Design, monitoring and analysis of randomized oncology clinical trials based on the restricted mean survival time

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Pfizer Inc.

ASA regulatory Industry Statistics workshop, Sep 25, 2019

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Acknowledgement

- Xiaodong Luo (Sanofi)
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- Pfizer BESPONSA® (inotuzumab ozogamicin) team: Jane Liang White, Tao Wang

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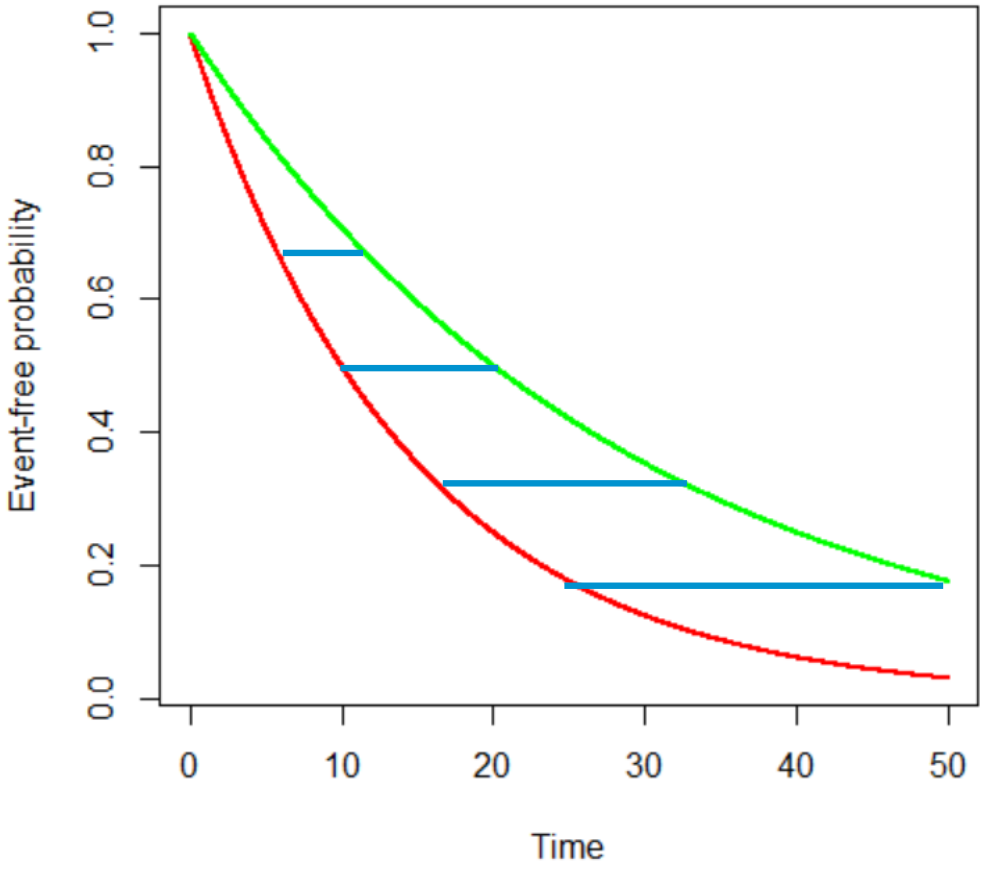
Scientific choice of summary measures for survival analysis



Based on horizontal separation of the curves (percentile of survival distribution):

