ISPOR acceptance code: MSR79
Abstract ID: 131655

Matching plus regression adjustment for the estimation of the average treatment effect on survival outcomes: A case study with mosunetuzumab in relapsed/refractory follicular lymphoma

Di Maio D,[a] Mitchell SA,[b] Batson S,[b] Keeney E,[c] Thom HHZ[d]

[a]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [b]Mtech Access, Bicester, Oxfordshire, UK; [c]Clifton Insight, Bristol, UK; [d]University of Bristol, UK

Introduction

- Follicular lymphoma (FL) is a low-grade, non-Hodgkin lymphoma, characterised by a chronic relapsing disease course with long overall survival (OS); relapses frequently occur following initial therapy, with progressively shorter durations of response
- There is currently no standard of care for relapsed refractory (RR) FL, but treatment most commonly includes rituximab/chemotherapy combination (R-chemo), particularly for later lines of therapy. Mosunetuzumab, a novel CD20/CD3 bispecific antibody, has recently been approved for third-line treatment and beyond (3L+), based on a single-arm Phase 1/2 study (1)
- The average treatment effect (ATE) represents the true causal effect of a treatment (2-4) and is also the estimand preferred by health technology assessment (HTA) bodies, such as the National Institute for Health and Care Excellence (NICE), for economic evaluations (5)
- Methods employing two different regression models – often referred to as 'doubly robust' – are increasingly common (6,7). However, supporting literature on their use for the estimation of the ATE is scarce, particularly for continuous survival outcomes (8)
- With non-randomised observational evidence increasingly being used in HTA, particularly in rare disease and oncology indications (2,4,5), there is a need to investigate robust new statistical approaches for estimating the ATE and minimise selection bias with survival outcomes

Objectives

- To investigate the adaptation of a doubly robust method, previously published by Austin et al (9), combining propensity score matching with regression adjustment, for the estimation of the ATE for survival outcomes
- To test the robustness of this method for modelling decisions and assumptions and to illustrate its implementation in a real-world HTA context, using the comparison of mosunetuzumab versus bendamustine + rituximab, as a proxy for R-chemo, in the 3L+ RR FL setting

Methodology

Data sources

- Individual patient data (IPD) were sourced from 3L+ FL RR cohorts from NCT02500407 for mosunetuzumab (n=90) (1) and a combination of two studies (NCT02187861 and NCT02257567) for bendamustine + rituximab (proxy for R-chemo; n=48) (10,11)
- Homogeneity across study populations was increased through application of common eligibility criteria; patients with Eastern Cooperative Oncology Group (ECOG) performance status ≥2 and patients who received >5 prior anti-cancer regimens were excluded from the R-chemo and mosunetuzumab cohorts, respectively

Outcomes

- Endpoints included OS and progression-free survival (PFS)

Statistical approach

- **Propensity score estimation:** Pre-specified prognostic factors and effect modifiers considered for inclusion in the propensity score (PS) model, ranked by level of priority, were informed by clinical expert opinion; the inclusion of clinically relevant 2-way interactions was considered
- **Propensity score matching:** Five PS matching methods were explored (1. nearest neighbour matching without replacement; 2. nearest neighbour matching with replacement; 3. optimal pair matching; 4. genetic matching; 5. full matching), and the method yielding the optimal covariance balance based on absolute standardised mean differences (threshold of 0.1) (12,13) (optimal pair matching) was selected as the preferred method
- **Regression adjustment:** Regression adjustment on the matched patient sample was used to estimate the counterfactual outcomes required to recover the ATE or local ATE (depending on matching method selected)
- Both missing potential outcomes under control for treated subjects and missing potential outcomes under treatment for controls were imputed
- An accelerated failure time parametric survival model (Weibull) was used to regress event times on baseline characteristics in each patient group (model specification was allowed to vary to increase flexibility). Comparison of Akaike information criteria (AIC) for all combinations of available factors (without interactions) informed covariate selection for the final regression model
- Event times longer than the maximum follow-up were censored (to account for potentially informative events in one arm related to imperfect matching, while avoiding predictions to fall excessively beyond the range of observed data)
- Imputed and observed outcomes for OS/PFS were combined and compared between treatments using standard survival analysis methods. The entire procedure was bootstrapped 2,000 times (to ensure >1,000 resamples)

