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ORIGINAL ARTICLE

Treatment efficacy of *HER2*-mutant lung adenocarcinoma by immune checkpoint inhibitors: a multicenter retrospective study

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Abstract

Background Despite the remarkable clinical advance of immune checkpoint inhibitors (ICIs) in the treatment of lung cancer, there are limited studies focused on evaluating efficacy of ICIs for patients with human epidermal growth factor receptor 2 (*HER2*)-mutant lung adenocarcinoma.

Methods We conducted a multicenter retrospective study of patients with *HER2*-mutant lung adenocarcinoma who received ICIs therapy at Shanghai Pulmonary Hospital, Shanghai Chest Hospital and the First Affiliated Hospital of Wenzhou Medical University between 2016 and 2021. Response was defined with reference to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

Results Among the 26 patients enrolled in our study, the overall objective response rate (ORR) was 38.5%, disease control rate (DCR) was 84.6% and median progression-free survival (PFS) was 7.4 months. Majority of patients were treated with immunochemotherapy combination regimens (16/26, 61.5%), with a median PFS of 8.4 months. Among the 9 patients receiving ICIs-based therapy as first-line treatment, 5 patients had partial response (PR) and 4 patients had stable disease (SD), with a median PFS of 9.1 months. Of the entire cohort, 5 patients who received ICIs before epidermal growth factor receptor (*EGFR)/HER2*-targeting drugs achieved a median PFS of 8.4 months.

Conclusion Our retrospective study provides clinical evidence that front line of ICIs-based therapy is also worth considering for the treatment to improve survival outcomes of patients with *HER2*-mutant lung adenocarcinoma.

Keywords *HER2*-mutant · Immune checkpoint inhibitors · Non-small cell lung cancer · Efficacy

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Abbreviations

CI	Confidence interval
DCR	Disease control rate
HER2	Human epidermal growth factor receptor 2
ICIs	Immune checkpoint inhibitors
PD-L1	Programmed cell death ligand 1
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate
PD-1	Programmed cell death protein 1
PFS	Progression-free survival

Introduction

Over the last ten years, oncogene driver-based therapies have improved outcomes for advanced non-small cell lung cancer (NSCLC), such as targeting epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*) and ROS proto-oncogene 1 (*ROS1*) [1]. However,

it remains unavoidable development of resistance and tumor recurrence in this setting. Moreover, there are limited targeted therapies for patients with rare oncogenic drivers. Similar to EGFR, human epidermal growth factor receptor 2 (HER2) is a member of the human epidermal growth factor receptor (HER/EGFR/ERBB) family. Patients harboring *HER2* mutations account for 1% to 4% in lung adenocarcinoma[2–5]. Nevertheless, despite *HER2*-targeting drugs such as pyrotinib and trastuzumab deruxtecan (T-DXd), have revealed promising efficacy in advanced NSCLC with *HER2* mutations[6, 7], there are no targeted drugs approved for this patient population.

Besides these molecularly targeted therapies, Immune checkpoint inhibitors (ICIs) like programmed cell death protein 1 (PD-1) inhibitors and programmed cell death ligand 1 (PD-L1) inhibitors have been approved as a standard of care in treatment for advanced NSCLC. Yet, the efficacy of ICIs in oncogene driven NSCLC remains uncertain, as most clinical trials were conducted without patients harboring known oncogenic mutations[8, 9]. There are limited number of studies reporting the clinical benefits of ICIs in *HER2*-positive NSCLC[10].

In this real-world retrospective cohort study, our efforts focused on investigating the potential benefits of ICIs treatment in patients with lung adenocarcinoma who harboring *HER2* mutation.

Material and methods

Patients

Records for patients with *HER2*-mutant lung adenocarcinoma who were treated with PD-1/PD-L1 inhibitors in Shanghai Pulmonary Hospital, Shanghai Chest Hospital and the First Affiliated Hospital of Wenzhou Medical University between 2016 and 2021 were reviewed. Patients were staged according to the eighth edition of the TNM staging system. Patients who had eligible imaging information for objective responses were enrolled. All of them received PD-1/PD-L1 inhibitors as monotherapy or in combination with chemotherapy or anti-angiogenesis or *EGFR/HER2*-targeting drugs regardless of treatment lines. Radiographic partial response (PR), stable disease (SD), and progression disease (PD) were defined with reference to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [11]. The objective response rate (ORR) and disease control rate (DCR) were defined as complete response (CR) plus PR, and CR plus PR plus SD, respectively. Participating centers were in charge of obtaining informed patient consent and institutional approval.