- Median is the most common percentile
- Infinite number of choices

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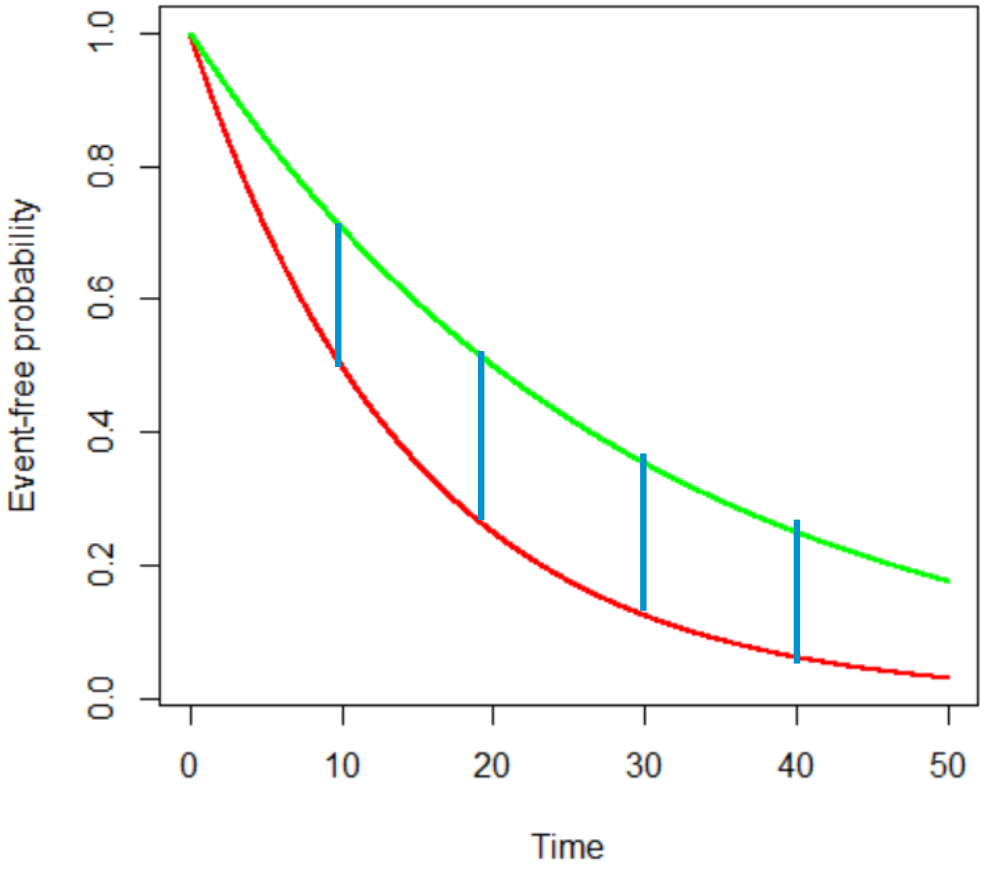
Scientific choice of summary measures for survival analysis



Based on vertical separation of the curves (event-free probability at specific time):

- 1-year survival rate, 5-year survival rate..
- Infinite number of choices

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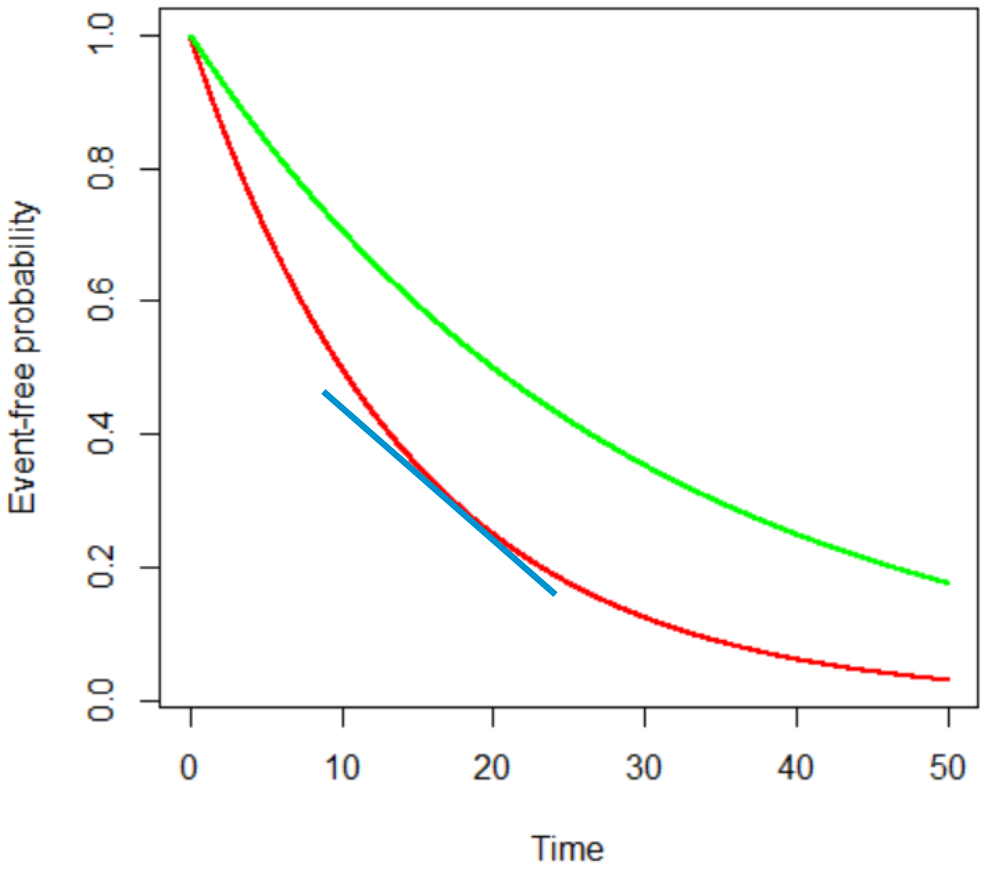

slope of the curves at any particular time point relative to the survival probability at that time point (hazard):

- Relative hazard: hazard ratio
- Average the HR over time with pre-selected weights
  - Under the semi-parametric PH model, the locally optimal weight leads to the LR test
  - Optimality under PH contributes to the popularity of the LR test

