Network meta-analysis of survival data using fractional polynomials; An example with first line metastatic renal cell cancer treatments

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Background

- First line targeted cancer therapies in treatment of metastatic renal cell cancer (mRCC) enabled an increment in progression-free survival (PFS) from 2 to 6 months

- An improvement in overall survival (OS) was not demonstrated in RCTs, or it was difficult to assess due to “cross-over” confounding

- Most of the evidence is available from registrational RCTs representing comparisons of a treatment of interest with previous therapeutic standard (interferon alpha)

Background

- Network meta-analysis (NMA) synthesizes direct and indirect evidence between ≥ 2 treatments linked by ≥ 2 RCTs

- Frequently NMA of survival data is based on simple adjustment of hazard ratio -> proprotional hazards (PH) assumption (e.g. all published NMAs in mRCC[1])

- Even survival modelling within single treatment appraisals in health economics is commonly founded on PH assumption (e.g. NICE appraisals of 32/45 of cancer drugs[2])

1 - Leung HWC et al. Molecular and clinical oncology 2 (2014): 858-864.; Mills et al. BMC Cancer 2009, 9:34
2 - Nicholas R. Latimer, Medical Decision Making, Aug 2013: 743-754.

Background

- What is wrong with PH assumption?

- Assuming constant ratio of hazards implies constant difference in effectiveness through time

- This is often implausible:
  - if evidence comes from many different RCTs (e.g. NMA)
  - if dealing with terminal disease (e.g. metastatic cancer)
  - if modelling is required far beyond the RCT's horizon (e.g. CEA)

Background

- Relaxing PH assumption can be achieved with fractional polynomials (FP) [1,2]
- Contrary to PH models (effect fixed, one dimensional - HR dependent), FP models estimate the hazard/survival through several parameters

Objective:

The aim is to apply FP in NMA of PFS and OS analysis of 1st line targeted cancer therapies for mRCC and to compare FP and PH approach in order to identify and explain the potential differences

1 - Royston P, Altman DG. Applied Statistics 1994, 43:429-467.
2 - Jansen JP. BMC Med Res Methodol. 2011;11:61..

1. Systematic literature review

RCTs' selection criteria:

a. A treatment examined in an RCT must be first line targeted therapy;
b. PFS and/or OS must be represented by reproducible Kaplan Meier curves accompanied by the numbers of patients at risk at least at two different time points;
c. The population examined in an RCT should be representative of the general mRCC population;
d. an RCT must be connected to the rest of RCTs in the NMA through at least one comparator (applied at the end of selection process);

2. Data extraction

- Number of patients at risk (R), number of patients experiencing event (D) and number of censored patients (C) at equal time intervals were needed

- At our disposal were treatment specific KM curves, followed by R per different time intervals (2, 3, 4, 5, 6 or 10 months)

- W/o informationa on C -> Assume constant rate of censoring within a time interval[1] -> improvements of existing method were needed for intervals not dividable by 2 (!)

1. Hoyle MW et Henley W. BMC Medical Research Methodology 2011, 11:139

3A. Survival analysis – FP model

- An FP function of second order can be utilised to estimate natural logarithm of *h*:

$$\ln (h(t)) = \beta_0 + \beta_1 t^{p1} + \beta_2 t^{p2}$$

- FP model with best fitting powers (DIC) from predefined set (-2,-1, -0.5, 0, 0.5, 1, 2, 3) for all RCTs is selected for further analysis of the effect (β parameter)

- Common parametric curves can be seen as special simplified cases of FP models (e.g. Exponential: $\beta_1 = \beta_2 = 0$; without p1 and p2; Weibull: $\beta1 \neq 0$; $\beta2 = 0$; p1=0; without p2;)

