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Case report

Dacomitinib exhibits promising activity against the rare *HER2* exon 20 insertion M774delinsWLV in lung cancer: A case report and literature review

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A R T I C L E I N F O

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A B S T R A C T

A775_G776insYVMA, the typical and predominant *HER2* exon 20 insertion variant in non-small cell lung cancer, exhibits relative insensitivity to covalent *HER2*-targeted tyrosine kinase inhibitors. However, other less common insertions have shown better responses to *HER2*-targeted inhibitors. M774delinsWLV is a rare *HER2* exon 20 insertion subtype and its clinical sensitivity to *HER2*-targeted inhibitors remains unclear. Furthermore, there is a lack of current studies to elucidate its structure and predict its sensitivity to *HER2*-targeted tyrosine kinase inhibitors. Herein, we presented a case of non-small cell lung cancer harboring M774delinsWLV who derived favorable response and significant survival benefit from *HER2*-targeted tyrosine kinase inhibitors. A 60-year-old male with metastatic lung adenocarcinoma carrying M774delinsWLV received pyrotinib monotherapy as first-line treatment. After rapid disease progression at three months, sequential combination therapy with pyrotinib and bevacizumab yielded promising antitumor activity and sustained progression-free survival benefits for nearly a year. Subsequent dacomitinib monotherapy displayed significant activity against this uncommon insertion, resulting in a rapid decrease in tumor markers and partial response, along with progression-free survival of one year. The molecular simulation revealed no significant differences in the overall protein structure and binding pocket region between M774delinsWLV and the *HER2* wild type. Drug binding dynamics simulation indicated that dacomitinib exhibited the most potent binding activity compared to afatinib, pyrotinib and poziotinib. Conclusively, dacomitinib exhibited promising efficacy against the rare *HER2* exon 20 insertion M774delinsWLV. Extensive investigation is needed to elucidate the effects of *HER2*-targeted tyrosine kinase inhibitors on non-small cell lung cancer with different *HER2* insertion subtypes.

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1. Introduction

Tyrosine kinase inhibitors (TKIs) targeting epidermal growth factor receptor (*EGFR*)-activating mutations or anaplastic lymphoma kinase (*ALK*) rearrangements have significantly improved prognosis and survival, establishing a standard of care for advanced non-small cell lung cancer (NSCLC) with specific oncogenic drivers [1]. Human epidermal growth factor receptor 2 (*HER2*, or *ERBB2*) alterations, present in 2%–4% of NSCLC patients [2], exhibit resistance to conventional *HER2*-targeted TKIs such as afatinib and dacomitinib due to the prevalent exon 20 insertion (ex20ins) variant A775_G776insYVMA [3–5].

Trastuzumab deruxtecan (T-DXd) is currently the sole approved *HER2*-targeted therapy for previously treated NSCLC patients with *HER2* mutations. It has achieved a confirmed objective response rate (ORR) of 54.9 %, and a median progression-free survival (PFS) of 8.2 months as evidenced in the phase II DESTINY-Lung01 trial [6]. The first and only randomized, blinded multicenter phase II trial DESTINY-Lung02, evaluated the effectiveness and safety of T-DXd in *HER2*-mutated NSCLC patients [7]. It showed considerable and enduring antitumor responses, with ORR of 49 % and 56 % at doses of 5.4 and 6.4 mg/kg, regardless of *HER2* mutation type, amplification status, and prior treatment [7]. In several countries, T-DXd, rather than *HER2*-targeted TKIs, has become the standard choice for second-line treatment in NSCLC patients with *HER2* mutations.

Several less common *HER2* ex20ins subtypes such as P780_Y781insGSP and G776delinsVC have been reported to exhibit a more favorable response to *HER2*-targeted TKIs in comparison to the YVMA insertion [8–10]. Here, we report the clinical outcome of different kinds of *HER2*-targeted TKIs pyrotinib and dacomitinib in a patient with lung adenocarcinoma harboring the rare *HER2* ex20ins variant M774delinsWLV. Notably, dacomitinib revealed significant efficacy as a subsequent-line treatment for this insertion. Furthermore, we conducted a thorough literature review and performed *in silico* analysis to investigate the structural characteristics and binding affinity of the M774delinsWLV insertion with currently approved *HER2*-targeted inhibitors.

