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# Local Therapy Improves Outcomes in Metastatic NSCLC with Atypical Response to PD-1/PD-L1 Inhibitors: A Multi-Center Retrospective Study

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## ABSTRACT

To investigate the clinical features, management strategies, and outcomes of metastatic non–small cell lung cancer (NSCLC) patients exhibiting atypical responses (AR) during PD-1/PD-L1 inhibitor therapy. We conducted a retrospective review of 926 patients with metastatic NSCLC treated with PD-1/PD-L1 inhibitors at three academic centers. Tumor responses were evaluated using RECIST version 1.1. AR was identified in 56 patients (6.1%), with a median onset of 2 months after initiating therapy. Patients with metastases in three or more organs at baseline were at higher risk for developing AR ($p = 0.038$). The most frequent sites of disease progression were the lymph nodes (33.8%) and lungs (29.7%). Most patients with AR (78.2%) had only one or two progressing lesions, predominantly arising from pre-existing tumors (89.1%). Survival outcomes did not differ significantly between AR and typical responders (TR). Importantly, receipt of local therapy targeting progressive lesions was independently associated with improved progression-free survival ($p = 0.025$). Atypical response is a notable phenomenon in metastatic NSCLC patients receiving PD-1/PD-L1 inhibitors and is associated with survival comparable to typical response patterns. Targeted local interventions for progressing lesions, without halting ongoing immunotherapy, may provide additional clinical benefit.

**Keywords:** Metastatic NSCLC, Atypical response, Immune checkpoint inhibitors, Local therapy, Progression-free survival, Overall survival

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## Introduction

The introduction of immune checkpoint inhibitors has markedly advanced the treatment landscape for advanced non–small cell lung cancer (NSCLC) [1–3]. PD-1/PD-L1 inhibitors, administered either alone or in combination with chemotherapy, have demonstrated improved overall survival (OS) in both treatment-naïve and previously treated stage IV NSCLC patients [1, 3, 4]. However, evaluating tumor response in patients receiving these agents can be complex due to the occurrence of atypical responses (AR), in which some lesions regress while others progress simultaneously [5]. This phenomenon complicates the assessment of treatment efficacy and the determination of subsequent therapeutic strategies. Although several imaging-response criteria have been proposed to address these immune-related response patterns [6, 7], comprehensive real-world data describing AR in NSCLC, including its clinical management and prognostic implications, remain limited. Existing reports suggest that patients with AR may have outcomes intermediate between those with typical progression and those exhibiting a conventional response (TR) [5, 8–10], but these studies were often small and insufficient to fully characterize AR. In particular, the radiographic patterns and clinical interventions for AR have been rarely explored.

Local consolidative therapy has garnered interest as a strategy for managing oligo-progressive disease and has increasingly been implemented in clinical practice. Evidence indicates that local treatment modalities can improve survival in NSCLC patients with oligometastatic or oligo-progressive disease [11–13]. Radiotherapy, in particular,

may enhance antitumor immunity, suggesting potential synergistic benefits when combined with immunotherapy [14, 15]. Nevertheless, guidance on optimal management for patients experiencing AR is scarce. To address this gap, we conducted a multicenter retrospective study to evaluate the clinical characteristics, treatment approaches, and survival outcomes of metastatic NSCLC patients exhibiting AR during PD-1/PD-L1 inhibitor therapy.

## Materials and Methods

*Patient selection*

In this study, AR was defined as the simultaneous occurrence of objective response in certain tumor lesions alongside progression in others during PD-1/PD-L1 inhibitor therapy, consistent with prior definitions [6]. Patients not meeting this criterion were categorized as exhibiting TR. We retrospectively reviewed medical records of advanced NSCLC patients treated with PD-1/PD-L1 inhibitors at Fudan University Shanghai Cancer Center, Fudan University Zhongshan Hospital, and Tongji Hospital affiliated with Huazhong University of Science and Technology between May 2018 and January 2022.

Two groups were established based on treatment response. The TR group included patients achieving complete response (CR), partial response (PR), or durable stable disease (SD ≥ 6 months), according to RECIST version 1.1 [16]. The AR group consisted of patients meeting the AR definition described above. All patients had NSCLC confirmed by pathology at the respective institutions. Histological subtypes were categorized as squamous cell carcinoma or non-squamous cell carcinoma (including adenocarcinoma, large cell carcinoma, and other variants). PD-L1 expression was assessed using the Dako 22C3 and 28-8 pharmDx assays, with tumor proportion score (TPS) cutoffs of 1% and 50% for low and high expression, respectively [17].

