Primary and secondary resistance mechanisms in EGFR mutated non-small cell lung cancer

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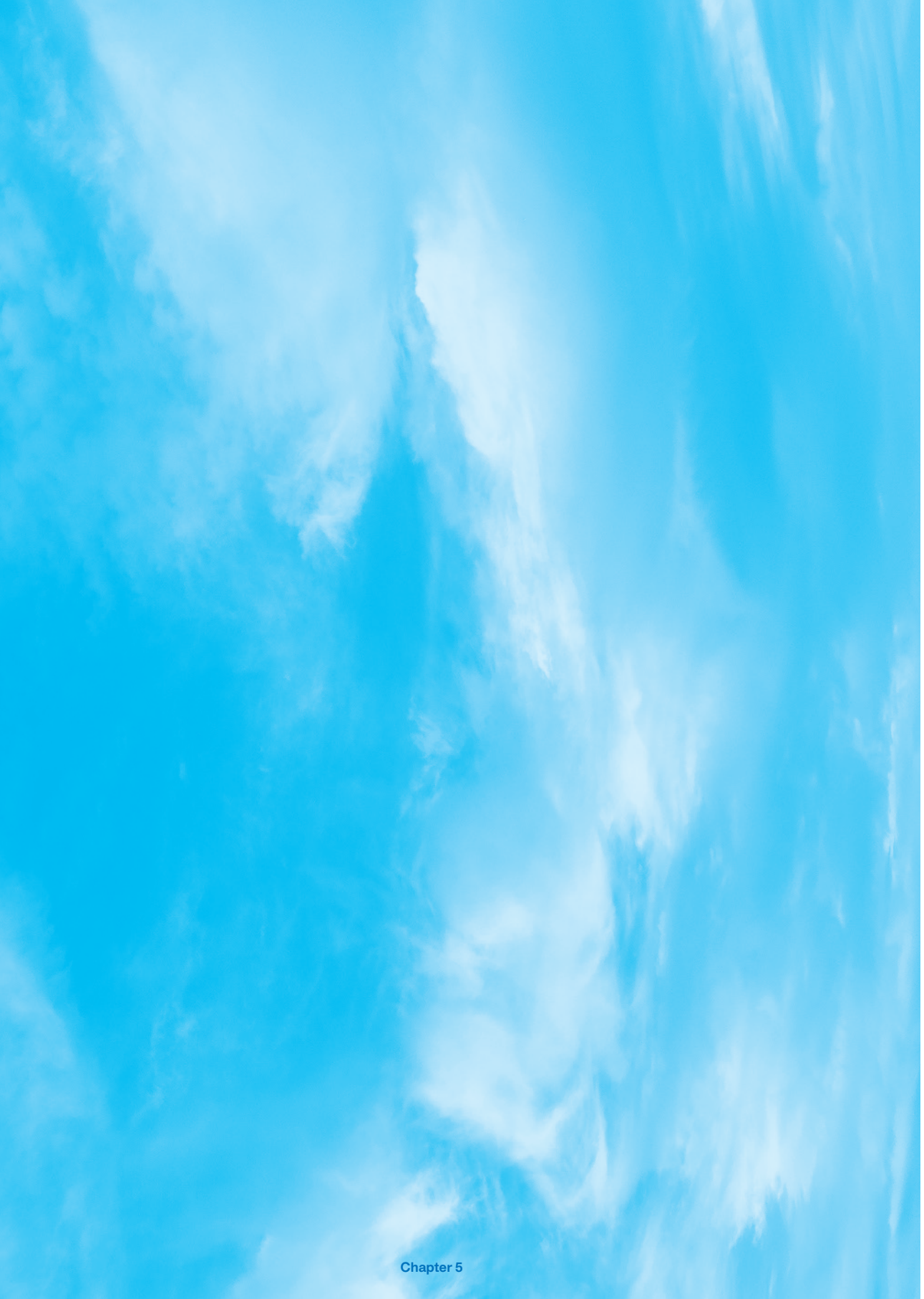

