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Survival extrapolation approaches: new era, new methods?

BREAKOUT SESSION 4, IP8
ISPOR COPENHAGEN
4 NOVEMBER 2019

MODERATOR: ELISABETH FENWICK
PANELLISTS: JOHN WHALEN, STEPHEN PALMER, SVEN KLIJN

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Speakers

- Elisabeth Fenwick
- *Moderator*

- John Whalen
- *Industry Perspective*

- Stephen Palmer
- *Policy Maker / Payer Perspective*

- Sven Klijn
- *Methodological Perspective*

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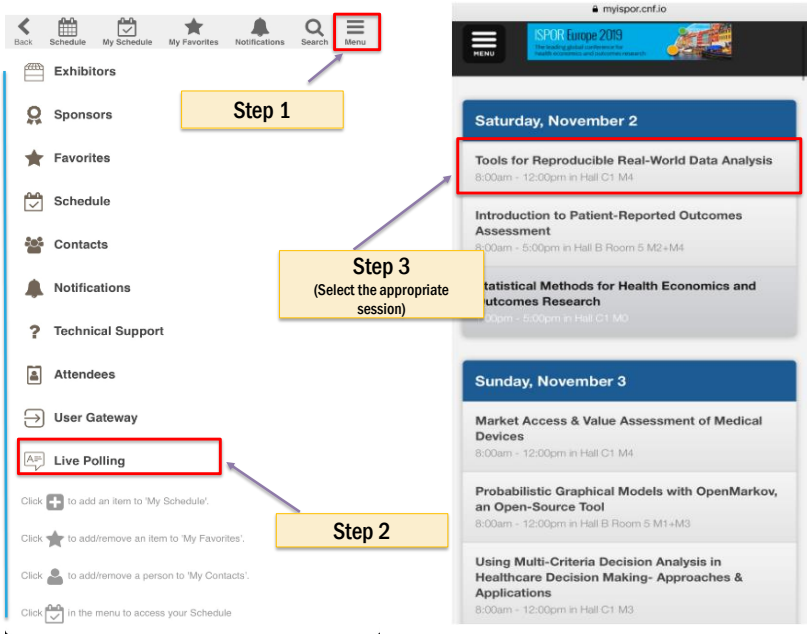
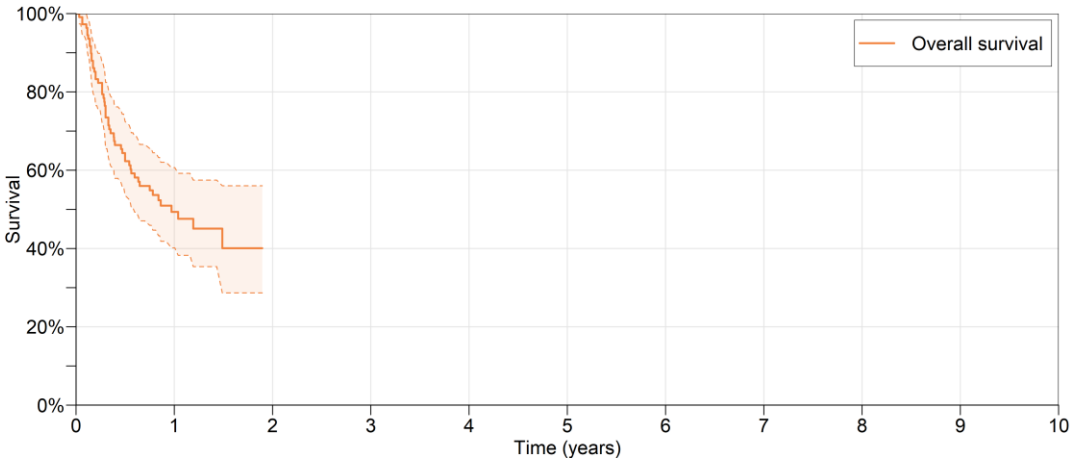
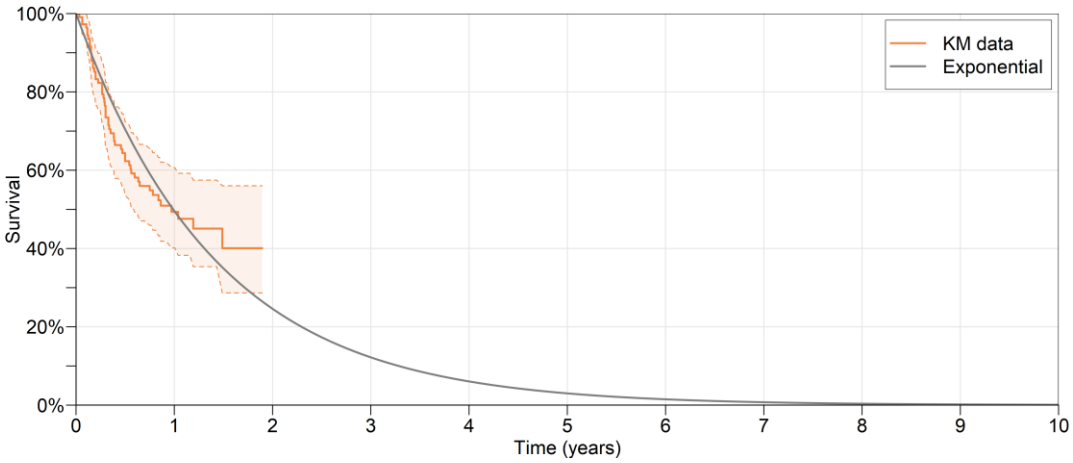


