Finding the Optimal Partner to Pair with Bispecific Antibody Therapy for Multiple Myeloma

Cedric Louvet, Omar Nadeem, and Eric L. Smith

**Summary:** BCMA/CD3ε-targeted bispecific antibody (BsAb) therapy represents a promising T-cell–redirecting immunotherapy to treat relapsed and refractory multiple myeloma. However, rational combination strategies will most likely be key to achieve a long-lasting immune response. In this issue, Meermeier and colleagues investigate BsAb therapy in a syngeneic multiple myeloma model and elucidate that partnering with cyclophosphamide is associated with tempered activation, mitigated exhaustion of T cells, and is superior to pomalidomide or bortezomib in enhancing durable anti–multiple myeloma efficacy.

See related article by Meermeier et al., p. 354 (6).

Multiple myeloma outcomes have improved significantly due to approval of numerous novel agents including next-generation proteasome inhibitors, immunomodulatory drugs (IMiD), and mAbs. Despite tremendous progress, the disease remains largely incurable, and there is marked heterogeneity in outcomes for patients. Poor prognosis of high-risk patients as defined by genetic translocations, TP53 loss, and markers of high tumor burden represents a particularly important area of unmet need, as is multiply relapsed and refractory disease. B-cell maturation antigen (TNFRSF17, BCMA) is a member of the TNF receptor superfamily and is selectively expressed on plasma cells, making it an ideal target for therapeutic development in multiple myeloma. Multiple BCMA-targeted approaches are currently under investigation including chimeric antigen receptor (CAR) T-cell therapies, bispecific antibodies (BsAb), and antibody–drug conjugates (ADC). The ADC belantamab mafodotin represents the first anti-BCMA–targeted therapy approved for use in relapsed and refractory multiple myeloma (RRMM), but its use is limited due to high rates of ocular toxicity. Idecabtagene vicleucel (Ide-cel) is the first CAR T-cell therapy approved for RRMM based on promising results from the pivotal KarMMa studies, demonstrating a median PFS ranging from 8.8 to 11.8 months in a heavily pretreated RRMM population (1). However, despite the majority of patients achieving a response to CAR T-cell therapy, including high rates of minimal residual disease (MRD) negativity, patients eventually relapse due to factors including antigen escape, T-cell exhaustion, and lack of functional persistence. There are additional approaches of novel CAR T-cell therapy in multiple myeloma, including non-BCMA (2) and dual-targeted approaches (3). While CAR T-cell therapy holds tremendous promise, there are barriers to widespread adoption including need for apheresis, manufacturing time, need for hospitalization, and referral to tertiary care center. BsAbs represent an alternative to delivering T-cell redirection therapy, with one end binding to a multiple myeloma cell–associated surface antigen (i.e., BCMA) and the other CD3ε, thereby bringing tumor cell and T-cell together and activating the T-cell receptor (TCR) in an HLA-independent manner. Several BCMA-targeted BsAbs are currently in clinical development, with encouraging results from early-phase studies (4). As a whole, BsAbs are well tolerated and induce high response rates. The durability of these responses and time to progression with BsAbs is unknown at this time and is an area of active investigation. Given that, to date, BCMA-targeted therapies are not curative for the vast majority of patients, and that combination therapy is advantageous in other settings for multiple myeloma, one of the most important questions in the field is: What is the optimal therapeutic class with which to partner BsAbs? For example, there is preclinical data in xenograft models suggesting enhanced potency of the BCMA-targeted BsAb AMG 701 with the addition of the IMiDs lenalidomide and pomalidomide (5). Additional investigation is needed to determine the optimal agent to partner with BsAbs for multiple myeloma.

