MIRROS: Phase 3 trial with time-to-event endpoint, a cure proportion, and a futility interim analysis using response

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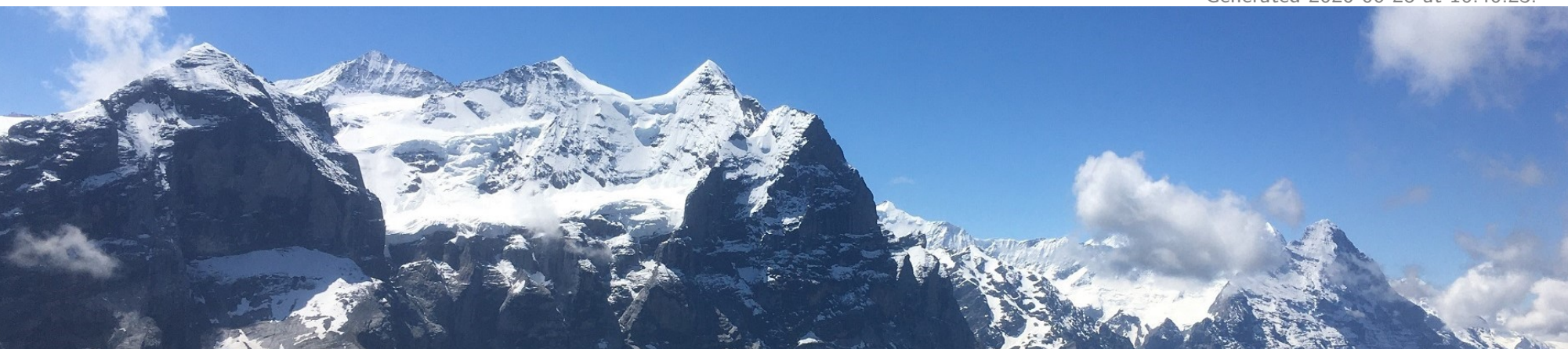


Agenda

1. Acute Myeloid Leukemia
2. Clinical development plan
3. Key questions of MIRROS
4. Implementation features
5. Health authority feedback
6. Conclusions

What MIRROS is NOT:

An adaptive trial.

A seamless phase 2/3 trial.

What MIRROS IS:

A phase 3 trial with a futility interim.

Acute Myeloid Leukemia

Acute Myeloid Leukemia

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.

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)

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

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)

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 (wild-type sample, + 66 mutant patients).

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

Key questions of MIRROS

Key questions of MIRROS

1. Primary endpoint OS. Sample size with **cure proportion** in both arms?
2. Base **interim** on OS or something else? If the latter, what?
3. How to compute **operating characteristics** of interim analysis?

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).

Cure proportion model – assumptions

What if we ignored cure proportions and simply computed necessary events d using Schoenfeld's formula?

- Study will (typically) be **underpowered**.
- Time to clinical cutoff will be **underestimated**.

