rijksuniversiteit groningen

Targeted therapies in oncology – a Serbian pharmacoeconomic perspective

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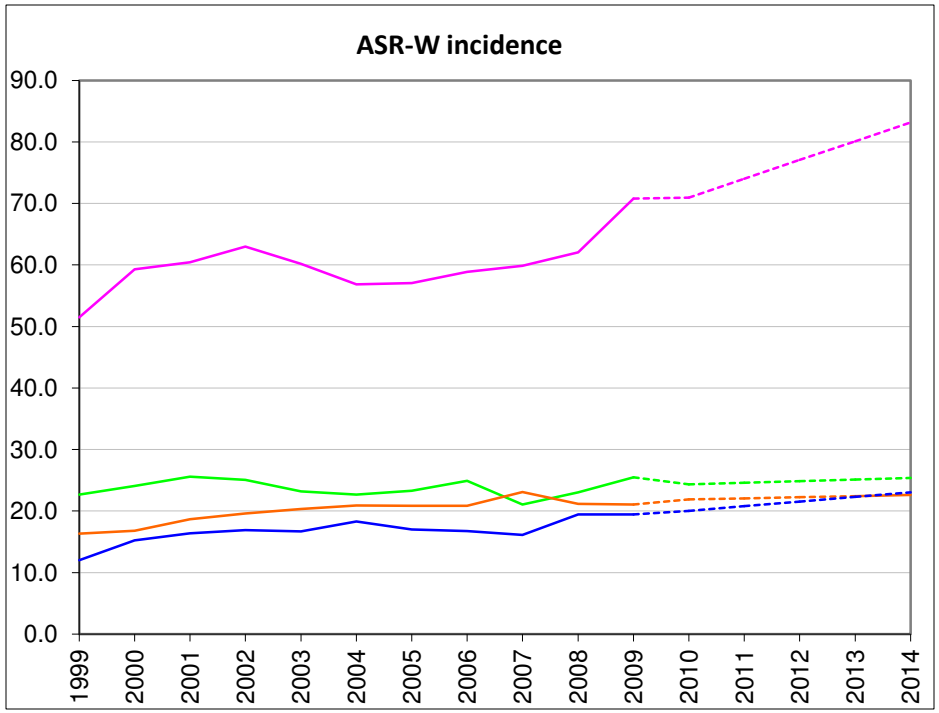
Outline

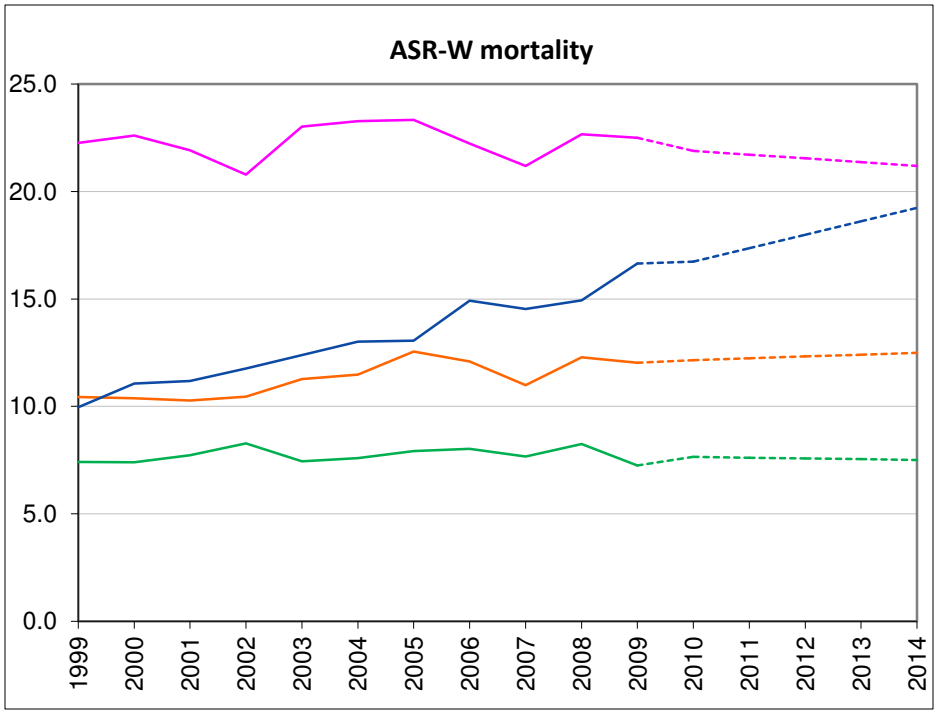
- Introduction
  - Serbia
  - Cancer epidemiology
  - Oncology care
- Targeted cancer therapies – policy issues
  - General reimbursement policy SRB
  - Comparison of TCT access - SRB, NL, SCO
- Cost effectiveness of TCTs – modelling issues
  - Everolimus CEA
  - 1st line mRCC therapies CEA in SRB and NL
- Conclusions

Population and economy - basic figures

- Population 7.2 million (census 2011)
- GDP per capita €4,450;
- Health care expenditure per capita €280 (6.3% GDP)
- Ageing population with the burden of disease switched towards non communicable diseases
- Main death causes: CV disease (37%), Cancer (18%), COPD (5%)
- 37,000 newly diagnosed cancer cases and 21,000 cancer deaths in 2011