Data collection

The recorded demographics and clinical characteristics included age, gender, smoking status, *HER2* alteration types, PD-L1 status and treatment data. *HER2* alteration was tested using amplification refractory mutation system (ARMS) and confirmed by DNA direct sequencing if necessary. PD-L1 status was assessed in formalin-fixed tumor samples according to local procedures. The follow-up end date was April 2021.

Statistical analysis

Progression-free survival (PFS) was calculated from initiation of ICIs treatment to disease progression or death from any causes. The Kaplan–Meier method was used to assess PFS for the entire cohort. Statistical analyses were performed with SPSS 23.0 (IBM, Armonk, NY, USA) and GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA, USA).

Results

Patient characteristics

The analysis included 26 patients with *HER2*-mutant lung adenocarcinoma managed in 3 medical centers (Tables 1, 2). Patients received PD-1/PD-L1 inhibitors therapy, including monotherapy (n = 5), combination with chemotherapy (n = 16), combination with anti-angiogenesis therapy (n = 3), combination with chemotherapy plus anti-angiogenesis therapy (n = 1), and combination with chemotherapy plus *HER2*-targeting drugs (n = 1). Our cohort was presented with a median age of 55 years (range 38 to 69 years), a higher proportion of never-smokers (n = 18, 69.2%), and a slightly higher proportion of male (n = 14, 53.8%). Of the 15 patients whose PD-L1 status were available, 7 patients had a PD-L1 tumor proportion score greater than 1%. 3 patients had history of pulmonary resection for lung cancer. Besides, PD-1/PD-L1 inhibitors were treated as first-line treatment in 9 patients (34.6%), and as second-line or later-line treatment in 17 patients (65.4%).

Patterns of HER2 variants

A total of 5 patterns of *HER2* variants were available in the 22 patients (Fig. 1), and 4 patients were lack of details genetic characteristics. A775_G776insYVMA was the most common *HER2* variant (n = 9), followed by Y772_A775dup (n = 5) and G776 mutation (n = 5, including G776 > VC and

Table 1 Baseline characteristics of the entire cohort

Variables	All (%) (N = 26)	Treatment data		*P*
		Group A (N = 16)	Group B (N = 10)	
Median age, years (range)	55 (38–69)	58 (38–69)	47.5 (40–68)	
Gender				0.422
Male	14 (53.8)	10 (62.5)	4 (40)	
Female	12 (46.2)	6 (37.5)	6 (60)	
Smoking history				0.420
Never smokers	18 (69.2)	10 (62.5)	8 (80)	
Former or current smokers	8 (30.8)	6 (37.5)	2 (20)	
ECOG PS				0.138
0–1	24 (92.3)	16 (100)	8 (80)	
≥ 2	2 (7.7)	0 (0)	2 (20)	
PD-L1 status				0.474
≥ 50%	1 (3.8)	1 (6.3)	0 (0)	
1–49%	6 (23.1)	4 (25)	2 (20)	
Negative	8 (30.8)	6 (37.5)	2 (20)	
Unknown	11 (42.3)	5 (31.3)	6 (60)	
History of pulmonary resection for lung cancer				0.538
Yes	3 (11.5)	1 (6.3)	2 (20)	
No	23 (88.5)	15 (93.8)	8 (80)	
Line of ICIs therapy				0.087
First-line	9 (34.6)	8 (50)	1 (10)	
> Second-line	17 (65.4)	8 (50)	9 (90)	
Best response to ICIs therapy				0.203
PR	10 (38.5)	6 (37.5)	4 (40)	
SD	12 (46.2)	9 (56.3)	3 (30)	
PD	4 (15.4)	1 (6.3)	3 (30)	
Objective response rate, %	38.5	37.5	40	1.000
Disease control rate, %	84.6	93.8	70	0.264

Group A: combination with chemotherapy; Group B: including monotherapy (n = 5), combination with anti-angiogenesis (n = 3), combination with chemotherapy plus anti-angiogenesis (n = 1), or combination with chemotherapy plus *HER2*-targeting drugs (n = 1)

ICIs, immune checkpoint inhibitors; ECOG PS, Eastern Cooperative Oncology Group performance status; PR, partial response; SD, stable disease; PD, progression disease

G776delinsVC). The other two patterns of *HER2* variants were G778_P780dup and L755P mutation (n = 2, n = 1, respectively). Among these 22 patients, a majority of them achieved PR or SD as best response(n = 18).

