Phase 3 trial of trastuzumab rezetecan vs standard of care for chemotherapy-refractory, HER2-positive, advanced colorectal cancer (HORIZON-CRC01)

Key Takeaways

Trastuzumab rezetecan achieved prolonged PFS and improved ORR compared with standard-of care (TAS-102, fruquintinib, or regorafenib) in chemotherapy-refractory HER2-positive advanced colorectal cancer.

Trastuzumab rezetecan could be a novel treatment option for chemotherapy-refractory HER2-positive advanced colorectal cancer .

Background

- Amplification or overexpression of HER2 has been identified as a key oncogenic driver in approximately 3-5% of patients with advanced colorectal cancer (CRC).[1-3]
- Trastuzumab rezetecan is an innovative antibody-drug conjugate (ADC) that integrates a humanized HER2-targeting monoclonal antibody with a DNA topoisomerase I inhibitor (SHR169265) through a cleavable tetrapeptide-based linker.[4]
- A phase I trial (NCT04513223) demonstrated that trastuzumab rezetecan had a manageable safety profile and promising antitumor activity in HER2-expressing advanced CRC.[5]
  - In HER2-positive CRC: ORR: 40.5% (95% CI: 22.9–57.9); median PFS: 9.5 months (95% CI, 7.3–11.2); median OS: 22.7 months(95% CI, 17.5–NR [not-reached]).
- This phase 3 randomized trial (NCT06199973) aimed to assess the efficacy and safety of trastuzumab rezetecan versus standard-of-care (SOC) in chemotherapy-refractory, HER2-positive, RAS and RAF wild-type advanced CRC.

Study design

- A randomized, open-label, active-controlled, multicenter, phase 3 study (NCT06199973; HORIZON-CRC01)

Key eligibility criteria

- Histologically or cytologically confirmed unresectable locally advanced or metastatic CRC;
- HER2-positive*, RAS and RAF wild-type;
- Had failed prior treatment with fluoropyrimidines, oxaliplatin, and irinotecan.
- dMMR or MSI-H tumors must have failed prior anti-PD-1 or anti-PD-L1 monoclonal antibody therapy;
- Previous HER2-targeted therapy was permitted;
- Had at least one measurable tumor lesion according to RECIST version 1.1;
- ECOG PS of 0 or 1.

R 2:1

Trastuzumab rezetecan group (N=86)

Trastuzumab rezetecan (4.8 mg/kg, IV, Q3W)

SOC group† (N=44)

TAS-102 (35 mg/m^2, bid, d1-5 and d8-12; PO, Q4W),
fruquintinib (5 mg, qd, d1-21; PO, Q4W),
or regorafenib (160 mg, qd, d1-21; PO, Q4W)

Until confirmed disease progression, intolerable toxicity, withdrawal of consent, loss to follow-up, or decision by the investigator

