Real-world treatment pattern and comprehensive comparative effectiveness of Endostar plus different chemotherapy in advanced patients with non-small cell lung cancer

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Recombinant human endostatin (Endostar) plus vinorelbine/cisplatin (NP) had been approved for the treatment of non-small cell lung cancers (NSCLC). But the real-world treatment pattern and effectiveness of Endostar plus other combination chemotherapy, namely docetaxel/platinum (DP), gemcitabine/platinum (GP), pemetrexed/platinum (PP), and paclitaxel/platinum (TP) in both treatment-naïve and re-treatment patients with advanced NSCLC were still unclear. A retrospective observational study was conducted based on the electronic medical record (EMR) system and advanced patients with NSCLC were identified from 7 cancer hospitals in China from 2012 to 2019. These patients were divided into five groups, Endostar plus NP, Endostar plus DP, Endostar plus GP, Endostar plus PP, and Endostar plus TP groups. The disease control rate (DCR), overall response rate (ORR), and the progression-free survival (PFS) were evaluated. Of the eligible 512 advanced patients with NSCLC, 10.35% were in Endostar plus NP group, while the numbers were 15.43%, 32.42%, 26.56%, 15.23% in Endostar plus DP group, Endostar plus GP group, Endostar plus PP group, and Endostar plus TP group, respectively. The ORRs were 31%, 28%, 22%, 41% and 27%, and the DCRs were 71%, 72%, 57%, 72% and 76%, respectively. The median of PFSs for the above groups were 7.9, 6.8, 5.6, 13.7, and 5.4 months. Compared with Endostar plus NP group, the hazard ratios (HRs) and 95%CIs of Endostar plus other chemotherapy were 1.86 (0.75–4.61), 2.15 (0.83–5.60), 1.33 (0.51–3.44), and 2.42 (0.86–6.81). This real-world study found the effectiveness of Endostar plus DP, Endostar plus GP, Endostar plus PP, and Endostar plus TP were of no statistically significant differences compared with Endostar plus NP and reflected the good effectiveness of Endostar plus different chemotherapy in advanced patients with NSCLC.

Lung cancer remains a great global health burden as the deadliest cancer with an estimated 2,206,771 new cases diagnosed and 1,796,144 deaths in 2020 worldwide, and 787,000 new cases diagnosed and 631,000 deaths in
China since 2015. Non-small cell lung cancers (NSCLC) comprise about 85% of all lung cancer, and the majority are diagnosed in late stage. Platinum-based chemotherapy remains the primary first-line treatment for the advanced NSCLC patients, but the efficacy is unsatisfactory. Thus, a new strategy, such as antiangiogenic therapy and immunotherapy, for NSCLC therapy is urgent. Recombinant human endostatin (Endostar), an angiogenesis inhibitor, has shown the effect of downregulating transplantation matrix metalloproteinases (MMP) and vascular endothelial growth factor (VEGF) to inhibit neovascularization and tumor growth. Endostar has also shown clinical efficacy in the treatment of advanced NSCLC in China.

Although clinical application of antiangiogenic therapy has brought promise for the treatment of NSCLC and Endostar plus vinorelbine/cisplatin (NP) were approved by the Chinese Food and Drug Administration (CFDA) in 2005, in real-world clinical practice, NSCLC patients are treated with different regimens according to their physical and economic status. Although studies were conducted focused on first-line treatment patients or early-stage patients, the real-world treatment pattern and evidence of the effectiveness of Endostar in combination with other chemotherapy regimens in advanced NSCLC patients remains unclear and need to be explored.

Therefore, this study aimed to evaluate the treatment pattern and effectiveness of Endostar plus different combination chemotherapy, such as Endostar plus docetaxel/platinum (DP), Endostar plus gemcitabine/platinum (GP), Endostar plus pemetrexed/platinum (PP) and Endostar plus paclitaxel/platinum (TP) compared with Endostar plus NP in treatment-naïve patients and re-treatment NSCLC patients with advanced-stage in real-world settings.

