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Exploring the impact of patient-specific clinical features on osimertinib effectiveness in a real-world cohort of patients with *EGFR* mutated non-small cell lung cancer

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Abstract

Osimertinib is prescribed to patients with metastatic non-small cell lung cancer (NSCLC) and a sensitizing *EGFR* mutation. Limited data exists on the impact of patient characteristics or osimertinib exposure on effectiveness outcomes. This was a Dutch, multicenter cohort study. Eligible patients were ≥18 years, with metastatic *EGFR*m+ NSCLC, receiving osimertinib. Primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS) and safety. Kaplan-Meier analyses and multivariate Cox proportional hazard models were performed. In total, 294 patients were included. Primary *EGFR*-mutations were mainly exon 19 deletions (54%) and p.L858R point mutations (30%). Osimertinib was given in first-line (40%), second-line (46%) or beyond (14%), with median PFS 14.4 (95% CI: 9.4-19.3), 13.9 (95% CI: 11.3-16.1) and 8.7 months (95% CI: 4.6-12.7), respectively. Patients with low BMI (<20.0 kg/m^2) had significantly shorter PFS/OS compared to all other subgroups. Patients with a high plasma trough concentration in steady state ($C_{min,SS}$; >271 ng/mL) had shorter PFS compared to a low $C_{min,SS}$ (<163 ng/mL; aHR 2.29; 95% CI: 1.13-4.63). A significant longer PFS was seen in females (aHR = 0.61, 95% CI: 0.45-0.82) and patients with the exon 19 deletion (aHR = 0.58, 95% CI:

Abbreviations: (a)HR, (adjusted) hazard ratio; BMI, body mass index; C_{max}, maximum concentration of a drug in blood; $C_{min,SS}$, plasma trough concentration during steady state.; CNS, central nervous system; CT, computed tomography; CYP, cytochrome P450; DCR, disease control rate; EGFR(m+), epidermal growth factor receptor (mutation-positive); kg, kilogram; m, meter; mg, milligram; mL, milliliter; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; MREC, Medical Research Ethics Committee; ND, not determined; ng, nanogram; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; QD, once a day; RCT, randomized controlled trial; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; TP53, tumor protein P53.

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0.36-0.92). A trend towards longer PFS was seen for *TP53* wild-type patients, while age did not impact PFS. Patients with a primary *EGFR* exon 19 deletion had longer PFS, while a low BMI, male sex and a high $C_{min,SS}$ were indicative for shorter PFS and/or OS. Age was not associated with effectiveness outcomes of osimertinib.

KEYWORDS
age, BMI, first-line treatment, lung cancer, observational study, osimertinib, plasma trough concentration, real-world treatment

What's new?

Patients with non-small cell lung cancer (NSCLC) and a sensitizing epidermal growth factor receptor mutation (EGFRm+) potentially benefit from treatment with the third-generation tyrosine kinase inhibitor osimertinib. Here, the authors evaluated the impact of NSCLC patient characteristics on outcomes associated with osimertinib. In osimertinib-treated patients with metastatic EGFRm+ NSCLC, male sex, low body mass index and high steady state osimertinib plasma trough concentration were associated with shorter survival. Meanwhile, increased progression-free survival was linked to female sex and primary EGFR exon 19 deletion, suggesting that osimertinib treatment strategies can be tailored to improve outcomes among EGFRm+ NSCLC patients.

1 | INTRODUCTION

For patients with non-small cell lung cancer (NSCLC) and a sensitizing epidermal growth factor receptor mutation (*EGFR*m+), several tyrosine kinase inhibitors (TKIs) have been approved resulting in considerably improved treatment outcomes.[1] Osimertinib is a third generation EGFR-TKI approved for the treatment of *EGFR*m+ NSCLC. In the metastatic setting, it has been approved in the first line or upon progression on first/second generation EGFR-TKI, if a patient developed the *EGFR* p.T790M-mutation. Recently, osimertinib has been approved in the adjuvant setting for patients with completely resected *EGFR*m+ stage IB-IIIA NSCLC.[2-5] Osimertinib is given as a flat dose of 80 mg once daily (QD), irrespective of patient characteristics or individual drug exposure (indirectly measured by steady state plasma trough level [$C_{min,SS}$]).

The characteristics of patients treated in clinical practice often differ from patients included in clinical trials.[6] This may cause worse treatment outcomes, previously described as the efficiency-effectiveness gap.[7] Clinical trial data alone, often do not accurately reflect the effectiveness of a drug in the real-world setting, due to strict inclusion and exclusion criteria. Therefore, the effectiveness of osimertinib in the real world has been evaluated in multiple retrospective studies, in the first-line treatment,[8-14] second-line treatment or beyond.[15-27] As first-line studies were mainly performed in Asian patients, and 62% of all patients in the FLAURA-trial[3,8,10-14] were Asian, there is a lack of outcome data in Caucasian patients. The effect of some patient characteristics, such as primary *EGFR*-mutation or *TP53*-status, has been described before.[22,28] However, for various other patient and treatment characteristics, such as age, body mass index (BMI) and plasma trough concentration ($C_{min,SS}$), limited information on their effect on osimertinib outcomes has been described[10,29-32] while they have shown to significantly impact the effectiveness of other anticancer treatments.[33,34]

Therefore, in our study we aim to explore the impact of patient-specific clinical features on osimertinib treatment outcomes in a real-world setting, focusing on age, BMI and osimertinib $C_{min,SS,}$ in primarily Caucasian patients.

