Disitamab vedotin (RC48), Tislelizumab, and S-1 as first-line therapy for HER2-overexpressing advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC): Updated survival and exploratory biomarker results from the RCTS trial

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BACKGROUND AND OBJECTIVES

- Anti-PD-1 antibodies have improved survival in patients with HER2-overexpressing, PD-L1 CPS ≥1 GC/GEJC when added to trastuzumab plus chemotherapy (KEYNOTE-811).
- HER2-targeting ADCs, such as disitamab vedotin (RC48) and trastuzumab deruxtecan, in combination with anti-PD-1 antibodies, have demonstrated promising efficacy in this patient population.
- We previously reported preliminary results of the RCTS trial (RC48 + tislelizumab + S-1) as 1L therapy for HER2-overexpressing GC/GEJC, with a confirmed ORR of 89.5%.

METHODS

- Single-arm, multicenter, phase II trial (NCT05586061) enrolling patients with unresectable or metastatic HER2-overexpressing (IHC 3+ or 2+, regardless of FISH status) GC/GEJC who had received no prior systemic therapy for advanced disease (**Figure 1**).
- Treatment: RC48 2.5 mg/kg + tislelizumab 200 mg IV on day 1, plus S-1 40-60 mg PO BID days 1-14, in 21-day cycles, until progression or intolerable toxicity.
- Primary endpoint: ORR (RECIST v1.1, ICR). Secondary: PFS, OS, DoR, safety. Exploratory: peripheral TCR sequencing (paired baseline / on-treatment) and longitudinal cfDNA tumor-fraction profiling. Data cutoff: Dec 31, 2025.

Key eligibility criteria
- Locally unresectable or metastatic GC/GEJC
- Treatment naïve
- HER2 IHC 3+ or 2+
- ECOG PS 0-1
- Measurable lesions

Treatment
- RC48 2.5 mg/kg IV
- Tislelizumab 200 mg IV
- S-1 40-60 mg bid D1-14 Q3W until PD or intolerance to toxicity

Primary endpoint
- ORR

Secondary endpoints
- DCR
- PFS, DOR, OS
- Safety

Exploratory endpoint
- Potential biomarkers

Figure 1. Study design

RESULTS

Patients

- 57 patients from 9 centers (Feb 2023 - Jul 2024). HER2: IHC 3+ 71.9%, IHC 2+/ISH+ 17.5%, IHC 2+/ISH- 10.5%. PD-L1: CPS ≥1 45.6%, CPS ≥5 17.5% (**Table 1**). All MMR-proficient and microsatellite-stable. Median follow-up: 28.2 months.

Table 1. Baseline demographic characteristics

Characteristic	Patients, n (%)
Median age, years (IQR)	65 (58–69)
Male / Female	46 (80.7) / 11 (19.3)
ECOG PS 0 / 1	17 (29.8) / 40 (70.2)
Primary site Gastric / GEJ	46 (80.7) / 11 (19.3)
Prior perioperative chemo	3 (5.3)
Prior gastrectomy	10 (17.5)
Metastatic / Locally advanced	53 (92.9) / 4 (7.0)
Organs with metastases ≤1 / >1	35 (61.4) / 22 (38.6)
HER2 IHC 3+/IHC 2+&ISH+/IHC 2+&ISH-	41 (71.9)/10 (17.5)/6 (10.5)
PD-L1 CPS <1 / ≥1	31 (54.4) / 26 (45.6)

Efficacy

- The confirmed ORR was 89.5% (51/57; 95% CI, 78.5-96.0), with a CR rate of 8.8% (5/57) and DCR of 98.2%. The best changes in target lesion diameters are shown in **Figure 2**. Median PFS (mPFS) was 13.8 months (95% CI, 10.3-24.0; **Figure 3A**), while median OS (mOS) reached 31.9 months (95% CI, 22.1-NR; **Figure 3B**). Median DoR was 13.3 months (95% CI, 9.6-NR).

