The Epidermal Growth Factor Receptor D761Y Mutation and Effect of Tyrosine Kinase Inhibitor

In Response: We appreciate the comments from Dr. Toyooka and his colleagues with regard to our article entitled “Novel D761Y and common secondary T790M mutations in epidermal growth factor receptor (EGFR)–mutant lung adenocarcinomas with acquired resistance to kinase inhibitors” (1). In response to their letter, we make the following points:

(a) We acknowledged in our article that lack of tumor DNA from a pretreatment specimen precluded our ability to determine whether the D761Y mutation was inherent or secondary. However, unlike the patient described by Tokumo and colleagues (2), the patient in whom we found the D761Y mutation had an initial partial response to gefitinib. The patient they described did not respond to first-line treatment with gefitinib. Taken together, these data further suggest that the patient we described did not have the D761Y mutation before treatment with gefitinib.

(b) We did not rely on a single assay to determine the effect of the EGFR D761Y mutation on sensitivity to gefitinib. Our findings in 293T cells suggested that the D761Y mutation, when combined with a drug-sensitive L858R mutation, modestly reduced sensitivity to gefitinib. However, to confirm results from this surrogate kinase assay, we carried out a more stringent test; we used a well-established Ba/F3 cell system to show that cells expressing both the L858R and D761Y mutations had a survival advantage in the presence of kinase inhibitors over cells expressing just the L858R mutation alone. Because the D761Y mutation was found in a growing brain lesion and because the concentration of gefitinib in the central nervous system can be 100-fold less than that in blood (3), even a slightly reduced sensitivity to drug could allow for growth of clones harboring the D761Y mutant within the brain of a patient receiving gefitinib.

(c) We agree that further investigation of patients undergoing treatment with gefitinib or erlotinib will yield clues for novel strategies to overcome inherent and acquired resistance. Neither of the studies (1, 2) can exclude the possibility that other molecular factors did not additionally contribute to drug resistance in the two patients with D761Y mutations.

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References
Response to CCR-07-0070

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