

Bevacizumab, Capecitabine, and Oxaliplatin As Neoadjuvant Therapy for Patients With Potentially Curable Metastatic Colorectal Cancer

Brigit Gruenberger, Dietmar Tamandl, Johannes Schueller, Werner Scheithauer, Christoph Zielinski, Friedrich Herbst, and Thomas Gruenberger

From the Department of Oncology, Rudolfstiftung Hospital; the Department of Internal Medicine I and Cancer Center, Medical University of Vienna; and the Department of General Surgery, Medical University of Vienna, Vienna, Austria.

Submitted August 14, 2007; accepted December 3, 2007.

Presented in part at the 42nd Annual Meeting of the American Society of Clinical Oncology, Atlanta, GA, 2006; the 43rd Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 1-5, 2007; the 8th World Congress on Gastrointestinal Cancer, Barcelona, Spain, June 28 to July 1, 2006; and the 31st European Society of Medical Oncology Conference, Istanbul, Turkey, September 29 to October 2, 2006.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Thomas Gruenberger, MD, Department of General Surgery, Waehringer Guertel 18-20, 1090 Vienna, Austria; e-mail: thomas.gruenberger@meduniwien.ac.at.

© 2008 by American Society of Clinical Oncology

0732-183X/08/2611-1830/\$20.00

DOI: 10.1200/JCO.2007.13.7679

A B S T R A C T

Purpose

Patients with colorectal cancer (CRC) and liver metastases have a poor prognosis, but can benefit from perioperative chemotherapy and disease resection. Bevacizumab improves outcomes in patients with metastatic CRC; however, its impact on surgical complications and hepatic regeneration after liver resection remains to be determined.

Patients and Methods

Fifty-six patients with metastatic CRC with liver metastases potentially curable by resection were eligible for this single-center, nonrandomized phase II trial. Eligibility criteria defined patients at high risk of early recurrence. Patients received biweekly bevacizumab plus capecitabine and oxaliplatin for six cycles. The sixth cycle of therapy did not include bevacizumab, resulting in 5 weeks between the last administration of bevacizumab and surgery.

Results

Objective response to neoadjuvant chemotherapy was achieved in 41 patients (73%). Fifty-two patients underwent liver resection including 11 with synchronous primary tumor resection. No increased intraoperative bleeding events or wound-healing complications were observed and only three patients (6%) required perioperative blood transfusions. Further surgery was necessary in a single patient. Postoperative liver function and regeneration were normal in all but one patient. No postoperative mortality occurred and morbidity was encountered in 11 patients (20%). The mean length of postoperative hospitalization was 9 days (\pm 4.0).

Conclusion

These data suggest that bevacizumab can be safely administered until 5 weeks before liver resection in patients with metastatic CRC without increasing the rate of surgical or wound healing complications or severity of bleeding. To our knowledge, they are also the first to show that neoadjuvant bevacizumab does not affect liver regeneration after resection.

J Clin Oncol 26:1830-1835. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Colorectal cancer (CRC) is a leading cause of cancer death, with approximately 350,000 new cases reported annually in Europe and the United States.¹ Median survival of patients with metastatic CRC treated with best supportive care is approximately 6 months.² Palliative chemotherapy considerably improves treatment outcome, with fluorouracil (FU) plus irinotecan and/or oxaliplatin extending median overall survival to approximately 20 months.³⁻⁷ Furthermore, several phase II/III clinical trials in patients with metastatic CRC have demonstrated that the addition of the novel antiangiogenic agent bevacizumab (Avastin; Genentech, San Francisco, CA) to standard first-line FU-based chemotherapy regi-

mens improves overall survival, progression-free survival, and response rates compared with chemotherapy alone.⁸⁻¹⁰

