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The Antibody Drug Conjugate, Belantamab-Mafodotin, in the Treatment of Multiple Myeloma: A Comprehensive Review

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Abstract: Despite recent advancements in treatments, including proteasome inhibitors, immunomodulators, and anti-CD38 monoclonal antibodies, multiple myeloma (MM) remains mostly incurable with patients frequently experiencing disease relapses due to therapy resistance. Hence there is an urgent need for innovative treatments for patients with relapsed and/or refractory MM (RRMM). This review examines Belantamab mafodotin, the first antibody-drug conjugate (ADC) targeting B-cell maturation antigen (BCMA), which has shown efficacy in pre-clinical and clinical settings for RRMM. BCMA, a type III transmembrane glycoprotein critical for B cell functions, is predominantly expressed in malignant plasma cells making it a promising therapeutic target. ADCs, comprising a monoclonal antibody, a cytotoxic payload, and a linker, offer a targeted and potent therapeutic approach to cancer treatment. Belantamab mafodotin integrates an afucosylated monoclonal antibody and monomethyl auristatin F (MMAF) as its cytotoxic agent. It induces apoptosis in MM cells by disrupting microtubule formation and interfering with important signaling pathways. The series of DREAMM (Driving Excellence in Approaches to MM) studies have extensively evaluated Belantamab mafodotin in various clinical settings. This review provides a comprehensive overview of pre-clinical and clinical data supporting Belantamab mafodotin as a future therapeutic option for RRMM.

Keywords: belantamab mafodotin, multiple myeloma, antibody-drug conjugate

Introduction

Multiple myeloma (MM), the second most prevalent hematological malignancy, accounts for 1% of all cancers.[1,2] It is marked by the proliferation of malignant plasma cells, resulting in their accumulation in the bone marrow and the overproduction of monoclonal (M) proteins or free light chains.[3] This overproduction can lead to severe end-organ damage, including anemia, renal insufficiency, hypercalcemia, and lytic bone disease.[3] In recent years, significant therapeutic advancements, such as proteasome inhibitors (bortezomib, carfilzomib, ixazomib), immunomodulators (thalidomide, lenalidomide, pomalidomide), and anti-CD38 monoclonal antibodies (daratumumab, isatuximab), have substantially improved the overall survival rates for MM patients.[4–8]

Despite these advancements, MM remains largely incurable, with most patients experiencing relapses and developing resistance to existing therapies.[9,10] This has underscored the urgent need for new treatments with novel mechanisms of action. Recent innovations in immunotherapy, including chimeric antigen receptor T-cells and T-cell engagers targeting the B-cell maturation antigen (BCMA) on plasma cells, have introduced a new arsenal of therapies for relapsed and refractory MM (RRMM).[10,11] This paper provides a comprehensive review of the pre-clinical and clinical data published and available on PubMed or other conference proceedings supporting the use of Belantamab Mafodotin, the sole antibody-drug conjugate targeting BCMA, as a promising therapeutic option for RRMM.

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B Cell Maturation Antigen (BCMA) Biology

BCMA (B-cell maturation antigen) was first identified in 1992 on chromosome 16p13.1 in malignant human T-cell lymphoma.[12] It is a type III transmembrane glycoprotein with six conserved cysteines in its extracellular domain, belonging to the tumor necrosis factor receptor (TNFR) superfamily, specifically TNFRSF17. Predominantly located in a perinuclear structure overlapping the Golgi apparatus, BCMA is also functional on the cell surface.[12–15] BCMA interacts with two related TNFR superfamily members: transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) and B-cell activation factor receptor (BAFF-R).[13,15,16] These receptors regulate numerous B cell functions, including proliferation, survival, maturation, and differentiation into plasma cells. Binding of BCMA to its ligands, BAFF and APRIL, activates signaling pathways such as NF-kB, p38, Elk-1, and JNK.[14,17–19] Additionally, a soluble form of BCMA (sBCMA), generated by γ-secretase, acts as a decoy by neutralizing APRIL, thus inhibiting BCMA pathway activation.[20] Elevated levels of sBCMA, often found in multiple myeloma (MM) patients, correlate with poor prognosis.[21,22] Previously, Carpenter et al[23] found BCMA cDNA in many hematologic tissues, such as blood leukocytes, bone marrow, lymph nodes, tonsils, and spleen. However, BCMA cDNA was not detected in other normal human tissues except for the testis, trachea, and some gastrointestinal organs. As a result, BCMA has been a desirable therapeutic target for treating MM.

Antibody-Drug Conjugate (Adc) Therapy and Their Mechanism of Action

An ADC consists of three essential components: a monoclonal antibody targeting a specific cell surface receptor, a highly potent cytotoxic payload, and a stable linker that connects the antibody to the drug. This advanced therapeutic approach addresses many challenges of traditional chemotherapy.[10] ADC payloads are designed to be highly potent, often active at picomolar concentrations, to counter the fact that only a small fraction of injected antibodies effectively reach tumor cells. These payloads typically target tubulin or induce DNA damage within targeted cells.[24–26]

The linker between the payload and the antibody is crucial for ADC effectiveness. It controls the release of the cytotoxic drug, directly impacting pharmacodynamics, pharmacokinetics, and the therapeutic index. A stable linker ensures controlled drug release at the target site, minimizing off-target effects. However, the stability of the linker must be carefully balanced: a too-weak linker may cause premature drug release, while an overly strong linker may hinder drug delivery. ADCs use both cleavable and non-cleavable linkers. Cleavable linkers respond to specific enzymatic conditions within endosomes, releasing the drug payload upon cleavage. Non-cleavable linkers rely on lysosomal degradation for drug release.[27,28] This sophisticated design allows ADCs to precisely target and destroy cancer cells while minimizing damage to healthy tissues.

Belantamab Mafodotin

Belantamab mafodotin (Blenrep), previously known as GSK2857916, is an innovative ADC designed for the treatment of RRMM. This ADC integrates a fully humanized IgG1 monoclonal antibody, a stable linker, and a cytotoxic payload.[10,29] The monoclonal antibody targets BCMA and is afucosylated to enhance its binding affinity to FcγRIIIa receptors on immune effector cells, such as macrophages and NK cells. This modification significantly improves antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), enhancing the immune response against BCMA-expressing multiple myeloma (MM) cells.[10,29]

The cytotoxic payload of Belantamab mafodotin is monomethyl auristatin F (MMAF), linked to the antibody via a non-cleavable maleimidocaproyl (MC) linker. Upon binding to BCMA on MM cells, the ADC is internalized through receptor-mediated endocytosis and transported to lysosomes (Figure 1). In the acidic lysosomal environment, the MC linker releases MMAF, which then binds to tubulin, disrupting microtubule formation. This disruption causes cell cycle arrest at the G2-M phase and triggers caspase-dependent apoptosis in MM cells.[10,29–31] Additionally, Belantamab mafodotin interferes with the NF-kB signaling pathway, crucial for MM cell survival. By blocking BCMA interactions with BAFF and APRIL, the ADC disrupts MM cell growth and survival signaling, promoting apoptosis.[10,29–31] Ongoing research is focused on developing anti-BCMA ADCs, with several candidates progressing through clinical trials. This targeted approach in cancer therapy represents a significant advancement, offering improved efficacy and reduced systemic toxicity compared to conventional chemotherapy.[10]

