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DESTINY CRC02

Trastuzumab deruxtecan (T-DXd) in patients with HER2-positive (HER2+) metastatic colorectal cancer (mCRC): Final analysis of DESTINY-CRC02, a randomized, phase 2 trial

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Declaration of Interests

Dr. Raghav discloses research grants from AbbVie, AstraZeneca, Bayer, Daiichi Sankyo, Grail, Guardant, Janssen, Merck, Pfizer, D3-Bio, MediLink, and Roche/Genentech; participation on an advisory board for AbbVie, Daiichi Sankyo, Janssen, Pfizer, and Jazz; and speaker roles for Jazz

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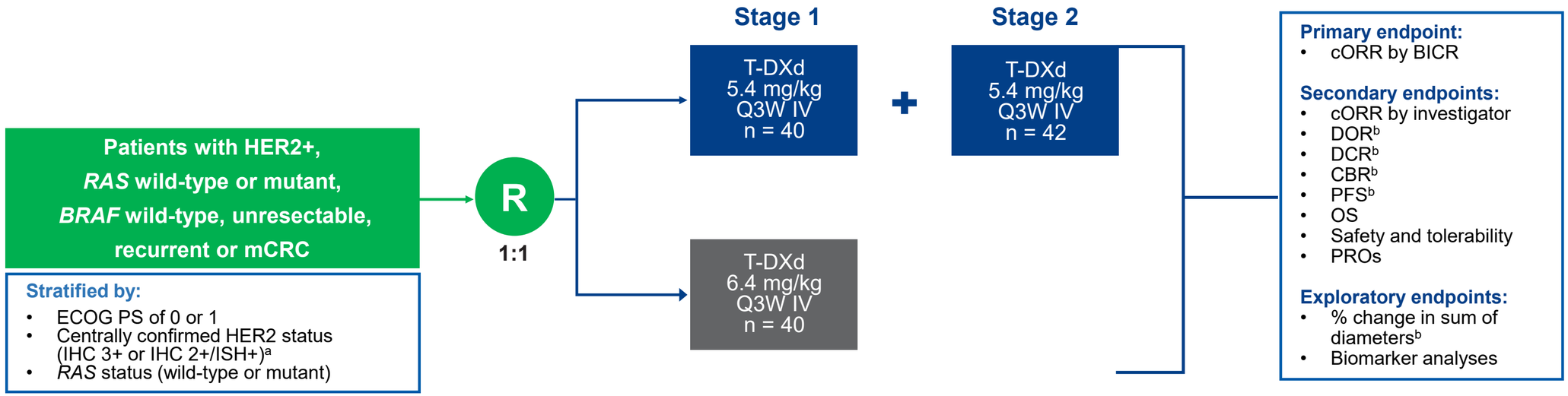
DESTINY-CRC02: A Multicenter, Randomized, 2-Stage, 2-Arm, Phase 2 Trial (NCT04744831)

Based in part on the results of DESTINY-CRC02, T-DXd has been approved in several countries for the treatment of patients with previously treated unresectable or metastatic HER2 IHC 3+ solid tumors, including CRC



This study was not powered to statistically compare the 2 arms.
The site staff were blinded to treatment assignment through the roles and permissions document in the interactive response technology system.
Treatment assignments were also unknown to patients, central imaging readers, and the interstitial lung disease adjudication committee.

Objective: To evaluate the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg at the final analysis of DESTINY-CRC02 (DCO, December 4, 2024)

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[a]HER2 status was assessed using the PATHWAY anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody (Roche Diagnostics), available in some regions as the VENTANA HER2 (4B5) Rabbit Monoclonal Primary Antibody RxDx (Roche Diagnostics). [b]By BICR and investigator.
BICR, blinded independent central review; CBR, clinical benefit rate; CRC, colorectal cancer; cORR, confirmed objective response rate; DCO, data cutoff; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan.

