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CASE REPORT

Overcoming T790M mutant small cell lung cancer with the third-generation EGFR-TKI osimertinib

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Abstract

A large number of *EGFR* mutant non-small cell lung cancer patients primordially benefit from first-line treatment with first-generation EGFR-tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib. However, multiple acquired resistance mechanisms have been described that limit the clinical efficacy of first-generation EGFR-TKIs. Herein, we report a rare case of lung adenocarcinoma harboring an *EGFR* exon 19-deletion mutation before the administration of target therapy. This patient acquired resistance to first-generation EGFR-TKIs through small cell lung cancer (SCLC) transformation accompanied by the T790M mutation. Unexpectedly, this SCLC patient maintained a sensitive response to the third-generation EGFR-TKI osimertinib. This special case may indicate that osimertinib represents an effective target drug for SCLC patients who harbor an *EGFR* T790M mutation.

Introduction

EGFR-TKIs have revolutionized the therapeutic field by inhibiting the *EGFR*-induced downstream signaling pathway in non-small cell lung cancer (NSCLC). However, most patients ultimately experience drug resistance and progression within two years, and several acquired resistance mechanisms have been identified, including *EGFR* T790M mutation, *MET* or *HER2* amplification, phosphoinositide 3-kinase pathway activation, and rare transformation from lung adenocarcinoma (LUAD) to small cell lung cancer (SCLC).[1–4] If an NSCLC patient has acquired a T790M mutation, the third-generation EGFR-tyrosine kinase inhibitor (TKI) osimertinib is recommended.[5]

Case report

A 46-year-old woman with a passive smoking history who presented with dyspnea and unintentional weight loss underwent chest computed tomography (CT) scanning that revealed a right middle lobe mass (51 x 61 mm) and multiple thorax and bone metastases. Her clinical stage was T4N2M1b (stage IV). Morphologically, immunohistochemistry showed a poorly differentiated adenocarcinoma that was diffusely positive for thyroid transcription factor 1 (TTF-1) and focally positive for Napsin A (Fig 1a–c). The tumor harbored a classic *EGFR* exon 19-deletion mutation, as shown by qualitative detection (amplification refractory mutation system PCR) (Fig 1a–d). The woman was subsequently treated with gefitinib and experienced significant regression of the mass.

Six months after her first exposure to gefitinib, the primary mass and metastatic nodules exhibited obvious enlargement, accompanied by gradually increasing bone pain. The patient subsequently underwent CT-guided percutaneous lung biopsy, which revealed SCLC transformation (Fig 2a). Given that sufficient biopsy tissue was not

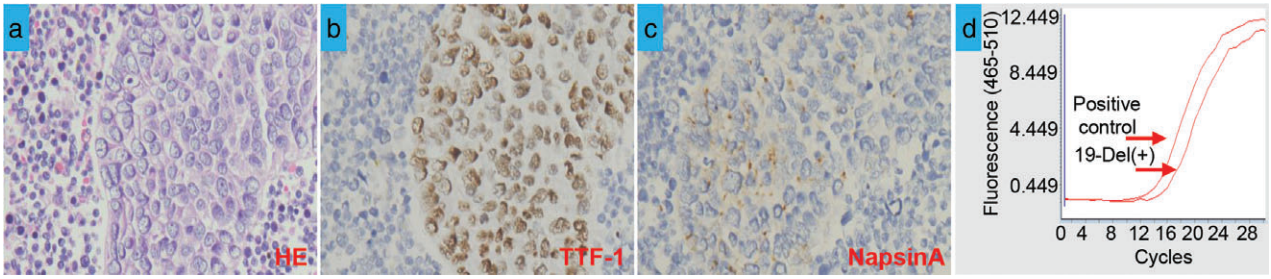

Figure 1 First biopsy specimen: (**a**) hematoxylin and eosin staining was diffusely positive for (**b**) thyroid transcription factor 1, (**c**) focally positive for Napsin A, and (**d**) harbored a classic *EGFR* exon 19-deletion mutation.

