Clinical trial design based on a multistate model that jointly models progression-free and overall survival

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Who

Meller *et al.* (2019):



Erdmann *et al.* (2023):



Power gains through exploiting correlations:

Group-sequential designs: over time.

Enrichment designs:
over nested subpopulations.

Goal:

design trial with PFS and OS

Co-primary (win both) or multiple (win ≥ 1)

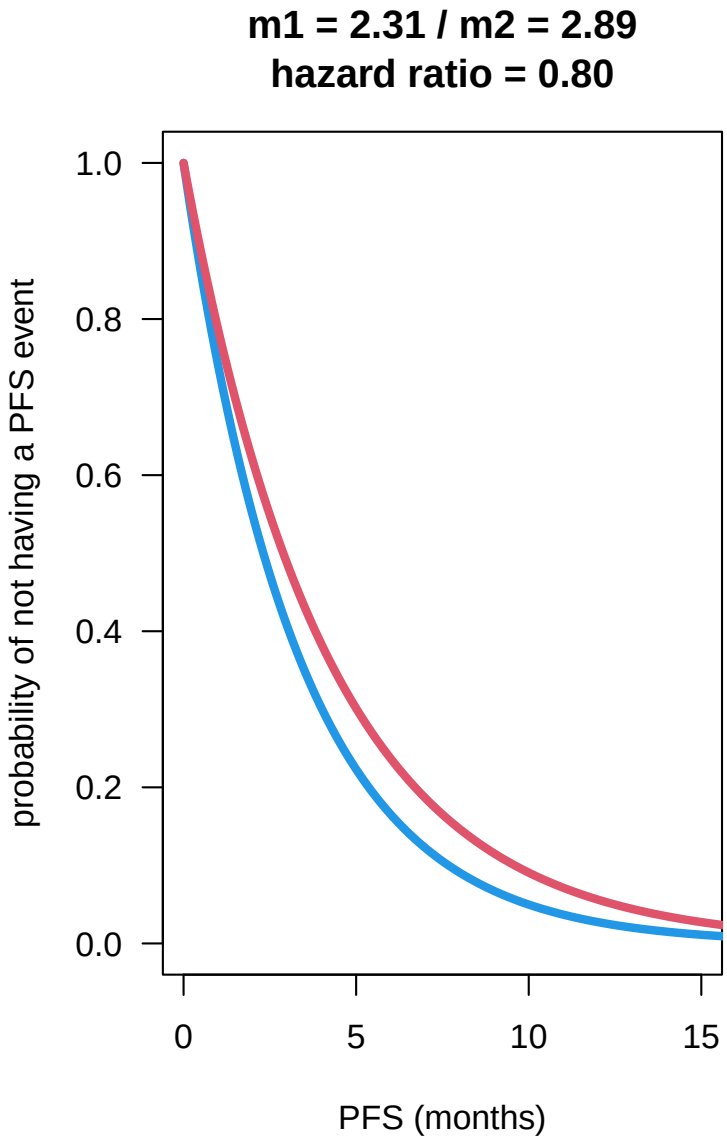
Typical approach:

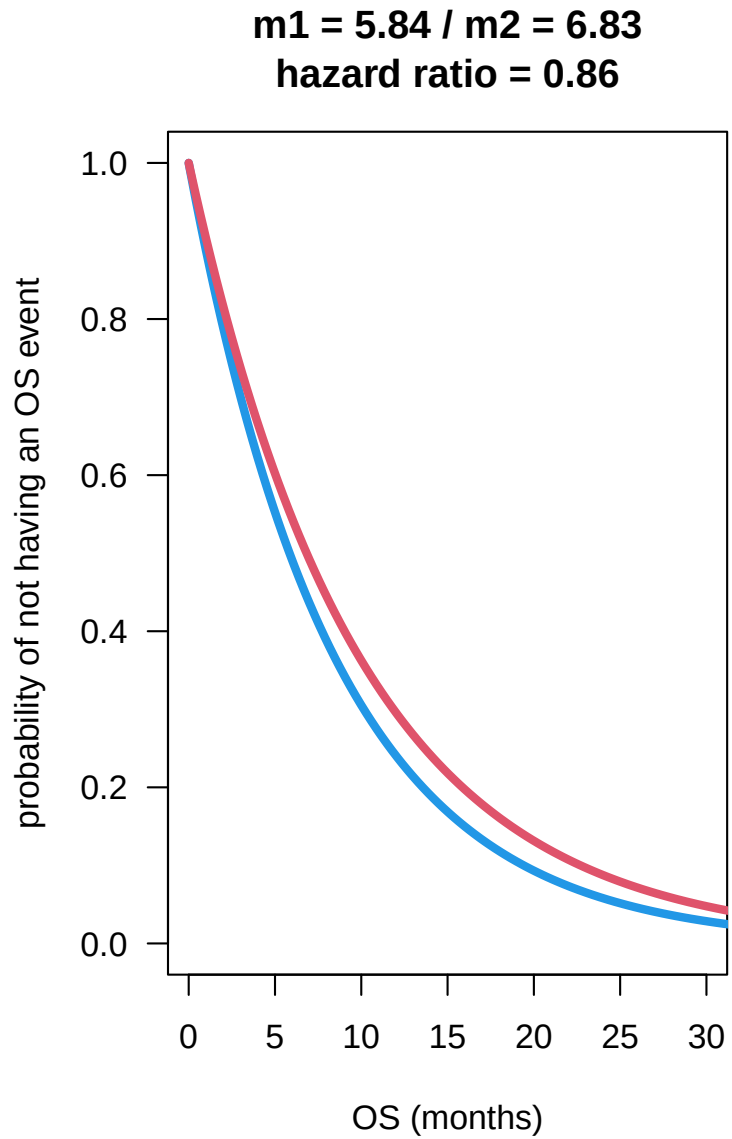
1) Split significance level

2) PFS: exponential, plan GSD

3) OS: exponential (or NPH), plan GSD, align OS interim with PFS final

Example: exponential for PFS and OS





Compute necessary #events based on α-split and GSD assumptions.