Inclusion criteria required adequate follow-up and at least one measurable lesion. Patients with secondary primary tumors, sensitizing driver mutations, or incomplete follow-up were excluded. Baseline clinical and pathological data—including age, sex, histology, smoking status, ECOG performance status, treatment regimen, and PD-L1 expression—were collected, along with dates of disease progression, last follow-up, and death. The study was approved by the institutional review boards of all participating centers (approval number: 2012228-3).

*Follow-up*

Follow-up generally included chest and abdominal CT scans or ultrasound every 6–12 weeks. Brain MRI, bone scans, and PET/CT were performed only if clinically indicated. Data were censored on January 31, 2022.

*Response assessment*

To account for potential variability in tumor response, the full spectrum of radiologic changes was evaluated at both lesion and organ levels to identify atypical responses (AR). Sequential imaging studies for each patient were independently reviewed by two experienced radiologists. Each measurable lesion was assessed separately. For patients demonstrating AR, the date of its first documentation was recorded. Tumor burden was quantified using unidimensional measurements (millimeters), and changes in size were expressed as absolute values and percentages, following RECIST version 1.1 criteria.

*Statistical analysis*

For patients exhibiting a typical response (TR), progression-free survival (PFS) was calculated from the start of PD-1/PD-L1 inhibitor therapy to the earliest occurrence of disease progression, death from any cause, or censoring at the data cutoff if no progression occurred. For AR patients, PFS was defined as the interval from therapy initiation to the first progression event following AR onset or death, irrespective of any progression before AR documentation. Overall survival (OS) was measured from treatment initiation to death from any cause or censored at the last follow-up.

Survival outcomes were estimated using the Kaplan–Meier method, and comparisons between groups were conducted with the log-rank test. Cox proportional hazards models were applied to determine hazard ratios (HRs) and 95% confidence intervals (CIs). Variables with $p < 0.10$ in univariate analysis were included in multivariate models. To minimize potential confounding, propensity score matching (PSM) was performed using one-to-one nearest neighbor matching with a caliper of 0.20 [18]. Statistical significance was defined as a two-sided $p < 0.05$. Analyses were conducted using SPSS version 22.0 (IBM, Chicago, IL, USA), while survival analyses were performed in R version 4.1.3 (R Foundation for Statistical Computing).

## Results and Discussion

*Patient characteristics*

Of the 926 metastatic NSCLC patients treated with immune checkpoint inhibitors, 327 met inclusion criteria and were analyzed, including 271 in the TR group and 56 in the AR group **(Figure 1)**. Among the overall cohort, 141 patients (43.1%) received PD-1/PD-L1 inhibitors as first-line therapy, whereas 186 (56.9%) were treated in second-line or later settings. Combination therapy was administered to the majority of patients (68.5%), while 31.5% received monotherapy. Baseline demographic and clinical characteristics of patients in the AR and TR groups are summarized in **Table 1**.

