# 22P Adding anlotinib in gradual or local progression on first-line EGFR-TKIs for advanced non-small cell lung cancer: a single-arm, multicenter, phase II trial (CTONG-1803/ALTER-L001)

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## BACKGROUND

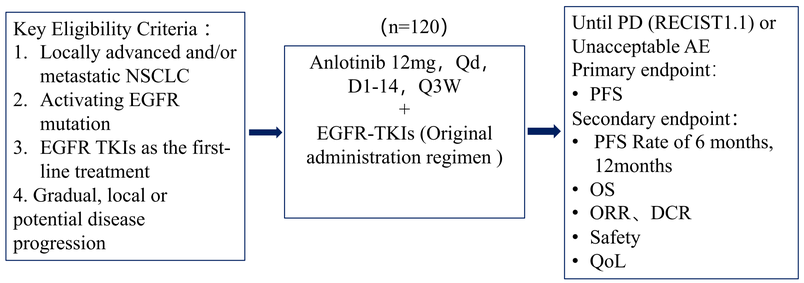
- Patients with EGFR activating mutations showed different clinical failure modes after first-line EGFR TKIs. Patients with gradual progression can still benefit from EGFR-TKIs continuation.
- Anlotinib was a multitarget tyrosine kinase inhibitor for tumor angiogenesis and proliferative signaling. Many clinical studies had shown a synergy of EGFR-TKIs and antiangiogenic agents.
- This study aimed to evaluate the efficacy and safety of combined EGFR-TKIs and anlotinib in patients with gradual, local or potential disease progression after the first-line EGFR-TKIs.

## METHODS

### Study Design

- This study was a single-arm, phase II, exploratory clinical trial done in 14 hospitals in China. Eligible patients were 18-75 years old with histologically or cytologically confirmed non-small cell lung cancer who were EGFR activating mutation positive and had received the first-line EGFR-TKIs, with ECOG PS of 0-1; had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1).The primary endpoint was median progression free survival. Clinical Trial: NCT04007835.

***Figure 1. Study Design***




**Gradual progression**: Disease control ≥ 6 months, the harm of tumor to the body is slightly increased compared with the previous evaluation (the cumulative tumor burden score ≤ 2 points), and the symptom score ≤ 1 points;
**Local progression**: Disease control ≥ 3 months, isolated extracranial progression or intracranial progression, symptom score ≤ 1 points;
**Potential disease progression**: Blood CEA<10.0ng/ml, the detection value ≥ 10ng/ml for two consecutive times (the detection interval is not less than 1 month); Or blood CEA ≥ 10ng/ml, gradually increasing after two consecutive tests (the test interval is not less than 1 month) .

Abbreviation: PFS, Progression free survival; OS, Overall survival; ORR, Objective response rate; DCR, Disease control rate; QoL, Quality of life; TRAE, Treatment-related adverse event; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; WBC, White Blood Cell.

## RESULTS

- From July 08, 2019 to December 15, 2022, 140 patients were screened and 120 were eligible for inclusion. All patients received at least one dose of study treatment. Baseline demographics and disease characteristics were in table 1. At date cutoff (December 31, 2022), median follow-up for PFS was 9.0 months (95% CI 6.3-11.7).

***Table 1. Patient Baseline Characteristics***

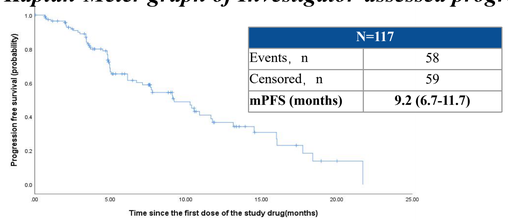
| | N=119* |
|---|---|
| Age, median (range), years | 58 (29-75) |
| Female, n(%) | 71 (59.7) |
| ECOG PS, n(%) | |
| 0 | 24 (20.2) |
| 1 | 95 (79.8) |
| Smoking status, n(%) | |
| Never | 89 (74.8) |
| Former | 26 (21.8) |
| Current | 4 (3.4) |
| Histology, n(%) | |
| Adenocarcinoma | 112 (94.1) |
| Non-Adenocarcinoma | 7 (5.9) |
| EGFR mutation type, n(%) | |
| 19 Del | 62 (52.1) |
| L858R | 50 (42.0) |
| 19del T790M | 4 (3.4) |
| L858R T790M | 1 (0.8) |
| G719S S768I | 1 (0.8) |
| G719C | 1 (0.8) |
| Progression , n(%) | |
| Gradual progression | 108 (90.8) |
| Local progression | 6 (5.0) |
| Potential progression | 5 (4.2) |
| Stable brain metastases, n(%) | 25 (21.0) |
| Prior EGFR-TKIs, n(%) | |
| The First or second generation | 87 (73.1) |
| Gefitinib | 40 (33.6) |
| Icotinib | 25 (21.0) |
| Erlotinib | 9 (7.6) |
| Afatinib | 8 (6.7) |
| Dacotinib | 5 (4.2) |
| The third generation | 32 (26.9) |
| Osimertinib | 31 (26.1)` |
| Almonertinib | 1 (0.8) |