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Efficacy and Safety of T-DXd at the Final Analysis Were Consistent With the Primary Analysis

	Primary analysis (DCO, November 1, 2022)		Final analysis (DCO, December 4, 2024)	
T-DXd dose	**5.4 mg/kg n = 82**	**6.4 mg/kg n = 40**	**5.4 mg/kg n = 82**	**6.4 mg/kg n = 40**
Treatment duration, median (range), mo	5.5 (0.7-13.2)	4.9 (0.7-13.8)	5.5 (0.7-34.3)[a]	4.9 (0.7-29.2)[a]
Follow-up, median (range), mo	8.9 (0.5-17.1)	10.3 (0.7-16.4)	14.2 (0.5-34.0)	12.7 (0.7-36.6)
cORR (95% CI), %	37.8 (27.3-49.2)	27.5 (14.6-43.9)	37.8 (27.3-49.2)	27.5 (14.6-43.9)
DOR, median (95% CI), mo	5.5 (4.2-8.1)	5.5 (3.7-NE)	5.5 (4.2-8.1)	5.5 (3.7-9.8)
PFS, median (95% CI), mo	5.8 (4.6-7.0)	5.5 (4.2-7.0)	5.8 (4.6-7.0)	5.5 (4.2-7.0)
OS, median (95% CI), mo	13.4 (12.5-16.8)	NE (9.9-NE)	15.9 (12.6-18.8)	19.7 (9.9-25.8)
Drug-related grade ≥3 TEAE,%[a]	41.0	48.7	42.2	48.7
Adjudicated drug-related ILD, %[a]	8.4 (1 grade 1; 6 grade 2)	12.8 (2 grade 1; 2 grade 2; 1 grade 5[b])	9.6 (2 grade 1; 6 grade 2)	17.9 (2 grade 1; 4 grade 2; 1 grade 5[b])

With longer follow-up, median OS with T-DXd was 15.9 and 19.7 months in the T-DXd 5.4- and 6.4-mg/kg treatment groups, respectively

