

Apatinib plus Chemotherapy as a Second-Line Treatment in Unresectable Non-Small Cell Lung Carcinoma: A Randomized, Controlled, Multicenter Clinical Trial

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TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT03256721
- **Sponsor:** Zongyang Yu
- **Principal Investigator:** Zongyang Yu
- **IRB Approved:** Yes

LESSONS LEARNED

- The efficacy of second-line treatment for advanced non-small cell lung carcinoma (NSCLC) without a sensitizing driver gene mutation is still unsatisfactory. The combination of apatinib and chemotherapy improved progression-free survival in the second-line therapy of advanced NSCLC without a sensitizing mutation.
- This study offers a new treatment strategy for second-line treatment of such patients but requires confirmation in a larger multi-institutional trial.

ABSTRACT

Background. This study explored the efficacy and safety of apatinib combined with single-agent chemotherapy versus single-agent chemotherapy in the second-line treatment of advanced non-small-cell lung carcinoma (NSCLC) without driver mutations.

Methods. In this double-arm, open label, exploratory clinical study, we enrolled patients with unresectable locally advanced or advanced NSCLC without driver mutations that had progressed following first-line chemotherapy. The subjects were allocated into an experimental group and a control group by 2:1. The experimental group received apatinib combined with four cycles of docetaxel or pemetrexed until disease progression, intolerable toxicity, or discontinuation at the patient's request. The control group only received

four cycles of docetaxel or pemetrexed. The primary endpoints were progression-free survival (PFS), and the secondary endpoints were overall survival (OS), disease control rate (DCR), and safety.

Results. Thirty-seven patients were enrolled. The efficacy of 33 patients was evaluated. The median PFS was 5.47 versus 2.97 months, the DCR was 95% versus 73%, and the objective response rate (ORR) was 27% versus 9% in the experimental versus control group. The OS was still under follow-up. The most common adverse effects included hypertension, hand-foot skin reaction (HFSR), and fatigue.

Conclusion. Apatinib combined with single-agent chemotherapy may be a novel option for second-line treatment of advanced NSCLC *The Oncologist* 2020;25:e1640–e1649

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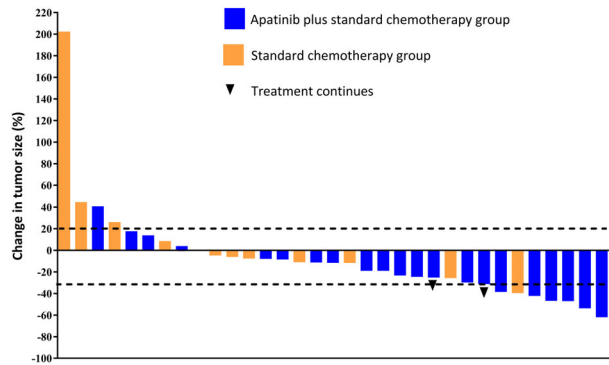


Figure 1. Waterfall plots of the largest percentage changes from the baseline in the sum of the longest tumor diameters for patients in the apatinib plus standard chemotherapy group and standard chemotherapy group.

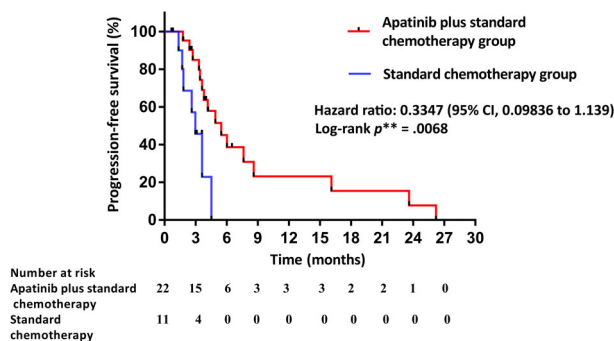


Figure 2. Kaplan-Meier curves for progression-free survival between the apatinib plus standard chemotherapy group and standard chemotherapy group. Abbreviation: CI, confidence interval.

DISCUSSION

The second-line treatment of locally advanced or advanced NSCLC without a driver gene predominantly included single-agent chemotherapy. At present, second-line chemotherapy is unsatisfactory, and scholars have conducted various investigations, including single-agent chemotherapy along with antiangiogenesis drugs. According to previous studies, chemotherapy combined

with antiangiogenesis agents has the prospect of broad application in the second-line treatment of cancer.

