

Lessons Learned from Checkpoint Blockade Targeting PD-1 in Multiple Myeloma

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Abstract

Immune checkpoints and agonists modulate ongoing, antigen-specific immune responses. Therapeutic blockade of CTLA-4, PD-1, and PD-L1 has proven to be an effective treatment approach for a subset of patients with a variety of cancers of epithelial, mesenchymal, or hematologic origin. In multiple myeloma, a B-cell lymphoid malignancy of terminally differentiated plasma cells, PD-1 pathway blockade is ineffective as a single agent. The initial promise in

combination approaches utilizing anti-PD-1 with the immunomodulatory drugs, lenalidomide or pomalidomide, was not confirmed in randomized trials. Here, we explore available data for and against manipulation of the PD-1 pathway and other immune checkpoints in myeloma and highlight several promising concepts and challenges that face ongoing development of immunotherapeutics for this disease.

Introduction

A broad range of infectious challenges can be eradicated by the immune system and elicit personalized long-term memory for future protection of the individual from rechallenge. Tumor immunologists have sought to translate observations from antimicrobial immune responses into therapies that elicit similar responses against self-derived cancer cells and that lead to long-lasting disease control. A recent focus on mechanisms of tolerance mediated by immune checkpoints has transformed cancer immunotherapy. The 2018 Nobel Prize in Medicine was awarded to James Allison for his discovery of the mechanism of action of CTLA-4 (the prototypical immune checkpoint) and to Tasuku Honjo for his discovery of the PD-1 receptor. Rapid clinical investigation focused on targeting immune checkpoints, especially with PD-1 pathway inhibitors, has revealed significant clinical activity in patients with various cancer types (1). Further combinatorial approaches built on knowledge of the human immune response, which have been derived from basic research, will continue to expand the benefits of immunotherapy to a growing number of patients with cancer. However, experience with checkpoint blockade in multiple myeloma (MM) has revealed some of the challenges of investigating immune modulators in a cancer with immune cell origin. Here, lessons from combination therapy approaches utilizing immune-checkpoint blockade (ICB), immunomodulatory

drugs (IMiD), and monoclonal antibodies will be reviewed.

Immune Checkpoints and Cancer Therapy

T-cell receptor (TCR) engagement with a specific peptide presented by MHC on antigen-presenting cells (APC) licenses T-cell activation. Interactions with additional signals, known as costimulation, shape the resulting effector and memory response. The classic costimulatory receptor on T cells is CD28, which engages B7 family members on APCs. This results in activation, proliferation, and secretion of cytokines. Activating costimulatory receptors on the T-cell surface such as ICOS, 4-1BB, or OX40 and inhibitory receptors such as CTLA-4, PD-1, or LAG-3 act to further augment or diminish T-cell responses (2). The inhibitory receptors, also known as immune checkpoints, are thought to mediate peripheral tolerance to antigens.

Initial studies of anti-CTLA4 revealed unique toxicities and novel response kinetics, including durable responses in sensitive patients. Key biomarker studies in solid tumor malignancies treated with ICB have lent mechanistic insight into how these agents work in the clinic. Analysis of baseline tumor-intrinsic factors (tumor mutation burden, PD-L1 expression, tumor antigen presentation machinery, and IFN γ responsiveness), immune microenvironment factors (tumor immune infiltrate—"cold" vs. "hot" tumors), and host factors (microbiome, FC γ R polymorphisms, and HLA haplotype) can predict sensitivity to ICB (extensively reviewed in ref. 3). However, it remains to be seen if these factors can be evaluated in a coordinated fashion to guide treatment decisions in patients.

ICB therapies in hematologic malignancies have also shown promise, especially in classic Hodgkin lymphoma (cHL). PD-1 blockade with nivolumab or pembrolizumab has been approved by the FDA for treatment of relapsed cHL based on high response rates (4). Tumor-intrinsic PD-L1/L2 upregulation via gene amplification of the 9p24.1 locus in cHL may be a potential driver of sensitivity to PD-1 pathway blockade. MHC II expression on Reed-Sternberg (RS) cells also correlates with survival in cHL, suggesting CD4⁺ T-cell activity is important (5).

