A Phase 3 trial with cure proportion, and some thoughts on NPH

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Who

Rufibach et al. (2020):



Meller et al. (2019):



Acute Myeloid Leukemia

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Rare malignant blood disease.

Most common leukemia, lowest survival rate in adults: **median survival $\leq$ 1y**.

Recurrent **life-threatening infections**.

Chemotherapy: modest benefit without cure.

Stem cell transplant:

- "Bridge-to-transplant": Goal of any therapy. Needs **complete response** (CR) to initial therapy.
- Only way to survive AML.

Mirros

MDM2 **I**dasanutlin in **R**elapsed **R**efractory AML for **OS**.

- **Population**: R/R AML.
- **Comparison**: **Idasanutlin** + cytarabine vs. placebo + cytarabine.
- **Phase III, 2:1 randomized, double-blind, placebo-controlled** clinical trial.
- Primary endpoint: **overall survival**.
- Planned recruitment: 374 patients.

`https://clinicaltrials.gov/ct2/show/NCT02545283`

How to plan RCT when some patients may be cured?

Cure proportion model

See e.g. Sun et al. (2018).

Let

- S_i^*, f_i^*: survival and density functions of **uncured** patients.
- p_i: proportions of patients cured.

Survival and hazard function in each treatment arm ($t \geq 0$):

$$\begin{aligned} S_i(t) &= p_i + (1-p_i)S_i^*(t), \\ h_i(t) &= \frac{(1-p_i)f_i^*(t)}{p_i + (1-p_i)S_i^*(t)}. \end{aligned}$$

Ratio of hazard functions:

$$\theta(t) = h_2(t)/h_1(t) = \left(\frac{1-p_2}{1-p_1}\right)\frac{f_2^*(t)}{f_1^*(t)}\left(\frac{p_1 + (1-p_1)S_1^*(t)}{p_2 + (1-p_2)S_2^*(t)}\right).$$

Even if both S_i^* exponential $\Rightarrow$ $\theta(t)$ **depends on time** (if ≥ 1 p_i is > 0).

What if we simply ignored cure proportions?

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- Median OS 6m.
- Cure: 0.080.

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Targeted effect size treatment arm (for 85% power, H_1):

- Median OS 9m.
- Cure: 0.161.

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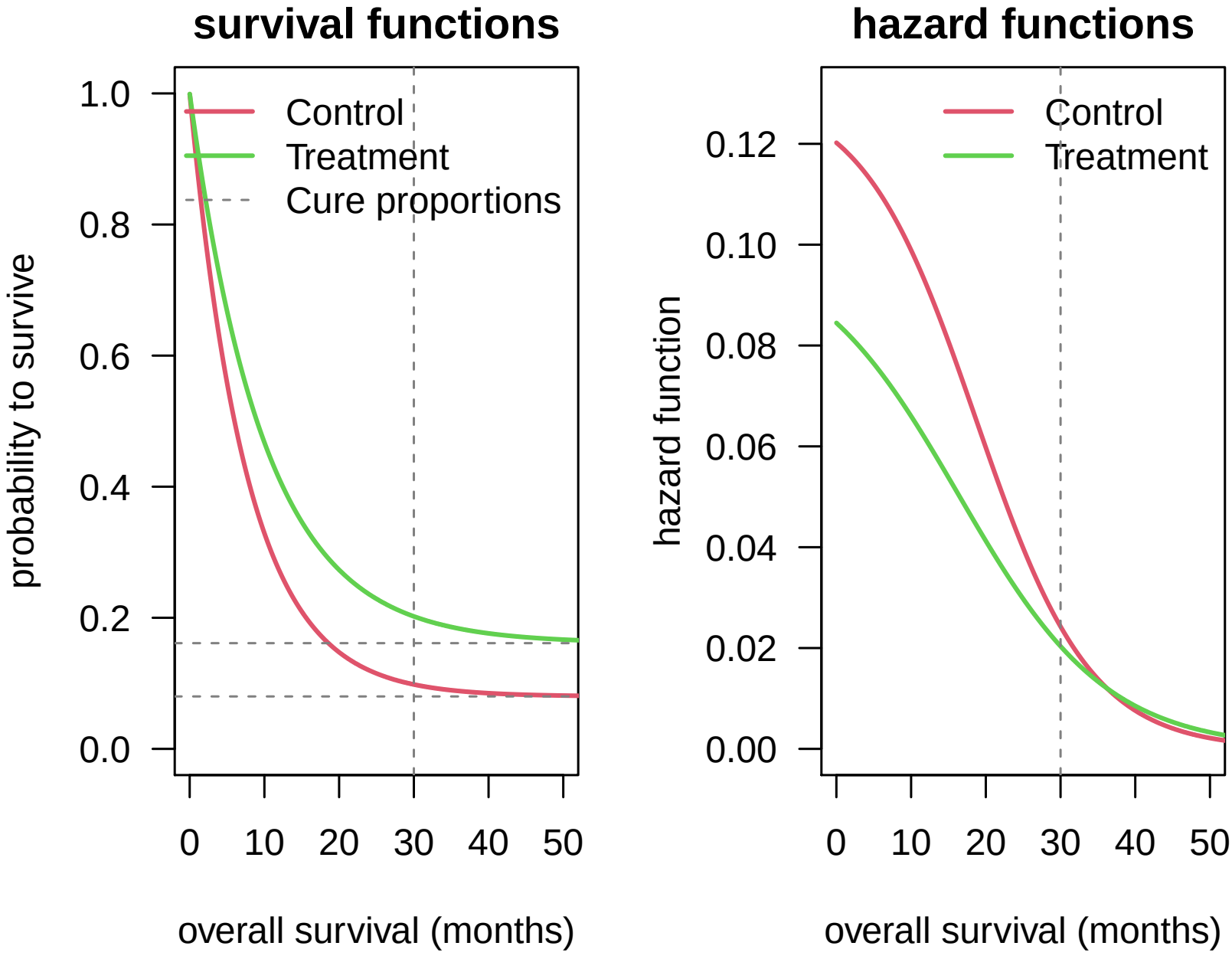

