Real-world therapeutic strategies and survival outcomes in advanced *HER2*-mutant non-small cell lung cancer

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Abstract

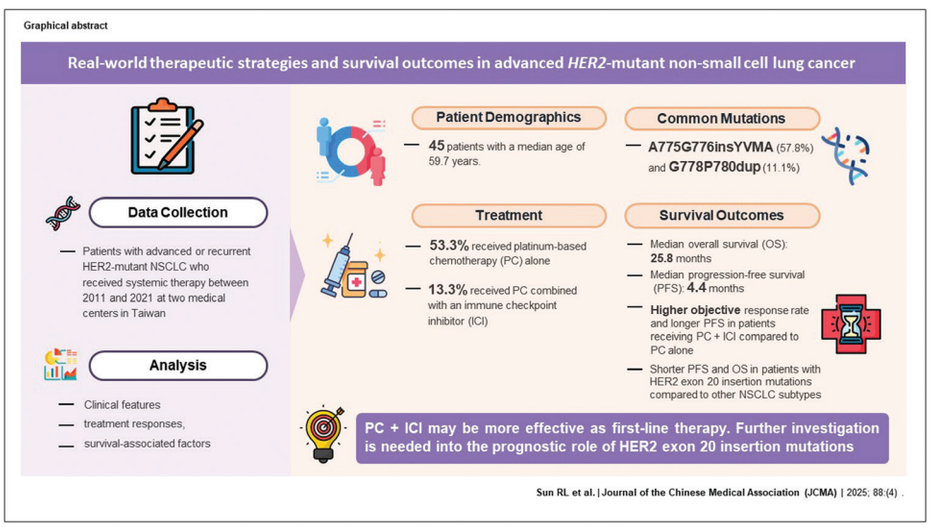
Background: Limited information is available regarding the clinical features and outcomes of advanced human epidermal growth factor receptor 2 (*HER2*)-mutant non-small cell lung cancer (NSCLC) in Taiwan, despite expanding treatment options for this distinct subtype. This study aimed to investigate the clinical characteristics and outcomes of HER2-mutant NSCLC in a real-world setting.

Methods: Relevant data were collected from patients with advanced or recurrent *HER2*-mutant NSCLC who received systemic therapy between 2011 and 2021 and were followed up until 2022 at two medical centers in Taiwan. Clinical features, treatment responses, and survival-related factors were analyzed.

Results: This study included 45 patients (median age: 59.7 [range: 41.3-78.7] years). A775_G776insYVMA was the most common HER2 mutation subtype (57.8%), followed by G778_P780dup (11.1%). Approximately 53.3% of the patients received first-line platinum-based chemotherapy (PC) alone, whereas 13.3% received PC combined with an immune checkpoint inhibitor (ICI). The median overall survival (OS) and progression-free survival (PFS) after first-line therapy were 25.8 and 4.4 months, respectively. The objective response rate was generally higher in patients receiving first-line PC + ICI than those receiving PC alone (33.3% vs 12.5%; $p = 0.269$). Furthermore, patients receiving PC + ICI had longer PFS than those receiving PC alone (9.5 vs 4.4 months; $p = 0.131$) and those receiving tyrosine kinase inhibitor/ICI monotherapy (9.5 vs 0.5 months; $p = 0.015$). Compared with patients having other NSCLC subtypes, those carrying *HER2* exon 20 insertion mutations had shorter median PFS (17.3 vs 2.9 months; $p = 0.043$) and OS (not reached vs 19 months; $p = 0.031$).

Conclusion: This study highlights the clinical features and outcomes of advanced *HER2*-mutant NSCLC in Taiwan. PC + ICI may be more effective than other regimens as first-line therapy. The prognostic impact of *HER2* exon 20 insertion mutations warrants further investigation.

Keywords: Immune checkpoint inhibitor; Non-small cell lung cancer; Prognostic; Progression-free survival; Tyrosine kinase inhibitor



1. INTRODUCTION

With the identification of tumor-specific mutations that deregulate molecular signaling, progress has been made in the care of patients with advanced non-small cell lung cancer (NSCLC). One such mutation occurs in the human epidermal growth factor receptor (EGFR) 2 gene (*HER2*; also called *ErbB2*). The prevalence of *HER2* mutation in patients with nonsquamous NSCLC is approximately 2% to 4%; it is slightly higher in Asian populations (1.4%-6.7%) than in European and American populations (1%-3%).[1–4]

HER2 targeting has significantly transformed the treatment landscape of breast and gastric cancers, and emerging clinical trials have reported promising results in NSCLC as well.[5,6] Although the American Society of Clinical Oncology does not recommend routine independent *HER2* molecular testing in patients with NSCLC, the society recommends it within a comprehensive panel, particularly at initial diagnosis or in patients with a negative test result in a conventional oncogenic assessment. Furthermore, the European Society for Medical Oncology Expert Consensus Statement now includes *HER2* mutation testing as part of the initial set of tests performed through next-generation sequencing (NGS). This inclusion is particularly important for patients with nonresectable stage III or IV NSCLC, provided they meet certain criteria, such as having a histological subtype of lung adenocarcinoma or adenosquamous carcinoma, having no history of smoking or being a light smoker, and being a woman.[7]

Although *HER2*-targeted agents have demonstrated promising tumor responses, they remain largely inaccessible in many countries, including Taiwan.[4,6] Consequently, patients with *HER2*-mutant NSCLC currently rely on conventional chemotherapy, which has varying efficacy in countries lacking approved *HER2*-targeted agents.[8–11] In patients with *HER2*-mutant NSCLC, the use of immune checkpoint inhibitors (ICIs) has resulted in inconsistent and diverse outcomes, with objective response rates (ORRs) ranging from 7% to 27%.[12,13]

In this retrospective study, we explored the current treatment approaches for advanced *HER2*-mutant NSCLC to identify effective management strategies.

