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!


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.
Introduction

There's too much uncertainty.

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?
A Bayesian framework for model-based interim analyses

Data available at an interim analysis

Control group

- Study entry
- Event time
- Censor time

Days since start of study

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A Bayesian framework for model-based interim analyses

A model-based approach

\[ f(OS, CTS, \text{covariates} \mid \theta, \gamma, \delta) = f(OS \mid CTS, \text{covariates}, \theta) \times f(CTS \mid \text{covariates}, \gamma) \times f(\text{covariates} \mid \delta) \]

- \( f(OS \mid CTS, \text{covariates}, \theta) \) is a disease-specific, drug-independent model
- \( f(CTS \mid \text{covariates}, \gamma) \) is a disease- and drug-specific model
- \( f(\text{covariates} \mid \delta) \) is a study population-specific model
A Bayesian framework using CTS and OS for interim monitoring of a controlled study

\[
f(OS, CTS, \text{covariates} \mid \theta, \gamma, \delta) = f(OS \mid CTS, \text{covariates}, \theta) \times f(CTS \mid \text{covariates}, \gamma) \times f(\text{covariates} \mid \delta)
\]

\[
\theta \sim g_\theta (\theta) \\
\gamma \sim g_\gamma (\gamma) \\
\delta \sim g_\delta (\delta)
\]

Given the data at the interim analysis, we then

- Sample from the posterior distribution for \( \theta, \gamma, \delta \)
- 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

- Simulate data from the left-truncated distribution posterior predictive distribution:
  \[ f(\text{OS}_i \mid CTS_i, \text{covariates}_i, OS_i^+, \text{all other IA data}) \]

For patients not yet enrolled before the IA

- Sample from the posterior predictive distribution:
  \[ f(\text{OS}, CTS, \text{covariates} \mid \text{all IA data}) \]
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 \((\sim 10 \text{ events})\)
- 8 week TS data for 280 patients \((\sim 50 \text{ events})\)
- 8 week TS data for 400 patients \((\sim 90 \text{ events})\)

Two simulation settings:
- **Base case:**
  - Median difference in PTR8 of 47% → HR of 0.67
  - → 80% power

- **Null case:**
  - No difference between groups in PTR8 or OS → HR of 1.0

\(N = 1000\) simulated trials for each setting.

R + OpenBUGS
Simulation model based on Wang et al. [7]

\[ f(OS \mid CTS, covariates, \theta) \]

\[ \log(OS_i) = \theta_1 + \theta_2 ECOG_i + \theta_3 TS0_i + \theta_4 PTR8_i + \epsilon_{OS,i} \]

\[ \epsilon_{OS,i} \sim N(0, \sigma^2_{OS}) \]

\[ f(TS \mid covariates, \gamma) \]

\[ TS_{ij} = \left( \gamma_{1,i} e^{-\gamma_{2,i}t_{ij}} + \gamma_{3,i} t_{ij} \right) e^{\epsilon_{TS,i}} \]

\[ \epsilon_{TS,i} \sim N(0, \sigma^2_{TS}) \]

\[ \log(\gamma_i) \sim N(\log(\gamma), \Omega) \]

\[ f(covariates \mid \delta) \]

\[ ECOG \sim \text{Multinomial}(\delta) \]
Simulation Study in NSCLC

Bayesian estimation model is similar

\[ f(OS \mid CTS, \text{covariates}, \theta) \]

\[
\log(OS_i) = \theta_1 + \theta_2 ECOG_i + \theta_3 TS0_i + \theta_4 PTR8_i + \epsilon_{OS,i}
\]

\[
\epsilon_{OS,i} \sim N(0, \sigma^2_{OS})
\]

\[ f(CTS \mid \text{covariates}, \gamma) \]

\[
PTR8_i = \gamma_1 I[trt_i = CTL] + \gamma_2 I[trt_i = INV] + \epsilon_{TS,i}
\]

\[
\epsilon_{TS,i} \sim N(0, \sigma^2_{TS})
\]

\[ f(\text{covariates} \mid \delta) \]

\[ ECOG \sim \text{Multinomial}(\delta) \]
Prior distributions

Priors for $\theta$

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

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

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

Priors for $\gamma$ and $\delta$

Non-informative prior distributions
Decision criteria

\[ H_0 : \text{hazard under INV} = \text{hazard under CTL} \]
\[ H_A : \text{hazard under INV} \neq \text{hazard under CTL} \]

