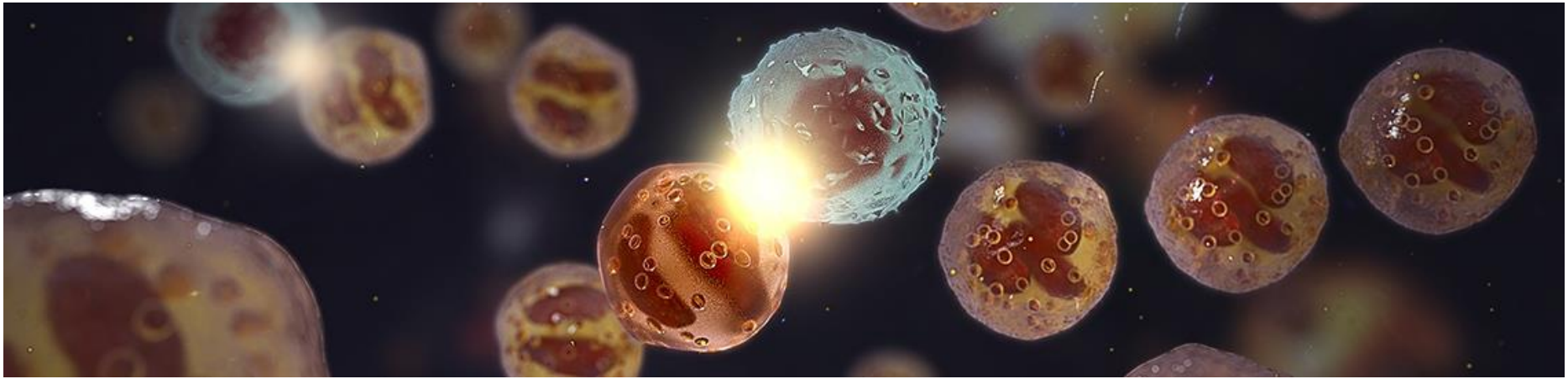
PSI Use of clinical opinion to support extrapolation of survival distributions



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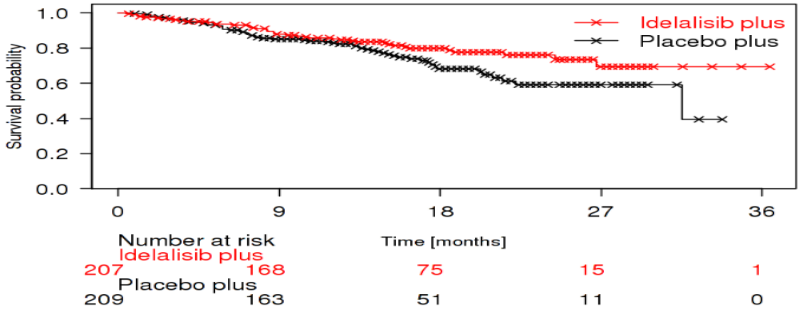
HTA: lifetime horizon evaluations

- In Health Technology Assessment (HTA) one is often interested in whether a new treatment should be reimbursed. If no reimbursement is granted, but EMA/FDA have approved the treatment, patients themselves could in theory buy the treatment, but there is usually no place in the patient's country where the treatment can be bought as the originator usually decides not to sell in the country

