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Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer – A randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO)

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ABSTRACT

Background: The value of second-line therapy for metastatic gastric cancer is unclear. So far there are no randomised phase III data comparing second-line chemotherapy to best supportive care (BSC). In this prospective, multicenter, open label, randomised phase III study we compared irinotecan to BSC to evaluate the impact on survival of second-line chemotherapy.

Methods: Eligible patients (pts) had metastatic or locally advanced gastro-oesophageal junction or gastric adenocarcinoma, objective tumour progression during or within 6 months after first-line chemotherapy and ECOG performance status 0–2. Stratification for time of progression after first-line therapy, ECOG PS and pretreatment secured even distribution of important prognostic factors.

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Treatment: Arm A: Irinotecan 250 mg/m^2 q3w (first cycle) to be increased to 350 mg/m^2, depending on toxicity. Arm B: BSC.
Findings: Between 10/2002 and 12/2006 40 pts were randomised. The study was closed prematurely due to poor accrual. *Response for arm A* (19 pts evaluable): No objective responses, SD 53%, PD 47%. Improvement of tumour related symptoms: Arm A 50% of pts, arm B 7%. *Overall Survival*: (all events in 40 pts have occurred): The hazard ratio for death was reduced to 0.48 (95%CI 0.25–0.92) in the irinotecan-arm ($p = 0.012$). Median survival arm A: 4.0 months (95% CI 3.6–7.5), arm B: 2.4 months (95% CI 1.7–4.9).
Interpretation: Irinotecan as second-line chemotherapy significantly prolongs overall survival compared to BSC in the studied pts. Second-line chemotherapy can now be considered as a proven treatment option for metastatic or locally advanced gastric cancer.
Funding: The study was supported by a research grant from Aventis and Pfizer.

1. Background

Gastric cancer is a significant global problem with more than 0.93 million new cases diagnosed annually.[1] As resection is curative in only about 30% of patients[2] the aim of therapy is mostly palliative. Four randomised trials demonstrated a statistically significant prolongation of survival achieved with first-line chemotherapy as compared to best supportive care (BSC),[3–6] although all of these studies only included a small number of patients (37, 40, 41 and 61 patients).

The availability of more active chemotherapeutics and targeted therapies opened the option for second line chemotherapy. The attitude towards second line chemotherapy differs dramatically between countries and between physicians. In the most recent first-line phase III trials subsequent use of second-line chemotherapy differed between 14% (REAL-2-study),[7] 42% in the ToGA Trial[8] and 75% in the SPIRITS study.[9] Therefore, it is important to answer the question whether second-line chemotherapy benefits the patient and prolongs survival.

So far, there is no published phase III study comparing second line chemotherapy to best supportive care in gastric cancer.

Several small phase II studies demonstrated second-line activity of taxanes and irinotecan as a monotherapy or in combination with fluropyrimidines.[10–15] ECOG performance status, progression free interval following first-line chemotherapy and platinum based first-line chemotherapy were suggested as factors to identify patients with the highest chance of a benefit from second line chemotherapy.[16,17]

In the current AIO-trial pretreated patients were randomised between irinotecan as second-line chemotherapy and BSC. The primary end-point of the study was overall survival. The trial focused on patients with a progression during or within 6 months after first-line chemotherapy. It, therefore, selects patients who are resistant to first-line chemotherapy. A possible benefit in patients with chemoresistant tumours should translate even more for patients with chemoresponsive disease and longer treatment free intervals after first-line.[16] To assure an even distribution of the most relevant prognostic variables patients were stratified for ECOC PS, pretreatment and timing of progression under first-line treatment. Irinotecan monotherapy was selected due to its lack of cross-resistance to common first-line regimens containing cisplatin/fluoropyrimidine or docetaxel. Irinotecan has proven activity in gastric cancer first-line therapy administered in a 3 weekly monotherapy regimen[18] or in combination with 5-fluorouracil.[19,20] Administration of irinotecan in a 3-weekly regimen starting the first cycle in a reduced dose and escalate to full dose depending on individual tolerability was based on published experience for optimal efficacy and tolerability.[21,22]

This is the first randomised trial which investigates whether second-line chemotherapy can prolong survival in gastric cancer.

