Evaluation of the efficacy of PD-1/PD-L1 inhibitor plus bevacizumab and chemotherapy for the treatment of patients with driver gene-negative advanced-stage lung adenocarcinoma: A retrospective cohort study

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Received February 22, 2024; Accepted May 10, 2024

DOI: 10.3892/ol.2024.14799

Abstract. Driver gene-negative advanced-stage lung adenocarcinoma is associated with a poor prognosis and insufficient treatment options. The present study aimed to evaluate the efficacy and safety profile of a programmed cell death protein 1/programmed death-ligand 1 inhibitor plus bevacizumab and chemotherapy (PBC) regimen for the treatment of patients with driver gene-negative advanced-stage lung adenocarcinoma under real-world clinical conditions. Data from 65 patients with advanced-stage lung adenocarcinoma without sensitizing epidermal growth factor receptor, ALK receptor tyrosine kinase or ROS proto-oncogene 1 receptor tyrosine kinase mutations who received a PBC regimen or only a BC regimen were reviewed in the present retrospective cohort study. The results revealed that the objective response rate was higher (70.4 vs. 47.4%; P=0.065) in the PBC group compared with that in the BC group, while not reaching statistical significance. Progression-free survival (PFS) time was longer in the PBC group than in the BC group [median PFS: 10.8 months (95% confidence interval (CI), 7.2-14.4) vs. 7.6 months (95% CI, 5.0-10.2); P=0.016], while overall survival (OS) exhibited a non-significant trend to be longer in the PBC group compared with that in the BC group [median OS: 20.6 months (95% CI, 16.8-24.4) vs. 15.9 months (95% CI, 11.8-20.0); P=0.115]. Following adjustment by multivariate Cox analysis, the PBC (vs. BC) regimen was found to be independently associated with an improved PFS time (P=0.045). The common adverse events in the PBC group were neutropenia, alopecia, leukopenia, nausea and vomiting, fatigue, anemia and peripheral neuropathy. Moreover, the incidence of each adverse event did not differ significantly between the PBC and BC groups. In conclusion, the present study demonstrated that the PBC regimen serves as a superior treatment option for patients with driver gene-negative advanced-stage lung adenocarcinoma; however, further verification of its efficacy is still required.

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Key words: programmed cell death protein 1/programmed death-ligand 1 inhibitor, bevacizumab, chemotherapy, driver gene-negative, advanced lung adenocarcinoma

Introduction

Lung cancer is the top cause of cancer-related mortality globally, accounting for 18.0% of the total cancer-related deaths in 2020, and lung adenocarcinoma is one of the most common lung cancer types (1,2). Benefiting from improved surgical techniques, strategic progress (such as novel, combined and personalized neoadjuvant therapies), novel drug development and precise medicine realization, the outcomes of patients with lung adenocarcinoma have continuously improved over the past several decades (3-5). However, a non-negligible proportion of patients with lung adenocarcinoma are diagnosed at an advanced/metastatic stage of the disease and are thus not eligible for surgery; even with neoadjuvant therapies, these patients have an unfavorable prognosis (6-8). With regard to patients with driver gene-positive advanced-stage lung adenocarcinoma harboring sensitizing epidermal growth factor receptor (EGFR), ALK receptor tyrosine kinase (ALK) or ROS proto-oncogene 1 receptor tyrosine kinase (ROS1) mutations, corresponding targeted therapy with or without chemotherapy effectively improves patient outcomes (9-11). As the most common driver gene, EGFR has distinct expression and polymorphisms in different regions of the world, which relate to the ethnic and demographic characteristics of the studied population (12-15). Meanwhile, the EGFR polymorphisms or variations help in predicting the outcomes and adverse effects

to some extent in patients receiving tyrosine kinase inhibitors (16,17). However, for patients with driver gene-negative advanced-stage lung adenocarcinoma, only a limited number of treatment options are available, which highlights the need for exploring further treatment strategies.

Chemotherapeutic regimens (such as pemetrexed plus cisplatin/carboplatin, gemcitabine plus cisplatin/carboplatin and paclitaxel plus carboplatin regimens) are currently the cornerstone for the treatment of patients with driver gene-negative advanced-stage lung adenocarcinoma (18,19). In addition to its use in combination with chemotherapy, bevacizumab has been shown to further improve the prognosis of patients with driver gene-negative advanced-stage lung adenocarcinoma (20,21). However, conventional chemotherapy affects antitumor immunosurveillance via its modification of regulatory T lymphocytes (22), and bevacizumab affects the immune system by repressing dendritic cell maturation and regulating regulatory T-lymphocyte proliferation (23-25). These findings suggest that the combination of immune therapy with bevacizumab and chemotherapy could further improve the outcomes of patients with driver gene-negative advanced-stage lung adenocarcinoma.

Programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors are immune checkpoint inhibitors that repress the immune escape of cancer cells to achieve antitumor activity and have been used in the treatment of various types of cancer, including lung cancer (26-28). In terms of advanced-stage lung adenocarcinoma, two previous trials have demonstrated that in addition to bevacizumab and chemotherapy, PD-1/PD-L1 inhibitors improve the progression-free survival (PFS) and/or overall survival (OS) of patients with driver gene-negative advanced-stage non-small cell lung cancer (NSCLC) (mostly patients with lung adenocarcinoma) (29,30). Nevertheless, to the best of our knowledge, only a limited number of related studies under real-world clinical settings have been reported.

Therefore, the present study retrospectively analyzed patients with driver gene-negative advanced-stage lung adenocarcinoma who were treated with the PD-1/PD-L1 inhibitor plus bevacizumab and chemotherapy (PBC) regimen or only the BC regimen to compare their treatment response, survival benefits and safety profiles under real-world clinical conditions.

Patients and methods

Patients. Between January 2019 and January 2021, 65 patients with driver gene-negative advanced-stage lung adenocarcinoma who received the PBC or BC regimen in Sichuan Cancer Hospital and Institute (Chengdu, China), and Sichuan Jianzhu Hospital (Chengdu, China) were retrospectively analyzed in the present cohort study. The eligible patients were screened from the database according to the following criteria: i) A confirmed diagnosis of lung adenocarcinoma; ii) age >18 years; iii) Tumor-Node-Metastasis (TNM) stage IIIB-IV disease (31); iv) confirmed driver gene-negative status (defined as patients without sensitizing EGFR, ALK or ROS1 mutations); v) treatment with the PBC or BC regimen; vi) available main clinical feature data, response assessment data, follow-up data and safety data available for analysis; and vii) no history of other fatal diseases. Among the 65 patients, 27 patients received PBC and were classified as the PBC group and 38 patients received BC without PD-1/PD-L1 inhibitors and were classified as the BC group. The driver gene status was detected by the amplification refractory mutation system-polymerase chain reaction method using the AmoyDx® Pan Lung Cancer PCR Panel Kit (cat. no. ADX-LG01; Amoy Diagnostics Co., Ltd.) according to the manufacturer's instructions. Briefly, the AmoyDx® tissue DNA kit (cat. no. 8.02.0078; Amoy Diagnostics Co., Ltd.) and AmoyDx® tissue RNA kit (cat. no. 8.02.0079; Amoy Diagnostics Co., Ltd.) were used to extract DNA and RNA from tissues. The AmoyDx® Pan Lung Cancer PCR Panel Kit (cat. no. ADX-LG01, Amoy Diagnostics Co., Ltd., China) was applied to analyze mutation. For reverse transcription, the RNA, LEG RT reaction Mix and LEG Reverse Transcriptase were mixed. The mixture was incubated at 42˚C for 1 h and at 95˚C for 5 min to generate cDNA. For mutation detection, the cDNA and DNA were mixed with LEG Reaction Mix A and LEG Reaction Mix B, respectively. Afterwards, the PCR was conducted and parameters were as follows: 42˚C for 5 min and 95˚C for 5 min, for 1 cycle; 95˚C for 25 sec, 64˚C for 20 sec and 72˚C for 20 sec, for 10 cycles; and 93˚C for 25 sec, 60˚C for 35 sec and 72˚C for 20 sec, for 36 cycles. A lightCycler480 II (Roche Diagnostics) was applied to complete PCR and collect data. The Institutional Review Board of Sichuan Cancer Hospital and Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China approved the study protocol. Written informed consent was obtained at the start of the retrospective study from each patient or from the patient's direct relatives if they were deceased.

