

# Impact of Using Relative Dose Intensity Versus Individual Patient Dosing: A Case Study Using Belantamab Mafodotin Data From the DREAMM-7 Study in Relapsed/Refractory Multiple Myeloma

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Estimated costs with BVd were substantially lower when applying dosing per IPD compared to overall mean/median RDI. Accurate methods that reflect observed dosing and treatment patterns, which are aligned to the observed safety and efficacy, are critical for payers and health technology assessment bodies to ensure robust cost-effectiveness evaluations

Digital poster



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Supplementary material

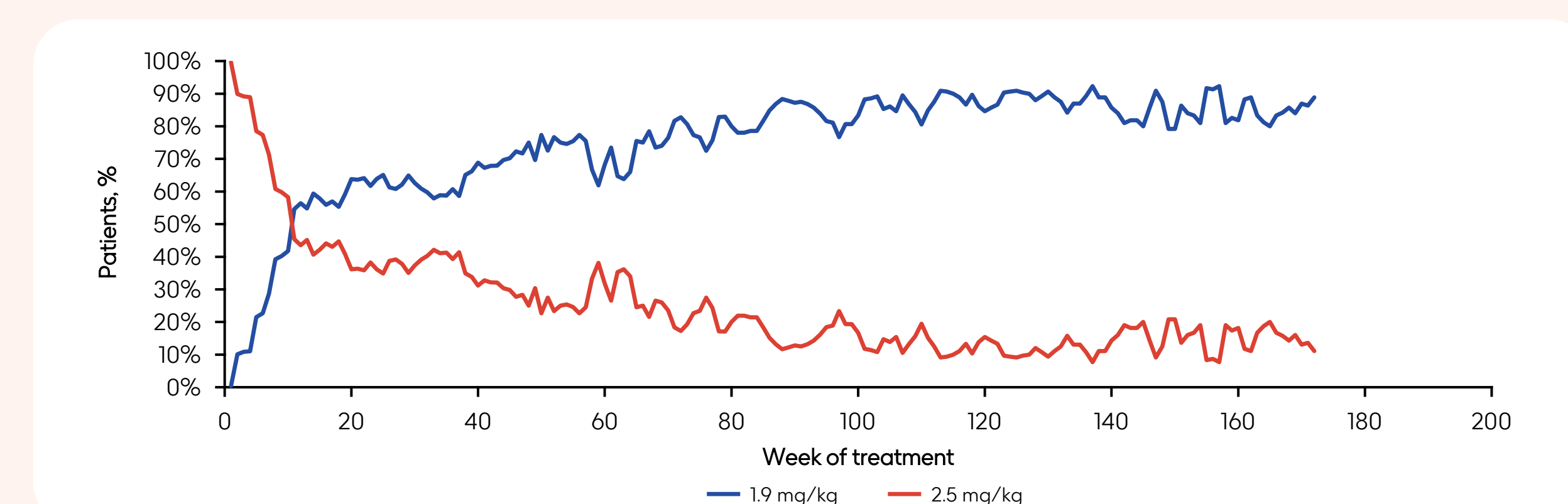


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## Background

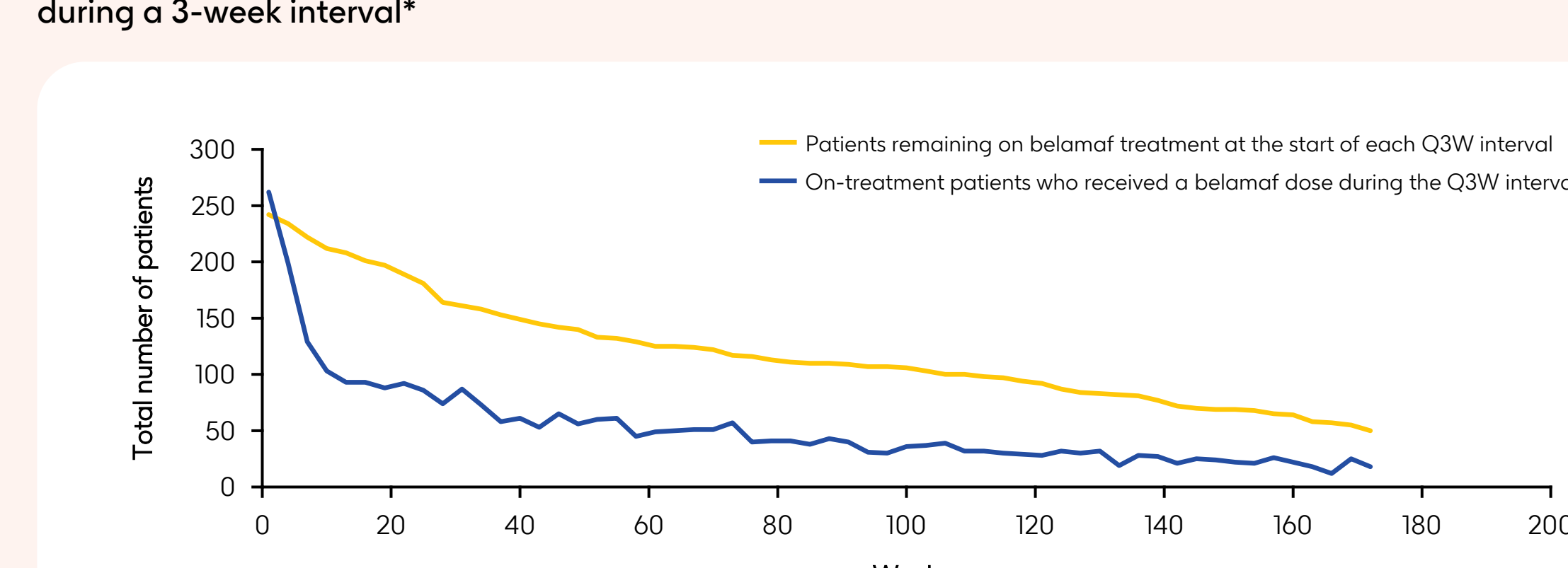
- With recent advancements in MM therapy, including transformative survival benefits shown by BCMA-targeting therapies<sup>1-3</sup> cost-effectiveness has become increasingly important when considering treatment selection<sup>4</sup>
- Relative dose intensity (RDI [ratio of the actual dose intensity to the planned dose intensity per protocol]) is used in cost-effectiveness models (CEMs) to calculate drug costs to account for deviations from trial protocol dosing.<sup>5</sup> However, drug/administration costs estimated using RDI may be confounded for treatments that have substantial dose modifications including dose reductions and varying dose intervals
  - RDI (%) = (total actual dose delivered / total planned dose) × 100
- In CEMs, the RDI is weighted by the number of patients on treatment in each model cycle, reflecting dosing among those still treated, rather than a simple per-cycle average
