Editorial

Is the third generation EGFR TKIs the solution for making EGFR mutant NSCLC a curable disease?

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Much promise and encouragement has been linked to the treatment of patients with advanced NSCLC harboring EGFR mutations. The first generation EGFR TKIs (e.g., erlotinib/gefitinib) gave promise as single agent therapy in the first-line setting (1). The second generation EGFR TKI with covalent irreversible binding to the receptor and with the potential to target heterodimers of the Erb-B receptors gave further promise regarding response, progression-free survival and overall survival, particularly in patients with exon 19 deletions (2-4). However, while significant improvement in outcome was achieved with these agents, no reports on cure have yet been seen! The main reason for that is the development of acquired resistant abnormalities with the most common resistant mechanism the development of T790M mutations (5). Most recently we learned about the third generation EGFR TKIs, which are designed to target the activating EGFR mutations as well as the resistance T790M mutation. AZ 9291 is one of these third generation EGFR TKIs and the results from the phase I/II study in patients with advanced NSCLC with EGFR Mutation and acquired resistance was presented at ASCO Annual Meeting 2014 by Dr. Janne *et al.* with very promising efficacy results in patients with T790M mutations (RSP: 64% and DCR: 94%) (6). The drug was well tolerated without any serious side effects. As a matter of fact, the new generation EGFR TKIs spares the EGFR wild type and, therefore, the patients will not suffer from the "traditional" EGFR side effects such as skin rash, diarrhea, hypomagnesemia, etc. Thus, much improvement has been achieved in this particular subgroup of advanced NSCLC patients. The current question is whether this therapy is enough to achieve long-term remissions and eventually cure by itself? Another question is of course whether the new generation EGFR TKIs is better than the previous generations in first-line therapy? A crucial element in this discussion is the fact that T790M mutations are not the only resistant mechanism. Several other mechanisms have been identified and more mechanisms for resistance to EGFR TKIs are expected to be learned in the future. Among already well known resistant mechanisms are activation of the MET pathway, transition to small cell carcinoma morphology, and based on preclinical data a possible role of FGFR, Mer and Axl as part of the acquired resistance to EGFR TKIs (5,7). Thus, while the development of the new generation EGFR TKIs represent a significant achievement in the fight for "curable" EGFR mutant tumors, most likely a partnership with other agents will be needed in order to achieve the goal.

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