Use of multistate models to jointly model progression-free and overall survival and improve decision-making in clinical trials

Kaspar Rufibach
Methods, Collaboration & Outreach Group, Department of Biostatistics, Roche Basel
MRC Biostatistics unit
14th November 2019, Cambridge, UK

Generated 2019-11-14 at 23:27:30.

Who

Meller *et al.* (2019):



Beyer *et al.* (2019):





Multistate model for PFS and OS

Introduction

Oncology endpoints:

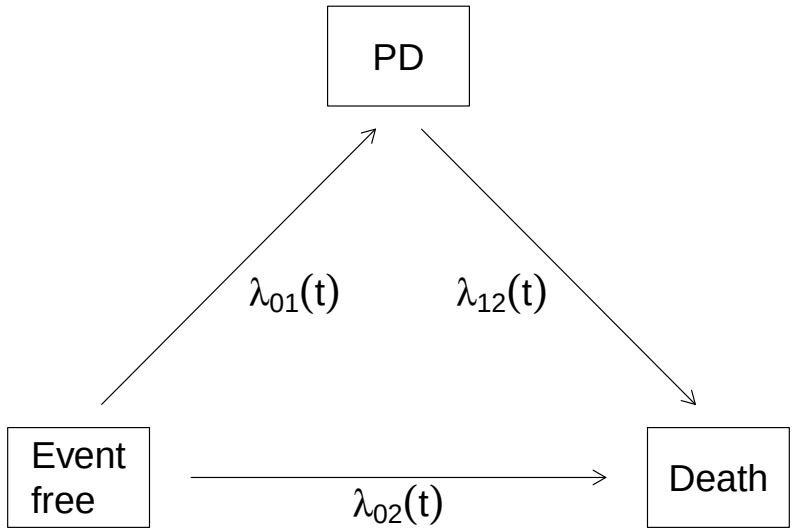
- Progression-free survival (PFS): Time from randomization to earlier of progression or death.
- Overall survival (OS): Time from randomization to death.

PFS common **surrogate** for OS in clinical trials.

Sophisticated methods to quantify amount of surrogacy, e.g. Buyse *et al.* (2016).

Correlation between PFS and OS important aspect, Li and Zhang (2015).

Multistate model for PFS and OS

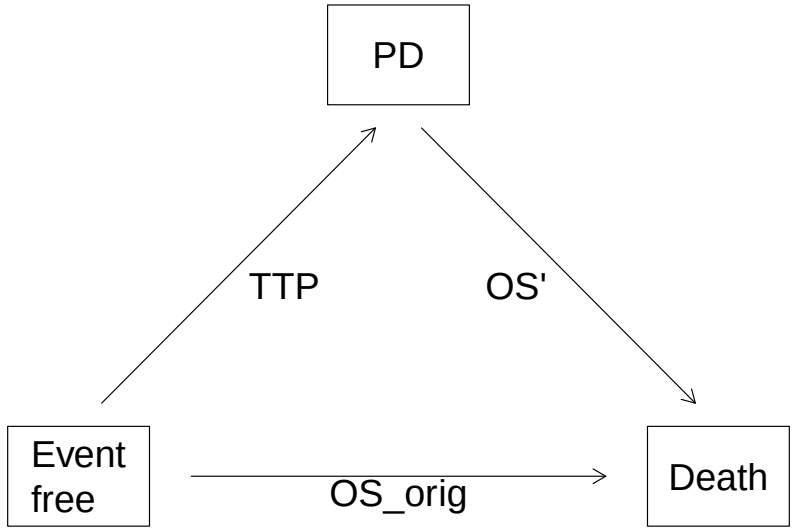


Standard **illness-death model without recovery**:

- 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, $\mathrm{OS} = \inf\{t : X(t) = 2\}$.

Alternatives

Latent failure time model



Latent failure time model (LFTM), Fleischer *et al.* (2009), Li and Zhang (2015):

- PFS = min(TTP, OS_{orig}).
- OS = PFS if PFS $\neq$ TTP, TTP + OS' else.

Challenges:

- **Impossible sampling space**: TTP $>$ OS_{orig} $\Rightarrow$ progression after death $\Rightarrow$ awkward idea.
- Issue with assumptions for estimation.

Copulas

Copulas, e.g. Burzykowski *et al.* (2001), Fu *et al.* (2013), Emura *et al.* (2017):

- Model general bivariate survival data (lifetimes of twins).

Challenges:

- PFS - OS structure more specific.
- PFS $\leq$ OS $\Rightarrow$ copulas do not place such a restriction on pair of event times.
- Reality: death without progression $\Rightarrow$ $P(\text{PFS} = \text{OS}) > 0$. Copula model with **continuous** "marginal" survival functions for PFS and OS: $P(\text{PFS} = \text{OS}) = 0$.

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).

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.

Exemplary application: **Pearson correlation**.

Multistate model for PFS and OS

Marginal distributions:

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

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.

Advantages of multistate model

Multistate model:

- Assumptions on $X(t)$ induce properties of transition intensities, (joint) probabilites, and thus PFS and OS.
- No progression after death.
- PFS = OS easily possible.
- Estimation: No assumption about "in-/dependence" of PFS and OS.

Multistate = (most?) parsimonious model

Correlation coefficient

Correlation coefficient

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

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

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

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

Proof: manipulations using law of total probability.

Estimation and inference for Markov models

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):

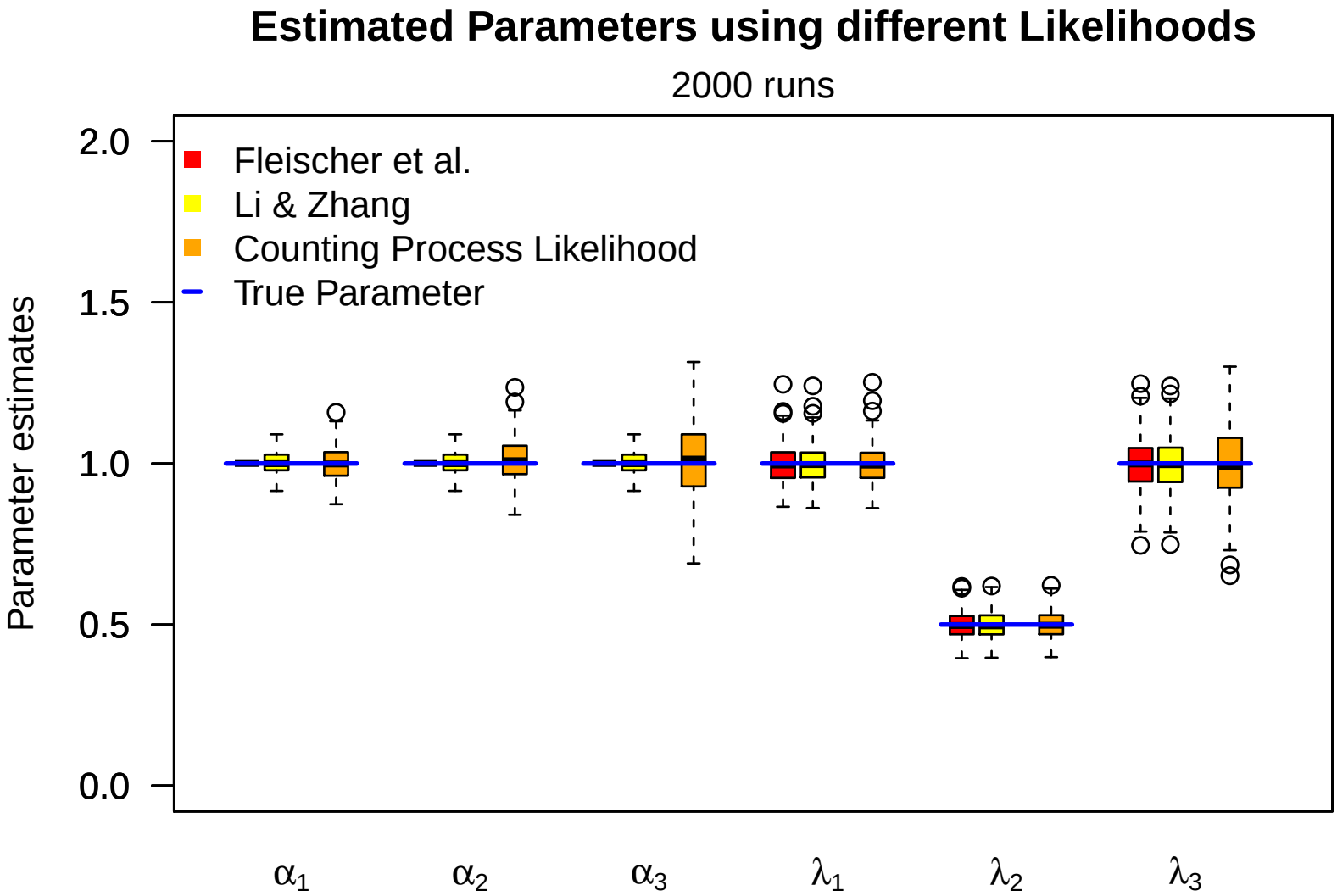
- Group patients depending on their path from 0 to 1 or 2, or censored.
- Likelihood uses **assumption of independence** of TTP, OS_{orig}. Cannot tell from (even uncensored!) data! Aalen (1987): "artificial problem", as LFTM not needed, see also Beyersmann *et al.* (2012).

Weber and Titman (2019):

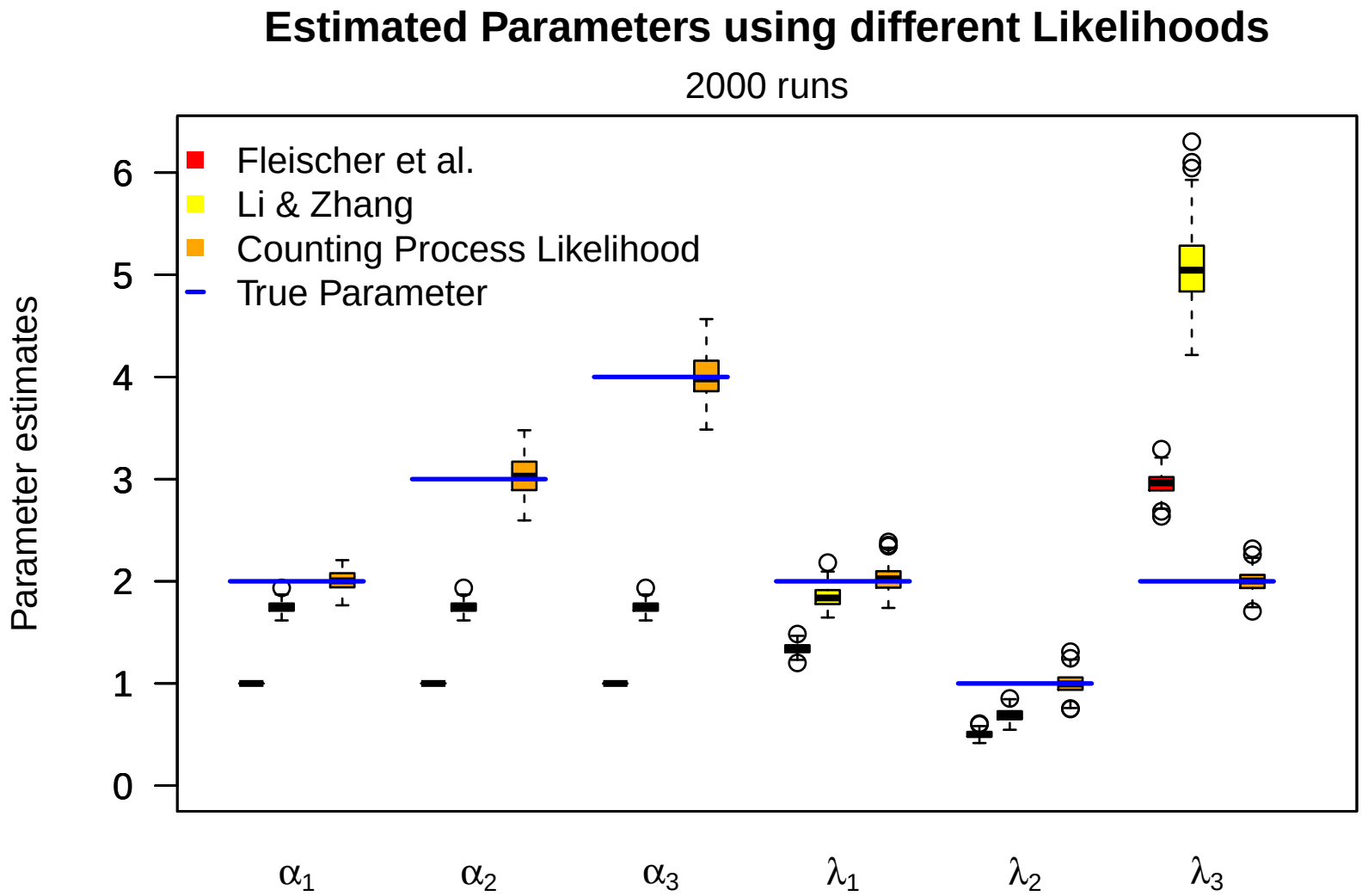
- Kendall's τ, based on multistate, nonparametric, and copula models.
- Use again LFTM for estimation.

Results

Results: estimated parameters Exponential



Results: estimated parameters time-inhomogeneous Weibull



Conclusions

Conclusions & outlook

Model PFS and OS within **illness-death without recovery multistate model**.

Advantages:

- Compared to LFTM avoids **questionable** and **uncheckable** assumptions,
- properties of PFS and OS induced through **transparent assumption on** $X(t)$,
- allows for **straightforward derivation** of survival functions and correlation for parametric models, e.g. no need to assume common Weibull shape parameter as in Li and Zhang (2015) to get tractable formulas,
- allows for **parametric** and **nonparametric** estimation and **inference** (at least) in Markov models using standard multistate modelling tools,
- engine to simulate PFS and OS times.

Outlook:

- How to best extrapolate tail of nonparametric survival function estimates?
- Shorten time for computation of bootstrap confidence intervals?
- R package?

Multistate models for early decision-making

How do we typically decide whether to move an oncology molecule into Phase 3?

Decision-making in early oncology development

1. Small single-arm trial for **experimental** drug (e.g. $n = 40$).
2. Response proportion, duration of response.
3. Compare to "corresponding" quantities from literature for **control** treatment.

But:

- **P(wrong decision)** may be high.
- Primary endpoint in Phase 3: **Overall survival**.

Proposal:

Decide in early phase based on OS prediction.

Decrease P(wrong decision).

Challenges and proposal

Challenges:

1. Response-type endpoint?
2. Surrogacy? **Poor** in many indications.
3. Immunotherapy (CIT): no effect on response, relevant OS effect.
4. **Non-randomized** comparison $\Rightarrow$ confounding.

Proposal: Base decision-making on **OS prediction from multistate model**.

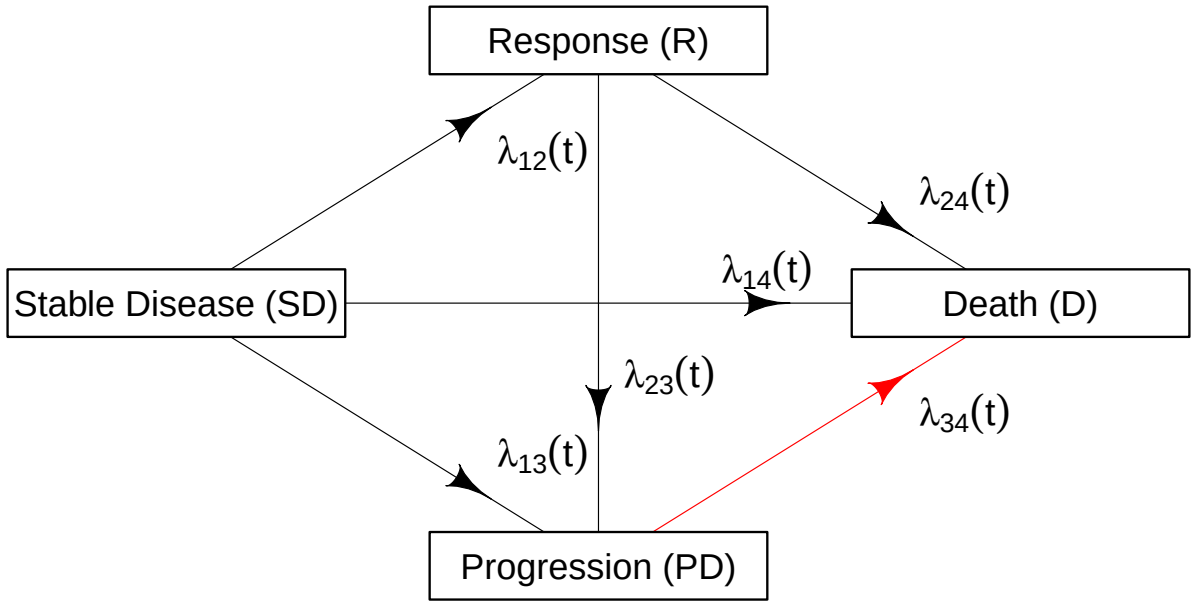
1. **Predicted survival function for experimental arm**.
2. Combine S_{exp} with S_{control} to get **predicted OS HR**.
3. Experimental drug might act on certain transitions only $\Rightarrow$ not captured through simple modelling of OS. Potential **efficiency gain**!
4. **Propensity scoring**.

Idealized scenario: Retrospective data from Phase 3 RCTs.

Long-term follow-up in both arms.

Randomization $\Rightarrow$ no confounding.

Multistate model for early decision-making



- Follow-up of patient until **PD or death without PD**.
- Post-progression hazard λ_{34}: **borrowing** from historical data.
- Transitions SD $\rightarrow$ D, R $\rightarrow$ D rare, hazards $\approx$ same in both arms.
- Markov assumption.

