# Metastatic breast cancer – Highlights

**In this concise summary, we highlight three of the key ESMO 2023 abstracts related to metastatic breast cancer, with a specific focus on antibody-drug conjugates.**

### Update of DESTINY-Breast04: a phase 3 trial of trastuzumab deruxtecan (T-DXd) in previously treated HER2-low metastatic breast cancer (1)

An update of the DESTINY-Breast04 trial, with a median follow-up of 32 months (95 % Confidence Interval [CI]: 31.0–32.8), was presented. The trial enrolled 557 patients with HER2-low metastatic breast cancer who had previously been treated with endocrine therapy and one or two lines of chemotherapy for metastatic breast cancer. Patients were randomly assigned to receive either T-DXd or their physician's choice of chemotherapy. The primary endpoint of this trial was progression-free survival (PFS) in patients with hormone receptor-positive (HR+) disease. PFS in all included patients (including a small subset of patients with HR-negative breast cancer) and overall survival (OS) were secondary endpoints.

In this update, treatment with T-DXd was still associated with a significant PFS benefit over physician's choice of chemotherapy in HR+ patients (Hazard Ratio [HR]: 0.37, 95 % CI: 0.30–0.46), median PFS: 9.6 (8.4–10.0) vs. 4.2 (3.4–4.9) months. Regarding OS, the benefit of T-DXd treatment was also significant (HR: 0.69; 95 % CI: 0.55–0.87; median OS: 23.9 [21.7–25.2] vs. 17.6 [15.1–20.2] months). These results and the toxicity profile were consistent with what was reported in the first report, in particular, 12.1 % (n = 45) of patients treated with T-DXd developing interstitial lung disease of any grade, 2.2 % (n = 8) grade 3 or higher, and 1.1 % (n = 2) grade 5. This update confirms the efficacy of T-DXd as second or third-line chemotherapy in patients with endocrine-resistant HR+ HER2-low metastatic breast cancer.

### DESTINY-BREAST01/02/03: Intracranial activity of trastuzumab deruxtecan in patients with brain metastases of HER2+ breast cancer: a retrospective pooled analysis (2)

A retrospective pooled analysis of patients with brain metastases (BMs) from the DESTINY-Breast 01, 02, and 03 clinical trials was conducted to evaluate the intracranial activity of T-DXd in patients with HER2+ metastatic breast cancer. DESTINY-Breast02 and 03 are randomized phase 3 trials assessing the efficacy of T-DXd as third and second lines of treatment for patients with HER2+ metastatic breast cancer, respectively. DESTINY-Breast01 is a single-arm phase 2 trial enrolling patients who had previously received TDM-1 treatment.

The pooled analysis of patients with BMs revealed an intracranial overall response rate (IC-ORR) of 45.2 % (n = 47/104) and 45.5 % (n = 20/44) in patients with treated/stable and untreated/unstable BMs, respectively. These IC-ORR values were substantially higher than those observed in the comparator arms, which included TDM-1, trastuzumab, or lapatinib and capecitabine (treated/stable BMs: 27.6 %, n = 16/58; untreated/stable BMs: 12 %, n = 3/25).

The IC-ORR observed with T-DXd was similar to that reported in the HER2CLIMB trial, which evaluated the combination of tucatinib, trastuzumab, and capecitabine (47.5 %). Despite the small sample size and the post-hoc nature of this analysis, which focused on a group that was not a stratification factor in the original randomized trials, it is reasonable to conclude that the IC-ORR of T-DXd is comparable to that of the HER-2CLIMB regimen and represents a valid and effective treatment option for patients with BMs from HER2+ breast cancer.

### First results of TROPION-Breast01, a randomized phase 3 trial of datopotamab-deruxtecan (Dato-Dx) in previously treated HR+/HER2- metastatic breast cancer (3)

The TROPION-Breast01 trial is a randomized phase 3 study that evaluated the efficacy of Dato-Dx, a TROP2-targeting antibody-drug conjugate, in patients with HR+/HER2- metastatic breast cancer who had progressed on endocrine therapy (ET) and at least one or two lines of chemotherapy. A total of 732 patients were randomly assigned 1:1 to either Dato-Dx or investigator's choice of chemotherapy (ICC) (eribulin, vinorelbine, gemcitabine, or capecitabine). The dual primary endpoints of TROPION- Breast01 are PFS and OS. Notably, the majority of patients had previously received CDK4/6 inhibitors (82 and 78 % in the experimental and control arms, respectively) and over 90 % had previously received taxanes and/or anthracyclines. Most participants had received only one line of chemotherapy (63 and 61 % in the experimental and control arms, respectively).

The investigators reported a statistically significant PFS benefit with Dato-Dx compared to ICC (HR: 0.63; 95 % CI: 0.52-0.76; $p < 0.0001$). However, this translated into a modest absolute difference of median PFS of 2 months (mPFS Dato-Dx: 6.9 months, 95 % CI: 5.7-7.4; mPFS ICC: 4.9 months; 95 % CI: 4.2-5.5). There was no clear heterogeneity of the PFS benefit for any of the presented subgroups, which were exclusively clinical and not biomarkerbased.

The overall response rate was 36.4 % (n = 133/365) in the Dato-Dx arm and 22.9 % (n = 84/367) in the ICC arm. Only 0.5 % (n = 2) of those treated with Dato-Dx had a complete response. Data for OS analysis is still immature at 9.7 months of median follow-up.

Regarding treatment-related adverse events (TRAEs), Dato-Dx treatment resulted in a 21 % rate of grade ≥ 3 TRAEs, mainly related to myelosuppression and gastrointestinal toxicity. Notably, interstitial lung disease was rare (3 %, n = 9) and only in 1 % (n = 2) was it grade ≥ 3.

The results of TROPION-Breast01 are similar to those of the TROPICS02 trial, which tested another TROP2 antibody-drug conjugate (sacituzumab govitecan) in the same setting. While the benefits in PFS in both trials (and of OS in TROPICs02) were significant, they may not translate into a substantial clinical benefit in real-world practice. Additionally, these results may be different in real-world settings, especially with the advent of multiple targeted options in the earlier lines of treatment and also in patients previously treated, if eligible, with other antibody-drug conjugates, such as T-DXd.

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**References:**

1. Modi S et al.: 3760 Trastuzumab deruxtecan (T-DXd) versus treatment of physician's choice (TPC) in patients (pts) with HER2-low unresectable and/or metastatic breast cancer (mBC): Updated survival results of the randomized, phase III DESTINY-Breast04 study. Ann Oncol. 2023;34:S334-S5.
2. Hurvitz S et al.: 3770 A pooled analysis of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) with brain metastases (BMs) from DESTINY-Breast (DB)-01,-02, and-03. Ann Oncol. 2023;34:S335-S6.
3. Bardia A et al.: LBA11 Datopotamab deruxtecan (Dato-DXd) vs chemotherapy in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2-) breast cancer (BC): Primary results from the randomised phase III TROPION-Breast01 trial. Ann Oncol. 2023;34:S1264-S5.