Apatinib mesylate is a novel small molecular anti-angiogenesis, Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) tyrosine kinase inhibitor (TKI) developed in China. The study of apatinib in the treatment of lung cancer has primarily been focused on three lines and after the third-line treatment with the single agent. The phase II clinical studies of advanced non-small cell non-squamous cell carcinoma after the progression of second-line chemotherapy showed that apatinib alone had a median PFS (mPFS) of 4.7 months and an ORR of 12.2%, both with significant efficacy.

In this study, we observed that the mPFS of the combined treatment group was significantly longer than that of the simple chemotherapy group (5.47 months vs. 2.97 months), reaching our planned primary endpoint (Fig. 2). In addition, our results also demonstrated that the mPFS of the single-agent chemotherapy group was 2.97 months, which was in agreement with the data reported globally. In the secondary endpoints, the DCR of the combined treatment group was also improved compared with the chemotherapy group. These results indicated that apatinib combined with chemotherapy could improve the PFS and DCR in the second-line treatment of patients with advanced NSCLC, and hence, further investigation with respect to the prolonged survival period was essential.

In terms of safety, the common adverse effects of the combined treatment group included hypertension, HFSR, and fatigue, which were similar to those observed with other antivasular targeted therapies. Patients with adverse effects were improved symptomatically after supportive treatment or suspension of medication, and no severe adverse event-related deaths occurred. The rate of overall adverse effects of the two groups was not significantly different, indicating that the safety of apatinib combined with single-agent chemotherapy was satisfactory and that the adverse effects were controllable.

Therefore, the results of our study indicated that the combination of apatinib and chemotherapy significantly improved the PFS time in the second-line therapy of advanced NSCLC without a sensitizing mutation. It was safe and well tolerated.

TRIAL INFORMATION	
Disease	Lung cancer – NSCLC
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	1 prior regimen
Type of Study	Phase II, randomized
PFS	<i>p</i> : .0068, HR: 0.3347
Primary Endpoint	Progression-free survival
Secondary Endpoints	Overall survival, disease control rate, safety

Additional Details of Endpoints or Study Design

Study Design and Eligibility Criteria

This study was a double-arm, open, multicenter, exploratory clinical study that included patients from six centers in Southeast China. The patients who fulfilled the inclusion criteria were stratified by 2:1 and assigned to the experimental and control groups based on factors such as performance status (PS), presence or absence of brain metastasis, and histological type.

The specific inclusion criteria were as follows: locally advanced or advanced primary NSCLC diagnosed by histology or cytology (account to American Joint Committee on Cancer version 7 stage, stage IIIB with unresectable, stage IV) that could not be surgically resected or recurred; age ≥ 18 years and ≤ 75 years; no epidermal growth factor receptor-sensitive mutations detected by molecular pathology; negative of anaplastic lymphoma kinase, or unknown; and had experienced progression of disease after chemotherapy or had discontinued therapy owing to intolerable adverse effects. Other inclusion criteria were as follows: at least one measurable lesion; Eastern Cooperative Oncology Group (ECOG) score 0–1; estimated survival time ≥ 3 months; and adequate hematologic, hepatic, and renal function. Patients with asymptomatic brain metastases were also included. Patients with uncontrolled blood pressure on medication ($>140/90$ mmHg), those with bleeding tendency, and those receiving thrombolytics or anticoagulants were excluded. The study was approved by the ethics committee. All patients provided written informed consent before participation in the study.

Study Assessments

The baseline assessment of the tumor was performed within 28 days prior to enrollment. Measurable lesions were determined by computed tomography (CT) or magnetic resonance imaging (MRI), followed by radiographic evaluation after every two cycles of treatment until disease progression. Efficacy was evaluated according to the RECIST standards (version 1.1) and divided into complete remission (CR), partial remission (PR), stable disease (SD), and progression of disease (PD). The adverse events were defined and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (version 4.03) and observed and evaluated at the beginning of the treatment as well as after 28 days. The primary research endpoint was PFS, whereas the secondary endpoints were total OS, DCR, and safety.

