Dynamic Assessment of a Multiple Myeloma Patient Access Scheme Using Real World Data and Bayesian Inference

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Introduction

- Novel multiple myeloma (MM) therapies are often initially available in England through the **Cancer Drugs Fund (CDF)**, a **patient access scheme (PAS)**, during an **evidence-gathering period** prior to NICE's final recommendation decision.
- A **Bayesian inferential approach** when analysing PAS data may allow for dynamic comparative effectiveness inference during the the data collection phase, as prior information can be integrated into analysis and **interim analysis is not penalised** as there is no reliance on null-hypothesis significance testing and therefore no concerns about multiple testing.
- Here, we have integrated **real-world and prior trial data** within a Bayesian framework to investigate the viability of **early decision making** based on assessment of daratumumab monotherapy for relapsed/refractory (RR) MM (NICE TA783[1]), with pomalidomide + dexamethasone (POM+DEX) as the NICE defined comparator.

Objectives

- Construct a **real world** cohort of patients receiving **daratumumab through the CDF**, and of patients receiving **POM+DEX at 4L** through **routine commissioning.**
- Identify **prior information regarding OS in daratumumab** treated patients from previous studies, and **prior information regarding OS treatment effects for novel MM therapies** from previous trials in RR MM.
- Perform **dynamic** longitudinal Bayesian assessment of the **probability of daratumumab reducing mortality** compared to POM+DEX.
- Assess the **time taken for this probability to be greater than 0.95** and compare this with the length of time daratumumab data was collected during CDF access.

Methods

1. **Patients with MM (ICD-10 code C90.0) (N = 2823)** were retrospectively identified between 2000 and 2023 from three NHS centres in the **Arcturis UK dataset** using de-identified secondary care EHR.

2. Data generated by patients receiving either **daratumumab through CDF during the data collection period** (2018/01/17 - 2021/06/02) or POM+DEX at 4L with a prior proteasome inhibitor and immunomodulator were retained for analysis.

3. **Dynamic time-to-event datasets** were created for **3 month periods** of the CDF data collection period of daratumumab by longitudinally updating each subject's survival outcome data.

4. **Bayesian parametric survival** models using an **exponential hazard** were constructed for **each month of daratumumab data collection** with POM+DEX exposure included as a covariate with a corresponding coefficient ($\beta_{POM+DEX}$)**.** Separate analyses were performed with an **informative** and a **diffuse prior** on baseline hazard.

5. A **prior distribution for baseline hazard** was constructed around a mean based on the median OS time from **previous daratumumab studies** (GEN501 and SIRIUS[2])

$$\lambda \sim \mathcal{N}(\mu = \ln(2)/-20.1, \sigma),$$
$$\beta_{POM+DEX} \sim \mathcal{N}(0, 0.325)$$

For the **diffuse prior** σ was set to 100, resulting in **little prior information** regarding the event rate for daratumumab exposure. For the **informed prior**, σ was set to 0.197 after assessment of the variance in median OS across RR MM trials.

6. The marginal posterior distribution for the treatment effect of POM+DEX was **assessed at each time point** to identify if $Pr(\beta_{POM+DEX} > 0) \geq 0.95$ **had been reached**, indicating a clear OS benefit for daratumumab over POM+DEX.

