Case Report: iMDT Corner

Successful treatment of lung squamous cell carcinoma with envafolimab, a PD-L1 inhibitor combined with chemotherapy: a case report

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Background: Metastatic non-small-cell lung cancer (NSCLC) represents a significant clinical challenge and is the leading cause of cancer-related death worldwide. Immune checkpoint inhibitors (ICIs), particularly those targeting the programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) pathway, have transformed the treatment of advanced-stage NSCLC; however, their efficacy varies, and optimal strategies following initial ICI failure remain undefined. Envafolimab, a novel humanized single-domain anti-PD-L1 antibody fragment fused to an Fc domain, is the first globally approved subcutaneous PD-L1 inhibitor. Its unique structure confers advantages in terms of tissue penetration and distribution compared to conventional monoclonal antibodies.

Case Description: This report details the case of a 66-year-old male diagnosed with stage IVB (cT4N2M1c) squamous cell carcinoma of the left upper lung with confirmed hepatic metastasis. Initial immunohistochemistry revealed a tumor proportion score for PD-L1 ≥1%, prompting the following standard first-line therapy as per the guidelines: three cycles of albumin-bound paclitaxel [470 mg, day (d)1], carboplatin (568 mg, d1), and pembrolizumab (200 mg, d1). This regimen yielded inadequate disease control. Subsequently, second-line therapy comprising two cycles of gemcitabine (1.6 g, d1; 1.4 g, d8), cisplatin (40 mg, d1–3), endostar (30 mg, d1–4), and subcutaneous envafolimab (200 mg, d1) was initiated. Follow-up computed tomography (CT) imaging revealed a notable reduction in the left hilar mass and significant alleviation of the bronchial obstruction. This therapeutic response was sustained for over 6 months during envafolimab monotherapy maintenance without recurrence.

Conclusions: This case shows the potential efficacy of envafolimab-based combination therapy in achieving a clinically significant and durable response for a patient with metastatic squamous NSCLC (sq-NSCLC) who showed disease progression on first-line pembrolizumab-containing chemotherapy. It suggests that envafolimab warrants consideration as a viable treatment option in this setting, particularly following the failure of PD-1 inhibitors. Further larger clinical trials need to be conducted to confirm these findings and define its optimal role in the NSCLC treatment sequence.

Keywords: Lung cancer; envafolimab; efficacy and safety; case report

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide, and non-small-cell lung cancer (NSCLC) accounts for about 85% of all lung cancer cases (1). Currently, surgical chemotherapy and radiotherapy remain the primary treatment options for NSCLC; however, they are not suitable for metastatic NSCLC. Over the last 20 years, the introduction of targeted therapies and immunotherapy has significantly transformed the treatment approach for advanced NSCLC (2). In recent years, immune checkpoint inhibitors (ICIs) like programmed cell death protein 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) have marked a transformative phase in immunotherapy for NSCLC (3).

Envafolimab was the first PD-L1 inhibitor approved in China and the first subcutaneously injectable PD-L1 inhibitor approved globally (4). It is an innovative fusion protein comprising two main components: a humanized single-domain anti-PD-L1 antibody and a human immunoglobulin G1 (IgG1) fragment crystallizable (Fc) fragment (5). Envafolimab has shown superior tissue penetration, allowing for consistent distribution in tumor tissues in contrast to conventional monoclonal antibodies (6). Preclinical research indicates that elevated levels of envafolimab successfully stimulate cytokine release in T cells, and envafolimab has enhanced anti-tumor effectiveness at similar doses compared to durvalumab (7).

This report examines a case involving a patient with metastatic NSCLC who underwent successful treatment using a combination of envafolimab and chemotherapy. This case study enhances our knowledge regarding the safety and efficacy of envafolimab in this specific group of patients. We present this article in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-2025-2073/rc).

Highlight box

Key findings

- A 66-year-old male with metastatic lung squamous cell carcinoma [programmed cell death-ligand 1 (PD-L1) tumor proportion score ≥1%] successfully underwent salvage therapy after pembrolizumab plus chemotherapy failure.

What is known, and what is new?

