

Second-generation epidermal growth factor receptor-tyrosine kinase inhibitors as a potentially cost-effective salvage option following third-generation resistance in patients with uncharacterized mechanisms: a retrospective propensity-matched analysis

Cuicui Zhang

The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Henan Academy of Innovations in Medical Science

Zhen HE

The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Henan Academy of Innovations in Medical Science

Xiance TANG

The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital

Xiaoqing YANG

The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital

Sen YANG

The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Henan Academy of Innovations in Medical Science

Shuxiang MA

The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Henan Academy of Innovations in Medical Science

Yuqing MO

The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Henan Academy of Innovations in Medical Science

Yufeng WU

The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Henan Academy of Innovations in Medical Science

Haiyang CHEN

The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Henan Academy of Innovations in Medical Science

Peng LI

The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Henan Academy of Innovations in Medical Science

Yingxi WU

The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Henan Academy of Innovations in Medical Science

Tong LIU

The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital

Wenyuan DUAN

The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital

Qiming WANG

qimingwang1006@126.com

The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Henan Academy of Innovations in Medical Science

Research Article

Keywords: Lung cancer, Rechallenge, Resistance, Second-generation EGFR-TKIs, Third-generation EGFR-TKIs

Posted Date: October 22nd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11025798/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Purpose

After acquired resistance to third-generation (3G) epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), the optimal strategy for patients with EGFR-mutated non-small cell lung cancer (NSCLC) who lack identifiable actionable resistance mechanisms remains uncertain. This study compared continuing 3G EGFR-TKI therapy (3 + 3 strategy) with switching to second-generation (2G) EGFR-TKIs (3 + 2 strategy) in this population.

Methods

In this single-center retrospective cohort study, patients with EGFR-mutated advanced NSCLC who progressed on 3G EGFR-TKIs (osimertinib, aumolertinib, or furmonertinib) between January 2015 and December 2024 were screened. Propensity score matching (1:1 nearest-neighbor without replacement, caliper 0.2) was used to balance baseline characteristics between the 3 + 2 group (dacomitinib or afatinib) and the 3 + 3 group. Objective response rate (ORR), disease control rate (DCR), time to treatment failure (TTF), and overall survival (OS) were compared.

Results

Among 1,934 patients screened, 60 matched pairs were analyzed. The 3 + 2 group showed a significantly higher ORR than the 3 + 3 group (18.3% vs. 3.3%, $P = 0.0082$), particularly in the dacomitinib subgroup (23.8% vs. 2.4%, $P = 0.0036$). However, no significant differences were observed in DCR (80.0% vs. 73.3%, $P = 0.3880$), median TTF (4.43 vs. 5.32 months, $P = 0.695$), or median OS (15.97 vs. 14.88 months, $P = 0.824$).

Conclusion

Switching to 2G EGFR-TKIs—particularly dacomitinib—yielded a higher response rate after 3G EGFR-TKI resistance without compromising TTF or OS; however, the absence of a survival benefit and the lack of comprehensive resistance mechanism data preclude a definitive recommendation. Biomarker-guided selection remains essential and requires prospective validation. Given their lower acquisition costs, 2G EGFR-TKIs may also reduce treatment-related financial burden, a hypothesis that merits formal pharmacoeconomic evaluation.

Trial registration

Not applicable (this study is a retrospective observational analysis, not a clinical trial).

Introduction

Third-generation epidermal growth factor receptor tyrosine kinase inhibitors (3G EGFR-TKIs)—including osimertinib, aumolertinib, and furmonertinib—have established themselves as the standard first-line therapy for EGFR-mutant advanced non-small cell lung cancer (NSCLC), demonstrating superior efficacy against sensitizing mutations (exon 19 deletions/L858R) and the resistant T790M mutation [1–3]. However, acquired resistance remains inevitable, with median progression-free survival (PFS) ranging from 18.9 months (FLAURA) to 20.8 months (AENEAS) [4, 5], leaving clinicians with substantial uncertainty regarding optimal post-progression management.

The resistance landscape after 3G EGFR-TKI failure is characterized by remarkable molecular heterogeneity. EGFR-dependent mechanisms—including C797S mutations and EGFR amplification—and EGFR-independent pathways—such as MET amplification, HER2 activation, histologic transformation, and PI3K pathway alterations—have been well characterized, particularly for osimertinib [6]. Emerging data also suggest differential resistance profiles among the three approved 3G agents: aumolertinib-resistant models demonstrate higher frequencies of MET amplification compared with osimertinib [7], whereas furmonertinib resistance may involve unique EGFR tertiary mutations [6]. This mechanistic diversity has catalyzed the development of precision-directed post-resistance strategies.

Indeed, the therapeutic armamentarium for 3G-resistant disease has expanded considerably. For patients with MET amplification, the combination of savolitinib and osimertinib has demonstrated meaningful clinical benefit in prospective trials. More broadly, antibody-drug conjugates (e.g., sacituzumab tirumotecan targeting Trop-2), immune checkpoint inhibitors combined with anti-angiogenic agents and chemotherapy (e.g., ivonescimab or sintilimab-based regimens), and other combination strategies have shown efficacy in biomarker-selected or unselected populations [8–11]. These advances have established a clear therapeutic hierarchy: patients with identifiable actionable resistance mechanisms should receive mechanism-directed therapy as the preferred standard of care.

Yet a substantial proportion of patients—estimated at 40% to 60% in real-world practice—fail to have actionable resistance mechanisms identified at the time of progression. For this population, the optimal sequencing strategy remains undefined. Chemotherapy remains the default option, but its tolerability and efficacy in heavily pretreated patients are often suboptimal. Against this backdrop, the potential role of second-generation EGFR-TKIs (2G EGFR-TKIs)—particularly dacomitinib, an irreversible pan-HER family inhibitor—warrants re-examination. Preclinical evidence suggests that certain resistance clones, such as those harboring C797S mutations or non-classical EGFR/ERBB2 alterations, may retain sensitivity to 2G agents through broader HER-family inhibition [12]. However, it is well established that switching to an alternative EGFR-TKI without characterizing the underlying resistance mechanism yields limited clinical benefit in unselected populations [13, 14]. Whether a subset of patients without actionable targets might derive meaningful benefit from 2G EGFR-TKI switching—and how such patients might be identified—remains an open clinical question.

Critically, no comparative real-world data currently exist to guide the choice between continuing 3G EGFR-TKI therapy (3 + 3 strategy) and switching to a 2G EGFR-TKI (3 + 2 strategy) in patients for whom molecular profiling of resistance to 3G EGFR-TKIs cannot be performed or are unsuitable for intensive combination regimens. The present study was designed to address this specific evidence gap. We evaluated a single-center retrospective cohort of 120 patients with EGFR-mutant NSCLC who progressed on 3G EGFR-TKIs, applying propensity score matching to compare outcomes between those who switched to 2G EGFR-TKIs and those who continued 3G therapy. Our primary objective was to assess whether 2G EGFR-TKI switching represents a viable oral therapeutic option for patients without actionable resistance targets—a population for whom standard precision-directed therapies are not applicable. We additionally sought to identify clinical and molecular features associated with response to 2G EGFR-TKIs in this setting, with the explicit understanding that these findings are hypothesis-generating and require prospective validation.

Materials and Methods

Study Design and Patient Selection

In this retrospective cohort study, 120 patients with EGFR-mutant advanced NSCLC who were treated at Henan Cancer Hospital between January 2015 and December 2024 were analyzed. The inclusion criteria were as follows:

- Histologically or cytologically confirmed stage IIIB–IV lung adenocarcinoma.
- Documented EGFR-sensitizing mutations (exon 19 deletion or L858R).
- Disease progression after treatment with 3G EGFR-TKIs (osimertinib, aumolertinib, or furmonertinib).
- Post-progression tumor biopsies with next-generation sequencing (NGS) were performed in 33 of 120 patients (27.5%) following failure of third-generation (3G) EGFR-TKI therapy.
- Post-progression on 3G EGFR-TKIs, patients who received either direct continuation or bridged therapy with other 3G or 2G EGFR-TKIs.
- A minimum of one follow-up assessment post-treatment.

To minimize confounding effects, the exclusion criterion was as follows:

- Patients who received investigational agents as TKI therapy.

