The immunotherapy era of myeloma: monoclonal antibodies, vaccines, and adoptive T-cell therapies

Valentina Hoyos and Ivan Borrello

Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD

The treatment of multiple myeloma has evolved significantly over the last decades from primarily alkylator-based chemotherapeutic agents with minimal efficacy to the introduction of more effective agents including immune modulators and proteasome inhibitors, which have changed the landscape of therapy for this disease. We are now entering a new era that will increasingly integrate immunotherapy into standard treatment. This review discusses the current immune-based strategies currently approved, as well as various immune approaches being actively investigated including monoclonal antibodies, checkpoint inhibitors, vaccines, and adoptive T-cell therapies. (*Blood*. 2016;128(13):1679-1687)

Introduction

The treatment of multiple myeloma (MM) has evolved significantly over the last decades from alkylating agents and steroids to an increasing compendium of agents that have improved the 5-year overall survival (OS) of patients from 29.7% in 1990% to 45.1% in 2007.[1] Some of the hurdles to long-term remissions/cures are a result of the inherent resistance of malignant plasma cells to conventional cancer treatments, as well as the genomic instability[2] and immune-deficient state[3] that characterize myeloma. The addition of the newer treatment options including proteasome inhibitors (PIs) and immune modulators (IMIDs) such as thalidomide and lenalidomide has improved OS, but again failed to provide a cure for the majority of patients, with >90% still dying of their disease.

Immunotherapy is rapidly establishing itself within the armamentarium of many diseases, from the first monoclocal antibody (mAb), such as rituximab, that revolutionized the treatment of lymphomas to the introduction of checkpoint inhibitors that have imparted impressive clinical results in diseases including melanoma, lung cancer, and Hodgkins lymphoma[4,5] and gene-modified T cells targeting CD19 in ALL showing durable responses in multiply relapsed patients.[6] Taken together, these results have ushered in a new era of treatment and led to significant interest and excitement in developing immunotherapeutic options for various malignancies, including MM, where it offers the benefit of a therapy that is non—cross-reactive with standard cytotoxic chemotherapy and capable of inducing long-term remissions with a potentially more tolerable toxicity profile.

This review highlights the immune based therapeutic options available and in development and attempts to place these within the context of current treatment paradigms.

Immunosuppressive mechanisms in myeloma

Myeloma is associated with profound immune dysfunction affecting both the innate and adaptive immune system.[7] Although this review does not aim to focus on these mechanisms, it is important to understand general concepts of immune suppression in MM to effectively develop strategies to overcome them.

Although many lymphoid malignancies, including MM, express HLA class II and may thus be capable of direct presentation, cross-presentation remains the dominant mechanism of tumor antigen priming[8]: a mechanism that can be augmented by the use of tumor targeting monoclonal antibodies.[9] As such, the functional status of antigen presenting cells (APCs) becomes critical. Dendritic cells (DCs) isolated from patients with MM are functionally impaired and express/produce lower levels of crucial molecules that initiate an immune response including interleukin 12 (IL-12), HLA-DR, CD40, CD86, and CD80.[10,11] This phenotype is likely due to exposure to cytokines produced by the cancer cells and its surrounding microenvironment including transforming growth factor β (TGFβ), IL-6, and IL-10.

Regulatory T cells have multiple mechanisms of immunosuppression including the production of the anti-inflamatory cytokines, IL-10 and TGFβ, and depletion of IL-2 from the bone marrow (BM).[12,13] Several groups have correlated the amount of regulatory T cells in MM (CD4$^+$CD25$^+$FoxP3$^+$) with disease stage and treatment response, although the exact role they play in disease progression remains unclear.[14,15]

Myeloid derived suppressor cells (MDSCs) are a heterogeneous population of immature myeloid cells that accumulate in the BM and peripheral blood of patients with MM and whose numbers correlate with a poor prognosis.[16] They inhibit T cells by producing arginase-1, reactive oxygen species, and nitric oxide.[17,18] Therapies targeting MDSCs are appealing as standard antimyeloma treatments have minimal effects on this population. However, some evidence suggests a role of lenalidomide.[19] Our group has previously reported the use of phosphodiesterase-5 inhibitors to reduce MDSC function and shown some activity in MM.[20]

Macrophages are the main source of the immunosuppressive cytokines IL-10, IL-1β, and tumor necrosis factor α within the tumor microenvironment. They also produce angiogenic factors, leading to tumor growth and invasion, such as vascular endothelial growth factor, IL-8, fibroblast growth factor-2, metalloproteinases, cycloxygenase-2, and colony-stimulating factor-1, and can also increase myeloma drug resistance through a direct cell–cell interaction.[16,21]

Myeloma cells also play an important role in maintaining immunosuppression. Their production of TGFβ and expression of
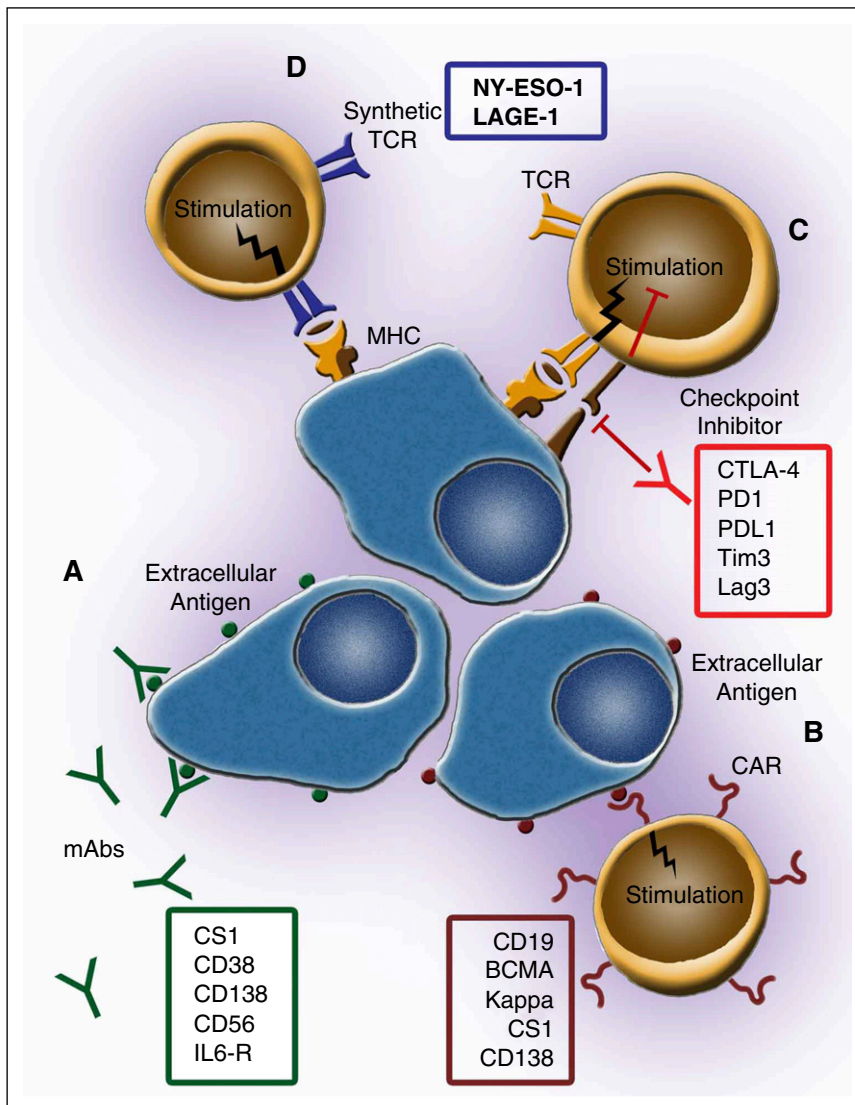
Figure 1. Immunotherapy targets in MM. (A) Monoclonal antibodies binding to targets present in the extracellular compartment of myeloma cells. Outlined are monoclonal antibody targets under clinical development. (B) Chimeric antigen receptors present on the surface of transformed T cells recognizing cell surface antigens on myeloma cells in an HLA-independent manner presentation. Outlined are current MM CAR target molecules. (C) Checkpoint inhibitors interrupting the T-cell inhibitory pathway. Outlined are the known checkpoint inhibitor target molecules. (D) Synthetic T cell receptors present on the surface of transformed T cells, recognizing targets presented in an HLA-restricted manner. Outlined are known synthetic TCR target molecules being examined in MM. mAbs, monoclonal antibodies.

