RWD18

Characterisation Of Time-To-Treatment-Discontinuation (TTTD) As A Proxy for Progression-Free Survival (PFS) In Real-World-Evidence (RWE) Based Analyses Of Relapsed-Refractory Multiple Myeloma (RRMM)

Joseph O'Reilly PhD[1], Alycia Perkins MSc[1], Filipa Tunaru MPhil[1], Jamie Wallis PhD[1], and Lewis Carpenter PhD[1]

[1] Arcturis Data, Building One, Oxford Technology Park, Technology Drive, Kidlington, OX5 1GN UK

Introduction

- Progression Free Survival (PFS) is often used as an endpoint in oncology trials, and is constructed from many biomarkers/imaging data types
- The **ability to construct PFS in real-world data (rwPFS) is constrained by what data is collected** in routine clinical practice, and what is recorded electronically
- Consequently, **time-to-treatment-discontinuation (TTTD) has seen use as a proxy for PFS** in real-world external control arm studies (and vice-versa for economic modelling)
- The ability of TTTD to act as a proxy for PFS requires characterisation
- The **large patient numbers**, **deep biochemistry data**, and **comprehensive anti-cancer therapy data** of the **Arcturis UK dataset** enable assessment of **the suitability of TTTD as a proxy for PFS**

Objectives

- **Construct cohorts** of RRMM patients who fulfilled the prior therapy requirements of **GEN501/SIRIUS**[1,2] and received subsequent daratumumab or **pomalidomide** at index
- **Build a framework** to approximate the HTA assessment of daratumumab as a novel therapy against a comparator therapy of pomalidomide (e.g., NICE TA7633)
- **Characterise the delay between progression and TTTD** and **identify patterns** across quantiles of time-to-progression and therapy type
- Compare the **treatment effect of daratumumab against pomalidomide** when the outcome is **rwPFS**, or when **TTTD is used in the pomalidomide** arm and **rwPFS is used in the daratumumab arm** (simulating a scenario in which an ECA cannot provide PFS)

Methods

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

2. **Arcturis' proprietary Lines of Therapy (LoT) algorithm** was applied to anti-cancer therapy data to construct patient lines of therapy.

3. **Inclusion and exclusion criteria** of SIRIUS+GEN501 were applied to RWD.

4. **rwPFS** was constructed by **applying IMWG criteria to real-world biochemistry and mortality data,** TTTD was constructed from anti-cancer therapy data

5. Differences between TTTD and time-to-progression were calculated by exposure status and quantile of time-to-progression

6. **Average treatment effect between daratumumab and pomalidomide was estimated** with IPTW weighted Cox-PH with rwPFS used in each arm, or **rwPFS in the daratumumab arm** and **TTTD in the pomalidomide arm**, with ATE as the target estimand

