J Cancer Allied Spec 2023;9(1):3

Original Article

Utilisation Patterns and Treatment Outcomes of EGFR-Tyrosine Kinase Inhibitors in EGFR-mutant Advanced Lung Carcinoma in the Pakistani-Asian Population: A Real-world Data Study

Kiran Munawar[1], Romena Qazi[2], Hassan Shahryar Sheikh[3]

[1]Department of Solid Tumour Oncology, St. Bartholomew's Hospital, Barts Health NHS Trust, London, United Kingdom, [2]Department of Pathology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, [3]Department of Medicine, Sheikh Shakbout Medical City, Abu Dhabi, United Arab Emirates

Received: 23 July 2022/Accepted: 10 November 2022

Correspondence:
Hassan Shahryar Sheikh, Department of Medicine, Sheikh Shakbout Medical City, Abu Dhabi, United Arab Emirates.
E-mail: hssheikh@ssmc.ae

Citation: Munawar K, Qazi R, Sheikh HS. Utilisation Patterns and Treatment Outcomes of EGFR-Tyrosine Kinase Inhibitors in EGFR-mutant Advanced Lung Carcinoma in the Pakistani-Asian Population: A Real-world Data Study. J Cancer Allied Spec [Internet]. 2023;9(1):1-9. https://doi.org/10.37029/jcas.v9i1.491

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interest: Nil.

Abstract

Introduction: Data on the utilisation of epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors (TKIs) and their clinical outcomes in a heterogeneous Pakistani-Asian population have not been previously reported. This manuscript presents the first account of the clinical outcomes of EFGR-TKIs in EGFR-mutant lung adenocarcinoma among Pakistani-Asians. **Materials and methods:** A real-world data study was conducted on all advanced lung cancer patients harbouring EGFR-mutations from the cancer registry of Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan. We identified three different patterns of the use of EGFR-TKIs (Groups 1, 2 and 3) that reflect the ground realities of cancer care and delivery in Pakistan. We also noted a significant proportion of patients (Group 4) without access to EGFR TKIs. We compared the objective response rates (ORR), progression-free survival (PFS) and overall survival (OS) of each of the four groups and reported their toxicity profile. **Results:** Within the limitations of a retrospective analysis, we saw differences in the frequency of EGFR mutations in this population. However, response rates and long-term outcomes of EGFR TKI therapy were comparable with the existing data. The overall use of EGFR TKIs led to a superior outcome in ORR, PFS and OS compared to chemotherapy alone; (77.8% vs. 50.0%, 16.3 vs. 10.7 months; $P = 0.099$; 85.6 vs. 25.9 months, respectively; $P = 0.13$). **Conclusion:** Except for modest differences, EGFR-mutant advanced lung adenocarcinoma outcomes among Pakistani-Asians are comparable to those of other populations.

Key words: Cancer, EGFR mutation, EGFR TKI, lung cancer, Pakistan

Introduction

Lung cancer remains the leading cause of cancer death, with an estimated 1.8 million deaths per year, according to GLOBOCAN 2020.[1] Many developing countries are experiencing an increasing trend in the incidence of lung cancer.[2] Low- and middle-income countries constitute more than 50% of all lung cancer deaths annually.[3] Non-small cell lung cancer (NSCLC) remains the most

common type, accounting for up to 80–90% of the cases.[4] Scientific advances in the understanding and diagnosis of lung cancer have revealed the presence of activating epidermal growth factor receptor (EGFR) mutations that are detected in approximately 40% and 20% of patients with non-squamous NSCLC in Asian and non-Asian populations, respectively.[5-7] The most common EGFR mutations in patients with NSCLC include short in-frame deletions in exon 19 and a specific point mutation in exon 21 at codon 858.[8] EGFR mutations are known to occur more frequently in patients of East Asian origin, who are female, non-smokers and with adenocarcinoma histology.[5] However, there is very little information about the occurrence of EGFR mutations in the Pakistani-Asian population. A single-institution and cross-sectional study conducted at a tertiary centre in Pakistan aimed to determine the frequency and type of EGFR mutation in primary lung adenocarcinoma in Pakistan.[9] It showed an *EGFR* mutation prevalence of 29% in 94 lung adenocarcinoma patient samples, with Exon 21 L858R being the most common mutation, followed by Exon 19 with a prevalence of 48% and 44%, respectively. While this study was not designed to capture the actual prevalence of EGFR mutations in the Pakistani population, it did compare favourably with the reported outcomes of EGFR mutation prevalence in other Asian countries that range between 27% and 60%.[10]

