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

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Who

Meller *et al.* (2019):

Beyer *et al.* (2019):

Multistate model for PFS and OS

Introduction

Oncology endpoints:

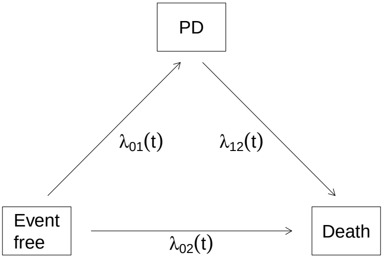
- Progression-free survival (PFS): Time from randomization to earlier of progression or death.
- Overall survival (OS): Time from randomization to death.

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

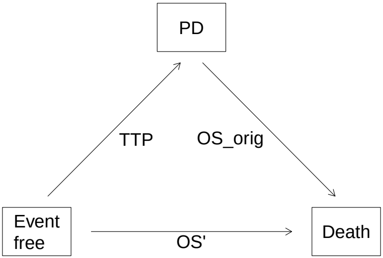


Standard **illness-death model without recovery**:

- 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).

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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**,
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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 **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.

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Multistate $=$ (most?) parsimonious model

Correlation coefficient

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

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

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

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

Proof: manipulations using law of total probability.

Estimation and inference for Markov models

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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):

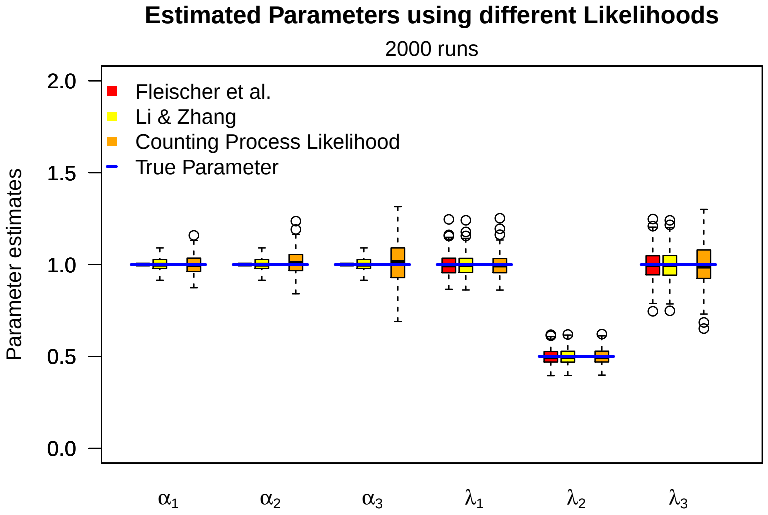
- Group patients depending on their path from 0 to 1 or 2, or censored.
- Likelihood uses **assumption of independence** of TTP, $\mathrm{OS}_{\mathrm{orig}}$. Cannot tell from (even uncensored!) data! Aalen (1987): "artificial problem", as LFTM not needed, see also Beyersmann *et al.* (2012).

Weber and Titman (2019):

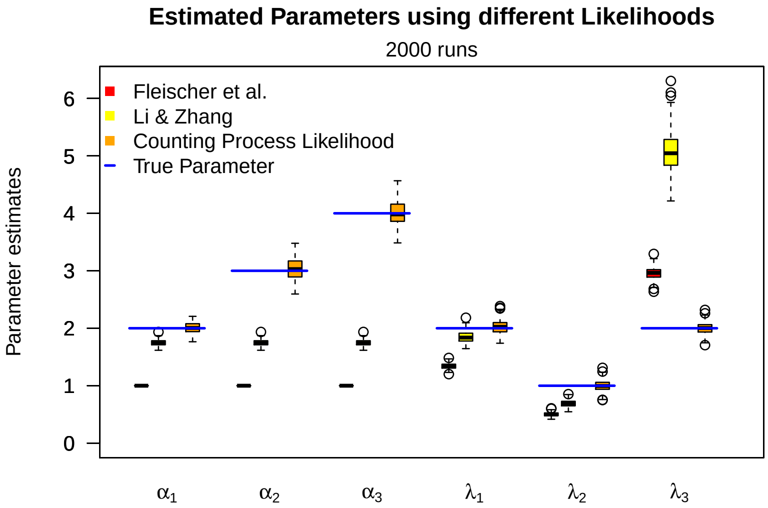
- Kendall's τ, based on multistate, nonparametric, and copula models.
- Use again LFTM for estimation.

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?

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But:

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

Proposal:

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Decide in early phase based on OS prediction.

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Decrease P(wrong decision).

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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**.

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Long-term follow-up in both arms.

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Randomization $\Rightarrow$ no confounding.

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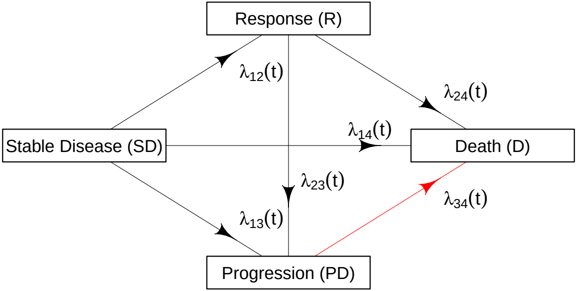

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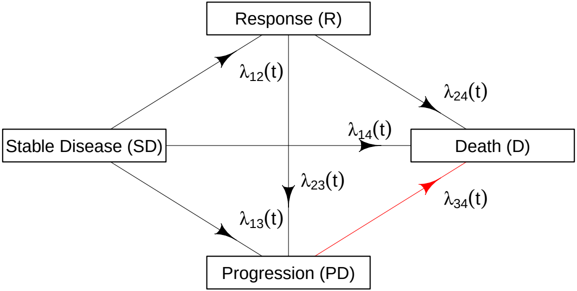

- Follow-up of patient until **PD or death without PD**.

