Study Design and Analysis in Late-Stage Cancer Immunotherapy Trials

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Disclosure

- Employment: currently employed by Bristol-Myers Squibb as Head of Global Biometric Sciences in Medical and Market Access

- The views expressed in this presentation are personal based on my experience and do not necessarily reflect the views of Bristol-Myers Squibb

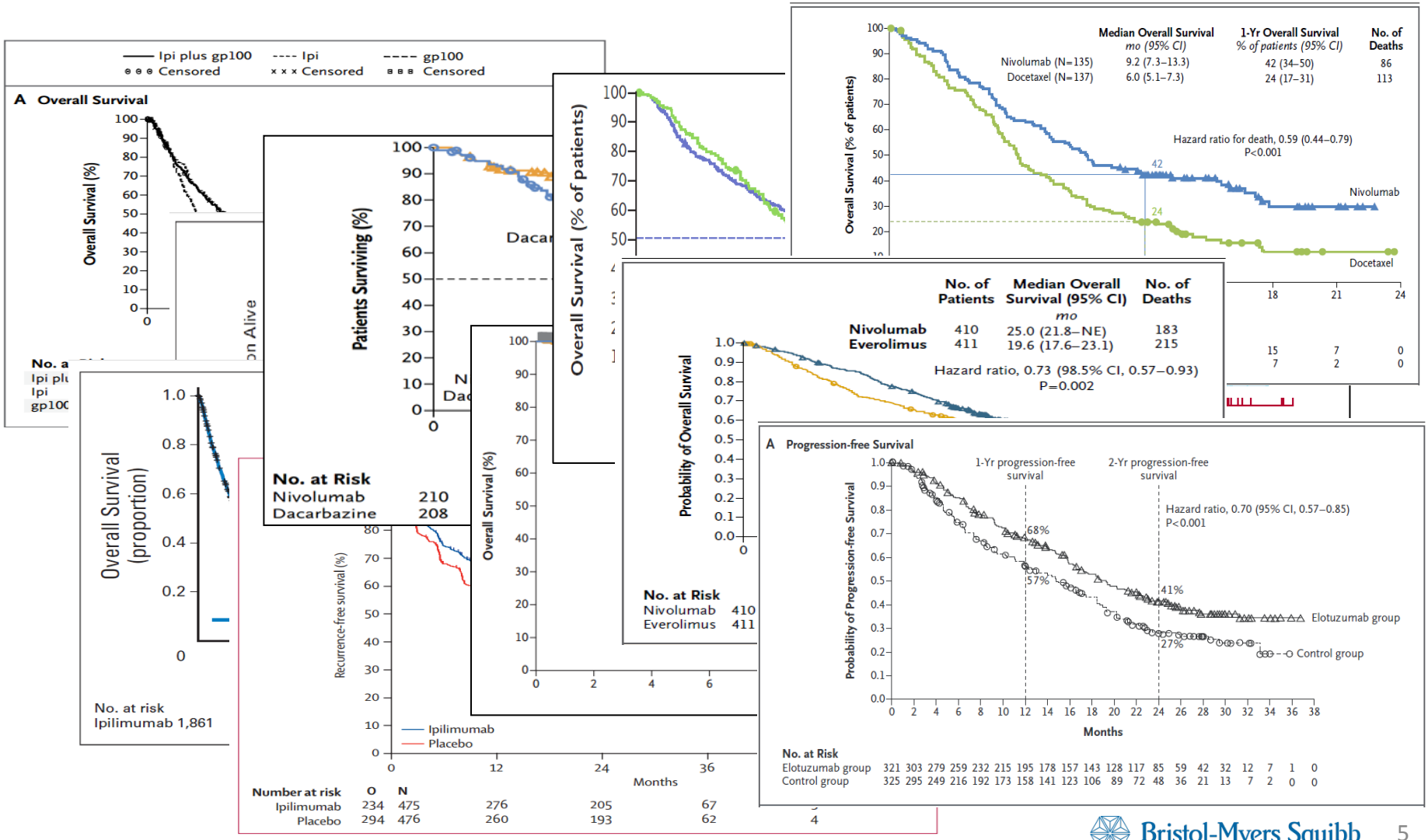
Outline

- Challenges in immuno-oncology
- Examples of efficacy outcomes in phase III randomized cancer immunotherapy trials
- Survival kinetics
- Impact caused by study design deviations
- Statistical consideration
  - Study Design
  - Statistical Analysis
- Concluding remarks

