

Phase II Study of Gefitinib, Fluorouracil, Leucovorin, and Oxaliplatin Therapy in Previously Treated Patients With Metastatic Colorectal Cancer

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ABSTRACT

Purpose

To investigate the gefitinib, fluorouracil (FU), leucovorin, and oxaliplatin regimen (IFOX) in previously treated patients with metastatic colorectal cancer.

Patients and Methods

Eligible patients had stage IV colorectal adenocarcinoma and had demonstrated progression or intolerance to a prior chemotherapy regimen not including oxaliplatin. Each cycle consisted of 14 days. Cycle 1 consisted of oxaliplatin 85 mg/m² intravenously (IV) during 2 hours on day 1, hours 0 to 2; leucovorin 200 mg/m² IV on days 1 and 2, hours 0 to 2; FU 400 mg/m² IV push on days 1 and 2; and FU 600 mg/m² IV on days 1 and 2, hours 2 to 24 (FOLFOX-4). All subsequent cycles consisted of FOLFOX-4 with gefitinib at 500 mg/d administered orally throughout the 14-day cycle.

Results

Twenty-seven patients were enrolled onto the study. The median number of prior chemotherapy regimens was two, and 74% of all patients received prior irinotecan. Nine of the 27 patients (33%) and six of the 20 patients (30%) who had prior FU and irinotecan had a partial response by Response Evaluation Criteria in Solid Tumors Group criteria. Median overall survival was 12.0 months. Median event-free survival was 5.4 months. Grade 3 to 4 toxicities included neutropenia (48%), diarrhea (48%), nausea (22%), and vomiting (15%).

Conclusion

IFOX is an active regimen in patients with previously treated metastatic colorectal adenocarcinoma, demonstrating higher response rates than those reported with FOLFOX-4 alone in a similar patient population.

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INTRODUCTION

The treatment of metastatic colorectal cancer (CRC) has changed dramatically during the last 5 years with the introduction of active new chemotherapeutic and biologically targeted agents. In 2000, the combination of irinotecan, bolus fluorouracil (FU), and leucovorin (IFL) was shown to be superior to FU and leucovorin alone.¹ Infusional FU was shown to have reduced toxicity while improving efficacy compared with bolus

FU.^{2,3} The addition of the platinum drug oxaliplatin to infusional FU led to the development of the infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) regimens for second-line treatment of metastatic CRC.⁴ In a phase III study in patients who had progression of metastatic CRC after IFL, the FOLFOX-4 regimen demonstrated a 10% objective response rate compared with a 1% response rates seen with FU/leucovorin or oxaliplatin.⁵ The FOLFOX-4 regimen also resulted in

superior time to progression (4.6 v 2.7 months) and improved relief of tumor-related symptoms as compared with FU/leucovorin.

Even with these advances, the response rate for second-line therapy in metastatic CRC remains low. The search for additional active treatment regimens in this setting has led to the investigation of new agents targeting cell-signaling molecules such as epidermal growth factor receptor (EGFR) tyrosine kinase. Preclinical studies inhibiting EGFR with either antibodies or small molecules demonstrated a dose-dependent inhibition of tumor cell growth in vitro and in animal models.⁶⁻¹⁰

EGFR expression has been demonstrated in up to 60% to 80% of CRC tumors,^{11,12} and has been associated with decreased survival.¹³ A recent phase III study demonstrated that the anti-EGFR antibody, cetuximab, in combination with irinotecan produced a 22% response rate in patients refractory to irinotecan-based chemotherapy, whereas cetuximab alone produced a 10% response rate.¹⁴ Preclinical models also demonstrate that inhibition of the EGFR signaling pathway can sensitize tumor cells to chemotherapy.¹⁵⁻¹⁷

Gefitinib (Iressa; ZD1839, Wilmington, DE), a potent small-molecule inhibitor of the tyrosine kinase domain of EGFR, has been studied extensively in patients with tumors of epithelial origin, such as lung and head and neck cancers, but studies in patients with CRC are limited.¹⁸⁻²³ Gefitinib is orally bioavailable, and is an attractive therapeutic option because of its biologic activity and ease of administration.

We recently completed a phase I study to determine the optimal doses of gefitinib, FU, leucovorin, and oxaliplatin (IFOX) therapy in patients with advanced solid malignancies.²⁴ On the basis of the results of our phase I study, we proceeded to a phase II study evaluating the efficacy of the IFOX regimen for the second-line treatment of patients with metastatic CRC.

