Adjuvant icotinib versus observation in patients with completely resected EGFR-mutated stage IB NSCLC (GASTO1003, CORIN): a randomised, open-label, phase 2 trial

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Summary

Background This phase 2 trial aimed to compare adjuvant icotinib with observation in patients with epidermal growth factor receptor (EGFR) mutation-positive resected stage IB non-small cell lung cancer (NSCLC).

Methods We performed a randomised, open-label, phase 2 trial from May 1, 2015 to December 29, 2020 at Sun Yat-sen University Cancer Center in China. Patients with completely resected, EGFR-mutant, stage IB (the 7th edition of TNM staging) NSCLC without adjuvant chemotherapy were randomised (1:1) to receive adjuvant therapy with icotinib (125 mg, three times daily) for 12 months or to undergo observation until disease progression or intolerable toxicity occurred. The primary endpoint was 3-year disease-free survival (DFS). CORIN (GASTO1003) was registered with Clinicaltrials.gov, with the number NCT02264210.

Findings A total of 128 patients were randomised, with 63 patients in the icotinib group and 65 patients in the observation group. The median duration of follow-up was 39.9 months. The three-year DFS was significantly higher in the icotinib group (96.1%, 95% confidence interval [CI], 91.3–99.9) than in the observation group (84.0%, 95% CI, 75.1–92.9; P = 0.041). The DFS was significantly longer in the icotinib group than in the observation group, with a hazard ratio (HR) of 0.23 (95% CI, 0.07–0.81; P = 0.013). The OS data were immature, with three deaths in the observation arm. In the icotinib group, adverse events (AEs) of any grade were reported in 49 patients (77.8%), and grade 3 or greater AEs occurred in four patients (6.3%). No treatment-related deaths occurred.

Interpretation Our findings suggested that adjuvant icotinib improved the 3-year DFS in patients with completely resected EGFR-mutated stage IB NSCLC with a manageable safety profile.

Funding This study was sponsored by Betta Pharmaceutical Co., Ltd.

Keywords: Icotinib; Adjuvant therapy; Stage IB NSCLC

Introduction

Lung cancer is the leading cause of cancer mortality worldwide, with an estimated 12.8 million deaths per year, accounting for approximately 1 in 5 cancer deaths.[1] Non-small cell lung cancer (NSCLC) is the most common pathological type and accounts for approximately 80% of all lung cancer cases.[2] Only 30% of patients with NSCLC are suitable for surgery, which is considered the most effective treatment option.[3,4] The absolute survival improvement at 5 years following adjuvant cisplatin-based chemotherapy in patients with early-stage NSCLC is 5.4%.[5] Although platinum-based

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Research in context

Evidence before this study

Increasing evidence suggests that adjuvant epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) may be effective in a selected population after resection of early-stage non-small cell lung cancer (NSCLC). However, prospective clinical trials of these regimens have largely excluded patients with stage IB disease. Despite of efficacy among patients with stage IB in the ADAURA study, rare trial was designed specifically for stage IB EGFR-mutant NSCLC. We searched PubMed using the terms "stage IB" and "EGFR-TKI" and "adjuvant" up to September 30, 2022, and we identified only a small number of clinical trials reporting the efficacy and safety of adjuvant EGFR-TKI therapies for treatment of stage IB NSCLC.

Added value of this study

To the best of our knowledge, this phase II trial is the first prospective, randomised study to evaluate the efficacy and safety of adjuvant icotinib in a patient population with completely resected stage IB (the 7th edition of TNM staging) NSCLC who had not received adjuvant chemotherapy or perioperative radiation therapy. Our study does provide important evidence that an EGFR-TKI, in the adjuvant setting, has anti-tumour efficacy and is generally well tolerated in patients with completely resected stage IB NSCLC.

Implications of all the available evidence

The results of the phase II trial suggest that adjuvant icotinib is a well-tolerated regimen for patients with completely resected stage IB (the 7th edition of TNM staging) NSCLC, with longer disease-free survival (DFS) in the icotinib group than in the observation group. These findings address an important knowledge gap for the treatment of completely resected stage IB NSCLC and also suggest that adjuvant EGFR-TKIs are a valuable therapeutic strategy. Given the limited studies on the role of adjuvant EGFR-TKIs in stage IB NSCLC, our results could directly improve clinical practise and broaden treatment options for patients with completely resected stage IB NSCLC.

chemotherapy following surgery improves survival in patients with stage II-IIIA NSCLC and in selected patients with IB disease, the survival outcomes are not satisfactory.[6] The 5-year survival rate following surgery and adjuvant chemotherapy ranges from 67% for stage IB disease to 39% for stage IIIA disease, and disease recurrence remains high across all disease stages.[7] Lung cancer screening has proven to reduce mortality by 20–30%, and more than a half of screening-detected lung cancers were stage I disease.[8,9] The increasing use of screening will lead to a substantial shift to early-stage (including stage IB) NSCLC, making adjuvant treatment for stage IB disease a major challenge.

