



LETTER

Immunotherapy rechallenge of patients with advanced NSCLC progression after sequential treatment with third-generation EGFR-TKI and immunotherapy

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Epidermal growth factor receptor (EGFR) mutations are among the most prevalent driver gene alterations in non-small cell lung cancer (NSCLC). Osimertinib, with or without chemotherapy, the first-line standard treatment for patients with advanced NSCLC bearing sensitive EGFR mutations, significantly prolongs the progression-free survival (PFS) to 25.5 months¹. Despite great breakthroughs in survival data, patients inevitably experience disease progression. A large meta-analysis has indicated that, compared with chemotherapy, immuno-based therapies achieve longer PFS in patients with EGFR mutation who progressed on third-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs)². Therefore, immunotherapies are often used after EGFR-TKI resistance is observed.

Multiple NSCLC studies have underscored the importance of immunotherapy rechallenge. In the phase III OAK trial, among 168 patients who continued to receive atezolizumab

after progression, 56% achieved control of target lesions. Patients with immune resistance caused by pseudoprogression or delayed response still benefit from continued immunotherapy³⁻⁵. Wang et al.⁶ have suggested that rechallenge combined with stereotactic body radiation therapy for patients with oligoprogression yields considerable survival benefits. In the MAPS1800A study, immunotherapy rechallenge combined with anti-angiogenic therapy significantly prolonged the OS⁷. Therefore, specific patient subgroups might benefit from immunotherapy rechallenge.

Whether immunotherapy rechallenge should be applied in such cases remains unclear. Therefore, we conducted a retrospective study to investigate the efficacy of immunotherapy rechallenge vs. no immunotherapy, and to identify the optimal candidate populations of patients who progressed after sequential treatment with EGFR-TKIs and immunotherapy.

This study included patients diagnosed with EGFR-mutant advanced NSCLC who progressed after treatment with third-generation EGFR-TKIs and immunotherapy between November 2018 and November 2023 at Jiangsu Cancer Center. The study was approved by Jiangsu Cancer Center (KY-2025-013). The study flowchart and statistical analysis methods are detailed in the **Supplementary Material**.

Among 134 enrolled patients, 71 received immunotherapy rechallenge, whereas 63 did not receive immunotherapy. The major results of the study are described below.

The baseline characteristics were essentially balanced and comparable between groups (**Figure 1A**). The overall objective

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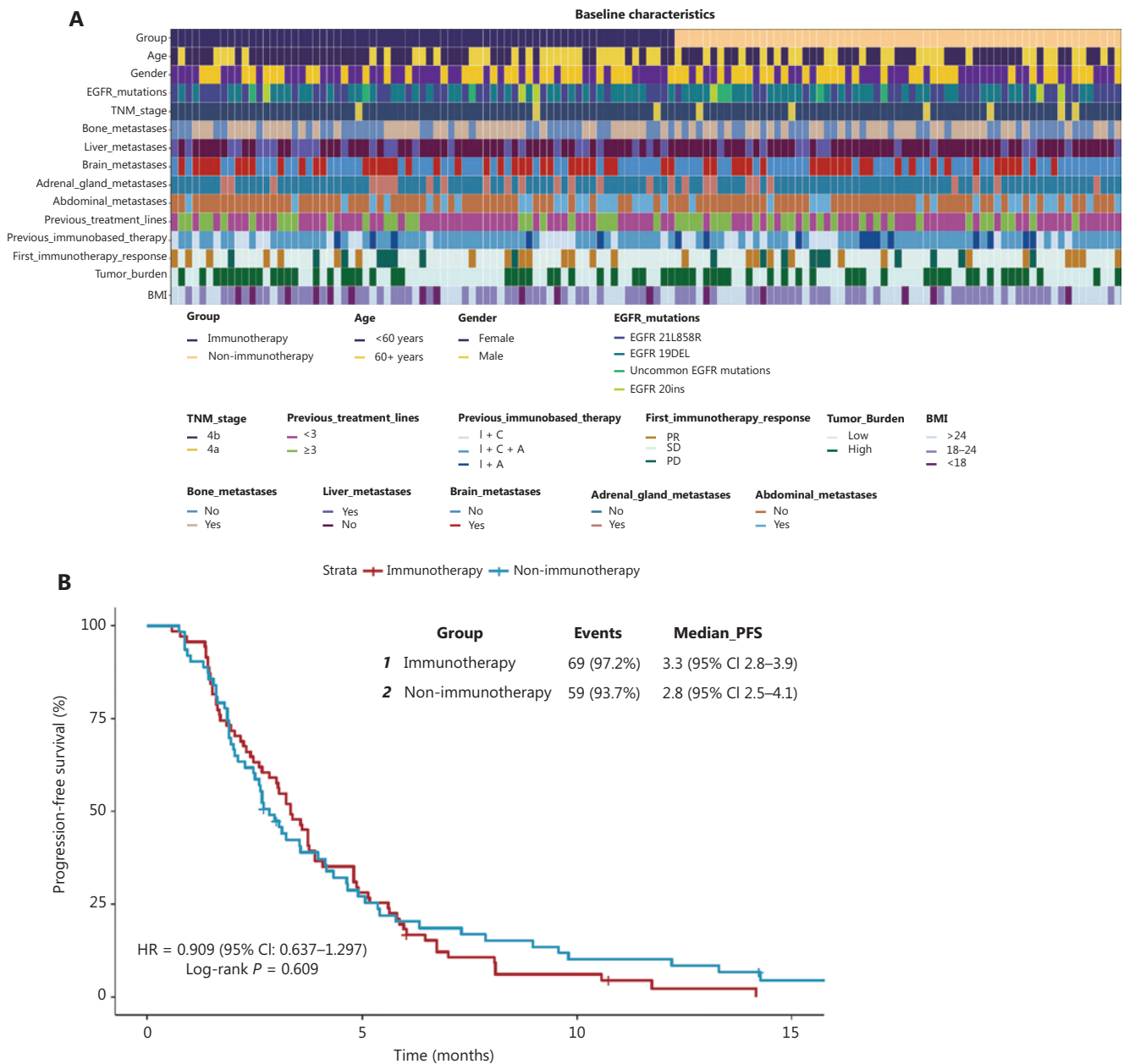


