



Perspective

# Customization of therapy for gastroesophageal adenocarcinoma patients

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## Abstract

Gastroesophageal adenocarcinomas (GEACs) remain a global health problem. These are most often diagnosed at advanced stage and the estimated 5-year relative survival rate is about 5%. Although cure is not possible for patients with advanced GEAC, systemic therapy (chemotherapy or biochemotherapy) can palliate symptoms, improve survival and provide a better quality of life. One of the most promising options for some patients with advanced stage GEAC is immunotherapy, which can result in durable responses. Numerous phase III trials evaluating targeted therapies in different lines are ongoing and it is hoped that better biomarkers will emerge to identify patients who can benefit from targeted agents and immunotherapy in the future. Surgery remains as the corner stone for localized GEAC and adjunctive therapies can increase the survival rates by about 10%. The high toxicity and low completion rates of adjuvant therapy led to the strategies of preoperative treatment. With the results of ongoing pre-operative therapy trials we will be able to determine the optimal adjunctive approach for resectable GEAC.

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## Introduction

Gastroesophageal adenocarcinomas (GEACs), originating from esophagus, esophagogastric junction (EGJ) and stomach, remain as a worldwide health problem with an estimated 1,407,400 new cases and 1,123,300 deaths in 2012, globally.<sup>1</sup> These are highly lethal cancer types and constitute about 15% of all cancer related deaths.<sup>1</sup> In recent decades, location of esophageal carcinoma has shifted from proximal to distal location and gastric cancer has migrated from distal location to proximal one in the West.<sup>2</sup> This trend is also found in Asia and South America.<sup>1</sup>

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Changes in the locations are mostly related to increased incidence of obesity, gastroesophageal reflux disease (GERD), Barrett's esophagus and decreased incidence of *H. Pylori* infection (Fig. 1).<sup>3–6</sup> This trend is occurring in other regions as well and EGJ adenocarcinoma (adenocarcinomas that have their epicenter in the 10-cm segment encompassing the 5 cm above and 5 cm below EGJ) constitutes the major burden of GEACs.<sup>2</sup> Selecting appropriate therapy for GEAC may be possible after accurate stage is determined and patients discuss with a multidisciplinary team consisting of medical oncologists, surgeons, radiation oncologists, radiologists, pathologists and supportive care specialists. With the American Joint Committee on Cancer (AJCC) 8th edition, staging and definition of esophageal, EGJ and gastric cancers are more clear.<sup>7</sup> According to the AJCC 8th edition, a tumor involving the EGJ with its epicenter  $\leq 2$  cm below EGJ, should be classified as esophageal cancer, all others below EGJ should be classified as gastric cancer. This classification is important to deciding on the right surgical approach. Surgery is the most important component of treatment for localized GEACs but unfortunately most of the patients are diagnosed with an advanced stage.<sup>3,4</sup> For intramucosal GEACs, minimally invasive approaches like endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) can be alternatives to surgery in experienced centers.<sup>8,9</sup>

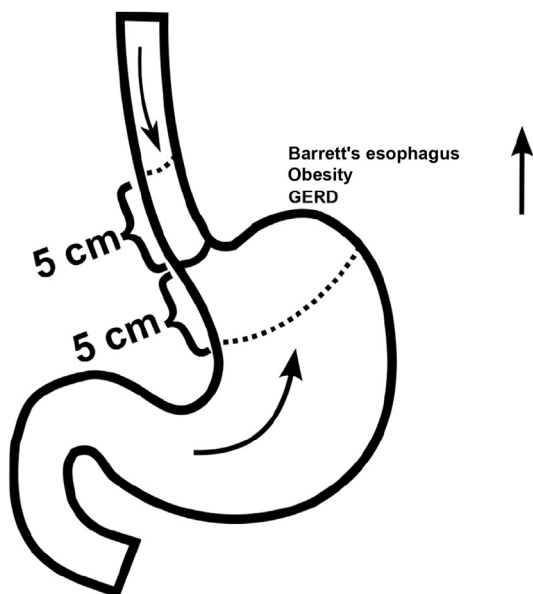


Fig. 1. The location changing trend of gastroesophageal adenocarcinomas. GERD: gastroesophageal reflux disease.

