

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of multiple myeloma

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ABSTRACT

Outcomes in multiple myeloma (MM) have improved dramatically in the last two decades with the advent of novel therapies including immunomodulatory agents (IMiDs), proteasome inhibitors and monoclonal antibodies. In recent years, immunotherapy for the treatment of MM has advanced rapidly, with the approval of new targeted agents and monoclonal antibodies directed against myeloma cell-surface antigens, as well as maturing data from late stage trials of chimeric antigen receptor (CAR) T cells. Therapies that engage the immune system to treat myeloma offer significant clinical benefits with durable responses and manageable toxicity profiles, however, the appropriate use of these immunotherapy agents can present unique challenges for practicing physicians. Therefore, the Society for Immunotherapy of Cancer convened an expert panel, which met to consider the current role of approved and emerging immunotherapy agents in MM and provide guidance to the oncology community by developing consensus recommendations. As immunotherapy evolves as a therapeutic option for the treatment of MM, these guidelines will be updated.

INTRODUCTION

Multiple myeloma (MM) is the second most commonly diagnosed hematological malignancy, with nearly 160 000 new cases worldwide in 2018.¹ Before the 21st century, most patients with MM died within a few years after diagnosis, yet outcomes have improved dramatically during the past two decades. Novel therapies including immunomodulatory agents (IMiDs), proteasome inhibitors (PIs) and monoclonal antibodies (mAbs) have been incorporated into standard treatment approaches, which had previously been limited to stem cell transplants, alkylating agents and steroids.^{2–6} Additionally, advances in risk stratification based on cytogenetics^{7,8} as well as the ability to detect minimal residual

disease (MRD) with a high degree of sensitivity using multicolor flow cytometry (MFC) or next-generation sequencing (NGS) technologies⁹ may further enhance the selection of treatment strategies both at initial diagnosis and relapse. Despite these breakthroughs, however, MM remains largely incurable, with the vast majority of patients experiencing relapse at some point.

Advances in understanding of the basic mechanisms of immune evasion and suppression in MM has led to new therapies with demonstrated benefits for patients. In 2015, the US Food and Drug Administration (FDA) approved two mAbs for the treatment of MM, daratumumab (dara) and elotuzumab,^{10 11} blazing a trail for the development of numerous other immunotherapies in this disease setting, including chimeric antigen receptor (CAR) T cells,^{12–15} antibody-drug conjugates (ADCs),^{16–18} bispecific T-cell engagers (BiTEs)^{19–21} and cancer vaccines.^{22 23} As the world's leading non-profit member-driven organization dedicated to advancing cancer immunotherapy, the Society for Immunotherapy of Cancer (SITC) develops Cancer Immunotherapy Guidelines for a variety of disease states. Previously, SITC published the first-ever consensus statement for the use of immunotherapy to treat hematological malignancies in 2016.²⁴

Immunotherapy is currently playing a pivotal role in MM treatment, necessitating clinical practice guidelines with detailed recommendations specific to these important, practice-changing modalities. Recognizing the rapid pace of advancement of the field, and a need to update the previously published consensus statement

with practical guidance on how to incorporate the ever-growing number of immunotherapeutic agents that have been approved or are in the final stages of clinical development into the treatment of MM, SITC convened an expert panel encompassing perspectives from hematology, medical oncology, hematopathology, nursing and patient advocacy to provide evidence-based recommendations for the oncology community. This panel met to consider issues related to patient selection, dosing and monitoring, toxicity management and quality of life (QoL), with the goal of preparing a consensus statement on clinical use of immunotherapy for patients with MM.

In recognition of the rapid pace of advancement of the immunotherapy field, this consensus statement will discuss emerging therapies that have not yet, at the time of publication, received United States Food and Drug Administration approval. As such, the manuscript is divided into two sections, based on FDA approval status at time of publication. Because recommendations concerning the use of IMiDs were published in the 2016 consensus statement on hematological malignancies,²⁴ those agents are not extensively discussed in these guidelines, except as components of combination regimens with antibody therapies. Additionally, although allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an important therapeutic option in the management of MM, other groups have published consensus recommendations regarding its use²⁵ and therefore a discussion of the approach was beyond the scope of these guidelines. As with any consensus statement, the recommendations contained within this paper are intended to provide guidance and are not a substitute for the professional judgment of individual physicians treating individual patients.

MATERIALS AND METHODS

SITC Multiple Myeloma Immunotherapy Guideline Expert Panel

The SITC Multiple Myeloma Immunotherapy Guideline Expert Panel consisted of 19 participants, including 17 medical oncologists, 1 nurse practitioner and 1 patient advocate. One hundred percent of clinical expert panel members reported previous experience/knowledge regarding the use of immuno-oncology therapy for the treatment of patients with MM. The panel communicated regularly via email and teleconference in addition to completing online surveys (see online supplementary file 1), addressing clinical topics concerning the use of cancer immunotherapy for the treatment of patients with MM, which helped form the basis for consensus recommendations.

Consensus statement policy

The Institute of Medicine's (IOM) Standards for Developing Trustworthy Clinical Practice Guidelines were used as a model to develop the consensus recommendations in this manuscript. IOM standards dictate that guideline development is led by a multidisciplinary team using a transparent process where both funding sources and

conflicts of interest are readily reported. Recommendations are based on literature evidence, where possible, and clinical experience, where appropriate.²⁶ For transparency, a draft of this consensus statement was made publicly available for comment after journal submission. All comments were considered for inclusion into the final manuscript. This consensus statement is intended to provide guidance and is not a substitute for the professional judgment of individual treating physicians.

Evidence and consensus ratings

Consensus recommendations were derived from evidence within the published literature along with responses to a clinical questionnaire that addressed current practices in the use or recommendation for use of immunotherapy agents (online supplementary file 1). SITC Cancer Immunotherapy Guidelines provide recommendations based on peer-reviewed literature and consensus within the expert panel. Consensus was defined as $\geq 75\%$ agreement among expert panel members.

Conflicts of interest policy

As per SITC policy, expert panel members managed potential competing interests through disclosure of all financial relationships that might result in actual, potential or perceived conflicts of interest. No commercial funding was provided to support the expert panel, literature review, or the preparation of this manuscript.

Literature review process

The MEDLINE database was used to search the scientific literature for current therapies related to MM and immunotherapy in humans and encompassed articles published from 2012 to 2019, including clinical trials, meta-analyses, practice guidelines and research in humans. The search terms included 'multiple myeloma' AND 'immunotherapy', 'daratumumab', 'elotuzumab', 'isatuximab', 'CAR T cell therapy', 'bispecific antibody', 'antibody-drug conjugate' and 'quality of life.' Articles were screened by expert panel members to include only papers with clinically accurate and relevant information and to remove duplicate articles from independent searches, resulting in a final citation list cataloged using EndNote X9. The citation list was supplemented with additional articles identified by the panel, as appropriate and necessary for a comprehensive literature review.

DARATUMUMAB

The integration of effective mAbs into the treatment of patients with MM has been in clinical development for >10 years.²⁷ The anti-CD38 therapy daratumumab is the first immunotherapeutic mAb to be clinically tested and to elicit durable responses as a single agent. This reported efficacy, in addition to its proven safety record and enhanced clinical benefit in combination with other antimyeloma therapies, has led to several FDA approvals for daratumumab in treating patients with MM. Such evidence, also demonstrating a

lack of overlapping toxicity, deep clinical response rates and long durations of response, places dara in a crucial position for the treatment of patients with MM in both the first-line and the relapsed/refractory setting.

Relapsed/Refractory setting

The phase III POLLUX study investigated dara plus lenalidomide and dexamethasone (D-Rd) versus Rd alone in relapsed or refractory multiple myeloma (RRMM). The dara regimen reduced the risk of disease progression or death by 63% and significantly increased overall response rate (ORR) in patients with RRMM compared with Rd alone (93% vs 76%; $p < 0.001$). Furthermore, when combined with standard-of-care regimens across multiple phase III studies including POLLUX and CASTOR (bortezomib+dexamethasone±dara), the addition of dara led to $\geq 50\%$ reductions in the risk of progression or death, doubled complete response (CR) rates and tripled MRD-negative rates at the 10^{-5} sensitivity threshold in patients with RRMM.^{28–30} A 4-year follow-up analysis of POLLUX examined 569 randomized patients (D-Rd, $n=286$; Rd, $n=283$). At a median follow-up of 51.3 months, D-Rd significantly prolonged progression-free survival (PFS) versus Rd (median 45.8 vs 17.5 months; HR 0.43; 95% CI 0.35 to 0.54; $p < 0.0001$).³¹ A PFS benefit for D-Rd versus Rd was also observed regardless of cytogenetic risk status. In the phase III CASTOR trial evaluating dara in combination with bortezomib and dexamethasone (D-Vd) compared with Vd alone, the 12-month rate of PFS was 60.7% in the dara group vs 26.9% in the control group. Additionally, the ORR was higher in the dara group than the control group (82.9% vs 63.2%).³²

The open-label, multicenter phase Ib EQUULEUS study (NCT01998971) evaluated dara in combination with various backbone regimens in patients with newly diagnosed MM as well as patients who had received prior therapy. In the dara plus pomalidomide and dexamethasone (D-Pd) treatment arm ($n=103$), only patients who had previous treatment were included (median number of prior therapies=4, range=1–13), all of whom had previous lenalidomide therapy. The ORR was 60% (95% CI 50.1 to 69.7) with 17 patients achieving CR or better and 5 (29%) of those patients achieving MRD negativity at the 10^{-5} threshold. Median PFS was 8.8 months (95% CI 4.6 to 15.4), and the 12-month PFS rate was 42% (95% CI 31.5 to 51.9). In exploratory analysis, PFS and ORRs were similar across patients with standard or high cytogenetic risk.³³ Based on data from the EQUULEUS study, the FDA approved D-Pd for the treatment of patients with MM who have received at least two prior therapies including lenalidomide and a PI in 2017.

Significant PFS benefit was demonstrated for the addition of dara to carfilzomib and dexamethasone (KdD) for the treatment of patients with RRMM with measurable disease who had received one to three prior lines of therapy in the randomized, open-label, phase III CANDOR study (NCT03158688). After a median follow-up of 16.9 months and 16.3 months for the KdD

and Kd arms, median PFS was not reached for the KdD arm vs 15.8 months for the control arm (HR 0.63; 95% CI 0.46 to 0.85; $p=0.0014$). The ORR was 84.3% vs 74.7% ($p=0.0040$), for KdD versus control, respectively, and the rate of CR or better was 28.5% vs 10.4% with an MRD-negative CR rate at 12 months of 12.5% for KdD vs 1.3% for Kd ($p < 0.0001$).³⁴

Frontline daratumumab Transplant-eligible patients

In an ongoing phase II, randomized study, the GRIFFIN trial (NCT02874742) compared the combination of dara, bortezomib, lenalidomide and dexamethasone (D-VRd) with VRd in 207 patients with newly diagnosed myeloma eligible for autologous HSCT. Patients received four induction cycles of D-VRd (or VRd) every 21 days followed by stem cell mobilization, high-dose therapy, and HSCT; two consolidation cycles of D-VRd (or VRd); and maintenance therapy with dara and lenalidomide (or lenalidomide alone) for 24 months.³⁵ At primary end point analysis, by the end of consolidation (cycle 6), the study met its prespecified one-sided alpha of 0.1 with a stringent complete response (sCR) rate of 42.4% for patients receiving D-VRd vs 32% in the VRd arm. Responses have continued to deepen throughout maintenance—rates of sCR improved for D-VRd versus VRd (62.6% vs 45.4%; $p=0.0177$), as did rates of MRD negativity at the 10^{-5} threshold (51.0% vs 20.4%; $p < 0.0001$).³⁶ Overall, the regimen with dara (D-VRd) was found to be safe and more effective than VRd alone, with an increase in any-grade infection rates of 91% vs 62%, largely due to grade 1/2 upper respiratory tract infections. Stem cell yield was adequate in both arms. At a median follow-up of 22.1 months, the 24-month PFS rate was 95.8% vs 89.8%, favoring the D-VRd combination.³⁷ Survival data have not yet matured at the time of this publication. A phase III study (PERSEUS) is ongoing to evaluate VRd versus D-VRd.³⁸

Data from the phase III CASSIOPEIA trial³⁹ of 1085 patients showed that incorporating dara into a regimen of bortezomib, thalidomide and dexamethasone (D-VTd) led to a 34% reduction in disease progression risk compared with the standard triplet therapy (VTd). The trial was divided into two parts, an induction and consolidation phase followed by maintenance treatment with dara or observation. In the induction phase, the addition of dara was associated with a 53% reduction in the risk of progression or death. At day 100 after transplantation, CR or better was observed in 39% of the patients in the dara-treatment group, with 64% achieving MRD-negativity, vs 26% and 44%, respectively, for those treated with VTd alone.⁴⁰ With a median follow-up of 18.8 months, the estimated 18-month PFS rate was 93% D-VTd vs 85% VTd (HR 0.47; 95% CI 0.33 to 0.67; $p < 0.0001$). Based on data from CASSIOPEIA, in September, 2019, the FDA approved D-VTd in newly diagnosed transplant-eligible patients.

Transplant-ineligible patients

The MAIA trial (NCT02252172) investigated the clinical benefit of adding dara to lenalidomide and dexamethasone (D-Rd) as part of a phase III, randomized trial in patients with transplant-ineligible untreated MM. The primary endpoint examined was PFS. At median follow-up of 28.0 months, of the 737 randomized patients, disease progression or death occurred in 26.4% of patients in the dara group and 38.8% in the control group. The estimated percentage of patients who were alive without disease progression at 30 months was 70.6% (95% CI 65.0 to 75.4) and 55.6% (95% CI 49.5 to 61.3) in the dara and control groups, respectively (HR 0.56; 95% CI 0.43 to 0.73; $p < 0.001$). The rates of CR or better were 47.6% and 24.9% in the dara and control groups ($p < 0.001$), respectively. A total of 24.2% vs 7.3% of patients in the dara and control groups, respectively, reported results below the threshold for MRD (one tumor cell per 10^5 total bone marrow cells) ($p < 0.001$).⁴¹ Results from this study further support the use of dara in combination with standard therapies in first-line treatment of patients with MM.

The ALCYONE trial (NCT02195479) assessed the addition of dara to the combination of bortezomib, melphalan and prednisone (D-VMP) in patients with treatment-naïve MM who are ineligible for HSCT in a phase III, randomized study.⁷ In this study, 706 patients received nine cycles of VMP either alone or with dara until disease progression. The primary endpoint was PFS. At a median follow-up of 40.8 months, the median PFS was 36.4 months with D-VMP vs 19.3 months in the control group (HR for disease progression or death 0.55; 95% CI 0.43 to 0.71; $p < 0.0001$). The estimated 36-month overall survival (OS) rate was 78% with D-VMP vs 68% with VMP, with a significant benefit for OS observed for D-VMP versus VMP alone (HR 0.60; 95% CI 0.46 to 0.80; $p = 0.0003$).⁴²

Other combination trials

An ongoing phase II trial (NCT03012880) is investigating the addition of dara to the triplet induction therapy of ixazomib, lenalidomide, and dexamethasone (IRd) to determine if the quadruplet regimen elicits enhanced efficacy with a feasible schedule. Patients with previously untreated MM were enrolled irrespective of their transplant eligibility and CR rate was the primary endpoint. Treatment consisted of ixazomib 4mg (days 1, 8, 15), lenalidomide 25 mg (days 1–21), dexamethasone 40 mg weekly and dara 16 mg/kg weekly for two cycles, every other week during cycles 3–6, and then every 4 weeks thereafter. As of the final assessment, all patients were alive and progression-free with a median follow-up of 5.2 months (median five cycles, range 2–13). One patient discontinued for alternate therapy. Responses proved rapid with a 90% partial response (PR) or better (32% very good partial response (VGPR)) after two cycles, and 100% PR or better (50% VGPR) for 32 patients who completed four cycles. The overall best confirmed

response rate among the 38 analyzed patients was 95%, including 11% CR and 47% VGPR.⁴³

Panel recommendations

Dara is FDA-approved and the panel recommends its use in the following settings:

- ▶ In combination with lenalidomide and dexamethasone (D-Rd) in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with RRMM who have received at least one prior therapy.
- ▶ In combination with bortezomib, melphalan, and prednisone (D-VMP) in newly diagnosed patients who are ineligible for autologous stem cell transplant.
- ▶ In combination with bortezomib, thalidomide, and dexamethasone (D-VTd) in newly diagnosed patients who are eligible for autologous stem cell transplant.
- ▶ In combination with bortezomib and dexamethasone (D-Vd) in patients who have received at least one prior therapy.
- ▶ In combination with pomalidomide and dexamethasone (D-Pd) in patients who have received at least two prior therapies including lenalidomide and a PI.
- ▶ As monotherapy, in patients who have received at least three prior lines of therapy including a PI and an IMiD or who are double-refractory to a PI and an IMiD.

Other combinations in newly diagnosed patients:

- ▶ Based on emerging data (e.g. from the Griffin trial³⁷), the panel was comfortable recommending D-VRd as one possible induction regimen option in newly diagnosed patients who are eligible for autologous stem cell transplant.
- ▶ A consensus could not be reached regarding the use of dara in combination with carfilzomib, lenalidomide and dexamethasone (D-KRd) in newly diagnosed patients who are eligible for autologous stem cell transplant.

Other combinations in RRMM:

- ▶ KdD is recommended for patients with RRMM in the USA that are refractory to immunomodulatory drugs and bortezomib, based on emerging data from the CANDOR trial.³⁴

Cytogenetic risk status

In both the CASTOR and POLLUX trials, dara combinations improved PFS regardless of the cytogenetic risk status.^{28 30} The antibody combination regimens seem to offer more benefit to the high-risk patients relative to the doublet-based regimens in RRMM in these studies.²⁹ In the phase III MAIA trial of newly diagnosed patients, the benefit of adding dara was more pronounced in the standard risk patients than the high-risk patients.⁴¹ However, no tests for interaction between cytogenetic risk and PFS were reported. Additionally, the subgroups with high-risk cytogenetics are relatively small (92 patients in MAIA, 168 patients in CASSIOPEIA), and power for comparison of PFS within these groups is not reported. At this juncture,

the data remain inconclusive on benefit from the addition of dara in the newly diagnosed induction setting for patients with high-risk disease.

Panel recommendations

- ▶ Until further phase III data become available, a consensus could not be reached to recommend that dara is the definitive choice for patients with high-risk cytogenetics, particularly in the frontline setting.

Dosing and administration

The dara package insert advises standard treatment with steroids, acetaminophen and antihistamines 1–3 hours prior to infusion to manage infusion-related reactions (IRRs).¹⁰ Across trials, the vast majority of IRRs occurred during the first dose.^{32–44} Additionally, a multicenter, open-label early access treatment protocol study found that IRR rate was one-third lower in patients who received 10 mg of the leukotriene receptor antagonist montelukast 30 min prior to dara dosing.⁴⁵

Panel recommendations

- ▶ Standard premedications as suggested below may be used to mitigate IRRs:
 - Dexamethasone, 20 mg intravenous (IV) (for dara monotherapy methylprednisolone, 100 mg is preferred).
 - Acetaminophen, 650–1000 mg oral.
 - Diphenhydramine, 25–50 mg oral or IV.
 - Montelukast, 10 mg, orally dissolving tablet (ODT) preferred, prior to first infusion.
- ▶ After cycle 2, steroids may be omitted if the patient has tolerated dara without IRRs.
- ▶ For patients with severe IRRs during dose or a history of respiratory comorbidities, oral corticosteroids (≤ 20 mg methylprednisolone or equivalent intermediate-acting or long-acting corticosteroid) should be administered per the prescribing label on each of the 2 days following dara infusions.
- ▶ Short-acting and long-acting bronchodilators and inhaled corticosteroids may be considered for patients with a long history of chronic obstructive pulmonary disease (COPD).

