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High dose osimertinib in patients with advanced stage EGFR exon 20 mutation-positive NSCLC: Results from the phase 2 multicenter POSITION20 trial

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ABSTRACT

Introduction: Patients with life-threatening advanced non-small cell lung cancer (NSCLC) who harbor an exon 20 deletion and/or insertion mutation (EGFRex20 +) have limited effective treatment options. The high dose 3rd generation tyrosine kinase inhibitor (TKI) osimertinib shows promising *in vitro* activity in EGFRex20 + NSCLC tumors.

Methods: The POSITION20 is a single arm phase II, multicenter study investigating 160 mg osimertinib in patients with EGFRex20+, T790M negative NSCLC. We allowed patients to be treatment naïve and to have asymptomatic brain metastases. The primary endpoint was overall response rate (ORR). Secondary outcomes were duration of response (DoR), progression free survival (PFS), overall survival (OS), and treatment related adverse events (trAEs).

Results: From June 2018 to October 2021, 25 patients were enrolled across five centers in the Netherlands. The median age was 70 years (range, 47–87), 20 patients (80%) were women, and the median number of previous lines of therapy was 1 (range, 0–3). The exon 20 mutations were clustered between A763 and L777. The most common exon 20 mutations were p.(N771_H773dup) (n = 3) and p.(A767_V769dup) (n = 3). The ORR was 28% (95% CI, 12–49%), including seven partial responses, with a median DoR of 5.3 months (range, 2.7–27.6). The median PFS was 6.8 months (95% CI, 4.6–9.1) and the median OS was 15.2 months (95% CI, 14.3–16.0). The most common trAEs were diarrhea (72%), dry skin (44%), and fatigue (44%). The primary reason for discontinuation was progressive disease in 14 patients (56%).

Conclusion: The POSITION20 study showed modest antitumor activity in patients with EGFRex20 + NSCLC treated with 160 mg osimertinib, with a confirmed ORR of 28% and acceptable toxicity.

1. Introduction

The treatment landscape of metastatic non-small cell lung cancer (NSCLC) changed radically in recent years, due to the identification of activating mutations within the tyrosine kinase domain of the epidermal growth factor receptor (*EGFR*) [1,2]. Patients with NSCLC with common *EGFR* mutations (exon 19 and 21, accountable for approximately 90% of all detected *EGFR* mutations) benefit from treatment with EGFR tyrosine

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kinase inhibitors (EGFR-TKIs) [3–5]. The third most common subset (4–12%) of *EGFR* activating mutations in patients with NSCLC are exon 20 deletion and/or insertion (EGFRex20 +) mutations [6,7]. Patients with NSCLC harboring an EGFRex20 + mutation lack clinical benefit to current 1st and 2nd generation EGFR-TKIs, with the general exception of the sensitive insertions in the αC-helix (for example, A763insFQEA) [8–10].

The inability to clinical benefit is most likely caused by the three-dimensional structure of the current EGFR-TKIs and the influence of the EGFRex20 + mutation on the kinetics of drug and ATP binding, which determines the resistance or sensitivity to *EGFR* inhibitors [11–13]. Therefore, new treatment options are needed to overcome the primary resistance of the EGFRex20 + mutation. Osimertinib is an oral, third-generation, irreversible EGFR-TKI approved for both classical- and *EGFR* T790M resistant mutations [14–18]. To date, the evidence regarding efficacy of osimertinib 80 mg daily in patients with EGFRex20 + NSCLC is disappointing [19–23,49] (see Supplementary Table 1, showing the efficacy of osimertinib in several trials). The results of the different studies showed that patients with EGFRex20 + NSCLC are heterogenous in their response to osimertinib 80 mg, in which patients harboring the A763_Y764insFQEA variant in the αC-helix showed better response in comparison to other near- and far loop EGFRex20 + mutations [24].

Higher dosage of osimertinib could be beneficial, as *in vitro* data hints [13,25]. A pharmacokinetic analysis revealed that geometric mean plasma concentrations for multiple dosing of osimertinib with daily 80 mg and 160 mg were around 500 nM and 1000 nM [25]. Thus, a higher dose of osimertinib will be necessary to effectively treat patients with EGFRex20 + NSCLC. In addition to preclinical research, the phase II ECOG-ACRIN 5162 trial assessed osimertinib 160 mg once daily in 20 patients with EGFRex20 + NSCLC who previously received at least one line of treatment and had Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1. The study showed an objective response rate (ORR) of 24% and a disease control rate (DCR) of 85% [26], in which the responders all harbored an EGFRex20 + mutation in the loop following C-helix (see Supplementary Table 2, showing the efficacy of osimertinib 160 mg for 21 patients with NSCLC EGFRex20 + within the study of Piotrowska et al., 2020). However, the ECOG-ACRIN 5162 trial does not provide evidence spanning the entire spectrum of exon 20 mutations (excluding the αC-helix), and patients were always pre-treated. In addition, we describe the results of the POSITION20 trial assessing the antitumor activity of osimertinib 160 mg in patients with EGFRex20 + NSCLC as first or second line treatment.