Why is this not necessarily optimal?

1) Ignores cor(PFS, OS).

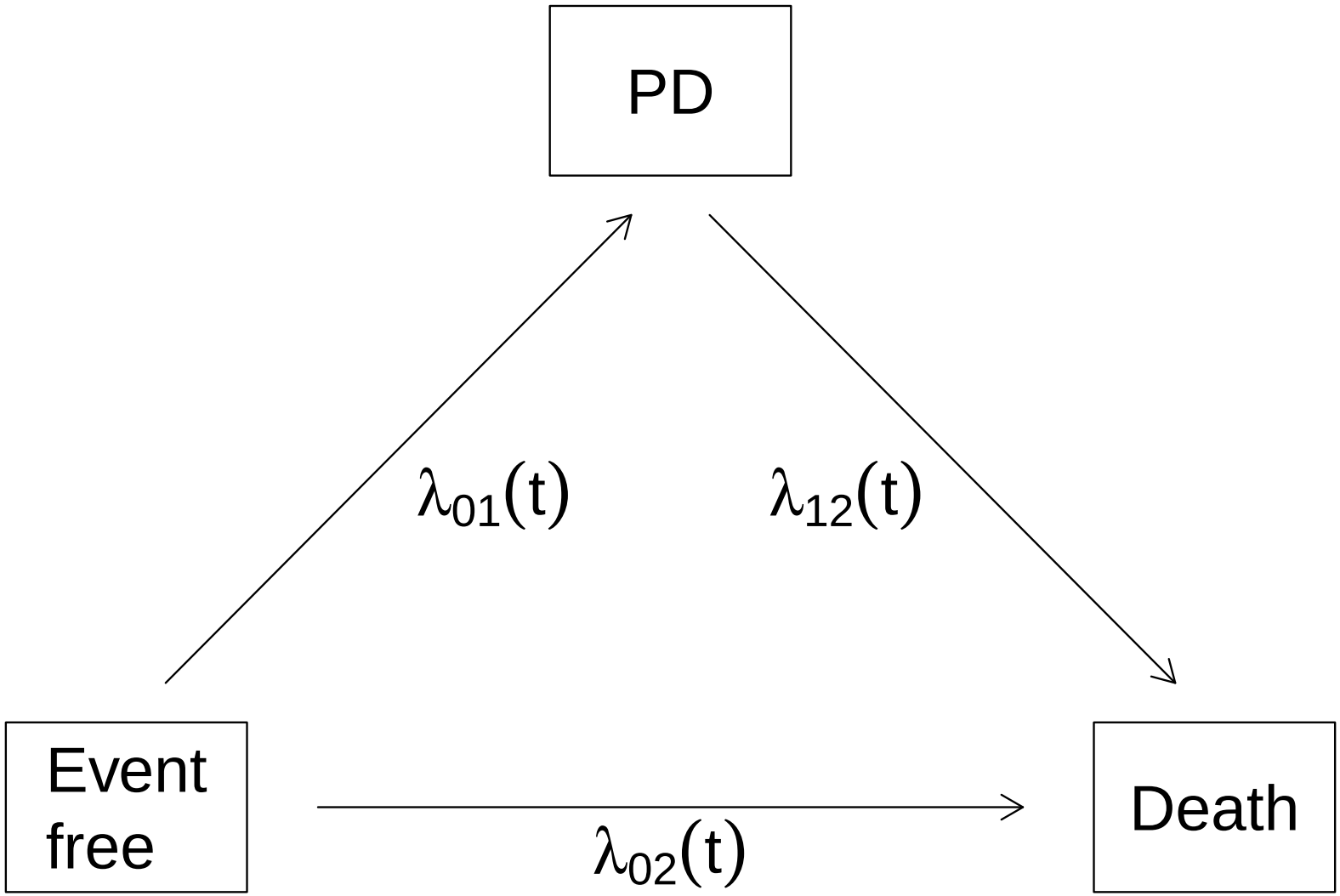
2) PFS + OS both involve death
$\Rightarrow$ OS not independent from PFS!

3) OS cannot be PH.

How can we fix that?

PFS and OS are connected through illness-death model.

Canonical extension of survival analysis



Illness-death multistate model for PFS and OS

Transition probabilities to move from state l at time s to state m at time t:

$$P_{lm}(s,t) \quad := \quad P(X(t) = m | X(s) = l, \text{history}).$$

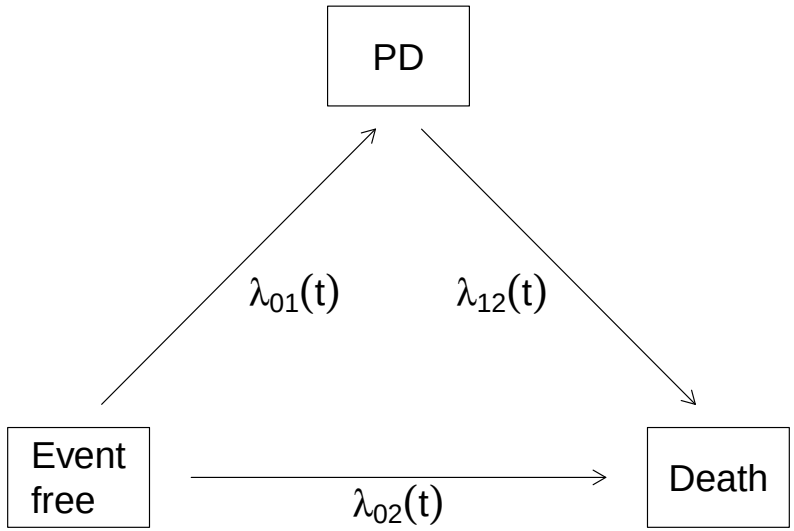
If $X(t)$ non-Markov: P_{11} and P_{12} depend on **PFS time** t_1.

Estimate P_{lm}'s **nonparametrically** by **Aalen-Johansen** estimator.

Illness-death model w/o recovery, P_{lm} as functions of transition intensities, Aalen *et al.* (2008):

$$\begin{aligned}
P_{00}(s,t) &= \exp\left(-\int_s^t \lambda_{01}(u) + \lambda_{02}(u)\, \mathrm{d}u\right), \\
P_{11}(s,t;\mathbf{t_1}) &= \exp\left(-\int_s^t \lambda_{12}(u;\mathbf{t_1})\, \mathrm{d}u\right), \\
P_{22}(s,t) &= 1, \\
P_{01}(s,t) &= \int_s^t P_{00}(s,u_-)\lambda_{01}(u)P_{11}(u,t;u)\, \mathrm{d}u, \\
P_{12}(s,t;\mathbf{t_1}) &= 1 - P_{11}(s,t;\mathbf{t_1}), \\
P_{02}(s,t) &= 1 - \Big(P_{00}(s,t) + P_{01}(s,t)\Big).
\end{aligned}$$

Illness-death model for PFS and OS



PFS: waiting time in initial state 0, $\mathrm{PFS} = \inf\{t : X(t) \neq 0\}$.

$$S_{PFS}(t) \quad = \quad P(\mathrm{PFS} > t) \; = \; P_{00}(0,t).$$

OS: time until reaching state 2, $\mathrm{OS} = \inf\{t : X(t) = 2\}$.

$$S_{OS}(t) \quad = \quad P(\mathrm{OS} > t) \; = \; P_{00}(0,t) + P_{01}(0,t).$$

(Non-)Proportional hazards

Induced survival functions

Meller *et al.* (2019):

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

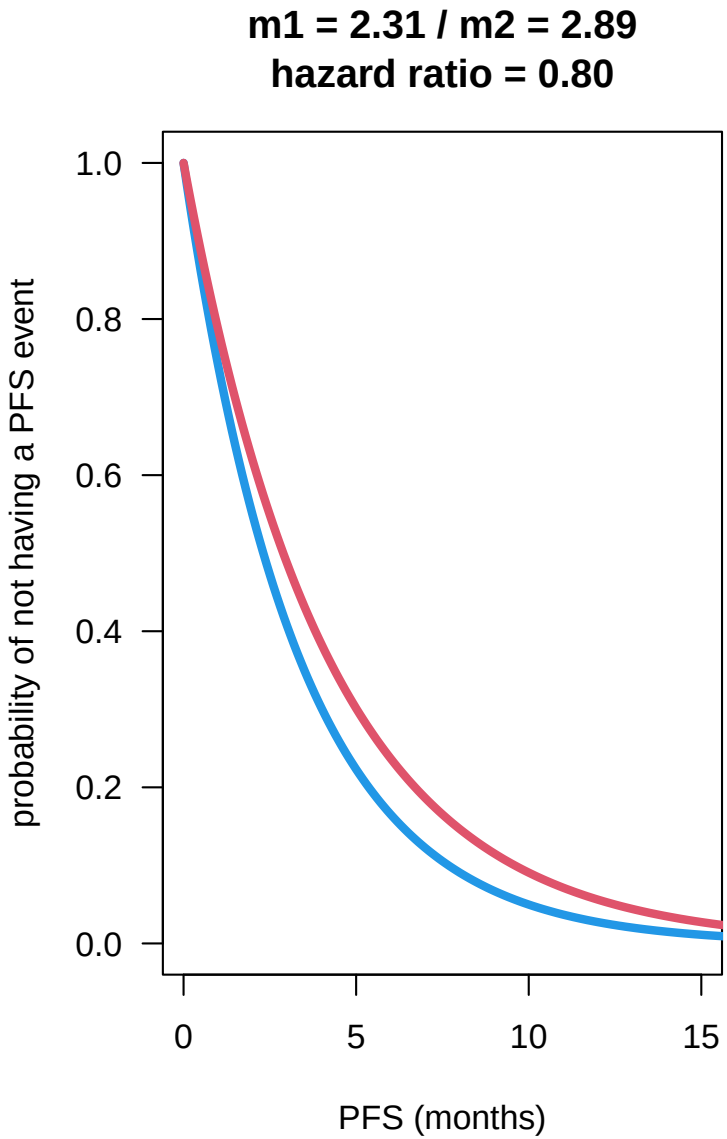
Assume **constant** transition hazards:

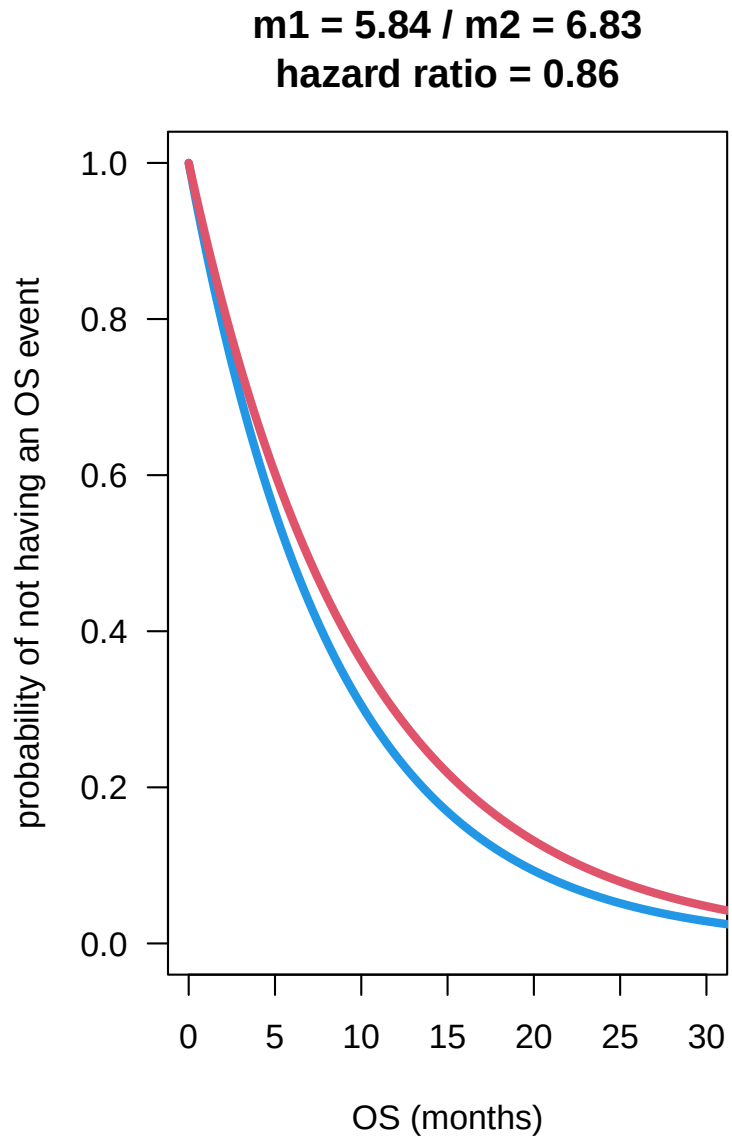
$$\begin{aligned} S_{PFS}(t) &= \exp\Big(-(\lambda_{01} + \lambda_{02})t\Big), \\ S_{OS}(t) &= \frac{S_{PFS}(t)}{\lambda_{012}}\Big(\lambda_{12} - \lambda_{02} - \lambda_{01}\exp(-\lambda_{012}t)\Big) \end{aligned}$$

with abbreviation $\lambda_{012} := \lambda_{12} - \lambda_{01} - \lambda_{02}$.

Hazard functions via $h(t) = -S'(t)/S(t)$.

