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RESEARCH ARTICLE

Osimertinib as a Potential Targeted Therapy for Non-Small Cell Lung Carcinoma (NSCLC) Patients with EGFR Exon 20 T790M

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Abstract

BACKGROUND: Emergence of drug resistance due to epidermal growth factor receptor (EGFR) Exon 20 T790M poses a challenge in the effective management of non-small cell lung carcinoma (NSCLC). Significant breakthrough in the management of NSCLC with a specific genetic alteration causes substantial condition improvement in patients whose cancer progressed after first-generation tyrosine kinase inhibitor treatment and who developed tumors with EGFR Exon 20 T790M mutation. The present study analyzed a cohort of NSCLC patients and investigated the incidence of the EGFR Exon 20 T790M status with Osimertinib therapy, along with its impact on survival rates.

METHODS: This was a retrospective cohort study on 22 NSCLC subjects who were genetically examined for EGFR status from plasmic cell free total nucleic acid. Subjects with EGFR Exon 20 T790M mutation were treated with/without Osimertinib. Demographic and clinical data were descriptively summarized, and the differences of each

variable and correlation between survival rate and EGFR Exon 20 T790M were analyzed.

RESULTS: Subjects with (n=13) and without (n=9) EGFR Exon 20 T790M had survival rates of 10.77 ± 2.45 and 4.78 ± 1.48 , respectively ($p=0.000$). Based on 1-year survival status of subjects with EGFR Exon 20 T790M, there were 3 Osimertinib-treated survivors and 2 Osimertinib-treated non-survivors. Eight subjects with EGFR Exon 20 T790M and without Osimertinib treatment did not survive ($p=0.001$).

CONCLUSION: Since the treatment of Osimertinib demonstrated a noteworthy survival rate among NSCLC subjects with EGFR Exon 20 T790M, thus Osimertinib could be suggested as a potential targeted therapy for NSCLC subjects with EGFR Exon 20 T790M.

KEYWORDS: non-small cell lung carcinoma, EGFR, Exon 20, T790M, osimertinib

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Introduction

The epidermal growth factor receptor (EGFR) mutation is an emerging and promising treatment target for non-small cell lung carcinoma (NSCLC).(1) This mutation is particularly prevalent in South-East Asian NSCLC patients, which is found in more than half of all NSCLC patients. Meanwhile it is also found in 10-20% of Caucasian patients.(2) NSCLC-associated EGFR mutation exhibits a higher incidence in women, non-smokers, and those with adenocarcinoma histology.(3) Fortunately, clinical outcomes for NSCLC patients have significantly improved since the introduction of tyrosine kinase inhibitors (TKIs) targeting EGFR.(4)

The initial generation of TKIs has shown remarkable results in prolonging patients' progression-free survival (PFS).(5,6) However, impact on overall survival (OS) may be limited due to disease progression. Recent findings have shed light on the differences in treatment response between the two most common types of EGFR mutations. Patients with Exon 19 deletion tend to have longer PFS on TKI treatment and show more extended OS compared to those with Exon 21 L858R point mutation.(7,8) Although there is an evidence suggesting that particular EGFR mutation had higher affinity with TKI (9), the true mechanism is still debated.

Despite the initial benefits observed with TKI therapy, a majority of NSCLC patients with active EGFR mutations develop resistance during treatment.(1) Since there has been a significant breakthrough in the management of NSCLC with a specific genetic alteration (10-12), there was substantial condition improvement in patients whose cancer progressed after first-generation TKI treatment and who developed tumors with EGFR Exon 20 T790M mutation.(13) The T790M mutation in NSCLC play role in reducing adenosine triphosphate (ATP)-competitive-kinase-inhibitor, so that the mutation can prevent the effect of inhibitor, thus EGFR-mediated signalling will not be defected.(14)

Based on above reasons, the present study was conducted to analyze a cohort of NSCLC patients and to investigate the incidence of the EGFR Exon 20 T790M status with Osimertinib therapy, along with its impact on survival rates. Understanding these factors will provide valuable insights in aiding the development of effective treatment strategies for NSCLC patients with EGFR mutations.

Methods

Subject and Data Collection

A retrospective cohort study was conducted on 22 NSCLC subjects within October 2019 and July 2022 in Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia, and its network centers. This study was approved by the Research Ethics Commission of the Faculty of Medicine, Universitas Hasanuddin (Approval No.: 270/UN4.6.4.5.31/PP36/2022). Demographic and clinical data including age, gender, body mass index, smoking status, Brinkman Index and family history were collected from subjects. Brinkman Index was calculated by multiplying average-cigarette-consumed-everyday with years-of-smoking, mild <200, moderate 200-600, severe >600.

EGFR Genetical Examination

All NSCLC subjects were genetically examined for EGFR status. From each NSCLC subject, 10 mL blood was collected. Blood sample was processed to collect plasmic cell free total nucleic acid (cfTNA) using MagMAX cell free total nucleic acid isolation kit (ThermoFisher, Waltham, MA, USA). DNA library was prepared Oncomine Lung cfDNA Assay (ThermoFisher). Then the sequencing was performed with Ion Torrent next-generation sequencing (NGS) (ThermoFisher). The NGS data was analyzed and interpreted with Ion Reporter and Oncomine Reporter.

Osimertinib Treatment and Survival Status

All NSCLC subjects were treated with Carboplatin and Paclitaxel in a cycle of 6-treatments and 21-days-interval. In the 6th month, EGFR genetical examinations were performed. Among the subjects with EGFR Exon 20 T790M, some received 80 mg Osimertinib for 1 dosage/daily (Tagrisso, AstraZeneca, Cambridge, UK), while others continued with the second cycle of Carboplatin and Paclitaxel treatment. The subjects were observed until they deceased. The subject survival status was recorded for further analysis.

Statistical Analysis

Demographic and clinical data were descriptively summarized and statistically analyzed using Chi-Square test. Correlation between survival rate and EGFR Exon 20 T790M was analyzed with Log Rank (Mantel-Cox) test. One-year survival status and EGFR mutation in different exons were statistically analyzed using Chi-Square test as well. Significant values were determined at $p < 0.05$. All

statistical analyses were performed using the Statistical Program for Social Sciences (SPSS) version 24.0 (IBM Corporation, Armonk, NY, USA).

Results

Based on the subjects' characteristic, there were 12 male and 10 female subjects with majority age of 45-65 years, non-smoking (Brinkman Index), and no family history of lung cancer (Table 1). Meanwhile, based on the EGFR mutation status, there were subjects with mutation of EGFR Exon 20 T790M and mutation of EGFR Exon 19 deletion (n=5) or EGFR Exon 21 L858R (n=8) (Table 2). There were also subjects without mutation of EGFR Exon 20 T790M but having mutation of EGFR Exon 19 deletion (n=5) or EGFR Exon 21 L858R (n=4).

Study subjects with (n=13) and without (n=9) EGFR Exon 20 T790M had a significant mean difference of 7.77 months with *p*-value of 0.000 (Table 3). As shown in Kaplan-Meier survival curve (Figure 1), subjects without EGFR Exon 20 T790M (blue line) had survival time <10 months, while subjects with EGFR Exon 20 T790M (red line) had survival time >10 months with 3 positive censored tick marks. Based on subjects' 1-year survival status, there were more non-survivor with EGFR Exon 20 T790M (n=10) compared with the survivor (n=3), while all subjects without EGFR Exon 20 T790M did not survive (Table 4).

Among the subjects with EGFR Exon 20 T790M, there were subjects treated with (n=5) and without (n=8) Osimertinib. Based on 1-year survival status of subjects with EGFR Exon 20 T790M, there were 3 Osimertinib-treated survivors and 2 Osimertinib-treated non-survivors

Table 1. The subject's characteristic based on EGFR Exon 20 T790M.

Variable	EGFR Exon 20 T790M [n (%)]		<i>p</i> -value [#]
	(+) (n=13)	(-) (n=9)	
Age			
<45 years old	-	2 (9.1)	0.204
45-65 years old	11 (50.0)	6 (27.3)	
>65 years old	2 (9.1)	1 (4.5)	
Gender			
Male	5 (22.7)	7 (31.8)	0.069
Female	8 (36.4)	2 (9.1)	
Body mass index			
Underweight	7 (31.8)	6 (27.3)	0.548
Normal	6 (27.3)	3 (13.6)	
Overweight	-	-	
Brinkman Index			
Non-smokers	7 (31.8)	2 (9.1)	0.003*
Mild	-	-	
Moderate	5 (22.7)	-	
Severe	1 (4.5)	7 (31.8)	
Family history			
Yes	4 (18.2)	2 (9.1)	0.658
No	9 (40.9)	7 (31.8)	

[#]Chi-Square test, **p*<0.05.

(Table 5). However, without any Osimertinib treatment, NSCLC subjects with EGFR Exon 20 T790M did not survive.

Discussion

Lung cancer is a complex disease that often involves genetic alterations affecting the EGFR tyrosine kinase

Table 2. Correlation of EGFR Exon 20 T790M with other EGFR mutations.

Other EGFR Mutation	EGFR Exon 20 T790M [n (%)]		<i>p</i> -value [#]
	(+) (n=13)	(-) (n=9)	
EGFR Exon 19 deletion	5 (22.7)	5 (22.7)	0.429
EGFR Exon 21 L858R	8 (36.4)	4 (18.2)	

[#]Chi-Square test.

Table 3. Survival rate related to EGFR Exon 20 T790M.

Group	Survival Rate (Month) [Mean±SD]	Mean Difference	<i>p</i> -value [#]
EGFR Exon 20 T790M (+) (n=13)	10.77±2.45	7.77	0.000*
EGFR Exon 20 T790M (-) (n=9)	4.78±1.48		

[#]Log Rank (Mantel-Cox), **p*<0.05.

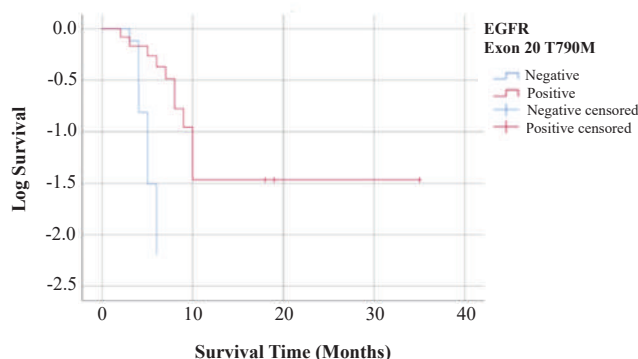


Figure 1. Kaplan-Meier survival curve of subjects with/without EGFR Exon 20 T790M.

signaling pathways, with approximately 75% of examined cases showing such changes.(15) Among these pathways, EGFR pathway is of particular interest with the most common mutations are in-frame deletions (85%–90%) of exon 19 deletion (45%–50%) and Exon 21 L858R mutation (40%–45%).(16) While targeted therapies like TKIs have shown promise in inhibiting tumor growth, the emergence of the EGFR Exon 20 T790M mutation has been identified as a common mechanism of resistance to these therapies. (17,18) The EGFR Exon 20 T790M competes with the TKI, reducing its efficacy and leading to treatment resistance.(14) Among the various post-TKI mutations, the EGFR Exon 20 T790M has the highest incidence.(1,17)

The EGFR Exon 20 T790M mutation is frequently observed in lung cancer patients who have previously undergone TKI therapy and developed resistance.(19) Interestingly, it tends to occur more often in individuals over the age of 40 and women.(20,21) In accordance, in this study, most subjects with EGFR Exon 20 T790M were in the age of 45-65 years old. Advanced age may be associated with a reduced function of tumor-suppressor genes (22), potentially contributing to the occurrence of the EGFR Exon 20 T790M.

In this study, smoking status, as assessed using the Brinkman index, non-smoker was correlated with the presence of the EGFR Exon 20 T790M. This result

Table 4. One-year survival status related to EGFR Exon 20 T790M.

One-year Survival Status	EGFR Exon 20 T790M [n (%)]		p-value [#]
	(+) (n=13)	(-) (n=9)	
Survivor	3 (13.6)	-	0.121
Non-survivor	10 (45.5)	9 (40.9)	

[#]Chi-Square test.

is in accordance with previous report, showing that the never smokers with EGFR Exon 20 T790M develop lung cancer more frequently than ever smokers. In addition, EGFR Exon 20 T790M was found more in female gender. (23) Similar data were also found in this study, most subjects with EGFR Exon 20 T790M were not smoking, and more female subjects (n=8) than male subjects (n=5) were detected with EGFR Exon 20 T790M. However, the underlying mechanism behind the higher occurrence of the EGFR Exon 20 T790M in non-smokers is not yet understood.

In this study, family history did not appear to have a significant association with the EGFR Exon 20 T790M, although there is a possibility of the mutation being inherited. (24) Additionally, the specific location of the mutation within the exon did not seem to be correlated. Although the EGFR Exon 20 T790M often coexists with other EGFR mutations, such as Exon 19 deletion and Exon 21 L858R mutation, the pathogenetic mechanism underlying this coexistence is still not fully understood.(25,26)

In this study, there was a significant difference in the survival rate of subjects with the EGFR Exon 20 T790M (10.77 months) than the one of subject without the mutation (4.78 months). These results were influenced by the Osimertinib treatment, since data of 1-year survival status showed that among 5 subjects treated with Osimertinib, 3 of them were survive (Table 5) with long survival time (Figure 1). These findings are consistent with similar studies which reported longer overall survival in subjects with EGFR Exon 20 T790M mutations who received EGFR-TKI treatment compared to those without the mutation and without EGFR-TKI treatment.(27)

There are some limitations of the current study. To overcome these limitations and gain a deeper understanding of the clinical outcomes and prognosis associated with the EGFR Exon 20 T790M, a multi-center study with a larger sample size is recommended. Such a study should also consider the type and duration of treatment provided, enabling a more robust analysis of the impact of the EGFR Exon 20 T790M on patient outcomes.

