

# Novel Method for Indirect Comparison of Treatment Sequences Using Averaged Parametric Survival Models with Application to Hepatocellular Carcinoma

Aceituno D<sup>1,2</sup>, Grossman J<sup>3</sup>, Paracha N<sup>4</sup>, Ozgurdal K<sup>5</sup>, Thom H<sup>1,6</sup>

1. Clifton Insight, Bristol, United Kingdom; 2. Pontificia Universidad Católica de Chile, Santiago, Chile; 3. Bayer HealthCare Pharmaceuticals, Whippany, NJ; 4. Bayer Pharmaceuticals, Basel, Switzerland; 5. Bayer Consumer Care, Basel, Basel, Switzerland; 6. University of Bristol, Bristol, United Kingdom

## BACKGROUND

- There is scarce methodological guidance to conduct indirect treatment comparisons (ITCs) of treatment sequences.
- Previous reviews in oncology have highlighted that ITC of sequential therapies usually evaluate each line of therapy independently.<sup>1,2</sup>
- In hepatocellular carcinoma (HCC), atezolizumab plus bevacizumab (*atezobev*) is now recommended as first-line treatment by current clinical guidelines.<sup>3</sup>
- Regorafenib was compared against best supportive care (BSC) on patients who progressed on sorafenib in the RESORCE trial and is only licensed for those who progress on sorafenib.<sup>4</sup>
- There are no licensed second-line therapies for progression on *atezobev*, leaving a decision between the sequence sorafenib followed by regorafenib (*sorego*) and single-line *atezobev*.