Extrapolating Survival



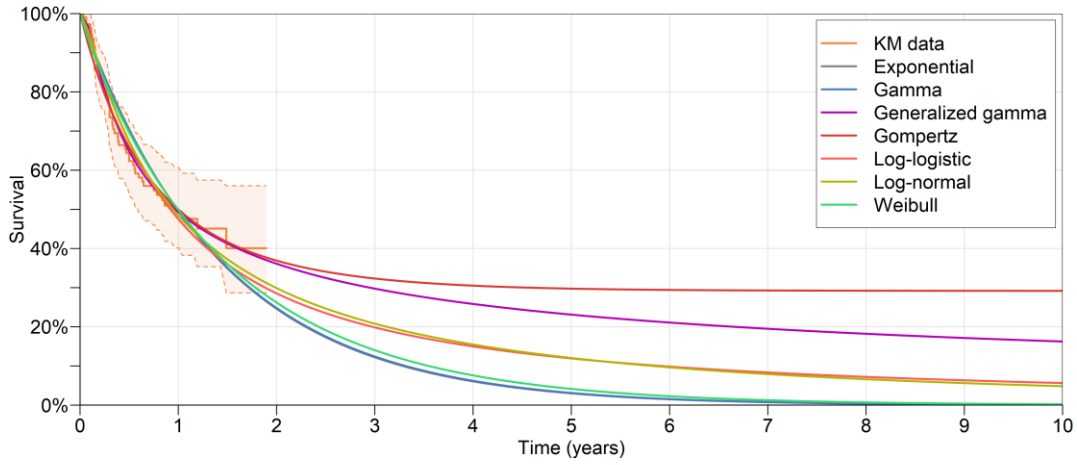
Data source: Tisagenlecleucel (Kymriah®) overall survival, as reported by Schuster et al. (2018). DOI: 10.1056/NEJMoa1804980
Data replication method: Guyot et al. (2012). DOI: 10.1186/1471-2288-12-9

