editorials

Testing Endocrine Response for Managing Primary Estrogen Receptor–Positive Breast Cancer

Mitch Dowsett, PhD[1]

Fifteen years ago, an international survey reported that identifying which patients with estrogen receptor–positive (ER+) human epidermal growth factor receptor 2–negative primary breast cancer could safely forego chemotherapy was oncologists' most important challenge for translational research.[1] At that time, the 21-gene Oncotype Recurrence Score test (RS) was already available,[2] but its application to many patients was uncertain, and the TAILORx and RxPONDER clinical trials were instigated to investigate this. The trials assessed the degree of benefit from chemotherapy in patients with RS 11-25 and 0-25 in N0 and N1 disease, respectively.[3,4] Most oncologists will be familiar with the major results: postmenopausal women with N0 or N1 disease and RS < 25 did not benefit from added chemotherapy; however, premenopausal patients with N0 disease and RS 16-20 gained absolute 2.7% in 5-year invasive disease-free survival (iDFS) and with RS 21-25 gained 5.8% in 5-year iDFS while those with N1 disease and RS 0-25 gained 4.9% in 5-year iDFS.

During the conduct of those studies, the ADAPT trialists created an ingenious multimodular study.[5] The endocrine trial within ADAPT has now been reported in the article[6] that accompanies this editorial (Fig 1). The aim was to describe the 5-year iDFS of patients with ER+ human epidermal growth factor receptor 2–negative pN0-1 breast cancer whose treatment was guided by a combination of RS and their endocrine therapy response (ET response). The latter was defined as Ki67 ≤ 10% after 3 weeks' presurgical endocrine therapy (ET; $Ki67_{post} \leq 10\%$). The primary comparison was between two groups of patients treated with ET alone: 868 patients with RS 0-11 (the control arm) and 1,422 patients with RS 12-25 and $Ki67_{post} \leq 10\%$ (the experimental arm). A third group of 694 patients with RS 12-25 and $Ki67_{post} > 10\%$ received chemotherapy before ET. The 5-year iDFS difference between the experimental and control arms was 1.3% (92.6% [90.8%-94.0%] *v* 93.9% [91.8%-95.4%], respectively) and just met the predefined boundary of noninferiority. Hence, without the addition of chemotherapy, patients with RS 12-25 and $Ki67_{post} \leq 10\%$ had an outcome not meaningfully different from those that had RS 0-11.

Presurgical ET is not routinely applied in clinical practice, so what information can be gained to make it worthwhile? Figure 2 illustrates the changes in Ki67 seen in 56 postmenopausal patients receiving 2 weeks of an aromatase inhibitor (AI) in the IMPACT trial.[7] Almost all tumors exhibited decreased Ki67—only four showed a numerical increase. A similar pattern was obtained with 2 weeks' tamoxifen, but the degree of suppression was significantly less.[7] This change or response in Ki67 reflects the biological sensitivity of individual tumors to ET and was found to predict the long-term clinical efficacy of the same therapy used postsurgically.[7-9]

The Ki67 value after 2 weeks' treatment can be considered an integration of the intrinsic prognostic information given by *baseline* Ki67 and the predictive value of *the change* in Ki67 over 2 weeks. Thus, the *2-week value* would be expected to, and has been shown to, relate to the residual risk of recurrence on ET.[10,11] The POETIC trial confirmed the greater prognostic information from Ki67 after 2 weeks' AI than at baseline.[11] Complete cell cycle arrest ($Ki67_{post} \leq 2.7\%$) is a prognostic term for those patients with exceptionally good prognosis on ET.[12]

Referring to patients with $Ki67_{post} \leq 10\%$ as endocrine responsive as in the ADAPT trial, and in some other studies,[13] can be conceptually confusing. In Figure 2, two cases are highlighted in blue that show substantial Ki67 suppression (response) with the AI but whose Ki67 values remain > 10% at 2 weeks, yet they would be called endocrine nonresponsive. The four cases highlighted in red have little or no change in Ki67, but their $Ki67_{post}$ is < 10%, yet they would be described as endocrine responsive. That is not to say making judgments based on residual Ki67 is incorrect, just that the terminology could be considered inaccurate. Although somewhat cumbersome, the subgroups would more accurately described as being at low or high residual risk.

