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REVIEW

Optimizing the Continuum of Care in Gastric Cancer

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Abstract: Gastric cancer (GC) still ranks as the fifth most common malignancy and the fourth leading cause of cancer-related death worldwide. Despite the recent progress in the therapeutic algorithm of the advanced disease with the advent of immune checkpoint inhibitors (ICIs) and next-generation HER2-directed therapies, survival rates remain poor, with a median survival hardly exceeding 12 months. Furthermore, only 40% of patients remain eligible for second- and later-line treatments due to the aggressiveness of the disease and the rapid deterioration of performance status (PS). Thus, current research is focusing either on the identification of novel treatment options or the development of personalized strategies to optimize the continuum of care and ultimately improve patients' outcome. In this article, we provide an overview of the current treatment landscape for advanced GC with a particular emphasis on later-line treatments and outline novel perspectives on the horizon.

Keywords: gastric cancer, gastroesophageal cancer, continuum of care, target therapies

Introduction

Over the Twentieth Century, a significant decrease in GC incidence and mortality has been observed thanks to better food preservation,[1] Helicobacter pylori eradication,[2] screening strategies in endemic areas[3,4] and the spread of the Mediterranean diet.[5,6] Nevertheless, GC still ranks as the fifth most common malignancy[7] and the fourth leading cause of cancer-related death worldwide,[8] mainly affecting men older than 60.[9] According to the ICBP SURVMARK-2 population-based study in 7 Western countries, more than half of patients with GC have a regional or distant disease at diagnosis, with proportions ranging between 56% and 90% across countries.[10] Furthermore, 40–50% of patients systemically relapse after radical surgery despite optimal multimodality management.[10]

Advanced gastric cancer (AGC) is one of the most aggressive cancer types, with a median overall survival (OS) of only 3 months in untreated patients.[11] Nowadays, chemotherapy represents the mainstay of palliative treatment for patients with AGC with the aim of prolonging OS, delaying disease progression and improving cancer-related symptoms.[12] Historical outcomes have been meager in this setting, apart from the minority subset of HER2-positive disease in which median OS (mOS) of 16 months has been reported in clinical trials with trastuzumab-based combinations.[13]

However, after decades of failures, the phase III CheckMate 649 is the first trial to overcome the barrier of 1 year in mOS for the vast proportion of HER2-negative AGC thanks to the addition of the anti-programmed cell death-1 (PD-1) nivolumab to platinum/fluoropyrimidine doublet.[14] Interestingly, other novel targets such as fibroblast growth factor receptor 2 (FGFR2b) and Claudin18.2 have been recently validated in first-line randomized phase III trials, thus further exploiting the emerging molecular segmentation of AGC.[15,16]

In parallel, the last few years have witnessed the advent of an expanding number of evidence-based options in the late-line setting, including the antiangiogenic agent ramucirumab, the new cytotoxics trifluridine/tipiracil and checkpoint

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inhibitors. Although only moderately active, these newly available compounds have significantly shown to prolong survival in second- and third-line trials depicting a continuum of care for AGC patients. Crucial to this concept are also a close tumour assessment for a prompt recognition of disease progression and the implementation of simultaneous care including the nutritional support early along patient's journey. As a result, a significantly higher proportion of patients go on to receive multiple lines of therapy and this treatment sequencing is favorably impacting the outcome leading to long-term survival in selected cases.

Notably, unprecedented results have been reported for the HER2-directed antibody-drug conjugated (ADC) trastuzumab deruxtecan (T-Dxd) in refractory patients with confirmatory randomized phase III trials data eagerly awaited.[17]

Here, we provide an overview of the current treatment landscape for AGC highlighting the most up-to-date evidence that is making the continuum of care a reality in this hard-to-treat cancer.

First-Line Setting

Combination chemotherapy has long been recognized as the standard-of-care for AGC with a platinum/fluoropyrimidine doublet being endorsed by international guidelines as the preferred first-line regimen for unresectable patients.[18] In 2008, the REAL-2 phase III trial proved that capecitabine-fluorouracil and oxaliplatin-cisplatin are equally effective in previously untreated esophagogastric cancer (HR 0.86, 95%CI 0.80–0.99 and HR 0.92, 95%CI 0.80–1.10, respectively).[19] Besides, the phase III GO2 study suggested that dose-reduced oxaliplatin-based chemotherapy (60% of standard doses of oxaliplatin 130 mg per square meter as per REAL-2 trial) is also feasible for elderly and/or frail patients, showing lesser toxicity and equivalent survival outcomes compared to conventional therapy.[20] Nonetheless, the current treatment armamentarium still provides a mOS ranging from 9 to 11 months and a 5-year OS of less than 10%. Furthermore, over the last two decades, several trials failed to identify viable targets in unselected AGC patients' populations,[21,22] with HER2-directed therapies being the only exception. We herein present the state of the art regarding first-line treatment. Table 1 will guide the reader through the major randomized phase III trials in this setting.

HER2-Negative Patients

Since the advent of checkpoint inhibitors has revolutionized the oncology arena, various chemo-immunotherapy combinations have been explored in AGC. The KEYNOTE-062 was the first global, randomized, phase III trial evaluating a ICI as a single agent or in combination with chemotherapy in HER2-negative AGC in the first-line setting.[30] In this study, pembrolizumab alone, chemotherapy alone (cisplatin plus fluoropyrimidine), or combined therapy was randomly assigned to 763 patients with previously untreated AGC or esophagogastric junction (EGJ) adenocarcinoma with a programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥1 (281 with a CPS ≥10). OS outcomes showed that, when compared to chemotherapy alone, pembrolizumab monotherapy was noninferior in the CPS ≥1 population (10.6 versus 11.1 months, HR 0.91, 99% CI 0.69–1.18) and was nonsuperior in combination with chemotherapy in both CPS ≥1 (12.5 versus 11.1 months, HR 0.85, 95% CI 0.70–1.03, p = 0.05) and ≥10 (12.3 versus 10.8 months, HR 0.85, 95% CI 0.62–1.17, p = 0 0.16) cohorts. Of note, it significantly improved mOS in the CPS ≥10 subgroup analysis (17.4 vs 10.8 months, HR 0.69, 95% CI 0.49–0.97), although this difference was not statistically tested.[30]

In contrast to the disappointing KEYNOTE-062, the CheckMate 649 trial recently reported practice-changing results for the front-line chemo-immunotherapy combination. In this multicenter phase III trial, 1581 patients with previously untreated, HER2-negative, AGC, EGJ, or esophageal adenocarcinoma (955 with CPS ≥ 5) were randomly assigned to receive nivolumab plus chemotherapy or chemotherapy alone (FOLFOX/XELOX).[14] Combined therapy was associated with a significantly better median progression-free survival (mPFS) and OS in all enrolled patients (mPFS 13.8 versus 11.6 months, HR 0.79, 95% CI 0.71–0.88, two-year survival 28 versus 19%). The primary endpoint of the study was met: patients with CPS ≥ 5, had a substantial gain in survival with the combinatory approach (mPFS 14.4 versus 11.1 months, HR 0.70, 95% CI 0.61–0.81, two-year OS 31% versus 19%). Nevertheless, in patients with CPS < 1 (mOS 13.1 versus 12.5 months, unstratified HR 0.95, 95% CI 0.73–1.24), <5 (mOS 12.4 versus 12.3 months, unstratified HR 0.94, 95% CI 0.79–1.11), or <10 (mOS 12.4 versus 12.5 months, HR 0.91, 95% CI 0.78–1.06) there was no survival advantage for nivolumab with chemotherapy compared to chemotherapy alone.[14] Based on these data, the Food and Drug

