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Position Paper

# Expert opinion on management of gastric and gastro-oesophageal junction adenocarcinoma on behalf of the European Organisation for Research and Treatment of Cancer (EORTC) - gastrointestinal cancer group

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ABSTRACT

A multidisciplinary approach is mandatory for patients with gastric cancer. Patients should be managed by an experienced team of physicians. The outcome of patients is related to the experience of the multidisciplinary team.

Surgery is the cornerstone of the management of patients with resectable gastric cancer. The standard recommendations for resectable gastric adenocarcinoma are free-margin surgery with at least D1 resection combined to removal of a minimum of 15 lymph nodes. It has been shown that the outcome of patients with resectable gastric cancer can be improved by a strategy of perioperative (pre- and postoperative) chemotherapy or by postoperative chemoradiotherapy. The evidence comes from large randomised phase 3 studies.

In the treatment of unresectable, locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma, no chemotherapy combination was accepted as the gold standard. Cisplatin/5-FU (CF) and ECF (epirubicin plus CF) regimens have been investigated widely in clinical studies and were until recently presented as the reference regimens. Despite a relative chemosensitivity of gastric cancer, a low rate of complete response was obtained, the response duration was short and patients' outcomes remained poor. Recently, new options have been introduced in the management of advanced gastric cancer. It has been shown that capecitabine is at least as good as 5-FU and that oxaliplatin at least as good as cisplatin in these combinations. It has also been demonstrated that the addition of docetaxel to CF resulted in statistically significant improved efficacy endpoints (including patient's quality of life), but also in an increased toxicity. The DCF regimen (docetaxel, cisplatin and 5-FU) has become, therefore, a new active option in advanced gastric cancer in selected patients in good condition.

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Further randomised trials are therefore to be designed to further improve chemotherapy by modifying and optimising the chemotherapy regimens, and investigating novel treatment combinations. The addition of biological agents to the optimal chemotherapy regimen may achieve further improvements in efficacy.



## 1. Introduction

Gastric cancer is a significant global problem. Recent figures indicate that 1.4 million new cases of gastro-oesophageal and gastric cancer are diagnosed annually and 1.1 million deaths are attributed to the disease.[1] While the rate of fundus and distal gastric cancers (often associated with Helicobacter pylori infection) has declined over past decades, the incidence of adenocarcinoma for the gastric cardia and gastro-oesophageal (GE) junction continues to rise. Areas with a particularly high incidence of gastric cancer include parts of Asia, Eastern Europe and South America with enormous differences between populations in the pathologic distribution and overall survival as shown by Maruyama et al.[2]

As with other malignancies, treatment for gastric cancer depends on the initial stage of the disease. Where possible, surgery is the cornerstone of treatment with curative intent, but recurrences frequently occur. Multiple clinical studies have therefore looked at whether adjuvant (and/or neo-adjuvant) chemotherapy can improve patient outcomes.

The European Organisation for Research and Treatment of Cancer (EORTC) Gastric Cancer Working Party took place at Nice (France) on 10 November 2006. Seven experts took part in the meeting and elaborated this review for gastric and (GE junction) adenocarcinoma management, as regards to literature or international meeting data using evidence-based medicine principles.

## 2. Diagnosis of gastric/GE junction adenocarcinoma

Diagnosis should be made from a gastroscopic or surgical biopsy and the histology given according to the World Health Organisation criteria. Particular attention is to be paid to familial history of gastrointestinal polyposis and/or gastrointestinal cancer [e.g. Hereditary Non Polyposis Colon Cancer (HNPCC)[3] or Hereditary Diffuse Gastric Cancer due to a mutation of the gene coding for E-Cadherin].

## 3. Staging and risk assessment

Initial staging consists of clinical examination including Virchow's lymph nodes and digital rectal examination, blood counts, liver and renal function tests, chest X-ray and (spiral) Computed Tomography (CT) scan of the abdomen and chest (if GE-junction cancer). Endoscopic ultrasound and laparoscopy may help to optimally determine resectability.

Further staging can include laparoscopy with peritoneal lavage for cytology to rule out peritoneal metastases, especially in case of T3–4 and/or subdiaphragmatic tumour.

Today there is no evidence to routinely perform Positron Emission Tomography (PET) scans, but the latter can contribute to the detection of metastases when CT-scan or Magnetic Resonance Imaging (MRI) are equivocal and might have an emerging role especially in GE junction tumours.

Barium X-ray has a limited role in gastric cancer and is more useful in GE junction tumours.

Tumour markers (e.g. CarcinoEmbryonic Antigen, CEA; Cancer Antigen, CA-19–9) are not useful for diagnosis and the question remains of their use for monitoring.

MRI may replace CT-scan in selected patients.

Bone scintigraphy and bone marrow aspiration are not routinely performed.

The stage is to be given according to the TNM 2002 system and the American Joint Committee on Cancer (AJCC) stage grouping.[4] Tumour stage assessed before any treatment is preceded by the small letter 'c' ('clinical'), postoperatively by a 'p' and staging performed during or after neoadjuvant treatment by the character 'y'.

An alternative Japanese Surgical Staging System considers serosal invasion instead of the T-stage, uses different definitions for N-stages, and considers the extent of peritoneal and hepatic metastases as well as peritoneal lavage cytology findings.[5]

## 4. Treatment plan

Multi-disciplinary treatment planning is mandatory.

### 4.1. *Treatment of localised disease*

Surgical resection is the only potentially curative option and is recommended for stages Tis-T3N0-N2M0 or T4N0M0. The extent of regional lymphadenectomy required for optimal results is still debated.

#### 4.1.1. *Surgical treatment*

In all cases, the surgeon is to be part of the multidisciplinary team. Surgery for gastric/GE junction cancer should be performed by well trained and experienced surgeons in centres of excellence. Gastric/GE junction surgery is to be standardised by quality control in order to reduce potential significant variations in patient outcome among surgeons.[6]

*4.1.1.1. Gastric/GE junction surgery.* The type of surgery depends on tumour characteristics and consists of total gastrectomy for proximal tumours and subtotal gastrectomy for distal tumours. Endoscopic mucosal resection or endoscopic submucosal dissection should be limited to mucosal cancers without ulcer or the well differentiated-type mucosal cancer with ulcers smaller than 2 cm .[7] Limited resection combined

with sentinel node resection for T1 tumours are to be left in experienced hands in order to have adequate locoregional control. The anatomic particularities of the oesophagus require mastery of all the different access routes to perform subtotal or distal oesophagectomy (e.g. Siewert type 1) in GE junction cancer.

4.1.1.2. *Lymphadenectomy*. Extent of lymph node dissection is an important issue as lymphatic spread of oesophagus/cardia cancer is an early event and the pattern of lymphatic dissemination difficult to predict. In Japan, three levels of lymph nodes dissection (D) were proposed[5]: either removal of perigastric lymph nodes (D1) or resection of perigastric lymph nodes plus those along the celiac axis and branches (left gastric, common hepatic and splenic arteries) (D2) or the latter plus removal of para-aortic lymph nodes (along common hepatic, prepancreatic, posterior pancreaticoduodenal and superior mesenteric arteries) (D3). However, it was unclear whether this operation should include an extended (D2) lymph-node dissection, as recommended by the Japanese medical community, or a limited (D1) dissection.

Two ancient randomised studies compared D1 resection to D2 lymph node removal (in 22 and 21 patients, respectively, over 5-year recruitment) and D1 to D3 resection (in 25 and 30 patients respectively with adenocarcinoma of the gastric antrum), respectively. In the former study,[8] the D2 group had a longer operating time ($p < 0.005$) than the D1 group, a greater blood transfusion requirement ($p < 0.005$), a longer hospital stay, re-operation in four patients, and no postoperative death. In the latter study,[9] there was a statistically significant longer operating time (140 versus 260 min; $p < 0.05$), a greater transfusion requirement (0 versus 2 units, $p < 0.05$) and a longer hospital stay (8 versus 16 days; $p < 0.05$) in the D3 group; fourteen patients developed subphrenic abscesses and one patient died from intra-abdominal sepsis in the D3 group whereas no major complications emerged in the D1 group.

In both studies, no advantage of extended lymphadenectomy was shown in terms of overall survival but both studies had a low power.

In the randomised Dutch gastric cancer group trial,[10–12] 1078 patients were included in 80 Dutch hospitals and randomly assigned to either D1 or D2 resection: 26 and 56 patients respectively were found not to satisfy eligibility criteria. In all, 771 patients were considered as resectable with a curative intent by one of the 12 referent surgeons: 380 patients underwent D1 resection by local surgeons and 331 patients D2 resection by a referent surgeon; all of them were prospectively followed for more than 10 years. Final results[12] showed a statistically significantly higher morbidity (43% versus 25%; $p < 0.001$) higher mortality (10% versus 4%; $p = 0.004$) and longer hospital stays (median, 16 versus 14 days; $p < 0.001$); in D2 than in the D1 group the relative risk ratio for morbidity and mortality was significantly higher for D2 dissection, splenectomy, pancreatectomy and age older than 70 years. No statistically significant difference was shown for overall survival (OS) with 5-year OS (47% versus 45%) and 11-year OS (35% versus 31%), $p = 0.53$. Of all subgroups analysed, only patients with N2 disease may benefit from a D2 dissection.

In the prospective MRC study[13] involving 32 European surgeons, 400 of 737 patients with histologically proven gastric adenocarcinoma were randomly assigned to either D1 or D2 lymph node resection after laparotomy staging (337 excluded patients for advanced disease). Five-year overall survival (OS) was similar between D1 (35%) and D2 (33%), Hazard Ratio (HR) = 1.10, (95% Confidence Interval (CI) [0.87–1.39] and Recurrence-Free Survival (RFS) was also identical (HR = 1.03, 95% CI.[0.82–1.29]. By multivariate analysis, clinical stages II and III, old age, male gender and removal of spleen and pancreas were independently associated with poor survival. However, the possibility that D2 resection without pancreatico-splenectomy may be better than standard D1 resection cannot be dismissed by the results of this trial.