Data Collection

Clinical and molecular data were extracted from electronic medical records and supplemented via telephonic follow-up when necessary.

Outcomes

The measured outcomes were as follows:

Objective Response Rate (ORR): The proportion of patients achieving a confirmed complete response (CR) or partial response (PR) as per RECIST 1.1.

Disease Control Rate (DCR): Included patients with CR, PR, or SD, as per investigator-assessed RECIST 1.1 criteria.

Time to Treatment Failure (TTF): The time from treatment initiation to discontinuation owing to disease progression (RECIST v1.1), unacceptable toxicity (CTCAE v5.0 $\geq$ Grade 3), patient withdrawal, or death from any cause.

Overall survival (OS): The interval between the initiation time of 2G/3G EGFR-TKIs after resistance to 3G EGFR-TKIs and death or censoring at data cutoff (April 10, 2025).

Statistical Analysis

The Kaplan–Meier method was used to assess the TTF, OS, and associated 95% confidence intervals (CIs). The log-rank test was used to compare the differences between both groups, and a Cox regression model was used to estimate hazard ratios (HRs) and corresponding 95% CIs. The Clopper–Pearson method was used to assess ORR, DCR, and associated 95% CIs. The Chi-square or Fisher’s exact test was used to compare the differences between the two groups.

In total, 1,934 patients met the initial screening criteria. Among them, 523 were preliminarily eligible for the “3+2/3+3” regimen. After rigorous selection, 454 patients were eligible for the “3+2/3+3” regimen. To accurately compare efficacy between the 3+2 and 3+3 groups while minimizing confounding variables, propensity score matching (PSM) [15] was conducted using the Greedy nearest neighbor algorithm 1-to-1 matching technique without replacement within a caliper width of 0.2 to balance baseline characteristics, including age, L858R mutations at initial diagnosis, systemic anti-angiogenic therapy (anlotinib/bevacizumab/endostar, etc.) combined with post-progression on 3G EGFR-TKI, and treatment strategy (sequential/bridging therapy). In addition, a multivariate logistic regression model was employed to estimate the propensity scores of patients in both groups. Eventually, 60 patients were successfully paired and included in 3+2 and 3+3 groups, respectively (Fig. 1).

Statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA). Nominal P values were used.

Results

Patient Characteristics

Age, L858R mutations at the time of initial diagnosis, nonclassical EGFR/ERBB2 mutations at the time of initial diagnosis, systemic anti-angiogenic therapy (anlotinib/bevacizumab/endostar, etc.) combined with

post-progression on 3G EGFR-TKI, and treatment strategy (sequential/bridging therapy) may serve as confounding factors. However, in the present study, to avoid potential bias and better compare the efficacy between the 3+2 and 3+3 groups, we balanced the baseline data via PSM. The following variables remained unbalanced after matching: initial adrenal gland metastasis, T790M mutations at the time of initial diagnosis, and nonclassical EGFR/ERBB2 mutations at the time of initial diagnosis (Table 1).

Efficacy Evaluation and Survival Analysis

The median follow-up time from lung cancer diagnosis to the data cutoff time (April 10, 2025) was 43.47 months.

ORR and DCR

Analysis of ORR and DCR Between the 3+2 and 3+3 Groups

To explore whether continuing with a 3G EGFR-TKI or switching to a 2G EGFR-TKI is more beneficial after resistance to 3G EGFR-TKI in patients with EGFR mutations, the patients were divided into two groups: the 3+2 and 3+3 groups. The ORR was significantly higher in the 3+2 group than in the 3+3 group (18.3% vs. 3.30%), with statistical significance ($P = 0.0082$). However, no statistically significant differences in DCR were observed between the two groups (80.00% vs. 73.30%; $P = 0.3880$) (Table 2).

Analysis of ORR and DCR Between the Dacomitinib-treated Subgroup in the 3+2 and 3+3 Groups

Next, we compared the ORR and DCR between the dacomitinib-treated subgroup in the 3+2 group and 3+3 groups. We observed that the ORR of the dacomitinib-treated subset was significantly higher in the 3+2 group than in the 3+3 group (23.8% vs. 2.4%); the difference was statistically significant ($P = 0.0036$). However, the DCR was similar in both groups (81.0% vs. 71.4%), with no significant statistical difference ($P = 0.3055$) (Table 3).

Additional analysis of ORR and DCR between Dacomitinib and Afatinib in the 3+2 Group

We further compared the ORR and DCR between the dacomitinib and afatinib subgroups in the 3+2 group. The ORR was higher in the dacomitinib subset than in the afatinib subgroup (23.80% vs. 5.60%). Meanwhile, the DCR was similar for both groups (81.00% vs. 77.80%), with no statistically significant difference (Online Resource 9).

TTF and OS

Comparison of TTF and OS Between the 3+2 and 3+3 Groups

The median TTF was 4.43 months (95% CI: 3.25–5.72) and 5.32 months (95% CI: 4.11–6.14) in the 3+2 and 3+3 groups, respectively; the difference was not statistically significant ($P = 0.695$) (Fig. 2). Similarly,

the median OS was 15.97 months (95% CI: 7.92–19.94) and 14.88 months (95% CI: 8.84–19.68), respectively; the difference was not significant ($P = 0.824$) (Fig. 3).

Exploratory Analysis of the 3+2 Treatment Group

Consequently, comprehensive subgroup analyses were performed to explore potential prognostic factors.

By Treatment Response:

Stratified by therapeutic efficacy during 2G EGFR-TKI treatment, the median TTF was 1.49 months (95% CI: 0.59–2.23), 8.51 months (95% CI: 3.25–20.99) and 4.93 months (95% CI: 3.75–7.13) in the PD, PR, and SD groups, with statistically significant difference ($P < 0.0001$) (Fig. 4A). Furthermore, the median OS was 4.99 months (95% CI: 2.37–24.08), 24.77 months (95% CI: 18.13–), and 12.71 months (95% CI: 6.67–19.25) in the PD, PR, and SD groups; the differences were not statistically significant ($P = 0.058$) (Fig. 4B).

By metastatic status at initial diagnosis:

Liver Metastasis:

The median TTF was 4.01 months (95% CI: 3.25–5.72) and 4.93 months (95% CI: 1.08–8.51) in patients without and with liver metastasis, respectively ($P = 0.593$) (Online Resource 1). Furthermore, the median OS was 15.97 months (95% CI: 7.92–24.08) and 19.19 months (95% CI: 2.89–19.94) in patients without and with liver metastasis, respectively ($P = 0.381$) (Online Resource 2).

Brain Metastasis:

The median TTF was 3.98 months (95% CI: 2.76–5.68) and 1.39 months (95% CI: 0.67–2.85) in patients without and with brain metastasis, respectively ($P = 0.373$) (Online Resource 3). Furthermore, the median OS was 12.71 months (95% CI: 5.72–20.60) and 18.56 months (95% CI: 6.24–26.51) in patients without and with brain metastasis, respectively ($P = 0.957$) (Online Resource 4).

Bone Metastasis:

The median TTF was 5.39 months (95% CI: 3.75–7.19) and 3.07 months (95% CI: 1.08–6.67) in patients without and with bone metastasis, respectively ($P = 0.272$) (Online Resource 5). Furthermore, the median OS was 19.19 months (95% CI: 8.28–24.77) and 7.52 months (95% CI: 3.61–15.97) in patients without and with bone metastasis, respectively ($P = 0.185$) (Online Resource 6).

Adrenal Metastasis:

The median TTF was 4.01 months (95% CI: 3.25–7.13) and 4.43 months (95% CI: 0.23–5.39) in patients without and with adrenal metastasis, respectively ($P = 0.083$) (Online Resource 7). Furthermore, the

median OS was 17.71 months (95% CI: 7.92–24.08) and 11.40 months (95% CI: 3.45–) in patients without and with adrenal metastasis, respectively ($P = 0.352$) (Online Resource 8).

Pleural Metastasis:

The median TTF was 4.93 months (95% CI: 3.88–7.13) and 2.96 months (95% CI: 1.91–5.68) in patients without and with pleural metastasis, respectively ($P = 0.023$) (Fig. 5A). Furthermore, the median OS was 19.19 months (95% CI: 7.92–24.77) and 15.97 months (95% CI: 4.99–18.56) in patients without and with pleural metastasis, respectively ($P = 0.211$) (Fig. 5B).