2. Material and methods

2.1. Study design and patients

The POSITION20 study was a single arm, phase II, multicenter study conducted in five institutes in the Netherlands. The study was approved by all medical research ethics committees at each site and informed consent was obtained from all patients according to the Declaration of Helsinki, prior to the study [27]. The study was listed in the Netherlands trial register (trialregister.nl), NL6705. AstraZeneca provided funding for and access to the study medication osimertinib. The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding- and first author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

General inclusion criteria included ≥ 18 years of age, ECOG PS 0–2 and being diagnosed with advanced NSCLC, harboring an EGFRex20 + mutation (deletion and/or insertion), T790M negative. Histological or cytological tumor samples from all patients were locally tested using next-generation sequencing (NGS) (e.g. single-molecule molecular inversion probes [smMIP] and Ion Torrent). We allowed patients to be pre-treated (chemo- or immunotherapy, multiple lines of treatment were allowed) and to have asymptomatic brain metastases. Patients pre-treated with other generation (EGFR-)TKIs or EGFR-MET bispecific antibody were excluded.

2.2. Procedure

Patients were treated with a double dosage of osimertinib 160 mg orally once daily until progression or unacceptable toxicity. The treatment started within 28 days of screening enrolment. Follow-up was done after 2 and 6 weeks, and thereafter every 6 weeks. Patients were monitored for ECG machine-derived QTc value changes at baseline, after 2 and 6 weeks, and further on indication in case of an abnormal QTc value.

The primary endpoint of this study was efficacy of osimertinib defined as ORR by investigator assessment using RECIST 1.1 [28]. Disease assessment using computed tomography (CT) and/or magnetic resonance imaging (MRI) was performed at baseline and every 6 weeks, until week 24. Thereafter, during the treatment phase every 12 weeks, until disease progression, discontinuation or withdrawal from the study. Brain imaging was not mandated at baseline, and only (subsequently) performed during the study at the discretion of the investigator when clinically indicated. Palliative radiotherapy to control symptoms (including gamma knife technique), e.g. to control brain disease, was permitted. Treatment beyond progression was allowed by investigators judgment in case of persistent clinical benefit. Secondary outcomes were treatment efficacy observed by duration of response (DoR), progression free survival (PFS), overall survival (OS) [28], clinical benefit rate (CBR), and safety endpoints defined as treatment related adverse events (trAEs). The CBR was defined as the proportion of patients with a complete or partial response (PR) or with durable stable disease (SD) ≥ week 24. Adverse events were reported and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (CTCAE) [29].

2.3. Statistical analysis

Descriptive statistics – median (IQR), n (%) – were used to describe patient and disease baseline characteristics. The association between characteristics and survival outcome was univariately assessed using a stratified Cox regression model. If possible, variables with a p-value ≤ 0.15 in the univariate analyses were analyzed in a multivariable stratified Cox regression model. The median PFS and median OS were estimated using the Kaplan–Meier method.

The trial aimed to show a confirmed ORR of 30%, adopting Simon's optimal two-stage design with a predefined one-sided alpha of 5% and a power of 80%. Twenty-five patients were planned to be recruited in total, if at least one patient showed a response in the first fifteen treated patients. Else, the study would be terminated. The ORR was estimated according to Clopper-Pearson. The Barnard's test was used to compare different ORR proportions. The efficacy data cutoff for the analyses was October 1, 2021.

3. Results

3.1. Patient characteristics

From August 2018 to August 2021, 29 patients were screened of whom 25 patients were enrolled and treated with 160 mg osimertinib once daily. The median follow-up time was 11.5 months (range, 0.8–32.0). The median age was 70 years (range, 47–87), 20 patients (80%) were woman and four patients (6%) never smoked (Table 1). Three patients (12%) had asymptomatic brain metastases at baseline, in which one patient (4%) had a history of treated brain lesions. Thirteen patients (52%) had undergone previous treatment. The median number of previous lines of therapy was 1 (range, 0–3). Two patients (8%) had received chemo-immunotherapy and 11 patients (44%) platinum-based

Table 1
Patient characteristics at baseline.