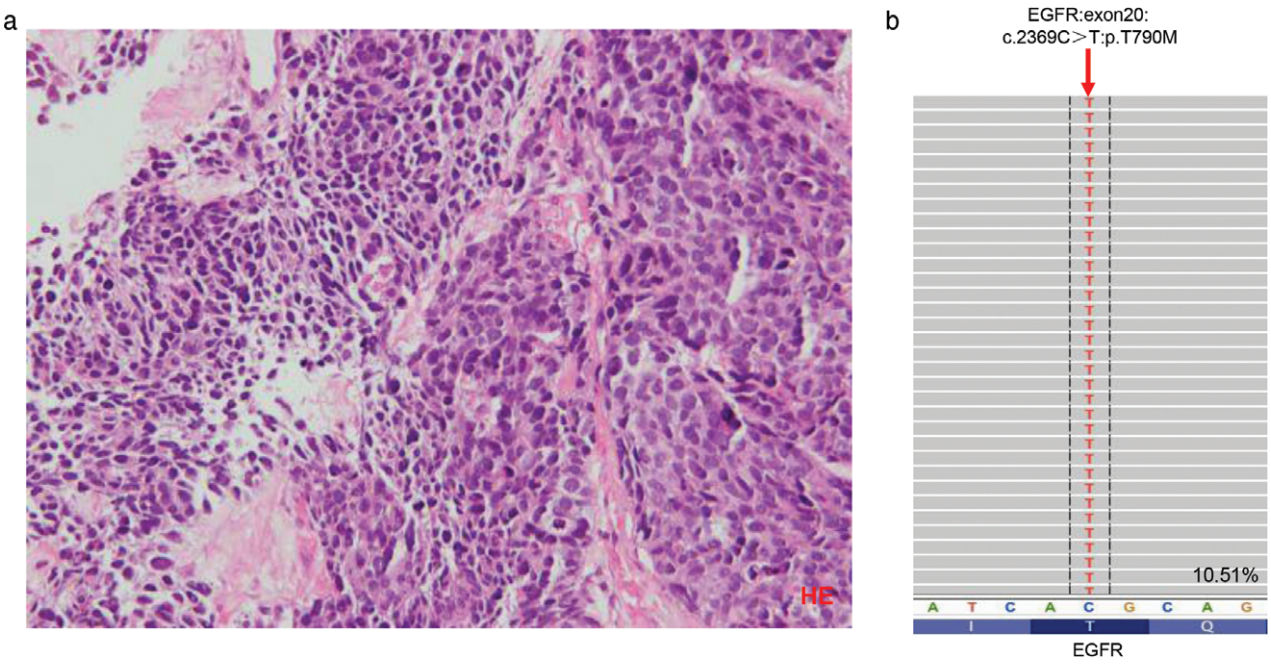

Figure 2 (**a,b**) Second biopsy specimen: hematoxylin and eosin staining exhibited *EGFR* T790M mutation.

obtained for immunohistochemistry staining and next generation sequencing (NGS), a blood sample was collected for driver gene testing and revealed that she harbored a new *EGFR*-T790M mutation (Fig 2b). She was then administered osimertinib therapy and experienced excellent improvement.

However, approximately five months after initial exposure to osimertinib, CT and whole-body bone scanning revealed further deterioration. Another CT-guided percutaneous lung biopsy specimen presented SCLC morphology with neuroendocrine markers, including diffuse positivity for Syn and focal positivity for CgA and CD56 (Fig 3). Additionally, peripheral blood was collected, and we defined circulating tumor cells (CK+/CD45-/4′,6-diamidino-2-phenylindole [DAPI]+) and white blood cells (CK-/CD45+/DAPI+) (Fig 4a). *RB1* and *TP53* inactivation mutations were definitively identified in this SCLC transformation (Fig 4b).[6] Additionally, tissue NGS also revealed that the *EGFR* exon 19 deletion (81.18%) and *EGFR* T790M mutation (3.10%) were retained, and some new mutation positions were detected, including *CTNNB1*, *FGFR2*, *HRAS*, *PIK3CA*, and *RET* mutations. The patient was administered a standard chemotherapy strategy with an intermittent etoposide-cisplatin regimen (EP) and continued to take osimertinib after each cycle of chemotherapy. After six cycles of chemotherapy, chest CT revealed obvious clinical responses, including shrinkage of the primary lung mass and metastatic nodules. The patient continued to take osimertinib, and achieved progression-free survival (PFS) of four months. In March 2018, the tumor progressed with a chest mass and multiple brain metastases. After written informed consent was obtained, a fourth biopsy of the progressing mass was performed, revealing Syn-positive, CgA-positive, and CD56-positive SCLC with

