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Regulatory Issues: EMA

EMA Review of Belantamab Mafodotin (Blenrep) for the Treatment of Adult Patients with Relapsed/Refractory Multiple Myeloma

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Belantamab mafodotin (Blenrep) • Multiple myeloma • B-cell maturation antigen • European Medicines Agency

Abstract

On August 25, 2020, a marketing authorization valid through the European Union was issued for belantamab mafodotin monotherapy for the treatment of multiple myeloma (MM) in adult patients who have received at least four prior therapies, whose disease is refractory to at least one proteasome inhibitor (PI), one immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody (mAb), and who have demonstrated disease progression on the last therapy. Belantamab mafodotin is an antibody-drug conjugate that combines a mAb, which binds specifically to B-cell maturation antigen, with maleimidocaproyl monomethyl auristatin F, which is a cytotoxic agent. It was evaluated in Study 205678 (DREAMM-2), an open-label, two arm, phase II, multicenter study in patients with MM who had relapsed following treatment with at least three prior therapies, who were refractory to an IMiD, a PI, and an anti-CD38 mAb alone or in combination. Patients were randomized to receive 2.5 mg/kg (n = 97) or 3.4 mg/kg (n = 99) belantamab mafodotin by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Belantamab mafodotin achieved an overall response rate (ORR) of 32% (97.5% confidence interval [CI]: 22–44) with a median duration of response (DoR) of 11 months (95% CI: 4.2 to not reached). The most frequently (≥20%) reported adverse reactions grades 3–4 with belantamab mafodotin were keratopathy (31%), thrombocytopenia (22%), and anemia (21%). With regard to the corneal risks associated with belantamab mafodotin, patients would need to undergo specific ophthalmic examinations so that any findings can be promptly and adequately managed. The scientific review concluded that a 32% ORR and a median DoR of 11 months observed with belantamab mafodotin was considered clinically meaningful. Given the manageable toxicity profile and considering that belantamab mafodotin has a mechanism of action that is different from that of authorized treatments in this group of highly pretreated patients whose disease is refractory to three classes of agents, the benefit risk for belantamab mafodotin monotherapy was considered positive, although the efficacy and safety evidence were not as comprehensive as normally required. ***The Oncologist*** 2021;26:70–76

Implications for Practice: Belantamab mafodotin (Blenrep, GlaxoSmithKline, St. Louis, MO, U.S.A) was approved in the European Union as monotherapy for the treatment of adult patients with refractory/relapsed multiple myeloma. Belantamab mafodotin resulted in durable response in highly pretreated patients whose disease is refractory to three classes of agents. Belantamab mafodotin is a monoclonal antibody against B-cell maturation antigen conjugated with the potent antimitotic agent maleimidocaproyl monomethyl auristatin. This is the first monoclonal antibody to target this antigen in multiple myeloma, which represents a true novelty from a pharmacological point of view.

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Background

Multiple myeloma (MM) is a rare and incurable plasma cell malignancy that typically affects adults older than 60 years of age. Its incidence in the European Union (EU) is 6.01/100,000/year, with a median age at diagnosis between 65 and 70 years [1]. Progress has been made over the last 15 years so that the median survival of patients with newly diagnosed MM has increased from 3 to 5 years [2, 3]. MM is characterized by bone marrow clonal plasma cell infiltration and overproduction of monoclonal immunoglobulin, while the production of normal immunoglobulins is impaired (immunoparesis).

The most common symptoms in patients with MM include persistent skeletal pain, pathological fractures and vertebral collapse, anemia, renal impairment, hypercalcemia, and recurrent or persistent bacterial infections. The Revised International Staging System (R-ISS) is now widely accepted for the estimation of prognosis, incorporating cytogenetics, lactate dehydrogenase, β2-microglobulin, and albumin levels [4]. At the time of diagnosis, patients are typically categorized according to R-ISS, their age, comorbidity, and their suitability for intensive treatment.