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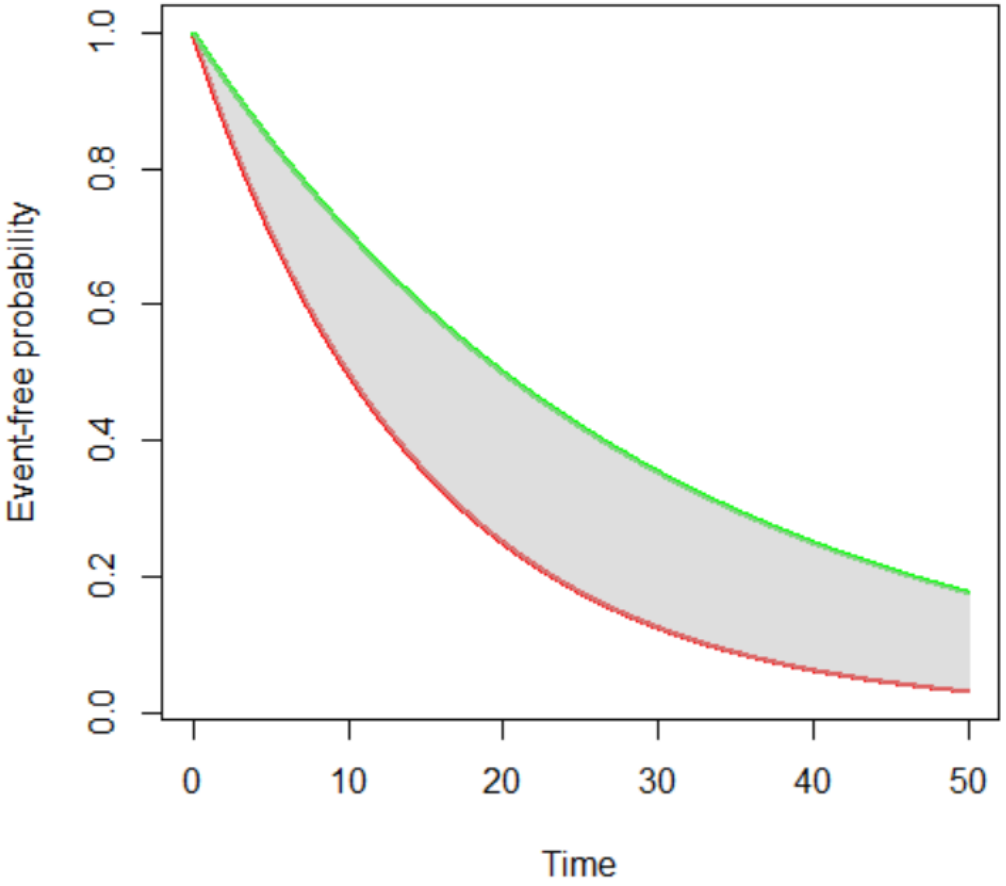
Limitation of Log-rank test, HR (from Cox model), medians, event-free probability

- The log-rank test is optimal under the proportional hazard (PH) assumption, but may lose power under NPH
- The power of log-rank test is event driven
  - Low power with small events; not sensitive to separated flat tails

- Interpretation of HR from Cox model is a problem under NPH
- Only a relative measure of effect

- Median/event-free prob: arbitrary percentile/timepoint
  - Not a global summary measure – does not capture what's before and after

Scientific choice of summary measures for survival analysis



Based on area under the curve (average survival time up to a specific timepoint):

- Restricted mean survival time (RMST)

$$\mathrm{RMST}(\tau) = \int_0^{\tau} S(t)dt$$

- $S(t)$ can be estimated by the KM estimator $\hat{S}(t)$. The variance of the RMST estimator:

$$\sum_{i=1}^{D} \left[\int_{t_i}^{\tau} \hat{S}(t)\, dt \right]^2 \frac{d_i}{Y_i(Y_i - d_i)}$$

