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Cadonilimab Combined with Chemotherapy Improves Survival as Second-Line Treatment in Immunotherapy-Pretreated Advanced HER2-Negative Gastric or Gastroesophageal Junction Cancer: A Real-World Study

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ABSTRACT

Immunotherapy has become a foundational component of first-line management for advanced gastric and gastroesophageal junction cancer (G/GEJC). After disease progression on such regimens, however, the optimal second-line approach remains uncertain. Because cadonilimab has demonstrated strong activity in initial treatment, this real-world analysis explored its use with chemotherapy in the second-line setting. We performed a retrospective review at a single institution involving patients with advanced G/GEJC who experienced progression following first-line immunotherapy. From October 2022 to April 2025, patients received either cadonilimab plus chemotherapy (Cohort A, n=50) or chemotherapy alone (Cohort B, n=62). The main outcome was overall survival (OS). Secondary measures consisted of progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and safety. Cohort A demonstrated noticeably better clinical performance. Median PFS reached 4.9 months (95% CI: 3.9–6.0) compared with 3.8 months (95% CI: 2.8–4.8) in Cohort B (p=0.024). Median OS was 10.3 months (95% CI: 8.8–11.8) versus 7.4 months (95% CI: 6.9–7.9) (p=0.046). ORR was 34.0% vs 17.7% (p=0.048), and DCR was 74.0% vs 54.8% (p=0.036). Adverse-event frequencies were comparable, and no deaths were attributed to treatment. Relative to chemotherapy alone, the combination of cadonilimab and chemotherapy yielded superior outcomes with manageable toxicity in patients who progressed after first-line immunotherapy. These observations suggest that cadonilimab-based regimens could serve as a promising second-line option. Prospective randomized trials will be necessary to verify these results.

Keywords: PD-1/CTLA-4 bispecific antibody, Cadonilimab, Advanced gastroesophageal junction cancer, Second-line therapy, Efficacy, Safety

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Introduction

Gastric cancer and gastroesophageal junction cancer (G/GEJC) remain major global health challenges, ranking fifth both in incidence and in cancer-related mortality [1]. In China, these malignancies constitute the third most common cause of cancer death, representing roughly 44% of worldwide diagnoses; only about 20% are detected early [2–4]. Consequently, patients continue to require more effective therapeutic strategies.

Over the past several years, immune-based treatments have reshaped the management of many solid tumors, including G/GEJC. Phase III studies such as CheckMate-649 [5], RATIONALE-305 [6], and KEYNOTE-859 [7] have established immunotherapy plus chemotherapy as the preferred first-line regimen for advanced HER2-negative disease. However, second-line benchmarks—largely derived from trials like REGARD [8] and RAINBOW [9], which focused on individuals progressing after chemotherapy—offer only limited benefit. Importantly, there is no standard second-line therapy for patients whose disease worsens following immunotherapy, highlighting a significant unmet clinical problem.

Cadonilimab (AK104), developed by Akeso Biopharma, is a dual-target antibody acting simultaneously on PD-1 and CTLA-4. It was engineered to deliver strong anti-tumor effects while mitigating immune-related toxicities. Clinically meaningful activity has been reported in multiple cancers, including cervical and hepatocellular carcinoma [10, 11]. Early investigations have also shown encouraging outcomes for cadonilimab combined with chemotherapy in the first-line management of advanced G/GEJC [12, 13]. Based on results from the COMPASSION-1 trial, the drug has been approved in China for first-line therapy in this setting [13].

Additionally, evidence from the AK109-201 trial indicated that the combination of cadonilimab, pulocimab (an anti-VEGFR-2 monoclonal antibody), and paclitaxel provided notable survival improvements as a second-line regimen for patients previously treated with immunotherapy. A Phase III study is currently underway to further evaluate this approach [14].

The scientific rationale for testing cadonilimab after PD-1–based therapy failure stems from the possibility that alternative inhibitory pathways, including CTLA-4, may become upregulated as tumors adapt to immune pressure. This process can deepen T-cell dysfunction. Dual checkpoint blockade targeting both PD-1 and CTLA-4 may reverse this state more effectively than inhibiting PD-1 alone, thereby supporting a strategy of immune rechallenge in the second-line context [15, 16].

