Advances in Time to Event Analyses in Clinical Trials

Pralay Mukhopadhyay

Otsuka America Pharmaceuticals, Inc.

15th Annual Conference on Statistical Issues in Clinical Trials

April 17th, 2023

Otsuka

NPH and 5-STAR (Devan Mehrotra)

- Standard tests (e.g., LRT) do not leverage ‘structured’ prognostic risk heterogeneity commonly anticipated in RCTs

- No (or inadequate) prognostic risk stratification can create non-PH conditions

- A 5-step approach is proposed that involves blinded “data driven” prognostic factor identification followed by treatment estimation in each risk stratum, and aggregating the overall effect

- Method appears to meaningfully improve power over standard tests based on multiple case studies and simulations

NPH and 5-STAR (Devan Mehrotra)

A few points to consider:

- Use of blinded data from same study to identify prognostic significance may give the perception of “data dredging”

- Not all sources of heterogeneity is prognostic in nature. Predictive factors can be source of NPH. Will be useful to explore this test in areas such as IO where NPH is prevalent

- Will data driven prognostic factors identified from study always make clinical/biological sense?

- Will replicability of study results be a problem?

- Will the method be easy to explain to clinicians/patients? Should it be used as primary or as a sensitivity analyses?

Design of IO trials under NPH (Zhenzhen Xu)

- Important to consider possible treatment delay during design stage

- Piecewise Weighted Log Rank Test (PWLRT) can be effective in preserving power loss
  - APPLE, SEPPLE

- Still leads to power loss if delay is mis-specified. Therefore, use generalized PWLRT (assumes random lag effect instead of fixed)
  - APPLE+, SEPPLE+

- Different patterns of treatment response can lead to heterogeneity and NPH in IO

- Therefore, incorporate response patterns (using Mixture model) to estimate treatment effect, test hypothesis, and compute sample size/power (PRIME+)

Design of IO trials under NPH (Zhenzhen Xu)

A few points to consider:

- Will be nice to understand power loss with GPWLRT under crossing KM curve

- May still be relevant to consider alternate tests to LRT (e.g., MaxCombo, MWLRT) during analysis to protect from misspecification of NPH pattern during design (e.g., crossing vs. delay)

- Important to identify biomarker signatures of resistance to IO therapy.
  - Can help with understanding underlying biological causes of rapid progression and therefore help better tailor treatments for patients (e.g., combination vs. monotherapy) and reduce NPH
  - Need availability of large number of datasets; potential use of AI/ML
  - A collaborative effort amongst pharma, FDA, consortiums can go a long way in this regard

Analyzing DOR in Oncology Trials (Lu Tian)

- Important to understand what is the question of interest. E.g.,
  - What is the chance of responding?
  - How soon will a patient respond?
  - How long will the response last?
- ORR still relevant despite cumulative ORR increases when many patients have stopped responding

- PBIR and RMDOR have clinically meaningful interpretation and addresses some of the statistical pitfalls of estimating DOR using standard KM estimates

- Important to consider what's most relevant from a physician and patient's perspective. What information can be included in the label.
  - A thorough evaluation of how PBIR and RMDOR compares with DOR can help with better adoption in practice