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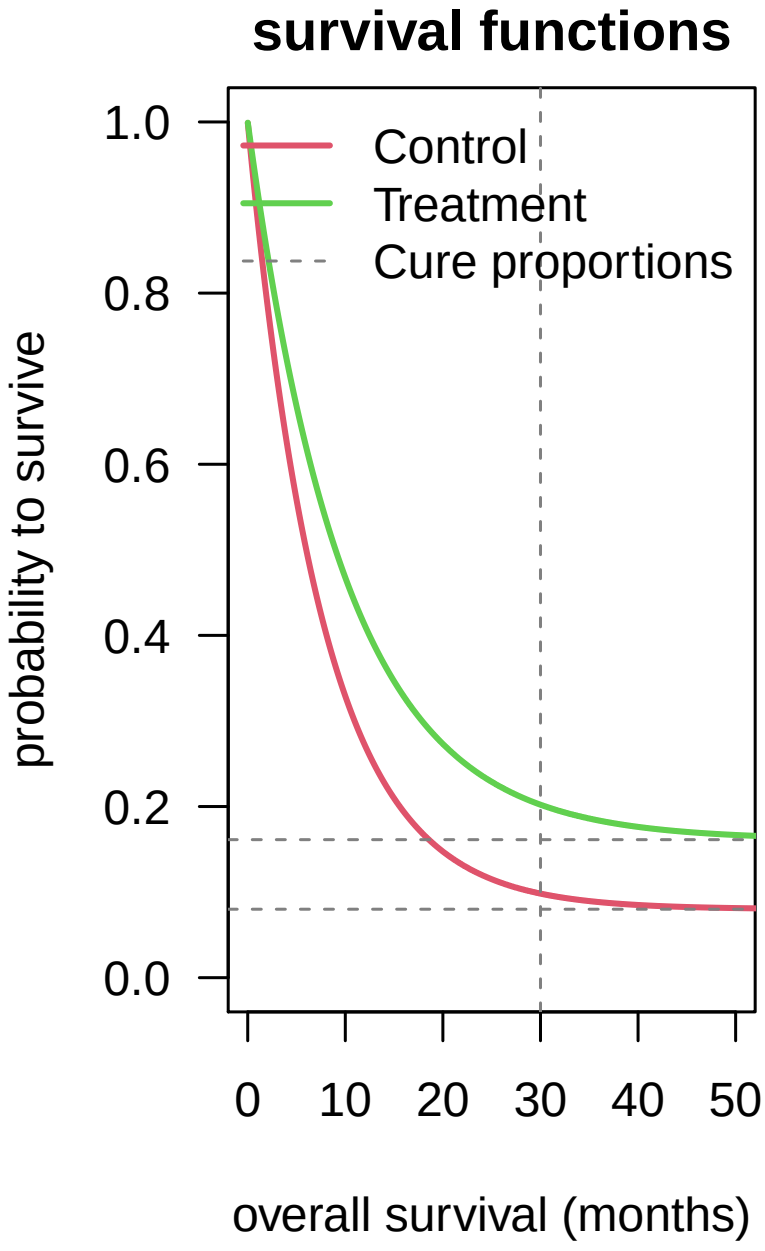

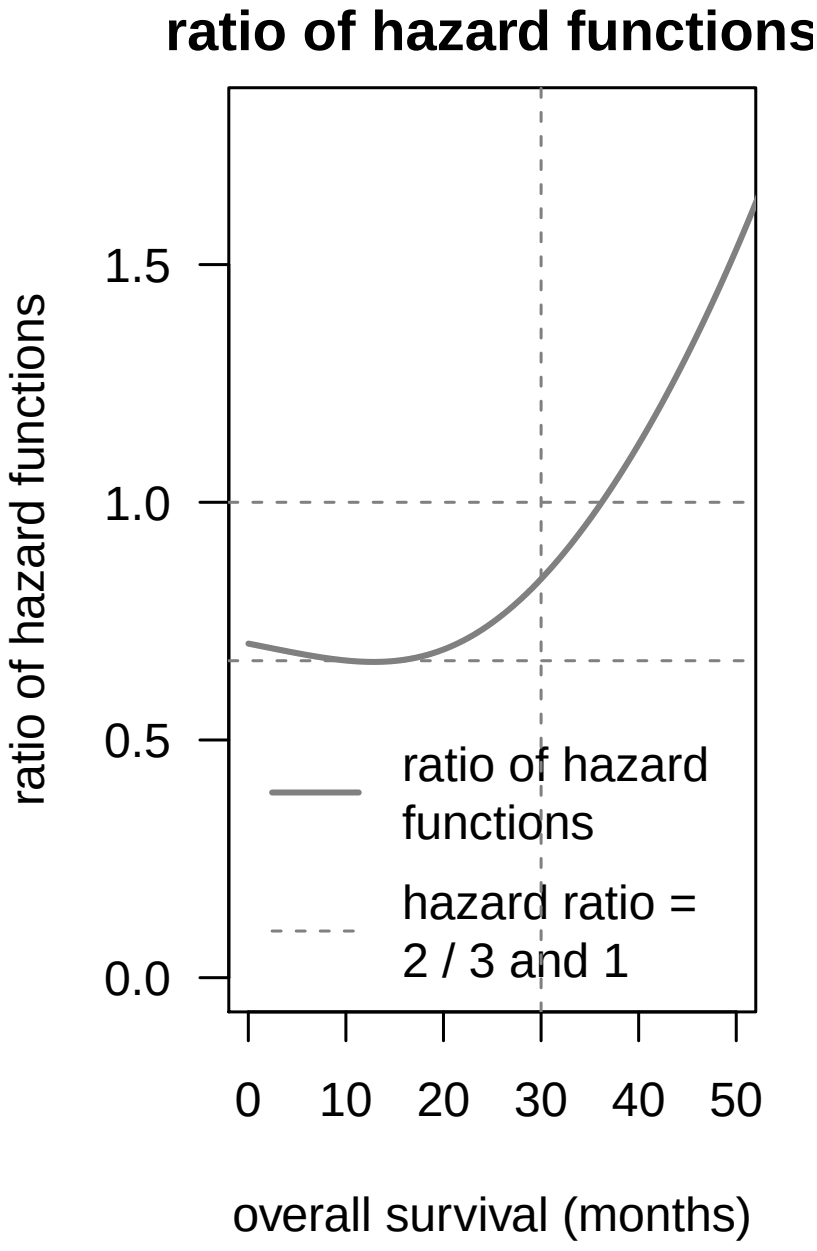

Cure proportion model – sample size

To find sample size:

- Compute necessary events d_0 using Schoenfeld's formula.
- **Simulate** from assumed S_i's, compute power for grid of $d = d_0, \ldots, d_1$.
- Choose d such that (unweighted) logrank test gives targeted power.

MIRROS: 2-sided $\alpha = 0.05$, $\beta = 0.15$, some accrual and drop-out assumption.

Assumption	$S_1^{-1}(0.5)$	$S_2^{-1}(0.5)$	p_1	p_2	d	power	time

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MIRROS with #events for (PH, no cure)	6.0	9.0	0.080	0.161	246	**0.810**	33.7

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Quantify effect using suitable **summary statistics**.

Cure proportion model – effect quantification

Cure proportion model – **no proportional hazards**. Unweighted logrank...

- ...**not most powerful** test, but loss modest (see above).
- ...**still valid** test, i.e. protects type I error.

How to quantify effect?