Treatment information. The treatment documents of the patients were reviewed, and the treatment information was collected as follows: In the PBC group (n=27), patients received one of the following PD-1/PD-L1 inhibitors: Sintilimab (200 mg per 3-week cycle), pembrolizumab (200 mg per 3-week cycle), camrelizumab (200 mg per 3-week cycle), durvalumab (10 mg/kg per 2-week cycle) or atezolizumab (1,200 mg per 3-week cycle) until unbearable toxic events or radiographically confirmed disease progression had occurred. The patients received bevacizumab (7.5-15.0 mg/kg per 3-week cycle) until unbearable toxic events or radiographically confirmed disease progression had occurred, plus chemotherapy with paclitaxel (175 mg/m^2 per 3-week cycle) and carboplatin (AUC 5-6 per 3-week cycle) for approximately six cycles depending on the patient's tolerance. In the BC group (n=38), patients underwent chemotherapy with paclitaxel (175 mg/m^2 per 3-week cycle) plus carboplatin (AUC 5-6 per 3-week cycle) for approximately six cycles depending on the patient's tolerance and continuously received bevacizumab (7.5-15.0 mg/kg per 3-week cycle) without PD-1/PD-L1 Inhibitors until unbearable toxic events or radiographically confirmed disease progression had occurred.

Efficacy, safety and survival assessment. The treatment response data of the patients were collected from the imaging assessment records, which were collected every 4 to 8 weeks after commencing therapy. The optimal treatment response was analyzed in the present study; patients were evaluated

referring to the Response Evaluation Criteria in Solid Tumors guidelines (31) and were concretely defined as having a complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) or unknown status (unpublished data or unevaluable data). The objective response rate (ORR) and disease control rate (DCR) were correspondingly calculated as follows: ORR=CR + PR and DCR=CR + PR + SD. The adverse events documented during the therapy were also collected for safety analysis and were graded in terms of the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (32). In addition, PFS and OS data were extracted from the follow-up records. PFS was defined as the time from treatment initiation to the time of cancer progression or death, and OS was defined as the time from treatment initiation to the time of death.

Statistical analysis. Clinical features were compared using the unpaired Student's t-test, the χ^2 test and Fisher's exact test. Treatment response was compared using the χ^2 test. PFS and OS were demonstrated using Kaplan-Meier curves and compared using the log-rank test. PFS- and OS-related factors were analyzed using multivariate Cox proportional hazards regression. Adverse events were compared using the χ^2 test or Fisher's exact test, as appropriate. SPSS 24.0 (IBM Corp.) and GraphPad Prism 7.02 (Dotmatics) software were used for the statistical analyses. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. Among the 65 enrolled patients with driver gene-negative, advanced-stage lung adenocarcinoma, the mean ages were 63.9±9.1 years (range, 43.0-80.0 years) and 64.9±8.2 years (range, 49.0-79.0 years) (P=0.643), and the male/female ratios were 70.4/29.6 and 78.9/21.1% (P=0.429), in the PBC group and the BC group, respectively. Moreover, no marked differences were found in the other characteristics such as TNM stage and lactate dehydrogenase (LDH) level between the PBC and BC groups (Table I).

Treatment response. The CR, PR, SD and PD rates were 7.4, 63.0, 14.8 and 3.7%, respectively, in the PBC group, while the rates were 0.0, 47.4, 28.9 and 10.5%, respectively, in the BC group. Further comparisons revealed that the treatment response (comparison of CR, PR, SD and PD rates between two groups) was higher in the PBC group than in the BC group (P=0.028; Fig. 1A). In addition, the ORR was higher in the PBC group compared with that in the BC group (70.4 vs. 47.4%; P=0.065), although this did not reaching statistical significance. Furthermore, the DCR did not differ markedly between the two groups (81.5 vs. 76.3%; P=0.618) (Fig. 1B).

