
Use of multistate models to improve decision-making in clinical trials

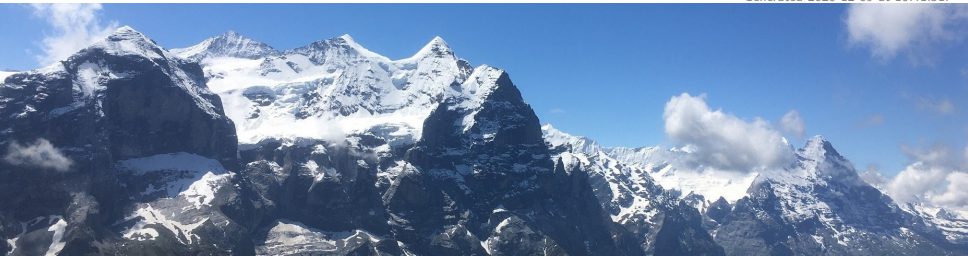
Kaspar Rufibach

Methods, Collaboration & Outreach Group, Department of Biostatistics, Roche Basel

Wiener Biometrische Sektion

9th December 2020

Generated 2020-12-09 at 10:41:51.



Who

Beyer *et al.* (2019):



Meller *et al.* (2019):



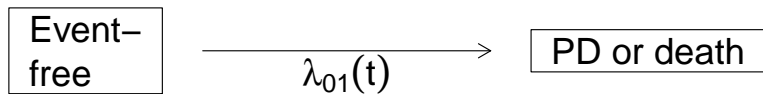
Oncology endpoints:

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

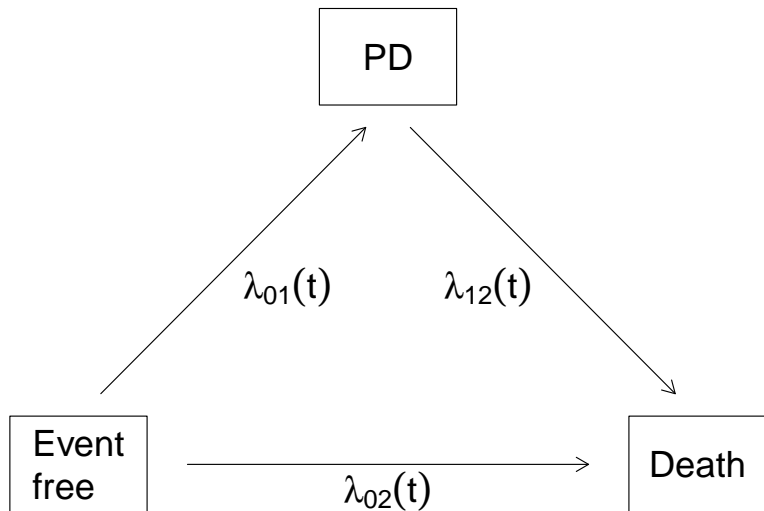
PFS common **surrogate** for OS in clinical trials.

Multistate models

Canonical extension of survival analysis



Canonical extension of survival analysis



Multistate models

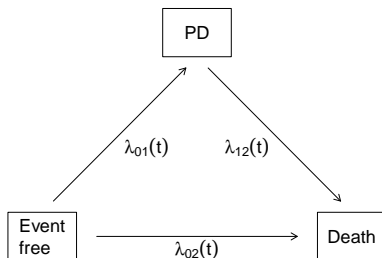
Multistate model:

- 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,

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

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

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, **PFS** = $\inf\{t : X(t) \neq 0\}$.
- OS: time until reaching state 2, **OS** = $\inf\{t : X(t) = 2\}$.

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!

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 $P(\text{wrong decision})$.

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**.

Oak

Previously treated non-small-cell lung cancer.

Rittmeyer *et al.* (2017).

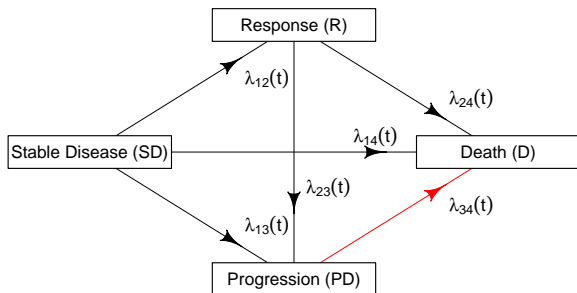
	Atezolizumab	Chemotherapy	Hazard ratio
Effect post-PD	expected	not expected	
Objective Response	58 (13.6%)	57 (13.4%)	
Duration of Response	26.3 (10 - ∞)	6.2 (4.9 - 7.6)	
Overall Survival			0.73 (0.62, 0.87)

**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**, at least for 6 months.
- 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.

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

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

How to compute transition probabilities?

Rigorously, Section A.2.5. in *Aalen et al. (2008)*:

- Write down transition intensity matrix.
- Solve Kolmogorov forward equation.