### Results

#### Real-world treatment pattern and baseline characteristics.

Table 1 showed the real-world treatment pattern and baseline characteristics of Endostar plus different chemotherapy in all patients.

| Variables                        | All patients | Endostar plus NP | Endostar plus DP | Endostar plus GP | Endostar plus PP | Endostar plus TP |
|----------------------------------|--------------|------------------|------------------|------------------|------------------|------------------|
| N (%)                            | 512          | 53 (10.35)       | 79 (15.43)       | 166 (32.42)      | 136 (26.56)      | 78 (15.23)       |
| Age, years                       |              |                  |                  |                  |                  |                  |
| Mean ± SD                        | 58.1 ± 10.0  | 57.0 ± 8.2       | 57.9 ± 9.6       | 59.2 ± 9.3       | 56.4 ± 11.7      | 59.3 ± 9.3       |
| Median (Q1-Q3)                   | 59.2 (51.3–65.0) | 56.1 (51.0–62.0) | 58.1 (50.3–65.6) | 60.1 (53.5–65.7) | 58.6 (48.0–65.0) | 59.6 (54.1–65.4) |
| Sex, n (%)                       |              |                  |                  |                  |                  |                  |
| Unknown                          | 14 (2.7)     | 2 (3.8)          | 2 (2.5)          | 5 (3.0)          | 1 (0.7)          | 4 (5.1)          |
| Male                             | 385 (75.2)   | 35 (66.0)        | 35 (69.6)        | 146 (88.0)       | 86 (63.2)        | 63 (80.8)        |
| Female                           | 113 (22.1)   | 16 (30.2)        | 22 (27.8)        | 15 (9.0)         | 49 (36.0)        | 11 (14.1)        |
| Smoking history                  |              |                  |                  |                  |                  |                  |
| No                               | 185 (36.1)   | 24 (45.3)        | 31 (39.2)        | 44 (26.5)        | 70 (51.5)        | 16 (20.5)        |
| Yes                              | 327 (63.9)   | 29 (54.7)        | 48 (60.8)        | 122 (73.5)       | 66 (48.5)        | 62 (79.5)        |
| Family history of lung cancer    |              |                  |                  |                  |                  |                  |
| No                               | 493 (96.3)   | 51 (96.2)        | 77 (97.5)        | 163 (98.2)       | 131 (96.3)       | 71 (91.0)        |
| Yes                              | 19 (3.7)     | 2 (3.8)          | 2 (2.5)          | 3 (1.8)          | 5 (3.7)          | 7 (9.0)          |
| Disease stage                    |              |                  |                  |                  |                  |                  |
| III                              | 188 (36.7)   | 21 (39.6)        | 33 (41.8)        | 83 (50.0)        | 21 (15.4)        | 30 (38.5)        |
| IV                               | 324 (63.3)   | 32 (60.4)        | 46 (58.2)        | 83 (50.0)        | 115 (84.6)       | 48 (61.5)        |
| Pathological type                |              |                  |                  |                  |                  |                  |
| Squamous cell carcinoma          | 181 (35.4)   | 20 (37.7)        | 36 (45.6)        | 99 (59.6)        | 6 (4.4)          | 20 (25.6)        |
| Adenocarcinoma                   | 205 (40.0)   | 19 (35.8)        | 37 (46.8)        | 8 (4.8)          | 116 (85.3)       | 25 (32.1)        |
| Unknown                          | 118 (23.0)   | 12 (22.6)        | 3 (3.8)          | 59 (35.5)        | 12 (8.8)         | 32 (41.0)        |
| Other                            | 8 (1.6)      | 2 (3.8)          | 3 (3.8)          | 0 (0)            | 2 (1.5)          | 1 (1.3)          |
| Patient type                     |              |                  |                  |                  |                  |                  |
| Treatment-naïve                  | 417 (81.4)   | 26 (49.1)        | 54 (68.4)        | 148 (89.2)       | 122 (89.7)       | 67 (85.9)        |
| Re-treatment                     | 95 (18.6)    | 27 (50.9)        | 25 (31.6)        | 18 (10.8)        | 14 (10.3)        | 11 (14.1)        |

Table 1. Real-world treatment pattern and baseline characteristics of Endostar plus different chemotherapy in all patients.
effectiveness analysis set with 25 in Endostar plus NP group, 49 in Endostar plus DP group, 90 in Endostar plus GP group, 89 in Endostar plus PP group and 39 in Endostar plus TP group.