Given this background, we conducted a retrospective analysis to assess both the therapeutic activity and safety of cadonilimab combined with chemotherapy in patients with advanced G/GEJC who had progressed on prior immunotherapy. Potential predictors of treatment response were also explored.

Materials and Methods

Patients

This analysis retrospectively examined individuals diagnosed with advanced G/GEJC who demonstrated progression after first-line immunotherapy. All cases were managed at the Affiliated Yantai Yuhuangding Hospital of Qingdao University from October 2022 to April 2025. The Clinical Research Ethics Committee approved the project (approval ID YYYIRB-IIT [2025]014), and all procedures followed the Helsinki guidelines. Because the work relied solely on previously documented clinical information, the need for consent was removed.

A total of 112 patients were included. Of these, 50 received a second-line regimen consisting of cadonilimab plus albumin-bound paclitaxel or irinotecan (Cohort A), and 62 were treated only with albumin-bound paclitaxel or irinotecan (Cohort B). Entry criteria required age 18 years or older, an ECOG status of 2 or less, prior exposure to immune checkpoint blockers, progression on initial immunotherapy, HER2-negative tumors, and measurable disease under RECIST 1.1. Patients were excluded if they had undergone anticancer treatment beyond neoadjuvant, adjuvant, or first-line therapy or had uncontrolled systemic illnesses.

Treatments

Participants were assigned either chemotherapy alone or chemotherapy combined with cadonilimab (10 mg/kg every 3 weeks). Chemotherapy options included nab-paclitaxel 260 mg/m² (Q3W), paclitaxel 175 mg/m² (Q3W), or docetaxel 75 mg/m² (Q3W). After completing 6–8 cycles, maintenance treatment consisted solely of cadonilimab until progression or intolerable adverse effects emerged.

Assessments

Tumor evaluation occurred every two treatment cycles using RECIST 1.1. Response categories were complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

Primary outcomes assessed were progression-free survival (PFS) and overall survival (OS). PFS represented the time from initiation of second-line therapy to progression or death; OS represented time from treatment start to death from any cause. Secondary outcomes included objective response rate (ORR), disease control rate (DCR), and safety evaluation. ORR referred to the percentage of patients with CR or PR, while DCR included those with CR, PR, or SD. Adverse events were graded following CTCAE 4.0.

Statistical analysis

Data analysis used SPSS 27.0 (IBM, New York, USA). All tests were two-sided with significance at $p < 0.05$. Depending on distribution patterns, categorical variables were analyzed via Chi-square testing or Fisher's exact test, the latter applied when any cell's expected frequency fell below 5. Survival curves for PFS and OS in both

cohorts were produced using the Kaplan–Meier method and reported as medians with 95% confidence intervals (CIs). Subgroup survival differences were evaluated with the Log-rank test. Hazard ratios (HRs) were determined first through univariate Cox proportional hazards models, followed by multivariate analyses to adjust for confounding variables.

Results and Discussion

Patient characteristics

From October 2022 to April 2025, 112 patients met the criteria for inclusion. Cohort A consisted of 50 patients receiving cadonilimab plus chemotherapy, whereas Cohort B contained 62 who received chemotherapy only. The median duration of follow-up reached 8.7 months in Cohort A and 7.3 months in Cohort B. Age, sex, ECOG performance scores, and other initial characteristics were balanced across both groups **(Table 1)**.

First-line immune therapies used previously included sintilimab (100/112, 89.3%), nivolumab (5/112, 4.5%), tislelizumab (5/112, 4.5%), and pembrolizumab (2/112, 1.8%). Patient flow is shown in **Figure 1**.

A total of 18 patients—10 in Cohort A and 8 in Cohort B—ended second-line therapy early due to toxicity, declining health, or personal choice. The typical number of cycles delivered was 6.

