Original Article

Panitumumab in Combination With Infusional Oxaliplatin and Oral Capecitabine for Conversion Therapy in Patients With Colon Cancer and Advanced Liver Metastases

The MetaPan Study

Francesco Leone, MD[1]; Salvatore Artale, MD[2]; Donatella Marino, MD[1]; Celeste Cagnazzo, PhD[1]; Stefano Cascinu, MD[3]; Carmine Pinto, MD[4]; Giuseppe Fornarini, MD[5]; Marco Tampellini, MD[6]; Francesca Di Fabio, MD[4]; Andrea Sartore-Bianchi, MD[2]; Luciano De Carlis, MD[2]; Raffaele Pugliese, MD[2]; Lorenzo Capussotti, MD[7]; Luisa Gioeni, PhD[1]; Salvatore Siena, MD[2]; and Massimo Aglietta, MD[1]

BACKGROUND: Preoperative chemotherapy improves the outcome in patients with colorectal cancer with liver metastases. In the current study, the authors evaluated the activity of a conversion treatment with the combination of capecitabine plus oxaliplatin (XELOX) used in association with panitumumab in patients with unresectable, liver-only, metastatic colon cancer. **METHODS:** Chemotherapy-naive patients with unresectable liver metastases from colon cancer with no other metastatic disease sites were enrolled. All patients received upfront therapy with XELOX plus panitumumab (P-XELOX) and were reevaluated for resectability every 4 cycles. The primary endpoint was the objective response rate (ORR). Secondary endpoints were overall survival (OS), progression-free survival, the percentage of patients whose disease became radically resectable, and the safety of the P-XELOX combination. **RESULTS:** A total of 49 patients were recruited, 35 of whom had wild-type KRAS (wtKRAS) and 14 of whom (who were enrolled before study amendment) had unknown (9 patients) or mutated (5 patients) KRAS mutational status. Forty-six patients were evaluable for response. After conversion P-XELOX therapy, the ORR in the general population was 54%, with 2 complete responses, 23 partial responses, and 14 cases of stable disease. In patients with wtKRAS, the ORR of the patients reached 65% (2 CRs and 19 PRs), which allowed 15 patients with initial unresectable liver metastasis to be reclassified as having resectable disease. Survival analysis demonstrated a median progression-free survival of 8.5 months and a median OS of 21.9 months. Patients who underwent surgery were found to have a significantly better OS when compared with those who did not undergo surgery ($P < .001$). Overall, toxicities were found to be predictable and manageable, with the most common being cutaneous, gastrointestinal, and neurologic toxicities. **CONCLUSIONS:** Conversion P-XELOX therapy yields high response and resectability rates for patients with metastatic colon cancer with extensive liver involvement. ***Cancer*** **2013;119:3429-35**. © *2013 American Cancer Society.*

KEYWORDS: colon cancer; liver metastasis; liver resection; panitumumab; capecitabine plus oxaliplatin (XELOX) chemotherapy.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide, with up to 1 million new cases diagnosed each year.[1] The standard treatment for metastatic disease involves chemotherapy based on fluoropyrimidines, oxaliplatin, and irinotecan (used in combination and sequentially), and monoclonal antibodies targeting vascular endothelial growth factor and epidermal growth factor receptor (EGFR).[2-7]

In selected patients, surgery can be included in the treatment plan for metastatic CRC (mCRC); in particular, the resection of hepatic metastases improves progression-free survival (PFS) and offers the chance for cure in approximately 10% to 20% of patients.[8,9] In patients with extensive metastatic involvement of the liver, neoadjuvant chemotherapy can result in tumor downsizing and lead to the reclassification of a percentage of patients considered to be unresectable to

Corresponding author: Francesco Leone, MD, Department of Medical Oncology, Piemonte Oncology Foundation, IRCC-Candiolo, Strada provinciale 142, km 3.95, 10060 Candiolo (TO) Italy; Fax: (011) 39 011 9933299; francesco.leone@ircc.it