Challenges in Immuno-Oncology

- Biomarkers
- Sequence or combinations of immunotherapies
- Endpoints
- Subgroup
- Study Design
- Statistical Analysis
- Relative effectiveness

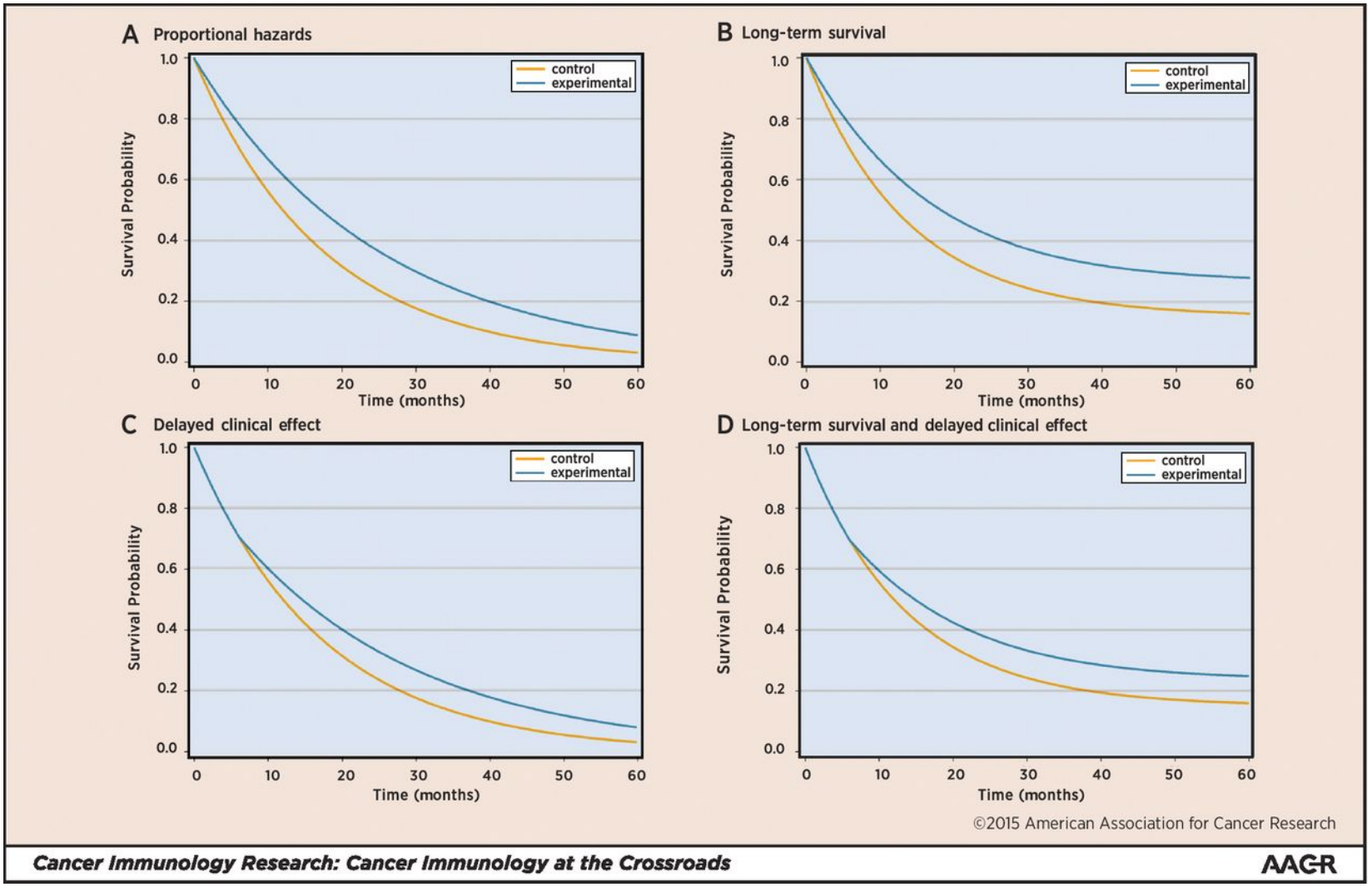
Examples from Phase III Cancer Immunotherapy Trials



Late-Stage Study Design (Time to Event as Primary Endpoint)

Conventional Late-Stage Study Design	Customized Late-Stage Study Design
▪ Exponential decay ▪ Proportional hazards ▪ Interim analysis with 50% events ▪ Event-driven ▪ Log-rank test	▪ Non-Exponential decay ▪ Nonproportional hazards ▪ Interim analysis with >50% events ▪ Time/event-driven ▪ Weighted log-rank test