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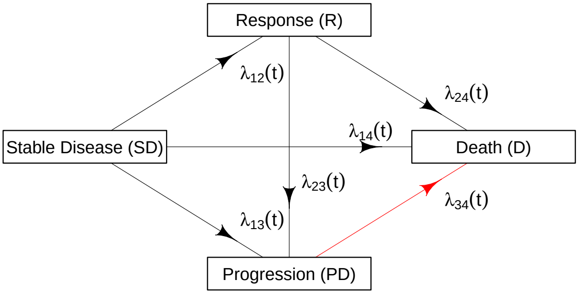

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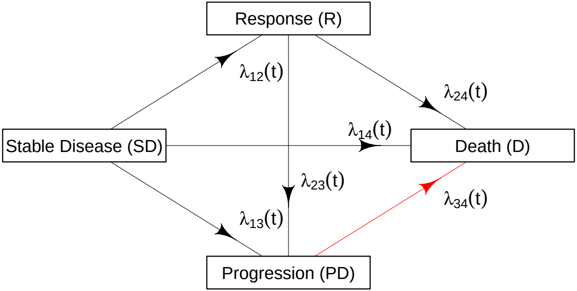

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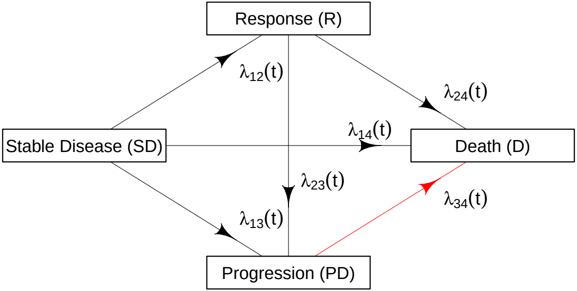

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- Transitions SD $\to$ D, R $\to$ D rare, hazards $\approx$ same in both arms.
- Markov assumption.

Predicted survival function in experimental arm, S_{exp}

Compute transition probabilities for each transition.

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

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**?

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No:

- E.g. chemotherapy or antibody-dependent cellular cytotoxicity.
- **Plug-in** hazard function estimate from historical control.
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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?

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Competitors used this mechanism of action.

OS prediction when post-PD hazards assumed proportional

Random variable:

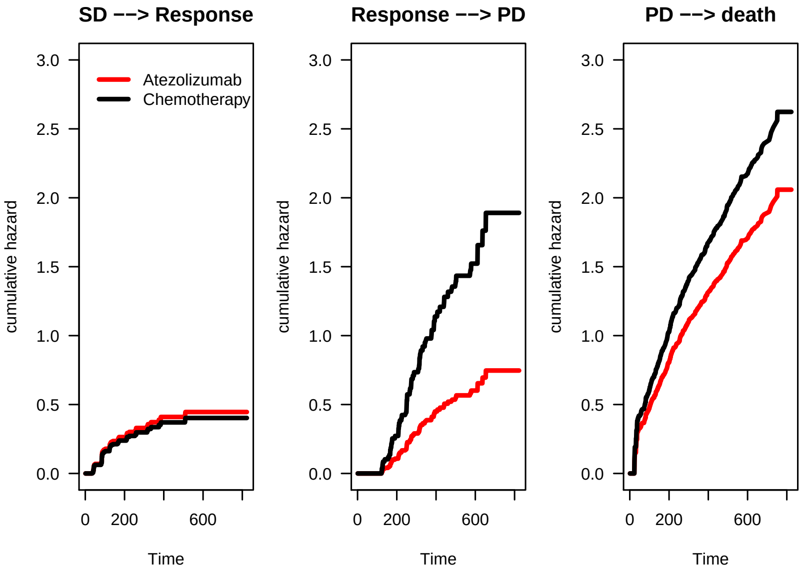
$$Z = \begin{cases} 0 & \text{if patient in control,} \\ 1 & \text{if in experimental group.} \end{cases}$$

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

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

Post-progression hazard ratio β_{34}?

Oak: raw cumulative hazard estimates (of interest)



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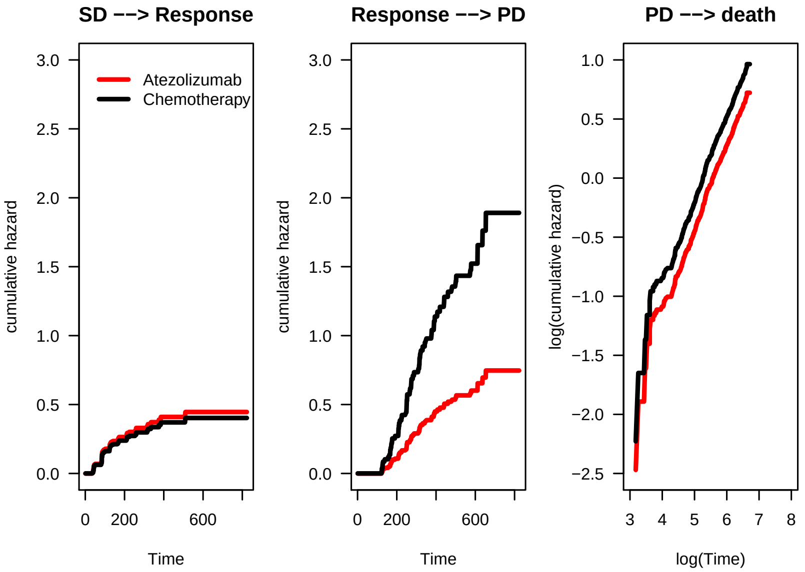

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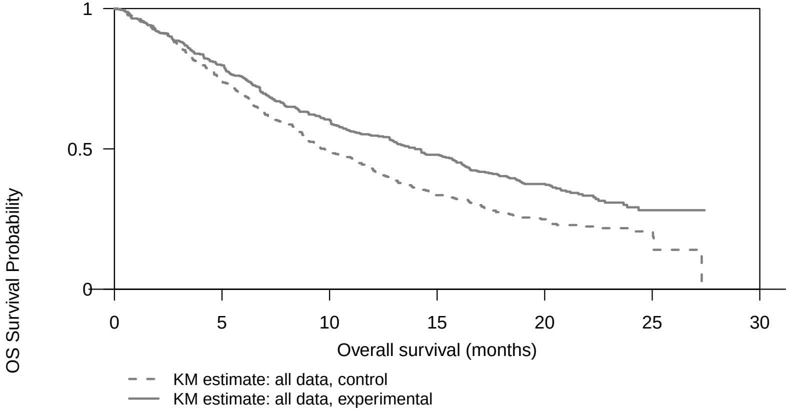

