Anlotinib hydrochloride consolidation after concurrent chemoradiotherapy in stage III non-small-cell lung cancer: a truncated, randomized, multicenter, clinical study (ALTER-L029)

Dan Yang[a,†], Xiaomin Li[b,†], Xiaoying Xue[c], Leilei Jiang[a], Anhui Shi[a,*] and Jun Zhao[d,*]

Anlotinib is an antiangiogenic drug that shows good efficacy and safety in patients with advanced non-small-cell lung cancer (NSCLC). This study aimed to explore the efficacy and safety of anlotinib for consolidation therapy in patients with stage III locally advanced, unresectable NSCLC after concurrent chemoradiotherapy (cCRT). This was a randomized, parallel-controlled, open-label, multicenter, phase II trial of patients with unresectable/nonoperated NSCLC treated with cCRT. The participants were randomized 2:1 to the anlotinib or control group. The primary endpoint was progression-free survival (PFS). The secondary endpoints were the disease control rate (DCR) and overall survival. This study was terminated early due to poor recruitment. Nine and two participants were randomly assigned to the anlotinib and control groups, respectively. One participant in the control group was excluded due to taking prohibited medications before the first efficacy evaluation. In the anlotinib group, the median age was 63 (range, 37–74) years. Two participants achieved partial response, six stable disease, and one progressive disease as best response. The DCR was 88.9%. The median PFS was 11.5 months, and the 12-month PFS rate was 33.9%. All related adverse events were grade 1 or 2. Two participants had a dose adjustment during the study. The evaluable data suggest that anlotinib alone was effective and tolerable in consolidation therapy after cCRT in patients with stage III unresectable NSCLC. The results need to be confirmed by a large-sample trial. This clinical trial was registered on www.clinicaltrials.gov (NCT03743129). Registration date: 6 September 2018.

Anti-Cancer Drugs 2024, **35**:680–685

Keywords: anlotinib, carcinoma, concurrent chemoradiotherapy, non, small, cell lung

[a]Department of Radiation Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, [b]Thoracic Radiotherapy Ward 2, Shanxi Province Cancer Hospital/Shanxi Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences/Cancer Hospital Affiliated to Shanxi Medical University, Taiyuan, [c]Department of Radiotherapy, The Second Hospital of Hebei Medical University, Shijiazhuang, [d]Department of Thoracic Oncology I, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China

Correspondence to Anhui Shi, MD, Department of Radiation Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing 100142, China
Tel: +86 139 0113 6511; fax: +86 139 0113 6511;
e-mail: anhuidoctor@163.com

*Anhui Shi and Jun Zhao contributed equally to this article.
†Dan Yang and Xiaomin Li contributed equally to this work and share first authorship.

Received 18 March 2024 **Revised form accepted** 19 March 2024.

Background

As GLOBOCAN estimated in 2020, lung cancer was the first cause of death and new cancer cases diagnosed in China [1]. Non-small-cell lung cancer (NSCLC) is the most frequent (85–90%) cause of malignant lung tumors, usually affecting adults who smoke and who are ≥65 years old [2]. According to the 2021 guideline of the National Comprehensive Cancer Network and based on the RTOG 9410 trial, concurrent chemoradiotherapy (cCRT) is recommended for unresectable stage III NSCLC [3,4]. Still, cCRT has limited efficacy, poor prognosis and short median progression-free survival (PFS) time at 5.6 months [5]. In order to prolong PFS, the strategy of consolidation therapy after cCRT has been explored, but the results showed that consolidation therapy using chemotherapy have no benefit [6–9]. Immune checkpoint inhibitors such as durvalumab are currently the recommended standard of care after cCRT for unresectable stage III NSCLC, and the efficacy of durvalumab was explored in a PACIFIC trial [5,10]. But some patients have contraindications, and durvalumab therapy as an injectable treatment is inconvenient for patients who are not suitable to go to the hospital in special situations. Therefore, other consolidation treatment options other than chemotherapy and immunotherapy need to be explored.

Anlotinib is an antiangiogenic agent that shows good efficacy and safety in patients with advanced NSCLC [11–13]. Retrospective studies showed that anlotinib could be used for maintenance treatment after chemotherapy for various solid tumors [14–17]. It was hypothesized that anlotinib could be used as a single agent for the consolidation treatment of unresectable NSCLC after cCRT.

