MIRROS: Planning a Phase 3 Trial with Time-to-event Endpoint, a Cure Proportion, and a Futility Interim Analysis using Response

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Who

Rufibach *et al.* (2020):



Acute Myeloid Leukemia

Acute Myeloid Leukemia

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

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).

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**)** $\Rightarrow$ minimize expected sample size.

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.

MIRROS: key questions

Key questions of MIRROS

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

Futility interim analysis

Futility interim analysis

Mitigate risk if drug does not work (sufficiently).

Planned after **120** patients are recruited.

Why not use OS for interim decision?

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

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

Intermediate endpoint

Complete response:

- Believed to be 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

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

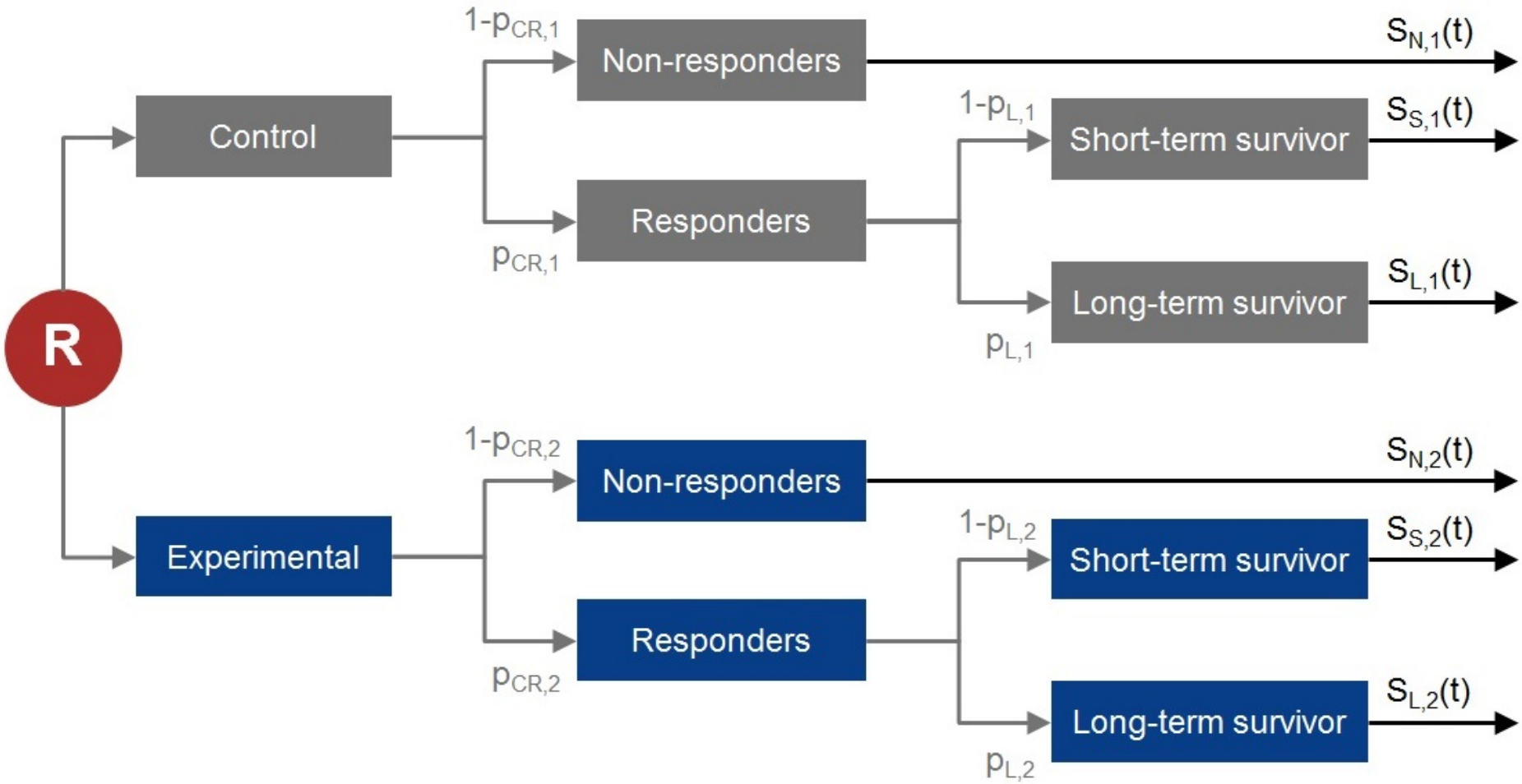
vs.