PDL-1 leads to significant T cells inhibition. Malignant plasma cells also shed the major histocompatibility complex (MHC) class I chain-related protein A (MICA), resulting in downregulation of NKG2D and impaired cytotoxicity.[22] The IL-17 pathway has also been involved in favoring MM cell growth,[23] as well as mediating osteoclast activation and lytic bone disease.[24] Taken together, these pathways all provide putative targets for immune-mediated targeted therapies.

Current immune approaches

MM immunotherapy can be divided into several categories (Figure 1): (1) monoclonal antibodies targeting surface molecules present on the myeloma cells; (2) monoclonal antibodies targeting checkpoint inhibitors on immune cells; (3) pharmacologic immunomodulation; (4) cancer vaccines; and (5) adoptive cellular therapy (ACT). Immune-based strategies in MM will undoubtedly require an integration of these various modalities. An understanding of their benefits and limitations is critical in developing effective therapies.

Monoclonal antibodies

Monoclonal antibodies have significantly altered the treatment landscape in cancer due to their high specificity and minimal side effect profile. The major obstacle to defining their efficacy includes finding the appropriate target molecule. In MM, several surface molecules have been explored as potential targets of monoclonal antibodies including SLAMF7 (CS1), CD38, CD40, CD138, CD56, CD54, IL-6, PD1, CD74, CD162, β2-macroglobulin, and GM-2. Here we will discuss monoclonal antibodies that are furthest along in their clinical development and that have the potential for significant clinical impact in the treatment of MM. Table 1 summarizes the clinical trials with these MM-targeting monoclonal antibodies.

SLAMF7 (CS1). SLAMF7 is a cell surface glycoprotein receptor highly expressed on MM cells mediating adhesion to BM stromal cells. It is selectively expressed on plasma and natural killer (NK) cells and lacks expression on other tissues.[25] Elotuzumab is an anti-SLAMF7 monoclonal antibody. Interestingly, SLAMF7 engagement induces both direct cell killing of MM cells and enhances NK cytotoxicity through upregulation of EAT-2[26] (adaptor protein present on NK cells).[27] A phase 1 dose escalation trial of 34 heavily pretreated patients demonstrated a safe toxicity profile limited

Table 1. Monoclonal antibodies in clinical development

Name	Target	Trials phase	Side effects	Monotherapy	Combination therapy	Comments
Elotuzumab	CS1 (SLAMF7)	3	Infusion reactions, lymphopenia, fatigue, pneumonia	No objective responses	With Rd: ORR: 84% with Vd: ORR 65% with PFS of 9.9 vs 6.8 months	FDA approved
Daratumumab	CD38	3	Infusion reactions, cytopenias	ORR 35% at 16 mg/kg 10% CR	With Rd: ORR 93% with Pd: ORR 58% with Vd: ORR 83%	FDA approved
Isatuximab	CD38	1/2	Fatigue, nausea, cytopenias, hyperglycemia, fever	ORR: At ≥10 mg/kg: 24%	With Rd: ORR 57%	
BT062 (indatuximab ravtansine)	CD138	1/2a	Nausea, fatigue, diarrhea, hypokalemia	Disease control (PR + SD) in 50% patients	With Rd: ORR 70-83% depending on dose and prior therapies	Conjugated with DM4
Lorvotuzumab	CD56	1	Cytopenias, peripheral neuropathy, fatigue, GI symptoms	Clinical benefit (≥stable disease): 41% including PR and and 4 mR	With Rd: ORR: 56.4% including 3% stringent complete remission, 28% VGPR and 26% PR	Conjugated with DM1
Siltuximab (CNTO 328)	IL-6	1, 2	Cytopenias, liver toxicity	No response	No advantage of combining with bortezomib	
Pembrolizumab	PD-1	1, 2	Cytopenias, diarrhea		With Rd: ORR 50% with Pomalidomide:ORR 50%	

mostly to infusion-related reactions. There were no objective responses, and stable disease (SD) was reported in 26% of patients.[28] However, in a phase 3 trial comparing elotuzumab, lenalidomide, and dexamethasone vs lenalidomide and dexamethasone (Rd), elotuzumab, lenalidomide, and dexamethasone showed an overall response rate (ORR) of 79% vs 66% and progression-free survival (PFS) of 41% vs 27%, respectively.[29]

In patients with relapsed/refractory MM (RRMM), elotuzumab + bortezomib/dexamethasone (EVd) was studied compared with Vd alone in a phase 2 randomized trial of 152 patients. Results showed minimal incremental toxicity and a median PFS of 9.9 months (EVd) vs 6.8 months (Vd).[30,31] The role of elotuzumab + lenalidomide, bortezomib, and dexamethasone in newly diagnosed MM showed no added toxicity. Efficacy data are currently not available.[32]

CD38. CD38 is a transmembrane receptor protein highly expressed on malignant plasma cells and on normal B cells during different stages of their maturation.[33] The intracellular presence of this molecule has been reported in normal tissues including brain, smooth muscle, and osteoclasts. $CD38^{-/-}$ mice exhibited marked deficiencies in antibody responses to T cell–dependent antigens, suggesting its role in regulating humoral immunity.[34] Its expression on activated T cells has been associated with reduced proliferative ability but increased production of Th1 cytokines.[35]