PATIENTS AND METHODS

Patients

Patients were considered eligible for this study if they were older than 18 years of age and had histologically confirmed metastatic colorectal adenocarcinoma with documented progressive disease after first-line chemotherapy. Patients receiving any prior therapy for metastatic disease or patients developing metastatic disease within 6 months of receiving adjuvant therapy were included. Other criteria for eligibility included measurable disease by Response Evaluation Criteria in Solid Tumors Group criteria, no more than three prior chemotherapy regimens, completion of prior chemotherapy ≥ 4 weeks before enrollment, no prior exposure to oxaliplatin or EGFR inhibitors, an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , adequate blood counts (neutrophils $\geq 1,500/\mu\text{L}$ and platelets $\geq 100,000/\mu\text{L}$), renal function within normal limits, total bilirubin ≤ 1.5 mg/dL, and aminotransferases $\leq 2.5\times$ the upper limit of normal.

Confirmation of tumor EGFR status was not required for inclusion in this study and there was no determination made of EGFR status before treatment initiation. All patients signed an informed consent form approved by the Stanford University Committee for the Protection of Human Subjects.

Treatment

The first cycle of treatment was FOLFOX-4 chemotherapy alone at dosages previously published.²⁵ This was done to obtain more experience with the acute toxicities of IFOX compared with FOLFOX-4 alone. On day 1, patients received oxaliplatin 85 mg/m² intravenously concurrent with leucovorin 200 mg/m² intravenously during 2 hours. Then, FU 400 mg/m² was administered by intravenous bolus injection followed by FU 600 mg/m² administered by continuous intravenous infusion during 22 hours. On day 2, leucovorin, bolus FU, and infusional FU was delivered at identical doses as day 1. Pretreatment with a 5-hydroxytryptamine-3 receptor antagonist and dexamethasone was administered before oxaliplatin.

In the second and subsequent cycles of treatment, patients received the IFOX regimen. Each cycle lasted 14 days. Thus, beginning with cycle 2 and for each subsequent cycle, gefitinib 500 mg/d orally was administered for the entire 14 days.

All toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (CTC) version 2.0, except for neurotoxicity (Table 1). Re-treatment at the start of each cycle required adequate hematologic function (absolute neutrophil count $\geq 1,500/\mu\text{L}$ and platelets $\geq 100,000/\mu\text{L}$) and resolution of all toxicities to CTC \leq grade 2.

During treatment, dose modifications for dermatitis, diarrhea, and myelosuppression were carried out as listed in Table 2. Daily gefitinib was continued if initiation of chemotherapy for the next cycle of treatment was delayed due to myelosuppression. Toxicity definitions and oxaliplatin dose modifications for neurotoxicity are outlined in Table 1. All treatment was withheld for toxicity CTC \geq grade 3 until resolution to CTC \leq grade 2, then treatment was restarted with the appropriate dose modification.

Treatment was continued until development of progressive disease or unacceptable toxicity, withdrawal of patient consent, or decision to perform surgical resection of disease.

Evaluation

Baseline tumor measurements by computed tomography were obtained within 28 days before study treatment was started. Physical examination, including medical history, laboratory studies, and assessment of performance status, were conducted at the beginning of each 2-week cycle. Patients were asked to keep a diary of daily gefitinib ingestion and record their experience of nausea and diarrhea.

Tumor response was evaluated approximately every 8 weeks by computed tomography imaging and tumor measurement performed using Response Evaluation Criteria in Solid Tumors Group criteria.²⁶ A response was defined as a reduction of $\geq 30\%$ in the sum of the longest diameters of all measured lesions, confirmed on a subsequent scan performed at least 4 weeks after the initial scan documenting the reduction.

Statistical Analysis

The primary end point of the study was to determine the objective response rate for patients with metastatic CRC treated with this study regimen. Secondary end points included determination of the safety profile of this regimen and determination of median event-free survival (EFS) and overall survival (OS) times.

