ORIGINAL ARTICLE

Salvage treatment with anlotinib for advanced non-small cell lung cancer

Di Wu, Jun Nie, Ling Dai, Weiheng Hu, Jie Zhang, Xiaoling Chen, Xiangjuan Ma, Guangming Tian, Jindi Han, Sen Han, Jieran Long, Yang Wang ⓘ, Ziran Zhang & Jian Fang ⓘ

Department of Thoracic Oncology II, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China

Abstract

Background: This real-world study assessed the efficacy and toxicity of anlotinib as salvage treatment in Chinese patients with advanced non-small cell lung cancer (NSCLC).

Methods: The medical records of 81 patients with advanced NSCLC who had failed at least two lines of chemotherapy were retrospectively collected. All patients were administered anlotinib treatment until disease progression or intolerance as a result of adverse events. Survival curves were created using the Kaplan–Meier method. The log-rank test was used for univariate analysis of progression-free survival (PFS) between groups. Cox regression was used to estimate the statistically significant factors based on univariate analysis.

Results: The median PFS was five months (95% confidence interval [CI] 3.5–6.5). The objective response rate (ORR) was 7% and the disease control rate (DCR) was 84%. The following subgroups of patients had longer PFS ($P < 0.05$): squamous cell carcinoma, no brain or liver metastases, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1, and no previous VEGF-tyrosine kinase inhibitor treatment. The results of Cox regression indicated that an ECOG PS of 0–1 (hazard ratio 0.152, 95% CI 0.057–0.403; $P = 0.00$) and patients without brain metastases (hazard ratio 0.421, 95% CI 0.195–0.911; $P = 0.028$) had longer PFS following anlotinib treatment.

Conclusion: Anlotinib, which is well tolerated, plays a significant role in the salvage treatment of advanced NSCLC. Patients with advanced NSCLC with an ECOG PS of 0–1 and no brain metastases achieved longer PFS following anlotinib salvage treatment.

Introduction

Both in China and globally, lung cancer has the highest morbidity and mortality among all cancer types.[1,2] Non-small cell lung cancer (NSCLC) accounts for approximately 80% of lung cancer cases. Because most early-stage lung cancer patients are asymptomatic, the diagnosis is usually made at locally advanced or advanced stages.[3,4] For locally advanced or advanced NSCLC, drug therapy, including chemotherapy, targeted therapy, and immunotherapy, is still the most important treatment. There are still some patients in good physical condition after recommended standard treatments who need safer and more effective new drugs.

Angiogenesis plays an important role in tumor occurrence, proliferation, and metastasis.[5,6] Clinical studies have shown that chemotherapy combined with bevacizumab significantly prolongs progression-free survival (PFS) and overall survival (OS) compared to chemotherapy in first-line treatment for advanced NSCLC patients.[7–9] Compared to docetaxel alone, docetaxel combined with ramucirumab significantly prolongs PFS and OS in patients for whom platinum-based treatment fails.[10] Most VEGF tyrosine kinase inhibitors (TKIs) prolong PFS, but not OS.[11,12]

A phase III trial of advanced NSCLC patients administered anlotinib – a novel TKI that targets VEGF receptor,

fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), and c-Kit – following third-line or further treatment resulted in longer PFS and OS than the group treated with a placebo.[13] The China Food and Drug Administration has approved the use of anlotinib for third-line treatment in advanced NSCLC patients. Furthermore, anlotinib also has a therapeutic effect in soft tissue sarcomas, medullary thyroid cancer, renal cell carcinoma, and other solid tumors.[14]

We assessed the efficacy and safety of anlotinib as salvage treatment in Chinese patients with advanced NSCLC in real-world practice and investigated the predictors of therapeutic efficacy.

