Moving from the hazard ratio to the difference in restricted mean survival time in IPD meta-analyses

Béranger Lueza

Statistical Methods and Designs in Clinical Oncology Symposium

October 20th 2016
Paris

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Inserm

Public Health Research Institute
IReSP

CONTRE LE CANCER
LA LIGUE
101 comités

Context

- ✓ **Difference in restricted mean survival time (rmstD)** is a commonly used survival measure in cost-effectiveness analyses
- ✓ **Cost-effectiveness analyses** based on individual patient data meta-analyses (IPD MA) are scarce
- ✓ **IPD MA** of randomized trials has become the gold standard = best evidence for treatment effects
- ✓ For this type of hierarchical data, statistical analyses are **stratified by trial** and **treatment effect heterogeneity** between trials is studied

Objectives

1. Investigate if the choice of the method used to estimate the *rmstD*(*t**) impacts the results of a cost-effectiveness analysis in the context of an IPD meta-analysis

   ➔ **Motivating case study**

2. Study and compare methods to estimate the *rmstD*(*t**) from an IPD meta-analysis

   ➔ **Simulation study**

3. Illustrate the use of the *rmstD*(*t**) as a measure for the treatment effect in an IPD meta-analysis

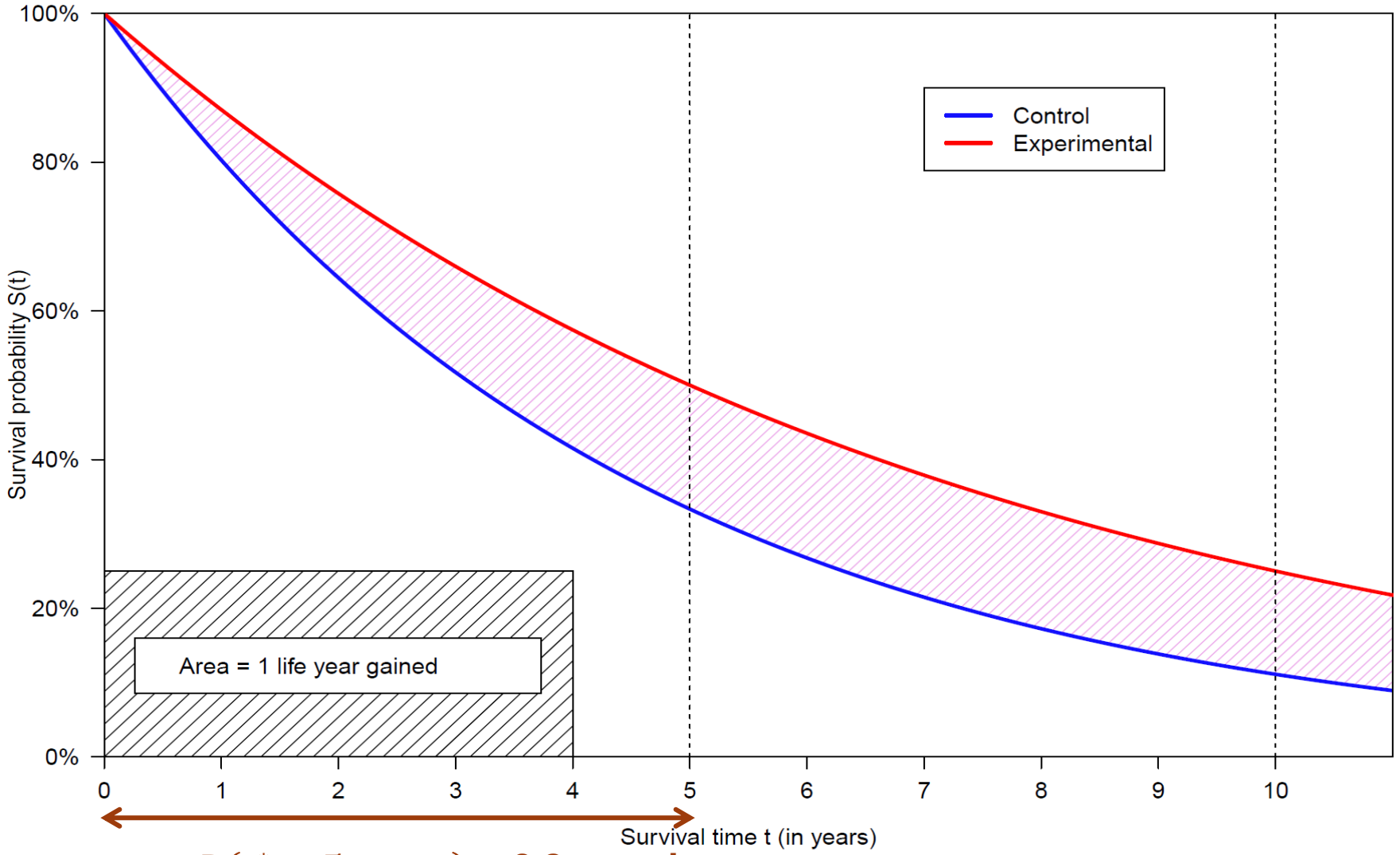
   ➔ **Application**

Methods

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Inserm

HR = 0.63: experimental arm always more efficient than control arm



$rmstD(t^* = 5 \text{ years})$ = 6,9 months

$rmstD(t^* = 10 \text{ years})$ = 16,4 months

Meta-analyses methodology

- ✓ **Stratification by trial**: comparison of patients in the experimental arm from a trial to patients in control arm **within the same trial** (comparison of like with like)
  ➔ respect the randomization

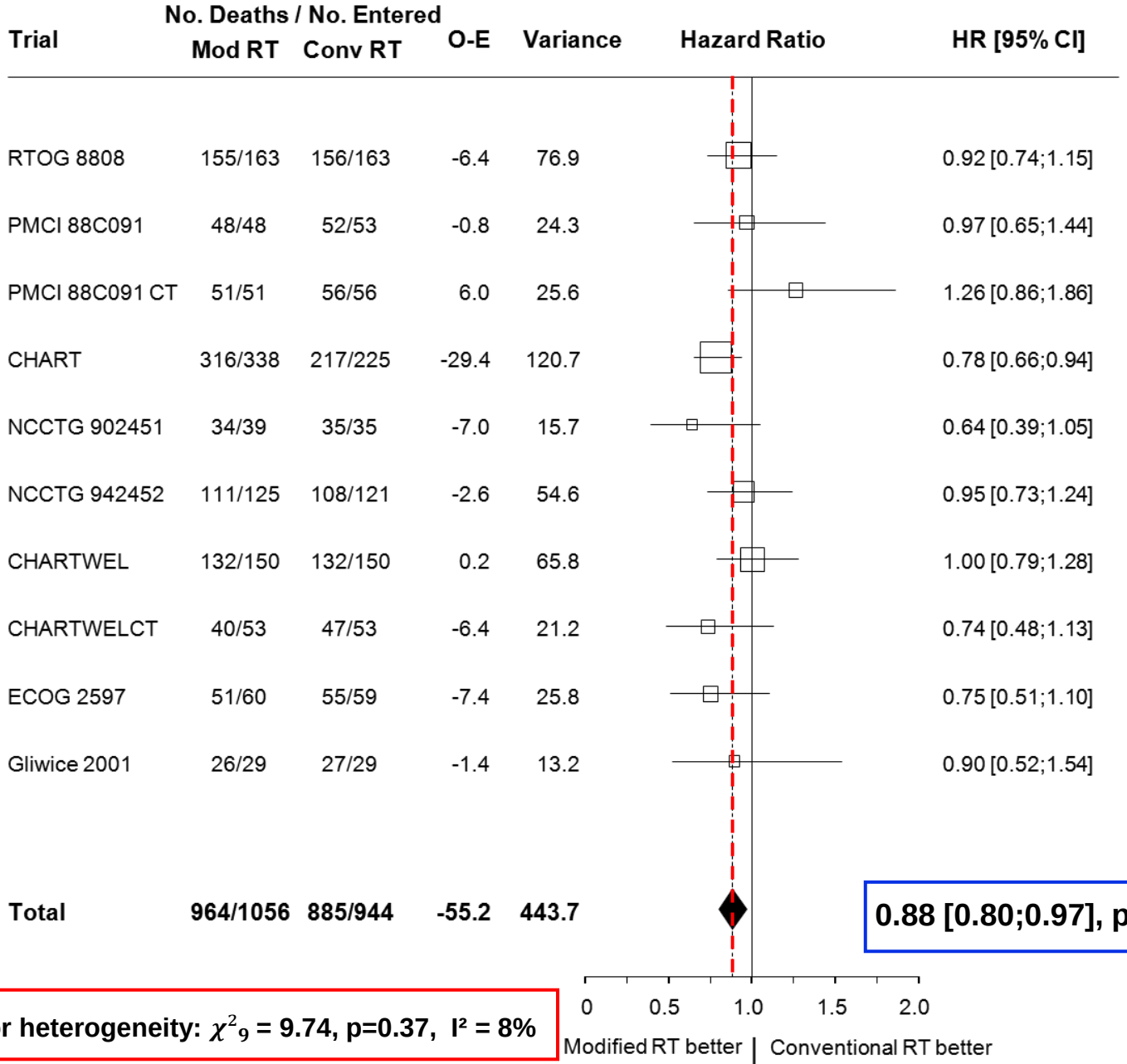
- ✓ Estimation of the **overall treatment effect** in 2 stages:
  1. Treatment effect estimation $\hat{\theta}_j$ in every trial *j*
  2. Weighted average : $\hat{\theta}_{overall} = \frac{\sum_{j=1}^{J} \hat{\theta}_j w_j}{\sum_{j=1}^{J} w_j}$

$\hat{\theta}_j = \log(\widehat{HR}_j)$ for survival data

$w_j = \frac{1}{\widehat{Var}(\hat{\theta}_j)}$ fixed effects

$w_j = \frac{1}{\widehat{Var}(\hat{\theta}_j)+\tau^2}$ random effects : τ^2 ⇔ **heterogeneity**

Forest-plot example (MAR-LC)