DOI: 10.1097/CAD.0000000000001617

Therefore, this study aimed to explore the efficacy and safety of anlotinib for consolidation therapy in patients with stage III locally advanced, unresectable NSCLC after cCRT. This study was terminated early due to poor recruitment and the preliminary result was reported here.

Methods

Study design

This was a randomized, parallel-controlled, open-label, multicenter phase II trial (ALTER-L029). This study was approved by the Ethics Committee of Beijing Cancer Hospital (approval number: 2018YJZ47) and written informed consent was obtained before each patient participated in the study. This clinical trial was registered on www.clinicaltrials.gov (NCT03743129). Registration date: 6 September 2018.

Participants

From December 2019 to March 2021, NSCLC patients after cCRT were recruited from five medical centers.

The inclusion criteria were (1) voluntarily participated in the study and signed the informed consent, (2) were able to cooperate with follow-up, (3) ≥18 years of age, (4) pathologically confirmed NSCLC patients with stage III disease [2,4], (5) unresectable disease, patient unsuitable for surgery or refused surgery, (6) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score is 0 or 1, (7) normal function of the main organs, (8) no disease progression after at least two cycles of cCRT and (9) life expectancy was at least 3 months.

The exclusion criteria were (1) previous exposure to any antiangiogenic drugs, (2) high risk of bleeding, (3) imaging showed central tumors that invaded local large blood vessels, obvious lung cavitation or necrotic tumors, (4) unresolved toxicity CTCAE > 2 in the previous cCRT or (5) serious or poorly controlled diseases such as hypertension, chronic obstructive pulmonary disease, hepatitis B, AIDS, etc.

Randomization

This study used stratified block randomization, with a block size of 6, and stratification indicators that included age (<65 years old or ≥65 years old), whether they received induction chemotherapy and whether they had a history of smoking. According to the ratio of 2:1, the participants were randomly allocated into the anlotinib and control groups.

Intervention

The anlotinib group started taking anlotinib (anlotinib hydrochloride capsules, Zhengda Tianqing Pharmaceutical, Zhengda Tianqing Pharmaceutical Company, China) 4 to 8 weeks after cCRT. Anlotinib had three dose levels (12, 10 and 8 mg). The initial dose was 12 mg qd, taken continuously for 2 weeks, followed by a 1-week pause [treatment cycles of 3 weeks (21 days)]. Then, the administration was continued until disease progression, intolerable toxicity, the patient requested to stop the drug or a maximum of 2 years.

The control group did not receive any antitumor consolidation treatment before disease progression.

For patients with hematological toxicity grade ≥3 or non-hematological toxicity grade ≥2 (except for controllable nausea, vomiting, alopecia, fever with a definite cause and grade 3/4 alkaline phosphatase elevation), anlotinib was reduced to 10 mg or 8 mg, if toxicity persisted after dosage adjustment, patients would discontinue the drug.

Endpoints

The primary endpoint of this clinical study was PFS. The secondary endpoints were the disease control rate (DCR), and 1- and 2-year overall survival (OS) rates. The tumor response was evaluated by the local investigators according to the response evaluation criteria in solid tumors version 1.1. PFS was defined as the date of first disease progression or death from any cause within the study period after randomization, whichever occurred first. DCR was defined as the proportion of patients with complete remission, partial remission (PR) and stable disease (SD) and maintained for more than 4 weeks after randomization among patients with evaluable efficacy. The OS rate was defined as the proportion of patients who die from any cause after randomization. The adverse events (AEs) during the study were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

