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Statins enhance trastuzumab deruxtecan efficacy: preclinical synergy in HER2-negative models and clinical benefit in HER2-positive metastatic breast cancer

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Abstract

Trastuzumab deruxtecan (T-DXd) has demonstrated significant efficacy in metastatic breast cancer (mBC) with varying HER2 expression. Statins have been shown to increase HER2 membrane localization and stability, potentially enhancing responses to HER2-targeted therapies. We investigated whether statins enhance T-DXd activity through a translational approach combining a preclinical HER2-negative model and a real-world HER2-positive mBC cohort. In the preclinical arm, 60 female Wistar albino rats were induced with mammary tumors using N-methyl-N-nitrosourea (MNU). Animals were randomized into five groups: Control, MNU-only, MNU + T-DXd, MNU+statin, and MNU + T-DXd+statin. In the clinical arm, 109 patients with HER2-positive mBC who received T-DXd were retrospectively analyzed. The combination of T-DXd and statin significantly reduced tumor volume compared to either monotherapy ($p < 0.0001$) in a preclinical rat model. HER2 protein levels were found to be elevated in the statin and combination groups, as demonstrated by both IHC and Western blot analyses. In a real-world cohort of 109 heavily pretreated patients with HER2-positive mBC receiving T-DXd, concomitant statin use was associated with significantly improved median progression-free survival (mPFS) and median overall survival (mOS). Our findings revealed that statin use significantly enhanced the efficacy of T-DXd in both a preclinical HER2-negative rat model and patients with HER2-positive mBC. Prospective clinical trials are warranted to validate these observations.

Keywords Trastuzumab deruxtecan, Statin, HER2-low, Breast cancer, Apoptosis, Synergistic effect

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To the Editor

Trastuzumab deruxtecan (T-DXd) has redefined the therapeutic landscape of metastatic breast cancer (mBC), demonstrating substantial efficacy in HER2-positive as well as HER2-low disease [1–3]. Nevertheless, treatment resistance and heterogeneity in HER2 expression remain clinically relevant challenges [4]. Loss of membranous HER2, altered receptor trafficking, and downstream signaling reactivation may attenuate antibody–drug conjugate (ADC) efficacy, ultimately limiting durable responses [5].

Statins exhibit pleiotropic anticancer properties, including the modulation of oncogenic signaling pathways [6]. Preclinical evidence demonstrates that statins may enhance HER2 membrane localization and stabilization by inhibiting Ras/Rho GTPase-mediated internalization, potentially sensitizing tumor cells to HER2-targeted therapies [7, 8]. We hypothesized that lovastatin might potentiate T-DXd efficacy across the HER2 expression spectrum.

A total of 60 female Wistar albino rats were included in the study and randomized into five groups ($n = 12$ per group): Control, MNU, T-DXd, Statin, and T-DXd + Statin. During the 28-day observation period, survival analysis revealed statistically significant differences among the groups ($p = 0.0199$) (Fig. 1A). Tumor volume was significantly lower in the T-DXd + statin group compared to all other groups ($p < 0.0001$) (Fig. 1B). Although tumor count reduction did not reach statistical significance, a clear trend favoring the combination was observed ($p = 0.0511$) (Fig. 1C).

At the molecular level, combination therapy markedly increased pro-apoptotic signaling. Tumors treated with T-DXd plus statin demonstrated significant upregulation of Bax and caspase-3/9 and downregulation of Bcl-2 relative to monotherapy groups ($p < 0.0001$ for all comparisons) (Fig. 2, FigS2). Furthermore, the T-DXd + Statin

