

Clinical Characteristics and Outcomes of Non-small Cell Lung Cancer Patients with *HER2* Alterations in Korea

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Purpose

Human epidermal growth factor receptor 2 (*HER2*) alterations are found in approximately 1%-3% of non-small cell lung cancers (NSCLCs). We evaluated the clinical features and outcomes of NSCLC harboring *HER2* alteration detected by next-generation sequencing (NGS) in Korea.

Materials and Methods

A total of 1,108 patients who were diagnosed with NSCLC between December 2015 and December 2017 were screened and analyzed by NGS. Medical records were reviewed retrospectively to analyze the clinical characteristics and outcomes from various treatments.

Results

HER2 alterations were identified in 36 NSCLC patients. Of the patients, 22 (61.1%) had an exon 20 in-frame insertion mutation, 15 (41.7%) had *HER2* amplification, and one had both. The median patient age was 58 years, 55.6% were male, and 50.0% were never-smokers. Adenocarcinoma was predominant (88.9%). The most common metastatic site was bone (58.3%), and 66.7% of patients were stage IV at initial diagnosis. Six patients (16.7%) had a coexistent sensitizing epidermal growth factor receptor (*EGFR*) mutation, and two patients (5.6%) had anaplastic lymphoma kinase (*ALK*) rearrangement. With a median 14 months of follow-up, the median progression-free survival of first-line treatment was 6 months (95% confidence interval, 4.172 to 7.828), and median overall survival was not reached. The proportions of adenocarcinoma, never-smokers, and metastasis to the liver were higher in the exon 20 in-frame insertion mutation group, whereas coexistence of *EGFR* mutation was more frequently found in the *HER2* amplification group.

Conclusion

HER2-altered NSCLC showed distinct clinical features. Moreover, different characteristics were identified between the *HER2* in-frame insertion mutation group and the *HER2* amplification group.

Key words

Non-small cell lung cancer, *HER2* mutation, *HER2* amplification

Introduction

The identification of oncogenic driver mutations has triggered the development of new treatments for non-small cell lung cancer (NSCLC). Targeted therapies have shown significant improvement of clinical outcomes in NSCLC patients with epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*), or *c-ros* oncogene1 (*ROS1*)

gene rearrangement.

With the advent of precision medicine using next-generation sequencing (NGS), other various genetic alterations can be detected. Human epidermal growth factor receptor 2 (*HER2*), also known as *NEU*, *EGFR2*, or *ERBB2*, is a member of the *EGFR* family of receptor tyrosine kinases. *HER2* alteration has been demonstrated to play important roles in the pathogenesis of certain human cancers, including breast cancer and gastric cancer, by activating downstream signaling

via the phosphatidylinositol 3-kinase (PI3K)–protein kinase B (AKT) and mitogen-activated protein kinase kinase (MEK)–extracellular signal-regulated kinase pathways.

HER2 alterations have emerged as novel oncogenic drivers and therapeutic targets in lung cancers [1]. The incidence of *HER2* mutation in lung adenocarcinoma is 1%-5%, and frequency of *HER2* amplification is 2%-5% [2]. Previous studies have identified distinct clinical features of NSCLCs with *HER2* alteration. Mazieres et al. [3] reported that *HER2*-altered NSCLC shows a high proportion of adenocarcinoma (100%), female patients (69.2%), and never-smokers (52.3%). Li et al. [4] also showed that *HER2* alteration occurs predominantly in never-smokers (100%) and female patients (87.5%). In contrast, Arcila et al. [5] reported that there were no associations between *HER2*-altered NSCLC and sex, race, or stage at diagnosis. Given the small number of patients analyzed in previous studies, the clinical features and outcomes have not been fully evaluated in advanced NSCLC harboring *HER2* alterations [6].

The aims of this study are to evaluate the characteristics and clinical outcomes of NSCLC patients harboring *HER2* alteration detected by NGS.

Materials and Methods

1. Patients

A total of 1,108 patients who were initially diagnosed with metastatic NSCLC was screened between December 2015 and December 2017 at Samsung Medical Center. All tissue samples were analyzed by NGS. For patients with *HER2* alterations, patient characteristics, histology, initial stage at diagnosis, sites of metastasis, and response to first-line systemic treatment for metastatic NSCLC were retrospectively analyzed.