# of events at t_i

# of pts at risk at t_i

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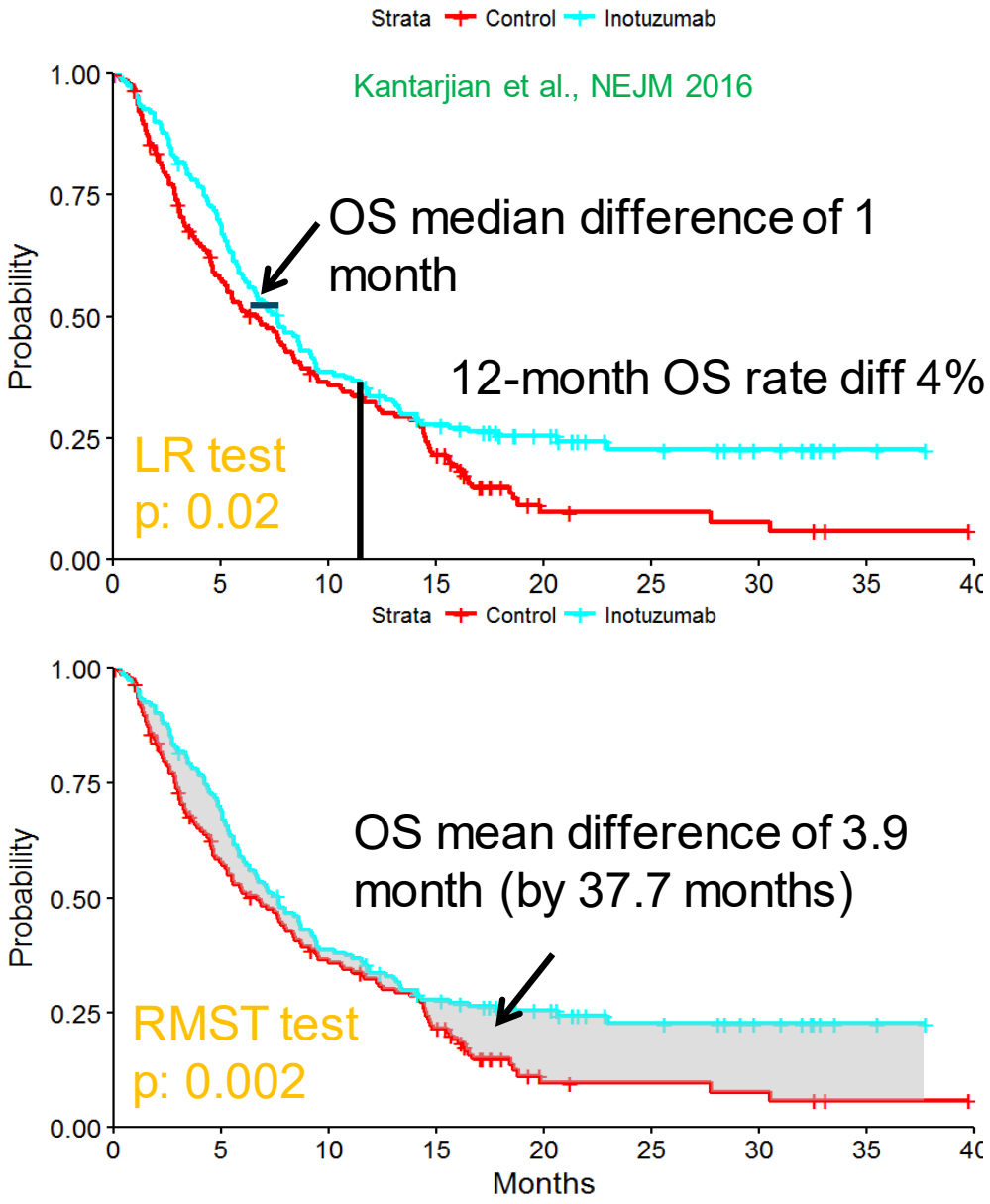
RMST vs. the HR, the median, t-time event-free probability

- **Versus the HR**
  - Clinical interpretation (whether or not PH holds)
  - Non-parametric
  - Dual presentation of relative and absolute effect
- **Versus the median/t-time event-free probability**
  - Informative global summary, no arbitrary percentile/cutoff
  - RMST curve: temporal profile by different truncation points



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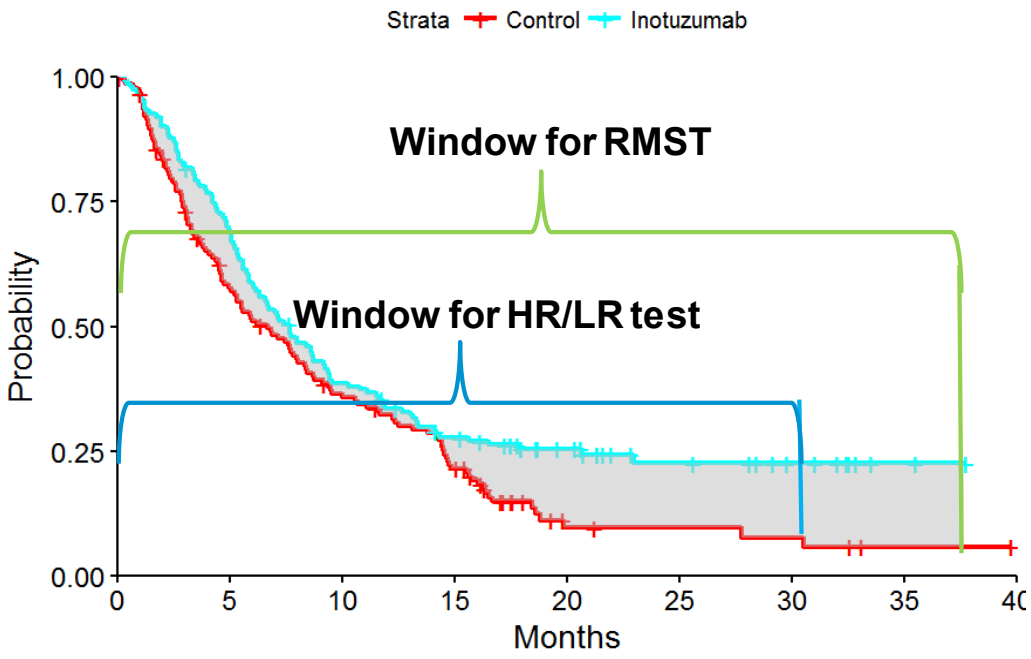
Time-window of RMST vs Time-window of HR/LR test

