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**Advanced gastric cancer: current treatment landscape and future perspectives**

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**Abstract**

Gastric cancer currently ranks fourth in global cancer mortality. In the western world, it is most often diagnosed at an advanced stage, after becoming metastatic at distant sites. Patients with advanced disease (locally advanced or metastatic) have a somber prognosis with a median overall survival between 10-12 mo and palliative chemotherapy is the mainstay of treatment. In recent years, novel approaches including inhibition of human epidermal growth factor receptor-2 (HER-2) demonstrated significant improvements in progression free- and overall survival as compared to chemotherapy alone in first-line treatment of patients with overexpression of HER-2. In addition, both second-line chemotherapy and treatment with the vascular endothelial growth factor receptor-inhibitor ramucirumab demonstrated significant benefits in terms of overall survival as compared to best supportive care in randomized studies. In addition, ramucirumab in combination with chemotherapy demonstrated further significant benefits in terms of progression-free and overall survival as compared to chemotherapy alone as second-line treatment for patients with metastatic gastric cancer. A recently published, molecular classification of gastric cancer is expected to improve patient stratification and selection for clinical trials and provide a roadmap for future drug development. Nevertheless, despite these developments the prognosis of patients with advanced gastric cancer remains poor. In this review we discuss current standards of care and outline major topics of drug development in gastric cancer.

**Key words:** Gastric cancer; phase III; clinical trials; chemotherapy; targeted therapy; perspectives

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**Core tip:** With the integration of both ramucirumab and transtuzumab, treatment options for advanced gastric cancer have increased significantly in recent years. Therefore a reconsideration of treatment options and results for gastric cancer is necessary. This paper discusses results of phase III trials for both - standard chemotherapy and targeted treatments in metastatic gastric cancer. Furthermore, results of selected early phase clinical trials, for example on immune checkpoint inhibitors, are discussed.

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**Introduction**

Gastric cancer (GC) currently ranks fourth in global cancer incidence and is the most common type of cancer among Japanese men[1,2]. In the last decades, epidemiologic changes in the anatomic distribution have converged with a decline of the incidence of distal (non-cardia) gastric cancer, notably in developed countries, and an increase in the incidence of adenocarcinoma of the proximal stomach. The origins of these changes are probably multi-factorial and linked to many risk factors, which includes *Helicobacter pylori* (*H. pylori*) infection incidence, dietary factors, obesity[3].

GC has a routine appearance of adenocarcinoma in 90% of cases and is divided into intestinal and diffuse type according to the Lauren classification[4]. The intestinal type is associated with *H. pylori* and dysplastic changes while the diffuse type is characterized by sheets of cells without gland formation and occasionally signet ring cells[5]. Diffuse type GC can also be associated with *H. pylori* infection, but not with intestinal metaplasia as precursor and is known to have a poorer prognosis.

Several attempts have been made to develop a molecular classification of gastric cancer based on genomic alterations. In 2012 Deng *et al*[6], identified 5 subgroups of gastric cancer defined by signature genomic alterations: FGFR-2 (9% of tumours), KRAS (9%), EGFR (8%), ERBB-2 (7%) and MET (4%). Interestingly, about 37% of GC had alterations of the receptor of tyrosine kinase RAS.

Recently, the Cancer Genome Atlas Research Network identified four molecular subtypes of gastric cancer through analysis of data from 295 primary tumors in six molecular platforms: (1) EBV-infected tumors (9%); (2) microsatellite unstable (MSI) tumors (22%); (3) genomically stable tumors (20%); and (4) chromosomally unstable tumors (50%). The researchers confirm that every subtype described has distinct genomic features:For example the group of EBV-infected tumors frequently harbors mutations of the *PIK3CA* gene (80% *vs* 3%-42% in the other subtypes), amplifications of the *JAK2* gene, and elevated PD-L1 expression. In this context, PIK3CA inhibitors and PD-L1 antagonists merit further investigation[7].

Tumors classified as chromosomally unstable are predominantly localized at the cardia or the gastrointestinal junction. This subtype is enriched for TP53 mutations and RTK-RAS activation.The microsatellite unstable subtype was present in 22% of cases and significantly associated with MLH1 silencing and genomic hyper mutation. Moreover, an amplification of the vascular endothelial growth factor A (*VEGFA*) gene was noticed, suggesting that anti-angiogenic therapy may represent an interesting therapeutic option for this subtype.Finally, the fourth subtype, the “genomically stable”, is associated with a histology of adiffuse type cancer, as wellas CDH1 and RHOA mutations.

Despite these major advances in our understanding of the biology of gastric cancer, median survival of patients with advanced GC currently remains less than 12 mo, and the development of personalized treatment strategies is the principal challenge. Primary aim of this review is to summarize data from recent phase III clinical trials on both chemotherapy and targeted therapies in advanced GC and discuss their impact on current clinical practice. Furthermore, we discuss selected recent phase II trials of special interest.

**FIRST LINE TREATMENT**

Before any systemic treatment for gastric cancer, determination of the human epidermal growth factor receptor-2 (HER-2) status is necessary. Treatment options for the about 20% of patients with HER-2 positive disease will be discussed in the paragraph on targeted therapies. The following section discusses the treatment of patients with HER-2 negative disease:

Chemotherapy is the standard first line treatment for patients with advanced GC and a good performance status. Available data from randomized clinical trials clearly demonstrate a statistically significant advantage of palliative chemotherapy as compared to best supportive care (BSC) in terms of palliation of symptoms and improvement of survival for patients with advanced GC[8] .