## Therapy for localized esophageal adenocarcinoma

Surgery remains as the corner stone treatment for operable esophageal adenocarcinoma (EAC). However, the reported median overall survival (OS) durations for patients treated only with surgery were less than 18 months in different trials.<sup>10,11</sup> Therefore, preoperative strategies have become popular. It was shown that post-treatment pathologic stage is the best prognosticator of survival for EAC and the OS was significantly better for patients with no residual carcinoma.<sup>12</sup>

Radiation Therapy Oncology Group trial 8911 (RTOG 8911) compared surgery alone with preoperative cisplatin plus fluorouracil (CF) in localized esophageal and EGJ tumors mostly composed of adenocarcinoma.<sup>10,13</sup> In this trial, adding CF to surgery did not prolong the survival [16.1 months for surgery-only group and 14.9 months for pre-operative CF group; hazard ratio (HR), 1.07; 95% CI: 0.87–1.32;  $P = 0.53$ ] and margin negative (R0) resection rates were similar for both groups (59% for surgery-only group and 62% for pre-operative CF group). However, a similar trial conducted by the United Kingdom Medical Research Council (OE02)<sup>11,14</sup> demonstrated longer OS for pre-operative CF patient group (13.3 months for surgery-only group and 16.8 months for pre-operative CF group; HR, 0.79; 95% CI: 0.67–0.93;  $P = 0.004$ ) and R0 resection rates were parallel (53% for surgery-only group and 60% for pre-operative CF group) with the rates reported by RTOG8911. The long-term follow-up of both of these studies showed that performing an R0 resection is the most important factor related with longer OS.<sup>13,14</sup> A recent study, OE05, compared two cycles of pre-operative CF with four cycles of pre-operative epirubicin, cisplatin, and capecitabine (ECX).<sup>15</sup> There was no survival benefit with intensified therapy (median OS; 23.4 months in the CF group and 26.1 months in the ECX group; HR, 0.90; 95% CI: 0.77–1.05;  $P = 0.19$ ). Moreover, the number of patients that could complete the pre-operative therapy was significantly higher in CF than ECX group (96% of CF group vs. 81% of ECX group;  $P < 0.0001$ ) and more patients discontinued the therapy due to toxicities in ECX group (10% vs. 2%).

In a study from France, peri-operative CF was compared with surgery alone in a patient group mostly consisting of patients with esophageal and EGJ adenocarcinoma.<sup>16</sup> It resulted in a longer OS benefit in favor of the peri-operative treatment group (HR, 0.69; 95% CI: 0.50–0.95;  $P = 0.02$ ). However, only 50% of the peri-operative treatment group could receive the planned post-operative treatment. This trial was

terminated early and had small number of patients for analysis.

The importance of R0 surgery to prognosis of localized EAC and the desire to reach higher local control rates, led to the evaluation of pre-operative chemoradiation for localized EAC. Earlier small studies had inconsistent results.<sup>17–20</sup> However, meta-analyses supported pre-operative chemoradiation.<sup>21,22</sup> In 2012, van Hagen et al<sup>23</sup> reported the “Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study” (CROSS) with 366 patients. The R0 resection rate was higher (92% of patients in the chemoradiotherapy—surgery group vs. 69% in the surgery-only group,  $P < 0.001$ ) and the median OS was longer (49.4 months vs. 24 months;  $HR$ , 0.657; 95%  $CI$ : 0.495–0.871;  $P = 0.003$ ) for pre-operative chemoradiation group. After CROSS, pre-operative chemoradiation followed by surgery has been the most commonly strategy for localized esophageal carcinoma. However, CROSS selected the best patient population and advantage for EAC is marginal.