Informal and intuitively:

$$P_{1 \rightarrow 4}(0, t) = \int_0^t P_{11}(0, u) \lambda_{14}(u) P_{44}(u, t) du.$$

- $P_{11}(0, u)$: probability to remain in State 1 from 0 to u .
- At u patient transitions to State 4 with intensity $\lambda_{14}(u)$.
- Remains in State 4 until t .
- State 4 (= death) absorbing $\Rightarrow P_{44}(u, t) \equiv 1$.

$$P_{1 \rightarrow 4}(0, t) = \int_0^t \exp(-\Lambda_{12}(u) - \Lambda_{13}(u) - \Lambda_{14}(u)) \lambda_{14}(u) du.$$

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:

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

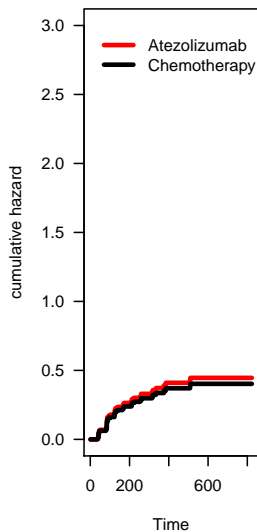
$$\lambda_{34}(t | Z) = \lambda_{34,0}(t) \exp(\beta_{34}Z)$$

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

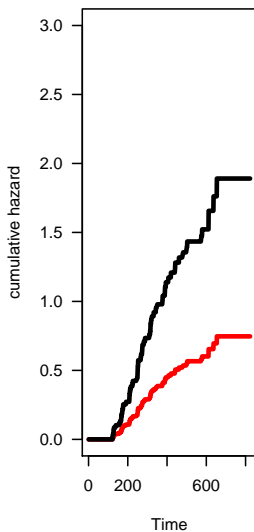
Post-progression hazard ratio β_{34} ?

Oak: raw cumulative hazard estimates (of interest)

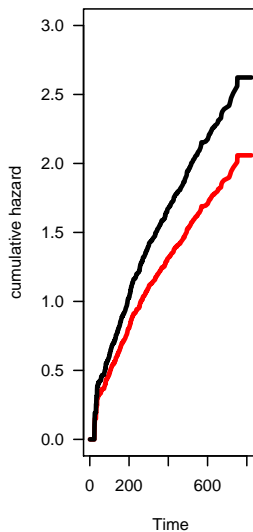
SD --> Response



Response --> PD

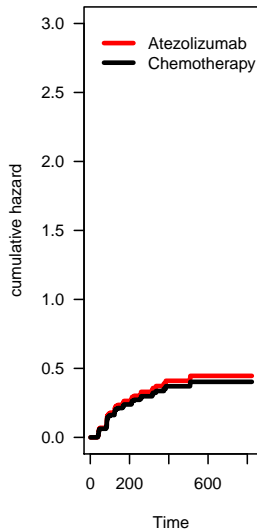


PD --> death

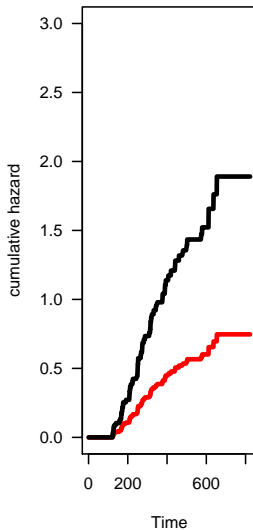


Oak: raw cumulative hazard estimates (of interest)