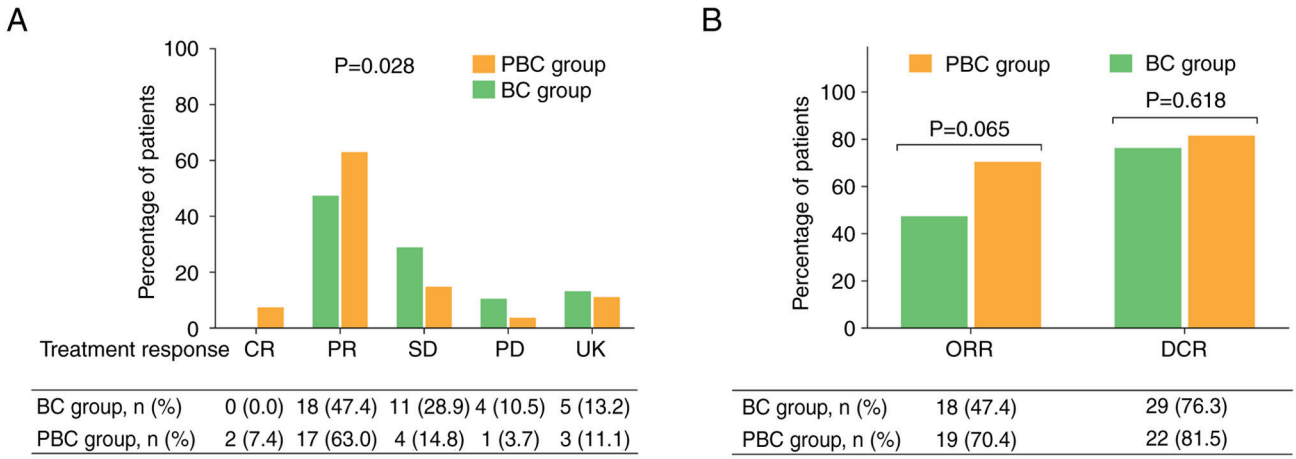
Survival profiles. PFS times was prolonged in the PBC group compared with that in the BC group [median PFS: 10.8 months (95% confidence interval (CI), 7.2-14.4) vs. 7.6 months (95% CI, 5.0-10.2); P=0.016; Fig. 2A], while the OS exhibited a non-significant trend for improvement in the PBC group compared with that in the BC group [median OS: 20.6 months (95% CI, 16.8-24.4) vs. 15.9 months (95% CI, 11.8-20.0); P=0.115; Fig. 2B].

Table I. Clinical characteristics.

Items	BC group (n=38)	PBC group (n=27)	P-value
Mean age ± SD, years	64.9±8.2	63.9±9.1	0.643
Sex, n (%)			0.429
Female	8 (21.1)	8 (29.6)	
Male	30 (78.9)	19 (70.4)	
Smoking status, n (%)			0.658
Never	12 (31.6)	6 (22.2)	
Former	21 (55.3)	16 (59.3)	
Current	5 (13.2)	5 (18.5)	
ECOG PS score, n (%)			0.750
0	14 (36.8)	11 (40.7)	
1	24 (63.2)	16 (59.3)	
TNM stage, n (%)			0.260
IIIB	3 (7.9)	5 (18.5)	
IV	35 (92.1)	22 (81.5)	
Bone metastasis, n (%)	6 (15.8)	7 (25.9)	0.314
Brain metastasis, n (%)	6 (15.8)	6 (22.2)	0.510
CEA level, n (%)			0.564
Normal	8 (21.1)	7 (25.9)	
Abnormal	29 (76.3)	18 (66.7)	
UK	1 (2.6)	2 (7.4)	
CA125 level, n (%)			0.520
Normal	13 (34.2)	11 (40.7)	
Abnormal	24 (63.2)	14 (51.9)	
UK	1 (2.6)	2 (7.4)	
LDH level, n (%)			0.681
≤ULN	22 (57.9)	17 (63.0)	
>ULN	16 (42.1)	10 (37.0)	
PD-L1 TPS, n (%)			0.450
<0%	11 (28.9)	10 (37.0)	
≥1%	13 (34.2)	11 (40.7)	
UK	14 (36.8)	6 (22.2)	

BC, bevacizumab and chemotherapy; PBC, programmed cell death 1/programmed cell death ligand 1 inhibitor plus bevacizumab and chemotherapy; SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, Tumor-Node-metastasis; CEA, carcinoembryonic antigen; CA125, cancer antigen 125; LDH, lactate dehydrogenase; ULN, upper limit of normal; UK, unknown; PD-L1, programmed death-ligand 1; TPS, tumor-cell proportion score.

