Abstract. In the setting of metastatic or inoperable gastric cancer, the current evidence shows that chemotherapy improves survival in comparison to best supportive care and that combination chemotherapy is superior to monotherapy in terms of survival, response rate and symptom control. Many randomized phase III trials tested different combinations of therapies showing better outcome for cisplatin-containing schedules. In recent years, new drugs, such as docetaxel, oxaliplatin, irinotecan, capecitabine and S1 have also been tested in phase III studies. Unfortunately, in all of these studies, but one, the median survival remained below one year. Although there are no internationally accepted standard regimens, in Europe, ECF (epirubicin, cisplatin, fluorouracil) has been considered the reference regimen; in the US cisplatin-fluoropyrimidine combinations are mainly used, while in Japan, cisplatin with S1 has become the standard. Currently, various targeted agents are being tested in clinical trials and promising data have been recently published for trastuzumab-containing therapy, with median survival exceeding one year. As regards progressive disease, about 20%-50% of patients receive second line chemotherapy and, although two phase III studies reported survival benefit with single-agent chemotherapy, the role of chemotherapy in this setting still needs to be defined. Despite the progress of recent decades, metastatic gastric cancer remains an incurable disease, and treatment options should primarily take into account the quality of life and quality-adjusted survival of patients. The hope for the future is that tailored interventions based on new cytotoxic drugs, targeted therapies and integration of molecular determinants may help to improve the current treatments.

Despite improvement in the diagnosis of gastric cancer, in the Western world, approximately two thirds of gastric cancer patients have inoperable locally advanced or metastatic disease at diagnosis or develop a recurrence after surgery. Patients with inoperable, recurrent or metastatic tumours are incurable and prognosis is of only few months with best supportive care (BSC). In this setting, systemic chemotherapy prolongs survival and improves symptom palliation, although these benefits are to be weighed against treatment-related toxicities.

The first-generation chemotherapy protocols were based on 5-fluourouracil (5-FU), the most extensively used single agent, cisplatin and anthracyclines. Recent phase III trials evaluated new drugs such as capecitabine, oxaliplatin, docetaxel, paclitaxel, irinotecan, S-1 and monoclonal antibodies (1-6); other new drugs are currently under evaluation in phase II and III clinical studies.

Although a large number of chemotherapy regimens have been tested in randomized studies, there is no internationally accepted standard of care and uncertainty remains regarding the most appropriate regimen.

In the setting of metastatic gastric cancer, the current evidence shows that: i) chemotherapy improves survival in comparison to BSC; ii) combination chemotherapy improves survival compared to single-agent 5-FU and produces a higher response rate, albeit, at the cost of higher toxicity.
Single-agent therapy versus combination therapy. A recent meta-analysis (10) demonstrated that combination chemotherapy had a statistically significant and consistent survival advantage compared with single-agent therapy (HR=0.80, 95% CI=0.72-0.89). Median survival was 8.3 vs. 6.7 months, median progression-free survival (PFS) 5.6 vs. 3.6 months and the pooled objective response rate 35% vs. 18% in the combination and single-agent arms, respectively. Overall, toxicity was higher with combination chemotherapy, but the difference was not statistically significant, probably because of dissimilarities in reporting. Death due to toxicity was different between treatment arms at 1.9% for combination and 0.9% for single-agent 5-FU (odds ratio, OR=1.69; 95% CI=0.58-4.94).

Combination regimens. Regimens not including cisplatin. The FAM regimen (5-FU, doxorubicin and mitomycin) was the first reference combination; preliminary studies reported