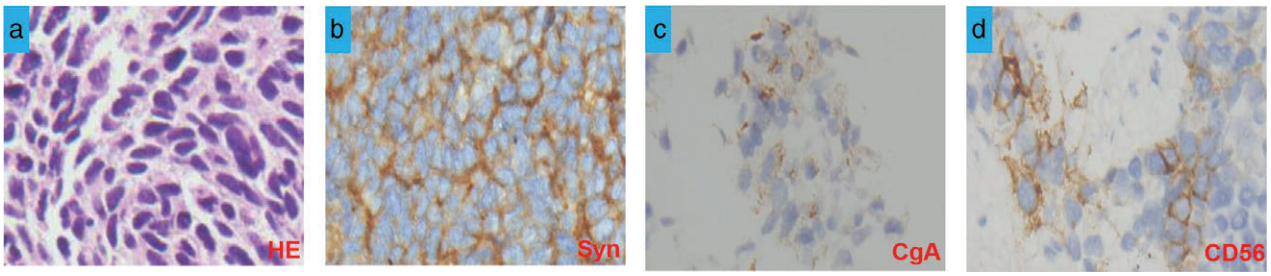

Figure 3 Third biopsy specimen: (**a**) hematoxylin and eosin staining was diffusely positive for (**b**) Syn and focally positive for (**c**) CgA and (**d**) CD56.

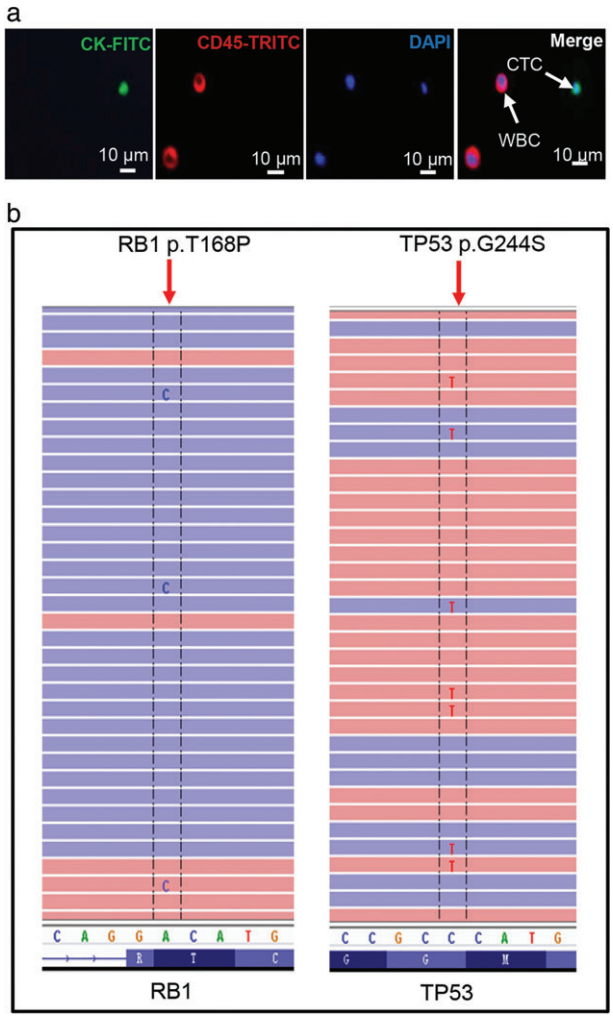

Figure 4 (**a**) Circulating tumor cells (CBCs) were positive for CK and 4′,6-diamidino-2-phenylindole (DAPI), white blood cells (WBCs) were positive for CD45 and DAPI and (**b**) harbored *RB1* and *TP53* inactivation mutations.

no evidence of adenocarcinoma histology (Fig 5a–d). Molecular analysis revealed that the T790M mutation was retained, and a new *EGFR* C797S mutation was identified (Fig 5e). Detailed driver gene information and biopsy, treatment, and image scanning history are presented in Figures 6 and 7.

