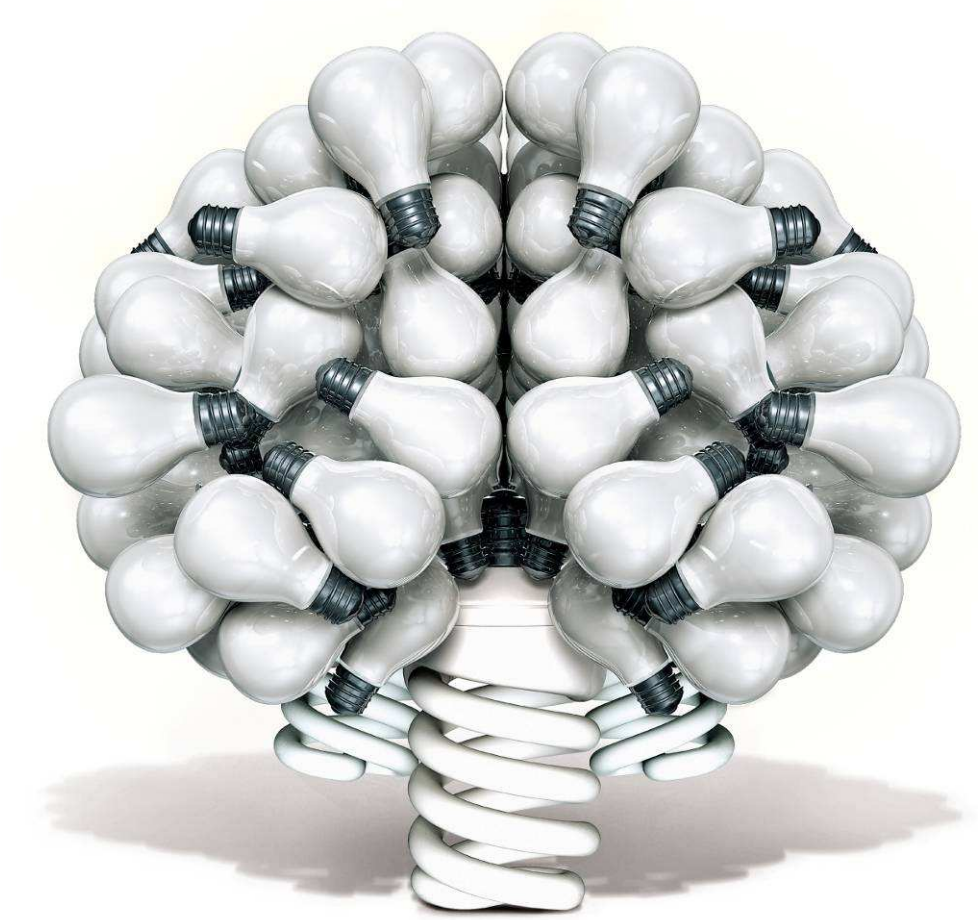
Statistical Modeling in the Context of Progression-free Survival

Dr. Frank Fleischer, Basel 12.03.2010



1. Introduction

Acknowledgements / Technical Remarks

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Thanks to Birgit, Julia, Karin and Erich !

Agenda

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2. Joint Modeling of PFS and OS
2.1 General model
2.2 Extensions
2.3 Case study (beta trial)
3. Investigator assessment vs Independent Review
3.1 General model
3.2 Quantification of bias caused by informative censoring
3.3 Numerical examples
4. Conclusions and Outlook

1. Introduction

Anti-cancer drug studies

- Most common (hard) endpoint overall survival (OS)
- Time to progression (TTP)

  Time from randomisation to progression

  Censoring of patients that die before progression
- Progression-free survival (PFS)

  Time from randomisation to earliest of progression and death: PFS = min(TTP, OS)

Progression e.g. based on RECIST criteria

1. Introduction

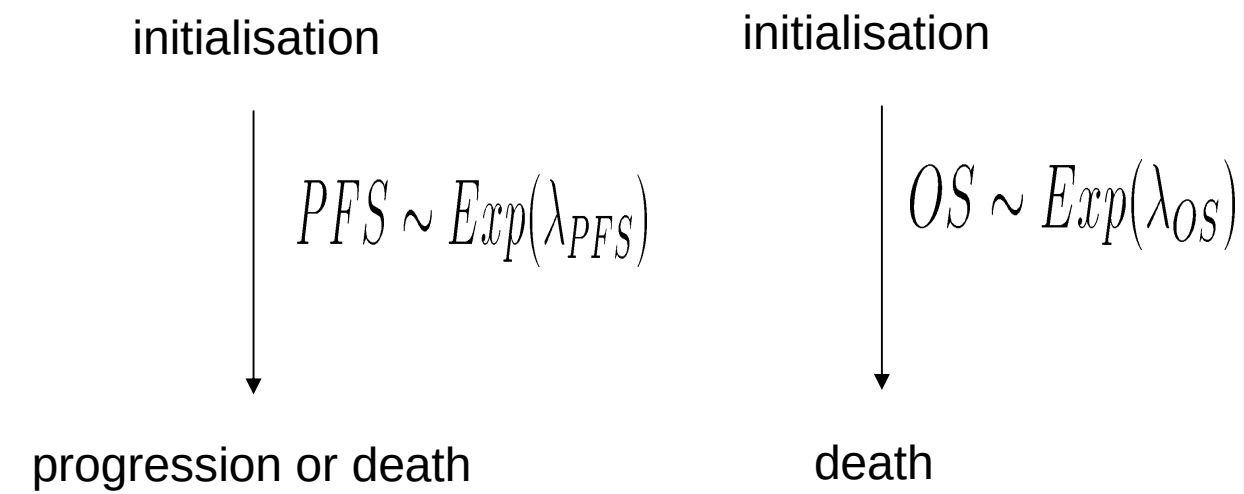
Two topics connected to PFS will be considered:

1) Joint modeling of PFS and OS
   - Sample Size calculation
   - Event monitoring and forecast
   - Quantification of confounding effects for OS
2) Informative censoring of PFS based on retrospective central review
   - Caused by errors in investigator assessment and retrospective mechanism
   - Quantification of bias introduced
   - Sensitivity analysis to cope with the bias

Statistical modeling might help…

2. Joint modeling of PFS and OS

PFS and OS are traditionally considered independently (sample size calculations)