### Table I. Principal characteristics of the randomized studies.

<table>
<thead>
<tr>
<th>Author, year (ref)</th>
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<tr>
<td>Wils et al., 1991 (14)</td>
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<td>Kelsen et al., 1992 (15)</td>
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<td>Van Cutsem et al., 2006 (4)</td>
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<td>Al-Batran et al., 2008 (1)</td>
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<tr>
<td>Dank et al., 2008 (3)</td>
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<td>Cunningham et al., 2008 REAL 2 (2)</td>
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GEJ: gastroesophageal junction tumor. *Statistically significant, †not inferior. NR: Not reported; RR: response rate; OS: overall survival, PFS: progression-free survival; TTP: time to progression. FAM (fluorouracil, doxorubicin and mitomycin), FAMTX (high-dose fluorouracil, adriamycin and methotrexate), EAP (etoposide, adriamycin, cisplatin), ECF (epirubicin, cisplatin, fluorouracil), PF (cisplatin and fluorouracil), ELF (etoposide, leucovorin, fluorouracil), PELF (cisplatin, epirubicin, leucovorin, fluorouracil), MCF (mitomycin, cisplatin, fluorouracil), DCF (docetaxel, cisplatin, fluorouracil), FLO (fluorouracil, leucovorin, oxaliplatin), FLP (fluorouracil, leucovorin, cisplatin), EOX (epirubicin, oxaliplatin, capecitabine), XP (capecitabine, cisplatin), P-S1 (cisplatin, S1), PX (cisplatin, capecitabine).
a response rate of more than 40%, with a favourable toxicity profile (11-12). However, a randomized three-arm trial performed by the North Central Cancer Treatment Group (NCCTG) including 305 patients with advanced gastric and pancreatic cancer, compared 5-FU single-agent, 5-FU plus doxorubicin, and FAM; however, response rates and survival were not statistically different (13).

The European Organization for Research and Treatment of Cancer (EORTC) then compared the FAM and FAMTX (high-dose 5-FU, adriamycin and methotrexate) regimens; FAMTX conferred a significantly superior response rate and improved overall survival (14). In turn, FAMTX was compared with other regimens (Tables I and II) (15-18).

Regimens including cisplatin. In a small U.S. study (15), FAMTX provided similar results to EAP (etoposide, adriamycin, cisplatin) but was significantly less toxic. In a UK trial (16) ECF (epirubicin, cisplatin, 5-FU) was superior both in terms of response rate (45% vs. 21%) and median survival (8.9 vs. 5.7 months); the authors concluded that the ECF regimen should be regarded as the standard treatment in advanced esophagogastric cancer.

### Table II. Results of the randomized studies.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>% response</th>
<th>Median PFS/TTP</th>
<th>Survival Median†</th>
<th>1-year</th>
<th>2-year</th>
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<tr>
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<td>PELF</td>
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<td>S-1</td>
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<td>6*</td>
<td>13*</td>
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<td>PF/PX</td>
<td>34.5</td>
<td>5.5</td>
<td>11.1</td>
<td>45</td>
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<td>Bang et al., 2010 ToGA (5)</td>
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<tr>
<td>PF/PX-trastuzumab</td>
<td>47.3*</td>
<td>6.7*</td>
<td>13.8*</td>
<td>57</td>
<td>25</td>
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<tr>
<td>PF/PX</td>
<td>29.5/37</td>
<td>5.3</td>
<td>10.1</td>
<td>42</td>
<td>17</td>
<td>Kang et al., 2010 AVAGAST (6)</td>
</tr>
<tr>
<td>PF/PX-bevacizumab</td>
<td>38*/46</td>
<td>6.7*</td>
<td>12.1</td>
<td>52</td>
<td>17</td>
<td>Kang et al., 2010 AVAGAST (6)</td>
</tr>
</tbody>
</table>

*Statistically significant; †months, unless specified differently; ‡derived from the curve; NR: Not reported; RR: response rate, PFS: progression-free survival; TTP: time to progression. For abbreviations see Table I.
In the EORTC trial (17), there were no statistical differences in response rate and survival between FAMTX, PF (cisplatin and 5-FU) and ELF (etoposide, leucovorin, 5-FU). An Italian trial (18) showed that PELF (cisplatin, epirubicin, leucovorin, 5-FU) was statistically superior in terms of response rate, but not survival.

A further UK study (19) compared ECF with the similar MCF regimen in which the doses of 5-FU were increased and epirubicin was substituted for mitomycin. Survival and response rate were not statistically different, but quality of life (QoL) was better with ECF. The study concluded that ECF should remain the reference regimen. In this study, one third of the patients had inoperable locally advanced disease; in this subset, median survival was 11.8 months with ECF and 12.6 months with MCF (p=0.4), one-year survival was 47.7% and 50.4% with ECF and MCF, respectively. This is the study with the highest percentage of patients with non-metastatic disease and the only one in which separate data for this subset have been reported; in general, the other series included fewer than 20% of patients with locally advanced disease.