2 | METHODS

2.1 | Study design and patients

Our study was performed in four centers in the Netherlands: two academic (Maastricht University Medical Centre and Erasmus Medical Centre) and two large teaching centers (St Antonius and Amphia Hospital). All patients treated with osimertinib in regular care between 2 January 2016 and 3 January 2022 were selected. In addition, eligibility criteria were age 18 years or older, a diagnosis of advanced or metastatic *EGFR*m+ NSCLC and at least one response assessment after the start of osimertinib. The first prescription of osimertinib determined the index date, and patients were followed until they die, were lost to follow-up or reached the end of study (3 January 2022).

2.2 | Data collection

Data on the use of osimertinib was extracted from the pharmacy information systems of the participating hospitals or patients were identified through participation in a clinical study (START-TKI, NCT05221372). Clinical data at index date (defined as start of osimertinib treatment) was retrieved from the electronic medical records and included demographic information, smoking status, disease characteristics (including location of metastases and localization in the central nervous system (CNS), grade (locally advanced or metastatic), type of primary *EGFR*-mutation, *TP53*-

status), co-medication and prior received treatments. The *EGFR*-mutation was evaluated before the start of osimertinib treatment for patients who received osimertinib in the first line and was re-evaluated for patients who received osimertinib in the second-line or later, after progression on a first- or second-generation EGFR-TKI. In the patients who received osimertinib in a later line, *EGFR*-mutation analysis was performed to evaluate for the presence of the T790M-mutation, which is required to receive reimbursement for osimertinib in the Netherlands. All evaluation CT scans were retrospectively evaluated and scored using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, by an experienced radiologist and/or pulmonologist (GV, AB, SD).[35] Response evaluations were performed every 8 to 12 weeks with at least a chest CT. CNS involvement was evaluated in case of symptomatic presentation or on routinely performed scans. CNS involvement was scored as yes (CNS metastasis on MRI or CT scan), no (no CNS metastasis on MRI or CT scan) or unknown (no MRI or CT brain scan available). The quantification of osimertinib in plasma was done for research purposes. Plasma concentrations for osimertinib were included for analysis in our study if (a) the patient did not receive a dose-reduction or -interruption of osimertinib to ensure the consistent use of 80 mg daily osimertinib over the whole treatment period, (b) data regarding the exact moment of blood withdrawal and accurate time frame of osimertinib intake was available, (c) blood withdrawal was performed at least 15 days after the start of osimertinib treatment, to ensure steady state concentrations, (d) blood withdrawal was performed at least 6 hours after the last intake of osimertinib and (e) the withdrawal took place at least 3 months before progression, as an increase of plasma trough concentration was seen shortly before, around and after progression which could bias the osimertinib plasma level (Figure A4). During the first 6 hours after osimertinib intake, osimertinib is absorbed from the gastrointestinal tract, and the maximum plasma concentration (C_{max}) has not been reached. After achieving the C_{max}, osimertinib is primarily eliminated, and the plasma concentration could be extrapolated to the $C_{min,SS}$ using the method described by Wang et al.[36]

2.3 | Outcomes

The primary efficacy endpoint was progression free survival (PFS), which was defined as the time in months since the index date until the occurrence of progression of disease, according to RECIST v1.1[35] or all-cause death. Patients were censored if the patient was lost-to-follow-up or the end of study was reached. Secondary outcomes were overall survival (time since index date until death, OS), best overall response, objective response rate (ORR), disease control rate (DCR) and safety. For safety, all adverse events that led to a hospital admission, dose reduction, interruption or definitive stop of osimertinib were collected. Interruption of osimertinib treatment was defined as a stop of at least 1 week. ORR and DCR were scored for intracranial and extracranial response. The extracranial response was scored for all patients, while intracranial response was scored for all patients with a CNS metastasis at the start of osimertinib treatment and the possibility to select a CNS metastasis as lesion according to RECIST v1.1.

2.4 | Statistical analysis

Patient demographics, disease specific information, other baseline characteristics and safety data were summarized using descriptive statistics. The Kaplan-Meier method was used to calculate the median PFS (mPFS) and OS (mOS) of the overall patient population. Furthermore, treatment outcomes were evaluated for specific subgroups (age, BMI, $C_{min,SS}$, treatment line, primary *EGFR*-mutation and *TP53*-status at index date). The following subgroups were used in the Kaplan-Meier analyses and Cox proportional hazards models: age—<65, 65-69, 70-74 and ≥75 years, furthermore <70 vs ≥70 years; BMI—<20.0, 20.0-24.9, 25.0-29.9 and ≥30.0 kg/m^2 and for plasma trough concentration—<163, 163-271 and >271 ng/mL. The subgroups for age and BMI were selected based on classifications commonly used in clinical research, for example, subgroups of 5-unit points (years or kg/m^2). The classification for plasma trough concentration was selected based on the 25th and 75th percentile calculated from all plasma trough concentrations that were included in the analysis. Additionally, the plasma trough concentration was analyzed as continuous variable, instead of a nominal value. This was not done for age and BMI, as no (inversely) proportional linear relation between parameter and outcome was expected or hypothesized. Multivariate Cox proportional hazards models were used to calculate hazard ratios (adjusted—aHR) for progression and all-cause mortality. HRs were adjusted for age, sex, primary *EGFR*-mutation, *TP53*-status, BMI, $C_{min,SS}$ and line of treatment, as those were known to have an impact on osimertinib treatment outcomes or were of special interest in our study. For the HRs: the lowest subgroup (age, BMI or $C_{min,SS}$) was used as reference group. As sensitivity analysis the cohort of patients was limited to only first-line users. All statistical analyses were performed using SAS 9.4 (SAS Institute).