Despite recent advances, MM remains incurable. Most patients eventually relapse, and with each successive relapse, the probability of response typically decreases, and the disease ultimately becomes refractory. Current therapeutic options comprise different combinations of glucocorticoids (dexamethasone, prednisolone, methylprednisolone), chemotherapy (melphalan, cyclophosphamide, doxorubicin, etoposide, cisplatin), proteasome inhibitors (PIs, such as bortezomib, carfilzomib, and ixazomib), immunomodulatory agents (IMiDs, such as thalidomide, lenalidomide and pomalidomide), monoclonal antibodies (mAbs, such as daratumumab, isatuximab, and elotuzumab), the histone deacetylase inhibitor panobinostat, and the XPO-1 inhibitor selinexor (approved in the U.S.). Of note, high-dose chemotherapy is also used as conditioning therapy for autologous stem cell transplantation (e.g., high-dose melphalan) or as treatment for fulminant disease (e.g., dexamethasone-thalidomide-cisplatin-doxorubicin-cyclophosphamide-etoposide).

After the approval of daratumumab (anti-CD38 mAb) and its wide use in earlier lines of therapy, a new population of patients has emerged, referred to as triple-class refractory, encompassing patients whose disease is refractory to at least one PI, one IMiD, and one anti-CD38 mAb. Most of these patients have also received alkylating agents, multiple courses of glucocorticoids, and other antimyeloma drugs. They also tend to have numerous comorbidities and require multiple concomitant medications. There is a clear unmet medical need for these patients because treatment options are very limited, and their overall survival is around 3–5 months [5, 6].

The review of this new drug application was conducted by the European Medicines Agency (EMA) Committee of Human Medicinal Products (CHMP). The CHMP recommended the granting of a conditional marketing authorization for belantamab mafodotin monotherapy for the treatment of MM in adult patients who have received at least four prior therapies, whose disease is refractory to at least one PI, one IMiD, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy. Conditional marketing authorization is one of the EU regulatory mechanisms to facilitate early access to medicines that fulfill an unmet medical need. This type of approval allows the Agency to recommend a medicine for marketing authorization with less complete data than normally expected, if the benefit of a medicine's immediate availability to patients outweighs the risk inherent to the fact that not all the data are yet available. The review was started on January 30, 2020, and a positive opinion was issued on July 23, 2020. The CHMP conducted accelerated assessment. Accelerated assessment reduces the timeframe for the EMA CHMP to review a marketing-authorization application to under 150 days, instead of 210 days using the standard timetable. Applications may be eligible for accelerated assessment if the CHMP decides the product is of major interest for public health and a therapeutic innovation. Table 1 presents a summary of key regulatory steps and procedures for belantamab mafodotin. The objective of this paper is to summarize the scientific review of the application leading to regulatory approval of belantamab mafodotin in the EU.

Table 1. Steps in the evaluation of the marketing authorization for Blenrep

Step/procedure	Date	Active review time
Initial marketing authorization application received	December 18, 2019	0
Adoption of the consolidated list of questions by the CHMP	April 28, 2020	90
Submission of responses by the applicant	May 24, 2020	
Adoption of the consolidated list of outstanding issues by the CHMP	June 23, 2020	120
Submission of responses by the applicant	June 30, 2020	
The CHMP adopted a positive opinion for granting a marketing authorization to Blenrep	July 23, 2020	150
The European Commission granted a marketing authorization valid across the EU	August 20, 2020	

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; EU, European Union.

Nonclinical Aspects and Clinical Pharmacology

Belantamab mafodotin is a humanized immunoglobulin G1 immunoconjugate that binds specifically to B-cell maturation antigen (BCMA). Upon binding to the cell surface, belantamab mafodotin is rapidly internalized and the active cytotoxic drug (cys-mcMMAF) is released inside the cell via proteolysis of the mAb component, resulting in cell killing through disruption of the microtubule network and leading to cell cycle arrest and apoptosis. Additionally, the antibody is afucosylated, which increases binding to FcγRIIIa receptors and enhances recruitment and activation of immune

effector cells. Immune effector cells can kill tumor cells by antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis. Moreover, antibody-dependent cellular-induced apoptosis by belantamab mafodotin was shown to be potentially immunogenic, as measured by cell surface externalization of calreticulin and secretion of high mobility group box 1 and adenosine triphosphate. Immunogenic cell death induced by belantamab mafodotin resulted in activation of dendritic cells in vitro and may contribute to a T-cell–mediated antitumor response.

