Clinical outcomes of patients with HER2-mutant advanced lung cancer: chemotherapies versus HER2-directed therapies

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Abstract

Background: Lung cancer is now the leading cause of cancer mortality worldwide for both men and women. In non-small cell lung cancer (NSCLC), matching a specifically targeted drug to the identified driver mutation in each patient resulted in dramatically improved therapeutic efficacy, often in conjunction with decreased toxicity. Mutations in HER2 have been identified as an oncogenic driver gene for NSCLC. This retrospective study was conducted to better understand the clinical outcomes of advanced lung cancer patients harboring HER2 mutations treated with chemotherapies and HER2-targeted agents, as well as the optimal clinical choice.

Methods: Patients who were diagnosed with advanced lung cancer (stage IIIb/IV) and had undergone molecular testing at Zhongshan Hospital, Fudan University, Shanghai, China from April 2016 to December 2018 were reviewed. For patients that had HER2 mutant advanced lung cancer, we analyzed their clinical and molecular features and clinical outcomes, including overall survival (OS), progression-free survival (PFS), disease control rate (DCR) and objective response rate (ORR).

Results: We identified 44 patients harboring HER2 mutations. Their median age was 56 years, with the majority being women (n = 24), never smokers (n = 32), and having the adenocarcinoma genotype (n = 42). Amongst the HER2 mutations present, a 12 base pair in-frame insertion in exon 20 with p.771insAYVM was the most common subtype in patients with known detail variants of HER2 mutation (9/27). The median OS from the date of advanced disease diagnosis was 9.9 months with 24 deaths, and a median follow-up of 12.7 months for survivors. For patients with a known HER2 exon 20 insertion mutation, OS tended to be superior (though not statistically) in the first-line HER2-TKI group to that in the group receiving chemotherapy (10.8 versus 9.8 months, p = 0.40). However, patients that received first-line chemotherapy had a median PFS of 5.9 months, numerically longer than that of the HER2-TKI group (4.6 months, p = 0.63). Patients who received HER2-targeted therapy as first-line therapy had an improved OS (10.8 versus 10.1 months, p = 0.30) and PFS (4.6 versus 2.8 months, p = 0.36) relative to those who received HER2-targeted therapy as subsequent-line therapy, although they did not meet the threshold for statistical significance. Furthermore, patients with AYVM mutation were associated with poor clinical outcomes.

Conclusion: Pemetrexed-based chemotherapy remains an important component of care for patients with HER2-mutant NSCLC. HER2-TKI given as an initial therapy may bring more clinical benefits than when given as a subsequent-line therapy. Refining the patient population based on patterns of HER2 variants may help improve the efficacy of anti-HER2 treatment in lung cancer. Developing highly effective and tolerable HER2-targeted agents is urgently needed for this population.

Keywords: HER2 mutation, lung cancer, chemotherapy, HER2-targeted therapy

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Introduction
Worldwide, lung cancer occurred in approximately 2.1 million patients in 2018 and caused an estimated 1.8 million deaths. Lung cancer is now the leading cause of cancer mortality worldwide for both men and women. The goals of patient management for patients with advanced lung cancer are to prolong survival and to maintain quality of life for as long as possible, while minimizing the side effects due to treatment. An improved understanding of the molecular pathways that drive malignancy in non-small cell lung cancer (NSCLC) has led to the development of agents, which target specific molecular pathways in malignant cells. Mutations in the human epidermal growth factor receptor 2 (HER2 (ERBB2)), an epidermal growth factor receptor (EGFR) family receptor tyrosine kinase, occur in approximately 1–3% of NSCLC tumors and have been identified as oncogenic drivers. They usually involve small in-frame insertions and point mutations in exon 20. HER2 mutations are more prevalent among female patients, never-smokers and those with lung adenocarcinomas. Patients with HER2-mutant advanced lung cancer have previously been reported as having a poorer prognosis compared with other oncogenic drivers. There are no approved agents for HER2-mutant lung cancers yet, though treatment responses to both chemotherapies and HER2-targeted therapies have been documented. HER2 mutations are currently emerging as a promising drug target, while the optimal choice of HER2-targeted agents remains unclear. Standard chemotherapy seems to be up-front for HER2-mutant advanced lung cancer patients.