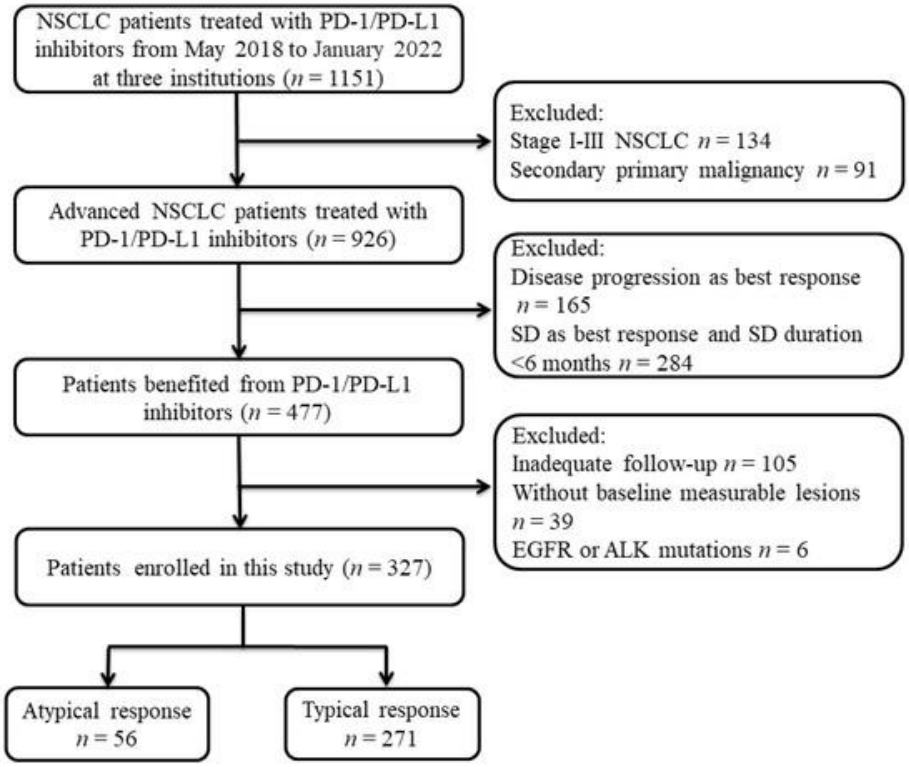



**Figure 1.** Flowchart of patient enrollment.

**Table 1.** Baseline characteristics and logistic regression analysis for predictors of atypical response.

| | AR | TR | Univariate Analysis | | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|---|---|---|
| | (N = 56) | (N = 271) | HR | 95% CI | | p | HR | 95% CI | p |
| Age, years | | | | | | | | | |
| ≤62 | 25 (44.6%) | 103 (38.0%) | 1 | | | | | | |
| >62 | 31 (55.4%) | 168 (62.0%) | 0.760 | 0.425 | 1.359 | 0.355 | | | |
| Gender | | | | | | | | | |
| Male | 45 (80.4%) | 217 (80.1%) | 1 | | | | | | |
| Female | 11 (19.6%) | 54 (19.9%) | 0.982 | 0.476 | 2.025 | 0.961 | | | |
| ECOG PS Score | | | | | | | | | |
| 0–1 | 52 (92.9%) | 252 (19.0%) | 1 | | | | | | |
| 2 | 4 (7.1%) | 19 (81.0%) | 1.020 | 0.333 | 3.123 | 0.972 | | | |
| Smoking status | | | | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ever | 26 (46.4%) | 152 (56.1%) | 1 | | | | | | | |
| Never | 30 (53.6%) | 119 (43.9%) | 0.903 | 0.507 | 1.609 | 0.73 | | | | |
| Histology | | | | | | | | | | |
| Squamous-cell Carcinoma | 14 (25.0%) | 105 (38.7%) | 1 | | | | 1 | | | |
| Non-squamous-cell Carcinoma | 42 (75.0%) | 166 (61.3%) | 1.898 | 0.988 | 3.644 | 0.054 | 1.853 | 0.946 | 3.628 | 0.072 |
| NO. of metastatic organs | | | | | | | | | | |
| ≤3 | 45 (80.4%) | 255 (94.1%) | 1 | | | | 1 | | | |
| >3 | 11 (19.6%) | 16 (5.9%) | 3.896 | 1.698 | 8.939 | 0.001 | 2.708 | 1.056 | 6.943 | 0.038 |
| NO. of metastatic sites | | | | | | | | | | |
| ≤3 | 29 (51.8%) | 181 (66.8%) | 1 | | | | 1 | | | |
| >3 | 27 (48.2%) | 90 (33.2%) | 1.872 | 1.046 | 3.351 | 0.035 | 1.425 | 0.731 | 2.777 | 0.298 |
| Treatment regimens | | | | | | | | | | |
| ICI alone | 23 (41.1%) | 80 (29.5%) | 1 | | | | 1 | | | |
| ICI combination | 33 (58.9%) | 191 (70.5%) | 0.601 | 0.332 | 1.087 | 0.092 | 0.575 | 0.309 | 1.071 | 0.081 |
| Treatment lines | | | | | | | | | | |
| 1st | 27 (48.2%) | 114 (42.1%) | 1 | | | | | | | |
| ≥2nd | 29 (51.8%) | 157 (57.9%) | 0.780 | 0.438 | 1.389 | 0.398 | | | | |
| PD-L1 expression, % | | | | | | | | | | |
| <1 | 4 (7.1%) | 18 (6.6%) | 1 | | | | | | | |
| 1–49 | 6 (10.7%) | 40 (14.8%) | 0.675 | 0.169 | 2.689 | 0.577 | | | | |
| ≥50 | 13 (23.2%) | 48 (17.7%) | 1.219 | 0.351 | 4.231 | 0.755 | | | | |
| Unknown | 33 (59.0%) | 165 (60.9%) | 0.900 | 0.286 | 2.831 | 0.857 | | | | |