Daratumumab is the first US Food and Drug Administration (FDA)-approved anti-CD38 antibody. Single agent daratumumab in 106 heavily pretreated patients (>3 prior regimens) shows a dose-dependent efficacy with 29% to 46% response rates at 16 mg/kg and an acceptable toxicity profile: mostly with most adverse events (AEs) associated to drug infusion and few serious AEs that mainly consisted of cytopenias. The reported ORR was 29.2%, with 3 stringent complete remission, 10 very good partial response (VGPR), and 18 partial response (PR). The median duration of response was 7.4 months, and the estimated 1-year OS was 65%.[36,37] In a phase 3 trial with lenalidomide and dexamethasone (DRd), daratumumab increased the ORR to 93% vs 76% Rd, with a complete response (CR) or better (43% vs 19%). Median PFS showed a 63% reduction in the risk of disease progression or death (hazard ratio = 0.37). Patients had a median of 1 prior therapy with 55% of patients having received prior IMID therapy.[38] Similarly, a randomized phase 3 trial of daratumumab with bortezomib and dexamethasone (DVd) vs Vd also showed an ORR of 83%, with DVd of 63% with an associated improvement in PFS. The

most benefit was seen in patients who had received 1 prior line of treatment, indicating that earlier treatment might provide the most benefit for patients with RRMM.[39]

Two additional anti-CD38 antibodies, isatuximab (SAR650984) and MOR03087, are currently being investigated in clinical trials.[40-42] Isatuximab + Rd in heavily pretreated RRMM patients (median 4-6 lines of therapy and 85% IMID refractory) showed a 57% ORR including 38% of patients achieving a VGPR or better.[41]

CD138. CD138 is found in the surface of MM cells and functions as a growth factor receptor. A conjugated anti-CD138 monoclonal antibody with cytotoxic maytansinoid derivatives (DM4) was developed: BT062.[43] A dose-escalating phase 1 trial of 29 patients with RRMM (failed IMID and PI treatment) reported a favorable safety profile, with nausea, anemia, diarrhea, and fatigue as the most common AEs. Only 1 patient had a PR (4%). SD was noted in 50% of patients.[44] As with the other monoclonal antibodies mentioned, combination with Rd improved the ORR in RRMM patients (median 3 prior therapies) to 78%.[45]

IL-6. IL-6 is a cytokine that has been implicated in the proliferation and survival of MM cells. Preclinical studies suggested that the combination of siltuximab (an anti–IL-6 monoclonal antibody) and bortezomib might have synergistic effects. However, the results of a randomized control trial in combination with bortezomib failed to report statistically significant differences in response rate, PFS, or OS, whereas it did increase the frequency of adverse events including cytopenias.[46-48] Currently it is being tested in patients with high-risk smoldering myeloma.

CD56. Lorvotuzumab mertansine is a humanized anti-CD56 monoclonal antibody conjugated to DM1 (cytotoxic maytansinoid derivative). CD56 is expressed on MM cells and NK cells and neural tissue. Phase 1 monotherapy trials in CD56-positive RRMM had an ORR of 7%. The toxicity profile was acceptable, consisting mostly of peripheral neuropathy, cytopenias, and fatigue.[49] Combination therapy with Rd also increased the ORR to 56%.[50]

Checkpoint inhibitors

T cells are major contributors of the antitumor immune response. A major determinant of their ability to generate clinically meaningful responses is dictated by the effective engagement of the T cell with
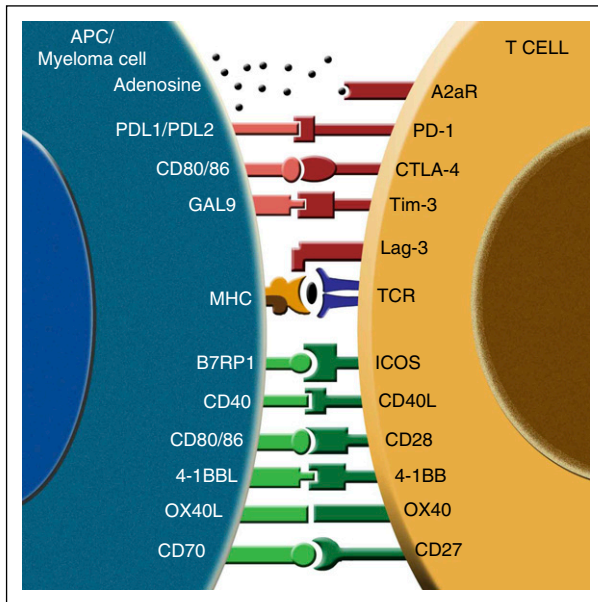
Figure 2. Signaling between T cells and APCs. This figure illustrates the different possible costimulatory and coinhibitory molecular interactions between T cells and APCs (or myeloma cell). The upper half (red) shows the inhibitory signals and the lower half (green) depicts the activating interactions.

its target. This interaction is regulated by a complex balance of costimulatory and coinhibitory bidirectional signals (Figure 2) whose physiologic role is the maintenance of self-tolerance and prevention of autoimmunity.

The checkpoint inhibitors anti–CTLA-4 and anti–PD-1 have shown impressive results as measured by both depth and durability of the response that has led to their FDA approval in a broad range of malignancies. Although single agent anti–CTLA-4 has not been significantly examined in MM, single agent PD-1 blockade has been disappointing, with 0 of 27 MM patients achieving sustainable responses.[51] More recently, the anti–PD-1, pembrolizumab, in combination with Rd (PRd), showed activity in 20 of 40 patients (50%) tested, with a 38% response rate (11 of 29) in lenalidomide-refractory patients with an acceptable toxicity profile.[52] A phase 1/2 study combining pembrolizumab with pomalidomide in 24 patients had a median number of prior therapies of 3 (1-6). Seventy-five percent of patients were double refractory to IMIDs and PIs. The overall response rate was 50% (11 of 22).[53] This has prompted a front-line PRd clinical study that is ongoing.[54] Taken together, these studies demonstrate a role of checkpoint inhibition in MM and underscore the need for immunomodulation by IMIDs to achieve this response. Checkpoint inhibition will likely play a key role in the treatment paradigm of myeloma in light of the results observed in these early studies.

Vaccines

Vaccines aim to increase the precursor frequency of antigen-specific T cells or antibodies through in vivo priming. Infectious vaccines are mostly administered to healthy individuals with relatively intact immune systems with the purpose of generating a humoral and/or cellular immune response in a disease-free setting. These vaccines are typically comprised of a multitude of antigens from live attenuated or killed organisms. Tumor vaccines, as currently used, face significantly greater hurdles that account for their limited efficacy. These primarily include the following: (1) the intrinsic immune dysfunction associated with cancer-bearing hosts; (2) the approach is used in a therapeutic setting in the presence of disease burden; and (3) many of these vaccine approaches attempt to target few antigens. To date, several vaccination approaches have been used for myeloma (Table 2).

Idiotype vaccines. The initial vaccines used to treat MM took advantage of the unique expression of a specific immunoglobulin by malignant plasma cells. These monoclonal immunoglobulins have somatically mutated variable regions and represent a unique antigen known as the idiotype (Id). These antigens can be expressed and presented in an HLA-restricted manner on the surface of malignant plasma cells, which enables them to serve as patient-specific tumor associated antigens. Furthermore, their HLA presentation enables plasma cells to serve as both a target and APCs for Id-specific T cells.[55,56] However, vaccines using only the Id were found to be weakly immunogenic and failed to elicit a response with a measurable clinical benefit even when combined with strong adjuvants such as granulocyte–monocyte colony-stimulating factor (GM-CSF), IL-12, and alum or keyhole limpet hemocyanine.

