

New Strategies in Multiple Myeloma: Immunotherapy as a Novel Approach to Treat Patients with Multiple Myeloma

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Abstract

Multiple myeloma is a B-cell malignancy characterized by proliferation of monoclonal plasma cells in the bone marrow. Although new therapeutic options introduced in recent years have resulted in improved survival outcomes, multiple myeloma remains incurable for a large number of patients, and new treatment options are urgently needed. Over the last 5 years, there has been a renewed interest in the clinical potential of immunotherapy for the treatment of multiple myeloma. Clinical progression of myeloma is known to be associated with progressive immune dysregulation and loss of immune surveillance that contribute to disease progression in association with progressive

genetic complexity, rendering signaling-based treatments less effective. A variety of strategies to reverse the multiple myeloma-induced immunosuppression has been developed either in the form of immunomodulatory drugs, checkpoint inhibitors, mAbs, engineered T cells, and vaccines. They have shown encouraging results in patients with relapsed refractory multiple myeloma and hold great promise in further improving patient outcomes in multiple myeloma. This review will summarize the major approaches in multiple myeloma immunotherapies and discuss the mechanisms of action and clinical activity of these strategies. *Clin Cancer Res*; 22(24); 5959–65. ©2016 AACR.

Background

Multiple myeloma is a neoplasia of terminally differentiated B cells (plasma cells), characterized by clonal expansion of plasma cells in the bone marrow and often complicated by osteolytic bone disease, infections, renal insufficiency, and bone marrow failure (1). Despite important advances in the treatment of multiple myeloma due to the introduction of immunomodulatory drugs (IMiD; ref. 2) and proteasome inhibitors (3), which have resulted in improved survival, multiple myeloma remains an incurable disease, and there is an urgent need for new therapeutic approaches.

Over the last 5 years, a better understanding of multiple myeloma biology and its immune dysregulation together with the development of several immune-based therapies have led to a renewed interest in the clinical potential of immunotherapy for the treatment of this disease.

Three main immunotherapeutic strategies are currently in development for multiple myeloma:

- (i) agents that reverse tumor-mediated immune paralysis, such as IMiDs and immune checkpoint inhibitors.
- (ii) agents that selectively target the malignant clone in the form of mAbs.

- (iii) agents that activate immune cells to target the tumor, such as chimeric antigen receptor (CAR) T cells, bispecific T-cell engagers (BiTE), and multiple myeloma vaccines.

The premise for utilizing immunotherapy in multiple myeloma is based on the fact that this disease is characterized by generalized immune suppression that contributes to susceptibility to infection, loss of immune surveillance, and tumor progression (4, 5). It is well established that in multiple myeloma, this "immunoparesis" is characterized by the loss of T-cell repertoire [regulatory T cells (Tregs) and Th-17], inhibition of antigen-presenting cells, such as dendritic cells (DC; refs. 6, 7), and increased presence of inhibitor pathways, such as the programmed death receptor-1/programmed death-ligand 1 (PD-1/PD-L1; ref. 8), that leads to immune suppression. The bone marrow microenvironment creates a protective niche maintained by the complex interplay of stromal elements and tumor cells that, through the secretion of cytokines and growth factors, promote disease progression and facilitate immune escape (9, 10). The interplay of TGFβ and IL6 affects generation of Th17 cells both directly or via engagement of other proinflammatory cytokines and, therefore, leads to immune deficiency in multiple myeloma (11). Myeloid-derived suppressor cells (MDSC) play a central role in mediating suppression of multiple myeloma-specific T-cell responses by induction of T-cell anergy and Treg development in the bone marrow (12). MDSCs are increased in patients with multiple myeloma and have bidirectional interactions with tumor cells that promote tumor growth by suppressing adaptive immunity and contribute to chemotherapy resistance (13, 14). Plasmacytoid DCs (pDC) are also involved in protective immunity and tumor immune escape (15). Chauhan and colleagues (10) found increased numbers of pDCs in the bone marrow of patients with multiple myeloma, where, by direct interaction with multiple myeloma cells and production of soluble factors, the pDCs promote multiple myeloma cell growth and confer drug resistance.

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To overcome this drug resistance, a number of therapeutic approaches have been developed in recent years (16). This review will summarize the major immunotherapeutic approaches available in the treatment of multiple myeloma and review the encouraging clinical results observed to date.