Table 3 showed the overall response rates (ORRs) for the above five groups were 28%, 22%, 41%, 27% and 31%, and the disease control rates (DCRs) were 72%, 57%, 72%, 76% and 74%, and the median of progression-free survivals (PFSs) were 7.9, 6.8, 5.6, 13.7 and 5.4 months, respectively. These differences of DCRs, ORRs and PFSs in Endostar plus different chemotherapy regimens groups were not statistically significant. Table 4 reported the DCRs, ORRs and PFSs of Endostar plus different chemotherapy in treatment-naïve patients and in re-treatment patients, and there were also no statistically significant differences. The Cox regression model revealed there were also no statistically significant differences in PFSs of Endostar plus other chemotherapy compared with Endostar plus NP group after adjusting age, sex, smoking history, family history of lung cancer, disease stage, pathological type and administration pathways. Figure 1 showed that the hazard ratios (HRs) (95%CI) of Endostar plus other chemotherapy were 1.86 (0.75–4.61), 2.15 (0.83–5.60), 1.33 (0.51–3.44) and 2.42 (0.86–6.81) as compared with Endostar plus NP group, and the re-treatment patients had decreased PFS as compared with treatment-naïve patients (HR = 0.84 [95% CI 0.75–0.95]). The exploratory subgroup analysis also demonstrated the PFSs of Endostar plus different chemotherapy groups were of no statistically significant differences, no matter in treatment-naïve patients or in re-treatment patients (Fig. 1).

Table 2. Real-world treatment pattern and baseline characteristics of Endostar plus different chemotherapy in treatment-naïve and re-treatment patients.

| Variables | Treatment-naïve patients (N = 417) | Re-treatment patients (N = 95) |
|-----------|----------------------------------|-------------------------------|
|          | Endostar plus NP | Endostar plus DP | Endostar plus GP | Endostar plus PP | Endostar plus TP |
| N (%)    | 26 (6.24) | 54 (12.95) | 148 (35.49) | 122 (29.26) | 67 (16.07) |
| Age, years | Mean ± SD | 57.2 ± 7.0 | 57.8 ± 10.2 | 59.5 ± 9.5 | 56.4 ± 11.6 | 53.7 ± 6.8 | 59.8 ± 9.2 | 56.8 ± 9.3 | 58.0 ± 8.4 | 57.5 ± 7.0 |
| Median (Q1-Q3) | 57.2 (52.4–61.4) | 58.9 (49.4–66.5) | 50.7 (53.6–66.7) | 56.4 (49.4–66.5) | 58.9 (48.8–52.6) | 55.0 (52.8–56.4) | 58.0 (52.4–64.3) | 57.6 (52.8–59.1) | 57.8 (54.5–63.1) | 56.5 (49.8–55.4) |
| Sex, n (%) | Unknown | 2 (7.7) | 2 (3.7) | 5 (3.4) | 1 (0.8) | 4 (6.0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
|           | Male     | 17 (65.4) | 38 (70.4) | 131 (88.5) | 76 (62.3) | 54 (80.6) | 18 (66.7) | 17 (68.0) | 15 (83.3) | 10 (71.4) |
|           | Female   | 7 (26.9) | 14 (25.9) | 12 (8.1) | 9 (9.3) | 13 (19.2) | 6 (22.2) | 13 (52.0) | 10 (55.6) | 9 (62.2) |
| Smoking history | No | 10 (38.5) | 22 (40.7) | 38 (25.7) | 63 (51.6) | 12 (17.9) | 14 (51.9) | 9 (36.0) | 6 (33.3) | 7 (50.0) |
|           | Yes      | 16 (61.5) | 32 (59.3) | 110 (74.3) | 59 (48.4) | 55 (82.1) | 13 (48.2) | 16 (64.0) | 12 (66.7) | 7 (50.0) |
| Family history of lung cancer | No | 26 (100.0) | 54 (100.0) | 145 (98.0) | 117 (95.9) | 61 (91.0) | 25 (92.6) | 23 (92.0) | 18 (100.0) | 14 (100.0) |
|           | Yes      | 0 (0) | 0 (0) | 3 (2.0) | 5 (4.1) | 6 (9.0) | 2 (7.4) | 2 (8.0) | 0 (0) | 0 (0) |
| Disease stage | III | 12 (46.2) | 21 (38.9) | 75 (50.7) | 17 (13.9) | 28 (41.8) | 9 (33.3) | 12 (48.0) | 8 (44.4) | 4 (28.6) |
|           | IV      | 14 (53.9) | 33 (61.1) | 73 (49.3) | 105 (86.1) | 39 (58.2) | 18 (66.7) | 13 (52.0) | 10 (55.6) | 10 (71.4) |
| Pathological type | Squamous cell carcinoma | 8 (30.8) | 23 (42.6) | 88 (59.5) | 3 (2.5) | 18 (26.9) | 12 (44.4) | 13 (52.0) | 11 (61.1) | 3 (21.4) |
|           | Adenocarcinoma | 5 (19.2) | 27 (50.0) | 5 (3.4) | 107 (87.7) | 18 (26.9) | 14 (51.9) | 10 (40.0) | 3 (16.7) | 9 (64.3) |
|           | Unknown  | 11 (42.3) | 1 (1.9) | 55 (37.2) | 11 (9.0) | 31 (46.3) | 1 (3.7) | 2 (8.0) | 4 (22.2) | 1 (7.1) |
|           | Other    | 2 (7.7) | 3 (5.6) | 0 (0) | 1 (0.8) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (7.1) |