There were no statistics differences with respect to PD-L1 status, tumor response or PFS between patients with A775_G776insYVMA and other *HER2* variant (Supplementary Table 1, Supplementary Fig. 1).

Treatment and survival of whole cohort

Among the 26 patients with *HER2*-mutant lung adenocarcinoma, the best response to PD-1/PD-L1 inhibitors is demonstrated in Tables 1, 2. Among the patients who received ICIs therapy, 6 patients are still receiving the treatment as of the last follow-up date (Fig. 2). About 10 out of 26 patients achieved PR and 12 patients achieved SD, achieving an ORR of 38.5% and DCR of 84.6%. As of data cutoff, 16 patients (61.5%, 16/26) had events of PFS, and median PFS was 7.4 months (95% confidence interval [CI], 4.4 to 10.4 months) (Fig. 3a). Meanwhile, patients who treated with ICIs therapy at earlier line tend to achieve longer PFS (Fig. 2). The median PFS from the initiation of first-line immunotherapy was 9.1 months (95% CI, 7.9–10.2) (Fig. 3c). In total of 17 patients (65.4%) received second or more lines of immunotherapy with a median PFS of 5.3 months (95% CI: 2.6–8.0) (Fig. 3c). Particularly, vast majority of patients were treated with

Table 2 Clinical details of patients

Patient number	Gender	Age	Smoking history	PD-L1 status	Patterns of HER2 Variants	Best response	Treatment lines	Combined therapy
P1	Female	68	No	Unknown	A775_G776insYVMA	PR	4	Anti-angiogenesis therapy
P2	Female	60	No	Unknown	L755P mutation	PR	1	Chemotherapy
P3	Male	58	Yes	Unknown	A775_G776insYVMA	PD	2	Chemotherapy
P4	Male	65	No	Negative	A775_G776insYVMA	PR	1	Chemotherapy
P5	Female	53	No	Unknown	A775_G776insYVMA	SD	3	Chemotherapy
P6	Male	47	Yes	Unknown	A775_G776insYVMA	SD	4	None
P7	Female	46	No	Negative	A775_G776insYVMA	PD	3	None
P8	Female	66	No	Unknown	Unknown	SD	1	Chemotherapy
P9	Male	62	Yes	1–49%	G776 > VC	SD	4	Chemotherapy
P10	Female	67	No	Unknown	G778_P780dup	PR	2	None
P11	Female	50	No	> 50%	Unknown	PR	1	Chemotherapy
P12	Male	40	No	Unknown	G778_P780dup	PD	3	None
P13	Male	58	Yes	1–49%	A775_G776insYVMA	SD	5	Chemotherapy
P14	Male	38	No	1–49%	A775_G776insYVMA	SD	4	Chemotherapy
P15	Female	68	No	Unknown	A775_G776insYVMA	SD	1	Anti-angiogenesis therapy
P16	Female	40	No	1–49%	Y772_A775dup	PD	2	Anti-angiogenesis therapy plus Chemotherapy
P17	Male	53	No	Unknown	Y772_A775dup	PR	2	None
P18	Male	69	No	Unknown	G776delinsVC	SD	1	Chemotherapy
P19	Female	44	No	1–49%	G776delinsVC	SD	1	Chemotherapy
P20	Male	48	Yes	1–49%	Y772_A775dup	SD	2	Anti-angiogenesis therapy
P21	Male	57	No	Negative	Y772_A775dup	PR	2	Chemotherapy
P22	Female	58	No	Negative	G776delinsVC	SD	2	Chemotherapy
P23	Female	45	No	Negative	G776delinsVC	PR	3	Chemotherapy plus *HER2*-targeting drugs
P24	Male	52	Yes	Negative	Y772_A775dup	SD	3	Chemotherapy
P25	Male	40	Yes	Negative	Unknown	PR	1	Chemotherapy
P26	Male	63	Yes	Negative	Unknown	PR	1	Chemotherapy