The liver is the most common site of metastasis with 25% of patients presenting with liver metastases at diagnosis; an additional 25% to 45% develop liver metastases on disease recurrence. These patients have poor prognosis, despite advances in survival with chemotherapy. Surgical resection of liver metastases is considered the only curative treatment option for patients with resectable liver metastases and no extrahepatic disease^{11,12} and is now an accepted practice. The current 5-year survival rates after resection of liver metastases are 25% to 40%.^{13,14} Unfortunately, a large proportion of patients (approximately 80%) are considered to be

unresectable at presentation due to extrahepatic disease involvement or insufficient remaining healthy liver tissue.¹¹ In addition, approximately 50% of patients experience disease recurrence which is confined to the liver.¹⁵

To address this issue, there has been an increased use of chemotherapy before potentially curative surgery. The theoretical advantages of preoperative chemotherapy in patients who are initially resectable include the treatment of undetected distant microscopic metastases, thus reducing the risk of disease recurrence after resection.¹⁶⁻¹⁸ Neoadjuvant chemotherapy may also be useful to determine chemoresponsiveness of the tumor to help select the optimal adjuvant therapy, as well as identify patients with particularly aggressive disease in whom surgery would be inappropriate. Furthermore, neoadjuvant chemotherapy is being increasingly used to downsize colorectal liver metastases and render 10% to 30% of initially unresectable patients potentially resectable.¹⁹

Perioperative morbidity after neoadjuvant treatment of liver metastases is a major issue, especially in patients with resectable disease. However, in the recently presented final analysis of the European Organisation for the Research and Treatment of Cancer (EORTC) 40983 trial, postoperative morbidity was observed in 25% of patients in the neoadjuvant chemotherapy-treated group,²⁰ which is comparable to the rate of complications seen with liver resection alone.

Bevacizumab combined with FU-based chemotherapy improves all efficacy outcomes, including response rate, in the first-line metastatic setting and therefore would be expected to also allow a higher proportion of patients to become resectable. Furthermore, from its known mechanism of action,²¹ bevacizumab would also be expected to have an effect on dormant micrometastases, promoting tumor shrinkage and inhibition of angiogenesis. However, the effects of bevacizumab therapy in the neoadjuvant setting are relatively unknown.

We report the results of a single-center, nonrandomized, phase II study designed to determine the feasibility, perioperative complication rate (including blood transfusions), and potential impact on postoperative liver regeneration with neoadjuvant capecitabine and oxaliplatin (XELOX) plus bevacizumab in patients with potentially curable metastatic CRC.

PATIENTS AND METHODS

Patients

The trial enrolled patients with histologically confirmed resectable CRC liver metastases who were at high risk of early recurrence defined as one or more risk factors according to Fong et al.¹⁵ These risk factors included: synchronous liver metastases; metastatic disease developed within 1 year after primary resection; lymph node–positive primary tumors; more than one liver metastasis; a liver metastasis larger than 5 cm; and a positive carcinoembryonic antigen level. Patients were also required to have an Eastern Cooperative

Oncology Group (ECOG) performance status of 0 to 1, adequate bone marrow reserve, and adequate renal and hepatic function.

Exclusion criteria included prior chemotherapy for metastatic disease; prior history of bleeding diathesis or coagulopathy; clinical evidence of CNS metastases; history of thromboembolic or hemorrhagic events within 6 months before treatment; clinically significant cardiovascular disease. All patients provided written informed consent before study entry according to institutional regulations. The study was approved by our institutional review board.

Treatment

Eligible patients received bevacizumab 5 mg/kg administered by intravenous infusion and oxaliplatin was administered at 85 mg/m² over a 2-hour period; both agents were given on day 1 of a 2-week cycle. Capecitabine was administered orally at a dose of 1,750 mg/m² twice per day on days 1 through 7 of a 2-week cycle. Treatment was administered for six cycles, but the sixth cycle of therapy did not include bevacizumab (Fig 1).