DC-based vaccines. A major mechanism of vaccine-mediated priming is through cross-presentation.[57] The antigens within the vaccine are taken up by resident APCs, traffic to draining lymph nodes, process and present antigen to T cells, and generate systemic immunity. DCs are the most efficient APCs,[58] and as such have also been used in vaccine formulations. One such approach was Myelovenge, in which DCs were pulsed with the patient's Id and vaccinated following an autologous stem cell transplantation (ASCT). The clinical responses were compared retrospectively to contemporaneous controls and they found an OS advantage of 5.3 vs 3.4 years with no differences in PFS.[59] This approach has not been further developed.

An alternative approach is fusion of DCs with patient-derived tumor cells. The rationale is to optimize antigen presentation and immune priming against the entire antigenic repertoire of each unique patients' tumor.[60] A phase 1 trial administering this vaccine following ASCT showed evidence of tumor-specific immunity and long-term disease stabilization in 3 of 17 patients.[61] These results have led to the development of an ongoing randomized trial.

Cancer testis antigens. Cancer testis antigens (CTAs) are normally expressed in male germ cells and are pathologically upregulated in a variety of tumors, including MM. In MM, CTAs fulfill several parameters, making them ideal antigens to target including their low expression on normal tissues and the association of their expression with more aggressive disease,[62] as well as advanced stage disease.[63] Vaccines using CTAs to generate tumor immunity have been tested. DCs pulsed with a CTA NY-ESO-1 peptide generated tumor-specific responses in vitro.[64]

A phase 2 trial in MM patients after ASCT was conducted with a MAGE-A3 peptide vaccine (compound GL-0817) combined with TLR-3 agonist (Hiltonol), GM-CSF, and ex vivo anti-CD3/CD28 costimulated autologous T cells. They found an 88% dextramer positivity in HLA-A2 patients but failed to prove a statistically significant correlation between vaccine specificity and clinical responses.[65]

GM-CSF–based cellular vaccines. The ability to prime immune responses toward a greater number of tumor-associated antigens maximizes the likelihood of achieving broader antimyeloma coverage. While the full antigenic repertoire of an autologous tumor is the best approach, this would inevitably limit vaccine strategies to patients in whom tumor could be collected and would only provide a finite amount of vaccine. The use of allogeneic cell lines offers several benefits: (1) they share common antigens with all myeloma patients; (2) they are an off-the-shelf product; (3) there is potentially an unlimited supply of vaccine; and (4) vaccine strategies can be used in settings in which obtaining autologous tumor is not feasible such as in minimal residual disease.

Myeloma GVAX is a GM-CSF–based vaccine consisting of 2 allogeneic cell lines: H929 and U266, coupled to a GM-CSF–secreting bystander cell line, K562/GM. This vaccine formulation has been tested

Table 2. Potential vaccine approaches

Type of vaccines
Idiotype (Id) vaccines + adjuvants
Dendritic cells + Id
Dendritic cell tumor fusion vaccine
Dendritic cells + cancer testis antigen
Dendritic cells electroporated with mRNA of target antigens
Peptide vaccine + adjuvant
Allogeneic myeloma cell lines with GM–CSF bystander line
Settings where vaccines are tested in clinical trials
Sustained near complete remission (nCR) for 4 months
Post auto-SCT
Post allo-SCT
Undergoing auto-SCT
Newly diagnosed on maintenance lenalidomide
Symptomatic MM
Off treatment with stable disease
Smoldering myeloma
Vaccine antigens tested in clinical trials
hTERT peptides: I540, R572Y, D988Y
Survivin peptide: Sur1M2, SVN53-67/M57,
KLH-Id
WT1 peptides: A1, 427, 331, 122A1
MAGE-A3: GL-0817, 168-176
NY-ESO-1: 1156-C165V,
XBP1: US(184-192), SP(367-375)
CD138: (260-268)
CS1: (239-247)
MUC1: BP25

in patients with a near complete remission, defined as the absence of an M-spike but persistence of detectable immunofixation (IFE) for 6 months. Of the patients initially identified as possible candidates, 50% were ineligible because of disease progression during the observation time (25%) or because they converted to IFE negativity (25%). These patients that were not vaccinated continued on all their therapy and had a median PFS of 17.9 months. In contrast, the 15 IFE-positive patients continued on lenalidomide alone and received vaccines. This group has not reached a median PFS with a median follow-up of >36 months.[66] This study suggests that the generation of tumor-specific immunity in a low disease burden state can significantly delay relapse. A larger randomized phase 2 study will attempt to answer this question.

Role of IMIDs

The agents described thus far target myeloma in an immune-specific manner. However, the global immune suppression present in

cancer-bearing hosts limits many immune-based approaches. Lenalido-mide (Len) was developed as a thalidomide analog with more immune-modulatory properties. Using the pneumococcal 7-valent conjugate vaccine (Prevnar; Pfizer, New York, NY), vaccine-specific humoral and cellular responses were augmented with Len in MM patients that provided evidence of in vivo immune modulation to vaccines in myeloma patients.[67]

Further evidence of these immunomodulatory properties has been discussed above in reference to the emerging combination with tumor targeting monoclonal antibodies, elotuzumab and daratu-mumab, where Len significantly provided or added antimyeloma activity, respectively,[29,36,68] as well as PD-1 blockade that went from no activity to a 50% response rate.[51,69]

The overall explanation for Len-based enhanced immunogenicity is likely multifactorial and includes T-cell activation through increased tyrosine kinase activity of the CD28 receptor,[70] downregulation of CD45RA on T cells,[71] and downregulation of SOCS1 on the stromal elements of the tumor microenvironment.[19]

ACTs

ACT aims to enhance T-cell antitumor activity through ex vivo manipulations. This can be achieved through nonspecific stimu-lation of CD3, resulting in activation and expansion,[72] specific stimulation by exposure to tumor antigens, or genetic engineering to express synthetic receptors that redirect T-cell specificity toward surface proteins (chimeric antigen receptors) or defined tumor-specific T-cell receptors (T-cell receptor transgenic T cells; Tables 3 and 4).