For McCulloch et al.,[14] who conducted a literature review of studies reporting node dissection technique, evidence for D2 dissection is inconclusive. No overall survival advantage has emerged, but some patients with intermediate stage disease may benefit. Excess operative mortality appears to be associated with pancreatico-splenectomy, low case volume and lack of specialist training.

In a single-centre, randomised, controlled trial,[15] 335 patients were registered. 221 patients were eligible with curative intent, 110 of them were randomly assigned to D1 surgery and 111 to D3 surgery and resections were performed by one of three referent surgeons having a previous experience of at least 25 D3 dissections. D3 nodal dissection compared with D1 offers a statistically significantly better overall survival: 59.5% (95% CI: 50.3–68.7) versus 53.6% (44.2–63.0) ($p = 0.041$ and a trend of 5-year Disease Free Survival (DFS): 50.6% (41.1–60.2) had a recurrence after D1 surgery and 40.3% (30.9–49.7) after D3 surgery ($p = 0.197$), while performed by well-trained surgeons. In a phase III trial (JCOG9501 study) 523 patients were randomised during surgery between D2 resection and D2 plus paraaortic lymph node dissection (PAND). Median operation time was 63 min longer and median blood loss was 230 ml larger in D2+PAND than in D2. There was no difference in the incidence of major surgical complications and hospital mortality (0.8% in both arms). No benefit could be demonstrated in terms of overall survival ($p = 0.57$, HR = 1.03, 95% CI: 0.77–1.37), the 3- and 5-year OS were 76% and 69% in D2 and 76% and 70% in D2+PAND arm, respectively.[16]

Gastric/GE junction surgery could be considered as a specialty surgery. D2 resection without splenopancreatectomy could be indicated in some particular young patients; risks are to be balanced on a case by case basis by well trained surgeons with wide experience in gastric/GE junction surgery. Splenectomy is to be avoided unless the tumour extends to the spleen; in that case, preventive treatment of respiratory infections,[17] including tobacco withdrawal advice, is to be established. Sentinel lymph node analysis is not to be performed routinely.

In conclusion, the standard recommendations for surgery of resectable gastric/GE junction adenocarcinoma could be free-margin surgery with at least D1 resection combined to removal of a minimum of 15 lymph nodes.

4.1.1.3. *Quality control of surgery*. The 'Maruyama Index of Unresected Disease' (MI) is an estimation of the likelihood of

disease in the regional lymph node stations left undissected by the surgeon. This index was obtained from a cohort of 3843 gastric cancer patients treated by D2 or D2+ lymphadenectomy at the National Cancer Centre in Tokyo; it is a computer-generated index by input of patient's age (±5 years), gender, tumour Bormann type, size (greatest dimension as measured on the luminal surface ±2.5 cm), location, estimated depth and histology. The performance characteristics of this program have been assessed in Japan and Germany.[18,19]

The prognostic value of this index was also validated in two large randomised Western trials. In the Intergroup 0116 (SouthWest Oncology Group, SWOG, trial 9008), a national, multicentre, two-armed, prospective, randomised trial of adjuvant postoperative chemoradiotherapy, D level was coded according to the Japanese general rules and the Maruyama program was used to estimate the MI in 553 of the 556 included patients (median MI: 70), before any survival analysis .[20,21] In contrast to D level, MI ($\geqslant 5/<5$) proved to be an independent prognostic factor for multivariate analysis of OS (HR = 1.9, 95% CI: 1.3–2.8) and RFS (HR = 2.0, 95% CI: 1.4–2.9), with T stage, number of nodes and randomisation arm put in the Cox model.

The prognostic value of the MI was tested using blinded reanalysis of the Dutch D1-D2 trial characterised by a patient cohort, presenting with a lower-stage disease than in the SWOG 90008 trial, treated with minimum D1 lymphadenectomy and no adjuvant chemoradiation. The MI was calculated for 648 of the original 711 patients treated with curative intent.[22] As expected, the median MI was 26, much lower than in the American SWOG study 9008. In contrast to the D level, MI < 5 proved to be a strong predictor of survival by both univariate and multivariate analysis. The MI was an independent predictor of both overall survival ($p = 0.016$; HR = 1.45; 95% CI; 1.07–1.95) and relapse risk ($p = 0.010$; HR = 1.72; 95% CI: 1.14–2.60). A strong dose-response reaction with respect to the MI and survival was also observed. Low MI surgery can be prospectively planned by using the Maruyama Computer Program preoperatively or intra-operatively.

A nomogram was developed by Kattan et al.[23] to predict 5-year disease-specific survival after R0 resection for gastric cancer on the basis of 1039 patients treated at a single American institution. Nomogram predictor variables include age, gender, primary site (distal third, middle third, proximal third and gastro-oesophageal junction), Lauren histotype (diffuse, intestinal, mixed), number of positive lymph nodes resected, number of negative lymph nodes resected, and depth of invasion. Nomogram discrimination was superior to predictive ability of American Joint Committee on Cancer staging with a concordance index of 0.8 versus 0.7, respectively ($p < 0.001$).

The accuracy of the nomogram was confirmed after application to 862 patients treated with R0 gastric cancer resection at a European high-volume centre.[24] Nomogram discrimination was superior to predictive ability of American Joint Committee on Cancer staging with a concordance index of 0.770 versus 0.756, respectively ($p < 0.008$). Heterogeneity in several of the AJCC stage groups, especially in the groups II and IIIA, was confirmed.

The need has resection and examination of at least 15 lymph nodes to be underlined for adequate estimation of outcome using the nomogram.

#### 4.1.2. *Adjuvant treatment*

As shown by Siewert et al.,[25] the proportion of patients with R0 resection decreases with tumour extension. Curative resection (R0) is the treatment of choice for gastric cancer and is a major predictive factor for survival.

Multiple clinical studies have therefore looked at whether adjuvant chemotherapy can improve patient outcomes. Unfortunately, many of them were underpowered for survival and the majority used 'old' chemotherapy regimens. Even more 'modern' trials[26] did not show a significant survival benefit. Nevertheless, these meta-analyses suggest a small relative (12% to 28%) reduction in the risk of death with adjuvant therapy versus no treatment.[27–30] It is estimated that an absolute survival benefit of 3–5% is obtained with an adjuvant chemotherapy. Meta-analyses alone are not sufficient to define the role of adjuvant chemotherapy.

In the large SWOG 9008/INT 0116 Phase III trial,[31] 556 patients with resected adenocarcinoma of the stomach or gastro-oesophageal junction were randomly assigned to surgery plus postoperative chemoradiotherapy or surgery alone. The adjuvant treatment consisted of 425 mg of fluorouracil/$m^2$/day plus 20 mg/$m^2$/day of leucovorin for 5 days, followed by 4500 cGy of radiation at 180 cGy per day, given 5 days per week for 5 weeks, with modified doses of fluorouracil and leucovorin on the first 4 and the last 3 days of radiotherapy. One month after the completion of radiotherapy, two 5-day cycles of fluorouracil (425 mg/$m^2$/day) plus leucovorin (20 mg/$m^2$/day) were given 1 month apart. The median overall survival was longer after complementary chemoradiation (36 months) than after surgery alone (27 months) with a HR for death of 1.35 (95% CI: 1.09–1.66, $p = 0.005$; and a HR for relapse equal to 1.52 (95% CI: 1.23–1.86, $p < 0.001$). Three patients (1%) died from toxic effects of the chemoradiotherapy; grade 3 toxic effects occurred in 41% of the patients in the chemoradiotherapy group, and grade 4 toxic effects occurred in 32% of patients. Although this study is clearly positive, it should be noted that about 54% of the patients underwent a less than D1 resection. It is therefore possible that the adjuvant radiotherapy compensated for insufficient surgery (like in lumpectomy for breast cancer) and its value in case of adequate surgical resection is a matter of debate.

A study, in 23 patients having undergone total gastrectomy with Roux-en-Y reconstruction,[32] showed that the mean number of ingested calories was 1458 kilocalories (kcal) at 1 month and 2118 kcal at 6 months with 23/23 and 9/23 patients with insufficient food intake, respectively. Usually adjuvant chemotherapy begins 8 weeks after surgery. Thus, poor nutritional status might explain the difficulty to administer adjuvant treatment.

A strict nutritional follow-up is very important after gastric surgery in order to obtain an adequate dietary intake.

Elderly can also benefit from adjuvant treatment if they are fit. Particular attention is to be paid to haematological parameters. Close management is needed in elderly with adequate nursing and dietary advice especially in outpatient setting.

#### 4.1.3. *Perioperative treatment*

In the MAGIC Trial conducted in the UK,[33] patients with resectable adenocarcinoma of the stomach, oesophago-gas-

tric junction, or lower oesophagus were randomly assigned to either perioperative chemotherapy and surgery (250 patients) or surgery alone (253 patients). Chemotherapy consisted of three preoperative and three postoperative cycles of intravenous epirubicin (50 mg/m$^2$) and cisplatin (60 mg/m$^2$) on day 1, and a continuous intravenous infusion of 5-fluorouracil (200 mg/m$^2$) for 21 days. The primary endpoint was overall survival. As compared with the surgery group, the perioperative-chemotherapy group had a higher likelihood of overall survival (HR for death = 0.75; 95% CI: 0.60–0.93, $p = 0.009$; 5-year survival rate, 36% versus 23%) and of progression-free survival (HR = 0.66; 95% CI: 0.53–0.81, $p < 0.001$). This trial showed the feasibility of neo-adjuvant treatment as 88% of patients completed the preoperative chemotherapy, 55% could start the adjuvant chemotherapy and 43% of patients completed the six planned cycles. The patients treated with preoperative chemotherapy had a statistically significantly lower tumour size and stage after neo-adjuvant treatment [maximal tumour diameter: 3 versus 5 cm, $p < 0.001$); (y)pT1/2: 51.7% versus 36.8%, $p = 0.002$ and (y)pN0/1: 84.4% versus 70.5%, $p = 0.01$] than after surgery alone. Similar rates of postoperative complications (46.6% versus 46.6%) and death within 30 days after surgery (6% versus 6%) were observed in both groups.

