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Durable Responses to Afatinib as First Line Therapy for HER2-Mutated Metastatic Non-Small Cell Lung Cancer

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Review comments:

We want to thank the reviewers for their detailed and thoughtful comments on our manuscript. We have made the requested revisions. Below is our point by point responses.

Reviewer #1: This case report demonstrated five HER2-mutated lung cancer patients and their response to first-line afatinib treatment. The manuscript was well written. And there are some points to be concerned.

Major concerns:

1. A major concern for TKI treated patients is the subsequent treatment choice on oligoprogression or oligometastases. In Case 1, the patient began to receive additional radiation for oligo-progressive organs after taking afatinib for 11 months and went on taking afatinib until substantial progression 14 months later. Had gene testing been taken on another biopsy on oligoprogression and substantial progression, respectively? If possible, it would be better to include oligoprogression or oligometastases in discussion.

The patient's sites of oligoprogression in the brain and lung were 2-4 mm in size and were not able to be biopsied. I have added information about oligoprogressive disease to the discussion.

2. The PFS of first-line afatinib in these cases was rather long, even comparable to chemotherapy. However, there might be some bias on treatment outcome. It would be intriguing if the authors could include more patients with less optimistic response to afatinib in first-line setting and compare 1) the clinical pathological differences between the responders and non-responders; 2) the different response rate toward later regimen including chemotherapy, other TKIs or antibodies and immunotherapy.

We agree that it would be ideal to include more patients, but we do not have more patients to include. Most patients were treated after receiving chemotherapy. To address this concern a retrospective multi-center registry approach would be needed.

3. It is interesting to see that case 2 and case 3 had comparable clinical features including age, gender, pathology, stage, dose and duration of afatinib. However, after progression on afatinib, patient 2 underwent chemotherapy plus trastuzumab and was alive after CR on immunotherapy, while patient 3 died almost seven months later. The authors did mention that the HER2 mutation type, tumor mutation load and treatment afterwards were different between the two patients, but more information could be provided concerning PD-L1 expression, progression site, co-mutation and so on.

Yes, these two patients are interesting for the reasons you have stated. I have added their PD-L1 expression levels to each case. Patient 2 had a PD-L1 expression level of 30% in her tumor while Patient 3's tumor did not express PD-L1. I clarified that Patient 2 progressed only at her known sites of disease while Patient 3 developed a new site of disease in the liver. Patient 3 was also not as healthy as Patient 2 i.e. chronic heart failure. They did have different co-mutations as listed in Table 1.

Minor concerns:

1. Table 1 -- The '*' and '**' could be labeled in a reversed way.

This has been changed.

2. The 'patient 4' in Page7 Line50 and Page8 Line24 should be 'patient 5'.

This has been corrected.

Reviewer #2: This is a nice case series though cases could be shortened slightly.

Thank you for the compliment. The cases were slightly shortened.

- 1) Is this every patient who received 1st line afatinib therapy for HER2 mutant NSCLC at UC Davis? How were the patients identified? What time period is covered? Please expand a bit on how the cohort was identified.

The patients were identified from our institutional Foundation Medicine database that was queried from 2015-2018. The treating physician was contacted requesting information on the initial treatment. I have added the time frame to the introduction.

There was one additional patient with a PS of 2-3 (versus PS 0-1 of all other patients) who took afatinib for a short time but then decided to go to hospice and is not included.

- 2) For Case 1 this can be shortened. The authors should consider mentioning duration of response instead of specific dates of treatment that might be used to identify the patient.

Case 1 has been shortened and the specific dates removed.

- 3) The clinical trial outcome data does not need to be included as it would be very easy for someone to see what Her2 trial is open at UCDavis and figure out what the patient is receiving. Thus the response data should not be in this report.

Thank you for bringing this to our attention. This has been deleted.

- 4) I would suggest mentioning the age at diagnosis for each patient instead of current age.

I mentioned the age at diagnosis in the table.

- 5) For this review the post-afatinib therapy is interesting but may detract from the message of the paper? Could shorten a bit.

We minimized the post-afatinib treatment description of the cases.

- 6) Is Cantonese a clearly established ethnicity? Perhaps just state Asian? And also would not reveal outcome from clinical trial, just that he is enrolled.

This has been corrected. This case has been updated to include the patient is now deceased.

- 7) Were RECIST criteria utilized to assess PR? Were all patients scanned at a particular frequency? If comparisons are made to other trial data (ie KN189) one must be careful as that is an apples to oranges comparison and you do not know how HER2 mutant NSCLC patients might have done on KN189. The comparison to the retrospective analysis is more appropriate.

Yes, RECIST criteria was used to assess response. This has been added. Four of the five patients were scanned at 6 weeks and one patient was scanned at 8 weeks.

We agree that the retrospective analysis is more appropriate because it includes only HER2 positive patients, but this analysis did not provide the data collection time frame and it was accepted for publication in 2015. We felt the control arm of KEYNOTE 189 provided a modern PFS benchmark but acknowledge its limitations. We modified this section.

- 8) The discussion can be shortened and perhaps does not need to dose discussion component as one area to remove.

The dosing discussion has been removed.

- 9) The authors should add the data from ASCO 2019 with TAK788.

This ASCO presentation was only on EGFR insertion 20 mutations. I included the data from the phase I study from ASCO 2018 which showed 1 unconfirmed response out of 5 evaluable patients with HER2 mutations.

