Med. J. Cairo Univ., Vol. 93, No. 1, Accepted 24/12/2024
DOI: 10.22608/MJCU. 109-114, March 2025
www.medicaljournalofcairouniversity.net

Osimertinib with Platinum Based Chemotherapy in Epidermal Growth Factor Receptor (EGFR)-Mutated Metastatic Non Small Cell Lung Cancer (NSCLC)

MOHAMED M. FAROUK AKL, M.D.

The Department of Clinical Oncology & Nuclear Medicine, Faculty of Medicine, Mansoura University

Abstract

Background: Osimertinib is a third-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI). Evidence suggests that Osimertinib plus chemotherapy may prolong the progression-free survival (PFS) in with EGFR-mutated metastatic NSCLC patients.

Aim of Study: To assess the efficacy outcome of Osimertinib plus platinum-based chemotherapy in EGFR-mutated metastatic NSCLC patients.

Patients and Methods: This is a retrospective analysis which included 21 patients with EGFR-mutated metastatic NSCLC, treated with combination therapy of osimertinib at 80 mg once daily plus gemcitabine at 1000mg/m^2 on D1 & D8 and carboplatin at an area under the curve 5 given every three weeks for four cycles.

Results: The median PFS for patients was 17 months (95% CI 13.5-20.5), while the median OR was 22 months (95% CI 15.9-28.1). The one year PFS was 64%, while the one year OS was 84%. The objective response rate was 76.2%. The commonest adverse effects, (AEs) were hematologic toxicity.

Conclusions: First-line treatment with osimertinib plus chemotherapy offered prolonged PFS in patients with EGFR-mutated metastatic NSCLC.

Key Words: *NSCLC – EGFR-mutated – Osimertinib – Metastatic.*

Introduction

LUNG cancer is the commonest cause of cancer-induced death globally, responsible for 1.8 million deathseveryyear **[1]**. Non-small cell lung cancer (NSCLC) constitutes 85% of primary lung tumors **[2]**. Nearly 20% to 25% ofpatients with NSCLC represented with locally advanced (LA) stage **[3,4]**. Unfortunately, the survival of metastatic NSCLC (mNSCLC) has abad prognosis, with 8% 5-year survival rate, despite the use of newer chemotherapeutics **[5]**.

Recently, new modalities have evolved and treatment plans have greatly changed, which results in an prolonged life expectancy and an improved quality of life **[6]**.

Tyrosine kinase inhibitors (TKIs) have made a revolution in treating metastatic NSCLC harboring EGFR mutation and anaplastic lymphoma kinase (ALK) rearrangement. First-generation EGFR- and ALK-TKIs as gefitinib, erlotinib, and crizotinib prolonged significantly the PFS and doubled the response rate in comparison to platinum based chemotherapy **[7-9]**.

Most EGFR-mutated NSCLC patients achieved response with 1st & 2nd generation EGFR TKIs, but usually express resistance after an average of one year. Third-generation TKIs aim mutant EGFR having T790M mutation.Osimertinib is an example, it is an oral, irreversible EGFR TKI, which is selective for EGFR TKI mutations & T790M resistance mutation **[4]**.

Osimertinib (Tagrisso), has prolonged PFS & OS, as compared to the standard TKIs, these studies involved stage IIIB and stage IV patients, with less number of stage IIIB **[10,11]**.

Tagrisso plus chemotherapy has granted priority review by the Food and Drug Administration (FDA) for locally advanced or metastatic EGFR-mutated NSCLC **[12]**.

