

A phase II randomized multicenter trial of gefitinib plus FOLFIRI and FOLFIRI alone in patients with metastatic colorectal cancer

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Received 18 February 2008; revised 22 May 2008; accepted 23 May 2008

Background: Gefitinib inhibits the epidermal growth factor receptor tyrosine kinase and preclinical studies indicate that it may enhance CPT-11 cytotoxicity. This randomized phase II trial investigates the feasibility and efficacy of gefitinib and 5-fluorouracil, folinic acid, irinotecan (FOLFIRI) in patients with metastatic colorectal cancer.

Patients and methods: Patients were randomized to FOLFIRI ± gefitinib 250 mg daily p.o. Patients randomized to FOLFIRI + gefitinib without disease progression after 6 months continued to receive gefitinib alone until disease progression.

Results: From October 2002 to September 2004, 100 patients were enrolled. Twenty-three patients (47.9%) in the FOLFIRI arm and 23 (45.1%) in the FOLFIRI + gefitinib arm experienced an objective response. The median progression-free survival and overall survival were 8.3 and 18.6 months in the FOLFIRI arm, and 8.3 and 17.1 months in the FOLFIRI + gefitinib arm, respectively. In the combination arm, grades 3–4 adverse events were experienced by 35 (67.3%) patients versus 25 patients (52.1%) in the FOLFIRI arm; 12 patients (23.1%) withdrew for an adverse event in the FOLFIRI + gefitinib arm and 5 (10.4%) in the FOLFIRI arm.

Conclusions: These data show that adding gefitinib to FOLFIRI does not improve the efficacy of FOLFIRI regimen. These disappointing results could be related to the high toxicity observed that led to significant dose reductions and delays.

Key words: colorectal cancer, EGFR, FOLFIRI, gefitinib, metastatic

introduction

Colorectal cancer (CRC) is a leading cause of cancer death in the developed world [1]. Although new chemotherapy regimens have improved the outcome of patients with metastatic disease in recent years, overall treatment results remain unsatisfactory and accelerated efforts of modulating drug resistance by combining standard and innovative therapeutic approaches are mandatory [2, 3].

Irinotecan (CPT-11) has been established as one of the most active drugs in the treatment of CRC. By combining CPT-11 with 5-fluorouracil (5-FU) and folinic acid (FA), Douillard [2] achieved an overall response rate (ORR) of 49% with a median time to progression of 6.7 months and an overall survival (OS) of 17.4 months. Toxicity of this regimen is manageable and includes diarrhea, nausea, vomiting, myelosuppression, and alopecia. Moreover, recent studies showed that bevacizumab

significantly enhances survival data of 5-FU- and CPT-11-based regimens [4]. Consequently, the combination of CPT-11 with 5-FU and FA alone or in combination with bevacizumab is a standard treatment of chemo-naïve patients with metastatic CRC.

Overexpression of the epidermal growth factor receptor (EGFR) has been reported in 60%–80% of CRC and was shown to be associated with a poor prognosis [5]. Accordingly, several antibodies and small molecules, which block EGFR signaling pathways, have been developed as potential therapies [6, 7].

Gefitinib (ZD 1839, Iressa, Astra Zeneca, London, UK) is an orally active, EGFR tyrosine kinase inhibitor (TKI) that blocks adenosine triphosphate-binding site of the catalytic domain of the receptor. In preclinical study, gefitinib showed activity against several human cancer cell lines and enhanced the antitumor effects of several chemotherapeutic agents [8–10].

In phase I studies, gefitinib showed a favorable toxicity profile characterized by diarrhea and skin rash, and its activity was demonstrated in phase II trials in advanced non-small-cell lung cancer (NSCLC) [11–13]. In this setting, gefitinib induced

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objective responses and improved tumor-related symptoms in patients pretreated with chemotherapy [14]. These data led to an accelerated US Food and Drug Administration approval as single agent in NSCLC in 2003.

Although the few preliminary preclinical and clinical data in CRC with gefitinib as single agent were less promising, preclinical studies clearly showed that gefitinib enhances antitumor effects of chemotherapy in colon cancer cell lines and xenograft of human cancer [15–18]. In particular, gefitinib has been shown to sensitize CRC cells to SN-38, the active metabolite of CPT-11, influencing molecular determinants of CPT-11 resistance and sensitivity [19–21].