In contrast, the benefit of combination – as compared to single-agent - chemotherapy is much smaller: A meta-analysis published in 2010 observed a modest survival benefit of approximately 1.5 mo for combination - as compared to single-agent chemotherapy. Of note, the combination chemotherapy regimens included in this analysis were mostly “older” regimens (combination of 5-FU/anthracyclines) and therefore might not have an optimal efficacy[9]. For example, in the Japanese phase III “SPIRITS” trial, 305 patients were randomly assigned to S-1(40-60 mg/m2, twice a day, on days 1-21 and cisplatin 60 mg/m2on day 8 every 5 wk) or S-1 alone (40 -60 mg/m2, twice a day, on days 1-28 every 6 wk). Both, progression-free survival (PFS) (6 mo *vs* 4 mo) and overall survival (OS) (13 mo *vs* 11 mo, HR = 0.77; 95%CI: 0.61-0.98) were significantly improved for the combination[10]. However, on the other hand, the Japanese phase III JCOG 9912 trial, which compared a continuous infusion of fluorouracil (800 mg/m2 per day, on days 1-5) every 4 wk with the combination of intravenous irinotecan (70 mg/m2, on days 1 and 15) and cisplatin (80 mg/m2, on day 1) every 4 wk or oral S-1 (40 mg/m2, twice a day, on days 1-28 every 6 wk as single-agent) did not confirm a superiority of this combination. While S-1 alone was non-inferior to 5-FU, patients receiving the combination of irinotecan plus cisplatin had a significantly better OS[11].

More than 50 years since its development, infusional 5-FU remains the backbone of most combination chemotherapy regimens in advanced GC. However, in recent years, two oral flouropyrimidines - capecitabine and S-1 - were shown to be at least equal alternatives to 5-FU. Capecitabine was shown to be non-inferior in two phase III trials.

Kang *et al*[12] conducted a randomized phase III-trial comparing cisplatin 80 mg/m2 on day 1, plus capecitabine 1000 mg/m2 bid on day 1 to 14 for a 21-d cycle to 5-FU 800 mg/m2 per day as a continuous infusion, on day 1 to 5. The trial met its primary endpoint and demonstrated non-inferiority of cisplatin plus capecitabine as compared to cisplatin plus 5-FU. While patients receiving capecitabine had better response rates (41% *vs* 29%) than those receiving 5-FU, PFS, response rates, as well as the toxicity profile were similar.

The oral fluoropyrimidine S-1 has been developed in Japan and – as single-agent or in different combinations - is a widely accepted treatment option for advanced gastric cancer in Japan. S-1 is a combination of tegafur with two enzyme inhibitors, the 5-chloro-2,4-dihydroxypyridine (CDHP), a reversible inhibitor of dihydropyrimidine dehydrogenase (DPD), which enhances the anticancer activity of tegafur by increasing its half-life, and potassium oxonate (Oxo), which reduces thegastrointestinal toxicity of tegafur. However, due to a higher activity of CYP2A6 in Caucasians, with a resulting more rapid conversion of tegafur to 5-FU than in Asians, separate studies in Caucasian populations were necessary before registration of S-1 in Europe and the United States.

The pivotal trial, which evaluated S-1 in a Western population, is the randomized phase III “FLAGS” trial. This trial compared a regimen of Cisplatin 75 mg/m2 on day 1, plus S-1 25 mg/m2 bid on day 1 to 21 for a 28-d cycle with 5-FU 1.000 mg/m2 per 24 h for 120 h and Cisplatin at 100 mg/m2 on day 1, repeated every 28 d.Although the comparison of the different fluoropyrimidines in this trial is limited by the different doses of cisplatin in both arms, the combination of Cisplatin/S-1 was as effective as Cisplatin/Fluorouracil (overall survival 8.6 mo *vs* 7.9 mo for S-1 *vs* 5-FU). Furthermore, patients receiving 5-FU experienced significantly more side effects than those treated with S-1: rates of grade 3/4 neutropenia were 32.3% *vs* 63.6%, rates of complicated neutropenia 5.0% *vs* 14.4%, rates of stomatitis 1.3% *vs* 13.6%[13].

***Platinum derivates - alternatives to cisplatin***

Several recent studies explored whether oxaliplatin may replace cisplatin in gastric cancer: cisplatin free regimens represent a more convenient therapeutic approach, which avoids the necessary hyper hydration and decreases the risk of renal and ototoxicity associated with cisplatin- at the price of increased neurotoxicity. Results of two phase III trials in GC demonstrated non-inferiority of oxaliplatin – as compared to cisplatin - in the treatment of advanced gastric cancer, while a third trial observed comparable results.

In a randomized phase III study conducted in Japan, the standard SP regimen (S-1 40 mg/m2 bid for 21 d and cisplatin 60 mg/m2 d8 q5wk) was compared to SOX (S-1 40 mg/m2 bid for 14d and oxaliplatin 100 mg/m2 d1 q3wk). 685 patients participated in this study, which reached its primary endpoint by showing non inferiority of SOX as compared to SP in terms of progression-free-survival (PFS). As expected, serious adverse events occurred more often in the group of patients treated with SP (29.3% *vs* 37.9%). Furthermore, the rate of treatment related deaths was twice as high in the patients treated with SP (2.4% *vs* 1.2%)[14].

