

SINTILIMAB PLUS CHEMOTHERAPY IN UNRESECTABLE GASTRIC/GEJ CANCER: A RETROSPECTIVE SAFETY AND EFFICACY ANALYSIS

SiYu Li

Department of Oncology, The Fifth Hospital of Anhui Medical University, Fuyang 236000, Anhui, China.

Abstract: To compare overall survival and safety of patients with metastatic gastric and gastroesophageal junction cancers treated with sintilimab with chemotherapy vs. chemotherapy only. In this study, we enrolled 60 with metastatic gastric cancer patients. Among them, 33 received treatment with chemotherapy combined with sintilimab, while the other 27 received chemotherapy alone. Demographic, clinical, and pathological data were analyzed. Of the 60 patients, 27 were treated with sintilimab plus chemotherapy and 33 with chemotherapy only. The addition of sintilimab increased the tumor response rate to chemotherapy (disease control rate [DCR]: 96.29% vs. 72.72%, $P = 0.017$). Furthermore, the combination therapy improved the progression-free survival (median: 8.41 months [95% CI: 5.59-11.22] vs. 6.03 months [95% CI: 3.90-8.16]) and overall survival (31.46 months [95% CI: 24.69-38.22] vs. 23.38 months [95% CI: 17.34-29.43]). Overall, the combined treatment group demonstrated good treatment tolerance. In patients with metastatic gastric and gastroesophageal junction cancers receiving first-line chemotherapy, the addition of sintilimab improved treatment outcomes compared with chemotherapy alone.

Keywords: Gastric cancer; Gastroesophageal junction cancer; Sintilimab; Immunotherapy

1 INTRODUCTION

More than one million people worldwide have been diagnosed with gastric and gastroesophageal junction cancer, making it the fifth most common malignancy globally and the fourth leading cause of cancer-related deaths. In China, approximately 44% of gastric cancer cases are diagnosed, and the country accounts for nearly 49% of all gastric cancer deaths [1]. For a long time, fluoropyrimidine- and platinum-based regimens have been the standard first-line treatment for advanced ERBB2 (formerly HER2)-negative gastric and gastroesophageal junction cancers. Despite therapeutic advances, patient outcomes remain unsatisfactory. The median survival is approximately 1 year, and the 5-year overall survival (OS) rate worldwide is only 10%–15% [2-3].

Immune checkpoint inhibitors (ICIs) bind to programmed cell death receptor-1 (PD-1), thereby blocking its interaction with ligands (PD-L1 and PD-L2) and restoring endogenous antitumor T-cell responses [4]. Trials such as ATTRACTION-2, KEYNOTE-062, and CheckMate 649 have shown promising results, and these agents are now routinely used in the management of advanced-stage gastric cancer [5-7].

Sintilimab is a fully human IgG4 monoclonal antibody that targets PD-1, similarly blocking the PD-1/PD-L1 interaction to rejuvenate antitumor immunity [8]. It has demonstrated excellent efficacy in various tumors, including lymphoma, lung cancer, liver cancer, colon cancer, and renal cancer [9]. The present study aims to evaluate the real-world efficacy and safety of sintilimab combined with chemotherapy in patients with advanced gastric cancer.

2 METHODS

2.1 Study Design

This single-center, retrospective study was conducted in the Fifth Affiliated Hospital of Anhui Medical University. This research was conducted in accordance with the Declaration of Helsinki guidelines.

2.2 Patients

We enrolled all patients with pathologically and radiologically confirmed unresectable, ERBB2-negative gastric or gastroesophageal junction cancer from January 1, 2017, to January 1, 2026. Patients who received standard fluoropyrimidine plus platinum chemotherapy were assigned to the chemotherapy group, whereas those who received sintilimab combined with the standard chemotherapy regimen were classified as the sintilimab group. Clinical staging was evaluated using computed tomography, magnetic resonance imaging, or positron emission tomography. Patient demographics, treatment course, progression-free survival (PFS), and overall survival (OS) were extracted from our hospital database. All enrolled patients were followed up until May 1, 2026.