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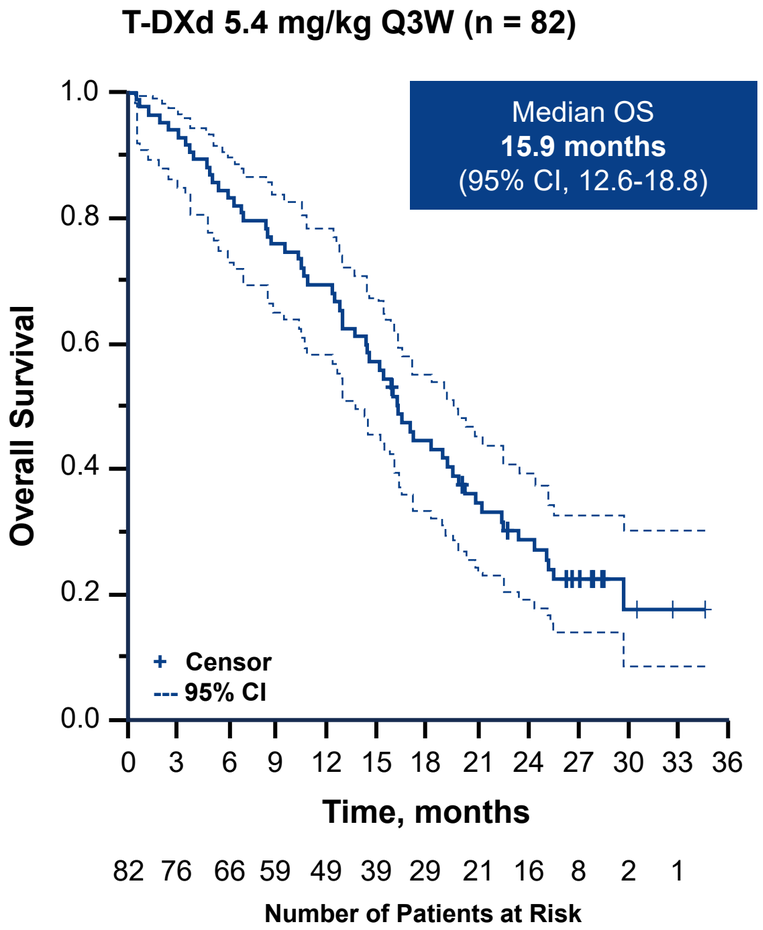
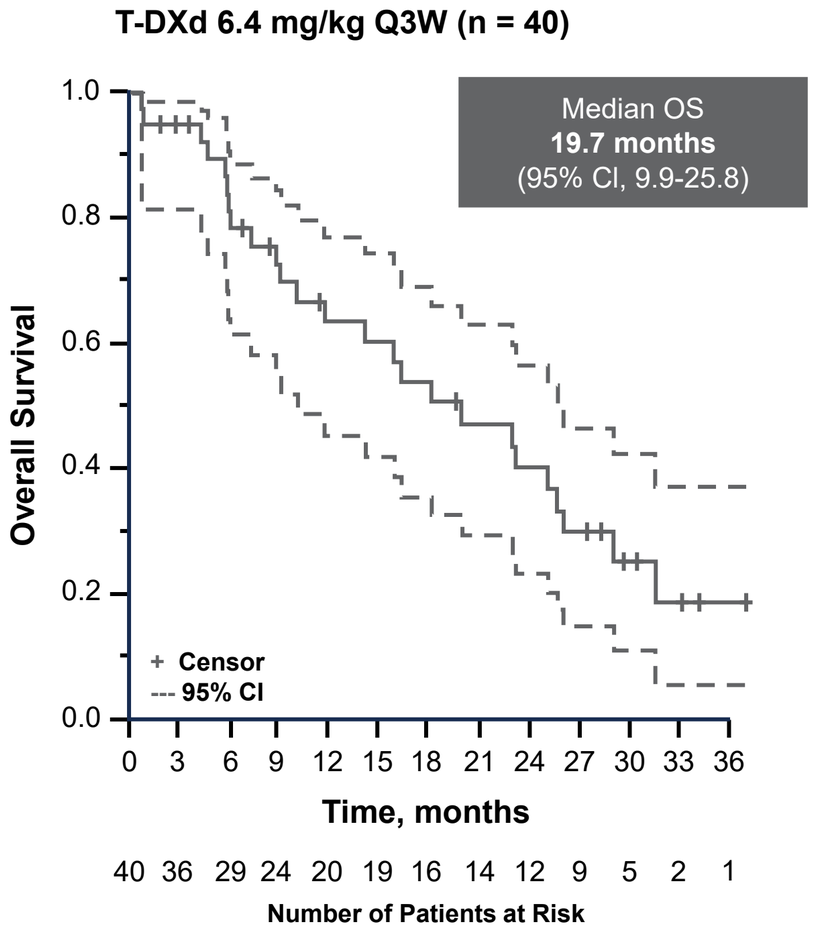
[a]Based on the total population treated with trastuzumab deruxtecan; 5.4 mg/kg, n = 83; 6.4 mg/kg, n = 39 (safety analysis set). [b]Adjudicated as drug-related grade 5 ILD by the ILD adjudication committee but assessed by the investigator as not related to study drug.
ILD, interstitial lung disease; mo, months; NE, not estimable; TEAE, treatment-emergent adverse event.

With Longer Follow-up at the Final Analysis, Median OS Was 15.9 Months and 19.7 Months in the T-DXd 5.4- and 6.4-mg/kg Groups





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OS Was Consistent in Key Subgroups

T-DXd dose	5.4 mg/kg n = 82		6.4 mg/kg n = 40	
	n	Median (95% CI), mo	n	Median (95% CI), mo
Overall	82	15.9 (12.6-18.8)	40	19.7 (9.9-25.8)
Region				
Asia-Pacific	47	16.8 (14.1-22.1)	24	19.7 (9.9-28.7)
Europe	29	12.2 (8.2-16.1)	14	25.4 (5.7-NE)
United States	6	NA[a]	2	NA[a]
ECOG performance status				
0	46	19.5 (15.7-25.1)	22	22.9 (14.0-31.2)
1	36	12.1 (6.2-14.1)	18	11.5 (5.8-24.8)
Primary tumor site				
Left	61	15.7 (12.6-19.9)	34	22.7 (9.9-28.7)
Right	21	15.9 (9.2-22.1)	6	NA[a]
Prior anti-HER2 treatment				
No	65	15.9 (12.6-19.2)	30	19.7 (8.7-25.4)
Yes	17	14.2 (8.2-25.1)	10	15.7 (0.7-NE)
Prior treatment with regorafenib or trifluridine and tipiracil				
No	48	16.1 (14.1-22.1)	27	22.7 (8.7-31.2)
Yes	34	13.0 (8.2-19.5)	13	15.7 (5.8-25.8)
HER2 IHC score status (central testing)				
3+	64	18.6 (14.9-22.1)	34	22.7 (14.0-25.8)
2+ and ISH+	18	6.8 (3.6-10.5)	6	NA[a]
***RAS* status (local testing)**				
Wild-type	67	16.7 (12.6-20.9)	34	19.7 (9.9-28.7)
Mutant	15	14.9 (2.9-16.1)	6	NA[a]
Presence of liver metastases at baseline				
No	23	16.7 (13.4-NE)	14	28.7 (8.9-NE)
Yes	59	15.7 (12.1-18.8)	26	15.7 (5.9-22.7)