Test for heterogeneity: χ^2_9 = 9.74, p=0.37, I^2 = 8%

Two approaches to estimating the overall *rmstD*(*t**) from an IPD meta-analysis

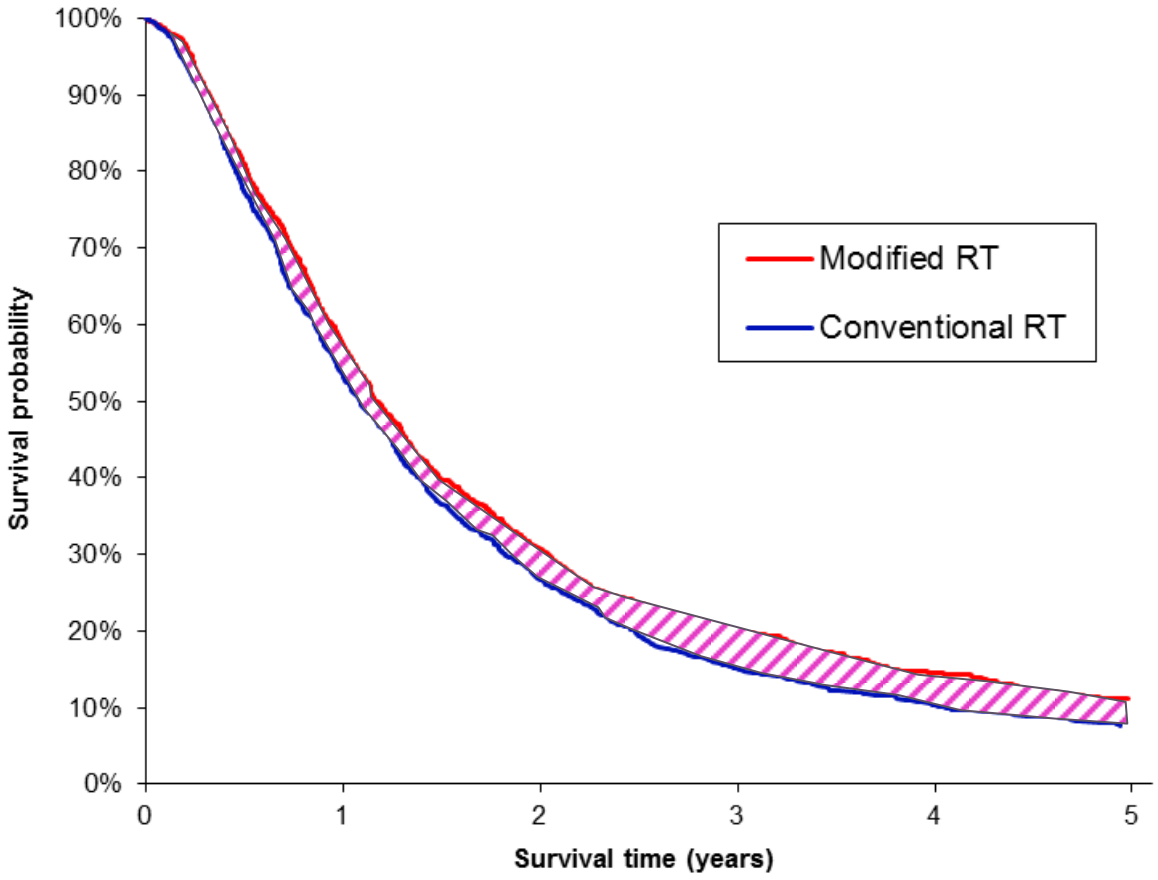
- Approach 1: *rmstD*(*t**) is estimated as the area between the two "pooled" survival curves summarizing the information from the *J* trials

- Approach 2:
  1. $rmstD_j(t^*)$ is estimated in each of the *J* trials
  2. Weighted average of the $rmstD_j(t^*)$ using fixed or random effects:

$$\widehat{rmstD}(t^*) = \frac{\sum_{j=1}^{J} \widehat{rmstD_j}(t^*) w_j}{\sum_{j=1}^{J} w_j}$$

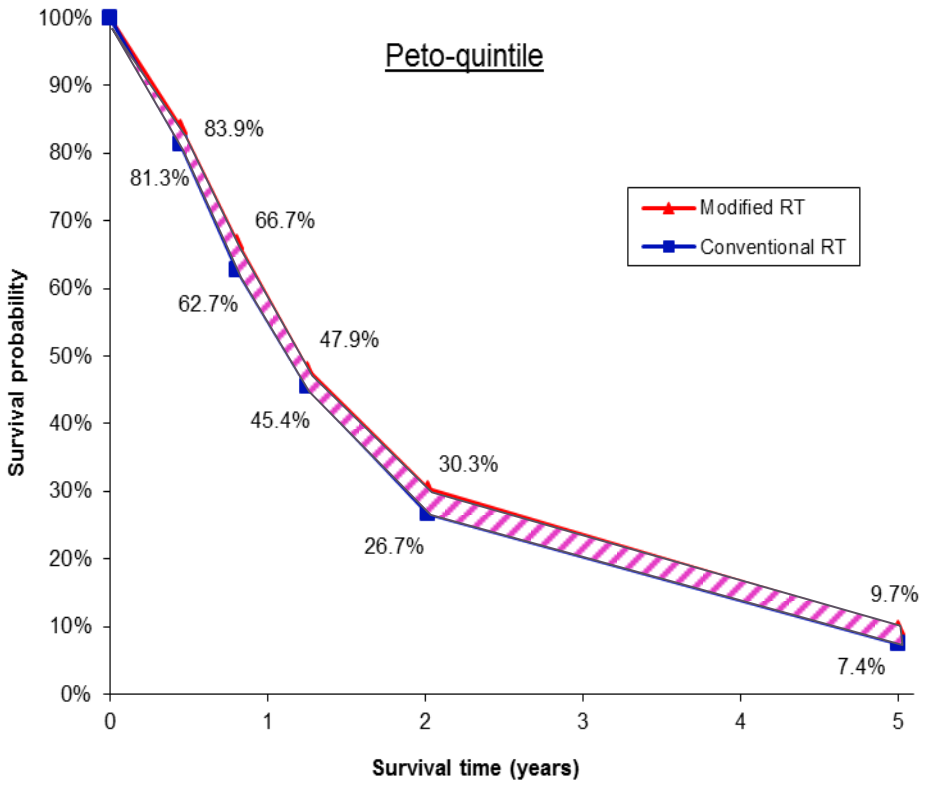
1st approach: Naïve Kaplan-Meier

Trials of the meta-analysis are considered as one and only trial; the overall *rmstD*(*t**) is estimated as the area between the two KM survival curves, thus ignoring trial effect



1st approach: Peto-quintile

Actuarial method developped by Richard Peto (EBCTCG, 1992) to take into account trial effect for representing suvival curves in IPD meta-analysis.



Time interval estimation is based on the quintiles of number of deaths until *t** ➔ each interval contains an equal number of events

2nd approach: Pooled Kaplan-Meier - Pooled Exponential

1. For each trial *j*, $rmstD_j(t^*)$ is estimated as the area between survival curves Kaplan-Meier or exponential
2. Then the $rmstD_j(t^*)$ are pooled using a fixed or random effects model

Motivating case study

Julia Bonastre, Audrey Mauguen, Jean-Pierre Pignon (Gustave Roussy, Inserm)
Oliver Rivero-Arias (Oxford University)

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

Inserm

Meta-Analysis of Radiotherapy in Lung Cancer (MAR-LC)

- ✓ IPD MA in non-small cell lung cancer (Mauguen 2012)
- ✓ N = 2,000 patients and 10 phase III trials comparing :
  - Conventional radiotherapy (RT)
  - Modified RT (hyperfractionated and/or accelerated)
- ✓ Modified RT improved overall survival:
  $HR_{overall}$ = 0.88 [IC 95%: 0.80-0.97; p = 0.009]

➔ Is modified radiotherapy cost-effective ?

rmstD(*t**) and Incremental Cost-Effectiveness Ratio

$$ICER = \frac{\bar{C}_{Mod\ RT} - \bar{C}_{Conv\ RT}}{\boldsymbol{rmstD}(\boldsymbol{t}^* = \mathbf{5})}$$

expressed as a cost per life year gained

- **Modified RT more expensive: 4 328 €** [1 830€ ; 6 804€]

Method	*rmstD*(*t**) (months) [95% CI]	ICER (k€) [95% CI]
Peto-quintile	1.7 [0.4 – 3.1]	35 [13 – 98]
Naïve Kaplan-Meier	2.2 [0.6 – 3.7]	27 [11 – 68]
Pooled Kaplan-Meier	2.3 [0.7 – 3.8]	26 [10 – 66]
Pooled Exponential	2.5 [0.7 – 4.2]	24 [10 – 59]

- The choice of a survival method to estimate overall *rmstD*(*t**) impacts the cost-effectiveness results

- These results were obtained based on a case study using an IPD meta-analysis with proportional hazards, no heterogeneity and a small treatment effect size

  ➔ need to investigate on other scenarios with simulation study

Ref: Lueza B, Mauguen A, Pignon JP, Rivero-Arias O, Bonastre J. Difference in Restricted Mean Survival Time for Cost-Effectiveness Analysis Using Individual Patient Data Meta-Analysis: Evidence from a Case Study. PLoS One 2016 11(3)

Simulation study

Julia Bonastre, Stefan Michiels,
Jean-Pierre Pignon, Federico Rotolo
(Gustave Roussy, Inserm)

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Inserm

Simulation of meta-analysis time-to-event data

- For a trial $j \in \{1,\ldots,J\}$, the hazard function is:

$$\lambda_j(t) = \lambda_0(t)exp\{a_j + (\beta + b_j)x\}$$

- $\lambda_0(t)$ = baseline hazard function (exponential distribut.)
- β = overall treatment effect
- x = treatment variable ($\pm 1/2$ ➔heterogeneity = 2 arms)
- $\mathrm{Var}(a_j) = \sigma^2 =$ baseline hazard heterogeneity
- $\mathrm{Var}(b_j) = \tau^2 =$ treatment effect heterogeneity

Ref: Lueza B, Rotolo F, Bonastre J, Pignon JP, Michiels S. Bias and precision of methods for estimating the difference in restricted mean survival time from an individual patient data meta-analysis. BMC Med Res Meth 2016 16(1):37.

