DOI: 10.7860/JCDR/2026/82906.23429

Original Article

Oncology Section

Efficacy of First Line Afatinib in Epidermal Growth Factor Receptor Mutation Positive Metastatic Non-squamous Non-small Cell Lung Cancer: A Prospective Cohort Single-arm Observational Study among Indian Patients

TRIVIKRAMA RAO MOPIDEVI[1], ANUSHREE CHATURVEDI[2], ANUJ SINGH[3], KM PARTHASARTHY[4], DENI GUPTA[5]

ABSTRACT

Introduction: Lung cancer remains a leading health burden in India, with Non-Small Cell Lung Cancer (NSCLC) being the most prevalent type. Epidermal Growth Factor Receptor (EGFR) mutations, commonly seen in non-smokers, offer an opportunity for targeted therapy. afatinib, a second-generation EGFR TKI, has shown improved outcomes over first-generation TKIs, but Indian data remains scarce.

Aim: To evaluate the safety and efficacy of first-line afatinib in Indian patients with metastatic EGFR mutation-positive Non-Squamous NSCLC (NS-NSCLC).

Materials and Methods: The present prospective, single-arm observational study was conducted from June 2016 to May 2018 at Dharamshila Narayana Superspeciality Hospital, New Delhi, India. Adults with Stage IV, EGFR mutation-positive NS-NSCLC were treated with oral afatinib (starting dose 40 mg/day). Responses were assessed every 12 weeks via Positron Emission Tomography-Computed Tomography (PET-CT) scan using Positron Emission Response Criteria in Solid Tumours (PERCIST) criteria. Patients progressing on treatment were evaluated for T790M mutation and switched to Osimertinib if found positive for mutation. Data were analysed using Statistical Package for Social Sciences (SPSS) version 21.0. Categorical variables were expressed as percentages, and continuous variables as mean±SD or median values. Survival outcomes were estimated using Kaplan-Meier analysis, with comparisons by log-rank test. A p-value <0.05 was considered statistically significant.

Results: Of the 217 patients screened, 27 were enrolled in the study. The median age was 55 years. Among them, 17 patients (62.96%) were female and 19 (70.37%) were never-smokers. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1 was observed in 20 patients (74.07%). The most common EGFR mutation was exon 19 deletion, present in 15 patients (55.56%). The median Progression-Free Survival (PFS) was 13.8 months, and 18 patients (66.67%) achieved one-year Overall Survival (OS). The Objective Response Rate (ORR) was 77.78% (n=21), with 25 patients (92.59%) achieving clinical benefit. The most common adverse events were diarrhoea in 21 patients (77.78%) and rash/acne in 20 patients (74.07%), though severe toxicities were uncommon. Dose reduction was required in 9 patients (33.33%), without any observed impact on PFS.

Conclusion: First-line afatinib was found to be effective and well tolerated in Indian patients with EGFR mutation-positive metastatic NS-NSCLC. It provided superior PFS compared with other first-generation TKIs like gefitinib and erlotinib, and with manageable adverse effects. afatinib also resulted in meaningful improvements in response rate, OS, and clinical benefit. These results support afatinib as a standard first-line treatment option in this patient population.

Keywords: Antineoplastic agents, Asian population, ErbB receptors, Molecular targeted, Precision oncology

INTRODUCTION

Lung cancer remains the most common cancer and leading cause of cancer-related death worldwide [1]. Its management, particularly medical treatment, has evolved significantly over recent decades. Lung cancer is broadly classified into Small Cell Lung Cancer (SCLC) and NSCLC, with NSCLC accounting for approximately 80% of cases [2,3].

Tobacco smoking is the primary cause of NSCLC, except in adenocarcinomas associated with specific genetic alterations such as EGFR mutations, EML4-ALK, ROS1, RET, MET, and HER2. These are more common in light or never-smokers, particularly East Asian women [4]. EGFR, a tyrosine kinase receptor, is a key therapeutic target in NSCLC. Sensitising mutations primarily exon 19 deletions and exon 21 L858R substitutions-occur in the tyrosine kinase domain and are present in about 90% of EGFR-mutant cases. Targeted EGFR-TKI therapy has revolutionised treatment, with multiple large clinical trials [5-10] showing superior PFS and response rates compared to chemotherapy in patients with advanced NSCLC harbouring sensitising EGFR mutations.

First-generation EGFR-TKIs like gefitinib and erlotinib offer PFS benefits of 9.5-13.7 months, but resistance inevitably develops [11]. Afatinib, an irreversible second-generation pan-ErbB inhibitor, was developed to address this limitation. The LUX-Lung trials have demonstrated its efficacy and safety as a first-line option, leading to Food and Drug Administration (FDA) approval for advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations.

However, data on afatinib's real-world safety and efficacy in the Indian population remain limited [1]. The present study aimed to

evaluate the safety and efficacy of first line Afatinib in patients with metastatic NS-NSCLC, with sensitising EGFR mutations, in Indian population at a tertiary cancer hospital in North India. The objective of this study was to assess PFS, response rate, Duration of Objective Response (DOR), and the adverse event profile in patients with EGFR mutation-positive metastatic NS-NSCLC treated with first-line afatinib.