4 most common/fatal CA in women



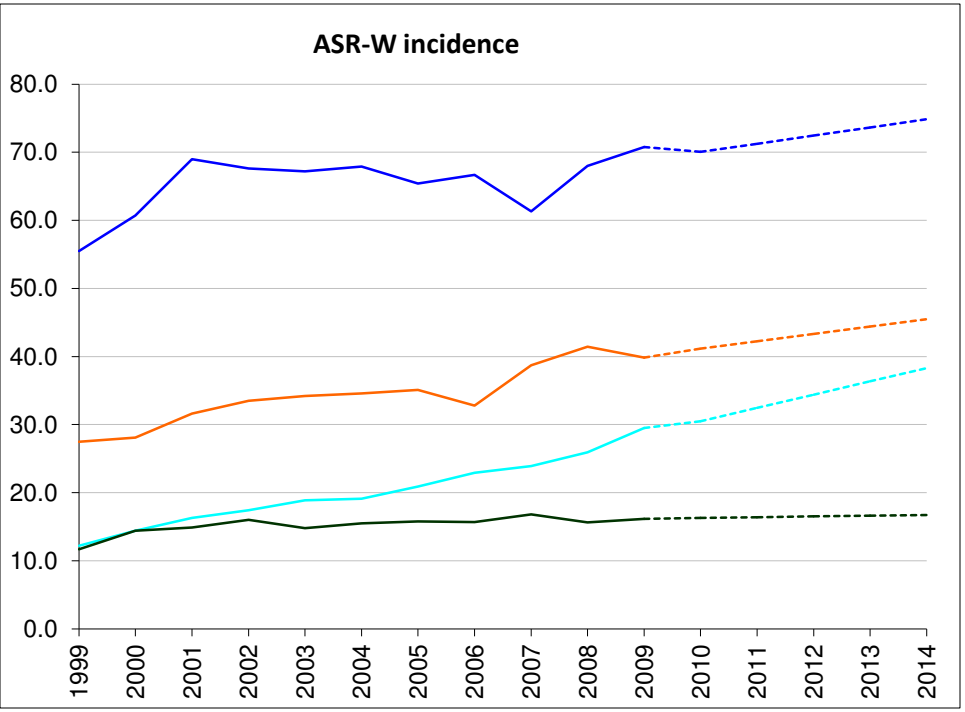


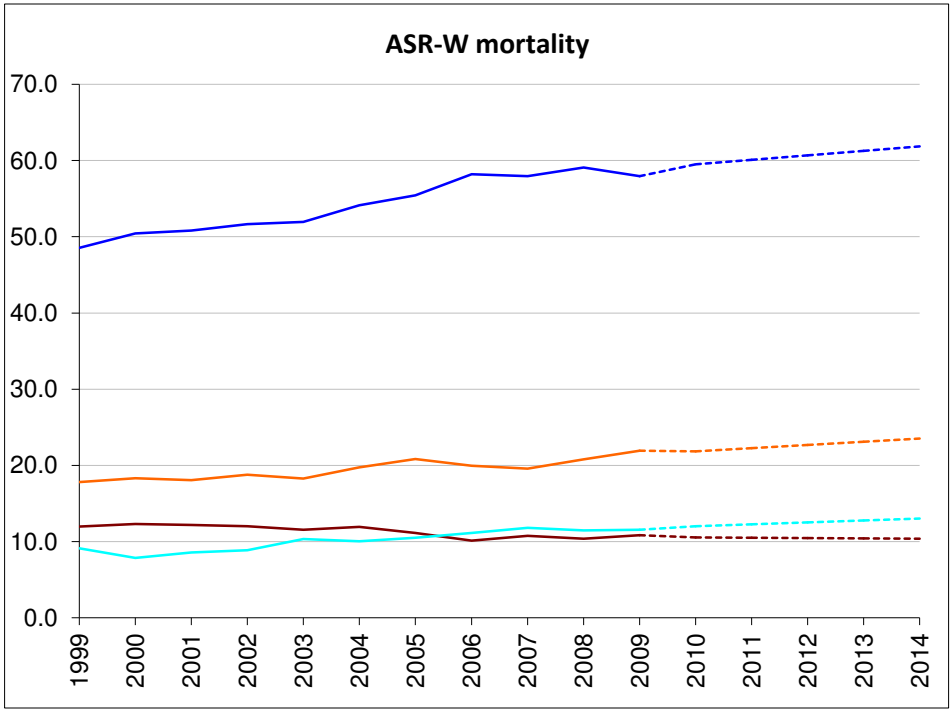
Breast CA
Cervical CA
Colorectal CA
Lungs CA

Still increasing trend of mortality !!!
in contrast to European countries

**Mihajlović J, Pechlivanoglou P, Miladinov-Mikov M, Živković S, Postma MJ. BMC Cancer, 13 (2013):18.*

4 most common/fatal CA in men





Lungs CA
Colorectal CA
Prostate CA
Bladder CA
Stomach CA

Still increasing trend of mortality !!!
in contrast to European countries

**Mihajlović J, Pechlivanoglou P, Miladinov-Mikov M, Živković S, Postma MJ. BMC Cancer, 13 (2013):18.*

Oncology care – organisation and economy

- “Cancer” is in title of **6 out of 8** National Programmes of the Ministry of Health (1 general strategy and 5 prevention programmes)
- National Health Insurance Fund (RFZO) is a sole provider of public (=elementary) health care insurance
- Oncology care is delivered almost exclusively within public health care institutions
- Hospitals financing based on annual RFZO plan, limitted by the budget contstraints, accounts for resources utilisation (no DRG sys), etc