In this issue of *Blood Cancer Discovery*, Meermeier and colleagues took advantage of a fully immunocompetent mouse model of multiple myeloma and a BCMA-targeted BsAb with murine reactivity to investigate this critical matter (6). The Vk*MYC model is particularly suitable to mirror human multiple myeloma, as BCMA is highly expressed at the mRNA level in both *de novo* and transplantable multiple myeloma cells, while detectable surface expression of the protein is low due to cleavage by endogenous gamma-secretases (GS) and subsequent shedding. Moreover, as observed in patients (7), the use of a GS inhibitor (GSI) enhances BCMA expression on Vk*MYC multiple myeloma cells. The authors then investigated a murine BCMA/CD3ε-targeted BsAb demonstrating dose-dependent tumor cell killing in the presence of whole splenocytes in *vivo*. This effect was dependent on the level of BCMA expression found across different cell lines. In *vivo* experiments were initially conducted in aged, *de novo* Vk*MYC mice and showed promising responses after only one dose of BsAb. However, mice with an initial high tumor burden...
eventually relapsed after treatment discontinuation. This observation was extended using aggressive transplantable multiple myeloma cells where only mice with an initial low tumor burden exhibit long-term, however transient, reduction in clonal multiple myeloma paraprotein (M-spike) levels. Interestingly, adding GSi treatment to increase BCMA surface expression did not result in a prolonged effect to extend survival.

These results perfectly set the stage for evaluating optimal partners for combination therapy with BsAbs. The authors first examined combination with IMiDs. Given their pleiotropic effects on both myeloma and immune cells, it is reasonable to hypothesize that IMiDs would synergize with BsAb therapy. As discussed above, others have reported that in xenograft models with human peripheral blood mononuclear cells, IMiDs did show substantial benefit when added to a BCMA-targeted BsAb in clinical use (5). As murine Cereblon (CRBN) is not susceptible to the IMiDs in clinical use, the human CRBN (hCRBN) amino acid sequence must be knocked into the murine ortholog locus to recapitulate the effect of IMiDs in a syngeneic murine system with an intact tumor microenvironment (8). Meermeier and colleagues replicated this approach in their genetic Vk*MYC model generating a novel mouse, Vk*MYChCRBN. These mice exhibit the desired responsiveness to IMiDs, including a direct and beneficial effect on cytolytic T cells.

As expected, pomalidomide clearly boosted activation and proliferation of hCRBN-expressing T cells when combined with murine BCMA/CD3ε-targeted BsAb, and this combination was efficient at slowing down tumor growth of aggressive transplantable multiple myeloma lines. Surprisingly, with or without tumor-intrinsic IMiD activity, this effect remained transient in vivo and no increased overall survival was observed. In addition, early mortality was noted in a fraction of the mice, suggesting a potential toxicity of this combination. Phenotypically, cotreatment with pomalidomide induced a sharp increase in IFNγ+ and granzyme B+ killer CD8+ T cells, but which rapidly contracted. Accordingly, the usual suspects of activation/exhaustion, such as PD-1 and LAG3, were found upregulated, suggesting that only short-lived effectors were produced, especially in a context of high tumor burden (Fig. 1A).

The authors then reasoned that avoiding T-cell hyperactivation might be beneficial to unleash the full potential of BsAb therapy and enable a long-lasting response. Cyclophosphamide (Cy) is a DNA-alkylating agent already used in multiple myeloma patients exhibiting a tumoricidal effect. Importantly, the fact that this molecule is often used in combination with fludarabine as a lymphodepleting regimen proved to be pivotal to allow CAR T-cell persistence, making it an attractive candidate to prepare the groundwork for optimal BsAb efficacy; however, because the effect of CD3ε-targeted BsAb relies on endogenous T cells, Cy may also antagonize this therapy. While Cy alone induced a strong but only transient reduction in multiple myeloma tumor cells, the authors find that the combination with BCMA/CD3ε-targeted BsAb resulted in an enhanced response, remarkably, associated with significantly increased overall survival. Cy expectedly

