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Abstract: Despite the recent approval of novel immunotherapies, as immunomodulatory drug, proteasome inhibitors and anti-CD38 monoclonal antibodies, Multiple Myeloma (MM) remains incurable and the acquisition of triple-refractoriness leads to really dismal outcomes, in even earlier lines of therapy. More recently, innovative therapeutic strategies targeting B cell maturation antigen (BCMA), highly expressed on the plasma cell surface, are drawing different future landscapes in terms of effectiveness and outcomes. Belantamab Mafodotin, a first-in-class anti-BCMA antibody drug conjugates, demonstrated good efficacy and safety profile in triple-refractory patients in the phase 2 DREAMM-2 trial and it was approved for the treatment of MM triple-exposed patients with >4 prior lines of therapy. Here, starting from Belantamab Mafodotin clinical trials also exploring combination studies and different schedules in order to improve its efficacy and toxicity, we focused on real life experiences all over the world, which have confirmed clinical trial data and encourage further Belantamab Mafodotin investigations.

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

1. Introduction

Multiple myeloma (MM) is the second most common hematological disease after diffuse large B-cell lymphoma, accounting for approximately 10% of all hematological malignancies and its incidence has increased over the last years. MM is typically an elderly hematologic disease, with the median age of patients at the diagnosis of about 65 years [1,2].

MM is a neoplastic disease characterized by abnormal plasma cells proliferation in the bone marrow, which produce an excessive of monoclonal protein (M-protein) detected in blood and urine. This M-protein causes specific organ damage resulting in MM signs and symptoms, tipically hypercalcemia, renal insufficiency, anemia and osteolytic bone lesions (named CRAB criteria) [3].

The therapeutical landscape of effective anti-myeloma drugs, both at diagnosis as well as in the relapse/refractory (RR) setting, has widely expanded in the last decade thanks to the introduction of proteasome inhibitors (PIs, such as bortezomib, carfilzomib and ixazomib), immunomodulatory drugs (IMiDs, such as thalidomide, lenalidomide and pomalidomide) and, recently, monoclonal antibodies (mAbs), such as elotuzumab, daratumumab and, lastly, isatuximab [3, 4]. The introduction of these agents has translated into prolonged progression free survival (PFS) as well as overall survival (OS) with significantly less toxicities and improved quality of life. Currently, thanks to the therapeutic first line approaches including quadruplet induction combination, high-dose chemotherapy, followed by autologous hematopoietic stem-cells transplantation (ASCT), and consolidation-maintenance, the 10-years overall survival (OS) probability is about 60% in patients eligible for ASCT. To date, approximately 50% of MM patients are still alive 5 years after the diagnosis, and one-third of the patients are still alive after 10 years, [5]. In non-transplant eligible (NTE) patients, therapeutical first line approaches based on doublet or triplet combination with PIs,

IMiDs and mAbs result in a prolonged OS, with a median OS of 5 years. To date, the addition of daratumumab, mAb specifically targeting CD38 antigen expressed on clonal plasma cells surface, to the standard of care regimen in first line therapy could improve outcome both for TE as well as for NTE patients.

However, MM still remains largely an incurable disease, with poor outcomes especially among patients who become resistant to therapies, underlying the need for a better understanding of pathobiology of the disease [6]. MM natural course can be described as an alternation of phases of remission, unfortunately followed by phases of relapse. In addition, it is known that the duration of the remission phases tends to progressively reduce during the history of the disease. The majority of patients becomes refractory to all available drugs. During the last years, scientific research has been oriented to immunotherapeutic approaches in order to identify specific target for MM clonal plasma cells and to obtain a deep, durable response, traducing in a possible cure for MM patients.

Immunotherapeutic approaches, both passive, for example, mAbs and cellular products targeting clonal plasma cells, or active (when patient's immune system is stimulated to induce an immune response against plasma cells), have been investigated to harness the patients' immune system to destroy clonal plasma cells and, nowadays, represent an effective strategy for the treatment of MM [3].

Clonal plasma cells express several antigens on its surface with the most important molecule under investigation as potential targets for mAbs, such as CD38, CD40, CD138, CD56, CD54, PD1, kappa light chain, B-cell maturation antigen (BCMA), and the signaling lymphocyte activation molecule F7 (SLAMF7). The optimal mAb-therapeutic targets should be expressed on clonal plasma cells surface and not on normal hematopoietic cells or non-hematopoietic tissue, in order to avoid off-target effects. Several mechanisms of action are described for mAbs therapies: a direct cytotoxic effects on the clonal plasma cell, an antibody-dependent cellular cytotoxicity (ADCC), an antibody-dependent cell-mediated phagocytosis (ADCP) and a complement-dependent cytotoxicity (CDC) [7].

Recently, these immunotherapy approaches have been investigated in monotherapy, firstly, and then in combination with other effective anti-plasma cells agents in order to improve outcomes, in terms of overall response and survival. Specifically, SLAMF7 and CD38 are two antibody targets of particular interest in MM. Elotuzumab, a humanized immunoglobulin IgG_1 monoclonal antibody binding SLAMF7, expressed both on MM and NK cells, is the first in class mAb to be explored in MM and to showed, in combination with lenalidomide and dexamethasone (Rd), a significant OS benefit in RRMM compared to Rd in phase II ELOQUENT-2 trial [8]. Furthermore, Elotuzumab has been investigated in association with pomalidomide and dexamethasone (Pd) and with bortezomib and dexamethasone, both resulting in superior outcomes compared with standard therapy Pd and Vd, respectively [9].

In the widely landscape of MM treatment, CD38 antigen expressed on plasma cell surface represent an ideal antibody target. For this purpose, several CD38-targeting antibodies have been developed. Daratumumab, the first-in class humanized IgG_1K monoclonal antibody targeting CD38, demonstrated impressive anti-MM efficacy as monotherapy firstly, as well as, in combination with other anti-myeloma drugs. Daratumumab exerts its specific mechanisms of action through different pattern: CDC, ADCC, ADCP, induction of direct plasma cell apoptosis, and through the modulation of CD38 enzyme activities [10]. After initial approval in heavily pretreated patients as monotherapy thanks to GEN501 and SIRIUS trials results [11, 12], daratumumab has been approved in combination with Rd and Vd for treatment of RRMM patients who have received at least one prior line of therapy, based on the results of phase III POLLUX and CASTOR trials [13, 14]. Recently, daratumumab has been investigated in RRMM patients in combination with Pd *versus* Pd or in combination with carfilzomib and dexamethasone (DKd) *versus* Kd in phase III APOLLO and CANDOR trials [15, 16]. Considering the efficacy data of these studies about the daratumumab-combination therapies, these two triplets are starting to become the new standard of care in RRMM patients.

More recently, based on the results of the pivotal phase III MAIA trial, daratumumab was approved, in combination with Rd, in newly diagnosed MM not eligible for ASCT [17]. Another daratumumab-based combination therapy has been recently approved, D-VMP, for newly diagnosed

MM patients not eligible to ASCT. [18]. Based on the results of phase III CASSIOPEIA study, the new standard of care for newly diagnosed transplant eligible MM patients is daratumumab in combination with VTd (bortezomib, thalidomide and dexamethasone) [19]. Currently, with daratumumab- based combination regimens mostly used in front-line therapy, the role of daratumumab in the relapse setting should be discussed, in the absence of clear evidence that retreatment with daratumumab can overcome prior daratumumab refractoriness.

Isatuximab, an IgG-k chimeric monoclonal antibody targeting a specific epitope on CD38, was investigated in combination with other drugs in relapsed/refractory setting. Based on the efficacy results, in terms of ORR and PFS, of phase III ICARIA study, the combination of isatuximab plus Pd was approved for RRMM patients who have received at least two prior lines of therapy, including lenalidomide [20]. Recently, the phase III pivotal trial IKEMA, demonstrated superior outcomes in terms of PFS for patients treated with isatuximab in combination with carfilzomib and dexamethasone (Kd) compared to patients treated with Kd [21]. Compared to daratumumab, isatuximab presents different mechanism: firstly, it has been demonstrated that it is able to induce a direct apoptosis in MM cells. Next, it is able to inhibit the enzymatic activity of CD38 more than daratumumab and is less effective to exert CDC. In addition, isatuximab improves NK and T-cell-mediated antitumor immune response [22]. Unfortunately, as with other agents, resistance to anti-CD38 monoclonal antibody therapy happened. To date, no standard of care has been established for RRMM patients who have been exposed to the three main classes of anti-myeloma drugs and these patients have limited treatment options representing an unmet medical need. The outcome of patients failing standard care regimens, defined as triple refractory (including PIs, IMiDs and mAbs), is poor, with a median PFS of 5 months and a median OS of 12 months [23]. For this purpose, there is a very urgent need to develop and introduce novel therapeutical approaches.