1.1. Case presentation

A 60-year-old male presented with shortness of breath and had a history of heavy smoking. A tumor was found in the left lung and a radical lobectomy was performed in March 2019. Postoperative pathology confirmed the adenocarcinoma at the lower lobe of left lung, with a tumor size of 2.7 × 2.1 × 1.8 cm (Fig. 1). The visceral pleura was invaded, and no metastatic lymph node was observed (p. T2aN0M0, TNM Stage IB). Afterwards, he received regular follow-ups without postoperative therapy for two years. In April 2021, positron emission tomography-computed tomography (PET-CT) examination revealed subpleural lesions in the left lung and metastatic disease in the left pleural effusion (Fig. 2A). Lung adenocarcinoma cells were detected in the drainage of the left pleural effusion, and hybridization-based enrichment was carried out by next-generation sequencing (NGS) in Geneseeq Technology Inc. Using Wash Reagents Kit (Integrated DNA Technologies) and 6-gene targeted panel covering *EGFR*, *ALK*, c-ros oncogene 1 (*ROS-1*), v-Raf murine sarcoma viral oncogene homolog B (*BRAF*), Kirsten rat sarcoma virus (*KRAS*), and *HER2*, which was sequenced on HiSeq4000 Illumina platform. The NGS testing via pleural effusion sample confirmed the presence of *HER2* ex20ins p.M774delinsWLV (c.2320A > TGGCTGG) (Fig. 2B).

The patient began pyrotinib (320 mg once daily) targeted therapy in May 2021. After one month, both the pleural metastases and left pleural effusion exhibited reduction (Fig. 3A), along with a significant decrease in the tumor marker carcinoembryonic antigen (CEA). However, the left pleural effusion increased, and the volume of multiple metastasized lesions enlarged after three months of pyrotinib treatment (Fig. 3B), accompanied by a gradual increase in CEA levels. Subsequently, the patient received a combination therapy of pyrotinib 320 mg once daily and bevacizumab 7.5mg/kg every three weeks starting in September 2021. Following one month of the combination therapy, the left pleural effusion disappeared, and the pleural metastases remained stable (Fig. 3C). In

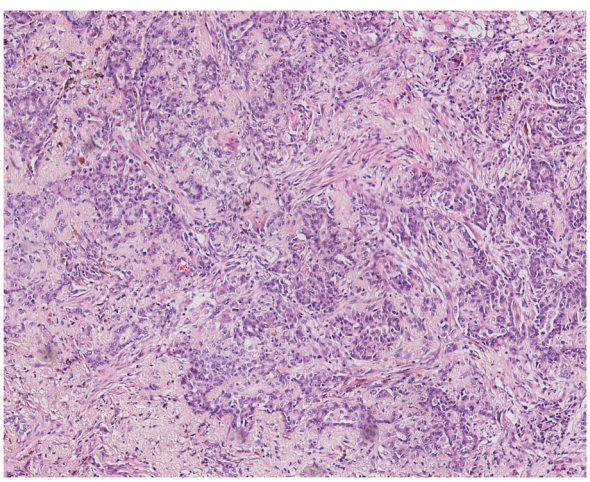

Fig. 1. Optical image of lung adenocarcinoma in Hematoxylin and Eosin staining with 10× magnification ratio in paraffin-embedded tissue after the radical resection of left lower lobe of lung.