- 10) The authors may consider referencing the following manuscript that discusses potential resistance mechanisms to HER2 directed therapy, though is not focused entirely on afatinib.
Chuang JC, Stehr H, Liang Y, Das M, Huang J, Diehn M, Wakelee HA, Neal JW. ERBB2-Mutated Metastatic Non-Small Cell Lung Cancer: Response and Resistance to Targeted Therapies. J Thorac Oncol 2017 May;12(5):833-842. doi: 10.1016/j.jtho.2017.01.023. Epub 2017 Feb 4.

Thank you for this reference. I added the following sentence to the discussion: We were not able to perform post-progression biopsies in any of our patients, but others have shown that *de novo* PIK3CA mutation and ERBB2 copy number gain are a possible resistance mechanism to HER2 directed therapies (Chuang)

- 11) The authors may consider concluding with more discussion of the more specific HER2 directed TKIs in development. There is some discussion but how afatinib may fit in the landscape could be expanded.

To my knowledge all known data with HER2 TKI i.e. poziotinib, pyrotinib and TAK-778 has been included in the discussion. We added to the discussion the limited future role for afatinib in this competitive landscape with more potent and selective second generation pan HER inhibitors.

Reviewer #3: Al-Obeidi and colleagues present a series of case reports of 5 patients with metastatic NSCLC with HER2 mutation treated with front line afatinib. Three patients demonstrated confirmed PR in this series. They review the literature surrounding TKI therapy for patients with HER2 mutated NSCLC. The authors should consider the following comments.

1. Since the focus of the case reports is front line HER2 therapy for metastatic disease, each can be shortened to present a more concise case of the diagnosis and therapy received with response. In addition, subsequent therapy can be removed from the cases.

The cases have been shortened. We respectfully believe it is important to include the subsequent therapies to show that additional HER2 directed therapies options are available, but we shortened their descriptions.

2. Please add a reference for the 3rd to last sentence in the introduction, starting, "In a small number of heavily pretreated..."

This has been corrected.

3. Case 1 would be enhanced by a timeline showing initial progression and treatment of oligometastatic disease while remaining on afatinib.

We added that the SRS was given 9 and 11 months after starting afatinib.

4. Case 1 mentions SBRT to the brain, which should be SRS.

This has been corrected to read SRS.

5. Please cite Fig 1a and 1b, 2a and 2b specifically in the text.

This has been corrected.

6. Table 1 would benefit from OS information.

OS information has been provided in Table 1.

7. Please include information regarding concurrent HER2 amplification if known.

NGS did not detect HER2 amplification in any patient. Patient 1 had ERB3 amplification.

8. Do you have any data regarding resistance mechanisms following progression?

Unfortunately, we do not have this information. No patient was re-biopsied at progression.

9. Please indicate whether the PRs noted in the cases were determined by RECIST.

Yes, the PRs were determined by RECIST, this has been added.

10. In the discussion, update the # PR to 3 since only 3 were confirmed.

This has been updated.

11. Please add a reference to the 5th sentence in the first paragraph of the discussion, starting, "Whether chemotherapy plus an immune..."

The following reference has been added: Mazieres J, Drilon AE, Mhanna L, et al. Efficacy of immune-checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC) patients harboring activating molecular alterations (ImmunoTarget). J Clin Oncol 36, 2018 (suppl; abstr 9010).

12. The discussion paragraph on afatinib dosing should be removed.

This paragraph has been removed.

13. The summary sentence should be modified to note modest effectiveness rather than "efficacious." The responses and durations in this series are modest.

This has been changed to include the word modestly.

14. Do you have any additional cases treated with afatinib that were not included in this series? How were these chosen?

Please see my answer to reviewer #2, question 1.

Durable Responses to Afatinib as First Line Therapy for *HER2*-Mutated Metastatic Non-Small Cell Lung Cancer

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Clinical Practice Points

- *HER2* mutated lung cancer occurs in 3% of patients with adenocarcinoma. Patients are typically never smoking women.
- Afatinib is an irreversible pan-HER inhibitor approved for the first line treatment of EGFR-mutated tumors. Its evaluation in *HER2* mutated disease has been sparse and limited to heavily pretreated patients. The response rates were low but disease control was consistently seen.
- Our case series demonstrated that first line afatinib produced durable responses. This finding coupled with its moderate toxicity profile and once daily oral administration suggests it is a reasonable treatment option for patients with *HER2* mutated tumors who prefer an alternative to chemotherapy-based regimens or who are not eligible for these regimens.
- Clinical trials evaluating more potent pan-HER inhibitors are showing promising efficacy in this molecularly defined subset of patients.

Introduction

Small molecule tyrosine kinase inhibitors (TKIs) are the agents of choice for the first line treatment of patients with metastatic oncogenic driven non-small cell lung cancers (NSCLC) harboring an epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1) or BRAF genetic alteration. Afatinib, a second generation TKI that irreversibly blocks homo- and hetero- receptor dimerization of the human epidermal growth factor (HER) family, is approved for the upfront treatment of EGFR mutated tumors. Afatinib's pan-HER properties suggests it could be effective in treating human epidermal growth factor receptor 2 (*HER2*) mutated lung cancer that occurs in approximately 3% of patients with adenocarcinoma.¹ All *HER2* mutations reported lead to constitutive activation of the receptor, and cells harboring these mutations are predicted to be sensitive to small-molecule TKIs. Indeed, preclinical studies have shown that afatinib produces growth inhibition in *HER2* mutated lung cancer cell lines and mouse models.² In a small number of heavily pretreated patients with this genomic feature, afatinib has demonstrated modest anti-tumor activity.³ Since clinical benefit with TKIs is higher in untreated patients, we reviewed our [local Foundation Medicine](#) database [from 2015-2018 to identify for](#) patients with *HER2* mutated lung tumors [and followed up with their treating physician.](#) Five evaluable patients were identified who received afatinib as first line therapy because they refused or preferred not to receive standard chemotherapy. Here we describe the outcomes of the five patients identified and review the literature.