Al-Batran *et al*[15] compared biweekly infusional fluorouracil and leucovorin either in combination with oxaliplatin (FLO) or cisplatin (FLP). This trial confirmed the better tolerability of oxaliplatin. While results for median OS (10.7 mo *vs* 8.8 mo) showed no significant differences between treatment arms, a trend towards better PFS was observed in the patients treated with FLO. However, as expected, rates peripheral neuropathy was significantly higher (63% *vs* 22%) in patients treated with FLO. Interestingly, in the subgroup analysis for patients older than 65 years,FLO resulted in significantly superior response rates and OS (13.9 mo *vs* 7.2 mo), forming the basis for the widespread use of this combination in elderly patients.

In the landmark REAL-2 trial, patients were randomized into four different regimens (epirubicin, oxaliplatin and capecitabine (EOX), epirubicin, oxaliplatin and 5-FU (EOF), epirubicin, cisplatin and 5-FU (ECF) and epirubicin, cisplatin and **c**apecitabine (ECX)) in a two-by-two factorial design. The results of this trial confirmed that oxaliplatin was non-inferior to cisplatin in combination with epirubicin and either 5FU or capecitabine. Furthermore, apart from the expected differences in toxicities between the two regimens, fewer thromboembolic events (7.6% *vs* 15%) were observed in the patients treated with oxaliplatin as compared to cisplatin[16]

Irinotecan is another alternative to platinum derivatives which has been evaluated in several randomized trials: In 2008, Dank *et al*[17] published a phase III trial comparing Irinotecan/5FU to cisplatin /5FU. Although the combination of Irinotecan/5-FUdid not show an improvement in time-to progression (TTP) as compared to cisplatin/5FU, it was better tolerated with a lower rate of patients who discontinued treatment due to toxicity (10% *vs* 22%). This observation has been confirmed in other randomized phase II trials[18].

For these reasons both oxaliplatin and irinotecan are adequate substitutes for CDDP in combination with fluoropyrimidines.

***What is the role of taxanes in gastric cancer?***

In the V-325 study, published by Van Cutsem *et al*[19], 445 patients were treated with cisplatin/FU, with or without docetaxel as first line therapy. Although response rate (37% *vs* 25%), time-to-progression (5.6 mo *vs* 3.7 mo) and 2-year overall survival rates (18% *vs* 9%) were improved by the addition of docetaxel, the absolute benefit in terms of survival was less than 4 wk, and was counterbalanced by a significant increase of grade 3-4 adverse events .

In view of the significant toxicities associated with this regimen, especially in the elderly population, several “modified DCF” regimens have been developed: One example of such a regimen is FLOT (docetaxel 50 mg/m2, infusional 5-FU 2.600 mg/m2, leucovorin 200 mg/m2, oxaliplatin 85 mg/m2) every 2 wk. Arandomized phase II study (*n =* 143) by Al-Batran *et al* addressed specifically the question whether the addition of docetaxel 50 mg/m2 to the two-drug combination of 5-FU, leucovorin and oxaliplatin is feasible in patients older than 65years: According to the results of this trial, FLOT was associated with significantly more adverse events grade 1-4 such as neutropenia, alopecia and diarrhea, but there were no differences between the two arms in terms of serious adverse events, discontinuation for toxicity or toxic deaths in this population[20]. Thus, the feasibility of this three-drug regimen could be demonstrated in this selected population of fit elderly patients. However quality-of-life was deteriorated in a greater proportion of patients treated with FLOT, as compared to FLO. Although the triplet combination demonstrated improved response rates (RR) (49% *vs* 28 %) as well as a trend towards better progression-free-survival (9.0 mo *vs* 7.1 mo, *p =* 0.79), there was no significant benefit in median overall survival (FLOT 17.3 mo, FLO 14.5 mo, *p =* 0.39 for the entire population of patients included in this trial. For this reason the authors conclude that “this study confirms the role of the doublet combination FLO as a tolerable and active treatment option for older adult patients with metastatic gastric cancer”. Of interest: according to subgroup analyses of this trial, patients with either locally advanced – as compared to metastatic - disease, and those younger than 70 years seem to have a greater benefit from treatment with the three-drug combination. However, this hypothesis needs prospective confirmation in further trials.

The phase III “START” trial, which compared S1 *vs* S1-docetaxel (S-1 at 80-120 mg/d d1-14 of a 21 d cycle, in combination with docetaxel 40 mg/m2 every 21 d *vs* S-1 alone d1-28 of a 42 d cycle)in 635 Japanese and Korean patients showed a significant benefit in terms of PFS (5.3 mo *vs* 4.2 mo) and OS (12.5 mo *vs* 10.8 mo) in favor of the combination. While the RR in the combination group was 38.8% (as compared to 26.8%in the single-agent arm), 58% of patients presented at least one grade 3 toxicity in the combination arm[21].

Another recent randomized phase II trial addressed the question whether 5-FU can be replaced by capecitabine in a three-drug regimen which includes as well docetaxel and oxaliplatin[22]. According to the results of this trial, patients treated with the combination of docetaxel, oxaliplatin and 5-FU (TEF) had a significantly better overall survival (14.6 mo *vs* 11.3 mo), PRS (7.6 mo *vs* 5.5 mo) and RR (46.6% *vs* 25.6%) comparing to the docetaxel, oxaliplatin and capecitabine group (TEX). Furthermore, the TEF regimen was associated with a better toxicity profile.

