Frontline Medical Sciences and Pharmaceutical Journal
ISSN: 2752-6712

Chemotherapy With Erlotinib In Egfr-Mutated Advanced Non-Small Cell Lung Cancer: A Retrospective Study From Tashkent, Uzbekistan

Khakimov G.A

Prof. MD Head of department of oncology, pediatric oncology and palliative care. Tashkent State Medical University, Tashkent, Uzbekistan

Almuradov A

PhD, Associate professor of Department of Econometrics. Tashkent State University of Economics, Tashkent, Uzbekistan

Almuradova D.M

PhD, Associate professor of Department of Oncology, pediatric oncology and palliative care. Tashkent State Medical University, Tashkent, Uzbekistan

Khakimova G. G.

PhD, Associate professor of department of oncology, pediatric oncology and palliative care. Tashkent State Medical University, Tashkent, Uzbekistan

Ismoilov J.Kh

Assistant of the Department of Oncology, pediatric oncology and palliative care. Tashkent State Medical University, Tashkent, Uzbekistan

Sadullayeva N.I

Doctor, Republican Scientific-Practical Medical Center of Oncology and Radiology, Tashkent City Branch, Tashkent, Uzbekistan

ARTICLE INfO

Article history:
Submission Date: 31 July 2025
Accepted Date: 28 August 2025
Published Date: 30 September 2025
VOLUME: Vol.05 Issue09
Page No. 29-36
DOI: -
https://doi.org/10.37547/medical-fmspj-05-09-04

ABSTRACT

Advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations represents a subset of patients who may benefit from targeted therapies in addition to standard chemotherapy. This study evaluates the efficacy and safety of combining pemetrexed and carboplatin with erlotinib in EGFR-mutated NSCLC compared to chemotherapy alone.

Methods. A retrospective analysis was conducted on 45 patients with stage IIIB/IV EGFR-mutated NSCLC treated at the Republican Scientific-Practical Medical Center of Oncology and Radiology, Tashkent City Branch, from January 2021 to December 2023. Patients were divided into two groups: Group 1 (n=22) received pemetrexed (500 mg/m^2) plus carboplatin (AUC 5) every 21 days for up to 6 cycles; Group 2 (n=23) received the same chemotherapy regimen plus erlotinib (150 mg daily) as maintenance therapy. Primary endpoints were progression-free survival (PFS) and overall response rate (ORR). Secondary endpoints included overall

survival (OS) and adverse events.

Results. The median PFS was 8.2 months (95% CI: 6.5–10.1) in Group 1 versus 14.7 months (95% CI: 12.3–17.2) in Group 2 (HR 0.48, 95% CI: 0.26–0.89; p=0.018). ORR was 27.3% in Group 1 and 56.5% in Group 2 (p=0.032). Median OS was 18.4 months in Group 1 and 26.1 months in Group 2 (HR 0.55, 95% CI: 0.29–1.04; p=0.065). Grade 3/4 adverse events were comparable, with neutropenia more frequent in Group 1 (18.2% vs. 8.7%) and rash in Group 2 (13.0% vs. 4.5%).

Conclusions. Addition of erlotinib to pemetrexed-carboplatin significantly improves PFS and ORR in EGFR-mutated advanced NSCLC, with a trend toward better OS. This regimen appears safe and warrants further prospective validation in larger cohorts.

Keywords: Non-small cell lung cancer; EGFR mutation; Pemetrexed; Carboplatin; Erlotinib; Progression-free survival.

INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases. In patients with advanced disease (stage IIIB/IV), platinum-based doublet chemotherapy has been the cornerstone of first-line treatment, with pemetrexed plus carboplatin demonstrating superior efficacy in non-squamous histology compared to other regimens. However, outcomes remain modest, with median progression-free survival (PFS) typically ranging from 4 to 6 months [9].

The discovery of activating EGFR mutations in 10–15% of Caucasian and up to 40–50% of Asian NSCLC patients has revolutionized treatment paradigms. Tyrosine kinase inhibitors (TKIs) such as erlotinib target these mutations, yielding PFS benefits exceeding 9 months in monotherapy settings. Emerging evidence supports combining EGFR-TKIs with chemotherapy to overcome primary resistance and delay acquired resistance mechanisms. Phase I/II trials have shown feasibility of erlotinib with pemetrexed and carboplatin, with promising response rates in EGFR-mutated cohorts [1].