Survival Kinetics



Cancer Immunology Research: Cancer Immunology at the Crossroads

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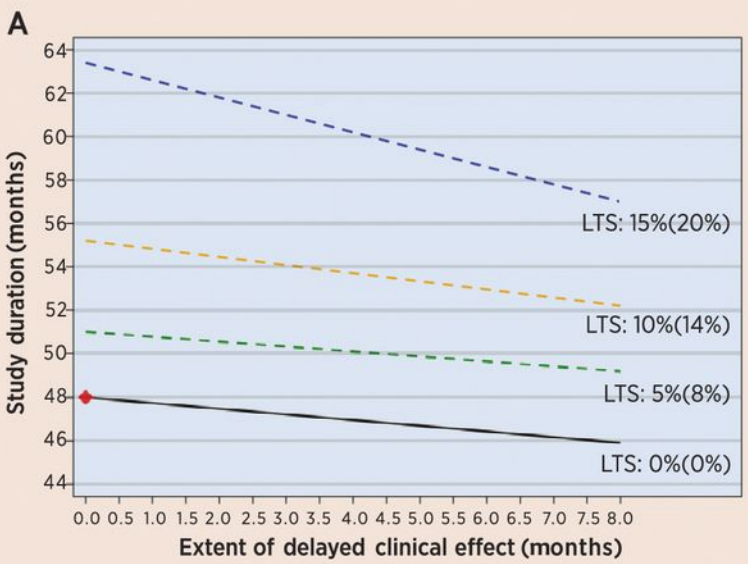
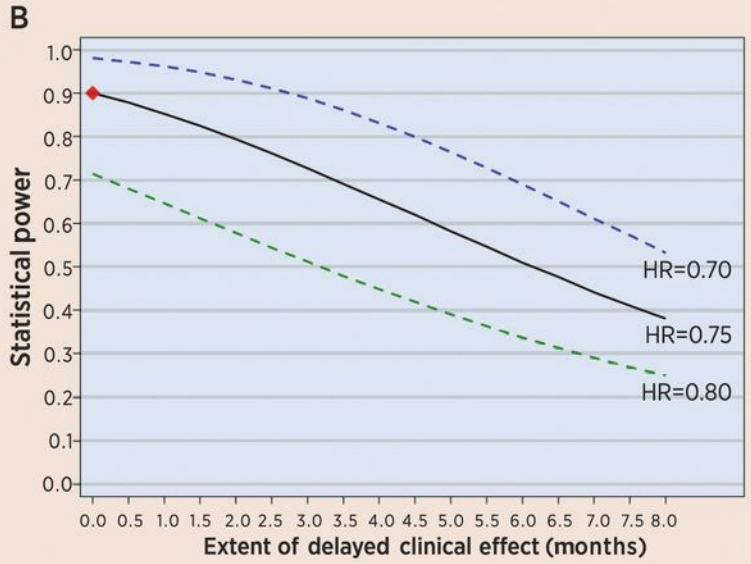
Impact Caused by Study Design Deviation





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Interim Analysis Strategy and Management

- Necessity of interim analysis
  - Interim analysis vs. final analysis only
- Timing of interim analysis
  - Information fraction (% of target events reached)
  - Early vs. late
- Population included in the interim analysis
  - All patients vs. a subset of patients
- Type of interim analysis
  - Superiority vs. futility