MATERIALS AND METHODS

The present hospital-based, single-centre, single-arm, prospective, observational study was conducted over a period of two years from 1st June 2016 to 31st May 2018, in Department of Medical Oncology at Dharamshila Narayana Superspeciality Hospital, New Delhi, India after approval by the Scientific Advisory and Ethics Committee of Dharamshila Hospital and Research Centre (IEC No. - ECR/226/Inst/DL/2013/RR-16) and in accordance with the 1964 Helsinki declaration and its later amendments. The mean follow-up duration for the study was 14 months till September 2018, indicating that patients were monitored for clinical response, disease progression, and survival outcomes over an average period of just over one year. This follow-up period was sufficient to assess treatment efficacy, tolerability, and one-year OS with afatinib therapy.

All adult Indian patients of both genders attending the Outpatient and Inpatients departments of the hospital with histologically confirmed stage IV NS-NSCLC and EGFR gene mutation positivity were included in the study.The results of the present study were compared with historic controls.

Sample size calculation: Based on previous Indian studies reporting a one-year survival rate of approximately 25-42% in advanced NSCLC [3] and using GLOBOCAN prevalence data [1], the minimum required sample size was calculated to be 94 (with a 10% margin of error and 5% significance level). However, due to time constraints, only 27 patients were enrolled. The sample size was calculated using the formula:

$$N \geq (p(1-p))/(ME/Z\alpha)^2,$$

(where, $Z\alpha$ is the Z-value for a two-sided alpha error of 5%, ME is the margin of error, and p is the prevalence)

Although limited, this sample provides valuable insights and a foundation for future large-scale studies.

Inclusion and Exclusion criteria: Adult patients (>18 years) with pathologically confirmed stage IV NS-NSCLC, ECOG PS 0-2 [12], and activating EGFR mutations (exons 18-21) confirmed by direct DNA sequencing, receiving afatinib as first-line therapy, were included. Patients were excluded if they had prior treatment with more than one cycle of cytotoxic chemotherapy, previous use of EGFR inhibitors (e.g., erlotinib or gefitinib), significant gastrointestinal disorders with baseline diarrhoea (CTCAE Grade>2), severe co-morbidities, or abnormal baseline laboratory parameters including ANC <1500/mm^3, platelet count <100,000/mm^3, serum bilirubin >1.5 mg/dL, AST or ALT >3× ULN (or >5× ULN with liver metastases), serum creatinine >1.5× ULN or creatinine clearance ≤45 mL/min. Patients with known pre-existing interstitial lung disease were also excluded.

Study Procedure

All patients underwent clinical examination, routine haematology (CBC), biochemistry (RFT, LFT), and biopsy with histopathology±IHC to confirm NS-NSCLC. EGFR mutation testing was performed. Staging involved whole-body PET-CT and brain MRI when indicated, following American Joint Committee on Cancer (AJCC) 7th edition TNM criteria [13].

Treatment: Patients were given oral afatinib 40 mg once per day. Patients were permitted to escalate dose to 50 mg daily after 21 days if they did not experience rash, diarrhoea, mucositis, or any other drug-related AE > grade 1 in severity. Treatment continued until progression of disease. Afatinib dose was reduced by 10 mg decrements down to 20 mg per day for treatment-related grade 3 or selected prolonged grade 2 AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4.0) [14].

Assessment during the course of study:

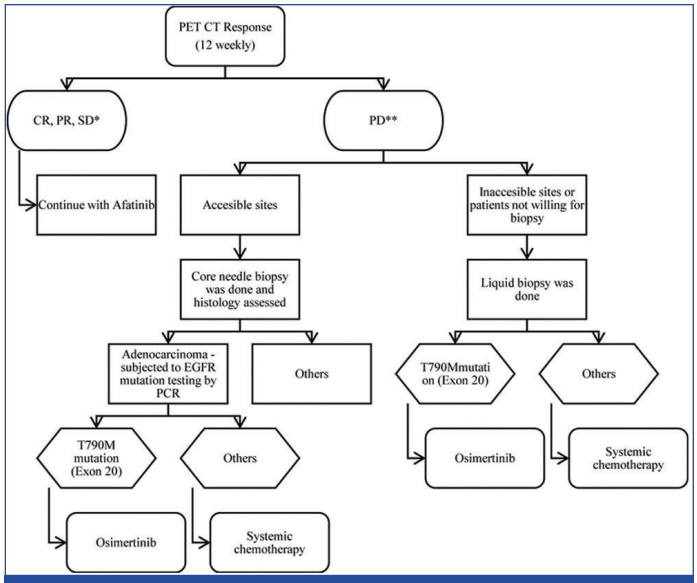
a) Vital signs, complete systemic examination, PS, haematology, serum chemistries were performed every four weekly.

b) Tumour response assessment was done by PET-CT every 12 weeks until disease progression or start of new anti-cancer therapy. Tumour response was independently reviewed in accordance with PET Response Criteria in Solid Tumors (PERCIST) criteria [15].

