Cancer Treatment Reviews 79 (2019) 101889

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Tumour Review

# Gastric cancer: Translating novels concepts into clinical practice

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ARTICLE INFO

*Keywords:*
Gastric cancer
Genomic tumour profiling
Immunotherapy
Targeted therapy
Biomarkers
Liquid biopsy

ABSTRACT

The overall 5-year survival of gastric cancer (GC) has change only little in the last decades and it remains the fifth leading cause of cancer-related death worldwide. However, in the past few years a more effective combination chemotherapy has raised the bar of curability of about 10% in resectable disease. Morever, a deeper knowledge of GC biology have unveiled biomarkers to help personalize adjunctive treatments in patients candidate to surgery. Despite a plateau in efficacy of fist-line treatment, incremental survival advantages have been recorded in unresectable advanced disease. The growing number of effective drugs in second and later lines along with a more judicious delivery of cytotoxics and early supportive interventions have enabled more patients to proceed beyond first-line. The continuum of care has become a reality in a considerable proportion of patients that offer opportunities to improve outcomes. Finally, the advent of the immune checkpoint inhibitors has brought great expectations in molecularly-defined subset of patients. This Review summarizes the state-of-the art in the management of GC together with novel concepts that have entered clinical development with the potential of change practice in the foreseeable future.

## Background

Gastric cancer (GC) remains a considerable health burden as it ranks as the sixth most common cancer and the fifth leading cause of cancer-related death worldwide [1]. In fact, despite a steadily decline in incidence overall, gastroesophageal junction cancers and cases in young-adults are on the rise, particularly in developed countries [2].

A multimodality treatment including surgical resection represents the only potentially curative standard of care for resectable T2–T4 and/or nodal-positive disease [3].

Nonetheless, 40% to 60% of resected patients eventually relapse and two-thirds of cases still present with de novo unresectable advanced disease [4,5]. In this setting, a systemic treatment consisting of platinum/fluoropyrimidine-based chemotherapy is the global standard of care with median overall survival (mOS) of 9–11 months in HER-2 negative disease [6], which extends to 14–16 months when trastuzumab is added to backbone chemotherapy in HER-2 positive cases [7].

After almost a decade of stagnation in survival, serial incremental advances are lately reshaping standards of care and treatment strategies in GC.

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https://doi.org/10.1016/j.ctrv.2019.101889
Received 17 June 2019; Received in revised form 10 August 2019; Accepted 12 August 2019

While adjuvant treatment intensification with combination regimens [8,9] and/or radiotherapy [10,11] has failed to provide an advantage in resectable disease, the fine-tuning of perioperative chemotherapy has been successful resulting in FLOT (5-fluorouracil, oxaliplatin, docetaxel) as the new reference regimen [12]. In addition, emerging biomarkers have been proposed that can refine treatment selection after surgery towards the goal of personalized medicine [13,14].

Conversely, the efficacy of combination chemotherapy has clearly plateaued in the first-line setting. However, an increasing number of "old" and "new" agents has proved effective and are expanding treatment options in second- and later lines. Among them are the anti-VEGFR2 monoclonal antibody ramucirumab [15,16], immune checkpoint inhibitors (ICIs) [17,18] and the oral cytotoxic trifluridine/tipiracil (also known as TAS-102) [19]. In parallel, a better delivery of systemic treatment and the implementation of simultaneous care have enabled more patients to preserve good general conditions across multiple lines of therapy. There is now convincing evidence that the administration of sequential treatments can improve patients' outcome thus supporting for the first time a continuum of care strategy in GC [20]. While the search for novel predictive biomarkers is actively pursued, MSI-h and EBV-positive tumours appear as the more likely to benefit from an immunotherapeutic approach.

In this article, we review major and most up-to-date clinical trials establishing the current standard management of GC along with new emerging concepts with the potential of personalizing and improving patients' outcome in the next future.

## Resectable disease

### *Standard management*

The historical high recurrence rates after curative-intent surgery alone with 5-year OS ranging from 23 to 49% highlighted the need for adjunctive treatment modalities in potentially resectable GC [21]. Perioperative chemotherapy, adjuvant chemotherapy and adjuvant chemoradiotherapy have been all evaluated over the years to improve survival. Of note, there is no widely accepted standard management in this setting and the best practice varies across different geographical regions [3].

The UK Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) represented the first practice-changing trial demonstrating the superiority of a multimodality strategy over surgery alone. Perioperative ECF produced a significant improvement in 5-year overall survival from 23% to 36% (HR 0.75; P = 0.009) [22]. Based on these results, a chemotherapy triplet consisting of a platinum compound, a fluoropyrimidine and epirubicin has been the perioperative reference regimen for a decade, though a superimposable survival gain was achieved in the ACCORD-07/FFCD 9703 trial without the anthracycline (from 24% to 38%, HR, 0.69; P = 0.02) [23].

Recently the docetaxel-based triplet FLOT (5-FU, folinic acid, oxaliplatin, docetaxel) outperformed the anthracycline-based regimen in the randomised phase II/III AIO-FLOT4 trial [12].