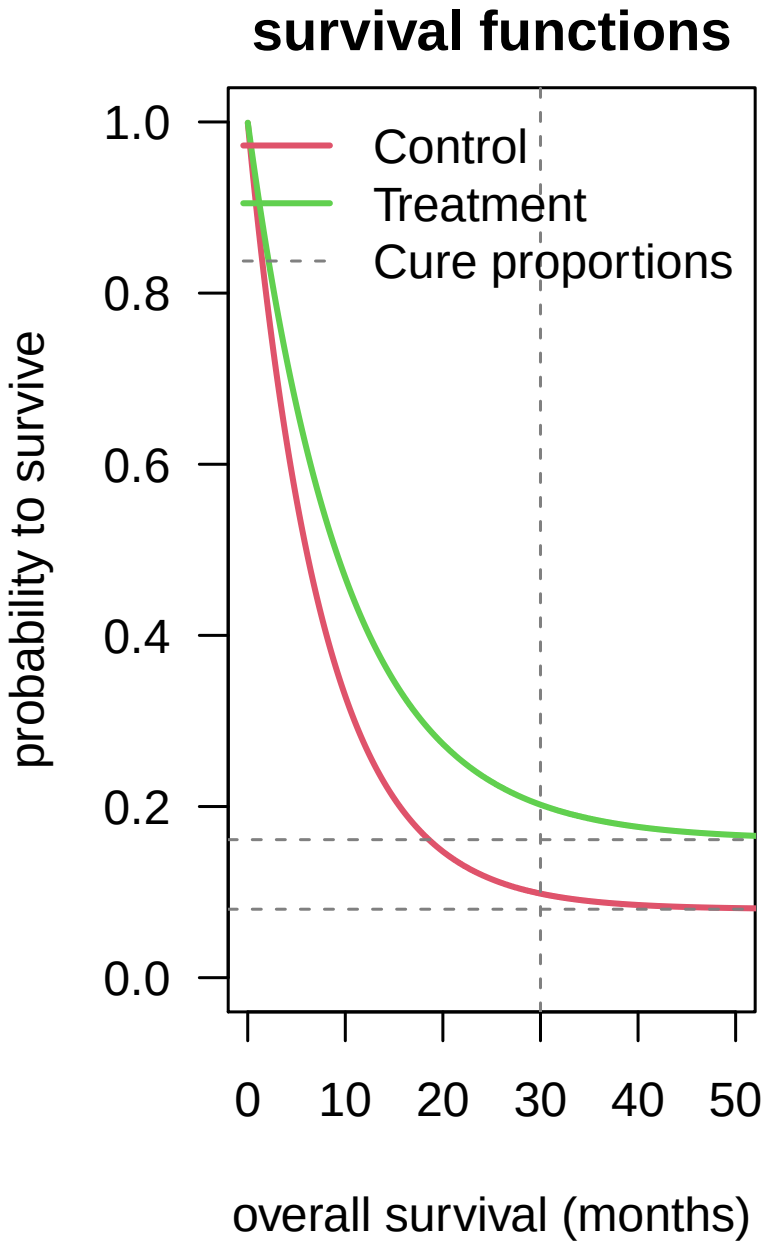
Control arm, based on **historical data**, H_0:

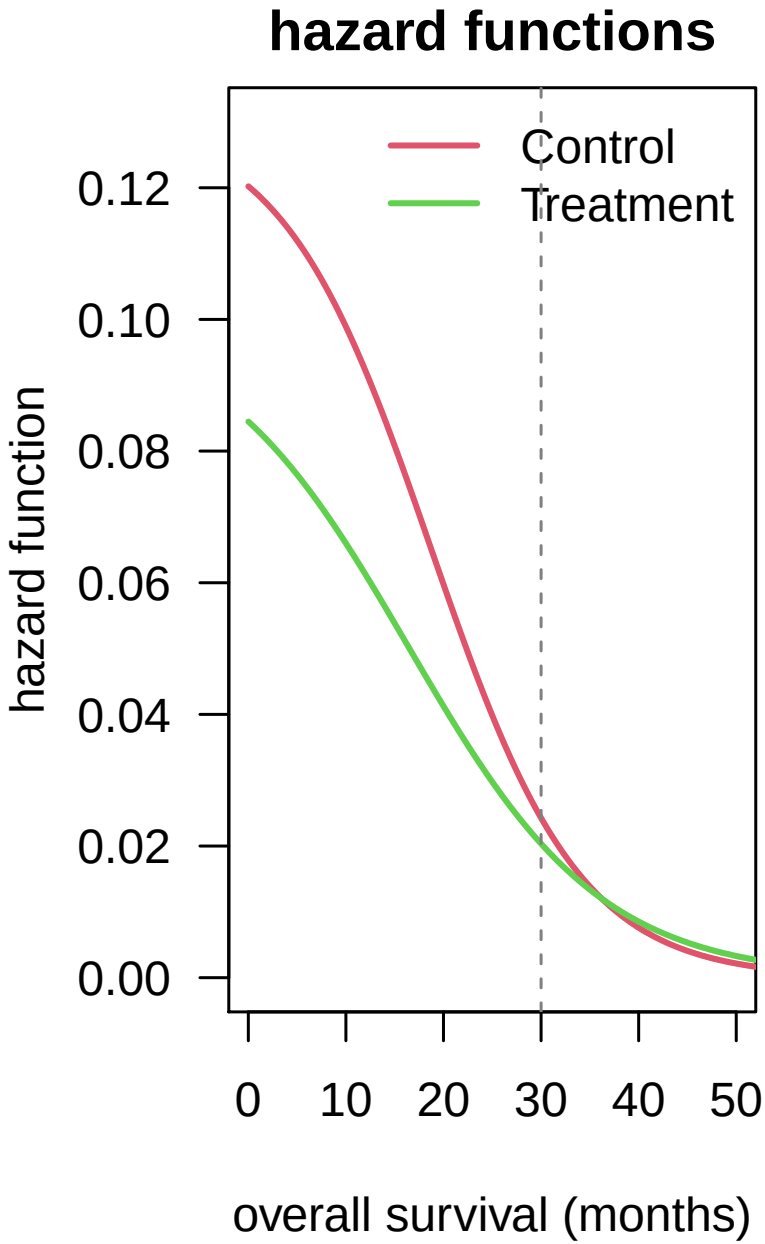
- Median OS 6m.
- Cure: 0.080.