Predicted survival function in experimental arm, S_{exp}

Compute transition probabilities for each transition.

$$S_{\text{exp}}(t) = 1 - \Big(P_{SD\to D}(0,t) + P_{SD\to \mathbf{PD}\to \mathbf{D}}(0,t) + P_{SD\to R\to D}(0,t) + P_{SD\to R\to \mathbf{PD}\to \mathbf{D}}(0,t)\Big).$$

λ_{34} corresponding to **PD** $\to$ **D** transition borrowed from historical data.

Historical borrowing for λ_{34}

Experimental treatment expected to provide benefit **beyond PD**?

No:

- E.g. chemotherapy or antibody-dependent cellular cytotoxicity.
- **Plug-in** hazard function estimate from historical control.
- No post-PD information required for experimental arm.

Yes:

- E.g. chemoimmunotherapy.
- Estimate post-PD hazard ratio assuming **proportionality**.
- How much post-PD deaths needed in experimental arm to reliably **estimate post-PD HR**?

Benefit beyond PD: Oak

Oak

Previously treated non-small-cell lung cancer.

Rittmeyer *et al.* (2017).

	Atezolizumab	Chemotherapy	Hazard ratio
Effect post-PD	expected	not expected	
Objective Response	58 (13.6%)	57 (13.4%)	
Duration of Response	26.3 (10 - ∞)	6.2 (4.9 - 7.6)	
Overall Survival			0.73 (0.62, 0.87)

If this were early phase data - would you initiate Phase 3?

Competitors used this mechanism of action.

OS prediction when post-PD hazards assumed proportional

Random variable:

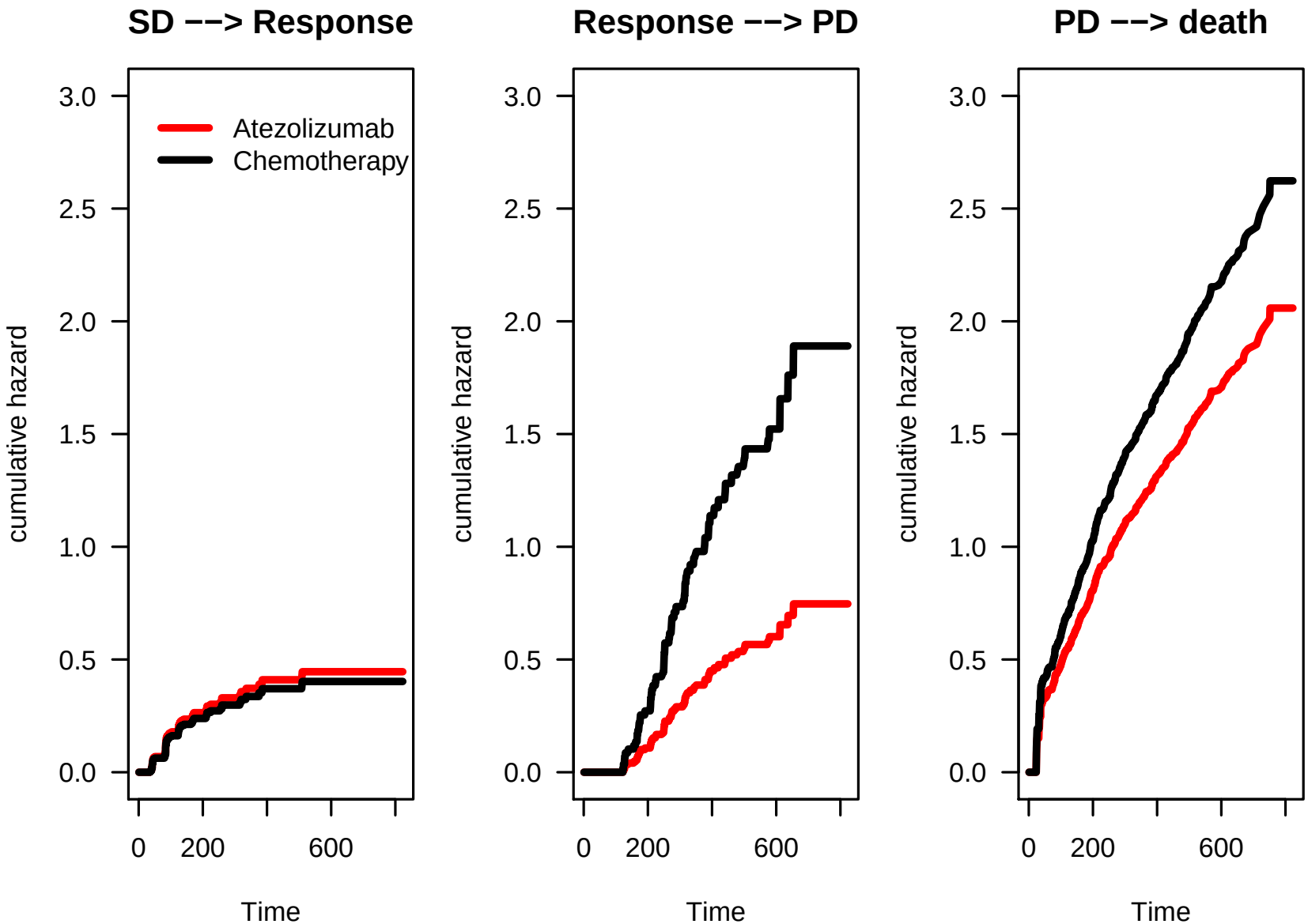
$$Z = \begin{cases} 0 & \text{if patient in control,} \\ 1 & \text{if in experimental group.} \end{cases}$$

$$\lambda_{34}(t \mid Z) = \lambda_{34,0}(t) \exp(\beta_{34} Z)$$

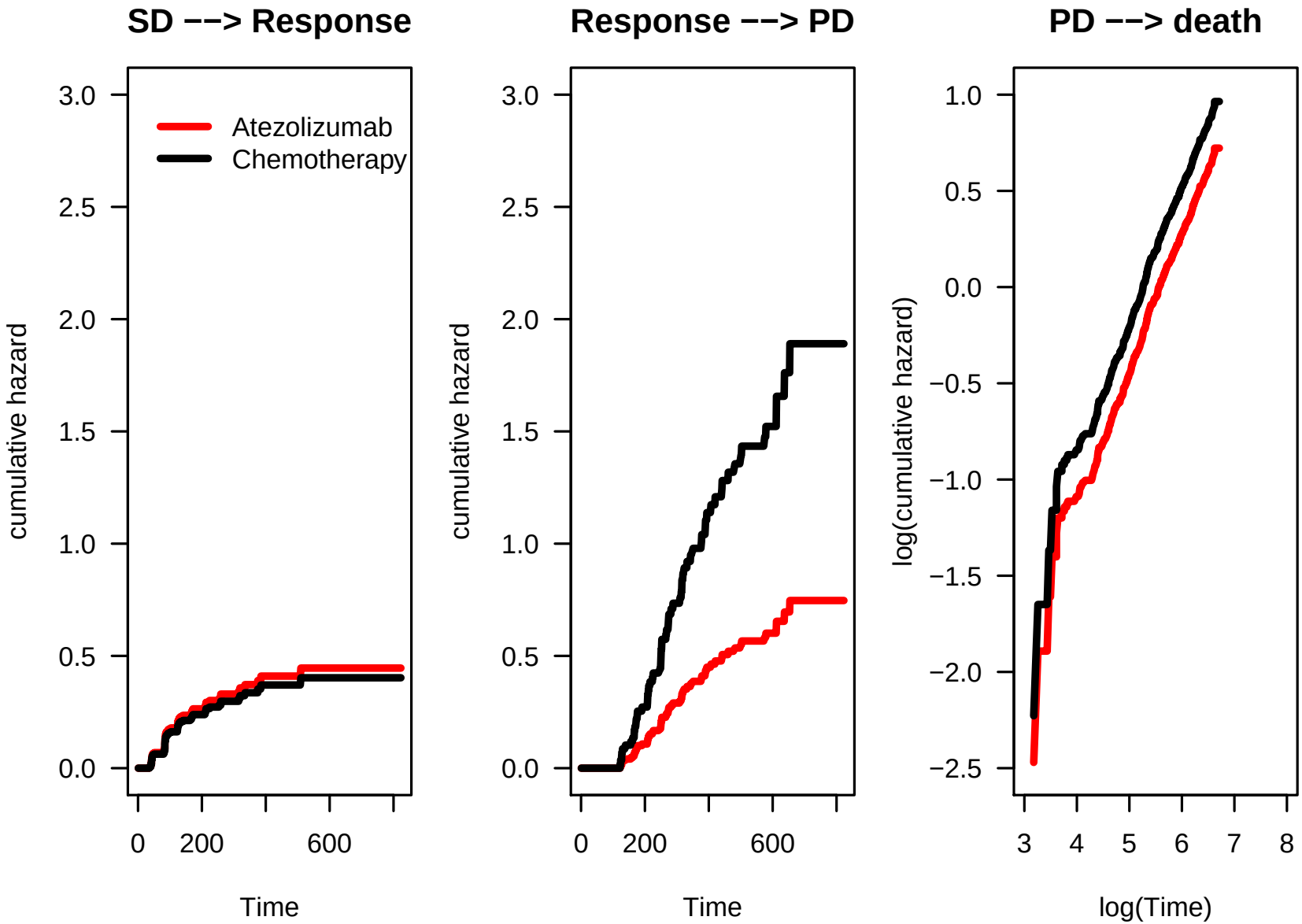
Baseline hazard $\lambda_{34,0}$ **estimated from both arms combined**.

Post-progression hazard ratio β_{34}?

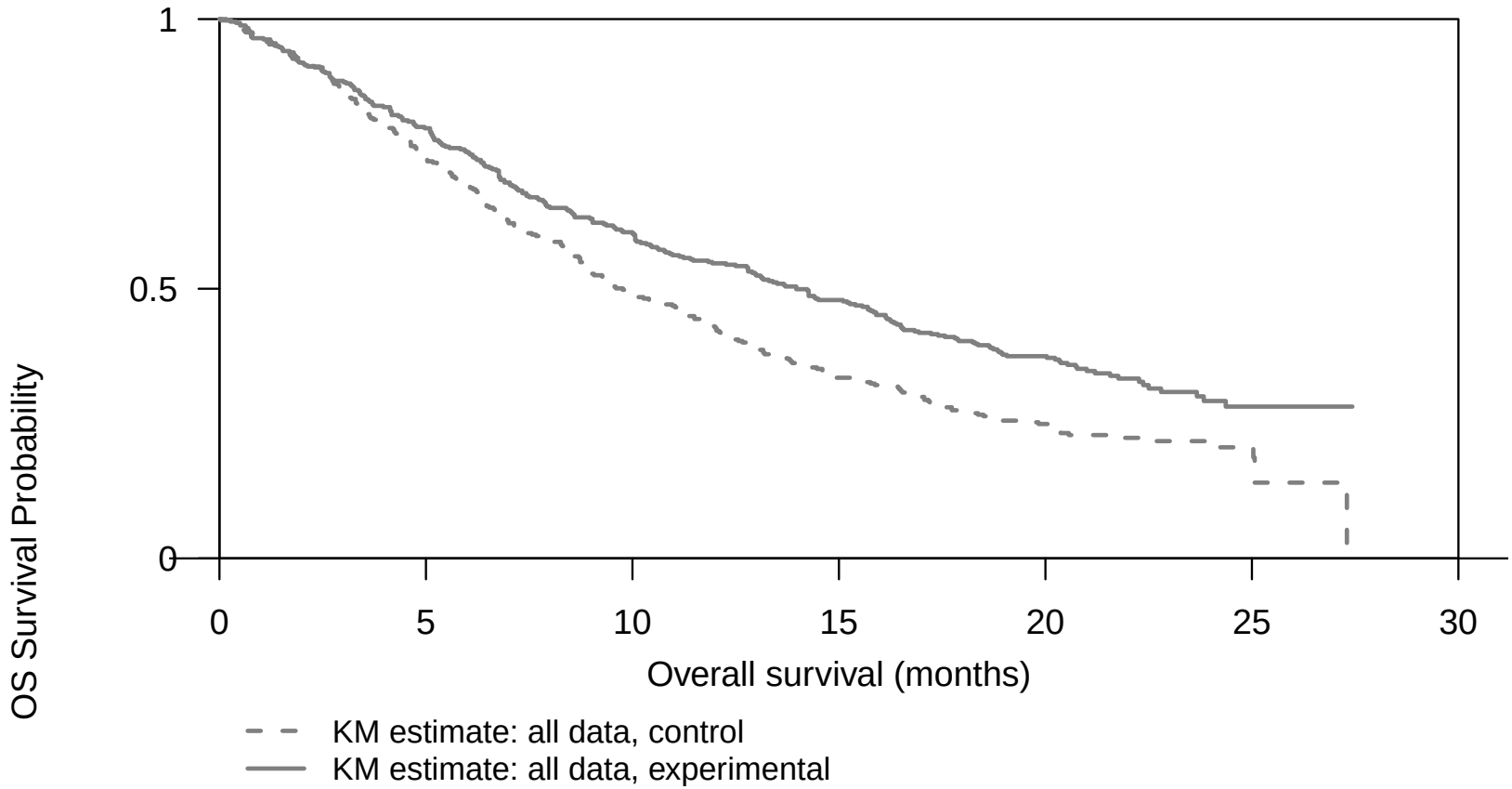
Oak: raw cumulative hazard estimates (of interest)



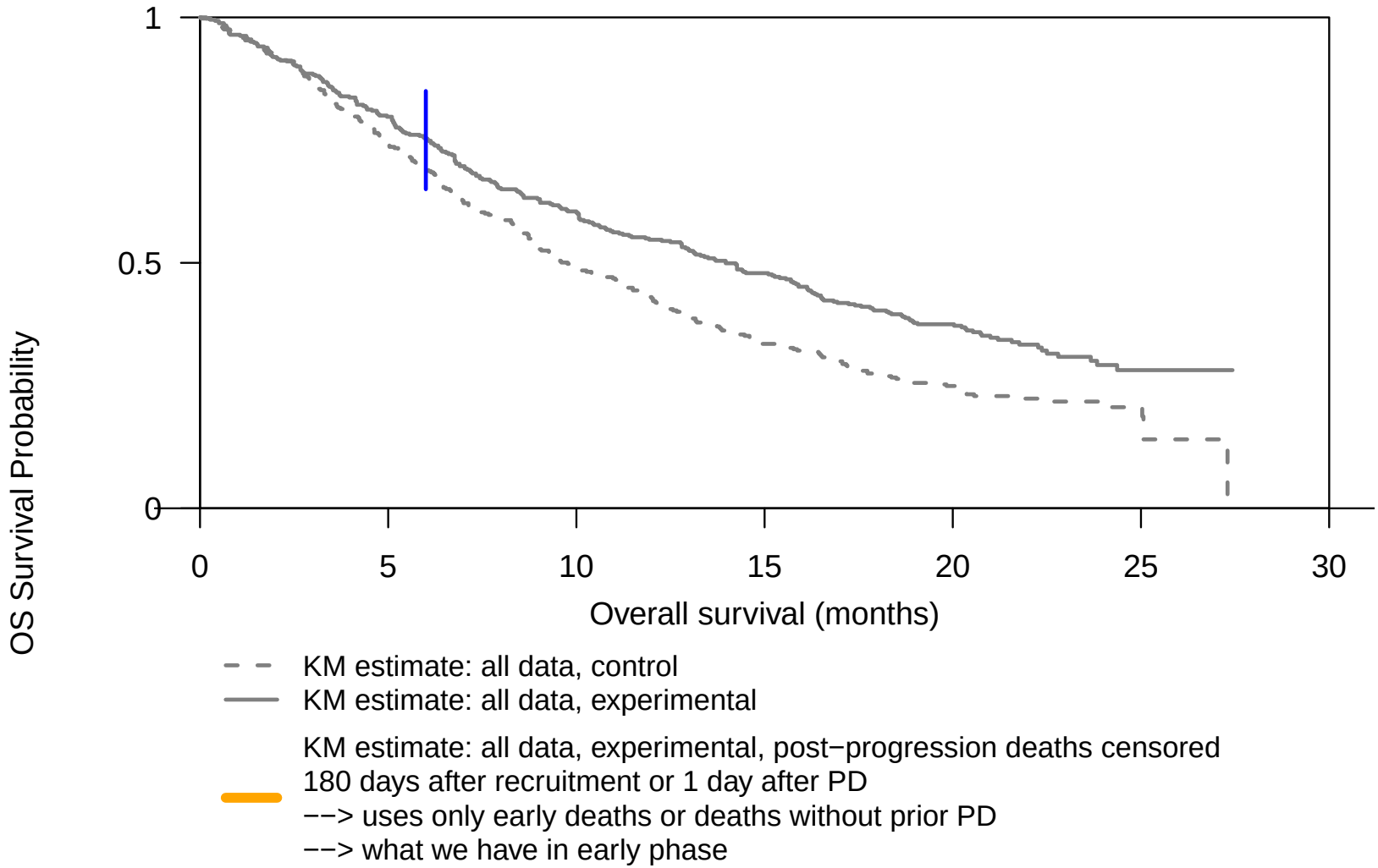
Oak: raw cumulative hazard estimates (of interest)