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

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

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

Mechanistic simulation model



Mechanistic simulation model

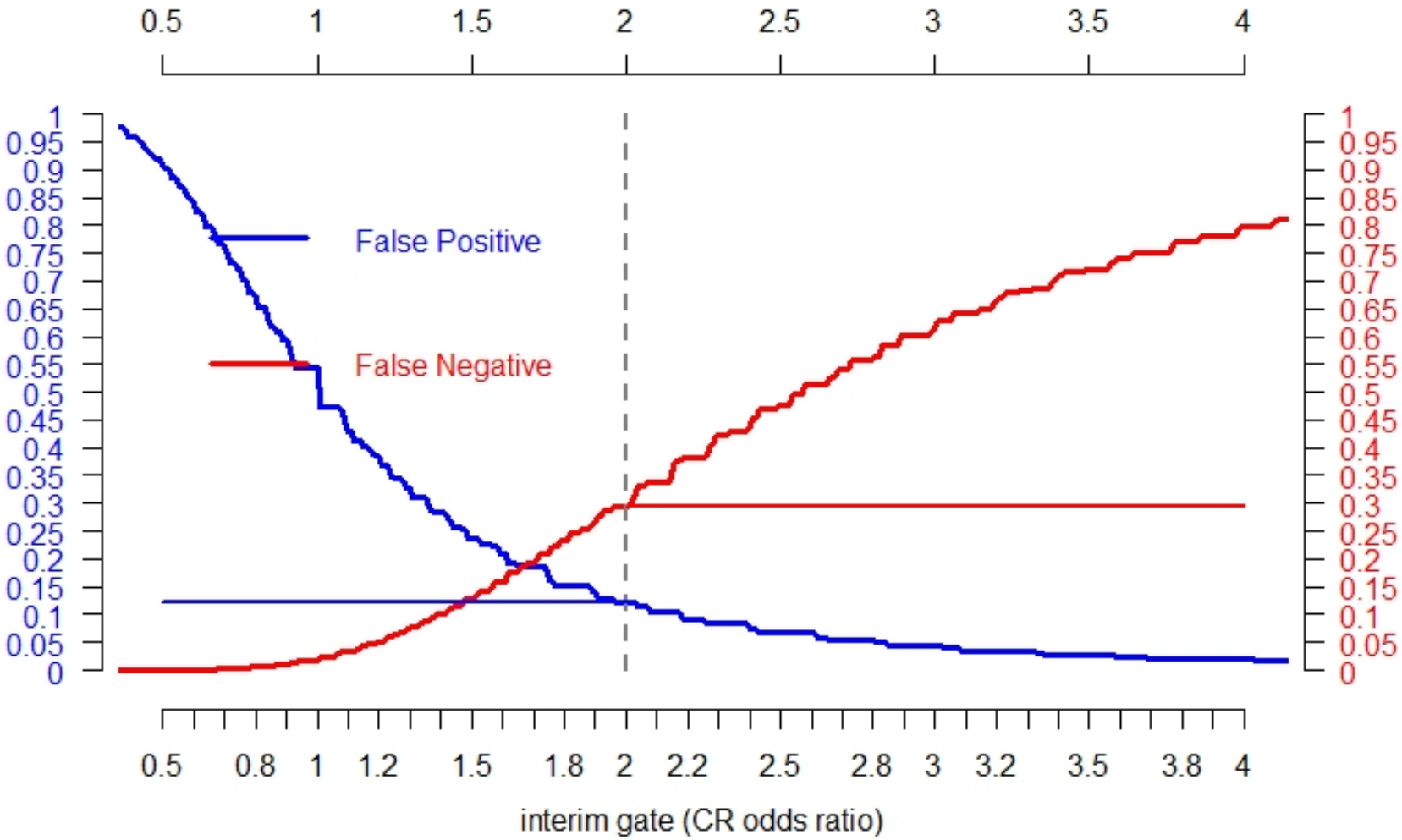
Connects CR to OS.