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Table 1. Selected ongoing studies utilizing ICB

NCI identifier	Trial title	Phase	Status	Patient cohort
NCT01592370	An Investigational Immuno-Therapy Study to Determine the Safety and Effectiveness of Nivolumab and Daratumumab in Patients with Multiple Myeloma	I	Open	Relapsed
NCT02431208	A Study of Atezolizumab (Anti-Programmed Death-Ligand 1 [PD-L1] Antibody) Alone or in Combination with an Immunomodulatory Drug and/or Daratumumab in Participants with Multiple Myeloma (MM)	Ib	Open	Relapsed
NCT03267888	Pembrolizumab and Radiation Therapy in Patients with Relapsed or Refractory Multiple Myeloma	I	Open	Relapsed
NCT03168438	NY-ESO-1 ^{4259T} Alone and in Combination with Pembrolizumab for Multiple Myeloma	II	Open	Relapsed
NCT03292263	ASCT with Nivolumab in Patients with Multiple Myeloma	I/II	Open	Newly diagnosed or relapsed
NCT03605719	Dexamethasone, Carfilzomib, and Nivolumab with Reovirus for Relapsed/Refractory Multiple Myeloma	I	Open	Relapsed
NCT03184194	Nivolumab Combined with Daratumumab with or without Low-Dose Cyclophosphamide	II	Open	Relapsed
NCT03634800	Radiotherapy with Immunotherapy for Systemic Effect in Myeloma (RISE-M) (RISE-M)	II	Open	Relapsed
NCT02681302	Check Point Inhibition after Autologous Stem Cell Transplantation in Patients at High Risk of Posttransplant Recurrence (CPIT001)	I/II	Open	Relapsed
NCT03312530	A Study of Cobimetinib Administered as Single Agent and in Combination with Venetoclax, with or without Atezolizumab, in Participants with Relapsed and Refractory Multiple Myeloma	I/II	Open	Relapsed
NCT03111992	Study of Single-Agent CJM112, and PDR001 in Combination with LCL161 or CJM112 in Patients with Multiple Myeloma	I	Open	Relapsed
NCT03194867	Isatuximab in Combination with Cemiplimab in Relapsed/Refractory Multiple Myeloma (RRMM) Patients	I/II	Open	Relapsed
NCT03782064	Dendritic Cell (DC)/Myeloma Fusions in Combination with Nivolumab in Patients with Relapsed Multiple Myeloma	II	Open	Relapsed

However, antigen presentation is often absent on RS cells due to mutations in β_2 -microglobulin (β_2M) or *CIITA* translocations, which limit expression of MHC I or II, respectively (4). Other non-Hodgkin lymphoma subtypes, such as primary mediastinal B-cell lymphoma, testicular lymphoma, and CNS lymphoma, have demonstrated evidence of PD-L1/L2 expression driven by 9p24.1 gene amplification and appear to also be sensitive to PD-1 blockade (4). Hints of clinical activity for single-agent PD-1 blockade in several non-Hodgkin lymphoma subtypes and in a few combinatorial strategies in acute myeloid leukemia have been seen, but limited activity has been a more common observation, and in some T-cell malignancies, increased disease progression raises the possibility that PD-1 blockade may be harmful (6–8). These clinical and correlative observations highlight major differences in the cell of origin of the tumor and the tumor microenvironment that distinguish treatment response in hematologic cancers from solid tumors.

The current challenge is how to incorporate ICB into immunologically sound combination therapies in a disease- and patient-specific manner. There are currently more than 1,000 trials evaluating ICB in combination with traditional chemotherapy, tumor microenvironment-directed agents, or cellular therapies across all cancers. A variety of combination approaches in MM have also been pursued (Table 1; Supplementary Table S1).

Immune Pathogenesis and Immune Surveillance in Myeloma

Chronic immune stimuli can potentially be a contributing driver of MM pathogenesis (Fig. 1). Development of plasma cell disorders has been linked with autoimmune disorders (9), obesity (10), and antibody response against phosphorylated

self-antigens. Analysis of paraprotein reactivity in patients with monoclonal gammopathy of unknown significance (MGUS)/MM identified that 4%, 15%, and 37% of individuals of Japanese, European, and African American descent, respectively, had reactivity to a hyperphosphorylated version of SLP-2, the most common of these phosphoantigens (11). A group of investigators also found that long-term stimulation of lipid-reactive NKT cells may be involved in the pathogenesis of one-third of sporadic MGUS and MM (12).