1,000 simulated meta-analyses per scenario

- ✓ **Baseline hazard and treatment effect heterogeneity:**

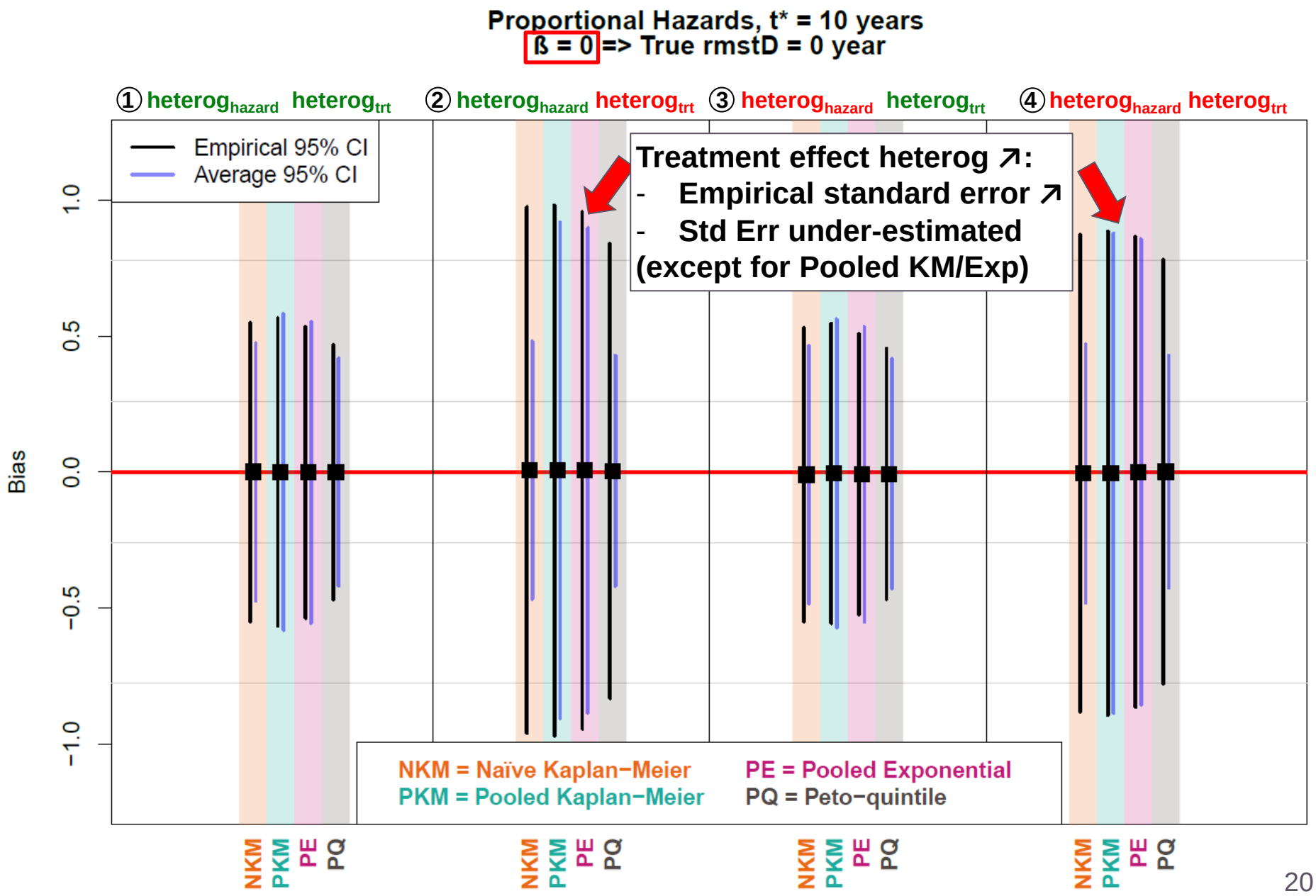
		Var(b_j) = τ^2 heterog$_{trt}$	
		Low (0.01)	High (0.10)
Var(a_j) = σ^2 heterog$_{hazard}$	Low (0.01)	①	②
	High (0.10)	③	④

- ✓ **Treatment effect size: β=0** (HR=1)/ **-0.2** (0.8) / **-0.7** (0.5)
- ✓ **Time horizon :**
  - ***t**** = 5 years : follow-up long enough for all trials**
  - ***t**** = 10 ans : too short follow-up for some trials**
- ✓ **Proportional or non-proportional hazards (piecewise exponential)**

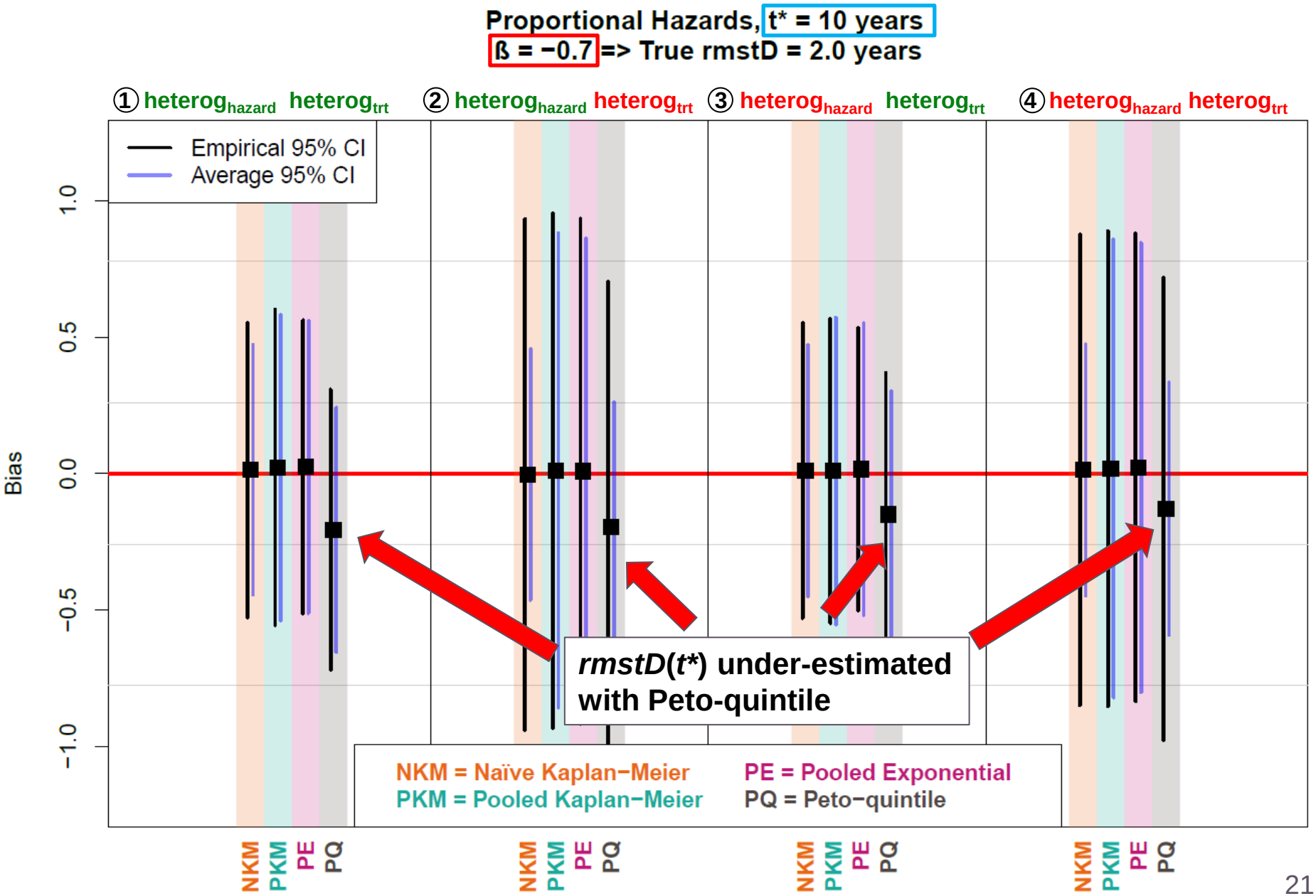
Compared methods and evaluation criteria

- **4 methods (fixed/random effects)**:
  - 1st approach (area between 2 « pooled » curves): Naïve Kaplan-Meier, Peto-quintile
  - 2nd approach (weighted average of areas): Pooled Kaplan-Meier, Pooled Exponential
- **Evaluation criteria:**
  - **Bias** = Average of the 1,000 estimated *rmstD*(*t**) - True *rmstD*(*t**)
  - **Empirical standard error** = Standard deviation of the *rmstD*(*t**) over the 1,000 replicates
  - **Average standard error** = Average of the 1,000 analytically estimated standard errors

