

Outcomes of Patients with *EGFR*-Mutant Advanced NSCLC in a Developing Country in Southeast Asia

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Background: Although first- and second-generation EGFR TKIs are considered first-line treatment in EGFRm+ NSCLC, most patients develop resistance and progress, commonly, EGFR *T790M* mutation. The third-generation EGFR-TKI has demonstrated efficacy in patients with progressive disease harboring the *T790M* mutation and in the first-line setting, bypassing this mode of resistance. The primary objectives of this study are to describe the proportion of EGFRm+ NSCLC patients treated with first-, second- and third-generation EGFR TKIs, and cytotoxic chemotherapy in the first-line setting, and the time on treatment for each category. Secondary objectives are to determine the dropout rate, the rates for *T790M* mutation testing at disease progression and the type of subsequent treatment.

Methods: This multicenter retrospective study utilized data from the Malaysian Lung Cancer Registry that actively registers all lung cancer patients ≥ 18 years, with primary lung cancer confirmed histologically or cytologically. All patients diagnosed with advanced stages (ie stages IIIB, IIIC and IV) EGFRm+ NSCLC from 1st of January 2015 to 31st December 2019 were included.

Results: Of 406 patients with EGFRm+ NSCLC, 351 were treated. Types of first-line treatment were as follows: EGFR-TKIs (first generation – 54.1%, second generation – 25.6% and third-generation – 12.5%) and chemotherapy (7.7%). The median time of treatment for each generation of EGFR-TKI was 12 months, 12 months and 24 months, and 2 months for chemotherapy. The dropout rate was 28.7% (n = 101). Nearly half (49.4%) of patients who were on first- or second-generation EGFR-TKI had further genetic testing via liquid or tissue biopsies upon disease progression. About 24.9% of those who developed disease progression after first- or second-generation EGFR TKI were started on a third-generation EGFR TKI.

Conclusion: In the real-world, the management of EGFRm+ advanced NSCLC patients in an Asian cost-restrictive setting may adversely affect the choice of first-line therapy, time on each line of treatment and subsequently the overall survival of patients.

Keywords: tyrosine kinase inhibitors, lung cancer, time on treatment, overall survival

Introduction

In 2018, the World Health Organization estimated that globally, lung cancer was the most common cancer (2.09 million cases) and the leading cause of cancer death (1.76 million deaths). The Malaysian National Cancer Registry published in 2016 showed that lung cancer is the third most common cancer (9.8%) in Malaysia with an incidence of 13.2 per 100,000

in males and 6.9 per 100,000 in females.¹ The Malaysian Study on Cancer Survival (2018) determined that the 1-year and 5-year overall survival rates in patients with lung cancer were 35.5% and 11.0%, respectively.²

A review of lung cancer research in Malaysia indicated that up to ~80.0% of lung cancer patients have non-small cell lung cancer (NSCLC).³ The estimated rate of *epidermal growth factor receptor* (*EGFR*) mutation (*EGFRm+*) in Malaysian lung cancer patients was 45.7% (n = 484).⁴ This finding was similar to an updated global analysis based on original studies from various countries, which determined that the prevalence of *EGFRm+* lung cancer was higher in parts of Asia (42.7%, p < 0.001).⁵ However, in a smaller prospective study of 151 multi-ethnic Malaysian patients,⁶ the *EGFRm+* rate was 36.4%, which is in line with the global median overall prevalence of 33.1%.⁵ There was also no significant difference among the different ethnic populations (p = 0.08).⁶ *EGFRm+* was found mainly in the adenocarcinoma subtype,⁴ which matches the global epidemiological data.⁵

With the advent of targeted therapy, the use of *EGFR* tyrosine kinase inhibitors (TKIs) is currently the recommended first-line treatment for *EGFRm+* NSCLC.⁷ First- and second-generation *EGFR*-TKIs have shown significant efficacy in this group of patients.^{8–11} However, most patients develop progressive disease (PD) within 9.0–14.7 months.^{12–15} The most common reason for PD is the development of *EGFR* TKI resistance, of up to 69.0% due to an acquired second mutation, ie pThr790Met point mutation (*T790M+*)^{13,15–17} In the Phase III randomized-controlled AURA 3 study,¹⁸ of 1036 patients with advanced or metastatic NSCLC and PD after first-line *EGFR* TKI therapy, more than half (52.0%) were *T790M+*.

A challenge of novel, molecular-targeted therapies is the access to the specific genetic testing required before initiating treatment, and the cost of the treatment itself.¹⁹ First- and second-generation *EGFR* TKIs being more accessible, are usually offered upfront instead of third-generation TKIs, even though the third-generation TKI osimertinib has been approved for use as a second-line treatment in Malaysia since May 2017 and as a first-line treatment since November 2018. For patients who progress on first- and second-generation *EGFR* TKI, many might not have access to third-generation *EGFR* TKI resulting in the utilization of chemotherapy or other alternatives. This lack of accessibility to third-generation *EGFR* TKI will impact their time on treatment (TOT) and the overall survival.