The malignant plasma cells found in MM and MGUS are genetically similar, supporting the notion that evolution to MM may require escape from immunosurveillance. Robust T-cell immune responses to MM antigens are detectable in the bone marrow of MGUS, but not MM patients (13). Loss of immunity to the embryonic stem cell antigen SOX2 correlates with progression of MGUS or smoldering MM (SMM) to MM (14). Malignant plasma cells also secrete larger amounts of soluble (s)MICA, a ligand for NKG2D, with progression of MGUS to MM, which is associated with decreased natural killer cell and CD8⁺ T-cell function (15). These observations suggest that restoring CD8⁺ T-cell and NK cell immunity against malignant plasma cells may be therapeutically beneficial.

Immune Checkpoints in Myeloma: Preclinical Studies

In mouse models, adoptive transfer of expanded PD-1⁺ T cells can eliminate established MM, suggesting these are antigen exposed (16). A combination of transplantation, whole-cell vaccination, and PD-L1 inhibition has also demonstrated preclinical efficacy (17). However, PD-1 blockade alone is not efficacious. CD137 agonists and other checkpoint inhibitors, such as anti-TIGIT, do appear to have efficacy in certain

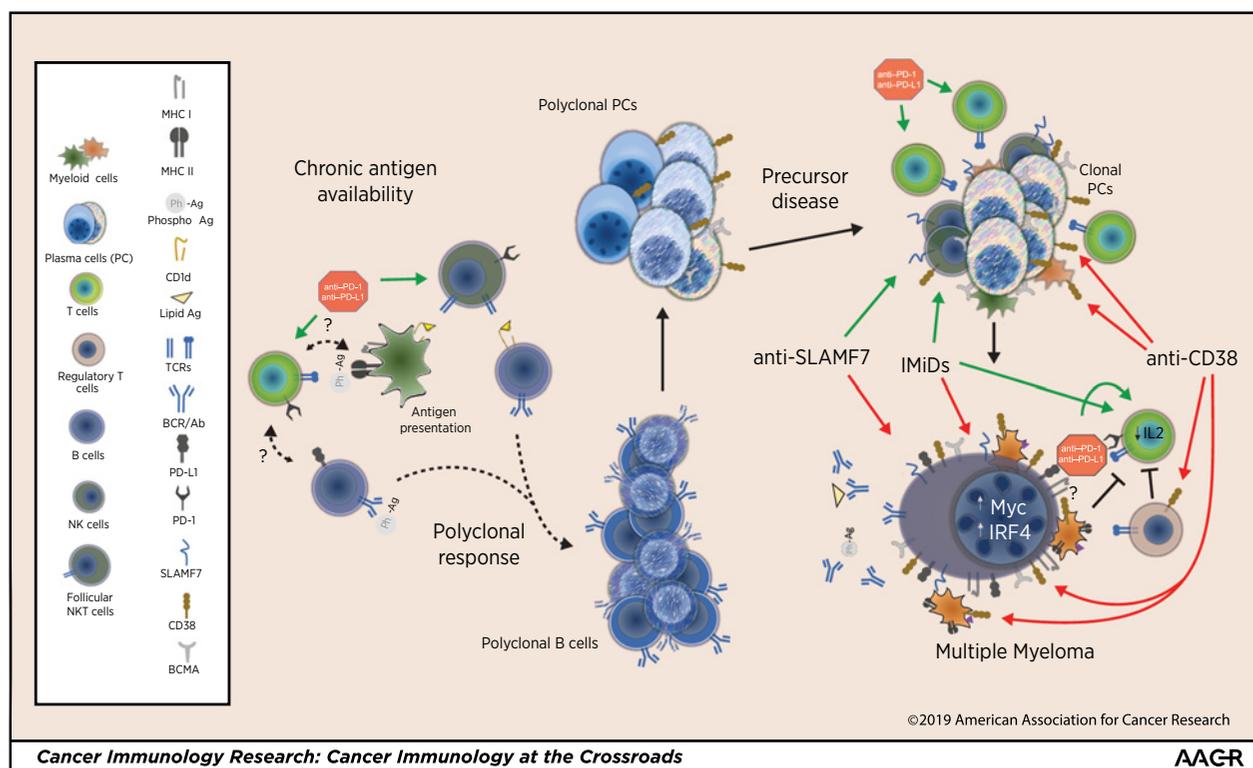


Figure 1.