Table 3. The ORRs, DCRs and PFSs of Endostar plus different chemotherapy in all patients. *Too few people to estimate confidence intervals.
tively collected EMR information might lead to bias, but in some extent, the bias was reduced because this study

tion regimen.

Lastly, this study was conducted in a larger sample than previous studies and to some extent, the effectiveness

including advanced-stage NSCLC patients with different pathological tissue typing and re-treatment patients.

was longer than that in gemcitabine and carboplatin regimen group with a statistically significant difference

NSCLC, Yu Xun etc. found that the PFS in Endostar combined with gemcitabine and carboplatin regimen group

treatment.

to different TNM stages, and this study focused on advanced-stage patients represented patients with systematic

effectiveness difference in Endostar plus NP group and Endostar plus DP group. The different result may be due

due to different patient types such as treatment-naïve patients and re-treatment patients.

particularly collected EMR information might lead to bias, but in some extent, the bias was reduced because this study

Table 4. The ORRs, DCRs and PFSs of Endostar plus different chemotherapy in treatment-naïve patients and

in re-treatment patients. *Too few people to estimate PFS and confidence intervals.

Discussion

Endostar is an effective angiogenesis inhibitor which can directly target new capillary endothelial cells around the
tumor. Study showed that median PFS in the Endostar plus NP regimen was significantly increased compared

with NP alone (6.3 and 3.6 months, \( P < 0.001 \)), as well as the ORR (35.4% and 19.5%, \( P < 0.01 \)). Endostar was

approved in combination with NP for the treatment of NSCLC by the Chinese Food and Drug Administration in

2005, but the treatment pattern and real-world evidence of different combined regimens were still unknown for

both treatment-naïve and re-treatment NSCLC patients with advanced stage. This study found that Endostar plus

GP, instead of Endostar plus NP which had been approved by the CFDA, was the domain combination regimens,
especially in treatment-naïve patients, and the effectiveness of Endostar plus DP, Endostar plus GP, Endostar

plus PP and Endostar plus TP weren’t statistically significant different compared with that of Endostar plus NP.

Recently, several studies had been performed to evaluate the effectiveness of Endostar combined with doc-
etaxel chemotherapy. For patients with stage I–IIIA postoperative NSCLC, QI Daliang etc. found that the PFS

of Endostar plus docetaxel and carboplatin was not statistically significant than that of docetaxel and carboplatin
alone. But our study found, in the advanced patients with NSCLC, there was also no statistically significant

effectiveness difference in Endostar plus NP group and Endostar plus DP group. The different result may be due

to different TNM stages, and this study focused on advanced-stage patients represented patients with systematic

treatment.

The better effectiveness of Endostar plus GP had been certified by several studies compared with GP alone

in small samples of patients with NSCLC. For example, in a study including 49 patients with advanced

NSCLC, Yu Xun etc. found that the PFS in Endostar combined with gemcitabine and carboplatin regimen group

was longer than that in gemcitabine and carboplatin regimen group with a statistically significant difference

\( P < 0.05 \)). This study included 512 NSCLC patients with advanced stage and showed the PFS of Endostar plus

GP was not significantly different from Endostar plus NP group. To some extent it can be said that this study

demonstrated the good effectiveness of Endostar plus GP in a large sample patient.

