Current Hematologic Malignancy Reports (2019) 14:1–10
https://doi.org/10.1007/s11899-019-0492-z

T-CELL AND OTHER LYMPHOPROLIFERATIVE MALIGNANCIES (J ZAIN, SECTION EDITOR)

Immunotherapeutic Approaches for Multiple Myeloma: Where Are We Now?

Myo Htut[1]

Published online: 21 January 2019

Abstract

Purpose of Review The treatment landscape for multiple myeloma has evolved rapidly with the availability of multiple new drugs; however, although patient survival has improved, the disease remains incurable. Multiple myeloma is characterized by the unregulated growth of malignant plasma cells accompanied by immune dysfunction as well as disrupted immune surveillance mechanisms. Here, we analyze clinical modalities, with a focus on monoclonal antibodies and adoptive cellular therapy that enhance patients' immune systems and overcome these defects.

Recent Findings Early clinical trials with PD-1 inhibitors were promising, but randomized phase III trials with immunomodulatory drugs showed increased toxicities. Monoclonal antibodies targeting surface antigens led to substantial clinical efficiency in relapsed myeloma. Chimeric antigen receptor (CAR) T cell therapy for multiple myeloma represents a significant advance, as exciting and dramatic responses in early clinical trials have been seen.

Summary Immunotherapeutic approaches are promising and can augment or replace the current standard of care, with the potential to offer extended survival for myeloma patients.

Keywords Adoptive cellular therapy · CAR T cells · Checkpoint inhibitors · mAbs · Multiple myeloma · Vaccine

Introduction

Both disrupted immune surveillance and immune escape have been postulated to promote disease progression in multiple myeloma (MM) via several mechanisms. Firstly, immune dysfunction can be associated with an increased chance of infections even in monoclonal gammopathy of undetermined significance (MGUS), the MM precursor stage [1]. Second, dysregulation of the T cell repertoire due to an abnormal CD4/CD8 ratio and a lower number of CD4+ T cells [2], an altered T helper (Th) 1/Th2 ratio in favor of the Th2 immune response [3], and a higher number of regulatory T cells (Tregs) [4] have been reported in MM patients. Thirdly, defective function of antigen presenting dendritic cells [5] has also been reported in MM cases. Forth, immune dysregulation in the permissive bone marrow microenvironment (stroma) allows MM cells to thrive and progress [6]. Furthermore, upregulation of programmed cell death ligand 1 (PD-L1) expression, which activates programmed cell death protein 1 (PD-1) and results in cytotoxic T cell inhibition, is noted in MM [7].

The graft-versus-myeloma effect after allogeneic hematopoietic cell transplantation (allo-HCT) and the effect of donor lymphocyte infusions first provided the supporting evidence of the role of immunotherapy in MM and its potential to provide cure in a select subsets of patients [8–10]. Substantial transplant-related toxicities and disease relapse after transplantation have limited the extensive use of this approach. Immunomodulatory drugs (IMiDs) such as thalidomide, lenalidomide, and pomalidomide have become one of the key backbones of anti-MM therapy [11]. Allo-HCT and IMiDs may broadly fit in the category of immune therapy.

There are several new strategies targeting MM, which will be the focus of this review: monoclonal antibodies directly targeting MM cell antigens, checkpoint inhibitors, and adoptive cellular therapy to overcome immune suppression.

This article is part of the Topical Collection on *T-Cell and Other Lymphoproliferative Malignancies*

✉ Myo Htut
mhtut@coh.org

[1] Department of Hematology/Hematopoietic Cell Transplantation, City of Hope National Medical Center, 1500 E Duarte Rd, Duarte, CA 91010, USA

Monoclonal Antibodies (mAbs) Targeting Surface Tumor Antigens

Some monoclonal antibodies (mAbs) induce cytotoxicity after targeting cancer cells via several mechanisms: antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), and direct effects on target cells via different signaling pathways. The clinical relevance of these mechanisms is uncertain as they are based on in vitro findings [12].

Although mAb therapy (e.g., rituximab) has been a crucial part of the treatment of B cell lymphoproliferative disorders, a similar approach was not available to MM patients until recently. The choice of specific antigens including B cell maturation factor (BCMA) on malignant plasma cells (PC), as well as off-target effects, will influence efficacy as well as the toxicity/safety profile of these mAbs. The ideal target antigen should be highly expressed on cancer cells without any expression on normal cells in order to prevent off-target side effects.

CD38-Targeting mAbs

CD38 is a potential target for MM treatment, as it is highly expressed in malignant PCs in the majority of MM patients [13], with relatively low level expression in normal myeloid and lymphoid cells and in some tissues of nonhematopoietic origin [14].

There are three different compounds in this class, daratumumab, isatuximab, and MOR22, that are clinically developed.

Daratumumab

Daratumumab is a human IgGκ monoclonal antibody. Single agent daratumumab was first tested in a phase I/II trial for relapsed/refractory MM (RRMM) patients who progressed after ≥ 2 lines of prior therapy. Thirty-two patients were enrolled in a dose escalation cohort (part 1), in which the maximum tolerated dose (MTD) was not identified. In part 2, enrolling a dose expansion cohort ($n = 72$), the overall response rate (ORR, ≥ partial response [PR] or better) was 36% in patients who received the highest dose level (16 mg/kg). Infusion-related reactions (IRRs) were common (71%, all grades), but severe reactions were rare (1% ≥ grade 3). The median progression-free survival (PFS) in the 16-mg/kg dose level cohort was 5.6 months. The most common toxicities of grade 3 or 4 were thrombocytopenia and pneumonia [15••].

In another phase II trial, single agent daratumumab (given at 16 mg/kg, $n = 106$) yielded an ORR rate of 29.2%. The median PFS for this group was shorter than in the previous study, at 3.7 months. The IRR rate was 42.5%, mostly representing grade 1/2 reactions during the first infusion [16]. The efficacy of daratumumab improved significantly after it was combined with lenalidomide and dexamethasone, leading to an ORR of 81% in patients with relatively less heavily treated MM [17].

These positive results lead to the POLLUX trial, a large phase III randomized trial evaluating the triple combination of daratumumab, lenalidomide and dexamethasone (DRd) versus standard lenalidomide and dexamethasone (Rd) in 569 patients with RRMM who were not refractory to lenalidomide. The ORR in the DRd group was 92.9% vs 76.4% in the Rd group. After a median follow-up of 13.5 months, 18.5% of patients in the DRd group developed disease progression or death, versus 41.0% in the control group (hazard ratio, 0.37; [$P < 0.001$]). The 12-month PFS was 83.2% in the DRd group vs 60.1% in the Rd group. Daratumumab-related IRRs occurred in 47.7% of the patients and were mostly of grade 1 or 2. A higher incidence of grade 3 or 4 neutropenia was noted in the DRd cohort (51.9%), compared to 37.0% in the Rd group [18••].