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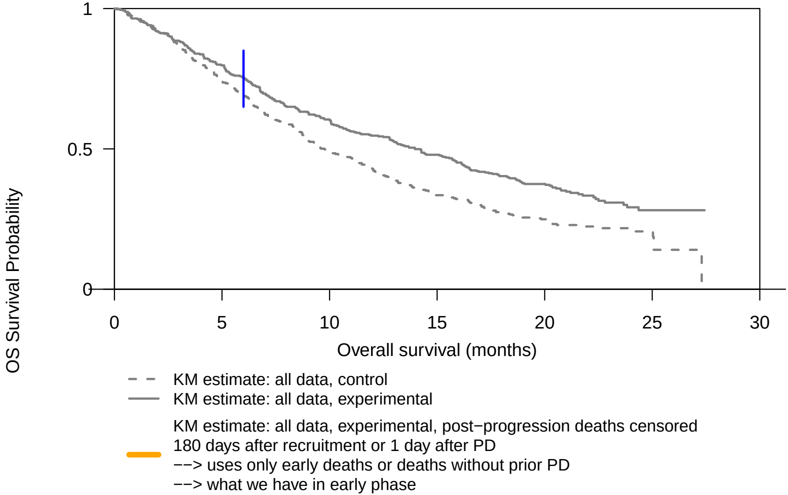

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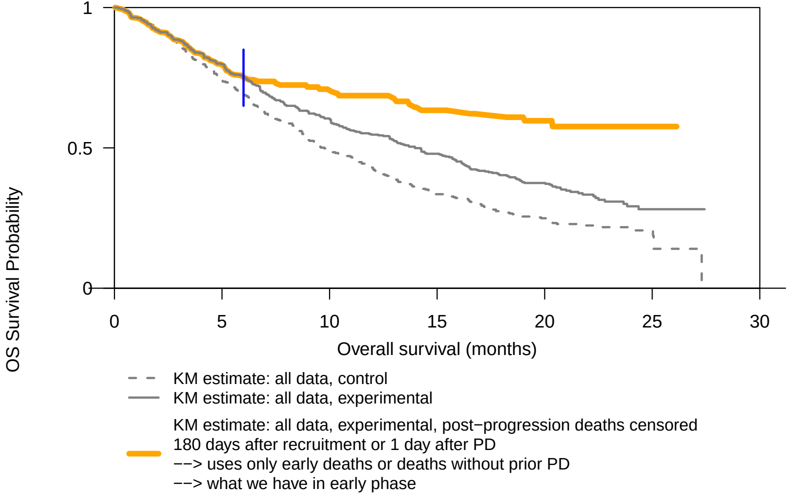

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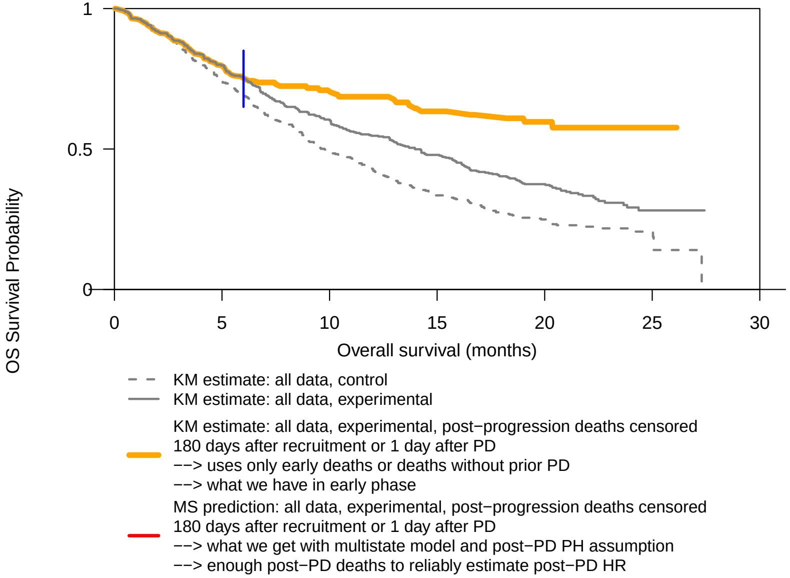

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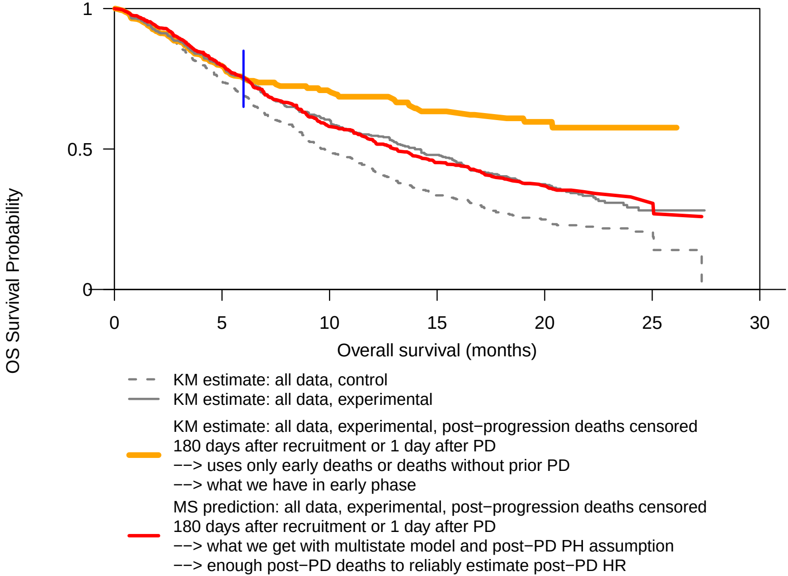

Early phase decision based on multistate prediction:

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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.

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

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Compute prediction of S_{exp}.

OS HR prediction based on early phase trial

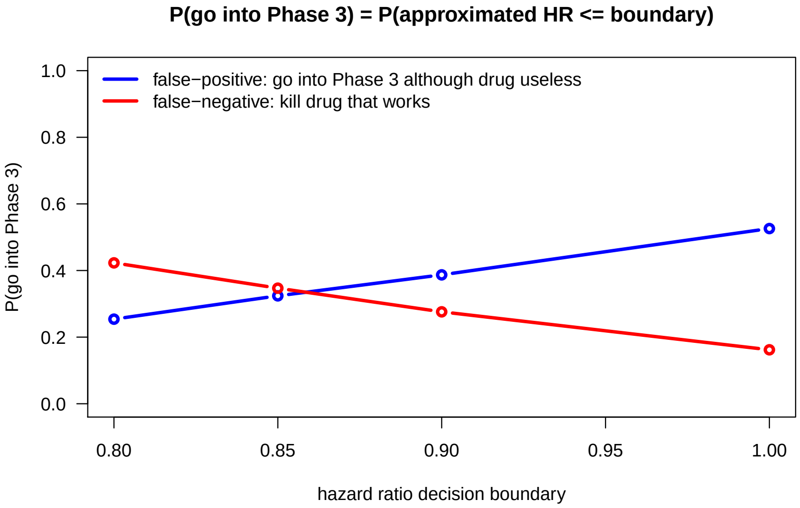
Approximate HR by fitting exponential distribution to both arms $\Rightarrow \widehat{HR}$.

