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Combination of icotinib and chemotherapy as first-line treatment for advanced lung adenocarcinoma in patients with sensitive EGFR mutations: A randomized controlled study

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ABSTRACT

Objective: To explore the efficacy and safety of icotinib with chemotherapy as first-line therapy for advanced lung adenocarcinoma in patients with sensitive epidermal growth factor receptor (EGFR) mutations.
Methods: This prospective, randomized, controlled trial was conducted in 10 general hospitals in Shandong Province, China. Previously untreated patients with advanced lung adenocarcinoma and sensitive EGFR mutations were recruited between January 16, 2014 and December 31, 2016 and randomly allocated to the combination group (icotinib plus pemetrexed and carboplatin) or the icotinib only group. The patients were followed up until May 23, 2018. The primary endpoint was progression-free survival (PFS).
Results: The efficacy analysis (intention-to-treat analysis) include 179 patients (n = 90 in the combination group and n = 89 in the icotinib only group). PFS was significantly longer in the combination group than in the icotinib only group (16.0 months vs. 10.0 months, hazard ratio [HR] = 0.59, 95% confidence interval [CI] 0.42–0.84, P = 0.003). The objective response rate and the disease control rate for the combination group were significantly higher than those for the icotinib only group (77.8% vs. 64.0%, χ^2 = 4.094, P = 0.043; 91.1% vs. 79.8%, χ^2 = 4.632, P = 0.031). However, overall survival did not differ between the two groups (36.0 months vs. 34.0 months, HR = 0.81, 95%CI 0.54–1.22, P = 0.309). The incidence rates of leukopenia and liver function damage of grades 3–4 were higher in the combination group than in the icotinib only group (12.2% vs. 0%, χ^2 = 11.086, P = 0.001; 12.2% vs. 3.5%, χ^2 = 4.488, P = 0.034). However, adverse events were resolved in most patients.
Conclusion: Use of the combination of icotinib and chemotherapy as first-line therapy significantly improved the PFS of advanced lung adenocarcinoma patients with sensitive EGFR mutations. Although the combination therapy increased the incidence of leukopenia and liver function damage, the observed adverse events were tolerable and manageable.

1. Introduction

Lung cancer has the highest incidence and mortality among malignant tumors, and lung adenocarcinoma is the most common type of lung cancer [1,2]. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs, hereinafter referred to as TKIs) offer significantly greater efficacy than chemotherapy in patients with TKI-sensitive EGFR mutations, and for this reason, TKIs are now the first-line therapy for advanced lung adenocarcinoma in patients with sensitive EGFR mutations [3,4]. Although the progression-free survival

Abbreviations: EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; PFS, progression-free survival; OS, overall survival; RECIST, Response Evaluation Criteria In Solid Tumors; ECOG, PS Eastern Cooperative Oncology Group performance status; ULN, upper limits of normal; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SPSS, Statistical Package for the Social Sciences; AUC, area under the curve; CEA, carcinoembryonic antigens; SCC, squamous cell carcinoma antigen; NSE, neuron-specific enolase; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; DCR, disease control rate; HR, hazard ratio; CI, confidence interval; NSCLC, non-small cell lung cancer

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(PFS) of these patients has been extended with the use of TKIs, after 10–14 months of treatment with first-generation TKIs, acquired resistance usually develops [5]. The phase 3 study of the second-generation TKIs (dacomitinib) showed a median PFS of 15months [6], while the study of the third-generation TKIs (osimertinib) showed a median PFS of 19 months [7]. At the time of conception of the study, it was assumed that the combination of TKIs with other treatment modalities might prolong PFS, and after progression, the third-generation TKIs might be effective in patients with T790M-positive. Therefore, treatment strategies are needed to prevent TKIs resistance and therefore prolong PFS and overall survival (OS).

Platinum combined with pemetrexed is a first-line chemotherapy regimen for lung adenocarcinoma [8]. Several studies have explored whether administration of TKIs in combination with chemotherapy can prolong PFS and OS in patients with advanced lung adenocarcinoma and sensitive EGFR mutations. For example, Han et al. found that gefitinib given together with chemotherapy resulted in a longer PFS than either chemotherapy or gefitinib alone [9]. Moreover, in patients with advanced lung adenocarcinoma and sensitive EGFR mutations, the NEJ005 study found that both PFS and OS were extended by concurrent combined treatment with gefitinib and chemotherapy [10,11] compared with the PFS and OS achieved with TKI monotherapy [12].

As another of the first-generation TKIs, icotinib shows no difference in efficacy and safety from gefitinib [13]. However, no studies have investigated whether first-line treatment with icotinib and chemotherapy in combination can improve the PFS and OS for advanced lung adenocarcinoma patients with sensitive EGFR mutations. An in vitro study reported that icotinib and pemetrexed can have a synergistic effect on cancer cells [14]. The present study was designed to investigate whether icotinib combined with chemotherapy (carboplatin/pemetrexed) can prolong PFS and OS in previously untreated patients with advanced lung adenocarcinoma and sensitive EGFR mutations and to explore the safety of this combination therapy.