On the Horizon

Several innovative approaches to reverse multiple myeloma-induced immunosuppression have been explored and can be divided in three major categories: agents that reverse tumor-mediated immune paralysis, agents that target the tumor, and agents that activate immune cells to target the tumor (Fig. 1).

Agents that reverse tumor-mediated immune paralysis

Multiple myeloma is associated with progressive immune dysregulation, resulting in a tumor microenvironment that promotes disease tolerance and progression. The upregulation of negative costimulatory signals induces a state of T-cell exhaustion and blocks T-cell-mediated killing of multiple myeloma (17). Immune checkpoint pathways that help maintain immune equilibrium in health are also upregulated in the presence of malignant plasma cells, fostering a state of immune tolerance (18). This understanding has led to the development of adjuvant immune-based therapies that, by activating stimulatory molecules or alternatively blocking inhibitory molecules, can act as immune boosters and enhance or unleash preexisting anticancer immune responses. One of the first examples of a biological modifier with both antiproliferative and immunomodulating properties used to treat multiple myeloma was IFN α . It has been used for more than 30 years in clinical practice, with single-agent response rate of 20% (19), but with moderate improvement in survival (20). To date, its wide clinical adoption in multiple myeloma has been limited due to its known toxicity and the availability of novel immunotherapeutics.

IMiDs. IMiDs, such as thalidomide, lenalidomide, and pomalidomide, exert significant activity in the treatment of multiple myeloma (2, 21, 22). They are recognized to bind to cereblon and induce degradation of transcriptional factors Ikaros and Aiolos (23). They have multifaceted mechanisms of action by mediating tumor cell killing via Myc and IRF4 downregulation (24) and enhancing immune function. In an Aiolos-dependent mechanism, IMiDs stimulate IL2 production, which in turn triggers the expansion of T cells as well as the activation and proliferation of natural killer (NK) cells. T and NK cells release IFN γ , which can induce the activation of DCs (25–27). They are also known to reduce the function of Tregs (28). Of note, Sehgal and colleagues (29) demonstrated *in vivo* the ability of pomalidomide to induce polyfunctional T-cell activation, with increased proportion of coinhibitory receptor BTLA⁺ T cells and Tim-3⁺ NK cells. These immunomodulatory effects are rapid, involve both adaptive and innate immunity, and correlate with clinical outcome, even in heavily pretreated multiple myeloma patients. These properties make IMiDs an attractive backbone in combination regimens with other immune-based therapies. The clinical effects of these combinations are discussed in more detail below.

Immune checkpoint inhibitors (PD-1/PD-L1 axis). PD-1 is a type I transmembrane protein expressed on the surface of activated T cells that, interacting with its ligands, PD-L1 and PD-L2, acts as an immunologic checkpoint to suppress antitumor immunity (30). Several studies have shown that PD-1 is largely expressed on tumor-infiltrating T cells and PD-L1 is detected on many different tumor cells, including multiple myeloma (18). PD-L1 expression on multiple myeloma cells is significantly upregulated compared with cells from patients with MGUS or healthy volunteers, and it increases with disease progression (31), allowing tumor cells to escape from host immune response. The interaction of PD-1⁺ T cells with PD-L1-expressing cells inhibits T-cell responses, by suppressing the secretion of stimulatory cytokines by T cells and by inhibiting tumor-reactive CD8⁺ cytotoxic T lymphocytes