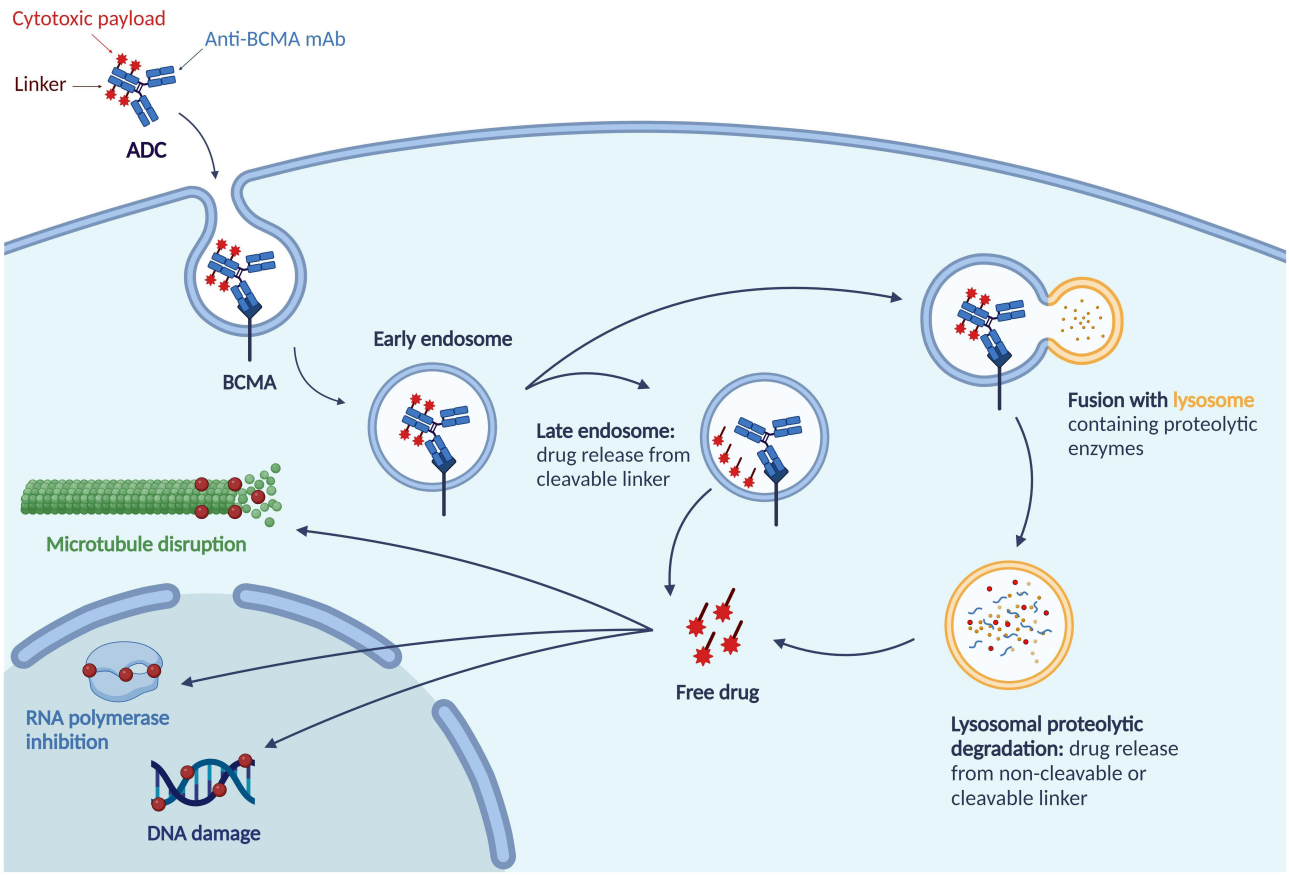

Figure 1 Mechanism of action of Belantamab mafodotin. In this figure, Belantamab mafodotin binds to the BCMA receptor on the target cell which then takes up the antibody-drug conjugate (ADC) by endocytosis. Within the target cell, aided by lysosomes, the MMAF drug will be released from the endosomes and they will bind and disrupt the microtubule structures leading to cell death.

Belantamab Mafodotin's Clinical Efficacy and Safety

Several clinical trials, including the critical DREAMM-1 and DREAMM-2 studies, have shown the efficacy of Belantamab mafodotin in heavily pretreated patients with RRMM who had received multiple prior lines of therapy, including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies.[10,29] The results demonstrated notable overall response rates (ORR), duration of responses (DoR), and depth of response including both complete responses (CR) and partial responses (PR), highlighting Belantamab mafodotin's efficacy in a challenging patient population and are reviewed in detail below and summarized in Table 1.

DREAMM-1

The DREAMM-1 study was conducted across multiple centers in the USA, Canada, and the UK. It was the first in human trial demonstrating the benefits of Belantamab mafodotin for RRMM.[32] The study was divided into two phases: dose escalation and dose expansion. In the initial phase (n=38), the primary objective was to determine the recommended dose of Belantamab mafodotin for Phase 2 (n=35). The subsequent phase focused on evaluating the safety, efficacy, tolerability, and pharmacokinetics of the established dose. After examining the primary outcomes, a dose of 3.4 mg/kg was established for the second phase of the study. The results regarding efficacy and safety in the second phase appear in Table 1. A dose of 3.4 mg/kg had significant activity in patients with heavily pretreated relapsed or refractory MM. After a 14-month follow-up, the median DoR was 14.3 months, and the median progression-free survival (PFS) was 12.0 months.[33] Additionally, the ORR was maintained, with responses deepening over time. Corneal events were reported in 69% of patients, with 51% experiencing blurred vision, 37% reporting dry eyes, and 29% reporting photophobia. Thrombocytopenia, anemia, and

Table 1 Summary of DREAMM Studies Conducted to Evaluate the Efficacy and Safety of Belantamab Mafodotin as Single Agent or in Combination Therapies

