on synthetic 2D mammograms, there is a risk of a kind of satisfaction of search (ie, the radiologist not searching those parts of the tomosynthesis stack rigorously).[7] In future, the combination of a radiologist and artificial intelligence might help to avoid such effects.

Encouraging findings from the To-Be trial are the lower proportion of recall and lower consensus for women screened with digital breast tomosynthesis versus digital mammography, and the higher positive predictive value for recalls for digital breast tomosynthesis compared with digital mammography, in concordance with many of the retrospective digital breast tomosynthesis studies done in the USA.[1] These are important outcomes in a screening scenario, and are contrary to most of the paired trials in which recall was increased with digital breast tomosynthesis; however, the baseline recall percentage with digital mammography was lower in these trials (2·5%[5] and 2·6%[9]) compared with the To-Be trial (4·0%) and the US studies.[1]

The To-Be trial is the first completed randomised, controlled trial with digital breast tomosynthesis, embedded in a real-world, population-based screening programme, and is an important contribution to the understanding and evidence of early implementation of digital breast tomosynthesis in breast screening. Given that this is the first randomised trial of this technology, it has the potential to contribute important future information on interval cancers. The study illustrates the complex interplay between new techniques and human readers in high-volume screening, and the challenges we will face in a possible future implementation phase of a new technology. The To-Be trial is probably not the beginning of the end of digital breast tomosynthesis screening, rather it heralds the arrival of randomised, controlled trials of tomosynthesis screening, with several now in progress.[10]

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I was involved as an external consultant for the planning of the To-Be trial in the initial phase of the protocol drafting. I have not since been involved at any time during the trial, analysis, or writing of the Article. I have received speaker's fees and travel support from Siemens Healthcare. I have a patent issued from the US Patent Office (US 9 833 203).

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Genetics to epigenetics: targeting histone deacetylases in hormone receptor-positive metastatic breast cancer

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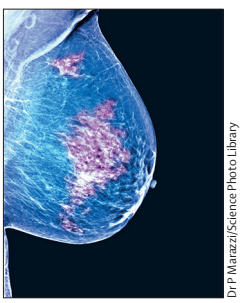
During the past decade, the use of combination targeted therapies for hormone receptor-positive, HER2-negative metastatic breast cancer has increased substantially. Besides approval of mTOR and CDK4 and CDK6 inhibitors in combination with endocrine therapy as second-line or later treatment,[1,2] positive results have been reported[3] with an α-specific PI3K inhibitor, alpelisib, in combination with endocrine therapy for patients with hormone receptor-positive, HER2-negative, metastatic breast cancer who have *PIK3CA* mutations. In addition to genetic alterations, epigenetic modification via histone deacetylases (HDACs) is another putative mechanism by which gene expression patterns can be changed, leading to cellular growth and proliferation.[4] In preclinical models of endocrine-resistant breast cancer, HDAC inhibition can restore oestrogen receptor dependency on, and

sensitivity to, anti-oestrogens,[5] highlighting the potential therapeutic role of HDAC inhibitors in endocrine-resistant metastatic breast cancer.

In *The Lancet Oncology*, Zefei Jiang and colleagues[6] present the results of a randomised, double-blind, placebo-controlled, phase 3 clinical trial (the ACE study) of the subtype-specific HDAC inhibitor tucidinostat (formerly known as chidamide) in combination with the steroidal aromatase inhibitor exemestane. Patients with hormone receptor-positive, HER2-negative metastatic breast cancer who had received at least one endocrine therapy were recruited at 22 centres in China. After a median follow-up of 13·9 months (IQR 9·8–17·5), median progression-free survival was 7·4 months (95% CI 5·5–9·2) in the tucidinostat plus exemestane group and 3·8 months (3·7–5·5) in the placebo plus exemestane group (hazard ratio [HR] 0·75 [95% CI 0·58–0·98]; p=0·033). Data for overall survival were not mature at the efficacy cutoff date. However, toxic effects—including cytopenias (eg, neutropenia, anaemia, thrombocytopenia), electrolyte abnormalities (eg, hypokalaemia, hypocalcaemia), and gastrointestinal side-effects (nausea and diarrhoea)—were more common with the combination of tucidinostat and exemestane than with placebo plus exemestane. 51 (21%) of 244 patients in the tucidinostat group had serious adverse events, compared with seven (6%) of 121 in the placebo group. As the authors state, the ethnic makeup of the cohort, mean age at diagnosis (breast cancer tends to be diagnosed at a younger age in China than in western countries), and the longer duration of follow-up in their trial compared with previous trials involving HDAC inhibitors could have had a role in the high frequency of adverse events.

