Interim Decisions in Adaptive Clinical Trials with Time-to-event Surrogate and Primary Endpoints

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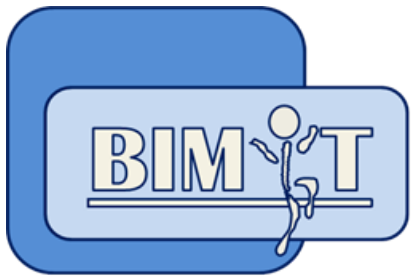

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Introduction

- Overall survival (OS) is often used as primary endpoint in phase 3 oncology trials
- Progression-free survival (PFS) is used
  - surrogate for OS
  - in phase 2 trials to inform the phase 3 go/no-go decision
  - make decisions in interim analyses in adaptive trials
- Surrogacy of PFS for OS usually not established
- Risk of false positives (effect in PFS, but no effect in OS)
- Evaluation of decision rules: Model of PFS and OS required

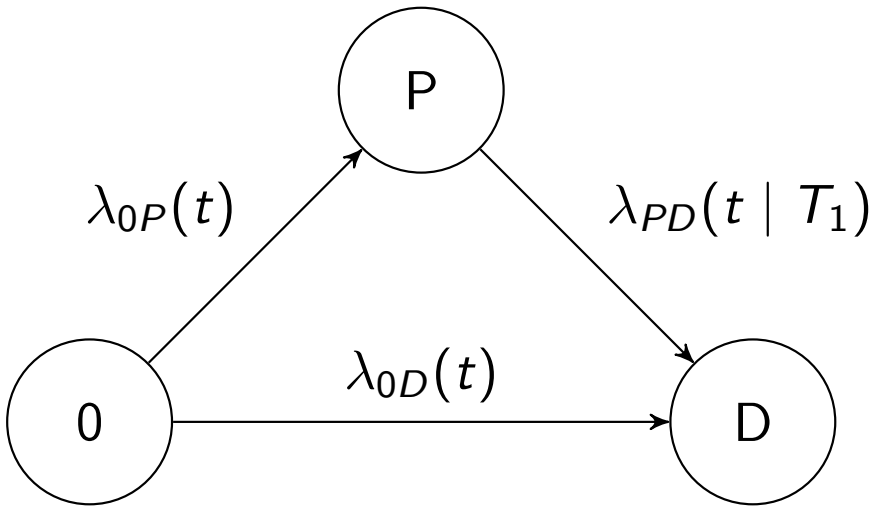
Modelling PFS and OS

Several approaches:

1. Model for treatment effects only: Bivariate normal distribution for log-HRs of PFS and OS
2. Bivariate survival distributions (e.g. copula approach)
3. Multi-state models

Multi-state model

Illness-death model without recovery:



P = Progression, D = Death

General illness-death models

- Assume independent and non-informative censoring
- Likelihood for transition $0 \to I$ ($I = P, D$):

$$L_{0I} \propto \prod_{i=1}^{n} f_{0I}(T_{1i})^{D_{0Ii}} S_{0I}(T_{1i})^{1-D_{0Ii}}$$
$$= \prod_{i=1}^{n} \lambda_{0I}(T_{1i})^{D_{0Ii}} \exp\left(-\int_0^{T_{1i}} \lambda_{0I}(t)dt\right)$$

- Likelihood for transition $P \to D$:

$$L_{PD} \propto \prod_{i=1}^{n} \lambda_{PD}(T_{2i} \mid T_{1i})^{D_{PDi}} \exp\left(-1\{s_{1i} = 1\} \int_{T_{1i}}^{T_{2i}} \lambda_{PD}(t \mid T_{1i})dt\right)$$

- Complete Likelihood (e.g. Hougaard (2012))

$$L \propto L_{0P} L_{0D} L_{PD}$$

Joint survival function of PFS and OS

Marginal survival function of PFS:

$$P_{00}(t) = P(PFS > t) = \exp\left(-\int_0^t \{\lambda_{0P}(s) + \lambda_{0D}(s)\}\, ds\right)$$

Theorem

$$\begin{aligned} S(t_1, t_2) &= P(PFS > t_1, OS > t_2) \\ &= \begin{cases} P_{00}(t_2) + \int_{t_1}^{t_2} \exp\left\{-\int_0^s \lambda_{0D}(u)du\right\} \int_{t_2-s}^{\infty} f(s,u)duds & t_1 < t_2 \\ P_{00}(t_1) & t_1 \geq t_2 \end{cases} \end{aligned}$$

where $f(s,u)$ is the joint density of TTP and PPS

Cox illness-death model

We assume a Cox proportional hazards models for each transition:

$$\lambda_{ml}(t \mid Z_i) = \lambda_{0;ml}(t \mid T_{mi}) \exp(\beta_{ml} Z_i)$$

Each factor of the likelihood can be written as a partial likelihood

$$L_{ml}(\beta_{ml}) = \prod_{i=1}^{n} \left\{ \frac{\exp(\beta_{ml} Z_i)}{\sum_{j \in R_{ml}(T_{m+1;i})} \exp(\beta_{ml} Z_j)} \right\}^{D_{mli}}$$

where $R_{ml}(t) = \{i : T_{mi} \leq t \leq T_{m+1,i}\}$ is the risk set at time t ($T_{0i} = 0$).