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response rate (ORR) was 8.20%, and the DCR was 58.96%. In the immunotherapy rechallenge group, the ORR was 8.45%, and did not significantly differ from that in the non-immunotherapy group (7.94%; $P = 0.914$). A similar trend was observed in the DCR (60.56% vs. 57.14%; $P = 0.688$). The median PFS of the total population was 3.13 months (95% CI: 2.67–3.73 months). The median PFS in the immunotherapy rechallenge group was 3.33 months (95% CI: 2.83–3.90 months) and did not significantly differ from that in the non-immunotherapy group (2.83 months, 95% CI: 2.47–4.13

months; $P = 0.609$) (**Figure 1B**). The PFS of patients in the EGFR-TKI-based group was 2.97 months (95% CI: 2.47–4.13 months), whereas the median PFS of patients in the other therapy group was 2.65 months (95% CI: 1.90–4.63 months) (**Figure 1C**). We observed no significant benefit in long-term prognosis (OS) [immunotherapy rechallenge group 11.47 (95% CI: 9.47–15.07) months vs. non-immunotherapy group 14.33 (95% CI: 10.97–19.27) months; $P = 0.986$].

We conducted survival follow-up on 71 patients who chose to undergo immunotherapy rechallenge. After a median

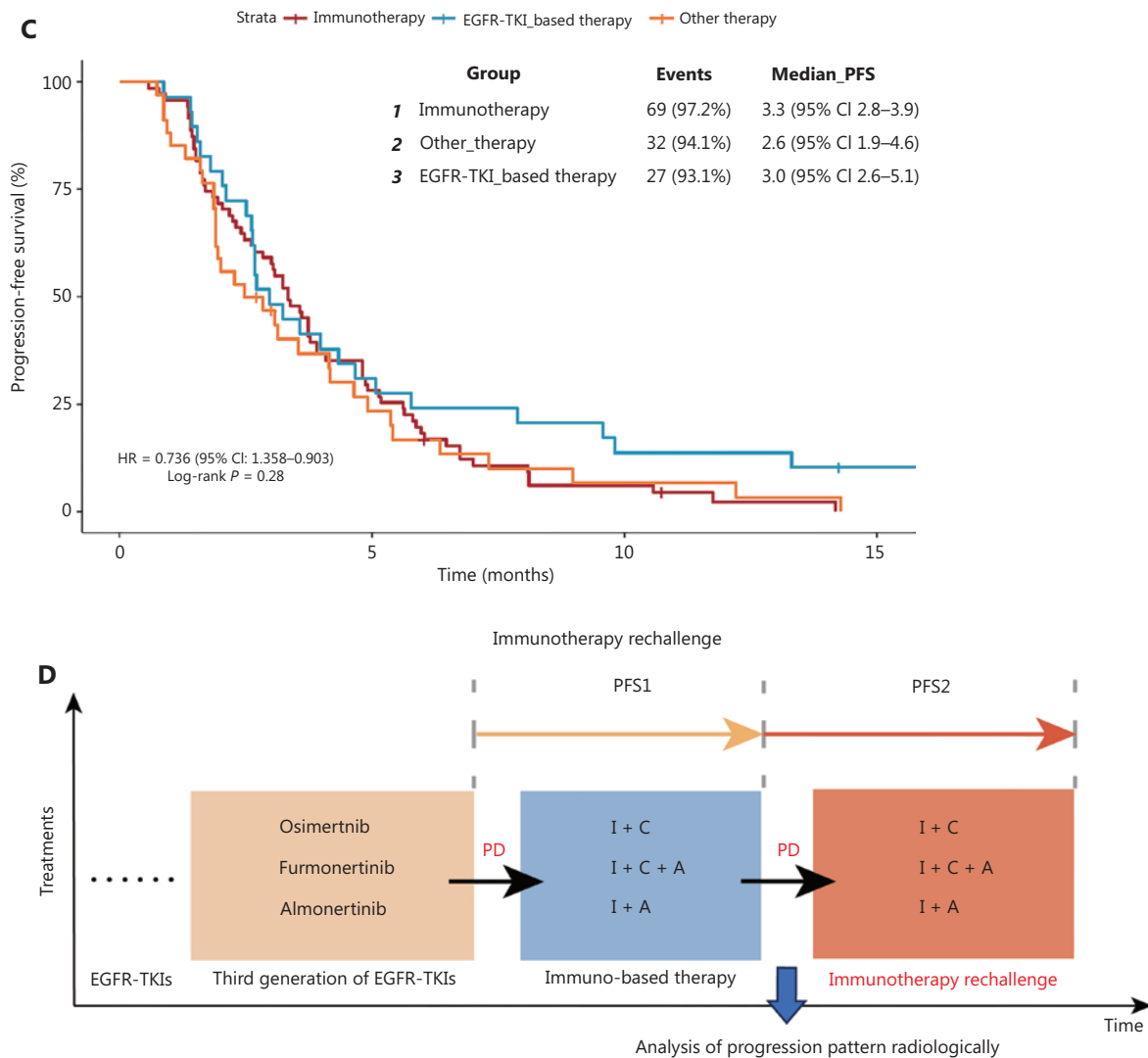


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follow-up time of 20.97 months (95% CI: 16.10–25.85 months), the median OS was 12.13 months (95% CI: 9.47–15.97 months). In addition, we evaluated the PFS1 + PFS2 of two lines of immunotherapy in patients, and observed a median PFS1 + PFS2 of 9.10 months (95% CI: 7.43–10.40 months) (**Figure 1D, E**).