Methods

Data source and study population

We retrospectively collected the medical data of NSCLC patients who were treated at Peking University Cancer Hospital between June 2018 and January 2019. Ninety-one patients were prescribed anlotinib; efficacy was not evaluated in eight patients and two patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 3 and were thus excluded. Eighty-one patients who were prescribed anlotinib met the following criteria: aged 18–80 years; recurrent or advanced NSCLC (stage IIIB, IIIC, or IV [American Joint Committee on Cancer Cancer Staging Manual, 8th edition]) with failure of at least two lines of chemotherapy; *EGFR*-sensitive mutations for which EGFR-TKIs and at least two lines of chemotherapy had failed (treatment failure was defined as disease progression or intolerance to chemotherapy or EGFR-TKIs); an ECOG PS of 0–2; and adequate liver and kidney function. Patients with centrally located lung squamous cell carcinoma, a risk of massive hemoptysis, a bleeding tendency, uncontrolled hypertension, and those administered thrombolytics or anticoagulants were excluded.

Treatment

All patients received anlotinib (one cycle of 12 mg daily for 14 days, discontinued for 7 days, and repeated every 21 days). Doses were reduced when patients experienced intolerable adverse events (AEs). Patients continued anlotinib until disease progression or intolerance as a result of AEs.

Study assessments

Therapeutic effect was assessed using Response Evaluation Criteria in Solid Tumors version 1.1 by computed tomography (CT) scans and nuclear magnetic resonance imaging (MRI) at baseline every two cycles or when clinical symptoms worsened. The data cutoff date was 10 April 2019. PFS was defined as the duration from the beginning of anlotinib administration to tumor progression or death. The safety of anlotinib treatment was assessed using Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis

Statistical analysis was processed using SPSS version 22.0. Survival curves were created using the Kaplan–Meier method. The log-rank test was used for univariate analysis of PFS between groups. Cox regression estimated the statistically significant factors in univariate analysis. Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics

Eighty-one advanced NSCLC patients were prescribed anlotinib between June 2018 and January 2019. The demographic and clinical characteristics of the patients were collected, including gender, age, pathologic type, *EGFR* status, clinical stage, number of distant metastases, brain metastases, liver metastases, smoking history (defined as a smoking index > 10 pack-years), ECOG PS, number of previous treatment lines, previous VEGF-TKI treatment, previous VEGF monoclonal antibody treatment, and previous EGFR-TKI treatment (Table 1).

Clinical outcomes

The median PFS was five months (95% confidence interval [CI] 3.5–6.5) (Fig 1a); the OS data were not mature at the end of follow-up. The best responses among the 81 patients were: partial response (PR, $n = 6$); stable disease (SD, $n = 62$); and progressive disease (PD, $n = 13$). The objective response rate (ORR) was 7% and the disease control rate (DCR) was 84%. Because some patients did not have measurable lesions or the imaging examinations in other hospitals were not available to determine changes in the lesions, the therapeutic effect in 15 patients was directly assessed by a physician based on imaging performance. A total of 65 patients had measurable lesions. The changes in measurable lesions from baseline are shown in Figure 2.

Univariate analysis showed that PFS was significantly prolonged in the following patient subgroups: squamous cell carcinoma, no brain or liver metastases, ECOG PS of 0–1, and no previous VEGF-TKI treatment ($P < 0.05$) (Fig 1b–f). Gender, age, *EGFR* status, clinical stage, number of distant metastases, previous history of hypertension, smoking history, number of previous treatment lines,

Table 1 Baseline demographic and clinical characteristics

Characteristic	Patients (*n* = 81)
Gender	
Male	47 (58)
Female	34 (41)
Age	
Median (years)	60
≤ 65	61 (75)
> 65	20 (25)
Pathologic type	
Adenocarcinoma	54 (67)
Squamous cell carcinoma	27 (33)
EGFR status	
Mutation	27 (33)
Wild type	40 (49)
Unknown	14 (18)
Clinical stage	
IIIB/IIIC	8 (10)
IV	73 (90)
Number of distant metastases	
0	25 (31)
1	37 (46)
≥ 2	19 (23)
Brain metastases	
Yes	23 (28)
No	58 (72)
Liver metastases	
Yes	11 (14)
No	70 (86)
Smoking history	
Yes	34 (42)
No	47 (58)
ECOG PS	
≤ 1	72 (89)
2	9 (11)
No. of previous treatment lines	
< 3	44 (54)
≥ 3	37 (46)
Previous VEGF-TKI treatment	
Yes	7 (9)
No	74 (91)
Previous VEGF monoclonal antibody treatment	
Yes	51 (63)
No	30 (37)
Previous EGFR-TKI treatment	
Yes	43 (53)
No	38 (47)