The ADAPT trial used 3 weeks of ET, and some other trialists[12] have used 2-4 weeks of presurgical therapy before assessing Ki67. There have been no systematic studies to determine whether Ki67 suppression is increased between 2 and 4 weeks. However, in

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THE TAKEAWAY

In the article[6] that accompanies this editorial, the ADAPT trialists report the results of the endocrine component of their trial that assesses the value of decision making that includes a presurgical Ki67-based test of endocrine responsiveness and the 21-gene Recurrence Score. Short-term presurgical therapy can provide useful added information around the Recurrence Score test cut point of 25 and is an excellent scenario for discovery of biomarkers of resistance to endocrine therapy that have the potential to guide the selection of agents alongside adjuvant endocrine treatment.

postmenopausal women, there is probably relatively little change in that period: in the IMPACT trial, the geometric mean Ki67 suppression with an AI at 2 weeks and 12 weeks was 76.0% and 81.6% and by tamoxifen was by 59.5% and 61.9%, respectively.[7]

Presurgical endocrine treatment of premenopausal patients in ADAPT was almost invariably with tamoxifen. The Ki67 suppression achieved was much less than that in the 9% of postmenopausal women treated with tamoxifen. In premenopausal women, tamoxifen leads to increased plasma estradiol levels of up to 3,000 pmol/L,[15] which is about 100-fold higher than mean levels in postmenopausal women. At steady state, after about 7 weeks, in postmenopausal women, tamoxifen and its metabolites achieve > 99.9% saturation of ER[14] compared with approximately 95% in premenopausal women. Thus, 3 weeks' tamoxifen may be insufficient to achieve maximal Ki67 suppression in premenopausal patients, and the low proportion with $Ki67_{post} \leq 10\%$ is likely to be at least partly explained by this.

Like $Ki67_{post}$, RS aims to estimate the residual risk of recurrence for patients taking adjuvant ET alone.[2] Approximately 20% of the prognostic information in the RS is provided by five proliferation-related genes (related to worse prognosis), and approximately 60% by four estrogen response–related genes (related to better prognosis).[16] Therefore, there are some similarities in the approaches of the RS and the $Ki67_{post}$ to estimating risk with both involving an assessment of proliferation and an estimate of the benefit from ET. Given these similarities and that they both aim to estimate residual risk on ET, one would expect a correlation between them. The data from ADAPT support this: $Ki67_{post}$ was ≤ 10% in 78.8% of RS 0-11, 62.2% in RS 12-25, and 32.7% in RS > 25. The degree to which ET response enhances the information from RS in the group 12-25 cannot be assessed because those with $Ki67_{post} > 10\%$ received chemotherapy.

It was notable in ADAPT that in patients with RS 12-25 $Ki67_{post} > 10\%$, 5-year iDFS was 90.3% (87.25%-92.6%) despite their receiving chemotherapy. However, in the neoadjuvant rather than adjuvant context, the Z1031B study reported that only 2 of 36 patients with $Ki67_{post} > 10\%$ achieved a pathologic complete response when switched to chemotherapy, despite these being least partially endocrine-resistant in patients with persistent high tumor cell proliferation.[12]

It is clear that molecular estimates of risk of recurrence are largely independent of those using clinicopathologic factors such as histologic grade, tumor size, and nodal status.[17] Integration of the RS with such factors to create the Recurrence Score Pathology-Clinical[18] and subsequently the

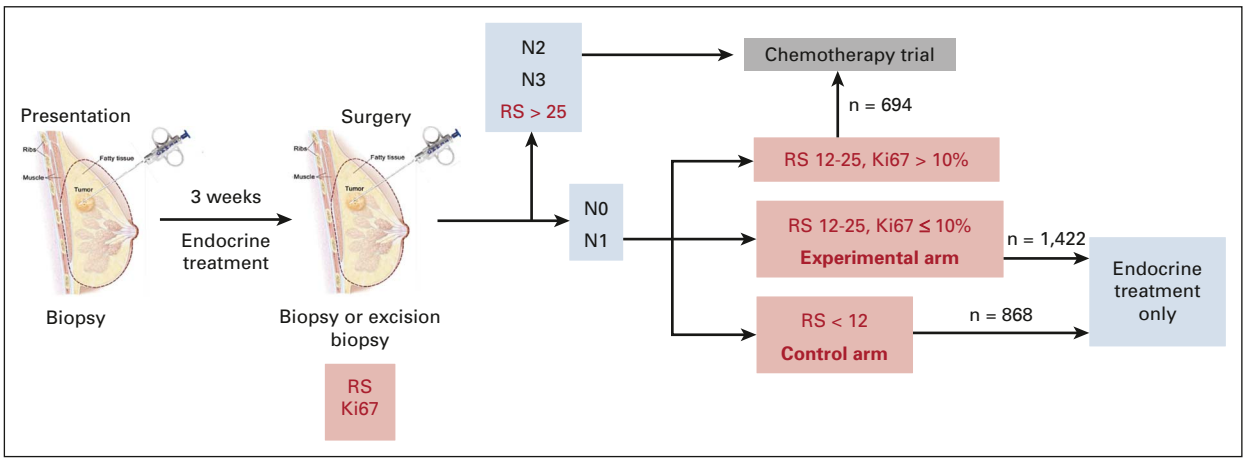

FIG 1. Schematic of the endocrine trial in ADAPT. The primary comparison was of the 5-year invasive disease-free survival in the experimental and control arms. RS, Recurrence Score test.

