Thoracic Cancer

Open Access

Thoracic Cancer ISSN 1759-7706

CASE REPORT

Afatinib as first-line treatment for advanced lung adenocarcinoma patients harboring *HER2* mutation: A case report and review of the literature

Yuequan Shi[1] & Mengzhao Wang[2]

1 Department of Critical Care Medicine, the First Hospital Affiliated to China Medical University, Shenyang, China
2 Department of Respiratory Disease, Peking Union Medical College Hospital, Beijing, China

Keywords
Afatinib; first-line treatment; HER2 mutation; lung cancer.

Correspondence
Mengzhao Wang, Department of Respiratory Disease, Peking Union Medical College Hospital, No.1 Shuaifuyuan Road, Dongcheng District, Beijing 100730, China.
Tel: +86 139 1123 5467
Email: mengzhaowang@sina.com

Received: 29 July 2018;
Accepted: 1 October 2018.

doi: 10.1111/1759-7714.12906

Thoracic Cancer **9** (2018) 1788–1794

Abstract

HER2 mutations are a rare group of driving genes that respond to HER2 targeted therapy, particularly afatinib. No more than 20 such cases have been reported, but afatinib was used after first-line chemotherapy. We present the case of a never-smoking female patient diagnosed with stage IV lung adenocarcinoma harboring a *Her2* exon 20 inserted mutation who achieved a durable response (12 months) to first-line afatinib treatment. We review the literature concerning afatinib therapy in this rare cohort of mutated lung cancer patients.

Introduction

Human epidermal growth factor 2 (HER2, erbB-2/neu) is a member of the erbB receptor tyrosine kinase family. It is a plasma membrane-bound receptor tyrosine kinase, containing extracellular ligand binding, transmembrane, and intracellular domains. *HER2* is activated by homodimerization or heterodimerization with other erbB-2 family members, especially *EGFR*.[1,2] *HER2* combined with *EGFR* can increase the potential for receptor phosphorylation and thus activate downstream signaling pathways, including mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K/Akt), phospholipase C γ, protein kinase C (PKC), and signal transducer and activator of transcription (STAT). These signaling pathways promote cell proliferation and resist apoptosis, which is correlated to uncontrolled cell growth in oncogenesis.[3,4] The principal mechanisms of oncogenic activation of HER2 are *HER2* gene amplification, gene mutation, and HER2 protein overexpression.[5] Oncogenic activity of *HER2* mutations have been reported in a large spectrum of malignancies including breast, ovarian, bladder, salivary gland, endometrial, pancreatic, and non-small cell lung cancers.[6]

Afatinib is an oral HER family blocker, which can covalently bind and irreversibly block ErbB receptor family members.[7] It displays a manageable toxicity profile and promising results in several retrospective studies targeting mutated *HER2* exon 20 in non-small cell lung cancer (NSCLC).[5]

Herein, we report a stage IV lung adenocarcinoma patient harboring a *HER2* exon 20 inserted mutation who was treated with afatinib as first-line treatment and achieved progression-free survival (PFS) of 12 months with ongoing treatment. To the best of our knowledge, this is the first report of first-line afatinib treatment achieving a partial response (PR) in an NSCLC patient with a *HER2* exon 20 insertion mutation.

Case report

A 57-year-old, non-smoking woman was diagnosed with stage IV lung adenocarcinoma in July 2017 after undergoing a left pleural biopsy by wedge resection of the lower lobe of the left lung. The tumor node metastasis

(TNM) classification of this patient was T3aN0M1a, because of ipsilateral lobe and pleural metastases. The pathological result from lung tissue biopsy was infiltrating lung adenocarcinoma. Immunohistochemical results showed positive thyroid transcription factor-1 (TTF-1), negative *ALK*, cytokeratin (CK)-7, and CK-10. No intracranial metastasis was observed on brain magnetic resonance imaging. A mutation frequency of 28.2% exon 20 ERBB2 activated mutation (p.G776delinsVC) was found in the tumor DNA extracted from the original diagnostic biopsy by next-generation sequencing (NGS), performed by Cancer-Hope (Genomicare, Shanghai, China). A CTNNB1 with p.S45P activated mutation was also detected at a frequency of 16.03%. Testing was conducted to identify any other common mutations, such as *EGFR*, *KRAS*, *NRAS*, *MET*, *ALK*, *ROS1*, and *RET*, however, the results were negative. The patient had not previously been administered chemotherapy or targeted therapy.

