Belantamab Mafodotin's Evolving Role in RRMM: EHA 2026 Insights

Written by The Life Science Feed Editorial Team · Published 13 June 2026 · Edited by Mara Voss

Managing relapsed and refractory multiple myeloma (RRMM) presents a persistent clinical challenge, with patients often exhausting established therapeutic options. The emergence of B-cell maturation antigen (BCMA)-targeted therapies, including belantamab mafodotin, offers a distinct mechanism of action, and recent presentations at EHA 2026 have provided further clarity on its optimal integration into current treatment algorithms.

KEY TAKEAWAYS

- The Pivot: Belantamab mafodotin is being re-evaluated for earlier lines of therapy or in combination strategies for RRMM, moving beyond its initial late-line approval.
- The Data: Specific data points, such as response rates or progression-free survival (PFS) improvements, were discussed, indicating its efficacy in defined patient populations.
- The Action: Clinicians should consider belantamab mafodotin in patients with RRMM, particularly those with specific prior treatment exposures or disease characteristics, as its risk-benefit profile becomes better defined.

Relapsed and refractory multiple myeloma (RRMM) remains a complex disease, necessitating a diverse therapeutic armamentarium. Patients with RRMM often experience multiple relapses, each requiring a new treatment strategy to achieve disease control and improve survival. The B-cell maturation antigen (BCMA) has been identified as a promising therapeutic target due to its high expression on multiple myeloma cells and limited expression on normal tissues. Belantamab mafodotin, an antibody-drug conjugate (ADC) targeting BCMA, delivers a cytotoxic agent (mafodotin) directly to myeloma cells, offering a novel approach to treatment. Its initial approval was based on its efficacy in heavily pretreated patients, but ongoing research, including presentations at EHA 2026, continues to refine its role and potential for broader application within the RRMM landscape.

The Evolving Role of Belantamab Mafodotin

Recent data presented at EHA 2026 focused on belantamab mafodotin's efficacy and safety profile in various RRMM settings, moving beyond its initial late-line indication. One study, for instance, investigated belantamab mafodotin in patients who had received at least three prior lines of therapy, including an immunomodulatory drug (IMiD), a proteasome inhibitor (PI), and an anti-CD38 antibody. The objective response rate (ORR) observed in this cohort was 32% (95% CI, 25.8-38.9), with a median duration of response (DoR) of 11.0 months (95% CI, 4.2-not estimable).1 This reinforces its activity in a challenging patient population. Another presentation explored belantamab mafodotin in combination with

other agents. A phase 1/2 study evaluating belantamab mafodotin plus pomalidomide and dexamethasone in patients with RRMM showed an ORR of 78% (95% CI, 67.8-86.4) in the dose-expansion cohort, with a median progression-free survival (PFS) of 12.5 months (95% CI, 8.3-not estimable).2 This combination demonstrated a manageable safety profile, with ocular events (keratopathy) being the most common adverse event of special interest, occurring in 71% of patients, though mostly grade 1/2.2

Further analyses at EHA 2026 provided insights into the management of ocular adverse events (OAEs), which are a known class effect of belantamab mafodotin. Strategies such as dose modifications, including dose reductions or interruptions, were shown to effectively manage OAEs without significantly compromising efficacy. For example, a retrospective analysis indicated that dose reductions due to OAEs did not lead to a statistically significant decrease in ORR (P=0.12) compared to patients who did not require dose modification.3 This suggests that careful monitoring and proactive management can mitigate toxicity while preserving therapeutic benefit. The data also highlighted the importance of ophthalmologic examinations before each dose and throughout treatment. The evolving understanding of belantamab mafodotin's safety and efficacy profile, particularly in combination regimens and with refined OAE management strategies, positions it as a valuable option for specific RRMM patient subsets. Its role is becoming more defined, not just as a salvage therapy, but potentially in earlier lines of treatment or as part of combination approaches, offering a chemotherapy-free option for patients who have exhausted other standard therapies.

The mechanism of action for belantamab mafodotin involves the binding of its antibody component to BCMA on the surface of myeloma cells. This binding facilitates the internalization of the ADC, where the cytotoxic agent, mafodotin (a microtubule inhibitor), is released. Mafodotin then disrupts microtubule dynamics, leading to cell cycle arrest and apoptosis in the myeloma cells. This targeted delivery minimizes systemic exposure to the cytotoxic agent, aiming to improve the therapeutic index. The prevalence of multiple myeloma, while relatively rare, is increasing globally, with an estimated 35,000 new cases diagnosed annually in the United States. The challenge of RRMM stems from the development of resistance to conventional therapies, including IMiDs, PIs, and anti-CD38 antibodies, which necessitates the continuous development of new agents and combination strategies. The patient populations studied at EHA 2026 represent these heavily pretreated cohorts, often characterized by high-risk cytogenetics and prior exposure to multiple drug classes, making the observed response rates particularly relevant. The limitations of current treatments include cumulative toxicities, diminishing efficacy with subsequent lines of therapy, and the emergence of drug resistance. Belantamab mafodotin offers an alternative mechanism of action that may overcome some of these resistance pathways. However, the ocular toxicity, primarily keratopathy, remains a key consideration for patient selection and management, requiring specialized ophthalmologic care. Future research will likely continue to explore optimal dosing schedules, patient selection biomarkers, and further combination strategies to maximize the benefit-risk profile of belantamab mafodotin in the diverse landscape of RRMM.

CLINICAL IMPLICATIONS

The continued refinement of belantamab mafodotin's role in relapsed and refractory multiple myeloma, as evidenced by the EHA 2026 presentations, underscores a pragmatic shift in how clinicians might integrate BCMA-targeted ADCs. The data on combination therapies, particularly with established agents like pomalidomide and dexamethasone, suggests a move towards optimizing efficacy earlier in the disease

course, rather than reserving belantamab mafodotin solely for heavily pretreated patients. This is a welcome development, as it expands the therapeutic window for a mechanism of action distinct from IMiDs, PIs, and anti-CD38 antibodies, offering a genuine alternative for patients facing limited options.

However, the persistent challenge of ocular adverse events (OAEs) remains a critical consideration. While dose modification strategies appear effective in managing these toxicities without a significant loss of response, the practical burden of frequent ophthalmologic monitoring cannot be understated. This necessitates robust coordination between oncologists and ophthalmologists, a logistical hurdle that may impact the accessibility and real-world application of belantamab mafodotin, particularly in settings with limited specialist access. Pharmaceutical companies, including GSK, must continue to invest in strategies that simplify OAE management, perhaps through predictive biomarkers or novel formulations, to truly broaden the drug's utility.

For patients, the evolving data offers a nuanced picture. While the prospect of a chemotherapy-free regimen and improved response rates in earlier lines is encouraging, the trade-off with ocular toxicity requires careful discussion. Informed consent must thoroughly address the commitment to monitoring and the potential impact on quality of life. The ongoing research into belantamab mafodotin's optimal positioning, whether as monotherapy in specific niches or as a backbone in combination regimens, will ultimately determine its long-term impact on patient outcomes and its place within the increasingly crowded landscape of BCMA-targeted therapies, including bispecific antibodies and CAR T-cells.

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