Limited number of studies compared the two accepted treatment approaches, namely pre-operative chemotherapy and pre-operative chemoradiation, for localized EAC. A phase III study evaluated the effect of adding chemoradiation to induction chemotherapy before surgery.<sup>24</sup> This study was closed early due to poor accrual and could not meet the primary endpoint of OS. However, chemoradiation group had a higher pathologic complete response rate (15.6% vs. 2%) and long-term follow-up demonstrated longer local progression-free survival (PFS) from chemoradiation ( $HR$ , 0.37; 95%  $CI$ : 0.16–0.85;  $P = 0.01$ ).<sup>25</sup> In a phase II study, Burmeister et al<sup>26</sup> compared pre-operative CF with pre-operative chemoradiation. There was no survival benefit for chemoradiation group but the pathological response rate was significantly higher in chemoradiation group. These studies have a number of shortcomings. Another phase II trial aimed to increase pathologic complete response rate by adding induction chemotherapy to pre-operative chemoradiation but did not reach a significant outcome (13% vs. 26%,  $P = 0.094$ ).<sup>27</sup> A recently reported multicenter trial comparing pre-operative chemotherapy with pre-operative chemoradiation met its primary endpoint of histologic complete response. Pathologic complete response rate was 28% after pre-operative chemoradiation and it was only 9% after pre-operative chemotherapy. However, there was no OS difference between the two arms.<sup>28</sup> Three phase III studies comparing pre-operative chemoradiation with peri-

operative regimens for resectable EAC are ongoing. The first is “Perioperative Chemotherapy Compared To Neoadjuvant Chemoradiation in Patients With Adenocarcinoma of the Esophagus” (ESOPEC) (NCT02509286), comparing peri-operative 5-fluorouracil (5-FU), leucovorin, oxaliplatin, docetaxel (FLOT) with CROSS protocol. The second is “NEOadjuvant Trial in Adenocarcinoma of the oEsophagus and oesophagoGastric Junction International Study” (Neo-AEGIS) which is comparing the MAGIC regimen [peri-operative epirubicin, cisplatin, and 5-FU (ECF)] with CROSS regimen (NCT01726452). The third compares three different arms, pre-operative CF versus pre-operative docetaxel, cisplatin, and 5-FU (DCF) versus radiotherapy with CF (JCOG1109, NExT study).<sup>29</sup> Results of these studies are awaited.

Preoperative approaches should be considered for localized EAC (Table 1). If surgery is done first, there may be a role for postoperative adjuvant chemoradiation particularly, if surgery was suboptimal.<sup>30,31</sup>

Definitive chemoradiation is often used for esophageal squamous cell carcinoma.<sup>32</sup> However, long-term results of a phase II study demonstrated favorable results in patients including EAC.<sup>33</sup> Definitive chemoradiation is an option for inoperable EAC or when patients decline surgery.

### Options for localized gastric adenocarcinoma

Complete resection with extended lymph node dissection in a high-volume center provides best outcome for localized gastric adenocarcinoma (GAC).<sup>34,35</sup> The number of involved lymph nodes determines prognosis and at least fifteen nodes should be removed/examined.<sup>36</sup> Despite the advances in surgical techniques, locoregional and distant recurrence rates remain high and survival rates remain low for localized GAC. By aiming to reduce recurrence rates, several different approaches have been studied.

Initial small studies failed to show benefit.<sup>37–40</sup> An adjuvant chemoradiation study conducted by Macdonald et al<sup>31</sup> [Southwest Oncology Group (SWOG) 9008/Intergroup trial 0116 (INT-0116)] accrued a total of 556 patients and randomized to observation after surgery or adjuvant chemoradiation. The relapse rate was higher in the observation group compared to the adjuvant therapy group ( $HR$ , 1.52; 95%  $CI$ : 1.23–1.86;  $P < 0.001$ ). The median duration of OS (36 months for adjuvant treatment group vs. 27 months for surgery-only group) and relapse-free survival (RFS) (30 months for adjuvant treatment group vs. 19 months

Table 1  
Survival outcomes of key studies evaluating the right therapy for localized esophageal adenocarcinoma.

