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Can methods based on existing models really aid decision making in non-small-cell lung cancer (NSCLC) trials?

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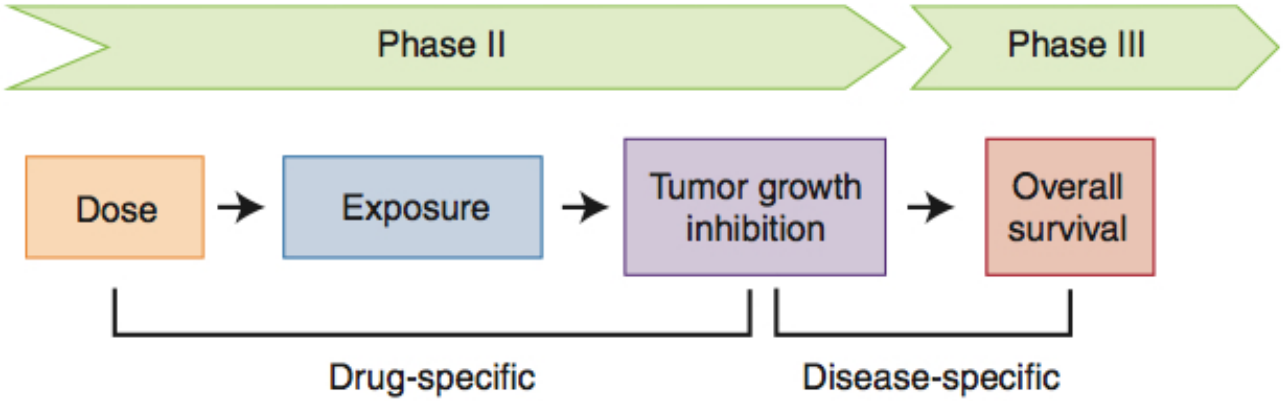
Model-based methods to the rescue!



Bruno, Mercier, & Claret. 2013. *Clin. Pharmacol. Ther.*

Models are being used to make early predictions/decisions about efficacy in Phase 1b/2 studies.

- Non-small cell lung cancer (NSCLC) [7, 4]
- Colorectal cancer [1, 2]
- Ovarian cancer [5]
- Multiple myeloma [3]
- Others . . .

Most of these models use fractional change in tumor size (CTS) at the end of cycle 2 (PTR8) to predict OS.


Our drug is different …
This doesn't apply to our MOA …
There's too much uncertainty

Objective

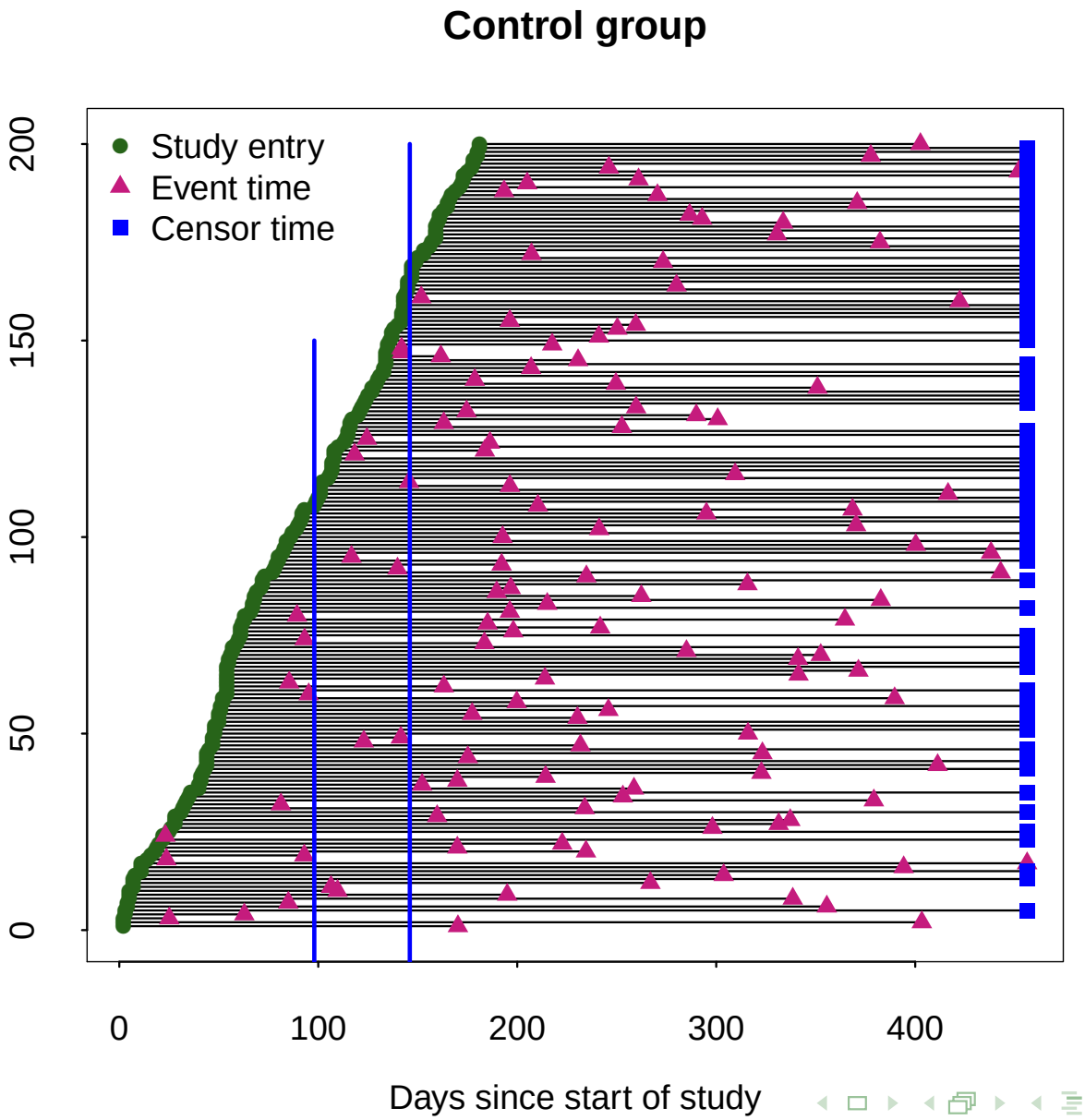
Can we use the accruing information *within a trial* to simultaneously address some of these concerns and provide better predictions?

