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A Multicenter, Multi-Cohort, Phase II Study of Sacituzumab Tirumotecan with or Without Tislelizumab in Patients with Advanced Thyroid Cancer

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1. Introduction

This Statistical Analysis Plan (SAP) describes the statistical methodology to be applied for analysis of efficacy, safety, and exploratory endpoints in this Phase II multi-cohort study.

This SAP is aligned with:

- ICH E9 Statistical Principles for Clinical Trials
- ICH E9(R1) Estimands and Sensitivity Analysis
- FDAAA 801 transparency requirements

2. Study Objectives

2.1 Primary Objectives

- ATC Cohort: Evaluate Overall Survival (OS)
- PDTC and RAIR-DTC Cohorts: Evaluate Progression-Free Survival (PFS)

2.2 Secondary Objectives

- To evaluate PFS in the ATC cohort.
- To evaluate OS in the PDTC and RAIR-DTC cohorts.

- To evaluate objective response rate (ORR), disease control rate (DCR), and duration of response (DoR) according to RECIST v1.1.
- To evaluate R0/R1 resection rate in PDTC patients who become surgically resectable during treatment.
- To evaluate safety and tolerability according to NCI CTCAE v6.0.

3. Study Design Summary

Open-label, multi-center, multi-cohort exploratory Phase II study.

Planned sample size:

- ATC: n = 40
- PDTC: n = 30
- RAIR-DTC: n = 24

No formal hypothesis testing for regulatory approval is planned.

4. Analysis Populations

4.1 Intent-to-Treat (ITT) Population

All enrolled patients who receive at least one dose of study treatment.

Primary efficacy analyses will be based on ITT population.

4.2 Per-Protocol (PP) Population

Subset of ITT without major protocol deviations that may impact efficacy evaluation.

Sensitivity analyses may use PP population.

4.3 Safety Population

All patients who receive at least one dose of study drug.

Safety analyses will use Safety population.

5. Estimand Framework (ICH E9 R1 Aligned)

5.1 Primary Estimand (ATC Cohort – OS)

- Population: ATC patients in ITT population
- Variable: Overall survival
- Intercurrent events:
    - Treatment discontinuation
    - Surgery
    - Subsequent anticancer therapy

- Strategy: Treatment policy strategy
- Summary measure: Median OS and Kaplan–Meier survival curve

5.2 Primary Estimand (PDTC / RAIR-DTC – PFS)

- Population: PDTC or RAIR-DTC ITT
- Variable: PFS per RECIST v1.1
- Intercurrent events:
    - Surgery (not considered PFS event)
    - Treatment discontinuation
    - New anticancer therapy
- Strategy: Treatment policy strategy
- Summary measure: Median PFS with 95% CI

6. Endpoint Definitions

6.1 Overall Survival (OS)

Time from first dose to death from any cause.

Patients alive at data cutoff will be censored at last known alive date.

6.2 Progression-Free Survival (PFS)

Time from first dose to first documented radiographic progression or death.

6.3 Objective Response Rate (ORR)

Proportion of patients achieving CR or PR per RECIST v1.1.

6.4 Disease Control Rate (DCR)

Proportion achieving CR, PR, or SD.

6.5 Duration of Response (DoR)

Time from first documented response (CR/PR) to progression or death.

7. Censoring Rules

OS

- Censored at last known alive date if no death observed

PFS

- If no progression or death → censored at last adequate tumor assessment
- If surgery (R0/R1) without progression → continue follow-up
- If lost to follow-up → censored at last tumor evaluation

8. Statistical Methods

8.1 Time-to-Event Endpoints

Estimated using Kaplan–Meier method.

95% confidence intervals calculated using Greenwood formula.

Median survival times reported with two-sided 95% CI.

8.2 Binary Endpoints (ORR, DCR)

Exact binomial confidence intervals (Clopper–Pearson method).

8.3 Descriptive Statistics

Continuous variables:

- Mean ± SD or median (min, max)

Categorical variables:

- Frequency and percentage

9. Missing Data Handling

No imputation will be performed for time-to-event endpoints.

Patients without post-baseline tumor assessment will be considered non-responders for ORR.

Sensitivity analyses may explore alternative censoring assumptions.

10. Sensitivity Analyses

- Per-Protocol population analysis
- Landmark analysis for surgery subgroup
- Alternative censoring at new therapy

11. Subgroup Analyses

Exploratory analyses by:

- TROP2 expression level
- ECOG status
- Prior therapy
- Molecular alteration status

Results interpreted descriptively.

12. Biomarker Analyses

Associations between TROP2、PD-L1 expression and response evaluated using:

- Logistic regression (for ORR)
- Cox proportional hazards models (for PFS/OS)

Exploratory and hypothesis-generating only.

13. Safety Analysis

Adverse events graded per NCI CTCAE v6.0.

Summaries include:

- TEAEs
- SAEs
- Treatment discontinuation due to AEs
- Laboratory abnormalities

14. Software

All analyses performed using:

- SAS version 9.2 or higher
- R version 4.4.3 or higher

15. Interim Analysis

No formal interim efficacy analysis is planned.

Safety data may be reviewed periodically.

16. Data Cut-Off

Primary analysis will occur after predefined follow-up period or sufficient number of events.

17. Regulatory Transparency Statement

This SAP is publicly posted in accordance with:

- FDA Amendments Act (FDAAA 801)
- 42 CFR Part 11
- EMA transparency policy