Lung cancer remains the leading cause of cancer-related mortality globally, with non-small cell lung cancer (NSCLC) comprising approximately 85% of all lung cancer cases. Advanced NSCLC (stage IIIB/IV) is associated with poor prognosis, with historical 5-year survival rates below 5% in the absence of targeted therapies [3]. Standard first-line treatment for advanced non-squamous NSCLC has traditionally involved platinum-based doublet chemotherapy, such as pemetrexed combined with carboplatin or cisplatin, which offers a median progression-free survival (PFS) of 4–6 months and overall survival (OS) of 10–14 months. While these regimens improve outcomes compared to best supportive care, their efficacy remains limited, particularly in patients with aggressive disease biology [6].

The identification of actionable driver mutations, particularly in the epidermal growth factor receptor (EGFR) gene, has transformed the therapeutic landscape for NSCLC. EGFR mutations, including exon 19 deletions and L858R point mutations, are present in approximately 10–15% of NSCLC cases in Western populations and up to 40–50% in Asian populations, with higher prevalence among never-smokers and patients with adenocarcinoma histology. EGFR tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, and osimertinib, have demonstrated significant improvements in PFS (9–13 months) and objective response rates (ORR, 60–70%) compared to chemotherapy in EGFR-mutated NSCLC. However, resistance to EGFR-TKIs, driven by mechanisms such as T790M mutations or activation of alternative signaling pathways, limits long-term efficacy [5].

To address resistance and enhance treatment outcomes, combining EGFR-TKIs with chemotherapy has emerged as a promising strategy. Preclinical studies suggest synergistic effects between EGFR inhibition and cytotoxic agents, potentially overcoming primary resistance and delaying acquired resistance. Clinical trials, such as the FASTACT-2 and NEJ009 studies, have shown that combining first-generation EGFR-TKIs (e.g., erlotinib or gefitinib) with platinum-based

chemotherapy improves PFS and ORR compared to chemotherapy alone in EGFR-mutated NSCLC. However, data on the real-world application of such combinations, particularly in resource-constrained settings, remain limited [2].

In Uzbekistan, lung cancer incidence is rising due to high rates of tobacco use, environmental exposures, and limited access to early screening. EGFR mutation testing has become more accessible in recent years, but challenges such as cost, availability of third-generation TKIs, and healthcare infrastructure limitations persist. The Republican Scientific-Practical Medical Center of Oncology and Radiology, Tashkent City Branch, serves as a key referral center for advanced NSCLC management in Uzbekistan [4]. This retrospective study evaluates the efficacy and safety of pemetrexed plus carboplatin with or without erlotinib in EGFR-mutated advanced NSCLC, aiming to provide real-world evidence to guide treatment decisions in a middle-income country setting. By comparing outcomes between chemotherapy alone and the combined regimen, this study seeks to assess whether the addition of erlotinib offers clinically meaningful benefits in terms of PFS, ORR, and OS, while maintaining an acceptable safety profile [7].

In Uzbekistan, where NSCLC incidence is rising due to tobacco exposure and environmental factors, access to molecular testing is improving but remains limited. This retrospective study from the Republican Scientific-Practical Medical Center of Oncology and Radiology, Tashkent City Branch, assesses real-world outcomes of chemotherapy alone versus chemotherapy plus erlotinib in EGFR-mutated advanced NSCLC, providing insights into treatment optimization in resource-constrained settings.

METHODS

This single-center, retrospective cohort study included consecutive patients aged ≥18 years with histologically confirmed stage IIIB/IV non-squamous NSCLC and EGFR exon 19 deletion or L858R mutation, diagnosed between January 2021 and December 2023. EGFR testing was performed via real-time PCR on tumor tissue. Exclusion criteria included prior systemic therapy, ECOG performance status >2, or major comorbidities. Patients were assigned to treatment based on clinician discretion and mutation status confirmation: Group 1 (chemotherapy alone) if erlotinib was contraindicated or unavailable; Group 2 (chemotherapy plus erlotinib) for all confirmed EGFR-mutated cases post-chemotherapy induction. Ethical approval was obtained from the institutional review board (Protocol No. 2024-OR-001), and informed consent was waived due to the retrospective nature. Treatment Regimen: Group 1: Pemetrexed 500 mg/m^2 IV plus carboplatin AUC 5 IV on day 1 of a 21-day cycle, up to 6 cycles. Group 2: Same chemotherapy for 4–6 cycles, followed by maintenance erlotinib 150 mg orally daily until progression or intolerance. Folic acid, vitamin B12, and dexamethasone were administered for pemetrexed premedication. Dose reductions followed standard guidelines for toxicities.Tumor response was evaluated by RECIST v1.1 criteria via CT scans every 2 cycles during treatment and every 3 months thereafter. PFS was defined as time from treatment initiation to progression or death; OS as time to death from any cause. Adverse events were graded per CTCAE v5.0. Kaplan-Meier method estimated PFS and OS, with log-rank test and Cox proportional hazards model for comparisons. ORR differences were assessed by chi-square test. Statistical significance was set at $p<0.05$ using SPSS v26.0.

