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Original Research

Afatinib in patients with metastatic or recurrent *HER2*-mutant lung cancers: a retrospective international multicentre study☆

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Abstract ***Introduction:*** *HER2* mutations occur in 1–3% of lung adenocarcinomas. With increasing use of next-generation sequencing at diagnosis, more patients with *HER2*-mutant tumours present for treatment. Few data are available to describe the clinical course and outcomes of these patients when treated with afatinib, a pan-HER inhibitor.

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HER2 mutation;
Multicentre study

Methods: We identified patients with metastatic or recurrent *HER2*-mutant lung adenocarcinomas treated with afatinib among seven institutions across Europe, Australia, and North America between 2009 and 2017. We determined the partial response rate to afatinib, types of *HER2* mutations, duration of response, time on treatment, and survival.

Results: We collected information on 27 patients with stage IV or recurrent *HER2*-mutant lung adenocarcinomas treated with afatinib. Of 23 patients evaluable for response, three partial responses were noted (13%, 95% confidence interval [CI] 4–33%). In addition, 57% of patients (13/23) had stable disease, and 30% (7/23) had progressive disease. We documented partial responses in patients with *HER2* exon 20 insertions, including two with YVMA insertion and one with VAG insertion. Two patients with partial responses were previously treated with trastuzumab and pertuzumab. Median duration of response to afatinib was 6 months (range 5–10); median time on treatment was 3 months (range 1–30) and median overall survival from the date of diagnosis of metastatic or recurrent disease was 23 months (95% CI 18–53 months).

Conclusions: Afatinib is modestly active in patients with *HER2*-mutant lung adenocarcinomas, including responses after progression on prior HER2-targeted therapies. However, investigations into the biology of *HER2*-mutant lung adenocarcinomas and development of better HER2-directed therapies are warranted.

1. Introduction

Research into the molecular basis of lung cancers has led to an improved understanding of pathways that are deregulated in the process of tumourigenesis. These key biological pathways are often deregulated through single-gene alterations, including mutations, amplifications, rearrangements or fusions, and this process has been described as an oncogene addiction model [1]. This model is well characterised in lung adenocarcinomas with approved targeted therapies for certain driver oncogenes including *EGFR*, *ALK*, *ROS1* and *BRAF*. Human epidermal growth factor 2 (*HER2*) has been identified as an additional key oncogenic driver in approximately 1–3% of lung adenocarcinomas [2–4].

HER2 is a member of the ErbB receptor tyrosine kinase family and acts through downstream effectors in the phosphoinositide 3-kinase-AKT and MEK-extracellular signal-regulated kinase pathways [5]. Most *HER2* mutations in lung cancer involve a 12–base pair (bp) in-frame insertion in exon 20, known as the YVMA mutation, which leads to constitutive activation of downstream effectors through the AKT and MEK pathways [6–8]. This mutation is most often found in female patients, never smokers and in patients with adenocarcinomas [6,9,10]. Overall, patients with *HER2*-mutant lung adenocarcinomas have previously been reported to have a median overall survival (OS) of 1.6–1.9 years from the date of metastatic or recurrent disease diagnosis and carry a poorer prognosis compared with other oncogenic drivers [2,3,10]. Treatment responses to both chemotherapy and HER2-targeted therapies have been reported, but there are no approved agents for *HER2*-mutant lung cancers, and there are limited data available to guide optimal treatments.

Afatinib is an irreversible ErbB family inhibitor that has been demonstrated to have preclinical activity in human lung cancer cell lines with an exon 20 insertion in *HER2* [11,12]. Along with other HER2-targeted agents including dacomitinib and trastuzumab, afatinib has been reported to have clinical activity in patients with *HER2*-mutant lung adenocarcinomas, although conclusions and recommendations for its clinical use are not possible because of the small sample size of these series [10,13–17].

To increase our sample size and to improve our understanding of the clinical activity of afatinib in this subset of patients with lung adenocarcinomas, we combined data from seven institutions. In this article, we present the results of our international multicentre study on clinical outcomes of patients with *HER2*-mutant lung adenocarcinomas who were treated with afatinib.