Table 1. Oxaliplatin Dose Modification Guidelines for Neurologic Toxicity

Toxicity	Duration of Toxicity		Persistent* Between Cycles
	1-7 Days	> 7 Days	
Paresthesias/dysesthesias† of short duration that resolve and do not interfere with function (grade 1)	No change	No change	No change
Paresthesias/dysesthesias† interfering with function, but not ADL (grade 2)	No change	No change	↓ to 65 mg/m ²
Paresthesias/dysesthesias† with pain or with functional impairment that also interfere with ADL (grade 3)	First time, ↓ to 65 mg/m ² ; second time, ↓ to 40 mg/m ²	First time, ↓ to 65 mg/m ² ; second time, ↓ to 40 mg/m ²	Stop
Persistent paresthesias/dysesthesias† that are disabling or life-threatening (grade 4)	Stop	Stop	Stop
Pharyngolaryngeal dysesthesias	No change	Duration of infusion to 6 hours	Duration of infusion to 6 hours

Abbreviation: ADL, activities of daily living.
 *Not resolved by the beginning of the next cycle.
 †May be cold induced.

EFS was defined as the interval of time from enrollment onto this study to the occurrence of the first event. In this study, an event was defined as death, any evidence of disease progression, withdrawal from study treatment because of toxicity, or proceeding to surgical resection or radiofrequency ablation of residual disease. The OS time was calculated as the interval of time from enrollment until the date of death as a result of any cause or until the date of the last follow-up, at which time the data were censored. Both the EFS and OS times were estimated by the Kaplan-Meier method.

To calculate the proposed sample size, we used the baseline response rate of 10% seen with FOLFOX-4 in the second-line setting as our null hypothesis. To detect a 20% improvement in response rate (10% v 30%) with the proposed regimen, with an $\alpha = .10$ and $\beta = .10$, we estimated accrual to be 35 patients in a two-stage design.²⁷ Because the response rate was slightly higher than expected (33% v 30%) and referral of patients declined because of the introduction of oxaliplatin in first-line regimens, the study was closed after the accrual of 27 patients.

RESULTS

Baseline Characteristics

Between April 2002 and May 2004, 27 patients were enrolled onto this study. Although two patients discontin-

ued chemotherapy before completion of two cycles and were lost to follow-up for nonmedical reasons, all 27 patients enrolled are included in the toxicity and efficacy analyses, on the basis of intention to treat. The baseline characteristics of the 27 assessable patients are listed in Table 3. All patients had an ECOG performance status of ≤ 1 , with 78% ECOG performance status of 0. The proportions of patients receiving one, two, or three prior therapies were similar, and 74% of patients (20 of 27) had received irinotecan. The median duration of first-line irinotecan-based treatment was 6 months and the majority of patients (15 of 20; 75%) showed evidence of progressive disease while receiving treatment.

Treatment Administration

The total number of cycles administered was 195, with a median of six cycles per patient (range, 1 to 15 cycles), and a mean of 7.2 cycles per patient.

Efficacy

The primary efficacy end point for this study was objective response rate. By intent-to-treat analysis, nine of 27 patients (33%) experienced a partial response, whereas another 12 of 27 (44%) had stable disease for at least four

Table 2. Dose Modification Guidelines for the IFOX Regimen

Toxicity	First	Second	Third	Fourth
Dermatitis \geq CTC grade 3	Reduce gefitinib to 250 mg PO daily	Discontinue gefitinib		
Diarrhea \geq CTC grade 3 refractory to oral antidiarrheal medication	Reduce FU bolus and infusion by 20%	Reduce gefitinib to 250 mg PO daily	Reduce oxaliplatin by 20%	Withdraw patient from study
Nadir ANC \leq 500/ μ L or nadir platelet \leq 50,000/ μ L	Reduce oxaliplatin by 20%	Reduce FU bolus and infusion by 20%	Further reduce oxaliplatin by 20%	Reduce FU or oxaliplatin at investigator discretion

Abbreviations: IFOX, gefitinib, fluorouracil, leucovorin, and oxaliplatin regimen; CTC, Common Toxicity Criteria; PO, orally; FU, fluorouracil; ANC, absolute neutrophil count.

