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Clinical Trial Results

Concurrent EGFR-TKI and Thoracic Radiotherapy as First-Line Treatment for Stage IV Non-Small Cell Lung Cancer Harboring EGFR Active Mutations

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT02353741
- **Sponsor:** Xinqiao Hospital of Chongqing
- **Principal Investigators:** Jianguo Sun, Yuzhong Duan, Bo Zhu
- **IRB Approved:** Yes

Lessons Learned

- This single-arm, phase II study shows that concurrent EGFR-tyrosine kinase inhibitor plus thoracic radiotherapy as the first-line treatment for stage IV non-small cell lung cancer harboring EGFR active mutations provides long-term control for the primary lung lesion, and 1-year progression-free survival (PFS) rate and median PFS are numerically higher than those of the erlotinib monotherapy.
- Serious adverse events are acceptable, although grade >3 radiation pneumonitis occurred in 20% of patients.

Abstract

Background. Studies show effective local control by EGFR-tyrosine kinase inhibitor (TKI) combined with radiotherapy at metastatic sites in advanced lung cancer harboring EGFR active mutations. Salvage local radiotherapy is associated with prolonged progression-free survival (PFS) in local disease during EGFR-TKI treatment. However, no prospective study has been reported on concurrent EGFR-TKI and radiotherapy for primary lung lesions. This study investigated the efficacy and safety of first-line EGFR-TKI combined with thoracic radiotherapy in treating stage IV non-small cell lung cancer (NSCLC) harboring EGFR active mutations.

Methods. We conducted a single-arm, phase II clinical trial. Each patient received EGFR-TKI (erlotinib 150 mg or gefitinib 250 mg per day) plus thoracic radiotherapy (54–60 Gy/27–30 F/5.5–6 w) within 2 weeks of beginning EGFR-TKI therapy until either disease progression or intolerable adverse events (AEs) appeared.

Results. From January 2015 to March 2018, 401 patients were screened, and 10 patients (5 male and 5 female) were eligible. These patients had a median age of 55 years (40–75) and median follow-up of 19.8 months (5.8–34). The 1-year PFS rate was 57.1%, median PFS was 13 months, and median time to progression of irradiated lesion (iTTP) was 20.5 months. Objective response rate (ORR), was 50% and disease control rate (DCR) was 100%. The most common grade ≥3 AEs were radiation pneumonitis (20%) and rash (10%). One patient died after rejecting treatment for pneumonitis. The others received a full, systematic course of glucocorticoid therapy. Pneumonitis was all well controlled and did not relapse.

Conclusion. Concurrent EGFR-TKI plus thoracic radiotherapy as the first-line treatment for stage IV NSCLC harboring EGFR active mutations shows a long-term control of primary lung lesion. The 1-year PFS rate and median PFS of this combined therapy are numerically higher than those of the erlotinib monotherapy. The risk of serious adverse events is acceptable. ***The Oncologist*** 2019;24:1031–e612

Discussion

Our previous study revealed that local radiation was associated with prolonged PFS in patients with EGFR-mutant advanced lung cancer who experienced local progression. It was also reported that EGFR-TKI could increase radiosensitivity and that radiotherapy could reduce EGFR-TKI resistance. Therefore, EGFR-TKI plus thoracic radiotherapy could be a promising strategy for treating patients with advanced NSCLC.

We conducted this prospective study to explore the efficacy and safety of concurrent EGFR-TKI plus thoracic

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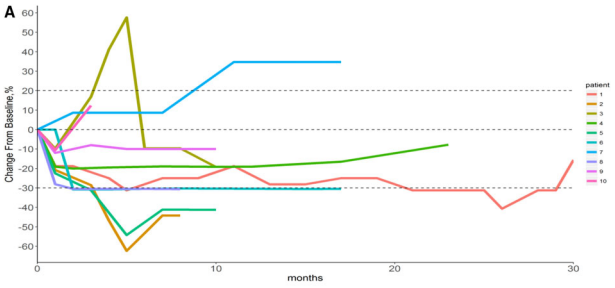
A



B

Tumor response	CR	PR	SD	PD	ORR	DCR
	0	5(50%)	5(50%)	0	5(50%)	10(100%)

C

	ORR(%)	DCR(%)
ENSURE	69(62.7)	98(89.1)
EGFR-TKI+TRT	5(50.0)	10(100)
p value	.428	.271

Figure 2. Tumor response. **(A):** Spider plot of dynamic changes in the maximum diameter of the tumor. **(B):** Best tumor response. **(C)**: Compared with the ENSURE study, there was no significant difference in ORR (50%, p = .43) or DCR (100%, p = .27). ORR = CR + PR; local control rate = CR + PR + SD.
Abbreviations: CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TRT, thoracic radiotherapy.

