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Editorial Board Member of *World Journal of Clinical Cases*, Raden Andri Primadhi, MD, PhD, Assistant Professor, Surgeon, Department of Orthopaedics and Traumatology, Universitas Padjadjaran Medical School, Hasan Sadikin Hospital, Bandung 40161, Indonesia. randri@unpad.ac.id

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## Response to dacomitinib in advanced non-small-cell lung cancer harboring the rare delE709\_T710insD mutation: A case report

Fei Xu, Meng-Ling Xia, Hui-Yun Pan, Jiong-Wei Pan, Yi-Hong Shen

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**Fei Xu, Meng-Ling Xia, Yi-Hong Shen**, Department of Respiratory Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310000, Zhejiang Province, China

**Hui-Yun Pan**, Department of Day Care Ward, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310000, Zhejiang Province, China

**Jiong-Wei Pan**, Department of Respiratory Diseases, Lishui City People's Hospital, Lishui 323000, Zhejiang Province, China

**Corresponding author:** Yi-Hong Shen, MD, Chief Doctor, Department of Respiratory Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, No. 79 Qingchun Road, Hangzhou 310000, Zhejiang Province, China. [drsyh@zju.edu.cn](mailto:drsyh@zju.edu.cn)

### Abstract

#### BACKGROUND

Tyrosine kinase inhibitors (TKI) have been the standard first-line therapy for advanced non-small cell lung cancer (NSCLC) of epidermal growth factor receptor (*EGFR*) sensitive mutations. Uncommon *EGFR* mutations are increasingly reported with the development of next-generation sequencing. However, their sensitivity to TKIs is variable with limited clinical evidence.

#### CASE SUMMARY

Here, we report a patient with the rare delE709\_T710insD mutation, who showed the favorable efficacy of dacomitinib and achieved a partial response with a progression-free survival of 7.0 mo.

#### CONCLUSION

To our knowledge, this is the first report displaying the clinical efficacy of dacomitinib for patients with delE709\_T710insD, which may help to provide alternatives in non-classical variant NSCLC patients. Further studies are warranted to make the optimal choice of *EGFR*-TKI for rare mutations.

**Key Words:** Next-generation sequencing; DelE709\_T710insD; Non-small-cell lung cancer; Dacomitinib; Uncommon *EGFR* mutation; Case report

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**Core Tip:** DelE709\_T710insD is an extremely rare complex in-frame deletion mutation in exon 18 and accounts for only 0.11% of epidermal growth factor receptor mutations. The development of next-generation sequencing enabled the more identification of rare variants. Our case is the first report describing the clinical efficacy of dacomitinib for delE709\_T710insD and achieved a progression-free survival of 7.0 mo. More patients with the rare variants may benefit from dacomitinib targeted therapy based on our study.

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## INTRODUCTION

Among non-small-cell lung cancer (NSCLC) patients with epidermal growth factor receptor (*EGFR*) mutations, the most common mutations are exon 19 deletions and exon 21 L858R point mutations, accounting for 80%-90% of all *EGFR* mutations[1]. With the development of next-generation sequencing (NGS), more rare or atypical mutations, such as *EGFR* exon 20 and exon 18, have been identified, but their responses to TKIs have been variable and less investigated.

Mutations in *EGFR* exon 18, including point mutations and deletion-insertion mutations, were observed in approximately 4% of patients with *EGFR* mutations[2]. DelE709\_T710insD is a rare complex in-frame deletion mutation in exon 18 and accounts for only 0.11% of *EGFR* mutations (33/31015) according to the Catalog of Somatic Mutations in Cancer (COSMIC) v.94 database[3]. Evidence regarding its response to available *EGFR*-TKIs is limited.

Here, we present a patient with advanced lung adenocarcinoma harboring the rare *EGFR* delE709\_T710insD mutation who responded well to the second-generation *EGFR* TKI dacomitinib.

## CASE PRESENTATION

### Chief complaints

A 56-year-old female patient presented with right chest discomfort for 3 mo.

### History of present illness

Chest computed tomography (CT) revealed a 1.9 cm × 2.1 cm mass in the anterior segment of the right upper lobe and multiple nodules in the bilateral lungs, accompanied by right pleural effusion. Moreover, the right hilar, mediastinal, and paratracheal lymph nodes (LNs) were found to be enlarged.

### History of past illness

The patient had no history of any other diseases.

### Personal and family history

The patient was free of any known congenital disease.