2. METHODS

2.1. Data source and study cohort

This study was conducted at two medical centers in Taiwan: Taipei Veterans General Hospital and Taichung Veterans General Hospital. We retrospectively reviewed the electronic medical records of patients with *HER2*-mutant NSCLC who received systemic therapy at one of the two aforementioned medical centers between January 2011 and December 2021. Patients who received a diagnosis of early-stage disease, underwent an unknown treatment course, or were monitored for <1 month were excluded from this study. Data on the included patients' survival status up to December 31, 2022, were collected.

2.2. Detection of *HER2* mutation

After routine testing for *EGFR*, *ALK*, and *ROS1* mutations yielded negative results, *HER2* mutations were investigated through NGS, as part of broad molecular profiling, or matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), based on the physician's judgment. In MALDI-TOF MS, a multiplexed genotyping technique, a laser pulse is used to generate ions, their flight times are measured, and a mass spectrum is obtained to enable precise molecular analysis. This technique is widely used in routine diagnostics because of its sensitivity, reliability, speed, and cost-effectiveness.[14–16]

2.3. Cancer staging and clinical outcomes

Clinicopathological staging was performed in accordance with the seventh edition (for diagnoses made before 2018) or the eighth edition (for diagnoses made in 2018 or later) of the tumor, node, and metastasis classification, as defined by the American Joint Committee on Cancer. The following clinical data were collected for all patients: age at diagnosis, diagnosis date, smoking history, performance status (PS; as defined by the Eastern Cooperative Oncology Group [ECOG]), tumor stage with initial metastasis sites, histologic tumor type, outcomes (recurrence and survival), and treatment regimen (chemotherapy, immunotherapy, antiangiogenic agents, and/or targeted therapy). Computed tomography of the thorax was performed at least every 12 weeks or as per clinical practice protocols. Treatment response, including partial response, stable disease, and progressive disease, was evaluated on the basis of the Response Evaluation Criteria in Solid Tumors version 1.1. The study protocol was approved by the ethics committees of Taipei Veterans General Hospital (approval number: 2022-07-028CC) and Taichung Veterans General Hospital (approval number: CE23476C).

2.4. Statistical analysis

Qualitative data are presented in terms of percentage values, and quantitative data are presented in terms of mean and SD values. The Mann-Whitney *U* test was used to analyze between-group differences in continuous variables. The chi-square or Fisher exact test was used for categorical variables, depending on the sample size. Survival curves were constructed and compared using the Kaplan-Meier method and log-rank tests. Overall survival (OS) was calculated from the date of diagnosis until either the date of death or that of the last follow-up. Progression-free survival (PFS) was defined as the interval between diagnosis and the earliest subsequent event: tumor progression, first-line therapy discontinuation, or death due to any cause. To identify factors associated with survival outcomes, Cox proportional-hazards models were used. Variables with a p value of <0.1 in univariate analyses were included in a subsequent multivariate analysis. All statistical analyses were conducted using SPSS (version 26.0; IBM Corporation, Armonk, NY).

3. RESULTS

3.1. Patient characteristics

The clinical characteristics of 45 patients with advanced *HER2*-mutant NSCLC were analyzed (Table 1; Fig. 1). Their median age was 59.7 (range: 41.3-78.7) years. Of these patients, 55.6% were women, and 62.2% were never smokers. Most patients

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Table 1

Patient characteristics (n = 45)

Characteristic	Number (percentage)
Age (median, range)	59.7 (41.3-78.7)
Sex, n (%)	
Male	20 (44.4)
Female	25 (55.6)
Smoking, n (%)	
Never smoker	28 (62.2)
Current smoker	14 (31.1)
Ex-smoker	3 (6.7)
ECOG PS at diagnosis, n (%)	
0	10 (22.2)
1	31 (68.9)
≥2	4 (8.9)
Histology at diagnosis, n (%)	
Adenocarcinoma	45 (100)
Stage (AJCC 8), n (%)	
III	2 (4.4)
Recurrence	7 (15.6)
IVA	13 (28.9)
IVB	23 (51.1)
Detection method, n (%)	
MALDI-TOF MS	5 (11.1)
NGS	35 (77.8)
MALDI-TOF MS + NGS	5 (11.1)
Baseline brain metastasis, n (%)	20 (44.4)
Baseline liver metastasis, n (%)	5 (11.1)
Baseline adrenal metastasis, n (%)	10 (22.2)
Baseline bone metastasis, n (%)	23 (51.1)
PD-L1 TPS, n (%) (n = 34)[a]	
<1%	18 (52.9)
1%-49%	12 (35.3)
≥50%	4 (11.8)
HER2 mutation type, n (%)	
A775_G776insYVMA	26 (57.8)
G776delinsVC	4 (8.9)
G778_P780dup	5 (11.1)
Other insertion	3 (6.7)
Missense mutation	7 (15.6)
Concomitant *HER2* amplifications	6 (13.3)
HER2 exon 20 insertion	38 (84.4)

AJCC 8 = American Joint Committee on Cancer, Eighth Edition; ECOG = Eastern Cooperative Oncology Group; MALDI-TOF MS = matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; NGS = next-generation sequencing; PD-L1 = programmed death ligand 1; PS = performance status; TPS = tumor proportion score.