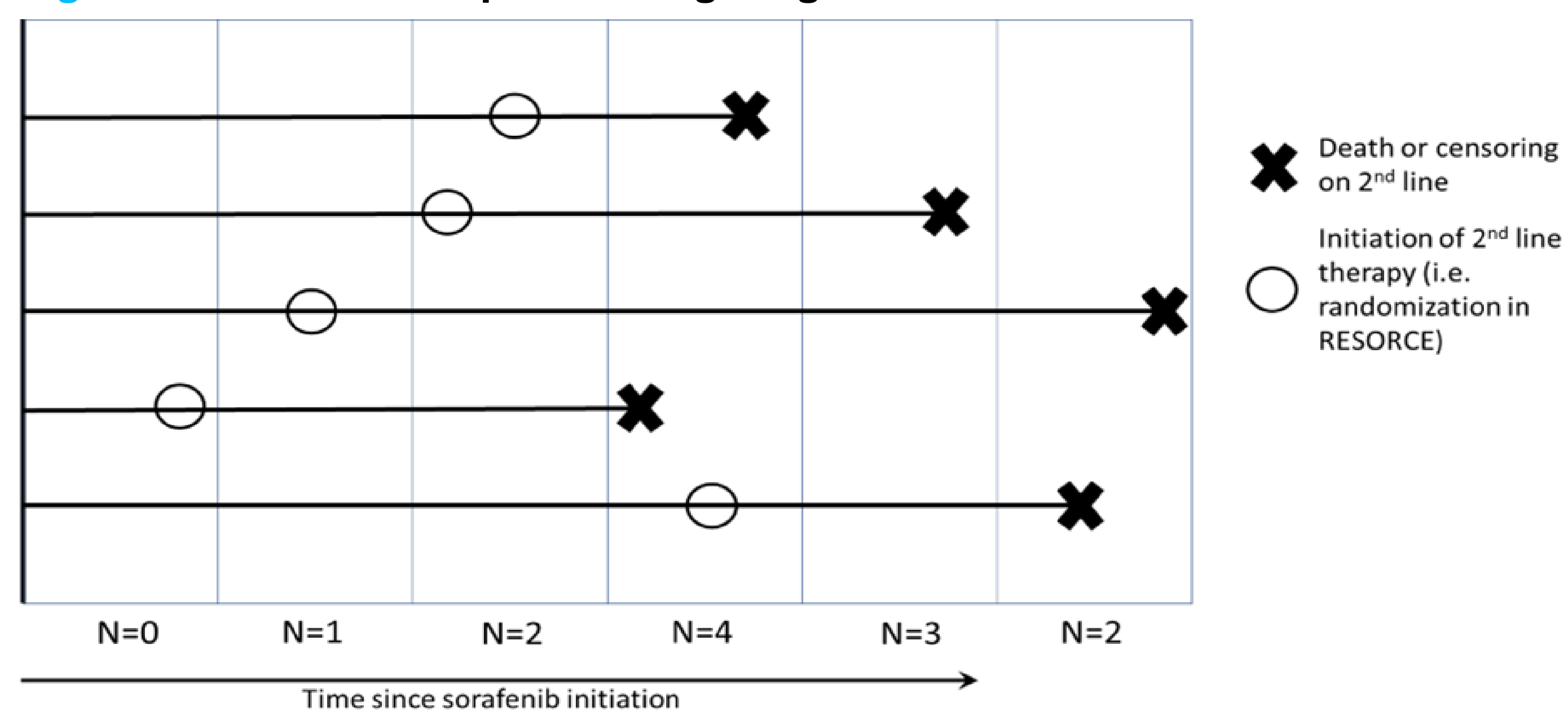
## OBJECTIVES

- Our aim was to develop a novel approach to ITC of overall survival (OS) on the sequence *sorego* against single-line *atezobev* in HCC, by averaging survival curves across lines of therapy.

## METHODS

- We first conducted an ITC of first-line treatments for HCC using fractional polynomial network meta-analysis, using RESORCE IPD and reconstructed IPD from digitized KM curves for comparators<sup>5,6</sup>, using a previously validated algorithm.<sup>7</sup>
- Then, we fit parametric models to second-line treatments in the RESORCE trial. RESORCE reported the time from initiation of first line sorafenib to randomisation, which we used to estimate time to initiate second line therapy.
- We then combined curves at first and second-line treatments using a weighted average of the first line and RESORCE curves, with weights defined as the inverse square root of number of patients on each line of therapy.
- As shown in Figure 1, the greater the sample size, the greater the weight of the second line curve. Weights of first-line fractional polynomials are total numbers of patients across first-line trials, which is done on the log hazard scale.

Figure 1. Treatment sequence weighting.



## RESULTS

- A lognormal model to fit RESORCE OS was selected using Akaike's information criteria (AIC) and clinical plausibility of extrapolations.
- The averaged curves showed that the *sorego* sequence had a marginally better OS (Figure 2).
- The time-varying hazard ratios (HRs) showed a benefit of *sorego* against *atezobev* over time, with a HR (95% credible interval [CrI]) of 0.98 (0.82-1.12) at 12 months, to 0.95 (0.84-1.09) at 24 months, and 0.87 (0.80-0.96) at 36 months.
- The results were sensitive to the selection of parametric model for RESORCE OS, as shown in Table 1, where the results shift in favour of *atezobev* if a Gamma distribution is fit.

## REFERENCES

- Huang, M. et al. Conceptual Framework and Methodological Challenges for Modeling Effectiveness in Oncology Treatment Sequence Models. *Pharmacoeconomics* 40, 257–268 (2022).
- Lewis, R. A., Hughes, D., Sutton, A. J. & Wilkinson, C. Quantitative Evidence Synthesis Methods for the Assessment of the Effectiveness of Treatment Sequences for Clinical and Economic Decision Making: A Review and Taxonomy of Simplifying Assumptions. *Pharmacoeconomics* 39, 25–61 (2021).
- Reig, M. et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J. Hepatol.* 76, 681–693 (2022)
- Bruix, J. et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 389, 56–66 (2017)
- Cheng, A.-L. et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J. Hepatol.* 76, 862–873 (2022)
- Kudo, M. et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 391, 1163–1173 (2018).
- Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol.* 2012; 12:9.

Figure 2. Kaplan-Meier curve comparing OS of different treatment sequences.