Myelomagenesis, myeloma, and modifying the immune response. Lipid antigen or phosphoantigen (Ph-Ag)-reactive B cells give rise to phosphoantigen- and/or lipid antigen-reactive plasma cells. Follicular NKT cells, which are typically PD-1^{high}, and possibly other helper T cells play a role. Ongoing chronic stimulation increases the potential for an emerging clonal myeloma precursor. T cell- and NK cell-mediated immune surveillance may limit myeloma progression. Frank progression to myeloma is associated with diminished T-cell and NK cell function and expansion of Tregs and MDSCs. IMiDs and mAbs lead to malignant plasma cell killing, which releases antigen and concurrently diminishes myeloma-driven suppressive mechanisms. Antigen release in the proper inflammatory milieu may elicit or expand an effector immune response. Anti-PD-1 could have pleiotropic effects, affecting both the effector response and follicular helper cell-mediated B-cell maturation. Combination strategies to shift the immune response toward an effector response could yield greatest clinical benefit. Green arrows: activation; red arrows: inhibition; blunted black lines: inhibition; (?): unknown effect.

models (18, 19). Patients with MM are older and have had a lifetime of antigen exposure; thus, PD-1 expression may indicate myeloma antigen-exposed T cells, viral antigen-specific memory T cells, or immune senescent cells (20). PD-1 upregulation is observed on CD8⁺ T cells, CD4⁺ T cells, NK cells, and bone marrow phosphoantigen-reactive V γ 9V δ 2 T cells in MM (21–23). Coexpression of other immune checkpoints, such as LAG-3 and TIGIT, on patient T cells suggests multiple pathways limiting T-cell responses. Blocking PD-1 *in vitro* can partially restore T-cell and NK cell function (21–23). Collectively, these observations suggest that PD-1 blockade is more likely to be effective in combinatorial approaches that focus on MM antigen-specific T cells.

PD-L1, the major ligand of PD-1, is upregulated on malignant plasma cells and can be upregulated by inflammatory cytokines or transcriptionally upregulated by both MYC and downstream effects of MAPK activation, both relevant genetic pathways in MM (24). Studies *in vitro* suggest that PD-L1⁺ plasma cells are more proliferative, resistant to T cell-mediated killing, and also resistant to traditional myeloma drugs (25). PD-L1 expression appears to be highest among drug-resistant cells present in the minimal residual disease state (26). Similarly, patients with SMM,

whose plasma cells express PD-L1, progress more quickly to symptomatic MM, suggesting PD-L1 may be a marker of a proliferative clone, as well as a potential mediator of immune evasion (14).

Combination Approaches Specific to Myeloma

Thalidomide, lenalidomide, or pomalidomide (IMiDs) function by enforcing ubiquitination and proteasomal degradation of Ikaros family proteins (IKZF1/IKZF3; ref. 27), which leads to plasma cell apoptosis. In immune cells, IKZF3 represses IL2 production, and, thus, IMiDs enhance secretion of IL2, leading to increased proliferation of T cells and NK cells, but diminished proliferation of regulatory T cells (Treg; ref. 28). IMiDs also enhance antigen presentation by releasing antigen through plasma cell death, upregulation of B7 expression, and enhancing immune synapse formation between T cells and APCs (29, 30). Pleiotropic effects of IMiDs on immune cells support the notion that greater anti-MM effect could be obtained through combination strategies with ICB independent of plasma cell-specific IMiD resistance.

