Gastric Cancer: Molecular Characterization, Therapeutic Innovations, and Perspectives

Emily Tonin da Costa[1] Sergio Jobim de Azevedo[1,2] Alexandre A. Jácome[3]

[1] Department Oncology, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil
[2] Seção de Oncologia Clínica, OC Oncoclínicas Moinhos de Vento, Porto Alegre, RS, Brazil
[3] Seção de Oncologia Clínica, Cancer Center Oncoclínicas, Belo Horizonte, MG, Brazil

Address for correspondence Alexandre A. Jácome, MD, PhD, Cancer Center Oncoclínicas, R. Roma, 561, Santa Lúcia, Belo Horizonte, MG, Brazil (e-mail: alexandre.jacome@medicos.oncoclinicas.com).

Braz J Oncol 2024;20:s00441790566.

Abstract

Introduction Gastric cancer is the fifth most common neoplasm and the fourth leading cause of cancer-related death in the world. The present review aims to offer to the oncologic community the molecular characterization of gastric cancer, the therapeutic innovations and the perspectives for the systemic therapy for gastric cancer.

Materials and Methods We searched for articles in the PubMed database using Medical Subject Headings (MeSH). The latest publications and proceedings of meetings were also reviewed.

Results The cornerstone of the systemic therapy for gastric cancer is the dual combination of fluoropyrimidines and platin-based chemotherapy. Nevertheless, it is recommended that gastric cancer patients are tested for human epidermal growth factor receptor 2 (HER2), high-frequency microsatellite instability (MSI-H), programmed cell death-ligand 1(PD-L1), and claudin 18.2 expression. If HER2-positive, trastuzumab plus pembrolizumab should be added to the doublet chemotherapy. Anti-programmed cell death-1 (anti-PD-1) therapy, such as nivolumab or pembrolizumab, should also be added to chemotherapy in MSI-H and in the PD-L1-positive patients. Patients who present overexpression of claudin 18.2 should be treated with the combination of zolbetuximab and oxaliplatin-based chemotherapy. Immunotherapy may also be considered in patients with high tumor mutational burden. Clinical trials evaluating fibroblast growth factor receptor 2 (FGFR2) inhibitors and the dual inhibition anti-PD-1 and anti-T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (anti-TIGIT) are promising.

Conclusions The clinical applicability of precision medicine in gastric cancer has risen in the past few decades, leading to substantial improvements in the efficacy of the systemic therapy. Testing patients for biomarkers is paramount for the appropriate management of advanced disease. Ongoing clinical trials evaluating new therapeutic strategies are promising and offer optimism for the patients affected by this challenging disease.

Keywords
- stomach neoplasms
- antineoplastic agents
- precision medicine

received
March 8, 2024
accepted
June 27, 2024

DOI https://doi.org/10.1055/s-0044-1790566.
ISSN 2526-8732.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Introduction

Gastric cancer (GC) is a heterogeneous disease characterized by high recurrence rates and unfavorable prognosis, ranking fifth in both incidence and cancer-related deaths worldwide.[1] The worldwide incidence of GC varies by geographic region, but low- and middle-income countries concentrate the majority of cases. In Brazil, the estimated yearly figure from 2023 to 2025 is of 21,480 new cases (13,340 cases in men and 8,140 cases in women), corresponding to the estimated risk of 9.94 cases per 100 thousand inhabitants.[2] Several risk factors have been implicated in the pathogenesis of this neoplasm, including obesity, smoking, alcohol consumption, and infections by the Epstein-Barr virus and *Helicobacter pylori*.[1,3] Most GCs arise sporadically, while hereditary cancer predisposition syndromes are responsible for a small portion of the cases.

Precision medicine was recently developed; it is innovative for this neoplasm, and it aims to adjust the clinical decision to the specific characteristics of individuals, such as the person's genetic characteristics and/or the genetic profile of the tumor. In the past few decades, the management of advanced GC has evolved largely due to therapeutic development tailored to actionable molecular abnormalities. A significant progress in the efficacy of systemic therapy has been observed with the clinical applicability of precision medicine (►**Figs. 1**–**2**). The objectives of precision medicine are to identify a target for prognostic and predictive stratification, and selection of treatment that provides improved responses with reduced toxicity. The development of the technology used for DNA sequencing, such as next-generation sequencing (NGS), which is capable of characterizing the tumor genome, has been vital for the identification of potential therapeutic targets and, consequently, to meet the objectives to offer better selective therapies with minimum adverse events.

Advanced GC portends a dismal prognosis, and the first therapeutic regimens used in the systemic therapy of the disease were characterized by poor efficacy and high toxicity.[4,5] The incorporation of targeted therapies and immunotherapy in the past few years has ushered in a new era in the systemic therapy of GC. The deeper understanding of the molecular biology of the disease and the advances observed in cancer therapies provide us optimism for the continuing improvement of the treatment of the GC in the next few years. The present review aims to describe the progress in the systemic therapies observed in the past few decades, as well as to present future perspectives for the treatment of this challenging disease.

Materials and Methods

We searched for articles in the PubMed database using the following search strategy and Medical Subject Headings (MeSH): *gastric cancer* AND *treatment* AND *molecular* AND *precision medicine*. The latest publications and meeting proceedings related to the topic were also reviewed.