The primary objectives of this multicenter, retrospective study are to describe the proportion of Malaysian NSCLC patients with *EGFRm+* according to the types of mutation (eg exon 19 deletion [Del19] and exon 20 L858R insertion) and describe the proportion of *EGFRm+* NSCLC patients treated with first-, second- and third-generation *EGFR* TKIs, and cytotoxic chemotherapy in the first-line setting, and the TOT in each treatment category. Secondary objectives are to determine the dropout rate, rates for *T790M+* testing at PD and subsequent treatment based on the presence or absence of *T790M+* as an acquired resistance. We aim to use data from a large, multicenter registry to highlight real-world prevalence and therapy outcomes in the setting of a resource challenged, developing country like Malaysia.

Materials and Methods

Study Design and Data Source

The data for this multicenter retrospective study were taken from the Malaysian Lung Cancer Registry. Eighteen major hospitals from the public, university and private sectors (75.0% contribution by public and university hospitals, and 25.0% from private hospitals) across Malaysia actively register all lung cancer patients 18 years and above, with a prior or current diagnosis of primary lung cancer confirmed histologically or cytologically since 1st January 2015. Electronic case report forms were used to collect data for the registry. The data collected include patients' baseline demographics, clinical characteristics such as smoking and Eastern Cooperative Oncology Group [ECOG] performance status, radiological and pathological findings, and treatment regimens of patients with *EGFRm+* NSCLC. For this study, informed consent was waived with approval by the University of Malaya Medical Centre Medical Research Ethics Committee as the individual patient medical information in the database was considered confidential and this was ensured using patient identification code numbers.

Study Population

All patients diagnosed with advanced stage (ie stages IIIB, IIIC and IV) *EGFR*m+ NSCLC patients from 1st of January 2015 to 31st December 2019 were included in this study. Clinical staging was based on the 8th edition of the International Association for the Study of Lung Cancer (IASLC) tumor, lymph node and metastasis (TNM) classification.²⁰ Patients with incomplete staging or treatment information were excluded from the analysis. Patients' *EGFR*m+ status was classified into Del19 (including patients with mixed exon 19 deletion and other co-mutations), L858R (including patients with mixed exon 21 L858R and other co-mutations) and rare mutations.

Data Collection

The electronic case report forms (eCRFs) retrieved from the Malaysian Lung Cancer registry were screened for any missing data. eCRFs of patients with missing data that could not be resolved after checking with the site investigator were excluded from analysis. Patients lost to follow-up and not contactable by phone at the time of analysis were excluded from OS analysis.

The demographic and the clinical characteristics of the patients, the type of treatment (chemotherapy or targeted therapy), time on treatment (TOT) on first-line treatment, PD, and median overall survival (OS) were documented. Type of treatment was categorized as first- and second-generation EGFR TKI with or without chemotherapy, third-generation EGFR TKI with or without chemotherapy, chemotherapy alone, and others which included any treatment that did not fall into the previous categories such as immune checkpoint inhibitor therapy with or without chemotherapy, bevacizumab with chemotherapy, and so on. TOT was defined as the duration from the first day of therapy to the day of the last dose of therapy. PD was evaluated clinically and radiologically every six weeks to three months depending on the individual center management protocols, and was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). OS was defined as the time from initiation of therapy until death from any cause.

Statistical Analysis

The analysis was then performed on complete eCRFs using IBM SPSS Statistics version 23. Descriptive analysis was performed for categorical variables and presented as percentages (%). Continuous variables including age and TOT were described using medians. Significance level was taken at alpha of 0.05, and all p values were reported to be 2-sided.

The Kaplan–Meier method was used to estimate TOT and OS, and Log rank test was used to test the TOT and survival differences between groups. All the assumptions were checked prior to analysis. Outcome was defined as when the patient changed treatment regime whilst censored was defined by the end of the study or when the patient was lost to follow up. Duration was expressed in months.

Results

A total of 406 patients with *EGFR*m+ NSCLC were registered in the Malaysian Lung Cancer Registry. Of these, 22 (5.4%) patients were excluded from analysis because of incomplete staging or treatment details (Figure 1). A total of 33 (8.6%) patients did not receive treatment after diagnosis, and the two most common reasons for non-treatment were death before treatment initiation (14 patients, 42.4%) and poor ECOG performance status at presentation (10 patients, 30.3%).

The baseline characteristics of the 351 patients included in the treatment and survival analyses are shown in Table 1. The majority (80.6%) of patients were non-smokers and female (61.5%). Del19 was the most common mutation in 195 (55.6%) patients followed by L858R mutation in 113 (32.2%) patients. Rare mutations were detected in 43 (12.3%) patients (G719X = 12, 20 insertion = 8, L861Q = 8, S768i = 4, T790M = 4, and others).