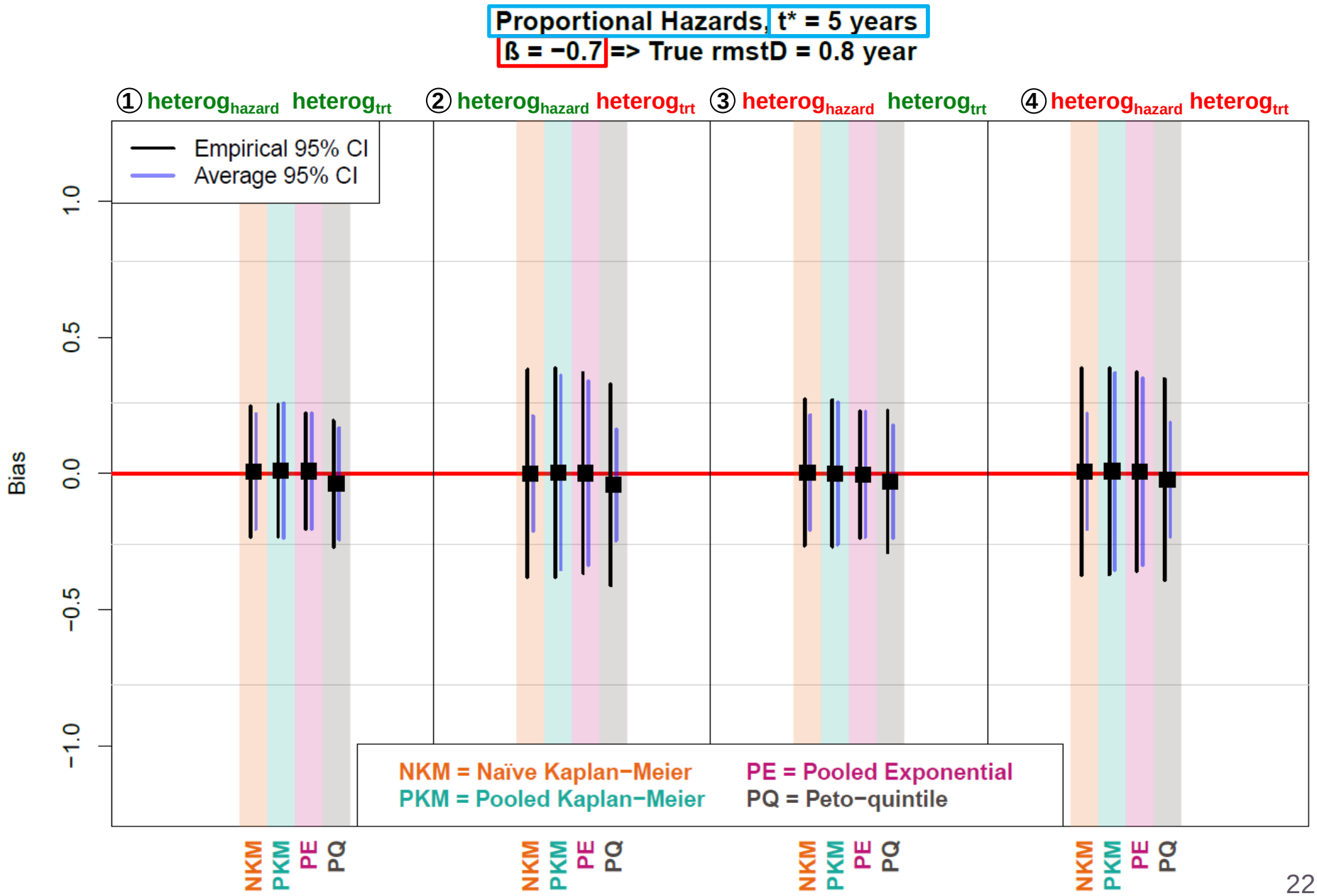
Standard error well estimated with Pooled KM/Exp



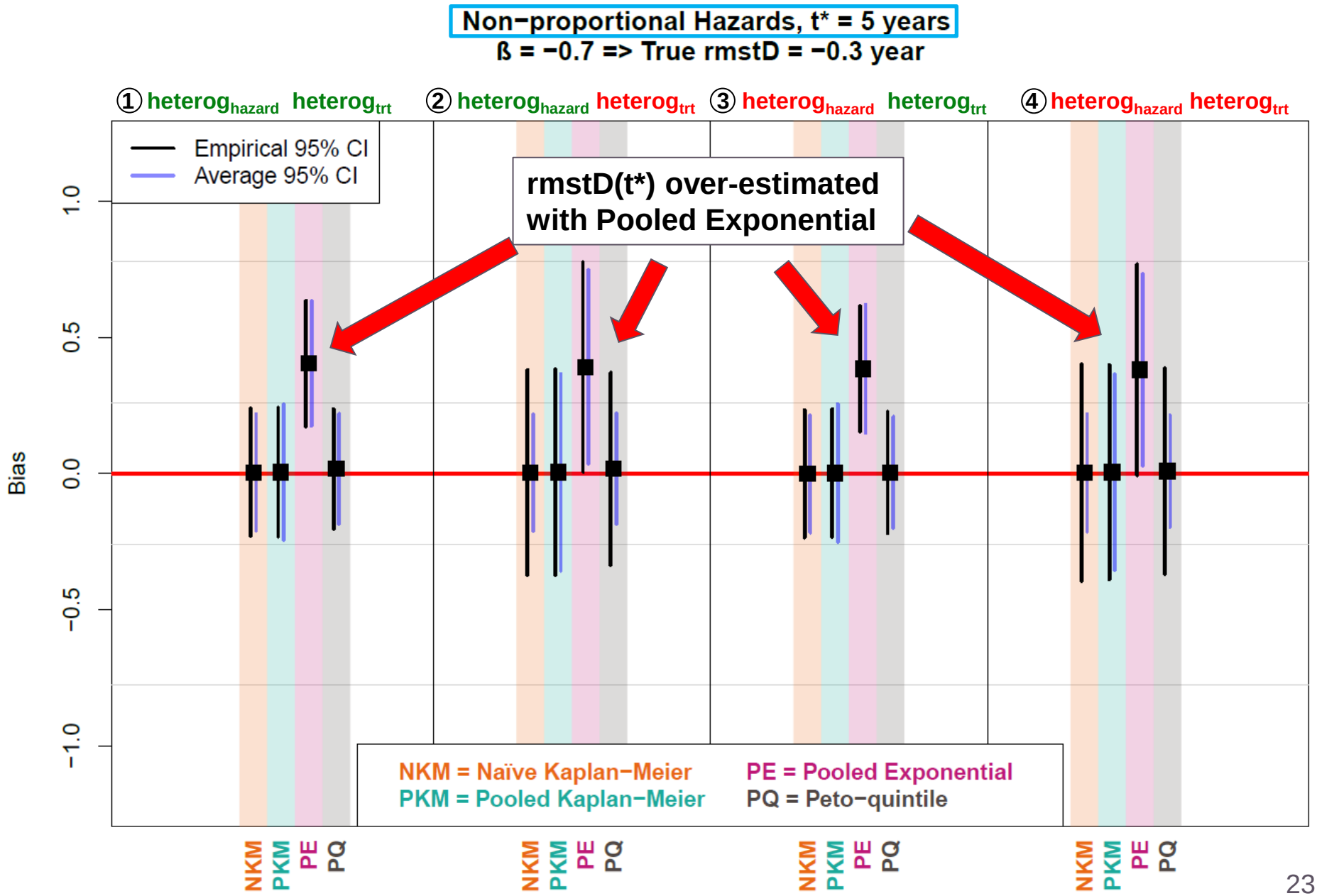
Peto-quintile biased when ß increases



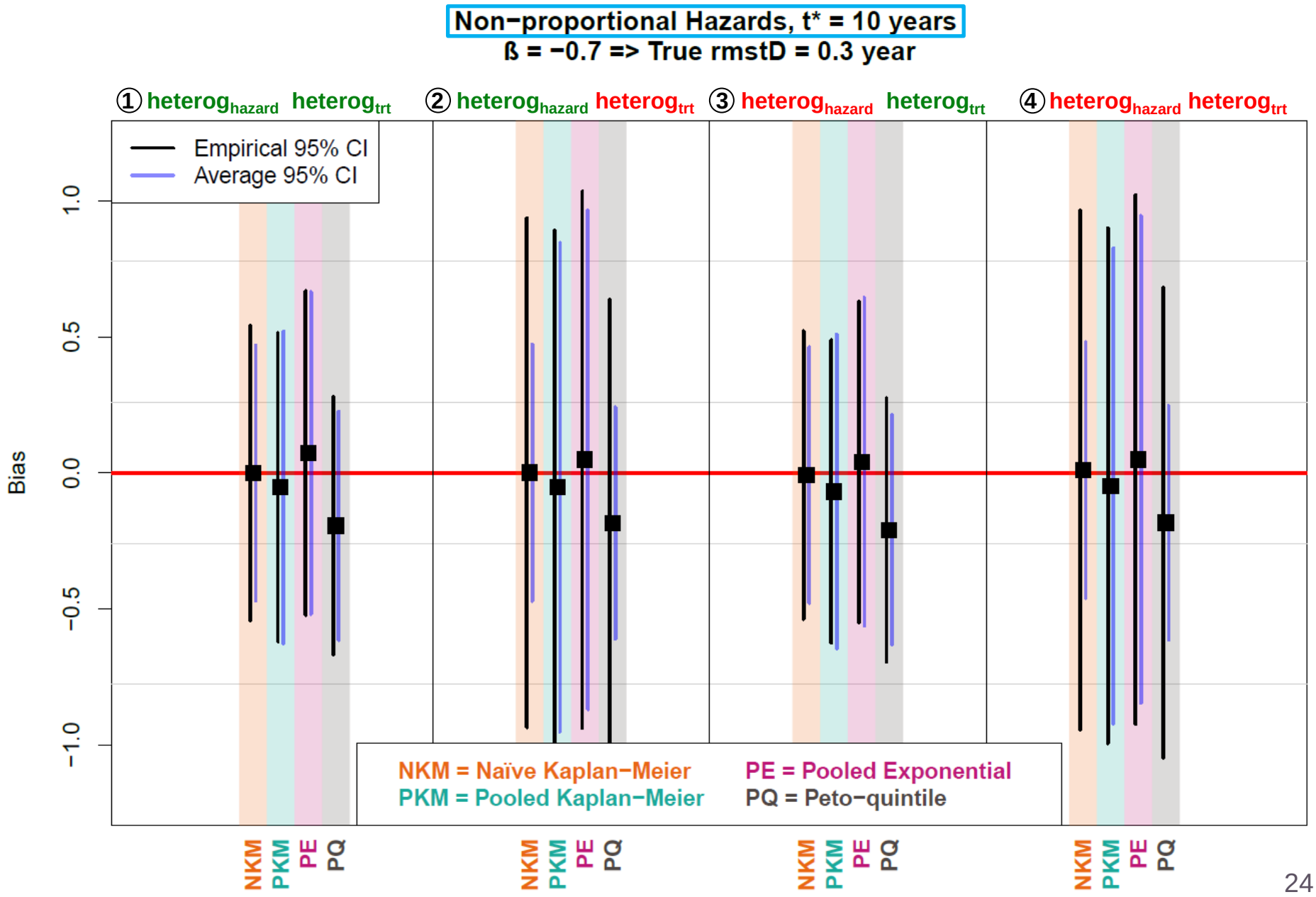
Similar results but smaller in magnitude (t*=5)