FDA approval depended on the results of the FLAURA2 Phase III trial. Tagrisso plus chemotherapy lessesns the incidence of progression or death by 38% in comparison to Tagrisso alone, which

Correspondence to: Dr. Mohamed M. Farouk Akl,
E-Mail: mohamedfaroukakl@gmail.com

is the 1st-line global standard of care. The median PFS was 25.5 months in the combined group, versus Tagrisso monotherapy (16.7 months), with 8.8-month improvement. At one year, the PFS rate was 80% in the Tagrisso plus chemotherapy arm vs 66% in the Tagrisso arm, and at 2 year, it was 57% vs 41%, respectively **[13].**

In December 2023, osimertinib (Tagrisso) plus chemotherapy was presented by the NCCN Clinical Practical Guidelines in Oncology for patients with NSCLC expressing EGFR exon 19 deletion or exon 21 L858R mutations **[14].**

Aim of work:

To assess the efficacy outcome of Osimertinib plus platinum-based chemotherapy in EGFR-mutated metastatic NSCLC patients with the PFS as a 1ry endpoint and the OS, objective response rate (ORR) and toxicity as secondary endpoints.

Patients and Methods

This is a retrospective analysis which included 21 patients with EGFR-mutated metastatic NSCLC treated at the Mansoura Health Insurance in the period between June 2022 – January 2024. Patients were treated with osimertinib at 80mg once daily plus gemcitabine at 1000mg/m^2 on D1 & D8 and carboplatin at an area under the curve 5 given once every 3 weeks for 4 cycles, followed by Tagrisso 80mg once daily as a maintenance, which was maintained until progressive disease or intolerable toxicity.

Data collected included age, sex, performance status (PS), histologic type of the tumor, metastatic sites and survival.

The primary end point was PFS, and the secondary end points were overall survival, objective response rate and treatment toxicity.

Adverse events were estimated according to the CTCAE version 6.

Agreement of the Mansoura Faculty of Medicine, institutional review board MFM IRB (R.24092791) has been obtained.

Inclusion criteria:

Patients with EGFR-mutated ex19del mutation and EGFR L858R mutation metastatic NSCLC.

Exclusion criteria: History of interstitial lung disease, uncontrolled medical illness, or inadequate bone marrow reserve or organ function, histopathologic tumors other than NSCLC and early stage NSCLC.

Statistical analysis:

Data was entered and analyzed using IBM-SPSS software Version 27.0. Also, Qualitative data was presented as frequency (N) and percentage (%). Quantitative data was initially tested for normality by Shapiro-Wilk's test with data being normally distributed if $p>0.050$. Quantitative data was presented as mean ± standard deviation (SD). For Survival analysis, Kaplan-Meier survival curves were used to estimate the probability of PFS & OS. Results were considered as statistically significant if p-value ≤ 0.050.

Results

About 85% of patients were male, the median age was 61 years, 95.3% of patients were found to have adenocarcinoma, 61.9% expressed EGFR ex19del mutation and 38.1% an EGFR L858R mutation, nearly 38% had brain metastasis and about 71.4% of patients presented with WHO performance status (PS). The patients characteristics are presented in Table (1).

The ORR was 76.2%. Complete response was observed in 4.8%, while 71.4% had partial response Table (2).

Table (1): Patients characteristics.

Characteristics	No. (%)
Age (years):	
Median	61
Range	(45-76)
Sex:	
Male	18 (85.7%)
Female	3 (14.3%)
ECOG performance status:	
0	1 (4.8%)
1	15 (71.4%)
2	5 (23.8%)
Histology:	
Adenocarcinoma	20 (95.3%)
Large cell ca	1 (4.8%)
EGFR mutation:	
ex19del	13 (61.9%)
L858R	8 (38.1%)
Met., site:	
Lung	9 (42.9%)
Liver	4 (19.1)
Bone	16 (76.2%)
CNS	8 (38.1%)
Adrenal	3 (14.3%)

Table (2): Tumor response.

Response	No.	%
Complete response	1	4.8
Partial response	15	71.4
Stable disease	4	19.1
Progressive disease	1	4.8

The median PFS was 17 months (95%CI 13.5-20.5), while the median OR was 22 months (95%CI 15.9-28.1). The 1year PFS was 64% and, while the year OS was 84% Figs. (1,2).

The commonest adverse effects (AEs) were hematologic toxicity. The most common non hematologic AEs included alopecia (62%), diarrhea (48%), nail toxicity (47.6%) and nausea (43.4%) Table (3).