On these bases, we designed a phase II randomized study to evaluate both efficacy and tolerability of the combination of gefitinib and FOLFIRI in chemo-naïve patients with metastatic CRC. Because no phase I studies were available at the time of the study design, we planned to assess the safety of the combination in the first six patients enrolled in the combination arm.

materials and methods

The study protocol was approved by the Independent Local Ethics Committee of each participating center and was conducted in accordance with The Declaration of Helsinki and according to the Good Clinical Practice–International Conference on Harmonisation (GCP–ICH) rules (study 1839IL/0138, sponsored by AstraZeneca).

Inclusion criteria in the trial were histologically confirmed metastatic adenocarcinoma of the colon or rectum with measurable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST), life expectancy of at least 12 weeks, age >18 years and Eastern Cooperative Oncology Group performance status of zero or one. No prior therapy for metastatic disease was allowed; patients may have received one prior course of 5-FU-based adjuvant chemotherapy and/or radiotherapy with the last dose administered at least 6 months before randomization. Patients had to provide written informed consent before the study entry. Exclusion criteria included absolute neutrophil count $<1.5 \times 10^9/l$, hemoglobin <8 g/dl or platelets $<75 \times 10^9/l$, serum bilirubin >1.25 times upper normal limit (UNL), serum creatinine >1.25 times UNL, alanine aminotransferase or aspartate aminotransferase >2.5 times UNL if no demonstrable liver metastases, or >5 times UNL in the presence of liver metastases.

This study is a randomized, multicenter, noncomparative phase II, parallel-group trial. The study was initially powered with the primary objective of estimating the ORR at trial closure according to the RECIST, for the combination of gefitinib and FOLFIRI regimen and for FOLFIRI alone, in patients with metastatic CRC. The study was not powered at conventional levels for a formal comparison between arms but was conducted to quantify the response rate, and other outcome data, on each arm. A randomized trial was preferred to a single-arm, uncontrolled trial as randomization serves to provide an internal control and lessens patient selection bias.

Gefitinib was administered orally once daily at the dose of 250 mg. A full safety evaluation was conducted when six patients completed one cycle of combination therapy, before further patients were enrolled into the trial.

According to FOLFIRI regimen, CPT-11 was administered at the dose of 180 mg/m^2 by i.v. infusion over 90 min on day 1; levo-FA was administered at 100 mg/m^2 by i.v. infusion over 120 min on days 1 and 2; and 5-FU was administered as a bolus injection at 400 mg/m^2 and as 22-h i.v. infusion at 600 mg/m^2 on days 1 and 2. Cycles were repeated every 2 weeks. Antiemetic prophylaxis with a 5-hydroxytryptamine₃ (5-HT₃) receptor antagonist and

dexamethasone and anticholinergic prophylaxis with atropine were used. Dose modification was made for myelosuppression, diarrhea, mucositis and skin rash.

Treatment was continued for a maximum of 12 cycles or until disease progression, unacceptable toxicity or withdrawal of consent. Patients without disease progression at the end of 12 cycles continued to receive gefitinib alone administered daily until disease progression, unacceptable toxicity or withdrawal of consent.

The aim of the study was to investigate the effects of the two treatments and to gather information so that a subsequent phase III study could be designed appropriately.

A sample size of 50 patients per arm was calculated in order to give at least an 87% probability of rejecting a baseline response rate of 35% with an exact 5% one-sided significance test when the true response is at the clinically relevant rate of 55%. Patients who have not progressed or died at the time of analysis have been censored at the time of their latest objective tumor assessment, including patients lost to follow-up or who withdraw consent.

The study started in October 2002. In May 2004, on the basis of preliminary phase II evidence of the efficacy and tolerability of gefitinib plus a 5-fluorouracil, folinic acid, oxaliplatin (FOLFOX) regimen as first-line therapy for CRC [22], the protocol for the current study was amended to allow it to be repowered for a primary end point of progression-free survival (PFS). An increase in the sample size of an additional 90 patients (to 190 in total) was calculated under the revised primary comparative end point.