In the FNLCC ACCORD 07/FFCD 9703 phase III trial, 224 patients with resectable gastric/GE junction adenocarcinoma were randomly allocated to either testing two preoperative cycles of the CF regimen (5-fluorouracil 800 mg/m$^2$/day from D1 to D5 and cisplatin 100 mg/m$^2$ on D1, every 28 days) followed by surgery; then four CF cycles in case of preoperative response or stable disease with pN+ ($n = 113$) versus surgery alone ($n = 110$).[34] The primary endpoint was OS. Baseline characteristics were equally balanced between arms. A statistically significant longer 5-year survival was found for patients treated with perioperative chemotherapy: 24% (16–33%) versus 38% (28–47%) (Hazard Ratio = 0.69; 95% CI: 0.50–0.95; logrank $p$ value = 0.021). The 5 year DFS was also improved: from 21% (14–30%) to 34% (26–44%) (Hazard Ratio = 0.65; 95% CI 0.48–0.89; logrank $p$ value = 0.0033). The curative resection rate was also significantly improved. Moreover, the SAKK group recently presented data that docetaxel based preoperative chemotherapy is better tolerated than postoperative chemotherapy.[35]

Based on the recently published trials, perioperative chemotherapy or postoperative chemoradiotherapy should therefore be recommended for patients presenting with resectable, locally advanced tumours of the stomach or the oesophagogastric junction (stages II and III). In Europe, the recommendation goes more towards a perioperative chemotherapy, consisting of 8–9 weeks of preoperative platin-fluoropyrimidine-based chemotherapy. The same duration of postoperative chemotherapy using the same regimen should be considered if this is tolerated by the patient. Postoperative chemoradiotherapy should be considered in patients who recovered from a gastrectomy and in whom a pT3 or pT4 or pTxN+ tumour was resected and if no preoperative chemotherapy was administered, especially if a less than optimal lymph node resection was performed.[36]

### 4.2. *Treatment of locally advanced disease (stage III: T3–4, N+) or metastatic disease (stage IV) or inoperable patients*

Frequently, patients with gastric cancer present with large, unresectable tumours at the time of diagnosis. For these patients, treatment is palliative and, in most cases, options are limited to systemic chemotherapy or supportive care.

A review and meta-analyses was recently published by Wagner et al.[37] in advanced gastric cancer. Conventional cytotoxic chemotherapy ($n = 103$) as compared to Best Supportive Care (BSC) ($n = 81$) can improve overall survival (HR = 0.39, 95% CI: 0.28–0.52, $p < 0.00001$), Quality of Life (QoL) (HR = 2.07, 95% CI: 1.31–3.28, $p = 0.002$) and symptom-free period (HR = 2.33, 95% CI: 1.41–3.87, $p = 0.001$).

A benefit of cytotoxic combinations ($n = 836$) was demonstrated a over single-agent ($n = 636$) regimen in terms of overall survival (HR = 0.83, 95% CI: 0.74–0.93, $p = 0.001$) by a meta-analysis of 11 trials conducted in advanced gastric cancer.

#### 4.2.1. *Cisplatin-based regimens*

Cisplatin based regimens have become a standard regimen in advanced gastric cancer. A randomised phase 2 study of the EORTC-GI group showed an efficacy benefit of the addition of cisplatin to weekly infused 5-FU/LV.[38] A meta-analysis of seven studies[37] confirmed the advantage of platinum-based regimen combined to 5-FU and anthracyclines ($n = 508$) over 5-FU-anthracyclines combinations ($n = 639$) on OS (HR = 0.83, 95% CI: 0.76–0.91, $p = 0.001$). In a randomised trial conducted in the United Kingdom,[39] patients suffering from advanced gastric cancer were randomly allocated to either the ECF (Epirubicin, Cisplatinum, 5-Fluorouracil) ($n = 130$) or FAMTX (5-FU, doxorubicin and methotrexate) ($n = 126$) regimen. A statistically significant higher response rate was shown in patients randomly allocated to the ECF regimen (45%) than in those of the FAMTX arm (21%), $p = 0.0002$ as well as longer Failure Free Survival (FFS) (median: 7.4 versus 3.4 months, $p = 0.00006$) and OS (median: 8.9 versus 5.8 months, $p = 0.00009$). In a prospective randomised study ,[40] previously untreated patients with advanced oesophagogastric cancer were assigned to receive either ECF (epirubicin 50 mg/m$^2$ every 3 weeks, cisplatin 60 mg/m$^2$ every 3 weeks and protracted venous infusion of 5-FU 200 mg/m$^2$/d) or MCF (mitomycin 7 mg/m$^2$ every 6 weeks, cisplatin 60 mg/m$^2$ every 3 weeks, and protracted venous infusion of 5-FU 300 mg/m$^2$/d) regimen. The overall response rate was 42.4% with ECF and 44.1% with MCF ($p = 0.692$), median OS 9.4 months with ECF and 8.7 months with MCF ($p = 0.315$) and median failure-free survival was 7 months with both regimens. Global QoL scores were better with ECF at 3 and 6 months. ECF resulted in more grade 3–4 neutropenia and grade 2 alopecia, but MCF caused more thrombocytopenia and plantar-palmar erythema. There is no general agreement on the contribution of epirubicin to cisplatin and 5-FU, although the Cochrane metaanalysis suggested a survival benefit of epirubicin.[41] Cisplatin-5-FU (CF) based and the ECF regimen have therefore been proposed until recently as reference regimens for clinical use and for protocols and cisplatin-5-FU combinations for regulatory purposes because they have been widely investigated in clinical studies and have demonstrated favourable survival outcomes. No combination has become accepted as

the gold standard. There are, however, shortcomings with the actual regimens in gastric cancer. Although gastric cancer is relatively chemosensitive, a low rate of complete response is obtained, the response duration is short and patients' outcomes remain poor despite toxic and/or heavy regimens. This has led to the development of new regimens.

#### 4.2.2. *Oxaliplatin*

Oxaliplatin is a platinum compound that is complexed to a diaminocyclohexane carrier ligand. Like other platinum compounds, oxaliplatin stimulates apoptosis and ultimately cell death by inhibition of DNA replication and repair by mean of adducts between pair bases. Oxaliplatin has demonstrated activity in tumours with intrinsic or acquired resistance to cisplatin.[42–44] Whereas cisplatin is associated with dose-limiting renal toxicity, peripheral neuropathy and cumulative ototoxicity,[45] the principal dose-limiting toxicity of oxaliplatin is cumulative sensory peripheral neuropathy, which usually resolves over time. Other oxaliplatin-associated toxicities include neutropenia, diarrhoea and vomiting, which can be managed with appropriate prophylaxis and treatment. Oxaliplatin has demonstrated *in vitro* anti-tumour activity in human gastric cancer cell lines.[46]

Results of several phase II studies using the FOLFOX regimen as first-line treatment in advanced gastric cancer were presented by several teams at the ASCO meeting in 2002.[47–50] Two other studies were published and recorded a 44.9% and 43% response rate, respectively, a median TTP of 6.2 months and median OS of 8.6 months in the French study[51] and a median OS of 9.6 months in the German study.[52] In a phase II study conducted in 48 patients with previously untreated metastatic gastric cancer,[53] weekly 5-FU-leucovorin-oxaliplatin (FUFOX) demonstrated a favourable toxicity profile and achieved an ORR of 54%, median TTP of 6.5 months and a median OS duration of 11.4 months. These small phase 2 studies showed relatively high degrees of activity.

Using ECF as a reference regimen, the UK National Cancer Research Institute's phase III REAL-2 study[54] was conducted in 1002 patients with previously untreated metastatic adeno-, squamous or undifferentiated carcinoma of the oesophagus, gastro-oesophageal junction or stomach. The study used a $2 \times 2$ factorial study design, in which patients were randomised to one of four treatment arms: ECF (epirubicin, cisplatinum, 5-FU), ECX (epirubicin, cisplatin, capecitabine); EOF (epirubicin, oxaliplatin, 5-FU), EOX (epirubicin, oxaliplatin, capecitabine) with epirubicin given at a dose of 50 mg/m$^2$, cisplatin 60 mg/m$^2$, oxaliplatin 130 mg/m$^2$, protracted venous infusion of 5-FU at 200 mg/m$^2$/day and oral capecitabine 625 mg/m$^2$ bid, for a total of eight 3-week cycles. Characteristics were well-balanced between treatment arms, 89% patients had Eastern Cooperative Oncology Group (ECOG) performance status 0–1 and 77% had metastatic disease. Primary endpoints were overall survival comparison for capecitabine versus 5-FU and oxaliplatin versus cisplatin (non-inferiority margin of 1.23) and between all four regimens (superiority) using stratification by centre, locally advanced/metastatic cancer, Performance Status (PS) 0–1/2.