Monoclonal antibodies (mAb) targeting CD38 and SLAMF7 proteins also have both direct anti-MM effects and immunomodulating effects. The CD38 mAb daratumumab has been shown to induce depletion of MDSCs, Tregs, and regulatory B-cell subsets and increase CD8⁺ T-cell number and clonality among responding MM patients (31). However, CD38 is expressed on T cells that are the targets for reinvigoration by anti-PD-1 in solid tumors (32). Thus, although the former observations provide support for combination with ICB in MM, whether this can be generalized to other cancers is not clear. Recently, a study (NCT03023423) combining daratumumab with PD-1 pathway blockade in lung cancer was halted due to lack of benefit. The anti-SLAMF7 antibody elotuzumab can also modulate the immune response via downstream activation of EAT2 on NK cells, suggesting a potential rationale for combinations that enhance NK cell function. Early studies evaluating combinations of elotuzumab with anti-KIR and 4-1BB agonists remain to be reported (NCT02252263).

In addition to IMiD- and mAb-based combinations, numerous bispecific T-cell engagers (BiTE), chimeric antigen TCR (CAR) therapies, and antibody–drug conjugates directed at the B-cell maturation antigen or other targets are showing promise in MM (33). Although many of these therapies are in early stages of clinical development, it is apparent that lack of persistent anti-MM T cells may be a contributing factor in disease relapse. Combination strategies incorporating ICB may be beneficial.

Immune Checkpoints in Myeloma: Clinical Studies

Initial studies of single-agent PD-1 blockade did not result in a clinical benefit. A phase Ib study of lenalidomide, dexamethasone, and pembrolizumab demonstrated a 50% overall response rate (ORR) and a 38% response rate in lenalidomide-refractory patients (34). Pembrolizumab in combination with pomalidomide and dexamethasone also appeared promising, demonstrating a 60% ORR (35). These results prompted investigation of these combinations in randomized phase III trials as follows: (i) lenalidomide and dexamethasone ± pembrolizumab (P-Ld vs. Ld) in newly diagnosed myeloma (Keynote-185); (ii) pomalidomide and dexamethasone ± pembrolizumab (P-Pd vs. Pd) in relapsed myeloma (Keynote-183); and (iii) pomalidomide and dexamethasone ± nivolumab in relapsed myeloma (Checkmate 602). A preplanned interim analysis in June 2017 revealed an imbalance in deaths in the two pembrolizumab-containing arms of the Keynote trials and the FDA issued a full clinical hold in September 2017 and also paused or halted multiple studies of PD-1 pathway blockade, including Checkmate 602 (36).

The Keynote-185 study targeted previously untreated, transplant-ineligible patients with myeloma. The study had a median follow-up time of 6.6 months and accrued 301 of 640 planned patients. Similar response rates of 64% versus 62% in the P-Ld ($n = 151$) versus Ld ($n = 150$) arms, respectively, and hazard ratio (HR) for 6-month progression-free survival (PFS) of 1.22 (95% CI, 0.67–2.22) and overall survival (OS) of 2.06 (95% CI, 0.93–4.55) were observed. The Keynote-183 study enrolled patients who had relapsed following two or more prior therapies. The study had a median f/u of 8.1 months and accrued 249 of 300

planned patients. Response rates of 34% versus 40% in the P-Pd ($n = 125$) versus Pd ($n = 124$) arms, respectively, and HR for PFS of 1.53 (95% CI, 1.05–2.22) and OS of 1.61 (95% CI, 0.91–2.85) were observed. Checkmate 602 had similar enrollment criteria to Keynote-183 and reopened for enrollment in May 2018 while a concurrent early futility analysis based on 170 of subjects enrolled was performed at the request of the FDA. Enrollment in Checkmate 602 was stopped in September 2018 based on the results of this analysis, with a median f/u of 9.3 months and HR for PFS of 1.08 (95% CI, 0.68–1.70) and OS of 1.19 (95% CI, 0.64–2.2) were observed with nivolumab-Pd (NPd) when compared with Pd alone. ICB has been associated with novel immune-mediated side effects that typically can be managed with appropriate vigilance and intervention (37). Adverse event frequency was similar between the anti-PD-1-containing cohorts and the IMiD/dexamethasone cohorts. However, in all three trials, serious adverse events were observed at higher frequency in the anti-PD-1-containing arms, including absolute frequency of fatalities. Immune-mediated causes of death, such as myocarditis and pneumonitis, were observed, but overall, a unifying cause for the imbalance in deaths as well as the imbalance in high-grade toxicities was not apparent.

