

Real-World Outcomes and Safety of PD-1 Blockade Rechallenge Strategies After Prior Immunotherapy in Advanced NSCLC: A Retrospective Cohort Study

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Objective: Evidence to guide treatment after progression on immunotherapy remains limited in advanced non-small cell lung cancer (NSCLC). We descriptively report real-world outcomes of two PD-1 rechallenge strategies (PD-1 plus chemotherapy and PD-1 plus anlotinib) using a contemporaneous docetaxel cohort as contextual reference.

Methods: Patients with advanced NSCLC who failed prior immunotherapy were screened retrospectively, 33 patients received PD-1 blockade plus chemotherapy, 31 received PD-1 blockade plus anlotinib and 63 patients treated with docetaxel monotherapy were served as a contextual reference cohort. Outcomes including objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and treatment-related adverse events (TRAEs) were summarized by cohort. Survival outcomes were estimated using Kaplan–Meier methods.

Results: ORR and DCR were 30.3% (95% CI: 15.6%–48.7%) and 84.8% (95% CI: 68.1%–94.9%) in PD-1 plus chemotherapy cohort, 22.6% (95% CI: 9.6%–41.1%) and 80.6% (95% CI: 62.5%–92.5%) in PD-1 plus anlotinib cohort, 15.9% (95% CI: 7.9%–27.3%) and 54.0% (95% CI: 40.9%–66.6%) in docetaxel cohort. Median DoR among responders was 6.9 months (95% CI: 0.7–13.1), 7.1 months (95% CI: 5.0–9.2), and 3.1 months (95% CI: 1.9–4.3), respectively. Median PFS was 7.0 months (95% CI: 0.7–13.3), 6.5 months (95% CI: 2.2–10.8), and 3.3 months (95% CI: 2.2–4.4), and median OS was 17.8 months (95% CI: 8.0–27.6), 16.8 months (95% CI: 13.9–19.7), and 9.5 months (95% CI: 4.8–14.2), respectively. Any-grade TRAEs occurred in 84.8%, 80.6%, and 81.0%, and grade ≥ 3 TRAEs were 42.4%, 41.9%, and 34.9%, respectively. No treatment-related deaths were observed.

Conclusion: PD-1 rechallenge strategies showed measurable antitumor activity and manageable safety profile in a subset of previously immunotherapy-treated advanced NSCLC. Limitations existed in this study and the findings were descriptive and hypothesis-generating and should be interpreted cautiously because treatment selection was non-random and important confounders might be incompletely captured.

Keywords: non-small cell lung cancer, previously immunotherapy-treated, PD-1 blockade, chemotherapy, anlotinib, docetaxel, therapeutic outcomes, safety

Introduction

Lung cancer remained the leading cause of cancer-related mortality worldwide with an estimated 2.48 million new cases and 1.80 million deaths in 2022.^{1,2} In China, there was an estimated 1.06 million new cases and 0.73 million deaths in 2022.³ Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers, and many patients present with advanced disease.⁴ Immune checkpoint inhibitors (ICIs) targeting programmed death-1 (PD-1) or programmed

death ligand-1 (PD-L1) have transformed the first-line therapy and can achieve durable response in a subset of patients.⁵ As a result, ICIs become the first-line standard of care for metastatic NSCLC without driver mutations, either alone or combined with chemotherapy, and a total of 9 ICIs-based regimens were approved as the first-line treatment by September 2025 in China.⁶ Unfortunately, fewer than 50% patients achieve an objective response, and only approximately 20–30% achieve survival beyond 36 months in unselected populations.⁷ Many patients ultimately experience progression due to primary or acquired resistance. The optimal therapeutic approach following progression on initial ICI therapy represents a critical unmet need in thoracic oncology.⁸ In routine practice, taxane-based chemotherapy remains commonly used after ICIs failure. Docetaxel, either as monotherapy or combined with ramucirumab, is frequently selected as a subsequent-line option and is consistent with guideline-concordant pathways.⁹ Historically, outcomes with second-line docetaxel have been modest (ORR ~10–15%, median PFS ~3.0–4.0 months, and median OS <10 months).¹⁰ In current therapeutic landscape, many patients receive ICIs with or without chemotherapy as initial treatment, upon progression, docetaxel is often used as salvage therapy. Unfortunately, outcome with docetaxel after immunotherapy failure is still disappointing. Retrospective study reported that docetaxel monotherapy in post-immunotherapy setting might yield ORR of 12.8%, median PFS of 3.7 months and median OS of 11.8 months,¹¹ underscoring an unmet need to improve disease control and survival beyond this benchmark. Attempts to surpass docetaxel in the post-ICIs setting yielded mixed outcomes: REVEL trial demonstrated that adding ramucirumab to docetaxel improved OS and PFS versus docetaxel alone.¹² More recently, antibody–drug conjugates (ADCs) demonstrated activity after platinum and ICIs. In TROPION-Lung01, the TROP2-directed ADC datopotamab deruxtecan significantly prolonged PFS versus docetaxel. However, the study did not meet its OS endpoint at the primary analysis, highlighting both incremental progress and the persistent limits of benefit in this setting.¹¹

Immunotherapy rechallenge has been explored as a potential strategy in selected patients, although its role remains uncertain. Retrospective series and real-world cohorts reported responses and survival estimates with ICIs rechallenge in selected patients, particularly those with prior clinical response to ICIs and preserved performance status.¹³ However, outcomes were heterogeneous, and the optimal rechallenge regimen (ICIs monotherapy vs combination approaches) remained unclear. Notably, one retrospective study reported limited activity with ICIs monotherapy rechallenge (ORR 2.9%, median PFS 2.7 months, and median OS 7.5 months).¹⁴ Therefore, combination approaches have been explored to evaluate whether outcomes may differ in selected settings. Cytotoxic chemotherapy may promote immunogenic cell death and increase tumor antigen release and presentation, which can enhance T-cell priming, chemotherapy may also reduce immunosuppressive cell populations (eg, myeloid-derived suppressor cells and regulatory T cells), potentially shifting the tumor microenvironment toward a more inflamed phenotype.¹⁵ Antiangiogenic agents such as anlotinib may normalize tumor vasculature and modulate the tumor microenvironment, which may influence immune activity.¹⁶ Preclinical and translational data suggests that VEGF-driven angiogenesis promotes an immunosuppressive microenvironment, whereas VEGF blockade may normalize abnormal tumor vasculature, facilitate infiltration of effector T cells and reduce immunosuppressive myeloid cells.¹⁶ The Phase III CONTACT-01 trial (atezolizumab plus cabozantinib vs docetaxel after prior chemo-immunotherapy) did not improve OS compared with docetaxel (median OS: 10.7 vs 10.5 months). And PFS was modestly longer (median PFS: 4.6 vs 4.0 months), highlighting the difficulty of improving outcomes in this setting.¹⁷ These findings indicate two key points: first, docetaxel remains an active and difficult-to-beat comparator after ICIs exposure; second, not all antiangiogenic partners are equivalent and regimen-specific biology and patient selection likely determine outcomes.

