Belantamab mafodotin: an important treatment option for vulnerable patients with triple class exposed relapsed and/or refractory multiple myeloma

by Maria Victoria Mateos, Katja Weisel, Evangelos Terpos, Sossana Delimpasi, Efstatios Kastritis, Elena Zamagni, Michel Delforge, Enrique Ocio, Eirini Katodritou, Francesca Gay, Alessandra Larocca, Xavier Leleu, Paula Rodriguez Otero, Fredrik Schjesvold, Michele Cavo, and Meletios A. Dimopoulos

Received: November 17, 2023.
Accepted: February 13, 2024.

Citation: Maria Victoria Mateos, Katja Weisel, Evangelos Terpos, Sossana Delimpasi, Efstatios Kastritis, Elena Zamagni, Michel Delforge, Enrique Ocio, Eirini Katodritou, Francesca Gay, Alessandra Larocca, Xavier Leleu, Paula Rodriguez Otero, Fredrik Schjesvold, Michele Cavo, and Meletios A. Dimopoulos. Belantamab mafodotin: an important treatment option for vulnerable patients with triple class exposed relapsed and/or refractory multiple myeloma. Haematologica. 2024 Feb 22. doi: 10.3324/haematol.2023.284694 [Epub ahead of print]

Publisher’s Disclaimer.

E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors’ final approval; the final version of the manuscript will then appear in a regular issue of the journal. All legal disclaimers that apply to the journal also pertain to this production process.
Belantamab mafodotin: an important treatment option for vulnerable patients with triple class exposed relapsed and/or refractory multiple myeloma

Running Title: Belantamab in triple class exposed relapsed and/or refractory MM.

Authors
Maria Victoria Mateos\textsuperscript{1,2}, Katja Weisel\textsuperscript{3}, Evangelos Terpos\textsuperscript{4}, Sossana Delimpasi\textsuperscript{5}, Efstathios Kastritis\textsuperscript{4}, Elena Zamagni\textsuperscript{6}, Michel Delforge\textsuperscript{7}, Enrique Ocio\textsuperscript{8,9}, Eirini Katodritou\textsuperscript{10}, Francesca Gay\textsuperscript{11,12}, Alessandra Larocca\textsuperscript{11,12}, Xavier Leleu\textsuperscript{13}, Paula Rodriguez Otero\textsuperscript{14-17}, Fredik Schjesvold\textsuperscript{18-20}, Michele Cavo\textsuperscript{21,22}, Meletios A. Dimopoulos\textsuperscript{4}

\textsuperscript{1}Hospital Universitario de Salamanca, Spain.
\textsuperscript{2}University of Salamanca, Spain.
\textsuperscript{3}University Hospital Hamburg-Eppendorf, Hamburg, Germany.
\textsuperscript{4}National and Kapodistrian University of Athens, Medicine School, Athens, Greece.
\textsuperscript{5}Evangelismos General Hospital, Athens, Greece.
\textsuperscript{6}University of Bologna, Italy
\textsuperscript{7}University Hospital Leuven, Leuven, Belgium
\textsuperscript{8}Hospital Universitario Marqués de Valdecilla (IDIVAL), Santander, Spain.
\textsuperscript{9}University of Cantabria, Santander, Spain.
\textsuperscript{10}Theageneion Cancer Hospital, Thessaloniki, Greece.
\textsuperscript{11}University of Turin, Italy.
\textsuperscript{12}AOU Città della Salute e della Scienza of Turin, Italy.
\textsuperscript{13}Hospital La Mileterie, France.
\textsuperscript{14}Clínica Universidad de Navarra, Pamplona, Spain.
\textsuperscript{15}Centro de Investigación Médica Aplicada (CIMA), Pamplona, Spain.
\textsuperscript{16}Instituto de Investigación Sanitaria de Navarra IDISNA, Pamplona, Spain.
\textsuperscript{17}Centro de Investigación Biomédica en Red en Cáncer (CIBERONC) Pamplona, Spain.
\textsuperscript{18}Oslo Myeloma Center, Oslo, Norway
\textsuperscript{19}Oslo University Hospital, Oslo, Norway
\textsuperscript{20}KG Jebsen Center for B Cell Malignancies, University of Oslo, Oslo, Norway.
\textsuperscript{21}IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia “Seràgnoli”, Bologna, Italy.
\textsuperscript{22}Università di Bologna, Bologna, Italy