Table 5. One-year survival status related to EGFR Exon 20 T790M with Osimertinib treatment.

One-year Survival Status	Osimertinib Therapy [n (%)]		p-value [#]
	(+) (n=5)	(-) (n=8)	
Survivor	3 (23.1)	-	0.001*
Non-survivor	2 (15.4)	8 (61.5)	

[#]Chi-Square test, * $p < 0.05$.

Conclusion

Since treatment of Osimertinib demonstrated a noteworthy survival rate among NSCLC subjects with EGFR Exon 20 T790M, thus Osimertinib could be suggested as a potential targeted therapy for NSCLC subjects with EGFR Exon 20 T790M.

Authors Contribution

NZZ involved in concepting and planning the research. NZZ, HI, NAT, AS, NL, and HAP performed the data acquisition data analysis. FS aided in interpreting the results. NZZ and FS drafted and revised the final the manuscript. All authors took parts in giving critical revision of the manuscript.

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RESEARCH ARTICLE

Osimertinib as a Potential Targeted Therapy for Non-Small Cell Lung Carcinoma (NSCLC) Patients with EGFR Exon 20 T790M

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Abstract

BACKGROUND: Emergence of drug resistance due to epidermal growth factor receptor (EGFR) Exon 20 T790M poses a challenge in the effective management of non-small cell lung carcinoma (NSCLC). Significant breakthrough in the management of NSCLC with a specific genetic alteration causes substantial condition improvement in patients whose cancer progressed after first-generation tyrosine kinase inhibitor treatment and who developed tumors with EGFR Exon 20 T790M mutation. The present study analyzed a cohort of NSCLC patients and investigated the incidence of the EGFR Exon 20 T790M status with Osimertinib therapy, along with its impact on survival rates.

METHODS: This was a retrospective cohort study on 22 NSCLC subjects who were genetically examined for EGFR status from plasma cell free total nucleic acid. Subjects with EGFR Exon 20 T790M mutation were treated with/without Osimertinib. Demographic and clinical data were descriptively summarized, and the differences of each variable and correlation between survival rate and EGFR Exon 20 T790M were analyzed.

RESULTS: Subjects with (n=13) and without (n=9) EGFR Exon 20 T790M had survival rates of 10.77±2.45 and 4.78±1.48, respectively (p=0.000). Based on 1-year survival status of subjects with EGFR Exon 20 T790M, there were 3 Osimertinib-treated survivors and 2 Osimertinib-treated non-survivors. Eight subjects with EGFR Exon 20 T790M and without Osimertinib treatment did not survive (p=0.001).

CONCLUSION: Since the treatment of Osimertinib demonstrated a noteworthy survival rate among NSCLC subjects with EGFR Exon 20 T790M, thus Osimertinib could be suggested as a potential targeted therapy for NSCLC subjects with EGFR Exon 20 T790M.

KEYWORDS: non-small cell lung carcinoma, EGFR, Exon 20, T790M, osimertinib

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CONCLUSION: Since the treatment of Osimertinib demonstrated a noteworthy survival rate among NSCLC subjects with EGFR Exon 20 T790M, thus Osimertinib could be suggested as a potential targeted therapy for NSCLC subjects with EGFR Exon 20 T790M.

KEYWORDS: non-small cell lung carcinoma, EGFR, Exon 20, T790M, osimertinib

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Introduction

The epidermal growth factor receptor (EGFR) mutation is an emerging and promising treatment target for non-small cell lung carcinoma (NSCLC).⁽¹⁾ This mutation is particularly prevalent in South-East Asian NSCLC patients, which is found in more than half of all NSCLC patients. Meanwhile it is also found in 10-20% of Caucasian patients.⁽²⁾ NSCLC-associated EGFR mutation exhibits a higher incidence in women, non-smokers, and those with adenocarcinoma histology.⁽³⁾ Fortunately, clinical outcomes for NSCLC patients have significantly improved since the introduction of tyrosine kinase inhibitors (TKIs) targeting EGFR.⁽⁴⁾

The initial generation of TKIs has shown remarkable results in prolonging patients' progression-free survival (PFS).^(5,6) However, impact on overall survival (OS) may be limited due to disease progression. Recent findings have shed light on the differences in treatment response between the two most common types of EGFR mutations. Patients with Exon 19 deletion tend to have longer PFS on TKI treatment and show more extended OS compared to those with Exon 21 L858R point mutation.^(7,8) Although there is an evidence suggesting that particular EGFR mutation had higher affinity with TKI ⁽⁹⁾, the true mechanism is still debated.

Despite the initial benefits observed with TKI therapy, a majority of NSCLC patients with active EGFR mutations develop resistance during treatment.⁽¹⁾ Since there has been a significant breakthrough in the management of NSCLC with a specific genetic alteration ⁽¹⁰⁻¹²⁾, there was substantial condition improvement in patients whose cancer progressed after first-generation TKI treatment and who developed tumors with EGFR Exon 20 T790M mutation.⁽¹³⁾ The T790M mutation in NSCLC play role in reducing adenosine triphosphate (ATP)-competitive-kinase-inhibitor, so that the mutation can prevent the effect of inhibitor, thus EGFR-mediated signalling will not be defected.⁽¹⁴⁾

Based on above reasons, the present study was conducted to analyze a cohort of NSCLC patients and to investigate the incidence of the EGFR Exon 20 T790M status with Osimertinib therapy, along with its impact on survival rates. Understanding these factors will provide valuable insights in aiding the development of effective treatment strategies for NSCLC patients with EGFR mutations.

Methods

Subject and Data Collection

A retrospective cohort study was conducted on 22 NSCLC subjects within October 2019 and July 2022 in Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia, and its network centers. This study was approved by the Research Ethics Commission of the Faculty of Medicine, Universitas Hasanuddin (Approval No.: 270/UN4.6.4.5.31/PP36/2022). Demographic and clinical data including age, gender, body mass index, smoking status, Brinkman Index and family history were collected from subjects. Brinkman Index was calculated by multiplying average-cigarette-consumed-everyday with years-of-smoking, mild <200, moderate 200-600, severe >600.

EGFR Genetical Examination

All NSCLC subjects were genetically examined for EGFR status. From each NSCLC subject, 10 mL blood was collected. Blood sample was processed to collect plasmic cell free total nucleic acid (cfTNA) using MagMAX cell free total nucleic acid isolation kit (ThermoFisher, Waltham, MA, USA). DNA library was prepared Oncomine Lung cfDNA Assay (ThermoFisher). Then the sequencing was performed with Ion Torrent next-generation sequencing (NGS) (ThermoFisher). The NGS data was analyzed and interpreted with Ion Reporter and Oncomine Reporter.

Osimertinib Treatment and Survival Status

All NSCLC subjects were treated with Carboplatin and Paclitaxel in a cycle of 6-treatments and 21-days-interval. In the 6th month, EGFR genetical examinations were performed. Among the subjects with EGFR Exon 20 T790M, some received 80 mg Osimertinib for 1 dosage/daily (Tagrissso, AstraZeneca, Cambridge, UK), while others continued with the second cycle of Carboplatin and Paclitaxel treatment. The subjects were observed until they deceased. The subject survival status was recorded for further analysis.

Statistical Analysis

Demographic and clinical data were descriptively summarized and statistically analyzed using Chi-Square test. Correlation between survival rate and EGFR Exon 20 T790M was analyzed with Log Rank (Mantel-Cox) test. One-year survival status and EGFR mutation in different exons were statistically analyzed using Chi-Square test as well. Significant values were determined at $p < 0.05$. All

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 statistical analyses were performed using the Statistical Program for Social Sciences (SPSS) version 24.0 (IBM Corporation, Armonk, NY, USA).

Results

Based on the subjects' characteristic, there were 12 male and 10 female subjects with majority age of 45-65 years, non-smoking (Brinkman Index), and no family history of lung cancer (Table 1). Meanwhile, based on the EGFR mutation status, there were subjects with mutation of EGFR Exon 20 T790M and mutation of EGFR Exon 19 deletion (n=5) or EGFR Exon 21 L858R (n=8) (Table 2). There were also subjects without mutation of EGFR Exon 20 T790M but having mutation of EGFR Exon 19 deletion (n=5) or EGFR Exon 21 L858R (n=4).

Study subjects with (n=13) and without (n=9) EGFR Exon 20 T790M had a significant mean difference of 7.77 months with *p*-value of 0.000 (Table 3). As shown in Kaplan-Meier survival curve (Figure 1), subjects without EGFR Exon 20 T790M (blue line) had survival time <10 months, while subjects with EGFR Exon 20 T790M (red line) had survival time >10 months with 3 positive censored tick marks. Based on subjects' 1-year survival status, there were more non-survivor with EGFR Exon 20 T790M (n=10) compared with the survivor (n=3), while all subjects without EGFR Exon 20 T790M did not survive (Table 4).

Among the subjects with EGFR Exon 20 T790M, there were subjects treated with (n=5) and without (n=8) Osimertinib. Based on 1-year survival status of subjects with EGFR Exon 20 T790M, there were 3 Osimertinib-treated survivors and 2 Osimertinib-treated non-survivors

Table 1. The subject's characteristic based on EGFR Exon 20 T790M.

Variable	EGFR Exon 20 T790M [n (%)]		<i>p</i> -value [#]
	(+) (n=13)	(-) (n=9)	
Age			
<45 years old	-	2 (9.1)	0.204
45-65 years old	11 (50.0)	6 (27.3)	
>65 years old	2 (9.1)	1 (4.5)	
Gender			
Male	5 (22.7)	7 (31.8)	0.069
Female	8 (36.4)	2 (9.1)	
Body mass index			
Underweight	7 (31.8)	6 (27.3)	0.548
Normal	6 (27.3)	3 (13.6)	
Overweight	-	-	
Brinkman Index			
Non-smokers	7 (31.8)	2 (9.1)	0.003*
Mild	-	-	
Moderate	5 (22.7)	-	
Severe	1 (4.5)	7 (31.8)	
Family history			
Yes	4 (18.2)	2 (9.1)	0.658
No	9 (40.9)	7 (31.8)	

[#]Chi-Square test, **p*<0.05.

(Table 5). However, without any Osimertinib treatment, NSCLC subjects with EGFR Exon 20 T790M did not survive.

Discussion

Lung cancer is a complex disease that often involves genetic alterations affecting the EGFR tyrosine kinase

Table 2. Correlation of EGFR Exon 20 T790M with other EGFR mutations.

Other EGFR Mutation	EGFR Exon 20 T790M [n (%)]		<i>p</i> -value [#]
	(+) (n=13)	(-) (n=9)	
EGFR Exon 19 deletion	5 (22.7)	5 (22.7)	0.429
EGFR Exon 21 L858R	8 (36.4)	4 (18.2)	

[#]Chi-Square test.

Table 3. Survival rate related to EGFR Exon 20 T790M.

Group	Survival Rate (Month) [Mean±SD]	Mean Difference	<i>p</i> -value [#]
EGFR Exon 20 T790M (+) (n=13)	10.77±2.45	7.77	0.000*
EGFR Exon 20 T790M (-) (n=9)	4.78±1.48		

[#]Log Rank (Mantel-Cox), **p*<0.05.

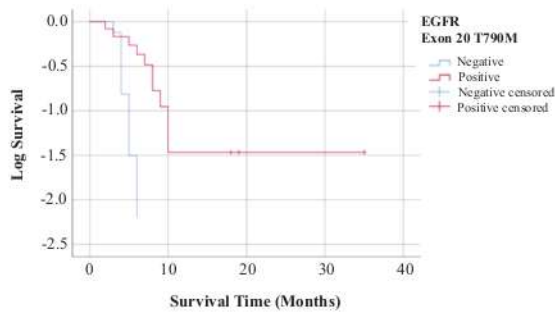


Figure 1. Kaplan-Meier survival curve of subjects with/without EGFR Exon 20 T790M.

signaling pathways, with approximately 75% of examined cases showing such changes.(15) Among these pathways, EGFR pathway is of particular interest with the most common mutations are in-frame deletions (85%–90%) of exon 19 deletion (45%–50%) and Exon 21 L858R mutation (40%–45%).(16) While targeted therapies like TKIs have shown promise in inhibiting tumor growth, the emergence of the EGFR Exon 20 T790M mutation has been identified as a common mechanism of resistance to these therapies.(17,18) The EGFR Exon 20 T790M competes with the TKI, reducing its efficacy and leading to treatment resistance.(14) Among the various post-TKI mutations, the EGFR Exon 20 T790M has the highest incidence.(1,17)

The EGFR Exon 20 T790M mutation is frequently observed in lung cancer patients who have previously undergone TKI therapy and developed resistance.(19) Interestingly, it tends to occur more often in individuals over the age of 40 and women.(20,21) In accordance, in this study, most subjects with EGFR Exon 20 T790M were in the age of 45-65 years old. Advanced age may be associated with a reduced function of tumor-suppressor genes (22), potentially contributing to the occurrence of the EGFR Exon 20 T790M.

In this study, smoking status, as assessed using the Brinkman index, non-smoker was correlated with the presence of the EGFR Exon 20 T790M. This result

is in accordance with previous report, showing that the never smokers with EGFR Exon 20 T790M develop lung cancer more frequently than ever smokers. In addition, EGFR Exon 20 T790M was found more in female gender.(23) Similar data were also found in this study, most subjects with EGFR Exon 20 T790M were not smoking, and more female subjects (n=8) than male subjects (n=5) were detected with EGFR Exon 20 T790M. However, the underlying mechanism behind the higher occurrence of the EGFR Exon 20 T790M in non-smokers is not yet understood.

