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1. Introduction

Despite significant advances in surgical technique, the overall survival of patients presenting with resectable gastric and gastroesophageal junction (GEJ) adenocarcinoma has remained unsatisfactory. Following state-of-the-art surgery including D2 lymphadenectomy, the vast majority of patients with initially localized disease will eventually relapse and ultimately succumb to the disease. Modern multimodal treatment plans integrate systemic chemotherapy and – in some cases – radiation therapy into treatment algorithms aiming to increase R0 resection rate, improve local control, and eradicate occult micro-metastatic disease. Treatment strategies for resectable non-metastatic gastric and GEJ adenocarcinoma have traditionally differed between continents and are constantly evolving in a highly dynamic and intensively researched field.

In Europe, the landmark phase III MAGIC trial [1] has set the stage for perioperative chemotherapy with ECF/ECX (Table 1) as standard-of-care for resectable gastric and GEJ cancers, while the more recently published CROSS trial [2,3] established neoadjuvant chemoradiation as a valid treatment option for esophageal adenocarcinoma and GEJ tumors. Most recently, the FLOT4 trial [4] proved superiority of perioperative chemotherapy with the taxane- and oxaliplatin-based FLOT regimen over ECF/ECX, both in terms of histopathological tumor response [5] and overall survival (Figure 1) broadly across all subgroups [4]. FLOT is now rapidly being adopted as a new standard-of-care across Europe.

Within the US, adjuvant chemoradiation following up-front resection based on the results of the Intergroup116 trial [6] had been an accepted standard-of-care. This trial has, however, been criticized for inadequate lymph node resection (<D2) arguing that the positive effect of radiotherapy might not be maintained in patients undergoing D2 lymphadenectomy. In line with this, subsequent trials including CALGB80101 [7], the Korean ARTIST trial [8], and the Dutch CRITICS study [9] did not show a survival benefit of postoperative radiation, triggering a decline of postoperative radiation use and a shift towards adjuvant or perioperative chemotherapy.

Eagerly awaited trials are currently evaluating the role of preoperative chemoradiation. The German phase III ESOPEC trial (NCT02509286) compares neoadjuvant chemoradiation with carboplatin and paclitaxel (CROSS protocol) to perioperative chemotherapy with FLOT in esophageal adenocarcinoma including GEJ cancers [10]. Other ongoing trials focus on the perioperative treatment of distinct molecular subgroups of gastric and GEJ cancers, evaluating the impact of personalized, molecularly stratified treatment approaches for resectable disease. Examples are trials for HER2/neu-positive tumors (INNOVATION, NCT02205047...
The perioperative treatment landscape for gastric/GEJ cancer is shifting from cisplatin- to oxaliplatin-based combination chemotherapy.

The landmark FLOT4 and CLASSIC phase III trials have shown superior PFS and OS for oxaliplatin combinations in the perioperative and adjuvant settings.

For advanced irresectable and metastatic gastric/GEJ cancer, 5 published randomized trials show non-inferior efficacy and an overall more favorable safety profile for oxaliplatin over cisplatin combinations.

Ongoing trials further evaluate the role of neoadjuvant chemoradia-
tion and explore the addition of molecularly targeted agents and immune checkpoint inhibitors to the FLOT backbone aiming to personalize perioperative treatment.

This box summarizes key points contained in the article.

**Article highlights**

- The perioperative treatment landscape for gastric/GEJ cancer is shifting from cisplatin- to oxaliplatin-based combination chemotherapy.
- The landmark FLOT4 and CLASSIC phase III trials have shown superior PFS and OS for oxaliplatin combinations in the perioperative and adjuvant settings.
- For advanced irresectable and metastatic gastric/GEJ cancer, 5 published randomized trials show non-inferior efficacy and an overall more favorable safety profile for oxaliplatin over cisplatin combinations.
- Ongoing trials further evaluate the role of neoadjuvant chemoradiation and explore the addition of molecularly targeted agents and immune checkpoint inhibitors to the FLOT backbone aiming to personalize perioperative treatment.