Corresponding author.
Maria Victoria Mateos
Hospital Universitario de Salamanca, University of Salamanca, Spain
mvmateos@usal.es

Contributions
All authors contributed to writing the letter. All authors critically revised and approved the final version of the letter and agree with presented format.
Data-sharing statement
No data will be shared.

Disclosures

**MVM** has received honoraria derived from lectures and participation in boards from Janssen, Celgene-BMS, GSK, Sanofi, Pfizer, AbbVie, Regeneron, Novartis.

**KW** has received research funding (to institution) from Abbvie, Amgen, BMS/Celgene, Janssen, GSK, Sanofi, Takeda; honoraria from Abbvie, Amgen, Adaptive Biotech, Astra Zeneca, BMS/Celgene, BeiGene, Janssen, GSK, Karyopharm, Novartis, Oncopeptides, Pfizer, Roche Pharma, Sanofi, Stemline, Takeda, Menarini; and consulting fees from Abbvie, Amgen, Adaptive Biotech, BMS/Celgene, BeiGene, Janssen, GSK, Karyopharm, Oncopeptides, Pfizer, Roche Pharma, Sanofi, Takeda, Menarini.

**ET** has received research funding from Amgen, GSK, Janssen, Sanofi, Takeda; honoraria from Amgen, BMS, Astra/Zeneca, EUSA Pharma, GSK, Janssen, Menarini/Stemli, Pfizer, Sanofi, Takeda; and travel expenses from Amgen, Astra/Zeneca, EUSA Pharma, Sanofi, Takeda.

**SD** has not conflict of interest to disclose.

**EK** has received honoraria derived from lectures and participation in boards from Janssen, GSK, Pfizer.

**EZ** has received honoraria and AB member from Janssen, BMS, Sanofi, Amgen, GSK, Pfizer, Oncopeptides, menarini-stemline.

**MD** have received speaker honoraria from BMS, GSK, Janssen, Stemline.

**EO** declares honoraria from Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Oncopeptides, Pfizer, Regeneron, Sanofi, and Takeda; consulting/advisory role from AbbVie, Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Menarini/Stemline Therapeutics, Oncopeptides, Pfizer, Sanofi, and Takeda; Speakers’ bureau from Janssen; and travel/accommodation expenses from Bristol Myers Squibb, GlaxoSmithKline, Janssen, and Lilly.

**Eirini K** declares Research Support/P.I from Amgen, Janssen, Takeda, Sanofi, Karyopharm, GSK, Abbvie, Pfizer and GSK; honoraria from Amgen, Genesis-Pharma, Janssen, Takeda, Integris-Pharma, Sanofi, Abbvie, GSK; and Scientific from Amgen, Janssen, Takeda and Sandoz.

**FG** declares honoraria/advisory board from Janssen, BMS, Takeda, Amgen, Sanofi, ROChe, Abbvie, GSK; and advisory from Pfizer, Oncopeptides.

**AL** declares honoraria and Scientific Advisory Board from: Janssen-Cilag, BMS, Amgen, Takeda, Oncopeptides, GSK, Sanofi, Karyopharm.

**XL** has received honorarium from Janssen, Takeda, Sanofi, Pfizer, Roche, BMS, GSK, Iteos, Abbvie, Regeneron, Amgen.

**PR-O** declares receiving honoraria from consulting activities from BMS, Janssen, Sanofi, Kite Pharma, Abbvie, Oncopeptides, Takeda, Pfizer, Roche, Pfizer and GSK, and from lectures from BMS, Janssen, Sanofi, GSK, Amgen, Regeneron and Takeda.

