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## Infusion-Related Reactions (IRRs) in the DREAMM-2 Study of Single-Agent Belantamab Mafodotin (Belamaf) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

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# Background

## DREAMM-2: analysis of IRRs

### Aim:

To assess the incidence of IRRs in patients treated with single-agent belantamab mafodotin (belamaf; BLENREP) at 2.5 mg/kg Q3W (the approved dose), after 13 months of follow-up in the DREAMM-2 study (NCT03525678)



### Belamaf

- Belamaf is a first-in-class, BCMA-targeting ADC containing MMAF that eliminates myeloma cells by a multimodal MoA<sup>1</sup>
- Belamaf was approved in August 2020 by the US FDA and EMA for the treatment of patients with RRMM<sup>2,3</sup>
- In the DREAMM-2 study, responses reported with belamaf 2.5 mg/kg Q3W in the primary analysis were sustained at 13 months (median DoR: 11.0 months, median OS: 13.7 months). Overall, belamaf had a manageable safety profile<sup>1,4</sup>
- The approved dose is 2.5 mg/kg administered as an IV infusion over a minimum of 30 minutes Q3W<sup>2,3</sup>

### Analysis of IRRs

- IRRs have been commonly reported by patients with RRMM receiving IV treatments with monoclonal antibodies<sup>5</sup>
- A post hoc analysis of the incidence and severity of IRRs in patients treated with belamaf in the DREAMM-2 study was warranted
- These data can inform strategies for the management of IRRs to ensure treatment continuity wherever possible
- Of note, owing to the low reported incidence of IRRs in Phase 1,<sup>6</sup> pre-medication to prevent IRRs was not mandatory in the DREAMM-2 study

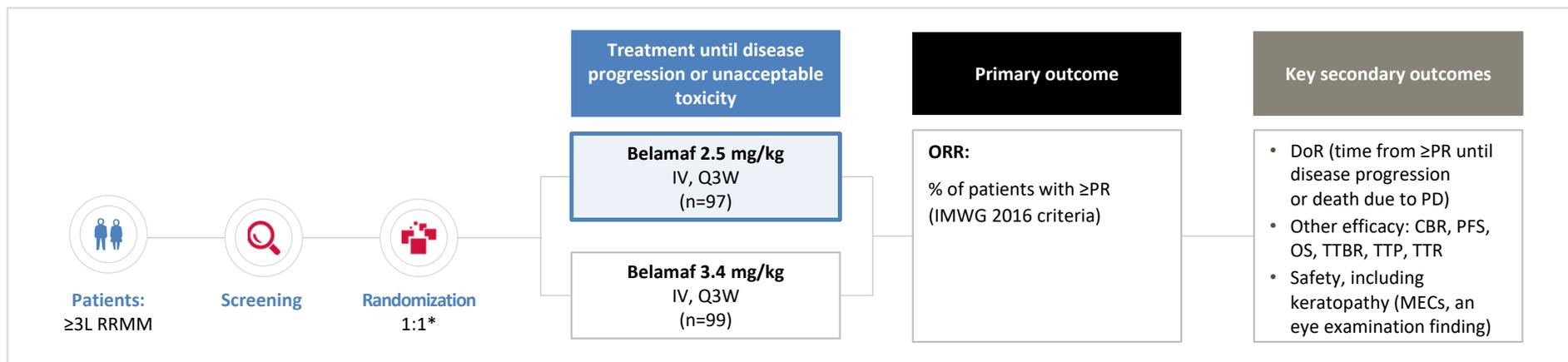
ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; DoR, duration of response; IRR, infusion-related reaction; IV, intravenous; MMAF, monomethyl auristatin F; MoA, mechanism of action; OS, overall survival; Q3W, every 3 weeks; RRMM, relapsed or refractory multiple myeloma.

1. Lonial S, et al. *Lancet Oncol.* 2020;21:207–21; 2. BLENREP Prescribing Information. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/761158s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761158s000lbl.pdf) [Accessed October 2020]; 3. BLENREP SmPC. Available at: <https://www.ema.europa.eu/en/medicines/human/EPAR/blenrep#authorisation-details-section> [Accessed October 2020]; 4. Lonial S, et al. ASCO 2020, Poster 436; 5. Nooka AK, et al. *J Oncol.* 2018;14:414–22; 6. Trudel S, et al. *Blood Cancer J.* 2019;9:37.