Cases

Case 1

The patient is a 73-year-old Caucasian male with no smoking history who [developed a cough and wheezing in the](#) [winter of 2014. A chest computed tomography \(CT\) revealed a mass in the left lower lobe and involvement of a](#) [left hilar lymph node which was confirmed on a positron emission tomography \(PET\) scan. He underwent a left](#) [lower lobe lobectomy and mediastinal lymphadenectomy in January 2015. Pathology revealed a moderately](#) [differentiated adenocarcinoma with involvement of four hilar and one mediastinal lymph nodes.](#) was found to [pathological stage was IIIA \(T3N2M0\) and he received four cycles of adjuvant cisplatin and pemetrexed](#) [chemotherapy. In December 2015 a surveillance CT scan have](#) [showed](#) two new nodules in the right lung on a

surveillance chest CT (computed tomography (CT) 11 months after his left upper lobe lobectomy and adjuvant chemotherapy for pIIIA(T3N2M0) adenocarcinoma in January 2015. A brain magnetic resonance imaging (MRI) also revealed four 2-3 mm lesions. A biopsy of one of the lung nodules showed adenocarcinoma consistent with his original tumor pathology. He underwent stereotactic Body Radiation radiosurgery Therapy (SBRTSRS) to the brain lesions. Meanwhile, his original tumor was sent for molecular analysis that revealed an *ERBB2* exon 20 P780_Y781insGSP mutation and an *ERBB3* amplification. He was treated with afatinib 40 mg orally once a day but required a dose reduction to 20 mg for rash and diarrhea. He had a confirmed partial response (PR) by Response Evaluation Criteria in Solid Tumors (RECIST) criteria and continued afatinib for 25 months. However, he received additional radiation for oligoprogressive disease in the right lung and brain 9 and 11 months after starting afatinib respectively. Fourteen months later he developed substantial progression in these locations. He received SRS to the brain lesions and continues to receive additional HER directed therapy.

Case 2

The patient is an 80-year-old white female, never smoker who was discovered to have a right upper lobe mass on chest radiograph in January 2016 for chronic right breast and chest pain. A biopsy of the lung mass showed a well-differentiated adenocarcinoma. A PET scan identified two additional lytic bone lesions in her right sacrum and hip (Figure 1a). She was diagnosed with Stage IV (T2bN0M1c) disease. Molecular profiling revealed an *ERBB2* exon 20 A775_G776insYVMA mutation. The patient initiated afatinib 30 mg per day. She had a radiographic confirmed PR by RECIST for 7 months (Figure 1b). Upon progression of known sites of disease she was switched to paclitaxel, carboplatin and trastuzumab but after two cycles she developed new sites of metastases and was treated on a clinical trial with immunotherapy. Notably, her tumor PD-L1 expression was 30%. to which she had a near complete response (CR). She completed the planned two years of trial treatment and is currently on observation.

Case 3

The patient is an 81-year-old never smoking, white female who was incidentally found to have lung nodules on a CT of the abdomen for abdominal pain in February 2016. A subsequent chest CT and a PET scan showed innumerable nodules (Figure 2a). A CT guided lung biopsy demonstrated a well-differentiated adenocarcinoma. Molecular profiling revealed an *ERBB2* D769Y mutation. Afatinib 30 mg was started in March. She had an impressive confirmed PR by RECIST criteria that lasted 7 months (Figure 2b) at which time she developed a new liver lesion. She was not eligible for other HER2 therapies due to her chronic heart failure. Her tumor did not express PD-L1 and she was treated with one cycle of pemetrexed and carboplatin. Unfortunately, she continued to decline and elected hospice care. She died in May 2017.

Case 4

The patient is a 67-year-old current smoking, Asian Cantonese male. In December 2017 he was evaluated in the emergency room for left sided chest pain. A chest radiograph showed a left lung mass worrisome for cancer. A staging PET revealed a left apical posterior pleura mass extending into the ribs and vertebral bodies with invasion into the neural foramina. A second left suprahilar mass extended into the mediastinum and pleura. Left supraclavicular and mediastinal lymphadenopathy and a pleural effusion were also noted. Biopsies showed adenocarcinoma consistent with a lung primary. Molecular profiling revealed an *ERBB2* exon 20 A775_G776insYVMA mutation. The patient received palliative radiation to his thoracic spine and was started on afatinib 40 mg in April. Repeat imaging in June revealed a partial response by RECIST however the next scan in October 2018 showed disease progression. The patient expired in May 2019 after failing subsequent chemotherapy and was recently enrolled on a clinical trial with a novel anti HER2 agent.

Case 5

The patient is a 72-year-old Caucasian female, with no smoking history who had a left upper lobe lobectomy in October 2015. Pathology revealed a poorly differentiated adenocarcinoma pT1bN0M0, stage 1A lung cancer. In May 2017 she underwent a work up for persistent low back pain. Scans revealed extensive liver and bone metastases that were confirmed by biopsy. Molecular profiling showed an *ERBB2* exon 20 A775_G776insYVMA

mutation. She underwent palliative radiation to the lumbosacral spine and was started on afatinib 40 mg per day.

