STATISTICAL ANALYSIS PLAN

Randomized, prospective, open-label phase II clinical study of adjuvant icotinib (12 months) versus observation in patients with stage IB epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) after complete resection **(CORIN Study)**

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2 Study Objectives

2.1 Primary Objective

To evaluate the efficacy of adjuvant icotinib, in terms of 3-year disease-free survival (DFS), for patients with completely resected stage IB non-small cell lung cancer (NSCLC).

2.2 Secondary Objectives

To evaluate the efficacy of adjuvant icotinib, in terms of DFS, for patients with completely resected stage IB NSCLC, as compared with observation.

To evaluate the efficacy of adjuvant icotinib, in terms of central nervous system (CNS)-related DFS, for patients with completely resected stage IB NSCLC, as compared with observation.

To evaluate the efficacy of adjuvant icotinib, in terms of overall survival (OS), for patients with completely resected stage IB NSCLC, as compared with observation.

To assess the safety and tolerability of adjuvant 12-month icotinib for patients with completely resected stage IB NSCLC, as compared with observation.

2.3Exploratory Objectives

To evaluate the efficacy of adjuvant icotinib for patients with completely resected stage IB NSCLC based on the AJCC 7th and 8th edition of staging.

To evaluate the efficacy of adjuvant icotinib for patients with completely resected stage IB NSCLC based on sensitive EGFR mutation and all EGFR mutations (including atypical EGFR mutations).

3 Study Design and Methods

3.1 Study Design

This is a phase II, open-label, randomized controlled study to evaluate the efficacy and safety of adjuvant icotinib for patients with completely resected stage IB NSCLC without adjuvant chemotherapy.

The decision of not receiving adjuvant chemotherapy will be according to physician and patient choices.

Eligible patients will be randomized in a 1:1 ratio to receive adjuvant therapy with icotinib (125 mg, three times daily) or to undergo observation. Treatment with icotinib will be given for up to 12 months or until discontinuation criteria are met. Therapy will be continued until disease progression or intolerable toxicity occurred. The first dose of study treatment should be taken no later than 7 days of randomization.

3.2 Randomization

Randomization will be performed by the study staff of the GASTO through a computer-generated sequence with a minimization method that balanced sex (male vs. female) and ECOG PS (0 vs. 1) for random assignment. Randomization will be performed just before the initiation of study administration. Eligible patients will be randomly assigned in a 1:1 ratio to either receive oral icotinib or undergo observation.

3.3 Blinding

Not applicable. This is an open-label study. All investigators, study personnel, and patients will be not masked to patient distribution.

4 Study Endpoints

4.1 Efficacy Endpoints

4.1.1 Primary Efficacy Endpoint

The primary endpoint are 3-year DFS, which is defined as the proportion of patients who were disease free at 3 years.

4.1.2 Secondary Efficacy Endpoints

The secondary endpoints included DFS (time from random assignment to documented disease recurrence or death, whichever occurred first), central nervous system (CNS)-related DFS (time from randomization to CNS recurrence or death, whichever occurred first), overall survival (OS, time from random assignment to death from any cause).

4.2 Safety Endpoints

All patients who receive at least 1 dose of study treatment will be evaluated for safety and tolerability. Safety and tolerability will be evaluated at every visit. All adverse events (AEs) will be classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Proportion of patients with AEs will be recorded for patients in the icotinib group. Grade 3 or greater AEs will be recorded. The number and percentage of subjects reporting serious adverse events (SAEs) will be summarized.

AEs will be managed according to the AE management protocol.

5 Sample Size

On the basis of the CALGB 9633 trial [1], we projected a 3-year DFS of 60% for patients with stage IB NSCLC. The study is designed to determine whether adjuvant icotinib would result in a 17% absolute improvement (from 60% to 77%) in 3-year DFS, with 80% power at a two-sided α of 0.1. This improvement corresponded to an HR of 0.5. Assuming an accrual time of 2 years, a follow-up time of 3 years, and an anticipated dropout rate of 5%, a total of 128 patients would be required to be randomly assigned. This sample size is sufficient to power this study at 80% with a two-sided type I error rate of 10%.

6 Patient characteristics

Patient demographics will be summarized. The patient demographics will include the following:

Age

Sex

Baseline ECOG PS

Smoking status

Disease characteristics will be summarized. Disease characteristics will include the following:

Pathological diagnosis

Primary tumor size

Tumor stage

Tumor grade

Tumor location

EGFR mutational status

Tumor stage will be derived based on pathological results.

7 Treatment Compliance

Treatment compliance of icotinib will be summarized. Compliance will be calculated as the ratio of total dose taken to the total assigned dose (minus any dose adjustments and doses omitted/withheld). The treatment time (days and months) will calculated.

8 Interim Analysis

Not applicable. No interim analyses were planned.

9 Subgroup Analysis

To investigate the interaction between treatment effect and the subpopulation, subgroup analyses will be conducted in an exploratory manner with respect to the following factors: sex (male vs. female) and EGFR mutation (exon 19 deletion vs. exon 21 L858R).

10 Statistical Considerations

The Intention-To-Treat Set (ITT) will include all randomized subjects. ITT will be used for the analysis of DFS and OS.

All analyses for efficacy are based on ITT population.

The Safety Analysis Set will include all subjects who received at least 1 dose of study drug and have a safety record after drug administration.

Descriptive statistics will be defined for continuous variables as number (n), median, mean, minimum and maximum, and as frequency and percentage for categorical variables.

The Kaplan-Meier method [2] will be used to estimate the point estimates of 3-year DFS for each group. The difference in 3-year DFS between groups will be compared by the Z test. The median DFS and OS will be estimated by the Kaplan–Meier method and the differences between median DFS and OS will be compared by the log-rank test.

Hazard ratios and their 95% confidence intervals for treatment effects are estimated using Cox proportional hazards models [3].

Unless otherwise specified, all statistical analyses will be performed using two-sided tests with a significance level of 0.05. All statistical analyses will be performed using SPSS and R.

11 Variables

Month=365/12 days.

Year=365 days.

Time since diagnosis to randomization = date of randomization – date of initial diagnosis) +1.

The duration of treatment was calculated as the (last dose date – first dose date) + 1.

Duration in study (days) = last day of known to be alive – date of randomization + 1

Follow-up time (days for DFS) = date of recurrence (patient who had recurrence) or date of last follow-up – date of randomization + 1.

Follow-up time (days for OS) = date of death (patient who died) or date of last follow-up – date of randomization + 1.

12 Missing data

No imputations will be made for missing data. Patients who does not have relapse or death will be censored at last follow-up.

13 References

1. Strauss GM, Herndon JE, 2nd, Maddaus MA et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008; 26: 5043-5051.

2. Kaplan EL, Meier P. Nonparametric estimation of incomplete observations. J Amer Stat Assoc. 1958; 53: 457-481.

3. Cox D. Regression models and life-tables. J Royal Stat Soc Ser B. 1972; 34: 187-220.