As a whole, the meta-analysis (10), comparing the three-drug (FU/cisplatin/anthracycline) with the two-drug regimens (5-FU/cisplatin or 5-FU/anthracycline) demonstrated a small, but statistically significant benefit in overall survival in favour of the three-drug combinations (2 months and 1 month, respectively).

**Regimens including new chemotherapy agents.** New agents, such as docetaxel, oxaliplatin, irinotecan, capecitabine, S-1 have been tested in randomized trials in the recent years. Many phase II studies have shown that taxanes (paclitaxel and docetaxel) produce response rates in the range of 22% to 65%. To date, no randomized phase III trials have been published with paclitaxel, while three phase II randomized studies demonstrated that docetaxel-based regimens had a response rate of approximately 40% and gave a median survival of 10 months (20-22).

Following these findings, docetaxel in combination with cisplatin and 5-FU (DCF) was tested in the V325 phase III trial against the US reference PF (4). The DCF arm demonstrated statistically superior time to progression (6.6 vs. 3.7 months), response rate (37% vs. 25%) and overall survival (9.2 vs. 8.6 months). DCF was also associated with a better preservation of QoL and maintenance of clinical benefit compared with PF (23, 24). Based on these results, the DCF regimen was approved for use by the US Food and Drugs Administration. However, it is of note that the DCF arm experienced a higher rate of complicated neutropenia (29% vs. 12%) necessitating granulocyte colony-stimulating factor prophylaxis. Moreover, the median patient age of 55 years was well below the median age of the patients included in other trials and needs to be considered when applying these findings to the general population.

The meta-analysis (10), pooling the results of three docetaxel-based protocols, reported that the HR for overall survival favoured the docetaxel-containing regimens; however, without reaching statistical significance (HR=0.93, 95% CI=0.75-1.15). PFS was, on the whole, not statistically different, but the results were flawed by the differences between the schedules. The objective response rate was 36% in the docetaxel-containing arms vs. 31% in the control arms, corresponding to an OR of 1.30 (95% CI=0.98-1.72), with a non-significant advantage for the docetaxel-containing regimens.

Al-Batran et al. (1) compared the FLO regimen (5-FU, leucovorin, oxaliplatin) vs. the FLP regimen (5-FU, leucovorin, cisplatin). There was only a trend in favour of FLO in PFS (the primary end point), but no difference in overall survival (OS). However, in the subset of patients older than 65 years, FLO resulted in significantly superior response rates (41.3% vs. 16.7%; p=0.012), time to treatment failure (5.4 vs. 2.3 months; p=0.001), PFS (6.0 vs. 3.1 months; p=0.029) and an improved OS (13.9 vs. 7.2 months) as compared with FLP. Overall, FLO was associated with reduced toxicity and seemed to be associated with improved efficacy in the elderly.

The REAL-2 (2), a UK non-inferiority phase III trial, compared ECF, ECX (X: capecitabine), EOF (O: oxaliplatin), and EOX (O: oxaliplatin; X: capecitabine). Median survival in the ECF, ECX, EOF and EOX groups was 9.9, 9.9, 9.3 and 11.2 months, respectively; one-year survival rates were statistically different. In the secondary analysis, OS was associated with reduced toxicity and seemed to be associated with improved efficacy in the elderly.

In the ML17032 trial with a prevalent Asian population, capecitabine with cisplatin showed significant non-inferiority for PFS vs. PF; the OS favoured the oral regimen (HR=0.85, 95% CI=0.65-1.11) with median survival times of 10.4 and 9.3 months in favour of capecitabine, without reaching, however, statistical significance (25).

These two trials (2, 25) consistently demonstrated the non-inferiority of capecitabine in comparison to 5-FU and also suggested better outcome in patients receiving capecitabine. This finding was confirmed by a recent meta-analysis (26) of individual patients data from the ML17032 and REAL-2 trials. The median OS was 285 days for patients treated with 5-FU and 322 days for patients treated with capecitabine, giving an unadjusted HR of 0.87 (95% CI=0.77–0.98) in favour of capecitabine (p=0.027). Besides the problem of whether one month gain in median OS is clinically relevant, additional advantages of capecitabine over continuous infusion of 5-FU include the convenience of oral chemotherapy, which is generally more acceptable to
patients, lack of potential morbidity associated with central venous access and the opportunity to make dose adjustments in order to manage toxicity.