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)



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Ask during Q&A.

Conclusions for early-decision making proposal

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- Recommendation **how much post-PD follow-up** needed to estimate β_{34}.

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- 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?

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Combine proposal with propensity scoring.

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- **Prediction** in well-specified, as opposed to black-box, model.

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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.

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Backup

Multistate models

Canonical extension of survival analysis

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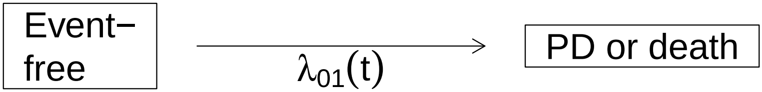

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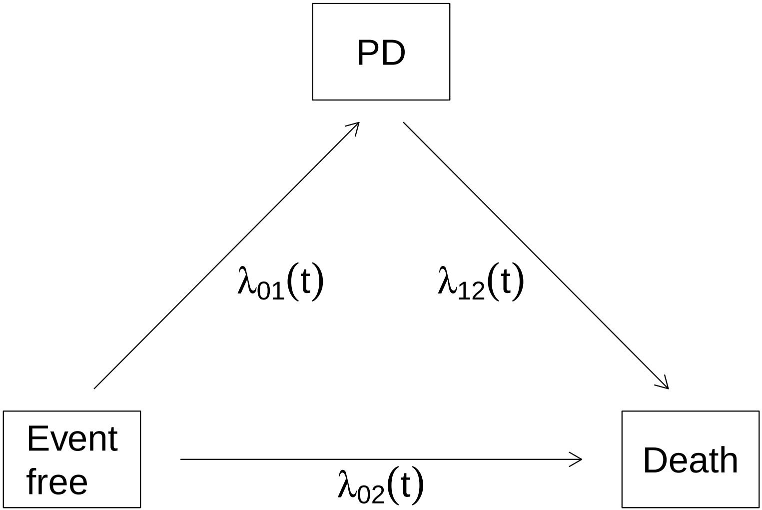

Multistate models

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):

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Prediction from multistate model!

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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

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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:

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

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\begin{aligned}
P(\mathrm{PFS} \le u, \mathrm{OS} \le 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; u) + P_{02}(0, u; u).
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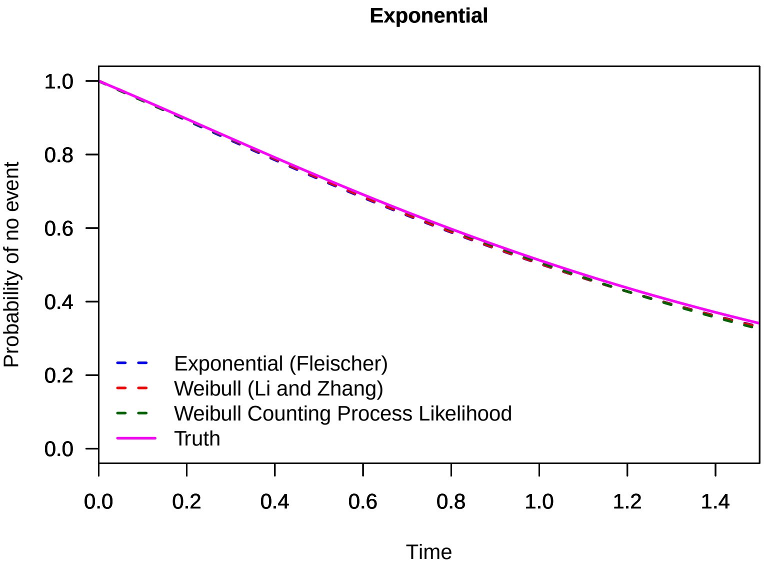
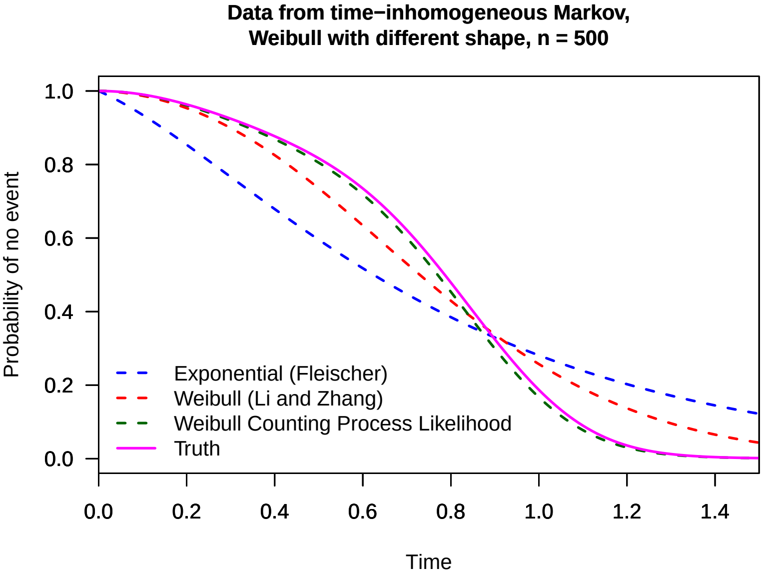
X **non-Markov**: integrate $P_{12}(u, v; t_1)$ over conditional distribution of all possible progression times $t_1 \le u \Rightarrow$ final formula tedious.

