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Original Article

Efficacy and safety of Endostar (recombinant human endostatin hormone) combined with docetaxel as second-or third-line therapy for patients with non-small-cell lung cancer

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Abstract: This study aimed to evaluate the efficacy and safety of Endostar (recombinant human endostatin hormone) in combination with docetaxel as a second-or third-line therapy for NSCLC. From September 2009 to December 2011, 42 patients with metastatic NSCLC were enrolled. Patients received docetaxel 75 mg/m^2 IV (day 1) and Endostar 7.5 mg/m^2 IV (days 1-14) every three weeks, for up to six cycles. Complete blood count was tested every other day during the first cycle and before the other cycles. Efficacy was evaluated every two cycles. Thirty-nine patients completed treatment with a median follow-up of 19 months. For the primary endpoint, patients under Endostar plus docetaxel had a median overall survival of 10.1 months (95% confidence interval (CI): 5.8-14.4). For the secondary endpoints, the mean disease control rate was 59.0% and median progression-free survival (mPFS) was 3.0 months (95% CI: 1.1-4.8). Multivariate analysis showed that age <55 was associated with mPFS (P=0.031, HR 0.429 95% CI 0.198-0.927). Toxicity was related to bone marrow suppression and transient cardiac toxicity. These results provide favorable evidence to perform large-scale clinical studies using Endostar plus docetaxel as second-or third-line therapy for patients with NSCLC.

Keywords: Carcinoma, non-small-cell lung, chemotherapy, second or third line therapy, endostar protein, docetaxel

Introduction

Among all malignant tumors, lung cancer is among the ones with the highest incidence in the world [1]. In China, there are more than 500,000 newly-diagnosed lung cancer cases annually [2]. Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers [1]. At the time of diagnosis, many lung cancer patients are already stage IIIB or IV [2], so treatment is unlikely to be curative and generally aims at prolonging survival and controlling disease-related symptoms [3]. Platinum-based two-drug combination chemotherapy is the standard first-line treatment for stage III and IV patients [4], but for patients with epidermal growth factor receptor (EGFR) mutations, EGFR-tyrosine kinase inhibitor (TKI)-based therapy may be used as first-line treatment [5, 6].

For patients with progression or relapse of NSCLC after first-line treatments, an alternative chemotherapy regimen is recommended to prolong survival [7, 8]. Commonly used second-line treatments for NSCLC include single-agent docetaxel, pemetrexed, and EGFR-TKI [7-9]. As a second-line chemotherapy for metastatic NSCLC, docetaxel has low efficacy (less than 10%), with median progression-free survival (mPFS) of 2.7-6 months and median overall survival (mOS) of 5.7-7.9 months [7, 8, 10]. To increase the efficacy of second-line docetaxel, many different chemotherapy drugs may be added [11]. NSCLC patients who fail to respond to second-line chemotherapy can still benefit from third-line chemotherapy, and EGFR-TKI, docetaxel, and S1 are commonly used [12].

Endostar is a recombinant human endostatin that has antiangiogenic effects [13]. Clinical

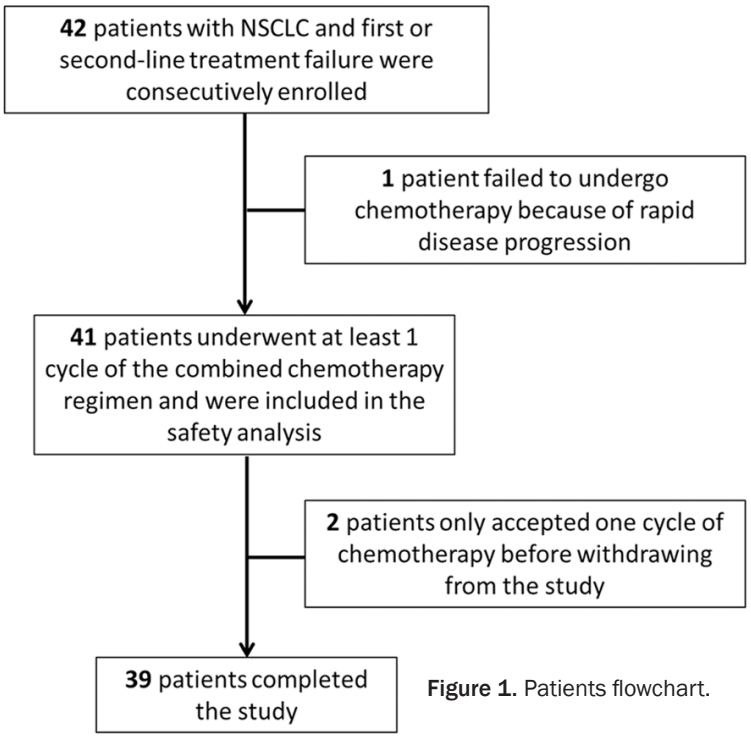

Figure 1. Patients flowchart.

