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ABSTRACT

Objectives: Epidermal growth factor receptor (*EGFR*) exon 20 insertions comprise 4–10 % of *EGFR* mutations in non-small cell lung cancer (NSCLC) and are associated with primary resistance to first and second generation EGFR tyrosine kinase inhibitors (TKIs). *In vitro* and preclinical animal studies have shown that osimertinib exerts antitumor activity against *EGFR* exon 20 mutation positive NSCLC. We report on a cohort of advanced stage NSCLC patients who harbor an *EGFR* exon 20 mutation and received osimertinib treatment.

Material and methods: Twenty-one patients were treated with osimertinib 80 or 160 mg once daily from April 2016 to June 2018, in four institutions in the Netherlands. Data were obtained retrospectively. Progression free survival (PFS), disease control rate (DCR), overall survival (OS) and objective response rate (ORR) were assessed using RECIST v1.1.

Results: Thirteen patients received prior platinum-based chemotherapy, and three patients a first – or second generation EGFR TKI. We observed 1 partial response, 17 patients with stable disease and 3 with progressive disease as best response to osimertinib (ORR 5 %). Median PFS was 3.6 (95 % CI, 2.6–4.5) months. PFS did not differ for patients with co-occurring *TP53* mutations (p = 0.937). The DCR at three months was 71 %. Median OS was 8.7 (95 % CI, 1.1–16.4) months.

Conclusion: Osimertinib has limited antitumor activity in patients with *EGFR* exon 20 mutated NSCLC, with an ORR of 5 %.

1. Introduction

Epidermal growth factor receptor (*EGFR*) exon 20 insertion mutations are identified as a subset (4–12 %) of *EGFR* mutation-positive non-small cell lung cancer (NSCLC) and are the third most common category of EGFR activating mutations [1–3]. *EGFR* exon 20 insertion mutations are heterogeneous at the molecular level but can be characterized as in-frame duplications (dup) or insertions (ins), or deletion/insertion (del-ins) mutations. *EGFR* exon 20 insertions are *EGFR* driver mutations that exhibit intrinsic resistance to first and second generation EGFR tyrosine kinase inhibitors (TKIs) with overall response rates of only 3–8 % [1,3]. In contrast to the common *EGFR* exon-19 deletion and L858R point mutations, *EGFR* exon 20 insertion mutations alter the α-C helix resulting in steric hindrance of the drug-binding pocket, that prevents binding of first and second generation EGFR TKIs [3,4]. Given the limited activity of first and second generation EGFR TKIs, new treatment options are needed to overcome primary resistance of *EGFR* directed treatment for tumors harboring an *EGFR* exon 20 insertion. Data about effectiveness of third generation EGFR TKIs are conflicting in preclinical studies. *In vivo*, *in vitro* and 3D modeling by Robichaux et al.

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showed that osimertinib lacks activity against cell lines harboring an *EGFR* exon 20 insertion, due to steric hindrance as a result of significant changes within the drug-binding pocket [4]. In contrast, a study by Floc'h et al. described anti-tumor activity of osimertinib across xenograft models, representing a variety of *EGFR* exon 20 insertions [5], in line with a previous report presenting *in vitro* activity of osimertinib in exon 20 insertion mutant cell lines [6]. Limited clinical data are available. Two cases with a clinical response to osimertinib have been published [7,8]. Recently, Fang et al. treated six Chinese patients with an EGFR exon 20 insertion mutation with osimertinib. This resulted in a median progression free survival (PFS) of 6.2 months [9]. Here, we report on a cohort of advanced stage *EGFR* exon 20 mutation positive NSCLC patients that were treated with osimertinib.