- **Kaplan-Meier** estimates provide entire information in data.
- Desire to summarize effect in one number.
- Hazard ratio from Cox regression and logrank test: if NPH, estimand and **power** depend on censoring distribution: accrual, dropout, follow-up pattern!

Rufibach (2019): extended discussion in **estimand** context.

Cure proportion model – estimation

Numerous parametric and nonparametric estimates of relevant quantities:
Cantor and Shuster (1992), Maller and Zhou (1992), Maller and Zhou (1996),
Tsodikov et al. (2003).

Obvious nonparametric estimate of cure proportion p, with $\widehat{S}$ Kaplan-Meier:

- $\widehat{S}(t_0)$ for some $t_0 > 0$.
- Maller and Zhou (1992): Kaplan-Meier evaluated at largest observed time, censored or event, consistently estimates p_0 under "sufficient follow-up" condition Tsodikov et al. (2003).
- Finite sample: likely not use latest observed time to evaluate the Kaplan-Meier estimate at. Rather **trade-off bias to reduce variability** of estimate.
- Choose milestone t_0 where clinically, cure seems very plausible.

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- Logrank test.
- Hazard ratio.
- Survival probabilities at milestones 6m, 12m, ...
- (Notorious) median OS.

What was NOT planned in MIRROS?

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Rerun of simulations with observed recruitment $\Rightarrow$ potential power impact.

Outcome of MIRROS

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Relative effect vs. control not big enough.

Immunotherapy:

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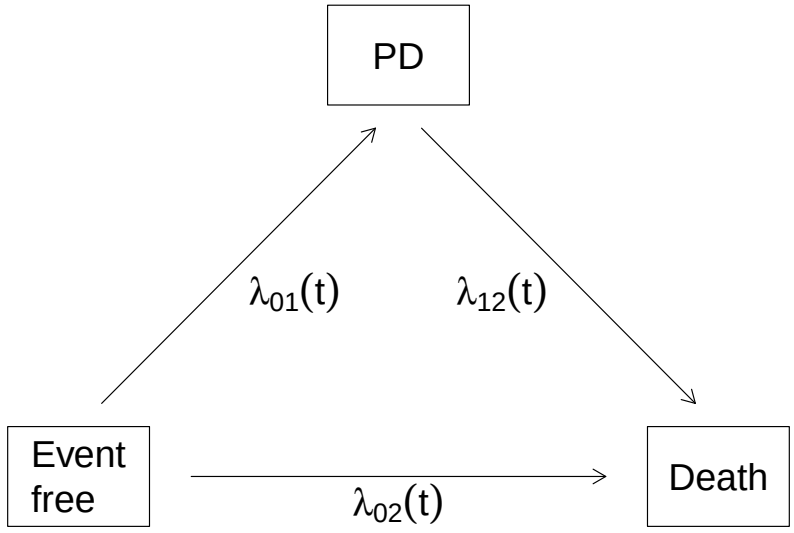
How to quantify effect?

Multistate model for PFS and OS



Standard **illness-death model without recovery**:

- Process $X(t) \in \{0, 1, 2\}, t \geq 0$ models the state occupied at time t.
- All patients in state 0 at time 0: $P(X(0) = 0) = 1$.
- PFS: waiting time in initial state 0, $\mathrm{PFS} = \inf\{t : X(t) \neq 0\}$.
- OS: time until reaching state 2, $\mathrm{OS} = \inf\{t : X(t) = 2\}$.

Multistate model formulation

Transition probabilities:

- **Full description** of multistate model by only assuming existence of intensities α_{01}, α_{02} and α_{12}.
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Meller et al. (2019):

- Formulas for P_{lm}'s assuming **Weibull** transition hazards for time-inhomogeneous Markov and semi-Markov.
- **Marginal** distributions:

$$\begin{aligned} S_{PFS}(t) &= P(\mathrm{PFS} > t) = P_{00}(0,t), \\ S_{OS}(t) &= P(\mathrm{OS} > t) = P_{00}(0,t) + P_{01}(0,t). \end{aligned}$$

- **Joint** distribution:

$$\begin{aligned} P(\mathrm{PFS} \leq u, \mathrm{OS} \leq v) &= P(X(u) \in \{1,2\}, X(v) = 2) \\ &= P(X(v) = 2 | X(u) = 1) \cdot P_{01}(0,u) + P_{02}(0,u). \end{aligned}$$

