MSR105

Construction of External Control Arms (ECA) in Relapsed and Refractory Multiple Myeloma (RRMM)

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Introduction

- **External Control Arms** (ECA) **can be constructed using real-world data** (RWD) to improve commonly applied indirect treatment comparison approaches when use a control arm poses logistical or ethical challenges or a randomized control trial (RCT) is not possible.
- **The use of RWD in regulatory submissions is increasingly common**, particularly in oncology.
- **Treatment for multiple myeloma (MM),** an incurable cancer of the bone marrow, **aims to increase survival and quality of life**; however, as patients relapse and become refractory to prior treatments, the availability of further treatment options reduces [1-4].
- Trials such as **ICARIA-MM** [5] and the pooled trials **SIRIUS+GEN 501** [6] **have investigated novel treatments** for use in the relapsed and refractory MM (RRMM) population with progression-free survival (PFS) and overall survival (OS) as outcomes.

Objectives

1. **Construct ECAs using RWD for each trial based on trial-specific inclusion and exclusion criteria** and assess baseline characteristics in each group;
2. **Compare the ECAs to the trial** control arms and the trial treatment arms for each trial **using KM curves**;
3. **Calculate overall survival (OS) and real-world progression-free survival (rwPFS)** using the ECA and compare to the trial OS and PFS for each trial.

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 each trial were applied to RWD to construct **ECAs** for the **ICARIA-MM** and pooled **SIRIUS+GEN 501** trials.

4. **Broad and narrow** ECA cohorts were constructed.
   - Broad: Patients with therapy exposure similar to trial participants, e.g. PI exposure.
   - Narrow: Patients in the broad cohort meeting the inclusion/exclusion criteria of each trial.

5. Outcomes of **rwPFS and overall survival** were identified using RWD equivalents of the International Myeloma Working Group (IMWG) criteria for progressive disease and the difference in time from diagnosis to death respectively.

6. **Baseline characteristics** in each **ECA** were compared with the respective trial to assess covariate imbalance in the absence of individual patient data (IPD) and **unadjusted Cox proportional hazards models** (or log-rank test if non-proportional) performed to assess the difference between **ECA** and trial populations.

