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ORIGINAL RESEARCH ARTICLE

Representativeness of Phase III Trial for Osimertinib in Pretreated Advanced EGFR-Mutated Non-small-cell Lung Cancer Patients and Treatment Outcomes in Clinical Practice

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Abstract

Background Overall survival (OS) data of osimertinib in pretreated non-small-cell lung cancer (NSCLC) in real-world practice is limited, and treatment benefits for patients not represented in the pivotal trials (ineligible) are unclear.

Objective To determine the representativeness of the AURA3 trial for NSCLC patients treated with osimertinib in a real-world setting and to determine outcomes of patients who were represented in the AURA3 trial (eligible) and those who were ineligible.

Methods Advanced NSCLC patients receiving post first-line osimertinib were included in this retrospective study and were divided into two groups based on eligibility criteria of the AURA3 trial. Progression-free survival (PFS) and OS were estimated using the Kaplan–Meier method. Cox models were used to estimate the association of eligibility criteria with OS.

Results 328 patients were included; 126 (38%) patients were eligible and 202 (62%) patients were ineligible. The most common ineligibility reasons were the number of earlier treatment lines and an Eastern Cooperative Oncology Group performance status (ECOG PS) > 1. PFS of eligible and ineligible patients was not statistically different (8.0 vs. 5.8 months, $p = 0.062$). Eligible patients had a longer OS (24.0 vs. 15.4 months, $p = 0.001$) compared to ineligible patients. ECOG PS was the best predictor for OS. An ECOG PS of 1 was already associated with poorer survival compared to an ECOG PS of 0 (hazard ratio 1.54; $p = 0.016$).

Conclusion The majority of the study population was not represented in the AURA3 trial. Survival outcomes of eligible patients are in concordance with the AURA3 trial, while OS of ineligible patients was significantly shorter compared to eligible patients.

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Key Points

Real-world outcomes of patients eligible for AURA3 were similar to AURA3 results.

Survival of patients in poor clinical condition was shorter, but still impressive.

Performance status was the best predictor for survival.

1 Introduction

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) have been provided to patients with advanced stage non-small-cell lung cancer (NSCLC) with

activating EGFR mutations for almost two decades now [1, 2]. The use of EGFR TKIs is, however, accompanied by the acquisition of drug resistance, meaning that all patients will eventually develop disease progression during treatment. The most commonly observed mechanism of resistance to first- and second-generation EGFR TKI treatment is the T790M mutation in EGFR exon 20, which is found in 50–60% of the NSCLC patients treated with a first- or second-generation EGFR TKI [3].

The third-generation EGFR TKI, osimertinib, was the first to overcome this T790M resistance mutation. It showed a significantly longer progression-free survival (PFS) compared to platinum-pemetrexed chemotherapy as second-line treatment after first-line treatment with a first-generation EGFR TKI in the AURA3 trial (NCT02151981) [4]. In the overall survival (OS) analysis, no statistically significant difference was observed between the study arms. This was attributed to a high crossover rate of patients from the chemotherapy arm to the osimertinib arm, suggesting that patients who progressed on platinum-pemetrexed chemotherapy also benefitted from osimertinib treatment as third-line treatment [5].

In addition to the AURA3 trial determining the efficacy of second-line osimertinib treatment, it is of relevance to perform observational cohort studies determining the effectiveness in a real-world setting [6]. The study population of randomized clinical trials (RCTs) is generally in a better health state compared to patient populations in clinical practice. This is the result of strict inclusion and exclusion criteria applied in RCTs to improve the valid estimation of treatment effects. The results of RCTs may, therefore, not be representative for patients in clinical practice [7–9]. In addition, treatment benefits are unclear for patients who were not represented in the RCTs [10].

Therefore, our study aimed to determine the representativeness of the AURA3 trial for NSCLC patients treated with osimertinib in routine clinical practice and to determine treatment outcomes of patients who were represented in the AURA3 trial (eligible) and those who were not represented (ineligible).