She did not tolerate treatment and a scan at 4 weeks showed progression. Treatment with a trastuzumab - containing regimen resulted in disease stabilization for 6 months. She subsequently received three additional regimens but died from disease 15 months later.

Discussion

Currently no TKI is approved for patients with *HER2* mutant NSCLC. Our small case series suggests afatinib is an efficacious upfront treatment for this subset of patients. Four of the five patients (3 with a confirmed PR and one with an unconfirmed PR) achieved durable clinical benefit lasting a minimum of 7 months (Table 1). This progression free survival (PFS) duration is similar to the 6 month PFS observed in a large retrospective analysis of 93 patients with *HER2* mutated disease who received a platinum doublet.³ It is also numerically higher than the median PFS of 4.9 months in the pemetrexed and carboplatin control arm of the KEYNOTE 189 trial.⁴ Although we do not know how patients with *HER2* mutated tumors performed in this study, it provides a modern PFS benchmark. Whether chemotherapy plus an immune checkpoint inhibitor (ICI) would further prolong PFS in our patient population is unknown but ICI monotherapy is relatively ineffective in most never smokers with oncogenic driven tumors.^{5 (5)} To our knowledge there are no prospective studies or retrospective analyses evaluating afatinib in untreated patients with a *HER2* driven lung cancer however two additional cases were identified (Table 1). The first case is an account of a never smoking female with a *HER2* V659E patient mutation who had a confirmed PR for five months, and the second case described a female never smoker with a *HER2* pG776delinsVC who achieved a PR for 12+ months.^{5,76} No other TKIs have been evaluated in the first line setting. In a basket trial of ado-trastuzumab two of three untreated patients enrolled achieved a PR. The PFS was not reported for these two patients but the median PFS for all eight previously untreated or treated responders was 6 months with a range of four months to not reached.³²

The sum of the clinical experience with afatinib is from small retrospective analyses and prospective trials in heavily pretreated patients. The two largest retrospective studies of 16 and 23 evaluable patients reported

objective response rates (ORR) of 19% (3/16 patients) and 13% (3/23 patients) and a disease control rates (DCR) of 70% (16/23 patients) and 69% (11/16 patients), respectively.^{8-9,10} The duration of response was not mentioned in the first study but was 6 months for the three responders in the second study. In the six responding patients, five had *HER2* exon 20 YVMA insertion and one patient had a M774dup. Two very small prospective trials have published results. De Grève conducted a phase II basket trial that included a cohort of seven patients with *HER2* mutated lung cancer.¹⁰⁻¹¹ Three patients had tumor shrinkage that did not meet RECIST defined PR criteria but had symptomatic improvement. The DCR was 71% (5/7 patients) with a median duration of 16 weeks. Recently the European Thoracic Oncology Platform (ETOP) reported the results of the NICHE trial.¹² This trial employed a two stage Simon design that required six of nine patients to achieve a 12-week DCR to continue the study which was not achieved. However, in all 13 enrolled patients the median PFS was 15.9 weeks with a 12-week DCR of 53.8% (7 patients) and one patient had a PR of 7.7%. Prospective studies of other agents in this class have shown similar results. Dacomitinib produced an ORR of 12% (3/26 patients) lasting 3+, 11 and 14 months.¹³ Although the basket study of neratinib demonstrated a low response rate of 3.6% (1/26 patients), the DCR was 46% and the median PFS was 5.5 months.¹⁴ Altogether, this data is not compelling for a therapeutic benefit with afatinib but hints of activity was seen suggesting more potent *HER2* directed inhibitors are needed.

Our patient's clinical characteristics are consistent with patients harboring *HER2* mutations, predominantly never smoking females with adenocarcinoma. The one interesting exception is the Asian male with a current smoking history. In the largest retrospective study of 101 patients with *HER2* mutations, 4% of patients were current smokers.³ This finding highlights the importance of molecular testing for all patients with adenocarcinoma regardless of smoking status. Afatinib demonstrated antitumor activity across the diverse mutational landscape of activating *HER2* exon 20 mutations. The most common insertion mutation A775_G776insYVMA was found in three tumors. Rarer mutations such as the insertion mutation P780_Y781insGSP and PG776delinsVC, a base substitution D769Y and a transmembrane domain mutation V659E were detected in each of the four remaining tumors. The most durable response was seen in patient 1 with a P780_Y781insGSP tumor mutation. The presence of glycine at position 770 has been associated with responsiveness to TKIs by enabling inhibitor binding.¹⁵ However, he did receive SRS to oligoprogressive sites of disease. The strategy of incorporating SRS and continuing the TKI is a

treatment option per NCCN guidelines with the rationale being to eradicate TKI resistant clones with radiation while maintaining control of sensitive clones with the TKI.^{16,17} Two recent retrospective analyses and one small prospective trial support this approach.^{18,19,20} The ongoing ETOP HALT study is evaluating the role of continuing targeted therapy with or without SRS in oligoprogressive disease for oncogene addicted tumors.

In contrast, patient 5 with the common A775_G776insYVMA mutation did not respond to afatinib. In addition to the *HER2* mutation she had several other genetic alterations including a p53 mutation and CDKN2A/B loss that may have influenced treatment responsiveness. Emerging data from many investigators suggest that co-mutations can influence treatment responsiveness to TKIs. Bivona and colleagues have shown that patients whose tumors harbor an EGFR sensitizing mutation plus alterations in p53 and/or CDKN2A/B are less responsive to EGFR-TKI and may have a more aggressive phenotype.^{21,46} This could be the case with our patient since she was the only patient with a p53 mutation. She also had CDKN2A/B loss that may have contributed to her poor outcome. Interestingly, two other patients had associated CDKN2A/B loss but were responders. We were not able to perform post-progression biopsies in any of our patients, but others have shown that *de novo* PIK3CA mutation and *ERBB2* copy number gain are possible resistance mechanism to HER2 directed therapies.²² These findings emphasize the need to acquire a deeper understanding of the mutations and their accompanied genetic alterations to better gauge TKI responsiveness.