The first cohort of 100 patients was enrolled by December 2004, after which recruitment restarted according to the modified sample size. A further 24 of the 90 additional patients were enrolled before the study closing early in March 2006 for reasons of slow recruitment and for changes in the standard of care in first-line CRC, making FOLFIRI no longer appropriate as a control arm. The early closure of the study did not allow to perform the comparative analysis on PFS and the data presented in this paper are for the first cohort of 100 patients.

The safety and tolerability of gefitinib plus FOLFIRI were assessed in the first six patients enrolled in the combination arm in a single institution before continuing the recruitment.

Pretreatment evaluations included past medical history, demography, assessment of tumor lesions and concurrent illness/therapy, physical examination, hematology, biochemistry, urinalysis, pregnancy test (if appropriate), and electrocardiogram. Tumor assessments were to be carried out every 8 weeks of therapy (four cycles) until progression. According to RECIST, assessments of objective responses must be confirmed a minimum of 4 weeks after the criteria for response are first met. For the purpose of this trial, any detrimental change in a patient's condition, after they enter the trial and during the 30-day follow-up period after the final treatment, was considered an adverse event as well as the development of a new cancer. Adverse events and laboratory values were graded according to the National Cancer Institute Common Toxicity Criteria 2.0 (NCI-CTC) [23].

All subjects who were enrolled in the first cohort of 100 patients and received study treatment are the intention-to-treat (ITT) population, considered for all efficacy outcome variables analysis. The ORR for each arm has been calculated. Durations of PFS and OS are analyzed using log-rank and also summarized by Kaplan–Meier methods.

results

The study started in October 2002. The safety and tolerability of the combination were assessed in an initial cohort of 11 patients, corresponding to six patients enrolled to FOLFIRI

plus gefitinib arm and five patients to FOLFIRI alone. The results of the initial safety analysis demonstrated that the association of gefitinib and FOLFIRI was well tolerated and no dose-limiting toxicity was reported; consequently, the enrollment restarted.

From October 2002 to September 2004, the planned 100 patients in the initial cohort were enrolled from nine Italian hospitals on to this study. The baseline characteristics of the enrolled patients were well balanced between the two randomized arms (Table 1). A total number of 911 chemotherapy cycles was administered either with or without gefitinib with a median of 12 cycles (range 1–12) in the FOLFIRI-alone arm and 10 cycles (range 1–12) in the FOLFIRI plus gefitinib arm. Overall, 721 cycles were administered at full dose and without delay [401 cycles (86.4%) in the FOLFIRI-alone arm and 320 cycles (71.6%) in the FOLFIRI plus gefitinib arm], 18 cycles were administered at a reduced dose, 142 were delayed, and 30 were administered at a reduced dose and delayed (Table 2). Gefitinib was temporarily interrupted in 13 patients (25%) due to an adverse event.

The primary efficacy end point of this study was the ORR defined as either complete or partial response according to RECIST criteria. One patient randomized to FOLFIRI plus gefitinib arm was found ineligible after randomization and never started the study treatment and was excluded from the ITT analysis. Overall, 96 patients (97.0%) are assessable for the tumor response and three patients (3.0%, two in FOLFIRI-alone arm and one in FOLFIRI plus gefitinib arm) withdrew from the trial therapy before the first planned tumor assessment: two patients for adverse event (one patient for

cardiomyopathy NCI-CTC grade 3 and one patient for febrile neutropenia NCI-CTC grade 4), and one patient died of an unknown cause. The ORR was 46.5% (46 patients): 47.9% (23 patients) in the FOLFIRI-alone arm and 45.1% (23 patients) in the FOLFIRI plus gefitinib arm. The disease control rate was of 81.8% (81 patients): 83.3% (40 patients) in the FOLFIRI-alone arm and 80.4% (41 patients) in the FOLFIRI plus gefitinib arm (Table 3). The median duration of tumor response was 6.8 months [95% confidence interval (CI) 5.7–9.2]: 6.2 months (95% CI 4.5–13.4) in the FOLFIRI-alone arm and 7.8 months (95% CI 5.7–9.2) in the FOLFIRI plus gefitinib arm.

