

Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-overexpressing/amplified (HER2+) metastatic colorectal cancer (mCRC): Primary results from the multicenter, randomized, phase 2 DESTINY-CRCO2 study.

Kanwal Pratap Singh Raghav, Salvatore Siena, Atsuo Takashima, Takeshi Kato, Marc Van Den Eynde, Maria Di Bartolomeo, Yoshito Komatsu, Hisato Kawakami, Marc Peeters, Thierry Andre, Sara Lonardi, Kensei Yamaguchi, Jeanne Tie, Cristina Gravalos Castro, John H Strickler, Daniel Barrios, Qi Yan, Takahiro Kamio, Kojiro Kobayashi, Takayuki Yoshino; The University of Texas MD Anderson Cancer Center, Houston, TX; Università degli Studi di Milano, Grande Ospedale Metropolitano Niguardia, Milan, Italy; National Cancer Center Hospital, Tokyo, Japan; National Hospital Organization, Osaka National Hospital, Osaka, Japan; Cliniques Universitaires St-Luc, Brussels, Belgium; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Hokkaido University Hospital, Sapporo, Japan; Kindai University Hospital, Osakasayama, Japan; UZ Antwerpen, Edegem, Belgium; Hôpital Saint-Antoine, Paris, France; Istituto Oncologico Veneto IRCCS, Padova, Italy; The Cancer Institute Hospital of JFCR, Tokyo, Japan; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; Hospital Universitario 12 de Octubre, Madrid, Spain; Duke University Medical Center, Durham, NC; Daiichi Sankyo Inc., Basking Ridge, NJ; Daiichi Sankyo Co, Ltd., Tokyo, Japan; National Cancer Center Hospital East, Kashiwa, Japan

Background: T-DXd (6.4 mg/kg, every 3 weeks [Q3W]) demonstrated antitumor activity in pts with HER2+ mCRC in DESTINY-CRCO1 (Siena et al. *Lancet Oncol.* 2021). We present primary results of DESTINY-CRCO2 (NCT04744831), which assessed the efficacy and safety of T-DXd (5.4 and 6.4 mg/kg) in pts with HER2+ mCRC. **Methods:** This was a multicenter phase 2 study. Eligible pts had centrally confirmed HER2+ (immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization [ISH]++) mCRC. Pts with RAS wild-type (wt) or mutant (m) mCRC were eligible. Pts had received prior standard therapy, unless contraindicated; prior anti-HER2 therapy was allowed. In stage 1, 80 pts were randomized 1:1 to 5.4 (n = 40) or 6.4 (n = 40) mg/kg T-DXd Q3W. In stage 2, an additional 42 pts received 5.4 mg/kg T-DXd. Primary endpoint was confirmed objective response rate (cORR) by blinded independent central review (BICR). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** At data cutoff (Nov 1, 2022), most pts in the 5.4 and 6.4 mg/kg T-DXd arms had HER2 IHC 3+ (78.0% and 85.0%), RAS wt tumors (82.9% and 85.0%), and a median of 3 and 4 prior lines of therapy, respectively. cORR was 37.8% (95% CI, 27.3-49.2%) in the 5.4 mg/kg arm and 27.5% (95% CI, 14.6-43.9%) in the 6.4 mg/kg arm (all partial responses in both arms). Key efficacy data are shown in the Table: Grade ≥ 3 treatment-emergent adverse events (AEs) were observed in 41/83 pts (49.4%) and 23/39 pts (59.0%) in the 5.4 and 6.4 mg/kg T-DXd arms, respectively. Serious AEs were observed in 20/83 pts (24.1%) and 12/39 pts (30.8%) in the 5.4 and 6.4 mg/kg arms, respectively. Independently adjudicated drug-related interstitial lung disease occurred in 7/83 pts (8.4%) with 5.4 mg/kg T-DXd and 5/39 pts (12.8%) with 6.4 mg/kg T-DXd, and most events were grade 1/2 (1 grade 5 in the 6.4 mg/kg arm). **Conclusions:** T-DXd showed promising antitumor activity in pts with HER2+ mCRC at both 5.4 and 6.4 mg/kg doses. Antitumor efficacy was observed irrespective of RAS mutation status at 5.4 mg/kg T-DXd, and in those with prior anti-HER2 therapy. Overall, safety was consistent with the known safety profile of T-DXd and favored the 5.4 mg/kg dose. Clinical trial information: NCT04744831. Research Sponsor: Daiichi Sankyo, Inc and AstraZeneca.

Efficacy summary.		
	5.4 mg/kg T-DXd n = 82	6.4 mg/kg T-DXd n = 40
Median follow-up, mo (range)	8.9 (0.5-17.1)	10.3 (0.7-16.4)
Median DoR by BICR, mo (95% CI)	5.5 (4.2-8.1)	5.5 (3.7-non-evaluable)
Median PFS, mo (95% CI)	5.8 (4.6-7.0)	5.5 (4.2-7.0)
Best overall response by BICR in subgroups, n/N (%) [95% CI]		
Prior anti-HER2 therapy	7/17 (41.2) [18.4-67.1]	4/10 (40.0) [12.2-73.8]
HER2 IHC 3+	30/64 (46.9) [34.3-59.8]	10/34 (29.4) [15.1-47.5]
HER2 IHC 2+/ISH+	1/18 (5.6) [0.1-27.3]	1/6 (16.7)
RAS wt	27/68 (39.7) [28.0-52.3]	11/34 (32.4) [17.4-50.5]
RASm	4/14 (28.6) ^a [8.4-58.1]	0/6

^aAll RASm responders were IHC 3+.