Allogeneic BM transplantation

Although nonspecific, the clinical responses observed in MM with allogeneic BM transplantation (BMT) provide support for the existence of a graft vs tumor effect. One approach to harness the graft vs tumor effect without the associated toxicity of myeloablative regimens has been the development of nonmyeloablative transplants. One large genetically randomized Italian study, comparing tandem autologous transplants to an ASCT followed by nonmyeloablative HLA-matched allo-BMT, showed significant improvement in disease-related mortality in favor of allo-BMT (43% vs 7%).[73] However, although a meta-analysis of 6 trials showed a higher CR rate in the auto-allo arms, it failed to show improvement in PFS but demonstrated a trend toward improved OS.[74] Although the long-term antitumor effect is questionable, the reduction in transplant-related mortality from 40%[75] to 8% to 12% can allow one to envision the use of this

Table 3. ACT approaches

ACTs	Advantages	Challenges	Disadvantages
TCR	Broader array of possible targets	Find target antigens that are tumor specific	Tumor escape
			MHC restricted
			Risk of cross-reactivity
			Require vectors
			Possible mispairing with endogenous TCR
CAR	Highly tumor specific	Find target antigens that are tumor specific	Tumor escape
	HLA independent		Cytokine storm
	Antigens recognized not limited to proteins		Limited to extracellular antigens
	Recognizes soluble antigen		Require vectors
MILs	No vectors involved in production	Identify antigens being recognized	Heterogeneous product
	Polyclonal (multiple targets)	Increase tumor specificity	Lower efficiency

Table 4. Currently active ACTs

Type of ACT	Setting in which tested
Activated MILs	After ASCT
CAR T cells anti–B-cell maturation antigen	RRMM
CAR T cells anti-NKG2D ligands	RRMM
CAR T cells anti-CD138	RRMM
CAR T cells anti–κ light chain	RRMM
NY-ESO-1– and LAGE-specific TCR-modified T cells	RRMM
T cells selected for NY-ESO-1, MAGEA4, PRAME, Survivin, and SSX specificity	Active myeloma after first line
Expanded haploidentical NK cells	After ASCT
NK cells from donor	After allo-SCT

modality as a foundation to build more effective tumor-targeted immune-based approaches.

Marrow infiltrating lymphocytes

Most ACTs used to date have used peripheral blood lymphocytes (PBLs). Although access to these cells is easy, a major limitation is their endogenous lack of tumor specificity. Our group has developed the use of marrow infiltrating lymphocytes (MILs).[76] In addition to being the site of disease, the BM also possesses a unique immune environment that enables us to obtain a lymphocyte product enriched for both tumor-specific and central memory T cells: 2 factors essential for effective ACT. In contrast to PBLs, MILs possess greater cytotoxicity and express CXCR4, which increases their likelihood of trafficking to the BM on reinfusion.[77] In the first clinical trial of 25 patients with active disease, MILs were expanded and administered after autologous SCT. Ex vivo tumor specificity of the expanded MILs product and tumor specificity of T cells obtained from the BM after transplant directly correlated with clinical outcomes.[78] Furthermore, the cells were administered with minimal, self-limiting toxicity. A randomized multicenter clinical trial is currently under way in patients with high-risk myeloma of ASCT ± MILs.

Chimeric antigen receptor T cells

Chimeric antigen receptor T cells (CARs) are engineered molecules that fuse the specificity of a monoclonal antibody with the activation of the T-cell receptor signaling domain. CARs usually recognize their target via a single-chain variable fragment (scFv) derived from a monoclonal antibody and possess a very high affinity for their target with a T-cell intracellular signaling domain consisting of CD3ζ alone or coupled to costimulatory domains such as CD28 or 4-1BB.[79] The largest success with this approach has been observed with CD19-directed CAR in chronic lymphocytic leukemia and ALL showing sustained remission in patients with advanced disease.[6] However, therapeutic efficacy has also been associated with a potentially life-threatening, IL-6–mediated, cytokine release syndrome (CRS), which appears to be related to the overall tumor burden[80] and responds to the anti–IL-6 antibody tocilizumab.[81]

A CD19 CAR approach in MM was reported in a patient with an immunoglobulin A myeloma, which interestingly had a very low level of CD19 expression as detectable by flow cytometry, and yet experienced a rapid and dramatic response to treatment.[82] Clinical studies are currently ongoing with this approach. Although our group has shown that the MM precursors represents a postgerminal B cell with CD19 expression,[83] the rapid decrease in the malignant plasma cell population would argue against having primarily targeted a precursor population.

B-cell maturation antigen is expressed on plasma cells and >70% of malignant MM cells with limited expression on normal B cells. As such, it represents an attractive target. A B-cell maturation antigen CAR trial at the National Cancer Institute has shown early evidence of dose-dependent activity in patients with advanced MM that was associated with a CRS.[84] Other targets being examined for CAR therapy include κ light chain,[85] CS-1,[86] CD138,[87] and CD38.[88] Although demonstrating powerful antitumor activity, the significant toxicity associated with the CRS thus far limits its use outside of the multiply-relapsed setting.

T-cell receptor-modified T cells

Unlike CARs, T-cell receptor-modified T cells (TCRts) are HLA restricted. The TCRs typically recognize peptides presented by HLA-A2 molecules as to maximize its use in the majority of patients. The first TCR used in MM recognizes the complex of HLA-A*0201 with a peptide shared by NY-ESO-1 and LAGE1. Of note, NY-ESO-1 expression is found in ~60% of advanced MM cases. The first 20 patients receiving NY-ESO-1 TCR-specific T cells (NY-ESOc259) experienced only grade 3 or lower AEs and no CRS. Persistence of NY-ESOc259 in the blood was observed up to 2 years after infusion. Sixteen of the 20 patients were heavily pretreated and showed a median PFS of 19.1 months and median OS of 32.1 months. Patients that exhibited PRs and those who eventually relapsed were found to have NY-ESO-1 antigen-negative disease, indicating the presence of antigen-escape variants and thus the need to target multiple antigens in the future to overcome tumor escape.[89]

Conclusion

Our increased understanding of the immune system and the availability of targeted reagents has now enabled immunotherapy to impart clinically meaningful responses. Immunotherapy is quickly establishing itself as a critical component of MM therapy. The current availability of various immune-based agents offers the possibility of numerous combinations to maximize their efficacy. Monoclonal antibodies will be incorporated into upfront cytoreductive regimens to deepen the initial response to therapy. Vaccines, in combination with immunomodulatory agents, may serve to achieve and/or maintain minimal residual disease with the hope of potentially prolonging PFS (and possibly OS). Finally, ACT therapy approaches could be integrated into 2 aspects of the treatment paradigm of MM: (1) in combination with high-dose therapy to further consolidate high-risk disease potentially using MILs or TCR ACT approaches where the overall toxicity is minimal or (2) in the setting of fulminant relapsed disease using CARs when there is a need for a rapid reduction in disease burden that would justify the associated toxicity. Whatever the final combination or actual reagents used, it is fair to say that we have now entered into a new era. Immunotherapy will increasingly play a role in MM treatment.

Authorship

Contribution: V.H. and I.B. wrote and edited the manuscript.

Correspondence: Ivan Borrello, Sidney Kimmel Comprehensive Cancer Center at John Hopkins, 1650 Orleans St, CRB-1, Room 453, Baltimore, MD 21231; e-mail: iborrell@jhmi.edu.

References

1. National Cancer Institute statistics. SEER Stat Fact Sheets: Myeloma. Available at: seer.cancer.gov/statfacts/html/mulmy.html. Accessed 10 May 2016.