  - In schedules with fixed intervals (such as Q3W), more patients received treatment per the fixed interval in earlier cycles; therefore, RDI is skewed toward earlier timepoints
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- Belantamab mafodotin (belamaf) is a BCMA-targeting ADC approved for RRMM in combination with bortezomib and dexamethasone (BVd) based on robust efficacy demonstrated vs daratumumab plus bortezomib and dexamethasone (DVd) in the phase 3 DREAMM-7 trial<sup>6</sup>
- In DREAMM-7, reactive belamaf dose modifications led to a declining dose and extended dosing intervals over time<sup>7</sup> after the starting dose of 2.5 mg/kg Q3W
- Starting from Week ~11 of belamaf treatment in DREAMM-7, there was transition to a higher proportion of patients receiving the lower dose of 1.9 mg/kg (Figure 1)
- Patients receiving daratumumab in DREAMM-7 generally received the protocol dose of 16 mg/kg throughout treatment, with ~90% of patients receiving this dose
- Early and sustained separation between patients remaining on belamaf treatment and those on-treatment receiving a daratumumab dose within each planned Q3W interval demonstrates frequent extensions to the dosing interval, which allows patients to remain on treatment; the separation stabilizes after ~Week 20 (Figure 2)
- Given the changes in belamaf dosage and administration frequency over time, applying a single RDI across the entire follow-up is inappropriate because it:
  - Fails to capture belamaf long-term dosing trends needed for extrapolation beyond the trial data
  - Misrepresents RDI as a simple time-averaged measure, rather than reflecting the evolving dose profile among patients who remain on treatment (Figure 3)