Characteristic	Efficacy population (N = 25)
Gender	
Male	5 (20%)
Female	20 (80%)
Age (median, range)	70 (47 – 87)
Ethnicity	
White	25 (100%)
Histology	
Adenocarcinoma	25 (100%)
Tumor samples	
Histology	20 (80%)
Cytology	5 (20%)
Smoking status	
Never	4 (6%)
Former	16 (64%)
Current	5 (20%)
ECOG performance status	
0	9 (36%)
1	15 (60%)
2	1 (4%)
Baseline brain metastases (asymptomatic)	3 (14%)
Prior lines of therapy (median, range)	1 (0 – 3)
Prior therapy	
Chemotherapy	10 (40%)
Chemo-immunotherapy	2 (8%)
Chemotherapy – TKI	1 (4%)
None	12 (48%)
EGFR exon20 mutation variants	p.(A767_V769dup) (12%)
(most common >1 are listed)	p.(N771_H773dup) (12%)
See Supplementary Table 3 for all EGFRex20 + mutation variants and co-occurring alterations in this study.	p.(S768_D770dup) (8%)
	p.(D770_N771insG) (8%)
	p.(N771_P772insH) (8%)
	p.(P772_H773dup) (8%)

Abbreviations: ECOG = Eastern Cooperative Oncology Group, TKI = tyrosine kinase inhibitor.

chemotherapy. Despite per-protocol exclusion criteria, one patient (4%) was treated with an EGFR-TKI in combination with an anti-EGFR monoclonal antibody (afatinib/cetuximab, partial response as best overall response [BOR]). Histological or cytological tumor samples from all patients were tested for at least BRAF, EGFR, HER2, HRAS, KIT, KRAS, MET, NRAS, and PIK3CA. The observed EGFRex20 + mutations were clustered between amino acids A763 and L777. The most common EGFRex20 + mutation variants were p.(N771_H773dup) (n = 3) and p.(A767_V769dup) (n = 3). Data regarding co-occurring alterations were available for 14 patients (56%). The tumor protein p53 (TP53) mutation was the most common type of co-occurring alteration detected (n = 5; 36%), (see Supplementary Table 3, for all EGFRex20 + mutation variants and co-occurring alterations in this study).

3.2. Clinical efficacy

Among the 25 patients, seven patients had a confirmed PR (ORR: 28%; 95% confidence interval [CI], 12–49). No complete responses were observed. Thirteen patients (52%) had SD, four patients (16%) were inevaluable (NE) for response due to symptomatic deterioration before the first radiological assessment, and one patient (4%) had progressive disease (PD) as BOR. The CBR was 60% (95% CI, 39–79). The median DoR was 5.3 months (range, 2.7–27.6), with five patients remaining on treatment after the data cutoff (Fig. 1). Eighty percent of the patients showed radiographically tumor shrinkage of any quantity (Fig. 2). When considering the treatment line (first-line vs. later line setting), there was no significant difference (p = 0,625) between the time to progression (see Supplementary Fig. 1). The ORR was 31% (95% CI 9–61) and 25% (95% CI 6–57) in patients receiving osimertinib 160 mg as first line or in later line setting (p = 0.464).

All three patients with brain metastases showed a decrease in brain lesion size during osimertinib treatment. Two patients had brain metastasis as target lesions with a brain lesion size decrease of 4% (SD as BOR) and 40% (PR as BOR). The patient with a decrease of 40% was pre-treated with radiotherapy. The third patient (PR as BOR) had non-target lesions as brain metastasis, which were at one point non-measurable. However, this patient experienced oligoprogression in the brain for which whole brain radiotherapy (WBRT) was indicated during osimertinib treatment. Hereafter, the patient remained stable on 160 mg osimertinib treatment for 5.3 months. The median duration of central nervous system (CNS) disease response was 6.6 (range, 2.8–7) months.

The primary reasons for discontinuation were PD in 14 patients (56%), symptomatic deterioration due to malignant disease in four patients (16%), and grade 3 trAEs in two patients (8%). Within the patients