Of the 351 patients who were treated, 92.3% were treated with first-line targeted therapy, including 10 patients who were treated first-line with a combination of chemotherapy and EGFR TKI (Figure 1). First-generation EGFR TKIs were the most frequently used (54.1%) followed by the second-generation EGFR TKI (25.6%). Only 12.5% patients were on first-line third-generation EGFR-TKI (osimertinib) and 7.7% were treated with chemotherapy alone. The median follow-up time for those on first- and second-generation EGFR TKIs was 24 months (95% CI 21.4, 26.6), on osimertinib was 23 months (95% CI 17.5, 28.5), and for those on chemotherapy was 21 months (95% CI 13.9, 28.1).

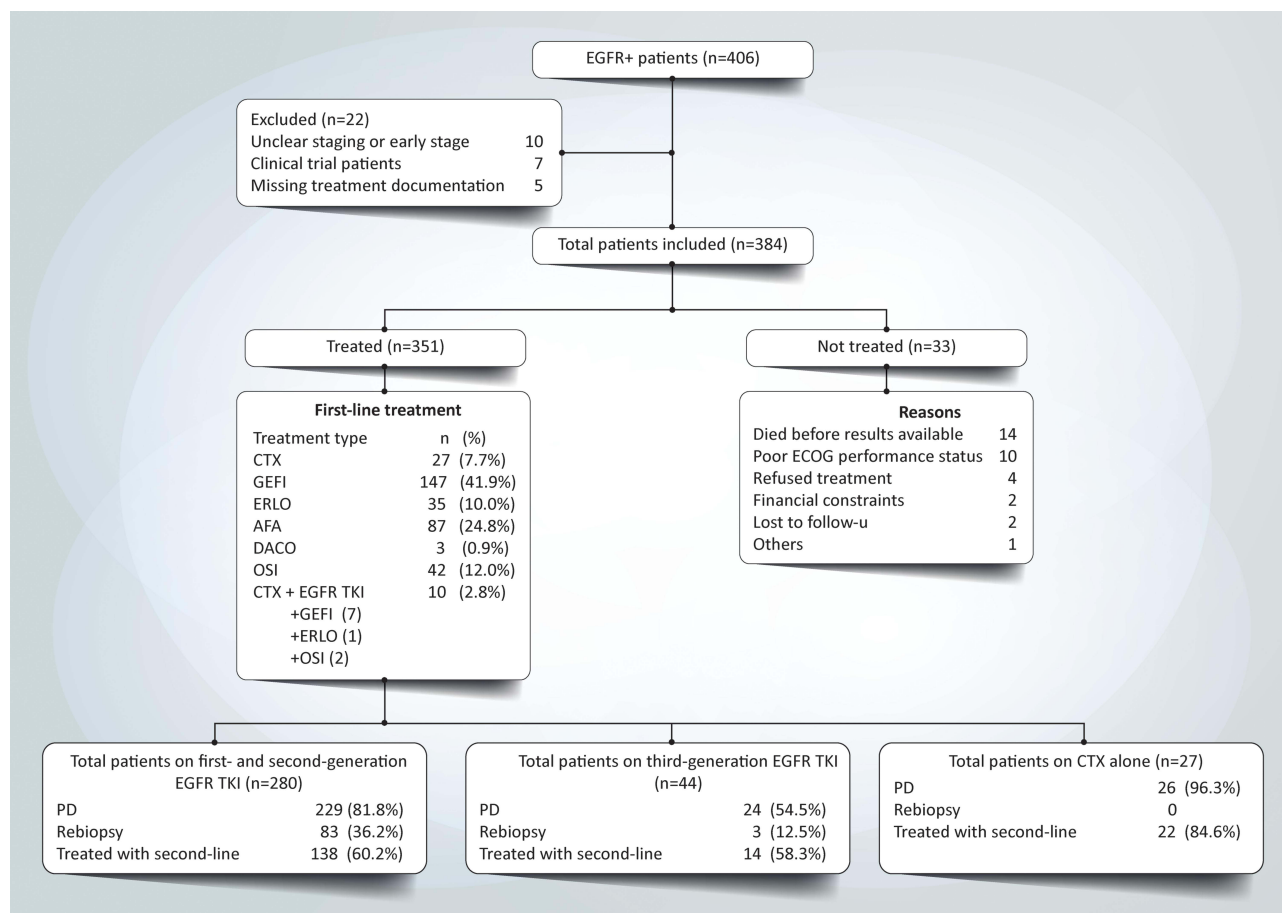


Figure 1 Patient flow.

Abbreviations: AFA, afatinib; CTX, chemotherapy; DACO, dacomitinib; ECOG, Eastern Cooperative Oncology Group; EGFR+, epidermal growth factor receptor positive; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; ERLO, erlotinib; GEFI, gefitinib; OSI, osimertinib; PD, disease progression.