[1]Department of Medical Oncology, Piemonte Oncology Foundation, IRCC-Candiolo, Candiolo, Italy; [2]Department of Oncology, Surgery, and Transplant, Niguarda Ca' Granda Hospital, Milan, Italy; [3]Medical Oncology Services, Riuniti Umberto I University Medical Center, Ancona, Italy; [4]UOC Medical Oncology Services, Azienda University Medical Center, S.Orsola-Malpighi Hospital, Bologna, Italy; [5]Medical Oncology Surgery Unit, A.O. U. San Martino Hospital, Genoa, Italy; [6]Department of Medical Oncology, San Luigi Gonzaga Hospital, Orbassano, Italy; [7]Department of Hepatobiliary and Digestive Surgery, Mauriziano Hospital, Torino, Italy

We would like to thank Radhika Srinivasan, PhD, for the extensive revision of the article.

DOI: 10.1002/cncr.28223, **Received:** February 18, 2013; **Revised:** April 23, 2013; **Accepted:** April 29, 2013, **Published online** July 18, 2013 in Wiley Online Library (wileyonlinelibrary.com)

resectable. However, the classification of liver metastases into clearly resectable, potentially resectable, or definitely unresectable is influenced by several variables, such as surgeon experience and innovative radiological and surgical techniques. Therefore, the criteria for defining resectability often differ in clinical studies and, as a consequence, the percentage of inoperable patients who undergo radical resection after frontline chemotherapy varies between 13% and 40%.[10-12] The optimization of the preoperative regimens is critical to the success of the curative strategy. In fact, a strong relationship between objective tumor response rate (ORR) and resection rates has been documented in patients with mCRC.[13]

A previous report has demonstrated that for patients with liver metastases who are refractory to conventional chemotherapy, combination therapy with cetuximab(Erbitux; ImClone LLC a wholly-owned subsidiary of Eli Lilly and Company, Branchburg, NJ) increases resectability rates.[14] In a phase 2 trial of cetuximab in combination with 5-fluorouracil and oxaliplatin as the first-line treatment of patients with mCRC, an ORR of 79% was reportedly obtained.[15]

Panitumumab (Vectibix; Amgen-Dompe, Milan, Italy) is a fully human antibody that binds to EGFR and prevents receptor dimerization, tyrosine autophosphorylation of EGFR, and the activation of downstream signaling molecules.[16] To our knowledge, the impact of panitumumab as a part of a conversion therapy in the metastatic setting has not been investigated to date.

We conducted this prospective, phase 2, multicenter study to investigate the activity, in terms of ORRs and conversion to resectable status, of the combination of panitumumab and capecitabine plus oxaliplatin (XELOX) chemotherapy (P-XELOX) in patients with colon cancer (CC) and synchronous unresectable liver metastases.

MATERIALS AND METHODS

Eligible patients had histologically confirmed metastatic, unresectable CC with liver involvement with or without involved perivisceral lymph nodes. Only patients with synchronous metastatic disease were enrolled to minimize the impact of previous adjuvant chemotherapy and to ensure a more homogenous population. Subjects with rectal cancer diagnosed within 12 cm from the anal verge were excluded because of the different therapeutic approach that is required in these cases.

Since November 2008, after it was discovered that wild-type KRAS (wtKRAS) was required for the clinical activity of panitumumab in patients with metastatic CC (mCC),[17] only patients bearing wtKRAS on codon 12 and 13 of exon 1 were included in the current study.

Liver metastases were considered unresectable in the simultaneous presence of multiple and bilateral lesions, with $< 50\%$ of the remnant healthy liver, specifically defined as > 3 liver metastases with $> 50\%$ hepatic involvement and requiring a major hepatectomy with contralateral wedge resection. In addition, any metastasis requiring resection that did not preserve at least 2 contiguous hepatic segments or adequate vascular inflow and outflow as well as biliary drainage was considered unresectable.

Other inclusion criteria were a minimum age of 18 years and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2. In addition, adequate hematologic, hepatic, and renal function were required.

Patients with extrahepatic metastasis, other than that of regional lymph nodes, were excluded.

The protocol was approved by the Institutional Review Boards at each participating institution and the study was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Treatment and Assessment

All patients received panitumumab administered by intravenous infusion at a dose of 9 mg/kg once every 3 weeks, in combination with oxaliplatin at a dose of 130 mg/m^2 on day 1 and capecitabine at a dose of 1000 mg/m^2 twice daily from days 1 to 14. Dose reductions or delays for both panitumumab and chemotherapy were provided in cases of toxicity according to the study protocol.