Table 1 Major Randomized Phase III Trials in the First-Line Setting

Target-therapy	Year	Pts (N)	Asian (%)	ESCC/GEJC (%)		Regimen	mOS (months)	Results	References
AVAGAST	2011	774	49%	13%		CF + Bevacizumab vs CF	12.1 vs 10.1	Neg	[21]
EXPAND	2013	904	38%	16%		CF + Cetuximab vs CF	9.4 vs 10.7	Neg	[22]
REAL-3	2013	553	/	70%		EOC + Panitumumab vs EOC	8.8 vs 11.3	Neg	[23]
RILOMET-1	2017	609	1%	31%		ECF + Rilotumumab vs ECF	8.8 vs 10.7	Neg	[24]
MET Gastric	2017	562	33%	23%		FOLFOX + Onartuzumab vs FOLFOX	11 vs 11.3	Neg	[25]
RAINFALL	2019	645	11%	25%		CF + Ramucirumab vs CF	11.2 vs 10.7	Neg	[26]
HER2-positive			**Asian (%)**	**ESCC/GEJC (%)**		**Regimen**	**mOS (months)**	**Results**	
TOGA	2010	594	52%	18%		CF + Trastu vs CF	13.8 vs 11.1	Pos	[13]
HELOISE	2017	248	30%	21%		CF + Trastu maintenance SoC (6 mg/kg) vs HD (10 mg/kg)	12.5 vs 10.6	Neg	[27]
LOGIC	2015	545	35%	12%		XELOX + Lapatinib vs XELOX	12.2 vs 10.5	Neg	[28]
JACOB	2018	780	47%	27%		Chemo + Trastu + Pertu vs Chemo + Trastu	17.5 vs 14.2	Neg	[29]
Immunotherapy			**Asian (%)**	**ESCC (%)**	**PD-L1**	**Regimen**	**mOS (months)**	**Results**	
KEYNOTE-062	2020	763	24%	31%	CPS ≥ 1	Pembro vs CF + Pembro vs CF	10.6 vs 12.5 vs 11.1	Neg	[30]
ChekMate 649	2021	1581	24%	30%	CPS ≥5	Chemo + Nivo vs Chemo	14.4 vs 11.1	Pos	[31]
						Nivo + Ipi vs Chemo	11.2 vs 11.6	Neg	
ORIENT-16	2021	650	100%	18%	CPS ≥5	XELOX + Sintilimab vs XELOX	18.4 vs 12.9	Pos	[32]
Javelin Gastric 100	2021	805	29%	23%	/	Maintenance Avelumab vs Chemo	10.4 vs 10.9	Neg	[33]
Combination Therapy			**Asian (%)**	**ESCC (%)**	**PD-L1**	**Regimen**	**mOS (months)**	**Results**	
INTEGA	2022	97	/	75%	CPS ≥1	Trastu+ Nivo + FOLFOX vs Trastu+ Nivo + Ipi	21.8 vs 16.4	Pos	[34]

Abbreviations: pts, patients; N, number; ESCC, esophageal squamous cell carcinoma; GEJC, gastroesophageal junction cancer; mOS, median overall survival; CF, cisplatin, 5-fluorouracil; vs, versus; neg, negative; EOC, epirubicin, oxaliplatin, capecitabine; ECF, epirubicin, cisplatin, 5-fluorouracil; FOLFOX, 5-fluorouracil, oxaliplatin; HER2, human epidermal growth factor receptor 2; Trastu, trastuzumab; pos, positive; SoC, standard of care; HD, high dose; XELOX, capecitabine, oxaliplatin; Chemo, chemotherapy; Pertu, pertuzumab; PD-L1, programmed cell death 1; CPS, combined positive score; Pembro, pembrplizumab; Nivo, nivolumab; Ipi, ipilimumab.

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Administration (FDA) approved nivolumab in combination with chemotherapy for metastatic gastric and EGJ cancer and esophageal adenocarcinoma irrespective of PD-L1 overexpression; whereas, the European Medicines Agency (EMA) restricted the approval only to patients with PD-L1 CPS ≥ 5.

Reasons of these disappointing data could be found in several factor.

First, the chemotherapy backbone was different in these two studies: in the KEYNOTE-062 a cisplatin-based backbone was used while in the CheckMate 649 was used as oxaliplatin backbone.

From some preclinical Oxaliplatin showed an induced immunogenic cell death by releasing tumor antigens, which led to the secretion of the danger-related molecules.[35]

On the other hand, cisplatin could down-regulate the activity of different immune cell subsets and immune phenotypes of tumor cells by enhancing antigen presentation and downregulating PD-L1 expression.[36]

In the two trials there were a different rate of histological diffuse type (40% in the KEYNOTE-062 and 29% in the CheckMate 649 trials), which could be an immune-resistant gastric cancer subtype.

Finally, rates of patients with GEJ adenocarcinomas were different (about 18% in the CheckMate 649 and about 33% in the KEYNOTE-062) and this different site could be less immunogenic.

The benefit of immuno-chemotherapy combinations has been assessed in two other studies. The first is the phase III KEYNOTE-590 trial, enrolling patients with previously untreated advanced/unresectable or metastatic esophageal adenocarcinoma, esophageal squamous cell carcinoma (SCC), or EGJ Siewert type 1 adenocarcinoma regardless of PD-L1 overexpression.[37] The OS benefit of pembrolizumab plus chemotherapy was seen in the overall population (6.3 months versus 5.8 months, HR 0.65, 95% CI 0.55–0.76), although the results were mainly driven by the CPS ≥ 10 SCC cohort (13.9 months versus 8.8 months, HR 0.57, 95% CI 0.43–0.75). While FDA-approved pembrolizumab in combination with chemotherapy in first-line treatment of metastatic or locally advanced esophageal or EGJ carcinoma (including adenocarcinoma) regardless of PD-L1 expression, EMA has restricted it to those with a PD-L1 CPS ≥ 10.