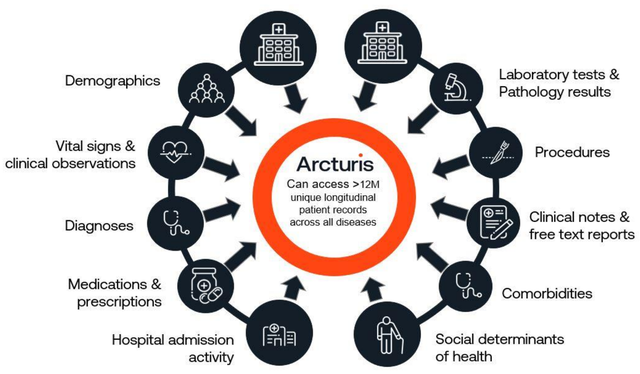

Figure 1. Types of data included in the Arcturis UK dataset

Results

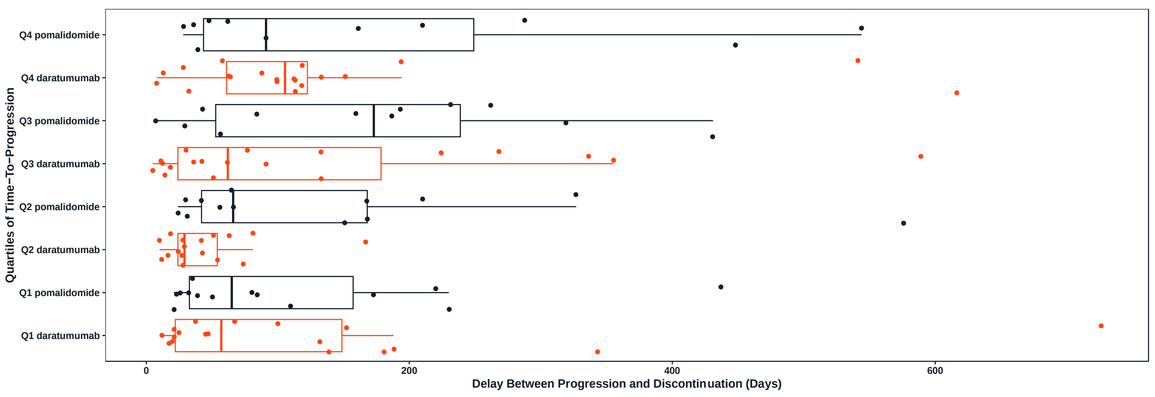

Figure 2. Distribution of delay from time-to-progression and TTTD, stratified by exposure therapy. **Pomalidomide** exposure is generally **associated with a larger time delay from progression to discontinuation** than **daratumumab,** particularly in **Q2** and **Q4**.

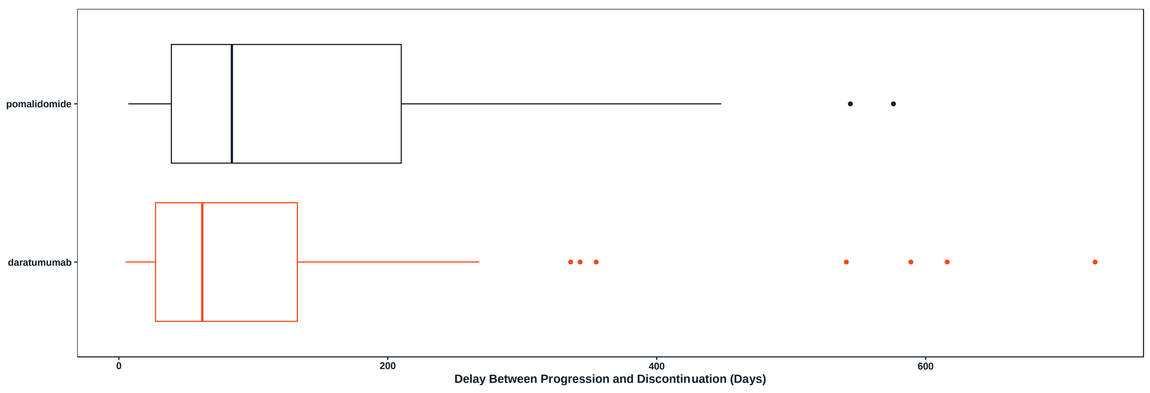

Figure 3. Distribution of delay from time-to-progression to TTTD amongst patients who had a progression event and subsequent discontinuation event, and who did not die on the date of progression, stratified by the quantile of time-to-progression and therapy type. **Pomalidomide** exposure is **associated with a larger time delay from progression to discontinuation** than **daratumumab**.