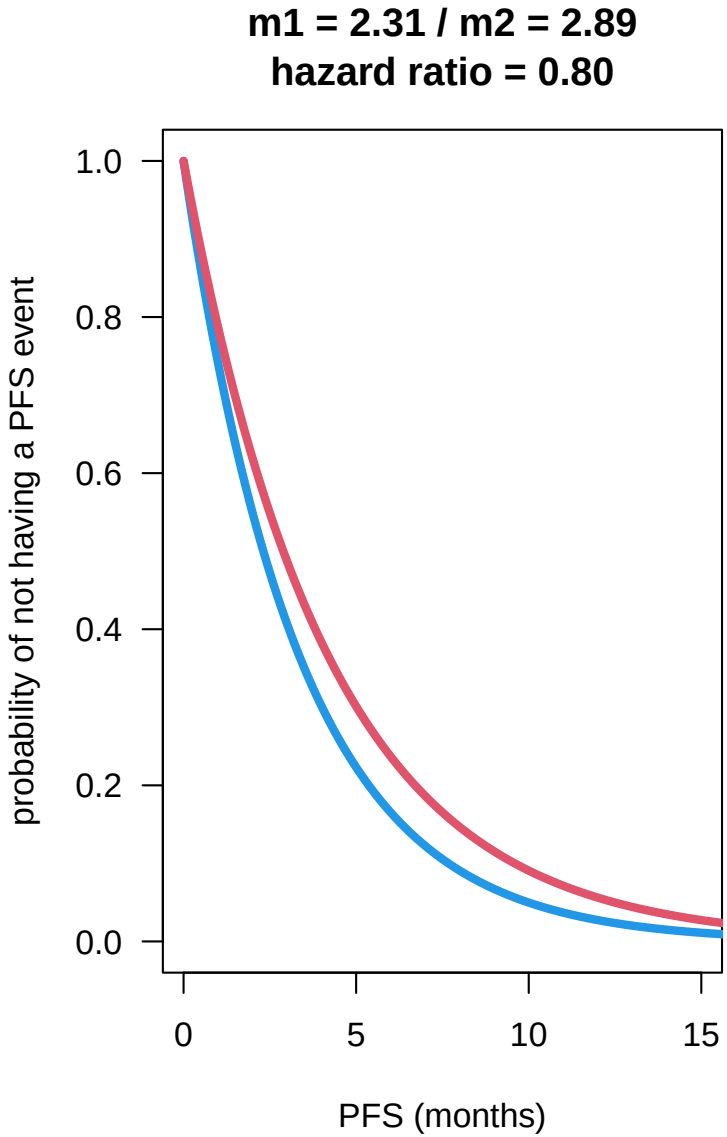
Example: exponential for PFS and OS

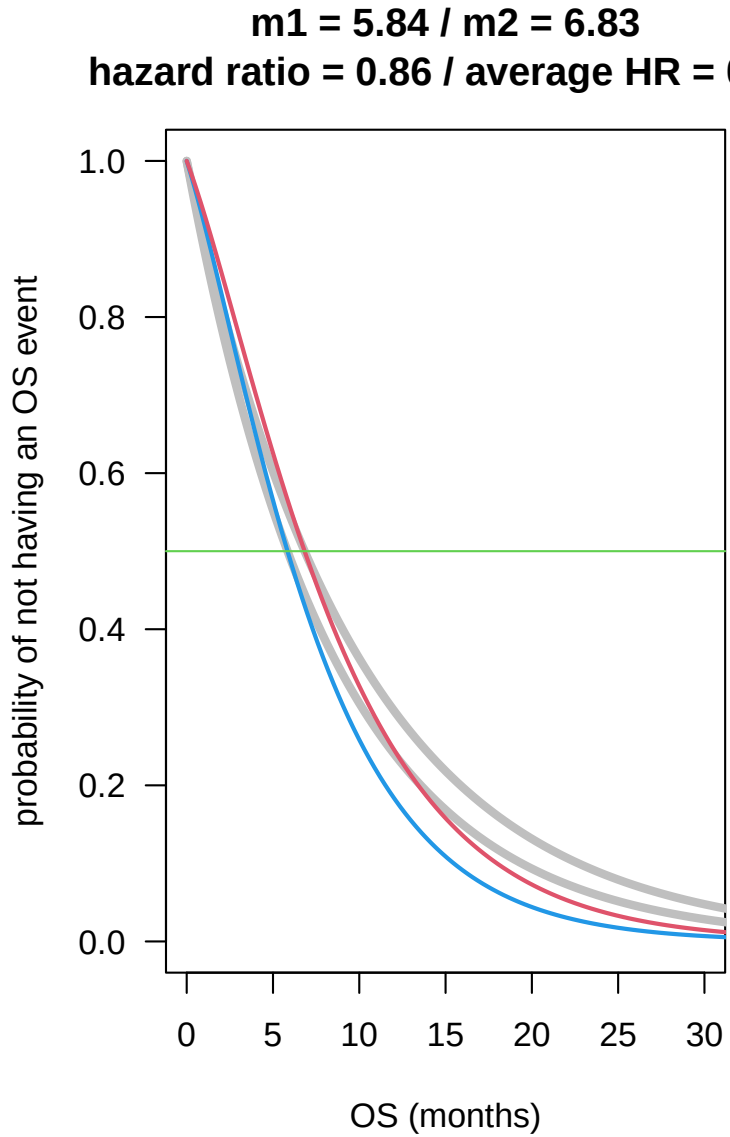




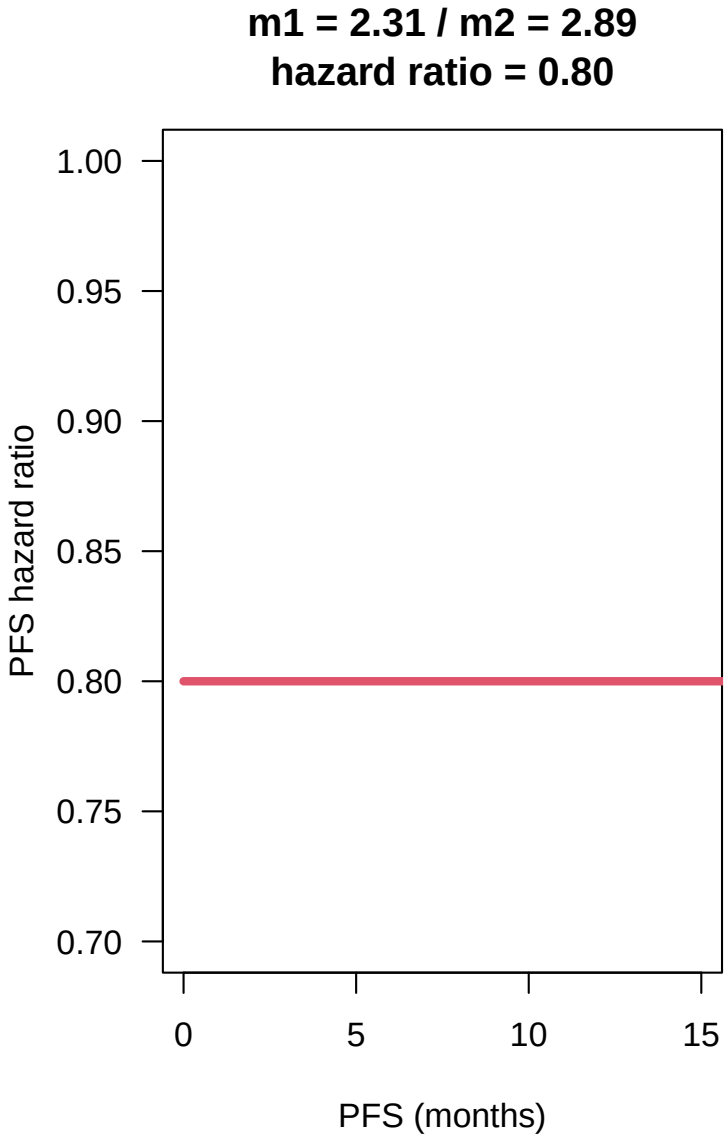
Compute necessary #events based on α-split and GSD assumptions.