[a]Eleven patients were not examined for PD-L1 expression.

had stage IV disease (stage IVA: 28.9%; stage IVB: 51.1%) and an ECOG PS of 1 on the date of diagnosis (68.9%). All tumors were adenocarcinomas. Information on programmed death ligand 1 (PD-L1) status was available for 34 (76%) patients. Of these patients, 52.9% exhibited <1% PD-L1 expression in tumor cells. Among patients with recurrence, six were classified as having stage IVB cancer because of distant metastasis, whereas one was classified as having stage IVA cancer with lung metastasis. Upon initial diagnosis or recurrence, brain metastases were discovered in 44.4% of the patients, whereas liver, adrenal, and bone metastases were found in 11.1%, 22.2%, and 51.1%, respectively. *HER2* mutations were detected through NGS in 35 (77.8%) patients, through MALDI-TOF MS in 5 (11.1%) patients, and through both approaches in 5 (11.1%) patients. All mutations were distinct from those noted in *EGFR* or *ALK*; *HER2* amplification was observed in six (13.3%) patients. A total of 38 patients carried *HER2* exon 20 insertions (exon20ins). A775_G776insYVMA was the most common subtype (n = 26 [57.8%]), followed by G778_P780 duplication (n = 5 [11.1%]). Supplementary Figure 1, http://links.lww.com/JCMA/A309, presents the co-mutation profiles of the included patients.

The patients were stratified by the percentage of PD-L1 expression (PD-L1 ≥1%), the presence of an A775_G776insYVMA mutation, and the presence of an *HER2* exon20ins mutation. No significant between-group difference was discovered in smoking status, sex, metastatic site, or ECOG PS (Supplementary Tables 1–3, http://links.lww.com/JCMA/A309).

3.2. First-line systemic therapy and outcomes

The median OS was 25.8 (95% CI, 14.1-37.6) months. The median number of treatment lines was two (range: 1-8). Among the patients who received at least one line of systemic therapy, the median PFS was 4.4 (95% CI, 2-6.7) months. A total of 26 (62.2%) patients received second-line therapy. Table 2 presents the patterns of the first two lines of therapy.

A total of 24 (53.3%) patients received platinum-based chemotherapy (PC) as first-line monotherapy, and 6 (17.8%) patients received PC combined with bevacizumab. Eight patients received ICIs either with PC (five patients received platinum-based doublet chemotherapy alone, and one received platinum-based doublet chemotherapy with bevacizumab [Supplementary Table 4, http://links.lww.com/JCMA/A309]) or as monotherapy (one patient received nivolumab and one received nivolumab + ipilimumab). Furthermore, two patients received the EGFR tyrosine kinase inhibitor (TKI) afatinib.

To determine the outcomes of the different first-line therapies, we stratified the patients into the following subgroups: patients receiving PC, patients receiving PC with an anti-vascular endothelial growth factor (VEGF) agent (PC + anti-VEGF agent), and patients receiving immunochemotherapy with or without an anti-VEGF agent (PC + ICI ± anti-VEGF agent). No significant difference in PD-L1 status was discovered between the PC alone and PC + ICI ± anti-VEGF agent groups (PD-L1 ≥1%: 47.1% vs 60% [p = 1.0]). Our results revealed a higher ORR and longer PFS in the patients receiving PC + ICI as first-line therapy than in those receiving PC alone (ORR: 33.3% vs 12.5% [p = 0.269]; PFS: 9.5 vs 4.4 months [p = 0.131]; Table 3; Fig. 2).

The median PFS was 4.5 (95% CI, 0.7-8.2) months for patients who received first-line chemotherapy and 0.5 (95% CI, 0-2.8) months for those treated with TKIs or ICIs alone (p = 0.021). The median OS was 28.2 (95% CI, 14.2-42.2) months for patients who received first-line chemotherapy and 15.7 (95% CI, 3.7-27.7) months for those who did not; however, the between-group difference was nonsignificant (p = 0.507; Supplementary Fig. 2, http://links.lww.com/JCMA/A309). A comparison of patients receiving first-line PC + ICI and those receiving TKIs or ICIs alone revealed a significant difference in PFS (9.5 vs 0.5 months [p = 0.015]) but not OS (not reached vs 15.7 months; p = 0.104 [Supplementary Fig. 3, http://links.lww.com/JCMA/A309]).