In the Intent-To-Treat set, median OS was 9.9 months for ECF, 9.3 months for EOF, 9.9 months for ECX and 11.2 months for EOX. The non-inferiory primary endpoint (OS) was met for both the fluoropyrimidine (HR = 0.92, 95% CI: 0.80–1.10) and platinum (HR = 0.86, 95% CI: 0.8–0.89) comparisons of the respective per-protocol populations. The survival benefit for EOX compared to ECF was statistically significant ($p = 0.020$), with a HR of 0.80 (95% CI: 0.66–0.97). The overall response (complete/partial response) rates (ORR) were consistently high at 40.7%, 46.4%, 42.4% and 47.9% for the ECF, ECX, EOF and EOX regimens, respectively, with no significant difference between groups. Grade 3–4 neutropenia was more commonly associated with cisplatin (ECF, 41.7%; ECX, 51.1%) than with oxaliplatin (EOF, 29.9%; EOX, 27.6%). Grade 3–4 non-haematological toxicity was reported for 36%, 33%, 42% and 45% of patients in the ECF, ECX, EOF and EOX groups, respectively .[54] The authors concluded that oxaliplatin may substitute for cisplatin and capecitabine for 5-FU without decreasing efficacy, with improved convenience and favourable safety; EOX seems to be associated with significantly improved efficacy compared to ECF.

In the German study FLO/FLP,[55] 112 patients were randomised to receive FLO (5-FU 2600 mg/m$^2$ 24-h infusion, leucovorin 200 mg/m$^2$, and oxaliplatin 85 mg/m$^2$, every 2 weeks) and 110 patients to FLP (5-FU 2000 mg/m$^2$ 24-h infusion, leucovorin 200 mg/m$^2$ weekly, and cisplatin 50 mg/m$^2$, every 2 weeks). The primary endpoint was TTP. In all, 162 patients (FLO, 80; FLP, 81) had disease progression with a median TTP of 5.7 months for FLO and 3.8 months for FLP (logrank $p = 0.081$, Wilcoxon $p = 0.019$). Median Time to Treatment Failure (TTF) was 5.3 months for FLO and 3.1 months for FLP (logrank $p = 0.028$). Response to FLO (34%) was superior to FLP (27%), with 15% and 30% of patients having disease progression as best response to FLO and FLP, respectively ($p = 0.012$). Median treatment duration was 4.3 months with FLO and 3 months with FLP. FLO was associated with significantly less NCI-CTC grade 1–4 leucopenia, nausea, alopecia, fatigue, and renal toxicity and FLP was associated with significantly less peripheral neuropathy ($p < 0.05$). Severe adverse events related to treatment were less frequent with FLO (8.9%) as compared to FLP (18.6%) ($p = 0.046$).[55]

In conclusion: oxaliplatin seems to be at least as active and less toxic compared to cisplatin in combinations regimens in gastric cancer and can therefore replace cisplatin.

#### 4.2.3. *Irinotecan*

Wagner et al.[37] has shown a small advantage of irinotecan ($n = 270$) over other regimens ($n = 266$) in a meta-analysis of two randomised phase II studies[56,57] and one randomised phase III study [58] in terms of overall survival (HR = 0.83, 95% CI: 0.73–1.06) but statistical significance was not reached ($p = 0.19$). The randomised phase III study, however, failed to show a superior efficacy of 5-FU/FA/irinotecan compared to cisplatin/5-FU. In this phase III study,[58] conducted in first-line advanced gastric cancer patients, 172 patients were randomised to irinotecan-based arm (irinotecan 80 mg/m$^2$ intravenously (iv) as 30-min infusion, followed by folinic acid 500 mg/m$^2$ iv over 2 h, followed by 5-FU 2000 mg/m$^2$ iv over 22 h weekly for 6 weeks) and 165 to CF arm (cisplatinum 100 mg/m$^2$ as 1–3 h intravenous infusion on day 1, followed by 5-FU 1000 mg/m$^2$/day continuous infusion over 5 days every 4 weeks). The main endpoint was TTP. In the 333 assessable

patients, median TTP was 5.0 months in irinotecan-based arm versus 4.2 months in CF arm ($p = 0.088$), median TTF 4 months versus 3.4 months ($p = 0.18$), median OS 9.0 months versus 8.7 months ($p = 0.53$) and ORR was 32% versus 26%.

#### 4.2.4. *Taxanes derivatives*

4.2.4.1. *Paclitaxel*. There are limited phase II data available for paclitaxel-platinum combinations in advanced gastric cancer. Phase III data are not available. Paclitaxel 175 mg/m$^2$ over 3 h on day 1 combined with 5-FU 750 mg/m$^2$ over 24 h on days 1–5 and cisplatin 20 mg/m$^2$ over 2 h on days 1–5, every 28 days, achieved an overall response rate of 51% and median survival duration of 6 months in a study of 41 patients with metastatic, unresectable advanced, or relapsed gastric cancer.[59] The main toxicity was myelosuppression, with grade 3–4 neutropenia reported in 34% of patients. Another study of 45 patients [60] in previously untreated, unresectable locally advanced or metastatic gastric cancer assessed 8-week cycles (6 weeks with therapy followed by 2-week rest) with paclitaxel 175 mg/m$^2$ as a 3-h infusion on days 1 and 22, cisplatin 50 mg/m$^2$ as a 1-h infusion on days 8 and 29, and 5-FU 2 g/m$^2$ given over 24 h, weekly, preceded by folinic acid 500 mg/m$^2$ over 2 h. The overall response rate was 51%, median PFS 9 months and OS 14 months. Grade 3–4 neutropenia was reported in seven patients (15%); other grade 3–4 toxicities included nausea/vomiting in five patients (11%), alopecia in 22 patients (49%), and diarrhoea in one patient (2%).

4.2.4.2. *Docetaxel*. Multiple phase II studies have investigated the efficacy of docetaxel as single agent in patients with advanced gastric cancer. Overall response rate ranged from 16–24% when docetaxel was used as front-line therapy and from 5–21% when given to pretreated patients. In both settings, a significant proportion of patients (close to 30%) achieved disease stabilisation. A phase II study[61] was undertaken by the Swiss Group for Clinical Cancer Research (SAKK) and European Institute for Oncology (EIO) to investigate the efficacy and tolerability of docetaxel (85 mg/m$^2$) in combination with cisplatin (75 mg/m$^2$) (DC) administered every 3 weeks for up to eight cycles in 48 patients with measurable, unresectable and/or metastatic gastric adenocarcinoma. In terms of efficacy, DC was associated with a favourable ORR of 56% (including two complete responses), a median time to progression (TTP) of 6.6 months and a median overall survival (OS) of 9 months. In addition, DC was well tolerated with a predictable and manageable toxicity profile. As expected, the vast majority of grade 3–4 toxicities were haematological (neutropenia 81%, anaemia 32%, thrombocytopenia 4%), and while there were nine episodes of febrile neutropenia, none was fatal. A phase I–II dose-finding study[62] was subsequently conducted by the same study group to establish the feasibility of adding a protracted continuous infusion of 5-FU 300 mg/m$^2$/day for 2 weeks to first-line DC (DCF) in patients with measurable, unresectable and/or metastatic gastric carcinoma. A similar ORR (51%; $n = 41$), median OS (9.3 months) and safety profile were observed with this DCF regimen.

Consequently, a randomised, three-arm phase II study (SAKK 42/99)[63] was conducted in first line treatment of advanced gastric cancer. Patients had bidimensionally measurable disease, PS 0–1, normal blood counts, hepatic and renal functions and were randomised to receive up to eight cycles every 3 weeks of either DC (docetaxel 85 mg/m$^2$, cisplatin 75 mg/m$^2$), DCF (like DC + continuous infusion of 5-FU 300 mg/m$^2$/d for 14 days) or ECF (epirubicin 50 mg/m$^2$, cisplatin 60 mg/m$^2$, continuous infusion 5-FU CI 200 mg/m$^2$/d for 21 days). The primary endpoint was ORR. Due to febrile neutropenia (ten occurrences in the first 21 included patients), the dose of docetaxel was decreased from 85 mg/m$^2$ to 75 mg/m$^2$, resulting in lesser febrile neutropenia occurrence. In all, grade 3–4 non-haematological toxicity was infrequent (less of 10% of patients) except alopecia (three arms), nausea (18% in DC and DCF arms) and diarrhoea (15% in DCF arm). Preliminary results on 119 patients (40 in ECF, 38 in DC and 41 in DCF) showed the highest ORR in DCF arm (36.6%) then ECF (25.0%) and DC (18.5%) and median time to progression of 7.8 months, 5.4 months and 4.4 months, respectively. Overall survival was higher in docetaxel-based regimens (median OS: 10.4 months and 11.0 months in DCF and DC, respectively) than in ECF arm (median OS: 8.2 months).