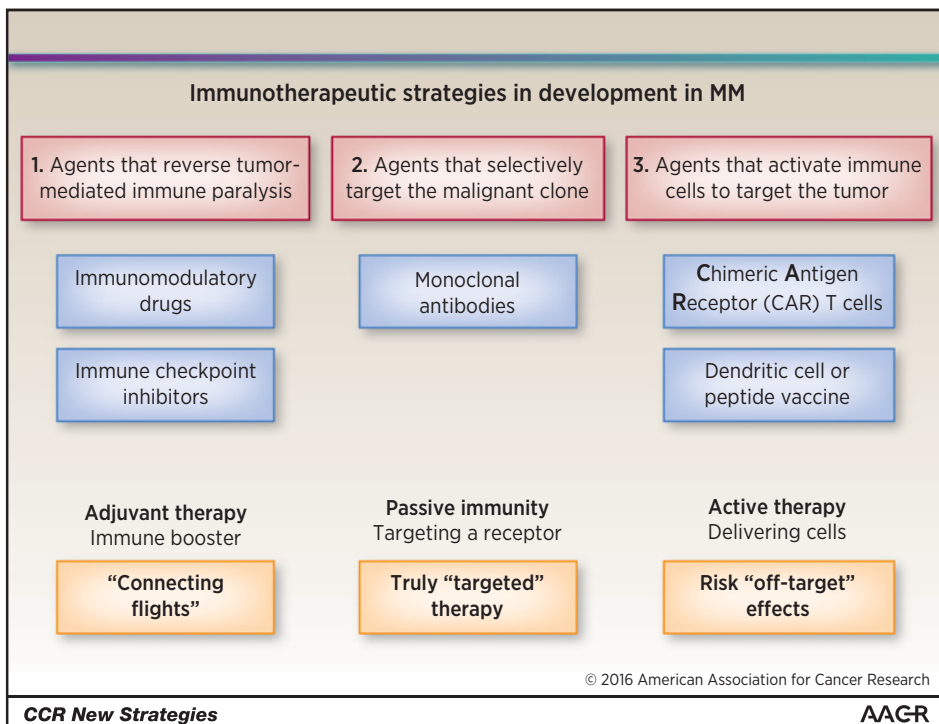


Figure 1. Immunotherapeutic strategies in development in multiple myeloma (MM). Myeloma immunotherapy agents may be broadly categorized into these three categories shown here.

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(32, 33). Recent work by Gorgun and colleagues (34) also demonstrated that PD-1/PD-L1 blockade induces anti-multiple myeloma immune response and lenalidomide further enhances effector cell-mediated cytotoxicity, providing the framework for clinical evaluation of combination therapy. At present, there are multiple clinical trials exploring the use of checkpoint inhibitors in patients with relapsed/refractory multiple myeloma (RRMM). Preliminary results of several phase I studies (35, 36) exploring the use of checkpoint inhibitors as single agents were disappointing, with no objective responses in patients with multiple myeloma, confirming the need for combinatory studies to antagonize additional inhibitory signals (37). Pembrolizumab is a highly selective anti-PD-1 mAb that has been recently evaluated in patients with RRMM in combination with IMiDs, due to their ability to enhance multiple myeloma-specific cytotoxic T cells. Preliminary results of a phase I trial exploring the safety, tolerability, and efficacy of pembrolizumab in combination with lenalidomide (Len)/dexamethasone (Dex) showed promising efficacy in heavily pretreated RRMM. The objective response rate (ORR) was 76%, including very good partial response (VGPR) and partial response (PR) also in patients with IMiD-refractory and double refractory disease (38). The combination also has a tolerable safety profile. The most common adverse events were anemia, pneumonia, neutropenia, thrombocytopenia, hyperglycemia, and dyspnea, and the immune-related side effects included pneumonitis, hypothyroidism, and hepatitis. Promising results are also expected from the phase II study evaluating the safety and efficacy of pembrolizumab with pomalidomide and dexamethasone in RRMM. Early evidence of deep, durable responses were observed in this heavily treated population. The ORR was 59% in all cohort of patients, and 50% in patients double refractory to proteasome inhibitors and IMiDs (39). The anti-PD-1 antibody nivolumab, alone or in combination with the CTLA4-blocking antibody ipilimumab or the killer cell immunoglobulin-like receptor-blocking antibody lirilumab, is also under evaluation in a phase I clinical trial in relapsed or refractory hematologic malignancies, including multiple myeloma (NCT01592370).

Immunotherapy agents targeting the tumor

mAbs. Direct targeting of the tumor has largely focused on the development of mAbs. This strategy is the most widely used form of cancer immunotherapy today and is a form of passive immunotherapy, as mAbs do not always require the patient's cellular immunity to take an active role in fighting the cancer, such is the case for mAbs capable of inducing complement-dependent cytotoxicity (CDC) and crosslinking-mediated apoptosis. It is considered a truly targeted therapy where the mAb is directed to a single target on a cancer cell, usually an antigen or a receptor site on the cancer cell, or it is directed at a cancer-specific enzyme or protein. Therefore, this approach depends on targets whose expression is relatively restricted to tumor cells and acts by coating tumor cells and promoting antibody-dependent mechanisms of cell death, including antibody-dependent cell-mediated cytotoxicity (ADCC) and CDC (40). For the purpose of this review, we will focus on the two mAbs that have already demonstrated promising clinical activity in multiple myeloma.

