Original Article

Immune checkpoint inhibitors combined with chemotherapy/bevacizumab therapy for patients with advanced lung cancer and heavily treated with EGFR mutation: a retrospective analysis

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Background: EGFR-mutated lung cancer poorly responded to anti-programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) monotherapy. Whether patients with EGFR-mutated lung cancer can benefit from anti-PD-1/PD-L1 therapy combined with other drugs remains controversial. We retrospectively evaluated the safety and efficacy of the PD-1 inhibitor combined with other drugs (chemotherapy and/or bevacizumab) in patients with EGFR-mutated lung cancer, who have progressed on EGFR–TKI treatment to determine the activity of the anti-PD-1/PD-L1 therapy combined with chemotherapy or/and bevacizumab therapy in heavily treated patients with EGFR-mutated lung cancer.

Methods: We identified 56 patients with EGFR-mutated lung cancer treated with PD-1/PD-L1 inhibitors alone or combined with the chemotherapy/bevacizumab therapy. The objective response rates were assessed using RECIST v1.1. Adverse events (AEs) were graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Academic Ethics Committee of Jiangsu Cancer Hospital. (NO. 2019 160), and individual consent for this retrospective analysis was waived.

Results: Objective responses were observed in 6 of 56 (10.7%) patients, and the disease control rate was 53.6% (30/56). The median progression-free survival (PFS) was 3.33 months with 95% CI of 1.58–5.08 months. No patient achieved a complete response. All six patients that achieved PR were treated with the PD-1 inhibitor combined with chemotherapy or bevacizumab therapy. Three of the six patients who achieved PR were treated with radiotherapy combined with PD-1 inhibitor-based therapy. Patients treated with the PD-1 inhibitor-based therapy as second-line therapy showed relatively longer PFS and higher objective response rates than those treated with PD-1 inhibitor-based therapy as third- or late-line therapy (PFS: 5.50 *vs.* 3.27 months, P=0.301; objective response rates: 25.0% *vs.* 6.82%, P=0.071). No additional AE profile was observed.

Conclusions: The PD-1 inhibitor combined with the chemotherapy/bevacizumab therapy showed acceptable toxicity profile and moderate efficacy on heavily treated advanced EGFR-mutated lung cancer after the exhaustion of target therapy.

Keywords: EGFR mutation; lung adenocarcinoma; programmed death-1 (PD-1); chemotherapy

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Introduction

Immune checkpoint inhibitors, especially anti-programmed death-1 (PD-1)/programmed death-ligand 1(PD-L1) antibody, serve as new standard of care for patients with advanced lung cancer without oncogenic driver alternation because of their efficacy and relatively low toxicity (1-3). The EGFR-mutated lung cancer is one of the most important oncogenic driver mutations in patients with lung cancer. Approximately 50% of patients with lung adenocarcinoma in Asia develops active EGFR mutation. The target therapy proves excellent efficacy in advanced lung cancer with EGFR mutation having ~70% response rate (4,5). However, almost all patients eventually develop resistance to the target therapy after treatment. Whether patients with lung cancer and EGFR mutation can benefit from anti-PD-1/PD-L1 therapy remains controversial (6).

Several phase 3 clinical trial subgroup analyses show that patients with EGFR-mutated lung cancer fail to receive a prolonged progression-free (PFS) or overall survival benefit from the anti-PD-1/PD-L1 therapy compared with docetaxel (2,7,8). The pooled and retrospective analyses confirm that the EGFR-mutated lung cancer cannot benefit from anti-PD-1/PD-L1 monotherapy (9-12). In a phase 2 clinical study with durvalumab as third- or late-line treatment for advanced EGFR-mutant lung cancer, the clinical activity supports previous reports with median a PFS of 1.9 month (13). In a phase 2 clinical trial, none of the naïve patients with EGFR-mutated tyrosine kinase inhibitor (TKI) and PD-L1 expression ≥50% can respond to the anti-PD-1 therapy (14). Hence, patients with EGFR-mutated lung cancer show lack of efficacy to the anti-PD-1/PD-L1 monotherapy, especially for naïve patients with EGFR–TKI treatment.

