



Treatment strategy of *EGFR*-mutated non-small cell lung cancer

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We read with great interest recent articles published in the International Multidisciplinary Team Discussion (iMTD) section of the *Journal of Thoracic Disease* (1-7). The authors and international experts provided valuable information and opinions on controversial clinical issues in the diagnosis and treatment of thoracic diseases including non-small cell lung cancer (NSCLC). Here, we focus on unmet medical needs in treating patients with NSCLC harboring mutations in the epidermal growth factor receptor (*EGFR*) gene, as is discussed in the majority of the articles (1-3,6,7).

Platinum-doublet chemotherapy had been recommended as first-line treatment for advanced NSCLC. However, the development of tyrosine kinase inhibitors (TKIs) for NSCLC harboring oncogenic driver alterations such as *EGFR*-mutations and re-arrangements of anaplastic lymphoma kinase (ALK) gene has become a “game-changer”. Several randomized clinical trials (RCTs) using first-generation and second-generation *EGFR*-TKIs for *EGFR*-mutated NSCLC showed superior tumor response and survival benefit as compared with platinum-doublet chemotherapy. Accordingly, systemic treatment with *EGFR*-TKIs has established as a standard treatment of care for patients with advanced NSCLC with common *EGFR*

mutations such as deletions in the exon 19 (Del19) and a point mutation in the exon 21 causing the substitution of arginine for leucine at position 858 (L858R) (8,9). Du and coworkers presented a case of double primary lung adenocarcinomas showing different efficacy, in which one tumor harboring L858R mutation in the left lower lobe responded well to systemic treatment using a first-generation *EGFR*-TKI (gefitinib) but another tumor without *EGFR*-mutation did not (1). Molecular characteristics and responses to targeting treatment may provide useful information in discrimination between multiple primary lung cancers and pulmonary metastases.

Several *EGFR*-TKI-based treatment options including combined therapy with a first-generation *EGFR*-TKI plus an antiangiogenic agent are currently available as first-line treatment for advanced *EGFR*-mutated NSCLC (*Figure 1*). Among them, monotherapy with a third-generation *EGFR*-TKI (osimertinib), which is a mutant-specific and irreversible inhibitor of *EGFR* kinase activity, is preferably prescribed due to its favorable toxicity profile and superior survival benefit over first-generation *EGFR*-TKIs (9-11). However, in daily clinical practice, we may encounter a variety of issues as follows.