An epidermal growth factor receptor (EGFR) shows a very high prevalence in patients from eastern Asia (40%–60%) compared with patients from Western countries (10%–15%).[10] EGFR tyrosine kinase inhibitors (TKIs) have been established for advanced EGFR-mutant NSCLC.[11] Many efforts have been made to explore the role of EGFR-TKIs as an adjuvant treatment for EGFR-mutant NSCLC.[12–19] A prior meta-analysis showed that EGFR-TKIs can significantly improve disease-free survival (DFS) and that TKIs are associated with fewer adverse events (AEs) in patients with resected EGFR-mutant NSCLC than chemotherapy in the adjuvant setting.[20] In the ADAURA trial, 3-year osimertinib in patients with resected EGFR-mutated stage IB-IIIA (the 7th edition of TNM staging) disease improved DFS compared with placebos, with a hazard ratio (HR) of 0.20.[21] Based on the results of the ADAURA study, the third-generation TKI osimertinib was approved by the FDA for NSCLC patients with sensitising EGFR mutations (exon 19 deletion or exon 21 L858R) in the adjuvant setting.[6,22]

Icotinib is a first-generation EGFR-TKI that shows similar efficacy but a good safety profile when compared with gefitinib in pretreated patients with advanced NSCLC in the ICOGEN trial.[23] In the CONVINCE trial, first-line icotinib significantly prolonged progression-free survival (PFS) and had a good tolerability profile in advanced EGFR-mutated lung adenocarcinoma compared with chemotherapy.[24] The recent EVIDENCE trial demonstrated that icotinib improves DFS and is associated with a more favourable safety profile in patients with resected EGFR-mutant stage II-IIIA NSCLC.[18] Based on the results from EVIDENCE, first-generation icotinib was approved in China for resected EGFR-mutant stage II-IIIA NSCLC in the adjuvant setting. However, no study has been designed specifically for stage IB NSCLC with EGFR mutations. This phase II study was designed to assess whether adjuvant therapy with first-generation icotinib can improve survival outcomes compared with observation in patients with resected EGFR-mutant stage IB (the 7th edition of TNM staging) NSCLC without adjuvant chemotherapy.

Methods

Study design and participants

CORIN (GASTO1003) was a randomised, open-label, phase 2 trial conducted at Sun Yat-sen University Cancer Center in China. Eligible patients were ≥18 years old; had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1; had completely resected (R0) stage IB disease (according to the 7th edition of the AJCC TNM staging system for lung cancer[25]); and had a confirmed EGFR mutation

(exon 19 deletion, exon 21 L858R, or uncommon EGFR mutations including exon 18 G719X, exon 20 S768I, and exon 21 L861Q). Additional eligibility criteria were a life expectancy of at least 1 year, adequate haematological function (absolute neutrophil count $\geq 2.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and haemoglobin ≥ 9 g/dL), adequate liver function (serum total bilirubin ≤ 1.5 times the upper limit of normal; aspartate aminotransferase and alanine aminotransferase ≤ 2.5 times the upper limit of normal), and adequate renal function (serum creatinine clearance ≥ 60 mL/min).

Key exclusion criteria included a second primary malignancy within 5 years (except for cured basal cell carcinoma of the skin or cured in situ carcinoma of the uterine cervix); prior treatment with antitumor agents or radiotherapy; a history of severe drug hypersensitivity; a history of interstitial pneumonitis; a history of myocardial infarction or angina within the past 6 months; any unstable systemic disease (such as unstable heart disease or uncontrolled hypertension); an active uncontrolled infection; and pregnancy or lactation. We excluded patients who had been treated with neoadjuvant chemotherapy, adjuvant chemotherapy, or perioperative radiation therapy. The decisions for not receiving adjuvant chemotherapy were made according to physician and patient choices.

The study was approved by the medical ethical committee of the Guangdong Association of Study of Thoracic Oncology (GASTO) and the Medical Ethics Committee of Sun Yat-sen University Cancer Center. The trial protocol and statistical analysis plan are available in the supplementary material. This trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practise guidelines and the policy of the trial sponsor, Betta Pharmaceuticals. This article was prepared in accordance with CONSORT guidelines (Supplementary Table S1). All patients provided written informed consent. CORIN (GASTO1003) was registered with Clinicaltrials.gov, with the number NCT02264210.

Randomisation and masking

Randomisation was performed by the study staff of the GASTO through a computer-generated sequence with a minimisation method that balanced sex (male vs. female) and ECOG PS (0 vs. 1) for random assignment. Eligible patients were randomly assigned in a 1:1 ratio to either receive oral icotinib or undergo observation. All investigators, study personnel, and patients were not masked to patient distribution.

Procedures

Baseline assessments before study entry included a full history and a physical examination, enhanced computed tomography (CT) scans of the chest and the upper abdomen, brain magnetic resonance imaging (MRI), and haematologic and biochemical testing. The baseline assessments were performed within 4 weeks before the administration of icotinib. Eligible patients received either 1 year of icotinib (125 mg thrice daily administered orally) or none. The start of treatment needed to be within 4 weeks after surgical resection. The therapy continued until disease progression or intolerable toxic effects occurred.

Follow-up assessments were scheduled at month 3 and month 6 after surgery, every 6 months until 5 years, and every 12 months thereafter. The follow-up assessments involved a physical examination and contrast-enhanced CT of the chest. Brain MRI was scheduled every 12 months. Bone scans and other examinations were performed based on symptoms. Disease recurrence was evaluated at follow-up visits and was determined according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 by the investigators. At disease relapse, the dates and sites of recurrence were recorded. Post-recurrence therapy was permitted.

Safety and tolerability were evaluated at every visit for the icotinib group. All AEs were classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. AEs were managed according to the AE management protocol.