3 | RESULTS

Data from 294 real-world osimertinib users was available, which were all included in our study. An overview of all baseline characteristics and per treatment line, is shown in Table 1. In short, 118 (40%), 134 (46%) and 42 (14%) patients were treated in first, second and third line or beyond, respectively. Median age was 67 years (range: 27-89), median BMI was 24.6 (range: 17.6-67.1). Exactly 92.9% of all patients were former or never smoker and 89.8% were Caucasian. Exon 19 deletions (53.7%) and the p.L858R point mutations (29.6%) were the most frequent activating primary *EGFR*-mutations, while 26.2% had a definitive registration of a CNS metastasis (first line—33.1%; second line—23.1% and third line or beyond—66.7%). No patients used a strong cytochrome P450 3A4 (CYP3A4) inhibitor or inducer during osimertinib treatment. Median follow-up time for the full cohort was 21.5 months (range: 0.2-65.5 months). The median follow-up time was shorter for patients who used osimertinib as first-line treatment (11.7 months; range: 0.2-43.7 months), compared to patients who were treated with osimertinib in the second line (28.8 months; range: 0.7-65.5 months) or the third line or later (30.0 months; range: 1.6-40.6 months).

TABLE 1 Baseline characteristics of all patients and stratified per treatment line.

	Total (N = 294)		1L (N = 118)		2L (N = 134)		3L+ (N = 42)	
	N	%	N	%	N	%	N	%
Age (years)	66.6		66.9		67.0		64.0	
Sex (female)	193	65.6	73	61.9	94	70.1	26	31.9
Smoking								
Never	120	40.8	48	40.7	59	44.0	13	31.0
Former	153	52.0	60	50.8	67	50.0	26	61.9
Current	16	5.4	10	8.5	4	3.0	2	4.8
Unknown	5	1.7	–	–	4	3.0	1	2.4
Race								
Caucasian	264	89.8	104	88.1	119	88.8	41	97.6
African American	5	1.7	4	3.4	1	0.7	–	–
Asian	21	7.1	10	8.5	11	8.2	–	–
Hispanic	1	0.3	–	–	–	–	1	2.4
Other/Unknown	3	1.0	–	–	3	2.2	–	–
CNS metastases								
Yes	77	26.2	39	33.1	31	23.1	28	66.7
No	108	36.7	28	23.7	52	38.8	7	16.7
Unknown	109	37.1	51	43.2	51	38.1	7	16.7
Primary *EGFR*m								
Exon 19 deletion (1)	158	53.7	67	56.8	72	53.7	19	45.2
L858R (2)	87	29.6	24	20.3	47	35.1	16	38.1
1 or 2 + second mutation	35	11.9	20	16.9	9	6.7	6	14.3
Other	14	4.8	7	5.9	6	4.5	1	2.4
TP53-status								
Positive	134	45.7	60	50.8	55	41.4	19	45.2
Negative	138	47.1	44	37.3	73	54.9	21	50.0
Unknown	22	7.2	14	11.9	6	3.8	2	4.8
Age (years)								
<65	114	38.8	44	37.3	53	39.6	17	40.5
65-69	56	19.0	23	19.5	25	18.7	8	19.0
70-74	51	17.3	21	17.8	20	14.9	10	23.8
≥75	73	24.8	30	25.4	36	26.9	7	16.7
BMI (kg/m^2)								
<20.0	24	8.2	10	8.5	12	9.0	2	4.8
20.0-24.9	136	46.3	61	51.7	58	43.3	17	40.5
25.0-29.9	85	28.9	34	28.8	40	29.9	11	26.2
≥30.0	37	12.6	12	10.2	18	13.4	7	16.7
Missing	12	4.1	1	0.8	6	4.5	5	11.9

Abbreviations: %, percentage; 1L, first line treatment; 2L, second line treatment; 3L+, third line treatment or beyond; BMI, body mass index; CNS, central nervous system; EGFRm, epidermal growth factor receptor mutation; kg, kilogram; m, meter; N, number.

3.1 | Sex, primary EGFR-mutation and TP-53 status

Characteristics that are known to be associated with treatment outcomes of osimertinib, were also indicative of treatment outcomes in our cohort. Female patients had a lower risk of progression as compared to men on osimertinib (aHR = 0.61, 95% CI: 0.45-0.82). This was also found for those with an exon 19 deletion as primary *EGFR*-mutation (compared to the group of patients with other EGFR-mutations): aHR = 0.58 (95% CI: 0.36-0.92). Furthermore, patients with a *TP53*-mutation at baseline had a trend for a higher risk for a shorter PFS on osimertinib: aHR = 1.31 (95% CI: 0.96-1.78).