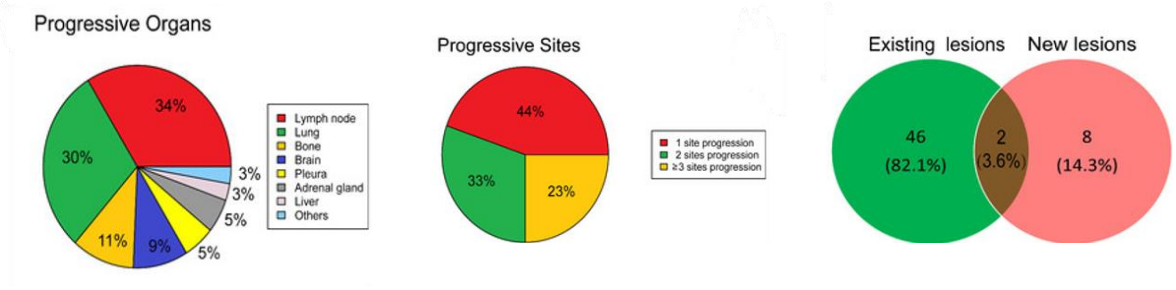
Abbreviations: ICI, immune checkpoint inhibitors; ECOG PS, eastern cooperative oncology group performance status; AR, atypical response; and TR, typical response.

*Clinical characteristics of atypical response*

In this cohort, AR was observed in 56 of 926 patients, corresponding to a frequency of 6.1%. The median interval from initiation of PD-1/PD-L1 inhibitor therapy to the first documentation of AR was 2.0 months (range: 1.0–5.0 months). At the time AR was initially recorded, RECIST version 1.1 assessments classified responses as partial response (PR) in 12 patients, stable disease (SD) in 35 patients, and disease progression in 9 patients.

For each AR patient, the number and anatomical location of progressive lesions that contributed to the classification of AR were carefully documented. The most frequently affected organs were lymph nodes (33.8%), lungs (29.7%), bones (10.8%), brain (9.5%), pleura (5.4%), adrenal glands (5.4%), and liver (2.7%) **(Figure 2a)**. Overall, 138 progressive lesions were identified among the 56 patients. A single progressive lesion was observed in 25 patients (44.6%), two lesions in 18 patients (32.2%), and three or more lesions in 13 patients (23.2%) **(Figure 2b)**.

Regarding the origin of progressive lesions, 46 patients (82.1%) developed progression from pre-existing tumor sites, whereas eight patients (14.3%) experienced AR due to newly emerged lesions. Two patients (3.6%) had progressive lesions arising both from pre-existing and new tumor sites **(Figure 2c)**.



