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

We, as leaders in the European myeloma clinical research community and from nine countries across the European Union, are writing in response to the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommendation to not renew the conditional marketing authorization of belantamab mafodotin issued on September 15, 2023.

Multiple myeloma (MM) is the second most frequent hematological cancer with four to five 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.[1]

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,[2] 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[3,4] or GPRC5D[5] 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[6-8] 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[9] 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% confidence interval [CI]: 4.2-19.3 months), and a tolerable safety profile.

We acknowledge that the phase III DREAMM-3 study[10] 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 trial11) and melflufen (OCEAN trial)[12] 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.[13] 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,[10] belantamab mafodotin demonstrated numerical improvement with a median progression-free survival (mPFS) of 11.2 months *versus* pomalidomide-dexamethasone at 7 months, and an improved hazard ratio (HR) of 0.90 after 10 months more of follow-up. Overall response rate (41%, 95% CI: 34.2-47.7 *vs*. 36%, 95% CI: 26.5-45.4), depth of response as measured by VGPR or better (25% *vs*. 8%) and DoR (25.6 months, 95% CI: 20.7-not reached [NR] *vs*. 10.4 months, 95% CI: 7.6-21.1) were markedly superior in the belantamab mafodotin arm *versus* pomalidomide-dexamethasone, supporting a meaningful treatment effect and potential clinical benefit.[10]

As investigators and physicians managing MM patients, we believe belantamab mafodotin provides an important treatment option for an 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 3 to 6 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 both the investigational[9,10] and real-world[14,15] settings. Eye-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

Table 1. Baseline characteristics and outcomes of the patients treated with belantamab mafodotin in DREAMM-2 trial and in the published real-world experience.

	DREAMM-2 trial	Spain	Israel	France IFM 2020-04	Mayo clinic	Italy	Athens
	N=97	N=156	N=106	N=97	N=36	N=28	N=27
Basal characteris tics of patients receiving belantamab mafodotin							
Age in years, median (range)	65 (60-70)	73 (40-89)	69 (36-88)	66 (37-82)	61 (37-83)	68 (51-83)	65 (41-81)
Sex: male, N (%)	51 (53)	82 (46)	60 (57)	49 (51)	23 (64)	16 (57)	14 (52)
Prior lines of tx., median (range)	7 (3-21)	5 (1-10)	6 (2-11)	5 (3-12)	8 (7-11)	6 (3-14)	5 (4-10)
ISS, % I II III	 22 34 43	 29 31 33	 43 30 26	 36 39 25	 25 17 33	 NR NR NR	 33 48 19
High-risk cytogenetics, N (%)	41 (42)	del17p, 17 t(4;14), 15 1q21+, 28 t(14;20), 1	27 (43)	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 tx., N (%) ASCT Carfilzomib Poma	 73 (75) 74 (76) 89 (92)	 101 (65) NR NR	 62 (59) 77 (73) 82 (77)	 70 (72) 11 (11) 60 (62)	 27 (75) 36 (100) 36 (100)	 20 (71) 24 (86) NR	 25 (93) 24 (89) 19 (70)
Median PFS in months	2.8	11	14.5	9.5	6.5	8	16
Efficacy outcomes							
Landmark mOS in months	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-Stathopoulus_Int. J. Mol. Sci. 2023[15]. ASCT: autologous stem cell transplant; ISS: international staging system; m: median; NR: not reported; OS: overall survival; ORR: overall response rate; PFS: progression-free survival; poma: pomalidomide; PR: partial response; tx: treatment; (s)CR: (stringent) complete response; VGPR: very good partial response.

217 patients entered in the DREAMM-3 trial).[10]
This safety profile is crucial when we manage heavily pretreated MM patients with severe immunosuppression and a previous history of infections because the other alternatives, like CAR T cells or bispecific antibodies, have reported a high incidence of severe infections, including those requiring hospitalizations.[16] 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.

Authors

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

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

Correspondence:
M. V. MATEOS - mvmateos@usal.es

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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

The data that support this manuscript are not openly available because they have not been generated by the auhtors but can be available from the corresponding author of each study, here referenced, and after a reasonable request.

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