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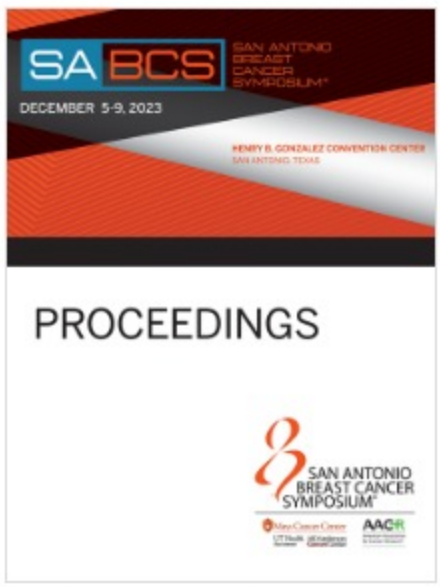

Article Contents

Abstract PO2-18-05: 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 FREE

Sofia Bruni; Florencia Mauro; Sofia Naveiro; Rosalia Cordo-Russo; Agustina Dupont; Mercogliano María Florencia; Roxana Schillaci

+ Author & Article Information
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Abstract

Background Trastuzumab deruxtecan (T-DXd) administration improves response for patients with HER2-positive metastatic breast cancer (HER2+ BC). Unfortunately, 50% of patients relapse after 2 years. T-DXd resistance mechanisms are being explored. For trastuzumab we have shown that mucin 4 (MUC4) expression is an independent predictor of poor response in HER2+BC patients. MUC4 is upregulated by soluble TNF (sTNF) secreted by the tumor, confers resistance to trastuzumab by hiding its epitope on the HER2, reducing its binding and decreasing anti-tumor phagocytic function. In preclinical models of de novo trastuzumab-resistant tumors, combination of a sTNF blocking agent INB03, (DN), with T-DXd decreases tumor growth compared to T-DXd alone. To

Methods Nude mice bearing HER2+MUC4+ JIMT-1 tumor, primary resistant to trastuzumab, pertuzumab and lapatinib, were treated with IgG 5 mg/kg, T-DXd 5 mg/kg (T-DXd 5), 2.5 mg/kg (T-DXd 2.5) or 1.25 mg/kg (T-DXd 1.25), DN 10 mg/kg or the combined therapies. T-DXd and IgG were administered i.v. on days 0, 7 and 14. DN was administered i.p. twice a week for 3 weeks. Tumor growth was monitored. Mitotic figures/field (mean) were analyzed in H&E tumor sections. Tumor-infiltrating macrophages were studied by flow cytometry. IFNɣ was determined in tumor extracts by ELISA. Internalization of T-DXd in JIMT-1 cells was studied in a S1 Incucyte along 18h by Fab-rhodo red labeling.

Results T-DXd dose-response curves showed inhibition in tumor growth of 83%, 61% and 37% for T-DXd 5, 2.5 and 1.25 mg/kg treatment respectively compared with IgG-treated tumors. DN alone exhibited no antitumor activity. T-DXd+DN increased the antitumor effect by 10%, 33% and 97% for T-DXd dose of 5, 2.5 and 1.25 mg/kg respectively. Tumor growth inhibition of T-DXd 5 was similar to combination of T-DXd1.25+DN. Addition of DN did not have toxicity. DN increases IFNɣ production in the TME of T-DXd treated tumors vs T-DXd alone and promoted macrophage recruitment to the tumor bed and polarization to the antitumor M1-like phenotype. Histopathological analysis of the tumor showed a significant decrease in proliferation in all the combined and in the T-DXd 5mg/kg (2.8-3.7 mitotic figures/field) vs IgG (6.0 mitotic figures/field). In vitro, JIMT-1 cells treated with DN internalized 40% more T-DXd than its vehicle-treated counterparts.

Conclusions Neutralizing sTNF with DN enhances T-DXd effect in a multiple HER2 targeted therapy resistant model of MUC4 expressing HER2+ BC. Combination of DN with T-DXd increases tumor response at all dose levels tested. The largest effect was seen at lower doses (T-DXd 1.25+DN), which mimicked the effect of 4 times the dose of T-DXd alone, suggesting significant synergy with DN as dose of T-DXd decreases. Combination of DN with T-DXd in MUC4 expressing HER2+ BC improves response to T-DXd alone by increasing T-DXd internalization and improving anti-tumor innate immune responses in the TME without increasing toxicity. The results suggest this combination should be investigated in clinical trials in patients who have MUC4 expressing tumors when T-DXd is started or become resistant to T-DXd therapy.

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