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EDITORIAL

Antibody—drug conjugates are active in patients with HER2-positive breast cancer brain metastases: where do we go from here?

In this issue of *ESMO Open*, Hurvitz and colleagues[1] report an exploratory analysis of trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine (T-DM1) in the subgroup of 82 patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer and baseline brain metastases (BrMs) from the landmark DESTINY-Breast03 clinical trial. Impressively, the intracranial response rate (i-ORR) was 65.7% with T-DXd versus 34.3% with T-DM1 confirming antibody—drug conjugates (ADCs) as a promising strategy in treating breast cancer BrMs.

Up to 50% of patients with advanced HER2-positive breast cancer will develop BrMs.[2] As patients survive longer, the need for multiple non-cross-resistant regimens with intracranial efficacy continues to increase, as do concerns about late toxicities from both local and systemic therapies. Historically, the evidence base for intracranial activity of tyrosine kinase inhibitors such as lapatinib, neratinib, and tucatinib has been the strongest.[3-6] However, accumulating data supporting the activity of HER2-targeted ADCs in patients with BrMs challenge the assumption that large molecules cannot have intracranial efficacy. Further, the intriguing efficacy signals observed to date raise pointed questions about how to integrate local and systemic therapies for patients with BrMs and how to better design current and future ADC clinical trials to account for the full range of patients seen in daily clinical practice.

Several aspects of the DESTINY-Breast03 study design bear special attention. Firstly, patients with clinically inactive/asymptomatic BrMs not requiring treatment with corticosteroids or anticonvulsants were eligible. The study initially allowed patients who had not received prior local therapy to BrMs to enroll; however, a later protocol amendment excluded these patients. Patients with progressive BrMs after prior local therapy were also excluded. Using the current U.S. Food & Drug Administration (FDA) definitions of active versus stable BrMs, 39 patients (20 treated with T-DXd and 19 treated withT-DM1) had asymptomatic locally untreated brain lesions that would be considered active; the remaining patients had stable/treated BrMs at study entry. Assessment of intracranial activity was not pre-planned but measurement of BrMs was carried out retrospectively by blinded independent central review. Brain magnetic resonance imaging scans were not required (computed tomography was allowed) despite their clearly greater sensitivity for identifying new lesions. Finally, it is not clear whether and how the central radiology reviewers accounted for lesions that had recently received prior local therapy.

Even with these caveats in mind, the data are compelling. The median progression-free survival (PFS) in patients with baseline BrMs in DESTINY-Breast03 was 15.0 months [95% confidence interval (CI) 12.5-22.2 months] for T-DXd versus 3.0 months (95% CI 2.8-5.8 months) for T-DM1 [hazard ratio (HR) 0.25, 95% CI 0.31-0.45].[7] These data confirm T-DXd as the strongly preferred second-line choice for patients with stable asymptomatic BrMs. Per protocol, central nervous system (CNS) lesions were considered non-target only, and so were not included in the RECIST measurements of target lesions; however, CNS non-target progression was counted as a PFS event. These data are in line with the PFS of the BrM subgroup reported in the DESTINY-Breast01 clinical trial of 18.1 months (95% CI 6.7-18.1 months).[8] In DESTINY-Breast03,[9] T-DXd led to an astounding median PFS in the intention-to-treat population of 28.8 months (95% CI 22.4-37.9 months), which indicates inferior performance of patients with baseline BrMs and highlights the continued needs of this population.

With respect to intracranial response, the observed i-ORR in DESTINY-Breast03 was 65.7% with T-DXd versus 34.3% with T-DM1 in this subset analysis. While the data are encouraging, it should be noted that there was only a minimum 2-week washout from stereotactic radiosurgery or whole-brain radiotherapy required before study entry, and the median time from prior CNS-directed radiation therapy to study entry was only 1.6 months (range 0.5-45.2 months) in the T-DXd arm and 3.4 months (range 0.5-80.1 months) in the T-DM1 arm. CNS outcomes in patients with or without prior CNS-directed local therapy were not separately reported. Thus, it is not possible with the data as presented to fully separate the causality of intracranial responses due to the systemic therapy versus prior local therapy versus the sequence of both modalities.

Measurement of intracranial response is particularly relevant for patients with active BrMs (untreated/asymptomatic or treated but progressive) for whom local therapy is either not an option or delayed in hopes of systemic treatment response in the CNS. TUXEDO-1 and DEBBRAH are both small single-arm trials of T-DXd in active HER2-positive breast cancer BrMs reporting intracranial response rates between 44.4% and 73.3% in patients with active BrMs.[10,11] As patients with treated but progressive BrMs were excluded from the DESTINY-Breast01, 02, and 03 trials, we await the results of the DESTINY-Breast12 trial

(NCT04739761), which has enrolled ∼250 patients with stable or active BrMs, to truly understand the efficacy in relevant subsets of patients with BrMs.

Can T-DXd prolong time until intracranial disease progression in patients with prior HER2-positive BrMs? CNS-PFS is the clinical endpoint assessing ability of systemic therapy to prolong progression in the brain. In a recent pooled analysis of 148 patients with baseline BrMs (treated/stable or untreated/asymptomatic) from the DESTINY-Breast01-03 trials, T-DXd resulted in a CNS-PFS of 12 months in the stable BrMs population and 18.5 months in the untreated/asymptomatic BrMs population outperforming the combined control cohorts.[12] These data also reflect the ability of T-DXd to prolong disease progression in the brain particularly in patients with asymptomatic/untreated BrMs, and evoke the desire to further study our ability to delay CNS radiation in such patients with multidisciplinary communication and close monitoring. Despite these promising data, over 40% of patients with BrM history on T-DXd still progressed first in the brain indicating the continued need for novel secondary prevention strategies as well as effective next-line therapies for patients with BrMs.