In this study, family history did not appear to have a significant association with the EGFR Exon 20 T790M, although there is a possibility of the mutation being inherited.(24) Additionally, the specific location of the mutation within the exon did not seem to be correlated. Although the EGFR Exon 20 T790M often coexists with other EGFR mutations, such as Exon 19 deletion and Exon 21 L858R mutation, the pathogenetic mechanism underlying this coexistence is still not fully understood.(25,26)

In this study, there was a significant difference in the survival rate of subjects with the EGFR Exon 20 T790M (10.77 months) than the one of subject without the mutation (4.78 months). These results were influenced by the Osimertinib treatment, since data of 1-year survival status showed that among 5 subjects treated with Osimertinib, 3 of them were survive (Table 5) with long survival time (Figure 1). These findings are consistent with similar studies which reported longer overall survival in subjects with EGFR Exon 20 T790M mutations who received EGFR-TKI treatment compared to those without the mutation and without EGFR-TKI treatment.(27)

There are some limitations of the current study. To overcome these limitations and gain a deeper understanding of the clinical outcomes and prognosis associated with the EGFR Exon 20 T790M, a multi-center study with a larger sample size is recommended. Such a study should also consider the type and duration of treatment provided, enabling a more robust analysis of the impact of the EGFR Exon 20 T790M on patient outcomes.

Table 4. One-year survival status related to EGFR Exon 20 T790M.

One-year Survival Status	EGFR Exon 20 T790M [n (%)]		p-value ^a
	(+) (n=13)	(-) (n=9)	
Survivor	3 (13.6)	-	0.121
Non-survivor	10 (45.5)	9 (40.9)	

^aChi-Square test.

Table 5. One-year survival status related to EGFR Exon 20 T790M with Osimertinib treatment.

One-year Survival Status	Osimertinib Therapy [n (%)]		p-value ^a
	(+) (n=5)	(-) (n=8)	
Survivor	3 (23.1)	-	0.001*
Non-survivor	2 (15.4)	8 (61.5)	

^aChi-Square test, *p<0.05.

Conclusion

Since treatment of Osimertinib demonstrated a noteworthy survival rate among NSCLC subjects with EGFR Exon 20 T790M, thus Osimertinib could be suggested as a potential targeted therapy for NSCLC subjects with EGFR Exon 20 T790M.

Authors Contribution

NZZ involved in conceptualizing and planning the research. NZZ, HI, NAT, AS, NL, and HAP performed the data acquisition data analysis. FS aided in interpreting the results. NZZ and FS drafted and revised the final the manuscript. All authors took parts in giving critical revision of the manuscript.

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Daria Gaut, Myung Shin Sim, Yuguang Yue, Brian R. Wolf et al. "Clinical Implications of the T790M Mutation in Disease Characteristics and Treatment Response in Patients With Epidermal Growth Factor Receptor (EGFR)-Mutated Non-Small-Cell Lung Cancer(NSCLC)", *Clinical Lung Cancer*, 2018

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Ferry Sandra <ferry@trisakti.ac.id>

[InaBJ] M2023140 Editor Decision Round 1 - Resubmit for Review

Secretariat of InaBJ <secretariatinabj@gmail.com>
To: ferry@trisakti.ac.id

Mon, Jul 24, 2023 at 7:32 AM

Dear Dr. Ferry Sandra,

Good day. We have reached a decision regarding your submission to The Indonesian Biomedical Journal, "**T790M mutation on Non-Small Cell Lung Carcinoma (NSCLC): A Retrospective Cohort Study**".

Our decision is: **Resubmit for Review.**

Find the file attached to see detailed comments from reviewers. Please make sure you read all the comments and revise the manuscript based on the suggestions given.

Revise this manuscript thoroughly before **August 7, 2023**. Mark/highlighted the revised part of the manuscript, so that the editor will notice the changes.

When you are done, you can upload it in: <https://inabj.org/index.php/ibj/author/submissionReview/2431>, or simply send us an email of your revised manuscript and response letter.

Please let us know when you have received this email. If you have any questions, do not hesitate to contact us. Thank you for your attention. We wish you a nice day.

Best Regards,

--

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Manuscript Review Form

Reviewer	: Reviewer 1
Manuscript #	: M2023140
Manuscript Title	: T790M mutation on Non-Small Cell Lung Carcinoma (NSCLC): A Retrospective Cohort Study

No.	Manuscript Components	Yes	No
1.	Does this manuscript present new ideas or results that have not been previously published?	Yes	
	Notes:		
2.	Are the title and abstract of the manuscript appropriate?	Yes	
	Notes:		
3.	Do the title and abstract reflect the study result/content?		NO
	Conclusion over estimate with result,		
4.	Is the significance of the study well explained at the Background?	Yes	
	Notes:		
5.	Are the research study methods technically correct, accurate, and complete enough to be reproduced/cited by other scientists?		No
	Notes: 1. need to be informed in greater detail about the molecular method that was used, how sensitively the mutation can be detected, and this information is very important in assessing how sensitively the method used distinguishes whether positive or negative results were obtained. 2. A very limited number of samples are available for analysis in order to determine		



	whether or not the effects of therapy have an impact on patient survival. We suggest add more sample to sufficient conclude the results.		
6.	Are the results, ideas, and data presented in this manuscript important enough for publication?	Yes	
	Notes:		
7.	Are all figures and tables necessarily presented?		No
	Notes: 1. table number 4 not clear. Are exon 19 & 21 positive or negative no information. 2. Over estimate survival time 19,88 month (this study only 9 months)		
8.	Is there a logical flow of argument in the Discussion which elucidate all the presented/obtained data?	Yes	
	Notes:		
9.	Are the conclusions and interpretations valid and supported by the data?		No
	Notes: 1. Only 3 subject survive so need more data to conclude 2. Calculation survival rate related to Osimertinib must be in positive T790M only because negative result not receive Osimertinib, please recalculate survival rate.		
10.	Is the manuscript clear, comprehensible, and written in a good English structure?	Yes	
	Notes:		

Specific Reviewer's Comments and Suggestions:

(These comments may be in addition to or in lieu of reviewer comments inserted into the text of the manuscript. Use as many lines as needed.)



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Reviewer's Recommendation (Please tick only one option)	
Accept Submission (No significant alterations suggested)	<input type="checkbox"/>
Revisions Required (Suggest changes to the manuscript as specified in this review)	<input type="checkbox"/>
Resubmit for Review (Major revisions should be made and suggestions as specified in this review must be addressed. Revised manuscript should be resubmitted to the reviewer for further review)	<input checked="" type="checkbox"/>
Decline Submission (Do not encourage a rewrite, manuscript is totally rejected)	<input type="checkbox"/>

Further Reviewer's Comments Regarding Disposition of the Manuscript:

Date and Sign:

June 20, 2023

Reviewer 1

1 **T790M mutation on Non-Small Cell Lung Carcinoma (NSCLC): A Retrospective**

2 **Cohort Study**

Comment [i1]: Title has to be revised to directly reflect the main findings of the study. A suggestion for title: "Non-Small Cell Lung Carcinoma (NSCLC) Subjects with T790M Positive Mutation Shows Better Survival Rate".

3 **Abstract**

4 **Background:** Mutations in the epidermal growth factor receptor (EGFR) tyrosine kinase
5 receptor have become a significant treatment target in non-small cell lung carcinoma
6 (NSCLC). However, the emergence of resistance due to T790M mutations poses a challenge
7 in the effective management of this disease. ~~While much~~ Though some information remains
8 unknown, various studies have demonstrated that patients ~~positive for~~ with the T790M-
9 positive mutation exhibit improved progression-free survival (PFS), overall survival (OS),
10 and better response to tyrosine kinase inhibitors (TKIs) treatment compared to T790M-
11 negative patients. This ~~to~~ study aimed to describe the effects of T790M mutation status in
12 lung cancer patients.

13 **Methods:** ~~This was a~~ retrospective cohort study on 22 NSCLC patients ~~aimed~~ to establish
14 correlations by collecting medical record data from patients who were examined for the
15 T790M mutation from blood circulating DNA (ctDNA) and analyzed by polymerase chain
16 reaction (PCR) between October 2019 and July 2022 in XXX Hospital and its network
17 hospital. Baseline data were descriptively summarized, and the differences in each variable
18 between groups were calculated as well as the survival rate of osimertinib therapy and
19 T790M mutation status.

Comment [i2]: Methods section needs to be majorly revised, many information necessary to be described. So after the revision of the Methods section, please also revise the Methods in Abstract.

20 **Results:** Our study found patients with the T790M mutation exhibited mean survival time of
21 19.88 months, compared to those without the mutation ($p = 0.005$) and significant association
22 between patients harboring the T790M mutation and receiving osimertinib therapy ($p =$
23 0.001).

24 **Conclusion:** T790M positive mutation and osimertinib therapy demonstrated a noteworthy
25 survival rate.

M2023140 - T790M Mutation of Lung Cancer

26 **Keywords:** non-small cell lung carcinoma, epidermal growth factor, T790M.

27

28 **Introduction**

29 Emerging as a promising treatment target for non-small cell lung carcinoma (NSCLC)
30 is the mutation of epidermal growth factor receptor (EGFR).^{1,2} This mutation is particularly
31 prevalent in Asian populations, present in up to half of NSCLC patients, and is found in about
32 10% of Western populations.³ NSCLC, associated with this molecular subtype of EGFR
33 mutation, exhibits a higher incidence in women, non-smokers, and those with
34 adenocarcinoma histology.^{4,5} Fortunately, the clinical outcomes for NSCLC patients have
35 significantly improved since the introduction of tyrosine kinase inhibitors (TKIs) targeting
36 EGFR.^{6,7}

37 The initial generation of TKIs has shown remarkable results in prolonging patients'
38 progression-free survival (PFS).^{8,9} However, the impact on overall survival (OS) may be
39 limited due to disease progression.¹⁰ Recent findings have shed light on the differences in
40 treatment response between the two most common types of EGFR mutations. Patients with
41 exon 19 deletions tend to have a longer PFS on TKI treatment and demonstrate a more
42 extended OS compared to patients with the TKI point mutation 21L858R.¹¹ Although, there
43 is evidence the mechanism involved.¹²

44 Despite the initial benefits observed with TKI therapy, a majority of NSCLC patients
45 with active EGFR mutations develop resistance during treatment.² However, there has been a
46 significant breakthrough in the management of metastatic NSCLC with a specific genetic
47 alteration.¹³⁻¹⁶ There was substantial improvement in their condition for patients whose
48 cancer progressed after first-generation TKI treatment and who developed tumors with the
49 T790M mutation.¹⁷

50 The aim of this study is to analyze a cohort of NSCLC patients and investigate the
51 incidence of the T790M mutation status with osimertinib therapy, along with its impact on
52 survival rates. Understanding these factors will provide valuable insights for pulmonology

53 and thoracic oncology experts, aiding in the development of effective treatment strategies for
 54 NSCLC patients with EGFR mutations.

55 **Methods**

56 *Subject's and data collections*

57 A retrospective cohort study was taken on 22 NSCLC patients with T790M mutation
 58 test (with targeted therapy EGFR-TKI and without) patients in XXX Hospital and its network,
 59 XXX, XXX, XXX. This study was approved by the Research Ethics Commission of XXX
 60 (No: XXX). Demographic and clinical data were collected by collecting medical record data
 61 from patients who were examined for the T790M mutation from blood circulating DNA
 62 (ctDNA) and analyzed and sequenced by polymerase chain reaction (PCR) between October
 63 2019 and July 2022 in Clinical Laboratory of XXX Hospital.

64 *Statistical analysis*

65 Baseline data were descriptively summarized, and the differences in each variable
 66 between age, gender, body mass index, smoking status, family history, exon location,
 67 survival in one-year with T790M mutation were calculated using Chi-Square tests.
 68 Correlation between SR and T790M mutation status were analyzed by Log Rank (Mantel-
 69 Cox). Significant values were determined at $p < 0.05$. The patient's SR were analyzed. Age,
 70 gender, and smoking status are also analyzed as control variables. All statistical analyses
 71 were performed using the Statistical Program for Social Sciences (SPSS) version 24.0 (IBM
 72 SPSS 24, IL Corporation, Armonk, NY, USA).

73 **Results**

74 Based on the study findings, the majority of patients included in the analysis were
 75 males aged between 45 and 65 years, who were underweight, smokers, and did not have a
 76 family history of lung cancer (Table 1). Our study found that patients with the T790M

Comment [i3]: In the Methods section, there is no information about osimertinib therapy. Did all subjects receive it? If not all subjects, then provide information which and how many subject has received it.

Comment [i4]: Eventhough this is a retrospective study, however author has to be able to provide clear information about how to collect the blood serum and what methods used for T790 mutation test.

Please also describe how to classify the subjects as T790-positive and T790-negative.

Comment [i5]: Demographic and clinical data including...? Add the parameters here.

Comment [i6]: Need to be briefly explained in the separate sub-section. Any use of tools, kit, and materials should also be mentioned completed with the information of the manufacturer company name, city, and country of location.

Comment [i7]: Does SR stands for survival rates? It has not been mentioned before, hence it has to be defined. And you have to be consistent whether to use the term 'overall survival' or 'survival rate' for this.

Comment [i8]: Use the term 'subjects' instead of 'patients' in the Results section.

77 mutation exhibited mean survival time of 19.88 months, compared to those without the
 78 mutation. The presence of the T790M mutation was found to be correlated with survival rate
 79 (Table 2 & Figure 1), although there ~~was~~are no correlation between T790M mutation with
 80 one-year survival rate and exon location (Table 3 & Table 4). Our study identified a
 81 significant association between patients harboring with the T790M mutation and receiving
 82 osimertinib therapy (p = 0.001). Significant association was observed between the
 83 administration of osimertinib therapy and improved one-year survival rates in these patients
 84 (Table 5).