Pooled Exponential strongly biased



Pooled KM/Expo and Peto-quintile biased (*t** = 10)



No major impact for other investigated scenarios

- ✓ **Negative correlation** between random effects a_j and b_j
- ✓ **Deleterious treatment effect**
- ✓ **Number of trials and nb patients per trial** fixed/random:
  - **5 trials and 200 patients per trial (N=1,000)**
  - **5 trials and nb patients random (N=1,000)**
  - **20 trials and 100 patients (N=2,000)**

Conclusion

- **Pooled Kaplan-Meier** with random effects formed the best compromise in terms of bias and variance

- **Treatment effect size:**
  - Bias for Peto-quintile which increases with effect size
- **High treatment effect heterogeneity**:
  - Empirical Std Err increases no matter the method
  - Std Err well estimated (empirical = average) only for Pooled Kaplan-Meier and Pooled Exponential
- **Non-proportional hazards**:
  - Strong bias for Pooled Exponential

Application to an IPD meta-analysis

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Inserm

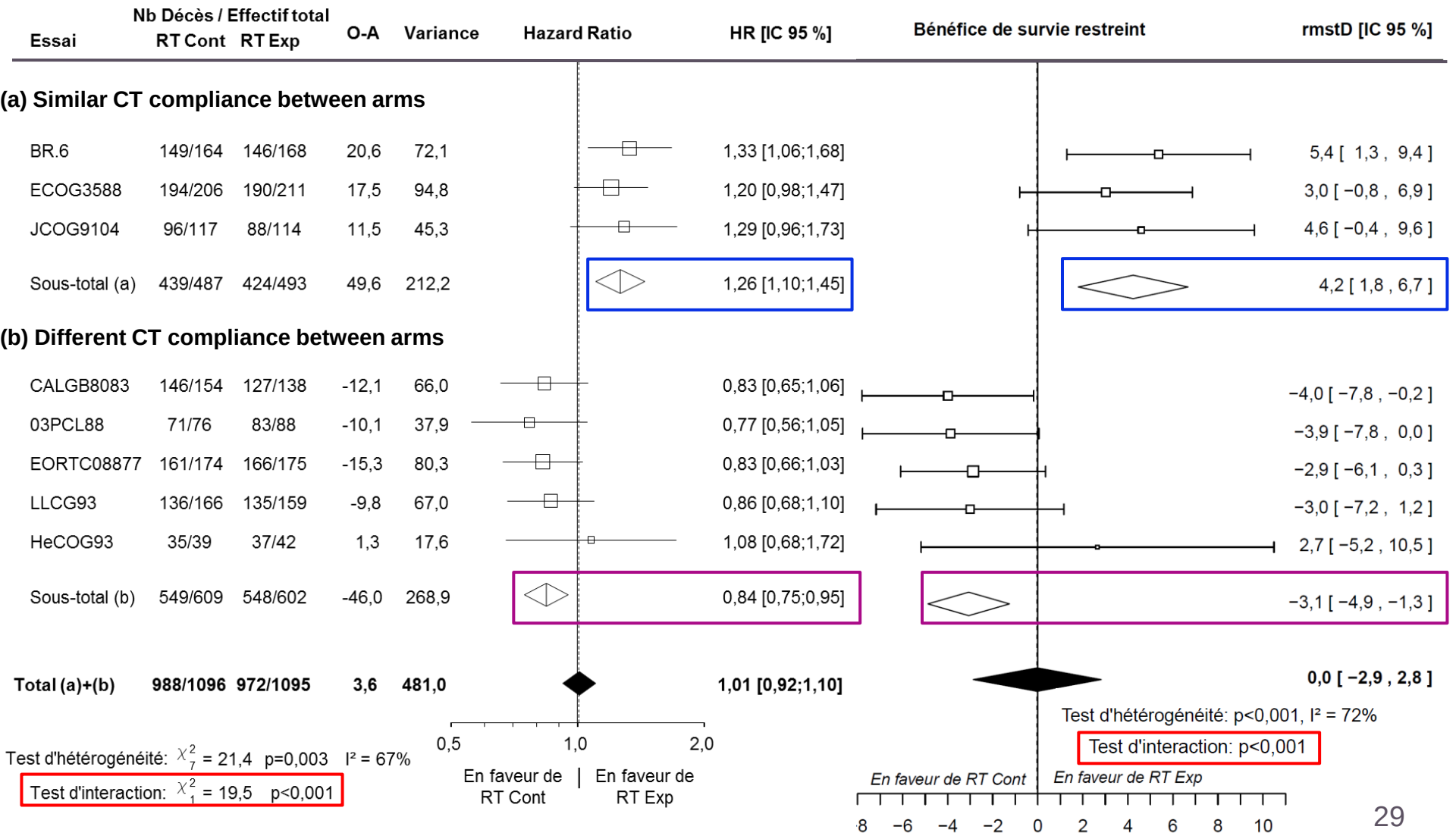
Radio-Therapy Timing in Small Cell Lung Cancer
RTT-SCLC

- ✓ IPD meta-analysis in small cell lung cancer, using both hazard ratio (primary measure) and *rmstD*(*t**) (secondary measure)
- ✓ Control RT versus experimental RT : HR = 1.01; p=0.87
- ✓ Strong treatment effect heterogeneity: p=0.003 ; I^2 = 67%

Ref: De Ruysscher D, Lueza B*, Le Péchoux C, et al. Impact of thoracic radiotherapy timing in limited-stage small-cell lung cancer: usefulness of the individual patient data meta-analysis. Annals of Oncology 2016 27(10), 1818–1828.*

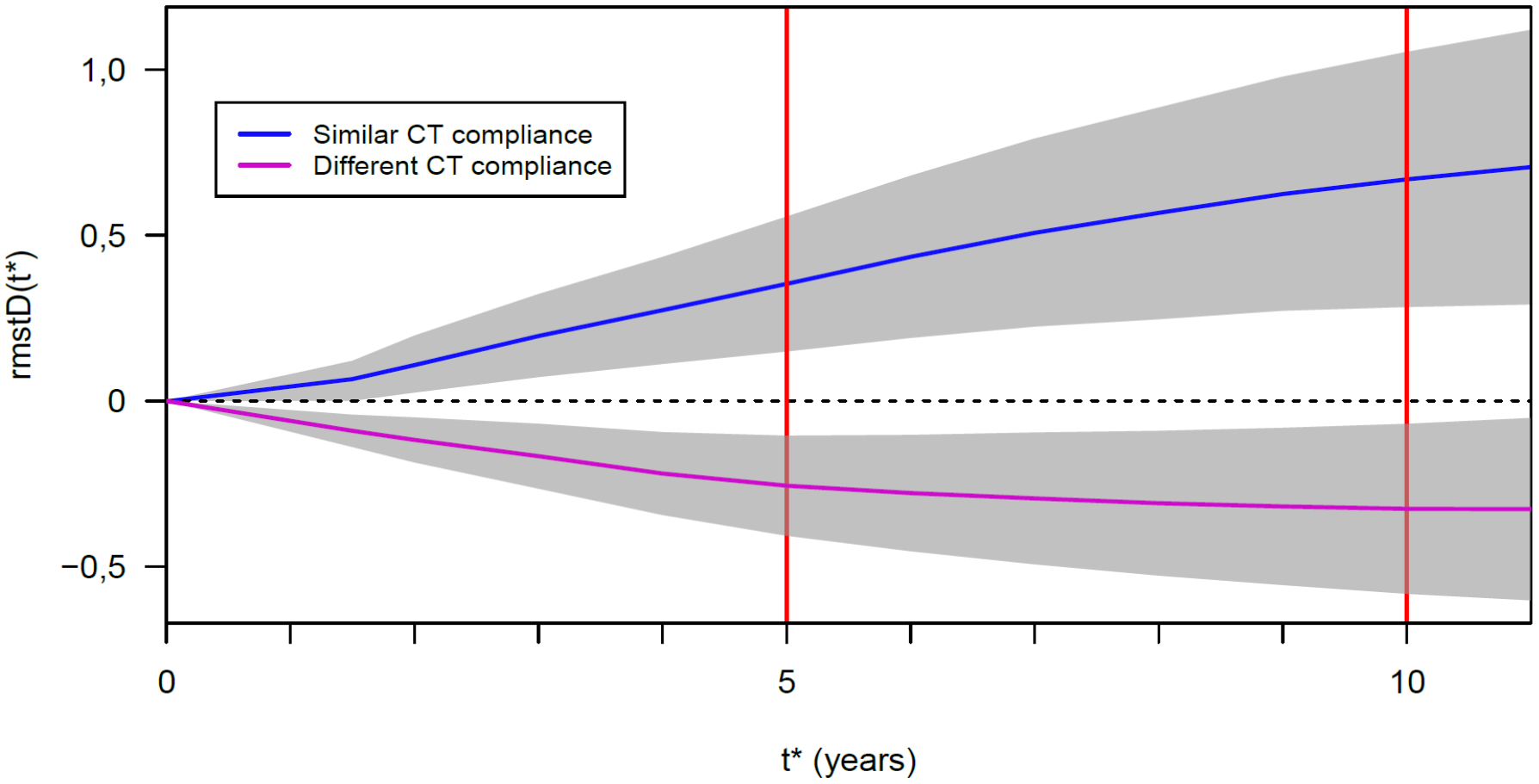
Interaction remains significant using rmstD

Same conclusions with either HR or *rmstD*(*t** = 5 years)



Varying time horizon *t**

- ✓ *rmstD*(*t**) estimated using Pooled Kaplan-Meier (random effects) varying *t**
- ✓ *rmstD*(*t**) significantly ≠ 0 and increases for *t** ϵ [0;10 yrs]



Discussion

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Inserm

Conclusion

- ✓ **Case study** showed that the choice of a method to estimate *rmstD*(*t**) exerts an impact on cost-effectiveness results in the context of an IPD meta-analysis
- ✓ **Simulation study**, through various scenarios, allowed us to recommend the Pooled Kaplan-Meier method with random effects which formed the best compromise bias / variance
- ✓ We have highlighted the **pros of using *rmstD*(*t**)** versus **HR** (non-proportional hazards, more intuitive) and have noted that **clinical conclusions** were similar with these two measures using 3 different IPD meta-analyses

Discussion

- ✓ PRISMA-IPD guidelines suggest to report both absolute and relatives measures (Stewart 2015)
- ✓ Royston and Parmar proposed to use the *rmstD*(*t**) to analyze and design a clinical trial (2011, 2013, 2016) + 1st simulation study for *rmstD*(*t**) in the context of meta-analysis using also flexible parametric model (Wei 2015)
- ✓ In a publication of a phase III RCT, for which Parmar was co-author, ***rmstD*(*t**) was the primary outcome measure** with non-proportional hazards (Oza 2015)
- ✓ To report the *rmstD*(*t**) in an article can also be usefull for future **economic evaluation**

Should RCT or IPD MA publications include ?