Selinexor, melfulflen, cerebron E3 ligase modulators (CELMoDs) and venetoclax represent very promising drugs for RRMM patients treatment.

The first in class oral selective inhibitor of nuclear export targeting exportin-1, selinexor, received FDA approval in combination with bortezomib and dexamethasone (SVd) for RRMM patients after the first line of therapy, based on the results of pivotal phase III BOSTON study [24, 25]. The median PFS for patients treated with SVd was 13.9 months compared to 9.5 months of patients treated with Vd. The most common reported adverse events were grade 3-4 thrombocytopenia and neutropenia (39% and 6%, respectively), and gastrointestinal toxicity (about 25%). In addition, selinexor was approved in combination with dexamethasone for triple refractory patients [26]. Melfulfen (melfuflen-flufenamide) is the first in class peptide-drug conjugate targeting aminopeptidases and releasing alkylating agents into clonal plasma cells [27]. The phase II HORIZON trial demonstrated melfulfen efficacy in association with dexamethasone, with a median PFS of 4.2 months in a very heavily pre-treated population [28]. Based on these results, it has been recently approved by FDA, in combination with dexamethasone, in patients who received at least four previous lines of therapy. Iberdomide, a first-in class CELMoDs, was an advanced IMiDs showing more efficacy compared to lenalidomide and pomalidomide [29]. Lastly, venetoclax, the oral BCL-2 targeted therapy used in CLL and AML, showed promising results in RRMM patients harboring t(11;14) or with high BCL-2 expression [30].

To date, novel immunotherapies, including antibody-drug conjugates (ADC), bispecific antibodies, and chimeric antigen receptor T-cell (CAR-T) represent an important option for relapsed or refractory disease resulting in high-quality, deep, and durable responses [31, 32].

B-cell maturation antigen (BCMA), a member of the tumor necrosis factor (TNF) superfamily, represents a promising new target for MM therapy and it was the first clonal plasma cell antigen to be targeted in CAR-T clinical trials for MM [33]. Frequent, deep, and durable responses with BCMA-directed CAR-T cells (idecabtagene-vicleucel) have been recently reported in MM patients who were triple-class exposed and refractory to their last regimen in the multicenter pivotal phase II KarMMa-2 trial [34]. This has led to the rapid approval by FDA and by EMA of the first product (idecabtagene vicleucel) for RR MM patients after three lines of therapy. On February 2022, FDA approved a second product, ciltacabtagene autoleucel, for the treatment of RR MM patients after four or more lines of

therapy, based on the results of the phase 1b/2 study CARTITUDE-1 [35]. Results from subcutaneous teclistamab, a T-cell redirecting bispecific antibody targeting BCMA, showed an impressive overall response rate (ORR) of 73% in heavily pre-treated patients with a median of 5 prior lines of therapy [36].

2. Belantamab Mafodotin

Belantamab Mafodotin is the first in class ADC targeting BCMA obtained FDA accelerated approval in August 2020, based on the results of phase II DREAMM-2 trial, for patients with RRMM who have received at least 4 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody [37]. On November 2022, FDA announced that the process for the withdrawal of the US marketing authorization for belantamab mafodotin has been initiated. This action is based on the results of the DREAMM-3 trial (NCT04162210), in which the primary endpoint of PFS was not met, with a hazard ratio of 1.03 (95% confidence interval, 0.72–1.47) in a head-to-head comparison of belantamab mafodotin versus Pd. A longer observed median PFS of 11.2 months was seen with belantamab mafodotin, compared with 7 months for Pd.

2.1. Mechanism of action

ADCs, an evolution of naked mAbs, consist of a mAb attached to a specific cytotoxic payload covalently conjugated through chemical linkers. The mechanism of action of ADCs is unique whereby the mAb binds a tumor-specific antigen on clonal plasma cells resulting in the cytotoxic payload internalization. Once the ADCs are intracellular, lysosomal degradation occurs causing the release of the toxic payload within the plasma cells. Then the free toxic payload enters the cytoplasm and/or nucleus, exerting its effect and causing apoptosis and cell death [38]. The first ADC approved by FDA for use in hematological malignancies was brentuximab vedotin in 2018. This ADC targets CD30 and it has been approved for Hodgkin's lymphoma selecting CD30 expressing T-cell lymphomas [39].

BCMA is a member of TNF receptor superfamily and can be an optimal target for ADCs in MM due to its high expression on clonal plasma cells. Indeed, it is a cell-surface receptor protein expressed almost in end-stage B lymphocytes and clonal plasma cells. Because of its unique expression on MM cells, BCMA has become of interest to develop specific targeted immunotherapies for MM. During malignant transformation of immature plasma cells, BCMA receptor and its ligand, named a proliferation-inducing ligand (APRIL) and B-cell activating factor (BAFF), overexpression activate several signal transduction pathways involved in oncogenesis, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), protein kinase B (AKT), signal transducer and activator of transcription 3 (STAT3), phosphoinositide 3-kinase (PI3K), and mitogen-activated protein kinases (MAPK) cascades. Thus, BCMA overexpression promotes tumor growth, survival, and drug resistance within malignant plasma cells. In addition, γ-secretase activity of the membrane receptor is bale to release soluble BCMA (sBCMA), which correlates with the phase of MM's history, increasing through progression from asymptomatic MGUS stage to smoldering myeloma and then to active MM, and should be helpful to monitor hematological response during treatment phase [33].

The most common naked mAbs used in MM treatment are humanized antibody or fully human immunoglobulin G subtype thanks to its long-circulating half-life in the bloodstream and lower immunogenicity. For ADCs the choice of the ideal antibody is important.

However, for the choice of ideal ADCs it is important, beyond the antibody structure, the covalent linker because, as mentioned, linkers play a crucial role in releasing the potent drug at target tumor cells. Indeed, it has to be able to avoid premature degradation in the plasma because it can cause release of cytotoxic payload with off-target effects on healthy cells. But, at the same time, it has to be able for degradation of the cytotoxic component in the pathologic cells once the ADC could be internalized in the malignant target cell [38, 39]. ADCs linkers are classified according to different categories in terms of the mechanism of drug release and their stability in circulation, including cleavable linkers and non-cleavable linkers. Cleavable linkers are designed to respond to a specific

physiological environment, such as there being high glutathione concentrations, low pH, and special protease, which could assist the linkers in enabling chemical or biochemical reactions by way of hydrolyzation or proteolysis. The second group is non-cleavable linkers that rely on the monoclonal antibody degradation after ADCs' internalization within the lysosomes and endosomes to generate the metabolites containing the active cytotoxic drugs with or without a portion of the linkers [40]. The choice of the optimal killing molecule is important too: indeed, it should be able to exert a direct cell toxicity and it should have an adequate site from where the conjugate releases the drug in the specific tumor cell. The most used payload in hematological malignancy are microtubule inhibitor agents as maytansinoids and auristatin (including monomethyl auristatin E and F), which are able to bind the tubulin, causing G2/M arrest and apoptosis. In addition, DNA-modifying drugs as calicheamicin, inducing cell death by DNA double-strand breaking, are other common form of payload used [41].

Belantamab mafodotin, also called Belamaf, (GSK2587916) is the first in class humanized IgG1 ADC that targets BCMA, approved for RRMM patients after four prior lines of therapy. This ADC is composed by an antibody, that it is able to bind BCMA, conjugated to a cytotoxic agent, monometil auristatin F (mafodotin), by a protease-resistant maleimidocaproyl linker. After binding BCMA on target cells, Belamaf is internalized and undergoes a process of proteolytic cleavage, releasing mafodotin. The released mafodotin disrupts microtubular cell network leading to cell cycle arrest and apoptosis [37, 42].