Extrapolating Survival

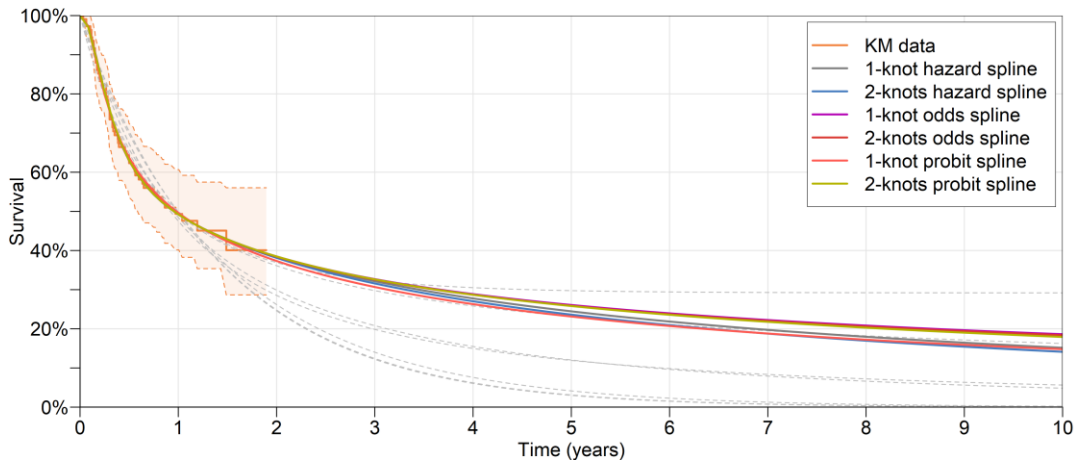


KM: Kaplan-Meier

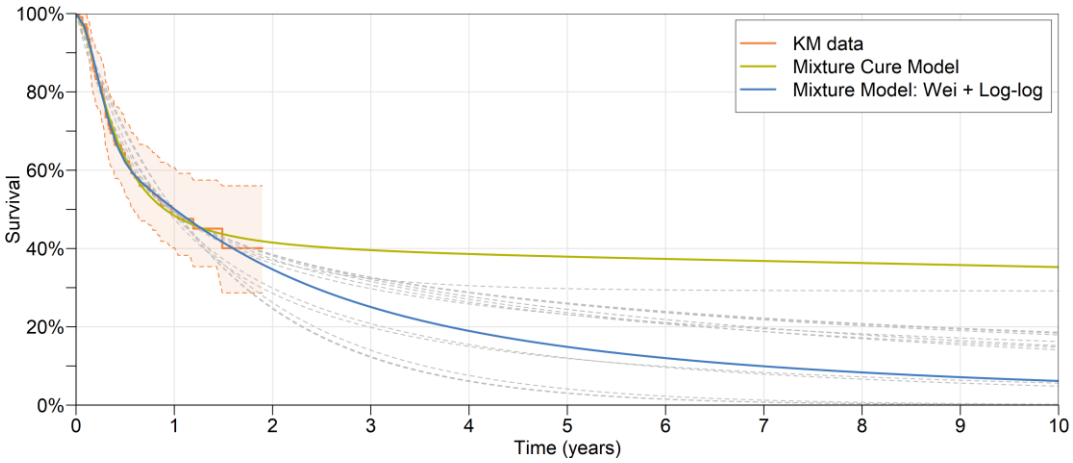
Extrapolating Survival



Extrapolating Survival



Extrapolating Survival



Overview of Methods

Homogeneous	Heterogeneous
Standard Parametric Distributions	Response-Based Landmark Models
	Mixture Cure Models
Splines	
	Parametric Mixture Models

This is a non-exhaustive overview of methods

Overview of Homogeneous Methods

Standard Parametric Distributions

- Exponential
- Gamma, Gompertz, Weibull
- Log-logistic, Log-normal
- Generalized Gamma

Splines

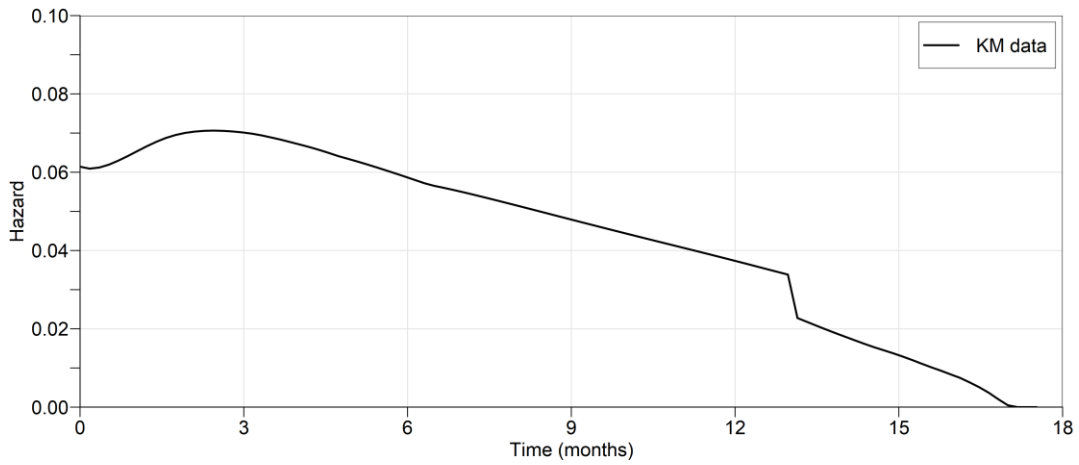
- 1-knot hazard, 1-knot odds, 1-knot probit
- 2-knots hazard, 2-knots odds, 2-knots probit