*One patient was found not to meet the inclusion criteria after being enrolled, and was later excluded.

### Efficacy

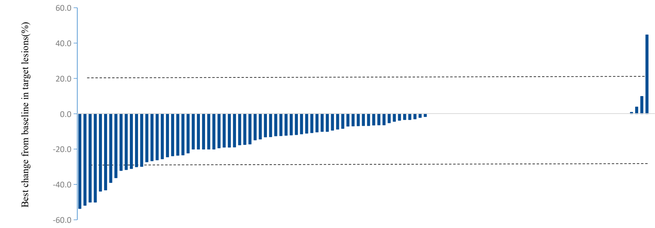
- 58 of 117 (2 patients without follow-up data) patients had disease progression or death. Median progression free survival was 9.2 months(95% CI 6.7-11.7) . The PFS rate at 6 and 12 months was 65.3% and 36.6% respectively. Among 85 patients with previous first or second-generation TKIs, the mPFS was 9.1 months (95% CI 6.1-12.1). Among 32 patients with previous third generation of TKIs, the mPFS was 10.4 months (95% CI 4.9-15.8).

***Figure 2. Kaplan-Meier graph of Investigator-assessed progression free survival***




- Six (5.1%) of 117 patients had a confirmed objective response. One hundred and three (88.0%) of 117 patients had a disease control. Sixty-eight (58.1%) of 117 patients showed tumour shrinkage.

***Figure 3. Best percentage change in tumor size from baseline***




### Safety

- At the time of date cutoff , 116 patients were available for safety assessment. Treatment-related adverse event occurred in 109 (94%) patients, and the incidence of grade 3 or higher TRAEs was 36.2%. Serious adverse event were observed in 15 (12.9%) patients. A dose reduction of anlotinib occurred in 26 (22.4%) patients. Dose interruption of anlotinib occurred in 28 (24.1%) patients. One death due to cerebral infarction occurred, the adverse event was possibly related to study treatment.

***Table2. TRAEs that occurred in at least ≥10% of all patients***

| Event | Any grade, n (%) | Grade 3 or 4, n (%) |
|---|---|---|
| Diarrhea | 55 (47.4) | 5 (4.3) |
| Hypertension | 49 (42.2) | 15 (12.9) |
| Proteinuria | 46 (39.7) | 2 (1.7) |
| Hypertriglyceridemia | 28 (24.1) | 3 (2.6) |
| Weight loss | 26 (22.4) | 0 (0.0) |
| Rash | 25 (21.6) | 4 (3.4) |
| Fatigue | 23 (19.8) | 1 (0.9) |
| Hand-foot syndrome | 23 (19.8) | 5 (4.3) |
| Platelet count decreased | 22 (19.0) | 0 (0.0) |
| Elevated AST | 21 (18.1) | 0 (0.0) |
| Elevated ALT | 17 (14.7) | 0 (0.0) |
| Nausea | 16 (13.8) | 1 (0.9) |
| WBC count decreased | 15 (12.9) | 0 (0.0) |
| Gum bleeding | 15 (12.9) | 0 (0.0) |
| Fecal occult blood | 14 (12.1) | 0 (0.0) |
| Dizziness | 14 (12.1) | 0 (0.0) |
| Conjugated bilirubin increased | 14 (12.1) | 0 (0.0) |
| Nasal bleeding | 14 (12.1) | 0 (0.0) |
| Neutrophil count decreased | 12 (10.3) | 1 (0.9) |

## CONCLUSIONS

- EGFR-TKIs plus anlotinib demonstrated meaningful clinical control in advanced NSCLC after gradual, local or potential disease progression to first-line EGFR-TKIs. And the toxicity was clinically manageable.

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