Afatinib + Cetuximab First-line in EGFR-Mutant Lung Cancer—Letter

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We read with great interest the article by Pirazzoli and colleagues on the ability of afatinib and cetuximab (AC) combination to delay resistance compared with afatinib alone (A) in a mouse model of EGFR-mutant lung adenocarcinoma (1). The main mechanism of resistance to AC in animals was the T790M mutation. It was detected in the same proportion than observed in human tumors that became resistant to first- or second-generation EGFR tyrosine kinase inhibitors (TKI). Assuming that no other new molecular alteration was associated with T790M mutation in the AC-resistant clones, these results suggest that the delayed appearance of resistance is not due to a shift toward other mechanisms of resistance associated with a more indolent disease but rather to the reduced ability of T790M clones to emerge. This may be due to the rapid and deep decrease of proliferated tumor cells that is achieved with AC limiting the emergence of resistance clones. This may also explain why AC is not more effective than A when a high number of resistant cells is already present in the tumor. The importance of rapidly and deeply reducing the pool of resistant clones from which resistance emerges has already been highlighted by the successful use of highly active antiretroviral therapy for HIV patients (2). Together with results from Meador and colleagues showing activity of third-generation TKIs in EGFR-resistant tumors, these data strongly support the evaluation of AC and colleagues showing activity of third-generation TKIs in AC-resistant tumors, these data strongly support the evaluation of AC in TKI-naïve rather than TKI-treated patients (3). Although toxicity of AC is significant, it has been evaluated only in heavily pretreated patients so far, and toxicity of EGFR TKIs is now better managed. Importantly, this approach should not preclude further efficacy of third-generation TKIs. Other perspectives for improvement of first-line treatment of EGFR-mutant adenocarcinoma include combination of bevacizumab to EGFR TKIs, which has shown encouraging results in selected Japanese patients from a phase II trial, and use of third-generation TKIs (4). However, this last approach may delay resistance only in patients who would have developed a T790M mutation, and may favor emergence of heterogeneous mechanisms of resistance which may be more difficult to control (5). For all these reasons, the French Cooperative Thoracic Intergroup IFCT will soon start the IFCT-1503 ACE-Lung study, a randomized phase II study evaluating AC combination as first-line treatment for EGFR-mutant non–small cell lung cancer patients.

Disclosure of Potential Conflicts of Interest

A.B. Cortot is a consultant/advisory board member for Boehringer Ingelheim. No potential conflicts of interest were disclosed by the other authors.

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