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Pre-treatment Neutrophil-to-Lymphocyte Ratio significantly affects progression free survival in positive EGFR mutation advanced lung adenocarcinoma with EGFR-TKI treatment in Bali, Indonesia

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Introduction: Today, recommendations about initial Response Evaluation Criteria in Solid Tumor (RECIST) and its frequency still vary, while early diagnosis of progression affects patient's prognosis and subsequent treatment options.

Methods: This study aims to examine Progression Free Survival (PFS) of positive EGFR mutations advanced lung adenocarcinoma receiving Tyrosine Kinase Inhibitor (TKI) and factors that influence it. This was an observational study with retrospective cohort design conducted at Prof IGNG Ngoerah Hospital from January to December 2021. Sample was data from Epidermal Growth Factor Receptor (EGFR) positive mutation advanced lung adenocarcinoma patient who were treated with EGFR-TKI at Prof IGNG Ngoerah Hospital, Denpasar, Bali from January 2017 to February 2021. Total sample was 63.

Results: Median PFS was 12 months (95% CI 10.28–13.71) and minimum PFS was 3 months. In univariate analysis, Hazard Ration (HR) of older age, smoker, distant metastasis, brain metastasis, increased Neutrophil-to-Lymphocyte Ration (NLR), and exon 21 mutation to shorter PFS was 0.99 (95% CI 0.95–1.02); 1.03 (95% CI 0.57–1.85); 1.45 (95% CI 0.85–2.49); 2.14 (95% CI 1.02–4.49); 1.08 (95% CI 1.03–1.13); and 1.21 (95% CI 0.67–2.18). Multivariate analysis showed only increased NLR affected PFS significantly with HR 1.06 (95% CI 1.007–1.13).

Conclusion: Median PFS of EGFR positive mutation advanced lung adenocarcinoma patients who received TKI was 12 months and minimum value was 3 months. Increased age, smoking, distant metastases, brain metastases, and exon 21 mutations were not associated with PFS. NLR significantly affected PFS.

Key words: adenocarcinoma, EGFR, Neutrophil-to-Lymphocyte Ratio, Tyrosine Kinase Inhibitor, Progression Free Survival.

INTRODUCTION

In the last decade, there has been significant increase in the findings of lung adenocarcinoma cases in the world [1]. Adenocarcinoma was found at 38.5% of all lung cancer patients [2]. TKI is first-line therapy in adenocarcinoma with EGFR mutation [3]. It provides good effectiveness, but also has high risk of developing resistance to cause disease progression. Resistance occurs by EGFR T790M mutation, MET amplification, transformation to SCLC, or PIK3CA mutation [4]. RECIST is a method used to evaluate therapy respond in solid tumors [5]. This is related to the progression that occurs especially in adenocarcinoma patients treated with EGFR-TKI as dominant asymptomatic [6, 7]. Therefore, RECIST is very important to be performed routinely to detect the progression of adenocarcinoma.

Recommendations about initial RECIST and its frequency are still variable. These are related to the finding of PFS variations according to certain areas or regions. PFS of NSCLC with EGFR mutation treated by TKI in the American population was 10.4 months, Portuguese population was 12 months, and in the Colombian population was 9.8 months [8]. A study by Barron *et al*. in Latin American populations (Mexico, Costa Rica, and Colombia) with EGFR positive mutation advanced lung adenocarcinoma with EGFR-TKI had a median PFS of 8.8 months (95% CI 7.9–9.7) [7]. Korean study conducted by Kim *et al*. on stage IIIB and IV NSCLC patients who received EGFR-TKI therapy had a median PFS 2.1 months [9].

Some studies also stated that PFS was influenced by several clinical and laboratory factors, such as age, smoking status, distant metastases, as well as laboratory components such as NLR, and the type of EGFR mutation [4]. In Indonesia, especially

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in Bali, there have been no studies that describe PFS in EGFR mutation positive lung adenocarcinomas who received TKI. This study aims to know PFS of patients with EGFR mutation positive advanced stage lung adenocarcinoma receiving TKI therapy and factors that influence it. In the future, it is hoped that the results of this study can be used when evaluating treatment by RECIST in EGFR mutation positive lung adenocarcinoma patients who were treated with TKI, information on treatment plans, and prognosis.

