



# Complete remission of advanced lung adenocarcinoma with first-line pembrolizumab monotherapy: Two case reports

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## ABSTRACT

Immune checkpoint inhibitors (ICIs) are clinically used for treating advanced lung cancer, and some patients have achieved complete remission (CR) with ICI therapy in clinical trials. However, reports summarizing the clinical courses of such patients are limited. We report two cases of lung adenocarcinoma in which CR was achieved with first-line pembrolizumab monotherapy, and the therapeutic effect was maintained after treatment completion. Specific patients can achieve CR, even those who do not meet the previously reported predictors of treatment response other than high programmed death-ligand 1 expression. Thus, biomarkers that can accurately predict the clinical efficacy of ICIs are warranted.

## 1. Introduction

Immunotherapy with immune checkpoint inhibitors (ICIs) is clinically used for treating advanced lung cancer. Pembrolizumab, an ICI, has been proven effective as a first-line treatment for advanced non-small-cell lung cancer (NSCLC) with high expression of programmed death-ligand 1 (PD-L1; tumor proportion score [TPS]:  $\geq 50\%$ ) in the KEYNOTE 024 trial [1]. The 5-year follow-up study of the trial revealed a favorable 5-year overall survival (OS) rate of 31.9% in the pembrolizumab arm, with a response rate of 82% and 4 of the 39 patients (10.3%) who completed a total of 35 cycles over 2 years of treatment achieving complete remission (CR) [2]. However, reports summarizing the clinical course of cases with CR are limited. Here, we report two cases of lung adenocarcinoma in which CR was achieved with first-line pembrolizumab monotherapy and the therapeutic effect was maintained after treatment completion (Table 1, Fig. 1).

## 2. Case report

**Case 1.** An 87-year-old man with a history of smoking of 45 pack-years presented with blood-tinged sputum. Chest computed tomography (CT) revealed a large mass (7 cm) in the left hilar region, which was

lumped together with the left hilar lymph nodes. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed on the hilar lymph nodes, and poorly differentiated lung adenocarcinoma was confirmed by immunohistochemistry. Biomarker analysis was negative for epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) translocation, and PD-L1 was highly expressed (TPS: 90%). The clinical stage after a systemic evaluation was cT4N2M0, stage IIIB. Pembrolizumab monotherapy was initiated because the patient was not eligible for curative radiation. Although tumor progression was observed immediately before treatment, partial response (PR) was achieved after two treatment cycles, and CR was achieved after nine cycles. After 35 cycles of pembrolizumab, the patient was found to have maintained CR during treatment-free follow-up, and currently, the patient is alive 36 months after treatment initiation.

**Case 2.** A 63-year-old man with a smoking history of 43 pack-years was referred to our hospital for a detailed examination of abnormal shadows on chest radiography. Chest CT revealed an irregular nodule (15 mm) in the right upper pulmonary lobe with lymphangitic carcinomatosis and multiple enlarged right hilar and mediastinal lymph nodes. EBUS-TBNA was performed for the sub-tracheal lymph nodes, and immunohistochemistry confirmed lung adenocarcinoma. Biomarker

**Abbreviations:** ALK, anaplastic lymphoma kinase; CR, complete remission; CT, computed tomography; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PD-L1, programmed death-ligand 1; PR, partial response; RR, response rate; TPS, tumor proportion score.

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**Table 1**

Clinical and disease characteristics of the series. ALK: anaplastic lymphoma kinase; CEA: carcinoembryonic antigen; CR: complete remission; CYFRA: cytokeratin 19 fragments; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; F: female; irAE: immune-related adverse event; M: male; PR: partial response; PD-L1: programmed death-ligand 1; TPS: tumor proportion score; WBC: white blood cell.

