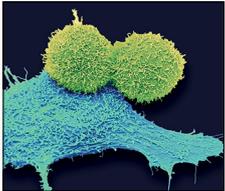




## Competing risks of extended adjuvant aromatase inhibitors



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See [Articles](#) page 88

The long-term risk of recurrence of hormone-receptor-positive breast cancer is well established. When competing risks of death are disregarded, there is an almost linear risk of recurrence over 20 years among women treated with 5 years of adjuvant endocrine therapy.<sup>1</sup> In women treated with 5 years of adjuvant tamoxifen, additional extended endocrine therapy with either tamoxifen or an aromatase inhibitor results in clinically meaningful reductions in the risk of recurrence and death from breast cancer.<sup>2,3</sup> However, until recently, little was known about the benefit of extending treatment in women who had received aromatase inhibitors within the first 5 years after diagnosis.

In *The Lancet Oncology*, Eleftherios Mamounas and colleagues report the results of the NRG Oncology/NSABP B-42 trial.<sup>4</sup> NSABP B-42 was a large, international, randomised, placebo-controlled trial of almost 4000 postmenopausal women who had completed about 5 years of endocrine therapy, including at least 2 years of treatment with an aromatase inhibitor, after diagnosis of early-stage breast cancer. Trial participants were randomly assigned to receive either an additional 5 years of letrozole or placebo. The trial did not meet its primary endpoint—disease-free survival was not significantly improved with letrozole compared with placebo. However, there were significant effects on the secondary efficacy endpoints of improved breast-cancer-free interval and reduced distant relapse, neither of which was an endpoint that included non-breast-cancer death as an event. These effects on breast cancer outcomes did not translate into any effect on overall survival. There was an increase in all-cause deaths in the letrozole group compared with placebo, an effect influenced predominantly by more non-breast cancer deaths in the letrozole group, although this increase was not statistically significant. Safety was similar to the known toxicity profile of aromatase inhibitors,<sup>5</sup> with a significantly increased risk of arterial thrombotic events after 2.5 years, and an increase, although not statistically significant, in osteoporotic fractures, perhaps reflecting screening and management of cancer therapy-induced bone loss.

The results of NSABP B-42 mirror those of other trials exploring the benefit of extending aromatase inhibitor-based therapy.<sup>6-8</sup> When including deaths

from any cause as the defining events of disease-free survival, individual studies report a non-significant 15–20% relative reduction in disease-free survival with aromatase inhibitors compared with no treatment. However, when excluding non-breast cancer deaths, there is a significant and larger magnitude of benefit from aromatase inhibitors. These findings highlight the importance of competing risks of death in the interpretation of long-term adjuvant breast cancer studies. Disease-free survival is a composite endpoint typically composed of loco-regional and distant recurrences, as well as contralateral breast cancers and death from any cause. Data show that with longer follow-up, the relative contribution of contralateral breast cancer and non-breast cancer death to defining events for disease-free survival increases. Concurrently, there is a reciprocal reduction in the contribution of loco-regional and distant recurrences.<sup>9</sup> Taken together, the evidence suggests that extended treatment with aromatase inhibitors improves breast cancer-specific outcomes, but an effect on disease-free survival is lost because of the contribution of non-breast cancer deaths. Such events are unlikely to be influenced favourably by extended endocrine therapy.

It has been argued that trials of extended adjuvant therapy should censor non-breast cancer deaths in primary analyses.<sup>6</sup> Although this approach results in a more focused assessment of the effect of therapy on breast cancer outcomes, it loses the capacity to explore the balance between benefits and risks of therapy. As described previously<sup>5</sup> and corroborated by the NSABP B-42 trial,<sup>4</sup> longer exposure to aromatase inhibitors results in adverse cardiovascular outcomes. Data show that in older women who have survived 5 years or more after diagnosis of breast cancer, cardiovascular disease exceeds breast cancer as the leading cause of death 10 years after diagnosis.<sup>10</sup> Excluding non-breast cancer deaths in the primary analysis would fail to capture the potentially adverse effect of aromatase inhibitors on cardiovascular mortality and might provide a biased interpretation of the balance between benefits and risks of treatment with extended aromatase inhibitors.

The NSABP B-42 trial highlights the importance of competing risks when making treatment decisions about the duration of adjuvant endocrine therapy. The

benefit of extended therapy is likely to be meaningful in patients at higher risk of recurrence (eg, those with nodal involvement or genomic risk signatures for late relapse) and in those who are less likely to have substantial competing risks of death (eg, younger patients and those without comorbidities, especially cardiovascular disease). Data from trials such as NSABP B-42 should be used to validate models incorporating breast cancer and competing risks, thereby allowing clinicians to tailor therapy to individual patients.

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## Exclusive MRI-targeted biopsy: not so fast

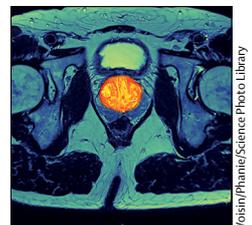
The MRI-FIRST trial reported by Olivier Rouvière and colleagues<sup>1</sup> in *The Lancet Oncology* is a thoughtfully designed, prospective investigation of men with suspected prostate cancer. This French multicentre study investigated the sensitivity of systematic versus targeted biopsy in the detection of clinically significant cancer. The greatest sensitivity in detecting prostate cancer was found by combining the two methods. Notably, only a third of clinically significant tumours were detected by either biopsy technique alone, which argues in favour of combining the two methods.

Previously, two of the most noteworthy investigations into MRI-guided prostate biopsy were the studies of Kasivisvanathan and colleagues (the PRECISION trial)<sup>2</sup> and Siddiqui and colleagues.<sup>3</sup> These studies both found that the proportion of prostate cancers detected by targeted biopsy was significantly greater than by systematic biopsy, thus providing a rationale for using targeted biopsy and omitting conventional systematic biopsy. However, in the PRECISION study,<sup>2</sup> men were randomly assigned to have either targeted or systematic biopsy. Combined biopsy was not done. In the study by Siddiqui and colleagues,<sup>3</sup> men with no MRI-visible lesions were excluded.

The design of the trial by Rouvière and colleagues differs from that of the aforementioned studies in

one important way: all men had systematic biopsy, regardless of MRI results, and if a lesion was visible on MRI, targeted biopsy was also done. Thus, a proportion of false-negative diagnoses could be calculated for men with no MRI-visible lesion. Furthermore, a comparison of targeted and systematic biopsies in the same individuals could be obtained. Of the 94 men diagnosed with clinically significant prostate cancer of International Society of Urological Pathology grade group 2 or higher, 13 were diagnosed by systematic biopsy only, 19 by targeted biopsy only, and 62 by combining both methods. By employing each patient as his own control, this study design provided a conclusion that was not apparent in either of the earlier investigations: although targeting might be somewhat more sensitive than systematic sampling, the combination of the two methods provides the greatest detection. These results are similar to those reported by Filson and colleagues in a large prospective study.<sup>4</sup>

It is not yet clear why MRI does not detect some foci of clinically significant prostate cancer. Many of the undetected lesions are small, and lesions less than 0.5 cc are often invisible on MRI.<sup>5</sup> Systematic biopsy will detect some of these foci because small-volume lesions might have relatively large surface areas. Specific morphologies of prostate cancer, such as the aggressive



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See [Articles](#) page 100