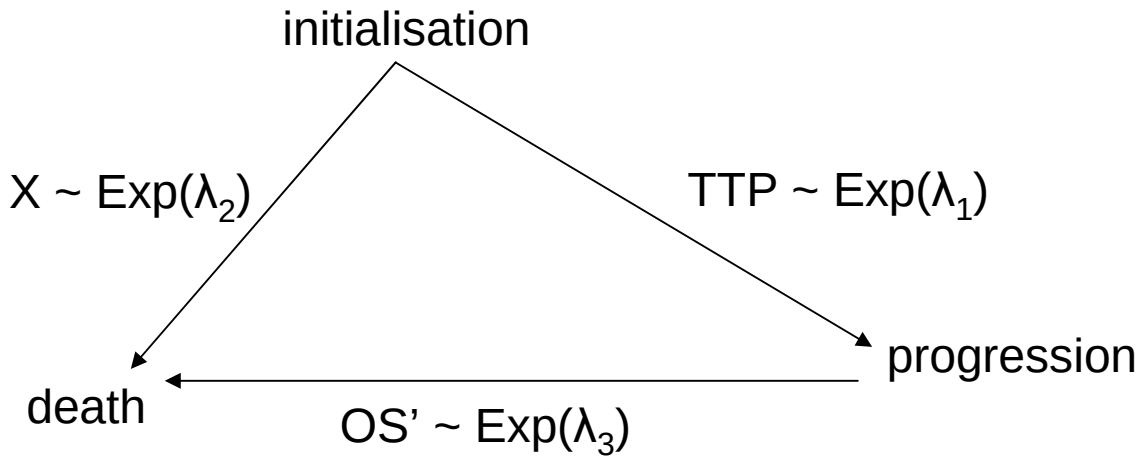
2.1. General model

Progression free survival

$$PFS = \min\{TTP, X\}$$

Overall survival

$$OS = \begin{cases} TTP + OS' & ,if\ PFS = TTP \\ X & ,if\ PFS = X \end{cases}$$



2.1. General model

Let TTP ~ Exp(λ_1), X ~ Exp(λ_2), OS' ~ Exp(λ_3). Furthermore let PFS=min(TTP, OS) and

$$OS = \begin{cases} TTP + OS' & ,if\ PFS = TTP \\ X & ,if\ PFS = X \end{cases}$$

Then

$$F_{OS}(x) = 1 - \frac{\lambda_1}{\lambda_1+\lambda_2-\lambda_3}\exp^{-\lambda_3 x} + \frac{\lambda_3-\lambda_2}{\lambda_1+\lambda_2-\lambda_3}\exp^{-(\lambda_1+\lambda_2)x}$$

2.1. General model

Let TTP ~ Exp(λ_1), X ~ Exp(λ_2), OS' ~ Exp(λ_3). Furthermore let PFS=min(TTP, OS) and

$$OS = \begin{cases} TTP + OS' & ,if\ PFS = TTP \\ X & ,if\ PFS = X \end{cases}$$

Then

$$\begin{aligned} Corr(PFS, OS) &= \frac{\lambda_3}{\sqrt{\lambda_1^2 + 2\lambda_1\lambda_2 + \lambda_3^2}} \\ &= \sqrt{\frac{Var(PFS)}{Var(OS)}} \end{aligned}$$

2.1. General model

Likelihood function:

$$L(\lambda_1, \lambda_2, \lambda_3) = \left(\lambda_1^{n_1} \exp(-\lambda_1 u)\right)\left(\lambda_2^{n_2} \exp(-\lambda_2 u)\right)\left(\lambda_3^{n_3} \exp(-\lambda_3 s)\right)$$

Maximum-Likelihood-Estimators of λ_1, λ_2 and λ_3 are:

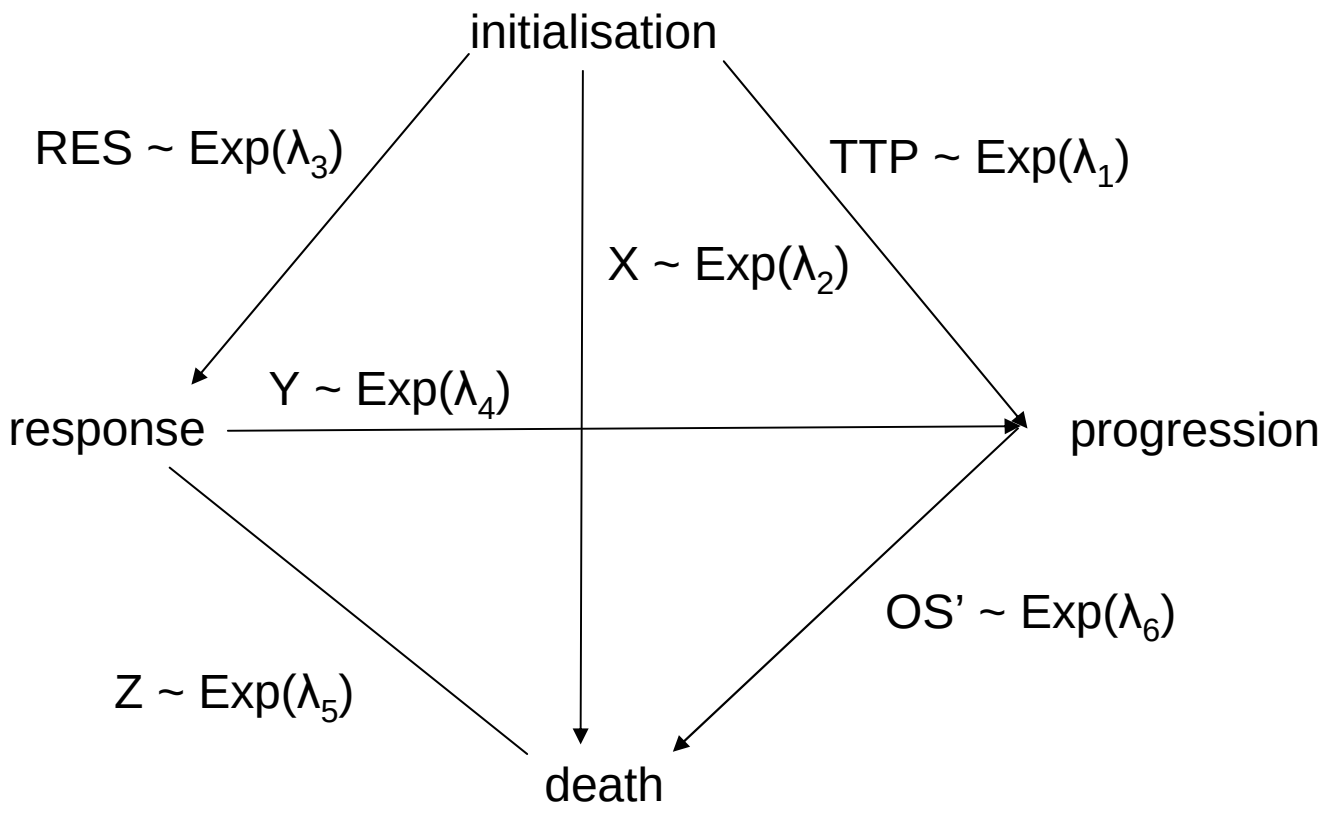
$$\hat{\lambda}_1 = \frac{n_1}{u}$$

$$\hat{\lambda}_2 = \frac{n_2}{u}$$

$$\hat{\lambda}_3 = \frac{n_3}{s}$$

Similar MLEs for extensions of the model

2.2 Extensions



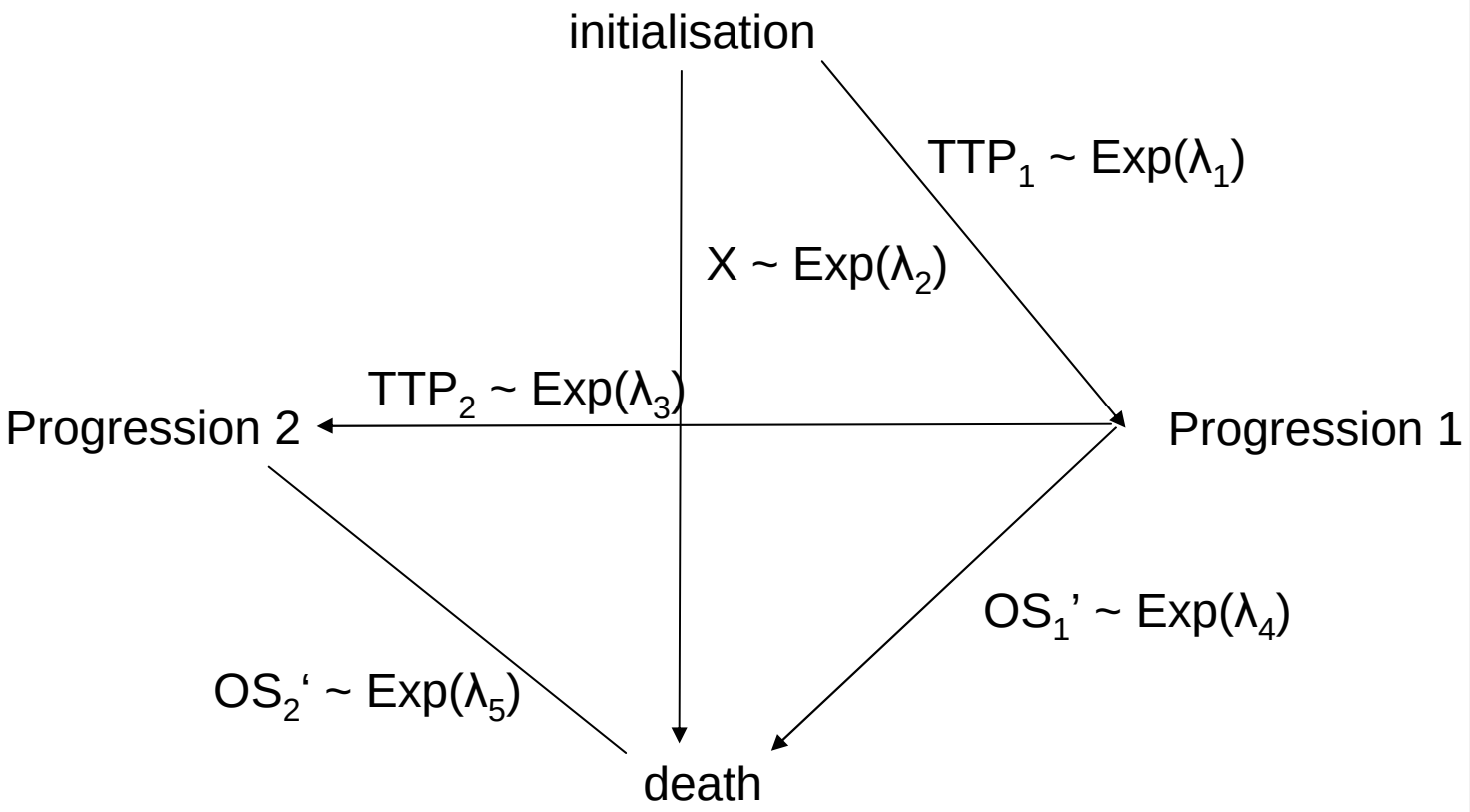
2.2 Extensions

Let TTP ~ Exp(λ_1), X ~ Exp(λ_2), RES ~ Exp(λ_3), Y ~ Exp(λ_4), Z ~ Exp(λ_5), OS' ~ Exp(λ_6). Furthermore let PFS=min(TTP,X,RES+X,RES+Y) and

$$OS = \begin{cases} TTP + OS' & , if\ PFS = TTP \\ X & , if\ PFS = X \\ (RES + Y) + OS' & , if\ PFS = RES + Y \\ RES + Z & , if\ PFS = RES + Z \end{cases}$$

$$\begin{aligned} F_{OS}(x) &= 1 - \left[\frac{(\lambda_1+\lambda_2+\lambda_3-\lambda_4-\lambda_5)(\lambda_2(\lambda_1+\lambda_2+\lambda_3-\lambda_6)-\lambda_1\lambda_6)}{(\lambda_1+\lambda_2+\lambda_3)(\lambda_1+\lambda_2+\lambda_3-\lambda_6)(\lambda_1+\lambda_2+\lambda_3-\lambda_4-\lambda_5)} \right. \\ &\quad \left. + \frac{\lambda_3\lambda_6(\lambda_4+\lambda_5)-\lambda_3\lambda_5(\lambda_1+\lambda_2+\lambda_3)}{(\lambda_1+\lambda_2+\lambda_3)(\lambda_1+\lambda_2+\lambda_3-\lambda_6)(\lambda_1+\lambda_2+\lambda_3-\lambda_4-\lambda_5)} \right] \exp^{-(\lambda_1+\lambda_2+\lambda_3)x} \\ &\quad - \frac{\lambda_1(\lambda_4+\lambda_5-\lambda_6)+\lambda_3\lambda_4}{(\lambda_1+\lambda_2+\lambda_3-\lambda_6)(\lambda_4+\lambda_5-\lambda_6)} \exp^{-\lambda_6 x} \\ &\quad + \frac{\lambda_3(\lambda_6-\lambda_5)}{(\lambda_1+\lambda_2+\lambda_3-\lambda_4-\lambda_5)(\lambda_4+\lambda_5-\lambda_6)} \exp^{-(\lambda_4+\lambda_5)x} \\ &= 1 - A\exp^{-(\lambda_1+\lambda_2+\lambda_3)x} - B\exp^{-\lambda_6 x} + C\exp^{-(\lambda_4+\lambda_5)x} \end{aligned}$$