After 4 cycles of chemotherapy, patients were evaluated for tumor response. Those who experienced stable disease (SD) or a partial response (PR) but were still considered unresectable after the first course of therapy received a second course of treatment (4 cycles) and a surgical reevaluation. In the case of a complete response (CR), patients continued chemotherapy for 8 cycles.

Patients who were considered eligible for surgery after treatment proceeded to undergo curative metastasectomy and received 4 additional postoperative cycles of P-XELOX chemotherapy.

Tumor response was assessed using modified Response Evaluation Criteria in Solid Tumors (m-RECIST). At baseline, computed tomography scans of the chest, abdomen, and pelvis, along with appropriate imaging of all other disease sites, were evaluated.

Safety was assessed on the basis of reports of adverse events, laboratory test results, and vital sign measurements. Toxicities were graded using version 3.0 of the National Cancer Institute's Common Toxicity Criteria (NCI-CTC), with the exception of skin-related or nail-related toxicities, which were graded using NCI-CTC version 3.0 with modifications.

Statistical Analysis

This phase 2 trial was designed using a Fleming single-stage design to assess the ORR. The null hypothesis is that the ORR is $\leq 25\%$. The alternative hypothesis is that the ORR is $\geq 45\%$. Requiring a 90% power against the alternative hypothesis and using a 5% significance level, the 'Hearn method indicates that 54 patients with wtKRAS are required.[18] Thus, patients with wtKRAS tumors who were enrolled before the approval of the amended protocol version 3 of 30 (November 2008) were considered part of the sample.

Efficacy analyses were performed according to the intent-to-treat principle.

Both PFS and overall survival (OS) were estimated using the Kaplan-Meier method.

RESULTS

Baseline Characteristics

From November 2007 to January 2011, 49 patients were enrolled in 6 different centers in Italy. The baseline characteristics of the patients are summarized in Table 1. Data collection was censored in August 2011.

Since November 2008, the protocol has been amended and wtKRAS included as a selection criterion. KRAS mutational status was performed, wherever possible, for patients who had been included in the study before the protocol amendment. In 9 cases, the KRAS mutational status was unknown. Of the remaining patients, 35 were classified as having wtKRAS mutational status and 5 patients who were enrolled before the protocol amendment were classified as having mutated KRAS. The median age of the patients was 60 years (range, 37 years-76 years). All patients had a good PS defined as ECOG 0 (34 patients) or ECOG 1 (15 patients); no patients with ECOG 2 were enrolled, although this was permitted by inclusion criteria. In 28 cases, patients had undergone colon surgery before study enrollment.

The median follow-up was 16.6 months (range, 1.1 months-38.9 months).

All patients received at least 1 cycle of P-XELOX, with a median of 6.3 cycles (range, 1 cycle-12 cycles).

TABLE 1. Patient Characteristics at Baseline

Characteristic		No.	%
Age, y	Median (range)	60 (37-76)	
Sex	Male	40	81.6
	Female	9	18.4
ECOG PS	0	34	69.4
	1	15	30.6
	2	0	0
Surgery of primary tumor		28	57.1
	pT1/2	1	3.6
	pT3/4	27	96.4
	pN0	8	28.6
	pN1	8	28.6
	pN2	12	42.8
KRAS	Wild-type	35	71.4
	Mutated	5	10.2
	Unknown	9	18.4

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

Efficacy

The primary endpoint of the current study was ORR. All data were analyzed separately for the entire study population and for those patients who had wtKRAS disease. The results are shown in Table 2. Tumor response was assessed in 46 patients (32 with wtKRAS mutational status) as the best response achieved during the treatment plan, excluding responses achieved with surgery. An ORR was recorded in 54% of patients with 2 CRs and 23 PRs. Fourteen patients (30.4%) achieved SD and 7 (15.2%) developed progressive disease.

As expected, the results from patients with wtKRAS demonstrated a better outcome. The overall disease control rate for patients with wtKRAS mutational status was 87.5%, with 2 CRs, 19 PRs, and 7 cases of SD.