At the median follow-up of 14.5 months, 78 (78.8%) patients progressed, while in the study, 35 (72.9%) in the FOLFIRI-alone arm and 43 (84.3%) in the FOLFIRI plus gefitinib arm. The median PFS in the FOLFIRI-alone arm was 8.3 months (95% CI 7.1–11.2) and in the FOLFIRI plus gefitinib arm was 8.3 months (95% CI 6.6–10.3). The PFS curves are shown in Figure 1.

At the cut-off date, 37 patients (37.4%) were alive, 19 (39.6%) in the FOLFIRI-alone arm and 18 (35.3%) in the FOLFIRI plus gefitinib arm. Overall, 57 of the 62 deaths (91.9%) were related to CRC. The causes of deaths unrelated to cancer were heart failure (one patient in the FOLFIRI plus gefitinib arm), road accident (one patient in the FOLFIRI-alone arm), suicide (one patient in the FOLFIRI-alone arm), and unknown (one patient in each of the two arms).

At trial closure, the median OS in the FOLFIRI-alone arm was 18.6 months (95% CI 14.1–29.0) and in the FOLFIRI plus gefitinib arm was 17.1 months (95% CI 13.8–26.5). The OS curves are shown in Figure 2.

Table 1. Baseline characteristics

	FOLFIRI (N = 48)		FOLFIRI + gefitinib (N = 51)	
	No.	%	No.	%
Sex				
Female	18	37.5	22	43.1
Male	30	62.5	29	56.9
Baseline ECOG PS				
0	37	77.1	41	80.4
1	11	22.9	10	19.6
Median age (range)	62.5 years	(49–75)	63 years	(41–78)
Site of primary tumor				
Colon	40	83.3	39	76.5
Rectum	6	12.5	9	17.6
Colon + rectum	2	4.2	3	5.9
Previous surgery				
Yes	42	87.5	42	82.4
No	6	12.5	9	17.6
Adjuvant chemotherapy				
Yes	12	25.0	10	19.6
No	36	75.0	41	80.4
Adjuvant radiotherapy				
Yes	3	6.3	2	3.9
No	45	93.7	49	96.1

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Table 2. Chemotherapy cycles

	FOLFIRI (N = 464)		FOLFIRI + gefitinib (N = 447)	
	No.	%	No.	%
Full dose, not delayed	401	86.4	320	71.6
Reduced dose	6	1.3	12	2.7
Delayed	45	9.7	97	21.7
Reduced dose and delayed	12	2.6	18	4.0

Table 3. Tumor response according to RECIST

	FOLFIRI (N = 48)		FOLFIRI + gefitinib (N = 51)	
	No.	%	No.	%
Overall response (CR + PR)	23	47.9	23	45.1
Stable disease	17	35.4	18	35.3
Disease control (CR + PR + SD)	40	83.3	41	80.4
Progressive disease	6	12.5	9	17.6
Not evaluable	2	4.2	1	2.0

CR, complete response; PR, partial response; SD, stable disease; RECIST, Response Evaluation Criteria in Solid Tumors.

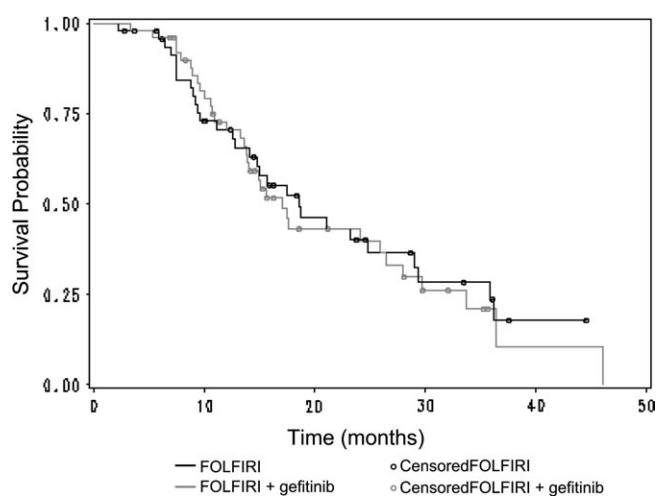


Figure 1. Kaplan–Meier curves for progression-free survival.

