Blending hazard method: A possible solution to modelling treatment effect waning in survival extrapolation

Student number: 22090905

University College London

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Health economic evaluation

- Systematic evaluation of health interventions
- Cost-effectiveness analysis (CEA):
  Compare the cost and benefits of interventions
- Production of health care is subject to finite resources, government intervenes the allocation of health care
- CEA informs policy makers to prioritise interventions that provide the best value of money
- NICE: CEA and provides recommendations on whether interventions should be reimbursed by the NHS

Survival extrapolation

- Survival: interventions aim to extend patient's survival (e.g. OS and PFS for oncology interventions)
- Survival data is not enough for CEA
- Effectiveness is measured in a lifetime horizon $\rightarrow$ estimation of lifetime survival $\rightarrow$ extrapolation!
- Conventional methods: assume the trend in hazard observed from short-term trials will continue in the long term

Treatment effect waning

- Immuno-oncology therapies: deep and durable response
- Treatment effect can wane slowly for several years after treatment discontinuation or disease progression
- Treatment effect changes beyond the trial
  $\rightarrow$ not reasonable to assume short-term trend in hazard will continue in the long term
  $\rightarrow$ biased estimate of lifetime survival
  $\rightarrow$ possibly wrong cost-effectiveness analysis!

Treatment effect waning

- No NICE TSD has provided guidance on how to model treatment effect waning
- Current solutions: proportional hazard models
  1. Set HR to 1 at some specific time point
  Limitation: abrupt change in hazard is not plausible
  2. Let HR gradually converge to 1
  Limitation: untestable assumption

TA	Waning assumption accepted by the committee
TA737	Gradual waning of hazard from year 5 to year 7
TA770	Equal hazard after 5 years
TA692	Equal hazard after 3 years
TA683	Gradual waning of hazard from year 2 to year 5
TA661	Equal hazard after 5 years
TA650	Equal hazard after 7 years
TA531	Equal hazard after 3 to 5 years

Blending hazard method

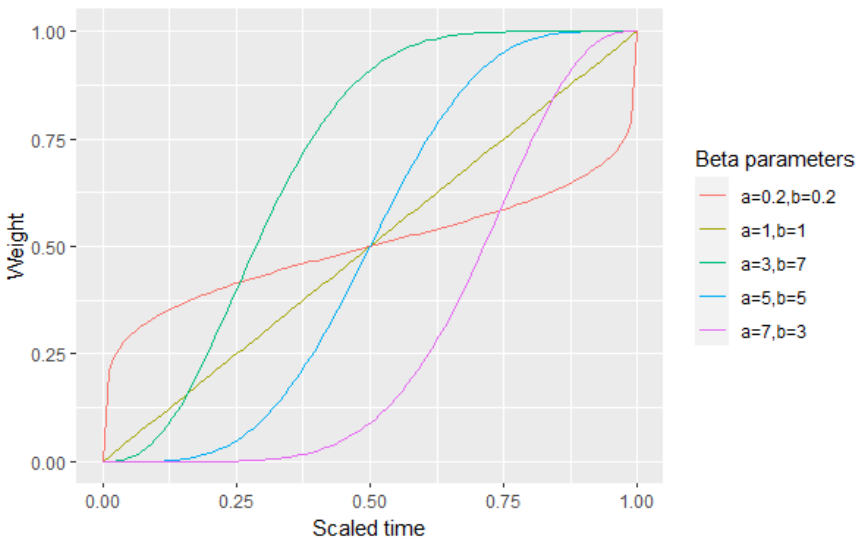
- Identify external data: represent long-term hazard when there is no treatment effect (HR=1, equal hazard)
- Model internal data from short-term trial for both arms
- Model external data
- For each arm, blend fitted internal hazard and fitted external hazard into a single hazard via a time-varying weight function

$$h_{blend}(t|\boldsymbol{\theta}) = [1 - \pi(t|t_1, t_2, a, b)] \times h_{int}(t|\theta_{int}) + \pi(t|t_1, t_2, a, b) \times h_{ext}(t|\theta_{ext})$$

