

CASE REPORT

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Conversion therapy with chemoimmunotherapy induced pCR in a stage IV lung squamous cell carcinoma patient harboring EGFR exon 20 insertion

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ABSTRACT

This case study details an innovative conversion therapy strategy in a 58-year-old Asian male with baseline stage cT₄N₁M_{1b} advanced lung squamous cell carcinoma (SCC) harboring a rare EGFR exon 20 insertion mutation with concurrent high PD-L1 expression who achieved a pathologic complete response (pCR) after preoperative immunotherapy plus chemotherapy. The patient initially presented with coughing and bloody sputum and was comprehensively diagnosed via PET/CT scanning, bronchoscopic biopsy and next-generation sequencing. After four cycles of platinum–paclitaxel chemotherapy plus immunotherapy with pembrolizumab (a PD-1 blockade), significant primary tumor shrinkage and the disappearance of oligometastasis in the right adrenal gland were discovered via CT scans. The subsequent salvage lung surgery resulted in a pCR, and the patient continued postoperative maintenance immunotherapy. No evidence of disease relapse or immune-related adverse events occurred after a post-surgery follow-up time of 9.4 months. This case highlights the potential value and challenges of immunotherapy plus chemotherapy as conversion therapy strategy in treating patients with non-small cell lung cancer (NSCLC) harboring rare EGFR exon 20 insertions.

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Introduction

Lung cancer remains the leading cause of cancer-related mortality globally, and non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases.^{1,2} Among NSCLCs, lung squamous cell carcinoma (SCC) represents a significant subtype characterized by distinct molecular profiles and clinical behavior compared with those of adenocarcinomas. Despite advances in targeted therapy and immunotherapy, the prognosis for patients with advanced lung SCC, especially those harboring specific genetic alterations, such as *epidermal growth factor receptor* (EGFR) exon 20 insertions (ex20ins), remains poor.^{3–5} EGFR ex20ins mutations (4%–12%) in lung cancer are less common than classical EGFR mutations (exon 19 deletions and L858R mutations)^{6,7} and have been shown to be associated with resistance to conventional EGFR tyrosine kinase inhibitors (TKIs), posing a significant challenge in the treatment of affected patients.^{8,9} Additionally, NSCLC patients harboring EGFRex20ins have a poorer prognosis than patients with other EGFR-TKI-sensitive mutations.¹⁰

The advent of immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis has revolutionized the treatment landscape for various malignancies, including lung SCC. In a clinical study that included patients with driver gene-negative resectable NSCLC, the perioperative use of nivolumab

plus chemotherapy resulted in a pathologic complete response in more patients than did chemotherapy alone.^{11,12} These results establish a new standard for the use of neoadjuvant immunotherapy combined with chemotherapy in the treatment of resectable driver mutation-negative NSCLC. However, whether neoadjuvant immunotherapy combined with chemotherapy benefits patients with driver mutation-positive NSCLC remains unknown, and the efficacy of these therapies, especially in patients with rare mutations such as EGFR ex20ins, is still under investigation.¹³

This is a case report of a patient with stage IV squamous lung cancer with an EGFR ex20ins mutation and concurrent high PD-L1 expression who underwent transformative surgery after chemotherapy combined with immunotherapy and achieved pathological complete response (pCR). Immunotherapy in combination with chemotherapy was used in this case for the first time as a new modality for oncogene mutation-positive patients to enable transformative surgery and achieve disease-free status.

Case presentation

A 58-year-old Asian male with a history of hypertension was admitted to the hospital on February 22, 2023, where he presented with a two-month history of coughing accompanied by

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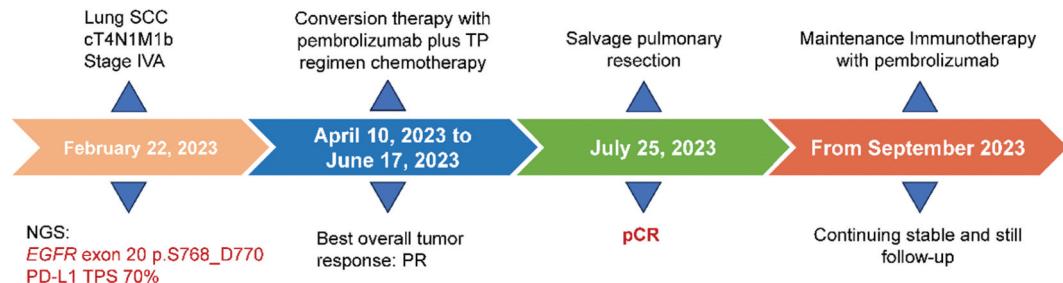


