Randomized Clinical Trial Design and Analysis Considerations in Neo-adjuvant Treatment

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Regulatory Approval Pathways

1. Accelerated Approval in serious or life-threatening disease: based on ”surrogate” endpoint reasonably likely to predict clinical benefit; improvement over available therapy; required confirmation of clinical benefit
   - Comparative efficacy
   - “surrogate” not necessarily validated; example: objective response rate in advanced stage disease setting with monotherapy in single arm studies
   - Uncertainty in the clinical benefit to patients

Regulatory Approval Pathways

2. Regular Approval: based on Clinical benefit (Survival benefit/patient benefit, or benefit in a validated surrogate marker).
   - Should be better than placebo
   - Validation of surrogate endpoint needed
   - Some intermediate endpoints are considered as clinical benefit endpoints; example: PFS in CML, DFS in adjuvant breast cancer, etc.

BEST (Biomarkers, EndpointS, and other Tools) Resource

(https://www.ncbi.nlm.nih.gov/books/NBK453485/)

- An endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint **is expected to be correlated** with an endpoint intended to assess clinical benefit in clinical trials, but **without sufficient clinical data** to show that it is a validated surrogate endpoint. Such endpoints may be used for accelerated approval for drugs and potentially also for approval or clearance of medical devices.

BEST (Biomarkers, EndpointS, and other Tools) Resource

(https://www.ncbi.nlm.nih.gov/books/NBK453484/)

- An endpoint supported by a clear mechanistic rationale and clinical data providing strong evidence that **an effect on the surrogate endpoint predicts a specific clinical benefit**. A validated surrogate endpoint can be used to support marketing approval of a medical or tobacco product in a defined context without the need for additional studies to demonstrate the clinical benefit directly.

Before Designing A Clinical Trial

- What is the definition of EFS?
- Is pCR associated with long-term clinical benefit (EFS and OS)?
- Which pCR definition is best associated with long-term clinical benefit?
- What magnitude of pCR improvement will predict long-term clinical benefit?
- Established treatment effect in advanced setting

Randomized Clinical Trial Design

Assuming pCR is well defined and acceptable as an endpoint for accelerate approval,

- Which population? – stage, molecularly defined, etc.
- What definition of EFS?
- What difference in pCR is meaningful?
- What difference in EFS/OS is meaningful?
- Post surgery adjuvant therapy?
- Single trial model or Two trials model? – Confirmation of benefit needed after accelerated approval

Single Trial Model

- pCR – intermediate endpoint to seek accelerated approval
- EFS – primary endpoint to confirm clinical benefit in the same trial
- Size the trial to demonstrate benefit in EFS
- Based on the meaningful difference in pCR to be detected, plan final analysis based on pCR
  - Note: a much smaller sample size needed to show improvement in pCR compared to improvement in EFS
- Re-randomization after surgery?

Two Trials Model

- One neo-adjuvant RCT to demonstrate meaningful, significant treatment effect based on pCR to seek accelerated approval
- A second post-surgery RCT to confirm/demonstrate meaningful, significant clinical benefit based on EFS/OS
  - Adjuvant RCT in the same population as the neo-adjuvant indication with/without any neo-adjuvant therapy
  - Adjuvant RCT in patients who did not achieve pCR from any neo-adjuvant therapy
- Two trials may be concurrently ongoing or staggered

Analysis Considerations

- Event before surgery
- Drop-out at any time during the study – event or censored observation?
- Differences in post-surgery therapy
- Timing of analyses
  - Interim or final
  - Recurrence early vs. late (early separation vs. late separation of survival curves

Concluding Remarks

- Consistent and reproducible definition of pCR and EFS
- Consensus on meaningful treatment effect
- Consideration of second randomization
- Clinical trial design options – pros and cons
- Treatment vs. Treatment sequencing
- Confirmation of clinical benefit – chance of withdrawal of AA

Thank You!


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