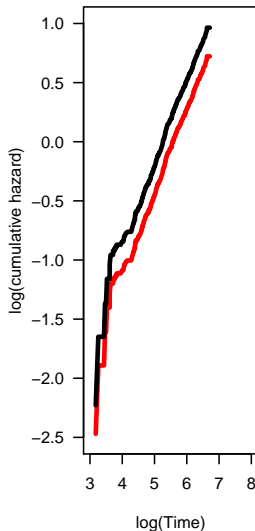
SD --> Response



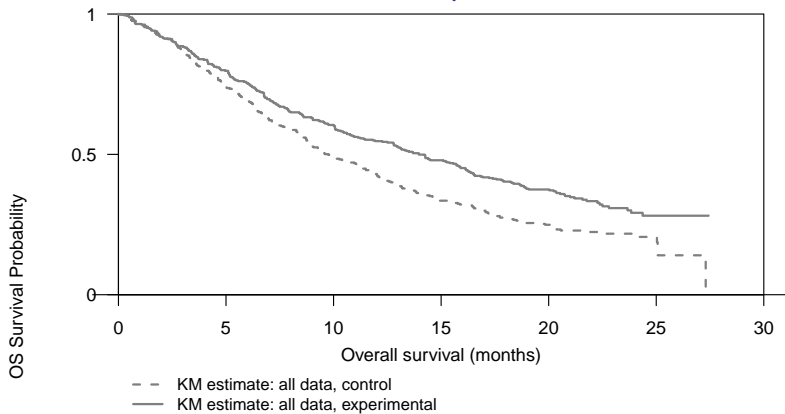
Response --> PD



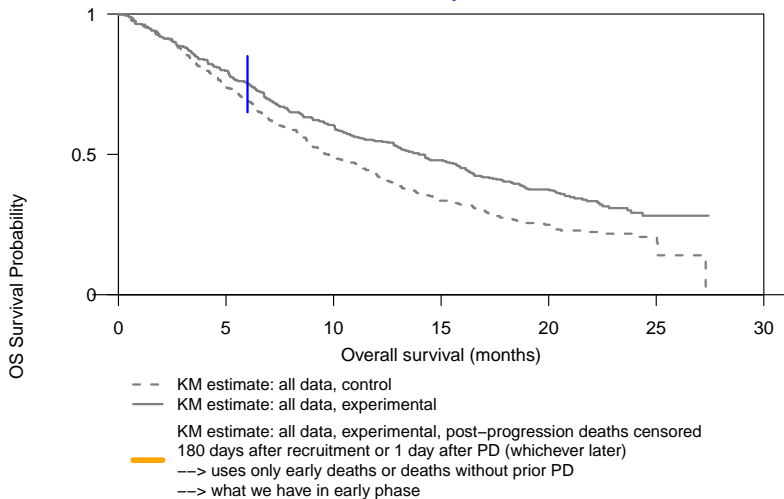
PD --> death



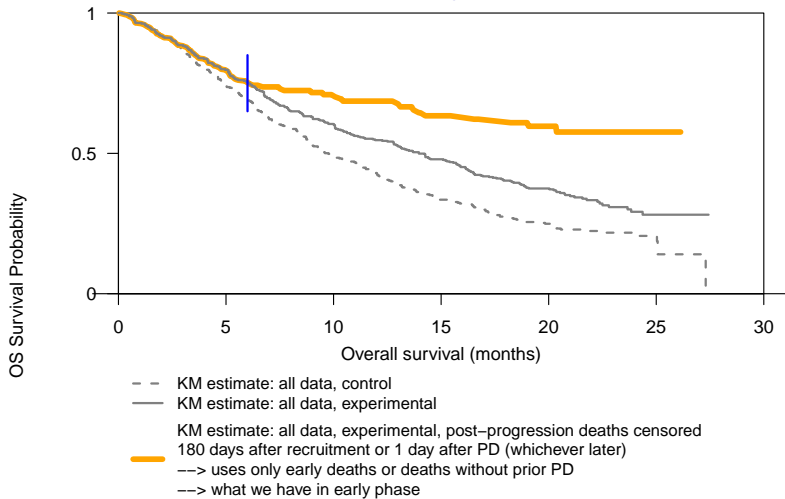
Oak: estimates / predictions of S_{exp}



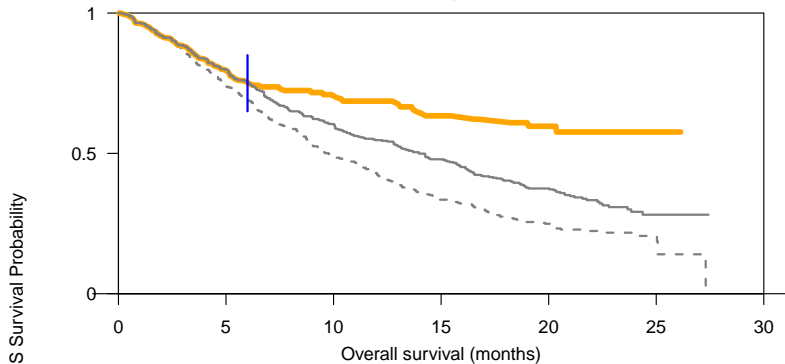
Oak: estimates / predictions of S_{exp}



Oak: estimates / predictions of S_{exp}

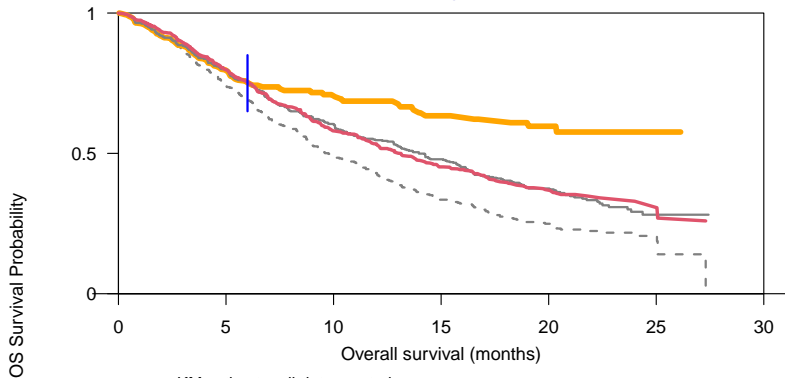


Oak: estimates / predictions of S_{exp}



- 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 (whichever later)
--> 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 (whichever later)
--> what we get with multistate model and post–PD PH assumption
--> enough post–PD deaths to reliably estimate post–PD HR

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 (whichever later)

--> 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 (whichever later)

--> 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:**

$P(\text{wrong decision})?$

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 $\Rightarrow \hat{\lambda}_{34}(t|Z)$.

Compute prediction of S_{exp} .

OS HR prediction based on early phase trial

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

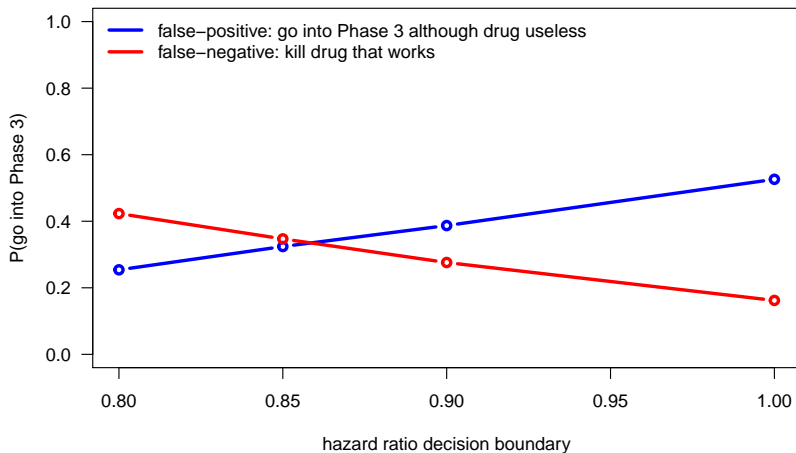
Decision to move to Phase 3: $\widehat{HR} \leq \text{boundary} \in \{0.80, 0.85, 0.90, 1.00\}$.

Repeat 1000 times.

Resampling \Rightarrow **quantification of uncertainty**.

Oak: P(wrong decision)

P(go into Phase 3) = P(approximated HR \leq boundary)



**How many post-PD deaths to
estimate HR of PD → 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

PFS - OS

Multistate vs. latent failure time model

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

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:

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

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 $1 \rightarrow 2$ transition only, as $0 \rightarrow 1, 2$ are rooted in initial state 0.