How do Jiang and colleagues' results compare with those of other trials of HDAC inhibitors? In a landmark randomised phase 2 trial,[7] the combination of entinostat (an oral drug with specificity for class 1 HDAC isoforms) and exemestane was compared with exemestane alone in postmenopausal women with hormone receptor-positive, HER2-negative, metastatic breast cancer that had progressed on a non-steroidal aromatase inhibitor. Median progression-free survival was 4·3 months (95% CI 3·3–5·4) in the entinostat plus exemestane group and 2·3 months (1·8–3·7) in the exemestane monotherapy group (HR 0·73 [95% CI 0·50–1·07]). The corresponding figures for median overall survival were 28·1 months (95% CI 21·2 to not reached) and 19·8 months (17·0–26·7), respectively (HR 0·59 [95% CI 0·36–0·97])—results which prompted the US Food and Drug Administration to grant entinostat breakthrough designation status. The follow-up randomised phase 3 study (E2112) of exemestane with and without entinostat in US patients with recurrent hormone receptor-positive breast cancer has completed accrual (NCT02115282).[8] Although final data from this pivotal trial have not yet been reported, a press release by the sponsor stated that the study did not meet its statistical co-primary endpoint of improvement in progression-free survival.[9] However, overall survival, which was also a co-primary endpoint, has not been reported and these data are needed before firm conclusions about efficacy can be drawn.


Dr P. Marazzi/Science Photo Library

Why are the results from the two pivotal clinical trials of HDAC inhibitors seemingly divergent? Care is needed when comparing the studies, in view of differences between the patient populations in median age at diagnosis, ethnicity, endocrine sensitivity, and drug tolerability. Additionally, there are potential differences in target selectivity and potency between tucidinostat and entinostat, which could affect efficacy and toxicity. Practice patterns, including exposure to previous systemic regimens, could also have affected clinical outcomes. Patients in the USA are more likely to have received previous CDK4 and CDK6 inhibitors than those in China (only seven patients in the ACE study had previously taken palbociclib, all in the context of a clinical trial). Because the molecular pathways governing resistance to combinatorial therapy with CDK4 and CDK6 blockade could be distinct from those promoting resistance to anti-oestrogen monotherapy,[2] previous exposure to CDK4 and CDK6 inhibitors could modulate therapeutic benefit with subsequent HDAC inhibition. Finally, tumour biology considerations cannot be ignored. For example, in the ACE trial, Jiang and colleagues noted that the combination of tucidinostat plus exemestane improved progression-free survival compared with placebo plus exemestane in patients with oestrogen receptor-positive, progesterone receptor-negative tumours (HR 0·51 [95% CI 0·29–0·90]) but not in those with oestrogen receptor-positive, progesterone receptor-positive tumours (0·80 [0·60–1·07]),[6] which probably reflects the role of HDAC in downregulation of oestrogen-independent pathways and the potential increased benefit of HDAC inhibitors in endocrine-resistant tumours. In 2017, a seminal

translational study[10] showed the complex interplay between the growth factor signalling pathway and epigenetic modifiers in mediation of the activation of oestrogen receptors. Additional biomarker studies assessing the potential contribution of alterations to oestrogen receptor sensitivity, PI3K and MAPK signalling, and the immune microenvironment, and the interplay of these factors with HDAC sensitivity, are warranted to gain further mechanistic insights and guide treatment sequencing and combination therapy in metastatic breast cancer. Additionally, predictive biomarkers, such as protein lysine hyperacetylation in peripheral blood cells, which have been associated with improved progression-free survival in patients given HDAC inhibitors, could be important for patient selection and triage in the era of precision medicine and multiple targeted therapies.

Overall, the results of the ACE trial represent an important step forward in the development of epigenetic therapy for endocrine-resistant breast cancer. Although further validation from additional studies, such as the overall survival results from E2112, is necessary before HDAC inhibitors can be incorporated into routine clinical practice, Jiang and colleagues' results provide important insight into the potential of epigenetic targeting to overcome anti-oestrogen resistance. Novel approaches are needed to improve clinical outcomes in patients with hormone receptor-positive metastatic breast cancer, and HDAC inhibitors could emerge as a new therapeutic tool in the rapidly evolving landscape of targeted therapies for this common disease.

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A new player in the treatment of HER2-positive tumours

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HER2 targeting is a remarkable example of how a therapeutic strategy can profoundly transform the natural history of a disease. The monoclonal antibody trastuzumab, the dual HER1 and HER2 inhibitor lapatinib, the monoclonal antibody pertuzumab, and the antibody-drug conjugate trastuzumab emtansine have improved the life expectancy of women with HER2-overexpressing or HER2-amplified (HER2-positive) breast cancer.[1,2] HER2 targeting has proven effective in other HER2-overexpressing cancers and, in gastric cancer, trastuzumab added to chemotherapy is now a standard first-line treatment.[3] Nevertheless, despite these therapeutic successes, HER2-driven diseases still cause a great deal of morbidity and many deaths each year. For this reason, efforts are ongoing to develop different classes of HER2-targeting compounds to treat resistant disease.