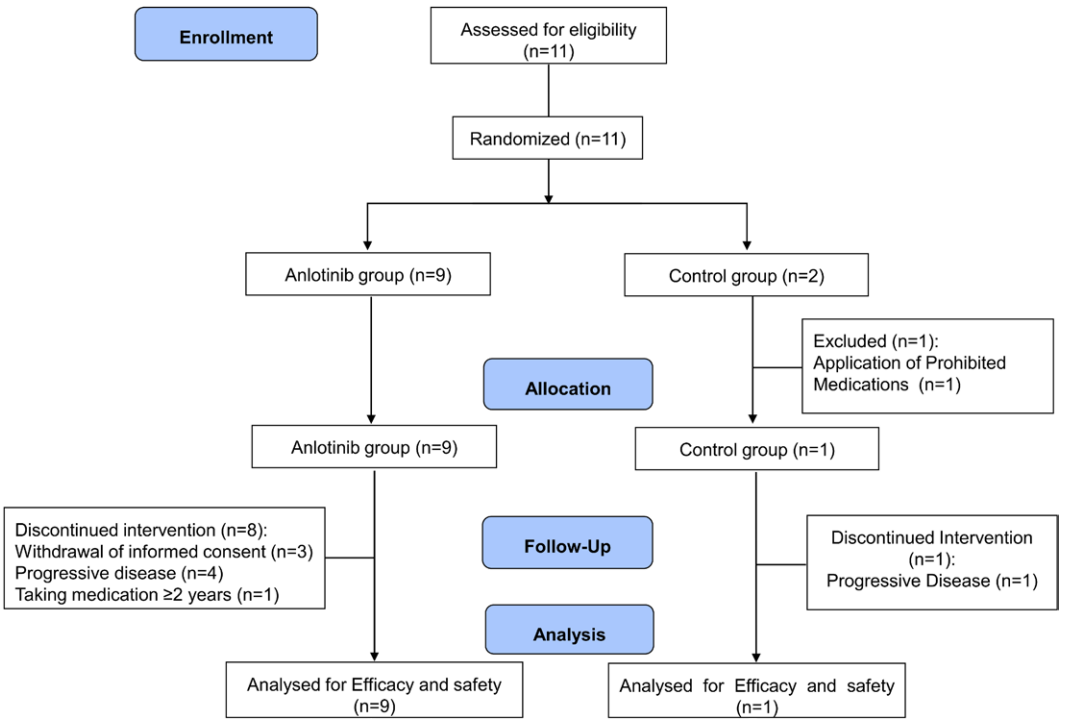
The first follow-up and imaging evaluations were carried out 3 months after enrollment. The imaging evaluation and follow-up were carried out every 3 months afterward. The bone scan was checked every 6 months or when symptoms appeared. Disease progression required a blinded IRC (BIRC) evaluation. If the BIRC result was inconsistent with the local investigator's evaluation result, the BIRC evaluation result prevailed. Anlotinib was not stopped during the BIRC evaluation period.

AEs that did not recover when the study drug was stopped were followed up, and a final evaluation was made. All patients were followed up once within 21 days after the last medication to observe eventual AEs.

Statistical analysis

In this study, blank treatment was used as the control, a superiority test was performed between groups, and the sample size was estimated with PFS. The study was expected to last 24 months, with 12 months of patient recruitment. Assuming that the median progression-free survival (mPFS) of anlotinib hydrochloride single-agent anlotinib group was 12 months, the mPFS of the control group was 6 months, one-sided $\alpha = 0.05$, power of 0.80,

Fig. 1



Study flowchart.

Table 1 Characteristics of the participants

Characteristics	Anlotinib group ($n = 9$)	Control group ($n = 1$)
Median age (years)	63 (37–74)	52
≥65 years old	4 (44.4%)	0
<65 years old	5 (55.6%)	1
Sex		
Male	8 (88.9%)	1
Female	1 (11.1%)	0
Smoking history		
Never smoked	1 (11.1%)	0
Ever smoked	8 (88.9%)	1
Previous induction chemotherapy	1 (11.1%)	1
Best response of cCRT		
PR	7	0
SD	2	1
ECOG score		
0	5 (55.6%)	1
1	4 (44.4%)	0
Pathological type		
Squamous carcinoma	6 (66.7%)	1
Adenocarcinoma	3 (33.3%)	0

The data are displayed as *n* (%) and median (range).
cCRT, concurrent chemoradiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; PR, partial remission; SD, stable disease.

randomization ratio of 2:1 and a loss to follow-up rate was 10%, a total of 90 patients were needed, including 60 in the anlotinib group and 30 in the control group. Unfortunately, the study was terminated early due to poor recruitment.

According to the principle of intention-to-treat, the full analysis set (FAS) included all participants who took at least one dose of the drug. No imputation was performed for missing data. The safety set (SS) included the participants who used the study medication at least once and had safety records after the medication.

All statistical analyses were performed using SAS 9.1.3 (SAS Institutes, Cary, New York, USA). The baseline data were analyzed according to the FAS. All efficacy analysis were performed in FAS. The safety analysis used the SS. The continuous data were described as means ± SD or median (minimum, maximum). Categorical data were described as *n* (%). The confidence intervals were calculated at the 95% level. The Kaplan–Meier method was used for the comparison of PFS and OS. Due to the small number of patients were included in the two groups, only descriptive statistics were employed and no comparison between groups was made in this study.