In this phase III study, 716 patients with stage IB-III GC and GEA (type I-III) were randomly allocated to either standard six cycles of perioperative ECF/ECX (epirubicin, cisplatin, capecitabine) or eight cycles of peri-operative FLOT. The latter resulted in a significantly higher proportion of patients achieving pathological complete regression (16% vs 6%, P = 0.02) and R0 resection than ECF/ECX (84% vs 77%, P = 0.01). More interestingly, FLOT prolonged OS compared to ECF/ECX, with an increase in median OS from 35 to 50 months (P = 0.012) which translated into 9% increase in projected 3-year OS (48% vs 57%). Notably, FLOT chemotherapy did not increase surgical morbidity nor mortality and demonstrated an acceptable safety profile. The report of grade 3–4 adverse events was consistent with the literature. Moreover, FLOT caused less nausea and vomiting (9% vs 24%), thromboembolic events (3% vs 6%) and anaemia (3% vs 6%) than ECF/ECX, though it more commonly resulted in neutropenia (51% vs 39%), infections (18% vs 9%) and diarrhoea (10% vs 4%). No primary prophylaxis with G-CSF was administered in the AIO-FLOT4 study. Importantly, patients treated with FLOT were more likely to start (60% FLOT vs 52% ECF/ECX) and complete (46% FLOT vs 37% ECF/ECX) the planned post-operative chemotherapy. Following these results, FLOT has become the new perioperative standard of care for patients deemed suitable for a triplet regimen, while platinum/fluoropyrimidine doublet is preferred for those not fit for the three-drug regimen.

Regarding post-operative approach, two individual patient-level meta-analyses of all randomised controlled trials reported a 15–18% reduction in the relative risk of death [24,25], resulting in an absolute improvement of about 6% in OS after 5 years for fluoropyrimidine-based adjuvant chemotherapy over surgery alone. It is worth mentioning that all Western trials failed to show a clear survival benefit for post-operative chemotherapy and these meta-analysis results are inflated by Asian studies. Notable trials from East Asia include the ACTS-GC and CLASSIC trials. The ACTS-GC evaluate S1 (for 1 year) versus surgery alone in 1059 patients with resected stage II or III gastric cancer. Five-year OS was improved from 61.1% to 71.7% (HR 0.67; 95% CI 0.54–0.83)[26]. The CLASSIC study randomized 1053 patient to receive oral capecitabine combined to oxaliplatin (XELOX for 6 months) versus surgery alone with an OS benefit for adjuvant chemotherapy from 69% vs 78% (HR 0.66; 95% CI 0.51–0.85) [27].This results led to the adoption of adjuvant S1 and XELOX as standard treatment in East Asia. Indeed, taking into account the different patient population, the adjuvant treatment has had a bigger impact in the East Asian population than in the Western counterpart. Finally, an intensive sequential chemotherapy regimen failed to improved survival against FU alone in the Western population [9].

From a practical perspective the question is whether the adjuvant therapy would be led to the same benefit as a perioperative regimen. A recent network meta-analysis established that taxane-containing perioperative chemotherapy is the most effective treatment compared to surgical alone [28]. However, when no neoadjuvant therapy has been given, an oxaliplatin-fluoropyrimidine doublet is the most promising adjuvant treatment after curative resection, although the use of adjuvant oxaliplatin has to be further verified in Western gastric cancer patients. On the other hand, the long-standing succesful experience and the greater benefit compared to adjuvant chemotherapy (absolute 5-year OS benefit of 9–14% vs 5.7%), have made perioperative chemotherapy the most adopted standard of care throughout Europe

Adjuvant chemoradiotherapy for resected gastric cancer is a widely adopted approach in the US on the basis of the results of the INT-0116 trial [29]. The three-year survival rates were 50% in the chemoradiotherapy group and 41% in the surgery-only group (P = 0.005); this survival benefit was maintained in more than 10-year median follow-up with improved relapse-free survival (P = 0.001) and overall survival (P = 0.0046)[30]. Several limitations including low-quality surgery with 54% of patients receiving less than a D1 dissection, old-fashioned technology and high toxicity rates, have hindered the widespread adoption of this approach outside North America. In addition, both the Korean ARTIST trial and the Dutch CRITICS trial failed to show an improvement in OS for adjuvant chemoradiotherapy compared to chemotherapy after D2 or > D1 dissection [10,11]. On this basis, it can be stated that chemoradiotherapy is not for all comers. Instead, it should be offered to patients who underwent suboptimal surgery and/or have a R-positive disease. To this end, interim results of a phase III trial ARTIST2 trial have been reported that show no difference in DFS between SOX and SOXRT was found (HR 0.910, P = 0.667) in patients with D2-resected, node-positive, stage II or III GC, to compare adjuvant chemotherapy versus chemoradiotherapy.

*Evolving concepts*

*Towards risk-adapted and personalised treatment strategies*

Latest results from clinical trials in the West reported still unsatisfying long-term outcomes after combined treatment approach, with estimated 5-year OS < 50%. Moreover, despite the improvement in adherence to post-operative treatment seen in the AIO-FLOT4 trial, most patients do not receive all the scheduled adjuvant chemotherapy. On the other hand, 5-year OS in the Asian CLASSIC trial was 69% in the surgery-only group, suggesting that a remarkable proportion of patients is cured by surgery alone and thereby might be unnecessarily over-treated with adjuvant chemotherapy. Hence, there exists an unmet need for a better risk-stratification of patients with resectable GC, in order to select those deemed to derive the greatest benefit from treatment and to spare toxicities to the remainders.

Ongoing endeavors are particularly heading to improve survival of patients at higher risk of relapse following surgery. Among them are those showing unfavorable clinicopathological features. In a retrospective translational study performed on MAGIC tissue material, lymph node status but not the pathologic response to chemotherapy was the only independent predictor of survival after chemotherapy plus resection [31]. Of interest, patients experiencing a poor pathological response to chemotherapy (TRG 3–4–5 according to Mandard system) and without lymph nodes metastases (ypN0) had similar survival to those who had an excellent pathological response (TRG 1–2 according to Mandard system) with no metastatic lymph nodes involvement (ypN0). This observation prompted a risk-adapted strategy currently under investigation in the EORTC VESTIGE trial (ClinicalTrials.gov Identifier: NCT03443856): randomisation to continue chemotherapy or switch to ipilimumab plus nivolumab as adjuvant component of a perioperative approach in node-positive or R1 resected GC.