2. Material and methods

This randomised multicenter open label investigator initiated phase III study of the AIO was approved by the local ethics committee, registered with the health authorities, published in http://www.clinicaltrials.gov (number NCT00144378) and performed according to the guidelines of good clinical practise and the Declaration of Helsinki.

2.1. *Patient eligibility*

Eligible patients had to have written informed consent, histologically proven adenocarcinoma of the stomach or gastro-oesophageal junction, metastatic or locally advanced with surgical incurability, no pretreatment with more than one prior palliative regimen of chemotherapy (neoadjuvant or adjuvant chemotherapy or radiation was permitted), documented objective imaging proven progression during or within 6 months after the end of a first-line chemotherapy. Further criteria were age $\leqslant$75 years, adequate bone marrow function, (leucocytes >3.0 Gpt/l, thrombocytes >100 Gpt/l), liver function (bilirubin <1.5 times the upper limit of normal (ULN), AST and ALT $\leqslant 3 \times$ ULN), kidney function (serum creatinine <1.25 ULN and creatinine clearance >60 ml/min (calculated according Cockroft-Gault), ECOG performance status $\leqslant$2, measurable or evaluable disease and adequate contraception. Exclusion criteria were prior second malignancy, uncontrolled infection, central nervous system metastases, other severe medical illness, major operation within the last 2 weeks, pretreatment with irinotecan, chronic diarrhoea,

and parallel treatment with any experimental or any other kind of antineoplastic therapy.

2.2. Statistics

The primary end-point of the trial was overall survival in the intention to treat population. The median survival of BSC after tumour progression on first-line therapy was extrapolated from several first-line chemotherapy trials and estimated at 2.5 months. A prolongation of overall survival by irinotecan from 2.5 to 4 months was considered clinically significant. 60 patients per arm, observed for at least one year, were required in order to significantly ($\alpha = 0.05$) show an improvement in overall survival of this magnitude with a power of 80%,[23] following an exponential distribution of survival data. Therefore, death is the event for the primary end-point and living patients would be censored at the time of their last follow up. All time to event curves were calculated according to the life-table method described by Kaplan and Meier,[24] and compared by a one-sided logrank-test,[25] corresponding to the one sided trial hypothesis.

Secondary end-points were response rate, time to tumour progression and toxicity.

Patients were stratified for (1) progression during or less than 3 months after first-line chemotherapy versus more than 3 months after the end of first-line chemotherapy, (2) ECOG performance status 0 or 1 versus 2; (3) pre-treatment with versus without cisplatin. The allocation ratio arm A:B was 1:1. Randomisation was done centrally. Randomisation blocks of four for each stratification arm were determined by using a coin.

Data were collected at the Charité, Berlin, Germany.

2.3. Treatment with irinotecan

Patients randomised to this arm were treated with BSC plus irinotecan (supplied by Aventis Pharma GmbH, Frankfurt, Germany, after 01.01.2005 by Pfizer, Berlin, Germany.)

Chemotherapy consisted of irinotecan 250 mg/m^2 in the first cycle which had to be increased to 350 mg/m^2 in subsequent cycles. Irinotecan was administered in 250 ml of normal saline over 30 min together with routine antiemetic cover (5-HT3 antagonists and dexamethasone) and subcutaneous atropine (0.25 mg) as prophylaxis against irinotecan induced cholinergic syndrome. Therapy was repeated every 3 weeks. The maximal dose was limited to a body surface area of 2.0 m^2.

Chemotherapy was administered until objective or clinical tumour progression, side effects, patient's wish or a maximum of 10 cycles.

Toxicity was graded according to National Cancer Institute Common Toxicity Criteria (CTC) Version 2.0. The dose of irinotecan was adjusted to the toxicity experienced. The dose in the second cycle was routinely increased to 350 mg/m^2 unless in his first cycle the patient experienced hematotoxicity grade 3 or 4 CTC or any other toxicity grade 2 CTC or higher despite of adequate prophylaxis. Chemotherapy was paused until all side effects regressed to $\leqslant$CTC grade 1. Irinotecan was reduced by 50 mg/m^2 in case of toxicity related dose delay of more than 2 weeks, CTC grade 4 leuko- neutro- or thrombocytopenia, or any other grade 3 or 4 toxicity.