Single-arm trials evaluating PD-1 pathway inhibition alone or in combinations with IMiDs in SMM, newly diagnosed, and some refractory MM patient settings have stopped accrual, have been redesigned, or were withdrawn in response to these findings (Supplementary Table S1). Intriguing results have been reported at conference proceedings, including a complete response in an SMM patient with pembrolizumab and encouraging durability for the combination anti-PD-L1 (atezolizumab) with daratumumab for a small number of patients treated prior to these FDA-mandated actions. Current studies evaluating IMiDs or anti-CD38–targeting agents in combination with PD-1 pathway blockade are exploring these agents in more advanced disease settings or in the context of randomization ± an anti-PD-1 agent (Table 1). Additional data on safety and efficacy will determine not only if these combinations continue to be explored, but also the development paths for newer combinations of PD-1 blockade that seek to enhance the efficacy of vaccination, radiation, engineered CARs, or BiTEs.

Summary and Future Directions

Phase III clinical trials evaluating the combination of IMiD, dexamethasone, and anti-PD-1 did not demonstrate improvement in disease response for patients with MM. The results also raise questions regarding a potential synergy in toxicities from this combination. Given the nature of the studies, it has not been possible to discern the specific contribution of each individual drug or patient characteristics to define either a toxicity risk or potential for benefit in a specific patient subset. For example, although IMiDs may promote an immune response, the degree to which dexamethasone may blunt this effect has not been assessed. Additional biomarker exploration from the phase Ib, II, and III trials of these combinations could be informative in this regard, if tissue samples are available. Drug exposure and overall follow-up on each of the studies is short in an era when MM patients are living many years, such that potential exploration of a hypothetical survival plateau was not possible. Taken together, the disparity in the results of the phase I/II and III trials of PD-1 blockade with IMiD and

dexamethasone in MM suggests that a more deliberate mechanism- or biomarker-driven approach may have identified a patient population with potential to derive clinical benefit from this treatment approach.

Obtaining adequate tissue samples for correlative studies to more fully understand how the endogenous immune response is altered is critically important as the field explores targets such as LAG-3, TIGIT, and others. Studies linking myelomagenesis with inflammation suggest a cautionary note regarding a theoretic possibility of promoting disease progression. IMiDs, proteasome inhibitors, mAbs, steroids, and traditional chemotherapeutics are all critical components of MM therapy in today's age. PD-1 blockade demonstrates clearly that safe and effective combinations of current MM treatment strategies with modalities that promote antigen-specific immune responses require a greater understanding of how the T cell–antigen interface affects MM development and is, itself, affected by current MM therapeutics (Fig. 1).

Exploration of combinations with the potential to change the MM treatment landscape is ongoing (Table 1). The relative paucity of mutated antigens, immune senescence, and lower relative frequency of bone marrow T cells means modalities to direct endogenous, adoptive, or engineered T cells against MM tumor-specific targets will be necessary. However, current data suggest that none of these alone are likely to result in durable remissions. ICB or immune agonist stimulation is a potent way to encourage an ongoing antigen-specific immune response toward greater clinical efficacy. Thus, despite initial setbacks, we should remain

undaunted in our efforts to explore all these available tools to realize the full potential of immunotherapy for the benefit of patients.

Disclosure of Potential Conflicts of Interest

A.M. Lesokhin reports receiving commercial research grants from Bristol-Myers Squibb and Janssen, has ownership interest (including stock, patents, etc.) in Seramatrix, Inc, and is a consultant/advisory board member for Bristol-Myers Squibb, Genmab, and Takeda. A.Z. Badros is a consultant/advisory board member for Celgene and Amgen. No potential conflicts of interest were disclosed by the other author.

Authors' Contributions

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Development of methodology: A.M. Lesokhin

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.M. Lesokhin, A.Z. Badros

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.M. Lesokhin

Writing, review, and/or revision of the manuscript: A.M. Lesokhin, S. Bal, A.Z. Badros

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.M. Lesokhin

Study supervision: A.M. Lesokhin

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