Under mild conditions on the censoring distribution:

- One can make inference on RMST up to **the last follow-up time (either event or censored) for the arm with shorter follow-up**

In contrast,

- For HR/LR test, one can only use data up to **the minimum of (last event time for any arm, the last follow-up time of the arm with the shorter follow-up)**



Reference:

- Tian L, Jin H, Uno H, Lu Y, Huang B, Anderson K, Wei LJ. On the Empirical Choice of the Time Window for Restricted Mean Survival Time. *To appear in Biometrics*.
- Huang B, Kuan P. (2018). Comparison of the Restricted Mean Survival Time with the Hazard Ratio in Superiority Trials with a Time-to-Event Endpoint, *Pharmaceutical Statistics* 17(3):202-13

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Trial design based on the RMST

Hypothesis Testing

- Assume we are interested in the difference in the RMST between the treatment arm and the control arm at truncation time τ
- H_0: RMST(τ) difference ≤ 0 versus H_1: RMST(τ) difference > 0
- We are interested in detecting a difference of Δ to achieve a desirable level of power

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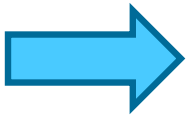
Trial design based on the RMST (cont'd)

- Empirical approach
  - Simulation based
  - Parametric assumption for simulated power

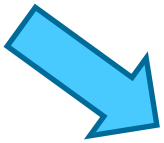
Pak K, Uno H, Kim DH, Tian L, Kane RC, Takeuchi M, Fu H, Claggett B, Wei LJ. Interpretability of Cancer Clinical Trial Results Using Restricted Mean Survival Time as an Alternative to the Hazard Ratio. JAMA Oncology. 2017;3(12):1692-6.

- Analytical approach
  - Simulation + analytic



Royston P, Parmar MK. 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 medical research methodology. 2013 Dec;13(1):152.

  - Fully analytic



Luo X, Huang B, Quan H. Design and monitoring of survival trials based on restricted mean survival times. Clinical Trials. 2019 Aug 26:1740774519871447.

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Analytic method

Luo X, Huang B, Quan H. Design and monitoring of survival trials based on restricted mean survival times. *Clinical Trials*. 2019 Aug 26:1740774519871447

CLINICAL TRIALS

- Design stage – due to the unknown distributions of event, censoring, accrual, the analytic derivation of RMST is intractable.
- Piecewise exponential distribution for event distribution and censoring distribution
- Piecewise uniform for accrual
- Variance-covariance structure derived analytically
- Interim monitoring: RMST(τ_i, t_i), *i=1,..k*

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Notations for the analytic method

Denote the survival distribution, censoring distribution and accrual distribution as S, G, G_E

The estimated RMST at study time t and truncation time τ based on the KM method is

$$\widehat{K}(\tau, t) = \int_0^{\tau} \widehat{S}(u, t) du$$

Consider the following RMST process indexed by both t and τ

$$\mathcal{A} = \{A(\tau, t) = n^{1/2}[\widehat{K}(\tau, t) - K(\tau)] : 0 < \tau \leqslant t\}$$

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Asymptotic property

Theorem. Let the at-risk probabilities $r(\tau, t) = \text{pr}\{Y_i(t) \geqslant \tau\} = S(\tau)G(\tau)G_E(t-\tau)$ for all $0 < \tau \leqslant t$. For any $\eta \in (0, 1)$, define the process $\mathcal{A}_\eta$ as

$$\mathcal{A}_\eta = \{A(\tau, t) \in \mathcal{A} : r(\tau, t) \geqslant \eta\}$$