The toxicology findings in nonclinical studies with belantamab mafodotin such as tubular degeneration/regeneration in the kidneys, seminiferous tubular changes in the testes, luteinized nonovulatory follicles in the ovaries, degeneration of the incisor ameloblast/odontoblast layers, increased liver enzymes with single-cell necrosis, and lymphocytolytic and/or cellularity alterations in the bone marrow, spleen, and eye were primarily related to the cytotoxic drug conjugate, cys-mcMMAF. The principal adverse findings directly related to belantamab mafodotin, at exposures of 1.2 and 1.9 times the recommended clinical dose of 2.5 mg/kg, in monkey and rat, respectively, were elevated liver enzymes sometimes associated with hepatocellular necrosis at ≥3 mg/kg in the monkey and increases in alveolar macrophages associated with eosinophilic material in the lung at ≥3 mg/kg in rat only.

Nonclinical safety studies have shown dose-dependent and reversible primary glomerular injury and tubular degeneration (in rat and monkey) directly related to belantamab mafodotin, accompanied by large molecular proteinuria (albuminuria) and enzymuria. Single-cell necrosis of the kidney and bladder urothelium was also noted in the 13-week monkey study. Severe tubular degeneration/regeneration and marked glomerulonephritis exacerbated by immune complex disease, likely associated with anti-drug antibody (ADA), following five weekly doses of 10 mg/kg, led to the early euthanasia of one monkey. Glomerulonephritis associated with immune complex formation is not expected to be reversible. Nephrotoxicity has been categorized as an important potential risk in the risk management plan.

Decreases in immunoglobulins were seen in monkeys at all doses. Decreased lymphoid cellularity/necrosis (dose responsive in severity) was noted in the spleen and/or lymph nodes at ≥3 mg/kg/week, which was associated with decreases in thymic cellularity in rats. Increased risk of infections due to immunosuppression and/or neutropenia has been categorized as an important potential risk.

Clinical Efficacy

The pivotal efficacy study was the DREAMM-2 Study (205678), a phase II, open-label, randomized, two-arm study to investigate the efficacy and safety of two doses of the belantamab mafodotin in participants with MM who had three or more prior lines of treatment, were refractory to a PI and an IMiD, and had failed an anti-CD38 mAb [7].

The study recruited patients with histologically or cytologically confirmed diagnosis of MM who had undergone stem cell transplant or were considered transplant ineligible and who had failed at least three prior lines of antimyeloma treatments, including an anti-CD38 mAb (e.g., daratumumab) alone or in combination, and were refractory to an IMiD (i.e., lenalidomide or pomalidomide) and to a PI (e.g., bortezomib, ixazomib, or carfilzomib). The number of prior lines of therapy was determined according to the guidelines [8].

Patients were randomized in a 1:1 ratio to receive 2.5 mg/kg (n = 97) or 3.4 mg/kg (n = 99) belantamab mafodotin by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity.

The selection of the 2.5 mg/kg and 3.4 mg/kg of belantamab mafodotin as an intravenous infusion once every 3 weeks dosing regimens for evaluation in the DREAMM-2 study was based on study BMA117159 (DREAMM-1) [9].

The primary efficacy endpoint of the study was overall response rate (ORR), defined as strict complete response + complete response + very good partial response + partial response, according to 2016 International Myeloma Working Group Response Criteria and as assessed by independent review committee based on intention-to-treat population [10].

Belantamab mafodotin monotherapy achieved an ORR of 32% (97.5% confidence interval [CI]: 22–44) with a median duration of response (DoR) of 11 months (95% CI: 4.2 to not reached [NR]) in the 2.5-mg/kg cohort (cutoff date January 31, 2020) (Figure 1).

The median progression-free survival in the 2.5-mg/kg cohort was 2.8 months. With regard to overall survival (OS), the median OS was 13.7 months (cutoff date January 31, 2020; data not shown).

A summary of the key favorable effects observed in the DREAMM-2 study is displayed in Table 2.

The supportive study DREAMM-1 was a phase I, open-label, dose-escalation study to investigate the safety, pharmacokinetics (PK), pharmacodynamics, immunogenicity, and clinical activity of belantamab mafodotin in participants with relapsed/refractory MM and other advanced hematologic malignancies expressing BCMA. The study consisted of the following two parts: Part 1 dose escalation phase and Part 2 expansion phase for safety confirmation and clinical activity testing. Subjects were scheduled to be administered belantamab mafodotin via 60-minute intravenous infusion once every 3 weeks (21-day cycle). In Part 1 (dose escalation), the ORR in the 2.5-mg/kg cohort (n = 8) was 13% (95% CI: 0.3–52.7), and in the 3.4-mg/kg cohort (n = 3), the ORR was 100% (95% CI: 29.2–100.0). In Part 2 (dose expansion, 3.4 mg/kg; n = 35), the ORR was 60% (95% CI: 42.1–76.1), and the median DoR was 14.3 months (95% CI: 10.6 to NR).

