Evaluation of treatment effect with paired failure times in a single arm phase 2 oncology trial

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Inserm

Phase 2 Trials endpoint

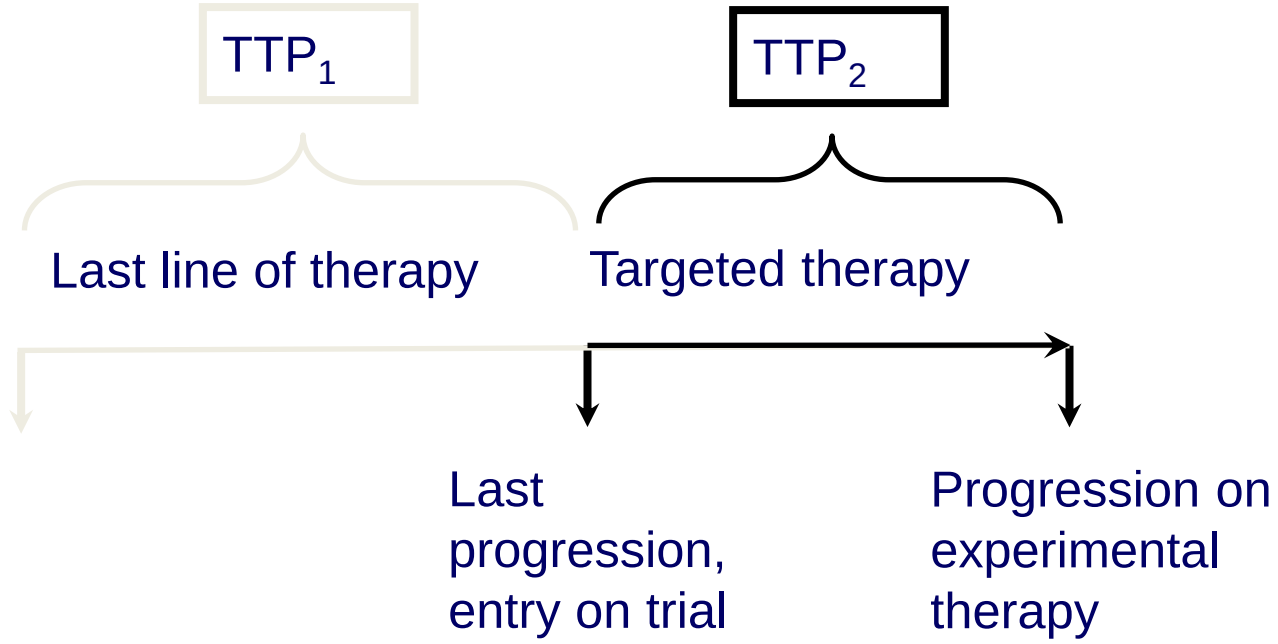
- Goal of phase 2 clinical trials:
  to estimate activity and toxicity of new anticancer agents

- For cytotoxic agents,
  most used endpoints are related to the tumor shrinkage

- The problematic is different with a cytostatic agents.
  Need for an endpoint which takes account of that change

Example of design in a multiple progression framework

- Reference *Von Hoff et al. (2010)*
- Purpose: To compare the time to progression (TTP) using the experimental treatment to the TTP with the most recent regimen on which the patient had experimented progression



Growth Modulation index

- The growth modulation index is defined as the ratio between the time to progression of 2 successive lines of treatment:
  GMI = TTP2 / TTP1

- The natural history of most advanced tumors suggests that GMI < 1 (patients tend to progress increasingly faster on successive lines of treatment)

- In Von Hoff's article, the trial designed to test the hypothesis that at least 15% of the patients have GMI > 1.3

- Need for correct estimate of the proportion of patients having a GMI superior to a given threshold

Aim of our work

- To propose statistical methods to estimate the proportion of patients having their GMI superior to a given threshold by handling censored observations

- To investigate design parameters which could influence the performance of these estimators

Methods

- We consider a study in which patients enter after having a first progression. Consequently, the time to progression at previous therapy (TTP_1) is always observed by design