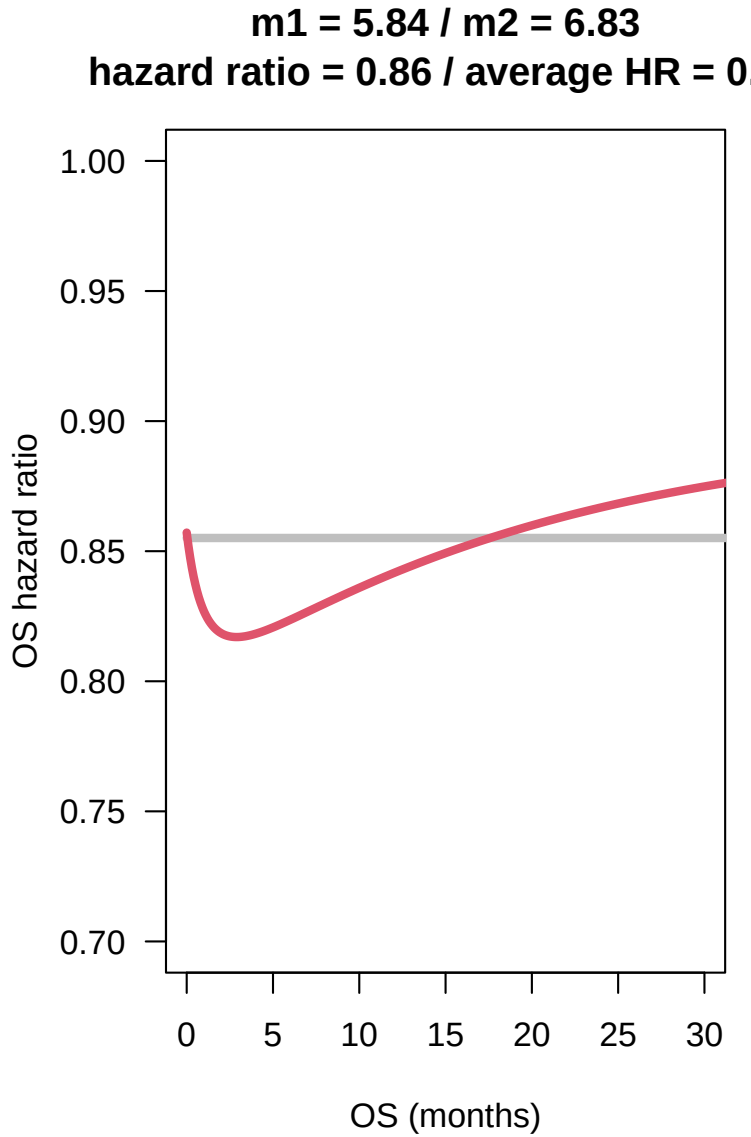
Example: median-matching survival functions induced by IDM





Example: hazard ratio as function of time - mind y-axis!





Proportional hazards for OS

PH for PFS for time-homogeneous transition hazards.

Hazard ratio for OS:

$$\begin{aligned} h_{OS}(t) &= \frac{(\lambda_{12}-\lambda_{02})(\lambda_{01}+\lambda_{02}) - \lambda_{01}\lambda_{12}\exp(-\lambda_{012}t)}{(\lambda_{12}-\lambda_{02}) - \lambda_{01}\exp(-\lambda_{012}t)}. \\ \theta_{OS}(t) &= h_{OS,A}(t)/h_{OS,B}(t). \end{aligned}$$

When is $\theta_{OS}(t)$ independent of t?

- $\lambda_{12} = \lambda_{02}$ **in both groups**: progression has no impact on death hazard.
- $\lambda_{01} = 0$ **in both groups**: no progression occurs.
- $\lambda_{012} := \lambda_{12} - \lambda_{01} - \lambda_{02} = 0$: denominator of h_{OS} equal to 0.

Assumption that we have PH for PFS AND OS
unrealistic to hold in real clinical trial.

Clinical trial design via simulation from IDM

Clinical trial planning

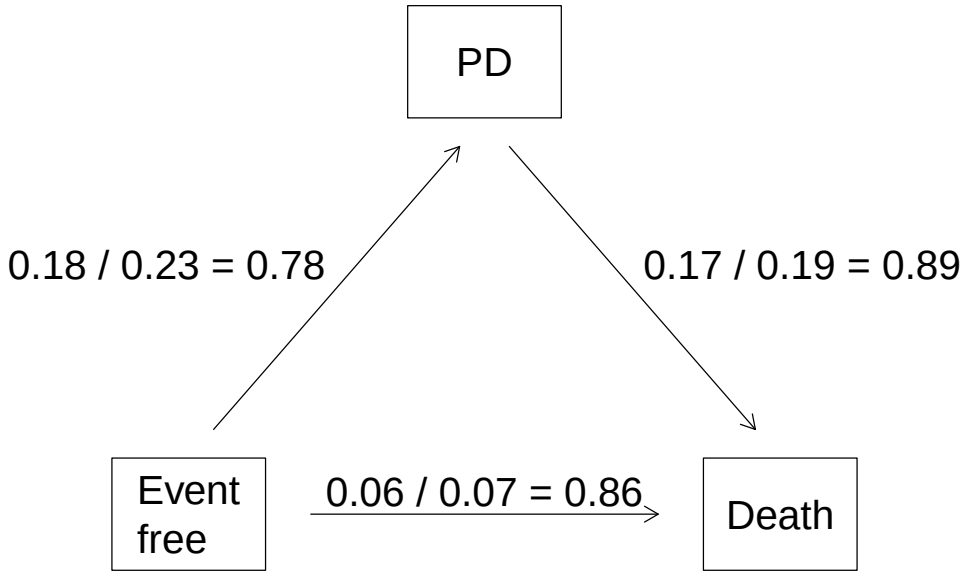
- Type I error: P(reject **at least** one H_0 irrespective of which are true).
- Power: assume ≥ 1 H_1 is true:
  - **Endpoint-specific**: P(reject H_0) for each endpoint separately.
  - **At least**: P(reject ≥ 1 H_0 of **PFS and OS**).
  - **Joint**: P(reject both H_0 for **PFS and OS**).