In previously immunotherapy-treated advanced NSCLC, PD-1 blockade can be combined with chemotherapy or anlotinib (an antiangiogenic TKI approved in China for third-line NSCLC). The phase III ALTER0303 trial demonstrated anlotinib significantly improved PFS and OS versus placebo in refractory NSCLC.¹⁸ A growing body of real-world evidence investigated anlotinib combined with PD-1 blockade after prior immunotherapy exposure. Several observational studies reported promising effectiveness and manageable safety profile for ICIs plus anlotinib in previously ICIs-treated advanced NSCLC, which found improved disease control rate (DCR) and PFS compared with historical expectations for PD-1 blockade rechallenge or for chemotherapy alone.¹⁹ A recent study retrospectively analyzed 107 advanced NSCLC patients who had progressed on prior ICIs and received either anlotinib-based regimens or single-agent chemotherapy. Anlotinib-based regimens showed higher disease control and longer survival versus chemotherapy (DCR: 79.6% vs

54.7%, $P=0.006$), median OS: 16.1 vs 10.1 months, $P=0.015$) with comparable safety, suggesting that anlotinib-based regimens were encouraging and tolerable.⁴ Another retrospective analysis found that patients with NSCLC who had received prior immunotherapy derived greater benefit from subsequent ramucirumab plus docetaxel treatment with median PFS of 5.7 months among prior ICIs exposure subgroup.²⁰ Despite heterogeneity and predominantly nonrandomized designs, the overall signal supports a biologic rationale whereby antiangiogenic modulation may recondition the tumor microenvironment and restore sensitivity to PD-1 blockade.

Additionally, rechallenge after immune-related adverse events (irAEs) requires careful risk-benefit assessment and multidisciplinary management. In carefully selected patients, ICIs may be restarted after resolution of grade 1–2 toxicities and steroid tapering. However, recurrence risk varies by irAEs type and severity, and robust prospective evidence in NSCLC is still lacking.²¹ Moreover, differences in prior ICIs exposure, initial response depth/duration, treatment-free intervals, and comorbidities complicate cross-trial comparisons, reinforcing the importance of real-world evidence that mirrors routine practice.

Given this rationale, we hypothesize that continuing PD-1 blockade-based regimens may provide potential anti-tumor activity in the post-immunotherapy setting. Therefore, this retrospective study is to explore the effectiveness and tolerability of PD-1 blockade plus chemotherapy and PD-1 blockades plus anlotinib combination in previously immunotherapy-treated advanced NSCLC using a contemporaneous docetaxel-treated cohort.

Materials and Methods

Study Design and Eligibility Criteria

This was a retrospective, observational cohort study describing real-world effectiveness and safety outcomes of PD-1 blockade plus chemotherapy and PD-1 blockade plus anlotinib combination in previously immunotherapy-treated advanced NSCLC using a contemporaneous docetaxel-treated cohort, which followed the strengthening the reporting of observational studies in epidemiology (STROBE) recommendations: the full checklist was consulted when planning the analysis set, defining variables and structuring the report.²² Medical records from October 2018 to March 2025 for patients with advanced NSCLC who previously received ICIs-based therapy and subsequently underwent either a PD-1 blockade-based regimens or docetaxel monotherapy were screened retrospectively. Key inclusion criteria were: (1) Histologically confirmed NSCLC, stage of IIIB–IV; (2) Prior exposure to ICIs treatment for at least one cycle (nivolumab, pembrolizumab, camrelizumab, sintilimab, toripalimab, tislelizumab, atezolizumab/durvalumab or other immunotherapy when applicable) with subsequent treatment failure due to disease progression or intolerance as documented by investigators; (3) After prior ICIs failure, receipt of ≥ 1 cycle of one index strategy (PD-1 blockade plus platinum or non-platinum chemotherapy or PD-1 blockade plus anlotinib) or docetaxel monotherapy in clinical practice; (4) ECOG performance status ≤ 2 score; (5) Age ≥ 18 years; (6) At least one measurable target lesion per RECIST v1.1; (7) Available clinical data for baseline characteristics, outcome assessment, safety reporting and follow-up. Main exclusion criteria were: (1) Another concurrent malignancy (other than NSCLC); (2) Life-threatening comorbidities expected to substantially limit survival independent of cancer; (3) Actionable oncogenic alterations for which targeted therapy would be standard (eg, EGFR, ALK, ROS1); (4) Concurrent systemic anticancer therapy administered during the index regimen (other than the components defining the index strategy); (5) Incomplete records precluding reliable ascertainment of key outcomes. Overall, 127 patients met the eligibility criteria and were included in the analysis (PD-1 blockade plus chemotherapy, $n=33$; PD-1 blockade plus anlotinib, $n=31$; docetaxel monotherapy, $n=63$). Treatment allocation was not randomized, it was based on physician's judgment and patient preference in real-world practice.

All included patients had previously received at least one cycle of ICIs-based therapy and subsequently experienced treatment failure, defined as either: (a) radiologically confirmed disease progression according to RECIST version 1.1, or (b) discontinuation of ICIs because of irAEs or other treatment intolerance documented by the investigators. RECIST v1.1 criteria were also used to evaluate the best tumor response and to define survival data in the present analysis.

The primary analysis of this study was OS, other analysis included ORR, DCR, duration of response (DoR), PFS and tolerability of the treatments. The study was approved by the institutional ethics committee of Fuwai Central China

Cardiovascular Hospital (Approved number: 202405). Due to the retrospective design, informed consent was waived for patients in accordance with the Declaration of Helsinki. All patient information was anonymized prior to analysis, and confidentiality was maintained throughout the study.

Analytic Framing

This retrospective cohort study was intended to be descriptive and hypothesis-generating. Because treatment assignment occurred in routine practice and important determinants of treatment choice might be incompletely captured, the contemporaneous docetaxel cohort was presented as a contextual reference rather than an evidentiary comparator. Accordingly, we emphasized strategy-specific outcome descriptions and avoided causal or comparative-effectiveness conclusions, consistent with observational reporting guidance.²²

Directed Acyclic Graph (DAG)-Style Causal Narrative (Textual)

In routine practice, selection of post-immunotherapy failure treatment strategies (PD-1 plus chemotherapy, PD-1 plus anlotinib or docetaxel) might be influenced by baseline prognosis and clinical context. We assumed that patient factors (age, gender, ECOG performance status, smoking history), disease factors (histology, stage, metastatic burden), and treatment-history factors (number of prior systemic therapy lines, characteristics and response to prior immunotherapy and duration of previous ICIs treatment) might affect both treatment selection and downstream outcomes (response and survival), and therefore represented potential confounders. Post-index therapies might lie on the causal pathway between the index strategy and OS and were considered potential mediators rather than baseline confounders. Thus, any between-cohort differences should be interpreted cautiously.

Treatments

Patients received one of the following index strategies per routine care: PD-1 blockade plus chemotherapy, PD-1 blockade plus anlotinib and Docetaxel monotherapy (contextual reference). PD-1 blockade included commercially available agents approved in China: tislelizumab, sintilimab, camrelizumab and pembrolizumab, which was administered intravenously at the dosage of 200 mg on day 1 of each 21-day cycle, continued until disease progression or unacceptable toxicity. Chemotherapy in PD-1 blockade plus chemotherapy included pemetrexed 500 mg/m² for non-squamous NSCLC or docetaxel 75 mg/m² for other types on day 1 of each 21-day cycle, continued until disease progression or unacceptable toxicity. Anlotinib in PD-1 blockade plus anlotinib was given orally at 8–12 mg once daily on a 2-weeks-on, 1-week-off cycle of each 21-day cycle, continued until disease progression or unacceptable toxicity. Patients in contemporaneous docetaxel-treated cohort received docetaxel typically at 75 mg/m² on day 1 of each 21-day cycle (with dose adjustments as needed). Treatment was continued until disease progression or unacceptable toxicity. Dose interruptions or reductions of treatment were recorded as per routine care.