'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
\[ P(\text{end-of-study p-value < 0.05 | IA data}) > \delta_{Bayes} \]

Cox model-based decision rules

Predict that the trial will reject \( H_0 \) if \( |\text{standardized log HR}| > \delta_{HR} \)
Simulation results

Performance of selected decision rules: Base case

\[
P(\text{True }+) = P(\text{Predict }+ \text{ at IA } | \text{ + at end of study })
\]

\[
P(\text{False }+) = P(\text{Predict }+ \text{ at IA } | \text{ - at end of study })
\]

Bayes rule with \( \delta_{\text{Bayes}} = 0.70 \)

<table>
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<th>End of study difference?</th>
<th>( N )</th>
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<tr>
<td>Yes</td>
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<td>607</td>
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<td></td>
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<td>85</td>
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<tr>
<td>No</td>
<td>Yes</td>
<td>209</td>
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<tr>
<td></td>
<td>No</td>
<td>99</td>
</tr>
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<td>Total</td>
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<td>816</td>
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</table>

\[
P(\text{True }+) = \frac{607}{816} = 0.74
\]

\[
P(\text{False }+) = \frac{85}{184} = 0.46
\]

CTS-based rule with \( \delta_{\text{CTS}} = 0.335 \)

<table>
<thead>
<tr>
<th>IA predicted difference?</th>
<th>End of study difference?</th>
<th>( N )</th>
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</thead>
<tbody>
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<td>123</td>
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<td>Yes</td>
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<tr>
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<td>816</td>
</tr>
<tr>
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<td>184</td>
</tr>
</tbody>
</table>

\[
P(\text{True }+) = \frac{613}{816} = 0.75
\]

\[
P(\text{False }+) = \frac{123}{184} = 0.67
\]
Simulation results: Base case IA1

ROC curve after first interim analysis (~10 events)
Simulation results: Base case IA2

ROC curve after second interim analysis (~50 events)

False Positive Rate
True Positive Rate

Bayes decision
Cox model decision
PTR8 decision
Simulation results: Base case IA3

ROC curve after third interim analysis (~90 events)

False Positive Rate

Cox model decision

Bayes decision

PTR8 decision

True Positive Rate

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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
L Claret, P Girard, and PM Hoff et al.  
Model-based prediction of phase iii overall survival in colorectal cancer based on phase ii tumor dynamics.  

L Claret, M Gupta, K Han, A Joshi, N Sarapa, J He, B Powell, and R Bruno.  
Evaluation of tumor-size response metrics to predict overall survival in western and chinese patients with first-line metastatic colorectal cancer.  

L Claret, F Jonsson, R Knight, and et al.  
A drug independent tumor burden reduction-survival model in patients with multiple myeloma to support early clinical development decisions.  

L Claret, J-F Lu, R Bruno, C-P Hsu, Y-J Hei, and Y-N Sun.  
Simulations using a drug-disease modeling framework and phase ii data predict phase iii survival outcome in first-line non-small-cell lung cancer.  


Simulation results: Null case IA1

ROC curve after first interim analysis (~10 events)

False Negative Rate
True Negative Rate
Bayes decision
Cox model decision
PTR8 decision
Simulation results: Null case IA2

ROC curve after second interim analysis (~50 events)

- False Negative Rate
- True Negative Rate

Bayes decision
Cox model decision
PTR8 decision

0.0 0.2 0.4 0.6 0.8 1.0
0.0 0.2 0.4 0.6 0.8 1.0
Simulation results: Null case IA3

ROC curve after third interim analysis (~90 events)

- Bayes decision
- Cox model decision
- PTR8 decision
One simulated study: Interim analyses

IA1

IA2

IA1

Fractional reduction in TS

Time (days)

Posterior predictive hazard ratio

Survival probability

HR = 1.35

HR = 0.85

HR = 0.59

PP HR = 0.69

PP HR = 0.68

PP HR = 0.65

diff = −0.35

diff = −0.36

diff = −0.37
One simulated study: Final analysis

![Survival probability graph](image)

- **HR = 0.65**
- Red line represents Investigational group.
- Black line represents Control group.

Time (days)

Survival probability