The second study is the randomized phase III ATTRACTION-4 trial, in which 724 Asian patients with HER2-negative advanced or recurrent gastric or EGJ adenocarcinoma were randomly assigned to chemotherapy (oxaliplatin plus either S-1 or capecitabine) plus placebo, or the same chemotherapy plus nivolumab.[38] When stratified according to PD-L1 overexpression, neither the PD-L1 expressors nor the PD-L1-negative patients had a survival benefit from the immune-chemotherapy combination. This trial used the tumor proportion score (TPS) instead of the CPS to designate the PD-L1 expression. W-811hile CPS represents the total number of PD-L1-positive cells (including tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells and multiplied by 100; TPS is the total number of PD-L1-positive tumor cells divided by the total number of viable tumor cells and multiplied by 100. Considering the results of the ATTRACTION-4 trial, TPS may not be as predictive as CPS in upper gastrointestinal tract adenocarcinomas. Furthermore, when analyzing the outcomes of immunotherapy-involving clinical trials, it should be considered that the PD-L1 parameter has some limitations: it is a dynamic marker that can change with local cytokines and the thresholds that separate "positive" and "negative" expression remains under debate.[39]

Beyond PD-L1, the status of mismatch repair (MMR) proteins/microsatellite instability (MSI) remains the most robust and validated biomarker predictive of immunotherapy response. To this end, the 50 patients with deficient MMR/high-MSI (dMMR/MSI-H) tumours and CPS ≥ 1 enrolled in the KEYNOTE-062 were included in a subgroup analysis. Compared to chemotherapy alone, combined therapy provided a significant benefit in OS (mOS not reached versus 8.5 months, 24-month survival 65 versus 26%) and PFS (mPFS not reached versus 6.6 months), and a twofold higher objective response rate (ORR) (65 versus 37%).[40] Furthermore, compared with chemotherapy alone, pembrolizumab monotherapy was also associated with a higher ORR (57 versus 37%), longer duration of response (21.2 versus 7 months), higher PFS (11.2 versus 6.6 months), and prolonged OS (mOS not reached versus 8.5 months, 12-month OS 79 versus 47%). Enhanced benefit for combined therapy among patients with dMMR/MSI-H tumours was also suggested in a subgroup analysis of the CheckMate 649 trial (mOS 38.7 versus 12.3 months, HR 0.38, 95% CI 0.17–0.84).[31]

HER2-Positive Patients

In the phase III ToGA trial, the combination of the anti-HER2 trastuzumab with standard first-line chemotherapy (six courses of cisplatin plus 5-fluorouracil) was assessed.[13] Immunohistochemistry (IHC) and fluorescence in situ

hybridization (FISH) were both used to determine the HER2 status of all tumors, and patients with IHC positive (IHC 3 +) or FISH positive tumors were eligible. At a median follow-up of 18 months, a significant increase in OS was found (13.8 versus 11.1 months, HR 0.74, 95% CI 0.60–0.91), and the ORR was greater with trastuzumab (47% versus 35%). Of note, the subgroup analysis showed that in patients with IHC 3+ tumors, trastuzumab was more effective (HR for death 0.66, 95% CI 0.50–0.87), with low efficacy in patients with IHC 2+ tumors (HR 0.78, 95% CI 0.55–1.10), and no activity in those with HER2 gene-amplified (FISH-positive) but non-protein-expressing (IHC 0 or 1+) tumors.[13] Therefore, platinum/fluoropyrimidine-based chemotherapy associated with trastuzumab represents the standard first-line therapy for HER2-positive (IHC 3+ and IHC 2+ with FISH positive) AGC.

Finally, the recent results on the use of immunotherapy in the HER2-positive setting should be mentioned. The safety and efficacy of combining pembrolizumab with first-line trastuzumab plus platinum-based chemotherapy were first shown in a single-arm open-label phase II trial of 37 previously untreated patients with HER2-positive esophageal, gastric, or EGJ cancer.[41] At a median follow-up of 13 months, 26 out of 37 patients (70%) did not progress after 6 months. Positive preliminary results were reported in the subsequent multicenter phase III KEYNOTE-811 study, in which 692 patients with HER2-positive AGC or EGJ adenocarcinoma were randomly assigned to pembrolizumab or placebo in association with trastuzumab plus chemotherapy.[42] In the interim analysis conducted after the first 264 patients (87% with PD-L1 CPS $\geq$ 1), the ORR was significantly higher in the experimental arm with the addition of pembrolizumab (74% versus 52%, complete responses 11% versus 3%). The median duration of response was 10.6 months with pembrolizumab versus 9.5 months, and more patients in the pembrolizumab group had an ongoing response of more than 6 months (70 versus 61%). Mostly based on this interim analysis, the FDA authorized the combination of pembrolizumab, trastuzumab, fluoropyrimidine, and platinum-based chemotherapy for treating patients with locally advanced or metastatic gastric or EGJ cancer who are ineligible for surgical resection or final chemoradiation. As of today, the Italian Drug Agency (AIFA) has not yet deliberated on the possible future indications of immunotherapy in AGC. However, similarly to EMA, we hope ICIs will be chosen in combination with chemotherapy in patients with high expression of PD-L1 (PD-L1 $\geq$5), regardless of HER2 status.

Second- and Later-Line Setting

Only in recent years, second-line therapy has become the standard of care for AGC progressing on or after platinum/fluoropyrimidine-based regimens due to the results of several randomized clinical trials[16,43–46] and a Cochrane review[47] showing improved OS and symptom control over best supportive care (BSC) alone. Convincing evidence from both clinical trials and real-world evidence has demonstrated that subsequent treatment favorably impacts on survival. Interestingly, post-progression survival has a stronger correlation with OS than PFS.

Of note, the uptake of sequential treatments has increased over time so that 40–60% of Western AGC remain candidate to further lines.[48–50] This is mainly the result of a rationale delivery of cytotoxics, more effective options, and early implementation of supportive measures.

In this section, we discuss more in detail the evolving field of second- and later-line treatment in AGC, highlighting the main drivers of treatment decision. In Table 2 major phase III trials in this setting are shown.

Chemotherapy

Second-Line monochemotherapy

Several randomized trials showed that monochemotherapy might be beneficial in selected patients compared to BSC alone. A German phase III trial[45] compared a 3-week schedule of irinotecan with BSC in patients who had a Eastern Cooperative Oncology Group (ECOG) PS of 0–2. Patients in this trial had received prior fluoropyrimidine/platinum combination and progressed during or within 6 months following first-line therapy. Due to poor accrual, the study terminated prematurely; however, a significantly longer mOS in the irinotecan arm than in the BSC arm was shown among 40 enrolled patients (4 versus 2.4 months, HR 0.48, p = 0.023).