Subcutaneous dosing

The PAVO trial (MMY1004), an open-label dose-escalation phase Ib study, evaluated subcutaneous delivery of dara in patients with RRMM. Results suggested that dara can be administered safely in a short time (3–5 min) as a subcutaneous formulation with lower rates of IRRs, yet retaining efficacy.⁴⁶ An ongoing phase III randomized multicenter study of subcutaneous versus IV administration of dara in patients with RRMM, the COLUMBA trial (NCT03277105), supports use of flat-dose 1800 mg dara subcutaneously. A total of 522 patients who had received a median of 4 prior lines of therapy including PIs and IMiDs were randomized to receive dara subcutaneously (n=263) or IV dara (n=259). The rates of all grade IRRs were 34.5% vs 12.7%, respectively and responses, median

PFS and 6-month OS rates were comparable between both groups.⁴⁷ Subcutaneous injection was non-inferior to IV dara across all body-weight subgroups, with subcutaneous being associated with lower rate of IRRs.⁴⁸ Importantly, patients also reported improved experience with subcutaneous dara, based on shorter administration time.⁴⁹ The phase II, open-label, multicenter PLEAIDES trial (NCT03412565) confirmed the safety profile of subcutaneous dara in combination with standard regimens such as VRd, Rd, or VMP in both the first-line and RR settings. Across groups, ORRs with subcutaneous dara-containing regimens were similar to those reported in IV dara trials (i.e. GRIFFIN for D-VRd, POLLUX for D-RD, ALCYONE for D-VMP). Importantly, the rate of IRRs across all cohorts receiving subcutaneous dara was 7.5% (15/199), with the majority (93.3%) being grade 1–2.⁵⁰ Based on results from COLUMBA and PLEAIDES, the FDA approved subcutaneous dara on May 1, 2020.

Panel recommendation

- ▶ The panel felt that the new subcutaneous formulation will provide a convenient option for patients.

Split dosing

Given that dara is only stable for 16 hours after reconstitution, the first dose of 16 mg/kg IV, with a median infusion time of 6–8 hours may result in drug remaining at the close of the infusion center that cannot be saved until the next day. Of note, stability data allow dara to be reconstituted in 4 mg/mL, thereby allowing volumes to be reduced.⁵¹

Panel recommendations

- ▶ For infusion centers with limited hours of operation, the first dose of dara can be split as 8 mg/kg across 2 days, which has a median infusion time of approximately 4 hours on each day. Nearly all IRRs occur on the first dose.
- ▶ For dose 4 and beyond, dara can be given safely over 90 min.⁵²
- ▶ Once subcutaneous dara is commercially available, the need to split dose will diminish.

Special considerations

Patients with severe renal insufficiency, defined as glomerular filtration rate < 30 , are typically excluded from clinical trials despite accounting for about 20% of patients with MM.⁵³ However, anti-CD38 antibodies are not metabolized by the kidney, and there are case reports of patients being safely treated in the setting of severe renal insufficiency.^{54–55}

Hepatitis B virus (HBV) reactivation carries significant risk of morbidity and mortality for patients receiving immune-modulatory and biological therapies. A large reservoir of individuals at risk for reactivation exists within the general population, including people currently infected and those with prior exposure.⁵⁶ Both the American Society of Clinical Oncology (ASCO) and the American Gastrological Association guidelines recommend all

patients with hematological malignancies receiving anti-cancer therapy should be screened for active or resolved HBV infection by blood tests for hepatitis B surface antigen (HepBsAg) and antibody to hepatitis B core antigen (HepBcAb).^{57 58} Two options exist for patients with evidence of prior exposure: serial monitoring for HBV DNA by PCR or initiation of prophylactic antivirals for patients deemed to be at high risk, such as those receiving biologics, high-dose chemotherapy or stem cell transplants.

Panel recommendations

- ▶ Although patients with renal failure, patients with COPD and patients with plasma cell leukemia are commonly excluded from clinical trials, the panel felt that these populations may safely be treated with dara.
- ▶ Before administering dara, patients should be tested for hepatitis B, given the potential risk of viral reactivation.
- ▶ For patients with no known hepatitis B exposure history, serum tests should be performed for HepBcAb, HepBsAb, and HepBsAg. In cases with evidence of hepatitis B exposure, a PCR test for hepatitis B genomes is recommended. For patients with positive serum tests for HepBcAb, entacavir should be considered.
- ▶ Prophylactic acyclovir should be administered to patients receiving dara.

Response evaluation, treatment duration

Because dara can render myeloma plasma cells CD38 negative by flow cytometry, treatment can hinder the ability to accurately ascertain MRD. Alternatives include evaluating for MRD by NGS or alternative anti-CD38 antibodies, such as vs38.^{59 60} Additionally, the Hydrashift 2/4 dara is an FDA-approved assay to mitigate antibody interference.⁶¹ Antibody interference testing is unnecessary for non-IgG kappa isotype patients, patients with detectable disease by free light chain (FLC) or Bence Jones protein (BJP), or patients with an M-spike >0.2 g/dL by serum protein electrophoresis (SPEP).⁶²⁻⁶⁴

Anti-CD38 antibodies such as dara interfere with blood bank testing by binding to CD38 on red blood cells (RBCs) and causing panagglutination on the indirect antiglobulin test.⁶⁵ Because many patients with MM have received multiple transfusions in the context of treatment and may in fact have RBC alloantibodies, a false-positive result should not be assumed solely on the basis of dara exposure. The most common and widely validated method of interrupting anti-CD38 antibody binding to RBCs is to treat with the reducing agent dithiothreitol (DTT).⁶⁶ Importantly, DTT has the potential to denature other clinically significant antigens including Kell and Yt.⁶⁵

All approved dara-containing regimens have used dara until progression, which for patients reaching 7 months and beyond is once monthly. Based on pharmacokinetic data, it appears that if dara is to be given as maintenance therapy, a 4-week schedule is likely to maintain

through levels better than 8-week intervals. Trials are ongoing investigating dara as maintenance therapy after autologous stem cell transplant (NCT03901963 and NCT03346135).⁶⁷ There is insufficient data to establish efficacy for retreatment with dara. However, a retrospective study of 34 patients with RRMM found that one third of patients refractory to both dara and pomalidomide responded when they were retreated with the combination.⁶⁸

Panel recommendations

- ▶ Response to dara should be monitored according to institutional protocols, most of which assay MM labs monthly. In patients with IgG kappa myeloma, serologic determination of CR can be confounded by the presence of dara.
- ▶ In the presence of a measurable M-spike, dara will have a minimal effect on disease measurement. When patients reach undetectable levels, however, mass spectrometry or other antibody interference testing methods should be considered.
- ▶ A consensus could not be reached to recommend retreatment with dara in patients relapsing on monthly dosing.
- ▶ Patients on dara should receive seasonal influenza vaccines.
- ▶ To manage infections following treatment, intravenous IgG (IVIG) should be administered according to established institutional criteria, which are not specific to dara.

ELOTUZUMAB

Elotuzumab is a mAb targeting signaling lymphocytic activation molecule F7 (SLAMF7) that elicits its antitumor effect through both direct activation of natural killer (NK) cells and antibody-dependent cellular toxicity.⁶⁹ Elotuzumab was first approved for MM on November 30, 2015.⁷⁰ Although no studies have found benefit for elotuzumab monotherapy, either in the advanced⁷¹ or smoldering⁷² settings, it has demonstrated significant activity in combination with IMiDs and other agents in the relapsed and refractory setting.⁷³ At the time of publication, elotuzumab has received FDA approval as combination therapy with lenalidomide and dexamethasone (E-Rd) for the treatment of adult patients with RRMM who have received one to three prior therapies or in combination with pomalidomide and dexamethasone (E-Pd) for adult patients who have received at least two prior therapies including lenalidomide and a PI.¹¹

Literature review

The ELOQUENT-2 trial (NCT01239797) was a phase III, randomized, open-label study that evaluated the efficacy and safety of E-Rd versus Rd alone in patients with MM who had received one to three prior lines of treatment and had documented disease progression after their most recent therapy. During the trial, 646 patients were randomized to E-Rd (n=321) or Rd (n=325), and in an extended

5-year follow-up, the longest median follow-up of any immuno-oncology agent in MM, 27% reduction in risk of progression or death was attained for E-Rd versus Rd (HR 0.73; 95% CI 0.60 to 0.87). The ORR was 79% (E-Rd) vs 66% (Rd).⁷⁴ Approximately 32% of patients had del(17)p and 9% of patients had t(4;14), and the outcomes in high-risk patients were comparable with those of the patients at standard risk.⁷⁵ The most common grade 3–4 adverse events (AEs) with E-Rd versus Rd were infections (35% vs 27%), neutropenia (26% vs 34%), anemia (17% vs 17%) and fatigue (10% vs 9%). Discontinuation of study regimens was mostly due to disease progression (55% vs 56% at the 5-year mark). Thus, E-Rd showed an overall sustained, durable improvement in PFS, reporting a 27% reduction in the risk of progression or death.⁷⁴

Based on the results from ELOQUENT-2, ELOQUENT-3 (NCT02654132) was initiated as a phase II, randomized, open-label trial investigating the addition of elotuzumab to pomalidomide plus dexamethasone (E-Pd vs Pd). The combination of pomalidomide and dexamethasone has previously been shown to be effective in patients with MM refractory to lenalidomide and a PI.⁷⁶ In ELOQUENT-3, a total of 117 patients were randomly assigned to receive either E-Pd (60 patients) or Pd alone (control; 57 patients) with the primary end point of investigator-assessed PFS.⁷⁷ After a minimum follow-up period of 9.1 months, median PFS was 10.3 months in the E-Pd group vs 4.7 months in the control group (HR 0.54; 95% CI 0.34 to 0.86; $p=0.008$), and ORR was 53% vs 26%, respectively (OR 3.25; 95% CI 1.49 to 7.11). Benefit from E-Pd was also demonstrated in patients who had received at least four previous lines of therapy, with a median PFS of 10.3 months (95% CI 3.7 to not reached) in the E-Pd group and 4.3 months (95% CI 1.9 to 9.3) in the control group (HR 0.51; 95% CI 0.24 to 1.08). The safety of E-Pd was notable, with grade 3/4 neutropenia occurring in 13% in E-Pd vs 27% for Pd and grade 3/4 infections occurring in 13% vs 22%. The main reason for discontinuation of the trial treatment was disease progression (43% of the treated patients in the E-Pd group and 56% of the treated patients in the control group).⁷⁷

A phase II trial (NCT01478048) evaluated the addition of elotuzumab to the combination of bortezomib and dexamethasone (Vd) in patients with MM with documented disease progression after one to three prior lines of therapy. The 1-year PFS rate was 39% (95% CI 28% to 50%) with E-Vd vs 33% (95% CI 22% to 44%) with Vd, yielding a 28% reduction in the risk of progression or death with E-Vd compared with Vd. Follow-up analysis at the 2-year point revealed more striking differences between subgroups stratified by FcγRIIIa V genotype, with a median PFS of 22.3 months for patients in the E-Vd group who were homozygous for the high-affinity FcγRIIIa V (VV) allele (13 patients) compared with 9.8 months in patients in the E-Vd group homozygous for the low-affinity FcγRIIIa F (FF) allele (24 patients) and a sizeable improvement over patients in the Vd group homozygous for the V allele (8.2 months). A trend toward longer

PFS with E-Vd was also observed across key subgroups, including in patients aged 65 years or older and in those who had received a prior PI or IMiD. Discontinuation in the overall population was mostly due to disease progression (57%). An increased rate of infections was observed for elotuzumab in combination with a PI: 67% vs 53% of all grade and 21% vs 13% of grade 3/4 for E-Vd versus Vd, respectively.⁷⁸

Elotuzumab has also been studied in combination with thalidomide and low-dose dexamethasone in a phase II single-arm safety study in the relapsed/refractory setting, where minimal toxicity was observed with the triple regimen and efficacy data suggested potential clinical benefit in a highly pretreated population. In the trial, grade 3 or higher non-hematological AEs were reported in 63% of patients, most commonly asthenia (35%) and peripheral edema (25%), and six patients (15%) had an infusion reaction. The ORR was 38%, with median PFS 3.9 months and median OS 16.3 months.⁷⁹ Another phase II trial (NCT03155100) evaluating the combination of elotuzumab, carfilzomib, pomalidomide and dexamethasone in RRMM is actively recruiting.

Patient selection

As of 2019, two phase III trials were exploring elotuzumab-containing regimens as a frontline option. ELOQUENT-1 (NCT01335399) is investigating the addition of E-Rd to treat newly diagnosed, non-transplant eligible MM.⁸⁰ The phase III GMMG-HD6 trial (NCT02495922) is investigating the efficacy of elotuzumab in combination with VRd induction/consolidation and lenalidomide maintenance in transplant-eligible patients as frontline therapy.⁸¹ Additionally, SWOG S1211 (NCT01668719) is a phase I/II trial evaluating for the first time a four-drug E-VRd induction regimen in high-risk newly diagnosed MM. Phase I has been completed and of the eight patients enrolled, the most common AEs were fatigue (100%), peripheral sensory neuropathy (83%), edema (83%), lymphopenia (66%) and leukopenia (50%), with one dose-limiting toxicity (grade 4 lymphopenia) observed.⁸² E-Rd is also being evaluated in patients with high-risk smoldering multiple myeloma (SMM). In a phase II trial, of the 34 evaluable patients enrolled to both arms of the study, the clinical benefit rate was 97% with an ORR of 71%, including 9 very good VGPRs (26%) and 15 PRs (44%) and at the 1-year mark, no patients progressed to active disease during, or after, protocol therapy.⁸³

No randomized studies have directly compared combination therapy with anti-CD38 antibodies (eg, dara and isatuximab) to elotuzumab-containing regimens. Given the temporary depletion of NK cells with anti-CD38 monoclonal antibodies, treatment with elotuzumab-containing (which may be dependent on NK cell function) regimens in the immediate next line of therapy has not been formally studied in prospective studies. The Monoclonal Antibodies in Multiple Myeloma: Outcomes after Therapy Failure study evaluated 275 patients with anti-CD38 refractory MM and found that the addition

of elotuzumab had an ORR of 21% with median PFS 2.6 months and OS 8.3 months.⁸⁴ A retrospective analysis of 50 heavily pretreated patients who received both elotuzumab and dara found that responses to elotuzumab decreased when given after dara, but responses to dara did not change regardless of the treatment sequence. No statistical difference was seen in ORR (78% for elotuzumab vs 89% for dara) for the initial antibody given, but a significant difference in ORR (61% for elotuzumab vs 88% for dara) was observed for the agent given second ($p=0.04$).⁸⁵ Another retrospective study that analyzed 86 patients who had progressed on elotuzumab in combination with an immunomodulatory drug reported a 35.6% ORR on subsequent treatment with an anti-CD38 mAb (dara or isatuximab) with a median PFS of 4.6 months (95% CI 1.6 to 7.6) and median OS of 15.3 months (95% CI 8.2 to 22.4).⁸⁶ A small retrospective analysis of 37 patients found significantly higher ORR and cumulative PFS for elotuzumab prior to dara (64.3% and 22.67%) compared with dara before elotuzumab ((34.8% and 10.5%).⁸⁷ It is important to note, however, the clear selection biases in analysis of real-world patients treated with an agent without single agent activity.

Panel recommendations

- ▶ E-Rd is approved in patients who have received one to three prior therapies.
- ▶ E-Pd is approved in patients who have received at least two prior therapies.
- ▶ Patients with high-risk cytogenetics may benefit from elotuzumab.
- ▶ At present, there is no approved indication for the use of elotuzumab in the initial management of myeloma.
- ▶ By consensus, elotuzumab-containing regimens may be considered for patients who have progressed on dara-containing regimens.
- ▶ Elotuzumab should not be used as a single agent.
- ▶ Prior treatment with elotuzumab is not a contraindication for treatment with anti-CD38 antibodies.
- ▶ By consensus, elotuzumab-containing regimens are not recommended for patients with a rapidly growing disease burden.

Administration, dosing, and monitoring

In the ELOQUENT-2 trial, IRRs were reported in 33 patients (10%) in the elotuzumab arm, with mostly grade 1/2 IRRs and no grade 4 or 5 events. The majority of IRRs occurred during the first infusion.⁷⁵ The prescribing information for elotuzumab recommends the premedication regimen developed during ELOQUENT-2: oral dexamethasone 28 mg 3–24 hours prior to each elotuzumab infusion and then an additional 8 mg administered intravenously 30–90 min before the infusion along with diphenhydramine (25–50 mg), ranitidine (50 mg) and acetaminophen (650–1000 mg).^{11 75} The prescribing information states that the infusion rate may be increased to 5 mL/min after four treatment cycles, however a phase II safety study found no increase in AEs with a faster

infusion of elotuzumab administered over 1 hour from the third dose onward.⁸⁸ ELOQUENT-2 and ELOQUENT-3 both gave elotuzumab at 10 mg/kg intravenous weekly for the first 8 weeks. However, in ELOQUENT-2, 10 mg/kg was continued every 2 weeks for cycles 3 and beyond whereas in ELOQUENT-3, elotuzumab was given 20 mg/kg intravenous every 4 weeks for cycle 3 and beyond.

Similar to other therapeutic antibodies, elotuzumab may interfere with protein electrophoresis or immunofixation measurements,⁸⁹ causing false positives for M-spike results in the peripheral blood and potentially affecting the assessment of response according to the International Myeloma Working Group (IMWG) criteria. Unlike with dara, gel-shift approaches have not yet been developed to eliminate false positives for elotuzumab. Possible workaround options for the measurement of elotuzumab-induced M-spikes or immunofixation electrophoresis include the SLAMF7⁹⁰ or mass spectrometry-based approaches.^{62 63}

Panel recommendations

- ▶ In published trials, infusion-related reactions (IRRs) have been most prevalent with the first infusion.
- ▶ The first dose of elotuzumab should start at 0.5 mL/min for the first 30 min, then 1 mL/min. The second dose should start at 3 mL/min for 30 min, then 4 mL/min and from the third dose on, the infusion can be given at 5 mL/min.
- ▶ Per prescribing information, patients should be premedicated 45–90 min prior to infusion with dexamethasone 8 mg, an H1 and H2 blocker and acetaminophen (650–1000 mg orally).
- ▶ For the most part, myeloma-specific immune responses should be measured with each cycle as per normal practice.
- ▶ In patients with IgG kappa myeloma, determination of CR can be confounded by elotuzumab.
- ▶ In the presence of a measurable M-spike, elotuzumab will have a minimal effect on disease measurement. When patients reach undetectable levels, however, mass spectrometry or other antibody-interference testing methods should be considered.

Other considerations

In the ELOQUENT-2 trial, serious AEs were reported in 65% and 57% of patients in the elotuzumab group and the control group, respectively⁷⁵ and the incidence of serious AEs was 53% in the elotuzumab group and 55% in the control group, respectively during the ELOQUENT-3 study.⁷⁷ The rates of anemia, neutropenia and thrombocytopenia were similar between the elotuzumab and control groups in both studies. In the ELOQUENT-2 trial, the incidence of grade 3 or 4 lymphocytopenia was significantly higher in the elotuzumab arm (77% vs 49%), however the rates were much lower and not significantly different between treatment arms during ELOQUENT-3 (8% vs 2%).^{75 77} Overall infection rates did not increase with the addition of

elotuzumab in the ELOQUENT-2 or ELOQUENT-3 trials.⁷⁵⁻⁷⁷ However, increased incidence of herpes zoster infections was noted in the elotuzumab groups in both studies (4.1% vs 2.2% and 5% vs 2%).⁹¹

Although the ELOQUENT-2 and ELOQUENT-3 trials excluded patients in renal failure, a phase Ib study of E-Rd in 26 patients with MM and various levels of renal impairment did not observe any statistically significant differences in maximum observed serum concentration, nor areas under the concentration-time curves between the groups with severe renal impairment (creatinine clearance (CrCl) <30 mL/min) and end-stage renal disease (requiring dialysis) compared with patients with normal renal function (CrCl ≥90 mL/min).⁹² One case report described fatal renal failure in a man aged 61 years with IgG kappa MM who developed tumor lysis syndrome 1 week after elotuzumab treatment,⁹³ but this has not been reported in any large clinical trials.