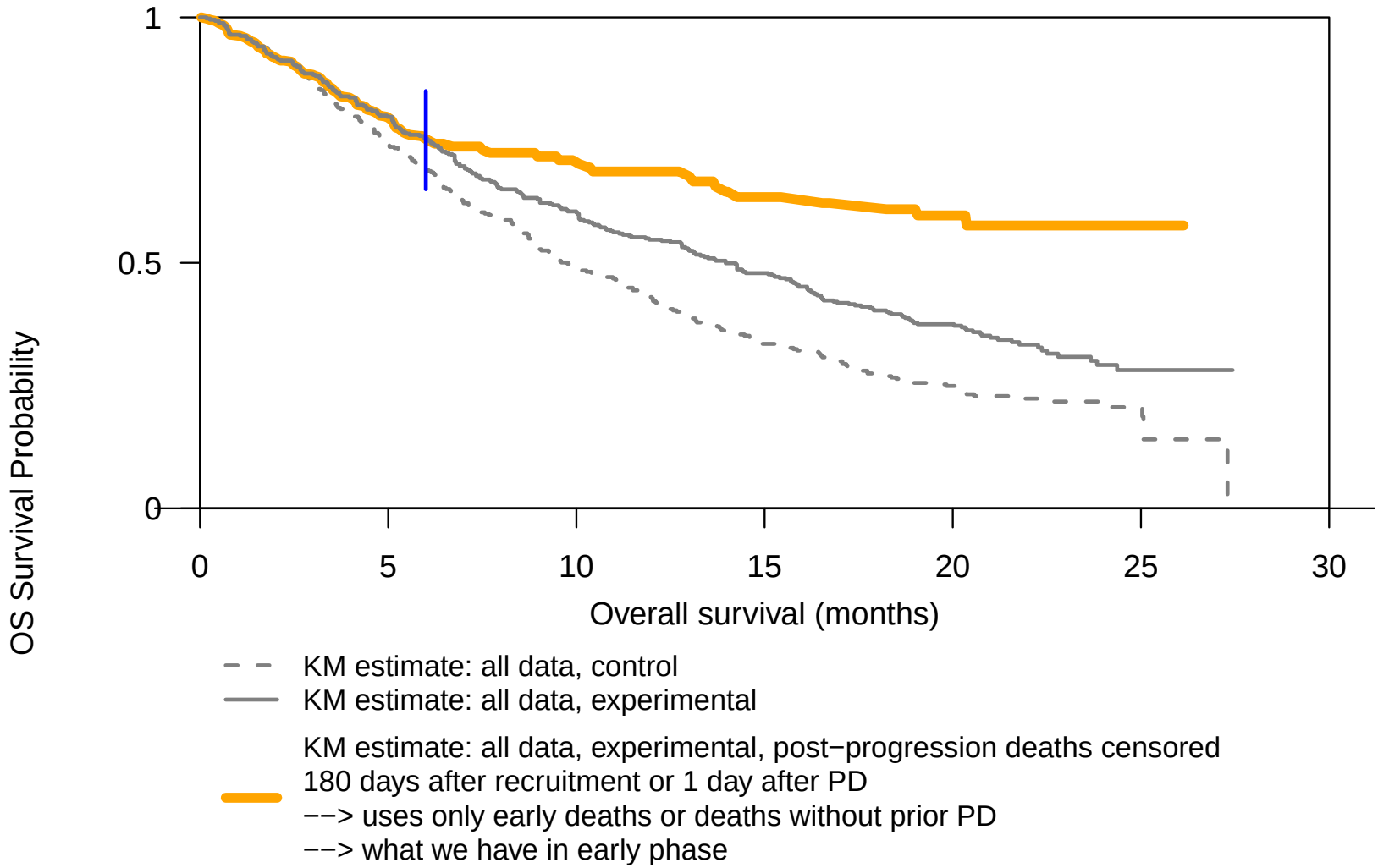
Oak: estimates / predictions of S_{exp}



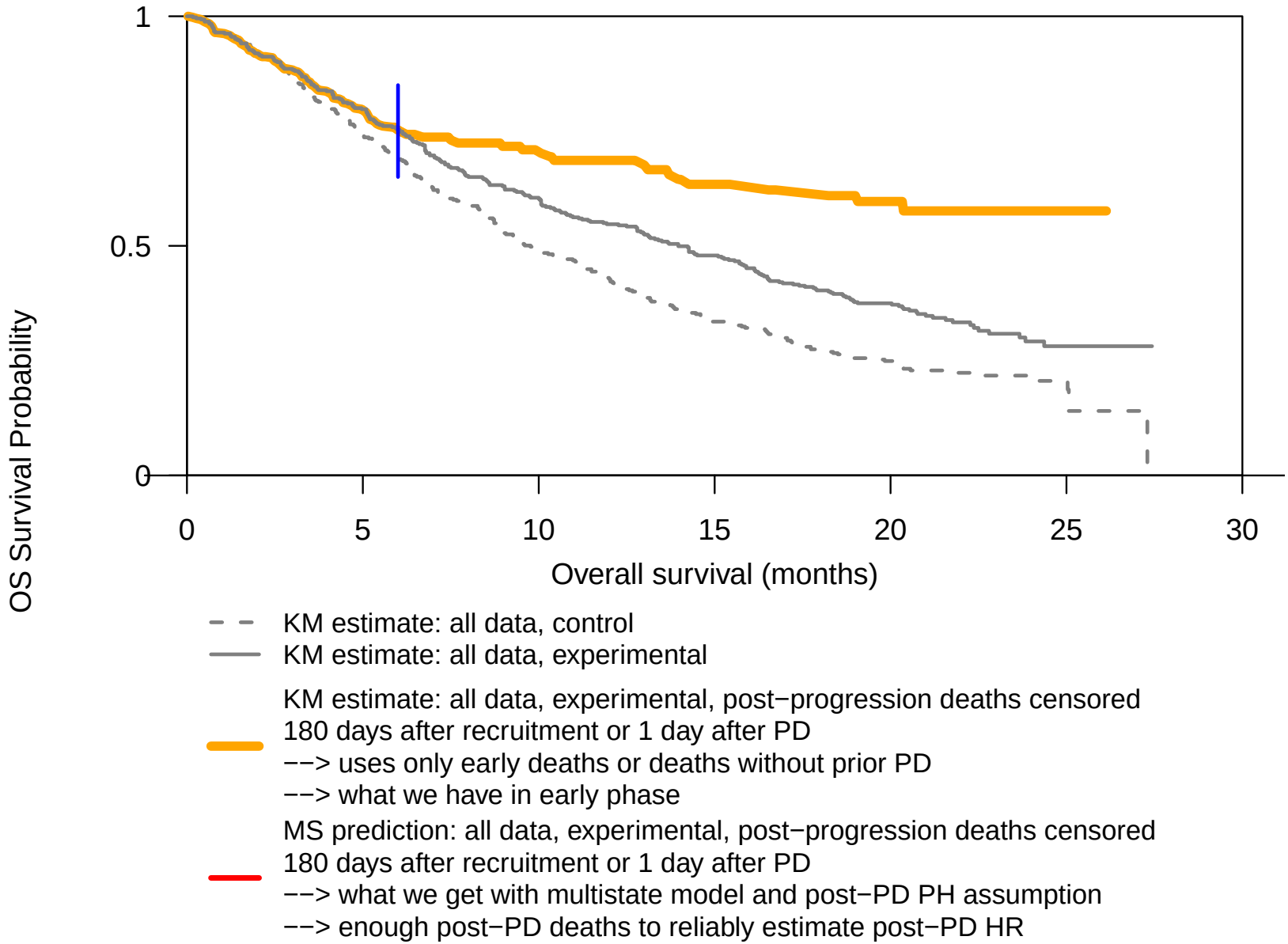
Oak: estimates / predictions of S_{exp}



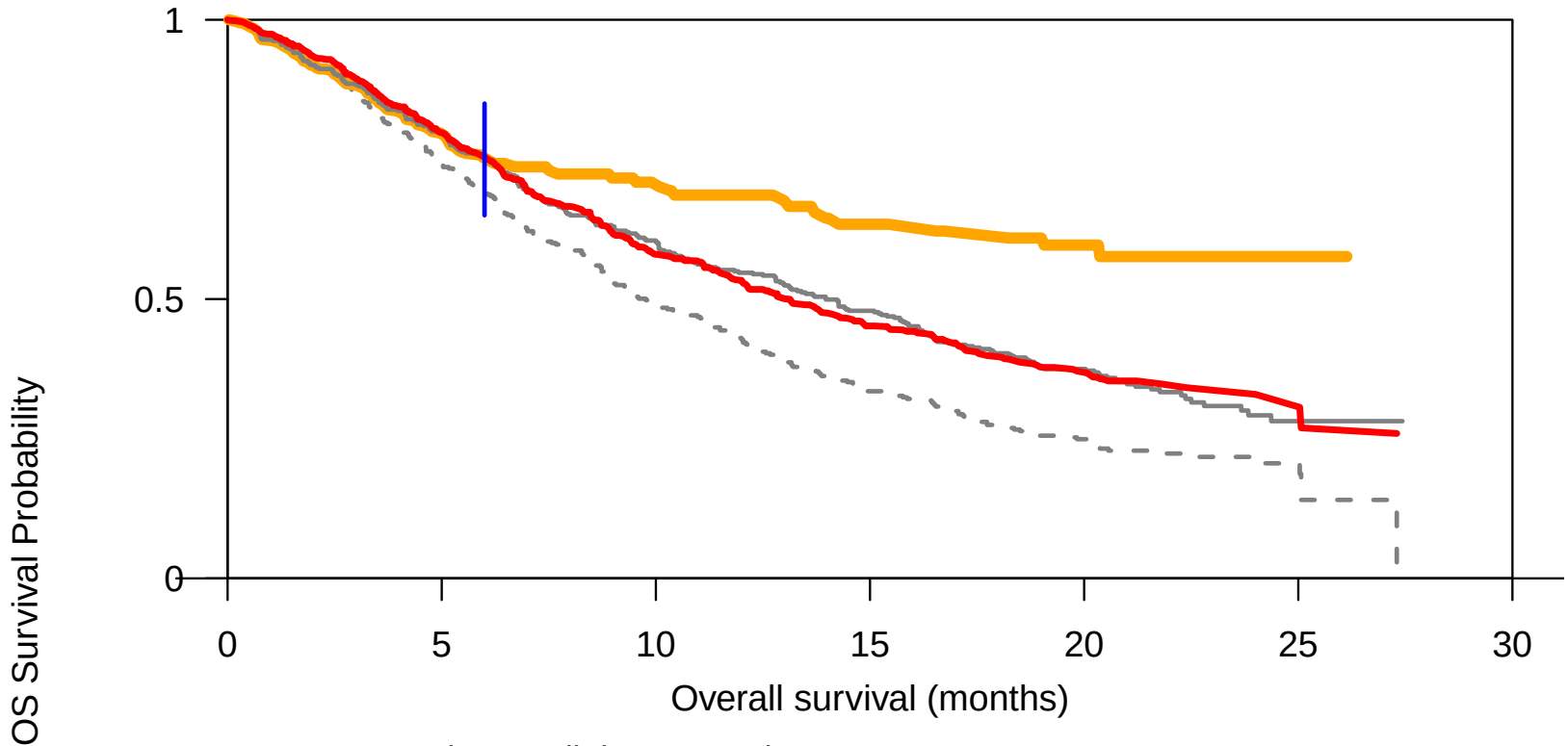
Oak: estimates / predictions of S_{exp}



Oak: estimates / predictions of S_{exp}



Oak: estimates / predictions of S_{exp}



KM estimate: all data, control
KM estimate: all data, experimental
KM estimate: all data, experimental, post−progression deaths censored 180 days after recruitment or 1 day after PD
−−> uses only early deaths or deaths without prior PD
−−> what we have in early phase
MS prediction: all data, experimental, post−progression deaths censored 180 days after recruitment or 1 day after PD
−−> what we get with multistate model and post−PD PH assumption
−−> enough post−PD deaths to reliably estimate post−PD HR

Early phase decision based on multistate prediction:

P(wrong decision)?

OS prediction from mimicked early phase data

Historical control: Oak control arm data.

False-positive decision: Sample early phase trial from Oak control arm.
False-negative decision: Sample early phase trial from Oak experimental arm.

Sample early phase trial:

- 40 patients,
- 6 months uniform recruitment,
- analysis 15 months after first patient entered,
- censor post-PD follow-up **one day after PD**,
- estimate $\lambda_{12}, \lambda_{13}, \lambda_{14}, \lambda_{23}, \lambda_{24}$ from this data.

Cox regression for post-PD transition $\Rightarrow \widehat{\lambda}_{34}(t|Z)$.

Compute prediction of S_{exp}.

OS HR prediction based on early phase trial

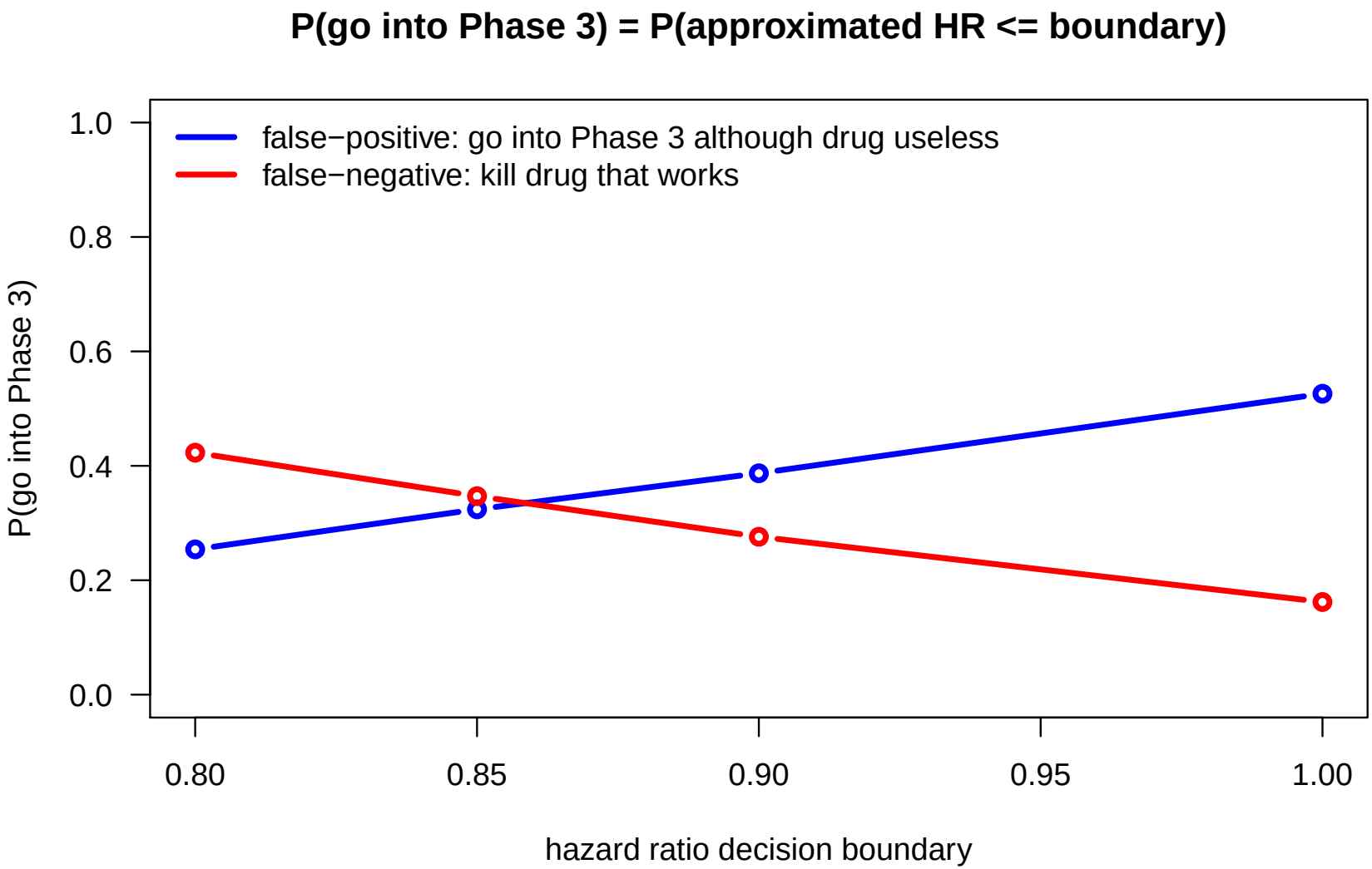
Approximate HR by fitting exponential distribution to both arms $\Rightarrow \widehat{HR}$.

Decision to move to Phase 3: $\widehat{HR} \leq$ boundary $\in \{0.80, 0.85, 0.90, 1.00\}$.

Repeat 1000 times.

Resampling $\Rightarrow$ **quantification of uncertainty**.

Oak: P(wrong decision)



How many post-PD deaths to estimate HR of PD $\rightarrow$ death transition?

How many post-PD deaths to estimate HR of PD $\rightarrow$ death transition?

Ask during Q&A.

Conclusions for early-decision making proposal

Conclusions

Early phase decision-making based on **multistate OS prediction**:

- Assumption on $\lambda_{34} \Rightarrow$ need to understand **disease and treatment**.
- **Avoids difficulty in interpretation of response-type endpoints**.
- Feasibility assessed in **idealized scenario**.
- Recommendation **how much post-PD follow-up** needed to estimate β_{34}.
- Needs **long-term individual-patient** data in control arm!

What about confounding?

Real-world data as historical control.

Combine proposal with propensity scoring.

Conclusions

Multistate models

Multistate models useful:

- Canonical **extension of survival analysis**.
- Get more **insight** in how disease and drug work.
- **Prediction** in well-specified, as opposed to black-box, model.
- **Jointly** model three key oncology endpoints: response, PFS, OS.
- Applications by no means restricted to oncology!

Many potential applications:

- Improved **early stage decision-making** ⇒ Beyer *et al.* (2019).
- Improved **communication** of effect and optimized **sample size** computation.
- Bivariate modelling of PFS and OS to help inform **surrogacy** questions ⇒ Meller *et al.* (2019).