Taxanes are well-recognized cytotoxics endowed with clinically meaningful antitumor activity in AGC. The randomized controlled COUGAR-02 study compared docetaxel and BSC in patients with a progression on a platinum plus fluoropyrimidine first-line regimen. In the docetaxel group, mOS was 5.2 months versus 3.6 months in the BSC group

Table 2 Major Randomized Phase III Trials in Second- and Later Lines Setting

Second-Line Setting								
	Year	**Pts (N)**	**Asian (%)**	**ESCC/GEJC (%)**	**Regimen**	**mOS (Months)**	**Results**	**References**
RAINBOW	2014	665	33%	20%	PTX + Ram	9.6 vs 7.4	Pos	[51]
REGARD	2013	355	16%	25%	Ram monotherapy	5.2 vs 3.8	Pos	[43]
Thuss-Patience et al	2011	40	na	43%	Irinotecan monotherapy	4 vs 2.4	Pos	[45]
COUGAR-02	2014	168	na	32%	Docetaxel	5.2 vs 3.6	Pos	[46]
KEYNOTE-158	2019	233	na	na	Pembrolizumab	11	Pos	[52,53]
Later lines setting								
			Asian (%)	**ESCC/GEJC (%)**	**Regimen**	**mOS (months)**	**Results**	
TAGS	2018	507	15%	29%	Trifluridine/tipiracil	5.7 vs 3.6	Pos	[54]
Jin Li et al	2016	267	100%	13%	Apatinib	6.5 vs 4.7	Pos	[55]

Abbreviations: pts, patients; N, number; ESCC, esophageal squamous cell carcinoma; GEJC, gastroesophageal junction cancer; mOS, median overall survival; PTX, paclitaxel; Ram, ramucirumab; pos, positive; na, not available.

(HR 0.67, p = 0.01). Despite docetaxel was associated with a higher incidence of grade 3–4 neutropenia and infections, patients in this group reported less pain and gastrointestinal symptoms (nausea/vomiting or constipation).[46]

When used in second-line treatment, some phase II trials showed the usefulness of three-weekly paclitaxel, which improved mOS and PFS in AGC patients who failed a prior line of chemotherapy.[56,57] A Japanese multicenter trial investigated the efficacy of biweekly paclitaxel in a cohort of AGC that received prior S-1-based treatment. Among the 41 patients enrolled, paclitaxel was administered at the dose of 140 mg/m2, intravenously on days 1 and 15 of a 28-day lasting cycle. The study showed a 70% disease control rate, mPFS was 111 days, and mOS was 254 days. Major adverse events (grade 3 or 4) were neutropenia (27.5%), anemia (12.5%), diarrhea (2.5%) and sensory neuropathy (2.5%).[58] Several phase II studies investigated the efficacy and safety of weekly paclitaxel at the dose of 70–80 mg/m2 h in AGC whose disease progressed after a platinum plus fluoropyrimidine (mostly S-1) or irinotecan first-line therapy.[59–62] The schedule had both a good safety profile and efficacy with a response rate (RR) of about 20%. Even though there are no comparison data between three-weekly paclitaxel, BSC and weekly regimen, this latter schedule seems to be more effective and tolerable in patients with poor PS in later lines of therapy. Due to the incidence of infusion-related reactions related to solvent-based paclitaxel, the efficacy and safety profile of nanoparticle albumin-bound paclitaxel (nab-paclitaxel), were investigated in a phase III trial.[63] In this study, the efficacy and safety of three-weekly or weekly nab-paclitaxel versus weekly solvent-based paclitaxel were compared and intravenous nab-paclitaxel (260 mg/m2 on day 1 of a 21-day cycle) was noninferior to weekly solvent-based paclitaxel in terms of mOS (10.3 months in the 3-weekly nab-paclitaxel group, 11.1 months in the weekly nab-paclitaxel group, and 10.9 months in the weekly solvent-based paclitaxel group). The most frequent grade 3–4 adverse event was neutropenia. The study suggested that nab-paclitaxel could be a reasonable choice in patients at risk of hypersensitivity reaction to taxanes.

Second-Line Polichemotherapy

Polichemotherapy, especially the combination of paclitaxel and ramucirumab, is considered the second-line standard of care in AGC. The randomized, placebo-controlled, phase III RAINBOW trial, enrolled patients with AGC or GEJ adenocarcinoma whose disease progressed on or within 4 months after first-line chemotherapy (platinum plus fluoropyrimidine with or without an anthracycline). They were randomly assigned to receive ramucirumab 8 mg/kg or placebo intravenously on days 1 and 15, plus paclitaxel 80 mg/m2 intravenously on days 1, 8, and 15 of a 28-days cycle. The

primary endpoint was OS. Efficacy analysis was by intention to treat (ITT). OS was longer in the ramucirumab plus paclitaxel group than in the placebo plus paclitaxel group (mOS 9.6 months versus 7.4, HR 0.807, p = 0.017). Grade 3 or higher adverse-events rate was more than 5% in the ramucirumab plus paclitaxel group and included neutropenia, hypertension, fatigue, anemia, and abdominal pain.[51] Besides, real-world data confirmed the efficacy and tolerability of this combination in unselected Western and Asian populations.[64–66] Altogether, these findings made paclitaxel and ramucirumab the gold standard second-line regimen, which should be considered for every fit patient.

Later-Line Chemotherapy

The TAGS study was a randomized, double-blind, placebo-controlled, phase III trial, which investigated the role of trifluridine/tipiracil in third-line therapy.[67] The trial enrolled patients with metastatic gastric adenocarcinoma (including adenocarcinoma of the GEJ) who progressed after at least two previous lines of therapy and randomized them to oral trifluridine/tipiracil (35 mg/m2 twice daily on days 1–5 and days 8–12 every 28 days) or placebo. mOS was 5.7 months in the trifluridine/tipiracil group and 3.6 months in the placebo group. Regarding the safety profile, an increase in hematological toxicity was reported (34% grade 3 neutropenia and 19% grade 3 anemia in the experimental drug versus 8% and 0% in the placebo arm). However, an early interruption of the treatment was reported in 13% of patients in the trifluridine/tipiracil group versus 17% of patients treated with placebo. The survival benefit was confirmed in subsequent subgroup analyses regardless of age and previous gastrectomy and was particularly evident in the third-line setting (mOS 6.8 months versus 3.2 months, HR 0.68, 95% CI 0.47–0.97), with also a significant benefit on time to deterioration of general conditions (4.8 months versus 2 months, HR 0.60, 95% CI 0.42–0.86).[54,68] The subsequent quality of life assessment by two different questionnaires (EORTC QLQC30 and QLQ-STO22) displayed interesting results:[69] no worsening was reported in the trifluridine/tipiracil cohort, with indeed a median time to deterioration in participants with ECOG PS > 2 of 4.3 months in the experimental group versus 2.3 months in the placebo group (HR 0.69, 95% CI 0.562–0.854) and maintenance of good PS (ECOG 0–1) in 74% of patients at the time of treatment discontinuation.[69] For these reasons, trifluridine/tipiracil should be considered the standard of care in the third-line setting for patients able to swallow pills.

Targeted Agents: Antiangiogenics

Ramucirumab is a fully human immunoglobulin IgG1 monoclonal antibody which targets vascular endothelial growth factor receptor 2 (VEGFR2). It showed improvement in OS when used in monotherapy in the phase III double-blind, placebo-controlled REGARD trial.[43] In this study, 355 patients whose disease progressed within 4 months on a fluoropyrimidine and platinum-containing first-line chemotherapy or within 6 months of completion of adjuvant therapy were randomized to ramucirumab 8 mg/kg intravenously every 2 weeks or placebo. mOS was 5.2 months in the ramucirumab group and 3.8 months in the placebo group (HR 0.776, p = 0.047). The survival benefit with ramucirumab was not related to other prognostic factors after a multivariable adjustment. The main adverse event was hypertension, which was higher in the ramucirumab group than in the placebo group (16% versus 8%). The mOS benefit was observed even in the sub-group of patients older than 65 years old, so this targeted therapy could be a good option for elderly patients not eligible for chemotherapy.