Although patients with EGFR-mutated lung cancer show poor response to anti-PD-1/PD-L1 monotherapy, the subgroup analysis of the IMpower 150 trial shows that they can benefit from the combination of atezolizumab, carboplatin, paclitaxel, and bevacizumab (15). This information provides guidance on the immunotherapy in patients with the EGFR-mutated lung cancer, but further confirmation is needed. Several phase 3 clinical trials (i.e., KEYNOTE 789, CheckMate 722, and ORIENT-31) are ongoing to assess the efficacy of the anti-PD-1/PD-L1 combined with chemotherapy on patients with EGFR mutation after the failure of target therapy. Therefore, whether patients with EGFR-mutated lung cancer can benefit from immunotherapy combined the chemotherapy and/or bevacizumab after the exhaustion of target therapy remains unknown.

This study aims to analyze the efficacy and safety of anti-PD-1 antibody combined with chemotherapy or/and bevacizumab therapy in heavily treated patients with EGFR-mutated lung cancer. In this retrospective study, we evaluated the activity of the PD-1 inhibitor combined with other agents (i.e., chemotherapy and/or bevacizumab) in 56 patients with EGFR-mutated lung cancer whose condition have progressed under EGFR–TKI treatment. We also determined which patients can easily benefit from this combination treatment.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-3520).

Methods

Patients

We reviewed the medical records of all patients with EGFR-mutant positive advanced lung cancer treated at the Jiangsu Cancer Hospital between March 2018 and December 2019 and identified patients who received the PD-1 inhibitor alone or in combination with chemotherapy and/or bevacizumab therapy during the course of their disease. Only patients who progressed after first or second generation of EGFR–TKI and T790M mutation negative subject and patients who carried the T790M mutation and failure after third generation TKI were included in this study. All patients included had at least one measurable disease. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Academic Ethics Committee of Jiangsu Cancer Hospital. (NO. (2019)160) and individual consent for this retrospective analysis was waived.

Data collection and response assessment

Medical records were reviewed and extracted on clinical pathologic features and treatment histories. Data and follow-up records were updated as of April 2019. The best response to PD-1 inhibitor-based therapy, defined as a complete or partial response and stable disease achieved at least once during the course of therapy, was assessed using the RECIST v 1.1 criteria. The PFS was defined from the time of treatment initiation to clinical or radiographic progression or death. Adverse events (AEs) were graded in

accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

Statistical analysis

Survival data were estimated using the Kaplan-Meier method or Cox survival regression model and compared using the log-rank test in overall cohort and other subgroups. The overall response rates (ORRs) of different subgroups were compared using chi-square test. Statistical analyses were performed using the SPSS version 22.0 (SPSS, Inc.). P≤0.05 was considered to indicate statistical significance.

Results

Patient characteristics

We identified 56 patients with EGFR mutations at Jiangsu Cancer Hospital who were treated with the PD-1 inhibitor alone or in combination with chemotherapy and/or bevacizumab therapy. Baseline clinical and pathologic features were summarized in *Table 1*. The majority of patients (92.9%, 52/56) was diagnosed with lung adenocarcinoma. Most EGFR mutation types were EGFR 19 deletion and L858R. An exon 18 mutation and exon 20 insertion were observed. Most (87.5%) patients had an ECOG performance status of 0 or 1.

Treatment characteristics

As shown in *Table 1*, most (78.6%, 44/56) patients received the PD-1 inhibitor-based therapy as third- or late-line therapy, indicating that they were heavily treated before. We divided patients into four groups in accordance with the different agents that were used to combine with the PD-1 inhibitor (*Table 1*). Seven patients received PD-1 inhibitor monotherapy. Exactly 21 patients received the PD-1 antibody combined with chemotherapy. Eight patients received the PD-1 antibody combined with bevacizumab. Twenty patients received the PD-1 antibody combined with chemotherapy and bevacizumab. The PD-1 inhibitors used in this study were pembrolizumab, nivolumab, camrelizumab, toripalimab, and sintilimab. Camrelizumab, toripalimab, and sintilimab were PD-1 inhibitors will clinical approval from the Chinese Food and Drug Administration. Besides chemotherapy and bevacizumab therapy, some (14.3%, 8/56) patients received radiotherapy during the PD-1 inhibitor-based therapy.