Data Collection and Outcomes Assessment

Baseline demographic and clinical characteristics were collected from the electronic medical records, including age, gender, smoking history, ECOG performance status, histology, disease stage, sites of metastasis, previous treatments, and time since the last immunotherapy. Tumor PD-L1 status and detailed response metrics to prior ICI therapy were not available for a substantial proportion of patients and were therefore not used as core baseline characteristics. Effectiveness outcomes included ORR, DCR, DoR, PFS and OS. Radiologic assessments were typically performed every 6–8 weeks per routine practice. Tumor responses were assessed according to RECIST 1.1 criteria: complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). ORR was defined as the proportion of patients achieving CR or PR. DCR was the proportion achieving CR, PR, or SD as best response. Patients who were not available for evaluable response data were considered non-responders and were treated in the denominator when calculating therapeutic response.

Index Date, Follow-Up and Censoring Rules

The index date was defined as the date of initiation of the index strategy after prior immunotherapy failure: PD-1 plus chemotherapy, PD-1 plus anlotinib or docetaxel (contextual reference cohort). Subsequently, follow-up started on the index date for all time-to-event endpoints by clinical visits or phone calls. This alignment of eligibility, treatment assignment and start of follow-up was chosen to avoid time-origin misclassification and reduce risk of immortal time bias. For patients who achieved an objective response, DoR was defined as the time from the first documented CR or PR to disease progression or any-cause death, responders without an event were censored at the last tumor assessment. PFS was defined as the time from index date to radiographic/clinical progression or death, whichever occurred first, patients without an event were censored at the date of last disease assessment. OS was defined as time from index date to death from any cause. Patients alive at last contact were censored at the date of last follow-up.²³ The data cut-off date of this study was August 25, 2025.

Safety Assessment

Safety was assessed from the treatment initiation date (first administration of the corresponding drugs) until the end of the last dose or last follow-up, whichever occurred first. Adverse events (AEs) were extracted from medical records and summarized separately for PD-1 plus chemotherapy, PD-1 plus anlotinib and docetaxel. Severity was graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0) where explicit grades were available.

Treatment-related adverse events (TRAEs) were defined as events documented by the treating physician as possibly, probably or definitely related to the study treatment. Composite categories were predefined: “hematologic toxicity” included anemia, leukopenia, neutropenia, and thrombocytopenia; “hepatotoxicity” included ALT/AST elevation and/or bilirubin elevation. When detailed CTCAE grading was not available for an event, the event was still captured as an all-grade AEs based on clinical documentation, this limitation was acknowledged.

In particular, we paid attention to irAEs in the PD-1 blockade plus chemotherapy or PD-1 blockade plus anlotinib group (such as pneumonitis, hepatitis and endocrinopathies), as well as classical chemotherapy toxicities (myelosuppression, neuropathy, etc). Any events leading to treatment discontinuation or any treatment-related deaths were recorded and analyzed. An adverse events table summarized the incidence of all-grade and grade ≥ 3 TRAEs in three cohorts.

Missing Data

Missing data was summarized for each variable and by cohort ([Table S1](#)). For descriptive summaries, observed data were reported. For tumor response assessment, patients without evaluable imaging due to early clinical progression or intolerance before the first scheduled radiological scan were coded as not available (NA) and were treated as non-responders in ORR/DCR calculations. Information on first subsequent-line therapy after the index regimen was incomplete for a subset of patients because of unavailable follow-up documentation in real-world records. Given the retrospective nature and limited sample size, we used observed-data summaries without multiple imputation and acknowledged the potential bias introduced by missingness.

Statistical Analysis

Statistical analyses were performed using SPSS v25.0 and Stata v14.0. All eligible patients who initiated an index strategy after prior ICIs failure were analyzed in the corresponding cohort: PD-1 blockade plus chemotherapy, PD-1 blockade plus anlotinib, or the docetaxel contextual-reference cohort. Baseline characteristics were summarized using counts (percentages) for categorical variables and median (range) for continuous variables as appropriate. To describe differences in baseline distributions across cohorts, we reported standardized mean differences (SMDs) rather than relying on hypothesis testing, which described the magnitude of imbalance and were less sensitive to sample size. Time-to-event outcomes (DoR, PFS, OS) were summarized descriptively using the Kaplan–Meier method, reporting medians with 95% confidence interval (CI) and presenting survival curves with numbers at risk.

Restricted mean survival time (RMST): as a robustness summary for OS, we estimated the RMST up to a prespecified truncation time (t), defined as the area under the Kaplan–Meier survival curve from 0 to t . RMST represented the average

survival time accrued within $[0, t]$ and provided an interpretable alternative summary when proportional hazards assumptions might be questionable. We prespecified $t=24$ months (RMST (24)), and RMST estimated were reported with 95% CI of the three cohorts using Stata v14.0.

A pre-specified confounder set was defined a priori based on clinical plausibility and factors expected to influence both treatment selection and outcomes. The covariates (where available) included: age, gender, smoking status, ECOG performance status, histology, staging, number of metastatic lesions, prior lines of systemic therapy, characteristics of prior immunotherapy exposure and relevant baseline laboratory/organ function indicators. This covariate set was used to contextualize treatment selection and, if exploratory adjusted analyses were performed, to adjust associations without causal interpretation. No single P threshold was used to claim statistical significance, where P was reported, they were presented as descriptive summaries and interpreted in the context of effect sizes and uncertainty.

Results

Baseline Characteristics

A total of 127 patients met eligibility criteria: 33 in the PD-1 plus chemotherapy cohort, 31 in the PD-1 plus anlotinib cohort, and 63 in the docetaxel cohort. Baseline demographics and disease characteristics demonstrated acceptable small difference between the PD-1 blockade rechallenge cohorts and docetaxel cohorts as shown in Table 1 (all $SMD < 0.200$). Several characteristics showed non-negligible differences across cohorts, consistent with non-random treatment selection in routine practice ($SMDs > 0.100$).

Table 1 Baseline Clinical Characteristics in the Three Cohorts

Baseline Characteristics	PD-1 plus Chemotherapy (N=33)	PD-1 plus Anlotinib (N=31)	Docetaxel (N=63)	SMD1	SMD2
Age (years)					
Median (range)	65 (22–80)	67 (24–82)	65 (19–79)	0.054	0.086
Gender					
Male	22 (66.7)	20 (64.5)	39 (61.9)	0.099	0.054
Female	11 (33.3)	11 (35.5)	24 (38.1)		
ECOG performance status					
0-1	23 (69.7)	21 (67.7)	45 (71.4)	0.038	0.080
2	10 (30.3)	10 (32.3)	18 (28.6)		
Pathological Staging					
IIIb	4 (12.1)	3 (9.7)	8 (12.7)	0.018	0.096
IV	29 (87.9)	28 (90.3)	55 (87.3)		
Histology					
Adenocarcinoma	19 (57.6)	17 (54.8)	34 (54.0)	0.073	0.018
Squamous carcinoma	14 (42.4)	14 (45.2)	29 (46.0)		
Smoking Status					
Non-smoker	5 (15.2)	3 (9.7)	8 (12.7)	0.071	0.096
Smoker	28 (84.8)	28 (90.3)	55 (87.3)		
Combination with local therapy					
Yes	7 (21.2)	6 (19.4)	15 (23.8)	0.062	0.108
No	26 (78.8)	25 (80.6)	48 (76.2)		
Previous treatment lines					
1	16 (48.5)	12 (38.7)	26 (41.3)	0.145	0.052
≥ 2	17 (51.5)	19 (61.3)	37 (58.7)		
Failure status of previous ICIs					
Progression	24 (72.7)	22 (71.0)	44 (69.8)	0.064	0.025
Intolerance	9 (27.3)	9 (29.0)	19 (30.2)		

(Continued)

Table 1 (Continued).