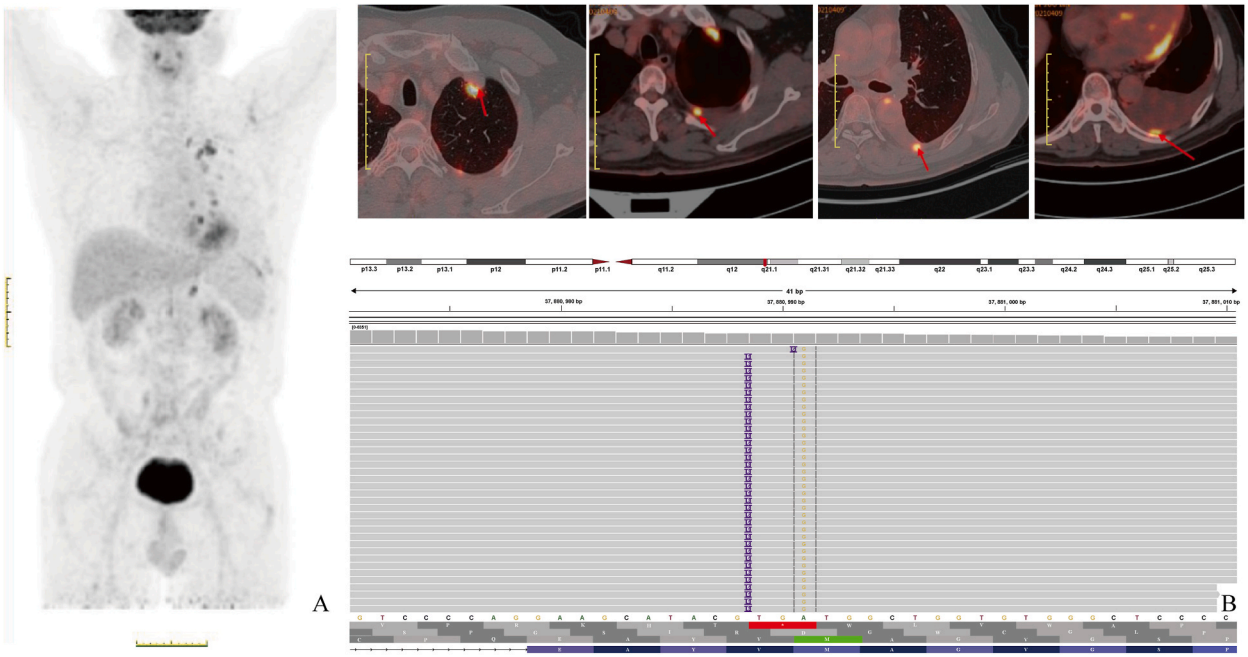

Fig. 2. The relapsed disease post surgical resection confirmed by the positron emission tomography-computed tomography examination (**A**). The integrative genomics viewer of *HER2* exon 20 insertion p.M774delinsWLV detected by the next-generation sequencing (**B**).