Patients who achieved Complete Response (CR), Partial Response (PR), or Stable Disease (SD) were continued on afatinib therapy. Upon disease progression, defined as progressive metabolic disease (PD), patients underwent core needle biopsy from an accessible site for histopathological evaluation.

Patients confirmed to have adenocarcinoma were further assessed for EGFR mutation status using Polymerase Chain Reaction (PCR)-based testing. In cases where tissue biopsy was not feasible due to inaccessible disease sites or patient unwillingness, liquid biopsy was performed.

Patients found to harbour the T790M mutation in exon 20 were treated with Osimertinib. Those without the T790M mutation received systemic chemotherapy tailored to their histological subtype as shown in [Table/Fig-1].



[Table/Fig-1]: Flowchart for treatment protocol.
*CR, PR, SD: Complete response, Partial response, Stable disease
**PD: Progressive disease

c) Adverse Effects were categorised and graded using NCI-CTCAE version 4.0 [14].

The study endpoints were either further disease progression, death of the patient and completion of the study tenure. One-year OS was also calculated for all eligible patients, as whether one year OS was attained or not by the study subjects.

1. Data collection and outcomes: Clinical data was collected prospectively from interviews and case records. Patients were followed till progression, death, start of another anti-cancer therapy or last date of tumour imaging for ongoing patients.

a) Progression-Free Survival (PFS): defined as the duration of time from the start of treatment until the day of objective tumour progression was confirmed by tumour imaging (PD according to PERCIST 1.0) or death.

b) Objective Response Rate (ORR): Percentage of participants with best OR: confirmed CR or confirmed PR according to PERCIST criteria.

c) Duration of OR (DOR): measured from the time the criteria for CR or PR (whichever is documented first) are first met until the first date that progressive disease or death is objectively documented.

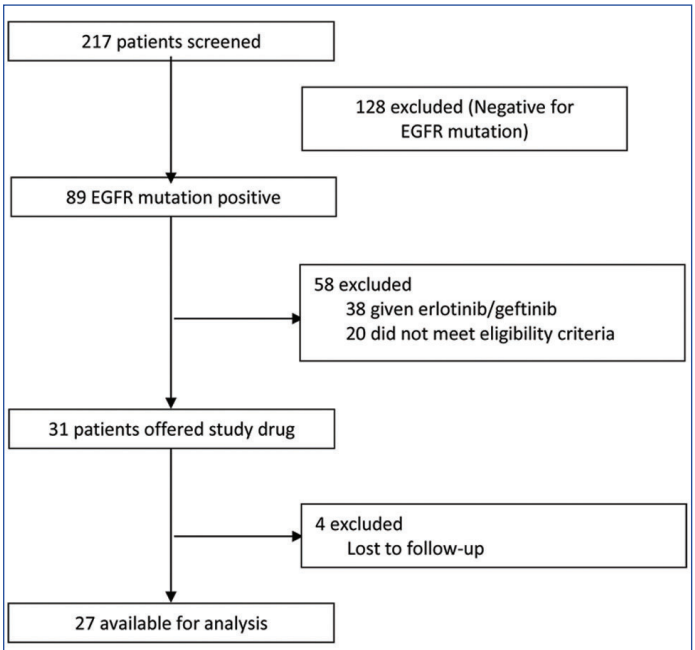
d) Adverse Effects (AEs).

STATISTICAL ANALYSIS

Categorical variables were presented as counts and percentages, while continuous variables were shown as mean±SD and median. Data normality was assessed using the Kolmogorov-Smirnov test. Appropriate statistical tests were applied: t-test or Mann-Whitney for two-group comparisons, Kruskal-Wallis for PFS across multiple groups, Chi-square/Fisher's-exact test for categorical variables, and Kaplan-Meier with log-rank test for PFS analysis. A p-value <0.05 was considered significant. Data were entered in MS Excel and analysed using SPSS v21.0.

RESULTS

CONSORT diagram is shown in [Table/Fig-2] below. Total 27 patients of EGFR mutation positive Stage IV NS-NSCLC fulfilling eligibility criteria were included in the study.Basic demographic and patient characteristics have been given [Table/Fig-3].

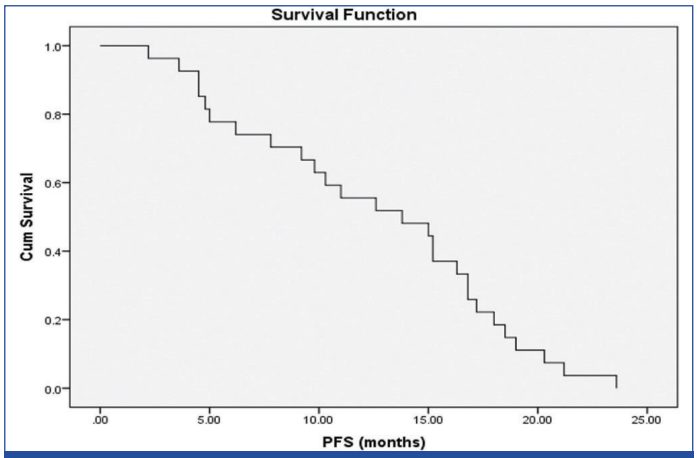


[Table/Fig-2]: CONSORT diagram.