When n increases, the process $\mathcal{A}_\eta$ converges in distribution to a mean-zero Gaussian process with a variance–covariance structure

$$\begin{aligned} cov\{A(\tau_1, t_1), A(\tau_2, t_2)\} &= B_2(\tau_1 \wedge \tau_2, t_1 \vee t_2) \\ &+ B_1(\tau_1 \wedge \tau_2, t_1 \vee t_2) \times \{K(\tau_1 \vee \tau_2) - K(\tau_1 \wedge \tau_2)\} \end{aligned}$$

$$= B_2(\tau, t), \text{ if } \tau_1 = \tau_2 = \tau, t_1 = t_2 = t$$

where, for any real numbers a and b, $a \wedge b = \min(a, b)$ and $a \vee b = \max(a, b)$ and

$$B_s(\tau, t) = \int_0^\tau \{K(\tau) - K(u)\}^s \frac{\lambda(u)}{r(u, t)} du, \quad s = 1, 2$$

Design Stage: Calculation of RMST and covariance structure

- When data are available, the RMST and var-cov matrix can be calculated based on the previous formulas
  - Estimated from the survival data
- **Challenge**: calculating these quantities at the design stage
- **Solution**: piecewise parametric distribution
  - Piecewise exponential distribution for event distribution and censoring distribution
  - Piecewise uniform distribution for accrual
- R package: PWEALL, available on CRAN

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Power and sample size calculation

For a randomized two-arm trial, we'd like to compare $K_1(\tau)$ and $K_0(\tau)$: $\boldsymbol{H_0: K_1(\tau) = K_0(\tau)}$ vs. $\boldsymbol{H_1: K_1(\tau) > K_0(\tau)}$

The sample size n $(n_0 + n_1)$ and study duration t need to satisfy the following equation

$$\frac{K_1(\tau) - K_0(\tau)}{\left\{\frac{\sigma_1^2(\tau,t)}{n_1} + \frac{\sigma_0^2(\tau,t)}{n_0}\right\}^{1/2}} = q_\alpha + q_\beta$$

where $\sigma_k^2(\tau,t)$ is the variance of $A_k(\tau,t)$ for the treatment group (k=1) and the control group (k=0)

Interim monitoring based on RMST

What if we want to do an interim analysis (or multiple) to stop the trial early?

$$Z_m = \frac{\widehat{K}_1(\tau_m, t_m) - \widehat{K}_0(\tau_m, t_m)}{\left\{\frac{\widehat{\sigma}_1^2(\tau_m, t_m)}{n_1} + \frac{\widehat{\sigma}_0^2(\tau_m, t_m)}{n_0}\right\}^{1/2}}, m = 1, \ldots, M$$

If there is only one interim analysis,

$$\begin{aligned}
&\Pr(Z_1 > C_{1U} | H_0) + \Pr(C_{1L} < Z_1 \le C_{1U}, \\
&\qquad Z_2 > C_2 | H_0) = \alpha \\
&\Pr(Z_1 > C_{1U} | H_1) + \Pr(C_{1L} < Z_1 \le C_{1U}, \\
&\qquad Z_2 > C_2 | H_1) = 1 - \beta.
\end{aligned}$$

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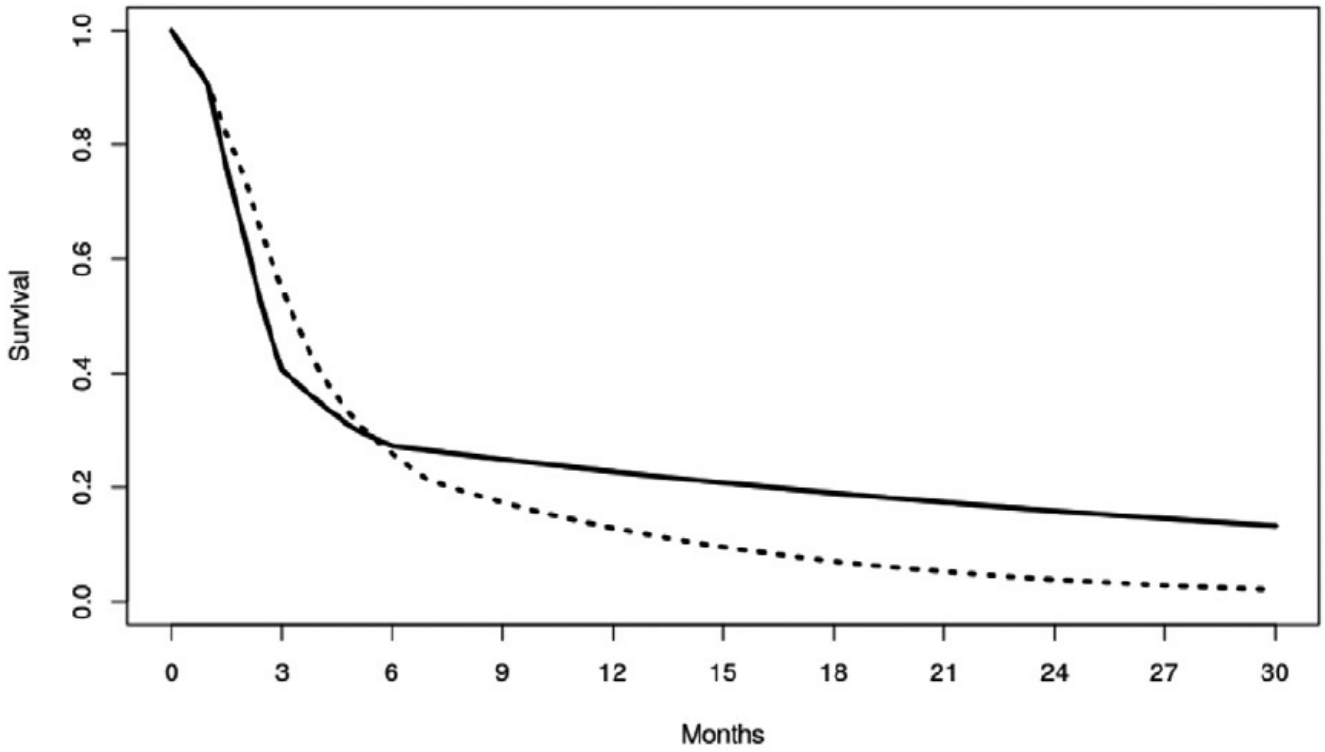
Example: Delayed treatment effect with crossing hazards