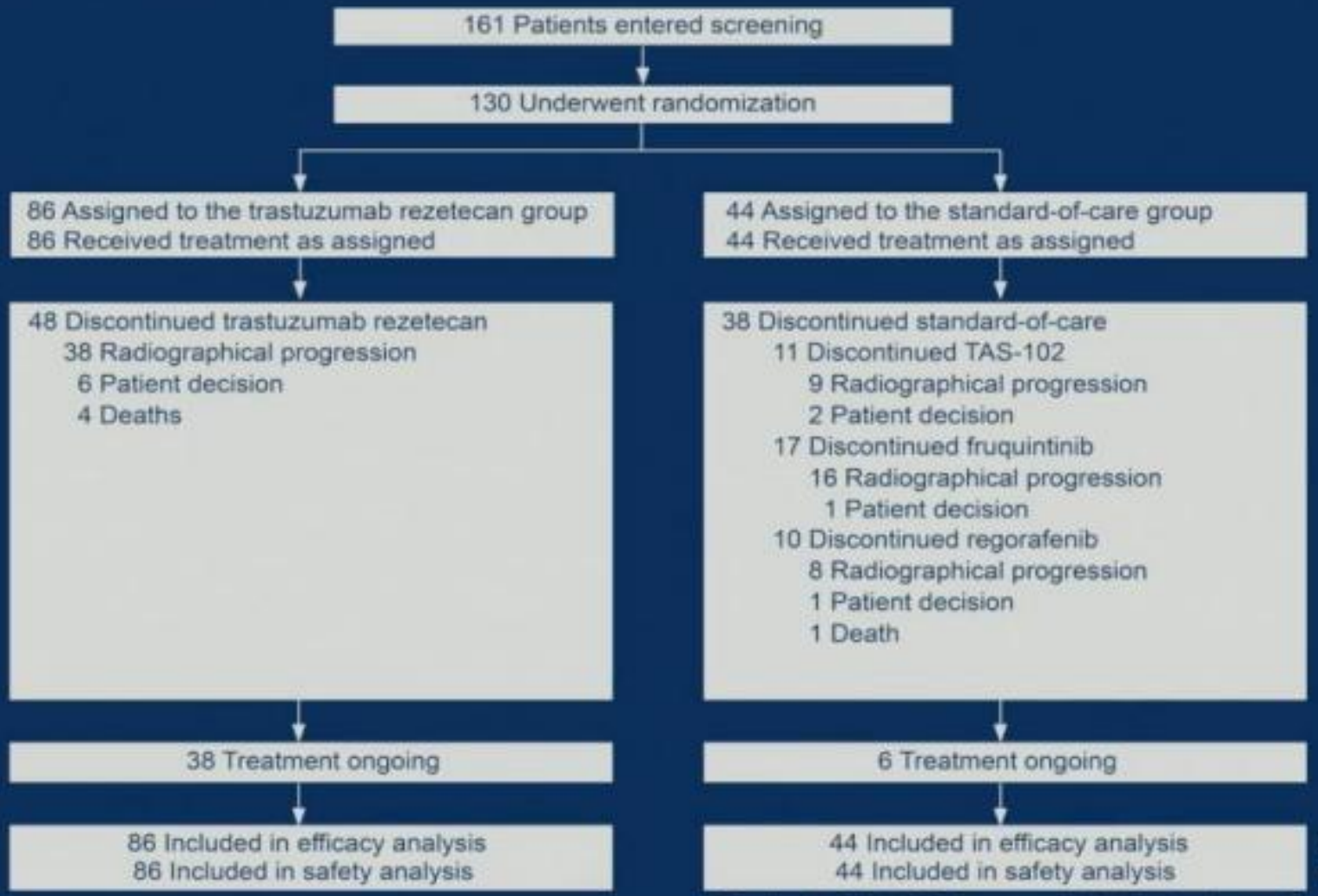
- **Randomization stratification factors:** HER2 status ([IHC 3+ vs IHC 2+/ISH+) and ECOG PS (0 vs 1).
- **Primary endpoint#:** PFS assessed by IRC.
- **Key secondary endpoint#:** OS.
- **Other secondary endpoints#:** PFS assessed by investigator; ORR and DoR, each assessed by IRC and investigator; safety.

Statistical Considerations

- **Estimated sample size: 120 patients**
  - The sample size was calculated based on the primary endpoint of PFS assessed by IRC;
  - A 2:1 randomization ratio (trastuzumab rezetecan group vs SOC group);
  - Assuming a median PFS of 4.0 months in the SOC group and a median PFS of 8.7 months in the trastuzumab rezetecan group (HR=0.46);
  - A total of 80 PFS events were required to achieve ≥90% power for demonstrating PFS superiority at a one-sided α level of 0.025 using the log-rank test;
  - Accounting for an annual PFS dropout rate of 8%, approximately 120 patients were planned for enrollment.

	Events	Planned analysis time	Superiority boundary of HR
PFS	80	22 months	0.628

Patient disposition



25 patients in the SOC group switched to trastuzumab rezetecan upon disease progression.

Cutoff date: Oct 31, 2025
Median follow-up (95% CI): 9.6 months (7.4-10.7)