85 Table 1. Patient's characteristic and T790M mutation

Variable	T790M mutation N(%)		Total	p-value
	Positive (+)	Negative (-)		
Age				
<45 years old	0 (0.0)	2 (9.1)	2 (9.1)	0.204
45-65 years old	11 (50.0)	6 (27.2)	17 (77.3)	
>65 years old	2 (9.1)	1 (4.6)	3 (13.6)	
Gender				
Male	5 (22.7)	7 (31.8)	12 (54.5)	0.069
Female	8 (36.4)	2 (9.1)	10 (45.5)	
Body mass index ^e				
Underweight	7 (31.8)	6 (27.3)	13 (59.1)	0.548
Normal	6 (27.3)	3(13.6)	9 (40.9)	
Overweight	0 (0.0)	0 (0.0)	0 (0.0)	
Smoking status				
Yes	6 (27.3)	7 (31.8)	13 (59.1)	0.170
No	7 (31.8)	2 (9.1)	9 (40.9)	
Brinkman Index				
Non-smokers	7 (31,8)	2 (9,1)	9 (40.9)	0.003*
Moderate	5 (22.7)	0 (0.0)	5 (22.7)	
Severe	1 (4.6)	7 (31.8)	8 (36.4)	
Family history				
Yes	4 (18.2)	2 (9.1)	6 (27.3)	0.658
No	9 (40.9)	7 (31.8)	16 (72.7)	

Chi-Square test, *significant if p<0.05.

Comment [i9]: n for each should be mentioned.

Comment [i10]: Has to be mentioned in the Methods before along with other parameter. And for Brinkman Index should be briefly explained what this index referring to and how to classify it.

86
87
88 Table 2. Survival rate related to T790M mutation status

Group	Survival rate (months)±SD	Mean difference	p-value
T790M (+)	19.88±3.36	9.81	0.005*
T790M (-)	5.74±0.49		

89 —Log Rank (Mantel-Cox), SD standard of deviation, MD mean difference, *significant if
 90 p<0.05.

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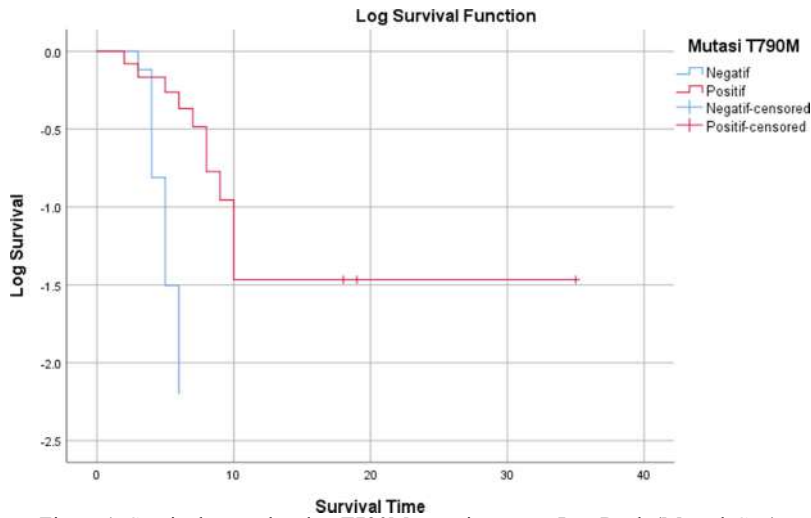


Figure 1. Survival rate related to T790M mutation status Log Rank (Mantel-Cox)

Table 3. One-year survival rate in T790M mutation

Survival status	T790M mutation N(%)		Total	p-value
	Positive (+)	Negative (-)		
Survivor	3 (10.5)	0 (0.0)	3 (13.6)	0.121
Non-survivor	10 (42.1)	9 (47.4)	19 (86.4)	

Chi-square, *significant if $p < 0.05$.

Table 4. Exon-related T790M mutation

Exon	T790M mutation N(%)		Total	p-value
	Positive (+)	Negative (-)		
Exon 19	5 (22.7)	5 (22.7)	10 (45.5)	0.429
Exon 21	8 (36.3)	4 (18.2)	12 (54.5)	

Chi-square, *significant if $p < 0.05$.

Table 5. One-year survival rate in NSCLC patients with and without T790M mutation with osimertinib therapy

Mutation of T790M status	Survival status	Therapy		Total	p-value
		Osimertinib	Without osimertinib		
Positive (+)	Survivor	3 (13.6)	0 (0.0)	3 (13.6)	0.001*
	Non-survivor	2 (9.1)	8 (36.6)	10 (45.5)	
Negative (-)	Survivor	0 (0.0)	0 (0.0)	0 (0.0)	
	Non-survivor	0 (0.0)	9 (40.9)	9 (40.9)	

Chi-square, *significant

Comment [i11]: Table 3 and Table 4 can actually be combined/merged into one table.

Discussion

Lung cancer is a complex disease that often involves genetic alterations affecting the tyrosine kinase signaling pathways, with approximately 75% of examined cases showing such changes.¹⁸ Among these pathways, the epidermal growth factor receptor (EGFR) pathway is of particular interest, with around 65% of lung cancer in tyrosine kinase pathways cases exhibiting EGFR mutations.¹⁹ While targeted therapies like tyrosine kinase inhibitors

106 (TKIs) have shown promise in inhibiting tumor growth, the emergence of the T790M
107 mutation has been identified as a common mechanism of resistance to these therapies.^{20,21}
108 The T790M mutation competes with the TKI, reducing its efficacy and leading to treatment
109 resistance. Among the various post-TKI mutations, the T790M mutation has the highest
110 incidence.²²

111 The T790M mutation is frequently observed in lung cancer patients who have
112 previously undergone TKI therapy and developed resistance.²³ Interestingly, it tends to occur
113 more often in individuals over the age of 40 and men. Advanced age may be associated with
114 a reduced ability of genes to suppress oncogenes, potentially contributing to the occurrence of
115 the T790M mutation. Additionally, epidemiological data suggest that men are more likely to
116 have familial lung cancer. However, the exact reasons for this gender disparity remain
117 unclear and warrant further investigation.²⁴

118 Smoking status, as assessed using the Brinkman index, has been correlated with the
119 presence of the T790M mutation. Prolonged smoking can trigger changes in cellular
120 differentiation patterns, which may influence the development of this mutation.²⁵ However,
121 the underlying mechanism behind the higher occurrence of the T790M mutation in non-
122 smokers is not yet understood.²⁶ Furthermore, body mass index (BMI) has not shown a
123 relationship with the T790M mutation.²⁷ On the other hand, family history does not appear to
124 have a significant association with the T790M mutation, although there is a possibility of the
125 mutation being inherited.^{28,29} Additionally, the specific location of the mutation within the
126 exon does not seem to be correlated. Although the T790M mutation often coexists with other
127 EGFR mutations, such as exon 19 deletion and exon 21 L858R mutation, the pathogenetic
128 mechanism underlying this coexistence is still not fully understood.^{30,31}

129 The study's results highlight a significant difference in the one-year survival rates of
130 lung cancer patients with the T790M mutation who received osimertinib compared to those

Comment [i12]: In your study results, there is significant correlation of Brinkman Index and the T790 mutation, please add more discussion about the mechanism.

Reference No.26 was published on 2018, you should look for more recent literatures to provide information about this.

131 without the mutation. Patients undergoing EGFR-TKI therapy exhibited an average survival
132 time of 19.88 months, with a mean difference of 9.81 months compared to patients without
133 the T790M mutation, who had an average survival time of 5.74 months. These findings are
134 consistent with similar studies which reported longer overall survival in patients with T790M
135 mutations who received EGFR-TKI therapy compared to those without the mutation.^{32,33}
136 Importantly, these improvements in survival have been observed across different age groups
137 and regardless of previous therapies received.^{34,35}

Comment [113]: Why? Explain a little about the possible correlation that allow subjects with EGFR-TKI therapy to have better OS in subjects with T790 mutation.

138 However, it is important to acknowledge the limitations of the current study. One
139 significant limitation is the need for more comprehensive data on the specific type of EGFR-
140 TKI administered to each patient. To overcome these limitations and gain a deeper
141 understanding of the clinical outcomes and prognosis associated with the T790M mutation, a
142 multi-center study with a larger sample size is recommended. Such a study should also
143 consider the type and duration of treatment provided, enabling a more robust analysis of the
144 impact of the T790M mutation on patient outcomes. By addressing these limitations,
145 researchers can further enhance our knowledge of the T790M mutation and its implications
146 for the management of lung cancer. Further research is necessary warranted to explore
147 optimal treatment strategies and improve patient outcomes in this subgroup.

148 **Conclusion**

149 T790M positive mutation and osimertinib therapy demonstrated a noteworthy survival
150 rate. These findings contribute to the potential benefits of targeted therapies for NSCLC
151 patients harboring T790M mutation. ~~Further research is warranted to explore optimal~~
152 ~~treatment strategies and improve patient outcomes in this subgroup.~~

153

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Ferry Sandra <ferry@trisakti.ac.id>

[InaBJ] M2023140 Editor Decision Round 1 - Resubmit for Review

Ferry Sandra <ferry@trisakti.ac.id>

Mon, Jul 24, 2023 at 7:45 PM

To: Secretariat of InaBJ <secretariatnabj@gmail.com>

Dear Secretariat of The Indonesian Biomedical Journal,

Please find the revision of the manuscript M2023140 that was previously titled "T790M mutation on Non-Small Cell Lung Carcinoma (NSCLC): A Retrospective Cohort Study" as well as the response letter addressing the reviewer's and editor's question. We have revised the manuscript accordingly. Thank you for your kind assistance.

Regards,

Ferry Sandra

[Quoted text hidden]

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Ferry Sandra, D.D.S., Ph.D.

Head of Medical Research Center

Universitas Trisakti

2 attachments**Round 1 Revision from Author.docx**

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**Round 1 Response Form from Author.xlsx**

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1 **Non-Small Cell Lung Carcinoma (NSCLC Subjects with T790M Positive Mutation**

2 **Shows Better Survival Rate**

3 **Abstract**

4 **Background:** Mutations in the epidermal growth factor receptor (*EGFR*) tyrosine kinase
5 receptor have become a significant treatment target in non-small cell lung carcinoma
6 (NSCLC). However, the emergence of resistance due to T790M mutations poses a challenge
7 in the effective management of this disease. Though some information remains unknown,
8 various studies have demonstrated that patients with T790M-positive mutation exhibit
9 improved progression-free survival (PFS), overall survival (OS), and better response to
10 tyrosine kinase inhibitors (TKIs) treatment compared to T790M-negative patients. This study
11 aimed to describe the effects of T790M mutation status in lung cancer patients.

12 **Methods:** This was a retrospective cohort study on 22 NSCLC subjects to establish
13 correlations by collecting data from subjects who were examined for the T790M mutation
14 from plasma circulating tumor DNA (ctDNA) with next-generation sequencing analysis
15 (NGS) and sequenced by Ion GeneStudio S5 with *EGFR* T790M (ThermoFisher, CA, United
16 States) between October 2019 and July 2022 in Dr. Wahidin Sudirohusodo Hospital and its
17 network hospital. Baseline data were descriptively summarized, and the differences in each
18 variable between groups were calculated as well as the survival rate of osimertinib therapy
19 and T790M mutation status.

20 **Results:** Our study found subjects with the T790M mutation exhibited mean survival time of
21 19.88 months, compared to those without the mutation ($p = 0.005$) and significant association
22 between subjects with the T790M mutation and receiving osimertinib therapy ($p = 0.001$).

23 **Conclusion:** T790M positive mutation demonstrated a noteworthy survival rate.

24 **Keywords:** non-small cell lung carcinoma, epidermal growth factor, T790M.

25 **Introduction**

26 Epidermal growth factor receptor (*EGFR*) mutation is an emerging and promising
27 treatment target for non-small cell lung carcinoma (NSCLC).^{1,2} This mutation is particularly
28 prevalent in Asian populations, present in up to half of NSCLC patients, and is found in about
29 10% of Western populations.³ NSCLC, associated with *EGFR* mutation, exhibits a higher
30 incidence in women, non-smokers, and those with adenocarcinoma histology.^{4,5} Fortunately,
31 the clinical outcomes for NSCLC patients have significantly improved since the introduction
32 of tyrosine kinase inhibitors (TKIs) targeting *EGFR*.⁶⁻¹⁰

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33 The initial generation of TKIs has shown remarkable results in prolonging patients'
34 progression-free survival (PFS).^{11,12} However, the impact on overall survival (OS) may be
35 limited due to disease progression.¹³ Recent findings have shed light on the differences in
36 treatment response between the two most common types of *EGFR* mutations. Patients with
37 exon 19 deletion tend to have a longer PFS on TKI treatment and show a more extended OS
38 compared to those with exon 21 L858R point mutation.¹⁴ Although, there is evidence the
39 mechanism involved in TKIs therapy on *EGFR* mutation is tighter covalent binding but the
40 true mechanism is still debated.^{15,16}

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41 Despite the initial benefits observed with TKI therapy, a majority of NSCLC patients
42 with active *EGFR* mutations develop resistance during treatment.² However, there has been a
43 significant breakthrough in the management of metastatic NSCLC with a specific genetic
44 alteration.¹⁷⁻²⁰ There was substantial condition improvement in patients whose cancer
45 progressed after first-generation TKI treatment and who developed tumors with T790M
46 mutation.²¹ T790M mutation in NSCLC play role as a genomic stability marker and reduce
47 adenosine triphosphate (ATP)-competitive kinase to prevent *EGFR*-mediated signalling.²²
48 This mutation is responsible for better prognosis in NSCLC patients.