Results

Characteristics of the participants

The trial was originally planned to recruit 90 participants, but due to poor recruitment, after recruiting 11 participants over 3 years, the study was terminated in November 2021. Nine participants were randomly assigned to the anlotinib group, and two were assigned to the control group. One participant in the control group was excluded from the study due to taking drugs prohibited by the protocol within 2 days of enrollment, and the efficacy and safety were not evaluated. As of November 2021, all

patients reached the endpoints. In the anlotinib group, three participants withdrew consent, and one participant had his medication suspended due to suspected intracranial hemorrhage and was subsequently reinstated, four participants showed disease progression but no deaths, and one participant took medication over 2 years without disease progression. The follow-up was 4–26 months. The nine participants in the anlotinib group could be analyzed. Figure 1 presents the participant flowchart.

The baseline characteristics are shown in Table 1. In the anlotinib group, the median age was 63 (range, 37–74) years. Of the nine participants, only one was female. Six participants were diagnosed with squamous cell carcinoma, and the remaining three had adenocarcinoma. Five participants had an ECOG PS score of 0, and 4 patients had a PS score of 1.

Efficacy

Table 2 shows the efficacy of anlotinib. Two participants achieved a PR, six achieved an SD, and one achieved PD as the best response. The objective remission rate was 22.2%, and the DCR was 88.9%. The median PFS was 11.5 months. The 12-month PFS rate was 33.9% (Fig. 2).

Table 2 Tumor response

Efficacy	Anlotinib group ($n = 9$)
CR, *n*	0
PR, *n*	2
SD, *n*	6
PD, *n*	1
ORR, *n* (%)	2 (22.2%)
DCR, *n* (%)	8 (88.9%)

CR, complete remission; DCR, disease control rate; ORR, objective remission rate; PD, progressive disease; PR, partial remission; SD, stable disease.

Safety

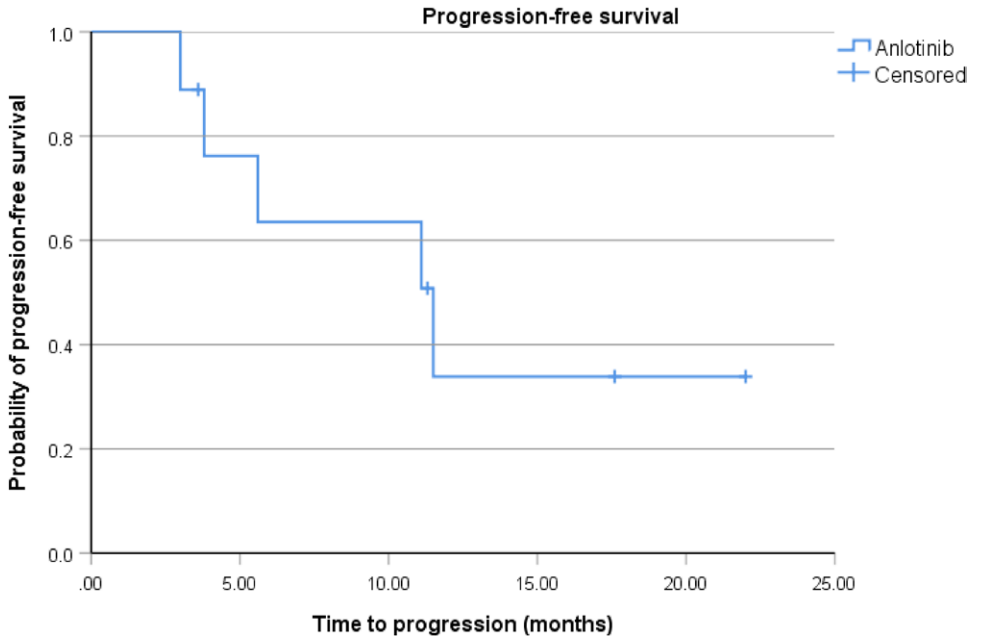
All related AEs were grade 1 or 2. Fatigue (44.4%), palmar-plantar erythrodysesthesia syndrome (44.4%) and cough (44.4%) were the most frequent AEs in the anlotinib group (Table 3). One participant was suspended due to suspected but nonconfirmed intracranial hemorrhage. Two participants had a dose adjustment during the study. Their doses were adjusted to 10 mg due to fatigue and elevated thyroid-stimulating hormone, respectively.