Low complexity

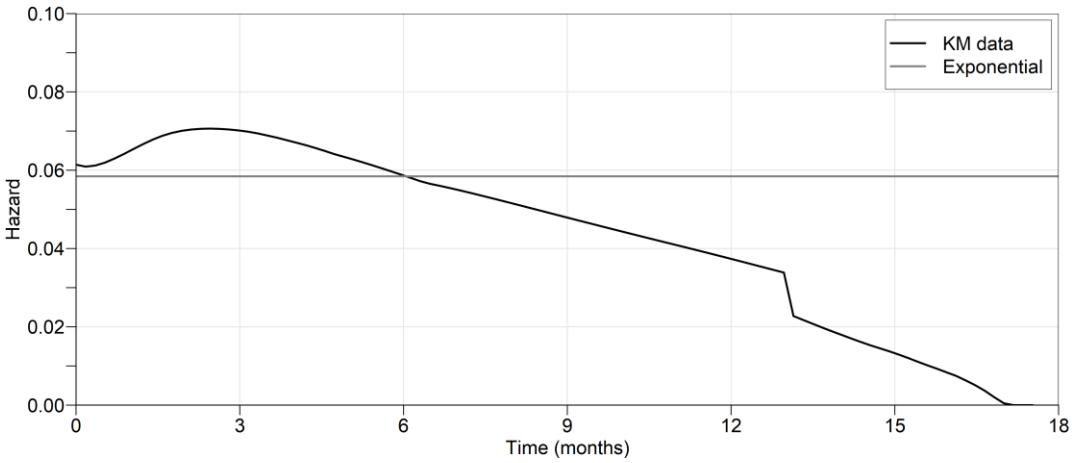
Increasingly complex hazard shape

High complexity

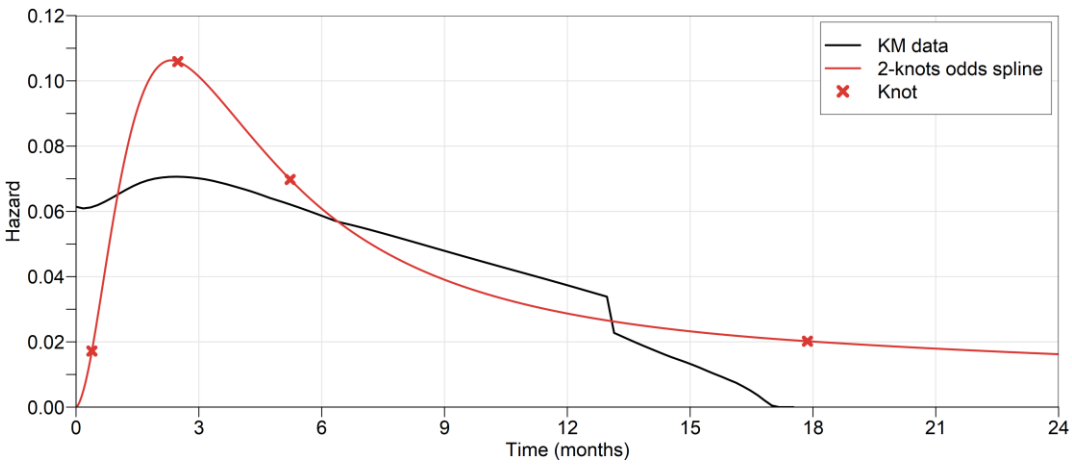
Hazards



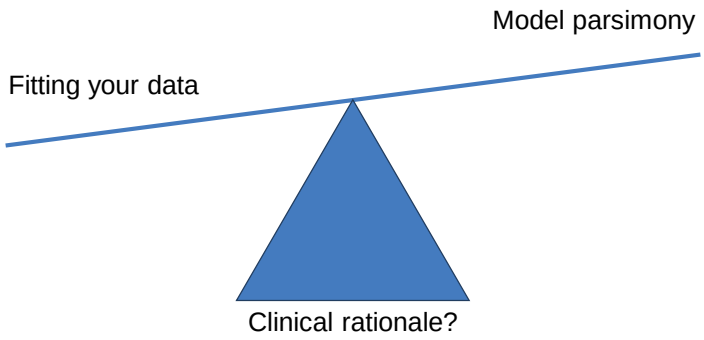
Constant Hazard



Complex Hazard



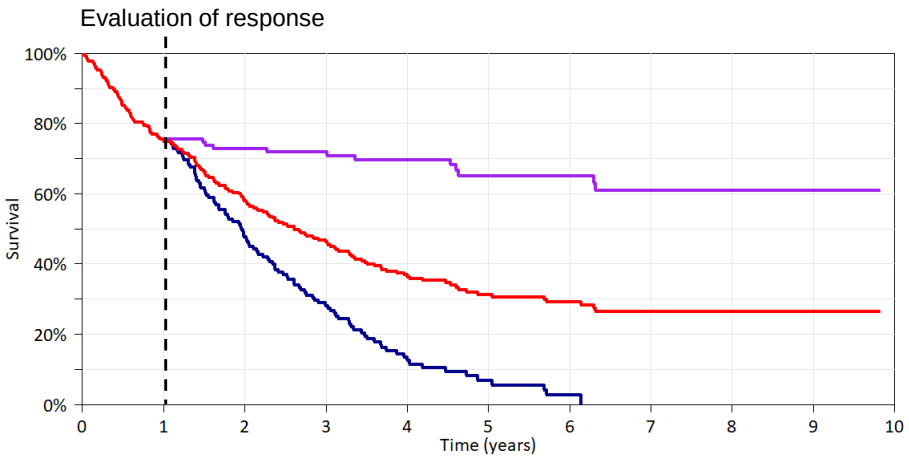
Reflection on Homogeneous Methods



Overview of Methods

Homogeneous	Heterogeneous
Standard Parametric Distributions	Response-Based Landmark Models
Splines	Mixture Cure Models
	Parametric Mixture Models