MATERIALS AND METHODS

Research design

This was an observational analytic study using a retrospective cohort. Study was conducted at Prof IGNG Ngoerah General Hospital, Denpasar, Bali from March to December 2021. Data were taken from medical records of outpatients and inpatients who were treated from January 2017 to February 2021. This study has been approved by Faculty of Medicine, Udayana University Ethics division with ethical approval number 2558/UN14.2.2.VII.14/LT/2021. Informed consent was not obtained because we used secondary data. We used 63 patient data who diagnosed advanced stage EGFR-positive lung adenocarcinoma and treated with EGFR-TKI at Prof IGNG Ngoerah Hospital, Denpasar, Bali, from January 2017 to February 2021. Patients who had other malignancy, history of chemotherapy before EGFR-TKI treatment, died before progression, and had not progressed until end of research observation were excluded from this research.

Advanced stage lung adenocarcinoma is the mean stage IIIB and IV according to the 8th edition of International Association for the Study of Lung Cancer (IASLC). PFS was length of time between the first time the patient received TKI and the occurrence of progressive disease (PD) as obtained from the information in medical records. Lung adenocarcinoma diagnosis was based on pathology anatomy results. We obtained smoking status from medical records. We only differentiated smoker and non-smoker without other quantification of smoking habit. Information about extra thorax metastasis was based on medical record information before patient got TKI. The value of NLR was obtained from the results of routine complete blood tests at the beginning of the patient receiving TKI therapy. We differentiate type of EGFR mutation between EGFR mutation exon 19 and 21 based on molecular test results in medical records. We also searched for information about patient symptom while progress is based on medical record and we differentiate it to symptomatic and asymptomatic as one of the demography characteristic. Symptomatic patient was patient who had worsening or new respiratory symptom (cough, dyspnea, chest pain, hemoptoe) and non-respiratory symptom (pain caused by metastatic process in bone, liver, and others organ) while progress was diagnosed by RECIST. All subjects were on EGFR-TKI 1st generation (Gefitinib or Erlotinib).

Data analysis

Data analysis was performed by statistical software SPSS 17.0. Descriptive statistical analysis was performed to find characteristics of the research sample (age, gender, ethnic, smoking status, distant metastasis, brain metastasis, performance status, NLR pre-treatment, EGFR mutation, and symptom presentation while progress). Progression Free Survival was analyzed by Kaplan Meier. Independent variables were age, smoking status, distant metastasis, brain metastasis, NLR pre-treatment, and EGFR mutation. Dependent variable was PFS. Confounding variables were gender, and performance status. We performed log rank test for bivariate analysis of nominal scale independent variables (smoking status, distant metastases, brain metastases, and type of EGFR mutation). Simple Cox regression analysis was performed to determine HR of each independent variable. Time independent Cox regression model analysis was done for multivariate analysis. Level of significance was <0.05 with 95% confidence interval.

RESULTS

Demographic characteristics and symptoms of progressive patients

Demographic characteristics of subjects can be seen in Table 1.

PFS patients with advanced stage EGFR positive mutation advanced lung adenocarcinoma treated with TKI therapy and factors affecting it

Median PFS of patients advanced stage EGFR positive mutation advanced lung adenocarcinoma with TKI was 12 months (95% CI 10.28–13.71), with minimum value three months and maximum value 35 months. Survival function can be seen in Figure 1.

Survival function and median PFS based on smoking status, distant metastasis, brain metastasis, and EGFR mutation can be seen in Figure 2 and Table 2.

Hazard Ratio (HR) for age, smoking status, distant metastasis, brain metastasis, NLR, and type of EGFR mutations can be seen in Table 3.

Table 1
Demography characteristics

Characteristic	N (%)	Mean	Median (±SD)	Minimal	Maximal
Age (years old)		**56.84**	**57.00±8.158**	**36**	**75**
Gender					
• Male	27 (42.9%)				
Ethnic					
• Bali	57 (90.5%)				
Smoking status					
• Smoker	15 (23.8%)				
EGFR mutation					
• 19	47 (74.6%)				
• 21	16 (25.4%)				
Distant metastasis					
• Yes	12 (19%)				
Brain metastasis					
• Yes	12 (19%)				
NLR		**5.20**	**12.00±5.23**	**3**	**35**
Status Performance					
• 0–1	**37 (58.7%)**				
• 2–4	**26 (41.3%)**				
Symptom					
• Symptomatic	30 (47.6%)				
• Asymptomatic	33 (52.4%)				

