First-line osimertinib treatment in a patient with lung adenocarcinoma with coexisting epidermal growth factor receptor G719S and de novo T790M mutations

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Abstract
Osimertinib is the standard first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) for treating non-small cell lung cancer (NSCLC) with an active EGFR mutation.1 In addition, osimertinib has been shown to be effective in patients with uncommon EGFR mutations.2 There has been a report presenting osimertinib as a first-line treatment for NSCLC with EGFR common and de novo T790M mutations. This report showed that partial response (PR) was observed in six out of seven cases.3 There is another report of three osimertinib-treated NSCLC cases with uncommon mutations, G719A and de novo T790M mutations.4,5

INTRODUCTION
Osimertinib is the standard first-line epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) for treating non-small cell lung cancer (NSCLC) with an active EGFR mutation.1 In addition, osimertinib has been shown to be effective in patients with uncommon EGFR mutations.2

There has been a report presenting osimertinib as a first-line treatment for NSCLC with EGFR common and de novo T790M mutations. This report showed that partial response (PR) was observed in six out of seven cases.3 There is another report of three osimertinib-treated NSCLC cases with uncommon mutations, G719A and de novo T790M mutations.4,5

This is the first report which highlights the efficacy of osimertinib in a patient with NSCLC and uncommon mutations—G719S and de novo T790M mutations.

CASE REPORT
A 71-year-old woman was diagnosed with clinical T1cN3M1c stage IVB lung adenocarcinoma (Fig. 1a); she was diagnosed with coexisting EGFR G719S and T790M mutations using a cobas EGFR assay of her mediastinal lymph node. First, she underwent whole-brain radiation therapy (WBRT, 30 Gy/10 Fr) for symptomatic brain metastases (Fig. 2). Osimertinib (80 mg/day) was initiated after WBRT. Head magnetic resonance imaging (MRI) showed

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that the size of the brain metastases decreased and partially disappeared 1 month after osimertinib initiation. Three months later, computed tomography (CT) showed shrinkage of the primary lesion and mediastinal lymph nodes; this was considered as PR. However, 5 months after osimertinib initiation, MRI or CT showed brain metastases, pulmonary lesions, enlarged mediastinal lymph nodes, and disseminated peritoneal lesions (Figs 1, 2).

First, we performed radiotherapy to treat the brain metastases and craniotomy for the right parietal lobe lesion. Although her performance score (PS) was three after the treatment for brain tumors, she and her family requested standard treatment for advanced NSCLC. Therefore, we reduced the chemotherapy dose to limit side effects and administered carboplatin (AUC 4) + nab-paclitaxel (80 mg/m²) + atezolizumab (1200 mg/bodyweight). After the first treatment course, CT showed marked reduction of the lesions. However, her PS dropped to 4; her condition was diagnosed as meningeal carcinomatosis. Next-generation sequencing (NGS) of the brain specimen revealed G719S and de novo T790M mutations, without newly acquired resistance mutations, including EGFR C797S.

**DISCUSSION**

This is the first report to show the efficacy of osimertinib in NSCLC with EGFR G719S and de novo T790M mutations. Osimertinib treatment resulted in a shorter PFS in our patient. In the three previously reported NSCLC cases with EGFR G719A and de novo T790M mutations, first-line osimertinib yielded an antitumor response (Table 1).

Osimertinib was also the primary treatment for our patient because it is reportedly very effective for CNS lesions. Osimertinib reportedly has a high response rate of 91% in EGFR mutation-positive NSCLC cases. Since osimertinib has a higher CNS penetration ability than afatinib, osimertinib was considered suitable for our patient. Moreover, a previous study showed that osimertinib had better clinical benefits than afatinib in patients with brain metastases.

Tumor shrinkage was observed only a few months after treatment initiation in our patient. To detect newly acquired resistant mutations, we performed NGS using Oncomine Dx Target Test Multi-CDx System (Ion Torrent PGM Dx Sequencer; Thermo Fisher Scientific), which is an NGS panel for detecting sequence variations in 46 genes using DNA and RNA in NSCLC. Therefore, whole genome mutations were not detected. However, the NGS revealed that the osimertinib-resistant brain metastases showed no new mutations (including C797S, MET amplification, KRAS, PIK3CA, etc).

We administered the IMpower130 regimen (carboplatin + nab-paclitaxel + atezolizumab) after disease progression occurred, and a marked improvement was observed. A phase
III study (IMpower150 study) showed that progression-free survival was higher in the atezolizumab + bevacizumab + carboplatin + paclitaxel (ABCP) group than in the bevacizumab + carboplatin + paclitaxel group for patients with EGFR or ALK genetic alternations. Therefore, the ABCP regimen was considered suitable for the patient. However, bevacizumab was considered to inhibit wound healing post-surgical resection of the brain metastases. Subsequently, we excluded pemetrexed-containing regimens due to her decreased renal function. In addition, a previous retrospective study investigated the efficacy

![Figure 2](image)

**Figure 2** Enhanced head magnetic resonance imaging showing brain metastases (arrows) (a) at diagnosis, (b) 1 month after initiation of osimertinib, and (c) 5 months after initiation of osimertinib