ECOG PS, Eastern Cooperative Oncology Group performance status; TKI, tyrosine kinase inhibitor.

previous VEGF monoclonal antibody treatment, and previous EGFR-TKI treatment did not influence PFS after anlotinib treatment (Table 2).

The results of Cox regression indicated that ECOG PS (hazard ratio [HR] 0.152, 95% CI 0.057–0.403; *P* = 0.00) and brain metastases (HR 0.421, 95% CI 0.195–0.911; *P* = 0.028) were predictive indicators of PFS following anlotinib treatment. There were no statistically significant differences between patients with and without liver metastases (HR 0.682, 95% CI 0.275–1.693; *P* = 0.409), squamous cell carcinoma and adenocarcinoma (HR 0.466, 95% CI 0.189–1.147; *P* = 0.097), or patients previously treated with and without VEGF-TKIs (HR 0.827, 95% CI 0.313–2.184; *P* = 0.701) (Table 3).

Safety

The most common AEs with an incidence of ≥ 5% were: hypertension (12%), hand-foot syndrome (6%), decreased appetite (6%), fatigue (5%), oral mucositis (5%), and hoarseness (5%). Only hypertension (7%), which was well controlled by anti-hypertensive drugs, was assessed as grade 3–4 with an incidence of > 5% (Table 4).

Discussion

In third-line or further treatments, if immune checkpoint inhibitors,[15–18] docetaxel, gemcitabine, or pemetrexed (non-squamous only),[19–22] have not already been administered, these therapies can be recommended for patients with advanced NSCLC, after which there are no additional standard treatment options.

The ALTER 0303 trial showed that PFS was significantly longer in the anlotinib group than the placebo group (5.4 vs. 1.4 months; *P* < 0.001). In addition, a considerable improvement in ORR (9.2% vs. 0.7%; *P* < 0.001) and DCR (81.0% vs. 37.1%; *P* < 0.001) was observed in the anlotinib group compared to the placebo group.[13] There are few real-world studies of anlotinib salvage treatment in advanced NSCLC patients. In the present study, we retrospectively assessed the real-world outcomes of anlotinib salvage treatment in Chinese patients with advanced NSCLC to evaluate efficacy and toxicity. The median PFS was five months (95% CI 3.5–6.5). In addition, the ORR and DCR were 7% and 84%, which were consistent with the results of the ALTER 0303 trial. Moreover, the PFS, ORR, and DCR results in the present study were not inferior to the results with second-line recommended drugs, such as docetaxel, pemetrexed,[19] immune checkpoint inhibitors,[16–18] and drugs with a similar mechanisms of action to apatinib.[12] These results show that in patients with advanced NSCLC, anlotinib treatment is an effective salvage therapy.