	Study	Sample size (N)	PFS	OS	DoR	Depth of response	MRD- status	Grade 3 or higher AEs	Corneal events	Infections Any
Belantamab mafodotin [32,33]	DREAMM-1	Part 1: 38 Part 2: 35 patients	12.0 months	N/A	14.3 months	**ORR**: 60% **sCR**: 6% **CR**: 9% **VGPR**: 40% **PR**: 6%	N/A	Part 1: **Thrombocytopenia**: 34% **Anemia**: 16% Part 2: **Any AE ≥3**: 83% **Thrombocytopenia**: 34% **Anemia**: 17% **Serious AE**: 49%	Part 1: **Corneal events**: 53% Part 2: **Corneal events**: 69% **Grade 1 or 2**: 54% **Grade 3**: 14% **Blurred vision**: 51% **Dry eyes**: 37% **Photophobia**: 29%	N/A
Belantamab mafodotin [34,35]	DREAMM-2	223	2.5mg/kg: 2.8 months 3.4 mg/kg: 3.9 months Lyophilized cohort (3.4 mg/kg): 5.7 months	2.5mg/kg: 15.3 months 3.4 mg/kg: 14.0 months Lyophilized cohort: 24.5 months	2.5mg/kg: 12.5 months 3.4 mg/kg: 6.2 months Lyophilized cohort: 9 months	**ORR** 2.5mg/kg: 32% 3.4 mg/kg: 35% Lyophilized cohort: 52% **sCR** 2.5mg/kg: 2% 3.4 mg/kg: 3% Lyophilized cohort: 0 **CR** 2.5mg/kg: 7% 3.4 mg/kg: 2% Lyophilized cohort: 0 **≥VGPR** 2.5mg/kg: 9% 3.4 mg/kg: 19% Lyophilized cohort: 24% **PR** 2.5mg/kg: 13% 3.4 mg/kg: 11% Lyophilized cohort: 28% **Clinical benefit rate** 2.5mg/kg: 36% 3.4 mg/kg: 40% Lyophilized cohort: 56%	**≥VGPR + MRD-** 2.5mg/kg: 36% 3.4 mg/kg: 23% Lyophilized cohort: N/A **≥CR+ MRD-** 2.5mg/kg: 44% 3.4 mg/kg: 67% Lyophilized cohort: N/A	**Grade 3 or higher AE** 2.5mg/kg: 84% 3.4 mg/kg:83% Lyophilized cohort: 88% **keratopathy** 2.5mg/kg: 31% 3.4 mg/kg: 25% Lyophilized cohort: 21% **Thrombocytopenia** 2.5mg/kg: 22% 3.4 mg/kg: 32% Lyophilized cohort: 21% **Anemia** 2.5mg/kg: 21% 3.4 mg/kg: 28% Lyophilized cohort: 21% **SAE** 2.5mg/kg: 45% 3.4 mg/kg: 54% Lyophilized cohort 63%	**Keratopathy** 2.5mg/kg: 71% 3.4 mg/kg: 75% Lyophilized cohort: 96% **Blurred vision** 2.5mg/kg: 25% 3.4 mg/kg: 36% Lyophilized cohort: 42% **Dry eye** 2.5mg/kg: 18% 3.4 mg/kg: 25% Lyophilized cohort: 25%	2.5mg/kg: 45% 3.4 mg/kg: 55% Lyophilized cohort: 46%
Belantamab mafodotin [36]	DREAMM-3	325	Belamaf: 11.2 months Pd: 7 months	Belamaf: 21.2 months Pd: 21.1 months	Belamaf: NR Pd: 8·5 months **12-month DoR** Belamaf: 77% Pd: 48%	**ORR** Belamaf: 41% Pd: 36% **CR and sCR** Belamaf: 10% PD: 3% **VGPR or better** Belamaf: 25% Pd: 8% **Clinical benefit rate** Belamaf: 47% Pd: 47%	Belamaf: 7% Pd: 0	**Grade 3 or higher AE** Belamaf: 77% Pd: 74% **SAE**: B: 43% P: 39%	**CTCAE scale** Belamaf: 66% (grade ≥3: 29%) Pd: 8% (grade ≥3: 0%) **KVA scale** B: 75% (grade ≥2 59%) P: 31% (grade ≥2 4%) **Keratopathy** B: 12% P: <1% **Blurred vision**: Belamaf: 40% Pd: 2%.	Belamaf: 41% Pd: 40% **Grade 3 or worse**: B: 13% P: 25%

Belantamab mafodotin with pembrolizumab [37]	DREAMM-4	34	3.4 months	N/A OS at 12 months: 85% OS at 18 months: 73%	8 months	**ORR**: 47% **CR**: 12% ≥**VGPR**: 29% **PR**: 18%	≥VGPR: 30%	74%	**Keratopathy**: 76% **Blurred vision**: 38% **Dry eye**: 21%	Serious infection: 6%
Belantamab mafodotin with nirogacestat [38]	DREAMM-5	10	N/A	N/A	N/A	**ORR**: 60% **VGPR**: 20% **PR**: 40%	N/A	80%	70% Keratopathy: 20%	N/A
Belantamab mafodotin with feladilimab (aICOS) [39]	DREAMM-5	23 Cohort A (Belamaf 1.9 mg/kg +aICOS 8mg) = 9 Cohort B (Belamaf 2.5 mg/kg +aICOS 8mg)= 10 Cohort C (Belamaf 2.5 mg/kg +aICOS 24mg)= 4	N/A	N/A	N/A	**Cohort A**: ORR: 44% sCR: 0 CR: 11% VGPR: 22% PR:11% Clinical benefit rate: 44% **Cohort B**: ORR: 50% SCR: 10% CR: 0 VGPR: 10% PR: 30% Clinical benefit rate: 50% **Cohort C**: ORR: 50% sCR: 0 CR: 0 VGPR: 25% PR: 25% Clinical benefit rate: 50% **Total population**: ORR: 48% sCR: 4% CR: 4% VGPR: 17% PR: 22% Clinical benefit rate: 48%	N/A	Cohort A: 67% Cohort B: 70% Cohort C: 50% Total population: 65%	Cohort A: 56% Cohort B: 80% Cohort C:75% Total population: 70%	N/A
Belantamab mafodotin, bortezomib, and dexamethasone [40]	DREAMM-6	ARM B: 18 patients in belamaf 2.5 mg/kg SINGLE + BorDex	N/A	N/A	N/A	**ORR**: 78% **VGPR**: 50% **PR**: 28% **Clinical benefit rate**: 83%	N/A	89%	MECs/ keratopathy occurred in all patients	N/A

(*Continued*)

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Table 1 (Continued).