EGFR mutations in advanced lung adenocarcinoma and their inhibition with specific tyrosine kinase inhibitors (TKIs) have been shown to generate clinically significant tumour responses.[11,12] Use of first-generation EGFR TKIs such as gefitinib has resulted in improved response rates and progression-free survival (PFS) in patients with advanced lung cancer harbouring activating EGFR mutations.[12] Newer third-generation EGFR TKIs such as osimertinib has additionally shown overall survival (OS) advantage as well and are approved for first-line therapy.[13]

The treatment outcomes of *EGFR* TKIs in advanced *EGFR* mutant lung carcinoma in a Pakistani population have not been previously reported to the best of our knowledge. Therefore, we conducted a real-world evidence study of the outcomes of *EGFR* mutant advanced lung cancer patients treated with and/or without *EGFR* TKI at our institution. We also evaluated the utilisation patterns of *EGFR* TKIs, patient characteristics, clinical features, toxicity profile and clinical outcomes of *EGFR* mutation-positive patients treated with or without TKIs.

Materials and Methods

A total of 1050 tests were performed assessing for EGFR mutations in samples of non-small cell lung carcinoma from 2013 to 2021 received at Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH). Three hundred and one cases (29%) were reported positive for EGFR mutations. Of these positive cases, we identified 37 patients, all treatment naïve, who registered for further treatment and management at our institution. Five patients were excluded from the study because of loss of follow-up before initiating any treatment, as shown in consort Figure 1. All remaining 32 patients were treated at SKMCH, Lahore, Pakistan, from January 2013 to October 2021. All patients had a biopsy-proven NSCLC. Tumour histology was classified using the WHO criteria.[8] Biopsy specimens were taken either from the primary lung tumour or pleural fluid. Multiplex

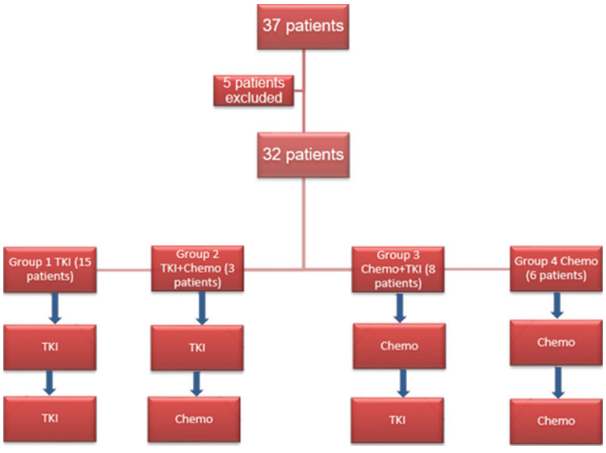


Figure 1: Overview of the study population (TKI: Tyrosine kinase inhibitors, Chemo: Chemotherapy)

real-time PCR was used to analyse EGFR mutation in tumour samples according to the manufacturer's instructions (Roche Diagnostics(R), USA). DNA from Fresh Frozen Paraffin-Embedded tissue was extracted and amplified with primers and probes specific to 43 different EGFR mutations in Cobas z 480 instrument. The assay detects 43 mutations in four exons (18–21) of the EGFR gene, including several point mutations, deletions and insertions. This study was approved by the institutional review board of our institute and informed consent was waived due to the retrospective nature of the study.

We categorised our patients into four groups based on the utilisation patterns of TKIs. Group 1 consisted of 15 patients who received first-generation TKI followed by third-generation TKI on progression. Group 2 consisted of three patients who received upfront first-generation TKI followed by conventional chemotherapy on progression. Group 3 consisted of eight patients who received upfront chemotherapy followed by a first-generation TKI on progression and Group 4 consisted of six patients who received upfront chemotherapy followed by second-line chemotherapy on progression.

Data on the clinical and pathologic characteristics of all patients were collected through the electronic medical record database at our institution. Information was collected on demographics such as age, sex, smoking status, ECOG PS, pathological features of tumour, AJCC stage, CNS metastasis, EGFR mutation status, response to first and second line therapy, PFS in first and second line treatments and OS. Data on the adverse effects of TKI observed in each patient were obtained through electronic medical records and toxicity evaluation was performed according to the CTC AE v3.0. Imaging studies such as computed tomography of the chest and abdomen, brain magnetic resonance imaging or whole-body positron emission tomography scans were reviewed at baseline, interim and end of treatment for response evaluation using the (Response Evaluation Criteria in Solid Tumours) version 1.1.[14] Evaluation of the response included complete response, partial response (PR), stable disease (SD) or progressive disease (PD).