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**Figure 1.** Optimal combination therapy for durable BCMA/CD3ε-targeted BsAb-mediated response in multiple myeloma (MM). A. The IMiD pomalidomide exerts its pleiotropic effect on both myeloma (cytotoxic) and immune (stimulating) cells but, paradoxically, favors a detrimental T-cell hyperactivation and exhaustion induced by BsAb treatment, ultimately leading to tumor relapse. B. Cyclophosphamide is an alkylating agent that leads to tumor debulking but is also a lymphodepleting agent that, when used in combination with BCMA/CD3ε BsAb, enables tempered T-cell activation, mitigates exhaustion, impacts the tumor microenvironment, and uniquely induces durable anti–multiple myeloma immunity. Treg, regulatory T cell.
impacted both tumor and T-cell numbers but induced a higher T cell–to–tumor cell ratio by the end of the concurrent treatment with BsAb, and was associated with a less exhausted and terminally differentiated phenotype. Most importantly, the long-term surviving mice were protected from tumor challenge 9 months after the initial treatment, strongly suggesting durable tumor-specific immunity. Furthermore, the authors found an increase in circulating memory and IFNγ-producing T cells; antigen-specific analysis or evidence of a potential oligoclonal TCR expansion could enhance these findings (Fig. 1B).

The exact mechanism by which Cy primes anti-BCMA/CD3ε BsAb therapy remains elusive. Cy has the potential to modulate cytokine levels and different immune cell types within the tumor microenvironment. For example, the impact on tumor-associated macrophages may enhance antitumor responses; however, Cy has also been shown to potentially promote expansion of tumor-supportive myeloid-derived suppressor cells (9). Overall, the most robust evidence exists that Cy induces preferential depletion of regulatory T cells (Treg), including in the relevant setting of blinatumomab bispecific T-cell engager (BiTE) therapy for relapsed/refractory B-precursor acute lymphoblastic leukemia (10). It is tempting to speculate that Treg depletion may be a key contributor to the improved antitumor immunity induced by Cy and could be key to successful BsAb therapies to treat multiple myeloma. Along this line, in contrast to Cy, the authors showed that the proteosome inhibitor bortezomib failed at enhancing the efficacy of BsAb, highlighting that the impact of Cy is not purely from reduction of tumor burden or alteration of effector-to-target ratio but likely of immunologic underpinning. Further mechanistic studies are, however, warranted to demonstrate if preferential Treg depletion is a causative factor in the success of this combination.

This study particularly points to the importance of relevant in vivo models to explore combination therapies. In particular, the data presented are another example that in vitro data may rarely predict persistent immune responses in vivo. The use of immunocompetent mouse models such as the Vk*MYChCRBN mouse developed by the authors thus proves highly valuable to emulate various and complex suppressive tumor microenvironments and evaluate novel immunotherapies. In this regard, a recent study by Riddell and colleagues made use of an elegant autochthonous mouse model of lung adenocarcinoma to reveal the superiority of the Cy + oxaliplatin regimen to enhance immunologic cell death and improve CAR T-cell efficacy, in particular, when combined with anti–PD-L1 (11). Taken together, the results of these two studies underscore the importance of further modulation of the immune system to obtain optimal results from T-cell redirected therapies.

While Cy appears as a unique and attractive drug to boost BsAb therapies in multiple myeloma, this finding paves the way for identifying more selective approaches to support initially tempered but long-lasting antitumor T-cell immunity.

In conclusion, BCMA-targeted BsAbs hold tremendous promise in multiple myeloma due to their impressive single-agent activity, lower toxicity compared with CAR T-cell therapy, and ease of administration due to their “off-the-shelf” availability and outpatient dosing schedule. However, durability of response is unknown at this time and rational combination strategies are needed to further maintain the immune response. With availability of several therapeutic classes in multiple myeloma with distinct mechanism of actions, future clinical studies, perhaps prioritized by these data, will be required to determine the ideal agents to partner with BsAbs.

**Authors’ Disclosures**

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