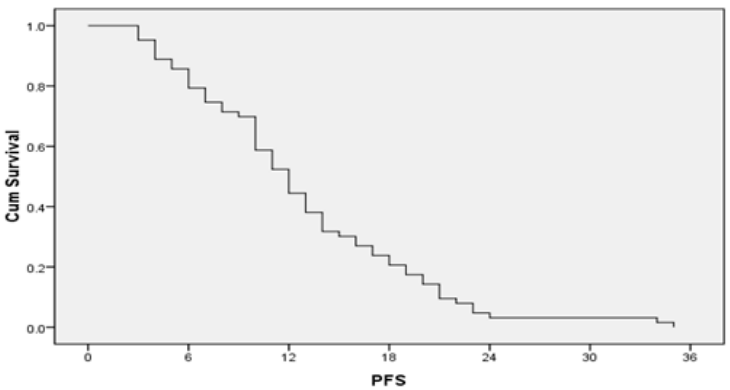

Fig. 1. *Survival Function* of PFS.

Table 2
Median PFS based on smoking status, distant metastasis, brain metastasis

Variable	Median PFS (95% CI)	P
Smoking status		
• Smoker	11.00 (9.10–12.89)	0.916
• Non Smoker	12.00 (9.73–14.26)	
Distant metastasis		
• Yes	10.00 (5.73–14.26)	0.914
• No	12.00 (10.44–13.55)	
Brain metastasis		
• Yes	10.00 (6.65–13.34)	0.011
• No	13.00 (11.26–14.73)	
EGFR mutation		
• Exon 19	12.00 (9.76–14.23)	0.499
• Exon 21	12.00 (10.18–13.81)	

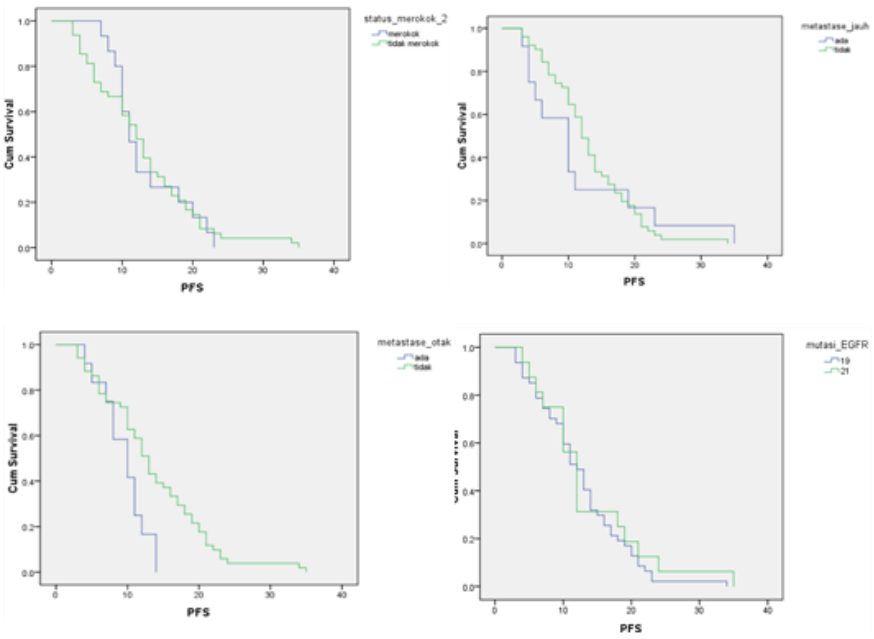

Fig. 2 PFS Based on a) smoking status (p = 0.916), b) distant metastasis (p = 0.914), c) brain metastasis (p = 0.011), d) EGFR mutation (p = 0.499).

Table 3
Bivariate and multivariate analysis of hazard ratio

Variable	Bivariate		Multivariate	
	HR (95% CI)	**P**	**HR (95% CI)**	**P**
Age	**0.99 (0.95–1.02)**	**0.57**		
Smoking status	**1.03 (0.57–1.85)**	**0.92**		
Smoker vs Non-smoker				
Distant metastasis	**1.03 (0.53–2.01)**	**0.91**		
Yes vs No				
Brain metastasis	**2.26 (1.15–4.46)**	**0.01**	**1.51 (0.66–3.43)**	**0.32**
Yes vs No				
NLR	**1.08 (1.03–1.13)**	**0.00**	**1.06 (1.005–1.124)**	**0.03**
EGFR mutation	**1.21 (0.67–2.18)**	**0.52**		
21 vs 19				
Gender*	**1.15 (0.69–1.91)**	**0.58**		
Male vs Female				
Performance score*	**0.68 (0.40–1.14)**	**0.14**	**0.83 (0.47–1.45)**	**0.51**
0–1 vs 2–4				