Another group, the TAX 325 Study Group, had also undertaken a multinational, randomised phase II/III study in order to determine the most efficacy regimen (DC or DCF) to be tested in a phase III trial against CF (cisplatin 100 mg/m$^2$ on day 1, and 5-FU 1000 mg/m$^2$/day as a continuous infusion on days 1–5 every 4 weeks), chosen as reference arm before the onset of phase II trial. CF was chosen as it was an accepted standard reference therapy for regulatory purposes, used worldwide and studied in advanced gastric cancer as well as the reference arm in two ongoing large phase III trials.[64,65]

In the phase II study,[66] 158 previously untreated patients with metastatic (accounting for 95% of patients) or locally advanced/recurrent gastric or gastro-oesophageal adenocarcinoma received either DCF (docetaxel 75 mg/m$^2$ on day 1, cisplatin 75 mg/m$^2$ on day 1, and 5-FU 750 mg/m$^2$/day as a continuous infusion on days 1–5) or DC (docetaxel 85 mg/m$^2$ and cisplatin 75 mg/m$^2$ on day 1), administered every 3 weeks until disease progression, unacceptable toxicity or consent withdrawal. The aim of the study was ORR and safety comparisons between the regimens. DCF was superior to DC for confirmed ORR (43% versus 26%, respectively) and median TTP (5.9 versus 5.0 months, respectively, equating to a 20% reduction in the risk of progression), while median OS was slightly longer in the DC group (10.5 months) than in the DCF group (9.6 months) with similar 1-year survival (41.7% versus 35.4%, respectively). The most frequent grade 3–4 toxicities were neutropenia (86% versus 87%) and gastrointestinal events (56% versus 30%); they were considered as manageable. In the phase III stage of the TAX 325 study,[67] DCF was selected for further investigation by an independent data monitoring committee. The TAX 325 phase III study is one of the most important clinical trials to have been undertaken in advanced gastric cancer during the past decade. The primary endpoint was TTP. Unlike most previous trials in this setting, almost all patients (97%) had metastatic disease (81% with at least two metastatic sites), indicating that patients had a very high tumour burden. In all, 227 patients were randomised to the DCF arm and 230 to the CF arm. Patients received a median of six cycles of DCF and four cycles of CF. DCF ($n = 221$) was statistically significantly superior to CF

($n = 224$) for TTP ($p = 0.0004$) with a risk reduction of 32% for progression (HR 1.46; 95% CI: 1.19–1.82; median TTP: 5.6 months versus 3.7 months), for OS ($p = 0.02$) with a risk reduction of 23% (median: 9.2 months versus 8.6 months; 1-year OS: 40% versus 32%; 2-year OS: 18% versus 9%), confirmed ORR (37% versus 25%, $p = 0.01$) and median TTF (4.0 months versus 3.4 months, $p = 0.03$).

Even though DCF was the more intense regimen, the difference between treatments was statistically significantly in favour of the DCF regimen for the primary QoL (time to 5% definitive deterioration of Global Health Status versus baseline: 6.5 months versus 4.2 months, $p = 0.0121$) and clinical benefit (time to definitive deterioration of Karnofsky Performance Status by one category versus baseline: 6.1 months versus 4.8 months, $p = 0.088$) endpoints. DCF was also statistically significantly superior to CF for nearly all secondary QoL analyses (time to definitive deterioration in social functioning, nausea/vomiting, appetite loss, pain and EuroQoL EQ-5D thermometer), with a trend for time to definitive deterioration in physical functioning ($p = 0.1349$), time to definitive 5% weight loss ($p = 0.0776$) and time to definitive worsening appetite ($p = 0.1143$). No difference between treatments was observed for pain-free survival and time to first cancer pain requiring opoids.[67–69]

DCF was associated with increased toxicity compared with CF especially grade 3–4 neutropenia (82.3% versus 56.8%) and febrile neutropenia/neutropenic infection (30% versus 13.5%), diarrhoea (20.4% versus 8.0%) and neurosensory toxicity (7.7% versus 3.1%). In contrast, grade 3–4 stomatitis (20.8% versus 27.2%) and anaemia (18.2% versus 25.6%) occurred less frequently than with CF. The main cause of toxic deaths was infection in both arms (7 of 8 in DCF and 8 of 12 in CF), and they mainly occurred during the first cycle of chemotherapy.

In all, 19% of patients in the DCF arm received secondary prophylaxis with granulocyte colony-stimulating factor (G-CSF) and 9% in CF arm: among them the incidence of febrile neutropenia/neutropenic infection was only 12% versus 15%, respectively. In patients aged at least 65 years, grade 3–4 infection (related to treatment) was more frequent with DCF (20%) than with CF (9%).[67]

Primary prophylaxis with G-CSF would dramatically reduce the rate of complicated neutropenia associated with DCF. This treatment strategy is consistent with new European and North American guidelines that recommend the routine use of primary G-CSF prophylaxis when using a chemotherapy regimen that is associated with a high (>20%) risk of febrile neutropenia, such as DCF.[70–72]

The TAX 325 study has demonstrated that the addition of docetaxel to CF resulted in improved efficacy suggesting that it should now be incorporated in front-line strategies used for the treatment of patients with advanced gastric or gastro-oesophageal cancer.

Although DCF is associated with a high risk of febrile neutropenia, this complication may be prevented by primary G-CSF prophylaxis, a treatment strategy advocated in current practice guidelines. Other haematological and non-haematological toxicities are predictable, acceptable and manageable. Moreover, overall toxicity management can be improved further through proper patient selection, early intervention, improved awareness of the treatment entity and better patient education involving close management by cancer nurses and general practitioners.

Following the results of TAX 325 and docetaxel approvals by the authorities in the USA and Europe, the docetaxel-cisplatin-5-FU (DCF) triplet has become a new reference regimen in advanced gastric cancer. Numerous studies are ongoing to try to optimise both the efficacy and safety of existing regimens and to investigate the potential of new drug combinations in gastric cancer. Potential modifications of the DCF regimen include variations in the DCF schedule, the substitution of cisplatin with oxaliplatin, the substitution of 5-FU with oral fluoropyrimidines, and the addition of biological agents.

The modified DCF regimen was tested in a randomised phase II[73] study conducted in 106 patients with previously untreated metastatic gastric or oesophageal carcinoma who received either mDCF (docetaxel 30 mg/m$^2$ on days 1 and 8, cisplatin 60 mg/m$^2$ on day 1, and 5-FU 200 mg/m$^2$/day continuous infusion) every 3 weeks or mDX (docetaxel 30 mg/m$^2$ on days 1 and 8 and capecitabine 1600 mg/m$^2$/day on days 1–14) every 3 weeks. The study showed a confirmed ORR (primary endpoint) of 47% for mDCF and 26% for mDX, median PFS 5.8 months versus 4.6 months for mDCF and mDX, respectively. Safety and tolerability were satisfactory in both treatment arms, with diarrhoea, hand foot syndrome and febrile neutropenia each reported in less than 10% of patients in each arm. In order to reduce docetaxel toxicity, weekly schedules were proposed since they were demonstrated to be effective and less toxic in other tumours. However, in two trials[74,75] conducted in first (weekly docetaxel in combination with capecitabine) and second (weekly docetaxel) line treatment, respectively, the doses and schedule investigated were safe, but did not show significant activity in patients with advanced gastric cancer.

To reduce the haematological toxicity while maintaining the efficacy of DCF, split doses of docetaxel, cisplatin, leucovorin, and fluorouracil.[76] Chemotherapy-naïve patients with advanced gastric or gastrooesophageal adenocarcinomas received docetaxel 50 mg/m$^2$ and cisplatin 50 mg/m$^2$ on days 1, 15 and 29 and leucovorin 500 mg/m$^2$ plus 5-FU 2000 mg/m$^2$ on days 1, 8, 15, 22, 29 and 36, every 8 weeks. Because significant dose reductions to <80% became necessary in most of patients, the regimen was amended after the first 15 patients to docetaxel 40 mg/m$^2$, cisplatin 40 mg/m$^2$, leucovorin 200 mg/m$^2$, and 5-FU 2000 mg/m$^2$. Sixty patients were enrolled: 24 had locally advanced tumours and 36 had metastatic disease. The overall response rate was 47%. Twenty-three patients with locally advanced disease underwent secondary surgical resection (96%); complete resection (R0) was achieved in 87%. Overall, median time to progression and overall survival were 9.4 and 17.9 months, respectively (8.1 and 15.1 months, respectively, for patients with metastatic disease).

Other modifications of the DCF are under investigation in order to maintain the activity and to improve the tolerance of the original DCF regimen: e.g. replacing cisplatin by oxaliplatin and 5-FU by capecitabine.

#### 4.2.5. *Oral fluoropyrimidines*

The REAL-2 study discussed in the chapter of oxaliplatin[54] showed that capecitabine is at least as active as 5-FU in

gastric adenocarcinoma and in GE junction adenocarcinoma and has a favourable toxicity profile. A phase III study was conducted in Korea, Asia and Latin America[77] also investigated the activity of capecitabine. In this non-inferiority study (primary endpoint PFS), 316 patients with previously untreated metastatic gastric adenocarcinoma were randomised to receive five cycles of either cisplatin (80 mg/m$^2$ on day 1) plus capecitabine (1000 mg/m$^2$ twice daily on days 1–14), every 3 weeks (XP), or the same regimen of cisplatin plus 5-FU (800 mg/m$^2$/day on days 1-5), every 3 weeks (FP). The XP regimen was clearly not inferior to FP ($p = 0.0008$; test for superiority $p = 0.0801$), with median PFS durations of 5.6 months (95% CI [4.9–7.3 months]) and 5.0 months (95% CI: 4.2–6.3), respectively. Moreover, XP was associated with improved median OS (10.5 months versus 9.3 months; $p < 0.008$) and objective response rate (41% versus 29%; $p = 0.030$) compared with FP, and had a similar safety profile except hand foot syndrome was more frequent in the XP arm (22%) than the FP arm (4%).

Several phase II studies have investigated the combination of docetaxel with capecitabine as first- or second-line therapy for advanced gastric cancer.[78–82] Although these were small studies, the cumulative evidence supports the feasibility of docetaxel-capecitabine in gastric cancer, with objective response rates generally ranging from 26 to 55%, median TTP ranging from 3.7 months to 6.2 months and median OS ranging from 8.4 months to 16.0 months. The main toxicities of this combination include acceptable levels of neutropenia, febrile neutropenia, diarrhoea, nausea, stomatitis and hand foot syndrome.

