Investigational New Drugs (2019) 37:731–737
https://doi.org/10.1007/s10637-019-00735-1

PHASE I STUDIES

Apatinib, a novel VEGFR inhibitor plus docetaxel in advanced lung adenocarcinoma patients with wild-type EGFR: a phase I trial

Jian-Chun Duan[1] · Zhi-Jie Wang[1] · Lin Lin[1] · Jun-Ling Li[1] · Yan Wang[1] · Hua Bai[1] · Xing-Sheng Hu[1] · Yu-Tao Liu[1] · Xue-Zhi Hao[1] · Hong-Yu Wang[1] · Rui Wan[1] · Xin Wang[1] · Jie Wang[1]

Received: 23 November 2018 / Accepted: 24 January 2019 / Published online: 1 February 2019

Summary

Background This phase I trial was primarily conducted to determine the maximum tolerated dose (MTD) of apatinib combined with docetaxel in advanced lung adenocarcinoma patients with wild-type EGFR who have failed to first-line platinum-based chemotherapy, and to evaluate the safety and tolerability of apatinib plus docetaxel. *Methods* This was a single-center, open-label, dose-escalating phase I trial. The study used a standard 3 + 3 dose escalation design with the primary aim of determining the MTD. Twelve patients with advanced lung adenocarcinoma were enrolled, the primary endpoint was safety. Two doses of apatinib, 250 mg/day (level 1) and 500 mg/day (level 2), were evaluated in combination with 60 mg/m^2 doxetacel every 3 weeks. Six patients have been treated at levels 1 and 2, respectively. Optimal dose of apatinib was determined by dose-limiting toxicity (DLT). *Results* Six patients have been treated at levels 1 and 2. At level 1, one of six patients experienced grade 3 acneiform rash as DLTs. At level 2, two patients experienced grade 3 hypertension and one experienced grade 3 nasal bleeding. MTD and recommended dose for phase II study was 250 mg/day. Most frequent adverse events of any grade were bilirubin elevation, hypertension, alanine aminotransferase elevation, transglutaminase elevation, hand foot syndrome and fatigue. The median progression-free survival was 2.76 month. Moreover, three patients had developed progressive disease and the mean duration of response was 2.79 months. *Conclusion* Apatinib plus docetaxel was well tolerated and showed promising efficacy in advanced lung adenocarcinoma. This combination therapy may represent a potent therapeutic option for advanced lung adenocarcinoma patients with wild-type EGFR.

Keywords Apatinib · Docetaxel · Lung adenocarcinoma · Wild-type EGFR

✉ Jie Wang
zlhuxi@163.com

Jian-Chun Duan
duanjianchun79@163.com

Zhi-Jie Wang
jie_969@163.com

Lin Lin
doctor.linlin@outlook.com

Jun-Ling Li
drlijunling@vip.163.com

Yan Wang
wangyanyifu@126.com

Hua Bai
baihuahb@sina.com

Xing-Sheng Hu
huxingsheng66@163.com

Yu-Tao Liu
13911901165@139.com

Xue-Zhi Hao
hxz1968@sina.com

Hong-Yu Wang
why6439@163.com

Rui Wan
wanrui243@163.com

Xin Wang
xiaowuxian2006@126.com

[1] State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center and Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17, Panjiayuan Nanli, Chaoyang District, Beijing 100021, China

Introduction

Lung cancer was the most frequently diagnosed cancer [19], and it was one of the leading causes of cancer death, with 5-years survival rate of 16.6% [14]. Lung adenocarcinoma, the most common subtype of non-small cell lung cancer (NSCLC), has been the leading cause of cancer death and responsible for more than 500,000 deaths per year worldwide [9, 18]. Moreover, the incidence of lung adenocarcinoma remains increasing, which reaches even more than 50% of NSCLC [3].

For patients with advanced NSCLC, platinum-based doublet chemotherapy is recommended as the first-line treatment [6]. However, the efficacy of platinum-based chemotherapy varies remarkably between individuals, which manifests as intrinsic or acquired resistance in some patients. Patients progressing after first-line chemotherapy should be offered second-line treatment, while limited options were recommended, including docetaxel, pemetrexed and epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI) [21]. Therefore, the development of new drugs and combination therapy was critical to the treatment of lung cancer.