2. Neri P, Bahlis NJ. Genomic instability in multiple myeloma: mechanisms and therapeutic implications. *Expert Opin Biol Ther.* 2013; 13(Suppl 1):S69-S82.

3. Pratt G, Goodyear O, Moss P. Immunodeficiency and immunotherapy in multiple myeloma. *Br J Haematol.* 2007;138(5):563-579.

4. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med.* 2012;366(26): 2443-2454.

5. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med.* 2015;372(4): 311-319.

6. Gill S, June CH. Going viral: chimeric antigen receptor T-cell therapy for hematological malignancies. *Immunol Rev.* 2015;263(1):68-89.

7. Romano A, Conticello C, Cavalli M, et al. Immunological dysregulation in multiple myeloma microenvironment. *Biomed Res Int.* 2014;2014: 198539.

8. Sotomayor EM, Borrello I, Rattis FM, et al. Cross-presentation of tumor antigens by bone marrow-derived antigen-presenting cells is the dominant mechanism in the induction of T-cell tolerance during B-cell lymphoma progression. *Blood.* 2001; 98(4):1070-1077.

9. Dhodapkar KM, Krasovsky J, Williamson B, Dhodapkar MV. Antitumor monoclonal antibodies enhance cross-presentation ofcCellular antigens and the generation of myeloma-specific killer T cells by dendritic cells. *J Exp Med.* 2002;195(1):125-133.

10. Brown RD, Pope B, Murray A, et al. Dendritic cells from patients with myeloma are numerically normal but functionally defective as they fail to up-regulate CD80 (B7-1) expression after huCD40LT stimulation because of inhibition by transforming growth factor-beta1 and interleukin-10. *Blood.* 2001;98(10):2992-2998.

11. Brimnes MK, Svane IM, Johnsen HE. Impaired functionality and phenotypic profile of dendritic cells from patients with multiple myeloma. *Clin Exp Immunol.* 2006;144(1):76-84.

12. von Boehmer H. Mechanisms of suppression by suppressor T cells. *Nat Immunol.* 2005;6(4): 338-344.

13. Nishikawa H, Sakaguchi S. Regulatory T cells in tumor immunity. *Int J Cancer.* 2010;127(4):759-767.

14. Giannopoulos K, Kaminska W, Hus I, Dmoszynska A. The frequency of T regulatory cells modulates the survival of multiple myeloma patients: detailed characterisation of immune status in multiple myeloma. *Br J Cancer.* 2012; 106(3):546-552.

15. Muthu Raja KR, Rihova L, Zahradova L, Klincova M, Penka M, Hajek R. Increased T regulatory cells are associated with adverse clinical features and predict progression in multiple myeloma. *PLoS One.* 2012;7(10):e47077.

16. Shay G, Hazlehurst L, Lynch CC. Dissecting the multiple myeloma-bone microenvironment reveals new therapeutic targets. *J Mol Med (Berl).* 2016;94(1):21-35.

17. Rodriguez PC, Quiceno DG, Zabaleta J, et al. Arginase I production in the tumor microenvironment by mature myeloid cells inhibits T-cell receptor expression and antigen-specific T-cell responses. *Cancer Res.* 2004;64(16):5839-5849.

18. Botta C, Gullà A, Correale P, Tagliaferri P, Tassone P. Myeloid-derived suppressor cells in multiple myeloma: pre-clinical research and translational opportunities. *Front Oncol.* 2014;4: 348.

19. Görgün G, Calabrese E, Soydan E, et al. Immunomodulatory effects of lenalidomide and pomalidomide on interaction of tumor and bone marrow accessory cells in multiple myeloma. *Blood.* 2010;116(17):3227-3237.

20. Noonan KA, Ghosh N, Rudraraju L, Bui M, Borrello I. Targeting immune suppression with PDE5 inhibition in end-stage multiple myeloma. *Cancer Immunol Res.* 2014;2(8):725-731.

21. Noonan K, Borrello I. The immune microenvironment of myeloma. *Cancer Microenviron.* 2011;4(3):313-323.

22. Jinushi M, Vanneman M, Munshi NC, et al. MHC class I chain-related protein A antibodies and shedding are associated with the progression of multiple myeloma. *Proc Natl Acad Sci USA.* 2008; 105(4):1285-1290.

23. Prabhala RH, Pelluru D, Fulciniti M, et al. Elevated IL-17 produced by TH17 cells promotes myeloma cell growth and inhibits immune function in multiple myeloma. *Blood.* 2010;115(26): 5385-5392.

24. Noonan K, Marchionni L, Anderson J, Pardoll D, Roodman GD, Borrello I. A novel role of IL-17-producing lymphocytes in mediating lytic bone disease in multiple myeloma. *Blood.* 2010; 116(18):3554-3563.

25. Hsi ED, Steinle R, Balasa B, et al. CS1, a potential new therapeutic antibody target for the treatment of multiple myeloma. *Clin Cancer Res.* 2008; 14(9):2775-2784.

26. Collins SM, Bakan CE, Swartzel GD, et al. Elotuzumab directly enhances NK cell cytotoxicity against myeloma via CS1 ligation: evidence for augmented NK cell function complementing ADCC. *Cancer Immunol Immunother.* 2013; 62(12):1841-1849.

27. Guo H, Cruz-Munoz ME, Wu N, Robbins M, Veillette A. Immune cell inhibition by SLAMF7 is mediated by a mechanism requiring src kinases, CD45, and SHIP-1 that is defective in multiple myeloma cells. *Mol Cell Biol.* 2015;35(1):41-51.

28. 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(3):552-559.

29. Lonial S, Dimopoulos M, Palumbo A, et al; ELOQUENT-2 Investigators. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med.* 2015;373(7):621-631.

30. Richardson PG, Jagannath S, Moreau P, et al; 1703 Study Investigators. 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-e527.

31. Palumbo A, Offidani M, Pegourie B, et al. Elotuzumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma: 2-year follow-up. In: Proceedings of the 57th American Society of Hematology; 5-8 December 2015; Orlando, FL. Abstract 510.

32. 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.

33. Malavasi F, Deaglio S, Funaro A, et al. Evolution and function of the ADP ribosyl cyclase/CD38 gene family in physiology and pathology. *Physiol Rev.* 2008;88(3):841-886.

34. Cockayne DA, Muchamuel T, Grimaldi JC, et al. Mice deficient for the ecto-nicotinamide adenine dinucleotide glycohydrolase CD38 exhibit altered humoral immune responses. *Blood.* 1998;92(4): 1324-1333.

35. Sandoval-Montes C, Santos-Argumedo L. CD38 is expressed selectively during the activation of a subset of mature T cells with reduced proliferation but improved potential to produce cytokines. *J Leukoc Biol.* 2005;77(4):513-521.

36. Lonial S, Weiss B, Usmani SZ, 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). In: Proceedings of the American Society of Clinical Oncology (ASCO) Annual Meeting; 29 May-2 June 2015; Chicago, IL. Abstract LBA8512.