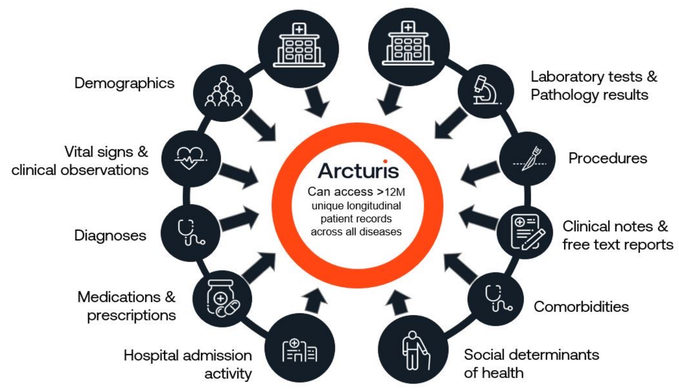

Figure 1. Types of data included in the **Arcturis UK dataset.**

Results

- A cohort of N = **115** (N = **88 CDF daratumumab**; N = **27 4L POM+DEX**) suitable subjects were identified in the Arcturis MM dataset. The two cohorts were broadly similar at baseline (Table 1).
- When the **prior on the baseline hazard** for daratumumab was **informed** by previous daratumumab and RR MM trial results, the marginal **probability of daratumumab providing an OS benefit was > 0.95** by the **sixth month** of data collection (Figure 2).
- This result was obtained after **just 14.6% of the data collection period used for NICE TA783[1]** had elapsed. This is equivalent to a **~7x improvement** in the time taken to observe a treatment benefit.
- The posterior distribution of the **treatment effect** of daratumumab **stabilised after 15 months** of data-collection.
- When a **diffuse prior** was applied on the baseline hazard, the probability of daratumumab providing an OS benefit was exceeded 0.95 at the sixth month of data collection, as observed with the informed prior.
- Recovery of similar results with a diffuse prior suggests that the **analysed data is driving the estimated treatment effect** when the informed prior was used (Figure 3).

Variable	Daratumumab Cohort	4L POM+DEX Cohort
N	88	27
Mean Age (SD), Years	69.2 (10.2)	73.4 (9.3)
Sex = Male, %	58.5	57.1
Mean Time from MM Diagnosis to Index Date (SD), Years	3.3 (2.7)	3.4 (1.8)
Median Index Date Year (IQR), Calendar Year	2019 (1)	2017 (2)

Table 1. Cohort characteristics for the real world cohort at index date, stratified by exposure group. The two exposure groups were broadly similar in terms of disease duration, sex distribution, and age at baseline. Index date was the date of first administration of either daratumumab or POM+DEX.

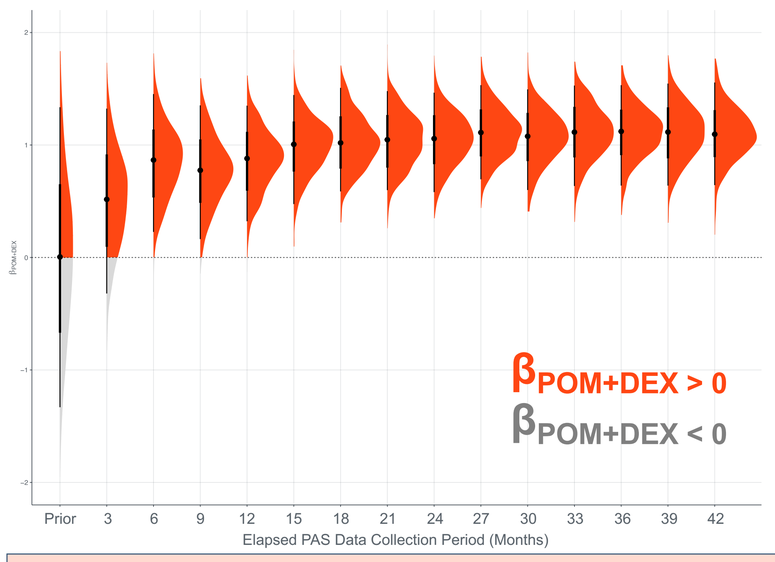

Figure 2. Marginal posterior distribution of $\beta_{POM+DEX}$ for overall survival (OS) estimated dynamically at 3-month intervals across the PAS data collection process for daratumumab funded through the CDF. Values greater than 0 demonstrate longer OS on daratumumab therapy than POM+DEX. Black points and bars represent the posterior median, and 50th and 95th percentile limits for the distribution.