The phase III, randomized CASTOR trial ($n = 498$) also showed similar impressive results. Daratumumab, bortezomib, and dexamethasone (DVd) were compared with bortezomib plus dexamethasone (Vd) in relapsed MM patients not refractory to bortezomib. Again, the daratumumab-containing arm (DVd) had superior ORR (82.9%) over the control group (63.2%). Twelve-month PFS was 60.7% in the DVd group versus 26.9% in the Vd group. The hazard ratio for progression or death with DVd versus Vd was 0.39 ($P < 0.001$) after a median follow-up of 7.4 months. The DVd cohort had higher rates of grade 3 or 4 thrombocytopenia and neutropenia. Daratumumab-related IRRs occurred in 45.3% of the patients; they occurred during the first infusion in 98.2% of patients [19••].

These positive results led FDA to approve daratumumab as a single agent for patients treated with ≥ 3 prior lines of therapy (including an IMiD and a proteasome inhibitor), and in combination with lenalidomide plus dexamethasone or bortezomib-dexamethasone in patients who have been treated with at least one prior line of therapy.

Daratumumab was also combined with other established backbone therapies for MM. Daratumumab was combined with pomalidomide and dexamethasone in a phase Ib study in RRMM patients with ≥ 2 prior lines of therapy ($N = 103$). The ORR was 60%, and after a median follow-up of 13.1 months, the median PFS was 8.8 months and the median overall survival was 17.5 months. The toxicity profile of this combination therapy is similar to that of pomalidomide-dexamethasone alone, except for daratumumab-related IRRs (50%) and a higher incidence of neutropenia without an increased chance of infections [20]. Another trial combined

daratumumab with carfilzomib and dexamethasone in 85 RRMM patients who were treated with 1–3 prior lines of therapy. Only carfilzomib naïve patients were enrolled. The ORR was 84%, with a 12-month PFS of 74% after a median follow-up of 4.5 months. Toxicities were consistent with that of the individual therapies [21]. A phase III study comparing daratumumab, carfilzomib, and dexamethasone versus carfilzomib-dexamethasone in RRMM (CANDOR; NCT03158688) is ongoing.

The combination of daratumumab with carfilzomib-lenalidomide-dexamethasone for newly diagnosed MM showed no additional toxicities and resulted in an ORR of 100% [22].

Subcutaneous injection of daratumumab has also been studied to reduce the infusion time. A phase Ib trial showed that it was well tolerated and caused lower than expected rates of IRRs. Once available, it may dramatically reduce infusion times (saving costs) and IRRs [23].

Isatuximab

In a single agent phase I trial, isatuximab was given at doses ranging from 0.3 to 20 mg/kg and the ORR was 24%. IRRs occurred mainly during the first infusion and were mostly grade 1/2 [24•].

Isatuximab was combined with pomalidomide and dexamethasone in a dose escalation phase Ib trial [25]. The study enrolled RRMM patients who received ≥ 2 prior lines of therapy. The ORR was 62% in 26 evaluable patients. IRRs developed in 42% of patients. Fatigue, upper respiratory tract infection, and dyspnea were the most common adverse events (AEs). Grade ≥ 3 neutropenia occurred in 83% of patients, with 56% having grade 4 neutropenia.

In a separate phase Ib dose-escalation trial ($n = 57$) of isatuximab, lenalidomide, and dexamethasone, the MTD was not reached, and the ORR was 56%. In lenalidomide-refractory patients, the ORR was 52%. IRRs (mostly grade 1/2) were noted in 56% of patients and predominantly occurred during the first infusion. The median PFS was 8.5 months. The most frequent grade 3/4 AEs were neutropenia (60%), leukopenia (53%), thrombocytopenia (38%), pneumonia (9%), and fatigue (7%) [26].

MOR202

MOR 202 does not stimulate the CDC pathway, which is thought to be responsible for the immune effect causing IRRs [27]. In a phase I/II trial, the ORR was 31% in a single agent MOR202 group ($n = 16$), 71% in an MOR202 + lenalidomide cohort ($n = 7$) and 60% in an MOR202 + pomalidomide group ($n = 5$). IRRs were noted in only 10% of patients, which is lower than that of daratumumab.

There are two unique problems with anti-CD38 mAbs. They can bind to CD38 on red blood cells, which also have CD38 expression, and interfere with blood compatibility testing. Blood banks should be notified of patient therapy such as daratumumab. Methods to neutralize this interference are available (e.g., dithiothreitol incubation of patients' red blood cells [28]. The second problem applies to all mAbs as they are all immunoglobulins (e.g., IgGκ) which can provide positive results for serum protein electrophoresis (SPEP) and immunofixation, confounding interpretation of disease assessment of MM.

SLAMF7 Antibodies

Signaling lymphocytic activation molecule family member 7 (SLAMF7), also known as CS1, is almost universally expressed in plasma cells and MM cells, with limited expression in NK and T cells [29]. It is a unique target for anti-MM therapy, as it plays a role in MM cell survival and growth and immune cell function regulation.

Elotuzumab is a humanized monoclonal IgG1 antibody directed against human SLAMF7. The first phase I single agent clinical trial showed no objective responses. Disappointingly, only 26.5% of patients achieved stable disease. No MTD was reached up to the maximum planned dose of 20 mg/kg every 15 days. Given the strong preclinical data, combinatorial therapy was planned [30].

In a phase II trial, RRMM patients ($n = 152$) who received 1–3 prior lines of therapy were randomized to receive elotuzumab with bortezomib and dexamethasone (EBd) or bortezomib and dexamethasone (Bd). The median PFS was longer with EBd patients (9.7 months) versus Bd patients (6.9 months), without additional significant adverse events. ORRs were similar at 66% in EBd and 63% in Bd. IRRs due to elotuzumab were low (only 5% of EBd patients) [31].

When elotuzumab was combined with lenalidomide and dexamethasone in a phase Ib/II trial, the ORR was higher, at 92% [32]. Of note, phase II patients were lenalidomide-naïve.