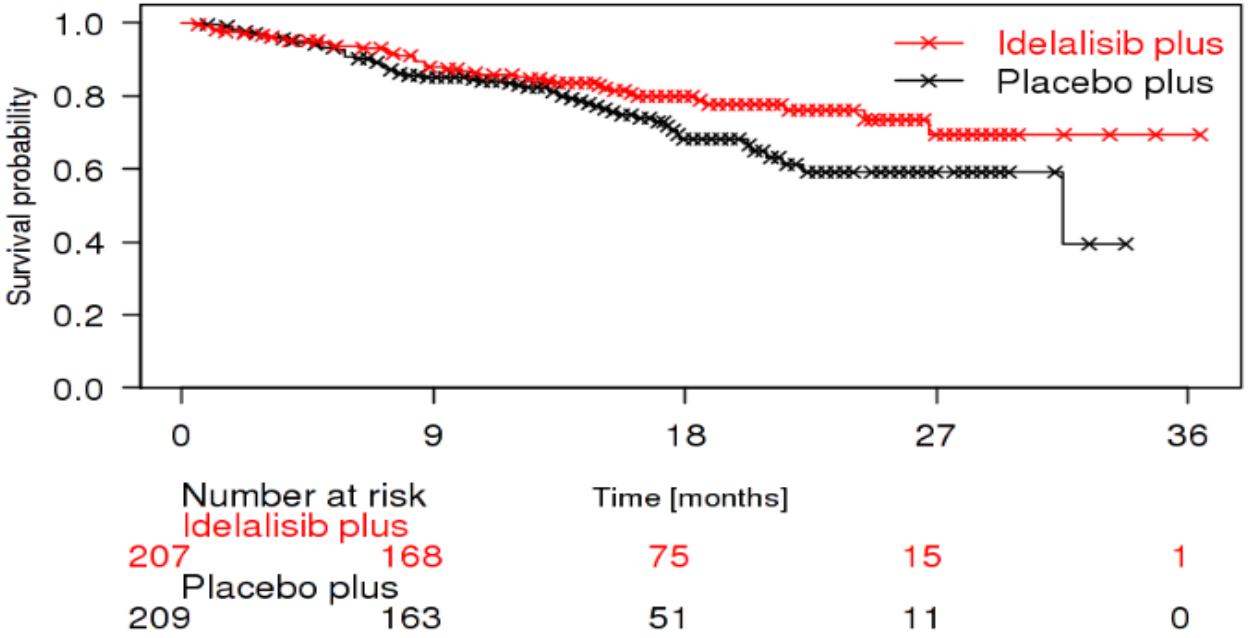
- Some countries like Germany are clinically driven when evaluating new treatments for reimbursement
- Some other countries like UK, Canada, Australia, evaluate the additional costs needed per additional life year in full quality of life, called the ICER (Incremental Cost Effectiveness Ratio)

Treatments influencing survival

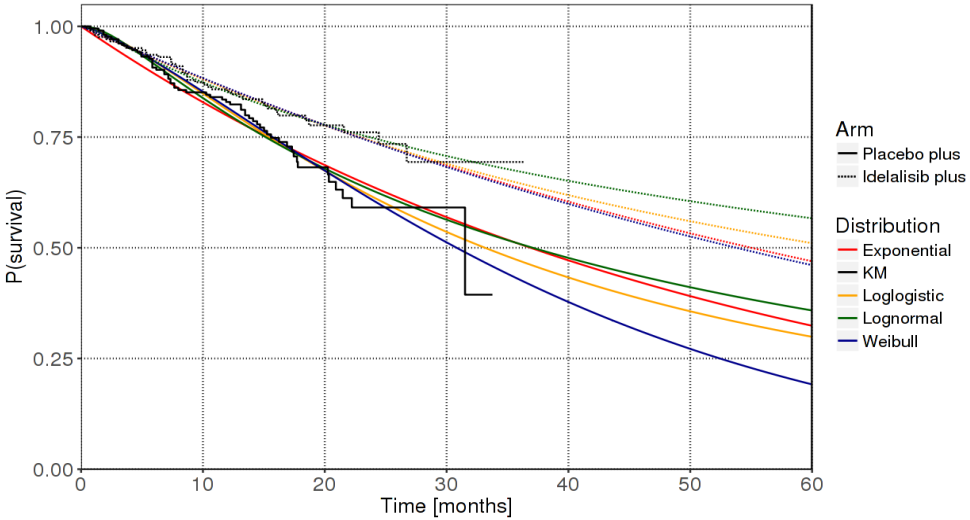


- For treatments influencing survival, the percentage patients alive at end of trial is usually different per treatment arm
- This means that cost and quality of life also differ across treatment arms for the post-trial period
- As such, UK, Canada, Australia and other countries in which cost-effectiveness is evaluated usually require extrapolation of trial-findings to longer time horizons, and probably to life time horizon.
- For these extrapolations, standard distributions are defined, being the Weibull, loglogistic, lognormal, exponential, Gompertz and generalized gamma