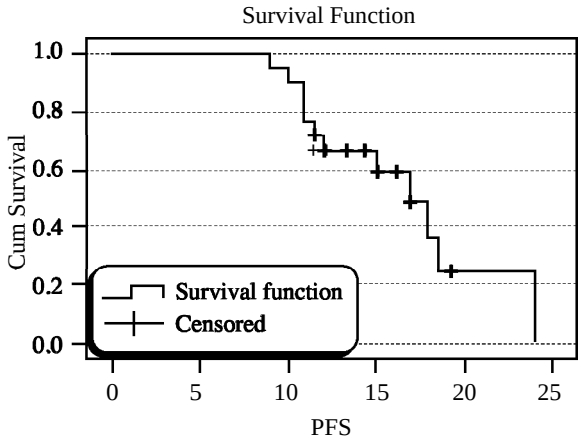

Fig. (1): Kaplan Meier survival curve of PFS.

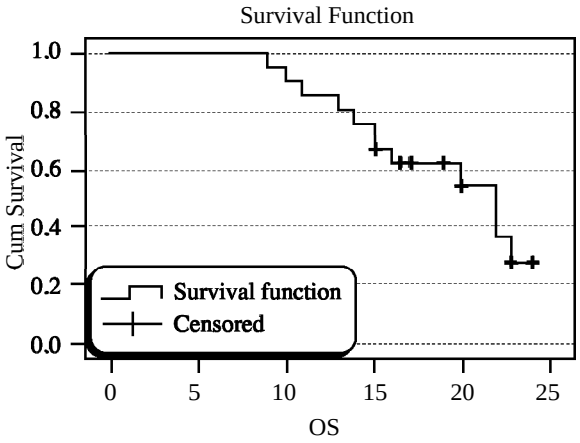

Fig. (2): Kaplan Meier survival curve of OS.

Table (3): Treatment-related toxicity.

Toxicities	Grade I		Grade II		Grade III		Grade IV	
	No.	%	No.	%	No.	%	No.	%
Haematological:								
Anaemia	12	57.1	9	42.9	3	14.8	0	0
Neutropenia	14	66.7	6	28.6	4	19.1	0	0
Thrombocytopenia	5	23.8	2	9.5	2	9.5	0	0
Non-hematological:								
Nausea	6	28.6	3	14.8	0	0	0	0
Alopecia	8	38.1	5	23.9	0	0	0	0
Diarrhea	7	33.3	3	14.8	0	0	0	0
Pneumonitis	1	4.8	0	0	0	0	0	0
Nail toxicity	10	47.6	0	0	0	0	0	0
Skin rash	1	4.8	0	0	0	0	0	0

Discussion

According to the cancer statistics, the incidence and death rates of lung cancer rank 2nd and 1st in all cancers, respectively *[15]*.

Patients are usually presented with advanced stages with restricted treatment modalities and bad prognosis. Lung cancer treatment has gained world attention because of its poor 5-year survival which is <15% *[16]*.

Fifteen percent of Caucasians and fifty percent of Asian patients presented with advanced stage NSCLC expressed EGFR mutations *[17]* these mutations, the 19 exon deletion and the 21 exon mutation of L858R represented 90% of EGFR mutations *[17]*.

Osimertinib has proved efficacy as a 1st line treatment in advanced NSCLC patients with EGFR TKI-mutations and had an acceptable safety *[18]*.

Tagrisso at a dose of 80mg once daily proved efficacy as a first line treatment in comparison to EGFR tyrosine kinase inhibitors as erlotinib or gefitinib in a randomized, double-blinded FLAURA trial which included 556 patients with advanced NSCLC, EGFR mutation *[7]*.