Several phase III studies have confirmed the efficacy of therapy combined antiangiogenic agents and docetaxel chemotherapy. Edward BG et al. indicated that treatment with docetaxel combined ramucirumab led to improved progression-free survival (PFS) and overall survival (OS) compared with docetaxel plus placebo for advanced NSCLC patients after disease progression on platinum based therapy [7]. Another international multicenter phase III study (LUME-lung-1) showed that docetaxel combined with nintedanib was also an efficacious option for patients after the first-line platinum-based double drugs chemotherapy [8]. Moreover, the combination therapy of docetaxel and nintedanib for advanced lung adenocarcinoma has been approved by European Medicines Agency [1]. The results of these clinical trials suggested that the combination therapy of antiangiogenic agents and docetaxel chemotherapy for lung adenocarcinoma has beneficial effect.

Apatinib is a novel oral antiangiogenic agent that targets the intracellular domain of vascular endothelial growth factor receptor (VEGFR)-2 and inhibits the tumor-induced angiogenesis by blocking the vascular endothelial growth factor (VEGF) signaling pathway. Several clinical studies reported that apatinib showed promising outcomes in treatment with liver cancer, gastric cancer and breast cancer [11, 24]. A randomized phase II trial of apatinib in patients with advanced non squamous NSCLC showed that apatinib significantly improved patients' survival outcomes compared with the placebo. Basic scientific research indicated that apatinib could reverse multidrug resistance (MDR) and may be useful in circumventing MDR to certain conventional antineoplastic drugs [13]. It was approved and launched in China in 2014 as the basic treatment strategy of patients with advanced gastric cancer refractory to second or more lines of prior chemotherapy [16]. Due to the beneficial outcomes of apatinib for cancer, we speculated that apatinib, as a novel oral antiangiogenic agent, plus docetaxel may be an effective alternative to other antiangiogenic agents (nintedanib, ramucirumab, etc) combined with docetaxel in the treatment of lung adenocarcinoma. Therefore, we conducted a clinical trial of apatinib combined with docetaxel in the treatment of lung adenocarcinoma.

The primary aim of our study was to determine the maximum tolerated dose (MTD) of apatinib in combined with docetaxel in lung adenocarcinoma patients with wild-type EGFR and recommended dose for phase II trial. Besides, a secondary objective was to assess the safety and tolerability of apatinib combined with docetaxel.

Materials and methods

Study design

This was a single-center, open-label, dose-escalating phase I trial of apatinib plus docetaxel in Chinese lung adenocarcinoma patients with wild-type EGFR. Patients were scheduled to receive 60 mg/m^2 docetaxel as 1-h intravenous infusion on day 1, every 21 days; Apatinib (level 1: 250 mg; level 2: 500 mg) was administered orally once daily on days 3–19. If patients did not experience a dose-limiting toxicity (DLT), apatinib treatment was continued until unacceptable toxicity, progression of disease (PD), serious protocol deviation, or withdrawal of informed consent occurred. Continuation of apatinib alone was allowed after at least 4 cycles of combination therapy without disease progression, based on investigator's decision. Each cycle was 21 days, and dose escalation was based on safety data from the first cycle of each cohort. Dose levels continued to be escalated until reaching the maximum tolerated dose (MTD). Apatinib (investigational drug) was provided by Jiangsu HengRui Medicine Co., Ltd. Docetaxel is commercially available (Jiangsu HengRui Medicine Co., Ltd).

Patients were treated according to a standard 3 + 3 dose escalation protocol with a fixed dose of docetaxel (60 mg/m^2 every 3 weeks). The escalation scheme was performed as follows. Initially, 3 patients are enrolled to dose level 1(250 mg/day), if none of the 3 patients experienced DLT during the first 21-day cycle, the dose escalation was permitted to continue; if one patient experienced DLT, an additional three patients were enrolled to the same dose; If no DLT experienced in the new enrolled patients, dose escalation is permitted to continue; If 2 or more patients experienced DLT during the first 21-day cycle, dose escalation was to be stopped and the previous level was declared the MTD.

Ethical considerations

This phase I trial (NCT02691871) was conducted in accordance with the ethical principles laid down in the Declaration of Helsinki, and the ethical Good Clinical Practice Guidelines. The ethical, medical, and scientific aspects of the study were reviewed and approved by the ethics committee of Cancer Institute and hospital, Chinese Academy of Medical Sciences. Written informed consent was obtained from all patients prior to any study-related procedure in the study.