Hospital care – an economic paradox

NL

>

SRB

<

Health care – non-economic prices

Stanje:	Struktura troška	Cena po mg/usluzi	Doza/usluga po ciklusu	Udeo pacijenata	Cena po ciklusu
Stabilna bolest (SB):	*Davanje terapije*				
	Plasiranje centralnog venskog katetera[2]	992.85	1.00	1.00	992.85
	Infuziona pumpa[2]	8,532.40	1.00	0.05	426.62
	Davanje IV infuzije	93.49	1.00	1.00	93.49
			Ukupno za davanje terapije:		*1,512.96*
	Korišćenje medicinskih resursa				
	Pregled onkologa	187.00	1.00	1.00	187.00
	Hospitalizacija (poluintenzivna nega)	2,474.19	1.00	0.30	742.26
	Ultrazvuk (ginekološki)	402.12	0.60	0.86	207.49
	Abdominalni/karlični CT	15,500.00	0.50	0.46	3,565.00
	MRI	10,990.00	1.20	0.04	527.52
	Rentgen pluća	105.32	0.50	0.60	31.60
	CA-125 marker	1,100.00	0.80	1.00	880.00
	Laboratorija - ukupna krvna slika	240.00	0.90	1.00	216.00
	Laboratorija - AST, ALT, Gama GT	580.00	0.90	1.00	522.00
			Ukupno za korišćenje medicinskih resursa:		*7,616.87*
				UKUPNO ZA STANJE PB:	***9,129.83***
Progresivna bolest (PB):	*Korišćenje medicinskih resursa*				
	Palijativna nega (dnevna bol., opšta)	1,363.28	14.07	0.22	4,296.62
	Palijativna nega (patronažna poseta)	130.18	12.00	0.10	153.09
	Palijativna radioterapija	113,447.80	1.00	0.01	1,588.27
	Ultrazvuk (ginekološki)	402.12	0.22	0.82	72.09
	Abdominalni/karlični CT	15,500.00	0.21	0.58	1,913.76
	MRI	10,990.00	0.20	0.22	486.87
	Rentgen pluća	105.32	0.10	0.80	8.73
	CA-125 marker	1,100.00	0.22	1.00	240.49
	Laboratorija - ukupna krvna slika	240.00	0.21	1.00	49.71
	Laboratorija - AST, ALT, Gama GT	580.00	0.23	0.80	106.78
				UKUPNO ZA STANJE PB:	**8,916.41**

~ €76
Stabile disease resource use

~ €74
Progress. disease resource use

**RFZO Official price lists of health care services. Updated on 8/2012*

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General reimbursement policy

A drug “application file“ submitted to RFZO

If complete

Assesment by Committee for therapeutic group
(Clinical efficacy, Safety)

If positive

Assesment by RFZO for pharmacoeconomics
(Cost Effectiveness, Budget Impact)

If positive

Central RFZO Committee makes a recommendation

RFZO Director and Executive Board decides upon recommendation

Pharmacoeconomics within reimbursement policy

- Rule book (4/2012; 4/2014; 6/2015) introduces pharmacoeconomic assesment – “CEA and BIA are needed, should be compared with existing RFZO trts”

- How it will be decided on CEA and BIA?
- Will these decisions be publicaly available?
- Threshold of cost-effectiveness?
- Appropriate RCT sources? Appropriate effectiveness modeling?
- Appropirate costs sources?
- Time horizon? Discount rates?

Targeted cancer therapies (TCT)

- The total number of TCT in 2010 was 22, while only four years later there are 44 registered TCT by EMA and FDA -> fastest growing drug market
- TCT brought clinically important gains in survival within the indications that did not see any improvements in past -> also at considerable cost
- Different policies in drugs' reimbursement among European countries led to significant imbalances in TCT access
- We identified 41 TCT for 70 indications within EMA database*
- We compared TCT reimbursement practice in SRB, SCO and the NL

**Mihajlović J, Dolk C, Tolley K, Simoens S, Postma MJ. Clin Ther 2015 Feb 1;37(2):474-480*

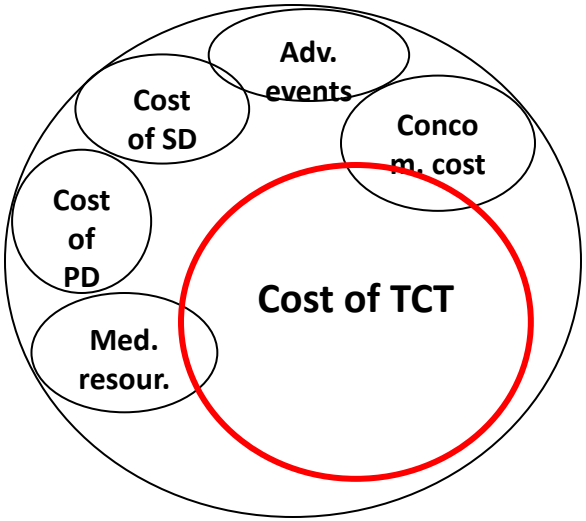
	TCT/i [accept./subm.]	Success rate
 ➢ Two special fast access policies for orphan&expensive hospital drugs ➢ Pharmacoeconomics requsted in t=4 ➢ No strict CE threshold	60/61	98%
 ➢ Pharmacoeconomics obligatory part of assessment process ➢ “Strictly” defined threshold - £30,000/QALY ➢ Rarely exemptions-decision modifiers	26/56	46%
 ➢ Pharmacoeconomics implemented, yet not sufficiently defined ➢ No cost-effectiveness threshold ➢ No specific policies for hospital drugs, TCTs	20/?	N/A

List of TCTs **with ICER<€20,000/QALY in SCO**, their reimbur. status in SRB and SCO