Our investigation established a definitive time point during immunotherapy when the absence of progression could be used to stratify patients as either sensitive or resistant to immunotherapy. We selected 7.7 months (approximately 10 cycles of immunotherapy) as the cutoff point, on the basis of prior modeling calculations. Patients with a PFS of >7.7 months after previous immunotherapy were defined as the sensitive group, whereas those with a PFS of <7.7 months were defined as the resistant group (**Figure 1F, G**). The PFS of immunotherapy rechallenge was 3.48 months (95% CI: 2.17–NA months) in the

sensitive group and 3.33 months (95% CI: 2.60–3.90 months) in the resistant group ($P = 0.046$). The OS was significantly longer in the sensitive group than the resistant group (16.8 months vs. 10.6 months; $P = 0.030$) (**Figure 1H, I**).

To better screen patients who showed progression on EGFR-TKIs and immunotherapy to identify the population benefiting from immunotherapy rechallenge, we collected 31 features extracted from the baseline information, treatment status, and progression patterns of 71 patients with immunotherapy rechallenge (**Figure 1J**). Through LASSO regression, we selected 8 features with significant effects on progression outcomes among 31 variables. We selected 4 important indicators (progression pattern, previous immunotherapy response, previous immunotherapy sensitivity, and EGFR mutation type) according to further Cox univariate analysis, multivariate