Thank you for your attention.

kaspar.rufibach@roche.com

http://www.kasparrufibach.ch

numbersman77

numbersman77

References I

- Aalen, O., Borgan, Ø., and Gjessing, H. (2008). *Survival and event history analysis: a process point of view*. Springer Science & Business Media.
- Aalen, O. O. (1987). Dynamic modelling and causality. *Scandinavian Actuarial Journal*, **1987**(3-4), 177–190.
- Aalen, O. O. and Johansen, S. (1978). An empirical transition matrix for non-homogeneous markov chains based on censored observations. *Scandinavian Journal of Statistics*, **5**(3), 141–150.
- Andersen, P. K., Borgan, Ø., Gill, R. D., and Keiding, N. (1993). *Statistical Models Based on Counting Processes*. Springer.
- Baselga, J. and Cortes, J. et. al. (2012). Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N. Engl. J. Med.*, **366**(2), 109–119.
- Beyer, U., Dejardin, D., Meller, M., Rufibach, K., and Burger, H. U. (2019). A multistate model for early decision making in oncology. *Biom J, to appear*.
- Beyersmann, J., Allignol, A., and Schumacher, M. (2012). *Competing Risks and Multistate Models with R*. Springer.
- Burzykowski, T., Molenberghs, G., Buyse, M., Geys, H., and Renard, D. (2001). Validation of surrogate end points in multiple randomized clinical trials with failure time end points. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, **50**(4), 405–422.

References II

- Buyse, M., Molenberghs, G., Paoletti, X., Oba, K., Alonso, A., Van der Elst, W., and Burzykowski, T. (2016). Statistical evaluation of surrogate endpoints with examples from cancer clinical trials. *Biom J*, **58**(1), 104–132.
- Emura, T., Nakatochi, M., Murotani, K., and Rondeau, V. (2017). A joint frailty-copula model between tumour progression and death for meta-analysis. *Stat Methods Med Res*, **26**(6), 2649–2666.
- Fleischer, F., Gaschler-Markefski, B., and Bluhmki, E. (2009). A statistical model for the dependence between progression-free survival and overall survival. *Stat. Med.*, **28**(21), 2669–2686.
- Fu, H., Wang, Y., Liu, J., Kulkarni, P. M., and Melemed, A. S. (2013). Joint modeling of progression-free survival and overall survival by a Bayesian normal induced copula estimation model. *Stat Med*, **32**(2), 240–254.
- 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.
- Li, Y. and Zhang, Q. (2015). A Weibull multi-state model for the dependence of progression-free survival and overall survival. *Stat Med*, **34**(17), 2497–2513.
- 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.

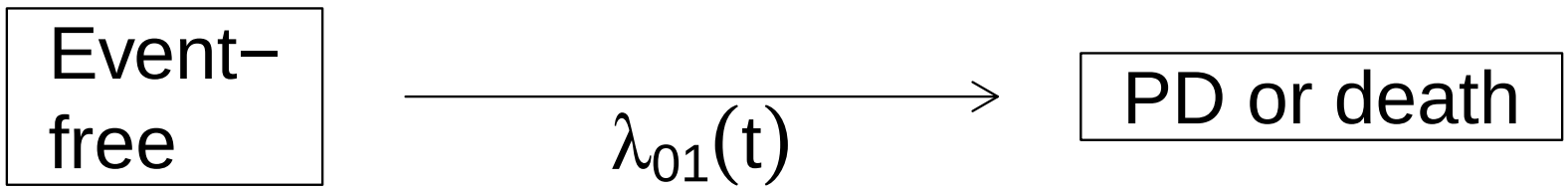
References III

- Rittmeyer, A., Barlesi, F., Waterkamp, D., Park, K., Ciardiello, F., Von Pawel, J., Gadgeel, S. M., Hida, T., Kowalski, D. M., Dols, M. C., *et al.* (2017). Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *The Lancet*, **389**(10066), 255–265.
- Swain, S. M. and Baselga, J. (2015). Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N. Engl. J. Med.*, **372**(8), 724–734.
- Weber, E. M. and Titman, A. C. (2019). Quantifying the association between progression-free survival and overall survival in oncology trials using kendall's τ. *Statistics in medicine*, **38**, 703–719.

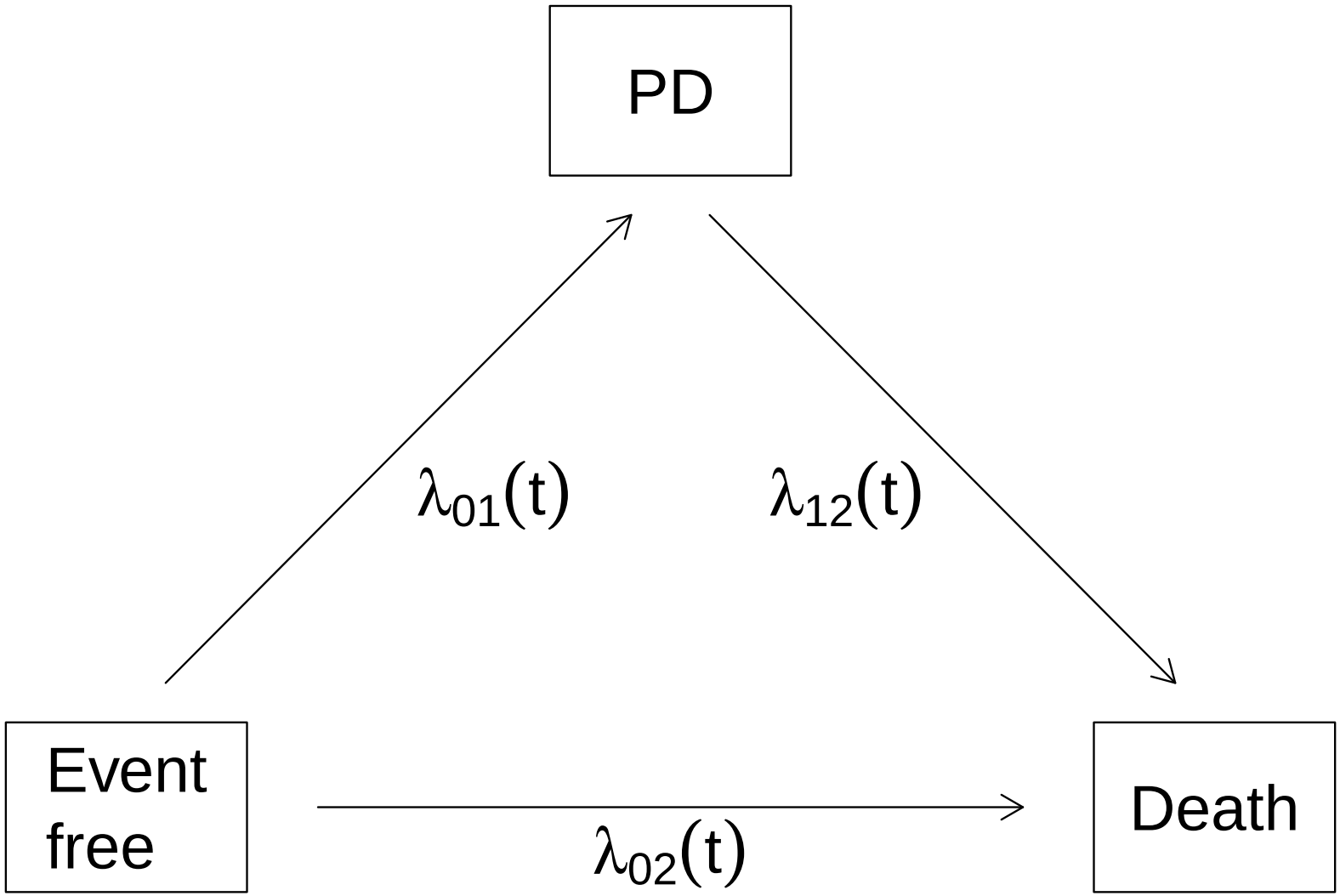
Backup

Multistate models

Canonical extension of survival analysis



Canonical extension of survival analysis



Multistate models

Multistate model:

- 1-1 correspondence **hazard - probability** breaks down.
- Transition probabilities: (Markov) process $X(t)_{t\geq 0}$ with state space $\{0,1,2\} = \{\text{event-free, progression, death}\}$. Then,

$$P_{lj}(s,t) \quad := \quad P(X_t = j | X_s = l, \text{Past}).$$

- Estimate P_{lj}'s **nonparametrically** by **Aalen-Johansen** estimator.
- PFS: Kaplan-Meier of time-to-progression simply censoring death is **biased**!
- OS: Aalen-Johansen offers **higher precision** compared to simple Kaplan-Meier estimate, Andersen *et al.* (1993) (p. 315 and Fig. IV.4.16).
- Markov assumption **stronger** than what is needed for Kaplan-Meier though.

Prediction in multistate models

Rates (hazards, intensities):

- Modelling of effects of covariates on **transition hazards**.
- Hazard ratios (HR) from Cox regression.

Transition probabilities look at **cumulative effects**:

- Effects on transition probabilities may be different from what HRs suggest.
- **Intermediate** events in multistate model also contribute to cumulative effects.
- How to estimate such cumulative effects?

Prediction from multistate model!

Prediction in multistate models

General problem: estimate **conditional probability of some future clinical event**, given

- event history,
- set of values for prognostic factors of a patient.

Derive formulas for these conditional probabilities, or simulate.

Final result: survival function for OS, as function of

- covariates and
- relevant **cumulative hazards**.

PFS - OS

Multistate vs. latent failure time model

Fleischer *et al.* (2009), Li and Zhang (2015): LFTM with **uncheckable** and **questionable** (**unrealistic**?) independence assumption.

Connections to multistate model? We are still figuring that out, work in progress.

Parametric models: formula for S_{PFS} identical for all three models below, and

- **Time-homogeneous Markov, Exponential**: model so simple that $\nexists$ time-inhomogeneous Markov process. S_{OS} identical to Exponential LFTM.
- **Time-homogeneous Markov, Weibull**: formula for S_{OS} identical to Weibull LFTM $\Rightarrow$ are model assumptions equivalent? **No**!
- **Time-inhomogeneous Markov, Weibull**: formulas for S_{OS} are **different**.

BUT: values of estimated parameters differ between LFTM and multistate for **all three parametric models**, as **likelihoods differ**!

Not clear (?) how to nonparametrically estimate LFTM $\Rightarrow$ possible for (Markov) multistate.

Assumptions for multistate model

Assumptions for multistate model

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

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

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, $\alpha_{12}(t; t_1) = \alpha_{12}(t)$ for all $t_1 < t$.
- **Homogeneous**: intensities are time-constant, i.e. **Exponential**, $\alpha_{ij}(t) = \alpha_{ij}, i, j = 0, 1, 2$.

$X(t)$ **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):

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

If $X(t)$ non-Markov:

- P_{11} and P_{12} depend on **PFS time** t_1.
- Although P_{01}, P_{02} depend on α_{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.

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

- $P_{00}(s,u_-)\alpha_{01}(u)$: "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.

Illness-death multistate model for PFS and OS

Marginal distributions:

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

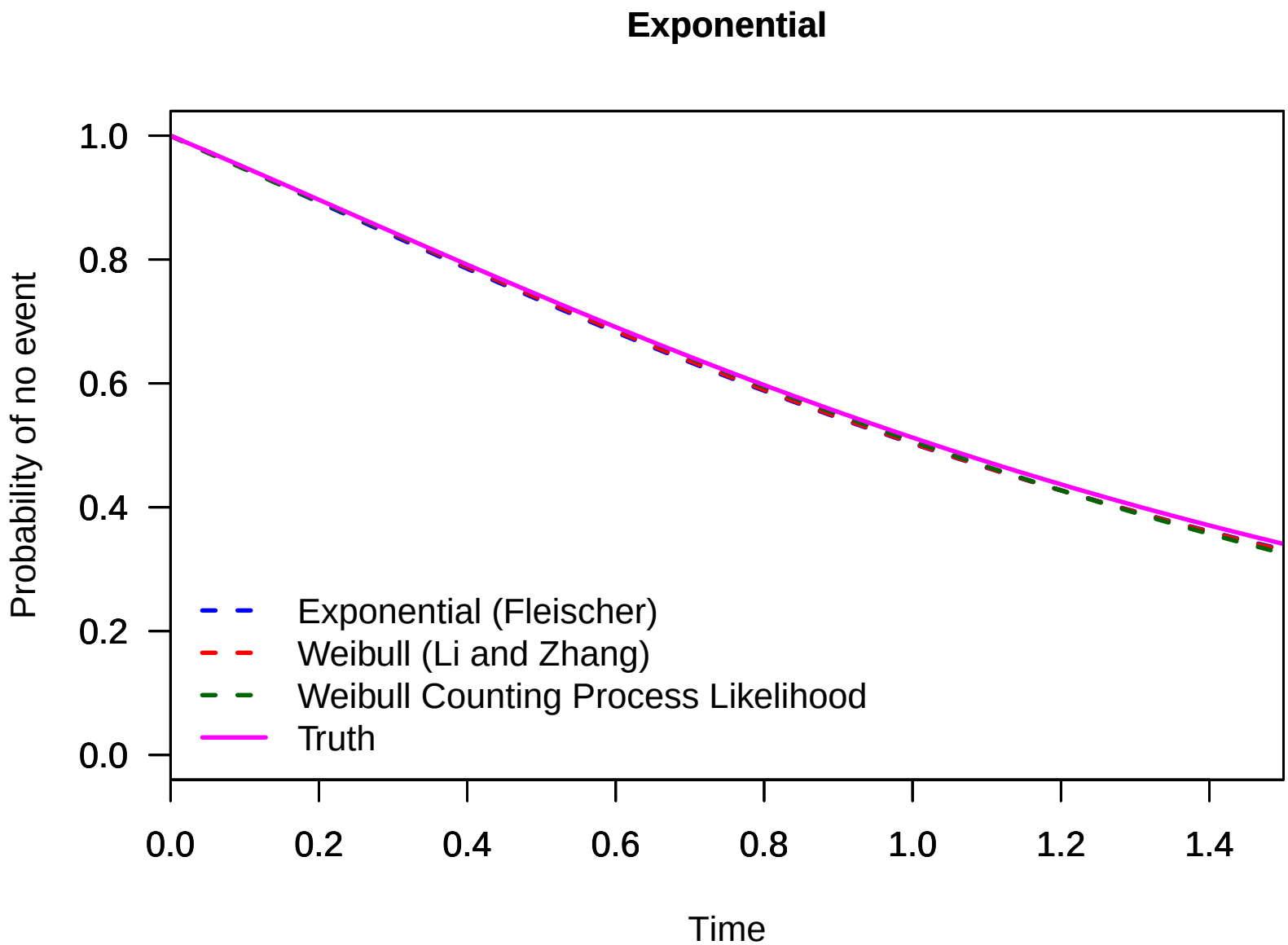
Joint distribution:

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

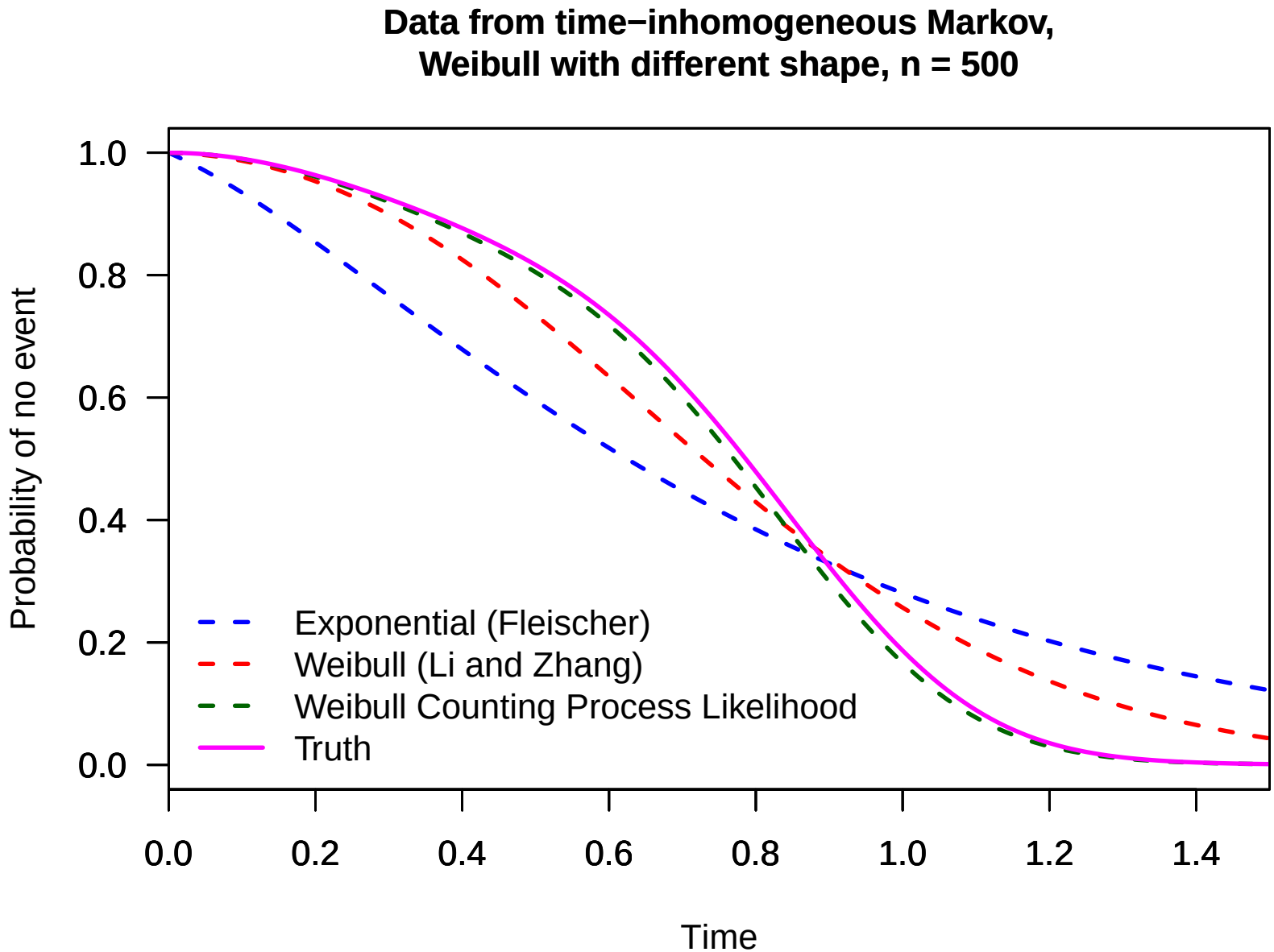
X **inhomogeneous Markov**: $P(X(v) = 2 | X(u) = 1) = P_{12}(u,v)$ independent of progression time $t_1 \leq u$.