Chapter 5

A phase II trial combining afatinib with cetuximab in patients with *EGFR* exon 20 insertion positive non-small cell lung cancer

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Abstract

Introduction: **Epidermal growth factor receptor (*EGFR*) exon 20 insertion (ex20ins) mutations are the third most common *EGFR* mutations in patients with non-small cell lung cancer (NSCLC) and are associated with primary resistance to EGFR tyrosine kinase inhibitors (TKIs). There is evidence of activity of combining EGFR TKIs with monoclonal antibodies. Here we report on the efficacy and safety of afatinib in combination with cetuximab.**

Methods: **In this single-arm phase II trial, patients with advanced NSCLC harboring an EGFR ex20ins mutation were treated with afatinib 40 mg once daily, in combination with cetuximab 500 mg/m2, every two weeks. The primary endpoint was disease control rate (DCR) after 18 weeks of treatment.**

Results: **Thirty-seven patients started treatment: median age 65 years (range 40 – 80 years), 78% female, 35 (95%) Caucasian. The study achieved its primary endpoint, with a DCR of 54% at 18 weeks, an overall response rate (ORR) of 43% and a 32% confirmed ORR. Best responses were partial (n=16), stable (n=16), progressive disease (n=2) or not evaluable (n=3). Median progression free survival was 5.5 months (95% CI: 3.7 – 8.3 months) and median overall survival was 16.8 months (95% CI: 10.7 – 25.8 months). Most common treatment related adverse events (TRAEs) were diarrhea (70%), rash (65%), dry skin (59%), paronychia (54%) and erythema (43%). Grade III TRAEs were reported in 54% of all patients.**

Conclusions: **Combination treatment with afatinib and cetuximab demonstrated antitumor activity with a DCR of 54% at 18 weeks and a 32% confirmed ORR. Toxicity was significant, however manageable after dose reduction.**

Introduction

Epidermal growth factor receptor (*EGFR*) exon 20 insertion mutations (ex20ins) comprise 4% to 12% of *EGFR* mutated non-small cell lung cancer (NSCLC) and approximately 2% of all NSCLC cases [1-4]. In contrast to the more common in-frame deletions in exon 19 and the L858R point mutation in exon 21, *EGFR* ex20ins are generally resistant to EGFR tyrosine kinase inhibitors (TKIs), except for the *EGFR* A763_Y764insFQEA variant [2, 5-8]. Targeting *EGFR* ex20ins is challenging because these mutations activate EGFR without diminishing ATP affinity, resulting in a small therapeutic window for EGFR TKIs [9]. Although there is progress in developing novel targeted therapies for these patients, currently platinum-based chemotherapy remains the first line treatment of choice [10-12].

EGFR ex20ins are unresponsive to EGFR TKIs in general, including afatinib, a second generation irreversible EGFR TKI, with overall response rates (ORR) below 10% [8]. In addition, a pooled analysis of 70 patients treated with afatinib monotherapy demonstrated modest activity with an ORR of 24.3% [13]. There is some evidence of increased anti-tumor activity when adding cetuximab to an EGFR TKI. Cetuximab, an anti-EGFR monoclonal antibody (mAb), binds with high affinity to the extracellular domain of the EGFR receptor, partially blocks the ligand-binding domain and sterically hinders EGFR dimer formation [14]. Cetuximab can also target EGFR by diminishing EGFR phosphorylation [15]. Consequently, in combination with an EGFR TKI, mAbs induce a more potent inhibitory effect *in vitro*, *in vivo* and in xenografts than either therapy alone [16]. In 2017, we described tumor responses in three of four *EGFR* ex20ins positive NSCLC patients after afatinib and cetuximab combination treatment [17]. In conclusion, there is evidence of activity of combining EGFR TKIs with EGFR monoclonal antibodies. However, the safety profile of this combination is of special interest, since treatment with afatinib and cetuximab led to high rates of EGFR-related toxicity, especially dermatological side effects and diarrhea [18, 19].