Statistical Analyses

Patients were stratified based on ECOG PS, presence or absence of brain metastasis, gender, smoking history, and histological type. In analyzing the data, we performed exploratory analyses comparing the two treatment arms. The primary research endpoint was PFS, whereas the secondary endpoints were OS, DCR, and safety. Between-group differences in patient characteristics were analyzed using the *t* test. The differences before and after treatment were determined by analysis of variance or the rank sum test. Median PFS and OS were estimated from Kaplan-Meier curves.

As to study design and size, this was an investigator-initiated exploratory study. Referring to the results of the LUME-Lung 1 trial, the control group of PFS was set to 2.7 months, and the experimental group of PFS was assumed to be 5.2 months. The unilateral threshold value and test efficacy was set to 10% and 80%, respectively, and 49 patients (33 in the experimental group and 16 in the control group) were scheduled to be enrolled. Owing to the geographical and epidemiological factors of the disease, the enrollment was slow and exceeded the expected enrollment time. We terminated the study when 37 patients were enrolled.

Investigator's Analysis

Active and should be pursued further

DRUG INFORMATION: CONTROL

Drug 1

Generic/Working Name	Pemetrexed sodium for injection
Dose	500 mg/m ²
Route	IV

Schedule of Administration

The control group received four cycles of docetaxel or pemetrexed single-agent chemotherapy and were monitored by regular follow-up. The withdrawal of drugs because of drug-related toxicity was for <14 days and not more than two times. The patients in the pemetrexed group were treated with 4 mg dexamethasone 1 day before administration, on the same day, and 1 day after administration, twice a day. At least five daily doses of folic acid (350–1000 μ g) were administered 7 days prior to the first treatment and continued until 21 days after the final pemetrexed dose. One thousand micrograms of vitamin B12 should also be injected intramuscularly within 7 days prior to the first pemetrexed administration and once every three cycles thereafter. The granulocyte colony-stimulating factor was permitted for prophylactic use in patients with granulocytopenia events or those that occurred during the previous cycle of treatment.

Drug 2

Generic/Working Name	Docetaxel injection
Dose	75 mg/m ²
Route	IV

Schedule of Administration

The control group received four cycles of docetaxel or pemetrexed single-agent chemotherapy and were monitored by regular follow-up. The withdrawal of drugs because of drug-related toxicity was for <14 days and not more than two times. The patients in the docetaxel treatment group received 8 mg dexamethasone 1 day before administration, on the same day, and 1 day after administration, twice a day. The granulocyte colony-stimulating factor was permitted for prophylactic use in patients with granulocytopenia events or those that occurred during the previous cycle of treatment.

DRUG INFORMATION: APATINIB**Drug 1**

Generic/Working Name	Apatinib mesylate tablets
Drug Type	Small molecule
Drug Class	VEGFR
Dose	500 mg per flat dose
Route	p.o.

Schedule of Administration

The experimental group received 500 mg apatinib once a day orally combined with four cycles of single-agent docetaxel (75 mg/m², every 21 days) or pemetrexed chemotherapy (500 mg/m², every 21 days, non-squamous cell carcinoma only) until disease progression or intolerable toxicity or in the event of discontinuation upon patient' request. Holding drugs as a result of drug-related toxicity was allowed for <14 days but not more than two times. The dose of the drugs could be decreased during treatment; apatinib was >375 mg once a day. The granulocyte colony-stimulating factor was permitted for prophylactic use in patients with granulocytopenia events or those that occurred during the previous cycle of treatment.

Drug 2

Generic/Working Name	Pemetrexed sodium for injection
Dose	500 mg per flat dose
Route	IV

Schedule of Administration

The experimental group received 500 mg apatinib once a day orally combined with four cycles of single-agent docetaxel (75 mg/m², every 21 days) or pemetrexed chemotherapy (500 mg/m², every 21 days, non-squamous cell carcinoma only) until disease progression or intolerable toxicity or in the event of discontinuation upon patient' request. Holding drugs as a result of drug-related toxicity was for <14 days and not more than two times. The patients in the pemetrexed group were treated with 4 mg dexamethasone 1 day before administration, on the same day, and 1 day after administration, twice a day. At least five daily doses of folic acid (350–1,000 µg) were administered 7 days prior to the first treatment and continued until 21 days after the final pemetrexed dose. One thousand micrograms of vitamin B12 should also be injected intramuscularly within 7 days prior to the first pemetrexed administration and once every three cycles thereafter. The granulocyte colony-stimulating factor was permitted for prophylactic use in patients with granulocytopenia events or those that occurred during the previous cycle of treatment.