2. Patients and methods

2.1. Study design and patient population

This prospective, randomized, controlled, open-label trial was designed to compare the efficacy and safety of first-line therapy with the combination of icotinib and chemotherapy to those of first-line therapy with icotinib only advanced lung adenocarcinoma in patients with TKI-sensitive EGFR mutations. Patients were screened for potential eligibility at 10 general hospitals in Shandong Province, China from January 16, 2014 to December 31, 2016. The inclusion criteria were as follows: 1) age ≥18 years; 2) pathology-based diagnosis of lung adenocarcinoma; 3) stage IIIB or IV disease or stage IIIA inoperable disease according to the 7th edition of the TNM staging criteria for lung cancer issued by the 2009 International Association for the Study of Lung Cancer; 4) positivity for a known TKI-sensitive EGFR mutation (exon-18, exon-19 or exon-21) on Amplification Refractory Mutation System real-time PCR detection; 5) no prior treatment with surgery, chemotherapy, radiotherapy, TKIs or immunotherapy before enrollment; 6) at least one accurately measured lesion according to the Response Evaluation Criteria In Solid Tumors (RECIST, version 1.1); 7) an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2 points; 8) routine blood test results of a leukocyte count $\geq 4.0 \times 10^9$/ L, a platelet count $\geq 100 \times 10^9$/ L, and a hemoglobin level ≥10.0 g/ dL; 9) liver function indices of a total bilirubin level ≤1.5 times the upper limit of normal (ULN) and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≤2.5 × ULN; 10) renal function indices of a creatinine level ≤1.25 × ULN and a creatinine clearance rate ≥60 ml/min. Patients were excluded according to the following criteria: 1) negative for EGFR mutation or the lack of EGFR gene detection; 2) previous treatment with surgery, chemotherapy, radiotherapy, TKIs or immunotherapy for target lesions; 3) allergy to platinum, pemetrexed, TKIs or related ingredients; 4) severe heart, liver or kidney disease; 5) history of other malignant tumors in the previous 5 years (except for cured skin basal cell carcinoma and cervical carcinoma in situ); 6) brain metastases or spinal cord compression; 7) current pregnancy or lactation; and 8) poor compliance. This study was registered at *ClinicalTrials.gov* (NCT02031601) and received approval from the ethics committees of the 10 participating hospitals. Written informed consent was obtained from all patients.

2.2. Treatment protocol

Eligible patients were randomly assigned in a 1:1 ratio to either the combination treatment group, which received icotinib and standard chemotherapy (referred to as the combination group), and to the icotinib only group (referred to as the icotinib group). Simple randomization was performed by the Statistical Package for the Social Sciences (SPSS) software (version 25.0) to produce the random allocation sequence. The envelope method was used to conceal the sequence, that is, to store a random grouping scheme in opaque envelopes. According to the order of enrollment, envelopes were opened and the subjects were randomly assigned to different treatment groups. The combination group first received pemetrexed (500 mg/m^2 on day 1) plus carboplatin (area under the curve [AUC] × [creatinine clearance rate + 25], AUC = 5, on day 1) and then oral icotinib (125 mg, three times per day, on days 2–19) until 2 days before the start of the next chemotherapy. This treatment was repeated every 3 weeks for up to six cycles, and patients who did not experience cancer progression were maintained in an icotinib dose of 125 mg given three times per day. Tropisetron and palonosetron were routinely administered during chemotherapy to prevent vomiting. Long-acting recombinant human granulocyte colony-stimulating factor was administered to reduce the incidence of myelosuppression after chemotherapy. The icotinib group received oral icotinib monotherapy (125 mg, three times per day, daily). All therapies were continued until disease progression, unacceptable toxicity or death.

If disease progression was observed, the second-line treatment was selected by the attending physician. Three main strategies were used: 1) testing for the T790 M mutation of the EGFR gene with peripheral blood specimen was performed, and patients positive for the mutation received oral osimertinib (80 mg, once per day, daily); 2) patients without the T790 M mutation received chemotherapy, radiotherapy or a local therapy (such as radiofrequency ablation, microwave ablation, etc.); and 3) in some patients without the T790 M mutation, chemotherapy, radiotherapy or local therapy were applied along with continuation of oral icotinib until the attending physician thought icotinib should be discontinued.

In all patients, the tumor response was assessed according to the RECIST (version 1.1) every 2 months based on the results of chest computed tomography, abdominal B-ultrasound, brain magnetic resonance imaging, emission computed tomography bone scanning, and measurement of blood tumor markers. The detected lung cancer tumor markers included carcinoembryonic antigen (CEA), CYFRA21-1, CA-125, squamous cell carcinoma antigen (SCC), and neuron-specific enolase (NSE). If a new lesion was found on abdominal B-ultrasound during the trial, its presence was confirmed using abdominal computed tomography or magnetic resonance imaging. In cases of disease progression, the patients were followed up every 2 months until death or the study follow-up deadline. The cutoff date for follow-up observation of PFS and OS was May 23, 2018.

The safety of the combined treatment was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.0). Routine blood tests were performed weekly during chemotherapy for the combination group and only once per month for the icotinib group. Liver function and renal function were assessed before the start of each cycle of chemotherapy and one week after the finish of each cycle of chemotherapy, and were

