Poster #: MSR134

Optimizing Fractional Polynomials by Using Variable Powers

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Background & Objective

- Fractional polynomials (FP) are traditionally calculated using a fixed set of numbers that covers the desired range, P = (-2;-1;-0.5; 0; 0.5; 1; 2; 3) due to computational power limits.
- This analysis investigated whether making the powers into variables had benefits in both terms of fit and computational speed that outweighed the penalty for these additional variables in a Bayesian setting.

Methods

- The standard code for FPs in a Bayesian network meta-analysis (NMA) setting has been extended to program powers as variables instead of parameters in RStan.
- A network of four trials in previously treated metastatic non-small cell lung cancer was used with programmed death-ligand 1 >1% comparing nivolumab, pembrolizumab, and atezolizumab (twice) individually with docetaxel.[1-4] The models were compared based on visual and statistical fit (using leave one out information criterion [LOOIC]) and the execution time.

Key Results

- The results of all 48 models were first reviewed by visual and statistical fit. The second-order FPs performed best, both with fixed- and variable-power FPs. There were minimal differences in visual and statistical fit between the best fixed- and variable-power FPs.
- Although the mean survival was slightly higher in the fixed-power FP, there was little difference in the incremental survival. The confidence interval was smaller in the variable-power FP.
- Total computational time for fixed powers and variable powers was 19.3 hours and 2.0 hours, respectively, with a reduction of 89.7%.

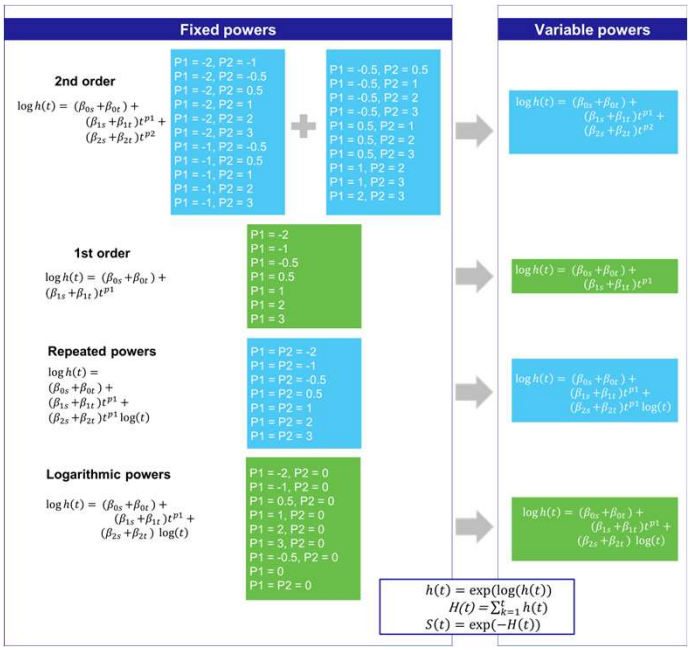
Conclusion

- The use of variable powers in FPs led to at least a similar-fitting model, while simultaneously yielding a huge reduction in computational time.

Methods

- There were eight elements in the set P = (-2;-1;-0.5; 0; 0.5; 1; 2; 3). Using the NMA definition by Jansen (2011),[5] the log hazard can be defined for a first-order, second-order and repeated-power FP (see Figure 1):
- There were 44 FPs possible using set P; eight first-order, 28 second-order and eight repeated-power FPs possible using set P, using log(t) when p = 0. An overview of the models is shown in Figure 1.
- When assuming p1 and p2 as variables, this was reduced to four FPs—a first-order, second-order, repeated-power, and logarithmic FP, where the latter was normally used for p = 0. There was a constraint where $p1 \leq p2$ to avoid that $p1$ and $p2$ can swap positions when optimizing (e.g., $p1$ = -3 and $p2$ = 2 vs. $p1$ = 2 and $p2$ = -3).

Figure 1. Overview of FP models for fixed and variable powers



Results

- The best-performing models in terms of LOOIC and visual fit were a fixed and variable second-order FP. The fixed FP had p1 = -0.5, p2 = 0.5, while the variable FP determined p1 = -0.60, p2 = 0.22.
- Although the mean survival was a bit higher for the fixed-power FP for all treatments, the incremental survival was comparable between the fixed and variable FPs (Table 1). The smaller confidence interval found in the variable FP was counterintuitive given the extra parameters in this model. This could mean that the fixed-power FP using set P was too restrictive and that a variable-power FP can lead to a better-fitting model with less uncertainty; it could also be due to the lower mean survival which gives less room for uncertainty. Extrapolation is shown in Figure 2.