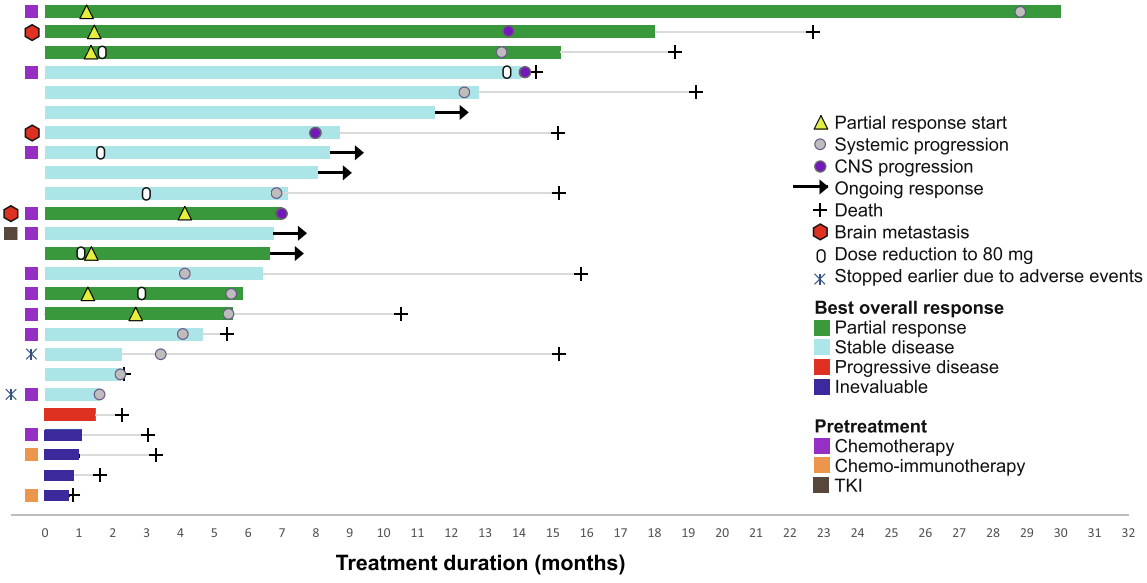

Fig. 1. Swimmers plot showing the duration of osimertinib treatment and responses for all evaluable patients. The lower four patients are inevaluable for response due to symptomatic deterioration before the first radiological assessment. Abbreviations TKI = tyrosine kinase inhibitor, CNS = central nervous system.

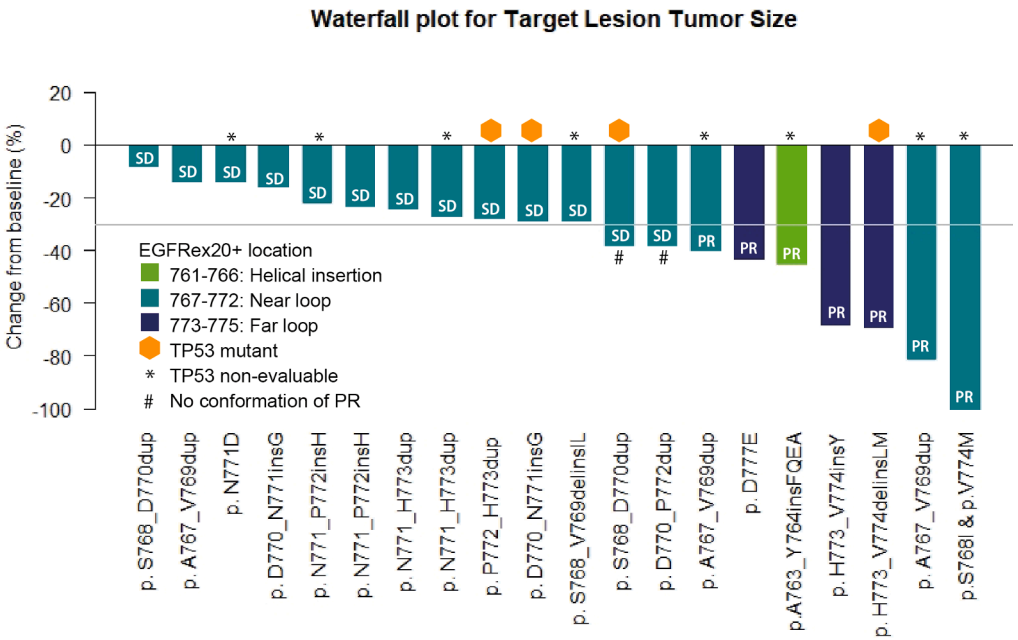

Fig. 2. Waterfall plot showing best percent change from baseline in sum of target lesion diameters by location of EGFRex20 + mutations for all evaluable patients. In addition, the best overall response for each patients is shown. Four patients were radiological non-evaluable, due to symptomatic deterioration before the first radiological assessment, and are not shown in the waterfall plot. The patient with PD as best response, showed pleural effusion on CT which was non measurable, and is therefore not shown in the waterfall plot. Two patients showed a percent change of more than 30% decrease in sum of target lesion diameters, but the decrease was not confirmed on the next time point. Therefore, the best responses of these patients is SD. The patients whose TP53 status is unknown are indicated with an asterisk. Abbreviations: SD = stable disease, PR = partial response, PD = progressive disease, EGFRex20+ = exon 20 deletion and/or insertion mutation.