2. Identification of *HER2* alteration

HER2 gene alterations were identified by NGS. The OncoPrint Focus Assay panel (Thermo Fisher Scientific, San Francisco, CA) or the CancerSCAN panel (LabGenomics, Seongnam, Korea) was used for analyzing *HER2* alterations, including *HER2* amplification and exon 20 in-frame insertion mutation.

CancerSCAN is a targeted sequencing platform, designed at Samsung Medical Center. This customized platform included target genes curated from the literature of requested by the researchers and clinicians and the selected genes covered variants associated with the targeted cancer therapies appro-

ved by the Korean Ministry of Food and Drug Safety and U.S. Food and Drug Administration. In this study, CancerSCAN version 2 was applied, encompassing 381 cancer-related genes. The genes contained in the panel are listed in S1 Table. The panel has been validated with data demonstrating 95% sensitivity and positive predictive value [7].

We also used OncoPrint Focus Assay (OFA) panel, which simultaneously detects hundreds of variants across 52 genes relevant to solid tumors [8]. The biomarkers included were selected based on information in the Ion Torrent OncoPrint Knowledgebase, one of the world's largest collections of curated oncology data. OFA has shown a precise, reproducible, sensitive, and accurate NGS assay for the detection of somatic genetic variants with nearly 99% of accuracy and specificity, which is commercially available [8].

Copy number variations (CNVs) of genes were detected using an in-house copy number caller. To identify somatic CNVs, we calculated the mean read depth at each exon, normalized by the coverage of the target regions in that sample. This normalized read depth was further standardized by dividing by the expected coverage for a normal individual (the expected coverage at each exon was taken to be the median of the read depth at that exon across a set of normal individuals). These steps account for the variability in capture efficiency and GC content at different exons. To infer the correct copy number, the amplitude of the copy numbers were then adjusted based on the estimated purity. Copy numbers greater than four were categorized as amplifications.

3. Statistical analysis

Medical records were reviewed to obtain clinical information. Descriptive statistics were used to analyze the demographics, histology, incidence of various sites of metastasis, *EGFR* mutation, and *ALK* rearrangement. Statistical significance was set at $p < 0.05$. All analyses were conducted using SPSS ver. 24.0 (IBM Corp., Armonk, NY). Either the chi-squared test or Fisher exact test was used, as appropriate, to analyze statistical significance among patient characteristics. Progression-free survival (PFS) was calculated from the time of first systemic treatment to radiographic progression or death. Overall survival (OS) was also calculated from the time of first systemic treatment to the date of death. PFS and OS were analyzed using the Kaplan-Meier estimation method.

4. Ethical statement

Institutional Review Board (IRB) approval was obtained from Samsung Medical Center (SMC, Seoul, Korea, SMC 2019-03-107-001). The IRB approved waiver of informed consent.

Table 1. Characteristics of the patients harboring *HER2* alteration

Characteristic	<i>HER2</i> altered (n=36)	Exon20 insertion (n=22)	<i>HER2</i> amplification (n=15)	p-value
Age at diagnosis (yr)	58	60.2	56.4	
Sex				0.093
Men	20 (55.6)	10 (45.5)	11 (73.3)	
Women	16 (44.4)	12 (54.5)	4 (26.7)	
ECOG PS				0.819
0	4 (11.1)	3 (13.6)	1 (6.7)	
1	30 (83.3)	18 (81.8)	13 (86.7)	
2	2 (5.6)	1 (4.5)	1 (6.7)	
Tobacco				0.084
Never	18 (50.0)	14 (63.6)	4 (26.7)	
Former	11 (30.6)	5 (22.7)	6 (40.0)	
Current	7 (19.4)	3 (13.6)	5 (33.3)	
Stage at diagnosis				0.753
I	5 (13.9)	2 (9.1)	3 (20.0)	
II	3 (8.3)	2 (9.1)	1 (6.7)	
III	4 (11.1)	2 (9.1)	2 (13.3)	
IV	24 (66.7)	16 (72.7)	9 (60.0)	
Metastasis sites				
Bone	21 (58.3)	14 (63.6)	8 (53.3)	0.531
Pleura	18 (50.0)	12 (54.5)	6 (40.0)	0.385
Brain	13 (36.1)	8 (36.4)	5 (33.3)	0.850
Contralateral metastasis	11 (30.6)	6 (27.3)	5 (33.3)	0.728
Liver	7 (19.4)	7 (31.8)	0	0.028
Distant LN	7 (19.4)	4 (18.2)	3 (20.0)	0.808
Adrenal	4 (11.1)	4 (18.2)	0	0.131
LMS	3 (8.3)	2 (9.1)	1 (6.7)	1.000
Thyroid	1 (2.8)	1 (4.5)	0	1.000
Histology				0.021
ADC	32 (88.9)	22 (100)	11 (73.3)	
SQC	4 (11.1)	0	4 (26.7)	
EGFR(+)				0.002
Wild type	30 (83.3)	22 (100)	9 (60.0)	
Mutation	6 (16.7)	0	6 (40.0)	
ALK(+)				0.505
Wild type	34 (94.4)	20 (90.9)	15 (100)	
Mutation	2 (5.6)	2 (9.1)	0	