The improved knowledge of GC biology has culminated in The Cancer Genome Atlas Research network classification with the identification of four distinct molecular subtypes of GC that may represent a platform to guide individualized treatment decision. To this end, mismatch repair deficiency (dMMR) and microsatellite instability (MSI)-high status have been demonstrated to be positively prognostic for survival in patients treated with surgery alone, whilst they were negative predictors in patients treated with perioperative chemotherapy [32]. Similar findings were replicated in a translational study of the Asian CLASSIC trial, showing that the benefit of adjuvant XELOX was confirmed only among MSI stable tumours [33].

A multinational individual patient data meta-analysis gathering together 1.552 patients with available MSI status from MAGIC, CLASSIC, ITACA-S and ARTIST trials were recently reported [34]. In MSI versus microsatellite stable (MSS) subgroups, 5-year DFS was 71.8% versus 52.3% (HR = 0.50, 95% CI 0.35–0.72; p < 0.001) and 5-year OS was 77.4% versus 59.2% (HR = 0.50, 95% CI 0.34-0-74; p < 0.001). The predictive role of MSI according to treatment received was assessed overall and in the 2 randomized controlled trials with a surgery alone arm (MAGIC and CLASSIC). In the MSS subgroups, 5-year OS was 62% vs 53% in patients treated with chemotherapy versus surgery alone, respectively; while in MSI 5-year OS was 63% vs 83% in those treated with chemotherapy compared to surgery only. Consequently, MSI has emerged as a predictive biomarker with the potential of improving treatment selection. This, together with the well-described sensitivity of MSI-high tumours to immune checkpoint inhibitors, paves the way for novel strategies investigating chemotherapy omission and/or immune checkpoint blockade in MSI-high GCs.

Remarkably, tumour genomic profiling is being increasingly applied to GC and it is showing a role in prognostication. A seven-gene signature (i.e. CDH1, ELOVL5, EGFR, PIP5K1B, FGF1, CD44v8 and TBCEL) was developed in 84 GC patients treated with neoadjuvant chemotherapy that identified a high- and low-risk group with a median OS of 10.2 and 80.9 months (P < 0.0001), respectively [14]. The risk groups turned out to be an independent predictor of OS and remained predictive even after controlling for lymph node status, that is the best-established prognostic factor in patients treated with perioperative chemotherapy. These findings were independently validated in an external cohort. The signature and associated assay have been proposed as a helpful tool for risk-stratify patients for post-operative chemotherapy in future trials.

Lately, a single patient classifier real-time PCR assay offered new insights into precision medicine for the adjuvant treatment selection of GC. This tool was made up with four genes displaying relevance in GC biology: GZMB (granzyme B), WARS (tryptophanyl-tRNA synthetase), SFRP4 (secreted frizzled-related protein 4), and CDX1 (caudal type homeobox 1) [13]. GZMB and WARS are related to immune regulation and inflammatory response, SFRP4 is a WNT signalling-associated EMT modulator, and CDX1 is a biomarker for gastric intestinal metaplasia, an intermediate, precancerous lesion in gastric carcinogenesis. The test was predictive for prognosis as it was able to differentiate between three groups with different survival (low, intermediate, and high risk) and for response to adjuvant chemotherapy (benefit and no benefit) in stage II-III resected Asian GC after D2 gastrectomy. These findings were validated in two independent cohorts of patients with GC.

Specifically, patients classified as immune high (GZMB- and WARS-positive) should not be treated with adjuvant chemotherapy based on their favourable prognosis with surgery alone and lack of response to post-operative treatment. In contrast, for patients in the immune low and epithelial high (CDX positive) subgroup adjuvant chemotherapy is highly recommended because their intermediate-risk prognosis is the result of a sizeable chemotherapy benefit. Future prospective validation of Western findings in Eastern population and vice versa is needed to confirm their reliability and generalizability.

## Advanced disease

*Standard management*

*First-line treatment*

In Western countries, 80% of patients present with unresectable advanced-stage disease or develop a recurrence within 5 years of curative-intent surgery [5].

Combination chemotherapy has shown to prolong survival and improve quality of life in this disease setting, though mOS has plateaued at 9–11 months despite the best regimen [6]. A platinum/fluoropyrimidine doublet chemotherapy is the preferred backbone of first-line treatment palliation in HER-2 negative GC across the globe. Of note, it has been shown that oxaliplatin and capecitabine can safely replace cisplatin and 5-FU respectively in combination regimens based on their non-inferiority and better risk-to-benefit ratio [35]. A valuable first-line alternative to platinum/fluoropyrimidine-based chemotherapy can be represented by FOLFIRI (5-FU, folinic acid, irinotecan) which was shown to be at least as effective as and better tolerable than CF and ECF [36].

The value of adding a third cytotoxic (either docetaxel or epirubicin) to doublet chemotherapy has long been investigated and debated. Indeed, both docetaxel- and epirubicin-containing triplets yield higher RRs than doublets, yet they produce significantly more toxicities [37]. Notably, the administration of regimens such as DCF [38] or modified schedules [39] should be carefully evaluated in light of potential cumulative toxicity and development of resistance to taxanes in potential candidate to second-line paclitaxel/ramucirumab. Also, the favourable impact on survival of epirubicin has never been convincingly demonstrated in a prospective randomized fashion [40].

When offering later lines to GC patients, the trade-off between survival gain, toxicity and impact on quality of life needs to be carefully evaluated. Hence, triplet chemotherapy can be justified in highly selected fit patients with unresectable locally advanced disease pursuing a “conversion intent” or those with metastatic disease in need of rapid tumour shrinkage.

