Progress in the Application of Immune Checkpoint Inhibitors in the Immunotherapy of Metastatic/Locally Advanced Gastroesophageal Junction Adenocarcinoma (Postprint)

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Abstract

Gastroesophageal junction (GEJ) adenocarcinoma has a poor prognosis, and the efficacy of traditional chemotherapy and targeted therapy is limited. Immune checkpoint inhibitors (ICIs) have brought breakthroughs in the treatment of advanced GEJ adenocarcinoma by blocking pathways such as programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1); however, their clinical application still faces challenges such as therapeutic heterogeneity, toxicity management, and drug resistance. This article systematically reviews the latest progress of ICIs in metastatic/locally advanced GEJ adenocarcinoma. Monotherapy (e.g., nivolumab, pembrolizumab) has become a standard late-line option, but its efficacy depends on biomarkers such as the PD-L1 combined positive score (CPS) and high microsatellite instability (MSI-H)/mismatch repair deficiency (dMMR). Combination therapy is the core strategy of current clinical treatment: ICIs combined with chemotherapy have significantly improved the survival of first-line human epidermal growth factor receptor 2 (HER2)-negative and positive patients, becoming the new standard for advanced gastroesophageal junction adenocarcinoma; ICIs combined with anti-angiogenic drugs (e.g., apatinib) and novel targeted drugs [e.g., anti-claudin 18.2 (CLDN18.2), fibroblast growth factor receptor 2b (FGFR2b) antibodies] have gradually demonstrated efficacy in GEJ adenocarcinoma, providing new directions for late-line treatment; dual immunotherapy (e.g., nivolumab combined with ipilimumab) has shown high pathological response rates in the dMMR/MSI-H population, though toxicity requires attention. Biomarkers such as [PD-L1 CPS, MSI-H/dMMR, and tumor mutational burden (TMB)] are crucial for predicting efficacy and optimizing patient stratification, and composite models need to be constructed in the future to improve predictive accuracy. Combination therapy is the mainstream direction for ICIs in treating GEJ adenocarcinoma, but

it remains necessary to explore multi-omics-guided individualized strategies, develop novel drug combinations, and optimize biomarker systems to overcome resistance, balance efficacy and toxicity, and ultimately achieve precision treatment.

Full Text

Preamble

Application Progress of Immune Checkpoint Inhibitors in the Immunotherapy of Metastatic/Locally Advanced Gastroesophageal Junction Adenocarcinoma

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Abstract

Gastroesophageal junction (GEJ) adenocarcinoma is characterized by a poor prognosis, with traditional chemotherapy and targeted therapies offering limited efficacy. Immune checkpoint inhibitors (ICIs) have achieved a breakthrough in the treatment of advanced GEJ adenocarcinoma by blocking pathways such as programmed cell death protein-1 (PD-1) and programmed cell death ligand-1 (PD-L1). However, their clinical application still faces challenges including therapeutic heterogeneity, toxicity management, and drug resistance. This paper systematically reviews the latest progress of ICIs in metastatic and locally advanced GEJ adenocarcinoma.

Monotherapy (e.g., nivolumab, pembrolizumab) has become a standard late-line option, though its efficacy depends on biomarkers such as the PD-L1 combined positive score (CPS) and high microsatellite instability (MSI-H)/mismatch repair deficiency (dMMR). Combination therapy is currently the core clinical strategy. ICIs combined with chemotherapy have significantly improved survival in first-line treatment for both human epidermal growth factor receptor 2 (HER2)-negative and HER2-positive patients, establishing a new standard of care for advanced GEJ adenocarcinoma. Furthermore, the efficacy of ICIs combined with anti-angiogenic agents (e.g., apatinib) and novel targeted drugs [e.g., antibodies against claudin 18.2 (CLDN18.2) and fibroblast growth factor receptor 2b (FGFR2b)] is gradually emerging, providing new directions for late-line treatment. Dual immunotherapy (e.g., nivolumab plus ipilimumab) has demonstrated high pathological response rates in dMMR/MSI-H populations, though toxicity remains a concern.

Biomarkers such as PD-L1 CPS, MSI-H/dMMR, and tumor mutational burden (TMB) are critical for predicting efficacy and optimizing patient stratification. Future research should focus on constructing combinatorial models to improve

predictive accuracy. While combination therapy remains the mainstream direction for ICIs in GEJ adenocarcinoma, it is essential to explore multi-omics-guided individualized strategies, develop novel drug combinations, and optimize biomarker systems to overcome resistance and balance efficacy with toxicity, ultimately achieving precision medicine.

Keywords: Gastroesophageal junction adenocarcinoma; Immune checkpoint inhibitors; Immunotherapy

Introduction

Gastroesophageal junction (GEJ) adenocarcinoma refers to tumors involving the anatomical border between the esophagus and the stomach. Due to its unique anatomical location and biological behavior, its incidence has been rising globally in recent years. For a long time, the treatment of advanced or metastatic GEJ adenocarcinoma relied primarily on platinum- and fluoropyrimidine-based chemotherapy. However, the median overall survival (OS) for these patients remained less than one year. Although the introduction of targeted therapies, such as those targeting HER2, improved outcomes for specific subgroups, the overall prognosis for the majority of patients remained poor.

In recent years, the rapid development of tumor immunology has established immune checkpoint inhibitors (ICIs) as a transformative force in the treatment of GEJ adenocarcinoma. By targeting inhibitory signaling pathways like PD-1/PD-L1 and CTLA-4, these agents reactivate the host' s anti-tumor immune response. This review summarizes the clinical application of ICIs as monotherapy and in various combination strategies, evaluates the role of predictive biomarkers, and discusses future directions for precision immunotherapy in GEJ adenocarcinoma.

Progress in ICI Monotherapy

Initial clinical trials focused on the efficacy of ICI monotherapy in heavily pretreated patients. Drugs such as nivolumab and pembrolizumab demonstrated durable responses in late-line settings. However, the benefit of monotherapy is often restricted to specific molecular subtypes. For instance, patients with MSI-H or dMMR status exhibit high sensitivity to PD-1 blockade due to high neoantigen loads. In contrast, for the unselected population, the objective response rate (ORR) of monotherapy remains relatively low, necessitating the identification of robust biomarkers like PD-L1 CPS to guide patient selection.