Drug 3

Generic/Working Name	Docetaxel injection
Dose	75 mg/m ²
Route	IV

Schedule of Administration

The experimental group received 500 mg apatinib once a day orally combined with four cycles of single-agent docetaxel (75 mg/m², every 21 days) or pemetrexed chemotherapy (500 mg/m², every 21 days, non-squamous cell carcinoma only) until disease progression or intolerable toxicity or in the event of discontinuation upon patient' request. The patients in the docetaxel treatment group received 8 mg dexamethasone 1 day before administration, on the same day, and 1 day after administration, twice a day. The granulocyte colony-stimulating factor was permitted for prophylactic use in patients with granulocytopenia events or those that occurred during the previous cycle of treatment.

PATIENT CHARACTERISTICS: CONTROL

Number of Patients, Male	8
Number of Patients, Female	3
Stage	Stage IIIB with unresectable, stage IV
Age	Median (range): 62 (41–74) years
Performance Status: ECOG	0 — 1 — 10 2 — 3 — Unknown —

Other

During the period from May 30, 2016, to March 27, 2019, 37 patients from six centers were enrolled in the present study. Twenty-six patients were included in the experimental group, and 11 patients were included in the control group (Fig. 3). The baseline and clinical characteristics of the two groups were well balanced, with no statistically significant differences (Table 1). Regarding the data cutoff (March 27, 2019), 11 patients in the control cohort had tissue or cytology available for testing.

Cancer Types or Histologic Subtypes	Nonsquamous cell, 8; squamous cell, 3
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PATIENT CHARACTERISTICS: APATINIB

Number of Patients, Male	18
Number of Patients, Female	4
Stage	Stage IIIB with unresectable, stage IV
Age	Median (range): 58.5 (31–73) years
Performance Status: ECOG	0 – 2 1 – 20 2 – 3 – Unknown –

Other

During the period from May 30, 2016, to March 27, 2019, 37 patients from six centers were enrolled in the present study. Twenty-six patients were included in the experimental group, and 11 patients were included in the control group (Fig. 3). The baseline and clinical characteristics of the two groups were well balanced, with no statistically significant differences (Table 1). Regarding the data cutoff (March 27, 2019), 26 patients had tissue cytology in the experimental group, 4 of which were not evaluated for efficacy. In patients without evaluation of efficacy, three patients were treated for less than one cycle because of adverse reactions, and one patient had not undergone imaging examination.

Cancer Types or Histologic Subtypes	Nonsquamous cell, 17; squamous cell, 5
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PRIMARY ASSESSMENT METHOD: CONTROL

Title	New assessment
Title	RECIST response
Number of Patients Enrolled	11
Number of Patients Evaluable for Toxicity	11
Number of patients Evaluated for Efficacy	11
Evaluation Method	RECIST 1.1
Response Assessment CR	$n = 0$
Response Assessment PR	$n = 1$
Response Assessment SD	$n = 7$
Response Assessment PD	$n = 3$
(Median) Duration Assessments PFS	2.97 months, CI: 2.02–3.92

Outcome Notes

In patients without evaluation of efficacy, three patients were treated for less than one cycle because of adverse reactions, and one patient had not undergone imaging examination. In the apatinib plus standard chemotherapy group, two patients continued to receive the treatment, and seven patients had undergone apatinib therapy for more than 6 months. PFS was significantly longer in the experimental group than in the control group (median PFS 5.47 months [95% confidence interval (CI): 3.21–7.73] vs. 2.97 months [95% CI: 2.02–3.92], hazard ratio [HR]: 0.3347, $p = .0068$; Fig. 2). ORR and DCR were 27% and 95% for the experimental group compared with 9% and 73% for the control group (Fig. 1; Table 2), respectively. Because the number of patients is too small, therapeutic effect evaluation and statistical analysis of subgroup are not performed temporarily.