- Fuller utilization of the trial data - using both the CTS and OS data
- Provide some flexibility in case the assumed model is wrong

Can we use a model-based framework for adaptive Phase 2/3 studies in oncology? [6]

- Can we make decisions about OS at an interim analysis based on CTS or CTS-OS data?

Data available at an interim analysis



A model-based approach

$$f(OS, CTS, covariates \mid \theta, \gamma, \delta) = f(OS \mid CTS, covariates, \theta) \times f(CTS \mid covariates, \gamma) \times f(covariates \mid \delta)$$

- $f(OS \mid CTS, covariates, \theta)$ is a disease-specific, drug-independent model
- $f(CTS \mid covariates, \gamma)$ is a disease- and drug-specific model
- $f(covariates \mid \delta)$ is a study population-specific model

A Bayesian framework using CTS and OS for interim monitoring of a controlled study

$$
\begin{aligned}
f(OS, CTS, covariates \mid \theta, \gamma, \delta) = \; & f(OS \mid CTS, covariates, \theta) \times \\
& f(CTS \mid covariates, \gamma) \times f(covariates \mid \delta) \\
\theta &\sim g_\theta(\theta) \\
\gamma &\sim g_\gamma(\gamma) \\
\delta &\sim g_\delta(\delta)
\end{aligned}
$$

Given the data at the interim analysis, we then

- Sample from the posterior distribution for θ, γ, δ
- For each posterior sample, 'complete' the study by sampling from the posterior predictive distribution for the future data.
- By analyzing each 'completed' study, we obtain the posterior predictive distribution for the OS hazard ratio or log-rank test statistic

How do you 'complete' the study?

For patients who have died before the interim analysis

- Use the observed OS and CTS

For the patients who have enrolled but not died before the IA

- Simuate data from the left-truncated distribution posterior predictive distribution:
  $f(OS_i \mid CTS_i, covariates_i, OS_i^+,$ all other IA data$)$

For patients not yet enrolled before the IA

- Sample from the posterior predictive distribution:
  $f(OS, CTS, covariates \mid$ all IA data$)$

A simulation study in first-line treatment of NSCLC

Conducting a Phase 3 study with:

- 400 patients randomized 1:1
- Recruitment period of 6 months
- Additional follow-up of 9 months

Three interim analyses:

- 8 week TS data for 80 patients ($\sim$ 10 events)
- 8 week TS data for 280 patients ($\sim$ 50 events)
- 8 week TS data for 400 patients ($\sim$ 90 events)

Two simulation settings:

- Base case:
  Median difference in PTR8 of 47% $\rightarrow$ HR of 0.67 $\rightarrow$ 80% power
- Null case:
  No difference between groups in PTR8 or OS $\rightarrow$ HR of 1.0

N = 1000 simulated trials for each setting.
R + OpenBUGS

Simulation model based on Wang et al. [7]

$f(OS \mid CTS, covariates, \theta)$

$$\log(OS_i) = \theta_1 + \theta_2 ECOG_i + \theta_3 TS0_i + \theta_4 PTR8_i + \epsilon_{OS,i}$$
$$\epsilon_{OS,i} \sim N\left(0, \sigma^2_{OS}\right)$$