For the efficacy of pemetrexed/cisplatin (PC), a trend of prolonged PFS was found in 56 previously untreated

patients with lung adenocarcinoma, although the difference was lack of statistical significance in Endostar plus

PC group compared with PC alone group. While this real-world study revealed the effectiveness in 136 patients

treated with Endostar plus PP was no statistically significant difference compared with Endostar plus NP group.

The different results may be due to different pathological tissue typing. For non-squamous advanced NSCLC,
pemetrexed/cisplatin still was a relatively modern regimen which needs to be further studied.

Paclitaxel-carboplatin (TC) approved by US Food and Drug administration was the first-line treatment for

NSCLC. In this real-world study, the PFS of Endostar plus TP group had no statistically significant difference

compared with that of Endostar plus NP group. Similarly, Ma Huifang etc. also revealed the Endostar plus TP

had better curative effect than TP alone in the lung adenocarcinoma patients with stage IIIb and IV. While

Han Baohui etc. found in previously untreated, advanced NSCLC patients, first-line treatment with Endostar

plus TC seemed to have an increased ORR compared with TC alone, but the differences in PFS or OS between

the two groups were not statistically significant. The contradictory findings about Endostar plus TP might be

due to different patient types such as treatment-naive patients and re-treatment patients.

Besides, the study has several advantages. Above all, this study firstly explored the real-world treatment pat-
ttern both in treatment-naïve patients and re-treatment patients and found that Endostar plus NP approved by

the CFDA wasn’t the main combination regimens. Secondly, the patients in this study were more representative,

including advanced-stage NSCLC patients with different pathological tissue typing and re-treatment patients.

Lastly, this study was conducted in a larger sample than previous studies and to some extent, the effectiveness

analysis result without statistically significance provided real-world evidence for the expansion of the combina-
tion regimen.

We acknowledge this study still has two limitations. Firstly, just as all the real-world studies, the retrospec-
tively collected EMR information might lead to bias, but in some extent, the bias was reduced because this study
### Figure 1. Forest plot of HR of PFS for all patients and subgroup patients.

#### a. Forest plot of HR of PFS for all patients

| Variables                                      | HR(95%CI)        | P Value |
|------------------------------------------------|------------------|---------|
| Age yrs                                        | 1.03(1.00–1.05)  | 0.0320  |
| Sex(Male vs Female)                            | 0.52(0.27–1.00)  | 0.0491  |
| Cancer stage(N vs III)                         | 1.25(0.73–2.14)  | 0.4269  |
| Smoking History(Y vs N)                        | 1.06(0.58–1.94)  | 0.8571  |
| Pathological type(Unknown vs Squamous cell carcinoma) | 0.59(0.27–1.30)  | 0.1926  |
| Pathological type(Other vs Squamous cell carcinoma) | 1.08(0.34–3.53)  | 0.9093  |
| Pathological type(Adenocarcinoma vs Squamous cell carcinoma) | 0.64(0.32–1.27)  | 0.2011  |
| Administration pathway(CIV vs IV)              | 0.90(0.53–1.54)  | 0.7089  |
| Administration pathway(Combined vs IV)         | 0.95(0.50–1.79)  | 0.8651  |
| Endostar plus DP vs Endostar plus NP           | 1.86(0.75–4.61)  | 0.1822  |
| Endostar plus GP vs Endostar plus NP           | 2.15(0.83–5.60)  | 0.1158  |
| Endostar plus PP vs Endostar plus NP           | 1.33(0.51–3.44)  | 0.5098  |
| Endostar plus TP vs Endostar plus NP           | 2.42(0.96–6.81)  | 0.0956  |

**Patient type(Re–treatment vs Treatment–naive)**

| Variables                                      | HR(95%CI)        | P Value |
|------------------------------------------------|------------------|---------|
| Age yrs                                        | 2.41(1.49–3.91)  | 0.0044  |