These findings led to the randomized phase III Eloquent-2 trial [33••] comparing elotuzumab and lenalidomide-dexamethasone (ERd) versus lenalidomide-dexamethasone (Rd). A total of 646 RRMM patients who had received one to three previous therapies were enrolled. Adding elotuzumab produced a better ORR (79 versus 66%) and a longer PFS (median 19.4 months versus 14.9 months, hazard ratio for progression or death in the elotuzumab group, 0.70; $P < 0.001$) after a median follow-up of 24.5 months. IRRs developed in 10% of patients with elotuzumab. The ERd cohort had higher incidence of zoster reactivation and lymphocytopenia, which may reflect changes in lymphocyte/natural killer cell trafficking. This study led to FDA approval

of ERd for RRMM patients who have received 1–3 prior lines of therapy.

Another randomized, open labeled phase II trial [34••] comparing elotuzumab and pomalidomide-dexamethasone versus pomalidomide-dexamethasone showed better PFS in elotuzumab cohort (10.3 months) compared to 4.7 months in the control group that led to FDA approval in RRMM patients who have received at least two prior therapies. The ORR was 53% in the elotuzumab group as compared with 26% in the control group.

Other mAbs

There are multiple mAbs currently under investigation. An anti-CD138 mAb shows clinical activity [35] as a single agent. It was combined with IMiDs (lenalidomide or pomalidomide) in RRMM patients; the ORR was 77% in patients who received at least two treatment cycles and were evaluable for response [36].

Targeting the bone marrow microenvironment (stroma) and inflammatory cytokines did not produce meaningful clinical benefit, even though they appear to play crucial role in MM disease progression. Antibodies targeting CD56, 40, and 74 are also in different stages of clinical development [37].

Bispecific T Cell Engagers (BiTEs)

Bispecific T cell engagers (BiTEs) are a form of bispecific antibodies (targeting two different antigens). BiTEs have two essential components; one involves engagement and activation of T cells via CD3, and the other recognizes tumor antigens such as BCMA, leading to T cell-mediated lysis of target tumor cells.

The first-in-human phase I dose escalation study in RRMM showed promising results with no significant toxicities in doses up to 400 μg/day, which is the recommended dose for further investigation. At this dose, an objective response is seen in 5/6 patients (83%). A higher dose level, 800 μg/day, was found to be unacceptably toxic. Treatment-related serious AEs were cytokine release syndrome (CRS), peripheral polyneuropathy, edema, and fever [38].

Checkpoint Inhibition to Overcome Immunosuppression

The human immune system has breaks (checkpoints) which control the intensity as well as the duration of immune responses [39]. These checkpoints function to prevent auto-immunity, but this regulatory mechanism is exploited by cancer cells including MM to escape immune surveillance [40]. There are two different types of checkpoint receptors: inhibitory receptors like CTLA-4 and PD-1, and stimulatory such as OX40 and CD 28 [41]. T cell function can be amplified by antibodies that block inhibitory receptors or by agonist antibodies activating stimulatory receptors.

PD-1 Pathway Inhibitors

Overexpression of PD-L1, reported in MM patients [7], activates PD-1 receptors on T cells as well as NK cells, rendering these immune cells functionally exhausted and leading to a reduction in proliferation, cytotoxicity, and cytokine production [42]. The clinical efficacy of PD-1 inhibitors for both solid tumors [43] and hematologic malignancies [44] together with preclinical evidence of anti-myeloma activities [45, 46], led to clinical trials for RRMM.

A single agent PD-1 receptor inhibitor, nivolumab (human, IgG K), provided stable disease in 67% of patients, without any objective responses in 27 relapsed MM patients [44].

The phase I KEYNOTE-023 trial evaluated pembrolizumab, a PD-1-antibody, with lenalidomide and dexamethasone in RRMM. The OOR was 50% in 40 response-evaluable patients. Immune-related AEs occurred in 10% of subjects [47].

This study was followed by a single center phase II trial ($n = 48$) of pembrolizumab combined with pomalidomide and dexamethasone, which showed an ORR of 60% in RRMM patients. Forty percent of patients developed grade 3 or 4 AEs. Autoimmune events were mostly ≥ grade 2, including pneumonitis (13%) and hypothyroidism (10%). Other significant toxicities (grade 3/4) were anemia, neutropenias, thrombocytopenias, lymphopenias, hyperglycemia, and pneumonia. The PFS was 17.4 months after a median follow-up of 15.6 months [48]. These findings led to several phase III trials but FDA halted two clinical trials in September 2017, due to safety concerns [49].

KEYNOTE-183

KEYNOTE-183 is a phase III, randomized controlled trial of pomalidomide and dexamethasone with and without pembrolizumab for patients with RRMM who had received at least two prior lines of therapy. Some of the causes of death (without MM progression) reported in the pembrolizumab arm were Stevens-Johnson syndrome, myocarditis, myocardial infarction, pericardial hemorrhage, cardiac failure, respiratory tract infection, respiratory failure, and sepsis. The summary of safety and efficacy analyses can be found in Table 1.

KEYNOTE-185

KEYNOTE-185 is a phase III, randomized controlled trial of lenalidomide and dexamethasone with and without

Table 1 Results of pembrolizumab + IMiDs trials (KEYNOTE 183 and 185)

Trial ID	Groups	Number of patients	Number of deaths	Hazard ratio of death	ORR (%)	Grade 3–5 toxicity (%)	Serious adverse effects (%)
183	Pem Pd	125	29	1.61 (95% CI 0.91, 2.85)	34	83	63
	Pd	124	21		40	65	46
185	Pem Rd	151	19	2.06 (95% CI 0.93, 4.55)	64	72	54
	Rd	150	9		62	50	39

Pem pembrolizumab, *P* pomalidomide, *d* dexamethasone, *R* revlimid, *ORR* overall response (≥ partial response)

pembrolizumab in patients with newly diagnosed MM who are not eligible for autologous stem cell transplantation. The following causes of death (excluding MM progression) were reported in the pembrolizumab arm: intestinal ischemia, large intestine perforation, cardio-respiratory arrest, pneumonia, pulmonary embolism, cardiac arrest, sudden death, myocarditis, suicide, and cardiac failure.

Although, at this time, correlative study data and detailed clinical data are not available, it is possible that the increased mortality may be related to autoimmune toxicities.

Nivolumab

The Checkmate 602 study (combining nivolumab, elotuzumab, pomalidomide, and dexamethasone in RRMM) was also permanently discontinued due to insufficient evidence of clinical benefit based on a futility analysis of interim PFS.