2. Material and methods

Twenty-one patients with advanced stage NSCLC harboring an *EGFR* exon 20 mutation were treated with osimertinib in four institutions in the Netherlands (Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, University Medical Center Groningen, Amsterdam UMC and Erasmus Medical Center). Data were obtained retrospectively. We started a search by identifying all patients treated with osimertinib from April 2016 to June 2018 in the four institutions. Then we selected the patients with an *EGFR* exon 20 mutation. Patients data were collected by searching electronic medical record databases. Histological or cytological tumor samples from all patients were tested for at least EGFR and KRAS mutation status. For 8 patients high resolution melting followed by Sanger sequencing was used to test for EGFR and KRAS mutations, while next-generation sequencing (NGS) with different panels was used to test for at the following mutations: BRAF, EGFR, HER2, KRAS, MET, PIK3CA. Patients were treated with commercially available osimertinib 80 mg or 160 mg once daily on an off-label basis. Response evaluation was performed every six to eight weeks, according to local practice. PFS, overall survival (OS), disease control rate (DCR) and objective response rate (ORR) were retrospectively assessed by the study team using Response Criteria in Solid Tumors (RECIST) version 1.1. PFS was defined as the interval between start of osimertinib treatment and radiological progression or death, whichever came first. PFS and OS data were calculated using Kaplan-Meier survival plots together with the median PFS or OS time and corresponding 95 % confidence intervals (CIs). P values for subgroups were calculated using the log rank test.

3. Results

3.1. Patient and tumor characteristics

Patient and tumor characteristics are summarized in Table 1. Median age was 63 years (range 38–82), 67 % of patients were female and median number of prior systemic treatments was 1 (range 0–3). Thirteen patients (62 %) received prior platinum-based chemotherapy. Three patients were treated with a first or second generation EGFR TKI, erlotinib (n = 1) or afatinib (n = 2); one patient experienced stable disease (SD) for 11 months after having received afatinib, while the other two patients had progression as best response. One patient was treated with luminespib (HSP-90 inhibitor) for nineteen months. Median time on the previous line of systemic treatment prior to osimertinib treatment was 4 months (95 % confidence interval [CI], 3.0–12.0). Eleven (52 %) of the treated patients had brain metastases at baseline. Cranial irradiation (whole brain radiotherapy (N = 1) or stereotactic radiotherapy (N = 2) was performed in three patients prior to starting osimertinib.

Response to osimertinib treatment and mutation findings are summarized in Table 2. All exon 20 mutations were clustered between Ala767 and Gly779. The most common mutation was p. Ala767_Val769dup (n = 4). No patients with the known sensitizing EGFR exon 20 insertion variant A763_Y764insFQEA were included in this cohort. Data about co-occurring genetic alterations and copy number variations were available for 13 patients (62 %). Tumor protein p53 (*TP53*) mutations were the most common type of co-occurring mutations detected (N = 8; 62 %), followed by other less common alterations in cyclin dependent kinase inhibitor 2A (*CDKN2A*), phosphatase and tensin homolog (*PTEN*), notch 1 gene (*NOTCH1*) and erb-b2 receptor tyrosine kinase 4 (*ERBB4*). In two patients (15 %) *EGFR* amplification was detected.

Table 1
Patient and tumor characteristics.

	Number	Percentage (%)
Age (years)	63	Range 38-82
Women	14	67
Histology		
Adenocarcinoma	20	95
Large cell neuroendocrine carcinoma	1	5
Tumor samples		
Histology	19	90
Cytology	2	10
Mutation type		
EGFR exon 20 insertion/duplication	17	81
EGFR exon 20 (bi/tri) nucleotide substitutions	4	19
Number of lines for advanced disease		
0	6	28.5
1	7	33.5
2	6	28.5
3	2	9.5
Prior platinum based chemotherapy	13	62
Prior TKI		
First generation	1	5
Second generation	2	10
Brain metastases at baseline	11	52

EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor.