- Statistic of interest:

$$S_{GMI}(\delta) = P\left[\frac{TTP_2}{TTP_1} > \delta\right], \qquad \delta \geq 0,$$

- δ is an arbitrary threshold which represents the sign of activity considered clinically relevant

Non-parametric approach

- The non-parametric approach, described in Kovalchik et al (2011), consists in using the ranks of each pair (TTP_1, TTP_2) to estimate $S_{GMI}(1)$.
  To handle censoring, we used midranks:

- $TTP_{1i}: [L_{1i};\ R_{1i}]$ and $TTP_{2i}: [L_{2i};\ R_{2i}]$

- $min_{ji}: R_{j(1)} \leq R_{j(2)} \leq \cdots \leq R_{j(min_i-1)} \leq L_{ji} \leq R_{j(min_i)} \leq \cdots \leq R_{j(2n)}$
- $max_{ji}: L_{j(1)} \leq L_{j(2)} \leq \cdots \leq L_{j(max_i)} \leq R_{ji} \leq L_{j(max_i+1)} \leq \cdots \leq L_{j(2n)}$

- Imputation of the midrank: $M_{ji} = \frac{min_{ji}+max_{ji}}{2}$

- $\hat{S}_{GMI}(1) = \frac{1}{n}\sum_{i=1}^{n} I(M_{2i} \geq M_{1i})$

Parametric approach

- By assuming a parametric distribution for the GMI, the probability of interest can be derived as a function of the estimated distribution parameters
- E.g., with Weibull distributed TTPs

$$f_j(x; a, b_j|u_i) = a(u_i b_j)^{-a} x^{a-1} \exp\{-[x/(u_i b_j)]^a\}$$

the GMI has a log-logistic distribution:

$$f(\delta; a, \kappa) = a\kappa^a \delta^{a-1}(1 + (\delta\kappa)^a)^{-2}, \delta \geq 0$$

- Maximum likelihood estimates of the parameters can be obtained and used to derive the estimated probability of interest

$$S_{GMI}(\delta;\ \hat{\alpha}, \hat{\kappa}) = (1 + (\delta^{\hat{\kappa}})^{\hat{a}})^{-1}$$

Simulation study

- Objectives: to evaluate the influence of the design parameters on the two estimators

- We varied:
  - The dependence between TTP_1 and TTP_2 (Kendall's τ)
  - The shape of the distribution of TTP
  - The relative effect of second line treatment compared to the first
  - The censoring rate

- The statistical properties were evaluated in terms of mean bias, average standard error and empirical standard error