2.4. Treatment with best supportive care

Patients randomised in the BSC-arm had to be kept under the care of the same physician who looked after the patients in the irinotecan-arm. Patients had to be examined and evaluated at the same frequency and by the same methods as in the irinotecan arm, described below. No crossover into the irinotecan arm was allowed.

2.5. Evaluation during therapy

Investigations scheduled for both treatment arms: Weekly full blood count and evaluation of side effects, three-weekly history and examination, evaluation of tumour related symptoms, blood chemistry. The advised imaging methods were chest X-ray and abdominal ultrasonography; abdominal and chest ct-scan was optional. Staging by imaging was mandatory every 6 weeks only in the irinotecan arm and optional in the BSC arm. It was felt to be emotionally harmful or distressing for BSC-patients to have to undergo mandatory regular imaging. Imaging, therefore, was optional in the BSC-arm. Due to this reason objective response and PFS could not be calculated for the BSC-arm.

After termination of irinotecan therapy patients should be seen every 3 weeks.

Tumour response was assessed according to WHO criteria.[26] Patients who received at least one cycle of chemotherapy were considered assessable for response and toxicity.

Tumour related symptoms were assessed by the treating physician every 3 weeks on direct questioning for fatigue, loss of appetite, nausea, weight loss, pain, epigastric fullness and difficulty swallowing or other and compared with the symptoms at baseline. Symptomatic improvement was defined as subjective improvement as stated by the patient of at least one tumour related symptom without worsening of any other symptom or appearance of any new tumour related symptom.

The overall survival was calculated from the time of randomisation to the time of death. The progression free survival (PFS) was calculated from the time of randomisation to the time of progression or death. PFS was only calculated for the irinotecan-arm.

2.6. Funding

The study was supported by a research grant from Aventis, Frankfurt and Pfizer, Berlin, Germany.

3. Results

From October 2002 until December 2006 a total of 40 patients were randomised; 21 into arm A (irinotecan) and 19 patients into arm B (BSC). The study was closed prematurely due to poor accrual (Fig. 1).

3.1. Patient characteristics

Stratification factors (performance status, pretreatment and time of progression on first-line chemotherapy) are equally distributed (see Table 1). Other criteria which might possibly

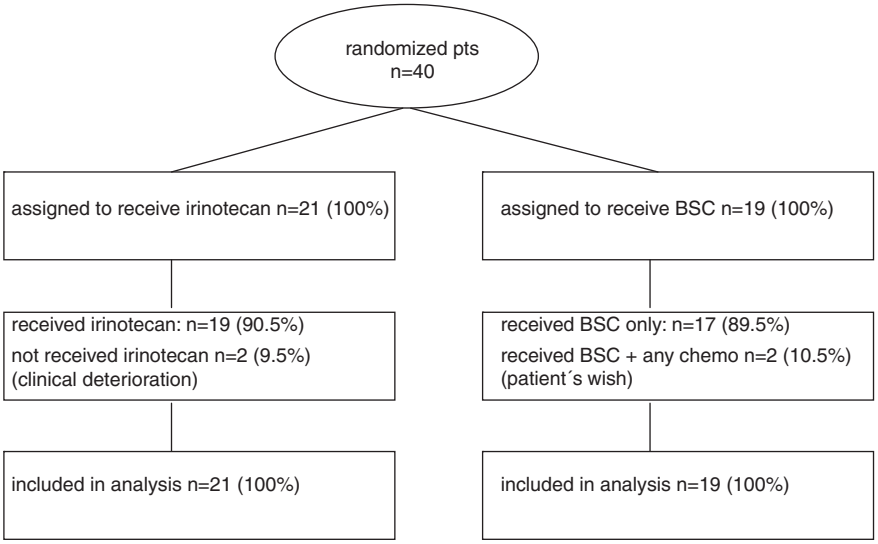

Fig. 1 – Profile of the trial.

