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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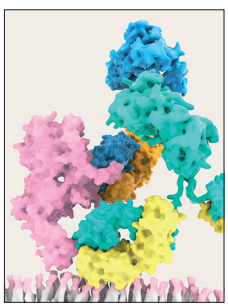
HER2 targeting is a remarkable example of how a therapeutic strategy can profoundly transform the natural history of a disease. The monoclonal antibody trastuzumab, the dual HER1 and HER2 inhibitor lapatinib, the monoclonal antibody pertuzumab, and the antibody-drug conjugate trastuzumab emtansine have 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.

In *The Lancet Oncology*, the safety and preliminary antitumor activity of one of these newer drugs, trastuzumab deruxtecan (DS-8201a), in HER2-positive breast cancer and gastric or gastro-oesophageal junction cancer are reported in two papers by Kenji Tamura and colleagues[4] and Kohei Shitara and colleagues.[5] Trastuzumab deruxtecan is an antibody-drug conjugate of trastuzumab and a potent topoisomerase 1 inhibitor, deruxtecan. Similar to trastuzumab emtansine, trastuzumab deruxtecan exploits the specific binding of trastuzumab to its epitope on the extracellular portion of the HER2 receptor to carry and release, by lysosomal cleavage, its toxic payload directly into cancer cells. The two papers describe patients with HER2-positve breast or gastric or gastro-oesophageal junction cancer from the same first-in-human phase 1 study of this compound in patients with cancer. This two-part (dose escalation and expansion), five-group trial also included patients with breast tumours who, despite showing supra-physiological HER2 expression (ie, immunohistochemical score 1+ and 2+), do not fulfil the guideline definition of HER2 positivity (part 2c).[6] The dose escalation results were previously published in *The Lancet Oncology*[7] and were the basis for trastuzumab deruxtecan recommended dosing in the five expansion groups.

Trastuzumab deruxtecan was reasonably well tolerated, with the only serious concern being interstitial lung disease or pneumonitis, which was the main cause of treatment discontinuation through adverse events (9 of 13 patients who discontinued treatment in the absence of disease progression in the breast cancer cohort).

In patients with HER2-positive breast cancer with trastuzumab emtansine-resistant disease, the proportion of patients who achieved an objective response (primary end-point) was 59·5% (95% CI 49·7–68·7) and median progression-free survival was 22·1 months (95% CI not estimable, range 0·8–27·9). Responses occurred quickly (median time to response 1·6 months [95% CI 1·4–2·8], with most responses registered at the first on-protocol tumour imaging) and were durable. These findings appear even more interesting considering that all patients had to have trastuzumab emtansine-resistant disease by protocol and most of them had also progressed on pertuzumab.

Although based on a smaller sample size, the results in the HER2-positive gastric cancer cohort are equally meaningful. By contrast with HER2-positive breast cancer, no anti-HER2 strategy other than trastuzumab has shown efficacy in these patients, and no HER2-targeting compound is currently approved to treat trastuzumab-resistant disease. Therefore, a proportion of patients who achieved objective response of 43·2% (95% CI 28·3–59·0), with apparently no differences according to previous exposure (and failure) to irinotecan (41·7%, 95% CI 22·1–63·4), is at the very least promising, as is the median duration of response of 7·0 months (95% CI 4·4–16·6).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If efficacy and manageability are confirmed in further studies, the implications of these results go beyond the treatment of HER2-positive cancers resistant to currently approved targeted treatments. The results presented here not only call for rapid exploration of trastuzumab deruxtecan in phase 3 trials in less pretreated patients, but also raise several scientific questions. The first, and probably most important from a strategic point of view, concerns the relative contribution of targeted delivery of potent cytotoxic drugs, antibody-dependent cell cytotoxicity, and interference with HER2 signalling to the final anti-tumour effect. Clarifying this issue is not simply a matter of scientific curiosity. Two other compounds, each acting more specifically on one of these mechanisms, have been reported as active in patients with HER2-positive breast cancer in whom registered treatment has failed: neratinib, which interferes with HER2 signalling by potent and irreversible tyrosine kinase inhibition,[8] and margetuximab,[9] a monoclonal antibody engineered to more efficiently engage antibody-dependent cell cytotoxicity. These agents might be other new players in HER2-positive breast cancer.

Several hints point to antibody–drug conjugates being active regardless of cancer cell dependence on aberrant HER2 signalling. For example, clinical studies have suggested alterations to *PIK3CA*, *Akt*, and *PTEN* as markers of resistance to trastuzumab, pertuzumab, and lapatinib but not trastuzumab emtansine.[10] Similarly, hormone receptor co-expression does not affect trastuzumab emtansine and trastuzumab deruxtecan antitumor activity, but does so in patients treated with trastuzumab, pertuzumab, and lapatinib. Both trastuzumab emtansine and trastuzumab deruxtecan are active in patients who have exhausted all other anti-HER2 treatments, with trastuzumab deruxtecan also active in patients with trastuzumab emtansine-resistant and pertuzumab-resistant breast cancer. Preliminary results show that supra-physiological HER2 expression

(as opposed to overexpression or amplification) seems to be sufficient for trastuzumab deruxtecan to induce meaningful tumour responses.[6] These and other advances suggest an expanded spectrum of HER2 druggable alterations encompassing HER2-activating mutations, supra-physiological HER2 expression, addiction to HER2 amplification, the presence of molecular resistance mechanisms to specific compounds, and tumour and patient immune status. This complex scenario will require adequate testing in rationally designed clinical trials, which is the greatest challenge for the immediate future.

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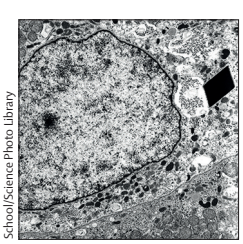
# Personalised management of alveolar soft part sarcoma: a promising phase 2 study



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For **NetSarc website** see https://netsarc.sarcomabcb.org/

Medical oncologists have identified approximately 100 different histological subtypes of sarcoma, each of which exhibit specific characteristics and outcomes and require a tailored approach. Accordingly, an accurate biopathological diagnosis of sarcoma is a mandatory first step towards personalised treatment.[1] However, approximately a third of sarcomas are misdiagnosed before the solicitation of an expert second opinion. In *The Lancet Oncology*, Breelyn A Wilky and colleagues[2] report on the remarkable results of a clinical trial assessing the combined activity of axitinib plus pembrolizumab for advanced sarcoma. The study cohort included 12 patients with alveolar soft part sarcoma (ASPS), which is one of the rarest subtypes of sarcoma and accounts for only 48 (0·5%) of 10 262 sarcomas in the French Nationwide NetSarc database as of December 2014.[3]

ASPS is usually diagnosed in adolescents and young adults and is associated with a high risk of lung and brain metastasis. Long-term follow-up is required because ASPS can relapse even several decades after initial treatment. For special cases, surgery or focal treatment during the oligometastatic stage might be feasible; otherwise, close monitoring is acceptable, given the spontaneous and indolent disease course and good survival prognosis (5-year overall survival exceeding 70% in many large case series).[4]

Although ASPS is considered refractory to classical chemotherapy, it is a so-called targetable sarcoma. This subtype is characterised by a persistent unbalanced translocation der(17)t(X;17)(p11;q25) and two mutually exclusive variants of the inherent chimeric fusion protein ASPSCR1-TFE3. In everyday practice, fluorescent in-situ hybridisation confirmation of this translocation