The article by Akamatsu and colleagues in this issue of JAMA Oncology describes a phase 2 randomized clinical trial that tests the value of adding the vascular endothelial growth factor inhibitor bevacizumab to osimertinib in 81 Japanese patients with EGFR mutation–positive advanced non–small cell lung cancer (NSCLC) and T790M mutation–positive acquired resistance on a prior epidermal growth factor receptor (EGFR) inhibitor. In contrast with what many of us may have expected, the data revealed no hint of a favorable signal for progression-free survival (PFS) or overall survival (OS) with the combination.

Notably, osimertinib is commonly administered as first-line treatment for EGFR mutation–positive advanced NSCLC today, in the wake of the observed significant efficacy benefit, including in OS, with osimertinib over a first-generation EGFR inhibitor in previously untreated patients with EGFR–mutated disease in the FLAURA trial. One might therefore argue that the results seen by Akamatsu and colleagues in patients with EGFR T790M–mutated disease with acquired resistance to a prior EGFR inhibitor may not apply to osimertinib/bevacizumab administered in the first-line setting. However, these negative results are consistent with those observed in the single-arm phase 1/2 trial conducted by Yu and colleagues of osimertinib with bevacizumab in previously untreated patients with advanced EGFR mutation–positive NSCLC. The investigators for this US-based trial demonstrated a median PFS of only 18.4 months, numerically inferior to the median PFS of 18.9 months with osimertinib alone in the global FLAURA trial. Meanwhile, studies from Japan of erlotinib with or without bevacizumab as first-line treatment for EGFR mutation–positive NSCLC have demonstrated a significant improvement in PFS not accompanied by an improvement in OS, nor have we yet seen a prolonged OS with the combination of erlotinib and ramucirumab over erlotinib alone.

Taken together, the available data on the combination of a vascular endothelial growth factor inhibitor with an EGFR inhibitor have not demonstrated a survival benefit over an EGFR inhibitor alone, and the emerging data with osimertinib/bevacizumab are best characterized as disappointing. Regardless, a phase 3 randomized clinical trial of osimertinib with or without bevacizumab (ClinicalTrials.gov Identifier: NCT04181060) is being conducted through ECOG-ACRIN, propelled by a presumption of benefit rather than an assessment of the clinical data available.

Unfortunately, we all too frequently see our optimistic hopes based on impressive data from phase 2 trials dispelled when these approaches are battle tested in a larger, multicenter trial; it is almost unprecedented to see results of a phase 3 trial emerge as far superior to those of a preceding phase 2 trial. Phase 2 trials are conducted to identify which strategies demonstrate such clear promise that they merit being explored in phase 3 trials, which require vast investment, including the opportunity for patients to participate in research that has a meaningful probability of becoming a significant clinical advance. It is regrettable if we bypass the critical step of awaiting the signal from smaller clinical trials, particularly if that signal is a warning sign of likely futility.