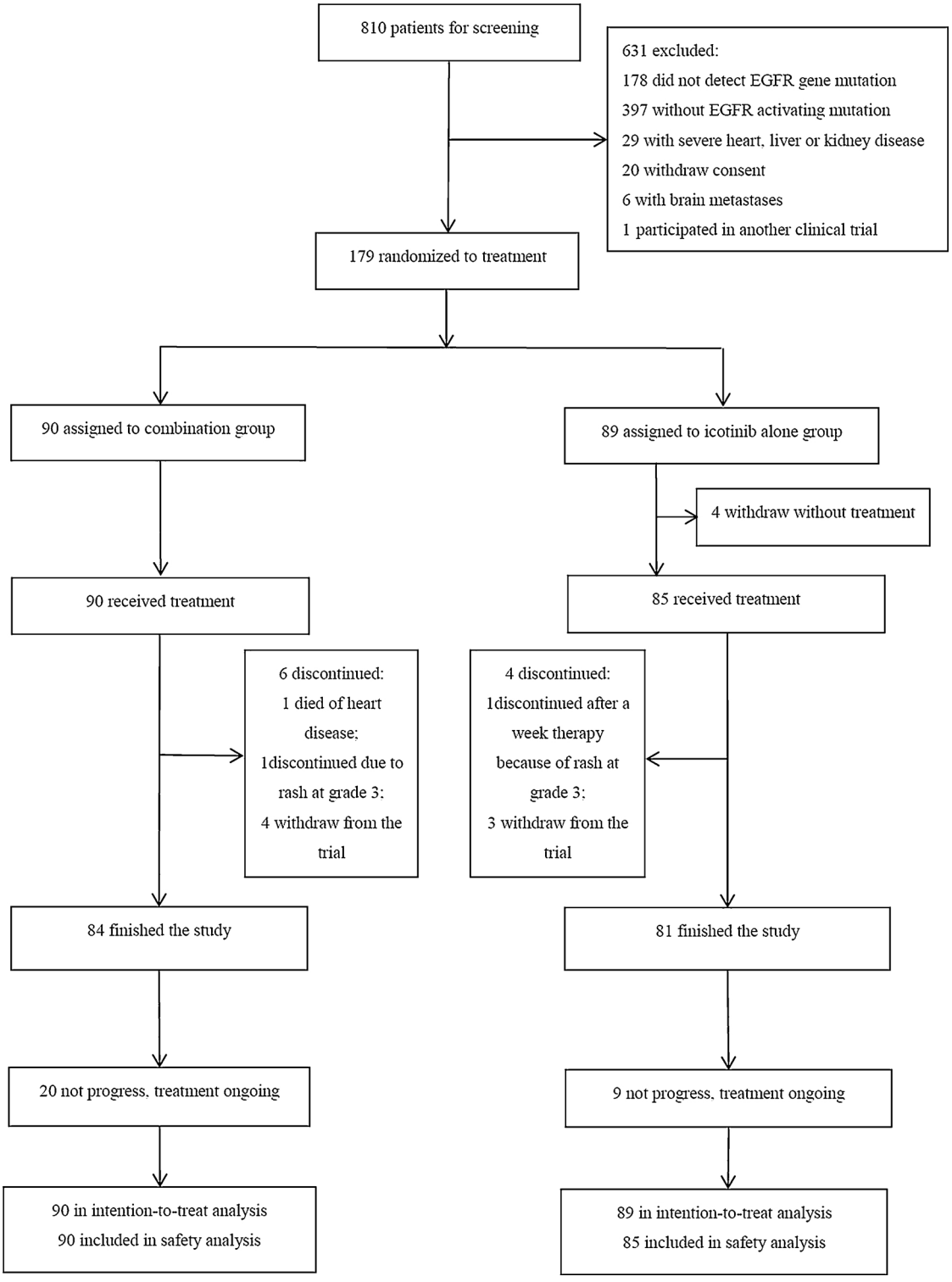

Fig. 1. Flow diagram of patient enrollment.

performed once per month when maintained with icotinib for the combination group. For the icotinib group, liver function and renal function were assessed once per month. All treatment-related adverse events in both groups were treated promptly. If a grade 3 or 4 toxic side effect occurred, either the dose of drug was reduced or the drug was discontinued. The carboplatin and pemetrexed doses were reduced by 20% of the original dose. Icotinib was reduced to the minimum dose (125 mg, once daily). Treatment might be discontinued depending on the patient's condition, but the longest treatment interruption could be no more than 2 weeks.

2.3. Outcome measures

The primary endpoint in this trial was PFS, which was defined as the time from the date of initiation of treatment to the first date of disease progression. For patients who did not experience disease progression before the end of the study or who were lost to follow-up, PFS was censored at the date of the last objective progression-free disease

Table 1
Comparison of patients' demographic and clinical characteristics between the combination group and icotinib group (intention-to-treat population).

Variable	Combination group (n = 90)	Icotinib group (n = 89)	χ^2 or t	P
Gender			2.439	0.118
Male	33 (36.7%)	23 (25.8%)		
Female	57 (63.3%)	66 (74.2%)		
Age (years)			0.278	0.598
≥65	29 (32.2%)	32 (36.0%)		
< 65	61 (67.8%)	57 (64.0%)		
Age (years)	58.6 ± 9.9	61.0 ± 9.5	−1.644	0.102
Smoking status			0.965	0.326
Ever smoker	26 (28.9%)	20 (22.5%)		
Never smoker	64 (71.1%)	69 (77.5%)		
TNM stage			2.377	0.305
IIIA	2 (2.2%)	6 (6.7%)		
IIIB	15 (16.7%)	16 (18.0%)		
IV	73 (81.1%)	67 (75.3%)		
ECOG PS			0.820	0.664
0	45 (50.0%)	39 (43.8%)		
1	39 (43.3%)	42 (47.2%)		
2	6 (6.7%)	8 (9.0%)		
EGFR mutation type			1.404	0.496
Exon-18 G719X	1 (1.1%)	0		
Exon-19 19-del	51 (56.7%)	52 (58.4%)		
Exon-21 L858R	38 (42.2%)	37 (41.6%)		
Specimen for EGFR mutation detection			4.182	0.759
Percutaneous lung biopsy	26 (28.9%)	29 (32.6%)		
Bronchoscopy biopsy	23 (25.6%)	26 (29.2%)		
Pleural effusion	18 (20.0%)	19 (21.3%)		
Peripheral blood	10 (11.1%)	8 (9.0%)		
Internal thoracoscopic biopsy	6 (6.7%)	2 (2.2%)		
Peripheral lymph node biopsy	5 (5.6%)	4 (4.5%)		
Bone marrow biopsy	1 (1.1%)	1 (1.1%)		
Lumbar puncture	1 (1.1%)	0		
Serum lung cancer tumor markers[a]			1.264	0.531
All normal	17 (18.9%)	16 (18.0%)		
CEA elevated, others normal	17 (18.9%)	23 (25.8%)		
Others elevated, CEA normal or elevated	56 (62.2%)	50 (56.2%)		

[a] Serum lung cancer tumor markers included CEA, CYFRA21-1, CA-125, squamous cell carcinoma antigen and neuron-specific enolase. Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; CEA, carcinoembryonic antigens.

assessment. Secondary endpoints included OS, the objective response rate (ORR), the disease control rate (DCR) and the incidence of adverse events. OS was defined as the time from the date of initiation of treatment to the date of death. For patients who remained alive at the end of the study or were lost to follow-up, OS was censored at the date of the last follow-up assessment. The ORR includes complete remission and partial remission, and the DCR considered complete remission, partial remission and stable disease.