Treatment with afatinib (40mg/day) was commenced in August 2017. One month later, computed tomography showed a radiological PR with the patient advising relief of the chest pain (Fig 1). She was followed-up at outpatient visits every two months and achieved a continuous PR until July 2018, the latest return visit. Afatinib treatment is ongoing. The major treatment-related side effects observed were diarrhea, oral ulcers, and grade 1 skin adverse events.

Discussion

HER2 kinase domain mutation occurs in 1–4% of lung adenocarcinomas as oncogenic driver mutations.[8]

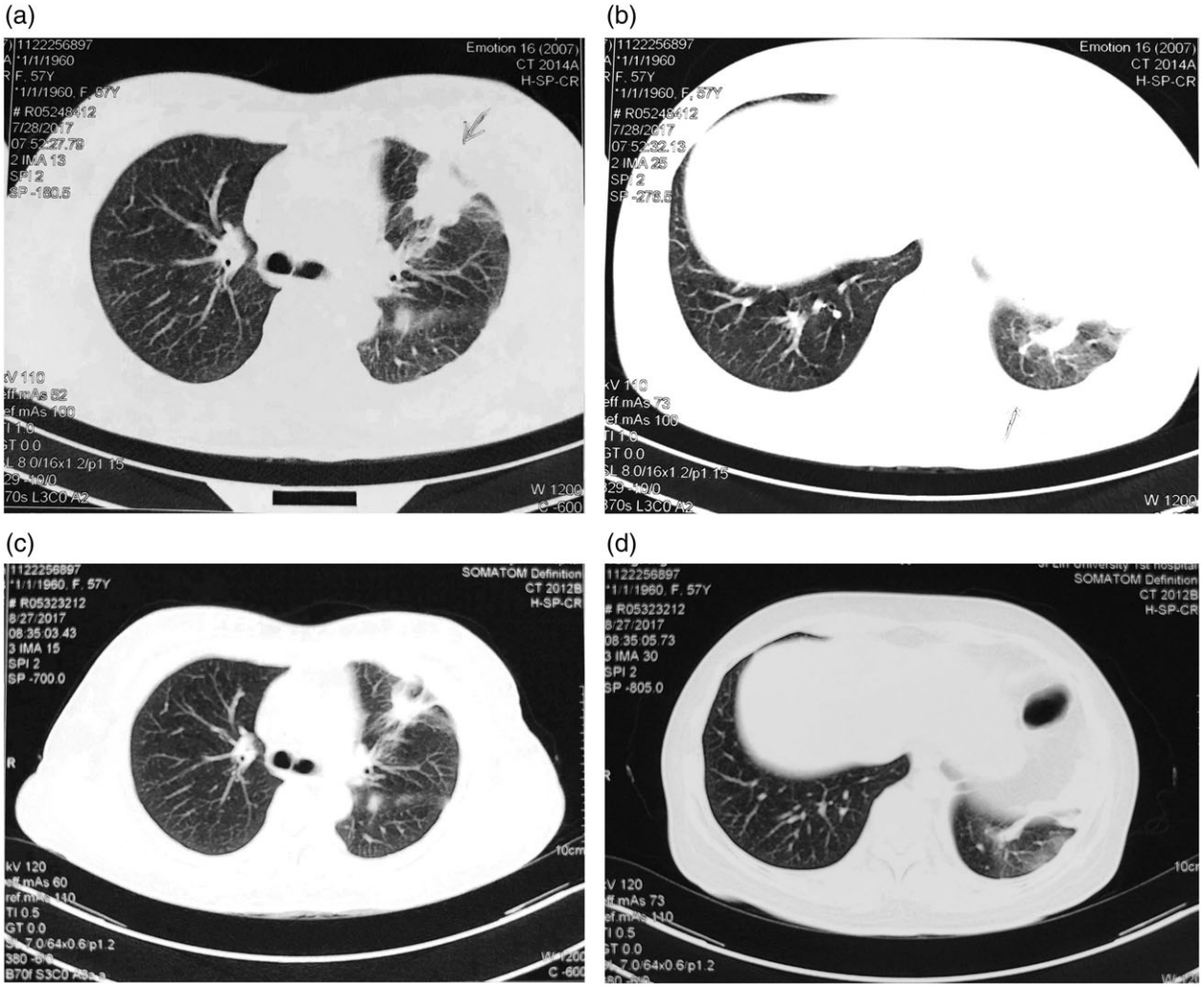

Figure 1 (**a,b**) Computed tomography (CT) images taken on 28 July 2017 when the patient arrived at our outpatient facility for the first time. Multiple lesions were observed on both sides of the lung. (**c,d**) CT images taken on 27 August 2017 after orally administration of afatinib 40 mg/day for one month. Shrinkage of the lesions was observed, particularly in the upper lobe of the left lung.

Oncogenic mutations of *HER2* mostly present in non-smoking female patients diagnosed with advanced lung adenocarcinoma.[9–14] Similar to *EGFR* mutations in NSCLC, *HER2* mutations most frequently occur in tyrosine kinase domains, but cases involving the extracellular domain and transmembrane domain (TMD) have been reported.[15] The most common subtype of *HER2* mutation is exon 20 in-frame YVMA insertion (*HER2*[YMVA]), which is found in over 50% of all *HER2* mutant lung cancer patients.[12] The percentage of exon 20 in-frame insertions has been reported to be as high as 89–100% by several large cohort studies.[13,14,16–18] Gow *et al*. retrospectively analyzed 888 Asian lung cancer patients via gene sequencing to detect a number of driver gene mutations, including *HER2*. Forty lung adenocarcinoma patients were *HER2* mutation positive and all were exon 20 insertion alterations. A775_G776ins YVMA and P780_Y781insGSP were the two most prevalent mutation subtypes (n = 22 and n = 4, respectively).[19]