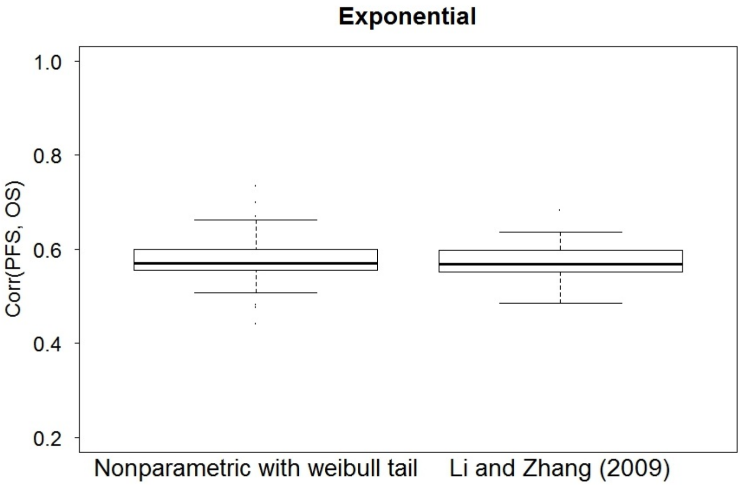
Results: S_{OS} for Exponential



Results: S_{OS} for Weibull



Results: correlations Exponential



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

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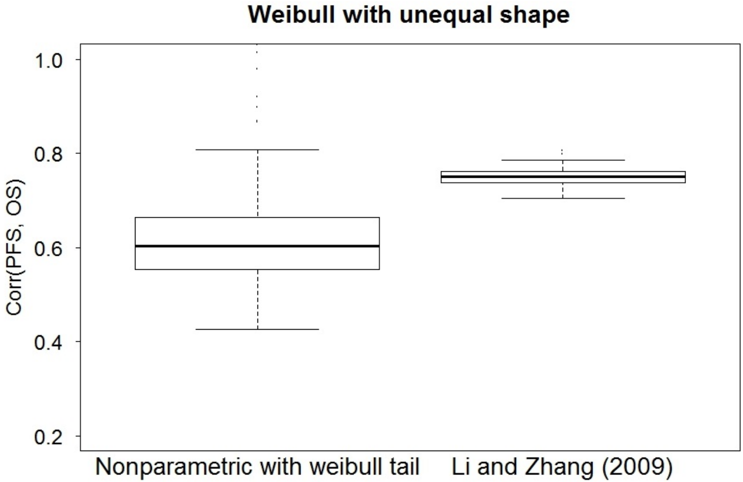

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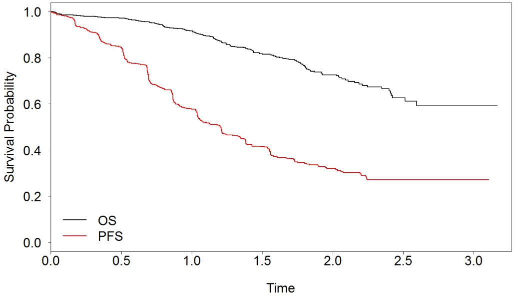
Results: CLEOPATRA, Baselga and Cortes (2012).



	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.

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Various scenarios for post-PD follow-up time.

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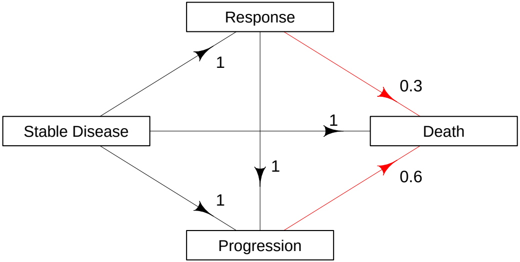

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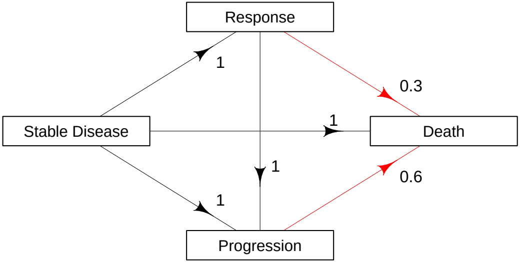

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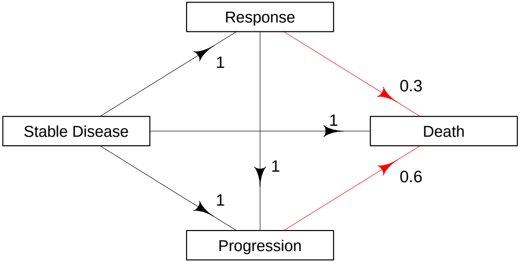

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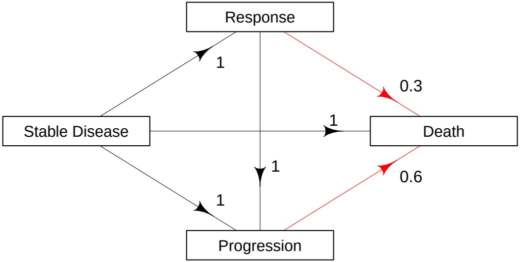

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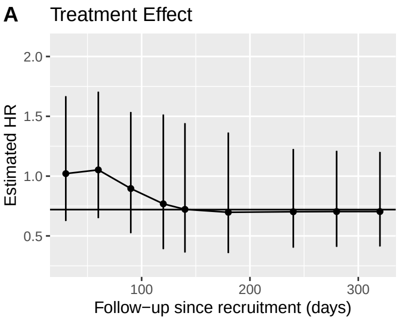
- Repeat 1000 times.

Stability of hazard ratio estimate



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

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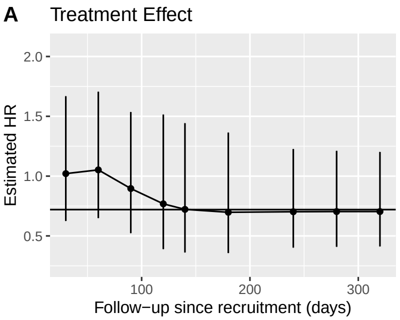

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Typical early phase follow-up: Post-PD deaths censored **180 days after recruitment** in experimental arm.

