The 9th Data Science Roundtable Discussion

Innovative Trial Design in Practice: Lessons from Virtual Cases

Note: The views and opinions expressed in this presentation are those of the presenter and do not necessarily reflect the official policy or position of any affiliated organization.

Purpose of discussion

- To evaluate the advantages and limitations of innovative clinical trial designs (e.g., external controls, surrogate endpoints) through the use of virtual cases in settings where randomized controlled trials (RCTs) are not feasible.
  - Case 1: Development of a new drug for high-risk neuroblastoma using external control
  - Case 2: Development of a new drug for multiple myeloma using surrogate endpoints

- To create opportunities for young statisticians to gain practical experience through simulated regulatory discussions and innovative trial design exercises.

Background of virtual case 1

- Development of a new drug for high-risk neuroblastoma following consolidation therapy, which is performed to prevent the recurrence.
  - Neuroblastoma is a pediatric cancer, with 150 patients diagnosed in Japan each year.
  - Consolidation therapy is performed on 20 to 30 neuroblastoma patients in Japan each year.
- The efficacies of two investigational drugs for high-risk neuroblastoma were evaluated in confirmatory studies using external control data.
  - Eflornithine (IWILFIN)
    - External control data is from ANBL0032 study, which included patients enrolled in the US between 2009 and 2015 and they were followed up for 10 years.
  - ^{131}I-Omburtamab
    - External control data is Central German Childhood Cancer（CGCC）registry, which included patients diagnosed in the Germany between 1990 and 2015.

Background of virtual case 1

- Virtual drug called yokunarumab is new compound.
  - Yokunarumab has not been approved for other diseases.
  - Phase I study of yokunarumab was performed, and MTD was defined.
- Sample size required for randomized clinical trial (RCT) is 332 patients in total.
  - Randomized ratio is 1:1
  - Primary endpoint is Event Free Survival (EFS)
  - 2-year EFS rate in control group is assumed to be 45%, based on ANBL0032 study result.
  - 2-year EFS rate in investigational drug group is to be assumed 60% (Hazard ratio of 0.64)
  - Significant level is 5% for both sides, and Power is 80%
- ANBL0032 study and CGCC registry are available as external control data.

We discussed the best plan for developing yokunarumab under this situation.

	Detail
Phase	3
Estimand	・Treatment : Yokunarumab add-on to standard of care (SoC) ・Population : High-risk neuroblastoma ・Variable : EFS ・Population-level summary : Hazard ratio ・Intercurrent event : Not considered
Study design	・Multi-regional clinical trial ・Hybrid control design that combines concurrent control (CC) data in RCT and ANBL0032 study data as external control (EC) by using Bayesian analysis. ⇒ Comparative analysis using propensity score with an external control cannot evaluate the effects of background differences between Japanese and non-Japanese participants in the control, and it cannot evaluate the effects of temporal shifts between CC and EC. ・Initial randomized ratio is 1:1, but it changes depending on the similarity between the CC and EC data at interim analyses. ・Randomized stratification factor is region. ・Sample size is approximately 200.

Assumption	Points to consider when interpreting results
・SoC does not change during the trial. ・Backgrounds of the study participants are be similar between CC and EC. ・Treatment effects are consist across regions. ・Temporal shifts between CC and EC are negligible.	Assumptions of background similarity, consistent treatment effects, and the ignorability of temporal shifts should be evaluated based on the results. If these assumptions are not met, it will be difficult to interpret the treatment effect for the Japanese population.

Background of virtual case 2

- In the development of a new drug for the treatment of multiple myeloma (MM), it is assumed that the traditional approach of designing and planning randomized controlled trials (RCTs) with overall survival (OS) and progression-free survival (PFS) as endpoints may not always be the optimal design. This is due to the excessive time and effort required, which can lead to high trial costs and ethical concerns about the time it takes to deliver the drug to patients.
- In addition to the traditional evaluation of treatment effects on MM using OS and PFS, the use of Minimal Residual Disease (MRD) for disease assessment is being considered. Based on materials published by the FDA's Oncologic Drugs Advisory Committee (ODAC), a meta-analysis on the surrogacy of MRD was introduced.
- Methods for adjusting multiplicity to evaluate multiple endpoints in a single trial and the 2-in-1 adaptive design that can handle them simultaneously were also introduced.

Background of virtual case 2

- Assuming the initial application for the new active ingredient, Anzentamab, for the treatment of multiple myeloma (MM).
  - Anzentamab has been approved for other cancers and has accumulated usage experience.
  - A similar compound has just been approved.
  - The optimal dosage of Anzentamab has been identified, and a validation trial to evaluate its efficacy is being considered.
  - The drug-related safety and convenience of administration of Anzentamab have been clearly improved compared to similar drugs.

In the discussion, it was considered to conduct a trial to verify the efficacy of this drug by setting MRD as the primary endpoint, assuming the following situations for each endpoint in comparison with similar drugs:

MRD@12mo: A significant difference between groups is expected, the detection power is considerably higher compared to PFS and OS, and the analysis timing is earlier.
PFS : A significant difference between groups is expected, the detection power is higher compared to OS, and it can be analyzed earlier than OS after MRD.
OS : A significant difference between groups is not expected, the detection power is quite low, events are less likely to occur, and the analysis takes time.

	Detail
Phase	3
Estimand	・Treatment : Anzentamab add-on to standard of care (SoC) ・Population : MM ・Variable : MRD and PFS (dual-endpoint) ・Population-level summary : percentage of MRD-@12mo and Hazard ratio of PFS ・Intercurrent event : Not considered
Study design	The sample size design is based on PFS, with MRD as the primary endpoint for interim analysis. If MRD is effective, early termination will be considered (with follow-up for PFS and OS). If MRD is negative at interim, evaluation will be done at the end with MRD. If MRD is positive at interim, evaluation will be done at the end with PFS. **Interim analysis:** Set at 1 year **Interim analysis:** MRD at 12 months (200 patients at 12-month follow-up), PFS (200 patients at 12-month follow-up) **Final analysis:** PFS **Multiplicity adjustment:** α-recycling (0.5% for MRD at 12 months, 4.5% for PFS), PFS interim analysis uses α-spending function **Sample size:** 400-500

Assumption

No new assumptions:

Initial application for the treatment of multiple myeloma

Usage experience of Anzentamab is available

A similar compound has just been approved

Side effects and compliance have improved. SAR is similar

MRD@12mo: PFS can be estimated reliably from MRD@12mo at a certain level

Recruitment is completed by the time of interim analysis

Points to consider when interpreting results

For the interim analysis, if the efficacy can be evaluated with MRD and the correlation between MRD and PFS is observed, an application for early termination will be submitted. Otherwise, the trial will continue with a sample size to evaluate efficacy with PFS.

OS will be used as a reference value. If the interim analysis results of MRD at 12 months show significant efficacy, an application for approval will be submitted.

Outcomes and insights from discussions

- The discussion enabled us to explore innovative methods that are not easily implemented in confirmatory trials, thereby bridging theory and practice.
  - We examined in detail the challenges of using external data and the approaches available for bias adjustment.
  - We considered the validity of surrogate endpoints and regulatory perspectives on early approval, aiming to balance trial efficiency with regulatory requirements.
- We compared multiple trial designs for a single case, clarifying the rationale and assumptions for each, and shared the selection process across industry, academia, and regulatory authorities.
  - We discussed the interpretation and assumptions of each design, taking into account practical decision-making under uncertainty and risk.
- By focusing on disease areas with significant constraints, the discussion provided insights applicable to future drug development strategies, statistical methodologies, and regulatory interactions.