2.4. Statistical analysis

The leading parameter for sample size calculation was PFS. According to previous reports, the median PFS with combined treatment was assumed to be 17 months and the median PFS with icotinib only was assumed to be 11 months [4,9,11]. The sample size needed to have a power of 80% to detect a hazard ratio (HR) of 0.65 with an α level of 0.05 was 160 patients in total according to a log rank test power analysis. All randomized patients (the intention-to-treat population) were included in the efficacy analysis. For those patients who discontinued or withdrew, follow-ups were performed as planned. Patients who did not reach first assessment after two months noted as being censored. Patients in the intention-to-treat population who received at least one dose of study drug were included in the safety analysis. Continuous data are expressed as the mean ± standard deviation and were compared using Student's t test. Categorical variables are expressed as a number (%) and were compared using χ^2 test. PFS and OS were described by Kaplan–Meier curves, and the log-rank test was used to explore differences in PFS and OS between the two groups. Subgroup analyses were performed using a Cox proportional hazard model to compare PFS between the two treatment groups, stratified by age, gender, ECOG PS score, smoking status, TNM stage, EGFR mutation type, and presence/levels of tumor markers. All statistical analyses were conducted with the SPSS software (version 25.0), and $P < 0.05$ was considered an indicator of statistical significance.

3. Results

3.1. Patients and treatment

A total of 810 patients were screened for participation in this study. There were 631 patients being excluded from the trial. Among those patients, 178 patients were excluded because they did not detect EGFR gene mutation; 397 patients were excluded due to the negative EGFR mutation; 29 patients with severe heart, liver or kidney disease were excluded; 20 patients were unwilling to participate in the trail; 6 patients with brain metastases were excluded; and 1 patients had participated in another clinical trial and was excluded. Finally, 179 patients were randomized to a treatment group from January 16, 2014 to December 31, 2016 (Fig. 1). The combination group consisted of 90 patients, whereas the icotinib group consisted of 89 patients. Six patients in the combination group discontinued (one patient died of coronary artery disease after one cycle of treatment and this death was regarded by investigators as not related to the study products; one patient discontinued therapy due to a rash of grade 3 that appeared after one 1 week of treatment, but follow-ups were performed as planned; one patients transferred to icotinib monotherapy after one cycle of treatment, but follow-ups were performed as planned; one patient accepted microwave ablation local treatment after one cycle of treatment and lost to follow; and two patients were no longer willing to participate after one cycle of treatment due to family financial burden and inconvenient transportation and lost to follow). Four patients in the icotinib group discontinued (one patient discontinued due to the appearance of grade 3 rash after 1 week of treatment, but follow-ups were performed as planned; three patients were no longer willing to participate after 4 weeks of treatment because of family financial burden, inconvenient transportation and poor compliance, and lost to follow); four patients in the icotinib group received no treatment and lost to follow (two patient suffered from rapid disease progression and consents were withdrawn; and two patients transferred to other clinical trials and consents were withdrawn). The attrition rates in the combination group and icotinib group did not differ statistically (6.7% vs. 9.0%; $\chi^2 = 0.335$, $P = 0.563$). Baseline data of the intention-to-treat population were balanced between two groups, including age, gender, ECOG PS score, smoking status, TNM stage, EGFR mutation type, EGFR gene test specimens, and serum lung cancer tumor markers (Table 1). The results of the per protocol analysis were added as the supplementary (supplementary Table 1).

In the combination group, 73 (81.1%) patients received at least four cycles of first-line chemotherapy, and the average number of first-line chemotherapy cycles in the combination group was 4.0 ± 1.5 cycles. The dose of icotinib was reduced to the minimum dose (125 mg/day) for 11 patients in the combination group and 6 patients in the icotinib group due to grade 3–4 rash, diarrhea or liver dysfunction (12.2% vs. 6.7%, $\chi^2 = 1.564$, $P = 0.211$). There were mainly five second-line treatment options: oral osimertinib; chemotherapy; radiotherapy or local therapy such as radiofrequency ablation or microwave ablation;

Table 2
Second-line treatments administered after disease progression in the combination and icotinib groups.

Treatment	Combination group (n = 66)	Icotinib group (n = 75)	χ^2	P
			0.791	0.940
Osimertinib	16 (24.2%)	18 (24.0%)		
Chemotherapy	20 (30.3%)	25 (33.3%)		
Continued oral icotinib	8 (12.1%)	6 (8.0%))		
Radiotherapy or local treatment	11 (16.7%)	14 (18.7%)		
Abandon treatment	11 (16.7%)	12 (16.0%)		

continued oral icotinib; and treatment cessation. The blood gene test for T790M was performed in 37 patients with disease progression in the combined group and in 36 patients with disease progression in the icotinib group. Sixteen cases in the combination group were positive for T790M mutation and received oral osimertinib, and while 18 cases in the icotinib group were positive for T790M mutation and received oral osimertinib (24.2% vs. 24.0%, $\chi^2 = 0.001$, P = 0.973). Second-line treatments administered after disease progression in the combination and icotinib groups were shown in Table 2. Notably, the second-line treatment regimen did not differ significantly between the two groups (Table 2).