*Confounding variable

DISCUSSION

Various studies on survival and characteristics of patients with adenocarcinoma have been conducted. Most of these studies have similar characteristics with this research [6, 10]. Median PFS in this study was 12 months (95% CI 10.28–13.71) with minimum PFS three months. A study by Douillard *et al*. in Europe had shorter median PFS, 9.7 months (95% CI 8.5–11 months). Racial differences were probably one of the causes of differences. Histological types used in this study were not only adenocarcinoma, but also 1.9% adenosquamous carcinoma, 0.9% large cell carcinoma, and 0.9% other histology. Other EGFR mutations also included in the study were L861Q (1.9%) and G719X (G719S/A/C) (1.9%) mutations [11]. Another study conducted in Japan by Igawa *et al*. resulted in shorter PFS, 9 months (95% CI 6.7–11.3 months). Shorter PFS

was possibly caused by the histological type of the subject which is not only adenocarcinoma, but there were 0.7% squamous cell carcinoma, 0.7% pleomorphic carcinoma, and 1.4% of patients were not specific [10]. Study by Rotella *et al*. in Italy had a median PFS similar to this study, 11.4 months [12]. A study by Yu *et al*. in China had similar PFS; median PFS was 12.5 months (95% CI 11.2–13.7 months) [13].

This study found that subjects who experienced progressivity were dominant asymptomatic (52.4%). This was similar to results of several previous studies [6, 7]. Therefore, regular and ongoing evaluation through the RECIST method is needed to see the progress of the disease, especially patients with advanced lung adenocarcinoma who are receiving EGFR-TKI therapy.

It was found that increasing age did not significantly affect the risk of rapid progression with HR 0.99 (95% CI 0.95–1.02, p = 0.56). Other studies have various results. A study by Ouyang *et al.* showed that age was not associated with risk of T790M mutation with HR 0.994 (95% CI 0.971–1.017, p=0.587). T790M mutation was one of the most common mechanisms of progression of EGFR-positive adenocarcinoma patients receiving TKI therapy [14]. Research conducted by Wheatley-Price *et al*. in Canada showed similar results, that age did not affect risk of progression with HR 0.91 (95% CI 0.73–1.13) [15]. Research by Rozensztajn *et al*. in Paris showed that age affects PFS of patients. Older age had lower risk of progression by 4% with an OR of 0.96 (95% CI 0.93–0.98, p = 0.005) [16]. Another study by Tsai *et al*. in Taiwan had different results from this study. Older age was defined as subjects who were 65 years old. PFS of older patients was significantly longer (10.5 months versus 5.5 months, p = 0.0320) compared to younger age [17].

This study found that median PFS of lung adenocarcinoma patients who did not smoke was longer than smokers, namely 12 months (95% CI 9.73–14.26) compared to 11 months (95% CI 9.10–12.89). Patients in the smoker group also had HR 1.03 (0.57–1.85) for progression but not significant statistically. A study by Igawa *et al*. in Japan found the median PFS of NSCLC patients who had never smoked was longer than smokers (10.7 months vs 5.4 months, p=0.0002). In this study, it was also found that therapeutic response was better in group of subjects who did not smoke (72.3% vs 55.8%, p = 0.04). Difference in statistical significance could be due to number of subjects and different definitions of smoker and non-smoker. Definition of non-smoker was patient who smokes <100 cigarettes throughout his life, or has stopped smoking for 15 years with a total pack-per year 10 while in this study definition history of smoker or not was only based on patient information in medical records [17].

This was related to smoking degree that can affect PFS, as evidenced by Zhang *et al*.'s retrospective cohort study in China. The study showed no difference in PFS between the non-smokers (median, 10.5 months) and light smokers (median, 11 months), but PFS was significantly longer in the non-smoker than heavy smoker group (median, 10.7 months vs 6 months, p<0.001). The study also found that heavy smoking (smoking 30 packs/year) was associated with shorter PFS (HR = 2.48, 95% CI 1.55–3.98, p<0.001) [18]. A meta-analysis of prospective randomized control trials by Hasegawa *et al.* in 2015 also showed a better benefit of EGFR TKI (as seen from PFS) in lung adenocarcinoma patients who had never smoked (HR 0.29 (95% CI 0.21–0.39) compared to smoker (0.54; 95% CI 0.38–0.76) [19].