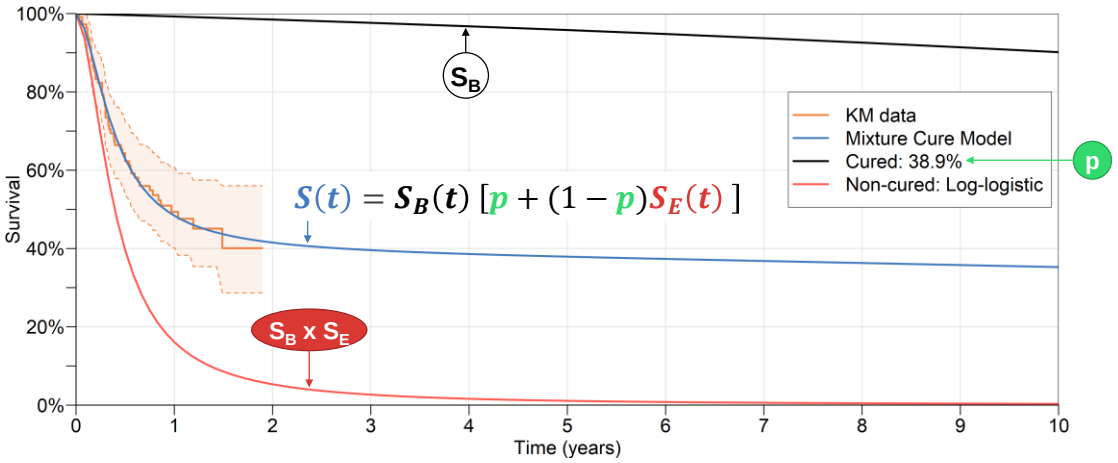
Response-Based Landmark Model



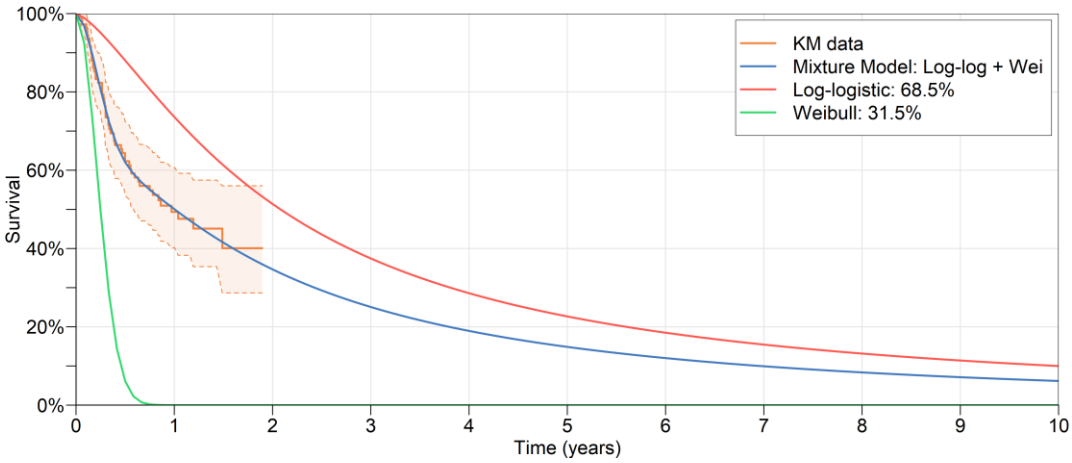
Overview of Methods

	Homogeneous	Heterogeneous	
	Standard Parametric Distributions	Response-Based Landmark Models	**Explicit**
	Splines	Mixture Cure Models	**Latent**
		Parametric Mixture Models	

Mixture Cure Model



Parametric Mixture Model

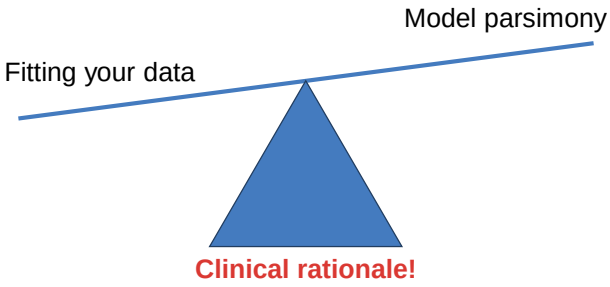


Overview of Methods

Homogeneous	Heterogeneous	
Standard Parametric Distributions	Response-Based Landmark Models	**Explicit**
Splines	Mixture Cure Models	**Latent**
	Parametric Mixture Models	

Final Thoughts

- This was a simplified overview. Other things to take into consideration:
  - Other methods
  - Treatment effects
  - Multiple time-to-event outcomes



Poll

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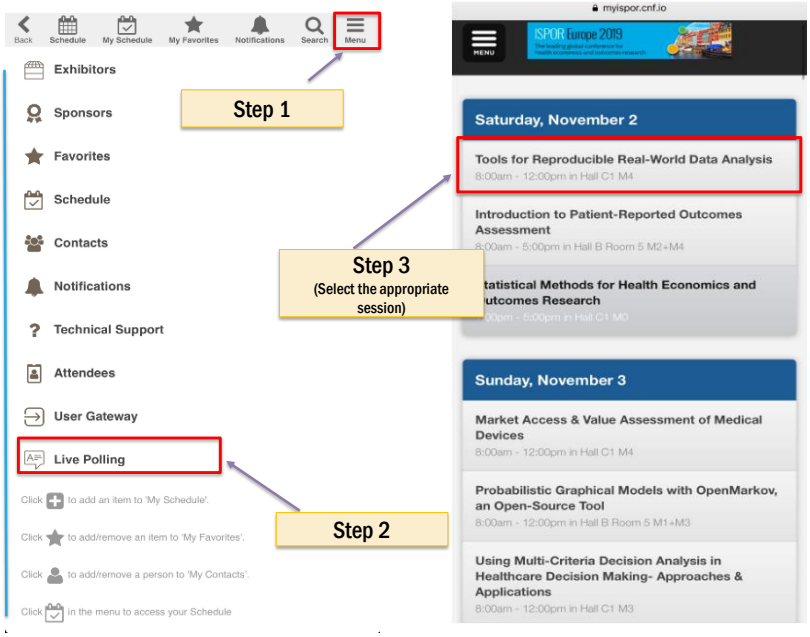

Live Content Slide

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Poll: What is your professional background?