Figure 1: Belamaf dose (mg/kg) received by patients remaining on treatment (3-week rolling average)\*



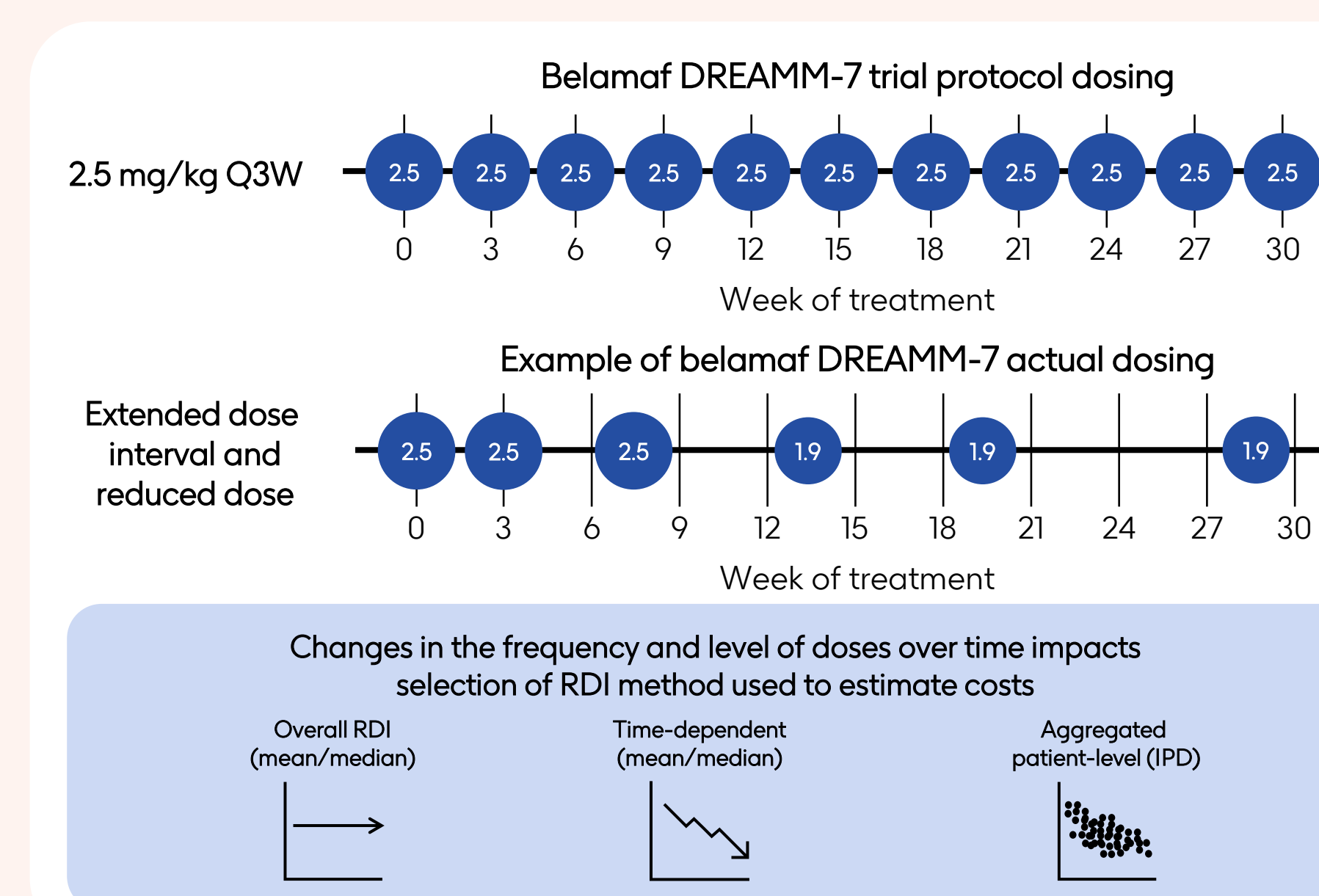
\*To preserve interpretability, the figure shows weeks up to the point when 50 patients remained on treatment (n=50); later weeks are omitted. The closest SmPC doses were used (1.9 mg/kg and 2.5 mg/kg), though actual doses received varied from 1.7 to 2.7 mg/kg.

