PD-1 Blockers: Staying Long in the Body and Delayed Toxicity Risks

To the Editor:

The programmed death-1 (PD-1) blockers, nivolumab and pembrolizumab, confer long-term survival benefits in various types of cancer. However, these drugs can induce immune-related adverse events, including those with late onset. Intriguingly, durable complete response, even after withdrawal of anti–PD-1 therapy, has been reported. In clinical trials, pharmacokinetic monitoring is not frequently conducted after treatment cessation; therefore, it remains unclear how long and how many anti–PD-1 antibodies remain beyond discontinuation. We have been conducting a clinical study to evaluate the pharmacokinetics of PD-1 blockers (methodological details are provided in Supplementary Appendix). So far, 205 patients receiving nivolumab or pembrolizumab have been enrolled, and one patient with lung cancer with sustained nivolumab exposure developed secondary adrenal insufficiency long after discontinuation of treatment, which is described as follows (Fig. 1A).

This 72-year-old man was diagnosed with stage IV lung adenocarcinoma. He was treated with six cycles of nivolumab (3 mg/kg every 2 weeks) as second-line treatment until disease progression, at which point he began treatment with docetaxel plus ramucirumab. After four doses, the patient’s performance status had considerably improved, and a complete response of hepatic metastases and partial responses of the primary lesion and lymph node metastases were confirmed by computed tomography scan. On the ninth infusion (335 days after the start of nivolumab treatment), the patient presented with fatigue, nausea, and anorexia, which resulted in discontinuation of chemotherapy. The next day, the patient visited the emergency room because of severe muscle weakness in the lower limbs, with worsening of the aforementioned symptoms. He was admitted to the hospital, and laboratory tests revealed eosinophilia (22.3%), hyperkalemia (5.8 mmol/L), hyponatremia (131 mmol/L), and hypoglycemia (79 mg/dL). Magnetic resonance imaging revealed no pituitary abnormalities. On the ninth hospital day, he presented with hypotension and decreased urine output, which required glucocorticoid replacement. He was discharged after 16 days of hospitalization and palliative care was given to the patient.

The peak (55.3 μg/mL) and trough (~60 μg/mL) plasma concentrations of nivolumab were similar to those reported in previous clinical trials (Fig. 1A). Nivolumab concentrations after discontinuation seemed to decline log-linearly with a slow elimination half-life ($T_{1/2}$; 40.3 d; Fig. 1B, Supplementary Fig. 1). Notably, nivolumab (0.2 μg/mL) was still detectable at diagnosis. Anti-nivolumab antibody was negative throughout follow-up.

Our overall study population of patients who had discontinued treatment demonstrated persistent drug
exposure until approximately 1 year after stopping nivolumab and pembrolizumab (Supplementary Table 2, Figs. 1B and C).

This study provides insights into the etiologic mechanisms underlying late-onset immune-related adverse events after discontinuation of anti–PD-1 therapies. Given the long-lasting drug exposure, the pharmacokinetic impact of PD-1 blockers on clinical efficacy and safety remains relevant in certain patients even after treatment cessation. This highlights the need to continuously monitor patients for delayed toxicity after discontinuing anti–PD-1 therapies.

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Supplementary Data
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References
Melanoregulin-Anaplastic Lymphoma Kinase (ALK), a Novel ALK Rearrangement That Responds to Crizotinib in Lung Adenocarcinoma

To the Editor:

The rearrangement of anaplastic lymphoma kinase (ALK) is a distinct driver in NSCLC, which is found in 3% to 5% of patients with NSCLC. In NSCLC, many fusion partners of ALK have been reported, and the most common ALK rearrangement is echinoderm microtubule–associated protein like 4–ALK. ALK rearrangements are correlated with response to ALK tyrosine kinase inhibitors (TKIs). Here, we report a novel melanoregulin (MREG)-ALK fusion, which is sensitive to crizotinib, in a patient with lung adenocarcinoma and brain metastasis.

A 65-year-old nonsmoking Chinese woman was admitted to the local hospital with cough since 2 months. She had no fever, expectoration, or headache. Computed tomography scans of her chest reported an irregular nodular mass in the left main bronchial wall and the left lingual lobe, with a narrowing of the left lower lobe bronchi (Fig. 1A). Meanwhile, cranial computed tomography and magnetic resonance imaging revealed a space-occupying lesion in the frontal lobe, accompanied by bone destruction, which was considered a metastatic tumor (Fig. 1B). A biopsy through fiberoptic bronchoscopy was performed, and pathologic analysis reported a poorly differentiated lung adenocarcinoma with mucin production in cytoplasm (Fig. 1C and D). Formalin-fixed, paraffin-embedded specimens from bronchoscopy biopsy were sent for genomic testing by next-generation sequencing. Results revealed that MREG promoter was fused to ALK exon 20, leading to a novel MREG-ALK fusion gene with a mutant allele frequency of 13.09% (Fig. 2A and B). At the same time, immunohistochemistry was performed with the Ventana D5F3 (Roche), revealing the diffuse expression of ALK in the cytoplasm of tumor cells (Fig. 2C). Break-apart fluorescent in situ hybridization probe (Vysis FISH, Abbott) reported a separation of ALK (Fig. 2D). The patient received an ALK TKI crizotinib orally at a dose of 250 mg (twice daily) after our pathologic diagnosis. The tumor size decreased both in the lung and in the brain with an impressive symptomatic improvement after 3 months of therapy (Fig. 1E and F).

Multiple ALK fusion partners have been reported in NSCLC, and break points vary across patients even with the same partner gene. These make it complicated when treatment and prognosis are concerned because responses to ALK TKIs are heterogeneous for different ALK fusion variants. To our knowledge, MREG has not been previously reported as a fusion partner of ALK. MREG, the product of the Mreg^dsu^ located at 2q35, has been shown to act as a factor in organelle biogenesis, maintain melanosome size and distribution, drive melanosome transfer from melanocytes to keratinocytes, regulate membrane fusion, and suppress the invasion and proliferation of thyroid cancer cells. In our present case, the break points of this fusion were located in the promoter of MREG and exon 20 of ALK. We speculate that the fusion of the MREG promoter activates the expression of ALK as indicated in other ALK fusion events. Moreover, the patient harboring MREG-ALK fusion reported a response to the ALK inhibitor crizotinib.

To our knowledge, this is the first case to present a patient with lung adenocarcinoma harboring a new fusion of ALK rearrangement (MREG-ALK) showing response to crizotinib. Our finding expands the spectrum of ALK fusion variants that should be added to the list of ALK fusion genes.

Disclosure: The authors declare no conflict of interest.

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