Patients

The main eligibility criteria were as follows: (1) age 18–65 years with anticipated life expectancy of >12 weeks; (2) histologically or cytologically confirmed stage IV lung adenocarcinoma with wild-type EGFR; (3) at least one measurable site of disease according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) without previous radiation therapy within at least 3 months; (4) disease progression during or after a single platinum-based chemotherapy; (5) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1; (6) had adequate organ function (neutrophil count $\geq 1.5 \times 10^9$ /L; platelet count $\geq 100 \times 10^9$ /L; hemoglobin ≥90 g/L; bilirubin ≤1.5 times the upper institutional limit; aspartate aminotransferase (ALT) or alanine aminotransferase (AST) ≤2.5 times the upper institutional limit or 5 times (if known hepatic metastases); serum creatinine ≤1 times the upper institutional limit and creatinine clearance rate ≥ 50 mL/min; international normalized ratio (INR) < 1.5).

Major exclusion criteria included: (1) uncontrolled pleural effusion, seroperitoneum, or pericardial effusion; (2) serious illness or other malignancies diagnosed within past 5 years; (3) previous radiation therapy, chemotherapy, targeted therapy within 3 weeks; and major surgery, serious nonhealing wound, ulcer or bone fracture within 4 weeks; and previous mitomycin or nitrosoureas injection within 6 weeks before enrollment; (4) clinically serious cardiovascular disease or uncontrolled hypertension; (5) previous treatment with docetaxel within 6 months before enrollment or VEGFR inhibitors (except bevacizumab); (6) receiving other anti-cancer therapy during the study; (7) symptomatic brain metastasis or leptomeningeal carcinomatosis, history or presence of hemoptysis or a coagulation disorder, tumor invading or abutting major blood vessels, tumor cavitation, or coexisting or previous other malignant tumors; (8) gastrointestinal disorder or other factors that affected drug absorption.

Tolerability, safety and efficacy assessment

The primary endpoint was the MTD, which defined as the highest dose level at which the posterior mean DLT rate ≥ 33%. The MTD would be considered the recommended dose of daily oral apatinib in combination with docetaxel therapy for phase II trial. Toxicity was assessed continuously according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. DLT will be evaluated during the first cycle of therapy. DLT was defined as any of the following adverse drug reactions: (1) grade 4 hematological toxicity including grade 4 neutropenia or grade 3 febrile neutropenia (≥38.5 °C); grade 4 thrombocytopenia or grade 3 thrombocytopenia in presence of bleeding and grade 4 anemia. (2) grade 3 or worse non-hematological toxicity except for electrolyte abnormalities, glutamyl transpeptidase elevation alone, nausea/vomiting that could be managed with supportive care, and fever induced by tumor, infection and elevated alkaline phosphatase. (3) grade 3 or worse gastrointestinal toxicity or hypertension despite optimal supportive care; grade 2 or worse ALT/AST elevation associated with bilirubin elevation. (4) Any adverse events that resulted in scheduled dose to be delayed for 2 weeks or more.

The secondary endpoints were progression-free survival (PFS), overall response rate (ORR), and disease control rate (DCR). PFS was defined as the time from the date of treatment initiation to the date of disease progression or death from any cause. DCR was defined as the number of patients with complete response (CR), partial response (PR), and stable disease (SD) among all patients. ORR was defined as the number of patients with the best tumor response (CR and PR) among all patients. Tumor responses was assessed radiologically (computed tomography or magnetic resonance imaging) every 2 cycles. All responses were defined according to the criteria of RECIST 1.1.

Statistical analysis

Sample size of the dose-escalation cohort was determined by a standard 3 + 3 phase I design for oncology drugs. All patients who received more than one dose of investigational drug were included in the safety analysis set. Tumor responses data were summarized for all patients with both baseline and more than one post-baseline imaging assessment. Quantitative data were described using mean, standard deviation, median, interquartile range, maximum and minimum value, while qualitative data were described by number or rate and ratio. The Kaplan-Meier were used to estimate PFS. All statistical tests were two-sided, significance set at $p < 0.05$ along with 95% confidence intervals (CI). Statistical analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

A total of 12 eligible patients with stage IV lung adenocarcinoma were enrolled in this study, with a median age of