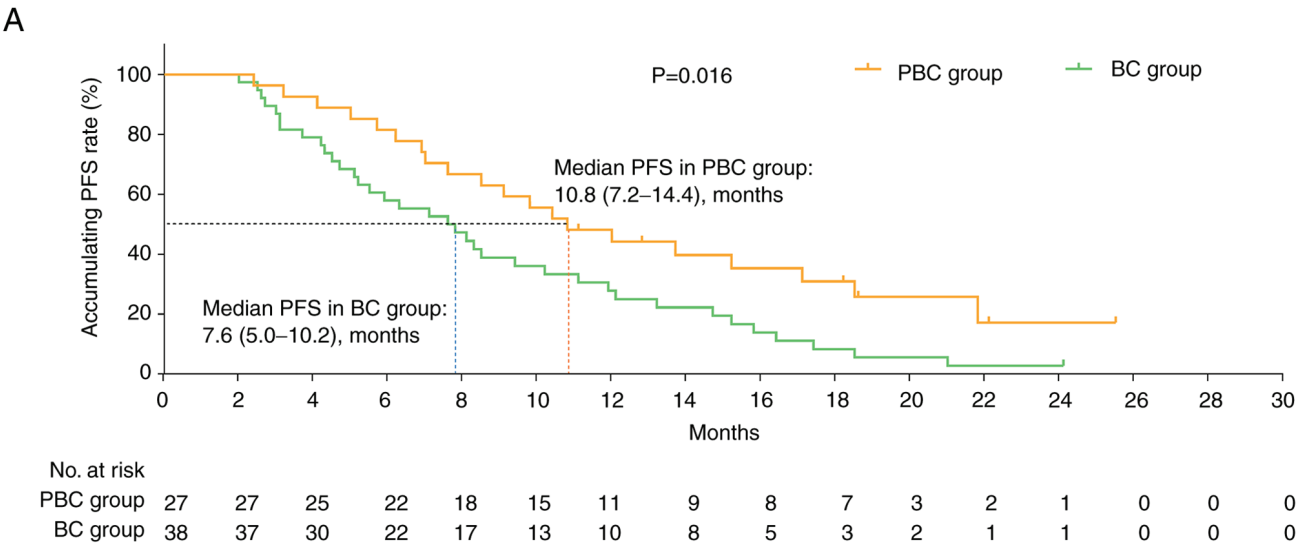
Adjustment by multivariate Cox analyses. To reduce the influence of compounding factors, multivariate Cox analyses were performed, which confirmed that the PBC regimen (vs. the BC regimen) was independently associated with an improved PFS time [hazard ratio (HR)=0.566; P=0.045], but not OS time (Table II). In addition, an increased TNM stage was independently associated with both a worse PFS (HR=5.092; P=0.008) and OS (HR=4.363; P=0.043) time (Table II).



BC group, n (%)	0 (0.0)	18 (47.4)	11 (28.9)	4 (10.5)	5 (13.2)
PBC group, n (%)	2 (7.4)	17 (63.0)	4 (14.8)	1 (3.7)	3 (11.1)

BC group, n (%)	18 (47.4)	29 (76.3)
PBC group, n (%)	19 (70.4)	22 (81.5)

Figure 1. Evaluation of the treatment response. (A) Detailed treatment response information for the PBC and BC groups. (B) Objective response rate and disease control rate in the PBC and BC groups. The optimal treatment response during therapy was used for evaluation. PBC, programmed cell death 1/programmed cell death ligand 1 inhibitor plus bevacizumab and chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; UK, unknown; ORR, objective response rate; DCR, disease control rate.