- Programmed cell death protein 1 (PD-1)/PD-L1 inhibitors (e.g., pembrolizumab) are the standard first-line therapy for metastatic non-small-cell lung cancer (NSCLC); however, treatment options are limited after immune checkpoint inhibitor failure.
- This was the first study to document the success of a subcutaneous PD-L1 inhibitor, envafolimab, post-pembrolizumab progression.

What is the implication, and what should change now?

- Envafolimab-based regimens should be considered for PD-1/PD-L1 inhibitor-refractory NSCLC.

Case presentation

Patient information

A 66-year-old male presented to Yangzhou Hospital of Traditional Chinese Medicine (Yangzhou, China) in June 2022 with a cough and sputum, along with a history of chronic obstructive pulmonary disease (COPD). Computed tomography (CT) showed that the left hilar region was occupied, and the bronchi in the left upper lobe were obstructed. Several lymph nodes were swollen in the mediastinum and left hilum. There were also liver lesions, likely originating from the lungs (*Figure 1*). His imaging and biopsy results revealed squamous cell carcinoma in the upper lobe of the left lung (cT4N2M1C, stage IVB) with possible metastasis to the liver and bones (*Figure 2*). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from the patient's relatives for publication of this case report and accompanying images. A copy of the written consent form is available for review by the editorial office of this journal.

Clinical findings

CT showed that the left hilar region was occupied by the tumor tissue, and the bronchi in the left upper lobe were obstructed (*Figure 3*). Several lymph nodes were swollen in the mediastinum and left hilum. The positron emission tomography-CT scan revealed the presence of lung cancer in the upper lobe on the left side, accompanied by localized

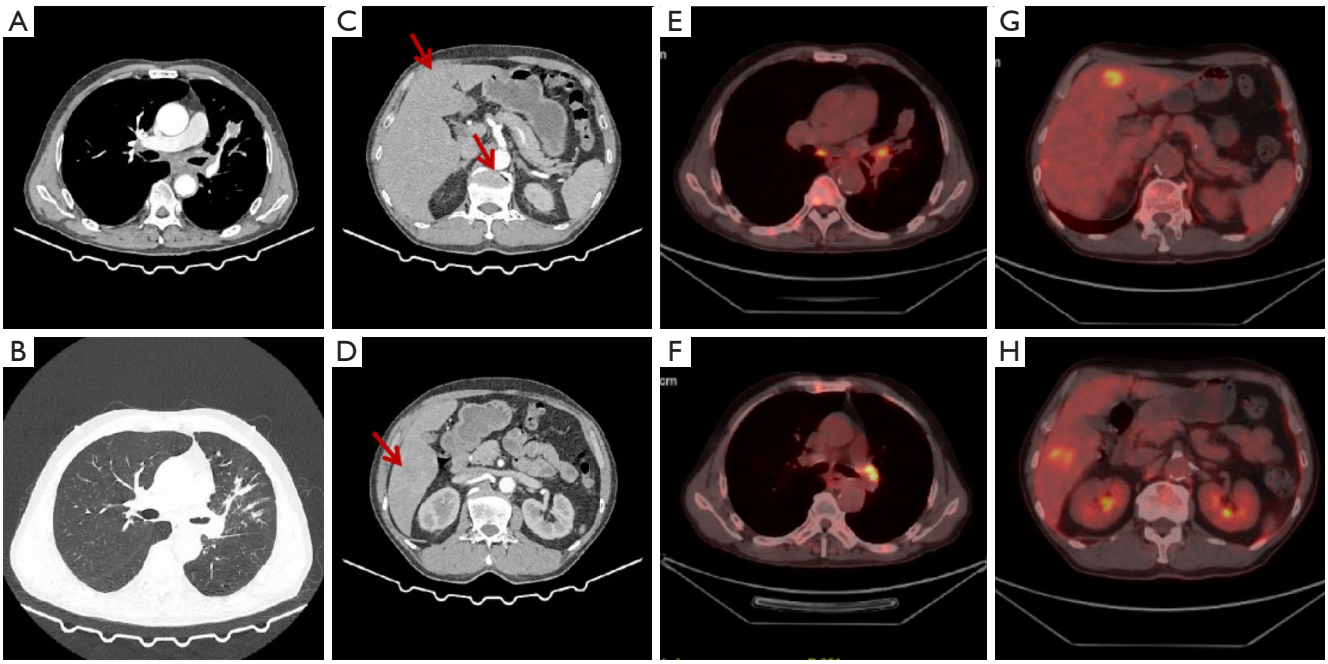

Figure 1 Chest CT and the positron emission tomography-CT before the chemotherapy. (A,B,E,F) The left hilar was occupied by the tumor tissue and part of the bronchi in the left upper lobe were obstructed. (C,D,G,H) Liver and bone metastasis. The arrows indicated the liver metastatic lesions. CT, computed tomography.