Baseline Characteristics

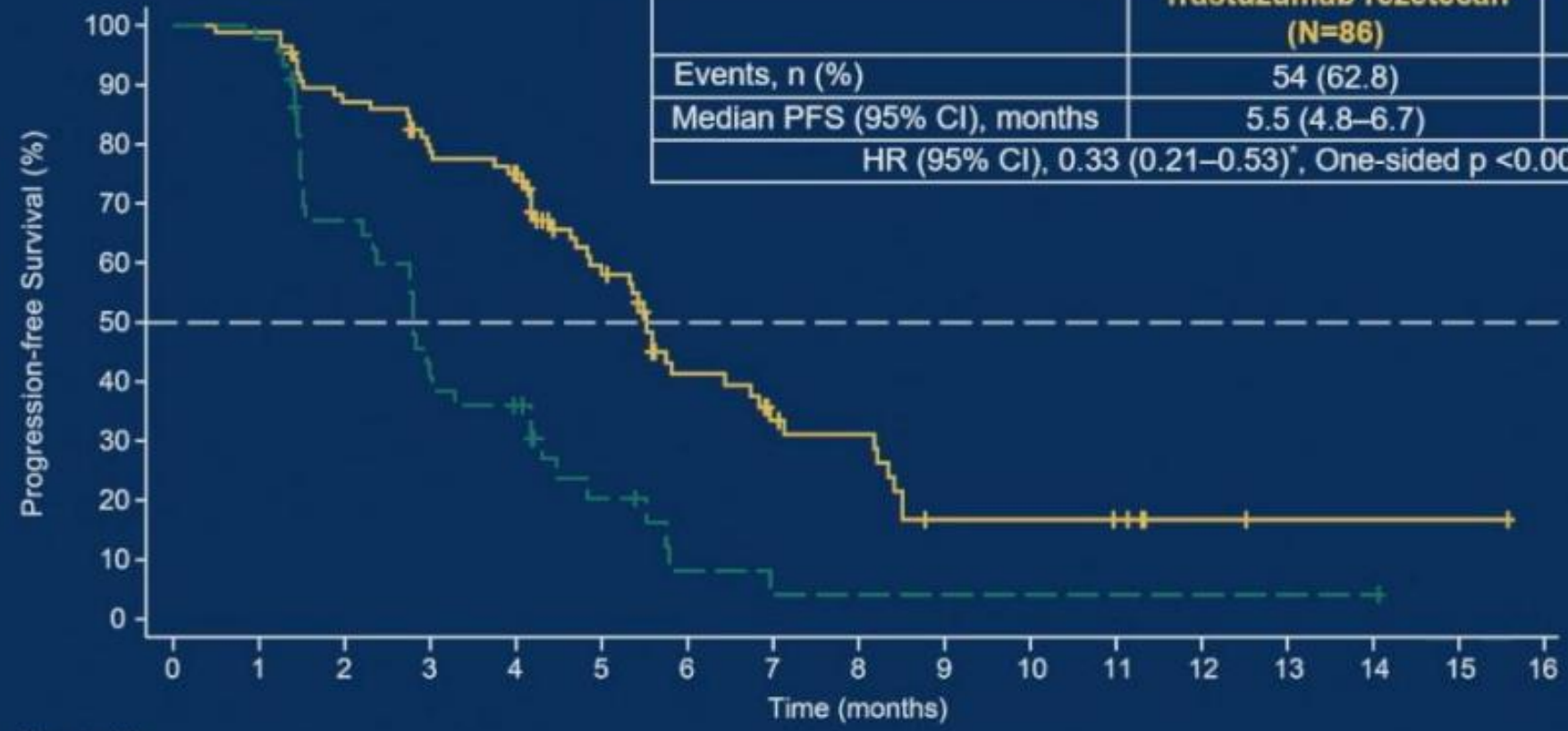
	Trastuzumab rezetecan (N=86)	SOC (N=44)
Age, years		
Median (range)	58.0 (24–75)	58.0 (33–74)
<65 years	63 (73.3)	33 (75.0)
≥65 years	23 (26.7)	11 (25.0)
Sex		
Male	54 (62.8)	29 (65.9)
Female	32 (37.2)	15 (34.1)
ECOG performance status		
0	36 (41.9)	19 (43.2)
1	50 (58.1)	25 (56.8)
HER2 status		
IHC 3+	61 (70.9)	31 (70.5)
IHC 2+ and ISH+	25 (29.1)	13 (29.5)
MMR/MSI		
pMMR/MSI-L/MSS	85 (98.8)	43 (97.7)
dMMR/MSI-H	1 (1.2)	0
Unknown	0	1 (2.3)
RAS wild type	86 (100)	44(100)
RAF wild type	86 (100)	44(100)

	Trastuzumab rezetecan (N=86)	SOC (N=44)
Location of primary lesion		
Left colon	73 (84.9)	39 (88.6)
Right colon	13 (15.1)	5 (11.4)
Clinical staging at screening		
IVA or IVB	60 (69.8)	34 (77.3)
IVC	26 (30.2)	10 (22.7)
No. of metastasis sites		
1	16 (18.6)	13 (29.5)
>1	70 (81.4)	31 (70.5)
Liver metastases at study entry	52 (60.5)	32 (72.7)
Lines of previous systemic therapy		
<3	44 (51.2)	25 (56.8)
≥3	42 (48.8)	19 (43.2)
Previous systemic therapies		
Chemotherapy	86 (100.0)	44 (100.0)
Immunotherapy	19 (22.1)	7 (15.9)
Anti-HER2 agents	16 (18.6)	8 (18.2)
Anti-VEGF antibody	46 (53.5)	24 (54.5)
Anti-EGFR antibody	76 (88.4)	36 (81.8)

Data are presented as n (%), unless otherwise specified.
d-MMR, deficient mismatch repair; MSI, microsatellite instability; MSI-H, MSI-high; MSI-L, MSI-low; MSS, microsatellite stable; p-MMR, proficient mismatch repair.