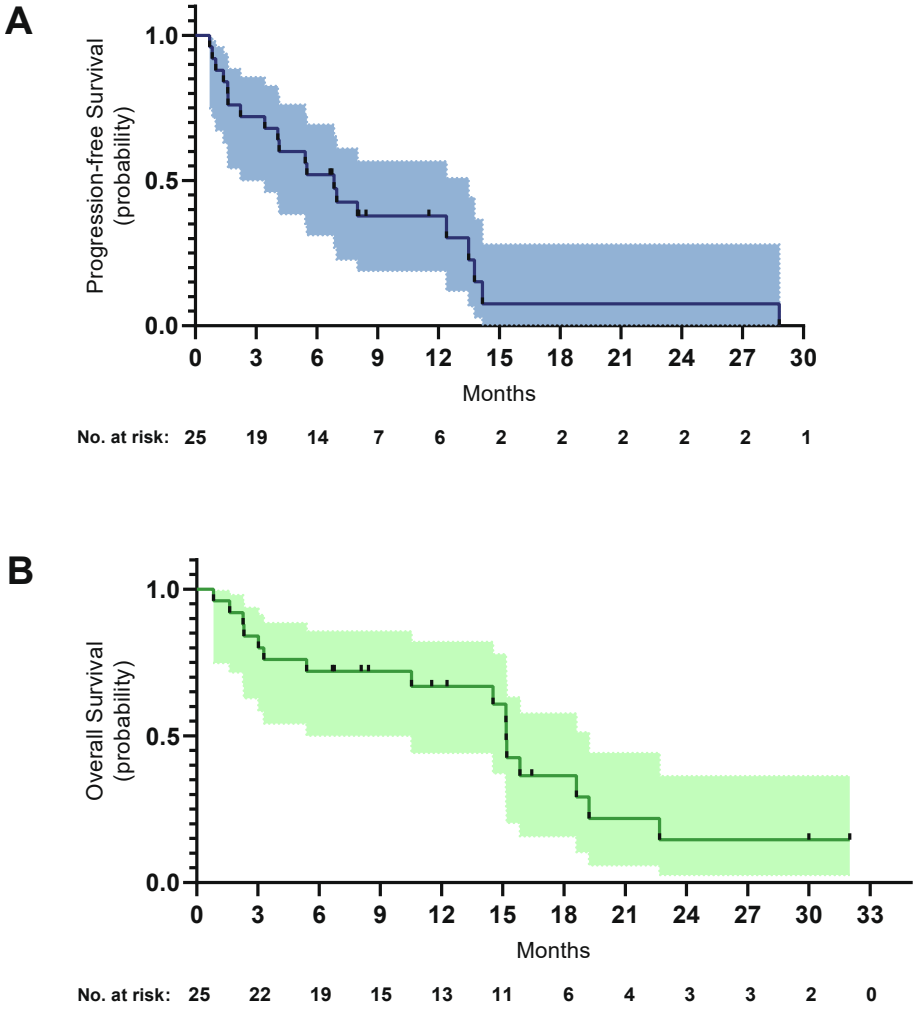

Fig. 3. Kaplan-Meier curve with 95% confidence interval showing progression-free survival (A) and overall survival (B).

who experienced PD, 10 patients (71%) had systemic progression and four patients (29%) had CNS disease progression (Fig. 1). At data cutoff, progression or death due to PD occurred in 20 patients (80%). The median PFS was 6.8 months (95% CI, 4.6–9.1) and the median OS was 15.2 months (95% CI, 14.3–16.0) (Fig. 3). We found no significant correlation between the time to progression and the different baseline characteristics (see Supplementary Fig. 1). There was no significant difference in antitumor responses ($p = 0.90$) between the helical region (known sensible insertion regions) or loop region (less sensible insertion regions) of the EGFRex20 + mutations. To distinguish further between the different mutations and co-occurring TP53 mutations, we compared the best percent change from baseline in sum of target lesion diameters to location of insertion regions and presence of TP53 shown in Fig. 2. The patient with the longest PFS (16.4 months) had a known sensible *EGFR* exon 20 insertion variant p.(A763_Y764insFQEA) (helical region) (Fig. 2).