2.3 Study Assessments

Efficacy was evaluated at least two weeks after treatment by two or more physicians, following the immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST) [10-11]. OS was defined as the time from diagnosis to death from any cause. PFS was measured from the first day of treatment to disease progression per iRECIST. Disease control rate (DCR) was defined as the proportion of patients achieving radiological complete response, partial response, or stable disease. Treatment-emergent adverse events (TEAEs) were graded using the Common Terminology Criteria for Adverse Events, version 4.0. Immune-related adverse events (irAEs) were identified as TEAEs with a potential immunological basis requiring close monitoring or intervention, according to established guidelines [12-13].

2.4 Statistical Analyses

Statistical analyses were performed using SPSS 25.0. Ordinal data were compared using the rank-sum test. Logistic regression models were employed to examine associations between variables and clinical response. OS and PFS probabilities were estimated using the Kaplan–Meier method, and differences were evaluated with the log-rank test.

3 RESULTS

3.1 Characteristics

The baseline characteristics of the 60 patients are summarized in Table 1. There were 48 males and 12 females. In the sintilimab group and chemotherapy group, there were 24 and 24 male participants, and 3 and 9 female participants, respectively. The mean age at diagnosis was 67.88 years (range, 38–83 years). The majority of patients (35/60) had a pathological diagnosis of poorly differentiated adenocarcinoma.

Table 1 Baseline Characteristics of the Enrolled Patients (N = 60)

Group	Sintilimab group	Chemotherapy group
Sum	27	33
Gender		
Male	24	24
Female	3	9
Age of first diagnosis		
Mean	69.74	66.36
Median	74	68
Range	50-83	38-82
Pathological grading		
G1-2	3	2
G3-4	16	19
Unknown	8	12

3.2 Efficacy

According to the RECIST 1.1 standard, 21 out of 60 patients achieved a partial response (PR), 30 had stable disease (SD), and 9 had progressive disease (PD). In the sintilimab group, 9 patients achieved PR, 17 had SD, and 1 had PD. In the chemotherapy group, the corresponding numbers were 12, 12, and 9, respectively. The DCR was significantly higher in the sintilimab group than in the chemotherapy group (96.29% vs. 72.72%), with a significant difference by chi-square test ($P = 0.017$). The best response data are presented in Table 2.

Table 2 The Best Efficacy After Relapse

Efficacy	Sintilimab group	Chemotherapy group
CR	0	0
PR	9	12
SD	17	12
PD	1	9

The sintilimab group showed a longer PFS compared with the chemotherapy group, as evidenced by Kaplan–Meier survival curves (Figure 1). After a median follow-up time of 9.795 months, the median PFS was 8.41 months (95% CI: 5.59-11.22) for the sintilimab group vs. 6.03 months (95% CI: 3.90-8.16) for chemotherapy group ($P = 0.146$). A similar trend was observed for OS (Figure 2): 31.46 months (95% CI: 24.69-38.22) for sintilimab group vs. 23.38 months (95% CI: 17.34-29.43), $P = 0.839$.

The differences in OS and PFS did not reach statistical significance, likely due to the relatively small sample size.

3.3 Safety

Overall, sintilimab combined with chemotherapy was well tolerated. Grade ≥ 3 adverse events occurred in 5/27 patients in the sintilimab group and 7/33 patients in the chemotherapy group. The most common adverse effect was leukopenia,

which occurred at a higher rate in the sintilimab group. In addition, hypothyroidism and hypopituitarism were observed only in the sintilimab group. Fortunately, most adverse reactions were grade 1–2 in severity (Table 3).