As soon as a quantity depends on **$1 \rightarrow 2$ 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 :

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

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

$$\begin{aligned}P_{00}(s, t) &= \exp\left(-\int_s^t \alpha_{01}(u) + \alpha_{02}(u) du\right), \\P_{11}(s, t; \mathbf{t}_1) &= \exp\left(-\int_s^t \alpha_{12}(u; \mathbf{t}_1) du\right), \\P_{22}(s, t) &= 1, \\P_{01}(s, t) &= \int_s^t P_{00}(s, u_-) \alpha_{01}(u) P_{11}(u, t; u) du, \\P_{12}(s, t; \mathbf{t}_1) &= 1 - P_{11}(s, t; \mathbf{t}_1), \\P_{02}(s, t) &= 1 - \left(P_{00}(s, t) + P_{01}(s, t)\right).\end{aligned}$$

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.

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

$$S_{PFS}(t) = P(\text{PFS} > t) = P_{00}(0, t),$$

$$S_{OS}(t) = P(\text{OS} > t) = P_{00}(0, t) + P_{01}(0, t),$$

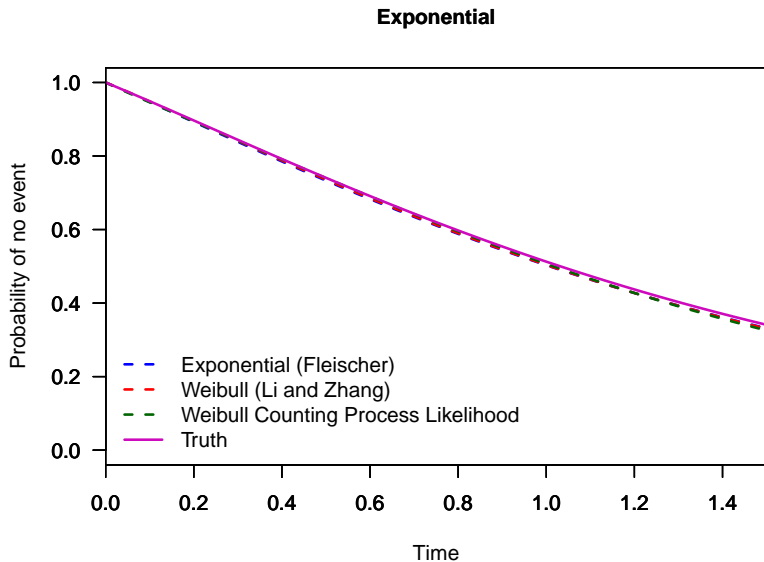
Joint distribution:

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

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

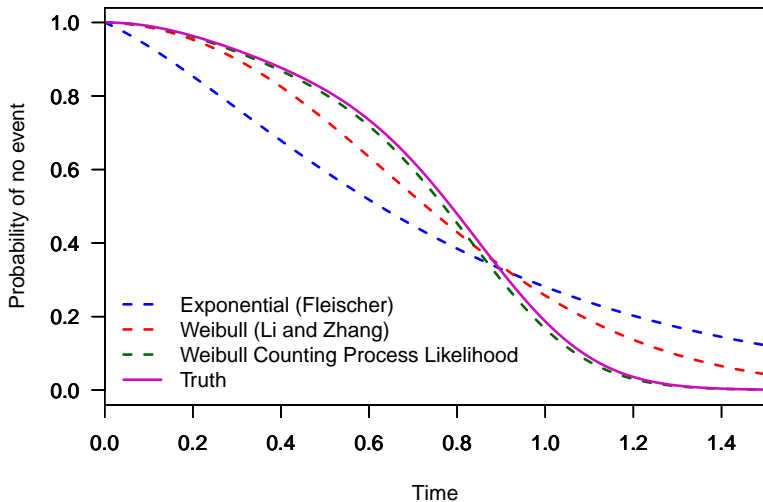
X **non-Markov**: integrate $P_{12}(u, v; t_1)$ over conditional distribution of all possible progression times $t_1 \leq u \Rightarrow$ final formula tedious.