- Changepoints: 1, 2, 3, 4, 5, 6, 7, 8, 9 months
- KM curves closely mimic the PFS KM curves in the CM-057 study
- 12m uniform accrual, 10% yearly dropout rate, 1000 pts (1:1)



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Example: Delayed treatment effect with crossing hazards

Calculated powers and simulated powers (RMST vs LR)

Months (t)	RMST Power(c)	RMST Power(s)	LR Power(c)	LR Power(s)
6	0.0	0.0	0.0	0.0
12	4.1	4.1	0.1	0.1
18	48.7	49.3	5.3	5.2
24	86.8	86.8	22.8	22.7
26	92.1	92.5	29.2	29.1
28	95.3	95.8	35.0	34.9
30	97.2	97.5	40.1	40.3

RMST: restricted mean survival time; Power(c): calculated power; Power(s): simulated power.
RMSTs are calculated at cut-points $t - 0.5$.
LR: log-rank test.

Example: Delayed treatment effect with crossing hazards

RMST differences, SE, correlation coefficients of Z_m

Months (t)	n	RMSTd	SE	z value	Correlation coefficient						
					$t = 6$	$t = 12$	$t = 18$	$t = 24$	$t = 26$	$t = 28$	$t = 30$
6	500	−0.32	0.14	−2.27	1	.76	.65	.62	.61	.60	.59
12	1000	0.06	0.29	0.22		1	.82	.79	.78	.78	.77
18	1000	0.72	0.37	1.93			1	.96	.95	.94	.93
24	1000	1.45	0.47	3.07				1	.99	.98	.98
26	1000	1.69	0.50	3.37					1	.99	.99
28	1000	1.92	0.53	3.64						1	.99
30	1000	2.15	0.55	3.87							1

RMSTd: the RMST difference; SE: the standard error of RMSTd; z value: z statistic; RMST: restricted mean survival time.
RMSTs are calculated at cut-points $t - 0.5$.

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Practical considerations for the RMST design and monitoring

- If the interim analyses and the final analysis are triggered by number of events or both num. of events and follow-up time, the the τ_m can be pre-specified as a fixed landmark time $t_m - t_0$, where t_0 is a constant, or the minimax follow-up time.
- The number of time intervals and hazard rates for the piecewise exponential distribution can be based on prior data, expert opinions
- Similar to the LR test, futility analysis at an early study time should be taken with caution, in particular when there is a high likelihood of late separation of KM curves
  - Non-binding?
- A wide range of scenarios should be evaluated at the design stage

Broader acceptance in the oncology community

JOURNAL OF CLINICAL ONCOLOGY

Moving Beyond the Hazard Ratio in Quantifying the Between-Group Difference in Survival Analysis

Hajime Uno, Brian Claggett, Lu Tian, Eisuke Inoue, Paul Gallo, Toshio Miyata, Deborah Schrag, Masahiro Takeuchi, Yoshiaki Uyama, Lihui Zhao, Hicham Skali, Scott Solomon, Susanna Jacobus, Michael Hughes, Milton Packer, and Lee-Jen Wei

JAMA Oncology July 2016

Describing Differences in Survival Curves

Rick Chappell, PhD; Xiaotian Zhu, PhD

Annals of Internal Medicine RESEARCH AND REPORTING METHODS

Alternatives to Hazard Ratios for Comparing the Efficacy or Safety of Therapies in Noninferiority Studies

Hajime Uno, PhD*; Janet Wittes, PhD*; Haoda Fu, PhD*; Scott D. Solomon, MD; Brian Claggett, PhD; Lu Tian, ScD; Tianxi Cai, ScD; Marc A. Pfeffer, MD, PhD; Scott R. Evans, PhD; and Lee-Jen Wei, PhD

JOURNAL OF CLINICAL ONCOLOGY

Comparison of Treatment Effects Measured by the Hazard Ratio and by the Ratio of Restricted Mean Survival Times in Oncology Randomized Controlled Trials

Ludovic Trinquart, Justine Jacot, Sarah C. Conner, and Raphaël Porcher

JOURNAL OF CLINICAL ONCOLOGY

Restricted Mean Survival Time: An Obligatory End Point for Time-to-Event Analysis in Cancer Trials?

