

Lung Section

Real-World Experience of First-Line Osimertinib in EGFR Mutated Non-Small Cell Lung Cancers from a Tertiary Cancer Center, India

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Abstract



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Osimertinib is approved in the first line in patients with mutations in the sensitive gene epidermal growth factor receptor (EGFR) mutation. There is lack of real-world evidence to illustrate the effectiveness and safety of osimertinib that can reflect the current medical practice especially in resource-constrained setting. A total of 129 patients with histology-proven metastatic non-small cell lung cancer with EGFR mutation registered at Tata Memorial Hospital between from March 2018 and May 2023 were analyzed. The parameters studied included demographics, outcomes, safety analysis, and secondary mutations. Most common EGFR mutation was exon 19 deletion 58.9% followed by EGFR exon 21 L858R 39.5% and others 1.5%. The overall median progression-free survival was 21.9 months (95% confidence interval [CI]: 16.0–58.1) and median overall survival was 31 months (95% CI: 17.8–45). The median duration of response was 21.3 months (95% CI: 17.1–25.5). Of 129 patients, 77.5% had partial response (PR), 10.1% had stable disease (SD), and 6.2% patients had progressive disease (PD) as the first best response with overall disease control rate was 87.2%. In patients with baseline central nervous system disease, 8.9% had complete response, 75.5% had PR and 8.9% had SD, and 2.2% had PD as best response. The overall intracranial response rate was 84.4% and disease control was 93.3%. Skin toxicities (27.1%) and gastrointestinal toxicities (17%) were most frequently observed toxicities. Overall, 63 patients had progression of disease on osimertinib. Subsequently, 58.7% ($n = 37$) patients received second line of therapy and 27% ($n = 17$) patients received third line of therapy. Platinum-based combination chemotherapy was the most common subsequent treatment after progression on osimertinib. Repeat biopsy was done in 33 patients (52.3%) and next-generation sequencing was done in 30 patients (47.6%). The most common resistance alteration

Keywords

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detected was TP53 in 30% cases followed by mesenchymal epithelial transition (MET) amplification which was seen in 20% cases. Our study confirms similar efficacy and safety of osimertinib as first-line treatment of mutated non-small cell lung cancer in real-world setting irrespective of the type of common EGFR mutation and similar intracranial activity as well.

Introduction

Metastatic non-small cell lung cancer (mNSCLC) is one of the most common malignancies and the leading cause of cancer-related deaths worldwide and in India.^{1,2} Outcomes for mNSCLC have improved in the past two decades with the identification of certain biomarkers drivers.³

In patients with advanced or metastatic NSCLC with mutations in the gene epidermal growth factor receptor (EGFR) that are sensitive to tyrosine kinase inhibitors (TKIs), EGFR-TKIs are the standard first-line therapy either alone or in combination with chemotherapy. The first-generation EGFR-TKIs erlotinib, gefitinib, and the second-generation EGFR-TKIs afatinib and dacomitinib were approved by the Food and Drug Administration as they showed an improvement in progression-free survival (PFS), overall survival (OS), and overall response rate (ORR).^{4–8}

However, most patients treated initially with first- or second-generation EGFR-TKIs have initial responses but ultimately acquire resistance, leading to progression of disease after median periods of 9 to 15 months.^{9,10} Most commonly, these patients harbor the EGFR T790M resistance mutation.^{9,11}

Osimertinib is a third-generation, potent, irreversible oral EGFR-TKI that inhibits both EGFR-TKI sensitizing and EGFR T790M-resistant mutations. Osimertinib showed efficacy in patients with central nervous system (CNS) metastasis. The FLAURA trial showed that treatment with osimertinib in the first line significantly improved PFS and OS against first-generation TKI. Consequently, osimertinib is now the preferred first-line EGFR-TKI in patients with EGFR-TKI sensitization and EGFR T790M mutations.^{12–14}

Though large phase 3 randomized trials are available, there is a lack of real-world evidence to illustrate the effectiveness and safety of osimertinib, which can reflect current medical practice. Thus, we conducted this retrospective study to assess the real-world clinical impact of osimertinib in patients with advanced NSCLC in our cancer center in India.

Materials and Methods

This study is a retrospective audit of a prospectively collected database at the Department of Medical Oncology, Tata Memorial Hospital, Mumbai, India. The details of the patients were obtained from the prospective lung cancer audit database. The lung cancer audit is an institutional ethics committee-approved observational protocol and is registered with the Clinical Trials Registry India (registration number: CTRI/2013/01/003335). Other relevant clinical details were obtained from hospital electronic medical records.