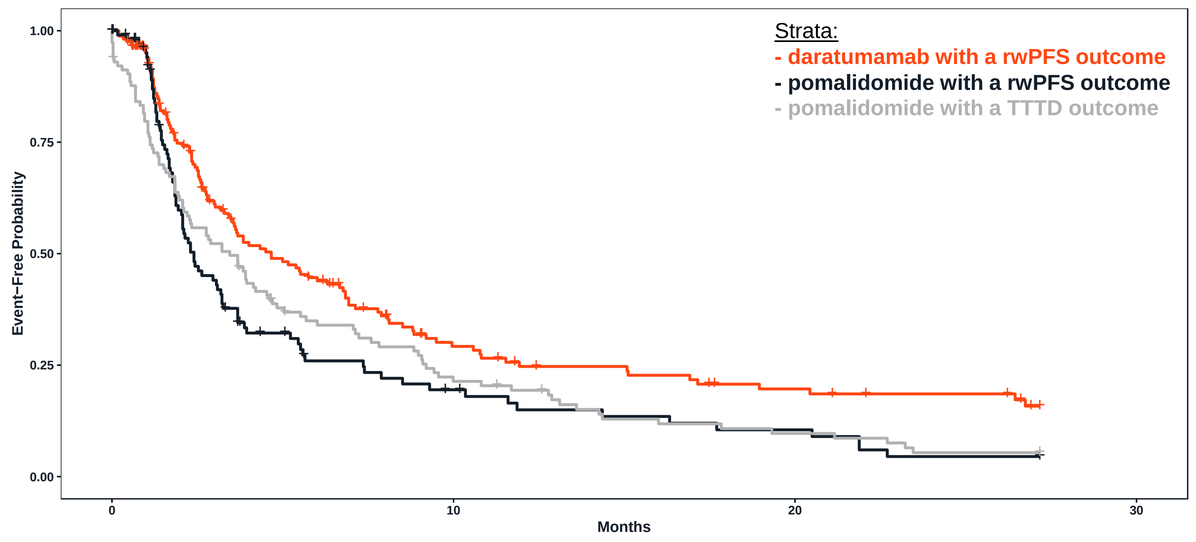

Figure 4. Kaplan-Meier estimated survival distributions for **daratumamab with a rwPFS outcome**, **pomalidomide with a rwPFS outcome** and **pomalidomide with a TTTD outcome**

	Daratumumab$_{rwPFS}$ Pomalidomide$_{rwPFS}$	Daratumumab$_{rwPFS}$ Pomalidomide$_{TTTD}$
Hazard Ratio (95% CI)	0.65 (0.49, 0.86)	0.71 (0.55, 0.93)
Schoenfeld Residual Test P-Value	0.78	0.28
ESS (N, Percentage of Observed Arm Size)	Pomalidomide: 113.14 (99.25%) Daratumumab: 176.36 (99.64%)	

Table 1. Weighted Cox-PH estimated hazard ratios, 95% CIs, p-values for tests of proportional hazards, effective sample size after weighting. In each analysis daratumamab is compared with a control of pomalidomide across pairs of outcomes (rwPFS, or rwPFS in the daratumumab arm and TTTD in the pomalidomide arm).

- A cohort of N = 291 (N = **177 daratumumab**; N = **114 pomalidomide**) suitable subjects were identified in the Arcturis MM dataset
- **Differences** in the delay between progression and discontinuation were seen **across exposure status and quantile of time to progression**, particularly in **Q2 and Q4**, with **pomalidomide** patients staying on therapy for longer after progression on average (Figure 2; Figure 3)
- Using rwPFS as the outcome in both arms demonstrates a superior progression free period in **daratumumab** treated subjects (Table 1)
- Using TTTD as a proxy for PFS in the control arm results in a smaller estimate of the treatment effect of **daratumumab**, both in the point estimate and 95% CI (Table 1)
- The similarity in the weighted effective sample size (ESS) and size of the unweighted **daratumumab** and **pomalidomide** arms reflects a **similar distribution of baseline covariates in these populations**
- Proportional hazards were maintained in all analyses

Conclusions

- The **delay between progression and discontinuation in real-world data varies** with the time taken to reach progressive disease and the type of therapy being administered
- Heterogeneity means that **TTTD suitability as a PFS proxy depends on the conte**xt
- Covariate balance in the pomalidomide and daratumumab arms was strong before weighting, and sample size was maintained after weighting
- **Use of TTTD as a proxy for PFS in real-world cohorts may bias estimates of comparative effectiveness**

Acknowledgements

This work uses data provided by patients and collected by the NHS as part of their care and support. We believe using patient data is vital to improve health and care for everyone and would, thus, like to thank all those involved for their contribution. A pseudonymised dataset for this study was provided by the West of Scotland Safe Haven research database service at NHS Greater Glasgow and Clyde under REC approval 22/WS/0163.

References

[1] Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet. 2016;387(10027):1551-1560. doi:10.1016/S0140-6736(15)01120-4
[2] Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. N Engl J Med. 2015;373(13):1207-1219. doi:10.1056/NEJMoa1506348
[3] NICE TA763, Daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable, Feb 02 2022

Arcturis