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

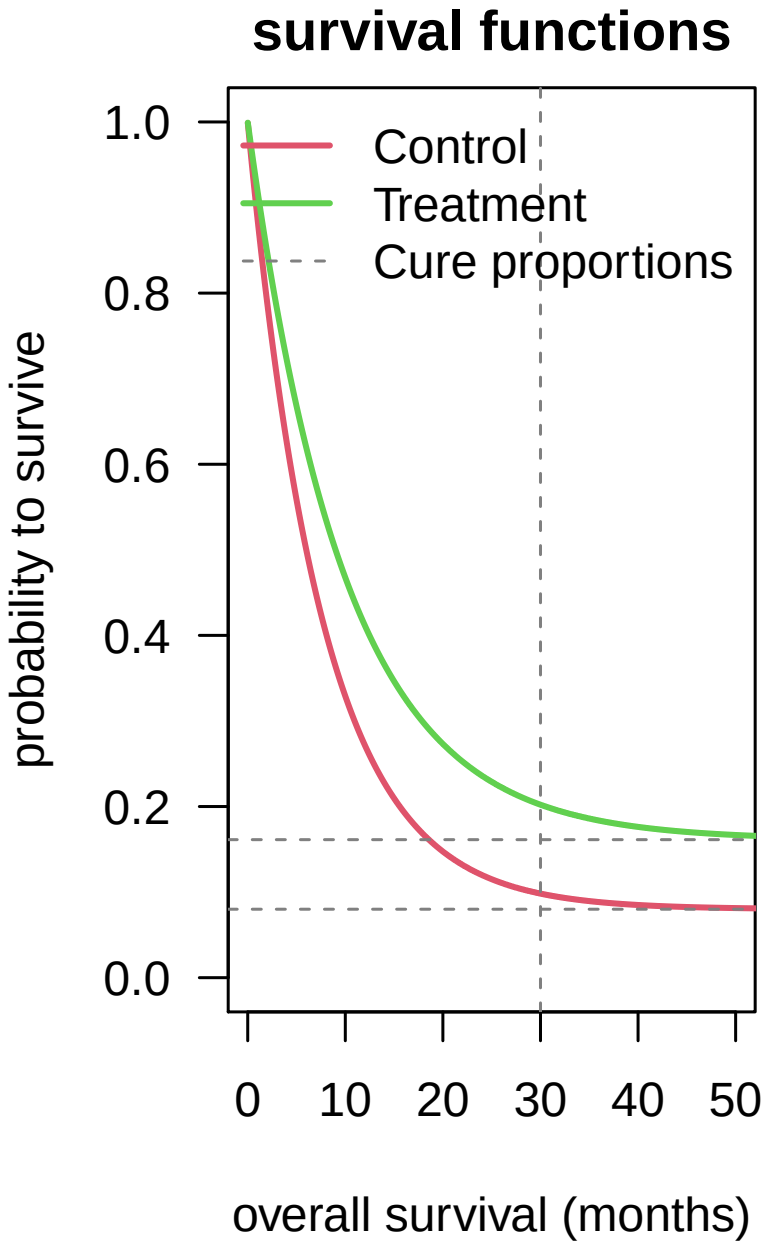
- Median OS 9m.
- Cure: 0.161 (see later for justification).

