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To Target or Not to Target, That Is the Question

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To the Editor: Ramalingam et al[1] recently reported the interesting results achieved with dacomitinib (PF-00299804), a pan–human epidermal growth factor receptor (HER) inhibitor. The authors demonstrated that dacomitinib was able to selectively, irreversibly (covalently) bind to the adenosine triphosphate domain of each of the three kinase-active members of the HER family: epidermal growth factor receptor (EGFR)/HER1, HER2, and HER4. In addition, dacomitinib demonstrated significantly improved progression-free survival compared with erlotinib in the treatment of non–small-cell lung cancer, with acceptable toxicity. The authors concluded that the progression-free survival benefit was observed in most clinical and molecular subsets, notably *KRAS* wild-type/*EGFR* any status, *KRAS* wild-type/*EGFR* wild-type, and *EGFR* mutants.

In this phase II trial, which was not powered for subgroup analysis, it is important to note that the significant imbalance (20.2% *v* 11.7%) in *EGFR* mutations in favor of dacomitinib may be principally responsible for the overall positive results. In fact, patients with *EGFR* mutations shift the risk of progression from a reduction of 34% to 30%, rendering the overall results not statistically significant. Similar results, also not statistically significant, are found if we consider only the subgroup of patients with wild-type *EGFR* mutations. However, an interesting benefit in wild-type *EGFR* mutations can be hypothesized, possibly driven by other biomarkers, such as the overexpression of HER2 or the activation of the phosphatidylinositol 3-kinase pathway.[2,3]

We agree that dacomitinib is an interesting drug, but its development should not be in an unselected patient population. Today, a target agent must be used for a particular target to avoid another "me too" drug for unselected patients.

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