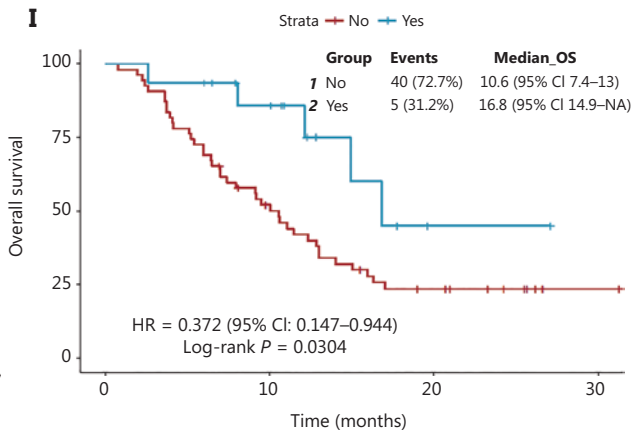
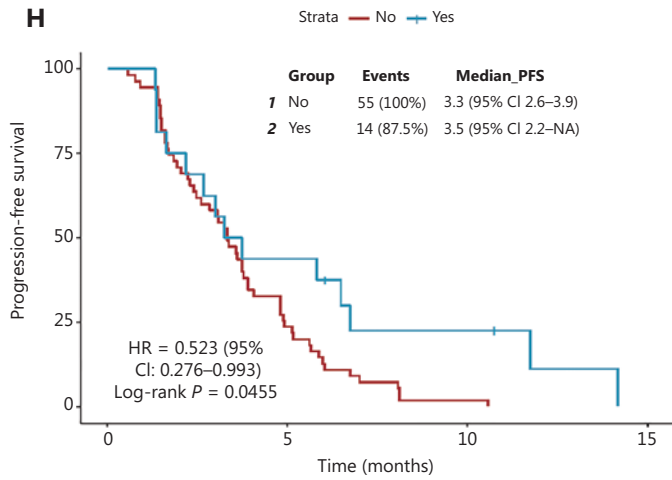
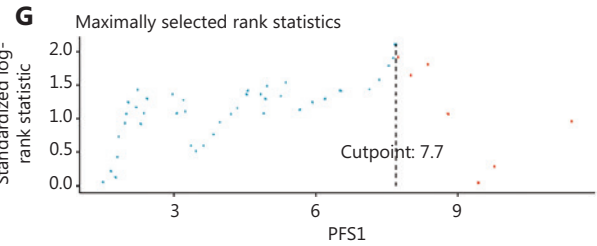
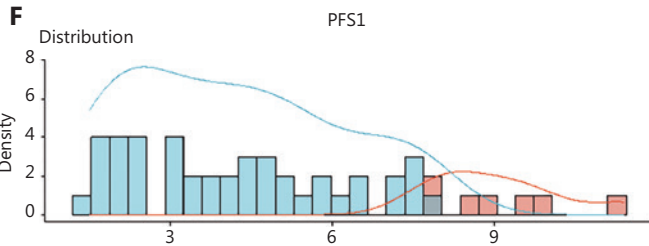
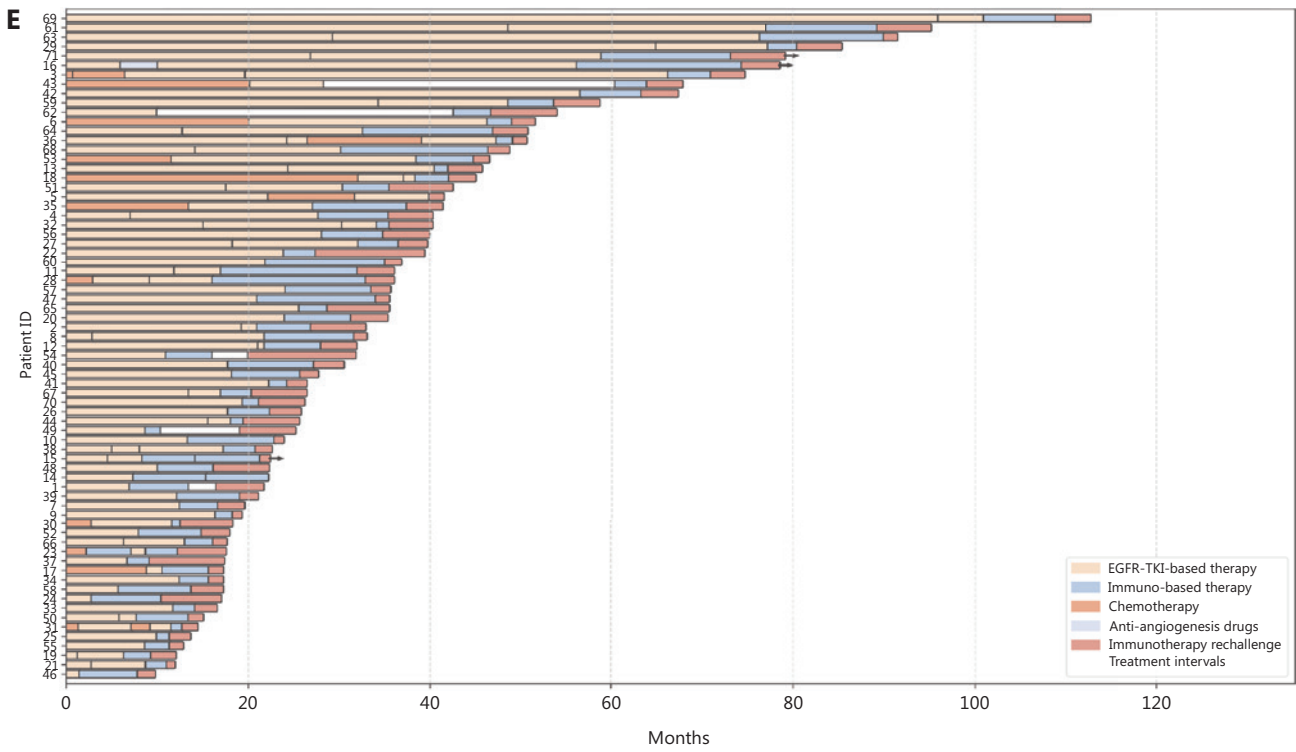