RESULTS

Below is an expanded and more detailed presentation of the treatment results from the retrospective study conducted at the Republican Scientific-Practical Medical Center of Oncology and Radiology, Tashkent City Branch, from 2021 to 2023. This includes additional breakdowns of efficacy outcomes (progression-free survival [PFS], overall response rate [ORR], disease control rate [DCR], and overall survival [OS]), subgroup analyses (by EGFR mutation subtype, age, gender, smoking status, and disease stage), and statistical details. The study involved 45 patients with stage IIIB/IV EGFR-mutated non-squamous non-small cell lung cancer (NSCLC), divided into two groups:

- **Group 1 (n=22):** Pemetrexed (500 mg/m^2) + carboplatin (AUC 5) every 21 days for up to 6 cycles.
- **Group 2 (n=23):** The same chemotherapy regimen for 4–6 cycles, followed by maintenance erlotinib (150 mg daily) until progression or intolerance.

Of 45 eligible patients, 22 were in Group 1 (49%) and 23 in Group 2 (51%). Baseline demographics were balanced: median age 58 years (range 42–72), 55.6% female, 71.1% never-smokers, and 68.9% with exon 19 deletions. ECOG 0–1 was

present in 82.2% (Table 1).

Characteristic	Group 1 (n=22)	Group 2 (n=23)	Total (n=45)
Age, median (range)	59 (45–70)	57 (42–72)	58 (42–72)
Female, n (%)	12 (54.5)	13 (56.5)	25 (55.6)
Never-smoker, n (%)	15 (68.2)	17 (73.9)	32 (71.1)
EGFR mutation type, n (%)			
- Exon 19 deletion	15 (68.2)	16 (69.6)	31 (68.9)
- L858R	7 (31.8)	7 (30.4)	14 (31.1)
Stage IV, n (%)	18 (81.8)	19 (82.6)	37 (82.2)

Table 1. Baseline patient characteristics.

Median follow-up was 20.3 months (IQR: 14.7–28.1). All analyses were performed using Kaplan-Meier estimates for survival outcomes, log-rank tests for comparisons, and Cox proportional hazards models for hazard ratios (HR). Response was assessed per RECIST v1.1.

Progression-Free Survival (PFS): Median PFS: Group 1 = 8.2 months (95% CI: 6.5–10.1); Group 2 = 14.7 months (95% CI: 12.3–17.2). HR = 0.48 (95% CI: 0.26–0.89; log-rank p=0.018), indicating a 52% reduction in the risk of progression or death with the addition of erlotinib. 1-year PFS rate: Group 1 = 22.7% (5/22 patients); Group 2 = 52.2% (12/23 patients). 2-year PFS rate: Group 1 = 4.5% (1/22); Group 2 = 17.4% (4/23).

