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## CASE REPORT

# Long response to camrelizumab in metastatic lung squamous cell carcinoma with high PD-L1 expression despite EGFR G719S mutation: A case report

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## *Abstract*

*Immune checkpoint inhibitors (ICIs) have been widely used in non-small cell lung cancer with wildtype EGFR/ALK genes. However, the effect of ICIs on advanced NSCLC with EGFR genes sensitive mutations has been controversial. There are no reports on whether ICIs monotherapy can be used in the treatment of NSCLC with EGFR sensitive mutations. A patient with metastatic lung squamous cell carcinoma with EGFR G719s mutations, high PD-L1 score and a tuberculosis history was given first-line treatment of afatinib, camrelizumab monotherapy (200 mg, intravenous, once every three weeks) from February 24,2020 to January 2023. The patient achieved partial response (PR) after treatment with camrelizumab. The progress-free survival (PFS) due to camrelizumab monotherapy was more than 34 months.It is concluded that camrelizumab has promising potential effectiveness as a treatment option for lung squamous cell cancer with EGFR G719 mutations and high PD-L1 score.*

***Keywords:*** *Prolonged response, Immuno-checkpoint suppressor, Lung cancer; EGFR mutation, Progress-free survival, Camrelizumab, Afatinib*



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## INTRODUCTION

At present, ICIs are widely used in the treatment of non-small cell lung cancer (NSCLC), whether as neoadjuvant therapy and postoperative adjuvant therapy for early-stage patients, or as first-line and secondary therapy for late-stage NSCLC. However, ICIs have produced clinical efficacy in patients with wildtype EGFR/ALK genes [1]. In NSCLC subjects having EGFR gene-sensitive mutation, ICI is ineffective in the first line of treatment, but the incidence of fatal adverse effects are also increased [2]. In the second-line and post-line treatment of NSCLC patients with EGFR gene-sensitive mutations, ICIs achieve certain efficacy only after TKI-targeted resistance therapy, in combination with chemotherapy and bevacizumab [3,4].

Therefore, in the second-line management of NSCLC patients with EGFR gene-sensitive mutations, the efficacy of ICIs alone has remained controversial, and no special clinical studies have been conducted in this respect.

Camrelizumab is a humanized monoclonal antibody against PD-1. It has produced good efficacy in first-line combined chemotherapy for non-small cell lung cancer without EGFR/ALK mutations [5,6]. As secondary treatment for NSCLC devoid of EGFR/ALK mutation, clinical studies have demonstrated that Camrelizumab is also an effective drug [7]. However, not much is known about its therapeutic effect in NSCLC patients having EGFR gene-sensitive mutations.

This case is that of a patient who had Metastatic Lung Squamous Cell Carcinoma （MLSCC） with EGFR G719 mutation and high expression of PD-L1. Afatinib-targeted treatment was given as first-line therapy. The second-line treatment was camrelizumab monotherapy, and the PFS exceeded 34 months.

## CASE PRESENTATION

The present investigation received approval from the ethical authority of Gaoxin Hospital of the First Affiliated Hospital of Nanchang University, Nanchang City, China (approval no. 1022033), and it met the guidelines of the Declaration of Helsinki [8]. The patient involved in this case report gave his informed consent authorizing use and disclosure of his health information.

The patient was a 78-year-old man with a history of tuberculosis and a poorly differentiated lung squamous cell carcinoma (Figure 1). The primary tumor appeared in the left upper lung (Figure 2 A). Numerous metastatic lesions were identified in pleural and bilateral mediastinal lymph nodes (Figure 2 B), left adrenal gland (Figure 2 C) and retroperitoneal lymph nodes (Figure 2 D).

Immunohistochemistry evaluation of lung-biopsy-tumor-tissue using PD-LI identified 98 % TPS (Figure 3). Using large gene new generation sequencing (NGS) panel analysis, molecular screening of lung-biopsy tumor tissue resulted in identification of EGFR gene G719S mutation with 14.45 % allelic frequency, and PIK3CA gene p.E545q mutation with 0.86 % allelic frequency.