2 Materials and Methods

2.1 Patients

This retrospective observational cohort study was conducted at the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital (NKI-AvL), Amsterdam. All patients with advanced stage EGFR mutation-positive NSCLC, who received osimertinib as post first-line treatment between July 2015 and October 2020 were included in this study. Patients who participated in the AURA3 trial were excluded. No other exclusion criteria were applied.

The eligibility criteria of the AURA3 trial were used to assign patients to either the eligible group or the ineligible group [4]. Patients were assigned to the ineligible group if they met one or multiple of the following criteria:

- Negative T790M status confirmed by either a circulating tumor DNA test or a tumor biopsy.
- First-line treatment was not an EGFR TKI or more than one prior treatment line was given.
- Eastern Cooperative Oncology Group performance status (ECOG PS) of > 1.
- Brain metastases that were unstable, symptomatic, or for which glucocorticosteroids were given within 4 weeks of start of osimertinib treatment.

Data on patient characteristics, tumor characteristics, treatments, and outcomes were extracted from the individual electronic medical records. The data cutoff was 8 March 2021. The conduct of this observational study was approved by the Investigational Review Board of the NKI-AvL and patients' permission to use their data for scientific research was obtained.

2.2 Outcomes

The primary endpoints were PFS and OS. PFS was defined as the time from treatment initiation until the first signs of disease progression by either radiology or clinical signs, or death by any cause in the absence of progression. Patients were evaluated for disease status every 3 months and in case of clinical symptoms or worsening of symptoms. OS was defined as the time from treatment initiation until death by any cause. In addition, it was determined whether patients experienced dose-limiting toxicities, which were defined as the need for dose reductions, dose interruptions, or permanent discontinuation of treatment due to adverse events.

2.3 Statistical Analysis

Descriptive statistics were reported using frequencies for categorical data and medians for continuous data. Median PFS and OS were calculated using the Kaplan–Meier method, including their 95% confidence intervals (CIs). Patients who did not have an event of progression or death were censored at the time of the last radiology scan or last follow-up date. A two-sided p-value < 0.05 was considered statistically significant. In addition, OS of patients with brain metastases and leptomeningeal (LM) metastases were determined regardless of eligibility group. The median follow-up time was estimated with the reverse Kaplan–Meier method [11].

Univariable and multivariable Cox proportional hazards regression models were used to estimate the association of exclusion criteria and other covariates with OS using the entire study population. The backwards elimination procedure was used starting with all variables of interest to determine the final multivariable model. A two-sided p-value < 0.05 was considered statistically significant. The proportional hazard assumption in the model was investigated using the scaled Schoenfeld residuals. All statistical analyses were performed in R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

3 Results

3.1 Characteristics of the Study Population

In total 328 patients were included in this study. Patient characteristics are depicted in Table 1. Of the patient population, 202 (62%) patients were considered to be ineligible. The majority of ineligible patients met one ineligibility criteria. Thirty-nine (19%) patients met two ineligibility criteria, whereas 19 (9%) met more than two of these criteria. The most common causes for ineligibility were the number of earlier treatment lines followed by an ECOG PS > 1 (Table 2).

3.2 Treatment Outcomes

The median duration of follow-up was 27.8 months (range 0–56 months). At the time of data cutoff, 93 patients were still on osimertinib treatment.

Disease progression occurred in 110 (87%) patients in the eligible group and in 176 (87%) patients in the ineligible group. Median PFS of the eligible group was not statistically significantly longer compared to the ineligible group, which was 8.0 months (95% CI 6.5–10.8) and 5.8 months (95% CI 4.4–8.0), respectively with a p-value of 0.062 (Fig. 1A).