Eligible patients were required to have histologically confirmed metastatic NSCLC detected with EGFR mutations. EGFR mutation analysis was done by reverse transcription polymerase chain reaction (RT-PCR) or next-generation sequencing (NGS). Patients who received chemotherapy while the results of EGFR mutation status were awaited and were symptomatic for disease and switched to osimertinib after molecular reporting was included in the analysis.

Patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0–3) were included. Patients with baseline CNS metastasis and leptomeningeal metastasis were also included.

Evaluation

Patients underwent a complete history and physical examination and routine blood testing (complete hemogram, renal and liver function tests), electrocardiogram, and two-dimensional-Echo before therapy. Demographic data, including smoking status and tobacco use, was collected. Tumor staging was performed by contrast-enhanced computed tomography of the chest and upper abdomen or whole-body fluorodeoxyglucose positron emission tomography-computed tomography and magnetic resonance imaging of the brain.

Statistical Analysis

All statistical calculations were performed using SPSS version 23 (Armonk, New York, United States) and RStudio. Descriptive statistics were performed for all the baseline characteristics. A median value with an interquartile range was provided for continuous variables. PFS was calculated in months from the date of start of osimertinib to the date of progression on osimertinib or death due to any reason or change in treatment. Patients who had not progressed at the time of the last follow-up were censored. OS was calculated in months from the date of the start of osimertinib until death. Patients who had not died at the time of the last follow-up were censored. The Kaplan–Meier method was used for the time-to-event analysis.¹⁵ The log-rank test was used for univariate analysis of PFS and OS.¹⁶

Results

The study included a total of 129 mNSCLC EGFR-mutated eligible patients who received osimertinib in the first-line setting from March 2018 to May 2023.

Demographic and Clinical Characteristics

The demographical and baseline clinical characteristics of patients are summarized in supplementary data ([–Supplementary Table S1](#) [available in the online version]).

The median age was 59 years (range: 26–78 years). The percentage of male and female patients were 54.3 and 45.7%, respectively. Patients with ECOG PS 0–3 were included; 97 patients (75.2%) had ECOG PS 1, whereas 21 patients (16.3%) had ECOG PS 2 and 6 patients (4.7%) had ECOG PS 3. The majority of the patients (85.3%) were nonsmokers, only 14.7% were current or ex-smoker.

Tumor Characteristics

All patients had EGFR-mutated stage IV mNSCLC. Adenocarcinoma was the most common histological subtype (96.1%). The CNS disease was present in 34.9% of the patients (n = 45), including 3.9% (n = 5) of those with baseline leptomeningeal disease and 34.1% (n = 44) with brain metastasis. EGFR testing was done by RT-PCR in 76% (n = 98) and by NGS in 24% (n = 31) of the patients. The most common EGFR mutation was exon 19 deletion in 76 patients (58.9%). Fifty-one patients (39.5%) had EGFR exon 21 L858R substitution mutation and two patients (1.6%) had other mutations.

Survival Outcome

Overall Population

In overall population, the median PFS was 21.9 months (95% confidence interval [CI]: 16.6–27.2) and median OS was 31.0 months (95% CI: 17.4–44.5) in our study with first-line osimertinib –Supplementary Fig. S1 and S2.

The median duration of response was 21.3 months (95% CI: 17.1–25.5) –Supplementary Fig. S3.

EGFR Exon 19 versus EGFR Exon 21

Median OS in patients with EGFR exon 19 was 28.9 months (95% CI: 25.87–33.88) and in EGFR 21 was 32.4 months (95%

CI: 10.46–54.32) with hazard ratio (HR) of 1.238 (95% CI: 0.678–2.263), p = 0.486 (–Fig. 1).

Similarly, median PFS was 22.3 (95% CI: 15.23–25.95) and 18.2 months (95% CI: 15.11–21.28), respectively for EGFR exon 19 and EGFR exon 21 mutations with HR of 1.387 (95% CI: 0.830–2.317), p = 0.209 (–Fig. 2).

Response Outcome

Of the 129 patients in this study, 100 (77.5%) had a partial response, 13 (10.1%) had stable disease, and 8 (6.2%) had progressive disease as the best response. So, the overall disease control rate (DCR) was 87.2%. Response evaluation was not available for eight patients (6.2%; –Table 1).

In patients with baseline CNS disease (n = 45) response evaluation was available for 43 patients. About 8.9% (n = 4) patients had a complete response, 75.5% (n = 34) patients had a partial response, and 8.9% (n = 4) patients had stable disease as their best response. Response evaluation was not available for 2 patients (4.5%). One patient (2.2%) had progression of disease on osimertinib. ORR was 84.4% and DCR was 93.3%. (–Table 1)

Post-Progression Details

Overall, 63 patients had progression of disease on osimertinib.

