Original Article

Drug-eluting beads bronchial arterial chemoembolization/ bronchial arterial infusion chemotherapy with and without PD-1 blockade for advanced non-small cell lung cancer: a comparative single-center cohort study

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Background: Drug-eluting beads bronchial arterial chemoembolization (DEB-BACE)/bronchial artery infusion chemotherapy (BAI) have been investigated as treatment options for advanced non-small cell lung cancer (NSCLC), especially for those patients who develop refractoriness to or are intolerant to systemic chemotherapy. This retrospective study aimed to compare the outcomes of DEB-BACE/BAI with and without programmed cell death protein 1 (PD-1) blockade for advanced NSCLC, and to investigate the effectiveness and safety of combination regimens.

Methods: This retrospective cohort study included advanced NSCLC patients who were intolerant to or were resistant to systemic chemotherapy, radiotherapy, or molecular targeted therapy and underwent DEB-BACE/BAI between October 2016 and October 2021 in Beijing Hospital, National Center of Gerontology. A total of 84 advanced NSCLC patients (DEB-BACE/BAI + PD-1 blockade group: group A, n=27; DEB-BACE/BAI: group B, n=57) were enrolled finally. The embolic agent CalliSpheres (100–300, 300–500, or 500–700 μm) loaded with gemcitabine (800 mg) was administered during the DEB-BACE procedure. The adverse events (AEs) and outcomes were compared. Of these, the median progression-free survival (PFS) and overall survival (OS) were compared via Kaplan–Meier (KM) methods. Univariate and multivariate Cox regression analyses were used to investigate the predictors of PFS and OS.

Results: KM methods showed that group A had longer median PFS (12.0 *vs.* 3.0 months, P<0.001) and OS (27.0 *vs.* 8.0 months, P<0.001) than group B. The predictors of PFS for DEB-BACE/BAI included tumor diameter (P=0.013), immunotherapy (P<0.001), and DEB-BACE/BAI cycles (P=0.012), whereas the predictors of OS included tumor diameter (P=0.021), extrapulmonary metastases (P=0.041), immunotherapy (P<0.001), and DEB-BACE/BAI cycles (P=0.020). The incidence rates of overall AEs in groups A and B were 40.7% (11/27) and 36.8% (21/57), respectively, and no significant difference was found (P=0.731). Group A

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had an incidence rate of 11.1% for grade 3 immunotherapy-related AEs (irAEs). There were no incidences of ectopic embolization or spinal artery injury.

Conclusions: Compared with DEB-BACE/BAI, PD-1 blockade plus DEB-BACE/BAI could improve the prognosis for advanced NSCLC despite the associated risk of grade 3 irAEs. The combination regimens are promising and safe approaches for advanced NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); drug-eluting beads; chemoembolization; immunotherapy

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Introduction

Primary lung cancer ranks first in cancer fatality and second in cancer incidence globally (1). In China, 85% of lung cancer cases have the subtype of non-small cell lung cancer (NSCLC), and almost 75% of patients are accompanied by local invasion or/and distant metastases when diagnosed (2). Therapeutic guidelines recommend tyrosine kinase inhibitors (TKIs) and systemic chemotherapy plus immunotherapy as the first-line treatments for advanced NSCLC according to whether oncogene mutations are harbored, which increases the median overall survival (OS) to 13 months (3,4). Nevertheless, most NSCLC patients who harbor a mutation of epidermal growth factor receptor (*EGFR*) could develop resistance to TKIs within a median period of 14 months (5), and the refractoriness to systemic chemotherapy can occur rapidly despite a satisfying initial response (6). With the aging of the population, the number of patients who cannot tolerate systemic chemotherapy is increasing continuously, which contributes to severe comorbidities, old age, or poor performance status (PS) (7). Local therapy such as radiotherapy or ablation can be used for advanced disease even if the patient is intolerant to systemic chemotherapy, despite the limited prognosis.

Immunotherapy has revolutionized cancer treatments, especially immune checkpoint inhibitors (ICIs). Programmed cell death protein 1 (PD-1) blockade is the predominant type, which alters the immune regulatory pathways and promotes T cell-mediated destruction (8). The KEYNOTE-024 trial demonstrated that the first-line treatment of PD-1 blockade has a survival advantage over systemic chemotherapy in advanced NSCLC, with a median OS of 30.0 months (9). Meanwhile, it has been reported that systemic chemotherapy-induced acute inflammation could promote antitumor immunity (10). Several trials have emphasized the superiority of ICIs plus systemic chemotherapy over mono-chemotherapy (11,12), which promotes the approval of combination therapy as the priority for advanced and oncogenes-wild NSCLC (4). Nevertheless, a meta-analysis summarized a higher incidence of severe adverse events (SAEs) for NSCLC treated with immunotherapy plus systemic chemotherapy, when compared with mono-immunotherapy (47.0% *vs.* 37.0%), and indicated better toxicity of the latter (13). However, in another study, only 20% of NSCLC patients responded to mono-immunotherapy (14).

Drug-eluting beads bronchial arterial chemoembolization (DEB-BACE) has been identified as a treatment option for NSCLC since it was first applied to NSCLC in 2019, especially for patients who are resistant or are intolerant to systemic chemotherapy, with a median progression-free survival (PFS) and OS of 6.3–11.0 and 8.0–29.6 months for all stages, respectively (15-17). A study reported that DEB-BACE was effective in controlling hemoptysis and tumor progression for patients with lung metastases (18,19). In 2021, Li *et al.* (20) attempted DEB-BACE/bronchial artery infusion chemotherapy (BAI) plus PD-1 blockade in advanced NSCLC and found that immunotherapy may improve the prognosis, and another study showed that immunotherapy was a predictor for prolonged OS in advanced NSCLC after DEB-BACE/BAI (15). The long-term outcomes of DEB-BACE/BAI combined with immunotherapy remain unclear. Therefore, we conducted a retrospective cohort study to compare the outcomes of DEB-BACE/BAI with and without PD-1 blockade for advanced NSCLC, and to investigate the effectiveness and safety of the combination regimens. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/

view/10.21037/qims-23-287/rc).