Trial	Arms	n	Outcome
RTOG 8911 <sup>10</sup>	Surgery vs. CF×3 → surgery	227 vs. 213	Median OS, 16.1 vs. 14.9 months; <i>HR</i> , 1.07; 95% <i>CI</i> : 0.87–1.32; <i>P</i> = 0.53
OE02 <sup>11</sup>	Surgery vs. CF×2 → surgery	402 vs. 400	Median OS, 13.3 vs. 16.8 months; <i>HR</i> , 0.79; 95% <i>CI</i> : 0.67–0.93; <i>P</i> =0.004
OE05 <sup>15</sup>	CF×2 → surgery vs. ECX×4 → surgery	451 vs. 446	Median OS, 23.4 vs. 26.1 months; <i>HR</i> , 0.90; 95% <i>CI</i> : 0.77–1.05; <i>P</i> = 0.19
FNCLCC/FFCD <sup>16</sup>	Surgery vs. CF×3 → surgery → CF×3	111 vs. 113	5-year OS rate, 24% vs. 38%; <i>HR</i> , 0.69; 95% <i>CI</i> : 0.50–0.95; <i>P</i> =0.02
CROSS <sup>23</sup>	Surgery vs. CRT (with carboplatin and paclitaxel) → surgery	188 vs. 178	Median OS, 24 vs. 49.4 months; <i>HR</i> , 0.657; 95% <i>CI</i> : 0.495–0.871; <i>P</i> = 0.003
POET <sup>24,25</sup>	Induction CT → surgery vs. induction CT → CRT → surgery	59 vs. 60	3-year OS rate, 27.7% vs. 47.7%; <i>P</i> = 0.07; study closed early due to poor accrual
Burmeister et al <sup>26</sup>	CT → surgery vs. CRT → surgery	36 vs. 39	Median OS, 29 vs. 32 months; <i>P</i> = 0.83
Ajani et al <sup>27</sup>	CRT → surgery vs. induction CT → CRT → surgery	63 vs. 63	Median OS, 45.62 vs. 43.68 months; <i>P</i> = 0.69
NeoRes <sup>28</sup>	CT → surgery vs. CRT → surgery	91 vs. 90	3-year OS rate, 49% vs. 47%; <i>P</i> = 0.77

RTOG 8911: Radiation Therapy Oncology Group trial 8911; CF: cisplatin plus fluorouracil; OS: overall survival; *HR*: hazard ratio; *CI*: confidence interval; ECX: epirubicin, cisplatin, and capecitabine; FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer; FFCD: Fédération Francophone de Cancérologie Digestive; CROSS: Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study; POET: PreOperative therapy in Esophagogastric adenocarcinoma Trial; CT: chemotherapy; CRT: chemoradiation therapy; NeoRes: Neoadjuvant Chemotherapy versus Chemoradiotherapy in Resectable Cancer of the Oesophagus and Gastric Cardia.

for surgery-only group) was longer in adjuvant therapy group. However, Grade 3–4 toxic effects were seen in 73% of patients in adjuvant therapy arm and only 64% of patients completed the treatment as planned. Despite the high toxicity rate, adjuvant chemoradiation has been a standard for resected GAC in the West. Only 10% of enrolled patients had a D2 dissection and the effect of adjuvant radiotherapy in D2 dissected patients was unclear.<sup>31</sup> The phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine-radiotherapy in completely resected GAC with D2 lymph node dissection [Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial] was designed to clarify that situation.<sup>41,42</sup> The 5-year OS rates were not different between adjuvant chemoradiation and adjuvant chemotherapy arms and results demonstrated that adjuvant radiation therapy is not effective in D2 dissected patients. The ongoing phase III ARTIST-II trial is comparing adjuvant chemotherapy with chemoradiation in D2 dissected patients with positive lymph nodes (NCT01761461). Recent adjuvant chemotherapy trials from Asia also supported the beneficial effects of adjuvant chemotherapy in patients that underwent D2 dissection and this approach is accepted as a preferable choice for D2 dissected patients.<sup>43–45</sup>

Response to preoperative chemotherapy was shown to be an important predictor of OS for resectable