Dose Adjustments

Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria (CTC) version 3.0. No dose modifications of bevacizumab were performed. If patients developed a grade 4 hematologic and/or grade 3 or higher nonhematologic adverse event, the dose of capecitabine and/or oxaliplatin was reduced by 25% for all subsequent cycles. In the case of persistent severe neurotoxicity, despite a 25% dose reduction, oxaliplatin was temporarily withdrawn, and maintenance therapy with capecitabine used until recovery. In patients who developed allergic reactions or laryngeal spasm syndrome, the duration of the oxaliplatin infusion was increased to 4 to 6 hours. Treatment was delayed for up to 2 weeks if the absolute neutrophil count was lower than 1,500/μL or the platelet count was lower than 100,000/μL. Subcutaneous erythropoietin was recommended for patients with hemoglobin lower than 10 g/dL. Patients who required more than 2 weeks recovery from an adverse reaction were excluded from this protocol.

Study Evaluations

Pretreatment evaluation included a complete medical history, physical examination, routine hematology and biochemistry analyses, and computed tomography (CT) scans of the thorax and abdomen to define the extent of disease. A multidisciplinary team of oncologists, liver surgeons, and radiologists confirmed that the patient was eligible for this single-center study. After the initial assessment, CBCs (including platelet and differential) and serum biochemistry analyses were obtained at least once every course of treatment. Carcinoembryonic antigen levels were assessed every 4 weeks. Subjective symptoms, physical examination results, performance status, and all adverse reactions were recorded before each treatment cycle according to the CTC.²² Tumor size was measured before and after the sixth cycle by CT scan or magnetic resonance imaging. Response rate was evaluated according to Response Evaluation Criteria in Solid Tumors by an independent radiologist.

Surgical Technique

Surgery was planned 2 weeks after the last dose of chemotherapy, resulting in a gap of 5 weeks between surgery and the last bevacizumab dose; patients must have recovered from any severe adverse effects of chemotherapy. Curative liver resection was obligatory, which included the resection of all liver metastases with a negative margin. Therapy with bevacizumab plus XELOX was restarted 5 weeks after surgery (after complete wound healing) for another six cycles (Fig 1).

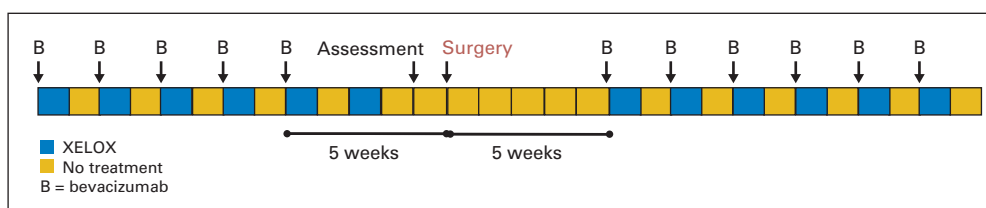


Fig 1. Treatment and surgery schedule. B, bevacizumab; XELOX, capecitabine and oxaliplatin.

Study End Points

The primary objective of this study was to assess the feasibility of bevacizumab therapy before surgery. Secondary end points included the evaluation of potential curative resection, hepatic regeneration, morbidity, and objective response rate. Efficacy and safety analyses were performed in all patients who received at least one dose of study drug.

Statistical Analysis

According to the design of this proof of concept study, the primary objective was to evaluate if the incidence of perioperative blood transfusions would not exceed an acceptable limit of 40%, based on our experience and the results of published studies.^{23,24} For a sample size of 50 patients (the number planned to be included), an incidence of events involving at least 13 patients (26%) would result in a 95% CI between 15% and 40%. A positive proof of concept result was accepted if the number of patients having bleeding events did not exceed 12 (24%), corresponding to a 95% CI of 13% to 38%.

RESULTS

From April 2005 to October 2006, 56 patients with CRC liver metastases potentially curable by resection (with or without primary in situ) were enrolled onto the study. Patient characteristics are listed in Table 1. The median age was 61.5 (standard deviation [SD] 10.5) years and the majority (89%) of the patients had ECOG performance status 0. In addition, a large proportion of patients had lymph-node-positive primary tumors (60.7%), synchronous liver metastases (60.7%), and bilobar liver metastases (51.8%).