The exploration of potential predictors for treatment efficacy of antiangiogenic drugs is valuable. In a randomized phase III trial of gastric cancer patients, plasma VEGF-A levels and tumor neuropilin-1 expression were identified as strong predictors of bevacizumab efficacy.[23] A study of predictive indicators showed that phosphorylated VEGFR2 and hypertension may be predictors of anti-angiogenic drugs in breast cancer.[24] A retrospective study
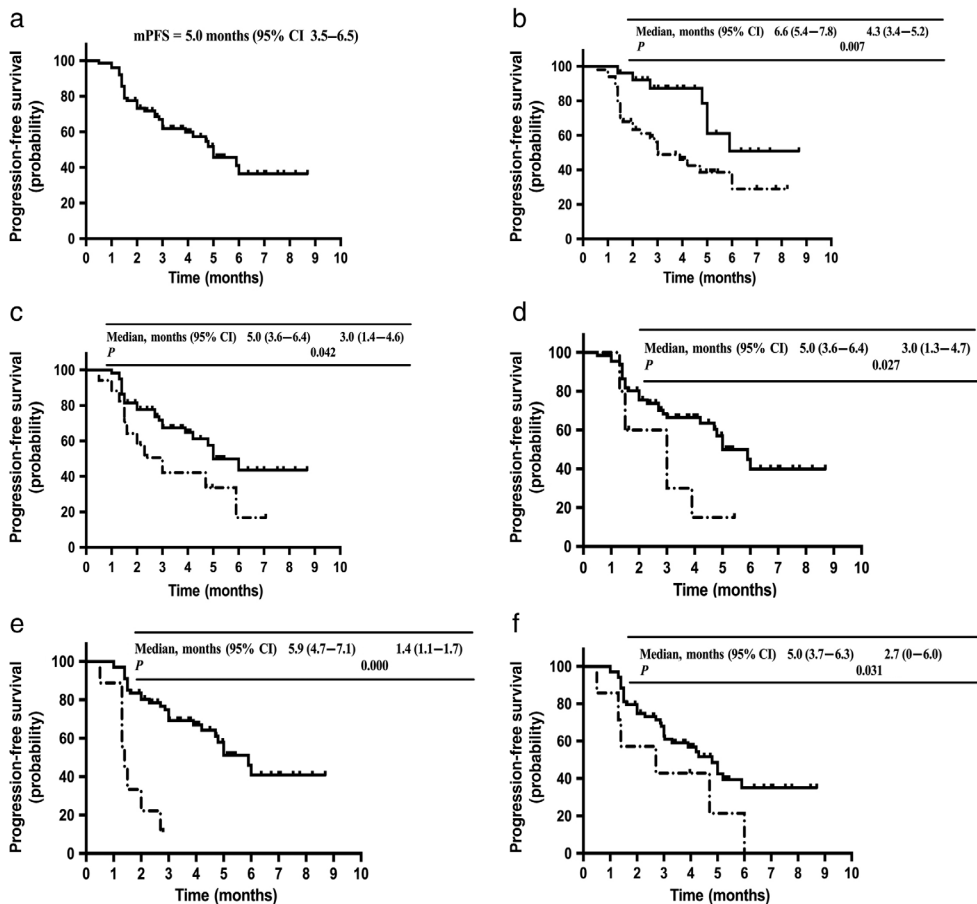
Figure 1 Efficacy results after the administration of anlotinib. Progression-free survival of: (**a**) all 81 patients; (**b**) stratified by pathologic type, (———) Squamous cell carcinoma and (—·—·) adenocarcinoma; (**c**) stratified by brain metastases, (———) No brain metastases and (—·—·) brain metastases; (**d**) stratified by liver metastases, (———) No liver metastases and (—·—·) liver metastases; (**e**) stratified by Eastern Cooperative Oncology Group (ECOG) performance status, (———) ECOG = 0–1 and (—·—·) ECOG = 2; and (**f**) stratified by previous VEGF-tyrosine kinase inhibitor (TKI) treatment, (———) No previous EGFR-TKI treatment and (—·—·) previous EGFR-TKI treatment. CI, confidence interval.
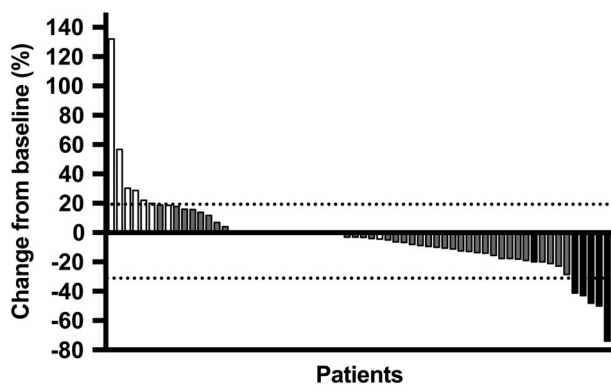