PD-L1, programmed cell death ligand 1; PR, partial response; SD, stable disease; PD, progressive disease

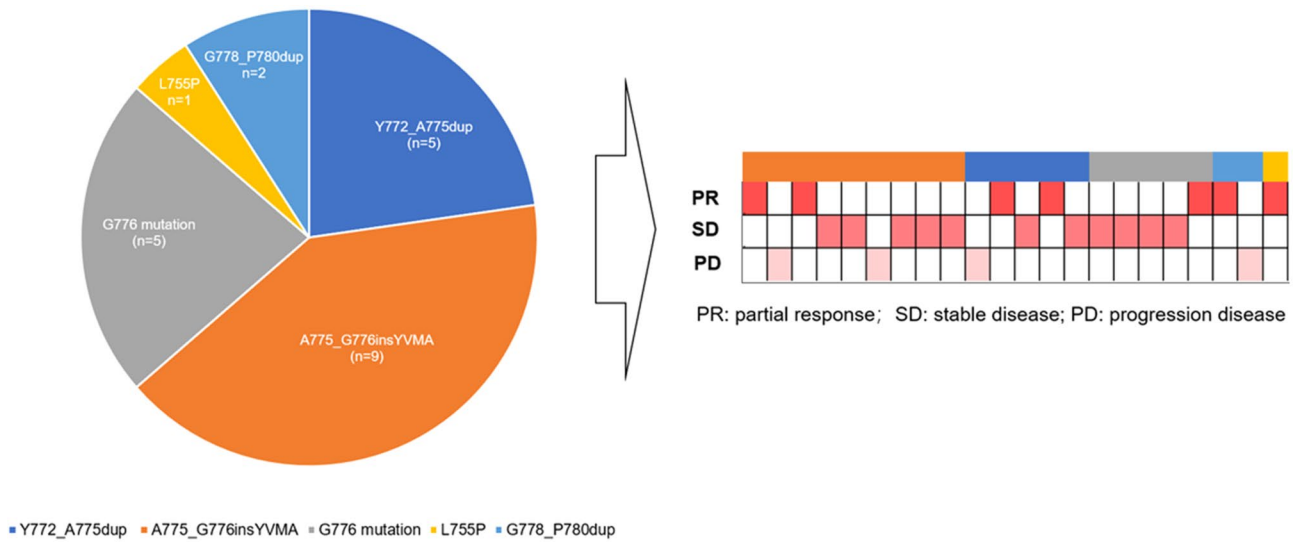

Fig. 1 Patterns of *HER2* variants and tumor responses(n = 22)

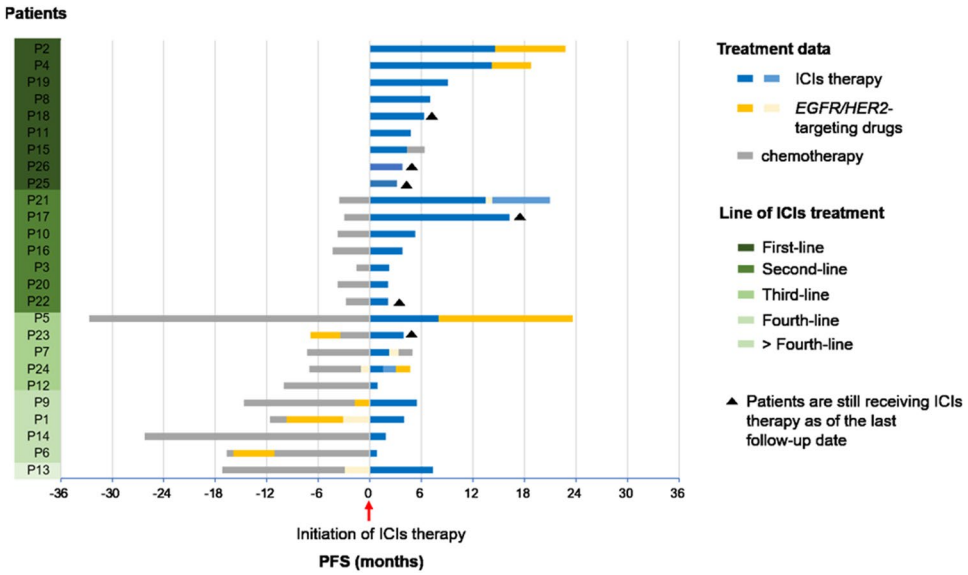

Fig. 2 Survival benefits based on treatment data and line of ICIs treatment (n = 26)