PFS was measured from the 1st day of treatment until radiologic or clinical progression or death. PFS1 was calculated for the front-line therapy and PFS2 was calculated for the second line of therapy. OS was measured from the date of diagnosis of NSCLC until the date of death. Patients without a known date of death were censored at the time of the last follow-up.

Participants' baseline characteristics are presented by descriptive statistics. Statistical analysis was done using SPSS (SPSS version 22.0, SPSS Inc. Chicago, IL, USA). Progression-free and OS were assessed using Kaplan-Meier curves and log-rank analysis, and comparisons were made between TKI and chemotherapy treatments.

Results

Of the 32 patients analysed, 56.3% were males. Twenty-eight patients (87.5%) presented with *de novo* Stage IV disease. Age ranged from 34 to 84 years [Table 1]. The frequency of Exon 19 deletion, Exon 21 L858R mutation, Exon18G7196 mutation and Exon 20 mutation was 56.3%, 31.3%, 9.4% and 3.1%, respectively. One patient had compound Exon18G719X and Exon20S7681 mutation [Table 1], and 4 patients (12.5%) had CNS metastasis at the initial presentation. Three-fourths of patients were never-smokers, while 12.5% and 12.5% were former and active smokers. Female never smokers constituted 43.8% of the study population.

In the first line setting of *EGFR* TKI, 77.8% of patients achieved a PR, 16.7% achieved SD and 5.7% developed PD. In the second line setting of *EGFR* TKI, 54.5% of patients achieved a PR, 27.3% achieved SD and 18.2% developed PD. These data and their chemotherapy comparators are shown in Table 2.

Median PFS on first-line treatment (PFS1) [Figure 2a] was 16.3 months in the upfront TKI group (56.2% of patients consisting of Groups 1 and 2) compared to 10.7 months in the upfront

Table 1: Demographic and baseline characteristics

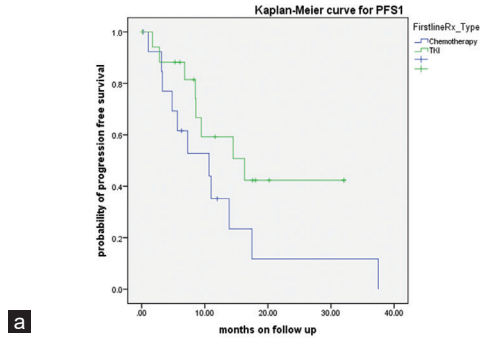
Characteristic	All patients	Group 1 (TKI) *n*=15	Group 2 (TKI + Chemo) *n*=3	Group 3 (Chemo + TKI) *n*=8	Group 4 (Chemo only) *n*=6
Age (years)					
Median (range)	68 (34–84)	64 (34–84)	62 (62–64)	55 (34–60)	64 (46–65)
Gender					
Male	18 (56.3)	6 (40.0)	3 (100.0)	5 (62.5)	4 (66.7)
Female	14 (43.8)	9 (60.0)	0 (0.0)	3 (37.5)	2 (33.3)
Smoking history (%)					
Active	4 (12.5)	2 (13.3)	0 (0.0)	1 (12.5)	1 (16.7)
Former	4 (12.5)	0 (0.0)	0 (0.0)	3 (37.5)	1 (16.7)
Never	24 (75)	13 (86.7)	3 (100.0)	4 (50.0)	4 (66.7)
WHO performance status (%)					
0	8 (25.0)	1 (6.7)	0 (0.0)	6 (75.0)	1 (16.7)
1	22 (68.8)	12 (80.0)	3 (100.0)	2 (25.0)	5 (83.3)
2	1 (3.1)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
3	1 (3.1)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
Histopathologic feature of tumour (%)					
Adenocarcinoma	31 (96.9)	15 (100.0)	3 (100.0)	8 (100.0)	5 (83.3)
Squamous cell carcinoma	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disease stage at presentation (%)					
III	4 (12.5)	1 (6.7)	0 (0.0)	1 (12.5)	2 (33.3)
IV	28 (87.5)	14 (93.3)	3 (100.0)	7 (87.5)	4 (66.7)
EGFR mutation					
exon 18	3 (9.4)	0 (0.0)	1 (33.3)	2 (25.0)	0 (0.0)
exon 19	18 (56.3)	10 (66.7)	0 (0.0)	6 (75.0)	3 (50.0)
exon 20	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
exon 21	10 (31.3)	5 (33.3)	2 (66.7)	0 (0.0)	2 (33.3)
CNS metastasis at presentation					
No	28 (87.5)	14 (93.3)	2 (66.7)	7 (87.5)	5 (83.3)
Yes	4 (12.5)	1 (6.7)	1 (33.3)	1 (12.5)	1 (16.7)

