BLOCKING “DON’T-EAT-ME” SIGNAL OF CD47-SIRPα BY ANTI-SIRPα ANTIBODY ENHANCES ANTI-TUMOR EFFICACY OF TRASTUZUMAB DERUXTECAN

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Background CD47-Signal-regulatory protein alpha (SIRPα) pathway is an emerging target for cancer immunotherapy. Preclinically, CD47-SIRPα blockers have been shown to enhance anti-tumor function of macrophages such as antibody-dependent cellular phagocytosis (ADCP). While in blood cancer patients, several CD47-SIRPα blockers have shown encouraging monotherapy activity, the monotherapy efficacy in solid tumors seems less promising, suggesting the need for combination drugs to fully exploit the myeloid immune checkpoint. We have established DS-1103a, a humanized IgG4 antibody against human SIRPα, and in this study we assessed whether trastuzumab deruxtecan (T-DXd; DS-8201a), a HER2-targeting antibody-drug conjugate (ADC), is a potential combination drug for DS-1103a. The antibody portion of T-DXd is a human IgG1, an ADCP-enabling Fc, which might show a combination benefit with DS-1103a.

Methods The binding of DS-1103a to human SIRPα and the inhibitory potency on CD47-SIRPα interaction was assessed by a cell-based binding assay. To test whether the combination of DS-1103a with T-DXd augments ADCP activity of macrophages, human monocyte-derived macrophages were co-cultured with JIMT-1 cells, HER2-expressing human breast cancer cells. The anti-tumor activity of T-DXd or trastuzumab in combination with MACK-8260a, an anti-mouse SIRPα antibody, was evaluated in a syngeneic mouse model bearing HER2-expressing mouse cancer cells.

Results DS-1103a successfully bound to human SIRPα and inhibited CD47-SIRPα interaction. In our ADCP assay, T-DXd induced modest ADCP (9.267% ± 1.249% of JIMT-1 cells were phagocytosed) of macrophages, compared to a control IgG-ADC (5.156% ± 0.571%, P = 0.0242). When combined, DS-1103a significantly enhanced the ADCP (40.860% ± 8.319%) compared to T-DXd monotherapy described above (P = 0.0025). Further, in our syngeneic mouse model with HER2-expressing CT26.WT cells, the combination of T-DXd with MACK-8260a prolonged the overall survival of animals compared to those of the monotherapy. By day 35 from the treatment initiation, 7/15, 13/15, and 15/15 of mice reached humane endpoint in the combination therapy, T-DXd, and MACK-8260a monotherapy group, respectively (P = 0.0232, combination vs T-DXd; P = 0.0006, combination vs MACK-8260a). Interestingly, trastuzumab failed to show such combination effect with MACK-8260a, suggesting that T-DXd is a better combination drug for DS-1103a than trastuzumab.

Conclusions Our in vitro and in vivo studies demonstrated that blocking CD47-SIRPα pathway by anti-SIRPα antibody enhances antitumor efficacy of T-DXd, warranting future clinical trials of the combination to assess the potential of DS-1103a to further enhance the efficacy of T-DXd.

Ethics Approval All the in vitro studies employing human blood obtained from healthy volunteers were approved by and conducted in accordance with the guidelines of Daiichi Sankyo Research Ethics Committee. All animal studies were approved by the Institutional Animal Care and Use Committee of Daiichi Sankyo.