2.2 Extensions



2.3 Case study (beta trial)

- Bevacizumab in NSCLC, Phase III, 2nd line
- Erlotinib/Bevacizumab vs. Erlotinib/Placebo

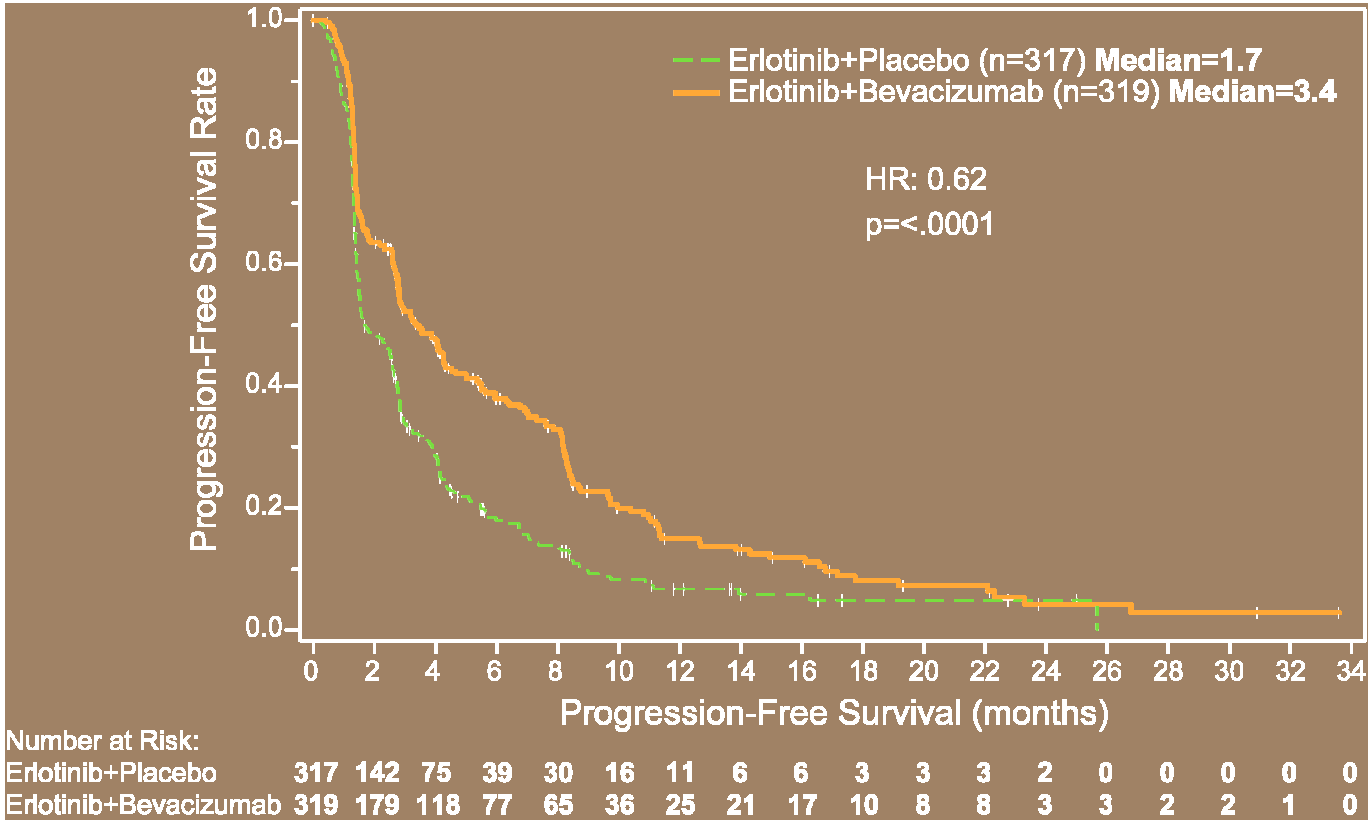
- Given data:

  n = 636 patients

- $med_{PFS,Bev}$= 3.4 months, $med_{OS,Bev}$ = 9.3 months and 75% quartile for OS = 4.1 months
- $med_{PFS,Plac}$= 1.7 months, $med_{OS,Plac}$ = 9.2 months and 75% quartile for OS = 4 months

- Significant advantage of Bevacizumab in PFS ($p<0.01$)
- No significant advantage of Bevacizumab in OS ($p=0.758$)

2.3 Case study (beta trial)



HR is estimated using stratified Cox model; P value is based on stratified Logrank test. Stratification factors are: ECOG PS, Smoking Status and Sex