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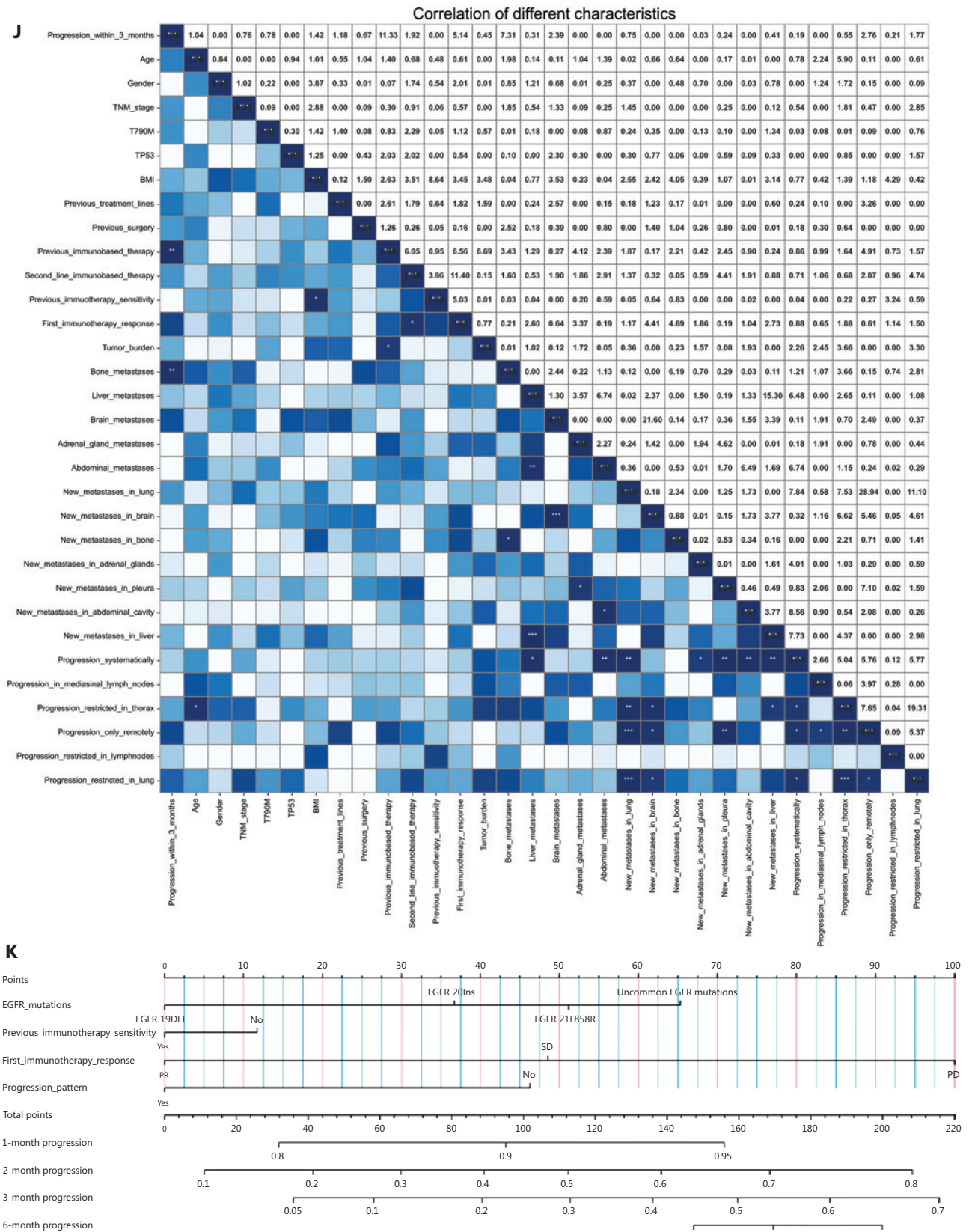