To better understand the clinical outcomes as well as to investigate the management of advanced lung cancer patients harboring HER2 mutations in a real-life setting, we conducted this retrospective study. The clinical outcomes of interest include overall survival (OS), progression-free survival (PFS), disease control rate (DCR) and objective response rate (ORR). We examined the clinical and molecular characteristics of HER2 mutations in advanced lung cancer patients.

Methods

Patient selection
Patients who were diagnosed with advanced lung cancer (stage III/IV) and had undergone molecular testing at Zhongshan Hospital, Fudan University, Shanghai, China from April 2016 to December 2018 were reviewed in our retrospective study. HER2 mutations were detected through the method of amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) by Multi-Gene Mutations Detection Kit (AmoyDx, Xiamen, China) or through next-generation sequencing (NGS) via Illumia Hiseq platform (Geneseeq, Nanjing, China). For patients that had HER2-mutant advanced lung cancer, we analyzed their clinical and molecular features, including age, gender, smoking status, tumor histology and genotype.

Clinical outcomes
Clinical outcomes included OS, PFS, DCR and ORR. OS was defined as the period of time from the diagnosis date of advanced lung cancer to death from any cause. Patients without a recorded death were censored at the last date of follow-up. PFS was defined as the time interval from the first day of treatment to documented disease progression or death from any cause. Disease progression was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. DCR was defined as the proportion of patients who had a best response rating of complete response (CR), partial response (PR), or stable disease. ORR was defined as the proportion of patients who had a best response rating of CR or PR.

Statistical analysis
Statistical analysis was performed using SPSS software. The Kaplan–Meier method was used to analyze the OS and PFS. A log-rank test was used to analyze OS and PFS between different groups. A p-value of less than 0.05 was considered statistically significant.

Results

Clinical and molecular characteristics
From April 2016 to December 2018, among all the 1497 patients who were diagnosed with advanced lung cancer and had undergone molecular testing in our department, we identified 44 (2.9%) patients with HER2 mutations. The baseline patient clinical characteristics are listed in Table 1. HER2 mutant lung cancer patients had a median age of 56 years (range: 32–76 years). A greater proportion of these patients were women.
(n = 24, 55%) and never-smokers (n = 32, 73%). These tumors were predominantly adenocarcinomas (n = 42, 95%). Twenty-seven of the 44 patients had tissue and blood samples available for next-generation sequencing and had particular HER2 mutation variants including 18 with a 12 base pair in-frame insertion in exon 20 (nine with p.771insAYVM, five with A775>G776insYVMA, two with p.Y772_A775dup, one with p.E770delinsEAYVM, one with p.772insYVMA), two with three base pair insertions in exon 20 (G776>VC) and seven with missense mutations (V777L in exon 20, W9G in exon 1, S310Y in exon 8, V659E in exon 17, R678Q in exon 17, R713W in exon 18, and L1173V in exon 27). One of the 44 patients had both an EGFR L858R mutation in exon 21 and a HER2 W9G mutation in exon 1. Two patients with EGFR sensitive mutations harbored HER2 mutations (one with L1173V in exon 27 and one with p.Y772_A775dup in exon 20) after resistance to first-line EGFR tyrosine kinase inhibitors (TKI) treatment. Thirty-eight of the 44 patients harbored mutations in HER2 exon 20, including one patient in which the mutation was detected after resistance to initial therapy.