**Table 1** Cases of de novo T790M + G719X mutation-positive lung cancers treated with osimertinib

| Age | Gender | EGFR mutations | Stage | Metastatic lesion | Best overall response | Progression-free survival (m) | Overall survival (m) |
|-----|--------|----------------|-------|------------------|----------------------|-----------------------------|---------------------|
| 70  | Male   | G719A + de novo T790M | IVA   | Pleura           | Partial response     | >4                          | >4                  |
| 33  | Female | G719A + de novo T790M | IVB   | Liver            | Partial response     | >5                          | >5                  |
| 51  | Female | G719A + de novo T790M | IVB   | Brain            | Stable disease       | 15                         | >15                 |
| 71  | Female | G719S + de novo T790M | IVB   | Brain            | Partial response     | 5                          | 8                   |
of immune checkpoint inhibitors (ICIs) in NSCLC with uncommon EGFR mutations after acquisition of resistance to EGFR-TKIs. This study showed that patients with uncommon mutations had a higher response rate to ICIs than those with common mutations (hazard ratio 0.047, 95% CI: 0.04–0.557, \( p = 0.015 \)). Based on these, we used the IMpower130 regimen for our patient.

To conclude, the efficacy of osimertinib in NSCLC with G719S and T790M mutations may be poor. Therefore, we should investigate the optimal treatment for these cases in future.

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REFERENCES
1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Non-Small Cell Lung Cancer Version 3. 2020. https://www2.tri-kobe.org/nccn/guideline/lung/english/non_small.pdf. Accessed November 13, 2021.
2. Cho JH, Lim SH, An HJ, Kim KH, Park KU, Kang EJ, et al. Osimertinib for patients with non-small-cell lung cancer harboring uncommon EGFR mutations: a multicenter, open-label, phase II trial (KC5G-LU15-09). J Clin Oncol. 2020;38(5):488–95. https://doi.org/10.1200/JCO.19.00931
3. Ramalingam SS, Yang JC, Lee CK, Kurata T, Kim DW, John T, et al. Osimertinib as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer. J Clin Oncol. 2018;36(9):841–9. https://doi.org/10.1200/JCO.2017.74.7576
4. Ancevski Hunter K, Friedland DM, Villaruz LC, Burns TF. First-line Osimertinib in patients with treatment-naïve somatic or germline EGFR T790M-mutant metastatic NSCLC. J Thorac Oncol. 2018;13(1): e3–5. https://doi.org/10.1016/j.jtho.2017.09.1963
5. Ikari T, Sakakibara-Konishi J, Yamamoto G, Kitai H, Mizugaki H, Asahina H, et al. Response to first-line Osimertinib treatment in non-small-cell lung cancer with coexisting G719A and primary T790M epidermal growth factor receptor mutations. Clin Lung Cancer. 2019;20(4):e531–3. https://doi.org/10.1016/j.cllc.2019.05.002
6. Masuzawa K, Yasuda H, Hamamoto J, Nukaga S, Hirano T, Kawada I, et al. Characterization of the efficacies of osimertinib and nazaritnib against cells expressing clinically relevant epidermal growth factor receptor mutations. Oncotarget. 2017;8(62):105479–91. https://doi.org/10.18632/oncotarget.22297
7. Campo M, Gerber D, Gainer JF, Heist RS, Temel JS, Shaw AT, et al. Acquired resistance to first-line Afatinib and the challenges of prearranged progression biopsies. J Thorac Oncol. 2016;11(1):2022–6. https://doi.org/10.1016/j.jtho.2016.06.032
8. Reungwetwattana T, Nakagawa K, Cho BC, Cabo M, Cho EK, Bertolini A, et al. CNS response to Osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. J Clin Oncol. 2018;36:3290–7. https://doi.org/10.1200/JCO.2018.78.3118
9. Colclough N, Chen K, Johnström P, Strittmatter N, Yan Y, Wrigley GL, et al. Preclinical comparison of the blood-brain barrier permeability of Osimertinib with other EGFR TKIs. Clin Cancer Res. 2021;27(1):189–201. https://doi.org/10.1158/1078-0432.CCR-19-1871
10. Ito K, Morise M, Wakuda K, Hataji O, Shimokawaji T, Takahashi K, et al. A multicenter cohort study of osimertinib compared with afatinib as first-line treatment for EGFR-mutated non-small-cell lung cancer from practical dataset: CJLSSG1903. ESMO Open. 2021;6(3):100115. https://doi.org/10.1016/j.esmoop.2021.100115
11. He J, Huang Z, Han L, Gong Y, Xie C. Mechanisms and management of 3rd-generation EGFR-TKI resistance in advanced non-small cell lung cancer (review). Int J Oncol. 2021;59(5):90. https://doi.org/10.3892/ijo.2021.5270
12. Socinski MA, Jotte RM, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018;378(24):2288–301. https://doi.org/10.1056/NEJMoa1759142
13. Yamada T, Hirai S, Katayama Y, Yoshimura A, Shiotsu S, Watanabe S, et al. Retrospective efficacy analysis of immune checkpoint inhibitors in patients with EGFR-mutated non-small cell lung cancer. Cancer Med. 2019;8(4):1521–9. https://doi.org/10.1002/cam4.2037

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