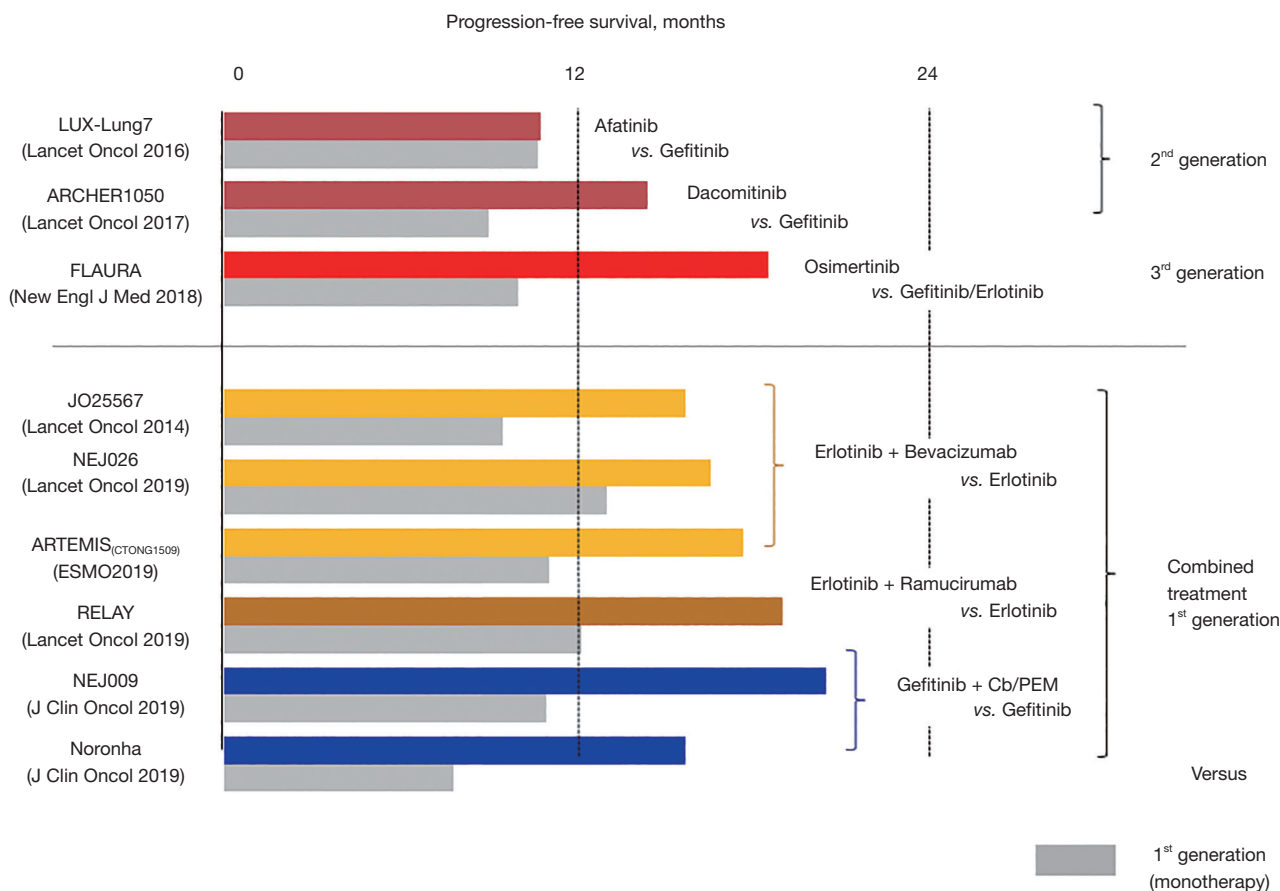


Figure 1 First-line treatment options for advanced *EGFR*-mutated non-small cell lung cancer. Comparison of progression-free survival in randomized controlled trials (RCTs).

Treatment for NSCLC with uncommon *EGFR* mutations

EGFR-TKIs generally provide significant clinical benefit for patients with NSCLC harboring common activating mutations (Del19 and L858R) that comprise 80-90% of *EGFR* mutations. The other uncommon mutations consist of insertions in the exon 20, activating point mutations in the exon 18-21 (G719X, S768I and L861Q), and point mutations associated with acquired resistance (T790M, C797X and L718Q), for which first-generation *EGFR*-TKIs may not be effective (2,3,7,9,12-14). A combined analysis of 3 RCTs showed that a second-generation *EGFR*-TKI (afatinib) was active for uncommon activating point mutations (G719X, S768I and L861Q) but less active for exon 20 insertions (13). For uncommon activating point mutations, osimertinib also showed a favorable clinical activity (14). Based on these results, afatinib or osimertinib

monotherapy may be offered for patients with advanced NSCLC harboring uncommon activating point mutations, and platinum-doublet chemotherapy is generally prescribed for patients with NSCLC harboring exon 20 insertions (9). Recently, a novel *EGFR*-TKI (mobocertinib) targeting exon 20 insertions as well as a bispecific antibody (amivantamab) targeting *EGFR* and mesenchymal-epithelial transition (MET) have been recently approved in the United States, which may provide a new insight in the treatment of *EGFR*-mutated advanced NSCLC (15).

Overcoming resistance to *EGFR*-TKIs

The second mutation in the exon 20, T790M, is responsible for acquired resistance in 50–60% of patients treated with a first-generation *EGFR*-TKI, as shown in a case presented by Zang and coworkers (7). Osimertinib may overcome T790M-mediated acquired resistance, and provide

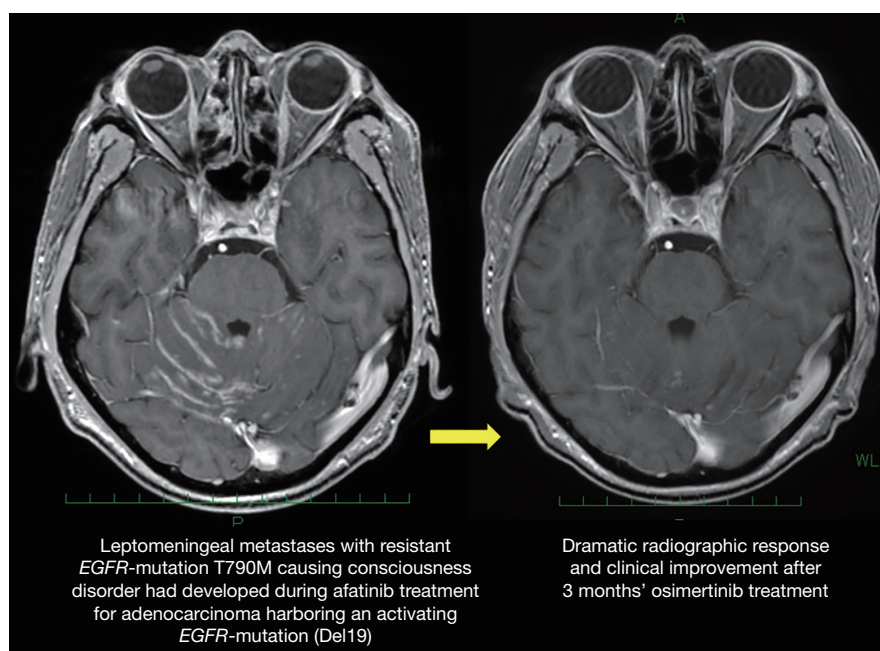


Figure 2 A case of leptomeningeal metastases successfully treated with osimertinib. A 51-year-old Japanese man presented with consciousness disorder caused by leptomeningeal metastases that had developed during systemic treatment using afatinib following multiple treatment including erlotinib plus bevacizumab, platinum-doublet chemotherapy plus bevacizumab, and docetaxel plus ramucirumab for adenocarcinoma harboring an activating *EGFR*-mutation (Del 19). A second *EGFR*-mutation (T790M) causing acquired resistance was detected. Clinical symptoms were dramatically improved after the initiation of osimertinib, and magnetic resonance imaging (MRI) also revealed good radiographic response.