Another novel oral fluoropyrimidine (S-1), providing a response rate exceeding 40% in phase II studies, has been tested in two randomized trials (27, 28).

The Japanese SPIRITS trial (27) compared S-1 plus cisplatin with S-1 alone. Median PFS (6.0 vs. 4.0 months; \(p<0.0001\)) and OS (13.0 vs. 11.0 months; \(p=0.04\)) were significantly longer in the combination group. Response was also significantly improved in patients with target tumors and assigned to S-1 plus cisplatin (54% vs. 31%). On the basis of these findings, the S-1 plus cisplatin has become the standard of care in Japan. A possible criticism of this study is the lack of information about the advantage of S-1 over 5-FU when each drug is combined with cisplatin.

In Western populations, the First-Line Advanced Gastric Cancer Study (FLAGS) compared S-1 with 5-FU, both when combined with cisplatin (28). Median OS was 8.6 months in the cisplatin/S-1 arm and 7.9 months in the PF arm \(p=0.2\). On the other hand, the study showed statistically significant safety advantages for the S-1-based combination, regarding the rates of G3-4 neutropenia (32% vs. 63.6%), stomatitis (1.3% vs. 13.6%), renal function (5.2% vs. 9.3%) and treatment related deaths (2.5% vs. 4.9%).

Although the SPIRITS trial was the first randomized trial to break the apparently inoperable wall of 12 months, this result was not repeated in FLAGS. This inconsistency in survival may be explained by some relevant differences between the two studies. In the SPIRITS trial, only 65% of patients had metastatic disease compared with 96% of those in FLAGS; 74% and 31% of patients, respectively, received second-line therapy; Japanese investigators are highly experienced with excellent facilities, while FLAGS was a non-Asian global trial; despite dose adjustment, different pharmacokinetics due to ethnic variations cannot be excluded.

Thus, the future role of S-1 in gastric cancer is still unclear, but its use in three-drug regimens in order to improve tolerability of DCF or ECF is worthy of study.

Recent data were reported on the use of weekly irinotecan in combination with 5-FU and leucovorin (IF protocol) vs. PF. Time to progression (TTP) and OS were similar in both arms and the results on the non-inferiority of IF were borderline. However, the toxicity profile favoured the irinotecan arm over the PF arm in terms of discontinuation due to toxicity (10.0% vs. 21.5%), febrile neutropenia (4.8% vs. 10.2%) and stomatitis (2% vs. 16.9%). The authors suggested that IF may provide a viable platinum-free treatment alternative (3).

As for irinotecan, the meta-analysis reported that the irinotecan-containing combinations resulted in improved, although not statistically superior, median survival times (9.8 vs. 8.3 months, \(HR=0.86, 95\% CI=0.73-1.02\)), objective response rates (40% vs. 30%, \(OR=1.77, 95\% CI=0.85-3.69\)) and a lower rate of treatment discontinuation and deaths due to toxicity. Therefore, irinotecan-containing regimens should be considered as suitable alternatives to platinum combinations in consideration of the results and of the different toxicity profile (i.e. absence of neurotoxicity, no significant renal toxicity, less nausea and vomiting, no need for hyperhydration).

In conclusion, cisplatin is the basis for combination regimens all over the world, with geographical variations for the partner drugs. In Europe, ECF has long been considered the reference regimen; in the US cisplatin-fluoropyrimidine is mainly used, while in Japan, cisplatin-S1 has become widely accepted.

**Regimens including targeted agents.** Phase III studies. In recent years, different classes of targeted agents, such as monoclonal antibodies directed against the epidermal growth factor receptor 1 (EGFR) and 2 (HER-2), tyrosine kinase inhibitors (TKIs) and angiogenesis inhibitors have been tested in clinical trials.