2. Material and methods

2.1. Patient selection

An international, multicentre network of seven institutions across Europe, Australia and North America combined data on patients with *HER2*-mutant lung adenocarcinomas who were treated with afatinib between April 2009 and May 2017. Patients were selected to be included in the study at each of the participating study centres through independent comprehensive chart reviews. Eligible patients had a pathologic diagnosis of advanced (stage IV or recurrent) lung adenocarcinoma and a *HER2* mutation by a validated molecular diagnostic test that was performed in an accredited local laboratory. Accepted test methods included reverse transcriptase polymerase chain reaction (PCR) or next-

generation sequencing (NGS). Patients were administered afatinib at a starting dose of 20 mg, 30 mg or 40 mg daily depending on the patient's performance status and other comorbidities. This retrospective study was approved by local institutional review boards. The study was an academic collaboration and not funded by industry, and all investigators were trained in good clinical practice.

2.2. Data collection and response assessment

Anonymised clinical data, including age, sex, *HER2* mutation subtype, tumour stage, date of diagnosis, initiation and discontinuation of afatinib therapy, duration of afatinib therapy, response to afatinib, disease progression and death, were recorded for all patients. Clinical data were collected by each contributing institution and pooled for analysis. All patients were treated outside of a clinical trial setting, and the date for data cut-off was May 25, 2017. Best response to afatinib, defined as a complete or partial response (PR) achieved at least once during the course of therapy, was determined using Response Evaluation Criteria in Solid Tumours (RECIST, v1.1) by dedicated study radiologists at each study centre [18]. The selection of target lesions was performed retrospectively.

2.3. Statistical methods

Data were summarised according to the frequency and percentage for qualitative variables and by medians and ranges for quantitative variables. OS was measured as the time from the date of initial diagnosis of metastatic disease to the date of death from any cause. Patients who were alive at the time of analysis were censored at their last follow-up. Survival rates were estimated by using the Kaplan–Meier method. Statistical analyses were performed using R software (version 3.3.2).

3. Results

3.1. Clinicopathologic and molecular features

We collected data on 27 patients who were diagnosed with metastatic or recurrent *HER2*-mutant lung adenocarcinomas and treated with afatinib (Table 1). The median age at diagnosis was 63 years (range, 40–84 years), and 59% (16/27) of patients were male. Most patients (67%; 18/27) were never smokers. Molecular testing for *HER2* mutations was performed locally via NGS or real-time PCR (Table 2). Twenty-one patients (78%; 21/27) had insertion mutations in *HER2* exon 20. The most common *HER2* mutation found was the YVMA mutation, a 12-bp insertion in *HER2* exon 20 (56%; 12/27). Five (19%; 5/27) had single bp substitutions, and one (4%; 1/27) had a single-nucleotide polymorphism (SNP).

Table 1
Clinicopathologic characteristics.

Clinicopathologic characteristics (n=27)	
Median age at diagnosis (%)	63 (range 40-84)
Sex (%)	
Female	11 (41)
Male	16 (59)
Histology (%)	
Adenocarcinoma	27 (100)
Cigarette smoking status (%)	
Former smokers	9 (33)
Never smokers	18 (67)
Reason for afatinib cessation (%)	
Progression of disease or death	19(70)
Toxicity	6 (22)
Unknown	1 (4)
Remains on afatinib (%)	1 (4)

Clinicopathologic characteristics of patients with stage IV or recurrent *HER2*-mutant lung cancers who were treated with afatinib (n = 27).

3.2. Outcomes with afatinib treatment in patients with HER2-mutant lung adenocarcinomas

Twenty-seven patients with advanced *HER2*-mutant lung adenocarcinomas received afatinib as a single agent. The median line of systemic therapy for afatinib was third line (range: first to sixth). Median time from the initial diagnosis of metastatic disease to the start of afatinib therapy was 11 months (range: 1–57 months).

Of the 27 patients, data on response to therapy by RECIST were available for 23 patients (Fig. 1). The best response to afatinib was PR in three patients (13%, 3/23, 95% confidence interval [CI] 4–33%), stable disease (SD) in 13 patients (57%), progressive disease (PD) in seven patients (30%) and not evaluable in four patients. All PRs were noted in patients with *HER2* exon 20 insertions, two with YVMA mutations and one with a VAG mutation (Table 3). Of the seven patients with PD, the following mutations were observed: YVMA (2); exon 20 insGSP (1); unspecific exon 20 insertion (1); exon 20 single bp substitutions (2) and an exon 17 single bp substitution (1) (Table 2). The median duration of response to afatinib was 6 months (range: 5–10 months). Two of three patients with PR were previously treated with HER2-targeted therapies; one experienced a PR to trastuzumab and the other had SD in response to pertuzumab given in combination with erlotinib as part of a clinical trial (Table 3) [16].