Combination of PFS and OS information

- Standardize log-rank (score) test statistics Z_{0P}, Z_{0D} and Z_{PD}
- Likelihood factorization $\Rightarrow$ Z_{0P}, Z_{0D} and Z_{PD} asymptotically independent
- Weights: $w_{0P}^2 + w_{0D}^2 + w_{PD}^2 = 1$
- $Z_w = w_{0P} Z_{0P} + w_{0D} Z_{0D} + w_{PD} Z_{PD}$
- Asymptotically standard normal if $H_0 : \beta_{ml} = 0 \quad \forall m, l$
- In the absence of prior knowledge about the treatment effects, we set all three weights to $1/\sqrt{3}$

Adaptive enrichment design with subgroup selection

- Subgroup S, complementary subgroup S^c
- We expect $HR_S < HR_{S^c}$
- Standardized effects Z_S and Z_{S^c}
- At interim analysis: Decision thresholds c_1 and c_2:

	$Z_{S^c} < c_2$	$Z_{S^c} \geq c_2$
$Z_S < c_1$	co-primary	subgroup S only
$Z_S \geq c_1$	full only	stop for futility

Adaptive enrichment design with subgroup selection

Z_S and Z_{S^c} are either

1. the standardized score from a Cox model for PFS or
2. the standardized score from a Cox model for OS or
3. the multi-state based score Z_w with all weights equal to $1/\sqrt{3}$

We will also consider Decision rule 1 from Jenkins et al. (2011):

	$HR_F < 0.9$	$HR_F \geq 0.9$
$HR_S < 0.7$	co-primary	subgroup S only
$HR_S \geq 0.7$	full only	stop for futility

Adaptive enrichment design with subgroup selection

- S only: Reject H_S if $C(pS_1, pS_2) < c_\alpha$ and $C(pSF_1, pS_2) < c_\alpha$
- F only: Reject H_F if $C(pF_1, pF_2) < c_\alpha$ and $C(pSF_1, pF_2) < c_\alpha$
- Co-primary:
  - Reject H_S if $C(pS_1, pS_2) < c_\alpha$ and $C(pSF_1, pSF_2) < c_\alpha$
  - Reject H_F if $C(pF_1, pF_2) < c_\alpha$ and $C(pSF_1, pSF_2) < c_\alpha$

Simulations

Setup similar to Jenkins et al. (2011):

- Exponential survival times ($Cor(PFS, OS) = 0.7$)
- Subgroup incidence 40%
- Interim analysis after 200 PFS events
- Patient-wise splitting
- Final analysis after 250 OS events in Stage 1 and
  - 200 OS events in stage 2 in case of S only decision
  - 500 OS events in case of full and co-primary decision
- Inverse-normal combination test + log-rank test of OS at final analysis ($\alpha = 0.025$)

Scenario 1

PFS: $HR_S = 1$, $HR_{S^c} = 1$, $HR_F = 1$

OS: $HR_S = 1$, $HR_{S^c} = 1$, $HR_F = 1$

	Selection Probability				Power		
Rule	stop	S only	F only	co-primary	H_S	H_F	Any
Jenkins	0.76	0.01	0.19	0.04	0.005	0.014	0.017
MS	0.79	0.10	0.10	0.01	0.009	0.007	0.016
PFS	0.81	0.09	0.09	0.01	0.007	0.008	0.014
OS	0.81	0.09	0.09	0.01	0.007	0.007	0.013

10000 simulations, thresholds $c_1 = c_2 = \Phi^{-1}(0.1)$

Scenario 2

PFS: $HR_S = 0.6$, $HR_{S^c} = 1$, $HR_F = 0.8$

OS: $HR_S = 0.6$, $HR_{S^c} = 1$, $HR_F = 0.8$

	Selection Probability				Power		
Rule	stop	S only	F only	co-primary	H_S	H_F	Any
Jenkins	0.17	0.10	0.13	0.59	0.69	0.61	0.80
MS	0.22	0.68	0.03	0.08	0.75	0.09	0.77
PFS	0.20	0.70	0.02	0.07	0.78	0.09	0.80
OS	0.37	0.53	0.04	0.06	0.59	0.09	0.62

10000 simulations, thresholds $c_1 = c_2 = \Phi^{-1}(0.1)$

Scenario 3

PFS: $HR_S = 0.7$, $HR_{S^c} = 0.7$, $HR_F = 0.7$

OS: $HR_S = 0.7$, $HR_{S^c} = 0.7$, $HR_F = 0.7$

	Selection Probability				Power		
Rule	stop	S only	F only	co-primary	H_S	H_F	Any
Jenkins	0.05	0.00	0.48	0.46	0.43	0.94	0.95
MS	0.14	0.17	0.30	0.40	0.53	0.70	0.86
PFS	0.12	0.18	0.29	0.41	0.54	0.70	0.87
OS	0.26	0.20	0.31	0.24	0.41	0.55	0.74

10000 simulations, thresholds $c_1 = c_2 = \Phi^{-1}(0.1)$

Scenario 4

PFS: $HR_S = 0.7$, $HR_{S^c} = 0.7$, $HR_F = 0.7$

OS: $HR_S = 1$, $HR_{S^c} = 1$, $HR_F = 1$

	Selection Probability				Power		
Rule	stop	S only	F only	co-primary	H_S	H_F	Any
Jenkins	0.14	0.01	0.54	0.32	0.008	0.018	0.023
MS	0.56	0.17	0.21	0.06	0.012	0.012	0.023
PFS	0.25	0.20	0.30	0.24	0.016	0.015	0.025
OS	0.81	0.09	0.09	0.01	0.008	0.006	0.014

10000 simulations, thresholds $c_1 = c_2 = \Phi^{-1}(0.1)$

Discussion

- Our method is more robust than relying on either PFS or OS only
- Choice of thresholds and weights could be improved using prior information about the treatment effects
- Proportional hazards assumption is not essential
- Dependent censoring of OS is no problem, when censoring is independent of OS conditional on TTP

References

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