In a Japanese phase III trial, the VEGFR2 tyrosine kinase inhibitor apatinib showed a significant benefit in OS (6.5 versus 4.7 months) and PFS (2.6 versus 1.8 months) compared to placebo in patients with AGC and EGJ cancer who received at least two prior lines of treatment.[55]

It is worth mentioning that at the recent ASCO GI, preliminary data from the Integrate IIa phase III trial were presented.[70] After 238 events, mOS was 4.5 months for the anti-angiogenic tyrosine kinase inhibitor regorafenib and 4.0 months for placebo (HR 0.70, 95% CI 0.53–0.92, p = 0.011), with almost one out of five patients alive in the study cohort at 12 months (19% versus 6%).[70]

Second-Line Therapy After Taxane-Based Perioperative Treatment

It is worth to mention that about 13% of the participants in the FLOT4 trial discontinued peri-operative chemotherapy due to progression or lack of efficacy.[71] The correct approach to patients who progress on perioperative chemotherapy is yet to be defined and a schedule that does not contain a used drug is to be considered. Monotherapy with

ramucirumab could be a reasonable option, as it showed advantages even in the subgroup of patients who progressed during adjuvant or neoadjuvant therapy, with good tolerability, even in those with ECOG PS ≥ 1 or older than 65 years.[43]

In the phase II RAMIRIS trial, the combination of FOLFIRI and ramucirumab obtained an ORR of 25% in patients pretreated with docetaxel-based chemotherapy.[72] To conclude, ramucirumab alone or in combination with FOLFIRI, if feasible, could represent an effective treatment option in patients with early progression during perioperative strategies. Irinotecan alone could be an alternative option for those who have contraindications to antiangiogenic treatment.

Second-Line Immunotherapy

For dMMR/MSI-H AGC that never received immunotherapy in previous lines, pembrolizumab could be a good option, as suggested in the subgroup analysis of the phase II KEYNOTE-158 study (ORR 45.8%, mPFS 11 months, mOS and median duration of response not reached).[52] Furthermore, an exploratory subgroup analysis of the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 clinical trials suggested a benefit in MSI-H AGC that received pembrolizumab with or without chemotherapy in later lines.[40]

Role of Radiotherapy and Surgery in AGC

As seen above, AGC also needs local treatments to improve palliation of symptoms or to actively support patients through cycles of systemic therapy.

Radiotherapy

Radiotherapy could help reduce localized symptoms, such as bleeding, pain, and obstruction.[73] There are no clear data about the efficacy of increased radiation dose.[74] Furthermore, concomitant chemoradiotherapy could also lead to better symptom control.[75]

Surgery

Surgery could help symptoms control and its palliative role is recommended by principal guidelines[76,77] . Active role of surgery in terms of improved mOS was investigated in the phase III REGATTA trial that showed no benefit in AGC with a single non-curable factor, which underwent gastrectomy followed by systemic chemotherapy.[78] These data showed a clear futility in terms of survival for gastrectomy in patients treated with chemotherapy, therefore this approach is not considered in clinical practice. Another surgical approach that has no clear benefit in terms of survival in AGC patients is Hyperthermic Intraperitoneal Chemotherapy (HIPEC) combined with surgery in patients with peritoneal metastasis only.[79–81]

Active Supportive Care Measures

Supportive care is a crucial part in AGC management and a key step for the continuum of care optimization, as underlined by a recent phase III randomized controlled trial, in which early integration of interdisciplinary supportive care conferred a 3 months survival benefit compared to standard oncologic care (mOS 14.8 versus 11.9 months, HR 0.68, 95% CI 0.51–0.9, p = 0.021).[82] Optimal supportive care should include not only symptom palliation, but also nutritional support, since early skeletal muscle mass depletion has a negative prognostic impact during chemotherapy.[83,84] Hence, early nutritional screening and prompt oral, parenteral, or enteral support are necessary to improve anti-cancer treatment which should be administered to every fit patient tolerability, quality of life, and disease outcomes in actively treated patients.[18]

Weight loss is a multifactorial process and is caused by both disease- and chemotherapy-related symptoms. Gastrointestinal symptoms, such as dysphagia, dyspepsia, nausea, and vomiting, are often linked to mechanical obstruction and can be handled either with a medical or interventional approach. Anti-emetic agents like prokinetics, dopamine antagonists, antihistamines, anticholinergics, and serotonin antagonists, are mainstays in clinical practice.[85] Dexamethasone and octreotide are also widely used, especially in bowel obstruction.[85] Dysphagia due to proximal

masses might also be relieved through endoscopic stenting or palliative radiotherapy.[86] The choice between these two approaches should be aided by life expectancy since symptom relief is expected immediately with the first and within 4 to 6 weeks with the latter.[87] Finally, palliative surgery may be considered in cases of severe and conservatively unsolvable bowel obstruction in patients with adequate life expectancy.[88]

Chemotherapy-related anorexia and gastrointestinal symptoms are other common issues that could compromise access to active treatment. Low dose of daily olanzapine showed promising results in terms of weight gain and appetite improvement, which could help increase nutritional and PS.[89]

Finally, palliative care as defined by the World Health Organization (WHO) should also consider emotional and spiritual needs.[90] Early integration of professional psychological and spiritual support should therefore be offered to every AGC diagnosis.

New Treatment Options

HER2-Negative Patients

The therapeutic algorithm of locally advanced and metastatic GC has recently been enriched by ICIs, with nivolumab and pembrolizumab approved in mono- and combination therapy in first- and third-line settings. Considering the positive results in advanced and metastatic GC that pembrolizumab has obtained in the phase II and III KEYNOTE-059,[91] KEYNOTE-061[92] and KEYNOTE-062[30] trials, the randomized phase III KEYNOTE-859 study aims to strengthen the evidence that adding pembrolizumab to standard-of-care first-line chemotherapy improves survival in HER2-negative patients.[93] Other novel anti-PD-1 agents, such as sintilimab and tislelizumab, are under investigation. The randomized phase III ORIENT-16 trial is currently evaluating the efficacy of sintilimab plus chemotherapy in the first-line setting. Preliminary results in 650 patients with AGC showed superior OS in combination therapy regardless of PD-L1 expression (mOS 15.2 versus 12.3 months, HR 0.77, 95% CI 0.63–0.94, p = 0.0090), with better outcomes in patients with CPS ≥ 5%.[32] The randomized phase III BEIGENE-305 trial aims to compare the addition of tislelizumab to chemotherapy versus chemotherapy plus placebo in 997 patients with AGC[94] and results are awaited soon. Promising results might also be obtained from the combination of ICI with anti-VEGF therapies since pre-clinical and clinical data hint that concurrent blockade of VEGFR-2 and PD-1 or PD-L1 enhances antigen-specific T-cell migration and antitumor activity with favorable toxicity.[95] A phase I trial showed that adding anti-VEGFR-2 ramucirumab to anti-PD-1 pembrolizumab had a manageable safety profile and favorable antitumor activity in patients with previously treated AGC and other malignancies.[95] The combination of the PD-L1 inhibitor avelumab with paclitaxel and ramucirumab is currently under investigation in the single-arm phase II RAP trial.[96] Lenvatinib and regorafenib, both antiangiogenic and oncogenic receptors multikinase inhibitors, have been evaluated in addition to immunotherapy in East Asian populations. Lenvatinib plus pembrolizumab showed safe and promising antitumor activity (ORR 69%, 95% CI 49–85) as first- and second-line treatment.[97] A phase III clinical trial evaluating the efficacy of first-line pembrolizumab plus lenvatinib plus chemotherapy is currently ongoing.[98] The addition of regorafenib to nivolumab had also encouraging antitumor activity and a manageable safety profile in a phase I study.[99]

