A parametric method for unanchored matching-adjusted indirect treatment comparison (MAIC) based on survival outcomes for health economic (HE) models in absence of proportional hazards (PH)

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Context

The hazard ratios (HR) obtained from MAICs are often applied in HE models to derive the MAIC-adjusted comparator curves. However, when the PH assumption is violated, using HRs for extrapolation is inappropriate. This study proposes a novel approach using unanchored MAIC outputs in HE models when PH is violated.

Objective

To explore a novel method for constructing comparator curves for HE models using unanchored MAIC results when non-PH presents. This novel method uses principles similar to those used in parametric network meta-analyses.

Conclusion

This novel approach is a promising method for extrapolating comparator curves using unanchored MAIC outputs when non-PH presents. Like the HR approach, by assuming shared effect modification assumption, it allows for the comparison of intervention and comparator consistently on the intervention population in HE models.

Background

- In the absence of head-to-head comparisons, unanchored MAICs are frequently conducted to estimate the relative treatment effect after correcting for population differences between trials.
- HRs obtained from the MAIC are often applied in HE models to derive the MAIC-adjusted treatment comparator curves.
- When the PH assumption is violated, however, using HRs for extrapolation is inappropriate.

Materials and Methods

DATA SOURCES

- Individual patient-level data (IPD) were obtained from the MagnetisMM-3 trial (NCT04649359).[1]
- The trial investigated the efficacy and safety of elranatamab among patients with multiple myeloma (MM) who were relapsed or refractory to at least one proteasome inhibitor, one immunomodulatory drug, and one anti-CD38 monoclonal antibody (i.e., triple exposed/refractory MM).
- The current study focused on cohort A of the trial, comprising patients who had not previously received a B-cell maturation antigen-directed therapy (n=123), at the clinical data-cut off (March 2023).[1]
- Aggregate data were obtained from LocoMMotion (NCT04035226, n=248),[2] a prospective, real-world study representing physicians' choice of treatment (PCT) for patients with triple-exposed MM.
- Progression-free survival (PFS) was used as the endpoint for the illustrative purpose.

STATISTICAL METHODS

Unanchored MAIC

- An unanchored MAIC was conducted to compare the relative treatment effect of elranatamab based on IPD from MagnetisMM-3 and PCT from aggregated LocoMMotion data.[3]
- The following key prognostic variables and effect modifiers were adjusted:
  - age,
  - median time since diagnosis,
  - International Staging System disease stage,
  - extramedullary disease,
  - number of prior lines of therapy,
  - Eastern Cooperative Oncology Group performance status,
  - creatinine clearance,
  - and penta-refractory status.
- These were selected based on statistical testing, previous literature reviews, and clinical opinions.
- After performing the MAIC, the summary statistics of the selected key prognostic variables and effect modifiers were comparable between the two studies.
- Weights were obtained subsequently and applied to the patient population of MagnetisMM-3.[3]

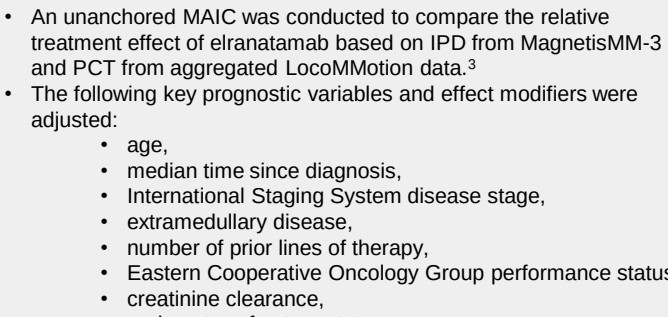
Testing PHs

- The PH assumption was tested based on the MAIC-weighted elranatamab data and LocoMMotion data.
- The Schoenfeld test was conducted, which was supplemented by the log-cumulative hazard plot.[4]

Novel approach and application to the HE models

- We estimated the treatment effect on both shape and scale parameters compared with the traditional HR approach where treatment effect is captured by the scale parameter only.
- These estimated treatment effect parameters were then subtracted from the distribution parameters of the unweighted elranatamab curve to derive the MAIC-adjusted parameters for LocoMMotion (Figure 1).
- This approach was tested on all parametric distributions, except for exponential distribution as it assumes constant hazard.