Table 2: Response rate of the participants after receiving TKIs

Response rate	First line TKI	Second line TKI	First line Chemo	Second line Chemo
CR	0/18 (0.0)	0/11 (0.0)	0/14 (0.0)	0/6 (0.0)
PR	14/18 (77.8)	6/11 (54.5)	7/14 (50.0)	2/6 (33.3)
SD	3/18 (16.7)	3/11 (27.3)	5/14 (35.8)	2/6 (33.3)
PD	1/18 (5.56)	2/11 (18.2)	2/14 (14.3)	2/6 (33.3)

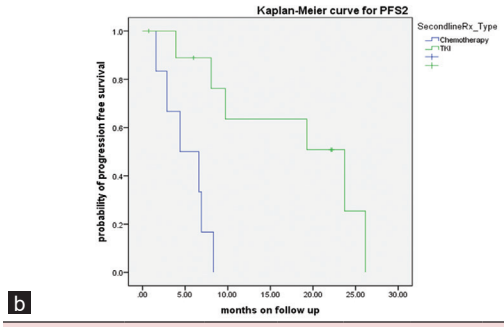
TKIs: Tyrosine kinase inhibitors, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

chemotherapy group (43.8% of patients consisting of Groups 3 and 4) (P = 0.099). Median PFS on second-line treatment (PFS2) [Figure 2b] was 23.7 months in the TKI group (groups 1 and 3)



a

Number at Risk					
Chemo	14	8	4	4	3
TKI	18	12	10	10	10



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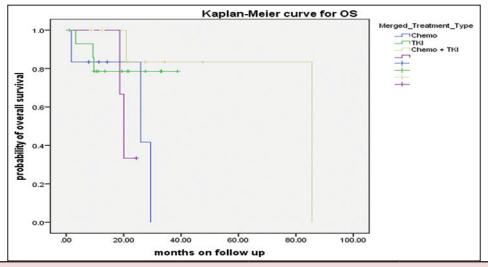
Number at Risk							
Chemo	6	3	0	0	0	0	0
TKI	10	9	7	7	6	5	4



c

Number at risk						
TKI	15	12	12	12	12	12
TKI+Chemo	3	2	1	1	1	1
Chemo + TKI	8	8	7	7	7	6
Chemo	6	5	3	3	3	3

Figure 2: (a) Progression-free survival (PFS) curves of first line (PFS1) TKI versus chemotherapy (TKI: TKIs, Chemo: Chemotherapy). (b) PFS curves of second line (PFS2) TKI versus chemotherapy (TKI: TKIs, Chemo: Chemotherapy). (c) Overall survival (OS) curves by treatment groups; TKI followed by TKI versus TKI followed by chemotherapy versus chemotherapy followed by TKI versus chemotherapy followed by chemotherapy

versus 4.4 months in the chemotherapy group (Groups 2 and 4) (P = 0.002).

Median OS [Figure 2c] in Groups 2, 3 and 4 was 20.0, 85.6 and 26.0 months, respectively, and not yet reached in Group 1 (P = 0.142). Our median follow-up duration was 19.7 months. We also looked at the outcomes of four patients with uncommon EGFR mutations. One patient harboured Exon 20 mutation, and two patients had Exon 18 mutation. One patient also had a complex exon 18 G7196 and exon 20 S7681 mutation. Exon 20 mutation-positive patients received chemotherapy alone and achieved a PFS of 11.9 months and OS of 14.29 months. Both Exon 18 mutation-positive patients received upfront chemotherapy followed by first-generation TKI, resulting in a PFS1 of 5.65 months and 10.68 months, PFS2 of 8.05 months and 22.24 months, and an OS of 21.42 months and 34.27 months, respectively. One patient with complex exon 18 G7196 and exon 20 S7681 mutation received upfront first-generation TKI with a PFS1 of 16.3 months and received chemotherapy on progression with a PFS2 of 4.4 months and OS of 24.41 months.