The identification of novel targetable biomarkers is also a crucial step in GC treatment development. Currently, the most promising targets are claudin 18.2 and FGFR2. Claudin 18.2 is a tight-junction protein confined to the gastric mucosa, whose epitopes are exposed on the cancer cell surface upon malignant transformation.[100] Claudin 18.2 positivity (defined as moderate-to-strong immunohistochemical staining in ≥75% of tumor cells) is found in 24–38% AGC patients.[101,102] Zolbetuximab, a chimeric monoclonal antibody that binds claudin 18.2, was well tolerated and exhibited antitumor activity both alone[103] and combined with chemotherapy in claudin 18.2 positive participants in the FAST phase II trial.[16] At the recent ASCO GI, primary results from the phase III SPOTLIGHT (zolbetuximab plus mFOLFOX6 versus placebo plus mFOLFOX6) were reported.[104] Both PFS and OS were improved with zolbetuximab + mFOLFOX6 vs mFOLFOX6 alone: mPFS 10.61 versus 8.67 months (HR 0.751, p = 0.0066) and mOS 18.23 versus 15.54 months (HR 0.750, p = 0.0053).[104]

The FIGHT phase II trial involved patients with FGFR2b overexpression (occurring in up to 60% of AGC cases) and demonstrated a benefit from the addition of the FGFR2b inhibitor bemarituzumab to mFOLFOX6,[15]

which led to the ongoing phase III trials FORTITUDE 101 (bemarituzumab + mFOLFOX6 versus placebo + mFOLFOX6) and FORTITUDE 102 (bemarituzumab + nivolumab + mFOLFOX6 versus nivolumab + mFOLFOX6) in previously untreated patients. Furthermore, in the second-line setting, the randomized K-Umbrella Gastric Cancer Study aimed to test optimal biomarker-driven targeted agent applications versus standard-of-care chemotherapy. Data presented at ASCO 2022 showed no benefit in the biomarker group over the control arm.[105]

Finally, given the encouraging results that the novel anti-Trop-2 ADC sacituzumab govitecan showed in the phase I/II IMMU-132-01 basket trial in various cancer cohorts, Trop-2 currently represents a viable target in solid tumours, including GC, regardless of their Trop-2 expression level.[106]

HER2-Positive Patients

Several preclinical and clinical analyses have suggested a synergistic activity between HER2-targeted treatments and ICI.[107] Based on the first interim analysis of the KEYNOTE-811 trial,[42] in May 2021 the FDA granted accelerated approval to the combination of pembrolizumab, trastuzumab and fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with advanced HER2-positive gastric or GEJ adenocarcinoma. This randomized phase III trial showed improvement of ORR by 22.7% (74.4% versus 51.9%) in the pembrolizumab arm compared to the placebo arm,[42] and data of PFS and OS are awaited soon.

Another compelling approach in HER2-targeted therapy of AGC is the use of T-Dxd, a second-generation ADC consisting of a humanized, monoclonal, anti-HER2 antibody bound to a cytotoxic topoisomerase I inhibitor. In the phase II DESTINY-Gastric01[17] trial, treatment with T-Dxd significantly improved OS (12,5 versus 8.4 months, HR 0.59, $p = 0.01$) with an impressing ORR (51% versus 14%, $p < 0.001$) compared with chemotherapy in third or later line eastern patients. Similar activity was confirmed also in a small group of Western patients in the phase II single arm Destiny-Gastric02 with an ORR of 39% in the second-line setting.[74]

Based on the results of these trials, T-Dxd recently gained FDA and EMA approval as monotherapy in HER2-positive patients who have received a prior trastuzumab-based regimen. The phase III DESTINY-Gastric04 trial is currently evaluating T-DXd compared with ramucirumab and paclitaxel in participants who have progressed on or after a trastuzumab-containing regimen and have not received any additional systemic therapy. The phase Ib/II clinical trial DESTINY-Gastric03 is also testing the efficacy of T-DXd in several combinations (chemotherapy and/or immunotherapy), with preliminary results showing tolerability and efficacy for the addition of fluoropyrimidine. Other HER2-ADC are RC48 (disitamab vedotin) and ARX788, which showed antitumor activity in phase I[108] and II[109] trials, and are currently being tested in phase III (NCT04714190 and ACE-Gastric-02).

Among monoclonal antibodies, margetuximab showed a synergistic effect in a single-arm, phase Ib/II trial with pembrolizumab[110] and is being further tested with anti-PD-1 retifanlimab and tebotelimab with or without chemotherapy in first-line setting.[111] There is also growing attention towards the HER2-targeted bispecific monoclonal antibodies ZW25 (zanidatamab) and KN026, which have proven safety and efficacy in early phase clinical trials.[112,113] Moreover, the CD47 inhibitor ALX148 (evorpacept) has obtained in 2020 fast track designations from FDA for the treatment of patients with gastric/GEJ adenocarcinoma based on an open-label, multicenter phase I clinical trial of ALX148 in combination with pembrolizumab or trastuzumab.[108] A phase II/III study to test evorpacept in combination with trastuzumab, ramucirumab, and paclitaxel in second- or third-line setting is ongoing (ASPEN-06).

Besides monoclonal antibodies, tucatinib, a highly selective HER2-directed tyrosine kinase inhibitor (TKI) widely approved for HER2-positive metastatic breast cancer, is being evaluated in the MOUNTAINEER-02 phase II/III study in addition to trastuzumab, ramucirumab and paclitaxel in HER2-positive GC in the second-line setting.[114]

Finally, future strategies might also involve vaccination against Her-2/neu[115] and cellular therapy, for example CT-0508[116] and CYNK-101, which lately received FDA fast-track designation.