Improving Immunity Using Vaccines

Vaccines targeting specific antigens that are highly and selectively expressed (thus preventing off-target effects) in a given cancer type are the key factors in the development of vaccine therapy. The target antigen should also be critical for cancer cell survival as well as highly immunogenic to produce effective vaccines. Several such antigens for MM have been identified, such as cancer testis antigens NY-ESO, WT1, MAGE, and XBP-1, for which peptide-based vaccination trials are ongoing, targeting different antigens alone or in combination [50–54].

The second approach uses the ability of dendritic cells (DC) to present several cancer antigens to host immune cells. In the first phase I dose escalation trial, active MM patients ($n = 16$) were treated with a DC/MM fusion vaccine given serially three times every 3 weeks [55]. The majority of patients achieved stable disease, and the vaccine was able to induce cellular and humoral immune responses to MM.

This study was followed by a phase II [56] trial using the same DC/MM fusion vaccine in the context of autologous stem cell transplantation ($n = 36$). It was found that 78% of patients achieved very good partial response (VGPR) or better. Also, 17% of patients upgraded their response only until after day 100 post-transplantation, suggesting a vaccine-mediated effect on residual disease. CTN 1401 (NCT02728102) is an ongoing phase III trial to confirm these results in the post-autologous transplant setting.

Adoptive Cellular Therapy

Another strategy to improve immunity against cancer is to use adoptive cellular therapy with chimeric antigen receptor (CAR) T cells, marrow infiltrating lymphocytes (MILs), and T cell receptor (TCR)-engineered T cells. The recent development of CAR T cells has been a remarkable success, with recent FDA approval of two CAR T cell therapies: axicabtagene ciloleucel for relapsed DLBCL and tisagenlecleucel for B-ALL and some forms of NHL.

CAR T Cell Therapy

CAR T therapy includes several steps: First, a patient's own lymphocytes are collected via an apheresis process. Then, T lymphocytes are genetically modified using a virus (usually a retrovirus/lentivirus), after which lymphocytes express CARs on their cell membrane. These modified cells are expanded and transfused back into the same patient, usually after a short course of lymphodepletion chemotherapy (mostly fludarabine and cyclophosphamide). The CAR itself contains a single chain variable fragment (scFv), which can be manufactured to target specific cell surface antigens such as BCMA. The CAR also has a transmembrane domain and an intracellular domain to produce downstream activation with a costimulatory signal once a target antigen binds the scFv. CAR T cells must expand in vivo and persist to control targeted cancer. Loss of persistence may cause relapse of the disease. Another mechanism for relapse after successful CAR T response is growth of malignant clones devoid of the antigen targeted by CAR T cells (antigen escape).

Activated CAR T cells may produce unique complications such as CRS and neurotoxicities. CRS may present with fever,

chills, and in severe cases, hypotension and hypoxia. Neurotoxicity can range from headache, confusion, aphasia, and seizures.

CD19

MM cells do not express CD19, but it was thought that MM stem cells may express CD19, and it is possible that they may express CD19 at levels not detectable by traditional methods. CD19-targeting CAR T cells were given after salvage high dose melphalan and ASCT [57•] in RRMM patients who progressed within 12 months of prior ASCT. Two of ten patients achieved a longer PFS after salvage ASCT + CD19 CAR T cells compared to that after the prior ASCT. This study is being succeeded by another trial (NCT02794246), in which CD19 CAR T cells will be infused as a consolidation therapy, 2 months after an upfront ASCT, with the goal of altering the natural history of MM.

CAR T cells targeting CD138 [58] as well as Kappa light chain [59] were well tolerated, but the majority of best responses have been stable disease. SLAMF7 (CS1) will be targeted in another phase I trial (NCT03710421).

BCMA

BCMA is highly expressed in MM and has limited expression on normal tissue, making it an attractive target [60]. Different CAR T trials targeting BCMA are summarized in Table 2.

These trials use different sources of scFv, either from a murine hybridoma or human library screening, the latter of which having the advantage of developing fewer anti-CAR host immune responses. Human library screening also allows investigators to select the most efficacious candidate among multiple scFvs.

National Cancer Institute (NCI)

NCI investigators reported 16 RRMM patients who received 9×10^6 CAR T cells/kg (highest dose level for the trial); 63% of patients achieved ≥ VGPR [61•]. Earlier-enrolled patients on the same trial who received lower doses of CAR T cells did not have a similar response (ORR 20%). High peak blood CAR T cell levels were correlated with anti-MM activities. The incidence of CRS was high, and the latter 14 patients were required to have BM plasmacytosis of < 30% before CAR T therapy. This CAR construct was licensed by Bluebird Bio for an ongoing multi-center trial.

Bluebird Bio

A phase I multi-center dose escalation trial of bb2121 showed an ORR of 100% in patients treated with doses of 150×10^6 CAR+ T cells or higher. CRS, primarily grade 1 or 2, was reported in 71% of patients [62].

Nanjing Legend (LCAR-B38M)

A total of 57 patients have been treated at the time of reporting; these patients are less heavily pretreated than those in other anti BCMA CAR T trials. Grade ≥ 3 AEs were observed in 65% of patients. Forty-two patients achieved a complete response (CR), and 39 of these patients were minimal residual disease (MRD) negative by eight-color flow cytometry. The median duration of response was 16 months [63]. Janssen has obtained a license from Nanjing Legend, and a multi-center clinical trial is ongoing (NCT03548207).

Table 2 BCMA targeted CAR T cell clinical trials for MM

Institution/company	NCI	Bluebird multicenter	Nanjing legend	UPenn	MSK	Juno therapeutics	Poseida therapeutics
scFv source	Murine hybridoma	Murine hybridoma	Murine hybridoma	Human library	Human library	Human library	Human library
Costimulatory molecule	CD28	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB
Gene transfer	Retrovirus	Lentivirus	Lentivirus	Lentivirus	Retrovirus	Lentivirus	PiggyBac DNA modification
BCMA expression required	> 50%	> 50%	"Clear expression"	No	> 1%	No	No
Median prior lines	9.5	7	3	7	6	7	3–9 prior lines
ORR (≥ PR)	81%	89%	88%	45%	64%	82%	83% (excluding 1st cohort)
Number of patients	16	18	57	21 (20 Evaluable)	11	44	12

NCI National Cancer Institute, *UPenn* University of Pennsylvania, *MSK* Memorial Sloan Kettering, *ORR* overall response (≥ partial response)

University of Pennsylvania (UPenn)

In this phase I trial, unlike other trials discussed, the first cohort treated did not receive any lymphodepletion chemotherapy. Three cohorts are being enrolled at the time of reporting [64]:

A). $1–5 \times 10^8$ CAR T cells alone. Six of nine patients responded (one stringent CR [sCR], two VGPR, one PR, two minimal responses [MR]). One patient has an ongoing sCR at 21 months, and other responses lasted 1.5 to 5 months.