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

Use "real-world data" (or basic epidemiology) to inform these.

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%.

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".
- **No option to stop for efficacy** $\Rightarrow$ no adaptive design theory for type I error correction needed.

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?

Cure proportion model – assumptions

Assume effect size for S_i^*.

Compute necessary events d using **Schoenfeld's formula**:

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

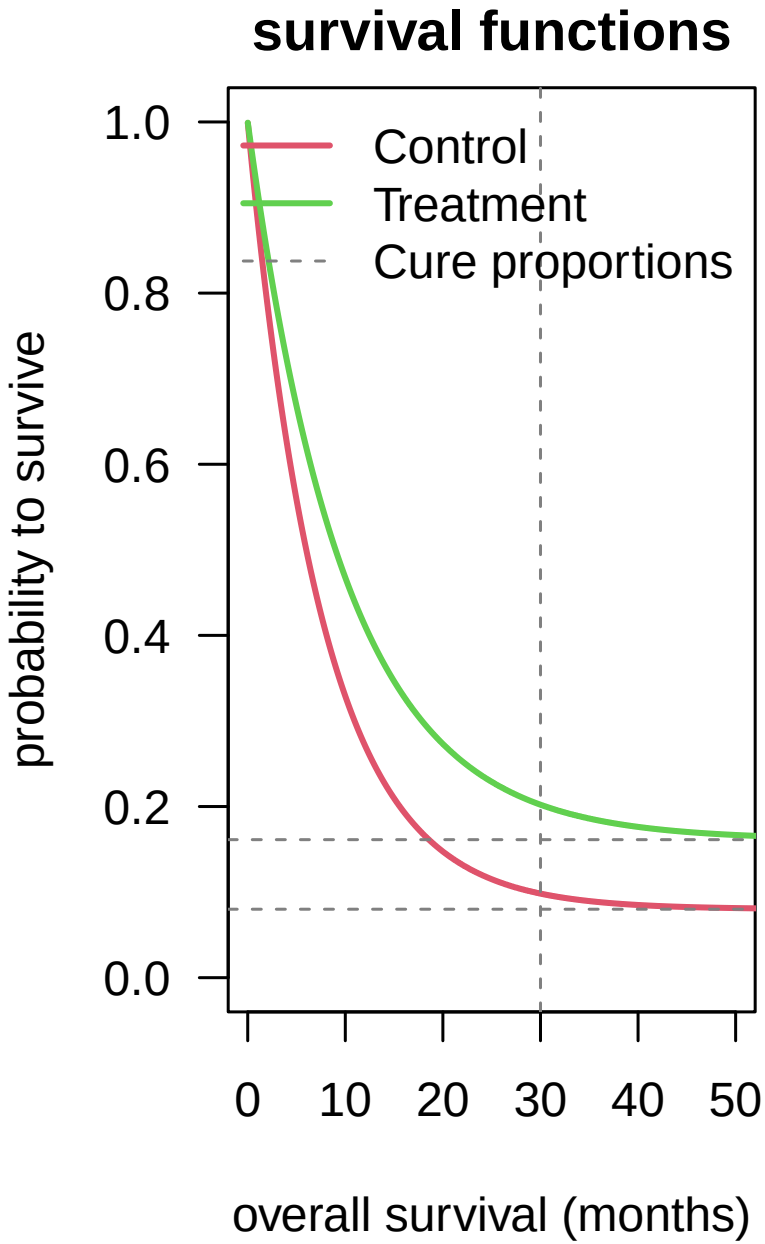
Control arm, based on **historical data**, H_0:

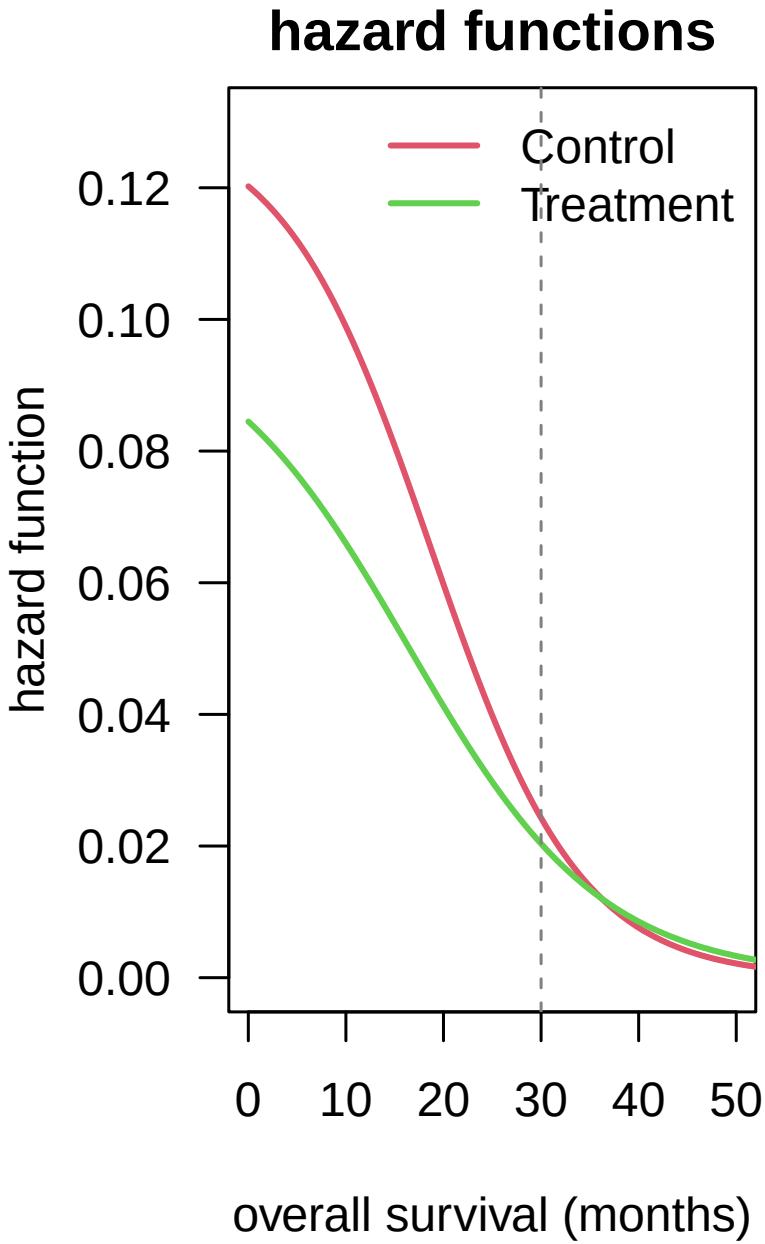
- Median OS 6m.
- Cure: 0.080.