Live Content Slide

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Poll: What is your level of experience with survival extrapolations?

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Poll: What would be the preferred method for extrapolating survival for novel therapies?

Mixture Cure Models (MCMs) for Economic Evaluations

John Whalen

ISPOR 4th Nov 2019

This presentation was prepared or accomplished in my personal capacity. The opinions expressed are my own and do not reflect the view of my employer.

What is required for economic models?

- Transparent / reproducible
- Flexible
- Consistent with Medical & Regulatory evidence

How do we model oncology therapies?

Model	Cohort partition	State transition
Transparent?		
Flexible?		
Consistent w/ Medical & Regulatory?		

What has changed?

- Number of treatment options
- Curative transplant procedures (stem cells, cell therapy)
- Advances in antibody development

Have MCMs been successful?

43 TAs

600, 584, 562, 558, 557, 554, 553, 540, 531, 525, 522, 520, 519, 517, 447, 428, 414, 410, 400, 396, 384, 366, 357, 268

Acute lymphoblastic leukemia (2)	tisagenlecleucel
Acute myeloid leukemia (2)	gemtuzumab ozogamicin
Head & neck (2)	cetuximab
Hodgkin lymphoma (2)	
Melanoma (11)	cobimetinib + vemurafenib
Merkel cell (1)	avelumab
NSCLC (9)	atezolizumab
RCC (8)	
Urothelial (6)	atezolizumab (x2)

Are MCMs face valid?

Cure fractions

- 554 tisagenlecleucel
- 517 avelumab
- 414 cobimetinib + vemurafenib
- 545 gemtuzumab ozogamicin

Accepted 

Cure fractions <5%

- 525 atezolizumab
- 520 atezolizumab
- 492 atezolizumab

ERG used piecewise instead

State transition

- 553 pembrolizumab
- 545 gemtuzumab ozogamicin
- 540 pembrolizumab
- 526 arsenic trioxide
- 462 nivolumab
- 432 everolimus
- ***400 nivolumab***
- 384 nivolumab

TA400: "model was unnecessarily complex and a simpler approach such as partitioned survival modelling could have been taken"

Are MCMs flexible?

	UK	Australia	Canada
TA 554 Tisagenlecleucel	Cure fraction (redacted)	Traditional	No (but unclear)
TA 492, 525 atezolizumab	Cure fraction: 0%	Traditional	No (but unclear)
TA 520 atezolizumab	Cure fraction: 2% ERG rejected MCM	Cost-minimization	Cure fraction: 1% pERC removed MCM
TA 414 cobimetinib + vemurafenib	Cure fraction (redacted)	Not mentioned	No (but unclear)
TA 545 gemtuzumab ozogamicin	Cure fraction (redacted)	--	(under review)
TA 145 cetuximab	Cure fraction: 23-36% ERG: "unable to provide any sensitivity analysis"	Traditional	--

Are MCMs consistent with medical & regulatory evidence?

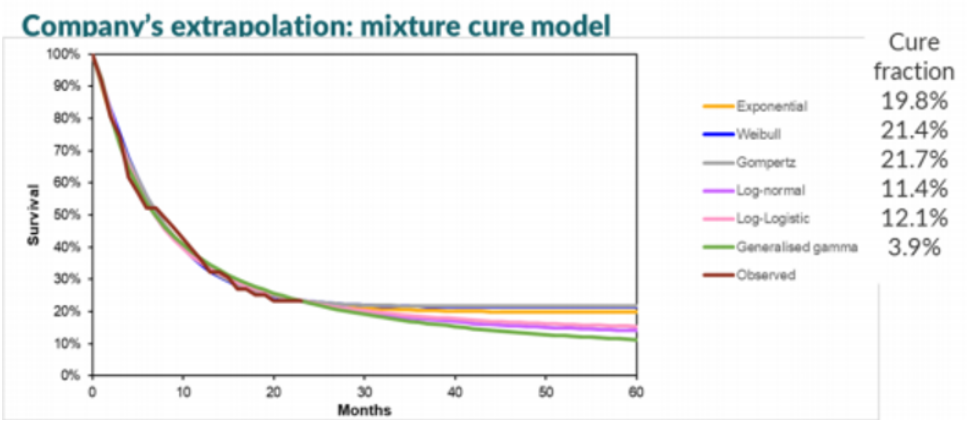
"Acceptable primary endpoints include cure rate, OS and PFS/DFS. […]

consider in the planning of the study whether it is at all possible to demonstrate a favourable effect on cure rate, i.e. in analyses conducted when recurrence rates have reached an apparent plateau"

- Guideline on the evaluation of anticancer medicinal products in man. September 2017. European Medicines Agency.