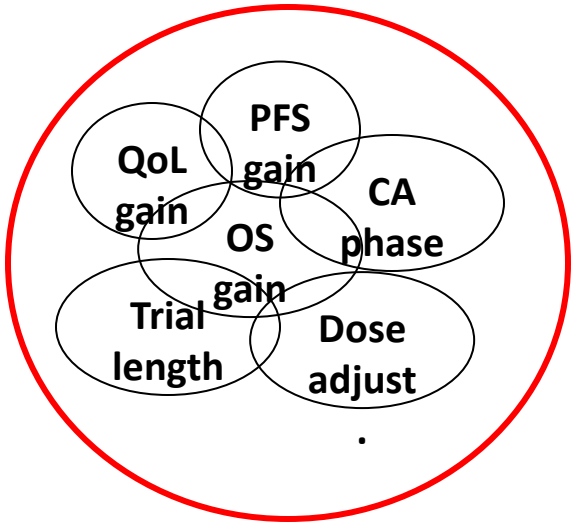
TCT name	TCT indication	ICER of CUA in Scotland	Reimbursement status in Scotland	Reimbursement status in Serbia
Rituximab	NHL - folicular lymphoma, relapsed/refractory	CUA - £7,721/QALY	**Recommended for reimbursement** under restriction (R)	**Reimbursed** under restriction (R)
Rituximab	NHL - folicular lymphoma, previously untreated	CUA - £7,417-10,472/QALY	**Recommended for reimbursement** under restriction (R)	**Reimbursed** under restriction (R)
Rituximab	NHL - folicular lymphoma, stabile disease; induction and maintenance therapy;	CUA - £15,978/QALY (maintenance phase); Not available (induction phase);	**Recommended for reimbursement** under restriction (R)	**Reimbursed**
Rituximab	CLL in previously untreated patients; with FC regimen;	CUA - £15,593/QALY	**Recommended for reimbursement** under restriction (R)	**Reimbursed** under restriction (R)
Rituximab	CLL in previously treated patients; with FC regimen;	CUA - £6,279/QALY	**Recommended for reimbursement** under restriction (R)	**Reimbursed** under restriction (R)
Trastuzumab	Early breast cancer	CUA (i.v. trastuzumab vs standard th) - <£3,000/QALY	**Recommended for reimbursement** under restriction (R)	**Reimbursed** under restriction (R)
Trastuzumab	Metastatic breast cancer	CMA (s.c. vs. i.v. trasutuzumab) proves s.c. trastuzumab cost saving (no information on i.v. vs. standard therapy)	**Recommended for reimbursement** under restriction (R)	**Reimbursed** under restriction (R)
Nilotinib	Chronic myelogenous leukemia	CUA - £11,000/QALY (when nilotinib is given in first and imatinib in second line)	**Recommended for reimbursement** when PAS applied	**Reimbursed** under restriction (R)
Cetuximab	Squamous cell cancer of the head and neck	CUA - £6,870/QALY	**Recommended for reimbursement** under restriction (R)	**Reimbursed** under restriction (R)
Imatinib	Multiple hematologic malignancies (ALL and CML)	CUA - £16,665/QALY	**Recommended for reimbursement** under restriction (R)	**Reimbursed** under restriction (R)

Rationale for reimbursement in SRB?

Are CE results for TCTs transferable?



COSTS



EFFECTIVENESS

ICER [€/QALY] = COSTS / EFFECTIVENESS

- **ANSWER: Y/N; Y - TCT cost correlates generally well with the ICER, <u>BUT</u>**
  N- this rationale <u>is not always</u> applicable -> can lead to wrong decision

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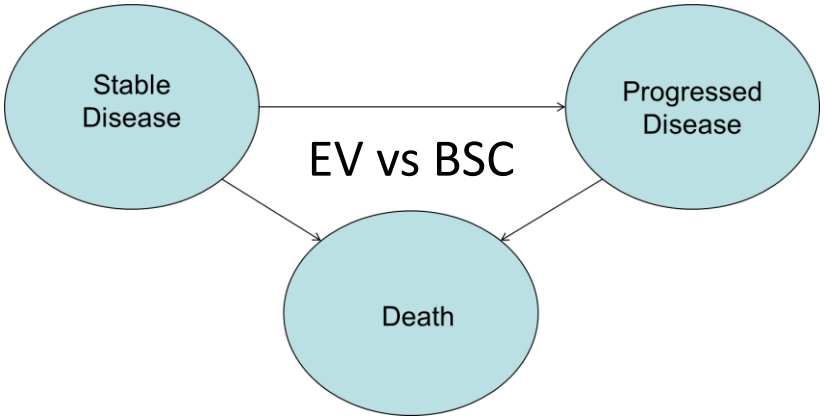
Cost effectiveness modelling of TCTs – a common example of area-under-the--curve model