Subsequent Treatment

The subsequent therapies are summarized in supplementary data (–Supplementary Table S2 and S3[available in the online version]). On progression, 37 patients (58.7%) received a second line of therapy, and 17 patients (27%) received a third line of therapy. In second line, 57% (n = 20) patients received platinum-based combination chemotherapy regimens, 18.9% (n = 7) received EGFR-TKI, 13.5% (n = 5) received

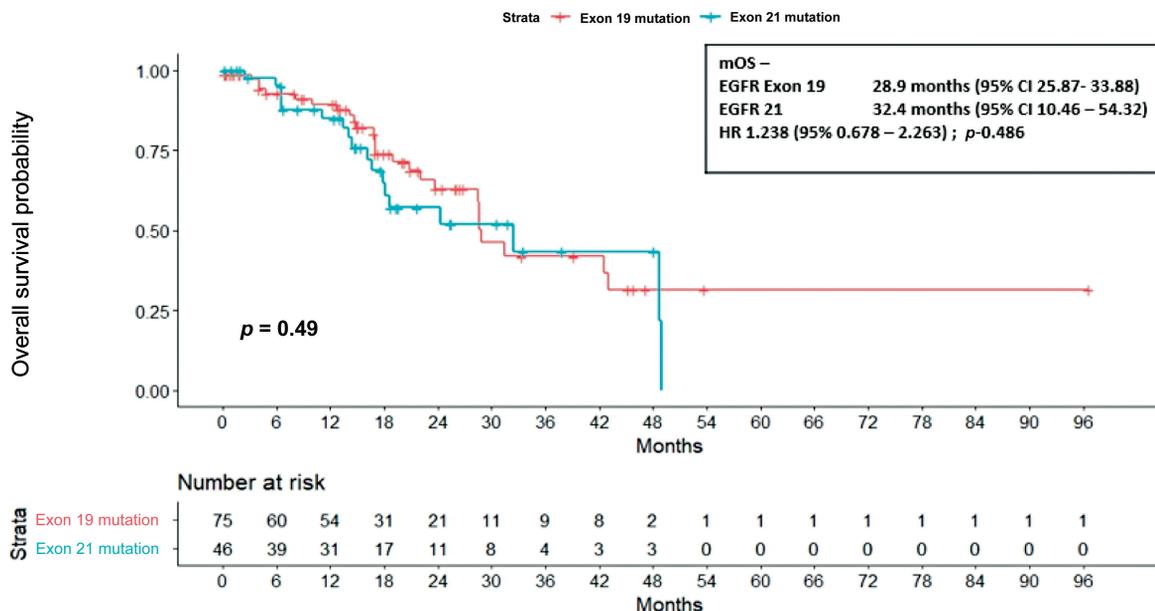


Fig. 1 Overall survival according to epidermal growth factor receptor (EGFR) mutation. CI, confidence interval; HR, hazard ratio.