51 years (range, 31–64 years). Table 1 showed the demographics and baseline characteristics of 12 eligible patients. Six of the twelve patients enrolled had an ECOG performance status of 0, others had an ECOG performance status of 1. Eleven of the twelve patients were wild-type EGFR. One of the twelve patients were EGFR exon 20 insertion mutation which was regarded as wild-type because it was not sensitive mutation to apatinib. Six patients were included in the apatinib 250 mg/day cohort, six patients in the 500 mg/day cohort. Among the 12 patients, 3 patients finished less than 2 cycles of the combined therapy due to toxicities and disease progression. Eight patients finished more than 2 months of the combined therapy. The longest treatment duration was 7.46 months at the 250 mg/day dose level (Table 2). All 12 patients were evaluable for safety and efficacy.

Table 1 Demographic and baseline characteristics

Characteristics	$N = 12$
Sex	
Male	8 (66.67%)
Female	4 (33.33%)
Age (years)	
Mean ± SD	51.08 ± 11.20
Median (Q1,Q3)	51.00 (41.50, 62.00)
Min, Max	31.00, 64.00
ECOG performance status	
0	6 (50.00%)
1	6 (50.00%)
Clinical stage	
IV	12 (100.00%)
Recurrence	0 (0.00%)
Smoking history	
Yes	6 (50.00%)
No	6 (50.00%)
Site of metastasis	
Lung	1 (8.33%)
Brain	2 (16.67%)
Spleen	1 (8.33%)
Pleura	1 (8.33%)
Adrenal gland	2 (16.67%)
Lymphnodes	10 (83.33%)
Bone	4 (33.33%)
Number of metastatic sites	
1	6 (50.00%)
2	3 (25.00%)
3	3 (25.00%)
EGFR status	
Wild type	11(91.67%)
Mutant *	1 (8.33%)

*EGFR exon 20 insertion mutation

MTD and DLTs

The DLTs were observed day 1–28 at each dose level. In the first dose level, three patients started apatinib treatment (250 mg/day cohort), and one patient experienced grade 3 acneiform rash. Since one of three patients enrolled at dose level 1(250 mg/day) experienced DLT, we enrolled next 3 patients at dose level 1. There was no DLT in this cohort (250 mg/day). Additional 3 patients were enrolled at dose level 2 (500 mg/day). Two of three patients at dose level 2 (500 mg/day) experienced grade 3 hypertension. Next, additional 3 patients were enrolled at the same dose level (500 mg/day). Since one of three patients experienced grade 3 nasal bleeding, dose escalation was stopped. Therefore, the MTD and recommended dose was determined to be 250 mg/day apatinib once daily combined with docetaxel.

Adverse events

The combination of apatinib and docetaxel was tolerated with no major hematological toxicities (no neutropenia) as detailed in Table 3. Most of low-grade non-hematologic toxicities were bilirubin (total, direct and indirect) elevation, hypertension, alanine aminotransferase elevation, transglutaminase elevation, hand foot syndrome (HFS) and fatigue, which were generally mild and reversible. The main grade 3 non-hematologic toxicities were hypertension (2 cases), nasal cavity bleeding (1 case), and acneiform rash (2 cases). No patient experienced grade 4 or 5 toxicity, and there were no treatment-related deaths in this phase I trial.

Treatment activity

All of the 12 patients were evaluable for response, and the response to apatinib in the intent-to-treat population is given in Table 4. None of patients attained a complete response (CR) and three patients had a partial response (PR) for an overall response rate (ORR) of 25.00% (95% CI: 5.49–57.19). There were 6 patients had stable disease (SD) and 3 patients had a disease progression (PD), and the disease control rate (DCR) was 75.00% (95% CI: 42.8–94.5%). The efficacy evaluation for the 12 response-evaluable patients is presented in Table 4. The median PFS was 2.76 months in all evaluable patients (95%: 1.38–3.25). The duration of response for the 3 patients with disease progression was 1.40 months, 1.33 months, and 5.63 months, respectively. The median duration of response was 2.79 months.