X **non-Markov**: integrate $P_{12}(u,v;t_1)$ over conditional distribution of all possible progression times $t_1 \leq u \Rightarrow$ final formula tedious.

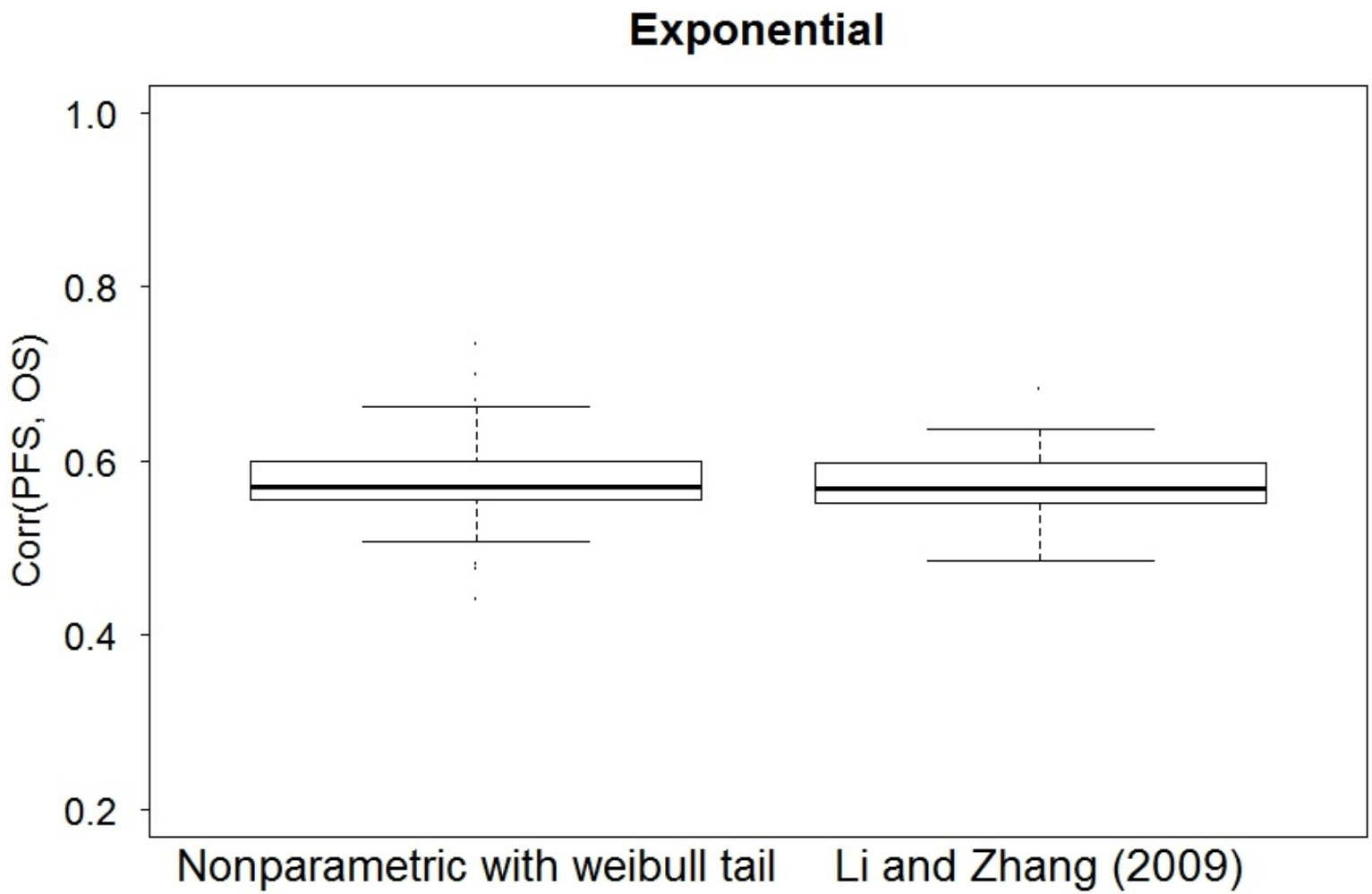
Results: S_{OS} for Exponential



Results: S_{OS} for Weibull

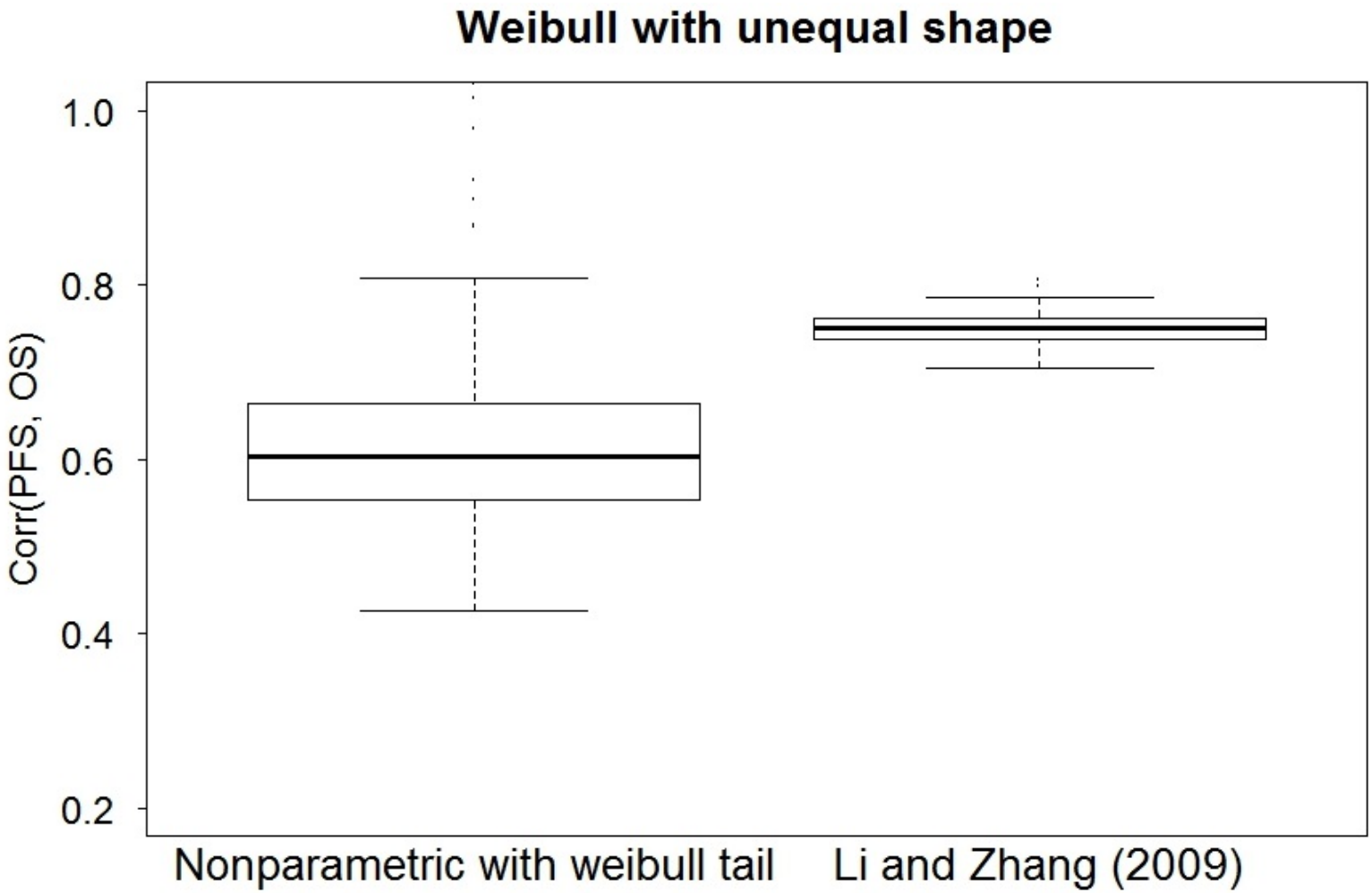


Results: correlations Exponential



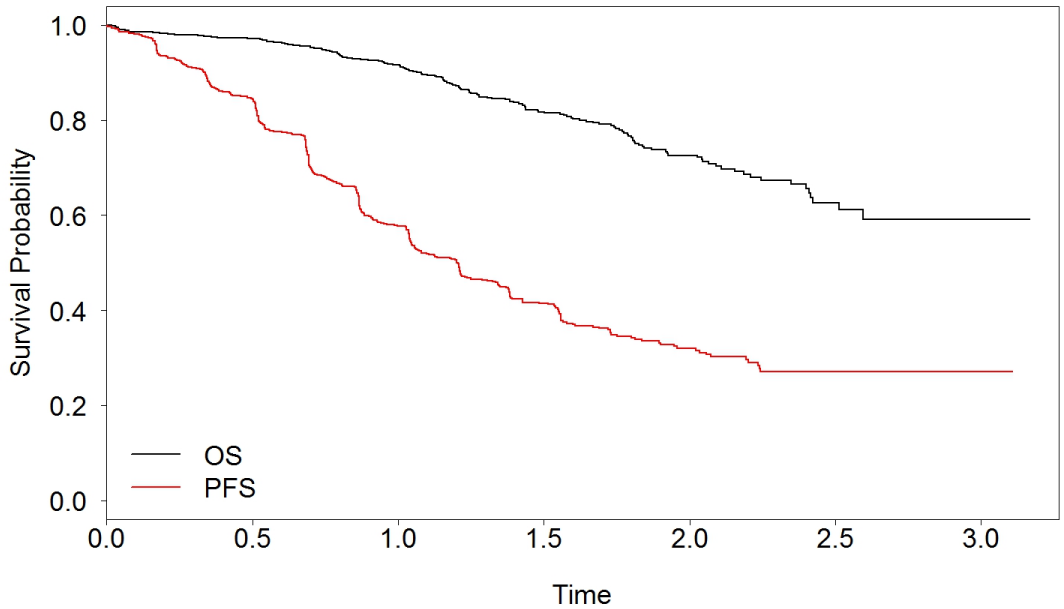
Corr(PFS, OS) for 200 simulated dataset from time-inhomogeneous Markov process.

Results: correlations Weibull



Corr(PFS, OS) for 200 simulated dataset from time-inhomogeneous Markov process.

Results: CLEOPATRA, Baselga and Cortes (2012).



	Exponential	Weibull	Weibull Markov	Nonparametric Markov
Corr(PFS, OS)	0.611	0.643	0.483	0.450
95% Bootstrap CI	[0.541; 0.673]	[0.584; 0.699]	[0.342; 0.643]	[0.297; 0.655]

Table: Correlation between PFS and OS in CLEOPATRA (1000 bootstrap samples).

Early decision-making

How many post-PD deaths needed?

Assumption:

$$\lambda_{34}(t \mid Z) \quad = \quad \lambda_{34,0}(t) \exp(\beta_{34} Z).$$

How many post-PD deaths needed in **experimental** arm to reliably estimate λ_{34}?

Planning stage: only data for control arm are available.

- Fit multistate model to control data.
- Assume transition-specific hazard ratios corresponding to **clinically meaningful OS effect**.
- **Simulate**.

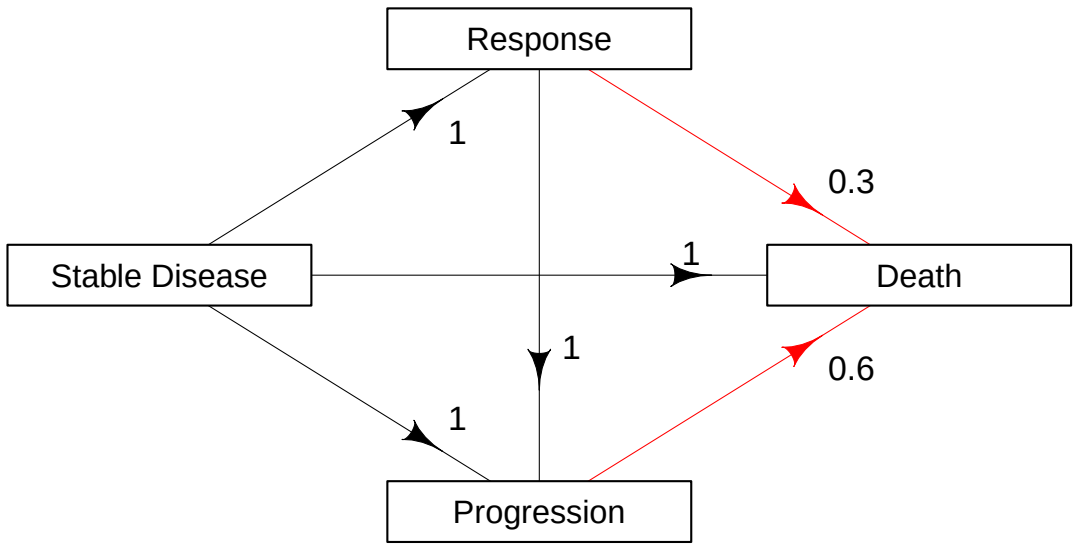
Various scenarios for post-PD follow-up time.

Simulation details – mimick Oak

NOT power computation for hypothesis test – sample size too small anyway.

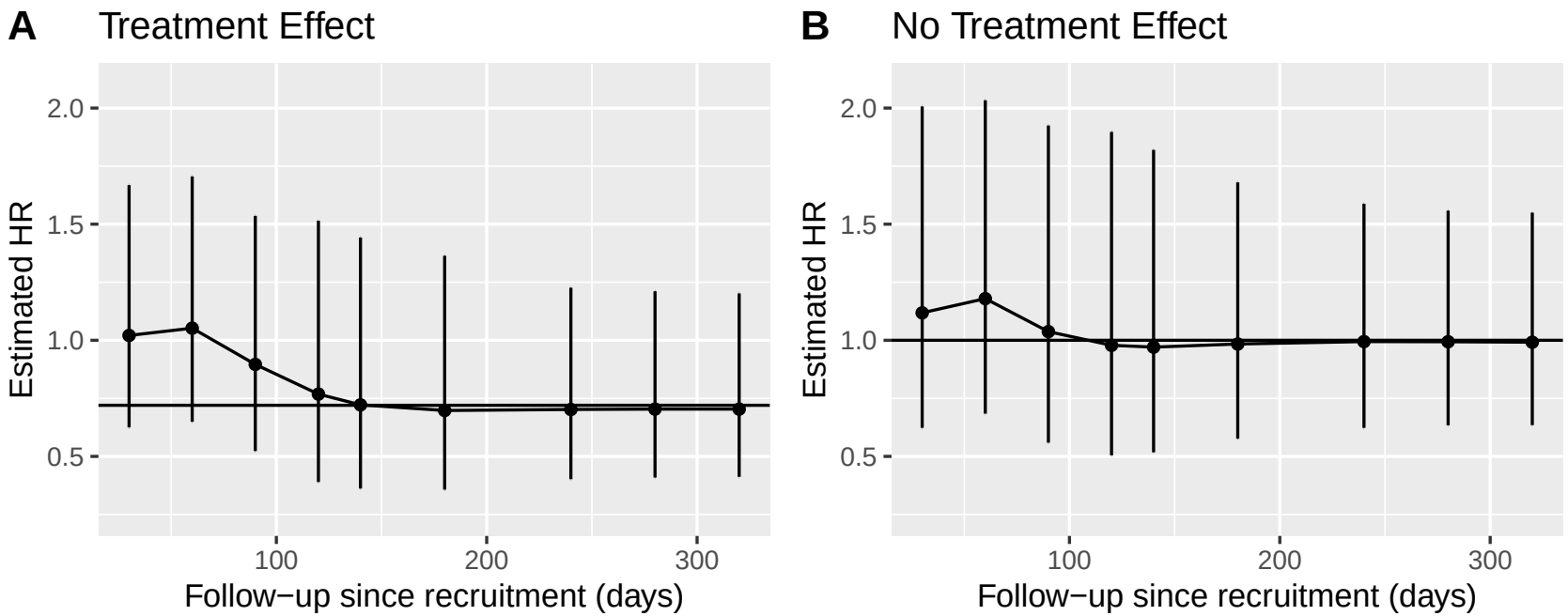
Rather: find cutoff timepoint from which on OS HR estimate remains **stable**.

- Simulate 40 patient from experimental arm as before.



- Resulting **OS HR = 0.73**. Close to Oak OS HR.
- Follow-up post-PD for experimental arm truncated at 30, 60, 90, 120, 150, 180 and 240 days after recruitment.
- Repeat 1000 times.

Stability of hazard ratio estimate



180-240 days sufficient to obtain stable point estimate over time.

Typical early phase follow-up: Post-PD deaths censored 180 **days after recruitment** in experimental arm.