Methods

Patient criteria and study design

All advanced NSCLC patients (stage IIIB to IVB) who underwent DEB-BACE/BAI between October 2016 and October 2021 in Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences were included. This retrospective single-center cohort study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics review board of Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, and individual consent for this retrospective analysis was waived. The indications for DEB-BACE/BAI included unresectable tumors, resistance or intolerance to standard treatments (systemic chemotherapy, radiotherapy, or TKIs), but the need to undergo systemic chemotherapy. The patients were classified into group A (DEB-BACE/BAI + PD-1 blockade) and group B (DEB-BACE/BAI). The inclusion criteria were as follows: (I) age ≥18 years; (II) unresectable and advanced NSCLC with intolerance of or resistance to systemic chemotherapy, radiotherapy, or TKIs; and (III) Eastern Cooperation Oncology Group (ECOG) PS of 0–3. The exclusion criteria were as follows: (I) local ablation was performed before DEB-BACE/BAI; (II) lost to follow-up; (III) period between DEB-BACE/BAI and immunotherapy longer than 1 month; and (IV) follow-up less than 1 year.

The intolerance or resistance to standard treatments was determined by the multidisciplinary treatment team. The intolerance to standard treatments was judged according to whether severe comorbidities [such as cardiocerebrovascular diseases, pulmonary fibrosis, or chronic obstructive pulmonary disease (COPD)], old age (≥75 years), or poor ECOG score (≥2) were present, which caused the patients to be intolerant to standard treatments, such as systemic chemotherapy. The resistance to standard treatments was judged as patients who developed local progression or distant metastases after standard treatments, such as systemic chemotherapy or TKIs. The evaluation of positron emission tomography (PET) or contrast-enhanced computed tomography (CT) was ahead of treatments, which assisted the tumor staging via the clinical tumor-node-metastasis (TNM) staging system (8th edition) (21).

DEB-BACE/BAI procedure

As described previously (22), DEB-BACE/BAI was performed under the guidance of digital subtraction angiography (DSA) by several experienced interventional radiologists. The procedures were performed under local anesthesia via right femoral artery approaches. Initial angiography was conducted to detect the tumor-feeding arteries via a pigtail catheter (5-French; PIG Impress; Merit Medical Systems, Inc., South Jordan, UT, USA). Features for tumor-feeding arteries included bronchial artery hypertrophy or tumor hypervascularity. Selection of tumor-feeding arteries was achieved by a 5-French cobra (CB 1 Impress; Merit) or left gastric catheter (Radifocus; Terumo Corporation, Tokyo, Japan), followed by the super-selective catheterization to facilitate endovascular therapy and avoid ectopic embolization via a microcatheter (1.98-French; Masters PARKWAY SOFT; Asahi Intec Co., Aichi, Japan). The subsequential BAI was performed before chemoembolization, with paclitaxel (100–200 mg; Keaili, CSPC Pharmaceutical Group Co., Shijiazhuang, China) was administered for patients who had a treatment history of platinum-based systemic chemotherapy, and nedaplatin (80–100 mg; Lubei, Qilu Pharmaceutical Co., Jinan, China) was administered for those patients without such a treatment history. Chemoembolization was performed using CalliSpheres (100–300 μm, 300–500 μm, or 500–700 μm, Jiangsu Hengrui Medical Co., Lianyungang, China) loaded with gemcitabine (800 mg; Hansoh, China). The microspheres were mixed with the drug at a temperature of 23–28 ℃ for 0.5 h. The contrast agent of the equal volume to DEB microsphere was also added. The DEB microsphere was injected into the target arteries slowly for chemoembolization, with the technical endpoints being reached when the complete stagnation of contrast agent in arteries or the disappearance of tumor staining was found. The repeated DEB-BACE/BAI was undergone at an interval of 1 month as demanded. Of these, DEB-BACE was considered for patients who still showed abundant tumor staining during angiography, whereas BAI alone was considered for those patients with tumor hypovascularity. In general, no more than 2 types of chemotherapeutic drugs were administered during DEB-BACE/BAI procedures.

Protocols of ICIs

The ICIs administered in this study was PD-1 blockade, which was considered for patients with high programmed cell death ligand 1 (PD-L1) expression but without a

treatment history of immunotherapy. For patients in group A, sequential PD-1 blockade was administrated intravenously within 1 month after the first DEB-BACE, and was repeated every 3–4 weeks. The types of PD-1 blockade included camrelizumab (200 mg; Hengrui), sintilimab (200 mg; Innovent Biologics Inc., Suzhou, China), tislelizumab (200 mg; BeiGene Inc., Beijing, China) and toripalimab (240 mg; Junshi Biosciences Co., Ltd., Shanghai, China). In general, the combination therapy of DEB-BACE/BAI and PD-1 blockade was performed in 2–3 cycles, and consolidation monotherapy of immunotherapy was maintained and ceased when progression or intolerance-related AEs occurred.

Further treatment

Radiotherapy was performed for patients with cerebral or bone metastases, whereas local interventional therapy was performed for patients with liver or other solid organ metastases as demanded (4,23). The best supportive care was considered for patients who experienced disease progression or intolerance-related AEs during the treatments.

Management of AEs

Immunotherapy-related AEs (irAEs) and DEB-BACE/BAI-related AEs were evaluated per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI CTCAE v 5.0) (24). For the management of AEs, antalgic, antipyretic, or anti-myelosuppression were administered for patients who presented with grade 2 DEB-BACE/BAI-related AEs or higher, whereas steroid therapy was considered for patients who developed grade 3–5 irAEs.

Prognostic analyses

CT reexaminations were performed every 3 months to evaluate the local efficacy, which was graded as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) (25). Disease control rate (DCR) was identified as the sum of CR, PR, or SD. PFS referred to the period between DEB-BACE and the progression or death, whereas the OS was calculated as the interval between DEB-BACE and death or the last follow-up (October 31, 2022). The censoring date was calculated as the last assessment date for patients who have neither mortality nor progression.

Statistical analyses

The software SPSS 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Demographic characteristics, AEs, and outcomes were compared, with Student's *t*-test or Mann-Whitney U test for analysis of continuous variables and chi-square test used for categorical variables. The median PFS and OS were compared via the Kaplan-Meier (KM) method. The potential predictors of PFS or OS included 18 parameters and were investigated by univariate and multivariate Cox regression analyses. P values <0.05 for the 2-sided test in the log-rank test were screened as potential variables for multivariate Cox regression analyses, which were confirmed as predictors when the variables revealed P values <0.05 for the 2-sided test in the multivariate analyses.

