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Heterogeneity in Tumors and Resistance to EGFR TKI Therapy— Letter

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We read with great interest a recently published article in your journal, entitled “Intratumoral Heterogeneity in *EGFR*-Mutant NSCLC Results in Divergent Resistance Mechanisms in Response to EGFR Tyrosine Kinase Inhibition,” by Soucheray and colleagues (1). Lung cancer cell lines with *EGFR* mutations have “favorite” acquired resistance mechanisms to EGFR-TKIs (2, 3), including PC9 cells in which the *EGFR* T790M secondary mutation emerges directly, while HCC4006 cells often utilize epithelial-to-mesenchymal transition (EMT). In this article, Soucheray and colleagues showed that combined inhibition of EGFR and TGF β receptor prevented the emergence of resistance via EMT in HCC4006 cells. HCC4006 cells, which acquired resistance to the combination therapy, instead, developed the T790M mutation. As the T790M mutation is a treatable resistance mechanism employing third-generation EGFR-TKIs (4), a reasonable treatment strategy would anticipate that lung cancer cells would eventually result in emergence of the T790M mutation (3).

Translating these findings to the clinic, however, it is essential to identify biomarkers that predict acquired resistance mechanism(s) to EGFR-TKIs prior to treatment. Because some resistance mechanisms are believed to occur through the “selection” of preexistent minor resistant clones, it is reasonable to analyze pretreatment samples using high-throughput methods (5). In their study, however, Soucheray and colleagues failed to adequately explain the emergence of T790M mutation by analyzing the prevalence of T790M allele in parental cells (1), in which the number of HCC4006 cells (0.0738%) was greater than PC9 cells (0.0360%), which often develop acquired resistance via T790M mutation (2). We therefore suggest that at least two additional factors should be considered. First, *EGFR* gene copy number gain (CNG) should be assessed to make an estimate for the prevalence of preexisting minor clones with T790M mutation. Because it is probable that T790M mutation exists in a part of *EGFR* allele with an activating mutation, as shown in Fig. 1A, *EGFR* CNG can project an apparent lower T790M allele ratio. Second, balances between the potential

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resistance mechanisms should be important to predict upcoming resistance mechanisms (Fig. 1B). Therefore, a biomarker(s) that may predict the emergence of resistance via EMT, for example, preexisting EMT cells, should be identified. In clinical settings, the prediction of resistance mechanisms should be more difficult due to the effect of the microenvironment (5).

EGFR-TKI has prolonged the survival of lung cancer patients with *EGFR* mutation. We believe that a rational upfront poly-therapy that cotargets EGFR and resistance mechanism(s) is a reasonable strategy to evaluate in future studies to further improve their outcomes.

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Figure 1.

Predicting the acquired resistance mechanism(s). A, *EGFR* gene CNG affect the T790M allele ratio. For example, in the case of a tumor that includes 0.1% minor clones with T790M mutation, the T790M allele ratio is 0.05% without *EGFR* CNG (left), whereas the ratio is 0.025% in a tumor in which cells harbor four copies of *EGFR* (right). B, schematic representation of potential resistance mechanisms in HCC4006 cells and PC9 cells.