37. Chari A, Lonial S, Suvannasankha A, et al. Open-label, multicenter, phase 1b study of daratumumab in combination with pomalidomide and dexamethasone in patients with at least 2 lines of prior therapy and relapsed or relapsed and refractory multiple myeloma. In: Proceedings from the 57th American Society of Hematology (ASH) Annual Meeting; 5-8 December 2015; Orlando, FL. Abstract 508.

38. Dimopoulos M, Oriol A, Nahi H, et al. An open-label, randomised phase III study of daratumumab, lenalidomide, and dexamethasone (DRd) versus lenalidomide and dexamethasone (Rd) in relapsed or refractory multiple myeloma (RRMM): pollux. In: Proceedings from the European Hematology Association 21st Congress; 9-12 June 2016; Copenhagen, Denmark. Abstract LB2238.

39. Palumbo A, Chanan-Khan AA, Weisel K, et al. Phase III randomized controlled study of daratumumab, bortezomib, and dexamethasone (DVd) versus bortezomib and dexamethasone (Vd) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): CASTOR study. In: Proceedings from the American Society of Clinical Oncology (ASCO) Annual Meeting; 2-7 June 2016; Chicago, IL. Abstract LBA4.

40. Raab MS, Chatterjee M, Goldschmidt H, et al. MOR202 alone and in combination with pomalidomide or lenalidomide in relapsed or refractory multiple myeloma: data from clinically relevant cohorts from a phase I/IIa study. In: Proceedings from the American Society of Clinical Oncology (ASCO) Annual Meeting; 2-7 June 2016; Chicago, IL. Abstract 8012.

41. Vij R, Lendvai N, Martin T, et al. A phase Ib dose escalation trial of isatuximab (SAR650984, anti-CD38 mAb) plus lenalidomide and dexamethasone (Len/Dex) in relapsed/refractory multiple myeloma (RRMM): Interim results from two new dose cohorts. In: Proceedings from the American Society of Clinical Oncology (ASCO) Annual Meeting; 2-7 June 2016; Chicago, IL. Abstract 8009.

42. Richter J, Martin T, Vij R, et al. Updated data from a phase II dose finding trial of single agent isatuximab (SAR650984, anti-CD38 mAb) in relapsed/refractory multiple myeloma (RRMM). In: Proceedings from the American Society of Clinical Oncology (ASCO) Annual Meeting; 2-7 June 2016; Chicago, IL. Abstract 8005.

43. Ikeda H, Hideshima T, Fulciniti M, et al. The monoclonal antibody nBT062 conjugated to cytotoxic Maytansinoids has selective cytotoxicity against CD138-positive multiple myeloma cells in vitro and in vivo. *Clin Cancer Res.* 2009;15(12): 4028-4037.

44. Heffner L, Jagannath S, Zimmerman T, 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. In: Proceedings from the 54th American Society of Hematology (ASH) Annual Meeting; 8-11 December 2012; Atlanta, GA. Abstract 4042.

45. Kelly K, Chanan-Khan AA, Heffner L, 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. In: Proceedings from the 56th American Society of Hematology (ASH) Annual Meeting; 6-9 December 2014; San Francisco, CA. Abstract 4736.

46. Voorhees PM, Manges RF, Sonneveld P, et al. A phase 2 multicentre study of siltuximab, an anti-interleukin-6 monoclonal antibody, in patients with relapsed or refractory multiple myeloma. *Br J Haematol.* 2013;161(3):357-366.

47. Orlowski RZ, Gercheva L, Williams C, et al. A phase 2, randomized, double-blind, placebo-controlled study of siltuximab (anti-IL-6 mAb) and bortezomib versus bortezomib alone in patients with relapsed or refractory multiple myeloma. *Am J Hematol.* 2015;90(1):42-49.

48. San-Miguel J, Bladé J, Shpilberg O, et al. Phase 2 randomized study of bortezomib-melphalan-prednisone with or without siltuximab (anti-IL-6) in multiple myeloma. *Blood.* 2014;123(26):4136-4142.

49. Chanan-Khan AA, Wolf J, Garcia J, et al. Efficacy analysis from phase I study of lorvotuzumab mertansine (IMGN901), used as monotherapy, in patients with heavily pre-treated CD56-positive multiple myeloma: a preliminary efficacy analysis. In: Proceedings from the 52nd American Society of Hematology (ASH) Annual Meeting; 4-7 December 2010; Orlando, FL. Abstract 1962.

50. Berdeja J, Hernandez-Ilizaliturri F, Chanan-Khan AA, et al. Phase I study of lorvotuzumab mertansine (LM, IMGN901) in combination with lenalidomide (Len) and dexamethasone (Dex) in patients with CD56-positive relapsed or relapsed/refractory multiple myeloma (MM). In: Proceedings from the 54th American Society of Hematology (ASH) Annual Meeting; 8-11 December 2012; Atlanta, GA. Abstract 728.

51. Lesokhin AM, Ansell SM, Armand P, et al. Preliminary results of a phase I study of nivolumab (BMS-936558) in patients with relapsed or refractory lymphoid malignancies. In: Proceedings from the 56th American Society of Hematology (ASH) Annual Meeting; 6-9 December 2014; San Francisco, CA. Abstract 291.

52. Mateos MV, Orlowski RZ, Siegel D, et al. Pembrolizumab in combination with lenalidomide and low-dose dexamethasone for relapsed/refractory multiple myeloma (RRMM): final efficacy and safety analysis. In: Proceedings from the American Society of Clinical Oncology (ASCO) Annual Meeting; 2-7 June 2016; Chicago, IL. Abstract 8010.

53. Badros A, Kocoglu M, Ma N, et al. A phase II study of anti PD-1 antibody pembrolizumab, pomalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM). In: Proceedings from the 57th American Society of Hematology (ASH) Annual Meeting; 5-8 December 2015; Orlando, FL. Abstract 506.

54. Palumbo A, Mateos MV, San-Miguel J, et al. KEYNOTE-185: a randomized, open-label phase 3 study of pembrolizumab in combination with lenalidomide and low-dose dexamethasone in newly diagnosed and treatment-naive multiple myeloma (MM). In: Proceedings from the American Society of Clinical Oncology (ASCO) Annual Meeting; 2-7 June 2016; Chicago, IL. Abstract TPS8069.

55. Weiss S, Bogen B. B-lymphoma cells process and present their endogenous immunoglobulin to major histocompatibility complex-restricted T cells. *Proc Natl Acad Sci USA.* 1989;86(1):282-286.

56. Yi Q, Dabadghao S, Osterborg A, Bergenbrant S, Holm G. Myeloma bone marrow plasma cells: evidence for their capacity as antigen-presenting cells. *Blood.* 1997;90(5):1960-1967.

57. Thomas AM, Santarsiero LM, Lutz ER, et al. Mesothelin-specific CD8(+) T cell responses provide evidence of in vivo cross-priming by antigen-presenting cells in vaccinated pancreatic cancer patients. *J Exp Med.* 2004;200(3): 297-306.