Baseline Characteristics	PD-I plus Chemotherapy (N=33)	PD-I plus Anlotinib (N=31)	Docetaxel (N=63)	SMD1	SMD2
Previous ICIs regimens					
PD-I	27 (81.8)	24 (77.4)	53 (84.1)	0.061	0.171
PD-L1	6 (18.2)	7 (22.6)	10 (15.9)		
Duration of previous ICIs treatment					
<6 months	18 (54.5)	17 (54.8)	31 (49.2)	0.107	0.113
≥6 months	15 (45.5)	14 (45.2)	32 (50.8)		
Number of metastatic lesions					
≤3	24 (72.7)	22 (71.0)	47 (74.6)	0.043	0.082
>3	9 (27.3)	9 (29.0)	16 (25.4)		

Notes: SMD1 and SMD2 represented PD-I plus chemotherapy versus docetaxel and PD-I plus anlotinib versus docetaxel, respectively. SMDs were reported to quantify between-cohort differences in baseline covariate distributions. Absolute SMD <0.200 were typically considered acceptable small differences.

Abbreviations: ECOG, eastern cooperative oncology group; ICIs, immune checkpoint inhibitors; PD-I, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; SMD, standardized mean difference.

For 33 patients on chemo-immunotherapy cohort, the chemotherapy partner was docetaxel in 19 patients (given concurrently with PD-1 blockade) and pemetrexed in 14 patients (adenocarcinoma cases). The PD-1 blockade used included tislelizumab (n=25, 39.1%), sintilimab (n=19, 29.7%), camrelizumab (n=11, 17.2%) and pembrolizumab (n=9, 14.1%). In docetaxel monotherapy cohort, all 63 patients received single-agent docetaxel as second-line or third-line therapy after immunotherapy.

Tumor Response Outcomes

All patients were evaluable for best tumor response except those who had clinical progression or intolerable toxicity before the first radiological scan (these were considered non-responders for ORR). As shown in Table 2, in the PD-1 plus chemotherapy cohort, best overall response included 0 CR, 10 PR, 18 SD, and 3 PD, response was not evaluable in 2 patients, achieving an ORR of 30.3% (95% CI: 15.6%–48.7%) and a DCR of 84.8% (95% CI: 68.1%–94.9%). In the PD-1 plus anlotinib cohort, best overall response included 0 CR, 7 PR, 18 SD, and 3 PD, response was not evaluable in 3 patients, yielding an ORR of 22.6% (95% CI: 9.6%–41.1%) and a DCR of 80.6% (95% CI: 62.5%–92.5%). In the docetaxel cohort, best overall response included 0 CR, 10 PR, 24 SD, and 22 PD; response was not evaluable in 7 patients, resulting in an ORR of 15.9% (95% CI: 7.9%–27.3%) and a DCR of 54.0% (95% CI: 40.9%–66.6%).

Among patients who achieved objective response (CR or PR), DoR was also evaluated. As exhibited in Figure 1, the median DoR of the 10 responders in PD-1 plus chemotherapy cohort, 7 responders in PD-1 plus anlotinib cohort and 10 responders in docetaxel cohort was 6.9 months (95% CI: 0.7–13.1 months), 7.1 months (95% CI: 5.0–9.2 months) and 3.1 months (95% CI: 1.9–4.3 months), respectively. Notably, several responses in PD-1 plus chemotherapy and PD-1 plus

Table 2 Therapeutic Outcomes in the Three Cohorts

Therapeutic Outcomes	PD-I plus Chemotherapy (N=33)	PD-I plus Anlotinib (N=31)	Docetaxel (N=63)
CR	0	0	0
PR	10	7	10
SD	18	18	24
PD	3	3	22
NA	2	3	7
ORR (95% CI)	30.3% (15.6%-48.7%)	22.6% (9.6%-41.1%)	15.9% (7.9%-27.3%)
DCR (95% CI)	84.8% (68.1%-94.9%)	80.6% (62.5%-92.5%)	54.0% (40.9%-66.6%)

Abbreviations: PD-I, programmed cell death protein 1; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not available; ORR, response rate; DCR, disease control rate; CI, confidence interval.

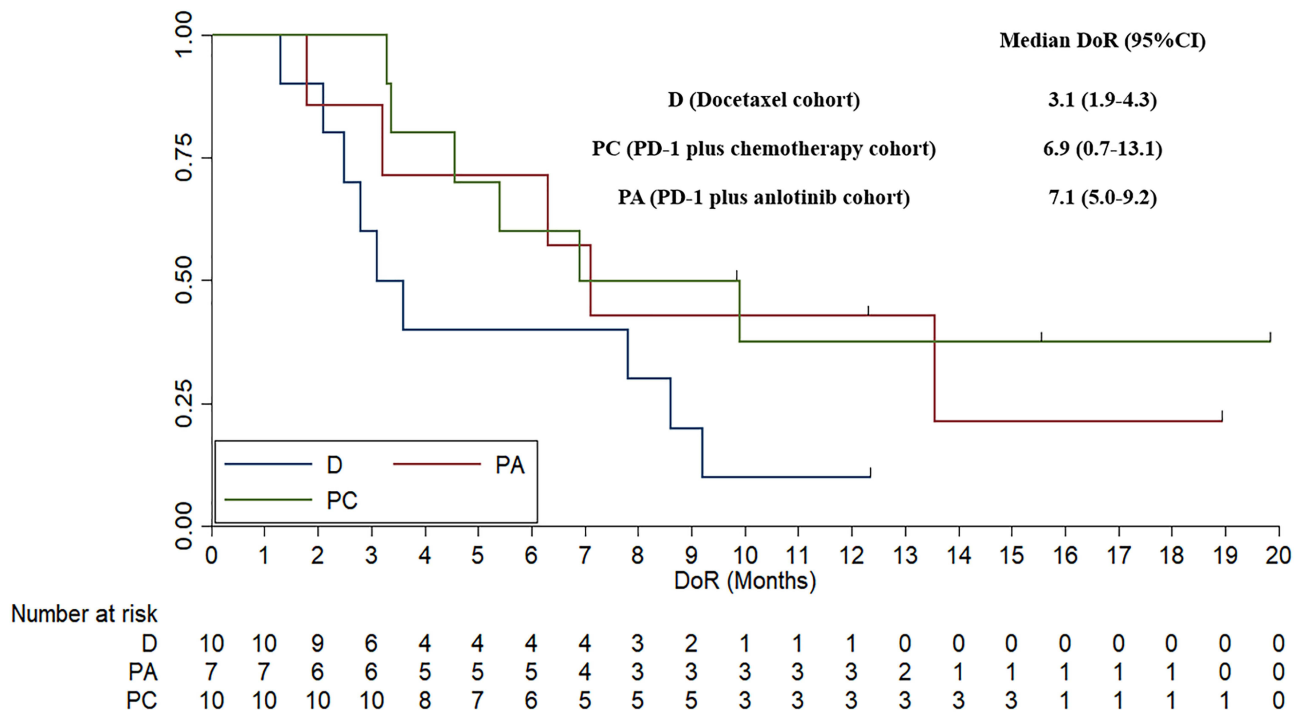


Figure 1 Kaplan-Meier Duration of response survival curves of responders in PD-1 plus chemotherapy, PD-1 plus anlotinib and docetaxel cohorts.

anlotinib cohort were ongoing beyond 12 months, whereas responses to docetaxel cohort were uniformly short-lived, often with progression at the next assessment.

