To Target or Not to Target, That Is the Question

**To the Editor:** Ramalingam et al. recently reported the interesting results achieved with dacomitinib (PF-00298804), 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% vs 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.

**REFERENCES**


DOI: 10.1200/JCO.2012.45.9818; published online ahead of print at www.jco.org on January 28, 2013