Combination Therapy Strategies

ICIs Combined with Chemotherapy

Combining ICIs with chemotherapy has become the new first-line standard of care. Chemotherapy can induce immunogenic cell death, increasing the release of tumor antigens and enhancing the efficacy of ICIs. Large-scale Phase III trials have demonstrated that adding PD-1 inhibitors to standard chemotherapy significantly extends OS and progression-free survival (PFS) in patients with advanced GEJ adenocarcinoma, particularly those with a PD-L1 CPS ≥ 5.

ICIs Combined with Targeted Therapy

The integration of ICIs with targeted agents is a rapidly evolving field. For HER2-positive GEJ adenocarcinoma, the combination of pembrolizumab, trastuzumab, and chemotherapy has shown superior efficacy compared to the standard trastuzumab-plus-chemotherapy regimen. Additionally, combining ICIs with anti-angiogenic agents (e.g., apatinib) can normalize tumor vasculature and improve the infiltration of immune cells into the tumor microenvironment. Emerging targets such as CLDN18.2 and FGFR2b are also being investigated in combination with ICIs, showing promising preliminary results in late-line settings.

Dual Immunotherapy

Dual checkpoint blockade, such as the combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4), aims to provide a synergistic immune response. While this approach has shown high pathological response rates in specific populations like MSI-H/dMMR patients, the increased risk of immune-related adverse events (irAEs) requires careful clinical management and patient selection.

Biomarkers for Efficacy Prediction

The identification of reliable biomarkers is essential for optimizing the use of ICIs. Currently, PD-L1 CPS, MSI-H/dMMR status, and TMB are the most widely used indicators in clinical practice. However, no single biomarker can perfectly predict the response to immunotherapy. Future research is moving toward multi-omics integration—combining genomic, transcriptomic, and proteomic data—to develop more precise predictive models that can account for the complexity of the tumor microenvironment.

Conclusion and Future Perspectives

Immunotherapy has fundamentally changed the treatment landscape for metastatic and locally advanced GEJ adenocarcinoma. While combination strategies involving ICIs and chemotherapy have established a new first-line standard, challenges such as primary and acquired resistance, as well as the

management of toxicities, persist. Future efforts should focus on: 1. Refining patient stratification through advanced biomarker panels. 2. Exploring novel combinations with next-generation targeted therapies. 3. Investigating the role of the microbiome and metabolic factors in modulating immune responses. 4. Developing individualized treatment protocols to maximize clinical benefit while minimizing adverse effects.

Abstract

Adenocarcinoma of the gastroesophageal junction (GEJ) has a poor prognosis, and conventional chemotherapy and targeted therapy have limited efficacy. Immune checkpoint inhibitors (ICIs), which block pathways such as PD-1/PD-L1, have brought breakthroughs in the treatment of advanced GEJ adenocarcinoma. However, their clinical application still faces challenges including heterogeneous response, toxicity management, and drug resistance. This article systematically reviews the latest advances of ICIs in metastatic/locally advanced GEJ adenocarcinoma. Monotherapy (e.g., nivolumab, pembrolizumab) has become the standard later-line option, but its efficacy is dependent on biomarkers such as PD-L1 combined positive score (CPS) and microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) status. Combination therapy is the current core strategy in current clinical practice. ICIs combined with chemotherapy (e.g., as demonstrated in the CheckMate-649 and KEYNOTE-811 trials) have significantly improved survival in first-line HER2-negative and HER2-positive patients, establishing a new standard

Chinese General Practice of care for advanced GEJ adenocarcinoma. ICIs combined with anti-angiogenic agents (e.g., apatinib) and novel targeted drugs (e.g., anti-CLDN18.2 and anti-FGFR2b antibodies) have shown promising efficacy in GEJ adenocarcinoma, offering new directions for later-line treatment. Dual immunotherapy (e.g., nivolumab combined with ipilimumab) demonstrates high pathological complete response (pCR) rates in dMMR/MSI-H populations, although its toxicity requires careful attention. Biomarkers [e.g., PD-L1 CPS, MSI-H/dMMR, tumor mutational burden(TMB)] are crucial for predicting efficacy and optimizing patient stratification; future efforts need to focus on constructing combinatorial models to enhance predictive accuracy. Combination therapy is the mainstream direction for ICI treatment in GEJ adenocarcinoma. Future strategies should involve exploring multi-omics-guided personalized approaches, developing novel drug combinations, and optimizing the biomarker system to overcome resistance, balance efficacy and toxicity, and ultimately achieve precision therapy.

Introduction

Adenocarcinoma of the gastroesophageal junction (GEJ) is a common malignancy of the digestive tract characterized by its unique anatomical location. Its incidence is currently trending upward on a global scale. According to 2020

global cancer statistics, there were 604,000 new cases and 544,000 deaths worldwide, ranking it among the leading causes of cancer incidence and mortality and posing a severe threat to human health. The primary treatment modalities for GEJ adenocarcinoma include surgery, chemotherapy, and targeted therapy. However, the prognosis for patients with advanced disease remains poor, with low five-year survival rates, highlighting an urgent need for new therapeutic strategies.

At the molecular level, GEJ adenocarcinoma can be classified into two subtypes: "esophageal adenocarcinoma-like" and "gastric adenocarcinoma-like." These subtypes exhibit significant differences in signaling pathway activation, gene copy number variations, and drug sensitivity, which increases the difficulty of implementing precision medicine. Traditional chemotherapy and targeted therapies generally face efficacy plateaus and resistance issues, resulting in limited long-term survival benefits for patients [**?**, **?**].

In recent years, immunotherapy—represented by immune checkpoint inhibitors (ICIs)—has brought about new breakthroughs for advanced GEJ adenocarcinoma. The mechanism of action for these agents stems from the regulation of the GEJ adenocarcinoma tumor immune microenvironment (TIME) and the mitigation of immune escape mechanisms. The programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway is a critical route for immune evasion in GEJ adenocarcinoma. Research indicates that GEJ adenocarcinoma tumor cells commonly express PD-L1 and exhibit low levels of T-cell infiltration, which together form the basis for immune escape. Furthermore, the TIME of GEJ adenocarcinoma is enriched with immunosuppressive cells, such as regulatory T cells and tumor-associated macrophages. These cells secrete immunosuppressive cytokines, further reinforcing the local immunosuppressive state and promoting immune evasion.