	Study	Sample size (N)	PFS	OS	DoR	Depth of response	MRD- status	Grade 3 or higher AEs	Corneal events	Infections Any
Belantamab mafodotin, lenalidomide and dexamethasone [41]	DREAMM-6	Arm A: 45 patients Belamaf 1.9 mg/kg Q8W: n=12 Belamaf 1.9 mg/kg Q4W: n=4 2.5 mg/kg Q4W: n=16 2.5 mg/kg Q4W split dose: n=13	Belamaf 1.9 mg/kg Q8W: NR Belamaf 1.9 mg/kg Q4W: 8.6 months 2.5 mg/kg Q4W: NR 2.5 mg/kg Q4W split dose: 9 months	Belamaf 1.9 mg/kg Q8W: NR Belamaf 1.9 mg/kg Q4W: NR 2.5 mg/kg Q4W: 32.1 2.5 mg/kg Q4W split dose: NR	Belamaf 1.9 mg/kg Q8W: NR Belamaf 1.9 mg/kg Q4W: 11.6 months 2.5 mg/kg Q4W: NR 2.5 mg/kg Q4W split dose: NR	**Belamaf 1.9 mg/kg Q8W**: ORR: 58% ≥VGPR: 42% ≥CR: 25% **Belamaf 1.9 mg/kg Q4W**: ORR: 75% ≥VGPR: 50% ≥CR:25% **2.5 mg/kg Q4W**: ORR: 69% ≥VGPR: 56% ≥CR:44% **2.5 mg/kg Q4W split dose**: ORR: 69% ≥VGPR: 38% ≥CR:15%	N/A	Belamaf 1.9 mg/kg Q8W: 83% Belamaf 1.9 mg/kg Q4W: 75% 2.5 mg/kg Q4W: 81% 2.5 mg/kg Q4W split dose: 100%	N/A	N/A
Belantamab Mafodotin, Bortezomib, and Dexamethasone [42]	DREAMM-7 NCT04246047	494 (243 BVd)	BVd: 36.6 months DVd: 13.4 months	OS 18 months: BVd: 84% DVd: 73%	BVd: 35.6 months DVd: 17.8 months	**sCR** BVd:14% DVd 5% **CR** BVd: 21% DVd: 12% **VGPR** BVd: 31 DVd: 29 **PR** BVd:17% DVd: 25% **Clinical benefit rate**: BVd: 86% DVd: 76%	**CR or better**: BVd: 25% DVd: 10% **VGPR or better**: BVd: 39% DVd: 17%	BVd: 95% BVd (serious AE: 50%) DVd: 78% (serious AE: 37%)	BVd: 79% (grade ≥3: 34%) DVd: 29% (grade ≥3: 3%) **Blurred vision**: BVd: 66% DVd: 11% **Dry eye**: BVd: 51% DVd: 7% **Photophobia**: BVd: 47% DVd: 2%	BVd:70% DVd: 67%
Belantamab Mafodotin, Pomalidomide, and Dexamethasone [43]	ALGONQUIN trial NCT03715478	87 RP2D (n=38)	Part 1: 20 months RP2D: NR All patients: 21.8 months	Part 1: 34 months RP2D: NYR All patients: 34 months	N/A	**ORR** Part 1: 89.8% RP2D: 85.3% All patients: 87.7% **CR/sCR** Part 1: 33.9% RP2D: 33.3% All patients: 33.3% **VGPR** Part 1: 40.7% RP2D: 42.4% All patients: 39.5% **PR** Part 1: 15.3% RP2D: 11.8% All patients: 14.8%	N/A	**Thrombocytopenia**: Part 1: 39.3 RP2D: 34.2 All patients: 33.3 **Neutropenia**: Part 1: 45.9 RP2D: 36.8 All patients: 41.4	**Keratopathy** Part 1: 78.7% RP2D: 65.8% All patients: 71.3% **Decreased visual acuity (BCVA)** Part 1: 83.6% RP2D: 71.1% All patients: 78.2%	Part 1: 50.8% RP2D: 47.4% All patients: 50.6%

Belantamab Mafodotin, Pomalidomide, and Dexamethasone in Multiple Myeloma [44]	DREAMM-8 NCT04484623	302	**Median PFS**: BPd: not reached PVd: 12.7 months **12-month estimated PFS** BPd: 71% PVd: 51%	N/A	**Estimated 12 months DoR**: BPd: 79% PVd: 61%	**sCR** BPd: 9% PVd: 3% **CR** BPd: 31% PVd: 14% **VGPR** BPd: 24% PVd: 22% **PR** BPd: 14% PVd: 34%	**CR or better plus MRD-**: BPd: 24% PVd: 5% **VGPR or better plus MRD-**: BPd: 32% PVd: 5%	BPd: 94% PVd: 76%	**Corneal event** BPd: 89% (grade 3 or 4 in 43%) PVd: 30% (grade 3 or 4 in 2%) **Blurred vision**: BPd: 79% PVd: 15 **Dry eyes**: BPd: 61% PVd: 10% **Photophobia** BPd:44% PVd: 4%	BPd: 82% (grade ≥3 49%) PVd: 68% (grade ≥3 26%)
Belantamab mafodotin, bortezomib, lenalidomide and dexamethasone[45]	DREAMM-9	93 **Cohort 1** 1.9 mg/kg Q3/4W (n=12) **Cohort 2** 1.4 mg/kg Q6/8W (n=12) **Cohort 3** 1.9 mg/kg Q6/8W (n=12) **Cohort 4** 1.0 mg/kg Q3/4W (n=15) **Cohort 5** 1.4 mg/kg Q3/4W (n=13) **Cohort 6** 1.4 mg/kg, then 1.0 mg/kg Q9/12W **Cohort 7** 1.9 mg/kg, then 1.4 mg/kg Q9/12W.	N/A	N/A	N/A	**Cohort 1** ORR: 100% ≥CR: 75% VGPR: 17% PR: 8% **Cohort 2** ORR: 92% ≥CR: 83% VGPR: 8% PR: 0 **Cohort 3** ORR: 100% ≥CR: 83% VGPR: 17% PR: 0 **Cohort 4** ORR: 80% ≥CR: 53% VGPR: 20% PR: 7 **Cohort 5** ORR: 92% ≥CR: 62% VGPR: 23% PR: 8% **Cohort 6** ORR: 79% ≥CR: 14% VGPR: 21% PR: 43% **Cohort 7** ORR: 53% ≥CR: 7% VGPR: 27% PR: 20%	**Cohort 1 MRD-** ≥CR: 75% ≥VGPR: 83% **Cohort 2 MRD-** ≥CR: 33% ≥VGPR: 33% **Cohort 3 MRD-** ≥CR: 58% ≥VGPR: 67% **Cohort 4 MRD-** ≥CR: 33% ≥VGPR: 33% **Cohort 5 MRD-** ≥CR: 46% ≥VGPR: 46% **Cohort 6 MRD-** ≥CR: 7% ≥VGPR: 14% **Cohort 7 MRD-** ≥CR: 0 ≥VGPR: 7	35%	**Grade ≥3**: Total: 53% Cohort 1: 83% Cohort 2: 58% Cohort 3: 92% Cohort 4: 57% Cohort 5: 85% Cohort 6: 7% Cohort 7: 0%	N/A

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neutropenia of any grade occurred in 63%, 29%, and 6% of patients, respectively. These results of the DREAMM-1 trials supported the benefits and acceptable safety profile of incorporating Belantamab mafodotin as a strategy for treating RRMM.

DREAMM-2

DREAMM-2 was an open-label, two-arm, phase 2 study that examined the safety profiles and efficacy of two doses of Belantamab (2.5 mg/kg and 3.4 mg/kg every 3 weeks)[46] in patients with RRMM. The median PFS was 2.8 months (95% CI: 1.6–3.6) and 3.9 months (95% CI: 2.0–5.8), while OS was 15.3 months (95% CI: 9.9–18.9) and 14.0 months (95% CI: 10.0–18.1) for the 2.5 mg/kg and 3.4 mg/kg doses, respectively.[34] The ORR was 32% (97.5% CI: 21.7–43.6) with a DoR of 12.5 months (95% CI: 4.2–19.3) for the 2.5 mg/kg dose, and 35% (97.5% CI: 24.8–47.0) with a DoR of 6.2 months (95% CI: 4.8–18.7) for the 3.4 mg/kg dose. As seen in previous studies, ocular events were commonly seen with 71% and 75% of patients in the 2.5mg/kg and 3.4 mg/kg arm having keratopathy. Corneal microcyst-like epithelial changes (MECs) were found to be present in 72% of patients receiving Belantamab mafodotin and were observed in 69% of the patients by the fourth dose.[47] At a 13-month follow-up, there were no new safety signals and clinical activity was sustained, responses to treatment even deepened over time in some patients.[48]

In a separate cohort of the DREAMM-2 clinical trials, Belantamab mafodotin was administered in a lyophilized preparation to compare it to the usual frozen-liquid preparation to provide a more convenient method for shipment and storage.[35] There was no significant difference between the pharmacokinetics of both presentations. The 2.5 mg/kg dose had a more favorable safety profile without compromising the anti-MM activity.[46] Due to these reasons, the lyophilized preparation and the 2.5 mg/kg dose was the recommended formulation and dosage for future clinical trials.