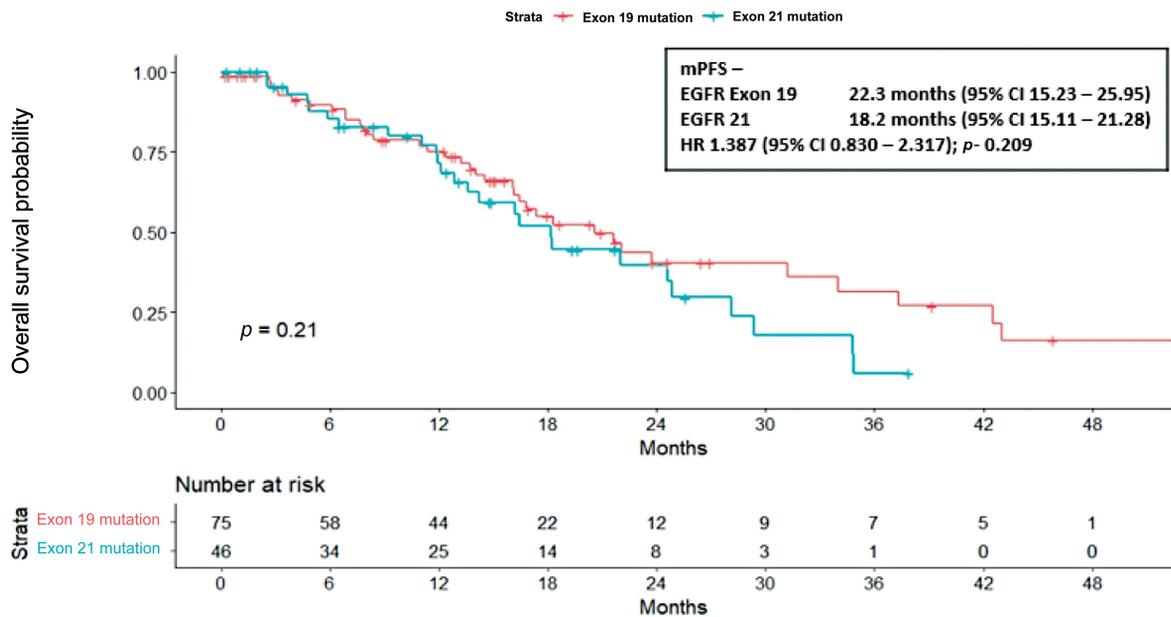


Fig. 2 Progression-free survival according to epidermal growth factor receptor (EGFR) mutation. CI, confidence interval; HR, hazard ratio.

Table 1 Objective response rate

	Response rate	CNS response
Complete response—no (%)	–	4 (8.9%)
Partial response—no (%)	100 (77.5%)	34 (75.5%)
Stable disease—no (%)	13 (10.1%)	4 (8.9%)
Progressive disease—no (%)	8 (6.2%)	1 (2.2%)
Not available—no (%)	8 (6.2%)	2 (4.5%)

Abbreviation: CNS, central nervous system.

chemoimmunotherapy combination regimen, and 8.1% ($n = 3$) patients received EGFR-TKI plus Met TKI combination therapy. In third line, nine patients (52.9%) received taxane-based chemotherapy, four patients (23.5%) received pemetrexed based chemotherapy, one patient (5.8%) received EGFR-TKI plus MET TKI combination therapy, one patient (5.8%) received BRAF V600E directed therapy, and one patient (5.8%) received PI3K inhibitor.

Rebiopsy and Resistance Mechanism Post-Progression

A repeat biopsy was performed in 52.3% ($n = 33$) and NGS was done in 47.6% ($n = 30$) patients. The most common resistance alteration detected was TP53 in 30% cases followed by MET amplification that was seen in 20% cases. Other alterations detected were CDK4 alteration (13.3%), RET mutation (6.7%), PIK3CA (6.7%), EGFR C797S (3.3%), EGFR amplification (3.3%), RET mutation (3.3%), BRAF (3.3%), ROS1 (3.3%), MET fusion (3.3%), and RB1/PTEN (3.3%; ▶Table 2).

Safety and Adverse Events

The adverse effects of osimertinib are depicted in ▶Table 3. Skin toxicities (27.1%) and gastrointestinal toxicities (17%) were the most frequently observed toxicities. About 7.7% of

Table 2 Resistance mechanism post-progression

	Number ($n = 33$)
TP53 mutation	9 (30%)
MET amplification	6 (20%)
CDK4 amplification	4 (13.3%)
RET mutation	2 (6.7%)
CDKN2A mutation	2 (6.7%)
PIK3CA	2 (6.7%)
Exon 20 substitution C797S	1 (3.3%)
MET fusion	1 (3.3%)
RB1/PTEN mutation	1 (3.3%)
BRAF	1 (3.3%)
ROS 1	1 (3.3%)
EGFR amplification	1 (3.3%)
No mutation	6 (20%)

Table 3 Adverse events

	Gd 3/4
Anemia	3 (2.3%)
Hyponatremia	2 (1.5%)
Thrombocytopenia	1 (0.7%)
Transaminitis	1 (0.7%)
Diarrhea	1 (0.7%)

the patients had hyponatremia. The incidence of hematological toxicities (7.1%) was also low. Cardiological toxicities were observed in three patients (2.3%) (2 patients had hypokinesia and 1 patient had QTc prolongation).

Only one patient discontinuing the drug because of grade 3 diarrhea. No other serious or fatal adverse events were observed.

Discussion

Third-generation EGFR-TKI osimertinib changed the outcomes of EGFR-mutated NSCLC.^{17,18} However, real-world data are lacking from lower middle-income countries (LMIC) like India regarding the use of osimertinib, its efficacy, and associated toxicities. To our knowledge, this is the first report of the use of osimertinib in the first-line setting in EGFR-mutated NSCLC from LMIC and Southeast Asian region.