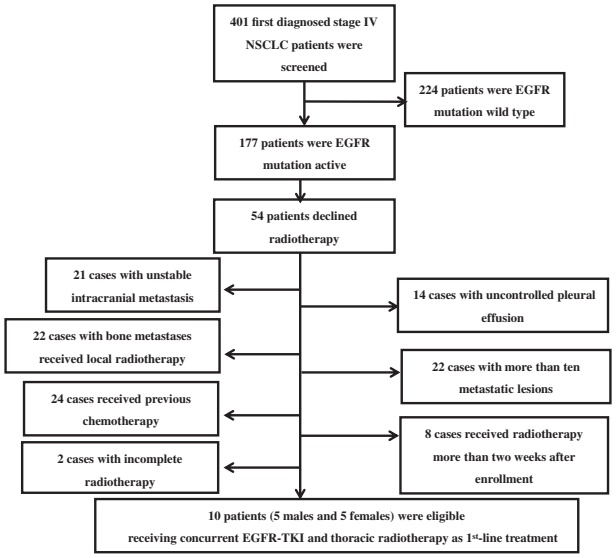


Figure 3. Flow chart of patient enrollment process.
Abbreviations: NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

radiotherapy as the first-line treatment for stage IV limited metastatic NSCLC harboring EGFR mutations (no more than ten distant lesions). The primary endpoint was 1-year PFS rate. In the ENSURE study, the 1-year PFS rate of patients treated with erlotinib monotherapy was 43%, and the median PFS was 11.0 months. In the current study, the estimated 1-year PFS rate was 60%. Considering a 20% dropout rate and one-sided α = .1, β = .2, a sample size of 47 patients was needed according to the Freedman rule from the Contract Research Organization of Brightech (Chengdu, China).

A total of 401 patients with NSCLC were screened. Ultimately, ten patients (five males and five females) with a median age of 55 (40–75) years were eligible. Tumors in four patients displayed an exon 21 L858R mutation, and six had exon 19 deletion. All patients had good baseline performance status (PS, 0–1). One patient received gefitinib, and the others received erlotinib. The radiotherapy design was 54–60 Gy/27–30 F/5.5–6 w. The median radiation dose to both lungs in all the recruited cases was as follows: normal bilateral lung volume receiving at least 20 Gy, 12% $\pm$ 4%; mean lung dose, 5.25 $\pm$ 3.75 Gy. All the patients completed radiotherapy. By October 8, 2018, the median follow-up time for all ten patients was 19.8 months (5.8–34.0 months). By the last follow-up, five patients were alive. One-year PFS was 57.1%. Kaplan-Meier analysis showed that the median PFS was 13.0 months (95% confidence interval [CI] 4.9–21.1 months), and the median iTTP was 20.5 months (95% CI, 10.6–25.5 months). Five patients were assessed as PR (50%), five as SD (50%), and no patient as PD. ORR was 50%, and DCR was 100%. Rash (5/10), radiation pneumonitis (4/10), and diarrhea (2/10) were the most common adverse events. Treatment-related grade ≥3 radiation pneumonitis occurred at a rate of 20% (2/10) and rash at 10% (1/10). Radiation pneumonitis occurred at an average 40 days after radiation. One patient died after rejecting any treatment for pneumonitis, whereas the others recovered after a full, systematic course of glucocorticoid therapy.

To the best of our knowledge, this is the first study to focus on the efficacy and safety of concurrent EGFR-TKI and thoracic radiotherapy as the first-line treatment for stage IV NSCLC harboring EGFR active mutations. Our study found that combined therapy can achieve long-term control of the primary lung lesion. The 1-year PFS rate and median PFS of this combined therapy are numerically higher than those of erlotinib monotherapy. The risk of serious adverse events is acceptable.