Discussion

This is the first phase I study that evaluated the safety and tolerability of apatinib and docetaxel combination therapy in

Table 2 Treatment condition of patients with advanced lung adenocarcinoma

No.	Age(y)	Sex	Dose (mg/day)	Suspension time of treatment (days)	Treatment duration (months)
1	31	M	250	N	2.66
2	62	M	250	Y(7d)	2.63
3	50	M	250	Y(12d)	2.76
4	39	F	500	Y(2d)	2.60
5	52	M	500	N	1.35
6	38	M	500	N	1.31
7	62	M	500	Y(2d)	2.99
8	44	F	500	N	2.69
9	49	M	500	N	6.24
10	60	M	250	Y(14d)	0.36
11*	62	F	250	Y(NA)	7.46
12	64	F	250	N	1.48

M male, *F* female, *N* no treatment suspension, *Y* treatment suspension, *NA* not available

* This subject continued to receive the apatinib treatment

advanced lung adenocarcinoma patients with wild-type EGFR. Docetaxel is the agent that is approved by U.S. Food and Drug Administration (FDA) for both the first- and second-line treatment of advanced NSCLC [15]. Besides, the use of apatinib single-drug therapy has also been widely investigated with a view to improving the therapeutic option for patients with advanced NSCLC. In the previous phase I studies of apatinib, Zeng et al. showed that apatinib as a single-drug might be a potential choice for the treatment of EGFR wild-type advanced lung adenocarcinoma patients [23]. It is worth noting that the efficacy of apatinib and docetaxel combination therapy has only been confirmed in A549 xenograft mice, and the result suggested that apatinib significantly enhanced the antitumor effect of docetaxel [5]. However, tolerability and efficacy of the combination therapy of apatinib and docetaxel and optimal dose for the patients with advanced lung adenocarcinoma has not been clear yet. Therefore, our study focused on determining the MTD of apatinib in combined with docetaxel in lung adenocarcinoma patients with wild-type EGFR and the recommended dose for phase II trial.

In this study, 250 mg/day apatinib combined with 60 mg/m^2 docetaxel was declared as MTD and the recommended dose for further phase II study. Despite we used a lower apatinib dose of 250 mg/d for advanced lung adenocarcinoma

Table 3 Adverse events graded based on NCI-CTC AE 4.0

Adverse event	Any Grade (n, %)	Grade 1 (n, %)	Grade 2 (n, %)	Grade 3* (n, %)
Total bilirubin	6 (50.00%)	4 (33.33%)	2 (16.67%)	0 (0.00%)
Direct bilirubin	5 (41.67%)	4 (33.33%)	1 (8.33%)	0 (0.00%)
Hypertension	5 (41.67%)	2 (16.67%)	1 (8.33%)	2 (16.67%)
Indirect bilirubin	4 (33.33%)	3 (25.00%)	1 (8.33%)	0 (0.00%)
Increased ALT	4 (33.33%)	4 (33.33%)	0 (0.00%)	0 (0.00%)
Increased transglutaminase	4 (33.33%)	2 (16.67%)	2 (16.67%)	0 (0.00%)
HFS	4 (33.33%)	3 (25.00%)	1 (8.33%)	0 (0.00%)
Fatigue	4 (33.33%)	4 (33.33%)	0 (0.00%)	0 (0.00%)
Increased AST	3 (25.00%)	3 (25.00%)	0 (0.00%)	0 (0.00%)
Neutropenia	3 (25.00%)	3 (25.00%)	0 (0.00%)	0 (0.00%)
Prothrombin time	3 (25.00%)	3 (25.00%)	0 (0.00%)	0 (0.00%)
Plasma D-dimer	3 (25.00%)	3 (25.00%)	0 (0.00%)	0 (0.00%)
Hoarseness	3 (25.00%)	3 (25.00%)	0 (0.00%)	0 (0.00%)
Lactic dehydrogenase	3 (25.00%)	3 (25.00%)	0 (0.00%)	0 (0.00%)
Fibrinogen	3 (25.00%)	3 (25.00%)	0 (0.00%)	0 (0.00%)
Leukopenia	2 (16.67%)	2 (16.67%)	0 (0.00%)	0 (0.00%)
Hemoptysis	2 (16.67%)	2 (16.67%)	0 (0.00%)	0 (0.00%)
Hyponatremia	2 (16.67%)	2 (16.67%)	0 (0.00%)	0 (0.00%)
Nasal mucosa dry	2 (16.67%)	2 (16.67%)	0 (0.00%)	0 (0.00%)
Hypoalbuminemia	2 (16.67%)	2 (16.67%)	0 (0.00%)	0 (0.00%)
Nasal cavity bleed	2 (16.67%)	1 (8.33%)	0 (0.00%)	1 (8.33%)
ECG T wave abnormality	2 (16.67%)	2 (16.67%)	0 (0.00%)	0 (0.00%)
Acneiform rash	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Platelet count	1 (8.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)