Belamaf improves additional anticancer effects such as antibody-dependent cellular toxicity (ADCC) and antibody-dependent cellular phagocytosis via recruitment of the immune system, thanks to afucosylation of antibody portion. *In vitro* preclinical studies demonstrated that ADCC is enhanced in combination with IMiDs. In addition, *in vitro* and *in vivo* studies showed that Belantamab mafodotin efficacy is characterized by higher T and NK lymphocyte concentration and an increase of markers of immunomediated tumor cell death [43].

2.2. Dosing and administration

Recommended dose for Belantamab mafodotin is 2.5 mg/kg administered once every 3 weeks and continued until disease progression or unacceptable toxicity. No dose modification is required for renal impairment if the estimated glomerular filtration rate (eGFR) is > 30 mL/min/1.73 m2 or for mild hepatic impairment where total bilirubin is ≤ 1.5 times upper limit of normal. However, no dosing recommendations have been established for patients with eGFR < 30 mL/min/1.73 m2, those with end- stage renal disease either with or without dialysis, or those with moderate to severe hepatic impairment. Therefore, due to the lack of safety and efficacy data for severe renal and hepatic impairment at this time, Belamaf should be considered contraindicated in these patients. Dose interruption, reduction, or discontinuation may be required for adverse events such as thrombocytopenia, infusion reactions, or ocular adverse events. Dose reduction for the first adverse event is Belamaf 1.9 mg/kg once every 3 weeks. Belamaf is administered as an intravenous infusion over 30 minutes and does not require any premedication. However, if patients experience an infusion reaction, then premedication should be administered for all subsequent infusions [44].

2.3. Toxicities

The most important adverse event related to Belamaf therapy is the ocular toxicity as reported by DREAMM-1 and DREAMM-2 clinical trials. Ocular events include keratopathy (defined as corneal epithelial changes named microcyst-like epithelial changes, MECs), best-corrected visual activity (BCVA) reduction and any other ocular symptoms, such as blurred vision, dry eye, and corneal ulceration [37].

ADC adverse events could be explained by on-target or off-target mechanisms: indeed, considering that the majority of the proteins targeted by these agents are not expressed in the cornea (such as BCMA), ocular events may represent a specific off-target mechanism.

Farooq et al.[45] reported that ADC could reach corneal epithelial cell through vascularized part of the limbus or through the tear film because it has been previously detected in animal tears, circumstantially pointing toward its off-target damage site as the cornea lacks BCMA.

Microtubule-disrupting monomethylauristatin-F (MMAF) is the cytotoxic component of Belamaf that is linked to a monoclonal antibody via protease-resistant maleimidocaproyl (mc) linker. MMAF is proposed as an attributable cause of ocular toxicity along with other ADCs that used the MMAF. Several factors are involved to promote off-target ocular toxicity by ADCs such as linker instability or premature cleavage in extracellular environments, linker-cytotoxin intracellular metabolism, and Fc-receptor mediated cellular uptakes. Belamaf induces apoptosis of myeloma cells but may cause a concomitant off-target apoptosis of corneal epithelial cells due to microtubulin inhibition caused by MMAF. MECs require medium to high magnification power when examined via slit lamp. On in-vivo confocal microscopy these changes may appear as hyper-reflective opacities. When Belamaf encroaches the cornea via limbus vasculature or tears, it undergoes the process of solute internalization or cellular uptake via macropinocytosis into in the limbal epithelial stem cells. Once Belamaf is internalized into corneal cells it inhibits their proliferation inducing apoptosis. The second step is the migration of the alive epithelial corneal cells toward the peripheral cornea: at this moment we can detect MECs using the slit lamp images in the absence of specific ocular symptoms, too. Belamaf-containing cells and MECs are initially found at the periphery of cornea but eventually migrate in a centripetal fashion and then vanish due to extrusion [45]. Then, when the migration of Belamaf-carrying cells reaches the central cornea, ocular symptoms are described by patients [46]. However, the exact mechanism of damage is not well defined and requires further elucidations. Investigation of the mechanism and pharmacokinetics of ocular toxicity are underway, as well as the evaluation of various mitigation and management strategies to prevent and treat this toxicity.

In part-1 of DREAMM-1 trial where Belamaf dose ranged from 0.03 mg/kg to 4.60 mg/kg, the ocular toxicity occurred more frequently at larger dose than a smaller dose [42].

In the pivotal phase II DREAMM-2 study, keratopathy was the most common ocular toxicity (73%) irrespective of its grades (71% in 2.5 mg/kg versus 75% in 3.4 mg/kg) and the most common complaints were also blurred vision (22% for 2.5 mg/kg versus 30% for 3.4 mg/kg) and dry eyes (14% for 2.5 mg/kg versus 23% for 3.4 mg/kg). When corneal changes occur in the form of keratopathy, most patients are symptomatic. Nevertheless, the absence of corneal symptoms does not rule out the existence of keratopathy as detected by the slit lamp and visual acuity testing data of DREAMM-2.

In the dosing cohort of 2.5 mg/kg of DREAMM-2, 72% of patients had MECs and 54% had vision changes. Contrarily, only 25% of those patients reported blurred vision and 15% reported dry eyes. Similarly, in the 3.4 mg/kg cohort of Belamaf, 77% of patients had MEC, but 33% of those reported blurred vision and 25% reported dry eyes. These data suggest that ocular toxicity requires active surveillance irrespective of symptoms. Even patients with grade G3 or 4 keratopathies, i.e., severe superficial keratopathy and corneal ulcers may be asymptomatic. Such patients may continue to receive Belamaf with ongoing toxicity unless screened via slit lamp. The median time to onset of MECs was 36 days and it is longer for other specific ocular symptoms, such as BCVA decline (median time of 64 days), blurred vision (median time of 52 days), and 42 for dry eyes. Globally, 3% of patients experienced ocular events led to treatment discontinuation. According to DREAMM-2 data, 48% of patients resolved MECs, and 82% of patients resolved BCVA reduction [37, 42].

The exposure-safety analyses of DREAMM-2 evaluated the likelihood of G2 and G3 corneal AEs and their relationship with Belamaf concentration. Ferron-Brady et al. [47] demonstrated that higher Belamaf Ctrough (the predicted concentration on day 21 at the end of first cycle) was associated with a higher probability of G2 or G3 corneal events or with an earlier onset of them. A history of dry eyes and lower baseline serum concentration of soluble sBCMA were associated with an increased risk of G2 and G3 corneal AEs. A history of dry eyes and baseline keratopathy prior to Belamaf use were associated with a higher risk of any grade of blurred vision. Baseline keratopathy was also associated with an earlier onset of blurred vision along with an increased probability of grade ≥2 blurred vision.

The sub-study analysis of DREAMM-2 for the management of ocular toxicities demonstrated that prophylaxis with steroids eye drops as mitigation strategy was ineffective as ocular prophylaxis [47]. It is strongly recommended the baseline ophthalmic examination prior to the first dose and then before each subsequent doses, even in the absence of symptoms. The use of cooling eye mask, vasoconstrictors prior to Belamaf infusion, is still unclear and should be used at the discretion of physician. The use of preservative-free artificial tears is strongly recommended for all patients, at least four times a day from the day of Belamaf infusion and throughout the treatment course [48].

Lin et al. [49] analyzed imipramine as a new potential drug against micropinocytosis in cellular and biological systems so, theoretically, the inhibition of Belamaf macropinocytosis might reduce occurrence of ocular toxicity but the practical role of such inhibition is limited [49]. To date, it has been demonstrated that dose delay or dose reduction are the only actions to reduce ocular toxicity, in order to allow appropriate time for replacement of corneal epithelial cells. However, no specific guidelines are yet available to apply effective dose delay or reduction. Several trials are ongoing to evaluate alternative dose reduction strategy. DREAMM-2 reported that treatment delay (more than 63 days) did not negatively impact on Belantamab mafodotin efficacy: of 16 patients, 38% deepened their response; 38% maintained the same response, and 13% showed an increase of serum monoclonal protein in the absence of criteria for disease progression [50].

Considering the high frequency of ocular symptoms with Belamaf treatment, patients should be monitored closely with ophthalmology and hematology to ensure the effective and safe use of Belamaf.