**FS** has received honoraria derived from lectures and participation in boards from Abbvie, GSK, Celgene, Takeda, Janssen, Oncopeptides, Sanofi, BMS, Amgen, BMS, Novartis, SkyliteDX, Pfizer, Daiki-Sankyo.
MC received honoraria from Janssen, Celgene/Bristol Myers Squibb, Sanofi, Takeda, Amgen, AbbVie, Adaptive, GSK, Pfizer, Menarini-Stemline and served on a speakers bureau for Janssen, Celgene/Bristol Myers Squibb, and Sanofi.

MAD has received honoraria from participation in advisory boards and satellite symposia from Amgen, Sanofi, Regeneron, Menarini, Takeda, GSK, BMS, Janssen, Beigene.

**Article Summary:**
- The recommendation for not renewing the conditional marketing authorization for belantamab mafodotin that EMA’s human medicines committee (CHMP) has given would entail the loss of the opportunity for treating a significant subgroup of patients with myeloma who have exhausted the available options.
- The results of belantamab mafodotin both as an investigational and in the real-world setting, justify maintaining it as a potentially beneficial therapeutic option for patients.

**Key words (3-5):** belantamab mafodotin; triple class exposed-refractory patients; BCMA-targeted therapy.
We, as leaders in the European myeloma clinical research community and from 9 countries across the European Union, are writing in response to the EMA’s Committee for Medicinal Products for Human Use (CHMP) recommendation to not renew the conditional marketing authorisation of belantamab mafodotin issued on September 15, 2023.

Multiple Myeloma (MM) is the second most frequent haematological cancer with 4-5 new cases per 100,000 inhabitants/year and although remarkable progress has occurred in the last years, it does remain for most patients an incurable disease.

There are three main drug classes used for the treatment of MM: proteasome inhibitors, immunomodulatory drugs and CD38 monoclonal antibodies, all of which are now part of the standard of care for patients with MM in early lines of therapy. However, when patients become triple class exposed and/or refractory to these treatments, they typically have poor outcomes, thus representing an unmet medical need with a lack of new standards of care options in this population.

New targets and new approaches have emerged to address this unmet need including new targets, like BCMA or GPRC5D and new modalities, like chimeric antigen receptor T-cell (CAR-T) therapies or bispecific monoclonal antibodies and all of them have shown to be effective in the triple class refractory population resulting in their approval. However, despite their proven benefit, safety concerns such as risk of serious infections and burden of administration often makes these agents less suitable for elderly patients or those with other comorbidities. Additionally, accessibility represents a significant hurdle for most patients in Europe, leaving many patients without viable options and without proven effective therapies.

Belantamab mafodotin is a BCMA-targeted therapy in the modality of an antibody drug conjugate and it was the first drug, in this category, approved for the treatment of triple class refractory MM patients. Although belantamab mafodotin is a BCMA-targeted therapy, its mechanism of action is different and makes it suitable for some MM patients not eligible for either CAR-T cells or bispecific antibodies. The rationale for the approval was the significant clinical benefit observed for those patients included in the DREAMM-2 clinical trial (overall response rate [ORR], 32%) and especially those who experienced a partial response or better with a durability of response of 12.5 months (median duration of responses [DoR], 95% CI [4.2–19.3] months), and a tolerable safety profile.