The recommended starting dose of afatinib is 40 mg orally once a day but 30 mg is frequently used. In our series afatinib 40 mg once a day was initiated in three patients and 30 mg once a day in two patients. Two patients who received 40 mg required dose reductions due to diarrhea and rash to 30 mg and 20 mg. The inability to tolerate afatinib 40 mg requiring a seven day treatment hold in patient 54 may have contributed to her progressive disease. No dose reductions were required for patients starting at 30 mg. The two patients from the literature who received afatinib as first line therapy both received afatinib 40 mg. One of the two patients required a dose reduction to 30 mg due to rash and paronychia. Afatinib 30 mg or 40 mg are acceptable starting doses.

The antitumor activity of afatinib in our patients with *HER2* mutated tumors provides incentive to develop more efficacious TKIs for these patients. Pozitotinib, ^{16,23} and pyrotinib ^{17,24} and TAK-788, are novel pan-HER TKIs that have demonstrated increased potency compared to afatinib in preclinical models of *HER2* and *EGFR* mutated tumors. In a small study with pozitotinib, two of six pretreated patients with *HER2* mutated lung cancer achieved a PR (30%) for 4.5 and 5.5 months. ^{16,23} A larger phase II trial evaluating pozitotinib in both untreated and treated patients with an *EGFR* or *HER2* insertion 20 mutation is ongoing (NCT03318939). A phase II study of pyrotinib has also reported encouraging efficacy. Eight of 15 previously treated *HER2* mutated NSCLC patients (53.3%) had a documented PR and the overall median PFS was 6.4 months. ^{17,24} Continued evaluation of pyrotinib in *HER2* positive lung cancer patients is proceeding (NCT02834936). A phase I study of TAK-778 in patients with *EGFR* or *HER2* Exon 20 mutations included 13 patients with *HER2* mutated tumors. One of five patients had an unconfirmed response at an early analysis. Accrual to a HER-2 specific dose expansion cohort is ongoing. ²⁵ Overall the preliminary data with second generation pan-HER inhibitors have produced numerically increased response rates and PFS durations compared to first generation afatinib in a previously treated patient population. This leads us to speculate that their efficacy would be even greater in the first line setting which would be consistent with several second and third generation TKIs in other molecularly defined cohorts and we anxiously await the trial results. Afatinib may ultimately have a limited and short-lived role in the treatment of *HER2* mutated lung cancer but we should not underscore its importance in the journey to bring effective TKI treatment to this group of patients.

In summary, afatinib is modestly efficacious in untreated patients with *HER2* mutated lung cancer and may be considered for patients who are not candidates for or who refuse standard therapies. Our data generates support and optimism for the continued evaluation of novel, more potent *HER2* TKI inhibitors for this molecularly defined subset of lung cancer patients.

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Table 1. Characteristics and Outcomes of Patients with *HER2* Mutated Tumors Treated with First line Afatinib

Case	Age at Diagnosis	Gender	Race	Smoking History	Lung Cancer Histology	PS*	<i>HER2</i> Mutation**	Other Mutations	Best Response to Afatinib	Duration on Afatinib	Current StatusOS ***
Case 1	7369	M	Caucasian	Never	Adenocarcinoma	0	<i>ERBB2</i> exon 20 P780_Y781insGSP	<i>ERBB3</i> amplification FLT3 R311Q	Confirmed PR	25 months	Alive 40+ months
Case 2	7880	F	Caucasian	Never	Adenocarcinoma	0	<i>ERBB2</i> exon 20 A775_G776insYVMA	VEGFA amplification CDKN2A/B loss TAF1 W565	Confirmed PR	8 months	Alive 37+ months
Case 3	8180	F	Caucasian	Never	Adenocarcinoma	1	<i>ERBB2</i> D769Y	CDKN2A/B loss DNMT3A E37* KDM6A loss exons 3-16 SMAD4 H371fs*14	Confirmed PR	7 months	Deceased 13.7 months
Case 4	6766	M	Asian	Active	Adenocarcinoma	1	<i>ERBB2</i> exon 20 A775_G776insYVMA	MDM2 amplification MEN1 splice site 669+1G>C FRS2 amplification ZNF217 amplification	Unconfirmed PR	7 months	Alive 17 months
Case 5	7268	F	Caucasian	Never	Adenocarcinoma	1	<i>ERBB2</i> exon 20 A775_G776insYVMA	RICTOR amplification CDKN2A/B loss FGF10 amplification TP53 C176F	Progression	.75 months	Deceased 18 months
Additional cases from the literature											
Case 6	57	F	Asian	Never	Adenocarcinoma	NR***	<i>ERBB2</i> exon 20 G776delinsVC	CTNNB1	Confirmed PR	12+ months	Alive
Case 7	62	F	Asian	Never	Adenocarcinoma	NR***	<i>ERBB2</i> V695E	NR***	Confirmed PR	7 months	NR***

*-Testing by Next Generation Sequencing
 **_PS-performance status
 **-Testing by Next Generation Sequencing
 ***NR-not reported
 ****from starting Afatinib

Figure 1. Case 2. ERBB2 exon 20 A775_G776insYVMA and a Low Tumor Burden. Positron Emission Tomography/Computed Tomography Scans. A) Pretreatment and B) 2 Months after Treatment with Afatinib.