AE adverse events, *ALT* alanine aminotransferase, *HFS* hand-foot syndrome, *AST* aspartate aminotransferase, *ECG* electrocardiogram

* There were no grade 4 or 5 adverse events

Table 4 Response and disease control rates

	No. of patients($n = 12$)	%
Complete response	0	0.00%
Partial response	3	25.00%
Stable disease	6	50.00%
Progressive disease	3	25.00%
Overall response rate (95% CI)	25.00% (5.49–57.19)	
Disease control rate (95% CI)	75.00% (42.8–94.5)	

patients than the recommended dose of 750 mg reported by Li et al. [12], the patients achieved a survival benefit with acceptable toxicity. Besides, a lower apatinib dose of 250 mg/d certainly resulted significantly fewer adverse events of any grade than high dose of apatinib [2]. At present, we have confirmed the MTD of apatinib in this combination therapy. However, further investigation remains needed to confirm the most suitable dose of apatinib plus docetaxel in advanced lung adenocarcinoma patients.

The result suggested that the most common adverse events from the combination of apatinib and docetaxel were hypertension, HFS, fatigue and clinically insignificant elevation in liver enzymes. However, the toxicity of apatinib was controllable and tolerable and the toxicities resolved soon with treatment interruption and symptomatic treatment. For example, two patients experienced grade 3 hypertension. One of the patients developed hypertension 1 month after treatment and recovered with orally administered nifedipine controlled release tablets and irbesartan for 15 days. Another patient developed hypertension 1 week after treatment and recovered with orally administered nifedipine controlled release tablets for 5 days. One patient experienced grade 3 nasal bleeding, which improved after local tamponade hemostasis for 2 h. One patient experienced grade 3 acneiform rash, and recovered with fusidic acid cream and ketoconazole cream for 9 days. In addition, no patient experienced grade 4 or 5 toxicity or serious adverse events. In fact, most of these toxicities were known and were resulted from the single drug alone, as reported in other studies [17, 20], such as hypertension, proteinuris and HFS for apatinib, and anemia, neutropenia and thrombocytopenia for docetaxel. So, this combination did not increase the risk of haematologic toxicity compared to either agent alone. In a word, this phase I study shows that apatinib and docetaxel combination can be delivered safely with acceptable toxicity in patients with advanced lung adenocarcinoma. However, more toxicity evaluation in phase II is needed to further refine the real toxicity that can be expected with prolonged administration with this dose schedule.

The efficacy was not the primary end point of this study, but the ORR and DCR in our study was 25.00% and 75.00%, respectively. They were better than the results of the previously clinical trials that reported the ORR and DCR were respectively 18.75% and 68.75% in EGFR wild-type advanced lung adenocarcinoma patients with apatinib monotherapy [23]. The better response rate might due to the mechanism that apatinib could significantly enhanced the antitumor effect of docetaxel reported by Feng et al. [5]. Apatinib could inhibit the function of P-glycoprotein (P-gp), meanwhile docetaxel was the substrate of P-gp. Combined treatment with apatinib down-regulated the expression of P-gp induced by docetaxel, which is in accordance with the increased tumor distribution of docetaxel. As a result, apatinib would increase the accumulation of docetaxel in tumors but exerted no obvious effect on the docetaxel concentrations in the plasma, kidney, lung, heart and liver. In addition, apatinib also tended to increase the sensitivity of docetaxel in cells. Moreover, the median PFS was 2.76 months in all evaluable patients, which was in accordance with the previous reports [4, 10, 22].

Although the combination of apatinib and docetaxel is feasible at the recommended phase I dose defined in this study, it is unclear the most suitable dose and definitive efficacy based on this small early phase trial. A more large scale study with multiple centers would be more convincing.

In conclusion, the results of the present study suggested that the MTD and recommended dose of apatinib for phase II study was defined as 250 mg/day. The combination therapy of apatinib with docetaxel, at dose of 250 mg/day apatinib and 60 mg/m^2 docetaxel, was well tolerated and feasible for patients with advanced lung adenocarcinoma. Although the number of patients enrolled is small to derive any meaningful conclusion regarding efficacy of the combination treatment, apatinib may provide an additional therapeutic option for patients with advanced lung adenocarcinoma, especially for those without a driver mutation.