#### b. Forest plot of HR of PFS for treatment-naive patients

| Variables                                      | HR(95%CI)        | P value |
|------------------------------------------------|------------------|---------|
| Age yrs                                        | 1.03(1.00–1.06)  | 0.0378  |
| Sex(Male vs Female)                            | 0.58(0.24–1.40)  | 0.2249  |
| Cancer stage(N vs III)                         | 1.06(0.54–2.09)  | 0.8895  |
| Smoking History(Y vs N)                        | 0.93(0.39–2.19)  | 0.8649  |
| Pathological type(Unknown vs Squamous cell carcinoma) | 0.69(0.25–1.88)  | 0.4672  |
| Pathological type(Other vs Squamous cell carcinoma) | 3.11(0.52–18.74) | 0.2154  |
| Pathological type(Adenocarcinoma vs Squamous cell carcinoma) | 0.41(0.15–1.13)  | 0.0853  |
| Administration pathway(CIV vs IV)              | 0.94(0.42–1.69)  | 0.6257  |
| Administration pathway(Combined vs IV)         | 1.18(0.57–2.44)  | 0.6699  |
| Endostar plus DP vs Endostar plus NP           | 3.64(0.42–31.56) | 0.2409  |
| Endostar plus GP vs Endostar plus NP           | 4.69(0.54–40.48) | 0.1600  |
| Endostar plus PP vs Endostar plus NP           | 3.26(0.36–30.36) | 0.2917  |
| Endostar plus TP vs Endostar plus NP           | 4.76(0.53–42.93) | 0.1647  |

#### c. Forest plot of HR of PFS for re-treatment patients

| Variables                                      | HR(95%CI)        | P value |
|------------------------------------------------|------------------|---------|
| Age yrs                                        | 1.02(0.97–1.06)  | 0.4058  |
| Sex(Male vs Female)                            | 1.33(0.32–5.47)  | 0.6958  |
| Cancer stage(N vs III)                         | 1.66(0.51–5.47)  | 0.4025  |
| Smoking history(Y vs N)                        | 0.37(0.09–1.56)  | 0.1749  |
| Pathological type(Unknown vs Squamous cell carcinoma) | 0.61(0.12–3.12)  | 0.5600  |
| Pathological type(Other vs Squamous cell carcinoma) | 0          | 0.9896  |
| Pathological type(Adenocarcinoma vs Squamous cell carcinoma) | 0.95(0.30–3.00)  | 0.9232  |
| Administration pathway(CIV vs IV)              | 1.06(0.40–2.77)  | 0.9081  |
| Administration pathway(Combined vs IV)         | 0.19(0.03–1.07)  | 0.0902  |
| Endostar plus DP vs Endostar plus NP           | 1.75(0.54–5.73)  | 0.3936  |
| Endostar plus GP vs Endostar plus NP           | 2.04(0.48–8.79)  | 0.3388  |
| Endostar plus PP vs Endostar plus NP           | 1.96(0.52–7.36)  | 0.3182  |
| Endostar plus TP vs Endostar plus NP           | 2.20(0.43–11.16) | 0.3411  |
identified patients from 7 cancer centers in China and the confounding factors were adjusted by Cox regression model. Secondly, the sample size of re-treatment patients was smaller than that of treatment-naïve patients, although this study was conducted in a larger sample patient compared with previous study.

In conclusion, this retrospective multi-center study showed in real-world practice, the Endostar plus GP was the domain combination regimens in advanced-stage NSCLC patients and revealed that Endostar plus other chemotherapy regimens also had good clinical benefits, with relatively high ORRs and DCRs.

Methods

Patients. A retrospective multi-center observational study was conducted based on electronic medical records (EMR) from 7 cancer hospitals in China, registered on Chinese Clinical Trial Registry (ChiCTR2000035129). This study was approved and waived informed consent by all the institutional and licensing committee [Ethics committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China (14/01/2020), Ethics committee of The Third Clinical College of Xinjiang Medical University, Urumqi, China (22/06/2020), Ethics committee of Yunnan Cancer Hospital, Kunming, China (29/03/2021), Ethics committee of Anhui Provincial Hospital, Hefei, China (10/06/2020), Ethics committee of Hunan Cancer Hospital, Changsha, China (10/03/2021), Ethics committee of Chongqing Cancer Hospital, Chongqing, China (22/05/2020), and Ethics committee of Shaanxi Provincial Cancer Hospital, Xi’an, China (25/03/2021)]. All research was performed in accordance with the the Declaration of Helsinki. Patients aged older than 18 years with clinical diagnosis of NSCLC, pathological stage III or IV [defined by American Joint Committee on Cancer tumor, node, metastasis (TNM) staging system version 7.0], and treated with Endostar combined with chemotherapy between 2012 and 2019 were included. According to the combination chemotherapy, the patients were furtherly divided into Endostar plus NP group, Endostar plus DP group, Endostar plus GP group, Endostar plus PP group and Endostar plus TP group. Treatment-naïve patients and re-treatment patients were separately defined as those who had Endostar administration during the 1st line therapy and those who had Endostar administration during 2nd line therapy or after, and exploratory subgroup analysis was furtherly performed.