3.2. Response to osimertinib treatment

Patients were treated with osimertinib 80 mg (N = 20) or 160 mg (N = 1) once daily. Osimertinib treatment was well tolerated with none of the patients requiring dose modification. Two patients experienced grade I nausea and three patients reported grade I skin toxicity. We observed one (5 %) partial response (PR), sixteen (76 %) patients with SD and four (19 %) with progressive disease (PD) as best response (Fig. 1). Median PFS was 3.6 (95 % CI, 2.6–4.5) months. The DCR at three months was 71 % (N = 15) (Fig. 2). After five months, eight patients (38 %) were still on osimertinib treatment. In 14 patients (67 %), osimertinib treatment resulted in tumor regression (range: -4 to -38 percent from baseline according to RECIST v1.1 [Fig. 1]). Two patients were not evaluable due to the absence of measurable lesions. Median OS was 8.7 (95 % CI, 1.1–16.4) months. Patients with co-occurring *TP53* mutations did not appear to fare better or worse than those without in terms of PFS (p = 0.937) or OS (p = 0.107). Three patients had brain metastases that showed a decrease in lesional size, including the patient with a partial response. There were no differences in PFS between patients with or without brain metastases; 3.4 and 3.6 months (95 % CI, 2.6–4.5; p = 0.740), respectively.

One patient, who progressed after 9.3 months osimertinib treatment, subsequently received carboplatin – gemcitabine. After progression, a higher dose of osimertinib (160 mg once daily) was re-introduced, with stable disease after six weeks and progression after three months of treatment.

A post-progression biopsy was available for the patient with a PR after osimertinib treatment. Besides the activating *EGFR* exon 20 mutation this biopsy revealed high *cMET* amplification, a known resistance mechanism to osimertinib treatment, with 34 copies of *cMET*, as assessed by whole genome sequencing. NGS at baseline, prior to platinum based chemotherapy and (unsuccessful) erlotinb treatment, did not

Table 2
Response to treatment and co-occurring mutations.

Patient	Mutation type	Best response	Best change from baseline according RECIST (%)	PFS (months)	Co-mutations
1	p.(His773_Val774delinsLeuMet)	PR	−38	8.3	TP53
2	p.(His773delinsTyrAsnProTyr)	SD	−26	3.6	TP53; PTEN
3	p.(Asn771delinsThrHis)	PD	−22	1.2	None
4	p.(His773_Val774insAlaHis)	SD	−21	6.5	N/A
5	p.(Gly779Phe)	SD	−19	2.7	TP53; EGFR amplification
6	p.(Ala767_Val769dup)	SD	−17	8.3	N/A
7	p.(Asn771_His773dup)	SD	−16	17.3	TP53
8	p.(Ser768_Asp770dup)	SD	−12	3.8	N/A
9	p.(Asn771_Pro772insHis)	SD	−11	11.4	TP53
10	p.(Asn771_Pro772insArgHis)	SD	−9	9.3	None
11	p.(Asn771delinsGlyTyr)	SD	−7	12.6	N/A
12	p.(Asn771_His773dup)	SD	−5	7.9	N/A
13	p.(Ser768_Val769delinsIleLeu)	SD	−5	2.6	N/A
14	p.(Ala767_Val769dup)	SD	−4	4.0	EGFR amplification
15	p.(His773_Val774delinsLeuMet)	SD	0	3.2	N/A
16	p.(His773_Val774insAlaHis)	SD	0	1.7	TP53
17	p.(Val769_Asp770insGlyGly)	SD	+6	3.7	Notch1
18	p.(Asn771delinsGlyHis)	SD	+12	3.0	None
19	p.(Val769_Asp770insSerPheLeu)	PD	+17	1.7	N/A
20	p.(Ala767_Val769dup)	PD	NE	3.1	TP53; CDKN2A
21	p.(Ala767_Val769dup)	PD	NE	0.7	TP53

NE: non-evaluable; N/A: not applicable; PD: progressive disease; PFS: progression free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease.

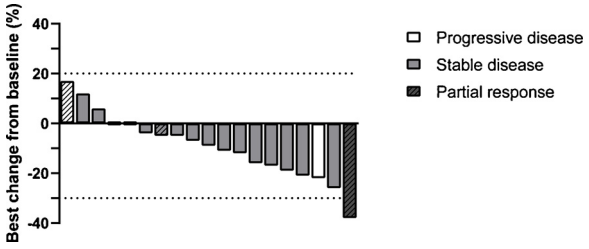

Fig. 1. Waterfall plot of best percentage change in tumor size during osimertinib treatment.
Two patients were non-evaluable according to RECIST version 1.1.
The patients who received a prior TKI are shaded with stripes.

show an increased c*MET* copy number.