Consequently, PD-1/PD-L1 inhibitors such as pembrolizumab and nivolumab function by blocking the binding of PD-1 to PD-L1, thereby releasing T-cell inhibition and restoring anti-tumor functions. Key Phase III clinical trials, including KEYNOTE-059, ATTRACTION-2, and CheckMate series, have confirmed the efficacy of pembrolizumab and nivolumab in advanced GEJ cancer. Related drugs have subsequently been approved for third-line, and even first-line or adjuvant treatment of recurrent/metastatic gastric (G) or GEJ adenocarcinoma, providing patients with new therapeutic options.

However, the clinical application of ICIs still faces core challenges. Their efficacy is heterogeneous and highly dependent on biomarkers such as PD-L1 expression and microsatellite instability-high (MSI-H) status. Identifying the optimal patient population with precision, overcoming primary or acquired resistance, and optimizing combination therapy strategies are current research hotspots and difficulties in the field. Therefore, systematically reviewing the clinical evidence for ICIs in metastatic/locally advanced GEJ adenocarcinoma and deeply exploring efficacy-predicting biomarkers, resistance mechanisms, and cutting-edge combination strategies is of significant value for advancing precision therapy.

This article aims to provide a comprehensive review of these aspects to offer a reference for clinical practice and suggest directions for future research.

1 文献检索策略

Computerized searches were conducted across both English and Chinese databases, including PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), and the Wanfang Data Knowledge Service Platform.

The search timeframe was set from January 1, 2020, to January 1, 2026; additionally, key authoritative literature published outside this range was manually traced and retained. Chinese search terms included: “胃食管结合部腺癌” (gastroesophageal junction adenocarcinoma), “胃食管结合部癌” (gastroesophageal junction cancer), “免疫检查点抑制剂”(immune checkpoint inhibitors), “免疫治疗”(immunotherapy), “纳武利尤单抗” (nivolumab), “帕博利珠单抗” (pembrolizumab), “信迪利单抗” (sintilimab), “卡瑞利珠单抗” (camrelizumab), “生物标志物” (biomarkers), and “微卫星不稳定性” (microsatellite instability). English search terms included: “Gastroesophageal Junction Adenocarcinoma,” “GEJ cancer,” “Immune Checkpoint Inhibitors,”“Immunotherapy,”“Nivolumab,”“Pembrolizumab,”“Sintilimab,”“Camrelizumab,” “Combination therapy,” “Biomarker,” “PD-L1,” and “Microsatellite Instability.” Inclusion criteria were defined as: (1) studies focusing on metastatic or locally advanced GEJ adenocarcinoma (or gastric/esophageal cancer studies including this population); (2) clinical research involving immune checkpoint inhibitors as monotherapy or in combination regimens (including Phase I-III clinical trials and real-world studies), or high-quality reviews and meta-analyses regarding relevant mechanisms and biomarkers. Exclusion criteria were: (1) case reports, conference abstracts, commentaries, and unrelated studies; (2) low-quality literature or studies with unclear methodological descriptions. Literature was screened by reviewing titles and abstracts.

摘要

After screening the full text, a total of 55 articles were ultimately included for systematic review and analysis.

2 ICIs

Progress in the Application of Later-line Treatments

The treatment options for later-line therapy in advanced gastroesophageal junction (GEJ) adenocarcinoma are limited. However, the emergence of immune checkpoint inhibitors (ICIs) has brought new hope to these patients. Among these, research related to nivolumab and pembrolizumab has established the foundational role of ICIs in later-line therapy. Key words: Gastroesophageal junction adenocarcinoma; Immune checkpoint inhibitors; Immunotherapy.

Key Phase III clinical trials and subsequent real-world studies have confirmed

that these two PD-1 inhibitors, when used as third-line or later-line treatment regimens, can provide significant survival benefits for patients while demonstrating controllable safety profiles. These findings have fundamentally shifted the treatment landscape for advanced GEJ adenocarcinoma.

Nivolumab

In the ATTRACTION-2 Phase III trial, nivolumab demonstrated that third-line treatment could significantly improve overall survival (OS) compared to placebo. The median OS was 5.26 months for the nivolumab group versus 4.14 months for the placebo group ($HR = 0.63, 95\%CI = 0.50 - 0.80$). Data from the Early Access to Medicines Scheme (EAMS) in the UK showed that the median progression-free survival (PFS) for third-line nivolumab treatment was 2.6 months, with a 6-month OS rate of 56.7%. Regarding safety, studies by YAMAGUCHI et al. reported that in the ATTRACTION-2 trial, the incidence of any-grade treatment-related adverse events (TRAEs) in the nivolumab group was approximately 43.0%, with grade $\geq$ 3 TRAEs at approximately 10.0%. Post-marketing surveillance in Japan showed a TRAE incidence of 31.5% and a grade $\geq$ 3 TRAE incidence of 11.2%, which is largely consistent with the ATTRACTION-2 trial results, suggesting favorable tolerability.

Pembrolizumab

In the KEYNOTE-059 study, pembrolizumab demonstrated a median OS of 8 months ($95\%CI = 5.8 - 11.1$) as a third-line treatment for patients with a Programmed Death-Ligand 1 (PD-L1) Combined Positive Score (CPS) $\geq$ 10. The objective response rate (ORR) was 17%, and the median duration of response (DOR) reached 21 months, reflecting durable antitumor activity. Subgroup analysis of the KEYNOTE-059 trial showed that the ORR for pembrolizumab in patients with high microsatellite instability (MSI-H) was 57.1% ($95\%CI = 18.4\% - 90.1\%$). This indicates that pembrolizumab can induce tumor remission even in later-line settings. In the KEYNOTE-061 trial for second-line treatment, pembrolizumab was compared with paclitaxel chemotherapy; the median OS was 10 months in the pembrolizumab group versus 8 months in the chemotherapy group ($HR = 0.64; 95\%CI = 0.41 - 1.02$), with ORRs of 25% and 9%, respectively. The significant difference in ORR highlights the advantage of pembrolizumab in the MSI-H subgroup. These data suggest that pembrolizumab offers a clear ORR advantage and OS improvement in MSI-H GEJ adenocarcinoma patients. In terms of safety, TRAEs associated with pembrolizumab in the KEYNOTE series trials were manageable, with common adverse events such as nausea and vomiting being mostly mild.

Limitations of Monotherapy

Currently, the application of ICI monotherapy in metastatic or locally advanced GEJ adenocarcinoma is primarily restricted to third-line and subsequent treatment regimens.