Afatinib exhibits antitumor efficacy by downregulating the phosphorylation of HER2 and EGFR, together with downstream signaling in *HER2* mutant NSCLC. Moreover, it induces an anti-proliferative effect through G1 arrest and apoptotic cell death.[20] Increased *HER2* phosphorylation, as well as increased sensitivity to afatinib, have also been observed in transfected Ba/F3 cells with *HER2* (P780_Y781insGSP) mutation, indicating the possible treatment efficacy of afatinib.[21]

De Greve *et al*. reported the first evidence of clinical benefit from afatinib treatment in 2011.[22] Three patients diagnosed with advanced lung adenocarcinoma were detected with *HER2* mutations. They were administered afatinib 50 mg/day (2 accompanied by paclitaxel) and all achieved significant tumor regression, with an afatinib-related PFS of 3–15 months. De Greve *et al*. subsequently conducted a phase II clinical study to evaluate the effects of afatinib or afatinib plus paclitaxel for the treatment of lung adenocarcinoma. Notably, one patient receiving afatinib monotherapy achieved a confirmed PR, as well as one patient treated with combination therapy who had a confirmed PR of 41.9 weeks.[23] Since these studies, few cases of lung adenocarcinoma patients harboring *HER2* mutation have been reported (Table 1). Of the 24 reported cases (F: 16 vs. M: 8), three patients were light smokers, one male patient was a heavy smoker, and the remaining 15 patients were never-smokers (5 were unclear). Seventeen (71%) patients' genetic sequences were altered with exon 20 insertions. Five harbored TMD mutations and also responded to afatinib, with no significant difference to those with exon 20 insertions. Unlike other patients who were treated with no more than 50 mg/day afatinib, three patients underwent pulse afatinib therapy with oral 280mg once a week. It is worth mentioning that these three patients did not experience any rash, which is a common drug-related side effect of afatinib. The PFS durations were 11 and 5 months; PFS was not available in the third patient.[25] Twenty patients achieved evaluable afatinib-related PR or stable disease (SD), with a median PFS of 5.25 months (range: 1–18).