PFS per IRC

	Trastuzumab rezetecan (N=86)	SOC (N=44)
Events, n (%)	54 (62.8)	36 (81.8)
Median PFS (95% CI), months	5.5 (4.8–6.7)	2.8 (2.2–4.2)
HR (95% CI), 0.33 (0.21–0.53)*, One-sided p <0.0001†		

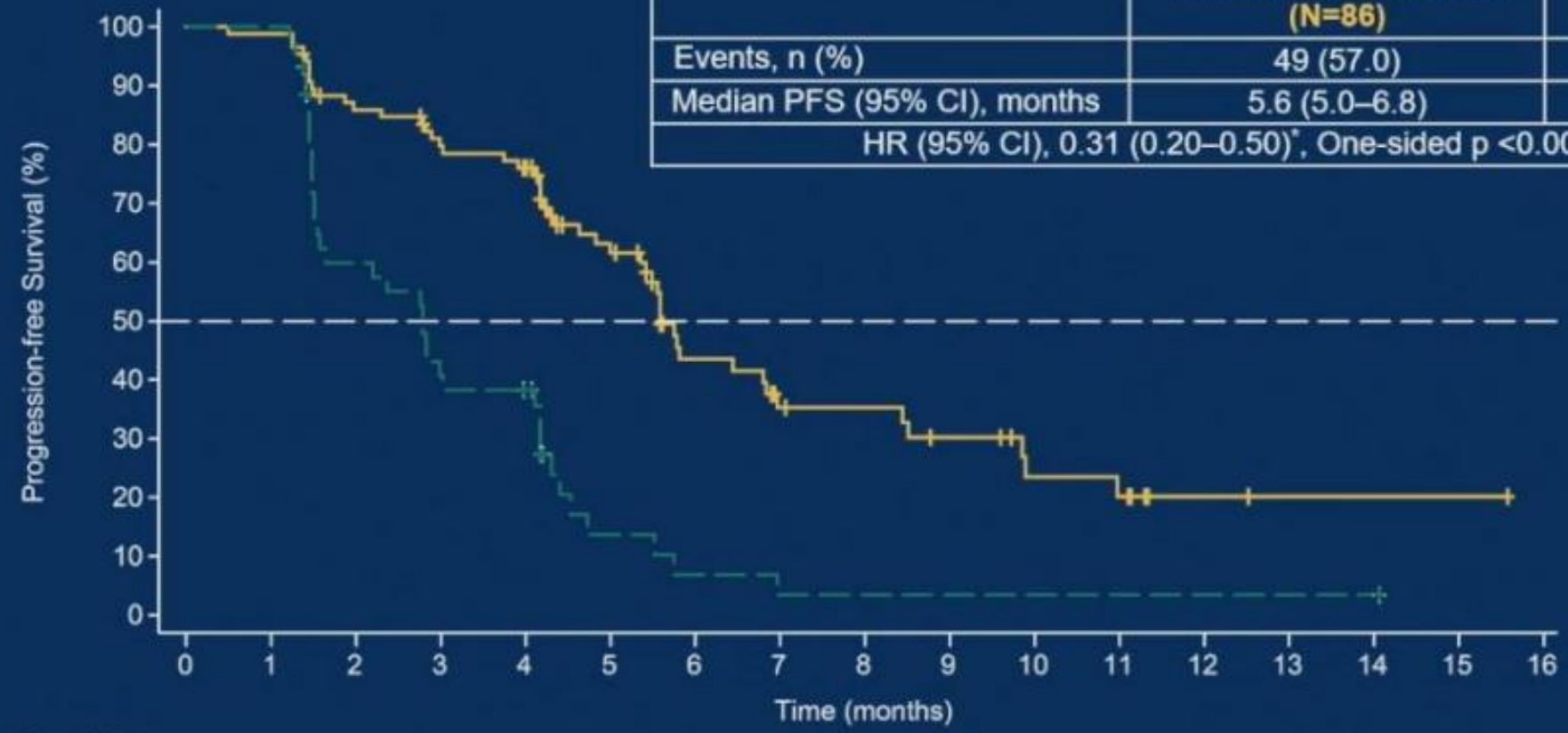


No. at risk

Trastuzumab rezetecan	86	85	74	64	60	38	22	15	13	6	6	5	2	1	1	1	0
Standard-of-care	44	43	28	17	14	6	2	1	1	1	1	1	1	1	1	0	