In Japan, several studies have shown the activity of the oral fluoropyrimidine S-1 in gastric cancer. Phase II studies have shown an impressive activity in combination with docetaxel or cisplatin. Randomised phase III studies are ongoing integrating S-1 combinations (e.g.: 5-FU/cisplatin versus S-1/cisplatin; S-1 versus S-1 plus docetaxel). Two randomised Japanese studies have shown the non-inferiority of S-1 compared to continuous IV-5-FU[83] and the high degree of activity of S-1 in combination with cisplatin.[84]

#### 4.2.6. *Oxaliplatin-docetaxel based regimens*

A new strategy under investigation in gastric cancer is the administration of oxaliplatin and docetaxel in combination. In addition to the known activity of both agents in advanced gastric cancer, the rationale for the docetaxel-oxaliplatin pairing includes their distinct and complementary mechanisms of action, lack of cross-resistance, different toxicity profiles. Several phase II studies have been conducted with promising results.

A large phase II study by the US oncology group[85] assessed first-line docetaxel (60 mg/m$^2$ intravenously over 1 h on day 1) combined with oxaliplatin (130 mg/m$^2$ iv over 2 h on day 1), every 3 weeks, in 71 patients with metastatic adenocarcinoma of the stomach and/or gastro-oesophageal junction. Confirmed ORR, the primary endpoint, was 38% and a further 52% of patients had stable disease. Median duration of response was quite long at 4.6 months (range, 2.7–18.3 months) and median OS was 9.2 months (95% CI, [6.5–11.2] months). The incidence of grade 3–4 non-haematological adverse events was acceptable; the most common events were vomiting in 17% of patients, nausea in 16% and dehydration, diarrhoea and fatigue in 13% each. Grade 3–4 neutropenia was observed in 70% of patients, but febrile neutropenia was reported in only 7% of patients. A second study[86] investigated the combination of docetaxel (75 mg/m$^2$ on day1) and oxaliplatin (80 mg/m$^2$ on day 2) every 3 weeks in 20 patients with advanced gastric cancer who had progressed on 5-FU-based chemotherapy (60% of patients received first-line ECF, 30% cisplatin plus infusional 5-FU and 10% irinotecan plus infusional 5-FU). An objective response was achieved in 15% of patients and 40% had stable disease. Median TTP was 4.8 months (range, 1–7 months) and median OS was 6.0 months (range 2–20 months). Grade 3–4 non-haematological toxicities were neurotoxicity and asthenia, each reported for 10% of patients. Grade 3–4 neutropenia was reported for 40% of patients but non had febrile neutropenia or other grade 3–4 haematological toxicities. The combination of docetaxel (50 mg/m$^2$ over 1 h) with modified FOLFOX 6 (oxaliplatin 85 mg/m$^2$ iv over 2 h plus 5-FU 400 mg/m$^2$ bolus then 3000 mg/m$^2$ iv over 48 h plus leucovorin 400 mg/m$^2$ iv over 2 h), all administered on days 1 and 14 every 3 weeks, was also investigated in a small phase II study of 16 patients with locally advanced or metastatic gastric cancer .[87] This regimen achieved a high objective response rate (44%; six partial responses, one complete response) and was well tolerated.

In advanced disease, an ongoing phase II study (GATE study) is investigating three cytotoxic combinations in 270 patients with previously untreated advanced gastric or gastro-oesophageal junction adenocarcinoma; the study includes two cohorts of patients with dose reduction for oxaliplatin and docetaxel in the first cohort. Three regimens are tested: docetaxel (75 mg/m$^2$ on day 1) and oxaliplatin (100 or 130 mg/m$^2$ on day 1) every 3 weeks; docetaxel (40 or 50 mg/m$^2$ on day 1, oxaliplatin (85 mg/m$^2$ on day 1, leucovorin (400 mg/m$^2$ on day 1) and 5-FU (2400 mg/m$^2$on day 1) every 2 weeks; and docetaxel (50 or 65 mg/m$^2$ on day 1) oxaliplatin (100 mg/m$^2$ on day 1) capecitabine (625 mg/m$^2$ bid continuously) every 3 weeks. The primary endpoint is TTP. In the neoadjuvant setting, the planned phase II EORTC study will investigate this strategy in the preoperative setting in a trial evaluating docetaxel-oxaliplatin-5-FU-leucovorin followed by concomitant oxaliplatin-5-FU plus radiotherapy and then surgery in patients with locally advanced gastric or gastro-oesophageal junction adenocarcinoma.

#### 4.2.7. *Biological agents*

Limited data with targeted agents are available in gastric cancer. These data are interesting and stimulate the further investigations of targeted agents in gastric cancer.

Results were presented recently for a phase II study[88] of docetaxel (35 mg/m$^2$ intravenously over 30 min on days 1, 8 and 15, every 4 weeks) combined with bevacizumab (5 mg/kg iv over 30–90 min on days 1 and 15, every 4 weeks) in 26 patients with previously treated advanced gastric or oesophageal cancer. Most patients had previously received irinotecan and/or cisplatin. Interim response data for 17 patients demonstrate the feasibility of this regimen which achieved a partial response in 4/15 patients (26.6%) and disease stabilisation in five patients (33.3%). Toxicity was acceptable; the main grade 3–4 toxicities were anaemia (15%), fatigue (15%),

neutropenia (10%), gastrointestinal bleed (15%) and arterial thrombosis (10%) – the latter two toxicities most likely related to bevacizumab.

First-line bevacizumab (15 mg/kg) on day 1, irinotecan (65 mg/m$^2$) and cisplatin (30 mg/m$^2$) on days 1 and 8 every 3 weeks, was investigated in a non-randomised phase II study in 47 patients with advanced gastric or gastro-oesophageal cancer.[89] The results suggest acceptable toxicity and improved efficacy for irinotecan-cisplatin plus bevacizumab compared with historical controls: with a median follow-up of 12.2 months, median TTP was 8.3 months (95% CI: 5.5–9.9 months); in 34 patients with measurable disease, the overall response rate was 65% (95% CI: 46–80%); median survival was 12.3 months (95% CI: 11.3–17.2 months).

Another interesting innovative approach was represented by Epidermal Growth Factor Receptor (EGFR) inhibition. While small molecules like erlotinib[90] and gefitinib.[91] did not show any clinical benefit for gastric cancer, anti-EQFR monoclonal antibodies (i.e. cetuximab) gave promising results. Nevertheless, in the erlotinib trial,[90] it was of note that this EGFR inhibitor was active in the gastro-oesophageal junction tumours with a 10% objective response rate versus 0% in the stomach, suggesting a different biology between gastric and gastro-oesophageal tumours. In a study[92] conducted in 38 patients with locally advanced (13.2%) or metastatic (86.8%) gastric (89.5%) or gastro-oesophageal junction (10.5%) adenocarcinoma, FOLFIRI plus cetuximab were administered as first-line treatment. The ORR was 44.1% (95% CI: 27.5–60.9%). The median TTP was 8 months (95% CI: 7–9 months). At the median follow-up time of 11 months, 55.3% of patients were alive, with a median expected survival time of 16 months (95% CI: 9–23 months). Treatment was well tolerated and the highest toxicity limited to neutropenia (grade 3–4: 42.1%). This approach deserves further investigations, and now a trial combining docetaxel and cetuximab is ongoing in Italy. In a study conducted by the German Arbeitsgemeinschaft Internistische Oncologie (AIO), 52 patients with advanced gastric cancer received FUFOX (oxaliplatin, leucovorin and continous infusion 5-FU) plus cetuximab.[93] Response was assessable in 46 patients showing an overall response rate of 65.2% (95% CI, [49.8–78.6%]) including four complete and 26 partial responses. Eighteen (39.1%) responses have been confirmed. The response rate according to the EGFR-status was 76.5% and 54.2% in tumours with undetectable and detectable level, respectively. Intention-to-treat analysis reveals a TTP of 7.6 months (95/ CI: 5.0–10.1 months) and an OS of 9.5 months (95% CI: 7.9–11.1 months).

### 4.3. *Follow-up*

There is no evidence that regular intensive follow up after initial therapy improves the outcome. Symptom-driven visits are recommended for most cases. History, physical examination, blood tests should be performed, if symptoms of relapse occur. Radiological investigations should be considered for patients who are candidates for palliative chemotherapy.

## Conflict of interest statement

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## REFERENCES

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006;**24**(14):2137–50.
2. Maruyama K, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. *World J Surg* 1987;**11**(4):418–25.
3. Olschwang S, Bonaiti C, Feingold J, et al. Identification and management of HNPCC syndrome (hereditary non polyposis colon cancer), hereditary predisposition to colorectal and endometrial adenocarcinomas. *Bull Cancer* 2004;**91**(4):303–15.
4. Stomach. In: American Joint Committee on Cancer: AJCC Cancer Staging Manual. 6th ed. New York, NY: Springer, 2002, pp 99–106.
5. Nishi M, Omori Y, Miwa Y. Japanese Research Society for Gastric Cancer "Japanese classification of gastric carcinoma. *2nd English ed" Gastric Cancer* 1998;**1**:11–24.
6. McArdle C, Hole D. Impact of variability among surgeons on postoperative morbidity and mortality and ultimate survival. *BMJ* 1991;**302**(6791):1501–5.
7. Ishikawa S, Togashi A, Innoue M, et al. Indications for EMR/ESD in cases of early gastric cancer: relationship between histological type, depth of wall invasion, and lymph node metastasis. *Gastric Cancer* 2007;**10**(1):35–8.
8. Dent D, Madden M, Price S. Randomized comparison of R1 and R2 gastrectomy for gastric carcinoma. *Br J Surg* 1988;**75**(2):110–2.
9. Robertson C, Chung S, Woods S, et al. A prospective randomized trial comparing R1 subtotal gastrectomy with R3 total gastrectomy for antral cancer. *Ann Surg* 1994;**220**(2):176–82.
10. Bonenkamp JJ, Songun I, Hermans J, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995;**345**(8952):745–8.
11. Bonenkamp JJ, Hermans J, Sasako M, et al. Dutch Gastric Cancer Group. Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999;**340**(12):908–14.
12. Hartgrink H, van de Velde C, Putter H, et al. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. *J Clin Oncol* 2004;**22**(11):2069–77.
13. Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. *Br J Cancer* 1999;**79**(9–10):1522–30.
14. McCulloch P, Niita M, Kazi H, Gama-Rodrigues J. Gastrectomy with extended lymphadenectomy for primary treatment of gastric cancer. *Br J Surg* 2005;**92**(1):5–13.
15. Wu C, Hsiung C, Lo S, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. *Lancet Oncol* 2006;**7**(4):309–15.
16. Sasako M, Sano T, Yamamoto S et al. Japan Clinical Oncology Group (JCOG). Randomized Phase III trial of standard D2 versus D2+para-aortic lymph node (PAN) dissection (D) for clinically M0 advanced gastric cancer: JCOG9501. J Clin Oncol 2006; Proc ASCO, 24(18S): LBA4015.
17. Davies J, Barnes R, Milligan D. British Committee for Standards in Haematology. Working Party of the Haematology/Oncology Task Force. Update of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. *Clin Med* 2002;**2**(5):440–3.
18. Kampschoer G, Maruyama K, van de Velde C, Sasako M, Kinoshita T, Okabayashi K. Computer analysis in making