Figure 2. Case 3 ERBB2 D769Y and a High Tumor Burden. Positron Emission Tomography/Computed Tomography Scans. A) Pretreatment and B) 3 Months after Treatment with Afatinib.

Durable Responses to Afatinib as First Line Therapy for *HER2*-Mutated Metastatic Non-Small Cell Lung Cancer

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Clinical Practice Points

- *HER2* mutated lung cancer occurs in 3% of patients with adenocarcinoma. Patients are typically never smoking women.
- Afatinib is an irreversible pan-HER inhibitor approved for the first line treatment of EGFR-mutated tumors. Its evaluation in *HER2* mutated disease has been sparse and limited to heavily pretreated patients. The response rates were low but disease control was consistently seen.
- Our case series demonstrated that first line afatinib produced durable responses. This finding coupled with its moderate toxicity profile and once daily oral administration suggests it is a reasonable treatment option for patients with *HER2* mutated tumors who prefer an alternative to chemotherapy-based regimens or who are not eligible for these regimens.
- Clinical trials evaluating more potent pan-HER inhibitors are showing promising efficacy in this molecularly defined subset of patients.

Introduction

Small molecule tyrosine kinase inhibitors (TKIs) are the agents of choice for the first line treatment of patients with metastatic oncogenic driven non-small cell lung cancers (NSCLC) harboring an epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1) or BRAF genetic alteration. Afatinib, a second generation TKI that irreversibly blocks homo- and hetero- receptor dimerization of the human epidermal growth factor (HER) family, is approved for the upfront treatment of EGFR mutated tumors. Afatinib's pan-HER properties suggests it could be effective in treating human epidermal growth factor receptor 2 (*HER2*) mutated lung cancer that occurs in approximately 3% of patients with adenocarcinoma.¹ All *HER2* mutations reported lead to constitutive activation of the receptor, and cells harboring these mutations are predicted to be sensitive to small-molecule TKIs. Indeed, preclinical studies have shown that afatinib produces growth inhibition in *HER2* mutated lung cancer cell lines and mouse models.² In a small number of heavily pretreated patients with this genomic feature, afatinib has demonstrated modest anti-tumor activity.³ Since clinical benefit with TKIs is higher in untreated patients, we reviewed our local Foundation Medicine database from 2015-2018 to identify patients with *HER2* mutated lung tumors and followed up with their treating physician. Five evaluable patients were identified who received afatinib as first line therapy because they refused or preferred not to receive standard chemotherapy. Here we describe the outcomes of the five patients identified and review the literature.

Cases

Case 1

The patient is a 73-year-old Caucasian male with no smoking history who was found to have two new nodules in the right lung on a surveillance chest computed tomography (CT) 11 months after his left upper lobe lobectomy and adjuvant chemotherapy for pIIIA(T3N2M0) adenocarcinoma in January 2015. A brain magnetic resonance imaging (MRI) also revealed four 2-3 mm lesions. A biopsy of one of the lung nodules showed adenocarcinoma consistent with his original tumor pathology. He underwent stereotactic radiosurgery (SRS) to the brain lesions. Meanwhile, his original tumor was sent for molecular analysis that revealed an *ERBB2* exon 20 P780_Y781insGSP mutation and an *ERBB3* amplification. He was treated with afatinib 40 mg orally once a day but required a dose

reduction to 20 mg for rash and diarrhea. He had a confirmed partial response (PR) by Response Evaluation Criteria in Solid Tumors (RECIST) criteria and continued afatinib for 25 months. However, he received additional radiation for oligoprogressive disease in the right lung and brain 9 and 11 months after starting afatinib respectively. Fourteen months later he developed substantial progression in these locations. He received SRS to the brain lesions and continues to receive additional HER directed therapy.

Case 2

The patient is an 80-year-old white female, never smoker who was discovered to have a right upper lobe mass on chest radiograph in January 2016 for chronic right breast and chest pain. A biopsy of the lung mass showed a well-differentiated adenocarcinoma. A PET scan identified two additional lytic bone lesions in her right sacrum and hip (Figure 1a). She was diagnosed with Stage IV (T2bN0M1c) disease. Molecular profiling revealed an *ERBB2* exon 20 A775_G776insYVMA mutation. The patient initiated afatinib 30 mg per day.. She had a radiographic confirmed PR by RECIST for 7 months (Figure 1b). Upon progression of known sites of disease she was switched to paclitaxel, carboplatin and trastuzumab but developed new sites of metastases and was treated on a clinical trial with immunotherapy. Notably, her tumor PD-L1 expression was 30%. She is currently on observation.

Case 3

The patient is an 81-year-old never smoking, white female who was incidentally found to have lung nodules on a CT of the abdomen for abdominal pain in February 2016. A subsequent chest CT and a PET scan showed innumerable nodules (Figure 2a). A CT guided lung biopsy demonstrated a well-differentiated adenocarcinoma. Molecular profiling revealed an *ERBB2* D769Y mutation. Afatinib 30 mg was started in March. She had an impressive confirmed PR by RECIST criteria that lasted 7 months (Figure 2b) at which time she developed a new liver lesion. She was not eligible for other HER2 therapies due to her chronic heart failure. Her tumor did not express PD-L1 and she was treated with one cycle of pemetrexed and carboplatin. Unfortunately, she continued to decline and elected hospice care. She died in May 2017.