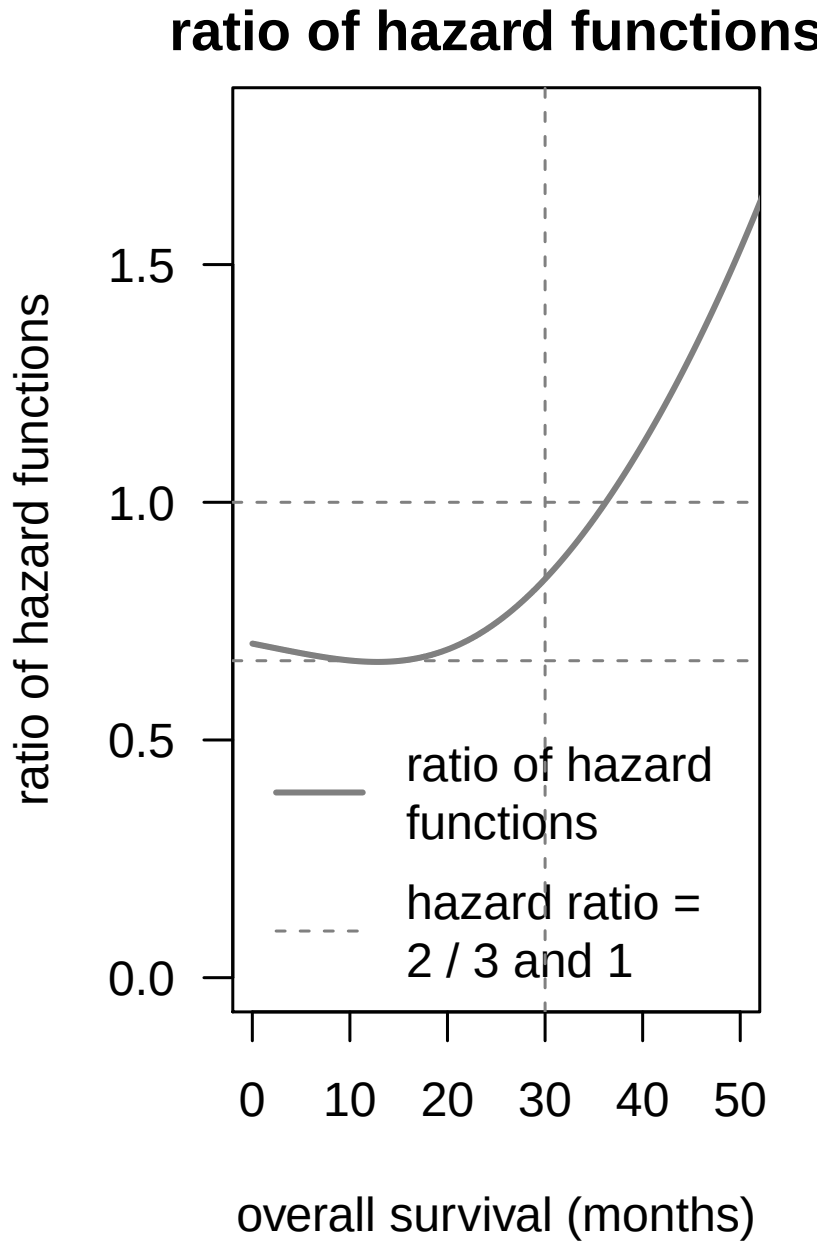
Cure proportion model – assumptions





Cure proportion model – assumptions





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
MIRROS	6.0	9.0	0.080	0.161	275	0.852	**38.8**
PH, no cure	6.0	9.0	0	0	246	0.858	**29.2**
MIRROS with #events for PH, no cure	6.0	9.0	0.080	0.161	246	**0.810**	33.7

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 and logrank test: if NPH, estimand depends on censoring distribution!
- Regulatory environment: typically accepted to reject H_0 using valid test, and then quantify effect differently.
- MIRROS: violation of PH only very late. Give hazard ratio, and estimate of cure proportion difference.

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

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.

Futility interim is **non-binding**. Why do we need to model it at all?

- How to choose interim boundary on CR?
- Decision-makers want to be able to trade-off