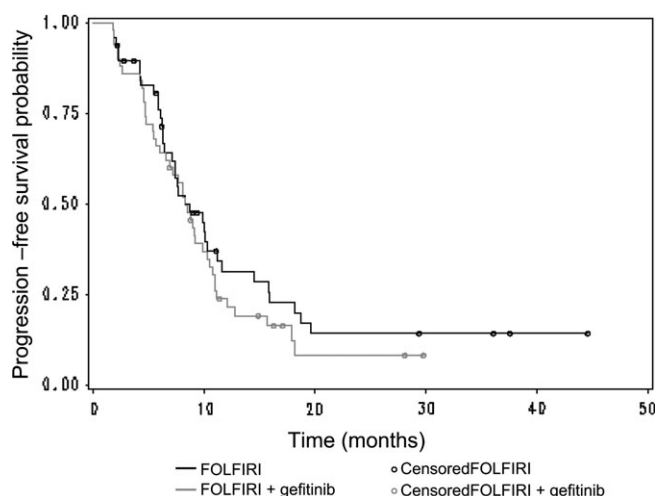


Figure 2. Kaplan–Meier curves for overall survival.

Thirty patients withdrew from the study for reasons other than progressive disease: 12 patients (25%) in the FOLFIRI arm and 18 (35.3%) in the combination arm. The reasons of withdrawal were adverse events or intolerance to therapies in 15 patients (29.4%) in the combination arm and in 6 patients (12.5%) in the FOLFIRI arm, respectively.

The toxicity of the combination of FOLFIRI plus gefitinib was acceptable although drug-related NCI-CTC grades 3–4 adverse events were experienced by 35 (68.6%) patients randomized to FOLFIRI plus gefitinib arm compared with 25 patients (52.1%) in the FOLFIRI-alone arm, serious adverse events by 13 (25.5%) patients randomized to FOLFIRI plus gefitinib arm versus 10 patients (20.8%) in the FOLFIRI-alone arm (Table 4). Most common drug-related NCI-CTC grades 3–4 adverse events included diarrhea (33.3% of patients in the FOLFIRI plus gefitinib arm versus 2.1% in the FOLFIRI-alone arm) and neutropenia (35.3% of patients in the FOLFIRI plus gefitinib arm versus 22.9% in the FOLFIRI-alone arm) (Table 4).

The patients randomized to FOLFIRI plus gefitinib arm experienced more skin toxicity (70.6% versus 35.4%) and

Table 4. Toxic effects

Adverse event	FOLFIRI		FOLFIRI + gefitinib		P value
	No. of patients	%	No. of patients	%	
Diarrhea					
Any grade	20	41.7	28	54.9	0.1879
Grades 3–4	1	2.1	17	33.3	<0.0001 ^a
Nausea					
Any grade	27	56.2	26	51.0	0.5993
Grades 3–4	2	4.2	–	–	0.2274
Neutropenia					
Any grade	19	39.6	25	49.0	0.3450
Grades 3–4	11	22.9	18	35.3	0.1762
Vomiting					
Any grade	18	37.5	16	31.4	0.5211
Grades 3–4	5	10.4	3	5.9	0.4786
Skin Toxicity					
Any grade	17	35.4	36	70.6	0.0005
Grades 3–4	1	2.1	5	9.8	0.2056 ^a
Asthenia					
Any grade	21	43.8	23	45.1	0.8927
Grades 3–4	3	6.3	2	3.9	0.6716 ^a
Mucositis					
Any grade	10	20.8	18	35.3	0.1103
Grades 3–4	2	4.2	1	2.0	0.6098 ^a
Leukopenia					
Any grade	10	20.8	11	21.6	0.9287
Grades 3–4	1	2.1	3	5.9	0.6179 ^a
Anemia					
Any grade	6	12.5	7	13.7	0.8568
Grades 3–4	1	2.1	3	5.9	0.6179 ^a
Abdominal pain					
Any grade	12	25.0	16	31.4	0.4817
Grades 3–4	2	4.2	1	2.0	0.6098 ^a
Constipation					
Any grade	8	16.7	10	19.6	0.7045
Grades 3–4	–	–	–	–	–
Anorexia					
Any grade	3	6.3	6	11.8	0.3088 ^a
Grades 3–4	–	–	1	2.0	0.4848 ^a
Fever					
Any grade	13	27.1	15	29.4	0.7971
Grades 3–4	–	–	–	–	–
Bleeding					
Any grade	1	2.1	8	15.7	0.0315 ^a
Grades 3–4	–	–	–	–	–
Neurological					
Any grade	11	22.9	4	7.8	0.0498 ^a
Grades 3–4	2	4.2	–	–	0.2325 ^a