be related to a different response to treatment like localisation of the primary tumour, histologic subtype, number of metastatic sites and response to first-line chemotherapy were well balanced between the two arms. There was, however, an imbalance in males: females in both arms. All patients were pretreated with cisplatin, 39 patients with a cisplatin/5-FU based combination, 1 patient with cisplatin/docetaxel. The majority of patients in both arms suffered from tumour progression whilst receiving first-line chemotherapy, 15 patients (71%) in the irinotecan-arm and 13 patients (68%) in the BSC-arm. Follow up was complete when the last patient died on the 10th of October 2007.

3.2. *Treatment*

Sixty eight cycles or irinotecan were administered with a median number of 2 cycles per patient (range 0 to 9). In 37% of patients the irinotecan dose could be escalated to 350 mg/m^2 according to the protocol. Two pts randomised to the irinotecan-arm did not receive any chemotherapy because of early clinical deterioration. In those patients death due to tumour progression occurred at day 27 and day 36 after randomisation. These 2 pts are included in the intention to treat (ITT) population for overall-survival. Three patients in the irinotecan-arm received a third line therapy after irinotecan (docetaxel, epirubicin/cisplatin/5-FU and mitomycin C, respectively). Two patients randomised into the BSC-arm received chemotherapy due to patient's wish or doctor's decision (irinotecan and paclitaxel, respectively). These patients are included in the ITT population of the BSC arm.

3.3. *Toxicity*

A total of 19 patients who received any dose of irinotecan were evaluable for toxicity (see Table 2). The main toxicity was diarrhoea, which occurred at grade 3/4 CTC in 5 of 19 patients (26%). Due to standardised initiation of loperamide diarrhoea was usually short lasting and there were no treatment related deaths.

3.4. *Quality of life*

Assessment of quality of life using the EORTC QLQ C30 questionnaire was planned but return of the forms was too poor to undertake meaningful analyses.

3.5. *Response*

3.5.1. *Objective response to irinotecan*

There was no objective tumour remission documented in the irinotecan arm according to WHO criteria in 19 pts evaluable. However, disease stabilisation for at least 6 weeks was seen in 53% of patients. Progressive disease as best response, either imaging proven or due to clinical deterioration was documented in 47% of patients.

3.5.2. *Response of tumour related symptoms*

In those patients who had tumour related symptoms at study entry ($n = 18$ in irinotecan arm; $n = 15$ in BSC arm) improvement of their symptoms was documented in 50% ($n = 9$) of patients in the irinotecan and 7% ($n = 1$) in the BSC-arm, respectively.

3.6. *Progression free survival*

PFS was calculated for the irinotecan arm, only. The median PFS for the intention to treat population of arm A (irinotecan) is 2.5 months (95% CI 1.6–3.9 months). The median PFS calculated for those patients who received irinotecan (per protocol-population) is 2.6 months (95% CI 1.7–4.3 months).

3.7. *Overall survival*

The overall survival is shown for the intention to treat population in Fig. 2. All patients in both arms have died, thus, all events have occurred. The hazard ratio for death is 0.48 with a 95% confidence interval of 0.25–0.92 favouring the active treatment with irinotecan ($p = 0.012$, one-sided logrank test, corresponding to a two-sided $p = 0.023$). The median survival

Table 1 – Patient characteristics.