Characteristics	No. of patients (percentage)
Age (years)	
≤50	7 (25.93)
51-60	12 (44.44)
>60	8 (29.63)
ECOG PS*	
0	8 (29.63)
1	12 (44.44)
2	7 (25.93)
Histopathology	
Well-differentiated adenocarcinoma	13 (48.15)
Moderately differentiated adenocarcinoma	7 (25.93)
Poorly differentiated adenocarcinoma	7 (25.93)
Type of EGFR mutation	
Exon 19 deletion	15 (55.56)
Exon 21 mutation	10 (37.04)
Exon G719A mutation	2 (7.41)
Site of metastasis	
Pleural effusion	12 (44.44)
Bone	9 (33.33)
Brain	8 (29.63)
Liver	6 (22.22)
Adrenal	5 (18.52)
Co-morbidities	
Diabetes	7 (25.93)
Hypertension	7 (25.93)
Coronary artery disease	2 (7.41)
COPD	1 (3.70)
Smoking	
Never Smokers	19 {4 male, 15 female} (70.37)
Smokers (Current and former)	8 {6 male, 2 female} (29.63)

[Table/Fig-3]: Patient characteristics.
*ECOG PS: Eastern cooperative oncology group performance status; COPD: Chronic obstructive pulmonary disease

Progression Free Survival (PFS): PFS was defined as the interval between the date of initiation of first-line afatinib therapy and the date of documented disease progression on PET-CT. The one-year OS was also calculated for all eligible patients to determine whether survival beyond one year was achieved. PFS was analysed using the log-rank test. The mean PFS was 12.53±6.14 months, and the median PFS was 13.8 months with a 95% Confidence Interval (CI) and a standard error of 3.46 months [Table/Fig-4-6].



[Table/Fig-4]: Kaplan-Meier plot for progression free survival shows survival probability against progression free survival given in months of afatinib.

Variables	Regression Coefficient (B)	Standard Error (SE)	p-value	Hazard ratio	95.0% CI for hazard ratio	
					Lower	Upper
Age distribution						
≤50				1		
51-60	1.471	0.664	0.027	4.355	1.185	16.008
>60	2.092	0.687	0.002	8.102	2.109	31.117
Gender						
Female				1		
Male	0.250	0.407	0.538	1.285	0.579	2.851
Histopathology						
Well Differentiated Adenocarcinoma				1		
Moderately Differentiated Adenocarcinoma	0.286	0.542	0.597	1.331	0.460	3.851
Poorly differentiated Adenocarcinoma	-0.924	0.544	0.089	0.397	0.137	1.152

Co-morbidities	1.092	0.432	0.012	2.981	1.277	6.959
Smoking status						
Current smoker				1		
Former smoker	-1.836	0.829	0.027	0.159	0.031	0.810
Never smoker	-1.628	0.601	0.007	0.196	0.061	0.637
ECOG PS						
0				1		
1	0.997	0.539	0.064	2.711	0.942	7.805
2	2.781	0.737	0.0002	16.135	3.807	68.383
Side						
Left				1.000		
Right	-0.396	0.408	0.333	0.673	0.302	1.499
LL/ML/UL						
Lower lobe				1		
Middle lobe	0.218	0.490	0.657	1.243	0.476	3.248
Upper lobe	-0.031	0.481	0.948	0.969	0.378	2.487
Site of Metastasis						
Pleural effusion	0.855	0.418	0.041	2.352	1.037	5.335
Bone metastasis	0.999	0.460	0.030	2.715	1.102	6.689
Brain metastasis	1.603	0.507	0.002	4.967	1.839	13.421
Liver metastasis	0.424	0.477	0.374	1.528	0.600	3.889
Adrenal metastasis	-0.459	0.505	0.364	0.632	0.235	1.702
Type of EGFR mutation						
Exon 18				1		
Exon 19	-1.591	0.831	0.056	0.204	0.040	1.038
Exon 21	-1.158	0.836	0.166	0.314	0.061	1.617

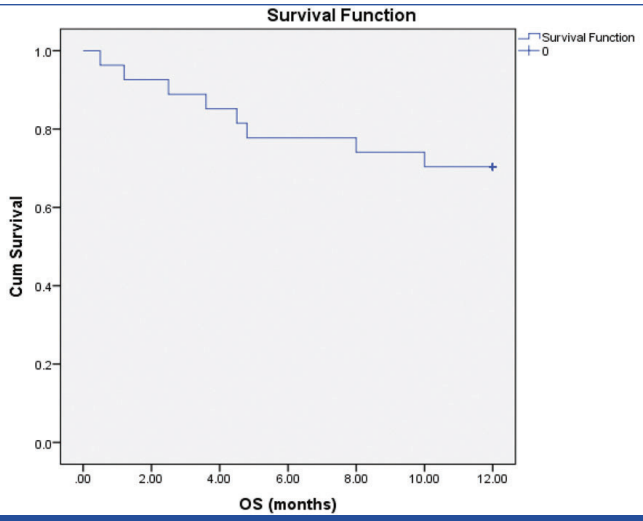
[Table/Fig-5]: Univariate Cox proportional hazard regression for PFS.