In HER-2 positive cases (15–20%), the anti-HER2 monoclonal antibody trastuzumab combined with fluoropyrimidine (capecitabine or 5-FU) plus cisplatin has shown to improve the overall response rate (ORR) (47% vs 35%, p = 0.0017), progression-free survival (PFS) (6.7 vs 5.5 months, p = 0.0002) and OS (13.8 vs 11.1 months, p = 0.0046) in the randomized phase III TOGA trial [7]. The greatest benefit was recorded for strongly (3 + ) HER2-overexpressing tumours (16 vs 11.8 months, p = 0.0046). The survival advantage of trastuzumab was maintained though reduced over time as shown by the decrease of HR for OS from 0.73 to 0.80 as well as the difference in median OS from 2.7 to 1.4 months on a longer follow-up [41].

Apart from trastuzumab, the addition of biologics to standard first-line chemotherapy has been largely unsuccessful. The final analysis of the RAINFALL trial was lately published showing the failure for ramucirumab, a VEGFR-2 antagonist monoclonal antibody to improve OS when combined with cisplatin/fluoropyrimidine [42].

*Second-line and beyond*

For patients failing first-line treatment and who maintain acceptable general conditions, ramucirumab, a fully human immunoglobulin IgG1 monoclonal antibody targeting VEGFR-2, has been shown to significantly improve survival either alone (5.2 vs 3.8 months, HR = 0.776, p = 0.047) or combined with paclitaxel (9.6 vs 7.4 months, HR = 0.807, p = 0.017), in two pivotal international phase III double-blind, placebo-controlled trials [15,16]. Real-world data have been shown to support efficacy and safety of ramucirumab also in daily practice [43].

Other valuable options in adequate patients are taxanes (docetaxel and paclitaxel) or irinotecan monotherapy, which have similar activity but increased toxicity compared with the anti-VEGFR-2 alone and a lower activity and an equivalent toxicity in comparison with paclitaxel/ramucirumab combination [44–48].

Until recently, there was no evidence supporting the role of third-line treatment in pretreated GC. In 2016, an Asian randomized phase III trial first demonstrated the superiority of the small molecule VEGFR-2 tyrosine kinase inhibitor apatinib over placebo (mOS 6.5 vs 4.8, HR 0.709, P = 0.149) in patients refractory to two or more lines of prior chemotherapy [49]. Then, other two randomized phase III trials showed a limited yet statistically significant role in third-line for the novel oral cytotoxic trifluridine/tipiracil (also known as TAS-102) [19] in a global population and the anti-PD1 agent nivolumab in a Japanese cohort [17]. Additionally, pembrolizumab was added to the third-line armamentarium by FDA in the US for patients with PD-L1-positive (CPS ≥ 1%) GC and MSI-H tumours [18]. Published randomized phase III trials of second- and later lines of treatment in GC are summarized in Table 1.

*Targeted therapy*

*Rethinking drug development*

With the exception of trastuzumab in the first-line and ramucirumab in the second-line setting, the drug development process involving molecularly targeted agents has proved largely disappointing in GC. Clinical trials targeting dual-HER2 [50], EGFR [51,52], MET [53,54], PI3K/mTOR [55] and PARP [56] have all yielded negative results. The lack of a proper molecular selection has certainly played a major role in these failures diluting potential treatment advantages. Moreover, intrapatient and interpatient heterogeneity has recently emerged as a barrier to the success of targeted therapy. Indeed, genomic instability with aberrations such as amplifications and co-amplifications of receptor tyrosine kinases is a molecular hallmark of GC which is involved in tumour initiation, progression as well as treatment resistance.

Interestingly, translational studies have shown that molecularly highly selected patients exist that may benefit from targeted therapies. For instance, studies are investigating the relationship between target gene amplification and benefit from targeted agent. ERBB2-amplified cases as defined by NGS derived the greatest benefit from trastuzumab-based therapy and it is a more robust biomarker of clinically meaningful response to HER2-directed agent [57]. Again [58], EGFR-amplified gastroesophageal adenocarcinomas have been shown to derive a remarkable benefit from anti-EGFR treatment. In a prospectively screened cohort of stage IV GC, 57% of objective response rate and 100% of disease control rate was observed with a mPFS of 10 months, in patients with EGFR copies ranging from 54 to 167. On a different approach, the AMNESIA panel which includes EGFR/MET/KRAS/PI3K mutations and EGFR/MET/KRAS amplifications has shown to predict primary resistance to trastuzumab in more than a half of HER2-positive metastatic patients in a case-control study [59].

Therefore, an accurate selection following the concept of “targeted agent in a targeted population” and next-generation clinical trials using expansion platform design provide a proper tool to address the issue of low-incidence druggable genomic aberrations in GC. This appears as the most reasonable road to fulfill the full potential of molecularly targeted therapeutics in GC.

Novel promising agents undergoing evaluation in GC include trastuzumab-deruxtecan [60] and fusion proteins such as M7824 [61]. The former is a HER2-targeted antibody-drug conjugate with a humanized HER2 antibody, topoisomerase I inhibitor payload and a cleavable peptide-based linker which showed an acceptable safety profile and promising antitumour activity in pretreated subjects with HER2+ GC who previously received trastuzumab. The randomized, phase II, multicenter, open-label, DESTINY-Gastric01 study will assess the efficacy and safety of trastuzumab deruxtecan in HER2-expressing GC. The latter is a bifunctional fusion protein targeting PD-L1 and TGF-β that displayed an encouraging clinical efficacy and a manageable safety profile in heavily pretreated Asian patients with gastric cancer.