Molecular Characterization of Gastric Cancer

A new classification based on the main molecular abnormalities was recently proposed by The Cancer Genome Atlas

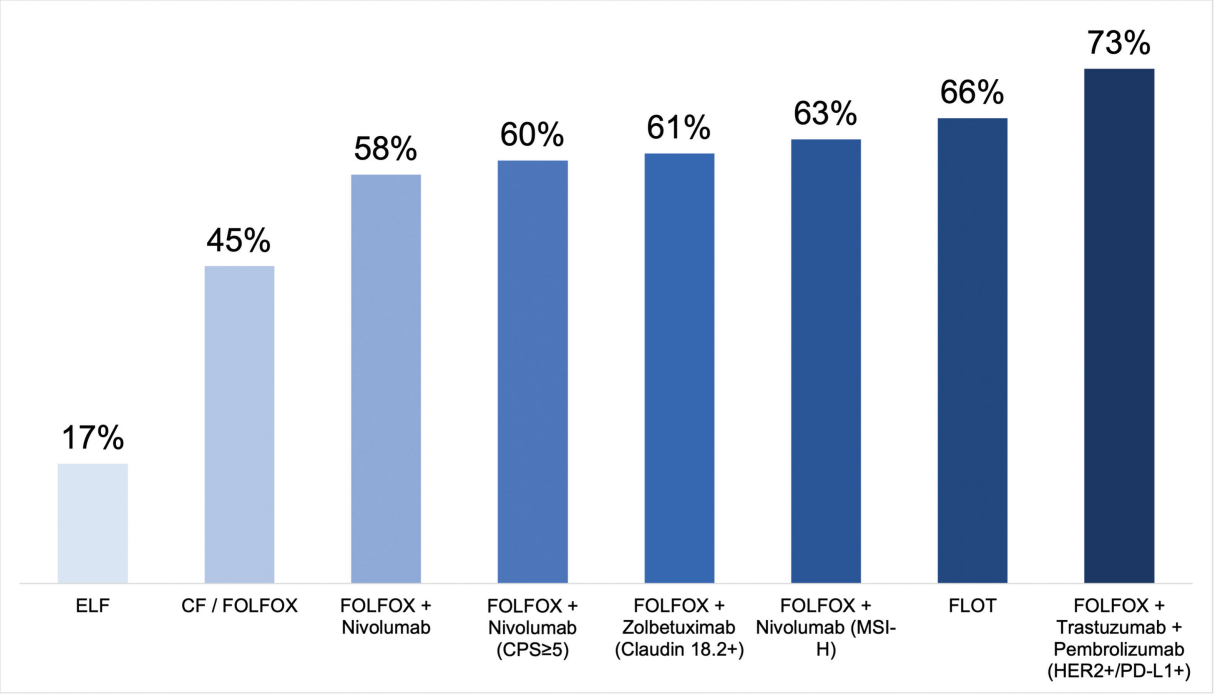

Fig. 1 Overall response rates of the therapeutic regimens used in advanced gastric cancer. **Abbreviations:** ELF, etoposide, leucovorin, 5-fluorouracil; CF, cisplatin, 5-fluorouracil; FOLFOX, 5-fluorouracil and leucovorin combined with oxaliplatin; CPS, combined positive score; MSI-H, high-frequency microsatellite instability; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; HER2, human epidermal receptor 2; PD-L1, programmed cell death-ligand 1.