e.g. - cost effectiveness of everolimus in SRB



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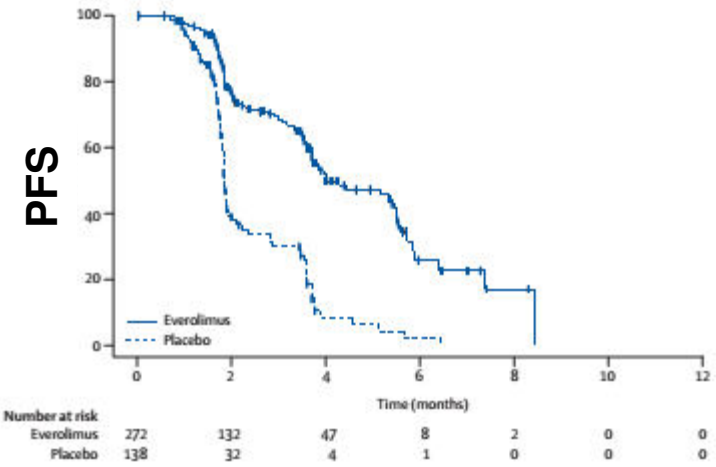
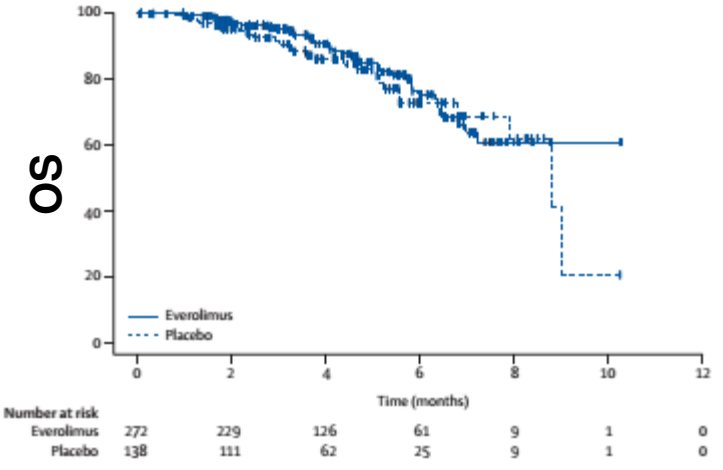


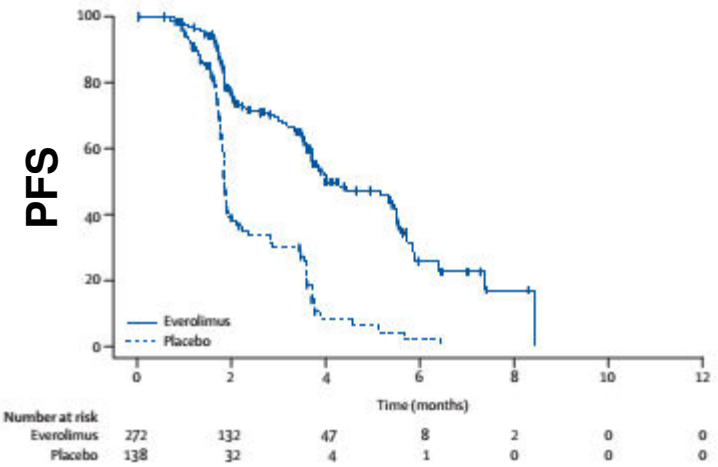


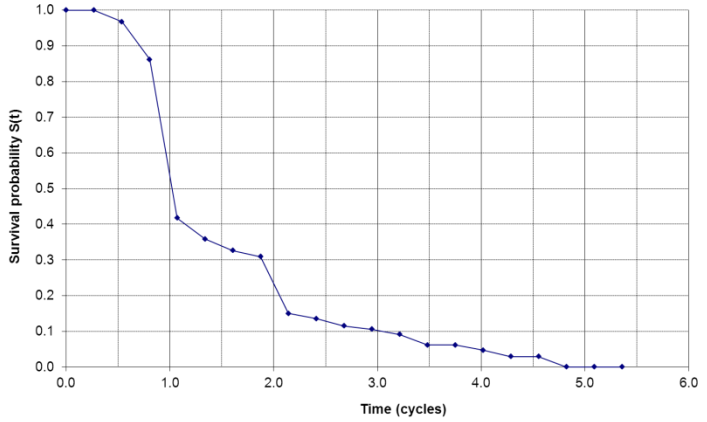
Common modelling issues

1) Censoring of pts through time

(a) assuming constant rate of censoring through time, (b) using No of pts at risk and (c) observing OS and PFS from KM curves at the same time points

We reproduced KM curves with acceptable accuracy*:





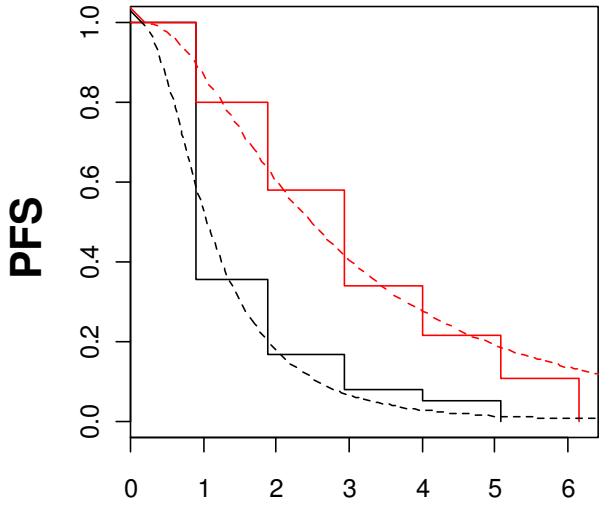
R code publicaly available from Hoyle et al 2011 – http://sites.pcmd.ac.uk/pentag