About hematologic toxicities, thrombocytopenia was reported as the most common adverse events during Belamaf treatment. In DREAMM-1 study grade 3-4 thrombocytopenia and anemia were reported in 35% and 15% of patients, respectively. This data was confirmed in DREAMM-2 trial: grade 3-4 thrombocytopenia was observed in 22% of patient treated in the 2.5 mg/Kg arm compared to 32% in the 3.4 mg/Kg arm [37]. Furthermore, thrombocytopenia was reported in DREAMM-6 study, leading treatment discontinuation and dose delay in 33% and 39% of patients, respectively. [50].

Other reported minor extra-hematological adverse events were pneumonia, GGT and ALT serum increase without liver dysfunction, hypertension, hypercalcemia, and fatigue.

As previously mentioned, premedication before each Belamaf infusion is not mandatory. In DREAMM-2 study, premedication was not mandatory, specifically it was administered in about ¼ of all patients but it did not reduce the rate of infusion related reactions (IRRs). IRRs were reported in 21% of patients treated in the arm of 2.5 mg/Kg and 16% of patients in the arm of 3.4 mg/Kg experienced IRRs, mostly during the first infusion and nearly all were grade 1-2.

3. Clinical trials on Belantamab Mafodotin

3.1. DREAMM-1, DREAMM-2 and DREAMM-3 studies

The first human phase I trial evaluating belamaf monotherapy was the international Driving Excellence in Approaches to MM (DREAMM-1) study [42]. No maximal tolerated dose was found in the dose-escalation phase of the study in which 38 patients, 76% of whom had received at least 5 prior lines of therapy, received from 0.03 mg/kg to 4.6 mg/kg intravenous belamaf every 3 weeks until progression..The dose of 3.4 mg/kg was the RP2D chosen in the dose expansion phase, in 35 patients, among whom 57% had received more than 5 prior lines of therapy, more than 90% were double-refractory and 40% were refractory to daratumumab. After a median follow-up of 12.5 months, patients enrolled in the part 2 of the trial had a ORR of 60%, with 55% achieving at least VGPR. Belamaf monotherapy was found active in double- (ORR = 56.3%) and triple-refractory (ORR = 38.5%) patients as well in those with more than 5 prior therapies (ORR = 50%) [42]. Median time to first response was 1.2 months, median duration of response was 14.3 months and median PFS 12 months, being 6.2 months in triple-refractory patients. As regard safety profile, the most common grade 3-4 adverse events were thrombocytopenia (35%), and cornel events occurring in 69% of patients, most commonly blurred vision (51%), dry eye (37%) and photophobia (29%). After DREAMM-1 study,

pivotal phase II, open-label, two-arm, multicenter DREAMM-2 trial [37] led to approval of belamaf in RRMM. This study enrolled RRMM patients who had received at least three prior lines of therapy, who were refractory to a PI and an IMiD and were refractory or intolerant to an anti-CD38 mAb. Patients whose median age was 66 years, were randomised to receive belamaf 2.5 (n = 97) or 3.4 mg/kg (n = 99) every 3 weeks until disease progression or unacceptable toxicity. As per baseline patient characteristics, patients received a median of 7 (3-21) and 6 (3-21) previous lines of therapy in the 2.5 mg/kg and 3.4 mg/kg cohort, respectively with 100% of patients refractory to daratumumab in the 2.5/kg cohort in which approximately 27% of patients were at high risk cytogenetic, harbouring t(4;14, t(14;16) or del(17p) and 23% had extramedullary disease. The primary endpoint DREAMM-2 trial was ORR and the final analysis [51] showed, after a median follow-up of 12.48 months for patients enrolled in the 2.5 cohort and 13.77 months for those randomized to 3.4 mg/kg cohort, an ORR of 32% and 35%, respectively. Among patients who obtained at least VGPR (19% in the 2.5 mg/kg group and 24% in the 3.4 mg/kg cohort) 36% and 23%, respectively, achieved MRD negativity. Median duration of response (DoR) and media PFS were 12.5 and 2.8 months in the 2.5 mg/kg cohort and they were 6.2 and 3.9 months in the 3.4 mg/kg group. Notably, median PFS was higher in patients achieving high quality response (≥ VGPR), being 14 months and 16.8 months for 2.5 mg/kg and 3.4 mg/kg cohorts, respectively. As regard OS, median estimated was 15.3 months in patients allocated to 2.5 mg/kg arm but it resulted to be 30.7 months in patients achieving at least VGPR. In patients receiving 3.4 mg/kg estimated median OS 14 months, being 35.5 in those with ≥ VGPR [51]. Among patients treated with belamaf 2.5 mg/kg, efficacy was documented either in patients with standard risk cytogenetics, defined as patients with none of t(4;14, t(14;16), del(17p) or 1q21+, in whom ORR was 34% and median DoR was not reached after a median follow-up of 13 months or in patients with high risk cytogenetic (with any of the above abnormalities) in whom ORR was 29% and median estimated DoR 10.3 months. Moreover, patients with mild or moderate renal impairment obtained similar ORR compared with those with nomal renal function[46].

In the DREAMM-2 study median time on therapy was 2.1 months (0.5-41 months) and 2.8 months (0.5-42.8) for patients randomized to 2.5 mg/kg and 3.4 mg/kg, respectively. As per safety profile, grade ≥ 3 adverse events occurred in 84% of patients receiving belamaf 2.5 mg/kg and 83% of those treated with 3.4 mg/kg, requiring dose reduction in 36% and 44% and permanent discontinuation of belamaf in 9% and 5% of patients, respectively [51]. The main grade ≥ 3 hematologic toxicities were anemia occurring in 21% and 28% of 2.5 mg/kg and 3.4 mg/kg cohorts whereas thrombocytopenia was documented in 19% and 29% of patients, respectively. Among nonhematologic adverse events, the most common was ocular toxicity whose rate observed in patients allocated to 2.5 mg/kg was similar to that of 3.4 mg/kg group. In the first cohort any grade keratopathy occurred in 71% of patients (grade ≥ 3 = 29%), blurred vision in 25% and BCVA reduced to 20/50 or worse in 48% of patients. Median time to keratopathy resolution was 120 days whereas median time to resolution of first BCVA event was 23 days. However, only 3% of patients in both study arms permanently discontinued treatment because of ocular events [51]. Based on results and the benefit-risk profile observed in the pivotal DREAMM-2 study, belamaf received accelerated approval on August 2020, at the dosage of 2.5 mg/kg every three weeks, for RRMM patients who have received at least four prior therapies including an anti-CD38 mAb, a PI and an IMiD [52]. The ongoing phase II randomized DREAMM-14 trial is recruiting RRMM patients with ≥3 prior lines of therapy in order to evaluate if modifying the dose of belamaf monotherapy, the schedule or both a reduction in the incidence of ocular events, the primary endpoint of the study, can be achieved.

The phase III, open-label, randomized DREAMM-3 trial, comparing single agent belamaf to pomalidomide/dexamethasone (Pd) in 325 who had received at least 2 prior lines of therapy including lenalidomide and a PI, failed its primary endpoint since, despite a longer PFS for patients enrolled in the belamaf arm compared with Pd arm (11.2 months vs 7 months), HR was 1.03 (95% CI: 0.72-1.47). However, at least VGPR was documented in 25% and 8% of patients receiving belamaf abd Pd, respectively, an safety profile was consistent with the one already known [53].