$f(TS|covariates, \gamma)$

$$TS_{ij} = \left(\gamma_{1,i} e^{-\gamma_{2,i} t_{ij}} + \gamma_{3,i} t_{ij}\right) e^{\epsilon_{TS,ij}}$$
$$\epsilon_{TS,i} \sim N\left(0, \sigma^2_{TS}\right)$$
$$\log\left(\gamma_i\right) \sim N\left(\log(\gamma)\ , \Omega\right)$$

$f(covariates \mid \delta)$

$ECOG \sim \text{Multinomial}(\delta)$

Bayesian estimation model is similar

$f(OS \mid CTS, covariates, \theta)$

$$\log(OS_i) = \theta_1 + \theta_2 ECOG_i + \theta_3 TS0_i + \theta_4 PTR8_i + \epsilon_{OS,i}$$
$$\epsilon_{OS,i} \sim N\left(0, \sigma^2_{OS}\right)$$

$f(CTS|covariates, \gamma)$

$$PTR8_i = \gamma_1 \mathrm{I}[trt_i = CTL] + \gamma_2 \mathrm{I}[trt_i = INV] + \epsilon_{TS,i}$$
$$\epsilon_{TS,i} \sim N\left(0, \sigma^2_{TS}\right)$$

$f(covariates \mid \delta)$

$ECOG \sim \text{Multinomial}(\delta)$

Prior distributions

Priors for θ

Weakly informative prior distributions centered at the estimated values from Wang et al. [7] .

$$\theta \sim MVN\left(\hat{\theta}, k_1\Sigma\right) \text{ with } k_1 > 1$$

$$\log(\sigma^2) \sim N\left(\log(\hat{\sigma}^2), k_2\omega^2\right) \text{ with } k_2 > 1$$

Priors for γ and δ

Non-informative prior distributions

Decision criteria

H_0 : hazard under INV $=$ hazard under CTL
H_A : hazard under INV $\neq$ hazard under CTL

'True' results based on two-sided log-rank test at end of study with $\alpha = 0.05$.

CTS-based decision rules

Predict that the trial will reject H_0 if $|\text{mean difference in PTR8}| > \delta_{CTS}$

Posterior-predictive distribution-based decision rule

Predict that the trial will reject H_0 if
$P(\text{ end-of-study p-value } < 0.05 \mid \text{ IA data}) > \delta_{Bayes}$

Cox model-based decision rules

Predict that the trial will reject H_0 if $|\text{standardized log HR}| > \delta_{HR}$

Performance of selected decision rules: Base case

$$P(\textit{True}+) = P(\text{Predict + at IA} \mid \text{+ at end of study})$$
$$P(\textit{False}+) = P(\text{Predict + at IA} \mid \text{- at end of study})$$

Bayes rule with $\delta_{Bayes} = 0.70$

		End of study difference?	
IA predicted difference?		Yes	No
	Yes	607	85
	No	209	99
	Total	816	184

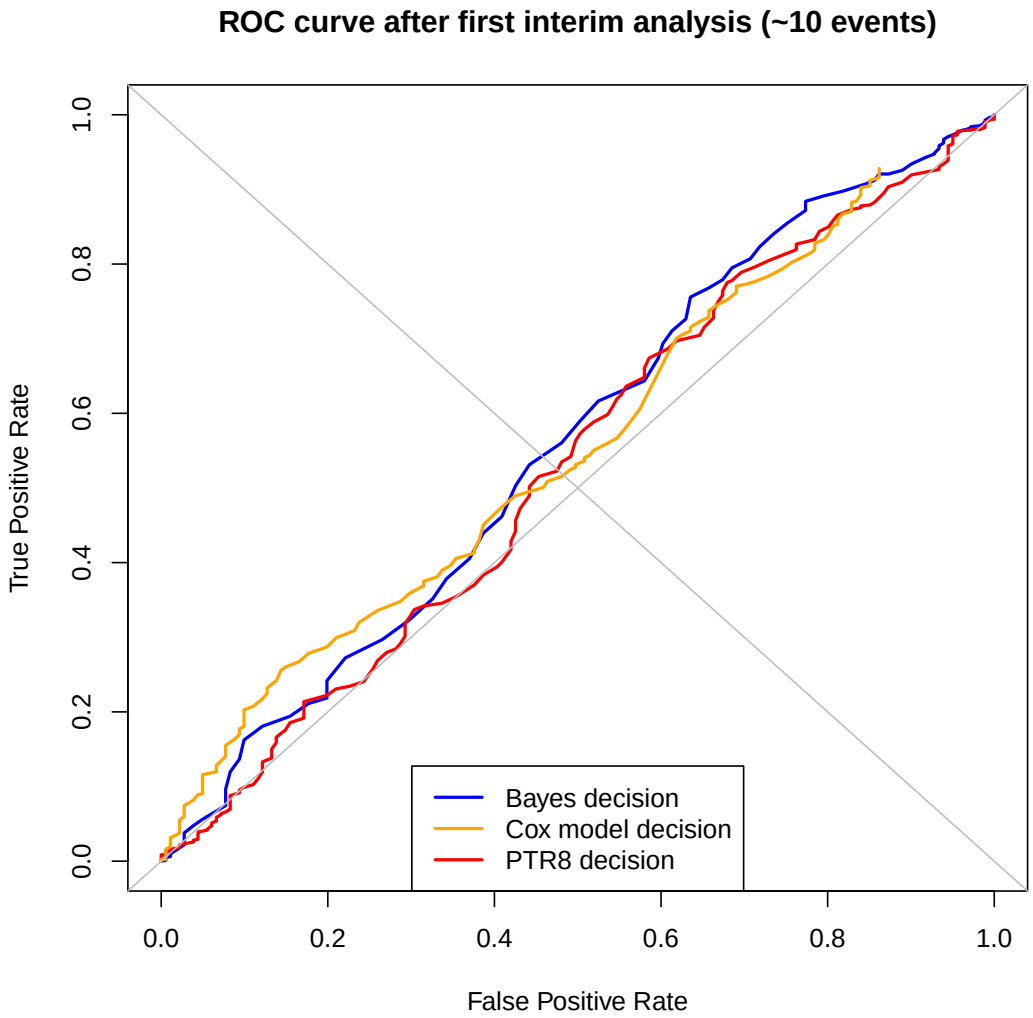
$P(\textit{True}+) = {}^{607}/_{816} = 0.74$
$P(\textit{False}+) = {}^{85}/_{184} = 0.46$