Fifteen patients, all of whom had wtKRAS tumors, underwent surgical resection of their liver metastasis: 10 patients after the first radiological assessment and 5 patients after the second. In 11 cases, a major hepatectomy, defined as a resection of ≥ 3 Couinaud segments, was performed. Ten patients received a median of 3.5 postoperative treatment cycles (range, 1 cycle-4 cycles).

TABLE 2. Response Rates

Response Rates Evaluable	Total Population (n = 49)			wtKRAS (n = 35)		
	No.	%	95% CI	No.	%	95% CI
Complete response	2	4.3	0-10.3	2	6.3	2.6-15.1
Partial response	23	50	35-65	19	59.4	41.4-77.4
Stable disease	14	30.4	16.6-44.2	7	21.9	6.7-37
Progressive disease	7	15.2	4.2-26	4	12.5	0-24.6
Total	46	93.8		32	91.4	

Abbreviations: 95% CI, 95% confidence interval; wt, wild-type.

TABLE 3. Approach Used and Outcome of Patients Treated With Liver Surgery

Patient No.	Previous Colon Surgery	Type of Liver Surgery	Margins	No. of Preoperative Cycles	No. of Postoperative Cycles	Site of Disease Recurrence	PFS, Months
1	Yes	Minor	R0	2	4	Lymph nodes	20.9
2	No	Major	UNK	8	0	Liver	7.4
3	No	Minor	R0	4	4	Lung and liver	11.3
4	No	Major	UNK	4	4	Liver	15
5	No	Major	R0	4	4	Lung	21
6	No	Major	UNK	7	0	Lymph nodes	8.3
7	No	Major	UNK	4	0	Liver	5.5
8	No	Minor	R0	5	3	Liver	10.1
9	No	Major	R0	4	3	Liver	13
10	No	Major	R2	8	0	Liver	9.2
11	No	Minor	R0	2	1	Lung	22.7
12	No	Major	R0	5	2	Liver	21.5
13	Yes	Major	R0	8	4	Lung and liver	14.7
14	Yes	Major	R0	4	0	Liver	16.7
15	Yes	Major	R0	6	2	Lung	13

Abbreviations: PFS, progression-free survival; UNK, unknown.

Among the patients who underwent surgery, R0 resection, defined as radical resection with histologically negative margins, was achieved in 10 of 15 patients. Colon surgery was performed at the same time as liver resection, if it had not been performed previously. No surgery-related deaths were recorded, nor were any second surgeries required due to complications. Details regarding the type of resection, number of perioperative chemotherapy cycles, and outcomes are shown in Table 3.

In the absence of radiologically visible disease, 2 patients with a radiological CR to chemotherapy did not proceed to liver resection.

Patients were evaluated for survival analysis; the median PFS in the entire population was 8.4 months (95% confidence interval, 6.8 months-9.9 months) and the median OS was 21.9 months (95% confidence interval, 13.3 months-30.6 months) (Fig. 1 Top and Bottom).

Patients who had undergone surgery for liver metastasis had a better survival outcome when compared with those who were treated only with palliative chemotherapy; the median PFS was 14.7 months for patients undergoing surgery and 7.3 months for unresected patients ($P = .079$). The median OS was not reached for resected patients and was 17.1 months for unresected patients ($P < .001$) (Fig. 2 Top and Bottom).

As expected, a survival benefit was noted for the wtKRAS subgroup when compared with those whose KRAS status was unknown or mutated ($P < .001$) (Fig. 3).

Safety

Adverse events that were noted are listed in Table 4. The most common toxicities reported were gastrointestinal, constitutional, cutaneous, and neurological. In particular, 25 patients experienced diarrhea, which reached grade 3 or higher in 10 cases. Nausea, vomiting, mucositis, and anorexia were reported in 23 patients, 7 patients, 8 patients, and 6 patients, respectively, but were generally of grade 1 to 2. Skin toxicity, mostly related to panitumumab, was commonly reported, occurring in up to 90% of patients; other forms of cutaneous toxicity that are typical of anti-EGFR agents were observed, in particular folliculitis (11 patients), pruritus (3 patients), conjunctivitis (5 patients), and ungual toxicity (3 patients).