Figure 1. Treatment process of this patient from the time of diagnosis.

bloody sputum. The patient had no history of smoking or alcohol consumption. The patient's integrated clinical care process is shown in Figure 1. Initial diagnostic efforts included a PET/CT scan on March 31, 2023, revealing a soft tissue mass in the anterior basal and lateral basal segments of the left lower lung lobe with increased glucose metabolism, suggesting malignancy with surrounding obstructive inflammation and atelectasis; possible involvement of the adjacent pleura and diaphragm; left pulmonary hilar lymph node metastasis; right adrenal metastasis; and left pleural effusion (Figure 2).

Subsequent pathological examination was undergone on April 4, 2023, which revealed poorly differentiated carcinoma at the opening of the anterior and lateral basal segments of the left lower lobe (Figure 3a). The lesion was further characterized as poorly differentiated squamous cell carcinoma through immunohistochemical staining [positive for P40 and CK5/6 and Ki-67 (60% positive) and negative for TTF-1, Napsin A, and CEA] (Figure 3b–g).

Following the diagnosis of cT₄N₁M_{1b} lung squamous cell carcinoma, the patient underwent the first cycle of chemotherapy (albumin-bound paclitaxel 400 mg and cisplatin 100 mg) on April 10, 2023 accompanied by symptom-based supportive care. Genetic testing via next-generation sequencing on April 14, 2023, revealed an *EGFR* exon 20 p.S768_D770 duplication (Table 1), and a PD-L1 tumor proportion score (TPS) of

70% was detected via immunohistochemical staining (DAKO, 22C3) (Figure 3h).

The subsequent treatment cycles commenced on April 29, May 24, and June 17, 2023 and involved a combination of chemotherapy and immunotherapy, specifically, albumin-bound paclitaxel 450 mg on Day 1 plus carboplatin 550 mg on Day 1 and pembrolizumab 200 mg every 3 weeks. The patient experienced severe grade IV myelosuppression during treatment, necessitating leukocyte-boosting therapy. After 4 cycles of chemotherapy combined with immunotherapy, the primary tumor shrank dramatically, and the right adrenal metastasis disappeared completely (Figure 4).

On 25 July 2023, the patient underwent conversion surgery after multidisciplinary treatment, consisting of a left lower lobectomy with lymph node dissection, left upper lobe wedge resection, and partial diaphragm resection under video-assisted thoracoscopic surgery, which was modified to an open-thorax operation due to severe pleural adhesions. Postoperative pathology revealed no cancer tissue in the left lower lobe and significant necrosis, inflammatory cell infiltration, perifibrotic tissue growth, foam cell aggregation, occasional multinucleated giant cells (indicative of chemotherapy effects), and chronic inflammation with fibrotic tissue growth in the left upper lobe. An examination of a frozen section of the bronchial stump of the left lower lobe and a diaphragmatic