3.2. Improvement in PFS with combination therapy

The shortest follow-up time was 17 months, and the longest follow-up time was 53 months. Sixty-six patients (73.3%) in the combination group experienced disease progression, whereas seventy-five patients (84.3%) in the icotinib alone group experienced disease progression. As shown by the data presented in Fig. 2A, the PFS in the intention-to-treat population of the combination group was significantly longer than of the icotinib group (16.0 months vs. 10.0 months, HR = 0.59, 95% confidence interval [CI] 0.42–0.84; χ^2 = 8.634, P = 0.003). Subgroup analyses of PFS by patient characteristics were generally consistent with the overall results (Fig. 3). The results suggested that patients aged ≥65 years might derive more benefit from combination therapy than from icotinib monotherapy (Fig. 3). For comparison, the results of the per protocol analysis were added as the supplementary (supplementary Figs. 1–3).

3.3. Greater efficacy of combination therapy versus icotinib monotherapy

In the combination group, 44 patients died; by comparison, in the icotinib group, 53 patients died (mortality rates of 48.9% vs. 59.6%, χ^2 = 2.049, P = 0.152). OS did not differ significantly between the two groups (36.0 months vs. 34.0 months, HR = 0.81, 95%CI 0.54–1.22; χ^2 = 1.035, P = 0.309; Fig. 2B). In the combination group, 2 patients (2.2%) achieved complete remission, 68 patients (75.6%) achieved a partial remission, 12 patients (13.3%) had stable disease, 3 patients (3.3%) experienced disease progression, and 5 patients (5.6%) could not be evaluated. In the icotinib group, 1 patient (1.1%) experienced complete remission, 56 (62.9%) achieved a partial remission, 14 patients (15.7%) had stable disease, 12 patients (13.5%) experienced disease progression, and 6 patients (6.7%) could not be evaluated. ORR and DCR for the combination group were significantly higher than those for the icotinib group (77.8% vs. 64.0%, χ^2 = 4.094, P = 0.043; 91.1% vs. 79.8%, χ^2 = 4.632, P = 0.031).

3.4. Comparable safety of combination therapy and icotinib monotherapy

A total of 175 patients were included in the safety analysis (90 patients in the combination group and 85 patients in the icotinib group). Grade 3–4 adverse events in the combination group included leukopenia (12.2%), elevated ALT or AST level (12.2%), rash (3.3%), nausea (4.4%), diarrhea (2.2%), fatigue (1.1%), and elevated total bilirubin (1.1%). In contrast, those in the icotinib group were rash (3.5%), elevated ALT or AST level (3.5%) and diarrhea (1.2%; Table 3). The incidence rates of grade 3–4 leukopenia and an elevated ALT or AST level were higher in the combination group than in the icotinib group (12.2% vs. 0%, χ^2 = 11.086, P = 0.001; 12.2% vs. 3.5%, χ^2 = 4.488, P = 0.034). However, upon reduction of the dose of carboplatin and pemetrexed or icotinib and administration of granulocyte stimulating factor or hepatoprotective drugs, patients in both groups experienced relief from the adverse events and completed the study. The incidence rates of grade 3–4 rash, nausea, diarrhea, fatigue and elevated total bilirubin did not differ significantly between the two treatment groups. One patient in each group withdrew from the study due to grade 3 rash, and other patients recovered after symptomatic treatment and drug dose reduction. No cases of interstitial pneumonia or renal dysfunction occurred in the two groups, and no grade 5 drug-related adverse events were observed in either group.

4. Discussion

The main findings of this randomized, controlled trial were as follows: the first-line combination therapy led to a significantly longer PFS than did icotinib therapy only, and the ORR and DCR with the combination therapy were significantly higher than those achieved with icotinib only; the results of subgroup analysis suggested that patients aged ≥65 years might derive more benefit from combination therapy than from icotinib monotherapy; OS did not differ significantly between the groups receiving the combination therapy or icotinib only; and finally, the incidence of leukopenia and liver function damage of grades 3–4 was greater with the combination therapy than with icotinib only, but these adverse effects could be tolerated and managed.

A retrospective analysis suggested that the PFS and OS achieved with icotinib combined with chemotherapy were significantly longer than those achieved with icotinib alone in a group of NSCLC patients with EGFR mutations [15]. In the present prospective, randomized, controlled trial, we found that PFS in the combination group was significantly longer than that in the icotinib group, and moreover, the ORR and DCR in the combination group were significantly higher than those in the icotinib group. The NEJ005 study compared a concurrent regimen and a sequential alternating regimen for the combination of gefitinib and chemotherapy [10,11]. Our in vitro studies suggested that the sequential administration of pemetrexed followed by icotinib exerted a synergistic effect on EGFR-mutant human lung adenocarcinoma cell lines [16], and that the volume and weight of tumor xenografts in the sequential pemetrexed followed by icotinib group were significantly smaller than sequential icotinib followed by pemetrexed group [14]. Therefore, we used an intercalated regimen for combined treatment with icotinib and chemotherapy. The possible theoretical basis was as followed. On one hand, antagonism may occur with simultaneous application of a TKI with chemotherapy or with chemotherapy given immediately after the TKI. In vitro studies showed that pretreatment with erlotinib caused arrest of cells in G1 phase, decreasing the cytotoxicity of chemotherapy and reducing apoptosis, which would negatively affect the efficacy of chemotherapy [17]. One the other hand, it was discovered that temporary discontinuance of TKIs before chemotherapy allows the cancer cells to re-enter the cell cycle, restoring their sensitivity to chemotherapy [18–20]. The strategy was also supported by FASTACT-2 and several other clinical researches [21–23]. However, the NEJ005 study showed improved OS for the concurrent schedule of gefitinib and chemotherapy [10,11]. Clinical studies might be affected by a variety of factors, which resulted in the inconsistent results with in vitro studies.