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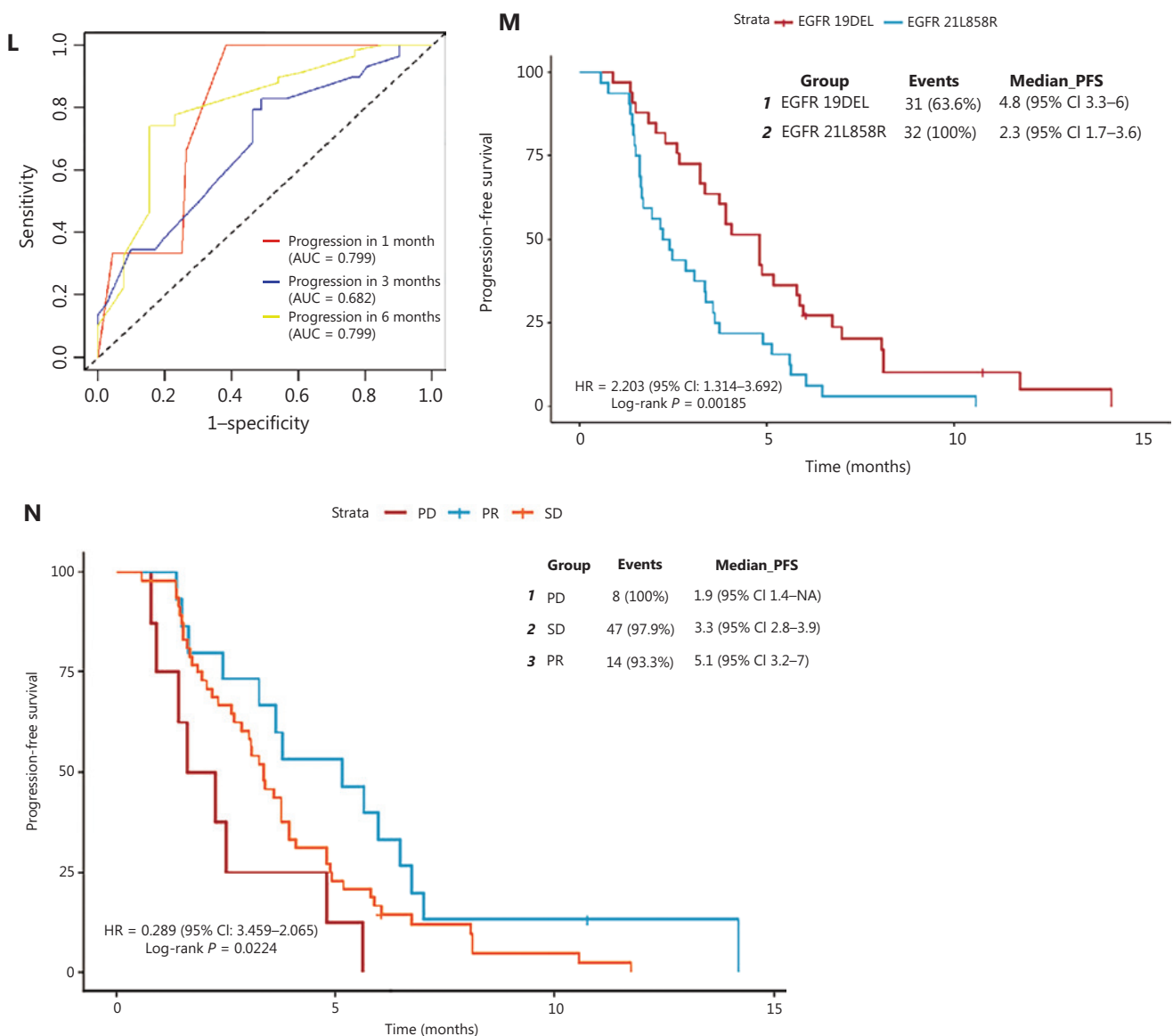


