Editorial

Multiple mutations in the *EGFR* gene in lung cancer is rare but should not be forgettable

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The authors should be congratulated for this paper entitled "Multiple mutations in the *EGFR* gene in lung cancer: a systematic review (1)". In this paper, the authors conducted a systemic review to describe the compound epidermal growth factor receptor (*EGFR*) mutations in non-small cell lung cancer (NSCLC) and revealed multiple *EGFR* mutations were found in less than 1%, the most frequent double mutations were T790M with L858R and exon 19 deletions with T790M, and the most common single mutation associated with double mutations was the mutation in T790M (de novo and acquired). The authors describe several important findings based on a systemic review, which enable us to make decisions in NSCLC treatment strategy with confidence.

First, multiple mutations in the *EGFR* gene are a rare event with its incidence of less than 1% (446 of 46,679 patients), which suggests a majority of patients having single *EGFR* mutation in clinical encounters. Exon 19 deletions and exon 21 L858R mutation are the most common *EGFR* mutations that constitute approximately 90% of all *EGFR* mutations (2,3). NSCLC harboring those common *EGFR* mutations have shown favorable treatment responses to EGFR-tyrosine kinase inhibitors (TKIs) (4). On the other hand, uncommon *EGFR* mutations, are considered to have a poor response to EGFR-TKIs, except for exon 18 G719 and exon 21 L861Q mutations (5). Patients with advanced NSCLC harboring *EGFR* mutations may develop disease progression mainly from secondary *EGFR* mutations. For example, the most frequent mutation after EGFR-TKIs treatment is exon 20 T790M mutation, and approximately 50% of patients receiving first- and second-generation EGFR-TKIs were reported to acquire T790M mutation, which is likely to be associated with drug resistance (6,7). Recent advances in tumor genotyping techniques provide not only accurate data, but also a higher probability of identifying atypical and multiple mutations in a single tissue or blood sample. Compound *EGFR* mutations, defined as double or multiple mutations in the EGFR tyrosine kinase domain, in which an EGFR-TKIs sensitizing mutation (such as G719X, exon 19 deletions, L858R, or L861Q) coexists with uncommon mutations involving other residues of the EGFR tyrosine kinase domain and show some sensitivity to EGFR-TKIs (5).

Identification of T790M mutation is essential in selection of appropriate EGFR-TKIs. Although treatment of *EGFR* mutation-positive stage IV NSCLC with EGFR-TKIs have improved long-term survival outcomes, acquired resistance to first- or second-generation EGFR-TKIs occurs approximately 10 months from initiation of therapy (8). Osimertinib, third-generation EGFR-TKI, is an oral, third-generation, irreversible EGFR-TKI that selectively inhibits both EGFR-TKI-sensitizing and *EGFR* T790M resistance mutations, with lower activity against wild-type *EGFR* (9). Among patients with *EGFR* mutation-positive

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(exon 19 deletions or exon 21 L858R) advanced NSCLC, the first line treatment with osimertinib had better efficacy and longer overall survival than those who received first-generation EGFR-TKIs (10,11). EGFR-TKIs as first-line treatment for postoperative recurrent *EGFR*-mutated NSCLC is also important in clinical practice. Since management of postoperative recurrent *EGFR*-mutated NSCLC is also important, our group has previously published 3 studies on the treatment and outcomes of patients with postoperative recurrent *EGFR*-mutated NSCLC and reported favorable survival outcomes, with a median progression-free survival ranging from 16.7 to 26.1 months (12-14).

Re-biopsy plays an important role in those who developed resistance to first- or second-generation EGFR-TKIs. In those situations, identification of T790M mutation will give us the reason for administering osimertinib. When an acquired resistance to first- or second-generation EGFR-TKIs is suspected, re-biopsy using a liquid sample or a tissue sample under the guidance of bronchoscopy-, thoracoscopy-, or computed tomography is highly recommended (15-17).

Overall, the recent contribution by Castañeda-González *et al.* was a seminal work that highlighted the importance of identifying T790M mutation in *EGFR*-mutated NSCLC. Further studies will be the next step to identify another target for patients who develop resistance to osimertinib.

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