietic stem cell transplantation (alloH SCT), which has shown potential in a subset of patients with multiple myeloma (fig 1). The treatment offers the opportunity
for sustained disease control with an immune mediated graft versus myeloma effect by establishing donor chimerism. AlloHSCTs are usually performed after achieving optimal cyto reduction with high dose chemotherapy or an autologous hematopoietic stem cell transplantation (autoHSCT). AlloHSCTs (or autoHSCTs and alloHSCTs in tandem) are an option for fit patients with relapsed disease that is refractory to standard options, and in rare situations such as clinical trials for young and fit patients with newly diagnosed multiple myeloma with high risk disease as a consolidation approach. This option, however, is not routinely recommended.10 11

Over the past decade, considerable improvements have been made in supportive care, typing, and use of the more tolerable reduced intensity conditioning regimens compared with the myeloablative regimens as conditioning treatment. Additional options for immunotherapy at relapse after allogeneic transplant include donor lymphocyte infusions, immunomodulatory drug maintenance, and withdrawal of immune suppression.12 However, allogeneic transplants do not have a defined role in multiple myeloma treatment, owing to the high mortality related to treatment and limited efficacy as well as the conflicting reports regarding long term outcomes from prospective studies.12 13 Another reason that alloHSCTs have fallen out of favor is the availability of effective novel treatments that are easier to tolerate, many of which we will discuss in this review.

### Immunomodulatory imide drugs

Until the early 2000s, treatment options for multiple myeloma were limited. For patients diagnosed before 2000, the relative survival at five years was less than 35%.6 The first use of thalidomide, an immunomodulatory imide drug, in the treatment of multiple myeloma in 1997 and its subsequent FDA approval in 2006 started an era of new drug approvals for myeloma including immunologic and other treatments (fig 1). A detailed review of currently available myeloma treatments is beyond the scope of this article, but we will highlight important studies informing the use of immunomodulatory imide drugs and monoclonal antibodies for treatment of multiple myeloma.

Immunomodulatory imide drugs that have been approved by the FDA in addition to thalidomide include lenalidomide in 2006 and more recently pomalidomide in 2013. These drugs exert their antitumor activity via multiple mechanisms. They bind to cereblon and thus increase the ubiquitination and proteasomal degradation of key transcription factors Ikaros (IKZF1) and Aiolos (IKZF3) that are important for the development of B cells and long lived plasma cells. They also have immunomodulatory effects including enhanced natural killer cell and T cell activity and an increase in interleukin 2 and interferon γ.14 15 Immunomodulatory imide drugs have been studied as a single agent16 17 and in combination with proteasome inhibitors18-23 in relapsed and refractory multiple myeloma, in newly diagnosed

**Fig 1 | Multiple myeloma treatments—timeline of drug discovery and five year relative survival (using data from the Surveillance, Epidemiology, and Ends Results program).**7 Data for year of diagnosis and relative survival are: 1975, 26.5% (observed); 1980, 26.0% (observed); 1985, 27.4% (observed); 1990, 29.9% (observed); 1995, 33.5% (observed); 2000, 34.6% (observed); 2005, 47.1% (observed); 2010, 53.6% (observed); 2015, 55.3% (modelled)
Multiple myeloma,20-26 as maintenance treatment after induction and autologous transplantation,27-29 and in smoldering multiple myeloma.30 Iberdomide (CC-220) and CC-92480 are novel cereblon E3 ligase modulators that have shown promise in overcoming prior immunomodulatory drug resistance.34-36

Monoclonal antibodies
In the past five years, additional immunotherapies became available with the approval of three monoclonal antibodies. Daratumumab (anti-CD38) and elotuzumab (anti-signaling lymphocytic activation molecule F7 (SLAMF7)) were approved by the FDA for the treatment of multiple myeloma in 2015, and isatuximab (anti-CD38) was most recently approved in 2020 (fig 1). These antibodies are effective via multiple processes, with some minor differences between their mechanisms. Similar mechanisms include direct tumor cell apoptosis; immune mediated mechanisms (including complement dependent cytotoxicity; antibody dependent cell mediated cytotoxicity via natural killer cells; and macrophage mediated, antibody dependent cellular phagocytosis); and immunoregulatory actions such as decreasing regulatory T cells, regulatory B cells, and myeloid derived suppressor cells.37,38 One of the differences is that daratumumab induces apoptosis via Fc receptor mediated crosslinking of tumor bound monoclonal antibodies,38 and isatuximab induces apoptosis without crosslinking via caspase dependent and lysozyme associated pathways leading to homotypic aggregation.39

Daratumumab monotherapy has shown a favorable safety profile and encouraging efficacy in initial phase I and II trials.40-42 It was then combined with standard treatments in randomized phase III studies (that is, immunomodulatory drugs, proteasome inhibitors, and alkylators; table 1). In randomized phase III studies of relapsed and refractory multiple myeloma, daratumumab and dexamethasone were combined with bortezomib (median progression free survival 16.7 v 7.1 months),43,44 lenalidomide (44.5 v 17.5 months),45,47 carfilzomib (not reached v 15.8 months),48 showing significant improvements in overall response rates and progression free survival. Daratumumab has also been combined with pomalidomide, based on phase Ib data43,44 and a non-randomized, multicohort multicenter phase II study.42 With this drug’s promising results in relapsed and refractory multiple myeloma, trials evaluating daratumumab in transplant ineligible patients with newly diagnosed multiple myeloma showed significantly improved overall response rates and progression free survival. In the MAIA trial, daratumumab was combined with lenalidomide and dexamethasone (not reached v 31.9 months),51 in the ALCYONE trial, daratumumab was combined with bortezomib, melphalan, and prednisone (D-VMP (36.4 v 19.3 months)).49,51 An updated analysis also showed an overall survival benefit in the D-VMP group at a median follow-up of 40.1 months (interquartile range 37.4-43.1), and a significant benefit in overall survival in the D-VMP group (hazard ratio 0.60, 95% confidence interval 0.46 to 0.80, P<0.001).50

