

EGFR Mutation and Response of Lung Cancer to Gefitinib

TO THE EDITOR: Kobayashi et al. (Feb. 24 issue)¹ report that a second mutation in the gene encoding the epidermal growth factor receptor (*EGFR*), one resulting in a threonine-to-methionine substitution at amino acid position 790 (T790M), was associated with acquired resistance to gefitinib in their patient and that this mutant gene had been absent from the primary non-small-cell lung cancer. In a reanalysis of the data from the 397 subjects we have previously described,^{2,3} we identified two women who had never smoked who had non-small-cell lung cancer and harbored two *EGFR* mutations — T790M and a leucine-to-arginine substitution at amino acid position 858 (L858R) — in resected tumor specimens before treatment with chemotherapy or radiotherapy. Both patients later had recurrent disease and eventually died — outcomes suggesting that tumors with both the L858R and T790M mutations are very aggressive. One patient was treated with gefitinib and had progression.

These findings indicate the existence of cases with inherent double mutations and provide evidence that the T790M mutant genotype is an important factor conferring resistance to gefitinib in non-small-cell lung cancers containing *EGFR* sensitivity mutations. In addition, detecting T790M may be useful for predicting pretreatment resistance to *EGFR* tyrosine kinase inhibitors. Our observation, together with data from recent reports,^{1,4} may help clarify the role of *EGFR* mutations in the development of *EGFR*-related non-small-cell lung cancer and help establish effective strategies against specific subtypes of non-small-cell lung cancer.

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THE AUTHORS REPLY: Dr. Toyooka and colleagues describe two patients whose lung tumors harbored a T790M mutation before treatment with chemotherapy or radiotherapy was begun and suggest that this mutation might be a marker of tumor aggressiveness as well as resistance to gefitinib therapy. In the cases we and others¹ have described, the T790M mutation was not found in specimens from untreated patients. Nevertheless, the possibilities do exist that this second mutation might be present in some tumors at a low frequency at the time of diagnosis and that tumor cells harboring the mutation might be enriched over time during treatment with gefitinib or erlotinib. By analogy, imatinib-resistant *BCR-ABL* mutations have, on occasion, been detected in specimens from patients with untreated chronic myeloid leukemia.^{2,3} We agree that such interesting findings should motivate further research to improve our understanding of the role of *EGFR* in non-small-cell lung cancers, to encourage the development of alternative *EGFR* inhibitors able to overcome such resistance mutations, and to incorporate the knowledge gained into clinical treatment.

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