PRIMARY ASSESSMENT METHOD: APATINIB

Title	RECIST response
Number of Patients Enrolled	26
Number of Patients Evaluable for Toxicity	26
Number of Patients Evaluated for Efficacy	22
Evaluation Method	RECIST 1.1
Response Assessment CR	<i>n</i> = 0
Response Assessment PR	<i>n</i> = 6
Response Assessment SD	<i>n</i> = 15
Response Assessment PD	<i>n</i> = 1
(Median) Duration Assessments PFS	5.47 months, CI: 3.21–7.73

Outcome Notes

In patients without evaluation of efficacy, three patients were treated for less than one cycle because of adverse reactions, and one patient had not undergone imaging examination. In the apatinib plus standard chemotherapy group, two patients continued to receive the treatment, and seven patients underwent apatinib therapy for more than 6 months. PFS was significantly longer in the experimental group than in the control group (median PFS 5.47 months [95% CI: 3.21–7.73] vs. 2.97 months [95% CI: 2.02–3.92], HR: 0.3347, *p* = .0068; Fig. 2). ORR and DCR were 27% and 95% for the experimental group compared with 9% and 73% for the control group (Fig. 1; Table 2), respectively. Because the number of patients is too small, therapeutic effect evaluation and statistical analysis of subgroup are not performed temporarily.

ADVERSE EVENTS: CONTROL**All Cycles**

Name	NC/NA	1	2	3	4	5	All grades
Cough	36%	55%	9%	0%	0%	0%	64%
Fatigue	82%	9%	9%	0%	0%	0%	18%
Febrile neutropenia	73%	9%	9%	9%	0%	0%	27%
Proteinuria	91%	9%	0%	0%	0%	0%	9%
Nausea	91%	9%	0%	0%	0%	0%	9%
Diarrhea	91%	9%	0%	0%	0%	0%	9%
Lung infection	91%	9%	0%	0%	0%	0%	9%
Hypoalbuminemia	91%	9%	0%	0%	0%	0%	9%
Hepatic infection	91%	9%	0%	0%	0%	0%	9%
Weight loss	91%	9%	0%	0%	0%	0%	9%
Bone marrow hypocellular	82%	0%	9%	0%	9%	0%	18%
Aspiration	82%	18%	0%	0%	0%	0%	18%

Adverse Events Legend

The adverse events that were more common in the experimental group than in the control placebo group were fatigue, hand-foot skin reaction (HFSR), hypertension, chest pain, proteinuria, diarrhea, and nausea. Although most of these adverse events were manageable with supportive treatment or dose reduction, two patients had to cease the treatment because of adverse events. Dose modifications resulting from toxicity were more common in the trial group than in the control group. Dose reduction was mainly attributed to HFSR and hypertension. Abbreviation: NC/NA, no change from baseline/no adverse event.

ADVERSE EVENTS: APATINIB**All Cycles**

Name	NC/NA	1	2	3	4	5	All grades
Fatigue	42%	35%	19%	4%	0%	0%	58%
Cough	61%	35%	4%	0%	0%	0%	39%
Weight loss	92%	0%	8%	0%	0%	0%	8%
Nausea	88%	4%	8%	0%	0%	0%	12%
Diarrhea	88%	8%	0%	4%	0%	0%	12%
Proteinuria	88%	12%	0%	0%	0%	0%	12%

Chest pain—cardiac	88%	12%	0%	0%	0%	0%	12%
Hypertension	80%	8%	8%	4%	0%	0%	20%
Febrile neutropenia	77%	15%	4%	0%	4%	0%	23%
Mucositis oral	92%	4%	4%	0%	0%	0%	8%
Lung infection	96%	4%	0%	0%	0%	0%	4%
Bone marrow hypocellular	92%	4%	0%	4%	0%	0%	8%
Hypoalbuminemia	96%	0%	4%	0%	0%	0%	4%
Hepatic infection	92%	8%	0%	0%	0%	0%	8%
Aspiration	84%	12%	4%	0%	0%	0%	16%
Skin and subcutaneous tissue disorders—hand-foot skin reaction	62%	23%	0%	15%	0%	0%	38%
Rash maculo-papular	92%	8%	0%	0%	0%	0%	8%

Abbreviation: NC/NA, no change from baseline/no adverse event.