*Liquid biopsy*

Liquid biopsies, particularly those involving circulating-tumour DNA (ctDNA) from plasma, are rapidly emerging as valuable and minimally invasive tools with numerous clinical applications in cancer. Indeed, ctDNA may provide the means to capture spatio-temporal heterogeneity and to account for genomic complexity arising from all disease sites [62]. In GC, it has been demonstrated high concordance between metastatic and ctDNA profiling with 17 out of 20 (85%) targetable gene amplifications (MET, ERBB2, FGFR2, EGFR, KRAS) in the metastasis detected also in ctDNA; moreover the detection rate is similar to improved with ctDNA analysis compared with tissue-based approaches [63]. In the context of metastatic GC, clinical sequencing of ctDNA can identify potentially targetable genetic alterations to select precision therapies. In a cohort of gastroesophageal patients treated with the anti-FGFR2 AZD4547, ctDNA analysis by ddPCR, turned out to be a viable strategy to screen for FGFR2 amplification and a predictive biomarker [64]. Indeed, in that study, all responding patients had high level clonal FGFR2 copy number change detectable in plasma. Another role for liquid biopsy is represented by monitoring response to targeted therapy and tracking emergence of resistance. A recent analysis from 24 *HER2*+ patients treated with trastuzumab, documented that the liquid biopsy-based ctDNA profiling can define patterns of resistance. Most patients with innate trastuzumab resistance presented high detection of somatic copy number alteration of *HER2* gene during progression compared to baseline, while *HER2* somatic copy number alteration decrease in patients with acquired resistance [65]. Moreover, in a patient with MET-amplified receiving the experimental MET kinase inhibitor AMG337, elevated MET copy number detectable in ctDNA decreased to near-normal levels during the first 2 months of therapy, indicating effective suppression of MET-amplified tumour clones and consistent with the radiological response [66]. Interestingly, in the same patient, increased EGFR copy number by ddPCR was observed as resistance mechanism responsible for targeted treatment failure, theoretically paving the way for EGFR-directed therapy. Recently,

**Table 1**
Published randomised phase III trials of second- and later lines of treatment in advanced gastric cancer.

| Trial | Setting | Study intervention | N. pts | PFS, median | OS, median | Grade ≥3 AEs in the experimental arm |
|---|---|---|---|---|---|---|
| Thuss-Patience et al. [39] | 2nd-line | Irinotecan + BSC vs BSC | 40 | 2.6 vs NR | 4.0 vs 2.4<br>HR 0.48, p = 0.012 | Diarrhoea 26%, leucopenia 21%, febrile neutropenia 16% |
| Kang et al. [40] | 2nd-line | Docetaxel or irinotecan vs BSC | 202 | NR | 5.3 vs 3.8<br>HR 0.65, p = 0.007† | Anaemia 31%, fatigue 18%, neutropenia 17% |
| Hironaka et al. [43] | 2nd-line | Paclitaxel vs irinotecan | 219 | 3.6 vs 2.3 | 9.5 vs 8.4<br>HR 1.13, p = 0.38 | Neutropenia 39.1%, anaemia 30%, anorexia 17.3% |
| Ford et al. [41] | 2nd-line | Docetaxel + BSC vs BSC | 168 | NR | 5.2 vs 3.6<br>HR 0.67, p = 0.01 | Neutropenia 15%, infection 19%, febrile neutropenia 7% |
| Fuchs et al. [15] | 2nd-line | Ramucirumab + BSC vs BSC | 355 | 2.1 vs 1.3 | 5.2 vs 3.8<br>HR 0.77, p = 0.047 | Hypertension 8%, fatigue 6%, abdominal pain 6% |
| Wilke et al. [16] | 2nd-line | Ramucirumab + paclitaxel vs paclitaxel | 665 | 4.4 vs 2.8 | 9.6 vs 7.4<br>HR 0.87, p = 0.017 | Neutropenia 41%, leucopenia 17%, hypertension 14% |
| Shitara et al. [63] | 2nd-line | Pembrolizumab vs Paclitaxel | 395 | 1.5 vs 4.1 | 9.1 vs 8.3<br>HR 0.82, p = 0.042 | Fatigue 12%, decreased appetite 8%, hypothyroidism 8% |
| Li et al. [44] | ≥2nd-line | Apatinib vs Placebo | 267 | 2.6 vs 1.8 | 6.5 vs 4.7<br>(HR 0.70,<br>p = 0.0156) | Hand-foot syndrome 8.5%, Hypertension 8%, Proteinuria 2.3%, |
| Shitara et al. [19] | ≥2nd-line | TAS vs Placebo | 507 | 2.0 vs 1.8 | 5.7 vs 3.6<br>(HR 0.69,<br>p = 0.00058 | Neutropenia 34%, anaemia 19% |
| Kang et al. [17] | ≥2nd-line | Nivolumab vs Placebo | 493 | 1.61 vs 1.45 | 5.26 vs 4.14<br>(HR 0.63,<br>p < 0.0001 | Diarrhoea 1%, fatigue 1%, decreased appetite 1% |

prognostic information have been derived from ctDNA analysis in GC. In a prospectively evaluated cohort of advanced GC, high (max VAF > median) baseline ctDNA burden has been shown to correlate with worse outcome (mOS 7.9 vs 15.1 mos, p = 0.0086). Notably, a serial decline in ctDNA (max VAF ≥ 50%) was prognostic for improved mOS (12 vs 7.7 mos, p = 0.00938) in the same population [67].

Although these findings have to be regarded as hypothesis-generating data in need of further clinical validation, ctDNA analysis offers new insight into precision and personalized medicine in GC.

*Immunotherapy*

The advent of immune checkpoints blockade (ICI) into oncology arena has finally involved also GC. Several trials have reported encouraging efficacy data together with a manageable safety profile in advanced GC.