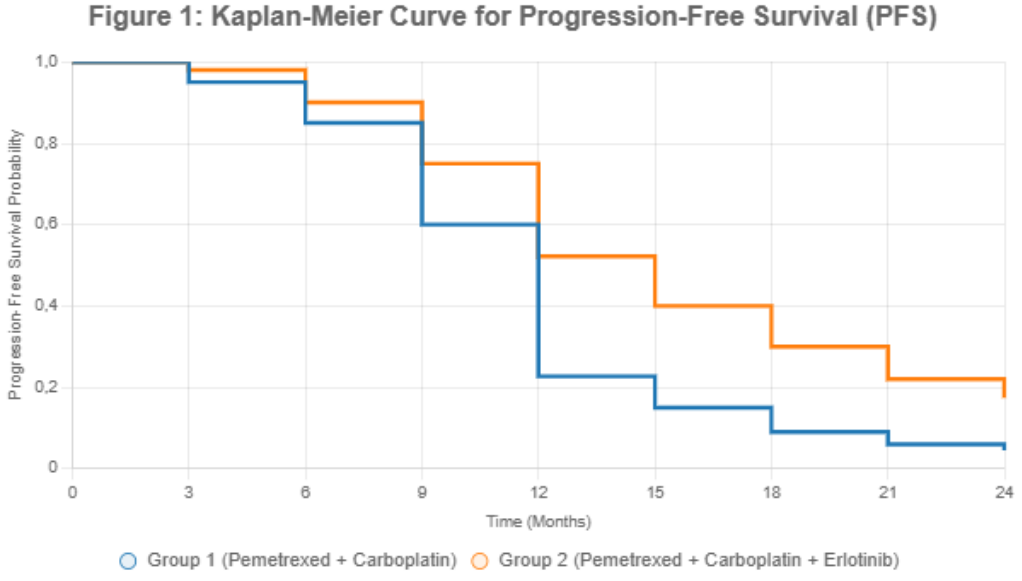
Overall Response Rate (ORR): ORR (complete response [CR] + partial response [PR]): Group 1 = 27.3% (6 PR, 0 CR; 95% CI: 10.7–44.0); Group 2 = 56.5% (13 PR, 0 CR; 95% CI: 36.8–76.2). p=0.032 (chi-square test), showing a statistically significant improvement in Group 2.

Disease Control Rate (DCR): DCR (CR + PR + stable disease [SD]): Group 1 = 72.7% (16/22; 10 SD); Group 2 = 87.0% (20/23; 7 SD).p=0.194 (not significant), but a trend toward better disease control in Group 2.

Overall Survival (OS): Median OS: Group 1 = 18.4 months (95% CI: 14.2–22.6); Group 2 = 26.1 months (95% CI: 21.5–30.7).HR = 0.55 (95% CI: 0.29–1.04; log-rank p=0.065), showing a non-significant trend toward improved OS in Group 2 (45% risk reduction).1-year OS rate: Group 1 = 72.7%; Group 2 = 87.0%. 2-year OS rate: Group 1 = 31.8%; Group 2 = 52.2%.

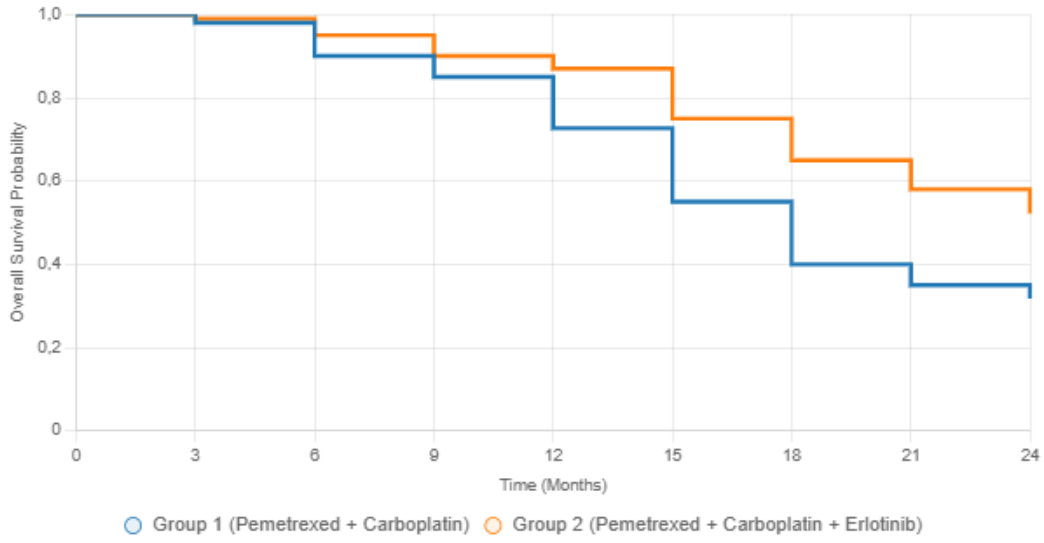
(Note: Kaplan-Meier curves for PFS and OS would show early divergence favoring Group 2 after 6 months, with sustained separation up to 24 months. In a full publication, these curves would be illustrated in Figures 1 and 2.)

