

# Predicting outcome of the comparison of time to death in an oncology clinical trial, using PFS and time to death data.

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# Introduction

Metastatic cancer clinical trials compare treatments through:

- Time to Death ( $D$ )
  - Progression Free Survival ( $P$ )  
defined as the time to first progression or death
  - Tumor response (response rate, duration of response, ...).
- 
- Mature  $P$  data are obtained before mature  $D$  data.

Question:

Can we use  $P$  to predict the difference in  $D$  between treatments ?

# Introduction

In the course of the trial:

- $P$  data can be analyzed earlier than  $D$ 
  - An interim analysis is conducted on  $P$  and  $D$  or
  - $P$  is analyzed as the primary endpoint and  $D$  is updated later
- Information on efficacy of treatment on  $D$  is available when  $P$  is analyzed.

Early information on the comparison of  $D$  would be useful

- For Data Monitoring Committee
- For assessment of risk / benefit to avoid exposition to a potentially ineffective treatment
- For assessment of risk of an early filing based on  $P$  to Health Authorities

Current practice:

- Predictive power and conditional power
- Available data analysis (based on early events)
- Medical experience to link all endpoints together to assess the effect of treatment

Methods do not combine statistically the knowledge on  $P$  with  $D$  data.

## Example: NSCL cancer trials

2 trials of first line therapies in advanced NCSL cancer (stage III, IV)

Treatments	Arm Size	Progression Median (mths)	Time to Death Median (mths)
<b>CA139165 - Primary endpoint: Time to Death</b>			
TAXOL + CISPLAPTIN vs ETOPOSIDE + CISPLAPTIN vs	198	4.3	9.3
TAXOL + CISPLAPTIN + G-CSF	200	2.7	7.4
	201	4.9	10.0
<b>CA139271- Primary endpoint: NI in Response Rate</b>			
TAXOL + CISPLAPTIN vs	309	4.2	9.8
TAXOL + CARBOPLATIN	309	3.0	8.5

# Outline of the Method

Method based on:

- 1 association between the endpoints
- 2 model for joint distribution between  $P$  and  $D$

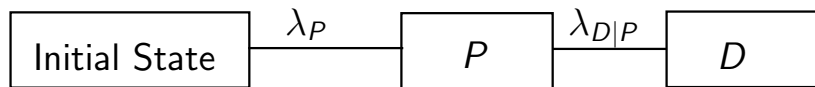
When  $P$  data are mature, we update prior distribution of the hazard ratio ( $\theta$ ) for  $D$  based on:

- 1 mature  $P$  data
- 2 early  $D$  data in both treatment arms

using Bayesian MCMC simulations.

## Joint Model of $P$ and $D$

The joint distribution between  $P$  and  $D$  is based on a progressive multi-state model.



- Association modelled through a subject-specific frailty term in transition hazards.
- $Z \sim$  Gamma with mean 1 and variance  $\delta$ .
- Transition hazards are proportional

$$\lambda_P(p) = Z\lambda_0(p) \quad \text{and} \quad \lambda_{D|P}(d|p) = ZI(p \leq d)e^\beta \lambda_0(d)$$

- $\lambda_0(t)$  is the baseline hazard e.g. a Weibull hazard:  $\nu\eta e^{\eta-1}$

## Joint Model of $P$ and $D$ (cont'd)

Measure of association : Kendall's  $\tau$ .

- No explicit formulation.
- Depends only on  $\beta$  and  $\delta$  (variance of the frailty term).

Further:

- This model takes into account ordering of  $P$  and  $D$
- We use interval censoring for  $P$ :
  - $P$  is assessed at fixed visits
  - take into account cases where  $P = D$

# Method: details

Step 1: Based on past trials in same setting, compute:

- $\beta$  : proportionality parameter
- $\delta$  : frailty variance

Parameters estimates and variance  $\Rightarrow$  association between  $P$  and  $D$  and its distribution

## Method (cont'd)

- Step 2:
- At the time with have mature  $P$  data
  - model the joint distribution in experimental arm using MCMC simulations
  - using mature  $P$  data and incomplete  $D$  data from experimental arm
  - use posterior of  $\beta$  and  $\delta$  from step 1 as prior
  - use an NI prior for  $\nu$  and  $\eta$  ( $\lambda_0$ )
  - obtain posterior distribution of the parameters  $\beta, \delta, \nu, \eta$

Parameters provide joint distribution in experimental arm  
 joint distribution  $\Rightarrow$  “extended” marginal distribution for  $D$

## Method (cont'd)

- Step 3:
- Assume proportionality ( $\theta$ ) between the hazards of  $D$  in both treatment arms
  - Assume NI prior for  $\theta$
  - $\beta$   $\delta$   $\nu$   $\eta$  not updated at this stage
  - fit, with MCMC, proportional distribution of the control, with  $\theta$  as parameter
- Posterior distribution of  $\theta$  (and estimates)

# Study 165

Aim: to predict comparisons in study -165, using study -271 as “historical” data:

$$① \theta_1 = \frac{\text{Hazard TAXCISP}}{\text{Hazard ETO} + \text{CISP}}$$

$$② \theta_2 = \frac{\text{Hazard TAXCISP}}{\text{Hazard TAXCISP} + \text{GCSF}}$$