CTS-based rule with $\delta_{CTS} = 0.335$

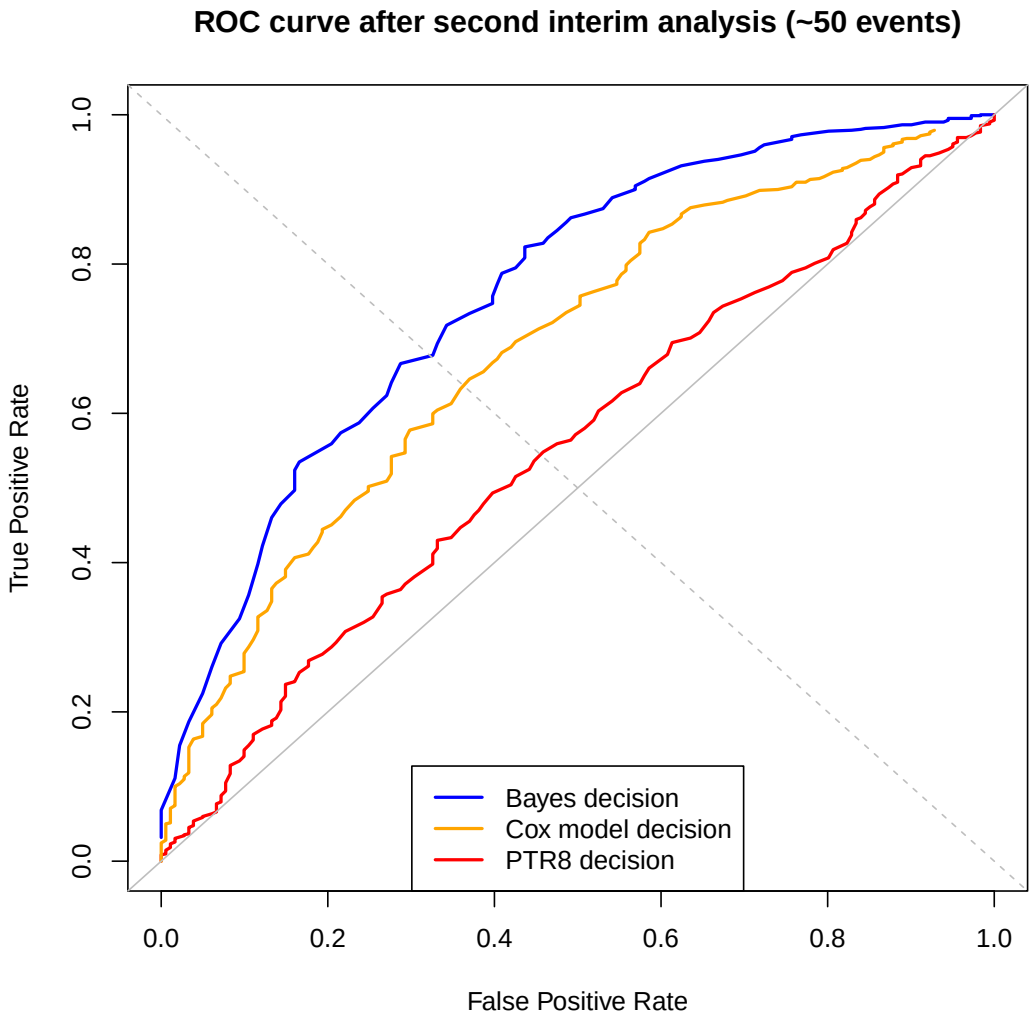
		End of study difference?	
IA predicted difference?		Yes	No
	Yes	613	123
	No	203	61
	Total	816	184