Clinical Safety

A total of 103 patients have been exposed to the recommended dose of 2.5 mg/kg as a single agent, the majority of them in the pivotal study DREAMM-2. In the 13-month follow-up (cutoff date January 31, 2020), the median number of treatment cycles was 3 (range 1–17), and the median time on treatment was 9.3 weeks. In the DREAMM-2 study, the median dose intensity was 2.39 mg/kg/3 weeks.

Grade 3–4 adverse events (AEs) were observed in 83% of patients, with keratopathy (31%), thrombocytopenia

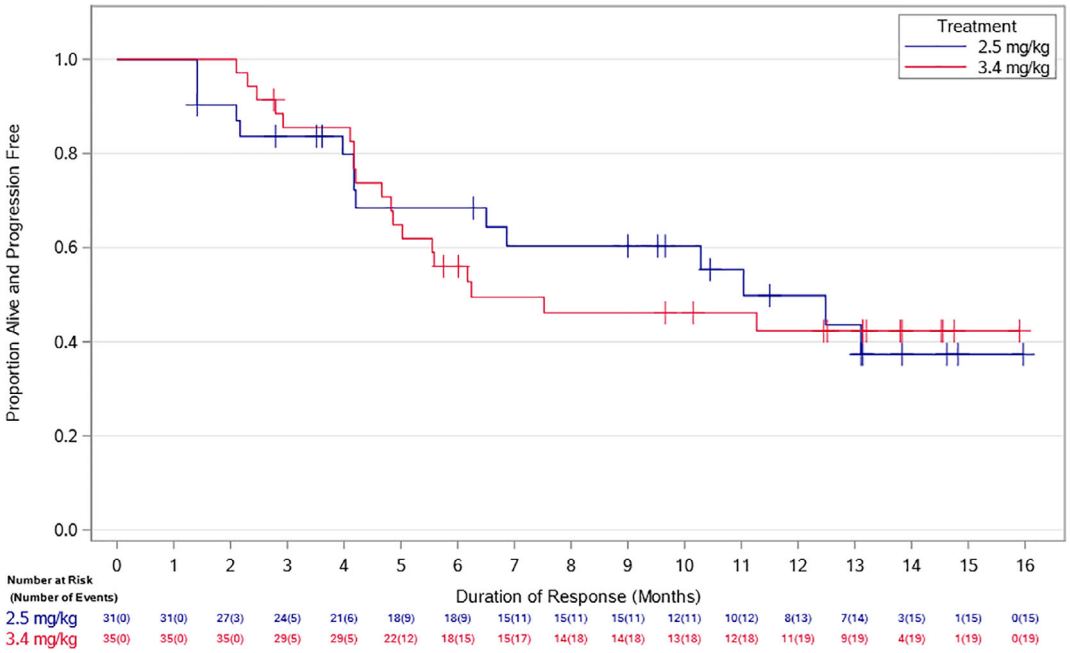

Figure 1. Kaplan-Meier analysis of independent review committee–assessed duration of response (DREAMM-2, 2.5-mg/kg cohort and 3.4 mg/kg cohort; cutoff date: January 31, 2020).

Table 2. Key favorable and unfavorable effects for belantamab mafodotin monotherapy in adult patients who have received at least four prior therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy (Study 205678, cutoff date: January 31, 2020)

Effect	Short description	Treatment (*n* = 97)	Result	Uncertainties/strength of evidence
Favorable effects				
ORR, %	Percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR, and sCR, according to the 2016 IMWG Response Criteria by IRC.	2.5 mg/kg	32	No control arm other than another dose cohort 97.5% CI: 22 to 44
DoR, median, months	Time from first documented evidence of PR or better until the earliest date of documented PD per IMWG, or death due to PD	2.5 mg/kg	11	95% CI: 4.2 to NR
Unfavorable effects[a], %				
Keratopathy	- All grades		71	
	- Grade 3–4		31	
Thrombocytopenia	- All grades		38	
	- Grade 3–4		22	
Anemia	- All grades		27	
	- Grade 3–4		21	
Lymphopenia	- All grades		20	
	- Grade 3–4		17	

[a]Two participants in the study DREAMM-3 were randomized but did not receive any study treatment. These participants were excluded from the safety population.
Abbreviations: CI, confidence interval; CR, complete response; DoR, duration of response; IMWG, International Myeloma Working Group; IRC, independent review committee; NR, not reached; ORR, overall response rate; PD, progression of disease; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

(22%), anemia (21%), lymphopenia (17%), and neutropenia (11%) occurring in more than 10% of patients.