This study found that median PFS of patients without distant metastasis before treatment was longer than patients with distant metastases (12 months vs 10 months). Based on the literature review, pathogenesis of distant metastases in patients with EGFR-positive adenocarcinoma mutations receiving EGFR TKI therapy can affect incidence of progression [20].

A retrospective study conducted by Taniguchi *et al*. in Japan showed bone metastasis associated with worse PFS with HR 2.11 (95% CI 1.44–3.09, p<0.001). Comparison of PFS of bone metastasis group and without bone metastasis before treatment was 8.8 months vs 15.4 months. Patients with liver metastasis also had shorter PFS (6.7 months vs 12.5 months) [18]. Differences in statistical significance can be caused by differences in the number of subjects in each group. In that study, comparison group was extra thoracic metastases in general, while, in this study, the comparison was used according to the presence or absence of metastases in each organ (bone, liver, and brain). In addition, other refractive factors such as ethnicity and median older age in the study may affect the results of the study. Routine screening for metastasis was not performed at the start of treatment in the patients in this study. Thus, it was possible for the patient to have extra thoracic metastasis at initial therapy but was not known.

In this study, there was a difference in PFS between the group of patients who did not have brain metastasis and those who had brain metastasis (13 months vs 10 months) with HR 2.26 (1.15–4.46), p = 0.01, but was not significant in multivariate analysis. A retrospective study conducted by Taniguchi *et al*. in Japan showed that group with brain metastases at time of diagnosis had significantly worse PFS than those without (8 months vs 13.2 months) [18]. A study by Hsu *et al*. conducted in the UK found that brain, liver, and bone metastases were associated with a poor prognosis in patients with positive EGFR mutations KPKBSK with HR of 1.73; 1.69; and 1.89 [21]. Differences in statistical significance in this study can be caused by differences in demographic characteristics, like ethnicity and extent of metastases. Routine screening for metastases was not performed at initiation of treatment in this study. Thus, it was possible for patient to have brain metastases at the start of therapy but unknown.

Pre-therapy NLR was one of the biomarkers thought to affect risk of progression in malignant patients. This study proves that there was a relationship between the NLR pre-therapy and incidence of

progression. In bivariate analysis, it was found that higher NLR increased the risk of short PFS by 8% (HR 1.08, 95% CI 1.03–1.13; p=0.00), a significant result was also obtained in multivariate analysis (HR 1, 06, 95% CI 1.005–1.124; p = 0.03).

Research by Xu *et al*. showed similar results. Study used cut-off NLR 2.57. Patients with higher NLR (≥ 2.57) showed significantly shorter PFS (8.8 versus 12.2 months, p<0.01) and reduced Disease Control Rate (DCR) at 8 and 10 months after therapy (62.5% vs 93.3%, p=0.014; 38.5% vs 77.8%, p=0.037) [22]. A meta-analysis study also obtained similar results; lower NLR predicts better PFS survival in NSCLC patients treated with EGFR-TKI. This meta-analysis used 10 studies with different NLR cut-offs. Patients with low NLR had better PFS (HR 1.67, 95% CI 1.16–2.39, p=0.005) [23]. A study by Phan *et al*. in Vietnam also demonstrated NLR as a prognostic factor for poor PFS. The study used an NLR cut-off of 2.96. In bivariate analysis, patients with high pretreatment NLR (≥ 2.96) were associated with a shorter PFS (HR = 2.67, 95% CI 1.41–5.03, p = 0.006) [24].

An increase in NLR can occur due to an increase of neutrophils or decrease of lymphocytes. Neutrophil protumor activity was influenced by two main components, TAN and serine proteases. TAN helps tumors progress through several pathways. TAN can secrete MMP-9 which releases VEGF from the ECM to promote angiogenesis. TAN can secrete cytokines (IL-1β, TNF-, IL-6, and IL-12) that induce a chronic inflammatory state and arginase 1, which inhibits CD8 T cells, and creates an immunosuppressive state. TAN also produces ROS, which can damage DNA, thereby inducing genotoxic effects on tumor cells. Serine proteases have a direct effect on tumor cells by inducing proliferation. Some tumors can induce neutrophils to produce Oncostatin, which is an IL-6-like cytokine that stimulates cancer cells to secrete VEGF to promote angiogenesis [25]. Decreased lymphocyte values are associated with decreased ability to eradicate tumors. TILs are components of TME that regulate the inflammatory response and have an important role in the eradication of tumor cells [23, 24].