PFS per investigator

	Trastuzumab rezetecan (N=86)	SOC (N=44)
Events, n (%)	49 (57.0)	37 (84.1)
Median PFS (95% CI), months	5.6 (5.0–6.8)	2.8 (1.5–4.1)
HR (95% CI), 0.31 (0.20–0.50)*, One-sided p <0.0001†		



No. at risk																	
Trastuzumab rezetecan	86	85	72	64	60	39	22	15	14	11	7	6	2	1	1	1	0
Standard-of-care	44	44	25	17	15	4	2	1	1	1	1	1	1	1	1	0	

Subgroup analyses of PFS per IRC

- The beneficial trend in IRC-assessed PFS favoring the trastuzumab rezetecan group over the SOC group was consistent across most predefined subgroups.

	No. of events/No. of patients		Hazard ratio (95% CI)	Hazard ratio (95% CI)
	Trastuzumab rezetecan	Standard-of-care		
Overall	54/86 (62.8%)	36/44 (81.8%)		0.37 (0.24–0.57)
Sex				
Male	31/54 (57.4%)	23/29 (79.3%)		0.37 (0.22–0.65)
Female	23/32 (71.9%)	13/15 (86.7%)		0.36 (0.18–0.78)
Age				
<65 years	38/63 (60.3%)	29/33 (87.9%)		0.29 (0.17–0.48)
≥65 years	16/23 (69.6%)	7/11 (63.6%)		0.70 (0.28–1.71)
ECOG performance status score				
0	21/36 (58.3%)	17/19 (89.5%)		0.23 (0.11–0.45)
1	33/50 (66.0%)	19/25 (76.0%)		0.49 (0.28–0.87)
HER2 status				
IHC 3+	36/61 (59.0%)	24/31 (77.4%)		0.37 (0.22–0.64)
IHC 2+ and ISH+	18/25 (72.0%)	12/13 (92.3%)		0.37 (0.17–0.78)
Clinical staging at screening				
Non-IVC	37/60 (61.7%)	26/34 (76.5%)		0.43 (0.26–0.73)
IVC	17/26 (65.4%)	10/10 (100.0%)		0.13 (0.05–0.35)
Lines of previous systemic therapy				
<3	27/44 (61.4%)	20/25 (80.0%)		0.35 (0.19–0.64)
≥3	27/42 (64.3%)	16/19 (84.2%)		0.38 (0.20–0.71)
Previous anti-HER2 agents				
Yes	10/16 (62.5%)	7/8 (87.5%)		0.36 (0.13–0.99)
No	44/70 (62.9%)	29/36 (80.6%)		0.38 (0.24–0.62)
Liver metastases at study entry				
Presence	34/52 (65.4%)	29/32 (90.6%)		0.29 (0.17–0.50)
Absence	20/34 (58.8%)	7/12 (58.3%)		0.66 (0.29–1.63)
Location of primary lesion				
Left colon	47/73 (64.4%)	31/39 (79.5%)		0.43 (0.26–0.66)
Right colon	7/13 (53.8%)	5/5 (100.0%)		0.15 (0.04–0.60)
No. of metastasis sites				
1	8/16 (50.0%)	10/13 (76.9%)		0.18 (0.06–0.54)
>1	46/70 (65.7%)	26/31 (83.9%)		0.43 (0.26–0.70)

Tumor response

	IRC-assessed		Investigator-assessed	
	Trastuzumab rezetecan (N=86)	SOC (N=44)	Trastuzumab rezetecan (N=86)	SOC (N=44)
Best overall response				
Complete response	0	0	1 (1.2)	1 (2.3)
Partial response	35 (40.7)	2 (4.5)	27 (31.4)	1 (2.3)
Stable disease	41 (47.7)	27 (61.4)	47 (54.7)	25 (56.8)
Progressive disease	8 (9.3)	15 (34.1)	9 (10.5)	17 (38.6)
Not evaluable	2 (2.3)	0	2 (2.3)	0
ORR	35 (40.7; 30.2–51.8)	2 (4.5; 0.6–15.5)	28 (32.6; 22.8–43.5)	2 (4.5; 0.6–15.5)
Rate difference	36.2 (24.1–48.2)		28.0 (16.4–39.7)	
One-sided p value*	<0.0001		0.0002	
Duration of response, median (95% CI), month	4.4 (3.3–NR)	3.4 (2.7–NR)	5.8 (4.2–NR)	1.4 (NR–NR)

*Stratified Cochran-Mantel-Haenszel test.
Data are presented as n (%), n (%; 95% CI), or % (95% CI), unless otherwise indicated.