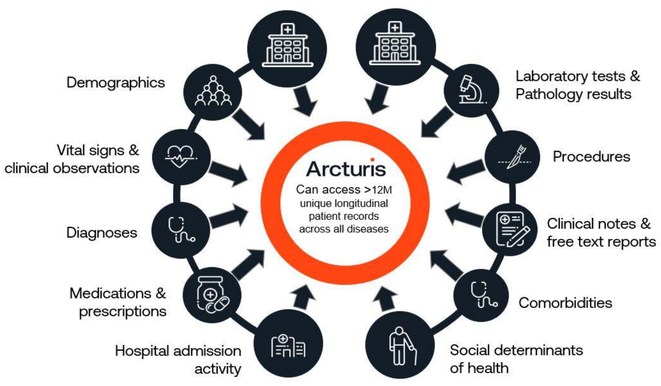

Figure 1. Types of data included in the Arcturis UK dataset

Results

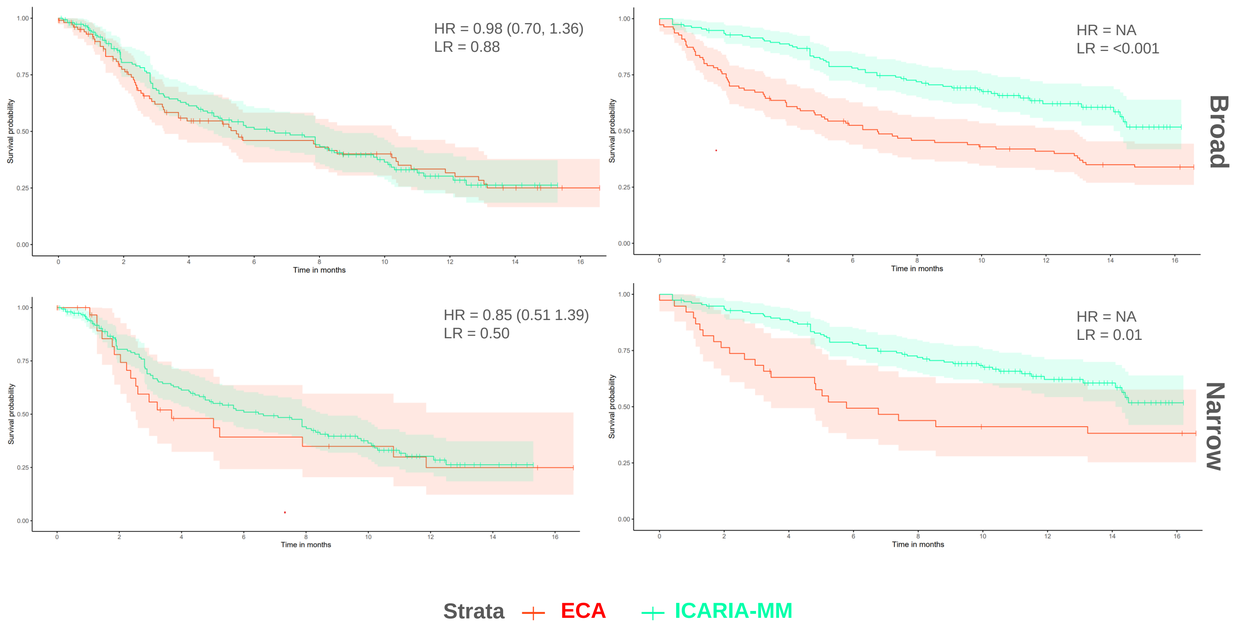

Figure 2. Comparison between the pomalidomide arm of ICARIA-MM and Arcturis' ECA constructed using the trial inclusion criteria, with PFS and OS as outcomes. The broad cohort fulfil the therapy inclusion criteria, the narrow fulfil a more extensive set of the ICARIA-MM inclusion criteria. Where proportional hazards was not observed a hazard ratio is not reported. HR = hazard ratio, LR – Log-rank p-value