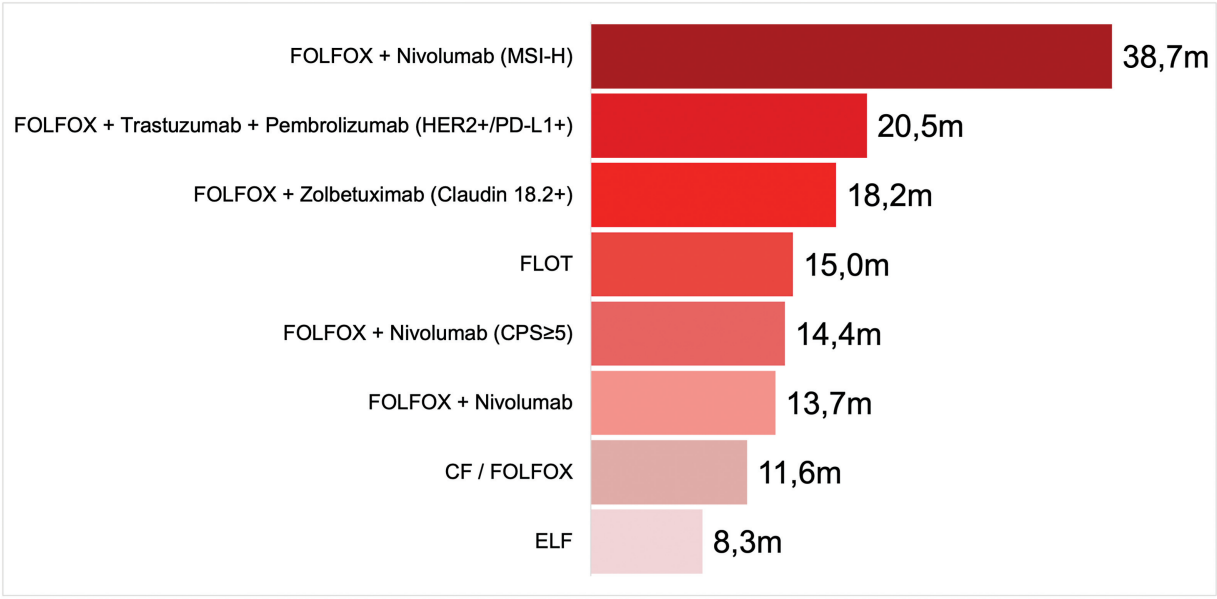

Fig. 2 Overall survival associated with the therapeutic regimens used in advanced gastric cancer. **Abbreviations:** ELF, etoposide, leucovorin, 5-fluorouracil; CF, cisplatin, 5-fluorouracil; FOLFOX, 5-fluorouracil and leucovorin combined with oxaliplatin; CPS, combined positive score; MSI-H, high-frequency microsatellite instability; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; HER2, human epidermal receptor 2; PD-L1, programmed cell death-ligand 1.

Table 1 Molecular characterization of gastric cancer

Molecular subtype	Frequency	Characteristics
Chromosomal instability (CIN)	50%	• The incidence is increased in esophagogastric tumors; • Usually present intestinal-type histology; • *TP53* mutations, and *HER2* and *KRAS* amplifications.
High-frequency microsatellite instability (MSI-H)	22%	• The incidence is higher in elderly patients; • Characterized by a high tumor mutational burden; • Frequent silencing of *MLH1*.
Genomically stable (GS)	20%	• Typically diagnosed at an earlier age; • Diffuse-type histology usually present; • Tends to be located at the distal portions of the stomach; • *CDH1*, *ARID1A*, and *RHOA* mutations.
Epstein-Barr virus (EBV)	9%	• Frequently located at the fundus and gastric body; • Lower rate of nodal metastases; • Better survival rates; • *PIK3CA* mutations and silencing of the *CDKN2A* promoter.

(TCGA) project[6] to identify possible therapeutic targets in four molecularly-distinct subtypes of GC (►**Table 1**).

In the current clinical practice, the molecular evaluation of GC must involve the test for overexpression/amplification of the human epidermal growth factor receptor 2 (HER2), high-frequency microsatellite instability (MSI-H), programmed cell death-ligand 1 (PD-L1) expression, and, more recently, claudin 18.2 expression. Such findings influence the decision-making process and therapy for metastatic disease.

Approximately 10 to 20% of GCs present amplification of the *HER2* gene, which results in the overexpression of HER2, a receptor tyrosine kinase member of the epidermal growth factor receptor (EGFR) family commonly found in the chromosomal-instability subtype.[6] These patients with advanced disease may benefit from the addition trastuzumab to chemotherapy, which is a recombinant humanized monoclonal antibody that targets the extracellular domain IV of the HER2 protein.[7]

Expression of PD-L1 and deficient DNA mismatch repair (dMMR) mechanism are also important predictive biomarkers in GC.[8,9] Programmed cell death receptor-1 (PD-1) is expressed in T-cells, and pembrolizumab and nivolumab, monoclonal antibodies targeting PD-1, provide antitumor activity by releasing function. Metastatic GC patients whose tumors exhibit dMMR and/or MSI-H, as well as those with high tumor mutational burden (TMB), may also experience clinical benefits from PD-1 inhibitors.[10] The identification of the predictive biomarkers to precisely select the patients who will derive clinical benefits from immunotherapy is one of the main current challenges in precision oncology, and it has been intensively investigated worldwide.

Therapeutic Targets and Results

PD-L1

The standard of care for unresectable locally-advanced or metastatic GC is the combination of fluoropyrimidines and platins. The addition of monoclonal antibodies will be based on the expression of biomarkers in the tumor tissue.

Expression of PD-L1 may be measured by the number of PD-L1-stained tumor cells divided by the total number of viable tumor cells and multiplied by 100, which is called tumor proportion score (TPS), or as the total number of lymphocytes, macrophages, and PD-L1-stained tumor cells divided by the total number of viable tumor cells and multiplied by 100, which is called combined positive score (CPS).[8,11] Studies on GC have predominantly used the CPS as the main score to measure PD-L1 expression. In the phase-III CheckMate 649 study,[8] 1,581 previously-untreated, unresectable and HER2-negative patients were randomized to receive nivolumab plus chemotherapy or chemotherapy alone (5-fluorouracil [5-FU] and leucovorin combined with oxaliplatin [FOLFOX] or capecitabine plus oxaliplatin [CAPOX]). Compared to chemotherapy alone, nivolumab plus chemotherapy significantly increased the overall survival (OS) in the whole population (median: 13.8 months versus 11.6 months; hazard ratio [HR]: 0.79; 95% confidence interval [95%CI]: 0.71–0.88) and progression-free survival (PFS) (median: 7.7 months versus 6.9 months; HR: 0.79; 95% CI: 0.70–0.89). In the analysis of OS in the CPS $\geq$ 5 population, which was the primary endpoint of the study,[8] the benefit was even greater, with a median OS of 14.4 months versus 11.1 months (HR: 0.70; 95%CI: 0.61–0.81), and a median PFS of 8.1 months versus 6.1 months (HR: 0.70; 95%CI: 0.60–0.81). Based on the CheckMate 649[8] findings, nivolumab was approved by the United States Food and Drug Administration (FDA) and by the Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária, ANVISA, in Portuguese) for every patient with advanced GC, regardless of the PD-L1 expression. On the other hand, European agencies, and the guidelines of the United States National Comprehensive Cancer Network (NCCN) and of the American Society of Clinical Oncology (ASCO) suggest that the immune checkpoint inhibitor should be added to chemotherapy only in patients with CPS $\geq$ 5.[12] The decision to add nivolumab in patients with CPS between 1 and 4 should be made in a case-by-case basis.