***Is triplet superior to doublet chemotherapy in advanced GC?***

When discussing triplet- *vs* doublet chemotherapy regimens we need to address the regimens, the outcomes and the patients.

Regarding the regimens: a superiority in terms of survival for three-drug regimens including 5-FU, an anthracycline and cisplatin (ECF) over the same regimens without an anthracycline; as well as ECF over the same regimen without cisplatin has been demonstrated in our meta-analyses published in 2006 and 2010[8,9]. However, the trials included in these comparisons have all been conducted more than 10 years ago. The most recent study included in these comparisons was published in 2003, at a time when second-line therapy was not generally available. Thus, it is unclear if the survival benefit observed in this meta-analysis is still valid in a time when second-line treatment is routinely administered, and up to approximately 50% of patients in European studies[23,24], and 80% of patients in Asian trials are treated with second-line chemotherapy routinely. The recently published phase III trial by Guimbaud *et al*[23], which compared the three-drug regimen of ECX in first line to FOLFIRI *vs* the reverse sequence, did not observe a survival benefit for patients treated with ECX, as compared to FOLFIRI, with a better tolerability of FOLFIRI. Furthermore, there were no differences in quality-of-life between study arms, and FOLFIRI was better tolerated. Other triplet chemotherapy regimens, such as DCF and FLOT, which have been discussed above, have both not demonstrated convincing benefits in terms of survival, but increased rates of toxicity in the overall population of patients included in these trials. For these reasons they are not generally accepted as standards of care. Results for other outcomes, such as quality-of life, were as well contradictory for different regimens:While treatment with DCF resulted in a significant delay in time to deterioration of quality of life as compared to CF, FLOT demonstrated a deterioration in the quality of life of the patients treated with this regimen, as compared to the patients treated with FLO[24,25].

The question whether subgroups, such as patients with locally advanced or limited metastatic disease, may have a greater benefit from these combinations, is currently under investigation.

**Second line and beyond:** As much as for first line treatment, the aim of second and later lines of treatment in advanced gastric cancer is to increase survival and to control the clinical symptoms of the disease, without or with as little as possible toxicity and no negative impact on quality of life. Several phase III clinical trials and a recent meta-analysis demonstrate a modest, but significant survival benefit of chemotherapy in this setting for patients in good performance status[26,27]. Both - single-agent therapy with irinotecan and taxanes have been shown to be effective. Therefore, the choice of the regimen should be guided by the previous lines of therapy and eventual residual toxicities (*e.g.,* neurotoxicity).

In a German (AIO) phase III study patients with advanced GC and a performance status of 0-2, who had failed first line treatment, irinotecan (250 mg/m2 on day 1 of a 21 d cycle, to be increased to 350 mg/m2 based on tolerance) showed a significant benefit in terms of OS (4 mo *vs* 2.4 mo, *p =* 0.012) and RR (44% *vs* 5%) as compared to BSC. Furthermore, although the study was closed prematurely due to poor accrual after inclusion of 40 patients, it demonstrated a significant advantage in terms of symptom control for the patients treated with irinotecan: an improvement of tumor-related symptoms was noted in 50% *vs* 7% of the patients treated with irinotecan, as compared to BSC[28].

The survival benefit of 2nd line or 3rd line chemotherapy was confirmed in a Korean phase III trial in patients with advanced GC after failure of fluoropyrimidines and platinum and a good performance status. In this trial (*n =* 202, patients were randomized in a 2:1 ratio to receive either chemotherapy (docetaxel or irinotecan) or BSC. Again, median OS was improved significantly in patients treated with chemotherapy (5.3 mo for patients with chemotherapy *vs* 3.8 mo with BSC). The efficacy of irinotecan and docetaxel were comparable[26].

Finally, the recently published phase III trial “COUGAR-02” confirmed a significant difference in OS in patients with a performance status of 0-2 who were treated with docetaxel as single-agent - as compared to active symptom control - after progression to previous platinum/fluopyrimidine chemotherapy. In this trial, 168 patients with a medium age of 65 years were treated with active symptom control, with or without docetaxel (75 mg/m2 in 21 d cycle)[29]. Although only 23% of patients received 6 cycles of docetaxel, and only 7% presented an objective response to docetaxel, a modest but significant benefit in OS (5.2 mo *vs* 3.6 mo, *p =* 0.01) was observed. Moreover, despite the fact that 21% of patients treated with docetaxel presented grade 4 toxicities, significant less pain and a trend for less dysphagia and nausea were reported for the patients treated with chemotherapy, while global quality of life scores showed comparable results in both trial arms.

With the publication of this well-conducted, large, randomized trial, the benefit of docetaxel as second line treatment - as compared to active symptom control - in terms of improvement of tumor-related symptoms as well as survival has clearly been established. For this reason, all patients in good performance status should be offered second line chemotherapy.

The activity of weekly paclitaxel 80 mg/m2 (on day 1, 8, 15 every 4 wk) and irinotecan 150 mg/m2 (on day 1, 15 in 28-d cycles) as second-line treatment were compared in another recent Japanese randomized phase III study in 223 patients with advanced gastric cancer that had progressed after fluoropyrimidine plus platinum chemotherapy[30]. Irinotecan was not superior to taxane monotherapy in terms of median PFS (2.3 mo *vs* 3.6 mo with paclitaxel; *P* < 0.33) and OS (8.4 mo *vs* 9.5 mo; *P =* 0.38), and treatment-related toxicity was comparable in both arms. Interestingly, third-line chemotherapy was administered in 97 patients (89.8%) after Paclitaxel treatment and in 80 patients (72.1%) after irinotecan treatment (*P =* 0.001). Thus, we agree with the author’s conclusion that both regimens are equal andvalid treatment choices for 2nd line.