3.2 | Outcome per treatment line

The mPFS were 14.4 months (95% CI: 9.4-19.3 months, first-line), 13.9 months (95% CI: 11.3-16.1 months, second line) and 8.7 months (95% CI: 4.6-12.7 months, third line or beyond). The mOS since the start of osimertinib were 34.5 months (first line; 95% CI: 34.5 to NR), 28.0 months (second line; 95% CI: 23.6-39.1 months) and 18.9 months (third line; 95% CI: 13.6-25.1 months). Detailed results for the cohort of first line users are summarized in Table A1.

3.3 | Outcome by age

Detailed baseline characteristics stratified by age group are listed in Table A2. Irrespective of treatment line, mPFS according to age groups was 11.5 months (<65 years; 95% CI: 8.2-13.9 months), 18.0 months (65-69 years; 95% CI: 13.5-21.4), 10.5 months (70-74 years; 95% CI: 5.9-19.1 months) and 13.1 months (≥75 years; 95% CI: 9.8-17.1 months). Compared to the youngest group there were no statistical differences in aHR, as can be seen in Table 2 and Figure A1A. The mOS was similar for three age groups: <65 years: 25.3 months (95% CI: 18.7-34.5), 70-74 years: 23.6 months (95% CI: 14.8-41.4 months) and ≥75 years: 25.5 months (95% CI: 20.4-30.9 months) but was increased in patients who were 65 to 69 years at the start of osimertinib: 42.3 months (95% CI: 26.2 to NR) (Table 3 and Figure A1B). For OS, patients between 65 and 70 years at the start of osimertinib had a longer mOS than patients that were younger than 65 at the start of osimertinib treatment (aHR = 0.52; 95% CI: 0.29-0.92).

3.4 | Outcome by BMI

Detailed baseline characteristics stratified by BMI subgroup are shown in Table A3. Irrespective of treatment line, mPFS was relatively short in the patients with a low BMI (8.1 months; 95% CI: 3.3-14.3 months) compared to the other three subgroups. The risk for progression was significant lower in two subgroups (20.0-24.9 kg/m^2—aHR = 0.55, 95% CI: 0.33-0.93 and 25.0-29.9 kg/m^2—aHR = 0.40, 95% CI: 0.23-0.71) compared to the lowest BMI subgroup (≤20.0 kg/m^2), while a trend for reduced risk of progression was seen for the highest BMI subgroup (≥30.0 kg/m^2, aHR = 0.57, 95% CI: 0.31-1.06) (Table 2 and Figure A2A). All BMI subgroups showed a reduced risk of mortality (mOS) as compared to BMI <20.0 kg/m^2; aHR = 20.0-24.9 kg/m^2-0.45, 95% CI: 0.23-0.87; 25.0-29.9 kg/m^2-0.41, 95% CI: 0.21-0.82; ≥30.0 kg/m^2-0.38, 95% CI: 0.17-0.86) (Table 3 and Figure A2B).

3.5 | Outcome by $C_{min,SS}$

All patients with a dose reduction or interruption (due to toxicity) were excluded from the $C_{min,SS}$ analyses (n = 45). In patients for whom multiple $C_{min,SS}$ values were available over time, we observed that the $C_{min,SS}$ increased 3 months before, at and after progression (Figure A4). As these measurements could bias the osimertinib plasma level interpretation, determination of the mean $C_{min,SS}$ for each patient was done based on the available $C_{min,SS}$ measurements up to 3 months before first ever recorded radiological progression. If more than one measurement was available within the allowed sampling time frame, the average $C_{min,SS}$ was used. Figure 1 shows the flowchart for the information regarding the $C_{min,SS}$ of all patients. Detailed baseline characteristics specified per $C_{min,SS}$ subgroup are shown in Table A4. In total, 25 patients (25.0%) had a low $C_{min,SS}$ (<163 ng/mL), 50 patients (50.0%) were in the middle group and 25 patients (25.0%) had a high $C_{min,SS}$ (>271 ng/mL). In patients with a high $C_{min,SS}$, mPFS was shortest, 8.8 months (95% CI: 5.9-10.2 months), which was significantly worse compared to the group of patients with a low $C_{min,SS}$ (aHR = 2.29, 95% CI: 1.13-4.63; Table 2 and Figure A3A). A similar trend was seen for mOS, although no significant difference was found (aHR—1.95, 95% CI: 0.83-4.61), compared to patients with a low $C_{min,SS}$ (Table 3 and Figure A3B). Additionally, the results of $C_{min,SS}$ as continuous variable are shown in Table A5.

3.6 | Severe adverse events

In total, 51 unique patients (17.3%) experienced a grade 3 adverse event that led to hospitalization, an interruption, a dose-reduction or a definitive stop of osimertinib. Safety issues resulted in an interruption of osimertinib in 34 patients (11.6%), led to a dose reduction in 36 patients (12.2%), caused hospitalization of six patients (2.0%) and provoked a definitive stop of osimertinib in nine patients (3.1%). The most frequent reasons were increased laboratory values (mainly deviating liver enzymes), skin toxicity and pneumonitis (Table 4).