We previously presented interim-data of the first 17 patients with *EGFR* ex20ins positive metastatic NSCLC who received afatinib in combination with cetuximab in our single arm, phase II trial (AFACET). The antitumor activity of this combination was demonstrated by a disease control rate (DCR) at 18 weeks of 59%, an ORR of 47% and median progression free survival (PFS) of 5.5 months. Almost 60% of patients experienced grade ≥3 toxicity [20]. Here, we report the final results of this trial.

Material and methods

Study Design and Patients

This single-arm, open-label, investigator-initiated phase II trial was conducted in five academic institutions in the Netherlands. Eligible patients had advanced NSCLC with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2 and had measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [21]. *EGFR* mutation status was locally tested using an amplicon based next-generation sequencing (NGS) hotspot panel that was validated for detection of *EGFR* ex20ins. Previous systemic therapy was allowed, but not mandatory. Key exclusion criteria were prior treatment with EGFR targeting antibodies (prior treatment with EGFR TKIs was allowed) and symptomatic brain metastases. Untreated asymptomatic brain metastases were allowed.

The protocol was approved by the medical research ethics committee. All patients provided written informed consent prior to study procedures and the study was done in accordance with the Declaration of Helsinki [22]. This study is registered with ClinicalTrials.gov, NCT03727724.

Treatment and Study Assessments

Patients received afatinib 40 mg orally once daily, in combination with cetuximab 500 mg/m^2 intravenously every two weeks, until disease progression or unacceptable toxicity. Patients who discontinued treatment for reasons other than disease progression continued with tumor assessments until disease progression. Supportive medication consisted of minocycline 100 mg once daily, loperamide as needed and emollient skin creams two-four times per day. Two dose reductions were allowed: firstly, a dose reduction of afatinib to 30 mg in combination with 400 mg of cetuximab, followed by a second dose reduction of afatinib 30 mg once daily and cetuximab 250 mg. If unacceptable toxicity recurred following two dose modifications, study treatment was permanently discontinued. Tumor assessments according to RECIST v1.1 were locally performed by an independent thoracic radiologist using computed tomography (CT) scans. CT scans were performed at baseline and every six weeks thereafter until radiographic progression. Magnetic resonance imaging (MRI) of the brain was performed at baseline, and thereafter every six weeks only in case brain metastases were present at screening. Selected patients were permitted to continue treatment beyond disease progression in case of ongoing clinical benefit.

Outcomes

The primary objective was to determine the DCR after 18 weeks of afatinib and cetuximab treatment. Secondary endpoints included investigator-assessed ORR, duration of response (DoR), PFS, overall survival (OS) and safety. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

Table 1: Baseline patient and tumor characteristics (n = 37)

Characteristics	Number of patients (%)
Median age, years (range)	65 (40 – 80)
Female	29 (78)
Histology	
Adenocarcinoma	36 (97)
Squamous cell carcinoma	1 (3)
Smoking status	
Never	13 (35)
Former	22 (59)
Current	2 (5)
Ethnicity	
Caucasian	35 (95)
African Descent	1 (3)
East/Southeast Asian	1 (3)
ECOG performance status	
0	11 (30)
1	23 (62)
2	3 (8)
Brain metastases at baseline	14 (38)
Local radiotherapy at baseline	2 (14)
Untreated asymptomatic brain metastases at baseline	12 (86)
Most common *EGFR* ex20ins mutations (>10%)	
S768_D770dup	7 (19)
A767_V769dup	4 (11)
D770_N771insG	4 (11)
Prior treatment	
Platinum based chemotherapy	10 (27)
Chemo-immunotherapy	6 (16)
Osimertinib	7 (19)
Median prior lines of therapy (range)	0 (0 - 5)
0	19 (51)
1	12 (32)
2	5 (14)
5	1 (3)

Abbreviations: ECOG: Eastern Cooperative Oncology Group; *EGFR* ex20ins: epidermal growth factor receptor exon 20 insertion.