Panel recommendations

- ▶ Although patients with renal impairment were excluded from clinical trials, the panel felt that elotuzumab may be used in patients with severe renal insufficiency (CrCL <30 mL/min).
- ▶ A consensus could not be reached to recommend using elotuzumab in patients with hepatic impairment or plasma cell leukemia.
- ▶ Antiviral prophylaxis is recommended for patients receiving elotuzumab.
- ▶ To manage infections following treatment, IVIG should be administered according to established institutional criteria, which are not specific to elotuzumab.
- ▶ At this time, no biomarkers of response or resistance to elotuzumab are known.

ISATUXIMAB

Isatuximab is a mAb that targets a distinct epitope on the plasma cell surface marker CD38, which promotes tumor cell killing through classic Fc-dependent immune-effector mechanisms, antibody-dependent cellular cytotoxicity, complement-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis.⁹⁴ Similar to dara, isatuximab has been shown to exhibit immunomodulatory effects in preclinical models through reducing the numbers of regulatory T cells (T_{regs}) as well as decreasing immune inhibitory cytokine production, including interleukin (IL)-10. Unlike dara, isatuximab was selected based on its ability to directly trigger MM cell death in the absence of cross-linking agents and independently of effector cells. In 2020, isatuximab was approved by the FDA in combination with pomalidomide and dexamethasone (I-Pd) for adult patients with MM who have received at least two prior therapies including lenalidomide and a PI based on results from the multicenter, multinational, randomized, open-label, two-arm, phase III ICARIA-MM study.

Literature review

Isatuximab is currently being evaluated in multiple ongoing phase III clinical trials in combination with current standard treatments for people with both RRMM and treatment-naïve MM. In the relapsed refractory setting, based on promising results from a phase Ib study where isatuximab combined with carfilzomib led to an ORR of 61% and a clinical benefit rate of 86%, the ongoing IKEMA study (NCT03275285) recruited 302 participants with RRMM to assess the clinical benefit of isatuximab combined with carfilzomib and dexamethasone (I-Kd) versus Kd alone.⁹⁵ In 2019, initial positive results from the randomized phase III ICARIA-MM (NCT02990338) trial⁹⁶ were presented at the ASCO Annual Meeting and the European Society of Hematology Annual Meeting, reporting benefits for I-Pd in RRMM. The trial found that I-Pd prolonged PFS by 5 months compared with Pd alone (HR 0.596; 11.53 vs 6.47 months; 95% CI 0.44 to 0.81, $p=0.001$) and ORR was also significantly greater with I-Pd compared with Pd (60% vs 35%; $p<0.0001$), similar to the results observed in the phase Ib study that preceded this trial.⁹⁷ The triplet regimen also demonstrated a significantly higher VGPR rate and a longer duration of response compared with Pd (31.8% vs 8.5%; $p<0.0001$ and median 13.27 vs 11.07 months, respectively). Among patients who achieved a response, I-Pd demonstrated faster median time to first response compared with Pd alone (35 vs 58 days). Moreover, time to next treatment was longer with I-Pd compared with Pd alone (HR 0.538; median not reached vs 9.1 months).⁹⁸ These results were the basis for FDA approval of I-Pd for RRMM in 2020.

In patients with newly diagnosed MM, isatuximab is being evaluated in combination with the standard of care triplet regimen of VRd in multiple ongoing trials. The phase III IMROZ trial (NCT03319667)⁹⁹ randomized 475 patients with newly diagnosed MM to receive either induction treatment with 4×6 week cycles with IV isatuximab+subcutaneous bortezomib+oral lenalidomide+IV or oral dexamethasone followed by continuous treatment with 4-week cycles with IV isatuximab+oral lenalidomide+IV or oral dexamethasone, or a control regimen of induction with VRd followed by continuous treatment with Rd. The primary outcome measure will be PFS and the estimated primary completion date is in December 2022. Another study evaluating the effect of isatuximab in combination with RVd induction therapy, GMMG HD7 (NCT03617731), had recruited 662 patients with newly diagnosed MM in 2019, and the trial will evaluate MRD negativity as well as PFS as primary outcome measures.

Panel recommendations

- ▶ I-Pd is approved and recommended by the panel for patients with RRMM who have received more than two prior lines of therapy.
- ▶ Although patients with renal failure, patients with COPD and patients with plasma cell leukemia were excluded from initial clinical trials, these populations may safely be treated with isatuximab.

Administration and dosing

In the phase Ib study of I-Rd, IRRs were observed in 83% of patients receiving isatuximab at an infusion rate of 250 mg/hour, prompting the adoption of a 175 mg/hour rate. The median durations for the first infusions were 3.7 and 3.1 hours, with shorter times for the second doses.¹⁰⁰ Across multiple trials, IRRs most commonly occurred during the first doses of isatuximab, and were substantially less frequent on subsequent infusions.^{95 97 100}

Panel recommendations

- ▶ In accordance with published protocols, isatuximab should be started at 175 mg/hour initial infusion rate with a duration range of 2–7 hours.
- ▶ Standard premedications are recommended up to 60 min prior to infusion to mitigate IRRs. Recommendations should be guided by label once approved by regulatory agencies. A suggested example is as follows:
 - Dexamethasone 40 mg IV or methylprednisolone 100 mg IV.
 - Diphenhydramine 50 mg IV or equivalent.
 - Ranitidine 50 mg IV or equivalent.
 - Acetaminophen 650–1000 mg oral administration.
- ▶ In patients with respiratory disease (eg, asthma or reduced forced expiratory volume in 1 s), consider adding an adrenergic bronchodilator (albuterol inhaler/nebulizer) as premedication.

Special considerations

Prior exposure to mAb therapies

No large, randomized studies have evaluated whether prior exposure to mAbs alters efficacy of subsequent lines of therapy directed against the same antigen in MM. Dara has been demonstrated to reduce CD38 expression on MM cells within hours of the first infusion in clinical trials, yet some patients with reduced CD38 expression achieved deep and durable responses with treatment.¹⁰¹ A case report has been published describing two partial remissions in two relapsed patients after retreatment with dara, and plasma cells from those patients did not display decreased CD38 expression.¹⁰² More studies will need to be done to determine if retargeting CD38 is a viable option.

Panel recommendations

- ▶ No consensus could be reached on using isatuximab in patients who had progressed on a dara-containing regimen.

Antibody interference in serum protein electrophoresis

Similar to dara, isatuximab may interfere with immunofixation results and appear as IgG kappa. Mass spectrometry, NGS or gel-shift approaches can help resolve antibody interference on SPEP. Antibody interference testing is unnecessary for non-IgG kappa isotype patients, patients with detectable disease by FLC or BJP or patients with an M-spike >0.2 g/dL by SPEP.^{62–64 89}

Panel recommendations

- ▶ For most patients, the panel recommends antibody interference testing by mass spectrometry for patients treated with isatuximab.

Infection care

The European Society of Clinical Microbiology and Infectious Disease Study Group for Infections in Compromised Hosts concluded that, based on available evidence, CD38-targeting therapies likely do not substantially increase patients' risk for bacterial infections.¹⁰³ Results from trials with dara suggest that patients on combination regimens may be at elevated risk for varicella zoster virus infection and cytomegalovirus (CMV) reactivation.^{103–105}

Panel recommendations

- ▶ Patients should receive seasonal influenza vaccines while on isatuximab.
- ▶ To manage infections following treatment, IVIG should be administered according to established institutional criteria, which are not specific to isatuximab.

Emerging therapies

Several promising new immunotherapy modalities are currently being evaluated in clinical trials for newly diagnosed as well as RRMM. Strategies include mAbs, CAR T cells, bispecific engagers of T cells, ADCs and cancer vaccines. Although the products described in subsequent sections have yet to be approved by the FDA at the time of publication, it is important for the oncology community to be familiar with emerging therapies, for possible consideration of referring their patients to an appropriate clinical trial or incorporating these new treatments into clinical practice, when they become available. Even though immune checkpoint inhibitors are FDA-approved for other disease settings and have been studied both as monotherapy and in combination with IMiDs for MM, safety signals observed in early trials and lack of clear clinical benefit motivated the panel to refer readers elsewhere for discussion of those agents.¹⁰⁶ Given the rapid pace of the field, therapies other than those described in this manuscript may advance through clinical trials soon after publication, and inclusion or absence of a specific agent herein should not be interpreted as an endorsement.

Emerging therapies targeting BCMA

Both CD38 (the antigen targeted by dara and isatuximab) and SLAMF7 (elotuzumab) are expressed in healthy tissues including hematopoietic lineages and immune effector cells.^{107 108} B cell maturation antigen (BCMA), by contrast, is a surface marker with highly restricted expression that is very frequently upregulated in MM cells. In healthy tissues, BCMA is only found on late memory B cells committed to plasma cell differentiation, where it is required for the survival of long-lived plasma cells.^{109 110} In MM, BCMA is associated with the proliferation and survival of cancer cells, and it is associated with the induction of an immunosuppressive bone marrow microenvironment.^{111 112} Membrane BCMA is

cleaved by the enzyme gamma secretase,^{113 114} leading to the formation of a soluble form (sBCMA), and elevated levels of sBCMA in patient serum have been correlated with disease status and poor prognosis.¹¹¹ The administration of an oral gamma secretase inhibitor to patients can significantly increase BCMA density on the surface of malignant plasma cells and reduce sBCMA levels.¹¹⁴

CAR T CELLS

Escalating pipelines of BCMA-targeting CAR T therapies for MM have posted encouraging results. In late 2019, >40 trials investigating BCMA-targeting CAR T cells were actively recruiting patients, with the majority in phase I or phase I/II. Agents further along the path toward FDA approval are bb2121 (idecabtagene vicleucel),^{12 115} a second-generation CAR containing a 4-1BB costimulatory motif, which received Breakthrough Therapy designation in 2017,¹¹⁶ and JNJ-68284528 (also called JNJ-4528, formerly LCAR-B38M), which binds to two distinct epitopes on BCMA,^{117 118} and has also been granted Breakthrough Therapy designation in addition to PRIME designation by the European Medicines Agency (EMA). Additionally, under investigation are cell-based therapies using NK cells¹¹⁹ as well as TCR-engineered T cells, such as the enhanced affinity NY-ESO-1 TCR.¹²⁰

Literature review

A phase I trial investigated the novel CAR T cell therapy, bb2121, in patients with heavily pretreated RRMM. For the first 33 consecutive patients who received a bb2121 infusion at the cut-off date of 6.2 months after last infusion, the ORR was 85% (95% CI 68.1 to 94.9), with 45% of patients having a CR (9%) or stringent CR (sCR 36%), respectively. Of the 15 patients with a CR, 6 relapsed. The median PFS was 11.8 months (95% CI 6.2 to 17.8). All 16 patients who had a response (PR or better) and who could be evaluated for MRD achieved MRD-negative status ($\leq 10^{-4}$ nucleated cells). Successful expansion of CAR T cells was associated with responses, during which expanded cells persisted up to 1 year after the infusion. Interestingly, response rates of 74% or higher were observed among patients with progressive disease during their most recent line of therapy, those who had received dara as part of their most recent line, those who did not receive bridging therapy and those who had extramedullary disease (plasmacytomas) at baseline.¹² Hematological toxic effects were the most common AEs of grade 3 or higher, including neutropenia (85% of patients), leukopenia (58%), anemia (45%) and thrombocytopenia (45%). Twenty-five patients (76%) experienced cytokine release syndrome (CRS) (grade 1–2 in 70% and grade 3 in 6% of patients). Neurological toxic effects occurred in 14 patients (42%) and were of grade 1–2 in 39% of patients. One patient (3%) had a reversible grade 4 neurological toxic effect.¹²

At the time of writing, several phase II trials are evaluating bb2121 in the RRMM setting, including KarMMA

and KarMMA-2 (NCT03361748 and NCT03601078). The KarMMA-1 trial has completed recruitment for patients who have received at least three prior lines of therapy, whereas the KarMMA-2 study is enrolling multiple cohorts including subjects with ≥ 3 prior antimyeloma treatment regimens, subjects with one prior antimyeloma therapy including autologous stem cell transplantation (ASCT) and with early relapse, subjects with one prior antimyeloma therapy not including ASCT and with early relapse, and subjects with inadequate response to ASCT during their initial antimyeloma therapy. Additionally, a multicenter, randomized, open-label, phase III study comparing the efficacy and safety of bb2121 vs standard triplet regimens in subjects with RRMM treated with two to four prior lines of therapy, the KarMMA-3 trial (NCT03651128), is ongoing. KarMMA-4, which is a phase I study with bb2121 to be given after four cycles of induction chemotherapy in newly diagnosed, high-risk MM, has started recruiting (NCT04196491).

The EVOLVE study is a phase I/II trial evaluating the safety and efficacy of JCARH125, a fully human CAR, in patients with RRMM (NCT0343001). In late 2019, 44 patients with highly refractory disease (median of nine prior therapies, 64% with high-risk cytogenetics) had received various doses of JCARH125. Overall, an ORR of 82% was achieved, with CR/sCR reported in 27% and VGPR or better in 48% of patients with limited follow-up. At the lowest dose of 50×10^6 total CAR T cells, the CR/sCR reported was 43%, with a trend of deepening responses over time. CRS was observed in 80% of patients, with 9% having a grade ≥ 3 AE. Neurotoxicity occurred in 18% of patients, with 7% reported to be grade ≥ 3 . The product received FDA orphan drug status in 2017.¹²¹

Another CAR T therapy in development is JNJ-4528 (identified as LCAR-B38M in China), which targets two distinct epitopes of BCMA. In early results from the LEGEND-2 phase I/II open study (NCT03090659) of 57 Chinese patients with RRMM treated with LCAR-B38M, the ORR was 88% and the CR rate was 68%. CRS was seen in 90% of patients, with 7% having grade 3 CRS. Only one patient developed neurotoxicity.¹¹⁷ At data cut-off, the OS rate at 18 months was 68% (range 54%–79%) with median duration of response (mDOR) 22 months (range 13–29). At 18 months, the rate of PFS was 50% (range 36–63) for all treated patients and 71% (range 52–84) for MRD-negative patients with CR. The median PFS for all treated patients was 20 months (range 10–28) and 28 months (range 20–31) for MRD-negative patients with CR. It is important to note that many therapies available in the USA are not routinely available in China, and these patients were significantly less heavily pretreated than the patients on US trials.¹²² The phase Ib/II CARTITUDE-1 study (NCT03548207) is evaluating JNJ-4528 in the USA and Europe, concomitantly with the ongoing phase II CARTIFAN-1 trial (NCT03758417) in China.¹²³ As of June 24, 2019, 25 patients had been infused with JNJ-4528 in the phase Ib portion of the study. In an update presented December 2019 at the American Society of Hematology

annual meeting, 21 patients were evaluable for response with a median follow-up of 3 months (range 1–10). Reduction in tumor burden was observed for all patients with ORR of 91% including 4 sCRs, 2 CRs, 7 VGPRs and 6 PRs. Of the 15 patients with evaluable bone marrow samples, 10 were MRD-negative at the 10^{-5} sensitivity level.¹²⁴

P-BCMA-101, a novel BCMA-targeting CAR T produced using the non-viral transposase-transposon piggyBac DNA Modification System,¹²⁵ has entered phase II testing. In a phase I trial with 11 patients, encouraging safety data was reported with only 1 case of suspected CRS that was minimal and short-lived. PR or better was obtained in 7 out of 10 patients. The manufacturing technology results in CAR T cell products with a high percentage of self-renewing, long-lived stem cell memory T cells due to the introduction of a selection gene along with the CAR. Second, the use of the protein Centyrin binder instead of a traditional antibody-based binder may yield a potentially less immunogenic product. Additionally, the small size of the Centyrin binder has allowed P-BCMA-101 cells to be engineered with a ‘safety switch’ gene to allow the cells to be eliminated if desired. The product received FDA RMAT designation in 2018 and orphan drug status in 2019.¹²⁶

Early promise has also been demonstrated through the combination of BCMA CAR T cells and an oral gamma secretase inhibitor (GSI; JSMD194) designed to increase surface density of the BCMA target. Among the eight patients reported to date on this phase I trial (NCT03502577), a median 20-fold increase in BCMA surface density was observed following three doses of the oral GSI, and although the data are not mature, an ORR of 100% was noted among evaluable patients, including those treated at the lowest BCMA CAR T-cell dose (50×10^6).¹²⁷

In the future, combination treatments using CAR T cells directed against BCMA as well as additional antigens may be needed to further improve clinical outcomes. A SLAMF7-targeting CAR, derived from elotuzumab, has been developed, and T cells transduced with the construct display anti-myeloma activity in vitro and in mouse models.¹²⁸ GPRC5D has been shown to be a potentially important target for the immunotherapy of MM, and GPRC5D-targeted CAR T cells demonstrate preclinical myeloma-directed activity in vitro and in vivo, including in a BCMA antigen-escape model.¹²⁹ Additionally, even though abnormal plasma cells in MM generally do not express CD19,¹³⁰ a very small proportion of cancer stem cells may retain the marker,¹³¹ opening the door to treatment with existing anti-CD19 CAR T therapies, such as tisagenlecleucel. In a study of 10 patients with RRMM who received high-dose melphalan and autologous stem cell transplant followed by infusion of CTL019 CAR T cells, 2 achieved longer PFS after HSCT+CTL019 compared with prior HSCT (479 vs 181 days and 249 vs 127 days). Durable response in this study was associated with the induction of T cells against SOX2, a stem-cell antigen.¹³² A study of 21 patients with RRMM who received infusions

of CD19-targeting and BCMA-targeting CAR T cells reported 20 ORs (95%), including 9 sCRs (43%), 3 CRs (14%), 5 VGPRs (24%) and 3 PRs (14%).¹³³ Another trial observed high initial response rates after administering a combination of CAR T-BCMA and CTL119 (an investigational product with a humanized CD19-targeting CAR) as consolidation therapy to 10 patients responding to third-line therapy, 4 of whom had high-risk cytogenetics. Absence of circulating B cells was observed in five patients, including two who had ongoing responses at 4 months and 1 year, hinting at the desirable long-term persistence of CAR T cells.¹³⁴

Patient selection

The most frequent setting for clinical trials (and the setting where the reported clinical results are the most mature) are in the multiply relapsed/refractory space, especially for trials in the USA. For inclusion in the phase II KarMMa-1 trial of the BCMA-directed CAR T-cell therapy bb2121, for example, patients must have received three prior regimens including an IMiD, PI and an anti-CD38 antibody, and have been refractory to the last regimen. Because of the clinical setting, many patients treated with CAR T cells have had MM with extensive prior therapy.^{12 14 115 117 135–137} To date, there is no data demonstrating differences in safety or efficacy based on cytogenetics. As safety and efficacy is becoming apparent, more advanced products are beginning to be explored clinically in earlier lines, such as one to three prior therapies, and in the upfront setting for high-risk patient populations.