An example: Zelenetz et al (2017) Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, double-blind, placebo-controlled trial



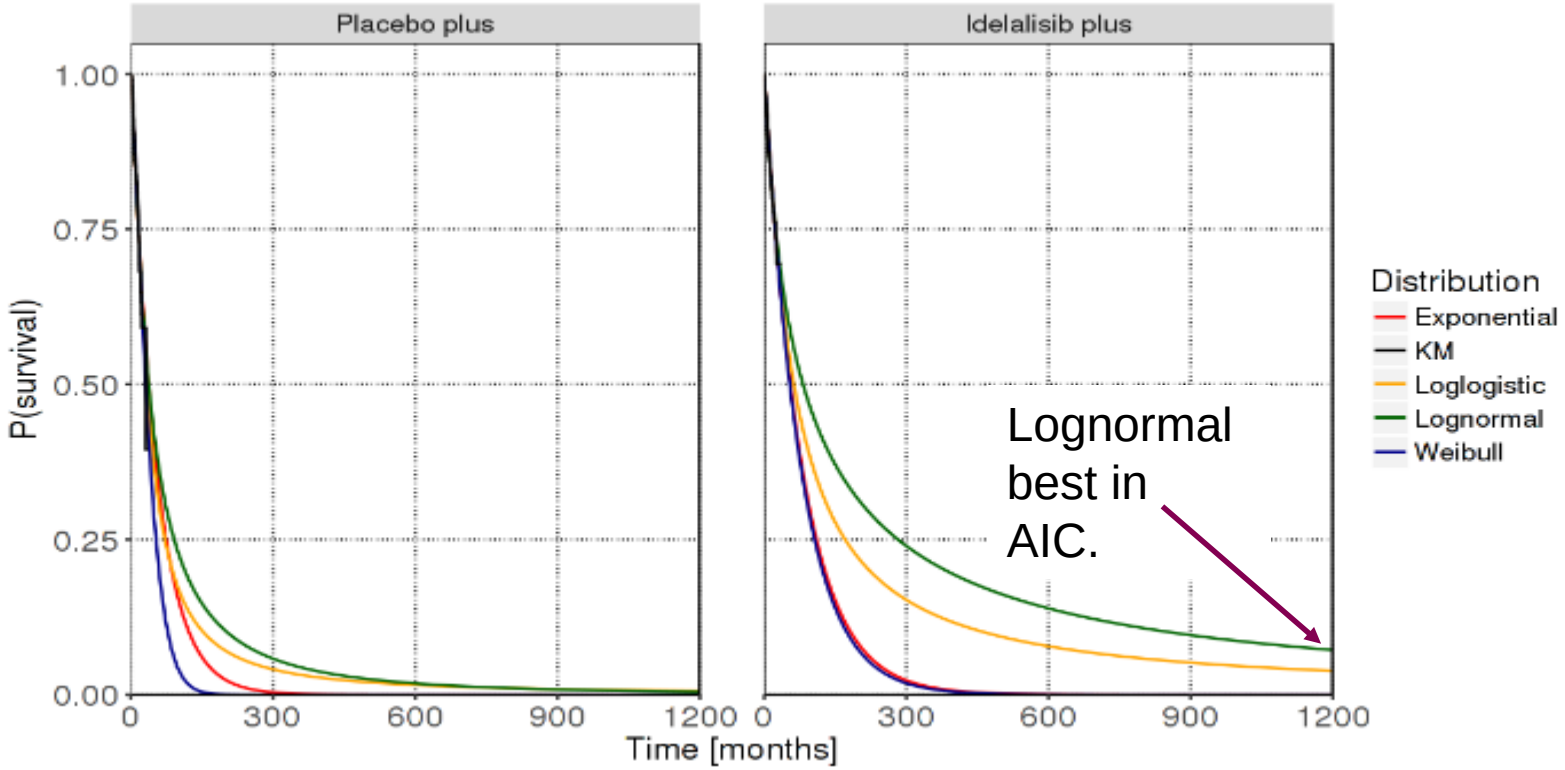
Fit to Kaplan Meier of lognormal, loglogistic, Weibull and exponential