At the time of analysis, 279 (79.5%) patients had PD. For the 24 patients treated with first-line osimertinib, only three (12.4%) patients had genetic testing performed at PD. Eighty-three (36.2%) of the 229 patients treated with first-line first- or second-generation EGFR TKIs had genetic testing upon progression (Figure 1). The most common genetic testing method was a blood liquid biopsy ($n = 65$; 78.3%) followed by a core tissue biopsy ($n = 18$; 21.7%) and cytological specimens were utilized for the remaining three patients. Tissue-based biopsies were performed using the cobas® version 2 (Roche Diagnostics) platform whilst liquid biopsies were performed using droplet digital polymerase chain reaction. Overall, EGFR T790M+ was detected in 54 of 83 (65.1%) patients who failed first- or second-generation EGFR TKI. EGFR T790M+ was detected in 41 of 65 (63.1%) using liquid biopsies and in 10 of 18 (55.6%) patients using core tissue biopsies (including one patient who had positive EGFR T790M from both liquid and tissue biopsy). All three patients who were tested using cytological specimens were EGFR T790M positive.

The median TOT for first-, second- and third-generation EGFR TKIs were 12.0, 12.0 and 24.0 months in the first-line setting, respectively. Since the median TOT for first- and second-generation EGFR-TKI in the first-line setting were the same (12.0 months), we combined their results when performing further analysis. Patients treated with first-line chemotherapy had significantly shorter TOT (2.0 months) compared to patients who were on first-line first- or second-generation (12.0 months), and third-generation (24.0 months) EGFR TKIs ($p < 0.001$, Figure 2). A hundred and one (28.8%) patients were lost to follow up at the time of analysis despite all efforts by their treating physicians to contact them. The median OS for the whole cohort ($n = 250$) was 30.0 months (95% CI, 25.4–34.6) (Figure 3). By category of treatment, patients on first-line chemotherapy and osimertinib had significantly longer median OS than those on first-line first- or second-generation EGFR TKI (median OS not reached vs 28.0 (95% CI, 22.1–34.0) months) (Figure 3). Among those who received first-line first- and second-generation

Table 1 Baseline Characteristics of Patients in the Analysis Set (N = 351)

| Characteristic | n (%) |
|--------------------------------------|-------------|
| Age (Mean, SD) | 63.2 (11.0) |
| Gender | |
| Male | 135 (38.5) |
| Female | 216 (61.5) |
| Ethnicity | |
| Malay | 137 (39.0) |
| Chinese | 180 (51.3) |
| India | 12 (3.4) |
| Non-Malaysian | 22 (6.3) |
| Smoking status | |
| Never smoker | 283 (80.6) |
| Ex-smoker | 59 (16.8) |
| Current smoker | 7 (2.0) |
| ECOG performance status | |
| 0 | 70 (19.9) |
| 1 | 173 (49.3) |
| 2 | 51 (14.5) |
| 3 | 33 (9.4) |
| 4 | 22 (6.3) |
| TNM stage | |
| IIIB and C | 12 (3.4) |
| IVA | 208 (59.3) |
| IVB | 131 (37.3) |
| Histological subtype of NSCLC | |
| Adenocarcinoma | 340 (96.9) |
| Non-adenocarcinoma | 11 (3.1) |
| EGFR mutation | |
| Ex19Del | 195 (55.6) |
| Ex21 L858R | 113 (32.2) |
| Others | 43 (12.3) |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TNM, tumour nodes and metastasis.

EGFR TKIs, initiating third-generation EGFR TKI as second-line treatment on PD doubled the median OS (60.0 months) compared to those who did not receive osimertinib as second-line treatment (Figure 4).

Upon PD on first-line treatment, 174 of 351 patients were started on second-line treatment at the time of analysis with 116 patients (66.7%) receiving second-line targeted therapy with or without chemotherapy and 53 patients (30.5%) treated with second-line chemotherapy alone (Table 2). Only two patients (1.1%) were started on immune checkpoint inhibitor with chemotherapy, and the remaining were given chemotherapy with bevacizumab or others. Of the 229 patients who developed PD on first- or second-generation EGFR TKI, 83 patients had genetic testing. Nearly half of these patients [41 of 83 (49.4%)] were started on the third-generation EGFR-TKI, osimertinib, while only 16 of 146 patients (11.0%) who did not have genetic testing received osimertinib. Of the 26 patients who had PD on first-line chemotherapy, 22 received second-line treatment with the majority [20 of 22 (90.9%)] receiving second-line EGFR TKI. Thirty-four of 138 (24.6%) patients who failed first-line first- or second-generation EGFR TKI received a different first- or second-generation EGFR TKI as second-line treatment.