Discussion

This study (ALTER-L029) was a randomized, parallel-controlled, open-label, multicenter exploratory phase II clinical trial, but this trial was terminated early due to poor recruitment. Nevertheless, the evaluable data suggest that anlotinib alone has some efficacy and good safety in consolidation therapy after cCRT in patients with stage III unresectable NSCLC. The results need to be confirmed by a large-sample trial.

The study was terminated early due to poor recruitment, which is the main reason for the early termination of randomized controlled trials [18,19]. Reasons for poor recruitment in this study were multiple. Although

Fig. 2



Progression-free survival (PFS) of patients in anlotinib group.

Table 3 Treatment-emergent adverse event

Symptoms	Anlotinib group ($n = 9$)[a]	Control group ($n = 1$)
Fatigue	4	
Palmar-plantar erythrodysesthesia syndrome	4	
Cough	4	
Toothache	3	
Chest pain	3	
Hoarseness	3	
Diarrhea	3	
Hypertriglyceridemia	3	
Tinnitus	2	
Anorexia	2	
Pharyngolaryngeal pain	2	
Abdominal pain	2	
Proteinuria	2	
Edema limbs	2	
hypertension	1	
Back pain	1	
Paresthesia	1	
Neck pain	1	
Cholesterol high	1	
Pneumothorax	1	
Pulmonary bullae	1	
Anemia	1	
Leg cramps	1	
Arthralgia (ankle)	1	
Epistaxis	1	
Low-density lipoprotein elevation	1	
Cholecystitis	1	
Hypothyroidism	1	1
Pain of skin	1	
White blood cell decreased	1	
Neutrophil count decreased	1	
Headache	1	
hyperglycemia	1	
Urinary tract infection	1	
Hypothyroid stimulating hormone decreased	1	
hypoalbuminemia	1	
Dyspnea	1	
Arthralgia (shoulder joint)	1	
myalgia	1	

TEAE, treatment-emergent adverse event.
[a]No ≥Grade 3 TEAEs were observed in the anlotinib group.

cCRT is the first-line treatment for unresectable locally advanced NSCLC, patients who received cCRT may be in poor condition, and it is not easy to recruit patients who meet the enrollment criteria. The number of patients suitable and willing to receive cCRT was small [20]. Another important reason for enrollment difficulties is that durvalumab, which was available in China in December 2019, was recommended by the guidelines as consolidation therapy for unresectable locally advanced NSCLC after cCRT, but the control group in this study was set to placebo. In addition, the COVID-19 pandemic complicated healthcare in China. Many patients were reluctant to return to the hospital for the study purpose.

The purpose of consolidation therapy is to prevent disease progression. In the present study, the median PFS was 11.5 months, and the 12-month PFS rate of the anlotinib group was 33.9%. Without consolidation therapy, the median survival time of stage III unresectable NSCLC is 14.6–17 months [3], and the median PFS was 5.6–8.1 months [5,9]. Consolidation with chemotherapy after cCRT yielded a 12-month PFS rate of 27% using docetaxel-carboplatin [6], a median PFS of 10.0 months with pemetrexed-cisplatin [7], a median PFS of 7.6 months with etoposide-cisplatin [7], a median PFS of 6.4 months with vinorelbine and cisplatin [8] and a median PFS of 9.1 months with docetaxel and cisplatin [9]. Hence, consolidation with chemotherapy is not satisfied.

Immune checkpoint inhibitors are promising as consolidation therapy after cCRT. Indeed, the PACIFIC trial showed that durvalumab could achieve a 12-month PFS rate of 55.9% [5]. Another trial of durvalumab showed similar results (12-month PFS rate of 65.9%) [21]. Anlotinib is effective and safe in patients with advanced NSCLC [22,23]. In the present study, anlotinib appears to achieve PFS rates similar to those achieved with durvalumab, but it needs to be confirmed in large-scale studies. Still, immune checkpoint inhibitors are expensive drugs with many contraindications, and their use were limited in China. Thus, as an antiangiogenic agent with a different mechanism of action to durvalumab, anlotinib might be a less expensive and more accessible option for the consolidation therapy of unresectable locally advanced NSCLC.