**Table 1. Pivotal phase III trials for locally advanced resectable gastric/GEJ cancers.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Patients (n)</th>
<th>HR</th>
<th>Regimens</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLOT4</td>
<td>2017*</td>
<td>716</td>
<td>0.77</td>
<td>FLOT</td>
<td>Perioperative CTX</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.63, 0.94)</td>
<td>ECF/ECX</td>
<td>Perioperative CTX</td>
</tr>
<tr>
<td>MAGIC</td>
<td>2006</td>
<td>503</td>
<td>0.75</td>
<td>ECF</td>
<td>Perioperative CTX</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.60, 0.93)</td>
<td>Surgery only</td>
<td>Perioperative CTX</td>
</tr>
<tr>
<td>OEOS</td>
<td>2017</td>
<td>897</td>
<td>0.90</td>
<td>S-FU/Cisplatin</td>
<td>Perioperative CTX</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.75, 1.05)</td>
<td>ECX</td>
<td>Perioperative CTX</td>
</tr>
<tr>
<td>FFCD9703</td>
<td>2011</td>
<td>224</td>
<td>0.69</td>
<td>S-FU/Cisplatin</td>
<td>Perioperative CTX</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.05, 0.96)</td>
<td>Surgery only</td>
<td>Perioperative CTX</td>
</tr>
<tr>
<td>ACTS-GC</td>
<td>2007</td>
<td>1059</td>
<td>0.68</td>
<td>Surgery + S1</td>
<td>Adjuvant CTX</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.52, 0.87)</td>
<td>Surgery only</td>
<td>Adjuvant CTX</td>
</tr>
<tr>
<td>CLASSIC</td>
<td>2012</td>
<td>1035</td>
<td>0.56</td>
<td>Surgery + CAPOX</td>
<td>Adjuvant CTX</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.44, 0.72)</td>
<td>Surgery</td>
<td>Adjuvant CTX</td>
</tr>
<tr>
<td>CROSS**</td>
<td>2012</td>
<td>366</td>
<td>0.66</td>
<td>RCTX + surgery</td>
<td>Neoadjuvant RCTX</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.50, 0.87)</td>
<td>Surgery only</td>
<td>Neoadjuvant RCTX</td>
</tr>
</tbody>
</table>

*Full publication pending

**Esophageal and GEJ cancers, n = 84 squamous cell histology**

3. **Clinical efficacy, safety, and tolerability of oxaliplatin for gastric/GEJ cancers**

3.1. **Oxaliplatin versus cisplatin for advanced gastric cancer**

For the advanced stage, irresectable gastric and GEJ adenocarcinoma, six randomized controlled trials (RCTs) directly compared the arrival of the FLOT regimen and of CAPOX based on the CLASSIC trial, the global treatment landscape is rapidly shifting towards oxaliplatin. Direct prospective comparisons between cisplatin and oxaliplatin within otherwise unchanged combination regimens are only available for patients with irresectable and metastatic disease, pointing to similar efficacy and distinct, overall reduced levels of toxicity for the oxaliplatin combinations [17–21]. Consequently, oxaliplatin has long been considered standard-of-care for patients with irresectable and metastatic gastric cancer. Within this drug profile, we highlight its pharmacological profile, summarize pivotal clinical data and discuss its future role for gastric/GEJ cancer perioperative treatment.