In the double-blind, placebo-controlled, phase III ATTRACTION-2 trial, the humanised IgG4 monoclonal antibody inhibitor of PD-1 nivolumab was investigated as third and beyond line therapy in Asian GCs and GEC [17]. A total of 493 were randomly allocated to either nivolumab 3 mg/kg of or placebo every 2 weeks. ORR was 11.2% vs 0% (P < 0.0001) with a median duration of response of 9.5 months and mOS was 5.3 vs 4.1 months (HR = 0.63, P < 0.0001). Interestingly, the significant improvement in survival was maintained with 2-year follow-up showing OS of 10.6% and 3.2% at 24 months, for nivolumab and placebo, respectively. Of note, no difference was seen according to PD-L1 status. To this end, PD-L1 positivity was defined as staining in 1% or more of tumour cells, using immunohistochemistry (28–8 pharmDxassay), though tumour samples was available in only 39% of patients. Most frequent adverse events (AEs) were mild in grade including pruritus, diarrhoea, rash, and fatigue; only 10% of patients treated with nivolumab experience grade 3–4 AEs compare to 4% in the placebo group. These results suggest that at least a proportion of GEAs achieved a durable OS advantage from nivolumab. Nivolumab has also been tested in non-Asian patients in the phase I/II CheckMate-032 trial [68]. In this non-randomized study, nivolumab alone and combined with the fully human IgG1 monoclonal antibody inhibitor of cytotoxic T-lymphocyte associated protein-4 (CTLA-4) ipilimumab was administered in chemo-pretreated PD-L1-unselected GECs. A total of 160 pretreated patients (among whom 79% received at least 2 lines) were enrolled onto three arms: nivolumab monotherapy 3 mg/kg (Group 1), nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (Group 2) and nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (Group 3). Notably, Group 1 and 2 showed ORR 12% and 24% and a median OS of 6.2 and 6.9 months, respectively. Grade 3–4 (AEs) were reported in 17% and 47% of patients. Objective responses were achieved regardless of tumour PD-L1 status and no difference was recorded between the monotherapy and combinatorial approach. Intriguingly, based on the similarity observed in objective responses and survival, the results from the Asian ATTRACTION-2 appear to be generalizable also to the non-Asian population. Another anti-PD-1 monoclonal antibody, pembrolizumab, demonstrated promising activity, in PD-L1 positive previously treated GC. Based on an ORR of 22% recorded in a phase 1b trial of 39 patients with PD-L1–positive advanced gastric or gastroesophageal junction adenocarcinoma (KEYNOTE-012 study) [69], pembrolizumab was tested in patients with advanced GC whose disease progresses after 2 or more lines of therapy. In this phase II trial, ORR was 11.6%, responses appeared more likely to occur (15.5% vs 6.4%) and to last longer (16.3 months) in PD-L1–positive patients [18]; however, patients with PD-L1–negative tumours still experienced objective responses. Of note, even if in the non-Asian randomized phase III trial KEYNOTE-061 pembrolizumab did not significantly prolong OS compared to weekly paclitaxel as second-line therapy [70], protocol-specified and post-hoc exploratory subgroup analyses suggest that the treatment effect of pembrolizumab might be more pronounced in patients with a ECOG PS 0, greater levels of PD-L1 expression (CPS > 10), and tumours with MSI-high. The anti-PD-L1 avelumab failed to improve OS or PFS compared to physician's choice of chemotherapy as third-line option in heavily pretreated patients.

Very recently, pembrolizumab granted US FDA approval for PD-L1 ≥ 1% as well as agnostic indication for unresectable or metastatic MSI-high or mismatch repair deficient (dMMR) solid tumours, including GC, without alternative options. With regards to chemo-immunotherapy combination, recently published interim results of the randomized phase II trial ATTRACTION-4 demonstrated promising efficacy and good tolerability for the combination of Nivolumab and S-1/capecitabine plus oxaliplatin (SOX) in patients with treatment-naïve HER2-negative GC [71]. Objective response rate was 57.1% with nivolumab plus SOX and 76.5% with nivolumab plus CapeOX and median PFS was 9.7 months and 10.6 months, respectively. Median overall survival was not reached (NR) in both groups. The part 2 (phase III) to compare nivolumab plus SOX/CapeOX versus placebo plus SOX/

CapeOX is underway. More interestingly, very encouraging data from the phase III randomized KEYNOTE-062 trial presented at the 2019 American Society of Clinical Oncology Annual Meeting. Pembrolizumab improved OS compared to standard chemotherapy in patients with CPS ≥ 10 (17.4 vs 10.8 months, HR, 0.69) and was non-inferior and significantly less toxic than cytotoxics in those with CPS ≥ 1 (10.6 vs 11.1 months, HR 0.91) [72].

Among the subset of HER-positive, the upfront combination of pembrolizumab with chemotherapy/trastuzumab turned out to be highly active yielding an ORR of 83% and laying the foundations for the ongoing phase III trial Keynote 811.

Ongoing studies are investigating ICIs either as maintenance therapy in patients showing disease control on mFOLFOX (JAVELIN Gastric 100; NCT02625610) or in combination with platinum/fluoropyrimidine doublets as the front-line treatment (NCT02494583; CheckMate 649, NCT02872116, NCT02746796). In the refractory setting, preliminary data of nivolumab combined with ramucirumab (NivoRam) and regorafenib (REGONIVO) study showed acceptable toxicity and encouraging anti-tumour activity. Other early-phase studies are testing the combination of ramucirumab with pembrolizumab (NCT02443324) and durvalumab (NCT02572687). Another phase I/II trial is currently recruiting GC patients to investigate the safety and efficacy of the triplet paclitaxel, ramucirumab, and nivolumab in those refractory or intolerant to platinum/fluoropyrimidine first-line chemotherapy (Clinical trial information: UMIN000025947).