To date, the Trastuzumab for gastric cancer (ToGA) trial (5) is the only phase III study already published which enrolled 594 patients with immunohistochemical overexpression of HER2 or gene amplification by fluorescence in situ hybridization (FISH). HER2 overexpression was positive in 21% of gastric carcinomas and in 33.2% of gastroesophageal junction carcinomas. The two treatment arms compared a chemotherapy regimen consisting of capecitabine or fluorouracil plus cisplatin with and without trastuzumab. The primary endpoint was OS. Median OS was 13.8 months (95% CI=12-16) in the trastuzumab arm compared with 11.1 months in the chemotherapy alone arm \(HR=0.74; 95\% CI=0.60-0.91; p=0.0046\). There was no difference in the rate of grade 3 or 4 adverse events and the percentage of cardiac events was identical in the two arms (<1%). The response rate was 47.3% and 34.5% \(p=0.0017\) in the trastuzumab arm and control arm, respectively. An explorative analysis showed that in the subgroup of tumors with high HER2 expression, the HR was 0.65 (95% CI=0.51-0.83) and median survival was 16.0 months (95% CI=15-19) in patients receiving trastuzumab, compared with 11.8 months (95% CI=10-13) for the controls. It has been proposed that trastuzumab be considered in combination with chemotheraphy as a new standard option for patients with HER2-positive advanced gastric or gastroesophageal junction cancer.

The anti-VEGF (vascular endothelial growth factor) monoclonal antibody bevacizumab was tested in the AVAGAST phase III trial (6) that enrolled 774 patients and compared the combination of cisplatin capecitabine (or fluorouracil) with and without bevacizumab. The primary end point was OS. The difference was not statistically significant and therefore the trial failed to met the primary endpoint; median OS was 10.1 and 12.1 months in the control and bevacizumab arms, respectively \(HR=0.87; p=0.1\); however, there was a significant improvement in PFS (5.3 vs. 6.7 months) and ORR (37% vs. 46%) with an
except for hypertension 6.2% vs. 0.5% and gastrointestinal (GI) perforation 2.3% vs. 0.3%.

Bevacizumab (anti-VEGFR monoclonal antibody) was tested in different schedules (fluorouracil/capecitabine plus oxaliplatin or irinotecan, docetaxel plus oxaliplatin) (32-35). The response rate was about 50% (range 41%-65%) and the TTP 6 months (range 5-8 months). The principal toxicities were neutropenia (40%) and acne-like rash (20%). A phase III trial of capecitabine and cisplatin with or without cetuximab is now recruiting patients (29).

Panitumumab (anti-EGFR monoclonal antibody) is currently being tested in combination with irinotecan-cisplatin (30) or with docetaxel-oxaliplatin (31), demonstrating a PFS and OS of 7-8 and of 11-12 months, respectively. The response rate was in the range of 65%-79%; the most relevant toxicities consisted of neutropenia (34%) and GI perforation (6%-8%).

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Phase II trials. Bevacizumab was tested in combination with irinotecan-cisplatin (30) or with docetaxel-oxaliplatin (31), demonstrating a PFS and OS of 7-8 and of 11-12 months, respectively. The response rate was in the range of 65%-79%; the most relevant toxicities consisted of neutropenia (34%) and GI perforation (6%-8%).

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Panitumumab (anti-EGFR monoclonal antibody) is currently being tested in combination with EOX in the REAL-3 phase III trial in which OS is the primary end point (29, 36).

Sunitinib (TKI) as a single agent was evaluated in ≥second line setting achieving mainly a disease stabilization in 33% of the patients (range 31%-34.7%) and a PFS of 1.4-2.3 months. However the clinical value of these results was deemed insufficient and the studies considered negative (37-38).

Sorafenib (TKI) in combination with docetaxel and cisplatin in first line achieved a response rate of 41%, a PFS of 5.8 months and an OS of 13.6 months; the toxicity was haematological, with 64% of severe neutropenia (39).

Everolimus (mTOR inhibitor) in second and third line settings (40) produced only disease stabilization in 56% of the patients without unexpected toxicities. PFS and OS were 2.7 and 10.1 months, respectively. Two phase III trials in pretreated patients are ongoing (29).

In summary, many randomized studies reported the inclusion also of adenocarcinoma of the gastroesophageal junction which represented a median of 20% of the patients (range 13%-28.9%) (1-6, 15, 16, 19, 28); two old studies also included esophageal cancer (16, 19). Since the 7th TNM Cancer Staging edition classified gastroesophageal junction tumours as esophageal cancer, in future trials it will be worthwhile having separate data in order to avoid possible confounding factors.

