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Safety and efficacy of the FLOT regimen in the Polish population - an analysis of the prospective trial

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As gastric cancer is associated with poor prognosis, the preferred management of locally advanced gastric cancer (GC) and gastroesophageal junction (GEJ) cancer in European patients is perioperative chemotherapy using the FLOT regimen. Previously published data demonstrate that such treatment is associated with improved disease-free survival (DFS) as well as overall survival (OS) compared to ECF/ECX regimen. In order to collect biomaterial for the identification of serum biomarkers of an early response to neoadjuvant chemotherapy, we performed a prospective study and here, we report the safety and clinical efficacy of this prospective cohort. It was an academic, nonrandomized, prospective study, conducted at Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw, Poland. Between January 2018 and November 2019, we analyzed a total of 61 patients aged 30-77 (median 63 years, 52.5% males and 47.5% females) with histologically confirmed GC or GEJ cancer. The patients were qualified by a multidisciplinary team for perioperative treatment (FLOT regimen). All cases of reported adverse events were recorded and analyzed. All patients received G-CSF prophylactically. After gastrectomy, an assessment of pathological regression was performed according to the Becker classification. A total of 93.4% (57) patients completed four cycles of preoperative chemotherapy and 78.7% (48) received postoperative chemotherapy. All of them experienced grade 1/2 toxicities. The common AE G1/G2 in preoperative versus postoperative chemotherapy were: fatigue (75% vs. 60%), anemia (64% vs. 62%), nausea (60% vs. 60%), peripheral neuropathy (60% vs. 60%), and oral mucositis (59% vs. 50%), respectively. Only 24.6% (15) had G3/4 adverse events during preoperative chemotherapy and only 20.8% (10) during postoperative chemotherapy. The estimated DFS at 3 years was 53% (95% CI 40.5–66.1%) and the estimated OS at 3 years was 60.2% (95% CI 45.1–72.3%). FLOT regimen significantly improved GC and GEJ cancer patients' prognosis with acceptable side-effect profiles.

Key words: gastric cancer, safety, efficacy, chemotherapy, FLOT, DFS, OS

Gastric cancer (GC) is an important problem influencing life expectancy and has a significant impact on overall health globally. GC has been reported as the fifth most common cancer and the fourth leading cause of cancer deaths worldwide [1, 2]. According to the World Health Organization GLOBOCAN 2020 database, the total number of newly diagnosed cases of GC was estimated at 1,089,103, which was 5.6% of all newly detected malignancies, and GC-related mortality was estimated at 768,793, which was 7.7% of cancer-related deaths. The age-standardized world incidence rate was 11.1/100,000 and the age-standardized world mortality rate was 7.7/100,000. Central and Eastern Europe had the second highest rate of GC after East Asia, with an estimated age-standardized incidence rate (ASIR) of 11.3/100,000 and an age-standardized mortality rate (ASMR) of 7.7/100,000. Medium levels of gastric cancer were observed in Western and Southern Europe (ASIR: 5.9 and 7.4/100,000, respectively).

GC most commonly occurs over the age of 60, with the incidence in men twice as frequent as in women [2]. Locally advanced disease is diagnosed in approximately 2/3 of western patients and prognosis is highly dependent on the tumor stage at presentation [3]. In addition, molecular heterogeneity is associated with clinical phenotype and plays a prognostic role. The best overall prognosis and the lowest frequency of recurrence (22%) have microsatellite-unstable and EBV-positive tumors, which is probably less frequent in the western population [4]. The worst prognosis and the

