A randomized phase II trial of capecitabine and two different schedules of irinotecan in first-line treatment of metastatic colorectal cancer: efficacy, quality-of-life and toxicity

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Abstract

To determine the efficacy, impact on quality-of-life (QoL) and tolerability of two different irinotecan administration schedules in combination with capecitabine as first-line treatment of metastatic colorectal cancer.


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A randomized phase II trial of capecitabine and two different schedules of irinotecan in first-line treatment of metastatic colorectal cancer: efficacy, quality-of-life and toxicity

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Background: To determine the efficacy, impact on quality-of-life (QoL) and tolerability of two different irinotecan administration schedules in combination with capecitabine as first-line treatment of metastatic colorectal cancer.

Patients and methods: We carried out a randomized phase II trial to select one of the following treatment regimens for further investigation: weekly irinotecan at a dose of 70 mg/m² days 1, 8, 15, 22, 29 (arm A) or 3-weekly irinotecan at a dose of 300/240 mg/m² day 1 and days 22 (arm B) in combination with capecitabine 1000 mg/m² twice daily days 1–14 and days 22–35 every 6 weeks.

Results: Seventy-five patients with good performance status entered the trial. The two arms were well balanced for relevant patient and disease characteristics. The most frequent toxic effects were grade 3/4 diarrhea (arm A: 34%, B: 19%), grade 3/4 neutropenia (A: 5%, B: 19%) and grade 2/3 alopecia (A: 26%, B: 65%). Other grade 3/4 toxic effects were rare (<5%). Response rates were 34% [95% confidence interval (CI) 20% to 51%] in arm A and 35% (95% CI: 20% to 53%) in arm B. Median time to progression was 6.9 (4.6–10.1) and 9.2 (7.9–11.5) months and median overall survival was 17.4 (12.6–23.0+) and 24.7 (16.3–26.4+) months. Patients with an objective tumor response reported better physical well-being (P < 0.01), mood (P < 0.05), functional performance (P < 0.05) and less effort to cope (P < 0.05) compared with the non-responders and stable disease patients.

Conclusions: The primary end point of this study was the objective response rate and based on the statistical design of the trial, the 3-weekly irinotecan schedule was selected over weekly irinotecan administration. The 3-weekly irinotecan schedule also seemed advantageous in terms of grade 3/4 diarrhea, time to progression, overall survival and patient convenience, but the study was not designed to detect differences in these parameters. In addition, tumor response was shown to have a beneficial effect on QoL indicators.

Key words: irinotecan, metastatic colorectal cancer, randomized phase II, schedule

Introduction

Irinotecan was the first drug to add survival to standard fluorouracil and leucovorin in first-line treatment of colorectal cancer [1, 2]. Different fluorouracil schedules were used in the two trials. The comparison of the toxicity data of both studies seemed to suggest a better tolerability in terms of gastrointestinal and hematological toxicity with the infusional schedule. However, an important drawback of continuous intravenous infusion is the need for implantable access devices and portable infusion pumps. The availability of oral fluoropyrimidines has very much improved the feasibility of prolonged fluoropyrimidine administration. Most patients clearly prefer oral fluoropyrimidine therapy over intravenous bolus fluorouracil [3]. Oral capecitabine is active in colorectal cancer and two large randomized studies have shown higher tumor response rates and at least equivalent time to disease progression and overall survival compared with intravenous bolus fluorouracil/leucovorin [4–6]. In addition, capecitabine was better tolerated with a significantly lower incidence of stomatitis, diarrhea, nausea and alopecia.