B). Cyclophosphamide 1.5 g/m^2 + $1–5 \times 10^7$ CAR T cells. Two of five patients responded (one PR, one MR) but progressed at 4 and 2 months, respectively. Of note, cell dose in this cohort is tenfold lower.

C). Cyclophosphamide 1.5 g/m^2 + $1–5 \times 10^8$ CAR T cells. At a median follow-up of 1 month at the time of reporting, five of six patients responded (one CR, three PR, one MR) and one was not yet evaluable.

Memorial Sloan Kettering (MSK)

MSK is conducting a phase I, first-in-human, dose escalation trial of MCARH171. Anti BCMA CAR T cells were given in one–two divided doses [65].

Juno Therapeutics

In a phase 1 dose escalation trial, clinical responses were noted even at the lowest dose level of 50×10^6 CAR T cells. At the time of reporting, 13 patients have been enrolled and 8 patients were evaluable for response assessment [66].

Poseida Therapeutics

In a dose escalating phase I trial [67], 12 patients have received CAR T cells and 9 patients were evaluable. Poseida anti-BCMA CAR T cells utilize an anti-BCMA Centyrin™ fused to a CD3ζ/4-1BB signaling domain. Centyrins are fully human, and they are less immunogenic and exhibit relatively high binding affinities. This method uses a piggyBac™ (PB) DNA modification system instead of a traditional viral method to transfer genetic materials. It is less costly and produces a more purified CAR T cell population, with the expectation of a greater therapeutic index than in other trials. Their CAR T product also has a safety switch, which can be activated to eradicate CAR T cells in cases of severe toxicity. The CRS incidence was low, as 8% (only 1 patient) developed limited grade 2 CRS without any neurotoxicities.

Marrow Infiltrating Lymphocytes (MILs)

Similar to tumor infiltrating lymphocytes (TILs), marrow infiltrating lymphocytes (MILs) are thought to be in an exhausted state in the immune suppressive bone marrow microenvironment in patients with hematological malignancies, including MM. Harvesting of these MILs and their ex vivo stimulation, expansion and reinfusion are postulated to generate anti-cancer immunity. In a phase I trial, these harvested MILs were activated with CD3/CD8 beads and IL2 in culture medium to reverse the exhausted phenotype. They were expanded (average fold expansion was 48.5), and activated MILs were reinfused 2 days after high-dose melphalan/ASCT, with evidence of anti-myeloma immunity, homing of MILs to bone marrow and correlation between disease response and myeloma-specific immunity, indicating the promise and feasibility of such therapy [68••].

TCR Engineered T Cell Therapy

This approach includes ex vivo manipulation of autologous T cells, resulting in genetically modified T cells with synthetic TCRs. Similar to CAR T cells, these modified T cells (obtained by an apheresis procedure) requires expansion and reinfusion. Synthetic TCRs can be affinity-enhanced in the laboratory to improve TCR interaction with target antigen, resulting in increased efficacy. These synthetic TCRs are HLA-restricted (unlike CAR T cells), and a patient needs to have a certain HLA type (e.g., HLA-A *02) to receive treatment with a particular synthetic TCR. These TCR engineered T cells can recognize intracellular antigens presented in HLA, unlike CAR T cells.

A clinical trial targeting NY-ESO/LAGE-1 antigen included infusion of modified TCR engineered T cells on day + 2 of ASCT after high dose melphalan. The patients were required to have HLA-A *02, and their MM cells must have expressed NY-ESO or LAGE-1 antigens. It was difficult to interpret the clinical benefit, as ASCT was a confounding factor. Seventy-five percent of patients were undergoing their first transplant [69••].

A similar trial targeting NY-ESO/LAGE-1 antigen (fludarabine-cyclophosphamide as lymphodepletion chemotherapy) in combination with a PD-1 inhibitor (pembrolizumab) is ongoing (NCT 03168438). Pembrolizumab is expected to potentiate activities of modified T cells.

Conclusion and Future Directions

Tumor antigen-targeting mAbs (e.g., daratumumab, elotuzumab) showed clear efficacy in relapsed MM. Multiple trials are ongoing to incorporate these drugs at a disease stage before development of a chemo-resistant state (earlier in the disease course). If these trials show clinical

benefits, we may be able to use them as first-line therapy (as part of induction chemotherapy), similarly to rituximab, which has been combined with chemotherapy as a first-line therapy for treating lymphomas.

The disappointing increased toxicities without significant benefits in phase III randomized trials of PD1 inhibitors (pembrolizumab) plus IMiDs are cause to explore the underlying biological mechanisms and to undertake combining PD-1 inhibitors with non-immunomodulatory agents such as bortezomib or anti-CD38 antibodies. We are still in the beginning stages of characterizing immune checkpoint inhibitors. There are many other antibodies, both inhibitory as well as stimulatory, as well as bispecific antibodies that await exploration. BiTEs are also at a very early phase of development, and it will be interesting to learn how these new classes of drug can be combined with other new drugs or established standard-of-care regimens.

CAR T cell therapy appears to be a particularly exciting development in MM, as rapid responses in RRMM patients with very heavy disease burden are observed. The persistence of CAR T cells has been a challenge, and further improvement in CAR T cell production is needed, including using fully human CARs. Other aspects to consider are optimizing the CD4/CD8 ratio [70] or selecting a particular phenotype such as the central memory phenotype [71•]. To prevent antigen escape, we could also generate CAR T cells targeting more than one antigen (e.g., targeting both BCMA and SLAMF7). We should also look into improving the efficiency of CAR T cells in vivo through combination with IMiDs [72] or PD-1 inhibitors.

Although there are numerous unanswered questions to address and define immunotherapy approaches for MM, new developments indicate that immunotherapy will evolve into a backbone of MM therapy.