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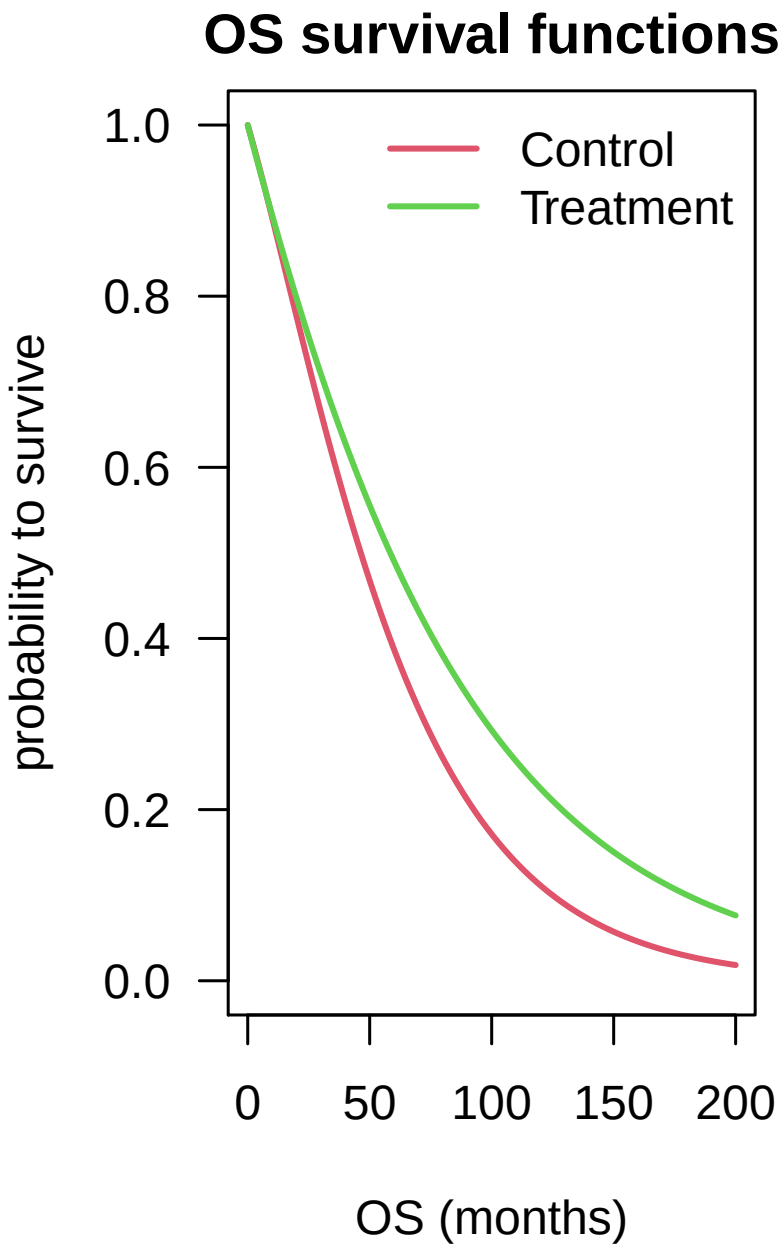
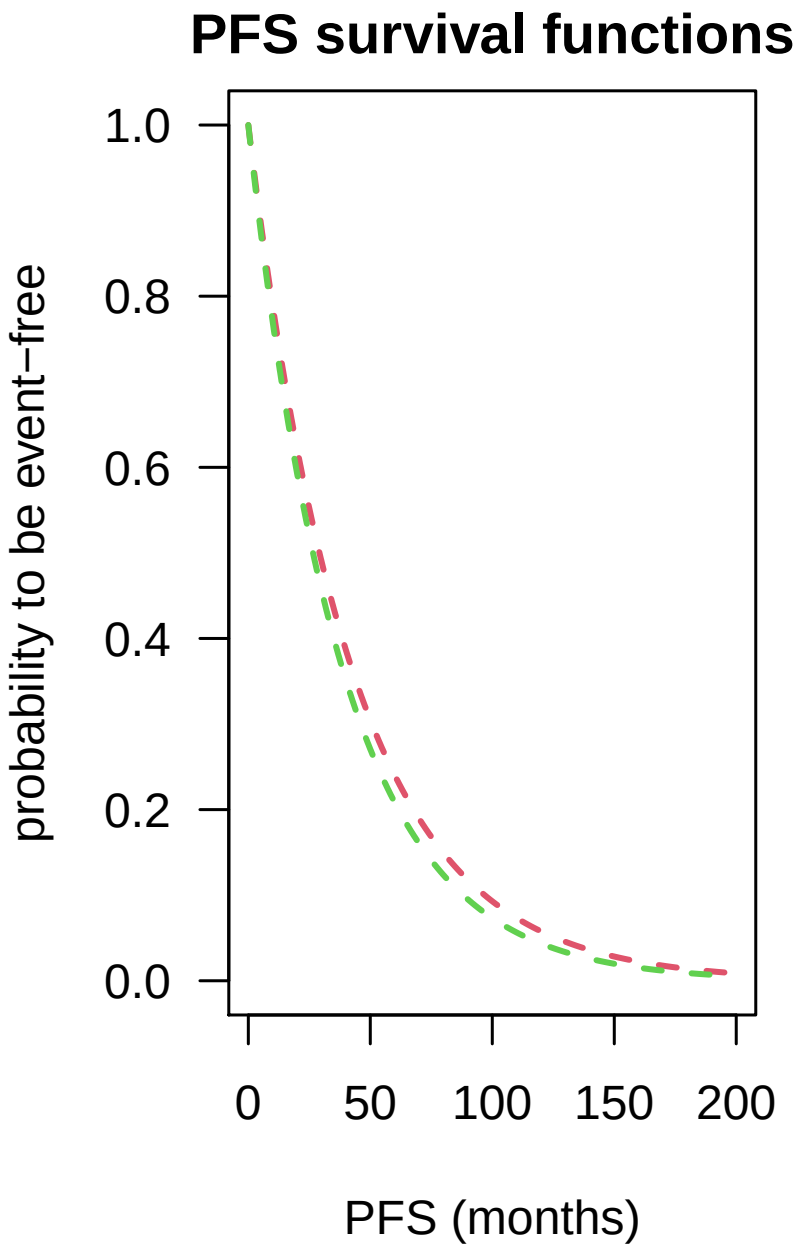
Proposal	focus	parameters to pre-specify	interpretation
Piecewise exponential hazard	estimation	interval limits, hazard ratio on each interval	✓
Subgroupwise hazard	estimation	prevalence of each sub-group, hazard ratio in each group	✓
Max-combo tests	testing	number of weight functions, one hazard ratio	?
RMST	both	upper limit, effect size	recalibration needed

(True) PFS and OS for hypothetical clinical trial





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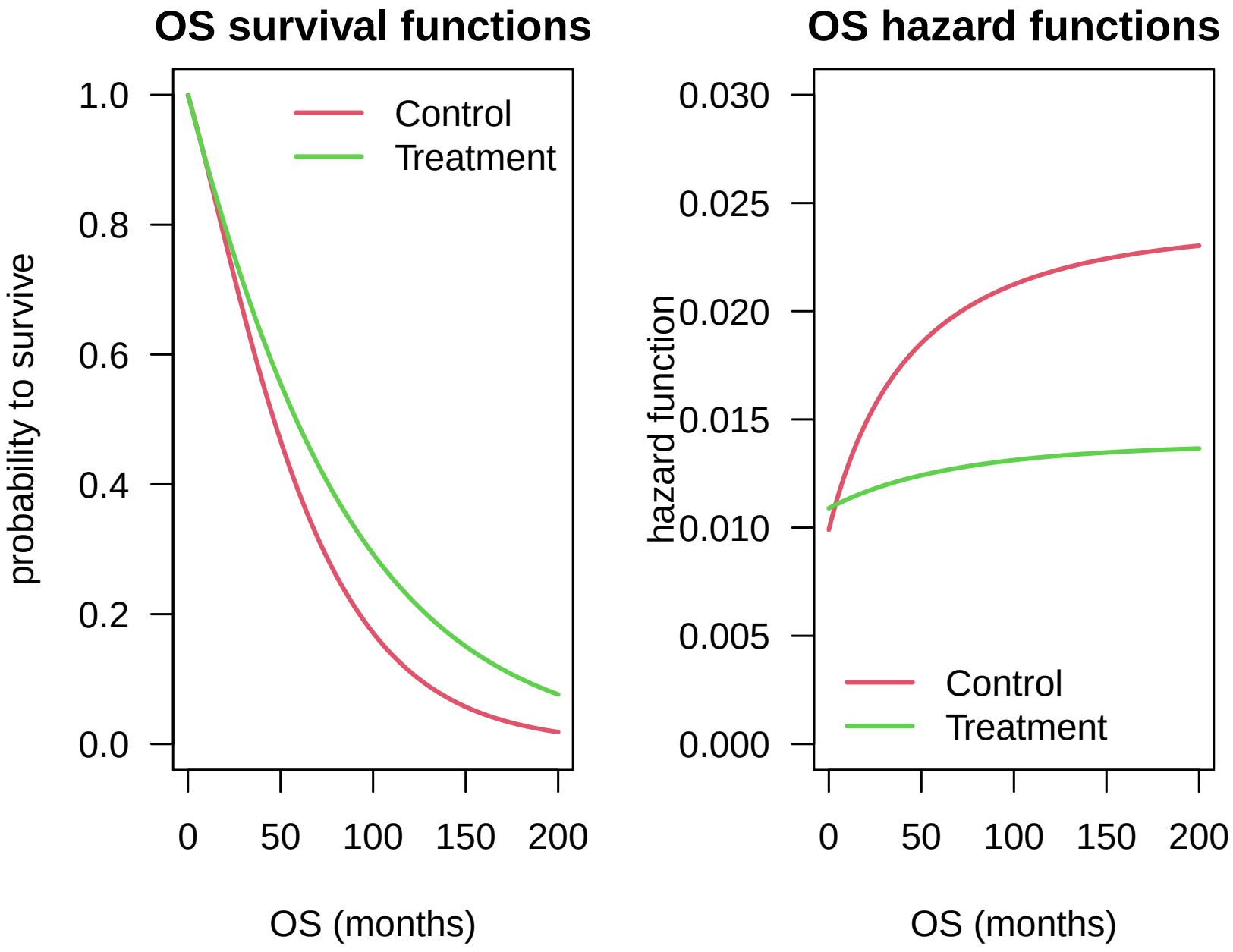