# Methods

## DREAMM-2: study design



### Eligibility Criteria

- ✓ Measurable disease<sup>†</sup>
- ✓ Refractory to immunomodulatory agents and PIs, and refractory and/or intolerant to an anti-CD38 mAb
- ✓ ECOG PS of 0–2
- ✓ Not exposed to a prior BCMA-targeted therapy
- ✓ ≥3 prior lines of therapy
- ✓ Prior ASCT allowed; allogeneic stem cell transplant excluded

\*Patients stratified based on number of previous lines of therapy (≤4 vs >4) and presence or absence of high-risk cytogenetic features; <sup>†</sup>measurable disease defined as serum myeloma protein (M-protein) ≥0.5 g/dL; urine M-protein ≥200 mg/24 h; serum FLC assay: involved FLC level ≥10 mg/dL and an abnormal serum FLC ratio (<0.26 or >1.65). 3L, third line; ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; CBR, clinical benefit rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FLC, free light chain; IMWG, International Myeloma Working Group; IV, intravenous; mAb, monoclonal antibody; MEC, microcyst-like epithelial changes; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitors; PR, partial response; Q3W, every 3 weeks; RRMM, relapsed or refractory multiple myeloma; TTBR, time to best response; TTP, time to progression; TTR, time to response. Lonial S, et al. ASCO 2020, Poster 436.

# Methods

## Recording and management of IRRs in DREAMM-2

IRRs were recorded and graded according to CTCAE version 4.03

IRRs were reported as an AE. In addition, all AEs reported from all participants were screened for specific clinical symptoms compatible with possible IRR symptoms, if they occurred within 24 hours of the start/completion of an infusion. These included pyrexia, chills, diarrhea, nausea, asthenia, hypertension, and tachycardia.

All IRRs were followed until resolution/stabilization

### IRR grade Management strategy in DREAMM-2\*

Per protocol, pre-medication was not a requirement, but was encouraged in patients who had already experienced an IRR on the study.

Medication to prevent IRRs (including analgesics, antihistamines, and steroids) could be administered at the investigator's discretion, including prior to the first infusion.

1	<ul style="list-style-type: none"> <li>• Continue study drug</li> <li>• Provide close follow-up to evaluate for increased severity</li> </ul>
2	<ul style="list-style-type: none"> <li>• Stop the infusion†</li> <li>• Provide medical treatment</li> <li>• Continue the infusion at half the original infusion rate after resolution to Grade ≤1</li> </ul>
3	<ul style="list-style-type: none"> <li>• Stop the infusion until recovery to Grade ≤1</li> <li>• After recovery, treatment to continue pending discussion with the study sponsor, with:               <ul style="list-style-type: none"> <li>– Pre-medication (also for all future infusions)</li> <li>– Longer infusion time (2–4 hours)</li> </ul> </li> </ul>
4	Patient permanently withdrawn from the study

\*The US PI contains the following guidance for IRRs: for Grade 2 (moderate) or Grade 3 (severe) IRRs, interrupt infusion and provide supportive care. Once symptoms resolve, resume at lower infusion rate; reduce the infusion rate by at least 50%. For Grade 4 (life-threatening) events, permanently discontinue belamaf treatment and provide emergency care.<sup>1</sup>

†If symptoms resolve within one hour of stopping infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise, dosing will be held until symptoms resolve and the participant must be pre-medicated for the next scheduled dose.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; IRR, infusion-related reaction; PI, prescribing information.

1. BLENREP Prescribing Information. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/761158s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761158s000lbl.pdf) [Accessed October 2020].



# Results

## Occurrence and consequences of IRRs

### Occurrence of IRRs

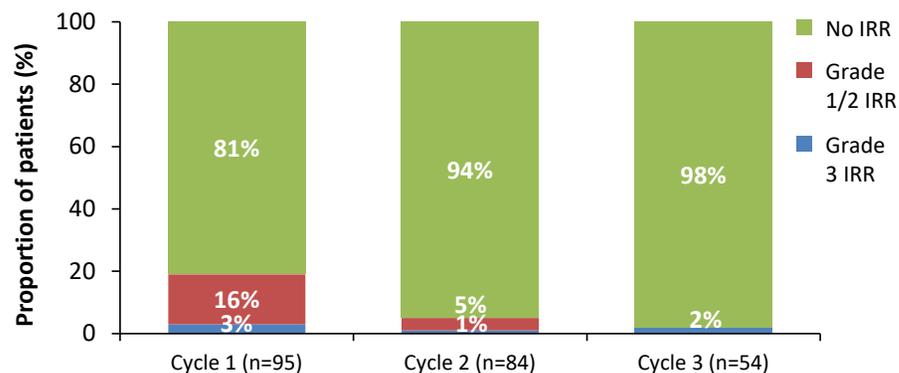
- IRRs occurred in 20 of 95 patients (21%)
- Most IRRs were mild or moderate, with no Grade 4 IRRs reported (Table)
- 12/20 patients (60%) experienced 1 IRR; 3 (15%) experienced 2 IRRs and 5 (25%) had ≥3 events
- Median time to onset of IRRs was 1 day; IRRs lasted for a median of 1 day (range: 1–3)
- The majority of IRRs occurred in Cycle 1 (Figure)