GAC.<sup>46</sup> “Peri-operative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer” [Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC)] trial compared peri-operative ECF (epirubicin, cisplatin, and 5-FU) regimen to surgery alone.<sup>47</sup> An estimated improvement of 13% points in the 5-year survival rate with 36.3% and 23.0% for peri-operative treatment and surgery-only groups was reported; however, these outcomes are very poor for both arms. Additionally, less than 50% of patients could complete post-operative treatment. Since the MAGIC trial, ECF has been standard of care in Europe for resectable GAC. In FLOT4-AIO phase III trial, Al-Batran et al<sup>48</sup> noted an increased rate of R0 surgery and prolonged PFS (18 months for ECF vs. 30 months for FLOT; *HR*, 0.75; 95% *CI*: 0.62–0.91; *P* = 0.004) and OS (35 months for ECF vs. 50 months for FLOT; *HR*, 0.77; 95% *CI*: 0.63–0.94; *P* = 0.012) for peri-operative FLOT compared to peri-operative ECF. However, FLOT is a toxic regimen and not recommended for every patient. FLOT results are also not mature. Only very fit patients may be offered this regimen and close monitoring is recommended.

In another study,<sup>49</sup> the addition of bevacizumab, that binds to vascular endothelial growth factor (VEGF), to peri-operative ECX for localized GEAC patients was studied but no benefit was noted (3-year OS rate, 50.3% in ECX alone group and 48.1% for ECX plus

bevacizumab group; *HR*, 1.09; 95% *CI*: 0.91–1.29; *P* = 0.36). More than 70% of all patients could receive post-operative therapies but wound healing complications were more prevalent in bevacizumab group (12% vs. 7%). The phase III studies evaluating adjunctive therapies in resectable GAC are listed in Table 2.

The US SWOG 9008/INT-0116 trial and European MAGIC trial have generated two accepted adjunctive modalities for localized GAC.<sup>31,47</sup> Adjuvant chemoradiation is falling out of favor and ECF or its modification should be abandoned entirely in favor of 5-FU, oxaliplatin, and leucovorin (FOLFOX).<sup>4</sup> The first randomized study comparing pre-operative RT with surgery alone, demonstrated significant benefit in resection rates and OS time in favor of the pre-operative radiotherapy arm.<sup>50</sup> In Phase II trial of pre-operative chemoradiation in patients with localized GAC (RTOG 9904), induction chemotherapy and chemoradiation were applied before gastric surgery.<sup>51</sup> The reported pathologic complete remission rate was 26% and R0 resection rate was 77%. Another phase II trial with pre-operative chemotherapy with irinotecan and cisplatin followed by concurrent chemoradiation supported the RTOG 9904 trial with a 65% R0 resection rate.<sup>52</sup> “The Neoadjuvant Chemotherapy Compared With Surgery Alone for Locally Advanced Cancer of the Stomach and Cardia” [European Organisation for Research and Treatment of Cancer (EORTC) 40954] trial intended to

evaluate the value of purely pre-operative chemotherapy with CF for resectable GAC.<sup>53</sup> The trial was closed early due to poor accrual and there was no survival benefit for pre-operative treatment. Two prospective trials are evaluating the role of preoperative chemoradiation in GAC. Trial of “Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma” (TOPGEAR) (NCT01924819) is a phase III trial comparing peri-operative ECF alone with pre-operative chemoradiation. The interim analysis of first 120 patients demonstrated that pre-operative chemoradiation can be safely applied to patients.<sup>54</sup> The Multicentric Randomised Trial for Resectable Gastric Cancer (CRITICS II) is a phase II trial comparing three investigational pre-operative treatment arms for resectable GAC (chemotherapy vs. chemotherapy and subsequent chemoradiotherapy vs. chemoradiotherapy) (NCT02931890). The results of TOPGEAR study with the outcome of CRITICS II study will determine the optimal adjunctive approach for resectable GAC.

### Approaches for unresectable gastroesophageal adenocarcinoma

GEACs are mostly diagnosed at advanced stage and the estimated 5-year relative survival rate at this stage is about 5%.<sup>55,56</sup> Although cure is not possible, systemic therapy can palliate symptoms, improve survival

Table 2  
Survival outcomes of key studies evaluating the right therapy for localized gastric adenocarcinoma.