### Table 1 | Randomized, multicenter phase III trials of monoclonal antibody treatment for multiple myeloma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient group (type of disease, No of prior lines of treatment)</th>
<th>Arm (No of patients)</th>
<th>Overall response rate (%)</th>
<th>Median progression free survival (months)</th>
<th>Hazard ratio (P value)</th>
<th>FDA approval</th>
<th>EMA approval</th>
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<td>CASTOR51,52</td>
<td>Relapsed and refractory disease, at least 1 prior line</td>
<td>D-Vd (n=251)</td>
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FDA=Food and Drug Administration; EMA=European Medicines Agency.

* D=daratumab; V=bortezomib; d=dexamethasone; R=lenalidomide; K=carfilzomib; M=melphalan; p=prednisone; T=thalidomide; SC=subcutaneous; IV=intravenous; E=elotuzumab; I=isatuximab; P=pomalidomide.

1Randomized phase II study.
Daratumumab has also been studied in transplant eligible patients with newly diagnosed multiple myeloma as a quadruple drug combination with bortezomib, thalidomide, and dexamethasone (VTD). The patients were treated with four cycles of the VTD combination, followed by autoHSCT and then two cycles of the VTD combination. Daratumumab was added to the six cycles of the VTD combination in the experimental arm (median progression free survival, not reached). In a randomized phase II study in transplant eligible patients with newly diagnosed multiple myeloma, patients were treated with lenalidomide, bortezomib, and dexamethasone (RVd) with and without daratumumab for four cycles followed by autoHSCT followed by two additional cycles of the RVd combination. Results showed an improvement in the overall response rate, stringent complete response rate, and rate of minimal residual disease negativity (median progression free survival, not reached).

A randomized phase III trial has shown that subcutaneous daratumumab was non-inferior to intravenous daratumumab in terms of efficacy and pharmacokinetics, and had an improved safety profile in relapsed and refractory multiple myeloma leading to its recent FDA approval in 2020 (median progression free survival 5.6 v 6.1 months). Although elotuzumab has limited activity on its own, it has shown significantly improved overall response rates and progression free survival when combined with immunomodulatory drugs lenalidomide in a randomized phase III trial (median progression free survival 19.4 v 14.9 months) and pomalidomide in a randomized phase II trial (10.3 v 4.7 months). Only 2% of patients in the elotuzumab arm and 4% in the control arm were exposed to prior daratumumab in the phase II trial.

Therefore, a recent randomized phase III study in high risk patients with newly diagnosed multiple myeloma compared the addition of elotuzumab to induction and maintenance of the RVd drug combination with no improvement in outcomes. Isatuximab is another anti-CD38 antibody that has been studied in combination with lenalidomide and dexamethasone as well as pomalidomide and dexamethasone in phase Ib studies. Isatuximab and dexamethasone with and without pomalidomide were studied in a randomized phase III study that showed a benefit in progression free survival (11.5 v 6.5 months), which led to their FDA approval in 2020 for relapsed and refractory multiple myeloma. Only one patient in the isatuximab arm had been previously treated with daratumumab.

Isatuximab has been studied in combination with carfilzomib and dexamethasone in another randomized phase III trial, which showed substantial benefit in progression free survival (not reached v 19.2 months).

Newer immunotherapies

Immunotherapies that are currently being studied in multiple myeloma are discussed in this section under four headings: checkpoint inhibitors, chimeric antigen receptor (CAR) T cells, bispecific antibodies, and antibody drug conjugates (fig 2).

Checkpoint inhibitors

Malignant plasma cells in most patients with multiple myeloma express the checkpoint programmed death-ligand 1, which is upregulated especially when exposed to inflammatory mediators such as interferon γ. Interaction of this checkpoint molecule with programmed cell death protein 1 on T cells limits their proliferation and cytotoxic activity.

The first study evaluating single agent nivolumab for relapsed multiple myeloma showed a response in only one of 27 patients. Despite a lack of single agent activity, single arm trials combining checkpoint inhibitors with immunomodulatory imide drugs and dexamethasone because of the potential synergy look promising.

With these clinical data, three large randomized phase III trials were halted by the FDA in 2017 because of increased serious adverse events and deaths as well as decreased overall survival in the checkpoint inhibitor arm (pomalidomide and dexamethasone with and without pembrolizumab) in relapsed and refractory multiple myeloma (hazard ratio 1.61, 95% confidence interval 0.91 to 2.85), pomalidomide and dexamethasone with and without nivolumab in relapsed and refractory multiple myeloma (1.19, 0.64 to 2.20), and lenalidomide and dexamethasone with and without pembrolizumab in transplant ineligible patients with newly diagnosed multiple myeloma (2.06, 0.93 to 4.55).

These trials encourage caution with expedited timelines for future combination studies for drugs with limited single agent activity.

Chimeric antigen receptor T cells

CAR T cells are human T cells that have been genetically modified and expanded in the laboratory before they are infused back into patients to target the tumor. The receptor on the surface of CAR T cells that targets the tumor antigens consists of several parts (fig 3): an extracellular, non-major histocompatibility complex restricted, targeting domain, usually derived from a single chain variable fragment of a monoclonal antibody; a spacer region; a transmembrane domain; an intracellular signaling domain including the CD3ζ activation domain; and a costimulatory domain (eg, CD28 or 4-1BB). The single chain variable fragment was originally derived from mice (hence the term chimeric), but many of the newer constructs are fully human.