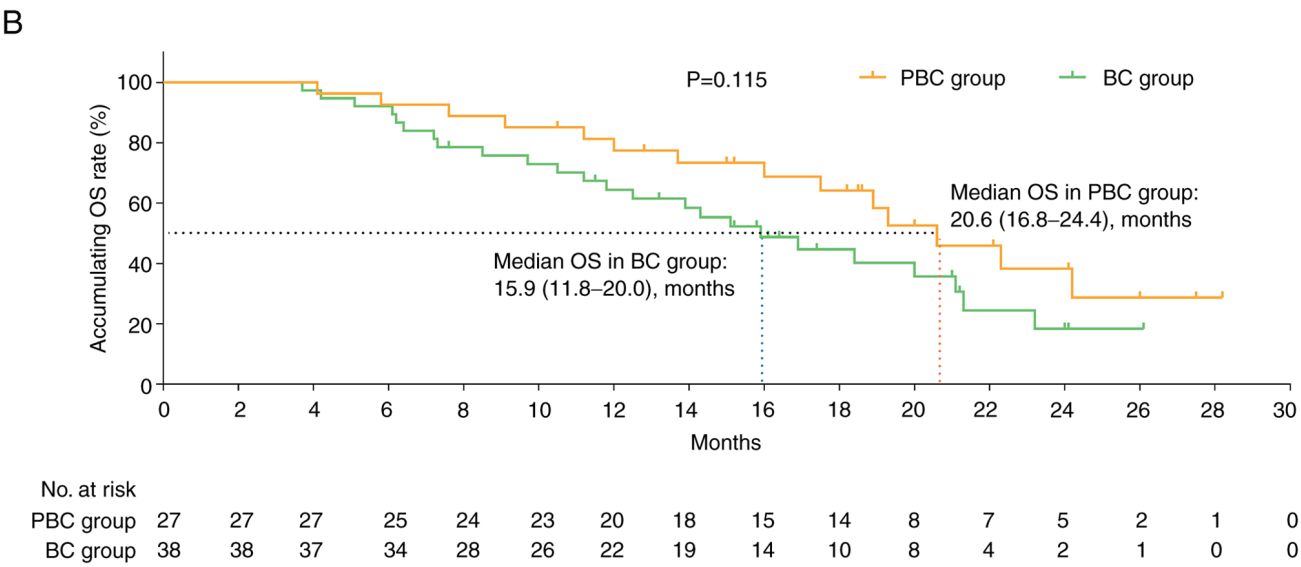


Figure 2. Evaluation of PFS and OS. (A) Comparison of the cumulative PFS rate between the PBC and BC groups. (B) Comparison of the OS rate between the PBC and BC groups. PFS, progression-free survival; OS, overall survival; PBC, programmed cell death 1/programmed cell death ligand 1 inhibitor plus bevacizumab and chemotherapy.

Table II. Multivariate Cox's proportional hazards regression analysis for PFS and OS.

A, Forward stepwise multivariate Cox's regression analysis for PFS

			95% CI	
Items	P-value	HR	Lower	Upper
Treatment (PBC vs. BC)	0.045	0.566	0.325	0.986
TNM stage (IV vs. IIIB)	0.008	5.092	1.524	17.013

B, Forward stepwise multivariate Cox's regression analysis for OS

			95% CI	
Items	P-value	HR	Lower	Upper
TNM stage (IV vs. IIIB)	0.043	4.363	1.046	18.191

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; PBC, programmed cell death 1/programmed cell death ligand 1 inhibitor plus bevacizumab and chemotherapy; BC, bevacizumab and chemotherapy; TNM, Tumor-Node-Metastasis.

Table III. Adverse events.

	BC group			PBC group			
Items	Total	Grade 1-2	Grade 3-4	Total	Grade 1-2	Grade 3-4	P-value
Neutropenia, n (%)	11 (28.9)	7 (18.4)	4 (10.5)	12 (44.4)	9 (33.3)	3 (11.1)	0.365
Alopecia, n (%)	14 (36.8)	14 (36.8)	0 (0.0)	11 (40.7)	11 (40.7)	0 (0.0)	0.750
Leukopenia, n (%)	12 (31.6)	9 (23.7)	3 (7.9)	10 (37.0)	6 (22.2)	4 (14.8)	0.674
Nausea and vomiting, n (%)	11 (28.9)	9 (23.7)	2 (5.3)	10 (37.0)	9 (33.3)	1 (3.7)	0.682
Fatigue, n (%)	11 (28.9)	11 (28.9)	0 (0.0)	9 (33.3)	9 (33.3)	0 (0.0)	0.706
Anemia, n (%)	6 (15.8)	6 (15.8)	0 (0.0)	8 (29.6)	6 (22.2)	2 (7.4)	0.169
Peripheral neuropathy, n (%)	3 (7.9)	3 (7.9)	0 (0.0)	6 (22.2)	5 (18.5)	1 (3.7)	0.099
Anorexia, n (%)	7 (18.4)	6 (15.8)	1 (2.6)	6 (22.2)	4 (14.8)	2 (7.4)	0.664
Elevated transaminase, n (%)	7 (18.4)	7 (18.4)	0 (0.0)	6 (22.2)	5 (18.5)	1 (3.7)	0.488
Rash, n (%)	7 (18.4)	5 (13.2)	2 (5.3)	5 (18.5)	3 (11.1)	2 (7.4)	0.918
Thrombopenia, n (%)	6 (15.8)	5 (13.2)	1 (2.6)	5 (18.5)	4 (14.8)	1 (3.7)	0.949
Elevated bilirubin, n (%)	5 (13.2)	5 (13.2)	0 (0.0)	5 (18.5)	5 (18.5)	0 (0.0)	0.729
Diarrhea, n (%)	5 (13.2)	5 (13.2)	0 (0.0)	5 (18.5)	5 (18.5)	0 (0.0)	0.729
Increased blood pressure, n (%)	7 (18.4)	7 (18.4)	0 (0.0)	4 (14.8)	4 (14.8)	0 (0.0)	0.751
Constipation, n (%)	3 (7.9)	3 (7.9)	0 (0.0)	3 (11.1)	3 (11.1)	0 (0.0)	0.686