Model	AIC	BIC
Lognormal	1031.33	1044.68
Loglogistic	1031.40	1044.75
Weibull	1031.79	1045.14
Exponential	1032.45	1039.13

- Lognormal has lowest AIC
- Lognormal and Weibull differ less than 0.5 point in AIC and BIC, not clearly distinguishing distributions for trial period

But: Difference in long term extrapolation



Difference in long term extrapolation

	Idelalisib		Placebo	
	5 years	10 years	5 years	10 years
Weibull	46%	21%	19%	2%
Exponential	47%	22%	32%	11%
Lognormal	57%	42%	36%	19%
Loglogistic	51%	33%	30%	14%

2% very low;
10-15% seen as more reasonable given other distributions

42% for lognormal at 10 years time frame is about double the percentages for Weibull and Exponential
15-30% seen as more realistic for Idelalisib

Note: Usually more knowledge about comparator than about active treatment, resulting in narrower intervals for comparator

Average (disease) 50 years survival estimates

	Exponential	Lognormal	Loglogistic	Weibull
Idelalisib	6.6	15.3	11.6	6.4
Placebo	4.5	6.7	5.6	3.1
Difference Idelalisib – Placebo	2.1	8.6	6.0	3.3

The difference in restricted 50 years mean survival of 8.6 for lognormal is more than four times the difference in average survival of 2.1 for exponential

Well, between brackets

- HTA agents may ask to discount life years and costs
- In the economic models, all cause mortality is usually build in, adjusting somewhat for too large tails
- Longer life is associated with higher quality adjusted life years, but also with larger costs, so total implications unknown

- We applied natural survival from UK lifetables, resulting in an adjusted difference in lognormal 50 years survival of 3 .6(vs 8.6) and exponential 50 years survival of 1.7 (vs 2.1)
- However, even after adjustment, we see that lognormal results in more than double difference in restricted mean survival

Jackson et al (Medical Decision Making 2017): Elicitation of expected survival

- *Eliciting expected survival $S(t|\alpha, \lambda) = \exp(-\lambda t^{\alpha})$ could provide a distribution for λt^{α}, but extra assumptions would be needed to obtain separate priors for λ and α. To our (Jackson et al) knowledge, there has been no investigation of this.*

Proposed approach step 1: Collect information to set x years expectations

- External data can be collected based on
  - RWE
    - May also consider treatments from same-drug-class
  - Historical trials
    - Consider phase II trials for investigational drug
    - Consider RCTs and long-term follow up from look-a-like products (about me-too) from the same class
    - Do the same for comparator
- Have an advisory board meeting and address expectations for e.g. 5 years and 10 years follow-up, in which one may present all relevant information, whether or not the information will be used