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

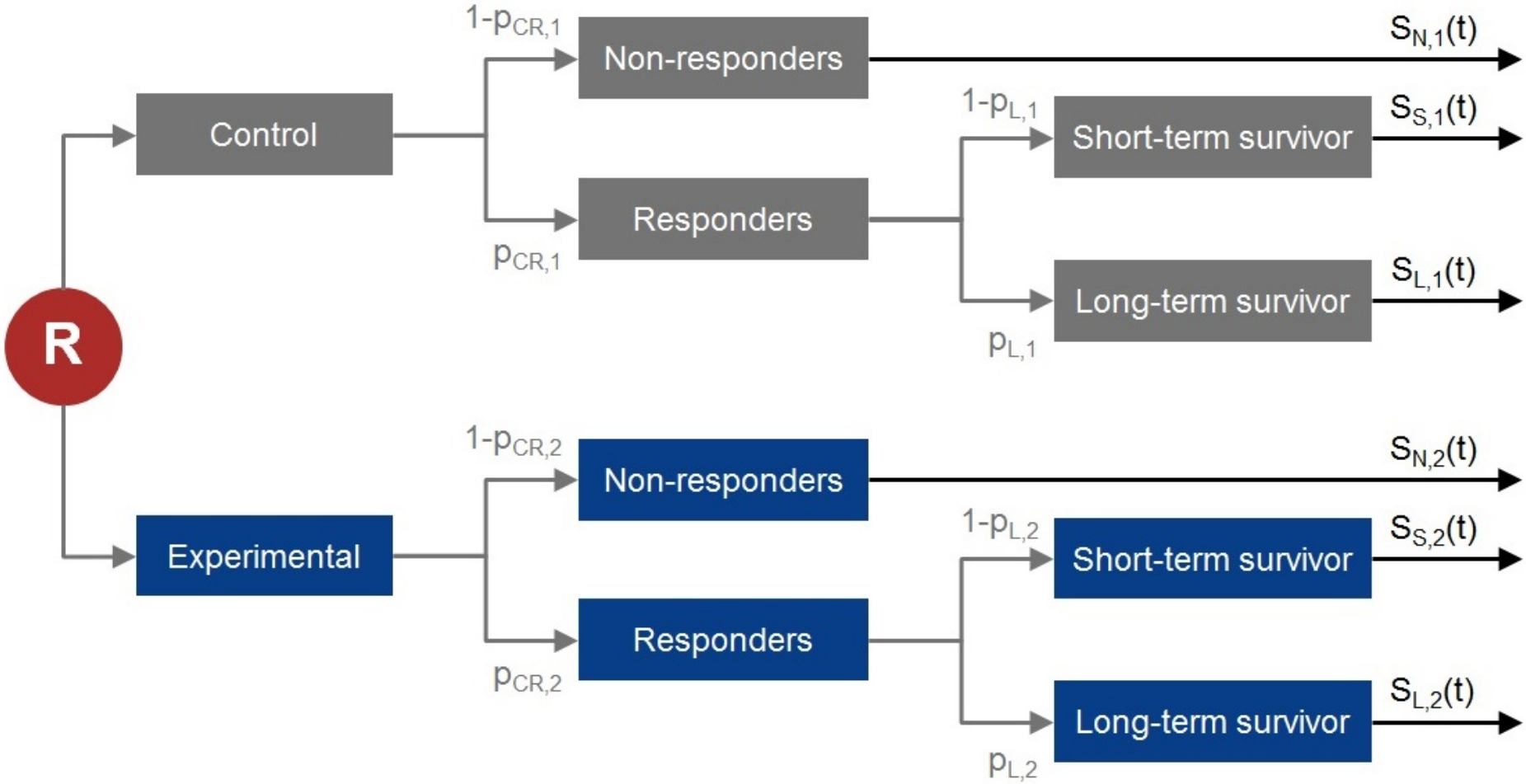
vs.

$$\textbf{False Negative} = \mathrm{P}(\text{stop @ interim} \mid H_1).$$

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.