CD3 positive T cells are obtained from patients (for autologous CAR T cells) or healthy donors (for allogeneic CAR T cells) via a process called leukapheresis. These T cells are expanded manifold
in culture and activated using beads coated with anti-CD3 or anti-CD28 monoclonal antibodies or cell based artificial antigen presenting cells. The T cells are then transduced with a vector (usually either lentiviral or retroviral) that carries the gene encoding a receptor to an antigen present on the surface of tumor cells. This manufacturing process takes up to four weeks at a good manufacturing practices facility, and the CAR T cells can then be stored until needed by the patient. This delay means that the disease must not be rapidly progressing, so that the patient is able to wait until the CAR T product is ready; otherwise the patient will need bridging chemotherapy. Two to seven days before CAR T cell infusion, a patient receives lymphotopeleting chemotherapy to make way for the CAR T cells that are subsequently given as an intravenous infusion. Once infused into patients, the CAR T cells encounter the antigen, proliferate, and kill the tumor cells (fig 4). These cells, therefore, combine the target specificity of a monoclonal antibody with the enhanced cytotoxicity of T cells without requiring human leucocyte antigen presentation of the target antigen.

An ideal antigen is one that is widely and exclusively expressed on cancer cells but not on normal cells to enhance efficacy and reduce toxicity. In multiple myeloma, most emerging immunotherapies (including CAR T cells) target B cell maturation antigen (BCMA), a type III transmembrane receptor, which is a promising target antigen. BCMA is also known as tumor necrosis factor receptor superfamily member 17 or CD269. It is expressed in nearly all plasma cells (normal and malignant) although its expression is variable. BCMA promotes plasma cell survival and is induced during plasma cell differentiation by binding to ligands (a proliferation inducing ligand (APRIL) and B cell activating factor (BAFF)) that are produced by osteoclasts. Increased levels of soluble BCMA are associated with high tumor burden in multiple myeloma and thus worse outcomes.

CAR T cells targeting CD19 were approved by the FDA in 2017 for refractory large B cell lymphoma and acute lymphoblastic leukemia, and are being used in clinical practice. The first study on CAR T cell treatment directed by BCMA opened in 2014 at the US National Cancer Institute. Since then, about a dozen of different early phase clinical trials have been conducted on CAR T cell treatment for advanced multiple myeloma. A detailed review outlining the differences in the construct, manufacturing, and clinical efficacy of these different products has been published previously.

This review focuses on four BCMA CAR T cell products that are currently being evaluated in registration (that is, for regulatory approval) phase I/II clinical trials for patients with relapsed and refractory multiple myeloma. These products include bb2121 (now known as idecabtagene vicleucel or ide-cel), JCARH125 (now known as orvacabtagene autoleucel or orva-cel), LCAR-B38M (now known as JNJ-4528), and P-BCMA-101. FDA approvals for some of these agents are anticipated in 2020-21 for...
relapsed and refractory multiple myeloma (fig 5; table 2). The high overall response rates of 60-100% seen in these trials in a highly refractory population is unprecedented, although the durability of these responses is still in question.

**Ide-cel**  
The most advanced CAR T cell treatment targeting a BCMA is ide-cel (bb2121), which uses a lentiviral vector for CAR insertion and includes a 4-1BB costimulatory domain as well as a murine single chain variable fragment. In a phase I non-randomized, open label, multicenter trial in relapsed and refractory multiple myeloma (≥3 prior lines of treatment) for 33 patients treated at various doses, researchers found an overall response rate of 85% with a median progression free survival of 11.8 months. A higher overall response rate was seen at the higher dose levels and doses of 150-450×10⁶ CAR T cells were defined as the active dose. This dose is being tested currently in a multicenter, single arm, open label trial to evaluate bb2121 CAR T cells further in relapsed and refractory multiple myeloma; the trial has completed enrolment of 149 patients worldwide. Preliminary results show an overall response rate of 73% (complete response rate 33%) and median progression free survival of 8.8 months in 128 patients treated at doses of 150-450×10⁶ cells (table 2). Fifty four patients treated at the highest dose level of 450×10⁶ cells had an overall response rate of 82% and a median progression free survival of 12.1 months. These results have been submitted to regulatory agencies including the FDA and European Medicines Agency for treatment for advanced multiple myeloma.

**Orva-cel**  
Orva-cel (JCARH125) is another second generation CAR product with a fully human B cell derived single chain variable fragment, a 4-1BB costimulatory domain, and optimized manufacturing (predefined CD4:CD8 ratio) that is derived from preclinical work at Memorial Sloan Kettering Cancer Center. The preliminary data for the multicenter phase I/II EVOLVE study were presented at the American Society of Clinical Oncology meeting in 2020. These patients had received a median of six prior treatments. They received escalating doses of 50-600×10⁶ cells. The results for 62 patients treated at the 300-600×10⁶ cells dose range showed an overall response rate of 92% (complete response rate 36%). The trial is currently enrolling at the recommended phase II dose of 600×10⁶ cells (table 2).

**JNJ-4528**  
The LCAR-B38M CAR construct was developed initially in China and is currently being pursued in the US and globally as JNJ-4528 (table 2). It consists of two llama derived variable-heavy chain only fragments that target two epitopes of BCMA designed to confer avidity. In a phase I/II study in China, researchers found deep durable responses with a median progression free survival of 19.9 months and a manageable safety profile in relapsed and refractory multiple myeloma, although the patients in this study were treated earlier in their disease course with a median of three prior lines of treatment and were therefore less heavily pre-treated. In the US and Europe, a multicenter phase I/II clinical trial of this CAR construct as JNJ-4528 in relapsed and refractory multiple myeloma (≥3
prior lines of treatment) was conducted to confirm the findings of the LEGEND-2 study. Preliminary results of the phase Ib portion showed an overall response rate of 100% (complete response rate 86%) in patients with a median of five prior lines of treatment (table 2). The phase II portion is fully enrolled, and phase II and III studies have been initiated.