Death was reported for 199 (61%) patients: 68 (54%) in the eligible group and 131 (65%) in the ineligible group. Median OS was 24.0 months (95% CI 21.0–29.5) in eligible patients and 15.4 months (95% CI 12.5–19.6) in ineligible patients, with a p-value of 0.001 (Fig. 1B). Patients with brain metastases had a median OS of 18.2 months (95% CI 13.5–21.8) and patients with LM metastases had a median OS of 10.1 months (95% CI 6.5–21.4).

The univariable and multivariable Cox models for the association of exclusion criteria and OS are shown in Table 3. Age, sex, LM metastases, ECOG PS, and EGFR mutation were relevant covariates and were taken into account in the multivariable model. Brain metastasis, T790M status, number of previous treatment lines, and smoking status did not have a significant effect in the

Table 1 Patient characteristics of eligible and ineligible patients

	Eligible ($n = 126$)	Ineligible ($n = 202$)
Age, years		
Median (range)	66 (42–87)	63 (24–85)
Female sex [no. (%)]	90 (72)	150 (74)
Smoking status [no. (%)]		
Never	74 (59)	123 (61)
Ever	51 (40)	75 (37)
Unknown	1 (1)	4 (2)
Histologic type [no. (%)]		
Adenocarcinoma	119 (94)	177 (88)
Other	7 (6)	25 (12)
EGFR mutation [no. (%)]		
Exon 19 deletion	79 (63)	117 (58)
Exon 21 L858R	42 (33)	59 (29)
Other	5 (4)	22 (11)
Unknown	–	4 (2)
T790M mutation [no. (%)]		
Positive	119 (94)	127 (63)
Negative	–	28 (14)
Unknown	7 (6)	47 (23)
Metastases [no. (%)]		
Brain	14 (11)	104 (52)
Leptomeningeal	3 (2)	38 (19)
Prior EGFR TKI use [no. (%)]		
Erlotinib	87 (69)	132 (65)
Gefitinib	30 (24)	48 (24)
Afatinib	9 (7)	32 (16)
Rociletinib	–	10 (5)
ECOG PS [no. (%)]		
0	42 (33)	48 (24)
1	82 (65)	81 (40)
2	–	51 (25)
3 or 4	–	22 (11)
NA	2 (2)	–

ECOG PS Eastern Cooperative Oncology Group performance status, *EGFR* epidermal growth factor receptor, *TKI* tyrosine kinase inhibitor

multivariable Cox model and were left out. Of the exclusion criteria applied in this study, a higher ECOG PS was correlated strongest with poorer survival, whereas sex, the presence of LM metastases, and the type of EGFR mutation also influenced OS significantly.

3.3 Toxicity and Adverse Events

There were no significant differences in the occurrence of dose-limiting toxicities between eligible and ineligible patients. The osimertinib dose was reduced in 35 (10.7%)

Table 2 Characteristics on which patients were deemed ineligible

Earlier treatment	110 (54%)
1[a]	12 (6%)
2	71 (35%)
3 or more	27 (13%)
ECOG PS > 1	73 (36%)
Brain metastases[b]	70 (35%)
Negative T790M status	28 (14%)
Total reasons for ineligibility	281 (139%)

ECOG PS Eastern Cooperative Oncology Group performance status

[a]First-line treatment was not with an earlier generation epidermal growth factor receptor tyrosine kinase inhibitor

[b]Unstable, symptomatic, or requiring corticosteroid use within 4 weeks of start osimertinib treatment

patients due to adverse events. Gastrointestinal toxicity, mainly diarrhea, was the reason for dose reductions in almost half of these cases. Treatment was interrupted in 19 (5.8%) patients, due to diarrhea, skin toxicity, reduced renal function, and pneumonitis. After dose interruption, the treatment was restarted at the initial dose or at a reduced dose. Osimertinib treatment was permanently discontinued in six (1.8%) patients. Three of them had an osimertinib-induced pneumonitis. The other reasons for discontinuation were cardiotoxicity, hepatotoxicity, and a combination of gastrointestinal symptoms with other adverse events, which were deemed unbearable by the patient.