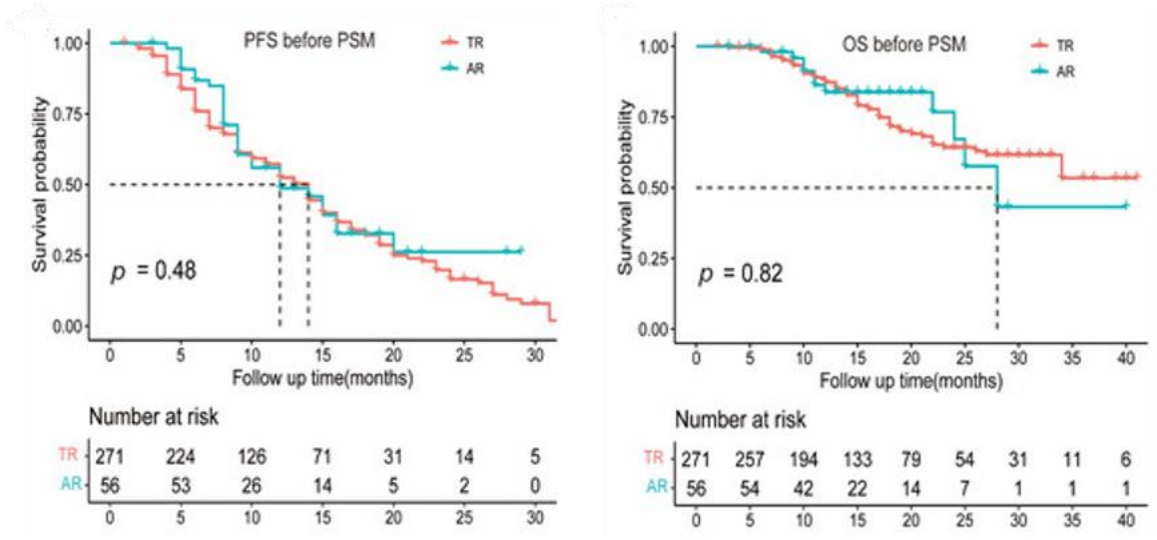

a) b) c)

**Figure 2.** Progressive patterns of AR. Locations (a), number (b), and originations (c) of the progressive tumor lesions in patients with AR.

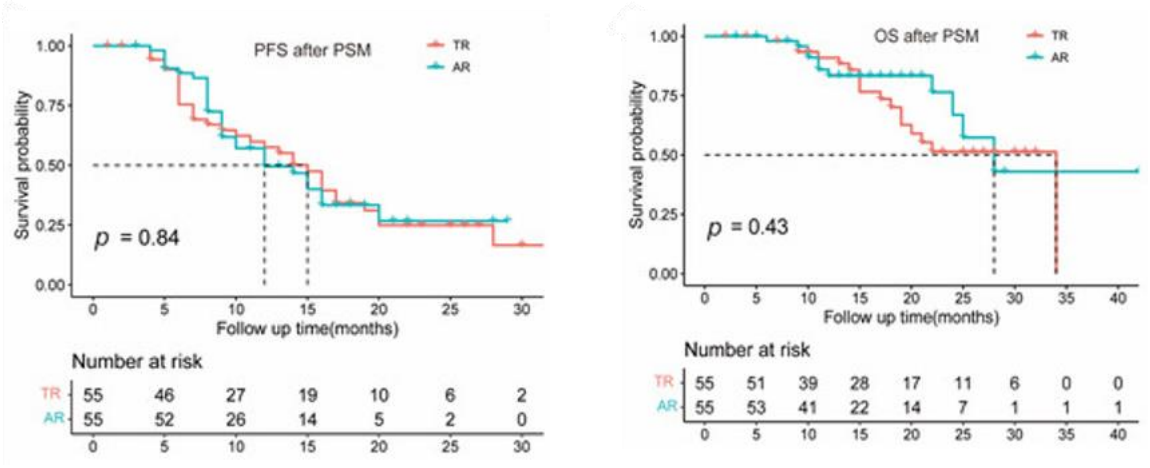
Univariate analysis showed that patients with a higher number of metastatic organs or metastatic sites at baseline were more likely to develop an atypical response. No statistically significant associations were observed between AR occurrence and other clinical factors such as age, sex, ECOG performance status, smoking history, tumor histology, treatment type, line of therapy, or PD-L1 expression. In the multivariate model, the number of metastatic organs at baseline remained a significant predictor of AR ($p = 0.038$) **(Table 1)**, which aligns with previous observations in metastatic melanoma cohorts [19].

*Impact of atypical response on survival*

Over a median follow-up of 16 months (ranging from 2 to 52 months), 199 patients experienced disease progression according to RECIST 1.1 criteria, and 75 patients died. For the entire cohort (n = 327), median overall survival was not reached, whereas median progression-free survival was 13.0 months (95% CI: 12.0–15.0). When comparing patients exhibiting AR to those with a typical response, no significant differences were found in either PFS **(Figure 3a)** or OS **(Figure 3b)**. Cox regression analyses further confirmed that the type of response (AR vs. TR) did not independently influence progression-free or overall survival.




a) b)