Heavy pretreatment, including prior allogeneic transplant or other BCMA-targeting therapies, does not necessarily preclude patients from CAR T treatment. Safety and possible efficacy was reported in a study by investigators from the Fred Hutchinson Cancer Research Center using a vector identical to JCARH125 with unique manufacturing. In this study, seven patients with a median of eight prior therapies, including autologous HSCT in 71% and allo-HSCT in 43% of subjects were treated, none of whom developed graft-versus-host disease (GVHD).¹³⁷ In the phase I trial of bb2121, the median number of previous regimens was seven in the dose-escalation cohort and eight in the expansion cohort, and manufacturing was successful for 100% of patients.¹² Regardless of prior therapies, an adequate number of lymphocytes can usually be collected, and CAR T cells have been successfully manufactured to the prespecified dose for most patients on most trials.^{12 14 115 117 135–138} However, the impact of previous chemotherapy on the quality of CAR T cells is not yet known. While more study is required to understand the benefit of repeat dosing at relapse with the same CAR T-cell product, there have been reports in the acute lymphoblastic leukemia (ALL) setting of clinical efficacy of retreatment in the presence of preserved antigen expression with an intensified lymphodepletion regimen.¹³⁹ For MM, responses have also been reported in relapsed patients treated with anti-BCMA CAR T cells,

even after prior treatment with different BCMA-targeting products, including CAR T cells.¹³⁷

Performance status may be an important consideration in recommending patients for trial enrollment. A study evaluating JCAR017, an anti-CD19 CAR T, in relapsed/refractory non-Hodgkin's lymphoma observed worse outcomes in patients with impaired performance status, defined as grade 2 on the Eastern Cooperative Oncology Group (ECOG) scale. The overall mDOR was 5.0 months, whereas the subset of patients scored ECOG 0–1 had an mDOR of 9.2 months. Similarly, the 6-month OS was 75% for all patients, and 88% for the ECOG 0–1 group.¹⁴⁰

Recommendations

- ▶ The decision of suitability for CAR T cell therapy is often based on the potential for toxicity. Thus, baseline bone marrow function, cardiopulmonary, hepatic and renal function as well as performance status and organ status with respect to ability to tolerate CRS should be evaluated and toxicities should be considered, especially prolonged cytopenias.
- ▶ Registration trial results and FDA labels should guide disease-specific characteristics such as number of prior antimyeloma therapies.
- ▶ For patients earlier in their disease course, the presence of high-risk disease is an unmet medical need, and may shift the benefit/risk calculation in support of enrollment on cellular therapy trials.
- ▶ Heavily pretreated patients, including those who have undergone allo-HSCT may be considered for CAR T cell therapy.
- ▶ No data have been reported indicating that prior bispecific antibody or ADC therapy impacts the potential efficacy of future CAR T cell therapy or vice versa, and the panel agreed that there is not enough data to report on a consensus. Future trials should seek to address this question.
- ▶ Myeloma disease progression kinetics and likelihood of control should be weighed against the manufacturing time when considering patient eligibility for collection and likelihood to be clinically stable for CAR T cell administration.

Administration, dosing and monitoring

CAR T cell therapy involves extensive collaboration across the healthcare team. At the present time patients should be referred to centers of experience for CAR T cell therapies. This may change as the community gains more experience with this therapeutic modality.¹⁴¹ Prior to infusion, lymphodepletion is integral to CAR T cell treatment, and an association between effective preconditioning and consistent BCMA-targeting CAR T cell expansion has been observed.¹⁴² The optimal conditioning regimen has yet to be established, however experience from CD19-targeting CAR T cell therapies indicates that a combination of fludarabine and cyclophosphamide yields added benefits over single-agent lymphodepletion.¹³ After dosing of CAR T cells, patients must be monitored closely for

toxicities, especially CRS and neurological events. Of the approved CD19 CAR T cell products, axicabtagene ciloleucel requires daily monitoring at the treatment center for 7 days after infusion,¹⁴³ whereas tisagenlecleucel may be given as outpatient, with patients being monitored 2–3 times during the first week following dosing.¹⁴⁴ Both instruct patients to stay within a 2 hours drive of the treatment facility for 4 weeks after infusion.

The characteristics of anti-BCMA CAR T therapy that are amenable for outpatient management include a low overall incidence of severe toxicities. For bb2121, most cases of CRS were Lee Criteria grade 1 or 2 and the frequency of grade 3 or 4 neurotoxicity was only 3%.¹² Additionally, when severe toxicities do present, the presentation typically has a slow, predictable progression over the course of days, such that worsening signs and symptoms can be addressed in a timely fashion.^{145 146}

However, treatment centers providing CAR T cell therapy as an outpatient regimen will need to have the proper infrastructure to support appropriate outpatient monitoring and rapid escalation to inpatient care, if needed.

The interpretation of bone marrow MRD status in MM is not as straightforward as with other treatment modalities. The patchy pattern of bone marrow infiltration typically observed in MM generally leads to a degree of uncertainty in the case of negative results.^{147 148} This is because MM bone marrow burden of disease is cleared rapidly in many cases, and clearance of the M-protein, which has a long half-life, often lags behind. This is not an issue for patients with light chain only disease, but for those with an M-protein a deepening of response by IMWG criteria is often seen over time, thereby confounding interpretation of persistent M-protein seen in patients with MRD-negative responses in the marrow. Combined bone marrow MRD assessment by MFC or NGS and ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET)/CT may yield more valuable information for predicting response duration. A retrospective analysis of 103 patients with newly diagnosed MM found significant differences in 4-year OS and PFS for patients who achieved negativity by both PET and MFC (median PFS for PET–/MFC–92 vs 28 months for PET+ patients; 4-year OS 94.2% for PET–/MFC– patients vs 73.8% for PET+ patients).¹⁴⁹ In addition, the presence of more than three avid lesions by PET/CT has been linked to inferior OS and shortened PFS in several studies.¹⁵⁰ However, this setting may not be applicable to patients with RR disease receiving CAR T cell therapy.

In the context of CAR T-cell therapy, in the bb2121 trial, achievement of MRD negativity was independent of depth of response at the first assessment. Of the 9 out of 10 patients who achieved MRD, 2 were in CR by IMWG criteria at the time of assessment and the remaining seven achieved deeper responses over time. However, 1 MRD-negative patient became MRD-positive after 12 months and 1 MRD-negative patient progressed as of the data cut-off.¹⁵¹ MRD negativity did appear to associate with improved outcomes, however, out of 9 patients

who achieved MRD negativity, 3 had at least 12-month follow-up without progression by IMWG criteria. Importantly, the panel felt that PET-CT can be considered as part of MRD evaluations, and FDG-avid disease should be considered for biopsy before concluding that it is residual or relapsing MM after CAR T cell therapy.

Panel recommendations

- ▶ Patients should be re-evaluated including disease restaging prior to lymphodepletion if they received cytotoxic bridging therapy or >30 days have passed since apheresis.
- ▶ Registration trial results and FDA labels should guide lymphodepletion regimens.
- ▶ The dose of fludarabine used for lymphodepletion in patients with renal insufficiency should be reduced per FDA prescribing guidelines.
- ▶ Evidence of adequate blood counts based on complete blood count should be present prior to lymphodepletion, unless impaired by disease burden.
- ▶ If bridging therapy induces a CR, while data are limited, the panel feels that the benefits of proceeding with planned CAR T cell therapy in the heavily pretreated RRMM setting regardless of CR outweighs the risk of lower disease burden limiting CAR T cell expansion.
- ▶ Patients may consider receiving CAR T cell therapy as outpatient provided all the following criteria are met:
 - Patient has appropriate caretaker who can provide 24/7 support when the patient is away from the outpatient facility.
 - Patient is compliant with medical management instructions.
 - Patient meets clinical criteria for outpatient monitoring including stable vital signs, maintaining oral intake and no impending clinical deterioration from myeloma.
 - Patient has no active infection, increased risk for CRS or neurotoxicity and no other clinical conditions requiring inpatient care.
 - Treatment center has appropriate infrastructure to expedite care to inpatient if clinically indicated 24/7.

Toxicities

The most commonly reported adverse event across all CAR T clinical trials is CRS, with rates ranging from 37% to 93% in patients with lymphoma treated with anti-CD19 CAR T cells and 77% to 93% in leukemia.^{152–157} CRS has also been observed in patients with RRMM treated with BCMA-directed CAR T cells.^{12 136–138} A consensus grading system for CRS has been developed by the American Society for Transplant and Cell Therapy (ASTCT),¹⁵⁸ and most clinical trials going forward in the MM setting are using the ASTCT criteria. In the phase I trial evaluating bb2121, 25 out of 33 patients experienced CRS, which was grade 3 in 2 patients.¹² Of the eight patients who have been treated in 2018 with bb21217, a CAR T product similar to bb2121 except that a PI3 kinase inhibitor is

included during manufacturing to induce more of a central memory phenotype, five developed CRS, with one grade 3 case.¹³⁶

Clinically, CAR T-associated CRS can range from mild flu-like symptoms to multiple organ failure. Recognition of CRS is vital in order to begin treatment, and high fevers, hypoxia and hypotension are frequently observed early symptoms. Severe CRS may be fatal and requires intensive management, but most cases do resolve if care is initiated quickly, including IL-6 blockade and steroids.^{153 156 157 159} The established protocol for IL-6 blockade involves tocilizumab, an antibody against the IL-6 receptor, initially developed for rheumatoid arthritis, which was approved in 2018 by the FDA for the treatment of CAR T cell-induced CRS.^{160 161} Although some concerns have been raised that steroids or IL-6/IL-6R axis blockade may impair T-cell proliferation, several reports have described successful management of severe CAR T cell-associated CRS using IL-6R-directed therapy and short-course corticosteroids without apparent compromise in expansion or therapeutic efficacy.^{156 162 163} Theoretically, the anti-IL-6 antibody siltuximab could also be used to modulate the damaging inflammatory pathology in CRS, although the evidence for its efficacy is limited to two case reports.^{164 165} Blockade of IL-1 has been demonstrated to alleviate CRS in mouse models,¹⁶⁶ however the use of IL-1-modulatory therapies in human patients treated with CAR T cells remains anecdotal.

Transient neurological events, including confusion or delirium, expressive aphasia, motor weakness, tremor, headache, seizures and depressed level of consciousness have been observed in nearly every trial targeting T cells to CD19.¹⁶⁷ The ASTCT criteria consider neurological events separately from CRS, with an independent grading system for immune effector cell-associated neurotoxicity syndrome (ICANS).¹⁵⁸ The pathophysiology of neurotoxicity remains poorly understood, but experience with CD19-targeting CAR T cells for leukemia and lymphoma suggest that elevated cytokine levels in the serum and central nervous system (CNS) as well as blood-brain barrier disruption play a role.^{145 146 168} Notably, in studies of CD19-targeting CAR T cells, tocilizumab treatment has not been associated with decreased incidence or severity of ICANS.^{146 154 169–172} Some centers have moved toward supportive care for CAR T cell-associated neurotoxicity, since most cases of low-grade ICANS resolve on their own, while others favor aggressive early intervention with steroids.^{146 165 173} In the majority of trials with BCMA-targeted CAR T cell therapy to date, severe CRS and neurotoxicity have been less commonly seen than in the registration trials for CD19-expressing malignancies.

Prolonged and recurrent cytopenias have also frequently been observed in the CAR T cell trials reported to date as a consequence of lymphodepleting chemotherapy, possibly compounded by a direct effect from the CAR T cells themselves. Patients often need RBC and platelet transfusion support within the first 3 months of therapy.^{174–176}

Panel recommendations

- ▶ The ASTCT consensus guideline grading system for CRS and ICANS should be used to assess CAR T cell toxicities in patients with myeloma.
- ▶ To treat patients with CRS who do not respond to tocilizumab and steroids, the panel could not reach a consensus as to whether anakinra or siltuximab is preferred.
- ▶ For grade 1 CRS, tocilizumab may be considered, especially in cases of patients with prolonged high fevers, elderly patients or patients with significant comorbidities.
- ▶ Grade 2 or higher CRS should be managed with prompt tocilizumab administration.
- ▶ All patients should undergo comprehensive baseline neurological assessment prior to CAR T cell dosing to enable assessment for neurotoxicity signs and symptoms after infusion.
- ▶ Initial management of neurotoxicity should be based on experience and guidelines from registration trials, with escalation from supportive management to steroids, based on severity of signs and symptoms.
- ▶ Levetiracetam should be administered if seizures or other evidence of severe neurotoxicity develop in the context of CAR T cell therapy. Although no consensus could be reached to recommend antiseizure medicines prophylactically, the panel was unanimous in the opinion that there are few downsides to treating with levetiracetam.
- ▶ Patients may have had a high number of prior therapies before receiving CAR T cells, therefore, for patients who have persistent cytopenia beyond 3 months, evaluation for other causes are recommended including infections such as CMV and parvovirus B19, and bone marrow examination to rule out myelodysplastic syndrome (MDS).
- ▶ If patients develop neutropenia during CAR T cell therapy, filgrastim can be considered.
- ▶ Patients should be monitored for blood count and IgG levels regularly post-CAR T cell infusion until recovery.
- ▶ IVIG supplementation should be considered for patients with severe hypogammaglobulinemia (IgG <400 mg/dL).
- ▶ Macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH)-like toxicity is potentially fatal, and for patients who do not respond to tocilizumab and steroids, anakinra can be considered.

Other considerations

- ▶ CAR T cell safety when CrCl is <20 mL/min has not been assessed and the majority of the panel would not feel comfortable recommending CAR T therapy for patients with renal failure or significant hepatic impairment.

- ▶ Viral prophylaxis should be administered during CAR T cell therapy, and maintained through the treatment period and the neutropenic period.
- ▶ *Pneumocystis jirovecii* pneumonia prophylaxis should be administered during CAR T cell therapy, although a consensus could not be reached on the optimal length of administration.
- ▶ A consensus could not be reached to recommend antifungal prophylaxis during CAR T cell therapy, however, as more data accumulate this may require further study.
- ▶ A consensus could not be reached to recommend antibacterial prophylaxis during CAR T cell therapy.
- ▶ During influenza season, all patients should receive the influenza vaccine prior to leukapheresis (if not already administered in the current season) and if lymphodepletion is not scheduled to start within 14 days. Influenza vaccines should be given with each influenza season thereafter.

BISPECIFIC T-CELL ENGAGERS

Bispecific dual-targeting antibody constructs are designed to help re-direct the immune system to carry out an attack on tumor cells without extracting cells from the patient. These agents often consist of mAbs with one binding site directed against the cytotoxic T lymphocyte-activating receptor CD3- ϵ and another against a tumor-specific antigen.¹⁷⁷ These ‘off-the-shelf’ therapies may present a more standard paradigm than treatment with CAR T cells, circumventing the current laborious and expensive procedures of extracting, engineering, and reinfusing cells for treatment. However, they require repeat dosing, and come with their own unique toxicities. Bispecific antibody and CAR T-cell therapies should not be considered as interchangeable, and their relative clinical efficacies are unknown.

Literature review

In 2019, only two bispecific antibody products were approved: catumaxomab in Europe, for the treatment of malignant ascites,¹⁷⁸ and blinatumomab for relapsed and refractory B-ALL.^{179 180} At the time of publication, several bispecific cell engagers for the treatment of MM are in development, listed in [table 1](#). These could eventually become options if results from early data are confirmed in larger studies. A CD38-targeting bispecific cell engager, GBR 1342, is undergoing a phase I clinical trial (NCT03309111).¹⁸¹ Another anti-CD38 bispecific cell engager, AMG 424, has demonstrated tumor-growth inhibition in mice and peripheral B-cell depletion in primates,¹⁸² and a phase I trial is underway (NCT03445663). A phase I trial (NCT03399799) is ongoing for JNJ-6440754, a bispecific T-cell engager targeting GPRC5D that has demonstrated tumor growth suppression in preclinical models.¹⁸³ A FcRH5-directed bispecific cell engager, BFCR4350A, is also being evaluated in a phase I, multicenter, open-label, dose-escalation study (NCT03275103).

Table 1 Bispecific antibodies in development for the treatment of multiple myeloma

Name	Target antigen	Company	Trial ID
AMG-420	BCMA	Amgen	NCT02514239
AMG-701	BCMA	Amgen	NCT03287908
CC-93269	BCMA	Celgene	NCT03486067
PF-06863135	BCMA	Pfizer	NCT03269136
REGN-5458	BCMA	Regeneron	NCT03761108
TNB-383B	BCMA	Tenebio	NCT03933735
JNJ-64007957	BCMA	Johnson & Johnson/Genmab	NCT03145181
JNJ-64007564	GPRC5d	Johnson & Johnson/Genmab	NCT03399799
GBR-1342	CD38	Glenmark	NCT03309111
AMG-424	CD38	Amgen	NCT03445663
BFCR4350A	FCRH5	Genetech	NCT03275103

The most clinically mature bispecific cell engagers target BCMA, with several agents in active phase I studies, including JNJ-64007957 (NCT03145181), PF-06863135 (NCT03269136), AMG 420 (previously known as BI836909), AMG 701 (NCT03287908), REGN5458 (NCT03761108) and REGN5459 (NCT04083534). In 2018, the FDA granted Fast Track Designation to AMG 420¹⁸⁴ after encouraging results were reported from a phase I first-in-human study. In the trial, there was a 70% (7/10) response rate at a dose of 400 µg/day (the recommended dose for further investigation), with 5 of 7 responders achieving sCR. As of February 2019, some responses had lasted longer than 1 year.²⁰ However, as AMG 420 is a dual-scFv 'BiTE' with short serum half-life, the requirement for continuous infusions halted its further development. An extended half-life derivative, AMG 701,¹⁸⁵ is currently being evaluated in a phase I clinical trial (NCT03287908). Interim analysis of a phase I trial of CC-93269, an asymmetric 2-arm humanized T-cell engager that binds bivalently to BCMA and monovalently to CD3, also reported promising efficacy and a manageable safety profile.¹⁸⁶

The first-in-human phase I dose-escalation study (NCT02514239) for the anti-BCMA bispecific cell engager AMG 420, demonstrated clinical activity in heavily pretreated patients with RRMM.²⁰ The study included at least five 6-week cycles of AMG 420 administered until PD, toxicity or consent withdrawal, followed by a potential five additional cycles for extended benefit. Patients were eligible if they had progressive disease after ≥2 lines of previous therapies, including PIs and IMiDs. Patients were treated for a mean of 2.5 cycles. A dosage of 400 µg/day (800 µg/day was determined intolerable, as two out of three patients receiving this dose had dose-limiting toxicities: one case of grade 3 CRS and one case of grade 3 peripheral neuropathy, both of which required hospitalization and subsequently resolved), this study reported an ORR of 7/10 (70%), with five MRD-negative sCRs, one VGPR and one PR. At the data cut-off date of December 2018, responses had lasted for 5.6–10.4 months with four

patients remaining on treatment. As of February 2019, some responses lasted over 1 year. In total, 13/42 patients demonstrated a response, with 6 sCRs, 3 CRs, 2 VGPRs and 2 PRs. Treatment-related serious AEs included two grade 3 peripheral neuropathies distinct from classic CNS toxicity and one edema. Grade 2–3 CRS was seen in three patients. Atypical infections including aspergillosis and fulminant hepatitis related to adenovirus infection were also observed.²⁰ Another bispecific cell engager, CC-93269, was evaluated in a phase I dose-finding trial (NCT03486067), where eligible patients had RRMM and had received ≥3 previous lines of treatment without prior BCMA-directed therapy. Of the 12 patients receiving doses ≥6 mg/kg, the ORR was 83.3% and the median time to response was 4.2 weeks (range 4.0–13.1). All 10 responses were ongoing with follow-up ranging from 2.1 to 4.7 months. Grade 3–4 treatment-emergent AEs were reported in 15 (78.9%) patients and included 10 (52.6%) patients with neutropenia, 8 (42.1%) with anemia, 5 (26.3%) with infections and 4 (21.1%) with thrombocytopenia. One patient who received 6 mg CC-93269 as first dose and 10 mg on cycle 1 day 8 died on study in the setting of CRS, with a potential infection as a contributing factor. No patients required dose modifications.¹⁸⁶

Patient selection

The efficacy and toxicity of bispecific cell engager therapy targeting BCMA has not been fully elucidated to guide a careful assessment of the risk/benefit ratio for participating populations. In general, the toxicities associated with bispecific cell engagers have largely mirrored those seen with other mAbs and T cell therapies including CRS.¹⁷⁷ However, notable unique toxicities, including atypical infections and peripheral neuropathies, have also been seen in trials. The population that has been studied to date had relapsed/refractory disease after more than two prior lines of therapy. Patients with plasma cell leukemia, extramedullary relapse, CNS involvement or prior allo-HSCT were excluded from the first-in-human study of AMG 420.²⁰ In the phase I trial of CC-93269, all 19

patients who were treated had myeloma refractory to their last line of therapy, with 16 (88.9%) refractory to dara, 17 (89.5%) to the most recently administered PI and 16 (84.2%) to the last IMiD. As more information becomes available, however, treatment at an earlier line of therapy or in the setting of high-risk disease will likely be evaluated.