Despite the breakthrough progress ICIs have made in treating advanced gastric cancer, the efficacy of monotherapy remains significantly limited. Research indicates that the ORR for ICI monotherapy is relatively low; in the KEYNOTE-061 study, the ORR for second-line pembrolizumab was 16% compared to 14% in the chemotherapy group, with no significant difference in OS ($HR = 0.92$). Furthermore, the unique toxicity profile of ICIs limits their application in certain patients. The incidence of TRAEs for third-line nivolumab was 31.5%, with grade $\geq$ 3 TRAEs at 11.2%; common events included hypothyroidism (4.2%) and diarrhea (3.7%). Meta-analyses have shown that ICI monotherapy can significantly improve alopecia [with Quality of Life Questionnaire (QLQ-STO22) scores decreasing by 23.2 points ($P < 0.001$)] and dysphagia (score improvement of 6.7 points, $P = 0.009$). However, the overall quality of life showed no statistical difference compared to chemotherapy [least squares mean (LSM) change: -3.54, 95%$CI = -8.92$ to 1.84] [**?**, **?**]. Additionally, the efficacy of monotherapy is highly dependent on biomarker status.

Among patients with PD-L1 CPS $\geq$ 10, third-line pembrolizumab treatment yielded a median OS of 8 months (95%$CI = 5.8 - 11.1$), whereas patients who were PD-L1 negative experienced limited benefit. MSI-H patients respond better to ICIs (ORR $>$ 40%). However, the existing biomarker system remains imperfect. Clinical practice has shown that some patients who are PD-L1 negative or have proficient mismatch repair (pMMR) status may still derive benefit from ICI treatment.

For instance, a patient with locally advanced PD-L1 negative/pMMR GEJ adenocarcinoma achieved a pathologic complete response (pCR) after receiving anti-PD-1 antibody combined with chemotherapy, suggesting that combination strategies may overcome the limitations of monotherapy. Therefore, focusing on the development of more effective biomarker detection systems and exploring combination strategies of ICIs with other therapeutic modalities is essential to achieving an optimal balance between efficacy and safety.

3 ICIs

Advances in Combination Therapy

The application of Immune Checkpoint Inhibitor (ICI) combination therapies has become a critical strategy for advanced gastroesophageal junction (GEJ) adenocarcinoma, aiming to overcome the bottlenecks of traditional treatments through synergistic effects. Based on existing clinical trial data, different combination regimens exhibit distinct efficacy and toxicity profiles (see for details), necessitating a priority analysis to optimize clinical decision-making.

In patients with human epidermal growth factor receptor 2 (HER2)-negative GEJ adenocarcinoma, the CheckMate-649 trial demonstrated that in patients with a PD-L1 Combined Positive Score (CPS) $\geq$ 5, nivolumab combined with chemotherapy significantly improved overall survival (OS; $HR = 0.71$,

98.4%CI = 0.59–0.86) and progression-free survival (PFS; HR = 0.68, 98%CI = 0.56–0.81) compared to chemotherapy alone. The objective response rate (ORR) increased to 60% (versus 45% in the chemotherapy group), and the duration of response (DoR) was extended to 9.5 months (versus 7.0 months for chemotherapy alone). Three-year follow-up data further confirmed long-term benefits: in patients with PD-L1 CPS $\geq$ 5, the 3-year OS rate reached 21% in the nivolumab group (versus 10% for chemotherapy), and the PFS rate was 13% (versus 8% for chemotherapy). In the overall randomized population, OS and PFS benefits remained consistent ($OS: HR = 0.79$; $PFS: HR = 0.77$), with a manageable safety profile; the incidence of grade 3–4 treatment-related adverse events (TRAEs) was 59% and 44%, respectively [**?**]. A subgroup analysis of Chinese patients (n = 208) further confirmed the OS benefit, with the median OS reaching 14.3 months in the nivolumab plus chemotherapy group (versus 10.2 months for chemotherapy; $HR = 0.61$).

In the Chinese subgroup, the median PFS was 8.3 months (versus 5.6 months for chemotherapy; HR = 0.57), and the ORR improved to 66% (versus 45% for chemotherapy). Quality of Life (QoL) assessments indicated that nivolumab combined with chemotherapy did not increase the symptom burden and delayed the time to deterioration in the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) scale (HR = 0.72). The ORIENT-16 study further validated the efficacy of sintilimab combined with chemotherapy in the Chinese HER2-negative population. The median OS for the overall population was 15.2 months (versus 12.3 months for chemotherapy; HR = 0.77), while the median OS in the PD-L1 CPS $\geq$ 5 subgroup reached 18.4 months (versus 12.9 months for chemotherapy; $HR = 0.66$). Cost-effectiveness analysis demonstrated its economic viability, with an incremental cost-effectiveness ratio (ICER) of \$25, 239.29 per quality-adjusted life year (QALY), which is below the Chinese threshold of \$38, 223.34 [**?**]. These data support ICIs combined with chemotherapy as the preferred first-line regimen for HER2-negative patients.

In patients with HER2-positive GEJ adenocarcinoma, the KEYNOTE-811 study established the value of pembrolizumab combined with trastuzumab and chemotherapy. The first interim analysis showed an ORR of 74.4% (95%CI = 65.8–81.1) for the combination therapy, a pathological complete response (pCR) rate of 11%, and a median tumor shrinkage rate of 47% (range: −100% to 60%), demonstrating powerful early anti-tumor activity. In the second pre-specified interim analysis, with a median follow-up of 28.3 months, the median PFS in the pembrolizumab group was 10.0 months (HR = 0.72, 95%CI, P = 0.0002), and OS showed a trend toward improvement (20.0 vs. 16.9 months; $HR = 0.87$, 95%CI = 0.72–1.06; $P = 0.084$).

Subsequent data updates with a median follow-up of 38.4 months maintained the PFS benefit (HR = 0.73), although OS did not reach the pre-specified significance level (HR = 0.84). Pre-specified subgroup analysis showed that patients with PD-L1 CPS $\geq$ 1 derived a more pronounced PFS benefit (HR = 0.69). Regarding safety, the incidence of grade 3 or higher TRAEs was 58% in

the pembrolizumab group and 51% in the chemotherapy group, with common events including diarrhea and anemia. Quality of life assessments indicated that the combination therapy did not lead to a deterioration in QoL; the difference between groups in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) global health status score was −1.16 (95%CI = −4.23–1.91), suggesting that quality of life was not negatively impacted. Furthermore, the KEYNOTE-585 study explored the application of perioperative pembrolizumab combined with chemotherapy in resectable GEJ cancer. The final analysis showed a median OS of 71.8 months (HR = 0.86) and an event-free survival (EFS) HR of 0.81, indicating patient benefit.

