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
- Exponential decay
- Proportional hazards
- Interim analysis with 50% events
- Event-driven
- Log-rank test

### Customized Late-Stage Study Design
- Non-Exponential decay
- Nonproportional hazards
- Interim analysis with >50% events
- Time/event-driven
- Weighted log-rank test
Survival Kinetics

A. Proportional hazards

B. Long-term survival

C. Delayed clinical effect

D. Long-term survival and delayed clinical effect

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Cancer Immunology Research: Cancer Immunology at the Crossroads
Impact Caused by Study Design Deviation

Cancer Immunology Research: Cancer Immunology at the Crossroads
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

Post-Separation HR

Pre-Separation HR

Time (Months)

Event-Free Survival

Time to Event (Control)  Time to Event (Treatment)
Change in Hazard Ratio
Change in Hazard Ratio (ECOG E4A03)
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


• Royston, P and Palmer, MKB. (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. BMRM, 13:152.