Clinical trial design

Design feature	Standard approach	Illness-death model
Assumptions to make	Control medians and hazard ratios for PFS and OS	Transition-specific hazards
#quantities	4	6
Cor(PFS, OS)	Not exploited	Explicitly modelled through IDM
Proportional hazards	Assumed for OS, although not met	NPH properly induced through IDM
α allocation	Bonferroni	Bonferroni
Number of events	Schoenfeld's formula	Tune through simulation
Power	Disjoint per endpoint	Any type of power

Simulation of PFS - OS

Scenario 4



Features:

- Drug effect on all transitions.
- PFS HR $= 0.8$.
- Average hazard ratio for OS: 0.832.

How to plan a trial?

Co-primary endpoints PFS and OS, one analysis each

Global significance level: 0.05.

Design feature	**PFS**	**OS**
Local significance level	0.01	0.04
Critical value	2.576	2.054
Hazard ratio	0.80	0.832 (AHR)
Power	80%	80%
Events using Schoenfeld	939	992
Simulate from IDM under H_0	Empirical type I error: 0.0499	
Joint power of Schoenfeld sample size with these critical values	Joint power: 0.708	
Tune number of events to get endpoint-specific power of 80%	939	905
Empirical power per endpoint	0.797	0.801
Empirical joint power	Joint power: 0.686	

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Before you ask...

...let me make a few comments

NPH for OS: should we use something else than logrank test and hazard ratio?

- Hypothesis test and effect quantification **independent** of MSM.

What is role of the **Markov** assumption?

- Markov assumption: probability of future transition only depends on (i) state currently occupied and (ii) time t.
- If violated: individual transition hazards random quantities through dependence on history.
- S_{PFS}, S_{OS}: estimation straightforward even if X non-Markov.
- Meller *et al.* (2019): joint distribution of PFS and OS for non-Markov. Can be leveraged.

...let me make a few comments

Do we always **gain power** for OS? **No!**

Power for OS depends on:

- **Knowledge of PFS to "predict" OS**.
- **Induced shape** of survival functions. Relative effect can be smaller than, e.g., that of median-matching exponential survival functions.

Interim analysis for OS: see paper.

Does the IDM approach make some "regulatory-incompatible" assumptions?

- In our opinion **not at all**.
- Need to assume 6 transition-specific hazards. Maybe more uncommon to inform, but **conceptually no different** from PFS / OS medians.
- Current approach: assumes PH for OS $\Rightarrow$ we know can't be true!
- $\pm$ Markov.

Conclusions

Conclusions and outlook

Conclusions:

- Illness-death model for PFS and OS:
  - Properly account for **induced** hazard ratio as a function of time, $\theta_{OS}(t)$, for OS.
  - Exploit correlation between PFS and OS.
- Sample size for OS might **decrease** or **increase**!
- **Proper simulation** of PFS and OS on patient-level.

Outlook:

- **Broadly applicable**: surrogacy, interim decisions based on PFS, OS prediction, ...
- Combine subpopulation + illness-death model for PFS - OS. **Tira trials**.
- Extendable to more states, Beyer et al. (2020).

Resources

Resources:

- Meller et al., Meller *et al.* (2019).
- Paper on arxiv.
- Package **simIDM** on github and CRAN. Exponential, Weibull, piecewise exponential transition hazards.
- Linkedin post.
- Further MSM resources:
  - Beyer et al. on use of MSMs for early-phase decision-making, Beyer et al. (2020).
  - MS example.
  - Material of BBS seminar "Competing Risks and Multi-State Models".
  - oncomsm: R package by Boehringer colleagues, "Bayesian Multi-State Models for Early Oncology".

Slides can be downloaded on
www.kasparrufibach.ch.

Thank you for your attention.

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http://www.kasparrufibach.ch

References I

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- Andersen, P. K., Borgan, **Ø**., Gill, R. D., and Keiding, N. (1993). *Statistical Models Based on Counting Processes*. Springer.
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- Gaschler-Markefski, B., Schiefele, K., Hocke, J., and Fleischer, F. (2014). *Multi-state Models Used in Oncology Trials*, pages 283–304. Springer Berlin Heidelberg, Berlin, Heidelberg.
- Meller, M., Beyersmann, J., and Rufibach, K. (2019). Joint modeling of progression-free and overall survival and computation of correlation measures. *Statistics in medicine*, **38**, 4270–4289.

Backup

Advantages of illness-death model for PFS and OS

Illness-death model:

- Assumptions on $X(t)$ **induce** properties of transition intensities, (joint) probabilities, survival functions of PFS and OS.
- Estimation of derived quantities straightforward by plugging in estimated intensities.
- Can reflect disease specifics and drug mode-of-action in transition hazards, see also Beyer et al. (2020).