Results

Demographic characteristics

There were 84 advanced NSCLC patients (group A: n=27; group B: n=57; *Figure 1*) enrolled in this study, with a tumor diameter of 6.5±2.7 cm. Of these, 45 patients (53.6%) were stage III, and 43 patients (51.2%) developed refractoriness to standard treatments, including 5 patients (6.0%) with surgery plus TKIs or chemotherapy, 12 patients (14.3%) with chemoradiotherapy, 8 patients (9.5%) with chemotherapy plus immunotherapy, 13 patients (15.5%) with TKIs, and 5 patients (6.0%) with mono-chemotherapy. Patient characteristics are presented in *Table 1*. No significant differences were found in the demographic characteristics, except for hypertension (P=0.044). In group A, PD-1 blockade began at 10.5±8.6 days after the first DEB-BACE/BAI.

Outcomes

In a mean follow-up period of 28.0±13.2 months, the median PFS and OS in group A were 12.0 and 27.0 months, respectively, whereas those in group B were 3.0 and 8.0 months, respectively. Group A had a significantly longer median PFS (P<0.001; *Figure 2A*) and OS than group B (P<0.001; *Figure 2B*). A higher 1-year PFS (44.4% *vs.* 14.0%; P=0.002) or OS rate (74.1% *vs.* 31.6%; P<0.001) was also found in group A. The overall DCR was 63.1% at 3 months after the first DEB-BACE/BAI (*Figure 3*), of which a higher DCR was observed in group A (96.3% *vs.* 47.4%; P<0.001). The detailed prognostic data are shown in *Table 2*.

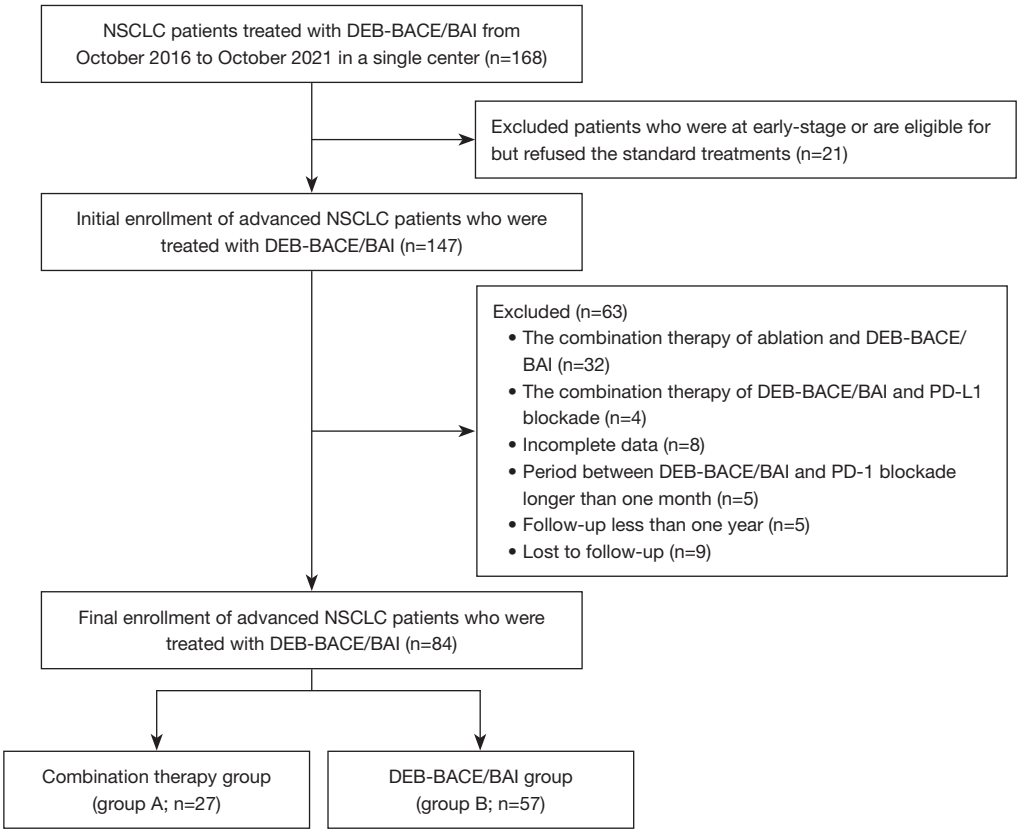

Figure 1 Patient selection flowchart. NSCLC, non-small cell lung cancer; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; BAI, bronchial artery infusion chemotherapy; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.

Survival analyses

The results of univariate and multivariate analyses are presented in *Tables 3*,*4*, respectively. Immunotherapy [hazard ratio (HR): 0.322; 95% confidence interval (CI): 0.182–0.569; P<0.001), tumor diameter (HR: 1.878; 95% CI: 1.140–3.092; P=0.013), and DEB-BACE/BAI cycles (HR: 0.536; 95% CI: 0.330–0.870; P=0.012) were the predictors of PFS (*Figure 4*). Extrapulmonary metastases (HR: 1.787; 95% CI: 1.024–3.118; P=0.041), immunotherapy (HR: 0.307; 95% CI: 0.160–0.589; P<0.001), tumor diameter (HR: 1.875; 95% CI: 1.102–3.190; P=0.021), and DEB-BACE/BAI cycles (HR: 0.527; 95% CI: 0.307–0.904; P=0.020) were the predictors of OS (*Figure 5*).

AEs

The incidence rates of overall AEs in groups A and B were 40.7% (11/27) and 36.8% (21/57), respectively, with no significant difference being found (P=0.731). Group A had an incidence rate of 11.1% for grade-3 irAEs, which belong to irAEs of immunotherapy-related pneumonia (IRP). For the management of severe irAEs, there were 3 patients (11.1%, 3/27) with IRP who received steroid therapy and ceased the immunotherapy. Detailed AEs are presented in *Table 5*, with no severe DEB-BACE-related AEs being found. No patient experienced ectopic embolization or spinal artery injury or AE-related mortality.