Parameters	Regression Coefficient (B)	Standard Error (SE)	p-value	Hazard ratio	95.0% CI for hazard ratio	
					Lower	Upper
Age distribution						
≤50						
51-60	0.819	0.727	0.260	2.267	0.546	9.420
>60	2.531	0.785	0.001	12.563	2.698	58.504
Co-morbidities	0.998	0.705	0.157	2.714	0.681	10.815
Smoking status						
Current smoker						
Former smoker	1.879	1.356	0.166	6.544	0.458	93.407
Never smoker	1.759	1.156	0.128	5.806	0.602	55.989
Site of metastasis						
Pleural effusion	0.676	0.602	0.261	1.967	0.605	6.393
Bone metastasis	1.698	0.705	0.016	5.466	1.372	21.768
Brain metastasis	1.593	0.764	0.037	4.921	1.101	21.994

[Table/Fig-6]: Multivariate Cox proportional hazard regression for PFS.

One-year OS: Eighteen (66.67%) patients survived beyond one year. Remaining 9 (33.33%) patients succumbed to disease within 12 months [Table/Fig-7,8].

Response Rate (RR): Response rates were calculated at the end of study with as the best response achieved by each individual patient. Out of 27 patients analysed in the present study, 25 (92.59%) patients achieved clinical benefit. Out of 25, 21 (77.78% overall) patients achieved OR. All these 21 (77.78% overall) patients achieved PR. None of the patients on afatinib in our study achieved CR. Four (14.81% overall) patients achieved SD as their best response [Table/Fig-9].



[Table/Fig-7]: Kaplan-Meier plot for Overall Survival (OS) shows survival probability against OS given in months of afatinib.

Parameters	Regression coefficient (B)	Standard Error (SE)	p-value	Hazard ratio	95.0% CI for hazard ratio	
					Lower	Upper
Age distribution						
≤50				1		
51-60	-0.476	1.414	0.737	0.621	0.039	9.935
>60	2.235	1.093	0.041	9.347	1.098	79.561
Gender						
Female				1.000		
Male	0.699	0.708	0.324	2.011	0.502	8.063
Histopathology						
Well Differentiated Adenocarcinoma				1		
Moderately Differentiated Adenocarcinoma	0.980	0.869	0.260	2.663	0.485	14.618
Poorly Differentiated Adenocarcinoma	-0.613	1.000	0.540	0.542	0.076	3.847
Co-morbidities	1.890	0.822	0.022	6.620	1.321	33.168
Smoking status						
Current smoker				1		
Former smoker	-0.769	1.157	0.506	0.464	0.048	4.477
Never smoker	-1.412	0.769	0.067	0.244	0.054	1.101
ECOG PS						
0				1		
1	10.884	153.932	0.944	53319.654	0001	
2	12.291	153.931	0.936	217712.668	0001	
Side						
Left				1		
Right	-0.130	0.731	0.859	0.879	0.210	3.681
LL/ML/UL						
Lower lobe				1		
Middle lobe	1.875	1.120	0.094	6.518	0.726	58.518
Upper lobe	1.354	1.155	0.241	3.873	0.403	37.264
Site of metastasis						
Pleural effusion	0.915	0.732	0.211	2.497	0.595	10.484
Bone metastasis	0.866	0.708	0.221	2.378	0.594	9.528
Brain metastasis	1.697	0.733	0.021	5.456	1.297	22.954
Liver metastasis	1.198	0.525	0.023	3.313	1.183	9.277
Adrenal metastasis	0.978	0.732	0.182	2.658	0.633	11.159
Type of EGFR mutation	-0.613	1.070	0.566	0.542	0.067	4.407

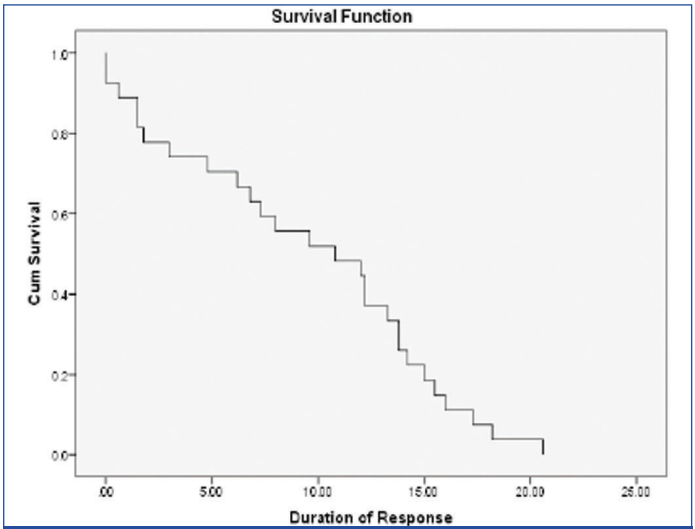
Exon 18				1		
Exon 19	-0.682	1.121	0.543	0.506	0.056	4.552
Exon 21	-0.447	1.157	0.699	0.640	0.066	6.181

[Table/Fig-8]: Univariate Cox proportional hazard regression for OS.

