Assessing Efficacy via Indirect Comparison of Single-Agent Belantamab Mafodotin (Belamaf; GSK2857916) in DREAMM-2 Versus STORM or MAMMOTH Studies in Relapsed/Refractory Multiple Myeloma (RRMM)

Poster No. MM-209

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Aims

To make an indirect comparison of the efficacy of single-agent belamaf vs. appropriate comparators and standard of care (SoC) in similar patient populations (received >3 prior lines of treatment, refractory to anti-CD38 therapies) in a post hoc analysis of DREAMM-2 (NCT03525678).

Background

- Patients with RRMM whose disease has progressed following SoC regimens have limited treatment options.[1,2] Improving the prognosis of patients with heavily pretreated RRMM is a significant challenge and remains an important unmet need in multiple myeloma (MM).[3]
- Belamaf is an antibody-drug conjugate that binds to B-cell maturation antigen (BCMA) and eliminates MM cells by multiple mechanisms of action.[4,5] Single-agent belamaf demonstrated clinically meaningful, deep and durable responses, along with a manageable safety profile in patients with heavily pretreated RRMM in the DREAMM-2 primary analysis and 13-month follow-up.[6,7]
- The efficacy of belamaf versus other treatments, including SoC, has not yet been assessed in head-to-head comparator studies.
- Matching-adjusted indirect comparison (MAIC) and Bucher indirect treatment comparison (ITC) analyses were conducted to compare the efficacy of belamaf with comparators and SoC.

Methods

Study design and population

- DREAMM-2 is a Phase II, open-label, randomized study of belamaf in patients with RRMM, who had previously received >3 lines of therapy, were refractory to an immunomodulatory agent and a proteasome inhibitor (PI), had prior exposure to an anti-CD38 monoclonal antibody (eg, daratumumab), and provided informed consent.[4,5]
  - Data from the 2.5-mg/kg arm (n=97) were used in this analysis (13-month follow-up), with a cut-off date of January 31, 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) to identify studies published between January 2008 to April 2019 that included patients with late-line RRMM with ≥3 prior lines of therapy.
- After screening, according to prespecified inclusion and exclusion criteria, only one study (STORM Part 2) with a comparable patient population was identified for inclusion in the MAIC.
- STORM Part 2 was a Phase II, open-label study of selinexor (80 mg) plus dexamethasone (20 mg; sel+dex) consisting of patients with RRMM who had received ≥3 prior lines of therapy and were refractory to daratumumab, immunomodulatory agents, and PIs.[8]

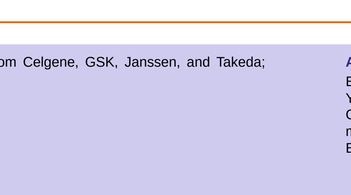
MAIC

- Population adjustment was carried out by matching populations on all available clinically validated effect modifiers and prognostic factors.
  - As both patient populations were comparable on refractory status to a PI, or an immunomodulatory agent, and daratumumab, there was no need for adjustment.[6,8]
  - The overall response rate (ORR), overall survival (OS), duration of response (DoR), progression-free survival (PFS), and time to response (TTR) of belamaf versus sel+dex were compared using MAICs.

Comparison with SoC

- Belamaf efficacy versus SoC was estimated by Bucher ITC of MAIC results using data derived from a previous study of sel+dex (STORM) versus SoC (MAMMOTH).[2,9]
  - The MAMMOTH study is a retrospective, natural history study of patients with RRMM following SoC.[2]
- In a comparative efficacy analysis, a subset of MAMMOTH patients who were refractory to a PI, an immunomodulatory agent, and daratumumab, and were comparable to patients in the STORM study, were compared.[9]
  - Bucher ITC estimates were derived using the covariate-adjusted hazard ratio (HR) reported in Costa et al. and the naïve/MAIC-adjusted HR of belamaf versus sel+dex. These HRs were derived on two different populations, and no population adjustment was carried out at this stage (**Figure 1**).

Figure 1. Bucher ITC: comparing belamaf vs. SoC from the MAMMOTH study



Results

Efficacy population

The baseline characteristics of the patients enrolled 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=97)	Belamaf 2.5 mg/kg DREAMM-2 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**

Estimates highlighted in ***bold*** and shaded in grey indicate characteristics included in the population matching model. *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+; §of which none were missing. ECOG, Eastern Cooperative Oncology Group; R-ISS, Revised International Staging System.

Efficacy analyses

Following population adjustments, the OS and DoR were significantly longer for belamaf compared with sel+dex (**Table 2, Figure 2,** and **Figure 3**).

TTR, PFS, and ORR values were not significantly higher for belamaf versus sel+dex (**Table 2**).