Treatment Received

All patients received up to six cycles (median, 6; SD \pm 1.41) of preoperative therapy before CT assessment and potentially curative surgery. The median number of bevacizumab cycles was five (SD \pm 1.07). Twenty-five patients (45%) received full-dose chemotherapy

Parameter	No.
No. of patients	56
Median age, years (\pm SD)	61.5 (\pm 10.5)
Sex	
Male	32
%	24
Female	57
%	43
ECOG performance status	
0	50
%	89
1	6
%	11
Site of primary tumor, %	
Colon	75
Rectum	25
Patients with primary tumor resected, %	80
Distribution of liver metastases	
Synchronous	34
%	60.7
Bilobar	29
%	51.8

Abbreviations: SD, standard deviation; ECOG, Eastern Cooperative Oncology Group.

before surgery. Twenty-three patients (41%) had dose reductions, including 19 with a dose reduction of capecitabine (34%), two with a dose reduction of oxaliplatin (4%), and two with a dose reduction of both agents (4%). Of the remaining patients, one withdrew before the end of the study due to personal reasons (2%) and seven received fewer than six cycles of therapy due to toxicity (12%).

Safety

The combination of bevacizumab plus XELOX was relatively well tolerated (Table 2). The most common grade 3/4 nonhematologic and hematologic adverse events were diarrhea (33%), peripheral neuropathy (10%), and neutropenia (10%). A low incidence of rare, serious adverse events that may be associated with bevacizumab included thromboembolic events (7%), hypertension (3%), and gastrointestinal perforation (2%). No grade 3/4 proteinuria or bleeding were observed and there were no treatment-related deaths.

Efficacy

All patients were evaluated for tumor response before resection of metastases and pathologic responses were assessed during histological work-up (Table 3). A total of 41 patients responded (objective response rate, 73.2%); five patients had a complete pathologic response (8.9%) and 36 had a partial response (64.3%); an impressive tumor response is illustrated in Figure 2. An additional 12 patients (21.4%) had stable disease and the overall disease control rate was 94.6%. Only three patients (5.4%) experienced progression during neoadjuvant therapy.

Surgery

The median time from the last dose of bevacizumab and capecitabine to surgery was 5 and 2 weeks, respectively. Potentially curative surgery (R0, histologically confirmed) was performed in 52 of 56 patients. This included 41 patients who underwent liver resection only and 11 patients who had synchronous primary tumor and liver resection. Major hepatectomies (resection of three or more segments of the liver) were performed in 36% of patients.

Of the remaining four patients, liver resection was suspended in one patient due to extrahepatic disease discovered during laparotomy and three patients did not undergo surgery due to progressive disease. These three patients received an irinotecan-based second-line chemotherapy regimen.

Grade 3/4 Event*	No.	%
No. of patients	56	
Neutropenia	6	10
Anemia	2	3
Peripheral neuropathy	6	10
Diarrhea	19	33
Thromboembolic	4	7
Hand-foot syndrome	2	3
Hypertension	2	3
Gastrointestinal perforation	1	2

NOTE. National Cancer Institute Common Toxicity Criteria version 3.0 was used.

Table 3. Tumor Response After Perioperative Therapy

Response	Assessable Patients (n = 56)	
	No.	%
Complete pathologic	5	8.9
Partial	36	64.3
Stable disease	12	21.4
Disease control rate*	53	94.6
Progressive disease	3	5.4

*Complete pathologic response + partial response + stable disease.

Postoperative Morbidity and Mortality

The median length of postoperative hospitalization was 8.8 days (SD ± 4.0). No patients died during the study or experienced increased bleeding events or wound-healing complications. Only three patients (6%) required blood transfusions (one unit in two patients, two units in a patient undergoing a third liver resection). According to this number of bleeding events (95% CI, 1% to 17%), no increase of bleeding events could be observed. A total of 42 patients (79%) experienced no complications after surgery (Table 4). Complications observed in the remaining 11 patients included sepsis (n = 3; 6%) and hyperbilirubinemia (n = 2; 4%), just one patient required further surgery. To date, peri- and postoperative complications are consistent with previous studies evaluating chemotherapy alone.