As shown in Fig. 3, compared with patients not carrying *HER2* exon20ins mutations, those carrying these mutations had significantly shorter PFS (17.3 vs 2.9 months; p = 0.043) and OS (not reached vs 19 months; p = 0.031). For patients carrying A775_G776insYVMA mutations, the median OS was 17.9 (95% CI, 6.2-29.7) months, and the median PFS was 3.3 (95% CI, 1.4-5.1) months. For the patients with other *HER2* mutation subtypes, the median PFS was 6.4 (95% CI, 0-13.1; p = 0.911) months, and the median OS was 25.8 (95% CI, 16.5-35.2; p = 0.135) months (Fig. 4).

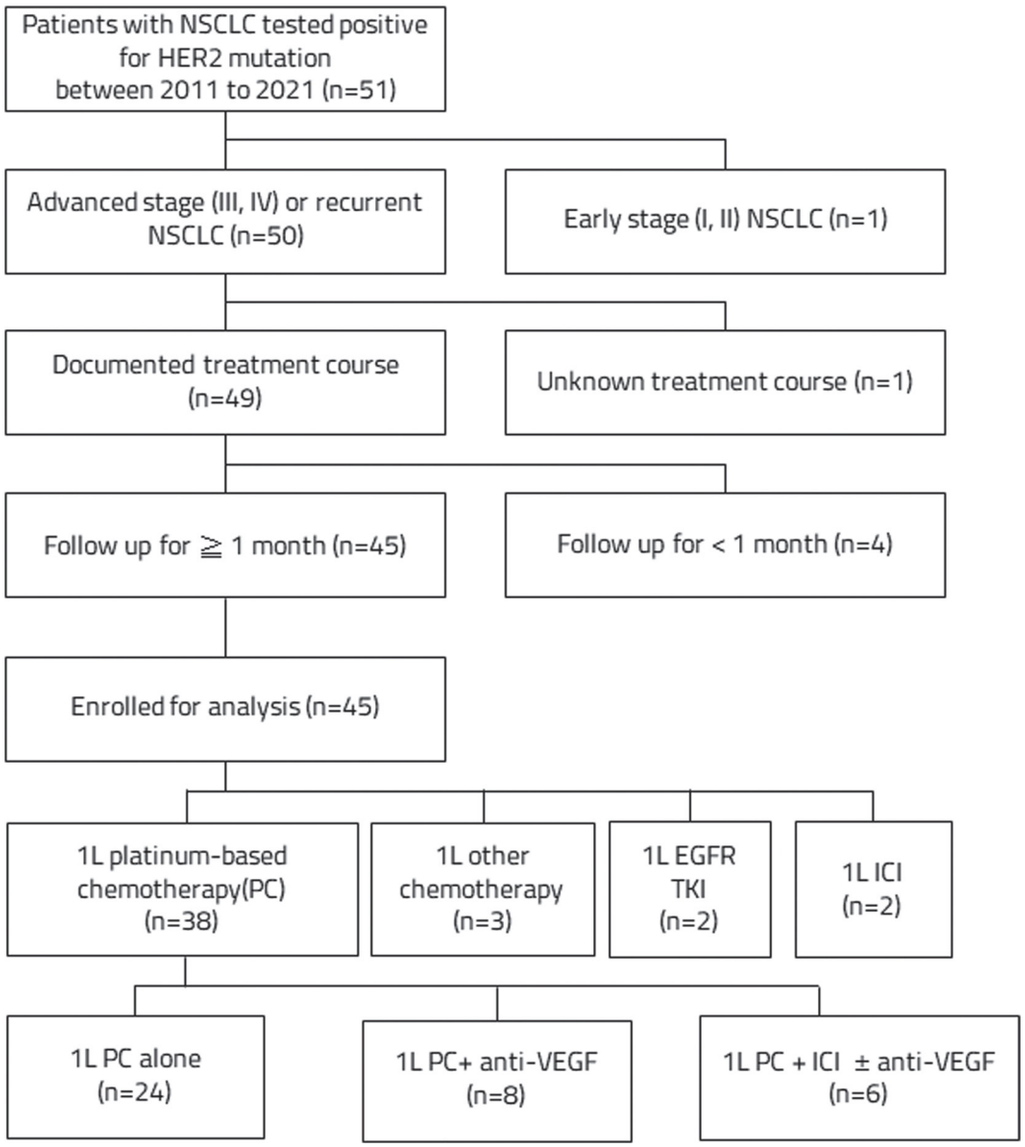

Fig. 1 Study cohort. 1L = first line; EGFR = epidermal growth factor receptor; ICI = immune checkpoint inhibitor; NSCLC = non-small cell lung cancer; PC = platinum-based chemotherapy; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

No major between-group difference was found in PFS or OS when the patients were stratified by their PD-L1 tumor proportion score (Supplementary Table 5, http://links.lww.com/JCMA/A309).

Six patients received *HER2*-targeted agents after third-line therapy. Information on treatment response was available for three patients, all of whom exhibited progressive disease with a median PFS of 1.6 (range: 1-2.5) months (Supplementary Table 6, http://links.lww.com/JCMA/A309).