Baseline covariates. Index date was defined as the date of first treatment with Endostar, and the baseline covariates data were collected, including birth date, sex, smoking history, family history of lung cancer, admission date and discharge date, tumor stage, pathological feature and administration pathways. The smoking history, family history of lung cancer, tumor stage and pathological feature were extracted by Natural Language Processing (NLP) from admission records and discharge note in EMR. 

Effectiveness evaluation. The Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 is used to evaluate the tumor response. ORR was defined as the percentage of patients who had complete response (CR) and/or partial response (PR). DCR was defined as the percentage of patients who had CR and/or PR and/or stable disease (SD). The PFS was defined as the interval(months) between first date of Endostar administration to the date of disease progression or death. In patients with progressive disease or death, the date of imaging progression or death was used as the endpoint date, and if PD and death were not observed, the date of the last evaluation was considered as the censored date.

Statistical methods. SAS 9.4 (SAS Institute INC., Cary, NC) was used to describe patient characteristics and compare the effectiveness among different treatment regimens. Quantitative variables, age, was described using Mean ± SD and Median(P25-P75), and qualitative variables, sex, tumor stage, family history of lung cancer, smoking history, administration pathways, and treatment regimen were described as count and component ratio. The Chi-squared test or Fisher exact test was used to compare ORRs and DCRs. The Kaplan–Meier method was used to describe PFSs and log-rank test was used to compare the differences in different groups. The HR (95%CI) of different chemotherapy groups were estimated by Cox regression model. A two-sided P<0.05 was considered statistically significant.

Ethics declarations and consent to participate. This study is a retrospective, non-interventional study, which does not interfere with routine diagnosis and treatment, does not affect any medical rights of patients, does not increase the medical risk of patients. At the same time, the study did not identify individual patients. In addition, most of the patients to be included in this study have died or lost to follow-up and their informed consents could not be obtained. For the above reasons, we applied for exempting informed consents of patients. In accordance with the Declaration of Helsinki.

The full name of all ethics committee that approved this study:

- Ethics committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China (14/01/2020).
- Ethics committee of The Third Clinical College of Xinjiang Medical University, Urumqi, China (22/06/2020).
- Ethics committee of Yunnan Cancer Hospital, Kunming, China (29/03/2021).
- Ethics committee of Anhui Provincial Hospital, Hefei, China (10/06/2020).
- Ethics committee of Hunan Cancer Hospital, Changsha, China (10/03/2021).
- Ethics committee of Chongqing Cancer Hospital, Chongqing, China (22/05/2020).
• Ethics committee of Shaanxi Provincial Cancer Hospital, Xi’an, China (25/03/2021).

Data availability
The data of this study is available upon request from the corresponding author [LW]. The data are not publicly available due to [state restrictions, “Where the information on human genetic resources of China is provided or opened for use to organizations, individuals or institutions established or actually controlled outside the country, it shall report in advance to the competent department of science and technology under The State Council and submit a copy of the information”. Adopted at the 22nd Session of the Standing Committee of the 13th National People’s Congress of the People’s Republic of China on October 17, 2020 and effective as of April 15, 2021].

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Author contributions
All authors have read and approved the manuscript. W.J. and W.S. equally contributed to the study conception, assessed the risk of bias of the studies, performed the data extraction and cleaning, conducted the statistical analyses, and drafted the manuscript. L.W. contributed to the study conception, supervised the statistical analyses, and reviewed the manuscript for important intellectual content. W.L., J.G., H.W., W.Z., and J.L. assisted in performing the search and reviewed the manuscript for important intellectual content. L.A. assisted in study conception and assessing the risk of bias of the studies.

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