Disitamab vedotin (DV) plus toripalimab (Tor) and chemotherapy (Chemo)/trastuzumab (Tra) for first-line (1L) HER2-expressing locally advanced or metastatic (la/m) gastric cancer (GC): Updated results from the RC48-C027 trial

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Background

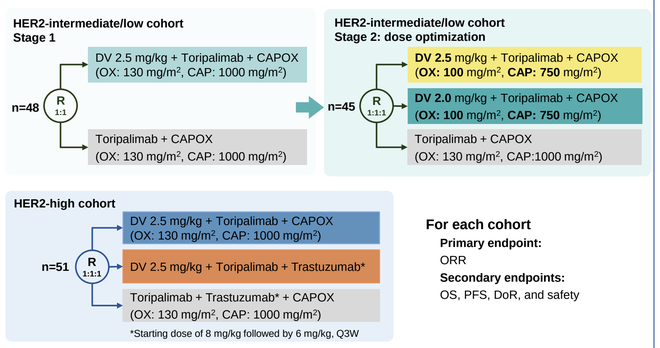
- For patients with HER2-high (defined as IHC 3+, or IHC 2+/FISH+ based on Chinese CSCO GC guidelines[1]) GC, current 1L therapy consisting of trastuzumab combined with pembrolizumab and chemotherapy offers limited efficacy.[2] For patients with HER2-intermediate/low (defined as IHC 2+/FISH- or IHC 1+ as per Chinese guidelines) GC, no HER2-targeted precision treatment is available.[3]
- Previous analysis of the RC48-C027 (NCT05980481) randomized phase 2 part showed notable objective response rates (ORRs): 82.4% with DV+Tor+Tra in patients with HER2-high GC; 72.0% with DV+Tor+CAPOX (oxaliplatin and capecitabine) in patients with HER2-intermediate/low GC, and lowering the CAPOX dose showed improved safety while maintaining efficacy (ORR: 71.4%).[4]
- We report here long-term efficacy and safety results with extended follow-up (data cutoff date: April 1, 2026).

Study Design

Key Eligibility Criteria:

- Histologically or cytologically confirmed unresectable locally advanced or metastatic G/GEJ adenocarcinoma (G/GEJA)
- No prior systemic chemotherapy for la/m G/GEJA
- ECOG PS 0 or 1
- HER2 expression for each cohort:
  - ✓ HER2-high† cohort: IHC 3+ or IHC 2+/FISH+
  - ✓ HER2-intermediate/low† cohort: IHC 2+/FISH- (median) or IHC 1+ (low)

†The term HER2-high corresponds to the conventional definition of HER2-positive. HER2-intermediate is defined as HER2 IHC 2+/FISH-. HER2-low is defined as IHC 1+.[1]



For each cohort

Primary endpoint:
ORR

Secondary endpoints:
OS, PFS, DoR, and safety

- DV and Tor (3.0 mg/kg) were administered IV Q2W. OX (IV, day 1), CAP (orally, days 1-14) and Tra (IV, day 1) were given every 3 weeks. Treatment was continued until disease progression, intolerable toxicity, or study termination.

DV dose cited here is based on calculations using bovine serum albumin (BSA)-based extinction coefficient (EC) implemented in China. Outside of China, DV dose calculation is based on DV EC which is equivalent to 1.07 (BSA-based EC) ÷ 1.41 (DV-based EC) X BSA-based EC dose. ECOG PS: Eastern Cooperative Oncology Group performance status; IHC: immunohistochemistry; FISH: fluorescence in situ hybridization; R: randomized; IV: intravenously; Q2W: once every 2 weeks; CAPOX: capecitabine (CAP) and oxaliplatin (OX); OS: overall survival; PFS: progression-free survival; DoR: duration of response.

Conclusions

- In patients with HER2-intermediate/low G/GEJA, DV+Tor+CAPOX demonstrated sustained efficacy vs PD-1+CAPOX. Lowering the dose of CAPOX improved tolerability without compromising efficacy, supporting it as the optimal combination regimen.
- In patients with HER2-high advanced G/GEJA, extended follow-up showed that DV+PD-1+Tra achieved sustained and clinically meaningful efficacy vs PD-1+Tra+CAPOX, with manageable safety.
- Two phase III studies are ongoing in China to validate the efficacy and safety of DV-containing regimens in 1L setting, with RC48-C039 (NCT06944496) evaluating DV+PD-1+CAPOX in HER2-intermediate/low G/GEJA, and RC48-C040 (NCT07315750) evaluating DV+PD-1+Tra in RC48-high G/GEJA. Both studies are currently actively recruiting participants.