Liver Regeneration

Postoperative liver function was assessed with routine blood tests (bilirubin, albumin, prothrombin time) and liver regeneration was assessed by CT scan 3 months after surgery. Normal function and regeneration were observed in 51 (98%) of 52 of the patients who underwent resection. Abnormal liver function/regeneration was observed in a single patient who experienced prolonged liver dysfunction due to steatohepatitis discovered during pathologic liver histology analysis.

Synchronous Resection Subgroup

Peri- and postoperative complications observed in the 11 patients who underwent synchronous resection are consistent with those patients who underwent liver resection only. None of the synchronous

Table 4. Complications After Liver Resection

Complication	No.	%
No complications	42	79
Complication	11	21
Anastomotic leak	1	2
Bile leak	1	2
Hyperbilirubinemia	2	4
Sepsis		
Positive blood count*	2	4
Intermittent renal failure†	1	2
Small bowel perforation (requiring re-operation)	1	2
Urinary tract infection	1	2
Wound hematoma	1	2
Wound infection	1	2

*Antibiotic treatment.
†Intensive care unit support.

resection patients experienced wound-healing or bleeding complications and no patient required perioperative blood transfusion. Only three patients experienced postoperative complications, which were single cases of wound infection, sepsis, and anastomotic leak. Similarly, the median length of hospitalization was 9.4 days (SD ± 3.5), which was consistent with the liver resection only patients.

DISCUSSION

Our data demonstrate that with appropriate management, preoperative bevacizumab can be used in combination with chemotherapy, with minimal risk of bleeding/wound-healing complications, in patients with metastatic CRC undergoing potentially curative liver resection. In patients who received bevacizumab until 5 weeks before liver resection, the rate of surgical (21% v 25%), wound healing (0% v 0%), or bleeding complications (0% v 3%) were not increased compared with historical data for chemotherapy alone.²⁰ In addition, a high objective response rate and disease control rate were observed in this study. This high level of efficacy may be due to the fact that only patients with metastatic CRC confined to the liver were included and all patients had a good performance status.

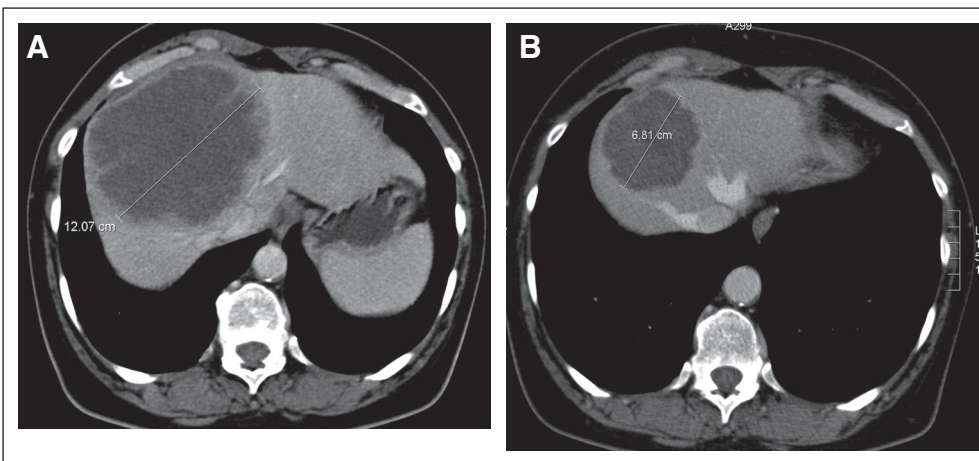


Fig 2. Tumor response (A) before and (B) after neoadjuvant treatment (post-therapy scan shown at a higher level illustrating the largest diameter of the remaining lesion).