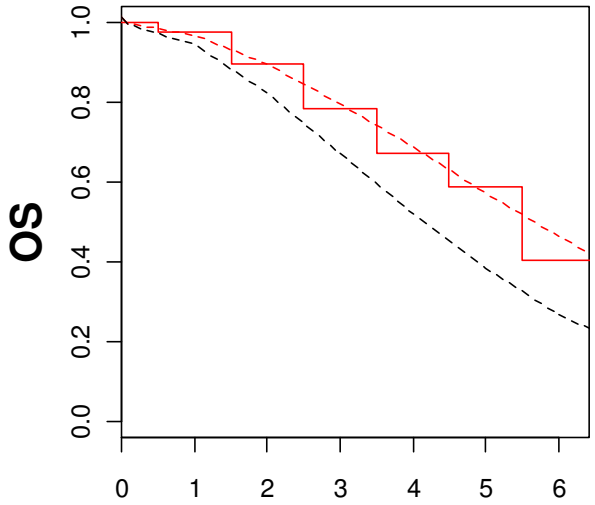
**Mihajlović, Pechlivanoglou, Sabo, Tomić, Postma. Clinical Therapeutics, 2013 Dec;35(12):1909-22.*

2) Fitting best distribution on top of reconstructed KM curves

3) Problem with cross over in OS data?

Unsolvable w/o pt level data → NICE estimate of HR





Outcome	Everolimus	BSC	Difference
Costs, €	16,828	640	16,188
Effectiveness	0.8113	0.5658	0.2455
LYG			
QALY	0.5804	0.3943	0.1861
ICER			
€/LYG	–	–	65,926
€/QALY	–	–	86,978

**Mihajlović, Pechlivanoglou, Sabo, Tomić, Postma. Clinical Therapeutics, 2013 Dec;35(12):1909-22.*

Common modelling issues

- Decision maker is interested in CEA and eff. comparison of all relevant TCTs for one indication
- TCTs are generally licenced with 1-2 RCT, and head-to-head eff. comparisons are rarely available
- Solution – Network Meta Analysis (NMA) including both direct and indirect evidence
- NMA should be based on systematically/critically selected data from the literature (RCTs), both survival end-points reported for TCTs (OS and PFS) should be included to obtain tps for standard 3-states CE models
- All included RCTs in NMA come with the shortcomings explained above !!!

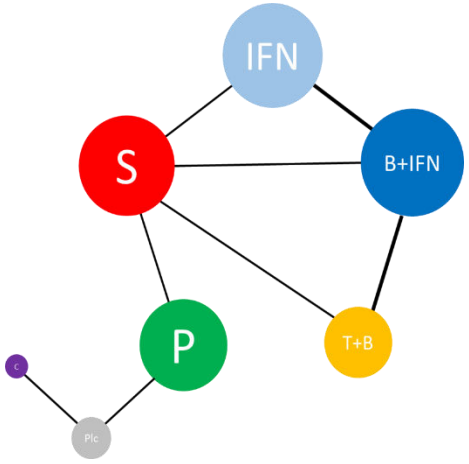
Common modelling issues

4) How to appropriately conduct NMA of PFS and OS for all available TCTs?

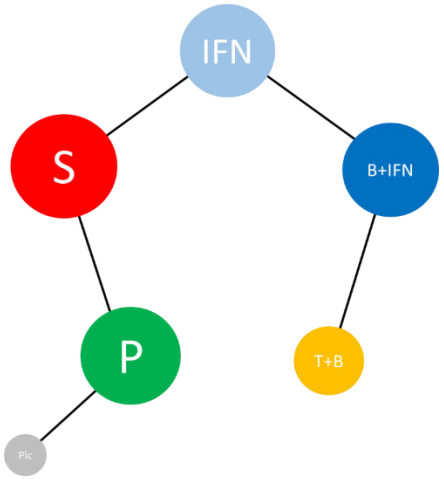
e.g. all available 1st line mRCC TCTs – sunitinib, pazopanib, bevacizumab, temsirolimus compared with previous th standard – IFN alpha (cediranib ?)

We examined differences in standard modelling approach **(proportional hazards)** and one novel modelling approach **(fractional polynomials)***