58. van Mierlo GJ, Boonman ZF, Dumortier HM, et al. Activation of dendritic cells that cross-present tumor-derived antigen licenses CD8+ CTL to cause tumor eradication. *J Immunol.* 2004; 173(11):6753-6759.

59. Lacy MQ, Mandrekar S, Dispenzieri A, et al. Idiotype-pulsed antigen-presenting cells following autologous transplantation for multiple myeloma may be associated with prolonged survival. *Am J Hematol.* 2009;84(12):799-802.

60. Avigan D, Vasir B, Gong J, et al. Fusion cell vaccination of patients with metastatic breast and renal cancer induces immunological and clinical responses. *Clin Cancer Res.* 2004;10(14): 4699-4708.

61. Rosenblatt J, Glotzbecker B, Mills H, et al. PD-1 blockade by CT-011, anti-PD-1 antibody, enhances ex vivo T-cell responses to autologous dendritic cell/myeloma fusion vaccine. *J Immunother.* 2011;34(5):409-418.

62. Condomines M, Hose D, Raynaud P, et al. Cancer/testis genes in multiple myeloma: expression patterns and prognosis value determined by microarray analysis. *J Immunol.* 2007;178(5):3307-3315.

63. van Baren N, Brasseur F, Godelaine D, et al. Genes encoding tumor-specific antigens are expressed in human myeloma cells. *Blood.* 1999; 94(4):1156-1164.

64. Batchu RB, Moreno AM, Szmania SM, et al. Protein transduction of dendritic cells for NY-ESO-1-based immunotherapy of myeloma. *Cancer Res.* 2005;65(21):10041-10049.

65. Rapoport AP, Aqui NA, Stadtmauer EA, et al. Combination immunotherapy after ASCT for multiple myeloma using MAGE-A3/Poly-ICLC immunizations followed by adoptive transfer of vaccine-primed and costimulated autologous T cells. *Clin Cancer Res.* 2014;20(5):1355-1365.

66. Borrello I, Noonan K, Huff CA, et al. Allogeneic myeloma GVAX with lenalidomide enhances progression free survival through the generation of tumor specific immunity in patients in near complete remission. In: Proceedings from the 57th American Society of Hematology (ASH) Annual Meeting; 5-8 December 2015; Orlando, FL. Abstract 4238.

67. Noonan K, Rudraraju L, Ferguson A, et al. Lenalidomide-induced immunomodulation in multiple myeloma: impact on vaccines and antitumor responses. *Clin Cancer Res.* 2012; 18(5):1426-1434.

68. Plesner T, Arkenau H, Lokhorst H, et al. Safety and efficacy of daratumumab with lenalidomide and dexamethasone in relapsed or relapsed, refractory multiple myeloma. In: Proceedings from the 56th American Society of Hematology (ASH) Annual Meeting; 6-9 December 2014; San Francisco, CA. Abstract 84.

69. San-Miguel J, Mateos MV, Shah JJ, et al. Pembrolizumab in combination with lenalidomide and low-dose dexamethasone for relapsed/refractory multiple myeloma (RRMM). In: Proceedings from the 57th American Society of Hematology (ASH) Annual Meeting; 5-8 December 2015; Orlando, FL. Abstract 505.

70. LeBlanc R, Hideshima T, Catley LP, et al. Immunomodulatory drug costimulates T cells via the B7-CD28 pathway. *Blood.* 2004;103(5): 1787-1790.

71. Neuber B, Herth I, Tolliver C, et al. Lenalidomide enhances antigen-specific activity and decreases CD45RA expression of T cells from patients with multiple myeloma. *J Immunol.* 2011;187(2): 1047-1056.

72. Levine BL, Bernstein WB, Connors M, et al. Effects of CD28 costimulation on long-term proliferation of CD4+ T cells in the absence of exogenous feeder cells. *J Immunol.* 1997; 159(12):5921-5930.

73. Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. *N Engl J Med.* 2007; 356(11):1110-1120.

74. Armeson KE, Hill EG, Costa LJ. Tandem autologous vs autologous plus reduced intensity allogeneic transplantation in the upfront management of multiple myeloma: meta-analysis of trials with biological assignment. *Bone Marrow Transplant.* 2013;48(4):562-567.

75. Björkstrand BB, Ljungman P, Svensson H, et al. Allogeneic bone marrow transplantation versus autologous stem cell transplantation in multiple myeloma: a retrospective case-matched study from the European Group for Blood and Marrow Transplantation. *Blood.* 1996;88(12):4711-4718.

76. Noonan KA, Borrello IM. Marrow infiltrating lymphocytes: their role in adoptive immunotherapy. *Cancer J.* 2015;21(6):501-505.

77. Noonan K, Matsui W, Serafini P, et al. Activated marrow-infiltrating lymphocytes effectively target plasma cells and their clonogenic precursors. *Cancer Res.* 2005;65(5):2026-2034.

78. Noonan KA, Huff CA, Davis 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.

79. Maus MV, June CH. CARTs on the road for myeloma. *Clin Cancer Res.* 2014;20(15): 3899-3901.

80. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood.* 2014;124(2): 188-195.

81. Barrett DM, Teachey DT, Grupp SA. Toxicity management for patients receiving novel T-cell engaging therapies. *Curr Opin Pediatr.* 2014; 26(1):43-49.

82. Garfall AL, Maus MV, Hwang WT, et al. Chimeric Antigen Receptor T Cells against CD19 for Multiple Myeloma. *N Engl J Med.* 2015; 373(11):1040-1047.

83. Matsui W, Wang Q, Barber JP, et al. Clonogenic multiple myeloma progenitors, stem cell properties, and drug resistance. *Cancer Res.* 2008;68(1):190-197.

84. Ali SA, Shi V, Wang M, et al. Remissions of multiple myeloma during a first-in-humans clinical trial of T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor. In:

Proceedings from the 57th American Society of Hematology (ASH) Annual Meeting; 5-8 December 2015; Orlando, FL. Abstract LBA-1.

85. Vera J, Savoldo B, Vigouroux S, et al. T lymphocytes redirected against the kappa light chain of human immunoglobulin efficiently kill mature B lymphocyte-derived malignant cells. *Blood.* 2006;108(12):3890-3897.

86. Chu J, He S, Deng Y, et al. Genetic modification of T cells redirected toward CS1 enhances eradication of myeloma cells. *Clin Cancer Res.* 2014;20(15):3989-4000.

87. Jiang H, Zhang W, Shang P, et al. Transfection of chimeric anti-CD138 gene enhances natural killer cell activation and killing of multiple myeloma cells. *Mol Oncol.* 2014;8(2):297-310.

88. Drent E, Groen RW, Noort WA, et al. Pre-clinical evaluation of CD38 chimeric antigen receptor engineered T cells for the treatment of multiple myeloma. *Haematologica.* 2016;101(5):616-625.

89. Rapoport AP, Stadtmauer EA, Binder-Scholl GK, et al. NY-ESO-1-specific TCR-engineered T cells mediate sustained antigen-specific antitumor effects in myeloma. *Nat Med.* 2015;21(8):914-921.