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CASE REPORT

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Unsuccessful rechallenge with nivolumab in a patient with advanced non-small cell lung cancer who had a 6-year complete response and treatment-free period: Case report

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Abstract

Several predictive factors of immune checkpoint inhibitor response have been reported, but there has not been sufficient exploration of which patients benefit from immune checkpoint inhibitor rechallenge. We report the case of a patient with non-small cell lung cancer who had 6 years of complete response with initial nivolumab treatment. After relapse, however, rechallenge with nivolumab did not result in tumour shrinkage or long-term response. Even in patients who had an exceptional response to the initial immune checkpoint inhibitor, long-term efficacy may not be achieved by immune checkpoint inhibitor rechallenge. Thorough investigation of biomarkers that predict efficacy of immune checkpoint inhibitor rechallenge is warranted.

KEYWORDS

long-term response, nivolumab, non–small cell lung cancer, rechallenge

INTRODUCTION

Immune checkpoint inhibitor (ICI) treatment is the standard of care for patients with advanced non-small cell lung cancer (NSCLC). In patients with advanced NSCLC treated with nivolumab, an ICI, the five-year pooled overall survival rate was reported as 13.4% and the five-year progression-free survival (PFS) rate was 8.0%.[1] However, disease progression often occurs despite the patients once achieving a durable response with ICIs. For such patients, it is unclear whether ICI rechallenge is effective treatment, although there are several reported resistance mechanisms to ICIs.[2] The efficacy of ICI rechallenge was suggested by previous reports to be limited in patients who required the cessation of ICI due to immune-related adverse events. Although the predictive factors of long-term response and efficacy of rechallenge with ICI have been reported in several studies, their exact values have not been established.[3] We report the case of a patient who was treated with nivolumab for 6 months and achieved 6 years of complete response (CR), but for whom rechallenge with nivolumab did not result in tumour shrinkage or long-term response.

CASE REPORT

The patient was a 61-year-old male with Eastern Cooperative Oncology Group Performance Status 1. He was diagnosed with stage IIIB lung adenocarcinoma. EGFR/ALK gene alterations were not detected, and PD-L1 IHC testing was not done. He received first-line treatment with cisplatin and pemetrexed followed by thoracic radiotherapy. After relapse, we administered second-line treatment with carboplatin and paclitaxel with bevacizumab.

After disease progression on CT scan (enlargement of multiple mediastinal lymph nodes), we initiated nivolumab (3 mg/kg) as the third-line treatment (Figure 1). After 6 months, the patient developed grade 2 interstitial lung disease. Nivolumab was discontinued and the patient responded to steroid therapy. Thereafter, without any anticancer treatment, the patient had sustained CR, and positron emission tomography-computed tomography (PET-CT) showed no fluorodeoxyglucose uptake for 6 years. However, CT scan again 6 years later showed enlargement of the right hilar lymph node. A transbronchial biopsy was performed from the right upper lobe of the lung where the same site as the

