27O-ISMS04 **The Profiles of Trastuzumab Deruxtecan (DS-8201a), Topoisomerase I Inhibitor Exatecan-Derivative Based HER2-Targeting Antibody-Drug Conjugate**

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Antibody-drug conjugates (ADCs) represent a promising drug class with wider therapeutic window than conventional chemotherapeutic agents that affect efficient and specific drug delivery to antigen-expressing tumor cells. Trastuzumab deruxtecan (DS-8201a) is a HER2-targeting ADC that is structurally composed of a humanized anti-HER2 antibody, an enzymatically cleavable peptide (Gly-Gly-Phe-Gly)-based linker, and a novel topoisomerase I inhibitor (DXd). A self-immolative amino methylene spacer was used for DS-8201a, which reduced hydrophobicity compared to the conventional p-amino benzyl spacer (pAB) and provided stability in systemic circulation. Therefore, this ADC achieves a high drug-to-antibody-ratio (DAR 8) with homogeneous conjugation with DXd. The preclinical profile of DS-8201a was assessed and its pharmacological advantage over T-DM1 was evaluated in in vivo xenograft studies. DS-8201a differed from T-DM1 in the following aspects: 1) effect on T-DM1-insensitive model, 2) effect on low HER2 expressing model, and 3) bystander effect. DS-8201a provided valuable therapy with a potential to respond to T-DM1-insensitive breast cancer and other cancers with low HER2 expression in clinical settings. Phase II DESTINY studies with DS-8201a are currently underway. The translation from the preclinical and phase I trials of this new topoisomerase I inhibitor-based ADC technology into the clinical proof-of-concept will be clarified in the study. The preclinical data indicate a possibility of combining the topoisomerase I inhibitor-based ADC technology with immuno-oncology therapy for better results and the clinical collaboration is being planned.