From the Editor

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In this month's AJHO, an important issue is addressed in a review on the recently approved cyclin dependent kinase (CDK) inhibitor, palbociclib. Why does a targeted drug seemingly have no target? Palbociclib is now used by many as the preferred therapy for one of the most common situations in oncology – first line hormonal therapy for hormone-sensitive breast cancer in the postmenopausal setting. Yet this CDK 4/6 inhibitor does not seem to have selectivity for CDK-driven tumors as would be predicted, such as those with cyclin D or CDK4 amplification. In fact, neither does the last approved hormone therapy "augmenter," everolimus. As an mTOR inhibitor, everolimus would be expected to be more effective in tumors driven by the relatively common driver lesion of this pathway, mutations in the p110α catalytic subunit of PI3 kinase (PIK3CA). But careful analysis of tumors obtained from the randomized BOLERO-2 study failed to demonstrate this. So what are we to make of these 2 major examples of "targetless" targeted drugs? They both clearly have a major impact in ER-positive breast cancer, doubling time to progression, but seemingly with no demonstrable benefit in overall survival. While the pivotal trials were not designed nor powered to demonstrate this, the number of events, at least in the case of everolimus, do not reveal the same types of survival impacts seen with antibody-based HER2 therapy. Could it be that growth factor pathways are simply too malleable, whereas therapies postulated to have an immune component, like trastuzumab and pertuzumab, are not as easily bypassed?

Nevertheless, we certainly welcome the change in the landscape of hormone receptor-positive breast cancer even though the initial lines of therapy have become more complicated, with new side effects, monitoring requirements, and of course, financial costs. The full impact on practice and the trickle down dilemmas surrounding decision-making for later lines of therapy in the absence of evidence with newer drugs will take some time to sort out. Trials will need to be done that may not necessarily be priorities for pharmaceutical companies—perhaps to be taken on by cooperative groups. It is not clear that such trials can keep up with the stream of drugs entering this space, such as inhibitors of PI3K, Akt, histone deacetylase, and TORC1/2. Still, these developments are important as the largest numbers of breast cancer deaths still occur in hormone-receptor-positive and HER2-negative cases. It could very well be that mortality reductions need to await the use of these drugs in the adjuvant setting—these trials are well underway with everolimus and palbociclib.