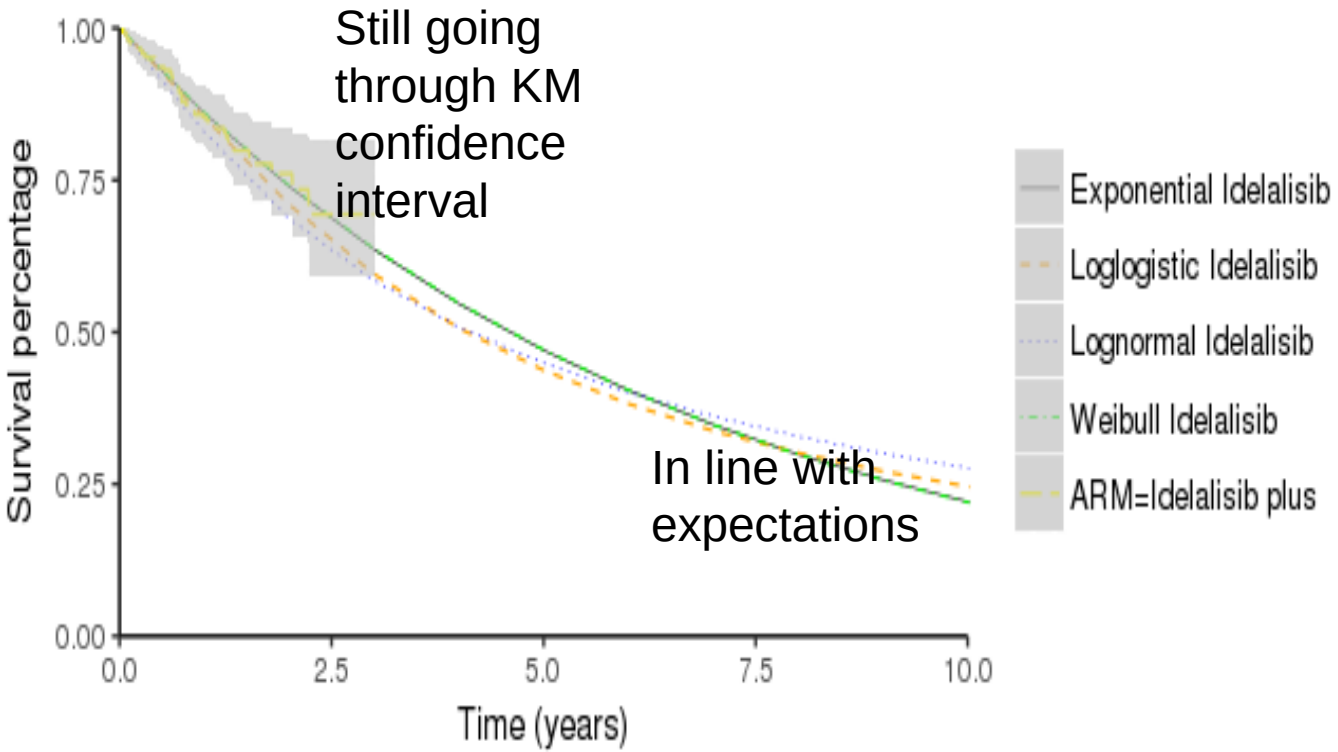
Proposed approach step 2: Bayesian analyses
Using some algebra to define prior distributions

- Suppose the information from previous slide results in a 10 years survival range from S_1 to S_2
- Suppose the range is seen as 95% ”confidence interval”
- Assume Weibull expression $\exp(-\lambda t^{\alpha})$ from the paper of Chris Jackson et al
- Take an arbitrary α
- The range S_1 to S_2 means for λ the following lower and upper bound given α
  - Upper bound: $\lambda_{S1} = -\log(S_1)/10^{\alpha}$
  - Lower bound: $\lambda_{S2} = -\log(S_2)/10^{\alpha}$
- Hence, sampling $\log(\lambda)$ from a normal distribution with boundaries of the 95% credibility interval $\log(\lambda_{S1})$ and $\log(\lambda_{S2})$ result in an a priori distribution for which the 10 years 95% “confidence interval” is equal to the interval from S_1 to S_2 given α
- By first sampling α and then sampling λ given α, we end up in having a prior distribution for the joint distribution, for which the information around S_1 to S_2 holds