Trial	Arms	<i>n</i>	Outcome
SWOG 9008/INT-0116 <sup>31</sup>	Surgery vs. surgery → CRT	275 vs. 281	3-year OS rate, 41% vs. 50%; <i>HR</i> , 1.35; 95% <i>CI</i> : 1.09–1.66; <i>P</i> =0.005
ARTIST <sup>42</sup>	Surgery (D2) → CT vs. surgery (D2) → CRT	228 vs. 230	5-year OS rate, 73% vs. 75%; <i>HR</i> , 1.130; 95% <i>CI</i> : 0.775–1.647; <i>P</i> = 0.5272
ACTS GC <sup>43,44</sup>	Surgery (D2) vs. surgery (D2) → S1	530 vs. 529	3-year OS rate, 70.1% vs. 80.1%; <i>HR</i> , 0.68; 95% <i>CI</i> : 0.52–0.87; <i>P</i> = 0.003
CLASSIC <sup>45</sup>	Surgery (D2) vs. surgery (D2) → XELOX	520 vs. 515	5-year OS rate, 69% vs. 78%; <i>HR</i> , 0.66; 95% <i>CI</i> : 0.51–0.85; <i>P</i> = 0.0015
MAGIC <sup>47</sup>	Surgery vs. ECF×3 → surgery → ECF×3	253 vs. 250	5-year OS rate, 23.0% vs. 36.3%; <i>HR</i> , 0.75; 95% <i>CI</i> : 0.60–0.93; <i>P</i> = 0.009
FLOT4-AIO <sup>48</sup>	FLOT×4 → surgery → FLOT×4 vs. ECF×3 → surgery → ECF×3	356 vs. 360	5-year OS rate, 45% vs. 36%; <i>HR</i> , 0.77; 95% <i>CI</i> : 0.63–0.94; <i>P</i> =0.012
ST03 <sup>49</sup>	(ECX + bevacizumab)×3 → surgery → (ECX + bevacizumab)×3 vs. ECX×3 → surgery → ECX×3	533 vs. 530	3-year OS rate, 48.1% vs. 50.3%; <i>HR</i> , 1.09; 95% <i>CI</i> : 0.91–1.29; <i>P</i> = 0.36

SWOG 9008/INT-0116: Southwest Oncology Group 9008/Intergroup trial 0116; CRT: chemoradiation therapy; OS: overall survival; *HR*: hazard ratio; *CI*: confidence interval; ARTIST: Adjuvant Chemoradiation Therapy in Stomach Cancer; CT: chemotherapy; ACTS GC: Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer; CLASSIC: Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer; XELOX: capecitabine/oxaliplatin; MAGIC: Medical Research Council Adjuvant Gastric Infusional Chemotherapy; ECF: epirubicin, cisplatin, and 5-fluorouracil; FLOT4-AIO: perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma; FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; ECX: epirubicin, cisplatin, and capecitabine; ST03: Chemotherapy With or Without Bevacizumab or Lapatinib to Treat Operable Esophagogastric Cancer.



and provide a better quality of life compared to the best supportive care.<sup>57</sup> Local consolidative therapies can be effective in a selected patient group after controlling the disease with extended (not less than 3 months) systemic treatment.<sup>58</sup>

Chemotherapy regimens including fluoropyrimidines and platinum derivatives are the most investigated combinations and are recommended as the first-line therapy by different guidelines.<sup>4,59,60</sup> In Western countries, 5-FU or capecitabine is the most commonly used fluoropyrimidines and two consecutive phase III studies showed that capecitabine is as effective as 5-FU in treating GEACs.<sup>61,62</sup> In Asian countries, S-1 which contains tegafur (a prodrug of 5-FU) has been the most popular companion to platinum derivatives after “S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS)” trial.<sup>63</sup> However, S-1 did not show the superiority to FU in western GEAC patients in the First-Line Advanced Gastric Cancer Study (FLAGS) trial.<sup>64</sup>

Oxaliplatin is equal to cisplatin in the first-line treatment of advanced stage GEAC patients with a better safety profile.<sup>65,66</sup> Today, oxaliplatin most often accompanies to fluoropyrimidines in the first-line treatment of advanced GEAC.