Discussion

Our study indicated a prognostic superiority of DEB-BACE/BAI plus PD-1 blockades to DEB-BACE/BAI in a longer follow-up, with an estimated median OS of 27.0 months for combination regimens. It should be noted that 55.6% of patients in group A remained alive, which indicated a potential longer OS if continuous follow-up could be

Table 1 Demographic characteristics between groups A and B

Variables	Overall (n=84)	Group A (n=27)	Group B (n=57)	P-value
Age (years)	67.3±9.2	65.3±8.3	68.2±9.6	0.181
Gender				0.536
Male	65 (77.4)	22 (81.5)	43 (75.4)	
Female	19 (22.6)	5 (18.5)	14 (24.6)	
ECOG				0.896
0	19 (22.6)	5 (18.5)	14 (24.6)	
1	26 (31.0)	8 (29.6)	18 (31.6)	
2	23 (27.4)	8 (29.6)	15 (17.9)	
3	16 (19.0)	6 (22.2)	10 (17.5)	
Hemoptysis	11 (13.1)	3 (11.1)	8 (14.0)	0.980
Comorbidity				
Hypertension	35 (41.7)	7 (25.9)	28 (49.1)	0.044
Diabetes	14 (16.7)	5 (18.5)	9 (15.8)	>0.999
Cardiocerebrovascular diseases	20 (23.8)	3 (11.1)	17 (29.8)	0.060
Pulmonary diseases	8 (9.5)	4 (14.8)	4 (7.0)	0.460
Tumor subtypes				0.405
Adenocarcinoma	33 (39.3)	8 (29.6)	25 (43.9)	
Squamous cell carcinoma	44 (52.4)	17 (63.0)	27 (47.4)	
Others	7 (8.3)	2 (7.4)	5 (8.8)	
Tumor stage				0.828
III	45 (53.6)	14 (51.9)	31 (54.4)	
IV	39 (46.4)	13 (48.1)	26 (45.6)	
Treatment history				
Previous chemotherapy	28 (33.3)	10 (37.0)	18 (31.6)	0.620
Previous radiotherapy	12 (14.3)	2 (7.4)	10 (17.5)	0.365
Previous TKIs	16 (19.0)	2 (7.4)	14 (24.6)	0.062
Previous immunotherapy	8 (9.5)	0	8 (14.0)	0.099
Radiological features				
Tumor diameter (cm)	6.5±2.7	6.6±2.9	6.4±2.6	0.677
Location				0.359
Lower or middle lobe	34 (40.5)	9 (33.3)	25 (43.9)	
Upper lobe	50 (59.5)	18 (66.7)	32 (56.1)	
Extrapulmonary metastases	28 (33.3)	8 (29.6)	20 (35.1)	0.620
Malignant pleural effusion	9 (10.7)	4 (14.8)	5 (8.8)	0.647
Tumor number				0.210
1	70 (83.3)	25 (92.6)	45 (78.9)	
≥2	14 (16.7)	2 (7.4)	12 (21.1)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Overall (n=84)	Group A (n=27)	Group B (n=57)	P-value
Laboratory examinations				
WBC (×10^9/L)	7.9±2.7	8.5±2.7	7.5±2.6	0.120
PLT (×10^9/L)	269.8±91.8	292±76.8	259.3±97.0	0.128
PT (s)	11.8±1.5	11.7±1.0	11.8±1.7	0.821
Immunotherapy related factors				
Types	/	/	/	/
Sintilimab	/	9 (33.3)	/	/
Camrelizumab	/	13 (48.1)	/	/
Others	/	5 (18.5)	/	/
Courses of PD-1 blockade	/	7.6±7.3	/	/
DEB-BACE/BAI related factors				
Diameter of microsphere (μm)				0.060
100–300	12 (14.3)	2 (7.4)	10 (17.5)	
300–500	70 (83.3)	23 (85.2)	47 (82.5)	
500–700	2 (2.4)	2 (7.4)	0	
Number of embolized arteries	1.2±0.4	1.3±0.4	1.1±0.4	0.230
DEB-BACE/BAI cycles	2.0±1.3	1.9±1.1	2.0±1.4	0.722
Cycles of combination therapy	/	2.5±1.8	/	/

Frequencies and percentages are reported for categorical variables and mean ± SD are reported for continuous variables. Group A: combination therapy group; Group B: DEB-BACE/BAI group. ECOG, Eastern Cooperation Oncology Group; TKIs, tyrosine kinase inhibitors; WBC, white blood cell; PLT, platelet; PT, prothrombin time; PD-1, programmed cell death protein 1; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; BAI, bronchial artery infusion chemotherapy.

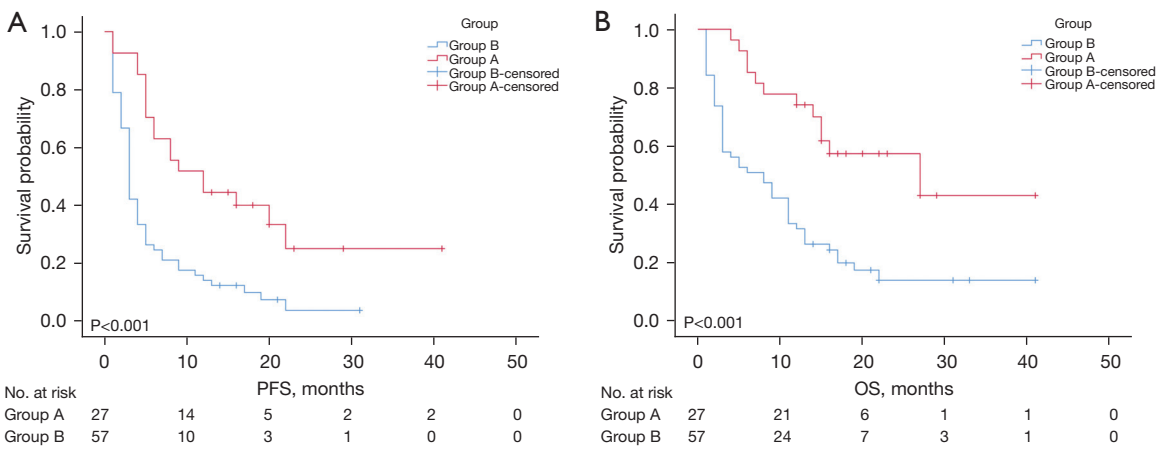

Figure 2 Comparison of median PFS or OS between groups A and B. (A) The estimated median PFS was 12.0 months for patients in group A, while that was 3.0 months for patients in group B. (B) The estimated median OS was 27.0 months for patients in group A, while that was 8.0 months for patients in group B. Group A: combination therapy group; Group B: DEB-BACE/BAI group. PFS, progression-free survival; OS, overall survival; NSCLC, non-small cell lung cancer; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; BAI, bronchial artery infusion chemotherapy.