Conclusion

Despite the recent progresses in the therapeutic algorithm of the advanced disease and the advent of target therapies and ICIs, much work still needs to be done to improve AGC patients' survival and quality of life. Our efforts need to

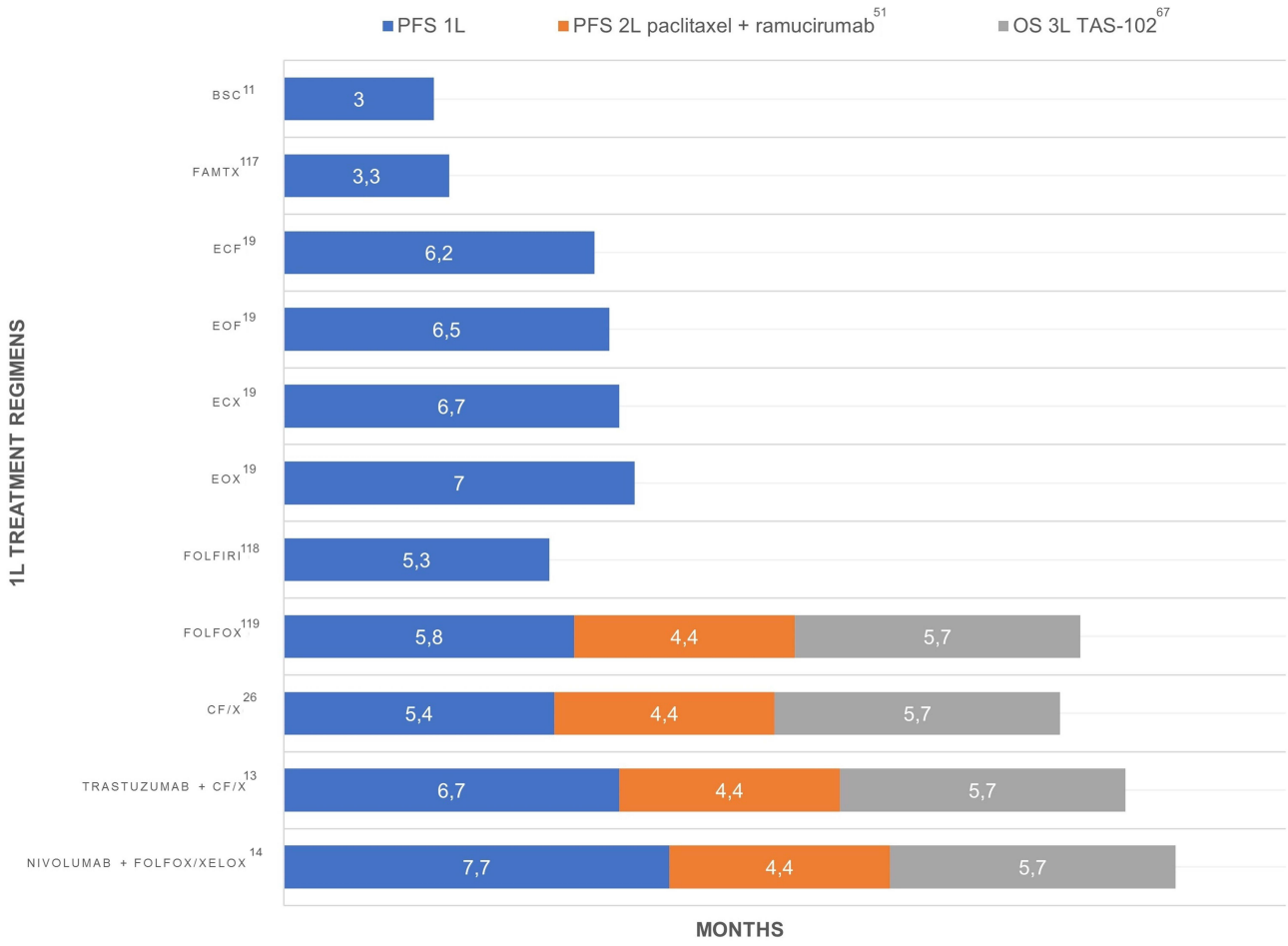

Figure 1 Best conceivable median overall survival from the start of first-line treatment.
Abbreviations: PFS, progression free survival; 1L, first line; 2L, second line; OS, overall survival; 3L, third line; BSC, best supportive care; FAMTX, fluorouracil, doxorubicin, methotrexate; ECF, epirubicin, cisplatin, 5-fluorouracil; EOF, epirubicin, oxaliplatin, 5-fluorouracil; ECX, epirubicin, cisplatin, capecitabine; EOX, epirubicin, oxaliplatin, capecitabine; FOLFIRI, 5-fluorouracil, irinotecan; FOLFOX, 5-fluorouracil; CF/X, cisplatin, 5-fluorouracil/capecitabine; XELOX, capecitabine, oxaliplatin.

concentrate on raising the bar beyond the 18 months of median survival (Figure 1). Currently, less than a half of patients who receive first-line therapy manage to receive effective second-line treatment. Thus, current and future research should focus not only on the identification of new treatment options, but also on the implementation of patient selection. A particular attention should be put on the detection of new clinicopathological prognostic and predictive biomarkers.

Table 3 Selected Ongoing Clinical Trials in AGC

Therapy Line	Agent	Trial	Study Design	Phase	Status	Estimated Study Completion date
HER2-NEGATIVE						
ICI						
I	Pembrolizumab	KEYNOTE-859 (NCT03675737)	Pembro + Chemo vs Placebo + Chemo	III	Active, not recruiting	Sep 28, 2024
I	Sintilimab	Orient-16 (NCT03745170)	Sintilimab + Chemo vs Placebo + Chemo	III	Active, not recruiting	Dec 31, 2022

(*Continued*)

Table 3 (Continued).

Therapy Line	Agent	Trial	Study Design	Phase	Status	Estimated Study Completion date
1	Tislelizumab	Beigene-305 (NCT03777657)	Tislelizumab + Chemo vs Placebo + Chemo	III	Active, not recruiting	Sep 2023
Combination of ICI and anti-VEGF						
2	Avelumab	RAP (NCT03966118)	Avelumab + Ram + PTX	II	Recruiting	Sep 2023
2	Pembrolizumab + Lenvatinib	LEAP-015 (NCT04662710)	Lenvatinib + Pembro + Chemo vs Chemo	III	Recruiting	Feb 2, 2026
2	Regorafenib + Nivolumab	INTEGRATEIIb (NCT04879368)	Regorafenib + Nivo vs Chemo	III	Recruiting	Jun 1, 2026
Other targets						
1	Zolbetuximab	SPOTLIGHT (NCT03504397)	Zolbetuximab + mFOLFOX6 vs Placebo + mFOLFOX6 in Claudin 18.2 positive pts	III	Active, not recruiting	Jan 31, 2025
1	Zolbetuximab	GLOW (NCT03653507)	Zolbetuximab + CAPOX vs Placebo + CAPOX in Claudin 18.2 positive pts	III	Active, not recruiting	Aug 31, 2024
1	Zolbetuximab	ILUSTRO (NCT03505320)	Zolbetuximab alone vs + Chemo vs + Pembro vs + Chemo and Nivo in Claudin 18.2 positive pts	II	Recruiting	Jul 31, 2024
1	Bemarituzumab	FORTITUDE-101 (NCT05052801)	Bemarituzumab + Chemo vs Placebo + Chemo in FGFR2b overexpressed pts	III	Recruiting	Aug 18, 2025
1	Bemarituzumab	FORTITUDE-102 (NCT05111626)	Bemarituzumab + Chemo + Nivo vs Chemo + Nivo in FGFR2b overexpressed pts	III	Recruiting	May 11, 2026
HER2-POSITIVE						
HER2 blockade						
2	T-DXd	DESTINY-Gastric04 (NCT04704934)	T-DXd vs Ram + PTX	III	Recruiting	Nov 15, 2024
2	Tucatinib	MOUNTAINEER-02 (NCT04499924)	Tucatinib + Tmab + Ram + PTX vs Ram + PTX	II/III	Recruiting	Mar 31, 2027
Combination of ICI and HER2 blockade						
1	Durvalumab + T-DXd	DESTINY-Gastric03 (NCT04379596)	T-DXd mono and combinations (Chemo and/or ICI)	Ib/II	Recruiting	Dec 31, 2024
1	Pembro + Tmab	KEYNOTE-811 (NCT03615326)	Pembro + Tmab + Chemo vs Placebo + Tmab + Chemo	III	Active, not recruiting	Dec 30, 2024
1	Retifanlimab + Tebotelimab + Margetuximab	MAHOGANY (NCT04082364)	Margetuximab, Ratifanlimab, Tebotelimab ± Chemo	II/III	Active, not recruiting	Dec 2023

