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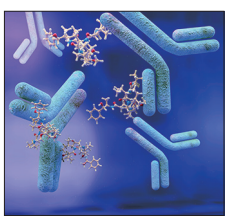
A new agent in the family of antibody–drug conjugates

Amplification of the *HER2* gene occurs in approximately 15% of breast cancers, defining HER2-positive disease. Patients whose tumour overexpresses the HER2 receptor derive benefit from trastuzumab-based treatments.[1] The emergence of antikinase treatments (eg, neratinib and lapatinib) and other antibodies (eg, pertuzumab) that target the HER2 receptor have enhanced this class of drugs and have substantially improved outcomes for patients with HER2-positive breast cancer.

HER2-positive breast cancers are heterogeneous. Genetic analysis has established that these tumours do not represent an intrinsic subtype but rather are distributed along the whole breast cancer spectrum,[2] which helps to explain why no predisposing factors for HER2-positive breast cancer have been detected.[3] Reported genome alterations accord with the luminal-to-basal phenotype. *HER2* amplification initially arises as a genetic incident from unknown causes, but the mechanism implicated in HER2 amplification has been identified in most cases as the breakage–fusion–bridge cycle.[2] However, the observed focal amplification suggests that other mechanisms might also be involved, such as formation of double-minute chromosomes. In some cases, several breakpoints associated with interchromosomal events indicate that amplification might have occurred on other chromosomes. Rarely, deleterious mutations could also cause HER2 overexpression without any amplification-supporting processes. Thus, the various mechanisms that lead to a HER2-positive status, combined with the heterogeneity of associated genetic breast cancer subtypes, suggests the need for tailored therapeutic strategies.

The most recent evolution in targeted treatment is antibody engineering, which permits a paradigm that might work independently of HER2 positivity or breast cancer subtypes. The chemical conformation of trastuzumab allows a cytotoxic agent to be linked to the antibody without affecting its ability to bind to HER2. Internalisation of the HER2 receptor triggered by binding of the antibody–drug conjugate allows delivery of the cytotoxic agent inside the cell—an innovative approach to target cancer. Trastuzumab emtansine was the first-in-class named antibody–drug conjugate available for routine use in patients with breast cancer.[4] The agent includes DM1—a microtubule inhibitor derived from maytansine—conjugated to trastuzumab via a stable linker. Randomised trials have shown that trastuzumab emtansine improves clinical outcomes for patients with HER2-positive metastatic breast cancer and has a more acceptable safety profile than standard treatment regimens.[5] Although standard trastuzumab-containing regimens in a neoadjuvant setting did not lead to pathological complete responses in patients with early-stage breast cancer, a switch to trastuzumab emtansine instead of pursuing adjuvant trastuzumab showed a survival benefit.[6] How trastuzumab emtansine could become the backbone of anti-HER2 treatment strategies is still a matter of debate.

Trastuzumab emtansine binds to HER2-expressing cells with similar affinity to trastuzumab alone. Both molecules can inhibit the PI3K signalling pathway and HER2 extracellular domain shedding and can elicit an antibody-dependent cellular cytotoxicity response on binding of the Fab region to HER2 on cancer cells and binding of the Fc region to FcγRs on immune-effector cells. The contributions of each mechanism to the efficacy of trastuzumab can be highly variable, due to the therapeutic partners (if any), the host predisposition, or the diversity of tumour subtypes. Trastuzumab emtansine provides a lower exposure to trastuzumab than does the antibody alone, which might reduce the magnitude of the previously described effects. However, the option of direct delivery of the cytotoxic agent needs to be added to the existing mechanisms of delivery. Based on the contribution of each mechanism to the



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final efficacy of trastuzumab, we could consider that trastuzumab alone for some patients might provide enough efficacy, but for other patients concomitant administration with other anticancer agents might be necessary. Furthermore, use of HER2-targeting antibody–drug conjugates might be the best option for some patients. The complexity of identifying the optimum option in clinical practice seems to be a huge challenge.

Several new HER2-targeting antibody–drug conjugates with different linkers and payloads are in clinical development, with promising results. In *The Lancet Oncology*, Udai Banerji and colleagues report the results of a phase 1, first-in-human, dose-escalation and dose-expansion trial of trastuzumab duocarmazine (trastuzumab covalently bound to a linker drug containing duocarmycin).[7] After binding to HER2 and internalising, the linker is cleaved in the lysosome by proteases that release the active toxin. Such proteases can exert activity extracellularly through secretion from malignant cells. This extracellular cleavage of the linker drug might, therefore, induce a cell-killing effect that is not HER2-mediated. In Banerji and colleagues' study, trastuzumab duocarmazine showed impressive clinical antitumour effects in several types of cancers, including breast cancer with varying expression of HER2. For example, in the dose-expansion phase using the recommended phase 2 dose of 1·2 mg/kg, 16 (33%, 95% CI 20·4–48·4) of 48 assessable patients with HER2-positive breast cancer achieved an objective response (all partial responses), as did six (40%, 16·3–67·6) of 15 patients with low expression of HER2 and hormone receptor-negative breast cancer. The drug also showed an acceptable tolerability profile, with few grade 3–4 adverse events and no treatment-related deaths in the dose-expansion phase.

The encouraging results from this first-in-human study with this new drug help to support the notion that the family of antibody–drug conjugates could serve as new agents with many modalities of anticancer activity, allowing for multiple new strategies in the treatment of cancer.

Xavier Pivot, Thierry Petit
Centre Paul Strauss, Porte de l'Hopital Strasbourg, Strasbourg 67065, France
xpivot@strasbourg.unicancer.fr

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Underdiagnosis is the main challenge in breast cancer screening

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In *The Lancet Oncology*, Sepideh Saadatmand and colleagues[1] present the results of a multicentre, randomised, controlled trial that compared the performance of MRI plus mammography with that of mammography alone for breast cancer screening in women aged 30–55 years with familial risk of breast cancer, but without a documented mutation in a breast cancer susceptibility gene. Participants were randomly allocated to receive either annual MRI and clinical breast examination plus biennial mammography (MRI group) or annual mammography and clinical breast examination (mammography group). To my knowledge, this is the first study of MRI screening that used a randomised design. Therefore, this study not only allows for comparison of respective cancer detection rate and diagnostic accuracy, as did all previous studies[2–5] on the screening performance of MRI versus mammography, but also provides important outcome measures useful to evaluate the oncological implications of the respective screening methods. Although the study follow-up time was still too short to assess the impact of each screening