	Arm irinotecan	Arm BSC
n	21	19
Median age [yrs] (range)	58 (43–73)	55 (35–72)
Sex		
Male	18 (86%)	11 (58%)
Female	3 (14%)	8 (42%)
Histology subtype		
Intestinal	5 (24%)	3 (16%)
Diffuse	14 (67%)	13 (68%)
Unknown	2 (10%)	3 (16%)
Localisation		
GE-junction	9 (43%)	8 (42%)
Gastric body	12 (57%)	11 (58%)
Stage		
Locally advanced	0 (0%)	0 (0%)
Metastatic	21 (100%)	19 (100%)
Metastatic sites		
Gastric (primary lesion)	11 (52%)	2 (11%)
Lung	4 (19%)	0 (0%)
Lymphnode	8 (38%)	6 (32%)
Peritoneal	9 (43%)	9 (47%)
Liver	8 (38%)	10 (53%)
Other	8 (38%)	6 (32%)
Number of sites involved		
1	6 (29%)	11 (58%)
2	8 (38%)	3 (16%)
3	4 (19%)	3 (16%)
$\geqslant 4$	3 (14%)	2 (11%)
Grading		
G1	0 (0%)	1 (5%)
G2	4 (19%)	2 (11%)
G3	12 (57%)	14 (74%)
G4	2 (10%)	0 (0%)
Unknown	3 (14%)	2 (11%)
ECOG PS		
0 and 1	17 (81%)	14 (74%)
2	4 (19%)	5 (26%)
Baseline CEA (optional)		
>50 ng/ml	6 (29%)	6 (32%)
$\leqslant$50 ng/ml	8 (38%)	10 (53%)
Unknown	7 (33%)	3 (16%)
Baseline haemoglobin		
>11.5 g/dl	8 (38%)	8 (42%)
$\leqslant$11.5 g/dl	13 (62%)	11 (58%)
Prior therapy		
Gastric operation (curative intent)	6 (29%)	6 (32%)
Adjuvant chemotherapy	2 (10%)	0 (0%)
Adjuvant chemoradiotherapy	1 (5%)	1 (5%)
Pretreatment		
With cisplatin	21 (100%)	19 (100%)
Without cisplatin	0 (0%)	0 (0%)
Kind of first-line palliative chemotherapy		
5-FU/FA/cisplatin***	16 (76%)	10 (53%)
ECF	5 (24%)	7 (37%)
Capecitabine/docetaxel		1* (5%)
Cisplatin/docetaxel		1 (5%)

(*continued on next page*)

Table 1 – *continued*

	Arm irinotecan	Arm BSC
Best response to first-line chemotherapy		
CR	1 (5%)	1 (5%)
PR	6 (29%)	3 (16%)
SD	4 (19%)	6 (32%)
PD	10 (48%)	9 (47%)
Progressive disease after first-line chemotherapy		
During or ⩽3 months after end of first-line	18 (86%)	17 (89%)
3–6 months after end of first-line	3 (14%)	2 (11%)
PFS under first-line chemotherapy**	5.46 months (95%CI: 3.42–9.44)	6.87 months (95%CI: 4.37–11.01)

* Pt had prior preoperative ECF.
** PFS under first-line chemotherapy defined as time between start of first-line and date of progression to first-line chemotherapy.
*** FA = folinic acid.

Table 2 – Toxicity (grade 3/4) in Arm A: Irinotecan.

	CTC grade 3	CTC grade 4
Evaluable pts n = 19		
Nausea	1 (5%)	–
Vomiting	1 (5%)	–
Diarrhoea	5 (26%)	–
Neutropenic fever	2 (11%)	1 (5%)
Leucocytopenia	3 (16%)	1 (5%)
Thrombocytopenia	–	–
Haemoglobin	2 (11%)	–