Outcomes

The primary endpoint was 3-year DFS, which was defined as the proportion of patients who were disease free at 3 years. 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 randomisation to CNS recurrence or death, whichever occurred first), overall survival (OS, time from random assignment to death from any cause), safety and tolerability.

Statistical analysis

On the basis of the CALGB 9633 trial, we projected a 3-year DFS of 60% for patients with stage IB NSCLC. The study was 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 hazard ratio (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.

The point estimates of 3-year DFS were calculated by the Kaplan–Meier method, and the difference in 3-year DFS between groups was compared by the Z test. The median DFS and OS were estimated by the Kaplan–Meier method and compared by the log-rank test. Cox proportional hazards models were used to estimate HRs with their 95% confidence intervals (CIs). Predefined subgroup comparisons of DFS were performed for sex

(male vs. female) and EGFR mutation (exon 19 deletion vs. exon 21 L858R). Subgroup analyses of age (≥65 vs. <65), smoking history (ever vs. never) and side (left vs. right) were done in a post hoc manner. All analyses for efficacy were based on intention-to-treat (ITT) population. Safety analysis included all patients in the icotinib group who received at least one dose of the study medication and had one or more safety follow-up visits. Patient characteristics and treatment-related AEs were analysed descriptively. The data cutoff date was July 30, 2022. All P values reported herein are two-sided, and P values less than 0.05 are considered to be significant.

Role of the funding source

The study sponsor (Betta Pharmaceuticals) was involved in the study design, data collection, analysis, interpretation, and the writing of this report. All authors had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

Results

Patients and treatment

From May 1, 2015 through December 29, 2020, 485 patients were screened, and 357 patients were excluded due to the following reasons: EGFR wild-type status (n = 249), adjuvant chemotherapy (n = 99), withdrawal of consent before randomisation (n = 3), unstable systemic disease (n = 2), double cancer within 5 years (n = 2), bone metastases before randomisation (n = 1), and stage other than stage IB (n = 1). Finally, 128 eligible patients with completely resected, EGFR-mutant stage IB NSCLC without adjuvant chemotherapy were enrolled and randomised to receive icotinib (n = 63) or undergo observation (n = 65). All 128 patients were included in the full analysis set (Fig. 1). Baseline characteristics were balanced between the two groups (Table 1). Overall, 58%–59% of the patients were female. Almost all surgical types were lobectomies in both arms. Patients with exon 21 L858R accounted for 46% and 52% of patients in the icotinib arm and in the observation arm, respectively. Of note, 3 patients with the uncommon EGFR mutation exon 18 G719X were also included in the full analysis set.

Regarding treatment compliance, 46 patients (73.0%) in the icotinib group completed the planned 1-year treatment, and none of the patients in the icotinib group were still receiving the study medication at the data cutoff. A total of 17 patients discontinued icotinib treatment because of patient decisions (n = 15) and AEs (n = 2). For patients who received icotinib, the median duration of treatment was 12.0 months (range 0.5–14.6).

Efficacy

The median follow-up in the full analysis set was 39.9 (IQR 25.7–59.4) months. By the data cutoff, three patients in the icotinib group and 13 patients in the observation group had had disease recurrence. The percentage of patients who were alive and disease-free at 3 years was significantly higher in the icotinib group (96.1%, 95% CI, 91.3–99.9) than in the observation group (84.0%, 95% CI, 75.1–92.9; P = 0.041; Fig. 2A). The DFS in the full analysis set was significantly longer for those assigned icotinib than for those assigned observation (HR 0.23; 95% CI, 0.07–0.81; P = 0.013; Fig. 2A). This HR equalled a 77% reduction in the risk of disease recurrence or death. The HR adjusted for sex and ECOG PS was 0.23 (95% CI, 0.06–0.79; adjusted P value, 0.020). Although the median DFS had not been reached in either group, the Kaplan–Meier curves showed early separation between the icotinib and observation groups and maintained this separation throughout the trial.

To rule out the possible influence of different editions of staging, we restaged all patients according to the 8th edition of the TNM classification and performed an exploratory analysis of DFS based on the AJCC edition of staging. Since we only enrolled patients without adjuvant chemotherapy, 123 patients remained in stage IB, and only 5 patients were reclassified as stage IIA (T2bN0) according to the 8th edition of the TNM staging system. Similar results were observed in patients with stage IB disease by the 8th edition of TNM staging (Fig. 2B). The 3-year DFS rates were 95.9% (95% CI, 90.9–99.9) in the icotinib group and 83.0% (95% CI, 73.7–92.4) in the observation group, and the results favoured the icotinib group (P = 0.041). The icotinib group also had a significantly lengthened DFS time compared with the observation group (HR, 0.25; 95% CI, 0.07–0.87; P = 0.018; Fig. 2B). This HR equalled a 75% reduction in the risk of disease recurrence or death. To rule out the possible influence of atypical EGFR mutations, we reanalysed the DFS results by excluding 3 patients with the exon 18 G719X mutation. As we expected, the DFS was also significantly different between the two groups (P = 0.005; Supplementary Fig. S1).

Subgroup analyses of DFS with respect to baseline characteristics are shown in Fig. 3. The DFS favoured icotinib in patients who had right-sided disease (P = 0.022). There were no significant differences between icotinib and observation in other factors, although the DFS had a trend toward favouring icotinib in patients who were nonsmokers (HR, 0.31; 95% CI, 0.08–1.14; P = 0.077). These results may be due to the small sample size and the short follow-up time.