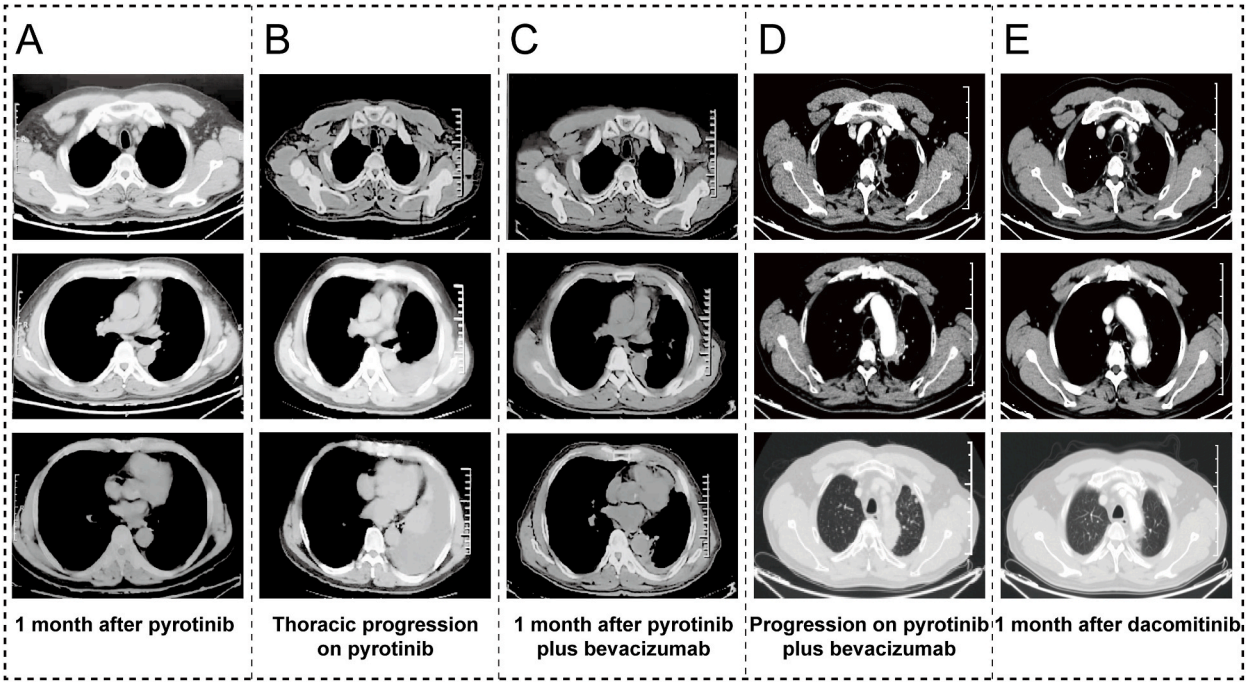

Fig. 3. Response evaluated by the chest computed tomography scan. One month after pyrotinib monotherapy (**A**), thoracic progression on pyrotinib treatment (**B**), one month after pyrotinib and bevacizumab treatment (**C**), progression on pyrotinib and bevacizumab treatment (**D**), and one month after dacomitinib monotherapy **(E)**.

August 2022, there was a recurrence of the disease, characterized by an increase in left pleural effusion and enlarged lymph nodes in the mediastinum (Fig. 3D). The combination of pyrotinib and bevacizumab resulted in an 11-month PFS for the patient. Afterwards, the patient received pemetrexed (500mg/m^2) plus carboplatin (area under the concentration-time curve, AUC 5.0) chemotherapy in

combination with bevacizumab 7.5mg/kg every three weeks. Despite stable imaging results, there was a gradual increase in the tumor marker CEA from September 2022. However, due to the Corona Virus Disease 2019 (COVID-19) outbreak in China in December 2022, the patient was unable to stay in hospital and had to discontinue chemotherapy. In December 2022, the patient was administered targeted therapy with dacomitinib 30mg once daily. After one month, he achieved partial response to dacomitinib therapy, with a significant reduction of lesions in the left pleura, left side of the aortic arch, and multiple metastatic lymph nodes in the mediastinum (Fig. 3E). In February 2023, there was a rapid decrease on CEA levels after two-month of dacomitinib therapy, from 230.77 ng/ml to 20.22 ng/ml. Since December 2022, the patient continued dacomitinib 30mg once daily targeted therapy, and sustained a partial response under regular follow-ups every two months until December 2023, with PFS benefit of 12 months. On December 5, 2023, he developed brain metastases, and received stereotactic radiotherapy by Leksell Gamma Knife. From December 18, 2023, T-DXd was administered at dose of 5.4mg/kg every three weeks. Up to the last follow-up on March 31, 2024, the patient continued T-DXd therapy, with a stable disease both in the pulmonary and brain metastases after five treatment cycles. The dynamic changes in the tumor marker CEA during the treatment process are depicted in Fig. 4.

In addition, we employed computational modeling to study the M774delinsWLV mutation, utilizing the crystal structure of the kinase domain of HER2 (PDB: 3PP0) via the Schrödinger software (2020-1 Release). The binding free energy (ΔG_{bind}) was calculated using the GlideScore method and the Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) method. Our analysis revealed that codon M774 was located at the end of the C-helix, which encoded residues I767-M774 of the *HER2* kinase domain (Fig. 5A). When compared to the wild-type *HER2* (Fig. 5B), the overall protein structure of M774delinsWLV, with the insertion of the three amino acids WLV (Tryptophan-Leucine-Valine, shown in red) in place of the original M774, showed no significant difference (Fig. 5C). Furthermore, the binding pocket region of M774delinsWLV was only slightly affected. Our simulations for ΔG_{bind} indicated that dacomitinib exhibited the most potent binding activity for M774delinsWLV compared to other *HER2* inhibitors (Table 1).