PBC, programmed cell death 1/programmed cell death ligand 1 inhibitor plus bevacizumab and chemotherapy.

Adverse events. The most common adverse events were neutropenia (44.4 vs. 28.9%), alopecia (40.7 vs. 36.8%), leukopenia (37.0 vs. 31.6%), nausea and vomiting (37.0 vs. 28.9%) and fatigue (33.3 vs. 28.9%) in the PBC and BC groups (Table III). The majority of the adverse events were grade 1-2, and only a few adverse events were grade 3-4, such as leukopenia, neutropenia, anemia and peripheral neuropathy.

Notably, the general incidence of each adverse event did not differ significantly between the PBC and BC groups (Table III). However, neutropenia (44.4 vs. 28.9%), anemia (29.6 vs. 15.8%), and peripheral neuropathy (22.2 vs. 7.9%) were more common in the PBC group than in the BC group, without reaching statistical significance (all P>0.05). In addition, the incidence of grade 3-4 adverse events was also greater in the PBC group than in the BC group; however, these differences were not statistically significant (all P>0.05).

Discussion

In contrast to the multiple treatment options available for patients with driver gene-positive advanced-stage lung adenocarcinoma, surrogate treatment modalities for patients with

driver gene-negative advanced-stage lung adenocarcinoma are limited, and mainly include platinum-doublet chemotherapy with or without bevacizumab (33-35). However, the emergence of immunotherapy has provided an alternative option for patients with driver gene-negative advanced-stage lung adenocarcinoma (26-28). In addition, inspired by the mutual effects of chemotherapy, bevacizumab and PD-1/PD-L1 on immunosurveillance, regimens that involve the combination of PD-1/PD-L1 inhibitors, bevacizumab and chemotherapy have been applied in the treatment of patients with driver gene-negative advanced-stage lung adenocarcinoma and have subsequently been recommended as first-line therapies (23-25,29,36-40). For example, the IMpower150 study revealed that the addition of atezolizumab to bevacizumab plus chemotherapy achieved an ORR of 63.5% (CR of 3.7% and PR of 59.8%) in patients with driver gene-negative advanced-stage non-squamous NSCLC (29). In addition, in the ONO-4538-52/TASUKI-52 study, the addition of nivolumab to platinum-doublet chemotherapy plus bevacizumab was associated with a notably greater ORR of 61.5% (vs. 50.5% in the placebo combination group) for patients with driver gene-negative metastatic non-squamous NSCLC (30). However, as PD-1/PD-L1 inhibitor therapy has not been used in China for that long, and as previous studies involve randomized controlled trials, the relevant efficacy and safety data for PD-1/PD-L1 inhibitors in the Chinese population are not sufficient, particularly in real-world clinical settings. Thus, the present real-world study was conducted with the aim of determining the efficacy and safety of the PBC regimen in Chinese patients with driver gene-negative advanced-stage lung adenocarcinoma. The PBC regimen achieved an ORR of 70.4%, which was greater than the 47.4% ORR in patients treated with the BC regimen; however, their DCR did not differ. These findings are similar to those of previous studies, except that in the present study, there was only an upward trend, not a significant difference, in the ORR in patients who received the PBC regimen compared with the patients who received the BC regimen alone. These findings may be explained by the small sample size of the present study, which caused a lower statistical power; thus, further studies with larger sample sizes are warranted. Another notable finding of the present study was that the ORR of 70.4% in patients treated with the PBC regimen was numerically greater than that reported in previous studies (29,30). These findings may be explained by the fact that the response rate evaluated in the present study was the optimal response rate, which corresponded to a longer evaluation period than that used in previous studies and was thus associated with a numerically elevated ORR.