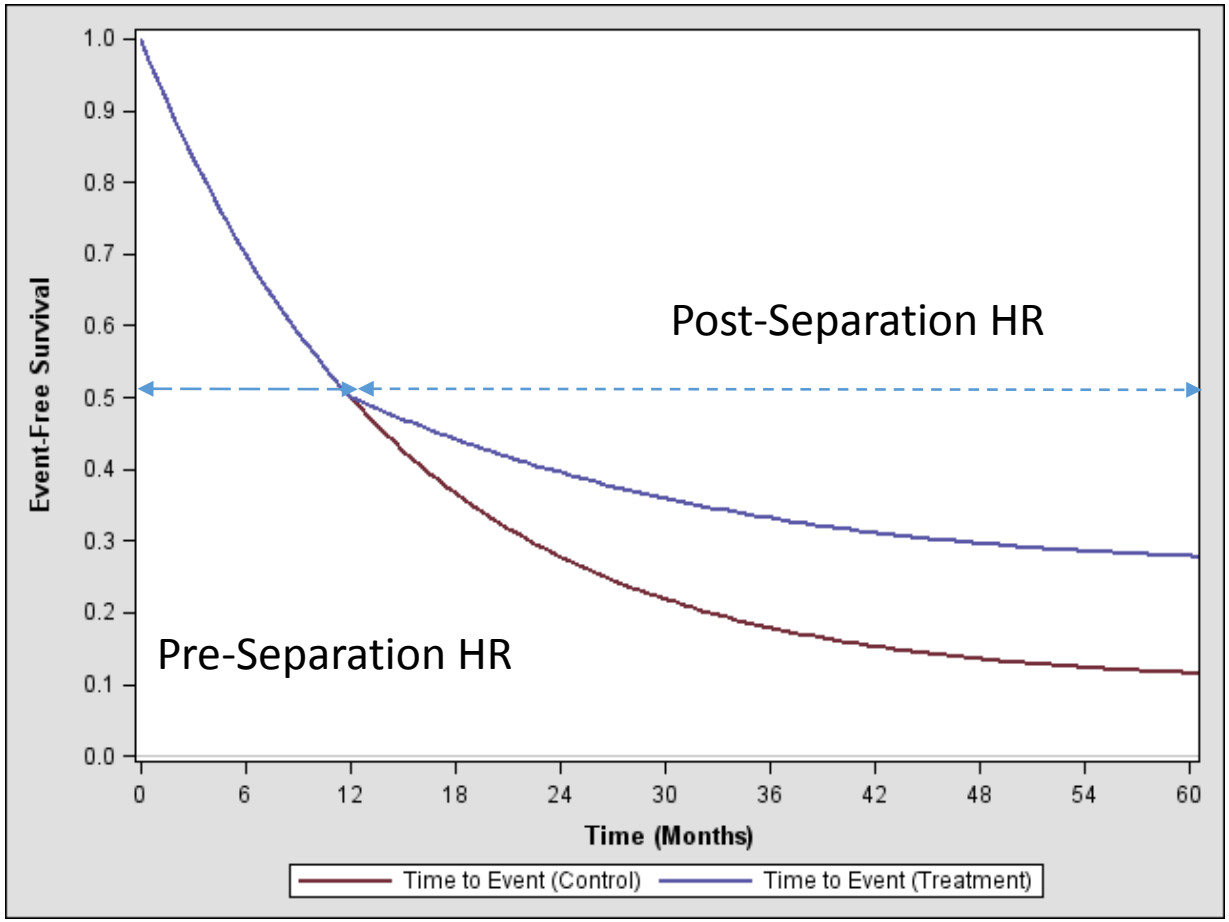
Lessons Learned (Event-Driven vs. Time-Driven Design)

- Ipilimumab in front-line metastatic melanoma
  - Estimated study duration: 3 years
- 3 years after study start
  - ~85% of anticipated number of events
  - Decreasing event rate
  - ~84% statistical power
- Study continued for another 1.5~2 years for the remaining 15% of number of events
- Unblinding occurred with a couple events short of design