**Clinical outcomes of patients treated with chemotherapy and HER2-targeted therapy as first-line therapy**

The median OS for patients with HER2-mutant advanced lung cancer was 9.9 months with 24 deaths and a median follow-up of 12.7 months for survivors. Patients with HER2 exon 20 mutation receiving HER2-TKI as an initial therapy had a numerically (though not statistically) longer OS than those receiving chemotherapy (10.8 versus 9.8 months, p = 0.40) (Figure 1(A)). In HER2 exon 20 mutant lung cancer, patients that had received first-line chemotherapy had a median PFS of 5.9 months, which was numerically longer than that of the HER2-TKI group (4.6 months, p = 0.78) (Figure 1(B)).

**Clinical outcomes of patients treated with HER2-targeted therapy and non-targeted therapy**

For patients with HER2 exon 20 mutations, the disease control rates of pemetrexed-based chemotherapy, HER2-TKI (afatinib and pyrotinib) and trastuzumab-based therapy were 89.7%, 64.0% and 33.3% (Table 2). For those receiving pemetrexed-based chemotherapy and those receiving HER2-TKI, the objective response rates were 6.9% and 8.0% (Table 2). For patients

### Table 1. Clinical characteristics of patients with HER2 mutations.

| Patient clinical characteristics |  |
|---------------------------------|--|
| Age at lung cancer diagnosis, median years (range) | 56 (32–76) |
| <65 | 33 (75%) |
| ≥65 | 11 (25%) |
| Gender |  |
| Male | 20 (45%) |
| Female | 24 (55%) |
| Smoking status |  |
| Non-smoker | 32 (73%) |
| Former smoker | 7 (16%) |
| Current smoker | 5 (11%) |
| Histology |  |
| Adenocarcinoma | 42 (95%) |
| Non-adenocarcinoma | 2 (5%) |
| HER2 alteration |  |
| Exon 20 | 38 (86%) |
| Non-exon 20 | 6 (14%) |
| Testing method |  |
| ARMS-PCR | 17 (39%) |
| NGS | 27 (61%) |
| Type of first-line treatment for HER2 exon 20 mutant advanced lung cancer |  |
| Chemotherapy | 27 (73%) |
| Targeted therapy | 8 (22%) |
| Supportive care | 2 (5%) |
| Line of HER2-targeted therapy |  |
| First line | 8 (28%) |
| Second line | 11 (38%) |
| Third line and above | 10 (34%) |

ARMS-PCR, amplification refractory mutation system-polymerase chain reaction; HER2, human epidermal growth factor receptor 2; NGS, next-generation sequencing.
receiving pemetrexed-based chemotherapy and HER2-targeted therapy, PFS was 5.8 and 2.1 months, respectively \( (p = 0.08) \) (Figure 2(A)). Patients who received HER2-targeted therapy as first-line therapy had an improved OS \( (10.8 \text{ versus } 10.1 \text{ months}, p = 0.30, \text{Figure 2(B)}) \), as well as the PFS \( (4.6 \text{ versus } 2.8 \text{ months}, p = 0.36, \text{Figure 2(C)}) \), relative to those who received HER2-targeted therapy as subsequent-line therapy, although they did not meet the threshold for statistical significance. For patients treated with immunotherapy, the median PFS was 1.7 months (range: 1–3.3 months) and the DCR was 75.0%. 

Clinical outcomes of patients with HER2 mutation: comparison among HER2 variants subgroups