Hainsworth J, ASTRO-IASLC 2008

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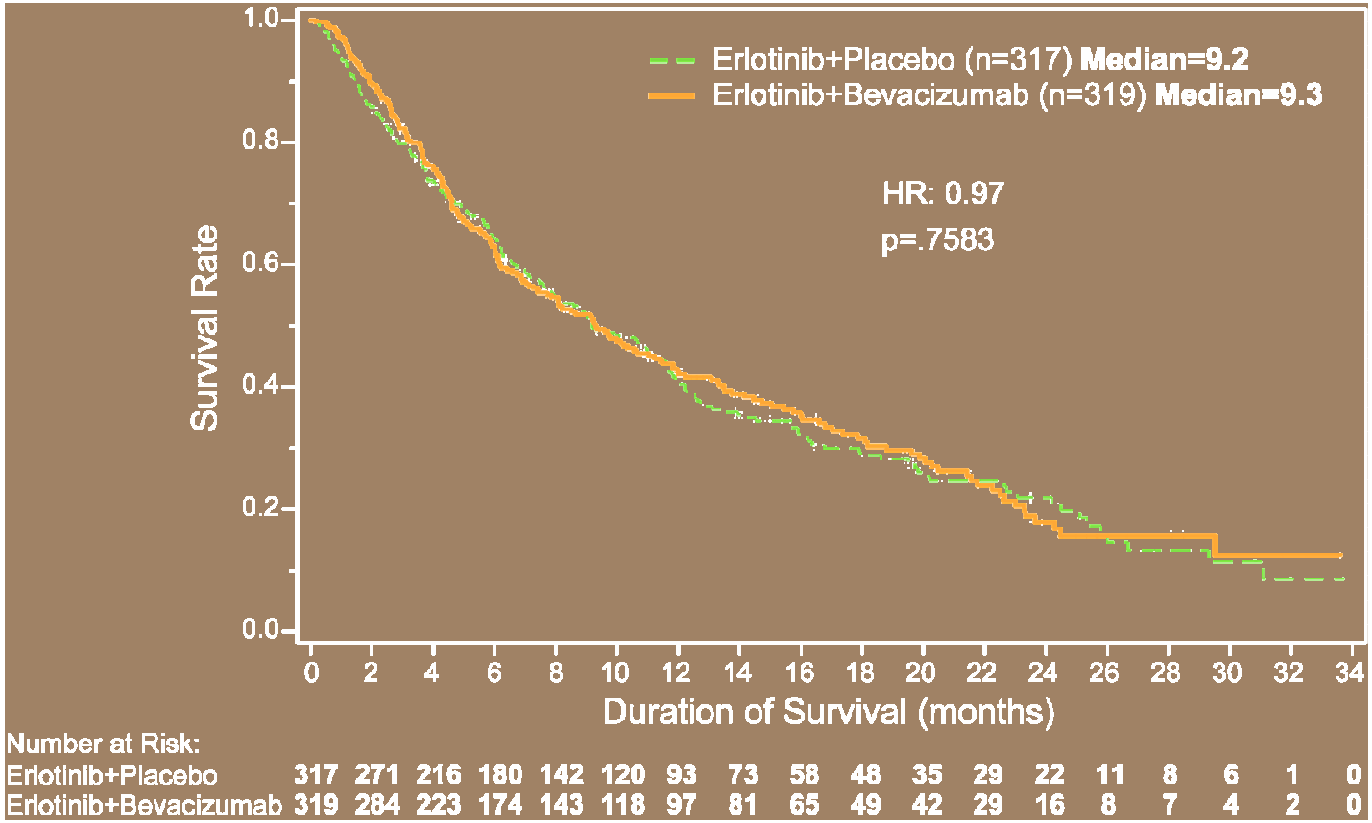
2.3 Case study (beta trial)



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2.3 Case study (beta trial)

	Erlotinib/Placebo	Erlotinib/Bevacizumab
•	$\lambda_{11} = 0.3420$	$\lambda_{21} = 0.1390$
•	$\lambda_{12} = 0.0648$	$\lambda_{22} = 0.0654$
•	$\lambda_{13} = 0.0797$	$\lambda_{23} = 0.0876$

- Probability of dying directly:

$$\frac{\lambda_{12}}{\lambda_{11} + \lambda_{12}} = 0.32 \qquad \frac{\lambda_{22}}{\lambda_{21} + \lambda_{22}} = 0.16$$

2.3 Case study (beta trial)

- **Question:**
- Where does the increased hazard of dying after progression in the Bevacizumab group come from?

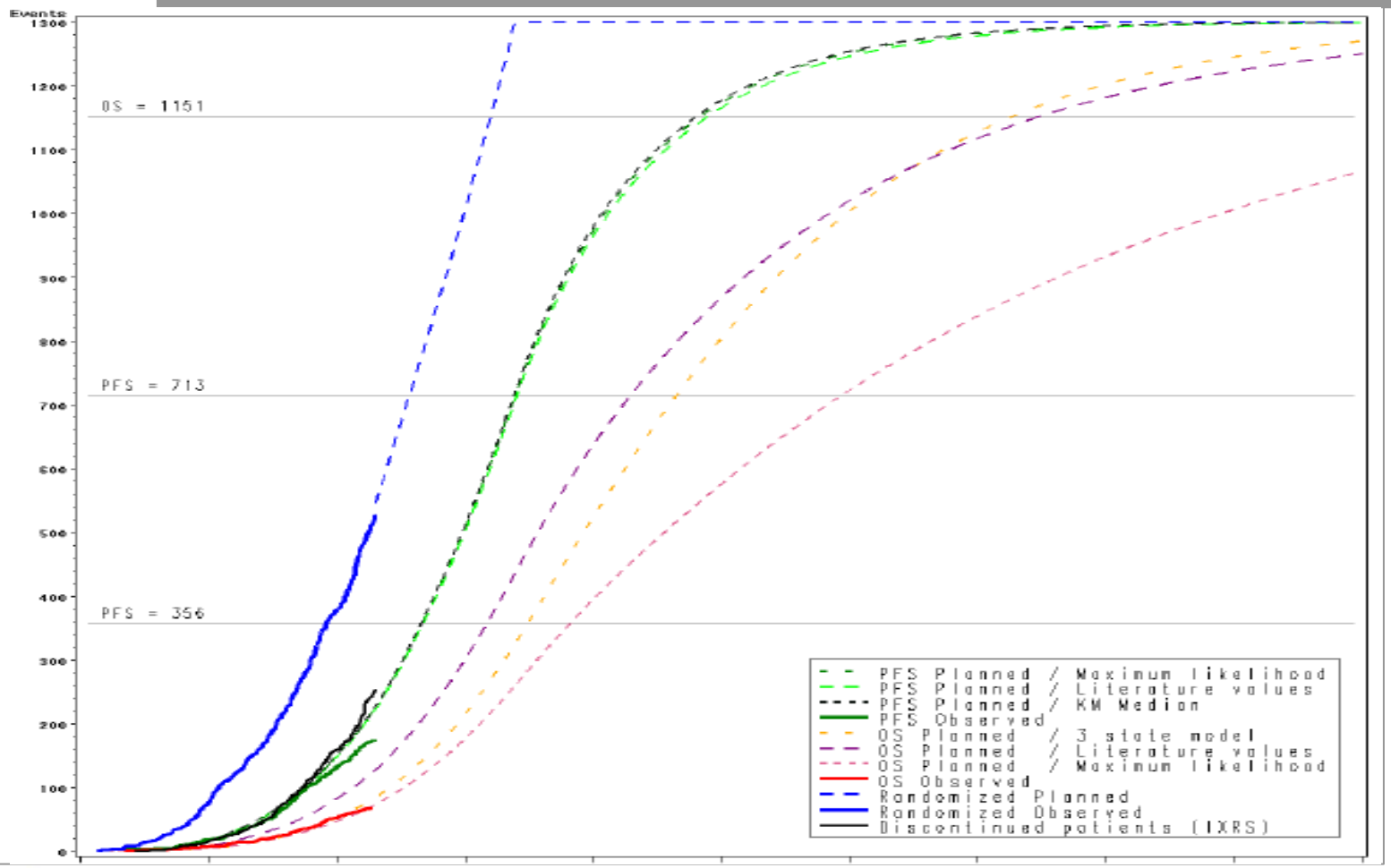
- **Possible explanation:**
- More or different subsequent treatment in the Placebo group compared to the Bevacizumab group