Pembrolizumab associated with oxaliplatin-based chemotherapy is another initial treatment option. In the phase-III KEYNOTE-859 study, with 1,579 HER2-negative patients, the addition of pembrolizumab to chemotherapy improved the median OS (12.9 months versus 11.5 months; HR: 0.78; 95%CI: 0.70–0.87) and PFS (6.9 months versus 5.6 months; HR: 0.76; 95%CI: 0.67–0.85) compared to the arm which received placebo associated with chemotherapy.[9] The benefits were consistent across all subgroups, including those with CPS $\geq$ 1 (HR: 0.74; 95%CI 0.65–0.84 for OS; and HR: 0.72; 95%CI: 0.63–0.82 for PFS), CPS $\geq$ 10 (HR: 0.65; 95% CI: 0.53–0.79 for OS; and HR: 0.62; 95%CI: 0.51–0.76 for PFS), and those with MSI-H (HR: 0.34; 95%CI: 0.18–0.66 for OS; and HR: 0.27; 95%CI: 0.14–0.53 for PFS). Neither the CheckMate 649 nor the KEYNOTE-859 demonstrated statistically significant benefits in terms of OS in the population of patients with CPS $<$ 1 for PD-L1 expression. Pembrolizumab as a single agent is not recommended based on the results of the KEYNOTE-062 study.[13] Among 763 patients with untreated, locally-advanced/unresectable or metastatic gastric/gastroesophageal junction cancer with CPS $\geq$ 1 for PD-L1 enrolled, pembrolizumab was noninferior to chemotherapy in terms of OS, which was the primary endpoint of the study (median: 10.6 versus 11.1 months; HR: 0.91; 95% CI: 0.69–1.18).[13] Pembrolizumab prolonged OS compared to chemotherapy in patients with CPS $\geq$ 10 (median: 17.4 versus 10.8 months; HR: 0.69; 95%CI: 0.49–0.97), but this difference was not statistically tested.

HER2

The addition of trastuzumab to chemotherapy is considered in patients with HER2-positive tumors, which are defined by 3+ immunohistochemistry (IHC) staining or 2+ and positive fluorescent in-situ hybridization (FISH). The addition of pembrolizumab to trastuzumab is also suggested, based on the phase-III KEYNOTE-811 study.[14]

The benefit of trastuzumab in advanced HER2-positive GC was addressed in the phase-III ToGA trial,[7] which compared standard chemotherapy (cisplatin plus infusional 5-FU or capecitabine) with or without trastuzumab. The objective response rate (ORR) and OS were higher with trastuzumab (47% versus 35%; 13.8 months versus 11.1 months; HR: 0.74; 95%CI: 0.60–0.91 respectively). An exploratory analysis of the subgroups defined by HER2 expression showed that trastuzumab was more effective in prolonging survival in individuals with 3+ IHC (HR: 0.66; 95%CI: 0.50–0.87) compared to patients with 2+ IHC (HR: 0.78; 95%CI: 0.55–1.10). The value of adding pembrolizumab to trastuzumab and chemotherapy was confirmed in the multicenter phase-III KEYNOTE-811 study,[14] in which 698 patients were randomized to receive pembrolizumab or placebo administered with trastuzumab plus platinum-containing cytotoxic chemotherapy. The ORR was significantly higher with pembrolizumab (73% versus 60%), as well as the rate of complete responses (17% versus 11%). A recently-published interim analysis[38] also demonstrated a significant increase in PFS, mainly in PD-L1-positive tumors (CPS $\geq$ 1), with a median PFS of 10.9 versus 7.3 months (HR: 0.71; 95%CI: 0.59–0.86).