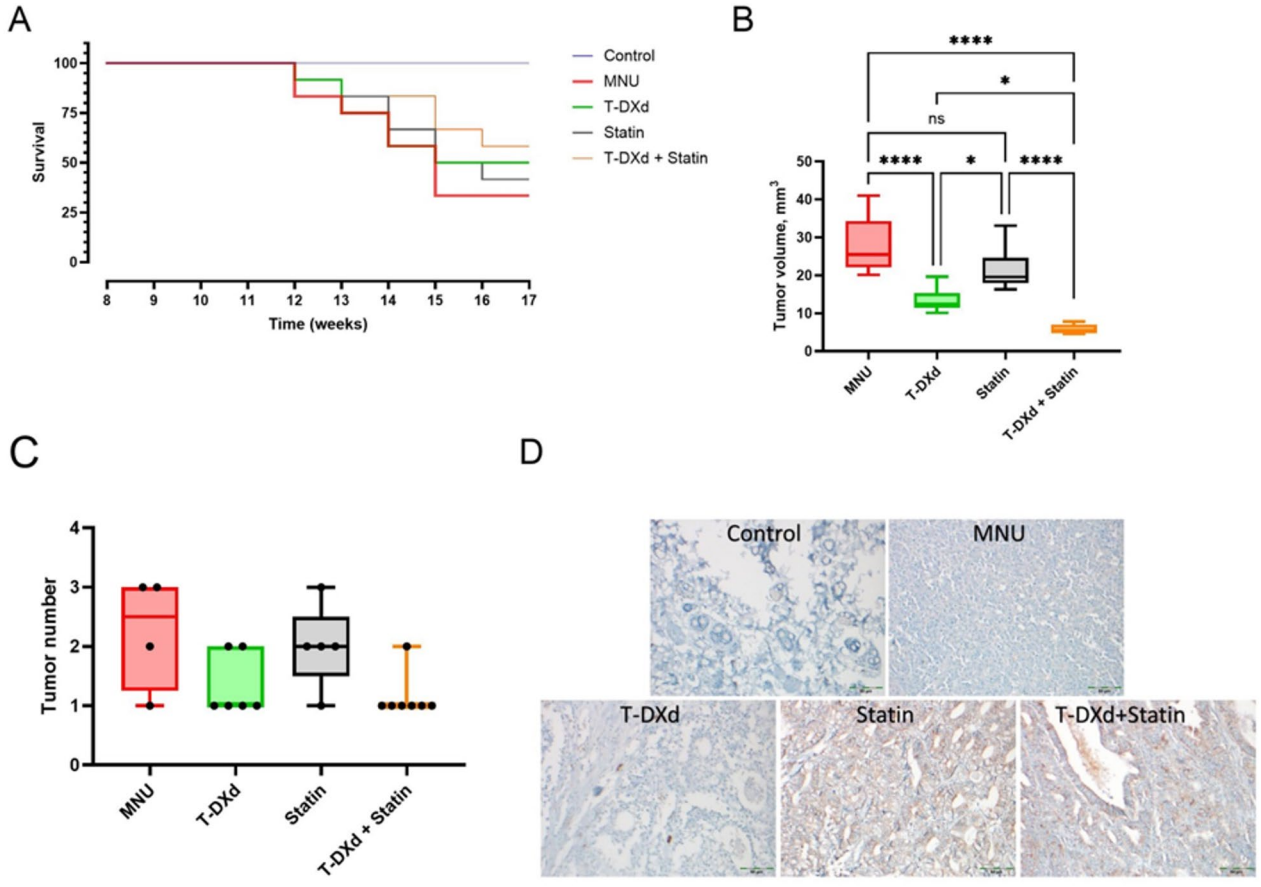


Fig. 1 **A** Kaplan-Meier survival curves of rats treated with MNU alone or with T-DXd and/or statin. **B** Tumor volume in mammary tissue of rats treated with MNU alone or with T-DXd and/or statin, presented as box-and-whisker plots. Asterisks indicate significance levels: $p < 0.05$ (*), $p < 0.0001$ (****), and "ns" indicates not significant. **C** Tumor number in mammary tissue of rats treated with MNU alone or with T-DXd and/or statin, shown as box-and-whisker plots. **D** Immunohistochemical 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. HER2 membrane expression was markedly increased in the Statin and T-DXd + Statin groups. Scale bar = 50 µm