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49 The present study was conducted to analyze a cohort of NSCLC patients and
50 investigate the incidence of the T790M mutation status with osimertinib therapy, along with

51 its impact on survival rates. Understanding these factors will provide valuable insights for
52 pulmonology and thoracic oncology experts, aiding in the development of effective treatment
53 strategies for NSCLC patients with EGFR mutations.

54 **Methods**

55 *Subject's and data collections*

56 A retrospective cohort study was taken on 22 NSCLC subjects (with osimertinib
57 therapy n=5, without n=17) with T790M mutation test subjects in Dr. Wahidin Sudirohusodo
58 Hospital and its network, Makassar, South Sulawesi, Indonesia. This study was approved by
59 the Research Ethics Commission of of the Faculty of Medicine, Hasanuddin University (No:
60 270/UN4.6.4.5.31/PP36/2022). Demographic and clinical data (age, gender, body mass index,
61 smoking status, Brinkman Index, family history and exon location) were collected by
62 collecting medical record data from subjects who were examined for the T790M mutation
63 from plasma (6 mL of plasma) circulating tumor DNA (ctDNA) with next-generation
64 sequencing analysis (NGS) and sequenced by Ion GeneStudio S5 with EGFR T790M
65 (ThermoFisher, CA, United States) between October 2019 and July 2022 in Prodia
66 Laboratorium and Clinic. The subjects observed until they pass away.

67 *Statistical analysis*

68 Baseline data were descriptively summarized, and the differences in each variable
69 between age, gender, body mass index, smoking status, Brinkman Index, family history, exon
70 location, survival in one-year with T790M mutation were calculated using Chi-Square tests.
71 Correlation between survival rate (SR) and T790M mutation status were analyzed by Log
72 Rank (Mantel-Cox). Significant values were determined at $p < 0.05$. The subject's SR were
73 analyzed. Age, gender, and smoking status are also analyzed as control variables. All

74 statistical analyses were performed using the Statistical Program for Social Sciences (SPSS)
 75 version 24.0 (IBM Corporation, Armonk, NY, USA).

76 **Results**

77 Based on the study findings, the majority of subjects included in the analysis were
 78 males aged between 45 and 65 years, who were underweight, smokers, and did not have a
 79 family history of lung cancer (Table 1). Our study found that subjects with the T790M
 80 mutation exhibited mean survival time of 19.88 months, compared to those without the
 81 mutation. The presence of the T790M mutation was found to be correlated with SR (Table 2
 82 & Figure 1), although there was no correlation between T790M mutation with one-year
 83 survival rate and exon location (Table 3). Our study identified a significant association
 84 between subjects with the T790M mutation and receiving osimertinib therapy (p = 0.001).
 85 Significant association was observed between the administration of osimertinib therapy and
 86 improved one-year survival rates in these subjects (Table 4).

87 Table 1. Subject's characteristic and T790M mutation

Variable	T790M mutation N(%)		Total	p-value
	Positive (+) (n=13)	Negative (-) (n=9)		
Age				
<45 years old	0 (0.0)	2 (9.1)	2 (9.1)	0.204
45-65 years old	11 (50.0)	6 (27.2)	17 (77.3)	
>65 years old	2 (9.1)	1 (4.6)	3 (13.6)	
Gender				
Male	5 (22.7)	7 (31.8)	12 (54.5)	0.069
Female	8 (36.4)	2 (9.1)	10 (45.5)	
Body mass index				
Underweight	7 (31.8)	6 (27.3)	13 (59.1)	0.548
Normal	6 (27.3)	3(13.6)	9 (40.9)	
Overweight	0 (0.0)	0 (0.0)	0 (0.0)	
Smoking status				
Yes	6 (27.3)	7 (31.8)	13 (59.1)	0.170
No	7 (31.8)	2 (9.1)	9 (40.9)	
Brinkman Index				
Non-smokers	7 (31,8)	2 (9,1)	9 (40.9)	0.003*
Moderate	5 (22.7)	0 (0.0)	5 (22.7)	
Severe	1 (4.6)	7 (31.8)	8 (36.4)	
Family history				
Yes	4 (18.2)	2 (9.1)	6 (27.3)	0.658
No	9 (40.9)	7 (31.8)	16 (72.7)	

88 Chi-Square test, *p<0.05, Brinkman index was calculated by multiply average
 89 cigar consumed everyday with years of smoking, mild <200, moderate 200-600,
 90 severe >600,

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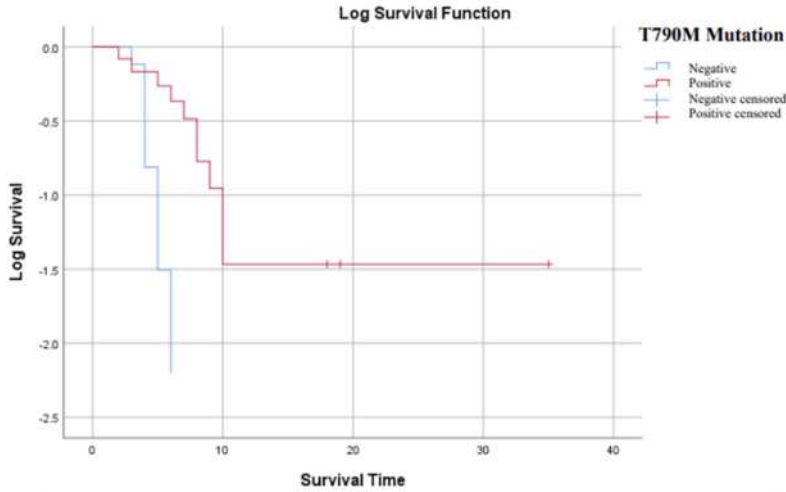
Table 2. Survival rate related to T790M mutation status

Group	Survival rate (months)±SD	Mean difference	p-value
T790M (+)	19.88±3.36	9.81	0.005*
T790M (-)	5.74±0.49		

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—Log Rank (Mantel-Cox), SD standard of deviation, MD mean difference, *p<0.05

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Figure 1. Survival rate related to T790M mutation status Log Rank (Mantel-Cox)

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Table 3. One-year survival rate and exon location in T790M mutation

Variable	T790M mutation N(%)		Total	p-value
	Positive (+) (n=13)	Negative (-) (n=9)		
Survival Status				
Survivor	3 (10.5)	0 (0.0)	3 (13.6)	0.121
Non-survivor	10 (42.1)	9 (47.4)	19 (86.4)	
Exon location				
Exon 19	5 (22.7)	5 (22.7)	10 (45.5)	0.429
Exon 21	8 (36.3)	4 (18.2)	12 (54.5)	

98

Chi-square, *p<0.05

99

Table 4. One-year survival rate in NSCLC subjects with osimertinib therapy

One-year survival rate	Therapy		Total	p-value
	Osimertinib (n=5)	Without osimertinib (n=17)		
Survivor	3 (13.6)	0 (0.0)	3 (13.6)	0.001*
Non-survivor	2 (9.1)	17 (77.3)	10 (86.4)	

100

Chi-square, *p<0.05

101 Discussion

102 Lung cancer is a complex disease that often involves genetic alterations affecting the
103 tyrosine kinase signaling pathways, with approximately 75% of examined cases showing

104 such changes.²³ Among these pathways, the epidermal growth factor receptor (EGFR)
105 pathway is of particular interest, with around 65% of lung cancer in tyrosine kinase pathways
106 cases exhibiting EGFR mutations.²⁴ While targeted therapies like tyrosine kinase inhibitors
107 (TKIs) have shown promise in inhibiting tumor growth, the emergence of the T790M
108 mutation has been identified as a common mechanism of resistance to these therapies.^{25,26}
109 The T790M mutation competes with the TKI, reducing its efficacy and leading to treatment
110 resistance. Among the various post-TKI mutations, the T790M mutation has the highest
111 incidence.²⁷

112 The T790M mutation is frequently observed in lung cancer patients who have
113 previously undergone TKI therapy and developed resistance.²⁸ Interestingly, it tends to occur
114 more often in individuals over the age of 40 and men. Advanced age may be associated with
115 a reduced ability of genes to suppress oncogenes, potentially contributing to the occurrence of
116 the T790M mutation. Additionally, epidemiological data suggest that men are more likely to
117 have familial lung cancer. However, the exact reasons for this gender disparity remain
118 unclear and warrant further investigation.²⁹

119 Smoking status, as assessed using the Brinkman index, has been correlated with the
120 presence of the T790M mutation. Prolonged smoking can trigger changes in cellular
121 differentiation patterns, which may influence the development of this mutation.³⁰ However,
122 the underlying mechanism behind the higher occurrence of the T790M mutation in non-
123 smokers is not yet understood.³¹ T790M mutation and smoking are inversely correlated.
124 Non-smoker have higher risk of this mutation. This is correlated with previous study that
125 conclude higher prevalence in non-smoker than higher Brinkman index population.¹⁰
126 Furthermore, body mass index (BMI) has not shown a relationship with the T790M
127 mutation.³² On the other hand, family history does not appear to have a significant association
128 with the T790M mutation, although there is a possibility of the mutation being inherited.^{33,34}

129 Additionally, the specific location of the mutation within the exon does not seem to be
130 correlated. Although the T790M mutation often coexists with other EGFR mutations, such as
131 exon 19 deletion and exon 21 L858R mutation, the pathogenetic mechanism underlying this
132 coexistence is still not fully understood.^{35,36}

133 The study's results highlight a significant difference in the one-year survival rates of
134 lung cancer subjects with the T790M mutation who received osimertinib compared to those
135 without the mutation. Subjects undergoing EGFR-TKI therapy exhibited an average survival
136 time of 19.88 months, with a mean difference of 9.81 months compared to subjects without
137 the T790M mutation, who had an average survival time of 5.74 months. These findings are
138 consistent with similar studies which reported longer overall survival in subjects with T790M
139 mutations who received EGFR-TKI therapy compared to those without the mutation.^{37,38} Two
140 mechanism that proposed EGFR-TKI affect T790M positive are covalent binding EGFR-TKI
141 therapy with T790M-positive are firmer and EGFR-TKI therapy also reduce ATP-
142 competitive kinase to prevent EGFR-mediated signalling. This two mechanism gave better
143 prognosis to subject T790M mutation.^{2,22} Importantly, these improvements in survival have
144 been observed across different age groups and regardless of previous therapies received.^{39,40}

145 However, it is important to acknowledge the limitations of the current study. One
146 significant limitation is the need for more comprehensive data on the specific type of EGFR-
147 TKI administered to each patient. To overcome these limitations and gain a deeper
148 understanding of the clinical outcomes and prognosis associated with the T790M mutation, a
149 multi-center study with a larger sample size is recommended. Such a study should also
150 consider the type and duration of treatment provided, enabling a more robust analysis of the
151 impact of the T790M mutation on patient outcomes. By addressing these limitations,
152 researchers can further enhance our knowledge of the T790M mutation and its implications

153 for the management of lung cancer. Further research is necessary to explore optimal
154 treatment strategies and improve outcome in this subgroup.

155 **Conclusion**

156 T790M positive mutation demonstrated a noteworthy survival rate among NSCLC
157 subjects. Osimertinib therapy may have potential beneficial effect on T790M mutation
158 NSCLC therapy. These findings contribute to the potential benefits of targeted therapies for
159 NSCLC subjects with T790M mutation.

160

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281

Response Form for Reviewer's Comments

Corresponding Author : Ferry Sandra
 Manuscript Code : M2023140
 Manuscript Title : T790M mutation on Non-Small Cell Lung Carcinoma
 (NSCLC): A Retrospective Cohort Study

No. (Reviewer and comments number code)	Comments (Comments/question from reviewer or editor)	Author's Response (Please write your response regarding the comment here)	Line Number (Please write the line number of the said revision)
R1 #1	Conclusion in the Abstract section is overclaimed. Please rewrite.	we re-conclude the conclusion	24
R1 #2	Please explain in a more detailed manner how molecular methods (for example: PCR) in this study were carried out. Briefly mention the protocol of each method.	we add the methods	63-7
R1 #3	A very limited number of subjects were included in this study to determine the effects of Osimertinib therapy on patient's survival. More subjects should be recruited to obtain representative results.	this case is very rare, we can't add more subject's	57-8
R1 #4	Do you overestimate the survival time? The survival time 19.88 months, but you only conducted the study for only 9 months.	9 months for sampling, the cohort is keep going in until subjects pass away	67
R1 #5	Only 3 survivors included in this study. More subjects should be recruited to obtain representative results.	this case is very rare, we can't add more subject's	100
R1 #6	Calculation of survival rate related to Osimertinib therapy should be performed only in subjects with positive T790M mutation, because subjects with negative T790M mutation did not receive Osimertinib. Please recalculate the survival rate.	we recalculate the one year survival rate with osimertinib therapy	100
R2 #1	Title has to be revised to directly reflect the main findings of the study. A suggestion for title: "Non-Small Cell Lung Carcinoma (NSCLC) Subjects with T790M Positive Mutation Shows Better Survival Rate".	we admit the new title	1
R2 #2	Methods section needs to be majorly revised, many information necessary to be described. So after the revision of the Methods section, please also revise the Methods in Abstract.	we revised the methods section	57-67
R2 #3	In the Methods section, there is no information about osimertinib therapy. Did all subjects receive it? If not all subjects, then provide information which and how many subject has received it.	not all subjects received osimertinib therapy	58