Discussion

In this case, this patient acquired resistance to first-generation EGFR-TKI through T790M mutation accompanied by SCLC transformation. Previous studies have demonstrated that T790M mutation is a major cause of resistance to gefitinib in NSCLC.[1] As another mechanism of resistance, SCLC transformation is reported to occur in 4–14% of LUAD cases.[7] SCLC transformation is associated with the rapid progression and deterioration of lung cancer. Furthermore, there are no ideal targeted drugs for SCLC patients. Although Okamoto *et al.* reported that SCLC harboring activating *EGFR* mutations exhibited a surprising response to gefitinib,[8] insufficient evidence is available to show that osimertinib could be a targeted candidate for SCLC. Despite SCLC transformation, this case of SCLC still presented sensitivity to osimertinib. We suggest that the T790M mutation may also underlie responsiveness to osimertinib in SCLC. The fourth biopsy in our patient revealed that SCLC harbored a new C797S mutation. Based on previous reports, C797S mutation contributes to osimertinib resistance in NSCLC.[1] Thus, C797S mutation may also play a significant role in osimertinib resistance in SCLC.

According to the classic theory of tumorigenesis, every subset of tumor cells unavoidably present characteristics of inter-tumor heterogeneity between primary tumors and their metastatic lesions, including histological and genomic heterogeneity. Currently, only one biopsy lesion is recommended for histological diagnosis and genomic analysis.[9] In our case, the primary mass, pleural effusion cytology, and metastatic lymph nodes simultaneously presented LUAD characteristics. Therefore these observations basically confirmed that this patient had LUAD before gefitinib therapy. PFS after gefitinib treatment was only six months. T790M mutation and SCLC transformation simultaneously accelerated gefitinib resistance.