Given the safety profile and notable clinical benefits observed in DREAMM-1 and 2, Belantamab Mafodotin was approved as a Breakthrough Therapy by the FDA in 2020 and as a Priority Medicine (PRIME) by the European Medicines Agency (EMA). It was indicated for use in patients with RRMM who have received a minimum of four prior therapies, including PIs, IMiDs, and anti-CD38 monoclonal antibodies.

DREAMM-3

In the DREAMM-3 study, 325 patients were randomized to two treatment groups: Belantamab mafodotin (n=218) and pomalidomide-dexamethasone group (n=107). Median PFS in the Belantamab mafodotin group was 11.2 months (95% CI: 6.4–14.5) compared to 7 months (95% CI: 4.6–10.6) in the pomalidomide-dexamethasone group (hazard ratio of 1.03 [95% CI: 0.72–1.47; p=0.56]. Although median OS was immature, the Belantamab mafodotin had a median OS of 21.2 months (95% CI: 18.7 - NR), while the pomalidomide-dexamethasone group had a median OS of 21.1 months (95% CI: 15.1 - NR) with a hazard ratio of 1.14 (95% CI 0.77–1.68). DoR was not reached (NR) in the Belantamab group, whereas the pomalidomide-dexamethasone group had 8.5 months (95% CI: 7.6 - NR). The Belantamab group and the pomalidomide-dexamethasone group had a partial response or better of 41% and 36%, VGPR or better of 25% and 8%, CR and stringent CR of 10% vs 3%, respectively. The occurrence of grade ≥3 adverse events, thrombocytopenia, anemia, and infections were similar between both groups. However, neutropenia and grade ≥3 infections were less prominent in the Belantamab group (11% vs 38%, 13% vs 25%, respectively). As expected, ocular events were more notable in the Belantamab group (66% vs 8%). Since single-agent Belantamab mafodotin did not meet its primary endpoint of PFS compared to Pomalidomide-dexamethasone, as a result, the FDA requested withdrawal of BLENREP (Belantamab mafodotin) on March 20, 2023 after the results of DREAMM-3 trial.[36]

Although Belantamab mafodotin as a monotherapy did not improve PFS compared to standard care, its effectiveness in combination therapies has been tested in DREAMM-4, DREAMM-5, DREAMM-6, DREAMM-7, DREAMM-8, DREAMM-9 clinical trials where Belantamab mafodotin is being used in combination with other agents such as pomalidomide, lenalidomide, pembrolizumab (anti-PD-L1), and nirogacestat (GS inhibitor). These trials aim to improve Belantamab mafodotin's efficacy further, expand its use across different lines of MM treatment, and mitigate potential adverse effects.[10,29]

DREAMM-4

The DREAMM-4 clinical trial examined the efficacy and safety profile of patients exposed to Belantamab mafodotin in combination with pembrolizumab, a PD-1 inhibitor.[37] Alike the DREAMM-1 trial, the study had a dose escalation phase to compare two doses (2.5 and 3.4 mg/kg) of Belantamab mafodotin with 200mg pembrolizumab to establish the recommended dose of the second phase, while the second phase addressed the clinical activity of the established dose. A dose of 2.5mg/kg of Belantamab mafodotin in combination with 200 mg of pembrolizumab was used for the second part of the study. The ORR was 47% with 29% achieving a VGPR or better response. The median DoR was 8 months (95% CI,2.1 - NR), while the OS was immature. The median PFS was 3.4 months (95% CI, 1.4–5.6). The most reported adverse events were ocular events, and no new safety concerns were identified. Keratopathy, blurred vision, and dry eyes occurred in 76%, 38%, and 21% of patients, respectively. Thrombocytopenia was observed in 35% of the patients, while anemia occurred in 26%. Even though Belantamab mafodotin with pembrolizumab showed improved ORR when compared to Belantamab alone in the DREAMM-3 trial (47% vs 41%),[36] the modest difference in clinical activity does not warrant further studies.

DREAMM-5

The DREAMM-5 is an ongoing Phase 1/2 study assessing Belantamab mafodotin in combination with other anticancer agents, including a GSK3174998 (an OX40 agonist), feladilimab (an inducible T-cell costimulatory (aICOS) receptor agonist), nirogacestat (a gamma-secretase inhibitor) and dostarlimab (a PD-1 blocker).[49] In a cohort within the dose expansion phase of the nirogacestat arm, 10 patients received 0.95 mg/kg Q3W (every 3 weeks) Belantamab mafodotin with 100 mg BID nirogacestat.[38] The ORR was 60%, with 20% of patients having a VGPR and 40% having a PR. Grade ≥3 occurred in 80% of patients, while ocular events of any grade were present in 70%. Keratopathy was reported in 20% of patients. Despite the small sample size, preliminary results of Belantamab mafodotin in combination with nirogacestat demonstrated promising clinical activity.

Another arm of the DREAMM-5 trial administered Belantamab mafodotin in combination with feladilimab, an inducible co-stimulatory T-cell molecule agonist (aICOS).[39] A total of 23 patients were assigned to three cohorts: Cohort A received Belantamab mafodotin 1.9 mg/kg + aICOS 8mg (n= 9), cohort B received Belantamab mafodotin 2.5 mg/kg + aICOS 8mg (n= 10), and cohort C received Belantamab mafodotin 2.5 mg/kg + aICOS 24mg (n= 4). In the preliminary analysis, the clinical benefit rate for the entire population was 48% (95% CI, 26.8–69.4). The ORR was 44%, 50%, and 50% for each of the cohorts, respectively. Grade 3 or 4 adverse events were seen in 65% of the total population, while 70% of patients had ocular adverse events of any grade. In this study, 56%, 80%, and 75% of patients in cohorts A, B, and C experienced ocular adverse events. Adverse events were managed with dose modifications. Although the cohort expansion phase of the DREAMM-5 is still ongoing, Belantamab Mafodotin in combination with anti-cancer treatment has shown clinical activity with a safety profile requiring clinical management in this preliminary analysis.

DREAMM-6

The DREAMM-6 clinical trials aimed to assess the possible synergistic effects of Belantamab mafodotin in combination with lenalidomide/dexamethasone or bortezomib/dexamethasone.[40,41] The first arm of the study addressed Belantamab mafodotin with lenalidomide and dexamethasone at two different dose levels at varied schedules: Belantamab 1.9 mg/kg Q8W (every 8 weeks) (n=12), Belantamab 1.9 mg/kg Q4W (every 4 weeks) (n=4), 2.5 mg/kg Q4W(n=16), and 2.5 mg/kg Q4W split dose(n=12).[41] The ORR was 58% with Belantamab mafodotin 1.9 mg/kg Q8W, while the ORR was 75% with Belantamab mafodotin 1.9 mg/kg Q4W. There was no drug-drug interaction between Belantamab mafodotin and lenalidomide. As expected, corneal events were the most evident adverse event. In arm B of the DREAMM-6 trial, 18 patients received a 2.5 mg/kg of Belantamab mafodotin dose plus bortezomib and dexamethasone.[40] Patients experienced a clinical benefit rate of 83%, with an ORR of 78%. The VGPR rate was 50%, while PR occurred in 28%. Corneal events were common, and microcystic epithelial changes (MECs) were noted in all patients in this arm. Thrombocytopenia was reported in 67% of patients. Belantamab in combination with bortezomib and dexamethasone showed favored outcomes adverse events.