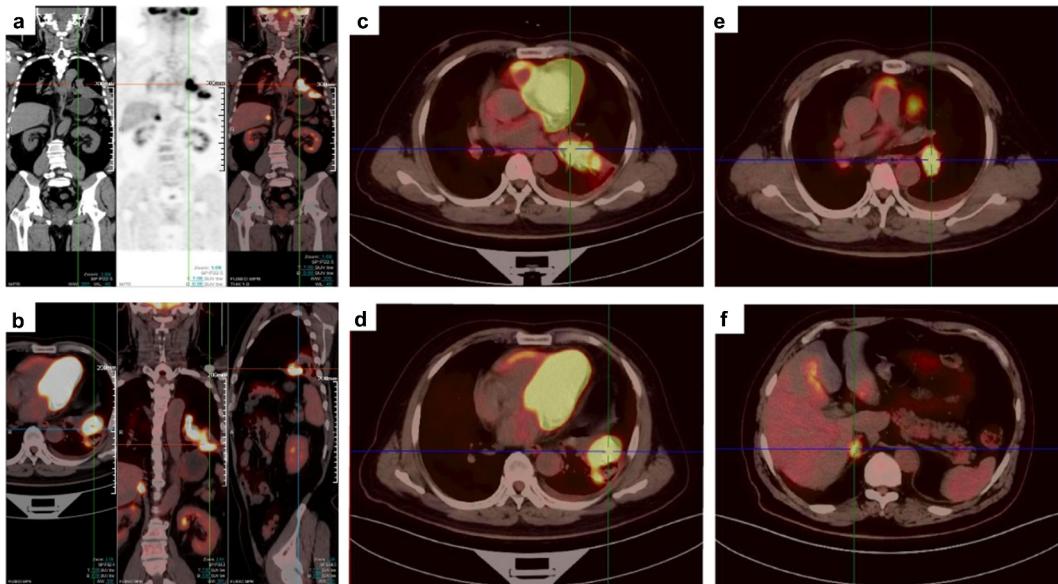


Figure 2. PET/CT examination at baseline. (a–b) Coronal imagings of tumor including soft tissue mass in the left lower lobe, lymph node metastasis and right adrenal metastasis. (c–d) Primary tumor at the left lower lobe. (e) Left pulmonary hilar lymph node metastasis. (f) Right adrenal metastasis.