Following these promising data, various trials are underway to assess the role of ICIs in resectable GC (Table 2). Given the low RR produced by immunotherapeutics, the incorporation of these agents into conventional chemotherapy regimens is the most pursued approach. To this end, the AIO-FLOT 8 DANTE trial (Clinical trial information: NCT03421288) is currently investigating the anti-PD-L1 atezolizumab plus FLOT as perioperative treatment in resectable GEC and the KEYNOTE 585 (ClinicalTrials.gov: NCT03221426) is evaluating pembrolizumab in combination with cisplatin/fluoropyrimidine doublet or FLOT regimen. Combinations of anti-PD1/PD-L1 antibodies with VEGFR-2 inhibitors or anti-CTLA4 are also being explorated.

The results of above-mentioned studies are eagerly awaited in order to ascertain the role of ICIs across clinical stages and settings in GEAs. Although IC blockade represents an unprecedented therapeutic breakthrough, its efficacy is limited to a proportion of GEAs that does not exceed 25%.

Thus, it exists an urgent need for predictive biomarkers assisting in treatment selection.

## *Evolving concepts*

### *From "the choice of the moment" to the "continuum of care" strategy*

The disappointments of targeted therapy development along with the plateau of chemotherapy efficacy have certainly represented setbacks in medical advances against GC.

Nonetheless, the scenario of advanced GC management is witnessing a paradigm shift towards a therapeutic journey for patients with advanced disease (Fig. 1). In the last 2 years, an unprecedented number of anti-cancer agents have proved effective in refractory settings thus expanding evidence-based treatment options beyond first-line. These include cytotoxic agents such as TAS-102 as well as anti-angiogenic drugs such as ramucirumab and immunotherapeutics such as apatinib and ICIs.

Moreover, the proportion of patients who remain fit to receive further lines has grown from 20% to 51% for the second-line [73] and from slightly above zero to 14% in third-line, in contemporary Western studies. The understanding of the nutritional issues of advanced GC patients and the proactive interventions including nutritional counseling and early supportive care have indeed resulted in better and safer delivery of therapies.

There is now evidence that the administration of sequential lines of treatment results in a gradual but progressive improvement in survival. In fact, a Royal Marsden experience reported an improvement in mOS from 8.3 months for patients receiving first-line only to almost 2 years for those treated with at least 3 lines during the period 2009–2015 [20].

It is clear that the administration of later line of therapy is clinically challenging because of chemotherapy- and disease-related symptoms are responsible for a deterioration of PS with a limitation in tolerance to treatment.

How to properly select patients the best candidates to later line treatments and how to choose the best drug/regimen are precision-medicine questions that have just begun to be addressed. The search for prognostic/predictive biomarkers is an area of active investigation that

**Table 2**
Selected ongoing trials of immune checkpoint inhibition in gastric cancer.

| Study | Phase | Setting | Stage | Study intervention | Planned accrual | Primary endpoint |
|---|---|---|---|---|---|---|
| *Resectable* | | | | | | |
| KEYNOTE 585 | III | Periop | cT2-4 and/or N + | FP ± Pem | 860 | OS, EFS, pCR |
| AIO DANTE | II | Periop | cT2-4 and/or N + | FLOTx4- > S- > FLOTx4<br>Vs<br>FLOTx4 + Atx4- > S- > FLOTx4 + Atx4- > Atx8 | 295 | PFS |
| EORTC VESTIGE | II | Adj | N + and/or R1 | Completion of periop<br>Vs<br>Nivo + Ipi → Nivo × 9 months | 240 | DFS |
| ATTRACTION-05 | III | Adj | pStage III | S-1 or CapeOX + Nivo<br>Vs<br>S-1 or CapeOX + Placebo | 700 | RFS |
| *Unresectable advanced or metastatic* | | | | | | |
| CheckMate 649 | III | I line | IV | Nivo + Ipi<br>Vs<br>Nivo + Oxa/FP<br>Vs<br>Oxa/FP | 2005 | PFS, OS |
| JAVELIN GASTRIC 100 | III | Maintenance | IV | Maintenance avelumab vs continuation of first-line Oxa/FP | 499 | OS |
| NCCH-1611 | I/II | II line | IV | Nivo + Ramu | 44 | DLT |
| I4T-MC-JVDJ | I | ≥II line | IV | Dur + Ramu | 114 | DLT |

**Abbreviations.** *Periop*, perioperative chemotherapy; *FP*, fluoropyrimidine/cisplatin; *Pem*, pembrolizumab; *OS*, overall survival; *EFS*, event-free survival; *pCR*, pathological complete response; *FLOT*, 5-fluorouracil, oxaliplatin, docetaxel; *S*, surgery; *At*, atezolizumab; *PFS,* progression-free survival; *Adj*, adjuvant chemotherapy; *Nivo*, nivolumab; *Ipi*, ipilimumab; *DFS*, disease-free survival; *CapeOx*, capecitabine/oxaliplatin; *RFS*, relapse-free survival; *Oxa*, oxaliplatin, *Ramu*, ramucirumab; *DLT*, dose-limiting toxicity; *Dur,* durvalumab.