2. Discussion

HER2-altered NSCLC is associated with an unfavorable prognosis, characterized by a median PFS of 4.9–5.9 months and a median overall survival (OS) of 9.9–10.7 months in first- or second-line treatment settings [11,12]. Several studies have demonstrated that *HER2* ex20ins in NSCLC are associated with a relatively poor response to covalent *EGFR/HER2* inhibitors, such as afatinib, dacomitinib, and neratinib, resulting in an ORR of 3.8%–11.5 % and a short PFS of 3–5.5 months [3,4,13]. The ZENITH20-2 study showed that the pan-*ErbB* inhibitor poziotinib achieved a median PFS of 5.5 months and improved the ORR to 35.1 % in previously treated NSCLC patients with *HER2* ex20ins [14]. Another multicenter study reported that pyrotinib monotherapy exhibited an ORR of 30.0 %, a median PFS of 6.9 months, and a median OS of 14.4 months in advanced NSCLC patients with *HER2* alterations who had experienced disease progression on platinum-based chemotherapy [15]. Currently, the first-line standard of care for *HER2*-altered NSCLC is platinum-based chemotherapy either alone or in combination with bevacizumab. The POLISH study reported a median PFS of 4.03 and 5.63 months, and a median OS of 31.67 and 36.27 months, respectively, for these therapies [16].

The M774delinsWLV subtype of *HER2* ex20ins is relatively rare, but it has shown a favorable response to dacomitinib as evidenced by a sustained PFS of over 23 months and a partial response duration lasting for more than 3 months [4]. Additionally, a preclinical

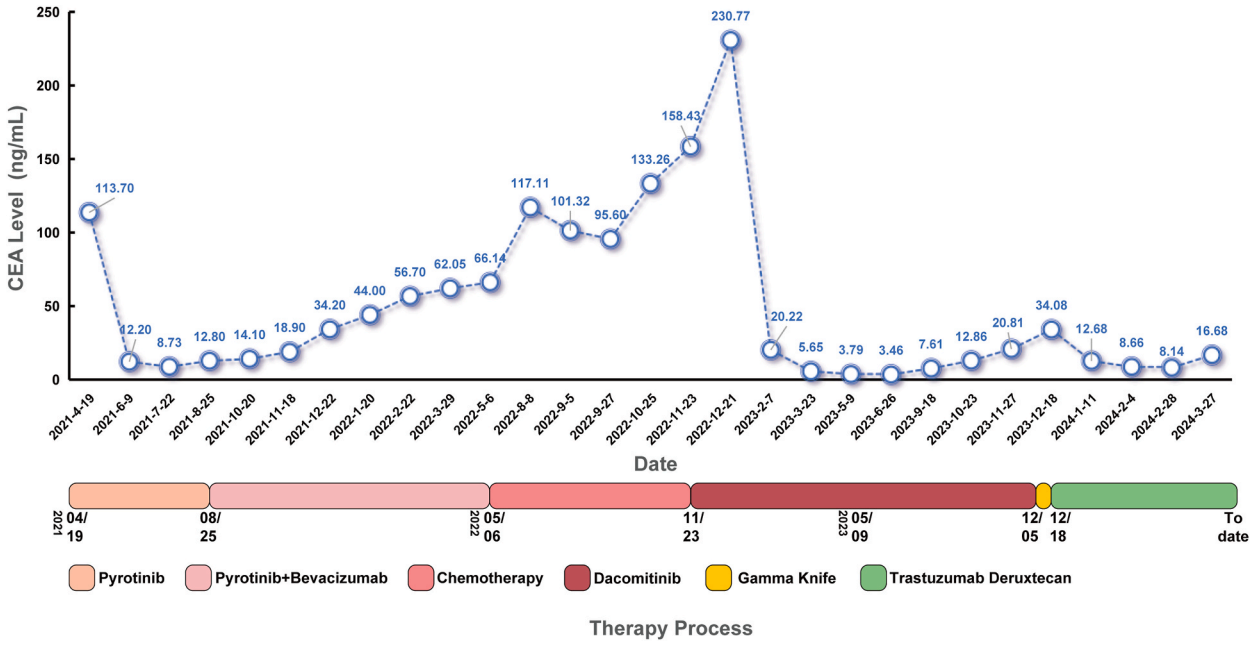

Fig. 4. The dynamic changes in the tumor marker carcinoembryonic antigen during the treatment process.