studies have shown that it has good anti-tumor efficacy in solid tumors with well-tolerated toxicity [14]. Endostar has shown some promising results as first-line treatment for NSCLC. Endostar plus vinorelbine and cisplatin (NP) regimen extended patients' time to tumor progression (TTP), but the mPFS and mOS were not significantly improved [14, 15]. Similar results were found with Endostar in combination with paclitaxel-carboplatin (TC) with improvements in overall response rates (ORR) but similar mPFS and mOS [16]. A recent phase II trial showed that Endostar in combination with docetaxel and cisplatin chemotherapy for locally advanced NSCLC patients was feasible and showed promising survival and local control rates [17]. A meta-analysis of Endostar combination therapies for NSCLC suggests that Endostar can improve the response rate without significantly increasing side effects [18], and may even increase TTP and disease control rate (DCR) with improvement in patients' quality of life [19].

Based on the efficacy of combination treatment with Endostar in first-line therapy, we hypothesized that Endostar in combination with standard docetaxel second-line therapy could improve the efficacy of second-and third-line therapy for NSCLC. The aim of this study was to investigate the benefits and side effects of Endostar plus docetaxel as second-or third-line treatment for patients with NSCLC.

Materials and methods

Study design and patients

This was a prospective study of 42 consecutive patients treated between September 2009 and December 2011 at the Shanghai Cancer Center, Fudan University. Inclusion criteria were: 1) definitive diagnosis of NSCLC according to pathological or cytological examination; 2) stage IIIB or IV NSCLC confirmed by imaging with at least one measurable lesion at baseline; lesion had to be ≥20 mm if assessed using X-ray, conventional computed tomography (CT), or magnetic resonance imaging (MRI), or ≥10 mm if assessed by spiral CT; 3) failure of first- or second-line therapy; 4) ECOG performance status of 0 or 1; 5) expected survival of at least 3 months; 6) aged 18-75 years; 7) no contraindication to chemotherapy; 8) white blood cells $\geq 3.5\times10^9$/L, platelets $\geq 80\times10^9$/L, hemoglobin ≥90 g/L, creatinine ≤2.0× the upper limit of normal (ULN), transaminases <1.5× ULN, and bilirubin <1.5× ULN; in the presence of liver metastases: transaminases <5× ULN and bilirubin <2.5× ULN; and 9) signed the informed consent form. Exclusion criteria were: 1) previously received docetaxel; or 2) vital organ dysfunction or failure.

The study was approved by the institutional review board of Shanghai Medical College, Fudan University. Written informed consent was obtained from all patients. All investigations were conducted according to the principles of the Declaration of Helsinki. The study was registered with ClinicalTrials. gov (NCT01192230).

Data collection

All patients underwent the docetaxel plus Endostatin treatment and the data were col-

Table 1. Baseline characteristics of the patients enrolled in the study

Variable	Observation	
Gender	Male	27 (69.2%)
	Female	12 (30.8%)
Age	Range	33-75
	Median	55
	Mean	54.1
Histological type	Squamous cell carcinoma	7 (17.9%)
	Adenocarcinoma	29 (74.4%)
	Poorly differentiated carcinoma	3 (7.7%)
Performance status	0	12 (30.8%)
	1	27 (69.2%)
Number of organs affected (local invasion or metastasis)	≤2	20 (51.3%)
	>2	19 (48.7%)
EGFR mutation	Positive	10 (25.6%)
	Negative	29 (74.4%)
Line of chemotherapy	Second	27 (69.2%)
	Third	12 (30.8%)
Previously received EGFR-TKI therapy	Yes	9 (23.1%)
	No	30 (76.9%)

Abbreviations: EGFR-TKI: epidermal growth factor-tyrosine kinase inhibitors.

lected prospectively. The primary endpoint of the study was OS. As per original study design, mOS over 10 months was considered satisfactory. The secondary endpoints were TTP and side effects. Progression was evaluated every two cycles according to RECIST 1.1 [20, 21]. Adverse effects were classified according to CTCAE 3.0 [22] in all patients that received at least one cycle of chemotherapy. DCR was defined as complete response (CR) + partial response (PR) + stable disease (SD) based on the RECIST evaluation of the lesions [20, 21].