The other highly active regimen for HER2-positive stable and active BrMs (including treated/progressive) is tucatinib/trastuzumab/capecitabine, as reported in the HER2CLIMB clinical trial.[13] The i-ORR of tucatinib, trastuzumab, and capecitabine was 47% in a more heavily pretreated population who had taxane, trastuzumab, pertuzumab, and T-DM1 exposure. Tucatinib also prolonged overall survival in the patients with BrMs with a median overall survival of 21.6 months for patients who received tucatinib versus 12.5 months for those who received placebo. Tucatinib also reduced the risk of developing new BrMs as the site of first progression or death by 45.1% (HR 0.55, 95% CI 0.36-0.85).[13] While cross-trial comparisons are tempting, it is critical to note several major differences in the patient populations enrolled in DESTINY-Breast03 versus HER2-CLIMB. Overall, patients with BrMs at baseline constituted ∼16% of the overall study population in DESTINY-Breast03, and the BrMs subset analysis included only 39 patients (20 patients treated with T-DXd) with previously untreated BrMs, and none with progressive BrMs after prior local therapy. This is in sharp contrast to HER2CLIMB, in which nearly half of the patients had history of BrMs, including 174 patients (28% of the overall study population) with active BrMs at study entry.

Based on the data, we believe that T-DXd and tucatinib/capecitabine/trastuzumab are both excellent options for patients with BrMs. We favor T-DXd in the second line for patients with extracranial progression who have stable BrMs with low brain metastasis velocity, or those with small asymptomatic/untreated lesions. We prefer tucatinib/capecitabine/trastuzumab for patients with previously treated but progressive lesions and those with high brain metastasis velocity due to a paucity of data for T-DXd in this population relative to the much larger published experience with tucatinib to date. However, we would favor T-DXd over other systemic options in patients who have progressed on a tucatinib-based regimen.

Finally, as we reflect upon these data and other accumulating evidence, what lessons can we apply to clinical trial design moving forward?

Firstly, although T-DM1 was inferior to T-DXd in this subset analysis, it is important to note that both ADCs demonstrated evidence of intracranial efficacy—indeed the i-ORR to T-DM1 was an impressive 34.3%. The next-generation properties of T-DXd such as potent chemotherapeutic payload and high drug—antibody ratio (DAR) likely contribute to its enhanced CNS efficacy.[14] ADC homogeneity and DAR are critical parameters for CNS penetration and brain tumor efficacy in preclinical models.[15] These data contribute to a growing wealth of evidence that ADCs, as a class, have CNS efficacy and strongly support the default inclusion of patients with active and stable/treated BrMs in all phases of ADC clinical trials, irrespective of the ability of the compounds to penetrate an intact blood—brain barrier in preclinical models. Indeed, preclinical models of BrMs appear to be much more predictive of clinical activity. Notably, in a large, population-based database, by start of second-line therapy (i.e. the patient population enrolled in DESTINY-Breast03), 18% of hormone receptor-positive/HER2-positive and 31% of hormone receptor-negative/HER2-positive have been diagnosed with BrMs.[16] Without more concerted efforts to include patients with active BrMs in ADC clinical trials, we are missing an important opportunity to understand the efficacy of a crucial class of anticancer agents in a patient population of high unmet medical need. In all recent pivotal ADC trials in breast cancer including DESTINY-Breast01-04, ASCENT, and TROPiCS-02, patients with active BrMs were excluded (with the exception of the few asymptomatic, previously untreated patients initially allowed on to T-DXd trials until protocol amendments to exclude them), so future prospective studies in this patient population must be carried out, which take years to complete. TUXEDO-4 (NCT06048718) is ongoing and will assess T-DXd in active HER2-low BrMs; DESTINY-Breast12 is assessing T-DXd in active HER2-positive BrMs; and DATO-BASE (NCT06176261) will assess efficacy of datopotamab deruxtecan in active triple-negative breast cancer, hormone receptor-positive/HER2-negative BrMs, and leptomeningeal disease. If these patients were allowed and enrolled up front, these studies would not be needed.

Next, we need to re-think the wording of eligibility criteria. In an era where systemic therapies can be sufficiently effective in patients with HER2-positive BrMs to allow safe deferral of local therapy, we should not require prior CNS-directed local therapy in order to deem eligibility for clinical trials. Finally, as we plan protocols, we should consider the data elements needed to conduct BrM subset analyses upfront—including definitions of active versus stable BrMs, frequency and type of required CNS imaging studies, collection of prior local therapy data, and pre-specified response endpoints. For those committed to making a change into the future, an increasing number of resources are available to

provide guidance in designing studies to better include patients with BrMs into clinical trials.[17,18]

In summary, this exploratory analysis of the DESTINY-Breast03 trial suggests that T-DXd is the premier ADC for the treatment of patients with HER2-positive breast cancer BrMs. The analysis underscores the pressing need to investigate T-DXd in patients with HER2-low expressing BrMs, active HER2-positive BrMs across other solid tumors, and leptomeningeal disease as the next crucial steps, as well as a move towards default inclusion of patients with BrMs into clinical trials of ADCs across the board. These investigations hold promise for improving outcomes and expanding therapeutic options for patients facing these challenging conditions as well as advancing our understanding of ADC potential in diverse clinical settings.

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