Figure 2 Measurable lesion changes from baseline. Among the 65 patients with measurable lesions, 6 achieved a partial response (PR), 52 achieved stable disease (SD), and 7 reported progressive disease (PD). (☐) PD, (▨) SD and (■) PR.

identified hypertension, proteinuria, and hand-foot syndrome emerging during the first cycle of apatinib treatment as viable predictive indicators of efficacy in gastric cancer patients.[25] Girard et al. reported that an ECOG PS of 0–1 was a predictor of prolonged survival after second-line therapy in patients with advanced NSCLC, which is a very important prognostic factor for survival in lung cancer.[26,27] In addition, studies have shown that liver and brain metastases might be negative predictors of OS in lung cancer patients.[28,29] In this study, univariate analysis showed that PFS in the squamous cell carcinoma subgroup was superior to that of the adenocarcinoma subgroup, which was different to the findings in the ALTER 0303 trial, but after Cox regression analysis, the results no longer differed between the two subgroups. Univariate analysis also showed that there was no significant association between PFS and gender, age, EGFR status, clinical stage, number of distant metastases, previous history of hypertension,

Table 2 Univariate analysis of PFS

Variable	PFS	95% CI	P
Gender			
Male	5.0	4.6–5.4	0.55
Female	5.9	1.7–10.1	
Age			
Median (years)			0.556
≤ 65	4.8	3.6–6.0	
> 65	6.0	2.7–9.3	
Pathologic type			
Adenocarcinoma	4.3	3.4–5.2	0.007
Squamous cell carcinoma	6.6	5.4–7.8	
EGFR status			
Mutation	4.8	3.5–6.1	0.158
Wild type	4.3	3.4–5.1	
Unknown	6.8	5.3–8.3	
Clinical stage			
IIIB	7.7	5.8–9.5	0.11
IV	4.8	4.0–5.5	
Number of distant metastases			
0	5.9	4.5–7.3	0.051
1	5.0	4.1–6.0	
≥ 2	3.1	2.3–3.9	
Brain metastases			
Yes	3.0	1.4–4.6	0.042
No	5.0	3.6–6.4	
Liver metastases			
Yes	3.0	1.3–4.7	0.027
No	5.0	3.6–6.4	
Previous history of hypertension			
Yes	5.0	3.7–6.3	0.855
No	4.8	2.8–6.7	
Smoking history			
Yes	5.6	4.4–6.8	0.481
No	4.6	3.7–5.6	
ECOG PS			
≤ 1	5.9	4.7–7.1	0.000
2	1.4	1.1–1.7	
No. of previous therapy lines			
< 3	4.8	3.5–6.1	0.901
≥ 3	5.9	4.1–7.7	
Previous VEGF-TKI treatment			
Yes	2.7	0–6.0	0.031
No	5.0	3.7–6.3	
Previous VEGF monoclonal antibody treatment			
Yes	5.0	4.0–6.0	0.835
No	5.9	3.0–8.8	
Previous EGFR-TKI treatment			
Yes	5.0	3.1–6.9	0.951
No	5.0	2.2–7.8	
Hypertension during medication			
Yes	2.7	1.5–3.9	0.446
No	5.0	4.6–5.4	

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Table 3 Cox regression of PFS

Factor	P	HR	95% CI
Pathologic type	0.097	0.466	0.189–1.147
Squamous cell carcinoma (vs. adenocarcinoma)			
Brain metastases: without (vs. with)	0.028	0.421	0.195–0.911
Liver metastases: without (vs. with)	0.409	0.682	0.275–1.693
ECOG PS: ≤ 1 (vs. 2)	0.000	0.152	0.057–0.403
Previous VEGF-TKI treatment: no (vs. yes)	0.701	0.827	0.313–2.184

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Table 4 Safety analysis

Adverse event	Patients (*n* = 81)	
	Any grade	Grade 3 or 4
Hypertension	10(12)	6(7)
Hand-foot syndrome	5(6)	1(1)
Decreased appetite	5(6)	1(1)
Fatigue	4(5)	0
Oral mucositis	4(5)	2(2)
Hoarseness	4(5)	0

smoking history, previous treatment lines, previous VEGF monoclonal antibody treatment, and previous EGFR-TKI treatment. Univariate analysis indicated that PFS was significantly prolonged in patients with squamous cell carcinoma, without brain or liver metastases, with an ECOG PS of 0–1, and not previously treated with VEGF-TKIs ($P < 0.05$). After Cox regression analysis, only an ECOG PS of 0–1 and no brain metastases achieved longer PFS after anlotinib salvage treatment in advanced NSCLC.