The results of subgroup analysis suggested that patients aged ≥65 years might derive more benefit from combination therapy than from icotinib monotherapy. However, interpretation of subgroup analyses is

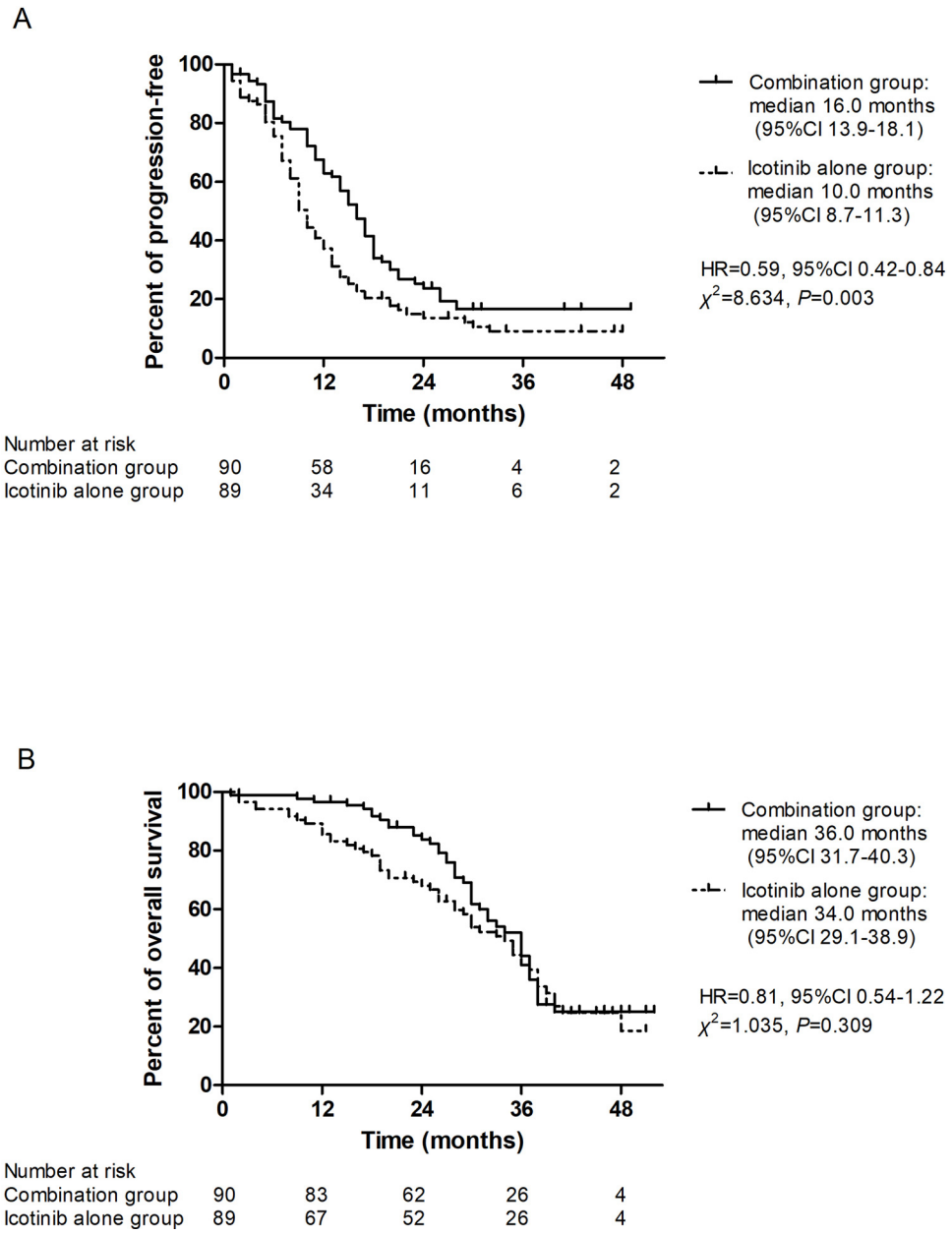

Fig. 2. PFS and OS for combination therapy versus icotinib monotherapy (intention-to-treat population).

limited by the small sample sizes and baseline imbalances. Larger sample size trails are needed for verification. Prior research found that increased levels of CEA, NSE and SCC were common in lung adenocarcinoma, small cell lung cancer and squamous cell carcinoma, respectively [24–26]. Additional studies explored the relationship between elevated tumor markers and the efficacy of chemotherapy or TKIs and found that the efficacy of chemotherapy in patients with a normal CYFRA21-1 level and elevated CEA level was better than that in patients with a normal CEA level and elevated CYFRA21-1 level [27–29]. Another study found that squamous cell carcinoma patients with elevated CYFRA21-1 and CEA levels benefited from adjuvant chemotherapy in addition to surgery [30]. However, the subgroup analysis in the present study showed no difference about the therapeutic benefits between patients with different tumor markers.

In the present study, the OS of the combination group was 36.0 months, which was shorter than that in the NEJ005 study (41.9 months) [10]. This difference might be related to the different maintenance treatment regimens applied. In the present study, patients in the combination group who did not experience disease progression received icotinib only as maintenance therapy, whereas patients in the NEJ005 study received TKIs and pemetrexed as maintenance therapy [10,11]. In addition, the NEJ005 study recruited some patients with post-operative recurrence, which contributed to the longer OS [10,11]. No intervene in second-line treatments of patients after disease progression might be another reason for the shorter OS. Unlike the NEJ005 study, the present study did not find a difference in OS between the two treatment groups. Several reasons contributed to the lack of significance in OS difference. Firstly, patients with ECOG PS of 2 points were included in the trial, while those patients were excluded in other trials. However, as shown in the subgroup analysis of PFS (Fig. 3), the HR was > 1 for patients with ECOG PS of 2 points. As a matter of fact, increased toxicity in those patients could also explain the lack of a difference in OS between the treatment groups. Secondly, the pathological type of lung cancer can change after treatment. In one case reported in the literature, the postoperative diagnosis was squamous cell carcinoma for a TNM IIIA patient who received adjuvant chemotherapy