Data generation

- Generation of a frailty term: $u_i \sim Gamma$

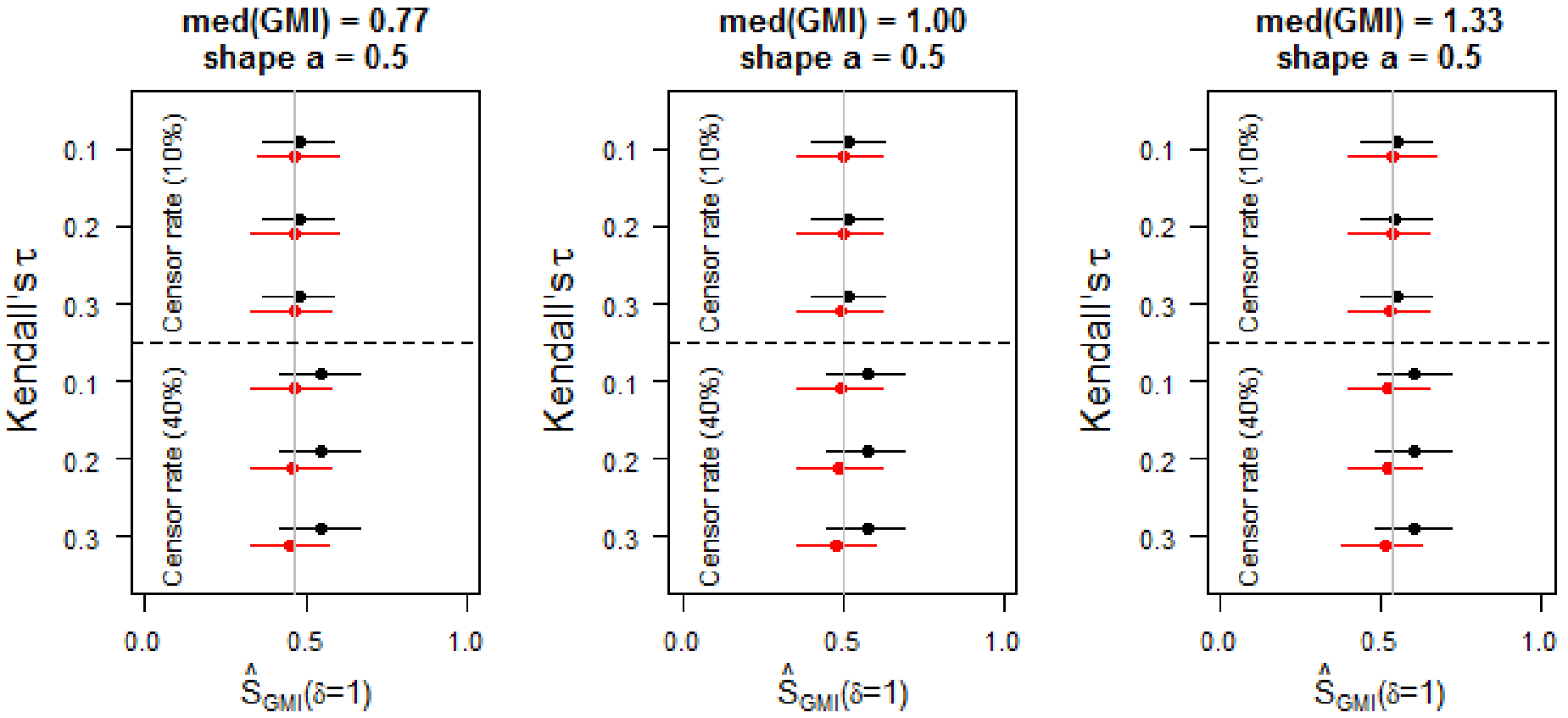
- Generation of TTP from Weibull distribution

$$f_j(x; a, b_j|u_i) = a(u_i b_j)^{-a} x^{a-1} \exp\{-[x/(u_i b_j)]^a\},\ j = 1, 2$$