Values are presented as number (%). *HER2*, human epidermal growth factor receptor 2; ECOG PS, Eastern Cooperative Oncology Group performance status; LN, lymph node; LMS, leptomeningeal seeding; ADC, adenocarcinoma; SQC, squamous cell carcinoma; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

Results

A total of 1,108 patients diagnosed with NSCLC were screened in this study. Tissue samples from all patients were analyzed by NGS. The NGS results showed that 36 patients (3%) had *HER2* alteration. The median age of *HER2*-altered

patients was 58 years (range, 35 to 79 years), 55.6% of the patients were male, and 50.0% were never-smokers. Adenocarcinoma was the predominant cancer type (88.9%), and there were four cases (11.1%) of squamous cell carcinoma. The most common metastatic site was bone (58.3%), followed by pleura (50%) and brain (36.1%). At initial diagnosis, 66.7% of patients were stage IV. Six patients (16.7%) had a coexis-

Table 2. Amino acid changes of *HER2* in-frame insertion mutation group

Patient No.	Amino acid change	Amino acid change	Total (n=22)
1	E770_A771insAYVM	E770_A771insAYVM	12
2	E770_A771insAYVM	E770delinsEAYVM	4
3	E770_A771insAYVM	G776delinsVC	3
4	E770_A771insAYVM	V777delinsVGSP	2
5	E770_A771insAYVM	A771_Y772insYVMA	1
6	E770_A771insAYVM	-	-
7	G776delinsVC	-	-
8	E770_A771insAYVM	-	-
9	E770_A771insAYVM	-	-
10	A771_Y772insYVMA	-	-
11	G776delinsVC	-	-
12	E770_A771insAYVM	-	-
13	E770_A771insAYVM	-	-
14	E770_A771insAYVM	-	-
15	E770delinsEAYVM	-	-
16	G776delinsVC	-	-
17	V777delinsVGSP	-	-
18	E770delinsEAYVM	-	-
19	E770delinsEAYVM	-	-
20	V777delinsVGSP	-	-
21	E770delinsEAYVM	-	-
36	E770_A771insAYVM	-	-

HER2, human epidermal growth factor receptor 2.

Table 3. Best response to the first-line treatment of *HER2* altered non-small cell lung cancer

Treatment	No. (%) (n=36)	Best response
Targeted therapy	5 (13.9)	
Erlotinib	1	PR
Gefitinib	2	SD (n=2)
Afatinib	1	PR
Crizotinib	1	PD
Cytotoxic chemotherapy	28 (77.8)	
Pemetrexed+cisplatin	23	PR (n=6), SD (n=15), PD (n=1), N/A (n=1)
Gemcitabine+cisplatin	4	PR (n=3), SD (n=1)
Pemetrexed monotherapy	1	N/A
Immunotherapy	3 (8.3)	
Durvalumab+tremelimumab+pemetrexed+cisplatin	1	SD
Ipilimumab+nivolumab	1	SD
Nivolumab	1	PR

HER2, human epidermal growth factor receptor 2; PR, partial response; SD, stable disease; PD, progressive disease; N/A, not acquired.