^aFisher's exact test two-tailed.

bleeding events (15.7% versus 2.1%), while more NCI-CTC grades 1–2 neurologic events were experienced in the FOLFIRI-alone arm (22.9% versus 7.8%).

The data regarding the additional 24 patients enrolled in the second part of the study and not included in the statistical analysis are consistent with the above-presented results of the first 100 patients.

discussion

In 2002, when this trial was started, there was a strong rationale to evaluate in a clinical study the efficacy and tolerability of the combination of gefitinib and FOLFIRI in advanced CRC. EGFR had been recognized as a target for the development of anticancer therapies and different EGFR inhibitors had shown preliminary promising results for the treatment of pretreated NSCLC and metastatic CRC, respectively. Moreover, preclinical studies had shown that gefitinib strongly sensitizes colon cancer cells to the CPT-11-active metabolite SN-38.

With the present randomized phase II trial, we investigated the efficacy and tolerability of the combination of gefitinib and FOLFIRI as a first-line regimen in patients with metastatic CRC.

Considering that at the time of the study no data were available on the clinical feasibility of the combination of gefitinib and FOLFIRI, we assessed safety and tolerability of the combination in an initial cohort of six patients in which we did not observe any relevant toxicity. These favorable preliminary results led us to complete the enrollment.

During the study time, disappointing results in CRC on the combination of EGFR TKIs and various chemotherapy regimens were published. Two phase I–II trials with the combination of gefitinib and FOLFIRI were early terminated due to an unfavorable toxicity profile, characterized by unexpected severe diarrhea, dehydration and neutropenia and a low level of activity [24, 25]. Also the combination of FOLFIRI and erlotinib, another EGFR TKI, caused excessive toxicity despite the use of reduced doses of drugs [26]. Many authors hypothesized a pharmacodynamic and/or pharmacokinetic interaction between gefitinib and CPT-11 but appropriate studies showed just an increase in steady-state concentration of EGFR TKIs that does not explain this high toxicity [26, 27]. A significant increase of toxicity was also documented in some studies with the combination of gefitinib- and oxaliplatin-based regimens [22, 28–30], although in two phase II studies these combinations were associated with efficacy outcomes superior to those historically reported with FOLFOX alone in a similar patient population [29, 30]. Finally, monotherapy with gefitinib and erlotinib failed to show any significant clinical activity in metastatic CRC [17, 18].

In the present study with the combination of gefitinib and FOLFIRI, we observed disappointing results in terms of toxicity, very similar to the data achieved in the phase I–II studies reported above [24, 25]. In particular, grades 3–4 diarrhea was documented in 33.3% of patients, grades 3–4 neutropenia in 35.3% of patients, and any grade skin toxicity in 70.6% of patients. The high toxicity rate observed determined a dose reduction and/or delay in 28.4% of cycles and this could have negatively affected the efficacy data which are very similar to the results obtained in the FOLFIRI arm.

Although we observed a limited improvement in duration of response in the combination arm, considering the lack of data in favor of gefitinib monotherapy in CRC, we do not feel that this drug may play a role in maintaining tumor response.

In our randomized study, the presence of the FOLFIRI control arm validates the high toxicity and the low efficacy of the combination arm. With the FOLFIRI regimen, we achieved

an ORR 47.9%, a median PFS of 8.3 months, and a median OS of 18.6 months. In terms of toxicity, grades 3–4 diarrhea was reported in 2.1% of patients, grades 3–4 neutropenia in 22.9%, and grades 3–4 skin toxicity in 2.1%. It is worth of note that the results achieved with FOLFIRI are very similar to those reported by several authors with the same regimen [2].