4 Discussion

This study investigated the clinical outcomes of pretreated EGFR mutation-positive NSCLC patients treated with osimertinib as post first-line treatment in a real-world setting. Approximately 60% of this study population was deemed ineligible according to the most important AURA3 trial eligibility criteria on which the registration of osimertinib for this indication was based. High ineligibility rates were also seen in other studies, in which the main reasons were poor ECOG PS, unstable or symptomatic brain metastases and specification of previous treatment lines [7–10].

For eligible patients, median OS was similar to the results obtained in the AURA3 trial for the non-Asian population (median OS 20.3; 95% CI 18.3–26.8) [5]. In addition to this trial, the results for patients with LM metastases closely resembled the results of the BLOOM trial (median OS 11.0; 95% CI 8.0–18.0) in which the efficacy of double dosage osimertinib was assessed in patients with LM metastases [12]. In another trial assessing the efficacy of double dosage osimertinib in patients with brain and LM metastases, the results for patients with brain metastases (median OS 16.9; 95% CI 7.9–NA) were similar to our results, whereas results of patients with LM metastases (median OS 13.3; 95% CI 9.1–NA) were slightly more favorable than ours [13]. However, it has to be noted that caution is still warranted in the comparison with the latter two trials due to differences in study populations, as both trials were performed in an Asian population with ECOG PS ≤ 2.

Treatment with osimertinib also showed clinical benefit for ineligible patients when comparing survival outcomes to literature. In a cohort study of Polish NSCLC patients, clinical outcomes of first- and second-generation EGFR TKIs as first-line treatment were studied. Median PFS and OS were 11.9 and 19.4 months, respectively, from the time of EGFR TKI treatment initiation, implying a duration of 7.5 months from the initiation of second-line treatment or best supportive care until death [14]. In a Swedish cohort study with NSCLC patient who were treated with first- and second-generation EGFR TKI treatment, the median OS was 15.5 months from the time of diagnosis. The majority of this cohort received a first- or second-generation EGFR TKI as first-line treatment, whereas patients who were diagnosed in the early years of the cohort study may have received chemotherapy as first-line treatment followed by an EGFR TKI as second-line treatment [15]. Taking into consideration that the ineligible patients in our study are the patients in clinical practice with the poorest health and that some of these ineligible patients received osimertinib as third-line treatment or further lines of treatment, the median OS observed for ineligible patients in our study is impressive.

In the multivariable Cox model, a higher ECOG PS was strongly correlated with a shorter survival in which the hazard ratios roughly doubled per change in ECOG PS. This same trend was seen in a prognostic model based on ECOG PS alone of Jang et al. [16]. Another noteworthy covariate is the difference in sex. Although women generally have better survival outcomes in NSCLC than men, the difference in this study seemed to be larger as compared to other studies [17, 18].

With regard to dose-limiting toxicities, it appears that dose reductions occur more often in clinical practice compared to the AURA3 trial, in which dose interruptions were more common compared to dose reductions. In the AURA3 trial, dose interruptions were applied first when patients experienced grade 3 or higher toxicities and/or unacceptable toxicity of any grade, after which osimertinib was restarted at the initial or a reduced dose. After additional analyses of the AURA and AURA2 studies, it became clear that osimertinib did not show an exposure-efficacy relationship at the approved dosing regimen, while it does show an exposure-toxicity relationship [19]. Therefore, dose reductions in clinical practice were applied more often to reduce toxicity, while the effectiveness of osimertinib was preserved.