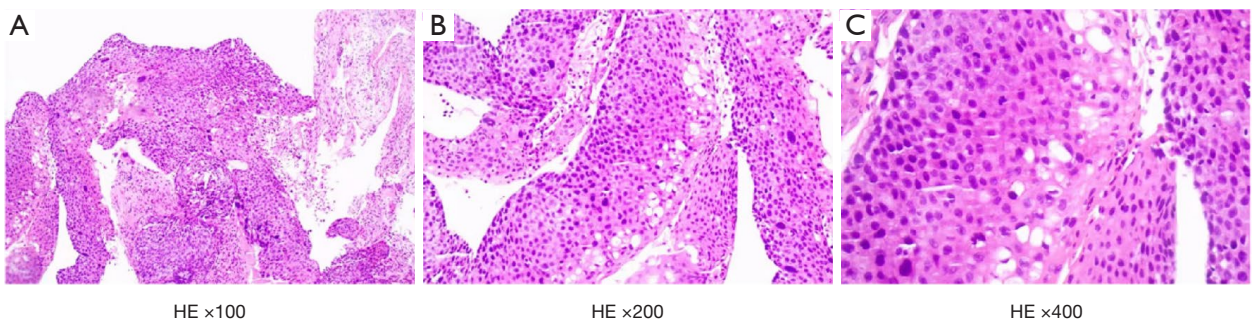

Figure 2 Pathological findings of the endobronchial ultrasound-guided biopsy. Histopathologic examination of the biopsy specimen obtained from the left upper lobe indicated squamous cell cancer. HE staining at a magnification of (A) ×100, (B) ×200, and (C) ×400. HE, hematoxylin and eosin.

obstructive inflammatory atelectasis. Lymphatic metastasis was detected in the mediastinum and the left hilar region. A liver puncture revealed the presence of malignant cells.

Timeline

A timeline for the patient is provided in *Table 1*. Notably, in June 2022, the patient presented to Yangzhou East Hospital with symptoms. In July 2022, the patient began a regimen comprising three cycles of albumin-bound paclitaxel, carboplatin, and pembrolizumab. However, this treatment proved ineffective. Sometime later, the patient commenced two cycles of a combination treatment that included gemcitabine, cisplatin, endostar, and envafolimab. The follow-up CT scan revealed a notable reduction in the mass in the left hilar region, along with a significant improvement in the bronchial obstruction. On January 13, 2023, the patient succumbed to coronavirus disease.