Three of the 24 patients received afatinib as first-line therapy, including our patient, who achieved PFS of 12 months with ongoing afatinib therapy. Of the other two patients, one harbored a TMD V659E mutation and the other an exon 20 insertion (YVMA776-779ins) and both had SD after afatinib treatment. Our patient is the only reported case with an exon 20 YVMA insertion to achieve a continuous PR.

Large cohort studies have reported similar clinical characteristics of lung cancer harboring *HER2* mutations as these case reports. Mazieres *et al*. retrospectively identified 65 NSCLC patients diagnosed with a *HER2* in-frame insertion in exon 20. Favorable responses were observed, with a 100% disease control rate in patients administered afatinib (n = 4, SD or PR).[13] Furthermore, Mazieres *et al*. also conducted the European EUHER2 study to determine the efficacy of multiple drug therapy for *HER2* exon 20 insertion mutated lung adenocarcinoma patients. Eleven patients were treated with afatinib and the median PFS was 3.9 months. No significant advantage of HER2-TKI treatment was observed compared to traditional chemotherapy.[14]

Although rarely occurring, mutations in the TMD have also attracted research attention. Ou *et al*. prospectively analyzed the tumor cells of 8551 lung adenocarcinoma patients and identified 15 cases of *HER2* TMD mutations (V659E/D, G660D), two of which harbored concurrent *ErbB2* receptor tyrosine kinase 2 gene amplification. Interestingly, three of the four patients with TMD mutations administered first or second-line afatinib developed partial or metabolic responses for 5–18 months, indicating the potential benefit not only to kinase domain but also TMD mutation patients.[33]

In conclusion, we report the only known case of a patient with the most common YVMA mutation, *HER2* alteration, administered first-line afatinib to achieve a continuous PR for at least 12months, which is longer than the median PFS (6.9 months) acquired by pemetrexed/cisplatin.[34] Our results, together with two other first-line afatinib treatment cases, indicate that large cohort studies should be conducted to investigate the efficacy and drug-related adverse events of first-line afatinib compared to traditional first-line chemotherapy with pemetrexed/cisplatin for the treatment of *HER2* positive lung adenocarcinoma patients.

Table 1 Summary of afatinib efficacy for the treatment of advanced lung adenocarcinoma harboring *HER2* mutation

No.	Age, y	Gender	Smoking status	Histologic subtype	Stage	*ERBB2/HER2* Alteration	Systemic Therapy	Best Response	PFS
1[22]	72	F	Never	Lung ADC	III	Exon 20 mutation (p. Tyr772_Ala775dup)	Carbo/Gem X8 cycles	Partial remission then SD	3 mo
							Afatinib *3 mo	PR then PD	
2[22]	62	F	Never	Lung ADC	pT2N1	Exon 20 mutation (p. Gly776Leu)	After surgery		8 mo
							Cis/Gem *4 cycles	SD	
							Docetaxel *6 cycles	SD	
							Gefitinib	PD	
							Tras/Paclitaxel	PR	
							Lapatinib	NA	
							Gem	NA	
							vinorelbine	NA	
							Afatinib *4 mo	PR	
							Afatinib/Paclitaxel *4 mo	PR	
3[22]	49	F	Never	Lung ADC	IV	Exon 20 insertional duplication (p.Gly778_Pro780dup)	Erlo*3 mo	PD	15 mo
							Cis/Gem	Objective response	
							Gem	PD	
							Carbo	Transient response	
							Vinorelbine	PD	
							Peme	Transient response	
							Cis	Objective response	
							Afatinib*4 mo	PR	
							Afatinib/Paclitaxel *11 mo	PR	
4[23]	48	F	Never	Lung ADC	IV	Exon 20 mutation (P780_Y781insGSP)	Peme/Cis *6 cycles	PR	4 mo
							Paclitaxel *2 cycles	PD	
							Gem/Cis *8 cycles	SD for first 4 cycles	
							Afatinib *4 mo	PR	
5[24]	55	M	Never	Lung ADC	IV	Exon 20 mutation (p.A775_G776insYVMA)	Carbo/Gem/Beva *5 mo	PR	10 mo
							maintenance Beva *13mo	PD	
							Erlo/Pertuzumab *2 mo	SD	
							Peme *5 mo	SD	
							Docetaxel *8 mo	SD	
							Dacomitinib/Placebo *2 mo	PD	
							Afatinib *10 mo	PR	
6[25]	65	M	Never	Lung ADC	IV	Exon 20 insertion (A775_G776insYVMA)	Carbo/Peme *5 mo	SD	
							Neratinib/temsirolimus *3 mo	SD	
							Brain radiotherapy		
							Afatinib (280 mg once weekly)	NA	
7[25]	64	F	5-pack-year	Lung ADC	IV	Exon 20 insertion (V747_G748insGSP)	Carbo/Peme *3 mo	NA	11 mo
							Afatinib (280 mg once weekly) *11 mo	PR	
8[25]	71	F	Never	Lung ADC	IV	Exon 20 insertion (E740_A741insAYVM)	Afatinib (280 mg once weekly) *5 mo	PR	5 mo