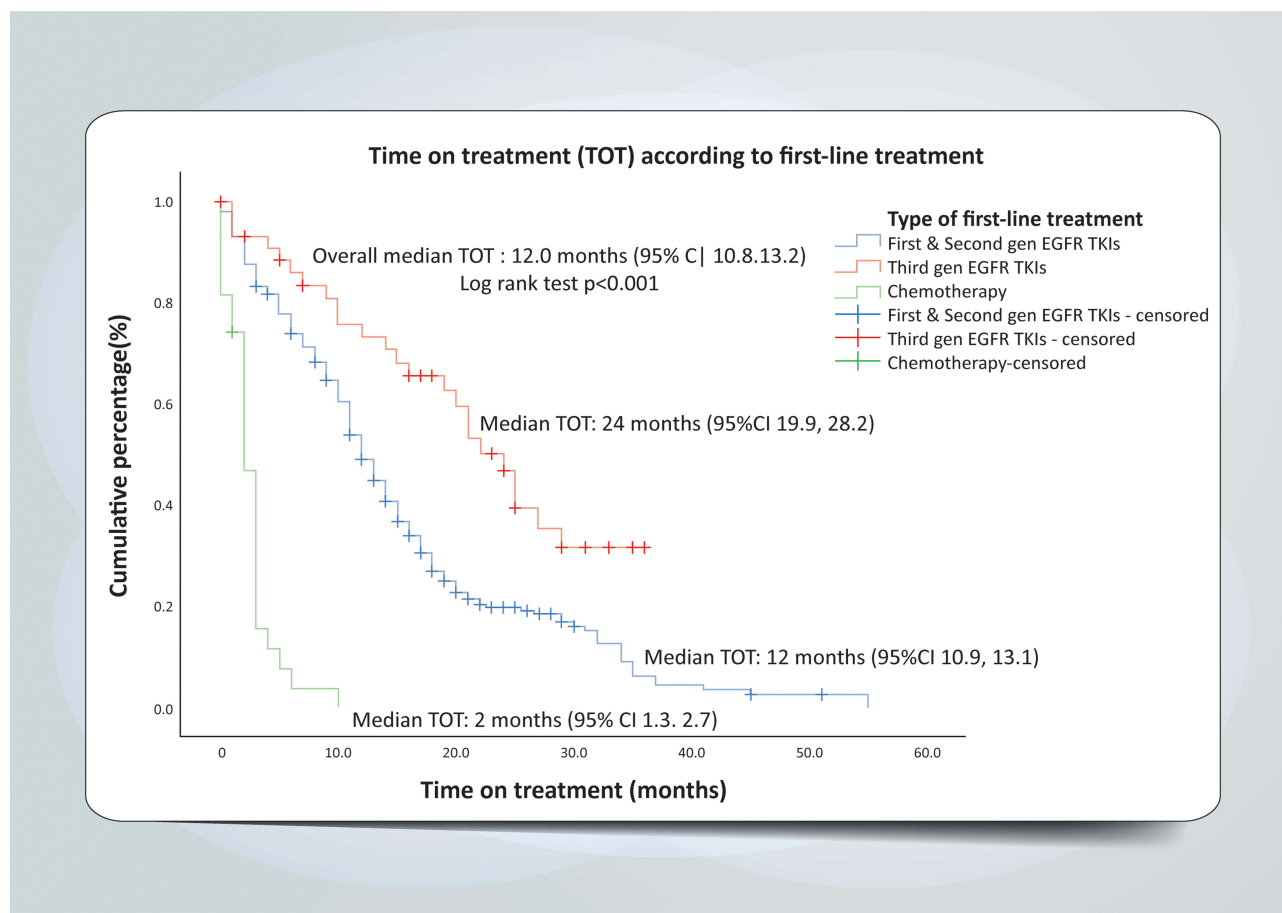


Figure 2 Time on treatment (TOT) according to first-line treatment excluding patients lost to follow-up (N=279).

Discussion

This multicenter registry-based, retrospective study aimed to highlight the treatment patterns of *EGFR*m+ advanced stage NSCLC patients in a real-world, resource-limited setting. Like other local and international studies,⁴⁻⁶ we found a higher proportion of female patients and those who never smoked with *EGFR*m+ NSCLC.

Though Malaysia is categorized as a developing country, most of our patients (92.3%) were treated with EGFR TKI compared to chemotherapy as the standard of care in the first-line setting.^{15,21} This is comparable to Singapore where 90.6% of *EGFR*m+ NSCLC patients received EGFR TKI monotherapy (88.6%) or in combination with chemotherapy (3.6%),²² and Taiwan where 95.7% of patients received EGFR TKI monotherapy.²³ Even though the third-generation EGFR TKI, osimertinib has shown superior treatment outcomes compared to first-generation EGFR TKI,²⁴ the proportion of our patients on first-line osimertinib was only 12.5%. First- and second-generation EGFR TKIs are reimbursed by the government, whereas the third-generation is self-funded. This is the most likely explanation for the preference of first- and second-generation EGFR TKIs in the first-line treatment setting and also explains the small uptake of patients treated with first-line third-generation TKI, namely osimertinib.