DREAMM-7

DREAMM-7 treated patients with at least 1 prior line of therapy for RRMM with Belantamab mafodotin, Bortezomib, and Dexamethasone (BVd) compared to those treated with Daratumumab, Bortezomib, and Dexamethasone (DvD).[42] A total of 494 patients were randomized into two arms: 243 patients in the BVd group and 251 patients in the DVd group. Patients receiving BVd regimen had a median PFS of 36.6 months (95% CI:, 28.4 - NR), while it was 13.4 months (95% CI, 11.1 to 17.5) in the DVd group. The hazard ratio for PFS was 0.41 (95% CI, 0.31–0.53; P<0.001). Of the total events of disease progression or death, 63% were in the DVd group. OS at 18 months for the BVd and DVd groups were 84% and 73%, respectively. The hazard ratio for OS was 0.57 (95% CI: 0.50–0.80; P<0.0005).

Patients treated with the BVd regimen were found to have a greater depth of response and a longer DoR than patients in the DVd group. In the BVd group, 83% of patients (95% CI, 77–87) achieved a PR or better to treatment, while 71% of patients (95% CI, 65–77) in the DVd group experienced similar outcomes. A CR or better was observed in 35% of patients in BVd group and 17% in the DVd. Additionally, 25% of patients in the BVd group and 10% in the DVd attained a CR or better along with MRD-negative status. Patients in the BVd had a median DoR of 36.5 months (95% CI, 30.5 to NR), while the DVd group had a median DoR of 17.8 months (95% CI, 13.8 to 23.6) (P<0.001). At the time of the data cutoff, most of the responses in the BVd were still ongoing. Patients in the BVd groups were more likely to experience grade 3 or higher adverse events than the DVd group (95% and 78%, respectively). Serious events occurred in half of the BVd group and 37% of the DVd group. In the BVd group, 69% experienced thrombocytopenia, 19% had anemia, and 70% had infections. In the DVd group, 50% experienced thrombocytopenia, 26% had anemia, and 67% had infections.

In the DREAMM-7 study, ocular adverse events of any grade were more prevalent in the BVd group (79% vs 29% in the DVd group). Ocular adverse events of grades 3 or 4 were seen in 34% of the patients in the BVd group and 3% in the DVd group. In the BVd group, ocular events caused 44% of patients to reduce their Belantamab mafodotin dose, 78% to experience delays, and 9% to discontinue the treatment altogether. As expected, ocular events were more prevalent in patients undergoing belantamab mafodotin treatment.

As a result, the median relative dose intensity (RDI) of belantamab mafodotin was 51% over the entire treatment period, with an RDI of 77% in the first 6 months, 68% between 6–12 months, and 28% after 12 months, reflecting dose interruptions due to corneal events. In contrast, the median RDIs of bortezomib and dexamethasone remained comparable between treatment groups, maintaining ≥75% during the first eight cycles. However, there was no major difference in the overall patient-reported quality of life over time.

DREAMM-8

The ALGONQUIN trial evaluated the efficacy and safety profile of Belantamab mafodotin plus pomalidomide and dexamethasone in a two-part study.[43] The first part demonstrated greater clinical efficacy with the 2.5 mg/kg dose compared with the 1.92 mg/kg dose. ORR, VGPR, mPFS for the 2.5mg/kg and 1.92mg/kg dose were 100% vs 66.7%, 100% vs 63.7%, and 25.3 months versus 19.9 months, respectively. The safety profile was consistent with single agent use of Belantamab mafodotin. As seen in previous studies, there was a trend in increased frequency and severity of ocular adverse events with increased doses. The administration of 2.5 mg/kg was only 37% of the intended dose due to increasing intervals and dose reductions to manage corneal toxicity. A summary of efficacy outcomes for part 2 (RP2D) of the trial is shown in Table 1. The ALGONQUIN trial shows promising results for the use of Belantamab mafodotin in a triplet regimen. However, the lack of a comparator highlights the need for a confirmatory study.

DREAMM-8 trial examined the effectiveness of Belantamab mafodotin plus Pomalidomide and Dexamethasone (BPd) versus Pomalidomide combined with Bortezomib and Dexamethasone (PVd).[44] In the study, 302 patients were randomized into the BPd group (n=155) and the PVd group (n=147). Although the median PFS duration was not reached in the BPd group, the 12-month estimated PFS was greater for the BPD group (71%, 95% CI: 63–78) than in the PVD group (51%, 95% CI: 42–60). Patients in the BPd group had a significantly lower risk of PFS than the PVd group (hazard ratio, 0.52; 95% CI: 0.37–0.73; two-sided P<0.001). Follow-up for OS is still ongoing, nevertheless, the BPd group had a greater 12-month overall survival than PVd group (hazard ratio, 0.77; 95% CI: 0.53–1.14). Depth of response and response duration were higher in the BPd group. For the BPd and PVd, 77% and 72% of patients had a PR or better

response, 50% and 16% had a CR or better, and 24% and 5% had a CR or better with MRD-negative status, respectively. A greater percentage of patients in the BPd group had a DoR of 12 or more months in the BPd group than the PVd group (79% vs 61%). In the BPd and PVd groups, 94% and 76% of patients experienced grade 3 or higher adverse events, while 63% and 45% of patients had serious adverse events, respectively. In the BPd and PVd groups, 79% and 15% of patients experienced blurred vision, 61% and 10% had dry eyes, 61% and 6% had foreign body sensations in the eyes, 48% and 34% had neutropenia, 36% and 30% had thrombocytopenia, 23% and 26% had anemia, and grade 3 or higher infections occurred in 49% and 26% of patients, respectively. Even though the presence of ocular events was common in the BPd group, they were managed by dose modifications and were characterized by high rates of resolutions, low treatment discontinuation rates, and no meaningful change from baseline in patients reported outcomes from the global health status and quality-of-life domains of the EORTC QLQ-C30. However, the protocol-recommended dose modifications to manage corneal events also resulted in a median RDI of 52.5% for belantamab mafodotin over the entire treatment course. Nevertheless, the lack of change in patients' reported health status in both DREAMM-7 and DREAMM-8 trials emphasizes the potential benefits of introducing Belantamab mafodotin as part of a triplet regimen in second-line treatment.

DREAMM-9

The DREAMM-9 is an ongoing phase 1 study that examines Belantamab mafodotin in combination with bortezomib, lenalidomide, and dexamethasone (VRd) in transplant-ineligible and newly diagnosed MM patients.[45] The study's primary aim is to establish a recommended dose for future trials. The primary outcome was safety, while the secondary outcomes were efficacy and tolerability. Patients (n=93) were randomized into 7 cohorts with varied doses: 1.9 mg/kg Q3/4W, 1.4 mg/kg Q6/8W, 1.9 mg/kg Q6/8W, 1.0 mg/kg Q3/4W, 1.4 mg/kg Q3/4W, 1.4 mg/kg then 1.0 mg/kg Q9/12W, and 1.9 mg/kg then 1.4 mg/kg Q9/12W. Grade ≥3 ocular adverse events occurred in 53% of all patients, with the highest incidence of 92% observed in the group receiving 1.9 mg/kg Q6/8W.