Table 3. Baseline Characteristics of Patients

Characteristic	No. of Patients	% (n = 27)
Age, years		
Median	57	
Range	37-79	
Sex		
Male	10	37
Female	17	63
Race		
White	17	63
Asian	7	26
Black	1	3.7
Hispanic	1	3.7
Native American	1	3.7
Performance status (ECOG)		
0	21	78
1	6	22
Number of prior therapies		
1	8	30
2	12	44
3	7	26
Prior irinotecan therapy	20	74

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

cycles (Table 4). When we consider only the 25 patients who were evaluated for response, 36% experienced a partial response, whereas another 48% had stable disease. For the 20 patients previously receiving irinotecan-based chemotherapy, the response rates were 30% partial responses and 45% stable disease. Response rates did not differ on the basis of the number of prior regimens the patients received.

The secondary efficacy end points were EFS and OS. The median EFS in this study was 5.4 months (95% CI, 4.0 to 5.8 months). Of the 27 patients, IFOX was stopped after six to 12 cycles in two patients (7%) with responding disease and two patients (7%) with stable disease to attempt definitive treatment with surgical resection or radiofrequency ablation of residual metastases (Table 5). Fifteen patients (56%) were taken off study treatment because of progressive disease, and six patients (22%) were taken off because of toxicity. For all 27 patients, median time to disease progression, including the four patients who discontinued IFOX to receive surgical resection or radioablation for re-

Table 4. Antitumor Response Rates to IFOX Therapy

Response	All Patients (n = 27)		Patients Receiving Prior Irinotecan (n = 20)	
	No.	%	No.	%
Partial remission	9	33	6	30
Stable disease	12	44	9	45
Progressive disease	6	22	3	25

Table 5. Events Leading to Discontinuation of Study Treatment

Event	No. of Patients	%
Surgery/RFA	4	15
Progressive disease	15	56
Toxicity	8	29

Abbreviation: RFA, radiofrequency ablation.

sidual metastases, was 8.0 months. The median OS for all assessable patients was 12.0 months (95% CI, 9.6 to 22.1 months; Fig 1). Survival analysis was also performed excluding the two patients who had surgical resection of their metastatic lesion after experiencing stable disease during treatment with IFOX. This was done to evaluate whether these two patients, who were likely in a more favorable category than the rest of the study population by virtue of their resectable disease at enrollment, significantly influenced the results. For the 25 patients in this secondary analysis, the EFS was unchanged at 5.4 months (95% CI, 3.4 to 5.8 months) and the OS was 11.1 months (95% CI, 8.8 to 20.6 months). The two survival curves were not significantly different ($P = .8$).

Toxicities

The toxicities of the study regimen were evaluated as a secondary end point of this study. The initial safety profile and maximum-tolerated dose of IFOX were previously established in a phase I study.²⁴ This study provides additional information on toxicities encountered with this regimen (Table 6). In this study, 48% of patients experienced grade 3 or 4 neutropenia and/or diarrhea at some point in the treatment course. Patients older than age 60 had more myelosuppression, with 88% experiencing grade 3 or 4 neutropenia compared with 32% of patients younger than 60 years ($P = .004$).

Additional toxicities included grade 2 dermatitis or dry skin attributable to gefitinib in 16 patients (59%), and grade 2 peripheral neuropathy attributable to oxaliplatin in three

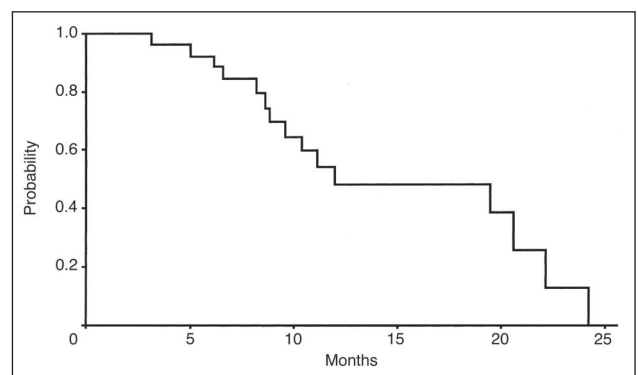
**Fig 1.** Kaplan-Meier curve of overall survival for all patients (median, 12.0 months; 95% CI, 9.6 to 22.1 months).