cCRT regimens are generally highly toxic [3,5–10,24,25]. Therefore, the selection of consolidation therapy should consider whether the patient can tolerate it. In this study, all AEs due to anlotinib were grade I–II, and the anlotinib dose had to be reduced in two patients without the need to stop it. In comparison, chemotherapy consolidation using docetaxel-carboplatin had a rate of grade ≥3 hematologic toxicity of 16% [6] or >5% [9], a rate of grade 3–4 treatment-emergent AEs of 61.4% or 91.3% with pemetrexed-cisplatin or etoposide-cisplatin [7], and grade 3–4 neutropenia and leukopenia of 22.1% and 26.7% with vinorelbine and cisplatin [8]. High grade 3–4 AE rates were also observed with durvalumab [5,21]. A better toxicity profile was observed with EGFR-TKI consolidation, with only grade 1–2 AEs reported [25,26]. Nevertheless, the present study showed that anlotinib is safe in patients with NSCLC, as supported by previous studies [11–16,22,23]. No new safety signals were found in this study.

This study had limitations. As discussed above, a major and critical limitation is poor recruitment and early termination, and no more reliable conclusions can be drawn from the results. In addition, the control group had a small number of patients, and none of the two patients could be included in the FAS or PPS. The efficacy and safety of anlotinib as consolidation therapy after cCRT for stage III NSCLC requires more studies.

Conclusion

In conclusion, the limited evaluable data suggest that anlotinib alone is effective and tolerable in consolidation therapy after cCRT in patients with stage III unresectable NSCLC. The results need to be confirmed by a large-sample trial.

Acknowledgements

This study was approved by the Ethics Committee of Beijing Cancer Hospital (approval number: 2018YJZ47) and written informed consent was obtained before each patient participated in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

D.Y. finished the majority of data entry and data analysis and composed the manuscript. X.L. and X.X. had provided part of the cases and profession advises on the treatment. L.J. reviewed the database prior to the data analysis. A.S. and J.Z. provided most of the cases and gave advice to data analysis and outcomes interpretation. All authors read, critically revised and approved the manuscript.

Conflicts of interest

There are no conflicts of interest.