About 38.5% of patients who received a TKI experienced some adverse effects [Table 3]. The most common adverse effects were skin and gastrointestinal system-related toxicities. About 19.2% of patients developed Grade I-II skin rash, while 3.8% developed Grade 3–4 skin rash. About 7.7% of patients developed Grade I-II diarrhoea and 11.5% experienced Grade 3–4 diarrhoea. A mild elevation in liver transaminases was noted. However, they only required observation. None of the patients reported peripheral oedema, dizziness, dysgeusia, visual disturbances, alopecia or photosensitivity. Overall, TKI therapy was very well tolerated and no new safety signals were reported in our study population. It is possible that due to the retrospective nature of the data, the toxicities are underreported.

Discussion

EGFR TKIs significantly improve outcomes in patients with advanced NSCLC with an activating

Table 3: Summary of adverse events experienced by the patients after undergoing TKI therapy

Adverse event	Group 1 (TKI) *n*=15		Group 2 (TKI followed by chemotherapy) *n*=3		Group 3 (Chemotherapy followed by TKI) *n*=8	
	All adverse events	Adverse events Grade 3–4	All adverse events	Adverse events Grade 3–4	All adverse events	Adverse events Grade 3–4
Skin rash	3 (20.0)	1 (6.70)	1 (3.3)	0	2 (25.0)	0
Diarrhoea	1 (6.7)	1 (6.70)	2 (6.7)	2 (6.7)	2 (25.0)	0
Nausea	2 (13.3)	0	1 (3.3)	0	3 (37.5)	1 (12.5)
Vomiting	0	0	1 (3.3)	0	1 (12.5)	0
Alopecia	0	0	0	0	0	0
Myalgia	0	0	1 (3.3)	0	3 (37.5)	0
Neutropenia	0	0	0	0	0	0
Any	0	0	1 (3.3)	0	0	0
Febrile	0	0	0	0	0	0
Anaemia	0	0	0	0	3 (37.5)	1 (12.5)
Bilirubin raised	1 (6.7)	0	1 (3.3)	0	1 (12.5)	1 (12.5)
ALT raised	0	0	0	0	0	0
AST raised	0	0	0	0	1 (12.5)	0
GGT raised	0	0	0	0	2 (25.0)	2 (25.0)

TKI: Tyrosine kinase inhibitor

mutation in EGFR compared with platinum-based chemotherapy doublets. Therefore, EGFR TKIs represent the standard first line therapy option for activating EGFR mutation-containing advanced lung cancer patients. Despite these significant benefits seen with *EGFR*, access to these novel agents has been limited to Pakistani-Asian populations due to reasons commonly occurring in low- and middle-income countries. As a result, many patients cannot start therapy with a TKI in the first-line setting or receive treatment based on the old standard of conventional cytotoxic chemotherapy alone. Information about the response to EGFR TKIs and their outcomes in an ethnically heterogeneous Pakistani-Asian population with EGFR mutant advanced lung carcinoma is not well known. To the best of our knowledge, this is the first study in a Pakistani-Asian population reporting on the real-world treatment outcomes of EGFR mutation-positive advanced non-squamous NSCLC treated with or without EGFR TKIs.

Around two-thirds of our EGFR mutation-positive study population consisted of never-smokers, slightly higher than 61% seen in a large Asian study (PIONEER) evaluating the frequency of EGFR mutations in Asian populations.[10] However, female never smokers constituted 43.8% of our study population, which was lower compared to the 62% seen in the PIONEER study. Furthermore, our study found the frequencies of deletion Exon 19 and Exon 21 L858R mutation at 56.3% at 31.3%, respectively. These data were compared differently from the previously reported Pakistani study that showed Exon 19 deletion frequency at 44% and Exon 21 L858R mutation frequency at 48%.[9] It also compared differently with the PIONEER study that showed almost similar prevalence of both mutations in the Asian population that is, Exon 19 deletion 47.8% and Exon 21 L858R mutation 45.4%.[10] Our results are likely to be affected by the small sample size than a meaningful difference in the biology of the disease.