Statistical Analysis

A Simon's two-stage optimal design was used for sample size determination. The null hypothesis was tested against a one-sided alternative, with α: 0.10, power of 90. The trial aimed to show a DCR of ≥ 40% at 18 weeks after treatment initiation. Seventeen patients were planned for inclusion in the first stage. If at least four patients experienced disease control after 18 weeks of treatment, the trial expanded to a total sample size to 37 patients. The study treatment was accepted for further development if at least 11 of 37 patients experienced disease control at 18 weeks. A uniform minimum variance unbiased estimator for the response rate was used on that matter proposed by Jung [23], and as a 95% confidence interval (CI) the Koyama et al [24] method was used on that purpose. The clinfun package, version 1.1.0, in R programming was used for that calculation, and specifically the twostage.inference function.

Overall response and disease control were estimated, including their two-sided 95% confidence intervals (CIs). DCR was defined as percentage of patients who had achieved complete response, partial response or stable disease at eighteen weeks of treatment. Time-to-event endpoints (PFS, DoR and OS) were analyzed using the Kaplan-Meier method. PFS was defined as the interval between initiation of study treatment and the date of radiological progression or death from any cause, whatever occured first. The data cutoff for the analyses was December 18, 2022. P values for subgroups were calculated using the log rank test. Statistical software program R was used for all the analyses.

Results

Patients

Between Jan 2019 and Dec 2021, 40 patients were screened. Three patients did not meet all inclusion criteria and were registered as screen failure. Thirty-seven patients were eligible and started study treatment. All patients had stage IV NSCLC harboring an *EGFR* ex20ins mutation based on NGS results of histological or cytological tumor samples. Baseline characteristics are shown in Table 1. The majority of patients (78%) were female and 35% had never smoked. Among fourteen patients (38%) with brain metastases at baseline, two were treated previously with local radiotherapy. The most common *EGFR* ex20ins mutation was S768_D770dup (19%, n = 7), followed by A767_V769dup (11%, n = 4) and D770_N771insG (11%, n = 4). No patients with the known sensitizing *EGFR* ex20ins variant A763_Y764insFQEA were included in this cohort. Eighteen patients (49%) received previous treatment with chemotherapy, chemo-immunotherapy and/or osimertinib. None of the patients received another (new-generation) EGFR TKI prior to enrollment in the study. The median number of previous lines of therapy was zero (range, 0 – 5).

Efficacy

The primary endpoint was met as disease control was achieved in 54% (95% CI: 25 – 63, n = 20) after 18 weeks of treatment. Best responses were partial (n = 16), stable (n = 16) or progressive disease (PD) (n = 2) (Figure 1). Three patients were not evaluable (NE) for response due to a treatment-related adverse event (TRAE) or symptomatic deterioration before the first radiological assessment. The ORR was 43%. Among the 16 patients with a PR, 12 were confirmed at subsequent imaging resulting in a confirmed ORR rate of 32% (95% CI, 20 – 49). Median DoR was 4.7 months (range 0.3 – 16.6 months), median PFS 5.5