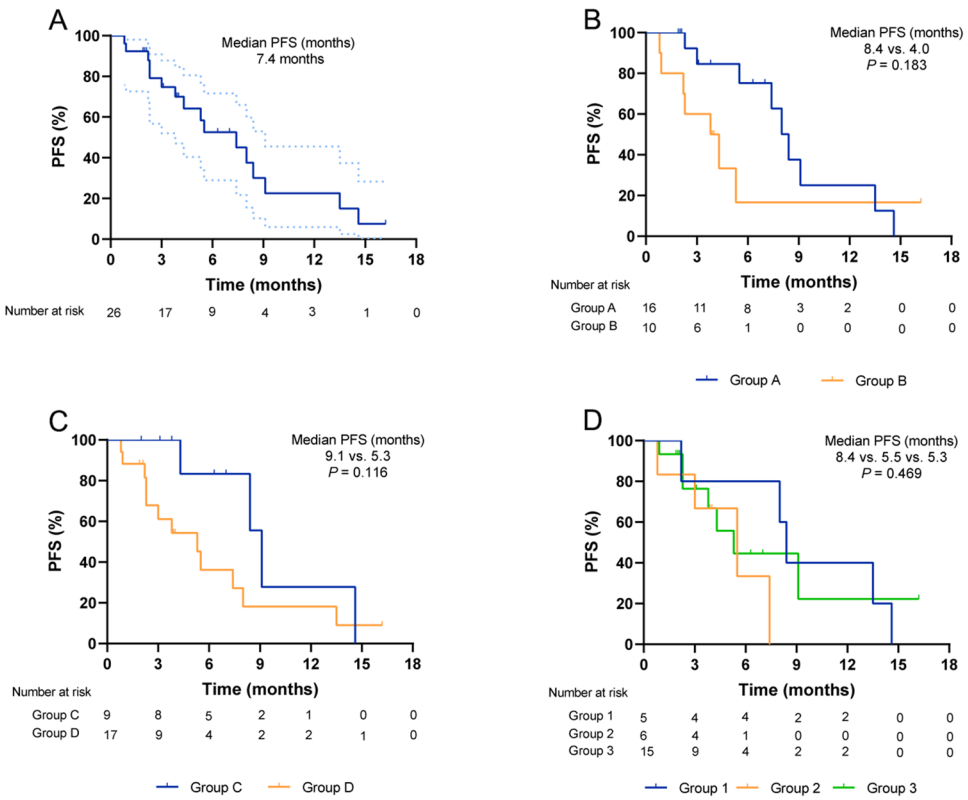

Fig. 3 Clinical outcomes on ICIs-based treatment. **a** Progression-free survival (PFS) from ICIs therapy initiation for the entire cohort. Dotted lines indicate 95% confidence intervals. **b** Group A: combination with chemotherapy; Group B: including monotherapy (n = 5), combination with anti-angiogenesis (n = 3), combination with chemotherapy plus anti-angiogenesis (n = 1), or combination with chemotherapy plus *HER2*-targeting drugs (n = 1). **c** Group C: Patients received ICIs as first-line treatment; Group D: Patients received ICIs as second or later-line treatment. **d** Group 1: Patients received ICIs before *EGFR/HER2*-targeting drugs; Group 2: Patients received ICIs after *EGFR/HER2*-targeting drugs; Group 3: patients never treated with *EGFR/HER2*-targeting drugs until the follow-up end date

first-line immunochemotherapy combination regimens (8/9, 88.9%) (Table 2). Of the entire cohort, 16 patients have been treated with immunochemotherapy combination regimens (16/26, 61.5%), achieving a median PFS of 8.4 months (95% CI: 7.1–9.6) (Fig. 3b, Table 1). Of interest, we observed a higher ORR (60%) and longer PFS (8.4 months) in patients receiving ICIs before EGFR/HER2-targeting drugs (Fig. 3d, Supplementary Table 2). However, there was no statistic difference of ORR or median PFS between those three groups (ORR: 60% versus 33.3% versus 33.3%, $P = 0.545$; PFS: 8.4 months versus 5.5 months versus 5.3 months, $P = 0.469$).