The median TOT for our patients treated with first-line first- or second-generation EGFR TKIs was comparable with that of other real-world studies showing a median TOT ranging from 12.1 to 17.9 months but falling at the lower end of this range.^{14,25,26} This could partly be due to 15.7% of our patient having poor ECOG performance status of 3 or 4. Interestingly, the median TOT in patients with poor ECOG performance status who were included in the study was 11.0 months. This suggests that patients with advanced *EGFR*m+ NSCLC despite having poor ECOG performance status, do derive OS benefits when treated with EGFR TKIs as previously reported.^{27,28}

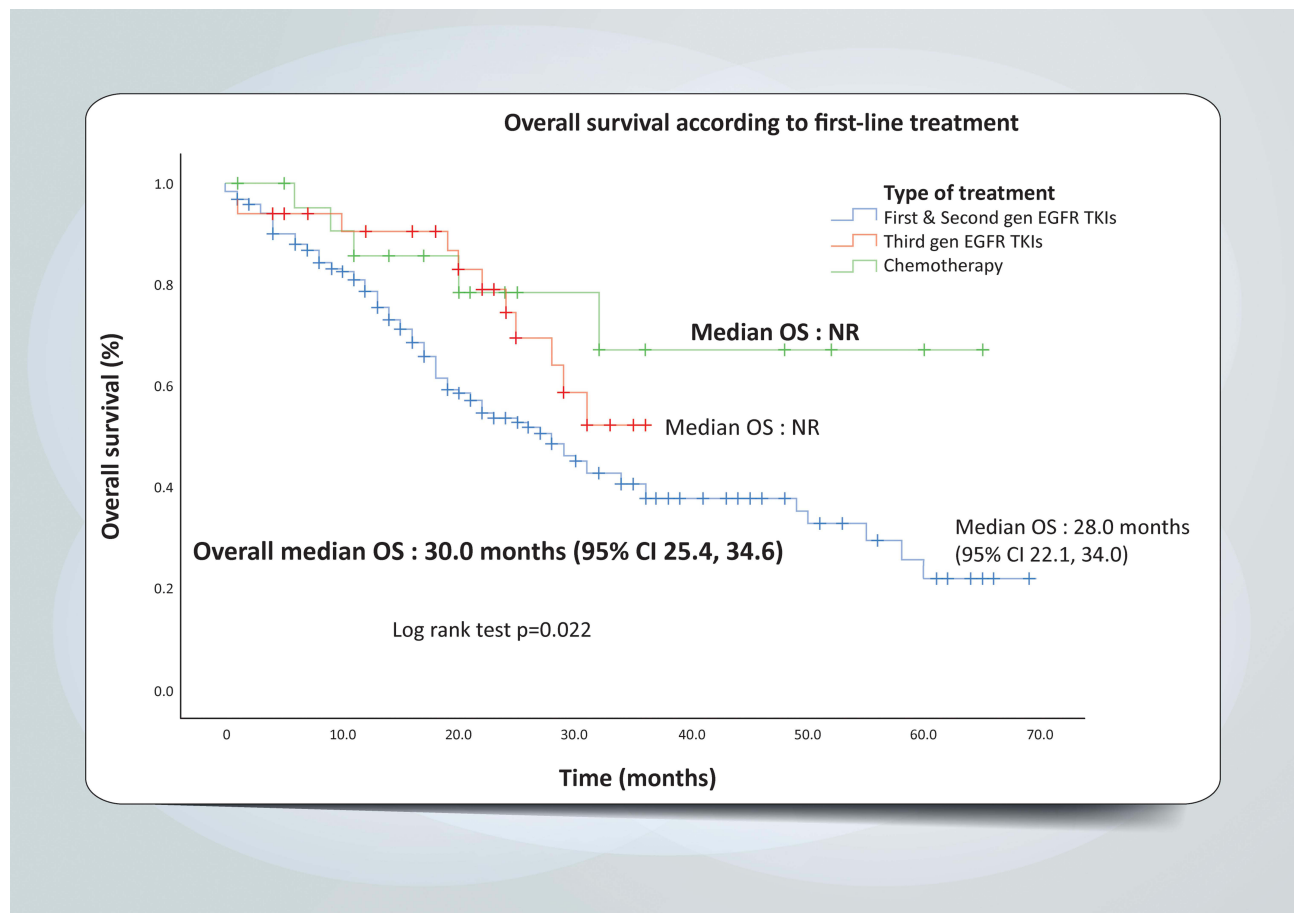


Figure 3 Overall survival (OS) according to first-line treatment excluding patients lost to follow-up (N=250).