CNS-related recurrence occurred in 0 of 63 patients in the icotinib group and in 6 of 65 patients (9.2%) in the observation group. The 3-year CNS-related DFS was significantly higher in the icotinib group (100%) than in the observation group (93.8%; Fig. 4A). The CNS-related DFS was significantly longer for those who received icotinib than for those who underwent observation (P = 0.018; Fig. 4A), although the median CNS-related

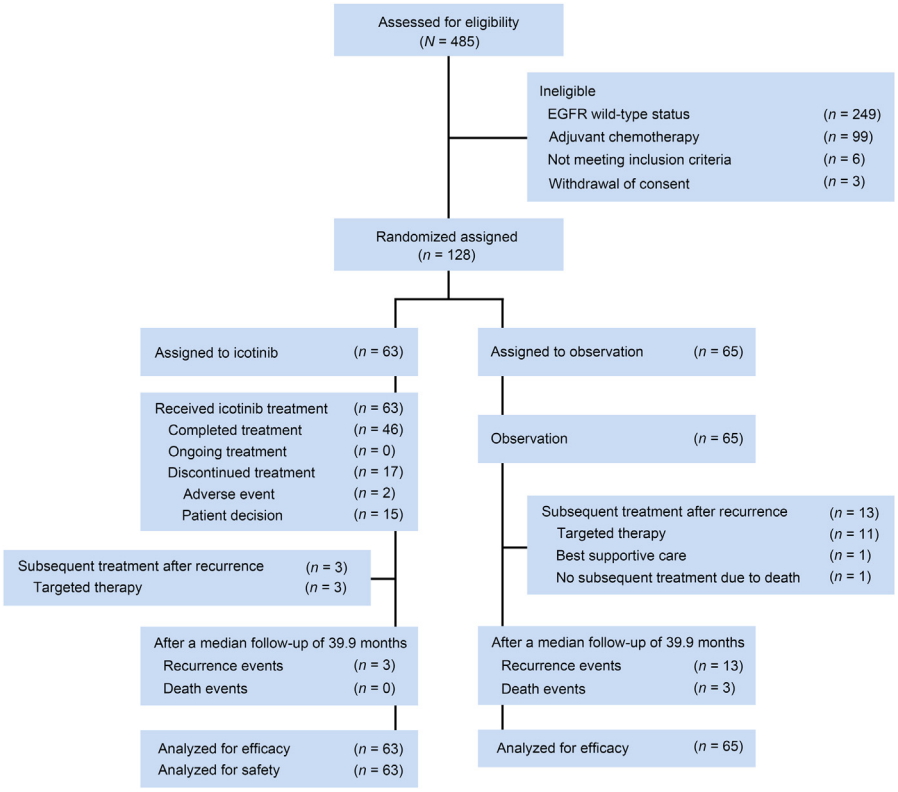

***Fig. 1:* Study profile.** Data cutoff on July 30, 2022. N, number; EGFR, epidermal growth factor receptor.

DFS was not reached in either group. Similar results were observed in patients with stage IB disease by the 8th edition of TNM staging. The icotinib group also had a significantly lengthened CNS-related DFS compared with the observation group (P = 0.030; Fig. 4B).

Subsequent treatments after recurrence were administered in 3 of 3 (100%) and in 12 of 13 (92.3%) patients in the icotinib and observation groups, respectively. Eleven of 13 patients who had relapsed in the observation group received EGFR-TKI treatment. All 3 patients who had had recurrence in the icotinib group received EGFR-TKI treatment.

A total of 3 death events had occurred by the data cutoff (icotinib, n = 0; observation, n = 3). The OS data are not mature. Although the preliminary analysis revealed that the Kaplan–Meier curves showed separation regardless of whether the 7th or 8th edition staging system was used, the OS was not significantly different between the two groups (P = 0.098 and P = 0.095; Supplementary Fig. S2).

Safety

All 63 patients in the icotinib group were included in the safety analysis set. Icotinib was well tolerated with no unexpected AEs, and there were no deaths that were deemed to be treatment-related. Overall, AEs of any grade were reported in 49 (77.8%) of 63 patients who had received icotinib (Table 2). The most common AEs reported were rash (25, 39.7%), diarrhoea (13, 20.6%), and pain (7, 11.1%). No cases of drug-induced interstitial lung disease were recorded.

Grade 3 or greater AEs occurred in 4 patients (6.3%) in the icotinib group, including rash in 2 patients (3.2%), diarrhoea in 1 patient (1.6%), and pain in 1 patient (1.6%). Dose discontinuation of icotinib owing to AEs occurred in 2 patients (3.2%). None of the patients had dose reductions.

Discussion

This phase 2, open-label, randomised CORIN (GASTO1003) trial examined the efficacy and safety of adjuvant icotinib in patients with completely resected, EGFR-mutant, stage IB NSCLC without adjuvant chemotherapy. Although the median DFS was not reached in either group at the data cutoff, the overall results demonstrated a positive effect of icotinib. The primary endpoint of CORIN, 3-year DFS, was significantly improved among patients who had been assigned to receive icotinib (3-year DFS, 96.1% vs. 84.0%).