The duration of afatinib therapy for each of the 27 patients is shown in Fig. 2. Median time on treatment with afatinib was 3 months (range 1–30 months). Five patients were treated for more than 6 months, including four patients with YVMA mutations and one with a single bp substitution in exon 8 (S310F). At data cut-off, one patient with SD (YVMA mutation) still remained on afatinib treatment after 30 months. Of the remaining 26 patients, six patients (22%) had discontinued treatment because of toxicity, with diarrhoea being the primary reported toxicity. None of the 27 patients were

Table 2
HER2 mutations.

HER2 mutation	Mutation amino acid change (nucleotide change)	Alternate nomenclature (HGVS guidelines)	Frequency (%)	Partial response	Progressive disease
Exon 20 insertion (12bp)	p.A775_G776insYVMA (c.2324_2325ins12)	p.Y772 A775dup (c.2313_2324dup)	15 (54)	n=2	n=2
Exon 20 insertion (12bp)	p.A775_G776insAVMA		1 (4)		
Exon 20 insertion (9bp)	p.A775_G776lnsVAG (c.2325_2326lns 9)		2 (7)	n=1	
Exon 20 insertion (9bp)	p.P780_Y781 insGSP (c.2339_2340ins 9)	p.G778 P780dup (c.2331_2339dup)	1 (4)		n=1
Exon 20 insertion (3bp)	p.G776>VC (c.2326_2327insTGT)	p.G776delinsVC (c.2326_2327insTGT)	1 (4)		
Exon 20 insertion (3bp)	Not specified	Not specified	1 (4)		n=1
Exon 20 single bp substitution	P.D769H (C.2305 G>C)		1 (4)		n=1
Exon 20 single bp substitution	p.L755F		1 (4)		n=1
Exon 17 single bp substitution	P.V659E (c.1976_1977delinsAA)		1 (4)		n=1
Exon 8 single bp substitution	P.S310F (c.929C>T)		2 (7)		
Single-nucleotide polymorphism	lle655Val		1 (4)		

Spectrum of mutations in patients with HER2-mutant lung cancers who were treated with afatinib (n = 27).