Twenty of the 44 patients had a known HER2 exon 20 variant when diagnosed with advanced lung cancer. According to the frequency of variants, they were divided into the exon 20 p.771insAYVM group \( (n = 9) \) and the other variants group \( (n = 11) \), five with A775_G776insYVMA, one with p.Y772_A775dup, one with p.E770delinsEAYVM, one with p.772insYVMA, two with G776>VC, and one with V777L. Median OS tended to be inferior in the p.771insAYVM group compared with the OS of the other variants group \( (9.3 \text{ versus } 12.4 \text{ months}, p = 0.48) \) (Figure 3(A)). Patients in the p.771insAYVM group had a median PFS of 3.6 months when treated with first-line chemotherapy, which was significantly shorter than that of the other variants group \( (7.1 \text{ months}, p = 0.02) \) (Figure 3(B)). When treated with HER2-TKI, median PFS tended to be inferior in the p.771insAYVM group compared with the median PFS of the other variants group, even though no significant difference existed between the two groups \( (2.6 \text{ versus } 4.4 \text{ months}, p = 0.24) \) (Figure 3(C)). Meanwhile, durable disease control was seen in two patients treated with afatinib as a first-line therapy \( (17.5 \text{ and } 13.3 \text{ months, respectively}) \), one with a G776>V mutation and the other with a YVMA insertion.

Discussion

In our retrospective study, mutations in the HER2 gene were detected in approximately 2.9% of unselected metastatic lung cancer using ARMS-PCR or NGS, which is comparable to previous
In accordance with prior reports, HER2 mutations tend to be more common in younger, female patients with no smoking history and adenocarcinoma histology. Most of the HER2 exon 20 mutations were exclusive, except for one patient with a concomitant EGFR sensitive mutation who harbored a HER2 exon 20 mutation after resistance to first-line EGFR-TKI. However, differently from previous studies, we found that a 12 base pair in-frame insertion with p.771insAYVM was the most common subtype, rather than A775_G776insYVMA⁵,⁷,⁸ in our study. Other, much rarer, subtypes of HER2 mutations were also detected, such as missense mutations in exons 1, 8, 17, 18 and 27.

Overall, patients with HER2-aberrant tumors have a significantly worse prognosis than those with EGFR and anaplastic lymphoma kinase (ALK)-positive tumors, possibly due to the low proportion of patients that received HER2-targeted therapies and the low response rate to HER2-targeted therapies in patients with HER2-mutant tumors.⁸ In a French real-life setting cohort, median OS of stage IV NSCLC patients harboring HER2 mutations was 10.7 months.⁹ As in our cohort, the median OS was 9.9 months with 24 deaths and a median follow-up of 12.7 months for survivors. Patil et al. reported that patients who received HER2-directed therapies had numerically longer median survival time.
relative to patients who received cytotoxic chemotherapy (65 versus 29 months). In our series, OS was numerically longer for patients treated with HER2-TKI as an initial therapy rather than chemotherapy (10.8 versus 9.8 months), although this did not meet the threshold for statistical significance. But we found that patients with advanced HER2 exon 20-mutant lung cancer derived a PFS benefit to first-line chemotherapy compared with first-line HER2-TKI (5.9 versus 4.6 months, \( p = 0.78 \)). In the current series, patients who received HER2-targeted therapies had a shorter median PFS relative to those who received pemetrexed-based therapy (2.1 versus 5.8 months, \( p = 0.08 \)), irrespective of the line of therapy. However, when HER2-targeted agents were given as an initial therapy rather than a subsequent-line therapy, patients derived a numerically longer OS (10.8 versus 10.1 months, \( p = 0.30 \)), as well as a numerically longer PFS (4.6 versus 2.8 months, \( p = 0.36 \)). When HER2-targeted agents were given as a subsequent-line therapy, a large proportion of patients derived short-term benefit or no benefits at all. As patients might derive more clinical benefits if they were treated at an earlier point in their disease course with a better performance status, assessments of the activity of HER2-targeted agents presented here and in the literature may be underestimates of their potential effectiveness.