Several schedules of irinotecan administration are in clinical use. Rothenberg et al. have established the ‘weekly’ schedule, administering irinotecan at a dose of 125 mg/m² weekly for...
was capecitabine 1000 mg/m² twice daily day 1–14 and day repeated day 50 [10]. The recommended dose from this study weekly irinotecan administered day 1, 8, 15, 22, 29 and 36, practicability of the treatment. Tewes et al. have carried out professional fluorouracil is an interesting alternative in view of the incidence of severe diarrhea with the weekly schedule. Combining irinotecan with oral capecitabine instead of infusional fluorouracil is an interesting alternative in view of the practicability of the treatment. Tewes et al. have carried out an extended phase I study of capecitabine in combination with weekly irinotecan administered day 1, 8, 15, 22, 29 and 36, repeated day 50 [10]. The recommended dose from this study was capecitabine 1000 mg/m² twice daily day 1–14 and day 22–36 in combination with irinotecan 70 mg/m² weekly. Still, 19% of the patients experienced grade 4 diarrhea at this dose level. Bajetta et al. have presented their pilot experience of capecitabine in combination with two schedules of irinotecan [11]. Capecitabine 1250 mg/m² twice daily day 2–15 was combined with irinotecan 150/120 mg/m² day 1 and 8 or irinotecan 300/240 mg/m² day 1 every 21 days. Grade 3/4 diarrhea occurred in 17% and 23% of the patients, respectively.

We carried out an exploratory analysis of the weekly and the 3-weekly irinotecan schedule in combination with capecitabine in a formal randomized phase II setting. The weekly irinotecan regimen described by Tewes et al. [10] was slightly modified to allow an identical capecitabine regimen in both treatment arms. Thus, the irinotecan administration schedule was the only variable between the two treatment arms. The goal of this trial was to select the combination regimen of capecitabine and irinotecan, which should be used in further studies of this group.

Materials and methods
Eligibility and patient evaluation
Eligible patients had histologically or cytologically confirmed advanced or metastatic adenocarcinoma of the colon or the rectum, which was no longer amenable to surgical treatment. Other eligibility criteria were measurability of tumor lesions, not pretreated with chemotherapy for metastatic cancer, age 18–75 years, WHO performance status of 0 or 1, adequate organ function and a life expectancy of at least 3 months. Stratification factors for randomization were performance status (0 versus 1), the presence of disease symptoms, weight loss ≥5% during the last 6 months or a tumor-free interval of >6 months (all yes versus no) [12]. The protocol was approved by local ethics review boards of all participating institutions, and all patients gave written informed consent before enrollment.

Pretreatment evaluation included a complete medical history and physical examination, a complete blood count, chemistry profile and CEA measurement, a chest X-ray and a radiological tumor parameter assessment. For patients in arm A (‘weekly’ irinotecan schedule), a complete blood count was obtained weekly throughout the treatment phase. For patients in arm B (3-weekly irinotecan schedule), a complete blood count was obtained weekly in the first two 3-week treatment cycles and thereafter before the start of each 3-week treatment cycle. A serum chemistry profile, CEA measurement, physical examination and toxicity assessment was done before the start of each 3-week cycle. Patients had radiological tumor parameter assessment every 9 weeks. Tumor response classification was based on standard World Health Organization criteria.

Response assessment
Computed tomography scans or magnetic resonance imaging of those patients with a CR, PR or minor response (at least a 25% decrease in tumor size) were reviewed by an independent radiology panel, which consisted of two experienced medical oncologists.

In arm A, scans of 21 patients were ordered according to the above criteria. Scans of three responding patients were not reviewed because of missing scan images, and a further two patients could not be assessed as their baseline target lesions were too small for evaluation (below 20 mm). In arm B, scans of 24 patients were ordered. Scans of one responding patient were not reviewed because of missing scan images.

Assessment of toxicity
Toxic effects were assessed according to the NCIC CTG expanded common toxicity grading. Hand–foot syndrome (palmar-plantar erythrodysesthesia) was classified as grade 1 (numbness, dysesthesia, painless swelling, erythema not disrupting normal activities), grade 2 (painful swelling, disrupting daily activities), or grade 3 (moist desquamation, ulceration, blisters, severe pain, inability to work or carry out daily living activities).