The median age in our study was 59 years, with a slightly higher male preponderance (54.3 vs. 45.7%). The majority of patients were nonsmokers (85.3%). Adenocarcinoma was the most common subtype. The EGFR exon 19 deletion and EGFR exon 21 mutation was the most frequently observed mutation. These demographic characteristics of our study are in line with those of the global and Indian populations of patients with EGFR mutation-positive advanced NSCLC.^{19–21}

In this study, the majority of patients were of ECOG PS 0–1, although a significantly higher number of patients with poor performance status of ECOG PS 2–3 (25.7%) were also included. As the majority of randomized trials usually include patients with good performance status (PS 0–1), in the real-world setting, a significant number of patients present poor performance status. Despite this the oncological outcome with osimertinib is not much significantly affected in our data.

The other important difference in the pivotal trial (the FLAURA trial) was the number of patients with baseline brain metastasis (19%) that was lower than our data (34%).^{13,22} The possible explanation is the exclusion of patients with unstable and symptomatic brain metastases from the FLAURA trial. Our study represents a more realistic representation of patients. Lorenzi et al found that in his study of osimertinib in NSCLC in the real world (FLOWER study), had a similar higher number of patients with brain metastasis (FLOWER study 30.2 vs. this study 34.9%).²³

Despite some differences in baseline characteristics, in our study, the ORR, DCR, PFS, and OS were comparable with published data. In our study, median PFS was 21.9 months and median OS was 31.0 months, which is comparable to the results of the phase III FLAURA trial (median PFS: 18.9 months and median OS: 38.6 months) and the FLOWER study (median PFS: 18.9 months and median OS not reached).^{13,22,23} The median duration of response was 21.3 months. Our study demonstrated an ORR of 77.5% and a DCR of 87.2%, whereas 6.2% of the patients progressed on osimertinib. When we compared the results of the FLAURA trial, ORR was 80% and DCR was 97%, which were higher than the results of our study. The possible explanation for this difference is that there were more patients with poor PS and CNS metastasis in our study.

In this study, median OS and median PFS in EGFR exon 19 and exon 21 were almost similar. This is odd against other standard data (FLAURA and FLOWER trail) where EGFR exon 21 mutation showing poorer outcome compared with EGFR exon 19 mutation.

As we know, third-generation EGFR-TKI osimertinib crosses the blood–brain barrier and has a better CNS control rate in comparison to first-generation EGFR-TKI. Our study has shown similar results. Despite the higher number of baseline CNS metastases, the CNS control rate was comparable to the results of previous landmark trials.^{13,22}

In our study, on progression of the disease, approximately 59% of patients received second-line therapy, and 27% received third-line therapy. The majority of the patients received chemotherapy as a subsequent therapy. Only a few patients received another EGFR-TKI. This is almost similar to data available from known trials where approximately only half of the patients receive subsequent therapies.

Our study showed that osimertinib was very well tolerated. Most of the toxicities were grades 1 and 2. The most common toxicities were skin toxicities. Only one patient discontinued treatment due to toxicity.

Resistance to osimertinib in patients who progressed on osimertinib remains a challenge.²⁴ In this study, 63 patients had progression of the disease. Out of these 63 patients, 33 underwent biopsy and 30 patients underwent NGS testing. The common resistance mechanisms include MET amplification and TP53 alteration with few other mutations occurring infrequently that leads to resistance to osimertinib. Histological transformation is another possible mechanism responsible for resistance. Our results also support the practice of doing the molecular analysis post-progression after EGFR-TKI therapy to know the resistance mechanism and feasibility for another targeted therapy.

Conclusion

Our study confirms the efficacy and safety of osimertinib in a real-world setting. However, cost still remains a challenging factor, leading to underutilization of drugs by most patients in LMICs like India.

Authors' Contributions

Atul Tiwari and Ajay Kumar Singh were involved in data curation, formal analysis, investigation, methodology, software, roles/writing, review and editing—original draft. Vanita Noronha was involved in conceptualization, investigation, supervision, and writing—review and editing. Vijay Patil helped in formal analysis, investigation, and writing—review and editing. Nandini Menon contributed to investigation and writing—review and editing. Minit J. Shah, Darshit Shah, Kunal Jobanputra, Mehak Trikhya, and Ahmad Ubharay helped in data curation, writing—review and editing.

Shashikant Yadav, Anuradha Majumdar, Pratik Chandrani, and Rajiv K. Kumar contributed to methodology and resources. Trupti Pai, Amit Janu, and Nilendu Purandare helped in investigation, methodology, and writing—review and editing. Kumar Prabhaskar was involved in conceptualization, project administration, resources, supervision, and writing—review and editing.

Conflict of Interest

None declared.

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