Elotuzumab (Elo) is a humanized mAb that specifically targets signaling lymphocytic activation molecule family member 7 (SLAMF7)—also known as CS1—a glycoprotein highly expressed on multiple myeloma and NK cells (41). It exerts a dual mechanism of action by directly activating NK cells and tumor cell

death via ADCC (42). As a single agent, elotuzumab has shown modest activity (43); recently, however, elotuzumab was combined with lenalidomide and dexamethasone and demonstrated encouraging results. The ELOQUENT-2 trial, a phase III randomized study comparing the efficacy and safety of Len-Dex with or without elotuzumab in RRMM patients, showed that the combination of Elo-Len-Dex demonstrated an ORR of 79% versus 66% in the Len-Dex arm and resulted in an extended progression-free survival (PFS) as compared with the control arm (19.4 months vs. 14.9 months, respectively), reducing the risk of progression or death by 30%. This benefit maintained regardless of patient age, number of prior lines of therapies, previous exposure to lenalidomide, or the presence of high-risk cytogenetics (44). On the basis of these results, elotuzumab was approved by the FDA in November 2015 for use with lenalidomide/dexamethasone in patients with RRMM and one to three prior therapies. A recent update of the ELOQUENT-2 trial also showed that at 3-year follow-up, patients receiving elotuzumab had 27% reduction in risk of progression or death versus lenalidomide/dexamethasone alone and had a median delay of 1 year in time to next treatment (45). Concerning safety profile, the most common side effects were lymphocytopenia, neutropenia, and fatigue. Infusion reactions to elotuzumab occurred in 10% of patients and were of mild grade. In a phase II trial patients who received elotuzumab in combination with bortezomib and dexamethasone showed an ORR of 66% versus 63% in patients treated with bortezomib and dexamethasone alone. The PFS was 9.7 months in the elotuzumab arm versus 6.9 months in the bortezomib arm (46). Infusion reactions occurred in 7% of patients in the elotuzumab arm, and the most common side effects were thrombocytopenia and infections.

Daratumumab is a humanized anti-CD38 mAb that not only targets tumor cells but also mediates the killing of CD38-expressing plasma cells via ADCC, antibody-dependent phagocytosis, CDC, and apoptosis (47). It also has an immunomodulatory mechanism of action due to its ability to induce the depletion of CD38⁺ immunosuppressive cells, which is associated with an increase in Th cells, cytotoxic T cells, T-cell functional response, and T-cell receptor (TCR) clonality (48). CD38 is an attractive target for immunotherapy treatment due to its high and uniform expression on multiple myeloma cells (49) and relatively low expression on normal lymphoid and myeloid cells and in some nonhematopoietic cells (50). As a single agent, in the phase II SIRIUS trial, daratumumab demonstrated an ORR of 29% and a median PFS of 3.7 months in patients with RRMM, all of whom had prior exposure to bortezomib and lenalidomide. The median time to response among responders was 1 month, and the median duration of response was 7.4 months (51). Patients experienced modest infusion-related reactions and manageable hematologic toxicity. On the basis of its favorable toxicity profile and efficacy, daratumumab was approved by the FDA in November 2015 for use in multiple myeloma patients with ≥ 3 prior therapies. Recent results of a phase I/II study (GEN503) of daratumumab in combination with lenalidomide/dexamethasone showed rapid, deep, and durable responses in RRMM patients. The ORR was 81%, including a 28% VGPR and a 34% complete response (CR)/stringent complete response (sCR), with a median follow-up of 15.6 months. At 18 months, the PFS was 72%, and the OS was 90%. The toxicity profile was similar to that reported by studies of daratumumab monotherapy (52). Two phase III studies of daratumumab are currently ongoing: one of daratumumab in