Discussion

With the widespread establishment of third-generation epidermal growth factor receptor tyrosine kinase inhibitors (3G EGFR-TKIs) as first-line therapy for EGFR-mutated advanced non-small cell lung cancer (NSCLC) [1,16], the selection of treatment strategies following acquired resistance has become a major clinical challenge [17,18]. This study provided the real-world cohort analysis to systematically compare the efficacy of switching to second-generation EGFR-TKIs (2G) (3+2 strategy) versus continuing third-generation agents (3+3 strategy) after progression on 3G EGFR-TKIs. The key finding was a significantly higher objective response rate (ORR) in the 3+2 group compared with the 3+3 group (18.3% vs 3.3%, $P=0.0082$), with the dacomitinib subgroup achieving an ORR of 23.8% (vs 2.4% in the 3+3 group, $P=0.0036$). However, this response advantage did not translate into significant differences in TTF or OS (median TTF: 4.43 vs 5.32 months; median OS: 15.97 vs 14.88 months; both $P>0.05$). This phenomenon of "response without survival benefit" suggests that 2G EGFR-TKIs retain target activity in a subset of patients with 3G resistance, but their clinical value requires biomarker-driven patient selection [5-7].

Previous study has provided preliminary evidence for the potential activity of 2G EGFR-TKIs after 3G resistance [13,19,20]. In vitro studies by Nishino et al. [21] demonstrated that first- and second-generation TKIs could restore EGFR pathway inhibition in cell models harboring acquired C797S mutations [21,22]. The ORR advantage observed with the 3+2 strategy in our study, particularly in the dacomitinib subgroup, aligns with this mechanistic hypothesis. Notably, dacomitinib is an irreversible pan-HER family inhibitor with activity against EGFR, HER2, and ERBB4 [23,24], whereas afatinib, although also irreversible, has a distinct affinity profile across HER family members [25,26]. The markedly higher ORR with dacomitinib (23.8%) compared with afatinib (5.6%) in our 3+2 cohort may reflect the broader HER-family inhibitory activity of dacomitinib in overcoming 3G-resistant clones, especially in patients with non-classical EGFR/ERBB2 mutations or HER-family bypass activation. However, the afatinib subgroup was small ($n=18$), and these data should be interpreted with caution due to limited statistical power.

In the current therapeutic landscape after 3G EGFR-TKI failure, several prospective phase III trials have established the efficacy of precision-directed regimens. For patients with MET amplification, savolitinib plus osimertinib (SACHI trial) achieved a median progression-free survival (PFS) of 8.2 months [27]. For broader resistance populations, ivonescimab plus chemotherapy (HARMONi-A trial) demonstrated a

median PFS of 7.1 months [28,29]; sintilimab plus bevacizumab biosimilar and chemotherapy (ORIENT-31 trial) achieved a median PFS of 7.2 months [30,31]; and sacituzumab tirumotecan (OptiTROP-Lung04 trial) achieved a median PFS of 8.3 months [32]. The ORR of these standard-of-care regimens generally ranges from 48% to 61%, substantially exceeding the 18.3% ORR observed with 2G EGFR-TKIs in our study. However, these approaches all require specific resistance mechanisms or biomarker status: MET amplification is detected in approximately 15%–30% of cases [4,33]; Trop-2 ADC is indicated after failure EGFR-TKI [32,34,35]; and immunotherapy combinations have shown limited benefit in EGFR-mutant populations with considerable toxicity [36]. Thus, for patients without identifiable actionable resistance mechanisms, or those unsuitable for or declining chemotherapy/immunotherapy-based combinations, switching to a 2G EGFR-TKI—particularly dacomitinib—offers an oral, accessible, and relatively tolerable alternative, especially for advanced patients whose primary treatment goals are disease control and symptom palliation [13,19].

The dissociation between improved ORR and unchanged TTF/OS in our study warrants careful interpretation. First, TTF encompasses treatment discontinuation due to disease progression, unacceptable toxicity, patient withdrawal, and death from any cause [37,38]. Dacomitinib, as a pan-HER inhibitor, is associated with higher rates of diarrhea and rash compared with 3G agents [24,39,40]; some patients may discontinue therapy due to toxicity rather than progression, potentially masking a true PFS benefit. Second, OS is heavily confounded by subsequent therapies—patients in both groups received chemotherapy, local therapies, and anti-angiogenic agents after progression on their assigned 2G or 3G regimen, and these crossover treatments may dilute any differential survival effect of the initial strategy. Third, the post-PSM sample size of 120 patients yielded limited OS events, providing insufficient statistical power to detect clinically meaningful survival differences [41]. Therefore, based on the current data, we cannot conclude that the 3+2 strategy is inferior or equivalent to the 3+3 strategy in terms of survival, nor can we assert a definitive survival advantage.

Our exploratory subgroup analyses offer several clinically relevant insights. Within the 3+2 treatment group, radiographic response to 2G EGFR-TKI (PR vs SD vs PD) was a strong predictor of TTF benefit ($P<0.0001$), suggesting that early imaging assessment may help identify patients likely to derive sustained benefit. Additionally, the presence of pleural metastasis at initial diagnosis was associated with shorter TTF on 2G EGFR-TKI therapy ($P=0.023$), whereas hepatic, brain, bone, and adrenal metastases did not show significant prognostic value. This finding may reflect an association between pleural dissemination and more aggressive tumor biology, and warrants validation in prospective studies.

Beyond clinical outcomes, the economic dimension of post-resistance treatment strategies deserves attention. In many healthcare systems, second-generation EGFR-TKIs such as afatinib and dacomitinib carry lower acquisition costs than third-generation agents, and several are available in generic form; where such a cost differential exists, switching to a 2G EGFR-TKI could reduce financial toxicity for patients while preserving disease control. Although cost data were not collected in the present study, our

findings provide a clinical rationale for future cost-effectiveness analyses comparing 3G EGFR-TKI rechallenge with a 2G switch strategy, particularly in resource-limited settings

This study has several important limitations. First, it is a single-center retrospective analysis, which is more susceptible to selection bias and confounding than prospective designs, and the findings may not be generalizable to other populations. Second, the re-biopsy rate after 3G EGFR-TKI resistance was low, with approximately 72.5% of patients lacking comprehensive post-resistance molecular profiling. It is well established across multiple studies that switching to another EGFR-TKI without characterizing the resistance mechanism yields limited clinical benefit [13,14,42]. Third, propensity score matching (PSM) substantially reduced the sample size from 454 to 120 cases, diminishing statistical power; moreover, several key variables remained imbalanced after PSM (e.g., non-classical EGFR/ERBB2 mutations, adrenal metastasis) [41,43]. Fourth, various bridging therapies (such as local ablation or intervening chemotherapy) may have confounded the interpretation of TTF. Finally, the OS follow-up duration may have been insufficient to observe mature survival differences between the two groups.

In conclusion, this real-world cohort study demonstrates that switching to 2G EGFR-TKIs—particularly dacomitinib—after 3G EGFR-TKI resistance yields a significantly higher objective response rate without compromising TTF or OS [13,19]. Molecular profiling (e.g., ERBB2 mutation status), early radiographic assessment during 2G TKI therapy, and the presence of pleural metastasis at initial diagnosis may help optimize patient selection. For patients without identifiable actionable resistance mechanisms, 2G EGFR-TKIs provide an oral and accessible treatment option. Larger-scale prospective studies with comprehensive resistance profiling are needed to definitively establish the role of 2G EGFR-TKIs in the post-3G therapeutic sequence.

Abbreviations

Non-small cell lung cancer: NSCLC

Epidermal growth factor receptor tyrosine kinase inhibitors: EGFR-TKIs

Third-generation: 3G

Second-generation: 2G

Epidermal growth factor receptor: EGFR

Progression-free survival: PFS

Overall survival: OS

Objective response rate: ORR

Disease control rate: DCR

Time to treatment failure: TTF

Declarations

Ethics approval and consent to participate: The study protocol was approved by the Institutional Review Board of The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital on November 25, 2024 (approval No. 2024-523-001). The study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Owing to the retrospective nature of this study, the requirement for written informed consent was waived by the Institutional Review Board.

Consent for publication: Not applicable.

Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Funding: This study was supported by the Key Research and Development Program of Henan Province in 2023—Key Technologies of Novel Precision Immunotherapy for Refractory Malignant Tumors (No. 231111313300), the Henan Province Health and Youth Subject Leader Training Project (No. [2020]60), the Key Project of Medical Science and Technology in Henan Province (SBGJ202101009), the Leading Talent Cultivation Project of Henan Health Science and Technology Innovation Talents (YXKC2020009), Zhongyuan Qianren Jihua (ZYQR201912118), the Wu Jie-Ping Clinical Research Fund (320.6750.2023-05-1), the Excellent Young Talent Cultivation Project of Henan Health Science and Technology Innovation Talents (No. YXKC2020046), the Henan International Joint Laboratory of Drug Resistance and Reversal of Targeted Therapy for Lung Cancer (No. [2021]10), the Henan Refractory Lung Cancer Drug Treatment Engineering Technology Research Center (No. [2020]4), the Henan Medical Key Laboratory of Refractory Lung Cancer (No. [2020]27), Henan Medical Researcher Overseas Training Program (HNMOT2025021) and the Henan Provincial Medical Science and Technology Key Research Program Projects (SBGJ202403049). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions: C.Z. and Q.W. conceived the study, curated the data, acquired resources, and supervised the study; C.Z., Z.H., X.T., X.Y., S.Y., S.M., Y.M., Yu.W., H.C., P.L., Yi.W., T.L., W.D., and Q.W. conducted the investigation and developed the methodology; X.T. performed the formal analysis; C.Z. wrote the original draft; Z.H., X.T., X.Y., S.Y., S.M., Y.M., Yu.W., H.C., P.L., Yi.W., T.L., W.D., and Q.W. reviewed and edited the manuscript. All authors read and approved the final manuscript.

Trial registration: Not applicable (this study is a retrospective observational analysis, not a clinical trial).

References

1. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113–25. <https://doi.org/10.1056/NEJMoa1713137>.
2. Lu S, Dong X, Jian H, et al. AENEAS: A randomized phase III trial of aumolertinib versus gefitinib as first-line therapy for locally advanced or metastatic non-small-cell lung cancer with EGFR exon 19 deletion or L858R mutations. *J Clin Oncol*. 2022;40:3162–71. <https://doi.org/10.1200/JCO.21.02641>.
3. Yan N, Guo S, Huang S, et al. The efficacy of furmonertinib in untreated advanced NSCLC patients with sensitive EGFR mutations in a real-world setting: A single institutional experience. *Front Oncol*. 2024;14:1331128. <https://doi.org/10.3389/fonc.2024.1331128>.
4. Leonetti A, Sharma S, Minari R, et al. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer*. 2019;121:725–37. <https://doi.org/10.1038/s41416-019-0573-8>.
5. Liu Q, Yu S, Zhao W, et al. EGFR-TKIs resistance via EGFR-independent signaling pathways. *Mol Cancer*. 2018;17:53. <https://doi.org/10.1186/s12943-018-0793-1>.
6. Wang Q, Yang S, Wang K, et al. MET inhibitors for targeted therapy of EGFR TKI-resistant lung cancer. *J Hematol Oncol*. 2019;12:63. <https://doi.org/10.1186/s13045-019-0759-9>.
7. Wu YL, Guarneri V, Voon PJ, et al. Tepotinib plus osimertinib in patients with EGFR-mutated non-small-cell lung cancer with MET amplification following progression on first-line osimertinib (INSIGHT 2): A multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2024;25:989–1002. [https://doi.org/10.1016/S1470-2045\(24\)00270-5](https://doi.org/10.1016/S1470-2045(24)00270-5).
8. Sidaway P. Patritumab deruxtecan shows activity in EGFR-mutant NSCLC. *Nat Rev Clin Oncol*. 2023;20:817. <https://doi.org/10.1038/s41571-023-00822-6>.
9. Wang M, Herbst RS, Boshoff C. Toward personalized treatment approaches for non-small-cell lung cancer. *Nat Med*. 2021;27:1345–56. <https://doi.org/10.1038/s41591-021-01450-2>.
10. Meyer ML, Fitzgerald BG, Paz-Ares L, et al. New promises and challenges in the treatment of advanced non-small-cell lung cancer. *Lancet*. 2024;404:803–22. [https://doi.org/10.1016/S0140-6736\(24\)01029-8](https://doi.org/10.1016/S0140-6736(24)01029-8).
11. Zhang Y, Xu Y, Xu J, et al. Osimertinib for EGFR-mutant NSCLC patients with acquired T790M and EGFR amplification after first-generation EGFR-TKI resistance. *Cancer Sci*. 2025;116:753–63. <https://doi.org/10.1111/cas.16437>.
12. Wu SG, Shih JY. Management of acquired resistance to EGFR TKI-targeted therapy in advanced non-small cell lung cancer. *Mol Cancer*. 2018;17:38. <https://doi.org/10.1186/s12943-018-0777-1>.
13. Sonehara K, Tateishi K, Yoh K, et al. Real-world study of EGFR-TKI rechallenge with another TKI after first-line osimertinib discontinuation in patients with EGFR-mutated non-small cell lung cancer: A subset analysis of the Reiwa study. *Thorac Cancer*. 2025;16:e15507. <https://doi.org/10.1111/1759-7714.15507>.
14. Passaro A, Leighl N, Blackhall F, et al. ESMO expert consensus statements on the management of EGFR mutant non-small-cell lung cancer. *Ann Oncol*. 2022;33:466–87. <https://doi.org/10.1016/j.annonc.2022.02.003>.

15. Griswold ME, Localio AR, Mulrow C. Propensity score adjustment with multilevel data: Setting your sites on decreasing selection bias. *Ann Intern Med.* 2010;152:393–5. <https://doi.org/10.7326/0003-4819-152-6-201003160-00010>.
16. McMahon DJ, John A, Popat S. Current and emerging treatment landscape of common EGFR-mutated advanced non-small cell lung cancer. *Target Oncol.* 2026;21:49–62. <https://doi.org/10.1007/s11523-025-01196-8>.
17. Saporita I, Farinea G, Lombardi E, et al. Tailored strategies to overcome third-generation TKI resistance in EGFR-mutated non-small cell lung cancer. *Expert Opin Ther Targets.* 2026;30:675–91. <https://doi.org/10.1080/14728222.2026.2706458>.
18. Liu S, Zhou L, He Y, et al. The resistance landscape of EGFR tyrosine kinase inhibitors in advanced non-small cell lung cancer: Molecular mechanisms and novel therapeutic strategies. *Transl Lung Cancer Res.* 2026;15:101. <https://doi.org/10.21037/tlcr-2025-1-1380>.
19. Wang Q, Yin X, Zhao K, et al. Dacomitinib for EGFR-L858R-mutated non-small cell lung cancer following acquired resistance to third-generation EGFR-TKIs: A retrospective real-world study. *Transl Lung Cancer Res.* 2026;15:121. <https://doi.org/10.21037/tlcr-2026-1-0153>.
20. Hata A, Katakami N, Takase N, et al. Afatinib plus bevacizumab combination after osimertinib resistance in advanced EGFR-mutant non-small cell lung cancer: Phase II ABCD-study. *Lung Cancer.* 2024;197:107988. <https://doi.org/10.1016/j.lungcan.2024.107988>.
21. Nishino M, Suda K, Kobayashi Y, et al. Effects of secondary EGFR mutations on resistance against upfront osimertinib in cells with EGFR-activating mutations in vitro. *Lung Cancer.* 2018;126:149–55. <https://doi.org/10.1016/j.lungcan.2018.10.026>.
22. Niederst MJ, Hu H, Mulvey HE, et al. The allelic context of the C797S mutation acquired upon treatment with third-generation EGFR inhibitors impacts sensitivity to subsequent treatment strategies. *Clin Cancer Res.* 2015;21:3924–33. <https://doi.org/10.1158/1078-0432.CCR-15-0560>.
23. Engelman JA, Zejnullahu K, Gale CM, et al. PF00299804, an irreversible pan-ERBB inhibitor, is effective in lung cancer models with EGFR and ERBB2 mutations that are resistant to gefitinib. *Cancer Res.* 2007;67:11924–32. <https://doi.org/10.1158/0008-5472.CAN-07-1885>.
24. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): A randomised, open-label, phase 3 trial. *Lancet Oncol.* 2017;18:1454–66. [https://doi.org/10.1016/S1470-2045\(17\)30608-3](https://doi.org/10.1016/S1470-2045(17)30608-3).
25. Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene.* 2008;27:4702–11. <https://doi.org/10.1038/onc.2008.109>.
26. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol.* 2013;31:3327–34. <https://doi.org/10.1200/JCO.2012.44.2806>.
27. Lu S, Wang J, Yang N, et al. Savolitinib plus osimertinib versus chemotherapy for advanced, EGFR mutation-positive, MET-amplified non-small-cell lung cancer in China (SACHI): Interim analysis of a

- multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2026;407:375–87. [https://doi.org/10.1016/S0140-6736\(25\)01811-2](https://doi.org/10.1016/S0140-6736(25)01811-2).
28. Fang W, Zhao Y, Luo Y, et al. Bispecific antibody ivonescimab added to chemotherapy in EGFR-variant non-small cell lung cancer: The HARMONi-A randomized clinical trial. *JAMA*. 2026;336:306–14. <https://doi.org/10.1001/jama.2026.7745>.
29. Fang W, Zhao Y, Luo Y, et al. Ivonescimab plus chemotherapy in non-small cell lung cancer with EGFR variant: A randomized clinical trial. *JAMA*. 2024;332:561–70. <https://doi.org/10.1001/jama.2024.10613>.
30. Lu S, Wu L, Jian H, et al. Sintilimab plus bevacizumab biosimilar IBI305 and chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer who progressed on EGFR tyrosine-kinase inhibitor therapy (ORIENT-31): First interim results from a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol*. 2022;23:1167–79. [https://doi.org/10.1016/S1470-2045\(22\)00382-5](https://doi.org/10.1016/S1470-2045(22)00382-5).
31. Lu S, Wu L, Jian H, et al. Sintilimab plus chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer with disease progression after EGFR tyrosine-kinase inhibitor therapy (ORIENT-31): Second interim analysis from a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2023;11:624–36. [https://doi.org/10.1016/S2213-2600\(23\)00135-2](https://doi.org/10.1016/S2213-2600(23)00135-2).
32. Fang W, Wu L, Meng X, et al. Sacituzumab tirumotecan in EGFR-TKI-resistant, EGFR-mutated advanced NSCLC. *N Engl J Med*. 2026;394:13–26. <https://doi.org/10.1056/NEJMoa2512071>.
33. Leonetti A, Verzè M, Minari R, et al. Resistance to osimertinib in advanced EGFR-mutated NSCLC: A prospective study of molecular genotyping on tissue and liquid biopsy. *Br J Cancer*. 2024;130:135–42. <https://doi.org/10.1038/s41416-023-02475-9>.
34. Fang W, Li X, Wang Q, et al. Sacituzumab tirumotecan versus docetaxel for previously treated EGFR-mutated advanced non-small cell lung cancer: Multicentre, open label, randomised controlled trial (OptiTROP-Lung03). *BMJ*. 2025;389:e085680. <https://doi.org/10.1136/bmj-2025-085680>.
35. Sands J, Ahn MJ, Lisberg A, et al. Datopotamab deruxtecan in advanced or metastatic non-small cell lung cancer with actionable genomic alterations: Results from the phase II TROPION-Lung05 study. *J Clin Oncol*. 2025;43:1254–65. <https://doi.org/10.1200/JCO-24-01349>.
36. Lee CK, Man J, Lord S, et al. Checkpoint inhibitors in metastatic EGFR-mutated non-small cell lung cancer-a meta-analysis. *J Thorac Oncol*. 2017;12:403–7. <https://doi.org/10.1016/j.jtho.2016.10.007>.
37. Blumenthal GM, Gong Y, Kehl K, et al. Analysis of time-to-treatment discontinuation of targeted therapy, immunotherapy, and chemotherapy in clinical trials of patients with non-small-cell lung cancer. *Ann Oncol*. 2019;30:830–8. <https://doi.org/10.1093/annonc/mdz060>.
38. Park K, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): A phase 2B, open-label, randomised controlled trial. *Lancet Oncol*. 2016;17:577–89. [https://doi.org/10.1016/S1470-2045\(16\)30033-X](https://doi.org/10.1016/S1470-2045(16)30033-X).

39. Corral J, Mok TS, Nakagawa K, et al. Effects of dose modifications on the safety and efficacy of dacomitinib for EGFR mutation-positive non-small-cell lung cancer. *Future Oncol.* 2019;15:2795–805. <https://doi.org/10.2217/fon-2019-0299>.

40. Yang Y, Huang Y, Wang Y, et al. A real-world pharmacovigilance study of dacomitinib based on FDA adverse event reporting system (FAERS) database. *Naunyn Schmiedebergs Arch Pharmacol.* 2026;399:16209–24. <https://doi.org/10.1007/s00210-026-05389-4>.

41. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivar Behav Res.* 2011;46:399–424. <https://doi.org/10.1080/00273171.2011.568786>.

42. Chang GC, Kapoor A, Lee CK, et al. Optimizing management of stage IV EGFR mutant non-small-cell lung cancer in Asia: An expert opinion. *Int J Cancer.* 2025;157:1648–61. <https://doi.org/10.1002/ijc.35512>.

43. Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. *Stat Med.* 2008;27:2037–49. <https://doi.org/10.1002/sim.3150>.

Tables

Table 1. Basic characteristics of participants.

	3+2(N=60)	3+3(N=60)	P-value
Age			
n	60	60	
Mean (SD)	56.7 (10.62)	57.3 (9.63)	
Median (Q1, Q3)	57.5 (48.5,65.0)	57.0 (52.0,65.0)	
Min, Max	35, 75	36, 74	
BMI			
n	57	60	
Mean (SD)	21.18 (3.878)	22.50 (3.469)	
Median (Q1,Q3)	20.80 (18.20,24.20)	22.60 (20.20,24.60)	
Min, Max	14.5, 34.6	14.9, 30.9	
Smoking history			0.4711
Never	48 (80.0)	51 (85.0)	
Current/Former	12 (20.0)	9 (15.0)	
Sex			0.4386
Female	42 (70.0)	38 (63.3)	
Male	18 (30.0)	22 (36.7)	
Histology			0.3153
Adenocarcinoma	59 (98.3)	60 (100)	
Adenosquamous carcinoma	1 (1.7)	0	
L858R mutations at the time of initial diagnosis			0.2314
No	20 (35.7)	28 (46.7)	
Yes	36 (64.3)	32 (53.3)	
T790M mutations at the time of initial diagnosis			0.0111
No	56 (93.3)	55 (91.7)	
Yes	0	5 (8.3)	
Missing	4 (6.7)	0	

	3+2(N=60)	3+3(N=60)	P-value
Nonclassical EGFR/ERBB2 mutations at the time of initial diagnosis			0.0129
No	42 (70.0)	54 (90.0)	
Yes	14 (23.3)	6 (10.0)	
Missing	4 (6.7)	0	
EGFR/ERBB2 amplification at the time of initial diagnosis			0.1260
No	54 (90.0)	58 (96.7)	
Yes	2 (3.3)	2 (3.3)	
Missing	4 (6.7)	0	
Off-target EGFR mutations at the time of initial diagnosis			0.1017
No	44 (73.3)	44 (73.3)	
Yes	12 (20.0)	16 (26.7)	
Missing	4 (6.7)	0	
TP53 mutation at the time of initial diagnosis			0.1247
No	47 (78.3)	51 (85.0)	
Yes	9 (15.0)	9 (15.0)	
Missing	4 (6.7)	0	
Initial M staging			0.5775
0	9 (15.0)	8 (13.3)	
1	50 (83.3)	52 (86.7)	
x	1 (1.7)	0	
Initial liver metastasis			0.1864
No	53 (88.3)	57 (95.0)	
Yes	7 (11.7)	3 (5.0)	
Initial brain metastasis			0.0917
No	49 (81.7)	41 (68.3)	
Yes	11 (18.3)	19 (31.7)	

