LBA3 **Plenary Session**

Trastuzumab deruxtecan (T-DXd) versus treatment of physician's choice (TPC) in patients (pts) with HER2-low unresectable and/or metastatic breast cancer (mBC): Results of DESTINY-Breast04, a randomized, phase 3 study.

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Background: About 55% of mBC typically categorized as HER2 negative, express low levels of HER2 (IHC 1+ or IHC 2+/ISH– by ASCO/CAP 2018 guidelines) with poor outcomes in later lines (Tarantino 2020). T-DXd has shown promising efficacy in HER2-low mBC in a phase 1 study (NCT02564900; Modi 2020). This is the primary report from DESTINY-Breast04 (NCT03734029), the first randomized, multicenter, open-label, phase 3 study comparing efficacy and safety of T-DXd vs TPC in pts with HER2-low mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting. **Methods:** 557 pts with centrally confirmed HER2-low mBC were randomly assigned 2:1 to T-DXd 5.4 mg/kg or TPC (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel). The primary endpoint was progression-free survival (PFS) determined by blinded independent central review (BICR) in pts with hormone receptor–positive (HR+) mBC. Key secondary endpoints (hierarchically tested after the primary endpoint) include PFS by BICR in the full analysis set (FAS; HR+/–) and overall survival (OS) in pts with HR+ mBC and in FAS. Other endpoints were objective response rate, duration of response, safety, and an exploratory analysis of pts with HR– mBC. **Results:** As of Jan 11, 2022, 373 and 184 pts (88.7% and 88.6% HR+ mBC) were assigned to T-DXd and TPC, respectively. Median follow-up was 18.4 months (mo; 95% CI, 17.9-19.1). Median treatment duration was 8.2 mo (range, 0.2-33.3) with T-DXd and 3.5 mo (range, 0.3-17.6) with TPC. Efficacy results are in the Table. 52.6% of pts with T-DXd vs. 67.4% of pts with TPC had grade (G) ≥ 3 treatment-emergent adverse events (TEAEs). With T-DXd, 45 pts (12.1%; 10.0% G1/2, 1.3% G3/4, 0.8% G5) had independently adjudicated drug-related interstitial lung disease [ILD]/pneumonitis vs. 1 pt (0.6% G1) with TPC. **Conclusions:** DESTINY-Breast04 is the first phase 3 trial of a HER2-directed therapy in pts with HER2-low mBC to show a statistically significant and clinically meaningful benefit in PFS and OS compared to standard-of-care treatment, regardless of HR status, with a generally manageable safety profile. Funding: Daiichi Sankyo, Inc., and AstraZeneca. Clinical trial information: NCT03734029. Research Sponsor: Daiichi Sankyo, Inc., and AstraZeneca.

Efficacy results.

	T-DXd (HR+) n = 331	TPC (HR+) n = 163	T-DXd (FAS) n = 373	TPC (FAS) n = 184	T-DXd (HR–) n = 42	TPC (HR–) n = 21
mPFS,[a] mo (95% CI)	10.1 (9.5-11.5)	5.4 (4.4-7.1)	9.9 (9.0-11.3)	5.1 (4.2-6.8)	6.6 (4.1-11.7)	2.9 (1.4-4.0)
Hazard ratio[b] (95% CI)	0.51 (0.40-0.64)		0.50 (0.40-0.63)		0.45 (0.23-0.87)	
p value[c]	< 0.0001		< 0.0001		0.0135	
mOS, mo (95% CI)	23.9 (20.8-24.8)	17.5 (15.2-22.4)	23.4 (20.0-24.8)	16.8 (14.5-20.0)	16.6 (11.3-NE)	10.3 (6.1-15.2)
Hazard ratio[b] (95% CI)	0.64 (0.48-0.86)		0.64 (0.49-0.84)		0.63 (0.32-1.23)	
p value[c]	0.0028		0.0010		0.1732	

m, median; NE, non-estimable.
[a]PFS by BICR.
[b]T-DXd vs. TPC.
[c]p values were determined by 2-sided log-rank test.