Table 1. Baseline Characteristics of Patients

Patient Characteristic	Cadonilimab + Chemotherapy (n=50)	Chemotherapy alone (n=62)	P value
Age, n (%)			0.802
<65 years	31 (62.0)	37 (59.7)	
≥65 years	19 (38.0)	25 (40.3)	
Gender, n (%)			0.640
Female	18 (36.0)	25 (40.3)	
Male	32 (64.0)	37 (59.7)	
ECOG performance status, n (%)			1.000
0–1	47 (94.0)	58 (93.5)	
2	3 (6.0)	4 (6.5)	
Number of metastatic sites, n (%)			0.769
<3	28 (56.0)	33 (53.2)	
≥3	22 (44.0)	29 (46.8)	
Liver metastases, n (%)			0.526
Absent	31 (62.0)	42 (67.7)	
Present	19 (38.0)	20 (32.3)	
Mismatch repair (MMR) status, n (%)			1.000
Proficient (pMMR)	47 (94.0)	58 (93.5)	
Deficient (dMMR)	3 (6.0)	4 (6.5)	
EBV status, n (%)			1.000
Negative	50 (100.0)	61 (98.4)	
Positive	0 (0)	1 (1.6)	
Primary tumor site, n (%)			1.000
Gastroesophageal junction (GEJ)	3 (6.0)	3 (4.8)	
Stomach	47 (94.0)	59 (95.2)	
Ki-67 proliferation index, n (%)			0.935
≤70%	27 (54.0)	33 (53.2)	

>70%	23 (46.0)	29 (46.8)	
Histologic differentiation, n (%)			0.327
Well or moderately differentiated	18 (36.0)	28 (45.2)	
Poorly differentiated	32 (64.0)	34 (54.8)	
PD-L1 combined positive score (CPS), n (%)			0.423
CPS <1	22 (44.0)	32 (51.6)	
CPS ≥1	28 (56.0)	30 (48.4)	

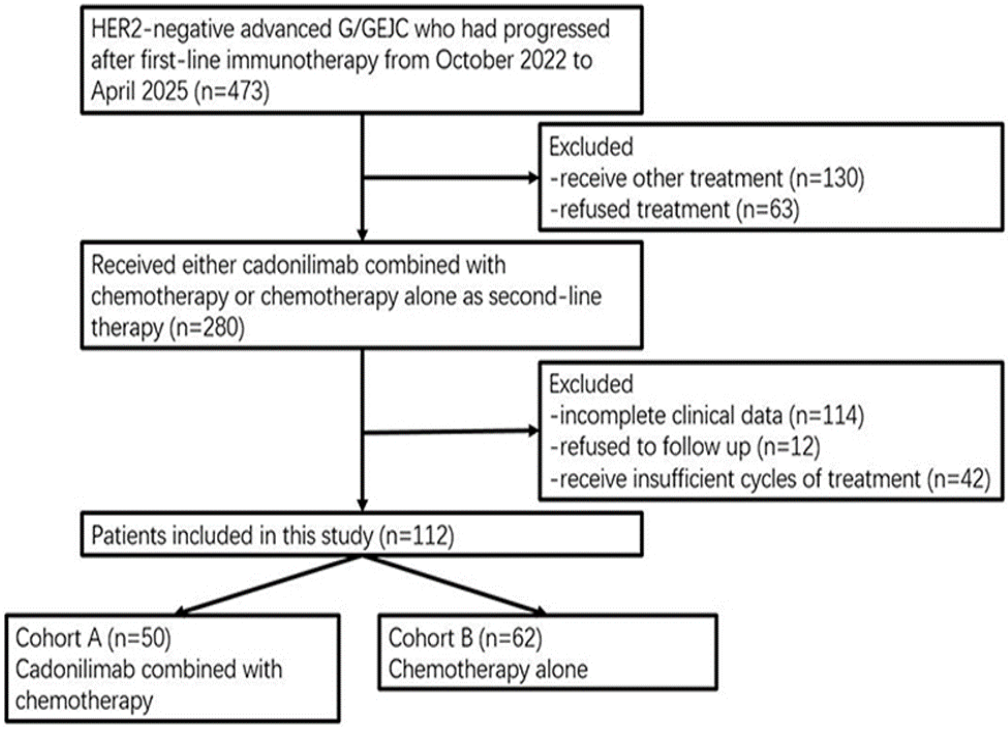


Figure 1. Overview of participant selection.

Efficacy and prognostic factors

By the time follow-up ended on April 30, 2025, the analysis showed that patients in Cohort A experienced a median PFS of 4.9 months (95% CI: 3.9–6.0), whereas those in Cohort B reached 3.8 months (95% CI: 2.8–4.8) **(Figure 2a)**. Median overall survival differed as well, with 10.3 months (95% CI: 8.8–11.8) recorded in Cohort A and 7.4 months (95% CI: 6.9–7.9) in Cohort B **(Figure 2b)**.