Although we did not test for EGFR expression, amplification or mutation in this trial, it is unlikely that this had a significant impact on the observed results. Overexpression of EGFR occurs in the majority of metastatic CRC and the clinical activity of agents that inhibit EGFR such as gefitinib does not appear to correlate with EGFR expression [18]. Although recent data have shown a correlation between an increased EGFR copy number assessed by FISH and clinical response to anti-EGFR monoclonal antibodies in patients with metastatic CRC [31], no data concerning EGFR TKIs are available in this setting.

In lung cancer, dramatic responses to EGFR TKIs have been observed in patients with activating mutations in the EGFR gene [32], although not all patients experiencing response to these agents harbor such mutations. Unfortunately, these mutations are rare in metastatic CRC and could represent one of the reasons of the reported low activity of EGFR TKIs in this disease [21].

In conclusion, our results showed disappointing results in terms of activity for the combination of gefitinib and FOLFIRI. One possible explanation for this might be the high toxicity observed that led to dose reductions and delays neutralizing the cytotoxic potential of the synergism between EGFR TKIs and chemotherapy. Alternatively, it might be that these combinations do not show synergy *in vivo*.

On the basis of the available data underlining the lack of activity and the unfavorable safety profile of gefitinib in combination with FOLFIRI in metastatic CRC, further development of this combination in this setting is not warranted.

references

1. Parkin DM, Bray F, Ferlay J et al. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; 55: 74–108.
2. Douillard JY. Irinotecan and high-dose fluorouracil/leucovorin for metastatic colorectal cancer. *Lancet* 2000; 355: 1041–1047.
3. Goldberg RM, Sargent DJ, Morton RF et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004; 22: 23–30.
4. Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350: 2335–2342.
5. Cohen RB. Epidermal growth factor receptor as a therapeutic target in colorectal cancer. *Clin Colorectal Cancer* 2003; 2: 246–251.
6. Vallbohmer D, Lenz HJ. Epidermal growth factor receptor as a target for chemotherapy. *Clin Colorectal Cancer Suppl* 2005; 1: S19–S27.
7. Vanhoefler U. Molecular mechanisms and targeting of colorectal cancer. *Semin Oncol* 2005; 32 (6 Suppl 8): 7–10.
8. Knight LA, Di Nicolantonio F, Whitehouse P et al. The *in vitro* effect of gefitinib ('Iressa') alone and in combination with cytotoxic chemotherapy on human solid tumours. *BMC Cancer* 2004; 4: 83.
9. Van Schaeybroeck S, Karaiskou-McCaul A, Kelly D et al. Epidermal growth factor receptor activity determines response of colorectal cancer cells to gefitinib alone and in combination with chemotherapy. *Clin Cancer Res* 2005; 11: 7480–7489.