Example 1: Cleopatra

Cleopatra

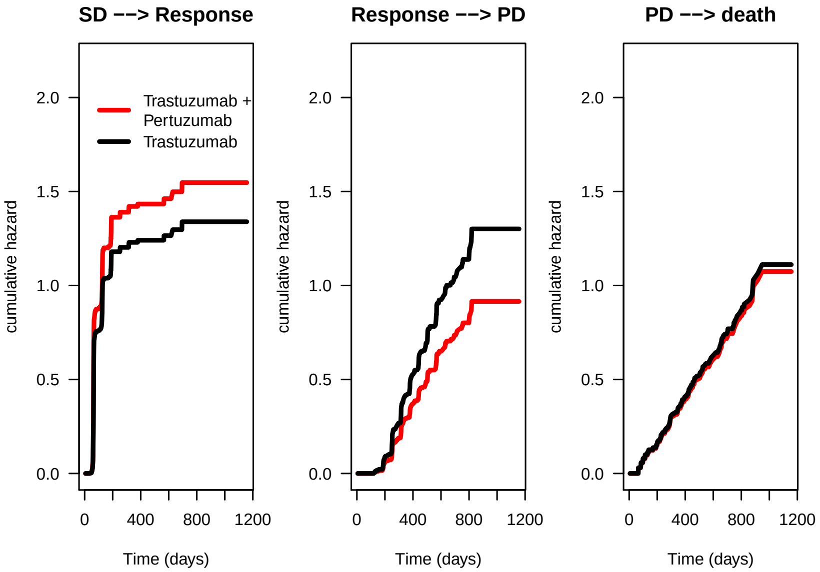
Baselga and Cortes (2012), Swain and Baselga (2015).

Previously untreated HER2-positive metastatic breast cancer patients.

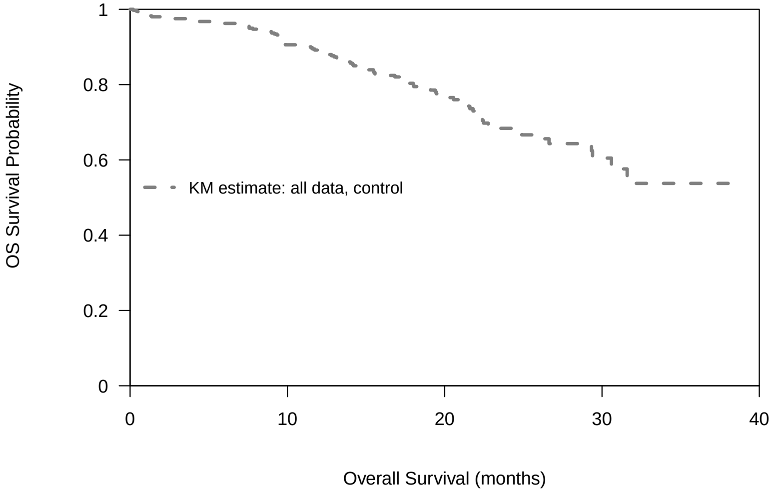
	Pertuzumab+Trastuzumab	Trastuzumab	HR (95% CI)
Survival	N=402	N=406	
Overall Survival			**0.64 (0.47,0.88)**
Progression-free Survival			0.62 (0.51,0.75)
Response	N=343	N=336	
Objective Response	275 (80.2%)	233 (69.3%)	
Stable Disease	50 (14.6%)	70 (20.8%)	
Progressive Disease	13 (3.8%)	28 (8.3%)	
Duration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

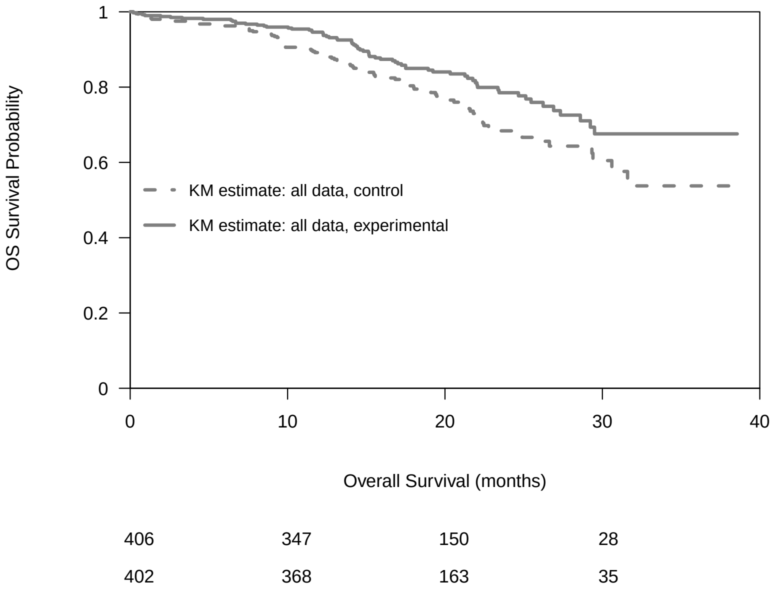


Cleopatra: estimates / predictions of S_{exp}



406	347	150	28
402	368	163	35

Cleopatra: estimates / predictions of $S_{\mathbf{exp}}$



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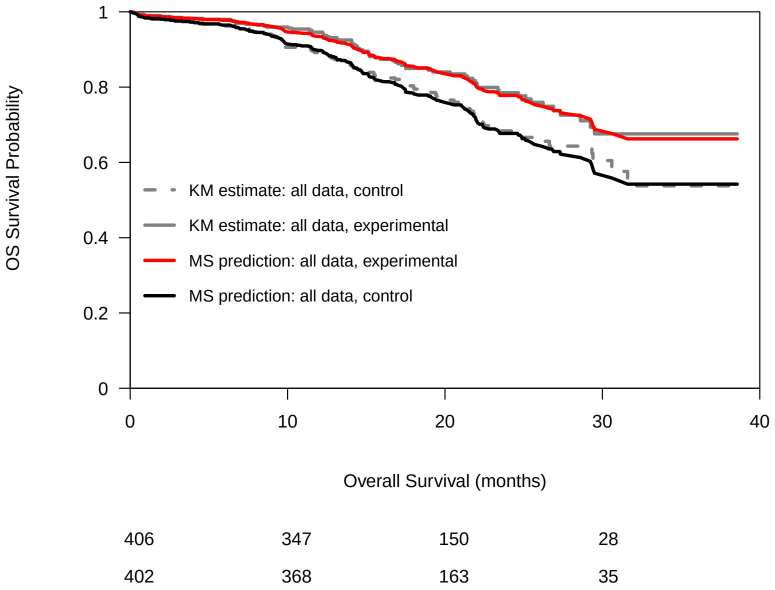