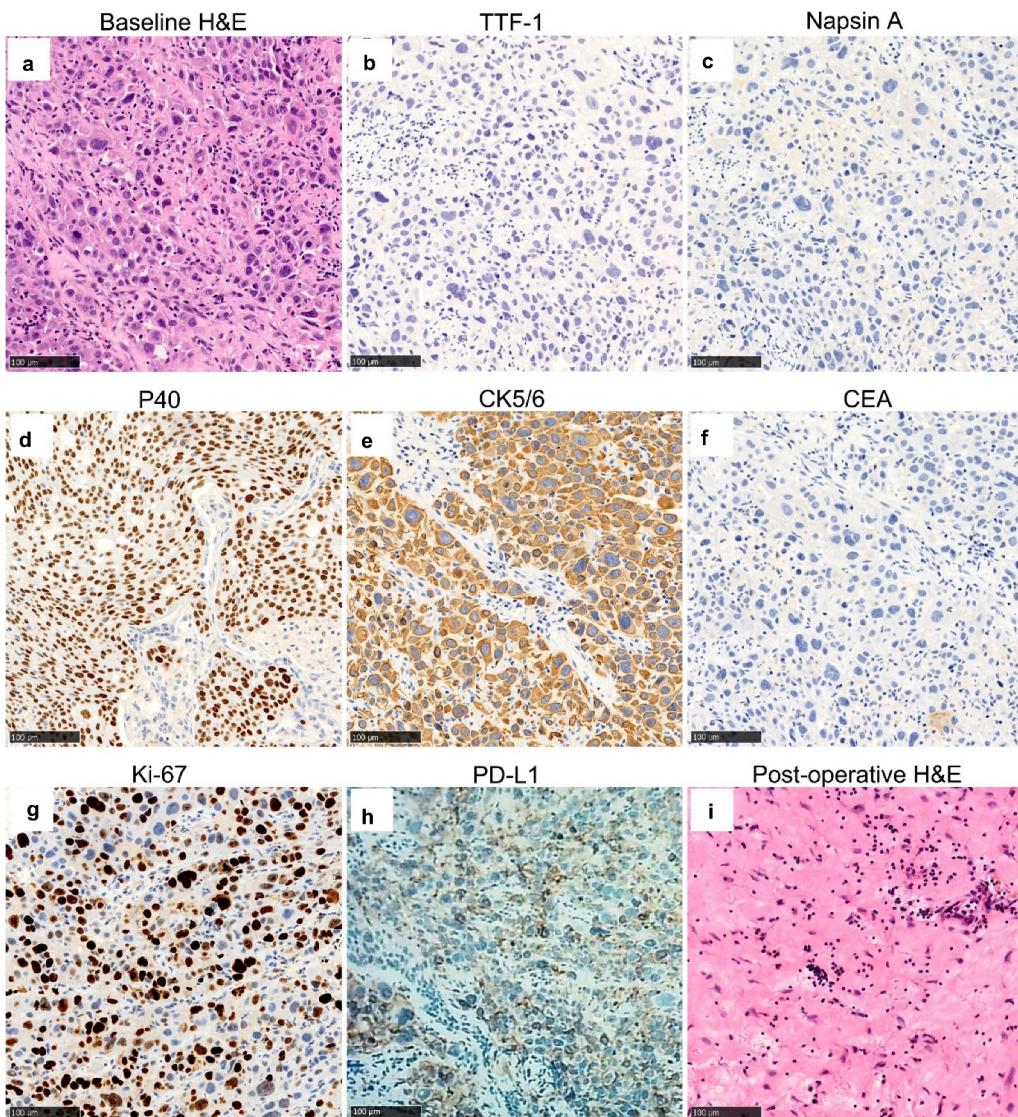


Figure 3. Histopathological H&E staining and immunohistochemical staining images of this patient. All these images were scanned using Nano Zoomer S210 (Hamamatsu). (a) H&E staining of bronchoscopic biopsy of primary tumor at baseline. (b–h) Immunohistochemical staining images of TTF-1 (negative), Napsin A (negative), P40 (positive), CK5/6 (positive), CEA (negative), Ki-67 (60% positive), and PD-L1 (TPS 70%) at baseline. (i) Post-operative H&E staining showed no residual tumor after conversion therapy.

Table 1. Genetic mutation profiles of the patient revealed by next-generation sequencing.

Gene	Transcript	Exon	Nucleotide change	Amino acid change	Mutation frequency
EGFR	NM_005228.4	exon20	c.2303_2311dup	p.S768_D770dup	29.49%
TP53	NM_000546.5	exon6	c.646G>A	p.V216M	23.38%
TP53	NM_000546.5	IVS5	c.560-1G>A	/	28.6%
NTRK1	NM_002529.3	exon8	c.1040G>A	p.R347H	8.38%
ROS1	NM_002944.2	exon31	c.5086T>G	p.Y1696D	18.40%

nodule revealed no cancer tissue, with fibrotic tissue growth and localized necrosis in the diaphragmatic nodule. All examined lymph nodes were free of cancer. The treatment outcome was evaluated as a pathological complete response (pCR) (Figure 3i). The tumor stage of this patient decreased from baseline cT₄N₁M_{1b} to post-operative ypT₀N₀M_x.

Following surgery, the patient resumed pembrolizumab monotherapy (200 mg IV drip every 3 weeks) from September 7, 2023. As of May 7, 2024, follow-up examinations of CT scans revealed no evidence of disease, and no immune-

related adverse effects including myocarditis, hepatitis, pneumonia, hypothyroidism and hyperthyroidism were discovered confirmed by the results of echocardiogram, complete blood count and comprehensive metabolic panel, CT scans, and thyroid functions, respectively.

Discussion

Neoadjuvant PD-1 blockade plus chemotherapy has become the standard treatment strategy for patients with oncogene