We acknowledge that the phase 3 DREAMM-3 study failed to meet its primary endpoint, but it is important to note that belantamab mafodotin is not indicated to replace pomalidomide in this current label but is a useful addition to the therapeutic armamentarium for patients with pomalidomide failure. Indeed, it has been shown to be effective in the pomalidomide-exposed patients as was demonstrated in the DREAMM-2 trial. Other trials assessing new agents such as venetoclax (CANOVA trial) and melflufen (OCEAN trial) have shown the challenges of doublet comparisons in the relapsed/refractory setting. However, the unmet medical need in specific sub-types of patients and especially in those who are not candidates for the currently approved therapies justify the possibility of having beneficial alternatives available to them, such as belantamab mafodotin and targeting BCMA as an antibody drug conjugate. Indeed, melflufen as a peptide drug conjugate, is currently fully approved in Europe given the results of the HORIZON study with the supportive results of OCEAN and based upon a similar premise. Moreover, as with belantamab mafodotin both venetoclax and
melflufen have been shown to be effective in pomalidomide-exposed patients and to be especially active in combination.

Despite not meeting its primary endpoint in the DREAMM-3 trial, belantamab mafodotin demonstrated numerical improvement with a median progression-free survival (mPFS) of 11.2 months vs. pomalidomide-dexamethasone at 7 months, and an improved HR of 0.90 after 10 months more of follow-up. Overall response rate (41%, [95% CI 34.2–47.7] vs. 36% [26.5–45.4]), depth of response as measured by VGPR or better (25% vs. 8%) and DoR (25.6 [95% CI 20.7- NR] vs. 10.4 [95 %CI 7.6-21.1] months) were markedly superior in the belantamab mafodotin arm vs. pomalidomide-dexamethasone, supporting a meaningful treatment effect and potential clinical benefit.

As investigators and physicians managing MM patients, we believe belantamab mafodotin provides an important treatment option for important subgroup of patients, such as the elderly and/or frail patients who may not tolerate the rigors of intensive therapies, as well as for individuals with renal impairment where other more intensive treatments targeting BCMA can be especially challenging, not least as this is a frequent complication of advanced MM. Moreover, patients who are unable to adhere to the demanding administration of bispecific antibodies and wish to avoid step up dosing and in patient hospitalization can benefit significantly from the more manageable dosing regimen of belantamab mafodotin, at a minimum of every three to six weeks or longer.

In addition, in cases of aggressive relapses where treatment should be initiated promptly, belantamab mafodotin in combination with other therapies can provide a rapid and successful alternative, bypassing the long delays associated with prolonged manufacturing process required for CAR-T cell therapies, as one example.

Considering the safety profile, belantamab mafodotin has been shown to be manageable in most patients in most patients in both the investigational and real-world settings. Eyes related side effects are proving better tolerated and reversible with a low rate of treatment discontinuation due to ocular adverse events now being reported (for example, 2% of the 217 patients entered in the DREAMM-3 trial).

This safety profile is crucial when we manage heavily pre-treated MM patients with severe immunosuppression and a previous history of infections because the other alternatives, like CAR-T cells or bispecifics, have reported a high incidence of severe infections, including those requiring hospitalizations. Other toxicities like cytokine release syndrome (CRS) and neurotoxicity, although manageable in most patients, are not associated with belantamab mafodotin, which further facilitates outpatient management of patients in clinical practice.

Furthermore, patients residing in remote areas, distant from academic centers where advanced therapies are administered, often face formidable barriers to treatment access. Patients lacking a robust caregiver or family support may face challenges with treatments that require significant monitoring and staying away from home for several weeks. Belantamab mafodotin, with its more manageable administration requirements, offers an option for these under-served populations alleviating some of these burdens.
In conclusion, we as authors and treating physicians endorsing this letter and firmly consider that belantamab mafodotin is a vital addition to treatment armamentarium of MM, particularly for our triple class exposed refractory patients with limited treatment options. The results published on real-world practice \(^{14,15}\) also support this conclusion (Table 1).

Its unique attributes address the specific needs of patients who have exhausted conventional available treatments and who may not find suitability with other recently approved therapies. It is important to keep in mind that despite the approvals of some of novel options mentioned before, their accessibility represents a significant hurdle for most patients in Europe, leaving many patients without viable options.