Overall clinical outcomes

As shown in *Figure 1A*, ORRs were observed in 6 of 56 (10.7%) patients, and the disease control rate (DCR) was 53.6% (30/56). No patient achieved a complete response. The median PFS was 3.33 months with 95% CI of 1.58–5.08 months (*Figure 1B*). All six patients that achieved PR were treated with the PD-1 inhibitor combined with chemotherapy or bevacizumab therapy. Three of six patients with PR were treated with radiotherapy combined with PD-1 inhibitor-based therapy. Notably, five patients (5/56, 8.9%) died because of rapid progression within three months after PD-1 inhibitor-based therapy.

Subgroup analyses

As shown in *Table 1* and *Figure 2A*, the ORR of patients who were treated with radiotherapy combined with PD-1 inhibitor-based therapy was significantly higher than that without radiotherapy (37.6% *vs.* 6.3%, P=0.008). In all patients treated with radiotherapy, the lesion evaluated for the efficacy of ICI therapy and irradiation site were observed on the same sites, and the treatment processes are shown in *Table 2*. None of the seven patients who received the PD-1 inhibitor monotherapy achieved complete or partial response. Patients with good performance had higher ORR than those with poor performance. However, no statistical difference was observed possibly because of the limited number of patients (*Figure 2B*). Patients treated with the PD-1 inhibitor-based therapy as second-line therapy showed relatively higher ORR and longer PFS than those treated with the PD-1 inhibitor-based therapy as third- or late-line therapy (ORR: 25.0% *vs.* 6.82%, P=0.071, *Figure 2C*; PFS: 5.50 months *vs.* 3.27 months, P=0.301, *Figure 3A*).

In multivariate analysis, the most important factors for PFS include combination therapy and ECOG performance status, as shown in *Table 3*. No significant difference was observed in the PFS of patients with EGFR 19 del and L858 mutation (*Figure 3B*, P=0.465). The PFS of patients treated with radiotherapy was higher than that without radiotherapy (5.50 months *vs.* 2.93 months, P=0.153, *Figure 3C*). No significant difference was observed in the ORR, DCR, or PFS under treatment with PD-1 antibody alone, PD-1 antibody combined with chemotherapy, PD-1 antibody combined with bevacizumab, and PD-1 antibody combined with chemotherapy and bevacizumab (*Figure 3D*)

Table 1 Clinical characteristics of patients and clinical activity of anti-PD-1 therapy

Characteristic	Patients number (%)	CR	PR	SD	PD	ORR (%)	P	DCR (%)	P
Sex									0.743
Male	31 (55.4)	0	3	13	15	9.7	0.813	51.6	
Female	25 (44.6)	0	3	11	11	12.0		56.0	
Histology									0.506
Adenocarcinoma	52 (92.9)	0	5	23	24	9.6	0.116	53.9	
Squamous	3 (5.6)	0	1	0	2	33.3		33.3	
Other	1 (1.8)	0	0	1	0	0		100	
EGFR mutation type									0.592
Exon 19 deletion	32 (57.1)	0	3	13	16	9.4	0.036	50.0	
L858R mutation	22 (39.3)	0	2	10	10	9.1		54.0	
Exon 18 mutation	1 (1.8)	0	0	1	0	0		100.0	
Exon 20 insertion	1 (1.8)	0	1	0	0	100		100.0	
ECOG performance status									0.014
0	11 (19.6)	0	3	7	1	27.3	0.207	90.9	
1	38 (67.9)	0	3	15	20	7.9		47.4	
2	7 (12.5)	0	0	2	5	0		28.6	
Prior lines of therapy									0.305
1	12 (21.4)	0	3	5	4	25.0	0.071	66.7	
≥2	44 (78.6)	0	3	19	22	6.8		50.0	
Combined with radiotherapy									0.189
Yes	8 (14.3)	0	3	3	2	37.6	0.008	75.0	
No	48 (85.7)	0	3	21	24	6.3		50.0	
Agents combined with PD-1 antibody									0.008
PD-1 antibody alone	7 (12.5)	0	0	0	7	0	0.091	0	
Combined with chemotherapy	21 (37.5)	0	4	11	6	19.0		71.4	
Combined with bevacizumab	8 (14.3)	0	2	1	5	25.0		37.5	
Combined with chemotherapy and bevacizumab	20 (35.7)	0	0	12	8	0		60.0	
Total	56	0	6	24	26	10.7		53.6	