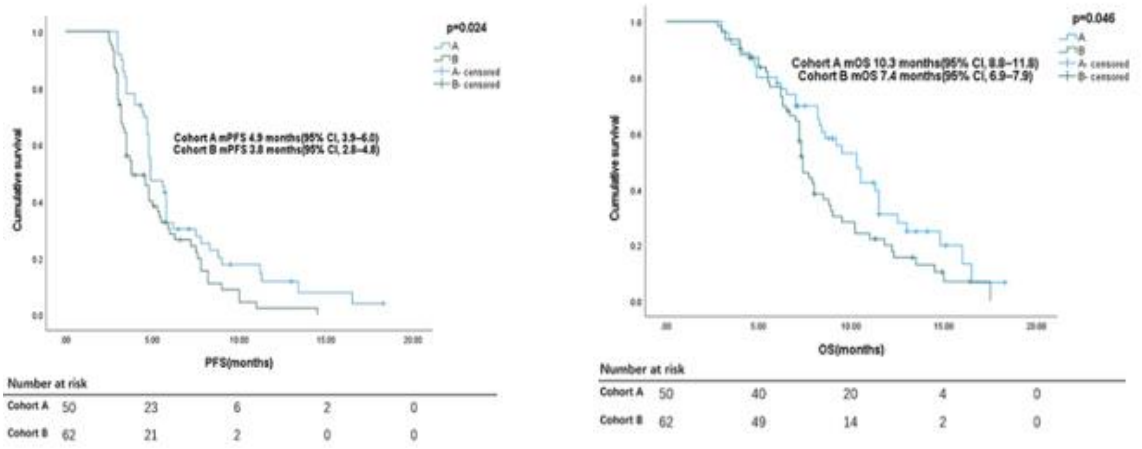
Within the 50 individuals assigned to Cohort A, outcomes included 17 partial responses (34.0%), 20 cases of stable disease (40.0%), and 13 progression events (26.0%). Among the 62 participants in Cohort B, 11 showed partial response (17.7%), 23 remained stable (37.1%), and 28 progressed (45.2%).

The ORR was 34.0% in Cohort A, nearly double that of Cohort B (17.7%, P = 0.048). The DCR was also higher for Cohort A at 74.0%, compared with 54.8% in Cohort B (P = 0.036) **(Table 2)**.

Table 2. Treatment Response Results

Efficacy Endpoint	Cadonilimab + Chemotherapy (n=50)	Chemotherapy alone (n=62)	P value
Complete response (CR), n (%)	0 (0)	0 (0)	–
Partial response (PR), n (%)	17 (34.0)	11 (17.7)	–
Stable disease (SD), n (%)	20 (40.0)	23 (37.1)	–
Progressive disease (PD), n (%)	13 (26.0)	28 (45.2)	–

Objective response rate (ORR), %	34.0	17.7	0.048
Disease control rate (DCR), %	74.0	54.8	0.036



a) b)

Figure 2. (a) PFS comparison; (b) OS comparison

Subgroup assessments were then carried out to determine which characteristics influenced treatment benefit. Kaplan–Meier curves combined with Log rank tests showed no meaningful influence from age, gender, Ki-67 levels, or tumor differentiation. In contrast, several subgroups displayed measurable advantages when treated with cadonilimab combinations.

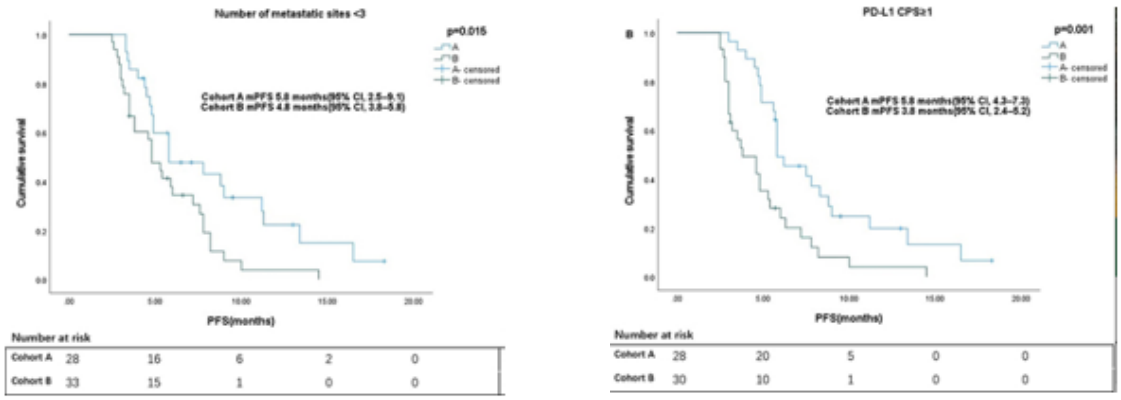
Patients presenting with <3 metastatic sites experienced longer PFS (5.8 vs 4.8 months; HR = 2.0, 95% CI: 1.1–3.6, p = 0.015).