	3+2(N=60)	3+3(N=60)	P-value
Initial bone metastasis			0.7019
No	40 (66.7)	38 (63.3)	
Yes	20 (33.3)	22 (36.7)	
Initial adrenal gland metastasis			0.0281
No	53 (88.3)	59 (98.3)	
Yes	7 (11.7)	1 (1.7)	
Initial pleural metastasis			0.6797
No	43 (71.7)	45 (75.0)	
Yes	17 (28.3)	15 (25.0)	
Third-gen EGFR-TKIs			0.6793
Furmonertinib	6 (10.0)	5 (8.3)	
Osimertinib	42 (70.0)	39 (65.0)	
Almonertinib	12 (20.0)	16 (26.7)	
L858R mutation after progression on 3rd-gen EGFR-TKIs			0.6364
No	5 (8.3)	8 (13.3)	
Yes	11 (18.3)	9 (15.0)	
Missing	44 (73.3)	43 (71.7)	
19del mutation after progression on 3rd-gen EGFR-TKIs			0.1226
No	15 (25.0)	11 (18.3)	
Yes	1 (1.7)	6 (10.0)	
Missing	44 (73.3)	43 (71.7)	
T790M mutation after progression on 3rd-gen EGFR-TKIs			0.2075
No	16 (26.7)	14 (23.3)	
Yes	0	3 (5.0)	
Missing	44 (73.3)	43 (71.7)	
Nonclassical EGFR/ERBB2 mutations after progression on 3rd-generation EGFR-TKI			0.3921

	3+2(N=60)	3+3(N=60)	P-value
No	9 (56.3)	12 (70.6)	
Yes	7 (43.8)	5 (29.4)	
EGFR/ERBB2 amplification after progression on 3rd-generation EGFR-TKI			0.5665
No	15 (25.0)	17 (28.3)	
Yes	1 (1.7)	0	
Missing	44 (73.3)	43 (71.7)	
Off-target EGFR mutations after progression on 3rd-generation EGFR-TKI			0.9501
No	11 (18.3)	11 (18.3)	
Yes	5 (8.3)	6 (10.0)	
Missing	44 (73.3)	43 (71.7)	
TP53 mutations after progression on 3rd-generation EGFR-TKI			0.6994
No	14 (23.3)	13 (21.7)	
Yes	2 (3.3)	4 (6.7)	
Missing	44 (73.3)	43 (71.7)	
Systemic anti-angiogenic therapy (anlotinib/bevacizumab/endostar, etc.) combined after third-generation EGFR-TKI progression			0.3153
No	40 (66.7)	45 (75.0)	
Yes	20 (33.3)	15 (25.0)	
Chemotherapy combined after third-generation EGFR-TKI progression			0.6242
No	51 (85.0)	49 (81.7)	
Yes	9 (15.0)	11 (18.3)	
EGFR-TKI combined after third-generation EGFR-TKI progression			0.7289
No	56 (93.3)	55 (91.7)	
Yes	4 (6.7)	5 (8.3)	

	3+2(N=60)	3+3(N=60)	P-value
Local therapies combined after third-generation EGFR-TKI progression (e.g., surgery, intrathecal injection, etc.)			0.3065
No	53 (88.3)	49 (81.7)	
Yes	7 (11.7)	11 (18.3)	
Non-EGFR targeted therapies combined after third-generation EGFR-TKI progression			0.0831
No	58 (96.7)	53 (88.3)	
Yes	2 (3.3)	7 (11.7)	
Treatment lines of second-generation EGFR-TKIs			0.6393
2	12 (20.0)	17 (28.3)	
3	15 (25.0)	15 (25.0)	
4	14 (23.3)	14 (23.3)	
5	11 (18.3)	8 (13.3)	
6	5 (8.3)	3 (5.0)	
7	0	2 (3.3)	
8	2 (3.3)	1 (1.7)	
9	1 (1.7)	0	
Intervening lines between 3rd-gen EGFR-TKI and 2nd-gen EGFR-TKI			0.9966
1	26 (43.3)	27 (45.0)	
2	25 (41.7)	24 (40.0)	
3	4 (6.7)	5 (8.3)	
4	3 (5.0)	2 (3.3)	
5	1 (1.7)	1 (1.7)	
6	1 (1.7)	1 (1.7)	
Treatment strategy			0.8541
Sequential therapy ^a	26 (43.3)	27 (45.0)	
Bridging therapy ^b	34 (56.7)	33 (55.0)	

Footnotes:

a: Sequential therapy: Treatment with 2nd/3rd-generation EGFR-TKIs immediately after resistance to 3rd-generation EGFR-TKIs.

b: Bridging therapy: Treatment with non-EGFR-TKI agents (e.g., chemotherapy or immunotherapy) prior to subsequent 2nd/3rd-generation EGFR-TKI administration following resistance to 3rd-generation EGFR-TKIs.

Table 2. ORR and DCR between the 3+2 and 3+3 groups.

	3+2 (n=60)(%)	3+3 (n=60)(%)	Total (n=120)(%)	P
ORR				0.0082
No	49(81.7)	58(96.7)	107(89.2)	
Yes	11(18.3)	2(3.3)	13(10.8)	
DCR				0.3880
No	12(20.0)	16(26.7)	28(23.3)	
Yes	48(80.0)	44(73.3)	92(76.7)	

Table 3. ORR and DCR between the dacomitinib-treated subgroup in the 3+2 and 3+3 groups.

	Dacomitinib of 3+2 (n=42)(%)	3+3 (n=42)(%)	Total (n=84)(%)	P
ORR				0.0036
No	32(76.2)	41(97.6)	73(86.9)	
Yes	10(23.8)	1(2.4)	11(13.1)	
DCR				0.3055
No	9(19.0)	12(28.6)	20(23.8)	
Yes	34(81.0)	30(71.4)	64(76.2)	