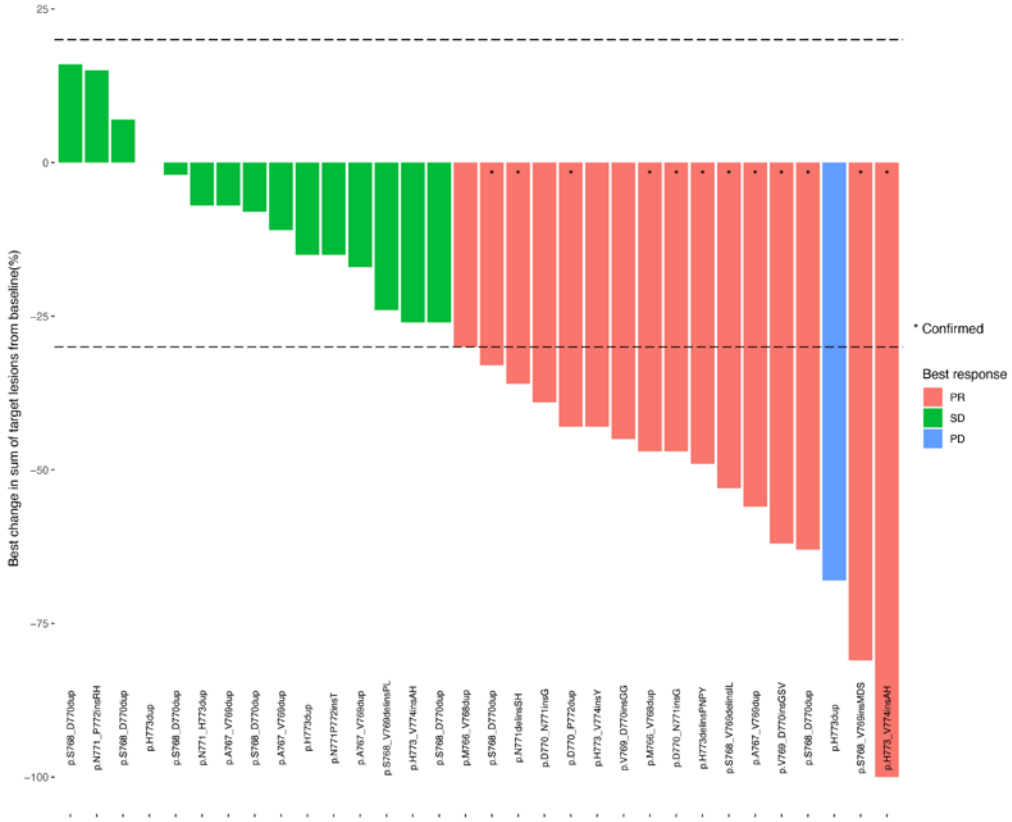

Figure 1. Tumor response to afatinib and cetuximab. Waterfall plot of the best percent change from baseline in the sum of target lesion diameters by locations of EGFR ex20ins mutations based on investigator assessment in patients with evaluable disease. The dashed lines at 20% and -30% indicate the thresholds for progressive disease and partial response, respectively, for RECIST response. Confirmed response rates are indicated with an asterisk. EGFR indicates epidermal growth factor receptor; ex20ins, exon 20 insertion; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