Combination with Targeted Therapies

The combination of ICIs and targeted drugs provides a new therapeutic strategy for advanced GEJ adenocarcinoma by synergistically modulating the tumor microenvironment. Anti-angiogenic drugs inhibit the VEGF/VEGFR signaling pathway, thereby reversing the immunosuppressive microenvironment and promoting T-cell infiltration, which can enhance the anti-tumor activity of ICIs.

3.2.1 ICIs 联合抗血管生成药物

Apatinib is an oral targeted therapeutic agent that inhibits tumor angiogenesis by potently suppressing vascular endothelial growth factor receptor 2 (VEGFR2). Research indicates that apatinib can enhance immune cell infiltration and alleviate immunosuppression. Studies have shown that apatinib monotherapy yields an objective response rate (ORR) of 6.38% to 13.04% and a median progression-free survival (PFS) of 3.67 months (95% CI: 2.17–6.80).

In the context of second-line and later-line therapy, a retrospective study evaluated the efficacy of apatinib in combination with PD-1 inhibitors for advanced gastric cancer or gastroesophageal junction (GEJ) adenocarcinoma. This single-center, retrospective observational study enrolled 24 patients with histologically confirmed unresectable locally advanced or metastatic HER2-negative gastric cancer (GC) or GEJ adenocarcinoma. These patients received a combination of a PD-1 inhibitor and apatinib as second- or third-line treatment. The results demonstrated that the combination therapy achieved an ORR of 26.3% and a disease control rate (DCR) of 63.2%. The PFS for this regimen was···

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The progression-free survival (PFS) ranged from 1.3 to 4.7 months, and the median overall survival (OS) was not reached. Compared to historical data for second-line therapy, which shows an objective response rate (ORR) of 6.8–25% and a PFS of 1.5–5.3 months, the combination regimen demonstrates a trend toward improved efficacy, albeit with higher toxicity. To further validate the feasibility of this approach, a real-world retrospective exploratory study was

conducted. This study included 39 patients with advanced gastric cancer (GC) or gastroesophageal junction (GEJ) adenocarcinoma who had received at least one prior line of systemic chemotherapy. Patients were treated with apatinib in combination with PD-1 inhibitors (camrelizumab, sintilimab, or nivolumab). The combination therapy achieved an ORR of 20.5% and a disease control rate (DCR) of 69.2%, with a median PFS of 3.9 months (95% CI = 2.74–5.06) and a median OS of 7.8 months (95% CI = 4.82–10.78).

Camrelizumab combined with apatinib has also shown prominent performance in third-line treatment. A study involving 19 patients with metastatic gastric cancer reported an ORR of 26.3%, a DCR of 68.4%, a median PFS of 7.0 months (95% CI = 2.9–11.0), and a median OS of 10.0 months (95% CI = 7.4–12.6). The incidence of grade 3 or higher treatment-related adverse events (TRAEs) was low, primarily consisting of hypertension (5.3%) and thrombocytopenia (5.3%). Furthermore, the synergistic effect of this combination strategy with chemotherapy has been validated in the second-line setting. A Phase II study of camrelizumab plus apatinib and S-1 as second-line therapy for 24 patients with advanced GEJ adenocarcinoma showed that the ORR increased to 29.2%, with a median PFS of 6.5 months and the median OS not yet reached. This demonstrates robust disease control and potential for survival benefit. The safety profile of this regimen was consistent with the known toxicities of the individual drugs, with a grade 3 or higher adverse event rate of 25.0% and no new safety signals observed. Ramucirumab, another monoclonal antibody targeting VEGFR2, also plays a critical role in the treatment of advanced G/GEJ adenocarcinoma. Ramucirumab monotherapy significantly improves median OS (HR = 0.77) and median PFS (HR = 0.48). Explorations in the pretreated HER2-positive population have shown that combining ramucirumab with trastuzumab and chemotherapy holds great potential. A multicenter Phase II clinical study evaluated the efficacy and safety of this regimen as second-line treatment in 50 patients with HER2-positive advanced G/GEJ cancer who were resistant to first-line trastuzumab-containing regimens. The results showed an ORR of 54%, a DCR of 96%, a PFS of 7.1 months, and a median OS of 13.6 months.

These findings confirm the clinical value of continuing trastuzumab treatment in combination with anti-angiogenic therapy following disease progression on first-line anti-HER2 therapy.

3.2.2 ICIs 联合新型靶向药物

Combination strategies involving novel targeted drugs and immune checkpoint inhibitors (ICIs) offer a new direction for breaking through the traditional treatment bottlenecks of gastroesophageal junction (GEJ) adenocarcinoma. Among these, claudin 18.2 (CLDN18.2) and fibroblast growth factor receptor 2b (FGFR2b) have emerged as two critical targets. Although efficacy and toxicity data remain immature, these targets have already demonstrated significant potential for clinical translation.

CLDN18.2 is a stomach-specific isoform of the tight junction protein claudin-18 (CLDN18). It is highly expressed in approximately 40% of gastroesophageal junction (GEJ) adenocarcinomas, particularly in patients with diffuse-type tumors or peritoneal metastases, making it a critical therapeutic target following HER2 [**?**]. Zolbetuximab, the world' s first monoclonal antibody targeting CLDN18.2, induces tumor cell death through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Research indicates that a subset of CLDN18.2-positive patients also express PD-L1 (CPS $\geq$ 1). For populations with high PD-L1 expression (CPS $\geq$ 10), immune checkpoint inhibitors (ICIs) provide more durable survival benefits; however, for those with low or no PD-L1 expression, zolbetuximab-based combination regimens offer a distinct advantage. Currently, several studies are evaluating combination strategies involving zolbetuximab and ICIs. Among these, the NCT03505320 trial aims to assess the synergistic effects of combining zolbetuximab with nivolumab and chemotherapy, exploring the dual enhancement potential of a "targeted + immunotherapy" model in CLDN18.2-positive patients.