***Is combination better than single-agent chemotherapy in second-line?***

Recently, a Japanese phase III trial conducted by the Tokyo Cooperative Oncology Group evaluated the role of a single-agent (irinotecan) *vs* irinotecan plus cisplatin combination chemotherapy as 2nd line treatment in patient’s refractory to S-1 based chemotherapy[31]. Interestingly, the combination of cisplatin/irinotecan demonstrated a PFS benefit without OS improvement. Thus, according to this trial, there is no evidence for a benefit of combination- *vs* single-agent chemotherapy.

**TARGETED THERAPIES**

Approximately 20% of GC are characterized by over-expression or/and amplification of the human epidermal growth factor receptor 2 (HER-2). HER-2 over-expression is more frequent in patients with intestinal – as compared to diffuse – type, as well as GEJ - as compared to distal - gastric cancers. Currently, its prognostic implication in GC is still controversial[32]. Combining chemotherapy with trastuzumab results in a significant improvement in survival in HER-2 positive gastric cancer:

In the international phase III, so-called “ToGA” trial, 594 previously untreated patients with advanced, HER2 positive (either IHC 3+ or IHC 2+ and FISH+) GC were randomized to chemotherapy with cisplatin 80 mg/m2 on day 1, and either capecitabine 1000 mg/m2 twice daily on day 1-14 every 3 wk or 5-FU 800 mg/m2 per day continuously for 3 wk, with or without trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every three weeks). Compared with chemotherapy alone, the combination resulted in a statistically significant and clinically relevant improvement of RR and OS in patients either IHC 3+ or FISH+/IHC 2+. This combination did not raise any new safety concerns; notably the incidence of cardio toxicity was equal in the 2 arms[33]. Recently, the HRQol analysis was published showing that the time to deterioration of HRQoL was prolonged in the combination arm[33,34]

Up to now, this is the only prospective randomized phase III trial exploring trastuzumab in combination with chemotherapy in gastric cancer, although phase II-data for example with XELOX or in combination with S1 and cisplatin has shown interesting clinical activity[35,36]. Therefore, the benefit of trastuzumab in combination with other chemotherapies needs further investigation. However,a non-interventional register studying the addition of Trastuzumab to different first line chemotherapies, and suggesting comparable results in terms of progression-free-survival (median 6.8 mo) for other chemotherapy-combinations with trastuzumab, for which the final results are still pending, needs to be mentioned in this context. Importantly, on the basis of pharmacokinetic data suggesting that the above mentioned dose of trastuzumab in combination capecitabine and cisplatin might not be optimal, a currently ongoing phase III trial named HELOISE is exploring two different dose schedules of trastuzumab (8 mg/kg loading dose, followed by 6mg/kg every three weeks or 8mg/kg followed by 10 mg/kg every 3 wk) in combination with cisplatin 80mg/m2 on d1 and capecitabine 800 mg/m2 twice daily on day 1-14 (NCT 01450696). Furthermore, the clinical value of the continuation of trastuzumab beyond first progression – a strategy with proven value in HER-2 positive breast cancer - needs to be defined[37].

***Second line treatment for HER-2 positive GC***

Lapatinib is a small molecule TKI that binds reversibly to EGFR 1 and EGFR-2 (HER-2), blocking the activation of downstream second messengers, which is approved for 2nd line treatment of HER-2 positive, advanced breast cancer[38].

Aphase III clinical trial “TyTAN”, evaluated the efficacy of lapatinib in combination with paclitaxel in the 2nd line setting in Asian patients with HER-2 positive, advanced gastric cancer. 261 HER-2 positive patients by FISH were randomized to lapatinib plus chemotherapy *vs* chemotherapy alone[39]. According to the results of this trial, the overall RRwas significantly higher in patients treated with lapatinib, but mPFS and OS showed no significant differences. However, in subgroup analyses, Asian patients, those with a score of 3 + at IHC, and those fewer than 60 years old seemed to benefit from the addition of lapatinib to paclitaxel.

The limited efficacy of lapatinib was confirmed in the first line setting in gastric cancer in the phase III “LOGIC” trial which investigated the activity of lapatinib in combination with capecitabine/oxaliplatin and demonstrated a non significant prolongation of OS[40].

***Future perspectives for HER-2 positive GC***

Currently, pertuzumab, a monoclonal antibody that binds to the dimerization domain of the HER2/HER-3 receptors, is investigated in GC: In HER-2 positive, metastatic breast cancer (BC), a recently published phase III trial comparing docetaxel in combination with trastuzumab, with either pertuzumab or placebo demonstrated a benefit in OS of 16 months (!) for patients treated with pertuzumab, without significant differences in toxicity, especially cardiac toxicity, for the addition of pertuzumab to trastuzumab plus docetaxel[41]. Based on preclinical data, targeting the dimerisation of HER-2/HER-3 has antitumoral activity as well in GC although the serum clearance seems to be higher in this setting[42]. On the basis of a randomized phase IIa trial (*n =* 30) exploring two different dose schedules of pertuzumab (840 mg for cycle 1 and 420 mg for cycles 2-6 *vs* 840 mg in cycles 1-6, in combination with chemotherapy), the dose of 840mg pertuzumab was selected for the ongoing international, randomized phase III “JACOB” trial (NCT 01774786), which explores the role of the combination of trastuzumab with chemotherapy, with or without pertuzumab, in advanced GC. Of note, response rates for patients treated with pertuzumab, in combination with trastuzumab and chemotherapy were 86% and 55% for the two doses in the above mentioned phase IIa trial[43].