preoperative decisions: a rational approach to lymph node dissection in gastric cancer patients. *Br J Surg* 1989;**76**(9):905–8.
19. Bollschweiler E, Boettcher K, Hoelscher A, et al. Preoperative assessment of lymph node metastases in patients with gastric cancer: evaluation of the Maruyama computer program. *Br J Surg* 1992;**79**(2):156–60.
20. Hundahl S, Macdonald J, Benedetti J, Fitzsimmons T. Southwest Oncology Group and the Gastric Intergroup. Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. *Ann Surg Oncol* 2002;**9**(3):278–86.
21. Hundahl S, Macdonald JS, Benedetti J. Durable survival impact of "low Maruyama Index surgery" in a trial of advjuvant chemoradiation for gastric cancer. ASCO Gastrointestinal Cancers Symposium, San Francisco, California, 22–24 January 2004 (abstract 48).
22. Peeters K, Hundahl S, Kranenbarg E, Hartgrink H, van de Velde CJ. Low Maruyama index surgery for gastric cancer: blinded reanalysis of the Dutch D1-D2 trial. *World J Surg* 2005;**29**(12):1576–84.
23. Kattan M, Karpeh M, Mazumdar M, Brennan M. Postoperative nomogram for disease-specific survival after an R0 resection for gastric carcinoma. *J Clin Oncol* 2003;**21**(19):3647–50.
24. Novotny A, Schuhmacher C, Busch R, Kattan M, Brennan M, Siewert J. Predicting individual survival after gastric cancer resection: validation of a U.S.-derived nomogram at a single high-volume center in Europe. *Ann Surg* 2006;**243**(1):74–81.
25. Siewert JR, Bottcher K, Stein HJ, Roder JD. Relevant prognostic factors in gastric cancer: ten-year results of the German Gastric Cancer Study. *Ann Surg* 1998;**228**(4):449–61.
26. Cascinu S, Labianca R, Barone C, et al. Adjuvant treatment of high-risk, radically resected gastric cancer patients with 5-fluorouracil, leucovorin, cisplatin, and epidoxorubicin in a randomized controlled trial. *J Natl Cancer Inst* 2007;**99**(8):601–7.
27. Hermans J, Bonenkamp J, Boon M, et al. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. *J Clin Oncol* 1993;**11**(8):1441–7.
28. Earle C, Maroun J. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. *Eur J Cancer* 1999;**35**(7):1059–64.
29. Mari E, Floriani I, Tinazzi A, et al. Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomised trials. A study of the GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente). *Ann Oncol* 2000;**11**(7):837–43.
30. Panzini I, Gianni L, Fattori P, et al. Adjuvant chemotherapy in gastric cancer: a meta-analysis of randomized trials and a comparison with previous meta-analyses. *Tumori* 2002;**88**(1):21–7.
31. Macdonald J, Smalley S, Benedetti J, Hundahl, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;**345**(10):725–30.
32. Braga M, Zuliani W, Foppa L, Di Carlo V, Cristallo M. Food intake and nutritional status after total gastrectomy: results of a nutritional follow-up. *Br J Surg* 1988;**75**(5):477–80.
33. Cunningham D, Allum W, Stenning S, et al. MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;**355**(1):11–20.
34. Boige V, Pignon J, Saint-Aubert B et al. Final results of a randomized trial comparing preoperative 5-fluorouracil(F)/ cisplatin (P) to surgery alone in adenocarcinoma of stomach and lower esophagus: FNLCC ACCORD07-FFCD9703 trial. J Clin Oncol, Proc ASCO 2005; 25: 18S: A4510.
35. Roth A, Biffi R, Stup R, et al. Comparative evaluation in tolerance of neoadjuvant versus adjuvant docetaxel based chemotherapy in resectable gastric cancer in a randomized trial of the Swiss Group for Clinical Cancer Research (SAKK) and the European Institute of Oncology (EIO). *Ann Oncol* 2007;**18**:S7. A-O-0019.
36. Van Cutsem E, Dicato M, Arber N, et al. The neo-adjuvant, surgical and adjuvant treatment of gastric adenocarcinoma. Current expert opinion derived from the Seventh World Congress on Gastrointestinal Cancer, Barcelona 2005. *Ann Oncol* 2006;**17**(6):vi13–8.
37. Wagner A, Grothe W, Haerting J, Kleber G, Grothey A, Fleig W. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol* 2006;**24**(18):2903–9.
38. Lutz MP, Wilke H, Wagener DJ, et al. Weekly infusional high-dose fluorouracil (HD-FU), HD-FU plus folinic acid (HD-FU/FA), or HD-FU/FA plus biweekly cisplatin in advanced gastric cancer: randomized phase II trial 40953 of the European Organisation for Research and Treatment of Cancer Gastrointestinal Group and the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2007;**25**(18):2580–5.
39. Webb A, Cunningham D, Scarffe J, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997;**15**(1):261–7.
40. Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. *J Clin Oncol* 2002;**20**(8):1996–2004.
41. Wagner AD, Grothe W, Behl S et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2005, 2, CD004064.
42. Mathe G, Kidani Y, Segiguchi M, et al. Oxalo-platinum or 1-OHP, a third-generation platinum complex: an experimental and clinical appraisal and preliminary comparison with cisplatinum and carboplatinum. *Biomed Pharmacother* 1989;**43**(4):237–50.
43. Raymond E, Faivre S, Woynarowksi J, Chaney S. Oxaliplatin: mechanism of action and antineoplastic activity. *Semin Oncol* 1998(suppl 5):4–12.
44. Raymond E, Faivre S, Chaney S, Woynarowski J, Cvitkovic E. Cellular and molecular pharmacology of oxaliplatin. *Mol Cancer Ther* 2002(3):227–35.
45. Hartmann J, Lipp H. Toxicity of platinum compounds. *Expert Opin Pharmacother* 2003;**4**(6):889–901.
46. Eriguchi M, Nonaka Y, Yanagie H, Yoshizaki I, Takeda Y, Sekiguchi M. A molecular biological study of anti-tumour mechanisms of an anti-cancer agent Oxaliplatin against established human gastric cancer cell lines. *Biomed Pharmacother* 2003;**57**(9):412–5.
47. Bang Y, Kang Y, Kang W, et al. Phase II study of oxaliplatin, 5-fluorouracil and folinic acid in recurrent or metastatic gastric cancer. *J Clin Oncol, Proc ASCO* 2002;**21**:A2249.
48. Chao Y, Yeh K, Chang C, et al. A Phase II study of oxaliplatin and weekly 24-hour infusion of high dose 5-fluorouracil and leucovorin (HDFL) in the first-line treatment of inoperable, locally advanced or recurrent/metastatic gastric cancers. *J Clin Oncol, Proc ASCO* 2002;**21**:A651.
49. Jin M, Chen Q, Cheng F, et al. Oxaliplatin (OXA) in combination with LV5FU2 in Chinese patients with advanced gastric cancer (AGC). *J Clin Oncol, Proc ASCO* 2002;**21**:A558.
50. Mauer A, Kraut E, Rudin C, et al. Phase II study of oxaliplatin (OX), fluorouracil (FU) and leucovorin (LV) in metastatic carcinoma of the esophagus/gastric cardia. *J Clin Oncol, Proc ASCO* 2002;**21**:A554.