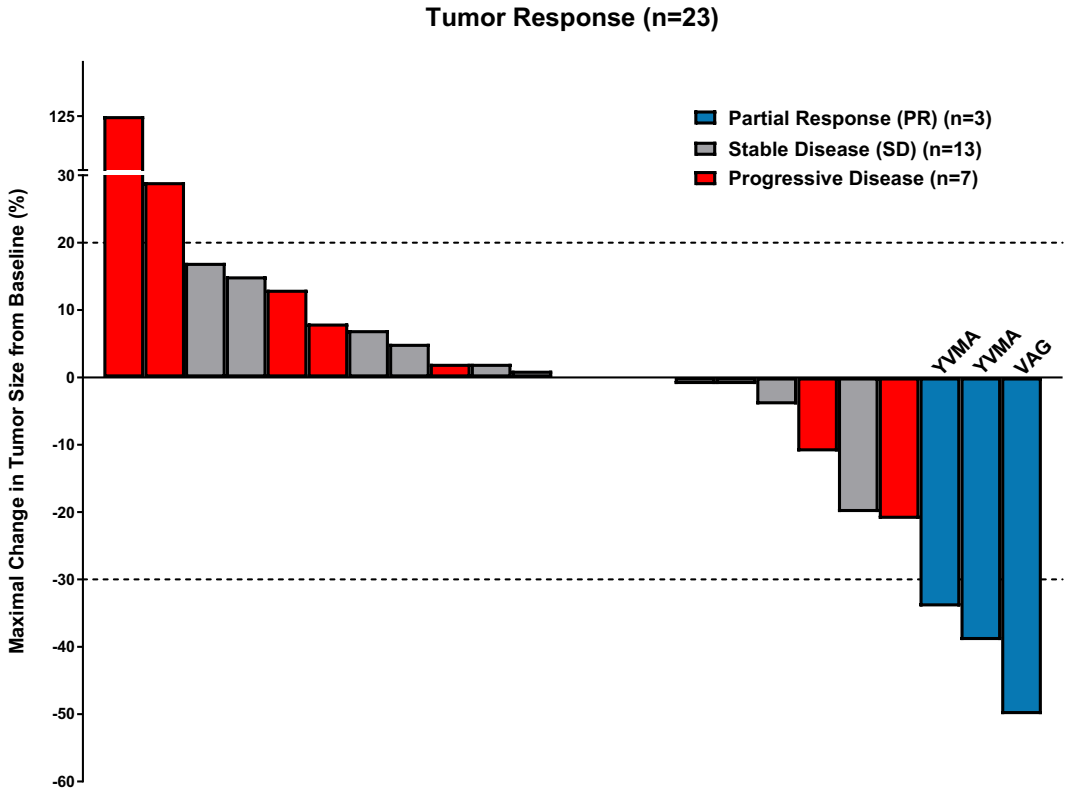

Fig. 1. Waterfall plot of overall response rate (ORR) to afatinib per RECIST, v1.1. ORR was 13% (three of 23 patients). RECIST was unable to be measured in four patients. RECIST, Response Evaluation Criteria in Solid Tumours.

treated with afatinib beyond disease progression. Five patients (19%) were alive at the time of data analysis. Median OS from the start of afatinib treatment was 7 months, while median OS from the date of metastatic disease diagnosis was 23 months (95% CI, 17.6–53.2 months). Kaplan–Meier survival curve is shown in Fig. 3.

4. Discussion

To the best of our knowledge, our study represents one of the largest single cohort of patients with *HER2*-mutant lung adenocarcinomas treated with afatinib. Although there are limitations in our retrospective series, it is one of the largest international efforts to date

Table 3
Molecular and clinical characteristics of partial responders.

Partial response to afatinib (n=3)							
Mutation	RECIST	Duration of PR to afatinib (months)	Line of treatment for afatinib	Reason for afatinib cessation	Response to prior HER2-targeted therapy	OS (months)	Vital status
insVAG	-50%	5	3	Death	N/A	62	Deceased
insYVMA	-39%	10	6	PD	Pertuzumab (SD)	73	Deceased
insYVMA	-34%	6	3	Death	Trastuzumab (PR)	23	Deceased

RECIST, Response Evaluation Criteria in Solid Tumours; PR, partial response; SD, stable disease; PD, progressive disease; OS, overall survival. Molecular and clinical characteristics of patients with *HER2*-mutant lung cancers who experienced partial responses when treated with afatinib (n = 3).

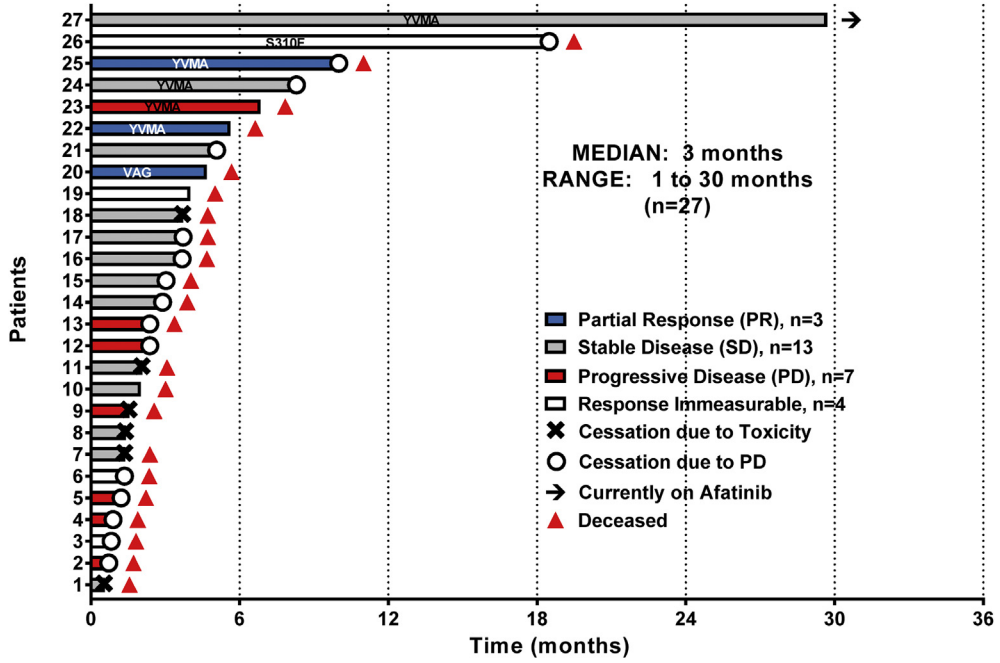

Fig. 2. Duration of treatment on afatinib in patients with *HER2*-mutant lung cancers from April 2009 through May 2017. Objective response as per RECIST could not be determined for four patients due to either the lack of the baseline imaging before starting afatinib or absence of on-treatment or post-treatment imaging. RECIST, Response Evaluation Criteria in Solid Tumours.

to assess the activity of afatinib in this uncommon molecular subset of lung cancers.