Figure 1: Novel Approach and Application



Abbreviations: MAIC, matching-adjusted indirect comparison

Results

- The baseline characteristics of elranatamab and LocoMMotion for the selected prognostic variables and effect modifiers adjusted in the MAIC are shown in Table 1.
- After the MAIC adjustment, the summary statistics of the selected prognostic variables and effect modifiers were comparable between the two studies.

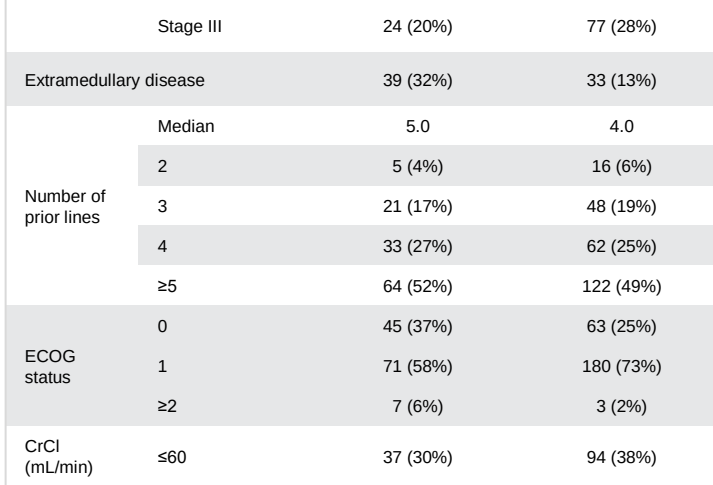
Table 1. Baseline Characteristics

Characteristics		MagnetisMM-3 (cohort A; n = 123)	LocoMMotion (n = 248)
Age	Median	68	68
Time since initial diagnosis (median, years)		6.1	6.3
ISS disease stage	Stage I	35 (28%)	70 (28%)
	Stage II	47 (38%)	70 (28%)
	Stage III	24 (20%)	77 (28%)
Extramedullary disease		39 (32%)	33 (13%)
Number of prior lines	Median	5.0	4.0
	2	5 (4%)	16 (6%)
	3	21 (17%)	48 (19%)
	4	33 (27%)	62 (25%)
	≥5	64 (52%)	122 (49%)
ECOG status	0	45 (37%)	63 (25%)
	1	71 (58%)	180 (73%)
	≥2	7 (6%)	3 (2%)
CrCl (mL/min)	≤60	37 (30%)	94 (38%)
Penta-drug refractory		52 (42%)	44 (18%)

Abbreviations: CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System

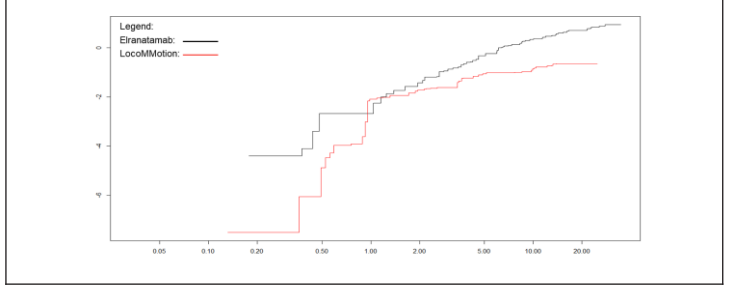
- The impact of the MAIC adjustment for PFS of elranatamab versus LocoMMotion are shown in Figure 2.
- After the adjustment for the selected variables shown in Table 1, the MAIC weighted PFS of elranatamab became longer.
- The Schoenfeld test showed that the PH assumption was violated (p = 0.00).
- Figure 3 shows the log-cumulative hazard plot, which confirms the violation of the PH assumption.