Results: S_{OS} for Exponential

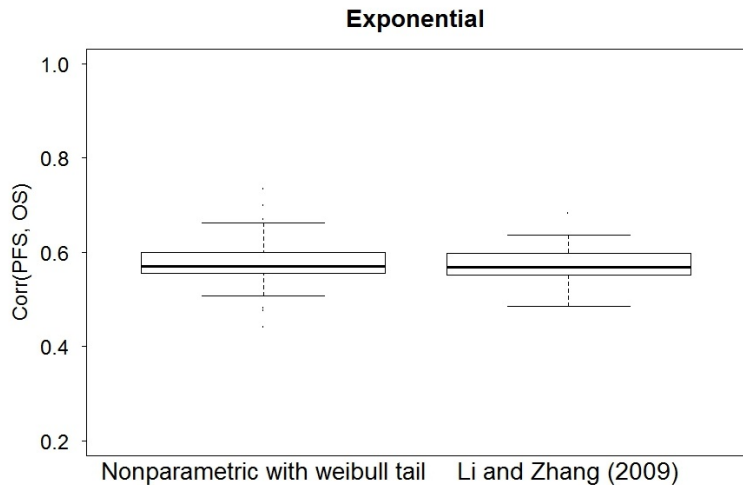


Results: S_{OS} for Weibull

Data from time-inhomogeneous Markov,
Weibull with different shape, $n = 500$

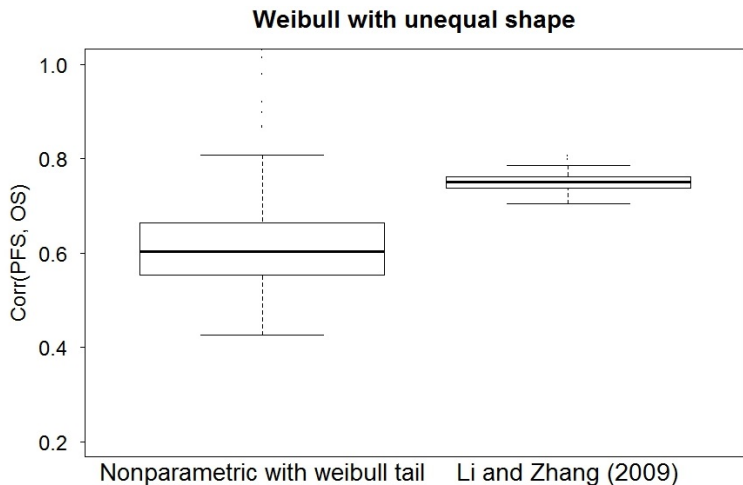


Results: correlations Exponential



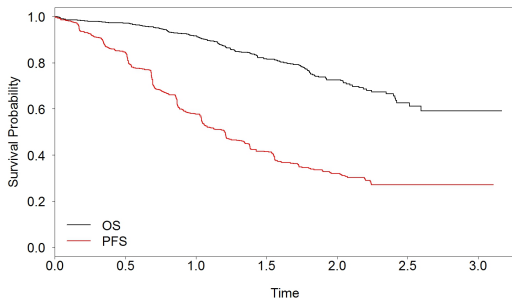
Corr(PFS, OS) for 200 simulated dataset from time-inhomogeneous Markov process.

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:

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

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**.

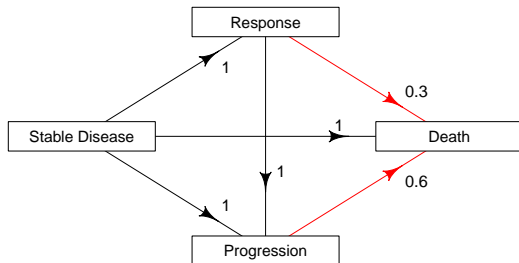
Various scenarios for post-PD follow-up time.

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**.

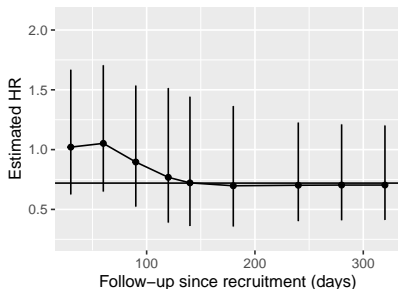
- Simulate 40 patient from experimental arm as before.



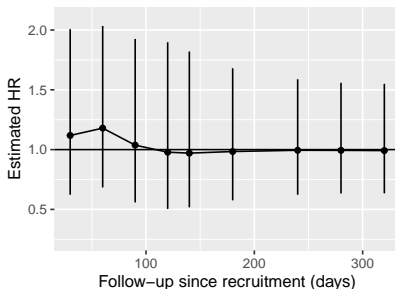
- Resulting **OS HR = 0.73**. Close to Oak OS HR.
- Follow-up post-PD for experimental arm truncated at 30, 60, 90, 120, 150, 180 and 240 days after recruitment.
- Repeat 1000 times.

Stability of hazard ratio estimate

A Treatment Effect



B No Treatment Effect



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

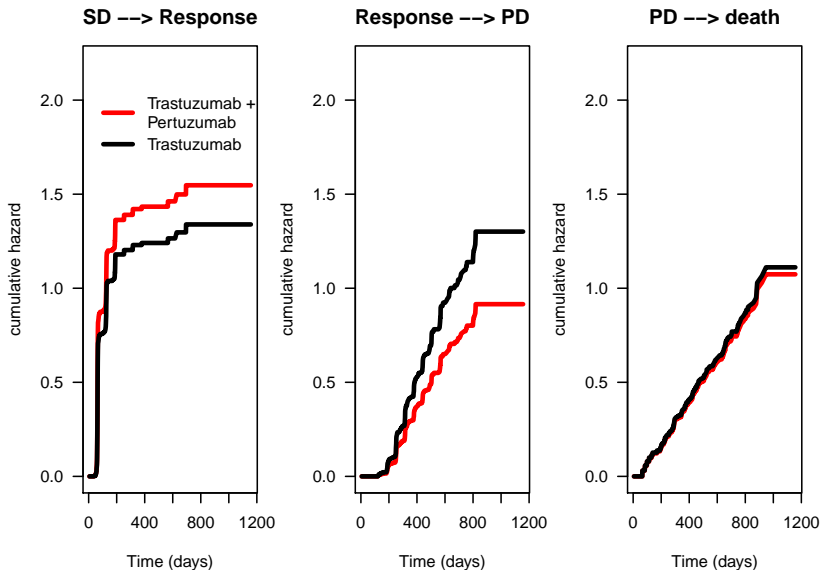
Baselga and Cortes (2012), Swain and Baselga (2015).

Previously untreated HER2-positive metastatic breast cancer patients.