PD-1, programmed death-1; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Safety

As shown in *Table 4*, 87.5% (49/56) of patients experienced treatment-related AEs. Several (42.9%, 24/56) patients experienced grade 3 or 4 treatment-related AE. One patient discontinued therapy because of grade 3 pneumonitis, which was related to anti-PD-1 therapy. The most common treatment-related AEs were leukopenia, anemia, elevated ALT or AST, fatigue, and decreased appetite. No grade 5 treatment-related AE was reported.

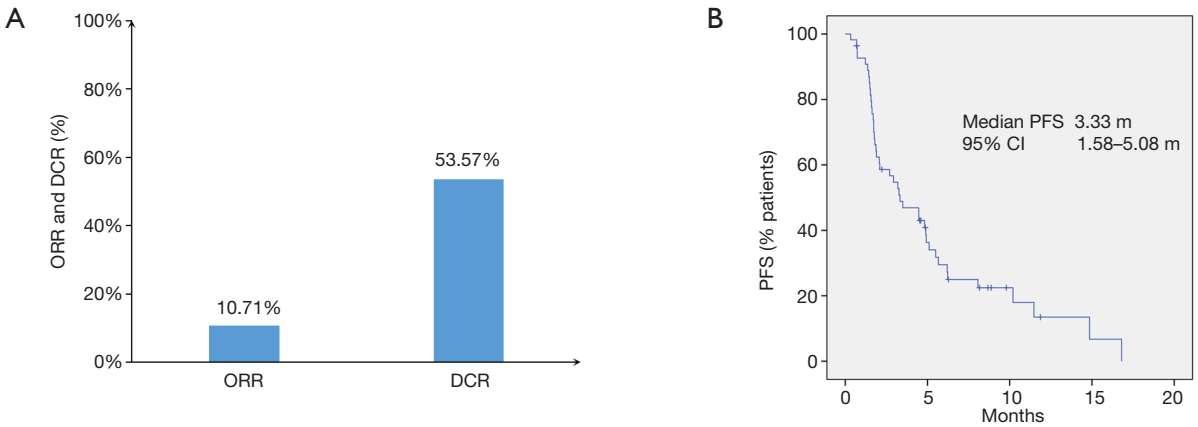

Figure 1 Overall clinical outcomes. (A) Objective response rate (ORR) and disease control rate (DCR) of all patients. (B) Progression-free survival (PFS) of all patients.