Acknowledgements We would like to thank Jiangsu HengRui Medicine Co., Ltd. for supporting our research. And we thank all participants and their families.

Funding This research was supported by Jiangsu HengRui Medicine Co., Ltd., and CAMS Innovation Fund for Medical Sciences (CIFMS) [number: 2017-12M-005].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Agency EM (2015) Vargatef (nintedanib): summary of product characteristics
2. Deng W, Qin S, Li J, Wen L, Wang J, Zhang G, Zhong H, Yang J, Ba Y, Bai Y, Lin X, Wang M, Wang L, Liu L, He Y, Tao M, Xie C, Ye F, Wu XY, Jia T (2018) Initial dose of apatinib in Chinese patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of stomach or gastroesophageal junction in third- or later-line setting: 500 mg or 850 mg? J Clin Oncol 36:35–35. https://doi.org/10.1200/JCO.2018.36.4_suppl.35
3. Devesa SS, Bray F, Vizcaino AP, Parkin DM (2005) International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising. Int J Cancer 117: 294–299. https://doi.org/10.1002/ijc.21183
4. Ding L, Li QJ, You KY, Jiang ZM, Yao HR (2016) The use of Apatinib in treating nonsmall-cell lung Cancer: case report and review of literature. Medicine (Baltimore) 95:e3598. https://doi.org/10.1097/md.0000000000003598
5. Feng SQ, Wang GJ, Zhang JW, Xie Y, Sun RB, Fei F, Huang JQ, Wang Y, Aa JY, Zhou F (2018) Combined treatment with apatinib and docetaxel in A549 xenograft mice and its cellular pharmacokinetic basis. Acta Pharmacol Sin 39:1670–1680. https://doi.org/10.1038/aps.2018.16
6. Garcia-Campelo R, Bernabe R, Cobo M, Corral J, Coves J, Domine M, Nadal E, Rodriguez-Abreu D, Vinolas N, Massuti B (2015) SEOM clinical guidelines for the treatment of non-small cell lung cancer (NSCLC) 2015. Clin Transl Oncol 17:1020–1029. https://doi.org/10.1007/s12094-015-1455-z
7. Garon EB, Ciuleanu T-E, Arrieta O, Prabhash K, Syrigos KN, Goksel T, Park K, Gorbunova V, Kowalyszyn RD, Pikiel J, Czyzewicz G, Orlov SV, Lewanski CR, Thomas M, Bidoli P, Dakhil S, Gans S, Kim JH, Grigorescu A, Karaseva N, Reck M, Cappuzzo F, Alexandris E, Sashegyi A, Yurasov S, Pérol M (2014) 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 384: 665–673. https://doi.org/10.1016/s0140-6736(14)60845-x
8. Gottfried M, Bennouna J, Bondarenko I, Douillard JY, Heigener DF, Krzakowski M, Mellemgaard A, Novello S, Orlov S, Summers Y, von Pawel J, Stöhr J, Kaiser R, Reck M (2017) Efficacy and safety of Nintedanib plus docetaxel in patients with advanced lung adenocarcinoma: complementary and exploratory analyses of the phase III LUME-lung 1 study. Target Oncol 12:475–485. https://doi.org/10.1007/s11523-017-0517-2
9. Imielinski M, Berger AH, Hammerman PS, Hernandez B, Pugh TJ, Hodis E, Cho J, Suh J, Capelletti M, Sivachenko A, Sougnez C, Auclair D, Lawrence MS, Stojanov P, Cibulskis K, Choi K, de Waal L, Sharifnia T, Brooks A, Greulich H, Banerji S, Zander T, Seidel D, Leenders F, Ansén S, Ludwig C, Engel-Riedel W, Stoelben E, Wolf J, Goparju C, Thompson K, Winckler W, Kwiatkowski D, Johnson BE, Jänne PA, Miller VA, Pao W, Travis WD, Pass HI, Gabriel SB, Lander ES, Thomas RK, Garraway LA, Getz G, Meyerson M (2012) Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. Cell 150:1107–1120. https://doi.org/10.1016/j.cell.2012.08.029
10. Li F, Zhu T, Cao B, Wang J, Liang L (2017) Apatinib enhances antitumour activity of EGFR-TKIs in non-small cell lung cancer with EGFR-TKI resistance. Eur J Cancer 84:184–192. https://doi.org/10.1016/j.ejca.2017.07.037
