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 Administration (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-

tients in the United States with cystic fibrosis are homozygous for this mutation, and more than 90% have at least one Phe508del allele. CFTR with this mutation presents a formidable challenge. Not only does it fold incorrectly, so that more than 98% is destroyed in the endoplasmic reticulum, but its "open probability" (i.e., the fraction of time that the CFTR channel is open) is reduced, and it is retrieved from the plasma membrane much more rapidly than normal CFTR; thus, this mutant protein spans mutant categories.[3] Ivacaftor can improve the open probability of this protein that is induced to reach the plasma membrane,[3,4] but it is ineffective in the treatment of patients who are homozygous for the Phe508del mutation. Another drug, lumacaftor, improves the processing of the mutant CFTR and prolongs its residence at the cell surface, but it does not improve its open probability.[3] When lumacaftor was combined with ivacaftor in vitro in cells that express Phe508del CFTR, chloride transport activity was greatly improved.[3]

In this issue of the *Journal*, Wainwright and colleagues[5] report the results of the TRAFFIC and TRANSPORT trials, two large studies conducted at cystic fibrosis centers around the world, in which they examined the effect of ivacaftor combined with lumacaftor in the treatment of patients who are homozygous for the Phe508del mutation. The two trials had similar results, which fosters increased confidence in their findings. The combination of lumacaftor and ivacaftor produced significant improvements in lung function and weight gain, as well as significant amelioration of respiratory symptoms and pulmonary exacerbations. However, the extent of improvement was not as great as that produced by ivacaftor alone in the treatment of patients with the Gly551Asp mutation. The forced expiratory volume in 1 second (FEV_1) increased by only about 3 percentage points, as compared with 11 percentage points with ivacaftor alone in patients with the Gly551Asp mutation.[2] To put these changes in context, approximately the same relative improvement was seen when inhaled DNase was introduced into the cystic fibrosis treatment armamentarium,[6] and greater improvement, about 10% of baseline FEV_1, was seen with inhaled tobramycin,[7] although neither drug addresses the basic defect in the protein.

Why was the response to ivacaftor combined with lumacaftor inferior to the response to ivacaftor alone? Drug–drug interactions between lumacaftor and ivacaftor, the former being a strong CYP3A inducer and the latter being a sensitive CYP3A substrate and weak inhibitor, not only necessitate higher doses of ivacaftor but also create potential difficulty with concomitant use of drugs that are commonly used to treat cystic fibrosis.[8] More effective treatment may require an individualized combination of doses rather than a single, fixed-dose combination. In addition, a critical interaction between ivacaftor and lumacaftor has been reported in two laboratory studies. In cell-culture models that express Phe508del CFTR treated with lumacaftor, prolonged exposure to ivacaftor interferes with the therapeutic effect of lumacaftor.[9,10] By 6 hours after exposure to the drug combination, 40% less protein escaped from the endoplasmic reticulum in the cultured cells, and there was concomitantly less chloride transport activity than was observed immediately after application of the drug combination. Although it is not certain that this interaction occurs in vivo, these observations provide a plausible explanation for the modest degree of improvement observed in the clinical studies despite good individual drug performance and expected synergy. Other drugs in combination might avoid these interactions.

Nevertheless, this is the beginning of effective therapy for cystic fibrosis associated with the most common mutant form of CFTR. With further drug development to avoid drug–drug interactions, even the challenging Phe508del *CFTR* mutation will almost surely come under excellent therapeutic control. The road to success has been long, despite diligence, enthusiasm, and excellent collaborative efforts among academics, industry, and patients. The report by Wainwright and colleagues is a celebration of the legions of investigators — involved in clinical and basic research, based in industry and academia — as well as the legions of patients all over the world, who together have paved the way for a new beginning in cystic fibrosis treatment.

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