In the FLAURA trial, nearly 38% of patients were male, with a median age of 64 years, most of them (98.5%) had adenocarcinoma, 95% presented with distant metastasisvs only 5% with locally advanced stage, 63% expressed EGFR ex19del mutation and 37% EGFR L858R mutation, approximately, 21% presented withbrain metastasis, and about 41 and 59% of patients had a PS of 0 & 1

[7]. Treatment was maintained until progression or unacceptable toxicity. Osimertinib represented a significant $p<0.001$ prolongation of median PFS in comparison to standard EGFR TKI *[7]*.

In LAURA, they involved EGFR-mutated, stage III NSCLC patients. Two hundred & sixteen patients who received chemoradio therapy were randomly included to receive Tagrisso (143 patients) or placebo (73 patients). The median PFS was 39.1 months in Tagrisso group vs 5.6 months in placebo *[19]*.

The percent of surviving patients & free from progression at year, was 74% (95% CI, 65 to 80) in Tagrisso groupvs 22% in placebo group. The 3 year OS was 84% with osimertinib and 74% with placebo. The rate of grade 3 toxicity or higher was 35% in the Tagrisso group vs 12% in the placebo group; pneumonitis G1 & 2 was recorded in 48% & 38%, respectively *[19]*.

The FLAURA trial, supported by data phase 1/2 AURA trial, which included patients with EGFR mutation-positive NSCLC *[11]*. The first cohort included thirty patients who received Tagrisso 80mg once a day, the ORR was 67%, the disease control rate was 93% *[11]*. The second cohort included 30 patients received Tagrisso 160mg once daily, the ORR was 87%, 100% had controlled disease, the median PFS was 22.1 months *[11]*.

In FLAURA trial in patients with provedbrain metastasis, Tagrisso showed PFS prolongation in comparison to with standard EGFR TKI, median brain PFS has not been reached vs. 13.9 months. The ORR in the Tagrisso vs standard TKI group were 57% & 40%, with an odds ratio 2.0, $p= 0.053$. The median response duration in the Tagrisso group was not obtained vs 14.4 monthsin the standard TKI group *[9]*.

FLAURA2 is a randomized, open-label, multi-center, global Phase III trial of 1st-line treatment of stage IIIB-IIIC or metastatic, EGFR mutation positive NSCLC. Patients were treated with oral Tagrisso 80mg once daily with pemetrexed at a dose of 500mg/m^2 plus cisplatin at a dose of 75mg/m^2 or carboplatin (AUC5) every 3 weeks for 4 cycles, followed by osimertinib with pemetrexed maintenance every 3 weeks *[13]*. Fifty-seven patients were randomized. The PFS showed significant prolongation in the combination group as compared to the Tagrisso group, $p<0.001$. At 2 year, 57% of patients in the combined group vs 41% of those in the Tagrisso group were surviving & free from progression *[13]*.

An objective response was detected in 83% of patients in the combined group vs 76% of patients in the Tagrisso group; with a median duration ofresponse 24 months and 15.3 months, respectively *[13]*.

The FDA has approved osimertinib plus platinum-based chemotherapy for treatment of patients with locally advanced or stage IVNSCLC expressing EGFR exon 19 deletions or exon 21 L858R mutations *[20]*.

In the current trial, the PFS and OS were prolonged in comparison to survival data in previous trials of stage 4 NSCLC whether treated with chemotherapy or immunotherapy. The median PFS for patients was 17 months (95% CI 13.5-20.5), while the median OS was 22 months (95% CI 15.9-28.1). The 1 year PFS was 64% and, while the 1 -year OS was 84% figure. A trial has compared chemotherapy and immunotherapy, the median OS in the immunotherapy arm was 16.4 months vs 11.6 months in the chemotherapy arm *[21]*.

In the current work, most of adverse events were of GI & II and tolerable, G 3 toxicity was nearly 34%, similarly, most of adverse events expressed with osimertinib were mild to moderate and did not necessitate therapy interruption, G 3 toxicity or higher was 35% in the osimertinib group vs 12% in the placebo group *[19]*.

Conclusion:

first-line treatment with osimertinib plus a platinum-based chemotherapy improved progression-free survival in patients with EGFR-mutated metastatic NSCLC.