- ✓ *rmstD*(*t**) should be a secondary measure **systematically** reported in addition of a hazard ratio
- ✓ **Proportional hazards test**

  ➔Only one HR ? Average HR? Time varying HR?
- ✓ **Restricted mean survival times** in the 2 arms and ***rmstD*(*t**)** considering different time horizons *t**
- ✓ Graphic with ***rmstD*(*t**) varying time horizon *t****

➔ **We now include *rmstD*(*t**)** in the protocols of the IPD meta-analyses performed at Gustave Roussy

Acknowledgements

MAR-LC, MAC-NPC and RTT-SCLC collaborative groups and trialists

Julia Bonastre, Stefan Michiels,

Jean-Pierre Pignon and Federico Rotolo

(Gustave Roussy - Inserm, France)

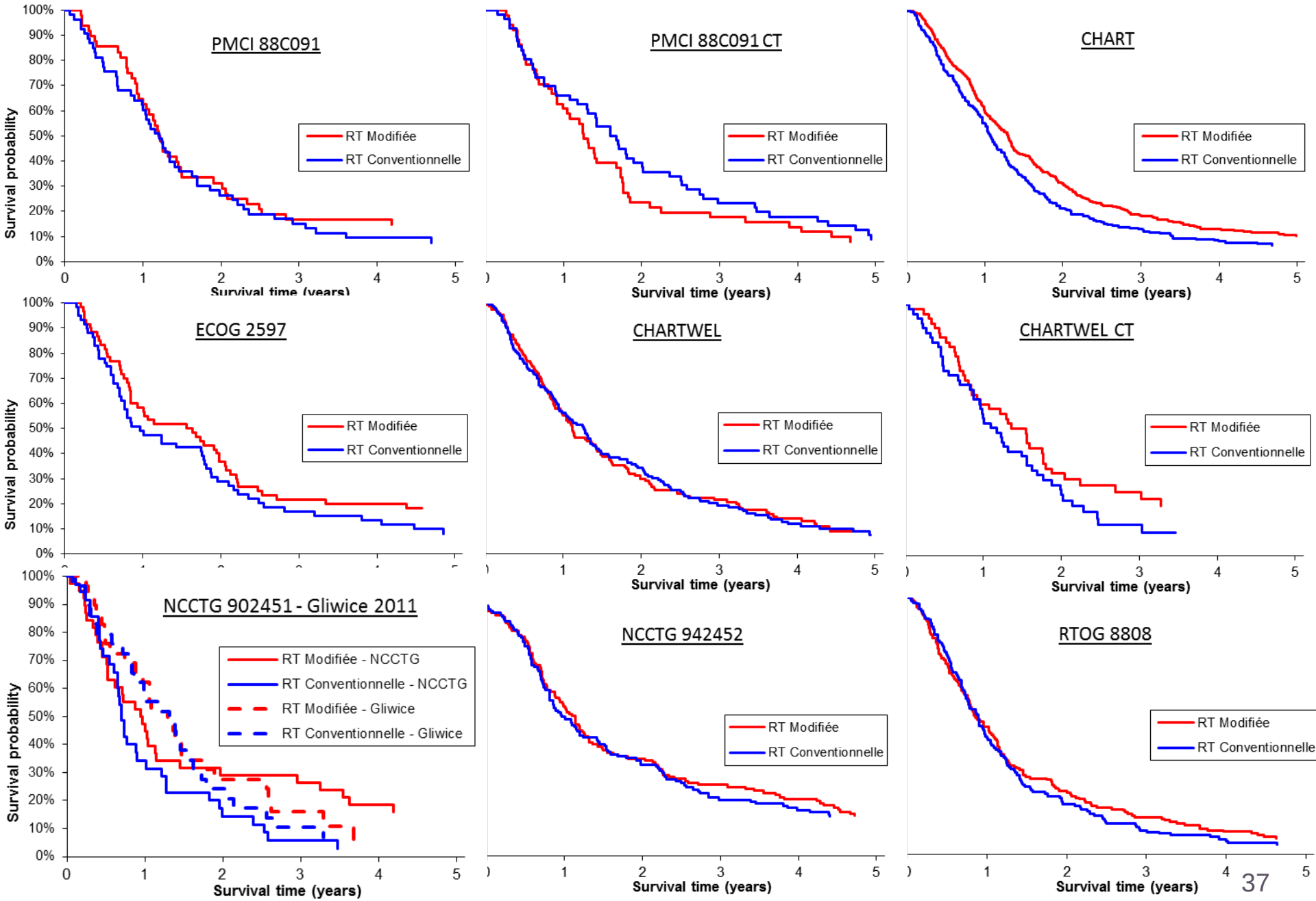
Oliver Rivero-Arias (Oxford University, UK)

IReSP, Ligue Nationale Contre le Cancer, Programme Hospitalier de Recherche Clinique

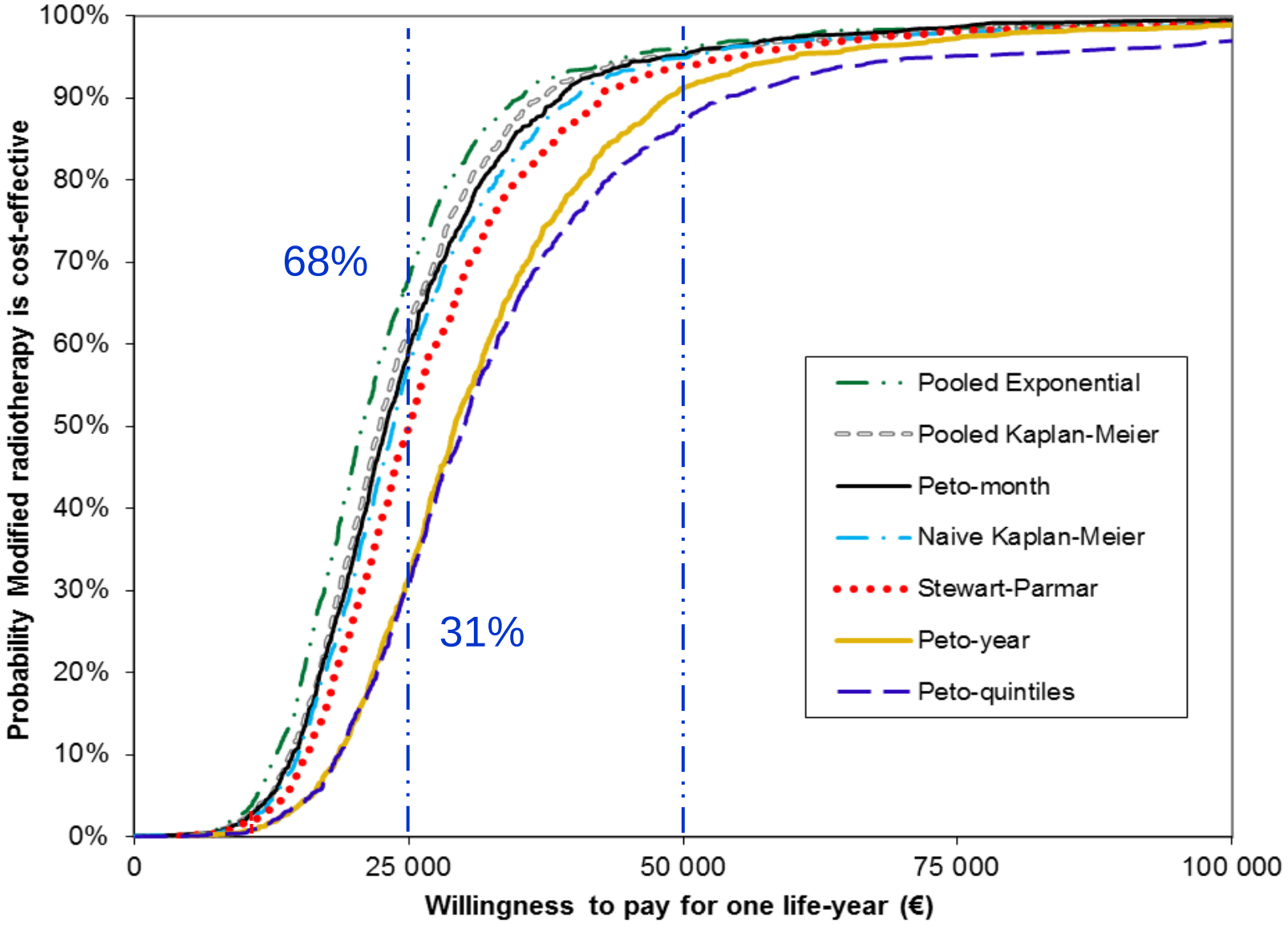
References

- Early Breast Cancer Trialists' Collaborative Group (1992) Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. *Lancet* ; 339.
- Mauguen A et al. (2012) Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. *J Clin Oncol* ; 30.
- Oza AM, Cook AD, Pfisterer J et al. (2015) Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): Overall survival results of a phase 3 randomised trial. *Lancet Oncol* ; 16, 928–936.
- Royston P, Parmar MKB (2002) Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med* ; 21, 2175–97.
- Royston P, Parmar M (2011) The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. *Stat Med*, 30, 2409–2421.
- Royston P, Parmar MK (2013) Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. *BMC Med Res Meth*, 13, 152.
- Royston P, Parmar MKB (2016) Augmenting the logrank test in the design of clinical trials in which non-proportional hazards of the treatment effect may be anticipated. *BMC Med Res Meth*; 16.
- Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF (2015) Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data. *JAMA*, 313, 1657.
- Trinquart L, Jacot J, Conner SC, Porcher R (2016) Comparison of Treatment Effects Measured by the Hazard Ratio and by the Ratio of Restricted Mean Survival Times in Oncology Randomized Controlled Trials. *J Clin Oncol* ; 34
- Wei Y, Royston P, Tierney JF, Parmar MKB (2015) Meta-analysis of time-to-event outcomes from randomized trials using restricted mean survival time: application to individual participant data. *Stat Med* ; 34, 2881–98.