The overall incidence of oxaliplatin-specific neuropathy was relevant (present in 30 patients), but was only reported as being serious (grade 3 or 4) in 3 patients. It is interesting to note that 7 patients had allergic reactions to oxaliplatin that required treatment interruption in 4 cases.

Overall, hematological toxicity was a minor event, with 6 cases of mild (grade 1 or 2) neutropenia and thrombocytopenia noted. No febrile neutropenia was reported.

All toxicities were managed with dose reduction or treatment interruption according to the study protocol. Twenty-one patients required dose reductions for panitumumab, and 22 patients for capecitabine and oxaliplatin.

Nearly 50% of patients received < 8 cycles of chemotherapy; 8 patients developed progressive disease before the second radiological reevaluation. Treatment interruption was due to adverse events in 7 patients or related to surgical procedures in 6 patients (inadequate recovery, timing of surgery, and investigator choice).

Other causes of treatment discontinuation were consent withdrawal, medical decision, and death unrelated to disease progression or treatment.

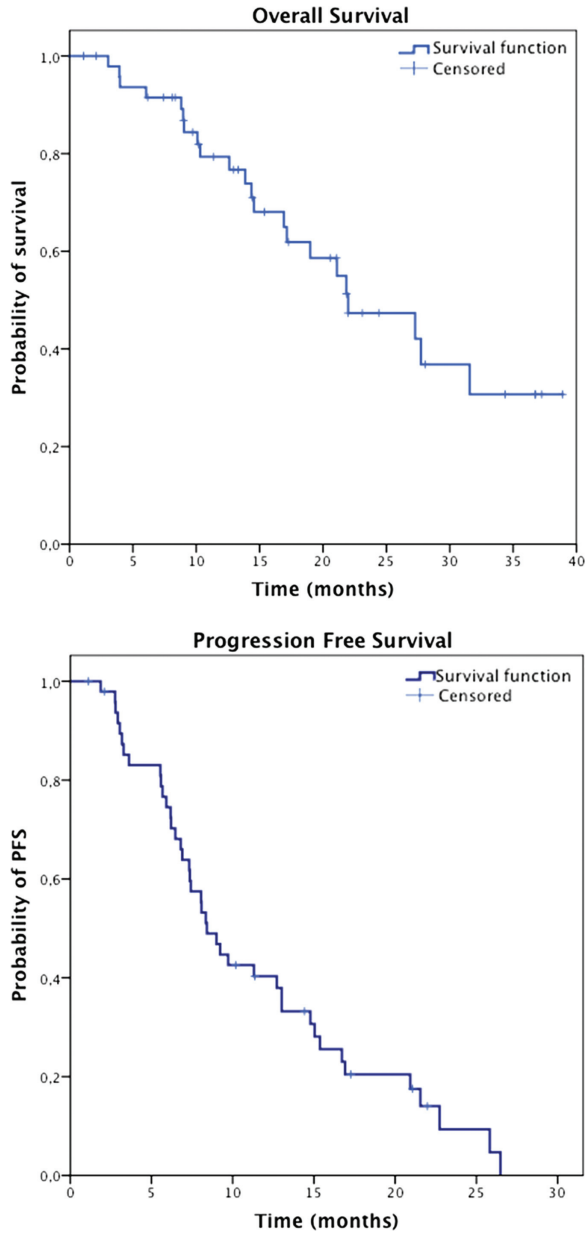

Figure 1. (*Top*) Overall survival and (*Bottom*) progression-free survival in the entire study population are shown.