**P-BCMA-101**

P-BCMA-101 is uniquely manufactured using the non-viral piggyBac gene editing system, which is less costly, produces cells with a high percentage of favorable stem cell memory phenotype T cells, and has the ability to include a safety switch. The binding molecule for this product is not a single chain variable fragment but a small fully human fibronectin domain (Centyrin) that has higher specificity and potentially less immunogenicity. In a phase I dose escalation trial, the overall response rate was 63% with a median progression free survival of 9.5 months in 19 evaluable patients (table 2).

**Toxicity**

CAR T cell treatments have a unique toxicity profile where patients can develop side effects such as cytokine release syndrome and neurotoxicity that has been recently termed immune effector cell associated neurotoxicity syndrome (ICANS). Cytokine release syndrome has been defined as a disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, or hypoxia caused by the release of cytokines from cells. The American Society for Transplantation and Cellular Therapy has developed a consensus grading system for cytokine release syndrome, which depends on the severity and presence of fever, hypotension, or hypoxia.

ICANS has been defined as a disorder involving the central nervous system following any immunotherapy that results in the activation or engagement of endogenous or infused T cells or other immune effector cells. Symptoms or signs can be progressive and could include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.

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**Fig 4** | Chimeric antigen receptor (CAR) T cell treatment for multiple myeloma—sequence of events. CRS=cytokine release syndrome; ICANS=immune effector cell associated neurotoxicity syndrome
It includes four grades that are determined by the ICE score (immune effector cell associated encephalopathy score, which provides objectivity to grading encephalopathy), level of consciousness, seizure, motor findings, and elevated intracranial pressure or cerebral edema (table 4). Management of ICANS and cytokine release syndrome is based on grading and involves supportive care, steroids, and interleukin blocking agents. Interleukin 6 blocking agents (tocilizumab and siltuximab) with or without steroids are the mainstay of management for cytokine release syndrome, whereas steroids are the mainstay for the management of neurotoxicity. Another potential agent for managing these symptoms includes the interleukin 1 blocking agent anakinra.

All the clinical trials on BCMA CAR T cell treatments had a high incidence of cytokine release syndrome (>80%) except for P-BCMA-101, which seemed to have a substantially lower incidence (10%). Despite this, severe cytokine release syndrome (that is, >grade 3) is seen in less than 10% of patients. Neurotoxicity was reported in less than 20% of patients with severe neurotoxicity (≥grade 3) in less than 7% of patients. Another common side effect is cytopenia, which has also been thought to be secondary to the lymphodepleting chemotherapy, ongoing CAR T cell activity, and disruption of hematopoiesis showing severe hypocellularity in the bone marrow, but most patients recover with time.

Management of toxicity

Early recognition of cytokine release syndrome and ICANS and prompt intervention after CAR T cell treatment is vital to prevent serious consequences, although the optimal timing for intervention and benefit of prophylactic treatment is yet unknown. The CAR T cell therapy associated toxicity (CARTOX) working group has developed a management approach for these syndromes, based on multidisciplinary grades. In cytokine release syndrome, patients with grade 1 are usually

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**Fig 5 |** Four major constructs of chimeric antigen receptor (CAR) T cells targeting B cell maturation antigens (BCMA), currently in multicenter clinical trials investigating multiple myeloma. This figure does not include all BCMA constructs in multiple myeloma. ScFv=single chain variable fragment; VH only=variable-heavy chain only fragments
managed with supportive care, those with grade 2 are managed with the anti-interleukin 6 receptor tocilizumab with or without steroids in addition to supportive care, and those with grade 3-4 are managed in the intensive care unit with aggressive supportive care, vasopressors, oxygen, tocilizumab, and steroids. Patients with grade 1 and 2 ICANS are managed supportively but an electroencephalogram is done to rule out electrical seizures and imaging of the brain to rule out edema. Patients with grade 3 and 4 ICANS need steroids and more aggressive supportive care.120

Bispecific antibodies including bispecific T cell engagers

Bispecific monoclonal antibodies direct a host’s immune system (more specifically cytotoxic T cells) against cancer cells by binding CD3 on T cells with a target protein on cancer cells (fig 6).124 A type of bispecific antibody is the bispecific T cell engager (BiTE), which differs from other bispecific antibodies by containing two different single chain variable fragments connected by a linker. BiTEs often have a short half life, requiring continuous infusion to maintain efficacy.125 The first BiTE to receive FDA approval for treatment in relapsed and refractory acute lymphoblastic leukemia is Blinatumomab, a bispecific antibody that engages T cells to CD19 positive cells.126 Because BiTEs engage and activate the patient’s own immune cells, they have a toxicity profile similar to CAR T cells including cytokine release syndrome and ICANS.116