- confounding effect

2.3 Case study (beta trial)

- **Size of the confounding effect:**
- Replace $\lambda_{13} = 0.0797$ in the Placebo group by $\lambda_{23} = 0.0876$ from the Bevacizumab group
- New $med_{OS,Plac} = 8.6$ months (old $med_{OS,Plac} = 9.2$ months)
- Confounding effect caused by subsequent treatment might be at most 0.6 months with respect to the median OS

2.3 Case study (event monitoring and forecast)



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3. Investigator assessment vs independent review

- Progression is assessed by independent review
  - Open-label trials
  - Potentially unblinding AE profile
  - To ensure quality of trial data
- Initial belief that assessment by independent review is superior to investigator assessment
  - Unbiased
  - Highly trained
  - Consistent

3. Investigator assessment vs independent review

- Independent review is usually performed retrospectively
  - No real-time assessments
  - Treatment decisions are investigator triggered
- Retrospective mechanism together with false investigator assessments can lead to
  - Informative censoring
  - Due to patients judged progressive by investigator but censored by independent review
  - Can lead to bias in PFS based on independent review

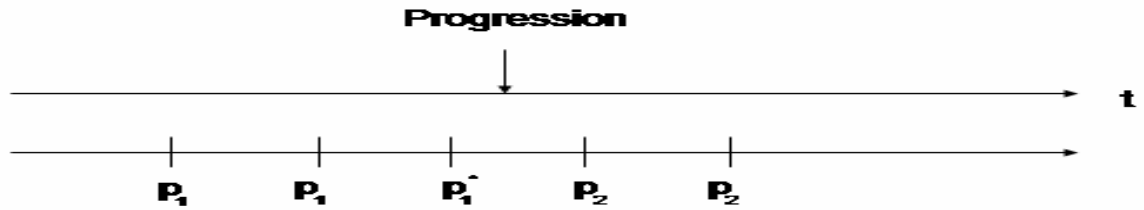
p_1

3.1 General model

- Assessment every v units (e.g. 1 month)
- Data available until PD by investigator is declared
- Underlying time-to-event T (e.g. Weibull-distributed)
- Error probabilities of investigator:
  - p_1^* False PD at assessment closest before T
  - p_1 False PD at other assessments
  - p_2 False Non-PD at assessment after T
- Independent review assesses perfectly for data available

p_1

3.1 General model



Error probabilites for investigator assessment based on real progression time point

3.2 Quantification of bias caused by informative censoring

- The hazard of becoming progressive is given by

$$\lambda_k = \frac{P((k-1)v \leq T < kv)}{P((k-1)v \leq T)} = \frac{S_T((k-1)v) - S_T(kv)}{S_T((k-1)v)}$$

- The hazard of being judged progressive by independent review is given by

$$\lambda_k^* = \frac{P(T_{ind} = kv, T_{ind} \text{ not censored})}{P(T_{ind} \geq kv)} = \frac{S_T((k-1)v) - S_T(kv)}{\frac{p_1^* - p_1}{1 - p_1^*} S_T(kv) + S_T((k-1)v)}$$

for $k \geq 2$ and $\lambda_1^* = \lambda_1$

3.2 Quantification of bias caused by informative censoring

- => In general $\lambda_k \neq \lambda_k^*$
  - Unless $p_1 = p_1^*$
  - => Bias in the independent review
  - Independent of p_2

- Difference between p_1 and p_1^* is the decisive factor in this model
  - No difference => no informative censoring => no bias
  - Large difference => informative censoring => bias

3.2 Quantification of bias caused by informative censoring

- What to do?
  - Discordance rate only helps partially
    - Low discordance => Small/no bias
    - High discordance does not necessarily indicate bias
- Sensitivity analysis
  - PD at next time-point (PDn) analysis
  - Patients censored by independent review but PD by investigator are considered PD at next scheduled time-point