Limitations: The retrospective design of the study and the small sample size.

References

1- ASCO: Lung Cancer - Non-Small Cell: Introduction. Available at: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/types-treatment. Accessed February 2024.

2- LUN Gevity Foundation, 2024. Types of Lung Cancer. Available at: https://lungevity.org/for-patients-caregivers/lung-cancer-101/types-of-lung-cancer. Accessed February 2024.

3- American Cancer Society,2024. What Is Lung Cancer? Available at: https://www.cancer.org/cancer/lung-cancer/about/what-is.html#:~:text=About%2080%25%20to%2085%25%20of,(outlook)%20are%20often%20similar. Accessed February 2024.

4- CROSS D.A., et al.: AZD9291, an Irreversible EGFR TKI, Overcomes T790M-Mediated Resistance to EGFR Inhibitors in Lung Cancer. Cancer Discov., 4 (9): 1046-1061, 2014. doi: 10.21037/tlcr.2019.06.01. [PMC free article] [PubMed] [CrossRef] [Google Scholar].

5- American Cancer Society: Lung cancer survival rates. https://www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/survival-rates.html, 2024.

6- World Health Organisation: International Agency for Research on Cancer. Lung Fact Sheet. Available at: https://

gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf. Accessed February 2024.

7- SORIA J.C., OHE Y., VANSTEENKISTE J., et al.: Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N. Engl. J. Med., 378 (2): 113–25, 2018.

8- PLANCHARD D., BOYER M., LEE J.S., et al.: Osimertinib vs standard of care (SOC) EGFR-TKI as first-line therapy in patients (pts) with untreated EGFRm advanced NSCLC: FLAURA post-progression outcomes [abstract no. 128O]. J. Thorac. Oncol., 13 (4 Suppl): S72–3, 2018.

9- VANSTEENKISTE J., REUNGWETWATTANA T., NAKAGAWA K., et al.: CNS response to osimertinib vs standard of care (SoC) EGFR-TKI as first-line therapy in patients (pts) with EGFR-TKI sensitising mutations (EGFRm)-postive advanced non-small cell lung cancer (NSCLC): Data from the FLAURA study [abstract]. In: European Society of Medical Oncology, Asia Conference. 2017.

10- LEIGHL N., KARASEVA N., NAKAGAWA K., et al.: Patient-reported outcomes from FLAURA: Osimertinib versus standard of care (SOC) epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) in patients with EGFR-mutated advanced non-small cell lung cancer (NSLC) [abstract no. 139PD]. J. Thorac. Oncol., 13 (4 Suppl): S81–S82, 2018.

11- RAMALINGAM S.S., YANG J.C., LEE C.K., et al.: Osimertinib as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer. J. Clin. Oncol., 36 (9): 841–9, 2018.

12- Tagrisso plus chemotherapy granted Priority Review in the US for patients with EGFR-mutated advanced lung cancer. News release. Astra Zeneca. October 16, 2023. Accessed October 16, 2023. https://bit.ly/3ZUDUm9.

13- JÄNNE PA, PLANCHARD D., CHENG Y., et al.: Osimertinib with / without platinum-based chemotherapy as first-line treatment in patients with EGFRm advanced NSCLC (FLAURA2). Presented at: International Association for the Study of Lung Cancer 2023 World Conference on Lung Cancer; September 9-12, 2023; Singapore. Abstract PL03.13.

14- NCCN, National Comprehensive Cancer Network® (NCCN®): Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer Version 1.2024.© National Comprehensive Cancer Network, Inc., 2024.

15- SIEGEL R.L., MILLER K.D., FUCHS H.E. and JEMAL A.: Cancer statistics, 2022. CA Cancer J. Clin., 72 7–33, 2022. doi: 10.3322/caac.21708. [PubMed] [CrossRef] [Google Scholar].

16- HERBST R.S., MORGENSZTERN D. and BOSHOFF C.: The biology and management of non-small cell lung cancer. Nature, 553: 446–454, 2018. doi: 10.1038/nature25183. [PubMed] [CrossRef] [Google Scholar].