AMG 420

AMG 420 (previously named BI 836909) is a novel BiTE targeting BCMA on myeloma cells and CD3ε on T cells, which has induced multiple myeloma cell lysis in preclinical models.127 In the first-in-human phase I study of AMG 420 in patients with at least two lines of treatment, AMG 420 was given as a continuous infusion with a pump for four week infusions, six week cycles, and a maximum of 10 cycles. The maximum tolerated dose was 400 µg/day; seven (70%) of 10 patients responded to this dose. Serious adverse events were seen in 48% of patients, which were most commonly infections; and two patients had reversible grade 3 polyneuropathies. Cytokine release syndrome developed in 38% of patients, with no toxicity in the central nervous system.109 A phase Ib trial with AMG 420 is currently ongoing and although this drug looks promising, the continuous intravenous infusions present logistical challenges for patients and healthcare systems (table 2). AMG 701 is a modified version of AMG 420 (by addition of an Fc domain) with an extended half life that is suitable for dosing once a week and is being investigated in a phase I study.128

**CC-93269**

Another BCMA bispecific antibody, CC-93269, is being studied in an ongoing phase I clinical trial. This humanized 2+1, immunoglobulin G 1 based, T cell engager binds to BCMA bivalently on myeloma cells and CD3ε monovalently on T cells. The bivalent binding could lead to improved potency, tumor

<table>
<thead>
<tr>
<th>Treatment agent, trial (No of participants)</th>
<th>Treatment type</th>
<th>Median No of prior lines of treatment</th>
<th>dose range</th>
<th>Overall response rate (%)</th>
<th>Median progression free survival (months)</th>
<th>Cytokine release syndrome (%), any grade (3-5)</th>
<th>Neurotoxicity (%), any grade (3-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bl2121 (ide-cel)</td>
<td>CAR T cell</td>
<td>6</td>
<td>150-450×10⁶ cells</td>
<td>73</td>
<td>88</td>
<td>84 (6)</td>
<td>18 (3)</td>
</tr>
<tr>
<td>KarMa (n=128)</td>
<td>CAR T cell</td>
<td>6</td>
<td>300-600×10⁶ cells</td>
<td>92</td>
<td>Not reached</td>
<td>89 (3)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>JCARH125 (ova-cell), EVOLVE (n=6.2)</td>
<td>CAR T cell</td>
<td>3</td>
<td>0.07-2.1×10⁶ cells/kg</td>
<td>88</td>
<td>19.9</td>
<td>90 (7)</td>
<td>2</td>
</tr>
<tr>
<td>LCAR-B38M, LEGEND-2 (n=57)</td>
<td>CAR T cell</td>
<td>5</td>
<td>0.52-0.89×10⁷ cells/kg</td>
<td>100</td>
<td>Not reached</td>
<td>93 (7)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>JN-4528, CARITUDE-1 (n=29)</td>
<td>CAR T cell</td>
<td>6</td>
<td>50-114×10⁶ cells</td>
<td>63 (100¶)</td>
<td>9.5</td>
<td>10 (0)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>P-BCMA-101, PRIME (n=19)</td>
<td>CAR T cell</td>
<td>6</td>
<td>150-450×10⁶ cells</td>
<td>73</td>
<td>8.8</td>
<td>84 (6)</td>
<td>18 (3)</td>
</tr>
<tr>
<td>AMG 420 (n=4.2)</td>
<td>Bispecific antibody (BiTE)</td>
<td>3.5</td>
<td>0.2-800 µg/day, week infusions every 6 weeks, 10 cycles</td>
<td>31 (70¶)</td>
<td>Not reached</td>
<td>38 (2)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>CC-93269 (n=30)</td>
<td>Bispecific antibody</td>
<td>5</td>
<td>0.15-10 mg weekly for 3 cycles, biweekly for 3 cycles then monthly</td>
<td>43 (89§)</td>
<td>Not reached</td>
<td>77 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Tecristamab (n=78)</td>
<td>Bispecific antibody (DuoBody)</td>
<td>6</td>
<td>0.3-720 µg/kg weekly</td>
<td>31 (67¶)</td>
<td>Not reached</td>
<td>56 (0)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Belantamab mafodotin, DREAMM-2 (n=156)</td>
<td>Antibody drug conjugate</td>
<td>7</td>
<td>2.5 mg/kg every 3 weeks</td>
<td>31</td>
<td>2.9</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Belantamab mafodotin and bortezomib, DREAMM-6 (n=18)</td>
<td>Antibody drug conjugate</td>
<td>3</td>
<td>2.5 mg/kg every 3 weeks</td>
<td>78</td>
<td>Not reached</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

BiTE = bispecific T cell engager.
*This list is not comprehensive.
1P-BCMA-101 overall response rate at highest reported dose of 857×10⁶ cells for 3 patients.
2AMG 420 overall response rate at maximum tolerated dose of 400 µg/day for 10 patients.
3CC-93269 overall response rate at highest reported dose of 10 mg for 9 patients.
4Tecristamab overall response rate at highest reported dose of 270 µg/kg for 12 patients.
targeting, and retention. All doses (range 0.15-10 mg) were given intravenously over two hours weekly for the first three cycles, every two weeks for the next three cycles, and then monthly. The most common treatment emergent adverse events of grade 3 or higher included neutropenia, anemia, and infections. Cytokine release syndrome was seen in 77% of patients, with all events developing after the first dose and less common with subsequent doses. The incidence increased with higher doses, and only one patient had cytokine release syndrome of grade 3 or higher leading to their death. In 30 patients treated, the overall response rate was 43.3% and dose dependent. The overall response rate was 88.9% in nine patients in the highest dose cohort.

**Teclistamab**

Teclistamab (JNI-64007957) is a humanized, immunoglobulin G4 based, bispecific DuoBody antibody that binds to BCMA and CD3 that is being studied in a phase I clinical trial. In the dose escalation part, 78 patients received doses ranging from 0.3 µg/kg to 720 µg/kg. The drug is given intravenously every week, with one to three step-up doses given within one week before the full dose. The overall response rate was dose dependent with no responses at doses 0.3-19.2 µg/kg, 30% at 38.4-180 µg/kg, and 67% at 270 µg/kg. Cytokine release syndrome was seen in 56% of patients overall and 65% patients at doses over 38.4 µg/kg. The most common adverse events at grade 3 or higher that were related to treatment were cytopenias and infections (table 2).