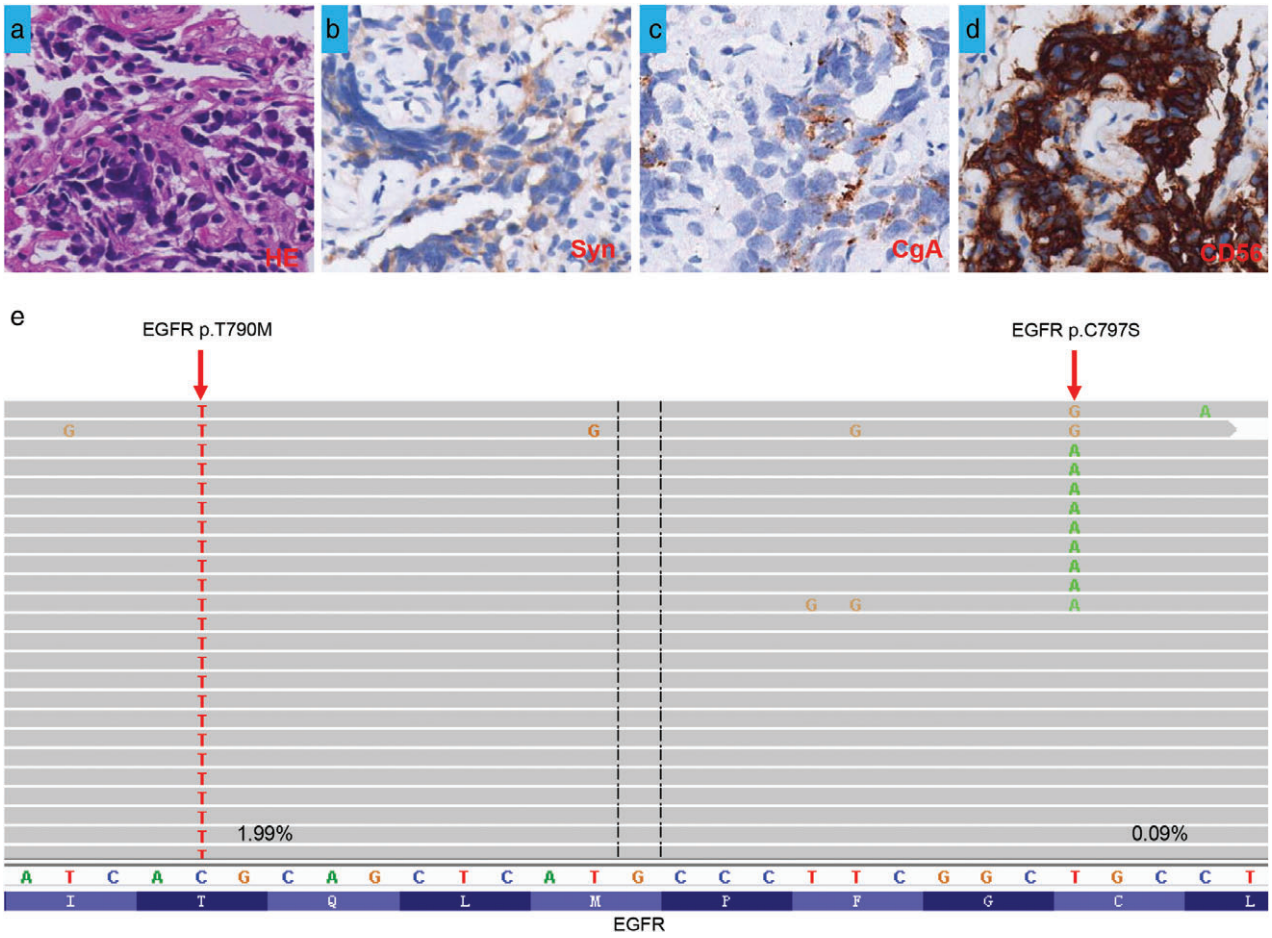

Figure 5 Fourth biopsy specimen: (**a**) hematoxylin and eosin staining was weakly positive for (**b**) Syn and (**c**) CgA, (**d**) diffusely positive for CD56, and (**e**) harbored *EGFR* T790M and *EGFR* C797S mutations. SCLC, small cell lung cancer.

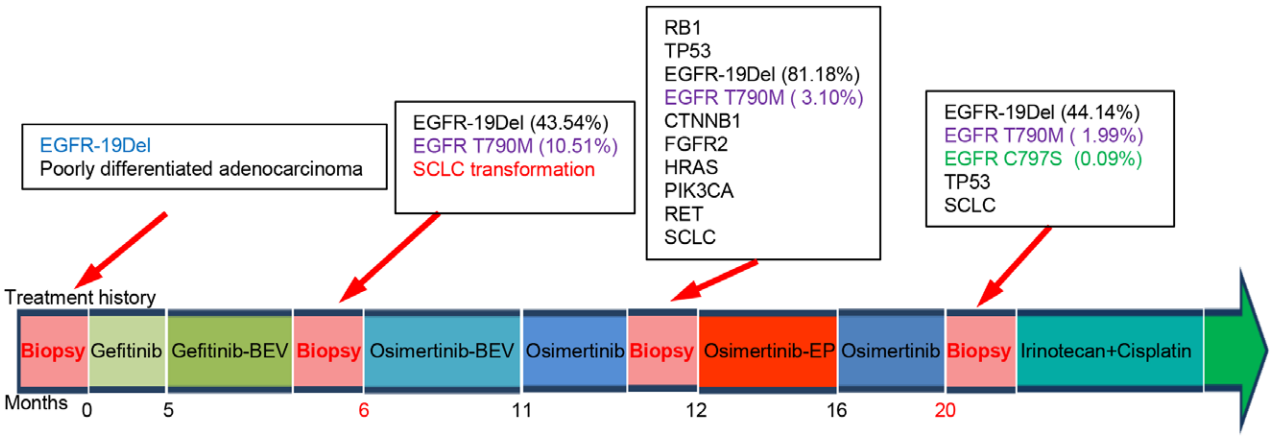

Figure 6 The course of treatment history and driver gene evolution.

After acquiring gefitinib resistance, a lung biopsy specimen presented SCLC morphology and *RB1* and *TP53* mutations; inactivation of both *RB1* and *TP53* is an effective predictor of transformation from LUAD to SCLC.[6] Therefore, the combined histological characteristics and *RB1*/*TP53* mutations in this case indicated SCLC (after gefitinib resistance) rather than LUAD before osimertinib therapy in the second biopsy. Osimertinib is an ideal target