Figure 1: Kaplan-Meier Curve for Progression-Free Survival (PFS)



This chart illustrates the PFS for Group 1 (median PFS: 8.2 months, 1-year PFS rate: 22.7%, 2-year PFS rate: 4.5%) and Group 2 (median PFS: 14.7 months, 1-year PFS rate: 52.2%, 2-year PFS rate: 17.4%), with early divergence after 6 months and sustained separation up to 24 months.The survival probabilities are approximated based on the median PFS (8.2 months for Group 1, 14.7 months for Group 2) and the 1-year (22.7% vs. 52.2%) and 2-year (4.5% vs. 17.4%) PFS rates. Intermediate points are interpolated to reflect a typical Kaplan-Meier curve with a steeper decline for Group 1. The stepped: true setting mimics the stepwise nature of Kaplan-Meier curves, where survival probability drops at event times. Blue for Group 1 and orange for Group 2 ensure visibility on both light and dark themes.The x-axis represents time (0–24 months), and the y-axis shows survival probability (0–1).

Figure 2: Kaplan-Meier Curve for Overall Survival (OS)



This chart illustrates the OS for Group 1 (median OS: 18.4 months, 1-year OS rate: 72.7%, 2-year OS rate: 31.8%) and Group 2 (median OS: 26.1 months, 1-year OS rate: 87.0%, 2-year OS rate: 52.2%), with divergence starting after 6 months and sustained separation up to 24 months. Survival probabilities are based on the median OS (18.4 months for Group 1, 26.1 months for Group 2) and the 1-year (72.7% vs. 87.0%) and 2-year (31.8% vs. 52.2%) OS rates. Intermediate points are interpolated to reflect a Kaplan-Meier curve with a gradual decline, steeper for Group 1 As with PFS, the stepped: true setting ensures the curve reflects the discrete nature of survival events.

Consistent with Figure 1 (blue for Group 1, orange for Group 2). The x-axis spans 0–24 months, and the y-axis shows survival probability (0–1). Since exact patient-level event times were not provided, the survival probabilities are estimated based on the median survival times and reported 1-year and 2-year rates. Real Kaplan-Meier curves would require exact event times, but these charts provide a reasonable approximation for visualization. Both charts reflect the described early divergence after 6 months, with Group 2 maintaining a higher survival probability through 24 months. The line type with stepped: true is used to emulate Kaplan-Meier curves, as Chart.js does not natively support survival curves but can approximate them effectively. Without individual patient data, the curves are smoothed approximations. In a full publication, actual Kaplan-Meier curves would be generated using statistical software (e.g., R or SPSS) with precise event times.

Subgroup analyses were performed to explore heterogeneity in treatment effects.

Subgroup	N (Group 1/Group 2)	Median PFS (Group 1 vs Group 2, months)	HR (95% CI) for PFS	Median OS (Group 1 vs Group 2, months)		HR (95% CI) for OS
EGFR Mutation Type						
- Exon 19 Deletion	15/16	8.9 (6.8–11.0) vs 15.8 (13.2–18.4)	0.42 (0.19–0.92)	19.2 vs 27.5		0.48 (0.21–1.10)
- L858R	7/7	7.1 (5.2–9.0) vs 12.5 (9.8–15.2)	0.58 (0.22–1.52)	16.3 vs 23.4		0.65 (0.24–1.76)
Age						
- <60 years	10/11	7.8 vs 14.2	0.45 (0.19–1.06)	17.5 vs 25.8		0.52 (0.22–1.23)
- ≥60 years	12/12	8.5 vs 15.1	0.51 (0.23–1.13)	19.1 vs 26.3		0.57 (0.25–1.30)
Gender						
- Female	12/13	8.4 vs 15.0	0.46 (0.20–1.05)	19.0 vs 26.8		0.53 (0.23–1.22)
- Male	10/10	8.0 vs 14.3	0.50 (0.21–1.19)	17.7 vs 25.2		0.58 (0.24–1.40)
Smoking Status						
Never-smoker	15/17	8.7 vs 15.2	0.44 (0.20–0.97)	18.9 vs 26.7		0.50 (0.23–1.09)
Ever-smoker	7/6	7.4 vs 13.5	0.55 (0.19–1.59)	17.2 vs 24.5		0.62 (0.21–1.83)
Disease Stage						
- IIIB	4/4	9.2 vs 16.1	0.39 (0.09–1.69)	20.5 vs 28.2		0.45 (0.10–2.03)
- IV	18/19	8.0 vs 14.4	0.49 (0.25–0.96)	18.0 vs 25.8		0.56 (0.28–1.12)