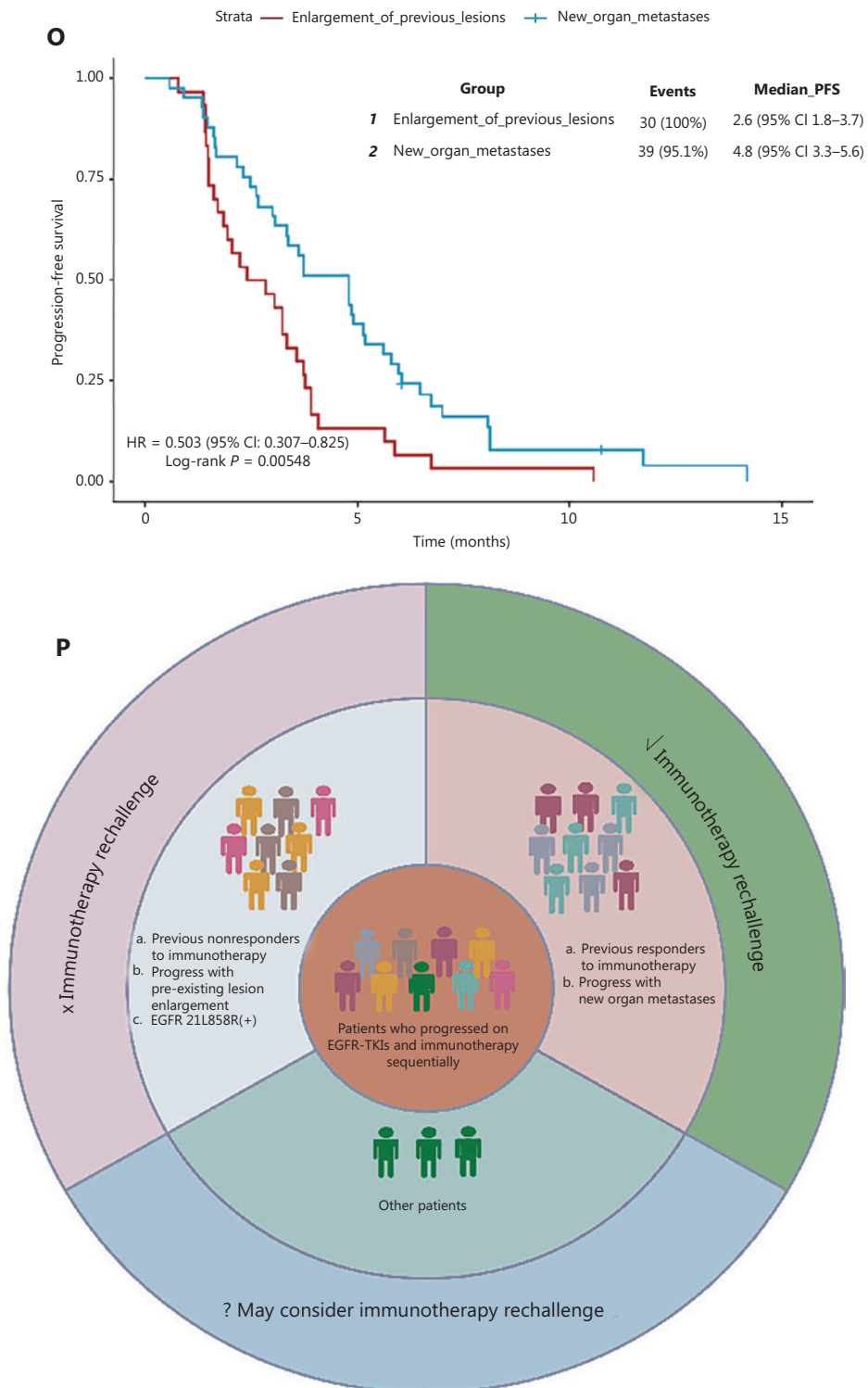
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analysis, and clinical practice. These indicators were used as grouping features (**Supplementary Method**) to build a Cox proportional hazards regression model (**Figure 1K**). We predicted the patients' progression risk within 1 month, 3 months, and 6 months according to this model, and determined AUC values of 0.80, 0.68, and 0.80, respectively (**Figure 1L**). According to the 4 important indicators, we plotted the Kaplan–Meier survival curves for the patients in different sub-groups (**Figure 1M, N, O**).