3.2. Ongoing studies with Belantamab Mafodotin-based regimens in relapsed/refractory MM

Phase I/II Algonquin study evaluated safety and efficacy of different doses and schedules of belamaf combined with Pd (Bela-Pd) in RRMM who had received at least one prior line of therapy, exposed to lenalidomide an PI, and pomalidomide naïve [54]. In the Part 1 of the study, a dose-escalation phase, patients were treated with pomalidomide 4 mg days 1-21, dexamethasone 40 mg weekly and belamaf as single dose of 1.92 mg/kg every 4 weeks, as single dose of 2.5 mg/kg every 4 weeks, every 8 weeks or every 12 weeks, or split on days 1 and 8 (2.5 mg/kg or 3.4 mg/kg) every 4 weeks. Considering the 54 triple-class exposed patients enrolled in the study, median age was 67.5 years, median number of prior lines of therapy was 3 (range 2-5) and 72.2% were triple-refractory. Across all cohorts, ORR was 86% and 60% of patients achieved at least a VGPR. As per outcome measures, after a median follow-up of 5.7 months, median PFS resulted to be 15.6 months, an imprressive results considering that in the prospective LocoMMotion study triple-class exposed patients treated with standard of care had a median PFS of 4.6 months [23]. Most common grade ≥ 3 adverse events included keratopathy (55%), neutropenia (37%), thrombocytopenia (27.5%) and decreased BCVA (23.5%). Other studies with belamaf including also patients with early relapse are ongoing. Phase I/II DREAMM-6 study is exploring safety and activity of up to 3 dose levels and up to dosing schedules of belamaf in combination with lenalidomide/dexamethasone (Rd, arm A) or bortezomib/dexamethasone (Vd, arm B) in patients with ≥ 1 prior line of therapy. Preliminary results of 18 patients with a median of 3 prior lines of therapy (range 1-11) enrolled in the arm B and receiving belamaf 2.5 mg/kg single dosing plus Vd showed an ORR of 78% with 67% of patients achieving at least VGPR. After a median of 25.5 weeks on treatment, median DoR was not reached. Grade ≥ 3 thrombocytopenia occurred in 66% of patients, grade 3 keratopathy in 61% whereas peripheral neuropathy (all grade ≤ 2) was observed in 33% of patients [50]. The international phase III DREAMM-7 trial is enrolling RRMM patients who have received at least 1 prior line of therapy, randomizing them between belamaf/bortezomib/dexamethasone (B-Vd) and daratumumab/bortezomib/dexamethasone (D-Vd) in. In the same setting of patients, phase III DREAMM-8, aiming to enroll 450 patients with RRMM worldwide, is comparing belamaf/pomalidomde/dexamethasone (B-Pd) vs pomalidomide/bortezomib/dexamethasone (PVd). In the Table 1 we summarized other ongoing clinical trials including belamaf in patients with RRMM.

Table 1. Other ongoing clinical trials including belamaf in patients with RRMM.

Trial	Phase	Population	Intervention	Trial ID
A study to investigate the safety and clinical activity of belantamab mafodotin + daratumumab, pomalidomide and dexamethasone in patients with RRMM previously treated with one line therapy who are lenalidomide refractory	I/II	RRMM with previous 1 line of therapy and lenalidomide-refractory	Bela-DPd	NCT05581875
Study of belantamab mafodotin in combination with Kd for the treatment of RRMM, refractory to lenalidomide	I/II	RRMM with 1-3 prior lines of therapy, refractory to lenalidomide	Bela-Kd	NCT05060627
Belantamab mafodotin maintenance therapy after salvage autologous hematopoietic cell transplantation in patients with RRMM	I	RRMM with ≥ 2 prior lines including PI, IMiD, and anti CD38 mAb	Belamaf	NCT05065047
Study of belantamab mafodotin with carfilzomib, pomalidomide, and dexamethasone in RRMM	II	RRMM with ≥ 2 prior lines including PI,	Bela-KPd	NCT05789303

		IMiD, and anti CD38 mAb		
DREAMM-12	I	Renal impairment RRMM with ≥ 2 prior lines including PIs and IMiDs	Belamaf	NCT04398745
DREAMM-13	I	Hepatic impairment RRMM with ≥ 2 prior lines including PIs and IMiDs	Belamaf	NCT04398680
A study of belantamab mafodotin and nirogacestat in people with MM that has not responded to treatment or has come back after treatment	I	RRMM with ≥3 lines including PI, IMiD, anti CD38 mAb	Belamaf + Nirogacestat	NCT05556798
DREAMM-4	I/II	RRMM with ≥3 lines including PI, IMiD, and anti CD38 mAb	Belamaf + Pembrolizumab	NCT03848845
DREAMM-5	I/II	RRMM with ≥3 lines including PI, IMiD, and anti CD38 mAb	Belamaf + innovative drugs	NCT04126200
DREAMM-20	I/II	RRMM with ≥3 lines including PI, IMiD, and anti CD38 mAb	Bela-xRd. X will be either a SoC or an emerging treatment	NCT05714839
Belantamab mafodotin, cyclophosphamide, and dexamethasone in RRMM	I/II	RRMM with ≥3 lines including PI, IMiD, and anti CD38 mAb	Bela-Cd	NCT04896658
Novel combination of belantamab mafodotin and elotuzumab to enhance therapeutic efficacy in multiple myeloma	I/II	RRMM with ≥3 lines including PI and IMiD	Belamaf + elotuzumab	NCT05002816
Master Protocol	I/II	RRMM with ≥3 lines including PI, IMiD, and anti CD38 mAb	Belamaf + novel agents	NCT04643002
EMBRACE	II	RRMM with ≥3 lines including PI, IMiD, and anti CD38 mAb	Maintenance with Belamaf after anti-BCMA CAR T cell therapy	NCT05117008

3.3. Sequencing of Belantamab Mafodotin with other BCMA-targeting immunotherapies

Availability of anti-BCMA immunotherapies as CAR-T cells products ide-cel [34] and cilta-cel [55] as well as the approval by FDA and EMA of bispecific antibody teclistamab [36] raised the question of the effectiveness of a retreatment with another product in patients already exposed to BCMA targeting immunotherapies. A recent analysis, using data from DREAMM-1 and DREAMM-2 trials, evaluated free sBCMA concentration at baseline, at achievement of best response and at latest progression in order to study BCMA expression during treatment with belamaf [56]. In 97% of patients who responded to treatment and later progressed in the DREAMM-2 trial, sBCMA level significantly decreased during response, returning to the baseline level at the time of progression,

suggesting that target loss does no represent the main mechanism of resistance in these patients. In the recent study by Cohen et al [57], 13 patients with advanced MM (previous lines of theapy = 8) received cilta-cel after belamaf, resulting in an ORR of 61.5% with 71% of evaluable patients achieving MRD negativity. After a median follow-up of 11,8 months, median DoR was 11.5 months and median PFS was 9.5 months. The opposite sequence can also be effective as shown by Gazeau et al [58] reporting a response that can be durable in patients receiving belamaf after CAR T cell therapy.

3.4. Belantamab Mafodotin in newly diagnosed MM

As well as for other novel immunotherapies, several clinical trials are exploring belamaf in the upfront setting. At the last ASH Meeting preliminary results from phase II Spanish GEM-BELA-VRd trial have been presented [59]. Treatment included 6 induction cycles with VRd plus belamaf 2.5 mg/kg every 8 weeks, high dose melphalan and ASCT followed by a consolidation with 2 cycles with Bela-VRd and and maintenance with lenalidomide until progression plus belamaf for 2 years. Among the 40 patients who received at least 4 cycles of induction, ORR was 82%, at least VGPR 69% and CR 13%. Ocular toxicity represented the most common toxicity since 77.5% of patients developed blurred vision and 60% any grade keratopahy. Neutropenia and thrombocytopenia were the most frequent hematologic adverse events.   In the same Meeting, Greek Group presented preliminary results of 36 transplant-ineligible patients (median age = 72.5 years) treated with the regimen Bela-Rd in a phase I/II study [60]. ORR was 97%, 72% of patients achieved at least VGPR and all patients were in response after a median follow-up of 9.5 months. Grade 3 visual acuity reduced occurred in 33% of patients whereas no patients developed grade 3-4 keratophaty as well as grade 3-4 thrombocytopenia were not documented. In the Table 2 we summarized main ongoing clinical trials with belamaf in NDMM.

Table 2. Main ongoing clinical trials with belamaf in NDMM.