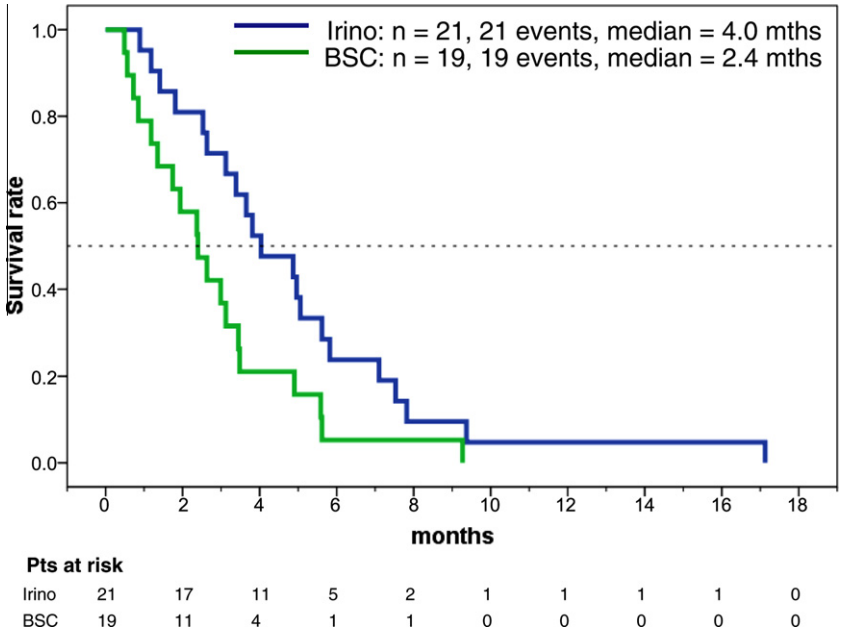

Fig. 2 – Overall survival (intention to treat population) Median survival Irinotecan: 4.0 months, BSC: 2.4 months; one sided logrank test: $p = 0.012$; HR: 0.48 (95% CI: 0.25–0.92).

is 4.0 months (95% CI 3.6–7.5) in the irinotecan arm and 2.4 months (95% CI 1.7–4.9) in the BSC-arm.

In an exploratory analysis the patients treated per protocol are investigated. If the 2 patients, who never received any

Table 3 – Univariate analyses for potential factors influencing overall survival.

Factor	*n*	HR	95% CI	*p* (two-sided)
Irinotecan versus BSC	40	0.48	0.25–0.92	0.023
Progression after end of first-line >3 months versus <3 months	40	0.34	0.12–0.99	0.039
Localisation GEJ versus stomach	40	0.79	0.42–1.52	0.49
Male versus female	40	0.49	0.24–1.03	0.056
Histology intestinal versus diffuse	35	0.48	0.21–1.07	0.069
ECOG PS 0/1 versus 2	40	0.53	0.24–1.15	0.10
Response during first-line chemo CR/PR/SD versus PD	40	0.55	0.28–1.09	0.086

irinotecan, are excluded from the irinotecan arm-A, the survival curve separates further. The hazard ratio decreases to 0.42 (95% CI: 0.22–0.82), one sided logrank test: $p = 0.0046$, and the median survival in the irinotecan arm is 4.9 months (95% CI 3.2–6.5) and in the BSC-arm 2.4 months (95% CI 1.7–4.9).

To identify potential factors influencing overall survival univariate analyses were performed (Table 3). In this analysis second-line treatment with irinotecan was the most significant prognostic factor for survival. Time of progression after first-line treatment of less versus more than three months was another significant prognosticator. This variable was equally distributed between the two treatment arms.

4. Discussion

The benefit of second line chemotherapy in gastric cancer is unclear. Therefore, this randomised phase III study was initiated to investigate the impact on survival of second-line irinotecan compared to best supportive care. It is the first randomised phase III trial comparing chemotherapy to BSC in gastric cancer. Accrual to this study was very difficult. A total of 30 centers in Germany acknowledged the importance of this study and registered to participate but only 10 centers included patients. The most frequent reason for low recruitment reported from different centers was patient refusal of randomisation. In several AIO meetings possible measures to improve accrual were discussed and undertaken but it was decided not to change the clear design and the BSC arm of the study. From this experience it seems unlikely that any other trial comparing second line chemotherapy to BSC can easily be conducted in Western patients. This probably also applies to Japanese and Korean patients where second-line chemotherapy is already used frequently.[9,27] BSC after progression on first-line-therapy should be even less acceptable for Western patients after publication of this trial. Nevertheless, although difficult to perform, a second confirmatory phase III trial could support the level of evidence.

All patients had metastatic disease and were pretreated with a potent, well established first-line cisplatin-containing chemotherapy. Tumour progression occurred in the majority of patients (approximately 70% in both arms) whilst they were receiving first-line chemotherapy. More than 85% of patients progressed within 3 months, all patients within 6 months after the end of first-line chemotherapy. Therefore, the patient population included was platinum and fluorouracil refractory with an unfavourable chance of responding to second line treatment.[16]

Stratification and randomisation assured a well balanced distribution of known or suspected prognostic variables.