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

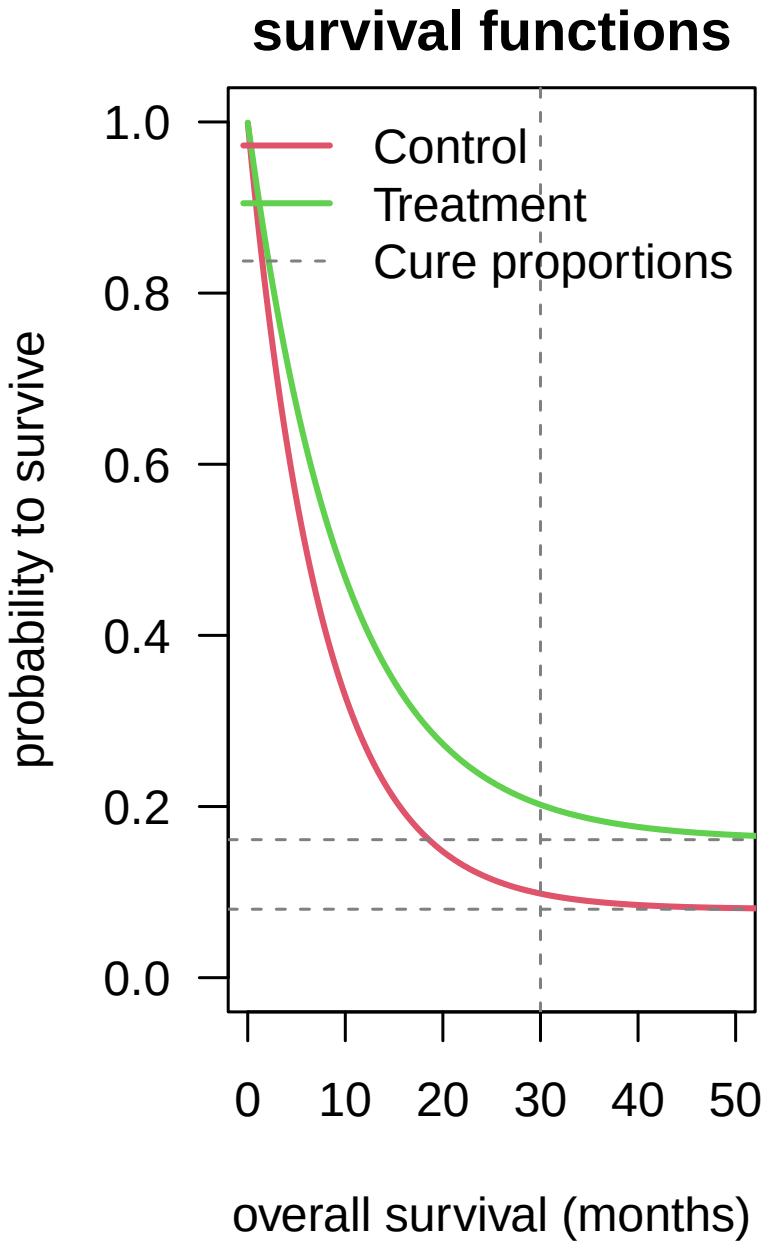
- Median OS 9m.
- Cure: 0.161.