Compliance with Ethical Standards

Conflict of Interest The author declares that there is no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Kristinsson SY, Tang M, Pfeiffer RM, Björkholm M, Goldin LR, Blimark C, et al. Monoclonal gammopathy of undetermined significance and risk of infections: a population-based study. Haematologica. Ferrata Storti Foundation. 2012;97(6):854–8.
2. Koike M, Sekigawa I, Okada M, Matsumoto M, Iida N, Hashimoto H, et al. Relationship between CD4(+)/CD8(+) T cell ratio and T cell activation in multiple myeloma: reference to IL-16. Leuk Res. 2002;26(8):705–11.
3. Ogawara H, Handa H, Yamazaki T, Toda T, Yoshida K, Nishimoto N, et al. High Th1/Th2 ratio in patients with multiple myeloma. Leuk Res. 2005;29(2):135–40.
4. Dosani T, Carlsten M, Maric I, Landgren O. The cellular immune system in myelomagenesis: NK cells and T cells in the development of myeloma [corrected] and their uses in immunotherapies. Blood Cancer J. 2015;5:e306.
5. Brown RD, Pope B, Yuen E, Gibson J, Joshua DE. The expression of T cell related costimulatory molecules in multiple myeloma. Leuk Lymphoma. 1998;31(3–4):379–84.
6. Romano A, Conticello C, Cavalli M, Vetro C, La Fauci A, Parrinello NL, et al. Immunological dysregulation in multiple myeloma microenvironment. Biomed Res Int. 2014;2014:198539.
7. Yousef S, Marvin J, Steinbach M, Langemo A, Kovacsovics T, Binder M, et al. Immunomodulatory molecule PD-L1 is expressed on malignant plasma cells and myeloma-propagating pre-plasma cells in the bone marrow of multiple myeloma patients. Blood Cancer J. 2015;5(3):e285.
8. Gahrton G, Iacobelli S, Bjorkstrand B, Hegenbart U, Gruber A, Greinix H, et al. Autologous/reduced-intensity allogeneic stem cell transplantation vs autologous transplantation in multiple myeloma: longterm results of the EBMT-NMAM2000 study. Blood. 2013;121(25):5055–63.
9. Sahebi F, Iacobelli S, Biezen AV, et al. Comparison of upfront tandem autologous-allogeneic transplantation versus reduced intensity allogeneic transplantation for multiple myeloma. Bone Marrow Transplant. 2015;50(6):802–7.
10. Auner HW, Szydlo R, van Biezen A, et al. Reduced intensity-conditioned allogeneic stem cell transplantation for multiple myeloma relapsing or progressing after autologous transplantation: a study by the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. 2013;48(11):1395–400.
11. Zhu YX, Kortuem KM, Stewart AK. Molecular mechanism of action of immune-modulatory drugs thalidomide, lenalidomide and pomalidomide in multiple myeloma. Leuk Lymphoma. 2013;54(4):683–7.
12. Shuptrine CW, Surana R, Weiner LM. Monoclonal antibodies for the treatment of cancer. Semin Cancer Biol. 2012;22(1):3–13.
13. Lin P, Owens R, Tricot G, Wilson CS. Flow cytometric Immunophenotypic analysis of 306 cases of multiple myeloma. Am J Clin Pathol. 2004;121(4):482–8.
14. Deaglio S, Vaisitti T, Billington R, Bergui L, Omede' P, Genazzani AA, et al. CD38/CD19: a lipid raft-dependent signaling complex in human B cells. Blood. 2007;109:5390–8.
15.•• Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, et al. Targeting CD38 with Daratumumab monotherapy in multiple myeloma. N Engl J Med. 2015;373(13):1207–19 **This study was one of the first to study daratumumab as single agent therapy and provided justification for the development of combinatorial therapies containing daratumumab.**
16. Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ, et al. Phase II study of daratumumab (DARA) monotherapy in patients with >= 3 lines of prior therapy or double refractory multiple myeloma (MM): 54767414MMY2002 (Sirius). ASCO Meet Abstr. 2015;33(18_suppl):LBA 8512.
17. Plesner T, Arkenau H-T, Lokhorst HM, Gimsing P, Krejcik J, Lemech C, et al. Safety and efficacy of Daratumumab with Lenalidomide and dexamethasone in relapsed or relapsed, refractory multiple myeloma. Blood. 2014;124(21):84.

18.•• Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, for the POLLUX Investigators, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016;375:1319–31. https://doi.org/10.1056/NEJMoa1607751 **Potentially practice-changing data in RRMM patients treated with daratumumab/lenalidomide-based backbone treatment.**

19.•• Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. Daratumumab, Bortezomib, and dexamethasone for multiple myeloma. N Engl J Med. 2016;375(8):754–66 **Potentially practice-changing data in RRMM patients treated with daratumumab/bortezomib-based backbone treatment.**

20. Chari A, Suvannasankha A, Fay JW, Arnulf B, Kaufman JL, Ifthikharuddin JJ, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood. 2017;130(8):974–81. https://doi.org/10.1182/blood-2017-05-785246.

21. Lonial S, San-Miguel JF, Martínez-Lopez J, Mateos M-V, Blade J, Benboubker L, et al. Daratumumab in combination with carfilzomib and dexamethasone in patients (pts) with relapsed multiple myeloma (MMY1001): an open-label, phase 1b study. Blood. 2017;130:1869.

22. Jakubowiak AJ, Chari A, Lonial S, Weiss BM, Comenzo RL, Wu K, et al. Daratumumab (DARA) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd) in patients (pts) with newly diagnosed multiple myeloma (MMY1001): An open-label, phase 1b study. J Clin Oncol. 2017;35(15_suppl):8000. https://doi.org/10.1200/JCO.2017.35.15_suppl.8000.

23. Chari A, Nahi H, Mateos M-V, Lokhorst HM, Kaufman JL, Moreau P, et al. Subcutaneous delivery of daratumumab in patients (pts) with relapsed or refractory multiple myeloma (RRMM): PAVO, an open-label, multicenter, dose escalation phase 1b study. Blood. 2017;130:838.

24.• Martin TG, Hsu K, Strickland SA, Glenn MJ, Mikhael J, Charpentier E. A phase I trial of SAR650984, a CD38 monoclonal antibody, in relapsed or refractory multiple myeloma. J Clin Oncol. 2014;32(15_suppl):8532. https://doi.org/10.1200/jco.2014.32.15_suppl.8532 **This study highlighted that other CD38-targeting agents aside from daratumumab hold clinical potential.**

25. Mikhael J, Richardson PG, Usmani Z, Raje N, Bensinger W, Kanagavel D, et al. A phase Ib study of isatuximab in combination with pomalidomide (Pom) and dexamethasone (Dex) in relapsed/refractory multiple myeloma (RRMM). 2017 ASCO Annual Meeting Abstracts. JCO. 2017;(35 suppl):abstr 8007.