Table 1 Continued

No.	Age, y	Gender	Smoking status	Histologic subtype	Stage	*ERBB2*/*HER2* Alteration	Systemic Therapy	Best Response	PFS
9[26]	58	F	NP	Solid predominant	NP	Exon 20 insertion (GSP781-783ins)	Gem/cis *4.6 mo Afatinib *5.5 mo	SD SD	5.5 mo
10[26]	70	F	NP	Papillary predominant	NP	Exon 20 insertion (YVMA776-779ins)	Peme/carbo*2.8 mo Afatinib *3.5 mo	SD SD	3.5 mo
11[26]	60	M	NP	Micropapillary predominant	NP	Exon 20 insertion (YVMA776-779ins)	Afatinib *4 mo	SD	4 mo
12[26]	66	M	NP	Papillary predominant	NP	Exon 20 insertion (YVMA776-779ins)	Docetaxel/platinum *1 mo Afatinib *1 mo	PD PD	NA
13[27]	67	F	Never	Lung ADC	NP	Exon 20 insertion (A775_G776insYVMA)	Carbo/Pem, then Pem maintenance *9 mo Tras/Docetaxel*8 mo Afatinib *1 mo	PR PR SD	1 mo
14[27]	36	F	Never	Lung ADC	NP	Exon 20 insertion (exact sequence unknown)	Carbo/Pem/Beva, then maintenance *4.5 mo Erlotinib *1 mo Afatinib*6.5 mo Tras/vinorelbine *6 mo Tras/Docetaxel* 4 mo Ado-tras *2 mo Nivolumab*1 mo Etirinotecan pegol *2 mo Afatinib/Bev *3 mo	PR PD PR PR SD PD PD PD Mixed response, with SD in lung and PD in liver	6.5 mo
15[28]	41	M	Heavy Smoker	Lung ADC	IV	HER2 exon 8 S310Y c.929C>A(p.Ser310Tyr)	Gem/Carbo *4 cycle Gem*3cycle Afatinib*7 mo	NA NA PR	7 mo
16[29]	50	F	Never	Lung ADC	IV	Exon 20 mutation (c.2437A>G)	Peme/Cis *4cycle Gefitinib *2 mo Afatinib *4 mo	SD NA PR	4 mo
17[30,31]	56	F	1,2-pack-year				Peme/Carbo Afatinib	PD PR	NA
18[30]	52	F	NA	Adeno of the ampulla of Vater	Metastatic to lung	G660D and S310F	Gem/Cis Afatinib	PD	NA
19[32]	45	F	Never	Lung ADC	Metastatic to bone	HER2 V777_G778insGSP	Cis/Peme*7 mo Docetaxel* 15 mo Vinorelbine/tras *2 cycles Afatinib*7 mo	PR PR PD PR	7 mo
20[33]	62	F	Never	NSCLC	NA	V659E	First-line afatinib	PR	5 mo
21[33]	54	M	Never	NSCLC	NA	V659E	Second-line afatinib	PR	18 mo