Although still a subject of exploration, bispecific cell engager therapy may also provide an effective option for patients in cytogenetically high risk subsets, as the features that render the disease more resistant to standard biologic therapy may not apply to cell-based immune therapies.^{187 188} Therefore, earlier therapy in high-risk disease may provide a unique opportunity to achieve more durable remission. Conversely, high-risk cytogenetics may be associated with higher levels of clonal diversity and proliferation that may also allow for escape mechanisms for T cell-mediated killing such as loss of antigen expression (as has been observed with BCMA-targeting CAR T cells¹⁸⁹), higher levels of immunomodulatory cells in the microenvironment,¹⁹⁰ upregulation of negative costimulatory molecules and loss of HLA-mediated presentation (as has been reported in patients with acute leukemia after stem cell transplantation¹⁹¹ as well as in mouse models of MM¹⁹²). As such, the efficacy of bispecific cell engager therapy will need to be assessed in different disease subgroups.

Panel recommendations

- To date, there is no consensus on the optimal indications for bispecific cell engager therapy. These agents have been studied in patients who have relapsed/progressed after standard treatments and were refractory to the last line of therapy, including PIs, IMiDs and CD38 antibodies.

Administration, dosing and monitoring

With limited clinical experience, there is no established dosing schedule for BCMA-targeting bispecific cell engagers. Some bispecifics have short serum half-lives, on the order of hours,¹⁹³ necessitating continuous infusions. AMG 420 was given as continuous infusion over 4 weeks,²⁰ which is also the recommended dosing schedule for blinatumomab.¹⁹⁴ However, an extended half-life BCMA-targeting bispecific, AMG 701, has been developed, which shows robust antimyeloma activity in vitro.¹⁸⁵ AMG 701 is currently being evaluated in a phase I clinical trial (NCT03287908). During the first-in-human trial of AMG 420, the maximum tolerated dose was 400 µg/day. For CC-93269, continuous infusions were not necessary and administration was intravenous over 2 hours on days 1, 8, 15 and 22 for cycles 1–3; days 1 and 15 for cycles 4–6; and on day 1 for cycle 7 and beyond, all in 28-day cycles. For dose escalation, CC-93269 was initially given in fixed doses and in the second stage, patients received a fixed first dose on cycle 1 day 1, followed by escalation on day 8. Doses ranged from 0.15 to 10 mg and the median duration of treatment was 14.6 weeks (range 1.6–32.0) with patients receiving a median of 4 cycles (range 1–8).¹⁸⁶

During the AMG 420 trial, two deaths occurred, neither of which were determined to be treatment related: one patient succumbed to acute respiratory distress arising from influenza and aspergillosis, the other experienced fulminant hepatitis related to adenovirus infection. Of the 21 serious AEs reported during the trial, 18 required hospitalization. The most common serious AEs were infections (12 patients) and polyneuropathy (2 patients). Grade 2–3 CRS was also seen in three patients.²⁰ For CC-93269, CRS was reported in 17 (89.5%) patients and the majority of cases were grade 1 (n=11 (57.9%)) or grade 2 (n=5 (26.3%)), occurring most frequently with the first or second dose (n=22 of 27 (81.5%)). Of the 27 total CRS events, 8 (29.6%) were managed with dexamethasone and 10 (37.0%) with tocilizumab. CRS prophylaxis with dexamethasone was subsequently implemented with the first dose. Other grade 3–4 AEs were reported in 15 (78.9%) patients, including 10 (52.6%) with neutropenia, 8 (42.1%) with anemia, 5 (26.3%) with infections and 4 (21.1%) with thrombocytopenia.¹⁸⁶

Experience with the approved bispecific, blinatumomab, as well as CAR T cell therapies may provide insight on potential toxicities, with the caveat that the more restricted expression profile of BCMA as compared with CD19¹¹² may alter toxicity profiles. Most cases of CRS in the trials leading to the approval of blinatumomab occurred during the first cycle, and during the phase III randomized TOWER study comparing blinatumomab with standard of care in relapsed and refractory acute lymphoblastic leukemia (RR ALL), the median time to first onset of any CRS event was 2 days and the median time to onset for grade ≥3 CRS events was 4 days.¹⁹⁵ Although no established biomarkers exist to predict CRS, patients with higher disease burden may be at increased risk.¹⁹⁶ Patients with CRS are at increased risk for infections, and the signs and symptoms of CRS can mimic those of sepsis, possibly delaying accurate diagnosis and treatment.¹⁵⁷ One patient in the CC-93269 trial died on study in the setting of CRS, with potential infection as a contributing factor.¹⁸⁶

Monitoring response to bispecific cell engager therapy is complicated by emerging data that MRD-negative responses can be independent of the depth of response for T cell redirecting therapies by classical IMWG criteria in the multiply RRMM population (see CAR T section for discussion). During the bb2121 trial, the MRD-negative patients who were not in CR by IMWG did achieve deeper responses over time.¹⁵¹ Potential biomarkers of response to bispecific cell engager therapy could include immunohistochemistry studies showing T cell localization into the tumor bed, which possibly may be further augmented by flow cytometric analysis of infiltrating T cell populations with respect to expression of activation and inhibitory markers as well as polarization as measured by cytokine expression profiling, but the prognostic value of such studies requires further investigation.

Panel recommendations

- ▶ The ASTCT consensus grading system for CRS and ICANS should be used to evaluate toxicities associated with bispecific cell engager therapy.
- ▶ Toxicities should be managed as per established or mandated investigational protocols.
- ▶ As these therapies may eventually be administered in the outpatient setting, it is important to recognize that time to onset of CRS is typically within the first 2 days of beginning treatment, but may be delayed.
- ▶ Atypical infections reported in one phase I trial of AMG 420 suggest that attention should be paid to monitoring for infectious sequelae.
- ▶ A consensus could not be reached regarding how to interpret MRD status as opposed to traditional IMWG response criteria in both CAR T cell therapy and bispecific antibody patients. However, there was general consensus that MRD status can be a useful tool for predicting favorable outcomes.

Other considerations

Patients with autoimmune disease were excluded from clinical trials for AMG 420, and the package insert for blinatumomab lists autoimmune disease, acute GVHD of grade ≥ 2 and active chronic GVHD as key exclusion criteria.^{20 194} Patients with renal failure are typically excluded from clinical trials, yet isatuximab, the CD38-directed antibody, can be dosed in renal failure. Additionally, blinatumomab has been used in patients with CrCL down to 30 mL/min. At present, little is known about the mechanisms by which resistance arises to bispecific cell engager therapies.

ANTIBODY-DRUG CONJUGATES

mAbs have become valuable components of combination regimens for the treatment of MM. Building on this success, a new class of agents called ADCs has begun to emerge for the treatment of hematological malignancies. Consisting of three components: a mAb directed against a tumor-specific antigen, a cytotoxic payload and a linker that connects the targeting moiety to the cancer-killing molecule,¹⁶ ADCs have demonstrated improved complete remission rates and PFS in the treatment of B-ALL and Hodgkin's lymphoma in phase III and phase II trials.^{197 198} In the MM setting, a few ADCs, directed against different cell-surface markers and carrying a variety of payloads, are being evaluated in clinical trials.¹⁶

Belantamab mafodotin (GSK2857916) is an investigational ADC involving a humanized anti-BCMA mAb conjugated to the cytotoxic agent monomethyl auristatin F (MMAF) via a non-cleavable linker.¹⁹⁹ In 2017, belantamab mafodotin was awarded Breakthrough Therapy designation from the FDA and PRIME designation from the EMA. Belantamab mafodotin is currently in clinical development in patients with RRMM and other advanced hematological malignancies expressing BCMA but is not yet approved for use.

Literature review

The first-in-human, open-label, two-part, phase I study DREAMM-1 (BMA117159; NCT02064387) investigated belantamab mafodotin in adult patients with RRMM after ASCT (or considered transplant ineligible), alkylators, PIs and IMiDs. In part 1 of the trial, 38 patients were treated with escalating doses from 0.03 to 4.6 mg/kg, with no dose-limiting toxicities identified. In part 2, patients received belantamab mafodotin 3.4 mg/kg once every 3 weeks for up to 16 cycles. Encouraging clinical responses were observed, with an ORR of 60% (95% CI 42.1 to 76.1), PFS of 12.0 months (95% CI 3.1 to not estimable (NE)), a mDOR of 14.3 months (95% CI 10.6 to NE) and median time to first response of 1.2 months (95% CI 0.7 to 1.4). A confirmed OR was observed in 18/32 (56.3%; 95% CI 37.7 to 73.6) patients refractory to both IMiDs and PIs, 15/21 (71.4%; 95% CI 47.8 to 88.7) patients without prior dara treatment and 5/13 (38.5%; 95% CI 13.9 to 68.4) patients refractory to both IMiD and PI with prior dara treatment.^{200 201} Overall, belantamab mafodotin was well tolerated with rapid, deep and durable responses in heavily pretreated patients with RRMM. Additional follow-up confirmed CRs and considerably longer PFS in the final analysis compared with interim analysis. Patient experience of clinical benefit and tolerability was also evaluated through optional daily patient-reported outcome (PRO) diaries and end-of-treatment interviews. Twelve out of thirteen (92%) of interviewed patients experienced a PR or greater by IMWG criteria. During the end-of-treatment interview, patients reported an average improvement in bone pain from 6.4 to 4.0 (scale 0–10). Fatigue ratings improved from 8.0 to 5.5. Only four (31%) patients stated a decreased independence while on treatment. Overall treatment satisfaction reached a mean of 8.1 (median=9.0) on a 0–10 point scale.^{17 202}

In the open-label, two-arm, phase II DREAMM-2 study (NCT03525678), 196 patients with RRMM with disease progression after three or more lines of therapy and refractory to IMiDs and PIs and refractory or intolerant (or both) to an anti-CD38 mAb were recruited, stratified by previous lines of therapy (≤ 4 vs >4) and cytogenetic risk status (42% and 47% with high-risk cytogenetics in the 2.5 mg/kg treatment group and 3.4 mg/kg treatment group, respectively) and randomized to receive 2.5 or 3.4 mg/kg belantamab mafodotin IV every 3 weeks on day 1 of each cycle. As of June 21, 2019 (the primary analysis data cut-off date), the ORR in the 2.5 mg/kg cohort was 31% (30 patients, 97.5% CI 20.8 to 42.6) and 34% (34 patients, 97.5% CI 23.9 to 46.0) in the 3.4 mg/kg cohort. Median PFS was 2.9 months in the 2.5 mg/kg group and 4.9 months in the 3.4 mg/kg group, and median OS was not reached.²⁰³ Various trials are also underway using belantamab mafodotin in multiple combinations, including with PIs (NCT03544281), IMiDs (NCT03715478), and checkpoint inhibitors (NCT03848845).

Patient selection

ADC therapy has been the subject of trials in patients with RRMM with progressive disease following IMiD, PI, anti-CD38 mAbs and stem cell transplant, if eligible.²⁰⁰ Subgroup analysis of part 2 of the DREAMM-1 trial found an ORR of 71% for patients without prior dara treatment and 38.5% in those patients with prior dara exposure. Median PFS in the dara-refractory group was 6.8 months and in the subset of patients with prior dara treatment and refractory to IMiDs and PIs, median PFS was 6.2 months—encouraging, given the generally low response rate seen in anti-CD38 refractory patients.²⁰¹ In the published results from the DREAMM-2 trial, although no hypothesis testing was done in the prespecified analysis of ORR in individual subcohorts, 100% of patients in the 2.5 mg/kg cohort and 97% of patients in the 3.4 mg/kg cohort were refractory to dara.²⁰³

Panel recommendations

- ▶ To date, there is no consensus on the optimal indications for ADC therapy. The agents have been studied in patients who have relapsed/progressed after standard treatments and were refractory to the last line of therapy, including PIs, IMiDs and CD38 antibodies.
- ▶ Patients with severe cytopenias (especially thrombocytopenia) or pre-existing corneal disease may be unsuitable for ADC therapy with belantamab mafodotin.
- ▶ Although patients with prior allo-HSCT were excluded from the DREAMM-1 and DREAMM-2 trials, based on the known mechanisms of action for ADCs, patients with prior allo-HSCT can be considered for treatment.

Administration, dosing and monitoring

In the phase II registration study for belantamab mafodotin, treatment continued until disease progression or unacceptable toxicity occurred. The 2.5 mg/kg dose was selected as the recommended dose for future monotherapy studies. During the trial, disease assessment was completed every cycle using the IMWG uniform response criteria.²⁰⁰ Premedication for IRRs was allowed on the second dose onward in DREAMM-1 but was not mandated in DREAMM-2. In the DREAMM-2 study, premedications for IRRs was not mandated per the protocol. Additionally, monitoring for corneal events is recommended with ADC therapy, based on the frequency of ocular AEs reported across clinical trials.²⁰⁴ All patients in the DREAMM-1 trial received steroid eye drops to mitigate corneal events.

Toxicities

All patients receiving the phase II dose in the DREAMM-1 trial experienced at least one adverse event. Grade 3 or 4 AEs were reported in 28 (80%) of 35 patients, most commonly thrombocytopenia (12 patients) and anemia (5 patients). The most common serious AEs were IRRs and lung infections. Ocular AEs were also common, with 16 patients (46%) reporting blurred vision and 12 (34%) experiencing dry eyes (although only 1 case of dry

eyes was grade 3).²⁰⁰ Ocular toxicities are a commonly reported adverse event with ADC treatment, although the precise mechanism remains unknown. AEs have been seen most frequently in ADCs using the combination of SPDB (a cleavable disulfide linker) and the maytansinoid DM4 or maleimidocaproyl (a non-cleavable linker) and the auristatin MMAF.²⁰⁴ Belantamab mafodotin carries MMAF as its toxic payload, and corneal events were common in the DREAMM-1 trial. Most patients did have corneal findings on examination, most commonly superficial punctate keratitis, although the majority were classified as mild in severity.²⁰⁰ In the DREAMM-2 trial, the most common grade 1–2 adverse event was keratopathy and the most common grade 3–4 AEs in the population were keratopathy in 26 (27%) and 21 (21%) of patients in the 2.5 and 3.4 mg/kg cohorts, respectively, thrombocytopenia (19 (20%) and 33 (33%)) and anemia (19 (20%) and 25 (25%)). Two potentially treatment-related deaths occurred: one case of sepsis in the 2.5 mg/kg cohort and one case of HLH in the 3.4 mg/kg cohort. Four patients (one in the 2.5 mg/kg cohort and three in the 3.4 mg/kg cohort) permanently discontinued treatment because of keratopathy. Among patients with keratopathy worse than baseline at the end of treatment, the events resolved in 9 (36%) of 25 patients in the 2.5 mg/kg cohort, with a median time to resolution of 71 days (interquartile range (IQR) 57–99), and 8 (28%) of 29 patients in the 3.4 mg/kg cohort, with a median time to resolution of 96 days (70–127). No benefit was observed for prophylactic steroid eyedrop administration, as median time to keratopathy was similar between eyes treated prophylactically with corticosteroid eye drops and without (24 (IQR 21–30) and 27 (21–42) days, respectively in the 2.5 mg/kg cohort and 25 (9–40) and 25 (21–40) days, respectively in the 3.4 mg/kg cohort).²⁰³

Panel recommendations

- ▶ Prior to receiving belantamab mafodotin the patient should receive a complete ophthalmological examination.
- ▶ Monitoring in the initial studies included weekly complete blood counts and complete metabolic panels. After the first few cycles or after blood counts normalize, testing can be reduced to occur every treatment cycle.
- ▶ Management of corneal toxicity includes use of preservative-free lubricant eye drops as needed for symptoms of dryness, blurry vision or photophobia.
- ▶ Management of moderate-to-severe corneal toxicity includes holding therapy until improvement of symptoms to grade 1 or less and improvement of corneal changes is confirmed by ophthalmological examination, then restarting with a one level dose reduction.
- ▶ During belantamab mafodotin treatment specifically, therapy can be restarted once keratopathy or other AEs (such as cytopenias) have resolved to grade 1 or less. Dose reduction from 3.4 to 2.5 mg/kg may be



considered. Further dose reductions to 1.9 mg/kg may be done if significant toxicity recurs.

- ▶ Since a proportion of patients may have delayed responses, it is recommended that ADC therapy be continued as long as patients exhibit stable disease or better responses and are tolerating therapy.

Other considerations

No validated biomarkers exist to predict response to ADC therapy. In the phase I DREAMM-1 trial, no clear association was observed between predose soluble BCMA concentrations and response to treatment.²⁰⁰ Patients with significant renal insufficiency, plasma cell leukemia and hepatic impairment were excluded from clinical trials of belantamab mafodotin. A trial of the ADC brentuximab vedotin in patients with CD30+ hematological malignancies and hepatic or renal impairment observed increased exposure to the cytotoxic payload molecule, MMAE, among patients with deficient liver or kidney function.²⁰⁵ Anecdotally, patients with chronic hepatitis B infection on entecavir have been successfully treated with ADCs and exhibited good tolerability and response.

Although belantamab mafodotin is the most clinically advanced, ADCs targeting other antigens and carrying other payloads have been investigated. Indatuximab ravtansine (BT-062) is an ADC carrying the microtubule-disrupting maytansinoid DM4 as payload and targeted to CD138, which is overexpressed on MM cells. In a phase I trial of 35 patients with RRMM, indatuximab ravtansine monotherapy resulted in a 5.9% ORR with no CR, although 61.8% of patients achieved stable disease. The median OS and PFS were 26.7 and 3 months, respectively.¹⁸ A phase I/II trial evaluating indatuximab ravtansine in combination with low-dose dexamethasone and lenalidomide in 47 patients with RRMM observed a median PFS of 16.4 months. Of the 43 who patients completed at least two treatment cycles and were evaluable for response, 33 achieved PR or better, with an ORR of 77% and a mDOR of 21.0 months.²⁰⁶ Despite these results, in 2017, ImmunoGen announced that it has elected not to exercise its late-stage co-development option with Biotest to develop BT-062 for the US market.²⁰⁷

Lorvotuzumab mertansine (IMGN901) is an anti-CD56 targeting mAb linked to the maytansinoid DM1. The agent demonstrated no clinical benefits in a phase II study evaluating combination therapy with carboplatin and etoposide in 141 patients with small-cell lung cancer.²⁰⁸ In RRMM, however, IMGN901 has delivered modest clinical benefits. In a phase I/II study, the objective response rate was only 5.7%, but stable disease or better was noted in 42.9% of patients treated with single agent lorvotuzumab mertansine, and the mDOR was 15.5 months.²⁰⁹ Another ADC, milatuzumab doxorubicin (hLL1-DOX), which delivers a DNA-damaging anthracycline molecule to cells expressing CD74, also maintained stable disease for longer than 3 months in 5 out of 19 patients with RRMM in a multicenter dose-escalation study.²¹⁰ However, a subsequent trial of hLL1-DOX, completed in

2015 (NCT01101594) posted no results, and no further studies have been registered with the agent.