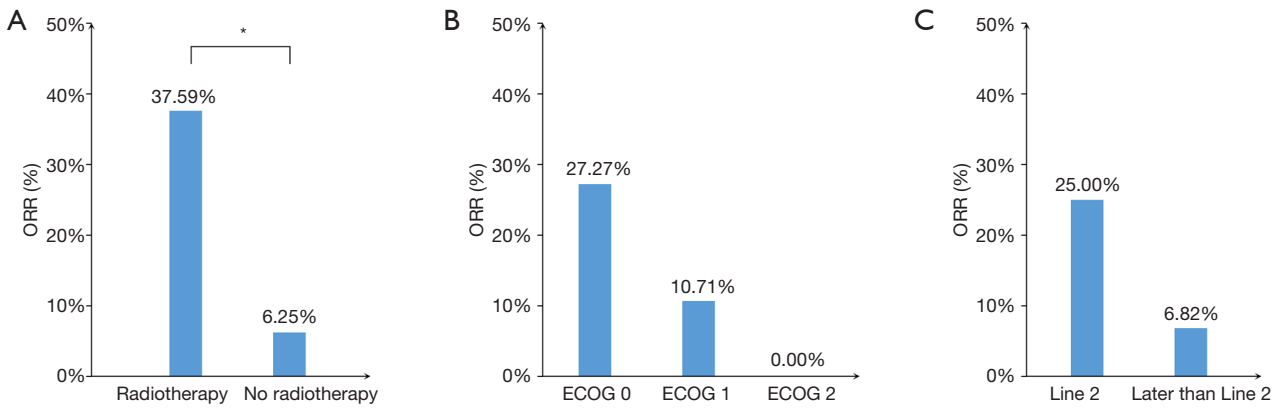

Figure 2 Objective radiographic responses. (A) Objective response rate (ORR) of patients with or without radiotherapy. (B) ORR of patients with different ECOG performance status. (C) ORR of patients treated with ICIs as second-line or later treatment. *, P<0.05.

Discussion

In this retrospective study, we evaluated the efficacy and safety of the PD-1 inhibitor combined with other therapies on heavily treated patients with advanced lung cancer and EGFR mutation after target therapy. Results show that the PD-1 inhibitor-based combination therapy and the EGFR wild-type lung cancer have similar AE profiles. This combination therapy shows longer PFS than the PD-1 inhibitor monotherapy reported before. However, the addition of chemotherapy and/or bevacizumab therapy to the anti-PD-1 therapy did not remarkably improved on heavily treated patients.

The EGFR-mutated lung cancer was thought to be an uninflamed "cold" tumor with low tumor-infiltrating CD8+ T cells (16,17). The conversion of this "cold" tumor into immunotherapy active "hot" tumor is vital in improving patients' immunotherapy efficacy. The EGFR pathway activation is responsible for the formation of the uninflamed tumor microenvironment (18,19). The treatment of EGFR blockage can modulate key EGFR signaling pathways and increase immune cell infiltration (20), indicating that the treatment of PD-1/PD-L1 inhibitor may have considerable efficacy on EGFR-mutated patients treated with a series of EGFR target therapies. However, the efficacy of the anti-PD-1/PD-L1 monotherapy did not show evident improvement on patients with EGFR mutation who have experienced EGFR–TKI therapy (13). Tumor cells can be killed using chemotherapy and release tumor antigen. These antigens can be presented by dendric cells to T cells

Table 2 Clinical characteristics, treatment process, clinical activity of patients treated with the radiotherapy

Patient	Metastases	Irradiation target	Irradiation area	Irradiation dose (Gy)	Irradiation times (f)	Clinical activity
1	Liver	PTV	Liver	36	18	PD
2	Brain	PTV	Brain	45	10	PR
3	Brain	PTV	Brain	54	20	SD
4	Lung	CTV	Lung	56	28	PR
5	Upper abdomen	PTV	Upper abdomen	45	25	PD
6	Lung	PTV	Lung	56	28	PR
7	Liver	PTV	Liver	36	6	PD
8	Lung	PTV	Lung	56	7	SD

PTV, planning target volume; CTV, clinical target volume; PD, progressive disease; PR, partial response; SD, stable disease.