Network of evidence (SLR) for PFS

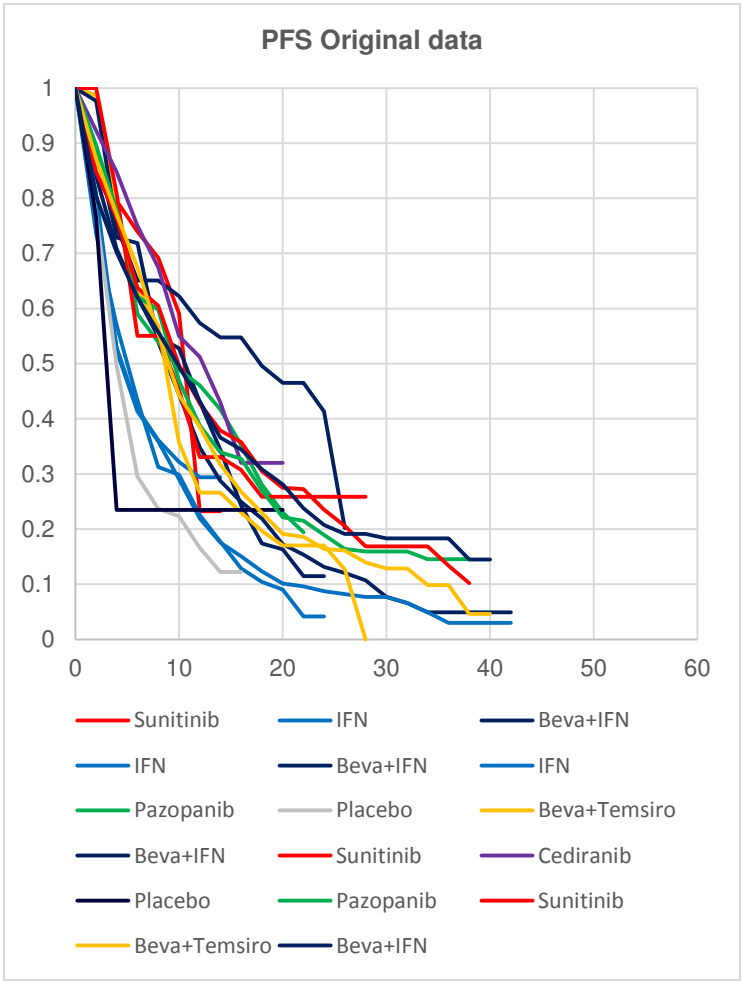


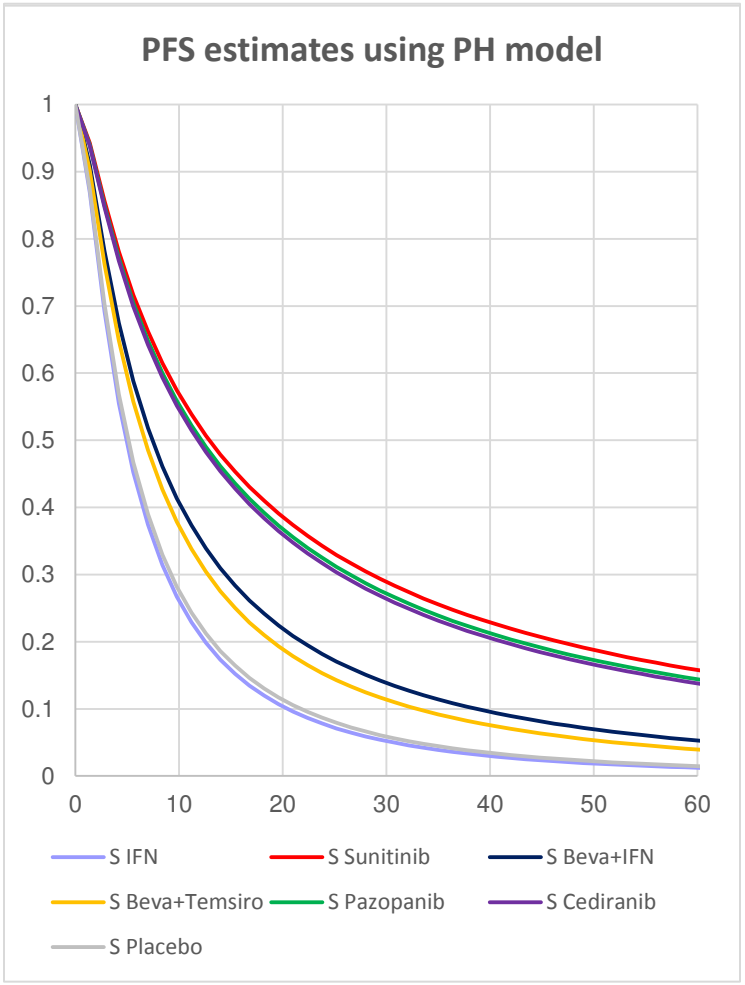
Network of evidence (SLR) for OS



*Mihajlović J, Pechlivanoglou P, Postma MJ. A network meta-analysis of summary survival in first line metastatic renal cell cancer targeted therapies; application of survival estimates in cost effectiveness analysis for Serbia and the Netherlands. *Submitted manuscript.*

e.g. Fractional polynomials vs Proportional hazards model*





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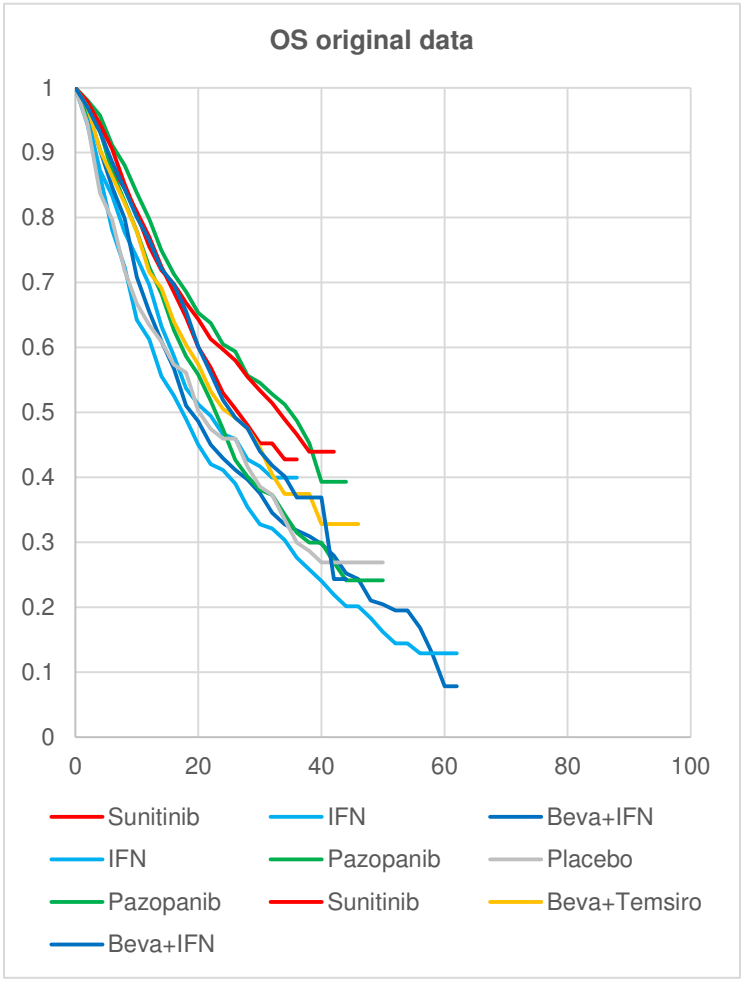