Despite the positive impact of chemotherapy, response was achieved in only about one third of the cases (median 31.5%, range 9%-54%).

The 15 studies had different end points: OS in 6, TTP/PFS in 4, RR in 3, OS and RR in 2. The results are shown in Table III. Whichever the primary end point, median survival was statistically superior in 5 studies (4, 5, 14, 16, 27) and showed non inferiority in 2 (2, 25). Regrettably, survival remained below 12 months in all but two trials (5, 27), and 1-year survival ranged from 7% to 57% (median 37%) (Table II). However the survival curves show no plateau and at 2 years, survival was only about 10% (range 0%-25%). It is still an open question whether the survival benefit achieved by three-drug vs. two-drug combinations compensates for the additional toxicity suffered by the patients.

Second-line Treatment

After disease progression, the role of second-line chemotherapy is even less defined than that of first-line, both in terms of efficacy and toxicity profile. However, this information is meaningful because 20%-50% of patients with advanced gastric cancer receive second-line chemotherapy (41-43). A pooled analysis of 1080 patients from phase III studies testing first-line fluorouracil-based regimens suggested that about 20% of patients with progressive disease received second-line treatment, with a response rate of 13.3% and median OS of 5.6 months since starting the second-line chemotherapy (44). It is important to note that most trials on second-line therapy have been conducted in Japan, Korea, and Italy, where the practice of offering second-line treatment to patients with advanced gastric cancer is common.

Phase III trials. The critical point is that only two phase III trials (45, 46) have been reported so far, while the remaining studies were phase II and did not provide direct comparison with BSC. A small study (45) compared irinotecan with BSC, but was prematurely closed due to poor accrual, with only 40 of an expected 120 patients enrolled. There was stabilization in 58% of patients, but no objective responses; on the other hand, there was a 44% improvement in symptoms in the active arm, compared to 5% in the control arm. OS, which was the primary end point, was 123 vs. 72 days in the treatment and control arm, respectively (p=0.003). Despite the small size of the study, the authors concluded that second-line chemotherapy could be considered as a proven option in gastric cancer.
Very recently, a Korean study (46) including 193 patients reported survival improvement in patients with progressive disease receiving chemotherapy (docetaxel or irinotecan) compared to those with BSC (5.1 and 3.8 months, respectively, \( p = 0.009 \)). However, no data regarding response rate, QoL or symptom control were reported.

These two studies showed that second-line chemotherapy has proven benefit and should be offered to medically fit patients willing to receive further treatment.

**Phase II trials.** Irinotecan has been tested mostly in combination with cisplatin and fluoropyrimidines (FOLFIRI/CAPIRI or similar schedules). The studies included a median of 33 patients each (range 8-131); on the whole the results were consistent over the studies showing a median response rate of about 21% (from 0% to 52%) and a disease control rate ranging from 0% to 77% (median 47%).

Median TTP and survival were reported to be approximately 3.3 (range 2.2-5.3) and 7.5 (range 5-10.9) months, respectively. Neutropenia was the most common relevant toxicity (11%-45%), followed by anaemia (3%-57%), diarrhoea (3% to 19%) and anorexia (12%-17%) (47-63, 76).

Docetaxel was mostly used in combination with other drugs (fluorouracil/capecitabine, cisplatin, epirubicin, oxaliplatin) achieving response rates ranging from 9% to 38% (median 17%), disease control rates of 50% (22%-80%), TTP of 3.9 (from 2.4 to 5.2) months and survival of 6.6 (from 6 to 8.9) months. The most frequent G3-4 toxicities consisted of neutropenia in about 27% (12%-71%) of the patients, febrile neutropenia in 11.5% and fatigue-asthenia in 32% (64-78).

Paclitaxel was prevalently used as weekly single agent and in a few studies it was combined with fluoropyrimidines. The studies included a median of 38 patients (from 4 to 85); the response rate was reported to be about 21% (0%-35%), disease control rate between 25% and 77% (median 63.5%), median TTP 3.6 (range 2.6-6.4) months and survival 7.8 (range 5-13.9) months. G3-4 toxicities were usually haematological, such as neutropenia in about 23% (2%-62%) and anaemia in 12% (1%-41%) of the cases; peripheral neuropathy was generally reported to be below 10% (65, 79-89).