Survival Outcomes

At the date of data cut-off (August 25, 2025), median follow-up duration was 13.8 months (range: 0.9–36.8 months) in PD-1 plus chemotherapy cohort, 15.1 months (range: 1.2–34.1 months) in PD-1 plus anlotinib cohort and 9.3 months (range: 0.7–33.4 months) in docetaxel cohort. A majority of patients in three cohorts had experienced disease progression, allowing for mature analysis of PFS, a total of 22 progression or death events (66.7%) in PD-1 plus chemotherapy cohort, 20 progression or death events (64.5%) in PD-1 plus anlotinib cohort and 49 progression or death events (77.8%) in docetaxel cohort was observed by the data cut-off date. Kaplan–Meier survival curves of PFS in the three cohorts was shown in [Figure 2](#), the median PFS of the 33 patients in PD-1 plus chemotherapy cohort, 31 patients in PD-1 plus anlotinib cohort and 63 patients in docetaxel cohort was 7.0 months (95% CI: 0.7–13.3 months), 6.5 months (95% CI: 2.2–10.8 months) and 3.3 months (95% CI: 2.2–4.4 months), respectively. And the 12-month PFS rates in the three cohorts were 43.6% (95% CI: 26.2%–59.8%), 41.9% (95% CI: 24.7%–58.3%) and 22.7% (95% CI: 12.7%–34.5%), respectively.

At the data cut-off, OS follow-up included 19 death events in PD-1 plus chemotherapy cohort (57.6%), 18 death events in PD-1 plus anlotinib cohort (58.1%) and 44 death events in docetaxel cohort (69.8%). The OS survival curves of the three cohorts were illustrated in [Figure 3](#). The median OS of the 33 patients in PD-1 plus chemotherapy cohort, 31 patients in PD-1 plus anlotinib cohort and 63 patients in docetaxel cohort was 17.8 months (95% CI: 8.0–27.6 months), 16.8 months (95% CI: 13.9–19.7 months) and 9.5 months (95% CI: 4.8–14.2 months), respectively. And the 24-month OS rates in the three cohorts were 42.7% (95% CI: 24.1%–60.1%), 39.5% (95% CI: 22.0%–56.5%) and 30.7% (95% CI: 18.4%–43.9%), respectively.

The first subsequent lines of therapy after index treatment were summarized in [Table 3](#). Subsequent therapy was documented in 18/33 (54.5%) patients in the PD-1 plus chemotherapy cohort, 17/31 (54.8%) in the PD-1 plus anlotinib cohort, and 27/63 (42.9%) in the docetaxel cohort. While subsequent therapy information was unavailable for 8/33 (24.2%), 6/31 (19.4%), and 15/63 (23.8%), respectively. Among patients with recorded subsequent therapy, the most

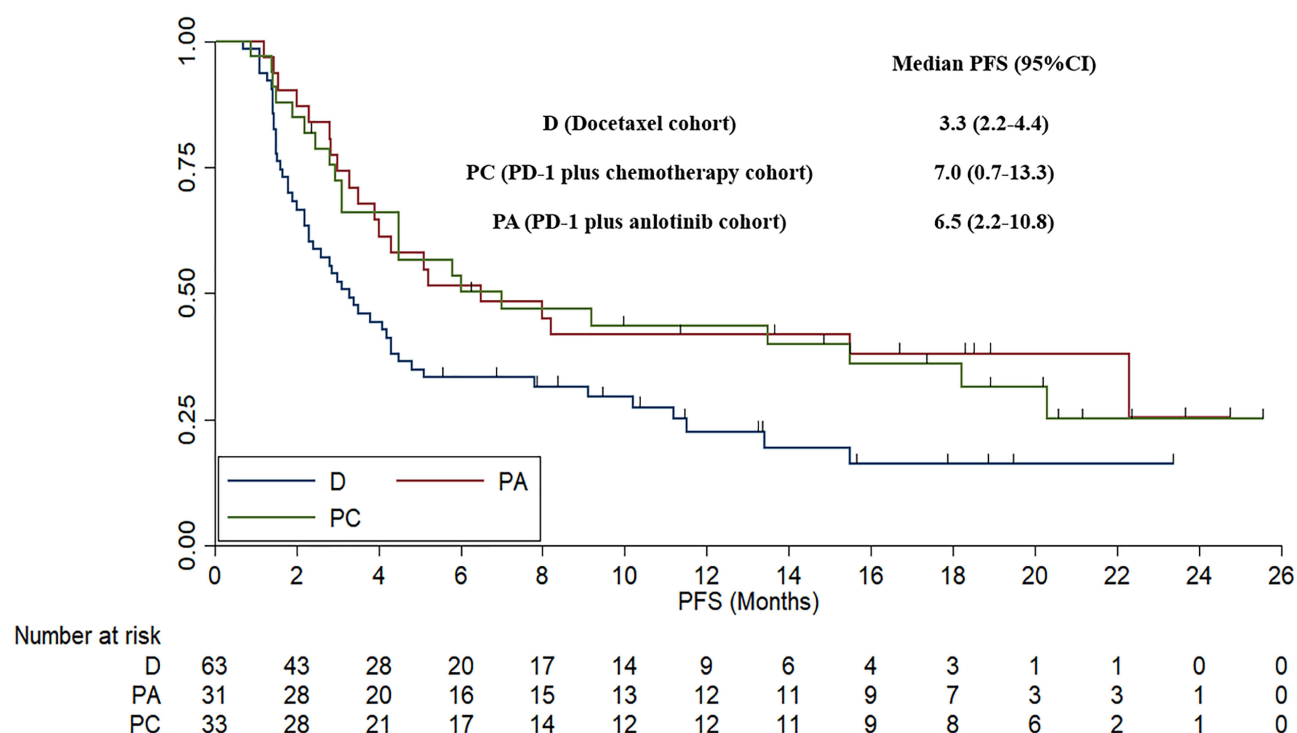


Figure 2 Kaplan-Meier Progression-free survival curves of PD-I plus chemotherapy, PD-I plus anlotinib and docetaxel cohorts.