Trial Information	
Disease	Lung cancer – NSCLC
Stage of Disease/Treatment	Primary
Prior Therapy	None
Type of Study - 1	Phase II
Type of Study - 2	Single arm
Primary Endpoint	1-year progression-free survival rate
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Overall survival
Secondary Endpoint	Safety

Secondary Endpoint	Overall response rate
Secondary Endpoint	Time to progression of irradiated lesion

Additional Details of Endpoints or Study Design

The study recruited patients with pathologically confirmed stage IV NSCLC harboring active EGFR mutations. The patients should not have received previous systemic therapy or treatment with any other investigational agents or have participated in any other clinical trials. Patients between the ages of 18 and 75, with Eastern Cooperative Oncology Group (ECOG) performance status 0~2, with no more than ten metastatic lesions, no brain metastases or serious functional damage of important organs were eligible. All patients signed an informed consent document after careful discussion of risk and potential benefit. Radiation therapy had to begin within 2 weeks of EGFR-TKI therapy.

Investigator's Analysis	Active and should be pursued further

Drug Information

Drug 1	
Generic/Working Name	Erlotinib
Drug Class	EGFR
Dose	150 milligrams (mg) per flat dose
Route	Oral (p.o.)
Schedule of Administration	150 mg per day until either disease progression or intolerable AEs appeared.
Drug 2	
Generic/Working Name	Gefitinib
Drug Class	EGFR
Dose	250 milligrams (mg) per flat dose
Route	Oral (p.o.)
Schedule of Administration	250 mg per day until either disease progression or intolerable AEs appeared.

Patient Characteristics

Number of Patients, Male	5
Number of Patients, Female	5
Stage	Stage IV
Age	Median (range): 55 (40–75) years
Number of Prior Systemic Therapies	Median (range): 0
Performance Status: ECOG	0 — 6 1 — 4 2 — 0 3 — 0 Unknown — 0
Cancer Types or Histologic Subtypes	Lung adenocarcinoma, 10

Primary Assessment Method

Title	New assessment
Number of Patients Screened	401
Number of Patients Enrolled	10
Number of Patients Evaluable for Toxicity	10
Number of Patients Evaluated for Efficacy	10
Evaluation Method	RECIST version 1.1

Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 5 (50%)
Response Assessment SD	*n* = 5 (50%)
Response Assessment PD	*n* = 0 (0%)
(Median) Duration Assessments PFS	13 months; CI, 8.4–15.4

Outcome Notes

From January 2015 to March 2018, 401 patients were screened, and 10 patients (5 male and 5 female) were eligible with a median age of 55 years (40–75) and median follow-up of 19.8 months (5.8–34). The 1-year PFS rate was 57.1%; median PFS was 13 months, and median iTTP was 20.5 months. ORR was 50%, and DCR was 100%. The most common grade ≥3 AEs were radiation pneumonia (20%) and rash (10%).

Adverse Events

All Cycles

Name	NC/NA, %	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5	All grades, %
Esophagitis	90	10	0	0	0	0	10
Vomiting	90	10	0	0	0	0	10
Diarrhea	80	20	0	0	0	0	20
Fatigue (asthenia, lethargy, malaise)	90	10	0	0	0	0	10
Pneumonitis or pulmonary infiltrates	60	10	10	10	0	10	40
Lymphopenia	90	10	0	0	0	0	10
Anorexia	90	10	0	0	0	0	10
Rash: acne/acneiform	50	40	0	10	0	0	50

Adverse Events Legend
Rash (5/10), radiation pneumonitis (4/10), and diarrhea (2/10) were the most common adverse events.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Events

Name	Grade	Attribution
Radiation pneumonitis	3	Possible
Rash	3	Possible

Serious Adverse Events Legend
Treatment-related grade ≥3 radiation pneumonitis occurred at a rate of 20% (2/10), and rash occurred in 10% (1/10).

Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Investigator's Assessment	Active and should be pursued further

Most patients receiving first-generation EGFR-tyrosine kinase inhibitor (TKI) undergo disease progression after 8.4 to 13.1 months of treatment, and the majority have local progression [1–3]. It has been reported that EGFR-TKI could increase radiosensitivity and that radiotherapy could reduce EGFR-TKI resistance [4, 5]. Moreover, several studies showed effective local control by EGFR-TKI combined with radiotherapy in metastatic sites of advanced non-small cell lung cancer (NSCLC) harboring EGFR active mutations [6–8]. Our previous study also revealed that local radiation prolonged progression-free survival (PFS) in patients with EGFR-mutant advanced lung cancer who acquired local progression after EGFR-TKI therapy [9]. Therefore, we hypothesized that there would be an improved efficacy in concurrent EGFR-TKI and local radiotherapy. No prospective study of concurrent EGFR-TKI and radiotherapy for primary lung cancer has yet been reported. Thus, we conducted this single-arm phase II study to investigate the efficacy and safety of EGFR-TKI with concurrent thoracic radiotherapy in newly diagnosed stage IV NSCLC harboring EGFR active mutations

From January 2015 to March 2018, a total of 401 patients with NSCLC were screened, including sequencing tumors to determine mutation status. EGFR mutation analysis was performed by staff members from Pathology Department of our hospital during screening using the SuperARMS assay (AmoyDx, Xiamen, China). Finally, ten eligible patients (five

male and five female) with a median age of 55 (40–75) years were enrolled (Fig. 1). The basic clinical characteristics of these ten cases are listed in Table 1. Nine patients had bone metastases, eight had lymph nodes metastases, and three had lung metastases. The trial was closed prematurely because of the low acceptance of thoracic radiotherapy plus EGFR-TKI treatment in patients.

One patient received gefitinib, and the others received erlotinib. EGFR-TKI was used until disease progression or intolerability of adverse events appeared. The plan of radiotherapy was 54–60 Gy/27–30 F/5.5–6 w. There was no limit to the maximum size of primary tumor, but normal bilateral lung volume receiving at least 20 Gy (V20) was strictly controlled to be less than 20%. Usually, primary tumors smaller than 7 cm in diameter were suitable to deliver concurrent EGFR-TKI plus thoracic radiotherapy. At the last follow-up on October 8, 2018, five patients were alive. We compared our results with those in the ENSURE study, which randomized first-line erlotinib against gemcitabine/cisplatin in stage IIIB/IV EGFR mutation-positive NSCLC. Concurrent EGFR-TKI plus thoracic radiotherapy as the 1st-line treatment for patients with stage IV NSCLC harboring EGFR active mutations showed numerically higher 1- year PFS rate (57.1% vs. 43%) and median PFS (13.0 vs. 11.0 months; Fig. 2). In addition to stage IV disease, patients with IIIB disease were enrolled into the ENSURE study, which may contribute to a longer PFS and therefore minimize the gain by the addition of radiation therapy. A spider plot was used to show the dynamic changes in the maximum diameter of primary lung lesion. Five patients were assessed as having partial response (50%), five as having stable disease (50%), and no patient as having progressive disease or complete response. Compared with the ENSURE study, there was no significant difference in objective response rate (50% vs. 62.7%, p = .43) or disease control rate (100% *vs.* 89.1%, p = .27; Fig. 3). Median time to progression of irradiated lesion in the current study was 20.5 months (95% confidence interval, 10.6–25.5 months). Similarly, Wang et al. [10] found that EGFR-TKI concurrent with thoracic radiotherapy in treating stage IIIB/IV NSCLC had a local control rate of 96% for thoracic tumor, with 1-year PFS rate of 42%. However, only one patient's EGFR mutation status was confirmed in that study.

In the current study, rash (5/10), radiation pneumonitis (4/10) and diarrhea (2/10) were the most common adverse events at any grade. The incidence of treatment-related grade ≥3 radiation pneumonitis and rash was 20% (2/10) and 10% (1/10), respectively (Table 2). Radiation pneumonitis occurred at an average 40 days after radiation. Two patients were assessed as grade 2 adverse events and one as grade 3 adverse event. One patient (grade 5) died, rejecting any treatment, whereas the others recovered after receiving a full, systematic course of glucocorticoid therapy. Previous studies also reported that the risk of radiation pneumonitis reached 22–32% during concurrent chemotherapy and radiotherapy, consistent with the current trial [11, 12]. The mean lung dose (MLD) and V20 were the two most important parameters of radiation pneumonitis [13, 14], which were strictly controlled in our study (MLD = 5.25 $\pm$ 3.75 Gy, V20 = 12 $\pm$ 4%). The incidence of rash in the current study was not higher than that in the study using erlotinib monotherapy [15]. Thus, the risk of serious adverse events is acceptable in concurrent EGFR-TKI and radiotherapy. Yoshida et al. [16] reported that lung was the most frequent site of treatment failures during EGFR-TKI treatment. Chen et al. [17] investigated the recurrence patterns of advanced non-small cell lung cancer of 318 patients treated with gefitinib and found that lung (62.34%) was the most common initial failure site. And patients with failure in the lung had a shorter median PFS time. Wang et al. [10] found that EGFR-TKI concurrent with thoracic radiotherapy in treating stage IIIB/IV NSCLC had a local control rate of 96% for thoracic tumor. We thus combined thoracic radiotherapy to control the primary lung lesions, finding that the median time to progression of irradiated lesion reached 20.5 months.