highest recurrence frequency (63%) has mesenchymal-like tumor [4]. Surgical treatment remains the best treatment modality for a potential cure. Despite developments in the surgical treatment, the efficacy of gastrectomy with extent lymph node dissection may be substantially limited by the risk of micrometastasis and peritoneal dissemination [5, 6]. Curative resection alone leads to a dismal outcome of gastric and GEJ adenocarcinoma, which points to the necessity of the application of perioperative chemotherapy. This approach in locally advanced, primary resectable GC and GEJ cancer has been established since both the MAGIC trial and the French FNCLCC/FFCD 97033 study. These studies revealed down-staging of the tumor, eliminating radiologically occult micrometastases, rapidly improving tumor-related symptoms, and significantly improving the OS (13–14%) [7, 8]. According to the report by Al-Batran et al. published in Lancet 2019, the FLOT regimen is a more effective type of chemotherapy, inducing more tumor responses than other regimens and improving the margin-free resection rate. FLOT is superior to ECF/ECX with respect to the complete pathological response (15% vs. 6%) and median OS (50 months vs. 35 months) with an acceptable toxicities profile [9].

Patients and methods

This nonrandomized, prospective study was conducted at the Maria Sklodowska-Curie National Research Institute of Oncology, in Warsaw, Poland. We aimed at a prospective study in order to collect biomaterial for the identification of serum biomarkers of early response to neoadjuvant chemotherapy. Here we report the safety and clinical efficacy of this prospective cohort. The trial was conducted in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the Local Bioethics Committee at the Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw (approval number 51/2016/2017).

Inclusion and exclusion criteria. The main inclusion criteria were as follows: written informed consent for participation in the trial, age ≥18 years old, patients with histopathologically confirmed gastric or gastroesophageal junction (GEJ) adenocarcinoma of a clinical stage cT2-T4/cN-any or cT-any/cN+, no evidence of distant metastasis, ECOG (Eastern Cooperative Oncology Group) performance status ≤2, adequate liver, kidney, and hematologic function. The main exclusion criteria were: prior chemotherapy or radiotherapy, active or documented prior autoimmune or inflammatory disorder, history of other primary malignancies, current or prior use of immunosuppressive medication or corticosteroids exceeding 10 mg/day of prednisone or its equivalent, allergy to an iodine contrast agent, concomitant disease (coronary heart disease, arrhythmia, stroke) preventing the administration of chemotherapy according to protocol, pregnancy, and breastfeeding.

Patient treatment. The clinical stage at the baseline was evaluated by physical examination, esophago-duodenoscopy, computed tomography (CT), or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis. In accordance with the Polish standards of care, diagnostic laparoscopy was recommended but was not mandatory and was not performed on any patient. FLOT administration consisted of four preoperative cycles and four postoperative cycles. During each 2-week cycle of the FLOT regimen, the following were administered: docetaxel 50 mg/m^2 on day 1, oxaliplatin 85 mg/m^2 on day 1, leucovorin 200 mg/m^2 on day 1, and 5-FU 2,600 mg/m^2 as a 24 h infusion on day 1. Patients were assessed according to their medical history, physical examination, weight, ECOG, performance status, complete blood count and blood chemical tests at baseline and before the start of every cycle. Adverse events were graded according to CTCAE (Common Terminology Criteria for Adverse Events) v 4.03 before each cycle. Granulocyte colony-stimulating factor (G-CSF) was used for primary prophylaxis of febrile neutropenia. All the patients received 6 mg of pegfilgrastim subcutaneously 24–72 h after the completion of each cycle of chemotherapy infusion. Chemotherapy was continued unless written informed consent was withdrawn, unacceptable toxicity occurred or progression of disease was observed. CT or MRI scan of the chest, abdomen, and pelvis was performed between 2 and 4 weeks following the completion of the last cycle of preoperative chemotherapy in order to confirm the absence of progression and metastasis. Surgery was scheduled for 4 to 6 weeks after the completion of the last cycle of chemotherapy. Subtotal or total distal gastrectomy with D2 lymphadenectomy was performed for gastric tumor. Transthoracic esophagectomy with resection of the proximal stomach and 2-field lymphadenectomy for type 1 GEJ cancers and gastrectomy with transhiatal distal esophagectomy plus D2 lymphadenectomy for type 2 and type 3 GEJ cancer were performed.