3.3. Safety

Among the 25 patients that were included in the safety analysis, adverse events of any cause were reported in all patients during the treatment (see Supplementary Table 4, showing adverse events regardless of causality in ≥ 1 patient). TrAEs of osimertinib of any grade were reported in 92% of the patients and are summarized in Table 2. The most common trAEs were diarrhea (72% of patients), dry skin (grouped term: 44% of patients), fatigue (44% of patients) and rash or acne (grouped term: 40% of patients). Five patients (20%) experienced grade 3 or worse trAEs. Serious adverse events (SAEs) were reported in nine patients (36%) (see Supplementary Table 5), in which three cases (12%) were considered treatment-related. These three SAEs included pneumonitis, dehydration, and hypokalemia caused by diarrhea. The patient who experienced pneumonitis did not receive immunotherapy in prior lines of treatment. Two patients discontinued treatment prior to progression due to SAE pneumonitis (n = 1) after 1.6 months and due to grade 3 trAE left ventricular systolic dysfunction (n = 1) after 2.3 months.

A dose interruption and/or reduction at any time during the treatment of osimertinib from 160 mg to 80 mg was required in eight patients (32%) (Fig. 1). Two patients required a dose interruption for only 2 weeks due to diarrhea or increased creatine kinase (CK) and continued thereafter with 160 mg. Two patients had to interrupt the regimen due to grade 3 trAEs hepatotoxicity and increased CK, and continued after the interruption without any sequels at a reduced dose of 80 mg. Four patients had a dose reduction to 80 mg (after 41-, 86-, 88- and 417 days) without interruption because of grade 2 fatigue, QTc prolongation, skin problems or nausea. No patient required a dose reduction to 40 mg. There were no new significant safety findings regarding treatment-related adverse events to osimertinib.

Table 2
Treatment-related adverse events (safety population).

Treatment-related adverse events	Safety population (N = 25) *Number of patients (percent)*				
	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Any adverse event	22 (88)	11 (48)	5 (20)	0	23 (92)
Diarrhea	14 (56)	3 (12)	1 (4)	0	18 (72)
Dry skin*	10 (40)	1 (4)	0	0	11 (44)
Fatigue	9 (36)	2 (8)	0	0	11 (44)
Rash or acne*	8 (32)	1 (4)	1 (4)	0	10 (40)
Dyspnea	8 (32)	1 (4)	0	0	9 (36)
Paronychia	9 (36)	0	0	0	9 (36)
Anemia	6 (24)	1 (4)	1 (4)	0	8 (32)
Coughing	7 (28)	0	0	0	7 (28)
Myalgia	4 (16)	2 (8)	1 (4)	0	7 (28)
Anorexia	3 (12)	3 (12)	0	0	6 (24)
CPK increased	3 (12)	1 (4)	2 (8)	0	6 (24)
Back pain	4 (16)	1 (4)	0	0	5 (20)
Dry eyes	5 (20)	0	0	0	5 (20)
Mucositis oral	4 (16)	1 (4)	0	0	5 (20)
Nausea	5 (20)	0	0	0	5 (20)
Platelets decreased	4 (16)	1 (4)	0	0	5 (20)
Dry mouth	3 (12)	0	0	0	3 (12)
Pruritus	0	3 (12)	0	0	3 (12)
Fissures	3 (12)	0	0	0	3 (12)

The adverse events that were considered by the investigators to be related to osimertinib treatment observed in at least 10% of the patients are recorded.
* This category is a grouped term.

4. Discussion

Patients with life-threatening advanced NSCLC who harbor a rare EGFRex20 + mutation (4–12%) have limited effective treatment options. This study aimed to investigate whether the increased dosage of osimertinib 160 mg once daily would induce a stronger anti-tumor response and prolong survival. Our confirmed ORR was 28% (95% CI 12–49). Whilst this study did not reach the ORR of 30% we assumed in our power calculation, the treatment did partially substantiate clinical benefit. We found that 20 (80%) patients experienced a decrease in tumor size. In addition, the confirmed CBR of our study is 60% (15 of 25 patients) at 6 months. Within the 15 patients who experienced CBR, 10 patients received osimertinib 160 mg as first line treatment suggesting a more effective strategy in first compared to second line.

Currently, this is the largest phase II study which investigated osimertinib 160 mg in patients with EGFRex20 + NSCLC. Similar studies with osimertinib in this subset of patients are being conducted (ClinicalTrials.gov, Identifier: NCT04974879) and are summarized in Supplementary Table 1. The evidence reviewed in our study suggests benefit for osimertinib 160 mg over 80 mg, with a confirmed ORR of 28% and a CBR of 60%. This study has found responses across the entire spectrum of the EGFRex20 + mutation (see Supplementary Table 3), including the helical region and point mutations. Comparison of our findings considering trAEs with studies evaluating osimertinib 80 mg daily, confirms that treatment with osimertinib 160 mg daily result in higher rates of diarrhea (72% any grade), fatigue (44% any grade), and acneiform rash (40% any grade). However, the occurred trAEs are tolerable and comparable with other new therapy strategies for EGFRex20 + NSCLC patients [30,31]. In comparison to the ECOG-ACRIN 5162, our study provides additional evidence that osimertinib 160 mg once daily shows a similar confirmed ORR in first-line setting. This combination of findings further supports the idea that osimertinib 160 mg is a relevant first-line treatment option for patients with EGFRex20 + NSCLC.