11. Li J, Qin S, Xu J, Xiong J, Wu C, Bai Y, Liu W, Tong J, Liu Y, Xu R, Wang Z, Wang Q, Ouyang X, Yang Y, Ba Y, Liang J, Lin X, Luo D, Zheng R, Wang X, Sun G, Wang L, Zheng L, Guo H, Wu J, Xu N, Yang J, Zhang H, Cheng Y, Wang N, Chen L, Fan Z, Sun P, Yu H (2016) Randomized, double-blind, placebo-controlled phase III trial of Apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. J Clin Oncol 34:1448–1454. https://doi.org/10.1200/jco.2015.63.5995
12. Li J, Zhao X, Chen L, Guo H, Lv F, Jia K, Yv K, Wang F, Li C, Qian J, Zheng C, Zuo Y (2010) Safety and pharmacokinetics of novel selective vascular endothelial growth factor receptor-2 inhibitor YN968D1 in patients with advanced malignancies. BMC Cancer 10:529. https://doi.org/10.1186/1471-2407-10-529
13. Mi YJ, Liang YJ, Huang HB, Zhao HY, Wu CP, Wang F, Tao LY, Zhang CZ, Dai CL, Tiwari AK, Ma XX, To KKW, Ambudkar SV, Chen ZS, Fu LW (2010) Apatinib (YN968D1) reverses multidrug resistance by inhibiting the efflux function of multiple ATP-binding cassette transporters. Cancer Res 70:7981–7991. https://doi.org/10.1158/0008-5472.CAN-10-0111
14. Network NCC (2014) Clinical practice guidelines in oncology-non small cell lung cancer (Version 4.2014)
15. Ramalingam S, Belani C (2008) Systemic chemotherapy for advanced non-small cell lung cancer: recent advances and future directions. Oncologist 13(Suppl 1):5–13. https://doi.org/10.1634/theoncologist.13-S1-5
16. Shukui QIN JL (2015) Expert consensus on clinical practice of Apatinib in treatment of gastric cancer. Chin Clin Oncol:841–847
17. Song Z, Yu X, Lou G, Shi X, Zhang Y (2017) Salvage treatment with apatinib for advanced non-small-cell lung cancer. OncoTargets Ther 10:1821–1825. https://doi.org/10.2147/OTT.S113435
18. The Cancer Genome Atlas Research N, Collisson EA, Campbell JD, Brooks AN, Berger AH, Lee W, Chmielecki J, Beer DG, Cope L, Creighton CJ et al (2014) Comprehensive molecular profiling of lung adenocarcinoma. Nature 511:543–550. https://doi.org/10.1038/nature13385
19. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A (2015) Global cancer statistics, 2012. CA Cancer J Clin 65:87–108. https://doi.org/10.3322/caac.21262
20. Wu D, Liang L, Nie L, Nie J, Dai L, Hu W, Zhang J, Chen X, Han J, Ma X, Tian G, Han S, Long J, Wang Y, Zhang Z, Xin T, Fang J (2018) Efficacy, safety and predictive indicators of apatinib after multilines treatment in advanced nonsquamous nonsmall cell lung cancer: Apatinib treatment in nonsquamous NSCLC. Asia Pac J Clin Oncol 14:446–452. https://doi.org/10.1111/ajco.12870
21. Xiuyi ZHIYS, Jinming YU (2015) China experts consensus on the diagnosis and treatment of advanced stage primary lung cancer (version 2015). Chin J Lung Cancer 37:433–436
22. Xu J, Liu X, Yang S, Zhang X, Shi Y (2017) Apatinib plus icotinib in treating advanced non-small cell lung cancer after icotinib treatment failure: a retrospective study. OncoTargets Ther 10:4989–4995. https://doi.org/10.2147/OTT.S142686
23. Zeng DX, Wang CG, Lei W, Huang JA, Jiang JH (2017) Efficiency of low dosage apatinib in post-first-line treatment of advanced lung adenocarcinoma. Oncotarget 8:66248–66253. https://doi.org/10.18632/oncotarget.19908
24. Zhang H (2015) Apatinib for molecular targeted therapy in tumor. Drug Des Devel Ther 9:6075–6081. https://doi.org/10.2147/DDDT.S97235