Example 1: Cleopatra

Cleopatra

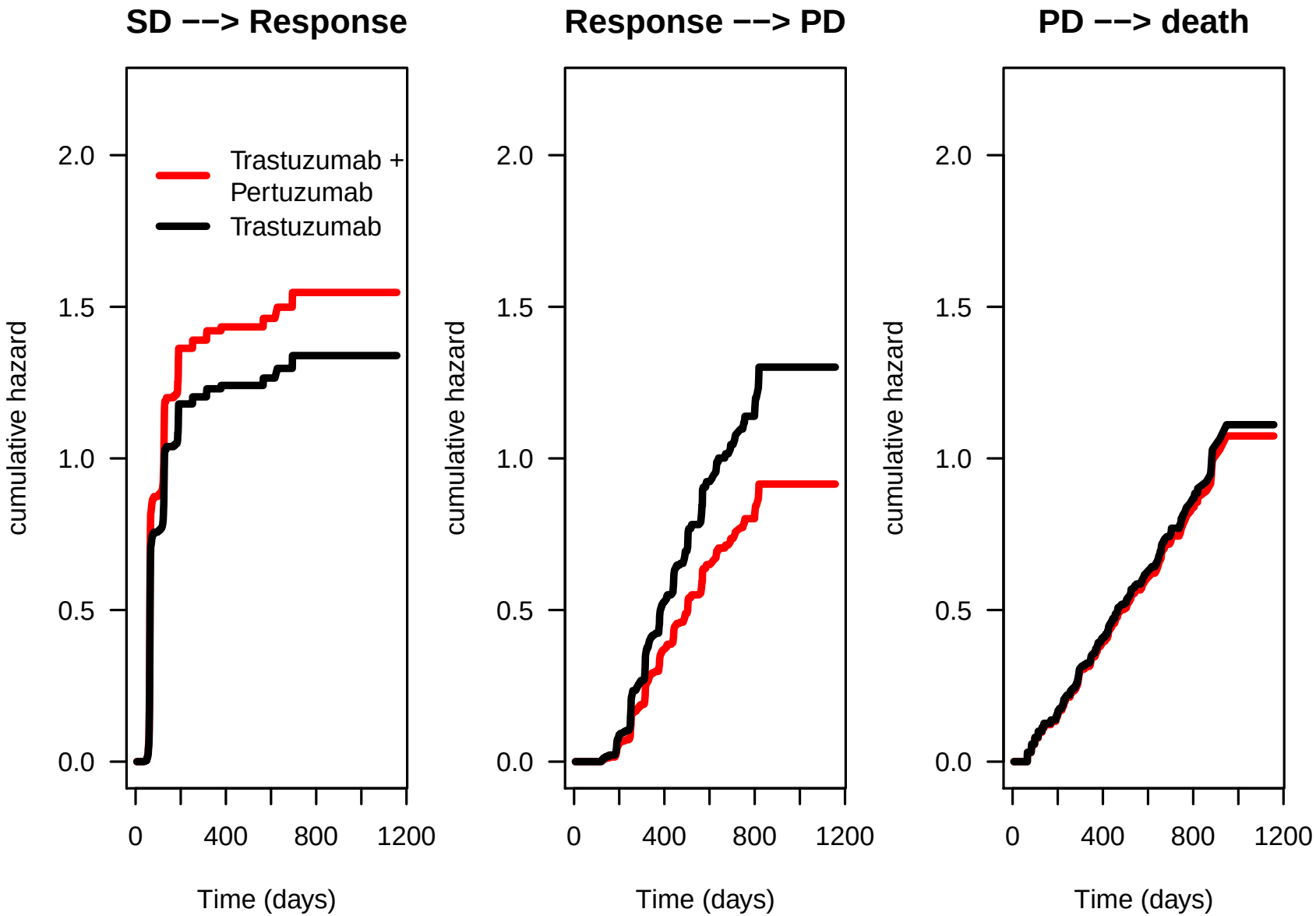
Baselga and Cortes (2012), Swain and Baselga (2015).

Previously untreated HER2-positive metastatic breast cancer patients.

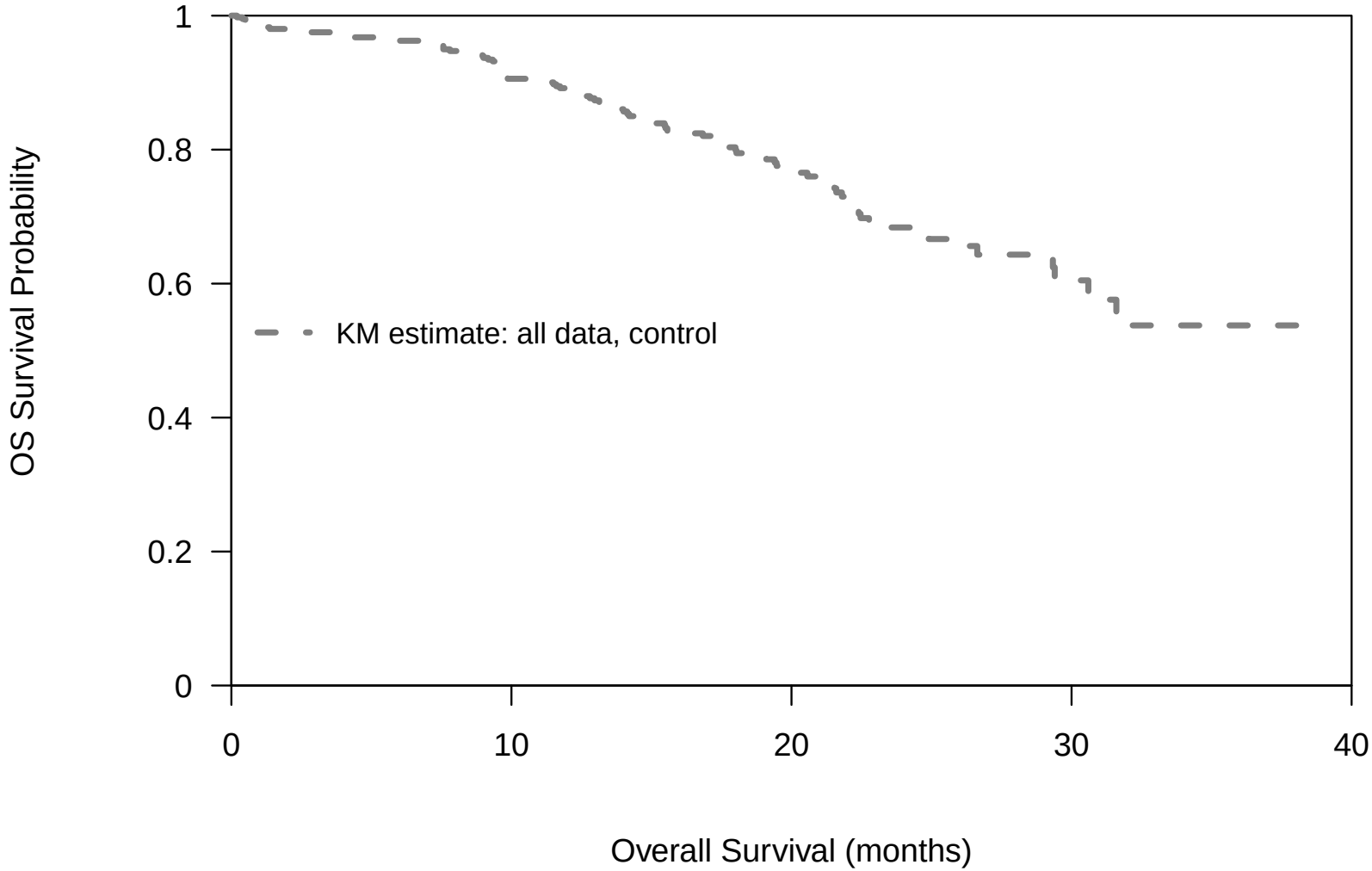
	Pertuzumab+Trastuzumab	Trastuzumab	HR (95% CI)
Survival	N=402	N=406	
Overall Survival			**0.64 (0.47,0.88)**
Progression-free Survival			0.62 (0.51,0.75)
Response	N=343	N=336	
Objective Response	275 (80.2%)	233 (69.3%)	
Stable Disease	50 (14.6%)	70 (20.8%)	
Progressive Disease	13 (3.8%)	28 (8.3%)	
Duration of Response	N=275	N=233	
Median (months, 95% CI)	**20.2 (16.0,24.0)**	**12.5 (10.0-15.0)**	

- Moderate difference in response.
- Prolonged **duration of response** in experimental arm.
- Clear OS benefit.
- Experimental treatment induces antibody-dependent cellular cytotoxicity $\Rightarrow$ no benefit beyond PD expected $\Rightarrow$ λ_{34} **same in both arms**.

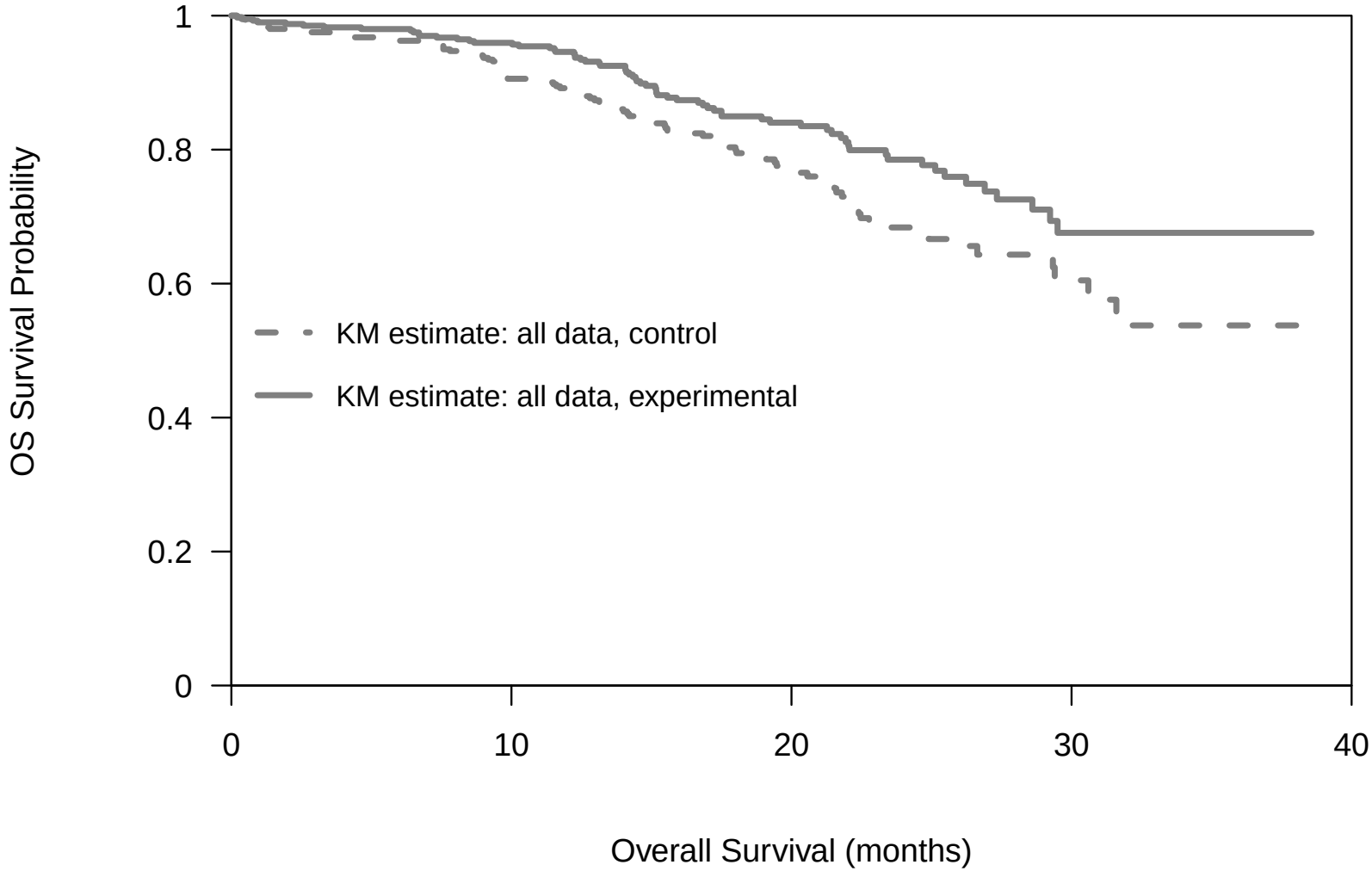
Cleopatra: raw cumulative hazard estimates (of interest)



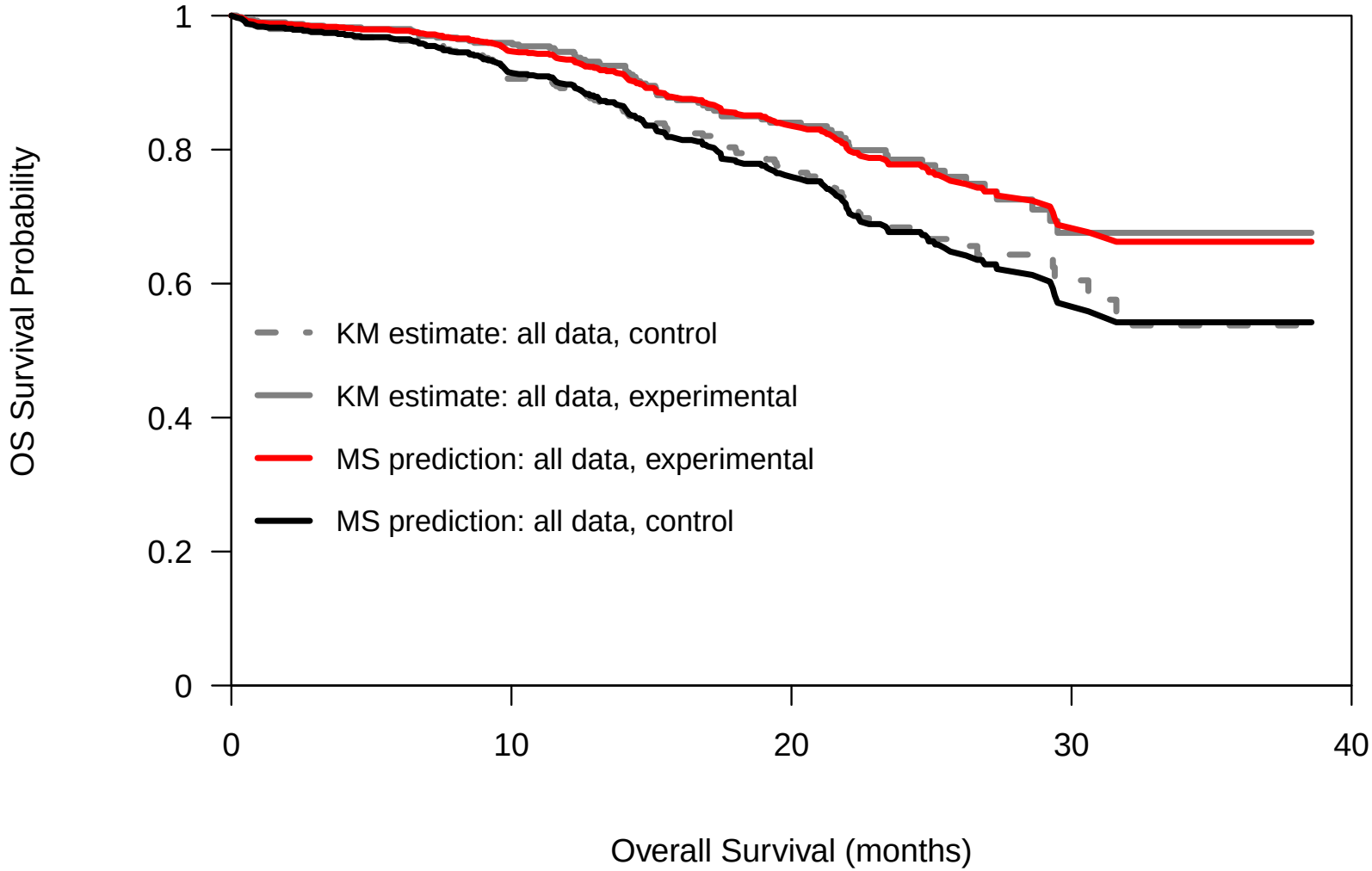
Cleopatra: estimates / predictions of S_{exp}



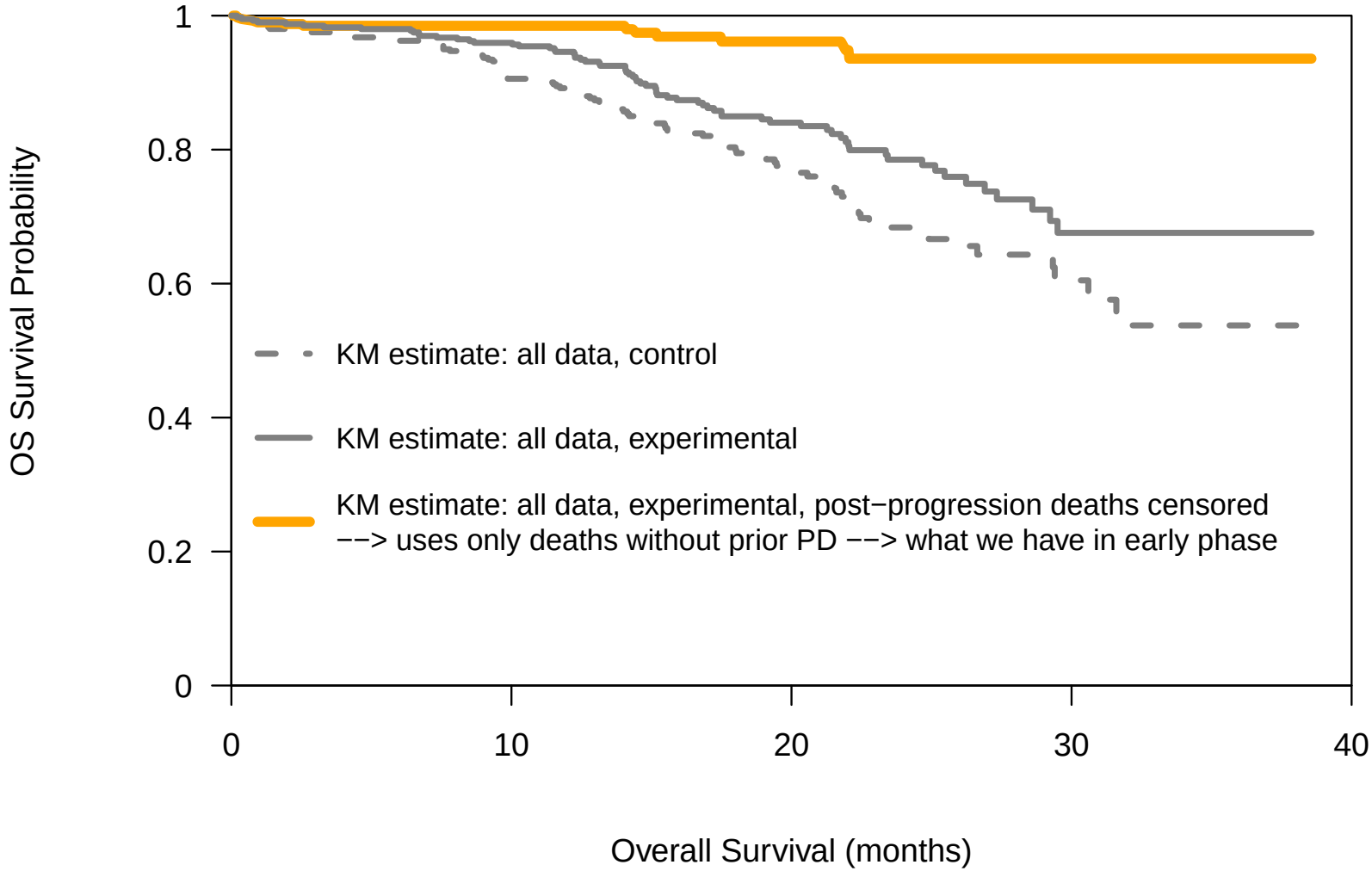
Cleopatra: estimates / predictions of S_{exp}