Statistical analysis. The pathological response of the primary tumor to neoadjuvant chemotherapy was evaluated according to Becker classification. This system classifies pathologic response as follows: TGR1a – no residual tumor/tumor bed, TGR1b – <10% residual tumor/tumor bed, TGR2 – 10–50% residual tumor/tumor bed, TGR3 – >50% residual tumor/tumor bed. Follow-up occurred every three months for 2 years and then every six months for 3 years, with chest, abdomen, pelvic CT or MRI scan, tumor marker (CEA, Ca 19.9), and clinical examination. Tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Overall survival and progression-free survival were calculated from the date of randomization until the date of death and the date of documentation of disease progression or death in patients without disease progression, respectively. Kaplan-Meier method was used to estimate overall survival and progression-free survival with 95% confidence intervals (CI). All analyses and figures were prepared using Stata ver. 15.

Results

The patients were enrolled in the study between January 2018 and November 2019. A total of 71 patients signed informed consent and started treatment. Two patients, having received two cycles of chemotherapy, failed to report to the center again and there was no further contact with them. Three patients, after four cycles of preoperative chemotherapy, did not report to surgery. Five patients were excluded from the final analysis (two patients did not consent to gastrectomy and were qualified for Macdonald radio-chemotherapy, two patients did not meet inclusion criteria as they were not primary resectable and were qualified for the CROSS protocol and one patient did not consent to continue treatment due to a poor response to preoperative chemotherapy and was qualified for Macdonald by MDT). The final data analysis was conducted on 61 patients aged 30–77 (median 63 years, 52.5% males and 47.5% females). The baseline characteristics of the patients are presented in Table 1. Full pre-operative treatment of four cycles of the FLOT regimen was administered to 93.4% (57) patients. A total of 6.6% (4) patients received three cycles of the FLOT regimen (2 due to toxicity and 2 at the patients' request). Dose reduction during one or more of the pre-operative cycles of chemotherapy was required in 54% (33) patients. Dose delays ≤7 days occurred in 26% (16) and dose delays >7 days occurred in 2% (1) patients due to fluid accumulation in the venous access port area. Hospitalization was required in 13% (8) patients as a result of the side effects of chemotherapy. No deaths occurred during preoperative chemotherapy. All patients experienced grade 1/2 toxicities. Adverse events associated with preoperative treatment are presented in Table 2. The most frequent of them were as follows: fatigue 75% (46), anemia 64% (39), nausea 60% (37), peripheral neuropathy 60% (37), and oral mucositis (59%). Only 24.6% (15) patients had any G3/4 adverse events. The most common of them were: nausea 11% (7), vomiting 10% (6), fatigue 6% (4), and diarrhea 5% (3). A preoperative CT scan was not performed in 11% (7) patients. The median time before the first cycle of preoperative chemotherapy and surgery was 13.1 weeks (9.1–20.9 weeks). A total of 87% (53) patients were resectable after preoperative chemotherapy. Margin-free resection (R0) was achieved in 85% (52) patients whereas R1 resection was achieved in 2% (1) patients. Surgical and pathology results of treatment are presented in Table 3. Pathological features indicating good prognosis such as histopathological tumor regression according to Becker classification TRG1a/b were found in 21 % (13) patients and ypN0 according to TNM AJCC 8th edition were found in 56% (34) patients. No response to preoperative chemotherapy was revealed in 13% (8) patients – 5% (3) patients as progression disease in CT and 8% (5) patients during surgery. Only palliative surgery was performed in the latter group. A total of 9.4% (5) patients were not qualified for postoperative chemotherapy due to postoperative complications (pancreatitis, duodenal stump blowout, gastric remnant necrosis, anastomotic leak, abscess, or postoperative bleeding) and four of them required reoperation. A total of 78.7% (48) received postoperative chemotherapy. Four cycles of the postoperative FLOT regimen were administered to 59% (28) patients, 4% (2) patients received 1 cycle of FLOT, 37% (18) patients received 2 or 3 cycles of postoperative chemotherapy due to late postoperative complications, lack of recovery after surgery, refusal to continue treatment, toxicity, and concomi-

Table 1. Baseline characteristics of the treatment group (n = 61).