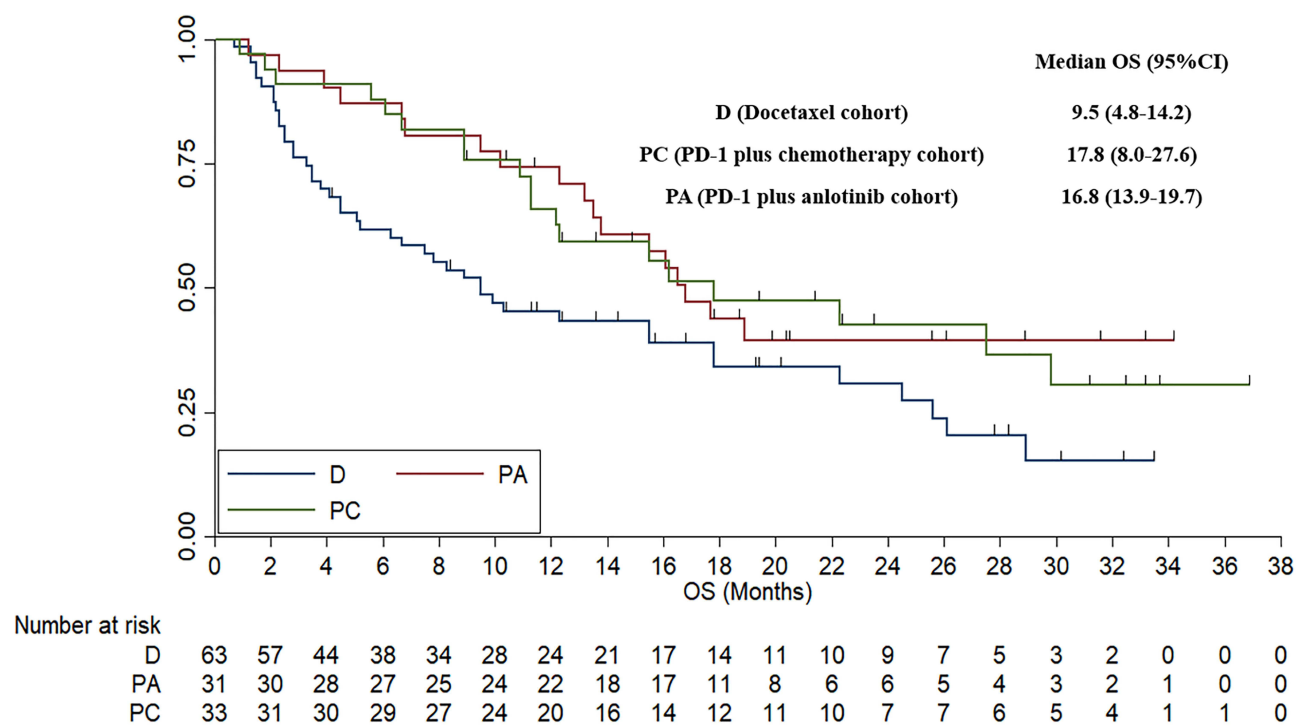


Figure 3 Kaplan-Meier Overall survival curves of PD-I plus chemotherapy, PD-I plus anlotinib and docetaxel cohorts.

Table 3 The First Subsequent Lines of Therapy in the Three Cohorts

Subsequent Therapy	PD-1 plus Chemotherapy (N=33)	PD-1 plus Anlotinib (N=31)	Docetaxel (N=63)
Yes	18 (54.5)	17 (54.8)	27 (42.9)
No	7 (21.2)	8 (25.8)	21 (33.3)
NA	8 (24.2)	6 (19.4)	15 (23.8)
First subsequent therapy regimens	N=18	N=17	N=27
Anlotinib ^a	10 (55.6)	2 (11.8)	13 (48.1)
Chemotherapy ^b	3 (16.7)	8 (47.1)	5 (18.5)
Immunotherapy-based treatment ^c	3 (16.7)	4 (23.5)	6 (22.2)
Traditional Chinese medicine ^d	2 (11.0)	3 (17.6)	3 (11.1)

Notes: ^aAnlotinib: anlotinib monotherapy or anlotinib-based regimen after index. ^bChemotherapy: gemcitabine, pemetrexed, paclitaxel or other chemotherapy. ^cImmunotherapy-based treatment: ICIs monotherapy or ICIs combination. ^dTraditional Chinese medicine: oral/injection approved traditional Chinese medicines with anti-tumor activity.

Abbreviations: PD-1, programmed cell death protein 1; NA, not available.

common first subsequent regimen categories differed across cohorts. In the PD-1 plus chemotherapy cohort (n=18), anlotinib was the most frequent first subsequent regimen (10/18, 55.6%), followed by chemotherapy (3/18, 16.7%) and immunotherapy-based treatment (3/18, 16.7%), with traditional Chinese medicine reported in 2/18 (11.0%). In the PD-1 plus anlotinib cohort (n=17), chemotherapy was most common (8/17, 47.1%), followed by immunotherapy-based treatment (4/17, 23.5%), traditional Chinese medicine (3/17, 17.6%), and anlotinib (2/17, 11.8%). In the docetaxel cohort (n=27), the leading first subsequent regimen categories were anlotinib (13/27, 48.1%), immunotherapy-based treatment (6/27, 22.2%), chemotherapy (5/27, 18.5%), and traditional Chinese medicine (3/27, 11.1%).

Missing data was limited for core baseline variables. However, evaluable tumor response was not available in 2/33 (6.1%), 3/31 (9.7%) and 7/63 (11.1%) patients in the PD-1 plus chemotherapy, PD-1 plus anlotinib and docetaxel cohorts, respectively. Additionally, first subsequent-line therapy information was unavailable in 8/33 (24.2%), 6/31 (19.4%), and 15/63 (23.8%) patients as shown in [Table S1](#).

RMST (24) was estimated as an exploratory summary for OS in [Table S2](#). RMST (24) was 16.4 months (95% CI: 13.6–19.2) in the PD-1 plus chemotherapy cohort, 16.3 months (95% CI: 13.6–19.0) in the PD-1 plus anlotinib cohort, and 12.4 months (95% CI: 10.1–14.7) in the docetaxel cohort (contextual reference). RMST (24) differences versus the contextual reference were 4.0 months (95% CI: 0.4–7.6) for PD-1 plus chemotherapy and 3.9 months (95% CI: 0.4–7.5) for PD-1 plus anlotinib. These estimates were exploratory and should be interpreted cautiously given non-random treatment selection and incomplete confounder capture.

Safety and Tolerability

Safety was assessed from treatment initiation date until end of the last dose or last follow-up, and TRAEs were summarized by cohorts with CTCAE grading where documented. TRAEs in three cohorts were summarized in [Table 4](#) separately. Overall, TRAEs of any grade were observed in 28/33 (84.8%) patients receiving PD-1 plus chemotherapy, 25/31 (80.6%) receiving PD-1 plus anlotinib and 51/63 (81.0%) receiving docetaxel. Grade ≥ 3 AEs occurred in 14/33 (42.4%), 13/31 (41.9%), and 22/63 (34.9%), respectively. TRAEs were categorized and graded according to the CTCAE v5.0, where available.

Across cohorts, the most frequently reported TRAEs (all grades) included fatigue (54.5%, 51.6%, and 49.2% in the PD-1 plus chemotherapy, PD-1 plus anlotinib and docetaxel cohorts, respectively) and nausea/vomiting (39.4%, 32.3%, and 47.6%). Hematologic toxicity (including anemia, leukopenia, neutropenia, and thrombocytopenia) was reported in 45.5% of the PD-1 plus chemotherapy cohort and 39.7% of the docetaxel cohort, compared with 12.9% in the PD-1 plus anlotinib cohort. Hepatotoxicity (including ALT/AST elevation and/or bilirubin elevation) occurred in 33.3%, 16.1%, and 30.2%, respectively. For grade ≥ 3 TRAEs, hematologic toxicity was the most common severe TRAE in the PD-1 plus chemotherapy cohort (24.2%) and the docetaxel cohort (19.0%), whereas no grade ≥ 3 hematologic toxicity was recorded in the PD-1 plus anlotinib cohort (0.0%). Hypertension was more frequent in the PD-1 plus anlotinib cohort (all grades:

Table 4 Safety Profile in the Three Cohorts

Adverse Events	PD-1 plus Chemotherapy (N=33)		PD-1 plus Anlotinib (N=31)		Docetaxel (N=63)	
	All Grades (N, %)	Grade ≥ 3 (N, %)	All Grades (N, %)	Grade ≥ 3 (N, %)	All Grades (N, %)	Grade ≥ 3 (N, %)
Any grade	28 (84.8)	14 (42.4)	25 (80.6)	13 (41.9)	51 (81.0)	22 (34.9)
Fatigue	18 (54.5)	4 (12.1)	16 (51.6)	3 (9.7)	31 (49.2)	6 (9.5)
Nausea and vomiting	13 (39.4)	5 (15.2)	10 (32.3)	3 (9.7)	30 (47.6)	8 (12.7)
Hematologic toxicity	15 (45.5)	8 (24.2)	4 (12.9)	0 (0.0)	25 (39.7)	12 (19.0)
Hepatotoxicity	11 (33.3)	3 (9.1)	5 (16.1)	1 (3.2)	19 (30.2)	6 (9.5)
Alopecia	7 (21.2)	1 (3.0)	1 (3.2)	0 (0.0)	15 (23.8)	4 (6.3)
Constipation	7 (21.2)	2 (6.1)	2 (6.5)	0 (0.0)	12 (19.0)	2 (3.2)
Hypertension	1 (3.0)	0 (0.0)	10 (32.3)	6 (19.4)	2 (3.2)	0 (0.0)
Rash	5 (15.2)	2 (6.1)	4 (12.9)	1 (3.2)	3 (4.8)	0 (0.0)
Stomatitis	5 (15.2)	0 (0.0)	0 (0.0)	0 (0.0)	9 (14.3)	0 (0.0)
Hand-foot syndrome	0 (0.0)	0 (0.0)	7 (22.6)	2 (6.5)	2 (3.2)	0 (0.0)
Pneumonia	3 (9.1)	1 (3.0)	3 (9.7)	0 (0.0)	1 (1.6)	0 (0.0)

Notes: Adverse events were collected from treatment initiation date until end of the last dose or last follow-up. Severity was graded using NCI CTCAE (version 5.0) when explicit grades were available. Hematologic toxicity included anemia, leukopenia, neutropenia and thrombocytopenia, hepatotoxicity included ALT/AST elevation and/or bilirubin elevation. TRAEs were events documented as possibly/probably/definitely related to treatment.

32.3%; grade ≥ 3 : 19.4%) compared with PD-1 plus chemotherapy (3.0%, grade ≥ 3 : 0.0%) and docetaxel (3.2%, grade ≥ 3 : 0.0%). Grade ≥ 3 nausea/vomiting was observed in 15.2%, 9.7%, and 12.7%, and grade ≥ 3 fatigue was 12.1%, 9.7%, and 9.5%, respectively. Grade ≥ 3 hepatotoxicity occurred in 9.1%, 3.2% and 9.5%, respectively.

Other notable TRAEs included hand-foot syndrome, which was more common in the PD-1 plus anlotinib cohort (all grades: 22.6%, grade ≥ 3 : 6.5%) than in the PD-1 plus chemotherapy cohort (0.0%) or docetaxel cohort (3.2%, grade ≥ 3 : 0.0%). Pneumonia occurred in 9.1%, 9.7%, and 1.6%, with grade ≥ 3 pneumonia documented in 3.0% in the PD-1 plus chemotherapy cohort and none in the other cohorts. Crucially, no treatment-related deaths occurred in three cohorts. There were no fatal pneumonitis or hematologic events attributable to therapy. Overall, the PD-1 plus chemotherapy and PD-1 plus anlotinib regimens exhibited tolerable safety profile among patients with advanced NSCLC after prior immunotherapy.

Discussion

Because this study was retrospective and treatment selection was non-random, we intentionally framed our findings as descriptive and hypothesis-generating. And because treatment selection was non-random with incompletely captured determinants, propensity score method intended for causal effect estimation was not performed. The docetaxel-treated cohort was presented for context rather than as an evidentiary comparator, and observed between-cohort differences should not be interpreted as causal treatment effects.

This study had several limitations, and the findings should be interpreted cautiously. Firstly, the retrospective design and lack of randomization introduced potential biases. Although baseline characteristics were similar across three cohorts, there might have unmeasured confounders influencing treatment assignment (for example, clinicians might be more likely to try PD-1 rechallenge in patients who were younger, more fit, or had better responses to prior immunotherapy). Secondly, the sample size was moderate, results should be considered hypothesis-generating. Thirdly, the follow-up duration, while sufficient to show a PFS/OS benefit, was still relatively short for long-term survival assessment. Some patients in the PD-1 cohorts remained on therapy. Therefore, the median OS for that arm might improve further with additional follow-up. We reported the medians available at data cutoff, but the true long-term survival difference might evolve. Additionally, there was some heterogeneity in the specific ICIs used before the study treatment (different PD-1/PD-L1 blockade and treatment lines). Although the distribution of prior agents was generally comparable across cohorts, such variability might have influenced subsequent treatment sensitivity and thus introduced potential

residual confounding. As a result, this study should be interpreted as hypothesis-generating and require confirmation in larger, prospectively collected datasets.

In this cohort of 127 previously ICIs-treated patients with advanced NSCLC, the median age across groups ranged from 65 to 67 years, and most patients had previously received PD-1 blockade. The distribution of key baseline variables was generally consistent with contemporary real-world practice in China.²⁴ The baseline characteristics of subjects in this study were in line with those included in a recent exploratory study initiated by Professor XS Fang.⁴ Interestingly, the predominance of prior PD-1 blockade therapy (around 80%) in our cohort aligned with contemporary standards of care for advanced NSCLC in China.²⁵ Approximately one-quarter of patients discontinued prior ICIs therapy because of intolerance, highlighting the clinical relevance of safety considerations in this setting.²⁶ Additionally, patients with duration of previous ICIs treatment <6 months accounted for approximately 50% of the subjects included across three cohorts. ESMO-aligned review noted that responses to rechallenge clustered in patients with longer prior ICIs benefit/intervals (often operationalized as ≥ 6 months). These patterns justified our planned adjustment and subgrouping using 6-month cut-point was suitable.²⁷ Taken together, this data also pointed to limited effectiveness of the antecedent ICIs therapy, in keeping with contemporary series in post-ICIs NSCLC.²⁸

ORR of 30.3% in PD-1 plus chemotherapy and 22.6% in PD-1 plus anlotinib in our cohorts was on par with ORR reported in other investigations. Dou et al (2024) observed an ORR of 23.9% in 67 previously immunotherapy-treated NSCLC patients receiving anlotinib plus PD-1 blockade.¹⁹ Wang et al (2021) reported an ORR of 28.4% for PD-1 blockade plus anlotinib in a mixed pretreated NSCLC population.¹⁶ ORR in this study was also comparable to the 20–30% ORR observed with docetaxel plus ramucirumab (an approved second-line regimen) in immunotherapy-naïve trials.^{12,29} In contrast, docetaxel monotherapy yielded a modest ORR of 15.9% in this study, consistent with historical controls (13–14% in second-line trials of Checkmate 017/057).³⁰ More striking was the difference in DCR: 84.8% in PD-1 plus chemotherapy, 80.6% in PD-1 plus anlotinib, 54.0% in docetaxel. This indicated that the combination stabilized disease in a substantially larger fraction of patients. Achieving stable disease was important in this salvage setting, as it often correlated with symptomatic relief and prolonged survival.³¹ Similar DCR was noted in related studies: Li et al reported a DCR of 86.6% with PD-1 blockade plus anlotinib,¹⁶ and anlotinib plus docetaxel showed a DCR of 79% vs 51% for docetaxel in a comparable retrospective analysis.³² Therefore, the efficacy results reinforced that combining PD-1 blockade with chemotherapy or anlotinib might achieve disease control in the majority of heavily pretreated NSCLC, whereas docetaxel alone benefited only about half. Another striking finding was the significantly longer DoR and tail of the survival curve with PD-1 rechallenge cohorts. Several patients achieved prolonged response and survival beyond 1–2 years with PD-1-based regimens, whereas long-term survivors on docetaxel were rare. However, the DoR was derived from only 10, 7 and 10 responders, respectively, this analysis was restricted to a small number of patients and therefore represented a fragile exploratory finding. It was well recognized that only a fraction of NSCLC were immuno-sensitive, characterized by factors like high PD-L1 expression, high tumor mutational burden, or inflamed tumor microenvironment.³³ Accordingly, patients who initially responded to immunotherapy might represent a subgroup with residual immune sensitivity despite subsequent progression.