$P(\textit{True}+) = {}^{613}/_{816} = 0.75$
$P(\textit{False}+) = {}^{123}/_{184} = 0.67$

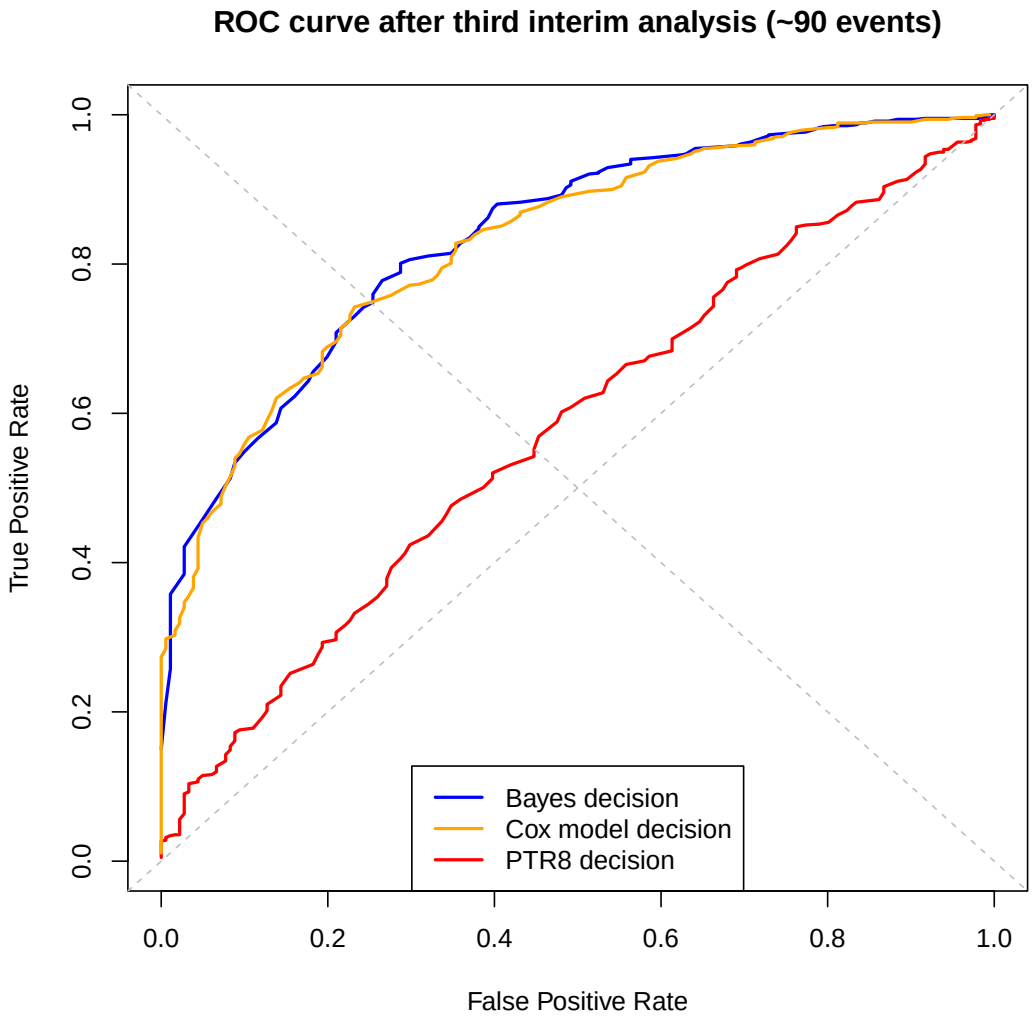
Simulation results: Base case IA1



Simulation results: Base case IA2



Simulation results: Base case IA3



Conclusions

- Under these simulation conditions,
  Bayes approach $>$ Cox model approach $>$ PTR8 approach
  for making decisions within a trial
- Differences in PTR8 does not adequately predict the statistical outcome of a trial for OS
  - Consistent with recent results reported by Claret et al. [4]
- The Bayes approach allows for some model mis-specification and can be made even more robust
- When enough information about survival accrues, decisions based on the log-rank statistic perform just as well as the Bayes approach.
  - After that point, there seems to be little benefit to including CTS to predict OS - the OS data overwhelms the benefit of the prediction

Future work

- Examine operating characteristics when the CTS-OS relationship is different than what is simulated
- Investigate sensitivity to enrollment and event rates
- Investigate second-line and mixed-line studies
- Investigate combinations of early looks at PTR8 and later looks using the Bayesian approach