3.2 Quantification of bias caused by informative censoring

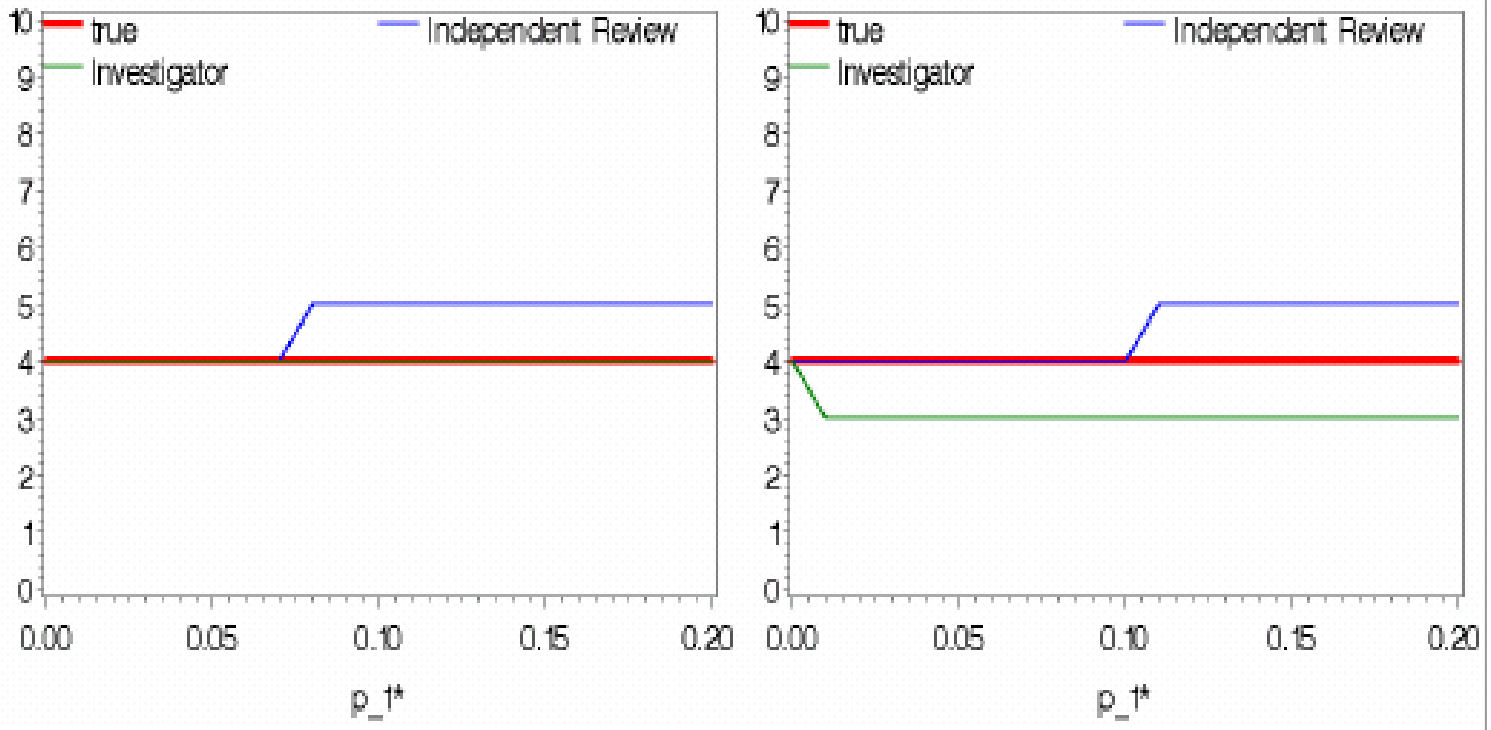
- Hazard for PDn-analysis

$$\lambda_k^{PDn} = \frac{P(T_{PDn}=kv)}{P(T_{PDn}\geq kv)} = \frac{S_T(k-1)v-(1-p_1)S_T(kv)}{S_T((k-1)v)}$$

- Useful sandwiching property if $p_1^* \geq p_1$

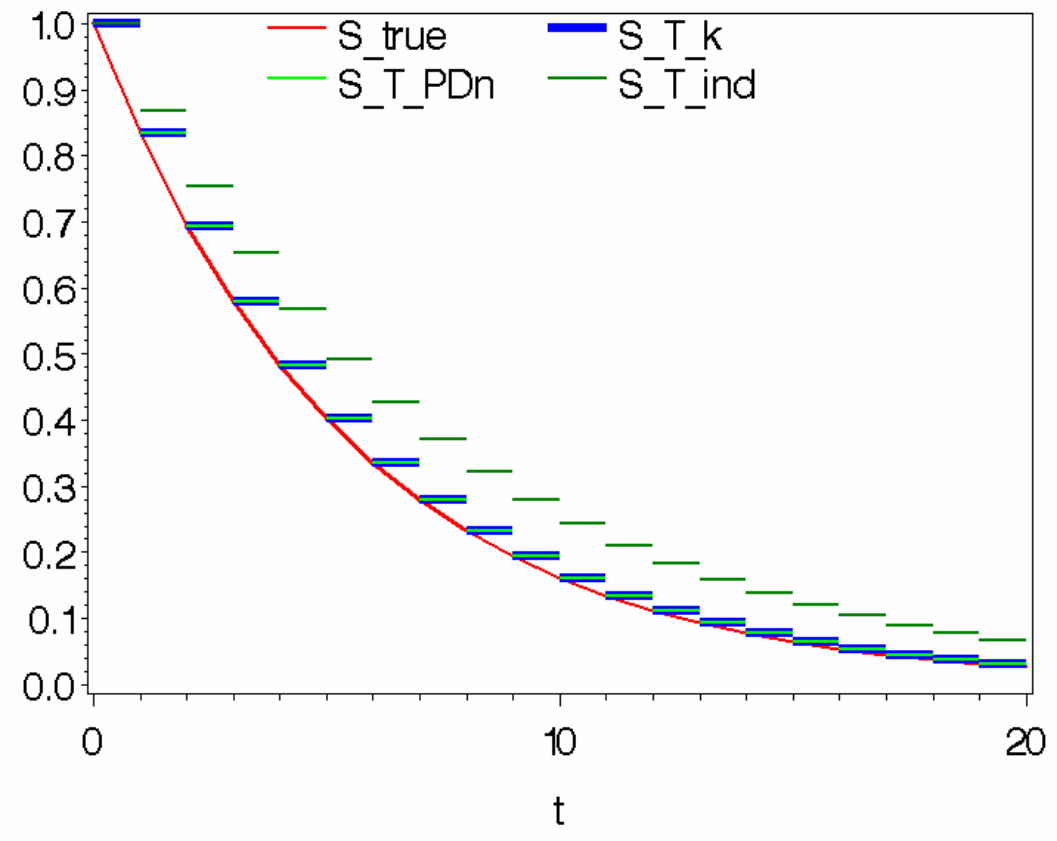
$$\lambda_k^{PDn} \geq \lambda_k \geq \lambda_k^*$$

3.3 Numerical examples



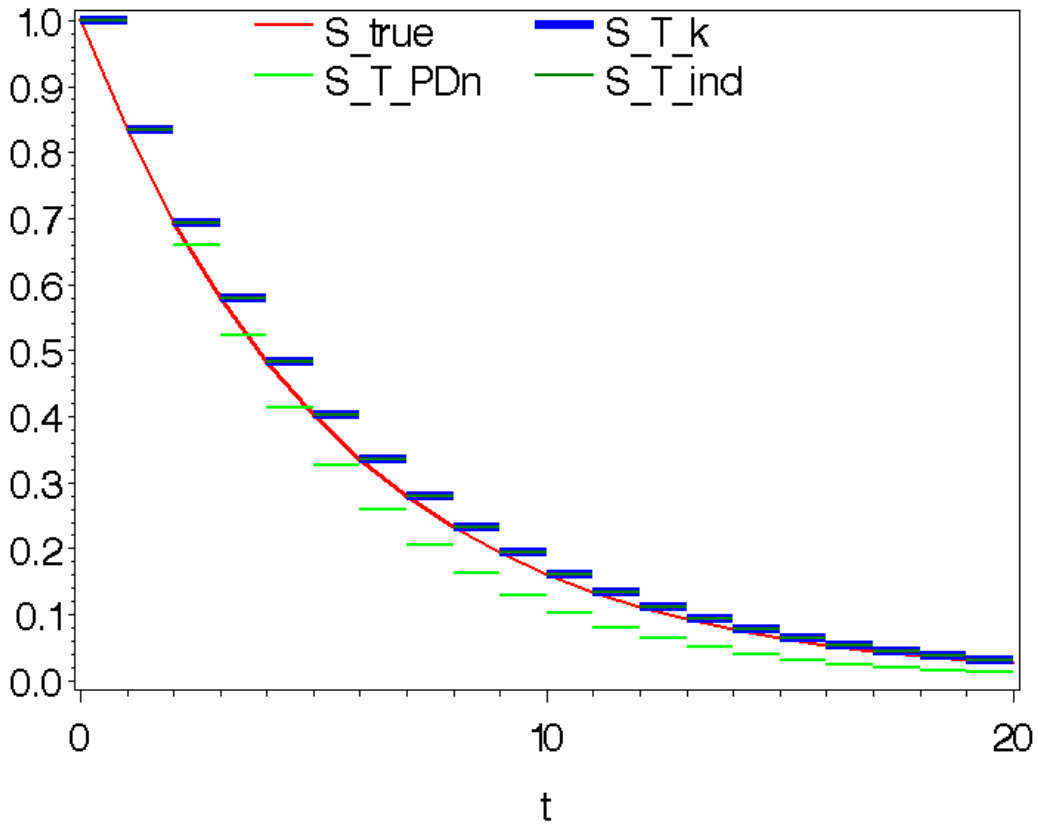
TTP medians under exponential distribution for $p_1 = 0.02$ and $p_1 = 0.05$