Those with liver metastases saw improved OS (10.3 vs 7.2 months; HR = 2.7, 95% CI: 1.4–4.3, p = 0.011).

The clearest positive effect appeared in individuals with PD-L1 CPS ≥1, who achieved both better PFS (5.8 vs 3.8 months; HR = 2.4, 95% CI: 1.4–4.3, p = 0.001) and longer OS (11.5 vs 7.4 months; HR = 2.9, 95% CI: 1.5–5.4, p < 0.001) **(Table 3 and Figures 3 and 4)**.

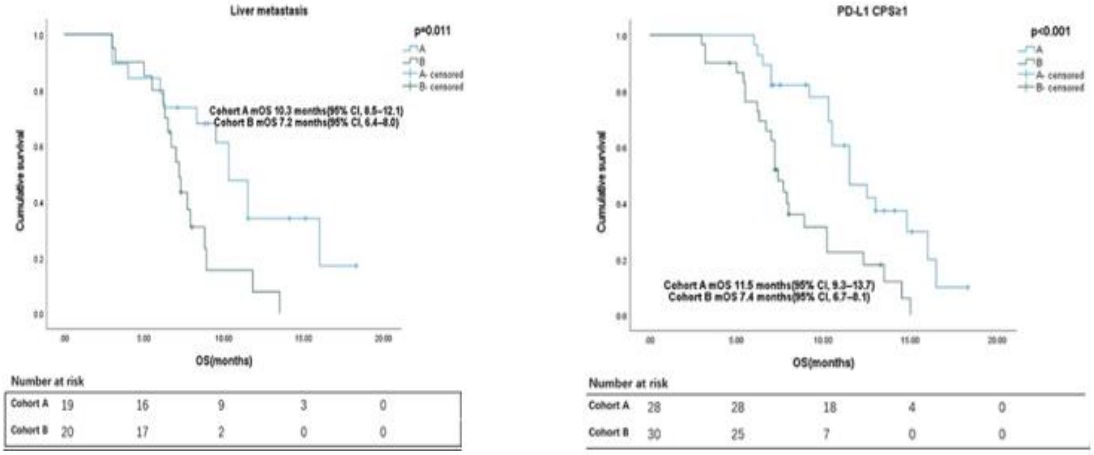
Table 3. Comparative summary of mPFS, mOS, and HR values

Subgroup / Endpoint	Cadonilimab + Chemotherapy (n=50)	Chemotherapy alone (n=62)	HR (95% CI)	P value
Progression-free survival (PFS)				
Overall PFS			1.6 (1.0–2.4)	0.024
Median PFS, months (95% CI)	4.9 (3.9–6.0)	3.8 (2.8–4.8)		
Patients with <3 metastatic sites			2.0 (1.1–3.6)	0.015
Median PFS, months (95% CI)	5.8 (2.5–9.1)	4.8 (3.8–5.8)		
PD-L1 CPS ≥1			2.4 (1.4–4.3)	0.001
Median PFS, months (95% CI)	5.8 (4.3–7.3)	3.8 (2.4–5.2)		
Overall survival (OS)				
Overall OS			1.5 (1.0–2.4)	0.046
Median OS, months (95% CI)	10.3 (8.8–11.8)	7.4 (6.9–7.9)		
Patients with liver metastasis			2.7 (1.2–5.9)	0.011
Median OS, months (95% CI)	10.3 (8.5–12.1)	7.2 (6.4–8.0)		
PD-L1 CPS ≥1			2.9 (1.5–5.4)	<0.001
Median OS, months (95% CI)	11.5 (9.3–13.7)	7.4 (6.7–8.1)		



a) b)

Figure 3. PFS subgroup analyses: (a) metastatic sites <3; (b) PD-L1 CPS ≥1



a) b)

Figure 4. OS subgroup analyses: (a) liver involvement; (b) PD-L1 CPS ≥1

To clarify whether these variables independently influenced survival, all significant factors were evaluated using multivariate Cox regression. After adjustment, three elements remained statistically relevant predictors: number of metastatic sites, presence of liver metastasis, and PD-L1 CPS category **(Tables 4 and 5)**. Analyses of ECOG performance and tumor origin were not feasible due to small subgroup sizes.