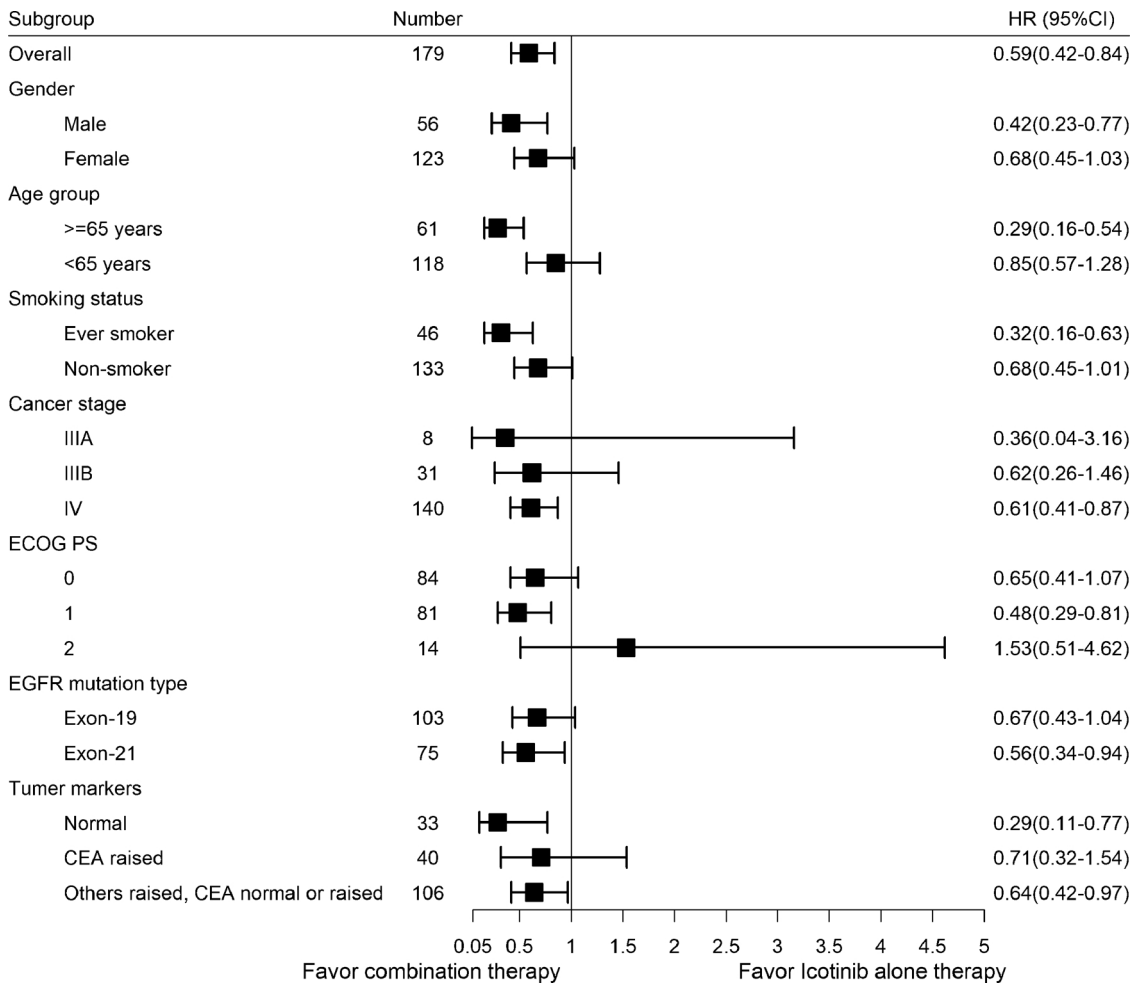

Fig. 3. Subgroup analysis of PFS (intention-to-treat population).

Table 3
Incidence of adverse reactions in the combination group and icotinib group.

Adverse reactions	Combination group (n = 90)		Overall incidence (%)	Icotinib group (n = 85)		Overall incidence (%)	χ^2	P*
	Grade 1–2	Grade 3–4		Grade 1–2	Grade 3–4			
Hematological toxicity								
Leukopenia	27(30.0%)	11(12.2%)	38(42.2%)	7(8.2%)	0	7(8.2%)	26.434	< 0.001
Anemia	21(23.3%)	0	21(23.3%)	4(4.7%)	0	4(4.7%)	12.387	< 0.001
Thrombocytopenia	8(8.9%)	0	8(8.9%)	1(1.2%)	0	0(1.2%)	6.079	0.014
Non-hematologic toxicity								
Loss of appetite	55(61.1%)	0	55(61.1%)	22(25.9%)	0	22(25.9%)	22.018	< 0.001
Fatigue	48(53.3%)	1(1.1%)	49(54.4%)	7(8.2%)	0(0)	7(8.2%)	42.896	< 0.001
Nausea	43(47.8%)	4(4.4%)	47(52.2%)	3(3.5%)	0	3(3.5%)	50.787	< 0.001
Vomiting	6(6.7%)	0	6(6.7%)	1(1.2%)	0	1(1.2%)	3.820	0.051
Rash	30(33.3%)	3(3.3%)	33(36.7%)	32(37.6%)	3(3.5%)	35(41.2%)	0.374	0.541
Diarrhea	29(32.2%)	2(2.2%)	31(34.4%)	27(31.8%)	1(1.2%)	28(32.9%)	0.044	0.833
Alopecia	13(14.4%)	0(0)	13(14.4%)	1(1.2%)	0(0)	1(1.2%)	10.456	0.001
Oral mucositis	7(7.8%)	0(0)	7(7.8%)	5(5.9%)	0(0)	5(5.9%)	0.246	0.620
Liver or kidney function								
Elevated ALT or AST	34(37.8%)	11(12.2%)	45(50.0%)	17(20.0%)	3(3.5%)	20(23.5%)	13.120	< 0.001
Elevated bilirubin	5(5.6%)	1(1.1%)	6(6.7%)	1(1.2%)	0	1(1.2%)	3.820	0.051
Elevated creatinine	0	0	0	0	0	0	–	–
Elevated blood urea nitrogen	0	0	0	0	0	0	–	–
Pulmonary fibrosis (radioactive change)	0	0	0	0	0	0	–	–

* The comparation of overall incidence between 2 groups. Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

and operation, but upon recurrence, biopsy using bronchoscopy indicated small cell carcinoma [31]. Other studies suggested that the transformation of adenocarcinoma into the small cell carcinoma pathology type might be a rare mechanism of TKI resistance [32,33]. However, it is often difficult to obtain the second biopsy after disease progression, because the location is difficult to biopsy or patients reject the biopsy. Thirdly, given that the PFS was the primary endpoint, the trial was not powered to show statistical significance in OS because of

the small sample size. Large sample size clinical trials are needed.