VACCINES

Cancer vaccines targeting MM represent an attractive strategy to reverse critical aspects of the immunosuppressive milieu of the tumor microenvironment and promote the activation and expansion of tumor-specific lymphocytes. Potential antigenic targets include the use of shared tumor antigens such as cancer testis antigens (NY-ESO), plasma cell-specific markers (BCMA), oncogenic drivers (MUC1) and the clonal idiotype. A growing area of interest is the use of neoantigens derived from unique mutational events. Several of the current vaccine strategies were reviewed in the prior SITC consensus statement on immunotherapy for the treatment of hematological malignancies.²⁴

One antigen-specific approach that is being explored in the setting of SMM is the PVX-410 vaccine, which consists of a cocktail of HLA-A2-derived peptides from X-box binding protein 1, CD138 and SLAMF7 antigens that can trigger activation of MM-specific T cells.²² Alternatively, investigators have examined strategies to load antigens derived from whole tumor cells onto antigen-presenting cells. In one approach, a personalized vaccine has been created in which hybridomas are created from patient-derived myeloma cells fused with autologous dendritic cells (DCs). In a phase I study, vaccination with the DC/MM fusions in conjunction with granulocyte macrophage colony-stimulating factor resulted in a durable expansion of myeloma-reactive CD4+ and CD8+ lymphocytes, and ongoing stable disease in three patients, with no evidence of progression at 12, 25 and 41 months.²³ Based on these results, this approach is now being tested in a randomized multicenter phase II clinical trial being conducted through the Clinical Trials Network cooperative group (CTN 1401, NCT02728102). Study enrollment of >200 patients has been completed with site-specific production of vaccine and centralized vaccine characterization and determination of immunological response.

The use of vaccine therapy will likely be most efficacious as a strategy to enhance native T cell immunity to target lower volume disease such as after autologous transplantation and as a potential combinatorial strategy to enhance effector cell therapies. As one example, the potential synergy between the DC/MM fusion vaccine and BCMA CAR T cells is being explored to assess whether vaccination may result in epitope spreading and greater persistence of the CAR T cell population.

Panel recommendations

- ▶ The panel did not make any recommendations regarding the use of vaccines in myeloma. Participation in well-designed clinical trials is encouraged.

QUALITY OF LIFE AND PATIENT ENGAGEMENT

Immunotherapy is changing the outlook for patients with MM. Data are limited on how immunotherapy affects QoL, but answering this question is increasingly important as our effective therapies evolve and the number of survivors grows. There is thus a need to identify late physiological effects and psychosocial needs, and develop evidence-based interventions.

Patient and caregiver education

Education for immunotherapies must emphasize the unique mechanisms of action and side-effect profiles, as they differ from chemotherapy and targeted therapies. Side effects vary among the various immunotherapy agents. Since immunotherapy is a complex modality with numerous agents and diverse side effects administered in different settings, all healthcare professionals must also be scrupulously educated. It is also important that patients with myeloma receive care from a specialist in hematological malignancies—a 2018 survey of 2382 patients with myeloproliferative neoplasms revealed that only one-third were treated by a specialist.²¹¹

For the current immunotherapies discussed in these SITC guidelines, the common immune related side effects include IRRs to antibodies (see ‘Daratumumab’, ‘Elotuzumab’, ‘Isatuximab’ and ‘Antibody-drug conjugates’ sections), as well as CRS and ICANS for CAR T cell and BiTE therapies (see ‘CAR T cells’ and ‘Bispecific T cell engagers’ sections). The majority of IRRs occur with the first or second exposure to antibodies, but they may also occur with any subsequent infusions. Some events, such as CRS and ICANS, may be delayed.

Panel recommendations

- ▶ Education must prepare the patient and caregivers for the timeline of expected side effects. It is critical to educate patients and caretakers about the signs and symptoms of immune-related side effects because early recognition is essential to effective treatment.
- ▶ Caregiver education is paramount as neurological toxic effects may impair a patient’s ability to recognize symptoms.
- ▶ It is crucially important to also coordinate education with the interdisciplinary care team. This may include provider, advanced practice provider, nurse, coordinator (research or non-research), social worker and pharmacist.

Quality of life considerations for administration, dosing and monitoring during immunotherapy

mAbs are associated with typical IRRs (see ‘Daratumumab’, ‘Elotuzumab’ and ‘Isatuximab’ sections). A clinical review of mAbs in myeloma²¹² emphasizes the need for appropriate preinfusion and postinfusion medications to lower the rates of IRRs and facilitate increases in infusion rates to enable shorter infusion time.

For cellular therapies, many institutions prefer continuous toxicity monitoring and have limited ambulatory

programs, so the majority of CAR T cell patients receive their initial care in the inpatient setting.²¹³ However, outpatient management is permitted on the label of at least one FDA-approved CAR T therapy for lymphoma. Research will need to identify methods to improve early detection and intervention for toxicities, such as an electronic medical record alert, medical alert bracelet, emergency department protocols for fast-tracking evaluation and admission and 24-hours access to specialized physicians for diagnosis and early management. Psychosocial criteria for CAR T cell therapy (such as proximity to treating institutions and need for a 24-hour caretaker) could potentially improve the promptness of medical attention, however, this needs to be studied.

In the long term, there is an effort to protect patients who are receiving genetically modified cellular therapy products. The FDA requires patients receiving tisagenlecleucel and axicabtagene ciloleucel to participate in 15 years of postmarketing participation in observational study for long-term safety and risk of secondary malignancies.^{143 144}

Panel recommendations

- ▶ Patient monitoring and management depends on the immunotherapy agent.
- ▶ All patients receiving immunotherapies should be given detailed call parameters specific to their treatment so patients can promptly communicate with their cancer care providers for direction.

Special considerations for quality of life

Clinical trials often have more frequent assessments and clinic visits than standard of care therapies. This places an additional burden on the patient—physically, emotionally and financially. Additionally, patients receiving treatment on an immunotherapy clinical trial may be required to remain in proximity to the treating institution and have a 24-hour caretaker for a period of time, which would further increase the burden.

Financial toxicity is an important side effect of cancer treatment and a psychological stressor.²¹⁴ Although at the time of this writing, there is not an FDA-approved CAR T cell therapy for myeloma, it can be surmised that a myeloma CAR T cell therapy would be similarly priced to the currently available commercial CAR T cell products. Cost of treatment alone, not including hospital care or services provided, for a course of tisagenlecleucel (Kymriah) or axicabtagene ciloleucel (Yescarta) for lymphoma is US\$373,000, and the price of tisagenlecleucel for B-ALL is US\$475,000. Ancillary expenses such as transportation, relocation costs and accommodations, food and child care²¹⁵ also contribute to financial distress. Kymriah and Yescarta Risk Evaluation and Mitigation Strategies (REMS) programs both instruct patients to remain within proximity of the treating institution for at least 4 weeks following infusion,^{143 144} and one could postulate a similar requirement for a myeloma therapy. This requirement obviously adds to the ancillary costs of treatment.

Panel recommendations

- ▶ Patients should be referred for a social work evaluation to assess needs and connect to available resources.
- ▶ It is especially important to provide whole-person care. Patients should be connected to other patients, survivors, support groups and online forums, and referrals should be made to social workers, chaplains and psycho-oncologists.
- ▶ Recommended advocacy groups include the International Myeloma Foundation (www.myeloma.org), Multiple Myeloma Research Foundation (www.themmr.org), Leukemia & Lymphoma Society (www.lls.org), Myeloma Crowd (www.myelomacrowd.org) and the SITC (sitc.org).
- ▶ Ideally, immunotherapy-specific survivorship programs should be developed or patients receiving immunotherapy should be included in existing programs.

Immunotherapy-specific quality of life

There are very limited data describing the impact of immunotherapy on QoL. In a secondary analysis of MAIA, which compared health-related quality of life (HRQoL) between treatment arms (D-Rd vs Rd), the D-RD arm demonstrated an improvement in HRQoL.²¹⁶ As assessed by the European Organization for Research and Treatment (EORTC) Quality-of-life Questionnaire Core 30 (QLQ-C30), improvement in Global Health Status occurred in both groups. However, the D-Rd arm demonstrated significantly greater improvement earlier (cycle 3) and increasing improvement over time. The D-Rd arm also showed significant improvement and clinically meaningful benefit in HRQoL as evaluated by the EQ-5D-5L Visual Analog Scale. This was evidenced by a longer time to worsening in the D-Rd arm and meaningful differences in pain symptoms and cognitive functioning, although the decline in cognitive functioning was not significant between arms.

Analysis of patient-reported health status in the ELOQUENT-3 trial as quantified by the MD Anderson Symptom Inventory MM module and the three-level version of the EuroQoL 5 Dimensions Questionnaire (EQ-5D-3L) in patients treated with elotuzumab compared with those receiving Pd alone showed no worsening of pain, fatigue or bone aches with elotuzumab treatment and minimal differences in QoL between patients who received EPd and Pd.²¹⁷

Data are lacking on the impact of CAR T cell therapies on short-term and long-term QoL. However, clinical trials are beginning to include QoL assessment in addition to efficacy. Preliminary data on QoL in CAR T cell patients, in comparison with HSCT patients, were presented at The 24th Congress of the European Hematology Association.²¹⁸ These data demonstrate that CAR T cell therapy at least does not significantly worsen QoL compared with autologous and allo-HSCT. Furthermore, in the short term there is some indication of improved physical well-being.

How and how often QoL should be assessed in patients receiving immunotherapy has not been established, although recommendations are starting to emerge. Level VI evidence (semi-structured interviews and focus groups encompassing 20 patients) from Osborne *et al* demonstrated that existing QoL measures developed and validated for MM do not capture all the QoL issues important for patients with myeloma. A new myeloma-specific QoL questionnaire designed specifically for use in the clinical setting—the MyPOS—was developed based on the findings of Osborne *et al*.²¹⁹ However, currently the EORTC QLQ-C30 is the most validated tool for HRQoL in myeloma. In 2018, the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) extended coverage for CAR T cell therapy for beneficiaries with advanced cancer, and the panel mostly endorsed the incorporation of Patient Reported Outcomes (PRO) tools for CAR T cell therapies. The MEDCAC voting members had highest confidence in the Patient-Reported Outcomes Measurement Information System (PROMIS).²²⁰ There are not yet validated PRO tools for CAR T cell therapy, but a recent review²²¹ advocates for the use of PROMIS as it has been universally validated for HSCT.

Panel recommendations

- ▶ Validated tools, including EORTC QLQ-C30 and PROMIS, should be considered in evaluation of effects of immune therapies on QoL.

Immune-related side effects and quality of life

Although some interview and focus group data²²² suggest that some patients' treatment decisions are impacted by treatment attributes, the panel's experience is that treatment efficacy is more important to patients than side effects. Significant associations have been seen between longer treatment-free intervals and better HRQoL for patients with MM,²²³ opening up the possibility that CAR T cell therapies and ADCs with finite treatment schedules could improve QoL.

As noted in previous sections, common side effects of immunotherapies that may persist after the initial treatment period include cytopenias, heightened risk for viral, bacterial and fungal infections, immunodeficiencies and fatigue. Treatment guidelines to manage these events are generally institution-specific (growth factors, prophylactic antimicrobial, transfusions, IVIG). However, it is important for providers to assess for these side effects with some frequency and to also work with local providers in following these toxicities closely.

Panel recommendations

- ▶ Patients should be educated on the potential need for prophylactic antimicrobials, IVIG and/or growth factor and transfusion support to manage cytopenias and immunodeficiency.
- ▶ Patients should also be educated that they may experience fatigue as a sequelae of cellular and immunotherapy. Pharmacological and non-pharmacological

interventions may be used to address fatigue, although it is important to avoid steroids as treatment because of the concern of T cell suppression.

CONCLUSIONS

With demonstrated clinical benefit including deep and durable responses in both the newly diagnosed and relapsed/refractory setting, immunotherapies are rapidly becoming mainstays in the treatment of MM. As more novel agents make their way through clinical trials, it will be important to characterize if and how prior treatment with one immunotherapeutic agent influences the efficacy of subsequent lines of therapy. Furthermore, with more approved options, trials evaluating combination regimens could examine potential synergies between immunotherapeutic agents. For example, bispecific T cell engager antibodies might enhance cytotoxic T cell activity when given after cancer vaccination or CAR T cell therapy. As with any regimen, however, rigorous randomized controlled trials will need to be performed to demonstrate safety and efficacy. Future studies will also need to address the interpretation of response criteria and MRD in the context of patients treated with immunotherapies. Finally, patient access to immunotherapy and QoL during and after treatment should not be ignored by practicing physicians. It is an exciting time for the MM field, as new agents are prolonging survival and improving outcomes in a disease that was once universally and rapidly fatal.

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REFERENCES

- 1 Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.
- 2 Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. *Blood* 2008;111:2521–6.
- 3 Fonseca R, Abouzaid S, Bonafede M, et al. Trends in overall survival and costs of multiple myeloma, 2000–2014. *Leukemia* 2017;31:1915–21.
- 4 Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia* 2014;28:1122–8.
- 5 Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008;111:2516–20.
- 6 Mateos M-V, Ludwig H, Bazarbachi A, et al. Insights on multiple myeloma treatment strategies. *Hemasphere* 2019;3:e163.
- 7 Rajkumar SV. Multiple myeloma: 2018 update on diagnosis, risk-stratification, and management. *Am J Hematol* 2018;93:1091–110.
- 8 Perrot A, Corre J, Avet-Loiseau H. Risk stratification and targets in multiple myeloma: from genomics to the bedside. *Am Soc Clin Oncol Educ Book* 2018;38:675–80.
- 9 Kazandjian D, Landgren O. A look backward and forward in the regulatory and treatment history of multiple myeloma: approval of novel-novel agents, new drug development, and longer patient survival. *Semin Oncol* 2016;43:682–9.
- 10 Biotech J. *Daratumumab highlights of prescribing information*. US: Food and Drug Administration, 2015.
- 11 Squibb B-M. *Highlights of prescribing information: EMLPICI (elotuzumab) for injection, for intravenous use U.S.* US: FDA, 2015.
- 12 Raju N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. *N Engl J Med Overseas Ed* 2019;380:1726–37.
- 13 Cohen AD. Car T cells and other cellular therapies for multiple myeloma: 2018 update. *Am Soc Clin Oncol Educ Book* 2018;38:e6–15.
- 14 Mikilineni L, Kochenderfer JN. Chimeric antigen receptor T-cell therapies for multiple myeloma. *Blood* 2017;130:2594–602.
- 15 Harrington K et al. Development of JCARH125: optimization of a fully human Anti-Bcma CAR for use in the treatment of multiple myeloma 2017;130:1813.
- 16 Yu B, Liu D. Antibody-Drug conjugates in clinical trials for lymphoid malignancies and multiple myeloma. *J Hematol Oncol* 2019;12:94.
- 17 Rakesh Popat NL, Trudel S, Voorhees PM, et al. *B-Cell maturation antigen antibody-drug conjugate (ADC), GSK2857916, in relapsed/refractory multiple myeloma (RRMM): final safety, efficacy and pharmacokinetic (pK) analyses from a phase I study, in 24th Congress of the European hematology association*. Amsterdam: EHA Library, 2019.
- 18 Jagannath S, Heffner LT, Ailawadhi S, et al. Indatuximab Ravtansine (BT062) monotherapy in patients with relapsed and/or refractory multiple myeloma. *Clin Lymphoma Myeloma Leuk* 2019;19:372–80.
- 19 Chen D, Zou J, Zong Y, et al. Anti-Human CD138 monoclonal antibodies and their bispecific formats: generation and characterization. *Immunopharmacol Immunotoxicol* 2016;38:175–83.
- 20 Topp MS, Duell J, Zugmaier G, et al. Evaluation of AMG 420, an anti-BCMA bispecific T-cell engager (bite) immunotherapy, in R/R multiple myeloma (Mm) patients: updated results of a first-in-human (FIH) phase I dose escalation study. *JCO* 2019;37:8007.
- 21 Zou J, Chen D, Zong Y, et al. Immunotherapy based on bispecific T-cell engager with hlgG1 Fc sequence as a new therapeutic strategy in multiple myeloma. *Cancer Sci* 2015;106:512–21.
- 22 Nooka AK, Wang ML, Yee AJ, et al. Assessment of safety and immunogenicity of PVX-410 vaccine with or without lenalidomide in patients with smoldering multiple myeloma: a nonrandomized clinical trial. *JAMA Oncol* 2018;4:e183267.
- 23 Rosenblatt J, Vasir B, Uhl L, et al. Vaccination with dendritic cell/tumor fusion cells results in cellular and humoral antitumor immune responses in patients with multiple myeloma. *Blood* 2011;117:393–402.
- 24 Boyiadzis M, Bishop MR, Abonour R, et al. The Society for immunotherapy of cancer consensus statement on immunotherapy for the treatment of hematologic malignancies: multiple myeloma, lymphoma, and acute leukemia. *J Immunother Cancer* 2016;4:90.
- 25 Gonsalves WL, Buadi FK, Ailawadhi S, et al. Utilization of hematopoietic stem cell transplantation for the treatment of multiple myeloma: a Mayo stratification of myeloma and Risk-Adapted therapy (mSMART) consensus statement. *Bone Marrow Transplant* 2019;54:353–67.
- 26 Graham R. *Clinical practice guidelines we can trust*. Washington, DC: The National Academies Press, 2011: 290.
- 27 Plesner T, Krejci J. Daratumumab for the treatment of multiple myeloma. *Front Immunol* 2018;9:1228.
- 28 Dimopoulos MA, San-Miguel J, Belch A, et al. Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX. *Haematologica* 2018;103:2088–96.
- 29 Bahlis N, Dimopoulos MA, White DJ, et al. Three-Year follow up of the phase 3 Pollux study of Daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (RD) alone in relapsed or refractory multiple myeloma (RRMM). *Blood* 2018;132:1996.
- 30 Spencer A, Lentzsch S, Weisel K, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. *Haematologica* 2018;103:2079–87.
- 31 Kaufman JL, Usmani SZ, San-Miguel J, et al. Four-Year follow-up of the phase 3 Pollux study of Daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (RD) alone in relapsed or refractory multiple myeloma (RRMM). *Blood* 2019;134:1866.
- 32 Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med* 2016;375:754–66.
- 33 Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. *Blood* 2017;130:974–81.
- 34 Usmani SZ et al. Carfilzomib, dexamethasone, and Daratumumab versus carfilzomib and dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma (RRMM): primary analysis results from the randomized, open-label, phase 3 study Candor (NCT03158688). *Blood* 2019;134.
- 35 Voorhees PM, Rodriguez C, Reeves B, et al. Efficacy and updated safety analysis of a safety Run-in cohort from Griffin, a phase 2 randomized study of Daratumumab (DarA), bortezomib (V), lenalidomide (R), and dexamethasone (D; Dara-Vrd) vs. Vrd in patients (PTS) with newly diagnosed (nd) multiple myeloma (Mm) eligible for High-Dose therapy (HDT) and autologous stem cell transplantation (ASCT). *Blood* 2018;132:151.
- 36 Voorhees PM, Kaufman JL, Laubach JP, et al. Daratumumab, Lenalidomide, Bortezomib, & Dexamethasone for Transplant-eligible Newly Diagnosed Multiple Myeloma: GRIFFIN. *Blood* 2020. doi:10.1182/blood.2020005288. [Epub ahead of print: 23 Apr 2020].
- 37 Voorhees PM, Kaufman JL, Laubach JP, et al. *Depth of response to Daratumumab (DarA), lenalidomide, bortezomib, and dexamethasone (RVd) improves over time in patients (PTS) with Transplant-Eligible newly diagnosed multiple myeloma (NDMM): Griffin study update, in ash 2019*. Orlando: Blood, 2019: 134. 691.
- 38 Sonneveld P, Broijl A, Gay F, et al. Bortezomib, lenalidomide, and dexamethasone (VRd) ± daratumumab (DarA) in patients (PTS) with transplant-eligible (te) newly diagnosed multiple myeloma (NDMM): a multicenter, randomized, phase III study (PERSEUS). *JCO* 2019;37:TPS8055.
- 39 Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. *Lancet* 2019;394:29–38.
- 40 Moreau P, Attal M, Hulin C, et al. Phase 3 randomized study of daratumumab (DarA) + bortezomib/thalidomide/dexamethasone (D-VTd) vs VTD in transplant-eligible (te) newly diagnosed multiple myeloma (NDMM): CASSIOPEIA Part 1 results. *JCO* 2019;37:8003.
- 41 Facon T, Kumar S, Plesner T, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med Overseas Ed* 2019;380:2104–15.
- 42 Mateos M-V, Cavo M, Bladé J, et al. Daratumumab plus bortezomib, melphalan, and prednisone versus bortezomib, melphalan, and prednisone in patients with transplant-ineligible newly diagnosed multiple myeloma: overall survival in Alcyone. *Blood* 2019;134:859.
- 43 Kumar SK, Kapoor P, Laplant B, et al. Phase 2 trial of Ixazomib, lenalidomide, dexamethasone and Daratumumab in patients with newly diagnosed multiple myeloma. *Blood* 2018;132:304.
- 44 Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med Overseas Ed* 2016;375:1319–31.
- 45 Chari A, Mark TM, Krishnan A, et al. Use of montelukast to reduce infusion reactions in an early access treatment protocol of Daratumumab in United States patients with relapsed or refractory multiple myeloma. *Blood* 2016;128:2142.