The multivariate analysis revealed that the following factors were associated with shorter OS: an age of ≥65 years (hazard ratio [HR]: 4.723; 95% CI, 1.631-13.68; p = 0.004), bone metastasis at baseline (HR: 4.313; 95% CI, 1.322-14.073; p = 0.015), and *HER2* exon20ins mutation (HR: 20.02; 95% CI, 2.185-183.47; p = 0.008). Notably, only ever smoking was significantly associated with both OS (HR: 3.012; 95% CI, 1.033-8.778; p = 0.043; Table 4) and PFS (HR: 2.527; 95% CI, 1.108-5.737; p = 0.028; Table 5).

4. DISCUSSION

To the best of our knowledge, this is the first study involving patients with *HER2*-mutant NSCLC from a single ethnic group in Taiwan. Despite the limitations inherent in the retrospective design of this study, the following characteristics of our patients are consistent with those reported in other studies on HER2-mutant NSCLC: female sex, nonsmoking status, exclusive adenocarcinoma subtype, and relatively low PD-L1 expression in tumor cells.[1,2,17–21]

The median OS estimated in this study (25.8 months) is consistent with that reported in other retrospective studies (approximately 2 years).[1,2,8] These studies have included diverse treatments, with various *HER2*-targeted agents, administered in different lines of therapy, either as combination therapy or as monotherapy. In our study, six patients (13.3%) received an *HER2*-targeted agent (trastuzumab-based drug) in nonprimary lines of therapy (Supplementary Table 6, http://links.lww.com/JCMA/A309). Whether this outcome is attributable to specific

Table 2

Patterns of the first-line and subsequent therapies (n = 45)

Number of lines (%), median (range)	2 (1-8)
1 line	17 (37.8)
2 lines	10 (22.2)
3 lines	5 (11.1)
≥4 lines	13 (29.9)
First-line systemic treatment category, n (%)	
Chemotherapy	24 (53.3)
Platinum combination	8 (17.8)
Platinum combination + anti-VEGF	3 (6.7)
Other chemotherapy	5 (11.1)
Immunotherapy-based regimen.	1 (2.2)
Platinum combination + ICI	1 (2.2)
Platinum combination + anti-VEGF + ICI	1 (2.2)
Double ICI	2 (4.4)
ICI single agent	
EGFR TKI	
Second-line systemic treatment category, n (%)	
No second-line treatment	17 (37.8)
Chemotherapy	8 (17.8)
Platinum combination	5 (11.1)
Chemotherapy + anti-VEGF agents	9 (20)
Other chemotherapy	4 (8.9)
Immunotherapy based regimen	2 (4.4)
Chemotherapy + ICI	
EGFR TKI	
History of TKI use, n (%)	11 (24.4)
History of ICI use, n (%)	15 (33.3)

ICI = immune checkpoint inhibitor; EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

characteristics of our cohort (eg, nonsmoking women with a high ECOG PS and access to treatment at a medical center) or reflects the natural course of advanced *HER2*-mutant NSCLC is unclear. Future studies should differentiate between the effect of patient characteristics and that of the disease's intrinsic nature on prognoses.

In this study, we evaluated the clinical outcomes of conventional PC combined with antiangiogenic agents or ICIs (with or without antiangiogenic agents). The median PFS with conventional chemotherapy is consistent with that observed in other studies: 5.1 months for patients receiving pemetrexed-based chemotherapy[22] and 6 months for those primarily receiving platinum-based doublet chemotherapy.[8] Yang et al[11] reported a median PFS of 5.63 months and a median OS of 36.27 months in patients with *HER2*-altered NSCLC who were treated with first-line chemotherapy plus an antiangiogenic agent; the researchers suggested that adding an angiogenesis inhibitor enhances survival by improving drug delivery to tumor sites through "vessel normalization." However, in our study, the PC + anti-VEGF agent group exhibited a trend toward a shorter median PFS (3.2; 95% CI, 1.2-5.2 months) and OS (9.8; 95% CI, 0-35.2 months) than those observed in the PC group. We found that adding an angiogenesis inhibitor to a chemotherapy regimen conferred no synergistic benefits, largely due to this study's small sample size and interpatient variations in baseline characteristics (Supplementary Tables 7 and 8, http://links.lww.com/JCMA/A309). The patients who were given such a regimen exhibited a tendency to have relatively poor ECOG PS (25% of the patients had an ECOG PS of ≥2), high prevalence of YVMA insertion mutation (75%), and high prevalence of *HER2* exon20ins mutation (87.5%), all of which are associated with poor prognosis.[22,23] Studies have reported varying response rates to first-line chemotherapy for advanced *HER2*-mutant NSCLC despite the incorporation of antiangiogenic agents; the ORR has ranged from 30% to 40%,[8,18,21,22,24] a higher range than that in our study. Nevertheless, first-line chemotherapy in this rare molecular subgroup appears to be as effective as that in patients without a targeted mutation.[25] In our cohort, patients who received first-line chemotherapy had significantly longer PFS than those who received either TKIs or ICIs (Supplementary Fig. 2,

Table 3

First-line PC with or without other agents

First-line treatment group	All	PC alone (n = 24)	PC+ anti-VEGF (n = 8)	PC + ICI ± anti-VEGF (n = 6)	*p*
ORR	20% (9/45)	12.5% (3/24)	37.5% (3/8)	33.3% (2/6)	0.269
DCR	60% (27/45)	58.3% (14/24)	62.5% (5/8)	100% (6/6)	0.354
Progression-free survival, mo, median (95% CI)	4.4 (2-6.7)	4.4 (2-6.7)	3.2 (1.2-5.2)	9.5 (0-19.9)	0.131
Overall survival, mo, median (95% CI)	25.8 (14.1-37.6)	31.2 (10.1-52.2)	9.8 (0-35.2)	35.3 (NR)	0.492

CI = immune checkpoint inhibitor; DCR = disease control rate; ICI = immune checkpoint inhibitor; NR = not reached; ORR = objective response rate; PC = platinum-based chemotherapy; VEGF = vascular endothelial growth factor.