Roger P. A'Hern

JAMA Oncology | Original Investigation

Interpretability of Cancer Clinical Trial Results Using Restricted Mean Survival Time as an Alternative to the Hazard Ratio

Kyongsun Pak, BPharm; Hajime Uno, PhD; Dae Hyun Kim, MD; Lu Tian, ScD; Robert C. Kane, MD; Masahiro Takeuchi, ScD; Haoda Fu, PhD; Brian Claggett, PhD; Lee-Jen Wei, PhD

Annals of Oncology

Treatment effects measured by restricted mean survival time in trials of immune checkpoint inhibitors for cancer

F Liang, S Zhang ✉, Q Wang, W Li

Article Type: Editorial Annals of Oncology

TITLE: ADDING A NEW ANALYTICAL PROCEDURE WITH CLINICAL INTERPRETATION IN THE TOOL BOX OF SURVIVAL ANALYSIS

H. Uno[1*], B. Claggett[2*], L. Tian[3], H. Fu[4], B. Huang[5], D. H. Kim[6,7 **], L.J. Wei[8 **]

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RMST extension (multi-state survival analysis)

A composite endpoint of duration of response in the ITT population

Research Letter

JAMA Oncology

June 2018

Evaluating Treatment Effect Based on Duration of Response for a Comparative Oncology Study

Bo Huang, PhD[1]; Lu Tian, ScD[2]; Enayet Talukder, PhD[1]; Mace Rothenberg, MD[3]; Dae Hyun Kim, MD, ScD[4]; Lee-Jen Wei, PhD[5]

Author Affiliations | Article Information

JAMA Oncol. 2018;4(6):874-876. doi:10.1001/jamaoncol.2018.0275

- Avelumab+axitinib EMA submission
- ASCO-GU (2019)
- ESMO (2019)

JOURNAL OF CLINICAL ONCOLOGY

Treatment-Free Survival: A Novel Outcome Measure of the Effects of Immune Checkpoint Inhibition—A Pooled Analysis of Patients With Advanced Melanoma

September 9, 2019:

Meredith M. Regan, ScD[1,2]; Lillian Werner, MS[1]; Sumati Rao, PhD[3]; Komal Gupte-Singh, PhD[3]; F. Stephen Hodi, MD[1,2]; John M. Kirkwood, MD[4]; Harriet M. Kluger, MD[5]; James Larkin, PhD, FRCP[6]; Michael A. Postow, MD[7,8]; Corey Ritchings, PharmD[3]; Mario Sznol, MD[9]; Ahmad A. Tarhini, MD, PhD[10]; Jedd D. Wolchok, MD, PhD[7,8]; Michael B. Atkins, MD[11]; and David F. McDermott, MD[2,12]

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Summary

- Conventional methods for TTE endpoints such as HR/median/LR tests have limitations
- RMST is an alternative method that may be more appealing in some scenarios
  - Traditionally used as a secondary/supportive analysis
- We develop the statistical framework for the design, monitoring and analysis of survival data based on RMST
- RMST can be extended to multi-state problems. Further research is warranted.

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BACK UP SLIDES

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Asymptotic property

Corollary Assume all the elements $A(\tau, t)$ mentioned below belong to $\mathcal{A}_\eta$. Suppose $\tau_1 \leqslant \tau_2$ and $t_1 \leqslant t_2$.

C4: The conditional distribution $\hat{K}(\tau_2, t_2)$ given $\hat{K}(\tau_1, t_1)$ is a normal distribution with mean μ_c and variance σ_c^2, where

$$\mu_c = K(\tau_2) + \left\{\hat{K}(\tau_1, t_1) - K(\tau_1)\right\} \times \frac{B_2(\tau_1, t_2) + \{K(\tau_2) - K(\tau_1)\}B_1(\tau_1, t_2)}{B_2(\tau_1, t_1)}$$

$$\sigma_c^2 = \frac{B_2(\tau_2, t_2)}{n} - \frac{[B_2(\tau_1, t_2) + \{K(\tau_2) - K(\tau_1)\}B_1(\tau_1, t_2)]^2}{nB_2(\tau_1, t_1)}$$