Figures

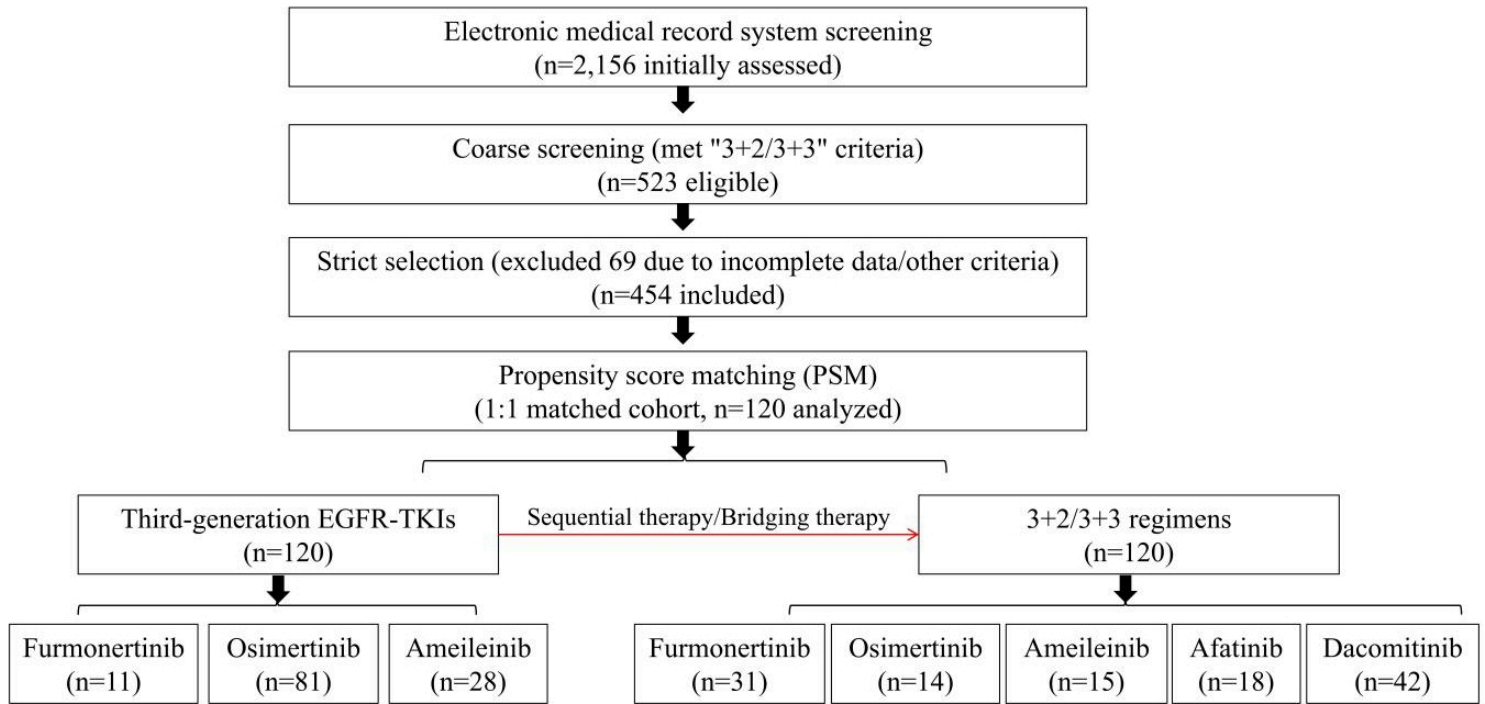


Figure 1

Flowchart of patient screening and treatment allocation. Between November 2015 and December 2024, electronic medical records from Henan Cancer Hospital were retrospectively reviewed to identify patients who had received either 3G EGFR-TKIs (osimertinib, aumolertinib, or furmonertinib) or 2G EGFR-TKIs (afatinib or dacomitinib); osimertinib received accelerated approval from the United States Food and Drug Administration on November 13, 2015 for T790M-positive metastatic NSCLC