4 | DISCUSSION

In this Dutch multicentre cohort study the treatment outcomes of 294 patients with metastatic *EGFRm+* NSCLC that were treated with osimertinib were assessed. We found that age was not associated with mPFS or mOS, while a low BMI (<20 kg/m^2) and a high $C_{min,SS}$ (>271.0 ng/mL) were associated with a higher risk of shorter PFS (both) and OS (BMI). Additionally, no new safety issues were identified, compared to reports from previously performed randomized controlled trials (RCTs) and/or real-world data studies. Factors that were already known to be associated with effectiveness outcomes of osimertinib, such as primary *EGFR*-mutation (exon 19 deletion) and female sex, were also found to significantly increase mPFS with osimertinib in our cohort, and a trend was seen for *TP53* wild-type patients. While this agrees with previous research,[22,28] data regarding *TP53* status was not available for all patients, which limits the number of patients that could be included in the analysis to evaluate the impact of *TP53* status on effectiveness outcomes of osimertinib.

TABLE 2 Adjusted hazard ratios for progression in patients treated with osimertinib in clinical practice, specified by age, BMI and the plasma trough concentration.

	Number of events	mPFS (months)	95% CI (months)		HR	95% CI		aHR	95% CI	
Age (years)										
<65	79	11.5	8.2	13.9	ref	ref	ref	ref	ref	ref
65-69	33	18.0	13.5	21.4	0.70	0.46	1.05	0.68	0.45	1.03
70-74	36	10.5	5.9	19.1	1.08	0.73	1.61	0.97	0.64	1.48
≥75	44	13.1	9.8	17.1	0.92	0.63	1.34	0.80	0.53	1.19
BMI (kg/m^2)										
<20.0	18	8.1	3.3	14.3	ref	ref	ref	ref	ref	ref
20.0-24.9	89	13.9	9.9	18.0	0.71	0.43	1.19	**0.55**	**0.33**	**0.93**
25.0-29.9	46	15.6	11.5	19.3	**0.54**	**0.31**	**0.93**	**0.40**	**0.23**	**0.71**
≥30.0	29	11.9	6.9	18.4	0.78	0.43	1.42	0.57	0.31	1.06
Unknown	10	8.2	2.8	17.8	0.92	0.40	2.08	0.66	0.28	1.57
Plasma trough concentration (ng/mL)										
<163	13	15.4	7.9	23.0	ref	ref	ref	ref	ref	ref
163-271	29	11.6	7.7	18.0	1.27	0.66	2.45	1.38	0.71	2.66
>271	22	8.8	5.9	10.2	1.92	0.96	3.83	**2.29**	**1.13**	**4.63**
Unknown	101	12.4	8.5	14.5	1.29	0.72	2.32	1.37	0.76	2.48

Note: Cox proportional hazard model: adjusted for primary EGFR-mutation, TP53 status, line of treatment, sex, age, body mass index and plasma trough concentration. aHRs and 95% CI in bold indicates a statistically significant different compared to the reference.
Abbreviations: 95% CI, 95% confidence interval; aHR, adjusted hazard ratio; BMI, body mass index; kg, kilogram; m, meter; mL, milliliter; mOS, median overall survival; mPFS, median progression free survival; ng, nanogram.

TABLE 3 Adjusted hazard ratios for mortality in patients treated with osimertinib in clinical practice, specified by age, BMI and the plasma trough concentration.

	Number of events	mOS (months)	95% CI (months)		HR	95% CI		aHR	95% CI	
Age (years)										
<65	51	25.3	18.7	34.5	ref	ref	ref	ref	ref	ref
65-69	16	42.3	26.2	NR	**0.57**	**0.32**	**0.99**	**0.52**	**0.29**	**0.92**
70-74	22	23.6	14.8	41.4	1.15	0.69	1.89	0.91	0.53	1.57
≥75	29	25.5	20.4	30.9	1.04	0.66	1.66	0.95	0.58	1.55
BMI (kg/m^2)										
<20.0	12	14.8	4.6	NR	ref	ref	ref	ref	ref	ref
20.0-24.9	52	28.4	21.8	42.3	0.58	0.31	1.09	**0.45**	**0.23**	**0.87**
25.0-29.9	31	26.2	21.9	38.2	0.55	0.28	1.07	**0.41**	**0.21**	**0.82**
≥30.0	15	23.6	19.8	NR	0.56	0.26	1.20	**0.38**	**0.17**	**0.86**
Unknown	8	10.9	5.6	NR	1.17	0.47	2.96	0.88	0.34	2.29
Plasma trough concentration (ng/mL)										
<163	8	28.9	15.4	NR	ref	ref	ref	ref	ref	ref
163-271	16	28.0	18.5	NR	1.20	0.51	2.82	1.13	0.56	3.11
>271	14	21.2	12.7	NR	1.94	0.81	4.64	1.82	0.75	4.42
Unknown	68	25.3	18.7	36.9	1.62	0.77	3.38	1.68	0.79	3.56

Note: Cox proportional hazard model: adjusted for primary EGFR-mutation, TP53 status, line of treatment, sex, age, body mass index and plasma trough concentration. aHRs and 95% CI in bold indicates a statistically significant different compared to the reference.
Abbreviations: 95% CI, 95% confidence interval; aHR, adjusted hazard ratio; BMI, body mass index; kg, kilogram; m, meter; mL, milliliter; mOS, median overall survival; mPFS, median progression free survival; ng, nanogram.