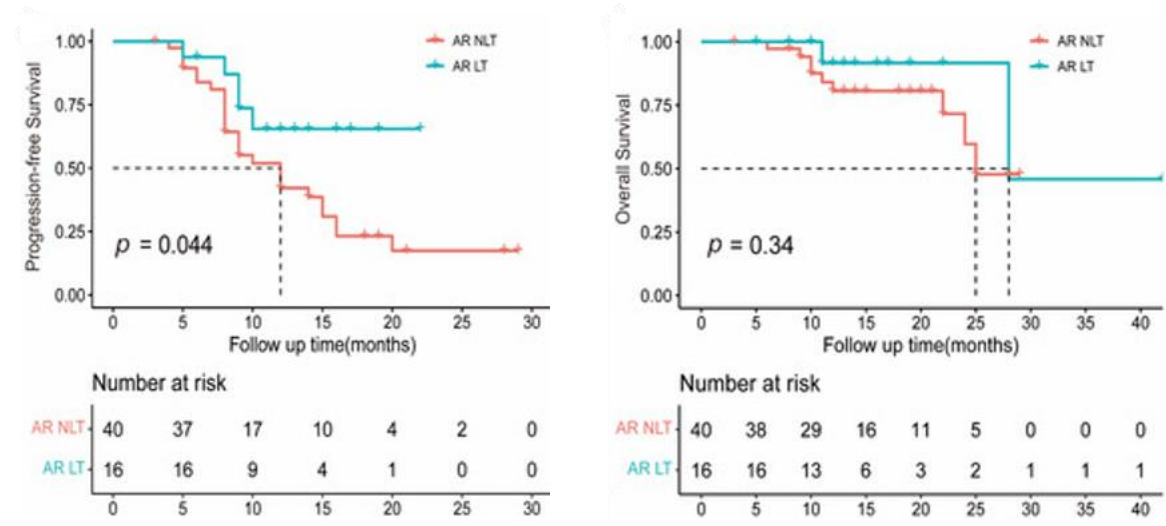

c) d)

**Figure 3.** Kaplan–Meier Estimates of Survival. Kaplan–Meier curves show progression-free survival (PFS) (a) and overall survival (OS) (b) for patients with atypical response (AR) versus typical response (TR) before propensity score matching (PSM), and PFS (c) and OS (d) after PSM

To address potential confounding factors between AR and TR groups, PSM was performed using four variables: sex, baseline number of metastatic organs, treatment type, and line of therapy. After matching, the characteristics between the two groups were well balanced. Post-matching analysis demonstrated no significant differences in PFS **(Figure 3c)** or OS **(Figure 3d)**.

*Effectiveness of local interventions in patients with AR*

All patients exhibiting AR remained on their initial PD-1/PD-L1 inhibitor regimen. Among these, 16 individuals (28.6%) received targeted local therapy directed at the progressive lesions, including radiotherapy in 13 cases, surgical excision in 2, and other localized procedures in 1 patient. The baseline characteristics between those receiving and not receiving local interventions were largely comparable. Administration of local therapy was associated with a substantial extension in PFS (median not reached vs. 12.0 months) **(Figure 4a)** and showed a trend toward improved OS (28.0 vs. 25.0 months) **(Figure 4b)**. Multivariate analysis indicated that local therapy independently predicted longer PFS among patients with AR.




a) b)

**Figure 4.** Kaplan–Meier analysis of PFS (a) and OS (b) in patients with AR who received local therapy or not. AR, atypical response; NLT, non-local therapy; and LT, local therapy.

*Discussion*

This multicenter retrospective study analyzed the clinical characteristics, prognostic implications, and management strategies for patients with stage IV NSCLC who exhibited an atypical response (AR) to PD-1/PD-L1 inhibitors. Our results indicate that the clinical outcomes of patients with AR were comparable to those of patients with typical responses (TR). Furthermore, local interventions directed at paradoxically progressing lesions were associated with improved survival outcomes, suggesting that targeted local therapy may provide additional benefit and merits further investigation.

Despite increasing recognition of AR, its clinical profile remains incompletely characterized. This study contributes important insights into the incidence and spatial-temporal patterns of AR among metastatic NSCLC patients treated with PD-1/PD-L1 blockade. Consistent with previous reports, AR occurred in approximately 6.1% of patients, falling within the previously reported range of 5–13% [5, 10, 20]. The median time to AR development was around 2 months, aligning with prior findings that AR generally manifests within the first 2–3 months of treatment [5, 9]. These observations underscore the need for cautious interpretation of early tumor progression, as a substantial subset of patients may actually be experiencing AR rather than conventional progression.