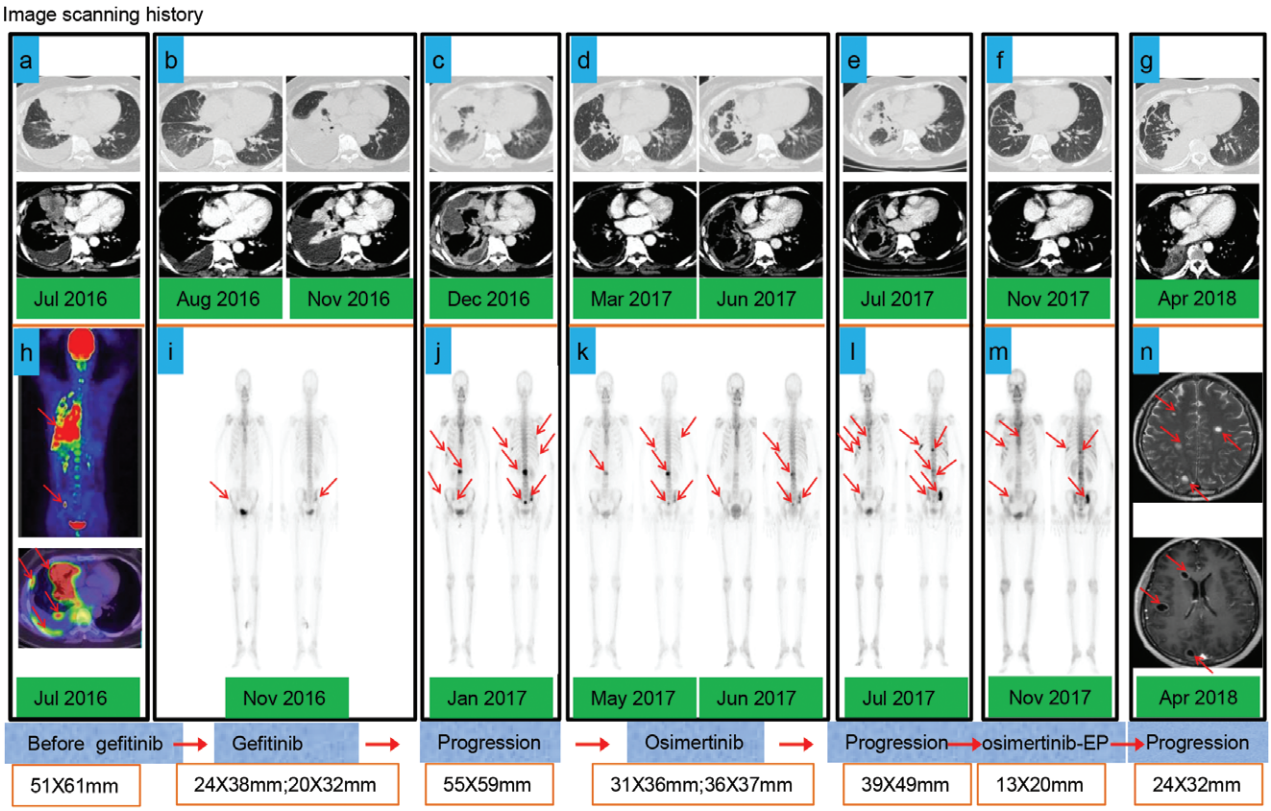

Figure 7 Image scanning history: (**a**,**h**) before gefitinib treatment; (**b**,**i**) response to gefitinib; (**c**,**j**) progression after acquired resistance to gefitinib; (**d**,**k**) response to osimertinib; (**e**,**l**) progression after transformation into small cell lung cancer; (**f**,**m**) response to osimertinib-etoposide-cisplatin (EP); and (**g**,**n**) progression after acquired resistance to osimertinib.

drug for gefitinib resistant-NSCLC patients who harbor *EGFR* T790M mutations; the median PFS is 10.1 months.[5] However, this SCLC case presented further deterioration at approximately five months rather than 10.1 months. We consider that SCLC is a highly aggressive malignant tumor with a rapid growth index and a routinely poor prognosis. The detailed molecular mechanism is very complicated. Further considerations are necessary to uncover the possible inter-tumor heterogeneity underlying this patient's treatment process. In particular, previous studies have demonstrated that SCLC transformation from adenocarcinoma retains the original *EGFR* mutation. We discovered that this SCLC maintained the *EGFR* 19-deletion in several subsequent biopsies, which is similar to the original *EGFR* mutation spectrum in LUAD. Thus, we speculate that the SCLC *EGFR* 19-deletion mutation in this case was inherited from the original adenocarcinoma.

In summary, our case highlights four points. First, few studies have reported the same patient undergoing four biopsies within the course of EGFR-TKI treatment with driver gene information. Second, concomitant SCLC transformation and T790M mutation as the manifestation of acquired resistance after first-line EGFR-TKI treatment is relatively rare. Third, a case of an osimertinib-responsive SCLC patient harboring a *T790M* mutation has not previously been reported, and this patient maintained a clinical response for six months. Fourth, this is the first case report of an SCLC patient with C797S mutation after acquired resistance to osimertinib. Overall, this case may significantly extend the therapeutic territory of osimertinib.

Acknowledgments

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Disclosure

No authors report any conflict of interest.

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