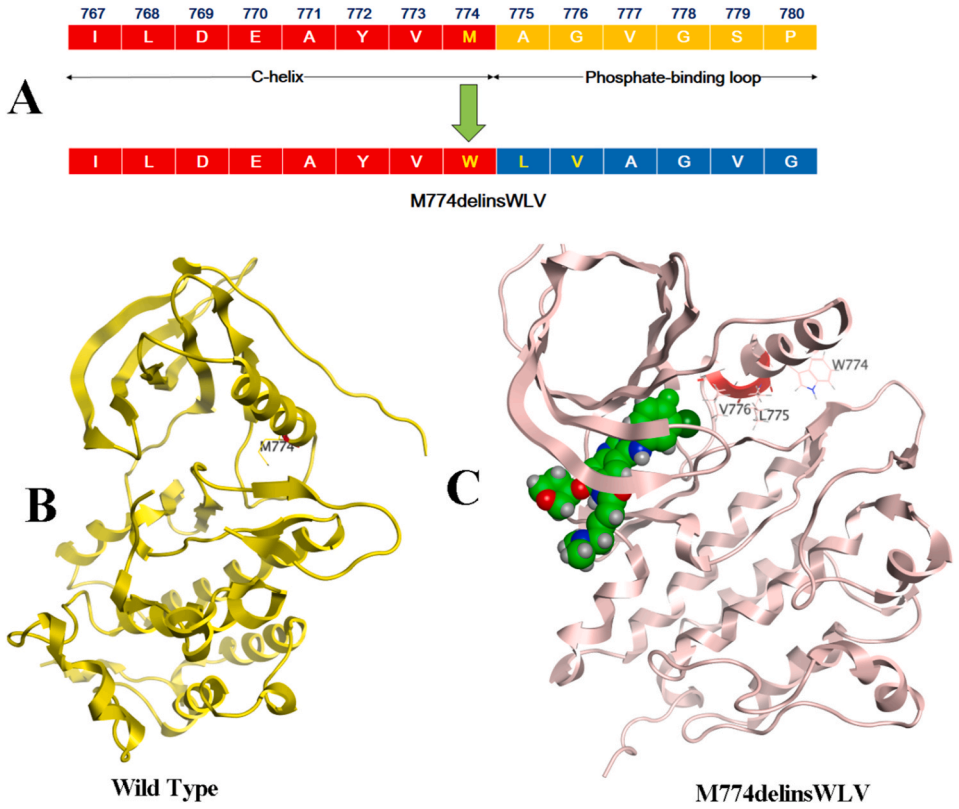

Fig. 5. The amino acid sequences of *HER2* wild-type and exon 20 insertion M774delinsWLV in the kinase domain (**A**). Computational protein structure of the *HER2* wild-type (**B**) and M774delinsWLV insertion (**C**).

Table 1
Computer-based binding free energy simulations of different HER2 inhibitors for M774delinsWLV insertion.

Molecule	M774delinsWLV	
	ΔG_{bind} Glide score (kcal/mol)	ΔG_{bind} MM/GBSA (kcal/mol)
Afatinib	**−9.463**	**−97.43**
Dacomitinib	**−10.086**	**−98.93**
Pyrotinib	**−8.953**	**−91.76**
Poziotinib	**−9.229**	**−91.51**

ΔG_{bind}, binding free energy; MM/GBSA, Molecular Mechanics/Generalized Born Surface Area.

study demonstrated that Ba/F3 cells carrying M774delinsWLV cells were highly sensitive to dacomitinib, with 50 % inhibiting concentration (IC_{50}) values of <1 nM [8]. Molecular simulation graphs by Yang et al. revealed a high sensitivity of dacomitinib, with a 90 % inhibiting concentration (IC_{90}) <1 nM towards M774delinsWLV [17]. However, the simulation only provided an approximate spatial location of M774delinsWLV, without representing its specific protein structure. Taken together, M774delinsWLV is an infrequently encountered subtype of *HER2* ex20ins, uniquely sensitive to dacomitinib, indicating potential clinical applications of dacomitinib for patients with this uncommon variant. Nonetheless, there is a lack of detailed structural analysis and exploration of the targeted activity of *HER2*-targeted TKIs towards M774delinsWLV insertion.