2. **Clinical pharmacology**

Oxaliplatin is a diaminocyclohexane-containing third-generation platinum compound with distinct structure (Figure 2), activity, and toxicity spectrum compared to cisplatin and carboplatin [24]. Oxaliplatin was first patented in 1976 and approved for medical use in 1996. Oxaliplatin has clinical activity as a mono-substance, but is typically used in combinations with other chemotherapeutic agents forming some of the most common chemotherapy regimens in modern oncology [25]. Doublet combinations are assembled with the fluoropyrimidines 5-FU/LV or capecitabine to form FOLFOX and CAPOX regimens. Triplet combinations for gastric and GEJ cancer further include the anthracycline epirubicin to form ECF/ECX protocols (Table 2). Triple combinations of 5-FU, oxaliplatin, and docetaxel have emerged in the wake of studies with 5-FU/cisplatin/taxane combinations such as DCF, which were found to be both highly efficacious and highly toxic [26,27]. The FLOT protocol was therefore introduced, replacing cisplatin with oxaliplatin, and early studies supported the hypothesis of excellent activity paired with acceptable safety and tolerability [28].
oxaliplatin to cisplatin in combination chemotherapy regimens [17–21]. Table 3 summarizes trial design and results, while Table 2 details components of chemotherapy combination protocols. Ten years ago, a large pivotal landmark study provided evidence for the non-inferiority of oxaliplatin in triple combination with epirubicin and 5-FU/capecitabine [18]. In the secondary analysis of this trial, EOX significantly improved overall survival compared to ECF, thereby establishing the EOX as a new standard-of-care for these patients. Moreover, oxaliplatin was associated with lower incidences of grade 3 or 4 neutropenia, alopecia, renal toxicity, and thromboembolism. Diarrhea and neuropathy, however, occurred more frequently with EOX [18]. A smaller German Phase III study compared the FLO (5-FU/LV+oxaliplatin) regimen with FLP (5-FU/LV+cisplatin). Again, side effects with oxaliplatin were generally milder with the exception of an increased rate of polyneuropathy with oxaliplatin, and efficacy was non-inferior for the overall population and superior with oxaliplatin for patients aged >65 years [17]. Several meta-analyses concluded that there exists a firm body of evidence supporting comparability of efficacy between oxaliplatin and cisplatin in the advanced stage and metastatic gastric and GEJ adenocarcinoma [29,30]. Within the same analysis, most grade 3/4 toxicities were significantly reduced with oxaliplatin, while sensory neurotoxicity was found increased with a hazard ratio (HR) of 8.68, p < 0.0001 [31]. A recent Cochrane meta-analysis comparing oxaliplatin vs. cisplatin in otherwise identical chemotherapy backbones for advanced and metastatic gastric/GEJ cancers found a statistically significant benefit in overall survival for...
oxaliplatin compared to cisplatin (HR 0.81). Data from the pivotal REAL trial [18], however had been excluded from the analysis [42]. The structural, molecular, cellular, and pharmacological basis for the differences in efficacy and toxicity of the two platinum compounds has been studied in much detail, however has remained incompletely understood [32].

3.2. Oxaliplatin-based combination chemotherapy in the perioperative setting

The FLOT protocol (Table 2) was introduced as alternative intensified taxane- and platinum-containing chemotherapy regimen by the German FLOT study group [28]. Several randomized phase II trials from the same group have since underlined the feasibility of perioperative treatment with FLOT for locally advanced [33,34] and oligometastatic resectable disease [35]. The pivotal Phase II/III FLOT4 trial enrolled patients with locally advanced resectable gastric and GEJ tumors (clinical stage cT2 or higher, and/or nodal positive (cN+) disease), and randomized them 1:1 between perioperative chemotherapy with FLOT (each 4 biweekly cycles pre- and postoperatively) and ECF/ECX (each 3 3-weekly cycles pre- and post-OP). The phase II part of the trial [5] enrolled 300 patients from 28 German centers and evaluated histopathological regression following the neoadjuvant part of the protocol (4 cycles of FLOT vs. 3 cycles of ECF/ECX). The study endpoint was met, and patients treated with FLOT showed a significantly higher complete histopathological response rate (16 vs. 6%, Figure 2). The phase III part of the trial [4] enrolled 716 patients from 38 German centers. Baseline characteristics were well balanced between treatment groups. Median age was 62 years; approximately 24%, 32%, and 44% of patients had GEJ Siewert I, GEJ Siewert II-III, and gastric cancer, respectively. The trial met its primary endpoint showing significantly improved overall survival for the FLOT arm (median OS 35 vs. >50 months, HR 0.77 (0.63–0.94), 3 year OS 48 vs. 57%). Resection rate, R0 resection, and progression-free survival were also significantly superior within the FLOT arm [4]. Subgroup analysis further highlighted superiority of the FLOT regimen for all groups including diffuse-type histology, GEJ I, and earlier stage (cT2N0) tumors. Perioperative morbidity and mortality were very similar between the treatment arms. The FLOT protocol was associated with significantly higher rates of grade 3/4 diarrhea (10 vs. 4%), neutropenia (51 vs. 39%), infections (18 vs. 9%) and sensory neuropathy (7% vs. 4%), while ECF/ECX more frequently caused nausea and vomiting (16 vs. 7% and 8% vs. 2%, respectively).