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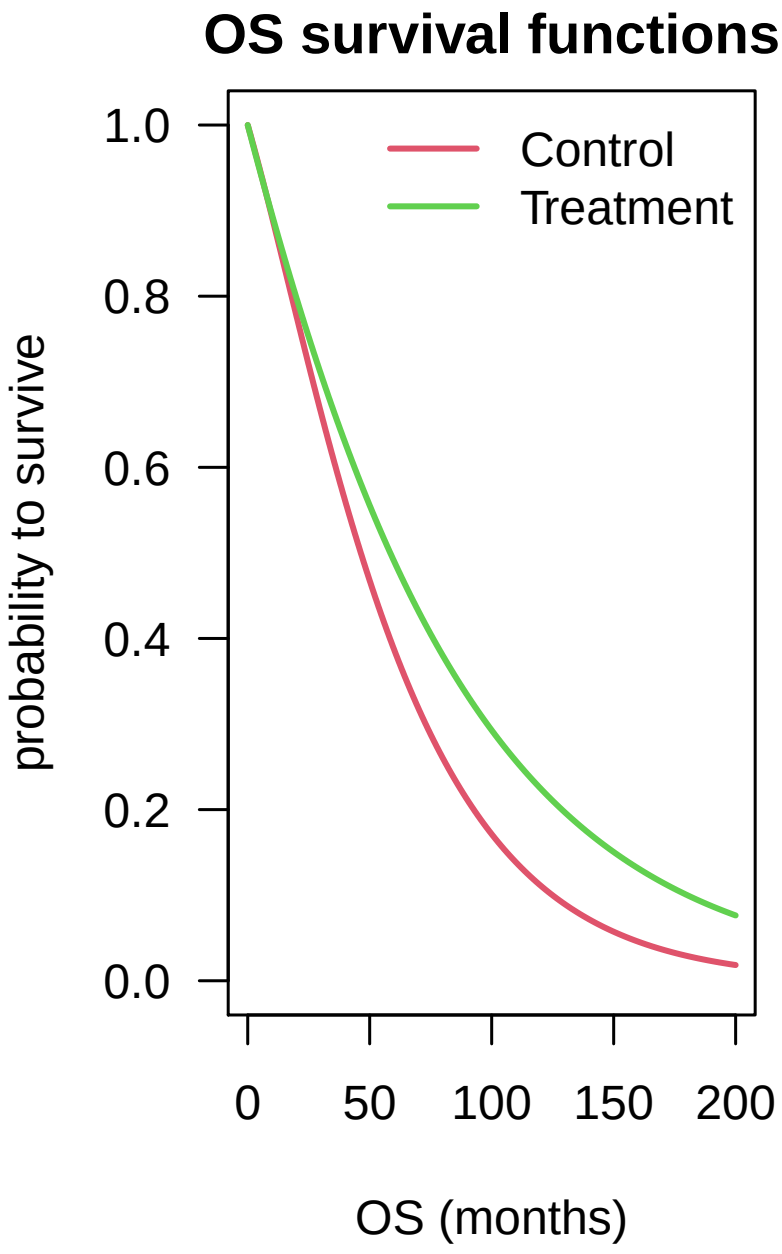