The median OS of ~17 months with PD-1-based therapy in our cohorts approached the survival one might expect in first-line immunotherapy trials for NSCLC.³⁴ Docetaxel monotherapy produced outcomes in line with published real-world post-immunotherapy data, underscoring the poor prognosis of ICIs-resistant NSCLC.³⁵ This aligned with emerging evidence favoring reintroduction of immunotherapy in certain patients. For example, Gandara et al reported that continuing atezolizumab beyond progression might extend OS in the OAK trial subset.³⁶ More recently, Feng et al (2023) performed a meta-analysis of ICIs rechallenge and found a pooled median OS of ~13 months, hinting at improved long-term outcomes compared to historical chemotherapy results.³⁷ However, OS in retrospective cohorts might be influenced by therapies received after the treatment. In our dataset, documented subsequent therapy was recorded more frequently in the PD-1 rechallenge cohorts (~55%) than in the docetaxel cohort (~43%). Differences in downstream treatment pathways and incomplete capture of subsequent therapy (unavailable in approximately one-fifth to one-quarter of patients) might affect OS interpretation. Therefore, OS findings should be considered descriptive and hypothesis-generating rather than causal. Additionally, RMST (24) was included as an interpretable survival summary within a fixed 24-month horizon and did not depend on proportional hazards assumptions. Even though RMST (24) estimates were

numerically longer in the PD-1 rechallenge cohorts, these RMST results should be interpreted as descriptive/hypothesis-generating associations, given the retrospective design and non-random treatment selection. In a similar vein, Zhou et al (2023) observed median OS of 13.5 months with anlotinib plus docetaxel vs 9.2 months with docetaxel in previously ICIs-treated NSCLC.³² XS Fang et al reported median OS of 16.1 months for anlotinib-based treatment, aligning with our estimate.⁴ These convergent data strongly hinted that rechallenging the PD-1 blockade in combination with systemic therapy might provide potential survival benefit.

A noteworthy aspect of our study was that the PD-1 blockade rechallenge was done in combination with another agent (chemotherapy or anlotinib) rather than as monotherapy. Rechallenging with ICIs monotherapy had limited efficacy historically (ORRs <5% in some series),³⁶ presumably because the tumor's resistance mechanisms to immunotherapy remained in place. By adding chemotherapy or antiangiogenic therapy, it might alter the tumor microenvironment or kill immunosuppressive cells, thereby overcoming adaptive resistance. From a biological standpoint, several mechanisms might explain why immunotherapy rechallenge with PD-1-based combinations might still be feasible and potentially beneficial after failure of prior ICIs therapy. Cytotoxic chemotherapy not only killed tumor cells but also induced immunogenic cell death, increased the release and presentation of tumor antigens, and modulated the tumor microenvironment by depleting regulatory T cells and myeloid-derived suppressor cells. These effects might enhance T-cell priming and function and thereby re-sensitize tumors to PD-1 blockade.³⁸ Additionally, anlotinib might normalize abnormal tumor vasculature, alleviate hypoxia and reverse VEGF-mediated immunosuppression, which facilitated the infiltration and activity of effector T cells and potentiated the efficacy of ICIs.³⁹ Although some retrospective analysis (Heraudet et al) did not find a statistically significant improvement in chemotherapy outcomes post-ICIs, they did note a trend toward longer OS in patients who received paclitaxel/bevacizumab after immunotherapy (HR=0.65, $P=0.17$).⁴⁰ These findings suggested a potentially synergistic sequence effect that, while not consistently reaching statistical significance across studies, remained biologically plausible. Essentially, PD-1 plus chemotherapy cohort indicated that the presence of PD-1 blockade added value beyond chemotherapy's own effect. Against this background, PFS/OS observed in our PD-1-based combinations cohorts should be interpreted as hypothesis-generating signals that merited further investigation, particularly given that CONTACT-01 trial demonstrated how challenging it was to achieve a survival benefit over docetaxel after prior chemo-immunotherapy.¹⁷

One of the major concerns with ICIs rechallenge was the potential risk of recurrent or more severe immune-related toxicity, especially in those who discontinued initial ICIs due to toxicity. Reassuringly, our study did not encounter any unexpected safety issues. Tolerability outcomes highlighted that the incidence of TRAEs in PD-1 plus chemotherapy was 84.8% with 42.4% of patients experiencing grade ≥ 3 , TRAEs in PD-1 plus anlotinib was 80.6% with 41.9% of patients experiencing grade ≥ 3 . In the docetaxel cohort, 81.0% of the patients experienced TRAEs, and 34.9% experienced grade ≥ 3 . The overall safety profile was in line with the previous study.⁴ We observed expected class-specific toxicities: hypertension and hand-foot syndrome from anlotinib, immune-mediated and general effects (like rash and pneumonia) from PD-1 blockade,⁴¹ and no overlapping organ toxicities that compounded. Furthermore, by combining with chemotherapy or anlotinib, we did not detect additive toxicity beyond what was expected from each component. Grade ≥ 3 TRAEs occurred in approximately 42% of patients receiving PD-1-based combinations in our study—comparable to rates observed with frontline chemo-immunotherapy and within the range reported for PD-(L)1-TKI strategies evaluated after prior ICIs exposure, underscoring both the tolerability and the ongoing need to balance benefits against toxicity in ICIs-refractory disease.⁴² In fact, some toxicities were less frequent in the combination arm compared to docetaxel (notably hematologic toxicity and alopecia), which might improve patient quality of life. This suggested that PD-1 blockade-based regimens might be a gentler alternative to more intensive chemotherapy-based salvage regimens. Of course, vigilant monitoring and management of liver function, rash, blood pressure, hand-foot syndrome and pneumonia were necessary, but oncologists were familiar with these from use of PD-1 blockade and anlotinib in clinical practice. By comparison, docetaxel—while familiar—carried clinically significant risks of myelosuppression, hepatotoxicity, alopecia, and stomatitis, which might be especially problematic in elderly patients. Therefore, PD-1 blockade-based regimens offered a different toxicity spectrum that might be preferable for some patients, and did not appear to add undue risk beyond the individual drugs. Nevertheless, our study was retrospective in nature with a moderate sample size and inevitable heterogeneity in prior ICIs regimens and combination strategies. Therefore, the safety profile of PD-1-based

combination cohorts should be considered exploratory and hypothesis-generating and required confirmation in larger prospective trials.

Conclusion

In this retrospective cohort of advanced NSCLC without targetable alterations who had previously received immunotherapy, two PD-1 rechallenge approaches (PD-1 plus chemotherapy and PD-1 plus anlotinib) demonstrated clinically meaningful activity with manageable toxicity in a subset of patients. Outcomes in the docetaxel cohort were included as a contemporaneous benchmark to contextualize routine salvage practices during the study period. Because treatment selection was non-random and important determinants of prognosis and treatment choice might be incompletely captured, between-cohort differences should be interpreted cautiously. Prospective studies were warranted to confirm effectiveness and to better define which patients were most likely to benefit from rechallenge strategies.

Ethics Statement

Despite the informed consent was waived by the Ethics Committee of Fuwai Central China Cardiovascular Hospital, we confirmed that the data of the patients included in this study was anonymized or maintained with confidentiality.

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Disclosure

The authors declare that there are no conflicts of interest.

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