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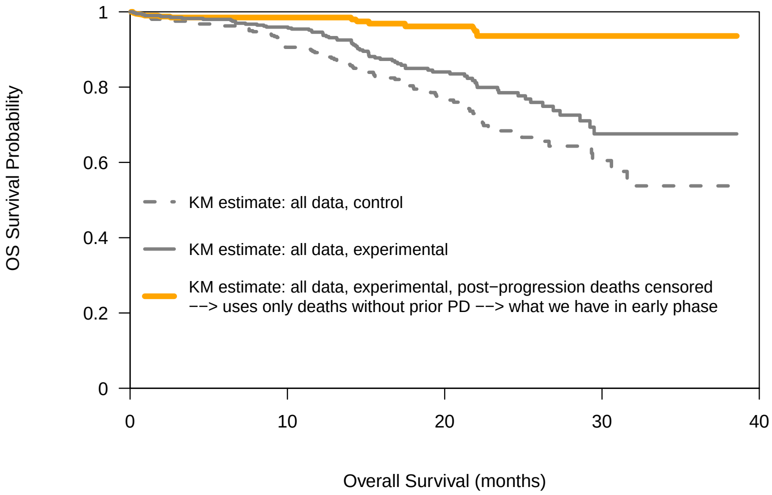

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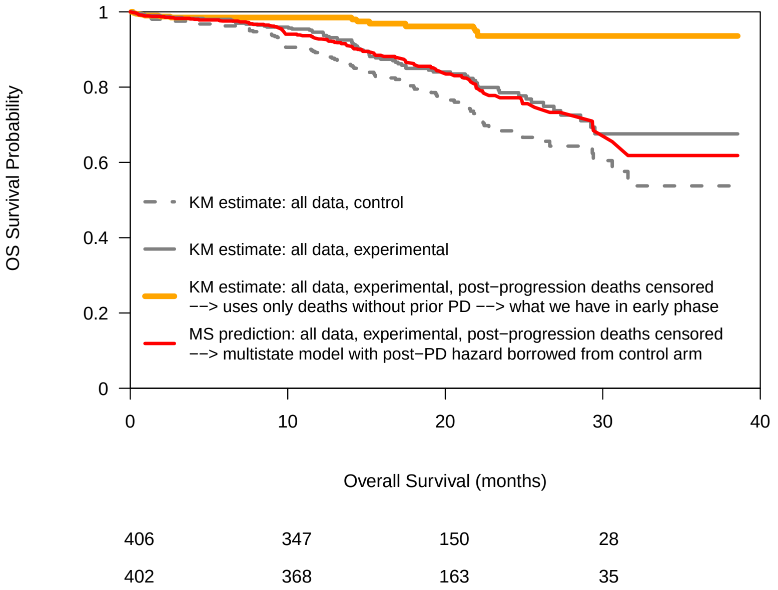

Conclusions for Cleopatra

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:

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

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- Use all data in control arm $\Rightarrow$ corresponds to historical control.

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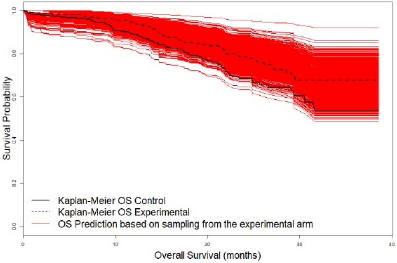
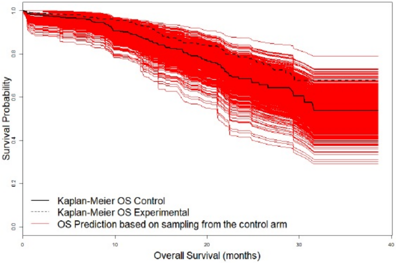
Resampling easily allows for **quantification of uncertainty**.

Cleopatra: operating characteristics

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





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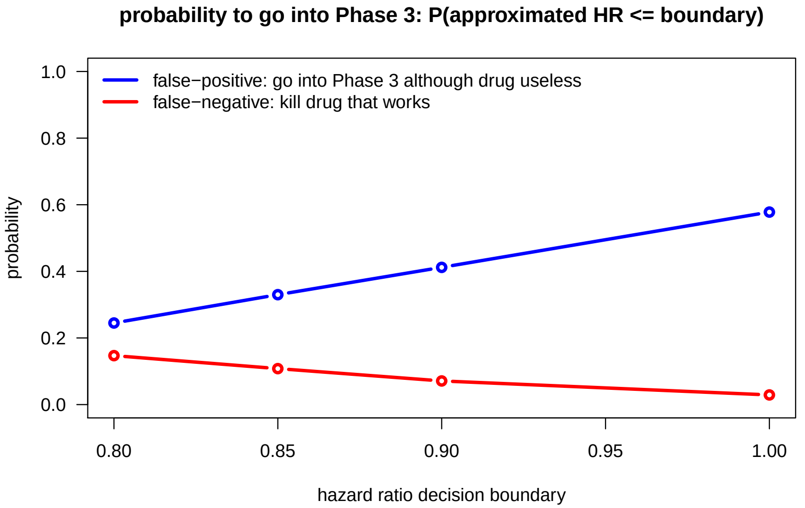
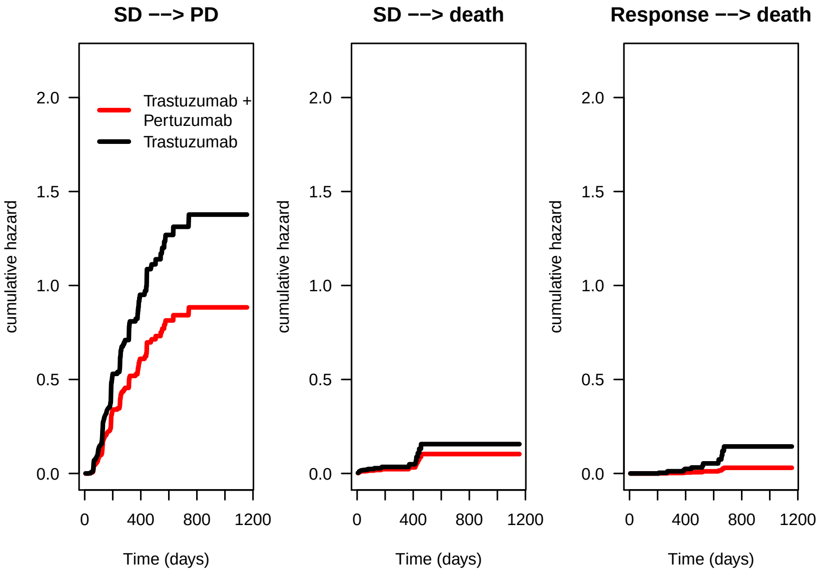


Decision based on response: $\approx$ 10% difference, some prolongation of DOR $\Rightarrow$ moved to Phase 3.