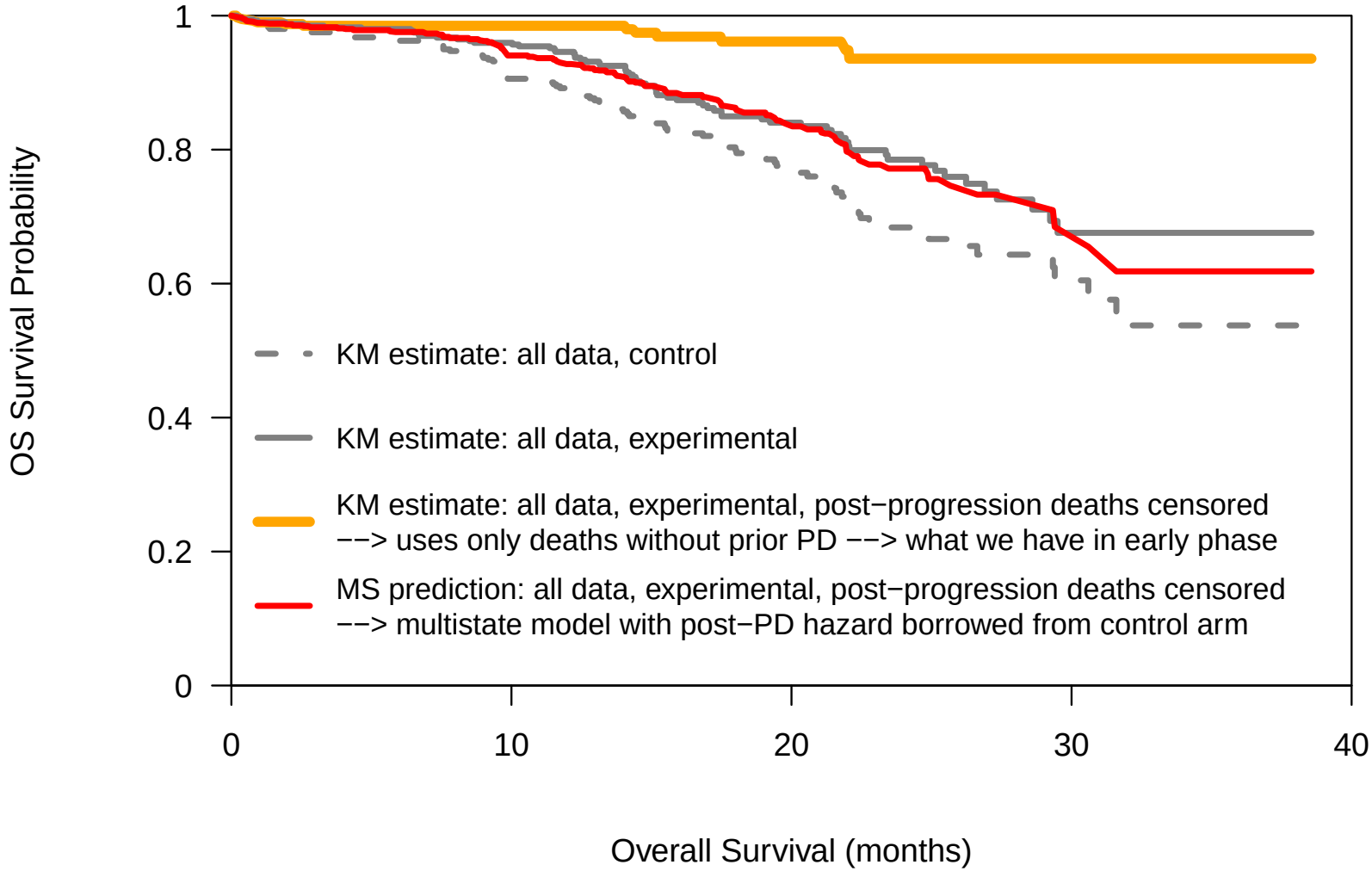
Cleopatra: estimates / predictions of S_{exp}



Cleopatra: estimates / predictions of S_{exp}



Cleopatra: estimates / predictions of S_{exp}



406	347	150	28
402	368	163	35

Conclusions for Cleopatra

For estimated / predicted survival function in experimental arm, based on **all data**:

- Majority of patients dies after observed PD.
- KM estimate of simply censoring post-PD deaths does not work $\Rightarrow$ very **few deaths observed**.
- Multistate model prediction assuming post-PD hazards as in control provides good prediction.

Early phase decision based on multistate prediction:

Operating characteristics?

OS prediction from mimicked early phase data

Sample early phase trial from **Cleopatra experimental arm**:

- 40 patients,
- 6 months uniform recruitment,
- analysis 15 months after first patient entered,
- censor post-PD follow-up **one day after PD**,
- estimate $\lambda_{12}, \lambda_{13}, \lambda_{14}, \lambda_{23}, \lambda_{24}$ from this data,
- **borrow $\widehat{\lambda}_{34}$ from historical data** = Cleopatra control arm in idealized scenario,
- compute prediction of S_{exp} as described above.

Resampling of operating characteristics

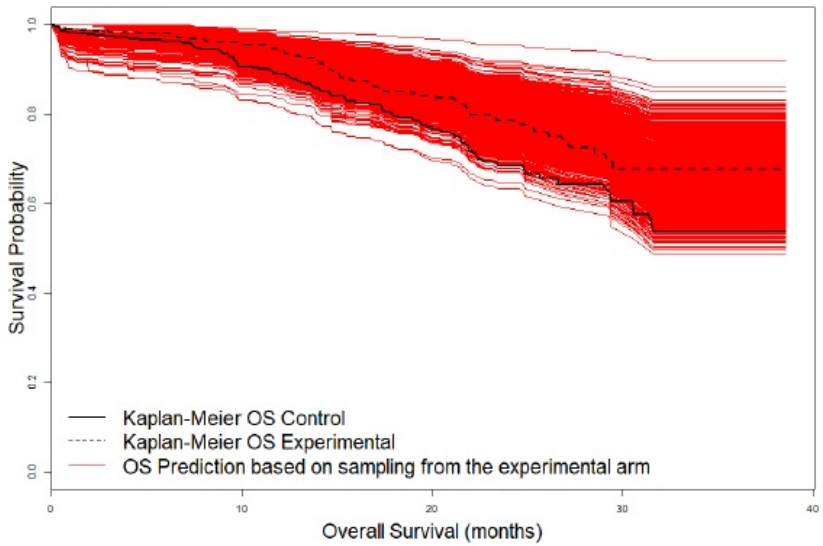
Setup:

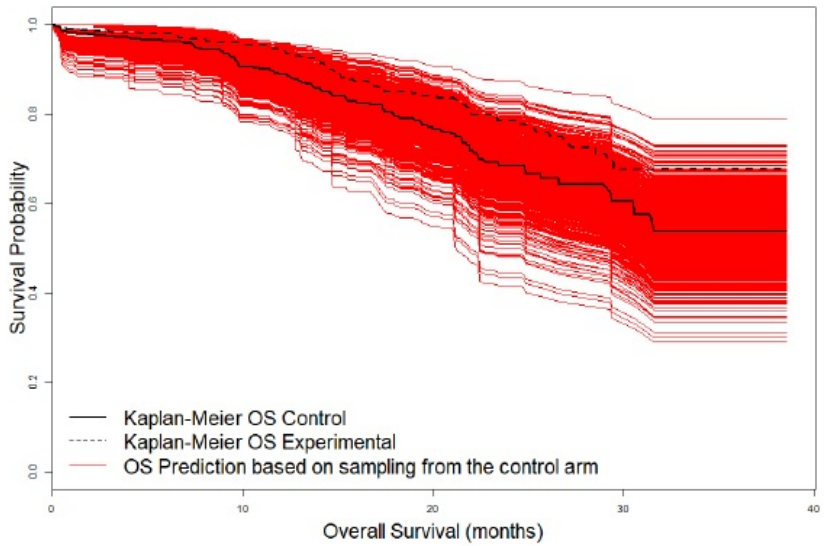
- Use all data in control arm $\Rightarrow$ corresponds to historical control.
- **False-positive** decision: Sample early phase trial from Cleopatra control arm.
- **False-negative** decision: Sample early phase trial from Cleopatra experimental arm.
- Approximate HR by fitting exponential distribution to both arms $\Rightarrow \widehat{HR}$.
- Decision to move to Phase 3: $\widehat{HR} \leq$ boundary $\in \{0.80, 0.85, 0.90, 1.00\}$.
- Repeat 1000 times.

Resampling easily allows for **quantification of uncertainty**.

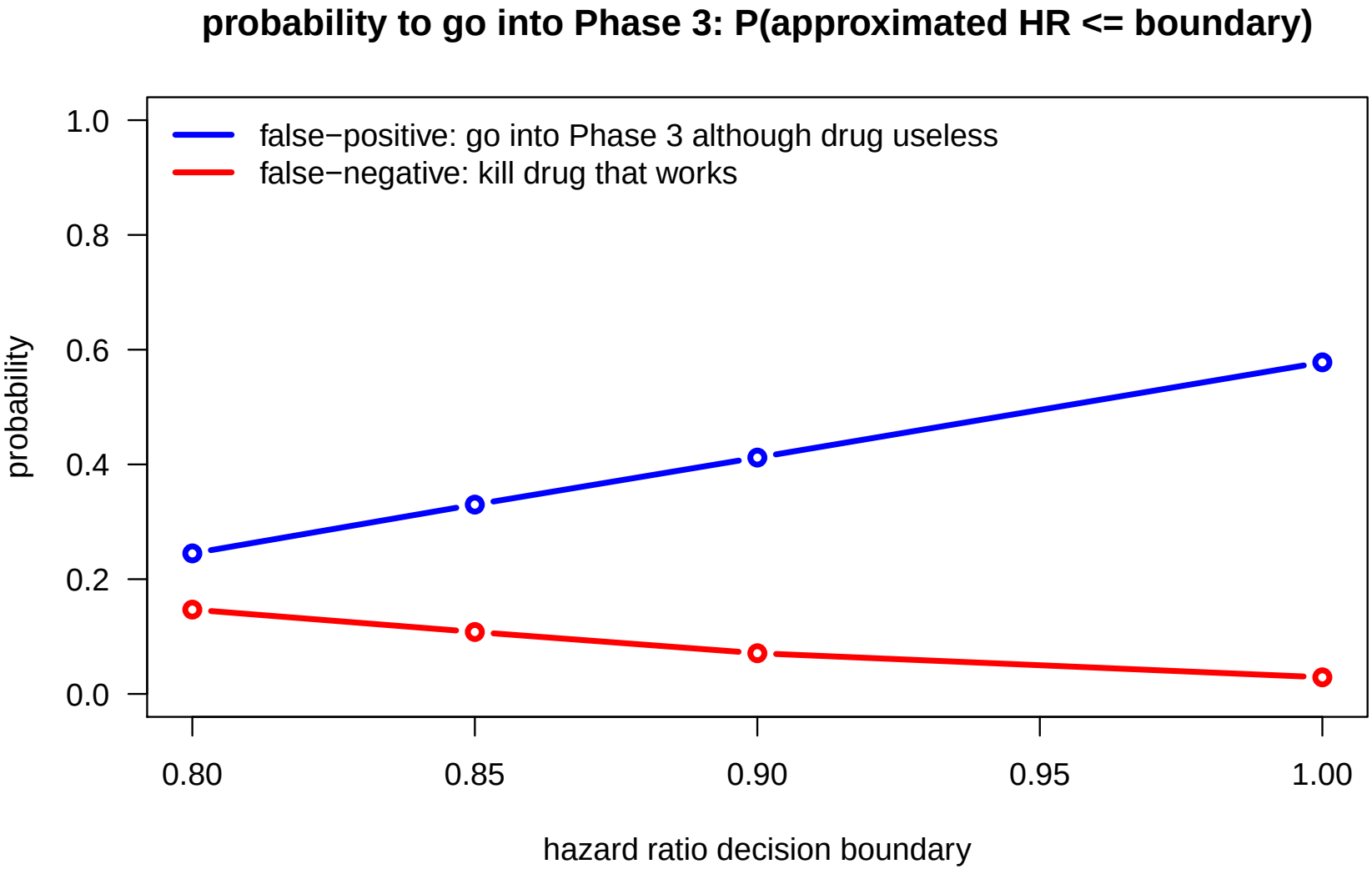
Cleopatra: operating characteristics

Sampled from **experimental** and **control** arm.



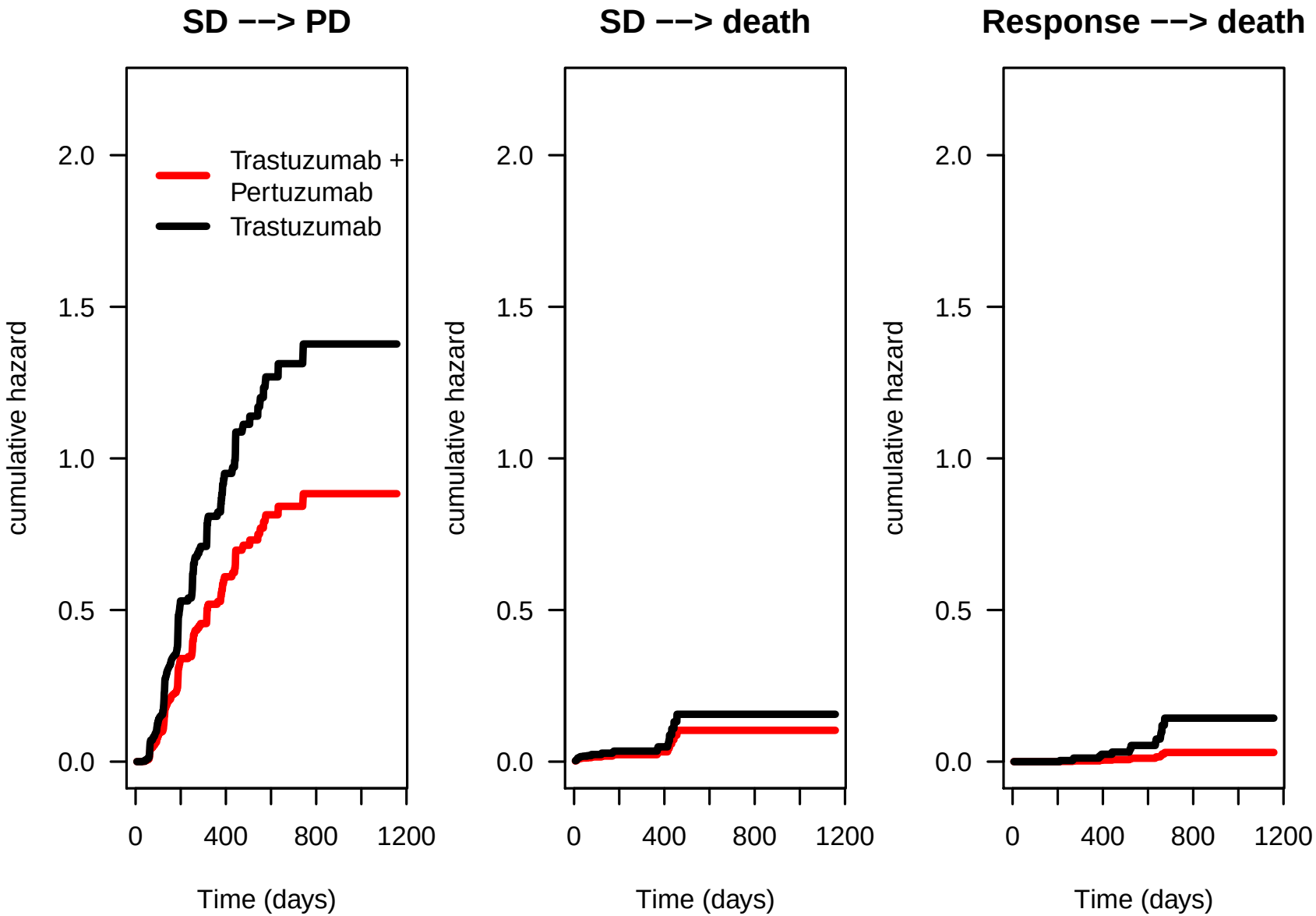


Cleopatra: operating characteristics



Decision based on response: $\approx 10\%$ difference, some prolongation of DOR $\Rightarrow$ moved to Phase 3.