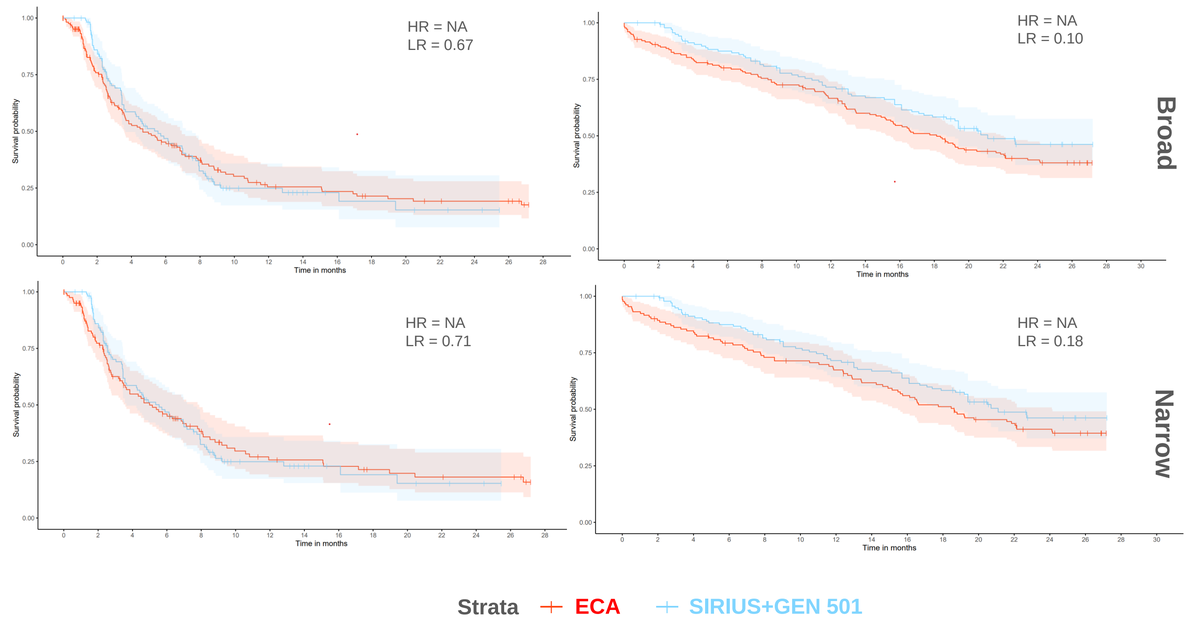

Figure 3. Comparison between the single daratumumab arm of SIRIUS+GEN501 and Arcturis' ECA constructed using the trial inclusion criteria, with PFS and OS as outcomes. The broad cohort fulfil the therapy inclusion criteria, the narrow fulfil a more extensive set of the SIRIUS+GEN501 inclusion criteria. Where proportional hazards was not observed a hazard ratio is not reported. HR = hazard ratio, LR – Log-rank p-value

- From a total of 6,749 MM patients, ECAs were constructed for ICARIA-MM (N Broad = 110, N Narrow = 38), and SIRIUS+GEN501 (N Broad = 177, N Narrow = 131).
- Despite fulfilling stringent inclusion criteria, **the ICARIA-MM ECA showed clear baseline demographic differences** (see Table 1) **to the original trial and exhibited a statistically similar PFS but longer OS** when compared to the trial control arm (Figure 2).
- **The PFS and OS distributions for the broad ECA for SIRIUS+GEN501 were similar to the trial arm**, with the null-hypothesis not rejected for any combination of cohort or outcome (Figure 3).

	ICARIA-MM			SIRIUS+GEN 501		
Covariate	**Arcturis' ECA Broad cohort**	**Arcturis' ECA Narrow cohort**	**Control arm**	**Arcturis' ECA Broad cohort**	**Arcturis' ECA Narrow cohort**	**Pooled control arm**
Age in years *	62 (59 – 66)	58 (56 – 60)	66 (59 – 71)	68 (44 – 84)	65 (44 – 84)	64 (31 – 84)
Male, n (%)	62 (56%)	20 (53%)	70 (46%)	102 (58%)	70 (53%)	78 (53%)
Time since diagnosis *	2.84 (2.1 – 4.3)	3.28 (1.7 – 4.1)	4.09 (2.9 – 7.0)	3.8 (0.1 – 17.3)	4.0 (0.5 – 17.3)	5.1 (0.8 – 23.8)
# prior LoT *	3 (2 – 4)	3 (2 – 4)	3 (2 – 4)	3 (1 – 8)	3 (1 – 7)	5 (2 – 14)
Prior PI, n (%)	110 (100%)	38 (100%)	153 (100%)	177 (100%)	131 (100%)	148 (100%)
Refractory to last LoT, n (%)	73 (66%)	27 (71%)	151 (99%)	130 (73%)	91 (69%)	135 (91%)

* ICARIA median (IQR), SIRIUS+GEN501 median (range)

Table 1. Baseline demographics in Arcturis' ECAs compared to trial data.

Conclusions

- **Construction of high-quality ECAs for RRMM is possible** with comprehensive secondary care data from a representative sample, **as demonstrated using data from the Arcturis data platform.**
- These **ECAs can be used in the absence of a trial control arm** to construct OS and rwPFS and to estimate a naive treatment effect of novel treatments.
- **ECAs constructed using stringent inclusion criteria can provide a better comparator to an intervention arm** when compared to indirect comparisons such as a matched adjusted indirect comparison (MAIC) analyses.
- **Subsequent comparative inference** to account for residual covariate imbalance **could be performed if IPD from the focal trial is also available**.

Acknowledgements

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References

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