Survival curves MAR-LC



Acceptability curves: 1,000 replicates bootstrap



Estimation des Coûts : perspective Assurance Maladie

Poste de coût	Ressource MAR-LC	Coût unitaire	Source	Pourcentage coût total
Traitement par radiothérapie	Nombre total de fractions reçues	1 004€ dosimétrie + 138€/fraction d'irradiation	PMSI 2012	21%
Transports pour la radiothérapie	Nombre total de fractions reçues	40€/fraction d'irradiation	Martin, 2003	5%
Traitement de la rechute	Temps de survie après rechute	3 073€/mois	Braud, 2003	73%
Traitement de l'œsophagite	Toxicité oesophagienne aigüe sévère	1 745€ si présence de toxicité	PMSI 2012	1%

- Conventionnelle = **25 331 €** ; IC95% [23 630€ ; 27 115€]
- Modifiée = **29 659 €** ; IC95% [27 845€ ; 31 507€]

7 methods to estimate the rmstD(t*)

Method	Take into account			
	Stratification by trial	Heterogeneity		Non-proportional hazards
		Treatment effect	Baseline hazard	
Naïve Kaplan-Meier	No	No	No	Yes
Stewart-Parmar	Yes	Yes	No	No[£]
Peto-month Peto-year Peto-quintile	Yes	Yes	No	Yes[µ]
Pooled Kaplan-Meier	Yes	Yes	Yes	Yes
Pooled Exponential	Yes	Yes	Yes	No

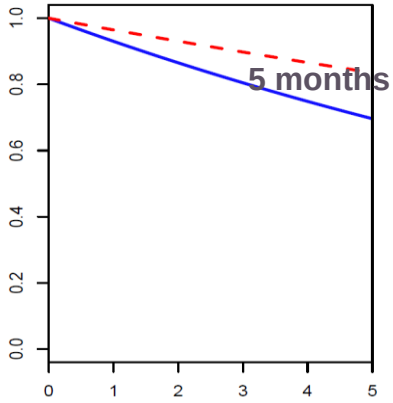
[£] Non-proportionality of hazards can however be taken into acocunt by using a time varying HR

[µ] $HR_{i,overall}$ can vary between time intervals

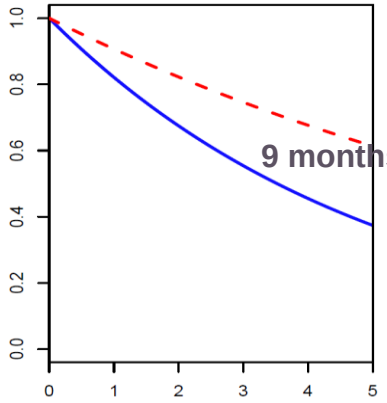
Varying the heterogeneity

$\lambda_j(t) = \lambda_0(t)exp\{a_j + (\beta + b_j)x\}$ (ici: β = -0,7 ➔ HR = 0,5)

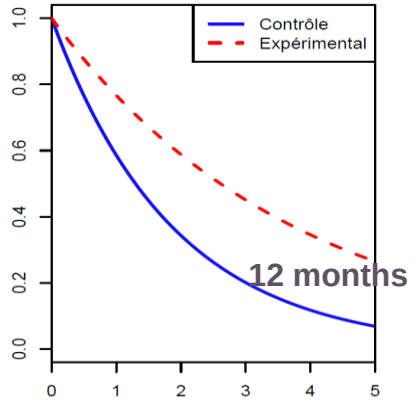
Trial 1 : a_j = -1



Trial 2 : a_j = 0



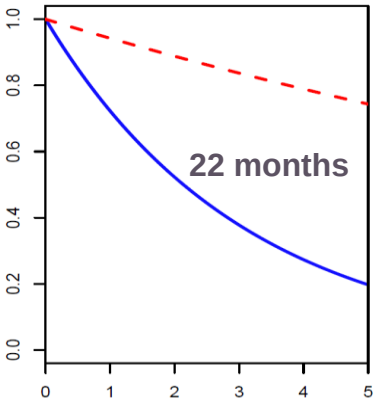
Trial 3 : a_j = 1



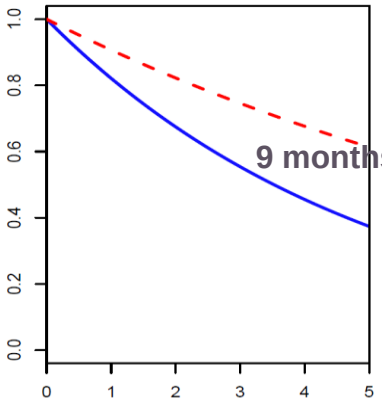
b_j = 0

➔ $\mathrm{Var}(a_j) = \sigma^2$: variation of baseline hazard heterogeneity

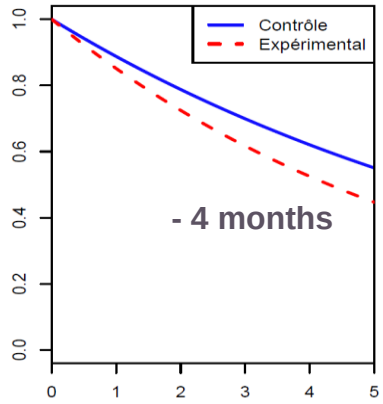
Trial 1 : b_j = -1



Trial 2 : b_j = 0



Trial 3 : b_j = 1



a_j = 0

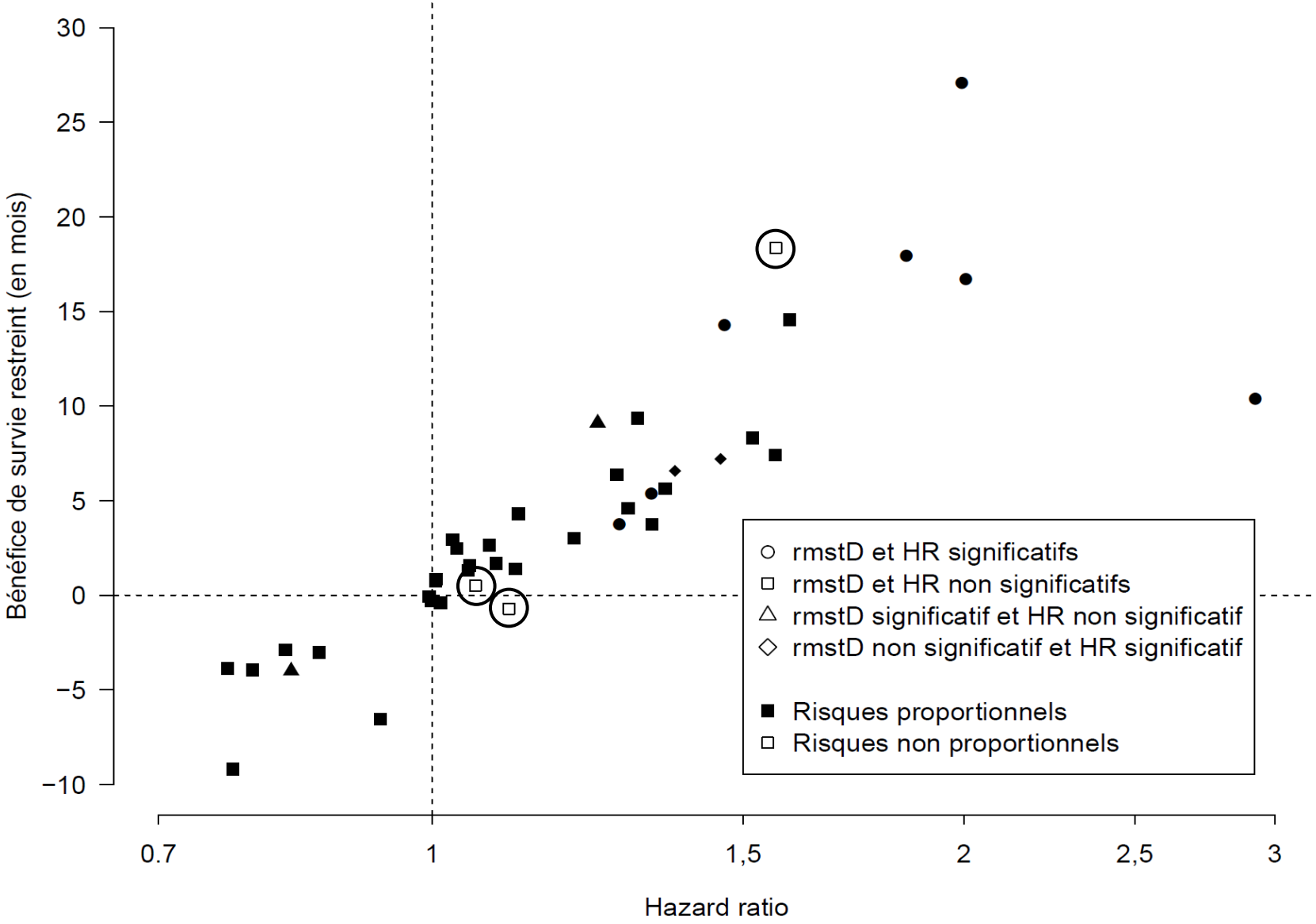
➔ $\mathrm{Var}(b_j) = \tau^2$: variation of treatment effect heterogeneity