Sensitivity analyses

- Analyses explored the robustness of the approach to the use of different assumptions for the event times distribution (log-normal, log-logistic and exponential) and model specifications (second, third and fourth lowest AIC)

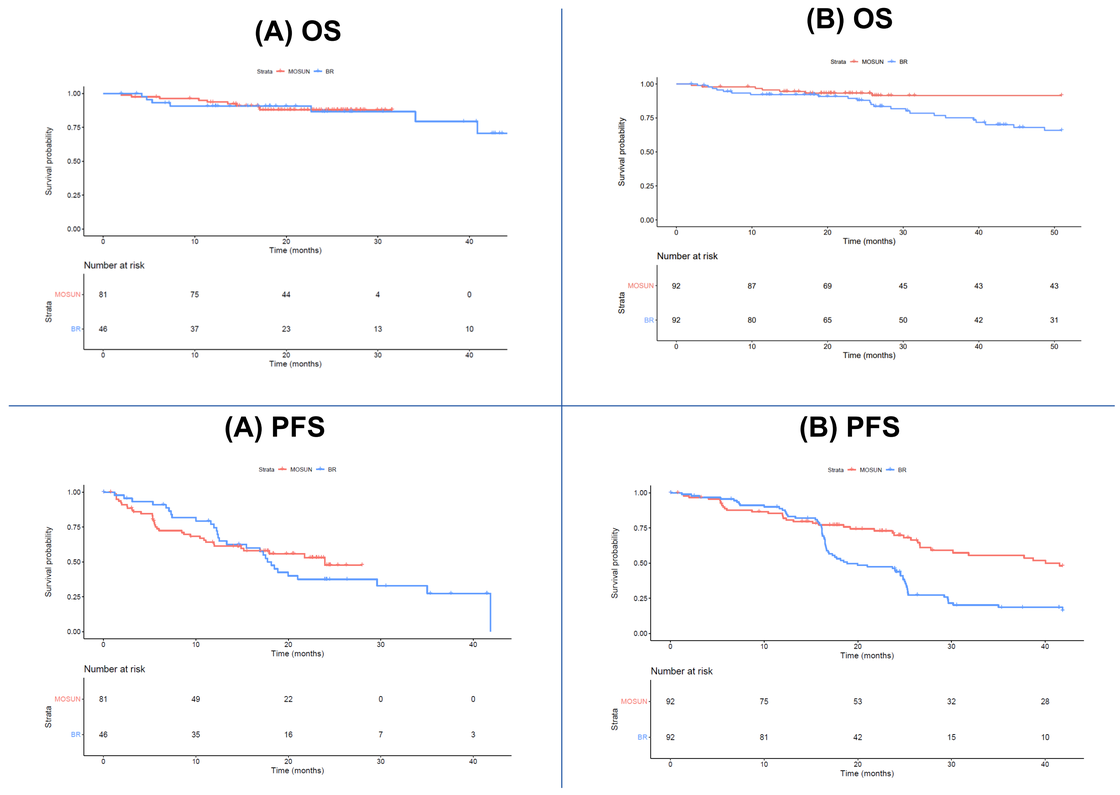
Results

In this case study comparing mosunetuzumab and bendamustine + rituximab for the treatment of 3L+ RR FL, the proposed matching plus regression adjustment approach yielded results that were relatively robust to variation in assumptions and statistical models

OS

- Hazard ratios (HRs) for OS numerically favoured mosunetuzumab versus R-chemo (HR <1) in all analyses, including the reference case (Weibull model and lowest AIC) and sensitivity scenarios (**Table 1**). Results showed a greater separation between the survival curves (**Figure 1**) and a hint of a potential numerical survival benefit with mosunetuzumab. However, confidence intervals (CIs) were wide due to the small number of events

Figure 1: KM plots of OS and PFS for (A) unadjusted and (B) matching plus regression adjustment samples



Abbreviations: BR, bendamustine + rituximab; KM, Kaplan–Meier; MOSUN, mosunetuzumab; OS, overall survival; PFS, progression-free survival.