Methods

- Now βs can be split to represent trial specific baseline (μ) and trial specific treatment effect (δ):

$$\begin{pmatrix} \beta_{0jk} \\ \vdots \\ \beta_{Mjk} \end{pmatrix} = \begin{cases} \begin{pmatrix} \mu_{0jb} \\ \vdots \\ \mu_{Mjb} \end{pmatrix} & \text{Baseline trt} \\ \begin{pmatrix} \mu_{0jb} \\ \vdots \\ \mu_{Mjb} \end{pmatrix} + \begin{pmatrix} \delta_{0jbk} \\ \vdots \\ \delta_{Mjbk} \end{pmatrix} & \text{Active trt} \end{cases}$$

- Each treatment's effect can be estimated through δ that is result of pooled estimates of δs specific for that treatment across included trials

- To determine the powers of best fitting FP model and to estimate the treatment effects (μs and ds), we relied on developed code[1] conducted 50,000 MCMC in WinBugs and R software

1 - Jansen JP. BMC Med Res Methodol. 2011;11:61..

3B. Survival analysis – PH model

- We fitted the most common parametric functions over hazard/survival data of a referent treatment and choose the best fitting distribution

- Tested were: Weibull, exponential, lognormal, logistic and loglogistic distributions

- Active treatments' effects were estimated through simple adjustment of HR across all trials as recommended by Bucher et al[1]

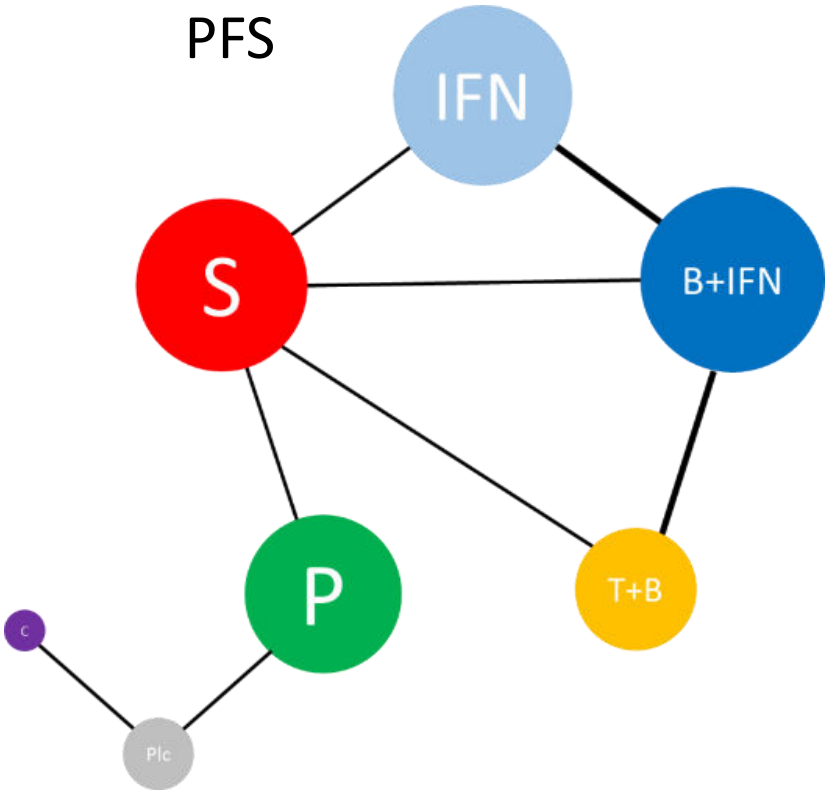
1. Bucher HC, Guyatt GH, Griffith LE et al. J Clin Epidemiol Vol. 50, No. 6, pp. 683-691, 1997.