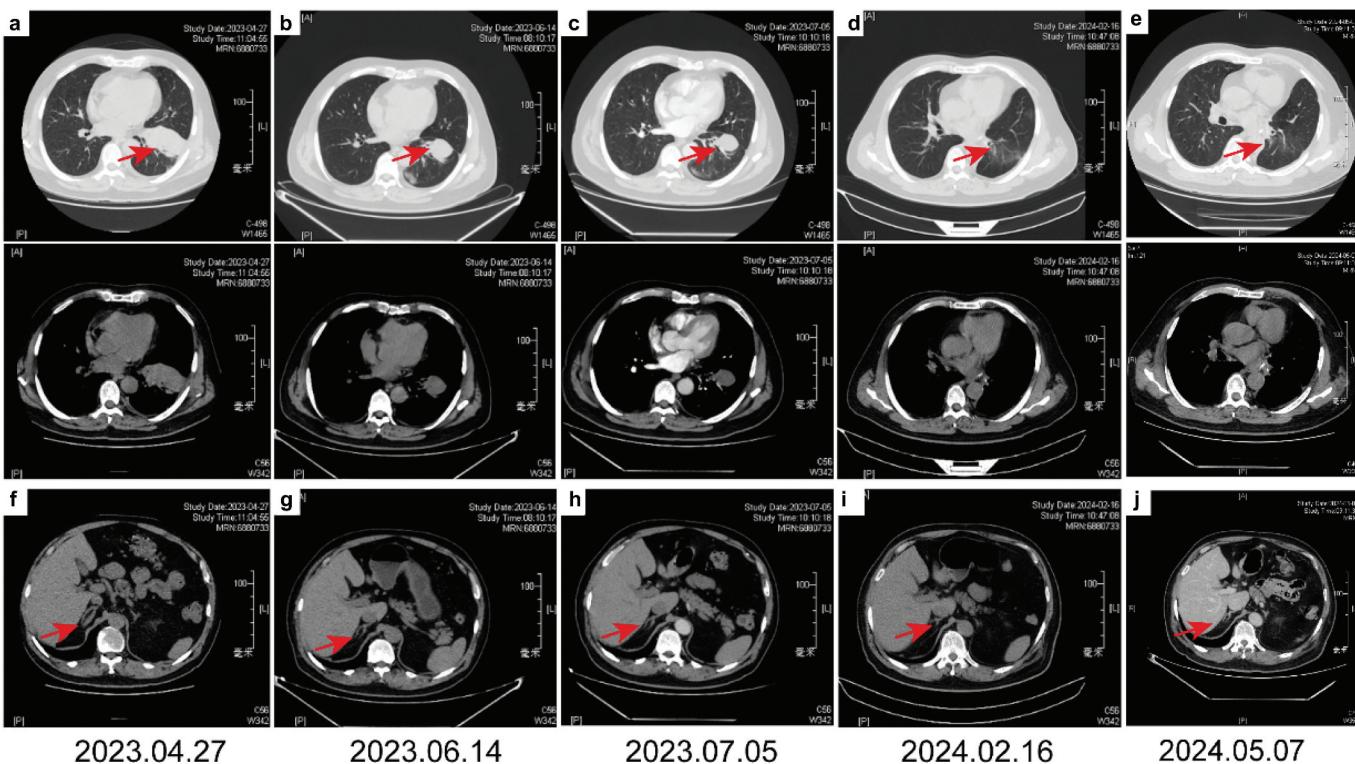


Figure 4. CT scanning of the patient. (a) After the first cycle of conversion therapy. (b) After the second cycle of treatment. (c) Significant decrease in primary tumor mass after the fourth cycle of treatment. (d–e) Post-operative follow-up. (f–h) Corresponding radiographic images of responses of the metastatic lesion in the right adrenal gland, with the presence of metastasis at baseline, and subsequent images showing post-treatment PR, and finally the absence of metastasis (cCR).

mutation-negative, potentially resectable stage IB-IIIA NSCLC on the basis of the results of recent phase III clinical trials,^{14,15} but these studies mostly excluded patients with oncogene mutations. For potentially resectable NSCLC patients harboring oncogene alterations, including *EGFR/ALK* alterations, neoadjuvant immunotherapy plus chemotherapy is not generally recommended, and only several phase II and retrospective studies have explored the efficacy and safety of neoadjuvant immunotherapy plus chemotherapy,^{16–19} as presented in Table 2. Additionally, the efficacy and safety of neoadjuvant targeted therapies with corresponding TKIs plus chemotherapy in this subgroup are not satisfactory and are still under exploration.^{20–22} In our previous study, we focused on the efficacy of different neoadjuvant treatment regimens in oncogene-positive NSCLCs, and we found that neoadjuvant chemoimmunotherapy had superior surgical outcomes (pCR/MPR rates) comparing with neoadjuvant chemotherapy/TKIs therapy, even though the sample size was limited.¹⁸ However, owing to the lack of subgroup analysis of patients harboring

EGFR ex20ins alterations in the above studies, whether pre-operative PD-(L)1 blockade-based immunotherapy will benefit patients with partially resectable NSCLC harboring *EGFR ex20ins* is not clear.

Currently, for advanced or unresectable NSCLC patients harboring *EGFR ex20ins* alterations, first-line treatment options include platinum-based chemotherapy alone or in combination with dual-drug targeted therapy or targeted therapy alone. The efficacy of PD-(L)1 blockade-based immunotherapy in these patients remains less clear owing to the lower immunogenicity of *EGFR-mutant* NSCLCs.²³ Targeted therapies for *EGFR ex20ins* alterations, including mobocertinib and amivantamab, both of which are indicated to have moderate efficacy in this subgroup.^{4,24} In the neoadjuvant setting, the selection of neoadjuvant therapy plans is primarily based on the tumor stage, whether the patients harbor oncogene alterations and what the specific oncogene alterations are, as well as the considerations from multidisciplinary discussions. Commonly, neoadjuvant chemotherapy combined with

Table 2. Summary of recent studies focusing on neoadjuvant PD-(L)1 blockade plus chemotherapy in *EGFR-mutant*, locally advanced NSCLC.