significant survival benefit for patients who have disease progression caused by T790M resistant-mutation during prior *EGFR*-TKI treatment (16). Osimertinib also may be effective for tumor progression in the central nervous system (CNS), as is characterized by high CNS penetration (17,18). In fact, Zheng and coworkers presented a case of successful treatment with osimertinib for T790M-mediated acquired CNS resistance (3). We also experienced a case of leptomeningeal metastasis with Del19 plus T790M that had developed during prior afatinib treatment and was successfully treated with osimertinib (Figure 2).

Acquired resistance to osimertinib is the most critical issues in the treatment of advanced *EGFR*-mutated NSCLC. A wide variety of mechanisms such as resistant *EGFR*-mutations (C797X and L718Q), mutations in genes other than *EGFR* (*PIK3CA*, *ALK*, *BRAF*, *KRAS*, and *TP53*), amplification of *MET* gene and human epidermal growth factor 2 (*HER2*) gene, and histological transformation are associated with acquired resistance to osimertinib (19). Platinum-doublet chemotherapy is generally prescribed at the time of tumor progression after osimertinib

treatment (9), which may provide an only modest survival benefit.

To elucidate precise molecular mechanisms of resistance during *EGFR*-TKI treatment, re-biopsy upon tumor progression is mandatory. However, in clinical practice, it is sometimes difficult to obtain adequate tumor tissues that are suitable for molecular characterization. In addition, tissue biopsy may represent only a snapshot of the biopsied part of tumor at the time of biopsy (20). Accordingly, liquid biopsy may be an alternative to monitor longitudinal gene-alteration status of circulating tumor DNA (ctDNA) during treatment, and several single-gene assays to detect *EGFR*-mutations in the plasma have been already approved (21). In addition, multi-gene assays using next generation sequencing (NGS) has been recently introduced into clinical practice (21), which may provide useful information to achieve long-term survival with precise medicine using the optimal drug at the optimal timing (20). In fact, Song and coworkers present a patient with metastatic lung adenocarcinoma with L858R who survived for 30 months despite development of multiple *EGFR*-TKI resistances

including T790M, C797S and L718Q. The patient was treated with sequential use of multiple drugs (EGFR-TKIs and chemotherapy), which was decided based on results of tissue and liquid biopsies (2).

Surgical treatment for EGFR-mutated NSCLC

Systemic tumor progression is commonly observed at the time of acquired resistance to EGFR-TKI. However, isolated tumor progression may occur on some occasions, which can be well controlled with local treatment such as surgery. Zang and coworkers presented a case of salvage surgery for solitary lung metastasis that progressed after 27 months' gefitinib treatment (7). Ohtaki and coworkers reported a nation-wide Japanese data of salvage surgery following systemic treatment using EGFR-TKI (n=33) or ALK-TKI (n=3), which showed that the 3-year overall survival (OS) rate after surgery was 75.1% and that no death was documented within 90days after surgery (22). These results may indicate that salvage surgery after EGFR-TKI treatment may be indicated in selected patients, which should be discussed by a multidisciplinary team (7). In addition, the safety of surgery after EGFR-TKI treatment, which was also reported by Du and coworkers (1), may support the use of an EGFR-TKI in neoadjuvant treatment of resectable *EGFR*-mutated NSCLC. An international RCT (NeoADAURA) will reveal the clinical efficacy of neoadjuvant osimertinib treatment (23).

The adjuvant use of EGFR-TKIs for resected early-stage *EGFR*-mutated NSCLC patients was evaluated in several RCTs (24). The ADAURA study is the landmark study to reveal the efficacy of adjuvant osimertinib treatment (25). The disease-free survival (DFS) among patients with pathologic stage II–IIIa disease was significantly prolonged (overall hazard ratio for disease recurrence or death, 0.17; $P < 0.001$). Based on the results, the adjuvant use of osimertinib after standard adjuvant chemotherapy has been approved worldwide (25). However, whether adjuvant use of osimertinib may improve the rate of “cure” remains unknown due to immaturity of overall survival data (25). The adjuvant use of osimertinib for should be considered according to the balance between toxicity and efficacy in each patient (6), as osimertinib may be also active at the time of recurrence.

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