combination with lenalidomide and dexamethasone versus lenalidomide and dexamethasone (MMY3003) and one of daratumumab in combination with bortezomib and dexamethasone (DvD) versus bortezomib and dexamethasone alone (Vd; MMY3004). Preliminary results of the MMY3003 study showed an unprecedented 63% reduction in the risk of progression or death in the daratumumab group compared with the lenalidomide and dexamethasone group. The ORR was 93% in the daratumumab group compared with 76% in the control group. Deep and durable responses were significantly more frequent in the daratumumab group, with higher rates of VGPR or better (76% vs. 44%) and a more than doubling of CR or better (43% vs. 19%). Median PFS had not been reached in the daratumumab arm and was 18.4 months in the control arm. Treatment was well tolerated in the daratumumab group, with adverse events consistent with the known profiles of the drugs in the combination (53). Promising results are also observed in the MMY3004 study, where daratumumab was added to the standard bortezomib and dexamethasone. With a median follow-up of 7.4 months, daratumumab significantly improved median PFS (61% reduction in risk of progression) and TTP for DvD versus bortezomib and dexamethasone. It significantly increased ORR (83% vs. 63%) and doubled rates of \geq VGPR (59% vs. 29%) and \geq CR (19% vs. 9%) for DvD versus Vd, respectively; median duration of response was not reached (NR) versus 7.9 months, respectively. Safety of DvD is consistent with the known safety profile of daratumumab and Vd (54). The combination of daratumumab with pomalidomide and dexamethasone is also being evaluated in an ongoing phase I trial. An early analysis showed rapid initial responses that are deepening over time. The ORR was 71% and 67% in patients double refractory to proteasome inhibitors/IMiDs, and the combination showed a tolerable safety profile (55). Additional trials investigating various daratumumab-based regimens for patients with newly diagnosed multiple myeloma are also ongoing, and results are eagerly awaited.

A summary of additional mAbs currently in clinical development for RRMM in combination with proteasome inhibitor or IMiD-based regimens is shown in Table 1.

Agents that activate immune cells to target the tumors

The detection of a graft-versus-myeloma effect exerted by donor-derived T lymphocytes after allogeneic stem cell transplantation (56) has demonstrated that multiple myeloma cells are susceptible to cellular immunity, but this immunologic efficacy is as yet insufficient to provide a clearly recognizable benefit for patients. With the aim of stimulating the immune system of multiple myeloma patients, several approaches to active immunotherapy have been explored. For the purpose of this review, data obtained on the use of CAR T cells and vaccine therapy against defined multiple myeloma-associated antigens will be reviewed.

CAR T cells. CAR T cells engineered to target antigens expressed on multiple myeloma cells also represent a promising new area of exploration. They lead to direct multiple myeloma cell killing and T-cell immunity stimulation. Autologous transplantation followed by treatment with CAR T cells against CD19 (CTL019) demonstrated significant activity in a patient with refractory multiple myeloma. It led to a CR lasting longer than previous remissions, but with subsequent relapse (57). Prom-

Table 1. Summary of additional mAbs under investigation in multiple myeloma

mAb	Target	Combination	Phase
Tabalumab	BAFF		II
Isatuximab	CD38	Len/Dex CFZ Pom/Dex	I
Indatuximab	CD138	Len/Dex	I/II
Milatumumab	CD74		I/II
MORO3087	CD38		I/II
Pidilizumab	PD-1	Len	I/II
Pembrolizumab	PD-1	Len/Dex Pom	I/II
Nivolumab	PD-1	Lirilumab	I
Atezolizumab	PD-L1	Len	I
Lirilumab	KIR	Elotuzumab	I
Urelumab	CD137	Elotuzumab	I

Abbreviations: Dex, dexamethasone; CFZ, carfilzomib; Len, lenalidomide; Pom, pomalidomide.

ising results are also coming from CAR T-cell therapy targeting BCMA, the B-cell maturation antigen expressed by normal and malignant plasma cells. Preliminary results of a phase I trial of the CAR-BCMA in patients with advanced multiple myeloma showed strong anti-multiple myeloma activity at higher dose levels, with durable sCR achieved in two patients with a high disease burden and chemotherapy-resistant disease. Substantial but reversible toxicity was observed. This included cytopenias attributable to chemotherapy, fever, and signs of cytokine-release syndrome (58). Additional studies of other CAR T-cell therapies targeting CD38, CD138, and CS1 are currently under evaluation in clinical trials.