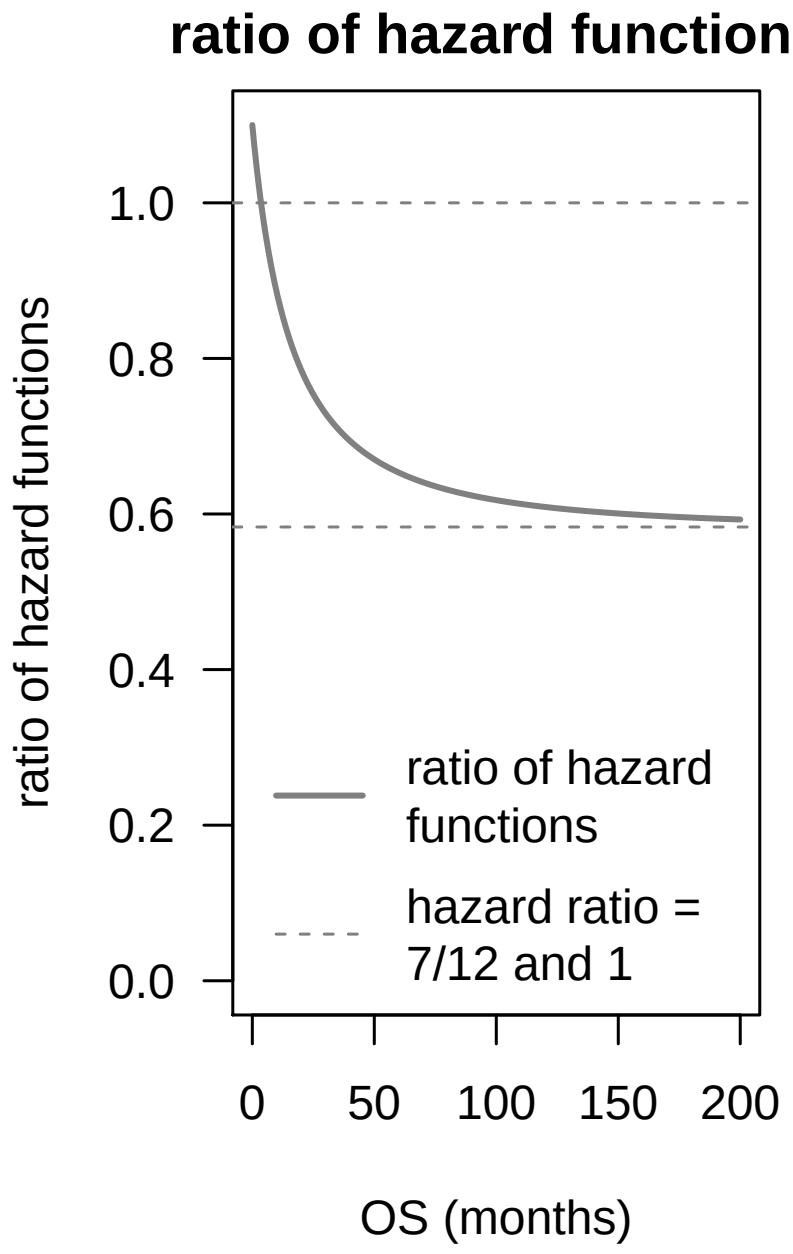

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$1 \to 2$	$\lambda_{12}^c = \log(2)/20$	$\lambda_{12}^t = \lambda_{12}^c \cdot \mathbf{0.4}$

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Power optimization $\Leftrightarrow$ pragmatism.

Resources

MIRROS trial design:

- Paper with Dominik Heinzmann and Annabelle Monnet: Rufibach et al. (2020).
- Reproduce simulations and **plan your own trial**: `https://github.com/numbersman77/integratePhase2.git`.

Multistate model for PFS and OS:

- Paper with Matthias Meller and Jan Beyersmann: Meller et al. (2019).

Thank you for your attention.

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Backup slides.

Standard of care

No standard regimen for relapsed or refractory (R/R) AML. Breems et al. (2005)

No new drug approved for treatment of AML in **over 50 years**! Bose et al. (2017)

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THIS is unmet medical need!

Idasanutlin

p53: Tumor suppressor, many mechanisms of anticancer function.

Mouse double minute 2 homolog (MDM2): Negative regulator of p53 tumor suppressor.

Idasanutlin: binds to MDM2 $\Rightarrow$ prevents p53 - MDM2 interaction $\Rightarrow$ (re-)activation of p53 $\Rightarrow$ **reinstalls anti-tumor capacity of p53**.

Clinical development plan for Idasanutlin

Need for acceleration:

- Very high unmet medical need in R/R AML.
- Early phase results with Idasanutlin encouraging.
- Competitive landscape and economic constraints: Lean program only way to receive internal approval for pivotal trial.
- Willingness to trade-off risk reduction from randomized P2 against increased speed.

Skip or integrate Phase 2?

Assume we have **successful P1**.

Purpose of futility interim: optimize **P(stopping @ interim | H_0)**.

Hunsberger et al. (2009):

- **Integrate** P2 into P3: futility interim based on **intermediate** endpoint.
- **Skip** P2: futility interim based on **P3 primary** endpoint.

If trial

- stops at futility interim: basically performed randomized P2.
- passes futility interim: P3 pivotal trial well on its way.

Key advantage of setup: Decision to proceed to full P3 part based on randomized comparison. Parmar et al. (2008)

Futility interim analysis

Mitigate risk if drug does not work (sufficiently).

Planned after **120** patients are recruited.

Why not use OS for interim decision?

- 53 (under H_0) and 46 deaths (under H_1) expected at interim. Substantial uncertainty.
- Cures have not happened yet at the interim.
- Confounding by early (mainly safety-related) deaths.

Bottom line: interim is **too early for OS** to be meaningful endpoint.

Intermediate endpoint

Complete response:

- Sufficiently associated with OS.
- CR **necessary** for good OS / cure: Patient needs CR to have chance for cure, via bridge-to-transplant.
- Odds ratio as effect measure.

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$$\textbf{False Positive} = \mathrm{P}(\text{continue @ interim} \mid H_0)$$

vs.

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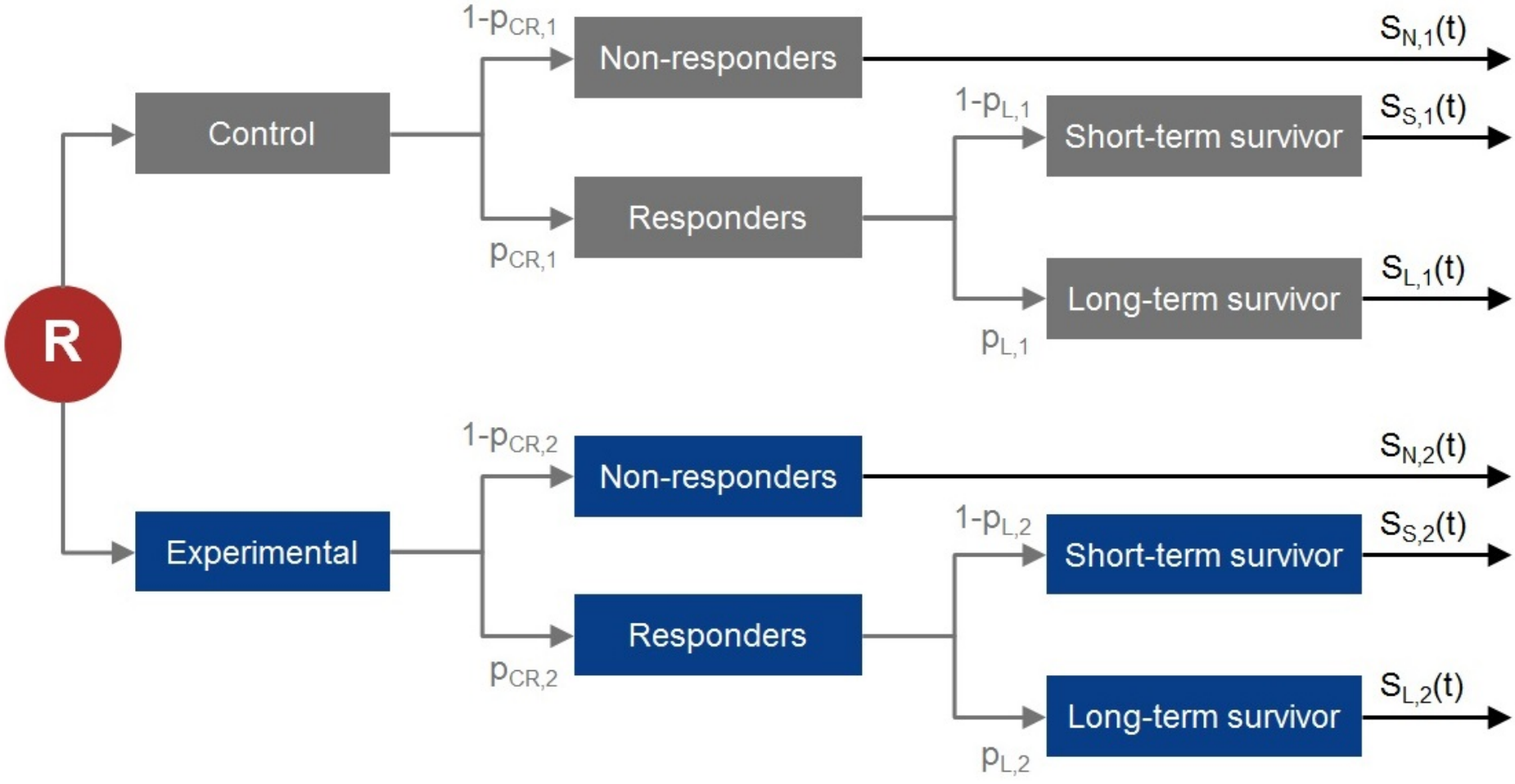
If futility based on OS $\Rightarrow$ conditional power.