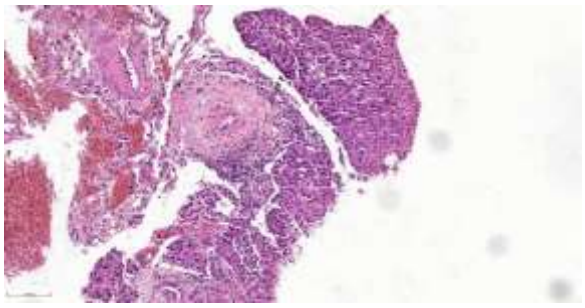

**Figure 1:** Pathological evaluation. Poorly-differentiated squamous cell carcinoma (x100)

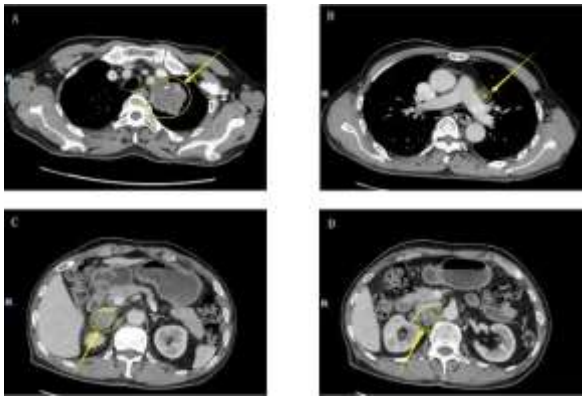

**Figure 2:** Initial computed tomography images. Computed tomography scans showing (A) left upper lung mass (5.8×5.1 cm); (B) mediastinal lymph node metastasis (1.3×1.6 cm); (C) right adrenal gland metastasis (3.3×2.5 cm), and (D) retroperitoneal lymph node metastasis (3.0×2.7 cm)

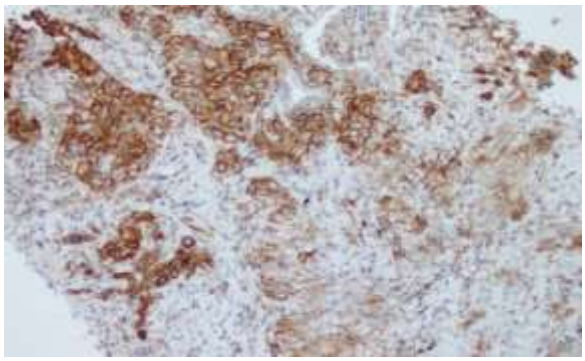

**Figure 3:** PD-L1 immunohistochemistry evaluation. TPS=98 % (x 100)

The EGFR gene G719S is a rare mutation site which accounts for only 2-3 % of EGFR-sensitive mutations in NSCLC [9]. It is even rarer in lung squamous cell carcinoma. The second and third-generation EGFR-TKI are effective drugs against this mutation site [10,11]. As first-line treatment, afatinib (40 mg, po, once a day) was given to the patient from September 20, 2019, to January 31, 2020. After 2 months of afatinib treatment, CT evaluation showed a partial response (Figure 4). On January 31, 2020, another CT evaluation indicated disease progression. The progress-free survival due to afatinib treatment was 4.1 months.

On February 20, 2020, NGS gene test on peripheral blood showed EGFR gene G719S mutation, while the other genes, i.e., ALK, ROS-1, RAS, BRAF, MET, PIK3CA, RET, NTRK1-3, and ERBB2 had no significant mutations. Considering the patient's advanced age, poor chemotherapy tolerance, refusal of chemotherapy, and PD-L1 (TPS = 98%), intravenous camrelizumab monotherapy (200mg)

was given once every three weeks, from February 24, 2020. After 3 cycles of camrelizumab monotherapy, CT was used to evaluate treatment efficacy, and it showed significant shrinkage of the tumor (Figure 5). After 2 years of camrelizumab treatment, the dose was adjusted to 200 mg q6w, to date. The disease is still responding to therapy. The progress-free survival due to camrelizumab monotherapy was more than 34 months.

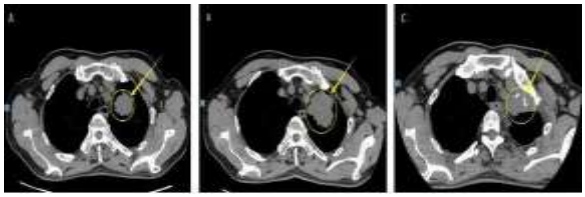

**Figure 4:** Re-examination of CT. A: After 2 months of afatinib treatment, CT showed that the mass in the left upper lung was reduced (4.5×3.9 cm), but it was increased after 4 months of Afatinib treatment (B, 5.2×4.4 cm). Then, after 2 months of treatment with camrelizumab, the mass was significantly decreased (C, 3.9×2.7 cm)