with $b_1 = e * b_2$

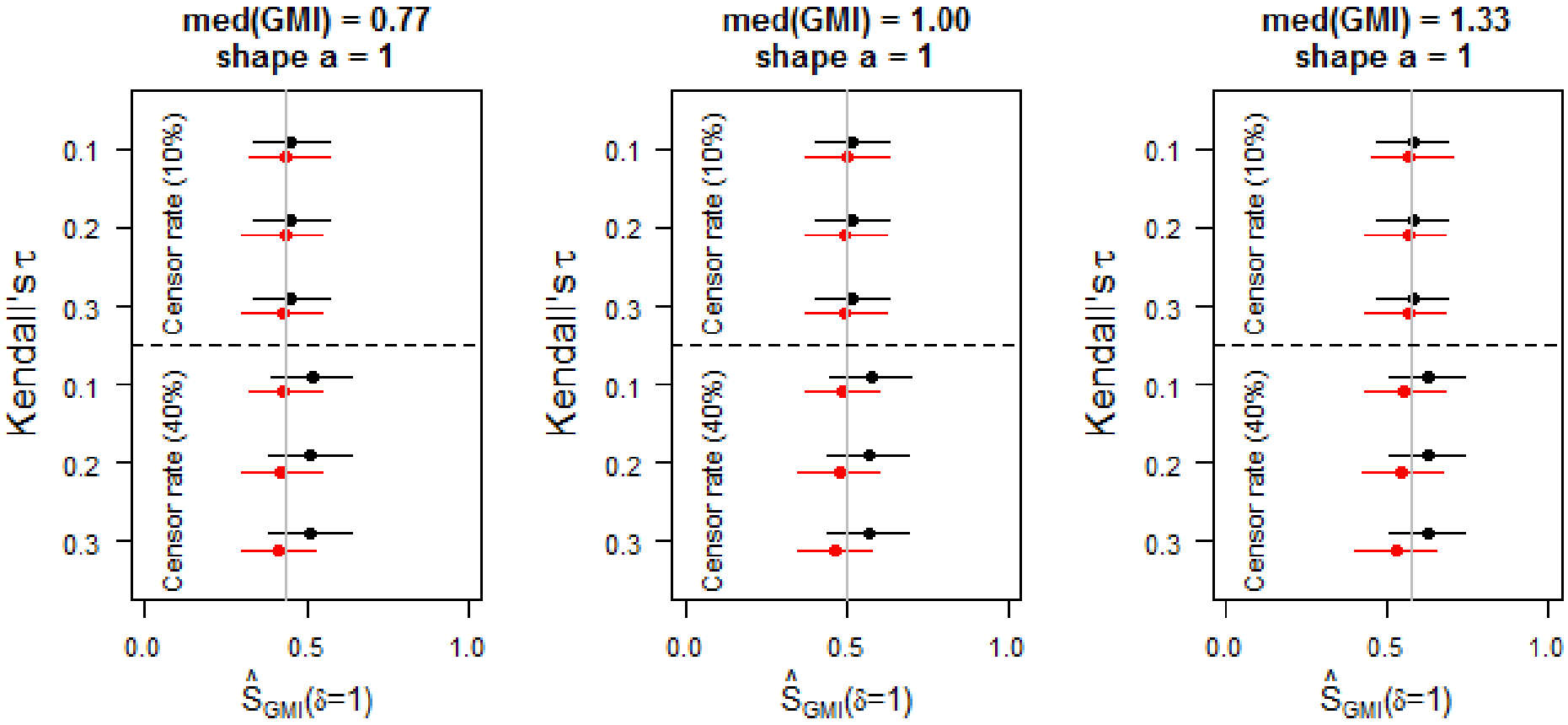
- Generation of censoring
(10% and 40% of censored observations)

Result of simulation (1)



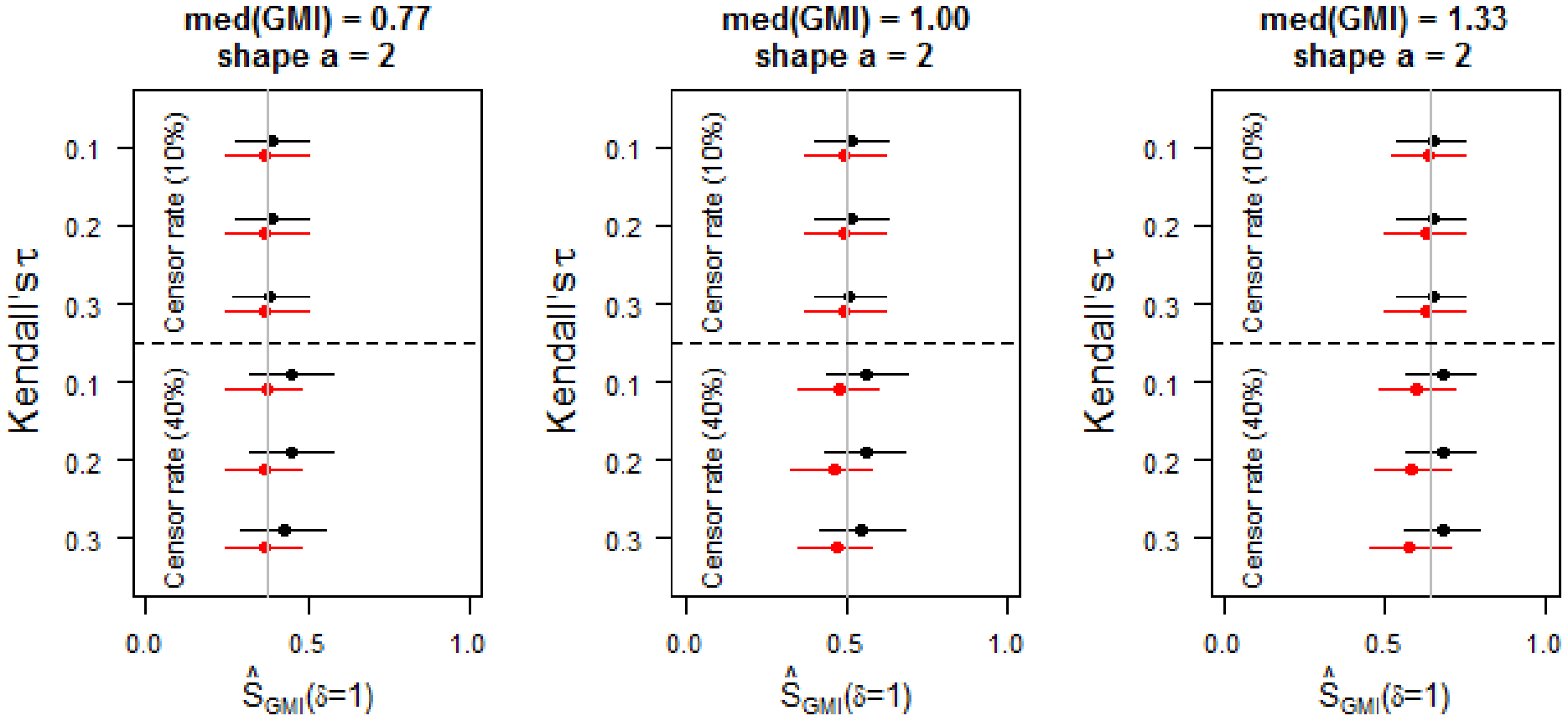
Probability $\hat{S}_{GMI}(\delta = 1)$ of GMI being greater than 1 estimated in the simulation study via the parametric (black) and non-parametric (red) methods. Normally approximate 95% confidence intervals using the empirical standard error