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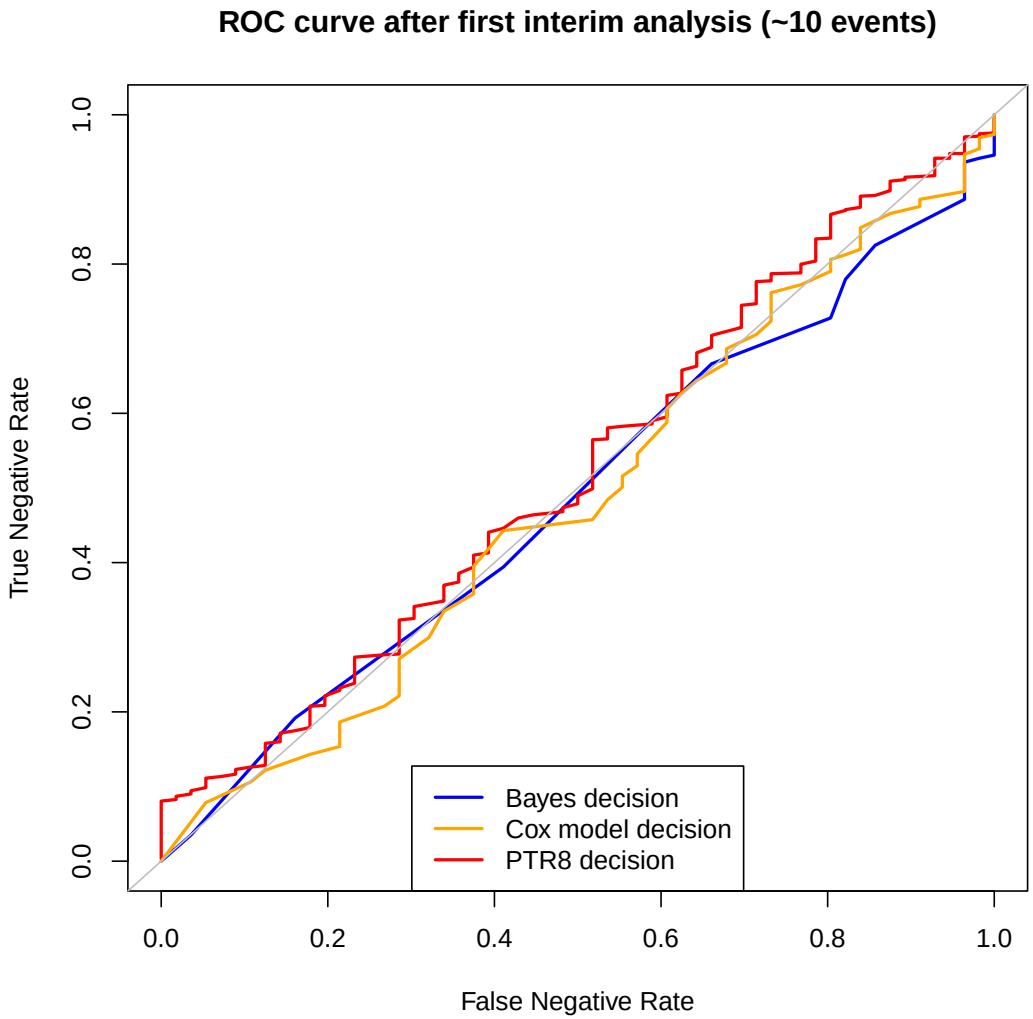
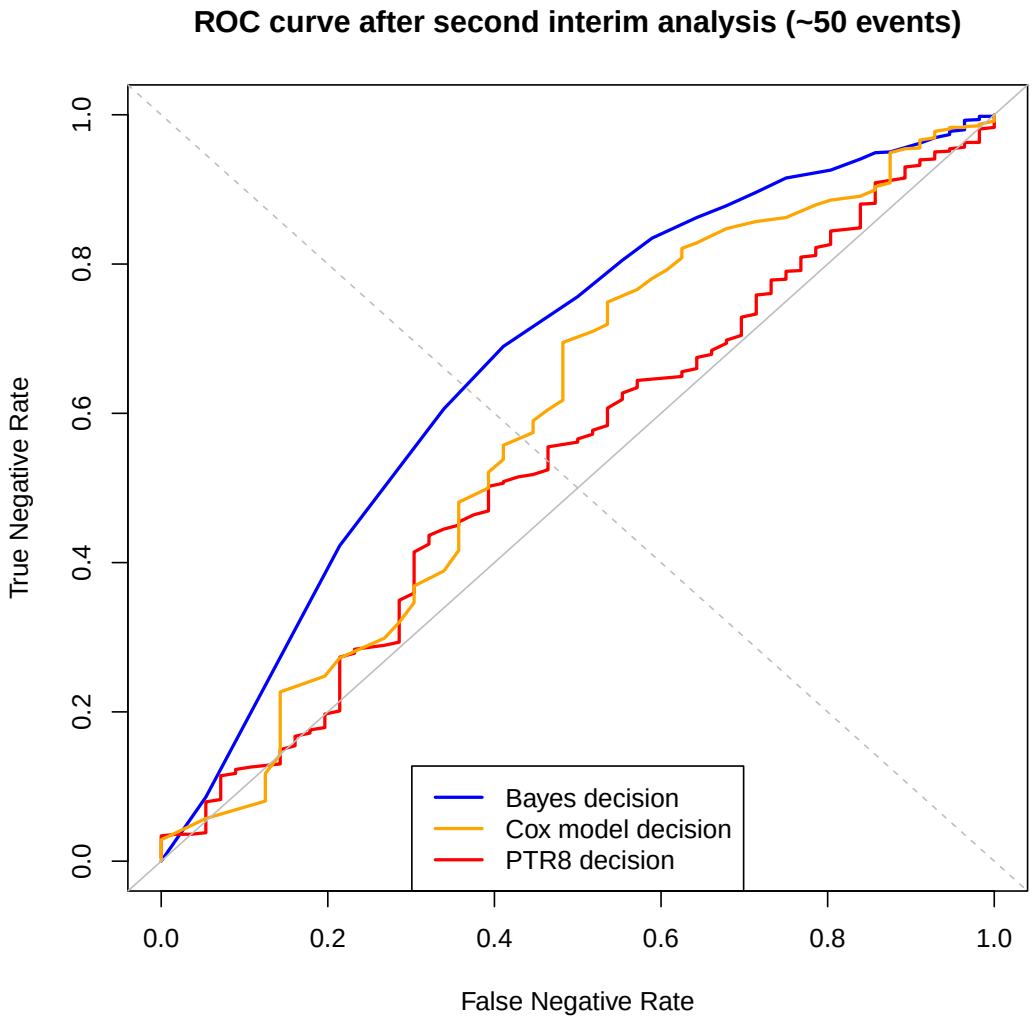
Back-up Slides

