Matching-Adjusted Indirect Comparisons (MAIC) of Safety Between Single-Agent Belantamab Mafodotin Versus Selinexor Plus Dexamethasone in Relapsed/Refractory Multiple Myeloma (RRMM)

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Background

- Patients with multiple myeloma (MM) who are refractory to an immunomodulatory agent, proteasome inhibitor (PI), and relapsed/refractory to an anti-CD38 monoclonal antibody (mAb), have poor prognosis and limited treatment options.[1,2]
- Improving the prognosis of heavily pretreated patients with relapsed/refractory multiple myeloma (RRMM) while maintaining tolerability is a significant challenge and remains an important unmet need in this population.[3]
  - Acceptable safety and tolerability are fundamental to treatment compliance and allow patients to complete their therapy and gain maximal clinical benefit.[4]
- Belantamab mafodotin (belamaf; BLENREP) is an antibody-drug conjugate that binds to B-cell maturation antigen, a membrane protein expressed on malignant plasma cells that supports myeloma cell proliferation and survival and eliminates MM tumour cells by multiple mechanisms of action.[5,6]
- Single-agent belamaf demonstrated deep and durable responses in heavily pretreated patients with RRMM in the DREAMM-2 primary analysis (NCT03525678).[7]
  - These responses were sustained at 13 months of follow-up with belamaf 2.5 mg/kg intravenously every 3 weeks; overall response rate was 32%, median duration of response (DoR) was 11.0 months, and estimated median overall survival (OS) was 13.7 months.[8]
- Belamaf has a manageable safety profile. The most commonly reported Grade 3–4 adverse events (AEs) with belamaf 2.5 mg/kg in the DREAMM-1 and DREAMM-2 studies included keratopathy (microcyst-like epithelial changes [MECs] defined as corneal epithelium changes identified on eye examination, with or without symptoms), anaemia, and thrombocytopenia.[7,9]
  - AEs were managed with dose delays and/or dose reductions, allowing most patients to continue treatment.[10]
- To date, the safety profile of belamaf versus other treatments has not been evaluated in head-to-head comparator studies.
- Matching-adjusted indirect comparison (MAIC) analyses were conducted to compare the efficacy and safety of single-agent belamaf with selinexor plus dexamethasone (sel+dex) in patients with heavily pretreated RRMM.
  - The efficacy results have been reported previously. Results demonstrated significant improvements in OS (adjusted hazard ratio [HR]=0.53, 95% confidence interval [CI] 0.34–0.83; p=0.005) and DoR (adjusted HR=0.32, 95% CI 0.13–0.75; p=0.009) with belamaf compared with sel+dex.[11]
  - Here we present the results of the safety MAIC analyses.

Aim

To perform an indirect comparison of the safety of single-agent belamaf versus appropriate comparators in similar patient populations (receiving ≥3 prior lines of treatment, refractory to anti-CD38 therapies) in a post hoc analysis of DREAMM-2.

Methods

Study design and population

- DREAMM-2 is a Phase 2, open-label, randomised study of belamaf in patients with RRMM, who had previously received ≥3 lines of therapy, were refractory to an immunomodulatory agent and a PI, had prior exposure to an anti-CD38 monoclonal antibody (mAb; e.g., daratumumab), and provided informed consent.[7]
  - Data from the 2.5 mg/kg arm (N=95) were used in this analysis, with a cut-off date of 31 January 2020.

Identification of an appropriate comparator: STORM Part 2

- Systematic searches were conducted in Embase, Medline, Cochrane Collection Central Register of Clinical Trials (CENTRAL), and the Database of Abstracts of Reviews of Effects (DARE) for studies published between January 2008 and April 2019 that included patients with late-line RRMM with ≥3 prior lines of therapy.
- After screening according to pre-specified inclusion and exclusion criteria, only one study with a comparable patient population was identified for inclusion in the MAIC.
- STORM Part 2 was a Phase II, open-label study consisting of patients with RRMM who had received ≥3 prior lines of therapy and were refractory to daratumumab, an immunomodulatory agent, and PIs.[12]

MAIC

- Population adjustment was carried out by matching populations on all available clinically validated effect modifiers and prognostic factors, as per National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) guidelines.[13]
- The cumulative incidences of any-grade or Grade 3–4 haematologic and non-haematologic treatment-emergent AEs (TEAEs) occurring in ≥5% of patients in the DREAMM-2 or STORM Part 2 were compared using MAIC.

