Changing the Survival Landscape in RRMM with Novel ADC

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Relapsed or refractory multiple myeloma (RRMM) remains characterized by repeated relapse, progressively shorter remission durations, and an ongoing need for regimens with high efficacy. With B-cell maturation antigen (BCMA) established as a validated therapeutic target, the clinical focus has shifted from whether BCMA-directed therapy works to how early it should be incorporated to maximize durable disease control and overall survival.

Belantamab mafodotin is a first-in-class BCMA-targeting antibody–drug conjugate (ADC) with a multimodal mechanism of action. In addition to direct cytotoxicity through intracellular delivery of monomethyl auristatin F (MMAF), belantamab mafodotin can promote immune effector functions such as antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP), and may induce immunogenic cell death (ICD), potentially supporting sustained antitumor immunity. Unlike cellular therapies or some T-cell–engaging approaches that often require intensive monitoring for cytokine release syndrome or neurotoxicity, belantamab mafodotin can be administered as an outpatient infusion and does not mandate such immune-toxicity surveillance.

In the phase 3 DREAMM-7 trial, patients with RRMM after at least one prior line were randomized to belantamab mafodotin plus bortezomib and dexamethasone (BVd) versus daratumumab plus bortezomib and dexamethasone (DVd). With a median follow-up of 39.4 months, BVd demonstrated a statistically significant and clinically meaningful overall survival (OS) benefit versus DVd (HR 0.58; 95% CI 0.43–0.79; p=0.0002), although median OS was not reached in either arm. BVd also achieved deeper and more durable responses, including higher rates of ≥CR with MRD negativity (25% vs 10%) and a substantially longer median duration of response (40.8 vs 17.8 months). Importantly, the clinical advantage of BVd was maintained beyond first progression, with improved PFS2 versus DVd. In the phase 3 DREAMM-8 trial, belantamab mafodotin in combination with pomalidomide and dexamethasone (BPd) likewise yielded markedly prolonged progression free survival (PFS) and higher MRD-negative deep responses compared with the control arm (PVd), including in clinically relevant subgroups such as patients with lenalidomide-refractory disease and those previously exposed or refractory to anti-CD38 antibodies.

Belantamab mafodotin has a distinct toxicity profile, most notably ocular toxicity that is mechanistically linked to the ADC payload and occurs more frequently in belantamab-containing regimens than comparator triplets. In DREAMM-7, ocular events were common and typically presented as keratopathy with associated changes in best-corrected visual acuity (BCVA), with blurred vision frequently reported; when BCVA decline to ≤20/50 occurs, the median time to onset is approximately 2–4 months. Most keratopathy improves with treatment interruption and/or interval extension, and over time, effective dosing intervals may drift to every 8–12 weeks in patients requiring repeated dose holds. Overall, these events are generally manageable with structured ophthalmologic monitoring and dose-modification algorithms, and treatment discontinuation due to ocular toxicity remains relatively infrequent.

In conclusion, the superior efficacy across OS, PFS and DOR in the DREAMM-7 and DREAMM-8 trials supports the potential for belantamab mafodotin-based combinations to become a new standard of care in the relapsed/refractory setting. The key implementation challenge is ocular toxicity; however, predictable onset patterns, high rates of improvement with dose holds/interval modification, and the feasibility of longer effective dosing intervals support practical, real-world integration when

proactive ophthalmologic collaboration and patient-centered toxicity management are embedded into care pathways.