Age (years)	
Median	63 (30–77)
<60	20 (33%)
60-69	30 (49%)
≥70	11 (18%)
Sex	
Male	32 (52.5%)
Female	29 (47.5%)
ECOG	
0	11 (18%)
1	50 (82%)
Location of tumor	
GEJ	14 (23%)
Stomach	47 (77%)
cT-stage	
T1	1 (2%)
T2	28 (46%)
T3	27 (44%)
T4	5 (8%)
cN-stage	
N0	30 (49%)
N1	11 (18%)
N2	11 (18%)
N3	9 (15%)
N-	30 (49%)
N+	31 (51%)
TNM according to AJCC – the 8th edition	
IIA	27 (44%)
IIB	18 (30%)
IIIA	5 (8%)
IIIB	7 (11%)
IIIC	4 (7%)
Lauren's type	
diffuse	17 (28%)
intestinal	23 (38%)
mixed	12 (19%)
Not evaluable according to Lauren	9 (15%)
Signed ring cell/poorly cohesive	22 (36%)
Grading according to WHO	
G1	1 (2%)
G2	21 (34%)
G3	28 (46%)
Not evaluable	11 (18%)

Table 2. Adverse events associated with perioperative treatment.

	Preoperative chemotherapy (n=61)		Postoperative chemotherapy (n=48)	
	any G1/G2 61 (100%)	any G3/G4 15 (24.6%)	any G1/G2 48 (100%)	any G3/G4 10 (20.8%)
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
Nausea	37 (60%)	7 (11%)	29 (60%)	4 (8%)
Vomiting	10 (16%)	6 (10%)	10 (21%)	4 (8%)
Diarrhea	19 (31%)	3 (5%)	14 (29%)	3 (6%)
Constipation	2 (3%)	0 (0%)	0 (0%)	0 (0%)
Stomatitis/mucositis	36 (59%)	1 (2%)	24 (50%)	2 (4%)
Peripheral neuropathy	37 (60%)	2 (3%)	29 (60%)	1 (2%)
Fatigue	46 (75%)	4 (6%)	29 (60%)	6 (12%)
Thrombocytopenia	11 (18%)	0 (0%)	4 (8%)	0 (0%)
Thromboembolic	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Anemia	39 (64%)	0 (0%)	30 (62%)	0 (0%)
Neutropenia	2 (3%)	3 (5%)	3 (6%)	1 (2%)
Leukopenia	5 (8%)	0 (0%)	3 (6%)	0 (0%)
Serum AST	22 (36%)	0 (0%)	12 (25%)	0 (0%)
Serum ALT	18 (29%)	0 (0%)	11 (23%)	1 (2%)
Serum creatinine	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Serum total bilirubin	1 (2%)	0 (0%)	0 (0%)	0 (0%)

tant disease. Scheme modification (FOLFOX, FLOT without docetaxel or oxaliplatin) was required in 12.5% (6) patients. Dose reduction during one or more of the postoperative cycles of chemotherapy was required in 54% (33) patients. Dose delays ≤7 days occurred in 26% (16) and delays >7 days occurred in 2% (1) patients. Adverse events associated with postoperative treatment are presented in Table 2. The most frequent of them included: anemia 62% (30), nausea 60% (29), peripheral neuropathy 60% (29), and fatigue 60% (29). Only 20.8% (10) patients had any G3/4 adverse events. The most common of them were: fatigue 12% (6), nausea 8% (4), vomiting 8% (4), and diarrhea 6% (3). Only 14.6% (7) of patients required hospitalization. No deaths occurred during postoperative chemotherapy. The estimated disease-free survival at 1-, 2-, and 3-year was 73.7% (95% CI 60.2–83.2%), 57.9% (95% CI 44.1–69.5%), and 54.2% (95% CI 40.5–66.1%) (Table 4). The estimated overall survival at 1-, 2-, and 3-year was 93.3% (95% CI 83.2–97.4%), 73.3% (95% CI 60.2–82.7%), and 60.2% (95% CI 45.1–72.3%) (Table 4).

