Statistical Analysis Plan (SAP)

Protocol Title: Anlotinib Combined With Chemotherapy as Neoadjuvant Therapy for Hormone Receptor-Positive HER-2 Negative Breast Cancer

Protocol Version: 2.0

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1. Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods to be used for the analysis of the clinical trial entitled "Anlotinib combined with chemotherapy as neoadjuvant therapy for hormone receptor-positive HER-2 negative breast cancer." The study is an open-label, single-arm, single-center, exploratory clinical trial.

The SAP defines the analysis sets, endpoints, statistical methodologies, and procedures for data handling to ensure a standardized and unbiased evaluation of the trial outcomes.

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2. Objectives and Endpoints

2.1 Primary Objective

To preliminarily assess the pathological complete response (pCR) rate of neoadjuvant therapy with Anlotinib and chemotherapy in patients with early-stage hormone receptor-positive, HER2-negative breast cancer.

- **Primary Endpoint:**
- pCR rate, defined as the absence of invasive cancer cells in the breast and axillary lymph nodes (ypT0/Tis, ypN0).

2.2 Secondary Objectives

- To evaluate the Objective Response Rate (ORR) based on RECIST v1.1.
- To assess Event-Free Survival (EFS).
- To evaluate the safety and tolerability of the treatment regimen.
- To explore additional pathological response measures:

- RCB 0/I rate
- breast pCR (bpCR, ypT0/Tis) rate
- axillary pCR (apCR, ypN0) rate

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3. Analysis Populations

- **Full Analysis Set (FAS):** All enrolled patients who received at least one dose of study treatment.
- **Per Protocol Set (PPS):** A subset of FAS who completed the treatment without major protocol deviations.
- **Safety Set (SS):** All patients who received any study treatment and had at least one post-baseline safety assessment.

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4. Statistical Methods

4.1 Descriptive Statistics

Unless otherwise specified, all data will be summarized using descriptive statistics based on data type:

- **Continuous variables** (e.g., age, laboratory values): Mean, Standard Deviation (SD), Median, Minimum, and Maximum.
- **Categorical and ordinal variables** (e.g., ECOG status, tumor stage, response categories): Frequency and percentage.
- **Confidence Intervals:** The overall 95% confidence interval (CI) will be provided for key efficacy endpoints.

4.2 Analysis of Primary Endpoint

- pCR rate will be calculated as the proportion of patients achieving ypT0/Tis and ypN0 among the FAS and PPS.
- A 95% confidence interval for the pCR rate will be computed using the Clopper–Pearson (exact) method.

4.3 Analysis of Secondary Endpoints

- **ORR:** Defined as the proportion of patients with Complete Response (CR) or Partial Response (PR) per RECIST v1.1. Will be presented with a 95% CI.

- **Event-Free Survival (EFS):** Defined as the time from initiation of treatment until the occurrence of any of the following events: disease progression, local or distant recurrence, second primary cancer, inability to undergo surgery as planned, or death from any cause.
- **Safety:** Adverse events (AEs) will be summarized by severity (NCI CTCAE v5.0) and relationship to study treatment. Frequency and percentage of patients with AEs, serious AEs (SAEs), and AEs leading to discontinuation will be presented.
- **Exploratory Pathological Endpoints:** Rates of RCB 0/I, bpCR, and apCR will be summarized using descriptive statistics.

4.4 Subgroup Analyses

Exploratory subgroup analyses for the primary endpoint will be performed based on:

- Axillary lymph node metastasis status (yes vs. no)
- Ki-67 index (high vs. low, if applicable)

4.5 Missing Data

- For the primary endpoint, patients with missing pCR data will be considered non-responders in the primary analysis.
- Sensitivity analyses may be performed to assess the impact of missing data.

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5. Software

All statistical analyses will be performed using validated statistical software (e.g., SPSS version 27 or R version 4.0 or higher).

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6. Data Handling

- All statistical tests will be two-sided, with a significance level of $\alpha = 0.05$, unless otherwise noted.
- No interim analysis is planned for this study.

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7. Amendments

Any changes to this SAP will be documented, dated, and justified in a formal SAP amendment.