Statistical Analysis Plan (SAP)

Study Title: A Study of Toripalimab in Adjuvant Therapy After Resection of High-risk Renal Cancer (TUORA)

Protocol Number: NCT06584435

Principal Investigator:

Sponsor: Tianjin Medical University Second Hospital

Statistical Analysis Plan Date: October 01,2022

1. Analysis Objectives and Hypotheses

1.1 Primary Objective

- Primary Endpoint: Disease-free survival (DFS), defined as the time from the first dose to disease recurrence (local or distant metastasis) or death from any cause.
- Hypothesis: Toripalimab adjuvant therapy can significantly improve DFS in high-risk patients, with the 24-month DFS rate expected to exceed 77%, surpassing historical data (e.g., 68.1% in the placebo group of KEYNOTE-564).

1.2 Secondary Objectives

- Overall Survival (OS): Time from the first dose to death from any cause.
- Safety Endpoints: Incidence and severity of adverse events (AEs), serious AEs (SAEs), and immune-related AEs (irAEs) graded per CTCAE v5.0.
- Patient-Reported Outcomes (PROs):
    - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)
    - Functional Assessment of Cancer Therapy-Kidney Symptom Index-15 (FKSI-15)

2. Analysis Populations

1. Full Analysis Set (FAS): All patients who provide informed consent and receive at least one dose of Toripalimab. Used for primary efficacy (DFS) analysis.
2. Per Protocol Set (PPS): Subset of FAS excluding major protocol deviations. Used for supportive efficacy analysis.
3. Safety Set (SS): All patients receiving ≥1 dose of Toripalimab with ≥1 post-baseline safety assessment. Used for safety analyses.

3. Statistical Methods

3.1 Primary Endpoint Analysis: DFS

- Method: Kaplan-Meier method to estimate DFS curves, reporting median DFS, 24-month DFS rate, and 95% confidence intervals (CIs).

- Historical Comparison: Compare with historical controls from our center (high-risk RCC patients without adjuvant therapy) using an adjusted Cox proportional hazards model (correcting for age, sex, tumor stage) to estimate hazard ratios (HRs) and 95% CIs.
- Sensitivity Analysis: Last observation carried forward for censored data.

3.2 Secondary Endpoint Analyses

- OS Analysis: Kaplan-Meier curves, median OS, and 24-month OS rate (95% CI).
- Safety Analysis:
    - Categorical variables (AE incidence) summarized as frequencies and percentages; continuous variables (lab parameters) as mean ± SD or median (range).
    - irAEs summarized by organ system.
- PRO Analysis: Longitudinal mixed models for EORTC QLQ-C30 and FKSI-15 scores, reporting least squares mean differences and 95% CIs.

3.3 Subgroup Analyses

- Prespecified Subgroups: Age (≤65 vs. >65 years), sex, tumor stage (M0 vs. M1 NED), ECOG performance status (0 vs. 1).
- Method: Cox model to estimate subgroup HRs and 95% CIs; interaction tests for subgroup differences.

3.4 Exploratory Analyses

- Limited to consistency of treatment effect across subgroups; no biomarker analyses.

4. Sample Size Justification

- Based on historical control data (24-month DFS rate ~68%), a 15% improvement with Toripalimab (α=0.05 one-sided, β=0.2) requires ~80 patients for 80% power.
- Actual enrollment: 40–100 patients; power will be reassessed at interim analysis.

5. Data Management and Handling

1. Missing Data:

- DFS: Censored at last follow-up.
- PROs: Mixed models under missing-at-random assumption.

2. Software: SAS 9.4 or R 4.0.
3. Independence: An independent data monitoring committee (IDMC) will review interim results.

6. Interim Analysis Plan

- Timing: One interim analysis when median follow-up reaches 12 months.
- Content: DFS Kaplan-Meier curves, 24-month DFS rate, and safety profile.
- Alpha Control: O'Brien-Fleming α-spending function (one-sided $\alpha=0.05$).
- Multiplicity: Fixed-sequence testing (DFS tested first).

7. Safety Analysis Plan

- AEs graded per CTCAE v5.0; focus on Grade ≥3 AEs and treatment discontinuations.
- irAEs (e.g., pneumonitis, colitis, hepatitis) managed per guidelines

8. Reporting and Visualization

- CONSORT flow diagram for patient screening, enrollment, and follow-up.
- Kaplan-Meier curves for DFS and OS.
- Tables for baseline characteristics, efficacy, and safety.
- PRO results presented as longitudinal plots.

9. Appendix: Reference Standards

1. Efficacy: RECIST v1.1.
2. Safety: CTCAE v5.0.
3. PRO Tools: EORTC QLQ-C30, FKSI-15.
4. Statistical Guidelines: ICH E9 and KEYNOTE-564 SAP.