The CALGB 9633 trial explored the role of chemotherapy in stage IB (6th edition of TNM staging) NSCLC.[26] Of note, the 6th edition of staging included

	Icotinib (n = 63)	Observation (n = 65)
Age, years	56 (35–75)	57 (32–75)
Sex		
Male	26 (41.3)	27 (41.5)
Female	37 (58.7)	38 (58.5)
ECOG PS		
0	63 (100.0)	64 (98.5)
1	0	1 (1.5)
Smoking status		
Never	48 (76.2)	46 (70.8)
Former	1 (1.6)	3 (4.6)
Current	14 (22.2)	16 (24.6)
Histology		
Adenocarcinoma	62 (98.4)	65 (100.0)
Adenosquamous carcinoma	1 (1.6)	0
Differentiation		
High/Moderate	48 (76.2)	50 (76.9)
Low	14 (22.2)	13 (20.0)
Unknown	1 (1.6)	2 (3.1)
Surgery type		
Lobectomy	63 (100.0)	64 (98.5)
Other	0	1 (1.5)
Side		
Left	26 (41.3)	25 (38.5)
Right	37 (58.7)	40 (61.5)
EGFR mutation		
Exon 19 deletion	32 (50.8)	30 (46.2)
Exon 21 L858R	29 (46.0)	34 (52.3)
Exon 18 G719X	2 (3.2)	1 (1.5)

Data are n (%) or median (range). ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor.

Table 1: **Demographic and clinical characteristics of patients (n = 128).**

lymph node–negative and invasion-negative (other than visceral pleura) tumours that were >3 cm in the greatest dimension.[27] Although a significant survival advantage was not observed in the entire population in CALGB 9633, chemotherapy demonstrated superiority in regard to OS in patients with tumours ≥4 cm.[26] The tumour size threshold was further verified in JBR-10, in which OS favoured patients with tumours ≥4 cm, whereas no benefit was observed in patients with tumours <4 cm. To utilise the above results in the 8th edition of the TNM staging system.[28] adjuvant chemotherapy is recommended for patients with stage IIA (T2bN0) or greater NSCLC. In our study, patients were enrolled based on the 7th edition of the TNM staging system. Since we only enrolled patients without adjuvant chemotherapy, 123 (96.1%) patients remained in stage IB according to the 8th edition of the TNM staging system.

There have been a few efforts to compare EGFR-TKIs as adjuvant therapy with chemotherapy in early-stage NSCLC. The ADJUVANT trial demonstrated that gefitinib improved DFS compared with chemotherapy for completely resected stage II–IIIA (N1–N2) EGFR-mutant NSCLC, but the DFS benefit did not translate into a significant OS difference.[16,29] The EVAN trial showed that adjuvant erlotinib improved the 2-year DFS compared with chemotherapy in resected stage IIIA EGFR-mutant NSCLC.[17] However, the IMPACT trial comparing gefitinib and vinorelbine plus cisplatin for patients with resected stage II-IIIA EGFR mutation-positive NSCLC failed to meet its DFS endpoint.[19] Icotinib showed its superiority in DFS for patients with completely resected stage II-IIIA NSCLC with EGFR mutations.[18] There are other studies that compared EGFR-TKIs with placebos or observation after chemotherapy, including the BR.19 study,[12] the RADIANT study,[14] Li's study,[13] and the ADAURA study.[21]

In the ADAURA trial, patients with completely resected EGFR-mutant stage IB-IIIA (7th edition of TNM staging) NSCLC were randomly assigned to receive either 3-generation osimertinib or placebos for 3 years. The primary endpoint was DFS among patients with stage II-IIIA disease. Postoperative adjuvant chemotherapy before randomisation was allowed but