Despite promising results, resistance and short duration of response is often noted with CAR-based immunotherapy. Loss of the CAR-specific antigen or limited proliferation of CAR T cells *in vivo* is often observed due to their inefficient activation or inhibition due to immunosuppressive microenvironment within the tumor stroma (59). This challenge seems to apply even more to multiple myeloma due to its phenotypic heterogeneity and the relative paucity of tumor-specific markers. To overcome these challenges, novel CAR designs are currently being tested, including an introduction of additional motifs from various costimulatory molecules into the intracellular chain of CAR or cotransduction of T cells with genes encoding for essential pro-survival T-cell cytokines (60).

BiTEs. BiTEs are generated to combine specificities of two antibodies by simultaneously binding to multiple epitopes, one of which involves the activation of T cells via their CD3 molecules (61). The first bispecific antibody generated specifically against multiple myeloma was developed by combining single-chain variable fragments (ScFv) of a mAb that binds normal and malignant plasma cells (Wue-1) and a mAb against CD3 (62). This led to design and development of other BiTEs. A promising molecule, currently under clinical investigation, targets BCMA via a defucosylated antibody that is conjugated to the monomethyl aurastatin F (MMAF). This antibody is currently under investigation in a phase I trial in patients with RRMM (NCT02064387).

Vaccine therapy. Another major area of investigation is the use of cancer vaccines to elicit a tumor-specific immune response without the need for alloreactive lymphocytes. Various strategies have been examined and can be broadly divided into noncellular approaches using antigen-specific peptides and cellular techniques using tumor lysates and whole-cell DCs (63, 64). Idiotype

proteins, derived from the variable region of the clonal immunoglobulin, were some of the first antigenic targets investigated. Unfortunately, due to the poor immunogenic nature of the protein and the low expression of these proteins on the plasma cell surface, this approach did not meet expectations. On the other hand, subsequent identification of tumor-associated antigens such as MAGE, hTERT, WT-1, XBP-1, CS1, and CTA as targets was able to generate cellular responses when used in preclinical studies (65, 66), but the clinical outcome is still lacking. Efforts to enhance the immunogenicity of these vaccines by combining T-cell therapy are currently ongoing.

The second vaccination approach involves patient-derived multiple myeloma cells fused with autologous DCs to take advantage of the ability of DCs to present several antigens from the cell to the host (67). In a phase I and II trial, this approach resulted in the expansion of autologous multiple

myeloma-specific T cells, was well tolerated, and demonstrated CRs in a quarter of the patients (68). A National Clinical Trials Network study (BMT CTN 1401) is currently underway, evaluating the efficacy of the DC/tumor vaccine with or without the presence of IMiDs in the post-autologous stem cell transplant setting.

A summary of novel immunotherapeutic targets and treatment options discussed in this review article is shown in Fig. 2.

Closing Remarks

The landscape of multiple myeloma treatment continues to change as we develop a deeper understanding of multiple myeloma biology and its tumor microenvironment, including host immunity. In this article, we have discussed the anti-multiple myeloma activities of a variety of immunotherapy agents and