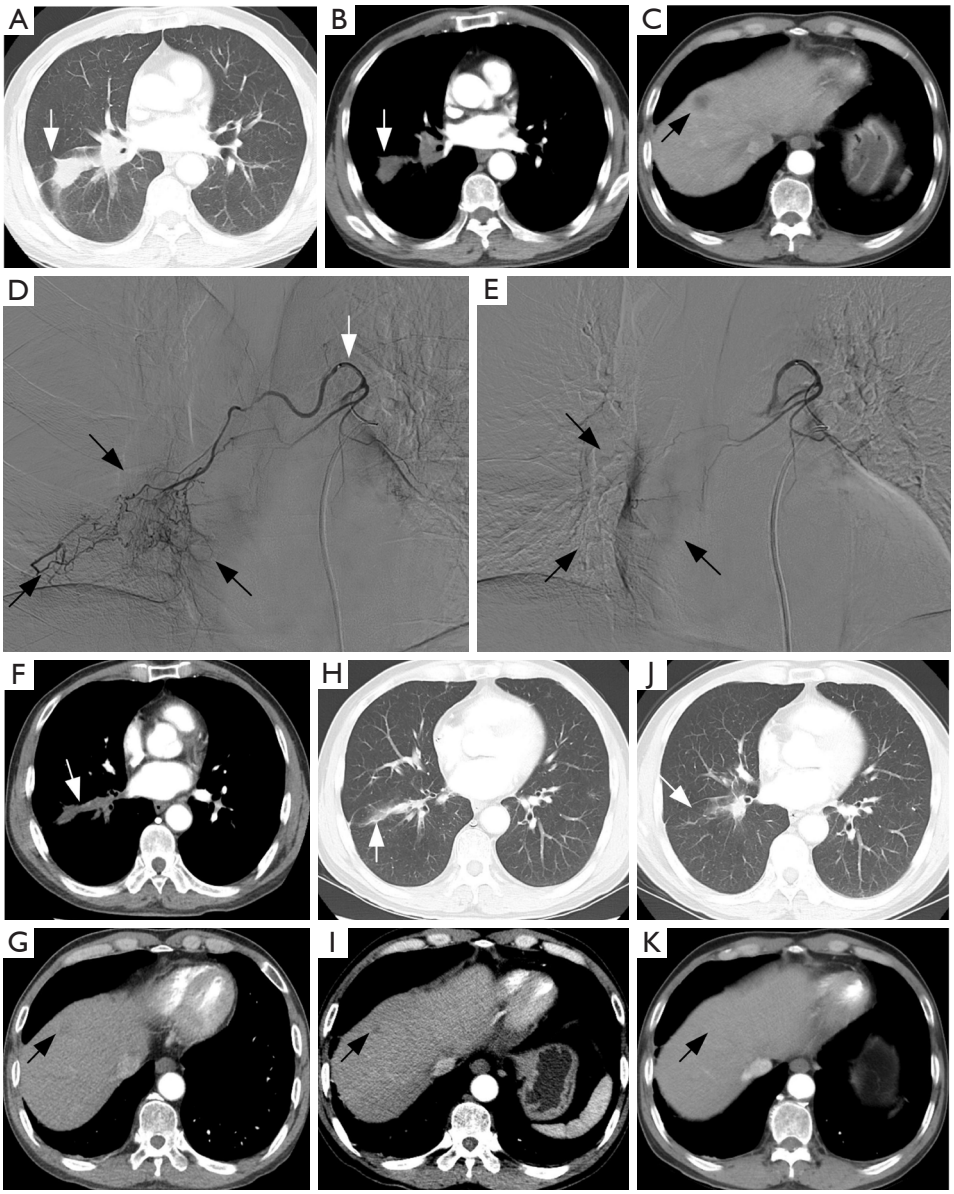

Figure 3 A typical case of advanced NSCLC treated with DEB-BACE/BAI plus PD-1 blockade. (A,B,C) A patient with tumor subtype of adenocarcinoma and primary tumor stage of IV (T1N2M1) has received first-line systemic chemotherapy (pemetrexed plus carboplatin) and anti-angiogenesis therapy (bevacizumab). The CT scans presented with the enlarged pulmonary lesion (white arrow), a new diagnosis of liver metastasis (black arrow), which reveals the resistance to standard treatments. (D) DEB-BACE/BAI was undergone, with a microcatheter being used for super-selective catheterization (white arrow). Right bronchial artery was detected as the tumor-feeding artery and abundant tumor staining was found during the angiography (black arrow). The 300–500 μm CalliSpheres microspheres loaded with gemcitabine (800 mg) were injected into the target arteries via microcatheter for chemoembolization (white arrow). (E) The procedure was terminated when the disappearance of tumor staining (black arrow). A total of 3 cycles of DEB-BACE/BAI and concurrent PD-1 blockades of camrelizumab (200 mg) were performed and additional 6 cycles of immunotherapy were administered per month. (F,G) The CT scans at 3 months after the first DEB-BACE/BAI revealed a decrease in tumor size (from 2.4 to 1.6 cm, white arrow) and extrapulmonary metastases (black arrow), and showed a PR in response. (H,I) The 6-month CT scans revealed a continued decrease in the primary lesion (white arrow) and metastases (black arrow). (J,K) The 15-month CT scans revealed a continuous reduction of tumor size (white arrow) and almost disappearance of extrapulmonary metastases (black arrow). NSCLC, non-small cell lung cancer; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; BAI, bronchial artery infusion chemotherapy; PD-1, programmed cell death protein 1; CT, computed tomography.

Table 2 Details of outcomes between groups A and B

Variables	Overall (n=84)	Group A (n=27)	Group B (n=57)	P value
Response, N (%)				<0.001
CR	/	/	/	/
PR	15 (17.9%)	11 (40.7%)	4 (7.0%)	
SD	38 (45.2%)	15 (55.6%)	23 (40.4%)	
PD	31 (36.9%)	1 (3.7%)	30 (52.6%)	
DCR (%)	63.1 (53/84)	96.3 (26/27)	47.4 (27/57)	<0.001
Status, N (%)				<0.001
Survival	25 (29.8%)	15 (55.6%)	10 (17.5%)	
Death	59 (70.2%)	12 (44.4%)	47 (82.5%)	
PFS rate (%)				
1 year	23.8 (20/84)	44.4 (12/27)	14.0 (8/57)	0.002
2 years	3.6 (3/84)	7.4 (2/27)	1.8 (1/57)	0.241
OS rate (%)				
1 year	45.2 (38/84)	74.1 (20/28)	31.6 (18/57)	<0.001
2 years	8.3 (7/84)	14.8 (4/28)	5.3 (3/57)	0.291

Group A: combination therapy group; Group B: DEB-BACE/BAI group. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; BAI, bronchial artery infusion chemotherapy.