Of the 81 patients, 7 had previously been administered VEGF-TKIs and 51 VEGF monoclonal antibodies. Cox regression analysis showed that there was no significant difference in PFS between patients previously treated with or without VEGF-TKIs. The univariate analysis also showed that there was no significant difference in PFS between patients previously treated with or without VEGF monoclonal antibodies. These findings suggest that there was no cross-resistance between anlotinib and other VEGF-TKIs or VEGF monoclonal antibodies.

Bleeding can be fatal in lung squamous cell carcinoma patients administered antiangiogenic drug treatment, thus monitoring such patients is critically important. Previous studies have reported life-threatening pulmonary hemorrhage in patients with squamous cell carcinoma when using VEGF monoclonal antibodies, such as bevacizumab, and VEGF-TKIs, such as sunitinib and sorafenib.[30]

Whether or not the pathologic type of squamous cell carcinoma or some other contributing factor, such as central location and cavitation, is an independent risk factor for hemoptysis with antiangiogenic therapy has not been established.[30] In the present study, only two patients with lung adenocarcinoma reported mild hemoptysis. Among the 27 patients with lung squamous cell carcinoma, no bleeding episodes were reported. Hypertension (7%), which was well controlled by anti-hypertensive drugs, was the only grade 3–4 AE with an incidence of > 5%. Compared to the AEs associated with anlotinib reported in previous studies, no new AEs were observed in the present study.[13,31]

In addition, only one patient underwent dose reduction because of third degree oral mucositis. Our results show that anlotinib is well tolerated in patients with advanced NSCLC.

There were some limitations to the present study. The OS data requires longer follow-up. A larger observational study should be conducted as a supplement to the phase III trial to confirm the efficacy and toxicity of anlotinib for the salvage treatment of patients with advanced NSCLC, and to identify the definite predictors of treatment efficacy.

In conclusion, the present study showed that anlotinib is effective and well tolerated for the treatment of advanced NSCLC. Advanced NSCLC patients with an ECOG PS of 0–1 and without brain metastases might achieve longer PFS following anlotinib salvage treatment.

Disclosure

No authors report any conflict of interest.

References

1 Ferlay J, Soerjomataram I, Dikshit R et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359–86.

2 Chen W, Zheng R, Baade PD et al. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; **66**: 115–32.

3 Howlader N, Noone AM, Krapcho M, et al. *SEER Cancer Statistics Review, 1975–2012*, 2015. Available from URL: seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015.

4 Miller KD, Siegel RL, Lin CC et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin* 2016; **66**: 271–89.

5 Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. *Cell* 2011; **144**: 646–74.

6 Hall RD, Le TM, Haggstrom DE, Gentzler RD. Angiogenesis inhibition as a therapeutic strategy in non-small cell lung cancer (NSCLC). *Transl Lung Cancer Res* 2015; **4**: 515–23.

7 Reck M, von Pawel J, Zatloukal P et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. (Published erratum appears in J Clin Oncol 2009; 27: 2415). *J Clin Oncol* 2009; **27**: 1227–34.

8 Zhou C, Wu YL, Chen G et al. BEYOND: A randomized, double-blind, placebo-controlled, multicenter, phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2015; **33**: 2197–204.

9 Sandler A, Gray R, Perry MC et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006; **355**: 2542–50.

10 Garon EB, Ciuleanu TE, Arrieta O et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): A multicentre, double-blind, randomised phase 3 trial. *Lancet* 2014; **384**: 665–73.