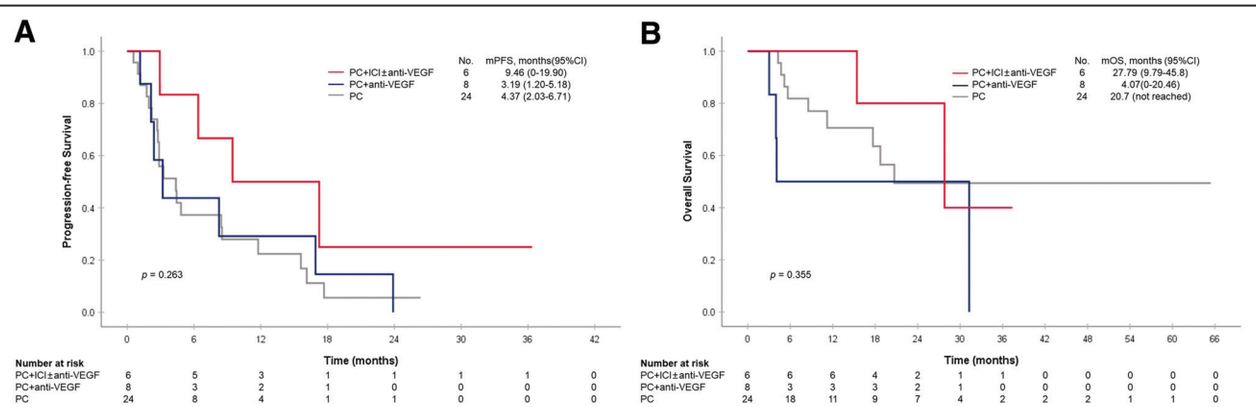

Fig. 2 (A) PFS and (B) OS in patients receiving first-line PC with or without other agents. OS = overall survival; PFS = progression-free survival.

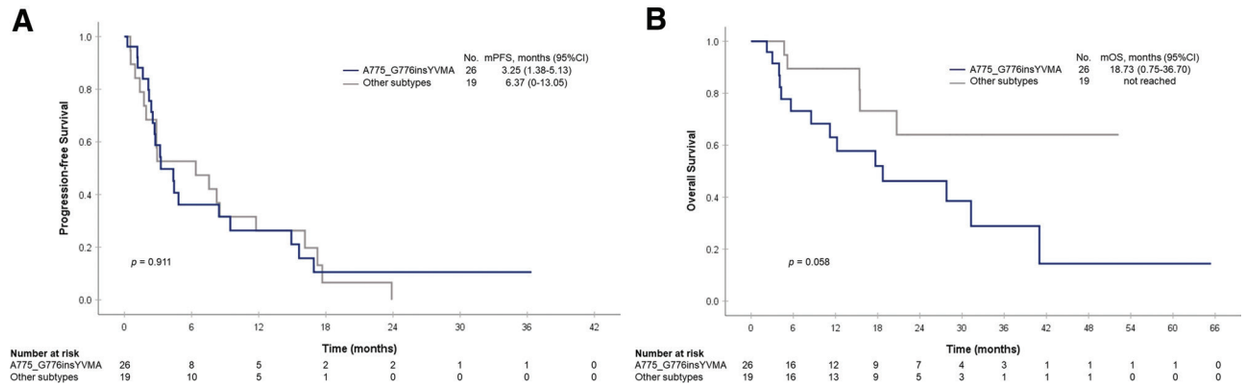

Fig. 3 (A) PFS and (B) OS in patients with *HER2* exon 20 insertion mutations and other *HER2* mutations. OS = overall survival; PFS = progression-free survival.

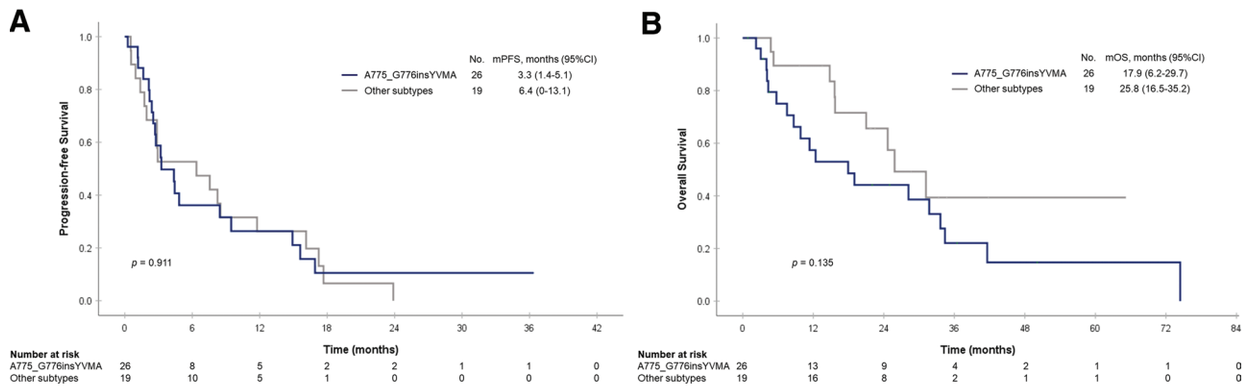

Fig. 4 (A) PFS and (B) OS in patients with the A775_G776insYVMA mutation and other subtypes. OS = overall survival; PFS = progression-free survival.