Our real-world data showed three different patterns of utilisation of EGFR TKIs, as reflected in treatment Groups 1–3. We compared Groups 1, 2 and 3, which incorporated an EGFR TKI in the treatment pathway with the old standard of platinum doublet chemotherapy consisting of Group 4 within the limitations of a retrospective review.

In the overall study population, only 81.24% of EGFR mutant advanced lung cancer patients received an EGFR TKI during the course of their treatment. Only 56.3% of patients received a TKI as their first line of treatment as per the best practice guidelines, while 25% received a TKI following front-line chemotherapy. Regarding the choice of TKI agent used, 83.3% of our patients received the first-generation TKI, Erlotinib, as first-line therapy, compared to 16.6% of patients receiving the third-generation TKI, osimertinib. Three patients (23%) received a third-generation TKI following progression on first-generation TKI (Group 1). It is pertinent to note that the study population underwent treatment during the era when first-generation TKI such as erlotinib, represented the standard of care as first-line therapy, followed by a third-generation TKI such as osimertinib on progression.

There are several observations to be made from our real-world data. The objective response rate (ORR) to TKI therapy in the first line (77.8%) was consistent with the high response rates seen in the previously published data from other Asian populations implying that our population compared favourably with the rest of the world. However, ORRs were lower (54.5%) if TKIs were used in the second line setting following conventional chemotherapy.

Similarly, there was a significant improvement in the PFS when TKI was used in first and second line therapy compared to chemotherapy in the corresponding setting that is, 16.3 months versus 10.7 months in first line and 23.7 months versus 4.4 months in second line therapy. These data are consistent with the published data in this population. Furthermore, median OS for the TKI only (Group 1) was not reached and further follow-up is ongoing. However, it showed a superior median OS compared to chemotherapy only (group 4); not yet reached versus 25.96 months; $P = 0.208$.

The median OS for the groups that contained a TKI (Groups 1+2+3) was superior (85.6 months) compared to the chemotherapy alone (25.96 months) (Group 4). However, it did not reach statistical significance due to the small sample size ($P = 0.131$). It implies that treatment with TKI at any point in the course was superior to not receiving a TKI.

There was a significant difference in the median OS between Groups 2 and 3; 20 months versus 85.6 months ($P = 0.081$) that is, patients who received first-generation TKI as first-line therapy and chemotherapy on progression versus patients who received chemotherapy upfront followed by first-generation TKI as second line therapy. These results are statistically non-significant and are likely influenced by the small sample size and the presence of one exceptional responder in Group 3.

Our real-world data showed that the use of EGFR TKIs was very well tolerated, with manageable adverse effects primarily consisting of manageable skin and gastrointestinal toxicities comparable to the published data. No new safety signals were noted in our population.

Our real-world evidence corroborates the superior outcomes in terms of ORR, PFS and OS seen with the use of EGFR TKIs in the published literature in advanced EGFR mutant lung adenocarcinoma and underpins the importance of access to EGFR TKIs in resource constraint countries.[13,15-18]

Our low utilisation of EGFR TKI in the overall population in this disease subset (81.24%) and the first line setting (56.3%) highlights the issues of access to EGFR TKIs in low- and middle-income countries. A recently published study evaluated the list of essential cancer medicines and their accessibility in routine clinical practice in different regions of the world. The authors reported that EGFR TKIs were not included in the WHO cancer essential medicine list (EML).[19] However, there

was a consensus among the oncologists from all across the strata of low- to high-income countries to include EGFR TKIs in the WHO EML. The study showed striking financial barriers to accessing these medicines, especially in low- and middle-income countries. Furthermore, access seemed to be limited by household affordability of medicine rather than their availability. Thus, improving access to EGFR TKIs as an essential cancer medicine requires policy and action at the government level to ensure universal access.

This study results are limited by several factors, principally due to the small sample sizes of the treatment groups and the overall study population. Other limitations inherent in real-world data analyses, such as non-randomisation of data, retrospective nature and selection bias, are also present in our study. Therefore, conclusions from this study should be drawn with caution. However, given the low occurrence of EGFR mutant lung cancer and the paucity of published data from Pakistan in this subset of patients, these observations, reported from the largest comprehensive cancer and referral centre in the country, are nonetheless informative.

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Author Contributions

Conceived and designed the analysis: HSS; Collected the data: KM and RQ; Contributed data or analysis tools: KM, RQ and HSS; Performed the analysis: KM, RQ and HSS; and Wrote the paper: KM, RQ and HSS.