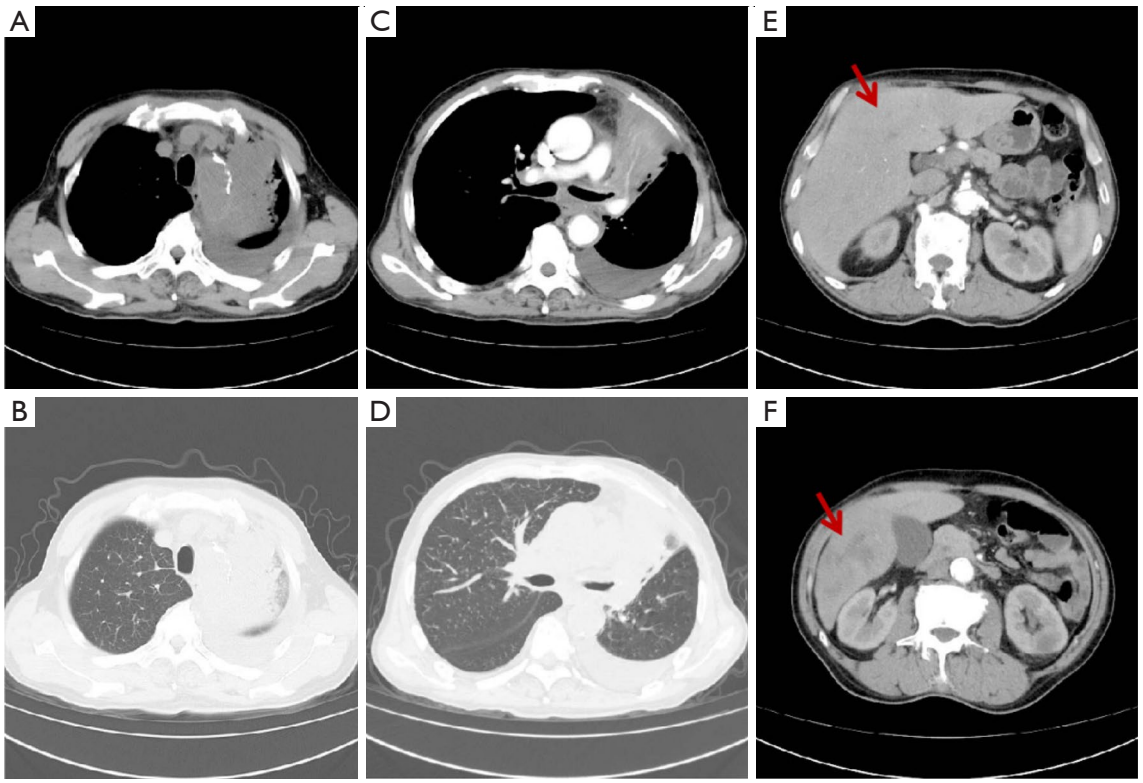

Figure 3 Chest CT after the pembrolizumab treatment. (A-D) The left hilar was occupied by the tumor tissue, which obstructed part of the bronchi in the left upper lobe. (E,F) Liver metastasis. The arrows indicated the liver metastatic lesions. CT, computed tomography.

Table 1 Timeline

Timeline	Clinical events	Interventions	Key findings
June 2022	Initial presentation with cough/sputum	Diagnostic workup	Left hilar mass with bronchial obstruction
July 2022	First-line therapy initiation	Albumin-bound paclitaxel + carboplatin + pembrolizumab (3 cycles)	Inadequate disease control
September 2022	Disease progression	Second-line: gemcitabine + cisplatin + endostar + envafolimab (2 cycles)	Significant tumor reduction
January 13, 2023	Mortality	Maintenance envafolimab	Sustained response for 6 months

Diagnostic assessment

The immunohistochemical analysis revealed that the patient's tumor proportion score for PD-L1 was at least 1%, suggesting that immunotherapy could be a viable treatment option. According to the NSCLC guidelines (version 3.2022), the recommended first-line therapy for metastatic NSCLC involves a combination of carboplatin with either paclitaxel or albumin-bound paclitaxel, alongside pembrolizumab for patients with advanced or metastatic NSCLC exhibiting PD-L1 levels between 1% and 49% (8).

Therapeutic interventions

The patient underwent three cycles of albumin-bound paclitaxel [470 mg, day (d)1], carboplatin (568 mg, d1), and pembrolizumab (200 mg, d1). Later, the patient underwent two cycles of a combination treatment that included gemcitabine (1.6 g, d1; 1.4 g, d8), cisplatin (40 mg, d1–3),