**Antibody drug conjugates**

Antibody drug conjugates are complex molecules composed of an antibody that targets cancer cells and are linked to a biologically active cytotoxic drug (known as the payload; fig 7). Belantamab mafodotin (GSK2857916) is a novel humanized and afucosylated (to improve antibody dependent cell mediated cytotoxicity) antibody drug conjugate that targets BCMA. It consists of an anti-BCMA monoclonal antibody conjugated to monomethyl auristatin F, a potent microtubule inhibitor. This antibody drug conjugate was shown to have selective myeloma cell killing in vitro and in vivo thus setting the stage for clinical trials.

Table 3 | American Society for Transplantation and Cellular Therapy consensus grading for cytokine release syndrome (CRS)

<table>
<thead>
<tr>
<th>CRS parameter</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever*</td>
<td>Temperature ≥38°C</td>
<td>Temperature ≥38°C</td>
<td>Temperature ≥38°C</td>
<td>Temperature ≥38°C</td>
</tr>
<tr>
<td>With hypertension</td>
<td>None</td>
<td>Not requiring vasoressor</td>
<td>Requires a vasoressor with or without vasoressor</td>
<td>Requires multiple vasoressors (excluding vasoressor)</td>
</tr>
<tr>
<td>And/or hypoxia</td>
<td>None</td>
<td>Requiring low flow nasal cannula or blow-by</td>
<td>Requiring high flow nasal cannula, facemask, non-rebreather mask, or Venturi mask</td>
<td>Requiring positive pressure (eg: CPAP, BiPAP, intubation, and mechanical ventilation)</td>
</tr>
</tbody>
</table>

CRS grade is determined by the more severe event: hypotension or hypoxia. For example, a patient with temperature of 39.5°C, hypotension requiring one vasoressor, and hypoxia requiring low flow nasal cannula would be classified as grade 3 CRS.

This antibody was studied in a two part phase I study. The drug was well tolerated with no dose limiting toxicities, although corneal events (such as blurry vision, dry eyes, photophobia) were seen in about 58% of patients; these events are a known toxicity of monomethyl auristatin F. In the dose expansion phase, 35 patients were treated, and the overall response rate was 60% with a median progression free survival 12 months. In a phase II, two arm study, the antibody was used in patients with relapsed and refractory multiple myeloma who had failed at least three lines of treatment. The overall response rate was 31% at the 2.5 mg/kg dose and 34% at the 3.3 mg/kg dose, which was significantly lower than the phase I study. The corneal changes or keratopathy were seen in 70% and 75% of patients, respectively. Owing to the similar response rates with the 2.5 mg/kg and 3.3 mg/kg doses and a more favorable side effect profile with the lower dose, 2.5 mg/kg will be the dose used for future studies.

Based on these data, belantamab is the first anti-BCMA treatment to be FDA approved for relapsed and refractory multiple myeloma patients who have received four prior treatments including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Preliminary results for another study with 18 patients treated on the belantamab, bortezomib, and dexamethasone arm was presented recently, with an overall response rate of 78%; however, all 18 patients developed grade 1-3 keratopathy. This visual toxicity is a unique but potentially serious side effect to this drug that needs close monitoring with an ophthalmologist. Another antibody drug conjugate, DFRF4539A, is an anti-FcRH5 (also known as FcRL5) antibody conjugated to monomethyl auristatin and has shown limited activity and high incidence of toxicity in a phase I study; therefore, it was unsuccessful for this disease.

**Future directions**

Although most immunotherapies are relatively new, this field is rapidly changing and many other immunotherapies are emerging, as are new indications and improved versions of current immunotherapies (some of which we have discussed here). Although having many drugs potentially available for patients with multiple myeloma is promising, one critical unanswered question is the...
pricing for these newer drugs. Historically, cost of multiple myeloma treatments has been a major barrier leading to disparities in cancer care. These treatments should be priced fairly so that they can be universally available to patients with the disease.

Monoclonal antibodies

More recent studies are now including the monoclonal antibodies daratumumab, elotuzumab, and isatuximab in the upfront setting as part of a quadruplet regimen that includes a monoclonal antibody with standard triplet combinations to improve depth of response and thus outcomes.

Two other newer monoclonal antibodies targeting CD38 include TAK-079, which only needs to be given in small volumes subcutaneously and is being studied as a single agent; and MOR202, which is being studied in combination with dexamethasone as well as immunomodulatory drugs. Furthermore, a phase I clinical trial looking at the first monoclonal antibody targeting BCMA (SEA-BCMA) is recruiting.
**Chimeric antigen receptor T cells**

Although a high proportion of patients with relapsed and refractory multiple myeloma have deep responses to BCMA CAR T cell treatment, relapses are common and the median progression free survival in early studies ranges from 8.8 months to 19.9 months. A key area of future research focuses on building on these early results to improve durability of responses. Some of the approaches being evaluated include the identification of additional targets for cellular treatment, improved manufacturing processes, use of CAR T cell treatment in earlier stages of multiple myeloma, combinations with other drugs, and off-the-shelf approaches including treatment with allogeneic CAR T cells and CAR natural killer cells.