Chemotherapy

Patients received docetaxel 75 mg/m^2 (day 1), and Endostar 7.5 mg/m^2 (IV, days 1-14) every three weeks per cycle for up to six cycles. Prophylactic granulocyte colony-stimulating factor (G-CSF) was not given at the first cycle. The patients were hospitalized during the first cycle and complete blood count was tested every day. If the patient experienced grade 4 neutropenia or febrile neutropenia, prophylactic G-CSF was added for the following cycles. Electrocardiogram (ECG) was monitored before each cycle, or if the patients experienced cardiac symptoms. Blood biochemistry was examined before each cycle.

Statistical analysis

All data are presented as mean ± standard deviation. Kaplan-Meier curves were used for survival analysis, and compared with the log-rank test. The Cox proportional hazards model was used for multivariate analysis. Factors with *P*-values <0.10 in univariate analyses were tested with the multivariate model. A standard least-squares method was used for multiple regression analyses. All statistical analyses were performed with SPSS 16.0 (IBM, Armonk, NY, USA). Two-sided *P*-values <0.05 were considered statistically significant.

Results

Characteristics of the patient

Figure 1 presents the patient flowchart. Among the 42 participants, one failed to undergo chemotherapy due to rapid progression of the disease, and two only accepted one cycle of chemotherapy before withdrawing from the study; the remaining 39 patients completed the whole treatment course with a median follow-up of 19 months.

The baseline characteristics of the patients are shown in **Table 1**. There were more males than

Table 2. Efficacy of the therapy

Variable	Observation	
No. of chemotherapy cycles	One	1 (2.6%)
	Two	17 (43.6%)
	Three	2 (5.1%)
	Four	15 (38.5%)
	Six	4 (10.3%)
	Median no. of cycles	3
Efficacy	Complete response (CR)	0 (0%)
	Partial response (PR)	3 (7.7%)
	Stable disease (SD)	20 (51.3%)
	Progressive disease (PD)	16 (41.0%)
	Disease Control Rate (DCR)	23 (59.0%)
Median progression-free survival (mPFS)	3.0 months	95% CI: 1.1-4.8
Median overall survival (mOS)	10.1 months	95% CI: 5.8-14.4

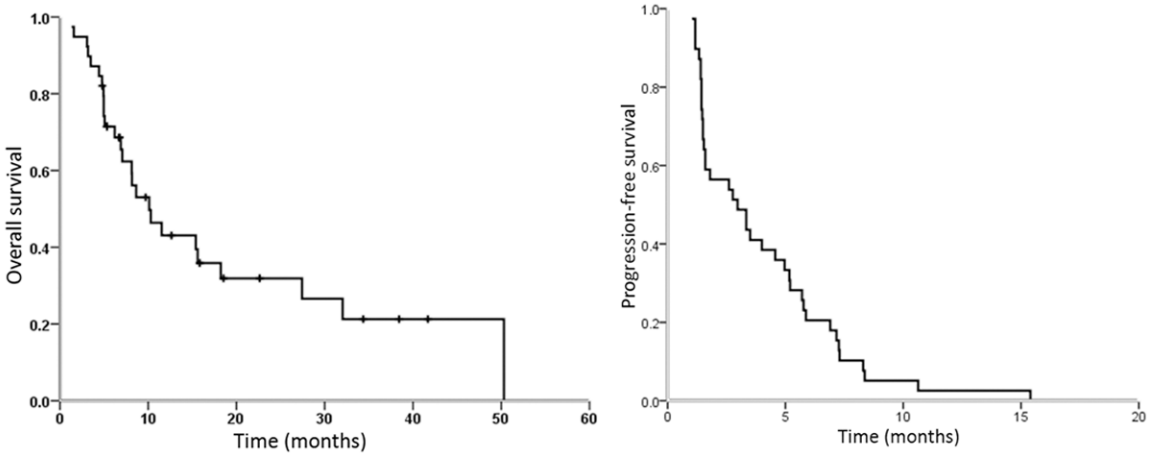

Figure 2. Survival curves of the patients who received docetaxel plus Endostar therapy. Progression-free survival (PFS) and overall survival (OS) of the 39 patients who received the combined regimen shown in months.

females (69.2%), with a mean age of 54.1 years. The most common histological type was adenocarcinoma (74.4%). The regimen was second-line for 69.2% of the patients.