The study had to be terminated prematurely due to poor accrual after 40 patients were included. Due to adequate follow up, the data for the primary end-point (survival) is definite and robust, as all events have occurred. Second line therapy with irinotecan significantly and meaningfully reduces the risk of death in gastric cancer with a hazard ratio of 0.48 (intent to treat and 0.42 as treated). As this trial could show that chemotherapy could significantly prolong survival even in the group of patients with an unfavourable chance to benefit from second line treatment, this effect may probably even be more pronounced or at least similar in those patients with more favourable prognostic factors.

In the study we reached almost exactly the estimated median survival in both arms and statistical significance ($p = 0.012$, one-sided) was reached already with 40 pts in contrast to the 120 pts planned. This somewhat counterintuitive result is due to the following three reasons: First, the 80% power included in the sample size calculation by principle leads to a much smaller p value than the planned α error level, if the actually recorded difference exactly corresponds to the pre-specified one. Second, the sample size calculation accounted for some censored cases, whilst in the final analysis death had occurred in all patients. Third, and most importantly, the statistical assumptions were based on median survival points and expected exponential survival curves. The actually observed overall treatment effect is better than what is reflected by simply comparing the two median survival points. Whilst the planned difference of 2.5 versus 4 months, based on exponential survival curves, would correspond to a hazard ratio of 0.625, the actually observed survival curves show a treatment effect which results in a HR of 0.48.

In an attempt to predict which patients may benefit from second-line chemotherapy Catalano et al.[28] suggested from a retrospective analysis to use performance status, haemoglobin, CEA level, number of metastatic sites, and time to progression under first-line therapy to calculate an index. Analysing our data for these parameters there is no imbalance between the treatment arms (see Table 1). Calculating the proposed index does not favour the irinotecan-group (risk index [Irino/BSC]: low 5%/11%, intermediate 43%/63%, high 38%/16%, not evaluable 14%/11% of patients).This underlines the robustness of our result.

In our trial no objective response in the irinotecan monotherapy could be documented. Nevertheless, disease stabili-

sation was achieved and tumour related symptoms were improved in 44% of patients. It seems unlikely, that the benefits of second-line chemotherapy will be restricted to the use of irinotecan monotherapy only. In several phase II trials irinotecan and a taxane as monotherapy or in combination with cisplatin or 5-FU have all shown activity in terms of tumour response in 12.5–29% and a median survival between 5.0–7.6 months[10–15] as reviewed recently.[29] The longer survival time in these phase II trials are probably due to selection of patients with more favourable prognostic factors.

Evidence from this phase III trial and cumulative data from phase II trials influenced the German national guideline committee to advice that second line treatment should be offered to patients with good performance status. The impact on survival of second line chemotherapy may need to be integrated into the design of future first-line chemotherapy studies. Also, BSC as a control arm may no longer be justified in any further randomised second-line trial.

In gastric cancer this is the first randomised phase III study comparing second-line chemotherapy against BSC. It demonstrates that irinotecan leads to a significant and meaningful reduction in the risk of death. In our interpretation the survival advantage shown for irinotecan suggests in principle the benefit of active non-crossresistant chemotherapy as second line in gastric cancer.

Second-line chemotherapy should routinely be offered to patients with good performance status suffering from gastric cancer.

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Disclosure of the authors

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Contribution of authors

	Conception and design	Financial support	Administrative support	Provision of study material or patients	Collection and assembly of data	Data analysis and interpretation	Manuscript writing	Final approval of manuscript
Thuss-Patience	x		x	x	x	x	x	x
Kretzschmar	x			x	x		x	x
Bichev					x	x	x	x
Deist				x	x		x	x
Hinke	x					x	x	x
Breithaupt						x	x	x
Dogan							x	x
Gebauer			x		x		x	x
Schumacher				x	x		x	x
Reichardt	x			x	x	x	x	x

Conflict of interest statement

None declared.

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