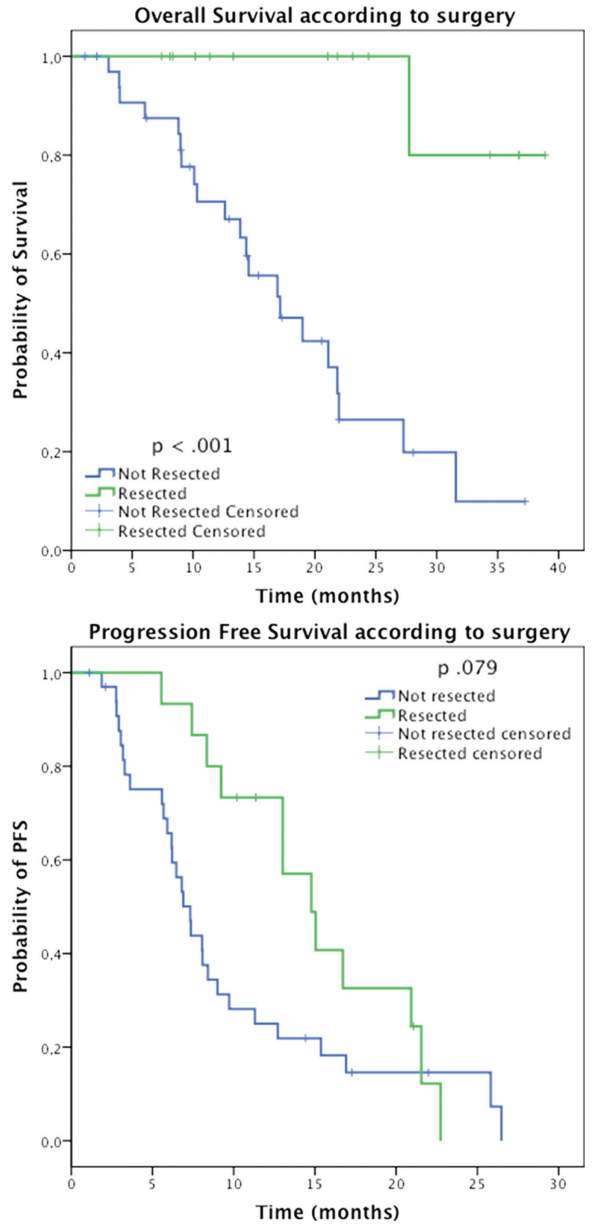

Figure 2. (*Top*) Overall survival and (*Bottom*) progression-free survival are shown in resected versus unresected patients.

DISCUSSION

To the best of our knowledge, the MetaPan study is, the first study of frontline treatment with the combination of a fluoropyrimidine, oxaliplatin, and panitumumab as neoadjuvant treatment in patients with liver-only, unresectable, synchronous mCC.

The role of anti-EGFR monoclonal antibodies in the induction of tumor shrinkage has become more defined, and currently this frontline treatment should preferably be performed in patients who might have a chance for resection. In patients with wtKRAS tumors, a high ORR is obtained using a treatment combining cetuximab with chemotherapy.[19-21] In particular, in the phase 2 randomized study of cetuximab plus FOLFOX or cetuximab plus FOLFIRI in the neoadjuvant treatment of nonresectable colorectal liver metastases (CELIM study), the ORRs were 68% and 57%, respectively, leading to a rate of R0 resection of 38%, and 30%, respectively, in patients with unresectable liver metastases.[19]

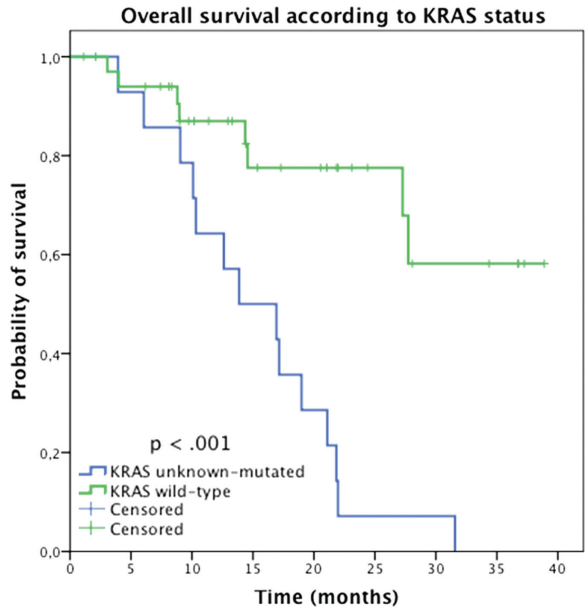

Figure 3. Overall survival in patients with wild-type KRAS versus those with unknown or mutated KRAS mutational status is shown.