Results – systematic literature review

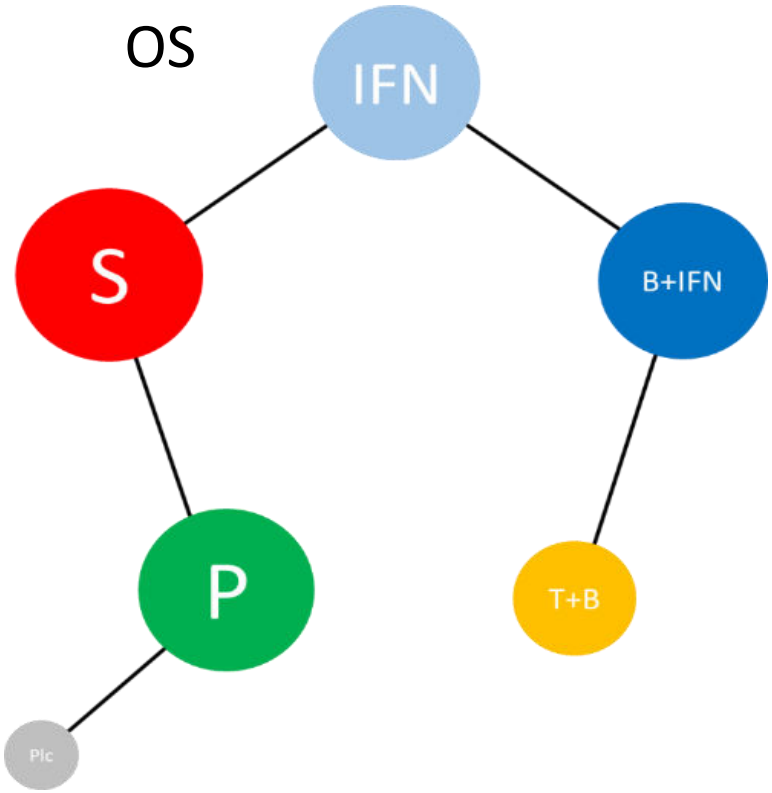
- 11 publications presenting 8 RCTs were included
- 8 publications reported PFS (4,709 pt) and 5 publications OS (3,818 pt)
- 7 compared treatments: sunitinib, pazopanib, interferon alpha (IFN), bevacizumab(beva)+IFN, temsirolimus+beva, cediranib and placebo
- 2 out of 5 OS studies allowed cross-over after progression (sunitinib vs IFN and pazoapnib vs PLC trials)