Our patient characteristics were similar to prior series of *HER2*-mutant lung cancers, including a similar median age of 63 years, primarily never smokers, and exclusively adenocarcinomas [6,10,17,19]. However, there were two key differences: our patients were predominantly male compared with predominantly female in previous studies and heavy smokers with up to 60 pack years were identified. Our study highlights that molecular testing for *HER2* mutations should be considered in all adenocarcinomas, even if patients do not fit the usual clinical profile of female and never smokers. Comparable to prior studies, most of our patients were found to have mutations involving exon 20 insertions in *HER2*, with the most common being the YVMA mutation.

The 13% overall response rate to afatinib is comparable to a 19% response rate reported by Peters *et al.* [20] in a separate retrospective series investigating the use of afatinib in more heavily pretreated patients with *HER2*-mutant lung adenocarcinomas. Our 13% response rate is also comparable to an earlier phase II trial that yielded a 12% response rate using dacomitinib, a selective and irreversible pan-HER inhibitor, in stage IIIB/IV patients with *HER2*-mutant lung adenocarcinomas [15]. Overall, the activity of afatinib seen in this study confirms the earlier reports of activity in small case series; De Greve *et al.* [13] reported PR in all of three patients on afatinib, and Mazières *et al.* [10] reported PR in one of three patients. While the common YVMA mutation was found in two of three responders to afatinib in our study, it was also found in two of seven patients with PD (Table 2). These findings emphasise the need for better understanding of the underlying biology of the various *HER2* mutation subtypes and potential differences in their response to HER2-targeted therapies.

One patient treated with afatinib was found to have an SNP in *HER2*, which resulted in the substitution of

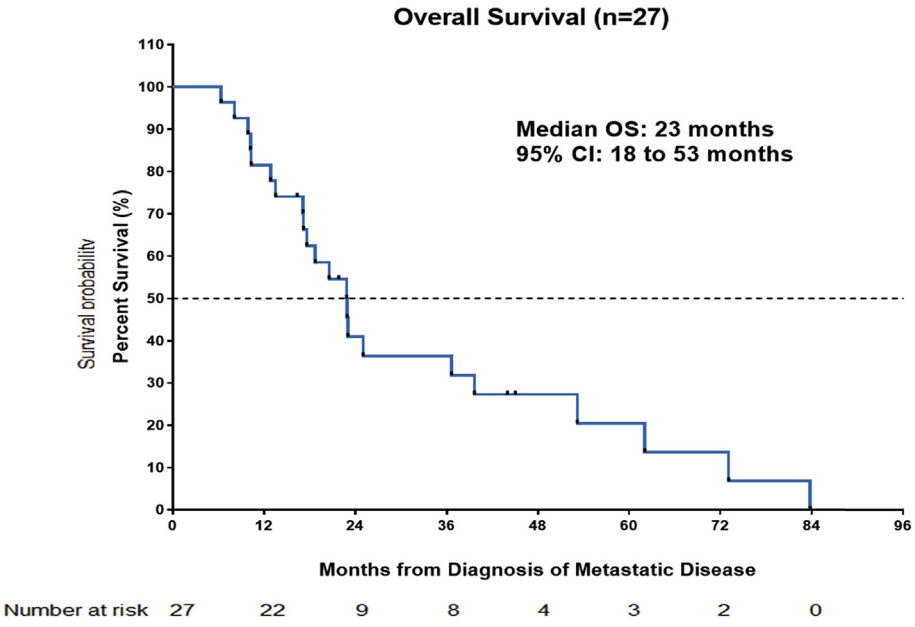

Fig. 3. Overall survival (OS) of patients with *HER2*-mutant lung cancers treated with afatinib between April 2009 and May 2017. OS was defined from the date of initial diagnosis of metastatic or recurrent disease. CI, confidence interval.

valine for isoleucine at codon 655 (Ile655Val) of the HER2 protein. The role of Ile655Val in driving oncogenesis has been explored in prior studies in patients with breast cancer with conflicting results, and this SNP has not been well characterised in *HER2*-mutant lung adenocarcinomas [21]. While RECIST data were unavailable for this patient, the patient experienced clinical benefit while on treatment with afatinib for 4 months. Thus, larger clinical series of this variant are needed to help draw conclusions regarding its predicted response to afatinib and other *HER2*-targeted agents. The identification of this SNP further underscores the molecular heterogeneity of *HER2* alterations in lung adenocarcinomas.