10. Xu JM, Azzariti A, Colucci G et al. The effect of gefitinib (Iressa, ZD1839) in combination with oxaliplatin is schedule-dependent in colon cancer cell lines. *Cancer Chemother Pharmacol* 2003; 52: 442–448.
11. Baselga J, Rischin D, Ranson M et al. Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. *J Clin Oncol* 2002; 20: 4292–4302.
12. Lorusso PM. Phase I studies of ZD1839 in patients with common solid tumors. *Semin Oncol* 2003; 30: 21–29.
13. Vokes EE, Chu E. Anti-EGFR therapies: clinical experience in colorectal, lung, and head and neck cancers. *Oncology (Williston Park)* 2006; 20 (5 Suppl 2): 15–25.
14. Cappuzzo F, Gregorc V, Rossi E et al. Gefitinib in pretreated non-small-cell lung cancer (NSCLC): analysis of efficacy and correlation with HER2 and epidermal growth factor receptor expression in locally advanced or metastatic NSCLC. *J Clin Oncol* 2003; 21: 2658–2663.
15. Daneshmand M, Parolin DA, Hirte HW et al. A pharmacodynamic study of the epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 in metastatic colorectal cancer patients. *Clin Cancer Res* 2003; 9: 2457–2464.
16. Lockhart AC, Berlin JD. The epidermal growth factor receptor as a target for colorectal cancer therapy. *Semin Oncol* 2005; 32: 52–60.
17. Mackenzie MJ, Hirte HW, Glenwood G et al. A phase II trial of ZD1839 (Iressa) 750 mg per day, an oral epidermal growth factor receptor-tyrosine kinase inhibitor, in patients with metastatic colorectal cancer. *Invest New Drugs* 2005; 23: 165–170.
18. Rothenberg ML, LaFleur B, Levy DE et al. Randomized phase II trial of the clinical and biological effects of two dose levels of gefitinib in patients with recurrent colorectal adenocarcinoma. *J Clin Oncol* 2005; 23: 9265–9274.
19. Braun AH, Stark K, Dirsch O et al. The epidermal growth factor receptor tyrosine kinase inhibitor gefitinib sensitizes colon cancer cells to irinotecan. *Anticancer Drugs* 2005; 16: 1099–1108.
20. Koizumi F, Kanzawa F, Ueda Y et al. Synergistic interaction between the EGFR tyrosine kinase inhibitor gefitinib ('Iressa') and the DNA topoisomerase I inhibitor CPT-11 (irinotecan) in human colorectal cancer cells. *Int J Cancer* 2004; 108: 464–472.
21. Ogino S, Meyerhardt JA, Cantor M et al. Molecular alterations in tumors and response to combination chemotherapy with gefitinib for advanced colorectal cancer. *Clin Cancer Res* 2005; 11: 6650–6656.
22. Cho CD, Fisher GA, Halsey J et al. Phase I study of gefitinib, oxaliplatin, 5-fluorouracil, and leucovorin (IFOX) in patient with advanced solid malignancies. *Invest New Drug* 2006; 24: 117–123.
23. National Cancer Institute. National Cancer Institute Common Toxicity Criteria version 2.0. http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf.
24. Veronese ML, Sun W, Giantonio B et al. A phase II trial of gefitinib with 5-fluorouracil, leucovorin, and irinotecan in patients with colorectal cancer. *Br J Cancer* 2005; 92: 1846–1849.
25. Hofheinz RD, Kubicka S, Wollert J et al. Gefitinib in combination with 5-fluorouracil (5-FU)/folinic acid and irinotecan in patients with 5-FU/oxaliplatin-refractory colorectal cancer: a phase I/II study of the Arbeitsgemeinschaft für Internistische Onkologie (AIO). *Onkologie* 2006; 29: 563–567.
26. Messersmith WA, Laheru DA, Senzer NN et al. Phase I trial of irinotecan, infusional 5-fluorouracil, and leucovorin (FOLFIRI) with erlotinib (OSI-774): early termination due to increased toxicities. *Clin Cancer Res* 2004; 10: 6522–6527.
27. Chau D, Cunningham D, Hickish T et al. Gefitinib and irinotecan in patients with fluoropyrimidine-refractory, irinotecan-naïve advanced colorectal cancer: a phase I-II study. *Ann Oncol* 2007; 18: 730–737.
28. Kindler HL, Friberg G, Skoog L et al. Phase I/II trial of gefitinib and oxaliplatin in patients with advanced colorectal cancer. *Am J Clin Oncol* 2005; 28: 340–344.
29. Kuo T, Cho CD, Halsey J et al. Phase II study of gefitinib, fluorouracil, leucovorin, and oxaliplatin therapy in previously treated patients with metastatic colorectal cancer. *J Clin Oncol* 2005; 23: 5613–5619.
30. Zampino MG, Magni E, Massacesi C et al. First clinical experience of orally active epidermal growth factor receptor inhibitor combined with simplified FOLFOX6 as first-line treatment for metastatic colorectal cancer. *Cancer* 2007; 110: 752–758.
31. Moroni M, Veronese S, Benvenuti S et al. Gene copy number for epidermal growth factor receptor (EGFR) and clinical response to antiEGFR treatment in colorectal cancer: a cohort study. *Lancet Oncol* 2005; 6: 279–286.
32. Rosell R, Taron M, Reguart N et al. Epidermal growth factor receptor activation: how exon 19 and 21 mutations changed our understanding of the pathway. *Clin Cancer Res* 2006; 12: 7222–7231.