Results – systematic literature review

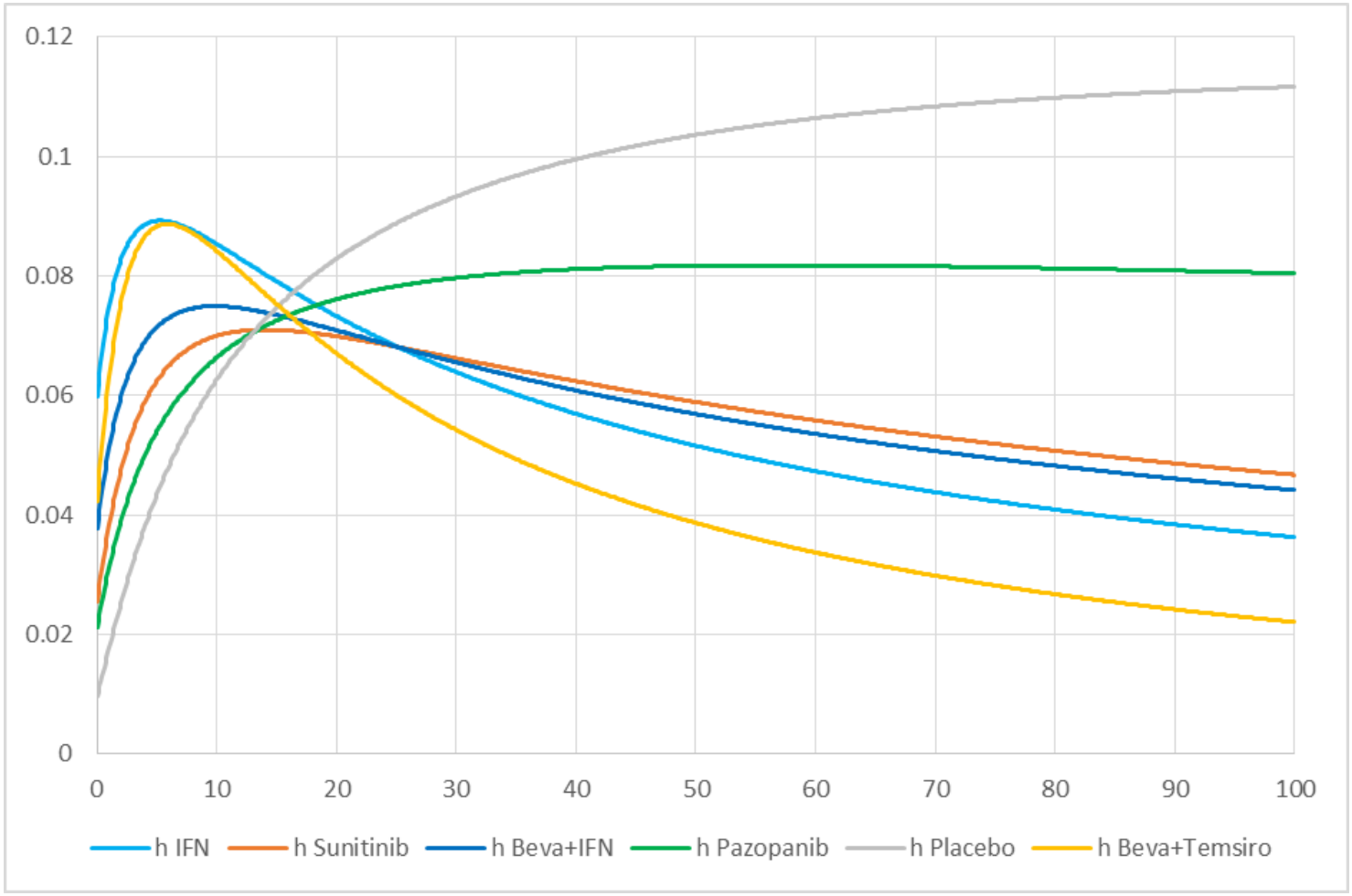
PFS



OS



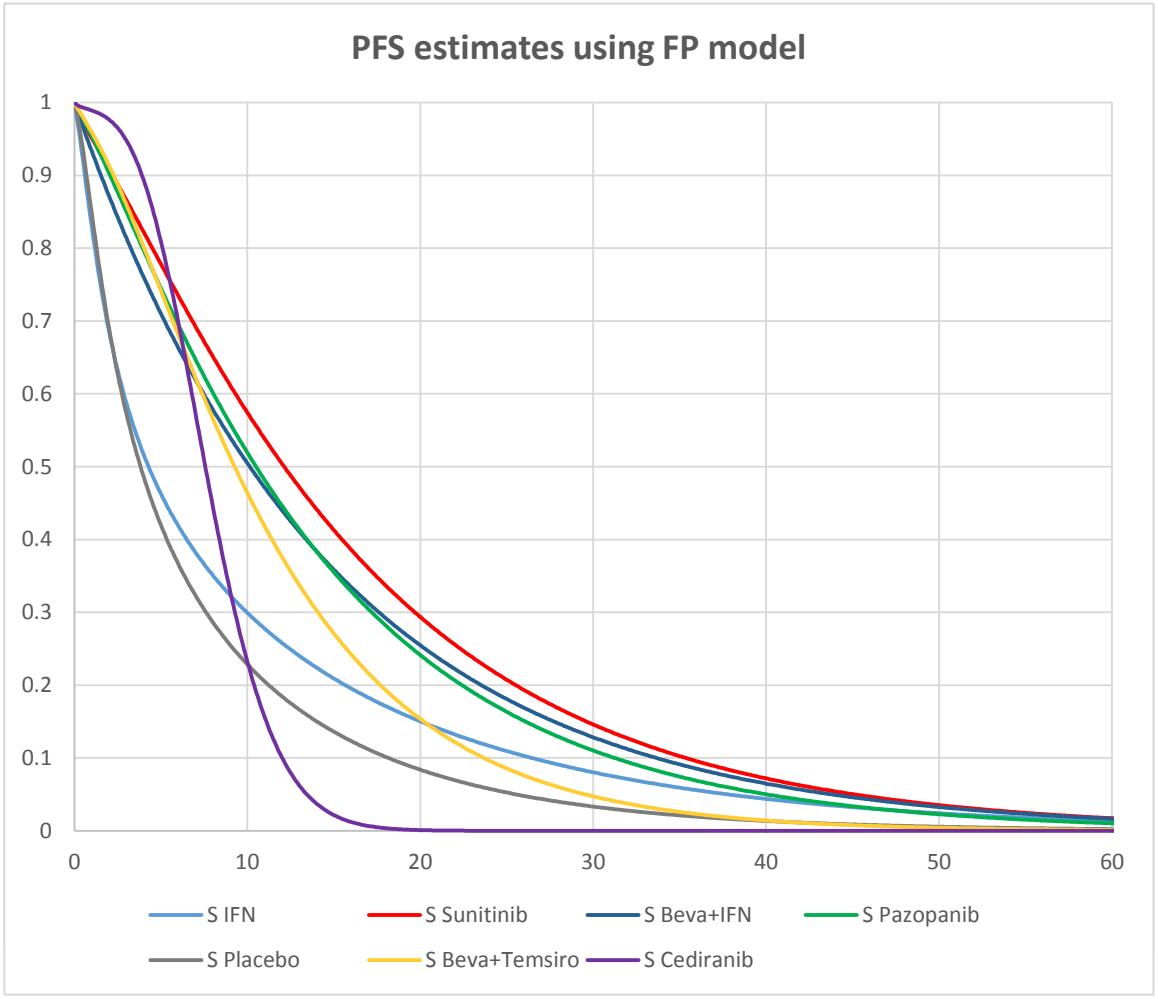
Results – hazard rates OS



Results – median survival estimatess

	Progression free survival			Overall survival		
	RCTs' estimates (mnths)	FP model (mnths)	PH model (mnths)	RCTs' estimates (mnths)	FP model (mnths)	PH model (mnths)
IFN	5.0-5.4	4.3	6	17.4-21.8	16.6	18.2
Sunitinib	8.2-11.0	12.1	12.6	26.4-29.3	21.4	22.4
Bevacizumab+IFN	8.5-16.8	10.1	7.3	18.3-25.5	19.7	21.5
Pazopanib	8.4-9.2	10.5	12.1	22.9-28.4	22	24.5
Placebo	2.8-4.2	3.8	5	20.5	20.7	22.4
Temsirolimus+Beva	8.2-9.1	9.3	6.6	25.8	17.4	21.5
Cediranib	12.1	7.6	11.6			

Results – PFS estimates (PH vs FP model)