### Physical examination

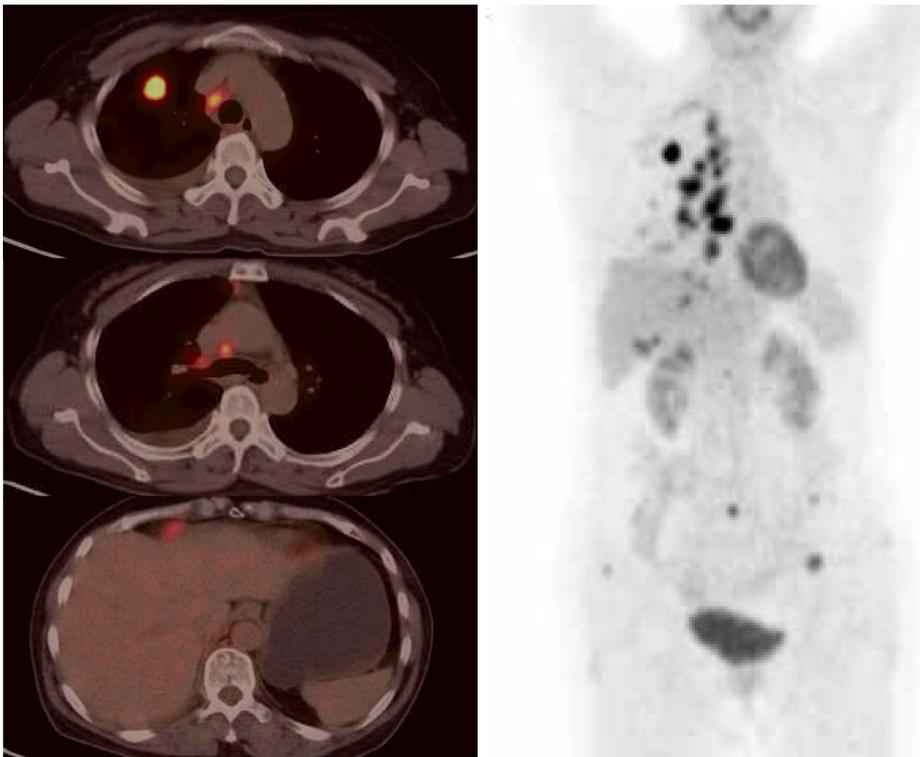
The right supraclavicular painless lymph node was palpated in the size of a soybean.

### Laboratory examinations

The laboratory test data revealed that the serum carcinoembryonic antigen level was 279.6 ng/mL.

### Imaging examinations

A positron emission tomography (PET) scan showed increased fluorodeoxyglucose (FDG) uptake in the right upper lobe mass, multiple pulmonary and subpleural nodules, and right supraclavicular, mediastinal, and right hilar lymph nodes. PET also indicated hypermetabolic nodules with low density in segment 6 of the liver and anterolateral area of the liver capsule, along with multiple bone destruction changes and high FDG uptake in T7 and T8 vertebral bodies and appendages, L5 spinous processes, and bilateral iliac bones (Figure 1). Magnetic resonance imaging of the brain was negative.



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Figure 1 Positron emission tomography scans at presentation.

## MULTIDISCIPLINARY EXPERT CONSULTATION

She subsequently underwent ultrasound-guided needle biopsy of the right supraclavicular lymph node and right closed thoracic drainage. Endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) was performed on LN 7 and 11R. Cancer cells were found both in the pleural effusion and clavicular lymph nodes. Pathological results of LN 11R were identified pulmonary adenocarcinoma, with P40 (-), CK7 (+), TTF-1 (+), Napsin A (+), CK5/6 (-), ALK Ventana (-), ALK-Negative (-) through immunohistochemistry (IHC). Genetic testing was performed on cell block samples from pleural effusion by polymerase chain reaction (PCR). Routine molecular genetic testing, including mutation of *EGFR*, *KRAS*, *NRAS*, *BRAF*, *HER2*, *MET*, and *PIK3CA*, and fusion of *ALK*, *RET*, and *ROS1*, were all negative. **Supplementary material** listed all gene and mutation sites of the PCR diagnostic kits.

## FINAL DIAGNOSIS

Based on this, the patient was identified as "driver gene-negative" right lung adenocarcinoma, cT1cN3M1c (TNM 8th Edition), stage IVB.