Results

Baseline demographics

- The baseline characteristics of the patients in DREAMM-2 before and after the MAIC adjustment and the corresponding aggregated characteristics for the STORM Part 2 patient population are provided in **Table 1**.

Table 1. Demographics and baseline characteristics in DREAMM-2 before/after MAIC adjustment, and baseline characteristics in STORM Part 2

Variable, % of patients*†	Level	Belamaf 2.5 mg/kg observed in DREAMM-2 (n=95)	Belamaf 2.5 mg/kg after MAIC weighting (n=63.46)	Sel+dex observed in STORM Part 2 (n=123)
Age, years	≥65–74 ≥75	40.2 13.4	36.1 14.8	36.1 14.8
Sex	Male	52.6	58.2	58.2
ECOG Performance Status	1 or 2	66.7	67.2	67.2
R-ISS stage	II III	60.8 24.7	63.9 18.9	63.9 18.9
Cytogenetic risk	High risk‡	42.3	53.3	53.3
Extramedullary plasmacytomas	≥1	22.7	23.2	Not reported
Lytic bone lesion	Yes	71.1	68.2	Not reported
Creatinine clearance, mL/min	≥60	72.0	66.4	66.4
Number of prior lines of therapy	≥5 ≥9	83.5 17.5	87.8 29.3	87.8 29.3
Refractory status	To last line of therapy	95.7	100	100

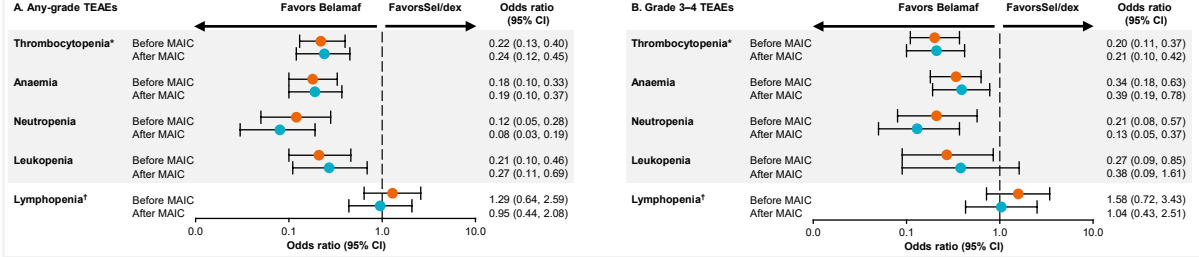
As both patient populations were comparable on refractory status to a PI, or an immunomodulatory agent, and daratumumab, there was no need for adjustment.[7,12] Extramedullary disease at baseline, presence of lytic bone lesions at baseline, and BCMA levels were reported in DREAMM-2 but not in STORM, hence no adjustment could be made for these variables. Additionally, patient populations could not be balanced with regard to time elapsed since MM diagnosis and mutation-specific factors. *Populations were matched for imbalances in age (<65, 65–74, ≥75 years old), sex, ECOG Performance Status (0 vs 1 or 2), creatinine clearance (normal or moderately impaired vs severely or very severely impaired), R-ISS (I vs II vs III), cytogenetics (high vs low risk), number of prior lines of therapy (≤4 vs ≥5, and ≤8 vs ≥9), and refractory status to the last line of therapy received; †after MAIC adjustment, an effective sample size of 63.46 was reached, which corresponded to 65% of the original population size; ‡defined as t(4;14), t(14;16), 17p13del or 1q21+. Estimates highlighted **in *bold*** and shaded in grey indicate characteristics included in the population matching model.

BCMA, B cell maturation antigen; ECOG, Eastern Cooperative Oncology Group; R-ISS, Revised International Staging System; sel+dex, selinexor 80 mg plus dexamethasone 20 mg.