Thrombocytopenia, constipation, diarrhea, and peripheral sensory neuropathy were reported in 46%, 36%, 34%, and 31% of the entire study population. Grade ≥3 adverse events occurred in 35% of patients. The highest CR rate of 83% was seen in cohort 2 and 3. In cohort 1, 83% of the patients exhibited MRD negative status plus ≥VGPR. The combination of Belantamab mafodotin plus VRd did not reveal new safety signals, while providing promising clinical activity. This Phase 3 study will determine if Belantamab mafodotin plus VRd provides statistically significant improvement in safety and efficacy when compared to VRd alone.[50]

Dose and Management of Corneal Events

Belantamab mafodotin is associated with specific side effects, mainly ocular toxicities due to its cytotoxic component, MMAF, which can accumulate in corneal epithelial cells, despite them not expressing BCMA, through nonspecific uptake or diffusion. This accumulation disrupts the epithelial cell function, leading to microcystic-like changes in the cornea, and manifesting as keratopathy characterized by corneal events such as superficial punctate keratitis, corneal opacities, epithelial edema, and stromal edema. These notable ocular events are usually managed through treatment strategies such as dose adjustments, interruptions, or supportive care using corticosteroid eye drops and preservative-free artificial tears.[10,29] A simulation framework was developed to address how belantamab mafodotin dose modification affects efficacy, ocular safety, and pharmacokinetics based on the data from DREAMM-1 and DREAMM-2 clinical trials.[51] A reduction in dose or dose frequency was associated with a lower risk of ocular events, probability of transitioning to a higher grade of adverse event, and time spent with grade 2+ or higher ocular events. In the DREAMM-1 trials, there was an evident tendency of increasing frequency of grade 3 or 4 corneal adverse events with increasing doses of Belantamab mafodotin.[32] The simulator framework also identified that the decrease in risk with a lower dose was much less than the reduction in efficacy. Split dosing, metronomic or more frequent schedules were not predicted to improve the benefit-risk profile. In another model, Corneal events and higher-grade adverse events occurred in higher frequency as Belantamab mafodotin trough concentration increases.[52] In addition, PFS was longer with increasing exposure to Belantamab mafodotin. Because exposure has a stronger association with safety factors than efficacy, dose management is an effective strategy for reducing the frequency of adverse events without greatly affecting

the efficacy of Belantamab mafodotin. These findings were consistent with the results of the DREAMM-3 clinical trials where dose modifications were effective in managing Belantamab mafodotin-related adverse events without disturbing clinical activity.[53]

Mechanisms of Resistance to Anti-BCMA ADC and Strategies to Overcome

The development of treatment resistance in myeloma patients remains a crucial challenge, usually indicating poor prognosis.[54] With the recent inclusion of anti-BCMA ADCs in MM treatment, the mechanisms behind resistance to these drugs are still not fully understood.[55] However, many potential mechanisms based on the ADC pathway have been proposed (Figure 2).[56] ADC must bind to myeloma cells by BCMA. Therefore, the loss or downregulation of BCMA on myeloma cells may lead to resistance. Also, due to the heterogeneous nature of MM, subclones lacking BCMA or with little BCMA might thrive during anti-BCMA ADC therapy. This has been observed in BCMA-specific CAR-T therapy, where myeloma cells lost surface BCMA.[57] Significantly elevated levels of soluble BCMA (sBCMA) in MM patients may also decrease anti-BCMA ADC efficacy via sequestering the anti-BCMA antibody, which prevents it from targeting MM cells.[10]

To address BCMA loss, new antibody formats can be incorporated into ADCs. Biparatopic and bispecific antibodies can improve targeting MM cells by recognizing the same or two different antigens. For instance, MEDI2228 binds strongly to membrane BCMA, with high sBCMA levels having a slight impact.[58] Furthermore, small-molecule gamma-secretase inhibitors (GSIs) can raise surface BCMA levels by decreasing its cleavage from the membrane, which