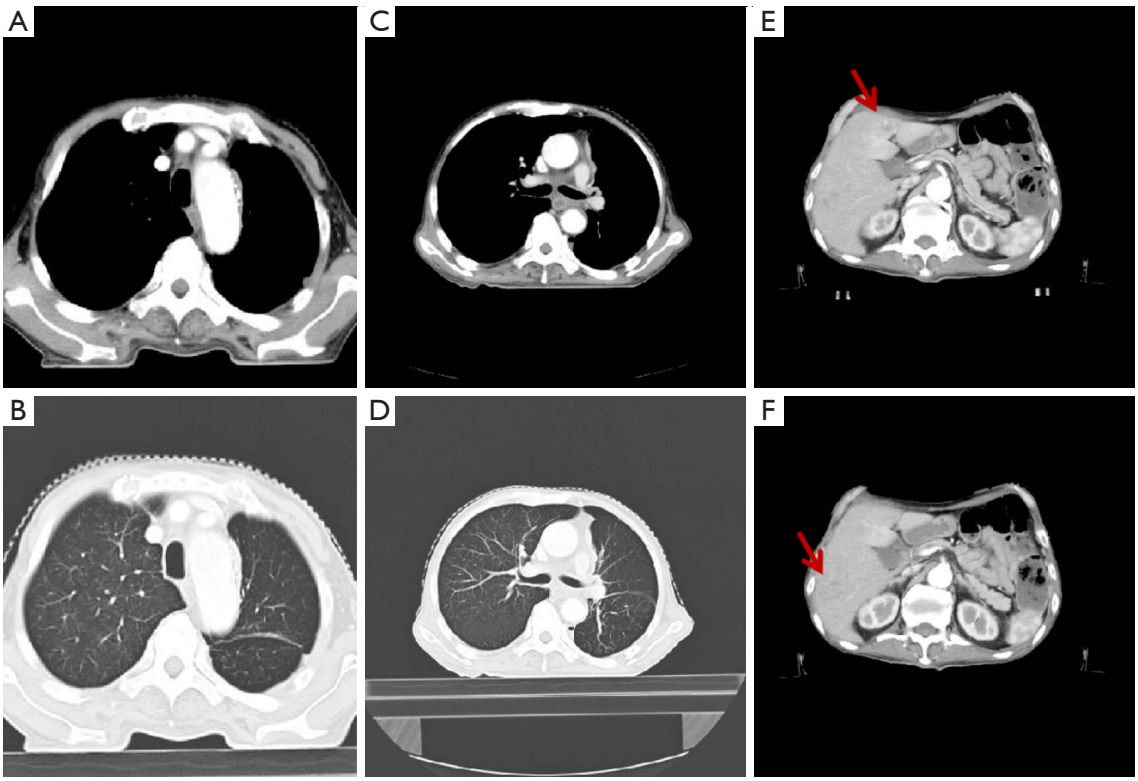

Figure 4 Chest CT after the treatment of envafolimab. (A-D) The occupying area in the left hilar was reduced, and the bronchial obstruction was distinctly alleviated. (E,F) Liver metastasis showed no significant improvement. The arrows indicated the liver metastatic lesions. CT, computed tomography.

endostar (30 mg, d1–4), and envafolimab (200 mg, d1).

Follow-up and outcomes

The follow-up CT scan revealed a notable reduction in the mass in the left hilar region, along with a significant improvement in bronchial obstruction (*Figure 4*). This therapeutic response was sustained for over 6 months without any signs of recurrence while the patient continued with envafolimab monotherapy.

International multidisciplinary team (iMDT) discussion

Discussion among physicians from Yangzhou Hospital of Traditional Chinese Medicine

Pneumology Department

Lung cancer is the leading cause of cancer-related death worldwide, and it accounts for a staggering 18% of all cancer-related deaths (9). Research has shown that ICIs substantially enhance the survival rates of NSCLC patients, including those treated with PD-1 and PD-L1 antibodies (10,11).

Recent approvals of various anti-PD-1 and anti-PD-L1 antibodies have marked a significant advance in the treatment of advanced solid tumors, boosting patients' chances of survival. Among these innovations is envafolimab, a novel concoction of a humanized PD-L1 antibody and an IgG1 Fc fragment, administered via subcutaneous injection. This heavy chain-only antibody, derived from camels, boasts a distinctive structure that sets it apart from its predecessors like pembrolizumab and nivolumab (12). The antigen-binding site is the key to its targeted action, effectively locking on and neutralizing the interaction between PD-1 and PD-L1 through its unique structure, thereby enhancing the immune response of immune system to tumors. To put it succinctly, envafolimab has a distinctive architecture, and its affinity with PD-L1 is a thousand times higher than that of PD-1 by enhancing the control of PD-L1, thereby improving its

effectiveness in immunotherapy. Its remarkable stability, lightweight nature, and deep tissue penetration make it an ideal candidate for administration via subcutaneous injection (6).

