Abstract TPS4245: Efficacy and safety of disitamab vedotin (DV) combined with trastuzumab, and tislelizumab versus chemotherapy (CAPOX) combined with trastuzumab ± pembrolizumab for patients with first-line HER2-high advanced gastric/gastroesophageal junction adenocarcinoma (G/GEJA): a randomized controlled phase 3 trial

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BACKGROUND

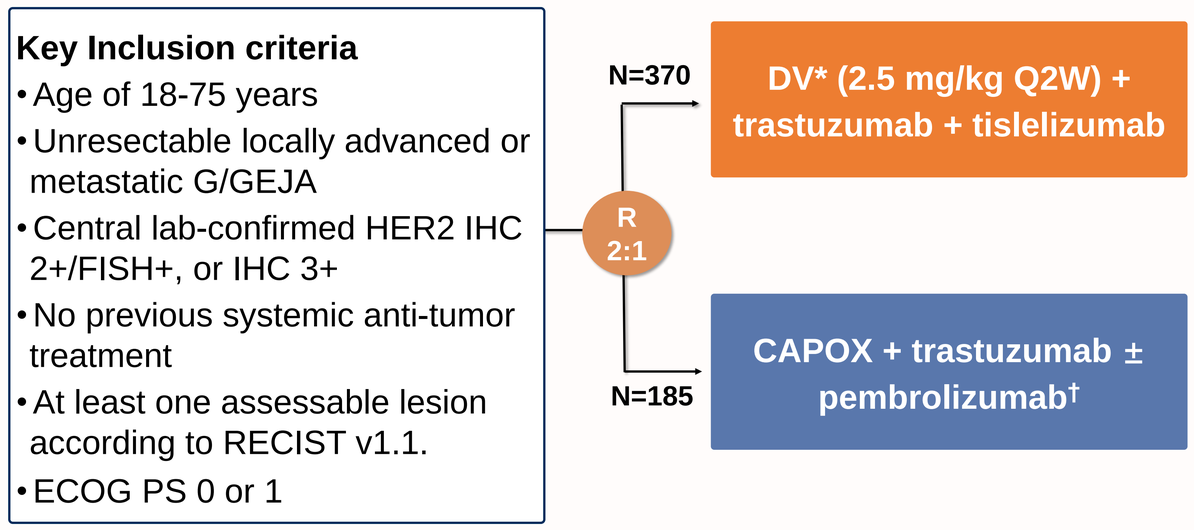
- Patients with HER2-high (defined as IHC 3+, or IHC 2+/FISH+ according to Chinese Society of Clinical Oncology Gastric Cancer Guidelines[1]) advanced G/GEJA continue to face a poor prognosis. Although adding pembrolizumab to trastuzumab and chemotherapy significantly improved overall survival in this patients population with a PD-L1 combined positive score (CPS) ≥1 in the first-line (1L) setting, there remains an unmet need for more effective treatment options.[2]
- DV, an anti-HER2 antibody-drug conjugate (ADC), has been approved as monotherapy for the later-line treatment of patients with HER2 IHC 2+/3+ advanced G/GEJA in China.[3]
- DV and trastuzumab bind to non-overlapping epitopes within domain IV of the HER2 molecule. This complementary binding may enhance antitumor activity through a synergistic effect.
- Previous data from the RC48-C027 randomized phase 2 part showed encouraging efficacy with DV + trastuzumab + an anti-PD-1 compared with trastuzumab + an anti-PD-1 agent + CAPOX agent in 1L HER2-high advanced G/GEJA.[4] Extended follow-up (as of April 1, 2026) have demonstrated sustained efficacy:
  - **ORR: 82.4% vs. 68.8%**
  - **Median DoR: not reached vs 13.9 months (hazard ratio [HR]: 0.56)**
  - **Median PFS: 18.0 vs 13.8 months (HR: 0.58); 12-month PFS rate: 67.0% vs 53.6%, 18-month PFS rate: 44.7% vs 33.5%**
- Building on the preclinical and clinical evidence, we designed this phase 3 RC48-C040 trial (NCT07315750) to assess the efficacy and safety of DV + trastuzumab + tislelizumab versus chemotherapy + trastuzumab ± pembrolizumab in patients with untreated, HER2-high, advanced G/GEJA.