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.

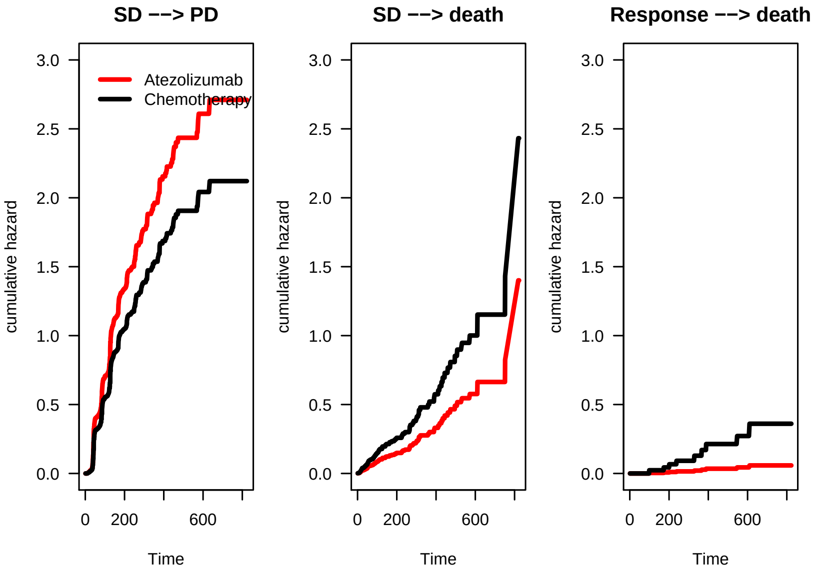
	Atezolizumab	Chemotherapy	HR (95% CI)
Survival	N=425	N=425	
Overall Survival			0.73 (0.62,0.87)
Progression-free Survival			0.95 (0.82,1.10)
Response	N=425	N=425	
Objective Response	**58 (13.6%)**	**57 (13.4%)**	
Stable Disease	150 (35%)	177 (42%)	
Progressive Disease	187 (44%)	117 (28%)	
Duration of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

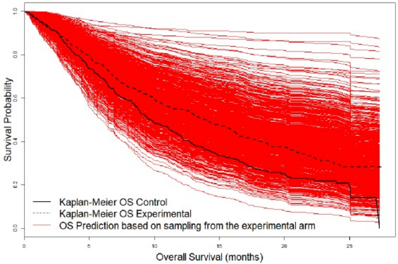
Clear survival benefit.

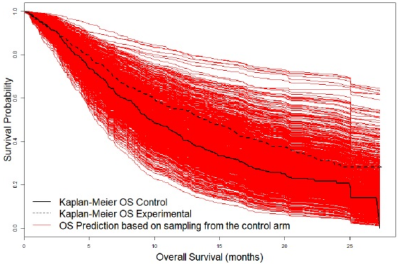
Oak: cumulative hazards of secondary interest



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.

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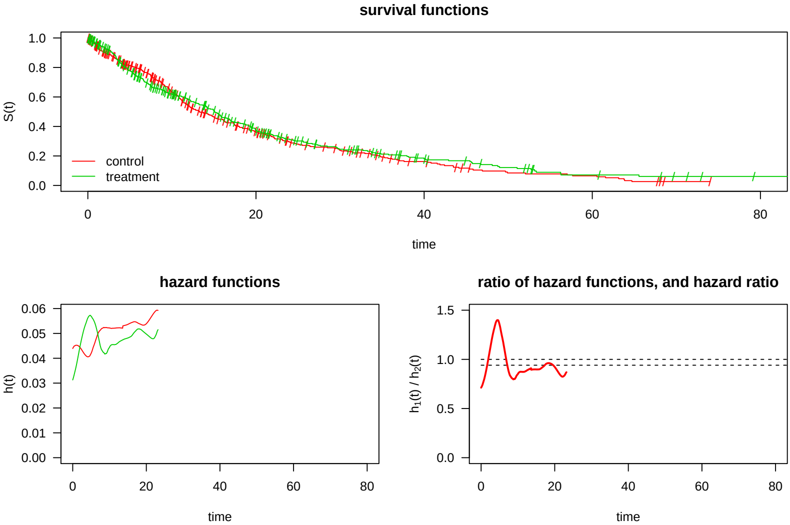
How to quantify effect?

A fictional clinical trial

Simulated clinical trial:

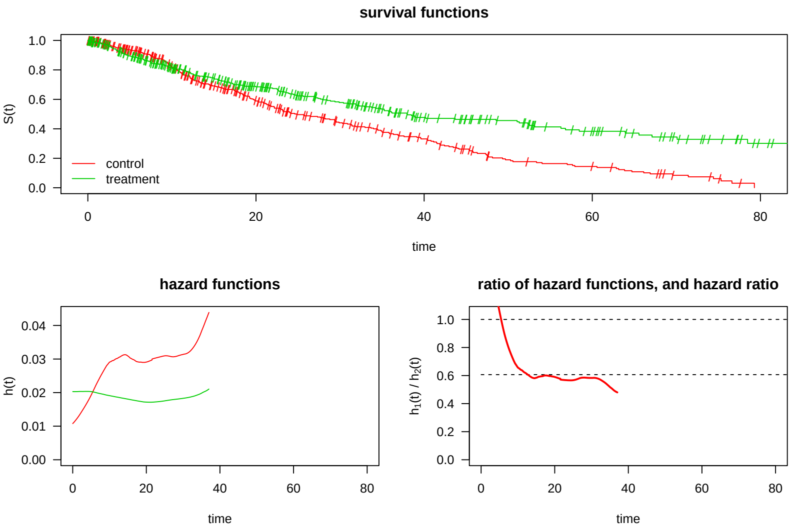
- 1:1 randomized, 400 and 400 patients per arm.
- No administrative censoring, but drop-out.

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?

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Data was generated according to:

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

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	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

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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

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