Figure 2: Patients remaining on belamaf treatment and on-treatment patients receiving a belamaf dose during a 3-week interval\*



\*Only time periods with ≥50 patients receiving a dose are shown. Doses received are summarized within a Q3W timeframe.

Figure 3: RDI methods to estimate costs

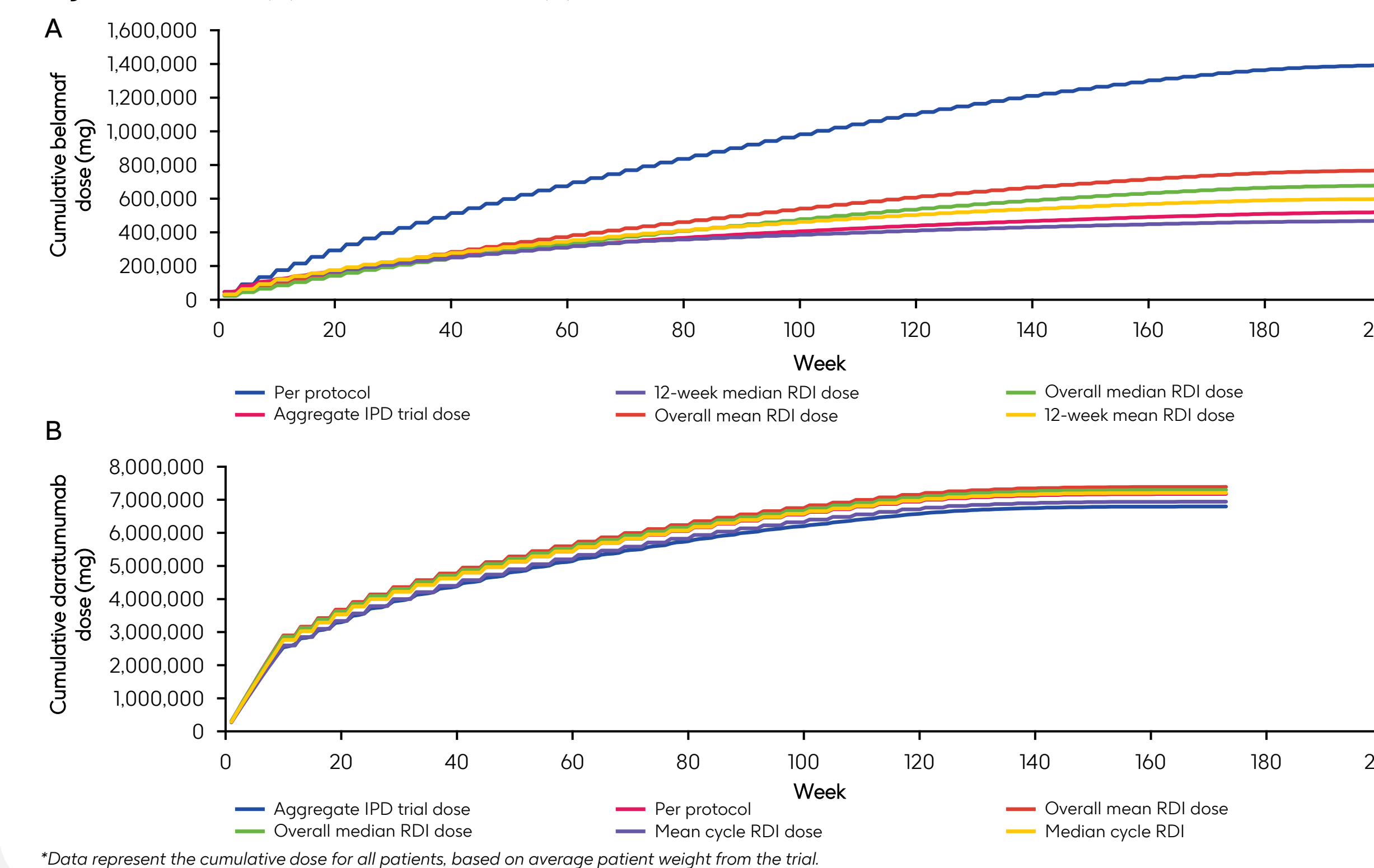


Changes in the frequency and level of doses over time impacts selection of RDI method used to estimate costs

## Results

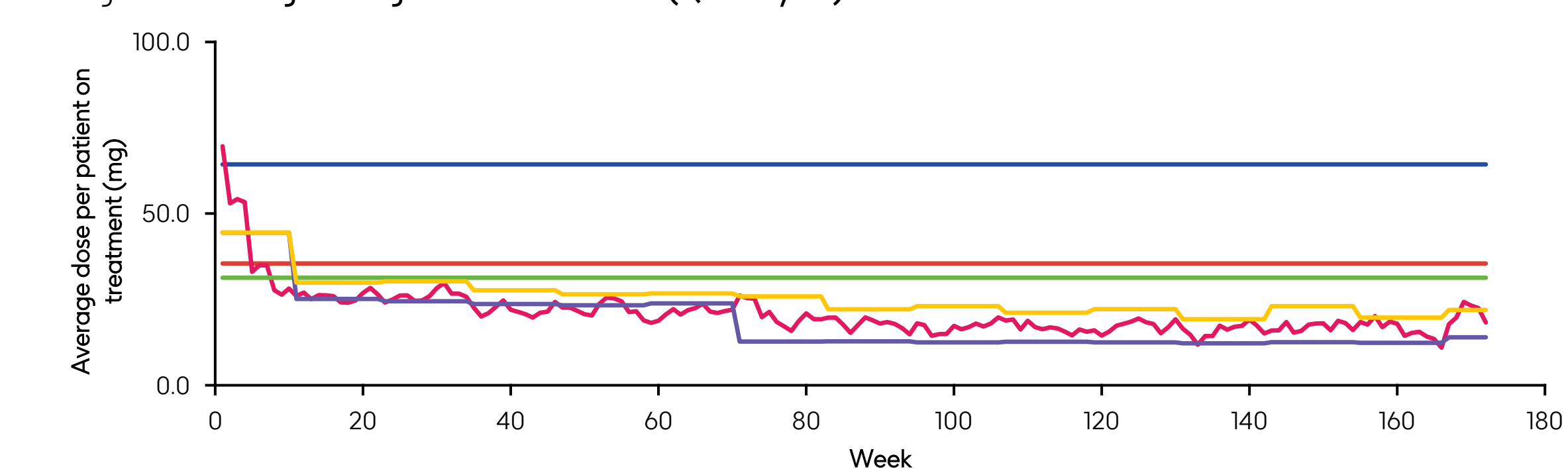
- Cumulative doses (mg) using RDI-based methods are summarized in Figure 5 (modeled for 242 patients for belamaf and 246 for daratumumab and aligned with the available dosing data prior to incorporating wastage). These estimates are compared to the total dose of belamaf and daratumumab administered to patients in the DREAMM-7 trial from the IPD data, and the protocol planned dose is included as a reference
- For belamaf, the dosing per IPD methodology closely aligned with the total administered dose from the trial, and the mean RDI method quickly overestimated belamaf administered dose. The 12-week interval dose was more closely aligned to the trial aggregate dose
  - It is therefore appropriate to use the time-varying analysis available from the IPD data to capture the true impact of dose reductions and dose schedule delays as seen in clinical practice
- For daratumumab, due to few dose reduction and dose schedule delays, the mean RDI and the aggregate IPD data were more closely aligned
- Median and mean RDIs were similar for belamaf and for daratumumab, though mean values were slightly higher than median values for belamaf, reflecting the wide range of dose modifications observed in DREAMM-7 (Figures 5–7)