Compared to the mPFS of 18.9 months (95% CI: 15.2-21.4) in the FLAURA study, the mPFS of first-line osimertinib users in our study was shorter (14.4 months, 95% CI: 9.4-19.3).[3] This difference could be caused by a higher proportion of patients in our study that had CNS involvement (33% vs 19%) or is due to the inclusion of real-life patients with uncommon *EGFR* mutations (other than solely exon 19 deletions or the p.L858R point mutation (Table A6; 22.8% vs 0.0%). Meanwhile, the mPFS of osimertinib in the second line was shorter in the AURA3 study compared to our study (10.1 months [95% CI: 8.3-12.3] vs 13.9 months [95% CI: 11.3-16.1]).[2] This could potentially be explained by the larger proportion of female patients in our study (70% vs 62%). However, other factors, such as broader inclusion of patients with uncommon primary *EGFR* mutations and patients with CNS metastasis in our study would hypothetically reduce osimertinib treatment outcomes in second-line users. Given these issues, the observed difference in mPFS requires further clarification and could be subject for future studies, while a potential explanation for the observed difference could be the higher frequency of radiological imaging, which was performed more strictly (every 6 weeks) in the AURA3 trial compared to our study. A detailed overview of the results of our study, compared to the large clinical trials, as well as other large observational series, is shown in Table A6.

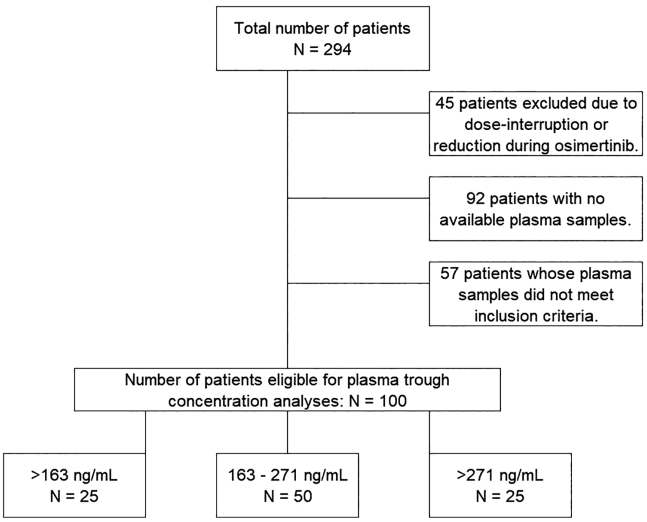

FIGURE 1 Flowchart describing eligible patients for the plasma trough concentration evaluations.

Similar to Yamamoto et al (N = 132),[10] we observed that elderly patients derive benefit from osimertinib. Furthermore, this was also seen in a smaller French study (N = 43), evaluating the effectiveness of osimertinib in second line or later.[32] However, both studies included elderly (>75 years/≥80 years, respectively) only, while we compared osimertinib treatment outcomes in different age groups. The mPFS was numerically better in the study by Yamomoto et al compared with our study (19.4 months[10] vs 14.4 months, 95% CI: 9.4-19.3 months) for all first-line users. Contrary to our study, they mainly included Asian patients, while our population was mostly Caucasian (90%). This difference could potentially influence mPFS, as better absolute mPFS with osimertinib was seen in Caucasian patients in the FLAURA study.[3] However, this did not translate into a similar trend in clinical practice as the opposite was true when comparing data published by Yamamoto with our study (Table A7).

TABLE 4 Adverse events of osimertinib responsible for hospitalizations, dose reductions, treatment discontinuation or definitive stop of osimertinib treatment.

	Hospitalization (N = 6)		Treatment interruption (N = 34)		Dose-reduction (N = 36)		Treatment stop (N = 9)	
	N	%	N	%	N	%	N	%
Cardiomyopathy	–	–	–	–	–	–	1	11.1
Deviant laboratory value	2	33.3	16	47.1	13	36.1	–	–
Diarrhea	–	–	3	8.8	2	5.6	–	–
Fatigue	–	–	4	11.8	3	8.3	–	–
Nausea	–	–	4	11.8	4	11.1	1	11.1
Overall deterioration	–	–	1	2.9	4	11.1	–	–
Pain	–	–	–	–	1	2.8	1	11.1
Palpitations	–	–	1	2.9	–	–	1	11.1
Paronychia	–	–	4	11.8	6	16.7	2	22.2
Pneumonitis	4	66.7	4	11.8	2	5.6	4	44.4
Pruritus	–	–	1	2.9	1	2.8	–	–
QTc-prolongation	–	–	–	–	1	2.8	–	–
Skin toxicity	–	–	6	17.6	6	16.7	–	–
Thrombocytopenia	–	–	–	–	1	2.8	–	–

Note: One patient could potentially experience multiple adverse events at the same time.
Abbreviations: %, percentage; N, number; QTc, QT-interval.