References

1. Chinese Society of Clinical Oncology Gastric Cancer Guidelines in 2025.
2. Janjigian YY, et al. The Lancet 2023; 402(10418): 2197-2208.
3. NCCN Gastric Cancer Guidelines in 2025.
4. Shen L, et al. J Clin Oncol 2025; 43: LBA4012.

Results

Efficacy in HER2-intermediate/low cohort – Stage 1

- The median follow-up was 23.1 months. The confirmed ORR (cORR) was 75.0% (95% CI: 53.3-90.2) vs 47.8 (95% CI: 26.8-69.4) with DV+Tor+CAPOX vs Tor+CAPOX; median DoR was 12.4 vs 10.0 months. PFS results showed favorable signals for DV+Tor+CAPOX (hazard ratio [HR]: 0.55).

Efficacy in HER2-intermediate/low cohort – Stage 2

- With long-term follow-up (median: 19.1 months), DV (2.5 mg/kg)+Tor+dose-reduced CAPOX continued to show a trend toward improved PFS compared with Tor+CAPOX (HR: 0.62). This favorable impact on PFS was further supported by a post-hoc sensitivity analysis (using Restricted Mean Survival Time [RMST]), showing a mean PFS improvement of 2.4 months for DV (2.5 mg/kg)+Tor+CAPOX versus Tor+CAPOX, with 19.6 months of follow-up.
- OS also showed favorable signals for DV (2.5 mg/kg)+Tor+dose-reduced CAPOX vs Tor+CAPOX (HR: 0.61).

Table 1. Efficacy summary and new anti-tumor treatment in HER2-intermediate/low cohort – Stage 2

	HER2-intermediate/low cohort stage 2 (intermediate: IHC 2+/FISH-; low: IHC 1+)		
	DV 2.5 mg/kg + Tor + CAPOX (OX 100 mg/m², CAP 750 mg/m²) N=14	DV 2.0 mg/kg + Tor + CAPOX (OX 100 mg/m², CAP 750 mg/m²) N=15	Tor + CAPOX (OX 130 mg/m², CAP 1000 mg/m²) N=16
cORR*, % (95% CI)	76.9 (46.2-95.0)	66.7 (38.4-88.2)	60.0 (32.3-83.7)
mDoR (95% CI), mo	NR	NR	10.6 (2.9-NE)
18-mo PFS rate, % (95% CI)	**39.7 (14.8-64.0)**	**33.3 (12.2-56.4)**	**20.0 (4.9-42.4)**
12-mo OS rate, % (95% CI)	**71.4 (40.6-88.2)**	**66.7 (37.5-84.6)**	**53.8 (26.8-74.8)**
18-mo OS rate, % (95% CI)	**63.5 (33.1-83.0)**	**59.3 (30.7-79.3)**	**47.1 (21.6-69.1)**
New anti-tumor treatment, n (%)			
Chemotherapy	5 (35.7)	2 (13.3)	6 (37.5)
PD-(L)1 inhibitor	1 (7.1)	1 (6.7)	3 (18.8)
Anti-HER2	0	0	0
VEGF/VEGFR inhibitor	1 (7.1)	1 (6.7)	2 (12.5)
Others†	3 (21.4)	2 (13.3)	6 (37.5)

*Analyzed in patients with at least one post-baseline tumor assessment. †Including other monoclonal antibody, antibody-drug conjugate, EGFR inhibitor, investigational drugs, etc.
cORR: confirmed objective response rate; mDoR: median duration of response; PFS: progression-free survival; OS: overall survival; CI: confidence interval; mo: months; NR: not reached; NE: not estimable.

Figure 1. PFS in HER2-intermediate/low cohort – Stage 2

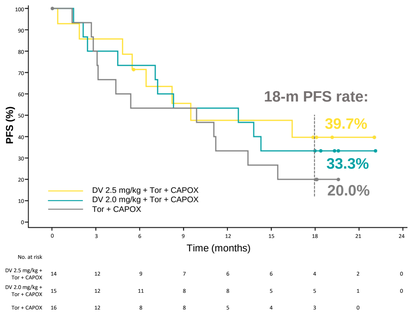
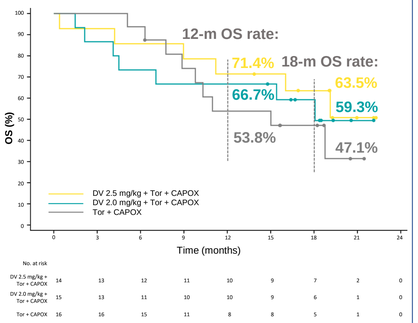