Trial	Phase	Population	Intervention	Trial ID
Study of belantamab mafodotin as pre- and post-autologous stem cell transplant and maintenance for MM	II	Transplant eligible	Belamaf pre (day -42) ASCT and after for 2 years	NCT04680468
Belantamab mafodotin and lenalidomide for the treatment of MM in patients with minimal residual disease positive after stem cell transplant	II	Transplant eligible	Belamaf + lenalidomide for 6 cycles if MRD positivity after ASCT	NCT04876248
Belantamab mafodotin, pomalidomide and dexamethasone for the treatment of high-risk MM	II	Transplant eligible High Risk cytogenetics	Bela-Pd maintenance after ASCT	NCT05208307
A study to investigate the safety and clinical activity of belantamab mafodotin in combination with daratumumab, lenalidomide and dexamethasone in patients with newly diagnosed MM transplant ineligible	I/II	Transplant ineligible	Bela-DRd	NCT05280275
A study to investigate safety and clinical activity of belantamab mafodotin in combination with lenalidomide, dexamethasone and nirogacestat in patients with transplant ineligible NDMM	I/II	Transplant ineligible	Bela-Rd + nirogacestat	NCT05573802
DEAMM-9	I	Transplant eligible and ineligible	Bela-VRd followed by Bela-Rd	NCT 04091126
Study of carfilzomib, lenalidomide, dexamethasone and belantamab mafodotin in MM	I/II	Transplant eligible and ineligible High Risk cytogenetics	Bela-KRd	NCT04822337

4. Real life data on Belantamab Mafodotin

4.1. USA real life experiences

Several American real life experiences have been published in order to better define efficacy and toxicity of belantamab outside clinical trials, which had restricted patients' selection, risking providing poorly reproducible data in real life settings.

Vaxman et al. [61] retrospectively identified 36 MMRR patients who received at least one dose of belantamab outside a clinical trial at all three Mayo Clinic sites, from September 2020 to June 2021, with a median follow up of 6 months. Patients' median prior lines of therapy was eight, more than DREAMM-2 trial, whose six patients (17%) received belantamab in combination with other agents (pomalidomide, cyclophosphamide and thalidomide) and seven patients (19%) had already received another anti BCMA agent (CART) prior to belantamab therapy. These features characterized a heavily pre-treated population, also BCMA-refractory, differently from the pivotal study. Median time from diagnosis to first belantamab dose was 7 years. They reported an ORR of 33% with a median PFS and OS for the whole cohort of 2 months and 6.5 months, respectively. Eighteen patients died, the all for disease progression. As for safety, keratopathy developed in 16 patients (44%), it was grade 1 in six patients, grade 2 in seven patients, grade 3 in three patients. Six patients reported decreased visual acuity. Two patients had grade 3 infusion related reactions and two had infections. Hospitalization rate was 33% and they were mostly related to MM complications (malignant ascites, hypercalcemia, pain management). The only previously unreported toxicity was seen in one patient hospitalized due to a suspected TLS. Five patients are still on therapy, treatment discontinuations were in 85% of patients, because of disease progression in 28 patients (77%) and keratopathy in three patients (8%). Despite the low number of enrolled patients, this was one of the first paper which confirmed efficacy and safety data of clinical trials in real world setting [61].

More recently, Abeykoon et al. [62] conducted a retrospective observational study on 38 RRMM patients, treated with belantamab at Mayo Clinic between January 2020 and January 2021, with a median follow up of 11 months, to evaluate the impact of belantamab mafodotin-induced ocular toxicity on outcomes of patients themselves. Authors found a 29% ORR, with a median PFS and OS of 2 and 7.2 months, respectively, in a really heavily pre-treated population (median prior lines of therapy 8, range 2-15), with 89% of patients having high risk disease characteristics and a median time from diagnosis to belamaf start of 7 years (range 1-19.7). Ocular toxicity was observed in 27 (75%) patients: keratopathy in 25 (69%), decreased BCVA in 21 (58), and/or ocular symptoms like xerophthalmia in 13 (36%). Ocular toxicity seemed to develop earlier in responders patients than non-responders. Authors found that keratopathy significantly complicated belamaf therapy mitigating its full potential effectiveness. For ocular toxicity, belantamab was permanently discontinued in 5 (14%) patients after a median of three doses (range: 2–3), delayed in 9 (25%) patients and reduced in doses in 4 (11%) patients. Belantamab discontinuation rate seemed to be 14-fold higher than in DREAMM-2 trial, probably because of the longer follow up may have captured more patients with keratopathy associated discontinuation. Moreover, only a few patients maintained their response (PR, 2 and VGPR, 2) during the prolonged keratopathy-related treatment interruption, compared to the 88% of patients maintaining their response in DREAMM-2, probably because real world population may be more heterogeneous, more heavily pre-treated with much more high risk diseases [62].

Becnel et al.[63] presented at ASCO 2022 data of a retrospective, single-center, real-world experience of belantamab mafodotin in 39 RRMM patients treated between November 2020 and November 2021 at MD Anderson Cancer Center in Houston. Overall population had 7 median prior lines of therapy (range 3-16) and 38% of whom had high risk FISH features, 38% extramedullary disease and 69% didn't met eligibility criteria for DREAMM-2 study, picturing a more difficult population to treat than the pivotal study. Moreover, 8 patients were even anti-BCMA-refractory, one of them obtained a PR and another a MR. Authors found a 27% ORR with a CBR of 35%. Median PFS was 1.8 months and median OS 9.2 months, with a not reached median DOR at a median follow up of 10.1 months. Twenty-five (76%) patients reported keratopathy, BCVA was described in 75% of patients, with a median time to first ocular adverse event of 1.3 months. However, there were not

information about recovery of these events. Authors specified that the most common reason for treatment discontinuation were disease progression in 75% and adverse events in 9% of patients. This retrospective study demonstrated a good efficacy and safety profile of belantamab in a real life population not eligible to clinical trials [63].

Hultcrantz et al. [64] presented data at ASH Meeting 2022 from a retrospective, single-center, observational study of 90 RRMM patients who have received at least one dose of commercial belantamab mafodotin at Memorial Sloan Kettering Cancer Center, between October 2020 and October 2022. Their median prior lines of therapy were 6 (range 2-14) and 19% of them was already BCMA-exposed (12 CART, 6 bispecific antibodies and 2 belantamab). No data were available about frailty of enrolled patients. ORR was 42%, with 36% having disease progression as best response, similar between BCMA-exposed and BCMA-naïve. Median PFS was 4 months with a median DOR of 13.1 months and median OS of 20.5 months. Ocular toxicity was reported in 58 (64%) patients globally, being keratopathy in 57 (63%) patients and BCVA reduction in 41 (46%) patients. Twenty-six (29%) patients reduced belantamab doses, 24 (27%) delayed doses and 9 (10%) discontinued treatment, for ocular toxicity. No new safety concerns were identified in this real life population, the majority of patients were able to continue belantamab and maintain a clinical response [64]. Hultcrantz et al. [65] also presented at the same meeting retrospective data of 137 RRMM patients who had ≥1 record for belantamab administration, from the US EHR-derived Flatiron Health Database, from January 2011 to December 2021. Among them, there were 40 (29.2%) penta-refractory patients, 64.2% of all patients had received at least 5 lines of therapy prior to belamaf start, being globally less pre-treated than patients in DREAMM-2. The median time from MM diagnosis to the first belantamab administration was 4.8 years, shorter than in DREAMM-2 study (5.49 years). But patients had a lot of comorbidities, more than 50% of patients had cardiovascular disease, 24% cardiac disease and 38% renal disease, but performance status was not reported. ORR was 30.2% at 6 months, similarly to pivotal DREAMM-2 study, and median PFS was 5.4 months, slightly longer. Among the whole population, 51.8% of patients had ocular toxicity (40.9% keratopathy, 64.2% blurred vision, while reduction in BCVA rate was not specified). Most ocular adverse events (58.5%), including keratopathy events (76.0%), were managed by therapy hold. The most common reasons of treatment discontinuation were disease progression (33.8%), treatment toxicity (19.7%), and a combination of both (15.5%). Authors confirmed in a numerous real world cohort of RRMM patients, slightly older than in DREAMM-2 (median age: 68 vs 65 years) and with multiple comorbidities, efficacy and safety data from pivotal study, suggesting that belantamab could help fill the unmet treatment need in this setting [65].