Efficacy of the therapy

Among the 39 patients that received the full docetaxel plus Endostar therapy and that were included in the efficacy evaluation, 38 received at least two cycles of chemotherapy. One patient had PD after the first cycle of chemotherapy, and was included in the efficacy evaluation. Results of therapy efficacy are shown in **Table 2**.

For the primary endpoint, mOS was 10.1 months (95% confidence interval (CI): 5.8-14.4). For the secondary endpoints, the mean DCR was 59.0% and mPFS was 3.0 months (95% CI: 1.1-4.8). **Figure 2** presents the survival curves and the data is summarized in **Table 3**.

This regimen was particularly effective for third-line patients with a DCR of 58.3% and the median progression-free survival (mPFS) of 3.0 months (**Table 3**). Subgroup analysis showed that younger patients (age <55) (**Figure 3** and **Table 3**) might be more likely to gain benefit from this regimen (P=0.054 and P=0.074 for mPFS and mOS, respectively).

The results of the multivariate analysis are presented in **Table 4**. The only factor that was iden-

Table 3. Summarized data for the Kaplan-Meier survival analysis

Subgroup		MPFS (months)	P	MOS (months)	P
Histological type	Non-SCC	3.0	0.103	8.2	0.389
	SCC	1.6		10.1	
Age	<55	3.5	0.054	18.2	0.074
	≥55	1.6		8.2	
Previously received EGFR-TKI therapy	Yes	2.6	0.555	11.5	0.618
	No	3.0		8.2	
Number of organs involved	≤2	3.3	0.516	11.5	0.817
	>2	2.8		8.2	
Line of chemotherapy	Second	2.8	0.941	10.3	0.919
	Third	3.0		8.2	
Performance status	0	4.0	0.488	15.6	0.399
	1	2.8		8.6	
Gender	Male	3.0	0.768	8.2	0.567
	Female	2.6		15.6	
Dose reduction due to toxicity	Yes	3.0	0.760	27.4	0.201
	No	2.8		8.6	

SCC: squamous cell carcinoma.

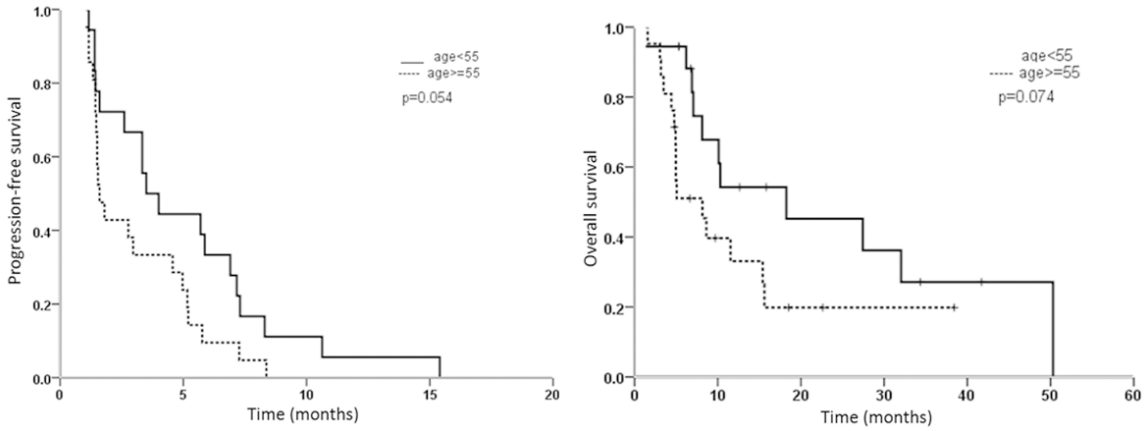

Figure 3. Overall survival of the patients of different ages (log-rank test). Overall survival is shown in months for patients <55 and ≥55 years old.

tified as being significant for PFS was age <55. This cut off point was selected because it was the median age of the patients.