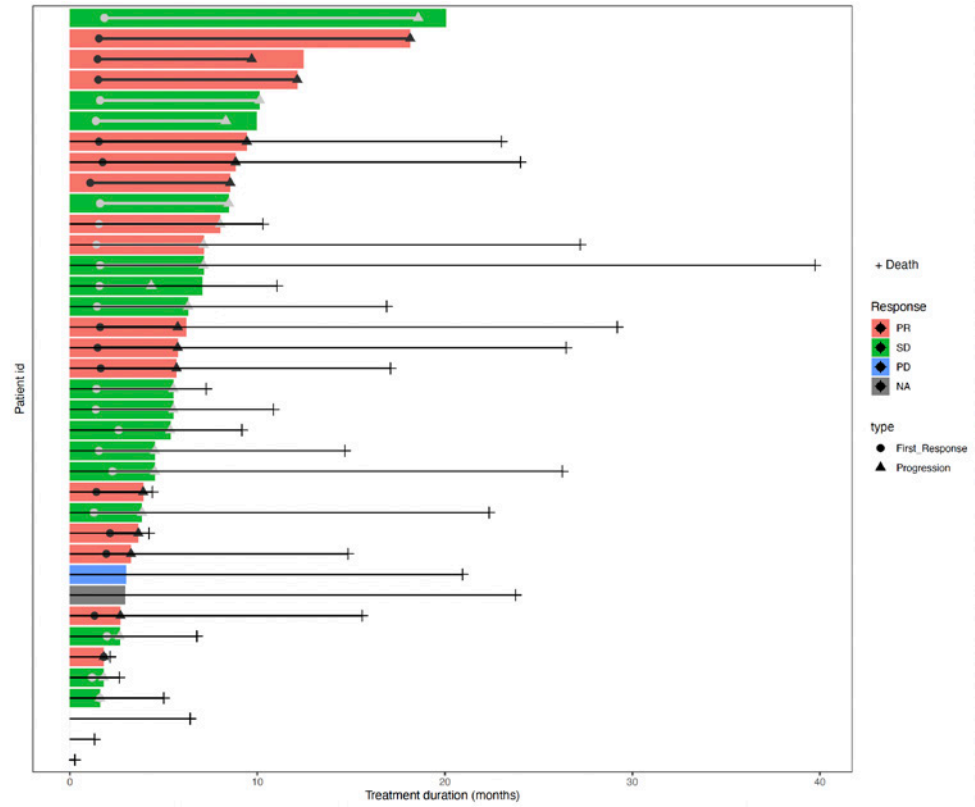

Figure 2. Duration of treatment. Duration of afatinib and cetuximab treatment in all treated patients (N = 37). Each bar represents one subject in the study. NA indicates nonapplicable; PD, progressive disease; PR, partial response; SD, stable disease.

months (95% CI: 3.7 – 8.3 months) and median OS was 16.8 months (95% CI: 10.7 – 25.8 months). At data cutoff (December 2022) all patients were off study treatment (Figure 2). The primary reasons for discontinuation were PD (73%) or adverse event(s) (22%). Two patients refused further treatment (5%).

In the subset of patients with brain metastases at baseline, the median PFS was similar to those without brain metastases (p-value = 0.87). Three patients continued study treatment beyond cerebral disease progression for a median of 7 weeks (range 6 – 14 weeks). One patient received whole brain radiotherapy during study treatment. Seven weeks later, treatment was permanently discontinued due to further progression. Of the patients with brain metastases at baseline, all patients (except two patients not evaluable for response) had cerebral progression as first site of progression.

Although one partial response was observed in the subgroup of patients pretreated with osimertinib (n = 9), patients pretreated with osimertinib did fare worse than those without in terms of PFS (p = 0.00055; Log-rank test).

When considering the treatment line, patients receiving study treatment as first line treatment showed a statistically longer PFS compared to later lines (p = 0.0001; Log-rank test).

Table 2: Mutation type and response to treatment

Insertion region	Mutation type	Best response	Best change from baseline according RECIST (%)	PFS (months)
Helical region n = 2 ORR 100%	p.M766_V768dup	PR	-30	5.5
	p.M766_V768dup	PR	-47	3.2
Near loop region n = 28 ORR 39%	p.A767_V769dup	SD	-11	19.6
	p.A767_V769dup	SD	-17	5.5
	p.A767_V769dup	PR	-56	8.5
	p.A767_V769dup	SD	-7	6.2
	p.S768_V769insMDS	PR	-81	5.5
	p.S768_D770dup	PR	-63	6.9
	p.S768_D770dup	SD	-8	3.7
	p.S768_D770dup	SD	7	9.7
	p.S768_D770dup	SD	-2	1.6
	p.S768_D770dup	SD	16	1.4
	p.S768_D770dup	SD	-26	5.5
	p.S768_D770dup	PR	-33	9.7
	p.S768_V769delinsIL	NE	NE	0
	p.S768_V769delinsIL	PR	-53	8.8
	p.S768_V769delinsPL	SD	-24	8.3
	p.V769_D770insGSV	PR	-62	18.0
	p.V769_D770insGG	PR	-45	1.6
	p.D770_N771insG	PD	NE	0
	p.D770_N771insG	PR	-47	12.0
	p.D770_N771insG	SD	NE*	12.7
	p.D770_N771insG	PR	-39	2.8
	p.D770_P772dup	NE	NE	3.0
	p.D770_P772dup	PR	-43	7.8
	p.N771delinsGY	NE	NE	1.0
	p.N771_P772insRH	SD	15	3.7
	p.N771_P772insT	SD	-15	3.9
	p.N771delinsSH	PR	-36	9.7
	p.N771_H773dup	SD	-7	2.1
Far loop region n = 7 ORR 43%	p.H773dup	PD	-68	1.4
	p.H773dup	SD	0	6.9
	p.H773dup	SD	-15	4.1
	p.H773delinsPNPY	PR	-49	9.2
	p.H773_V774insY	PR	-43	2.1
	p.H773_V774insAH	SD	-26	4.6
	p.H773_V774insAH	PR	-100	3.7