Discussion

In our trial we achieved satisfactory survival data in patients with GC or GEJ cancer, with acceptable side effects. It should be noted that there were differences in analyzed patients (ITT analysis vs. selected analysis) with regard to tumor clinical stages.

Adverse event grade 3 or 4 were observed in only 24.6% of patients in preoperative chemotherapy and in only 20.8% of patients in postoperative treatment. Due to GCS-F primary prophylaxis, neutropenia G1/G2 occurred in 3% vs. 6% and G3/G4 was observed in 5% vs. 2 % in preoperative and postoperative treatment, respectively. There were no cases of febrile neutropenia or infections. In the study by Al-Batran et al. neutropenia G3/4 was as high as 51% and infections G3/4 occurred in as many as 18% of patients but GCS-F prophylaxis was not mandatory [9]. In future trial, G-CSF prophylaxis could be considered a standard of care during the FLOT regimen chemotherapy. We reported an estimated 2- and 3-year disease-free survival of 57.9% (95% CI 44.1–69.5%) and 54.2% (95% CI 40.5–66.1%) as well as estimated 2- and 3-year overall survival of 73.3% (95% CI 60.2–82.7%) and 60.2% (95% CI 45.1–72.3%), respectively. We achieved a higher estimated overall survival rate than Al-Batran et al., who reported an estimated 2- and 3-year overall survival of 68.0% (95% CI 63.0–73.0%) and 57% (95% CI 52.0–62.0%), respectively. The difference might result from different baseline clinical stages of tumors of the enrolled patients. Comparing the group analyzed in our study with the FLOT4-AIO trial, we included more patients with tumor stage T2 (46% vs. 16%) and nodal negative stage N0 (49% vs. 22%), and fewer patients with tumor stage T3 (44% vs. 75%). The dominant localization in our study was stomach 77% while in Al-Batran's study it was GEJ tumor 56% [9]. We should bear in mind that the overall survival rate and disease-free survival rate are an estimation and could change with longer follow-up. A total of 85% of patients underwent margin-free surgical resection (R0), which was comparable with the results of the FLOT4-AIO trial and significantly exceeded the results of the MAGIC trial (79.3%). Complete histopathological tumor regression TGR1a according to the Becker et al. system (which was designed specifically for assessment in chemotherapy-treated patients with gastric cancer) was achieved in 11% and subtotal histopathological

Table 3. Surgical and pathology results of treatment.

Variable	
Surgery	
Tumor curative surgery R0-margin free	52 (85%)
Tumor surgery R1	1 (2%)
Palliative surgery	5 (8%)
No surgery	3 (5%)
Histopathological tumor regression according to Becker classification	
Complete-TRG1a	7 (11%)
Subtotal-TRG1b	6 (10%)
Complete or subtotal-TRG1a/b	13 (21%)
Partial-TRG2	14 (23%)
Minimal or none-TRG3	26 (43%)
Palliative surgery-not evaluated TGR	5 (8%)
Tumor stage (ypT)	
Tx	7 (11%)
T1	11 (18%)
T2	9 (15%)
T3	23 (38%)
T4	3 (5%)
ypT no available	8 (13%)
Nodal status (ypN)	
N0	34 (56%)
N1	5 (8%)
N2	6 (10%)
N3	8 (13%)
ypN no available	8 (13%)
Maximum tumor diameter	
0.0-3.9 cm	29 (47%)
4.0-7.9 cm	13 (21%)
8.0-11.9 cm	2 (3%)
12.0-15.9 cm	1 (2%)
> 16.0 cm	0 (0%)
No available	16 (26%)
Lympho-vascular invasion-LVI	
Yes	20 (33%)
No	32 (52%)
No available	9 (15%)
Perineural invasion-PNI	
Yes	7 (11%)
No	45 (74%)
No available	9 (15%)

Table 4. Efficacy of the perioperative FLOT regimen-DFS and OS.