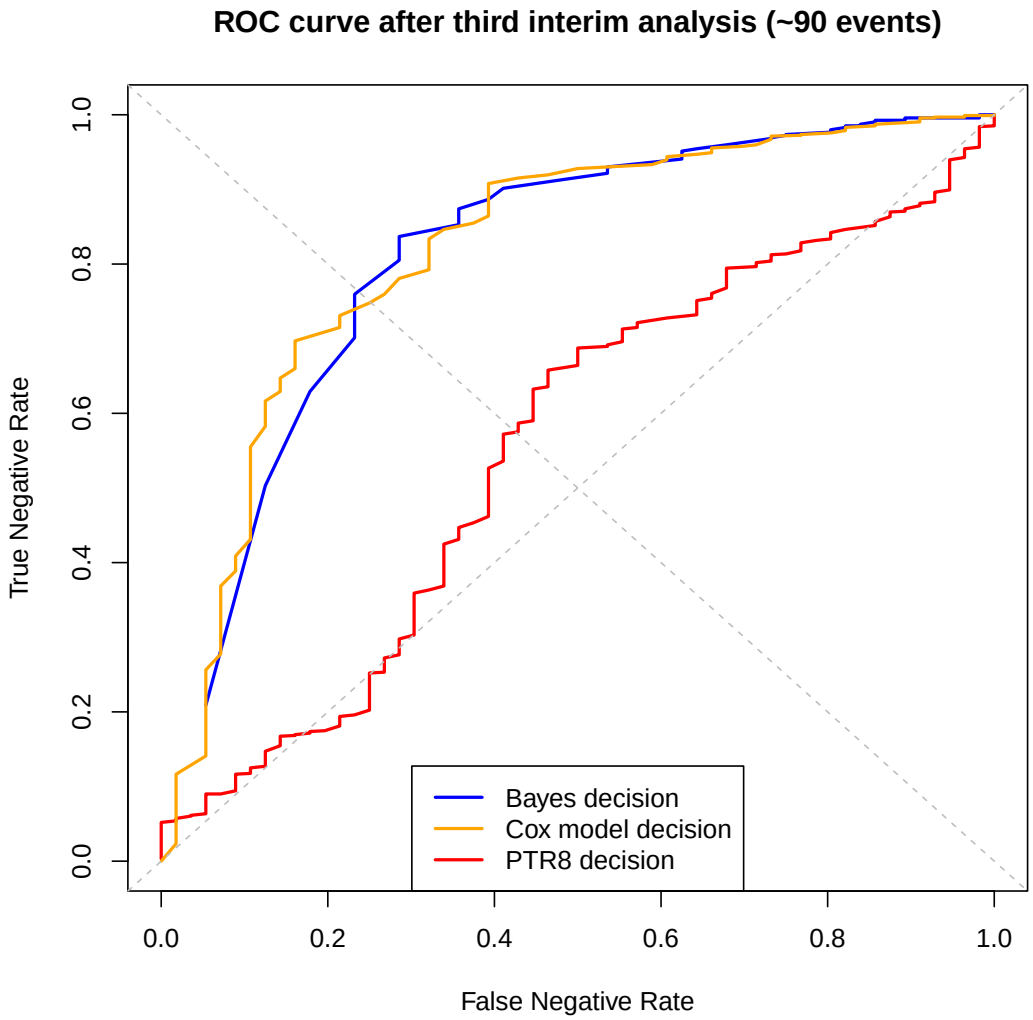
Simulation results: Null case IA1



Simulation results: Null case IA2

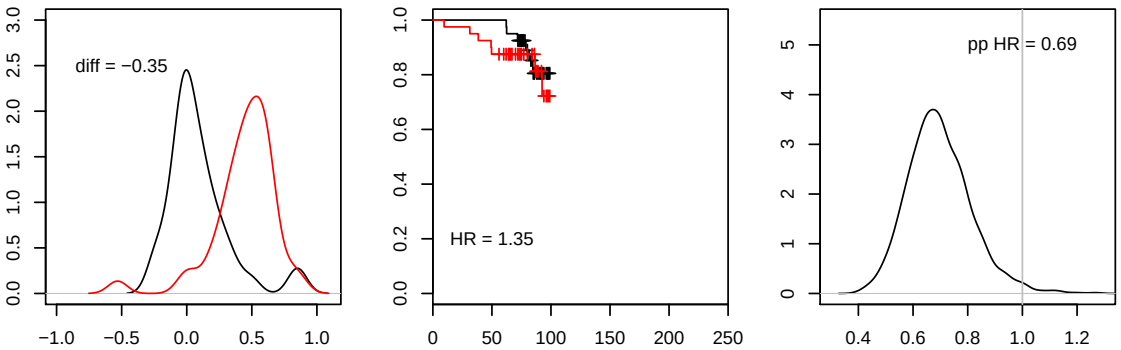


Simulation results: Null case IA3

