Preclinical and clinical efficacy of trastuzumab-deruxtecan in breast cancer brain metastases: a new insight on central nervous system activity

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Central nervous system (CNS) is a frequent metastatic site in human epidermal growth factor receptor 2 positive (HER2$^+$) advanced breast cancer (BC) patients. The presence of brain metastases (BMs) is associated with poor prognosis. Until recently, little was known about brain activity from anti-HER2 targeted therapy. The main reason was non-inclusion of patients with CNS metastasis in clinical trials. Since patients with HER2$^+$ advanced BC are living longer, this unmet need became more evident.

This paradigm of excluding patients with BMs from clinical trials started to change with LANDSCAPE trial, a single-arm phase II trial that investigated the role of lapatinib and capecitabine in previously untreated BMs from HER2$^+$ BC. This trial demonstrated CNS response in 65.9% of the included patients (1). More recently, HER2CLIMB tested the role of tucatinib with trastuzumab and capecitabine for previously treated advanced BC. This trial allowed inclusion of patients with BMs. For the subgroup of patients with baseline BMs (either active or stable), the addition of tucatinib resulted in a quite impressive 1-year CNS-progression free survival of 0% *vs.* 40.2% [hazard ratio (HR) 0.32, P<0.001] (2). This data highlighted the intracranial activity of tucatinib.

In contrast with lapatinib and tucatinib, which are small molecules, trastuzumab is an antibody with a high molecular weight. This characteristic was taught to limit blood-brain barrier (BBB) penetration and, consequently, its therapeutic action in CNS. However, it was already shown that the presence of CNS disease strongly correlates with CNS uptake of trastuzumab (3). This might be due to BBB disruption caused by BMs.

Trastuzumab-deruxtecan (T-Dxd) is an antibody-drug conjugate, that combines trastuzumab with a topoisomerase I inhibitor through a tetrapeptide-based linker. It has proven its efficacy for the treatment not only of HER2$^+$ advanced BC (4,5), but also for HER2-low advanced BC (6). To our knowledge, there is not much data on the mechanism of action of T-DXd in CNS, but similarly to trastuzumab, penetration of higher molecular rate agents might be due to BBB disruption. Once inside, we believe these agents might have the same mechanism of action as outside CNS.

In this paper, Kabraji and colleagues describe the activity

of T-Dxd in growth and survival of orthotopic patient-derived xenografts (PDX) of HER2$^+$ and HER2-low BC BMs and provide a retrospective cohort study of 17 patients with stable or active BMs treated with T-Dxd (7). A reduction in tumour growth and prolonged survival in both PDX models of HER2$^+$ and HER2-low BC were demonstrated. Interestingly, in the HER2$^+$ PDX, it was suggested that this effect was related with cell death induction, by increased expression of apoptosis markers. The uttermost importance of this research is the *in vivo* proof of efficacy of T-Dxd in CNS disease that expresses HER2$^+$ protein at some degree—either HER2$^+$ or HER2-low. These findings also provide biological rationale for the studies that are investigating T-Dxd in CNS disease, in patients with either HER2$^+$ or HER2-low advanced BC.

In the retrospective analysis on the outcomes of 17 patients with stable or active BMs treated with T-Dxd, the majority of patients had HER2$^+$ metastatic BC, and one patient had a HER2-low BC BM. All patients were previously treated with systemic therapy. In this pre-treated population, CNS overall response rate (RR), evaluated in patients with CNS measurable disease, was 73%, by Response Assessment in Neuro-Oncology (RANO)-BM criteria. Even with a small number of patients included, this impressive RR highlights the intracranial activity of this drug. Median time on treatment with T-Dxd was 8.9 months, which is quite similar to previously described in Destiny-Breast 02 (4). It should be emphasised that this latter trial did not allow inclusion of patients with untreated or symptomatic BMs, and the median treatment duration was 10 months.

The results of this retrospective cohort are also concordant with two phase II prospective trials that tested the role of T-Dxd in BMs from BC. TUXEDO, an Austrian trial, included HER2$^+$ BC patients with newly diagnosed untreated BMs or BMs progressing after local therapy, previously treated with trastuzumab and pertuzumab. In the 15 patients of the intention-to-treat population, the intracranial RR by RANO-BM was 73.3% (8)—which is interestingly similar to the RR achieved in this retrospective cohort by Kabraji and colleagues. The DEBBRAH trial, developed by our group, is also assessing the role of T-Dxd in patients with HER2$^+$ and HER2-low BMs and/or leptomeningeal carcinomatosis, either previously treated, untreated or progressing after local therapy. Patients are stratified in five cohorts and all were previously treated for their advanced disease. For the HER2$^+$ population with measurable disease, the intracranial objective response rate (ORR) in patients with active BMs was 46.2%, by RANO-BM criteria (9). For the HER2-low population, we found an intracranial ORR of 66.7%, by RANO-BM criteria, in 4 patients with HER2-low advanced BC with untreated BMs (exploratory analysis) and of 33.3% in 6 patients with HER2-low advanced BC BMs progressing after local therapy (10). Both these trials included a small number of patients but pave the way for additional studies on T-Dxd in patients with previously untreated or progressing BMs.

What is also interesting to highlight is that the intracranial activity seems to be similar to their extracranial activity, with responses seen either in CNS and extracranial metastasis.

Limited data also highlight that it might be worthy to investigate the role of T-Dxd in leptomeningeal carcinomatosis (11,12). Our DEBBRAH trial is prospectively accessing the role of T-Dxd in a cohort of patients that have developed this ominous condition.

With accumulating evidence on the efficacy of these newer drugs in BMs, an important question also can be raised: whether BMs should be screened at diagnosis of metastatic disease. Indeed, at least two clinical trials are ongoing and specifically addressing the role of magnetic resonance (RMN) at diagnosis of metastatic disease (13,14). Another ongoing trial to be noted is the phase 3b/4 Destiny-Breast 12 (15). This trial uses screening brain RMN or computed tomography, and subdivide patients into: no evidence of BM, or untreated BM, not needing immediate local therapy or previously-treated stable or progressing BM. Results of this trial are awaited, so more definitive conclusions on the benefit of T-Dxd for patients with BMs can be drawn.

Finally, we and other groups have been working on trials that focus on patients with CNS disease, but for the future, the path might be more similar to the one in HER2CLIMB: to use BMs as a stratification factor and not an inclusion or exclusion criteria. Also, the CNS endpoints need to be standardised. Indeed, the more recent trials and/or trials which includes only patients with CNS disease, tend to use RANO-BM criteria—which also takes into account clinical status and corticosteroids use and, as a result, might be more informative.

Additional studies with these newer drugs, either alone or in combination, might improve clinical results in HER2$^+$ and HER2-low advanced BC patients, which would translate into better care of these patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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