Table 3 Univariate and multivariate analyses for PFS in advanced NSCLC treated with DEB-BACE/BAI

Variables	Univariate analysis		Multivariate analysis	
	Estimated median PFS (95% CI), months	P value*	HR (95% CI)	P value**
Immunotherapy		<0.001		<0.001
Yes	12.0 (5.252–18.748)		0.322 (0.182–0.569)	
No	3.0 (2.478–3.522)		1	
Tumor diameter		0.013		0.013
<6 cm	6.0 (2.557–9.443)		1.878 (1.140–3.092)	
≥6 cm	4.0 (3.209–4.791)		1	
Tumor number		0.001		
1	5.0 (3.982–6.018)			
≥2	2.0 (0.533–3.467)			
DEB-BACE/BAI cycles		0.003		0.012
1	3.0 (2.256–3.744)		1	
≥2	8.0 (4.349–11.651)		0.536 (0.330–0.870)	

*, log-rank test was used; **, Cox proportional hazards regression analysis was used. PFS, progression-free survival; NSCLC, non-small cell lung cancer; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; BAI, bronchial artery infusion chemotherapy; CI, confidence interval; HR, hazard ratio.

Table 4 Univariate and multivariate analyses for OS in advanced NSCLC treated with DEB-BACE/BAI

Variables	Univariate analysis		Multivariate analysis	
	Estimated median OS (95%CI), months	P value*	HR (95%CI)	P value**
Immunotherapy		<0.001		<0.001
Yes	27.0 (5.267–48.733)		0.307 (0.160–0.589)	
No	8.0 (3.382–12.618)		1	
Extrapulmonary metastases		0.017		0.041
Yes	3.0 (0.000–6.111)		1	
No	13.0 (8.530–17.470)		1.787 (1.024–3.118)	
Tumor diameter		0.017		0.021
<6 cm	17.0 (8.700–25.300)		1.875 (1.102–3.190)	
≥6 cm	7.0 (3.285–10.715)		1	
Tumor number		0.037		
1	11.0 (5.896–16.104)			
≥2	3.0 (0.000–10.334)			
DEB-BACE/BAI cycles		<0.001		0.020
1	3.0 (0.961–5.039)		1	
≥2	15.0 (10.991–19.009)		0.527 (0.307–0.904)	

*, log-rank test was used; **, Cox proportional hazards regression analysis was used. OS, overall survival; NSCLC, non-small cell lung cancer; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; CI, confidence interval; HR, hazard ratio; BAI, bronchial artery infusion chemotherapy.

performed. In addition, our study also included patients with ECOG score of 3 and old age (≥75 years) and found that these 2 factors were not correlated with the PFS or OS, which indicated that the combination regimens were also effective for those patients. In terms of AEs, the combination therapy of DEB-BACE/BAI and PD-1 blockades did not increase the overall incidence rate of AEs when compared with DEB-BACE/BAI, which indicated the safety.

ICIs are mainly based on the mechanisms that (I) PD-L1 is expressed on tumor cells whereas PD-1 is expressed on the T cell surface, the binding of PD-1/PD-L1 lead to immune avoidance, and (II) ICIs could inhibit the binding and improve the immune response (8). In 2015, the KEYNOTE-001 trial attempted pembrolizumab in 495 advanced NSCLC patients with PD-L1 expression ≥50%, and found a median OS of 12.0 months, which contributed to the approval of PD-1 blockade as a treatment option for advanced NSCLC (26), and was further validated by KEYNOTE-010 and KEYNOTE-024 that compared the pembrolizumab with systemic chemotherapy in NSCLC, with the 5-year OS rate up to 32% (27,28). In addition, several trials have verified the effectiveness of camrelizumab for advanced NSCLC with treatment history, or sintilimab as an effective neoadjuvant approach for resectable NSCLC (29,30).

Some chemotherapeutic agents (such as gemcitabine) could exhaust myeloid-derived suppressor cells without effects on T cells, whereas some agents (such as anthracycline and cyclophosphamide) could increase T cells and downregulate Tregs (31). Several clinical trials have revealed 2-year OS rates of 37–45% after immunotherapy plus systemic chemotherapy in advanced NSCLC and 23–29% after mono-immunotherapy for NSCLC cases with a treatment history, and 18–29% and 8–16% after mono-chemotherapy in treatment-naïve and previously treated NSCLC patients, respectively (12,32). In addition, the ORIENT 11 and 12 trials indicated a longer median PFS, and the median OS reached 24.2 months for sintilimab plus systemic chemotherapy when compared with placebo or mono-chemotherapy in advanced NSCLC (33,34), whereas a longer median PFS of 8.5–11.3 months after the first-line treatment of camrelizumab plus systemic chemotherapy was