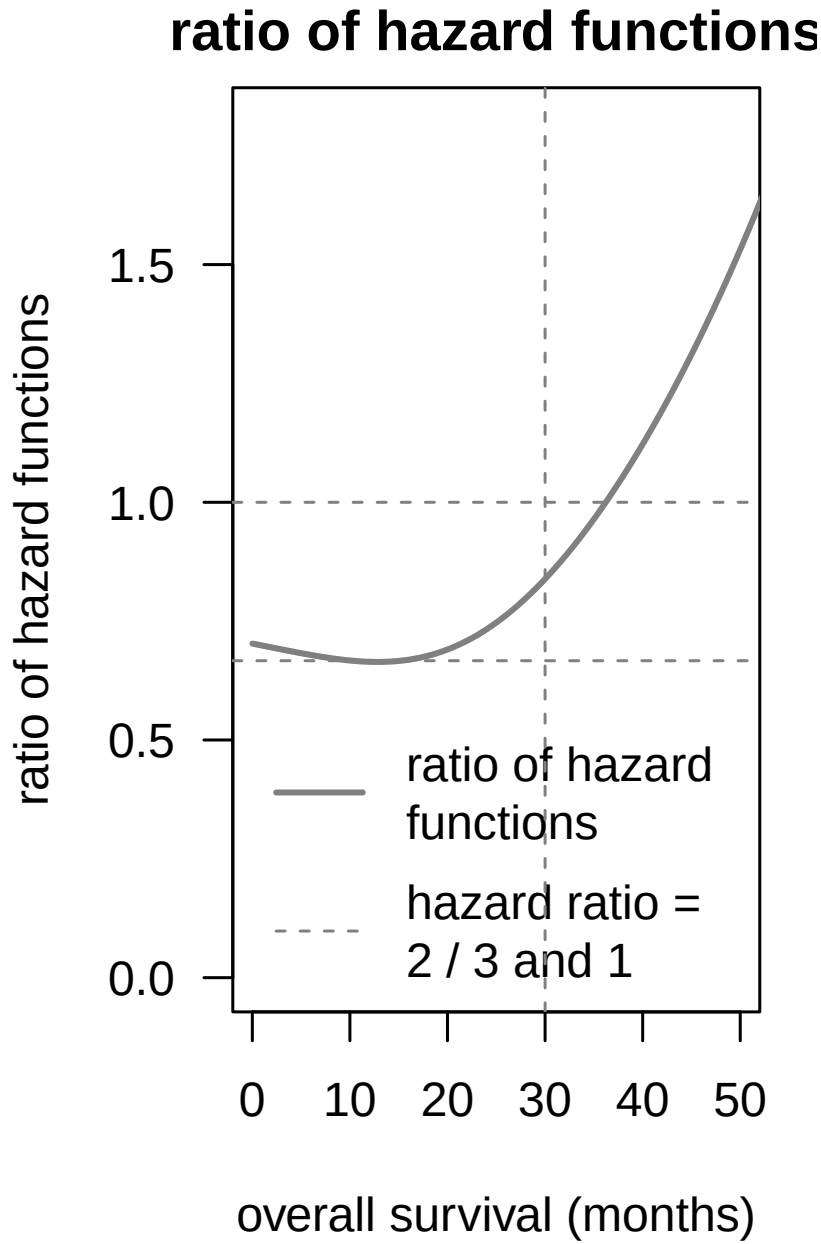
Cure proportion model – assumptions





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 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.

Regulatory view on effect quantification

(European) health authorities: Emphasized many times that effect quantification in label must **not necessarily**

- be tied to hypothesis test,
- provide inference with "significant" p-value.

Reject H_0 using valid test.

Quantify effect using suitable **summary statistics**.

What was done in MIRROS?

Violation of PH only **very late**.

Power loss modest.

MIRROS statistical analysis plan:

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

What was NOT planned in MIRROS?

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

Health authority feedback

Health authority feedback to design

FDA:

- **Preferred randomized P2**.
- 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, supported hazard ratio as appropriate effect measure.

Running the trial

Outcome

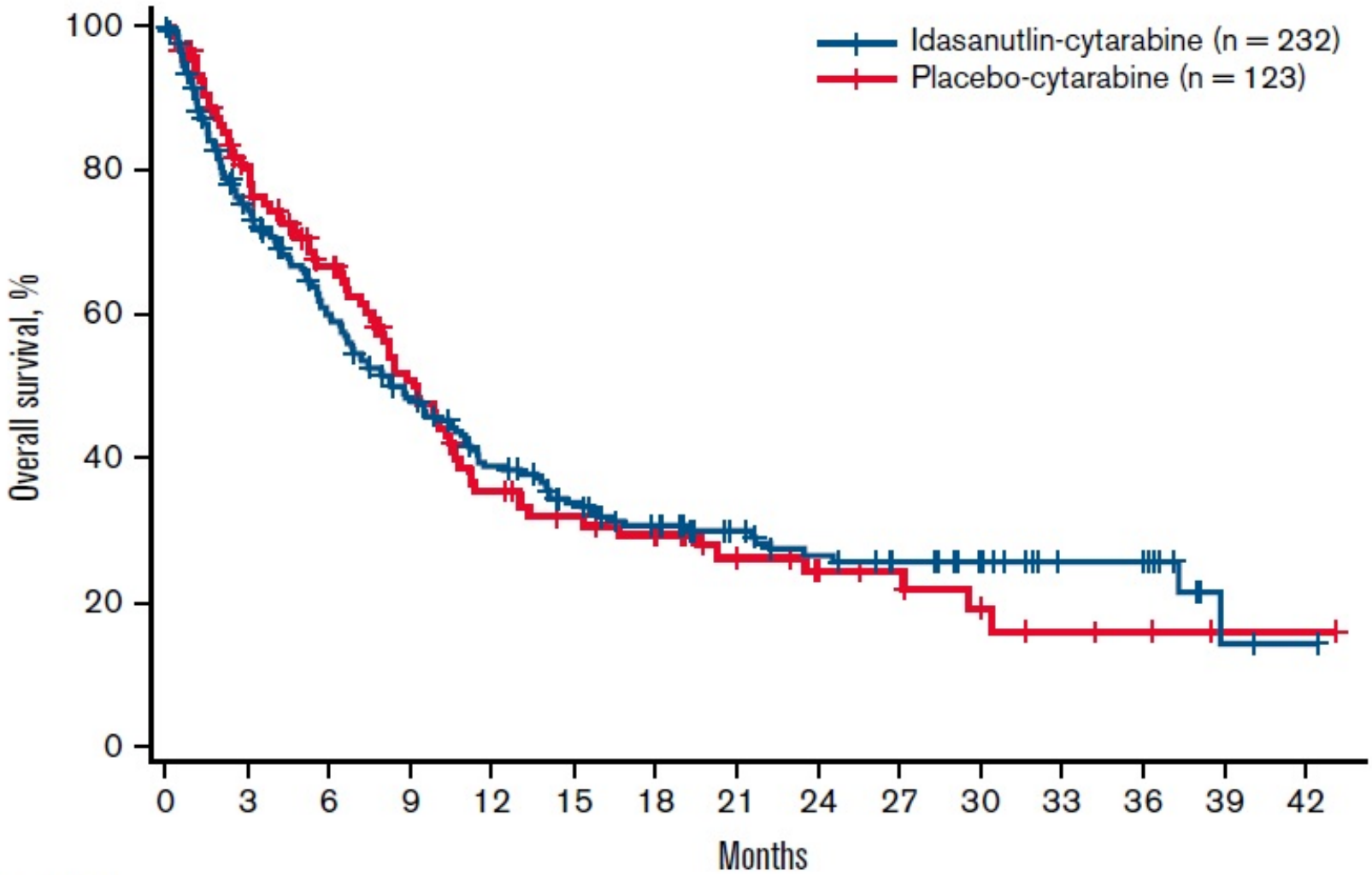
Futility interim was **passed**.