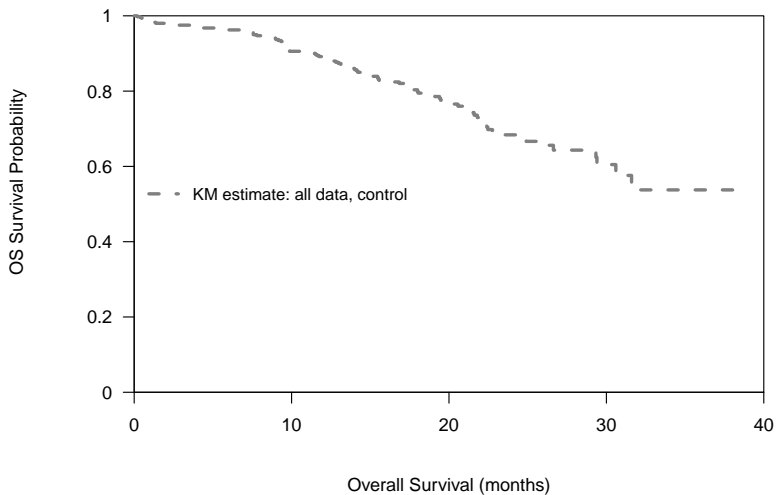
	Pertuzumab+Trastuzumab	Trastuzumab	HR (95% CI)
Survival	N=402	N=406	
Overall Survival			0.64 (0.47,0.88)
Progression-free Survival			0.62 (0.51,0.75)
Response	N=343	N=336	
Objective Response	275 (80.2%)	233 (69.3%)	
Stable Disease	50 (14.6%)	70 (20.8%)	
Progressive Disease	13 (3.8%)	28 (8.3%)	
Duration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



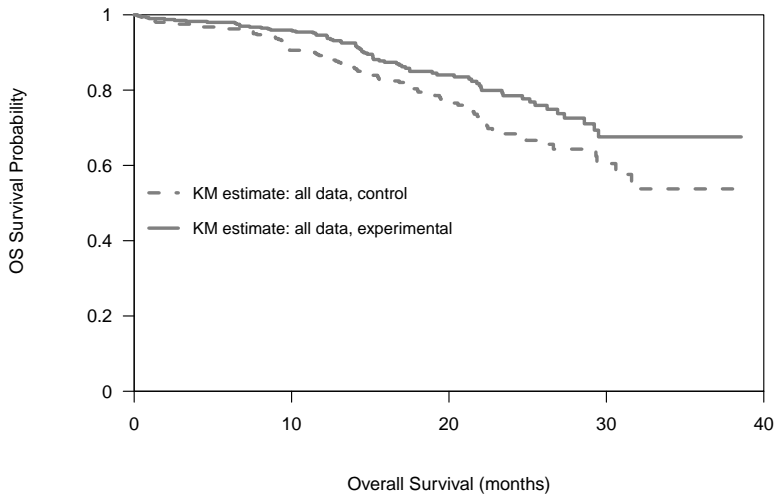
Cleopatra: estimates / predictions of S_{exp}



406 347 150 28

402 368 163 35

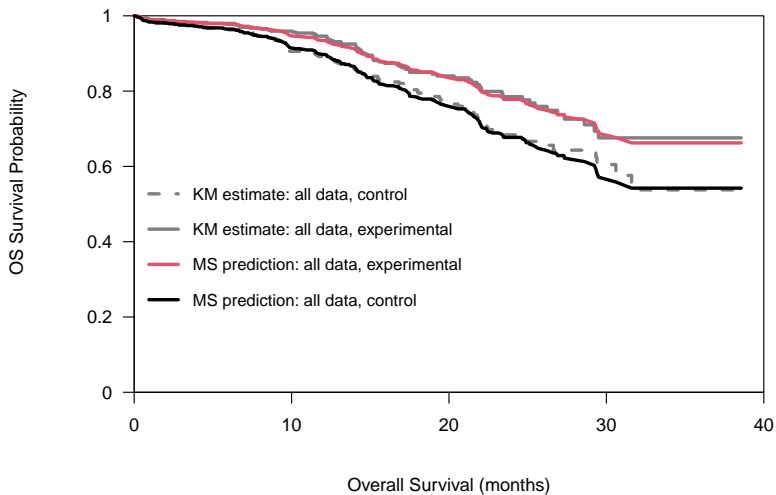
Cleopatra: estimates / predictions of S_{exp}



406 347 150 28

402 368 163 35

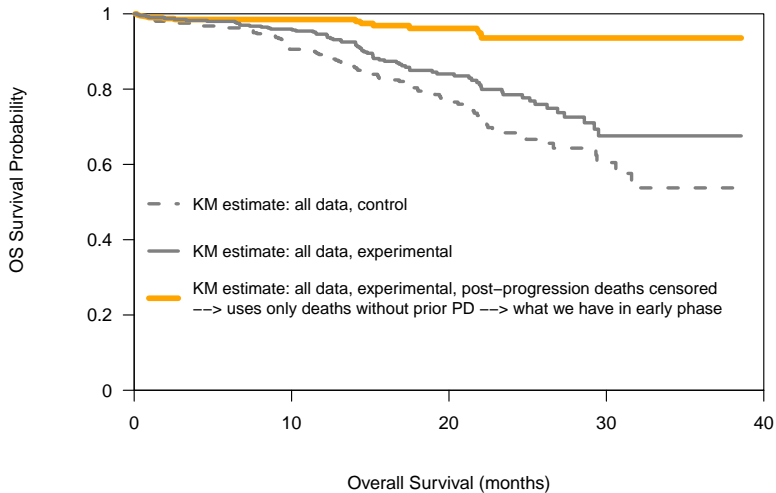
Cleopatra: estimates / predictions of S_{exp}