## TREATMENT

The patient then started chemotherapy with pemetrexed plus carboplatin and bevacizumab in September 2020. A CT scan after 2 cycles showed a reduction in the mass in the right upper lobe, but disease progression was observed in February 2021. The progression-free survival<sup>1</sup> (PFS<sup>1</sup>) is 5 mo, and the best response was reduced stable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria. To seek more effective and potential treatment, CT-guided transthoracic lung biopsy was taken from the right upper lobe as her family demanded. A 12-gene NGS panel (Shanghai Yikon Genomics Inc. China) for lung cancer revealed the *EGFR* Del18 (delE709\_T710insD) mutation. However, there are no recommended targeted drugs for this rare mutation. Dacomitinib 30 mg/d was administered as the second-line treatment, starting in February 2021.

**Table 1 Studies of epidermal growth factor receptor-tyrosine kinase inhibitors response for delE709\_T710insD**

Ref.	Patient No.	Gender	Age (yr)	Smoking	Stage	Histologic type	TKI used/line	Response	PFS (m)	OS (m)
Wu <i>et al</i> [7], 2011	1	F	61	No	IV	AD	Gefitinib/NA	SD	5.1	22.7
	2	M	65	Yes	IV	AD	Gefitinib/NA	PD	0.9	11.1
Ackerman <i>et al</i> [9], 2012	3	F	88	No	IV	AD	Erlotinib/1 <sup>st</sup>	PR	6	NA
Kobayashi <i>et al</i> [19], 2015	4	M	63	NA	IV	AD	Erlotinib/3 <sup>rd</sup>	SD	NA	NA
							Afatinib/4 <sup>th</sup>	PR	NA	
Wu <i>et al</i> [6], 2016	5	F	57	No	IV	AD	Gefitinib/NA	PD	0.6	24.1
	6	M	79	Yes	IV	AD	Gefitinib/NA	SD	6.2	6.2
	7	M	68	Yes	IV	AD	Gefitinib/NA	PD	2.3	29.5
Klughammer <i>et al</i> [10], 2016	8	F	50	No	III/IV	NSCLC	Erlotinib/2 <sup>nd</sup>	PD	1.3	1.7
Ibrahim <i>et al</i> [13], 2017	9	F	52	No	IV	AD	Afatinib/1 <sup>st</sup>	PR	NA	NA
An <i>et al</i> [14], 2019	10	M	56	No	IV	AD	Afatinib/2 <sup>nd</sup>	PR	11	More than 21
Iwamoto <i>et al</i> [15], 2019	11	F	56	No	IV	AD	Afatinib/6 <sup>th</sup>	PR	7	NA
D'Haene <i>et al</i> [16], 2019	12	F	57	No	III	AD	Afatinib/2 <sup>nd</sup>	PR	12	36
Martin <i>et al</i> [11], 2019	13	M	60	No	IV	AD	Erlotinib/NA	PD	1	3
Isaksson <i>et al</i> [12], 2020	14	NA	NA	NA	IV	NA	Erlotinib/1 <sup>st</sup>	PD	8	NA
Sousa <i>et al</i> [8], 2020	15	F	66	Yes	IV	AD	Gefitinib/1 <sup>st</sup>	PD	3	24
	16	F	46	Yes	II	AD	Erlotinib/2 <sup>nd</sup>	PD	4	26
	17	F	57	No	IV	AD	Erlotinib/2 <sup>nd</sup>	PD	3	18
Wei <i>et al</i> [17], 2021	18	F	70	No	II	NSCLC	Afatinib/1 <sup>st</sup>	PR	23	On going
Jelli <i>et al</i> [18], 2021	19	F	57	No	IV	AD	Afatinib/1 <sup>st</sup>	CR	17 (On going)	17 (On going)
Xu <i>et al.</i> , 2021 (this case)	20	F	56	No	IV	AD	Dacomitinib/2 <sup>nd</sup>	PR	7	On going