In analogy to the “EMILIA” trial in breast cancer, a randomized phase III trial comparing T-DM1 (trastuzumab emtansine, an antibody-drug conjugate that links the monoclonal antibody trastuzumab with the microtubule inhibitor DM1, a maytansine derivative, to deliver both the anti-HER2 agent and chemotherapy directly into the cancer cells) to the combination of and capecitabine in pretreated, HER-2 positive breast cancer, the ongoing phase III GATSBY trial is evaluating the T-DM1 *vs* a taxane (docetaxel or paclitaxel) in previously treated metastatic HER-2 positive gastric cancer (NCT01641939) .

***Targeting EGFR 1 in advanced gastric cancer***

Despite the high rate of EGFR expression in GC, which is approaching 50%, targeting the EGFR, has not proven to be a successful strategy, at least in an unselected population of patients with gastric cancers: The so-called “EXPAND”-trial, which evaluated the addition of cetuximab to first-line chemotherapy with capecitabine or 5-FU in patients with advanced GC failed to improve both PFS or OS, independent of the expression of EGFR[44].

The lack of activity of targeting EGFR in a non selected population of patients with gastric cancer was confirmed in another phase III, the REAL 3 trial. In this trial, panitumumab or placebo was added to 1st line chemotherapy with EOX[45]. This study was terminated prematurely due to a significantly worse median OS (8.8 mo *vs* 11.3 mo) in the patients treated with EOX and panitumumab. Predictive biomarkers for the efficacy of panitumumab (mutations in KRAS, BRAF, PIK3CA or loss of PTEN expression) could not be identified.

Nevertheless, in patients with advanced NSCLC, high EGFR expression (> 200 score assessed by IHC) seems to be a predictor of survival for patients treated with the combination of 1st line chemotherapy plus cetuximab[46]. Currently, data for patients with GC and high tumor EGFR expression is pending. However a small randomized phase II trial demonstrated that in a subgroup of patients with IHC2+/3+ EGFR metastatic gastric cancer adding nimotuzumab, an EGFR monoclonal antibody, to irinotecan might improve the antitumoral activity[47]. Based on these results, a randomized phase III trial investigating this combination in EGFR overexpressing GC in 2nd line setting is ongoing in Japan and Korea (ENRICH trial)(NCT 01813253).

***Role of angiogenesis***

Angiogenesis has become an important target in the treatment of several solid tumors. In gastric cancer, increased VEGF-A expression has been correlated with poor prognosis. Therefore, several studies tried to explore the role of anti-angiogenic therapies in this context[48,49].

Results from the international phase 3 “AVAGAST”study, whichassessed the benefit of adding bevacizumab, a monoclonal antibody targeting VEGF, toa cisplatin/capecitabine combination chemotherapy regimen[50], showed only a modest improvement of PFS rates (6.7 mo *vs* 5.3 mo) without OS benefit (12.1 mo *vs* 10.1 mo). Nevertheless, in an unplanned subgroup analysis, OS was significantly improved in non-Asian populations, in the diffuse subtype, and in distal GC. Furthermore, recent data demonstrated a clear benefit of targeting angiogenesis in the 2nd line setting: In contrast to bevacizumab, ramucirumab is a Ig1 monoclonal antibody and antagonist of the VEGF-receptor 2, which blocks the binding of VEGF A, C and D.The phase III “REGARD”-trial evaluated ramucirumab monotherapy (8 mg/kg every 15 d) *vs* placebo in 355 patients[51] after failure of first-line chemotherapy. Ramucirumab increased mOS by 37% (5.2 mo *vs* 3.8 mo, HR = 0.776, 95%CI: 0.603-.998) as well as PFS (2.1 mo *vs* 1.3 mo, HR = 0.483, 95%CI: 0.376-0.620). Importantly, ramucirumab was well tolerated, with hypertension (8% grade ≥ 3) being the most important side effect. Rates of grade > 3 arterial and venous thromboembolism were 1% *vs* 0% and 1% *vs* 4% respectively in both patient groups[43].

The activity of ramucirumab as second-line treatment of GC was confirmed by another phase III, the “RAINBOW”-trial, in combination with chemotherapy: In this study, 665 patients were randomized to receive paclitaxel 80 mg/m2 d1-8-15, with or without ramucirumab (8 mg/kg every 15 d). Again, patients treated with ramucirumab in addition to paclitaxel had significant improvements in median OS of 9.6 *vs* 7.4 mo,HR = 0.807 (95%CI: 0.678-0.962), PFS (4.4 mo *vs* 2.9 mo, HR = 0.635, 95%CI: 0.539-0.752, *p* < 0.0001) and response rate (28% *vs* 54%, *p =* 0.0001)[52].