51. Louvet C, Andre T, Tigaud J, et al. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. *J Clin Oncol* 2002;**20**(23):4543–8.
52. Al-Batran S, Atmaca A, Hegewisch-Becker S, et al. Phase II trial of biweekly infusional fluorouracil, folinic acid, and oxaliplatin in patients with advanced gastric cancer. *J Clin Oncol* 2004;**22**(4):658–63.
53. Lordick F, Lorenzen S, Stollfuss J, et al. Phase II study of weekly oxaliplatin plus infusional fluorouracil and folinic acid (FUFOX regimen) as first-line treatment in metastatic gastric cancer. *Br J Cancer* 2005;**93**(2):190–4.
54. Cunningham D, Rao S, Starling N, et al. NCRI Upper GI Study Group. Randomised multicentre Phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric (OG) cancer: The REAL 2 trial. *J Clin Oncol, Proc ASCO* 2006;**24**:18S. LBA4017.
55. Al-Batram S, Hartmann J, Probst S, et al. A randomised Phase III trial in patients with advanced adenocarcinoma of the stomach receiving first-line chemotherapy with fluorouracil, leucovorin and oxaliplatin (FLO) versus fluorouracil, leucovorin and cisplatin (FLP). *J Clin Oncol, Proc ASCO* 2006;**24**:18S. LBA4016.
56. Bouche O, Raoul J, Bonnetain F, et al. Federation Francophone de Cancerologie Digestive Group. Randomized multicenter Phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study-FFCD 9803. *J Clin Oncol* 2004;**22**(11):4319–28.
57. Moehler M, Eimermacher A, Siebler J, et al. Randomised Phase II evaluation of irinotecan plus high-dose 5-fluorouracil and leucovorin (ILF) vs 5-fluorouracil, leucovorin, and etoposide (ELF) in untreated metastatic gastric cancer. *Br J Cancer* 2005;**92**(12):2122–8.
58. Dank M, Zaluski J, Barone C, et al. Randomized Phase 3 trial of irinotecan (CPT-11) + 5FU/folinic acid (FA) vs CDDP + 5FU in 1st-line advanced gastric cancer patients. *J Clin Oncol, Proc* 2005;**23**:16S. A4003.
59. Kim Y, Shin S, Kim B, et al. Paclitaxel, 5-fluorouracil, and cisplatin combination chemotherapy for the treatment of advanced gastric carcinoma. *Cancer* 1999;**85**(2):295–301.
60. Kollmannsberger C, Quietzch D, Haag C, et al. A Phase II study of paclitaxel, weekly, 24-hour continuous infusion 5-fluorouracil, folinic acid and cisplatin in patients with advanced gastric cancer. *Br J Cancer* 2000;**83**(4):458–62.
61. Roth A, Maibach R, Martinelli G, et al. Docetaxel (Taxotere)-cisplatin (TC): an effective drug combination in gastric carcinoma. Swiss Group for Clinical Cancer Research (SAKK), and the European Institute of Oncology (EIO). *Ann Oncol* 2000;**11**(3):301–6.
62. Roth A, Maibach R, Fazio N, et al. 5-Fluorouracil as protracted continuous intravenous infusion can be added to full-dose docetaxel (Taxotere)-cisplatin in advanced gastric carcinoma: a Phase I-II trial. *Ann Oncol* 2004;**15**(5):759–64.
63. Roth A, Maibach R, Falk S, et al. Docetaxel-cisplatin-5FU (TCF) versus docetaxel-cisplatin (TC) versus epirubicin-cisplatin-5FU (ECF) as systemic treatment for advanced gastric carcinoma (AGC): A randomized Phase II trial of the Swiss Group for Clinical Cancer Research (SAKK). *J Clin Oncol* 2007;**25**(22):3217–23.
64. Vanhoefer U, Rougier P, Wilke H, et al. Final results of a randomized Phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin, and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: A trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. *J Clin Oncol* 2000;**18**:2648–57.
65. Ohtsu A, Shimada Y, Shirao K, et al. Japan Clinical Oncology Group Study (JCO G9205). Randomized Phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). *J Clin Oncol* 2003;**21**:54–9.
66. Ajani J, Fodor M, Tjulandin S, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. *J Clin Oncol* 2005;**23**:5660–7.
67. Van Cutsem E, Moiseyenko V, Tjulandin S, et al. V325 Study Group. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006;**24**:4991–7.
68. Ajani J, Moiseneyenko V, Tjuladin S, et al. Quality of life with docetaxel plus cisplatin and fluorouracil compared with cisplatin and fluorouracil from a phase III trial for advanced gastric or gastroesophageal adenocarcinoma: the V-325 Study Group. *J Clin Oncol* 2007;**25**:3210–6.
69. Ajani J, Moiseneyenko V, Tjuladin S, et al. Clinical benefit with docetaxel plus fluorouracil and cisplatin compared with cisplatin and fluorouracil in a phase III trial of advanced gastric or gastroesophageal cancer adenocarcinoma: the V-325 Study Group. *J Clin Oncol* 2007;**25**:3205–9.
70. Aapro M, Cameron D, Pettengell R, et al. European Organisation for Research and Treatment of Cancer (EORTC) Granulocyte Colony-Stimulating Factor (G-CSF) Guidelines Working Party EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. *Eur J Cancer* 2006;**42**(15):2433–53.
71. National Comprehensive Cancer Network. Myeloid growth factors. Available at: http://www.nccn.org. Accessed 11 July 2006.
72. Smith T, Khatcheressian J, Lyman G, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006;**24**(19):3187–205.
73. Tebbutt N, Sournina T, Strickland A, et al. ATTAX: Randomised Phase II study evaluating weekly docetaxel-based chemotherapy combinations in advanced oesophago-gastric cancer: final results of an AGITG trial. *J Clin Oncol, Proc ASCO* 2007;**25**:18S. A4528.
74. Orditura M, Martinelli E, Galizia G, et al. Weekly docetaxel and capecitabine is not effective in the treatment of advanced gastric cancer: a phase II study. *Ann Oncol* 2006;**17**(10):1529–32.
75. Graziano F, Catalano V, Baldelli A, et al. A phase II study of weekly docetaxel as salvage chemotherapy for advanced gastric cancer. *Ann Oncol* 2000;**11**(10):1263–6.
76. Lorenzen S, Hentrich M, Haberl C, et al. Split-dose docetaxel, cisplatin, and leucovorin/fluorouracil as first-line therapy in advanced gastric cancer and adenocarcinoma of the gastroesophageal junction: Results of a phase II trial. *Ann Oncol* 2007;**18**(10):1673–9.
77. Kang Y, Kang W, Shin D, et al. Randomized Phase III trial of capecitabine/cisplatin (XP) vs. continuous infusion of 5-FU/cisplatin (FP) as first-line therapy in patients (pts) with advanced gastric cancer (AGC): Efficacy and safety results. *J Clin Oncol, Proc ASCO* 2006;**24**:18S. LBA4018.
78. Chun J, Kim H, Lee J, et al. Weekly docetaxel in combination with capecitabine in patients with metastatic gastric cancer. *Am J Clin Oncol* 2005;**28**(2):188–94.

79. Lorenzen S, Duyster J, Lersch C, et al. Three-weekly Docetaxel (T) plus Capecitabine (X) in 1st and 2nd Line Metastatic Esophageal Cancer (MEC): Final Results of the Phase II DACAPO Trial. *J Clin Oncol, Proc ASCO* 2005;**23**:16S. A4142.
80. Kim J, Sohn S, Kim D, et al. Phase II study of docetaxel and capecitabine in patients with metastatic or recurrent gastric cancer. *Oncology* 2005;**68**(2–3):190–5.
81. Thuss-Patience P, Kretzschmar A, Loew A, et al. Capecitabine and docetaxel in advanced gastric adenocarcinoma, an ongoing Phase II study. *J Clin Oncol, Proc ASCO* 2005;**23**:16S. A4224.
82. Giordano K, Jatoi A, Stella P, et al. North Central Cancer Treatment Group. Docetaxel and capecitabine in patients with metastatic adenocarcinoma of the stomach and gastroesophageal junction: a Phase II study from the North Central Cancer Treatment Group. *Ann Oncol* 2006;**17**(4):652–6.
83. Boku N, Yamanoto S, Shirao K, et al. Randomized phase III study of 5-fluorouracil (5-FU) alone versus combination of irinotecan and cisplatin (CP) versus S-1 alone in advanced gastric cancer (JCOG9912). *J Clin Oncol, Proc ASCO* 2007;**25**:18S. LBA 4513.
84. Narahara H, Koizumi W, Hara T, et al. Randomized phase III study of S-1 + cisplatin in the treatment for advanced gastric cancer (the SPIRITS trial). *J Clin Oncol, Proc ASCO* 2007;**25**:18S. A4514.
85. Richards D, Wilfong L, Reznick D, et al. Phase II multicenter trial of docetaxel + oxaliplatin in stage IV gastroesophageal and/or stomach cancer. *J Clin Oncol, Proc ASCO* 2006;**24**:18S. A4071.
86. Barone C, Basso M, Quirino et al. Docetaxel and oxaliplatin combination as second line treatment in patients with advanced gastric cancer. ASCO Gastrointestinal Cancers Symposium Florida, 27–29 January 2005, A27.
87. Dima G, Caputo A, De Simone R, et al. Phase II study of docetaxel, oxaliplatin, and folinic acid in locally advanced or metastatic gastric cancer patients. *Ann Oncol* 2005;**15**(l 7):A E27.
88. Enzinger P, Fidias P, Meyerhardt J et al. Phase II study of bevacizumab and docetaxel in metastatic esophageal and gastric cancer. ASCO Gastrointestinal Cancers Symposium, San Francisco, California, 26-28 January 2006, A68.
89. Shah M, Ramanathan R, Ilson D, et al. Multicenter phase II study of irinotecan, cisplatin and bevacizumab in patients with gastric or gastroesophageal junction adenocarcinoma. *J Clin Oncol* 2006;**24**(33):5201–6.
90. Dragovich T, McCoy S, Fenoglio-Preiser C et al. Phase II trial of erlotinib in gastroesophageal junction and gastric adenocarcinomas: SWOG 0127. J Clin Oncol 2006, 24(30), 4922-4927. Erratum in: J Clin Oncol 2007, 25(16), 2334.
91. Rojo F, Tabernero J, Albanell J, et al. Pharmacodynamic studies of gefinitib in tumor biopsy specimens from patients with advanced gastric carcinoma. *J Clin Oncol* 2006;**24**:4309–19.
92. Pinto C, Di Fabio F, Siena S, et al. Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma (FOLCETUX study). *Ann Oncol* 2007;**18**(3):510–7.
93. Lordick F, Lorenzen S, Hegewisch-Becker S, et al. Cetuximab plus weekly oxaliplatin/5FU/FA in 1st line metastatic gastric cancer. Final results from a multicenter phase II study of the AIO upper GI study group. *J Clin Oncol, Proc ASCO* 2007;**25**:18S.A4526.