Abnormal activation of the FGFR2b signaling pathway drives tumor progression in GEJ adenocarcinoma and is associated with a poor prognosis. Bemarituzumab is the first monoclonal antibody targeting FGFR2b, and its efficacy was validated in the Phase II FIGHT study. This study evaluated bemarituzumab in combination with a modified 5-fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) regimen as a first-line treatment for patients with HER2-negative advanced GEJ adenocarcinoma overexpressing FGFR2b. The results demonstrated that the combination therapy provided significant clinical benefits compared to chemotherapy alone. In terms of the objective response rate (ORR), the bemarituzumab group reached 47%, compared to 33% in the placebo group. Survival analysis showed that the combination therapy significantly extended both progression-free survival (PFS) and overall survival (OS). The median PFS in the bemarituzumab group was 9.5 months, superior to the 7.4 months in the placebo group (HR = 0.68). Furthermore, the median OS was extended to 19.2 months, compared to 13.5 months in the placebo group (HR = 0.77).

These findings confirm the therapeutic potential of targeting FGFR2b in specific GEJ adenocarcinoma populations. However, the efficacy of small-molecule FGFR inhibitors as monotherapy for patients with $FGFR2$ amplification remains limited. A Phase II study showed that the small-molecule FGFR inhibitor futibatinib achieved an ORR of only 17.9% and a median PFS of just 2.9 months in 28 patients with $FGFR2$-amplified advanced GEJ adenocarcinoma. This indicates insufficient single-agent activity, suggesting that combination strategies are a necessary direction for future development. Preclinical studies have shown that FGFR inhibitors can reverse immunosuppression within the tumor microenvironment and enhance T-cell infiltration, providing a mechanistic rationale for their use in combination with ICIs.

Currently, the Phase Ib/III study (FORTITUDE-101) evaluating bemar-

ituzumab in combination with nivolumab and chemotherapy is ongoing (NCT05052801), which is expected to provide a new therapeutic option for FGFR2b-positive patients.

Matrix Metalloproteinase 9 (MMP9) has emerged as another novel target showing unique potential in the treatment of gastroesophageal junction (GEJ) adenocarcinoma. MMP9 is a zinc-dependent protease involved in extracellular matrix remodeling, tumor growth, and metastasis; its high expression in gastric cancer is associated with a poor prognosis. Preclinical studies have demonstrated that inhibiting MMP9 can reverse immunosuppression and promote T-cell infiltration, thereby enhancing the antitumor activity of immune checkpoint inhibitors (ICIs). A Phase Ib study evaluated the safety and preliminary efficacy of the anti-MMP9 antibody andecaliximab in combination with nivolumab for Japanese patients with GEJ adenocarcinoma. The results showed an objective response rate (ORR) of 50% (5/10) and a progression-free survival (PFS) of 4.6 months. The median overall survival (OS) was not reached, and the combination demonstrated a favorable safety profile with no dose-limiting toxicities observed, highlighting the therapeutic potential of combining MMP9-targeted therapy with ICIs.

Dual Immunotherapy Combinations

Dual ICI strategies and their integration with other treatment modalities represent a new direction for the management of advanced GEJ adenocarcinoma. In the field of dual immune checkpoint inhibition, the synergistic effect of nivolumab combined with ipilimumab has been validated in specific patient populations. The GERCOR NEONIPIGA Phase II study focused on patients with locally advanced resectable mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) GEJ adenocarcinoma. This study evaluated neoadjuvant nivolumab plus ipilimumab followed by adjuvant nivolumab monotherapy. Among the 32 enrolled patients, the incidence of grade 3–4 adverse events related to neoadjuvant therapy was 19%. All 29 patients who underwent surgery achieved R0 resection, with a pathologic complete response (pCR) rate as high as 58.6% (90% CI: 41.8–74.1). At a median follow-up of 14.9 months, no patients had experienced recurrence.

These results indicate that dual immunotherapy as a neoadjuvant treatment is highly effective in the dMMR/MSI-H population. However, safety remains a critical concern, as the surgical complication rate reached 55% (including one postoperative death). This suggests a need for rigorous patient selection and optimization of perioperative management. Balancing the predictive efficacy of dual immunotherapy regimens with their associated toxicity remains a significant clinical challenge.

Exploratory analysis from the CheckMate 032 study suggests that utilizing the Combined Positive Score (CPS) rather than the Tumor Proportion Score (TPS/TC) to evaluate PD-L1 expression provides a superior prediction of ef-

ficacy for nivolumab with or without ipilimumab. In populations with CPS ≥ 5 and ≥ 10, the objective response rates (ORR) reached 19% and 26%, respectively, which were significantly higher than those observed in populations defined by corresponding TC thresholds.

However, dual immunotherapy regimens are associated with a higher risk of immune-related adverse events (irAEs). A network meta-analysis demonstrated that among all immune checkpoint inhibitor (ICI) regimens, the combination of nivolumab and ipilimumab ranked highest for the incidence of Grade 3–5 irAEs (Surface Under the Cumulative Ranking curve [SUCRA] = 21.6%), which was significantly higher than the rates observed in chemotherapy groups (2.25% vs. 7.35%). Common irAEs include skin reactions (15.76%), hypothyroidism (9.73%), and pneumonitis (4.45%), necessitating enhanced toxicity monitoring and proactive management.

In summary, the combination of Immune Checkpoint Inhibitors (ICIs) and chemotherapy is recommended as a standard treatment strategy for patients with HER2-negative status.

The standard first-line treatment regimen remains the preferred choice due to its definitive efficacy and acceptable safety profile. For specific patient populations, such as those with CLDN18.2-positive tumors, the combination of immune checkpoint inhibitors (ICIs) and CLDN18.2 inhibitors represents a promising future direction, though further clinical data are required for validation. In addition to these systemic strategies, local interventions such as radiotherapy and interventional therapy may enhance the efficacy of ICIs by modulating the tumor immune microenvironment. However, high-level evidence supporting these combined approaches is currently lacking.

In the future, it will be necessary to explore personalized combination strategies guided by biomarkers to balance efficacy and toxicity, thereby optimizing clinical practice.

4 生物标志物

Biomarker systems play a critical role in the treatment of gastroesophageal junction (GEJ) adenocarcinoma with immune checkpoint inhibitors (ICIs). These markers can optimize patient stratification and clinical decision-making by predicting treatment response and resistance (see Table 2 for details). However, single-biomarker predictions have inherent limitations, necessitating the integration of multi-dimensional markers to improve precision. Future research should explore biomarker combination strategies to achieve individualized treatment.