METHODS

Study design and patients

- This is an open-label randomized controlled phase 3 study conducted in China.

Figure 1. Study design



Stratification factors

- HER2 expression (IHC 2+/FISH+ vs IHC 3+)
- PD-L1 expression (CPS<1 vs 1≤CPS<10 vs CPS≥10)
- Liver metastasis (present vs absent)

Endpoints

- Primary: BIRC-assessed PFS
- Secondary: OS; investigator-assessed PFS; BIRC/investigator-assessed ORR, DCR, and DoR; PROs; safety; pharmacokinetics; immunogenicity

- Oxaliplatin will be given for up to 6 doses, and tislelizumab/pembrolizumab for up to 2 years; other drugs will be administered until occurrence of disease progression, intolerable toxicity, or initiation of new anti-tumor treatment.

*Patients who has discontinued DV due to intolerable toxicity may receive capecitabine. †Only patients with central lab-confirmed CPS ≥1 will receive pembrolizumab.

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.

Abbreviations: IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; RECIST: Response Evaluation Criteria in Solid Tumors; ECOG PS, Eastern Cooperative Oncology Group performance status; R, randomized; Q2W, once every 2 weeks; CAPOX, capecitabine (CAP) and oxaliplatin (OX); PFS, progression-free survival; OS, overall survival; BIRC, Blinded Independent Review Committee; ORR, objective response; DCR, disease control rate; DoR, duration of response; PROs, patient-reported outcomes.

METHODS

Key eligibility criteria

Key inclusion criteria

- Histopathologically confirmed locally advanced or metastatic G/GEJA
- No prior systemic treatment for advanced G/GEJA
- Central lab-confirmed HER2-high: IHC 2+/FISH+, or IHC 3+
- At least one assessable lesion (measurable or immeasurable) according to RECIST v1.1 criteria
- ECOG performance status: 0 or 1
- Adequate hematological, hepatic, renal, and cardiac function
- Expected survival period >12 weeks

Key exclusion criteria

- Presence of central nervous system metastasis and/or carcinomatous meningitis
- CTCAE grade >1 peripheral neuropathy
- Interstitial lung disease, or severely impaired lung function
- Uncontrolled systemic diseases
- Prior treatment of any ADC or HER2-targeted agents (except for HER2-targeted treatment for breast cancer 5 years prior to first diagnosis of G/GEJA)

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

Tumor assessment by both BIRC and investigators

- Tumors will be assessed, according to RECIST v1.1, every 6 weeks for the first 60 weeks, and then every 12 weeks until occurrence of disease progression, initiation of new anticancer therapy, or meeting other criteria for study withdrawal, whichever occurs first.

Statistical consideration

- This study plans to enroll 555 patients to obtain approximately 372 PFS events (HR=0.7, power=90%) across the two arms at final PFS analysis.
- The overall alpha was 0.05 (two-sided) for PFS analysis.

INNOVATION of STUDY DESIGN

Dual HER2 blockades without conventional chemotherapy

- Novel dual HER2-blockade strategy with potential great efficacy.
- Potential to reduce toxicity and improve quality of life.
- Potential alternative to conventional chemotherapy in advanced HER2-high GC.

2:1 randomization

- Allows more patients benefit from the novel regimen.
- Larger experimental arm enables a more robust safety evaluation and more detailed subgroup analyses.

STUDY STATUS

- This trial is actively recruiting patients across 78 sites in China and has enrolled 39 patients as of May 7, 2026.

REFERENCES

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CONTACT and SUPPORT

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