Case 4

The patient is a 67-year-old current smoking, Asian male. In December 2017 he was evaluated in the emergency room for left sided chest pain. A chest radiograph showed a left lung mass worrisome for cancer. A staging PET revealed a left apical posterior pleura mass extending into the ribs and vertebral bodies with invasion into the neural foramina. A second left suprahilar mass extended into the mediastinum and pleura. Left supraclavicular and mediastinal lymphadenopathy and a pleural effusion were also noted. Biopsies showed adenocarcinoma consistent with a lung primary. Molecular profiling revealed an *ERBB2* exon 20 A775_G776insYVMA mutation. The patient received palliative radiation to his thoracic spine and was started on afatinib 40 mg in April. Repeat imaging in June revealed a partial response by RECIST however the next scan in October 2018 showed disease progression. The patient expired in May 2019 after failing subsequent chemotherapy and a novel anti HER2 agent.

Case 5

The patient is a 72-year-old Caucasian female, with no smoking history who had a left upper lobe lobectomy in October 2015. Pathology revealed a poorly differentiated adenocarcinoma pT1bN0M0, stage 1A lung cancer. In May 2017 she underwent a work up for persistent low back pain. Scans revealed extensive liver and bone metastases that were confirmed by biopsy. Molecular profiling showed an *ERBB2* exon 20 A775_G776insYVMA mutation. She underwent palliative radiation to the lumbosacral spine and was started on afatinib 40 mg per day. She did not tolerate treatment and a scan at 4 weeks showed progression. Treatment with a trastuzumab - containing regimen resulted in disease stabilization for 6 months. She subsequently received three additional regimens but died from disease 15 months later.

Discussion

Currently no TKI is approved for patients with *HER2* mutant NSCLC. Our small case series suggests afatinib is an efficacious upfront treatment for this subset of patients. Four patients (3 with a confirmed PR and one with an unconfirmed PR) achieved durable clinical benefit lasting a minimum of 7 months (Table 1). This progression free survival (PFS) duration is similar to the 6 month PFS observed in a large retrospective analysis of 93 patients with

HER2 mutated disease who received a platinum doublet.³ It is also numerically higher than the median PFS of 4.9 months in the pemetrexed and carboplatin control arm of the KEYNOTE 189 trial.⁴ Although we do not know how patients with *HER2* mutated tumors performed in this study, it provides a modern PFS benchmark. Whether chemotherapy plus an immune checkpoint inhibitor (ICI) would further prolong PFS in our patient population is unknown but ICI monotherapy is relatively ineffective in most never smokers with oncogenic driven tumors.⁵ To our knowledge there are no prospective studies or retrospective analyses evaluating afatinib in untreated patients with a *HER2* driven lung cancer however two additional cases were identified (Table 1). The first case is an account of a never smoking female with a *HER2* V659E mutation who had a confirmed PR for five months, and the second case described a female never smoker with a *HER2* pG776delinsVC who achieved a PR for 12+ months.^{6,7} No other TKIs have been evaluated in the first line setting. In a basket trial of ado-trastuzumab two of three untreated patients enrolled achieved a PR. The PFS was not reported for these two patients but the median PFS for all eight previously untreated or treated responders was 6 months with a range of four months to not reached.⁸

The sum of the clinical experience with afatinib is from small retrospective analyses and prospective trials in heavily pretreated patients. The two largest retrospective studies of 16 and 23 evaluable patients reported objective response rates (ORR) of 19% (3/16 patients) and 13% (3/23 patients) and a disease control rates (DCR) of 70% (16/23 patients) and 69% (11/16 patients), respectively.^{9,10} The duration of response was not mentioned in the first study but was 6 months for the three responders in the second study. In the six responding patients, five had *HER2* exon 20 YVMA insertion and one patient had a M774dup. Two very small prospective trials have published results. De Grève conducted a phase II basket trial that included a cohort of seven patients with *HER2* mutated lung cancer.¹¹ Three patients had tumor shrinkage that did not meet RECIST defined PR criteria but had symptomatic improvement. The DCR was 71% (5/7 patients) with a median duration of 16 weeks. Recently the European Thoracic Oncology Platform (ETOP) reported the results of the NICHE trial.¹² This trial employed a two stage Simon design that required six of nine patients to achieve a 12-week DCR to continue the study which was not achieved. However, in all 13 enrolled patients the median PFS was 15.9 weeks with a 12 week DCR of 53.8% (7 patients) and one patient had a PR of 7.7%. Prospective studies of other agents in this class have shown similar results. Dacomitinib produced an ORR of 12% (3/26 patients) lasting 3+, 11 and 14 months.¹³ Although the basket

study of neratinib demonstrated a low response rate of 3.6% (1/26 patients), the DCR was 46% and the median PFS was 5.5 months.¹⁴ Altogether, this data is not compelling for a therapeutic benefit with afatinib but hints of activity was seen suggesting more potent HER2 directed inhibitors are needed.