The value and limitations of the PD-L1 Combined Positive Score (CPS) as a predictive biomarker for ICIs in the treatment of GEJ adenocarcinoma have become a central focus of research. PD-L1 expression is quantified via CPS, with a CPS ≥ 1 established as the minimum threshold for pembrolizumab use in patients with gastric or GEJ cancer; however, studies suggest that higher

thresholds may offer greater predictive power. Das et al. reported a case of GEJ cancer with a CPS of 70 where peritoneal metastases disappeared following pembrolizumab treatment, suggesting that high CPS values (e.g., ≥ 70) may identify beneficiaries even among traditionally "immune-cold" tumors. Nevertheless, the controversy surrounding the cutoff values between CPS ≥ 1 and ≥ 5 presents limitations. While the CheckMate 649 trial established CPS ≥ 5 as the criterion for benefit from nivolumab plus chemotherapy, in real-world practice, patients with CPS ≥ 1 may also respond. This reflects the instability of PD-L1 as a biomarker, likely due to its expression heterogeneity and dynamic changes [**?**]. In clinical practice, a study by Mildanoglu et al. involving 153 patients with metastatic gastric/GEJ adenocarcinoma and PD-L1 CPS ≥ 5 found that nivolumab combined with chemotherapy yielded a median progression-free survival (PFS) of 11.06 months, an overall survival (OS) of 16.03 months, and an objective response rate (ORR) of 64%. Multivariate analysis identified PD-L1 CPS and the Systemic Immune-Inflammation Index (SII) as independent predictors of treatment response.

OS: 14.4 months vs. 11.1 months, HR = 0.71 (98.4% CI = 0.59–0.86); PFS: 7.7 months vs. 6.05 months, HR = 0.68 (98% CI = 0.56–0.81); ORR: 60% (226/378) vs. 45% (177/391).

OS in the total population: 15.2 months vs. 12.3 months (HR = 0.77, 95% CI = 0.63–0.94); OS in the PD-L1 CPS ≥ 5 subgroup: 18.4 months vs. 12.9 months (HR = 0.66, 95% CI = 0.50–0.86).

ATTRACTION-2: ICI monotherapy (Nivolumab vs. Placebo) for third-line treatment of advanced GEJ adenocarcinoma ($n = 330$ vs. 163); OS: 5.26 months vs. 4.14 months (HR = 0.63, 95% CI = 0.51–0.76). KEYNOTE-059: ICI monotherapy (Pembrolizumab) for third-line treatment of advanced GEJ adenocarcinoma; ORR: 11.6% (95% CI = 8.0–16.1); median PFS: 2.0 months (95% CI = 2.0–2.0); median OS: 5.5 months (95% CI = 4.2–6.7).

First-line treatment for HER2-negative advanced GEJ adenocarcinoma, PD-L1 CPS ≥ 5 ($n = 473$ vs. 482).

First-line treatment for HER2-positive advanced GEJ adenocarcinoma ($n = 217$ vs. 216); ORR: 74.4% (99/133) vs. 51.9% (68/131). Second- or third-line treatment for HER2-negative advanced GC/GEJ adenocarcinoma; ORR: 26.3% (5/19); DCR: 63.2% (12/19); median PFS: 3.0 months. Camrelizumab combined with Apatinib study (Immune-targeted combination therapy): Camrelizumab + Apatinib for third-line treatment of metastatic gastric cancer; ORR: 26.3% (5/19); DCR: 68.4% (13/19); median PFS: 7.0 months; median OS: 10.0 months. Second-line treatment for trastuzumab-resistant HER2-positive advanced GEJ adenocarcinoma; ORR: 54% (27/50); DCR: 96% (48/50); median PFS: 7.1 months; median OS: 13.6 months.

First-line treatment for FGFR2b-overexpressing, HER2-negative advanced GEJ adenocarcinoma ($n = 77$ vs. 78); ORR: 47% vs. 33%; PFS: 9.5 months vs. 7.4

months (HR = 0.68, 95% CI = 0.44–1.04); OS: 19.2 months vs. 13.5 months (HR = 0.77, 95% CI = 0.72–1.14).

MMP9 targeting study (Immune-targeted combination therapy): Andecaliximab + Nivolumab Phase 1b trial in patients with gastric or GEJ adenocarcinoma; ORR: 50% (5/10); median PFS: 4.6 months.

Phase II trial: dMMR/MSI-H locally advanced resectable GEJ adenocarcinoma ($n = 32$); pCR: 58.6% (17/29) (90% CI = 41.8%-74.1%).

Note: GEJ = gastroesophageal junction; ICIs = immune checkpoint inhibitors; OS = overall survival; PFS = progression-free survival; ORR = objective response rate; DCR = disease control rate; pCR = pathologic complete response; MSI-H = microsatellite instability-high; dMMR = deficient mismatch repair; PD-L1 = programmed death-ligand 1; CPS = combined positive score; HER2 = human epidermal growth factor receptor 2; GC = gastric cancer; FGFR2b = fibroblast growth factor receptor 2b.

In a study published in the *Chinese General Practice*, SII (OR = 3.93, 95% CI = 1.40–10.99) and CPS (OR = 0.64, 95% CI = 0.43–0.94) were analyzed; however, CPS itself did not emerge as an independent prognostic factor for OS or PFS, suggesting its predictive value is limited to specific contexts. Consequently, while PD-L1 CPS offers threshold-dependent advantages in identifying populations that benefit from ICIs—particularly with CPS ≥ 5 optimizing clinical decision-making—its heterogeneity and contextual limitations necessitate comprehensive evaluation alongside other biomarkers. MSI-H/dMMR is a molecular subtype with clear predictive value in GEJ adenocarcinoma. Arising from DNA mismatch repair defects that lead to microsatellite instability, the underlying mechanism involves MMR system dysfunction and the inability to correct DNA replication errors. This results in the accumulation of high-frequency mutations, increased tumor mutational burden (TMB), the generation of neoantigens, and enhanced tumor immunogenicity [**?**]. Although MSI-H/dMMR accounts for only about 10% of GEJ adenocarcinomas, this population shows a significant response to ICIs. For instance, the NEONIPIGA Phase II trial demonstrated that neoadjuvant nivolumab plus ipilimumab for 29 patients with locally advanced dMMR/MSI-H GEJ adenocarcinoma achieved a pCR rate of 58.6% with manageable safety, highlighting the potential of MSI-H/dMMR-based patient selection for ICI therapy. MSI-H status correlates with high TMB and can compensate for negative PD-L1 expression, supporting its role as a vital component of integrated predictive models.