The number of overweight and obese patients is rising worldwide, and consequently the average BMI increases.[37] BMI has shown to be associated with shorter OS in patients with NSCLC (both underweight and morbid obese patients) as well as OS with immunotherapy (longer OS in patients with baseline BMI ≥30 kg/m^2).[33,38] We found that a low BMI (<20.0 kg/m^2) was associated with shorter mPFS and mOS. A potential explanation for the lower effectiveness outcomes of osimertinib in patients with low BMI could be the occurrence of cachexia, which is characterized by substantial weight loss, primarily related to loss of skeletal muscle mass and body fat but is also associated with worse survival outcomes.[39,40] Unfortunately, we were unable to incorporate an indirect measure of cachexia in our analysis. Furthermore, the decrease in effectiveness outcomes in the low BMI subgroup could also be caused by the general effect on mortality that was previously seen in patients with a low BMI.[41] Patients with a low BMI have a higher probability for all-cause mortality, independent from other factors, such as comorbidity or mental health. This could potentially be caused by a higher risk of infection among elderly patients with a low BMI,[42] which is in concordance with the population that was included in our study, as more than 65% of the patients in the low BMI subgroup was older than 70 years. The influence of BMI on treatment outcomes with osimertinib had previously been evaluated in a small retrospective study by Ono et al (N = 47), using a cut-off of 21.5 kg/m^2 as threshold for low and high BMI and no difference was found between the two groups.[29] In our study, patients were divided into different BMI subgroups based on a classification that is used more routinely in clinical research. Furthermore, our study included considerably more patients (N = 294, of whom 282 had a known BMI; Table A7).

A low $C_{min,SS}$ (<163 ng/mL) seemed to be indicative of better osimertinib treatment outcomes, as mPFS in this subgroup was significantly better compared to patients with a high $C_{min,SS}$ (>271 ng/mL), but not compared to patients with a $C_{min,SS}$ between 163 and 271 ng/mL. A similar relation has recently been reported by Boosman et al[30] and by Rodier et al.[31] In the study by Boosman, patients with a $C_{min,SS}$ below 166 ng/mL were compared to patients with a $C_{min,SS}$ above 166 ng/mL. The threshold of 166 ng/mL in the study of Boosman et al was selected based on the geometric mean as reported by the Food and Drug Administration (FDA) and is based on results from the AURA studies. However, the median $C_{min,SS}$ found by Boosman et al was 211 ng/mL, and the median and mean $C_{min,SS}$ in our data were 216 ng/mL and 238 ng/mL, respectively. Therefore, we believe that the actual mean $C_{min,SS}$ is higher than originally reported by the FDA. This difference may be caused by limited osimertinib stability in plasma at room temperature, making adequate sample handling crucial and prone to deviations.[43,44] Furthermore, interracial differences in CYP3A genotype and/or phenotype may potentially contribute to the observed variation, as 90% of all patients in our study were Caucasian, while this was 32% in the AURA3 trial.[2,45-47] Nevertheless, also Boosman et al reported that patients with a $C_{min,SS}$ below 166 ng/mL had longer mPFS than patients with a $C_{min,SS}$ above 166 ng/mL, but this did not lead to statistical significance in the multivariate analysis. In the study by Rodier et al, a similar association between $C_{min,SS}$ and osimertinib effectiveness was found compared to our study. Patients with a high $C_{min,SS}$ (fourth quartile, >235 ng/mL) had a significant shorter mOS (Table A7). Similar to the analysis of Rodier et al, we divided $C_{min,SS}$ values into quartiles and used the 25th and 75th percentile as threshold values for low and high exposure, respectively. We decided to compare multiple subgroups (low, middle and high) as we were interested in evaluating the effect of the $C_{min,SS}$ over the whole range of $C_{min,SS}$ that was measured in our cohort, instead of using one previously defined hypothetical threshold value, as was done in both the study by Rodier et al, and the study by Boosman et al $C_{min,SS}$ values were corrected for time of blood withdrawal and time of osimertinib intake. Blood samples that were collected within 6 hours of the last osimertinib intake were excluded, due to uncertainty in the extrapolation for the $C_{min,SS}$. This was contrary to the approach used in the other two studies,[30,31] where blood samples collected within 6 hours of the last osimertinib intake were incorporated as well, which could have impacted the accuracy of the extrapolation. Another study, by Agema et al,[48] found that patients with a plasma trough concentration higher than 259 ng/mL are more likely to experience severe toxicity. It should be noted that a substantial part of these patients was also included in our dataset (54%), although the focus of both studies differed (ie, osimertinib toxicity vs efficacy analysis). Boosman et al hypothesized that higher cancer-induced inflammation (associated with poorer survival)[49,50] could lead to lower CYP-activity, and therefore lower osimertinib clearance, resulting in higher plasma trough concentrations.[30] Unfortunately, we were unable to incorporate inflammation markers (such as c-reactive protein or the neutrophil-to-lymphocyte ratio) in our analyses, as these were not routinely registered. In addition, other factors that could not be included in our analyses, may contribute to the lower survival seen in patients with a high osimertinib $C_{min,SS}$. Cachexia, for example, which is correlated with poor response and survival, leads to higher inflammation, reduced CYP-activity and loss of body mass, thereby changing the body distribution of osimertinib and its $C_{min,SS}$.[51,52] While in a limited number of patients, Boosman et al found no obvious effect of sarcopenia on the association between osimertinib effectiveness outcomes and its $C_{min,SS}$.[30] The potential impact of cachexia on the effectiveness of osimertinib has not been evaluated extensively. Therefore, to elucidate which underlying factors could explain the paradoxical correlation between a high osimertinib $C_{min,SS}$ and low mPFS, cachexia may be of interest for further research. For the near future, the scientific basis to incorporate TDM as standard practice in the treatment with osimertinib is missing and more, prospective research is needed to elucidate a potential role for TDM in the treatment of osimertinib.