Department of Oncology

As the initial intradermal PD-L1 blocker, envafolimab has shown superior efficacy and safety outcomes compared to other authorized PD-1/PD-L1 immunomodulators (13). Following disappointments with other PD-1 inhibitors, which often fell short of expectations due to issues like disease advancement or immune-related adverse events (irAEs), envafolimab has emerged as a promising alternative after other immunotherapy drugs have failed. Previous research has shown that in patients treated with pembrolizumab, roughly 2–7% experienced immune enteritis, and 1–5% suffered from pneumonia; however, such complications were not observed among those who received envafolimab (5). This difference may be associated with the varying interactions of PD-1 and PD-L2 (14). Given these considerations, envafolimab may be more appropriate for vulnerable populations, including older adults suffering from interstitial lung disorders (15).

Akin to other PD-1 blockers, envolizumab works to combat cancer by targeting the PD-1/PD-L1 pathway. By binding to the PD-L1 expressed on tumor and immune cells, it effectively blocks the interaction between PD-L1 and the PD-1 receptor on T cells. This action lifts the tumor's hold on the T cells via the PD-1/PD-L1 signaling mechanism, and thus boosts the immune response (16). A pivotal preclinical trial (6) investigated the anti-tumor efficacy of envolizumab by analyzing T-cell responses and tumor growth suppression, and found that envolizumab has the capacity to stimulate T cells to manufacture cytokines in a concentration- and time-sensitive manner during *in vitro* mixed lymphocyte reactions. This cytokine factor is akin to that of duvaliumab; however, envolizumab has shown a robust anti-tumor response at comparable dosages, which suggests that it is a highly effective inhibitor of the PD-1/PD-L1 pathway.

In our research, we found that lung cancer patients undergoing two rounds of envafolimab therapy had significantly better outcomes than those receiving pembrolizumab. This improvement may be attributed to the targeted nature of subcutaneous administration. For metastatic NSCLC patients who also have a history of COPD, envafolimab could prove to be a more advantageous option. To sum up, envafolimab demonstrates enhanced safety and efficacy for NSCLC patients.

Several issues regarding the diagnosis and treatment of this patient were further discussed as follows

How does envafolimab compare to other PD-1/PD-L1 inhibitors in the treatment of lung squamous cell carcinoma (LUSC) in terms of its efficacy and safety?

Rossana Berardi: Envafolimab is a subcutaneous PD-L1 inhibitor that doesn't yet have phase III, lung-squamous-specific efficacy data or regulatory approval for NSCLC, so—unlike pembrolizumab, cemiplimab, atezolizumab, or nivolumab—its benefit in LUSC remains unproven. Safety so far looks similar to other PD-L1 drugs.

Atsushi Osoegawa: In a phase II study for advanced squamous NSCLC (sq-NSCLC), a triplet regimen including the novel PD-L1 inhibitor envafolimab (17) demonstrated numerically superior efficacy compared to the standard-of-care, pembrolizumab plus chemotherapy (18). The envafolimab combination achieved a median overall survival of 24.6 months, substantially longer than the 17.2 months reported for the pembrolizumab regimen in its pivotal trial. However, these results are significantly confounded by the inclusion of the anti-angiogenic agent rh-endostatin, making it difficult to isolate envafolimab's specific contribution to the enhanced efficacy. The safety profile of the envafolimab combination was manageable, with an irAE rate of 33.3%, comparable to that observed with the pembrolizumab combination. Envafolimab's primary advantages over other PD-1/PD-L1 inhibitors are its unique single-domain antibody structure, which may improve tumor penetration, and its subcutaneous administration, offering greater patient convenience than intravenous infusions. Definitive conclusions on its comparative efficacy await a randomized Phase III trial to validate these promising but preliminary findings.

Fumihiro Yamaguchi: Envafolimab is distinguished by its ultra-small single-domain structure capable of recognizing the target antigen PD-L1. This single-domain antibody has an exceptionally low molecular weight of approximately 15 kDa, which facilitates enhanced penetration into tumor tissues. It has also been reported to possess high stability under thermal and pH variations, thereby conferring favorable pharmaceutical stability. Consequently, it can be stored at room temperature and administered subcutaneously within approximately 30 seconds, which represents a significant practical advantage. Furthermore, because intravenous infusion is not required, the risk of

infusion-related reactions is effectively eliminated.

What are the common adverse effects associated with envafolimab therapy in LUSC patients?