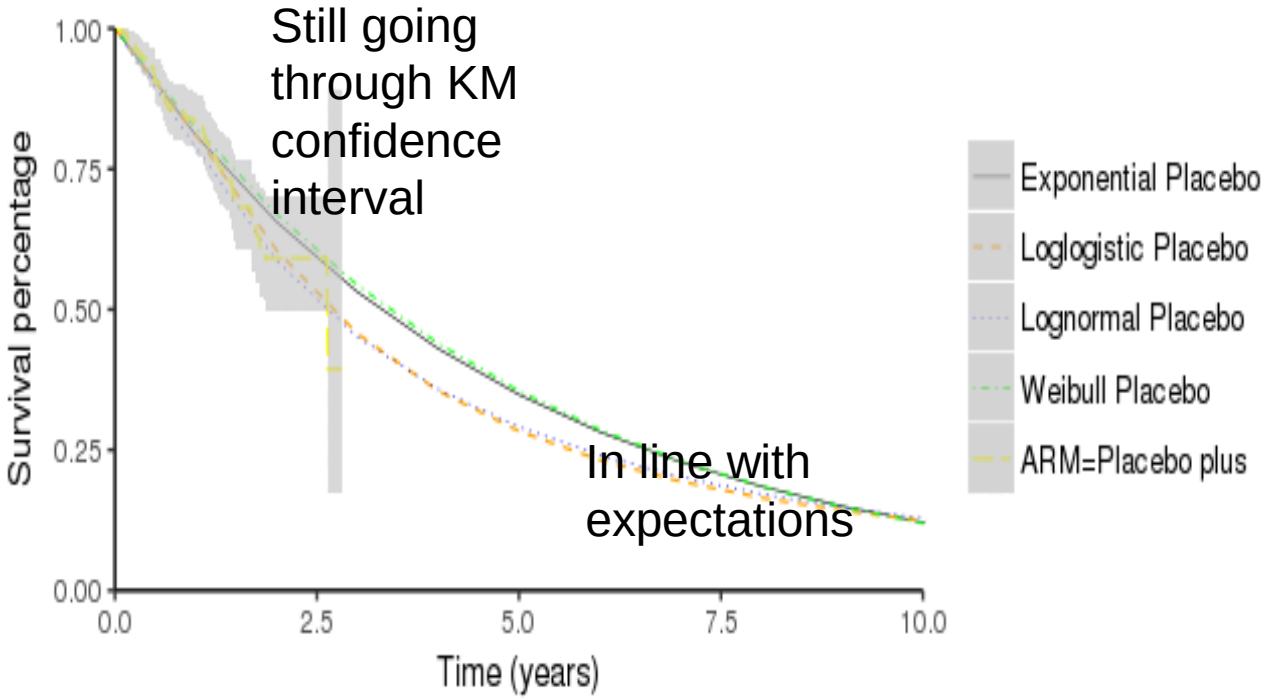
Proposed approach step 2: Bayesian analyses

- For lognormal, loglogistic and Gompertz distribution, the same holds
- The main concept is to limit the scale in its distribution conditional on first having sampled the shape
- FYI: we used an uninformative distribution for the shape here but could use informative priors based on external data as well

Results idelalisib



Results placebo



Difference in estimated 50 years restricted surival

- Without adjustment for all-cause mortality
  - Lognormal from 8.6 to 4.5
  - Exponential from 2.1 to 1.9
  - Before: 4.1 times larger, after 2.4

- With adjustment for all-cause mortality
  - Lognormal from 3.6 to 2.3
  - Exponential from 1.7 to 1.4
  - Before 2.1 times larger, after 1.6 times larger
    Still, 30% difference between adjusting and not adjusting, where ICER is usually close to willingness to pay value

Some (important) notes

- A few considerations:
  - By having equal shapes for both treatment arms, one generates the situation of constant Hazard Ratios/acceleration factor
  - By using the shapes from external data, power is increased
  - However, if we don’t believe in the shapes from external data, the a priori distribution can be chosen to be informative, using the point estimate from external data and the uncertainty, or even larger uncertainty
  - The prior for the scale can additonally be limited by considering external data

Take home message

- Although stated by Chris Jackson et al that no one has used this, it appeared after a long research period to be relatively straightforward to generate a priori distributions taking into account x years expectations

- We want to get this used for HTA, as one thing is that it is possible to use it, another thing is that it will be accepted by HTA

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