Disease-free survival-DFS		
Sample size (n)	57	
Progression	24	42.1%
Progression or death	26	45.6%
Observation time [year]		
Median	2.4 (0.1–3.8)	
Interquartile range	0.9–2.8	
1-year DFS 73.7%	95% CI 60.2–83.2%	
2-year DFS 57.9%	95% CI 44.1–69.5%	
3-year DFS 54.2%	95% CI 40.5–66.1%	
Overall survival - OS		
Sample size (n)	60	
Death	24	40.0%
Observation time [year]		
Median	2.6 (0.5–3.8)	
Interquartile range	1.8–3.0	
1-year OS 93.3%	95% CI 83.2–97.4%	
2-year OS 73.3%	95% CI 60.2–82.7%	
3-year OS 60.2%	95% CI 45.1–72.3%	

tumor regression TGR1b in 10% of patients. The results were lower than in the FLOT4-AIO trial, which were 16% and 21%, respectively [9]. The ECF/ECX regimen achieved only 6–11% pathological complete response. Node-negative ypNO was reported in 56% of cases in the postoperative histopathological report, which was similar to the FLOT4-AIO trial, where it was 59%. As is known from the analysis by Smyth et al., high TRG and lymph node metastases are negatively related to survival (Mandard TRG 3, 4, or 5: hazard ratio [HR], 1.94; 95% CI, 1.11–3.39; p=0.0209; lymph node metastases: HR, 3.63; 95% CI, 1.88–7.0; p=0.001) [9, 10]. Node-positive non-responders' prognosis is relatively poor. On multivariate analysis, lymph node status but not tumor regression is independently predictive of OS (HR, 3.36; 95% CI, 1.70–6.63; p=0.001) [10]. Ever since both the MAGIC trial and the French FNCLCC/FFCD 97033 study, perioperative chemotherapy has been an established standard of care due to the survival benefits that it provides. Despite the fact that currently we have more effective chemotherapy, i.e., FLOT regimen, the 5-year recurrence rate remains high and the 5-year estimated overall survival (OS) is 45% (95% CI 38–51%), which is still dismal for patients with resectable GC and GEJ tumor. More than half of the patients will develop recurrence despite margin-free surgical resection. Moreover, despite the use of preoperative chemotherapy, no surgery or only palliative surgery can be performed in 10–15% of patients due to the progression of the disease [9]. Therefore, it is extremely important to research a new therapeutic approach for patients with locally advanced, resectable GC and GEJ tumors. The European Organization for Research and Treatment of Cancer is currently conducting the phase II randomized EORTC VESTIGE trial (NCT03443856) for patients with a poor response to neoadjuvant chemotherapy and an incomplete (R1) resection or metastatic lymph nodes in the resection specimen (N+). The group of patients with a high risk of recurrence will be randomized to either adjuvant chemotherapy (the same as prior to surgery) or to immunotherapy with nivolumab and low dose ipilimumab (nivolumab 3 mg/kg IV Q2W plus Ipilimumab 1 mg/kg IV Q6W for 1 year). Furthermore, studies are being conducted which combine the use of perioperative chemotherapy with immunotherapy [11]. The randomized, double-

blind, placebo-controlled, phase 3 MATTERHORN study will analyze the efficacy and safety of neoadjuvant-adjuvant durvalumab and the FLOT regimen chemotherapy in resectable gastric and gastroesophageal junction cancer [12]. The phase III KEYNOTE-585 study will assess the safety and efficacy of pembrolizumab with chemotherapy compared to placebo with chemotherapy as a neoadjuvant/adjuvant treatment for GC or GEJ adenocarcinoma [13].

It is crucial to conduct studies on the application of biomarkers in GC and GEJ cancer. There are currently no biomarkers that would allow clinical practitioners to predict early response to the induction treatment. In a situation when treatment is not effective such markers could enable clinicians to avoid exposing patients to the potential toxicity of unnecessary chemotherapy and perform earlier surgery.