Case	1	2
Age (years)	87	63
Sex (M/F)	M	M
ECOG PS	1	1
Smoking history	Former smoker	Current smoker
Pack-years	45	43
Histology	Adenocarcinoma	Adenocarcinoma
PD-L1 TPS	90%	70%
EGFR mutations	Negative	Negative
ALK translocations	Negative	Negative
TNM	cT4N2M0	cT3N3M1c (LYM)
Stage	IIIB	IVB
Comorbidity		
Interstitial pneumonia	None	None
Others	Diabetes mellitus	Diabetes mellitus, shoulder arthritis
WBCs (/ $\mu$ L)	7800	8700
Neutrophils (/ $\mu$ L)	6030	5420
Lymphocytes (/ $\mu$ L)	1010	2580
CEA (ng/mL)	1.7	9.0
CYFRA (ng/mL)	4.1	6.8
Treatment	Pembrolizumab	Pembrolizumab
Time to PR (months)	1.5	1.5
Time to CR (months)	6.8	9.0
irAE	None	None
Outcome	Patient maintained CR and is alive 36 months	Patient maintained CR and is alive 42 months

tests were negative for both EGFR mutation and ALK translocation, and PD-L1 was highly expressed (TPS: 70%). The clinical stage after a systemic evaluation was cT3N3M1c (LYM), stage IVB with cervical lymph node metastasis. Pembrolizumab monotherapy was initiated. PR was observed after two cycles, and CR was achieved after 12 cycles. After completion of 34 cycles of pembrolizumab (the patient skipped one cycle for his own convenience), the patient was found to have maintained CR during treatment-free follow-up and is currently alive 42 months after the start of treatment.

### 3. Discussion

The two cases described herein provide two important clinical suggestions. First, a specific group of patients with advanced NSCLC can achieve CR with pembrolizumab treatment. The superiority of first-line pembrolizumab monotherapy over platinum-based chemotherapy in patients with metastatic NSCLC having PD-L1 TPS  $\geq$ 50% and no sensitizing EGFR/ALK alterations has been demonstrated [1]. The median OS, 5-year OS rate, 3-year progression-free survival rate, response rate (RR), and median response duration were 26.3 months, 31.9%, 22.8%, 46.1%, and 29.1 months, respectively. Furthermore, CR was noted in seven patients (4.5%) in the pembrolizumab monotherapy group [2]. Regarding the patients who completed the predetermined 35 treatment courses (N = 39), the RR was 82% and CR was noted in four patients (10.3%).

Second, CR may be achieved in older patients and in those who do not meet the previously reported predictors of treatment response other than high PD-L1 expression. In the KEYNOTE 024 trial, the oldest pembrolizumab-treated patient was 90 years of age; however, the individual clinical outcome was not available due to the nature of clinical trials. The first patient reported herein was 87 years of age and achieved CR without any notable adverse events. High PD-L1 expression, a low pretreatment neutrophil-to-lymphocyte ratio (NLR), post-treatment

NLR, pretreatment radiotherapy, and immune-related adverse reactions have been reported as possible predictors of response to ICI therapy [3–8]. In both the cases reported herein, high PD-L1 expression was noted. Further, only the second patient had a low pretreatment NLR. However, no predictive biomarkers have been established for the clinical efficacy of ICI therapy, and the reason that CR was achieved in our patients remains unknown.

In summary, we reported two cases of lung adenocarcinoma in which CR was achieved with pembrolizumab monotherapy. A specific group of patients can achieve CR, even those who do not meet the previously reported predictors of treatment response other than high PD-L1 expression. Therefore, biomarkers that can accurately predict the clinical efficacy of ICIs are warranted.