Treatment
This trial was conducted at eight centers. Patients were randomized centrally before starting treatment. In arm A, patients received irinotecan at a dose of 70 mg/m²/day given as a 1-h infusion on day 1, 8, 15, 22 and 29 repeated every 6 weeks. In arm B, patients received irinotecan at a dose of 300 mg/m²/day given as a 1-h infusion on day 1 repeated every 3 weeks. After December 20, 2001 (date of the amendment to the study protocol), the irinotecan dose in arm B was reduced to 240 mg/m²/day because of the report by Bajetta et al. [11]. Eighteen patients in arm B were randomized before December 20, 2001, eight of them finished treatment before irinotecan reduction. Treatment was continued until disease progression, unacceptable adverse effects, or withdrawal of consent by the patient.

Dose modifications
Capecitabine and irinotecan administration were interrupted in case of grade ≥2 non-hematological toxicity and were not resumed until the adverse effect improved to grade ≤1. The doses were reduced by 25% in the subsequent treatment cycles in case of grade 3 non-hematological toxicity or by 50% in case of grade 4 hematological toxicity.

Quality-of-life assessment
The objective of the quality-of-life (QoL) study was to evaluate patients’ QoL by tumor response and to describe QoL within and between the treatment groups. All randomized patients were asked to complete the QoL form at baseline, at day 1 of any subsequent 6-week cycle and at the first visit following treatment failure. To eliminate any differential anticipatory effects on baseline scores, the baseline QoL form had to be completed before randomization. The subsequent QoL forms were to be completed before diagnostic procedures and treatment administration.

Key components of QoL were assessed with linear analog self-assessment (LASA) indicators. This comprised global indicators for physical
well-being, mood, coping effort (PACIS) and functional performance [13–15]. We selected physical well-being as primary end point for evaluating the impact of tumor response. In addition, we asked the patient, “Overall, how much are you bothered by any treatment related difficulties?” [14] as primary end point for evaluating side-effects. This global indicator was designed to be responsive to the whole spectrum of toxicity and thus to be a comparative measure of overall burden. Finally, LASA indicators specific to symptoms of nausea and vomiting, diarrhea and hair loss were included. All LASA indicators range from 0 to 100, with higher values indicating better QoL (e.g. less side-effects).

Statistical analysis

The randomized two-arm phase II design was used to select the more promising schedule of the two in terms of response [16]. In this design, the schedule with the higher response rate is to be selected, irrespective of the difference. To have at least 90% probability of selecting the truly better schedule when the absolute difference in true response proportions (complete response + partial response) is 15% or greater, 37 patients are needed for each arm. Additionally, a stopping rule was included: A trial arm would have been stopped if there was no response in the first 14 patients. Since a selection design was chosen, no formal statistical comparisons between the arms were planned. Time to treatment failure was measured from randomization to treatment stop from any cause, time to progression from randomization to progression, and overall survival from randomization to death. Time to event data were analyzed by the Kaplan–Meier method. Confidence intervals for response rates and selected toxicity rates were calculated by the Clopper–Pearson method [17].

QoL indicators were descriptively evaluated as changes from baseline. The effects of tumor response, treatment, time and treatment–time interactions were longitudinally analyzed by a non-parametric mixed effects model using all available data within the observation period. As a general measure for a clinically meaningful effect between groups, we defined a difference in median changes from baseline of > 8% of full scale range for at least two succeeding time points, based on the difference in nausea/vomiting between observation only and 5-FU 600 mg/m\(^2\) 2 months after the beginning of adjuvant therapy in patients with early colon cancer made for multiple testing. The evaluation of the primary end point response rate. No adjustment was needed for each arm. Additionally, a stopping rule was included: A trial arm would have been stopped if there was no response in the first 14 patients. Since a selection design was chosen, no formal statistical comparisons between the arms were planned. Time to treatment failure was measured from randomization to treatment stop from any cause, time to progression from randomization to progression, and overall survival from randomization to death. Time to event data were analyzed by the Kaplan–Meier method. Confidence intervals for response rates and selected toxicity rates were calculated by the Clopper–Pearson method [17].