Oxaliplatin-fluorouracil combinations have also been tested as a second- and third-line regimens for advanced gastric cancer with response rates from 4% to 26%, disease control rates of about 50%, TTP of 3 to 4 months and survival of about 7 months. Severe neutropenia was reported to be about 15% (90-92).

Some reports have been published with single agent S-1 (93-94), S-1 plus mitomycin (95) and fluorouracil plus mitomycin (96). The disease control rate was about 50% and the TTP 3 months.

In summary, two randomised phase III studies support the use of single agent chemotherapy (irinotecan or docetaxel) in progressing patients with good performance status; however, since the survival gain is only of 4 to 6 weeks, further research should also focus on QoL items in order to ensure that treated patients do not suffer from unnecessary toxicities. In the clinical setting, the decision about treating patients with progressive disease should rely on careful selection based on performance status, history of agents used, degree of response to the first-line therapy and amount of metastatic disease.

In conclusion, despite the progress of recent decades, metastatic gastric cancer remains an incurable disease; although small subsets of patients may benefit from survival prolongation, the overall survival benefit achieved is small and does not exceed a couple of months in first-

### Table IV. Results of the phase II studies.

<table>
<thead>
<tr>
<th>Drug/combo</th>
<th>Number of studies</th>
<th>Median number of patients</th>
<th>RR, % (range)</th>
<th>DCR, % (range)</th>
<th>TTP, months (range)</th>
<th>OS, months (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan (48-51, 58, 60-63)</td>
<td>9</td>
<td>29 (8-87)</td>
<td>25.5 (0-52)</td>
<td>55 (0-64.2)</td>
<td>3.5 (2.6-5.3)</td>
<td>8 (5-10.6)</td>
</tr>
<tr>
<td>FOLFIRI/CAPIRI (47, 52-57, 59, 76)</td>
<td>9</td>
<td>38 (29-131)</td>
<td>18 (10-29)</td>
<td>46 (31-71)</td>
<td>3.2 (2.2-4.1)</td>
<td>6.5 (5-10.9)</td>
</tr>
<tr>
<td>Paclitaxel (65, 79-89)</td>
<td>12</td>
<td>38.5 (4-85)</td>
<td>20.6 (0-26)</td>
<td>57.5 (25-77)</td>
<td>3.5 (2.1-6.4)</td>
<td>7.8 (5-13)</td>
</tr>
<tr>
<td>Docetaxel (64-78)</td>
<td>15</td>
<td>34 (20-154)</td>
<td>17 (9.4-38)</td>
<td>55 (22-80)</td>
<td>3.95 (2.5-5.2)</td>
<td>6.5 (5-8.3)</td>
</tr>
<tr>
<td>S-1 (93-95)</td>
<td>3</td>
<td>32 (21-43)</td>
<td>16.5 (0-26.5)</td>
<td>48 (47-56)</td>
<td>3 (2.7-3.3)</td>
<td>8.1 (7.2-9)</td>
</tr>
<tr>
<td>FOLFOX/FLOX (90-92)</td>
<td>3</td>
<td>52 (26-59)</td>
<td>23 (4-26)</td>
<td>4 (35-58)</td>
<td>3 (2.5-4.3)</td>
<td>7.3 (6.6-8)</td>
</tr>
</tbody>
</table>

FOLFIRI: Fluorouracil, leucovorin, irinotecan; CAPIRI: capecitabine, irinotecan; FOLFOX: fluorouracil, leucovorin, oxaliplatin; FLOX: fluorouracil, leucovorin, oxaliplatin; RR: response rate; DCR: disease control rate; TTP: time to progression; OS: overall survival after starting second-line therapy.
and even less in second-line therapy. Because of the toxicity suffered by the patients, it remains an open question, whether these results are clinically relevant. The hope for the future is that tailored interventions based on new cytotoxic drugs, targeted therapies, identification of predictive or prognostic markers and integration of molecular determinants may help to select patients likely to benefit from treatment.

References