**Novel targets**

CAR T cells directed towards targets other than BCMA in multiple myeloma are being developed. These targets include CD38,148 149 GPRC5D,150 and SLAMF7,151 and clinical trials are ongoing. Another method to potentially decrease the risk of relapse and maximize treatment effect is the use of a combination of two CAR T products, or the development of CAR T cells that target two antigens (BCMA combined with CD19, GPRC5D, CS1, or TACI), and early results from phase I trials demonstrate feasibility and safety of this approach.81 152-156

**Improved manufacturing**

Newer transduction systems (including non-viral methods such as the piggyBac system) and alternatives to single chain variable fragments (such as Centyrin in P-BCMA-101) are being evaluated. With promising preliminary results from the phase I study, a phase II trial of P-BCMA-101 CAR T cells in patients with at least three prior lines of treatment has been initiated with an estimated enrollment of 100 patients.81 108 157 The ratio of CD4:CD8 T cells is undefined in most CAR T cell products and is determined by the ratio in the sample collected during leukapheresis; however, some CAR T products (eg, orva-cel) have predefined ratios of CD4 and CD8 T cells to evaluate whether this would improve their efficacy.100 158 159 Other products such as bb21217 have been modified to improve persistence, given that patients have limited persistence of CAR T cells at the time of relapse. Bb21217 includes T cells that have been cocultured with a phosphoinositide 3 kinase (PI3K) inhibitor bb007 to generate a product with enhanced memory-like phenotype. A trial with bb21217 is currently ongoing with an estimated enrolment of 74 patients.81 160 161

**Earlier lines of treatment**

Newer, multicenter clinical trials with products ide-cel and JNJ-4528 are opening to treat patients with CAR T cell products in combination with standard myeloma regimens in earlier lines of treatment. These studies include the KarMMa-2, KarMMa-3, and KarMMa-4 studies with ide-cel and the CARTITUDE-2 and CARTITUDE-4 studies with JNJ-4528. KarMMa-2 is a multicenter, multicohort phase II study in high risk relapsed myeloma. KarMMa-3 is a randomized phase III study comparing bb2121 with standard triplet regimens such as daratumumab, pomalidomide, and dexamethasone; or daratumumab, bortezomib, and dexamethasone; or ixazomib, lenalidomide, and dexamethasone in patients with two to four prior lines of treatment.
KarMMa-4 is a phase I study to evaluate bb2121 in high-risk patients with newly diagnosed multiple myeloma after four cycles of induction treatment. CARTITUDE-2 is a phase II multicohort study looking at JNJ-4528 in relapsed and refractory multiple myeloma including cohorts with high risk disease as well. CARTITUDE-4 is a randomized phase III trial of 600 patients with relapsed and refractory multiple myeloma who will be treated with JNJ-4528 or standard triplet regimens (pomalidomide, bortezomib, and dexamethasone; or daratumumab, pomalidomide, and dexamethasone) in patients with one to three prior lines of treatment.

**Combination with other drugs**

CAR T cells are being tested in combination with other drugs such as the immunomodulatory drugs (lenalidomide or iberdione),\(^{162, 163}\) checkpoint inhibitors (pembrolizumab)\(^{164}\) or a gamma secretase inhibitor (JSMD194) that increases BCMA expression on tumor cells. As patients could have downregulation of BCMA expression at the time of expression on tumor cells. As patients could have downregulation of BCMA expression at the time of relapse, JSMD194 is a unique approach to relapses after CAR T cell treatment.\(^{165, 166}\)

**Armor chimeric antigen receptor T cells**

So-called armored CAR T cells have been engineered to secrete proinflammatory cytokines such as interleukin 12 or ligands designed to further improve CAR T cell efficacy. These cells enhance anti-tumor efficacy and have the potential to overcome the hostile tumor microenvironment via different mechanisms.\(^{167}\) This approach has shown promise in CD19 positive cancers.\(^{168}\) Similar approaches will likely be tested in the future in multiple myeloma, particularly for patients with extramedullary disease.

**Other CAR approaches**

**Allogeneic (off-the-shelf) chimeric antigen receptor T cells**

Allogeneic CAR T cells could resolve some of the challenges with autologous CAR T cell treatment, including the delays (and costs) associated with individualized manufacturing of cells, the T cells from patients with multiple myeloma might be more exhausted, and the limited ability to give multiple doses. However, the challenges include graft versus host disease (that is, allogeneic CAR T cells attacking healthy organs such as skin), and host versus graft response (that is, the recipient immune system rejecting the allogeneic CAR T cells).\(^{169}\) Multiple groups have worked to overcome these challenges, and allogeneic CAR T cells targeting BCMA (P-BCMA-ALLO1\(^{170}\) and ALLO-715\(^{171}\)) and targeting CS1/SLAMF7 (UCARTCS1\(^{81,172}\)) are currently in clinical trials.

**Chimeric antigen receptor, natural killer cells**

An alternate off-the-shelf approach would be to use natural killer cells for manufacturing CAR. Unlike T cells, natural killer cells are not restricted by human leukocyte antigen and can therefore be produced from natural killer cell lines or cord blood, leading to inherent advantages such as off-the-shelf products and reduced toxicity and cost. Preliminary results from a first-in-human trial of anti-CD19 CAR natural killer cells for B cell cancers showed promising efficacy, with eight (73%) of the first 13 patients responding and no evidence of cytokine release syndrome, neurotoxicity, or graft versus host disease.\(^{173}\) Preclinical data for CAR natural killer cells in multiple myeloma targeting CS1, BCMA, CD138, and NKG2D ligands are promising and clinical data are awaited.\(^{174-176}\)

**Bispecific antibodies**

Given the logistical difficulty with continuous infusions of AMG 420, ongoing phase I trials are evaluating the efficacy of intermittent dosing of AMG 420 and evaluating the half life extended BCMA BiTE molecule (AMG 701). AMG 701 is a modified, newer generation version of AMG 420; it contains an Fc domain leading to a longer half life. Other bispecific antibodies targeting BCMA in phase I/II trials include REGN5458,\(^{177}\) JNJ-64007957, TNB-383B,\(^{178}\) and PF-06863135.\(^{179}\)