3.3 Numerical examples



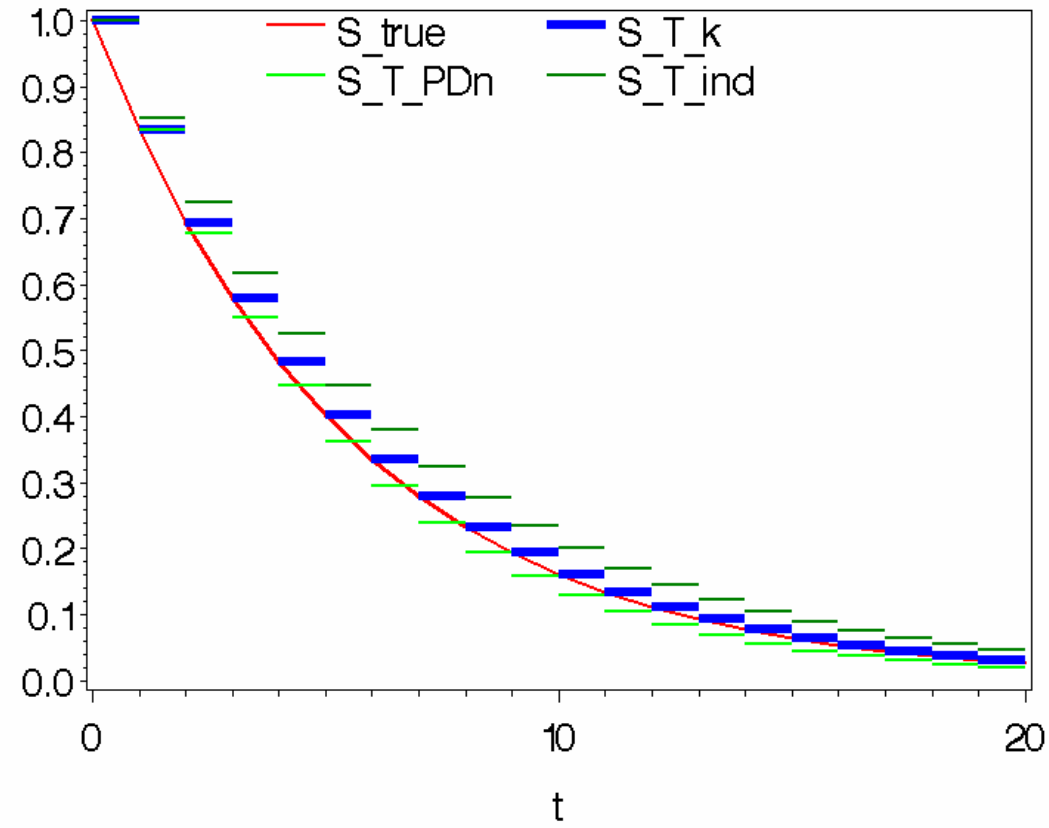
Expected TTP survival function for heavy informative censoring

3.3 Numerical examples



Expected TTP survival function for no informative censoring

3.3 Numerical examples



Expected TTP survival function for medium informative censoring

4. Conclusions and Outlook

- Statistical modeling can be of help in various topics related to PFS
  - Joint modeling of PFS and OS
  - Bias of retrospective independent review due to errors in investigator judgement
- Can help to come up with
  - More precise sample size estimates
  - Monitoring and forecast of events
  - Sensitivity analyses and when to apply them
  - Quantification of possible bias and confounding effects

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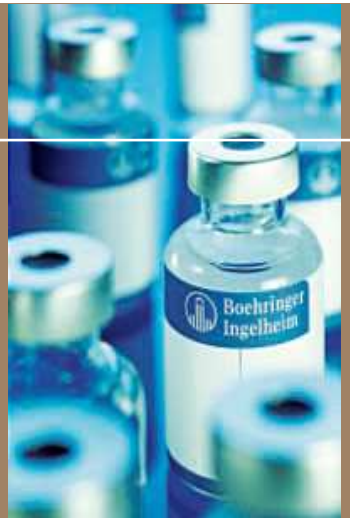

Questions?

Literature

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- Fleischer, F., Gaschler-Markefski B., Bluhmki E. *A statistical model for the dependence between progression-free survival and overall survival.* Statistics in Medicine 2009; 28: 2669-2686.
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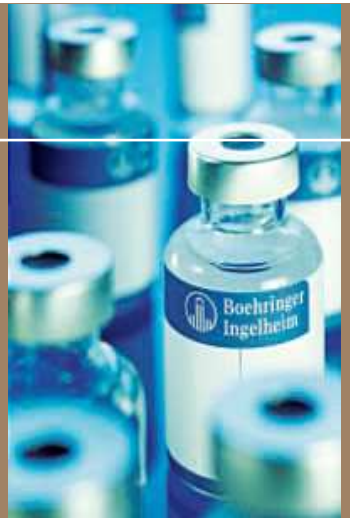

Back-up

2.3 Extensions

Let

- u be the sum of all observed times to the first event, including the observed times of patients censored while in the initial state
- s the sum of all times from progression to death, including the times of patients censored while in progression
- n be the number of patients in the study
- n_1 be the number of patients, who progress
- n_2 be the number of patients, who die directly without progression
- n_3 be the number of patients, who progress and then die