11 Villaruz LC, Socinski MA. The role of anti-angiogenesis in non-small-cell lung cancer: An update. *Curr Oncol Rep* 2015; **17**: 26.

12 Zhang L, Shi M, Huang C et al. A phase II, multicenter, placebo-controlled trial of apatinib in patients with advanced nonsquamous non-small cell lung cancer (NSCLC) after two previous treatment regimens. *J Clin Oncol* 2012; **30** (15 Suppl): Abstract): 7548.

13 Han B, Li K, Wang Q 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**: 1569–75.

14 Shen G, Zheng F, Ren D et al. Anlotinib: A novel multi-targeting tyrosine kinase inhibitor in clinical development. *J Hematol Oncol* 2018; **11**: 120.

15 Rittmeyer A, Barlesi F, Waterkamp D et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): A phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017; **389**: 255–65.

16 Herbst RS, Baas P, Kim DW et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. *Lancet* 2016; **387**: 1540–50.

17 Borghaei H, Paz-Ares L, Horn L et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015; **373**: 1627–39.

18 Brahmer J, Reckamp KL, Baas P et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015; **373**: 123–35.

19 Weiss JM, Stinchcombe TE. Second-line therapy for advanced NSCLC. *Oncologist* 2013; **18**: 947–53.

20 Kawaguchi T, Ando M, Asami K et al. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line

therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). *J Clin Oncol* 2014; **32**: 1902–8.

21 Langer CJ, Mok T, Postmus PE. Targeted agents in the third-/fourth-line treatment of patients with advanced (stage III/IV) non-small cell lung cancer (NSCLC). *Cancer Treat Rev* 2013; **39**: 252–60.

22 Noble J, Ellis PM, Mackay JA, Evans WK, Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: A systematic review and practice guideline. *J Thorac Oncol* 2006; **1**: 1042–58.

23 Van Cutsem E, De Haas S, Kang YK *et al.* Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: A biomarker evaluation from the AVAGAST randomized phase III trial. *J Clin Oncol* 2012; **30**: 2119–27.

24 Fan M, Zhang J, Wang Z *et al.* Phosphorylated VEGFR2 and hypertension: Potential biomarkers to indicate VEGF-dependency of advanced breast cancer in anti-angiogenic therapy. *Breast Cancer Res Treat* 2014; **143**: 141–51.

25 Liu X, Qin S, Wang Z *et al.* Early presence of anti-angiogenesis-related adverse events as a potential biomarker of antitumor efficacy in metastatic gastric cancer patients treated with apatinib: A cohort study. *J Hematol Oncol* 2017; **10**: 153.

26 Girard N, Jacoulet P, Gainet M *et al.* Third-line chemotherapy in advanced non-small cell lung cancer: Identifying the candidates for routine practice. *J Thorac Oncol* 2009; **4**: 1544–9.

27 Sculier JP, Chansky K, Crowley JJ, van Meerbeeck J, Goldstraw P, International Staging Committee and Participating Institutions. The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th Edition of the TNM Classification of Malignant Tumors and the proposals for the 7th Edition. *J Thorac Oncol* 2008; **3**: 457–66.

28 Castanon E, Rolfo C, Vinal D *et al.* Impact of epidermal growth factor receptor (EGFR) activating mutations and their targeted treatment in the prognosis of stage IV non-small cell lung cancer (NSCLC) patients harboring liver metastasis. *J Transl Med* 2015; **13**: 257.

29 Sørensen JB, Hansen HH, Hansen M, Dombernowsky P. Brain metastases in adenocarcinoma of the lung: Frequency, risk groups, and prognosis. *J Clin Oncol* 1988; **6**: 1474–80.

30 Piperdi B, Merla A, Perez-Soler R. Targeting angiogenesis in squamous non-small cell lung cancer. *Drugs* 2014; **74**: 403–13.

31 Sun Y, Niu W, Du F *et al.* Safety, pharmacokinetics, and antitumor properties of anlotinib, an oral multi-target tyrosine kinase inhibitor, in patients with advanced refractory solid tumors. *J Hematol Oncol* 2016; **9**: 105.