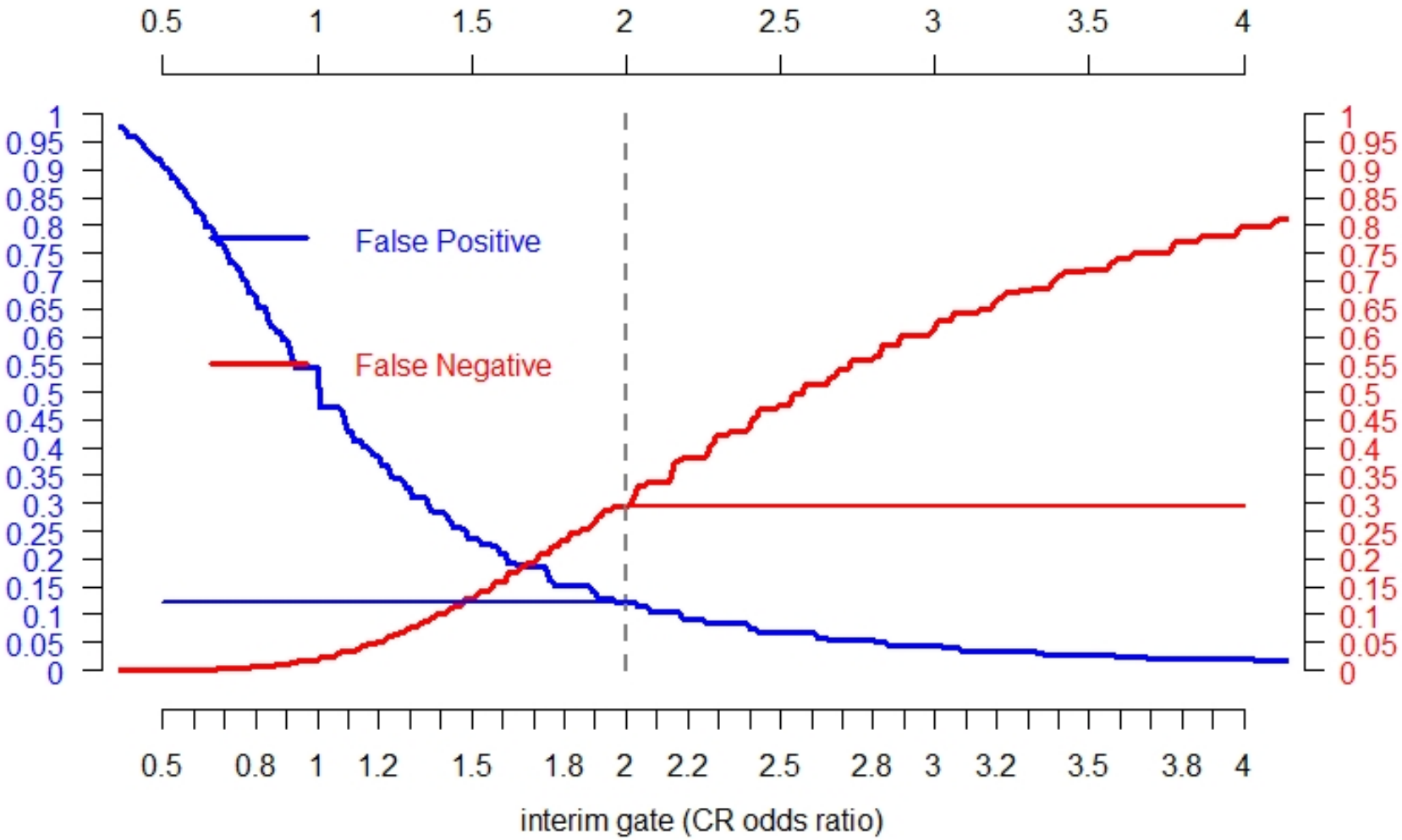
Need to inform all assumptions:

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.

Power loss of adding futility interim

Can easily get that from simulations.

- Targeted power: 85%.
- Power taking into account futility interim: **63%!**
- Illustrates risk-appetite. Futility interim somehow becomes "informal efficacy interim".
- 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

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).

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

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.

Conclusions

Current status of MIRROS

Interim analysis passed on 17th Sept 2017.

Final analysis cutoff projected for **Q4 2019**.

Conclusions

- Account for power loss and timing delay if you have cure proportions.
- Think about how to quantify effect.
- Skipping / integrating P2 into P3 allows for **acceleration** and **risk-mitigation**. If you stop at interim not much is lost in fact.
- Mechanistic simulation model allows to associate binary intermediate to time-to-event primary endpoint and explore interim analysis **operating characteristics**.

We have implemented this in a REAL trial!

Resources

Paper (under revision): Rufibach et al. (2019), available at `https://arxiv.org/abs/1901.01308`.

Code to reproduce simulations and **plan your own trial** on github: `https://github.com/numbersman77/integratePhase2.git`.

BBS seminar on synthetic controls

Basel Biometric Section spring seminar: **Synthetic controls - what do we need and how far can we go?**

- Basel.
- **May 10th**, 2019, 9:00-16:00.
- Speakers from industry, Flatiron, European regulators.
- Rejoinders by regulators: Norbert Benda (BfArM), Jan Müller-Berghaus (PEI), Anja Schiel (Norwegians Medicine Agency & Chair BSWP), Kit Roes (UMC Utrecht MEB and EMA BSWP), Meinhard Kieser (University of Heidelberg).
- Panel discussion with all speakers.

`http://bbs.ceb-institute.org`

Thank you for your attention.

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Backup slides.

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 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.

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.

Doing now what patients need next

R version and packages used to generate these slides:

R version: R version 4.0.0 (2020-04-24)

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

Other packages: biostatKR / survival / rpact / reporttools / xtable / probSuccess / cubature / pracma / mvtnorm / dplyr / readxl

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