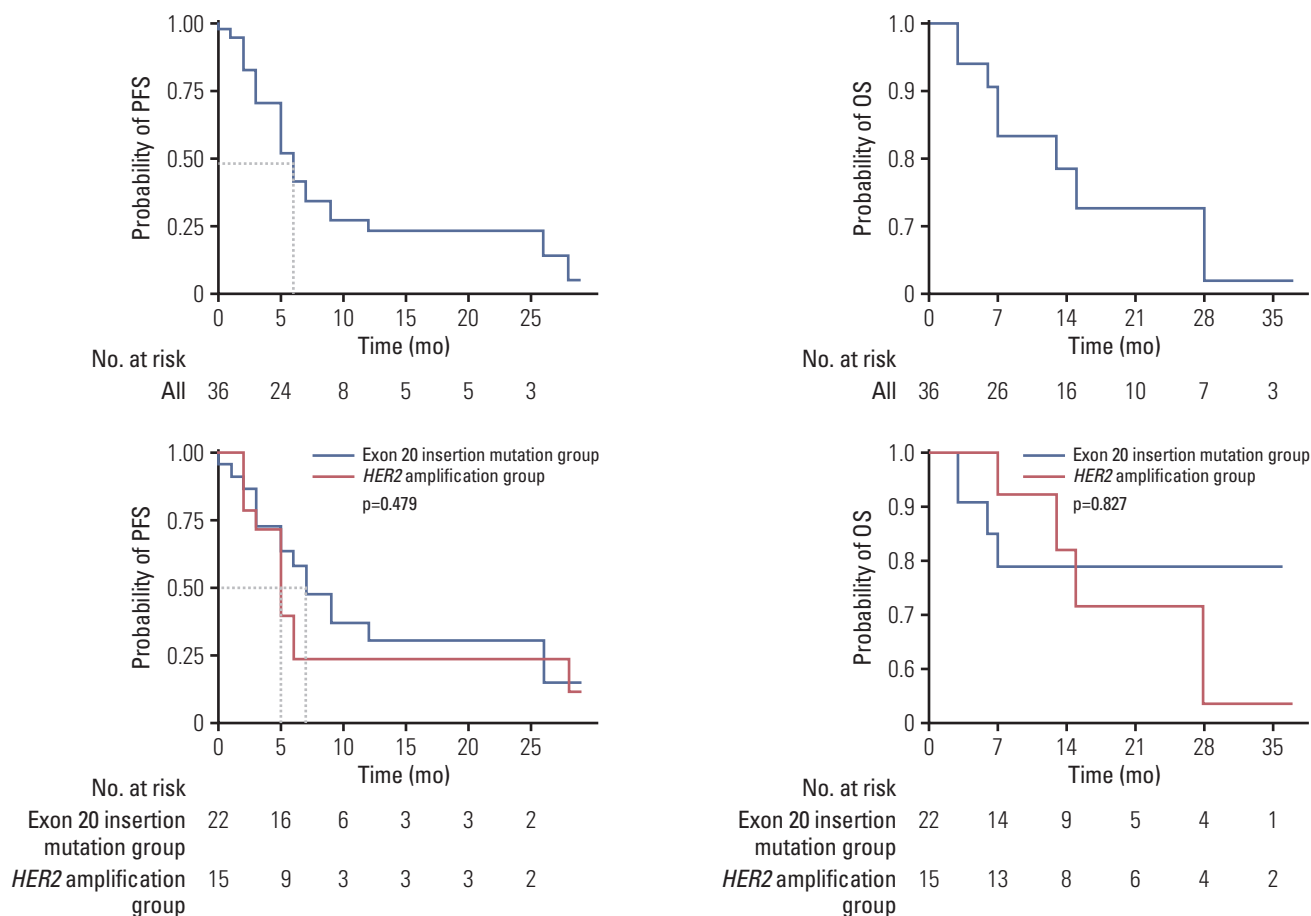


Fig. 1. Progression-free survival (PFS) and overall survival (OS) of human epidermal growth factor receptor 2 (*HER2*)-altered non-small cell lung cancer patients.

tent sensitizing *EGFR* mutation, and two patients (5.6%) had *ALK* rearrangement (Table 1). The *EGFR* mutations consisted of three exon 21 L858R mutations, one exon 19 deletion, and two compound mutations (exon 18 E709K+G719A [n=1] and exon 18 G179C+exon 20 S768I [n=1]). Five of the six *EGFR* mutations (83.3%) were detected by NGS. The other *EGFR* and two *ALK* rearrangements were found by peptide nucleic acid-mediated polymerase chain reaction (PCR) clamping method and fluorescent *in situ* hybridization (FISH), respectively.