TA554: tisagenlecleucel for R/R B-cell ALL

"wide range of cure fractions predicted by the model" - ERG report



Is MCM the solution?

- Sensitivity analysis

Why?

- Uncertain acceptability ex-UK
- Potential flexibility issues: how to adjust for later lines?
- Alignment with medical evidence

SURVIVAL EXTRAPOLATION APPROACHES: NEW ERA, NEW METHODS?
Policy maker/payer perspective

Stephen Palmer
Professor of Health Economics
Centre for Health Economics
University of York, UK

ISPOR Europe 2019, Copenhagen, Denmark

Background

- Development of novel (and high cost) targeted anti-cancer agents – different mechanisms
  - *Possible delayed clinical effects*
  - *Subset of long term survivors*
- Regulatory developments leading to earlier (conditional) approval for innovative treatments
  - Less mature evidence
- HTA agencies playing catch up
  - Over reliant on methods/processes more appropriate to conventional cytotoxic regimens and 'mature' Ph3 trials
- How are novel methods and approaches being considered by HTA agencies?

Current state of the art for guiding extrapolation choice?

NICE DSU TECHNICAL SUPPORT DOCUMENT 14: SURVIVAL ANALYSIS FOR ECONOMIC EVALUATIONS ALONGSIDE CLINICAL TRIALS - EXTRAPOLATION WITH PATIENT-LEVEL DATA

REPORT BY THE DECISION SUPPORT UNIT

June 2011
(last updated March 2013)

Nicholas Latimer

School of Health and Related Research, University of Sheffield, UK

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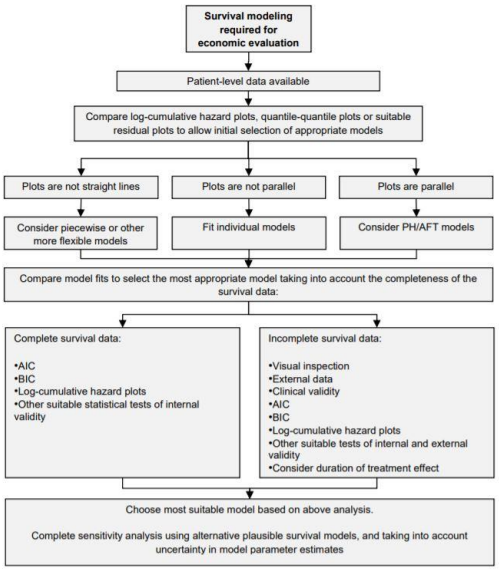

Increasing awareness of importance of structural assumptions

NICE DSU TECHNICAL SUPPORT DOCUMENT 19: PARTITIONED SURVIVAL ANALYSIS FOR DECISION MODELLING IN HEALTH CARE: A CRITICAL REVIEW

REPORT BY THE DECISION SUPPORT UNIT

2 June 2017

Beth Woods[1], Eleftherios Sideris[1], Stephen Palmer[1], Nick Latimer[2], Marta Soares[1]

[1]Centre for Health Economics, University of York, York, UK
[2] School of Health and Related Research, University of Sheffield, UK

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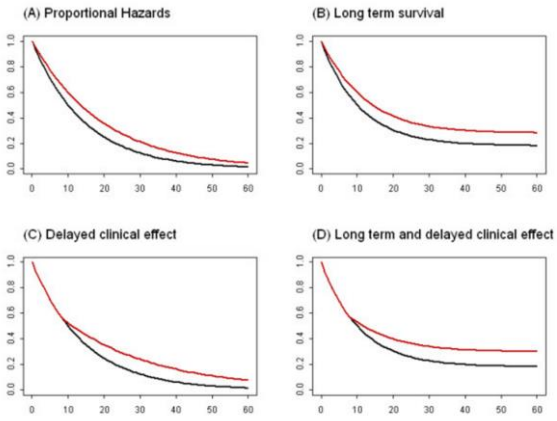
- Main structural limitation – <u>independence between survival endpoints</u>
- *'Limits degree to which the biological and clinical plausibility can be subject to scrutiny and sensitivity analysis'*
- *'Extrapolating without considering the underlying disease process, may not produce appropriate extrapolations'*

Why are immuno-oncology and cell & gene therapies different?