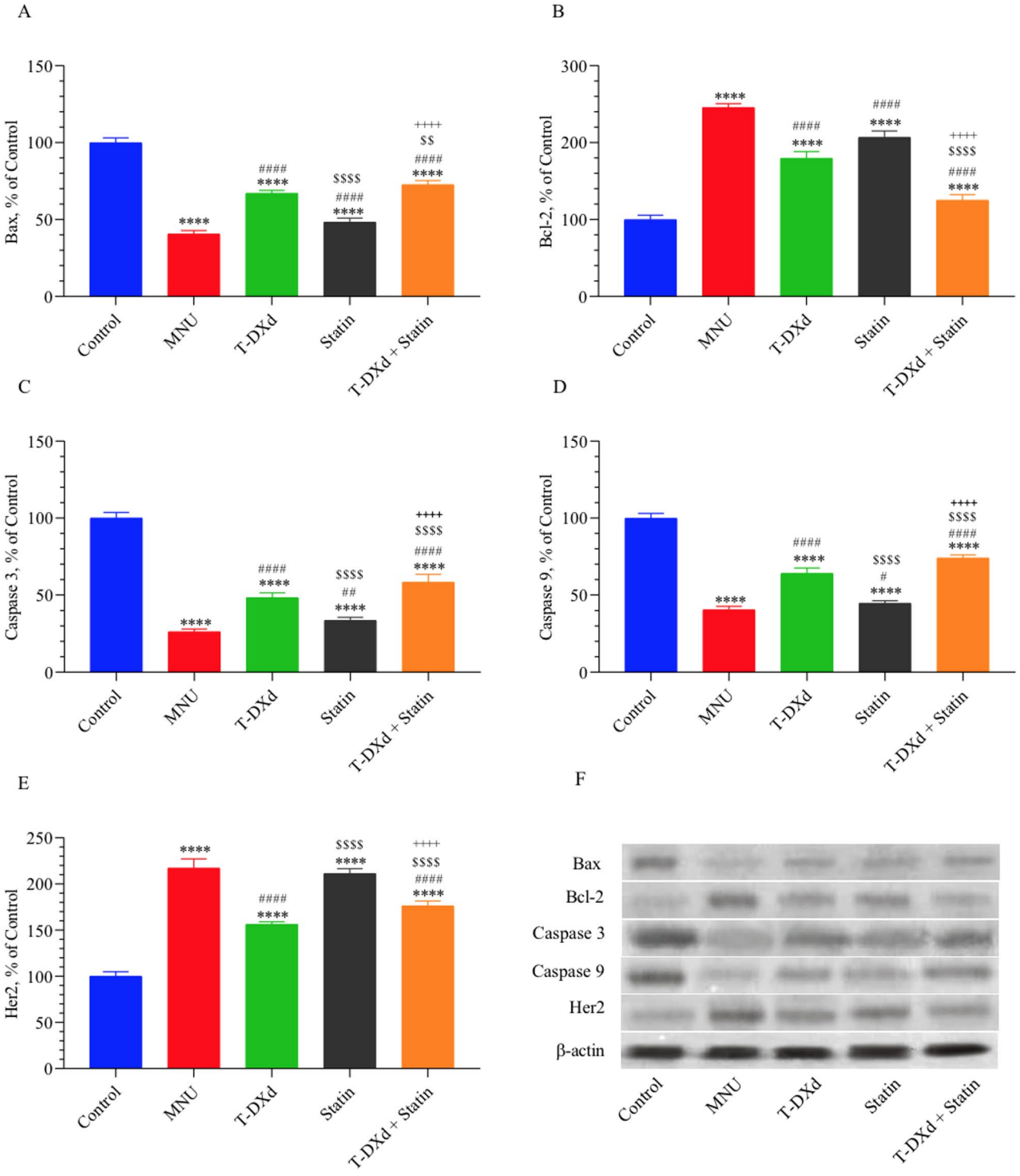


Fig. 2 Effects of T-DXd and Statin on protein levels of Bax (A), Bcl-2 (B), Caspase-3 (C), Caspase-9 (D), and Her2 (E) in mammary tissue of rats with MNU-induced breast cancer. Representive Western blot bands are presented (F). All groups normalized according to housekeeping protein β-actin (F), and ANOVA and Tukey's *post-hoc* test were used for comparing the results among different treatment groups. 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

group showed marked suppression of both p-AKT and p-ERK relative to all other groups (FigS3, FigS4).

Importantly, statin exposure was associated with increased HER2 protein expression in both the statin and T-DXd + statin groups compared to the MNU group (Fig. 2). IHC confirmed enhanced HER2 membrane localization in these groups, with particularly strong staining in the T-DXd + Statin group (Fig. 1D). Histopathology revealed marked tumor regression with preserved glandular architecture and the lowest Ki-67 proliferative index in the T-DXd plus statin group compared with monotherapy and control arms (FigS5, FigS6).

The clinical arm included 109 patients with HER2-positive mBC treated with T-DXd in a multicenter real-world setting (Table S1). With a median follow-up of 22.1 months, median PFS was significantly longer in statin users (21.83 months) compared with non-users (14.02 months; $p = 0.049$) (FigS7). Median OS was not reached in the statin group and was 19.68 months in non-users ($p = 0.023$). In multivariable Cox regression analyses adjusting for clinically relevant covariates, statin use remained independently associated with improved PFS (HR:0.27, 95%CI:0.10–0.74) and OS (HR:0.11, 95%CI:0.01–0.85) (Table S2, Table S3). Objective response and disease control rates were numerically higher among statin users (FigS8).