Safety profile

Forty-one patients received at least one cycle of combined chemotherapy and were included in the safety evaluation. Thirty-three patients (80.5%) developed grade 3-4 neutropenia; 21 (51.2%) of them experienced grade 4 neutropenia. Thirteen (31.8%) patients experienced febrile neutropenia; 12 of them (29.3%) were given a reduced dose of docetaxel and one patient withdrew from the study. They did not have another episode of febrile neutropenia by decreasing the dose of docetaxel, without changing the dose of Endostar.

Two patients had palpitations during the first cycle of Endostar administration. Four patients (9.8%) had chest pain at the first cycle treatment, but the symptom did not reappear in the subsequent cycles. One patient developed paroxysmal atrial fibrillation in the first circle; the patient had grade 1 palpitation and the symptoms improved after Endostar withdrawal and amiodarone administration, but the symptoms

Table 4. Multivariate Cox proportional hazards model analyses of various factors affecting PFS

Factor	HR (95% CI)	*P*
Gender		0.734
Male	1.0	
Female	1.138 (0.526-2.461)	
Performance Status		0.069
1	1.0	
0	0.444 (0.185-1.064)	
Previously received EGFR-TKI therapy		0.692
No	1.0	
Yes	1.202 (0.483-2.990)	
Number of organs involved		0.802
>2	1.0	
≤2	0.916 (0.462-1.816)	
Age		0.031
≥55	1.0	
<55	0.429 (0.198-0.927)	
Histological type		0.352
Non-SCC	1.0	
SCC	1.673 (0.566-4.947)	
Dose reduction due to toxicity		0.683
Yes	1.0	
No	1.187 (0.521-2.702)	
Line of chemotherapy		0.452
Second	1.0	
Third	0.717 (0.301-1.707)	

PFS: progression-free survival; EGFR-TKI: epidermal growth factor-tyrosine kinase inhibitors; SCC: squamous cell carcinoma.

did not reappear in the following cycles of Endostar. Grade I liver dysfunction was observed in one patient after the first cycle, which was managed with glutathione administration. Renal malfunction and hypertension were not observed throughout the study.

Discussion

Single-agent docetaxel is the standard second-line treatment for NSCLC patients [7, 23]. The primary endpoint of this study was to evaluate the efficacy (based on mOS) of docetaxel plus Endostar in patients with NSCLC for which first- or second-line chemotherapy had failed. The results showed that Endostar plus docetaxel had a DCR of 59.0% and was particularly effective for third-line patients with a DCR of 58.3% and mPFS of 3.0 months. Subgroup analysis showed patients <55 years were more likely to benefit from the regimen. Toxicity was manageable.

The present study suggested that the docetaxel plus Endostar regimen provided comparable clinical outcomes to that of second-line docetaxel monotherapy (75 mg/m^2), as observed in previous studies [7, 8, 24-28]. In addition, the docetaxel and Endostar combination could improve the clinical outcome of third-line NSCLC patients with higher DCR and longer mPFS. In the present study, mOS was over 10 months, which was higher than the present 10-month target that was pre-defined in study design. As the efficacy of docetaxel alone for second-line therapy is disappointing, other combined therapies have also been investigated and some have progressed to phase II clinical trials such as AT-101, which showed no improvement over single agent docetaxel in terms of PFS [25], or intermittent administration of erlotinib that also showed no additional benefit [28]. However, some agents showed good results in combination with docetaxel. Indeed, a phase III trial of docetaxel plus ramucirumab vs. docetaxel plus placebo showed that the combination improved survival (PFS of 4.5 vs. 3.0 months) of patients with NSCLC as second-line treatment, with manageable toxicity [27]. Another trial of docetaxel plus nintedanib vs. docetaxel plus placebo showed that the combination was an effective second-line treatment for NSCLC, with a PFS of 3.4 vs. 2.7 months and manageable toxicities [28]. A meta-analysis of 14 trials suggests that a combination of docetaxel with targeted therapy as second-line treatment of NSCLC increased response rates and PFS, but without effect on OS and with more toxicities [29]. The present study did not include a control group, preventing the evaluation of gained efficacy. There is no data from randomized controlled trials about the efficacy of the docetaxel plus Endostar combination for the treatment of NSCLC or of any other type of cancer, but a meta-analysis showed that the combination of Endostar with platinum-based chemotherapy improved DCR in NSCLC [19]. Additional studies are needed to establish if there is or not a