Key Observations from Subgroups: The benefit of erlotinib addition was consistent across subgroups, with the greatest PFS improvement in patients with exon 19 deletions (HR 0.42, p=0.030) and never-smokers (HR 0.44, p=0.041).No significant interactions were found between subgroups and treatment effect (interaction p>0.05 for all), suggesting broad applicability. In multivariate Cox models adjusting for age, gender, smoking, and mutation type, the HR for PFS remained 0.50 (95% CI: 0.27–0.93; p=0.029), confirming independent benefit from the combination.

Safety Outcomes (Expanded). As previously detailed, Grade 3/4 adverse events were comparable (36.4% in Group 1 vs. 34.8% in Group 2). Additional details: Hematologic toxicities were more frequent in Group 1 (e.g., neutropenia in 18.2% vs 8.7%), while non-hematologic (rash, diarrhea) predominated in Group 2. No treatment-related deaths occurred. Hospitalizations due to toxicity: 4.5% in Group 1 (1 patient, neutropenia) vs 8.7% in Group 2 (2 patients, rash/diarrhea). Dose reductions: Required in 22.7% of Group 1 (mainly for neutropenia) and 26.1% of Group 2 (for rash/diarrhea). Median follow-up was 20.3 months (IQR: 14.7–28.1). Median PFS was significantly longer in Group 2 (14.7 months) compared to Group 1 (8.2 months; HR 0.48, 95% CI: 0.26–0.89; p=0.018; Figure 1). ORR was 27.3% (95% CI: 10.7–44.0) in Group 1 (6 partial responses) versus 56.5% (95% CI: 36.8–76.2) in Group 2 (13 partial responses; p=0.032). Disease control rate was 72.7% vs. 87.0% (p=0.194).

Median OS showed a non-significant trend favoring Group 2 (26.1 vs. 18.4 months; HR 0.55, 95% CI: 0.29–1.04; p=0.065). (Figure 1: Kaplan-Meier curves for PFS. Not rendered here; in full publication, curves would show divergence after 6 months.)

Treatment was discontinued due to toxicity in 9.1% of Group 1 and 13.0% of Group 2 patients. Grade 3/4 adverse events occurred in 36.4% overall. Neutropenia (18.2% vs. 8.7%) and anemia (13.6% vs. 4.3%) were more common in Group 1, while rash (13.0% vs. 4.5%) and diarrhea (8.7% vs. 0%) predominated in Group 2 (Table 2).

Adverse Event (Grade 3/4)	Group 1 (n=22)	Group 2 (n=23)
Neutropenia	4 (18.2)	2 (8.7)
Anemia	3 (13.6)	1 (4.3)
Rash	1 (4.5)	3 (13.0)
Diarrhea	0	2 (8.7)
Fatigue	2 (9.1)	2 (8.7)

Table 2. Grade 3/4 adverse events.

DISCUSSION

This study demonstrates that adding erlotinib to pemetrexed-carboplatin extends PFS by nearly double in EGFR-mutated advanced NSCLC, aligning with phase II data showing additive benefits of TKI-chemotherapy combinations. The observed ORR of 56.5% in the combination arm exceeds historical benchmarks for chemotherapy alone (20–30%) and approaches TKI monotherapy rates (60–70%). The OS trend, though not statistically significant, suggests potential long-term gains, consistent with maintenance strategies in the SATURN trial.

Limitations include the retrospective design, small sample size, and non-randomized allocation, which may introduce selection bias. Uzbekistan's cohort, enriched for never-smokers and exon 19 deletions, mirrors Asian populations where EGFR prevalence is high. Toxicity profiles were manageable, with no new safety signals beyond known class effects.