If CR is intermediate endpoint: **mechanistic simulation model**.

Mechanistic simulation model



Mechanistic simulation model

Connects CR to OS.

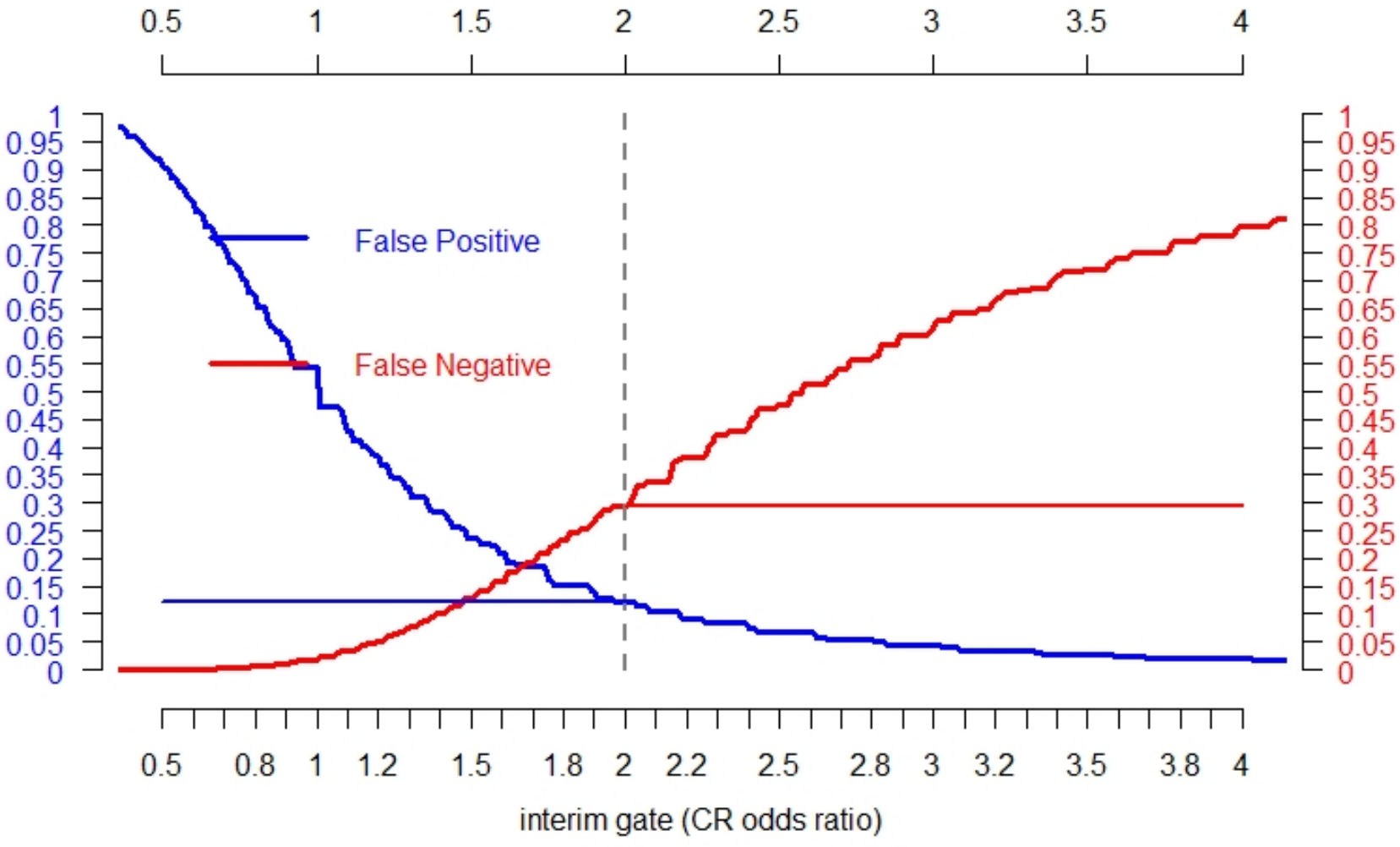
Need to inform all assumptions:

Quantity	Control arm	Treatment arm
Survival function of non-responders	$S_{N,1}$	$S_{N,2}$
Probability to have CR	$p_{CR,1}$	$p_{CR,2}$
Probability to be long-term responder | CR	$p_{L,1}$	$p_{L,2}$
Survival function of short-term responders	$S_{S,1}$	$S_{S,2}$
Survival function of long-term responders	$S_{L,1}$	$S_{L,2}$
#patients recruited per month	n_{1j}	n_{2j}
Months of recruitment	$j = 1, \ldots, N$	
Total #patients recruited	$n_1 = \sum_{j=1}^{N} n_{1j}$	$n_2 = \sum_{j=1}^{N} n_{2j}$
Drop-out rate per month	τ_1	τ_2

Align parameters such that **mechanistic simulation model can reproduce sample size**!

P(CR) control: 0.16. Assume OR = 2.5 to improve on this with treatment $\Rightarrow$
P(CR tmt) = 0.323. P(longterm survivor) = 0.5. This gives cure proportions.

Operating characteristics of various interim boundaries



False Positive = P(continue @ interim | no effect)
False Negative = P(stop @ interim | alternative used for powering)

Operating characteristics of various interim boundaries

Sweet spot: **odds ratio of 2**,

- False Positive = P(continue @ interim | no effect) $\approx$ 12%,
- False Negative = P(stop @ interim | alternative assumed for powering) $\approx$ 30%.

Interim decision:

- Based on independent data monitoring committee (iDMC) recommendation, i.e. sponsor **blinded**,
- **non-binding**,
- included safety criterion (molecule class toxicity) and criteria for early deaths $\Rightarrow$ OS component.

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Can easily get that from simulations.

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- Do we always compute the power loss when adding futility interims? Do we **increase number of events** to account for it?