In a phase III study from Europe, irinotecan combined with 5-FU and folinic acid (FOLFIRI) compared to standard CF combination and FOLFIRI was defined as a safe first-line treatment option that can be applied to patients who cannot tolerate platinum compounds.<sup>67</sup>

Adding a third cytotoxic agent to fluoropyrimidine and platinum derivate combination in the first-line setting does not seem beneficial. In the V325 study, adding docetaxel to cisplatin and 5-FU combination (DCF) ended up with less than 1 month prolongation in OS (9.2 months for DCF vs. 8.6 months for CF; *HR*, 1.29; 95% *CI*: 1.0–1.6; *P* = 0.02) with 82% grade 3–4 neutropenia rate in docetaxel arm.<sup>68</sup> Anthracyclines are not very effective for GEACs and toxicity rate is very high which is not bearable for this patient group.<sup>69</sup>

So far, the only established target for the first-line treatment of advanced GEAC is human epidermal growth factor receptor 2 (HER2). In “Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal cancer [Trastuzumab for Gastric Cancer (ToGA)]” phase III trial, adding trastuzumab to standard fluoropyrimidine plus platinum combination in HER2 expressing advanced GEAC patients was evaluated.<sup>70</sup> The median OS was 13.8 months in trastuzumab plus chemotherapy arm and 11.1 months in only chemotherapy arm (*HR*, 0.74; 95% *CI*: 0.60–0.91;

*P* = 0.0046). Today, trastuzumab is a standard component of first-line treatment of HER2 expressing advanced GEACs. Other agents targeting HER2,<sup>71</sup> epidermal growth factor receptor (EGFR),<sup>72,73</sup> vascular endothelial growth factor (VEGF),<sup>74,75</sup> and MET/hepatocyte growth factor (HGF)<sup>76,77</sup> did not show any beneficial effect in first-line treatment of advanced GEAC.

For the second-line treatment of GEACs, ramucirumab and paclitaxel combination is the best option for today. Ramucirumab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody against vascular endothelial growth factor receptor 2 (VEGFR-2). In “Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW)” trial, ramucirumab plus paclitaxel combination was compared with paclitaxel plus placebo after progression on first line therapy.<sup>78</sup> The median OS was 9.6 months in ramucirumab arm and 7.4 months in placebo arm (*HR*, 0.807; 95% *CI*: 0.678–0.962; *P* = 0.017).

A recent report showed that for advanced stage GEAC patients who can tolerate further treatment, third-line and beyond treatments can improve survival.<sup>79</sup> Irinotecan can be a preferable option for the third-line treatment with a response rate similar to taxanes for advanced stage GEACs.<sup>80</sup> A novel VEGFR-2 tyrosine kinase inhibitor apatinib is also an option that showed significantly improved OS compared to placebo in an Asian patient population.<sup>81</sup> Another and more promising option is immunotherapy which can provide more durable responses. Early phase studies did not show any significant activity of ipilimumab [an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody] on advanced stage GEACs.<sup>82,83</sup> However, anti-programmed death 1 (PD-1) antibody pembrolizumab resulted in a 22% response rate in patients with programmed death ligand 1 (PD-L1)-positive GEACs in KEYNOTE-012 phase 1b study.<sup>84</sup> Phase 1/2 CheckMate-032 study demonstrated a 26% overall response rate with nivolumab (anti-PD-1 antibody) and ipilimumab combination.<sup>85</sup> Recently, Kang et al<sup>86</sup> reported the results of phase III “Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens” (ONO-4538-12, ATTRACTION-2) trial. In this heavily pre-treated Asian patient group, the median OS was longer in nivolumab arm compared to placebo (5.26 months in the nivolumab group and 4.14 months in the placebo group; *HR*, 0.63; 95% *CI*: 0.51–0.78; *P* < 0.0001). In the subset analysis by PD-L1 expression, they demonstrated that benefit is irrespective of PD-L1 expression.<sup>87</sup> Outcomes of key studies for advanced stage GEAC are listed in [Table 3](#).