Our analysis also revealed that patients with more than three metastatic organs or sites at baseline were more likely to develop AR, highlighting the role of disease burden in the emergence of atypical patterns. The distribution and number of progressing lesions observed in AR closely resembled patterns reported for acquired resistance to PD-1/PD-L1 inhibitors [5, 21–25], with lymph nodes and lungs being the most frequently involved sites. Notably, most patients exhibited only one to three progressing lesions, which were often located at preexisting tumor sites. This pattern suggests a possible shared mechanism involving intra-tumoral heterogeneity and immune evasion pathways in metastatic NSCLC [22, 26–28]. Prior studies have demonstrated that local treatment of these limited progressing sites, in combination with ongoing PD-1/PD-L1 blockade, can prolong disease control, consistent with the findings presented here [22].

The biological mechanisms underlying AR remain poorly defined. Intratumoral heterogeneity among metastatic lesions likely contributes to divergent responses, where some tumors regress while others progress. Delayed activation of the immune system and complex tumor–immune interactions may also explain the simultaneous shrinkage and growth of lesions or the emergence of new lesions over time [20]. PD-L1 expression, a key biomarker for immune checkpoint inhibitor responsiveness, has been shown to vary across different tumor sites within the same patient, emphasizing the significance of intratumoral immune heterogeneity [29–31]. Additionally, local tumor microenvironment factors, such as T cell infiltration and immune cell recruitment, can differ across metastatic organs and influence therapeutic efficacy [32].

Clinically, patients with AR may benefit from continuation of PD-1/PD-L1 inhibitors beyond initial RECIST-defined progression. Observations of concurrent regression in some lesions and progression in others suggest that ongoing immunotherapy can still exert meaningful antitumor effects. This supports the rationale for maintaining PD-1/PD-L1 blockade rather than discontinuing therapy and switching to alternative treatments prematurely [23, 33–35]. Therefore, extending PD-1/PD-L1 therapy beyond conventional progression criteria appears to be a reasonable strategy for managing AR in advanced NSCLC.

The role of local therapy in stage IV NSCLC patients exhibiting atypical response (AR) to PD-1/PD-L1 inhibitors has been infrequently explored. Previous retrospective evidence suggests that local interventions, such as radiotherapy, directed at solitary or oligo-progressive lesions can extend the duration of PD-1/PD-L1 inhibitor therapy, particularly in cancers with relatively indolent biology, such as renal cell carcinoma [24]. In NSCLC, surgery and radiotherapy are increasingly recognized as important modalities for managing oligo-progressive disease [36]. Clinical studies have demonstrated that local consolidative therapy, with or without maintenance systemic treatment, in patients with up to three metastases who did not exhibit disease progression following initial therapy can significantly improve both progression-free survival (PFS) and overall survival (OS) compared with maintenance therapy alone [13, 37].

In our cohort, the majority of progressive lesions in AR patients originated from preexisting tumor sites. Appropriately applied local therapy targeting these lesions may prolong PFS and thereby extend the duration of PD-1/PD-L1 inhibitor treatment, which is generally associated with lower toxicity and better quality of life relative to conventional chemotherapy [1]. The observed clinical benefits of local therapy in patients with AR align with findings reported in NSCLC patients developing acquired resistance to PD-1/PD-L1 blockade [22, 23, 38]. By eradicating tumor clones resistant to PD-1/PD-L1 inhibitors, local treatments such as radiotherapy may not only control focal disease but also potentiate systemic antitumor immunity through synergistic effects with immunotherapy [38–40]. To our knowledge, this study represents one of the first reports demonstrating the

potential benefit of local therapy for progressive or newly emergent lesions in patients with AR, emphasizing the need for further investigation.

Several limitations should be acknowledged. First, the retrospective design introduces potential selection bias and unmeasured confounding factors between subgroups, despite the use of Cox regression and propensity score matching to minimize imbalance. Therefore, these findings require confirmation in prospective, randomized studies. Second, detailed toxicity data were not consistently available, limiting the evaluation of safety when local therapy is combined with PD-1/PD-L1 inhibitors; this warrants further prospective assessment.

## Conclusion

In summary, AR is not an uncommon occurrence among metastatic NSCLC patients receiving PD-1/PD-L1 inhibitors, and its prognosis is comparable to that of typical responders. Local therapy directed at progressive lesions while maintaining ongoing PD-1/PD-L1 blockade appears to be a feasible management approach for patients with AR and merits further evaluation in future studies.

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**Conflict of Interest:** None

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**Ethics Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Fudan University Shanghai Cancer Center, the Fudan University Zhongshan Hospital, and the Tongji Hospital affiliated with Tongji Medical College of Huazhong University of Science and Technology (approval number: 2012228-3). Patient consent was waived due to the retrospective nature.

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