Nonclinical safety assessment of trastuzumab deruxtecan (T-DXd; DS-8201), a HER2 targeting antibody-drug conjugate

Kazuyoshi KUMAGAI
Medicinal Safety Research Laboratories, Daiichi Sankyo Co., Ltd.

Trastuzumab deruxtecan (T-DXd; DS-8201) is a HER2-targeting antibody-drug conjugate composed of a humanized anti-HER2 antibody and an exatecan derivative (DXd), a topoisomerase I inhibitor, which are bound together by a cleavable peptide-based linker. Before clinical trials, 6-week toxicity studies (every 3 weeks totaling 3 doses) with T-DXd were conducted in cynomolgus monkeys (cross-reactive species) and in rats (non cross-reactive species). The major target organs/tissues in rats and monkeys were the intestines and bone marrow. This effect seemed to be attributable to the cytotoxic effects of DXd and typical dose-limiting factors in the clinical use of topoisomerase I inhibitors. T-DXd caused pulmonary toxicity in monkeys at ≥30 mg/kg, although it was not observed in rats. In a 3-month monkey toxicity study (T-DXd every 3 weeks for a total of 5 doses), pulmonary toxicity was observed at 30 mg/kg (the highest dose). An extended dosing period did not increase the severity of lesions. While comprehensive mechanisms of the pulmonary toxicity remain unclear, this finding in monkeys could be relevant to the understanding of mechanism of interstitial lung disease (ILD) in patients treated with T-DXd. In this presentation, nonclinical toxicity data are reviewed with an emphasis on relevant safety findings.
Trastuzumab deruxtecan (T-DXd; DS-8201) is a HER2-targeting antibody-drug conjugate composed of a humanized anti-HER2 antibody and an exatecan derivative (DXd), a topoisomerase I inhibitor, which are bound together by a cleavable peptide-based linker. Before clinical trials, 6-week toxicity studies (every 3 weeks totaling 3 doses) with T-DXd were conducted in cynomolgus monkeys (cross-reactive species) and in rats (non cross-reactive species). The major target organs/tissues in rats and monkeys were the intestines and bone marrow. This effect seemed to be attributable to the cytotoxic effects of DXd and typical dose-limiting factors in the clinical use of topoisomerase I inhibitors. T-DXd caused pulmonary toxicity in monkeys at ≥ 30 mg/kg, although it was not observed in rats. In a 3-month monkey toxicity study (T-DXd every 3 weeks for a total of 5 doses), pulmonary toxicity was observed at 30 mg/kg (the highest dose). An extended dosing period did not increase the severity of lesions. While comprehensive mechanisms of the pulmonary toxicity remain unclear, this finding in monkeys could be relevant to the understanding of mechanism of interstitial lung disease (ILD) in patients treated with T-DXd. In this presentation, nonclinical toxicity data are reviewed with an emphasis on relevant safety findings.