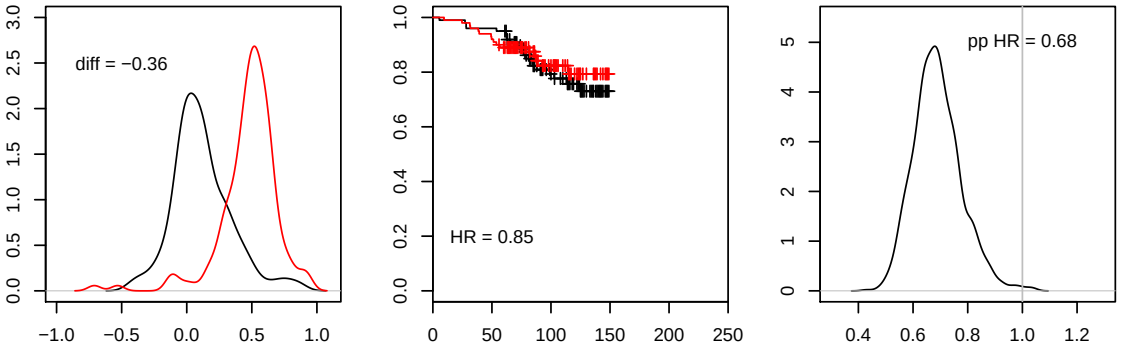


One simulated study: Interim analyses

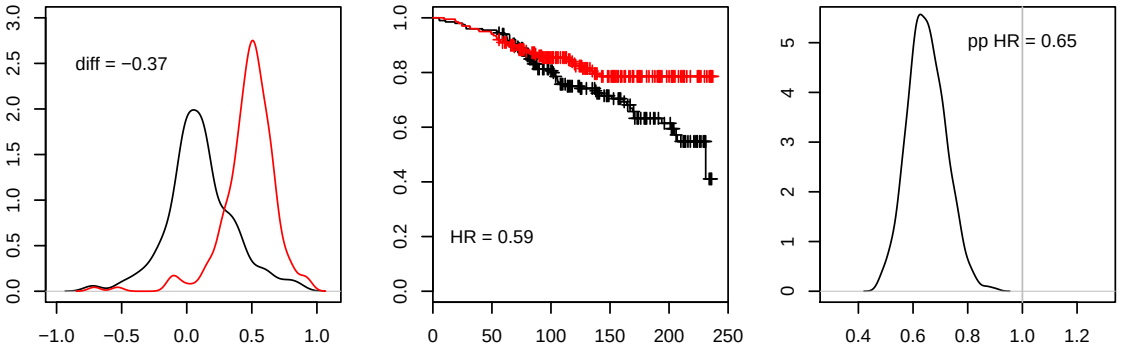
IA1



IA2



IA1



One simulated study: Final analysis