Table 6. Grade 3 or 4 Adverse Events Related to Treatment

Adverse Event	All Patients (n = 27)		Patients Older Than 60 Years (n = 8)	
	No.	%	No.	%
Neutropenia	13	48	7	88
Diarrhea	13	48	4	50
Nausea	6	22	1	13
Vomiting	4	15		
Dehydration	3	11	1	13
Hypokalemia	3	11	2	25
Increase in aminotransferases	3	11		
Fatigue	3	11	2	25
Infection	2	7		
Anemia	2	7	2	25
Thrombocytopenia	1	4		
Anorexia	1	4	1	13
Ileus	1	4		
Hand-foot syndrome	1	4		
Abdominal pain	1	4		

patients (11%). A greater number of patients experienced toxicity in cycles 2 and 3 (FOLFOX with gefitinib) than in cycle 1 (FOLFOX alone). The most significant differences were observed for myelosuppression, diarrhea, and dermatitis, as listed in Table 7.

A total of 17 patients (63%) underwent at least one dose reduction of oxaliplatin (Table 8) because of grade 3 or 4 neutropenia (29%), grade 3 nausea or vomiting (18%), grade 2 peripheral neuropathy (18%), or grade 2 increase in aminotransferases. Thirteen patients (48%) underwent a dose reduction of FU because of grade 3 diarrhea (85%), grade 3 hand-foot syndrome (8%), or grade 4 neutropenia (8%). Six patients (22%) underwent a dose reduction of gefitinib because of grade 3 diarrhea (50%) or grade 2 dermatitis or dry skin (50%).

One patient was removed from the study because of the development of asymptomatic interstitial pneumonitis after 12 cycles of treatment. Bronchoscopic washings and blood studies were negative for infectious etiologies of the pneumonitis, and the patient's radiographic abnormalities

improved after the discontinuation of IFOX therapy. The manifestations of this pneumonitis were consistent with a drug-induced toxicity, which has been described previously with gefitinib monotherapy.²⁸

DISCUSSION

The recent advent of several new agents for the treatment of metastatic CRC has markedly enhanced the therapeutic armamentarium for this disease. Oxaliplatin in combination with infusional FU in the FOLFOX-4 regimen has been shown to be effective in achieving an improved response and time to progression compared with FU/leucovorin in the second-line setting when progressive disease occurs after irinotecan-based regimens.⁵ The monoclonal antibodies cetuximab (which targets EGFR) and bevacizumab (which targets vascular endothelial growth factor) have also demonstrated therapeutic efficacy in CRC, and many studies to optimize their use in combination with chemotherapies are underway.

The high level of EGFR expression in CRC specimens has sparked great interest in using this target to develop more directed and specific therapies. To date, positive results with EGFR inhibition in CRC have only been reported for the monoclonal antibody cetuximab in combination with irinotecan-based regimens using bolus FU.¹⁴ The combination of EGFR inhibition with FOLFOX-4 is being investigated currently in a randomized phase III trial of FOLFOX chemotherapy with and without cetuximab. However, although cetuximab and gefitinib target the same cellular pathway, small-molecule inhibitors of EGFR have not yet been tested in combination with chemotherapy in CRC.

Despite preclinical evidence for chemotherapy sensitization of human tumor xenografts, four major randomized trials have shown no benefit for the addition of gefitinib or erlotinib to standard chemotherapy for non-small-cell lung cancer.^{20,21} Our data suggests that colorectal cancers differ substantially from non-small-cell lung cancers in the ability of EGFR inhibitors to enhance the effects of chemotherapy.

Table 7. Differences in Selected Adverse Events Between Cycle 1 and Cycles 2/3

Toxicity	No. of Patients Experiencing Toxicity					
	Cycle 1		Cycle 2		Cycle 3	
	No.	%	No.	%	No.	%
Any grade 3/4 toxicity	6	22	11	44	18	72
Neutropenia	2	7	7	28	4	16
Diarrhea	1	4	4	16	9	36
Nausea/vomiting	1	4	0	0	4	16
Grade 2 dermatitis	0	0	4	16	5	20

Table 8. Frequency and Cause of Drug Dose Reductions

Agent	Dose Reduction Required		Most Common Reasons for Dose Reduction			
	No. of Patients	%				
Oxaliplatin	17	63	Neutropenia (29%)	N/V (18%)	Neuropathy (18%)	AST/ALT (18%)
FU	13	48	Diarrhea (85%)	HFS (8%)	Neutropenia (8%)	
Gefitinib	6	22	Diarrhea (50%)	Dermatitis (50%)		

Abbreviations: N/V, nausea and vomiting; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FU, fluorouracil; HFS, hand-foot syndrome.