406 347 150 28

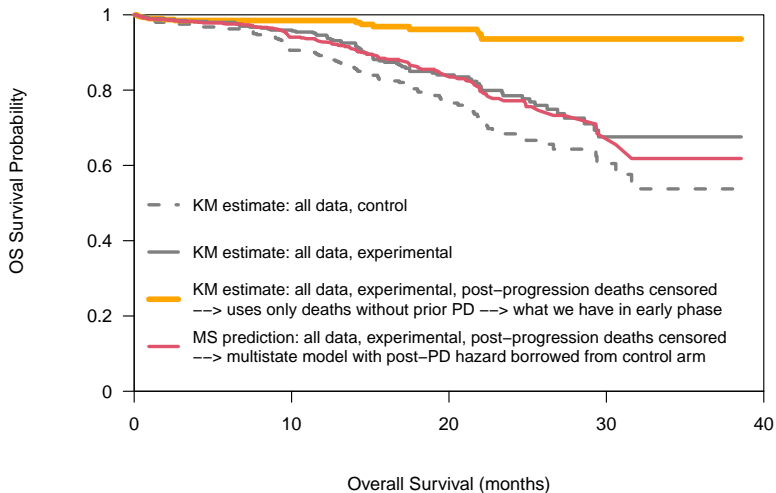
402 368 163 35

Cleopatra: estimates / predictions of S_{exp}



406	347	150	28
402	368	163	35

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 $\hat{\lambda}_{34}$ from historical data** = Cleopatra control arm in idealized scenario,
- compute prediction of S_{exp} as described above.

Resampling of operating characteristics

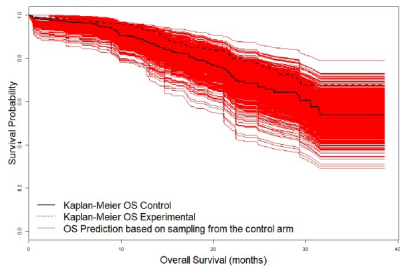
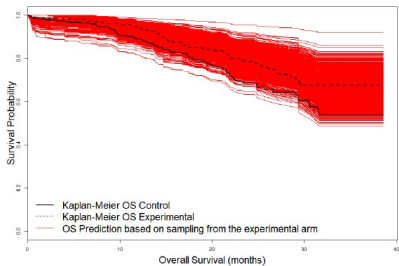
Setup:

- 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: $\widehat{HR} \leq \text{boundary} \in \{0.80, 0.85, 0.90, 1.00\}$.
- Repeat 1000 times.

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

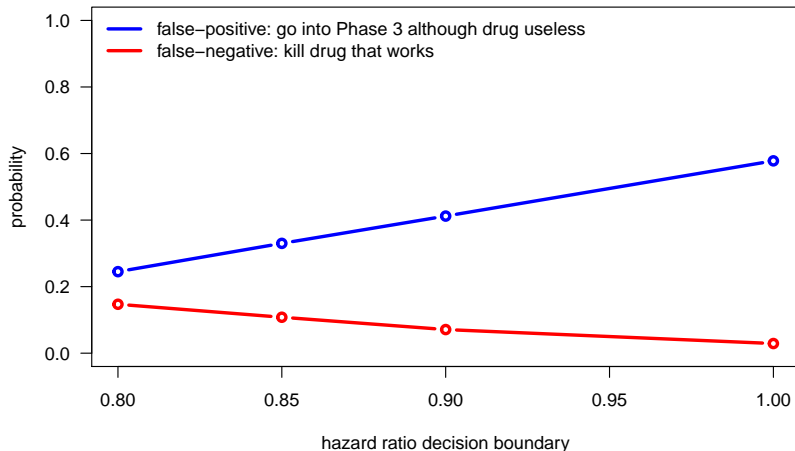
Cleopatra: operating characteristics

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



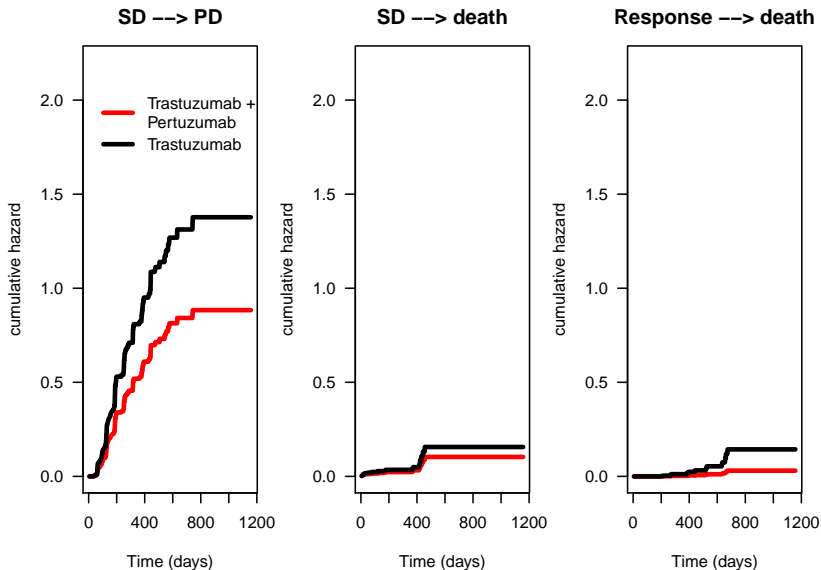
Cleopatra: operating characteristics

probability to go into Phase 3: $P(\text{approximated HR} \leq \text{boundary})$



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.