The efficacy and safety of trastuzumab deruxtecan (T-Dxd), an antibody-drug conjugate, were evaluated in patients with HER2-positive GC whose disease progressed after the initial trastuzumab-based therapy.[15,16] In a non-randomized phase-II study (DESTINY-Gastric02),[16] T-Dxd demonstrated ORR of 42% as second-line therapy. In a randomized trial (DESTINY-Gastric01) evaluating patients whose disease had progressed after two previous therapies,[15] which included trastuzumab, fluoropyrimidines, and platins, the subjects were randomized to receive T-Dxd or chemotherapy, and there was an improvement in OS (13.0 months versus 8.0 months) and PFS (5.6 versus 3.5 months). Based on these data, T-Dxd was approved in the United States and Brazil for

Table 2 Ongoing phase-III clinical trials evaluating systemic therapy in advanced gastric cancer (clinicaltrials.gov)

Clinical setting	Study number (and/or name)	Intervention/Treatment
HER2		
First line	NCT05152147 (HERIZON-GEA-01)[39]	Trastuzumab, zanidatamab, tislelizumab, chemotherapy
Second line	NCT05427383	KN026, chemotherapy
Second line	NCT05002127 (ASPEN-06)	Evorpacept (ALX148), trastuzumab, ramucirumab, chemotherapy
Second line	NCT04704934 (DESTINY-Gastric04)	Trastuzumab deruxtecan, ramucirumab, chemotherapy
VEGFR		
First line	NCT05919381	Gentuximab, chemotherapy
Second line	NCT03081143 (RAMIRIS)	Ramucirumab, chemotherapy
Third line	NCT04879368 (INTEGRATE IIb)	Regorafenib, nivolumab, chemotherapy
FGFR2		
First line	NCT05052801 (FORTITUDE-101)	Bemarituzumab, chemotherapy
First line	NCT05111626 (FORTITUDE-102)	Bemarituzumab, nivolumab, chemotherapy
Anti-PD-1/PD-L1		
First line	NCT05918094	Sintilimab, chemotherapy
First line	NCT05008783	AK104, chemotherapy
First line	NCT05677490	Nivolumab, chemotherapy
First line	NCT05568095 (STAR-221)	Domvanalimab, zimberelimab, nivolumab, chemotherapy
Unselected population		
First line	NCT03801668	Chemotherapy (albumin-bound paclitaxel, oxaliplatin, S-1)

Abbreviations: FGFR2, fibroblast growth factor receptor 2; HER2, human epidermal receptor 2; NCT, National Clinical Trial; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; VEGFR, vascular endothelial growth factor receptor.

the treatment of cases of advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma that has experienced disease progression while on trastuzumab.

Regarding bispecific antibodies, zanidatamab, which targets 2 distinct HER2 epitopes, was evaluated in a phase-I study,[17] in which this monoclonal antibody was well tolerated and yielded long-lasting responses in pretreated GC patients. In a phase-II study,[18] an ORR of 79% was demonstrated with zanidatamab plus chemotherapy. Based on these findings, a phase-III study (HERIZON-GEA-01) (►**Table 2**) was designed to evaluate the efficacy and safety profile of zanidatamab plus chemotherapy with or without tislelizumab, an anti-PD-1 monoclonal immunoglobulin G4 antibody, versus the standard of care (trastuzumab plus chemotherapy) as a first-line treatment for patients with advanced/metastatic HER2-positive gastroesophageal adenocarcinomas (GEAs)[39].

dMMR/ MSI-H

In cases of dMMR/MSI-H GEA identified through immunohistochemistry, it is highly recommended that the patients receive immune checkpoint inhibition. The greater benefit of the combination therapy was suggested in a subgroup analysis of the CheckMate 649 trial,[8] since among 44 patients with dMMR/MSI-H tumors who were randomized to receive nivolumab plus chemotherapy, the median OS was of 38.7 months versus 12.3 months among the patients submitted to chemotherapy alone (HR: 0.38; 95%CI: 0.17-0.84), and the benefit was even greater in the subgroup of patients with CPS $\geq$ 5 and dMMR (median OS: 44.8 months versus 8.8 months; HR: 0.32).

As with the first-line therapy, the second-line therapy also aims to control symptoms and increase survival. For patients with dMMR/MSI-H GEA, pembrolizumab remains as an option if it has not been administered as the first-line therapy. It has been subsequently established[10] that immune checkpoint inhibition appears to benefit a subset of patients with dMMR tumors, regardless of the anatomical site of origin or tissue histology. Therefore, in 2017, the FDA approved pembrolizumab for the treatment of advanced solid tumors that harbor dMMR/MSI-H and have progressed after the first-line treatment (treatment-agnostic approval).

TMB

Between 5% and 19% of gastric adenocarcinomas have high levels of TMB, which represents the number of mutations per megabase (mut/Mb) harbored by tumor cells.[10] It appears to be an independent biomarker of benefit for immunotherapy if TMB $\geq$ 10 mut/Mb after progression while on standard regimens. In the phase-II KEYNOTE-158 study,[10] which enrolled 24 GC patients, there were 11 objective responses (45.8%), 4 of which were complete, and the median PFS was of 11 months.

Claudin 18.2

New diagnostic techniques have contributed to the characterization of the genetic profile of GC and to the identification of new potential molecular targets. Claudin 18.2, a component of intercellular junctions, is commonly expressed in multiple cancers, including GC, and is not expressed in any healthy tissues, apart from the gastric mucosa. Zolbetuximab, an experimental monoclonal antibody that targets claudin 18.2, was evaluated in combination with oxaliplatin-based chemotherapy in the SPOTLIGHT[19] and GLOW[20] trials and demonstrated an improvement in survival (18.2 versus 15.5 months; HR: 0.750; $p = 0.0053$; and 14.3 versus 12.1 months; HR: 0.771; $p = 0.0118$ respectively) in the population of patients with locally-advanced or unresectable, HER2-negative, treatment-naïve GC.