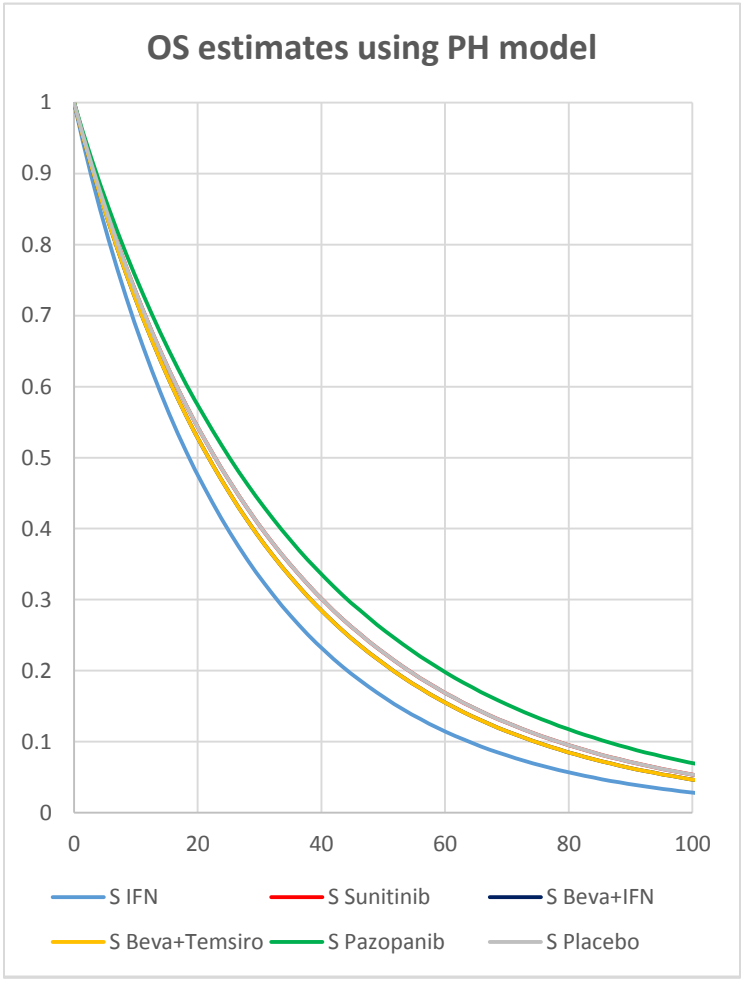

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e.g. Fractional polynomials vs Proportional hazards model ICER RESULTS*

	Estimates of FP model				Estimates of PH model			
Compared treatments:	Sunitinib	Pazopanib	Bevacizumab	Temsiro+Beva	Sunitinib	Pazopanib	Bevacizumab	Temsiro+Beva
Cost of compared trt [€]	37,784	35,866	59,656	73,213	61,469	63,179	62,288	84,272
Cost of baseline trt [€]			5,807				5,471	
Incremental cost [€]	31,976	30,058	53,848	67,405	55,998	57,708	56,817	78,801
LYG with compared trt	2.4359	2.2363	2.3410	2.5001	2.5194	2.7416	2.4143	2.4143
LYG with baseline trt			2.1854				2.0932	
Incremental LYG	0.2505	0.0509	0.1556	0.3147	0.4262	0.6484	0.3211	0.3211
QALY with compared trt	1.8345	1.6873	1.7263	1.8186	1.9909	2.1500	1.7832	1.7714
QALY with baseline trt			1.5871				1.5176	
Incremental QALY	0.2474	0.1003	0.1392	0.2315	0.4733	0.6324	0.2656	0.2538
ICER [€/QALY]	129,245	299,795	386,765	291,125	118,306	91,250	213,927	310,475

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CONCLUSIONS

1) Cancer is one of the leading death causes in Serbia with significant trend of increase, **LEGISLATION IS NOT ENOUGH** for efficient preventive and curative oncology care

2) Creating non-economic surrounding in Serbian state health care led to **HUGE UNDERESTIMATION OF MEDICAL COSTS** and threathens to lower quality of such care

3) TCTs present demanding task for pharmacoeconomic (PE) assessment even in developed countries, and **CEA APPEARS AS ONE OF THE MOST DECISIVE ELEMENTS** in TCT market access

4) **CONSISTENT PE EVALUATION** should be one of foundations of Serbian reimbursement policy, as this is the most rational (mathematical) way of accounting for comparative effectiveness

CONCLUSIONS

5) **MODELLING OF TCT SURVIVAL** (and therefore CEA) is **DEMANDING METHODOLOGICAL TASK**, judging its quality requires ability to completely replicate and evaluate submitted models (detailed guideline on TCT CEA?)

6) **CEA RESULTS** in area of TCT seem **RELATIVELY TRANSFERABLE** between countries; with common threshold of 3xGDP/c (WHO) small number of TCTs would appear cost effective within presented analyses;

7) Once general reimbursement system is appropriately put into practice, **SPECIFIC GUIDELINE FOR TCTs REIMBURSEMENT** should be considered (cost effectiveness threshold?, conditional approvement?, separate budget?)

Questions?

MIHAJLOVICHEALTHANALITICS