The added value of our study is the large cohort of 294 patients who were treated with osimertinib in clinical practice, with 118 patients receiving osimertinib as first line treatment. And additionally, our study contains a large cohort of patients who received osimertinib in a later line, which leads to an extensive picture of osimertinib effectiveness outcomes in clinical practice. Also, all treatment responses were retrospectively reviewed and scored using RECIST 1.1, to ensure uniformity in treatment evaluation. Furthermore, all $C_{min,SS}$ values were accurately extrapolated using the method

described by Wang et al.[36] All samples were collected during steady state, and samples obtained around progression were excluded, as an increase in $C_{min,SS}$ was observed around this time, which is shown in Figure A4. However, our study also has some limitations. As this was an observational study, not all subgroups consisted of a comparable number of patients, which impacts the certainty of the observed results. Furthermore, using data from patients that were treated with osimertinib in clinical practice, we were limited to the data that was registered for regular care. Therefore, not all characteristics of interest (extensive information on co-medication, inflammation and cachexia parameters) could be included in our analyses. Additionally, 102 patients died during the study period, which equals 34.7%. The relatively low number of events make the results for the OS immature, and caution should be applied when drawing definitive conclusions. However, data regarding the primary outcome is clear, and an extensive data collection was performed to minimize missing data in other variables.

Results from our study can help clinicians to adequately inform patients with NSCLC in clinical practice. Furthermore, we identified meaningful effects of patient-specific clinical features on osimertinib effectiveness, which can be used to develop or improve a reliable decision support system for NSCLC patients in real-world practice. Previous research already resulted in the development and implementation of such a tool.[53] Additional information about the impact of patient-specific clinical features (such as age and BMI), may be helpful in further tailoring this tool for patients treated with osimertinib, which then has to be tested and validated in a prospective study.

5 | CONCLUSION

Osimertinib treatment outcome in clinical practice was not associated with age, while shorter mPFS and/or mOS were seen in patients with a low BMI (<20.0 kg/m^2), male sex and a high $C_{min,SS}$ (>271 ng/mL). Patients with *EGFR* exon 19 deletion or *TP53* wild-type status had longer mPFS. Patient-specific clinical features affecting the response to osimertinib identified from this real-world data analysis can eventually help clinicians to adequately inform patients with NSCLC about what may be expected from osimertinib treatment.

AUTHOR CONTRIBUTIONS

Ard van Veelen: Conceptualization, methodology, software, formal analysis, investigation, data curation, writing – original draft, project administration. **G. D. Marijn Veerman:** Investigation, writing – review & editing; **Marjon V. Verschueren:** Investigation, writing – review & editing; **Judith L. Gulikers:** Software, validation, investigation, writing – review & editing; **Christi M. J. Steendam:** Investigation, writing – review & editing; **Anita J. W. M. Brouns:** Investigation, writing – review & editing; **Safiye Dursun:** Investigation, writing – review & editing; **Marthe S. Paats:** Investigation, writing – review & editing; **Vivianne C. G. Tjan-Heijnen:** Writing – review & editing, supervision; **Cor van der Leest:** Writing – review & editing; **Annemarie C. Dingemans:** Writing – review & editing, supervision; **Ron H. J. Mathijssen:** Writing – review & editing; **Ewoudt M. W. van de Garde:** Writing – review & editing, supervision; **Patrick Souverein:** Methodology, software, formal analysis, writing – review & editing; **Johanna H. M. Driessen:** Methodology, software, formal analysis, data curation, writing – review & editing; **Lizza E. L. Hendriks:** Methodology, writing – review & editing; supervision; **Robin M. J. M. van Geel:** Conceptualization, methodology, writing – review & editing; supervision; **Sander Croes:** Conceptualization, methodology, writing – review & editing; supervision. The work reported in the article has been performed by the authors, unless clearly specified in the text.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The research protocol and data collection were approved by the institutional medical research assessment committees (MREC), both in Maastricht (review numbers: 2016-643 and 2019-1080) and Rotterdam and Breda (START-TKI, NCT05221372). As this was an observational study, the necessity to obtain written informed consent was

waived for the data collection from the electronic health records. However, the quantification of osimertinib in plasma for research purposes was performed only if patients provided written informed consent to draw blood samples, additionally to the blood samples needed for routine clinical practice care.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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