VEGF/VEGFR

Inhibition of the vascular endothelial growth factor (VEGF) receptor (VEGFR) reduces tumor growth and vascularization.[21] The benefit of bevacizumab (a monoclonal antibody that binds to soluble VEGF and prevents binding to VEGFR) for gastric adenocarcinomas and GEAs is uncertain. An improvement in survival after adding bevacizumab to capecitabine plus cisplatin could not be shown in the global phase-III AVAGAST trial.[22]

Ramucirumab is a recombinant monoclonal antibody that binds to VEGF receptor 2 (VEGFR2), blocking receptor activation. At least two trials, REGARD[23] e RAINBOW,[24] demonstrated an improvement in survival with the ramucirumab therapy, either as a monotherapy or in combination with paclitaxel in patients with previously-treated advanced GEA. Folinic acid, fluorouracil, and irinotecan (FOLFIRI) plus ramucirumab is a reasonable alternative to ramucirumab plus paclitaxel.[25] Additionally, results from the phase-III INTEGRATE IIa study[26] presented at the ASCO 2023 Gastrointestinal Cancers Symposium showed that regorafenib significantly improved OS (4.5 months versus 4.0 months; HR: 0.70; 95%CI: 0.53–0.92) in patients under later-line treatment for advanced GEA.

FGFR2

Different types of agents targeting fibroblast growth factor receptors (FGFRs) have been explored, however, without robust clinical evidence. Bemarituzumab has shown some promising results as the first-line treatment for metastatic GC. The phase-II FIGHT study[27] was designed to evaluate the efficacy of the bemarituzumab plus oxaliplatin-based chemotherapy regimen and demonstrated a 2-month improvement in PFS (9.5 months in the bemarituzumab group and 7.4 months in the placebo group; HR: 0.68; 95%CI: 0.44–1.04).

MET

Activation of the MET proto-oncogene pathway is associated with tumor invasiveness and poor disease prognosis. The anti-MET monoclonal antibody onartuzumab was studied in combination with FOLFOX versus placebo plus FOLFOX in metastatic HER2-negative GEA patients, and the addition of anti-MET did not improve the outcomes in the general population or in MET-positive patients identified by through immunohistochemistry.[28] Rilotumumab, a fully-humanized monoclonal antibody that neutralizes the hepatocyte growth factor (HGF), thus preventing MET activation, was also studied in association with chemotherapy in the same patient profile, and neither was it effective in improving results.[29–31]

TIGIT

The phase-III STAR-221 trial[40] evaluated the safety and efficacy of various combinations of anti-T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (anti-TIGIT; domvanalimab) and anti-PD-1 (zimberelimab) monoclonal antibodies in patients with unresectable or metastatic locally-advanced GEA (►**Table 2**). The combination of domvanalimab and zimberelimab with FOLFOX achieved an 80% ORR in patients with positive PD-L1 (tumor positivity area $\geq$ 5%).

NTRK Gene Fusions

Neurotrophic tropomyosin-related kinase (*NTRK*) gene fusions (*NTRK1*, *NTRK2*, and *NTRK3*) lead to the expression of constitutively-active chimeric tropomyosin receptor kinase (TRK) proteins (TRKA, TRKB, and TRKC), which act as potential oncogenic drivers across various types of tumors. In GC, *NTRK* fusions are exceedingly rare, but they may indicate an aggressive phenotype. Larotrectinib and entrectinib, both TRK inhibitors, have shown remarkable efficacy against *NTRK* fusion-positive tumors, regardless of tumor type ("tumor-agnostic").[33] In 2018, the FDA approved larotrectinib for the treatment of solid tumors with *NTRK* gene fusions in adult and pediatric patients, based on data from three multicenter clinical trials.[34] These trials treated 55 patients with metastatic or unresectable solid tumors harboring *NTRK* gene fusions, achieving a 75% ORR with a complete response rate of 22%.[34] In 2019, entrectinib received FDA approval for the same indications, supported by data from three clinical trials[35] involving 54 treated patients, demonstrating an ORR of 57% with a complete response rate of 7%. Both drugs have shown durable and clinically-significant responses with manageable safety profiles, making them recommended second-line or subsequent treatment options for patients with gastric tumors positive for *NTRK* gene fusions.

Unselected Population

Substantial advances have been made in the treatment of GC; however, more research is needed to optimize treatment

strategies. For patients with gastric adenocarcinoma who do not overexpress HER2 and are not candidates for immunotherapy (CPS < 5–low or absent PD-L1 expression), the choice should be a dual classic combination containing platinum and fluoropyrimidine (such as FOLFOX or CapOX).