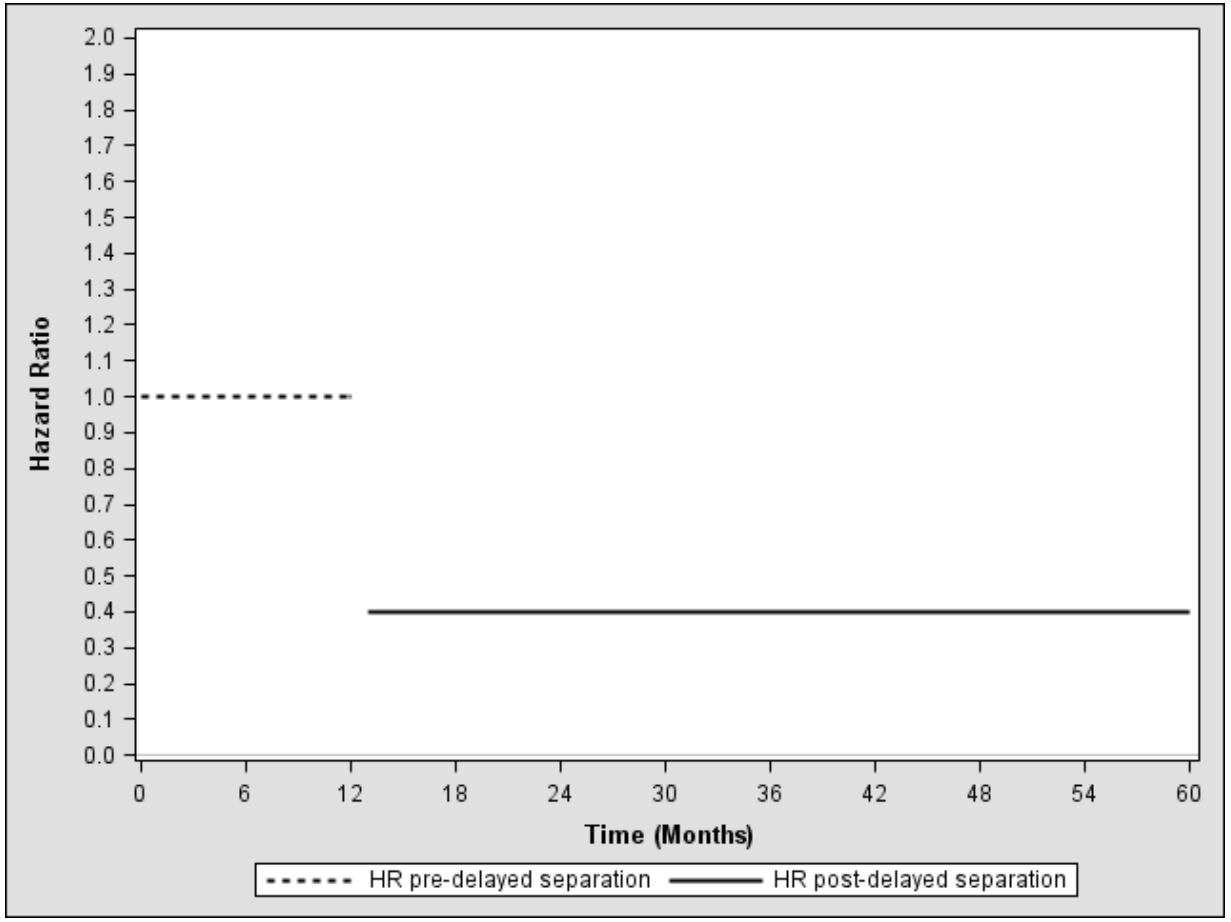
Weighted Log-Rank Test

- An alternative test procedure to be considered in study design
- WLR is more powerful than LR (log-rank) in the presence of delayed clinical effect
- Choice of weights depends on
  - Accumulated knowledge of class of therapy
