The one-size-fits-all approach for drug development of targeted agents in solid tumors has shown disappointing results in recent years. Although some new drugs have been approved, for most of them, the clinical benefit demonstrated in pivotal phase III trials has been small. Interestingly, even for drugs tested in enriched populations for a specific target, the improvement in clinical benefits was tiny. These results, in association with the high cost of these medicines, have been the topic of a recent controversial debate in the oncology community and also the focus of some commentaries in *Journal of Clinical Oncology*. These articles called for a reduction in the cost of these drugs and a change in the design of clinical studies with the intention of detecting more clinically meaningful benefits. Although we agree with the aspects mentioned in these articles, we will like to add some suggestions that in our view could enrich the ideas mentioned in them.

In most of the studies of targeted drugs in solid tumors, patient populations were not enriched on the specific drug targets because of unavailability of validated predictive biomarkers. Without any selection, it is unlikely that targeting of only one oncogenic pathway in the context of a complex aberrant biologic scenario (which applies to solid tumors) will be able to produce significant antitumor responses. In this context, preclinical evidence suggests that clinical cocktails with drug combinations against important oncogenic events could improve the antitumor activity of single agents. Moreover, the appearance of compensatory activating pathways as mechanisms of resistance to targeted agents, such as *MET* amplification or epidermal growth factor receptor secondary mutations to tyrosine kinase inhibitors in lung cancer, further suggest that adequate therapy of solid tumors must rely on combinations of targeted drugs. The main challenge is how to identify the right combinations, which, in principle, should be supported by strong preclinical data. This should not be confounded with the administration of targeted drugs without biologic evidence using the classical way chemotherapy combinations have been tested. Two successful examples of this approach are identification of phosphatidylinositol 3-kinase (PI3K) activation in K-RAS-driven tumors and the rationale for the combination of PI3K and mitogen activated protein kinase pathway inhibitors, and identification of the activity of poly adenosine diphosphate (ADP)-ribose polymerase inhibitors in tumors lacking some of the DNA mechanisms of repair (such as tumors with *BRCA1* and *BRCA2* mutations) and their synergistic action with platinum-based agents.

In solid tumors, most of the pivotal randomized phase III studies, which led to the approval of new compounds in the metastatic setting, required a large number of patients (between 500 and 800) to detect a small clinical benefit. Interestingly, in phase III clinical trials in which selection of patients was enriched on target (eg, human epidermal growth factor receptor 2 for trastuzumab and lapatinib, and c-Kit for sunitinib), a smaller number of patients was needed (approximately 400) to detect clinical benefits. Indeed, for the approval of imatinib in gastrointestinal stromal tumor, no randomized phase III trial was needed as a result of the important antitumor activity observed. In addition, studies without selection of patients on the basis of a specific target detected, smaller differences (hazard ratio approximately 0.60 to 0.80; risk reduction 40% to 20%) compared with those against a known target (hazard ratio approximately 0.30 to 0.50; risk reduction 70% to 50%). If combinations of new targeted drugs have a potential to increase the antitumor activity, smaller clinical trials should be able to detect benefits of new drugs in clinically more relevant end points (eg, overall survival). An example is the phase III registration trial for the poly adenosine diphosphate (ADP)-ribose polymerase inhibitor BSI-201 in triple-negative breast cancer, which is planned to enroll 420 patients with a primary end point of overall survival. In contrast, the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) phase III clinical trial is testing everolimus with exemestane after progression to letrozole or anastrozole in estrogen receptor–positive metastatic breast cancer with an estimated enrollment of 705 patients, and a primary end point of progression-free survival instead of overall survival. We envision that drug combinations based on the identification of the right biologic scenario will lead to a reduction of the time needed for drug approval (eg, estimated time of accrual for BSI-201, 36 months v BOLERO-2, 54 months), and finally to a lower cost of the medication.

Commercial strategies associated with pharmaceutical companies have been the main reason for the limited drug combination studies with novel targeted agents. Given that drugs are usually developed by different companies, concerns about toxicity and intellectual property are always alleged. To overcome this situation, agreements between pharmaceutical companies are mandatory, and some examples of these are emerging. Thus, AstraZeneca and Merck announced a phase I trial combining compounds from both companies to cotarget the PI3K-AKT and mitogen activated protein kinase pathways, and the same approach has been taken by Novartis and GlaxoSmithKline. Although this approach could be considered risky, we should learn from previous experiences such as the clinical development of antiviral combinations against AIDS, where a platform involving many industries was created to test medications with successful results.
In conclusion, biologic evidence, clinical data, and previous experience in other disease areas propose that it is time for a change in the current way drug development is done. To benefit cancer patients, better clinical studies should be based on strong preclinical evidence and be focused on testing combinations of targeted drugs in selected populations of patients. In addition, rational drug combinations could result in shorter time needed to develop targeted drugs and in lower drug cost. Fortunately, the one-size-fits-all approach in the drug development is coming to its end.