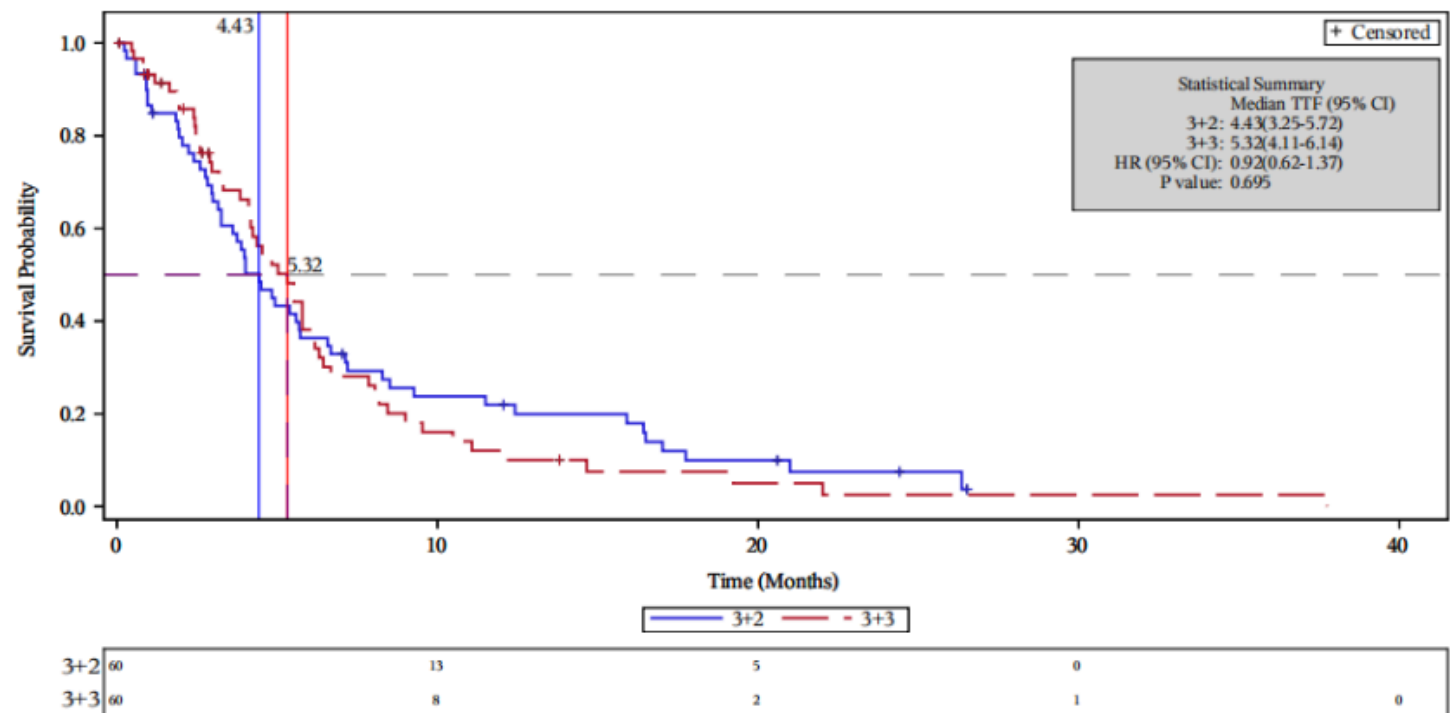


Figure 2

Comparison of time to treatment failure (TTF) between the 3+2 and 3+3 groups

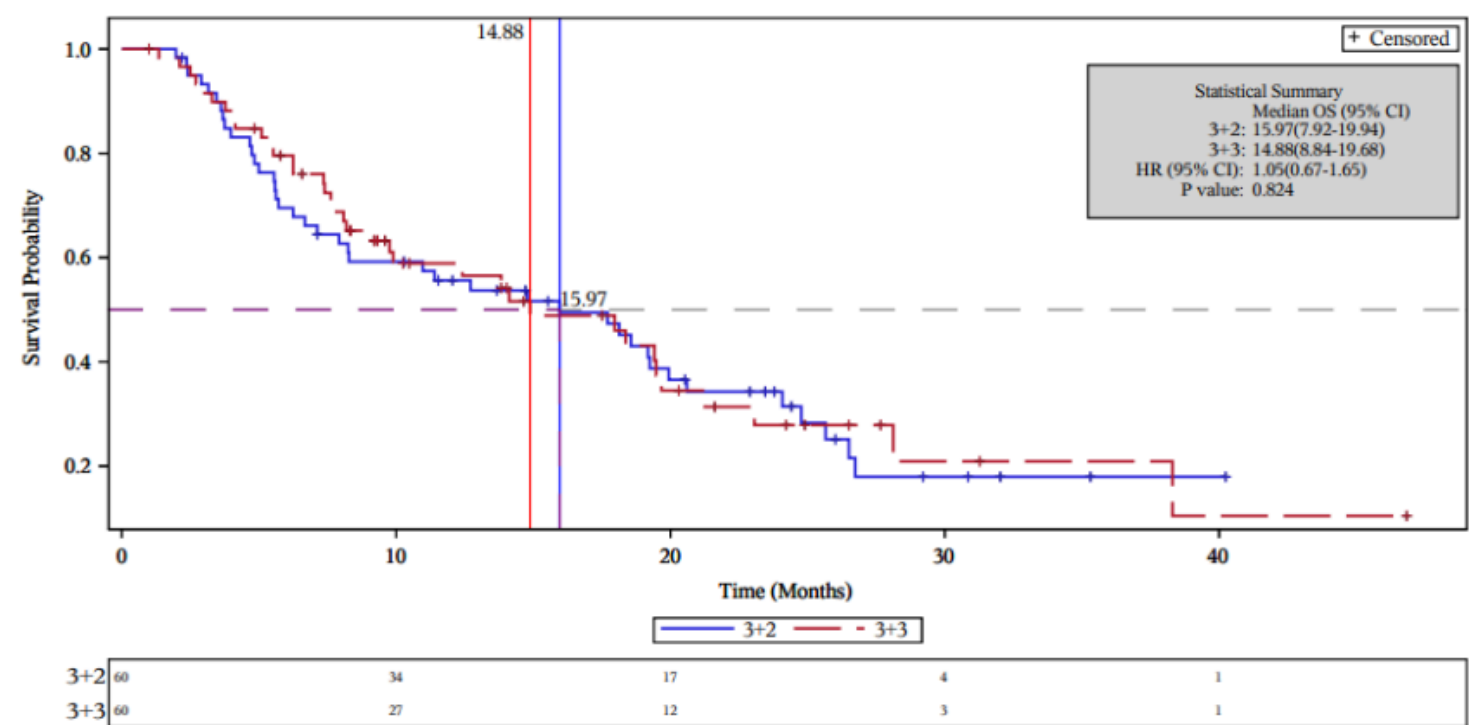


Figure 3

Comparison of overall survival (OS) between the 3+2 and 3+3 groups

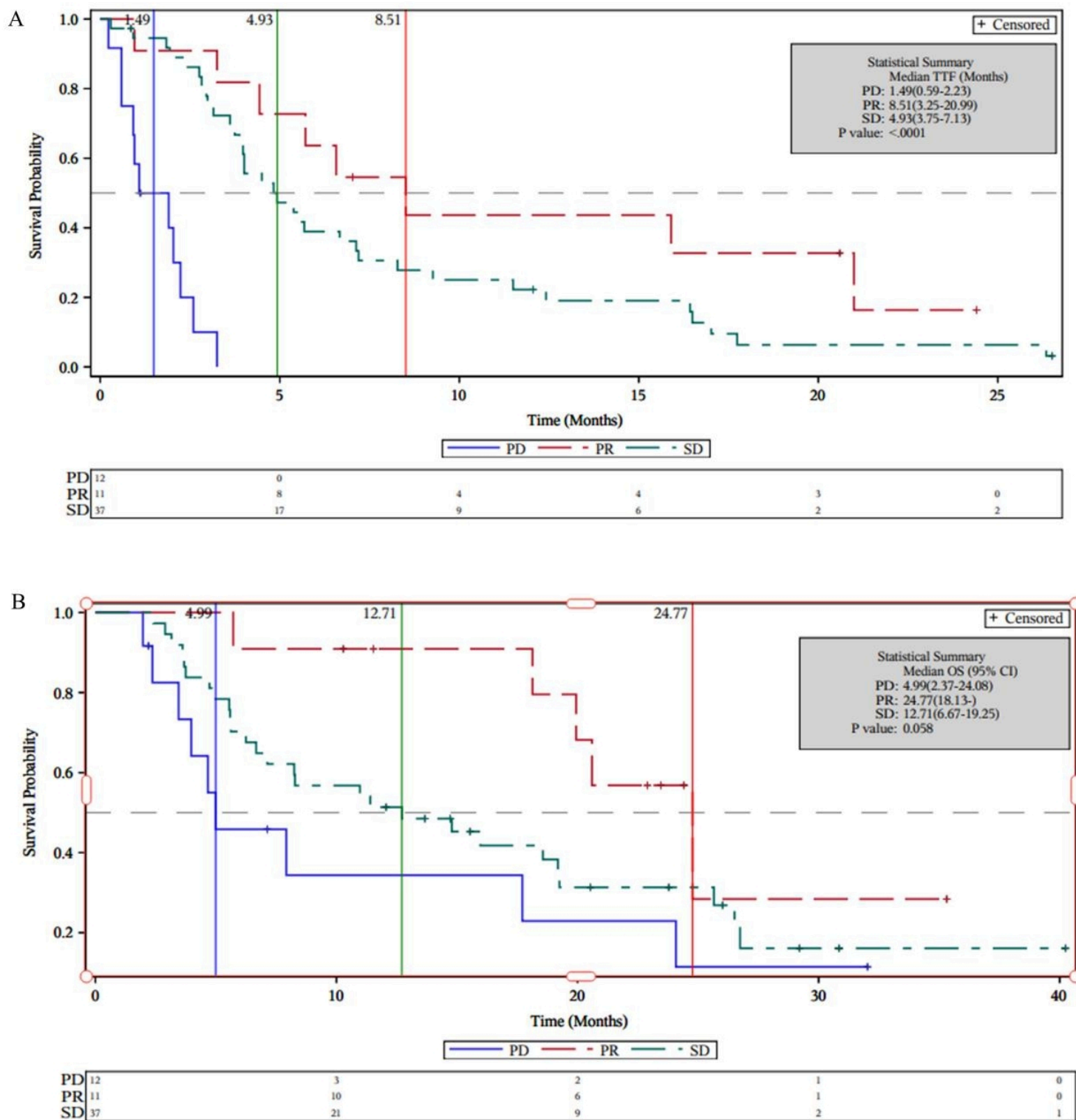


Figure 4

Exploratory analysis of the 3+2 treatment group: Kaplan–Meier plots of TTF and OS according to treatment response. (A) TTF by treatment response; (B) OS by treatment response

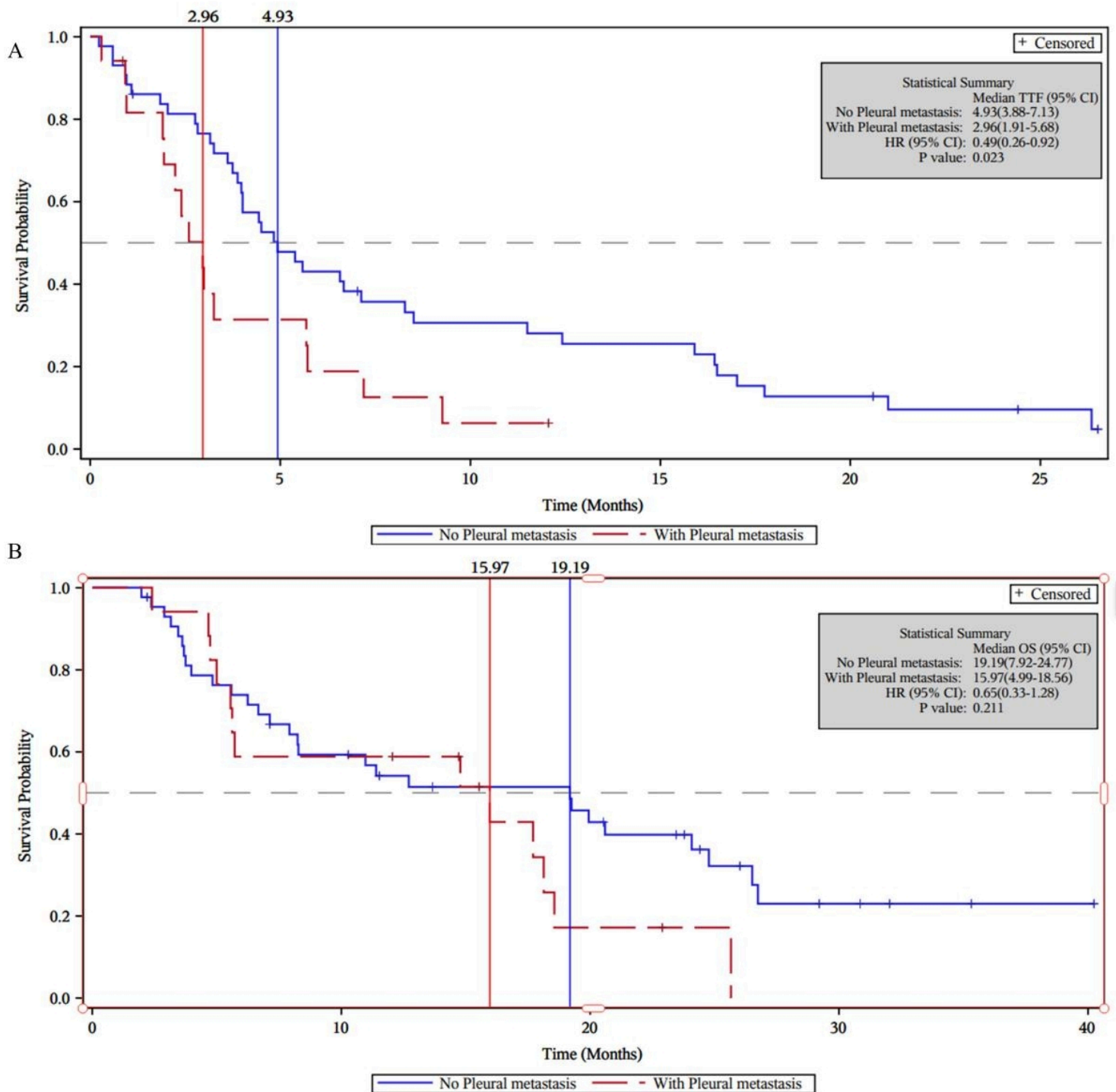


Figure 5

Exploratory analysis of the 3+2 treatment group: Kaplan–Meier plots of TTF and OS according to pleural metastasis status. (A) TTF by pleural metastasis; (B) OS by pleural metastasis

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [OnlineResource.docx](#)