Results of simulation (2)



Probability $\hat{S}_{GMI}(\delta = 1)$ of GMI being greater than 1 estimated in the simulation study via the parametric (black) and non-parametric (red) methods. Normally approximate 95% confidence intervals using the empirical standard error

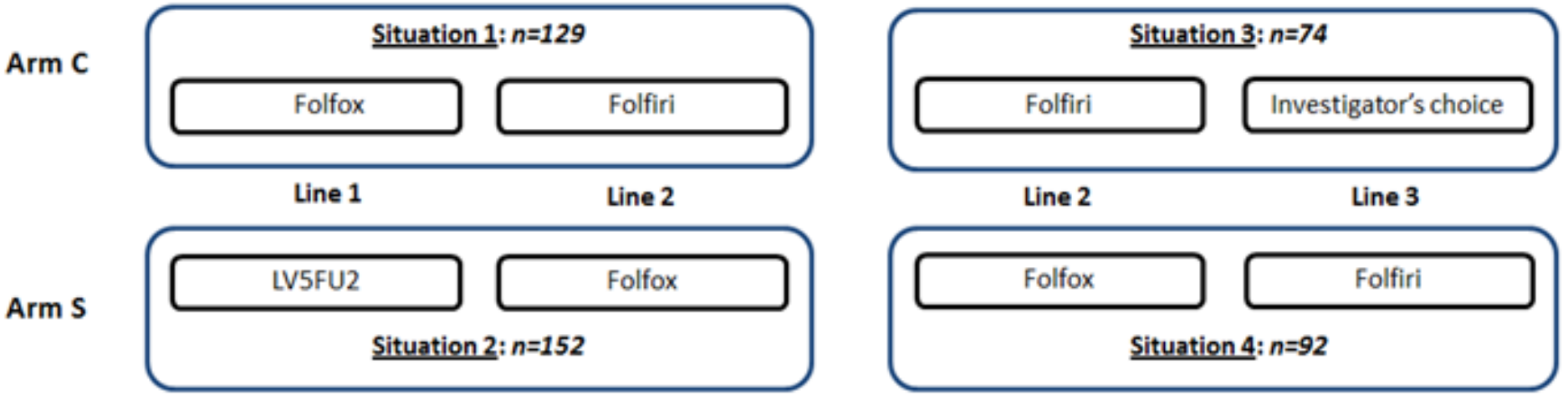
Results of simulation (3)