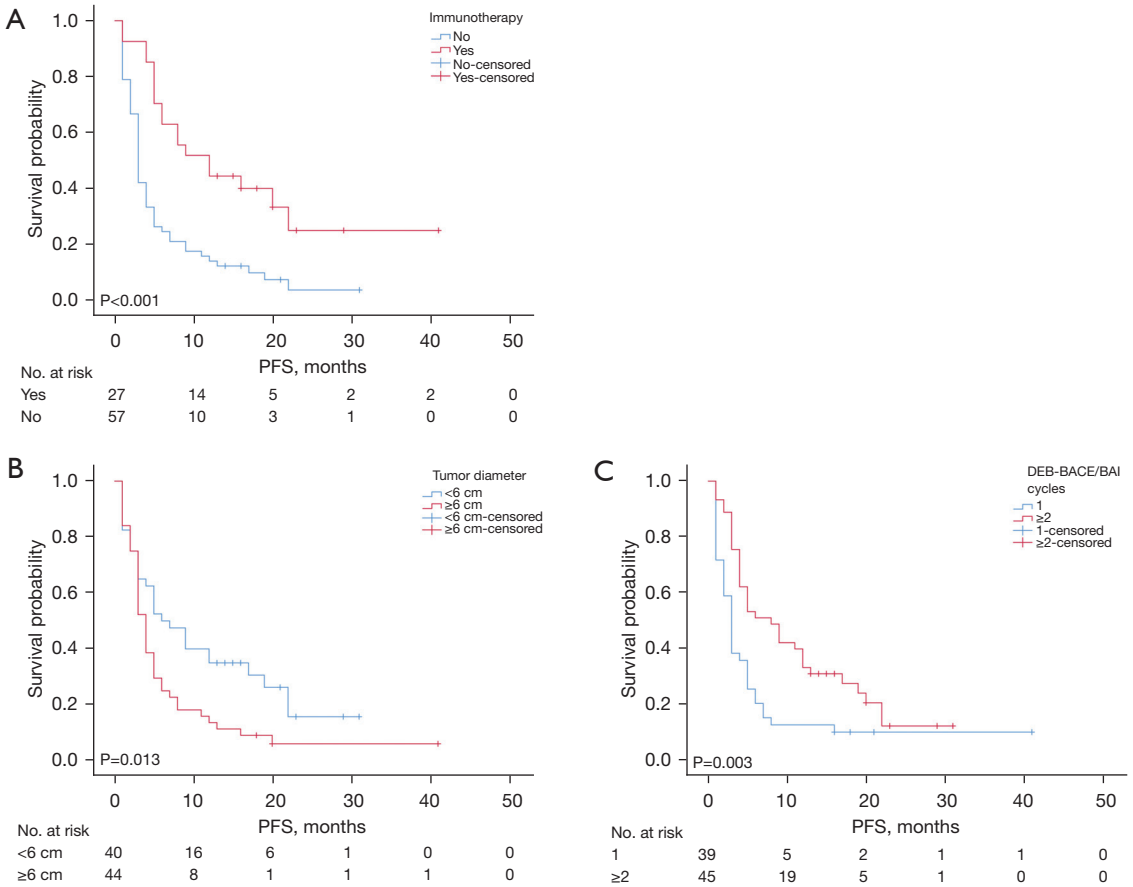

Figure 4 Kaplan-Meier analyses of PFS in advanced NSCLC treated with DEB-BACE/BAI. (A) The estimated median PFS was 12 months for patients treated with immunotherapy, compared with 3 months for those patients without. (B) The estimated median PFS was 6 months for patients with tumor diameter <6 cm, compared with 4 months for patients with tumor diameter ≥6 cm. (C) The estimated median PFS was 3 months for patients treated with a single cycle of DEB-BACE/BAI, compared with 8 months for those patients treated with multiple cycles. PFS, progression-free survival; NSCLC, non-small cell lung cancer; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; BAI, bronchial artery infusion chemotherapy.

also found in advanced NSCLC (35,36). In recent years, systemic chemotherapy plus ICIs was recommended as the first-line treatment for advanced and oncogenes-wild NSCLC (4). Nevertheless, 2 meta-analyses found that the incidence rate of SAEs was 64.9% for NSCLC treated with PD-1 blockades plus systemic chemotherapy whereas it was 37.0% for NSCLC treated with mono-chemotherapy (13,37), which indicates the limited tolerance of the former. In the KEYNOTE-042 trial, pembrolizumab monotherapy showed a similar median OS (13.4 *vs.* 12.1 months) but a significantly lower incidence of SAEs (18% *vs.* 41%) when compared with mono-chemotherapy, which reveals that mono-immunotherapy might be suitable for patients who are intolerant to systemic chemotherapy (38). Despite all this, patients with older age, major comorbidities, or poor PS are usually excluded from clinical trials because these factors may cause physiological modifications and affect the pharmacokinetics and pharmacodynamics of the drugs. Immunosenescence refers to the changes in immune components and pathways that are correlated with aging. This process may increase the naïve T cells and upregulate the circulating senescent T cells, while reducing the ability to distinguish the antigenic diversity of immune cells (39). Whether immunotherapy is effective for older patients or patients with poor PS remains debatable. In a retrospective study, Nebhan *et al.* (40) analyzed 345 geriatric NSCLC patients (aged ≥80 years) treated with immunotherapy, and found a median OS of 10.9 months, which indicated that