As we strive for more inclusive and effective treatments, the accessibility, and clinical benefits of belantamab mafodotin should remain an option for this vulnerable patient population, as with other more convenient outpatient options in this setting.
References:
Table 1: Baseline characteristics and outcomes of the patients treated with belantamab mafodotin in DREAMM-2 trial and in the published real-world experience.

| Basal characteristics of patients receiving belantamab mafodotin | DREAMM-2 trial | Published Real world evidence |
|---|---|---|---|---|---|---|---|
| | Spain | Israel | France IFM 2020-04 | Mayo clinic | Italy | Athens |
| | n=97 | n=156 | n=106 | n=97 | n=36 | n=28 | n=27 |
| Age, years (Median (range)) | 65 (60–70) | 73 (40–89) | 69 (36–88) | 66 (37–82) | 61 (37–83) | 68 (51–83) | 65 (41–81) |
| Gender; Males n (%) | 51 (53) | 82 (46) | 60 (57) | 49 (51) | 23 (64) | 16 (57) | 14 (52) |
| Prior lines of tx. n (range) | 7 (3–21) | 5 (1–10) | 6 (2–11) | 5 (3–12) | 8 (7–11) | 6 (3–14) | 5 (4–10) |
| ISS, % | | | | | | | |
| I | 22 | 29 | 43 | 36 | 25 | NR | 33 |
| II | 34 | 31 | 30 | 39 | 17 | NR | 48 |
| III | 43 | 33 | 26 | 25 | 33 | NR | 19 |
| High-risk cytogenetics n (%) | 41 (42) | del17p, 17q12t(4;14), 15q21+ | 27 (43) | t(14;20), 1q21+ | 27/66 (41) | 14 (41) | NR | 6/15 (40) |
| Triple-class refractory n (%) | 97 (100) | 125 (80) | 77 (73) | 55 (56) | 36 (100) | 28 (100) | 27 (100) |
| Prior txs. n (%) | | | | | | | |
| ASC T | 73 (75) | 101 (65) | 62 (59) | 70 (72) | 27 (75) | 20 (71) | 25 (93) |
| Carfilzomib | 74 (76) | NR | 77 (73) | 11 (11) | 36 (100) | 24 (86) | 24 (89) |
| Poma | 89 (92) | NR | 82 (77) | 60 (62) | 36 (100) | NR | 19 (70) |
| mPFS, mo | 2.8 | 3.6 | 4.7 | 3.2 | 2 | 3 | 2 |
| Efficacy outcomes | | | | | | | |
| Landmark mOS, mo | 13.7 | 11 | 14.5 | 9.5 | 6.5 | 8 | 16 |
| ORR, n (%) | 31 (32) | 14 (42) | 46 (46) | 37 (38) | 12 (33) | 11 (40) | 14 (52) |
| sCR/CR, n (%) | 7 (7) | 4 (12) | 4 (4) | 8 (8) | 2 (6) | 3 (11) | 3 (11) |
| VGPR, n (%) | 11 (11) | 2 (6) | 14 (14) | 11 (11) | 3 (8) | 3 (11) | 5 (19) |
| PR, n (%) | 13 (13) | 8 (24) | 28 (28) | 18 (19) | 7 (19) | 5 (18) | 6 (22) |
| Safety outcomes | | | | | | | |
| Keratopathy n (%) | 68 (72) | 73 (88) | 65 (68) | 39 (38) | 15 (43) | 9 (32) | 9 (33) |
| Infusion-related reaction, n (%) | 20 (21) | NR | 8 (8) | 10 (10) | 2 (5) | 0 | 1 (4) |

Adapted from Ntanasis-Stathopoulos Int. J. Mol. Sci. 2023

ASCT: autologous stem cell transplant; ISS: international staging system; m: median; mo: months; NR: not reported; OS: overall survival; ORR: overall response rate; PFS: progression-free survival; Poma: pomalidomide; PR: partial response; tx: Treatment; sCR: stringent complete response; VGPR: very good partial response