In addition to PD-L1 CPS and MSI-H/dMMR, novel markers such as TMB and circulating tumor DNA (ctDNA) monitoring are demonstrating potential in GEJ adenocarcinoma. As a quantitative measure of tumor mutations, high TMB typically reflects a higher neoantigen load, thereby enhancing tumor immunogenicity and correlating with improved ICI response rates. The U.S. Food and Drug Administration has approved TMB ≥ 10 mut/Mb as a companion diagnostic marker for pembrolizumab across various solid tumors. Goodman

et al. pooled data from 151 patients with various cancers and found that those with TMB $\geq$ 20 mut/Mb achieved an ORR of 58%, significantly higher than the 20% observed in the low TMB group ($P = 0.0001$). However, some high-TMB patients still fail to respond, suggesting that TMB must be integrated with microenvironmental factors to improve predictive accuracy. As a liquid biopsy tool, ctDNA allows for the dynamic monitoring of tumor genomic variations. Blood-based tumor mutational burden (bTMB) adjusted by ctDNA can mitigate interference from overall tumor burden. Nie et al. validated in the OAK and POPLAR cohorts ($n = 853$) that ctDNA-adjusted bTMB, using a threshold of 8 mut/Mb $\times$ ng, identified patients receiving atezolizumab who had significantly higher ORR and durable clinical benefit rates compared to the low-value group ($P < 0.05$), indicating its ability to further refine ICI response stratification.

Single-biomarker predictions have limitations. Future efforts should focus on constructing integrated models that combine multi-dimensional markers—such as PD-L1 CPS, MSI-H, and TMB—alongside dynamic ctDNA monitoring to achieve real-time optimization of treatment strategies. This approach will facilitate more precise individualized immunotherapy for GEJ adenocarcinoma.

Biomarkers

方法

Clinical Applicability

Expression heterogeneity; a subset of patients with CPS $<$ 1 may still derive clinical benefit.

PD-L1 CPS IHC optimizes patient selection for immune checkpoint inhibitors (ICIs), with priority given to those with CPS $\geq$ 5.

MSI-H/dMMR screening identifies high-response populations; however, results are influenced by tumor burden and should be integrated with the microenvironment.

TMB NGS serves as a supplementary predictive tool, with priority given to patients with TMB $\geq$ 10 mut/Mb.

Dynamic monitoring and refined stratification of ICI response; eliminating the interference of tumor burden requires standardized bTMB and ctDNA-adjusted assessments.

分析

Abstract

Human epidermal growth factor receptor 2 (HER2) is a critical driver gene and therapeutic target in gastric cancer (GC) and gastroesophageal junction (GEJ) cancer. Currently, the standard clinical method for determining HER2 status

relies on immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). However, these tissue-based assays are limited by the inherent spatial and temporal heterogeneity of the tumor. With the rapid advancement of liquid biopsy technologies, circulating tumor DNA (ctDNA) has emerged as a promising non-invasive alternative for detecting HER2 amplification and monitoring treatment response. Furthermore, tumor mutational burden (TMB) has been identified as a potential biomarker for predicting the efficacy of immune checkpoint inhibitors (ICIs). This study explores the clinical utility of next-generation sequencing (NGS) in assessing HER2 status and TMB in patients with gastric and gastroesophageal junction cancers.

1. Introduction

Gastric cancer remains one of the most prevalent malignancies worldwide, particularly in East Asia. The overexpression or amplification of HER2 occurs in approximately 10% to 20% of GC and GEJ cancer cases. The ToGA trial established the combination of trastuzumab and chemotherapy as the first-line standard of care for HER2-positive advanced gastric cancer. Despite this, therapeutic resistance frequently develops, often driven by the loss of HER2 expression or the emergence of bypass signaling pathways.

Traditional tissue biopsies are invasive and may fail to capture the complete genomic landscape of the tumor due to intratumoral heterogeneity. In contrast, ctDNA analysis via NGS offers a comprehensive, real-time snapshot of the tumor' s molecular profile. Additionally, the integration of immunotherapy into the treatment paradigm for GC/GEJ cancer has necessitated the identification of predictive biomarkers such as TMB. High TMB (TMB-H) is often associated with increased neoantigen load and improved response to ICIs.

2. Materials and Methods

2.1 Patient Selection and Sample Collection

This study enrolled patients diagnosed with advanced GC or GEJ cancer. Paired tumor tissue and blood samples were collected. Tissue HER2 status was initially determined using standard IHC and FISH protocols. Blood samples were processed to isolate plasma for ctDNA extraction.

2.2 NGS Sequencing and TMB Calculation

Targeted NGS was performed using a comprehensive gene panel. For tissue samples (tTMB), the number of somatic mutations per megabase (mut/Mb) was

5 结束语

Currently, immune checkpoint inhibitor (ICI) monotherapy provides a new option for late-line treatment; however, its efficacy exhibits significant biomarker dependence, with factors such as PD-L1 CPS and MSI-H/dMMR status serving as critical predictors. The integration of ICIs with chemotherapy has successfully transitioned into first-line treatment, significantly improving survival outcomes for both HER2-negative and HER2-positive patients and establishing this combination as the new standard of care. Concurrently, explorations into immunotherapy combined with targeted therapies, as well as dual-immunotherapy strategies, offer promising new directions for overcoming drug resistance and reversing the immunosuppressive microenvironment.

Nevertheless, current clinical practice still faces numerous challenges. The existing biomarker framework remains incomplete, as its predictive value is limited by heterogeneity and dynamic changes. Furthermore, the toxicity management of certain combination strategies—particularly dual-immunotherapy regimens and combinations with targeted drugs—requires careful consideration. Future immunotherapy for gastroesophageal junction (GEJ) adenocarcinoma must become more precise. This will necessitate the construction of a more refined molecular subtyping system based on multi-omics technologies, the implementation of dynamic treatment monitoring using tools such as liquid biopsy, and the active exploration of combination models involving ICIs and novel agents, such as bispecific antibodies and antibody-drug conjugates (ADCs). Ultimately, by optimizing biomarker-guided individualized treatment strategies, it will be possible to break through existing efficacy bottlenecks, achieve an optimal balance between efficacy and safety, and maximize survival benefits for patients.

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Note: Figure translations are in progress. See original paper for figures.