Study	Oncogene mutations	Number of patients	MPR rates	pCR rates
CTONG2104. ¹⁹	<i>EGFR 20ins</i>	8	37.5% (1/8)	12.5% (1/8)
	<i>EGFR 19del/21L858R</i>	10	30.0% (3/10)	20.0% (2/10)
	Other uncommon	4	50.0% (2/4)	25.0% (1/4)
Zhang et al. ¹⁶	<i>EGFR 17-25ins</i>	4	0	0
	<i>EGFR 19del/21L858R</i>	15	53.3% (8/15)	13.3% (2/15)
Zhao et al. ¹⁷	<i>EGFR 17-25ins</i>	4	0	0
	<i>EGFR 19del/21L858R</i>	7	0	0
Zhang et al. ¹⁸	<i>EGFR 19del/21L858R</i>	2	50.0% (1/2)	0
	Uncommon	1	0	0

immunotherapy are not recommended for the resectable NSCLC patients harboring sensitive *EGFR* mutations and *ALK* rearrangements. While the treatment strategies for *EGFR* ex20ins-mutant, locally advanced NSCLCs remain under exploration. In this case report, we highlight a novel approach for treating an NSCLC patient harboring *EGFR* ex20ins with concurrent high PD-L1 expression who achieved a pCR following preoperative conversion therapy with immunotherapy plus chemotherapy, suggesting the potential efficacy of chemoimmunotherapy in locally advanced NSCLCs harboring rare or complex mutations, including *EGFR* ex20ins.

In the neoadjuvant setting, a high PD-L1 TPS has been proven to be associated with a better tumor response with higher pCR and major pathological response (MPR) rates,²⁵ but the correlations in oncogene-mutant cohorts are unclear. In this case, the patient had high PD-L1 expression with a TPS of 70% and a satisfactory tumor response to preoperative PD-1 blockade with pembrolizumab plus chemotherapy, suggesting that immunotherapy plus chemotherapy is a neoadjuvant option for similar patients, especially those with rare oncogene alterations and concurrent high PD-L1 expression. Moreover, the researches of tumor immune microenvironment may reveal why some patients harboring oncogene alterations can respond well to neoadjuvant chemoimmunotherapy.

For NSCLC patients with isolated adrenal, bone, or brain metastatic lesions, surgical operations should be strongly considered if the primary tumor in the lung is considered potentially resectable. In this case, although the primary lesion of the patient (T₄N₁) was initially unresectable, significant tumor downstaging of the primary tumor was achieved, and disappearance of the oligometastatic lesion in the right adrenal gland was observed after four cycles of preoperative chemoimmunotherapy, ultimately allowing for successful surgical resection, which resulted in a pCR. These findings emphasize the importance of considering conversion therapy in stage IV NSCLC patients with isolated metastases.²⁶

Notably, this patient achieved a clinical complete response (cCR) in the metastatic lesion in the right adrenal gland after four cycles of conversion immunotherapy plus chemotherapy, and subsequent maintenance immunotherapy with pembrolizumab was administered instead of local consolidation therapy. Even though this patient achieved a no evidence of disease status following preoperative chemotherapy plus immunotherapy, the appropriate duration of maintenance immunotherapy remains to be determined. Considering that this patient had baseline stage IV disease, the treatment duration of pembrolizumab should be prolonged to two years according to the pattern of advanced NSCLCs in the KEYNOTE-407 trial,²⁷ rather than the adjuvant pattern of earlier-stage NSCLCs in the KEYNOTE-671 trial.^{15,28} Additionally, incorporating novel minimal residual disease (MRD) testing could aid in guiding postoperative adjuvant therapy and monitoring disease relapse, potentially allowing timely intervention.^{29,30}

Conclusion

In conclusion, this successfully treated case highlights the challenges and potential value of neoadjuvant immunotherapy plus chemotherapy for the treatment of *EGFR* exon 20 insertion-

mutant lung cancer, and prospective clinical trials with larger sample sizes are warranted to validate these findings in the future.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Notes on contributor

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Author contributions

Mingjin Xu, data curation, writing – original draft. Xingfa Huo, data curation, visualization and writing – original draft. Chuantao Zhang, data curation and writing – original draft. Xuchen Zhang, writing – original draft. Huiyun Wang, data curation. Hongmin Yang, data curation. Nan Ge, data curation. Yongjie Wang, data curation. Helei Hou, conceptualization, data curation, funding acquisition, validation, writing – review & editing. All authors read and approved the final manuscript.

Compliance with ethical standards

The protocol of this case report study was reviewed and approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (Approval No. QYFWZLL27970). The subject gave informed consent for inclusion before participated in the study. The study was conducted in accordance with the Declaration of Helsinki.

Data availability statement

All relevant data are within the paper.

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