Among the 36 *HER2*-altered NSCLC patients, 22 patients (61.1%) had exon 20 in-frame insertion mutation, 15 patients (41.7%) had *HER2* gene amplification, and one patient had both. The most frequently inserted amino acid sequence was E770_A771insAYVM (55%), followed by E770delinsEAYVM, G776delinsVC, and V777delinsVGSP (Table 2). Demographics, including Eastern Cooperative Oncology Group performance status, stage at diagnosis, and the *ALK* rearrangement incidence were similar between the exon 20 in-frame inser-

tion mutation group and the *HER2* amplification group. However, patients with adenocarcinoma were significantly more predominant in the exon 20 in-frame insertion mutation group than the *HER2* amplification group (100% vs. 73.3%, respectively, $p=0.021$). The proportion of never-smokers and frequency of metastasis to the liver were also higher in the exon 20 in-frame insertion mutation group (63.6% vs. 26.7%, $p=0.027$; 31.8% vs. 0%, $p=0.025$, respectively). In contrast, *EGFR* mutation was more frequent in the *HER2* amplification group (40% vs. 0%, $p=0.002$), and the proportion of male patients tended to be higher in the *HER2* amplification group (73.3% vs. 45.5%, $p=0.093$), although the difference was not statistically significant (Table 1).

As the initial treatment, 28 patients (77.8%) were treated with cytotoxic chemotherapy (pemetrexed/cisplatin [n=23], gemcitabine/cisplatin [n=4], pemetrexed monotherapy [n=1]), and the median PFS of these patients was six months (95% confidence interval [CI], 3.969 to 8.031). Of the six patients with coexisting sensitizing *EGFR* mutations, four