The feasibility and effectiveness of preoperative bevacizumab and chemotherapy are supported by the results of the open-label, community setting trial of bevacizumab plus standard first-line chemotherapy (First BEAT). In this trial, surgery with curative intent was performed in 215 (11.2%) of 1,914 patients (R0 resection rate, 8.9%) who were considered to be unresectable at diagnosis of metastatic disease.²⁵ In addition, in a large subgroup of patients with metastatic disease confined exclusively to the liver and ECOG performance status 0 (n = 484), hepatic metastasectomy with curative intent was performed in 17.4% of patients, including 26.6% of patients receiving bevacizumab plus continuous oxaliplatin and FU (FOLFOX).²⁶

The toxicity profile of biweekly bevacizumab plus XELOX as used in our study indicates that the combination regimen was well tolerated. The incidence of hematologic adverse events was consistent with previous studies of bevacizumab plus XELOX.^{27,28} However, due to the reporting of grade 3/4 diarrhea in 33% of the patients, we decided to reduce the dose of capecitabine to 3,000 mg/m²/d in our currently ongoing multicenter study. Most patients (85%) received six cycles of therapy before surgery, including 45% without dose reduction. In addition, the observed low rate of adverse events associated with bevacizumab was effectively managed using standard therapy. Furthermore, a low rate of postsurgical morbidity and mortality was noted, including no perioperative deaths, severe bleeding events, or wound-healing complications. These data support previous neoadjuvant bevacizumab data, including First BEAT, where no increase in wound-healing complications or bleeding events were observed, compared with historical data for chemotherapy alone.²⁰ Moreover, single-institution retrospective data of 125 patients who underwent hepatic surgery showed that neoadjuvant bevacizumab plus chemotherapy did not increase the rate of any (49% v 43%; P = .51), hepatobiliary (5% v 11%; P = .20), or wound-healing complications (28% v 25%; P = .68) compared with neoadjuvant chemotherapy alone.²⁹

Bevacizumab is a potent inhibitor of VEGF activity, and thus it has been suggested that use of bevacizumab in the neoadjuvant setting could potentially impact on postsurgical wound healing and hepatic regeneration.^{16,21} Based on early clinical data/experience and the half-life of bevacizumab, it is currently recommended that, to avoid the potential of wound healing/bleeding complications, bevacizumab is suspended for at least 6 weeks before elective surgery; should not be reinitiated for at least 28 days after major surgery; and any surgical incisions should be completely healed.³⁰ Our data show that a gap of 5 weeks between bevacizumab therapy and liver resection does not increase the rate of complications in patients with metastatic CRC and should not prohibit or delay surgery. In addition, we provide the first clinical data to indicate that bevacizumab in combination with chemotherapy does not appear to affect liver regeneration after resection.

Patients with synchronous primary CRC and liver metastases have poor prognosis and may benefit from an aggressive treatment strategy of perioperative chemotherapy and resection of tumor sites.¹⁶ In this study, potentially curable resection was achieved in all patients with synchronous metastases, and similar to those who underwent liver resection only, no bleeding or wound-healing complications were observed in this subgroup. These data indicate that synchronous primary and liver metastases should not preclude potentially curative liver resection, if a response is achieved with neoadjuvant treatment.

The optimal neoadjuvant chemotherapy regimen has not been determined. There are few trials which have evaluated XELOX in the

neoadjuvant setting. Recent data from NO16966 showed that bevacizumab in combination with XELOX or FOLFOX allowed surgery with curative intent in 59 (6.1%, intent-to-treat population) of 699 patients and 34 (19.2%, liver metastases only) of 177 patients.¹⁰ Neoadjuvant therapy in this study appeared well tolerated and only one patient experienced pathologic hepatic toxicity, but further randomized trials are required to define the safety and efficacy profile of XELOX in this setting. The most common regimens combine fluoropyrimidines with oxaliplatin or irinotecan. These chemotherapy regimens, particularly FOLFOX, provide higher response rates and are therefore widely accepted as the most effective. However, accumulating data indicate that oxaliplatin- and irinotecan-based regimens are commonly associated with pathological hepatic toxicity, including steatohepatitis, which is characterized by inflammation of the liver with concurrent fat accumulation, which may compromise liver tolerance to resection.^{16,31} In addition, data suggest that chemotherapy induced hepatotoxicity increases with dose and/or number of treatment cycles. Therefore, the improved efficacy of bevacizumab combination therapy may result in a reduced dose of chemotherapy and/or number of treatment cycles required to achieve resectability.