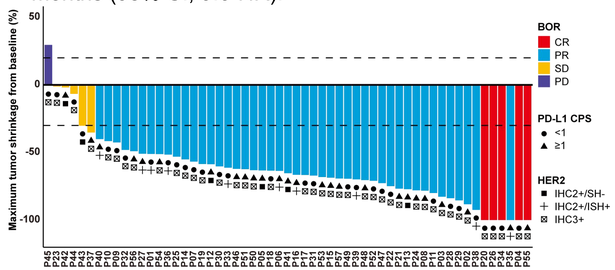

Figure 2. Waterfall plot for best percent change in lesion size

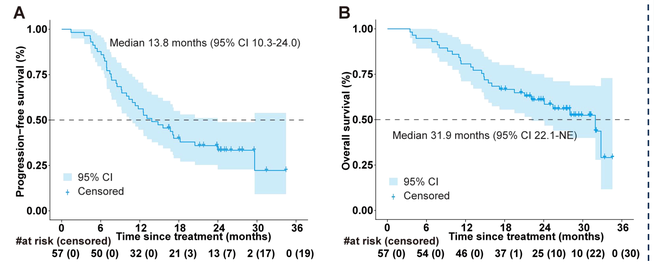

Figure 3. Kaplan-Meier curves of PFS (A) and OS (B)

Subgroup analysis

- In HER2-positive (IHC 3+ or IHC 2+/ISH+) and HER2-negative (IHC 2+/ISH-) subgroups, ORR was 92.2% vs 66.7%; mPFS was 13.8 vs 18.3 months; and mOS was 31.9 months vs not reached, respectively (**Table 2**).
- In PD-L1 CPS ≥1 vs CPS <1 subgroups, ORR was 92.3% vs 87.1%; mPFS was 16.7 vs 10.0 months; and mOS was 31.9 vs 25.4 months, respectively (**Table2**). Among CPS ≥5 patients (n=10), mPFS reached 24.0 months.

Table 2. Subgroup analysis by HER2 or PD-L1 CPS

	Pos	Neg	OR/HR	≥1	<1	OR/HR
ORR, %	92.2	66.7	5.9(0.9-44.0)	92.3	87.1	1.8 (0.3–10.6)
mPFS, mo	13.8	18.3	0.9(0.3–2.5)	16.7	10.0	0.8(0.4–1.5)
mOS, mo	31.9	NR	1.3(0.3–5.4)	31.9	25.4	0.6(0.3–1.3)

Safety

- The rate of grade ≥3 treatment-related AEs (TRAEs) was 64.9% (**Table 3**). The most common AEs were decreased neutrophil count, anemia, and asthenia/fatigue. Pneumonitis occurred in 12.3% (one G3). Six patients (10.5%) discontinued treatment due to TRAEs. No new safety signals.

Table 3. Safety summary

Safety summary	n (%)
Any AE	57 (100.0%)
TRAE	56 (98.2%)
AE grade ≥3	38 (66.7%)
TRAE grade≥3	37 (64.9%)
Serious AE	15 (26.3%)
Treatment-related serious AE	11 (19.3%)
TRAE associated with treatment discontinuation	6 (10.5%)

EXPLORATORY BIOMARKERS

- Paired peripheral blood TCRβ sequencing was performed at baseline and after 1 cycle of treatment in 32 patients (**Figure 4A**). A Clonal Expansion Score (CEscore) was calculated to quantify treatment-induced T-cell clonal expansion.CEscore-high patients had significantly improved PFS (HR 0.34, 95% CI 0.14-0.82, P=0.017; **Figure 4B**) and OS (HR 0.33, 95% CI 0.12-0.94, P=0.037; **Figure 4C**).
- Longitudinal cfDNA profiling was performed using whole-genome methylation and copy-number analysis. Tumor fraction (TF) tracked radiographic burden and rose before imaging-defined progression in 6 of 7 progressors, with a median lead time of 1.4 months.

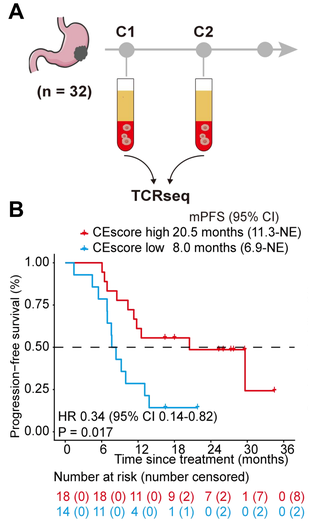

Figure 4. TCR sequencing (A), Kaplan-Meier curves of PFS (B) and OS (C) stratified by CEscore

CONCLUSIONS

- First-line RC48 + tislelizumab + S-1 produced durable benefit (mOS 31.9 mo) in HER2-overexpressing GC/GEJC, with activity preserved in PD-L1 CPS <1. Treatment-induced TCR clonal expansion (CEscore) identified long-term responders, supporting evaluation in the randomized RCTS2 trial (NCT06730373).

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