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BREAST CANCER

# Short-term NAT reveals resistance

Many breast-cancer-related deaths are attributable to recurrence of resected oestrogen receptor positive (ER+) tumours after adjuvant endocrine therapy. A study in 143 women with stage I–III ER+/HER2– breast cancer indicates that short-term neoadjuvant therapy (NAT) followed by genetic tumour profiling can not only uncover, but also offers the potential to avert, endocrine resistance.

The women received the aromatase inhibitor letrozole for 10–21 days before surgery, and the resected tumours were classified as 'sensitive', 'intermediate', or 'resistant' based on the level of positivity for the proliferation marker Ki67. Notably, 21% of tumours were 'resistant', with a high Ki67 index revealing ongoing cellular proliferation.

Whole-exome sequencing of 54 specimens revealed four *ESR1* (ER) fusions, all in resistant tumours. Amplifications of *CCDN1* (cyclin D1) and/or *FGFR1*, as well as *FGF3/4/19*, were also enriched in resistant tumours. These cyclin D1 and FGF-pathway aberrations are potentially targetable. Indeed, CDK4/6 and FGFR1 inhibition with palbociclib and lucitanib, respectively, synergistically abrogated the oestrogen-independent growth of *CCDN1*/*FGFR1*-co-amplified cancer cells. These aberrations were also detected in metastatic recurrences, suggesting they are drivers retained during the evolution of drug-resistant tumours. By contrast, *ESR1* point mutations, which are often detected at metastatic recurrence, occurred in only one tumour and, thus, might arise later in the disease course.

Carlos Arteaga, who led the study, concludes: "In patients with operable ER+ breast cancer, we can deprive the tumour of oestrogens for a brief period while the operation is planned, and the effect on tumour-cell proliferation can easily be assessed in the resected cancer; those with cancers in which cell proliferation is not inhibited harbour resistance mechanisms and might be at risk of early recurrence. This information can, in turn, be factored into subsequent systemic therapy: patients with a very good response to NAT might do well with adjuvant antioestrogen therapy alone, whereas those with resistant tumours might benefit from additional therapies."

*David Killock*

**ORIGINAL ARTICLE** Giltnane, J. M. *et al.* Genomic profiling of ER$^+$ breast cancers after short-term estrogen suppression reveals alterations associated with endocrine resistance. *Sci. Transl Med.* **9**, eaai7993 (2017)