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Results

Patients and treatment

From February 2001 until May 2002, a total of 75 patients were randomized to one of the two treatment arms. All patients were eligible. Table 1 lists the demographic data and baseline disease and pretreatment characteristics for all patients. Patients were well balanced for these characteristics with the exception of the number of metastatic sites per patient. Twenty-nine per cent of patients in arm A had more than one metastatic lesion compared with 46% in arm B. Fifty-

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weekly irinotecan (n = 38)</th>
<th>3-weekly irinotecan (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range)</td>
<td>58 (36–74)</td>
<td>61 (47–74)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td>65</td>
<td>11</td>
<td>29</td>
</tr>
</tbody>
</table>

Table 1. Patient and disease characteristics

<table>
<thead>
<tr>
<th>Site of primary</th>
<th>Weekly irinotecan (n = 38)</th>
<th>3-weekly irinotecan (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. ascendens</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td>C. transversum</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>C. descendens/sigmoidum</td>
<td>13</td>
<td>34</td>
</tr>
<tr>
<td>Rectum</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td>No information</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Metastatic at diagnosis</td>
<td>28</td>
<td>74</td>
</tr>
<tr>
<td>Adjuvant radiotherapy</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>6</td>
<td>16</td>
</tr>
</tbody>
</table>

*Each patient may have more than one localization.

eight per cent of the patients had liver metastases only in arm A compared with 49% in arm B.

The median number of 3-week cycles received was six (range 1–15) for arm A and eight (range 1–23) for arm B. The median dose intensity for capecitabine and irinotecan in the first eight treatment cycles is summarized in Table 2. The randomized two-arm phase II design was used to select the more promising schedule of the two in terms of response [16]. In this design, the schedule with the higher response rate is to be selected, irrespective of the difference. To have at least 90% probability of selecting the truly better schedule when the absolute difference in true response proportions (complete response + partial response) is 15% or greater, 37 patients are needed for each arm. Additionally, a stopping rule was included: A trial arm would have been stopped if there was no response in the first 14 patients. Since a selection design was chosen, no formal statistical comparisons between the arms were planned. Time to treatment failure was measured from randomization to treatment stop from any cause, time to progression from randomization to progression, and overall survival from randomization to death. Time to event data were analyzed by the Kaplan–Meier method. Confidence intervals for response rates and selected toxicity rates were calculated by the Clopper–Pearson method [17].

QoL indicators were descriptively evaluated as changes from baseline. The effects of tumor response, treatment, time and treatment–time interactions were longitudinally analyzed by a non-parametric mixed effects model using all available data within the observation period. As a general measure for a clinically meaningful effect between groups, we defined a difference in median changes from baseline of ≥8% of full scale range for at least two succeeding time points, based on the difference in nausea/vomiting between observation only and 5-FU 600 mg/m\(^2\) 2 months after the beginning of adjuvant therapy in patients with early colon cancer within a randomized trial [13]. Based on the decline in patients with 5-FU 600 mg/m\(^2\) over this period, we estimated a median change of ≥5% for at least two succeeding time points as a minimal clinically relevant change. All tests were two-sided. All treated patients were included in the evaluation of the primary end point response rate. No adjustment was made for multiple testing. The \(P\) values have descriptive value only in this phase II trial. Statistical analyses were carried out using SAS 8.1 (SAS Institute Inc., Cary, NC, USA), S-PLUS 6.1 (Insightful Corporation, Seattle, WA, USA) and StatXact 5.0 (Cytel Software Corporation, MA, USA).

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be given with only slight dose modifications. The median cycle duration remained stable at 21 days from the first to the sixth treatment cycle for arm A and arm B. Seven per cent of the cycles in arm A and 13% of the cycles in arm B were delayed (duration >25 days). Besides other reasons, the most frequent reasons for treatment delays were hematological toxicity (arm B) and diarrhea (both arms, mainly arm A). Sixty-three per cent of patients in arm A and 57% of patients in arm B received oxaliplatin containing second-line treatment.