Figure 5: Belamaf (A) and daratumumab (B) cumulative doses\*



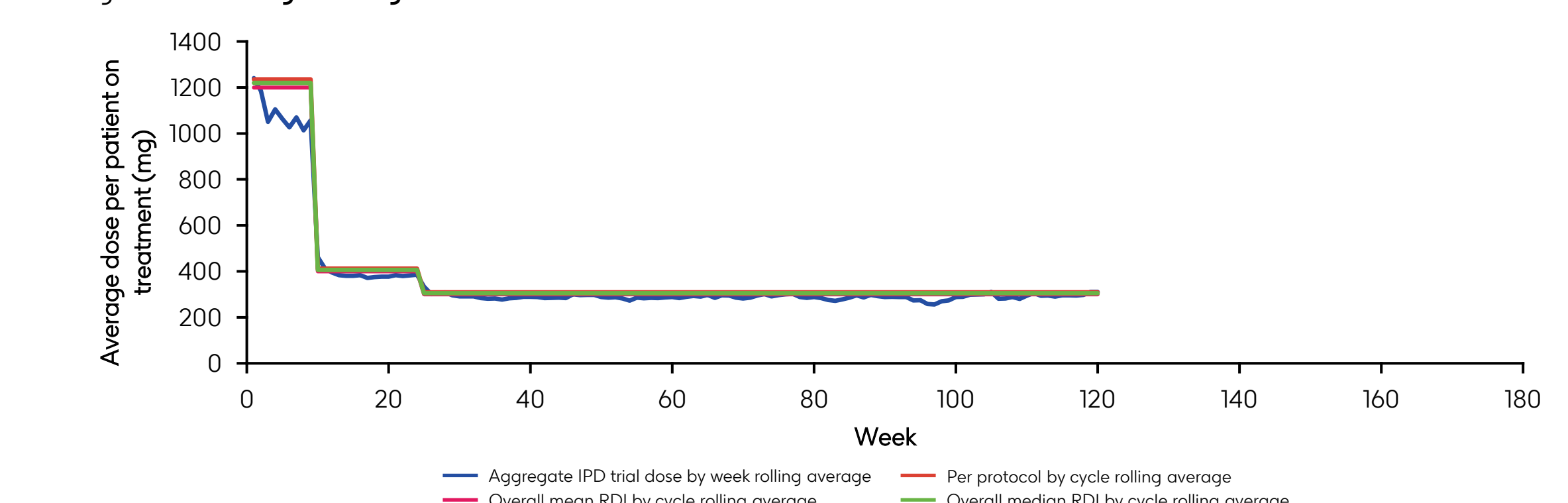
\*Data represent the cumulative dose for all patients, based on average patient weight from the trial.

Figure 6: Rolling average of belamaf dose (Q3W cycle)



- RDI will under-estimate the drug cost at the early time periods, but will quickly over-estimate the overall drug costs (Figure 6)
- Smaller-interval RDIs were more reflective of the actual dose received by patients than overall RDI

Figure 7: Rolling average of daratumumab dose



- For daratumumab, mean and median RDIs were consistent with the trial dose (Figure 7)

Table 2: Cost comparison

| Cost difference versus IPD | BVd  | DVd  |
|----------------------------|------|------|
| Median overall RDI         | +41% | +10% |
| Mean overall RDI           | +57% | +9%  |
| Median 12-week RDI         | +21% | NA   |
| Mean 12-week RDI           | +37% | NA   |

- Compared to dosing based on IPD, estimated lifetime BVd drug and administration costs were substantially higher using overall RDI methods, while DVd costs remained relatively consistent (Table 2)

## Aim

Data from the intent-to-treat population of the phase 3 DREAMM-7 trial of BVd versus DVd in RRMM were used to evaluate alternative methods for estimating lifetime drug acquisition and administration costs in a cost-effectiveness model, particularly when dosing intervals increase over time compared with the planned protocol dose