  - Timing of delay
  - Thorough assessment via statistical simulations

Hazard Ratio



Change in Hazard Ratio



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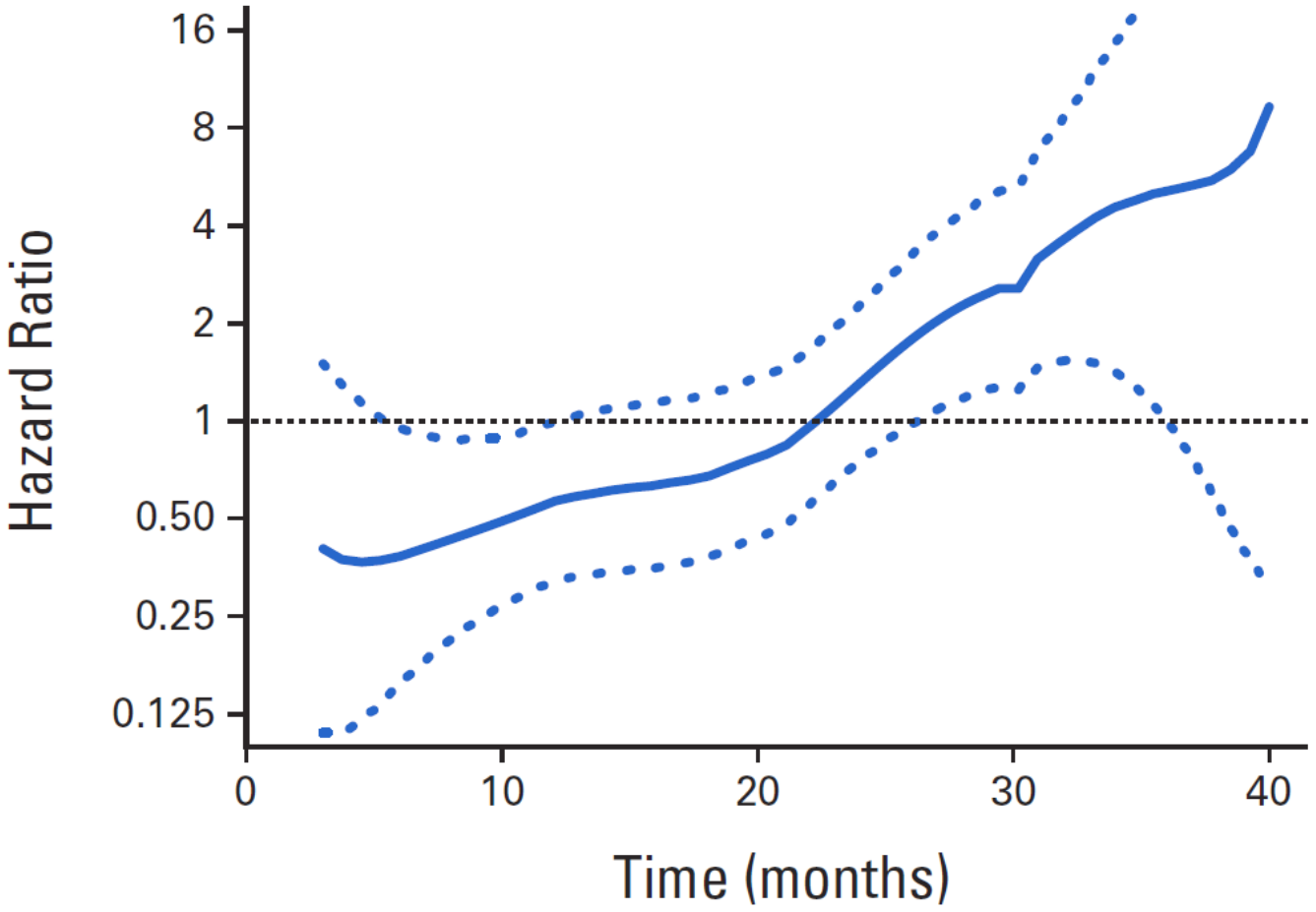
Change in Hazard Ratio (ECOG E4A03)