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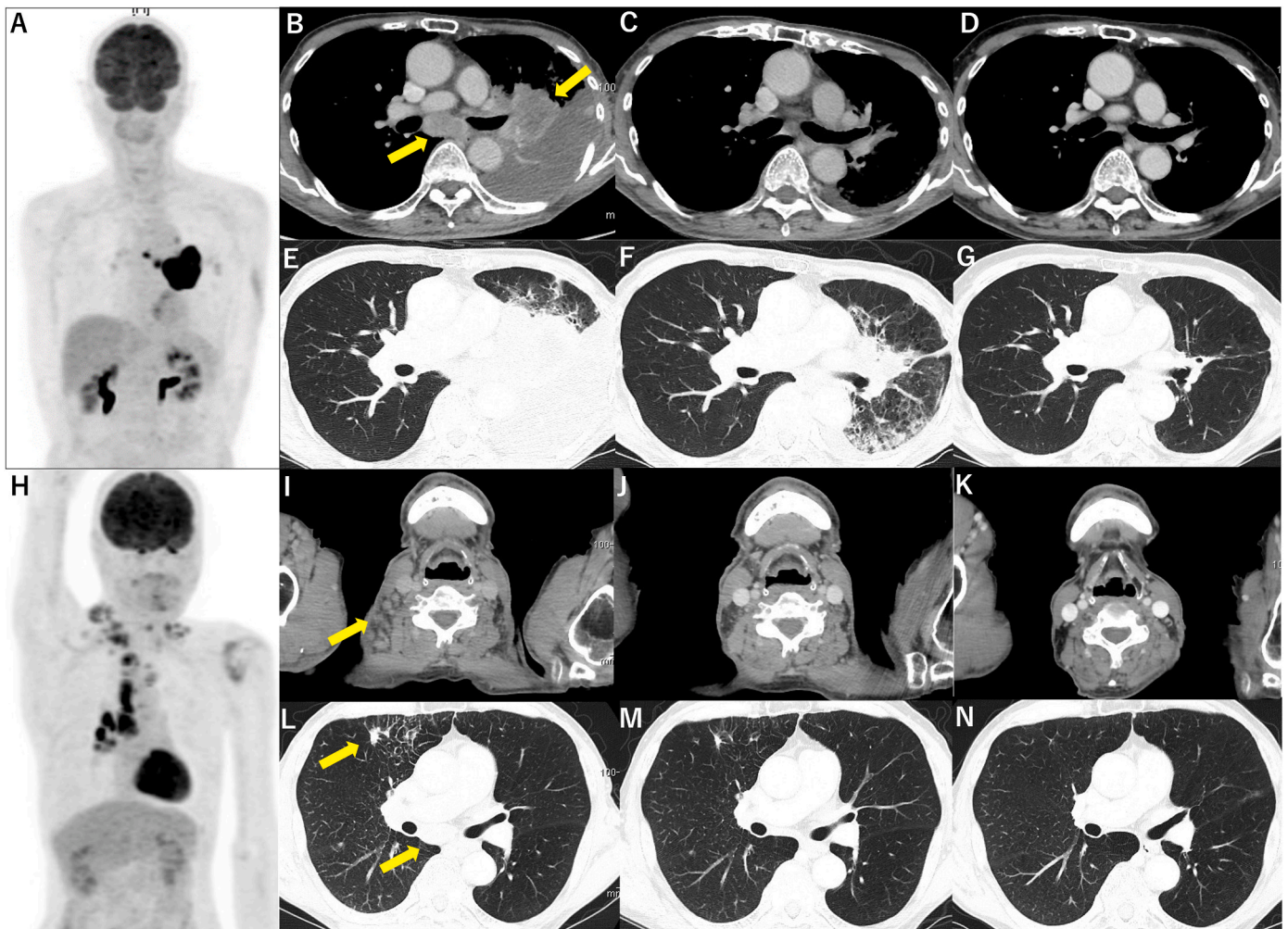
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### Author contributions

K.G. and A.O. wrote the initial draft of the manuscript. A.O. was responsible for drafting and image modification. A.O. and Y.T. performed the bronchoscopy. K.I. and K.S. were directly involved in the treatment. All authors critically revised the manuscript and approved its final version.

### Declaration of competing interest

The authors declare that there is no conflict of interest.



**Fig. 1.** Clinical course of Case 1 (A–G) and Case 2 (H–N). Case 1. Pretreatment FDG-PET showing lung cancer in the left hilar region along with left hilar and mediastinal lymph node metastases (A). Chest CT showing tumor and sub-tracheal nodules metastasis (arrowhead) worsening at the start of treatment (B, E), PR obtained after two treatment cycles (C, F), and CR maintained after the completion of 35 cycles of pembrolizumab treatment (D, G). Case 2. Pretreatment FDG-PET showing lung cancer of the right upper lobe with right hilar, mediastinal, bilateral supraclavicular, and right cervical lymph node metastases (FDG accumulation in the left shoulder is due to shoulder arthritis) (H). Chest CT showing the primary lesion and metastasis to the right cervical lymph node and sub-tracheal lymph node (arrowhead) before treatment (I, L) remarkably improving after two cycles of pembrolizumab treatment (J, M), and CR maintained after treatment completion (K, N). CR: complete remission; CT: computed tomography; FDG-PET: fluorodeoxyglucose-positron emission tomography; PR: partial response.

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