http://links.lww.com/JCMA/A309). Although this finding was not confirmed by the multivariate analysis (Table 5), the difference in PFS indicates potential advantages of chemotherapy over TKI or ICI monotherapy in patients with *HER2*-mutant NSCLC.

Inconsistent results have been reported regarding the efficacy of ICIs in treating *HER2*-mutant NSCLC. For instance, Guisier et al[13] reported that the median PFS and OS were 4.9 and 13.4 months, respectively, in patients receiving ICI monotherapy. Mazieres et al[12] revealed an ORR of 7% and a PFS similar to that observed in patients with *EGFR*-mutant NSCLC. By contrast, Yang et al[11] reported no significant difference in median PFS (5 months) between patients with *HER2*-mutant NSCLC who received combined therapy and those who received monotherapy (chemotherapy). A single-arm meta-analysis of studies evaluating the efficacy of immunotherapy in treating *HER2*-mutant NSCLC reported an ORR of 26% and a median PFS of 5.4 months; in patients receiving immunochemotherapy, the ORR was higher at 37%, and the median PFS was longer at 7.1 months.[26]

In our cohort, the ORR was higher, and PFS was longer in patients receiving first-line PC + ICI than in those receiving PC alone. The median PFS was similar to that in treatment-naïve patients receiving contemporary immunochemotherapy for advanced *HER2*-mutant NSCLC (median PFS: 6 months; ORR: 52%) or *HER2*-altered NSCLC (median PFS: 7.8 months; ORR: 50%).[10,24] Among the six patients receiving first-line PC + ICI, the patient with the longest median PFS (36.9 months) had high PD-L1 expression (100%). However, we found no durable effect of ICIs on OS, attributable to the wide 95% CI of the HR in the Cox proportional-hazards model. Moreover, OS could not be analyzed because of the limited availability of comprehensive data in the aforementioned meta-analysis,[26] necessitating further investigations. Because of the limited sample size, we could not compare different ICI combinations or determine whether PD-L1 expression can indicate treatment response in this PC + ICI subgroup. Nonetheless, our findings support the rationale for an ongoing clinical trial evaluating combinations of ICIs with *HER2*-targeted therapy and chemotherapy for *HER2*-mutant NSCLC (NCT04686305). Heterogeneous modifications in the tumor microenvironment affect cytotoxic cells and cytokine signaling; this highlights a need for tailored ICI combination therapy.[27] PC + ICI may be prescribed to patients lacking access to novel *HER2*-targeted agents.

In our study, most *HER2* mutations were exon20ins. A775_G776insYVMA is the most common *HER2* mutation identified to date.[28] Patients with exon20ins mutations had significantly shorter PFS and OS than those with other *HER2* mutations. Similarly, patients with YVMA insertion exhibited a trend toward worse outcomes. These findings are consistent with the short PFS reported by other studies exploring YVMA insertion.[22,23] *HER2* exon20ins mutations lead to constant ligand-independent kinase activation, triggering downstream signaling pathways.[29] Another possible explanation is that YVMA insertion induces conformational rigidity in the ATP-binding site, which may be associated with an increased baseline and lifetime incidence of brain metastases,[23] making it less accessible to small-molecule TKIs.[28] Future drug development studies should target *HER2* exon20ins mutations and prioritize blood-brain barrier activity.

TP53 is the most frequently co-mutated gene in individuals carrying *HER2* mutations (69%); the presence of *TP53*

Table 4

Factors associated with overall survival

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Age ≥65	1.993 (0.901-4.411)	0.089	4.723 (1.631-13.68)	0.004
Male	0.959 (0.446-2.061)	0.914		
Ever smoking	2.785 (1.263-6.144)	0.011	3.012 (1.033-8.778)	0.043
ECOG PS ≥2	1.61 (0.478-5.426)	0.443		
Stage IVB	3.678 (1.54-8.785)	0.003	0.979 (0.319-3)	0.97
Baseline brain metastasis	0.955 (0.434-2.102)	0.909		
Baseline liver metastasis	4.55 (1.618-12.792)	0.004	1.126 (0.266-4.775)	0.872
Baseline adrenal metastasis	2.769 (1.251-6.127)	0.012	1.703 (0.527-5.503)	0.374
Baseline bone metastasis	2.255 (1.031-4.932)	0.042	4.313 (1.322-14.073)	0.015
History of TKI use	0.996 (0.443-2.24)	0.993		
History of ICI use[a]	0.609 (0.272-1.361)	0.227		
First-line ICI use	0.607 (0.209-1.758)	0.357		
First-line chemotherapy	0.698 (0.240-2.028)	0.509		
TP53[b]	0.453 (0.156-1.321)	0.147		
HER2 exon20ins	6.734 (0.91-49.8)	0.062	20.02 (2.185-183.47)	0.008
A775_G776insYVMA	1.831 (0.819-4.094)	0.141		
PD-L1 TPS >1%[c]	0.730 (0.289-1.841)	0.505		

ECOG = Eastern Cooperative Oncology Group; exon20ins = exon 20 insertion; ICI = immune checkpoint inhibitor; PD-L1 = programmed death ligand 1; PS = performance status; TKI = tyrosine kinase inhibitor; TPS = tumor proportion score; VEGF = vascular endothelial growth factor.