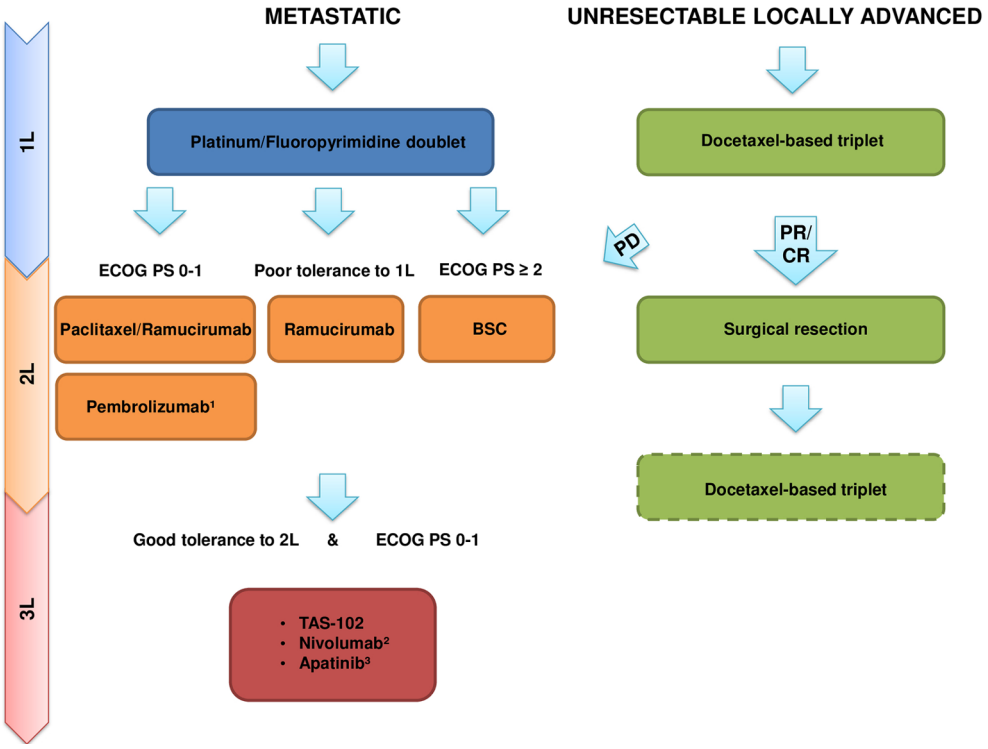


**Fig. 1.** The continuum of care: possible treatment algorithm for HER2-negative advanced gastric cancer. Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; BSC, best supportive care. [1]FDA-approved, CPS > 10% and EBV-positive cases. [2]Approved in Japan. [3]Approved in China. Dash line indicates optional treatment based on patient's conditions.

is moving from clinical features to biological determinants.

Polichemotherapy (compared to monochemotherapy) and response to previous treatments (PFS to first- and second-line) have been associated with the highest chance of benefit to third-line chemotherapy [74]. MSI-high status, EBV-positivity and high tumour mutational burden are promising predictive biomarkers to anti-PD(L)-1 treatment. In patients with MSI-high and EBV-positive tumours an outstanding activity was recorded for anti-PD1 agent (pembrolizumab) with ORR of 85.7% and 100%, respectively [75]. Likewise, among patients treated with ICIs, a more favourable OS was recorded in those with tumour nonsynonymous mutational burden > 9.7 mut/Mb [76]. Conversely, mesenchymal subtype at gene expression profiling level has been shown to be a negative predictive factor in patients receiving ICIs. These provide intriguing insights into patient selection that need to be pursued in future studies.

## Concluding remarks

Historically, late diagnosis due to lack of screening in Western countries, high post-surgical recurrence rates, and poor response to conventional treatments have made GC one of the biggest killers worldwide. The refinement of combination chemotherapy has led to FLOT regimen as a new perioperative standard of care able tocure more patients than older regimens. Furthermore, the improved understanding of the molecular underpinnings of GC has unveiled its marked heterogeneity thus providing reasons for targeted therapy failures and a framework for a more rationale and precise drug development. Again, ICI have demonstrated a meaningful activity in a subset of patients with advanced disease and are currently under investigation in earlier stages. More interestingly, a growing proportion of selected advanced patients may benefit from a sequenced treatment approach incorporating multiple lines of evidence-based therapies. Ongoing studies are evaluating predictive biomarkers and novel combinations both in the resectable and advanced setting, thus raising great expectations in the oncology community.

## Declaration of Competing Interest

**Elisabeth Smyth:** honoraria for advisory role from Astellas, Celgene, Five Prime, Gritstone Oncology, Servier. Lecture fees: BMS, Servier. Travel BMS, Servier. **Giordano Beretta**: *advisory board Roche, Lilly, Servier, Merck; travel expenses Roche, Celgene, Ipsen, Sanofi, Servier.* **Ferdinando De Vita**: advisory board Roche, Lilly, Servier, Celgene. **Maria Di Bartolomeo:** consulting/advisory board Lilly, Servier, Merck Serono, MSD; travel expenses from Roche. **Federica Morano:** *Honoraria from Servier.* **Filippo Pietrantonio** *consultancy role/honoraria from Amgen, Merck-Serono, Roche, Sanofi, Eli-Lilly, Bayer, Servier; research grants from BMS.* **Sara Lonardi:** *Consulting or Advisory Role for Amgen, Merck Serono, Lilly; Speakers' Bureau for Roche, Lilly, Bristol-Myers Squibb, Servier, Merck Serono; Research Funding from Amgen, Merck Serono.* **Carmine Pinto:** *honoraria for speaking or Advisory Board: BMS, Bayer, Astra-Zeneca, Lilly, Merck, Novartis, Roche, Servier.* **Lorenza Rimassa**: *consulting/advisory role from Lilly, Bayer, Sirtex, Medical, Italfarmaco, Sanofi, ArQule, Baxter, Ipsen, Exelixis, Amgen, Celgene, Incyte, Eisai, Hengrui Therapeutics; lecture fees from AstraZeneca, AbbVie, Gilead, Roche; non-financial support (travel expenses) from ArQule and Ipsen. Consulting/advisory role from MS.* **Caterina Vivaldi:** *non-financial support (travel expenses) from Bayer.* **Alberto Zaniboni:** *consulting/advisory role from Bayer, Amgen, Sanofi, Servier, Lilly, Merck Serono.*

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