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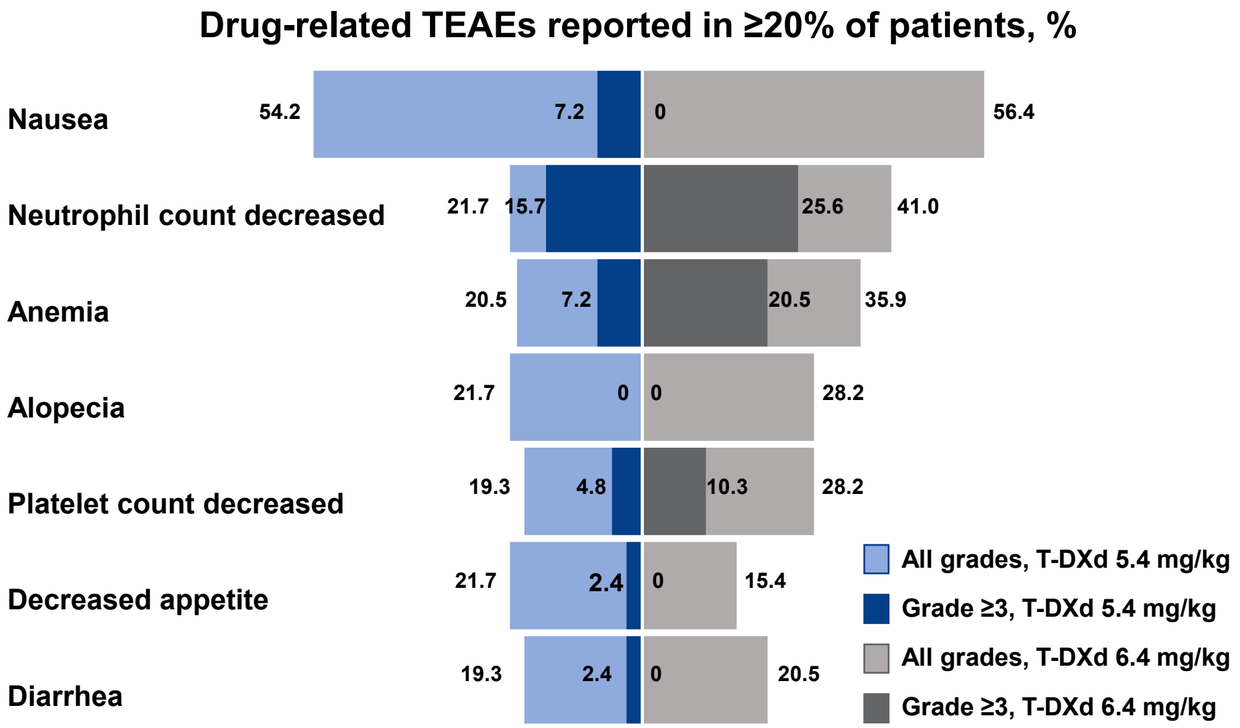
[a]Not available (median and 95% CI are only provided when there are at least 10 responders in a subgroup).