Probability $\hat{S}_{GMI}(\delta = 1)$ of GMI being greater than 1 estimated in the simulation study via the parametric (black) and non-parametric (red) methods. Normally approximate 95% confidence intervals using the empirical standard error

Application

- The FFCD 2000-05 trial was a randomized trial conducted by the French Federation of Digestive Oncology, which included 410 patients with advanced colorectal cancer



- Estimation of the dependence between TTP_1 and TTP_2 (Kendall's τ) by modeling the risks of progression by shared frailty models

Dependence between PFS_1 and PFS_2

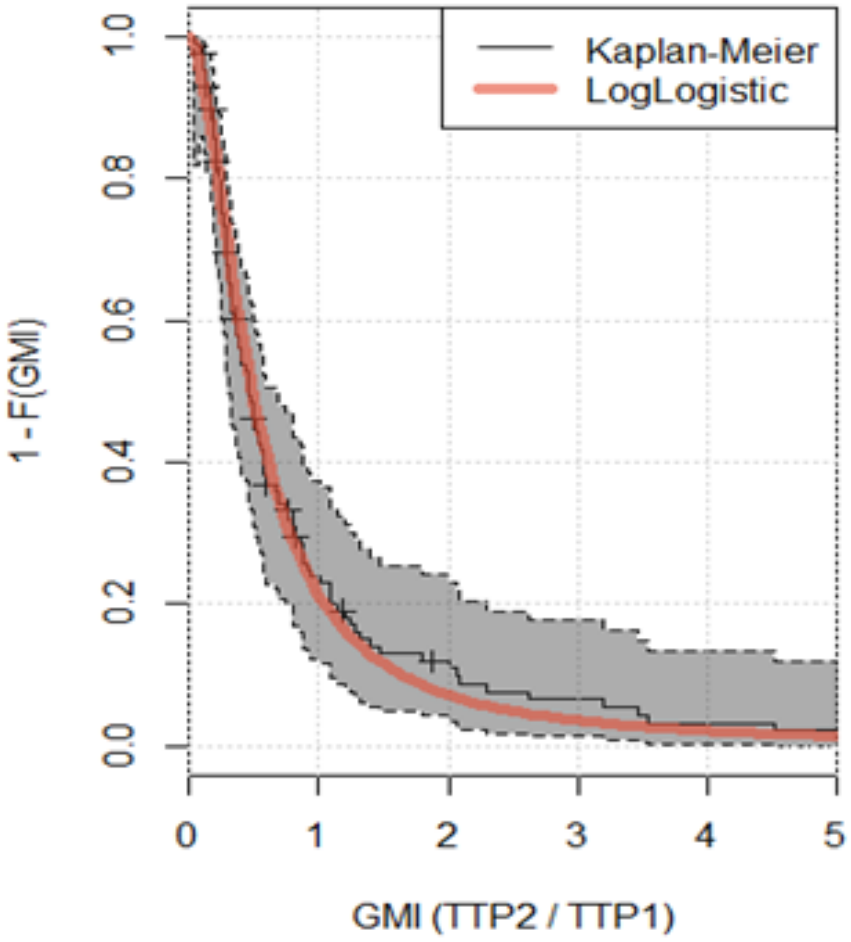
- Estimation of the Kendall's τ for the 4 situations
  by modeling the risks of progression by shared frailty models