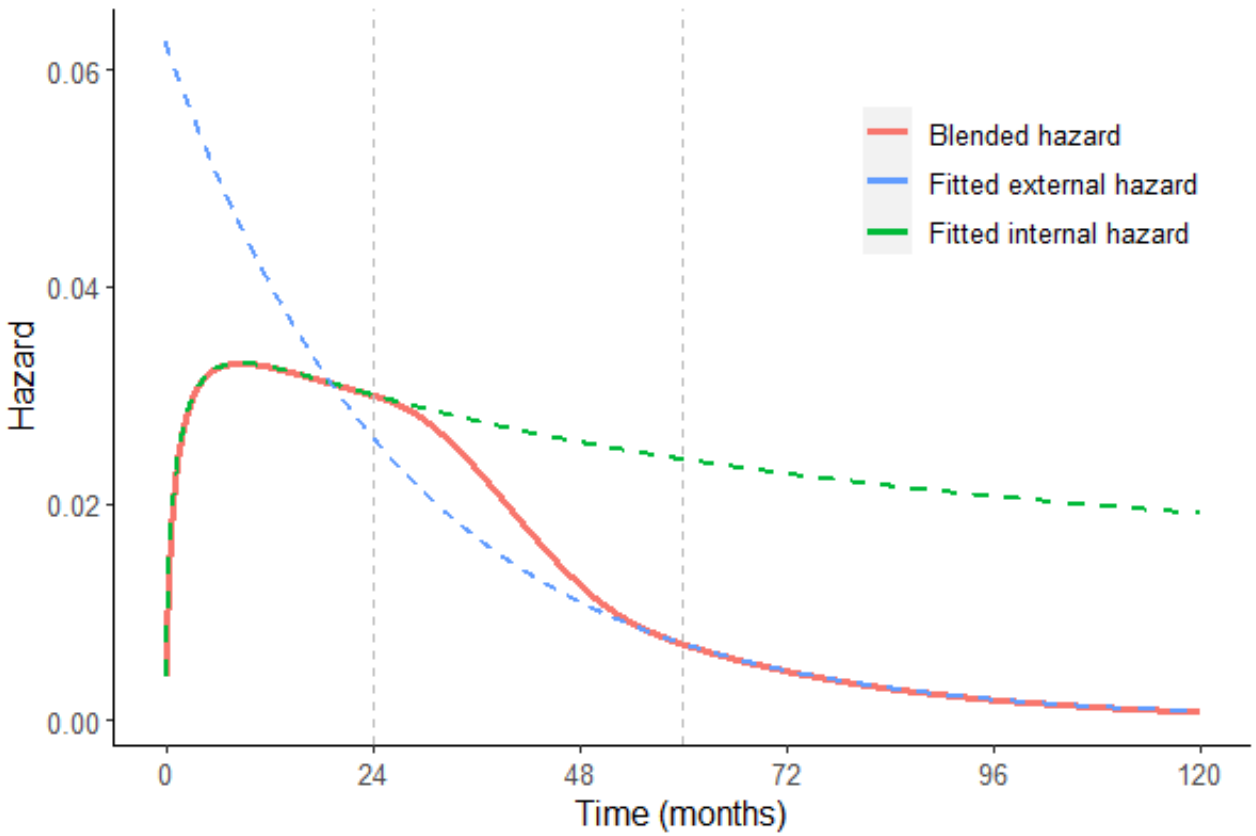
where $\boldsymbol{\theta} = (\theta_{int}, \theta_{ext}, t_1, t_2, a, b)$

Weight function

- $$\pi(t|t_1, t_2, a, b) = \begin{cases} 0 \quad \text{for } 0 \leq t < t_1 \\ \mathrm{F}_{\mathrm{Beta}}\left(\frac{t-t_1}{t_2-t_1} \,\middle|\, a, b\right) \quad \text{for } t_1 \leq t < t_2 \\ 1 \quad \text{for } t \geq t_2 \end{cases}$$
- t_1, t_2 are the start and the end of blending interval
  $\rightarrow$ control the time of blending
- a, b are Beta parameters
  $\rightarrow$ control the rate of blending



Graphical representation



4 key components

- Internal model $h_{int}(t|\theta_{int})$
  Top priority: provide good fit to short-term internal data
  Escalate flexibility gradually until reasonable good fit
- External model $h_{ext}(t|\theta_{ext})$
  Top priority: provide good fit to long-term external data
  Landmark model rebased at the median follow-up
- Blending interval (t_1, t_2): multiple scenarios
  t_1: start to not fully believe fitted internal hazard
  t_2: no treatment effect, HR=1 (3y-5y for IO treatments)
- Beta parameters a, b: multiple scenarios