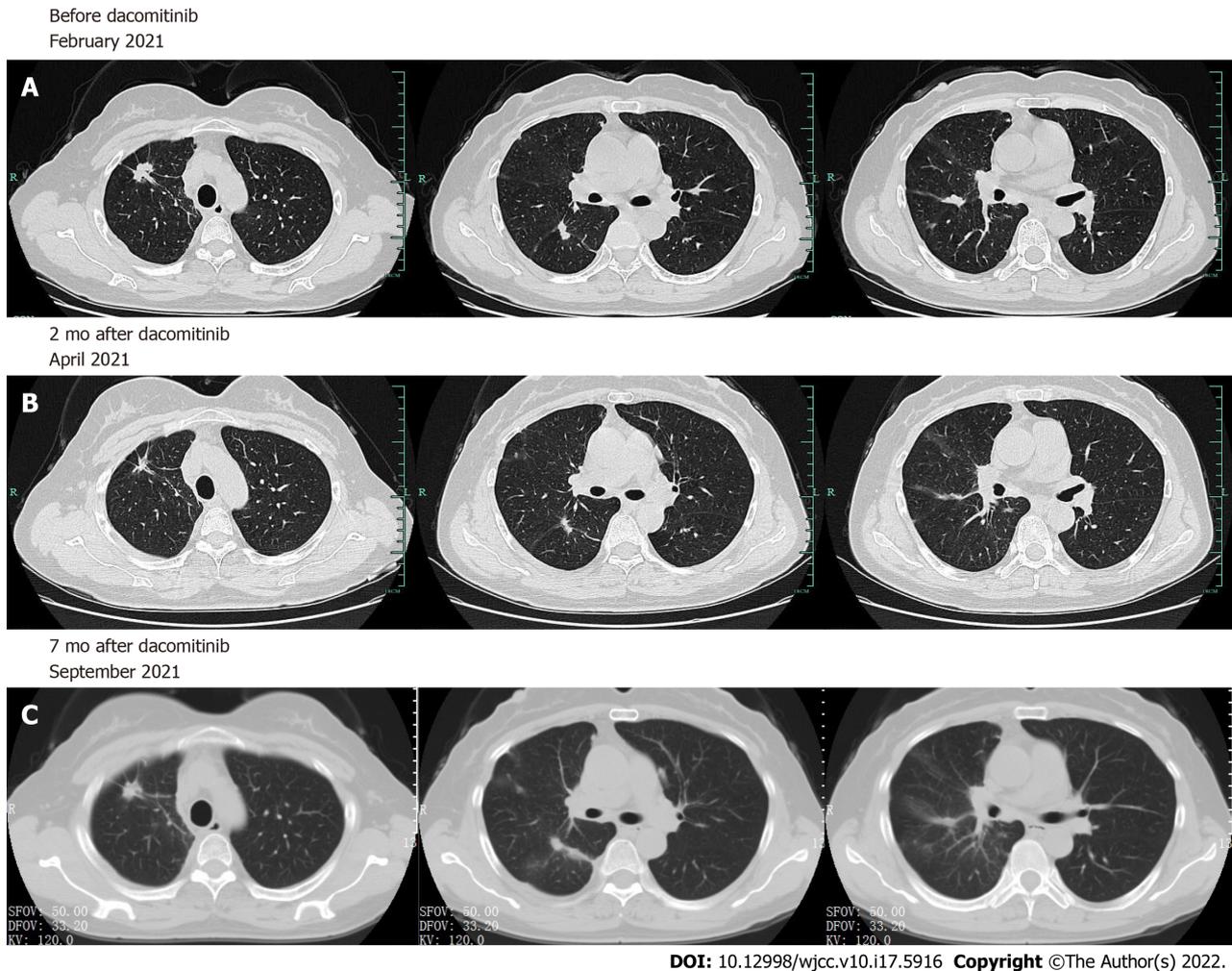
F: Female; M: Male; NA: Data not-available; PFS: Progression-free survival; OS: Overall survival; TKI: Tyrosine kinase inhibitor; AD: Lung adenocarcinoma; NSCLC: Non-small cell lung cancer; PR: Partial response; SD: Stable disease; PD: Progression disease.

## OUTCOME AND FOLLOW-UP

A CT scan revealed that the primary lesion significantly decreased in size after 2 mo, and a partial response (PR) was achieved (Figure 2). There were no significant adverse effects of dacomitinib therapy. Nevertheless, recent CT showed that the mass of the right upper lobe grew larger, which met the RECIST criteria for progressive disease (PD) after 7.0 mo of dacomitinib treatment.