Phase-III studies on second-line metastatic therapy showed that paclitaxel, docetaxel, and irinotecan increase OS in relation to clinical support, with similar results. One of these studies[36] included 202 patients and compared second-line chemotherapy (docetaxel or irinotecan) versus best supportive care. The median OS favored the chemotherapy arm (5.3 versus 3.8 months; HR: 0.65; $p = 0.007$), with no difference observed between docetaxel and irinotecan (OS of 5.2 versus 6.5 months; $p = 0.116$).[36]

The combination of trifluridine and tipiracil hydrochloride forms TAS-102, an oral agent that is an option for third-line or subsequent therapy in patients who maintain good performance status after undergoing treatment with two or more agents. The effectiveness of the regimen was suggested in the TAGS trial.[37] In this study with 507 heavily-pretreated GEA patients (more than 60% in each group had previously received 3 or more chemotherapy regimens), TAS-102 significantly improved OS relative to placebo (median: 5.7 versus 3.6 months) and was reasonably well tolerated.[37]

Perspectives

Gastric cancer is a markedly heterogeneous disease whose epidemiological, histological and molecular characteristics must be comprehensively understood for a successful therapeutic development. Novel therapeutic targets have been identified in the past few years, with several ongoing studies evaluating targeted therapies (►**Table 2**).

Precision medicine has gradually evolved, following advances in genomics, molecular biology and diagnostic technologies. It aims to offer more efficient and personalized treatment for patients, seeking to identify the therapeutic target and perform prognostic and predictive stratifications to achieve better survival results with minimal toxicity.

The fact that GC presents genetic variations among different patients and/or in the same patient during the course of the disease should drive investigations into the molecular characteristics present in the tumor tissue and evaluations of the use of circulating biomarkers to predict and monitor disease progression, as well as the response to treatment. Targeted therapies are considered one of the key points in new effective antitumor drug development, and they should be available to patient subgroups that could benefit from them.

Despite the advances in personalized medicine, Brazil still has many obstacles to the application of personalized treatment, such as difficulty in accessing laboratory tests and medications, as well as poor infrastructure. In summary, we expected that extensive research combined with clinical trials will lead to advances in the diagnosis and treatment of such a complex disease, hopefully, with significant improvements in the access of the population to the innovations that aim to increase survival and improve quality of life with minimal toxicity burden.

Author's Contributions
ETC, SJA, and AAJ: collection and assembly of data, conception and design, data analysis and interpretation, final approval of the manuscript, manuscript writing, and provision of study materials or patient.

Funding
The authors declare that they did not receive funding from agencies in the public, private or non-profit sectors to conduct the present study.

Clinical Trials
None.

Conflict of Interests
The authors have no conflict of interests to declare.

References

1 Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74(03): 229–263. Doi: 10.3322/caac.21834
2 de Oliveira Santos M, de Lima FCdS, Martins LFL, Oliveira JFP, de Almeida LM, de Camargo Cancela M. Estimativa de incidência de câncer no Brasil, 2023–2025. Rev Bras Cancerol 2023;69(1)
3 Lordick F, Carneiro F, Cascinu S, et al; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2022;33(10):1005–1020
4 Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer 1993;72; (01):37–41. Doi: 10.1002/1097-0142(19930701)72:1<37:aid-cncr2820720109>3.0.co;2-p
5 Moehler M, Eimermacher A, Siebler J, et al. Randomised phase II evaluation of irinotecan plus high-dose 5-fluorouracil and leucovorin (ILF) vs 5-fluorouracil, leucovorin, and etoposide (ELF) in untreated metastatic gastric cancer. Br J Cancer 2005;92(12): 2122–2128. Doi: 10.1038/sj.bjc.6602649
6 Network CGARCancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014;513(7517):202–209. Doi: 10.1038/nature13480
7 Bang Y-J, Van Cutsem E, Feyereislova A, et al; ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376(9742): 687–697
8 Janjigian YY, 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. Lancet 2021;398(10294):27–40
9 Rha SY, Oh DY, Yañez P, et al; KEYNOTE-859 investigators. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2023;24(11):1181–1195. Doi: 10.1016/S1470-2045(23)00515-6
10 Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol 2020;38(01):1–10. Doi: 10.1200/JCO.19.02105

11 Doki Y, Ajani JA, Kato K, et al; CheckMate 648 Trial Investigators. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. N Engl J Med 2022;386(05):449–462. Doi: 10.1056/NEJMoa2111380

12 Shah MA, Kennedy EB, Alarcon-Rozas AE, et al. Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer: ASCO Guideline. J Clin Oncol 2023;41(07):1470–1491. Doi: 10.1200/JCO.22.02331

13 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 Oncol 2020;6(10):1571–1580

14 Janjigian YY, Kawazoe A, Yañez P, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. Nature 2021;600(7890):727–730. Doi: 10.1038/s41586-021-04161-3

15 Shitara K, Bang YJ, Iwasa S, et al; DESTINY-Gastric01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. N Engl J Med 2020;382(25):2419–2430. Doi: 10.1056/NEJMoa2004413

16 Van Cutsem E, di Bartolomeo M, Smyth E, et al. Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal junction cancer with disease progression on or after a trastuzumab-containing regimen (DESTINY-Gastric02): primary and updated analyses from a single-arm, phase 2 study. Lancet Oncol 2023;24(07):744–756. Doi: 10.1016/S1470-2045(23)00215-2

17 Meric-Bernstam F, Hamilton EP, Beeram M, et al. Zanidatamab (ZW25) in HER2-expressing gastroesophageal adenocarcinoma (GEA): Results from a phase I study. J Clin Oncol 2021;39(3, suppl) 164

