afatinib reduction. The patient continued on afatinib 30 mg daily up to now (September 26, 2019, the cutoff day), with a progression-free survival of more than 3.8 months.

Although the combination of afatinib 20 mg and osimertinib 80 mg has been used to treat a patient with EGFR G724S/19del and achieved disease control, the patient experienced progressive disease rapidly. Whether afatinib monotherapy could retain sensitivity with standard dose in EGFR G724S/19del mutant patients remains unclear. To the best of our knowledge, this case is the first to elicit clinical response of afatinib monotherapy in EGFR G724S/19del adenocarcinoma after progression on osimertinib. Despite afatinib reduction due to intolerable rash, continued response was still observed. In conclusion, this case showed promising antitumor activity of afatinib in EGFR G724S/19del mutant NSCLC patients after resistance to osimertinib, providing a clinical strategy for such a subset of patients.

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References

A 76-year-old man was admitted to the Affiliated Wuxi People’s Hospital of Nanjing Medical University with left lower lung occupation for 1 month. A chest computed tomography scan revealed the existence of an eccentric cavity with speculation sign in the lower lobe of his left lung. After thoracoscopic radical resection of lower left lung cancer, stage IIb lung adenocarcinoma was diagnosed from surgical pathology. The specimen was then subjected to NGS analysis, and a novel intergenic region between TMED2 and ALK fusion was identified (Fig. 1). The fusion of TMED2-ALK included exons 3-4 of TMED2 and exons 20-29 of ALK, and the complete kinase structure of ALK protein was retained. Split signal was observed with a frequency of 74% in fluorescence in situ hybridization (FISH) image and immunohistochemistry (IHC) staining indicated a weakly ALK protein expression (>5%) (Fig. 2). ALK-positive was considered. Although several ALK inhibitors have been approved for the treatment of lung cancer patients with ALK-positive cases, the tumor response is heterogeneous. One

TMED2-ALK, a Novel ALK Fusion Gene Identified in a Patient With Lung Adenocarcinoma

To the Editor
Diverse ALK receptor tyrosine kinase (ALK) fusion partner genes have been identified, such as EML6-ALK, FBX011-ALK, and CUX1-ALK with the development of next-generation sequencing (NGS).1,2 Herein, we report a patient with lung adenocarcinoma harboring a novel TMED2-ALK fusion gene identified by NGS.

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explanation is that the response of ALK inhibitors to different ALK fusion types differs. Other possible reasons includes the existence of other driver mutations or primary resistance mutations in the kinase structure of ALK protein. At present, FISH and IHC approaches are routinely applied in clinical practice, although neither could identify specific ALK fusion types. Although FISH is recognized as a clinical gold standard method for ALK status detection, it has a certain false-positive possibility.

It is necessary to comprehensively understand ALK fusion information; NGS could serve as a supplementary approach for ALK status detection for its high-throughput molecular analysis ability to detect gene copy number alterations, deletions, insertions, and fusions simultaneously. A weak ALK protein expression (>5%) is observed with this patient, and one study indicated that patients with negative IHC might still benefit from ALK inhibitor therapy as long as FISH or NGS testing is positive. Our case reports a novel fusion for ALK and enriches the ALK fusion spectrum, which was confirmed by FISH and IHC. ALK inhibitors might be effective in later treatment for this patient.

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Severe Immune-Related Hepatitis Treated With Plasma Exchange

To the Editor:
A 77-year-old man diagnosed with stage IV lung adenocarcinoma had a tumor proportion score for programmed cell death-ligand 1 (PD-L1) of 0% (clone 22C3), manifested disease progression after four courses of carboplatin and pemetrexed, and then underwent treatment with atezolizumab. Thirteen days after the onset of atezolizumab treatment, he was admitted to our hospital with fever and elevated liver enzymes. He was diagnosed with grade 3 hepatitis (aspartate aminotransferase level, 760 U/L; alanine aminotransferase level, 441 U/L), with a liver biopsy revealing severe hepatitis with centrilobular necrosis (Fig. 1). He was closely monitored, and these abnormalities normalized in 2 weeks. Six days later, laboratory tests revealed aspartate aminotransferase, alanine aminotransferase, creatinine, amylase, and C-reactive protein levels of 2172 U/L, 1153 U/L, 4.43 mg/dL, 1246 U/L, and 23.7 mg/dL, respectively. Computed tomography revealed swelling of the kidneys and pancreas. On the basis of these clinical features, the patient was diagnosed with immune-mediated organ injury associated with acute liver failure (ALF) induced by atezolizumab. Methylprednisolone (1000 mg/d) was administered followed by plasma exchange (PE), with 40 units of plasma administered as replacement fluid for three consecutive days. The patient experienced a gradual clinical improvement and was switched to oral prednisolone. As relapse of liver enzyme elevation became apparent during steroid tapering, azathioprine was added to his treatment regimen (Fig. 2). He was discharged with prednisolone (15 mg/d) and azathioprine (50 mg/d) treatment.

Currently, there are no clinical recommendations regarding the management of immune-related hepatitis beyond the administration of steroids and immunosuppressive agents such as mycophenolate mofetil.1 In general, multiorgan dysfunction in ALF is thought to be attributable to a systemic inflammatory response triggered by the release of cytokines and damage-associated molecular patterns,2 with PE being a therapeutic option to attenuate innate immune activation by removing plasma cytokines and adhesion molecules.2 A recent prospective, multicenter study has indicated that PE removes cytokines and consequently improves survival in patients with ALF.3 Nevertheless, there is little evidence regarding the role or benefit of PE in the management of severe immune-related hepatitis. PE has been reported to improve steroid- and mycophenolate mofetil–refractory immune-related hepatitis caused by anti–cytotoxic T-lymphocyte-associated protein 4 therapy.4 To the best of our knowledge, the present case is the first of immune-related hepatitis caused by anti–PD-L1 therapy that has been managed with PE.

Serum analysis revealed that the levels of tumor necrosis factor-α, interferon-γ, and interleukin-6 were greatly increased before PE and declined after PE in association with clinical improvement (Table 1). These findings support the notion that the severe immune-related hepatitis developed as a result of the release of inflammatory cytokines and that the removal of these cytokines by PE contributed to the therapeutic effect; however, steroid therapy might also have had an impact on cytokine production.

References