Figure 2. OS in HER2-intermediate/low cohort – Stage 2



Efficacy in HER2-high cohort

- With a median follow-up of 24.5 months, the previously observed trend toward favorable PFS with DV+Tor+Tra versus Tor+Tra+CAPOX was maintained (HR: 0.58).[4]
- OS also showed a trend toward favoring DV+Tor+Tra versus Tor+Tra+CAPOX (HR: 0.42).

Table 2. Efficacy summary and new anti-tumor treatment in HER2-high cohort

	HER2-high cohort (IHC 3+ or IHC 2+/FISH+)		
	DV 2.5 mg/kg + Tor + CAPOX N=18	DV 2.5 mg/kg + Tor + Tra N=17	Tor + Tra + CAPOX N=16
cORR, % (95% CI)	66.7 (41.0-86.7)	82.4 (56.6-96.2)	68.8 (41.3-89.0)
mDoR (95% CI), mo	NR	NR	13.9 (3.7-NE)
18-mo PFS rate, % (95% CI)	**67.0 (37.9-84.7)**	**44.7 (18.9-67.7)**	**33.5 (12.2-56.6)**
12-mo OS rate, % (95% CI)	**88.9 (62.4-97.1)**	**100.0 (100.0-100.0)**	**68.8 (40.5-85.6)**
24-mo OS rate, % (95% CI)	**59.5 (33.2-78.3)**	**68.0 (38.4-85.6)**	**48.2 (22.2-70.2)**
New anti-tumor treatment, n (%)			
Chemotherapy	2 (11.1)	7 (41.2)	5 (31.3)
PD-(L)1 inhibitor	1 (5.6)	3 (17.6)	2 (12.5)
Anti-HER2	3 (16.7)	4 (23.5)	4 (25.0)
VEGF/VEGFR inhibitor	0	1 (5.9)	0
Others†	2 (11.1)	0	1 (6.3)

All patients across the three groups had at least one post-baseline tumor assessment. †Including other monoclonal antibody, antibody-drug conjugate, EGFR inhibitor, investigational drugs, etc.
cORR: confirmed objective response rate; mDoR: median duration of response; PFS: progression-free survival; OS: overall survival; CI: confidence interval; mo: months; NR: not reached; NE: not estimable.

Figure 3. PFS in HER2-high cohort

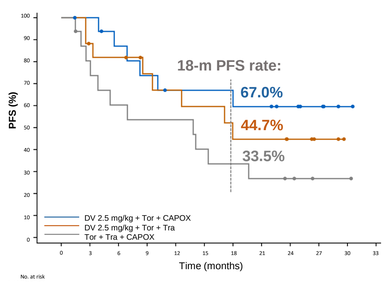
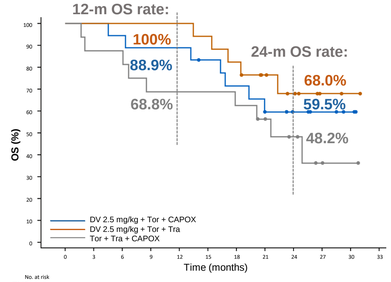


Figure 4. OS in HER2-high cohort



Safety for both HER2-intermediate/low and HER2-high cohorts

- In HER2-intermediate/low cohort, with extended follow-up, DV+Tor+dose-reduced CAPOX showed better tolerability than DV + Tor + full-dose CAPOX. No new safety signals were observed.[4]
  - The most common grade ≥3 treatment-related adverse events (TRAEs) with DV+Tor+dose-reduced CAPOX were neutrophil count decreased, white blood cell count decreased, decreased appetite, diarrhoea, platelet count decreased, nausea, and hypokalaemia.
- In HER2-high cohort, the safety profiles were consistent with previous report.[4]
  - The most common grade ≥3 TRAEs with DV+Tor+Tra were neutrophil count decreased, anemia, white blood cell count decreased, lipase increased, hypokalaemia, and hypertriglyceridaemia.

Abstract number: LBA4026 (2026 ASCO annual meeting). Correspondence to Dr. Lin Shen (linshenpku@163.com) and Dr. Zhi Peng (zhipeng@bjmu.edu.cn).

This study was funded by RemeGen Co., Ltd., Yantai, China.