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Background: Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate comprising an anti-HER2 antibody (trastuzumab) linked to a potent topoisomerase I inhibitor (DXd). T-DXd has been approved to treat HER2-positive metastatic breast cancer (United States [US], Japan, Europe, Israel) and advanced gastric cancer (US, Japan, Israel). It is currently being evaluated in other solid tumor types including colorectal cancer. The phase 2 DESTINY-CRC01 study included patients with *RAS* wild-type mCRC, with a median 4 (range, 2-11) prior lines of therapy. Preliminary results in patients with HER2-overexpressing (IHC 3+ or IHC 2+/ISH+) mCRC showed T-DXd treatment (6.4-mg/kg intravenously [IV] every 3 weeks [Q3W]) resulted in a confirmed objective response rate (ORR) of 45.3% (24/53; 95% CI, 31.6-59.6%) and a median progression-free survival (PFS) of 6.9 months (95% CI, 4.1-not estimable; Siena *J Clin Oncol*. 2020). Activity was also seen in patients treated with prior anti-HER2 therapy. Although 5.4-mg/kg and 6.4-mg/kg doses of T-DXd have shown clinical efficacy in multiple cancer indications, the lower dose has not yet been tested in patients with HER2-overexpressing mCRC. Preliminary data also suggest T-DXd may be active in *RAS* mutant mCRC, unlike other anti-HER2 therapies. The DESTINY-CRC02 study aims to determine efficacy and safety of T-DXd in patients with HER2-overexpressing, *RAS* wild-type or mutant mCRC at 5.4-mg/kg and 6.4-mg/kg doses. **Methods:** DESTINY-CRC02 (NCT04744831) is a multicenter, randomized, double-blind, 2-arm, parallel phase 2 study that will be conducted in 2 stages. Eligible patients (≥18 years; ≥20 years in Japan, Taiwan, and Korea) will have HER2-overexpressing (IHC 3+ or IHC 2+/ISH+) locally advanced, unresectable or metastatic CRC and have previously received chemotherapy, anti-EGFR therapy, anti-VEGF treatment, and/or anti–PD-1/PD-L1 therapy, as clinically indicated. Prior anti-HER2 therapy will be allowed. In stage 1, patients will be randomly assigned 1:1 to receive T-DXd IV Q3W at a dose of 5.4-mg/kg (n = 40; arm 1) or 6.4-mg/kg (n = 40; arm 2). Randomization will be stratified by ECOG PS (0 or 1), HER2 status (IHC 3+ or IHC 2+/ISH+), and *RAS* status (wild-type or mutant). After stage 1 enrollment is complete, eligible patients in stage 2 (n = 40) will receive T-DXd 5.4 mg/kg until disease progression or other treatment discontinuation criteria are met. The study is actively enrolling and aims to enroll 120 patients across 60 sites. The primary objective is to assess efficacy of T-DXd at the 5.4-mg/kg and 6.4-mg/kg doses, with a primary endpoint of confirmed ORR by blinded independent central review. Secondary endpoints include investigator-assessed ORR, PFS, duration of response, disease control rate, clinical benefit rate, overall survival, pharmacokinetics, and safety. Clinical trial information: NCT04744831.

DOI: 10.1200/JCO.2022.40.4_suppl.TPS224 Journal of Clinical Oncology 40, no. 4_suppl