Completion rates of pre-OP chemotherapy were 90/91%, with adherence to postoperative chemotherapy was rather low for both arms (37% for ECF/ECX vs. 46% for FLOT).

In summary, the landmark FLOT4 trial established a new standard-of-care for locally advanced gastric/GEJ cancers. While the major difference between FLOT and ECF/ECX arguably lies in the exchange of an anthracycline for a taxane, FLOT also replaces cisplatin with oxaliplatin, thereby avoids the high toxicity of 5-FU/cisplatin/taxane combinations such as DCF [26,27]. Ongoing studies of the FLOT study group explore FLOT ± surgical resection of both primary tumor and metastatic lesions in oligometastatic disease (FLOT5 RENAISSANCE, phase III, NCT02578368), the addition of trastuzumab and pertuzumab to perioperative FLOT for HER2-positive tumors (FLOT6 PETRARCA, phase II/III, NCT02581462), the potential of the anti-VEGFR2 antibody ramucirumab added to perioperative FLOT (FLOT7 RAMSES, phase II/III, NCT02661971), as well as the addition of the anti-PD-L1 antibody atezolizumab to perioperative FLOT (FLOT8 DANTE, phase II, NCT03421288). With all these results pending, it appears likely that the FLOT backbone will continue to dominate perioperative chemotherapy for gastroesophageal adenocarcinoma in the foreseeable future.

3.3. Oxaliplatin-based adjuvant chemotherapy

Standard-of-care for resectable gastric and GEJ cancer in Asian countries is upfront tumor resection followed by adjuvant chemotherapy. This is mainly based on two randomized phase III trials, the ACTS-GC [14] study conducted in Japan, and the CLASSIC trial conducted in South Korea, China, and Taiwan [36]. The ACTS-GC trial recruited over 1000 patients who had undergone D2 gastrectomy for stage II-IIIB gastric cancer. These patients were randomized between 1 year of adjuvant S-1 and observation alone. Five-year outcomes showed that adjuvant S-1 is associated with improved 5-year progression-free survival (65.4% vs. 53.1%; HR 0.65) and OS (71.7% vs. 61.1%; HR 0.68) compared to observation alone. Based on these results adjuvant S1 is still a commonly used approach for adjuvant therapy in Asia.

The more recent CLASSIC trial [36] randomized a similarly defined patient group to either 6 months of adjuvant capecitabine and oxaliplatin (CAPOX) or observation. This trial also met its primary endpoint of 3-year disease-free survival and superior OS for patients who received chemotherapy; 5-year

Table 3. Clinical trials evaluating oxaliplatin- vs. cisplatin-based chemotherapy for gastric/GEJ Cancer.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Phase</th>
<th>Patients (n)</th>
<th>HR (95% CI)</th>
<th>Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamada et al. [21]</td>
<td>2015</td>
<td>III</td>
<td>641</td>
<td>0.96 (0.80–1.14)</td>
<td>S-1/Oxaliplatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>S-1/Cisplatin</td>
</tr>
<tr>
<td>Kim et al. [19]</td>
<td>2014</td>
<td>II</td>
<td>77</td>
<td>0.90 (0.59–1.41)</td>
<td>Docetaxel/Oxaliplatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Docetaxel/Cisplatin</td>
</tr>
<tr>
<td>Al-Batran et al. [17]</td>
<td>2008</td>
<td>III</td>
<td>220</td>
<td>0.82 (0.47–1.45)</td>
<td>5-FU/Oxaliplatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-FU/Cisplatin</td>
</tr>
<tr>
<td>Cunningham et al. [18]</td>
<td>2008</td>
<td>III</td>
<td>964</td>
<td>0.92 (0.80–1.10)</td>
<td>Epirubicin/Oxaliplatin/S-FU-Cap</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Epirubicin/Cisplatin/S-FU-Cap</td>
</tr>
<tr>
<td>Hironaka et al. [41]</td>
<td>2016</td>
<td>II</td>
<td>95</td>
<td>0.59 (0.37–0.93)</td>
<td>S-1/Oxaliplatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>S-1/Cisplatin</td>
</tr>
<tr>
<td>Popov et al. [20]</td>
<td>2008</td>
<td>II</td>
<td>72</td>
<td>0.70 (0.54–0.90)</td>
<td>5-FU/Oxaliplatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-FU/Cisplatin</td>
</tr>
</tbody>
</table>
DFS was also improved (68% vs. 53%; HR 0.58) [16]. Subgroup analysis of both trials suggests that CAPOX might be particularly beneficial in nodal positive disease while adjuvant S1 performed well in the N0 setting, leading to the frequently adapted approach to treat nodal-positive disease with CAPOX and nodal negative disease with S1.