Safety analyses

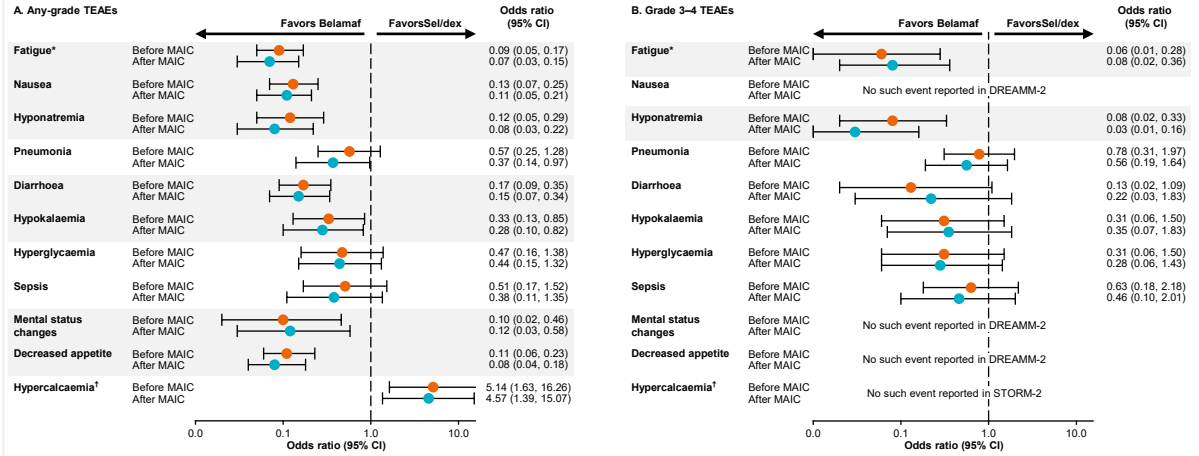
- The cumulative incidence of any-grade and Grade 3–4 haematologic TEAEs was significantly lower with belamaf compared with sel+dex (**Figure 1**), with the exception of lymphopenia, where treatments were found to be similar; however, the difference was not significant.
  - Belamaf was found to have a generally more favourable safety profile than sel+dex.
- The cumulative incidence of most any-grade non-haematologic TEAEs including fatigue, nausea, hyponatremia, pneumonia, diarrhoea, hypokalaemia, mental status changes, and decreased appetite were significantly lower in patients receiving belamaf compared with sel+dex (**Figure 2**).
  - The cumulative incidence of hypercalcaemia (commonly reported as a symptom of RRMM)[14] was significantly lower with sel+dex.
  - There was no difference in the cumulative incidence of hyperglycaemia or sepsis between treatments.
- Belamaf appeared to be significantly safer than sel+dex on onset of Grade 3–4 fatigue and hyponatremia. Trends in favour of belamaf were observed for other AEs; however, no significant difference could be detected and due to the overall low number of events observed the uncertainty is high.
- Keratopathy (MECs) was the most frequent TEAE in DREAMM-2 (any-grade keratopathy was observed in 72% of patients and Grade 3–4 in 46% of patients who received belamaf 2.5 mg/kg)[8] but no such event has been reported in the STORM Part 2 study, therefore an odds ratio could not be derived.

Figure 1. Forest-plots comparing cumulative incidence of haematologic TEAEs with belamaf vs sel+dex



OR <1 favours belamaf; OR <0.5, risk 50% lower with belamaf. TEAEs highlighted in grey boxes were significantly different. *Includes preferred terms thrombocytopenia, platelet count decreased; †includes preferred terms lymphopenia and lymphocyte count decreased.
Belamaf, belantamab mafodotin; TEAE, treatment-emergent adverse event; MAIC, matching-adjusted indirect comparison; sel+dex, selinexor plus dexamethasone.

Figure 2. Forest-plots comparing cumulative incidence of non-haematologic TEAEs with belamaf vs sel+dex



OR <1 favours belamaf; TEAEs highlighted in grey boxes were significantly different. OR <0.5, risk 50% lower with belamaf. *Include preferred terms fatigue and asthenia; †Hypercalcaemia is also a commonly reported symptom of RRMM.[14]

Conclusions

- This MAIC based on the 13-month follow-up of the DREAMM-2 study of single-agent belamaf, demonstrated a more favourable safety profile for belamaf than sel+dex for comparable haematologic and non-haematologic TEAEs reported in the DREAMM-2 and STORM Part 2 studies, respectively.
  - Keratopathy (MECs, an eye examination finding) was the most common AE in DREAMM-2, but was not reported in STORM Part 2.
- The results complement the MAIC efficacy analysis, which demonstrated significant improvements in the OS and DoR with single-agent belamaf versus sel+dex in patients with heavily pretreated RRMM.
- Single-agent belamaf represents a new treatment option for heavily pretreated patients with RRMM.

Disclosures

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