Parameters	n	Percentage
Clinical Benefit	25	92.59%
Objective Response (OR)	21	77.78%
Complete Response (CR)	0	0%
Partial Response (PR)	21	77.78%
Stable Disease (SD)	4	14.81%
Progressive disease	2	7.41%

[Table/Fig-9]: Response rates.

Duration of Objective Response (DOR): The DOR was defined as the time interval between the first documentation of tumour response and the date of disease progression, as confirmed by PET-CT. In this study, the mean DOR was 9.48±6.2 months, with a 95% CI of 7.14-11.82 months and a standard error of 1.19 months. The median DOR was 10.8 months, with a 95% CI of 4.02-17.59 months and a standard error of 3.46 months. These findings indicate a sustained therapeutic response to first-line afatinib in a significant proportion of patients [Table/Fig-10].



[Table/Fig-10]: Kaplan-Meier plot for duration of response shows survival probability against duration of response given in months of afatinib.

Side-effect profile: Diarrhoea, rash, and decreased appetite were the most common patient-reported side effects; most were grade 1-2, with few grade 3 events [Table/Fig-6] while raised SGOT/SGPT and anaemia were the most frequent lab abnormalities; mostly grade 1-2, with few grade 3 cases [Table/Fig-11,12].

Symptoms	All grades n (%)	Grade 1-2 n (%)	Grade 3 n (%)
Diarrhoea	21 (77.78)	19 (70.37)	2 (7.41)
Rash/Acne	20(74.07)	15 (55.56)	5 (18.52)
Decreased appetite	15 (55.56)	12 (44.44)	3 (11.11)
Mucositis	13 (48.15)	11 (40.74)	2 (7.41)
Fatigue	10 (37.04)	9 (33.33)	1 (3.7)
Paronychia	7 (25.93)	7 (25.93)	-
Nausea	5 (18.52)	5 (18.52)	-
Epistaxis	3 (11.11)	3 (11.11)	-
Pruritis	3 (11.11)	2 (7.41)	-
Vomiting	2 (7.41)	2 (7.41)	-
Constipation	1 (3.7)	1 (3.70)	-

[Table/Fig-11]: Side-effect profile-patient reported outcomes.
*There were no Grade 4 and Grade 5 side-effects

Laboratory adverse events	All grades n (%)	Grade 1-2 n (%)	Grade 3 n (%)
Raised SGOT/SGPT	7 (25.93)	6 (22.22)	1 (3.70)
Anaemia	5 (18.52)	4 (14.81)	1 (3.70)
Hypokalaemia	1 (3.70)	1 (3.70)	-
Neutropaenia	1 (3.70)	1 (3.70)	-

[Table/Fig-12]: Side-effect profile- laboratory adverse events.
*There were no Grade 4 and Grade 5 laboratory adverse events
**None of the patients had hyponatraemia or thrombocytopaenia

DISCUSSION

Lung cancer, especially in developing counties like India, is diagnosed in the later stages of disease in majority (60%) of the cases [1,2]. The main goal of the treatment strategies in metastatic lung cancer remains to prolong survival as long as possible with maintaining best quality of life [4]. Targeted treatment regimen has become new standard of care in EGFR mutation positive lung cancers [5-10]. The ease of oral treatment and significant prolongation of PFS and OS have made targeted treatment new 1st line standard of care in eligible patients [5-10].

EGFR-TKIs for lung cancer have advanced significantly over the past two decades, with newer second- and third-generation agents improving OS and PFS in advanced disease [11]. However, stage IV NSCLC remains incurable, and progression after first-line therapy is inevitable. Therefore, using newer-generation TKIs upfront offers better survival outcomes than first-generation TKIs.

Afatinib, a second-generation EGFR-TKI, has shown promise as a first-line treatment for metastatic NS-NSCLC with sensitising EGFR mutations, offering significant improvements in PFS and OS while maintaining a favourable safety profile and quality of life. It is FDA-approved for this indication as well as for treating SCLC following progression on platinum-based chemotherapy [16]. The present study aimed to evaluate first-line afatinib in Indian population to evaluate its efficacy and adverse effects in NS-NSCLC patients whose tumours have non-resistant EGFR mutations. In the present study, of stage IV NS-NSCLC patients with non-resistant EGFR mutations, afatinib showed superior PFS, over 60% one-year OS, and was well tolerated with mainly grade 1/2 toxicities.

The present study included only stage IV NS-NSCLC patients, unlike LUX-Lung 3 [17] and 6 [18] trials, which also included 7-9% stage IIIB cases.

The median age of the study population was 55 years, with three patients aged ≥65 years. Among the 27 patients analysed, 10 (37.04%) were male and 17 (62.96%) were female. The age and gender distribution in this study closely aligns with key landmark trials. In LUX-Lung 3 [17] and LUX-Lung 6 [18], the median ages in the afatinib arms were 62 and 58 years, respectively, with 36% males and 64% females in both trials. Similarly, in the LUX-Lung 7 [19] trial, the median age was 63 years with 43% males and 57% females in the afatinib group.