Who cares anyway $\Rightarrow$ interim **passed**!

Implementation features

A (industry) clinical trial is **not a pre-specified static** undertaking!

- Not clear whether p53 mutant patients (≈15%) also benefit from Idasanutlin.
  - Still included, as evidence unclear and high unmet medical need.
  - But testing too late for randomization, i.e. could not stratify for p53 status.
  - Adds uncertainty to recruitment assumptions.
- Decision-makers sceptical about interim gate based on CR only. Additionally engineered EFS criterion (not discussed here).
- Evolvement of gating criteria:

Date	Milestone	OR CR $\geq$ 2.5	OR CR $\geq$ 2 + EFS HR $\leq$ 1	OS HR $\leq$ 0.9	OS HR $\leq$ 0.8
22.04.2014	CHMP meeting	x	x		
27.01.2015	FDA type C mtg	x	x		
08.04.2015	LSPC team proposal			x	
09.04.2015	LSPC decision				x
24.04.2015	CHMP BP	x	x		x
27.08.2015	LSCP decision	x	x		

Implementation features

A (industry) clinical trial is **not a pre-specified static** undertaking!

- Biomarker development: typically in Phase 2! Recommendation on biomarker development by iDMC.
- Seamless designs in general: sponsor does not get to see data for a **long time**. Unease for decision-makers.
- No accrual suspension for interim $\Rightarrow$ data cleaning and decision needs to come fast.

Health authority feedback

FDA:

- **Preferred randomized P2**.
- Challenged lack of stratification on p53 mutation status.
- Companion Diagnostic component with blinded P2 data $\Rightarrow$ not clear how to decide on development.
- **Challenged assumptions**, asked for additional sensitivity analyses.
- Concerns of early events driving interim analysis. OS not part of futility decision, but early tox deaths are.
- US sites only opened after passing the IA.

EMA:

- Agreed to accelerated development due to high unmet need.
- PH assumption discussed, support hazard ratio as appropriate effect measure.

Why two models?

We have two models:

- Cure proportion model to derive sample size,
- mechanistic simulation model to explore interim operating characteristics.

Why?

Reasons:

- Futility interim analysis has no implication on type I error $\Rightarrow$ independent of key design characteristic.
- Cure proportion model:
  - Simple,
  - depends on less assumptions than mechanistic model,
  - Robust model to plan sample size.
- Mechanistic simulation model:
  - Interim setup has potential to be changed before or while study is running. Prefer not to have these changes interfere with sample size.
  - Only used for (internal) decision-making via iDMC, no filing relevance $\Rightarrow$ can "afford" more modeling.

Advantages of multistate model

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Multistate = (most?) parsimonious model

Correlation coefficient

$$\mathrm{Corr}(\mathrm{PFS}, \mathrm{OS}) \quad = \quad \frac{\mathrm{Cov}(\mathrm{PFS}, \mathrm{OS})}{\sqrt{\mathrm{Var}(\mathrm{PFS})\,\mathrm{Var}(\mathrm{OS})}} \quad = \quad \frac{\mathbb{E}(\mathrm{PFS} \cdot \mathrm{OS}) - \mathbb{E}(\mathrm{PFS})\,\mathbb{E}(\mathrm{OS})}{\sqrt{\mathrm{Var}(\mathrm{PFS})\,\mathrm{Var}(\mathrm{OS})}}.$$

Mean, variance of PFS and OS: via survival functions.

$\mathbb{E}(\mathrm{PFS} \cdot \mathrm{OS})$: Use

$$P(\mathrm{PFS} \cdot \mathrm{OS} > t) \quad = \quad P(\mathrm{PFS} > \sqrt{t}) + \int_{(0,\sqrt{t}]} P_{11}(u, t/u; u) P(\mathrm{PFS} > u-) \alpha_{01}(u)\ \mathrm{d}u.$$

Proof: manipulations using law of total probability.

Estimation and inference for Markov models

Parametric:

- Plug parametric assumption in formulas for $P_{lm}(s,t)$, S_{PFS}, S_{OS}, $\mathrm{Corr}(\mathrm{PFS},\mathrm{OS})$.
- Estimate parameters using **Counting Process Likelihood**, Andersen et al. (1993). Product of patient-specific likelihood-contributions to each state transition.
- Inference via delta method or bootstrap (results comparable).

Nonparametric:

- Transition probabilities: Aalen-Johansen estimator, Aalen and Johansen (1978).
- Plug in estimates into formulas for $\mathrm{PFS}, \mathrm{OS}, \mathrm{Corr}(\mathrm{PFS},\mathrm{OS})$.
- Challenge: need to **extrapolate tail beyond where we have data**.
- Inference via bootstrap.

Estimation and inference for Markov models

LFTM in Fleischer et al. (2009) and Li and Zhang (2015):

- Group patients depending on their path from 0 to 1 or 2, or censored.
- Likelihood uses **assumption of independence** of TTP, OS_{orig}. Cannot tell from (even uncensored!) data! Aalen (1987): "artificial problem", as LFTM not needed, see also Beyersmann et al. (2012).

Weber and Titman (2019):

- Kendall's τ, based on multistate, nonparametric, and copula models.
- Use again LFTM for estimation.

Multistate model formulation

Transition probabilities:

- **Full description** of multistate model by only assuming existence of intensities α_{01}, α_{02} and α_{12}.
- Formulas, even for **non-Markov** case: Aalen et al. (2008).

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- Embed PFS and OS in multistate model framework,
- formulas for P_{lm}'s assuming **Weibull** transition hazards for time-inhomogeneous Markov and semi-Markov (explicit),
- inference via **counting process likelihood**,
- $P(\mathrm{PFS} \leq u, \mathrm{OS} \leq v)$ for X non-Markov (generic).

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Exemplary application: **Pearson correlation**.

Multistate model for PFS and OS

Marginal distributions:

$$\begin{aligned} S_{PFS}(t) &= P(\mathrm{PFS} > t) = P_{00}(0,t), \\ S_{OS}(t) &= P(\mathrm{OS} > t) = P_{00}(0,t) + P_{01}(0,t), \end{aligned}$$

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Joint distribution:

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X **inhomogeneous Markov**: $P(X(v) = 2 | X(u) = 1) = P_{12}(u,v)$ independent of progression time $t_1 \le u$.

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X **non-Markov**:

- Integrate $P_{12}(u,v;t_1)$ over conditional distribution of all possible progression times $t_1 \le u$.
- Formula tedious (see Meller et al. (2019)) $\Rightarrow$ **simulate** in applications.

Doing now what patients need next

R version and packages used to generate these slides:

R version: R version 4.0.5 (2021-03-31)

Base packages: stats / graphics / grDevices / utils / datasets / methods / base

Other packages: MASS / mstate / prodlim / reporttools / xtable / biostatKR / survival

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