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## Insights Into the Role of Progesterone Receptors in Breast Cancer

**TO THE EDITOR:** We have several issues with the comments of Olivotto et al and believe that there are compelling

reasons that justify the continued use of progesterone receptors (PR) in our armory of breast cancer management and treatment decisions.

The authors state, "breast tumors that are ER [estrogen receptor] -negative are so often also PR-negative that PR testing is no longer useful in clinical decision-making."<sup>1</sup> They also state, "Historically, the primary reason to perform PR testing was to identify ER-negative patients who may respond to hormonal therapy." These statements, in our opinion, represent a misunderstanding of the reasons for measuring PR—PR are *not* only measured to distinguish among ER-negative tumors, and while ER-/PR+ patients represent only 3% to 5% of patients, it is still an important group to identify. Rather, PR are primarily measured to distinguish two subsets of ER-positive tumors, with ER+/PR- tumors much less likely to respond to hormonal therapies, especially tamoxifen, than ER+/PR+ tumors.<sup>2</sup>

With regard to the latter, is the authors claim that "PR testing also does not influence therapy decision-making in ER-positive patients," based on the results of the Early Breast Cancer Trialists' Collaborative Study<sup>3</sup> in which PR status was defined by "any such measurement," and in which PR measurements were generally not available. Two recent studies challenge this claim. First, when accurately measured, PR status is an independent predictive factor for benefit from adjuvant endocrine therapy with tamoxifen.<sup>4</sup> In this study, approximately 30% of patients were biochemically ER+/PR- and responded poorly to tamoxifen; this is not a trivial percentage of patients in the context of cost-effectiveness. Although the molecular mechanisms associated with the resistant phenotype of ER+/PR- patients have yet to be elucidated, it has been suggested that low PR may reflect enhanced growth factor signaling and enhanced tumor aggressiveness<sup>5</sup>—a hypothesis that can be readily tested. Second, are the recent provocative results from the Arimidex or Tamoxifen Alone or in Combination (ATAC) study showing only a modest advantage for anastrozole compared to tamoxifen in the ER+/PR+ group, while there was a major benefit for anastrozole in the ER+/PR- subgroup.<sup>6,7</sup> Although this study is undoubtedly preliminary and awaits confirmation, it did involve thousands of patients and supports the data from Bardou et al.<sup>4</sup> Finally, in view of recent trials showing a significant advantage for the sequence of tamoxifen followed by an aromatase inhibitor, it is an intriguing possibility that PR status could be used to select initial therapy. ER- and PR-positive tumors might be best treated by tamoxifen followed by an aromatase inhibitor, while ER+/PR- tumors might receive initial treatment with an aromatase inhibitor because of their relative resistance to tamoxifen. This hypothesis should be tested in ongoing clinical trials.

We also want to point out that we do not yet appreciate the clinical significance of weak PR positivity. No large retrospective studies have validated the clinical significance

of PR assessment by immunohistochemistry (IHC). An important study that defined the lower limit of ER positivity in breast tumors as 1% to 10% weakly positive cells (based on a univariate cut point analysis of all possible IHC scores and disease-free survival in patients receiving adjuvant tamoxifen therapy) decisively demonstrated that calibration of receptor positivity with improved treatment outcomes was optimal.<sup>8</sup> Based on these data, it is therefore unjustified to “adopt a low threshold to discontinue hormonal therapy among patients with weak ER-positive tumors. . .” as suggested by the authors.<sup>1</sup> As yet, there is no such standard for assessing PR IHC status, and unfortunately, diverse methodologies and arbitrary cut points are being employed in the clinical setting. A more prudent approach is warranted when offering PR status determination by IHC and its use in decision-making.

Finally, one also needs to consider a recent pilot study examining the role of the two different PR isoforms as predictive biomarkers; patients with high PR-positive tumors and high PR-A isoform expression were significantly more likely to relapse with tamoxifen therapy.<sup>9</sup> These data support other work indicating that PR-A-rich tumors have heightened aggressiveness, and that abnormal PR-A excess is found in the healthy breasts of women with *BRCA1/2* mutations.<sup>10</sup> As we begin to individualize treatment decisions based on the subclassification of breast cancer into its many clinical and molecular entities, we cannot overlook the value of any measurements in even small populations of patients. It is unwarranted at this time to abandon PR in clinical treatment decisions, especially in light of the recent exciting studies provoking new interest and understanding of its clinical utility.

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**IN REPLY:** Fuqua et al describe a number of interesting pieces of preliminary data regarding the value of progesterone receptor (PR) testing in patients with estrogen receptor (ER) –positive breast cancer qualified by biochemical assays. The point of our study was to highlight the lack of additional value of PR testing among patients with ER-negative disease quantified by immunohistochemistry (IHC).<sup>1</sup> Although past reports suggest that ER–/PR+ disease made up 3% to 5% of breast cancers, our study of 192 ER-negative patients found that less than 1% were PR-positive cases, suggesting that in the era of IHC hormone receptor testing, PR testing adds little information to this subset of patients. Similarly, Bardou et al noted that PR status added limited prognostic information in untreated breast cancer patients. In their study, disease-free survival and overall survival were not significantly different for untreated patients with ER+/PR+ tumors compared with patients with ER+/PR– tumors.<sup>2</sup>

The question of whether PR status should influence adjuvant hormone selection is interesting. Bardou et al found that in patients treated with endocrine therapies, ER+/PR+ tumors were associated with a better prognosis