In our trial, we achieved satisfactory benefits of perioperative chemotherapy FLOT regimen in patients with GEJ or GC cancer with acceptable side effects.

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References

[1] CHAU I, NORMAN AR, CUNNINGHAM D, WATERS JS, OATES J et al. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer--pooled analysis from three multicenter, randomized, controlled trials using individual patient data. J Clin Oncol 2004; 22: 2395–2403. https://doi.org/10.1200/JCO.2004.08.154

[2] GLOBOCAN 2020 database https://www.uicc.org/news/globocan-2020-new-global-cancer-data/ https://gco.iarc.fr/today/data/factsheets/cancers/7-Stomach-fact-sheet.pdf

[3] GREENLEE RT, MURRAY T, BOLDEN S, WINGO PA. Cancer statistics, 2000. CA Cancer J Clin 2000; 50: 7–33. https://doi.org/10.3322/canjclin.50.1.7

[4] THE CANCER GENOME ATLAS RESEARCH NETWORK. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014; 513: 202–209. https://doi.org/10.1038/nature13480

[5] FUJIWARA Y, DOKI Y, TANIGUCHI H, SOHMA I, TAKIGUCHI S et al. Genetic detection of free cancer cells in the peritoneal cavity of the patient with gastric cancer: present status and future perspectives. Gastric Cancer 2007; 10: 197–204. https://doi.org/10.1007/s10120-007-0436

[6] BOKU T, NAKANE Y, MINOURA T, TAKADA H, YAMAMURA M et al. Prognostic significance of serosal invasion and free intraperitoneal cancer cells in gastric cancer. Br J Surg 1990; 77: 436–439. https://doi.org/10.1002/bjs.1800770425

[7] CUNNINGHAM D, ALLUM WH, STENNING SP, THOMPSON JN, VAN DE VELDE CJ et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355: 11–20. https://doi.org/10.1056/NEJMoa055531

[8] YCHOU M, BOIGE V, PIGNON JP, CONROY T, BOUCHE O et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011; 29: 1715–1721. https://doi.org/10.1200/JCO.2010.33.0597

[9] Al-BATRAN SE, HOMANN N, PAULIGK C, GOETZE TO, MEILER J et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 2019; 393: 1948–1957. https://doi.org/10.1016/S0140-6736(18)32557-1

[10] SMYTH EC, FASSAN M, CUNNINGHAM D, ALLUM WH, OKINES AF et al. Effect of Pathologic Tumor Response and Nodal Status on Survival in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy Trial. J Clin Oncol 2016; 34: 2721–2727. https://doi.org/10.1200/JCO.2015.65.7692

[11] SMYTH E, KNODLER M, GIRAUT A, MAUER M, NILSSON M et al. VESTIGE: Adjuvant Immunotherapy in Patients With Resected Esophageal, Gastroesophageal Junction and Gastric Cancer Following Preoperative Chemotherapy With High Risk for Recurrence (N+ and/or R1): An Open Label Randomized Controlled Phase-2-Study. Front Oncol 2020; 9: 1320. https://doi.org/10.3389/fonc.2019.01320

[12] JANJIGIAN Y, VAN CUTSEM E, MURO K, WAINBERG ZA, AL-BATRAN SE et al. MATTERHORN: Efficacy and safety of neoadjuvant-adjuvant durvalumab and FLOT chemotherapy in resectable gastric and gastroesophageal junction cancer-A randomized, double-blind, placebo-controlled, phase 3 study. J Clin Oncol 2021; 39: TPS4151–TPS4151. https://doi.org/10.1200/JCO.2021.39.15_suppl.TPS4151

[13] BANG YJ, VAN CUTSEM E, FUCHS CS, OHTSU A, TABERNERO J et al. KEYNOTE-585: Phase III study of perioperative chemotherapy with or without pembrolizumab for gastric cancer. Future Oncol 2019; 15: 943–952. https://doi.org/10.2217/fon-2018-0581