New directed treatment strategies, including poziotinib and mobocertinib, attempt to overcome steric hindrance at the active site of the EGFRex20 + mutation, while minimizing toxicity by preserving selectivity against the wild type *EGFR* [30,31]. Poziotinib showed an average potency 100 times greater than osimertinib in EGFRex20 + *in vitro* [31], but an ORR of 14.8% among 115 patients with EGFRex20 + NSCLC [32]. Another group of 114 patients with EGFRex20 + NSCLC, progressing on platinum-based chemotherapy, were treated with mobocertinib and showed a confirmed ORR of 28% (95% CI, 20–37) by IRC assessment and 35% (95% CI, 26–45) by investigator assessment, with a DoR of 17.5 months (95% CI, 7.4–20.3) [33]. Due to the encouraging duration of the responses, mobocertinib was granted FDA accelerated approval in September 2021 [34]. Unfortunately, mobocertinib could not preserve selectivity against the wild type *EGFR* and provoked grade ≥ 3 trAEs in 46% of the patients and diarrhea in 90% (21% trAEs grade 3–4). Taken together, treatment with osimertinib 160 mg shows no improvement regarding ORR by investigator assessment, but less clinical burden for patients in terms of less severe trAEs compared to poziotinib and mobocertinib.

The exploratory CHRYSALIS single arm phase II study evaluated the intravenous treatment amivantamab in 81 patients who were pretreated with chemotherapy [35]. Park et al. (2021) reported an ORR of 40% with a median DoR of 11.1 months, a median PFS of 8.3 months,

and an expected safety profile associated with dual inhibition of *EGFR* and MET with grade 3–4 trAEs reported in 16% of all patients. Based on these results, amivantamab was granted FDA accelerated approval in May 2021 and EMA approval in December 2021 for patients with EGFRex20 + NSCLC with disease progression on or after platinum-based chemotherapy [36,37]. However, the treatment failed to address yet the clinical activity in CNS disease since it was an exclusion criteria [35]. Our study showed a decrease in brain lesion size in all patients with CNS disease, suggesting benefit of osimertinib for this subgroup. Another disadvantage of amivantamab is the possible adverse clinical burden due to more hospital visits because of the intravenous treatment, with associated infusion-related reactions (IRRs). Therefore, the disadvantages of amivantamab treatment raises the possibility that osimertinib 160 mg oral can be a good alternative for patients with EGFRex20 + NSCLC with CNS disease and deteriorated ECOG performance status.

Recently, more exciting new treatment options are being established for patients with EGFRex20 + NSCLC. Clinical data from a phase I study (ClinicalTrials.gov, Identifier:NCT04036682) evaluating CLN-081 (TAS6417) reported 13 confirmed PR and 8 unconfirmed PR among the 42 evaluable patients [41]. The findings from the phase II portion indicated 54% of patients experienced a PR (six confirmed, one unconfirmed) following treatment with a 100 mg twice daily dose of CLN-081, granting a breakthrough therapy designation from the FDA in January 2022 [42,43]. Another promising breakthrough treatment option is the selective, irreversible *EGFR* inhibitor DZD9008 [44]. In a cohort of 97 patients treated at the recommended phase 2 dose of 300 mg once daily, the ORR was 48.4%, and the disease control rate was 90.3% [45]. DZD9008 is currently being evaluated in phase II clinical development (ClinicalTrials.gov, Identifier:NCT03974022) for the treatment of patients with EGFRex20 + NSCLC and HER2-mutated NSCLC.

The effect of co-occurring alterations, for example TP53, PTEN or STK11 mutations, or the different EGFRex20 + mutation variants is not well identified [24,46]. In this study, four out of five patients, showed at least 25% of tumor shrinkage while harboring the TP53 co-occurring alteration. With a small sample size, caution must be applied. Furthermore, there was no significant difference in antitumor responses between the EGFRex20 + mutation variants. However, the uncommon *EGFR* mutation is characterized as heterogenous showing different sensitivity among the mutational spectrum [47,48]. A further larger study and review with more focus on the co-occurring alterations and the EGFRex20 + mutation variants is therefore suggested and will help define unmet needs for future therapeutic advances.

