Statins Enhance Trastuzumab Deruxtecan Efficacy: Preclinical Synergy in HER2-Negative Models and Clinical Benefit in HER2-Positive Metastatic Breast Cancer

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BACKGROUND

Trastuzumab deruxtecan (T-DXd) has demonstrated significant clinical efficacy in metastatic breast cancer (mBC). Statins have been shown to increase HER2 membrane localization and stability, potentially enhancing responsiveness to HER2-targeted therapies. Given this rationale, we assessed the potential of statins to enhance T-DXd activity through a translational approach combining a preclinical HER2-negative breast cancer model and a real-world cohort of patients with HER2-positive mBC treated with T-DXd.

MATERIALS & METHODS

Sixty female Wistar albino rats were induced with mammary tumors using N-methyl-N-nitrosourea (MNU) and then randomized into five groups: control, MNU only, T-DXd, statin, and combination therapy **(Figure 1).** T-DXd (3 mg/kg, i.v., Q3W) and lovastatin (8.3 mg/kg, oral, daily) were administered for 28 days. Tumor volumes were measured, and tissues underwent histopathological and IHC analyses, including HER2 and Ki-67 staining to evaluate treatment effects. Protein expression analyses were performed via Western blotting to assess apoptotic and signaling markers (Bax, Bcl-2, Caspase-3/9, HER2, p-Akt, and p-ERK1/2)

In the clinical part, a multicenter retrospective study included patients with HER2-positive metastatic breast cancer treated with T-DXd. Patients were stratified according to statin use at T-DXd initiation.

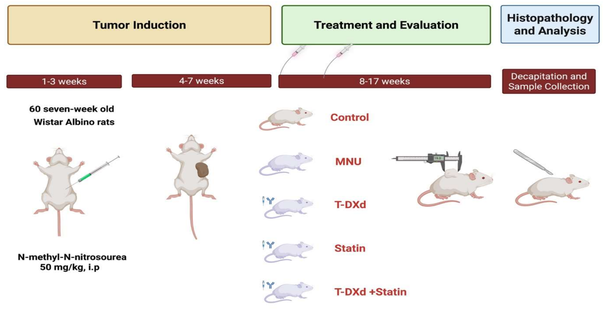


Figure 1. Experimental timeline of the preclinical rat model.

RESULTS

A total of 60 female Wistar albino rats were included in the study and randomized into five groups (n = 12 per group). Tumor volume was significantly lower in the T-DXd + statin group compared to all other groups ($p < 0.0001$) **(Figure 2a).** Although the T-DXd + Statin group exhibited the lowest median tumor count, the difference among groups did not reach statistical significance (p=0.0511) (**Figure 2b**).

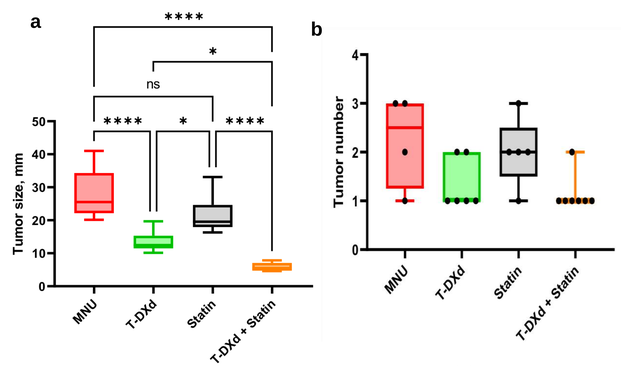


Figure 2. Representative box-and-whisker plots showing (a) tumor size and (b) tumor number in mammary tissues of rats. Asterisks indicate statistical significance (*$p < 0.05$, ****$p < 0.0001$), while “ns” denotes non-significance.