Trial was **negative**.

Assumption on shape of S in treatment arm quite accurate.

Control arm did better than assumed: Relative effect vs. control not big enough.

OS survival function estimates



No. at risk															
Idasanutlin-cytarabine	232	163	123	95	73	56	46	37	30	25	19	11	10	2	1
Placebo-cytarabine	123	88	67	48	33	27	24	16	12	10	6	4	3	1	1

Conclusions

Conclusions futility interim

Skipping / integrating P2 into P3 allows for **acceleration** and **risk-mitigation**:

- If you stop at interim not much is lost.
- If you continue you accelerate potentially dramatically.

Mechanistic simulation model:

- Associate binary intermediate to time-to-event primary endpoint.
- Explore interim analysis **operating characteristics**.

Conclusions effect quantification in cure model

- Account for **power loss** and **cutoff delay** if you have cure proportions (or NPH).
- NPH $\Rightarrow$ large zoo of alternatives $\Rightarrow$ assumption needed on shape of survival functions $\Rightarrow$ use **simulations extensively**!
- Think about **how to quantify effect**.
- Number of events: metric related to PH! **Delayed separation** $\Rightarrow$ number of events not necessarily sufficiently informative.
- Power optimization $\Leftrightarrow$ assumptions might also be off!

Power optimization $\Leftrightarrow$ pragmatism.

Resources

MIRROS trial design:

- Design and statistical methodology: Rufibach *et al.* (2020).
- Reproduce simulations and **plan your own trial**: `https://github.com/numbersman77/integratePhase2.git`.
- Clinical paper describing futility interim: Montesinos *et al.* (2020).
- Clinical paper with final analysis: Konopleva *et al.* (2022).

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MAIN PAPER

WILEY

Integrating phase 2 into phase 3 based on an intermediate endpoint while accounting for a cure proportion—With an application to the design of a clinical trial in acute myeloid leukemia

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Thank you for your attention.

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Backup slides.

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**.

Cure proportion model – estimation

Numerous parametric and nonparametric estimates of relevant quantities: Cantor and Shuster (1992); Maller and Zhou (1992, 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.

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 4.1.1 (2021-08-10)

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

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

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