References

1 Qiu H, Cao S, Xu R. Cancer incidence, mortality, and burden in China: a time-trend analysis and comparison with the United States and United Kingdom based on the global epidemiological data released in 2020. *Cancer Commun (Lond)* 2021; **41**:1037–1048.
2 Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, *et al.*; ESMO Guidelines Committee. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; **27**:v1–v27.
3 Curran WJ Jr, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, *et al*. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst* 2011; **103**:1452–1460.
4 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). *Non-Small Cell Lung Cancer. Version 1.2022*. National Comprehensive Cancer Network; 2021.
5 Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, *et al.*; PACIFIC Investigators. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2017; **377**:1919–1929.
6 Jain AK, Hughes RS, Sandler AB, Dowlati A, Schwartzberg LS, Dobbs T, *et al*. A phase II study of concurrent chemoradiation with weekly docetaxel, carboplatin, and radiation therapy followed by consolidation chemotherapy with docetaxel and carboplatin for locally advanced inoperable non-small cell lung cancer (NSCLC). *J Thorac Oncol* 2009; **4**:722–727.
7 Wang L, Wu YL, Lu S, Deng L, Ahn MJ, Hsu FM, *et al*. An East Asian subgroup analysis of PROCLAIM, a phase III trial of pemetrexed and cisplatin or etoposide and cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small cell lung cancer. *Asia Pac J Clin Oncol* 2016; **12**:380–387.
8 Flentje M, Huber RM, Engel-Riedel W, Andreas S, Kollmeier J, Staar S, *et al*. GILT--A randomised phase III study of oral vinorelbine and cisplatin with concomitant radiotherapy followed by either consolidation therapy with oral vinorelbine and cisplatin or best supportive care alone in stage III non-small cell lung cancer. *Strahlenther Onkol* 2016; **192**:216–222.
9 Ahn JS, Ahn YC, Kim JH, Lee CG, Cho EK, Lee KC, *et al*. Multinational randomized phase III trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III non-small-cell lung cancer: KCSG-LU05-04. *J Clin Oncol* 2015; **33**:2660–2666.
10 Faivre-Finn C, Vicente D, Kurata T, Planchard D, Paz-Ares L, Vansteenkiste JF, *et al*. Four-year survival with durvalumab after chemoradiotherapy in stage III NSCLC-an update from the PACIFIC trial. *J Thorac Oncol* 2021; **16**:860–867.
11 Zhou M, Chen X, Zhang H, Xia L, Tong X, Zou L, *et al*. China National Medical Products Administration approval summary: anlotinib for the treatment of advanced non-small cell lung cancer after two lines of chemotherapy. *Cancer Commun (Lond)* 2019; **39**:36.
12 Han B, Li K, Wang Q, Zhang L, Shi J, Wang Z, *et al*. Effect of anlotinib as a third-line or further treatment on overall survival of patients with advanced non-small cell lung cancer: the ALTER 0303 phase 3 randomized clinical trial. *JAMA Oncol* 2018; **4**:1569–1575.
13 Han B, Li K, Zhao Y, Li B, Cheng Y, Zhou J, *et al*. Anlotinib as a third-line therapy in patients with refractory advanced non-small-cell lung cancer: a multicentre, randomised phase II trial (ALTER0302). *Br J Cancer* 2018; **118**:654–661.
14 Wang HY, Chu JF, Zhang P, Wang JQ, Yan Z, Yao SN, *et al*. Safety and efficacy of chemotherapy combined with anlotinib plus anlotinib maintenance in Chinese patients with advanced/metastatic soft tissue sarcoma. *Onco Targets Ther* 2020; **13**:1561–1568.
15 Ni J, Cheng X, Chen J, Guo W, Dai Z. Anlotinib as exploratory therapy for platinum-resistant ovarian cancer: a retrospective study on efficacy and safety. *Onco Targets Ther* 2020; **13**:9857–9863.
16 Liu Z, Yao W, Zhao Y, Liu O, Zhang P, Ge H. Efficacy and safety of anlotinib combined with liposomal doxorubicin followed by anlotinib maintenance in metastatic soft tissue sarcomas. *Cancer Manag Res* 2021; **13**:1009–1016.
17 Liu J, Deng YT, Jiang Y. Switch maintenance therapy with anlotinib after chemotherapy in unresectable or metastatic soft tissue sarcoma: a single-center retrospective study. *Invest New Drugs* 2021; **39**:330–336.
18 Kasenda B, von Elm E, You J, Blumle A, Tomonaga Y, Saccilotto R, *et al*. Prevalence, characteristics, and publication of discontinued randomized trials. *JAMA* 2014; **311**:1045–1051.
19 Briel M, Olu KK, von Elm E, Kasenda B, Alturki R, Agarwal A, *et al*. A systematic review of discontinued trials suggested that most reasons for recruitment failure were preventable. *J Clin Epidemiol* 2016; **80**:8–15.
20 Cardenal F, Nadal E, Jove M, Faivre-Finn C. Concurrent systemic therapy with radiotherapy for the treatment of poor-risk patients with unresectable stage III non-small-cell lung cancer: a review of the literature. *Ann Oncol* 2015; **26**:278–288.
21 Dickson FAB, Raez LE, Dumais K, Powery HW, Walker D. Outcomes of patients with unresectable stage III non-small cell lung cancer treated with durvalumab and subsequent therapies after disease progression. *J Clin Oncol* 2021; **39**:e20531–e20531.
22 Zhang K, Ma X, Gao H, Wang H, Qin H, Yang S, *et al*. Efficacy and safety of anlotinib in advanced non-small cell lung cancer: a real-world study. *Cancer Manag Res* 2020; **12**:3409–3417.
23 Zhong Q, Liu Z. Efficacy and safety of anlotinib in patients with advanced non-small cell lung cancer: a real-world study. *Cancer Manag Res* 2021; **13**:4115–4128.
24 Bradley JD, Hu C, Komaki RR, Masters GA, Blumenschein GR, Schild SE, *et al*. Long-term results of NRG Oncology RTOG 0617: standard- versus high-dose chemoradiotherapy with or without cetuximab for unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 2020; **38**:706–714.
25 Wu R, Yu S, Ye J, Wang Y, Zhao Z, Liu H, *et al*. A multicenter retrospective study on the prognosis of stage III unresectable mutant non-small cell lung cancer with tyrosine kinase inhibitors therapy. *Front Oncol* 2021; **11**:692703.
26 Feng S, Wang Y, Cai K, Wu H, Xiong G, Wang H, *et al*. Randomized adjuvant chemotherapy of EGFR-mutated non-small cell lung cancer patients with or without icotinib consolidation therapy. *PLoS One* 2015; **10**:e0140794.