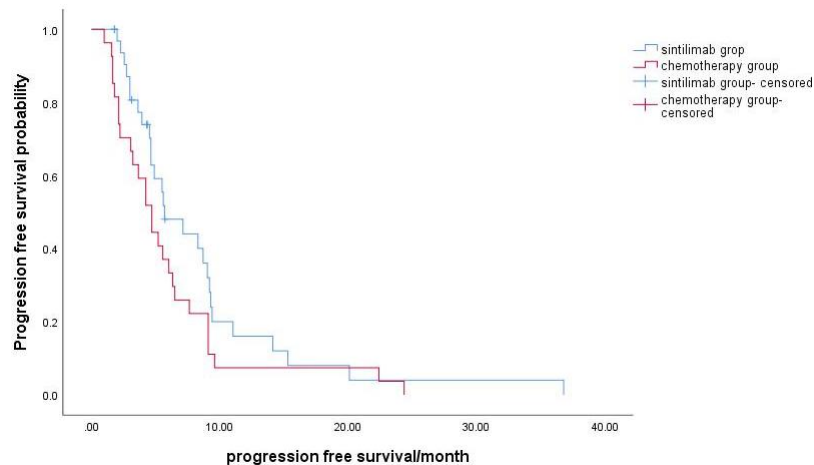


Figure 1 Progression-Free Survival of Sintilimab Group and Chemotherapy Group

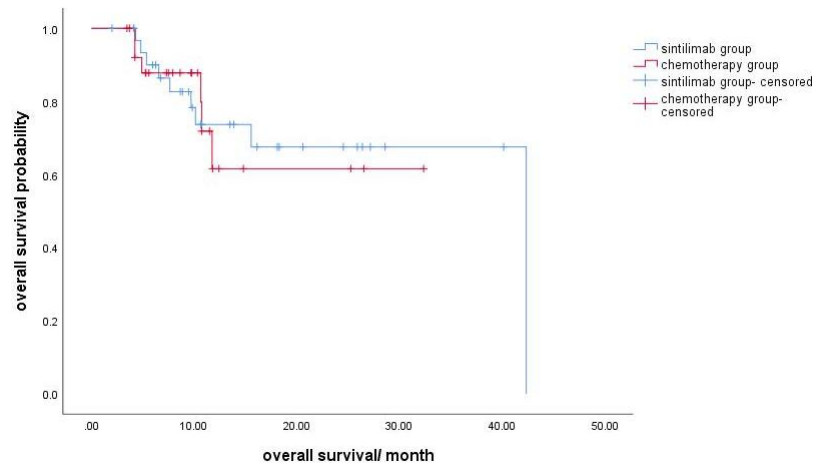


Figure 2 Overall Survival of Sintilimab Group and Chemotherapy Group

Table 3 Side Effect of Sintilimab Group and Chemotherapy Group

	Sintilimab		Chemotherapy group	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Leukopenia	11	3	13	4
Anemia	9	2	13	1
Thrombocytopenia	6	3	4	1
Transaminitis	3	1	9	0
Nausea	4	0	9	2
Weak	3	0	6	2
Hypothyroidism	3	0	0	0
Hypopituitarism	2	0	0	0

4 DISCUSSION

Since 2021, based on the results of the CheckMate 649 study, combination therapy with PD-1 inhibitors and chemotherapy has become the global standard of care for advanced gastric or gastroesophageal junction adenocarcinoma and has been incorporated into treatment guidelines [5, 14].

Given the known heterogeneity of gastric cancer, there is an urgent need to identify patients who may derive greater benefit from immunotherapy. The CheckMate 649 trial showed that in patients with a CPS of 5 or higher, as well as in the overall enrolled population, nivolumab plus chemotherapy significantly improved OS and PFS compared with chemotherapy alone. The ORIENT-16 study also demonstrated similar efficacy for sintilimab in patients with CPS ≥ 5 [15]. Furthermore, multiple studies have indicated that multifactor models incorporating baseline HER2 and CTNNB1 mutation status are associated with treatment sensitivity and prognosis [16-17]. However, in real-world practice, especially in remote areas, not every patient can be assessed using such predictive models. Our research indicates that

sintilimab can confer survival benefits to the entire population. For patients whose prognosis cannot be predicted by these models, sintilimab combined with chemotherapy represents an excellent treatment option.

In this study, the average patient age was as high as 67 years, yet they still exhibited acceptable tolerance to the combination regimen. The safety profile was generally similar between the sintilimab and chemotherapy groups. The most common adverse events were hematological and gastrointestinal toxicities, which we speculate are more closely related to the chemotherapy component.

This study has several limitations. First, it is a single-center, retrospective study with numerous confounding factors and a small sample size. Although it reflects real-world practice, the limited cohort likely contributed to the lack of statistical significance in some survival comparisons. Second, we did not stratify patients based on CPS score or MSI status; incorporating these factors might have better predicted therapeutic response. Third, tumor response was not evaluated by a blinded independent central review, which may have introduced bias in determining PFS.