Case study: TA366

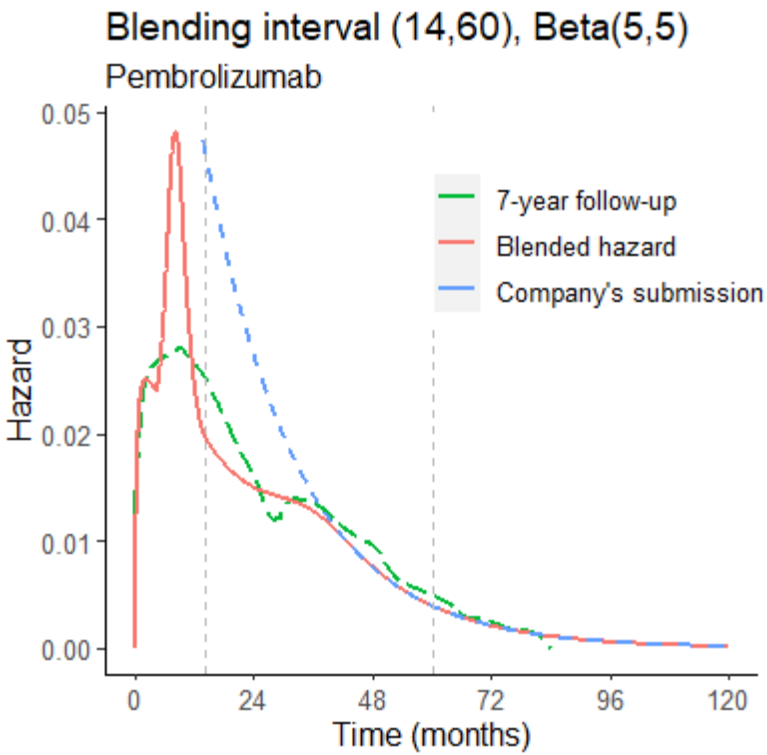
- Pembrolizumab for advanced melanoma not previously treated with ipilimumab
- 2-year stopping rule is proposed
- Main trial: KEYNOTE-006, pembrolizumab vs ipilumumab
- External data: Schadendorf treatment-naive data (a pooled study on ipilumumab for advanced melanoma)

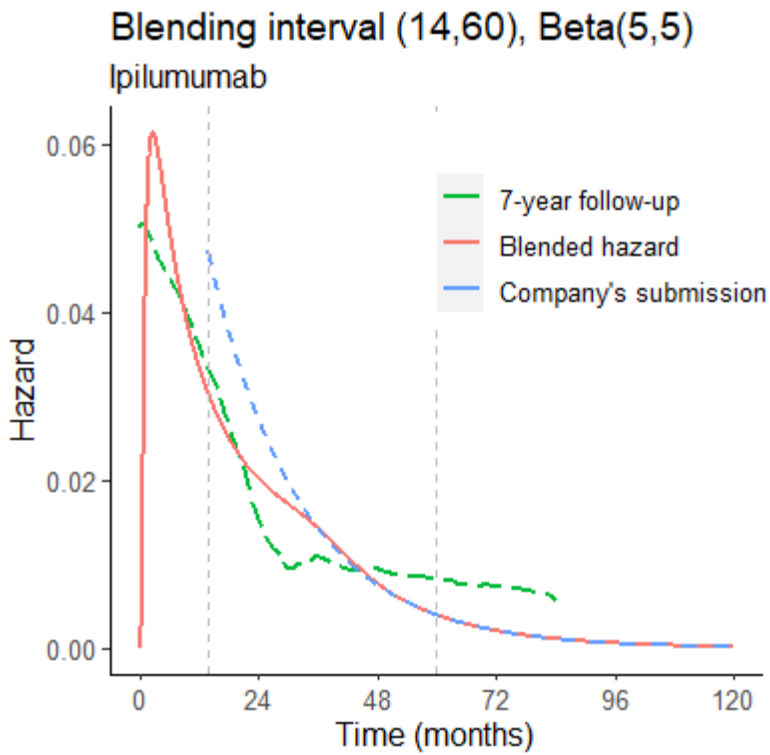
Case study: TA366

- Internal model:
  pembrolizumab - 3-knot spline normal model
  ipilumumab - Generalised Gamma
- External model:
  landmark Gompertz model rebased at median follow-up of the internal KEYNOTE-006 trial (14 mo)
- Blending interval:
  t_1: 14 mo (median follow-up), 24 mo (stopping rule)
  t_2: 36 mo (3 years), 60 mo (5 years)
  4 scenarios - (14,36), (14,60), (24,36), (24,60)
- Beta parameters:
  4 scenarios - (0.2,0.2), (5,5), (3,7), (7,3)
- 16 scenarios of weight function. e.g.
  $\pi(t|t_1 = 14, t_2 = 60, a = 5, b = 5)$

Case study: TA366

Extrapolation is compared with:
(1) the updated 7-year follow-up data
(2) company's base case method





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