(i) Different patterns of survival



Ref: Chen (2013). J Immunother Cancer. doi: 10.1186/2051-1426-1-18

(ii) Implications for trial design

	PHM	PHCRM	NPHM	NPHCRM
Cure rate	–	0.10 vs. 0.18	–	0.10 vs. 0.17
Delayed clinical effect (month)	–	–	3	3
Sample size	680	680	680	680
Number of events	512	512	512	512
Hazard ratio (pre- and post- separation)	0.75	0.75	1/0.75	1/0.75
Type I error	0.05	0.05	0.05	0.05
Power	0.90	0.90	**0.70**	**0.70**
Accrual duration (month)	34	34	34	34
Study duration (month)	48	**55**	47	**54**

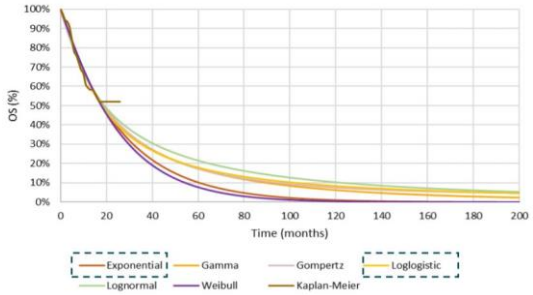
PH/NPH=Proportional/Non-Proportional; CR = Cure rate

NICE Appraisals: Same product, different approaches

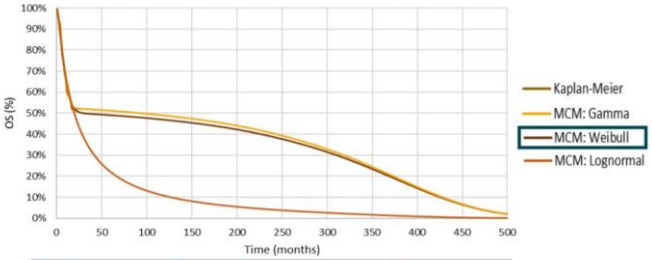
Product	Approach to OS extrapolation	Issues raised by external review group (ERG)
Nivolumab for treating advanced melanoma (2016)	• Partitioned survival approach • Conventional parametric curve up to 3 years • External pooled survival data (12 ipilimumab trials) beyond year 3	• ERG preferred simpler extrapolation based on trial data
Nivolumab with ipilimumab for advanced melanoma (2016)	• Semi-Markov • Conventional extrapolation of PFS • Post-progression survival from external data (ipilimumab trials)	• Too complex and over reliant on assumptions
Nivolumab for treating locally advanced unresectable/ metastatic urothelial carcinoma (2018)	• Landmark-response approach • Parametric curves fitted to PFS and OS based on response status	• No mathematical justification provided • Unnecessary complexity • Standard approaches sufficiently flexible
Nivolumab with ipilimumab for advanced renal cell carcinoma (2019)	• Partitioned survival with additional 'immunological' effect assumed after specific time point • 50% probability that durable responders are cured	• Not a recognised cure model • No evidence that 'cure' results in same mortality rate as general population

NICE Appraisal: CAR-T for lymphoma

(i) Conventional parametric



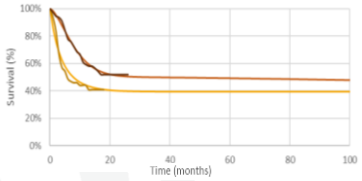
(i) Cure fraction



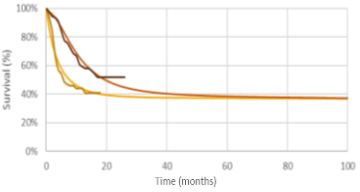
Distribution	Lognormal	Weibull	Gamma
Cure Fraction	1%	50%	53%

Alternative modelling approaches explored

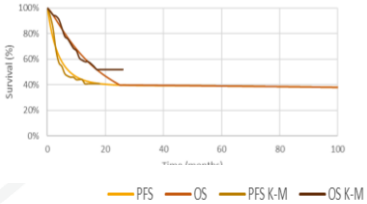
Company – partitioned survival approach



Company – state transition approach



ERG – alternative base case 'hybrid' approach



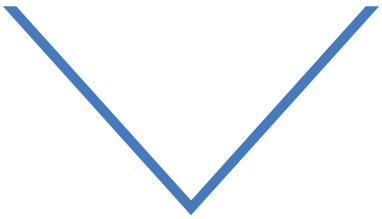
ERG:

- Overall survival data for axi-cel is immature
- No single approach to modelling is 'optimal'
- PFS and OS appear to converge at a later time point with state transition approach
- All should be considered in CE modelling

ERG critique of company ACD comments: https://www.nice.org.uk/guidance/ta559/documents/committee-papers-2

Conclusions

- HTA methods and processes need to adapt
  - Lack of guidance a challenge
  - Pragmatism being shown but lack of consistency in approaches/critique
- Companies need to be more proactive in identifying challenges at trial design stage
  - Implications for follow-up and power
  - Most of challenges due to immaturity of RCT evidence and reliance on external data/assumptions
- New methods may provide additional insights for clinical analysis and economic modelling
  - No single optimal method
  - Approach needs to be fully justified and alternatives explored
  - Uncertainties inevitably remain



Plenary Discussion

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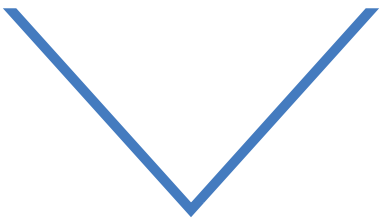
Poll: HTA agencies and industry are too hesitant in adopting new approaches



How can we move forward together?

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Survival extrapolation approaches: new era, new methods?

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