Table 1 Continued

No.	Age, y	Gender	Smoking status	Histologic subtype	Stage	*ERBB2/HER2* Alteration	Systemic Therapy	Best Response	PFS
						G660R			
22[33]	73	M	Never	NSCLC	NA	V659E	Third-line afatinib	5 mo of symptomatic improvement and metabolic response	5 mo
23[33]	53	M	Positive history	NSCLC	NA	G660D	Second-line afatinib	PD	10 weeks
24	57	F	Never	Lung ADC	IV	Exon 20 mutation (p. G776delinsVC)	First-line afatinib	PR	12 mo

ADC, adenocarcinoma; Beva, bevacizumab; Carbo, carboplatin; Cis, cisplatin; Erlo, erlotinib; Gem, gemcitabine; Mo, month(s); NA, not available; NSCLC, non-small cell lung cancer; PD, progressive disease; Peme, pemetrexed; PFS, progression-free survival; PR, partial response; SD, stable disease; Tras, trastuzumab.

Disclosure

No authors report any conflict of interest.

References

1 Rusnak DW, Affleck K, Cockerill SG *et al.* The characterization of novel, dual ErbB-2/EGFR, tyrosine kinase inhibitors: Potential therapy for cancer. *Cancer Res* 2001; **61**: 7196–203.

2 Oxnard GR, Binder A, Janne PA. New targetable oncogenes in non-small-cell-lung-cancer. *J Clin Oncol* 2013; **31**: 1097–104.

3 Gutierrez C, Schiff R. HER2: Biology, detection, and clinical implications. *Arch Pathol Lab Med* 2011; **135**: 55–62.

4 Roy V, Perez EA. Beyond trastuzumab: Small molecule tyrosine kinase inhibitors in HER-2-positive breast cancer. *Oncologist* 2009; **14**: 1061–9.

5 Peters S, Zimmermann S. Targeted therapy in NSCLC driven by HER2 insertions. *Transl Lung Cancer Res* 2014; **3**: 84–8.

6 Scholl S, Beuzeboc P, Pouillart P. Targeting HER2 in other tumor types. *Ann Oncol* 2001; **12** ((Suppl 1)): S81–7.

7 Solca F, Dahl G, Zoephel A *et al.* Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. *J Pharmacol Exp Ther* 2012; **343**: 342–50.

8 Shigematsu H, Takahashi T, Nomura M *et al.* Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. *Cancer Res* 2005; **65**: 1642–6.

9 Stephens P, Hunter C, Bignell G *et al.* Lung cancer: Intragenic ERBB2 kinase mutations in tumors. *Nature* 2004; **431**: 525–6.

10 Buttitta F, Barassi F, Fresu G *et al.* Mutational analysis of the HER2 gene in lung tumors from Caucasian patients: Mutations are mainly present in adenocarcinomas with bronchioloalveolar features. *Int J Cancer* 2006; **119**: 2586–91.

11 Tomizawa K, Suda K, Onozato R *et al.* Prognostic and predictive implications of HER2/ERBB2/neu gene mutations in lung cancers. *Lung Cancer* 2011; **74**: 139–44.

12 Arcilla ME, Chaft JE, Nafa K *et al.* Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. *Clin Cancer Res* 2012; **18**: 4910–8.

13 Mazieres J, Peters S, Lepage B *et al.* Lung cancer that harbors an HER2 mutation: Epidemiologic characteristics and therapeutic perspectives. *J Clin Oncol* 2013; **31**: 1997–2003.

14 Mazieres J, Barlesi F, Filleron T *et al.* Lung cancer patients with HER2 mutations treated with chemotherapy and HER2-targeted drugs: Results from the European EUHER2 cohort. *Annal Oncol* 2016; **27**: 281–6.

15 Garrido-Castro A, Felip E. HER2 driven non-small cell lung cancer (NSCLC): Potential therapeutic approaches. *Transl Lung Cancer Res* 2013; **2**: 122–7.