Previous trials have revealed that the PBC regimen can achieve a promising survival profile compared with BC regimens alone in patients with driver gene-negative advanced-stage lung adenocarcinoma (29,30,41,42). A previous phase Ib study demonstrated that nivolumab combined with platinum-doublet chemotherapy plus bevacizumab was associated with a long PFS time (41,42). Moreover, in the IMpower150 study, the addition of atezolizumab to bevacizumab plus chemotherapy prolonged the PFS time by 1.5 months (median PFS time: 8.3 vs. 6.8 months) and OS by 4.5 months (median OS time: 19.2 vs. 14.7 months) compared with the bevacizumab plus chemotherapy alone in patients with driver gene-negative advanced-stage non-squamous NSCLC (29). In addition, in the ONO-4538-52/TASUKI-52 study, the addition of nivolumab to platinum-doublet chemotherapy plus bevacizumab was associated with an even longer PFS time (median PFS time: 12.1 vs. 8.1 months) compared with platinum-doublet chemotherapy plus bevacizumab for patients with driver gene-negative metastatic non-squamous NSCLC (30). In the present study, it was found that the PFS time was longer in the PBC group than that in the BC group, while the OS time did not differ between these two groups. A possible explanation for this may be that due to the relatively short follow-up period, a significant difference in OS time was not detected between these two groups. Moreover, the OS could be affected by the treatment regimens after tumor progression, which weakened the difference in the OS time between the PBC and BC groups in the current study. For instance, some of the patients in the BC group received PD-1/PD-L1 inhibitor after the tumor progression, which affected the comparison of OS between the PBC and BC groups. However, since a proportion of patients received subsequent treatment in other hospitals, the detailed information of further treatment regimens after tumor progression was not analyzed in the study (the accurate information of treatment regimen after progression was confirmed in only 19 patients, while the data for the majority if patients was not available or could not be accurately confirmed).

In terms of safety profiles, preceding studies have demonstrated that treatment with the PBC regimen is well tolerated and that no new adverse events have occurred compared with those for the BC regimen, but only in patients with driver gene-negative advanced-stage lung adenocarcinoma (29,30,41,42). In line with the findings of these previous studies (29,30,41,42), the present study revealed that the adverse event rates did not differ significantly between the PBC and BC groups. The most common adverse events of the PBC regimen included neutropenia, alopecia, leukopenia, nausea and vomiting, fatigue, anemia, peripheral neuropathy, anorexia, elevated transaminase levels, rash, thrombopenia, elevated bilirubin levels, diarrhea, increased blood pressure and constipation. Furthermore, the majority of the adverse events were grade 1 or 2. These data indicated that the PBC regimen had acceptable safety profiles in patients with driver gene-negative advanced-stage lung adenocarcinoma.

Notably, a recent study observed that the measurement of blood inflammatory cytokines helped to predict the efficacy and adverse events of PD-1 inhibitor treatment in patients with metastatic melanoma (43), which could also be evaluated in the future in patients with driver gene-negative advanced-stage lung adenocarcinoma. It has also been reported that an LDH measurement is able to predict the response and outcome in patients with lung cancer receiving PD-1 inhibitor or PD-L1 inhibitor treatment (44,45); however, the present study observed that LDH proportion did not differed between the PBC and BC groups, indicating that it would not affect the findings.

The present study had several limitations that should be mentioned: i) As a real-world study, the sample size of 65 patients was insufficient; ii) the follow-up duration was short and could be further prolonged to determine the difference in OS time between the PBC and BC regimens; and iii) selection bias may have been present due to the study being in

a single institute, and more centers could be invited to join a real-world study in the future to reduce this.

In conclusion, the present study demonstrated that the PBC regimen serves as a superior treatment option with promising efficacy and tolerable safety in patients with driver gene-negative advanced-stage lung adenocarcinoma. However, further large-scale, multicenter real-world studies with longer follow-up periods are required to verity the findings presented.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XY, XL, KH and XZ contributed to the study conception and design. XY, XL and KH performed material preparation, and data collection and analysis. The first draft of the manuscript was written by XY, and all authors commented on previous versions of the manuscript. XZ and XY confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The Institutional Review Board of Sichuan Cancer Hospital and Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China (Chengdu, China) approved the protocol (approval no. SCCH EC-01A-2020-010). Written informed consent was obtained from the patient or the patient's direct relative.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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