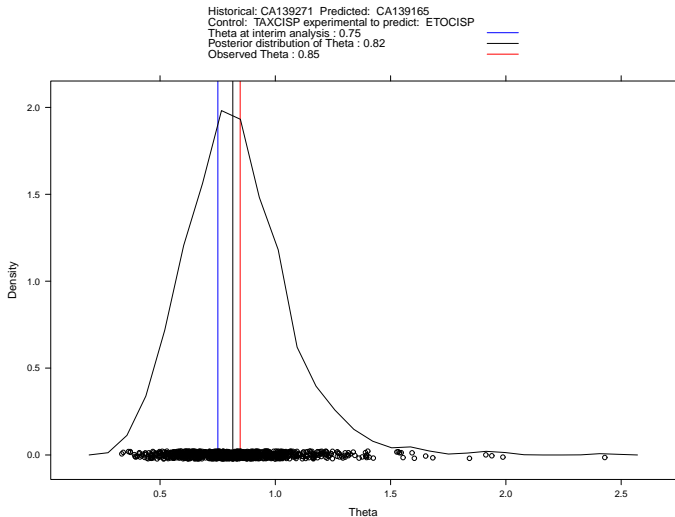
- Choose to predict based on data at 14 mths after first randomization (i.e. 2 months prior to last randomization)

We start with deriving the association for each study:

arms	Pooled (std)	Kendall's $\tau$	
		in TAXCISP	in comparator
<b>STUDY 165</b>			
TAXCISP vs ETOCISP	0.47 (0.020)	0.48	0.44
TAXCISP vs TAXCISP+G			0.48
<b>STUDY 271</b>			
TAXCISP vs TAXCARB	0.43 (0.020)	0.45	0.43

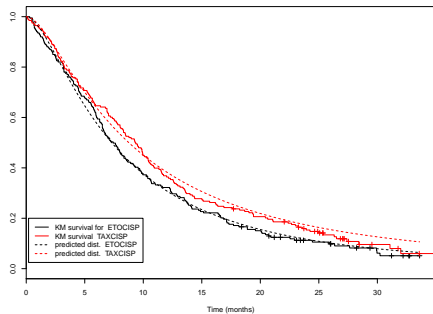
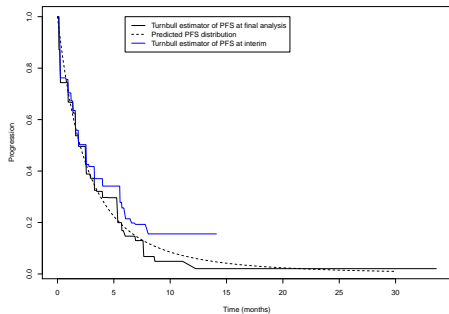
- association is similar across studies
- association is similar across treatment arms

# Prediction of $\theta_1$

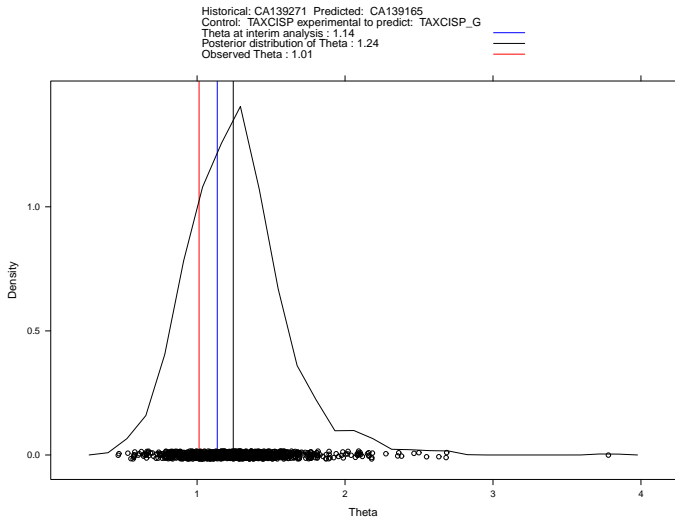


Events in ETOCISP	Interim (14 mths)	Final
$P$	113	194
$D$	68	183

Progression in ETOCISP

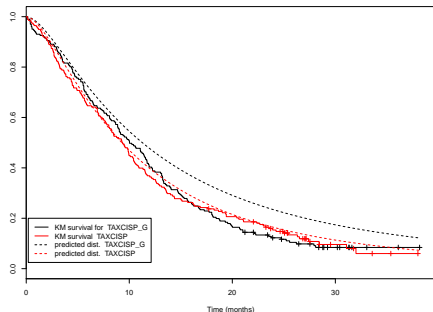
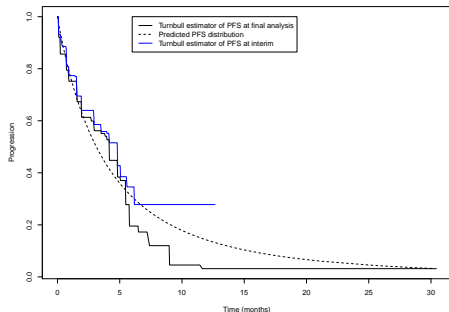


# Prediction of $\theta_2$



Events in TAXCISP +GCSF	Interim (14 mths)	Final
$P$	97	191
$D$	46	182

Progression in TAXCISP\_G



## Discussion

Method allows to “extend”  $D$  distribution based on mature  $P$  data and derive treatment difference.

- In current analysis and analyses not shown: improves on the estimates at interim
- Could be part of a package of techniques for early assessment of treatment effect on  $D$
  
- By incorporating all sources of variations: wide HPD interval
- Relies on proportional hazards for  $D$  between the treatment arms
- Parametric assumptions:
  - Baseline hazard, could be relaxed using piecewise constant hazard
  - Frailty distribution
  - Proportionality of transition hazards: important assumption to generalize the association

Our example:

- Association between  $P$  and  $D$  is not large

Thank you for your attention

Acknowledgment:

We thank Bristol-Myers Squibb Company for providing the NSCL Cancer Datasets