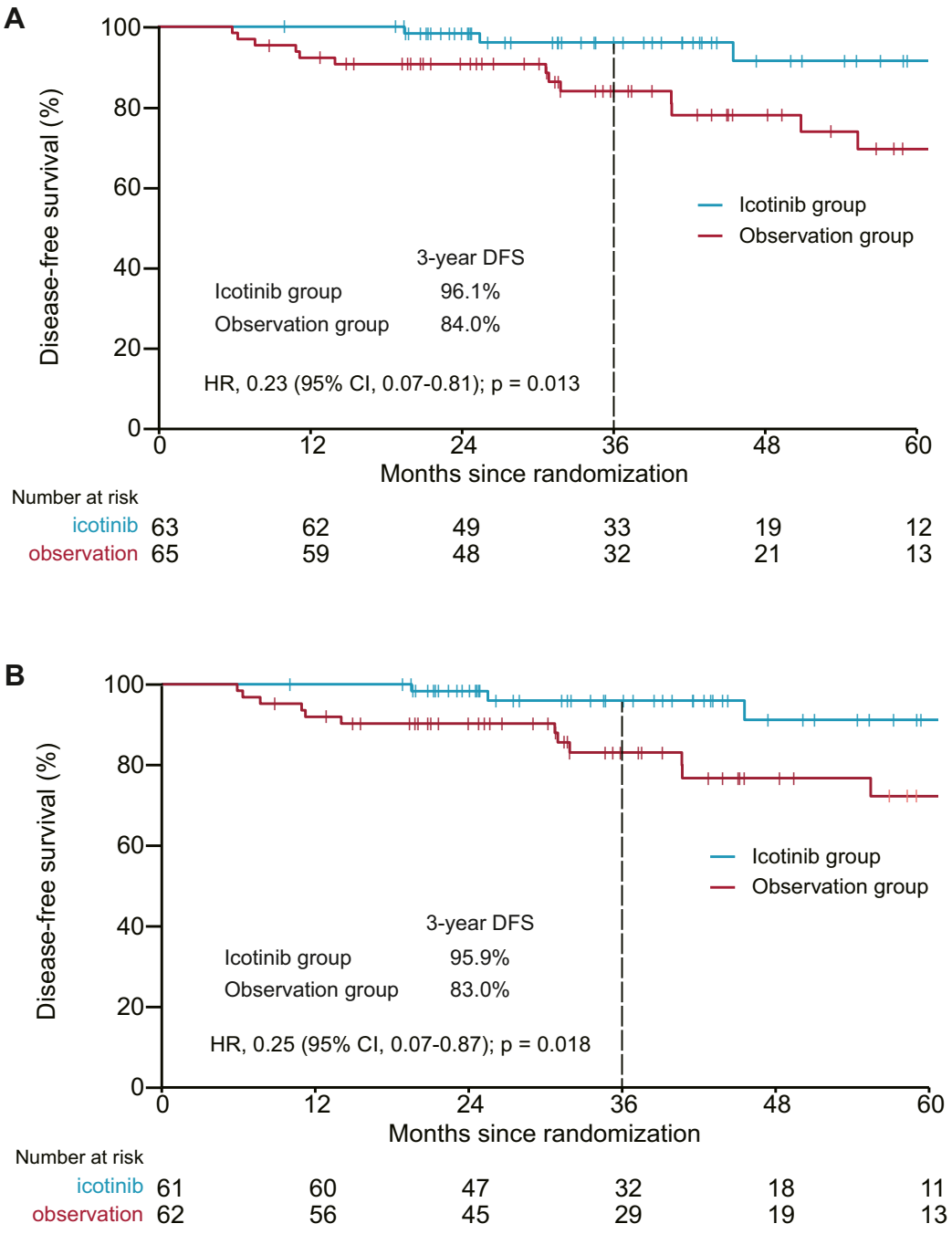

***Fig. 2:* Kaplan–Meier curves for disease-free survival in the overall population based on (A) 7th edition of TNM staging system and (B) 8th edition of TNM staging system.** DMS, disease-free survival; HR, hazard ratio; CI, confidence interval.

not mandatory. In the stage IB-IIIA population, osimertinib was associated with an 80% reduction in the risk of disease relapse or death, and the 1-year DFS rates were 89% in the osimertinib group and 52% in the placebo group.[21] Based on the results from ADAURA, osimertinib became the first approved targeted drug for NSCLC in the adjuvant setting. In exploratory analyses, the DFS in the stage IB population was similarly improved for patients who had received osimertinib, with an HR of 0.39 (95% CI, 0.18–0.76). An exploratory analysis of DFS based on the AJCC 8th edition TNM staging system also favoured osimertinib in the stage IB

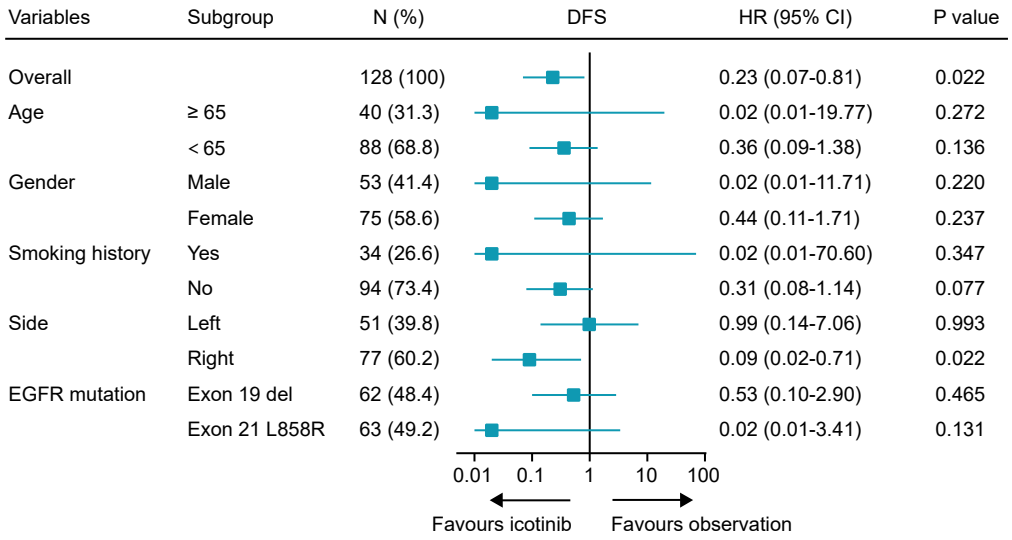

***Fig. 3:* Subgroup analyses of disease-free survival with respect to baseline characteristics.** N, number; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; EGFR, epidermal growth factor receptor.