16 Eng J, Hsu M, Chaft JE, Kris MG, Arcila ME, Li BT. Outcomes of chemotherapies and HER2 directed therapies in advanced HER2-mutant lung cancers. *Lung Cancer* 2016; **99**: 53–6.
17 Wu SG, Kuo YW, Chang YL *et al*. EML4-ALK translocation predicts better outcome in lung adenocarcinoma patients with wild-type EGFR. *J Thorac Oncol* 2012; **7**: 98–104.
18 Shan L, Qiu T, Ling Y *et al*. Prevalence and clinicopathological characteristics of HER2 and BRAF mutation in chinses patients with lung adenocarcinoma. *PLoS One* 2015; **10**: e0130447.
19 Gow CH, Chang HT, Lim CK, Liu CY, Chen JS, Shih JY. Comparable clinical outcomes in patients with HER2-mutant and EGFR-mutant lung adenocarcinomas. *Gene Chromosomes Cancer* 2017; **56**: 373–81.
20 Suzawa K, Toyooka S, Sakaguchi M *et al*. Antitumor effect of afatinib, as a human epidermal growth factor receptor 2-targeted therapy, in lung cancers harboring HER2 oncogene alterations. *Cancer Sci* 2016; **107910**: 45–52.
21 Gow CH, Liao WY, Liu YN *et al*. Discordant HER2 exon 20 mutation status determines a differential sensitivity to afatinib. *J Thorac Oncol* 2014; **10**: e58.
22 Greve DJ, Teugels E, Geers C *et al*. Clinical activity of afatinib (BIBW2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. *Lung Cancer* 2012; **76**: 123–7.
23 De Greve J, Moran T, Graas MP *et al*. Phase II study of afatinib, an irreversible ErbB family blocker, in demographically and genotypically defined lung adenocarcinoma. *Lung Cancer* 2015; **88** (1): 63–9.
24 Li BT, Lee A, Toole SO *et al*. HER2 insertion YVMA mutant lung cancer: Long natural history and response to afatinib. *Lung Cancer* 2015; **90**: 617–9.
25 Costa DB, Jorge SE, Moran JP *et al*. Pulse afatinib for ERBB2 exon 20 insertion mutated lung adenocarcinomas. *J Thorac Oncol* 2016; **11**: 918–23.
26 Song Z, Yu X, Shi Z, Zhao J, Zhang Y. HER2 mutations in Chinese patients with non-small-cell lung cancer. *Oncotarget* 2016; **7**: 78152–8.
27 Chuang JC, Stehr H, Liang Y *et al*. ERBB2-mutated metastatic non-small cell lung cancer: Response and resistance to targeted therapies. *J Thorac Oncol* 2017; **12**: 833–42.
28 Wang J, Wen Y, Ding G *et al*. Efficacy generated by afatinib in a lung adenocarcinoma patient harboring HER2 S310Y mutation. *Cancer Biol Ther* 2018; **21**: 1–4.
29 Park CK, Hur JY, Choi CM *et al*. Efficacy of Afatinib in a previously treated patient with non-small cell lung cancer harboring HER2 mutation: Case report. *J Korean Med Sci* 2018 Jan 1; **33** (1): e7.
30 Yamamoto H, Toyooka S, Ninomiya T *et al*. Therapeutic potential of Afatinib for cancers with ERBB2(HER2) transmembrane domain mutations G660D and V659E. *Oncologist* 2018; **23**: 150–4.
31 Yamamoto H, Higasa K, Sakaguchi M *et al*. Novel germline mutation in the transmembrane domain of HER2 in familial lung adenocarcinoma. *J Natl Cancer Inst* 2014; **106**: djt338.
32 Kosaka T, Tanizaki J, Paranal RM *et al*. Response heterogeneity of EGFR and HER2 exon 20 insertions to covalent EGFR and HER2 inhibitors. *Cancer Res* 2017; **77**: 2712–21.
33 Ou SI, Schrock AB, Bocharov EV *et al*. HER2 transmembrane domain mutations (V659/G660) that stabilize homo- and Heterodimerization are rare oncogenic drivers in lung adenocarcinoma that respond to afatinib. *J Thorac Oncol* 2017; **12**: 446–57.
34 Kato T, Yoshioka H, Okamoto I *et al*. Afatinib versus cisplatin plus pemetrexed in Japanese patients with advanced non-small cell lung cancer harboring activating EGFR mutations: Subgroup analysis of LUX-lung 3. *Cancer Sci* 2015; **106**: 1202–11.