In this case, we employed computational modeling of M774delinsWLV to gain initial insights into its structural features. We observed that codon M774 was located at the end of the C-helix of *HER2* kinase domain, which is crucial for enzyme regulation, as kinase activation is frequently associated with changes in its orientation [18]. In comparison to the *HER2* wild-type protein, M774delinsWLV exhibited no substantial differences in either the protein structure or the binding pocket region. Subsequent simulations for TKI-binding indicated that dacomitinib exhibited the most potent activity for M774delinsWLV. Our TKI-binding dynamics simulation strongly supported the structural observations of M774delinsWLV, aligning well with the aforementioned studies [4,8,17].

In this case, pyrotinib was administered as first-line therapy, targeting the *HER2* M774delinsWLV insertion, a novel mutation not previously reported globally. However, there was rapid progression after three months. Sequential combination therapy of pyrotinib with the antiangiogenic agent bevacizumab demonstrated promising antitumor activity and ongoing PFS benefit for 11 months. In our

previous PEARL study, the ORR of patients with *HER2*-mutant NSCLC who received pyrotinib combined with antiangiogenic agents was numerically higher than those with pyrotinib monotherapy (29.2 % *vs.* 9.1 %) [10]. Previous evidence has confirmed that the combination of *EGFR*-TKIs and antiangiogenic agents can inhibit tumor angiogenesis and provide significant survival benefits in *EGFR*-positive NSCLC [19–21]. Furthermore, vascular endothelial growth factor (*VEGF*) expression is also modulated by *HER2* signaling [22], thus further suppression of *VEGF* activity may enhance the antitumor effects of *HER2*-targeted inhibitors. Additionally, the combination of pyrotinib and the antiangiogenic TKI apatinib has been reported to demonstrate potent antitumor activity in metastatic NSCLC with *HER2* amplification or activating mutations, showing an improved ORR of 45.5 % compared to pyrotinib alone [15,23]. Surprisingly, dacomitinib demonstrated significant and sustained activity against the M774delinsWLV insertion in our case, with PFS benefit of one year, despite being administered later in the treatment course with the patient having received extensive prior treatments. This observation is consistent with previous reports on dacomitinib [4,8].

It cannot be ignored that longer follow-up and survival analysis is needed. This is an exploratory analysis only based on the protein structure and molecular dynamics simulation, and cannot fully represent the actual effect of *HER2*-targeted TKIs on M774delinsWLV insertion in clinical practice. More clinical evidence as well as cell lines and patient-derived xenograft models are still needed to correspond our findings and to draw a clear conclusion. Nevertheless, we believe that our case provides valuable evidence to guide meaningful targeted therapy regarding rare subtypes of *HER2* ex20ins in NSCLC.

3. Conclusion

Dacomitinib exhibited promising efficacy against the rare *HER2* ex20ins M774delinsWLV mutation. Extensive investigation is needed to elucidate the effects of *HER2*-targeted inhibitors on NSCLC with different *HER2* insertion subtypes.

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4. Ethics declarations

The patient provided informed consent for the publication of his anonymised case details and images.

Data availability statement

Data presented in this case is included in article, and will be made available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Guangjian Yang: Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Runze Liu:** Validation, Software, Formal analysis. **Xiaoyong Tang:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

ALK	anaplastic lymphoma kinase
AUC	area under the concentration-time curve
BRAF	v-Raf murine sarcoma viral oncogene homolog B
CEA	carcinoembryonic antigen
COVID-19	Corona Virus Disease 2019
EGFR	epidermal growth factor receptor
ex20ins	exon 20 insertion

HER2	human epidermal growth factor receptor 2
IC_{50}	50 % inhibiting concentration
IC_{90}	90 % inhibiting concentration
KRAS	Kirsten rat sarcoma virus
MM/GBSA	Molecular Mechanics/Generalized Born Surface Area
NGS	next-generation sequencing
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
ROS-1	c-ros oncogene 1
T-DXd	trastuzumab deruxtecan
TKIs	tyrosine kinase inhibitors
VEGF	vascular endothelial growth factor
ΔG_{bind}	binding free energy

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