Cleopatra: cumulative hazards of secondary interest



Oak

Previously treated non-small-cell lung cancer. Rittmeyer *et al.* (2017).

- Control: no benefit post-PD expected.
- Experimental: CIT $\Rightarrow$ benefit post-PD expected.

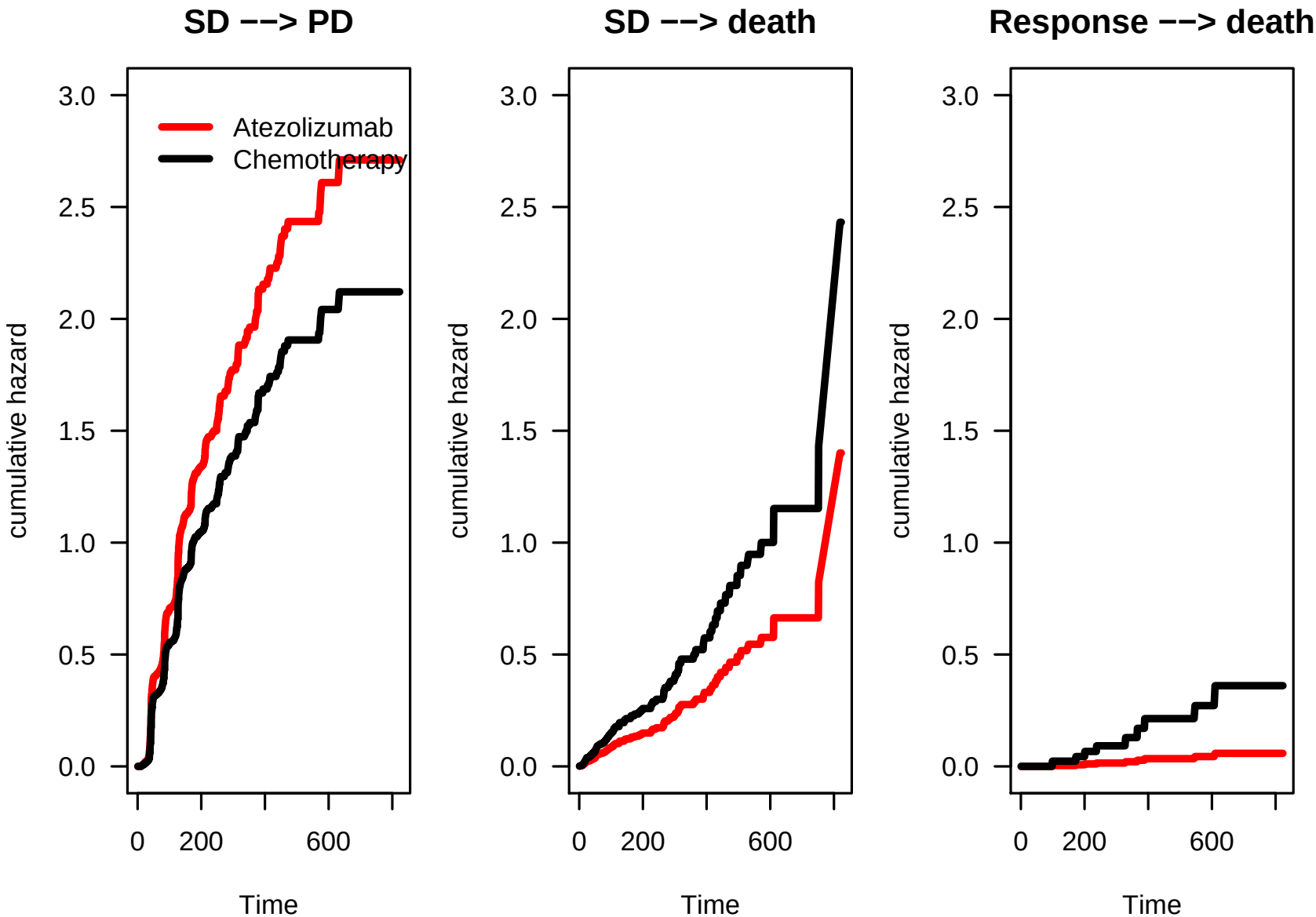
	Atezolizumab	Chemotherapy	HR (95% CI)
Survival	N=425	N=425	
Overall Survival			0.73 (0.62,0.87)
Progression-free Survival			0.95 (0.82,1.10)
Response	N=425	N=425	
Objective Response	**58 (13.6%)**	**57 (13.4%)**	
Stable Disease	150 (35%)	177 (42%)	
Progressive Disease	187 (44%)	117 (28%)	
Duration of Response	N=58	N=57	
Median (months, 95% CI)	26.3 (10,NE)	6.2 (4.9-7.6)	

No observed difference in response.

Prolonged duration of response in experimental arm.

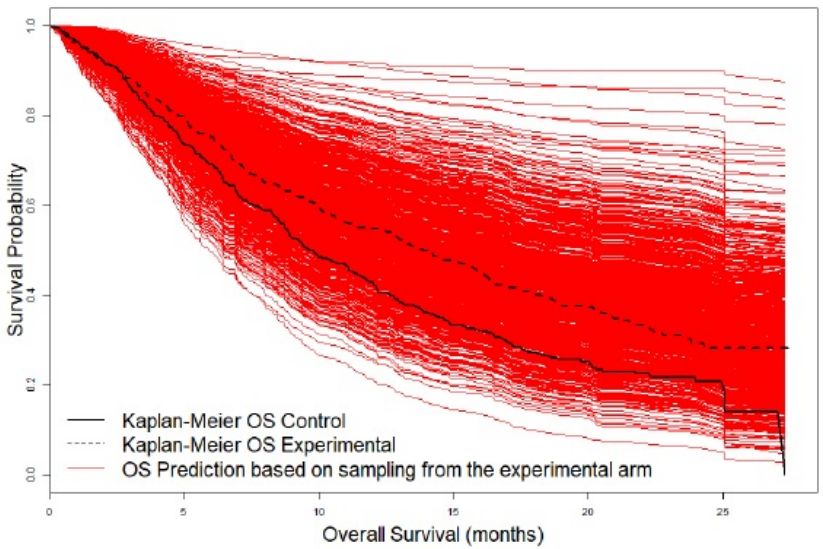
Clear survival benefit.

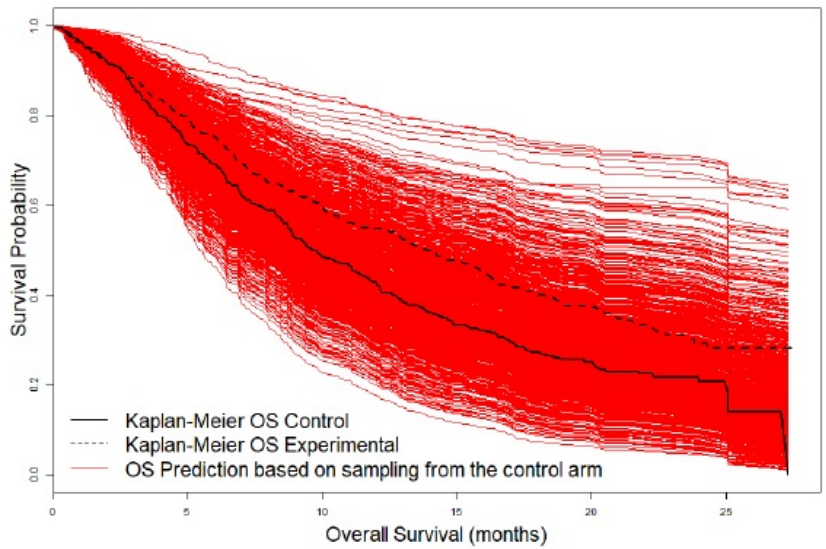
Oak: cumulative hazards of secondary interest



Oak: operating characteristics

Sampled from **experimental** and **control** arm.





Non-proportional hazards via multistate model

Immunotherapy:
1) no difference in PFS,
2) non-proportional hazards for OS.

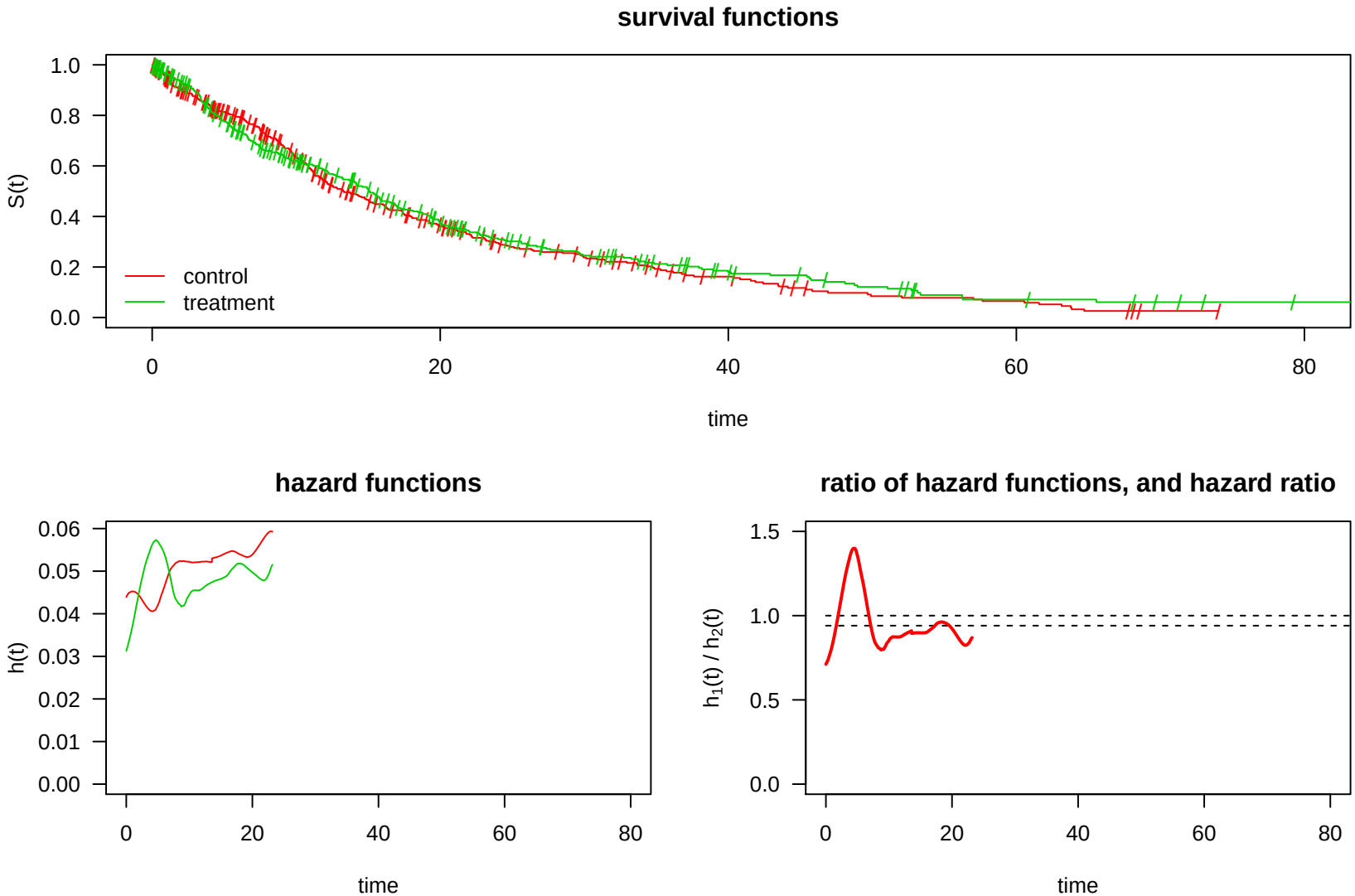
How to quantify effect?

A fictional clinical trial

Simulated clinical trial:

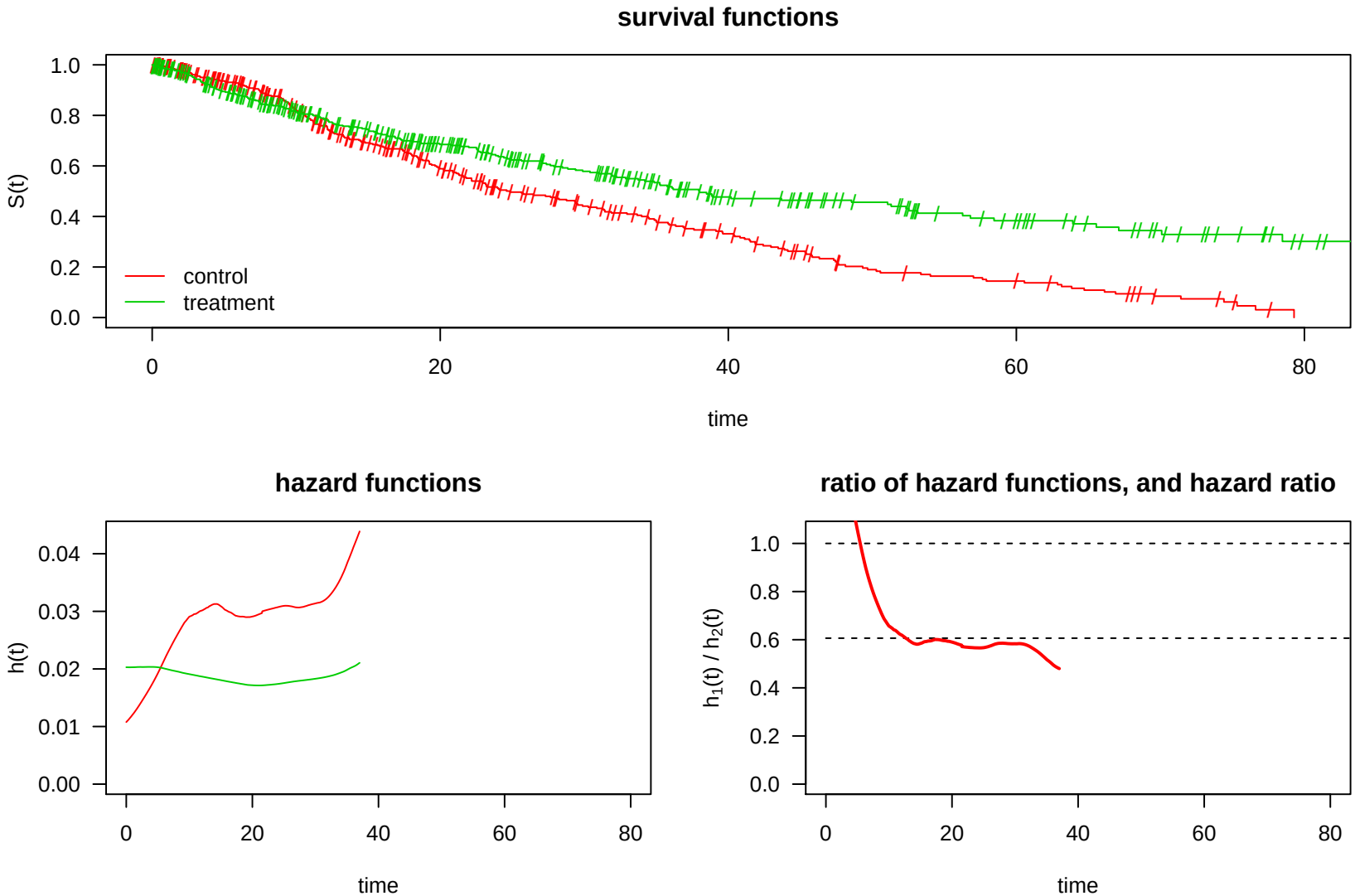
- 1:1 randomized, 400 and 400 patients per arm.
- No administrative censoring, but drop-out.

PFS for simulated clinical trial



- Estimated hazard ratio: 0.94, 95% confidence interval [0.80, 1.11].
- Hypothesis test for PH: $p = 0.24$.

OS for simulated clinical trial



- Estimated hazard ratio: 0.61, 95% confidence interval [0.50, 0.74].
- Hypothesis test for PH: $p < 0.0001$.

Summarize treatment effect

Non-proportional hazards for OS. How to summarize effect of treatment?

Data was generated according to:

Transition	Control arm	Treatment arm
$0 \to 1$	$\lambda_{01}^c = \log(2)/25$	$\lambda_{01}^t = \lambda_{01}^c \cdot \mathbf{1}$
$0 \to 2$	$\lambda_{02}^c = \log(2)/30$	$\lambda_{02}^t = \lambda_{02}^c \cdot \mathbf{0.8}$
$1 \to 2$	$\lambda_{12}^c = \log(2)/15$	$\lambda_{12}^t = \lambda_{12}^c \cdot \mathbf{0.4}$

	coef	HR = exp(coef)	95% CI	p-value
transition event-free –> PD	-0.04	0.96	[0.77, 1.19]	0.72
transition event-free –> death	-0.09	0.91	[0.70, 1.18]	0.49
transition PD –> death	-1.09	0.34	[0.24, 0.46]	< 0.0001

Gaschler-Markefski *et al.* (2014).

Big vs. small data

Big vs. small data

Often, information removed/altered in **small data**:

- (Artificial) response cateogries instead of actual measurements: **dichotomization**,
- response proportions only: **ignoring the dynamics between states**,
- complicated subsets, e.g. those that respond only: **selection bias**,
- effect quantification in **one** number where biological process might suggest few numbers,
- ...

Maximize information from **small** data. AND look at **BIG** data.

Biostatisticians ideally placed to contribute to this!

Doing now what patients need next

R version and packages used to generate these slides:

R version: R version 3.6.0 (2019-04-26)

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

Other packages: nls2 / proto / diagram / shape / ggplot2 / rocheBCE / muhaz / flexsurv / reporttools / xtable / mstate / etm / dplyr / mvna / prodlim / biostatKR / survival

This document was generated on 2019-11-14 at 23:27:30.