Consistent with the results of previous studies, the present study found that the incidence of leukopenia and liver damage of grades 3–4 was greater among patients who received the combination therapy than among those who received icotinib monotherapy [9,10]. However, after reduction of the dose of chemotherapy and treatment with granulocyte-stimulating factor drugs or liver protective drugs, most patients recovered from these adverse effects and finished the study. Therefore, although icotinib combined with chemotherapy was associated with an increased incidence of adverse effects of myelosuppression and liver dysfunction, the adverse events were tolerable and manageable. In this study, the incidences of adverse events of grades 3 and 4 were consistent with Han et al. [9] But the incidences of grade 3–4 leukopenia, anemia, thrombocytopenia and diarrhea in the combination group were lower than the NEJ005 study [11]. Preventive treatments for adverse events after chemotherapy might explain the lower incidence of grade > 3 adverse events. To reduce the incidence of myelosuppression after chemotherapy, patients in the trial were rejected with the long-acting recombinant human granulocyte colony-stimulating factor to enhance and protect the function of the hematopoietic system. In addition, patients received palonosetron for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. It was assumed that the administration of antiemetic drugs during and after chemotherapy might ensure successful completion of the treatment.

In the FLAURA study, osimertinib showed efficacy superior to that of gefitinib and erlotinib in the first-line treatment of EGFR mutation–positive advanced NSCLC [7]. The National Comprehensive Cancer Network incorporated osimertinib as a first-line option for advanced NSCLC in patients with sensitive EGFR mutations in its guidelines [34]. Currently, there are several first-line treatment options for NSCLC patients with positive EGFR mutations. According to the results of the trial and other researches, the combination of TKIs and chemotherapy significantly prolonged the PFS. The overall survival of a patient depends largely on the patient's efficacy at the time of initial treatment. Therefore, more trials are needed to explore the optimal treatment to achiever the longer OS for patients in future. In addition, further researches will explore the second-line treatments after resistance to osimertinib.

To the best of our knowledge, our trial is the first to find that the first-line combination of icotinib and chemotherapy might improve the PFS of patients with TKI-sensitive EGFR mutations in China. Several limitations of this trial must be considered though. First, all study participants came from the same province in China, and thus, the study population reflects a rather homogenous patient population. The treatment efficacy might differ in patients from different geographic regions. Moreover, the sample size was small, which might also have influenced the trial results. Although there were 810 patients being screened for participating in this study, only 179 patients were included and randomized. Most of those patients were excluded due to the negative EGFR gene mutation or lack of the detection of the EGFR gene mutation. Therefore, larger trials with a more heterogenous patient population are needed to validate our results. Secondly, because the choice of second-line treatments might be affected by many factors (such as patients' personal will, patients' financial burden, and adverse reactions, etc.), this trial did not intervene in second-line treatments of patients after disease progression. The testing for T790 M gene mutation was not performed in all patients who experienced disease progression. At the time of trial initiation, osimertinib was not widely used and was expensive [35]. Some patients were unable to pay the cost of three-generation TKI osimertinib due to family financial burden, so they refused to perform T790 M testing after the disease progressed. Some of the patients who were not tested for T790 M, if they indeed had the mutation, might have experienced longer OS if they had received osimertinib. Thirdly, some patients in this study continued oral icotinib after disease progression, which might not have improved their survival. The IMPRESS study reported that for NSCLC patients who experience disease progression after first-line treatment of gefitinib, PFS and OS might be shortened with second-line treatment with gefitinib plus chemotherapy [36]. Therefore, physicians should be warned against the continuation of treatment with first-generation TKIs after disease progression when second-line chemotherapy is initiated. Fourthly, patients with asymptomatic brain metastases were not allowed in the trial. At the time of conception of the study, there were still some controversies to use an TKI as first-line treatment for metastatic brain tumors [37,38]. However, at present, a phase 3 study demonstrated that icotinib was associated with significantly longer intracranial PFS than whole-brain irradiation plus chemotherapy in patients with EGFR-mutant NSCLC and multiple brain metastases [39]. TKIs have promising clinical activity in EGFR-mutant NSCLC patients with brain metastases. Fifthly, health-related quality of life should be assessed for patients with cancer in addition to efficacy and safety analysis of treatments. It is essential to ensure that any clinical gains do not come at the expense of intolerable reductions in quality of life [40]. Further studies should explore the quality of life of lung cancer patients with treatments.

5. Conclusion

In conclusion, the first-line combination of icotinib and chemotherapy significantly improved the PFS, ORR and DCR among advanced lung adenocarcinoma patients with sensitive EGFR mutations. Although the combination therapy increased the incidence of leukopenia and liver function damage of grades 3 and 4, the observed adverse events were tolerable and manageable.

Ethics approval and consent to participate

This study was registered at *ClinicalTrials.gov* (NCT02031601) and received approval from the ethics committees of the 10 participating hospitals. Written informed consent was obtained from all patients.

Availability of full trial protocol

The full trial protocol is available from the corresponding author on reasonable request.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.05.008.

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