These proof-of concept trials for theinhibition of angiogenesis in metastatic gastric cancer were confirmed by another phase III trial evaluating apatinib, an oral VEGR-2 tyrosine kinase inhibitor after failure of 2nd linechemotherapy[53]. In this study, 293 heavily pretreated Chinese patients were randomized to apatinib (850 mg/d) *vs* placebo. While median PFS (as assessed by the investigators) was 2.6 mo in the experimental group and 1.8 mo in the placebo group (HR = 0.44);median OS was 6.5 and 4.7 mo respectively (HR = 0.71). However, objective response rates were 3% *vs* 0% in the placebo group. Furthermore, 9% of patients treated with apatinib developed a hand and foot syndrome grade 3/4.

These data confirm the importance of angiogenesis as a pathway and support further development of anti-angiogenic treatments in GC.

**FUTURE PERSPECTIVES**

For the moment, several novels targets are under investigation (Table 1). For example, the PI3K/AKT/mTOR pathway plays a crucial role in multiple cellular functions including proliferation, angiogenesis and cell growth. The results of a phase III-trial, GRANITE-1 were recently released. This study compared everolimus, a mTOR inhibitor with placebo in pretreated advanced GC and did not show an improvement of OS in the patients treated with everolimus (5.4 mo *vs* 4.3 mo) [54].

Hepatocyte growth factor (HGF), as well as its receptor MET (mesenchymal epithelial transition factor) have key roles in gastric cancer[55,56].Rilotumumab, a fully human, IgG2monoclonal antibody against HGF demonstrated promising preliminary results in combination with EOX in a randomized phase II study[57]. Furthermore, recent data showed that MET-positive patients respond better to the combination of rilotumumab and ECX[58].Due to increased toxicity and treatment related deaths in the combination group in RILOMET-1, all clinical trials investigating the role of rilotumumab in GC including the phase III RILOMET-1 (with epirubicin, cisplatin, and capecitabine ECX) and RILOMET-2 trials (in combination with cisplatin and capecitabine (CX)) have been stopped early.Results of the RILOMET-1 trial have been presented atthe ASCO 2015 Annual Meeting: BothOS and PFS were statistically worse in the rilotumumab arm independent of MET expression[59]. In addition, preliminary results of another phase II trial presented at the2015 ASCO Annual meeting and evaluating onartuzumab, another monoclonal antibody designed specifically to target the MET receptor, failed to show PFS benefit when added to mFOLFOX in 1st line setting in patients with HER-2 negative metastatic gastric cancer[60].

Cancer immunotherapy has seen major advances in the last 10 years. Checkpoint inhibitors have become the cornerstone in the treatment of melanoma and – when compared to docetaxel - demonstrated a significant improvement in overall survival in a randomized phase III trial (brahmer, NEJMJULY 2015) in NSCLC[61]. Early results of “KEYNOTE-012” a phase Ib trial evaluating pembrolizumab, a humanized anti–PD-1 monoclonal antibody were initially presented at the [2015 ASCO Gastrointestinal Cancers Symposium](http://meetinglibrary.asco.org/subcategories/2015%20Gastrointestinal%20Cancers%20Symposium) and update data was reported in 2015 Asco Annual Meeting. In this trial, 39 chemo refractory patients with advanced gastric cancer,good PS and either distinctive stromal or≥ 1% of tumor nest cell PD-L1-staining were eligible and were treated with pembrolizumab 10 mg/kg every 2 wk until complete response, disease progression, or unacceptable toxicity[62]. With a 22.2% objective response rate, as assessed by central review after a median follow-up of 8.8 mo, pembrolizumab demonstrated promising anticancer activity in this heavily pretreated population. 13 patients (33%) remain on therapy. A total of 53.1% of patients with measurable disease displayed some degree of tumor shrinkage from baseline.

At 6 mo, 69% of patients remain alive and the median progression-free survival reached 1.9 months with a median OS at 11.4 mo[63].The incidence of side effects was low, and only 3 patients presented toxicities grade ≥ 3.Further trials with different checkpoint inhibitors in gastric cancer are in preparation.

This trial is one example of identification of identifying molecular subtypes of GC may help to better understand this heterogeneous cancer leading to the development of novel therapeutic strategies and to improvement the survival of patients. The discovery of key driver genes in these subgroups (such as TP53 in microsatellite stable tumors, ARID1A in EBV positives tumors) reveals important molecular biomarkers and the development of novel targeted therapeutic strategies is ongoing.

For example, JAK2 amplification was seen in 6% of EBV promising tumors leading to activation of JAK/STAT and PI3K/Akt/mTOR pathway opening to new perspectives for the design of clinical trial with JAK2 inhibitors.

**CONCLUSION**

The treatment of advanced Gastric cancer remains a major challenge, and many questions remain unresolved. While significant progress has been made in the last years by routinely treating patients with second- and further lines of chemotherapy, as well as integration of HER-2 targeting drugs and ramucirumab in the routine care of patients with advanced gastric cancer many phase III trials, for example with EGFR-inhibitors or everolimus, have had negative results, and others (*e.g.,* RILOMET) had to be closed prematurely doe to unexpected toxicity. Among the unresolved issues is the question whether some subgroups of patients benefit more than others from certain chemotherapy regimens (*e.g.,* doublet- *vs* triplet regimens).