Table 4. Multivariable Cox Model for PFS

Subgroup (for PFS)	Hazard Ratio (95% CI)	P value
Fewer than 3 metastatic sites	1.9 (1.1–3.4)	0.032
PD-L1 combined positive score ≥1	3.1 (1.7–5.7)	<0.001

Table 5. Multivariable Cox Model for OS

Subgroup (for overall survival)	Hazard Ratio (95% CI)	P value
Presence of liver metastasis	2.6 (1.2–5.8)	0.018
PD-L1 CPS ≥1	2.9 (1.5–5.6)	0.001

Safety

All treatment-related and immune-related toxicities detected during therapy are listed in **Table 6**. In Cohort A, the events seen most often were reduced neutrophils (20/50, 40%) and anemia (18/50, 36.0%). For grade 3–4 toxicity, the primary findings were liver dysfunction (6/50, 12.0%) and neutrophil decline (5/50, 10.0%).

Cohort B most frequently experienced anemia (18/62, 29.0%) and decreased neutrophils (16/62, 25.8%). High-grade adverse reactions in this group included neutrophil loss (4/62, 6.5%) and anemia (4/62, 6.5%).
Statistical comparisons in **Table 6** show that none of the recorded treatment-related events differed significantly between the two cohorts. No deaths were attributed to treatment during the study period.

Table 6. Treatment-Related Adverse Events

Treatment-Emergent Adverse Event	Cadonilimab + Chemotherapy (n=50)	Chemotherapy alone (n=62)	P value
Neutropenia	20 (40.0)	16 (25.8)	0.110
Grade 1–2	15 (30.0)	12 (19.4)	
Grade ≥3	5 (10.0)	4 (6.5)	
Anemia	18 (36.0)	18 (29.0)	0.433
Grade 1–2	15 (30.0)	14 (22.6)	
Grade ≥3	3 (6.0)	4 (6.5)	
Elevated liver enzymes / Abnormal liver function	17 (34.0)	12 (19.4)	0.079
Grade 1–2	11 (22.0)	7 (11.3)	
Grade ≥3	6 (12.0)	5 (8.1)	
Decreased appetite	15 (30.0)	13 (21.0)	0.272
Grade 1–2	15 (30.0)	12 (19.4)	
Grade ≥3	0 (0)	1 (1.6)	
Fatigue	14 (28.0)	12 (19.4)	0.281
Grade 1–2	14 (28.0)	12 (19.4)	
Grade ≥3	0 (0)	0 (0)	
Diarrhea	12 (24.0)	11 (17.7)	0.415
Grade 1–2	10 (20.0)	7 (11.3)	
Grade ≥3	2 (4.0)	4 (6.5)	
Rash	10 (20.0)	7 (11.3)	0.202
Grade 1–2	9 (18.0)	5 (8.1)	
Grade ≥3	1 (2.0)	2 (3.2)	
Thrombocytopenia	9 (18.0)	10 (16.1)	0.793
Grade 1–2	7 (14.0)	9 (14.5)	
Grade ≥3	2 (4.0)	1 (1.6)	
Nausea and vomiting	9 (18.0)	7 (11.3)	0.313
Grade 1–2	7 (14.0)	5 (8.1)	
Grade ≥3	2 (4.0)	2 (3.2)	
Stomatitis	8 (16.0)	6 (9.7)	0.315
Grade 1–2	7 (14.0)	5 (8.1)	
Grade ≥3	1 (2.0)	1 (1.6)	
Pyrexia	8 (16.0)	8 (12.9)	0.642
Grade 1–2	8 (16.0)	8 (12.9)	
Grade ≥3	0 (0)	0 (0)	
Peripheral neuropathy / Neurotoxicity	7 (14.0)	7 (11.3)	0.666
Grade 1–2	6 (12.0)	5 (8.1)	