4.2. Asian real life experience

Shragai et al. [66] published data from an Israelian observational multicenter real-life study treating 106 RRMM patients with belantamab between 2019 and 2021, during the compassionate programme, with or without steroid. Baseline population characteristics were similar to DREAMM-2 study, but patients had lower median prior lines of therapy (6 vs 7). Differently from the pivotal study, there was 32% of penta-refractory patients, and median age was little higher (69.4 vs 65 years). ORR was 45.5% and this rate was maintained among different subgroups (age, sex, triple-or penta-refractoriness, ISS, R-ISS, high-risk cytogenetics, EMD). At a median follow up of 11.9 months, median PFS was 4.7 months in the whole population, while it was 8.8 months in responders, confirming the significant association between response deepness and outcomes, already reported in DREAMM-2. There was no difference in PFS between the whole cohort and triple-refractory or penta-refractory patients. Median DOR was 8.1 months and median OS 14.5 months, without differences based on cytogenetic risk or refractoriness status, but better in responders than not responders. As for safety, the most common adverse event was ocular, 65 (68.4%) patients experimented keratopathy, of whom 63.4% resolved to grade 1 or less. Ocular symptoms were reported in 36.8% of evaluable patients. Discontinuations due to ocular toxicity were 4 (3.8%), similarly to DREAMM-2, and delays were 82 (70.7%), without correlation between proportion of dose delay and response rate. Other safety concerns were thrombocytopenia in 29 (27.4%) patients, 17.9% grade ≥3, infections

(11.3%, with 2 cases of hepatitis B reactivation) and anemia (11.3%). Considering that these patients had fewer prior lines of therapy, more patients with >75 years (23% vs 13%) and the presence of penta-refractory patients (32 vs 0) than DREAMM-2, without patients with severe renal failure or Cytopenic because they were excluded from the compassionate programme, ORR seemed to be higher in the real world experience, with similar outcomes. Interestingly, both ORR and outcomes didn't seem worse in penta-refractory patients than the overall cohort, encouraging anti-BCMA retreatment in the challenging setting of penta-refractory patients. No new safety signals were reported in real life, and Authors confirmed the reversibility of ocular findings. This paper reported for the first time 2 cases of tumor lysis syndrome, highlighting the need to select patients who could receive adequate prophylaxis [66].

4.3. European real life experiences

Offidani et al. [67] reported data from an observational, multicentre, retrospective real life study on 67 RRMM patients treated with belantamab in compassionate use programmes as Named Patient Program (NPP) and Expanded Access Program (EAP) in different Italian centers, under the aegis of European Myeloma Network (EMN). Compared to DREAMM-2, this cohort had fewer previous lines of therapy (5 vs 7) but similar median age, with similar general characteristics. Authors found similar ORR (31%) and CBR (37%). Median PFS was 3.7 months, median OS 12.9 months and median DOR 13.8 months, they seemed higher than the pivotal study. Authors confirmed that ocular toxicity was the most common, mostly grade <3 (87%), with keratopathy reported in 23 (74%) patients, ocular symptoms in 5 (16%) and changes in BCVA in 3 (10%), all reversible during the follow up. Moreover, drug was discontinued in 45% of cases and 13% of cases needed only a dose reduction. Thrombocytopenia was the second most common adverse event, reported in 14 (87.5%) patients, always reversible. Infections, infusion reactions and one case of secondary gallbladder cancer were described as less frequent adverse events. The most common cause for drug discontinuation was disease progression (75%). Authors demonstrated in explorative univariate analysis that PFS was negatively affected by patient characteristics, like age > 65 years (p=0.094) and ECOG $\geq$ 2 (p=0.012), rather than classical prognostic features, paving the way for future investigations on the best applicability of this drug [67].

Iula et al. published data of an observational, multicentre real life study on 28 RRMM patients treated with belantamab in four Hematology Units of the Campania region in Italy. Their median prior lines of therapy were 6 and their general characteristics were quite similar to DREAMM-2 patients, except for number of patients with severe renal failure (9% in the evaluable population vs 2% in DREAMM-2). Authors reported 40% ORR, without difference in different subgroups based on renal failure severity. Interestingly, patients with renal impairment were 20 (71%), they were classified based on the severity of renal failure in 8 patients with mild dysfunction (60 $\leq$ GFR< 90 ml/min), 8 with moderate (30 $\leq$ GFR > 60 ml/min) and 4 with severe (GFR < 30 ml/min), that were slightly higher rates than DREAMM-2. Patients with mild, moderate or severe renal failure showed an ORR of 50%, 25% or 50%, respectively, similar to that reported in DREAMM-2 and Mayo clinic trials, even considering the special population of the DREAMM-2 trial with mild (49%), moderate (25%) and severe (2%) renal dysfunction. These results are really important because patients with severe renal dysfunction are always poorly represented in published clinical trials, suggesting belantamab could be safely administered in MM patients with severe renal impairment without reducing clinical benefits, probably because the drug is mainly degraded and eliminated through internalization and intracellular proteolysis [68]. Median PFS and OS were 3 and 8 months, respectively, at a median follow up of 6.5 months. Median DOR was not reached. Selecting overall population by best response, median PFS was not reached in the subgroup who obtained a VGPR (vs 11 months in patients with PR), endorsing the association between deep responses and better outcomes, even in real life setting. ORR remained the only factor impacting outcomes in univariate analysis. Thrombocytopenia was the most frequent adverse event (46%), mostly grade < 3 (14% grade 3-4), followed by keratopathy (32%) that was always reversible and grade $\geq$ 3 in only 11% of cases, leading to drug discontinuation. Authors describe clinical ocular management of patients, which

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provided an ophthalmological visit only in case of ocular problems during the course of treatment, except for one center where the ophthalmological visit was made every three months after starting belantamab administration. Authors specified that there were no standardized procedures across different centers for keratopathy diagnosis and management, and this could have underestimated the real rate of silent corneal damages. This is very important in a real life study, because it better mirrors real life clinical management, as a close interdisciplinary assessment could be difficult to organize based on ophthalmologist availability and patients' clinical conditions [69].

De La Rubia et al.[70] presented at ASH Meeting 2022 data from an observational, retrospective and multicenter study which included 126 RRMM patients from 59 centers, who received at least one dose of belantamab within compassionate use or expanded access programs in Spain, between November 2019 and June 2021. Overall population was older than DREAMM-2 one (median age 72.5 vs 65 years), with severe renal failure in more cases (8% vs 2%), more extramedullary disease rate (31.4% vs 23%) and 34.6% of patients were penta-refractory. But, median prior lines of therapy were less than the clinical trial (5 with a range from 4 to 6 vs 7). ORR was 46.4%, really higher than in DREAMM-2, and it was maintained in triple-refractory and penta-refractory patients. Likewise, there were no differences in response rate among different age subgroups. Median PFS and OS were 3.6 and 11.1 months, respectively, at a median follow up of 13 months in the overall population. Authors also demonstrated the significant correlation between outcomes and deepness of response, like in DREAMM-2, being median PFS 14.4 vs 1.6 months and OS 23.3 vs 3.9 months, in patients who obtained a response ≥MR vs <MR, respectively. In patients achieving at least MR, median DoR was 13.9 months. Ocular adverse events were reported in 53.2% of patients, with keratopathy being the most frequent (46.8%), in most cases grade <3 (82%), causing the drug discontinuation in only 2 patients. Thrombocytopenia was described in 15.4% of patients, being of grade ≥3 in 10.9% of cases. Infections were the most important non-hematological toxicity, it was reported in 15% of cases, 5.6% of whom grade ≥3. In conclusion, Spanish real life experience documented an efficacy and safety profile similar to the pivotal trial, with slightly higher ORR, even if it was used in a cohort of patients with really fewer median lines of prior therapies but with more aggressive disease characteristics [70]. Roussel et al. presented at [71] ASH Meeting 2022 results of ALFA study, a non-interventional, retrospective study of 184 RRMM patients who started belamaf in 46 centers in France during early access programs, from April 2020 to June 2021. Study population was older than DREAMM-2 one (median age 70.3 vs 65 years) with more frailty features (12.3% vs 2% of patients with severe renal failure were included, 11.5% of patients with ECOG≥3). Importantly, 78.8% of patients were penta-exposed, without information about refractoriness status. Fifty-eight percent of patients received ≥5 prior lines of therapy, lower than in DREAMM-2. ORR was 32.7% with a median CBR of 36.4%. Interestingly, both ORR and CBR were 0% in the subgroups of patients with extramedullary disease (only 15 patients). Median PFS was 2.4 months in the overall population, when it was stratified by the best response, it was 20.6 months in patients with ≥VGPR, 7.1 months in patients with PR, and 1.6 months in others, demonstrating again the significant correlation between outcomes and deepness of disease response. The same was for median OS, which was 8.8 months for the full cohort of patients, 17.5 months in patients with PR, 14.1 months in MR, 9.5 months in SD and 5.6 months in the other patients; median OS in progressive disease was drastically lower (3.3 months). The most frequent adverse events were ocular (56%), most of them grade <3 (71.5%). Keratopathy was reported in 41.8% of patients, only 8.2% grade ≥3, decreased visual acuity in 10.9% and other ocular disorders in 13%. Ocular adverse events caused permanent drug discontinuation in 12.5% of cases, dose modification in 19.6% and temporary interruption in 11.4%, with a median duration of delay of 32 days. Thrombocytopenia occurred in 13.6% of patients and infusion reactions were reported in 3.3% of patients. The results of ALFA study were similar to them of DREAMM-2 trial, even if the population was older and more frail, but less pre-treated [71].