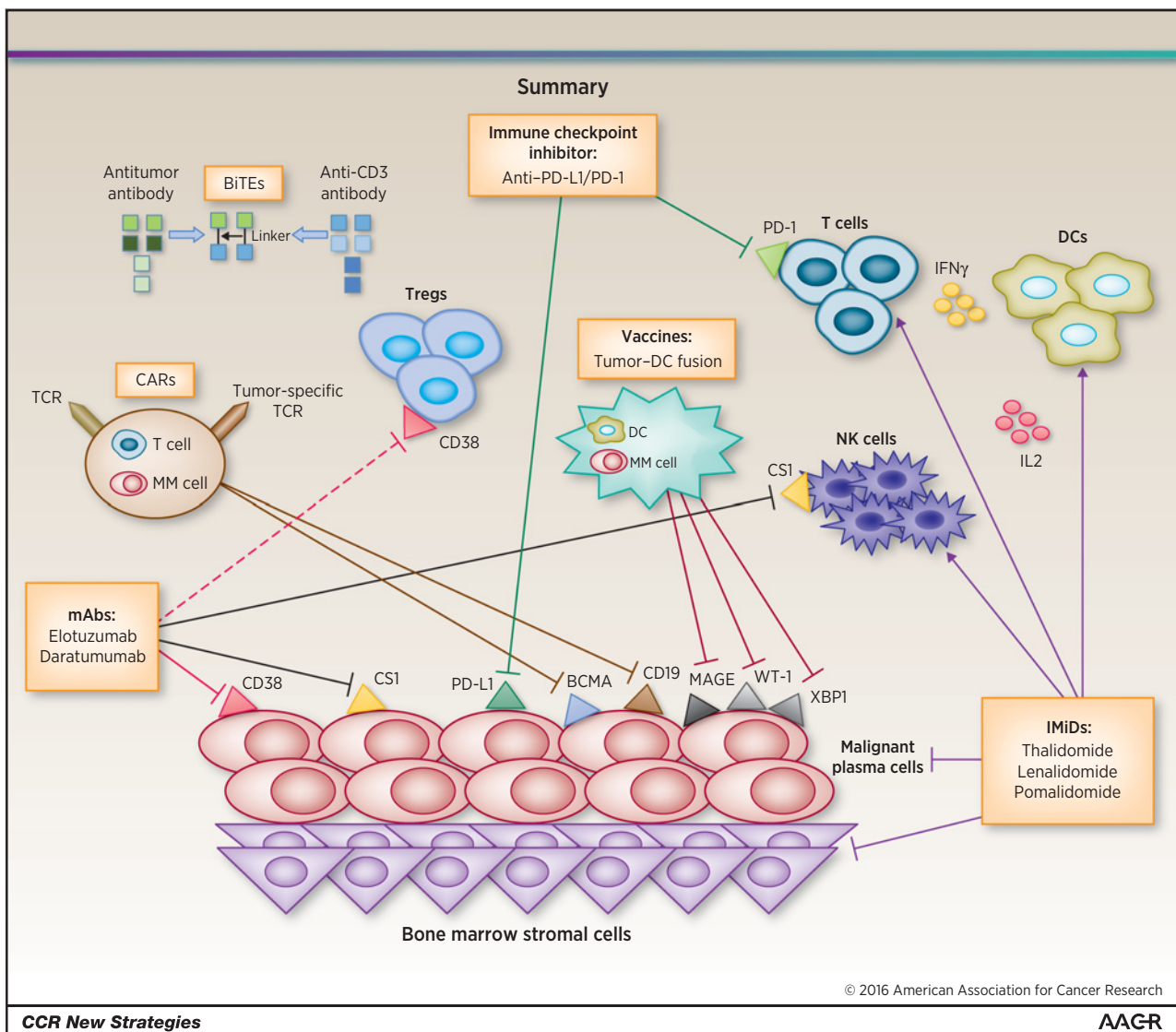


Figure 2. Overview of novel immunotherapeutic approaches in multiple myeloma (MM). Shown here are the cellular components of the bone marrow microenvironment and host immunity. The novel immunotherapeutic targets and treatment options discussed in this review article are highlighted here.

clearly established immunotherapy as an important treatment modality for patients with multiple myeloma. This approach holds the promise of selective targeting of malignant cells and the induction of a sustained response due to ongoing immune surveillance. Understanding the primary factors contributing to the immunosuppressive milieu in multiple myeloma is critical to achieve this goal. mAbs, checkpoint inhibitors, engineered T cells, and vaccines hold promise as exciting treatment options. In the future, further improvements in clinical outcomes and cures are expected with the combination of these immunotherapy strategies. As such, the use of combination therapies that at different levels stimulate an effective anti-multiple myeloma immune response should be incorporated into the early treatment of the disease to improve therapeutic efficacy and prevent progression to active disease. Identification of robust predictive biomarkers that can accurately measure determinants of immune responsiveness of tumors is also needed to guide development and personalization of combination immunotherapy strategies that will ultimately improve patient outcomes.

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Disclosure of Potential Conflicts of Interest

N.J. Bahlis reports receiving speakers bureau honoraria from Amgen, Celgene, and Janssen and is a consultant/advisory board member for Celgene and Janssen. S. Lonial is a consultant/advisory board member for Bristol-Myers Squibb, Celgene, Janssen, Merck, Millennium, Novartis, and Onyx. No potential conflicts of interest were disclosed by the other author.

Authors' Contributions

Conception and design: P. Neri, N.J. Bahlis, S. Lonial
 Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Lonial
 Writing, review, and/or revision of the manuscript: S. Lonial
 Study supervision: P. Neri
 Other (wrote and edited the manuscript): N.J. Bahlis

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