

EDITORIALS



Palbociclib — Taking Breast-Cancer Cells Out of Gear

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Palbociclib is a first-in-class inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). In some but not all cell types, these proteins regulate the transition from the G1 phase to the S phase of the cell cycle. CDK4 and CDK6 regulate proliferation in some types of epithelial cells, including estrogen-receptor–positive luminal cells.¹ In estrogen-receptor–positive breast cancers, estrogen induces CDK4 and CDK6 activity, leading to hyperphosphorylation of RB (the gene encoding retinoblastoma protein) and promotion of cell-cycle traversal; this is the rationale for testing CDK4 and CDK6 inhibitors in estrogen-receptor–positive breast cancer.

In this issue of the *Journal*, Turner and colleagues report the results of the PALOMA3 trial,² a double-blind, placebo-controlled, randomized, phase 3 study of palbociclib added to the estrogen-receptor down-regulator fulvestrant in previously treated estrogen-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative metastatic breast cancer. The addition of the CDK4 and CDK6 inhibitor more than doubled the median progression-free survival as compared with fulvestrant alone, from 3.8 months to 9.2 months. The rate of objective response with palbociclib–fulvestrant (10%) was not much higher than the rate with placebo–fulvestrant (6%), but the rate of clinical benefit (response or prolonged stable disease) at 6 months was significantly higher with palbociclib–fulvestrant (34%, vs. 19% with placebo–fulvestrant). There was no significant between-group difference in overall survival, but it is too early to expect such a difference. Palbociclib had a similar effect when added to a nonsteroidal aromatase inhibitor in the first-line setting in the randomized, phase 2 PALOMA1 trial,³ which was the basis for

the Food and Drug Administration granting palbociclib accelerated approval in 2015. With the PALOMA3 trial, palbociclib has now been shown to improve outcomes when added to two different endocrine therapies and in both previously untreated patients and previously treated patients with estrogen-receptor–positive metastatic breast cancer. For context, there are about 40,000 new patients with metastatic breast cancer per year in the United States.

Although these results are very promising, there are reasons to be cautious. Estrogen-receptor–positive breast cancer is biologically heterogeneous, and many patients do well with minimal treatment for many years. Palbociclib adds considerable cost and toxic effects, including mechanism-based myelosuppression, some fatigue, nausea, and an increased risk of infection. Ideally, we should seek to identify patients with an excellent prognosis with endocrine therapy alone as well as predictive biomarkers for palbociclib to have a benefit.

Prognostic biomarkers help to select patients with estrogen-receptor–positive breast cancer who are candidates for adjuvant endocrine therapy alone, and the same markers might be relevant in the metastatic setting.^{4,5} Several factors may predict the benefit of CDK4 and CDK6 inhibitors, including RB loss, RB phosphorylation, inactivation of CDK4 and CDK6 inhibitors such as p16^{INK4a} (CDKN2A), and amplification of cyclin-dependent kinases or the cyclins themselves. Inactivation of RB appears to predict resistance to CDK4 and CDK6 inhibitors, but two of the most promising biomarkers, loss of p16^{INK4a} and gains of cyclin D1, failed to predict a benefit for palbociclib in estrogen-receptor–positive breast cancer.³ This finding raises the question of

whether most or all of these cancers are dependent on CDK4 and CDK6, including those that are not cyclin D1–amplified or have no p16^{INK4a} loss. A molecular analysis of the cyclin D–p16^{INK4a}–RB pathway in breast cancer from the Cancer Genome Atlas supports this hypothesis,⁶ suggesting that most estrogen-receptor–positive breast cancers have intact RB. If so, then the focus may need to be on biomarkers of estrogen-independent growth, such as loss of RB by mutation, DNA copy-number loss, microRNA function, or other causes. For example, RB deficiency is predictably seen within a subset of rapidly proliferating luminal B breast cancers.⁷

For now, the “biomarker” for palbociclib efficacy appears to be the presence of hormone receptors, which encompasses most breast cancers and does not help us narrow the population that may benefit from this intervention to a significant degree. There are real costs to this lack of biomarker selectivity. In the PALOMA1 study, 10% of patients treated only with letrozole were still receiving protocol-directed treatment more than 2 years later. Simply adding palbociclib to letrozole in those patients from the beginning would have added toxic effects and approximately \$250,000 in costs per patient, without clear additional benefit.

We have many treatment options for estrogen-receptor–positive, HER2-negative metastatic breast cancer, including two drugs — everolimus and palbociclib — that augment progression-free survival when added to conventional endocrine therapies. What we don’t yet have is a strategy and a target population in whom to use these

drugs most effectively. This is important now but will have even greater implications if CDK4 and CDK6 inhibition lives up to its promise in the adjuvant setting, in which endocrine therapy is currently recommended to nearly 150,000 women in the United States per year. In that setting, it will be crucial to identify patient populations and tumor features predictive of benefit and, at the same time, to identify persons who would do well with endocrine therapy alone.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Another Beginning for Cystic Fibrosis Therapy

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Treatments for the fundamental defect in cystic fibrosis are beginning to come to fruition. Cystic fibrosis, an autosomal recessive disease of epithelial chloride transport, can be caused by more than 1000 mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (*CFTR*). However, these mutations fall into six functional categories,¹ which gives hope that therapies specific to particular mutant categories can be developed. The first success, ivacaftor, was approved by the Food and Drug Adminis-

tration (FDA) in 2012 for treatment of the 4 to 5% of patients who have the Gly551Asp mutation in *CFTR* and later for patients with other mutations in which the protein reaches the plasma membrane but does not open appropriately. In patients with the Gly551Asp mutation, ivacaftor corrects the sweat chloride defect, improves pulmonary function and patient-reported respiratory symptoms, and results in substantial weight gain.²

The prime therapeutic target, however, is the Phe508del mutation in *CFTR*. About half of pa-