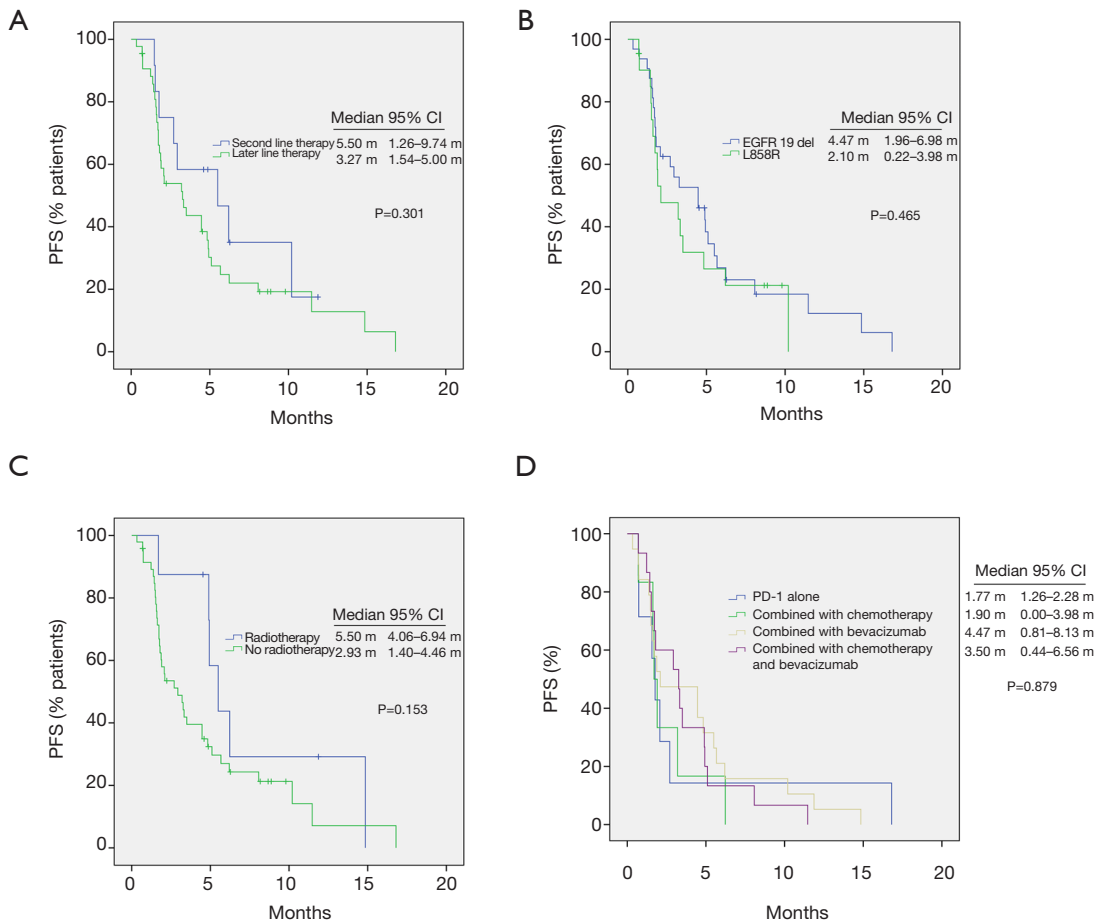

Figure 3 Kaplan-Meier curves. (A) Progression-free survival (PFS) of patients treated with ICIs as second-line or later treatment. (B) PFS of patients with EGFR 19 del and L858 mutation. (C) PFS of patients with or without radiotherapy. (D) PFS of different combination groups.

Table 3 Univariate analysis and multivariate analysis of factors of progression-free survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	0.963 (0.905–1.024)	0.228		
Gender	1.003 (0.445–2.260)	0.995		
EGFR mutation type	1.029 (0.459–2.311)	0.944		
Lines of therapy	0.960 (0.377–2.441)	0.931		
Radiotherapy *vs.* no radiotherapy	2.087 (0.490–8.884)	0.32		
Combination therapy versus monotherapy	2.828 (1.083–7.388)	0.034	3.698 (1.329–10.285)	0.012
ECOG performance status				
0	Reference		Reference	
1	0.118 (0.037–0.381)	<0.001	0.082 (0.024–0.285)	<0.001
2	0.080 (0.022–0.288)	<0.001	0.041 (0.010–0.170)	<0.001

