Poster 10: Trastuzumab deruxtecan induces immunogenic cell death, immune cell activation and -migration in viable human breast cancer slices

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Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate composed of a humanized immunoglobulin G1 monoclonal antibody specifically targeting HER2, a tetrapeptide-based cleavable linker, and a potent topoisomerase I inhibitor payload (DXd). It is approved for several indications including adult patients with HER2-positive and HER2-low breast cancers. While immune activation by T-DXd was reported in mouse models, it has not yet been shown in patient samples. We hypothesize that generation of an anti-tumor immune response could exist in patients' tumors treated with T-DXd,

In this preclinical research study, we used primary human breast cancer tissue to evaluate the cell types which can internalize T-DXd in culture, induction of immunogenic cell death within tumor cells, intra-tumoral immune cell activation and autologous immune cell migration.

Viable human tumor slices (VHTS) were prepared from surgically removed, primary tumors from breast cancer patients using a vibratome. For each readout, we analyzed three to seven samples from an overall pool of five HER2-positive and 16 HER2-low patient samples (three neoadjuvantly treated). To analyze internalization, VHTS were cultured overnight in presence of fluorescently labeled T-DXd or control IgG (10-15 µg/ml). For functional assays, VHTS were cultured up to five days in the presence of unlabeled T-DXd (15 or 150 µg/ml), DXd (30 or 100 nM) or left untreated. After that the culture supernatants were collected for cytokine analyses and the slices were dissociated and submitted to flow cytometry analyses.

As a result, it was observed that T-DXd was internalized into tumor cells in a target-dependent manner. Compared to untreated slices, T-DXd-treated VHTS showed significantly enhanced levels of the apoptosis marker active/cleaved caspase-3 within tumor cells, significantly reduced HER2-harbouring tumor cell counts, and in some patient samples increased release of HMGB1 in culture supernatants indicating the induction of immunogenic cell death. In addition, we observed increased immune cell activation upon T-DXd incubation manifested by upregulation of CD86 levels, potentiated antigen presentation demonstrated by elevation of MHC class II on macrophages and MHC class I on tumor cells as well as increases of granzyme B+ cytotoxic T cell frequencies. In line with this, cytokine analysis of supernatants revealed higher levels of pro-inflammatory cytokines including GM-CSF, TNFα and IFN-γ. Finally, we also observed enhanced immune cell infiltration of autologous PBMCs into T-DXd-treated VHTS.

These results suggest that T-DXd has immune activating effects in human HER2-positive and HER2-low breast cancer tissues. Further studies are needed to assess the use of T-DXd as a complementary treatment to immuno-oncology drugs in patients.