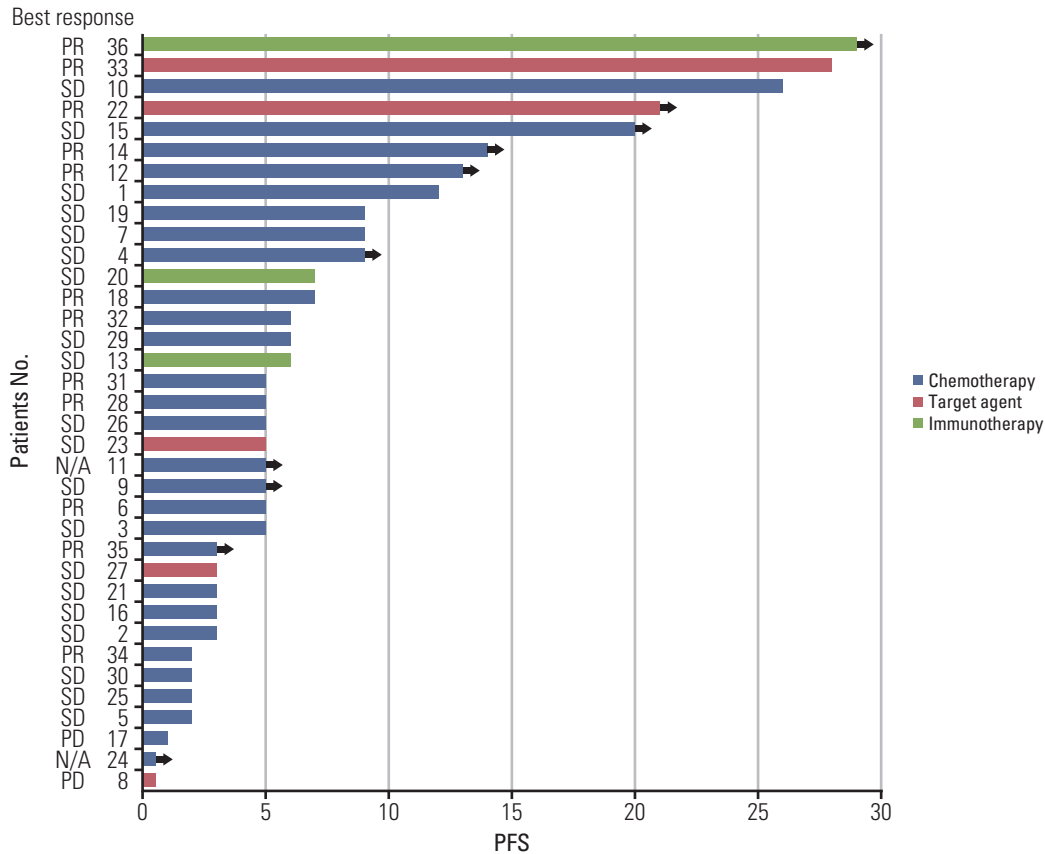


Fig. 2. Swimmers plot of progression-free survival (PFS) of first-line treatment. PR, partial response; SD, stable disease; N/A, not acquired.

patients were treated with EGFR tyrosine kinase inhibitors (TKIs) as first-line treatment (erlotinib [n=1], gefitinib [n=2], or afatinib [n=1]). Two patients showed PFS of 5 months and 3 months and achieved the best response of stable disease. Another two patients showed PFS of more than 21 months with partial response. The other two patients with EGFR mutations were treated with EGFR-TKI (gefitinib [n=2]) as second-line treatment, and the PFS were 33 and 15 months, respectively. One of the two patients with *ALK* rearrangement was initially treated with crizotinib, and the PFS was one month.

Of the 28 patients without coexisting sensitizing *EGFR* mutation or *ALK* rearrangement, three (two with exon 20 insertion mutation, one with both *HER2* alterations) were able to participate in a clinical trial and were treated with immunotherapy (durvalumab/tremelimumab/pemetrexed/cisplatin [n=1], ipilimumab/nivolumab [n=1], nivolumab [n=1]) (Table 3). Two of these patients showed PFS of 6 months and 7 months, and one patient showed sustained treatment response for 29 months until the data cut-off date. Overall, with 14 months of median follow-up (95% CI, 8.039

to 19.961), the median PFS of first-line treatment was six months (95% CI, 4.172 to 7.828), and the median OS had not been reached. There was no statistically significant difference between the exon 20 in-frame insertion mutation group and *HER2* amplification group in terms of PFS or OS (PFS, 7 months vs. 5 months, respectively; $p=0.479$) (Fig. 1).

Discussion

In our study, *HER2*-altered NSCLC was associated with a higher rate of adenocarcinoma (88.9%) and never-smokers (50%). This result is consistent with previous studies performed in Europe and Asia [3-5]. By contrast, there was no relationship between *HER2* alteration and sex, unlike the previous studies. Given that previous studies included smaller numbers of patients and were based on results from FISH or PCR, we could emphasize closer associations of adenocarcinoma histology and smoking history with the incidence of

HER2-altered NSCLC based on our NGS results. Early studies described *HER2* mutations as mutually exclusive with other oncogenic driver mutations, such as *EGFR* mutations [6]. However, recent reports suggested that concomitant *EGFR* mutation or *ALK* rearrangement is more common [9], and we found a relatively high rate of coexistence in this study (22.2%). Most of coexistent *EGFR* mutations (83.3%) were detected by NGS solely, not PCR. NGS seems to have better sensitivity in detecting *EGFR* mutations, which can be a key target for treatment. On the other hand, one *EGFR* mutation and two *ALK* rearrangements were found in PCR and FISH, respectively, not NGS. It means NGS is not a perfect test, and we need a better NGS panel to detect broader mutations, including rare ones.

HER2 alteration consists of *HER2* amplification and *HER2* mutation, which have been revealed as in-frame insertion mutation. Li et al. [10] showed that *HER2* mutations were not associated with *HER2* amplification and suggested a distinct disease entity and therapeutic target for each alteration. Of the 36 *HER2*-altered patients in our study, 35 patients had either *HER2* mutation or *HER2* amplification. One patient harbored both gene alterations. We found distinct clinical features between the *HER2* mutation and *HER2* amplification groups. The proportions of never-smokers, adenocarcinoma, and metastasis to the liver were more frequent in the exon 20 in-frame insertion mutation group, while the *HER2* amplification group showed a high proportion of *EGFR* mutation. Although these discrepancies should be confirmed with a bigger study, their different clinical features imply different pathogenesis and treatment strategies in NSCLC.