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion

Study completed

Investigator's Assessment

Active and should be pursued further

The second-line treatment of locally advanced or advanced non-small cell lung carcinoma (NSCLC) without a driver gene predominantly includes single-agent chemotherapy [1, 2]. According to one meta-analysis, the median objective response rate is approximately 6.8% (range, 0.8–12.2), whereas the median disease control rate (DCR) was 42.4% (range, 30.9–58.5), and the median survival time was 6.6 (range, 5.4–10.2) months in the second-line chemotherapy for advanced NSCLC [3]. Thus, second-line chemotherapy is overall unsatisfactory, and various investigations have been conducted in an effort to improve on these data, including single-agent chemotherapy along with antiangiogenesis drugs [4, 5]. According to previous studies, chemotherapy combined with antiangiogenesis therapy has the possibility of broad application in second-line treatment but needs further randomized data for confirmation [6–11].

The study included patients with non-small cell lung cancer, including squamous cell and adenocarcinoma. According to previous research data and clinical guidelines (National Comprehensive Cancer Network and Chinese Society of Clinical Oncology, etc.), pemetrexed and docetaxel have been the standard second-line treatment for patients with non-small cell lung cancer. The data from this study were consistent with the previous data of chemotherapy for second-line treatment of NSCLC.

In this study, we observed that the median progression-free survival (mPFS) of the combined treatment group was significantly longer than that of the simple chemotherapy group (5.47 months vs. 2.97 months), reaching the primary endpoints. In the CheckMate 057 trial, mPFS was not favorable to nivolumab compared with docetaxel (median, 2.3 months and 4.2 months, respectively), although the rate of progression-free survival at 1 year was higher with nivolumab than with docetaxel (19% and 8%, respectively) [12]. In the REVEL trial, the mPFS was 4.5 months for the ramucirumab plus docetaxel group compared with 3.0 months for the docetaxel group [13]. In the LUME-Lung 1 trial, the mPFS was 3.4 months

versus 2.7 months in the docetaxel plus nintedanib group versus the docetaxel plus placebo group [14]. In addition, our results also demonstrated that the mPFS of the single-agent chemotherapy group was 2.97 months, which was in agreement with the data reported globally [12, 15, 16]. In the secondary endpoints, the DCR of the combined treatment group was also improved compared with the chemotherapy group. These results indicated that apatinib-combined chemotherapy could improve the PFS and DCR in the second-line treatment of patients with advanced NSCLC, and hence, further investigation with respect to the prolonged survival period was essential.

Previous studies on antiangiogenesis therapeutic drugs mostly excluded patients with squamous cell carcinoma because of the potential risk of life-threatening pulmonary hemorrhage [17–20]. However, the present study included patients with lung squamous cell carcinoma, but no fatal bleeding events were observed. Owing to the small number of cases in this study, a larger sample size study was imperative to further elucidate the efficacy and safety of apatinib in patients with lung squamous cell carcinoma.

In terms of safety, the main adverse effects of the combined treatment group included hypertension, hand-foot skin reaction, fatigue, rash, diarrhea, proteinuria, and bone marrow suppression, which were similar to those observed in other antivasculature targeted therapies [14, 21–23]. The symptoms of patients with adverse effects were improved after symptomatic treatment or suspension of medication, and no severe adverse event-related deaths occurred. The rate of overall adverse effects of the two groups was not significantly different, indicating that the safety of apatinib combined with single-agent chemotherapy was satisfactory and that the adverse effects were controllable.

Therefore, the results of our study suggested that the combination of apatinib and chemotherapy significantly improved the PFS in the second-line therapy of advanced NSCLC without a sensitizing mutation. It was safe and well tolerated.

This study was an investigator-initiated exploratory study. Based on the LUME-Lung 1 trial, PFS for the control group was expected to be 2.7 months, and if successful, the experimental group PFS would be or exceed 5.2 months. The study planned to enroll 49 patients (33 in the experimental group and 16 in the control group), but enrollment was slow and exceeded the expected enrollment time. We terminated the study when 37 patients were enrolled. We consider the results of this study to be valid, as the control group data were consistent

with those of previous clinical studies, and the experimental group had significant survival benefits compared with the control group. Although the sample size is small, it still has certain guiding significance for clinical treatment.