18 Elimova E, Ajani JA, Burris HA III, et al. Zanidatamab+ chemotherapy as first-line treatment for HER2-expressing metastatic gastroesophageal adenocarcinoma (mGEA). American Society of Clinical Oncology; 2023

19 Shitara K, Lordick F, Bang Y-J, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. Lancet 2023; 401(10389):1655–1668

20 Shah MA, Shitara K, Ajani JA, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nat Med 2023; 29(08):2133–2141

21 Lieto E, Ferraraccio F, Orditura M, et al. Expression of vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) is an independent prognostic indicator of worse outcome in gastric cancer patients. Ann Surg Oncol 2008;15(01): 69–79. Doi: 10.1245/s10434-007-9596-0

22 Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 2011;29(30):3968–3976. Doi: 10.1200/JCO.2011.36.2236

23 Fuchs CS, Tomasek J, Yong CJ, et al; REGARD Trial Investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383(9911):31–39. Doi: 10.1016/S0140-6736(13)61719-5

24 Wilke H, Muro K, Van Cutsem E, et al; RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15(11): 1224–1235. Doi: 10.1016/S1470-2045(14)70420-6

25 Lorenzen S, Thuss-Patience P, Pauligk C, et al. FOLFIRI plus ramucirumab versus paclitaxel plus ramucirumab as second-line therapy for patients with advanced or metastatic gastro-esophageal adenocarcinoma with or without prior docetaxel - results from the phase II RAMIRIS Study of the German Gastric Cancer Study Group at AIO. Eur J Cancer 2022;165:48–57

26 Pavlakis N, Shitara K, Sjoquist KM, et al. INTEGRATE IIa: A randomised, double-blind, phase III study of regorafenib versus placebo in refractory advanced gastro-oesophageal cancer (AGOC)—A study led by the Australasian Gastro-intestinal Trials Group (AGITG). American Society of Clinical Oncology; 2023

27 Wainberg ZA, Enzinger PC, Kang Y-K, et al. Bemarituzumab in patients with FGFR2b-selected gastric or gastro-oesophageal junction adenocarcinoma (FIGHT): a randomised, double-blind, placebo-controlled, phase 2 study. Lancet Oncol 2022;23(11): 1430–1440

28 Shah MA, Cho J-Y, Tan IB, et al. A randomized phase II study of FOLFOX with or without the MET inhibitor onartuzumab in advanced adenocarcinoma of the stomach and gastroesophageal junction. Oncologist 2016;21(09):1085–1090

29 Iveson T, Donehower RC, Davidenko I, et al. Rilotumumab in combination with epirubicin, cisplatin, and capecitabine as first-line treatment for gastric or oesophagogastric junction adenocarcinoma: an open-label, dose de-escalation phase 1b study and a double-blind, randomised phase 2 study. Lancet Oncol 2014;15(09):1007–1018. Doi: 10.1016/S1470-2045(14)70023-3

30 Malka D, François E, Penault-Llorca F, et al. FOLFOX alone or combined with rilotumumab or panitumumab as first-line treatment for patients with advanced gastroesophageal adenocarcinoma (PRODIGE 17-ACCORD 20-MEGA): a randomised, open-label, three-arm phase II trial. Eur J Cancer 2019;115:97–106

31 Catenacci DVT, Tebbutt NC, Davidenko I, et al. Rilotumumab plus epirubicin, cisplatin, and capecitabine as first-line therapy in advanced MET-positive gastric or gastro-oesophageal junction cancer (RILOMET-1): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18(11):1467–1482

32 Klempner SJ, Shitara K, Sison A, et al. STAR-221: A randomized, open-label, multicenter, phase 3 trial of domvanalimab, zimberelimab, and chemotherapy versus nivolumab and chemotherapy in previously untreated, locally advanced, unresectable or metastatic gastric, gastroesophageal junction, and esophageal adenocarcinoma. American Society of Clinical Oncology; 2023

33 Kim M, Seo AN. Molecular Pathology of Gastric Cancer. J Gastric Cancer 2022;22(04):273–305. Doi: 10.5230/jgc.2022.22.e35

34 Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378(08):731–739

35 Doebele RC, Drilon A, Paz-Ares L, et al; trial investigators. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21(02):271–282

36 Kang JH, Lee SI, Lim DH, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 2012;30(13):1513–1518. Doi: 10.1200/JCO.2011.39.4585 Erratum in: J Clin Oncol. 2012 Aug 20;30 (24):3035

37 Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2018;19(11):1437–1448

38 Janjigian YY, et al. "Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial.". Lancet (London, England) vol. 402,10418 (2023): 2197–2208 Doi: 10.1016/S0140-6736(23)02033-0

39 Tabernero J, et al. “HERIZON-GEA-01: Zanidatamab + chemo ± tislelizumab for 1L treatment of HER2-positive gastroesophageal adenocarcinoma.”. Future oncology (London, England) vol. 18,29 (2022): 3255–3266 Doi: 10.2217/fon-2022-0595

40 Janjigian YY, et al. EDGE-Gastric Arm A1: Phase 2 study of domvanalimab, zimberelimab, and FOLFOX in first-line (1L) advanced gastroesophageal cancer. JCO 41, 433248-433248(2023). Doi: 10.1200/JCO.2023.41.36_suppl.433248