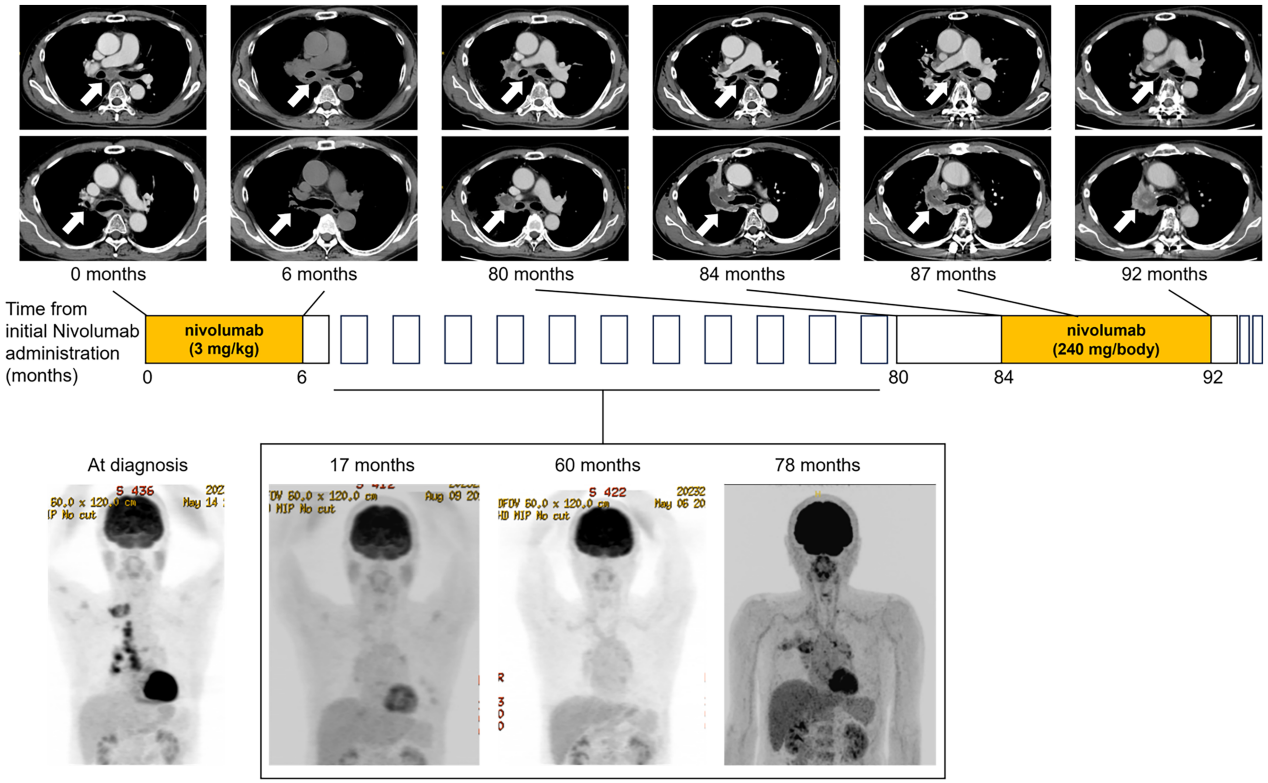

FIGURE 1 Timeline from initial nivolumab administration. The figure incorporates treatment and imaging. PET-CT revealed CR for 6 years. PET-CT, positron emission tomography/computed tomography; CR, complete response.

first biopsy and the pathological diagnosis was morphologically undifferentiated NSCLC; not otherwise specified. EGFR/ALK gene alterations were not detected, and PD-L1 tumour proportion score was 95%. Rechallenge with nivolumab (240 mg/body) was started, but it did not result in radiological shrinkage. After 8 months of treatment, CT showed enlargement of the right hilar lymph node.

DISCUSSION

Following 6 months of nivolumab treatment, our patient with NSCLC had 6 years of CR without any anticancer treatment. However, rechallenge with nivolumab did not result in tumour shrinkage or long-term efficacy. In contrast with previous reports, a treatment-free period lasting several years was not a predictor of ICI rechallenge in our patient.[3]

A phase II study of the rechallenge with ICI in patients with advanced NSCLC showed limited efficacy (ORR of 8.5% and median PFS of 2.6 months), wherein five responders showed 11.1 months of median PFS. Longer ICI-free interval (>9.2 months) was the only predictor of efficacy of an ICI rechallenge.[3] Elsewhere, a retrospective study showed that ICI rechallenge in eight patients with advanced melanoma with CR for more than 1 year to initial ICI therapy achieved CR or PR in five patients (ORR 63%). Four of the five responders had sustained tumour shrinkage for more than 1 year.[4] The reported efficacy of ICI rechallenge in patients with long ICI-free interval to initial ICI is encouraging, but nevertheless, our patient had no tumour shrinkage and PFS was only 8 months. Prospective data is required to identify biomarkers that predict efficacy of ICI rechallenge.