Although HER2 mutations appear to be an emerging and promising drug-targetable NSCLC marker, the optimal choice for targeted therapy...
remains poorly defined. For patients receiving afatinib and trastuzumab-based chemotherapy, the EUHER2 study demonstrated that response rates were 18% and 50%, disease control rates were 64% and 75% and PFS was 3.9 and 5.1 months, respectively. In our study, we observed that for patients treated with HER2-TKI and trastuzumab-based therapy, disease control rates were 64.0% and 33.3%, irrespective of the line of therapy. The ORR of HER2-TKI was 8% in our patients. However, durable clinical benefit from afatinib as a first-line therapy was also seen in two patients (17.5 and 13.3 months, respectively) in our study, one with a G776>V mutation and the other with a YVMA mutation. An ongoing treatment of afatinib for a patient with a YVMA mutation at 30 months was documented in a retrospective international multi-center study. Fang et al. reported that G778_P780dup and G776delinsVC derived the greatest benefit from afatinib among HER2 variants. This demonstrates that afatinib has the potential for durable disease control in a subset of patients with HER2-mutant lung cancer. Furthermore, we found for the first time that patients with AYVM insertion were associated with poor clinical outcomes. Given our small sample size and limited number of patients subjected to NGS, we were unable to differentiate responses to HER2-directed therapies based on specific insertion mutations, though this is an area of importance. These findings highlight the need for a better understanding of the underlying biology of the various HER2 mutation subtypes and potential differences in their response to therapies.

There are issues that need to be taken into consideration when administering HER2-targeted therapies. Toxicities of afatinib, including diarrhea and mucositis, can be dose-limiting. Tolerability of these medications may be a challenge for patients. Other irreversible pan-HER receptor family inhibitors of potential therapeutic roles, such as dacomitinib, neratinib, pyrotinib and poziotinib, are all under study. Dacomitinib showed a modest response rate of 11.5% (3/26) in patients with tumors harboring HER2 exon 20 mutations in a phase II trial. The preliminary results of neratinib in combination with temsirolimus from a phase II trial reported a response rate of 18.6% (8/43) in HER2-mutant lung adenocarcinoma. Pyrotinib, a promising small-molecular inhibitor, demonstrated a response rate of 53.3% (8/15) and median PFS of 6.4 months in an early-phase clinical trial. Poziotinib has reported efficacy in HER2 exon 20 insertion NSCLC (NCT03318939). Another potent and selective EGFR/HER2-TKI, TAK-788 (AP32788), has shown antitumor activity in preclinical studies involving HER2 exon 20 insertion-mutant cancer cell lines.

Apart from small molecular inhibitors, ado-trastuzumab emtansine (also known as T-DM1), a HER2-targeted antibody–drug conjugate, has shown promise in treating patients with HER2-mutant advanced lung cancer. A previous study reported limited efficacy of T-DM1 for HER2-positive NSCLC, which confirmed that HER2 IHC was not the ideal biomarker in lung cancers. In a recent separate phase II trial of T-DM1 for patients with HER2-mutant lung cancers, the objective response rate was 44%, median PFS was 5 months and the median duration of response was 4 months. T-DM1 has been incorporated as a treatment recommendation for HER2-mutant lung adenocarcinomas by the 2018 National Comprehensive Cancer Network Clinical Practice Guidelines. A further expansion study of T-DM1 in both HER2-amplified and HER2-mutant solid tumors is ongoing (NCT02675829). [Fam]-trastuzumab deruxtecan (DS-8201a), a novel HER2-targeted antibody–drug conjugate, has a confirmed objective response rate of 58.8% (10/17) in HER2-expressing or -mutated NSCLC and 72.7% (8/11) response rate in HER2-mutated NSCLC in an ongoing phase I trial, with a manageable safety profile. A phase II study of DS-8201a in HER2-overexpressing or -mutated advanced NSCLC is also ongoing (NCT03505710).