- 46 Usmani SZ, Nahi H, Mateos M-V, *et al.* Open-Label, multicenter, dose escalation phase 1B study to assess the subcutaneous delivery of Daratumumab in patients (PTS) with relapsed or refractory multiple myeloma (PAVO). *Blood* 2016;128:1149.
- 47 Usmani SZ, Mateos M-V, Nahi H, *et al.* Randomized, open-label, non-inferiority, phase 3 study of subcutaneous (Sc) versus intravenous (IV) Daratumumab (DarA) administration in patients with relapsed or refractory multiple myeloma: Columba update. *Blood* 2019;134:1865.
- 48 Mateos M-V, Usmani SZ, Grosicki S, *et al.* Randomized, open-label, non-inferiority, phase 3 study of subcutaneous (Sc) versus intravenous (IV) Daratumumab (DarA) administration in patients (PTS) with relapsed or refractory multiple myeloma (RRMM): body weight subgroup analysis of Columba. *Blood* 2019;134:1906.
- 49 Mateos MV. *Efficacy and safety of the randomized, open-label, non-inferiority, phase 3 study of subcutaneous (Sc) versus intravenous (IV) daratumumab (DarA) administration in patients (PTS) with relapsed or refractory multiple myeloma (RRMM): Columba, in American Society of clinical oncology meeting.* Chicago, US, 2019. al., C.A.e. *Subcutaneous (Sc) Daratumumab (DarA) in combination with standard multiple myeloma (Mm) treatment regimens: an open-label, multicenter phase 2 study (PLEIADES), in 17th International myeloma workshop.* Boston, MA, 2019: 24.
- 51 Chari A, Martinez-Lopez J, Mateos M-V, *et al.* Daratumumab plus carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma. *Blood* 2019;134:421–31.
- 52 Barr H, Dempsey J, Waller A, *et al.* Ninety-minute daratumumab infusion is safe in multiple myeloma. *Leukemia* 2018;32:2495–518.
- 53 Heher EC, Rennke HG, Laubach JP, *et al.* Kidney disease and multiple myeloma. *Clin J Am Soc Nephrol* 2013;8:2007–17.
- 54 Cejalvo MJet al. Activity and safety of Daratumumab Monotherapy in patients with relapsed and refractory multiple myeloma requiring dialysis: preliminary results of Spanish, retrospective. *Multicenter Trial* 2017;130:1866.
- 55 Rocchi S, Tacchetti P, Pantani L, *et al.* Safety and efficacy of daratumumab in dialysis-dependent renal failure secondary to multiple myeloma. *Haematologica* 2018;103:e277–8.
- 56 Loomba R, Liang TJ. Hepatitis B reactivation associated with immune suppressive and biological modifier therapies: current concepts, management strategies, and future directions. *Gastroenterology* 2017;152:1297–309.
- 57 Hwang JP, Somerfield MR, Alston-Johnson DE, *et al.* Hepatitis B virus screening for patients with cancer before therapy: American Society of clinical oncology provisional clinical opinion update. *JCO* 2015;33:2212–20.
- 58 Law MF, Ho R, Cheung CKM, *et al.* Prevention and management of hepatitis B virus reactivation in patients with hematological malignancies treated with anticancer therapy. *World J Gastroenterol* 2016;22:6484–500.
- 59 Mizuta S, Kawata T, Kawabata H, *et al.* VS38 as a promising CD38 substitute antibody for flow cytometric detection of plasma cells in the daratumumab era. *Int J Hematol* 2019;110:322–30.
- 60 Oberle A, Brandt A, Alawi M, *et al.* Long-Term CD38 saturation by daratumumab interferes with diagnostic myeloma cell detection. *Haematologica* 2017;102:e368–70.
- 61 Thoren KL, Pianko MJ, Maakaroun Y, *et al.* Distinguishing drug from disease by use of the Hydrashift 2/4 Daratumumab assay. *J Appl Lab Med* 2019;3:857–63.
- 62 Mills JR, Kohlhagen MC, Willrich MAV, *et al.* A universal solution for eliminating false positives in myeloma due to therapeutic monoclonal antibody interference. *Blood* 2018;132:670–2.
- 63 Moore LM, Cho S, Thoren KL. Maldi-ToF mass spectrometry distinguishes daratumumab from M-proteins. *Clin Chim Acta* 2019;492:91–4.
- 64 van de Donk NWCJ, Otten HG, El Haddad O, *et al.* Interference of daratumumab in monitoring multiple myeloma patients using serum immunofixation electrophoresis can be abrogated using the daratumumab IFE reflex assay (DIRA). *Clin Chem Lab Med* 2016;54:1105–9.
- 65 Lancman G, Arinsburg S, Jhang J, *et al.* Blood transfusion management for patients treated with Anti-CD38 monoclonal antibodies. *Front Immunol* 2018;9:2616.
- 66 Chapuy CI, Aguad MD, Nicholson RT, *et al.* International validation of a dithiothreitol (DTT)-based method to resolve the daratumumab interference with blood compatibility testing. *Transfusion* 2016;56:2964–72.
- 67 Thomas Lin SH, Krey R, Pei H, *et al.* *Daratumumab plus lenalidomide versus lenalidomide alone as maintenance treatment in patients with newly diagnosed multiple myeloma after frontline transplant: a multicenter, randomized, phase 3 study (AURIGA), in 17th International myeloma workshop.* Boston, MA, 2019.
- 68 Nooka AK, Joseph NS, Kaufman JL, *et al.* Clinical efficacy of daratumumab, pomalidomide, and dexamethasone in patients with relapsed or refractory myeloma: utility of re-treatment with daratumumab among refractory patients. *Cancer* 2019;125:2991–3000.
- 69 Ritchie D, Colonna M. Mechanisms of action and clinical development of Elotuzumab. *Clin Transl Sci* 2018;11:261–6.
- 70 Lonial S, Dimopoulos M, Palumbo A, *et al.* Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med* 2015;373:621–31.
- 71 Zonder JA, Mohrbacher AF, Singhal S, *et al.* A phase 1, multicenter, open-label, dose escalation study of elotuzumab in patients with advanced multiple myeloma. *Blood* 2012;120:552–9.
- 72 Jagannath S, Laubach J, Wong E, *et al.* Elotuzumab monotherapy in patients with smouldering multiple myeloma: a phase 2 study. *Br J Haematol* 2018;182:495–503.
- 73 Magen H, Muchtar E. Elotuzumab: the first Approved monoclonal antibody for multiple myeloma treatment. *Ther Adv Hematol* 2016;7:187–95.
- 74 Lonial S, Dimopoulos MA, Weisel K, *et al.* Extended 5-y follow-up (Fu) of phase 3 ELOQUENT-2 study of elotuzumab + lenalidomide/dexamethasone (ELD) vs LD in relapsed/refractory multiple myeloma (RRMM). *JCO* 2018;36:8040.
- 75 Lonial S, Dimopoulos M, Palumbo A, *et al.* Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med Overseas Ed* 2015;373:621–31.
- 76 Miguel JS, Weisel K, Moreau P, *et al.* Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2013;14:1055–66.
- 77 Dimopoulos MA, Dytfield D, Grosicki S, *et al.* Elotuzumab plus Pomalidomide and dexamethasone for multiple myeloma. *N Engl J Med* 2018;379:1811–22.
- 78 Jakubowiak A, Offidani M, Pégourie B, *et al.* Randomized phase 2 study: elotuzumab plus bortezomib/dexamethasone vs bortezomib/dexamethasone for relapsed/refractory MM. *Blood* 2016;127:2833–40.
- 79 Mateos M-V, Granell M, Oriol A, *et al.* Elotuzumab in combination with thalidomide and low-dose dexamethasone: a phase 2 single-arm safety study in patients with relapsed/refractory multiple myeloma. *Br J Haematol* 2016;175:448–56.
- 80 Dimopoulos MA, Facon T, Richardson PGG, *et al.* ELOQUENT-1: a phase III, randomized, open-label trial of lenalidomide/dexamethasone with or without elotuzumab in subjects with previously untreated multiple myeloma (CA204-006). *JCO* 2012;30:TPS8113.
- 81 Salwender H, Bertsch U, Weisel K, *et al.* Rationale and design of the German-speaking myeloma multicenter group (GMMG) trial Hd6: a randomized phase III trial on the effect of elotuzumab in VRD induction/consolidation and lenalidomide maintenance in patients with newly diagnosed myeloma. *BMC Cancer* 2019;19:504.
- 82 Usmani SZ, Sexton R, Ailawadhi S, *et al.* Phase I safety data of lenalidomide, bortezomib, dexamethasone, and elotuzumab as induction therapy for newly diagnosed symptomatic multiple myeloma: SWOG S1211. *Blood Cancer J* 2015;5:e334.
- 83 Ghobrial IM, Badros AZ, Vredenburgh JJ, *et al.* Phase II trial of combination of Elotuzumab, lenalidomide, and dexamethasone in high-risk smoldering multiple myeloma. *Blood* 2016;128:976.
- 84 Cornell RF, Gandhi UH, Lakshman A, *et al.* Subsequent treatment outcomes of multiple myeloma refractory to CD38-Monoclonal antibody therapy. *Blood* 2018;132:2015.
- 85 Becnel MR, Rubin ML, Nair R, *et al.* Effect of timing of monoclonal antibody therapy on the time to next treatment and response rate in heavily pre-treated patients with myeloma who separately received both Daratumumab and Elotuzumab-Based regimens. *Blood* 2018;132:3258.
- 86 Varnado W, Jagosky MH, Gahvari Z, *et al.* Natural history of patients with multiple myeloma refractory to Elotuzumab and outcomes of subsequent therapy with Anti-CD38 monoclonal antibodies. *Blood* 2018;132:3303.
- 87 Hoylman E, Brown A, Perissinotti AJ, *et al.* Optimal sequence of daratumumab and elotuzumab in relapsed and refractory multiple myeloma. *Leuk Lymphoma* 2020;61:691–8.
- 88 Berenson J, Manges R, Badarinarath S, *et al.* A phase 2 safety study of accelerated elotuzumab infusion, over less than 1 H, in combination with lenalidomide and dexamethasone, in patients with multiple myeloma. *Am J Hematol* 2017;92:460–6.
- 89 Mills JR, Murray DL. Identification of Friend or foe: the laboratory challenge of differentiating M-proteins from monoclonal antibody therapies. *Jrnl App Lab Med* 2017;1:421–31.

- 90 Postelnek J, Neely RJ, Robbins MD, *et al.* Development and validation of electrochemiluminescence assays to measure free and total sSLAMF7 in human serum in the absence and presence of Elotuzumab. *Aaps J* 2016;18:989–99.
- 91 Trudel S, Moreau P, Touzeau C. Update on elotuzumab for the treatment of relapsed/refractory multiple myeloma: patients' selection and perspective]]>. *Oncotargets and therapy* 2019;12:5813–22.
- 92 Berdeja J, Jagannath S, Zonder J, *et al.* Pharmacokinetics and safety of Elotuzumab combined with lenalidomide and dexamethasone in patients with multiple myeloma and various levels of renal impairment: results of a phase Ib study. *Clin Lymphoma Myeloma Leuk* 2016;16:129–38.
- 93 Atchison DK, Humes HD. A case of tumor lysis syndrome and acute renal failure associated with elotuzumab treatment in multiple myeloma. *Clin Nephrol Case Stud* 2017;5:78–81.
- 94 Moreno L, Perez C, Zabaleta A, *et al.* The mechanism of action of the Anti-CD38 monoclonal antibody Isatuximab in multiple myeloma. *Clin Cancer Res* 2019;25:3176–87.
- 95 Chari A *et al.* Phase Ib study of isatuximab+ carfilzomib in relapsed and refractory multiple myeloma (RRMM). American Society of Clinical Oncology, 2018.
- 96 Richardson PG, Attal M, Campana F, *et al.* Isatuximab plus pomalidomide/dexamethasone versus pomalidomide/dexamethasone in relapsed/refractory multiple myeloma: Icaria phase III study design. *Future Oncol* 2018;14:1035–47.
- 97 Mikhael J, Richardson P, Usmani SZ, *et al.* A phase 1B study of isatuximab plus pomalidomide/dexamethasone in relapsed/refractory multiple myeloma. *Blood* 2019;134:123–33.
- 98 Richardson PG, Attal M, Rajkumar SV, *et al.* A phase III randomized, open label, multicenter study comparing isatuximab, pomalidomide, and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM). *JCO* 2019;37:8004.
- 99 Orłowski RZ, Goldschmidt H, Cavo M, *et al.* Phase III (IMROZ) study design: Isatuximab plus bortezomib (V), lenalidomide (R), and dexamethasone (D) vs VRd in transplant-ineligible patients (PTS) with newly diagnosed multiple myeloma (NDMM). *JCO* 2018;36:TPS8055.
- 100 Martin T, Baz R, Benson DM, *et al.* A phase 1B study of isatuximab plus lenalidomide and dexamethasone for relapsed/refractory multiple myeloma. *Blood* 2017;129:3294–303.
- 101 Krejci J, Frerichs KA, Nijhof IS, *et al.* Monocytes and granulocytes reduce CD38 expression levels on myeloma cells in patients treated with Daratumumab. *Clin Cancer Res* 2017;23:7498–511.
- 102 Alici E, Chrobok M, Lund J, *et al.* Re-challenging with anti-CD38 monotherapy in triple-refractory multiple myeloma patients is a feasible and safe approach. *Br J Haematol* 2016;174:473–7.
- 103 Drgona L, Gudiol C, Lanini S, *et al.* ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Agents targeting lymphoid or myeloid cells surface antigens [I]: CD22, CD30, CD33, CD38, CD40, SLAMF-7 and CCR4). *Clin Microbiol Infect* 2018;24 Suppl 2:S83–94.
- 104 Ticona K, Tun A, Guevara E. Risks of upper respiratory tract infection and pneumonia in patients with multiple myeloma receiving Daratumumab: a systematic review and meta-analysis of randomized controlled trials. *JCO* 2018;36:e20005.
- 105 Laubach JP, van de Donk N, Davies FE, *et al.* Practical considerations for antibodies in myeloma. *Am Soc Clin Oncol Educ Book* 2018;38:667–74.
- 106 Costa F, Das R, Kini Bailur J, *et al.* Checkpoint inhibition in myeloma: opportunities and challenges. *Front Immunol* 2018;9:2204.
- 107 Morandi F, Horenstein AL, Costa F, *et al.* Cd38: a target for immunotherapeutic approaches in multiple myeloma. *Front Immunol* 2018;9.
- 108 Taniwaki M, Yoshida M, Matsumoto Y, *et al.* Elotuzumab for the treatment of relapsed or refractory multiple myeloma, with special reference to its modes of action and SLAMF7 signaling. *Mediterr J Hematol Infect Dis* 2018;10:e2018014.
- 109 Coquery CM, Erickson LD. Regulatory roles of the tumor necrosis factor receptor BCMA. *Crit Rev Immunol* 2012;32:287–305.
- 110 Lightman SM, Utlei A, Lee KP. Survival of long-lived plasma cells (LLPC): piecing together the puzzle. *Front Immunol* 2019;10:965.
- 111 Cho S-F, Anderson KC, Tai Y-T. Targeting B cell maturation antigen (BCMA) in multiple myeloma: potential uses of BCMA-Based immunotherapy. *Front Immunol*;9.
- 112 Tai Y-T, Anderson KC. Targeting B-cell maturation antigen in multiple myeloma. *Immunotherapy* 2015;7:1187–99.
- 113 Laurent SA, Hoffmann FS, Kuhn P-H, *et al.* γ -secretase directly sheds the survival receptor BCMA from plasma cells. *Nat Commun* 2015;6:7333.
- 114 Pont MJ, Hill T, Cole GO, *et al.* Gamma-Secretase inhibition increases efficacy of BCMA-specific chimeric antigen receptor T cells in multiple myeloma. *Blood* 2019;134:1585–97.
- 115 Friedman KM, Garrett TE, Evans JW, *et al.* Effective targeting of multiple B-cell maturation Antigen–Expressing hematological Malignances by Anti-B-Cell maturation antigen chimeric antigen receptor T cells. *Hum Gene Ther* 2018;29:585–601.
- 116 Corporation C. Celgene Corporation and bluebird bio announce bb2121 Anti-BCMA CAR-T cell therapy has been granted breakthrough therapy designation from FDA and prime eligibility from EMA for relapsed and refractory multiple myeloma. Business Wire: businesswire.com, 2017.
- 117 Zhao W-H, Liu J, Wang B-Y, *et al.* A phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell maturation antigen, in patients with relapsed or refractory multiple myeloma. *J Hematol Oncol* 2018;11:141.
- 118 Deepu Madduri SZU, Sundar Jagannath IS, Zudaire E, *et al.* Results from CARTITUDE-1: a phase 1b/2 study of JNJ-4528, a CAR-T cell therapy directed against B-cell maturation antigen (BCMA), in patients with relapsed and/or refractory multiple myeloma (R/R Mm) in ASH2019. Orlando, FL: Blood, 2019.
- 119 Khan AM, Devarakonda S, Bumma N, *et al.* Potential of NK cells in multiple myeloma therapy. *Expert Rev Hematol* 2019;12:425–35.
- 120 Zhao L, Cao YJ. Engineered T cell therapy for cancer in the clinic. *Front Immunol* 2019;10:2250.
- 121 Mailankody S, Htut M, Lee KP, *et al.* JCARH125, Anti-BCMA CAR T-cell therapy for relapsed/refractory multiple myeloma: initial proof of concept results from a phase 1/2 multicenter study (evolve). *Blood* 2018;132:957.
- 122 Wang B-Y, Zhao W-H, Liu J, *et al.* Long-Term follow-up of a phase 1, first-in-human open-label study of LCAR-B38M, a structurally differentiated chimeric antigen receptor T (CAR-T) cell therapy targeting B-cell maturation antigen (BCMA), in patients (PTS) with relapsed/refractory multiple myeloma (RRMM). *Blood* 2019;134:579.
- 123 European Medicines Agency. GrantsJanssenPRIME Designationfor JNJ-68284528(LCAR-B38M), an Investigational BCMA CAR-T Therapy Discovered by Legend Biotech. Johnson & Johnson, 2019.
- 124 Madduri D, Usmani SZ, Jagannath S, *et al.* Results from CARTITUDE-1: a phase 1b/2 study of JNJ-4528, a CAR-T cell therapy directed against B-cell maturation antigen (BCMA), in patients with relapsed and/or refractory multiple myeloma (R/R Mm). *Blood* 2019;134:577.
- 125 Cadiñanos J, Bradley A. Generation of an inducible and optimized piggyBac transposon system. *Nucleic Acids Res* 2007;35:e87.
- 126 Costello CL, Gregory TK, Ali SA, *et al.* Phase 2 study of the response and safety of P-Bcma-101 CAR-T cells in patients with relapsed/refractory (r/r) multiple myeloma (Mm) (prime). *Blood* 2019;134:3184.
- 127 Cowan AJ, Pont M, Sather BD, *et al.* Efficacy and safety of fully human BCMA CAR T cells in combination with a gamma secretase inhibitor to increase BCMA surface expression in patients with relapsed or refractory multiple myeloma. *Blood* 2019;134:204.
- 128 Gogishvili Tet al. SLAMF7-CAR T cells eliminate myeloma and confer selective fratricide of SLAMF7⁺. *Normal lymphocytes* 2017;130:2838–47.
- 129 Smith EL, Harrington K, Staehr M, *et al.* Gprc5D is a target for the immunotherapy of multiple myeloma with rationally designed CAR T cells. *Sci Transl Med* 2019;11:eaau7746.
- 130 Tembhare PR, Yuan CM, Venzon D, *et al.* Flow cytometric differentiation of abnormal and normal plasma cells in the bone marrow in patients with multiple myeloma and its precursor diseases. *Leuk Res* 2014;38:371–6.
- 131 Hajek R, Okubote SA, Svachova H. Myeloma stem cell concepts, heterogeneity and plasticity of multiple myeloma. *Br J Haematol* 2013;163:551–64.
- 132 Garfall AL, Stadtmauer EA, Hwang W-T, *et al.* Anti-Cd19 CAR T cells with high-dose melphalan and autologous stem cell transplantation for refractory multiple myeloma. *JCI Insight* 2019;4. doi:10.1172/jci.insight.127684. [Epub ahead of print: 21 Feb 2019].
- 133 Yan Z, Cao J, Cheng H, *et al.* A combination of humanised anti-CD19 and anti-BCMA CAR T cells in patients with relapsed or refractory multiple myeloma: a single-arm, phase 2 trial. *Lancet Haematol* 2019;6:e521–9.
- 134 Garfall AL, Cohen AD, Lacey SF, *et al.* Combination Anti-Bcma and anti-CD19 CAR T cells as consolidation of response to prior therapy in multiple myeloma. *Blood* 2019;134:1863.