Regarding the initial ICI administration, a previous study showed that non-squamous histology and depth of response were the predictive factors of long-term response, which is similar to our case.[5] In addition, the translational approach reported that higher tumour mutation burden was related to long-term efficacy with ICI, whereas high PD-L1 expression did not. On the other hand, a recent study revealed that acquired genomic mutations (i.e., loss of function mutations in *STK11*, *B2M*, *APC*, *MTOR*, *KEAP1*, and *JAK1/2*) and decreases of tumour infiltrating lymphocytes were found in patients who had become resistant to PD-L1 inhibitor.[2] Clarifying the mutational status and microenvironmental circumstances among patients who receive ICI rechallenge is still difficult, but this effort could result in important clues to identify appropriate patient populations.

AUTHOR CONTRIBUTIONS

Toshiaki Takakura: Writing–original draft, Investigation, Data curation. **Atsushi Washioka, Eriko Murakami, Ryota Shibaki, Toshio Shimizu, Yasuhiro Koh, Nobuyuki**

Yamamoto: Investigation, Data curation. **Hiroaki Akamatsu**: Supervision, Writing–review and editing, Conceptualization.

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CONFLICT OF INTEREST STATEMENT

Dr Takakura, Dr Washioka, Dr Murakami, Dr Koh declare no conflict of interest. Dr Akamatsu: Grants or contracts: Amgen Inc., Chugai Pharmaceutical Co. Ltd. Honoraria: Amgen Inc., Boehringer Ingelheim Japan Inc., Chugai Pharmaceutical Co. Ltd., MSD K.K., Novartis Pharma K.K., Pfizer Inc., Taiho Pharmaceutical Co. Ltd., AstraZeneca K.K., Bristol-Myers Squibb., Eli Lilly Japan K.K., Nippon Kayaku. Co. Ltd., Ono Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd. Advisory Board: Amgen Inc, Janssen Pharmaceutical K.K., Sandoz, MSD. Committee: WCLC Patient Advocacy Committee. Dr Shibaki: Honoraria: AstraZeneca KK, Chugai Pharmaceutical Co. Ltd, MSD KK, Taiho Pharmaceutical Co. Ltd, Ono Pharmaceutical Co Ltd, Daiichi Sankyo Co., Ltd., Boehringer Ingelheim Japan Inc. Dr Shimizu: Grants: AbbVie, Eli Lilly, LOXO Oncology, Novartis, Daiichi-Sankyo, Takeda Oncology, Bristol-Myers Squibb, Eisai, Incyte, AstraZeneca, Pfizer, Chordia Therapeutics, Astellas, Parexel, IQVIA. Consulting fees: AbbVie, Chordia Therapeutics, Chugai, Daiichi-Sankyo, Kyowa Kirin. Honoraria: Chugai, Taiho, MSD, IQVIA. Advisory Board: AbbVie, Chordia Therapeutics, Chugai, Daiichi-Sankyo, Kyowa Kirin. Committee: ESMO Targeted Anticancer Therapies (TAT) Scientific Committee, Joint Scientific Committee Review External IRB Member of Phase 1 Trials in Hong Kong, HKSAR, China, Executive Committee of Asia Pacific Oncology Drug Development Consortium (APODDC). Dr Yamamoto: Grants: AstraZeneca, Chugai, MSD, Taiho Pharmaceutical, Boehringer Ingelheim, Novartis, Abbvie, Amgen, Asahi Kasei, Janssen, Bristol-Myers Squibb Japan, IQvia, EPS Corporation, Amgen, A2 Healthcare, Mebix, Ono Pharmaceutical. Consulting fees: AstraZeneca, Chugai, MSD, Lilly Japan, Amgen, Novartis, Ono Pharmaceutical. Honoraria: AstraZeneca, Chugai, MSD, Takeda, Acuuray, Abbvie, Amgen, Ono Pharmaceutical, Guardant Health, Kyorin, Daiichi Sankyo, Taiho Pharmaceutical, Tsumura & Co., TERUMO, Lilly Japan, Boehringer Ingelheim Japan, Novartis, Pfizer, Miyarisan Pharmaceutical, Merck Biopharma, Janssen. Advisory Board: AstraZeneca.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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