IHC analysis indicated increased HER2 expression in both the statin and T-DXd + statin groups compared to the MNU group **(Figure 3)**

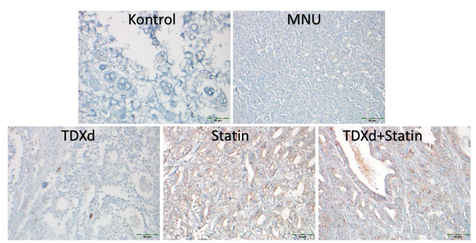


Figure3. IHC analysis of HER2 expression in rat mammary tumors across treatment groups. Representative IHC images demonstrate HER2 staining in Control, MNU, T-DXd, Statin, and T-DXd + Statin groups

Western blot analyses were conducted to assess the expression of apoptosis-related proteins in tumor tissues, including Bax, Bcl-2, caspase-3, and caspase-9. Results indicated a substantial increase in pro-apoptotic Bax expression in the T-DXd + Statin group compared to all other treatment arms ($p < 0.0001$ for all comparisons**, Figure 4**). The expression of caspase-3 and caspase-9 were similarly elevated in the combination group ($p < 0.0001$), while anti-apoptotic Bcl-2 levels were significantly reduced in the combination group ($p < 0.0001$ vs. MNU; $p < 0.01$ vs. T-DXd).Western blotting results indicated increased HER2 expression in both the statin and T-DXd + statin groups compared to the MNU group **(Figure 4).**

Figure 4. Effects of T-DXd and Statin on protein levels of Bax (A), Bcl-2 (B), Caspase-3 (C), Caspase-9 (D), and Her2 (E) in mammary tissue of rats with MNU-induced breast cancer. Statistical significance between groups is shown by: **** $p<0.0001$ compared to the control group, $^{\#}p<0.05$, $^{\#\#}p<0.01$ and $^{\#\#\#\#}p<0.0001$ compared to the MNU group; $^{\$\$}p<0.05$ and $^{\$\$\$\$}p<0.0001$ compared to the T-DXd group; $^{++++}p<0.0001$ compared to the Statin group.

The retrospective cohort included 109 patients with HER2-positive metastatic breast cancer treated with T-DXd, of whom 12 (11%) were concurrently receiving statin therapy. With a median follow-up of 22.1 months, patients receiving statins demonstrated a significantly longer median progression-free survival (21.83 vs. 14.02 months, p = 0.049) and overall survival benefit (not reached vs. 19.68 months, p = 0.023) compared with non-users **(Figure 5).** Statin users also showed a higher overall response rate (50.0% vs. 37.1%) and disease control rate (83.3% vs. 77.3%), suggesting enhanced clinical efficacy of T-DXd in patients receiving concurrent statin therapy.

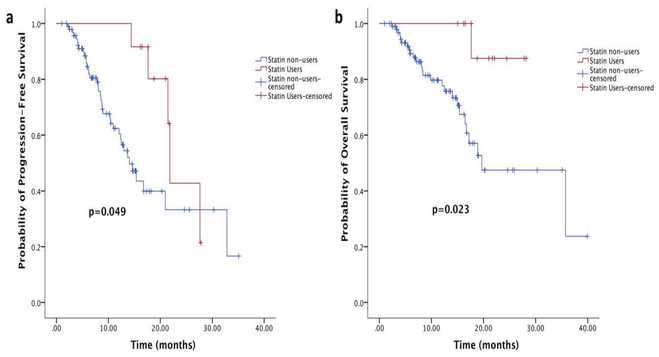


Figure 5. Kaplan-Meier curves for PFS(a) and OS(b) in HER2-positive mBC patients treated with T-DXd, stratified by statin use.

CONCLUSIONS

Our findings demonstrated that statin use significantly enhanced the efficacy of T-DXd across preclinical and clinical settings. These results provide a rationale for the potential role of statins as cost-effective and widely available agents to potentiate HER2-targeted therapies. These findings provide a compelling rationale for the prospective evaluation of statins as adjunctive agents to optimize the therapeutic efficacy of HER2-targeted ADCs.

DISCLOSURE: We have no conflict of interest to disclose.

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