Furthermore, the optimal duration of chemotherapy remains unclear: should we stop after 6-8 cycles, continue until progression, or just continue with maintenance therapy? Furthermore, valid biomarkers other than HER-2 are required to select patients for clinical trials in molecular defined subtypes of this disease. The presentation of the results of the KEYNOTE-2 trial has provided a first signal of the efficacy of immunotherapy in advanced gastric cancer. However, further trials, and especially longer follow up is necessary to validate the efficacy of this approach.Currently, there are hints that MEK inhibitors as well as immunotherapy may open a new exciting era of the treatment of advanced gastric cancer.

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**Table 1 several novels targets are under investigation**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Name of trial** | **Regimen** |  | **No. of patients** | **Primary endpoint** | **NCT number** | **Country** |
| **GO2 - Alternative chemotherapy for frail or elderly patients with advanced gastric or oesophageal cancer** | Best supportive care (BSC): Participants randomised to receive BSC will be treated according to local policy.  OxCap 100%: Oxaliplatin 130 mg/m2 day 1 Capecitabine 625 mg/m2 bd x 21 d OxCap 80%: Oxaliplatin 104 mg/m2 day 1 Capecitabine 500 mg/m2 bd x 21 d  OxCap 60%: Oxaliplatin 78 mg/m2 day 1 Capecitabine 375 mg/m2 bd x 21 d | http://www.isrctn.com/ISRCTN44687907?q=gastric cancer phase III&filters=&sort=&offset=4&totalResults=29&page=1&pageSize=10&searchType=basic-search | 530 | Chemotherapy intensity comparison:  Progression free survival   Chemotherapy vs best supportive care comparison Overall survival |  | United Kingdom |
| **Efficacy and Safety Study of Olaparib in Combination With Paclitaxel to Treat Advanced Gastric Cancer** | Drug: Olaparib  Tablets-at a dose of 100 mg orally twice daily, throughout each cycle (28 d); Once paclitaxel dosing is stopped, the planned monotherapy olaparib dose will be 300 mg twice daily. Drug: Paclitaxel  IV infusion over 1 hour at 80 mg/m2 weekly on days 1, 8 and 15 of a 28 d schedule | https://www.clinicaltrials.gov/show/NCT01924533 | 500 | Overall survival | NCT01924533 | China: South Korea: Japan:  Taiwan |
| **HELOISE Study: A Study of Herceptin (Trastuzumab) in Combination With Cisplatin/Capecitabine Chemotherapy in Patients With HER2-Positive Metastatic Gastric or Gastro-Esophageal Junction Cancer** | Drug: capecitabine  1600 mg/m2 orally daily Days 1-14 of each 3-wk cycle, 6 cycles Drug: cisplatin  80 mg/m2 iv on Day 1 of each 3-wk cycle, 6 cycles Drug: trastuzumab [Herceptin]  8 mg/kg iv loading dose, followed by 6 mg/kg iv every 3 wk | https://www.clinicaltrials.gov/show/NCT01450696 | 400 | Overall survival | NCT01450696 | 120 location |
| **A Study of Trastuzumab Emtansine Versus Taxane in Patients With Advanced Gastric Cancer (phII/III)** | Standard taxane (docetaxel or paclitaxel) according to investigator choice/Drug: trastuzumab emtansine  trastuzumab emtansine 2.4 mg/kg once a week/stuzumab emtansine 3.6 mg/kg every 3 wk | <https://www.clinicaltrials.gov/show/NCT01641939> | 412 | Overall survival | NCT01641939 | 150 location |
| **Phase 3 Study of Nimotuzumab and Irinotecan as Second Line With Advanced or Recurrect Gastric and Gastroesophageal Junction Cancer (EGFR + IHC)** | Irinotecan 150 mg/m2 IV once every 2 wk until progression or unacceptable toxicity develops with or without Nimotuzumab  400 mg IV once weekly until progression or unacceptable toxicity develops | https://clinicaltrials.gov/ct2/show/NCT01813253 | 400 | Overall Survival | NCT01813253 | Japan, South Korea |
| **A Study of Ramucirumab (LY3009806) in Combination With Capecitabine and Cisplatin in Participants With Stomach Cancer (RAINFALL)** | 80 mg/m2 cisplatin given IV on day 1 of each 21 d cycle (for up to 6 cycles) and 1000 mg/m2 capecitabine given orally twice a day on days 1 through 14 with or without ramucirumab 8 mg/kg given intravenously (IV) on days 1 and 8 | https://clinicaltrials.gov/ct2/show/NCT02314117?term=Ramucirumab+gastric&rank=5 | 616 | PFS | NCT02314117 | The world |
| **A Randomized, Double Blind Study Evaluating Paclitaxel With and Without RAD001 in Patients With Gastric Carcinoma After Prior Chemotherapy (AIO-STO-0111)** | Paclitaxel 80 mg/m2 on day 1, day 8 and day 15 of every 28-d cycle with or without Everolimous 10 mg (2 x 5 mg tablets per day) d1-d28 | <https://clinicaltrials.gov/ct2/show/NCT01248403> | 480 | Overall survival | NCT01248403 | Germany |
| **A Study of BBI608 Plus Weekly Paclitaxel to Treat Gastric and Gastro-Esophageal Junction Cancer (BRIGHTER)** | Paclitaxel 80 mg/m2 I.V. infusion on Days 1, 8, and 15 of every 4-wk cycle with or without BBI608 480 mg orally two times daily (960 mg total daily dose) | <https://clinicaltrials.gov/ct2/show/NCT02178956?term=BBI608+GASTRIC&rank=1> | 680 | Overall survival | NCT02178956 | United States |