PFS

- HRs for PFS were <1 in all analyses, showing a larger numerical benefit in PFS for mosunetuzumab compared with R-chemo (**Table 1; Figure 1**). These observed strong trends were consistent, with some variability, across all sensitivity analyses performed, with none of the HR CIs including 1

Table 1: Matching plus regression adjustment results for mosunetuzumab versus R-chemo (bendamustine + rituximab)

Method for estimating HRs	HR (95% CI)	
	OS	PFS
Unadjusted	0.94 (0.31, 2.81)	0.90 (0.54, 1.50)
Base case (regression adjustment using lowest AIC and assuming Weibull distribution of event times)	0.30 (0.04, 4.93)	0.43 (0.04, 0.70)
Regression adjustment (using second lowest AIC model† and assuming Weibull distribution of event times)	0.41 (0.06, 6.34)	0.44 (0.04, 0.73)
Regression adjustment (using third lowest AIC model† and assuming Weibull distribution of event times)	0.30 (0.06, 5.44)	0.62 (0.09, 0.73)
Regression adjustment (using fourth lowest AIC model† and assuming Weibull distribution of event times)	0.27 (0.06, 5.86)	0.42 (0.04, 0.71)
Regression adjustment (regression adjustment using lowest AIC, assuming log-normal distribution of event times)	0.27 (0.05, 2.11)	0.28 (0.01, 0.60)
Regression adjustment (regression adjustment using lowest AIC, assuming log-logistic distribution of event times)	0.29 (0.05, 2.64)	0.25 (0.01, 0.60)
Regression adjustment (regression adjustment using lowest AIC, assuming exponential distribution of event times)	0.50 (0.07, 1.69)	0.47 (0.06, 0.59)

†Without convergence issues.
Abbreviations: AIC, Akaike information criteria; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Conclusion

- Adaptation of the method from Austin et al (9) may represent a suitable indirect comparison approach for the estimation of the (local) ATE for survival outcomes in HTA applications
- This may be particularly beneficial when individual 'doubly' adjusted survival estimates are needed for subsequent modelling, such as the extrapolation of survival curves via parametric methods in cost-effectiveness analyses

ISPOR Europe 2023,
12–15 November 2023,
Copenhagen, Denmark

Abbreviations:

3L+: third line and beyond
AIC: Akaike information criteria
ATE: average treatment effect
BR: bendamustine + rituximab
CI: confidence interval
ECOG: Eastern Cooperative Oncology Group
FL: follicular lymphoma
HR: hazard ratio
HTA: health technology assessment
IPD: individual patient data
KM: Kaplan–Meier
MOSUN: mosunetuzumab
NICE: National Institute for Health and Care Excellence
OS: overall survival
PFS: progression-free survival
PS: propensity score
R-chemo: rituximab/chemotherapy combination
RR: relapsed refractory

References:

1. Budde LE, et al. Lancet Oncol. 2022;23(8):1055-65.
2. Xu J, et al. BMC Med Res Methodol. 2022;22(1):337.
3. Cheng D, et al. Biometrics. 2020;76(3):767-77.
4. Gong Q, et al. Biometrics. 2017;73(1):134-44.
5. National Institute of Health and Care Excellence. NICE DSU Technical Support Document 17. 2015. Available from: https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD17-DSU-Observational-data-FINAL.pdf
6. Funk MJ, et al. Am J Epidemiol. 2011;173(7):761-7.
7. Kreif N, et al. Health Serv Outcomes Res Method. 2013;13:174-202.
8. Denz et al. Stat Med. 2023;42:1461–1479
9. Austin PC, et al. Stat Methods Med Res. 2020;29(3):728-51.
10. Zinzani PL, et al. Blood. 2020;136(23):2628-37.
11. Sehn LH, et al. J Clin Oncol. 2020;38(2):155-65.
12. Franklin JM, et al. Stat Med. 2014;33(10):1685-99.
13. Stuart EA, et al. J Clin Epidemiol. 2013;66(8 Suppl):S84-S90 e1.