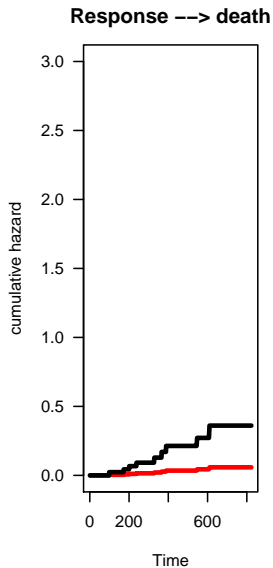
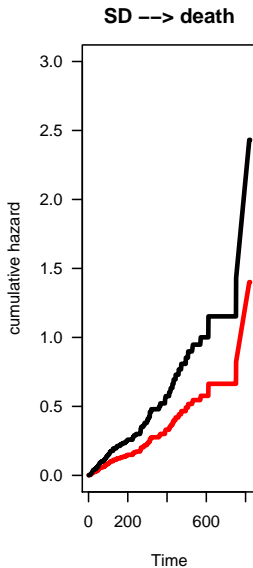
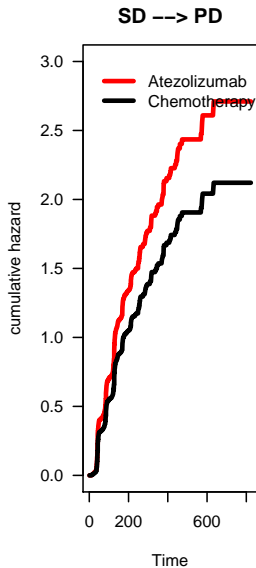
	Atezolizumab	Chemotherapy	HR (95% CI)
Survival	N=425	N=425	
Overall Survival			0.73 (0.62,0.87)
Progression-free Survival			0.95 (0.82,1.10)
Response	N=425	N=425	
Objective Response	58 (13.6%)	57 (13.4%)	
Stable Disease	150 (35%)	177 (42%)	
Progressive Disease	187 (44%)	117 (28%)	
Duration of Response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

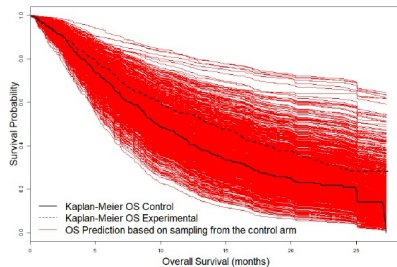
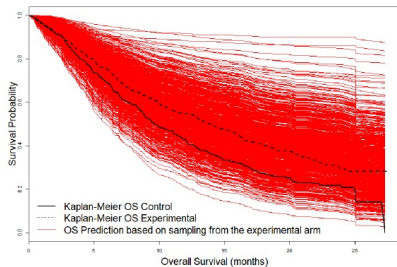
Clear survival benefit.

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.**

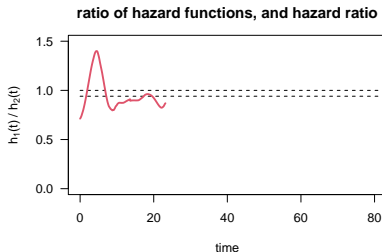
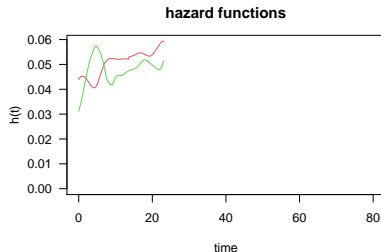
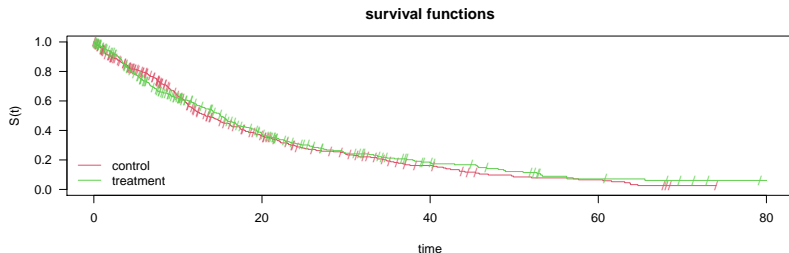
How to quantify effect?

A fictional clinical trial

Simulated clinical trial:

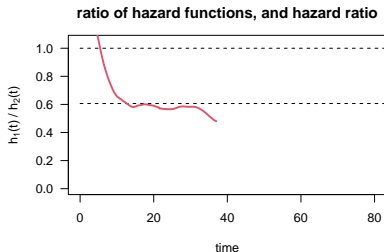
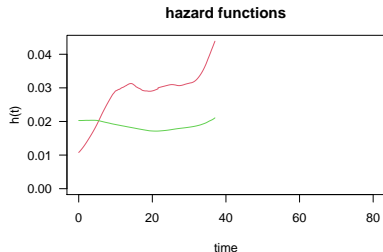
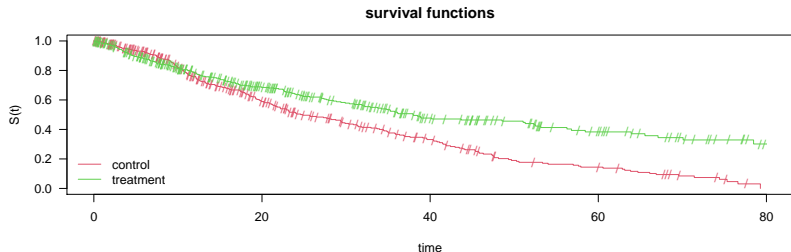
- 1:1 randomized, 400 and 400 patients per arm.
- No administrative censoring, but drop-out.

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 → 1	$\lambda_{01}^c = \log(2)/25$	$\lambda_{01}^t = \lambda_{01}^c \cdot \mathbf{1}$
0 → 2	$\lambda_{02}^c = \log(2)/30$	$\lambda_{02}^t = \lambda_{02}^c \cdot \mathbf{0.8}$
1 → 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).

Doing now what patients need next

R version and packages used to generate these slides:

R version: R version 4.0.3 (2020-10-10)

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 2020-12-09 at 10:41:51.