Multistate model formulation

Transition probabilities:

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

Meller *et al.* (2019):

- 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).

Allows derivation of any functional of PFS and OS.

Assumptions for multistate model

Multistate model **sufficiently smooth** so that following intensities exist:

$$\begin{aligned}
\lambda_{0j}(t) &= \lim_{\Delta t \searrow 0} \frac{P(\mathrm{PFS} \in [t, t+\Delta t), X(\mathrm{PFS}) = j \,|\, \mathrm{PFS} \geq t)}{\Delta t}, \; j = 1, 2, \\
\lambda_{12}(t; t_1) &= \lim_{\Delta t \searrow 0} \frac{P(X(t+\Delta t) = 2 \,|\, X(t-) = 1, \mathrm{PFS} = t_1)}{\Delta t} \\
&= \lim_{\Delta t \searrow 0} \frac{P(\mathrm{OS} - \mathrm{PFS} \in [t - t_1, t - t_1 + \Delta t) \,|\, \mathrm{OS} \geq t, \mathrm{PFS} = t_1)}{\Delta t} \quad \text{for } \mathbf{t_1 < t}.
\end{aligned}$$

t_1: observed PFS time, i.e. time when leaving state 0.

Assumptions for multistate model

$X(t)$ **Markov**:

- **Time-inhomogeneous**: intensity of death after progression does not depend on time of progression, $\lambda_{12}(t; t_1) = \lambda_{12}(t)$ for all $t_1 < t$.
- **Homogeneous**: intensities are time-constant, i.e. **Exponential**, $\lambda_{ij}(t) = \lambda_{ij}, i, j = 0, 1, 2$.

$X(t)$ **non-Markov** (= semi-Markov for illness-death model without recovery):

- Intensities depend on state patient is in at s and entire history $\leq s$, i.e. all transitions.
- Relevant for $1 \to 2$ transition only, as $0 \to 1, 2$ are rooted in initial state 0.

As soon as a quantity depends on $1 \to 2$ **transition** we need to be specific about assumption on $X(t)$.

Illness-death multistate model for PFS and OS

Transition probabilities to move from state l at time s to state m at time t:

$$P_{lm}(s,t) \quad := \quad P(X(t) = m | X(s) = l, \text{history}).$$

Illness-death model w/o recovery, P_{lm} as functions of transition intensities, Aalen *et al.* (2008):

$$\begin{aligned}
P_{00}(s,t) &= \exp\left(-\int_s^t \lambda_{01}(u) + \lambda_{02}(u)\,\mathrm{d}u\right), \\
P_{11}(s,t;\mathbf{t_1}) &= \exp\left(-\int_s^t \lambda_{12}(u;t_1)\,\mathrm{d}u\right), \\
P_{22}(s,t) &= 1, \\
P_{01}(s,t) &= \int_s^t P_{00}(s,u_-)\lambda_{01}(u)P_{11}(u,t;u)\,\mathrm{d}u, \\
P_{12}(s,t;\mathbf{t_1}) &= 1 - P_{11}(s,t;\mathbf{t_1}), \\
P_{02}(s,t) &= 1 - \Big(P_{00}(s,t) + P_{01}(s,t)\Big).
\end{aligned}$$

If $X(t)$ non-Markov:

- P_{11} and P_{12} depend on **PFS time** t_1.
- Although P_{01}, P_{02} depend on λ_{12} they **do not depend on** t_1.

Intuition behind transition probabilities

$P_{00}(s,t)$, $P_{11}(s,t;t_1)$: exp of cumulative hazards $\Rightarrow$ standard survival functions.

$P_{01}(s,t) = \int_s^t P_{00}(s,u_-)\lambda_{01}(u)P_{11}(u,t;u)\,\mathrm{d}u$: integral of

- $P_{00}(s,u_-)\lambda_{01}(u)$: "infinitesimal probabilities" to move from 0 to 1 at time u, $u \in (s,t]$,
- $P_{11}(u,t;u)$: subsequently stay in state 1 until at least time t, with progression happened in u.

Multistate model for PFS and OS

Joint distribution:

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

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

X **non-Markov**:

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

Simulation of PFS and OS on patient level

In the past when simulating PFS and OS how did you make sure...

- ...PFS $\leq$ OS for each patient,
- ...PFS $=$ OS possible,
- ...association between PFS and OS transparent.

Simulation of (Markov) MSM:

- **Nested series of competing risk experiments**.
- MSM trajectors of individual in IDM can generated:
  1. Waiting time t_0 in initial state: Generated from CDF $F(t) = 1 - P_{00}(0, t)$.
  2. State entered at t_0: binomial experiment which decides with probability $\frac{\lambda_{01}(t_0)}{\lambda_{01}(t_0)+\lambda_{02}(t_0)}$ on State 1. If death $\Rightarrow$ stop,
  3. otherwise waiting time t_1 in State 1 is generated from CDF $F(t) = 1 - \exp(-\int_{t_0}^{t_0+s} \lambda_{12}(u)\ \mathrm{d}u)$.
  4. Death will happen at time $t_0 + t_1$.
- Add **drop-out** (random censoring) and **administrative censoring**.
- Non-Markov: model λ_{12} as function of entry time t_0 and time since time origin in Step 3 above.
- All implemented in **simIDM** on github and CRAN.

Doing now what patients need next

R version and packages used to generate these slides:

R version: R version 4.2.3 (2023-03-15 ucrt)

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

Other packages: checkmate / survival / rpact / reporttools / xtable / prodlim / simIDM

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