In the DREAMM-2 13-month follow-up (data cutoff January 31, 2020) and at the 2.5-mg/kg cohort, at least one serious AE (SAE) was reported for 40 (42%) participants and at least one treatment-related SAE was reported for 11 (12%) participants. At the time of the primary analysis at the 2.5-mg cohort, (data cutoff June 21, 2019), the most

commonly reported treatment-related SAEs by preferred term were infusion-related reaction, reported for three (3%) participants, followed by pyrexia and sepsis, each reported for two (2%) participants.

In the DREAMM-2 9-month follow-up (data cutoff date September 20, 2019), 31 (33%) participants died during the study. The primary cause of death was disease under study, reported for 25 (26%) participants. There was one (<1%) participant who had a fatal SAE that was considered to be related to study treatment: sepsis; and there were two (2%) participants whose primary cause of death (both myocardial infarction) was considered unrelated to the disease under study and unrelated to study treatment. The remaining three (3%) participants' primary cause of death was reported as unknown, with no fatal SAEs reported for these participants.

Corneal events were the most frequently reported AEs associated with belantamab mafodotin and included keratopathy, blurred vision, and dry eyes. Keratopathy or microcyst-like epithelial changes in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, and dry eye symptoms were considered an important identified risk based on the changes in the corneal epithelium on ocular examination that have frequently been observed with belantamab mafodotin.

In the DREAMM-2 13-month follow-up; blurred vision events were mostly grade 1 or 2. Four (4%) participants experienced blurred vision with a maximum severity of grade 3, all of whom had recovered/resolved by the data cutoff. No participant experienced an SAE of blurred vision. The dose was reduced or delayed owing to blurred vision for 8 (8%) participants, and there were 15 (16%) participants whose blurred vision events had recovered/resolved.

Dry eye events were mostly grade 1 or 2. One (1%) participant experienced a dry eye event with a maximum severity of grade 3 that led to a dose delay and was recovered/resolved by the data cutoffs. The participant discontinued the treatment because of disease progression and remained in follow-up. No participant experienced an SAE of dry eye.

Participants who experienced a definite worsening of visual acuity had a median time to onset of 64 days and a median duration of 22 days for their first event. Most participants who experienced a definite worsening of visual acuity experienced one or two events (96%). As of the 13-month data cutoff, while 42 (43%) patients were still on study, the worsening of visual acuity resolved in the majority of participants prior to the end of treatment exposure (67%) and 30% of participants' worsening visual acuity resolved after the end of treatment exposure. Most patients with treatment delays due to ocular toxicities were able to reinitiate treatment. Detailed warnings about the risks are available in the product information.

A summary of the key unfavorable effects is displayed in Table 2.

Benefit–Risk Assessment

An ORR of 32% observed with belantamab mafodotin 2.5 mg/kg in the pivotal study DREAMM-2 was considered clinically relevant in adult patients with MM who have received at least four prior therapies, whose disease is refractory to at least one PI, one IMiD, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy. This antitumor activity was durable as the median DoR was 11 months.

There were concerns regarding the indication proposed by the applicant, which included adult patients with relapsed or refractory MM who have received three prior lines of therapy including an anti-CD38 mAb, a PI, and an IMiD. There were only five patients in the pivotal study who fulfilled these criteria, and the majority of the patients were heavily pretreated (at least four lines of prior treatment). All participants enrolled into the DREAMM-2 study were double refractory to immunomodulators and PI treatment and were previously treated with an anti-CD38 mAb, and all patients randomized to the 2.5-mg/kg dose arm were refractory to an anti-CD38 mAb treatment. Therefore, the CHMP concluded that the indication should be revised to include adult patients with MM who have received at least four prior therapies, whose disease is refractory to at least one PI, one IMiD, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy.