[a]ICI use, ICI ± chemotherapy ± anti-vascular endothelial growth factor agent.

[b]Data were available for 25 patients with at least one co-mutation.

[c]Data were available for 34 patients with available data on PD-L1 TPS.

Table 5

Factors associated with progression-free survival during first-line therapy

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Age ≥65	1.184 (0.607-2.311)	0.621		
Female	1.234 (0.645-2.359)	0.525		
Ever smoking	1.828 (0.943-3.544)	0.074	2.527 (1.108-5.767)	0.028
ECOG PS ≥2	2.234 (0.748-6.671)	0.150		
Stage IVB	2.549 (1.272-5.109)	0.008	1.824 (0.789-4.218)	0.16
Baseline brain metastasis	1.315 (0.691-2.503)	0.404		
Baseline liver metastasis	2.798 (0.948-8.259)	0.062	1.446 (0.275-7.614)	0.663
Baseline bone metastasis	1.653 (0.856-3.195)	0.135		
Baseline adrenal metastasis	1.958 (0.937-4.093)	0.074	0.62 (0.217-1.767)	0.371
First-line ICI use[a]	0.550 (0.229-1.323)	0.182		
First-line anti-VEGF agents	1.071 (0.353-1.358)	0.863		
First-line chemotherapy	0.306 (0.105-0.891)	0.03	0.3 (0.064-1.405)	0.126
HER2 exon20ins	2.465 (1-6.057)	0.049	2.492 (0.938-6.62)	0.067
TP-53[b]	0.746 (0.315-1.765)	0.505		
A775_G776insYVMA	0.964 (0.508-1.830)	0.911		
PD-L1 TPS ≥1%[c]	0.941 (0.445-1.992)	0.874		

ECOG = Eastern Cooperative Oncology Group; exon20ins = exon 20 insertion; ICI = immune checkpoint inhibitor; PD-L1 = programmed death ligand 1; PS = performance status; TPS = tumor proportion score; VEGF = vascular endothelial growth factor.

[a]ICI use, ICI ± chemotherapy ± anti-vascular endothelial growth factor agent.

[b]Data were available for 25 patients with at least one co-mutation.

[c]Data were available for 34 patients with available data on PD-L1 TPS.

mutations indicates an unfavorable prognosis in patients with *HER2* exon20ins mutations.[30] A study reported that 50.9% of all patients with *HER2* mutations concomitantly carried *TP53* mutations.[31] In our study, we observed comparable proportions of *TP53* mutations in patients with exon20ins and those with YVMA (Supplementary Tables 2–3, http://links.lww.com/JCMA/A309). Our multivariate analysis revealed that the presence of *TP53* mutations exerted no significant effect on PFS or OS. The results of co-mutation analysis were not available for all patients. Thus, future studies should explore the correlation between *HER2* mutation variants and clinical outcomes.

This study has several limitations. First, it was retrospective in nature and lacked a central radiological review. Second, the sample size was small, and the follow-up duration was short. Thus, large-scale, long-term studies should be conducted in the future. Given the increasing implementation of comprehensive genomic profiling upon lung cancer diagnosis in Taiwan, large-scale

studies are expected in the future. Finally, most patients in our cohort received conventional therapy. Although six patients received novel *HER2*-targeted agents, their responses were unfavorable because of extensive pretreatment. Only one patient received the approved drug trastuzumab deruxtecan.[6] The introduction of *HER2*-targeted agents and novel TKIs, which exert broad antitumor effects, has reshaped frontline treatment strategies. However, data from real-world applications remain limited, necessitating further investigations.[4,32,33] As we anticipate a shift toward specialized therapies for advanced *HER2*-mutant NSCLC, new treatment options must be balanced with practical patient care needs.

Overall, first-line PC + ICI (with or without antiangiogenic agents) is associated with a high ORR (33.3%), a high disease control rate (100%), and long PFS (9.5 months) in patients with advanced *HER2*-mutant NSCLC. Multiple novel *HER2*-targeted agents have been associated with promising ORRs; these regimens may enhance the current standard of care and inform future comparative trials in treatment-naïve patients with HER2-mutant NSCLC. Immunotherapy may be useful when combined with standard chemotherapy or when no alternatives are available. Comprehensive research is required to identify optimal therapeutic strategies.

In conclusion, as the development of *HER2*-targeted drugs and antibody–drug conjugates for *HER2*-mutant NSCLC continues, PC + ICI remains an effective first-line therapeutic regimen for this disease.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A309.

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