Table 3

Outcomes of key studies evaluating the right therapy for advanced gastroesophageal adenocarcinoma in different lines.

Trial/line	Arms	n	Outcome
Cunningham et al <sup>61</sup> /first line	ECF vs. ECX vs. EOF vs. EOX	1002	Median OS, 9.9 vs. 9.9 vs. 9.3 vs. 11.2 months; $P > 0.05$
Kang et al <sup>62</sup> /first line	XP vs. FP	316	Median OS, 10.5 vs. 9.3 months; $HR, 0.85; 95\% CI: 0.64-1.13; P = 0.008$
Koizumi et al <sup>63</sup> /first line	S1+cisplatin vs. S1	305	Median OS, 13 vs. 11 months; $HR, 0.77; 95\% CI: 0.61-0.98; P = 0.04$
Al-Batran et al <sup>65</sup> /first line	FLO vs. FLP	220	Median OS, 10.7 vs. 8.8 months; $P > 0.05$
Dank et al <sup>67</sup> /first line	IF vs. CF	333	Median OS, 9 vs. 8.7 months; $HR, 1.08; 95\% CI: 0.86-1.35; P = 0.53$
Van Cutsem et al <sup>68</sup> /first line	DCF vs. CF	445	Median OS, 9.2 vs. 8.6 months; $HR, 1.29; 95\% CI: 1.0-1.6; P = 0.02$
Guimbaud et al <sup>69</sup> /first line	ECX vs. FOLFIRI	416	Median OS, 9.5 vs. 9.7 months; $HR, 1.01; 95\% CI: 0.82-1.24; P = 0.95$
Bang et al <sup>70</sup> /first line	Trastuzumab + CF vs. CF	594	Median OS, 13.8 vs. 11.1 months; $HR, 0.74; 95\% CI: 0.60-0.91; P = 0.0046$
Wilke et al <sup>78</sup> /second line	Ramucirumab + paclitaxel vs. placebo + paclitaxel	665	Median OS, 9.6 vs. 7.4 months; $HR, 0.807; 95\% CI: 0.678-0.962; P = 0.017$
Hironaka et al <sup>80</sup> /second line	Paclitaxel vs. irinotecan	223	Median OS, 9.5 vs. 8.4 months; $HR, 1.13; 95\% CI: 0.86-1.49; P = 0.38$
Li et al <sup>81</sup> /third line and more	Apatinib vs. placebo	267	Median OS, 6.5 vs. 4.7 months; $HR, 0.709; 95\% CI: 0.537-0.937; P = 0.0156$
Kang et al <sup>86</sup> /third line and more	Nivolumab vs. placebo	493	Median OS, 5.26 vs. 4.14 months; $HR, 0.63; 95\% CI: 0.51-0.78; P < 0.0001$

ECF: epirubicin, cisplatin, and 5-fluorouracil; ECX: epirubicin, cisplatin, and capecitabine; EOF: epirubicin, oxaliplatin, and 5-fluorouracil; EOX: epirubicin, oxaliplatin, and capecitabine; OS: overall survival; XP: capecitabine and cisplatin; FP: 5-fluorouracil and cisplatin; HR: hazard ratio; CI: confidence interval; FLO: 5-fluorouracil, leucovorin, and oxaliplatin; FLP: 5-fluorouracil, leucovorin, and cisplatin; IF: irinotecan and 5-fluorouracil; CF: cisplatin plus 5-fluorouracil; DCF: docetaxel, cisplatin, and 5-fluorouracil; FOLFIRI: 5-fluorouracil, leucovorin, and irinotecan.

Numerous phase III trials evaluating targeted therapies in different lines are ongoing and we will be able to determine the most appropriate patient group that can benefit from various targeted agents and immunotherapy in the future.<sup>88</sup>

### Conflicts of interest

The authors have no conflicts of interest to declare.

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