Figure 2. Kaplan-Meier Curve of PFS: elranatamab vs LocoMMotion



Abbreviations: PCT, physician's choice of treatment; PFS, progression-free survival

Figure 3. Log-cumulative Hazard Plot



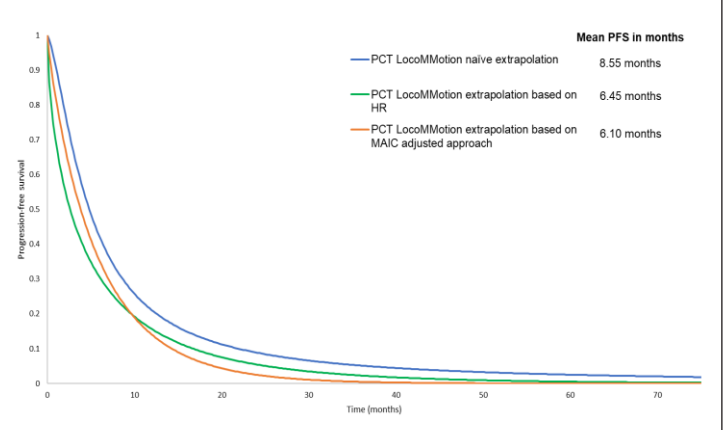
- Following the method steps shown in Figure 1, we first obtained the shape and scale parameters of elranatamab based on the unweighted data (Table 2).
- Then the treatment effect on shape and scale of elranatamab compared with LocoMMotion were estimated based on the MAIC weighted data (Table 2).
- The parameters for the MAIC-adjusted LocoMMotion arm were derived by subtracting the weighted treatment effect on both shape and scale from the unweighted shape and scale from elranatamab (Table 2).
- These parameters were further used to derive the LocoMMotion MAIC adjusted curve in HE models.
- The comparison of the LocoMMotion curves derived based on different approaches is shown in Figure 4.

Table 2. MAIC-adjusted Curve Parameters

	Unweighted shape and scale parameters of intervention	Weighted treatment effect on shape and scale based on MAIC	Derived shape and scale parameters for adjusted LocoMMotion arm
Shape	**-0.43**	**-0.34**	**-0.09**
Scale	**3.31**	**1.56**	**1.74**

Abbreviations: MAIC, matching-adjusted indirect comparison

Figure 4. Extrapolations of LocoMMotion PFS curves



Abbreviations: HR, hazard ratio, MAIC, matching-adjusted indirect comparison, PCT, physician's choice of treatment, PFS, progression-free survival

Discussion

- This novel approach is a promising method for extrapolating comparator curves using unanchored MAIC outputs when non-PH presents.
- By assuming the shared effect modification assumption,[3] it allows the comparison of the intervention and comparator to occur on the intervention population in HE models.
- Additionally, with the application of this method, there is no need to constrain the selection of the parametric extrapolation for the comparator arm to be the same as the selection of the parametric extrapolation of the intervention arm (which is the case for the traditional HR approach).
- However, there are some limitations. For one, the exponential distribution cannot be used with this method as it assumes proportionality. More importantly, shared effect modification must be assumed. Yet, this assumption also needs to be held for traditional HR approaches.

1. Lesokhin AM, Tomasson MH, Arnulf B, Bahlis NJ, Miles Prince H, Niesvizky R, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med. 2023; 2. Mateos MV, Weisel K, De Stefano V, Goldschmidt H, Delforge M, Mohty M, et al. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. Leukemia. 2022;36(5):1371-6. 3. Phillippo D, Ades T, Dias S, Palmer S, Abrams KR, Welton N. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. University of Sheffield: NICE Decision Support Unit; 2016. 82 p. 4: Grambsch, P. M., & Therneau, T. M. (1994). Proportional Hazards Tests and Diagnostics Based on Weighted Residuals. Biometrika, 81(3), 515–526. https://doi.org/10.2307/2337123

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