Immunotherapy with anti-programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 has emerged as a standard of care in advanced lung cancer treatment over the past 5 years. The role of immune checkpoint inhibitors (ICIs) alone, or with chemotherapy, in patients with known oncogenic drivers continues to evolve. In a single-center retrospective study, no patient with atypical EGFR (a-EGFR; G719X, exon 20, L861Q) or HER2 alterations (exon 19, exon 20, amplifications) had a RECIST response to single-agent ICI. Patients with a-EGFR and HER2 alterations who received ICI with platinum doublet chemotherapy had significantly improved PFS relative to single-agent ICI (7 versus 2 months). Mazieres et al. found that PFS to single-agent ICI ranged from 2 to 3.4 months among those with HER2 alterations.
et al. reported in a retrospective multi-center study that the response rates of anti-PD-1 immunotherapy for \( \text{BRAF-V600}, \text{BRAF-non-V600}, \text{HER2}, \text{MET} \) and \( \text{RET} \)-altered NSCLC – which were 26%, 35%, 27%, 36% and 38%, respectively – seemed close to that observed in unselected patients with NSCLC.\(^{24} \) Four patients received immunotherapy of anti-PD-1 as a subsequent-line of therapy in our study. DCR of immunotherapy was 75%. PFS to single-agent ICI as a subsequent-line of therapy ranged from 1 to 3.3 months in our cohort. These results suggest that it would be interesting to observe the clinical outcomes of immunotherapy in patients with \( \text{HER2} \)-mutant lung cancer. Large prospective studies are needed to reveal ICI efficacy in these rare patient subsets.

We note several limitations in our study. First, this was a retrospective and observational single-institution study and was therefore prone to selection bias. Additionally, collected patient information was not always complete. Second, the patient number was limited (\( n = 44 \)) in our cohort. This is partly due to the fact that a portion of the patients were subjected to hot spot molecular profiling, which may not have included \( \text{HER2} \), while it presented the real-world nature in the Chinese population given the study inclusion period. Third, 39% of the molecular testing (17/44) was performed using ARMS-PCR, which was not able to determine the particular variant of \( \text{HER2} \) mutation present and thus may have led us to miss some rare mutations. This also tempered our ability to draw strong conclusions regarding the potential differences of various \( \text{HER2} \) mutation subtypes in their responses to therapies, although this is an area ripe for future exploration. Finally, another limitation is that we only have experience with afatinib, pyrotinib and trastuzumab (in combination with chemotherapy) as these are the available treatments in China currently. No patients received other available or experimental \( \text{HER2} \)-targeted agents. However, because of the rarity of \( \text{HER2} \)-mutated advanced lung cancer, we think that our study provides valuable real-life information about treatments received and the outcomes of these patients in the Chinese population.

**Conclusion**

\( \text{HER2} \) is a targetable driver mutation. We recommend testing for \( \text{HER2} \) mutations in addition to other uncommon, potentially targetable, genetic alterations for patients whose tumors are negative in \( \text{EGFR}, \text{ALK} \) and c-ros oncogene 1 receptor tyrosine kinase (\( \text{ROS1} \)). Pemetrexed-containing chemotherapy seemed to be the prior regimen for patients with \( \text{HER2} \) exon 20 mutant adenocarcinomas so far. Currently available \( \text{HER2} \)-targeted agents may provide an additional option for those patients. Patients treated with \( \text{HER2} \)-TKI earlier in their disease course may derive more clinical benefits. Refining the patient population based on patterns of \( \text{HER2} \) variants may help to improve the efficacy of anti-\( \text{HER2} \) treatment in lung cancer. Developing highly effective and tolerable \( \text{HER2} \)-targeted agents is urgently needed for this population.

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**Author contribution**

JZ contributed to preparing and conducting this research. ND, XX, YZ, MY, and CL provided the patient information. JH designed the research. All authors read and approved the final manuscript.

**Conflict of interest statement**

The authors declare that there is no conflict of interest.

**Ethics statement**

The study protocol was approved by the ethics committee of Zhongshan Hospital, Fudan University (No. B2017-142R).

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**Informed consent**

Informed consent, covering the study background, objective, process, risk and benefit, and personal information safety, was obtained from all individual participants included in the study.

**Supplemental material**

Supplemental material for this article is available online.

**Reference**

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