Most of the *HER2*-altered patients (77.8%) were treated with cytotoxic chemotherapy as first-line treatment due to the unavailability of targeted agents. The median PFS of the patients was 6 months, which was similar to previous studies [11]. Other patients who were treated with *EGFR*-TKI, *ALK* inhibitor, or immunotherapy showed diverse responses (Fig. 2). There was no significant difference between the *HER2* mutation group and the *HER2* amplification group in terms of clinical outcomes.

Many clinical trials have attempted to find the best treatment for *HER2*-altered NSCLC. Although most of the studies used *HER2* TKI or *HER2*-targeted monoclonal antibody (trastuzumab), which yielded disappointing results, some recent studies have produced encouraging results. A phase-II basket trial showed a therapeutic benefit of adotrastuzumab emtansine (T-DM1) for NSCLC patients with *HER2* mutations, who achieved a median 5-month PFS with acceptable toxicity [12]. Although the study size was small, based on this result, National Comprehensive Cancer Network guideline suggests T-DM1 as an available targeted agent for *HER2*-mutant NSCLC. In addition, afatinib and dacomitinib, which are pan-HER inhibitors and have been

approved as first-line treatments for metastatic *EGFR*-mutant NSCLC, have shown promising results in phase-II studies [13,14]. Ogoshi [15] also showed that neratinib inhibited the growth of *HER2*-altered NSCLC cell lines. Other therapies for *HER2* alteration in lung cancer are still being introduced [16,17], and in clinical trials (NCT03505710, NCT02535507).

In our study, two patients showed an outstanding therapeutic response. One patient (No. 22 in Fig. 2) harboring *HER2* amplification with L858R mutation was treated with afatinib and showed a partial response after initial therapy. The therapeutic effect was sustained until the data cut-off date, for 21 months. Even considering the *EGFR* mutation, the PFS was much longer than the results of previous LUX-lung trials [18,19]. Previously, Fang et al. [20] showed a divergent therapeutic benefit from afatinib according to mutation type of *HER2*-altered NSCLC. Patients with G776delinsVC and G778_P780dup derive the greatest benefit from afatinib, while patients with A775_G776insYVMA, co-mutations in the TP53 and PI3K/AKT/mammalian target of rapamycin (mTOR) pathway show primary resistance to afatinib [20]. One preclinical study reported the efficacy of afatinib for NSCLC with *HER2* amplification [21]. Although further research is needed, based on our experience, we suggest that afatinib seems to have a sustained therapeutic effect for NSCLC patients with *HER2* amplification.

Another patient (No. 36 in Fig. 2) was treated with nivolumab and showed the most significant PFS of more than 29 months. The patient did not have any *EGFR* mutations, *ALK* rearrangement, or programmed death 1/programmed death-ligand 1 overexpression. Interestingly, he had both *HER2* amplification and exon 20 insertion mutation, and the inserted amino acid was E770_A771insAYVM. One previous case report showed that a *HER2* mutant patient with exon 20 insertion (M774_A775insAYVM) exhibited a great response to nivolumab [22]. However, the coexistence of *HER2* mutation and amplification has been reported with low incidence in several studies [3,23,24], and *HER2* amplification was assessed by different methods in each study, which could have a big impact on results and interpretation [10]. Therefore, the exact roles of the coexistence and certain mutation types of *HER2* require further study.

This study has one important limitation. Given the high incidence of *EGFR* mutations in Korea, a reflex test for *EGFR* and *ALK* alterations is routine practice, while NGS is performed mostly for *EGFR*/*ALK*-negative patients. Therefore, *HER2*-alteration incidence might have been overestimated in this study. Nevertheless, this is the biggest study to evaluate the clinical features of *HER2*-altered NSCLC in an Asian population, as detected by NGS.

In conclusion, NSCLC patients with *HER2* alterations have distinct clinical features, and NSCLC patients with *HER2* in-frame insertion mutation and *HER2* amplification exhib-

ited unique characteristics. Given the limited number of available effective agents to target *HER2*-altered NSCLC, further investigation with novel agents is needed.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (<https://www.e-crt.org>).

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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