3501 **Oral Abstract Session**

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-CRC02 study.

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Background: T-DXd (6.4 mg/kg, every 3 weeks [Q3W]) demonstrated antitumor activity in pts with HER2+ mCRC in DESTINY-CRC01 (Siena et al. *Lancet Oncol.* 2021). We present primary results of DESTINY-CRC02 (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]
***RAS*m**	4/14 (28.6)[a] [8.4-58.1]	0/6

[a]All *RAS*m responders were IHC 3+.