R2 #4	Even though this is a retrospective study, however author has to be able to provide clear information about how to collect the blood serum and what methods used for T790 mutation test. Please also describe how to classify the subjects as T790-positive and T790-negative.	we revised the methods section	57-67
R2 #5	Demographic and clinical data including...? Add the parameters here.	we add the parameters	61-2
R2 #6	Need to be briefly explained in the separate sub-section. Any use of tools, kit, and materials should also be mentioned completed with the information of the manufacturer company name, city, and country of location.	we add the methods	63-6
R2 #7	Does SR stands for survival rates? It has not been mentioned before, hence it has to be defined. And you have to be consistent whether to use the term 'overall survival' or 'survival rate' for this.		72
R2 #8	Use the term 'subjects' instead of 'patients' in the Results section.		
R2 #9	The total number of subjects (n) with positive (n=13)and negative (n=9) mutation should be mentioned in the table heading.		87, 97
R2 #10	Has to be mentioned in the Methods before along with other parameter. And for Brinkman Index should be briefly explained what this index referring to and how to classify it.		
R2 #11	Table 3 and Table 4 can actually be combined/merged into one table.	we merged the table	
R2 #12	In your study results, there is significant correlation of Brinkman Index and the T790 mutation, please add more discussion about the mechanism. Reference No.26 was published on 2018, you should look for more recent literatures to provide information about this.		
R2 #13	Why? Explain a little about the possible correlation that allow subjects with EGFR-TKI therapy to have better OS in subjects with T790 mutation.	we reexplain the discussion about egfr tki	139-144
SE #1	Incomplete sentence. What mechanism do you refer to in this sentence? Please revise this sentence.	we complete the sentence	39-40
SE #2	Please add more explanations about T790M mutation and its role in NSCLC in the Introduction section.		46-8
SE #3	Some annotations in Figure 1 is still using bahasa Indonesia. Please use English instead.	we remake the diagram	94

SE #4	Please cite the following articles as your references: https://doi.org/10.21705/mcbs.v1i2.10 https://doi.org/10.21705/mcbs.v6i2.246 https://doi.org/10.21705/mcbs.v6i2.232	We add these references	181-8
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Note : R1 = Reviewer 1
R2 = Reviewer 2
SE = Section Editor



Ferry Sandra <ferry@trisakti.ac.id>

[InaBJ] M2023140 Editor Decision Round 2 - Revisions Required

Secretariat of InaBJ <secretariatinabj@gmail.com>
To: ferry@trisakti.ac.id

Fri, Aug 11, 2023 at 11:21 AM

Dear Dr. Ferry Sandra,

Good day. We have reached a decision regarding your submission to The Indonesian Biomedical Journal, "**Non-Small Cell Lung Carcinoma (NSCLC) Subjects with T790M Positive Mutation Shows Better Survival Rate**".

Our decision is: **Revisions Required.**

Find the file attached to see detailed comments from reviewers. Please make sure you read all the comments and revise the manuscript based on the suggestions given.

Revise this manuscript thoroughly before **August 25, 2023**. Mark/highlighted the revised part of the manuscript, so that the editor will notice the changes.

When you are done, you can upload it in: <https://inabj.org/index.php/ibj/author/submissionReview/2431>, or simply send us an email of your revised manuscript and response letter.

Please let us know when you have received this email. If you have any questions, do not hesitate to contact us. Thank you for your attention. We wish you a nice day.

Best Regards,

--

Secretariat of The Indonesian Biomedical Journal

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Manuscript Review Form

Reviewer	: Reviewer 1
Manuscript #	: M2023140
Manuscript Title	: Non-Small Cell Lung Carcinoma (NSCLC) Subjects with T790M Positive Mutation Shows Better Survival Rate

No.	Manuscript Components	Yes	No
1.	Does this manuscript present new ideas or results that have not been previously published?		
	Notes:		
2.	Are the title and abstract of the manuscript appropriate?		
	Notes:		
3.	Do the title and abstract reflect the study result/content?		
	Notes:		
4.	Is the significance of the study well explained at the Background?		
	Notes:		
5.	Are the research study methods technically correct, accurate, and complete enough to be reproduced/cited by other scientists?		
	Notes:		
6.	Are the results, ideas, and data presented in this manuscript important enough for publication?		
	Notes:		



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7.	Are all figures and tables necessarily presented?		
	Notes:		
8.	Is there a logical flow of argument in the Discussion which elucidate all the presented/obtained data?		
	Notes:		
9.	Are the conclusions and interpretations valid and supported by the data?		
10.	Is the manuscript clear, comprehensible, and written in a good English structure?		
	Notes:		

Specific Reviewer's Comments and Suggestions:

(These comments may be in addition to or in lieu of reviewer comments inserted into the text of the manuscript. Use as many lines as needed.)

All corrections and clarifications have been accepted.

Reviewer's Recommendation (Please tick only one option)	√
Accept Submission (No significant alterations suggested)	√
Revisions Required (Suggest changes to the manuscript as specified in this review)	
Resubmit for Review (Major revisions should be made and suggestions as specified in this review must be addressed. Revised manuscript should be resubmitted to the reviewer for further review)	
Decline Submission (Do not encourage a rewrite, manuscript is totally rejected)	



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Further Reviewer's Comments Regarding Disposition of the Manuscript:

All corrections and clarifications have been accepted.

Date and Sign:

August 11, 2023

Reviewer 1



Manuscript Review Form

Reviewer	: Reviewer 2
Manuscript #	: M2023140
Manuscript Title	: Non-Small Cell Lung Carcinoma (NSCLC) Subjects with T790M Positive Mutation Shows Better Survival Rate

No.	Manuscript Components	Yes	No
1.	Does this manuscript present new ideas or results that have not been previously published?		
	Notes:		
2.	Are the title and abstract of the manuscript appropriate?		
	Notes:		
3.	Do the title and abstract reflect the study result/content?		
	Notes:		
4.	Is the significance of the study well explained at the Background?		
	Notes:		
5.	Are the research study methods technically correct, accurate, and complete enough to be reproduced/cited by other scientists?		
	Notes:		
6.	Are the results, ideas, and data presented in this manuscript important enough for publication?		
	Notes:		



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7.	Are all figures and tables necessarily presented?		
	Notes:		
8.	Is there a logical flow of argument in the Discussion which elucidate all the presented/obtained data?		
	Notes:		
9.	Are the conclusions and interpretations valid and supported by the data?		
10.	Is the manuscript clear, comprehensible, and written in a good English structure?		
	Notes:		

Specific Reviewer's Comments and Suggestions:

(These comments may be in addition to or in lieu of reviewer comments inserted into the text of the manuscript. Use as many lines as needed.)

Reviewer's Recommendation (Please tick only one option)	√
Accept Submission (No significant alterations suggested)	
Revisions Required (Suggest changes to the manuscript as specified in this review)	√
Resubmit for Review (Major revisions should be made and suggestions as specified in this review must be addressed. Revised manuscript should be resubmitted to the reviewer for further review)	
Decline Submission (Do not encourage a rewrite, manuscript is totally rejected)	



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Further Reviewer's Comments Regarding Disposition of the Manuscript:

There are some issues that still need to be confirmed/answered by the author(s).

Date and Sign:

August 11, 2023

Reviewer 2

1 **Non-Small Cell Lung Carcinoma (NSCLC) Subjects with T790M Positive Mutation**

2 **Shows Exhibits Better Survival Rate**

3 **Abstract**

4 **Background:** Mutations in the epidermal growth factor receptor (*EGFR*) tyrosine kinase
5 receptor have become a significant treatment target in non-small cell lung carcinoma
6 (NSCLC). However, the emergence of resistance due to T790M mutations poses a challenge
7 in the effective management of this disease. Though some information remains unknown,
8 various studies have demonstrated that patients with T790M-positive mutation exhibit
9 improved progression-free survival (PFS), overall survival (OS), and better response to
10 tyrosine kinase inhibitors (TKIs) treatment compared to T790M-negative patients. This study
11 aimed to describe the effects of T790M mutation status in lung cancer patients.

12 **Methods:** This was a retrospective cohort study on 22 NSCLC subjects with/without
13 osimertinib therapy. to establish correlations by collecting data from subjects who were
14 Secondary data from subjects underwent the examined for the T790M mutation from plasma
15 circulating tumor DNA (ctDNA) with next-generation sequencing analysis (NGS) and
16 sequenced by Ion GeneStudio S5 with *EGFR* T790M (ThermoFisher, CA, United States)
17 were collected between October 2019 and July 2022 in Dr. Wahidin Sudirohusodo Hospital
18 and its network hospital. Baseline data were descriptively summarized, and the differences
19 ofin each variable between groups were calculated, as well as the correlation between
20 survival rate of osimertinib therapy and T790M mutation status.

21 **Results:** ~~Our study found~~The result of this study showed that subjects with the T790M
22 mutation exhibited mean survival time of 19.88 months, compared to those without the
23 mutation ($p = 0.005$) and significant association between subjects with the T790M mutation
24 and receiving osimertinib therapy ($p = 0.001$).

25 **Conclusion:** T790M positive mutation demonstrated a noteworthy survival rate.

26 **Keywords:** non-small cell lung carcinoma, epidermal growth factor, T790M.

27 **Introduction**

28 Epidermal growth factor receptor (*EGFR*) mutation is an emerging and promising
29 treatment target for non-small cell lung carcinoma (NSCLC).^{1,2} This mutation is particularly
30 prevalent in Asian populations, present in up to half of NSCLC patients, and is found in about
31 10% of Western populations.³ NSCLC, associated with *EGFR* mutation, exhibits a higher
32 incidence in women, non-smokers, and those with adenocarcinoma histology.^{4,5} Fortunately,
33 the clinical outcomes for NSCLC patients have significantly improved since the introduction
34 of tyrosine kinase inhibitors (TKIs) targeting *EGFR*.⁶⁻¹⁰

35 The initial generation of TKIs has shown remarkable results in prolonging patients'
36 progression-free survival (PFS).^{11,12} However, the impact on overall survival (OS) may be
37 limited due to disease progression.¹³ Recent findings have shed light on the differences in
38 treatment response between the two most common types of *EGFR* mutations. Patients with
39 exon 19 deletion tend to have a longer PFS on TKI treatment and show a more extended OS
40 compared to those with exon 21 L858R point mutation.¹⁴ Although, there is evidence the
41 mechanism involved in TKIs therapy on *EGFR* mutation is tighter covalent binding but the
42 true mechanism is still debated.^{15,16}

43 Despite the initial benefits observed with TKI therapy, a majority of NSCLC patients
44 with active *EGFR* mutations develop resistance during treatment.² However, there has been a
45 significant breakthrough in the management of metastatic NSCLC with a specific genetic
46 alteration.¹⁷⁻²⁰ There was substantial condition improvement in patients whose cancer
47 progressed after first-generation TKI treatment and who developed tumors with T790M
48 mutation.²¹ T790M mutation in NSCLC play role as a genomic stability marker and reduce
49 adenosine triphosphate (ATP)-competitive kinase to prevent *EGFR*-mediated signalling.²²
50 This mutation is responsible for better prognosis in NSCLC patients.

51 The present study was conducted to analyze a cohort of NSCLC patients and
52 investigate the incidence of the T790M mutation status with osimertinib therapy, along with
53 its impact on survival rates. Understanding these factors will provide valuable insights for
54 pulmonology and thoracic oncology experts, aiding in the development of effective treatment
55 strategies for NSCLC patients with EGFR mutations.

56 **Methods**

57 *Subject's and data collections*

58 A retrospective cohort study was taken on 22 NSCLC subjects (with osimertinib
59 therapy n=5, without n=17) with T790M mutation test subjects in Dr. Wahidin Sudirohusodo
60 Hospital and its network, Makassar, South Sulawesi, Indonesia. This study was approved by
61 the Research Ethics Commission of of the Faculty of Medicine, Hasanuddin University (No:
62 270/UN4.6.4.5.31/PP36/2022). Demographic and clinical data (age, gender, body mass index,
63 smoking status, Brinkman Index, family history and exon location) were collected by
64 collecting medical record data from subjects who were examined for the T790M mutation
65 from plasma (6 mL of plasma) circulating tumor DNA (ctDNA) with next-generation
66 sequencing analysis (NGS) and sequenced by Ion GeneStudio S5 with EGFR T790M
67 (ThermoFisher, CA, United States) between October 2019 and July 2022 in Prodia
68 Laboratorium and Clinic. The subjects observed until they pass away.

69 *Statistical analysis*

70 Baseline data were descriptively summarized, and the differences in each variable
71 between age, gender, body mass index, smoking status, Brinkman Index, family history, exon
72 location, survival in one-year with T790M mutation were calculated using Chi-Square tests.
73 Correlation between survival rate (SR) and T790M mutation status were analyzed by Log
74 Rank (Mantel-Cox). Significant values were determined at $p < 0.05$. The subject's SR were

Comment [NMD1]: Eventhough you have stated the laboratory where you conduct the analysis, however the methods used is still needed to be briefly explained in the separate sub-section.

75 analyzed. Age, gender, and smoking status are also analyzed as control variables. All
 76 statistical analyses were performed using the Statistical Program for Social Sciences (SPSS)
 77 version 24.0 (IBM Corporation, Armonk, NY, USA).

78 **Results**

Comment [NMD2]: Author may needs to add more narration and explanation regarding the data in the Results section.

79 Based on the study findings, the majority of subjects included in the analysis were
 80 males aged between 45 and 65 years, who were underweight, smokers, and did not have a
 81 family history of lung cancer (Table 1). Our study found that subjects with the T790M
 82 mutation exhibited mean survival time of 19.88 months, compared to those without the
 83 mutation. The presence of the T790M mutation was found to be correlated with SR (Table 2
 84 & Figure 1), although there was no correlation between T790M mutation with one-year
 85 survival rate and exon location (Table 3). ~~A Our study identified a~~ significant association
 86 between subjects with the T790M mutation and receiving osimertinib therapy **was found** (p =
 87 0.001). Significant association was observed between the administration of osimertinib
 88 therapy and improved one-year survival rates in these subjects (Table 4).