One of the main uncertainties was the absence of a comparator arm in the study DREAMM-2. Although the observed durable response in highly pretreated patients whose disease is refractory to three classes of agents was considered a clinically meaningful benefit, there is a need to further quantify the efficacy of belantamab mafodotin in the approved indication in a comparative trial because the treatment effect in terms of ORR was comparable to other available alternatives. Therefore, additional controlled data were considered necessary to confirm the benefit of belantamab mafodotin. The company was therefore requested, as a specific obligation for approval, to provide the clinical data from the study 207495 (DREAMM-3), a phase III study of single-agent belantamab mafodotin versus pomalidomide plus low-dose dexamethasone in participants with relapsed/refractory MM. The DREAMM-3 study will include patients who have been previously treated with at least two prior therapies, including both lenalidomide and a proteasome inhibitor, and whose disease is progressing on or within 60 days of completion of the last treatment. However, data in earlier treatment lines could be applied to further characterize the clinical benefit of belantamab mafodotin monotherapy in advanced last-line disease setting. Results from DREAMM-3 are expected by July 2024. In addition, the CHMP considered that the applicant company should submit the final results of the pivotal study DREAMM-2, which will also provide comprehensive data suitable to confirm the positive benefit–risk balance of belantamab mafodotin. Final results from DREAMM-2 are expected by April 2021.

Ocular toxicity and its clinical management were the most important safety concern. The corneal events and visual changes can be managed in clinical practice through appropriate monitoring, as well as dose modifications, and additional risk minimization measures have been implemented in order to mitigate the possible risks of keratopathy. The additional risk minimization measures

include health care professionals (hematologists/oncologists/eye care professionals) and patient educational materials. Patients will receive educational materials to help them understand the corneal risks and potential visual impairment associated with taking belantamab mafodotin. This includes guidance on screening exams as well as treatment with preservative-free artificial tears, and how to speak with their doctors about their symptoms. Oncologists will receive educational materials to help them understand the corneal risks associated with prescribing belantamab mafodotin and how this risk is best managed and mitigated. They will be encouraged to work closely with the eye care professional because their treatment plan may be impacted by the eye care professional's exam findings. Eye care professionals will receive educational materials to help them understand the corneal risks associated with belantamab mafodotin with the aim to optimize symptom recognition and reporting. They will be encouraged to work closely with the treating oncologist as their findings may impact the oncologist's treatment plan. However, the applicability of the proposed follow-up measures and the toxicity profile observed in clinical practice remains to be tested in the postmarketing setting. Data from the ongoing pivotal study and confirmatory study DREAMM-3 will provide additional data on the current recommendations and prevention measures.

Hematological toxicities are also significant, both due to overlapping toxicity profile with previous treatments and disease under study and due to possibly serious clinical consequences. However, the follow-up and dose modification recommendations included in the product information are considered sufficient to manage the observed toxicity profile.

Missing information concern the safety in patients with severe renal impairment and in patients with hepatic impairment. It is unknown if there is increased risk to patients with severe renal impairment who may receive belantamab mafodotin or if patients with renal compromise are at higher risk for adverse events; however, data in patients with mild/moderate renal impairment do not indicate increased safety risk in this population. A renal impairment study is planned to evaluate the potential impact of severe renal impairment on the PK and safety of belantamab mafodotin and to provide dosing guidance if needed. The final study report will be submitted by September 2024. It is also unknown if there is an increased risk to patients with hepatic impairment who may receive belantamab mafodotin; therefore, a hepatic impairment study is planned to determine if any dose adjustments are needed. The final study report will be submitted by December 2026.

The scientific review concluded that Blenrep has a mechanism of action that is different from that of authorized treatments and has shown to be associated with a 32% ORR and a median DoR of 11 months in this group of highly pretreated patients whose disease is refractory to three classes of agents. Belantamab mafodotin has a distinct toxicity profile including significant toxicities like corneal toxicity and hematological toxicity. Adverse effects of belantamab mafodotin are mostly reversible. Treatment is tolerated when adverse effects are closely monitored and actively managed, mainly by dose modifications. Therefore, belantamab mafodotin can be considered a major therapeutic advantage in the proposed target population for whom there are very limited and often no other treatment options available, in particular when available options are unlikely to be efficacious, or when it is the preferred option in view of its efficacy and safety profiles.