In this study, statins potentiated the antitumor activity of T-DXd in both preclinical and clinical settings. In the animal model, the combination showed the greatest improvements in survival, tumor regression, and proliferation compared with monotherapy or control groups. These findings were corroborated by real-world data, in which statin use during T-DXd therapy was independently associated with improved PFS and OS.

Statins may potentiate HER2-targeted therapies by modulating membrane cholesterol content and altering HER2 receptor localization and trafficking [9, 10]. By inhibiting the mevalonate pathway, statins disrupt lipid raft integrity and interfere with caveolin-mediated internalization, thereby increasing HER2 retention at the cell surface [11]. Enhanced membrane availability of HER2 can improve antibody binding and facilitate ADC internalization [11, 12]. Preclinical studies have shown that lovastatin increases HER2 density and augments the efficacy of HER2-directed agents, including T-DM1 [11, 13]. Consistent with these findings, our data demonstrated increased HER2 expression and membranous localization in tumors exposed to statin therapy.

Beyond receptor modulation, statins amplify pro-apoptotic signaling when combined with T-DXd, as evidenced by increased Bax and caspase activation and decreased Bcl-2 expression. The combination also resulted in stronger inhibition of PI3K/AKT and MAPK/ERK pathways, reflecting enhanced suppression of survival signaling [6]. Collectively, these mechanistic insights provide a biological rationale for integrating statins into HER2-targeted treatment strategies to enhance efficacy and potentially overcome resistance.

Several limitations merit consideration. The clinical cohort was retrospective with a small number of statin users, and residual confounding, heterogeneity in statin exposure, and indication bias cannot be excluded. The preclinical findings rely on a single model and may not fully capture the complexity of human HER2-low disease. In addition, formal analyses to distinguish synergistic from additive effects were not performed, and HER2 levels were assessed in whole-cell lysates rather than membrane-specific fractions. Nonetheless, the consistency between mechanistic findings and survival outcomes strengthens the biological plausibility of the association.

Our findings demonstrated that statin use significantly enhanced the efficacy of T-DXd in both a HER2-negative preclinical rat model and in patients with HER2-positive mBC. These findings provide a compelling rationale for the prospective evaluation of statins as adjunctive agents to optimize the therapeutic efficacy of HER2-targeted ADCs.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Author contributions

Taha Koray Sahin: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. Cemal Orhan: Methodology, Investigation, Data curation, Formal analysis, Writing – review & editing. Ibrahim Hanifi Ozercan: Methodology, Investigation, Data curation, Writing – review & editing. Harun Muglu: Data curation, Investigation, Writing – review & editing. Besir Er: Investigation, Methodology, Writing – review & editing. Arif Akyildiz: Data curation, Formal analysis, Writing – review & editing. Salih Tunbekici: Investigation, Data curation, Writing – review & editing. Ahmet Oruc: Investigation, Data curation, Writing – review & editing. Musa Baris Aykan: Investigation, Data curation, Writing – review & editing. Bahadir Koylu: Investigation, Data curation, Writing – review & editing. Orhun Akdogan: Investigation, Data curation, Writing – review & editing. Ilknur Deliktas Onur: Investigation, Data curation, Writing – review & editing. Ozturk Ates: Investigation, Data curation, Writing – review & editing. Ozan Yazici: Investigation, Data curation, Writing – review & editing. Fatih Selcukbiricik: Investigation, Supervision, Writing – review & editing. Nuri Karadurmus: Investigation, Supervision, Writing – review & editing. Murat Araz: Investigation, Data curation, Writing – review & editing. Dilek Erdem: Investigation, Data curation, Writing – review & editing. Erdem Goker: Investigation, Data curation, Writing – review & editing. Ahmet Bilici: Investigation, Supervision, Writing – review & editing. Sercan Aksoy: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. Deniz Can Guven: Conceptualization, Supervision, Methodology, Writing – original draft, Writing – review & editing, Project administration.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
This study was approved by the Fırat University Animal Experiments Local Ethics Committee (Protocol No: 32617) for the preclinical experiments, which were conducted in accordance with the ARRIVE guidelines, and by the Hacettepe University Ethics Committee for the retrospective analysis of clinical data (SBA:24/1019).

Competing interests
The authors declare no competing interests.

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