The response rate achieved in this study is encouraging compared with reported results with FOLFOX-4 alone in a similar setting, and suggests that gefitinib exerts a chemotherapy-sensitizing effect in CRC. This is consistent with the findings of a previous phase III trial using cetuximab, in which that EGFR inhibitor combined with irinotecan produced a 22% remission rate in patients with prior irinotecan resistance.¹⁴ The relative lack of single-agent activity of gefitinib in CRC also supports a chemotherapy-sensitizing role in this disease.

In this study we report on EFS as a secondary end point rather than time to progression because 44% of patients discontinued treatment because of a reason other than progressive disease. Four patients were taken off study with either stable or responding disease, so that surgical resection or radiofrequency ablation could be performed. These four patients remain without evidence of disease with a median follow-up of 12.3 months. The overall median time to progression in our study population was 8.0 months, when calculated regardless of any subsequent therapy after discontinuation from the study treatment. FOLFOX alone in the second-line setting was reported to result in a median time to progression of 4.6 months.⁵

As would be expected with combination therapy, certain toxicities were significantly increased compared with the published data from several studies using FOLFOX alone. Adverse events known to be increased by gefitinib from other phase I and II studies include diarrhea and skin changes (either acneiform rash or dry skin). Thus, grade 3 diarrhea was experienced in 48% of patients receiving our study treatment compared with 11% reported previously, suggesting an additive toxicity of gefitinib and FU on the lower GI tract.⁵ Grade 3 or 4 neutropenia was not enhanced compared with historical controls (48% for IFOX v 44% for FOLFOX alone). There was more myelosuppression in patients older than 60 years of age, with 88% developing grade

3 or 4 neutropenia at some point in their treatment course, suggesting that early, preemptive dose modification of oxaliplatin in this population may be warranted.

In this study, we also compared acute toxicities of IFOX and FOLFOX alone by withholding gefitinib until the second cycle of chemotherapy. There was an increase in neutropenia and diarrhea in cycles 2 and 3 (with gefitinib) as compared with cycle 1 (without gefitinib), but some of these changes are likely due to cumulative toxicities of oxaliplatin and FU, rather than additive toxicity of gefitinib.

In conclusion, this phase II study demonstrated that EGFR tyrosine kinase inhibition with gefitinib may enhance the antitumor efficacy of FOLFOX-4 chemotherapy in patients with previously treated metastatic CRC. This study adds to the growing body of evidence that inhibition of the EGFR pathway in CRC can sensitize some colorectal cancers to cytotoxic drugs and provide substantial benefits to patients.

With the increasing use of oxaliplatin-based regimens for first-line treatment because of the demonstrated improved efficacy of FOLFOX compared with IFL, additional investigation of EGFR inhibition in this setting is warranted. To this end, we continue to accrue patients to a parallel study using IFOX for first-line therapy of metastatic CRC.

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Authors' Disclosures of Potential Conflicts of Interest

Although all authors have completed the disclosure declaration, the following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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REFERENCES

1. Saltz LB, Cox JV, Blanke C, et al: Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 343:905-914, 2000

2. Lokich JJ, Ahlgren JD, Gullo JJ, et al: A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: A Mid-Atlantic Oncology Program Study. *J Clin Oncol* 7:425-432, 1989

3. Falcone A, Ciani C, Pfanner E, et al: Continuous-infusion 5-fluorouracil in metastatic colorectal cancer patients pretreated with bolus 5-fluorouracil: Clinical evidence of incomplete cross-resistance. *Ann Oncol* 5:291-293, 1994

4. Maindrault-Goebel F, de Gramont A, Louvet C, et al: Evaluation of oxaliplatin dose intensity in bimonthly leucovorin and 48-hour 5-fluorouracil continuous infusion regimens (FOLFOX) in pretreated metastatic colorectal cancer: Oncology Multidisciplinary Research Group (GERCOR). *Ann Oncol* 11:1477-1483, 2000

5. Rothenberg ML, Oza AM, Bigelow RH, et al: Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: Interim results of a phase III trial. *J Clin Oncol* 21:2059-2069, 2003

6. Kawamoto T, Sato JD, Le A, et al: Biological effects in vitro of monoclonal antibodies to human epidermal growth factor receptors. *Mol Biol Med* 1:511-529, 1983