89 Table 1. Subject's characteristic and T790M mutation

Variable	T790M mutation N(%)		Total	p-value
	Positive (+) (n=13)	Negative (-) (n=9)		
Age				
<45 years old	0 (0.0)	2 (9.1)	2 (9.1)	0.204
45-65 years old	11 (50.0)	6 (27.2)	17 (77.3)	
>65 years old	2 (9.1)	1 (4.6)	3 (13.6)	
Gender				
Male	5 (22.7)	7 (31.8)	12 (54.5)	0.069
Female	8 (36.4)	2 (9.1)	10 (45.5)	
Body mass index				
Underweight	7 (31.8)	6 (27.3)	13 (59.1)	0.548
Normal	6 (27.3)	3(13.6)	9 (40.9)	
Overweight	0 (0.0)	0 (0.0)	0 (0.0)	
Smoking status				
Yes	6 (27.3)	7 (31.8)	13 (59.1)	0.170
No	7 (31.8)	2 (9.1)	9 (40.9)	
Brinkman Index				
Non-smokers	7 (31.8)	2 (9.1)	9 (40.9)	0.003*
Moderate	5 (22.7)	0 (0.0)	5 (22.7)	
Severe	1 (4.6)	7 (31.8)	8 (36.4)	
Family history				
Yes	4 (18.2)	2 (9.1)	6 (27.3)	0.658
No	9 (40.9)	7 (31.8)	16 (72.7)	

90 Chi-Square test, *p<0.05, Brinkman index was calculated by multiply average
 91 cigar consumed everyday with years of smoking, mild <200, moderate 200-600,
 92 severe >600,

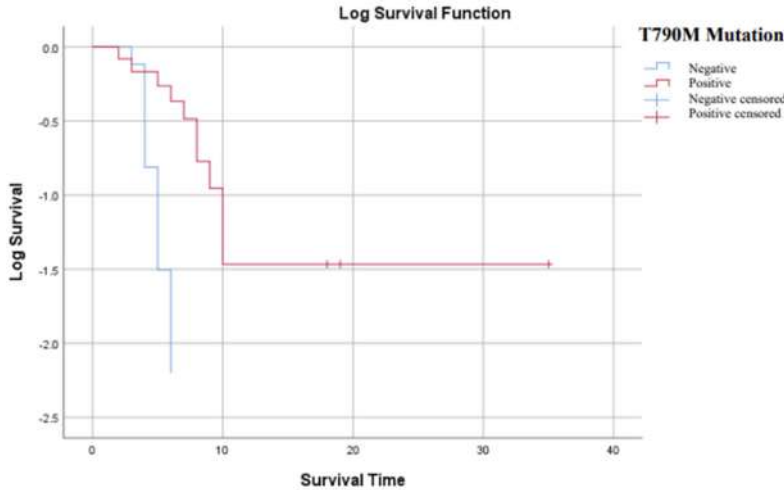
M2023140 - T790M Mutation of Lung Cancer

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Table 2. Survival rate related to T790M mutation status (n=22).

Group	Survival rate (months)±SD	Mean difference	p-value
T790M (+)	19.88±3.36	9.81	0.005*
T790M (-)	5.74±0.49		

Log Rank (Mantel-Cox), SD standard of deviation, MD mean difference, *p<0.05



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98
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Figure 1. Survival rate related to T790M mutation status Log Rank (Mantel-Cox)

Table 3. One-year survival rate and exon location in T790M mutation

Variable	T790M mutation N(%)		Total	p-value
	Positive (+) (n=13)	Negative (-) (n=9)		
Survival Status				
- Survivor	3 (10.5)	0 (0.0)	3 (13.6)	0.121
- Non-survivor	10 (42.1)	9 (47.4)	19 (86.4)	
Exon location				
- Exon 19	5 (22.7)	5 (22.7)	10 (45.5)	0.429
- Exon 21	8 (36.3)	4 (18.2)	12 (54.5)	

Chi-square, *p<0.05

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Table 4. One-year survival rate in NSCLC subjects with osimertinib therapy

One-year survival rate	Therapy		Total	p-value
	Osimertinib (n=5)	Without osimertinib (n=17)		
Survivor	3 (13.6)	0 (0.0)	3 (13.6)	0.001*
Non-survivor	2 (9.1)	17 (77.3)	10 (86.4)	

Chi-square, *p<0.05

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103 Discussion

104 Lung cancer is a complex disease that often involves genetic alterations affecting the
105 tyrosine kinase signaling pathways, with approximately 75% of examined cases showing

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Comment [NMD3]: Why did you combine the survival rate between the T790M-positive and T790-negative?

Meanwhile in the narration of results section you mentioned that a significant association between subjects with the T790M mutation and receiving osimertinib therapy was found (p = 0.001). How can you come to this conclusion when the comparison between the negative and the positive was not provided?

106 such changes.²³ Among these pathways, the epidermal growth factor receptor (EGFR)
107 pathway is of particular interest, with around 65% of lung cancer in tyrosine kinase pathways
108 cases exhibiting EGFR mutations.²⁴ While targeted therapies like tyrosine kinase inhibitors
109 (TKIs) have shown promise in inhibiting tumor growth, the emergence of the T790M
110 mutation has been identified as a common mechanism of resistance to these therapies.^{25,26}
111 The T790M mutation competes with the TKI, reducing its efficacy and leading to treatment
112 resistance. Among the various post-TKI mutations, the T790M mutation has the highest
113 incidence.²⁷

114 The T790M mutation is frequently observed in lung cancer patients who have
115 previously undergone TKI therapy and developed resistance.²⁸ Interestingly, it tends to occur
116 more often in individuals over the age of 40 and men. Advanced age may be associated with
117 a reduced ability of genes to suppress oncogenes, potentially contributing to the occurrence of
118 the T790M mutation. Additionally, epidemiological data suggest that men are more likely to
119 have familial lung cancer. However, the exact reasons for this gender disparity remain
120 unclear and warrant further investigation.²⁹

121 Smoking status, as assessed using the Brinkman index, has been correlated with the
122 presence of the T790M mutation. Prolonged smoking can trigger changes in cellular
123 differentiation patterns, which may influence the development of this mutation.³⁰ However,
124 the underlying mechanism behind the higher occurrence of the T790M mutation in non-
125 smokers is not yet understood.³¹ T790M mutation and smoking are inversely correlated.
126 Non-smoker have higher risk of this mutation. This is correlated with previous study that
127 conclude higher prevalence in non-smoker than higher Brinkman index population.¹⁰
128 Furthermore, body mass index (BMI) has not shown a relationship with the T790M
129 mutation.³² On the other hand, family history does not appear to have a significant association
130 with the T790M mutation, although there is a possibility of the mutation being inherited.^{33,34}

131 Additionally, the specific location of the mutation within the exon does not seem to be
132 correlated. Although the T790M mutation often coexists with other EGFR mutations, such as
133 exon 19 deletion and exon 21 L858R mutation, the pathogenetic mechanism underlying this
134 coexistence is still not fully understood.^{35,36}

135 The study's results highlight a significant difference in the one-year survival rates of
136 lung cancer subjects with the T790M mutation who received osimertinib compared to those
137 without the mutation. Subjects undergoing EGFR-TKI therapy exhibited an average survival
138 time of 19.88 months, with a mean difference of 9.81 months compared to subjects without
139 the T790M mutation, who had an average survival time of 5.74 months. These findings are
140 consistent with similar studies which reported longer overall survival in subjects with T790M
141 mutations who received EGFR-TKI therapy compared to those without the mutation.^{37,38} Two
142 mechanism that proposed EGFR-TKI affect T790M positive are covalent binding EGFR-TKI
143 therapy with T790M-positive are firmer and EGFR-TKI therapy also reduce ATP-
144 competitive kinase to prevent EGFR-mediated signalling. This two mechanism gave better
145 prognosis to subject T790M mutation.^{2,22} Importantly, these improvements in survival have
146 been observed across different age groups and regardless of previous therapies received.^{39,40}

147 However, it is important to acknowledge the limitations of the current study. One
148 significant limitation is the need for more comprehensive data on the specific type of EGFR-
149 TKI administered to each patient. To overcome these limitations and gain a deeper
150 understanding of the clinical outcomes and prognosis associated with the T790M mutation, a
151 multi-center study with a larger sample size is recommended. Such a study should also
152 consider the type and duration of treatment provided, enabling a more robust analysis of the
153 impact of the T790M mutation on patient outcomes. By addressing these limitations,
154 researchers can further enhance our knowledge of the T790M mutation and its implications

155 for the management of lung cancer. Further research is necessary to explore optimal
156 treatment strategies and improve outcome in this subgroup.

157 **Conclusion**

158 T790M positive mutation demonstrated a noteworthy survival rate among NSCLC
159 subjects. Osimertinib therapy may have potential beneficial effect on T790M mutation
160 NSCLC therapy. These findings contribute to the potential benefits of targeted therapies for
161 NSCLC subjects with T790M mutation.

162

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[InaBJ] M2023140 Editor Decision Round 2 - Revisions Required

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Sun, Oct 1, 2023 at 5:17 PM

To: Secretariat of InaBJ <secretariatinabj@gmail.com>

Dear Secretariat of The Indonesian Biomedical Journal,

Good day. I apologize for the delay, but I've completed the revision of manuscript M2023140. I've made several changes to the document and addressed all the reviewers' comments as requested.

Thank you.

Regards,

Ferry Sandra

[Quoted text hidden]

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**Round 2 Revision from Author.docx**

146K

1 Osimertinib as a Potential Targeted Therapy for Non-Small Cell Lung Carcinoma

2 (NSCLC) Patients with EGFR Exon 20 T790M

3

4 Abstract

5 **Background:** Emergence of drug resistance due to epidermal growth factor receptor (EGFR)
6 exon 20 T790M poses a challenge in the effective management of non-small cell lung
7 carcinoma (NSCLC). Significant breakthrough in the management of NSCLC with a specific
8 genetic alteration causes substantial condition improvement in patients whose cancer
9 progressed after first-generation tyrosine kinase inhibitor treatment and who developed
10 tumors with EGFR Exon 20 T790M mutation. The present study analyzed a cohort of
11 NSCLC patients and investigated the incidence of the EGFR Exon 20 T790M status with
12 osimertinib therapy, along with its impact on survival rates.

13 **Methods:** This was a retrospective cohort study on 22 NSCLC subjects who were genetically
14 examined for EGFR status from plasmic cell free total nucleic acid. Subjects with EGFR
15 Exon 20 T790M mutation were treated with/without osimertinib. Demographic and clinical
16 data were descriptively summarized, and the differences of each variable and correlation
17 between survival rate and EGFR Exon 20 T790M were analyzed.

18 **Results:** Subjects with (n=13) and without (n=9) EGFR Exon 20 T790M had survival rates
19 of 10.77 ± 2.45 and 4.78 ± 1.48 , respectively ($p=0.000$). Based on 1-year survival status of
20 subjects with EGFR Exon 20 T790M, there were 3 osimertinib-treated survivors and 2
21 osimertinib-treated non-survivors. Eight subjects with EGFR Exon 20 T790M and without
22 osimertinib treatment did not survive ($p=0.001$).

23 **Conclusion:** Since treatment of osimertinib demonstrated a noteworthy survival rate among
24 NSCLC subjects with EGFR Exon 20 T790M, thus osimertinib could be suggested as a
25 potential targeted therapy for NSCLC subjects with EGFR Exon 20 T790M.

26 **Keywords:** non-small cell lung carcinoma, EGFR, Exon 20, T790M, osimertinib

27 Introduction

28 Epidermal growth factor receptor (EGFR) mutation is an emerging and promising
29 treatment target for non-small cell lung carcinoma (NSCLC).(1) This mutation is particularly
30 prevalent in South-East Asian patients, found in more than half of all NSCLC patients, while
31 found in 10-20% of Caucasian patients.(2) NSCLC associated with EGFR mutation exhibits a
32 higher incidence in women, non-smokers, and those with adenocarcinoma histology.(3)
33 Fortunately, the clinical outcomes for NSCLC patients have significantly improved since the
34 introduction of tyrosine kinase inhibitors (TKIs) targeting EGFR.(4)

35 The initial generation of TKIs has shown remarkable results in prolonging patients'
36 progression-free survival (PFS).(5,6) However, the impact on overall survival (OS) may be
37 limited due to disease progression. Recent findings have shed light on the differences in
38 treatment response between the two most common types of EGFR mutations. Patients with
39 exon 19 deletion tend to have a longer PFS on TKI treatment and show a more extended OS
40 compared to those with exon 21 L858R point mutation.(7,8) Although there is an evidence
41 suggesting that particular EGFR mutation had higher affinity with TKI (9), the true
42 mechanism is still debated.

43 Despite the initial benefits observed with TKI therapy, a majority of NSCLC patients
44 with active EGFR mutations develop resistance during treatment.(1) Since there has been a
45 significant breakthrough in the management of NSCLC with a specific genetic alteration (10-
46 12), there was substantial condition improvement in patients whose cancer progressed after
47 first-generation TKI treatment and who developed tumors with EGFR exon 20 T790M
48 mutation.(13) The T790M mutation in NSCLC play role in reducing adenosine triphosphate
49 (ATP)-competitive-kinase-inhibitor, so that the mutation can prevent the effect of inhibitor,
50 thus EGFR-mediated signalling will not be defected.(14)

51 The present study was conducted to analyze a cohort of NSCLC patients and to
52 investigate the incidence of the EGFR exon 20 T790M status with osimertinib therapy, along
53 with its impact on survival rates. Understanding these factors will provide valuable insights in
54 aiding the development of effective treatment strategies for NSCLC patients with EGFR
55 mutations.