Overall Safety at the Final Analysis Was Generally Consistent With the Known Safety Profile of T-DXd

TEAE, n (%)	T-DXd 5.4 mg/kg n = 83[a]	T-DXd 6.4 mg/kg n = 39[a]
Any	**82 (98.8)**	**39 (100)**
Drug-related	77 (92.8)	37 (94.9)
Grade ≥3	**42 (50.6)**	**23 (59.0)**
Drug-related	35 (42.2)	19 (48.7)
Serious	**21 (25.3)**	**12 (30.8)**
Drug-related	11 (13.3)	6 (15.4)
Associated with drug discontinuation	**8 (9.6)**	**4 (10.3)**
Drug-related	6 (7.2)	3 (7.7)
Associated with drug interruption	**40 (48.2)**	**19 (48.7)**
Drug-related	24 (28.9)	10 (25.6)
Associated with dose reduction	**18 (21.7)**	**11 (28.2)**
Drug-related	17 (20.5)	10 (25.6)
Associated with death	**4 (4.8)**	**3 (7.7)**
Drug-related	1 (1.2)[b]	0
Adjudicated drug-related ILD		
Any grade	8 (9.6)	7 (17.9)
Grade 1	2 (2.4)	2 (5.1)
Grade 2	6 (7.2)	4 (10.3)
Grade 3 or 4	0	0
Grade 5	0	1 (2.6)[c]



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[a]One patient randomly assigned to receive T-DXd 6.4 mg/kg was mistakenly given T-DXd 5.4 mg/kg and was counted in the 5.4-mg/kg group safety analysis set. [b]Assessed by the investigator as drug-related hepatic failure.
[c]Adjudicated as drug-related grade 5 ILD by the ILD adjudication committee but assessed by the investigator as not related to study drug.

Conclusions

- Results of the DESTINY-CRC02 final analysis were consistent with those of the primary analysis, showing **single-agent T-DXd 5.4 mg/kg to be effective in patients with HER2+ mCRC**
- **Safety was generally consistent with the known safety profile of T-DXd**
- **T-DXd 5.4 mg/kg, the approved dose for patients with HER2+ (IHC3+) solid tumors, had a favorable benefit-risk profile**, and there were no new safety signals

Supplementary content is available
• Plain language summary

These findings support T-DXd 5.4 mg/kg as the optimal single-agent dose for patients with previously treated HER2+ mCRC, irrespective of *RAS* mutations and prior anti-HER2 therapy

This study is sponsored by Daiichi Sankyo. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).
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Supplementary

Plain Language Summary

Why did we perform this research?

- Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate designed to target and kill cancer cells that express a protein called human epidermal growth factor receptor 2 (HER2). In about 3%-11% of cases of colorectal cancer (CRC), cancer cells produce high levels of the HER2 protein.[1,2] In the phase 2 DESTINY-CRC02 clinical trial, T-DXd 5.4 mg/kg demonstrated encouraging antitumor activity and a favorable safety profile in patients with previously treated HER2-positive CRC tumors that were not surgically removable or had spread to other sites in the body (metastatic).[3] This presentation reports final efficacy and safety results from DESTINY-CRC02

How did we perform this research?

- T-DXd was evaluated in patients with HER2-positive metastatic CRC. This was a 2-stage study: in stage 1, patients were randomly assigned to receive T-DXd 5.4 mg/kg or 6.4 mg/kg every 3 weeks. In stage 2, patients were added to the 5.4-mg/kg treatment group only. In both stages of the study, the efficacy and safety of T-DXd were evaluated

What were the findings of this research and what are the implications?

- Results of the DESTINY-CRC02 final analysis were consistent with those reported previously from the primary analysis,[3] and efficacy was generally similar between the 5.4- and 6.4-mg/kg doses of T-DXd. At the final analysis, patients treated with T-DXd survived for a median of 15.9 months in the 5.4-mg/kg group and 19.7 months in the 6.4-mg/kg group. T-DXd 5.4 mg/kg demonstrated promising antitumor activity and a favorable safety profile, with no new safety signals emerging. These findings highlight the potential of T-DXd as a promising single-agent treatment for patients with HER2-positive metastatic CRC

Where can I access more information?

- To learn more about the phase 2 DESTINY-CRC02 trial please visit: https://clinicaltrials.gov/study/NCT04744831

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1. Uzunparmak B et al. Ann Oncol. 2023;34:1035-1046. 2. Ingold Heppner B et al. Br J Cancer. 2014;111:1977-1984. 3. Raghav K et al. Lancet Oncol. 2024;25(9):1147-1162.

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