population, with an HR of 0.38 (0.17–0.84).[22] Of note, adjuvant chemotherapy was administered to approximately one-quarter (26%) of patients with stage IB disease. Unlike the ADAURA study, CORIN is a trial designed specifically for stage IB EGFR-mutant NSCLC. To preclude confoundment by adjuvant chemotherapy, we only enrolled patients who had not received adjuvant chemotherapy according to physician and patient choices. In our study, icotinib was associated with a 75%–77% reduction in the risk of disease relapse or death, with an HR of 0.23 (95% CI, 0.07–0.81) for the 7th edition of TNM staging and an HR of 0.25 (95% CI, 0.07–0.87) for the 8th edition of TNM staging. Compared with the results of stage IB disease from the ADAURA trial, a great treatment effect on DFS was observed in our study. One important possible reason is that 96% patients were restaged as IB stage (8th edition of staging) in CORIN, whereas only about 50% were restaged as IB stage in ADAURA. Direct comparisons of different EGFR-TKIs in the adjuvant setting of NSCLC are needed. The OS data of CORIN are not mature and the OS was not significantly different between the two groups now. Actually, DFS benefit also did not translate into a significant difference in OS in ADJUVANT, ADAURA, and EVIDENCE, supporting DFS being a surrogate for OS in the adjuvant setting of NSCLC. The OS improvement of adjuvant EGFR-TKIs was only reported in the EVAN trial.[30]

In ADAURA, the treatment duration of osimertinib was set to be 3 years, and the median treatment duration was 22.5 months.[21] However, some patients in ADAURA seem to have been overtreated for years at a high cost to society and have suffered from AEs.[31] Using third-generation osimertinib in the adjuvant setting may lead to emerging patterns of acquired resistance.[32] In the EVIDENCE trial, patients in the TKI arm were planned to receive first-generation icotinib for 2 years, and the median treatment duration was 22.2 months.[18] In our study, the treatment duration of icotinib was set as 1 year. AEs were more frequent in ADAURA and EVIDENCE; grade ≥3 AEs were observed in 20% of patients in the osimertinib arm in ADAURA, 11% of patients in the icotinib arm in EVIDENCE, and 6.3% of patients in the icotinib arm in our study. The type and grade of AEs recorded in our study are consistent with the known safety profiles of icotinib.[23] Notably, interstitial lung disease occurred in 3% of patients in ADAURA, whereas no interstitial lung disease was recorded in EVIDENCE or our study. It seems that a shorter treatment duration is associated with fewer toxicities. The therapy duration and the selection of appropriate EGFR-TKIs should balance the anticipated treatment benefit and harm. Circulating tumour DNA (ctDNA) has shown potential value in guiding early individualised cancer interventions for early-stage NSCLC.[33,34] Longitudinal ctDNA positive was associated with inferior DFS for resected stage IA-IIIA EGFR-mutant NSCLC.[35] The optimal treatment duration and medicine choice of adjuvant EGFR-TKIs and the role of ctDNA in adjuvant EGFR-TKIs treatment remain to be determined.

Caution should be taken when interpreting our results in view of the fact that this is an open-label and single-centre phase 2 study focusing on stage IB NSCLC patients without chemotherapy. The main limitations of this study include the relatively small sample size and the immature OS data. The follow-up will continue, and the survival results might be updated. Furthermore, patients with uncommon EGFR mutations were allowed