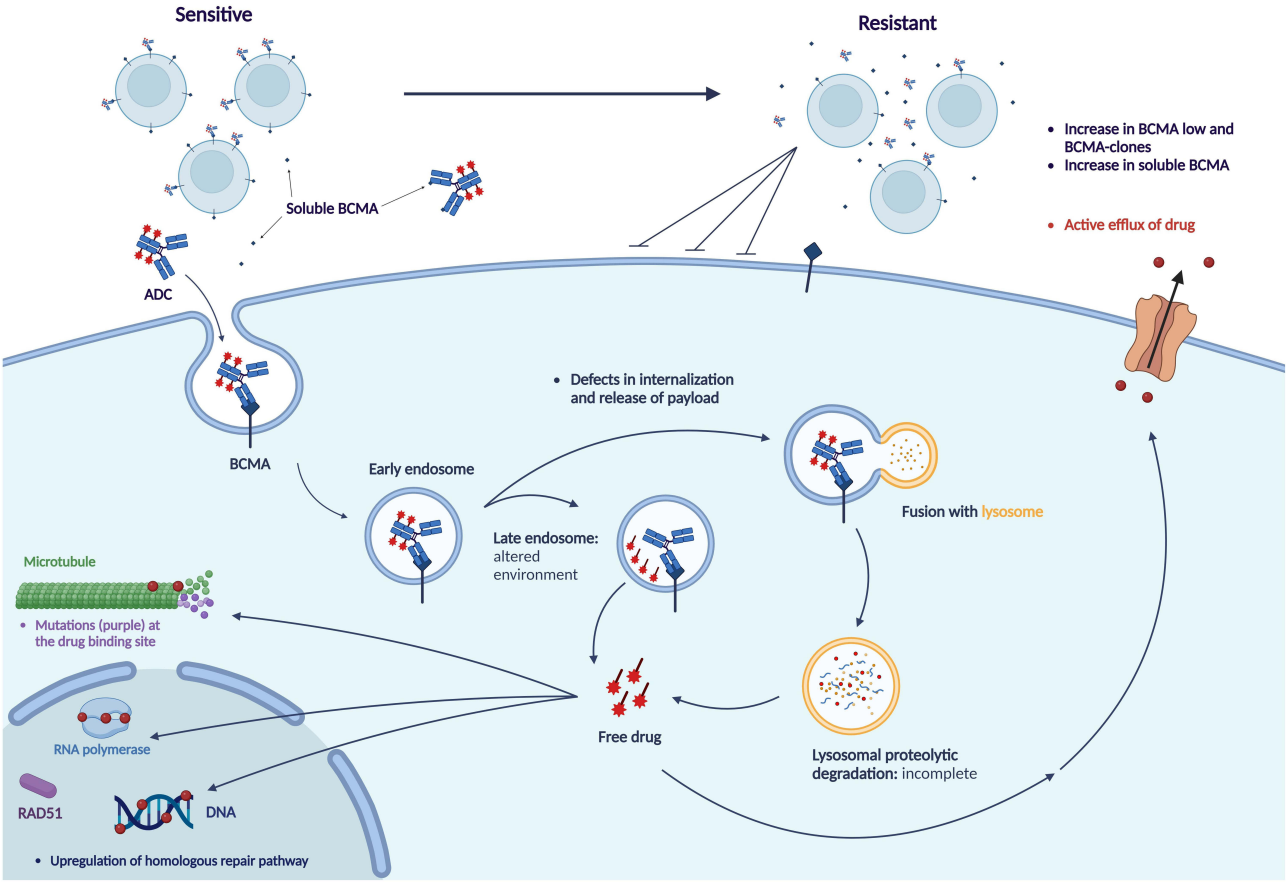

Figure 2 Mechanisms of resistance to Belantamab Mafodotin. In this figure, the following mechanisms can contribute to resistance to belantamab mafodotin: a) increase in BCMA-low or BCMA-negative MM cell clones, 2) increase in soluble BCMA that compete for the binding to Belantamab mafodotin, 3) increase in the active efflux of MMAF out of the cells, 4) increase in pathways involved in DNA repair and 5) mutations in MMAF binding sites limiting its adequate binding to the target.

enhances MM cell recognition by anti-BCMA ADCs. GSIs have improved anti-BCMA CAR-T therapy effectiveness in vivo.[59] Also, several clinical trials are exploring their combination with anti-BCMA CAR-T therapy to potentially improve anti-BCMA ADC therapy.[10]

After binding to BCMA ADCs are internalized into the cell via clathrin-mediated, caveolin-mediated, or clathrin-caveolin-independent endocytosis. Cleavage may occur in the endosome for ADCs with cleavable linkers. If not, the endosome fuses with a lysosome, which leads to complete ADC degradation and payload release.[56,60,61] Any impairment in these processes may prevent the payload from executing its cytotoxic function. To illustrate, in T-DM1-resistant cells, altered lysosomal pH blocked T-DM1 degradation. Using a protease-cleavable linker resolved this issue in several resistant cell models.[62,63]

Even if the payload is released, it must stay inside the cell to function properly. ATP-binding cassette (ABC) transporters can decrease chemotherapeutic agents' efficacy by expelling them from the cytoplasm actively.[64] It is likely that conjugated cytotoxins are substrates of ABC transporters, resulting in a significant resistance. This can be mitigated by changing the payload to one with a low affinity for efflux pumps. For example, vadastuximab talirine, an anti-CD33 ADC, uses pyrrolobenzodiazepines (PBD) instead of gemtuzumab ozogamicin (GO) because PBD is a poor substrate for drug efflux pumps. Moreover, PBD has demonstrated anti-leukemia activity in multidrug-resistant AML models, including those resistant to GO.[65] Furthermore, reducing the cytotoxic compound's hydrophobicity is considered an alternative approach to overcome resistance. This is because hydrophobic compounds are good substrates for multidrug resistance protein (MDR) transporters. In a study with antibody-maytansinoid conjugates, a hydrophilic maytansinoid metabolite produced via a hydrophilic linker was more effective in killing MDR-expressing cells than other metabolites from nonpolar linkers.[66]

If an ADC successfully binds to an MM cell, releases its payload, and avoids active efflux, the cell may still survive via activating survival pathways. In MM, drug resistance is usually linked to activated DNA repair pathways.[67,68] One key DNA repair pathway is homologous recombination (HR), which causes the recruitment of the protein RAD51.[69] RAD51 serves a key role in repairing DNA lesions, such as interstrand cross-links, double-strand breaks, and stalled/damaged replication forks. Elevated RAD51 levels aid the cells in evading DNA damage induced by radiation or chemotherapy, leading to resistance and poor patient survival.[70] During ADC treatment, upregulation of RAD51 and elevated HR were observed in a clinical trial with MEDI2228. Adding DNA damage repair checkpoint inhibitors, such as AZD1775 (WEE1i), AZD0156 (ATMi), and AZD6738 (ATRi), synergized with MEDI2228 to increase cytotoxicity.[71] Finally, ADC resistance can also stem from a mutation in the targets of the cytotoxic drugs. However, no mutations have been seen in tubulin, topoisomerase I, or RNA polymerase II in ADC-resistant models.[55]

Other ADC Drugs for Multiple Myeloma Treatment

Numerous promising ADCs are being studied and developed for MM treatment. MEDI2228, targeting BCMA with pyrrolobenzodiazepine (PBD) tesirine, showed a 65.9% overall response rate (ORR) when it was given to heavily pretreated patients, though it was withdrawn due to safety and efficacy concerns. AMG224, another BCMA-targeted ADC using mertansine, showed a 23% ORR in a Phase I trial, with side effects, such as thrombocytopenia and neutropenia. Other important ADCs include TAK-169 and TAK-573. TAK-169 utilizes a Shiga-like toxin A subunit, and it targets CD38 particularly. TAK-573, which also targets CD38 and is conjugated to interferon-alpha 2b, demonstrated a promising effect in heavily pretreated patients, including those exposed to CAR-T therapy.[10,29] FOR46 targets CD46 and relies on MMAF as its toxic payload, showing notable effectiveness in patients with chromosome 1q gain. HDP-101 targets BCMA with alpha amanitin and is effective in deletion 17p pathology, potentially targeting both dormant and proliferating myeloma cells. Indatuximab maytansine (BT062) targets CD138 along with DM4, showing promising results, especially when it's combined with Dex and IMiDs. Lastly, Lorvotuzumab mertansine (IMGN901), targeting CD56 with DM1, showed an expected toxicity profile and potential for further investigation. These ADCs represent an innovative and diverse approach to treating MM patients, offering hope for improved outcomes in RRMM patients.[10,29]

Conclusion

MM remains a challenging and often incurable disease, despite significant advances in treatment. Targeting BCMA has proven to be a promising approach, due to its high expression on malignant plasma cells and limited expression on normal tissue. Belantamab Mafodotin has demonstrated substantial efficacy in preclinical and clinical trials, offering hope for heavily pretreated patients with RRMM. However, challenges such as ocular toxicities and mixed results in monotherapy trials have led to regulatory setbacks. Following the publication of the DREAMM-3 results, the FDA rescinded the accelerated approval of Belantamab mafodotin, leading to its withdrawal from the market. Nonetheless, ongoing research of Belantamab mafodotin as part of combination therapies in the DREAMM-7 and DREAMM-8 studies has seen statistically significant results in clinical activity with an improvement in progression-free survival with an expected safety profile. Dose modification has been effective in reducing the occurrence of ocular adverse events associated with Belantamab mafodotin use. In the future, the availability of belantamab mafodotin within the therapeutic arsenal will enable optimal sequencing for patients with relapsed/refractory multiple myeloma (RRMM) alongside approved anti-BCMA CAR-T cell therapies and T-cell engagers. Its off-The-shelf accessibility offers substantial value for patients needing immediate treatment, especially those unable to endure the extended manufacturing timelines required for CAR-T cell therapy or the gradual dosing escalation necessary with T-cell engagers. In the meantime, continued research and clinical trials remain vital to fully comprehend the potential of BCMA-targeted therapies and improve outcomes for patients with RRMM.

Author Contributions

Adrian A Almodovar Diaz and Samhar Alouch are co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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