**Table: IRR by grade (all cycles)**

	Patients with IRR, n (%)
<b>All Grades</b>	20 (100)
Grade 1	6 (30)
Grade 2	11 (55)
Grade 3	3 (15)

\*IRR included the following preferred terms: pyrexia (n=5/20); chills (n=2/20); diarrhea (n=2/20); nausea (n=2/20); asthenia (n=1/20); hypertension (n=1/20); lethargy (n=1/20); tachycardia (n=1/20); IRR (n=16/20); †Two patients whose IRRs were not categorized as “resolved” at data cutoff were as follows: one patient had Grade 1 diarrhea in conjunction with a Grade 2 IRR, which started the same day as the first dose of belamaf. The IRR resolved that day, but the Grade 1 diarrhea remained ongoing. The second patient had Grade 2 pyrexia and a viral infection, both of which were ongoing at the time of death 35 days later. IRR, infusion-related reaction.

**Figure: Proportion of patients with IRR\* per cycle**  
2.5 mg/kg group (N=95) after 13-month follow-up



### Consequences of IRRs

- Belamaf treatment was permanently discontinued due to IRRs in one patient (Grade 3 IRR at first and second infusion)
- Belamaf treatment could continue as planned in all other patients, with appropriate management of IRRs
- IRRs were considered recovered/resolved in 18/20 patients (90%) at the data cutoff†

# Results

The most common pre-medications given to prevent IRRs were antihistamines, analgesics, and steroids

Cycle 1*	n (%)
Patients with IRR who received pre-medication <sup>†</sup>	8/18 (44)
Antihistamine	6/8 (75)
Analgesic	6/8 (75)
Steroid	4/8 (50)
Dopamine antagonist	1/8 (13)
Electrolyte solution	1/8 (13)
Serotonin antagonist	1/8 (13)
Unknown	0

All cycles	n (%)
Patients with IRR who received pre-medication <sup>‡</sup>	11/20 (55)
Antihistamine	6/11 (55)
Analgesic	7/11 (64)
Steroid	6/11 (55)
Dopamine antagonist	1/11 (9)
Electrolyte solution	1/11 (9)
Serotonin antagonist	1/11 (9)
Unknown	3/11 (27)

\*In Cycle 1, 73/95 (77%) patients did not receive pre-medication; of these, 12 (16%) experienced an IRR. A total of 22/95 (23%) patients received a pre-medication in Cycle 1; of these, 8 (36%) had an IRR.

<sup>†</sup>A total of 22 patients received pre-medication. Eighteen patients had an IRR<sup>1</sup>, of whom 8 had received pre-medication.

<sup>‡</sup>A total of 30 patients received pre-medication.<sup>1</sup> Twenty patients had an IRR, of whom 11 had received pre-medication.

1. Lonial S, et al. *Lancet Oncol.* 2020;21:207–21. IRR, infusion-related reaction.

# Conclusions

## DREAMM-2: analysis of IRRs

IRRs in patients receiving belamaf 2.5 mg/kg Q3W in the DREAMM-2 study were generally mild-to-moderate and manageable

- In this post hoc analysis, IRRs were reported in 20 of 95 patients (21%) receiving belamaf 2.5 mg/kg Q3W in the DREAMM-2 study
- IRRs were typically mild-to-moderate in severity, with no Grade 4 events
- The majority of IRRs occurred in Cycle 1, within 1 day of infusion
- Medication to prevent IRRs was not mandatory in the DREAMM-2 protocol, but could be administered at the investigator's discretion. It was encouraged in patients who had already experienced an IRR on the study
- The most common pre-medications were antihistamines, analgesics, and steroids
- IRRs Grade <4 were managed with either an adjustment to infusion time, pre-medication, or both

### Implications for managing belamaf-treated patients

To manage any potential risk, patients treated with belamaf should be monitored for IRRs. Management strategies include infusion interruption and supportive treatment until the IRR has resolved, and subsequent reduction of infusion rate by  $\geq 50\%$ . Pre-medication can be administered as needed. In severe cases, treatment discontinuation may be required

IRR, infusion-related reaction; Q3W, every 3 weeks.



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