Neoadjuvant therapy before potentially curative surgery will soon be recognized as new standard of care for patients with metastatic CRC and potentially resectable metastases, based on the final results of the randomized phase III EORTC 40983 trial that were recently presented by Nordlinger et al²⁰ at the Annual Meeting of the American Society of Clinical Oncology. This trial showed that perioperative chemotherapy followed by surgery and postoperative chemotherapy significantly improved 3-year progression-free survival in all eligible (36.2% v 28.1%; P = .041) and all resected patients (42.4% v 33.2%; P = .025) compared with surgery alone.

Our trial showed that bevacizumab plus XELOX allowed potentially curative resection in approximately 95% of patients and not a single patient experienced increased bleeding events or wound-healing complications. In conclusion, we and others have produced a wealth of data, in approximately 400 patients, which suggest that bevacizumab plus standard chemotherapy is a feasible, safe, and effective neoadjuvant regimen in patients with metastatic CRC and liver metastases undergoing potentially curative liver resection.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. 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.

Employment or Leadership Position: None **Consultant or Advisory Role:** Christoph Zielinski, F. Hoffmann-LaRoche Ltd (U) **Stock Ownership:** None **Honoraria:** Werner Scheithauer, F. Hoffmann-LaRoche Ltd; Christoph Zielinski, F. Hoffmann-LaRoche Ltd; Thomas Gruenberger, F. Hoffmann-LaRoche Ltd **Research Funding:** Werner Scheithauer, F. Hoffmann-LaRoche Ltd; Christoph Zielinski, F. Hoffmann-LaRoche Ltd; Thomas Gruenberger, F. Hoffmann-LaRoche Ltd **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Thomas Gruenberger
Administrative support: Johannes Schueller
Provision of study materials or patients: Johannes Schueller, Werner Scheithauer, Friedrich Herbst, Thomas Gruenberger

Collection and assembly of data: Brigit Gruenberger
Data analysis and interpretation: Brigit Gruenberger, Dietmar Tamandl, Thomas Gruenberger
Manuscript writing: Brigit Gruenberger
Final approval of manuscript: Brigit Gruenberger, Dietmar Tamandl, Johannes Schueller, Werner Scheithauer, Christoph Zielinski, Friedrich Herbst, Thomas Gruenberger