Abbreviations: HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; Pembro, pembrolizumab; Chemo, chemotherapy; VEGF, vascular endothelial growth factor; Ram, ramucirumab; PTX, paclitaxel; Nivo, nivolumab; mFOLFOX6, 5-fluorouracil, oxaliplatin; pts, patients; CAPOX, capecitabine, oxaliplatin; FGFR2b, fibroblast growth factor receptor 2b; T-DXd, trastuzumab deruxtecan; Tmab, trastuzumab.

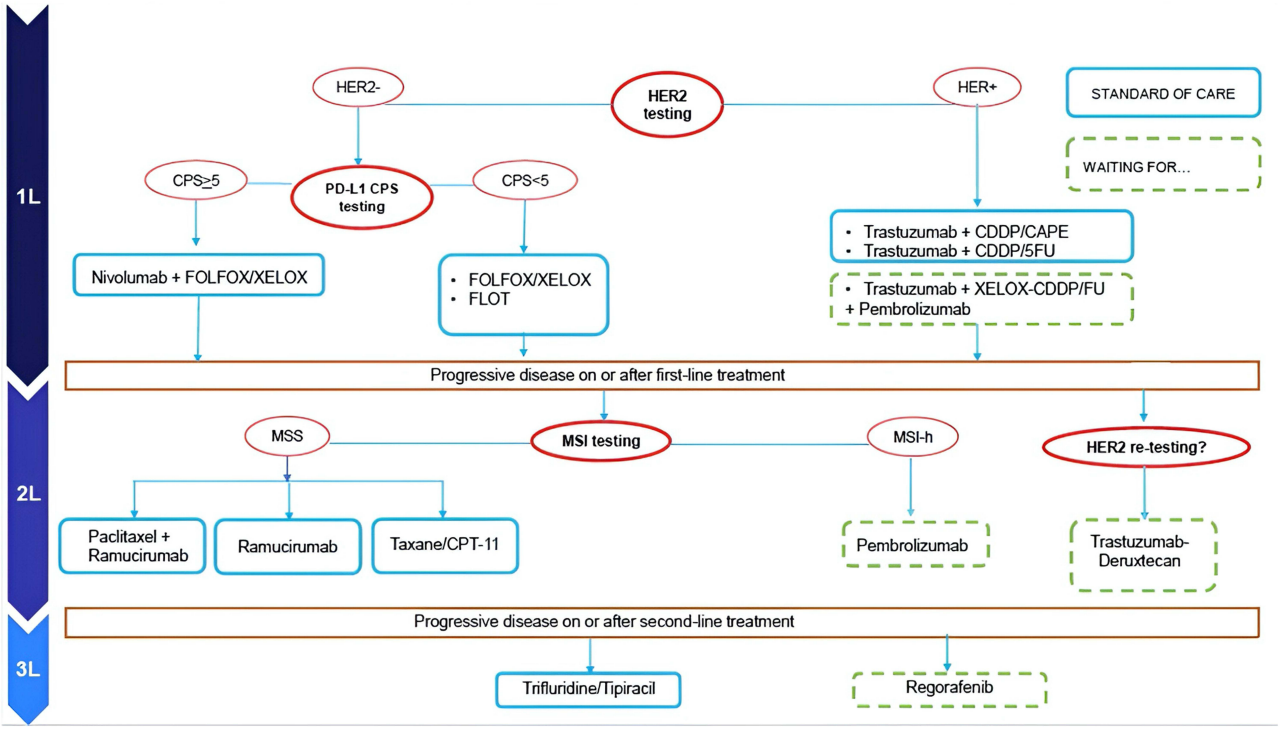

Figure 2 The evolving standard of care for advanced gastric cancer in Western Countries.
Abbreviations: HER2, human epidermal growth factor receptor 2; PD-L1 programmed cell death ligand 1; CPS, combined positive score; FOLFOX, 5-fluorouracil, oxaliplatin; XELOX, capecitabine, oxaliplatin; FLOT, fluorouracil, oxaliplatin, docetaxel; CDDP, cisplatin; cape, capecitabine; 5FU, 5-fluorouracil; MSI, microsatellite instability; MSS, microsatellite stable; MSI-h, MSI high; CPT-11, irinotecan.

Furthermore, considering the strong impact that sarcopenia has on prognosis and chemotherapy tolerance and efficacy, efficient collaboration between oncologists and clinical nutritionists should be emphasized to reduce the percentage of malnourished patients that still receive inadequate nutritional support.

Several clinical trials are ongoing and aim at strengthening and widening the current treatment armamentarium (Table 3). We developed a new treatment algorithm that will be implemented based on the results of the upcoming clinical trials (Figure 2).

Abbreviations

GC, gastric cancer; ICIs, immune checkpoint inhibitors; PS, performance status; AGC, advanced gastric cancer; OS, overall survival; mOS, median overall survival; PD-1, programmed cell death 1; FGFR2, fibroblast growth factor receptor 2; ADC, antibody drug conjugate; T-Dxd, trastuzumab deruxtecan; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; ORR, objective response rate; EGJ, esophagogastric junction; PD-L1, programmed cell death ligand 1; CPS, combined positive score; mPFS, median progression-free survival; FDA, Food and Drug Administration; EMA, European Medicines Agency; SCC, squamous cell carcinoma; TPS, tumor proportion score; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, High-microsatellite instability; AIFA, Agenzia Italiana del Farmaco; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; RR, response rate; VEGFR-2, vascular endothelial growth factor receptor 2; ITT, intention to treat; TKI, tyrosine kinase inhibitor.

Data Sharing Statement

All data supporting the results reported in the manuscript can be found in https://pubmed.ncbi.nlm.nih.gov

Consent for publication

The details of any images can be published, and the authors provide consent the article contents to be published.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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