Patients with an ECOG PS ≥3 were excluded from the study. The majority of patients, 44.44% (n=12), had ECOG PS 1; 29.63% (n=8) had PS 0; and 25.93% (n=7) had PS 2. Unlike the LUX-Lung 3 [17], LUX-Lung 6 [18], and LUX-Lung 7 [19] trials which included only patients with PS 0 or 1 (approximately 20-40% PS 0 and 60-80% PS 1) The present study included a higher proportion of patients with poorer PS 2. All patients had EGFR mutations: 55.56% with Exon 19 deletions, 37.04% with Exon 21 (L858R), and 7.41% with Exon 18 G719A. This closely mirrors LUX-Lung trials, which reported similar distributions.

In the present study, 12 patients (44.44%) had pleural effusion at diagnosis, consistent with the reported incidence of 41-55%. Metastatic sites included bone in nine patients (33.33%), brain in 8 (29.63%), liver in 6 (22.22%), and adrenal glands in 5 (18.52%). Compared to LUX-Lung 7 [19] which reported 50% bone, 16%

brain, 10% liver, and 8% adrenal metastases, our study showed a notably higher incidence of brain and liver metastases.

In this study, 19 patients (70.37%) were never smokers, 5 (18.52%) were current smokers, and 3 (11.11%) were former smokers. This distribution is comparable to LUX-Lung 3 [17] (67% never, 30% former, 2% current), LUX-Lung 6 [18] (75% never, 18% former, 7% current), and LUX-Lung 7 [19] (66% never, 13% light ex-smokers, 21% other smokers).

The PFS in this study was longer than in previous trials. The mean PFS was 12.53±6.14 months, and the median PFS was 13.8 months (95% CI, SE 3.46), which is higher than that reported in LUX-Lung 3 [17] (11.1 months), LUX-Lung 6 [18] (11.0 months), and LUX-Lung 7 [19] (11.0 months).

Lung cancer carries a poor prognosis, with over half of patients dying within a year and a 5-year survival rate below 18%. In this study, 1-year OS on first-line afatinib was 66.67% (n=18), while 33.33% (n=9) died before completing one year. This is slightly lower than the ~80% 1-year survival reported in LUX-Lung trials.

The mean duration of OR was 9.48±6.2 months, while the median duration of response was 10.8 months (SE 3.46), while median PFS was 13.8 months.

Response assessment: In this study, 21 patients (77.78%) achieved PR, 4 (14.81%) had SD, and 2 (7.41%) showed progressive disease as their best response. While no CRs were observed, the PR and progression rates were higher compared to LUX-Lung 6 [18] (1.2% CR, 65.7% PR, 21.5% SD, 3.7% PD) and LUX-Lung 7 [19] (1% CR, 69% PR, 21% SD, 6% PD).

Dose reduction: Afatinib 40 mg/day is the approved first-line dose for EGFR mutation-positive NSCLC. While effective, its use can lead to AEs requiring dose adjustments. In cases of grade ≥3 or prolonged grade 2 AEs, dose reduction by 10 mg increments (to a minimum of 20 mg) is recommended. In our study, 9 of 27 patients (33.33%) required a dose reduction to 30 mg due to grade ≥3 AEs. There was no significant difference in PFS between those who required dose reduction and those who did not (p=NS). No dose increases to 50 mg were made. In comparison, dose reductions were reported in 53.3% (122/229) of patients in LUX-Lung 3 [17] and 28.0% (67/239) in LUX-Lung 6 [18], with most occurring within the first six months (86.1% and 82.1%, respectively).

Safety analysis: Most of the patients tolerated treatment well with manageable grade1 or grade 2 toxicities. Most common symptoms reported by the patients were diarrhoea in 77.78% patients (n=21) and rash/acne in 74.07% (n=20) patients. Nonetheless these were mostly well manageable grade 1 or 2 adverse reactions. Other documented grade1or 2 adverse events were decreased appetite, mucositis, fatigue, paronychia, nausea, epistaxis, pruritis, vomiting, constipation. The laboratory side effect profile includes raised SGOT/SGPT, anaemia, hypokalaemia, neutropaenia, hyponatraemia, and thrombocytopaenia. A 7.41% (n=2) patients had grade 3 diarrhoea, 18.52% (n=5) patients had grade 3 rash/acne, 11.11% (n=3) patients had grade 3 reduced appetite, 7.41% (n=2) patients had grade 3 mucositis, 3.7% (n=1) patients had grade 3 fatigue, 3.7% (n=1) patients had grade 3 elevated SGOT/SGPT and 3.7% (n=1) patients had grade 3 anaemia. None of the patients had grade 4 or grade 5 (death) toxicity. In LUX-Lung 3 [17] trial, 95.2% patients had diarrhoea, 89.1% patients had rash/acne, 72.1% patients had stomatitis/mucositis and 56.8% patients had paronychia of all grades. In LUX-Lung 6 [18] trial, 88.3% patients had diarrhoea, 80.8% patients had rash/acne, 51.9% patients had stomatitis/mucositis and 32.6% patients had paronychia. In LUX-Lung 7 [19] trial, 78% patients had diarrhoea, 79% patients had rash/acne, 60% patients had stomatitis and 54% patients had paronychia. The toxicities in the present study are comparable or less to that of those studied in LUX-Lung 3, 6 and 7 [17-19], except for reduced appetite and fatigue which are reported more in the present study, are probably because of disease per se rather than the drug afatinib. This variability can also be explained by small sample size.