Only about 30.0% of our patients treated with first-line EGFR TKI who had PD underwent further genetic testing for acquired T790M mutation. One possible explanation for this low percentage is that while this registry was started in 2015, second-line osimertinib was only approved in Malaysia in May 2017. Although there was an expanded early access program for second-line osimertinib from 2016 to early 2017, the scope for access was not universal. The second reason is the high cost of second-line osimertinib treatment, which has to be self-funded for most patients. Nevertheless, our data revealed that those who had genetic testing to detect acquired T790M mutation were more likely to receive second-line osimertinib. The type of testing performed was mostly liquid biopsy. Although liquid biopsy is less sensitive and cannot detect small cell transformation, and there is a strong recommendation for tissue biopsy,²⁹ patients and treating physicians seemed to prefer liquid biopsy. Physicians prefer liquid biopsy as it is less invasive, costs less and is easier to organize especially in a busy hospital setting. In the real-world FLATIRON study conducted in the US, the frequency of testing for T790M+ was only 39.4% after failure of first-line EGFR TKI therapy.³⁰ A real-world study looking at T790M+ testing in advanced NSCLC patients in Japan²⁹ revealed a much higher rate of 86.9% (of 236 patients) with the majority (58.1%) tested using liquid biopsy. Regardless, the positive rate for T790M+ in the patients treated with first- and second-generation EGFR TKI in our study is similar to that reported by other studies.^{13,15–17} Patients who fail first- and second-line osimertinib should ideally undergo tissue rebiopsy to detect targetable resistance molecular alterations such as *MET* amplification^{13,15,16} but only 12.5% of our patients who failed first-line osimertinib underwent a tissue rebiopsy. This can be attributed to the non-availability of next-generation sequencing testing during the study period, as well as its high cost (~USD 2500 per test), and the lack of molecular targeted treatment either commercially or in clinical trials post-osimertinib.

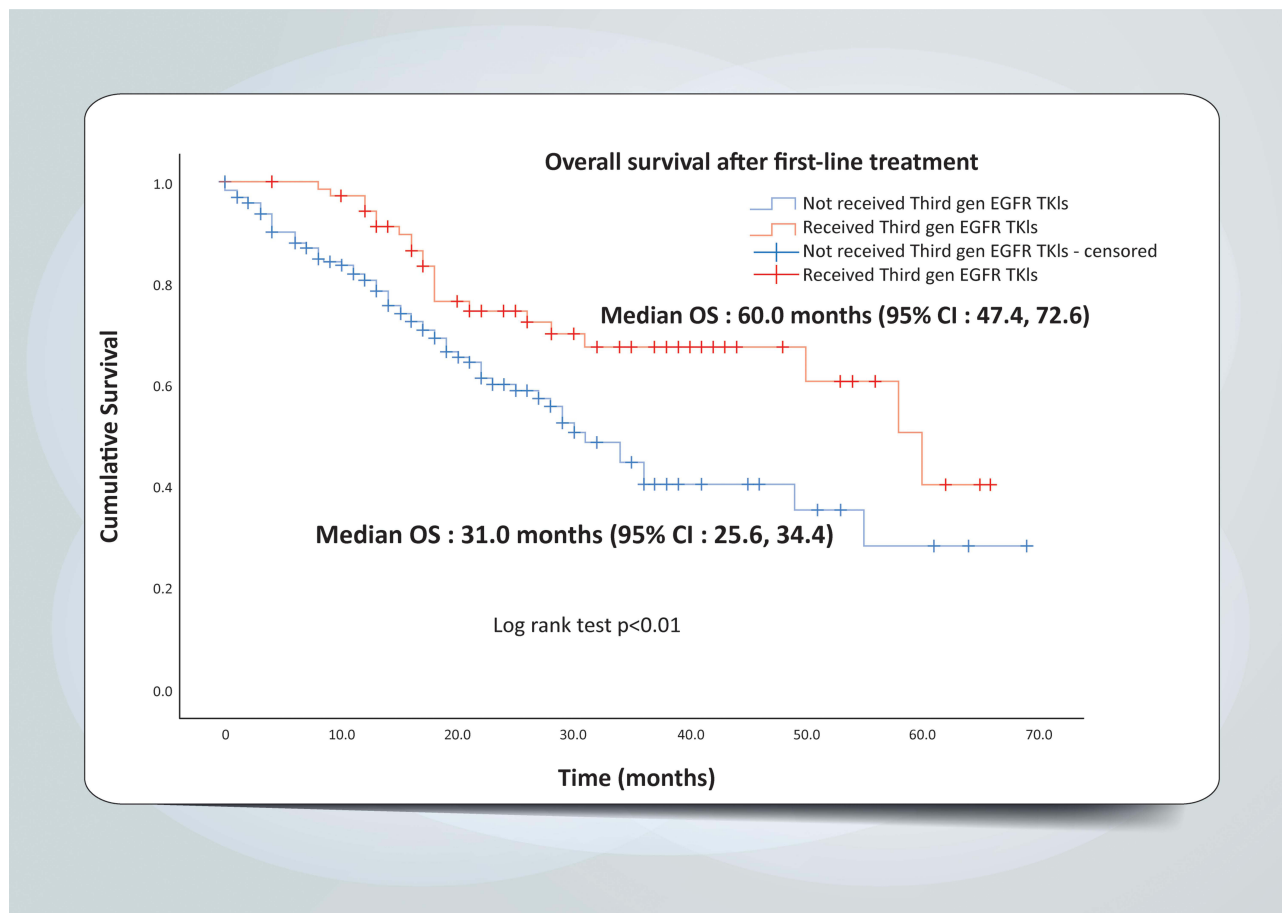


Figure 4 Overall survival (OS) after first-line first- and second-generation EGFR TKIs with and without third-generation EGFR-TKI.