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DISCLOSURES

The authors indicated no financial relationships.

FIGURE AND TABLES

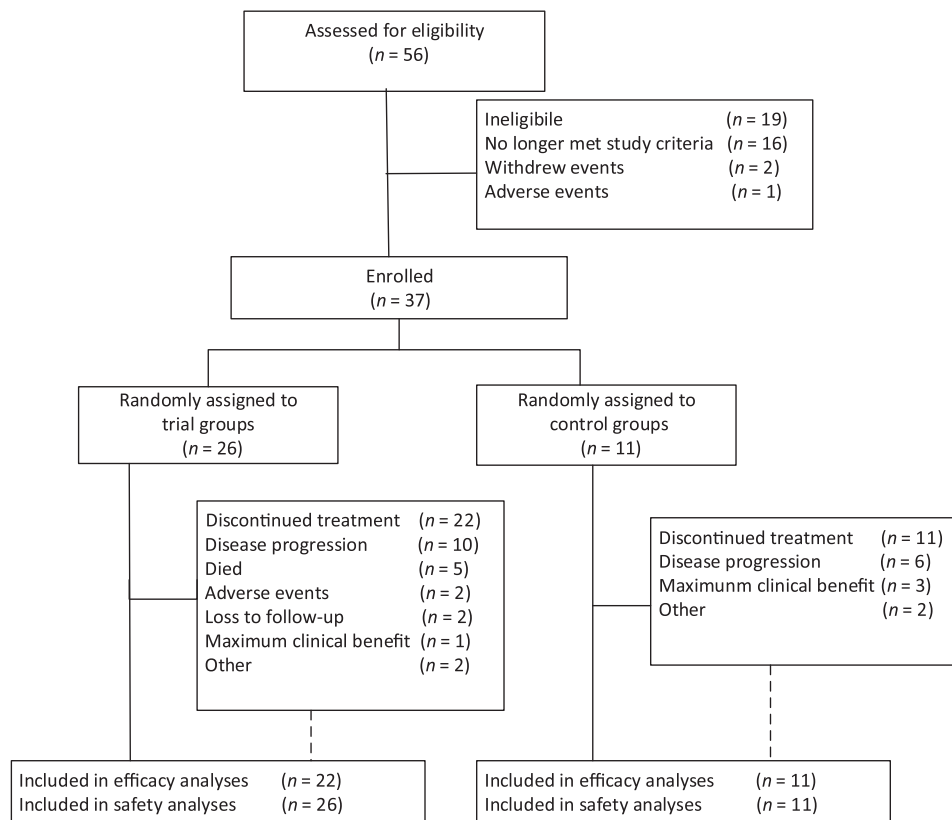


Figure 3. Research flow chart.

Table 1. Baseline characteristics of patients

Patient characteristics	Trial group (n = 22)	Control group (n = 11)
Gender, n (%)		
Male	18 (82)	8 (73)
Female	4 (18)	3 (27)
Age, years		
Median	58.5	62
Range	31–73	41–74
Performance status (ECOG), n (%)		
0	2 (9)	1 (9)
1	20 (91)	10 (91)
Operation history, n (%)		
Never had an operation	3 (14)	1 (9)
Had an operation	19 (86)	10 (91)
Radiation history, n (%)		
Had radiation	7 (32)	5 (45)
Never had radiation	15 (68)	6 (55)
Smoking history, n (%)		
Never smoker	10 (45)	6 (55)
Smoker	12 (55)	5 (45)
Pathological type, n (%)		
Non-squamous cell	17 (77)	8 (73)
Squamous cell	5 (23)	3 (27)
Brain metastases, n (%)		
Yes	2 (9)	1 (9)
No	20 (91)	10 (91)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. The best confirmed tumor response of the two groups

Response	Trial group (n = 22)	Control group (n = 11)
ORR, %	27	9
DCR, %	95	73
CR, n	0	0
PR, n	6	1
SD, n	15	7
PD, n	1	3

Abbreviations: CR, complete remission; DCR, disease control rate; ORR: objective response rate; PD, progression of disease; PR, partial remission; SD, stable disease.

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