We collected treatment-related adverse events in patients who received immunotherapy rechallenge. The incidence

of all treatment-related adverse events and those exceeding grade 3 was 71.83% and 53.52% in the immunotherapy rechallenge group. No treatment-related deaths were detected.

This study, to our knowledge, is the first comparative analysis of immunotherapy rechallenge vs. non-immunotherapy regimens in patients with EGFR-mutant NSCLC after progression on third-generation EGFR-TKIs and prior immunotherapy. The immunotherapy rechallenge cohort, compared with the non-immunotherapy group, exhibited a modestly, but non-significantly, prolonged median PFS. This finding underscores the need for identifying the beneficiary population in



progression within 3 months (numbers in the grid represent the chi-square values between 2 features). (K) Construction of a nomogram to predict progression risk in patients undergoing immunotherapy rechallenge. (L) ROC curves of the nomogram. (M) Kaplan–Meier estimates of immunotherapy rechallenge PFS in patients with EGFR 19 DEL or EGFR 21 L858R mutations. (N) Kaplan–Meier estimates of immunotherapy rechallenge PFS in patients with various prior immunotherapy responses. (O) Kaplan–Meier estimates of immunotherapy rechallenge PFS in patients with various progression patterns. (P) Treatment selection recommendations for patients.

this setting. According to the expert consensus on immunotherapy rechallenge in NSCLC, patients with a previous immunotherapy duration of >3 months have prolonged PFS2 during immunotherapy rechallenge⁸. A meta-analysis involving 2,100 cases of immunotherapy rechallenge has suggested that patients with a longer PFS1 (>2 years) have significantly more favorable ORR, DCR, and PFS2 than those with a shorter PFS1 (<1 year)⁹. This finding is consistent with the trends observed in our study. Patients who did not progress within 7.7 months (approximately 10 cycles of immunotherapy) had longer PFS and OS than those who showed progression, thus indicating the consistency of their response to immunotherapy. However, the specific time point for defining sensitivity requires further verification.

Through our Cox proportional hazards regression model, we screened out four important characteristics (EGFR mutations, previous immunotherapy sensitivity, first immunotherapy response and progression pattern) that helps to identify potential beneficiaries of immunotherapy rechallenge. Patients developing new organ metastases demonstrated greater suitability for immunotherapy rechallenge, whereas those with pre-existing lesion enlargement derived limited benefit¹⁰. These findings might stem from biological differences between metastatic and primary lesions¹¹. The emergence of new metastases does not necessarily reflect systemic immunotherapy resistance. In cases in which baseline lesions remain controlled, new lesions may still be effectively managed through sustained immunotherapy combined with localized therapies (e.g., radiotherapy). In contrast, progression of existing lesions suggests a loss of immunogenic control necessitating alternative therapeutic strategies¹².

We also found that patients who achieved PR/SD in previous immunotherapy were more suitable for immunotherapy rechallenge. Other studies have reported similar results indicating that patients who achieved tumor remission during the first course of immunotherapy still obtained an ORR of 40–60% during immunotherapy rechallenge^{13,14}. In a Japanese retrospective study among 17 patients with NSCLC, 7 patients showing favorable benefits (including sustained SD) from

the initial immune checkpoint inhibitor (ICI) treatment still achieved PR or SD after ICI rechallenge¹⁵.

Given the limited sample size of patients with the EGFR 21 L858R mutation included in this study, immunotherapy rechallenge for this subgroup should be considered with caution. The exact underlying reasons require further investigation; however, our data suggested that EGFR-TKI-based combination therapy might be a favorable treatment option for these patients.

In conclusion, patients who responded to previous immunotherapy (PR/SD or PFS over 7.7 months) or progressed with new organ metastases were found to be more suitable for immunotherapy rechallenge, whereas patients who were resistant to previous immunotherapy, who bore the EGFR 21 L858R mutation, or whose disease progressed with enlargement of pre-existing lesions were found to be less suitable for immunotherapy rechallenge (**Figure 1P**). Large-scale prospective studies are needed to further confirm these findings.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conception and design: Shuyi Hu, Xinhong Shi, Xiaohua Wang, Guoren Zhou, Cheng Chen, Zipeng Wu, Yingying Dai. Administrative support: Xiaohua Wang, Cheng Chen, Chengyun Yao, Meiqi Shi, Bo Shen, Guoren Zhou. Collection and assembly of information: All authors. Manuscript writing: Shuyi Hu, Xiaohua Wang, Qin Hu. Final approval of the manuscript: All authors.

Data availability statement

The data generated in this study are available upon request from the corresponding author.

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