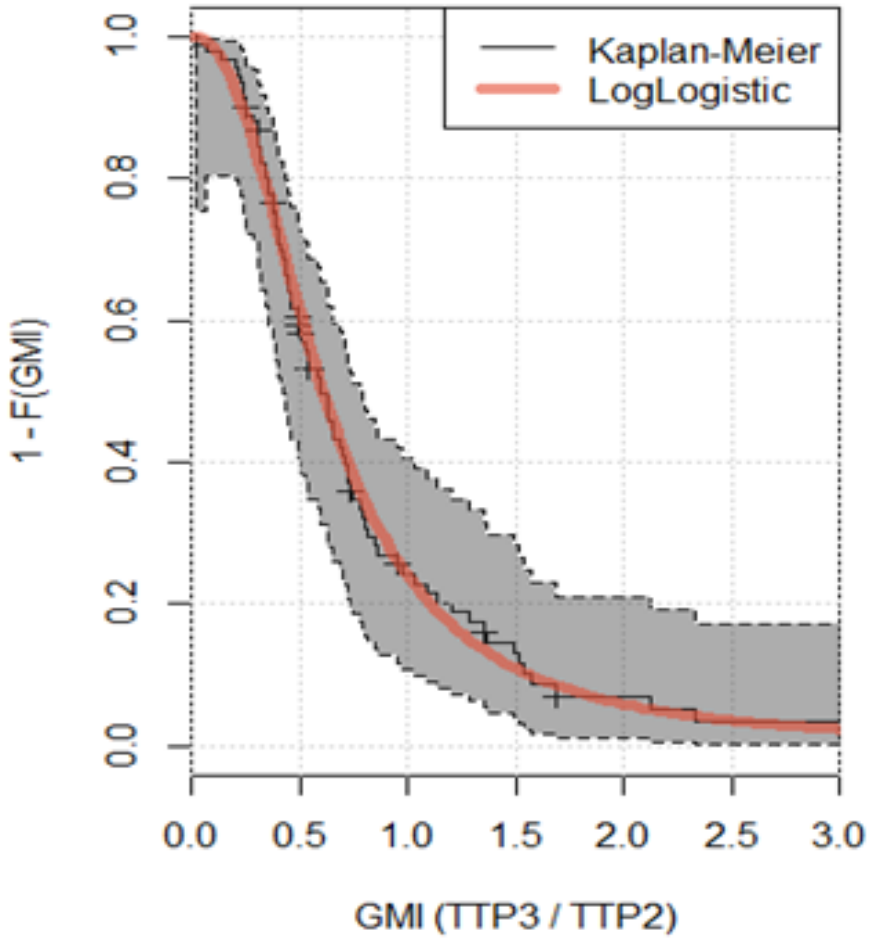
$$h_{ij}(t|u_i) = h_{0j}(t)u_i \exp(x_{ij}^T \beta)$$

- Gamma distribution assumed for the frailty term
- Weibull distribution assumed for the baseline hazard function

	Kendall's τ
Arm C	
Situation 1	0.195
Situation 3	0.152
Arm S	
Situation 2	0.142
Situation 4	0.225

Estimation of $\hat{S}_{GMI}(1)$





Survival function estimate of the growth modulation index (situation 1 on the left, situation 4 on the right) via the Kaplan-Meier method and via a log-logistic distribution. The gray area is the 95% confidence band for the Kaplan-Meier estimate.

Estimation of $\hat{S}_{GMI}(1)$

	Treatment				Estimator	
	Line 1	Line 2	N	Events	Parametric	Non parametric
Arm C						
Situation 1	FOLFOX	FOLFIRI	129	114	0.21 [0.14; 0.29]	0.24 [0.17; 0.31]
Situation 3	FOLFIRI	Investigator	74	59	0.52 [0.41;0.63]	0.54 [0.43; 0.65]
Arm S						
Situation 2	LV5FU2	FOLFOX	152	122	0.54 [0.46; 0.62]	0.48 [0.40;0.56]
Situation 4	FOLFOX	FOLFIRI	92	79	0.24 [0.15; 0.33]	0.27 [0.18; 0.36]

Estimation of $S_{GMI}(\delta = 1) = P(GMI > 1)$ for the four situations in the FFCD 2000-05 trial

Discussion

- Few published clinical trials using the GMI as a criterion of activity
  - Rather low correlation of the paired time-to-progression
  - At least in some of them, this may be due to the heterogeneity of the first-line treatment or to the localization of the tumor

- In phase II trials, progressions are generally assessed at fixed times, What about the effect of interval censoring on these methods?

- An increasing number of clinical trials and the EMA admits its use to compare two successive therapies

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