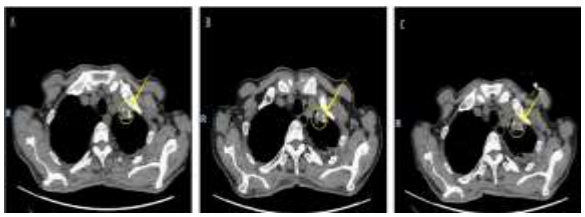

**Figure 5:** Re-examination of tumor using CT**.** After 1 year of camrelizumab treatment, the mass in the left upper lung was shrunk (A, 2.2×1.5 cm), and it remained well-controlled after 2 years (B, 2.2×1.4 cm). The last re-examination was on September 14, 2022, 3 years after diagnosis, and the mass in the left upper lung was still in a stable state (C, 2.4×1.5 cm)

## DISCUSSION

In NSCLC, the incidence of EGFR gene-sensitive mutation is very low, accounting for only 3 - 6.9 %, while in lung adenocarcinoma, the incidence of EGFR gene-sensitive mutation may reach 50 - 60 % [10]. Mutations in G719S of EGFR gene account only for 2 - 3 % of EGFR-sensitive mutations [9]. In non-small cell lung cancer, only 29.6 % of the population have PD-L1 expression greater than 50 % [1,12]. The subject in this study is an extremely rare case of an elderly patient with metastatic lung squamous cell carcinoma complicated with EGFR gene G719S mutation and PD-L1 expression of up to 98 %.

Targeted therapy still remains the 1st-line treatment for lung squamous cell carcinoma with EGFR/ALK/ROS-1 sensitive mutation. For EGFR gene G719S mutation, the objective response rate of afatinib treatment reached 77.8 %, with a PFS of 13.8 months and an OS of 26.9 months [11]. In this case, the PFS of afatinib was only 4.1 months, which was considered to be related to the presence of PIK3CA mutation. The PIK3CA mutation is associated with TKI drug resistance [13].

The present treatment strategy for NSCLC with gene-sensitive mutation after resistance to first-line TKI therapy requires repeated biopsy and re-genetic testing to find out whether there are available therapeutic targets. If there is still no opportunity for targeted therapy, the treatment model of patients with negative driver genes should be combined with chemotherapy. Chemotherapy alone, chemotherapy in combination with immunotherapy, or chemo-therapy in combination with bevacizumab is used. In the IMPOWER150 study [3], Atezolizumab was used in combination with Bevacizumab, and chemotherapy showed better efficacy in patients with TKI resistance and liver metastases. In the ORIENT-31 study [4], Sintilimab was used in combination with Bevacizumab and chemotherapy, and it further confirmed that the four-drug regimen was significantly superior to chemotherapy alone after TKI resistance. However, it is still unclear whether PD1/PD-L1 inhibitor immunotherapy monotherapy may be used. From the studies on first-line immunotherapy for NSCLC patients with positive driver genes, immunotherapy is not only ineffective, but it also has fatal adverse reactions [2]. As a result, no researcher has tried PD1/PD-L1 inhibitor immunotherapy monotherapy for NSCLC subjects having EGFR gene-sensitive mutations.

Camrelizumab, a PD1 monoclonal antibody, has shown good anti-tumor effect in first-line combined chemotherapy for NSCLC, both in squamous cell carcinoma [6] and non-squamous cell carcinoma [5]. In addition, combined use of Camrelizumab with Apatinib prolonged PFS and OS of patients in second-line treatment, and showed a higher objective response rate in patients with STK11/KEAP1 mutation [7]. In this study, single-agent Camrelizumab was used as second-line therapy because of the patient's advanced age, poor tolerance to combined chemotherapy, and the patient's refusal to receive chemotherapy. Camrelizumab monotherapy was tried after the patient and family agreed and signed the informed consent form, and very good curative effect was achieved. The PFS of Camrelizumab was more than 31 months, and it remained in response. This indicates that in NSCLC patients with EGFR-sensitive mutations and high PD-L1

expression, immunotherapy alone is also a feasible treatment option. However, it remains to be seen whether this is an isolated case, or whether this effect can be achieved in other patients. There is need to confirm this through randomized controlled studies. We hope that the present case can bring hope and inspiration to researchers around the world, so as to enable them do clinical research on immunotherapy single agent after progressing in targeted therapy for NSCLC patients with EGFR-sensitive mutations.

## CONCLUSION

The results obtained in this study suggest that patients with EGFR G719 mutations and high PD-L1 score may benefit from immunotherapy, and should not be excluded from trials or clinical applications of immune checkpoint inhibitors.

## DECLARATIONS

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### *Ethical approval*

None provided.

### *Availability of data and materials*

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### *Conflict of Interest*

No conflict of interest associated with this work.

### *Contribution of Authors*

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Yuhua Wang conceived and designed the study, and drafted the manuscript. Ke Fang collected, analyzed and interpreted the experimental data. Yuhua Wang and Ke Fang revised the manuscript for important intellectual content. Both authors read and approved the final manuscript.



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