Rossana Berardi: Envafolimab's safety profile mirrors other PD-1/PD-L1 inhibitors, and the most common TEAEs (incidence ≥10%) are:

- Hematological: anemia, decreased platelet count, decreased white blood cell count;
- Non-hematological: loss of appetite, elevated blood bilirubin, elevated liver transaminases, hyperglycemia, asthenia, decreased glomerular filtration rate, nausea, fever, skin rash, increased creatinine;
- Injection site reactions.

Atsushi Osoegawa: Based on clinical trial data, irAEs of any grade occurred in 33.3% of patients in a key trial (17), and no unexpected safety signals were identified. A separate real-world study of patients with various advanced lung cancers, including squamous cell carcinoma, provided more detail on specific envafolimab-related toxicities (19). In that study, the most common treatment-emergent adverse events related to envafolimab were rash (12.1%), pneumonitis (8.6%), increased alanine aminotransferase (an indicator of liver stress) (5.2%), and anorexia (5.2%). The most frequent types of irAEs observed were dermatologic, pulmonary, hepatic, gastrointestinal, and musculoskeletal toxicities. Considering the promising efficacy of envafolimab after the failure of a first-line ICI, as seen in the case report, the low frequency of irAEs associated with its subcutaneous injection is truly acceptable.

Fumihiro Yamaguchi: The pivotal trial supporting the approval of envafolimab was a single-arm phase II study conducted in China, enrolling patients with advanced solid tumors harboring mismatch repair deficiency or high microsatellite instability (13). Notably, no clinically significant irAEs—such as interstitial pneumonitis, colitis, severe hepatic or renal dysfunction, or serious endocrine disorders—were reported in this study.

Are there any biomarkers or predictive factors that could be used to identify which LUSC patients would respond better to envafolimab?

Rossana Berardi: Potential biomarkers or predictive factors for identifying which LUSC patients—or more broadly, NSCLC patients—might respond better to envafolimab. Among the others:

- Tumor mutational burden (TMB), microsatellite instability-high (MSI-H)/mismatch repair deficiency (dMMR), and potentially PD-L1 expression may hold predictive value for envafolimab—but strong, lung-squamous–specific validation is lacking.
- Prognostic indicators like poor performance status, advanced stage, or later-line therapy correlate with worse outcomes but aren't predictive of drug sensitivity.
- Validation in LUSC is still needed through dedicated trials to confirm whether these biomarkers truly predict benefit from envafolimab.

Atsushi Osoegawa: Envafolimab's effectiveness after resistance to a PD-1 inhibitor likely stems from three key factors. First, by selectively targeting PD-L1, it does not block the PD-1/PD-L2 interaction, potentially circumventing resistance mechanisms not solely dependent on the PD-L1 pathway and contributing to a different safety profile. Second, its unique single-domain antibody structure is smaller than conventional antibodies, allowing for superior and more rapid penetration into dense tumor tissue. Additionally, envafolimab inhibits T-cell suppression through a dual mechanism, blocking both the PD-1/PD-L1 and the PD-L1/CD80 signaling pathways. Together, these properties of a distinct target, superior tissue access, stronger binding, and dual-pathway inhibition likely combine to overcome resistance developed against prior PD-1 therapy.

Fumihiro Yamaguchi: At present, as in other solid tumors, mismatch repair deficiency and high microsatellite instability may serve as potential predictive biomarkers of therapeutic efficacy in pulmonary squamous cell carcinoma as well.

Conclusions

This case report shows the promising efficacy of envafolimab-based combination therapy in a 66-year-old male with metastatic sq-NSCLC who showed disease progression on first-line pembrolizumab-containing chemotherapy. The patient achieved a clinically significant and durable response, including a marked reduction in the left hilar mass and an alleviation of the bronchial obstruction, which were sustained for over 6 months during maintenance therapy.

The findings suggest that envafolimab, as the first subcutaneous PD-L1 inhibitor, may represent a viable treatment option for patients in whom PD-1 inhibitors fail. It may be that its unique single-domain antibody structure enables superior tissue penetration. This case supports the

favorable safety profile of envafolimab; no reported irAEs were observed.

While limited by its single-case nature, this report provides preliminary clinical evidence warranting larger trials to confirm the role of envafolimab in the NSCLC treatment sequence, particularly for PD-1/PD-L1 inhibitor-refractory cases.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-2025-2073/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from the patient's relatives for publication of this case report and accompanying images. A copy of the written consent form is available for review by the editorial office of this journal.

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