More recently, Talbot et al. [72] published results from IFM 2020-04 real-world study on the efficacy and safety of Belantamab in 106 RRMM, based on data from the nominative ATU (authorisation temporaire d'utilisation) in France, from November 2019 to December 2020. Their median age was 66 years and their median number of prior lines of therapy was 5 (range 3-12). All

patients were triple-exposed but only 55.6% were triple-refractory, there was 11.3% of penta-refractory patients, that were the two most relevant differences between this and DREAMM-2 study. So, ORR was 38.1%, higher than DREAMM-2 trial, but outcomes remain similar with a median PFS of 3.5 months, OS 9.2 months and DOR 9 months. Interestingly, in subgroups analysis, no significant difference was observed in terms of outcomes based on the presence of extramedullary disease, cytogenetic risk or refractoriness status, except a significant difference in OS between fit and unfit patients (OS 16.8 vs 5 months, p=0.01), probably not only related to Belantamab effect. This paper confirmed the significant correlation between outcomes and deepness of response, with an HR of 3.05 for OS and 2.91 for PFS. Ocular toxicity was confirmed to be the most frequent (48%), grade 3 in 40.8% of patients, and keratopathy was reported in 37.5% of patients. Ocular events resulted in delayed treatment administration or in a dose reduction in 30% of patients. Thrombocytopenia was the second most relevant toxicity, reported in 43.8% of patients grade ≥3. No new concerns were highlighted in this real life experience [72].

Table 3. MRD rates in 3-drugs and 4-drugs clinical trials.

Title	Patients (n)	Population: median of prior lines of therapy (range), median age (range)	Outcomes (ORR, mPFS, mDOR)	Safety: keratopathy grade ≥3 (%)	Therapy discontinuation for toxicity (%)
USA experiences					
"Real-life" data of the efficacy and safety of belantamab mafodotin in relapsed multiple myeloma—the Mayo Clinic experience[61]	36	8 (7-11) 61 (37-83)	33 2 14.3	8	50
Impact of belantamab mafodotin-induced ocular toxicity on outcomes of patients with advanced multiple myeloma[62]	38	8 (2-15) 67 (49-90)	-	14	14
Retrospective, single-center, real-world experience of belantamab mafodotin in relapsed/refractory multiple myeloma[63]	39	7 (3-16) 66 (39-89)	32 2.8 11	12	9
Belantamab mafodotin in patients with relapsed/refractory multiple myeloma, a real-world single center experience[64]	90	6 (2-14) 68 (37-88)	42 4 13.1	16	10
Belantamab Mafodotin (Belamaf) for Relapsed/Refractory Multiple Myeloma (RRMM): A Real-World Observational Study[65]	137	5 (4-7) 68 (±10)	30.2 5.4 -	38.6	19.7
Asian experiences					
Real-world experience with belantamab mafodotin therapy for relapsed/refractory multiple myeloma: A multicentre retrospective study[66]	106	6 (2-11) 69 (36-88)	45.5 4.7 8.1	24	-
European experiences					
Belantamab mafodotin in patients with relapsed and refractory multiple myeloma who have received at least one PI, one IMID and one anti-cd38 mAb: a retro-	67	5 66 (42-82)	31 3.7 13.8	13	45

prospective italian observational study[67]					
Efficacy and safety of belantamab-mafodotin in triplerefractory multiple myeloma patients: A multicentric real-life experience[69]	28	6 (3-14) 67.5 (51-83)	40 3 -	11	11
Belantamab Mafodotin in Patients with Relapsed/Refractory Multiple Myeloma Included in the Compassionate Use or the Expanded Access Program. Experience with a Spanish Cohort[70]	156	5 (4-6) 72.5 (64-77)	46.4 3.6 13.9	17.9	7.9
Effectiveness and Safety of Belantamab Mafodotin in Patients with Relapsed or Refractory Multiple Myeloma in Real-Life Setting: The ALFA Study[71]	184	5 70 (63-76)	32.7 2.4 -	8.2	12.5
Real-world study of the efficacy and safety of belantamab mafodotin (GSK2857916) in relapsed or refractory multiple myeloma based on data from the nominative ATU in France: IFM 2020-04 study[72]	106	5 (3-12) 66 (37-82)	38.1 3.2 9	37.5 (overall)	-

5. Conclusions and Future Directions

The increasing number of patients receiving all classes of drugs as IMiDs, PIs and mAbs, acquires multi-refractoriness status and requires development of novel therapeutic strategies that try to overcome clonal complexity and heterogeneity of MM. Besides naked mAbs, among new immunotherapies, Belantamab Mafodotin has been the first-in-class anti-BCMA ADC to be approved for advanced RRMM. In DREAMM-2 study [37] Belamaf monotherapy was able to induce substantial ORR in patients who had received more than 5 prior lines of therapy, showing activity either in standard or in high risk RRMM patients [51], with a remission duration of quite one year. Notably, these results have been confirmed also in the real-world experiences. Impressive anti-myeloma activity has been documented with bispecific antibodies and CAR T cell therapies but these immunotherapies are not yet available in many countries and, concerning CAR T cells, they required personalized manufacturing time with a median period from leukapheresis to infusion for ide-cel of 40 days [34], making this therapy challenging in patients with rapidly progressive disease. Other limitations should be taken into account as the presence of an adequate composition of T cell populations in the patients, the need for bridging therapy and good performance status, the need for family support and, last but not least, very high cost of therapy. Moreover, both CART cells and bispecific antibodies as teclistamab, the only one approved for RRMM, necessitate hospitalization to manage possible early severe toxicities as CRS (cytokine release syndrome) and ICANS (immune effector cell associated neurotoxicity syndrome). The main advantages in using Belamaf in triple-refractory patients are the immediate availability and no need for hospitalization. Moreover, while retreatment with anti-CD38 mAb is not effective, the other anti-BCMA immunotherapies can be administered after Belamaf leading to a significant duration of response in very heavily pretreated MM patients [57]. Ocular toxicity represents a peculiar side effect of belamaf but a close monitoring and collaboration between hematologists and ophthalmologists is making this toxicity easier to predict and manage. Moreover, several ongoing studies are evaluating different Belamaf doses and schedules in order to reduce its incidence. Within the next years we expect that triplets including Belamaf such as Bela-Pd and others under evaluation enter the treatment landscape of less advanced

RRMM and that exploring lower doses of Belamaf translates into an improved tolerability in order to prolong therapy and consequently to obtain a long-lasting response.

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Conflicts of Interest: Sonia Morè: Honoraria from Amgen, Janssen. Laura Corvatta: Honoraria from Celgene, Janssen, Amgen; Massimo Offidani: Honoraria from and Advisor for AbbVie, Amgen, BMS, Celgene, GSK, Janssen, Roche, Sanofi, Takeda; Maria Teresa Petrucci: Honoraria from Janssen-Cilag, Celgene-BMS, Amgen, Sanofi, GSK, Takeda; Advisor for Janssen-Cilag, Celgene-BMS, Amgen, Sanofi, GSK, Takeda, Roche, Karyopharm; Support for attending meetings and/or travel from Janssen-Cilag, Celgene-BMS, Amgen, Sanofi, Takeda. Francesca Fazio: Advisor for Takeda, Sanofi, Honoraria from GSK, Janssen, Amgen.

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