In our study, afatinib was used primarily in a heavily pretreated population and may underestimate the activity of afatinib, as patients might derive more clinical benefit if they were treated at an earlier point of their disease course with a better performance status. Although the number of patients is small, we also note that two of three patients with PR were previously treated with HER2-targeted therapies. This suggests that afatinib can still induce a PR in patients who have previously progressed on other HER2-targeted therapies, including trastuzumab and pertuzumab.

While the median duration of treatment on afatinib for all patients was 3 months, the range varied from 1 month to ongoing treatment at 30 months (YVMA mutation). Five patients (19%; 5/27) remained on treatment for more than 6 months, including a patient with an YVMA mutation who experienced PR. This demonstrates that afatinib has the potential for durable disease control in a subset of patients with *HER2*-mutant lung adenocarcinomas. Median OS of all patients treated with afatinib in our study was 23 months, which was comparable to prior studies that examined survival of advanced stage (stages IIIB-stage IV) *HER2*-mutant lung adenocarcinomas [6,10,17].

There are several limitations to this study due to its retrospective nature, including reporting bias, a lack of central molecular assessment and variable imaging intervals. Nevertheless, as our study was conducted in a heavily pretreated patient population with higher likelihood for development of drug resistance, it is unlikely to overestimate the efficacy of afatinib. Moreover, our study was conducted outside of a clinical trial, which broadens its applicability and generalisability to patients worldwide who have either a poor performance status or a lack of access to therapies on clinical trial. The use of afatinib in *HER2*-mutant lung adenocarcinomas currently is being studied in two separate prospective phase II clinical trials: the ETOP-NICHE trial (NCT02369484) in Europe and the NCI-MATCH trial (NCT02465060) in the US. Interim results from the ETOP-NICHE trial were reported at the 2017 ASCO Annual Meeting and did not demonstrate the expected ability of afatinib to control disease, and the final results of the study are still yet to be reported [22]. These upcoming results may help to confirm our findings of afatinib use outside of a clinical trial in a real-world setting.

Other HER2-targeted agents are being explored in patients with *HER2*-mutant lung adenocarcinomas. Single-agent neratinib recently demonstrated only a 4% overall response rate for *HER2*-mutant lung adenocarcinomas in a phase II basket trial, and the combination of neratinib with trastuzumab is being explored in a cohort expansion of the trial (NCT01953926) [23]. Neratinib is also being tested in combination with

temsirolimus, and the preliminary results from a phase II trial testing this combination in *HER2*-mutant lung adenocarcinomas reported a response rate of 19% (eight of 43 patients) (NCT NCT01827267) [24]. In addition, the early results from a phase II study examining the effects of poziotinib, a novel irreversible pan-HER inhibitor, reported a PR in eight of 11 (73%) patients with lung adenocarcinomas harbouring *EGFR* exon 20 insertions (NCT03066206) [25]. In a recent study published by Oh *et al.*, poziotinib was found to induce PR in two patients and SD in three of six total treated patients [26]. Owing to these promising results, poziotinib is currently being tested in patients with lung adenocarcinomas harbouring *HER2* exon 20 mutations (NCT03318939). Similarly, pyrotinib, another irreversible pan-HER inhibitor, is also being investigated in a phase I trial cohort expansion for *HER2*-mutant lung adenocarcinomas (NCT02500199). Recently, a phase II trial using ado-trastuzumab emtansine (T-DM1) in patients with *HER2*-mutant lung adenocarcinomas reported an overall response rate of 44%, and this has been incorporated as a treatment recommendation for *HER2*-mutant lung adenocarcinomas by the 2018 National Comprehensive Cancer Network Clinical Practice Guidelines [27]. A further expansion study of T-DM1 in both *HER2*-amplified and *HER2*-mutant solid tumours is ongoing (NCT02675829).

Afatinib demonstrated modest activity in a subset of patients with *HER2*-mutant lung adenocarcinomas and is a viable treatment option even after prior HER2-targeted agents. Our experience with afatinib confirms that *HER2*-mutant lung adenocarcinomas are clinically actionable and emphasises the need to identify *HER2* mutations in lung adenocarcinomas early in the patients' disease course. Moreover, our study underscores the unmet clinical need for novel HER2-targeted therapies to improve patient outcomes.

Conflict of interest statement

N.P. has received consulting fees from Boehringer Ingelheim; all other authors declare no competing interests.

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