Grade ≥3	1 (2.0)	2 (3.2)	
Hand-foot syndrome	6 (12.0)	5 (8.1)	0.487
Grade 1–2	6 (12.0)	5 (8.1)	
Grade ≥3	0 (0)	0 (0)	
Hypokalemia	6 (12.0)	4 (6.5)	0.306
Grade 1–2	5 (10.0)	3 (4.8)	
Grade ≥3	1 (2.0)	1 (1.6)	
Immune-related adverse events			
Hyperthyroidism or hypothyroidism	13 (26.0)	0	
Grade 1–2	13 (26.0)		
Grade ≥3	0 (0)		
Immune-mediated pneumonitis	3 (6.0)	0	
Grade 1–2	2 (4.0)		
Grade ≥3	1 (2.0)		

In this investigation, the two therapeutic groups showed clear separation in clinical outcomes. Patients receiving the combined regimen achieved longer PFS and OS than those given chemotherapy alone (PFS: 4.9 months vs 3.8 months, HR = 1.6, 95% CI 1.0–2.4, p = 0.024; OS: 10.3 months vs 7.4 months, HR = 1.5, 95% CI 1.0–2.4, p = 0.046). Differences were also seen in ORR (34.0% vs 17.7%, p = 0.048) and DCR (74.0% vs 54.8%, p = 0.036). These outcomes indicate that cadonilimab offers substantial therapeutic activity with tolerable toxicity in patients with advanced G/GEJC previously exposed to immunotherapy.

For second-line management of advanced G/GEJC, the commonly adopted approaches include chemotherapy alone or its combination with ramucirumab [17, 18]. After the RAINBOW study was published in 2014, [9] ramucirumab-containing regimens became a benchmark, though widespread clinical use remains inconsistent. Over recent years, the introduction of immune checkpoint inhibitors has reshaped the first-line treatment landscape. Pembrolizumab, cadonilimab, tislelizumab, nivolumab, and sintilimab have each shown compelling first-line activity [5–7, 13, 19, 20], resulting in a second-line population that has already encountered both chemotherapy and immunotherapy. What to offer these patients once frontline immunotherapy loses effectiveness remains an unresolved challenge. Given its dual-target mechanism against PD-1 and CTLA-4, cadonilimab represents a logical candidate for re-initiating immunologic responses. The present study aimed to examine whether combining cadonilimab with chemotherapy could provide a meaningful benefit in this setting.

The RAINBOW trial [9] demonstrated that paclitaxel plus ramucirumab exceeded paclitaxel plus placebo in PFS (4.4 vs 2.9 months; HR=0.635, 95% CI 0.536–0.752, p<0.0001) and OS (9.6 vs 7.4 months; HR=0.807, 95% CI 0.678–0.962, p=0.0169). Results from the FRUTIGA trial [21] also favored the fruquintinib–paclitaxel combination, which improved PFS (5.6 vs 2.7 months; HR=0.57, p<0.0001), ORR (42.5% vs 22.4%, p<0.0001), and DCR (77.2% vs 56.3%, p<0.0001), but without an OS advantage. Among patients with prior immunotherapy in FRUTIGA, PFS gains were even more striking (6.4 vs 1.8 months; HR=0.38, p=0.0003), although OS did not differ. Crucially, RAINBOW involved patients relapsing after chemotherapy alone, and FRUTIGA did not demonstrate OS benefit in immunotherapy-pretreated cases. In contrast, our cohort—composed entirely of individuals who progressed on first-line immunotherapy—showed that adding cadonilimab significantly extended both PFS and OS relative to chemotherapy alone.

Additional evidence supporting this strategy comes from dual-checkpoint blockade studies. In the AK109-201 trial, cadonilimab combined with pulocimab and paclitaxel in patients who had already failed immunotherapy led to an ORR of 48.0%, a DCR of 96.0%, and a median PFS of 6.8 months, reinforcing the rationale for cadonilimab-centered regimens [14].