Our patient's clinical characteristics are consistent with patients harboring *HER2* mutations, predominantly never smoking females with adenocarcinoma. The one interesting exception is the Asian male with a current smoking history. In the largest retrospective study of 101 patients with *HER2* mutations, 4% of patients were current smokers.³ This finding highlights the importance of molecular testing for all patients with adenocarcinoma regardless of smoking status. Afatinib demonstrated antitumor activity across the diverse mutational landscape of activating *HER2* exon 20 mutations. The most common insertion mutation A775_G776insYVMA was found in three tumors. Rarer mutations such as the insertion mutation P780_Y781insGSP and PG776delinsVC, a base substitution D769Y and a transmembrane domain mutation V659E were detected in each of the four remaining tumors. The most durable response was seen in patient 1 with a P780_Y781insGSP tumor mutation. The presence of glycine at position 770 has been associated with responsiveness to TKIs by enabling inhibitor binding.¹⁵ However, he did receive SRS to oligoprogressive sites of disease. The strategy of incorporating SRS and continuing the TKI is a treatment option per NCCN guidelines with the rationale being to eradicate TKI resistant clones with radiation while maintaining control of sensitive clones with the TKI.^{16,17} Two recent retrospective analyses and one small prospective trial support this approach.^{18,19,20} The ongoing ETOP HALT study is evaluating the role of continuing targeted therapy with or without SRS in oligoprogressive disease for oncogene addicted tumors.

In contrast, patient 5 with the common A775_G776insYVMA mutation did not respond to afatinib. In addition to the *HER2* mutation she had several other genetic alterations including a p53 mutation and CDKN2A/B loss that may have influenced treatment responsiveness. Emerging data from many investigators suggest that co-mutations can influence treatment responsiveness to TKIs. Bivona and colleagues have shown that patients whose tumors harbor an EGFR sensitizing mutation plus alterations in p53 and/or CDKN2A/B are less responsive to EGFR-TKI and may have a more aggressive phenotype.²¹ This could be the case with our patient since she was the only patient with a p53 mutation. She also had CDKN2A/B loss that may have contributed to her poor outcome. Interestingly,

two other patients had associated CDKN2A/B loss but were responders. We were not able to perform post-progression biopsies in any of our patients, but others have shown that *de novo* PIK3CA mutation and *ERBB2* copy number gain are possible resistance mechanism to HER2 directed therapies.²² These findings emphasize the need to acquire a deeper understanding of the mutations and their accompanied genetic alterations to better gauge TKI responsiveness.

The antitumor activity of afatinib in our patients with *HER2* mutated tumors provides incentive to develop more efficacious TKIs for these patients. Pozotinib, pyrotinib and TAK-788 are novel pan-HER TKIs that have demonstrated increased potency compared to afatinib in preclinical models of *HER2* and *EGFR* mutated tumors. In a small study with pozotinib, two of six pretreated patients with *HER2* mutated lung cancer achieved a PR (30%) for 4.5 and 5.5 months.²³ A larger phase II trial evaluating pozotinib in both untreated and treated patients with an *EGFR* or *HER2* insertion 20 mutation is ongoing (NCT03318939). A phase II study of pyrotinib has also reported encouraging efficacy. Eight of 15 previously treated *HER2* mutated NSCLC patients (53. 3%) had a documented PR and the overall median PFS was 6.4 months.²⁴ Continued evaluation of pyrotinib in *HER2* positive lung cancer patients is proceeding (NCT02834936). A phase I study of TAK-778 in patients with *EGFR* or *HER2* exon 20 mutations included 13 patients with *HER2* mutated tumors. One of five patients had an unconfirmed response at an early analysis. Accrual to a *HER2* specific dose expansion cohort is ongoing.²⁵ Overall the preliminary data with second generation pan-HER inhibitors have produced numerically increased response rates and PFS durations compared to first generation afatinib in a previously treated patient population. This leads us to speculate that their efficacy would be even greater in the first line setting which would be consistent with several second and third generation TKIs in other molecularly defined cohorts and we anxiously await the trial results. Afatinib may ultimately have a limited and short-lived role in the treatment of *HER2* mutated lung cancer but we should not underscore its importance in the journey to bring effective TKI treatment to this group of patients.

In summary, afatinib is modestly efficacious in untreated patients with *HER2* mutated lung cancer and may be considered for patients who are not candidates for or who refuse standard therapies. Our data generates support

and optimism for the continued evaluation of novel, more potent HER2 TKI inhibitors for this molecularly defined subset of lung cancer patients.

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Case 2	78	F	Caucasian	Never	Adenocarcinoma	0	<i>ERBB2</i> exon 20 A775_G776insYVMA	VEGFA amplification CDKN2A/B loss TAF1 W565	Confirmed PR	8 months	37+ months
Case 3	80	F	Caucasian	Never	Adenocarcinoma	1	<i>ERBB2</i> D769Y	CDKN2A/B loss DNMT3A E37* KDM6A loss exons 3-16 SMAD4 H371fs*14	Confirmed PR	7 months	13.7 months
Case 4	66	M	Asian	Active	Adenocarcinoma	1	<i>ERBB2</i> exon 20 A775_G776insYVMA	MDM2 amplification MEN1 splice site 669+1G>C FRS2 amplification ZNF217 amplification	Unconfirmed PR	7 months	17 months
Case 5	68	F	Caucasian	Never	Adenocarcinoma	1	<i>ERBB2</i> exon 20 A775_G776insYVMA	RICTOR amplification CDKN2A/B loss FGF10 amplification TP53 C176F	Progression	.75 months	18 months
Additional cases from the literature											
Case 6	57	F	Asian	Never	Adenocarcinoma	NR***	<i>ERBB2</i> exon 20 G776delinsVC	CTNNB1	Confirmed PR	12+ months	Alive
Case 7	62	F	Asian	Never	Adenocarcinoma	NR***	<i>ERBB2</i> V695E	NR***	Confirmed PR	7 months	NR***

*PS-performance status

**Testing by Next Generation Sequencing

***NR-not reported

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