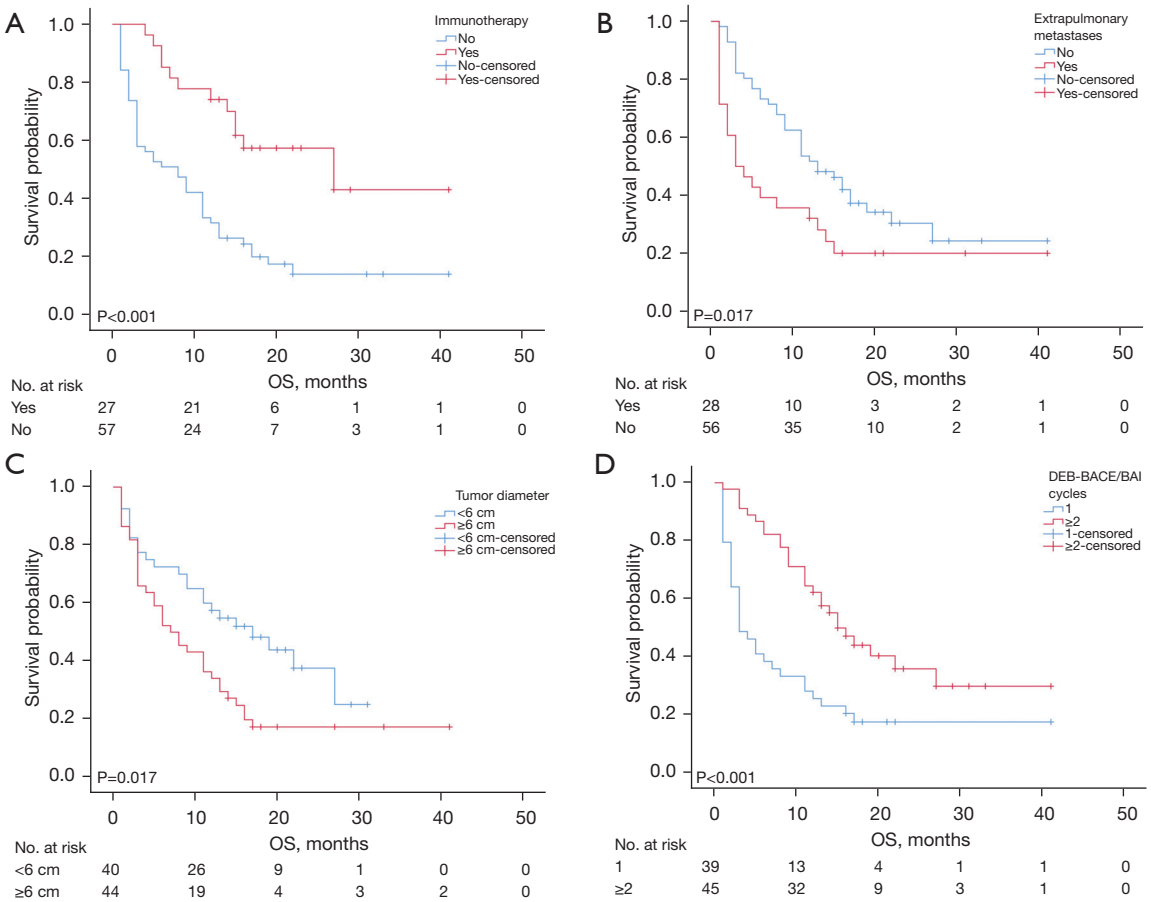

Figure 5 Kaplan-Meier analyses of OS in advanced NSCLC treated with DEB-BACE/BAI. (A) The estimated median OS was 27 months for patients treated with immunotherapy, compared with 8 months for those patients without. (B) The estimated median OS was 3 months for patients with extrapulmonary metastases, compared with 13 months for those patients without. (C) The estimated median OS was 17 months for patients with tumor diameter <6 cm, compared with 7 months for patients with tumor diameter ≥6 cm. (D) The estimated median OS was 3 months for patients treated with a single cycle of DEB-BACE/BAI, compared with 15 months for those patients treated with multiple cycles. OS, overall survival; NSCLC, non-small cell lung cancer; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; BAI, bronchial artery infusion chemotherapy.

mono-immunotherapy did not show inferiority in geriatric patients when compared with younger patients. However, another study reported that only 20% of NSCLC patients responded to mono-immunotherapy (14).

Bronchial artery is the predominantly supplied artery for NSCLC, which lays a foundation for BACE/BAI in NSCLC treatment, with a median OS of 13.1–25.0 months being provided (15). Different from the transient cytotoxic effects of BAI, the DEB microsphere brought about a sustainable method of drug delivery, and precise embolization of tumor-feeding arteries, which lead to tumor ischemia or necrosis and elevated local drug concentration while reducing systemic toxicity (41). Bie *et al.* (16) were the first to attempt gemcitabine-loaded DEB-BACE in 6 NSCLC patients, which achieved a median OS of 16.5 months. Sequential studies have summarized a median PFS and OS of 6.3 and 8.0–15.6 months for advanced NSCLC (15-17). Of these, most patients were systemic chemotherapy refractory/intolerant or refused to receive standard treatments. To some extent, the DEB-BACE/BAI are treatment options with satisfying local efficacy but limited long-term efficacy, and are likely to be improved when combined with a tolerant systemic treatment. In 2021, Li *et al.* (20) attempted DEB-BACE/BAI plus PD-1 blockade in 10 advanced NSCLC patients and found a median PFS of 11.0 months, despite the

Table 5 Details of AEs and between groups A and B

Variables	Overall (n=84)	Group A (n=27)	Group B (n=57)	P value
irAEs				
Grade 1	/		/	/
RCCEP	/	2 (7.4%)	/	/
Colitis	/	1 (3.7%)	/	/
Grade 2	/		/	/
Leukopenia	/	1 (3.7%)	/	/
RCCEP	/	2 (7.4%)	/	/
Pneumonia	/	2 (7.4%)	/	/
Grade 3	/		/	/
Pneumonia	/	3 (11.1%)	/	/
DEB-BACE/BAI related AEs				
Grade 1				
Chest congestion or pain	9 (10.7%)	3 (11.1%)	6 (10.5%)	>0.999
Fever	6 (7.1%)	2 (7.4%)	4 (7.0%)	>0.999
Vomit	2 (2.4%)	1 (3.7%)	1 (1.8%)	0.597
Grade 2				
Chest congestion or pain	5 (6.0%)	2 (7.4%)	3 (5.3%)	>0.999
Fever	6 (7.1%)	2 (7.4%)	4 (7.0%)	>0.999
Myelosuppression	4 (4.8%)	1 (3.7%)	3 (5.3%)	>0.999

Group A: combination therapy group; Group B: DEB-BACE/BAI group. AEs, adverse events; irAEs, immune-related adverse events; RCCEP, reactive cutaneous capillary endothelial proliferation; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; BAI, bronchial artery infusion chemotherapy.

limited follow-up. Then, another study revealed that immunotherapy was associated with a prolonged OS after DEB-BACE for advanced NSCLC (15). The potential mechanisms of superiority for DEB-BACE/BAI combined with PD-1 blockades in this study included the following: (I) chemoembolization-induced tumor necrosis could increase the tumor-associated antigens, recruit antigen-presenting cells (APCs), lower the immune-exhausted effector cytotoxic T cells and Tregs, and upregulate the pro-inflammatory pathways; (II) chemoembolization-induced tumor inflammation contributed to immune recognition and enhanced the antitumor effects; and (III) DEB microspheres delivered gemcitabine sustainably, which might upregulate immunogenic cell death markers based on the chemotherapy-induced inflammation (42).

The incidence rate of SAEs after platinum-based systemic chemotherapy was 37%, as previously reported (13), whereas a milder degree of grade 1–2 DEB-BACE/BAI-related AEs of 36.8% was found in our study. Of these, grade 3–5 irAEs occurred in 11.1% of patients, which was comparable to that of 5–28% as reported (43). All the severe irAEs were IRP, and were significantly lower than the incidence rate of 61.4% for IRP after camrelizumab plus platinum-based chemotherapy as previously reported (37). IRP occupies 35% of immunotherapy-related mortality, with the risk factors of underlying pulmonary diseases (such as interstitial lung diseases, pulmonary fibrosis, and COPD) and tumor invasion into the central airway (44). Generally, grade 3 IRP or higher required steroid treatment, and 70–87% of the patients could recover or improve (44).

Several limitations in this study should be noted. First, there may have been selection bias due to the retrospective nature. Second, this study included patients who were intolerant or resistant to standard treatments,

and heterogeneity may have existed. Third, a comparative group of patients treated with mono-immunotherapy was absent. Fourth, the incomplete information on PD-L1 expression prevented the subgroup analyses, which might reveal a different prognosis after combination regimens. Fifth, this study consists of PD-1 blockades from different manufacturers, and heterogeneity may exist. Finally, a multi-center study with more cases is warranted to validate these findings.

Conclusions

In conclusion, compared with DEB-BACE/BAI, PD-1 blockade plus DEB-BACE/BAI could improve the prognosis for advanced NSCLC despite the associated risk of grade 3 irAEs. The combination regimens are promising and safe approaches for advanced NSCLC.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-287/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-287/coif). 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 institutional ethics review board of Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences. The requirement for patient written informed consent was waived for this retrospective analysis.

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