Our study has several limitations. Firstly, it should be acknowledged that the distribution of EGFRex20 + mutation variants in this cohort is skewed towards near-loop mutations, with only three far-loop insertions. The responses almost all occur in EGFRex20 + mutation variants reported as sensitive to osimertinib in preclinical models, including the sensitizing variant p.(A763_Y764insFQEA). This knowledge should be taken into account while interpreting the survival data and therefore the different EGFRex20 + mutation variants were extensive elaborated. Secondly, a potential source of bias for the study is the influence the researchers had upon the response review, since the trial's lack of central review. Thirdly, the sample size of our cohort is relatively small, exists of only White patients with EGFRex20 + NSCLC, and are all being treated in a single country. In spite of its limitations, this prospective phase 2 POSITION20 study evaluates a relatively large case series of patients with EGFRex20 + NSCLC treated with 160 mg osimertinib, providing valuable insights. [42].

It is important to test and characterize the different EGFRex20 + mutation variants, co-occurring alterations, and evaluate the performance status of the patient to target the EGFRex20 + tumor effectively, and achieve clinical benefit. Osimertinib cannot be routinely recommended at either 80 or 160 mg daily for patients with EGFRex20 + NSCLC, but further development of higher dosing schemes is warranted. Approved and/or newer drugs in clinical trials should be considered first. Osimertinib 160 mg once daily can only be considered in patients who cannot access clinical trials and do not have other standard-of-care options available, particularly if CNS disease is present.

5. Conclusion

In conclusion, osimertinib 160 mg showed modest antitumor activity in patients with EGFRex20 + NSCLC, with a confirmed ORR of 28% and acceptable toxicity.

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CRediT authorship contribution statement

Fenneke Zwierenga: Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Project administration. **Bianca van Veggel:** Investigation, Writing – review & editing. **Lizza E.L. Hendriks:** Investigation, Writing – review & editing. **T. Jeroen N. Hiltermann:** Investigation, Writing – review & editing. **Birgitta I. Hiddinga:** Investigation, Writing – review & editing. **Lucie B.M. Hijmering Kappelle:** Investigation, Writing – review & editing. **Arja ter Elst:** Data curation, Writing – review & editing. **Sayed M.S. Hashemi:** Investigation, Writing – review & editing. **Anne-Marie C. Dingemans:** Investigation, Writing – review & editing. **Cor van der Leest:** Conceptualization, Methodology, Writing – review & editing. **Adrianus J. de Langen:** Investigation, Writing – review & editing. **Michel M. van den Heuvel:** Conceptualization, Methodology, Writing – review & editing. **Anthonie J. van der Wekken:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

FZ has no conflict of interest; **BV** has no conflict of interest; **LLH** reports research funding: Roche Genentech, Boehringer Ingelheim, AstraZeneca (all institution, Takeda and Beigene under negotiation); advisory board: BMS, Eli Lilly, Roche Genentech, Pfizer, Takeda, MSD, Merck, Novartis, Boehringer Ingelheim, Amgen, Janssen (all institution, Roche one time self); speaker: MSD, Lilly (institution); travel/conference reimbursement: Roche Genentech (self); mentorship program with key opinion leaders: funded by AstraZeneca; fees for educational webinars: Benecke, Medtalks, VJOncology (self), high5oncology (institution); interview sessions funded by Roche Genentech, Bayer, Lilly (institution); local PI of clinical trials: AstraZeneca, Novartis, BMS, MSD /Merck, GSK, Takeda, Blueprint Medicines, Roche Genentech, Janssen Pharmaceuticals, Mirati, outside the submitted work; **TH** reports research funding: Roche, Boehringer Ingelheim, AstraZeneca (all institution); advisory board: BMS, Roche, Merck, Pfizer; local PI of clinical trials: AstraZeneca, GSK, Novartis, Merck Serono, Roche, BMS, outside the submitted work; **BH** has no conflict of interest; **LH** has no conflict of interest; **AE** has no conflict of interest; **SH** reports advisory board/ grants: Abbvie, AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, Janssen, GSK, Loxo, MSD, Novartis, Roche, Takeda, outside the submitted work; **AD** reports research support from Amgen; consulting fees from Roche, Boehringer Ingelheim, AstraZeneca, Pharmamar, Bayer, Sanofi, and Amgen; payment for lectures or presentations from Eli Lily, AstraZeneca, Chiesi, Pfizer, Takeda and Jansen; participation in data safety monitoring board for Roche and Takeda., outside the submitted work; **CL** reports participation in advisory boards: Amgen, AstraZeneca, BMS, MSD, Roche, outside the submitted work; **AL** reports grants: BMS, MSD, Boehringer Ingelheim, AstraZeneca (all institution); non-financial support from Merck Serono, Roche, outside the submitted work; **MH** reports research support from Astrazeneca, BMS, Janssen, Stichting

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Appendix A. Supplementary data

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