Fig. 1 Kaplan–Meier curves for **a** progression-free survival (PFS) and **b** overall survival (OS) according to eligibility. *CI* confidence interval
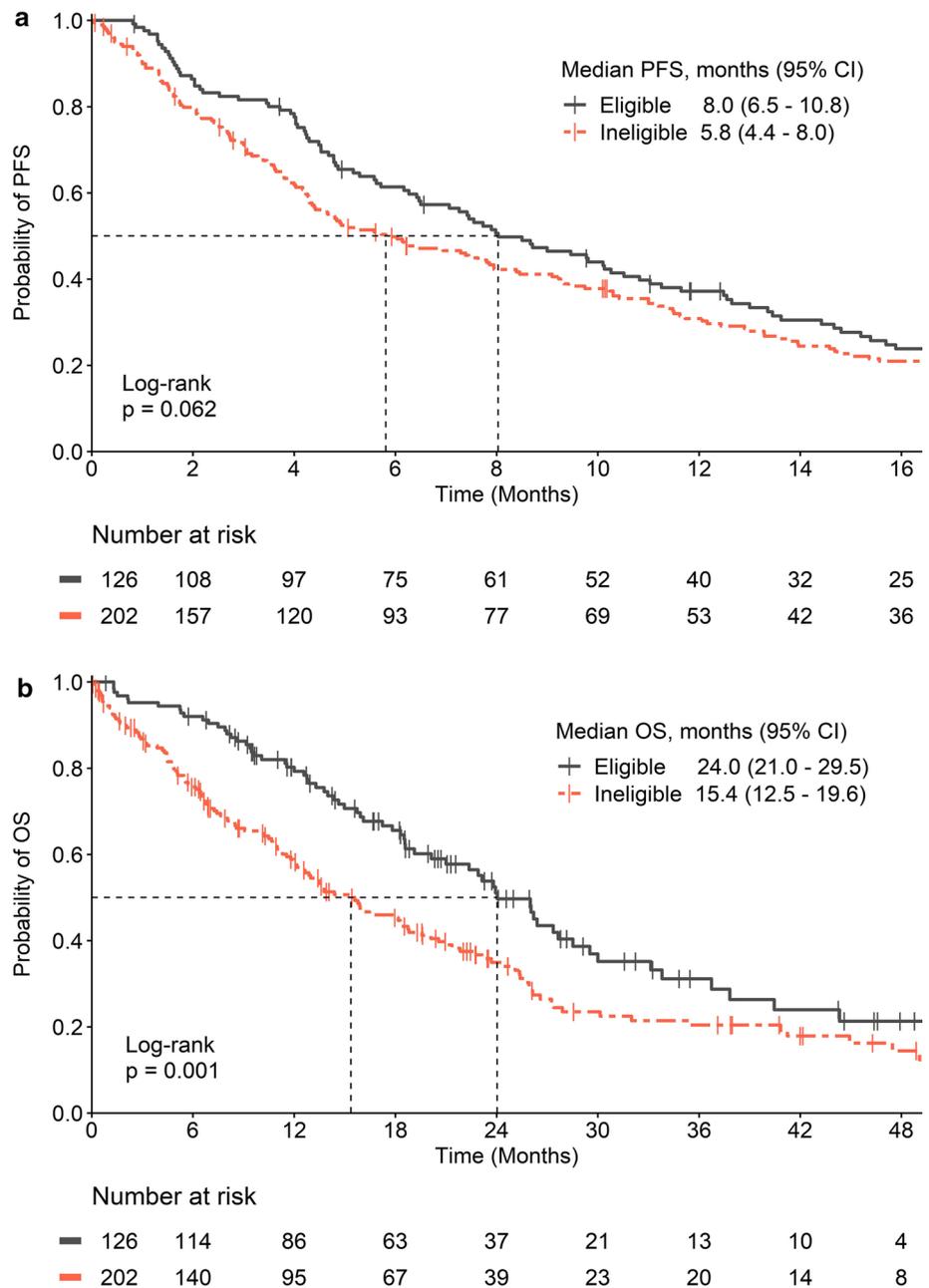
The number of included patients is relatively large, which is a strength of this study. Despite the large study population, data from other centers are needed to determine whether data are in accordance with ours and to study the differences between ethnicities in a real-world setting [5]. The most important limitation of this study is its retrospective nature, complicating the application of all eligibility criteria of the AURA3 trial. In the current study, patients were deemed ineligible only if this was apparent from the available data. Due to this conservative approach, it is possible that even a larger proportion of the patient population was actually ineligible, and that the benefits of osimertinib treatment in both groups is underestimated in this study.