56 **Methods**

57 *Subject and Data Collection*

58 A retrospective cohort study was conducted on 22 NSCLC subjects within October
59 2019 and July 2022 in Dr. Wahidin Sudirohusodo Hospital and its network, Makassar, South
60 Sulawesi, Indonesia. This study was approved by the Research Ethics Commission of the
61 Faculty of Medicine, Hasanuddin University (No: 270/UN4.6.4.5.31/PP36/2022).
62 Demographic and clinical data including age, gender, body mass index, smoking status,
63 Brinkman Index and family history were collected. Brinkman index was calculated by
64 multiplying average-cigarette-consumed-everyday with years-of-smoking, mild <200,
65 moderate 200-600, severe >600.

66

67 *EGFR Genetical Examination*

68 All NSCLC subjects were genetically examined for EGFR status. From each NSCLC subject,
69 10 mL blood was collected. Blood sample was processed to collect plasmic cell free total
70 nucleic acid (cfTNA) using MagMAX cell free total nucleic acid isolation kit (ThermoFisher,
71 Waltham, MA, USA). DNA library was prepared Oncomine Lung cfDNA Assay
72 (ThermoFisher). Then the sequencing was performed with Ion Torrent next-generation
73 sequencing (NGS) (ThermoFisher). The NGS data was analyzed and interpreted with Ion
74 Reporter and Oncomine Reporter.

75

76 *Osimertinib Treatment and Survival Status*

77 All NSCLC subjects were treated with carboplatin and paclitaxel in a cycle of 6-treatments
78 and 21-days-interval. In the 6th month, EGFR genetical examinations were performed.
79 Among the subjects with EGFR Exon 20 T790M, some received 80 mg osimertinib 1
80 dosage/daily (Tagrisso, AstraZeneca, Cambridge, UK), while others continued with the
81 second cycle of carboplatin and paclitaxel treatment. The subjects were observed until they
82 deceased. The subject survival status was recorded for further analysis.

83

84 *Statistical analysis*

85 Demographic and clinical data were descriptively summarized and statistically
86 analyzed using Chi-Square test. Correlation between survival rate and EGFR Exon 20
87 T790M was analyzed with Log Rank (Mantel-Cox) test. One-year survival status and EGFR
88 mutation in different exons were statistically analyzed using Chi-Square test as well.
89 Significant values were determined at $p < 0.05$. All statistical analyses were performed using
90 the Statistical Program for Social Sciences (SPSS) version 24.0 (IBM Corporation, Armonk,
91 NY, USA).

92

93 **Results**

94 Based on the subject characteristic, there were 12 male and 10 female subjects with
95 majority age of 45-65 years, non-smoking (Brinkman Index), and no family history of lung
96 cancer (Table 1). Meanwhile, based on EGFR mutation status, there were subjects with
97 mutation of EGFR Exon 20 T790M and mutation of EGFR Exon 19 deletion (n=5) or EGFR
98 Exon 21 L858R (n=8) (Table 2). There were also subjects without mutation of EGFR Exon

99 20 T790M but having mutation of EGFR Exon 19 deletion (n=5) or EGFR Exon 21 L858R
100 (n=4).

101 Subjects with (n=13) and without (n=9) EGFR Exon 20 T790M had mean difference
102 of 7.77 months with p-value of 0.000 (Table 3). As shown in Kaplan-Meier survival curve
103 (Figure 1), subjects without EGFR Exon 20 T790M (blue line) had survival time <10 months,
104 while subjects with EGFR Exon 20 T790M (red line) had survival time >10 months with 3
105 positive censored tick marks. Based on 1-year survival status, there were more non-survivor
106 with EGFR Exon 20 T790M (n=10) compared with the survivor (n=3), while all subjects
107 without EGFR Exon 20 T790M did not survive (Table 4).

108 Among the subjects with EGFR Exon 20 T790M, there were subjects treated with
109 (n=5) / without (n=8) osimertinib. Based on 1-year survival status of subjects with EGFR
110 Exon 20 T790M, there were 3 osimertinib-treated survivors and 2 osimertinib-treated non-
111 survivors (Table 5). However, without osimertinib treatment, subjects with EGFR Exon 20
112 T790M did not survive.

113
114 Table 1. Subject's characteristic based on EGFR Exon 20 T790M

Variable	EGFR Exon 20 T790M (n (%))		# p
	(+) (n=13)	(-) (n=9)	
Age			
<45 years old	-	2 (9.1)	
45-65 years old	11 (50.0)	6 (27.3)	0.204
>65 years old	2 (9.1)	1 (4.5)	
Gender			
Male	5 (22.7)	7 (31.8)	
Female	8 (36.4)	2 (9.1)	0.069
Body mass index			
Underweight	7 (31.8)	6 (27.3)	
Normal	6 (27.3)	3 (13.6)	0.548
Overweight	-	-	
Brinkman Index			
Non-smokers	7 (31.8)	2 (9.1)	
Mild	-	-	
Moderate	5 (22.7)	-	0.003*
Severe	1 (4.5)	7 (31.8)	
Family history			
Yes	4 (18.2)	2 (9.1)	
No	9 (40.9)	7 (31.8)	0.658

#Chi-Square test, *p<0.05

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Table 2. Correlation of EGFR Exon 20 T790M with other EGFR mutations

Other EGFR Mutation	EGFR Exon 20 T790M (n (%))		#p
	(+) (n=13)	(-) (n=9)	
EGFR Exon 19 deletion	5 (22.7)	5 (22.7)	0.429
EGFR Exon 21 L858R	8 (36.4)	4 (18.2)	

119

#Chi-square

120

121

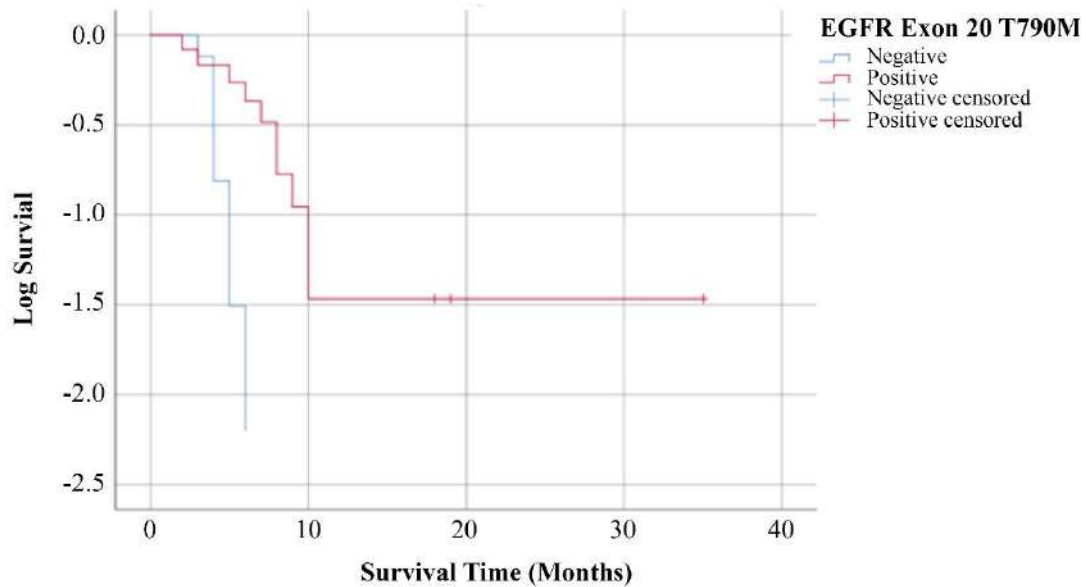
Table 3. Survival rate related to EGFR Exon 20 T790M

Group	Survival Rate (Month) Mean±SD	Mean Difference	#p
EGFR Exon 20 T790M (+) (n=13)	10.77±2.45	7.77	0.000*
EGFR Exon 20 T790M (-) (n=9)	4.78±1.48		

122

#Log Rank (Mantel-Cox), *p<0.05, SD: standard deviation

123



124

125

Figure 1. Kaplan-Meier survival curve of subjects with/without EGFR Exon 20 T790M

126

127

Table 4. One-year survival status related to EGFR Exon 20 T790M

One-year Survival Status	EGFR Exon 20 T790M (n (%))		#p
	(+) (n=13)	(-) (n=9)	
Survivor	3 (13.6)	-	0.121
Non-survivor	10 (45.5)	9 (40.9)	

128

#Chi-square

129

130

Table 5. One-year survival status related to EGFR Exon 20 T790M with osimertinib treatment

One-year survival status	Osimertinib Therapy (n (%))		#p
	(+) (n=5)	(-) (n=8)	
Survivor	3 (23.1)	-	0.001*
Non-survivor	2 (15.4)	8 (61.5)	

131

#Chi-square, *p<0.05

132 Discussion

133 Lung cancer is a complex disease that often involves genetic alterations affecting the
134 EGFR tyrosine kinase signaling pathways, with approximately 75% of examined cases
135 showing such changes.(15) Among these pathways, EGFR pathway is of particular interest
136 with the most common mutations are in-frame deletions (85%–90%) of exon 19 deletion
137 (45%–50%) and exon 21 L858R mutation (40%–45%).(16) While targeted therapies like
138 TKIs have shown promise in inhibiting tumor growth, the emergence of the EGFR Exon 20
139 T790M mutation has been identified as a common mechanism of resistance to these therapies.
140 (17,18) The EGFR Exon 20 T790M competes with the TKI, reducing its efficacy and leading
141 to treatment resistance.(14) Among the various post-TKI mutations, the EGFR Exon 20
142 T790M has the highest incidence.(1,17)

143 The EGFR Exon 20 T790M mutation is frequently observed in lung cancer patients
144 who have previously undergone TKI therapy and developed resistance.(19) Interestingly, it
145 tends to occur more often in individuals over the age of 40 and women.(20,21) In accordance,
146 in this study, most subjects with EGFR Exon 20 T790M were in the age of 45-65 years old.
147 Advanced age may be associated with a reduced function of tumor-suppressor genes (22),
148 potentially contributing to the occurrence of the EGFR Exon 20 T790M.

149 In this study, smoking status, as assessed using the Brinkman index, non-smoker was
150 correlated with the presence of the EGFR Exon 20 T790M. This result is in accordance with
151 previous report, showing that the never smokers with EGFR Exon 20 T790M develop lung
152 cancer more frequently than ever smokers. In addition, EGFR Exon 20 T790M was found
153 more in female gender.(23) Similar data were also found in this study, most subjects with
154 EGFR Exon 20 T790M were not smoking, and more female subjects (n=8) than male
155 subjects (n=5) were detected with EGFR Exon 20 T790M. However, the underlying

156 mechanism behind the higher occurrence of the EGFR Exon 20 T790M in non-smokers is not
157 yet understood.

158 In this study, family history did not appear to have a significant association with the
159 EGFR Exon 20 T790M, although there is a possibility of the mutation being inherited.(24)
160 Additionally, the specific location of the mutation within the exon did not seem to be
161 correlated. Although the EGFR Exon 20 T790M often coexists with other EGFR mutations,
162 such as exon 19 deletion and exon 21 L858R mutation, the pathogenetic mechanism
163 underlying this coexistence is still not fully understood.(25,26)

164 In this study, there was a significant difference in the survival rate of subjects with the
165 EGFR Exon 20 T790M (10.77 months) than the one of subject without the mutation (4.78
166 months). These results were influenced by the osimertinib treatment, since data of 1-year
167 survival status showed that among 5 subjects treated with osimertinib, 3 of them were survive
168 (Table 5) with long survival time (Figure 1). These findings are consistent with similar
169 studies which reported longer overall survival in subjects with EGFR Exon 20 T790M
170 mutations who received EGFR-TKI treatment compared to those without the mutation and
171 without EGFR-TKI treatment (27).

172 There are some limitations of the current study. To overcome these limitations and
173 gain a deeper understanding of the clinical outcomes and prognosis associated with the EGFR
174 Exon 20 T790M, a multi-center study with a larger sample size is recommended. Such a
175 study should also consider the type and duration of treatment provided, enabling a more
176 robust analysis of the impact of the EGFR Exon 20 T790M on patient outcomes.

177 **Conclusion**

178 Since treatment of osimertinib demonstrated a noteworthy survival rate among
179 NSCLC subjects with EGFR Exon 20 T790M, thus osimertinib could be suggested as a
180 potential targeted therapy for NSCLC subjects with EGFR Exon 20 T790M.

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Ferry Sandra <ferry@trisakti.ac.id>

[InaBJ] M2023140 Editor Decision - Manuscript Accepted

Secretariat of InaBJ <secretariat@inabj@gmail.com>
To: ferry@trisakti.ac.id

Mon, Oct 9, 2023 at 9:42 AM

Dear Dr. Ferry Sandra,

Good day. We have reached a decision regarding your submission to The Indonesian Biomedical Journal, "**Osimertinib as a Potential Targeted Therapy for Non-Small Cell Lung Carcinoma (NSCLC) Patients with EGFR Exon 20 T790M.**"

Our decision is to: **Accept Manuscript.**

Your manuscript will be sent to our publisher for typesetting and you should receive the proofreading in due course.

Congratulations on your interesting research, and thank you for allowing us to publish this valuable material. Please let us know once you have read this email. We wish you a nice day.

Best Regards,

--

Secretariat of The Indonesian Biomedical Journal

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