This study showed that there was no difference in PFS in the exon 19 mutation group and the exon 21 mutation group (12.00 (9.76–14.23) versus 12.00 (10.18–13.81), p = 0.499). Studies' results regarding relationship between types of EGFR mutations and progression of lung adenocarcinoma are still inconclusive. Research by Won *et al*. obtained different results. In that study, PFS of NSCLC patients with exon 19 mutations was significantly longer than patients with exon 21 mutations (9.3 months vs 6.9 months, p=0.02). Exon 21 mutations were predictors of short PFS with HR in multivariate analysis was 1.91 (1.10–3.29) p = 0.021 [26]. A study by Jiang et al. found that patients with exon 19 deletions had a better response rate (75.7% versus 51.4%, p=0.032), better disease control rate (89.2% versus 68.6%, p= 0.031), and a longer PFS of 13.2 months versus 10.8 months, p = 0.30) [27]. The difference in results could be due to differences in the subjects' characteristics, such as 50% more of the study subjects had undergone sequential chemotherapy and/or sequential surgery.

A study conducted by Matsuo *et al*. found that T790M mutation was more common in patients with exon 19 EGFR deletion mutations (63%) compared to exon 21 L858R mutations (38%) with p = 0.035. EGFR T790M mutation is associated with acquired resistance in patients [28]. The insignificant difference in PFS in the types of EGFR mutations could also be caused by multiple mutations occurring in the patients. A case report by Riza and Maranatha presents a case of lung adenocarcinoma with three different mutations, exons 18 (G719S), 20 (T790M), and 21 (L858R). The occurrence of these three mutations causes decrease of TKI effectiveness and poses a high risk of progression [28]. This was associated with lung adenocarcinoma which is a histological type that has highest EGFR mutation rate and each cell has a natural trait to continue growing and develop into a new drug-resistant type.

This is the first study to describe PFS of patients with advanced stage EGFR-positive mutation lung adenocarcinoma who received EGFR TKI in Bali. In the future, it is hoped that the data can become a reference for clinical management, help provide information about prognosis and other research bases.

There are several limitations in the implementation of this research. First, this study used secondary data, thus there was some information that cannot be well-documented, such as information on smoking status. Second, the research sample only came from one center, thus it cannot provide an overview of similar events in the general population. Third, the absence of evaluation of metastases prior to treatment in patients with lung adenocarcinoma who have asymptomatic metastases can be a bias in this study.

CONCLUSION

Median PFS of patients with advanced stage EGFR-positive mutation lung adenocarcinoma who received TKI therapy was 12 months with a minimum PFS of 3 months. Age, smoking status, distant metastases, brain metastases, and type of mutation had no significant association with PFS. NLR pre-treatment value significantly affected PFS. Patients who progressed were dominantly asymptomatic.

Introducere: *Astăzi recomandările despre răspunsul inițial terapeutic din tumorile solide (RECIST) variază, aceasta în condițiile în care diagnosticul precoce afectează prognosticul și opțiunile terapeutice.*

Metode: *Studiul își propune să evalueze PFS (supraviețuirea fără progresie) la pacienții cu adenocarcinom pulmonar cu mutații EGFR pozitiv, aflați sub tratament cu inhibitori de tirozin kinază (TKI). A fost realizat un studiu observațional de cohortă în spitalul Prof IGNG Ngoerah desfășurat în perioada ianuarie–decembrie 2021. Pacienții au provenit din cohorta pacienților tratați cu EGFR-TKI din spitalul Prof IGNG Ngoerah, Denpasar, Bali (ianuarie 2017–februarie 2021). Au fost incluși în studiu 63 de pacienți.*

Rezultate: *PFS mediană a fost de 12 luni (95% CI 10.28–13.71) cu valoarea minimă 3 luni. În analiza univariată vârsta înaintată, fumatul, metastazele la distanță și cele cerebrale, NLR crescut și mutațiile exonului 21 s-au asociat cu o durată mai scurtă a PFS (HR=0,99 (95% CI 0,95–1,02); 1,03 (95% CI 0,57–1,85); 1,45 (95% CI 0,85–2,49); 2,14 (95% CI 1,02–4,49); 1,08 (95% CI 1,03–1,13); respectiv 1,21 (95% CI 0,67–2,18)). Analiza multivariată a arătat numai NLR asociat independent cu PFS HR=1,06 (95% CI 1,007–1.13).*

Concluzii: *Valoarea mediană a PFS la acești pacienți a fost de 12 luni. NLR s-a asociat independent cu PFS.*

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Conflict of interest disclosure: The author declares that there were no conflicts of interest in this study.

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