7. Masui H, Kawamoto T, Sato JD, et al: Growth inhibition of human tumor cells in athymic mice by anti-epidermal growth factor receptor monoclonal antibodies. *Cancer Res* 44:1002-1007, 1984

8. Yang XD, Jia XC, Corvalan JR, et al: Eradication of established tumors by a fully human monoclonal antibody to the epidermal growth factor receptor without concomitant chemotherapy. *Cancer Res* 15:1236-1243, 1999

9. Pollack VA, Savage DM, Baker DA, et al: Inhibition of epidermal growth factor receptor-associated tyrosine phosphorylation in human carcinomas with CP-358774: Dynamics of recep-

tor inhibition in situ and antitumor effects in athymic mice. *J Pharmacol Exp Ther* 291:739-748, 1999

10. Lichtner RB, Menrad A, Sommer A, et al: Signaling-inactive epidermal growth factor receptor/ligand complexes in intact carcinoma cells by quinazoline tyrosine kinase inhibitors. *Cancer Res* 61:5790-5795, 2001

11. Messa C, Russo F, Caruso MG, et al: EGF, TGF-alpha, and EGF-R in human colorectal adenocarcinoma. *Acta Oncol* 37:285-289, 1998

12. Porebska I, Harlozinska A, Bojarowski T: Expression of the tyrosine kinase activity growth factor receptors (EGFR, ERB B2, ERB B3) in colorectal adenocarcinomas and adenomas. *Tumour Biol* 21:105-115, 2000

13. Mayer A, Takimoto M, Fritz E, et al: The prognostic significance of proliferating cell nuclear antigen, epidermal growth factor receptor, and mdr gene expression in colorectal cancer. *Cancer* 71:2454-2460, 1993

14. Cunningham D, Humblet Y, Siena S, et al: Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 351:337-345, 2004

15. Ciardiello F, Caputo R, Bianco R, et al: Antitumor effect and potentiation of cytotoxic drugs activity in human cancer cells by ZD-1839 (Iressa), an epidermal growth factor receptor-selective tyrosine kinase inhibitor. *Clin Cancer Res* 6:2053-2063, 2000

16. Sirotnak FM, Zakowski MF, Miller VA, et al: Efficacy of cytotoxic agents against human tumor xenografts is markedly enhanced by coadministration of ZD1839 (Iressa), an inhibitor of EGFR tyrosine kinase. *Clin Cancer Res* 6:4885-4892, 2000

17. Prewett MC, Hooper AT, Bassi R, et al: Enhanced antitumor activity of anti-epidermal growth factor receptor monoclonal antibody IMC-C225 in combination with irinotecan (CPT-11) against human colorectal tumor xenografts. *Clin Cancer Res* 8:994-1003, 2002

18. Herbst RS, Maddox AM, Rothenberg ML, et al: Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non-small-cell lung cancer and other solid tumors: Results of a phase I trial. *J Clin Oncol* 20:3815-3825, 2002

19. Kris MG, Natale RB, Herbst RS, et al: Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: A randomized trial. *JAMA* 290:2149-2158, 2003

20. Giaccone G, Herbst RS, Manegold C, et al: Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: A phase III trial—INTACT 1. *J Clin Oncol* 22:777-784, 2004

21. Herbst RS, Giaccone G, Schiller JH, et al: Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: A phase III trial—INTACT 2. *J Clin Oncol* 22:785-794, 2004

22. Cohen EE, Rosen F, Stadler WM, et al: Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol* 21:1980-1987, 2003

23. 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* 20:4292-4302, 2002

24. Cho CD, Fisher GA, Halsey J, et al: Phase I study of gefitinib, oxaliplatin, 5-fluorouracil, and leucovorin (IFOX) in patients with advanced solid malignancies. *Invest New Drugs*, in press

25. Andre T, Bensmaine MA, Louvet C, et al: Multicenter phase II study of bimonthly high-dose leucovorin, fluorouracil infusion, and oxaliplatin for metastatic colorectal cancer resistant to the same leucovorin and fluorouracil regimen. *J Clin Oncol* 17:3560-3568, 1999

26. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 92:205-216, 2000

27. Simon R: Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 10:1-10, 1989

28. Inoue A, Saijo Y, Maemondo M, et al: Severe acute interstitial pneumonia and gefitinib. *Lancet* 361:137-139, 2003