Less than 50.0% of our patients received osimertinib as second-line treatment. This percentage is low compared to other countries where the rate is 73.0–95.7%.^{29–31} The reason for the low uptake is mainly the cost of osimertinib in Malaysia. Approximately 20.0% of our patients who progressed on first-line first- or second-generation EGFR TKI were switched to a different first- or second-generation EGFR TKI with or without chemotherapy. This was a common practice before the availability of osimertinib in Malaysia and still is despite its availability because of its high cost. In clinical practice, first- and second-generation EGFR TKIs are often used beyond PD in patients who have asymptomatic progression and have been shown to prolong OS compared to switching to chemotherapy.¹⁵ The National

Table 2 Second-Line Treatment in Patients Who Progressed After First-Line Treatment

| First-Line Treatment | N | PD | Genetic Testing** | Second-Line Treatment | | | | |
|-------------------------------------|-----|-----|-------------------|-----------------------|-----|----------------------------|---------------------|--------|
| | | | | Yes | CTX | EGFR TKI | | Others |
| | | | | | | 1st or 2nd Generation ±CTX | 3rd Generation ±CTX | |
| CTX* | 27 | 26 | 0 | 22 | 2 | 19 | 1 | 0 |
| 1st or 2nd generation EGFR TKI ±CTX | 280 | 229 | 83 | 138 | 45 | 34 | 57 | 2 |
| 3rd generation EGFR TKI±CTX | 44 | 24 | 3 | 14 | 6 | 4 | 1 | 3 |
| Total | 351 | 279 | 86 | 174 | 53 | 57 | 59 | 5 |

Note: *CTX alone; **Number of patients with no genetic testing in each category of first-line treatment regime= number of patients with PD minus number of patients with genetic testing.

Comprehensive Cancer Network also recommends continuing first- and second-generation EGFR TKIs in combination with local therapy in patients with asymptomatic or minimally symptomatic progression.³²

The median OS in our cohort of patients was 30.0 months, which is comparable to the Japanese real-world study (median OS 29.7 months, 95% CI 28.1–31.4).²⁶ The median OS for patients treated with both first-line third-generation EGFR TKI and first-line chemotherapy had not been reached at the time of analysis. The OS benefit among the patients who received first-line chemotherapy who did as well as osimertinib was interesting. However, this apparent good outcome of those on first-line chemotherapy is most likely because more than 90.0% of these patients were switched to second-line EGFR TKI therapy upon progression of disease. Additionally, the proportion of patients on first-line chemotherapy was proportionally smaller than those who received first- or second-line EGFR TKI (27 vs 280). The shorter median OS of patients on first-line first- or second-generation EGFR TKI is most likely due to only 60.2% of them going on to receive second-line treatment. Hence, we cannot conclude that chemotherapy as first-line therapy is better than the EGFR TKIs. It also suggests that subsequent lines of therapy, whether it is with targeted therapies, chemotherapy or immune checkpoint inhibitor combinations, are vital for prolonging OS in these patients.

Two separate phase III randomized trials of the same design conducted in Japan³³ and India³⁴ illustrate the importance of access to a subsequent line of treatment in prolonging the OS. The objective of the Japanese NEJ009 study and the Indian study was to compare the efficacies of gefitinib versus gefitinib plus chemotherapy in patients with *EGFRm+* advanced NSCLC. The median OS in both studies were drastically different. The median OS of the gefitinib arm was 38.8 months in the Japanese study compared to only 17.0 months in the Indian study. This is because more patients (23.3%) in the Japanese study received osimertinib on PD compared to only 11.0% in the Indian study. We postulate that the difference in the OS between the Japanese and Indian studies was likely due to a difference in access to second-line osimertinib determined by its cost and reimbursement in the two countries.

The limitation of our study is that it is retrospective, which is true for most real-world studies. Although the Malaysian Lung Cancer Registry has an active participation from many centers across Malaysia, it is limited by incomplete eCRFs and a high loss to follow-up rate. These deficiencies could be attributed to the time constraints of the busy participating clinicians and the lack of dedicated human resources to monitor the patients' follow-up appointment.

Conclusion

Overall accessibility to first-line EGFR TKI is high but limited to first- or second-generation TKI. Patients who received chemotherapy as first-line therapy may have a good OS if they receive targeted therapy subsequently. The percentage of patients undergoing genetic testing following progression on first-line EGFR TKI remains modest. Liquid biopsy is a preferred option among treating physicians. The lack of accessibility to effective but costly newer treatments in the first- and second-line settings can adversely affect survival.

Our study suggests that in the real-world, the management of *EGFRm+* advanced NSCLC patients in an Asian cost-restrictive setting can adversely affect the choice of first-line therapy, time on each line of treatment and subsequently overall survival of the patient.

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