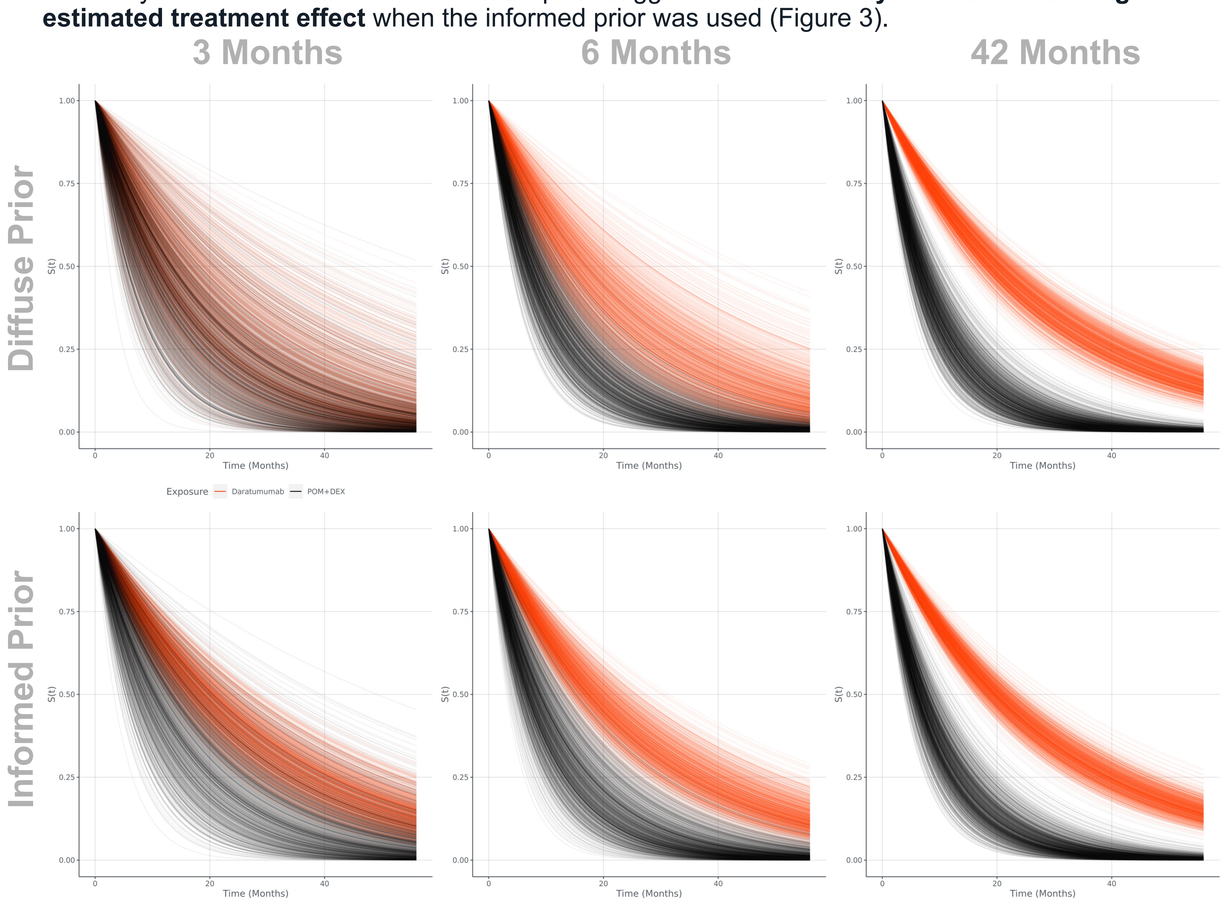

Figure 3. Posterior samples of modelled overall survival (OS) obtained using either an informed or diffuse prior on the baseline hazard, after 3 months, 6 months, and 42 months of data collection. After 3 months of data collection the informed prior provides a clearer picture of differential outcomes, by 6 months an OS benefit for daratumumab over POM+DEX is clear, by 42 months convergence across prior distributions shows that the survival estimates are completely driven by the analysed data.

Conclusions

- A **Bayesian inferential framework can be applied** to **dynamically assess** patient access scheme data as it is being collected in **real-time.**
- Inference regarding the **relative effect** on clinical outcomes can be **achieved before the end of the pre-defined data collection period.**
- Bayesian inference is **not restricted to comparative effectiveness**, this framework can be applied to **extrapolation of survival curves** or other aspects which may **influence economic modelling.**
- Future analysis will **relax the assumption of constant hazard**, and **adjus**t for potential **confounding covariates.**

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[2] Usmani SZ, Nahi H, Plesner T, et al. Daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma: final results from the phase 2 GEN501 and SIRIUS trials. Lancet Haematol. 2020;7(6):e447-e455.