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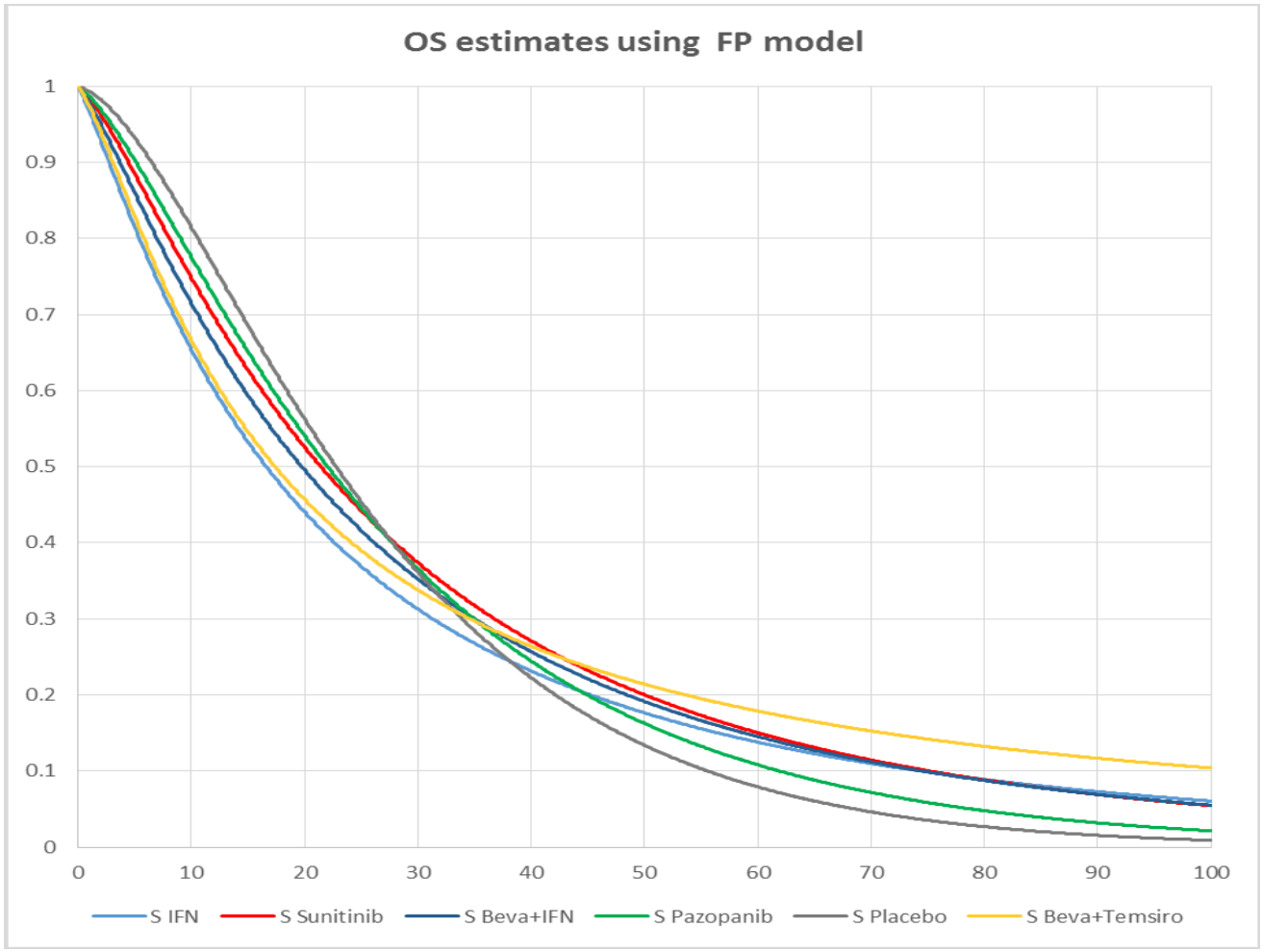
Results – OS estimates (PH vs FP model)



Conclusions

1. **PH assumption was violated** in NMA of PFS and OS estimations
2. **Median survival estimates were almost always lower with FP vs PH model** (PH overestimates ?)
3. **Sunitinib was the most effective treatment on PFS** in both models (heavily overestimated in long term by PH)
4. **Unclear effect on OS in both models** (FP – sunitinib; PH – pazopanib), impact of cross over

Future research

- Resolving issues on models' uncertainty
- Transfering effectiveness NMA data to CEA in settings of Serbia and the Netherlands

1. Cope S and Jansen JP. BMC Medical Research Methodology 2013, 13:147

Questions?

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