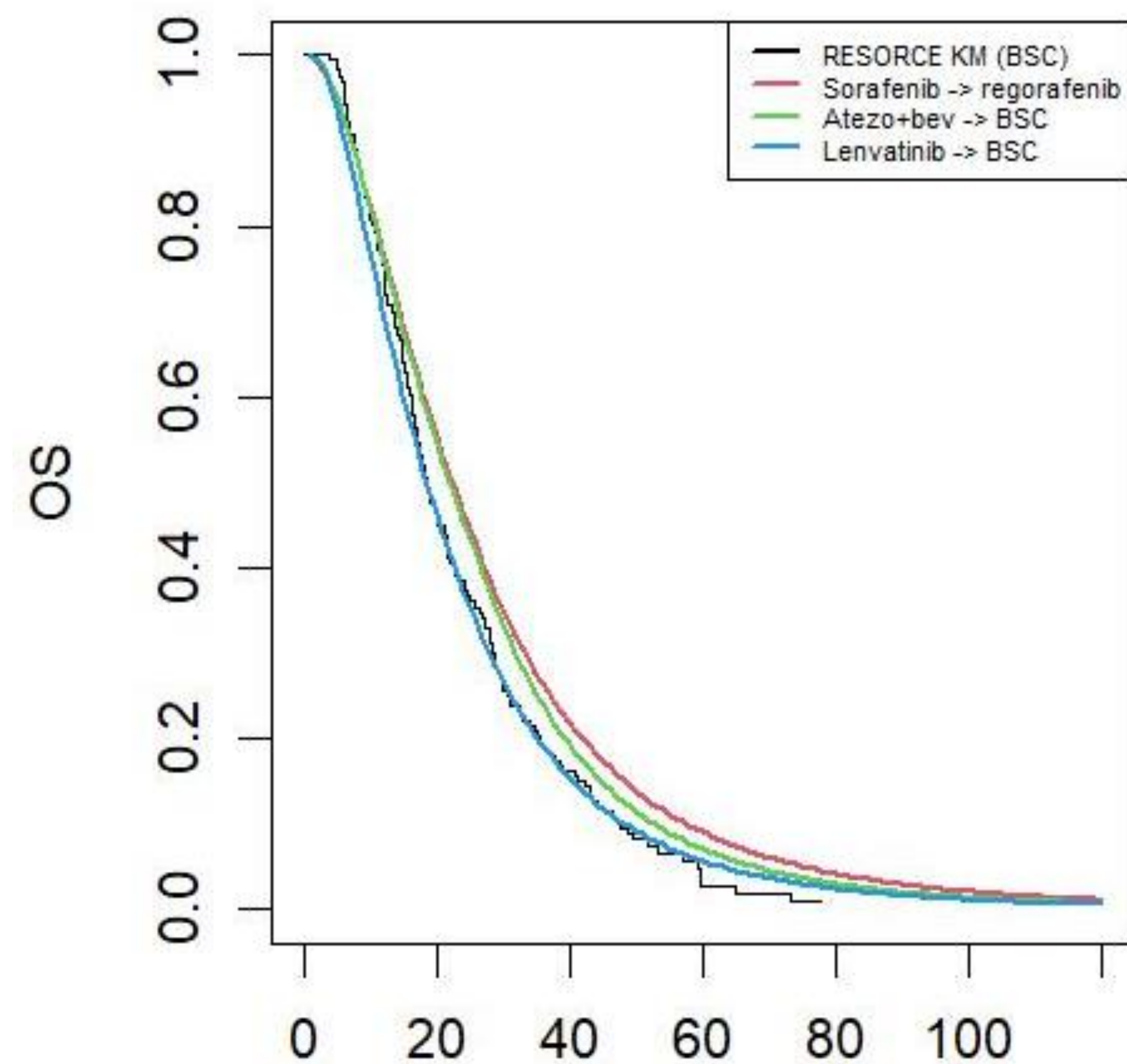


Table 1. Time-varying HRs by different second-line parametric models

Distribution	AIC	6 months HR (95% CrI)	12 months HR (95% CrI)	24 months HR (95% CrI)	36 months HR (95% CrI)	48 months HR (95% CrI)
Exponential	4407.64	1.18 (0.95, 1.35)	0.99 (0.85, 1.16)	0.89 (0.75, 1.05)	0.82 (0.68, 0.95)	0.81 (0.68, 0.95)
Weibull	4283.32	1.04 (0.85, 1.21)	1.08 (0.95, 1.22)	1.27 (1.10, 1.59)	1.39 (1.13, 1.76)	1.55 (1.18, 2.11)
Gamma	4251.48	1.66 (1.27, 1.93)	1.44 (1.20, 1.62)	1.29 (1.13, 1.48)	1.13 (1.07, 1.18)	1.10 (1.05, 1.13)
Log-logistic	4232.36	1.02 (0.83, 1.18)	1.19 (1.03, 1.33)	1.33 (1.15, 1.61)	1.26 (1.11, 1.43)	1.25 (1.10, 1.40)
Lognormal	4219.68	0.99 (0.78, 1.20)	0.98 (0.82, 1.12)	0.95 (0.84, 1.09)	0.87 (0.80, 0.96)	0.88 (0.82, 0.97)

Hazard ratio (HR) < 1 favours the sequence *sorego* against *atezobev*  
CrI: credible interval

## LIMITATIONS

- Approach cannot evaluate progression free survival (PFS) as progression at first-line is not comparable to progression at second-line.
- No adjustments were made for imbalance in potential effect modifiers between first-line studies or between first-line studies and RESORCE.
- Performance of method is unknown in other settings

## CONCLUSIONS

- We proposed a novel parametric ITC methodology to estimate overall efficacy of sequences of treatments, rather assuming independent effects.
- In this application, the *sorego* sequence showed a marginally OS benefit over *atezobev*, although the results were subject to structural uncertainty.
- Further applications are needed to test this method in other treatment sequences.