### Toxicity

The incidence of grade 3/4 toxicity is summarized in Table 3. The main toxicity was grade 3/4 diarrhea, which occurred in 34% of patients in arm A and 19% of patients in arm B. Severe (grade 3/4) neutropenia occurred in 5% and 19% of patients in arm A and B, respectively, during the first two treatment cycles. The information on the hematological toxicity in later cycles is limited since weekly blood counts were not mandatory. Severe hand–foot syndrome occurred in 5% and 8% of the patients. Severe alopecia, neuropathy, anemia and thrombopenia were not observed with this treatment combination. Generally, patients >65 years experienced more severe toxicity compared with younger patients. One sudden death occurred in arm A during the third treatment cycle due to a rupture of an aortic aneurysm. This event was considered treatment unrelated by the investigator. Other severe toxic effects in arm A were a myocardial infarction (cycle 2, possible related to study treatment), an arterial thromboembolism (cycle 2, probably related to study treatment), a deep vein thrombosis (cycle 1, unlikely related to study treatment), and unexplained renal failure (cycle 2). In arm B, a deep vein thrombosis (cycle 2, unlikely related to study treatment), three events of bowel obstruction (cycle 1 and 2), and one patient with acute cholecystitis were observed. Unacceptable toxicity was given as the reason for treatment failure in 26% of patients in arm A and 19% of patients in arm B. Among the seven patients in arm B with unacceptable toxicity as the reason for treatment failure, two stopped treatment before December 20, 2001 (date of the amendment).

### Efficacy end points

Response rates as indicated by the investigators were 34% [95% confidence interval (CI) 20% to 51%] in arm A and 35% (95% CI: 20–53%) in arm B. The confirmed response rate by independent radiology review was 18% (95% CI 8% 

### Table 2: Cycle number and median dose intensity

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Weekly irinotecan (n = 38)</th>
<th>3-weekly irinotecan (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Capecitabine 2000a</td>
<td>Irinotecan 70</td>
</tr>
<tr>
<td>1+2</td>
<td>1953b</td>
<td>69</td>
</tr>
<tr>
<td>3+4</td>
<td>1946</td>
<td>68</td>
</tr>
<tr>
<td>5+6</td>
<td>1946</td>
<td>68</td>
</tr>
<tr>
<td>7+8</td>
<td>1953</td>
<td>69</td>
</tr>
</tbody>
</table>

aPlanned dose.  
bEffectively administered dose.  
Capecitabine: mg/m²/day; irinotecan: mg/m²/infusion.

### Table 3: Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Weekly irinotecan (n = 38, courses = 251)</th>
<th>3-weekly irinotecan (n = 37, courses = 301)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Patients</td>
<td>% Courses</td>
</tr>
<tr>
<td>NCIC CTG grade 3 toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td>By age 65/&gt;65 years</td>
<td>26/36</td>
<td>5/7</td>
</tr>
<tr>
<td>By irinotecan 300/240 mg/m²</td>
<td>n.a.a</td>
<td>n.a.a</td>
</tr>
<tr>
<td>Alopecia</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Lethargy</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia in cycle 1</td>
<td>5</td>
<td>n.a.a</td>
</tr>
<tr>
<td>By age 65/&gt;65 years</td>
<td>0/18</td>
<td>n.a.-</td>
</tr>
<tr>
<td>NCIC CTG grade 4 toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>By age 65/&gt;65 years</td>
<td>4/9</td>
<td>&lt;1/2</td>
</tr>
<tr>
<td>By irinotecan 300/240 mg/m²</td>
<td>n.a.a</td>
<td>n.a.a</td>
</tr>
<tr>
<td>Alopecia</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lethargy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia in cycle 1</td>
<td>0</td>
<td>n.a.-</td>
</tr>
<tr>
<td>By age 65/&gt;65 years</td>
<td>0/0</td>
<td>n.a.-</td>
</tr>
<tr>
<td>Cardiovascular toxicity</td>
<td>5</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