## Methods

- Three methods for estimating lifetime drug and administration costs were evaluated in a CEM from a UK perspective. The first method used overall RDI, the second used aggregate individual patient-level dosing (IPD [dosing data collected from individual patients in DREAMM-7 and then pooled]), and the third, explored only for belamaf, used a 12-week RDI
  - Costs were based on administrative healthcare resource utilization per SmPCs, infusion costs from the UK National Health Service, and drug vial prices from the UK list price<sup>8-12</sup>
- The model used a 1-week cycle length and adopted a UK National Health Service and Personal Social Services perspective over a lifetime horizon, with outcomes discounted at 3.5%
- DREAMM-7 protocol dosing**
  - BVd: belantamab mafodotin 2.5 mg/kg IV infusion Q3W for all treatment cycles, bortezomib administered for the first 8 treatment cycles only
  - DVd: daratumumab 16 mg/kg IV infusion weekly in treatment cycles 1–3, Q3W from Cycles 4–8, and Q4W from Cycle 9+
  - Patients in both arms were treated until the earlier of progressive disease, death, unacceptable toxicity, withdrawal of consent, or loss to follow-up

### Methods used to determine RDI

#### 1. Overall RDI method

- Dose reductions and dose delays were modeled by estimating the drug usage using a constant RDI from DREAMM-7. RDI values were applied by multiplying the RDI by the dose recommended in the administration schedule. For example, with 55.1% mean RDI applied to the protocol dose of 2.5 mg/kg, the dose was reduced to 1.4 mg/kg. This dose was used to calculate the weekly drug and administration cost in the model. Mean and median RDIs were explored, and values are presented in Table 1

Table 1: Overall RDI in the DREAMM-7 study

| Overall RDI | Belamaf (BVd) | Daratumumab (DVd) |
|-------------|---------------|-------------------|
| Mean (SD)   | 55.1% (30.7%) | 97.1% (5.3%)      |
| Median      | 48.7%         | 98.8%             |

#### 2. Aggregate patient-level data method

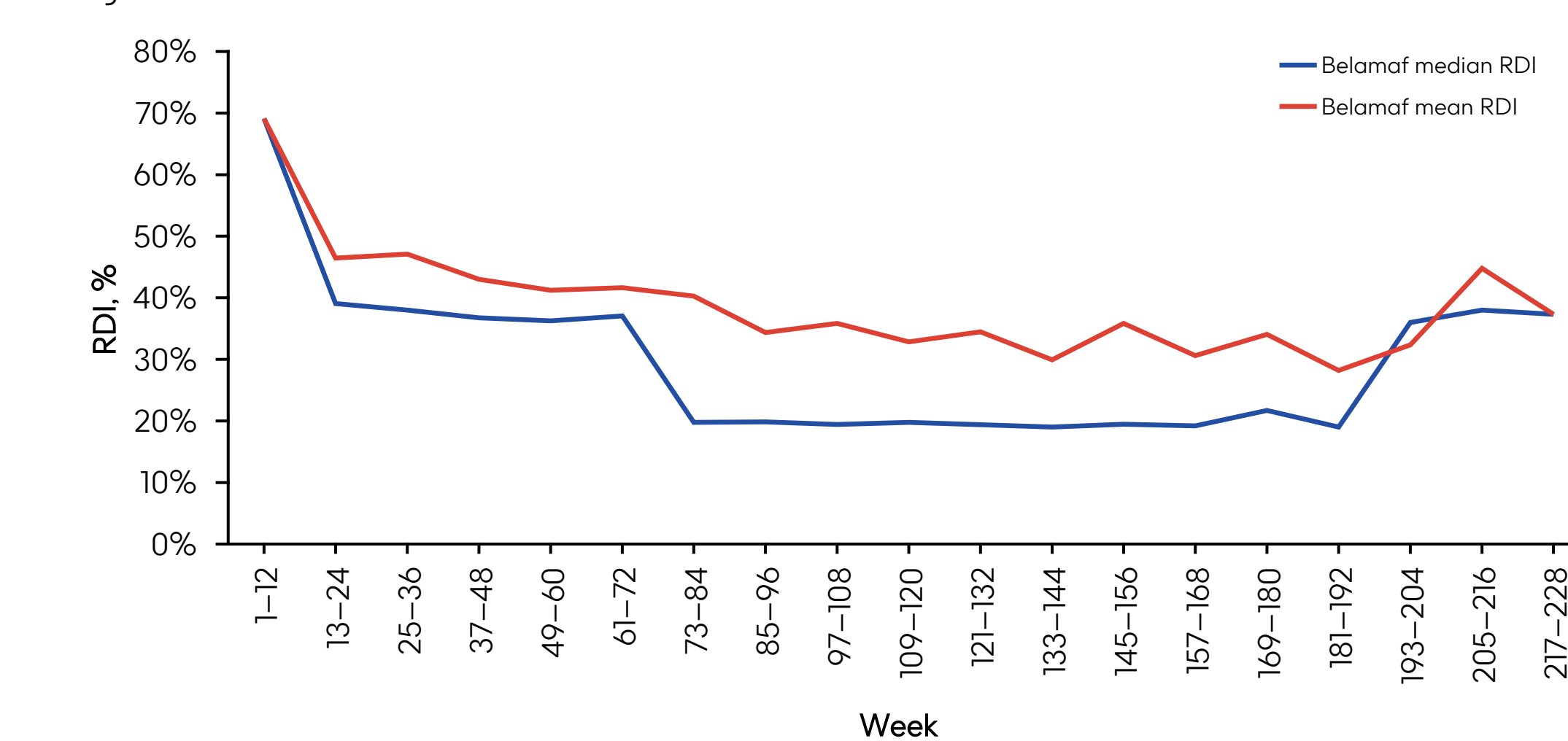
- IPD provide weekly data detailing the number of patients on treatment, the number of patients receiving any belamaf dose or daratumumab dose, and the number of patients receiving each treatment dose
- Summaries of administered belamaf and daratumumab dose levels by week are available in Supplementary Tables 1 and 2
- The percentage of patients receiving each dose was used to calculate the weighted belamaf/daratumumab acquisition cost per weekly model cycle for each dose, which was then used to calculate the total treatment acquisition cost per cycle. The per cycle treatment acquisition cost was calculated as follows:

$$X \text{ mg/kg acquisition cost per cycle} = \% \text{ of patients receiving } X \text{ mg/kg} \times \text{acquisition cost of } X \text{ mg/kg}$$

#### 3. 12-week RDI

- For belamaf, an option to account for dose delays and reductions using median and mean RDIs from the DREAMM-7 trial reported in 12-week intervals (Figure 4) was included to capture the changes in dose intensity over time

Figure 4: Belamaf 12-week RDI in DREAMM-7\*



\*Data from later timepoints are limited by smaller patient numbers.

## Conclusions

Belamaf dosing based on IPD aligned with trial administration while RDI overestimated the administered dose. This led to substantially lower cost estimates with BVd when applying IPD compared to overall RDI, whereas DVd costs were estimated to be similar

These results indicate that for agents with varying doses and dosing intervals over time, applying an overall RDI can inaccurately estimate long-term drug and administration costs compared to IPD

As treatment options continue to expand and improve outcomes for MM, accurate methods that reflect observed dosing and treatment patterns are critical for payers and health technology assessment bodies to ensure robust cost-effectiveness evaluations

## Abbreviations

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; belamaf, belantamab mafodotin; BVd, belantamab mafodotin, bortezomib, dexamethasone; CEM, cost-effectiveness model; DVd, daratumumab, bortezomib, dexamethasone; IPD, individual patient dosing; IV, intravenous; MM, multiple myeloma; NA, not applicable; QxW, every X weeks; RDI, relative dose intensity; RRMM, relapsed/refractory multiple myeloma; SD, standard deviation; SmPC, summary of product characteristics

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- <https://bnf.nice.org.uk/drugs/daratumumab/medicinal-forms/>

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## Disclosures

YS, MP, NB, SM, and GK are employees of and hold financial equities in GSK. AB is a former employee of and holds financial equities in GSK. ED is an employee of FIECON. DL is an employee of PenTAG, University of Exeter, and provides consultancy to FIECON.