TABLE 4. Adverse Events[a]

Adverse Event	Any Grade	Grade ≥3
Anorexia	6 (12.2 %)	2 (4.1 %)
Mucositis	8 (16.3 %)	0
Nausea	23 (46.9%)	3 (6.1 %)
Vomiting	7 (14.3 %)	1 (2 %)
Abdominal pain	5 (10.2 %)	0
Constipation	4 (8.2 %)	0
Diarrhea	25 (51 %)	10 (20.4 %)
Asthenia	29 (59.2 %)	6 (12.2 %)
Neutropenia	6 (12.2 %)	0
Thrombocytopenia	6 (12.2 %)	1 (2 %)
Ungual toxicity	3 (6.1 %)	0
Cutaneous toxicity	44 (89.8 %)	11 (22.4 %)
Folliculitis	10 (20.4 %)	1 (2 %)
Itch	3 (6.1 %)	0
Hepatic toxicity	5 (10.2 %)	0
Neurological toxicity	30 (61.2 %)	3 (6.1 %)
Conjunctivitis	5 (10.2 %)	0
Allergic reaction	7 (14.3 %)	3 (6.1 %)

[a] Toxicities were graded using version 3 of the National Cancer Institute's Common Toxicity Criteria (NCI-CTC), with the exception of skin-related or nail-related toxicities, which were graded using NCI-CTC version 3.0 with modifications.

A phase 3 randomized study demonstrated that panitumumab, in combination with FOLFOX4, improves the median PFS when compared with treatment with FOLFOX4 alone (9.6 months vs 8.0 months; $P = .02$) in previously untreated patients with mCRC.[22] In addition, a survival advantage was observed in association with FOLFIRI as a second-line treatment or used alone in patients with chemotherapy-refractory mCRC.[23,24]

It is difficult to compare our clinical results with those of other studies, mainly because of the different definitions of resectability. In fact, other studies[12,20,25] have considered the cutoff point of 5 liver metastases as the limit for defining resectability. However, the presence of large, multiple, or bilateral metastases is no longer considered an absolute contraindication to surgery, provided that radical resection is deemed possible. In the current study, a very strict definition of unresectable liver metastases was adopted to consider all enrolled patients as unequivocally excluded from upfront surgery. No upper limits to metastatic involvement were defined. Thus the population of patients with mCC enrolled in the current study included both patients potentially amenable to surgery once downsizing was obtained and those patients with unresectable disease independent of the degree of tumor shrinkage.

Consequently, it is not surprising that, unlike other studies of preoperative therapy, the rate of disease progression in the current study was 15%, and that in some cases a clinical progression anticipated the time of the first radiological evaluation. However, the P-XELOX combination resulted in a high ORR (54.3%) and an impressive rate of conversion from unresectable to resectable disease (30.6%). With regard to survival analysis, the results of 21.9 months for OS and 8.4 months for PFS are satisfactory if we consider the baseline characteristics of these patients. All patients had synchronous CC with major liver involvement, and were usually characterized as having a very poor prognosis.[8]

In patients who underwent surgery, the comparison between OS and PFS allowed us to support the use of surgery whenever feasible. Disease recurrence occurs after the first surgery in the majority of patients; however, these patients will most likely benefit from additional surgery or second-line chemotherapy.[26] This may explain why there was a statistically significant difference in the current study with regard to OS but not PFS between patients who did and those who did not undergo surgery.

Results according to KRAS mutational status appear to be clinically relevant. In the wtKRAS population, the ORR reached 65%, with a disease control rate of 87.5% and a conversion rate of 42.8%. However, given that this type of study did not include a comparison group, this observation suffers from selection biases, as do other noncomparative studies.

The small size of the population is a limiting factor of the current study. When it was designed, the role of KRAS mutational status as a predictive factor of response to anti-EGFR agents had not been clearly defined, and

therefore was not required for enrollment. After the discovery that wtKRAS status is required for the determination of panitumumab activity in patients with mCRC,[17] an amendment to the study protocol was made, adding wtKRAS status as an inclusion criterion. This had significant consequences on patient accrual: the time needed to determine the KRAS mutational status occasionally conflicted with the urgent need for treatment among some patients. For this reason, the accrual proceeded slowly and the preplanned number of subjects was not reached.