Table 5. Comparable results between this study and other published studies

	N	CR (%)	PR (%)	SD (%)	PD (%)	PFS (m)	OS (m)	Grade3/4 Neutropenia (%)	Febrile neutropenia (%)	Cardiac toxicity (%)
Shepherd et al. [7]	55	0	7.1	47.3	32.7	2.7	7.5	67.3	1.8	9.1
Fossella et al. [24]	124	0	6.7	36	57.3	2.1	5.7	54	8	N/A
Hanna et al. [8]	276	8.8		46.4	44.8	2.9	7.9	40.2	12.7	N/A
Ready et al. [25]	52	0	2.1	46.8	51.1	1.7	5.9	13.5	N/A	13.4 (EKG QT prolonged)
Herbst et al. [26]	697	0.9	9.3	44.3	45	3.2	9.9	24	7	N/A
Garon et al. [27]	625	0.3	13.3	39.0	33.0	3.0	9.1	39	10	N/A
Reck et al. [28]	659	0.2	21	37.9	45.2	2.7	9.1	12.1	4.7	8.6-9.5
Our study	39	0	7.7	51.3	41.0	3.0	10.1	80.5	31.8	14.6

N: number of subjects; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; PFS: progression free survival; OS: overall survival; N/A: not available.

superiority of docetaxel plus Endostar vs. other types of chemotherapy for NSCLC.

Nevertheless, combining Endostar with chemotherapy seems reasonable because of the possible complementary action mechanisms. In recent years, immune checkpoint inhibitors have shown encouraging results in treating NSCLC [30, 31]. However, the response rate of this kind of treatment used alone is only about 19-20% [30, 31]. Endostar may play a role in regulating immune checkpoints, leading to further shrinking of the tumor through inhibition of angiogenesis. It should be noted that the studies listed in **Table 5** evaluated the efficiency of docetaxel as second-line therapy, but in the present study, the efficacy of the combined therapy for second-line or third-line NSCLC patients was evaluated. The DCR of NSCLC generally decreases with every treatment line from the first one and it has been highlighted that more effective therapies for patients with NSCLC that have failed second-line treatment are needed [30]. These results suggest that Endostar combination therapy could benefit these patients.

Patients in this study had a relatively high incidence of grade 3-4 bone marrow suppression and febrile neutropenia. These rates are much higher than those seen in studies of docetaxel (**Table 5**), and may be of concern for the further development of this combination therapy. This high incidence could be related to docetaxel or to Endostar administration, but it would be contradictory to other studies using Endostar in combination with first-line chemotherapy [18, 19]. However, because the patients in this study were treated because they had relapsed, they may not have fully recovered from their previous chemotherapy treatment. Therefore, in particular for third-line patients, tolerance to the regimen would be expected to be lower. Furthermore, because all patients in this study were hospitalized throughout the first cycle of chemotherapy, blood tests were closely monitored every other day and bone marrow toxicity was more likely to be detected than in patients that had fewer blood tests (e.g., once every cycle).

Six patients in the present study experienced symptoms suggesting cardiac toxicity during Endostar administration. These symptoms were, however, transient and disappeared after appropriate treatments. These rates are slightly higher than in previous studies that provided data for cardiac symptoms [7, 25, 28], but the transient symptoms did not prevent the use of Endostar.

This study has some limitations. The sample size was small, and all patients received the combined therapy without any randomized placebo control. Therefore, the results should be treated as preliminary and only the first step towards further clinical trials. There were disparities between the general study population analyses and the age subgroup analyses, which is probably due to the small sample size and the general condition of the patients. As the study was started in 2009, i.e. before the common use of TKI maintenance medication, nine cases who had received TKI therapy previously did not continue to receive TKI despite the fact that current opinion would consider adding TKI to the regimen. Mean age was 54 years, which is comparable to previous Asian and Chinese

studies [31, 32], but younger to American populations [33, 34], limiting the generalizability of the results and comparisons among studies. Finally, adverse events could not be separated as docetaxel-induced and Endostar-induced since there was no control group (docetaxel only).

Endostar plus docetaxel regimen as second or third line treatment of NSCLC could have some benefit on DCR. Patients who received the therapy as third line treatment had a mPFS of 3 months. Adverse events were infrequent and manageable. These results provide favorable evidence to perform large-scale clinical studies using Endostar plus docetaxel as second or third line therapy for patients with NSCLC.

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Disclosure of conflict of interest

None.

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