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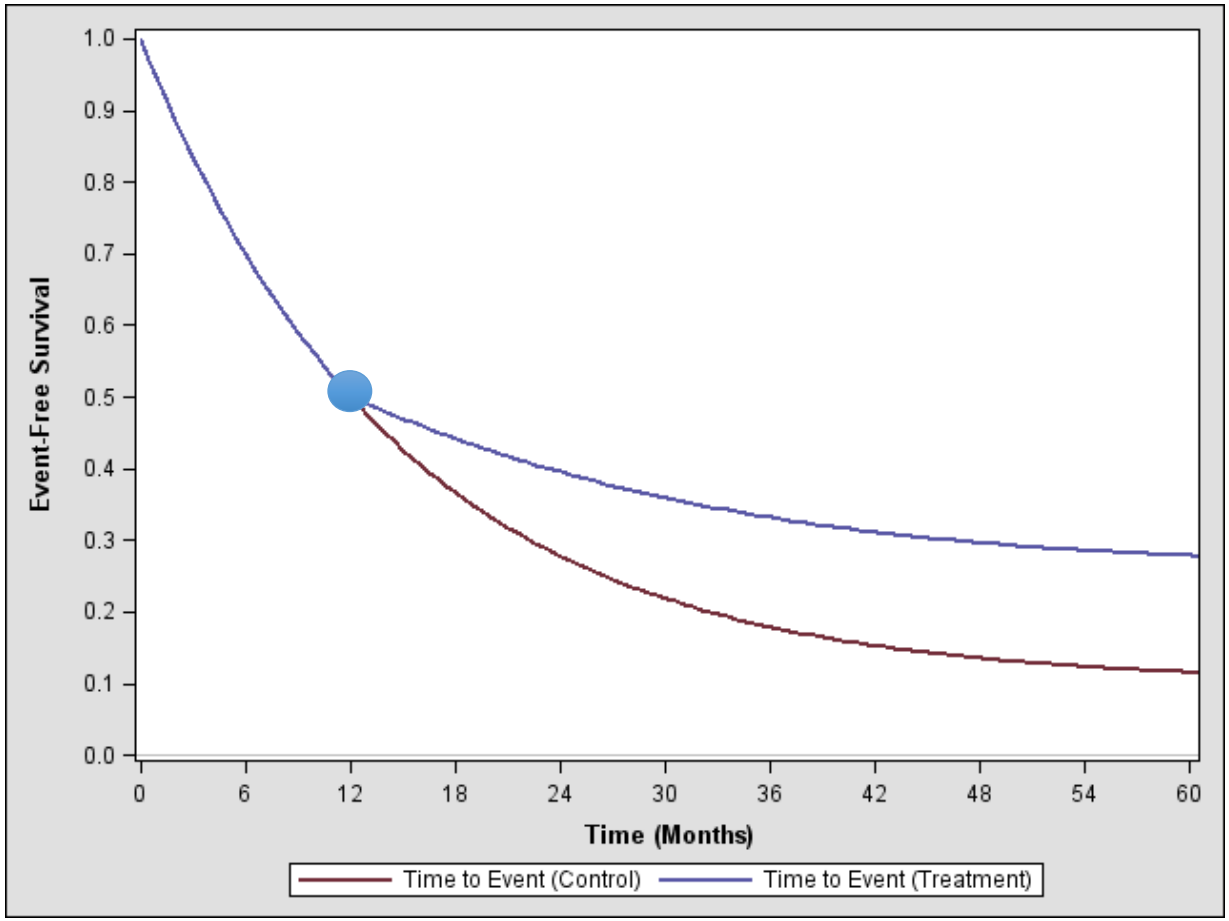
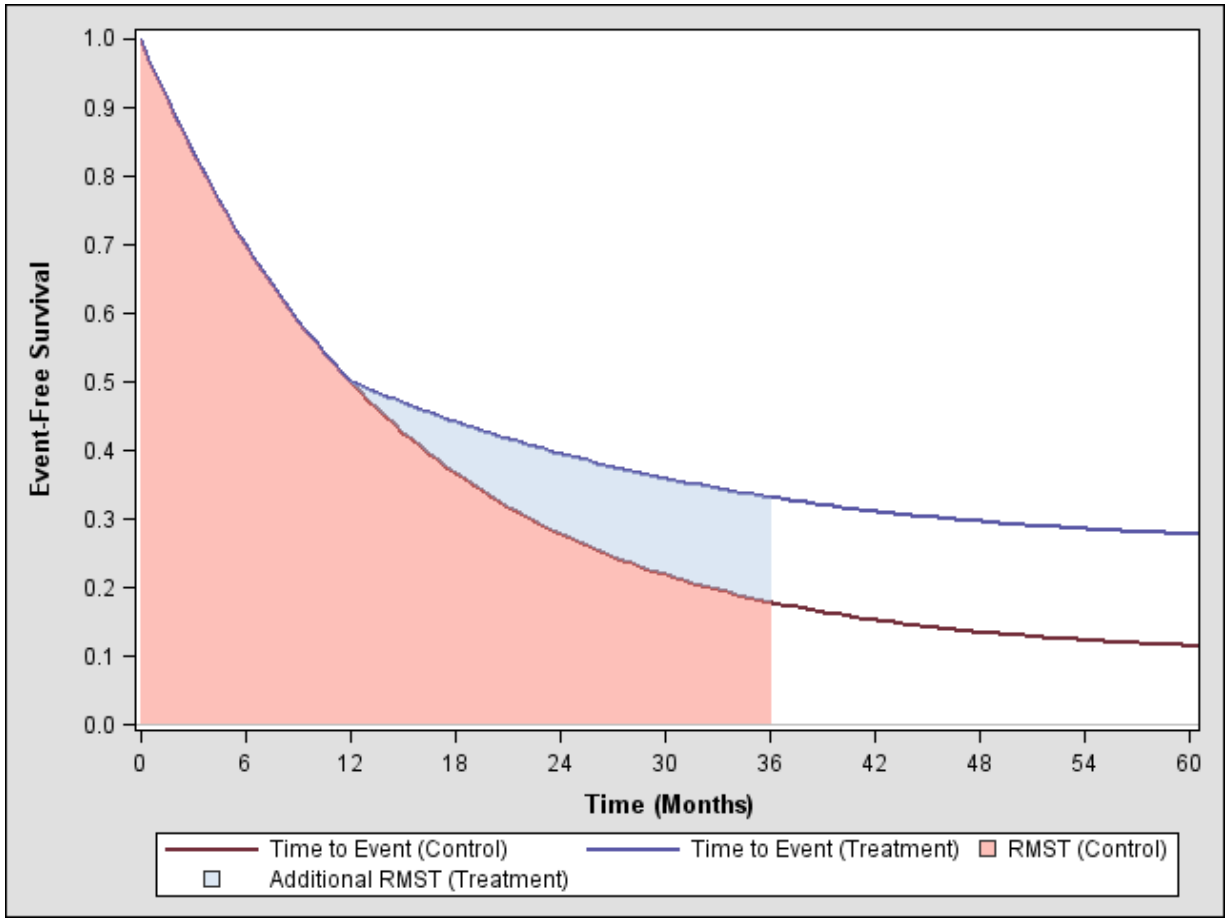
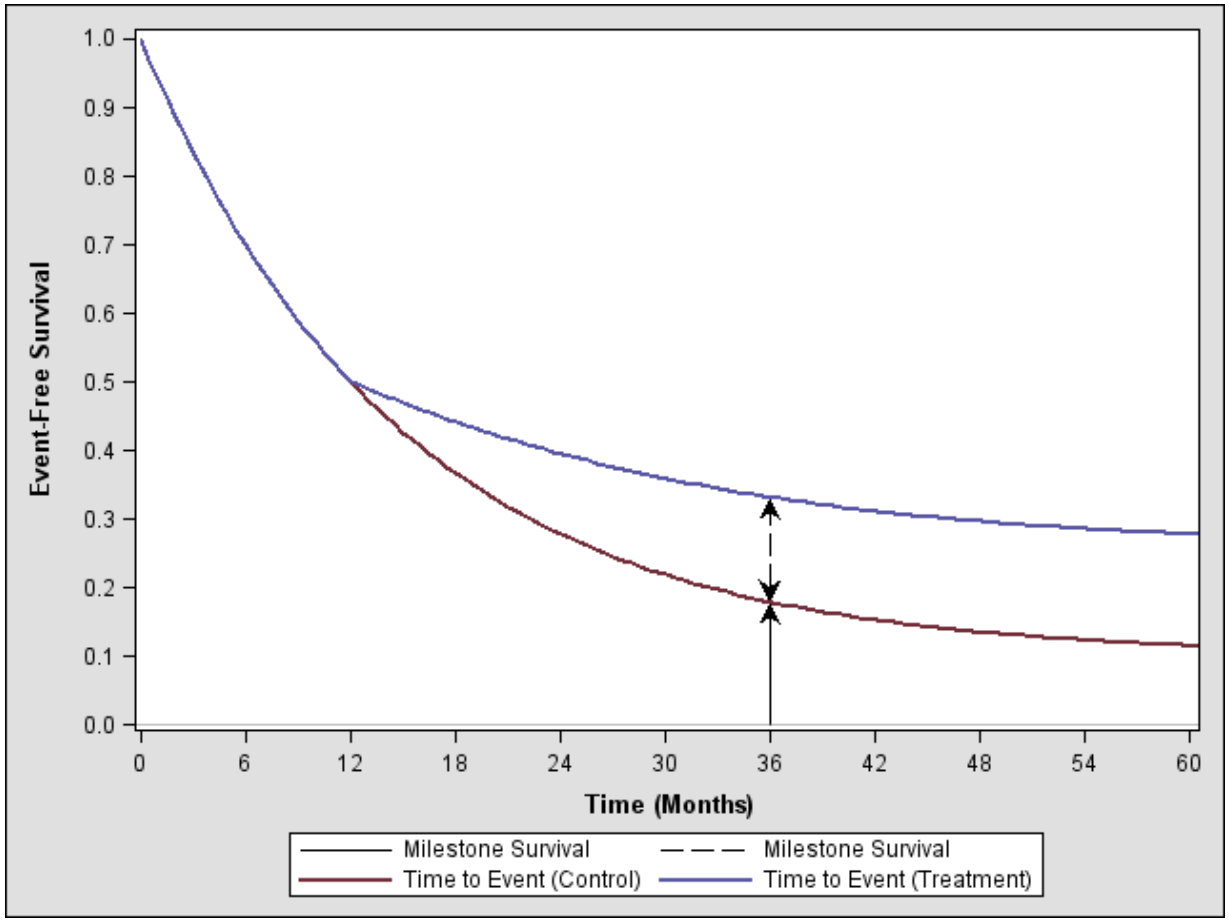
Median Survival Time



Restricted Mean Survival Time



Milestone Survival



Concluding Remarks

- Customized statistical approach needed in cancer immunotherapy research
- Unique survival kinetics, i.e., delayed effect and long-term survival need to be built into design and analysis
- Time-driven vs. Event-driven study design
- Weighted log-rank test is a viable alternative
- Median time may not be the optimal summary of treatment effect
- Other informative summary statistics: change in hazard ratio, milestone survival or restricted mean survival
- Designs using other endpoints possible, such as milestone survival or restricted mean survival time

Reference

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