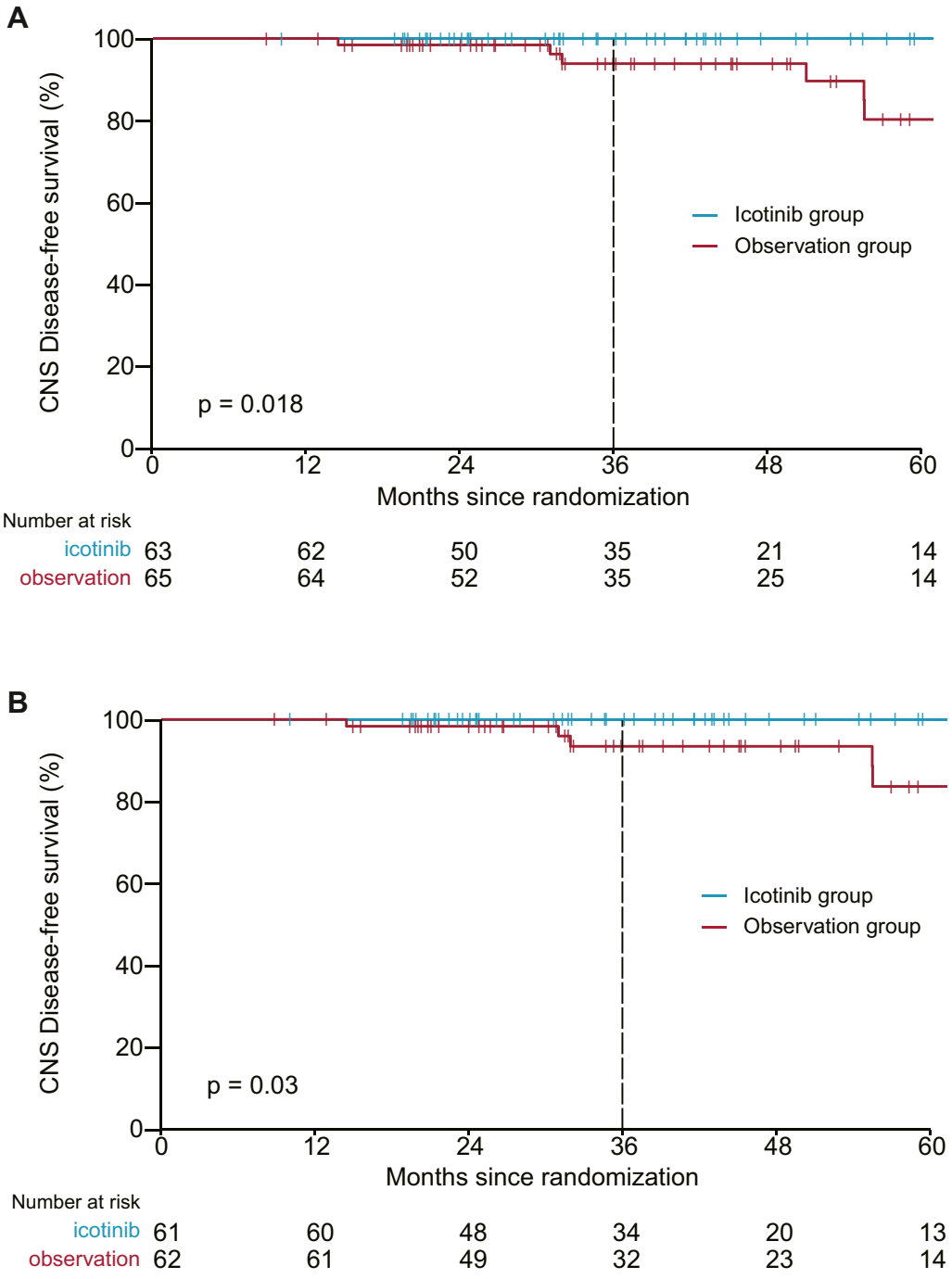

Fig. 4: **Kaplan–Meier curves for central nervous system (CNS) disease-free survival in the overall population based on (A) 7th edition of TNM staging system and (B) 8th edition of TNM staging system.**

in this study, although an exploratory analysis of DFS in patients with sensitive EGFR mutations confirmed the superiority of icotinib. Because icotinib was only approved in China for resected EGFR-mutant stage II-IIIA non-small cell lung cancer (NSCLC) in the adjuvant setting, we only included Chinese patients in this study, which may not be generalisable in other populations. However, these limitations do not seem to have distorted our findings. Despite these limitations, our data still support important evidence on adjuvant

	AEs		
	Any grade	Grade 1-2	Grade ≥3
Total[a]	49 (77.8%)	45 (71.4%)	4 (6.3%)
Rash	25 (39.7%)	24 (38.1%)	2 (3.2%)
Diarrhoea	13 (20.6%)	12 (19.0%)	1 (1.6%)
Pain	7 (11.1%)	7 (11.1%)	1 (1.6%)
Elevated ALT	6 (9.5%)	6 (9.5%)	0
Decreased appetite	5 (7.9%)	5 (7.9%)	0
Insomnia	4 (6.3%)	4 (6.3%)	0
Fatigue	4 (6.3%)	4 (6.3%)	0
Nausea	3 (4.8%)	3 (4.8%)	0
Leukopenia	3 (4.8%)	3 (4.8%)	0
Oral ulcers	3 (4.8%)	3 (4.8%)	0
AST increased	3 (4.8%)	3 (4.8%)	0
Vomiting	2 (3.2%)	2 (3.2%)	0
Cough	2 (3.2%)	2 (3.2%)	0
Pruritus	2 (3.2%)	2 (3.2%)	0
Dizziness	2 (3.2%)	2 (3.2%)	0
Anaemia	1 (1.6%)	1 (1.6%)	0
Constipation	1 (1.6%)	1 (1.6%)	0

Data are n (%). All AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0). AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate transaminase. [a]Total patients who had at least one AE; some patients had more than one AE.

Table 2: **Adverse events in the icotinib group (n = 63).**

EGFR-TKIs for patients with resected stage IB NSCLC with EGFR mutations. The ADAURA2 trial (NCT05120349) comparing 3-year osimertinib and observation in stage IA2-IA3 EGFR-mutant NSCLC is currently recruiting patients. The ICTAN (GASTO1002) trial (NCT01996098) comparing chemotherapy followed by 6-month or 12-month icotinib with chemotherapy as adjuvant therapy in stage IIA-IIIA NSCLC harbouring EGFR mutations is underway to further investigate the role of icotinib in the adjuvant setting for NSCLC.

In conclusion, to our knowledge, CORIN is the first prospective study to demonstrate that adjuvant icotinib improves 3-year DFS compared with observation for patients with stage IB EGFR-mutant NSCLC after complete resection, with acceptable safety and tolerability. Thus, icotinib provides a treatment option for such patients. Further studies to elucidate individualised strategies for adjuvant EGFR-TKI therapy in patients with early-stage NSCLC are warranted.

Contributors

SYW and LMD designed the research. WO, NL, BXW, TFZ, WGC, ZHC, XXH and SYW performed the research and collected data. All authors analysed and interpreted the data. WO, NL and SYW have verified the underlying data. WO, NL, and BXW draughted the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

Data sharing statement

The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (www.researchdata.org.cn), with the approval RDD number as RDDA2022873224. The datasets used and/or analysed during the current study are available from the corresponding author on a reasonable request.

Declaration of interests

LMD and ZLS are employees of Betta Pharmaceuticals Co., Ltd. TW and YP are employees of Hangzhou Repugene Technology Co., Ltd. Other co-authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101839.

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