Conclusion

Based on the review of data on quality, safety, and efficacy, the EMA CHMP concluded by consensus that the risk–benefit balance of belantamab mafodotin monotherapy for adult patients with MM who have received at least four prior therapies, whose disease is refractory to at least one PI, one IMiD, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy was favorable and hence recommended the granting of the conditional marketing authorization.

A conditional approval is reserved for medicinal drugs that treat, prevent, or diagnose seriously debilitating diseases or life-threatening diseases, or rare diseases (orphan medicinal products) or drugs to be used in emergency situations in response to threats. With this approval, the applicant company is obliged to submit additional data, with a view to confirming that the benefit–risk balance is positive. A conditional approval is only valid for 1 year but can be renewed. The renewal is given on the basis of the confirmation of the benefit–risk balance, taking into account the specific obligations and the timeframe for their fulfilment. Once it is judged that remaining data have been provided or are no longer required, the approval can be converted to a "standard" approval. If at any time the benefit–risk is considered to be negative, the marketing authorization can be suspended or revoked.

The most recent information on this medicinal product is available on the EMA website (https://www.ema.europa.eu/en/medicines).

Acknowledgments

The scientific assessment summarized in this report is based on important contributions from the rapporteur and corapporteur assessment teams, CHMP members, and additional experts following the application for a marketing authorization from the company. This publication summarizes, but is not limited to, the European Public Assessment Report (EPAR), the summary of product characteristics, and other published product information. The EPAR is published on the EMA website (www.ema.europa.eu). For the most current information on this marketing authorization, please refer to the EMA website. The authors of this paper remain solely responsible for the opinions expressed in this publication.

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Disclosures

The authors indicated no financial relationships.

References

1. Sant M, Allemani C, Tereanu C et al. Incidence of hematologic malignancies in Europe by morphologic subtype: Results of the HAEMACARE project. Blood 2010;116:3724–3734.

2. Kyle RA, Gertz MA, Witzig TE et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003;78:21–33.

3. Turesson I, Bjorkholm M, Blimark CH et al. Rapidly changing myeloma epidemiology in the general population: Increased incidence, older patients, and longer survival. Eur J Haematol 2018;101:237–244.

4. Palumbo A, Avet-Loiseau H, Oliva S et al. Revised international staging system for multiple myeloma: A report from International Myeloma Working Group. J Clin Oncol 2015;33:2863–2869.

5. Usmani S, Ahmadi T, Ng Y et al. Analysis of real-world data on overall survival in multiple myeloma patients with ≥3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or double refractory to a PI and an IMiD. ***The Oncologist*** 2016;21:1355–1361.

6. Mikhael J. Treatment options for triple-class refractory multiple myeloma. Clin Lymphoma Myeloma Leuk 2020;20:1–7.

7. Lonial S, Lee HC, Badros A et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): A two-arm, randomised, open-label, phase 2 study. Lancet Oncol 2020;21:207–221.

8. Rajkumar SV, Dimopoulos MA, Palumbo A et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;15:e538–e548.

9. Trudel S, Lendvai N, Popat R et al. Targeting B-cell maturation antigen with GSK2857916 antibody-drug conjugate in relapsed or refractory multiple myeloma (BMA117159): A dose escalation and expansion phase 1 trial. Lancet Oncol 2018;19:1641–1653.

10. Kumar S, Paiva B, Anderson KC et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016;17:e32–e46.

For Further Reading:

Sotirios Michaleas, Elisabeth Penninga, Doris Hovgaard et al. EMA Review of Daratumumab (Darzalex) for the Treatment of Adult Patients Newly Diagnosed with Multiple Myeloma. ***The Oncologist*** 2020;25:1067–1074.

Implications for Practice:

A set of extensions of indication was recently approved for daratumumab (Darzalex) in the setting of newly diagnosed multiple myeloma in combination with established regimens. Results of the MMY3006, MMY3007, and MMY3008 trials have shown enhanced efficacy and a favorable side effect profile of several daratumumab-based combinations in patients both ineligible and eligible for transplant, without compromising transplant ability. The combinations of daratumumab with either lenalidomide and low-dose dexamethasone or bortezomib, melphalan, and prednisone were approved for transplant-ineligible patients. The combination of daratumumab with bortezomib, thalidomide, and dexamethasone was approved for transplant-eligible patients. These combinations are expected to improve the survival outlook for patients with multiple myeloma, without an unacceptable risk of increase in adverse events, and updated information on progression-free survival and overall survival is expected from the above trials.