Among patients with PD-L1 CPS ≥1, cadonilimab-based therapy resulted in notably longer PFS and OS compared with chemotherapy alone, suggesting the drug may counteract mechanisms responsible for immunotherapy resistance in this biomarker-defined subgroup. Elevated PD-L1 and CTLA-4 expression has been linked with poor outcomes in gastric tumors [22]. Tumor cells escape immune attack in part by increasing PD-1 and CTLA-4

expression on T cells [23, 24]. Blocking PD-1 enhances reactivation of exhausted or previously stimulated T cells, while CTLA-4 inhibition promotes early-stage T-cell priming and expansion, though at the cost of potential immune-related toxicity [15]. These complementary effects may help reverse T-cell dysfunction and re-establish anti-tumor immunity. Cadonilimab, a tetravalent bispecific molecule directed at PD-1 and CTLA-4, is engineered to overcome resistance to single-pathway blockade by restoring the activity of T cells co-expressing both receptors. It augments CD8+ T-cell responsiveness even when antigen density is low. The antibody lacks Fc-mediated functions—ADCC, ADCP, and CDC—reducing the likelihood of high-grade immune toxicities. Its design also favors accumulation in areas with strong PD-1/CTLA-4 expression, concentrating its action within tumors while minimizing systemic effects [25]. Conversely, patients with PD-L1 CPS <1 did not experience measurable improvements in either PFS or OS, highlighting the persistent gap in effective second-line options for this biomarker-negative group.

Patients who had been exposed to cadonilimab and presented with fewer than 3 metastatic lesions experienced longer PFS than those in the comparison group (5.8 vs 4.8 months; HR=2.0, 95% CI 1.1–3.6, p=0.015). This pattern implies that individuals with limited metastatic spread may be more responsive to cadonilimab, possibly because reduced tumor dissemination allows for more effective immune reactivation. Similar observations were highlighted by Wei *et al*., who noted that individuals with lower disease burden tend to experience stronger therapeutic responses to immunotherapy [26].

A particularly noteworthy advantage emerged in patients with liver involvement, where OS was notably prolonged with the cadonilimab regimen (10.3 vs 7.2 months; HR=2.7, 95% CI 1.4–4.3, p=0.011). Liver metastasis generally predicts poor outcomes and diminished immunotherapy responsiveness, a phenomenon often linked to immunosuppressive cell populations concentrated within hepatic metastatic niches [27, 28]. Tumor infiltration of the liver may also initiate tolerance-inducing pathways unique to hepatic immunity, thereby suppressing systemic anti-tumor reactions and reducing treatment efficacy [29]. Evidence suggests that bispecific CTLA-4/PD-1 blockade may counteract this resistance more effectively than PD-1 monotherapy by simultaneously influencing Tregs, MDSCs, and effector T cells within the metastatic microenvironment [29]. Consistent with this, the COMPASSION-15 study also reported better treatment results in the liver-metastasis subgroup [13]. Cadonilimab's dual-checkpoint mechanism, therefore, appears promising for a group of patients traditionally considered difficult to treat.

Looking ahead, both our dataset and results from the AK109-201 study support cadonilimab as a practical therapeutic choice for individuals previously treated with immunotherapy. Further large-scale investigations are needed to confirm these outcomes and to discover biomarkers that perform better than PD-L1 alone. Since access to certain drugs varies geographically, future research should also examine combinations involving cadonilimab with widely available agents such as ramucirumab or fruquintinib together with chemotherapy.

This research is not without limitations. Conducted at a single institution and retrospective in design, the study's modest sample size may limit its broader applicability. Additional contributors to prognosis—such as tumor mutational burden—could not be assessed due to incomplete data collection inherent to retrospective studies. Small subgroup sizes may also weaken statistical confidence. These limitations underscore the need for prospective, multicenter trials to obtain larger, more representative datasets. Moreover, the biological processes through which cadonilimab reverses resistance to earlier immunotherapies remain unclear and warrant more mechanistic exploration.

Conclusion

For patients with advanced G/GEJC who previously received immunotherapy, adding cadonilimab to chemotherapy in the second-line setting produced marked improvements in PFS, OS, ORR, and DCR when compared with chemotherapy alone. Individuals with PD-L1 CPS ≥1 derived especially pronounced benefit, showing significant gains in both PFS and OS, while those with CPS <1 did not demonstrate such advantages. Treatment effects also varied by metastatic pattern: patients with fewer than 3 metastatic sites achieved better PFS, and those with liver metastases experienced notably enhanced OS. Collectively, these findings indicate that cadonilimab combined with chemotherapy may be a strong candidate for immunotherapy rechallenge in second-line G/GEJC management.

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