## DISCUSSION

EGFR mutations are observed in up to 50% of Asian non-small-cell lung cancer (NSCLC) patients and approximately 10%-20% of non-Asian patients. EGFR-TKIs have become the standard first-line treatment for EGFR sensitizing mutations (del18 and L858R) NSCLC based on Phase III trials vs platinum-based doublet chemotherapy[4], which has revolutionized the management of EGFR-mutated NSCLC. Uncommon mutations or less frequent alterations involving exons 18 and 20 in EGFR account for 10-20% of all EGFR mutations in NSCLC. Individuals with uncommon EGFR mutations seem to be a



**Figure 2 Chest computed tomography scans.** A: Chest computed tomography scans before (A) and after dacomitinib therapy; B and C: The patient achieved partial response 2 mo after the initiation of dacomitinib therapy and progressed at 7 mo later.

heterogeneous group exhibiting differential sensitivity to *EGFR* inhibitors, but clinical evidence is scarce [5].

Studies on the delE709\_T710insD mutation and its response to *EGFR*-TKIs, including gefitinib, erlotinib, and afatinib, have been reported sporadically in recent years (Table 1). Wu JY *et al*[6] reported that the prevalence of delE709\_T710insD is 0.16% (5/3146) in *EGFR* mutations. Six gefitinib-treated patients harboring delE709\_T710insD were nonresponders, with a median PFS of 2.65 mo[6-8]. Erlotinib was administered in previous case reports[8-12], which also seemed to be a frustrated treatment for delE709\_T710insD. One had a PR, 5 had PD, and the response rate was only 25% (1/6). Afatinib was proven to be effective for such rare variants[13-18]. Among the 6 patients receiving afatinib, one achieved a complete response (CR), and 5 achieved a PR. More significantly, 1 patient with E709\_T710delinsD mutations showed a survival benefit of afatinib after erlotinib treatment failed[19]. The overall response rate of afatinib for delE709\_T710insD was 100% (7/7). According to the analysis by Rubiera-Pebe R *et al*[20], the median PFS comparison between first-generation TKIs and afatinib for patients with delE709\_T710insD is 3.1 mo *vs* 7.0 mo, respectively. *In vitro*, a study by Kobayashi Y *et al* [19] investigated the sensitivities of exon 18 mutations to various *EGFR*-TKIs and suggested that second-generation *EGFR*i have broader inhibitory profiles than other TKIs for rare mutations.

Like afatinib, dacomitinib is a second-generation pan-HER inhibitor that irreversibly binds to all three kinase-active members of the ErbB family (*HER1/EGFR*, *HER2*, and *HER4*), leading to more efficient *EGFR* inhibition. The efficacy of dacomitinib on patients acquiring Ex18 G719A as later-line therapy has been reported by Morita A *et al*[21]. In addition, dacomitinib *in vitro* has an IC<sub>50</sub>=29 nM for Ba/F3 cells expressing exon 18 delE709\_T710insD[19], indicating the potential activity of this nonclassical mutation. The results of a phase 3 trial of dacomitinib (NCT01774721, ARCHER 1050) indicated that first-line dacomitinib significantly improved PFS and OS *vs* gefitinib, and the adverse events were manageable [22]. Based on these findings, dacomitinib seemed to be a promising candidate for *EGFR*-positive advanced NSCLC, including less common mutations. However, limited clinical data have shown the effect of dacomitinib on rare mutations.

## CONCLUSION

In our study, we reported that a patient with *EGFR* delE709\_T710insD achieved PR after the initiation of dacomitinib, with a PFS2 of 7 mo. To the best of our knowledge, this is the first report describing the clinical efficacy of dacomitinib for *EGFR* delE709\_T710insD. The efficacy of dacomitinib on rare mutations needs to be evaluated *in vivo* or *in vitro* by further studies. In addition, appropriate genetic diagnosis methodologies will provide patients with more opportunities for targeted therapy. Our report may help to provide new treatment options for NSCLC patients with nonclassical variants.

## FOOTNOTES

**Author contributions:** Shen YH initiated the case report and supervised the entire study; Xu F collected patient data, performed a literature review and wrote the manuscript; Xia ML obtained and analyzed the next-generation sequencing results; Pan HY reviewed the histological pathological examination of the biopsy; Pan JW was involved in patient follow-up after discharge; all authors read and approved the final manuscript.

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**Country/Territory of origin:** China

**ORCID number:** Fei Xu 0000-0003-4200-1485; Meng-Ling Xia 0000-0002-0182-7400; Hui-Yun Pan 0000-0002-2536-5773; Jiong-Wei Pan 0000-0002-4077-2561; Yi-Hong Shen 0000-0002-7815-9973.

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