4. Expert opinion
Multimodal treatment of gastroesophageal adenocarcinoma is an extremely challenging field of oncology. Since the publication of the landmark MAGIC trial in 2006, substantial progress had been lacking with many unexpectedly disappointing results from phase III trials. Against this background, the results of the FLOT4 study are groundbreaking and trigger a paradigm shift, replacing epirubicin and cisplatin in gastric/GEJ cancer perioperative treatment regimens for docetaxel and oxaliplatin. FLOT significantly prolonged PFS and OS in comparison to ECF/ECX, and its superiority was maintained across all relevant subgroups, including diffuse-type histology, small tumors (cT2N0) and distal esophageal adenocarcinomas. Maybe most importantly, the FLOT protocol was overall well tolerated and will be suitable as chemotherapy backbone onto which molecularly targeted agents and immune checkpoint inhibitors can be added, aiming to further improve efficacy and to better personalize treatment according to the molecular make-up of individual tumors.

Still, many questions remain: given that less than half of patients tolerated postoperative chemotherapy, should more cycles be added to neoadjuvant treatment? What is the role and effect of the adjuvant part of the protocol [37]? Which adjuvant treatment should we offer to poor responders to neoadjuvant treatment? Should distinct molecular subtypes of gastric cancer be treated differently [38]? What is the role of neoadjuvant chemoradiation in GEJ tumors [39]? Many of these questions are currently being addressed in a flurry of exciting clinical trials in the field.

5. Five-year view
The upcoming five years will see results of many of the aforementioned pivotal studies, several of which will definitely further advance the field. The global oncology community will continue to adopt the FLOT protocol and cisplatin doublet or triplet combinations will become less commonly used if not obsolete in the perioperative setting. Precision medicine is arriving at a rapid pace and will have its impact on perioperative treatment. Comprehensive molecular analysis, including liquid biopsy and assessment of tumor mutational burden (TMB) will move closer to clinical routine and clinical decision-making will be based on these informations. Several phase III trials addressing the impact of chemoradiation in the neoadjuvant setting (ESOPEC [10], CRITICS-II and TOPGEAR [40]) will further refine multimodality treatment. In summary, chances are excellent for treatment strategies around the globe to further evolve over the next five years, in order to ultimately further improve patient outcome.

Declaration of interest
No potential conflict of interest was reported by the authors.

References
Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.


•• This landmark study (MAGIC) provided the rational for perioperative treatment for resectable gastroesophageal cancer.


• This study (CROSS) established neoadjuvant chemoradiation as standard-of-care for esophageal and GEJ cancers.


•• This landmark study (FLOT4) established perioperative FLOT as novel standard-of-care for resectable gastroesophageal cancer.


• **Landmark study (CLASSIC) establishing adjuvant CAPOX as standard-of-care following primary resection in Asian patients.**


• **One of the rare studies directly comparing cisplatin vs. oxaliplatin within otherwise unchanged combination regimens.**


• **The first study directly comparing cisplatin vs. oxaliplatin within otherwise unchanged combination regimens.**


38. Leong T, Smithers BM, Haustermans K, et al. TOPGEAR: a randomized, phase III trial of perioperative ECF chemotheraphy with or without preoperative chemoradiation for resectable gastric cancer: interim results from an international,
