Blocking soluble TNF to improve potency of trastuzumab deruxtecan by increasing internalization and antitumor innate immune response in a resistant HER2-positive breast cancer model

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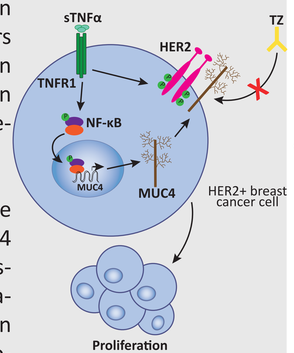
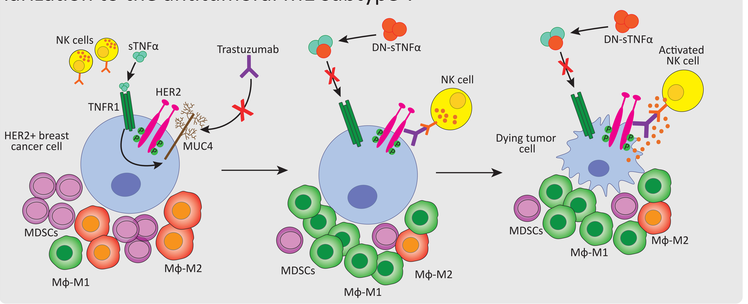
INTRODUCTION AND BACKGROUND

HER2+ is a breast cancer subtype characterized by the overexpression/amplification of HER2. Patients receive trastuzumab (Tz) but about 27-42% do not achieve an objective response. Clinical trials showed that trastuzumab deruxtecan (T-DXd) provides durable responses for patients with HER2+ and HER2 low metastatic breast cancer (BC), determined by immunohistochemistry. Approximately 50% of patients with HER2+ metastatic BC were still alive and progression-free at 24 months (DESTINY-Breast03)[1].

We have demonstrated that the overexpression of TNFα induces Tz resistance in HER2+ tumors by upregulating the membrane glycoprotein mucin 4 (MUC4), which masks Tz epitope on HER2, impairing its binding and reducing its therapeutic effects[2].

We have also proved that blocking the soluble TNFα isoform with INB03 (DN) reduces MUC4 expression, overcomes Tz resistance and unleashes an antitumor innate immune response characterized by an increase in NK cell activation and degranulation and a macrophage (Mϕ) polarization to the antitumoral M1 subtype[3].

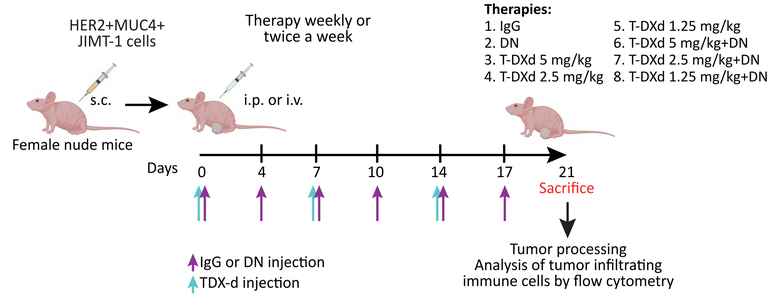


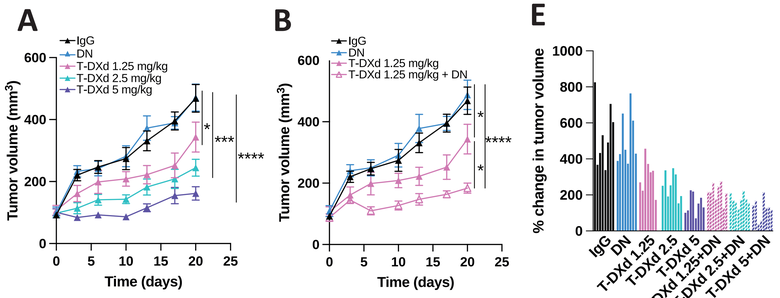


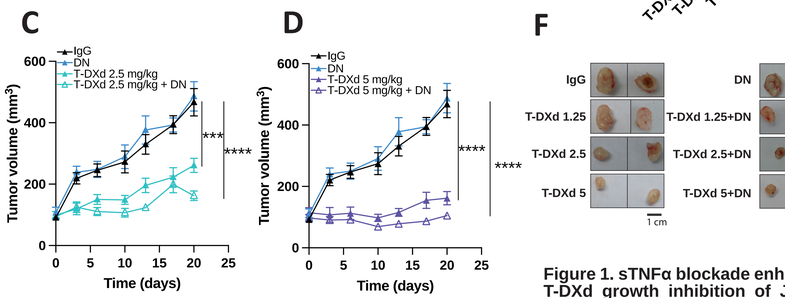
OBJECTIVE

To study whether DN improves internalization of T-DXd in tumor cells and modifies the innate immune response to enhance T-DXd antitumor effects in a multiple HER2-targeted therapy-resistant model.