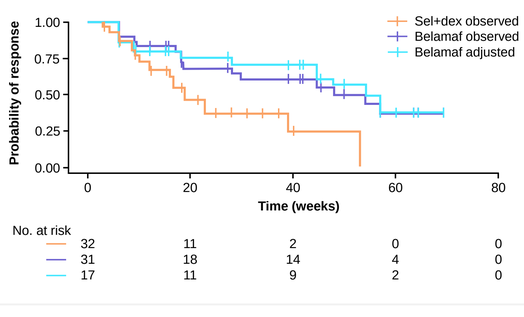
- Differences in schedules of progression assessment may have affected PFS and TTR, as initial assessments were performed 3 and 4 weeks after treatment initiation in DREAMM-2 and STORM Part 2, respectively.
- Although response rates were equivalent between belamaf and sel+dex, patients achieved deeper responses with belamaf compared with sel+dex (58% vs. 25% of responses were ≥very good partial response for belamaf and sel+dex, respectively [data on file]).

Table 2. Naïve and MAIC-adjusted estimates of HR of OS, DoR, TTR, and PFS, and OR of ORR for belamaf 2.5 mg/kg (DREAMM-2) vs. sel+dex (STORM Part 2)

Outcome*	Model (measure)	Belamaf 2.5 mg/kg vs. sel+dex	95% CI	*P*-value
OS estimate†	**Naïve (HR)** **Adjusted (HR)**	**0.60** **0.53**	**0.41–0.88** **0.34–0.83**	**0.010** **0.005**
DoR estimate	**Naïve (HR)** **Adjusted (HR)**	**0.41** **0.32**	**0.21–0.83** **0.13–0.75**	**0.013** **0.009**
TTR‡	**Naïve (HR)** **Adjusted (HR)**	0.65 0.71	0.39–1.10 0.43–1.15	0.110 0.165
PFS†‡	**Naïve (HR)** **Adjusted (HR)**	1.15 1.29	0.80–1.66 0.87–1.92	0.438 0.199
ORR§	**Naïve (OR)** **Adjusted (OR)**	1.32 1.00	0.73–2.38 0.52–1.91	0.355 0.996

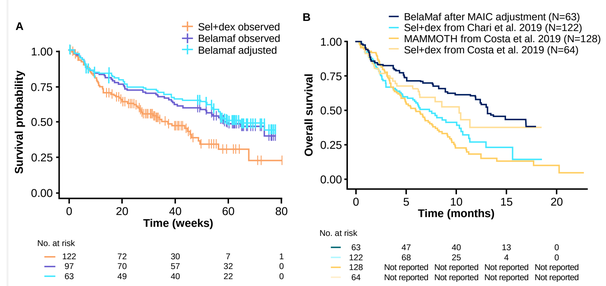
*HR<1 (except for TTR, HR>1) and OR>1 favor belamaf (shaded in grey and **bold** text indicates outcomes for which belamaf was more efficacious than sel+dex); †HR should be interpreted with caution due to the crossing of the curves; ‡suspicion of assessment-time bias; §ORR was defined as achieving partial response or above. CI, confidence interval; OR, odds ratio.

Figure 2. DoR Kaplan–Meier plot for belamaf 2.5 mg/kg (DREAMM-2) observed and MAIC-adjusted vs. sel+dex (STORM Part 2) observed



- Following the MAIC adjustment, the belamaf OS curve was shifted upward, demonstrating longer survival than sel+dex in STORM Part 2 (**Figure 3A**).
- Belamaf was found to significantly prolong OS against SoC from the MAMMOTH (**Figure 3B**).

Figure 3. OS Kaplan–Meier plots for belamaf 2.5 mg/kg (DREAMM-2) (A) before and after adjustment vs. sel+dex (STORM Part 2) observed and (B) vs. the SoC from the MAMMOTH study; overlay of the estimates from the different sources



The Bucher ITC analysis also suggested significantly longer OS with single-agent belamaf versus SoC (**Figure 3B**):

- Naïve, HR (95% CI): 0.33 (0.18–0.59), $p<0.001$ (using the naïve HR vs. sel+dex and covariate-adjusted HR of sel+dex vs. MAMMOTH);
- MAIC, HR (95% CI): 0.29 (0.16–0.54), $p<0.001$ (using MAIC-adjusted HR vs. sel+dex and covariate-adjusted HR of sel+dex vs. MAMMOTH).

Limitations

In the MAIC, 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.

In the Bucher ITC analysis, limitations included the shared-effect modifier assumption, imbalances in treatment-effect modifiers between compared treatments, and comparison against real-world studies.

Conclusions

MAIC analyses indicated significant improvements in OS and DoR with single-agent belamaf versus sel+dex in patients with heavily pretreated RRMM.

Subject to the shared treatment effect modifiers assumption, Bucher ITC suggested significantly improved OS with belamaf versus SoC.

Additional analyses will inform safety comparisons.

Disclosures

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Further analyses of DREAMM-2 are presented at this meeting (posters MM-219 and MM-250).

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