4. Discussion

EGFR exon 20 insertions represent a heterogeneous group of genomic aberrations with an unmet clinical need in precision oncology. *EGFR* exon 20 insertions after residue 764 are resistant to first and second generation EGFR TKIs [1]. Data about effectiveness of third generation EGFR TKIs are limited. Our series describes the results of osimertinib treatment, a third generation EGFR TKI, in 21 patients with advanced stage NSCLC harboring an *EGFR* exon 20 mutation. Despite the low response rate of 5 %, 14 of 21 patients (67 %) experienced a decrease in tumor size (Fig. 1). The DCR at three months was 71 %. In addition, a subgroup of patients (38 %) derived durable disease stabilization of five months and beyond. However, the median PFS of the treatment line prior to osimertinib was 4 months, so it is questionable if this represents osimertinib efficacy or natural evolution of the disease. Recently, a series of six Chinese patients with an *EGFR* exon 20 insertion mutation, treated with osimertinib 80 mg once daily was published. Four patients achieved a PR (including one patient with a known sensitizing variant A763_Y764insFQEA in combination with a *T790M* mutation after gefitinib treatment) and the other two patients showed stable disease as best response [9]. One patient with a PR harbored the same *EGFR* exon 20 mutation (p.A767_V769dup) as a patient in our cohort with SD as best response.

Together, the results of these two case series show that osimertinib has limited efficacy in patients with *EGFR* exon 20 insertion mutations with sized based tumor responses in the majority of patients. However, the results of osimertinib treatment do not even approach those that can be obtained for patients with *EGFR* exon 19 deletion and exon 21 L858R mutations.

Our results show that patient with exactly the same insertion

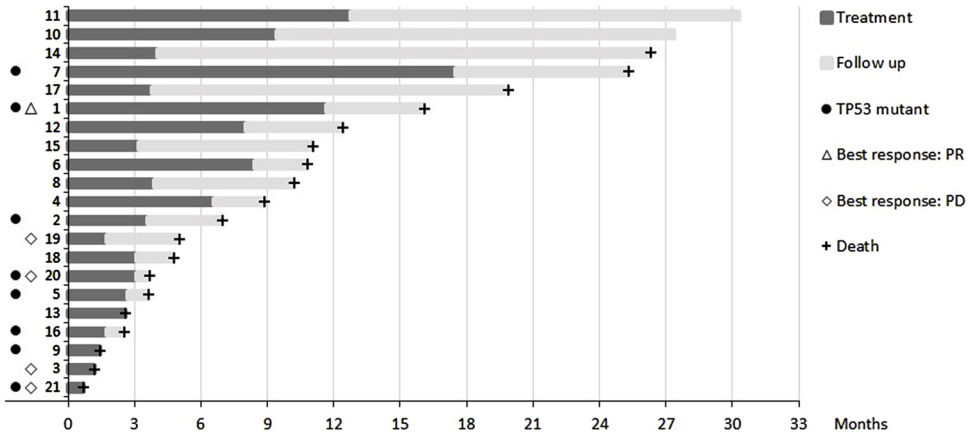

Fig. 2. Swimmerplot of progression-free survival and overall survival after osimertinib treatment.

mutation can have different treatment outcomes. The potential role of co-occurring aberrations like *TP53* during EGFR TKI treatment is not well characterized [10]. In this small series, there was no association between reduction in efficacy of osimertinib treatment and co-occurring *TP53* mutations. Analysis of the post-progression biopsy of the only patient with a PR after osimertinib treatment, revealed *cMET* amplification, suggestive of *cMET* bypass track resistance, a known resistance mechanism to EGFR TKIs.