In conclusion, concurrent EGFR-TKI plus thoracic radiotherapy as the first-line treatment for stage IV NSCLC harboring EGFR active mutations shows a long-term control of primary lung lesion. The 1-year PFS rate and median PFS of this combined therapy are numerically higher than those of erlotinib monotherapy. The risk of serious adverse events is acceptable. A multicenter randomized controlled clinical trial with a larger sample size is needed to confirm the efficacy and safety of first-line concurrent EGFR-TKI and thoracic radiotherapy for stage IV NSCLC.

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Disclosures

The authors indicated no financial relationships.

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Figure and Tables

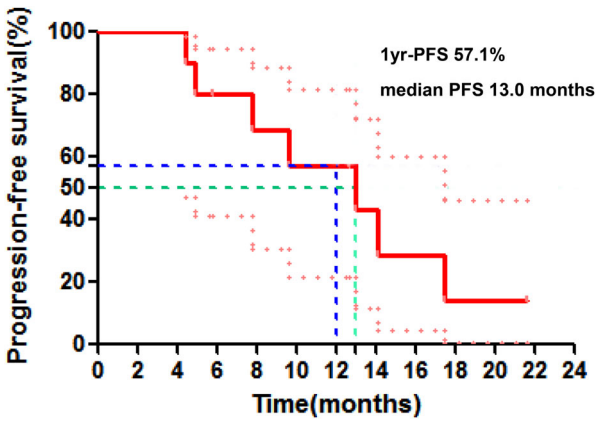

Figure 1. Progression-free survival.
Abbreviation: PFS, progression-free survival.

Table 2. Adverse events

Adverse event	All grades, *n* (%)	Grade ≥3, *n* (%)
Rash	5 (50)	1 (10)
Vomiting	1 (10	0
Anorexia	1 (10)	0
Fatigue	1 (10)	0
Radiation pneumonitis	4 (40)	2 (20)
Lymphocytopenia	1 (10)	0
Esophagitis	1 (10)	0
Diarrhea	2 (20)	0

Table 1. Basic clinical characteristics

Patient	Gender	Age, years	PS	Smoking status	Primary lesion	EGFR status	EGFR-TKI	Total dose/ fraction, Gy/F	Best response	Progression site	Alive
1	Male	59	0	Never	Left lung	21Mt	Erlotinib	60/28	PR	Lymph nodes	No
2	Male	56	1	Former	Right lung	21Mt	Erlotinib	60/30	PR	Pleura	No
3	Female	51	0	Never	Right lung	21Mt	Erlotinib	60/30	SD	Right lung	Yes
4	Male	40	1	Never	Right lung	19Del	Gefitinib	60/30	SD	Bone	No
5	Male	55	0	Former	Right lung	21Mt	Erlotinib	54/27	PR	Pleura	Yes
6	Male	57	0	Former	Right lung	19Del	Erlotinib	54/27	PR	—	Yes
7	Female	42	0	Never	Right lung	19Del	Erlotinib	54/27	SD	Liver	Yes
8	Female	75	0	Never	Right lung	19Del	Erlotinib	54/27	PR	—	Yes
9	Female	48	1	Never	Left lung	19Del	Erlotinib	60/30	SD	Bone	No
10	Female	55	1	Never	Right lung	19Del	Erlotinib	54/27	SD	—	Yes

Abbreviations: PR; partial response; PS, performance status; SD; stable disease; TKI; tyrosine kinase inhibitor.