5 CONCLUSION

In summary, this small-sample retrospective study aimed to report the real-world efficacy and safety of sintilimab combined with chemotherapy in patients with gastric or esophagogastric junction cancer. We conclude that sintilimab plus chemotherapy provides survival benefits for ERBB2-negative gastric cancer patients, with manageable and acceptable side effects.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

REFERENCES

- [1] Sung H, Ferlay J, Siegel R L, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, 2021, 71(3): 209-249. DOI: 10.3322/caac.21660.
- [2] Shah M A, Bang Y J, Lordick F, et al. Effect of Fluorouracil, Leucovorin, and Oxaliplatin With or Without Onartuzumab in HER2-Negative, MET-Positive Gastroesophageal Adenocarcinoma: The METGastric Randomized Clinical Trial. *JAMA Oncology*, 2017, 3(5): 620-627. DOI: 10.1001/jamaoncol.2016.5580.
- [3] Muro K, Van Cutsem E, Narita Y, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic gastric cancer: a JSMO-ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS. *Annals of Oncology*, 2019, 30(1): 19-33. DOI: 10.1093/annonc/mdy502.
- [4] Vafaei S, Zekiy A O, Khanamir R A, et al. Combination therapy with immune checkpoint inhibitors (ICIs); a new frontier. *Cancer Cell International*, 2022, 22(1): 2. DOI: 10.1186/s12935-021-02407-8.
- [5] Janjigian Y Y, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *The Lancet*, 2021, 398(10294): 27-40. DOI: 10.1016/S0140-6736(21)00797-2.
- [6] Shitara K, Van Cutsem E, Bang Y J, et al. Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer: The KEYNOTE-062 Phase 3 Randomized Clinical Trial. *JAMA Oncology*, 2020, 6(10): 1571-1580. DOI: 10.1001/jamaoncol.2020.3370.
- [7] Kang Y K, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*, 2017, 390(10111): 2461-2471. DOI: 10.1016/S0140-6736(17)31827-5.
- [8] Shiravand Y, Khodadadi F, Kashani S M A, et al. Immune Checkpoint Inhibitors in Cancer Therapy. *Current Oncology*, 2022, 29(5): 3044-3060. DOI: 10.3390/curroncol29050247.
- [9] Zhang L, Mai W, Jiang W, et al. Sintilimab: A Promising Anti-Tumor PD-1 Antibody. *Frontiers in Oncology*, 2020, 10: 594558. DOI: 10.3389/fonc.2020.594558.
- [10] Eisenhauer E A, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European Journal of Cancer*, 2009, 45(2): 228-247. DOI: 10.1016/j.ejca.2008.10.026.
- [11] Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *The Lancet Oncology*, 2017, 18(3): e143-e152. DOI: 10.1016/S1470-2045(17)30074-8.
- [12] Qin S, Guo J, Li J, et al. Management of immune checkpoint inhibitor-related toxicity of the Chinese Society of Clinical Oncology (CSCO). *People's Medical Publishing House*, 2019: 1-116.
- [13] National Comprehensive Cancer Network. Management of immunotherapy-related toxicities version 2.2019 NCCN clinical practice guidelines in oncology (NCCN guidelines). 2019.
- [14] Ajani J A, D'Amico T A, Bentrem D J, et al. Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*, 2022, 20(2): 167-192. DOI: 10.6004/jnccn.2022.0008.

- [15] Xu J, Jiang H, Pan Y, et al. Sintilimab Plus Chemotherapy for Unresectable Gastric or Gastroesophageal Junction Cancer: The ORIENT-16 Randomized Clinical Trial. *JAMA*, 2023, 330(21): 2064-2074. DOI: 10.1001/jama.2023.19918.
- [16] Chen Z, Chen Y, Sun Y, et al. Predicting gastric cancer response to anti-HER2 therapy or anti-HER2 combined immunotherapy based on multi-modal data. *Signal Transduction and Targeted Therapy*, 2024, 9(1): 222. DOI: 10.1038/s41392-024-01932-y.
- [17] Zhao Y, Li D, Zhuang J, et al. Comprehensive multi-omics analysis of resectable locally advanced gastric cancer: Assessing response to neoadjuvant camrelizumab and chemotherapy in a single-center, open-label, single-arm phase II trial. *Clinical and Translational Medicine*, 2024, 14(5): e1674. DOI: 10.1002/ctm2.1674.