With regard to safety, no unexpected toxicities were recorded and the treatment was globally manageable with dose reductions. Although toxicity can never be underestimated, in patients with exclusive metastatic liver involvement in whom surgery may play a critical role, the results in terms of ORR justify the use of an aggressive upfront treatment.

The P-XELOX combination has proven to be a promising frontline treatment in patients with extensive liver involvement from CC and deserves further investigation.

FUNDING SUPPORT

All investigators acknowledge Amgen for funding support. This work was supported by grants from "Progetti di Ricerca Rete Oncologia Piemonte-Valle d'Aosta" and "Associazione Italiana Ricerca sul Cancro-AIRC 5X1000" and "Progetto Terapia Molecolare dei Tumori della Oncologia Ca' Granda Onlus (OCGO) Fondazione.

CONFLICT OF INTEREST DISCLOSURES

Dr. Sartore-Bianchi is a member of the board of Aventis and has acted as a member of the Speakers' Bureau for Bayer, Roche, and Amgen. Dr. Siena is a member of the boards of Amgen, Sanofi-Aventis, Roche, AstraZeneca, Merck, and Bayer, and has acted as a member of the Speakers' Bureau for Bayer and Amgen.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005;55:74-108.
2. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol.* 2004;22:229-237.
3. Rougier P, Van Cutsem E, Bajetta E, et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet.* 1998; 352:1407-1412.
4. Fuchs CS, Moore MR, Harker G, Villa L, Rinaldi D, Hecht JR. Phase III comparison of 2 irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. *J Clin Oncol.* 2003;21:807-814.
5. 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.
6. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med.* 2004;351:337-345.
7. Andre T, Louvet C, Maindrault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. GERCOR. *Eur J Cancer.* 1999;35:1343-1347.
8. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg.* 1999;230:309-318; discussion 318-321.
9. Vigano L, Russolillo N, Ferrero A, Langella S, Sperti E, Capussotti L. Evolution of long-term outcome of liver resection for colorectal metastases: analysis of actual 5-year survival rates over two decades. *Ann Surg Oncol.* 2012;19:2035-2044.
10. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg.* 2004;240:644-657; discussion 657-658.
11. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol.* 2007;25:1670-1676.
12. Wong R, Cunningham D, Barbachano Y, et al. A multicentre study of capecitabine, oxaliplatin plus bevacizumab as perioperative treatment of patients with poor-risk colorectal liver-only metastases not selected for upfront resection. *Ann Oncol.* 2011;22:2042-2048.
13. Folprecht G, Grothey A, Alberts S, Raab HR, Kohne CH. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol.* 2005;16:1311-1319.
14. Adam R, Aloia T, Levi F, et al. Hepatic resection after rescue cetuximab treatment for colorectal liver metastases previously refractory to conventional systemic therapy. *J Clin Oncol.* 2007;25:4593-4602.
15. Tabernero J, Van Cutsem E, Diaz-Rubio E, et al. Phase II trial of cetuximab in combination with fluorouracil, leucovorin, and oxaliplatin in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol.* 2007;25:5225-5232.
16. Foon KA, Yang XD, Weiner LM, et al. Preclinical and clinical evaluations of ABX-EGF, a fully human anti-epidermal growth factor receptor antibody. *Int J Radiat Oncol Biol Phys.* 2004;58:984-990.
17. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol.* 2008;26:1626-1634.
18. A'Hern RP. Sample size tables for exact single-stage phase II designs. *Statist Med* 2001;20:859-866.
19. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol.* 2010;11:38-47.
20. Garufi C, Torsello A, Tumolo S, et al. Cetuximab plus chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemotherapy in colorectal liver metastases: POCHER trial. *Br J Cancer.* 2010;103:1542-1547.
21. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med.* 2009;360:1408-1417.
22. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol.* 2010;28:4697-4705.
23. Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol.* 2010;28:4706-4713.
24. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol.* 2007;25:1658-1664.
25. Van Cutsem E, Lang I, Folprecht G, et al. Cetuximab plus FOLFIRI: final data from the CRYSTAL study on the association of KRAS and BRAF biomarker status with treatment outcome [abstract]. *J Clin Oncol.* 2010;28(suppl):Page. Abstract 3570.
26. Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol.* 2009;27:3677-3683.