In this study, 7 patients (26.9%) were recorded to develop any-grade adverse events (AEs), including 3 patients (11.5%) with grade 3–4 AEs (one each neutropenia, thrombocytopenia and liver function test abnormality).

Discussion

This retrospective study included patients with *HER2*-mutant advanced lung adenocarcinoma treated with ICIs therapy. The proportion of male and never-smoker was higher, 53.8% and 69.2%, respectively. More than half of patients received PD-1/PD-L1 inhibitors combined with chemotherapy. Overall, patients who received ICIs-based therapy achieved a median PFS of 7.4 months and the ORR was 38.5%. Besides, the median PFS was 9.1 months among patients who received ICIs as first-line treatment. Patients who received ICIs before EGFR/HER2-targeting drugs achieved a median PFS of 8.4 months. A majority of the patients harbored with 12-bp exon 20 insertion (A775_G776insYVMA). Meanwhile, a large proportion of them had PR or SD as best response to ICIs therapy.

In our study, the clinical characteristics were as anticipated to a cohort of patients with *HER2* alterations, including a higher percent of never-smokers[12, 13]. However, there was a lower proportion of female in our cohort (12/26, 46.2%). One possible reason is the differences in selection of patient population for receiving ICIs treatment in clinical practice. As for *HER2*-mutant type, we observed 5 patterns of *HER2* variant, including A775_G776insYVMA, Y772_A775dup, G776 mutation, G778_P780dup and L755P mutation. It was consistent with the other report that A775_G776insYVMA is the most common variant[14]. Among the patients with available patterns of *HER2* variant, we observed an encouraging clinical response to ICIs therapy, in which most of them had PR or SD as best responses (18/22).

As for our cohort, we observed longer PFS in patients undergoing ICIs-based therapy than was reported in prior studies[13, 15, 16], in which PFS was only 2.2–3.6 months for receiving single-agent ICIs or combination with cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors. Of particular interest, 9 of 26 patients treated with ICIs in the first-line setting, in which 5 patients had PR as best response. It might be correlated to the higher percent of patients received PD-1/PD-L1 inhibitors combined with chemotherapy (n = 16, 61.5%) and 8 patients were treated in first-line setting (8/16, 50%). A recent study observed a median PFS of 6 months among NSCLC patients with *HER2*-mutation, who received ICIs in combination with chemotherapy as first-line treatment[17]. Similarly, a case series indicated that the combination of ICIs and chemotherapy may be a promising first-line treatment choice, with a median PFS of 8 months among NSCLC patients with *HER2*-alterations[18]. Chemotherapeutic agents may enhance the strength of effector T cells by upregulating the expression of co-stimulatory molecules (B7-1) or downregulating co-inhibitory molecules (PD-L1) on cancer cells[19]. Alternatively, some chemotherapy drugs can stimulate the release of tumor antigens and potentially upregulate the expression of major histocompatibility complex (MHC) class I molecules, which might enhance tumor antigen presentation and then enhance the response to ICIs therapy[19, 20]. Although the mechanisms underlying the response to ICIs therapy among *HER2* mutation remain elusive, our findings do not support inferior outcomes of ICIs-based therapy, including immunochemotherapy combination regimens, in patients with *HER2*-mutant lung adenocarcinoma.

Despite our clinically relevant findings based on a multicenter patient population, the conclusion is limited by the retrospective nature and small number of patients enrolled in this cohort that causes bias in patient selection. Moreover, one of the strengths about our study is the enrollment of a real-word cohort composed of patients with *HER2* mutations receiving ICIs therapy, a rare population in clinical trials. Taken together, our findings provide a new clinical therapeutic insight for lung adenocarcinoma harbored with *HER2*-mutant.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00262-021-03100-5.

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Data availability material The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of interest The authors declare no potential conflict of interest.

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