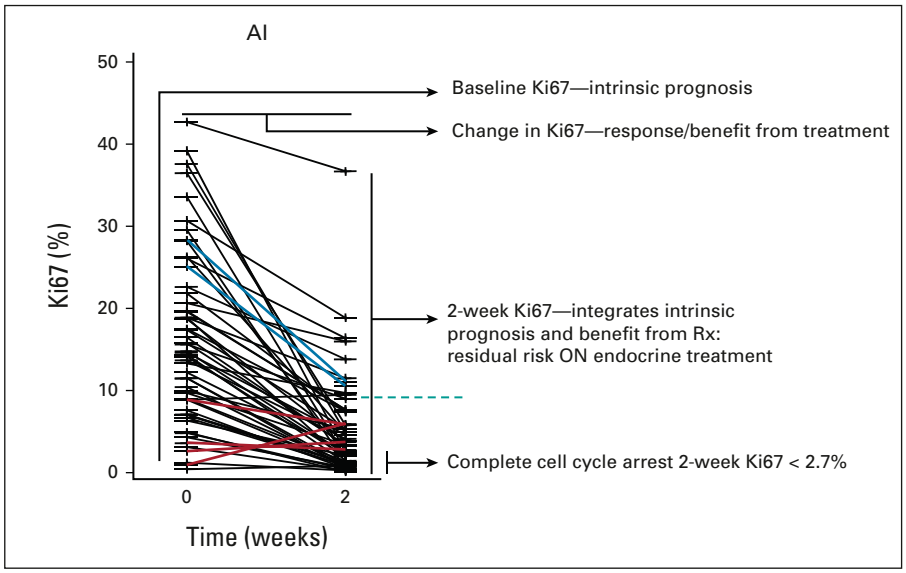

FIG 2. Individual Ki67 values before and after 2 weeks' treatment of 56 postmenopausal patients with an AI in the IMPACT trial.[7] Cases with $Ki67_{post}$ above or below the teal line would be referred to as ET nonresponsive or ET responsive, respectively. Cases highlighted in blue and red where this terminology is inaccurate. AI, aromatase inhibitor; ET, endocrine therapy.

RSClin[19] for patients with N0 substantially enhances the accuracy of prognosis beyond that with the RS alone. Tumor size (pT2-4 *v* pT0-1) and lymph node status (LN3 *v* LN0-2) contributed to a multivariate prognostic model for iDFS in ADAPT. Integrating such factors with $Ki67_{post}$ would create a more accurate tool for estimating risk than $Ki67_{post}$ alone and is arguably necessary for presurgical therapy for determining prognosis to be incorporated into routine care.

Measurement of Ki67 in breast cancer is subject to major variability between centers predominantly because of differences in visual scoring.[20] Within-individual pathologist scoring is, however, much more reproducible. In ADAPT, Ki67 staining and scoring was performed centrally by an unusual approach: Two pathologists created semiquantitative scores independently and then agreed a consensus result taking into account of the result from a digital pathology platform. It is clear that values derived at local centers often differed markedly from centrally measured values in ADAPT: The Spearman correlation was only 0.628. For local Ki67 analysis to be reliable, improved quality control and quality assessment schemes need to be implemented probably alongside straightforward image analysis to eliminate the subjective aspect of scoring.

As noted above, neither N0 nor N1 postmenopausal patients with RS 0-25 were found to benefit from added chemotherapy.[3,4] Thus, a view could be taken that there can be little value in ET response for determining chemotherapy use in such patients. However, given the implausibility that there is an absolute threshold for benefit at RS 25,[21] integrating RSs around that level with the ET response and other prognostic factors could provide more accurate risk assessment and improved decision making.

In premenopausal women with RS 0-25, it is plausible that it could bring useful additional information. However, given the above-mentioned concern about completeness of Ki67 suppression with 3 weeks' tamoxifen and that the adjuvant endocrine treatment may include ovarian suppressants ± AI or tamoxifen, much thought would be needed to determine the most informative presurgical endocrine intervention.

What is incontrovertible is that short-term presurgical therapy provides an excellent scenario for discovery of biomarkers of resistance to ET.[13,22] This has already been realized in other data from ADAPT.[23] These studies have the potential to identify resistance mechanisms in those patients with high $Ki67_{post}$ and to guide the selection of agents targeted to the respective mechanism alongside their adjuvant endocrine treatment.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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