17- SUN C., GAO W., LIU J., CHENG H. and HAO J.: FGL1 regulates acquired resistance to Gefitinib by inhibiting apoptosis in non-small cell lung cancer. Respir. Res., 21: 210, 2020. doi: 10.1186/s12931-020-01477-y. [PMC free article] [PubMed] [CrossRef] [Google Scholar].

18- TAN C.S., KUMARAKULASINGHE N.B., HUANG Y.Q., ANG Y.L.E., CHOO J.R., GOH B.C. and SOO R.A.: Third generation EGFR TKIs: Current data and future directions. Mol. Cancer, 17: 29, 2018. doi: 10.1186/s12943-018-0778-0. [PMC free article] [PubMed] [CrossRef] [Google Scholar].

19- LU S., KATO T., DONG X., et al.: The LAURA Trial Investigators,2024. Osimertinib after Chemoradiotherapy in Stage III EGFR-Mutated NSCLC. NEJM; Published online 2 June 2024. DOI: 10.1056/NEJMoa2402614.

20- FDA: FDA approves osimertinib with chemotherapy with chemotherapy for EGFR-mutated non-small cell lung cancer.Accessed February 16, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-osimertinib-chemotherapy-egfr-mutated-non-small-cell-lung-cancer, 2024.

21- BELAROUSSI Y., BOUTEILLER F., BELLERA C., PASQUIER D., PEROL M., DEBIEUVRE D., FILLERON T., GIRARD N., SCHOTT R., MATHOULIN-PÉLISSIER S., MARTIN A.L. and COUSIN S.: Survival outcomes of patients with metastatic non-small cell lung cancer receiving chemotherapy or immunotherapy as first-line in a real-life setting, Scientific Reports, Volume 13, Article number: 9584, 2023.

أوزيميرتينيب مع العلاج الكيميائى القائم على البلاتين فى سرطان الرئة غير صغير المنتشر المتحور بمستقبل عامل نمو البشرة (EGFR)

الخلفية: أوزيميرتينيب هو مثبط كيناز التيروزين لمستقبل عامل نمو البشرة من الجيل الثالث فى مرضى سرطان الرئة غير صغير الخلايا النقيلى المتحور بمستقبل عامل نمو البشرة. المرض تشير الأدلة إلى أن أوزيميرتينيب بالإضافة إلى العلاج الكيميائى قد يطيل من فترة البقاء الخالى من تقدم المرض. (EGFR)

المرضى والطرق: هذا تحليل رجعى شمل ٢١ مريضًا مصابًا بسرطان الرئة غير صغير الخلايا النقيلى المتحور بمستقبل عامل نمو البشرة، عولجوا بعلاج مركب من أوزيميرتينيب بجرعة ٨٠ مجم مرة واحدة يوميًا بالإضافة إلى جيمسيتا بين بجرعة ١٠٠٠ مجم/م٢ فى اليوم الأول واليوم الثامن وكاربوبلاتين فى منطقة تحت المنحنى ٥ كل ثلاثة أسابيع لمدة أربع دورات.

النتائج: كان متوسط البقاء الخالى من التقدم للمرضى ١٧ شهرًا، بينما كان متوسط عمر المرضى ٢٢ شهرًا وكان معدل البقاء الخالى منتقدم. المرضعند عام ٦٤٪، بينما كان معدل البقاء الإجمالى عند عام ٨٤٪. وكان معدل الاستجابة الموضوعى ٧٦,٢٪. وكانت الآثار الجانبية الأكثر شيوعًا هى السمية الدموية.

الاستنتاجات: يوفر العلاج الأولى باستخدام أوزيميرتينيب بالإضافة إلى العلاج الكيميائى إطالة فترة البقاء الخالى من تقدم المرض لدى المرضى المصابين بسرطان الرئة غير صغير الخلايا النقيلى المتحور بجين عامل نمو البشرة.