*There was no measurable lesion conforming to RECIST at baseline

NE: non-evaluable; ORR: overall response rate; PD: progressive disease; PFS: progression free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease

Table 3: Summary of TRAEs of any grade reported in 10% or more of patients or grade 3 or higher.

	Patients, No. (%)			
TRAE ≥ 10%	**Total**	**Grade 1**	**Grade 2**	**Grade ≥ 3**
Diarrhea	26 (70)	19 (51)	2 (5)	5 (14)
Rash*	24 (65)	8 (22)	11 (30)	5 (14)
Dry skin	22 (59)	10 (27)	7 (19)	5 (14)
Paronychia	20 (54)	9 (24)	10 (27)	1 (3)
Erythema multiforme	16 (43)	8 (22)	6 (16)	2 (5)
Fatigue	14 (38)	9 (24)	5 (14)	0 (0)
Hypertrichosis	13 (35)	11 (30)	2 (5)	0 (0)
Nausea	13 (35)	6 (16)	6 (16)	1 (3)
Anorexia	9 (24)	5 (14)	4 (11)	0 (0)
Mucositis	9 (24)	2 (5)	6 (16)	1 (3)
Dysgeusia	8 (22)	7 (19)	1 (3)	0 (0)
Pruritus	7 (19)	4 (11)	2 (5)	1 (3)
Dry mouth	6 (16)	6 (16)	0 (0)	0 (0)
Chills	5 (14)	4 (11)	1 (3)	0 (0)
Dry eye	5 (14)	4 (11)	1 (3)	0 (0)
Infusion related reaction	5 (14)	0 (0)	5 (14)	0 (0)
Headache	4 (11)	2 (5)	2 (5)	0 (0)

Abbreviations: TRAE: treatment-related adverse event
*Rash is defined by rash papulopustular, rash, maculo-papular, dermatitis and rash acneiform.

Responses were observed across the entire spectrum of *EGFR* ex20ins mutations (Table 2). There were no differences in ORR within the near-loop and far-loop regions of exon 20. Only two patients harbored an EGFR ex20ins within the helical region with an ORR of 100%.

Safety

Most common TRAEs were diarrhea (70%), rash (65%), dry skin (59%), paronychia (54%) and erythema (43%). Grade III TRAEs were reported in 54% of patients. Grade III TRAEs ≥ 10% included diarrhea (n=5; 14%), rash (n=5; 14%) and dry skin (n=5; 14%). All TRAEs of any grade reported in 10% or more or grade three or higher TRAEs are listed in Table 3. No grade IV treatment-related toxicity was observed. One patient died due to respiratory failure after the first infusion of study medication, probably related to disease progression, possibly treatment related. Two other patients died during study treatment due to non-treatment related events, respectively COVID-19 infection and cardiac arrest. Twenty-five (68%) patients required a dose reduction, including five patients (14%) who had two dose reductions. Rate of treatment discontinuation due to TRAEs was 16% (n=6), including one grade III allergic reaction after the first infusion of cetuximab.