Table 4 Treatment-related adverse events

Event	Total patients (n=56)	
	Any grade	Grade 3 or 4
Any event	49 (87.5)	24 (42.9)
Fatigue	17 (30.4)	4 (7.1)
Decreased appetite	12 (21.4)	3 (5.6)
Nausea	10 (17.9)	1 (1.8)
Pyrexia	6 (10.7)	1 (1.8)
Pneumonitis	10 (17.9)	1 (1.8)
Rash	5 (8.9)	1 (1.8)
Gingival bleeding	2 (3.6)	0
Anemia	22 (39.3)	3 (5.6)
Leukopenia	37 (66.1)	9 (16.1)
Thrombocytopenia	10 (17.9)	2 (3.6)
Elevated ALT or AST	17 (30.4)	4 (7.1)
Hypothyroidism	3 (5.6)	0

Number of patients with an event (percent). ALT, alanine aminotransferase; AST, aspartate transaminase.

and improve the efficacy of immunotherapy. Therefore, chemotherapy and immunotherapy may have synergistic effects. The combination of the PD-1 inhibitor and chemotherapy may improve the efficacy on patients with EGFR mutation after target therapy. Our study first proves that the combined therapy may result in better response than anti-PD-1 monotherapy but did not show remarkable efficacy on patients with EGFR mutation.

The median PFS is approximately two months for patients with EGFR mutation treated with PD-1/PD-L1 monotherapy (11,12). In our study, the median PFS was 3.3 months and was improved compared with PD-1/PD-L1 monotherapy. However, this improvement is not dramatic, possibly because most patients are heavily treated, and some

patients have poor performance status before they start to receive the PD-1 inhibitor-based therapy. We performed subgroup analysis and found that patients with good performance status, who received the PD-1 inhibitor-based therapy as second-line therapy or who were treated with the radiotherapy during the treatment of immunotherapy, may show good response. The results will determine which patients are more likely to benefit from the PD-1 inhibitor-based treatment. However, this trend did not have statistical difference possibly because of the limited number of patients included in this study. The high PD-L1 expression on tumor tissues indicates improved response to anti-PD-1 therapy. However, only the PD-L1 expression levels of 10 patients are available in this study. Therefore, we have not determined the efficacy difference at different PD-L1 expression levels. Considering that most of the patients' gene mutation status is not available in this study, we have not analyzed the association between the efficacy and certain gene mutation.

In the 2019 World Conference on Lung Cancer, the result of a phase 2 study of toripalimab, a PD-1 monoclonal antibody, in combination with the chemotherapy in patients with EGFR-positive advanced lung cancer have failed to prior EGFR–TKI therapies. Forty patients were included in this study (21). This study had a relatively high response rate of the PD-1 inhibitor-based therapy on patients with EGFR mutation (ORR =50.0%, DCR =87.5%). The median duration of the response is 7.0 months. The results of the clinical trial are superior to our study, possibly because the patient compositions of these two studies are different. In their study, 97.5% of patients have received the combination therapy as second-line therapy, and only one patient has received combination therapy as third-line therapy. Besides, the ECOG performance status of all patients in their study is 0 or 1. However, in our study, only 21.4% of patients have received combination therapy as second-line therapy. Most patients have received anti-PD-1 therapy as third- or even late-line therapy. Approximately 12.5% of patients have poor performance status. The difference in patient composition may contribute to the difference in results of these two studies. Notably, these studies involved limited number of patients, which may result in statistical bias. Therefore, further randomized controlled phase 3 study is needed to confirm whether patients with EGFR-mutated lung cancer can benefit from PD-1 inhibitor-based combination therapy.

In summary, our study proves that the PD-1 inhibitor therapy combined with chemotherapy and/or bevacizumab therapy shows acceptable toxicity profile and moderate efficacy on heavily treated patients with advanced EGFR-mutated lung cancer after target therapy.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/jtd-20-3520

Data Sharing Statement: Available at http://dx.doi.org/10.21037/jtd-20-3520

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-3520). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Academic Ethics Committee of Jiangsu Cancer Hospital. (NO. (2019)160) and individual consent for this retrospective analysis was waived.

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