The dose of osimertinib might be a relevant factor in the treatment of patients with an *EGFR* exon 20 insertion mutation. Pharmacokinetic analysis revealed that geometric mean plasma concentrations for osimertinib doses of 80 mg and 160 mg once daily are around 500 nM and 1000 nM, respectively [11]. Hirano et al. used *in vitro* models to identify the therapeutic window of osimertinib for *EGFR* exon 20 alterations. The IC50 values of osimertinib for the tested *EGFR* exon 20 insertion mutations were 10–100 fold higher compared to classic *EGFR* mutations. Thus, a higher dose of osimertinib greater than an 80 mg oral dose may be necessary to effectively treat patients with *EGFR* exon 20 mutations [6]. In our experience, one patient received osimertinib 160 mg after having progressed on osimertinib 80 mg and another patient, included in this cohort, started with osimertinib 160 mg. Neither of the two patients showed a radiological response.

Currently, two phase 2 trials are active to investigate the efficacy of this higher dose (NCT03191149 and ESR-16-12212). Also, the results of a prospective phase II study with 80 mg osimertinib are awaited (NCT03414814).

In addition, multiple clinical trials are pending with EGFR TKIs that were specifically designed to target *EGFR* and *HER2* exon 20 insertion mutations. The clinical activity of poziotinib was evaluated in a single arm phase 2 trial with an ORR of 43 %. Poziotinib is a small and flexible molecule that can circumvent the steric changes of *EGFR* exon 20 insertions. However, toxicity was substantial with 60 % grade ≥ 3 toxicity, mainly skin toxicity and diarrhea. Despite the high response rate, median PFS was 5.5 months [12]. A phase I/II trial with another EGFR TKI, TAK-788, showed a 43 % confirmed ORR and 7.3 months median PFS. Toxicity profiling showed 40 % treatment related grade ≥ 3 toxicity, mainly diarrhea and nausea [13]. The combination of afatinib and cetuximab resulted in a partial response in 3 out of 4 patients and a median PFS of 5.4 months in a retrospective case series [14]. This combination treatment is being prospectively evaluated in a single arm phase two trial (NCT03727724).

Our study has several limitations. At first hand, because of the retrospective nature of this study. Data about co-occurring genetic alterations were available for only 62 % of patients. Also, the sample size of our cohort is relatively small. However, to our knowledge this is the largest case series of patients with *EGFR* exon 20 mutation positive NSCLC, treated with osimertinib.

5. Conclusion

In conclusion, our study shows that osimertinib 80 mg once daily has limited antitumor activity in patients with *EGFR* exon 20 mutated NSCLC, with an ORR of 5 %.

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CRediT authorship contribution statement

B. van Veggel: Conceptualization, Data curation, Formal analysis, Writing - original draft, Methodology. **J.F. Vilacha Madeira R Santos:** Writing - review & editing. **S.M.S. Hashemi:** Data curation, Writing - review & editing. **M.S. Paats:** Data curation, Writing - review & editing. **K. Monkhorst:** Writing - review & editing. **D.A.M. Heideman:** Data curation, Writing - review & editing. **M. Groves:** Writing - review & editing. **T. Radonic:** Writing - review & editing. **E.F. Smit:** Conceptualization, Supervision, Writing - review & editing. **E. Schuuring:** Writing - review & editing. **A.J. van der Wekken:** Conceptualization, Data curation, Supervision, Writing - review & editing. **A.J. de Langen:** Conceptualization, Writing - original draft, Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interest

Dr. de Langen reports grants from Boehringer, grants from AstraZeneca, non-financial support from Roche, grants and personal fees from Merck / MSD, grants and personal fees from BMS, outside the submitted work.

Dr. Heideman is minority shareholder of Self-screen B.V., a spin-off company of VU University Medical Center (currently known as Amsterdam UMC, Vrije Universiteit Amsterdam). She has been on the speakers bureau of QIAGEN and serves occasionally on the scientific advisory boards of Pfizer and Bristol-Myers Squibb.

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