26. Martin T, Baz R, Benson DM, Lendvai N, Wolf J, Munster P, et al. A phase 1b study of isatuximab plus lenalidomide and dexamethasone for relapsed/refractory multiple myeloma. Blood. 2017;129(25):3294–303. https://doi.org/10.1182/blood-2016-09-740787.

27. Raab MS, Chatterjee M, Goldschmidt H, Agis H, Blau I, Einsele H, et al. A phase I/IIa study of the CD38 antibody MOR202 alone and in combination with pomalidomide or lenalidomide in patients with relapsed or refractory multiple myeloma. Blood. 2016;128:1152.

28. Chapuy CI, Nicholson RT, Aguad MD, Chapuy B, Laubach JP, Richardson PG, et al. Resolving the daratumumab interference with blood compatibility testing. Transfusion. 2015;55(6 Pt 2):1545–54. https://doi.org/10.1111/trf.13069.

29. Veillette A, Guo H. CS1, a SLAM family receptor involved in immune regulation, is a therapeutic target in multiple myeloma. Crit Rev Oncol/Hematol. 2013;88:168–77.

30. Zonder JA, Mohrbacher AF, Singhal S, Van Rhee F, Bensinger WI, Ding H, et al. A phase 1, multicenter, open-label, dose escalation study of elotuzumab in patients with advanced multiple myeloma. Blood. 2012;120(3):552–9.

31. Jakubowiak A, Offidani M, Brigitte P, La Rubia JD, Garderet L, Laribi K, et al. Randomized phase 2 study: elotuzumab plus bortezomib/dexamethasone vs bortezomib/dexamethasone for relapsed/refractory MM. Blood. 2016;127(23):2833–41.

32. Richardson PG, Jagannath S, Moreau P, Jakubowiak AJ, Raab MS, Facon T, et al. Elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma: final phase 2 results from the randomised, open-label, phase 1b-2 dose-escalation study. Lancet Haematol. 2015;2(12):e516–27.

33.•• Lonial S, Dimopoulos M, Palumbo A, White D, Grosicki S, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2015;373:621–31. https://doi.org/10.1056/NEJMoa1505654 **Potentially practice-changing data in RRMM patients treated with elotuzumab-/lenalidomide-based backbone treatment.**

34.•• Dimopoulos MA, Dytfeld D, Grosicki S, Moreau P, Takezako N, et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. N Engl J Med. 2018;379:1811–22 **Potentially practice-changing data in RRMM patients treated with elotuzumab-/pomalidomide-based backbone treatment.**

35. Heffner LT, Jagannath S, Zimmerman TM, Lee KP, Rosenblatt J, Lonial S, et al. BT062, an antibody-drug conjugate directed against CD138, given weekly for 3 weeks in each 4 week cycle: safety and further evidence of clinical activity. Am Soc Hematol Annu Meet Proc. 2012;120(21):653.

36. Kelly KR, Chanan-Khan A, Heffner LT, Somlo G, Siegel DS, Zimmerman T, et al. Indatuximab Ravtansine (BT062) in combination with Lenalidomide and low-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma: clinical activity in patients already exposed to Lenalidomide and Bortezomib. Blood. 2014;124(21):4736.

37. Kumar SK, Anderson KC. Immune therapies in multiple myeloma. Clin Cancer Res. 2016;22(22):5453–60.

38. Topp MS, Duell J, Zugmaier G, Attal M, Moreau P, Langer C, et al. Treatment with AMG 420, an anti-B-cell maturation antigen (BCMA) bispecific T-cell engager (BiTEs) antibody construct, induces minimal residual disease (MRD) negative complete responses in relapsed and/or refractory (R/R) multiple myeloma (MM) patients: results of a first-in-human (fih) phase i dose escalation study. ASH Annual meeting. 2018:abstract 1010.

39. Tamura H, Ishibashi M, Yamashita T, Tanosaki S, Okuyama N, Kondo A, et al. Marrow stromal cells induce B7-H1 expression on myeloma cells, generating aggressive characteristics in multiple myeloma. Leukemia. Nature Publishing Group. 2012;27(2):464–72.

40. Liu J, Hamrouni A, Wolowiec D, Coiteux V, Kuliczkowski K, Hetuin D, et al. Plasma cells from multiple myeloma patients express B7-H1 (PD-L1) and increase expression after stimulation with IFN-γ and TLR ligands via a MyD88-, TRAF6-, and MEK-dependent pathway. Blood. 2007;110(1):296–304.

41. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011;480(7378):480–9.

42. Hallett WHD, Jing W, Drobyski WR, Johnson BD. Immunosuppressive effects of multiple myeloma are overcome by PD-L1 blockade. Biol Blood Marrow Transplant. 2011;17(8):1133–45.

43. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373:23–34.

44. Lesokhin AM, Ansell SM, Armand P, Scott EC, Halwani A, Gutierrez M, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase ib study. J Clin Oncol. 2016;34(23):2698–704.

45. Görgün G, Samur MK, Cowens KB, et al. Lenalidomide enhances immune checkpoint blockade-induced immune response in multiple myeloma. Clin Cancer Res. 2015;21(20):4607–18.

46. Benson DM Jr, Bakan CE, Mishra A, Hofmeister CC, Efebera Y, Becknell B, et al. The PD-1/PD-L1 axis modulates the natural killer