Discussion

In this phase II trial, combination treatment with afatinib and cetuximab was effective for patients with *EGFR* ex20ins mutated NSCLC, resulting in a DCR of 54% after 18 weeks and a confirmed ORR of 32%. The median PFS was 5.5 months. Twenty-eight (76%) patients experienced a decrease in tumor size.

Multiple other TKIs, specifically designed to target *EGFR* ex20ins, have recently been tested in clinical trials. This led to the FDA approval of mobocertinib, for patients harboring an *EGFR* ex20ins mutation, who progressed on or after prior platinum-based chemotherapy. The ORR was 28% with a median PFS of 7.3 months [25, 26]. Poziotinib, another EGFR ex20ins-directed TKI demonstrated a 14.8% ORR [27]. In addition, the EGFR-MET bispecific antibody amivantamab was active in pretreated patients with an ORR of 40% and median PFS of 8.3 months [28]. Although progress has been made in the treatment of previously considered untargetable *EGFR* ex20ins, the effectiveness of these new agents is not on the same level as the treatment options for classical *EGFR* mutations and toxicity remains a major concern.

EGFR ex20ins mutations lack the therapeutic advantage of increased affinity for TKI versus ATP. Therefore, these mutations have a small therapeutic window for EGFR TKIs, resulting in high rates of typical EGFR related toxicity. In our study, grade III or higher TRAEs were reported in 54% of all patients, mostly consisting of diarrhea and skin toxicity. As a result, 68% of patients required a dose reduction and 16% percent discontinued treatment due to adverse events. With close monitoring, dose reductions and timely referral to a dermatologist, skin-related toxicity was generally manageable. However, this also clearly shows that adding an anti-EGFR mAb to afatinib enhances on-target side effects associated with inhibition of EGFR. Previous studies with TKI-antibody combinations already showed an increase in TRAEs, resulting in more than 50% grade ≥ III toxicity [29, 30].

In addition, other TKIs like poziotinib and mobocertinib, specifically designed to target *EGFR* ex20ins mutations, could not preserve selectivity against wild type EGFR. During poziotinib treatment, 28% and 26% of patients had grade ≥ 3 rash and diarrhea TRAEs, respectively [27]. Results from the expanded access program showed 66% grade ≥ 3 TRAEs[31]. These high toxicity rates led to a new trial to evaluate a lower dose and twice daily dosing. Mobocertinib

resulted in 46% grade ≥ 3 TRAEs [26]. Toxicity of these new agents seems comparable to our study. Possibly, a lower starting dose of afatinib 30 mg daily will lead to fewer serious adverse events, while maintaining effectiveness [32].

Most of the clinical trials regarding new *EGFR* ex20ins directed therapies excluded patients with active or untreated brain metastases. Therefore, the intracranial activity of these agents is largely unknown. Regarding intracranial activity in our study, the majority of patients with brain metastases at baseline were untreated (n=12). Although most patients experienced some decrease of tumor shrinkage at the first tumor evaluation, all of these patients had first progression in the brain, suggesting brain radiotherapy is required before start treatment with afatinib plus cetuximab.

Our study has several limitations, including the lack of a control arm and an independent blinded radiological review. In addition, no previous line of treatment was required. Patients treated with afatinib and cetuximab as first line treatment showed a statistically longer PFS compared to later lines. Therefore, comparison to other predominantly second line studies involving new EGFR ex20ins directed targeted treatment options is difficult.

In conclusion, combination treatment with afatinib and cetuximab demonstrated antitumor activity in patients with *EGFR* ex20ins positive NSCLC, with a DCR of 54% at 18 weeks and a 32% confirmed ORR. EGFR-related toxicity was significant, however manageable after dose reduction.

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