Safety

Summary

	Trastuzumab rezetecan (N=86)	SOC (N=44)
TEAEs	**86 (100.0)**	**44 (100.0)**
Grade 3–5	47 (54.7)	28 (63.6)
Serious	28 (32.6)	12 (27.3)
Leading to death	4 (4.7)	2 (4.5)
TRAEs	**85 (98.8)**	**43 (97.7)**
Grade 3–5	42 (48.8)	22 (50.0)
Serious	17 (19.8)	7 (15.9)
Leading to treatment discontinuation of study drug	0	0
Leading to dose reduction of study drug	15 (17.4)	14 (31.8)
Leading to interruption of study drug	27 (31.4)	21 (47.7)
Leading to death	2 (2.3)	0

Data are presented as n (%).

TRAEs occurring in ≥15% of patients in either group

	Trastuzumab rezetecan (N=86)		SOC (N=44)	
	All grade	Grade ≥3	All grade	Grade ≥3
Any	85 (98.8)	42 (48.8)	43 (97.7)	22 (50.0)
Neutrophil count decreased	66 (76.7)	31 (36.0)	12 (27.3)	7 (15.9)
White blood cell count decreased	65 (75.6)	14 (16.3)	13 (29.5)	3 (6.8)
Anemia	63 (73.3)	16 (18.6)	17 (38.6)	4 (9.1)
Platelet count decreased	30 (34.9)	7 (8.1)	14 (31.8)	2 (4.5)
Nausea	29 (33.7)	1 (1.2)	14 (31.8)	1 (2.3)
Alopecia	28 (32.6)	0	2 (4.5)	0
Hypoalbuminemia	23 (26.7)	0	7 (15.9)	0
Decreased appetite	23 (26.7)	2 (2.3)	10 (22.7)	0
AST increased	21 (24.4)	0	8 (18.2)	2 (4.5)
Diarrhea	20 (23.3)	1 (1.2)	11 (25.0)	2 (4.5)
Vomiting	18 (20.9)	1 (1.2)	4 (9.1)	1 (2.3)
ALT increased	16 (18.6)	0	8 (18.2)	3 (6.8)
Asthenia	16 (18.6)	1 (1.2)	6 (13.6)	0
Constipation	14 (16.3)	0	5 (11.4)	0
Fatigue	13 (15.1)	0	7 (15.9)	0
GGT increased	11 (12.8)	0	9 (20.5)	3 (6.8)
Blood bilirubin increased	4 (4.7)	1 (1.2)	7 (15.9)	1 (2.3)
Hypertension	2 (2.3)	0	9 (20.5)	4 (9.1)
PPE syndrome	1 (1.2)	0	11 (25.0)	1 (2.3)

Data are presented as n (%).

Conclusions

- **Trastuzumab rezetecan achieved prolonged PFS and improved ORR compared with SOC in chemotherapy-refractory HER2-positive advanced CRC.**
  - Median PFS (per IRC): 5.5 vs 2.8 months; HR, 0.33 (95% CI, 0.21–0.53), P <0.0001;
  - Median PFS (per investigator): 5.6 vs 2.8 months; HR, 0.31 (95% CI, 0.20–0.50), P <0.0001;
  - Median OS: Although median OS were immature, risk of death with trastuzumab rezetecan was reduced by 23% compared with SOC (HR, 0.77 [95% CI, 0.35-1.73]);
  - ORR: per IRC, 40.7% vs 4.5%; per investigator, 32.6% vs 4.5%.
- **The safety profile was manageable.**
  - No new safety signals were identified;
  - The most common grade ≥3 TRAEs associated with trastuzumab were hematological;
  - No patient discontinued trastuzumab rezetecan due to any TRAEs.
- **Trastuzumab rezetecan could be a novel treatment option for chemotherapy-refractory HER2-positive advanced CRC.**