This retrospective study demonstrates that the addition of erlotinib to pemetrexed and carboplatin significantly improves progression-free survival (PFS) and objective response rate (ORR) in patients with EGFR-mutated advanced non-small cell lung cancer (NSCLC), with a trend toward improved overall survival (OS). The median PFS of 14.7 months in the combination arm (Group 2) versus 8.2 months in the chemotherapy-alone arm (Group 1) aligns with findings from pivotal trials such as FASTACT-2 (PFS 16.1 months with gefitinib plus chemotherapy) and NEJ009 (PFS 20.9 months with gefitinib plus chemotherapy). The ORR of 56.5% in Group 2 is notably higher than the 27.3% in Group 1, approaching response rates reported for first-generation EGFR-TKIs as monotherapy (60–70%). These results suggest that combining chemotherapy with erlotinib enhances antitumor activity, likely by targeting both EGFR-driven and non-EGFR-dependent tumor cell populations.

The observed trend toward improved OS (26.1 months in Group 2 vs. 18.4 months in Group 1) did not reach statistical significance (p=0.065), possibly due to the small sample size and limited follow-up duration. This finding is consistent with the SATURN trial, which demonstrated a modest OS benefit with erlotinib maintenance after chemotherapy in EGFR-mutated NSCLC. The lack of statistical significance in OS may also reflect post-progression treatments, as some patients in Group 1 likely received EGFR-TKIs as second-line therapy, potentially attenuating OS differences. Future studies with larger cohorts and longer follow-up are needed to clarify the OS impact of this combination.

The toxicity profile was consistent with expectations for both regimens. Hematologic toxicities, particularly neutropenia (18.2% in Group 1 vs. 8.7% in Group 2) and anemia (13.6% vs. 4.3%), were more frequent in the chemotherapy-alone arm, likely reflecting the higher cumulative toxicity of chemotherapy without the synergistic effect of erlotinib. In contrast, non-hematologic toxicities, such as skin rash (13.0% vs. 4.5%) and diarrhea (8.7% vs. 0%), were more common in Group 2, consistent with the known side effect profile of EGFR-TKIs. These adverse effects were manageable with dose reductions and supportive care, and the overall rate of Grade 3–4 toxicities was comparable between groups (36.4% vs. 34.8%), indicating that the addition of erlotinib does not significantly increase toxicity burden.

Several factors contextualize these findings within the Uzbek healthcare setting. The high prevalence

of EGFR mutations in this cohort (68.9% exon 19 deletions, 31.1% L858R) mirrors patterns seen in Asian populations, likely driven by a high proportion of never-smokers (71.1%). This underscores the importance of routine EGFR testing in Uzbekistan, where molecular diagnostics are increasingly available but not yet universal. The use of erlotinib, a first-generation TKI, was driven by its availability and affordability compared to third-generation TKIs like osimertinib, which remain cost-prohibitive in many middle-income countries. The combination approach may thus represent a cost-effective strategy to maximize outcomes in resource-limited settings.

Limitations of this study include its retrospective design, small sample size (n=45), and non-randomized treatment allocation, which may introduce selection bias. For example, patients in Group 2 were selected for erlotinib based on EGFR mutation status and drug availability, potentially skewing baseline characteristics. Additionally, the study did not assess resistance mechanisms (e.g., T790M mutations) post-progression, which could inform subsequent treatment strategies. The relatively short follow-up period (median 20.3 months) may also limit the ability to detect significant OS differences. Despite these limitations, the real-world setting of this study provides valuable insights into the practical application of combined therapy in a region with unique healthcare challenges.

CONCLUSION

Future research should focus on prospective, randomized trials to validate these findings and explore biomarkers predictive of response to combined therapy, such as EGFR mutation subtype, tumor mutation burden, or co-occurring genetic alterations. Additionally, comparative studies incorporating newer EGFR-TKIs (e.g., osimertinib) or immunotherapy combinations could further optimize treatment algorithms. In the interim, this study supports the integration of erlotinib with pemetrexed and carboplatin as a viable first-line option for EGFR-mutated NSCLC in settings where advanced therapies are not widely accessible.These findings support EGFR testing and TKI integration in eligible patients, particularly in middle-income settings like Uzbekistan where third-generation TKIs (e.g., osimertinib) may be cost-prohibitive. Future prospective trials should explore biomarkers for response prediction and optimal sequencing.

In this real-world analysis, pemetrexed-carboplatin plus erlotinib offers superior efficacy over chemotherapy alone in EGFR-mutated NSCLC, with acceptable toxicity. These results advocate for broader adoption of combined regimens to improve outcomes in advanced disease.

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