Although BCMA has been the main target of interest, researchers have looked at bispecific antibodies targeting other molecules such as CD38. CD38 is universally expressed and has also been targeted with other effective drugs such as daratumumab for multiple myeloma.\(^{40}\) AMG 424 is an anti-CD38/CD3 bispecific antibody with the ability to kill cancer cells with high and low levels of CD38 expression in vitro and in animal models without triggering excessive cytokine release.\(^{180, 181}\) With these findings, AMG 424 is currently being studied in a first-in-human phase I, two part study in patients with relapsed and refractory multiple myeloma. Clinical trials of a bispecific antibody targeting other molecules such as GPRC5D (JNJ-64007564) and FcRH5 (BFCR4350A) are also under way.

**Antibody drug conjugates**

Further clinical trials exploring belantamab mafodotin as a single agent or in combinations are under way such as the DREAMM-3 study, which is a randomized phase III trial comparing single agent belantamab mafodotin with pomalidomide and low dexamethasone. Other trials combining this drug with pembrolizumab (DREAMM-4), other cancer drugs (DREAMM-5), and with lenalidomide dexamethasone or bortezomib dexamethasone (DREAMM-6) in relapsed and refractory multiple myeloma; or with bortezomib, lenalidomide, and dexamethasone in transplant ineligible patients with newly diagnosed multiple myeloma (DREAMM-9) are also ongoing. Other antibody drug conjugates targeting BCMA in clinical trials include MEDI2228\(^{182, 183}\) and CC-99712. Ongoing trials are also targeting proteins other than BCMA and CD38 such as CD48, CD46, CD56, and CD74.\(^{125}\)
Other approaches—vaccination
Cancer vaccines have been shown to generate potent immune responses that can translate into clinically meaningful improvements in outcomes for patients. In multiple myeloma, many such approaches have been tested including an idiotype DNA vaccine, peptide derived from Bcl-2 family vaccine, gene transduced tumor cell vaccine (GVAX), idiotype loaded antigen presenting cells, and whole cell dendritic cell/myeloma fusion vaccine. Most recently, multipeptide vaccine was safe and immunogenic. BMT CTN 1401 is a randomized phase II multicenter trial that has enrolled 203 patients, results for which are awaited. The trial randomizes patients to vaccination with (1) dendritic cell/myeloma fusion vaccine with granulocyte macrophage colony stimulating factor (GM-CSF) adjuvant plus lenalidomide maintenance treatment versus (2) maintenance treatment alone or with GM-CSF after autologous transplant as part of an upfront treatment of multiple myeloma.

Guidelines
Early clinical trials of CAR T cell treatment uncovered greater toxicities related to generalized immune system activation (cytokine release syndrome and ICANS) than those seen with other cellular treatments. Investigators followed the National Cancer Institute’s Common Terminology Criteria for Adverse Events to assess severity and struggled with the terminology because it did not directly apply to CAR T cell treatments. As a result, many institutions treating patients with these cell treatments developed their own grading systems, making comparisons difficult between trials and centers. The American Society for Transplantation and Cellular Therapy therefore developed consensus grading systems incorporating data from these prior individualized grading criteria. These guidelines for grading cytokine release syndrome (table 3) and ICANS (table 4) have now been adopted widely in the management of toxicities associated with CAR T cell treatment.

Conclusion
Substantial progress has been made in the care of patients with multiple myeloma over the past two decades resulting in a longer overall survival. Despite this, an unmet need still exists for newer treatments as patients eventually relapse. The landscape for treatment options in multiple myeloma is rapidly changing with many drugs in the pipeline, most of them being immunotherapies. The monoclonal antibodies have shown remarkable efficacy with minimal toxicity and have thus been widely adopted to treat multiple myeloma in relapsed patients initially. Trials looking at monoclonal antibodies in newly diagnosed multiple myeloma are promising and additional large randomized trials are ongoing.

Questions for future research
- Despite high overall response rates, many of these treatments still have only a modest progression free survival. What are the mechanisms that lead to relapse with these immunotherapies and how can they be overcome?
- Will using these drugs in earlier lines of treatments improve outcomes further?
- Although these novel drugs are effective, they are cost prohibitive and questions arise as to the affordability for the broader myeloma population worldwide.
- The field is dominated by multiple BCMA directed treatments in the pipeline, but how can these drugs can be sequenced, and can they retain their efficacy after another prior BCMA directed treatment?

Although this field of immunotherapy is promising, not all treatments are successful in multiple myeloma and some might also be harmful, as seen by the lack of response to single agent checkpoint inhibitors and the increased rate of serious adverse events and deaths in clinical trials combining checkpoint inhibitors with immunomodulatory drugs.

More recently, several large multicenter trials of BCMA targeted CAR T cell treatment have shown unprecedented overall response rates between 60-100% in patients with highly relapsed and refractory multiple myeloma; however, their progression free survival is relatively short (8-20 months). Therefore, much research is still needed into improving duration of response as well as developing products that can be off the shelf (such as CAR natural killer cells and allogeneic CAR T cells). Other BCMA treatments with promise include the bispecific antibodies AMG 420, teclistamab, and CC-93269 and the antibody drug conjugate belantamab mafodotin, among many others. Ultimately, which BCMA directed treatment will become prominent in multiple myeloma will depend on several factors, such as reduced toxicity, higher efficacy, lower cost, and ease of use, and whether different BCMA treatments given sequentially will continue to be effective.

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