cell versus multiple myeloma effect: a therapeutic target for CT-011, a novel monoclonal anti-PD-1 antibody. Blood. 2010;116:2286–94.
47. Ocio EM, Mateos M-V, Orlowski RZ, et al. Pembrolizumab plus lenalidomide and low-dose dexamethasone for relapsed refractory multiple myeloma : Efficacy and biomarker analyses. J Clin Oncol. 2017;35(15_suppl):8015. https://doi.org/10.1200/JCO.2017.35.15_suppl.8015.
48. Badros A, Hyjek E, Ma N, Lesokhin A, Dogan A, Rapoport AP, et al. Pembrolizumab, pomalidomide, and low-dose dexamethasone for relapsed/refractory multiple myeloma. Blood. 2017;130(10):1189–97. https://doi.org/10.1182/blood-2017-03-775122.
49. FDA news release: August 31, 2017. https://www.fda.gov/Drugs/DrugSafety/ucm574305.htm
50. Bae J, Song W, Smith R, Daley J, Tai YT, Anderson KC, et al. A novel immunogenic CS1-specific peptide inducing antigen-specific cytotoxic T lymphocytes targeting multiple myeloma. Br J Haematol. 2012;157(6):687–701.
51. McCann KJ, Godeseth R, Chudley L, et al. Idiotypic DNA vaccination for the treatment of multiple myeloma: safety and immunogenicity in a phase I clinical study. Cancer Immunol Immunother. 2015;64(8):1021–32.
52. Rapoport AP, Aqui NA, Stadtmauer EA, Vogl DT, Xu YY, Kalos M, et al. Combination immunotherapy after ASCT for multiple myeloma using MAGEA3/Poly-ICLC immunizations followed by adoptive transfer of vaccine-primed and costimulated autologous T cells. Clin Cancer Res. 2014;20(5):1355–65.
53. Szmania S, Gnjatic S, Tricot G, Stone K, Zhan F, Moreno A, et al. Immunization with a recombinant MAGEA3 protein after high-dose therapy for myeloma. J Immunother. 2007;30(8):847–54.
54. Tsuboi A, Oka Y, Nakajima H, Fukuda Y, Elisseeva OA, Yoshihara S, et al. Wilms tumor gene WT1 peptide-based immunotherapy induced a minimal response in a patient with advanced therapy-resistant multiple myeloma. Int J Hematol. 2007;86(5):414–7.
55. Rosenblatt J, Vasir B, Uhl L, Blotta S, MacNamara C, Somaiya P, 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(2):393–402.
56. Rosenblatt J, Avivi I, Vasir B, Uhl L, Munshi NC, Katz T, et al. Vaccination with dendritic cell/tumor fusions following autologous stem cell transplant induces immunologic and clinical responses in multiple myeloma patients. Clin Cancer Res. 2013;19(13):3640–8.
57.• Garfall AL, Maus MV, Hwang W-T, Lacey SF, Mahnke YD, Melenhorst JJ, et al. Chimeric antigen receptor T cells against CD19 for multiple myeloma. N Engl J Med. 2015;373(11):1040–7 **This study was one of the first to investigate CAR T cells for MM and demonstrated efficacy in a subset of patients despite the lack of CD19 expression in most MM cells.**
58. Guo B, Chen M, Han Q, Hui F, Dai H, Zhang W, et al. CD138-directed adoptive immunotherapy of chimeric antigen receptor (CAR)-modified T cells for multiple myeloma. J Cell Immunother. 2016;2(1):28–35.
59. Ramos CA, Savoldo B, Torrano V, Ballard B, Zhang H, Dakhova O, et al. Clinical responses with T lymphocytes targeting malignancy-associated κ light chains. J Clin Invest. 2016;126(7):2588–96.
60. Seckinger A, Delgado JA, Moser S, Moreno L, Neuber B, Grab A, et al. Target expression, generation, preclinical activity, and pharmacokinetics of the BCMA-T cell bispecific antibody EM801 for multiple myeloma treatment. Cancer Cell. 2017;31(3):396–410.
61.• Brudno JN, Maric I, Hartman SD, Rose JJ, Wang M, Lam N, 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(22):2267–80. https://doi.org/10.1200/JCO.2018.77.8084 **An early trial of BCMA-directed CAR T cells, demonstrating responses in the majority of patients.**
62. Berdeja JG, Lin Y, Raje N, Munshi N, Siegel D, Liedtke M, et al. Durable clinical responses in heavily pretreated patients with relapsed/refractory multiple myeloma: updated results from a multicenter study of bb2121 anti-BCMA CAR T cell therapy. Blood. 2017;130:740.
63. Zhao W-H, Liu J, Wang B-Y, Chen Y-X, et al. Updated analysis of 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/refractory multiple myeloma. 2018 ASH annual meeting. Abstract – 955.
64. Cohen AD, Garfall AL, Stadtmauer EA, Lacey SF, Lancaster E, Vogl DT, 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.
65. Mailankody S, Ghosh A, Staehr M, et al. Clinical responses and pharmacokinetics of MCARH171, a human-derived BCMA targeted CAR T cell therapy in relapsed/refractory multiple myeloma: final results of a phase I clinical trial. 2018 ASH Annual meeting. Abstract 959.
66. Mailankody S, Htut M, Lee K, Bensinger W, DeVries T, Piasecki J, et al. First-in human multicenter study of JCARH125, anti-BCMA CAR T-cell therapy for relapsed/refractory multiple myeloma. 2018 ASH annual meeting. Abstract: 957.
67. Gregory T, Cohen AD, Costello CL, Ali SA, Berdeja JG, Ostertag EM, et al. Efficacy and safety of P-BCMA-101 CAR-T cells in patients with relapsed/refractory (r/r) multiple myeloma (MM): ASH; 2018. abstract 1012
68.•• Noonan KA, Huff CA, Davis J, Lemas MV, Fiorino S, Bitzan J, et al. Adoptive transfer of activated marrow-infiltrating lymphocytes induces measurable antitumor immunity in the bone marrow in multiple myeloma. Sci Transl Med. 2015;7(288):288ra78 **The first clinical trial using marrow infiltrating lymphocytes in MM, demonstrating feasibility and efficacy.**
69.•• Rapoport AP, Stadtmauer EA, Binder-Scholl GK, Goloubeva O, Vogl DT, Lacey SF, et al. NY-ESO-1-specific TCR-engineered T cells mediate sustained antigen-specific antitumor effects in myeloma. Nat Med. 2015;21(8):914–21 **Supports that encouraging clinical responses can be associated with T cells engineered to express an affinity-enhanced T cell receptor.**
70. Turtle CJ, Hanafi L-A, Berger C, Hudecek M, Pender B, Robinson E, et al. Immunotherapy of non-Hodgkins lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified Tcells. Sci Transl Med. 2016;8(355):355ra116.
71.• Sommermeyer D, Hudecek M, Kosasih PL, Gogishvili T, Maloney DG, Turtle CJ, et al. Chimeric antigen receptor-modified T cells derived from defined CD8+ and CD4+ subsets confer superior antitumor reactivity in vivo. Leukemia. 2015;30(2):492–500 **Suggests that CAR T cells derived from defined subsets may improve activity and provide uniform potency.**
72. Wang X, Walter M, Urak R, Weng L, Huynh C, Lim L, et al. Lenalidomide enhances the function of CS1 chimeric antigen receptor-redirected T cells against multiple myeloma. Clin Cancer Res. 2018 Jan 1;24(1):106–19.