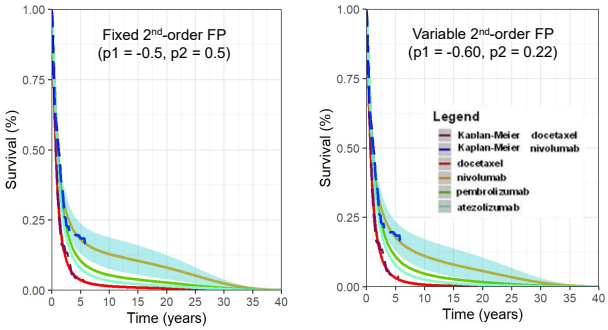
Results (cont.)

Table 1. Mean and incremental survival for best-fitting fixed and variable FPs

	Fixed power (2nd order)		Variable power (2nd order)	
	Mean survival (95% CI)	Incremental survival (95% CI)	Mean survival (95% CI)	Incremental survival (95% CI)
Docetaxel	1.31 (0.93, 2.04)	0.00 (0.00, 0.00)	1.18 (0.91, 1.71)	0.00 (0.00, 0.00)
Nivolumab	4.16 (2.81, 5.61)	2.81 (1.33, 4.37)	3.67 (2.44, 5.20)	2.46 (1.16, 4.05)
Pembrolizumab	2.54 (1.37, 4.55)	1.20 (0.23, 2.88)	2.36 (1.43, 4.13)	1.16 (0.38, 2.65)
Atezolizumab	2.00 (1.09, 4.32)	0.67 (-0.24, 2.71)	1.85 (1.16, 3.68)	0.65 (0.03, 2.26)

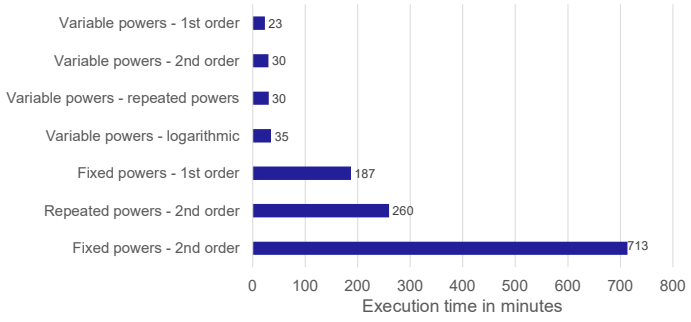
Abbreviation: CI, confidence interval

Figure 2. Extrapolation of best-fitting models for fixed and variable FPs



- The total execution time per model type was 2.0 hours for variable FPs vs. 19.3 hours for fixed FPs with sequential execution, a reduction of 89.7%. The best-fitting models (second order) showed a huge difference between fixed and variable FPs (Figure 3).

Figure 3. Total execution time per model type (in minutes)



References

1. Borghaei H, et al., Five-Year Outcomes From the Randomized, Phase III Trials CheckMate 017 and 057: Nivolumab Versus Docetaxel in Previously Treated Non–Small-Cell Lung Cancer. Journal of Clinical Oncology, 2021. 39(7): p. 723-733; 2. Herbst RS, et al., Long-Term Outcomes and Retreatment Among Patients With Previously Treated, Programmed Death-Ligand 1–Positive, Advanced Non–Small-Cell Lung Cancer in the KEYNOTE-010 Study. J Clin Oncol, 2020. 38(14): p. 1580-1590; 3. Fehrenbacher L, et al., *Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial.* The Lancet, 2016. **387**(10030): p. 1837-1846; 4. Fehrenbacher L, et al., Updated Efficacy Analysis Including Secondary Population Results for OAK: A Randomized Phase III Study of Atezolizumab versus Docetaxel in Patients with Previously Treated Advanced Non-Small Cell Lung Cancer. J Thorac Oncol, 2018. 13(8): p. 1156-1170. 5. Jansen JP. Network meta-analysis of survival data with fractional polynomials. *BMC medical research methodology* 11.1 (2011): 1-14.

Disclosures

This study was investigator-initiated and received no funding.