Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have changed the strategy of treatment for advanced or postoperative recurrent non-small cell lung cancer (NSCLC). The first-generation TKI, gefitinib, appeared in 2002, and verified the relationship between EGFR mutation and its efficacy in 2004 (1). Several EGFR-TKIs have been developed and approved for the treatment of advanced/postoperative recurrent NSCLC worldwide to date, including gefitinib and erlotinib as first-generation TKIs, afatinib and dacomitinib as second-generation TKIs, and osimertinib as third-generation TKI. Compared to first-generation TKIs, second-generation TKIs as first-line therapy for advanced NSCLC with EGFR mutations improved patients’ survival in clinical trials. In the LUX-Lung 7 trial, patients treated with afatinib showed longer progression-free survival (PFS) than those treated with gefitinib (2). In the ARCHER 1050 trial, patients treated with dacomitinib showed longer PFS and overall survival (OS) than those treated with gefitinib (3,4). According to these results, second-generation TKIs rather than first generation should be used as first-line therapy for patients with advanced NSCLC with EGFR mutation; however, it is often difficult in clinical practice to follow this principle because of their peculiar side effects (e.g., heavy diarrhea of afatinib and dermatitis aciform of dacomitinib). Further, EGFR-TKIs eventually acquire resistance, even if they were effective for a while. According to Yu et al. (5), the mechanisms of acquired resistance are mainly T790M mutation (63%), followed by HER2 amplification (13%), MET amplification (5%), and small cell histologic transformation (3%). Osimertinib was developed as an irreversible EGFR-TKI that is selective for both EGFR and T790M resistance mutations, and first, it was shown to be superior to platinum-doublet in the treatment for patients with T790M-positive NSCLC in AURA3 trial (6). Thereafter, osimertinib was also shown to be superior to gefitinib in the treatment of patients with advanced NSCLC with EGFR mutation (Ex21L858R mutation or Ex19 deletion) in the FLAURA trial (7) and is now recognized as a drug for first-line molecular-targeted therapy for patients with advanced NSCLC with EGFR mutation. A summary of the prognostic benefit of second- and third-generation EGFR-TKIs over the first-generation TKIs is shown in Table 1 (2-4,7,8).

Zheng et al. presented a patient who received first-line therapy with gefitinib for postoperative recurrence of NSCLC with pulmonary metastasis and single brain metastasis. However, disease progression occurred approximately 2 years after the administration of gefitinib, and anlotinib was administered without confirmation of the T790M mutation due to patients’ refusal of biopsy, and consequently, the patient withdrew from the treatment due to side effects. In this case, we consider that osimertinib should be administered as a first-line therapy, if possible, as Dr. Arulananda and Dr. Um recommended in this article. Because the PFS benefit of osimertinib in patients with
brain metastasis was reported in the FLAURA trial (7), and moreover, Colclough et al. (9) verified the higher blood-brain-barrier permeability of osimertinib than that of other TKIs in their in vivo and in vitro preclinical models, osimertinib might be preferred for this case.

As for the confirmation of the T790M mutation, it is essential to consider second-line therapy after developing resistance to EGFR-TKIs. Osimertinib becomes the ray of hope for patients if the mutation is detected, but it is useless if not detected. For patients whose metastatic nests are difficult to biopsy or who refuse invasive biopsies, such as transbrachial lung biopsy, liquid biopsy is a useful substitute. Takahama et al. (10) evaluated the efficacy of osimertinib in patients with T790M mutation-positive NSCLC detected by liquid biopsy. In their study, T790M mutation was detected in 74 of 276 patients, and the overall response rate in this population was 55.1% with the median DFS of 8.3 months. According to the preferable results, the authors should consider the use of liquid biopsy before administering anlotinib.

Although no detailed data about the lung metastatic lesions were reported in this article, we might consider surgical or radiotherapeutic intervention for single lung metastasis. Recently, some researchers advocated the concept of “oligo-recurrence” (11) and reported the efficacy of local therapy for such a limited recurrent status of postoperative NSCLC. Niibe et al. (12) reported that patients with NSCLC who received stereotactic radiotherapy for brain-only oligo-recurrence showed a favorable prognosis, and Hishida et al. (13) reported that initial definitive local therapy was associated with improved post-recurrence survival in patients with oligo-recurrence. Both were conducted among patients with oligo-recurrence restricted to a single organ; however, Sonoda et al. (14) reported in their study that among patients receiving radical local therapy, post-recurrence survival was particularly longer in patients with one or two recurrences that was not restricted to a single organ, and these patients were able to aim for post-recurrence cure. Although the efficacy of local therapy for postoperative recurrent NSCLC is not certain because the concept of “oligo-recurrence” appears recently and has non-uniform definition, it might be worth to consider applying local therapy (i.e., stereotactic radiotherapy for brain metastasis and partial resection for lung metastasis) for this case, if the lung metastasis was single.

In contrast, immune checkpoint inhibitor (ICI) therapy, another interesting therapeutic agent for advanced or postoperative recurrent NSCLC, as a second-line therapy for patients with NSCLC with EGFR mutation is somewhat disappointing. In their meta-analysis, Lee et al. (15) reviewed three studies that used ICI monotherapy as a second-line therapy for patients with NSCLC with EGFR mutation and had no positive impact on OS compared to docetaxel. Although studies have reported the efficacy of ICI + cytotoxic agent therapy compared with cytotoxic agents alone in a subset cohort of patients with previously treated advanced NSCLC with EGFR mutation (16,17), the administration of

### Table 1
The summary of prognostic benefit of second- and third-generation EGFR-TKIs over the first-generation TKIs

| Study phase | LUX-Lung 7 (2,8) | ARCHER 1050 (3,4) | FLAURA (7) |
|-------------|-----------------|-------------------|------------|
| Group       | Afatinib vs. gefitinib | Dacomitinib vs. gefitinib | Osimertinib vs. gefitinib/erlotinib |
| Number of patients | 160 vs. 159 | 227 vs. 225 | 279 vs. 277 |
| ORR         | 70% vs. 56%; OR =1.87 (95% CI: 1.18–2.99); P=0.0083 | 75% vs. 70%; P=0.2224 | 80% vs. 76%; OR =1.27 (95% CI: 0.85–1.90); P=0.24 |
| PFS         | 11.0 vs. 10.9 months; HR =0.73 (95% CI: 0.57–0.95); P=0.017 | 14.7 vs. 9.2 months; HR =0.59 (95% CI: 0.47–0.74); P<0.0001 | 18.9 vs. 10.2 months; HR =0.46 (95% CI: 0.37–0.57); P<0.001 |
| OS          | 27.9 vs. 24.5 months; HR =0.86 (95% CI: 0.66–1.12); P=0.2580 | 34.1 vs. 26.8 months; HR =0.760 (95% CI: 0.582–0.993); P=0.0438 | Not reached |

EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; ORR, objective response rate; OR, odds ratio; CI, confidential interval; PFS, progression-free survival; HR, hazard ratio; OS, overall survival.
The management of postoperative recurrence of NSCLC harboring EGFR mutations is still uncertain, and the recommendations in NSCLC guidelines are drastically changed almost every year (18). Many strategies, including definitive local therapy, exist, and the treatment strategy for each patient must be considered through multidisciplinary discussions among the experts of lung cancer treatment.

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Footnote

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