aNot applicable because irinotecan reduction only in the 3-weekly arm.  
bNot applicable because several patients reduced from 300 to 240 mg/m².  
cNot applicable because measurements only for cycle 1.
to 34%) in arm A and 35% (95% CI 20% to 53%) in arm B. The reasons for this discrepancy, which mainly affected arm A, were technicalities such as missing scans, including missing response confirmation. There were no response reclassifications by the reviewers due to measurement discrepancies with the investigators. Study treatment allowed resection of liver metastases for two patients in each arm. Seven patients were not assessable for response in arm A due to early treatment stop because of toxicity (six) and one patient undergoing elective reanastomosis surgery. In arm B, four patients had early treatment stop due to toxicity and one patient suffered from bowel obstruction deemed independent of the study treatment by the investigator. All patients were included in the response calculation. Stabilization of disease was observed in 26% of patients in arm A and 34% in arm B.

The median follow-up time for alive patients was 16.1 months (range 11.2–26.4). The Kaplan–Meier curve for overall survival is depicted in Figure 1. The median overall survival was 17.4 months (95% CI 12.6–23.0+) for arm A and 24.7 months (95% CI: 16.3–26.4+) for arm B. The median time to treatment failure (defined as stop of treatment due to any reason, progression or death) was 4.6 months (95% CI 3.6–6.6) for arm A and 5.8 months (95% CI 4.4–7.0) for arm B (Figure 2). The median time to progression was 6.9 months (95% CI 4.6–10.1) for arm A and 9.2 months (95% CI 7.9–11.5) for arm B (Figure 3).

### Quality of life

Pre-failure QoL data were evaluated up to and including week 24 (i.e. day 1 of cycle 5); thereafter, too few patients were left on trial. Of all expected QoL forms in this period, 246 (95%) were received, 74 (99%) at baseline and 172 (94%) under treatment. Timing deviations between QoL assessment and day 1 of cycle were balanced between the arms; the median difference across all assessments and both treatment arms was 0 days (25–75% range = 3 days). After treatment failure, 51 QoL forms (70%) were available. Almost all missing data were due to local administrative failure; one patient refused the QoL assessment, and two assessments were not done due to medical complications.

At baseline, patients reported moderately to substantially impaired physical well-being (n=74, median = 84), mood (n=74, median = 69) and functional performance (n=72, median = 82), a low treatment burden (n=58, median = 89) and considerable coping effort (n=73, median = 55). Overall, there was an indication for less coping effort (P<0.05) and more treatment burden (P<0.01) over the first 6 months on study treatment. The only substantial treatment difference was in hair loss, with more hair loss (P<0.01) in Arm B over cycles 2–5.

Over this period, across both treatments, patients with tumor response reported better physical well-being (P<0.01), mood (P<0.05), functional performance (P<0.05) and coping (P<0.05) compared with the non-responders and stable disease patients. Figure 4 shows the changes in physical well-being. It has to be noted that there is considerable overlap of the two groups due to the small sample sizes. All of these indicators fulfilled our criterion of a clinically meaningful

![Figure 1. Overall survival.](http://annonc.oxfordjournals.org/)

![Figure 2. Time to treatment failure.](http://annonc.oxfordjournals.org/)

![Figure 3. Time to progression.](http://annonc.oxfordjournals.org/)
Discussion

The results of this trial demonstrate that two different regimens of irinotecan in combination with oral capcitabine can be safely and effectively combined in first-line treatment of metastatic colorectal cancer. Treatment with 3-weekly irinotecan led to a slightly higher tumor response rate, and the chosen selection design therefore leads to the recommendation to prefer this schedule. In support of this decision, the 3-weekly irinotecan arm yielded less severe diarrhea. Time to tumor progression, time to treatment failure and overall survival were also longer in the 3-weekly irinotecan arm. However, the observed differences should not be over-interpreted due to the selected study design.