As there seems to be a large gap between patient populations in RCTs and the patient population in clinical practice, further real-world studies are needed to determine the effectiveness of treatments in ineligible patients to support decision making in clinical practice. This can be quite challenging since oncology is a fast-developing field and the standard of care changes accordingly. Studies comparing the previously standard-of-care treatment with the newly introduced treatment are prone to bias as other changes in the standard of care may act as confounders, which cannot be accounted for to the full extent [6]. In the

Table 3 Univariable and multivariable Cox model of the association of exclusion criteria and covariates on overall survival

	Univariable			Multivariable		
	n	HR (95% CI)	*p*-value	*n*	HR (95% CI)	*p*-value
CNS						
Absent	198	1				
Asymptomatic	74	1.13 (0.80–1.60)	0.473			
Symptomatic	56	2.07 (1.41–3.03)	< 0.001			
LM						
Absent	287	1		282	1	
Present	41	2.04 (1.36–3.04)	0.001	40	2.23 (1.42–3.49)	< 0.001
ECOG PS						
0	90	1		88	1	
1	163	1.52 (1.07–2.14)	0.018	161	1.54 (1.08–2.19)	0.016
2	51	2.84 (1.86–4.35)	< 0.001	51	3.02 (1.96–4.65)	< 0.001
3 or 4	22	6.49 (3.58–11.8)	< 0.001	22	6.50 (3.46–12.2)	< 0.001
T790M status						
Positive	246	1				
Negative	28	1.65 (0.99–2.73)	0.053			
Unknown	54	1.83 (1.26–2.67)	0.002			
Treatment lines						
1	230	1				
2	71	0.88 (0.63–1.24)	0.469			
3 or more	27	1.48 (0.94–2.33)	0.090			
Age (years)	328	1.01 (1.00–1.02)	0.104	322	1.02 (1.01–1.03)	0.003
Sex						
Male	88	1		85	1	
Female	240	0.59 (0.44–0.80)	0.001	237	0.54 (0.39–0.74)	< 0.001
EGFR mutation						
Exon 19 del	196	1		194	1	
Exon 21 L858R	101	1.38 (1.02–1.88)	0.038	101	1.52 (1.12–2.08)	0.008
Other	27	3.14 (2.01–4.90)	< 0.001	27	3.46 (2.17–5.52)	< 0.001

CI confidence interval, *CNS* central nervous system, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EGFR* epidermal growth factor receptor, *HR* hazard ratio, *LM* leptomeningeal

case of osimertinib, it would also be of interest to determine the effectiveness of first-line treatment in patients who were not represented in the respective Phase III trial, as treatment outcomes are potentially even better than the results of the ineligible patients in our study.

In addition, future research investigating the use of observational data as synthetic control arms in RCTs would be of interest, especially since only a limited set of exclusion criteria was applied in our study compared to the AURA3 trial and the results of eligible patients were similar to the AURA3 trial. The main advantage of these synthetic controls is the need for a smaller study population in RCTs, in which more patients can be allocated to the intervention arm. A small proportion of patients can then be allocated to the control arm, which will be combined with observational data from clinical practice [20].

In conclusion, the majority of patients with EGFR mutation-positive NSCLC who received osimertinib as post first-line treatment at our institution were not represented in the AURA3 trial. The treatment outcomes of eligible patients are in accordance with the results of the AURA3 trial, while OS of ineligible patients was significantly shorter as compared to eligible patients. However, considering that these patients are in poorer health, the survival outcomes of ineligible patients are impressive.

Declarations

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