METHODS







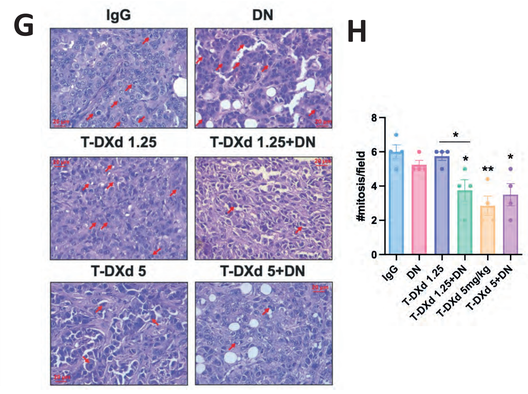
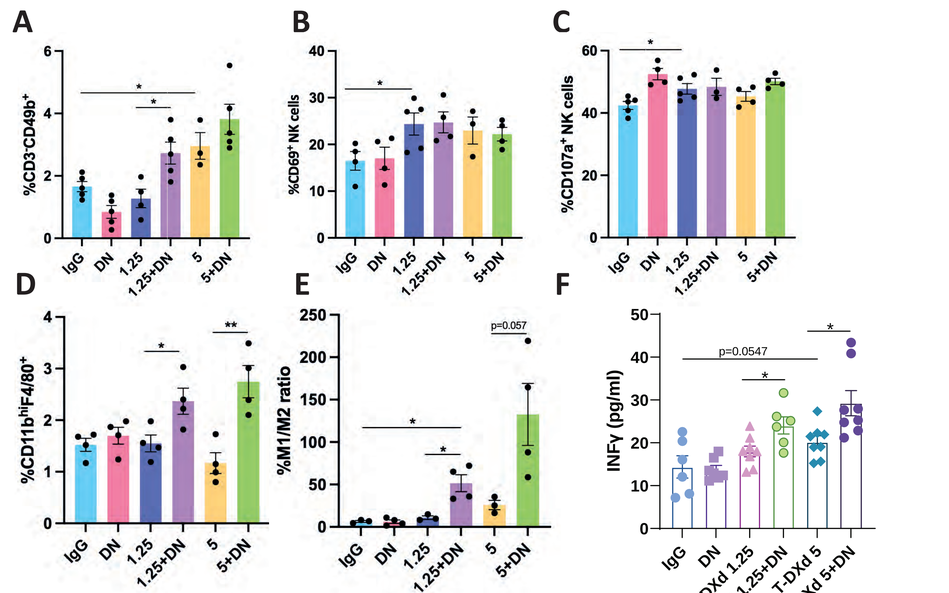


Figure 1. sTNFα blockade enhances T-DXd growth inhibition of JIMT-1 tumor. Female nude mice were injected with 3x10^6 JIMT-1 cells s.c. and mice were randomized and treated as shown in methods. Tumor growth was monitored routinely. Dose-response curves of T-DXd **(A)**. T-DXd in combination with DN **(B-D)**. Percentage change in tumor volume was calculated for each tumor with respect to the pre-treatment volume at endpoint **(E)** and tumors were photographed **(F)**. Mitotic numbers of representative tumor samples were studied. DN potentiates T-DXd reduction in tumor mitotic numbers **(G-H)**. Data represents mean ± SEM. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 vs. IgG, unless indicated otherwise.

RESULTS



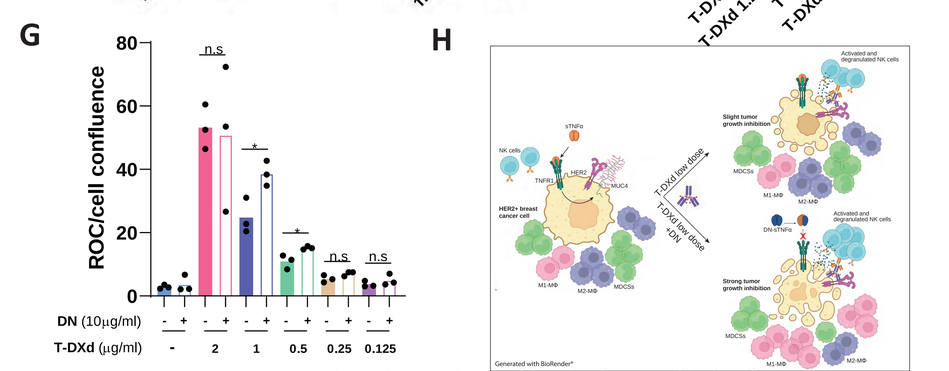


Figure 2. sTNFα blockade enhances T-DXd internalization and boosts the associated antitumor immune response. Tumor infiltrating cells from each experimental group shown in Figure 1 were determined by immunofluorescence staining and flow cytometry. NK cells referred to the total leukocyte population **(A)** and activation **(B)** and degranulation **(C)** are shown. Total macrophages **(D)** and M1/M2 ratio **(E)** are shown. IFNγ production in tumor lysates **(F)** and T-DXd internalization in JIMT-1 cells treated or not with INB03 **(G)** are shown. **(H)** Working model. Addition of DN to low-dose T-DXd treatment transforms the tumor microenvironment to potentiate the antitumor innate immune response. Data represents mean ± SEM and p values were calculated by one-way ANOVA coupled with Tukey post hoc test. Data represents mean ± SEM. *p<0.05, **p<0.01 vs. IgG, unless indicated otherwise. ROC: red object count determined by Incucyte at 18h.

CONCLUSIONS

- sTNFα blockade:
  - increases T-DXd internalization
  - allows a 4-time de-escalation of T-DXd dose, preserving similar antitumor effects
  - transforms the TME to an antitumor one with a reinforced immune response with increased IFNγ secretion.
- Neutralization of sTNFα may open new therapeutic strategies for treatment of patients who present MUC4 expression or have progression on T-DXd therapy or trastuzumab-based therapies

FINANCIAL SUPPORT AND REFERENCES

References:
1. Hurvitz et al. Lancet. 2023
2. Mercogliano et al. Clin Cancer Res 2017
3. Bruni et al. J Immunother Cancer 2023