Since a selection design was chosen, no formal statistical comparisons between the arms were planned. The small sample size of the study could have led to an imbalance of major prognostic factors affecting outcome independently of the assigned treatment. Looking at the patient and disease characteristics of the study population, an obvious source of bias could not be identified. The only clear imbalance was the higher percentage of patients with more than one metastatic site in arm B. The number of metastatic sites is an important prognostic factor for survival in advanced colorectal cancer [18], which would have favored longer survival in the weekly irinotecan arm. Liver metastases, another negative prognostic factor in the study by Kohne et al. [18], were also more prevalent in arm B (92%) than in arm A (79%). Thus, the imbalance of these prognostic factors between the treatment arms cannot explain the better outcome with 3-weekly irinotecan in this study.

Other investigators have found comparable response rates of 31–44% with weekly irinotecan [10, 11, 19, 20] and 47–50% with 3-weekly irinotecan [11, 21, 22] in combination with capcitabine. Although we planned to validate our results by carrying out an independent response review, the relevance of this review was severely hampered by the few missing scans in arm A. In addition, the measurements of the investigators were confirmed by the reviewers, suggesting good investigator assessment quality and no additional benefit by carrying out this review.

A recent meta-analysis supports the view that the tumor response rate is a clinically meaningful end point. These analyses confirmed that an increase in tumor response rate translates into an increase in overall survival for patients with first-line chemotherapy for advanced colorectal cancer [23]. Objective tumor response proved to be a meaningful end point also from patients’ subjective point of view in our trial. Over the first 6 months on treatment, patients with objective tumor response indicated better QoL performance compared with non-responding patients. A similar association between tumor response and QoL as perceived by the patient has recently been presented in another colorectal cancer trial [24]. Based on patients’ responses, the detrimental impact of more severe hair loss of the 3-weekly schedule was outweighed by the beneficial impact of better antitumor activity. In individual decision making, the differential impact on hair loss needs to be addressed.

Toxicity was manageable in both treatment arms. Potentially life-threatening toxicity consisted mainly of diarrhea and was more frequent in the weekly irinotecan arm as assessed by the investigators. This is consistent with the results of a recently published randomized phase III study on two different irinotecan second-line dosing regimens in metastatic colorectal cancer. In this trial, Fuchs et al. [9] found that 3-weekly irinotecan was associated with a significantly lower incidence of severe diarrhea compared with weekly irinotecan. Others, exploring comparable schedules of the irinotecan plus capcitabine combination, described similar experiences in terms of toxicity. The recommended dose from the phase I study by Tewes et al. was 1000 mg/m² twice daily capcitabine and 70 mg/m² irinotecan weekly [10]. Still, 19% of the patients experienced dose-limiting grade 4 diarrhea at this dose level. Bajetta et al. recently reported the results of a randomized phase II study comparing weekly 2 out of 3 weeks irinotecan and 3-weekly irinotecan in combination with capcitabine [11]. An interim analysis of this study was the basis of our dose reduction amendment since severe diarrhea occurred in 17% and 36% of the patients, respectively. Despite the fact that dose reductions were made for capcitabine and irinotecan in both treatment arms in that study, decreased occurrence of diarrhea was only observed in the 3-weekly irinotecan arm.
We have also found a reduction of toxicity after dose modification in the 3-weekly irinotecan arm. This translated into a higher dose intensity of both drugs as shown in Table 2. As compared with the 2 out of 3 weeks schedule of Bajetta et al. [11], our weekly irinotecan schedule seemed less toxic.

It will be important to prove that capecitabine can replace the established infusional fluorouracil plus leucovorin combinations without negatively affecting efficacy and toxicity. In terms of patient convenience, the oral fluoropyrimidine is clearly advantageous [3]. In this respect the results of EORTC 40015 are eagerly awaited, which compares capecitabine plus irinotecan with infusional fluorouracil/leucovorin plus irinotecan. As a consequence of the results presented here, the 3-weekly irinotecan schedule in addition to capecitabine will be used for further comparative trials of our group.

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