- 135 Garfall AL, Maus MV, Hwang W-T, *et al.* Chimeric antigen receptor T cells against CD19 for multiple myeloma. *N Engl J Med* 2015;373:1040–7.
- 136 Shah N, Alsina M, Siegel DS, *et al.* Initial results from a phase 1 clinical study of bb21217, a next-generation anti BCMA CAR T therapy. *Blood* 2018;132:488
- 137 Green DJ, Pont M, Sather BD, *et al.* Fully human BCMA targeted chimeric antigen receptor T cells administered in a defined composition demonstrate potency at low doses in advanced stage high risk multiple myeloma. *Blood* 2018;132:1011.
- 138 Brudno JN, Maric I, Hartman SD, *et al.* T cells genetically modified to express an Anti-B-Cell maturation antigen chimeric antigen receptor cause remissions of poor-prognosis relapsed multiple myeloma. *JCO* 2018;36:2267–80.
- 139 Shalabi H *et al.* Intensification of Lymphodepletion optimizes CAR Re-Treatment efficacy 2017;130:3889.
- 140 Abramson JSet *al.* High durable Cr rates in relapsed/refractory (R/R) aggressive B-NHL treated with the CD19-Directed CAR T cell product JCAR017 (TRANSCEND NHL 001): defined composition allows for dose-finding and definition of pivotal cohort 2017;130:581.
- 141 Elverum K, Whitman M. Delivering cellular and gene therapies to patients: solutions for realizing the potential of the next generation of medicine. *Gene Ther* 2019. doi:10.1038/s41434-019-0074-7. [Epub ahead of print: 25 Apr 2019].
- 142 Cohen A *et al.* Safety and Efficacy of B-Cell Maturation Antigen (BCMA)-Specific Chimeric Antigen Receptor T Cells (CART-BCMA) with Cyclophosphamide Conditioning for Refractory Multiple Myeloma (MM). *Blood* 2017;130:505.
- 143 U.S.F.a.D. administration. *Kite, Yescarta package insert*, 2017.
- 144 U.S. FDA. *Novartis, Kymriah package insert*, 2017.
- 145 Neelapu SS, Tummala S, Kebriaei P, *et al.* Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol* 2018;15:47–62.
- 146 Santomasso B, Bachier C, Westin J, *et al.* The other side of car T-cell therapy: cytokine release syndrome, neurologic toxicity, and financial burden. *Am Soc Clin Oncol Educ Book* 2019;39:433–44.
- 147 Kothari S, Hillengass J, McCarthy PL, *et al.* Determination of minimal residual disease in multiple myeloma: does it matter? *Curr Hematol Malig Rep* 2019;14:39–46.
- 148 Paiva B, van Dongen JJM, Orfao A. New criteria for response assessment: role of minimal residual disease in multiple myeloma. *Blood* 2015;125:3059–68.
- 149 Alonso R, Cedena MT, Gómez-Grande A, *et al.* Imaging and bone marrow assessments improve minimal residual disease prediction in multiple myeloma. *Am J Hematol* 2019;94:853–61.
- 150 Zamagni E, Cavo M, Fakhri B, *et al.* Bones in multiple myeloma: imaging and therapy. *Am Soc Clin Oncol Educ Book* 2018;38:638–46.
- 151 Munshi NC, Berdeja JG, Lin Y, *et al.* Early MRD negativity to predict deepening myeloma response in relapsed/refractory multiple myeloma (RRMM) patients treated with bb2121 anti-BCMA CAR T cells. *JCO* 2018;36:8024.
- 152 Acharya UH, Dhawale T, Yun S, *et al.* Management of cytokine release syndrome and neurotoxicity in chimeric antigen receptor (CAR) T cell therapy. *Expert Rev Hematol* 2019;12:195–205.
- 153 Baer B, Dudley CV, Simons RM. Management principles associated with cytokine release syndrome. *Semin Oncol Nurs* 2019;35:150931.
- 154 Chou CK, Turtle CJ. Insight into mechanisms associated with cytokine release syndrome and neurotoxicity after CD19 CAR-T cell immunotherapy. *Bone Marrow Transplant* 2019;54:780–4.
- 155 Lee DW, Gardner R, Porter DL, *et al.* Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014;124:188–95.
- 156 Maude SL, Barrett D, Teachey DT, *et al.* Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer J* 2014;20:119–22.
- 157 Shimabukuro-Vornhagen A, Gödel P, Subklewe M, *et al.* Cytokine release syndrome. *J Immunother Cancer* 2018;6:56.
- 158 Lee DW, Santomasso BD, Locke FL, *et al.* ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant* 2019;25:625–38.
- 159 Frey N, Porter D. Cytokine release syndrome with chimeric antigen receptor T cell therapy. *Biol Blood Marrow Transplant* 2019;25:e123–7.
- 160 Kotch C, Barrett D, Teachey DT. Tocilizumab for the treatment of chimeric antigen receptor T cell-induced cytokine release syndrome. *Expert Rev Clin Immunol* 2019;15:813–22.
- 161 Le RQ, Li L, Yuan W, *et al.* Fda approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. *Oncologist* 2018;23:943–7.
- 162 Brentjens RJ, Davila ML, Riviere I, *et al.* CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. *Sci Transl Med* 2013;5:177ra38.
- 163 Grupp SA, Kalos M, Barrett D, *et al.* Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med* 2013;368:1509–18.
- 164 Maude SL, Frey N, Shaw PA, *et al.* Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med* 2014;371:1507–17.
- 165 Teachey DT, Bishop MR, Maloney DG, *et al.* Toxicity management after chimeric antigen receptor T cell therapy: one size does not fit 'ALL'. *Nat Rev Clin Oncol* 2018;15:218.
- 166 Giavridis T, van der Stegen SJC, Eyquem J, *et al.* Car T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. *Nat Med* 2018;24:731–8.
- 167 Bedoya F, Frigault MJ, Maus MV. The Flipside of the power of engineered T cells: observed and potential toxicities of genetically modified T cells as therapy. *Mol Ther* 2017;25:314–20.
- 168 Gust J, Hay KA, Hanafi L-A, *et al.* Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. *Cancer Discov* 2017;7:1404–19.
- 169 Gofshteyn JS, Shaw PA, Teachey DT, *et al.* Neurotoxicity after CTL019 in a pediatric and young adult cohort. *Ann Neurol* 2018;84:537–46.
- 170 Hunter BD, Jacobson CA. Car T-cell associated neurotoxicity: mechanisms, clinicopathologic correlates, and future directions. *J Natl Cancer Inst* 2019. doi:10.1093/jnci/djz017. [Epub ahead of print: 11 Feb 2019].
- 171 Rice J, Nagle S, Randall J, *et al.* Chimeric antigen receptor T cell-related neurotoxicity: mechanisms, clinical presentation, and approach to treatment. *Curr Treat Options Neurol* 2019;21:40.
- 172 Santomasso BD, Park JH, Salloum D, *et al.* Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. *Cancer Discov* 2018;8:958–71.
- 173 Maude SL, Laetsch TW, Buechner J, *et al.* Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med* 2018;378:439–48.
- 174 Fried S, Avigdor A, Bielorai B, *et al.* Early and late hematologic toxicity following CD19 CAR-T cells. *Bone Marrow Transplant* 2019;54:1643–50.
- 175 Hill JA, Li D, Hay KA, *et al.* Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. *Blood* 2018;131:121–30.
- 176 Schaefer A, Saygin C, Maakaron J, *et al.* Cytopenias after chimeric antigen receptor T-cells (CAR-T) infusion; patterns and outcomes. *Biology of Blood and Marrow Transplantation* 2019;25:S171.
- 177 Sedykh SE, Prinz VV, Buneva VN, *et al.* Bispecific antibodies: design, therapy, perspectives. *Drug Des Devel Ther* 2018;12:195–208.
- 178 Linke R, Klein A, Seimetz D. Catumaxomab: clinical development and future directions. *MAbs* 2010;2:129–36.
- 179 Przepiorka D, Ko C-W, Deisseroth A, *et al.* Fda approval: Blinatumomab. *Clin Cancer Res* 2015;21:4035–9.
- 180 Pulte ED, Vallejo J, Przepiorka D, *et al.* Fda supplemental approval: Blinatumomab for treatment of relapsed and refractory precursor B-cell acute lymphoblastic leukemia. *Oncologist* 2018;23:1366–71.
- 181 Richter JR, Wermke M, Kauh JS, *et al.* Phase 1, multicenter, open-label study of single-agent bispecific antibody T-cell engager GBR 1342 in relapsed/refractory multiple myeloma. *JCO* 2018;36:TPS81.
- 182 Zuch de Zafra CL, Fajardo F, Zhong W, *et al.* Targeting multiple myeloma with AMG 424, a novel Anti-CD38/CD3 bispecific T-cell-recruiting antibody optimized for cytotoxicity and cytokine release. *Clin Cancer Res* 2019;25:3921–33.
- 183 Kodama T, Kochi Y, Nakai W, *et al.* Anti-GPRC5D/CD3 bispecific T-Cell-Redirecting antibody for the treatment of multiple myeloma. *Mol Cancer Ther* 2019;18:1555–64.
- 184 Amgen. *Amgen Announces first-in-human data evaluating investigational novel BiTE® immunotherapies AMG 420 and AMG 330 at ash 2018*, 2018.
- 185 Cho S-F, Lin L, Xing L, *et al.* Anti-BCMA BiTE® AMG 701 potently induces specific T cell lysis of human multiple myeloma (Mm) cells and immunomodulation in the bone marrow microenvironment. *Blood* 2018;132:592.
- 186 Costa LJ, Wong SW, Bermúdez A, *et al.* First clinical study of the B-cell maturation antigen (BCMA) 2+1 T cell Engager (TCE) CC-

- 93269 in patients (PTS) with relapsed/refractory multiple myeloma (RRMM): interim results of a phase 1 multicenter trial. *Blood* 2019;134:143.
- 187 Nooka AK, Lonial S. New targets and new agents in high-risk multiple myeloma. *Am Soc Clin Oncol Educ Book* 2016;35:e431–41.
- 188 Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working group. *Blood* 2016;127:2955–62.
- 189 Brudno JN, Maric I, Hartman SD, et al. T cells genetically modified to express an Anti-B-Cell maturation antigen chimeric antigen receptor cause remissions of poor-prognosis relapsed multiple myeloma. *J Clin Oncol* 2018;36:2267–80.
- 190 Malek E, de Lima M, Letterio JJ, et al. Myeloid-Derived suppressor cells: the green light for myeloma immune escape. *Blood Rev* 2016;30:341–8.
- 191 Vago L, Perna SK, Zanussi M, et al. Loss of mismatched HLA in leukemia after stem-cell transplantation. *N Engl J Med* 2009;361:478–88.
- 192 Klippel ZK, Chou J, Towler AM, et al. Immune escape from NY-ESO-1-specific T-cell therapy via loss of heterozygosity in the MHC. *Gene Ther* 2014;21:337–42.
- 193 Baeuerle PA, Reinhardt C. Bispecific T-cell engaging antibodies for cancer therapy. *Cancer Res* 2009;69:4941–4.
- 194 Amgen. *Highlights of prescribing information: blincyto® (blinatumomab) for injection for intravenous use*, 2014.
- 195 Stein A, Franklin JL, Chia VM, et al. Benefit-Risk assessment of Blinatumomab in the treatment of relapsed/refractory B-cell precursor acute lymphoblastic leukemia. *Drug Saf* 2019;42:587–601.
- 196 Jain T, Litzow MR. No free rides: management of toxicities of novel immunotherapies in all, including financial. *Blood Adv* 2018;2:3393–403.
- 197 Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol* 2012;30:2183–9.
- 198 Yurkiewicz IR, Muffly L, Liedtke M. Inotuzumab ozogamicin: a CD22 mAb-drug conjugate for adult relapsed or refractory B-cell precursor acute lymphoblastic leukemia. *Drug Des Devel Ther* 2018;12:2293–300.
- 199 Tai Y-T, Mayes PA, Acharya C, et al. Novel anti-B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. *Blood* 2014;123:3128–38.
- 200 Trudel S, Lendvai N, Popat R, et al. Targeting B-cell maturation antigen with GSK2857916 antibody-drug conjugate in relapsed or refractory multiple myeloma (BMA117159): a dose escalation and expansion phase 1 trial. *Lancet Oncol* 2018;19:1641–53.
- 201 Trudel S, Lendvai N, Popat R, et al. Antibody-Drug conjugate, GSK2857916, in relapsed/refractory multiple myeloma: an update on safety and efficacy from dose expansion phase I study. *Blood Cancer J* 2019;9:37.
- 202 Rakesh Popat JBO, Eliason L, Wilson J, et al. *Amanda Bruno patient reported experience from Part 2 of the first time in human study of the BCMA antibody drug conjugate GSK2857916 for advanced relapsed refractory multiple myeloma (DREAMM-1), in 24th Congress of the European hematology association*. Amsterdam: EHA Library, 2019.
- 203 Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *Lancet Oncol* 2020;21:207–21.
- 204 Eaton JS, Miller PE, Mannis MJ, et al. Ocular adverse events associated with antibody-drug conjugates in human clinical trials. *J Ocul Pharmacol Ther* 2015;31:589–604.
- 205 Zhao B, Chen R, O'Connor OA, et al. Brentuximab vedotin, an antibody-drug conjugate, in patients with CD30-positive haematologic malignancies and hepatic or renal impairment. *Br J Clin Pharmacol* 2016;82:696–705.
- 206 Kelly KR, Siegel DS, Chanan-Khan AA, et al. Indatuximab Ravtansine (BT062) in combination with low-dose dexamethasone and lenalidomide or Pomalidomide: clinical activity in patients with relapsed / refractory multiple myeloma. *Blood* 2016;128:4486.
- 207 AG B, Biotest AG. *Immugen has elected not to exercise its late stage co-development option for the US-Market with Biotest's antibody-drug conjugate (BT-062)*. Dissemination of a Corporate News, transmitted by DGAP - a service of EQS Group AG, 2017.
- 208 Socinski MA, Kaye FJ, Spigel DR, et al. Phase 1/2 study of the CD56-Targeting antibody-drug conjugate Lorvotuzumab Mertansine (IMGN901) in combination with Carboplatin/Etoposide in small-cell lung cancer patients with extensive-stage disease. *Clin Lung Cancer* 2017;18:68–76.
- 209 Ailawadhi S, Kelly KR, Vescio RA, et al. A phase I study to assess the safety and pharmacokinetics of single-agent Lorvotuzumab Mertansine (IMGN901) in patients with relapsed and/or refractory CD-56-positive multiple myeloma. *Clin Lymphoma Myeloma Leuk* 2019;19:29–34.
- 210 Kaufman JL, Niesvizky R, Stadtmauer EA, et al. Phase I, multicentre, dose-escalation trial of monotherapy with milatuzumab (humanized anti-CD74 monoclonal antibody) in relapsed or refractory multiple myeloma. *Br J Haematol* 2013;163:478–86.
- 211 Senyak Z, Mesa RA, Kroeger N, et al. Results from the myeloproliferative neoplasm patient care survey: patient care opportunities and challenges. *Blood* 2018;132:4289.
- 212 Nooka AK, Gleason C, Sargeant MO, et al. Managing infusion reactions to new monoclonal antibodies in multiple myeloma: Daratumumab and Elotuzumab. *J Oncol Pract* 2018;14:414–22.
- 213 Smith S, Essell J, Sandy Smith JE. Evolving the delivery of car T-cell therapies to the outpatient setting. *Journal of Clinical Pathways* 2018;4:42–7.
- 214 Chino F, Peppercorn JM, Rushing C, et al. Out-Of-Pocket costs, financial distress, and underinsurance in cancer care. *JAMA Oncol* 2017;3:1582–4.
- 215 Board, P.D.Q.A.T.E. *Financial Toxicity and Cancer Treatment (PDQ(R)): Health Professional Version, in PDQ Cancer Information Summaries*. National Cancer Institute (US: Bethesda (MD), 2002.
- 216 Perrot A, Facon T, Plesner T, et al. Faster and sustained improvement in health-related quality of life (HRQoL) for newly diagnosed multiple myeloma (NDMM) patients ineligible for transplant treated with daratumumab, lenalidomide, and dexamethasone (D-Rd) versus RD alone: Maia. *JCO* 2019;37:8016.
- 217 Weisel K, Paner A, Engelhardt M, et al. Quality-Of-Life outcomes in patients with relapsed/refractory multiple myeloma treated with Elotuzumab plus Pomalidomide and dexamethasone: results from the phase 2 randomized Eloquent-3 study. *Blood* 2018;132:2288.
- 218 Surbhi Sidana AD, Burtis M, Griffin J, et al. *Quality of life in patients undergoing chimeric antigen receptor (car) - t cell therapy vs. autologous and allogeneic stem cell transplant for hematologic malignancies, in 24th EHA Congress*. Amsterdam: EHA Library, 2019.
- 219 Osborne TR, Ramsenthaler C, Schey SA, et al. Improving the assessment of quality of life in the clinical care of myeloma patients: the development and validation of the myeloma patient outcome scale (MyPOS). *BMC Cancer* 2015;15:280.
- 220 Tamara Syrek Jensen JC, Ashby LM, Hakim R, et al. *Decision MEMO for chimeric antigen receptor (CAR) T-cell therapy for cancers CMS*, 2019.
- 221 Chakraborty R, Sidana S, Shah GL, et al. Patient-Reported outcomes with chimeric antigen receptor T cell therapy: challenges and opportunities. *Biol Blood Marrow Transplant* 2019;25:e155–62.
- 222 Parsons JA, Greenspan NR, Baker NA, et al. Treatment preferences of patients with relapsed and refractory multiple myeloma: a qualitative study. *BMC Cancer* 2019;19:264.
- 223 Acaster S, Gaugris S, Velikova G, et al. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. *Support Care Cancer* 2013;21:599–607.