HR vs *rmstD*(*t**) (MAR-LC, MAC-NPC 2 and RTT-SCLC)

- ✓ Similarly to the work by Trinquart *et al* (2016) : comparison of treatment effect measured by
  - Hazard ratio (Peto estimator)
  - *rmstD*(*t**) (Kaplan-Meier + Brown)
- ✓ **42 trials** included in 3 meta-analyses
- ✓ t^* = 5 years (MAR-LC, RTT-SCLC) or 10 years (MAC-NPC2)
- ✓ Test for hazards proportionality: Grambsh and Therneau test (1994) threshold = 5%

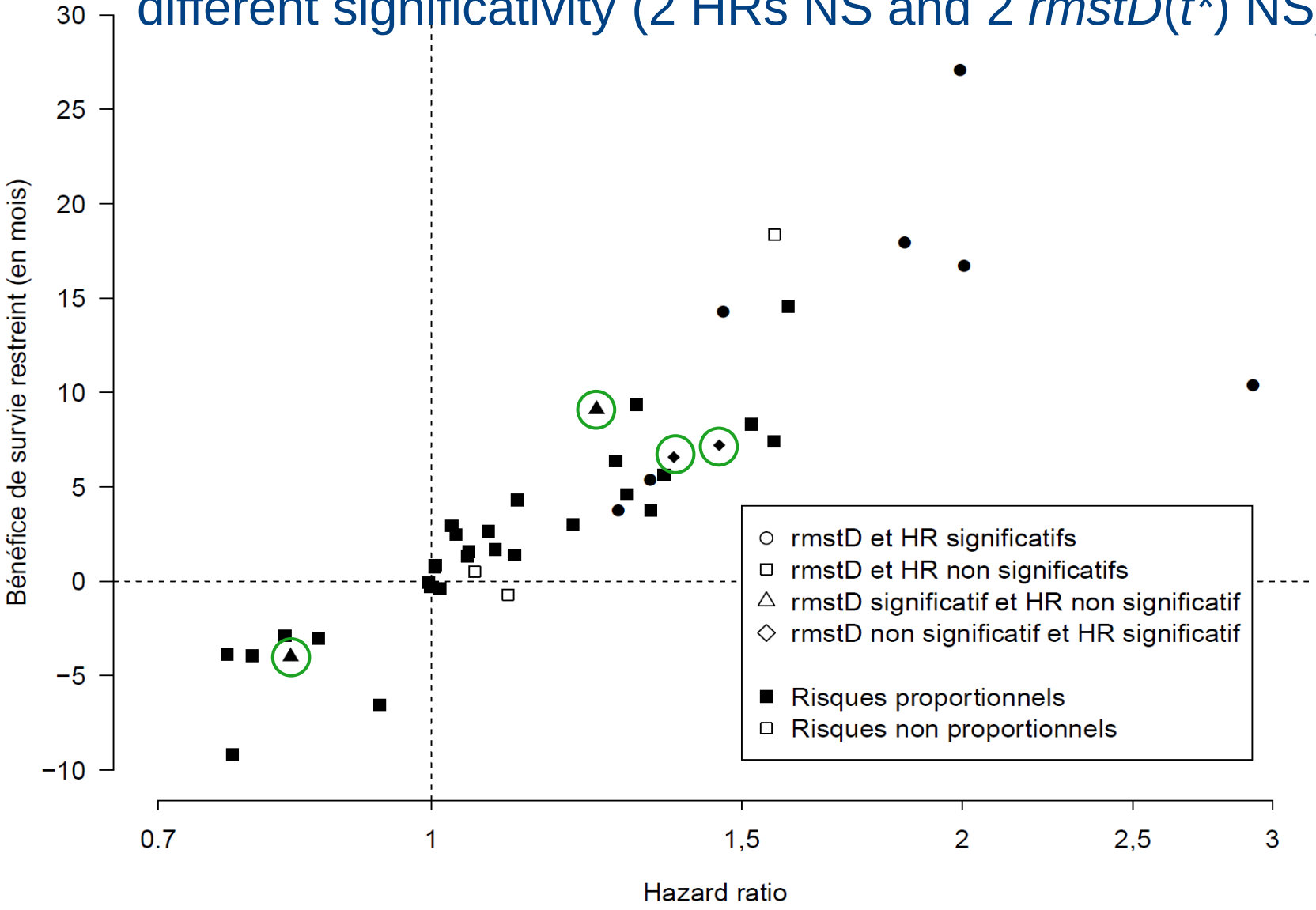
HR vs *rmstD*(*t**) (MAR-LC, MAC-NPC 2 and RTT-SCLC)

3 trials (7%) with non-proportional hazards



HR vs *rmstD*(*t**) (MAR-LC, MAC-NPC 2 and RTT-SCLC)

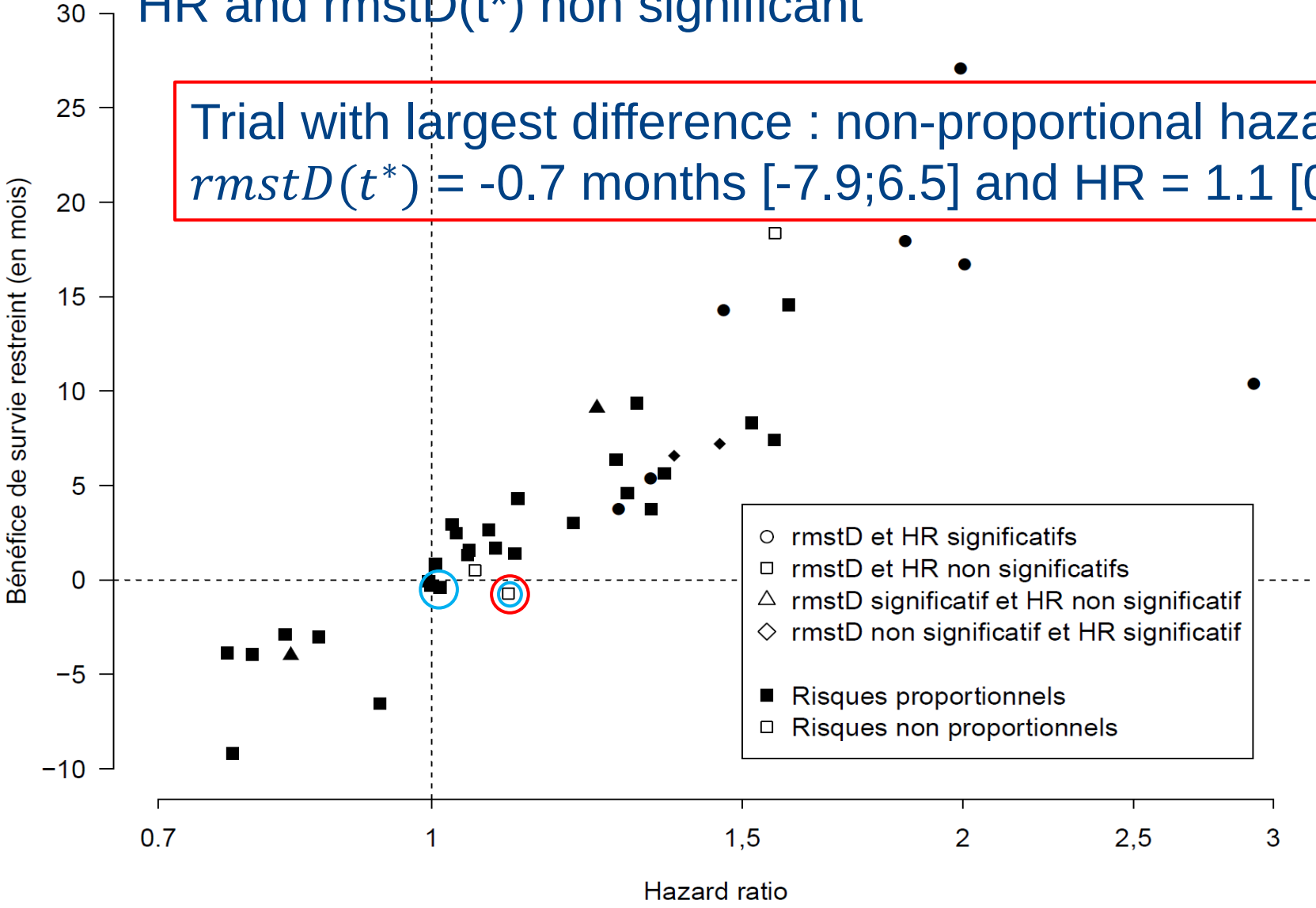
4 trials (10%) same direction of treatment effect but different significativity (2 HRs NS and 2 *rmstD*(*t**) NS)



HR vs *rmstD(t*)* (MAR-LC, MAC-NPC 2 and RTT-SCLC)

2 trials with different direction of treatment effect but both HR and rmstD(t*) non significant

Trial with largest difference : non-proportional hazards
$rmstD(t^*)$ = -0.7 months [-7.9;6.5] and HR = 1.1 [0.8;1.6])



Formules

- Cochran test for heterogeneity:

$$Q = \sum_{j=1}^{J} w_j \left(\hat{\theta}_j - \hat{\theta}_{overall,fixed}\right)^2 \sim \chi^2_{J-1}$$

- Random effecs model:

$$\hat{\theta}_{overall} = \frac{\sum_{j=1}^{J} \hat{\theta}_j w_j}{\sum_{j=1}^{J} w_j}$$

with:

- $w_j = \frac{1}{\widehat{Var}\left(\hat{\theta}_j\right) + \hat{\tau}^2}$
- $\hat{\tau}^2 = \frac{Q - (J-1)}{\sum_{j=1}^{J} w_j - \frac{\sum_{j=1}^{J} {w_j}^2}{\sum_{j=1}^{J} w_j}}$

- $\hat{\tau}^2$ is estimated by the method of moments from DerSimonian and Laird

- I² Higgins : $I^2 = \frac{Q-(J-1)}{Q} \times 100$ with *J* the number of trials