After progression on afatinib, patients were subjected to tissue biopsy from the accessible site, and those who were not willing for tissue biopsy were subjected to liquid biopsy. Those whose tissues or liquid biopsies are positive for T790M mutation were offered Osimertinib. Those whose biopsies were negative for T790M or those which are positive for T790M and not affording Osimertinib were treated with platinum doublet chemotherapy, preferably pemetrexed based. Of the 27 patients analysed, a total 20 (74.07%) patients progressed and 7 (25.93%) patients expired while on afatinib. Of the 20 patients progressed, 4 (20%) patients underwent liquid biopsy and the rest 16 (80%) underwent tissue biopsy. Two (50%) out of four liquid biopsies and 3 (18.75%) out of 16 tissue biopsies came out to be positive for T790M mutation and they all were offered Osimertinib.

Limitation(s)

The present study has several limitations, including its single-arm observational design and small sample size, influenced by the limited study duration and affordability of afatinib. Tumour response evaluations were performed every 12 weeks, which may have affected PFS estimation, and OS was assessed only at one year. Despite these constraints, the study offers meaningful preliminary insights and highlights the need for larger, multicentre randomised trials to validate these findings.

CONCLUSION(S)

First-line afatinib was found to be effective and well tolerated in Indian patients with EGFR mutation-positive metastatic NS-NSCLC. It provided superior PFS compared with other first-generation TKIs like gefitinib and erlotinib, and with manageable adverse effects. afatinib also resulted in meaningful improvements in response rate, OS, and clinical benefit. These results support afatinib as a standard first-line treatment option in this patient population.

REFERENCES

[1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-E386.

[2] Parikh PM, Ranade AA, Govind B, Ghadyalpatil N, Singh R, Bharath R, et al. Lung cancer in India: Current status and promising strategies. South Asian J Cancer. 2016;5(3):93-95.

[3] Noronha V, Patil VM, Joshi A, Menon N, Chougule A, Mahajan A, et al. Clinical outcomes in advanced non-small cell lung cancer: Real-world data from India. Lung India. 2017;34(4):334-41.

[4] Janne PA, Engelman JA, Johnson BE. Epidermal growth factor receptor mutations in non-small-cell lung cancer: Implications for treatment and tumour biology. J Clin Oncol. 2005;23(14):3227-34.

[5] Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947-57.

[6] Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open-label, randomised phase 3 trial. Lancet Oncol. 2010;11(2):121-28.

[7] Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362(25):2380-88.

[8] Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation–positive non–small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011;12(8):735-42.

[9] Han JY, Park K, Kim SW, Lee DH, Kim HY, Kim HT, et al. First-SIGNAL: First-line single-agent Iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J Clin Oncol. 2012;30(10):1122-28.

[10] Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13(3):239-46.

[11] Joshi M, Rizvi SM, Belani CP. Afatinib for the treatment of metastatic non-small cell lung cancer. Cancer Manag Res. 2015;7:75-82.

[12] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

[13] Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
[14] National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [Internet]. Bethesda (MD): National Cancer Institute; 2009 [cited 2016 May 5]. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf.
[15] Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumours. J Nucl Med. 2009 May;50(Suppl 1):122S-150S.
[16] FDA approval for Afatinib Dimaleate [Internet]. Bethesda (MD): NCI; [cited 2018 Jan 16]. Available from: https://www.cancer.gov/about-cancer/treatment/drugs/fda-afatinibdimaleate.
[17] Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, 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(27):3327-34.
[18] Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): An open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(2):213-22.
[19] Park K, Tan EH, O'Byrne K, Zhang L, Boyer M, Mok T, 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(5):577-89.

PARTICULARS OF CONTRIBUTORS:
1. Consultant, Department of Medical Oncology, American Oncology Institute, Hisar, Haryana, India.
2. Assistant Professor, Department of Medical Oncology, NIMS University, Jaipur, Rajasthan, India.
3. Associate Professor, Department of Surgical Oncology, NIMS University, Jaipur, Rajasthan, India. **ORCID ID: 0000-0001-9607-0588.**
4. Senior Consultant and Head, Department of Medical Oncology, Dharamshila Narayana Superspeciality Hospital, New Delhi, India.
5. Senior Consultant, Department of Medical Oncology, Dharamshila Narayana Superspeciality Hospital, New Delhi, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Anuj Singh,
OPD 3, BSTCRI, NIMS Hospital, Delhi Jaipur Highway, Jaipur-303002, Rajasthan, India.
E-mail: dranujsingh1@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 24, 2025
- Manual Googling: Nov 26, 2025
- iThenticate Software: Nov 29, 2025 (3%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Aug 23, 2025**
Date of Peer Review: **Oct 18, 2025**
Date of Acceptance: **Dec 02, 2025**
Date of Publishing: **May 01, 2026**