REFERENCES

- Boyle P, Leon ME: Epidemiology of colorectal cancer. *Br Med Bull* 64:1-25, 2002
- Scheithauer W, Rosen H, Kornek GV, et al: Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. *BMJ* 306:752-755, 1993
- Douillard J, Cunningham G, Roth A, et al: Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomised trial. *Lancet* 355:1041-1047, 2000
- Colucci G, Gebbia V, Paoletti G, et al: Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: A multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol* 23:4866-4875, 2005
- 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* 22:23-30, 2004
- Grothey A, Sargent D, Goldberg RM, et al: Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol* 22:1209-1214, 2004
- 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* 25:1670-1676, 2007
- Hurwitz H, Fehrenbacher L, Novotny W, et al: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for the treatment of metastatic colorectal cancer. *N Engl J Med* 350:2335-2342, 2004
- Kabbinavar FF, Schulz J, McCleod M, et al: Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: Results of a randomized phase II trial. *J Clin Oncol* 23:3697-3705, 2005
- Saltz L, Clarke S, Diaz-Rubio E, et al: Updated efficacy results from XELOX-1/NO16966, a randomised phase III trial in first-line metastatic colorectal cancer: Analysis of bevacizumab in combination with XELOX or FOLFOX-4. *Ann Oncol* 18:vii21, 2007 (suppl 7; abstr O-0032)
- Adam R: Chemotherapy and surgery: New perspectives on the treatment of unresectable liver metastases. *Ann Oncol* 14:ii13-ii16, 2003 (suppl 2)
- Van Cutsem E, Nordlinger B, Adam R, et al: Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. *Eur J Cancer* 42:2212-2221, 2006
- Choti MA, Sitzmann JV, Tiburi MF, et al: Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg* 235:759-766, 2002
- Fong Y, Cohen AM, Fortner JG, et al: Liver resection for colorectal metastases. *J Clin Oncol* 15:938-946, 1999
- Fong Y, Fortner J, Sun RL, et al: Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: Analysis of 1001 consecutive cases. *Ann Surg* 230:309-318, 1999
- Chong G, Cunningham D: Improving long-term outcomes for patients with liver metastases from colorectal cancer. *J Clin Oncol* 23:9063-9066, 2005
- Ellis LM, Curley SA, Grothey A: Surgical resection after downsizing of colorectal liver metastasis in the era of bevacizumab. *J Clin Oncol* 23:4853-4855, 2005
- Leichman L: Neoadjuvant chemotherapy for disseminated colorectal cancer: Changing the paradigm. *J Clin Oncol* 24:3817-3818, 2006
- Nordlinger B, Van Cutsem E, Rougier P, et al: Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group. *Eur J Cancer* 43:2037-2045, 2007
- Nordlinger B, Sorbye H, Collette L, et al: Final results of the EORTC Intergroup randomized phase III study 40983 [EPOC] evaluating the benefit of peri-operative FOLFOX4 chemotherapy for patients with potentially resectable colorectal cancer liver metastases. *J Clin Oncol* 25:2s, 2007 (suppl; abstr LBA5)
- Tobolem G: VEGF: A key therapeutic target for the treatment of cancer—insights into its role and pharmacological inhibition. *Targeted Oncology* 2:153-164, 2007
- MacDonald J, Haller D, Mayer R: Grading of toxicity, in MacDonald J, Haller D, Mayer R (eds): *Manual of Oncologic Therapeutics*. Philadelphia, PA, Lippincott, 1995, pp 519-523
- Karoui M, Penna C, Amin-Hashem M, et al: Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg* 243:1-7, 2006
- Tamandl D, Gruenberger B, Herberger B, et al: Selective resection of colorectal liver metastases. *Eur J Surg Oncol* 33:174-182, 2007
- Berry S, Cunningham D, Michael M, et al: Preliminary efficacy of bevacizumab with first-line FOLFOX, XELOX, FOLFIRI and fluoropyrimidines for mCRC: First BEAT. *Eur J Cancer Suppl* 5:241, 2007 (abstr 3020)
- Rivera F, Van Cutsem E, Kretzschmar A, et al: Preliminary efficacy of bevacizumab with first-line FOLFOX, XELOX, FOLFIRI and monotherapy for mCRC: First BEATrial. *Ann Oncol* 18:vii19, 2007 (suppl; abstr O-0025)
- Hochster HS, Hart L, Ramanathan RK, et al: Safety and efficacy of oxaliplatin/fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer (mCRC): final analysis of the TREE Study. *J Clin Oncol* 24:148s, 2006 (suppl; abstr 3510)
- Bendell JC, Fernando N, Morse M, et al: A phase II study of oxaliplatin (OX), capecitabine (CAP), and bevacizumab (BV) in the treatment of metastatic colorectal cancer. *J Clin Oncol* 24:156s, 2006 (suppl; abstr 3541)
- Kesmodel SB, Ellis LM, Lin E, et al: Complication rates following hepatic surgery in patients receiving neoadjuvant bevacizumab for colorectal cancer liver metastases. Presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium, Orlando, FL, January 19-21 2007
- Roche: Bevacizumab (Avastin) Summary of Product Characteristics. <http://www.roche.com>
- Nordlinger B, Benoist S: Benefits and risks of neoadjuvant therapy for liver metastases. *J Clin Oncol* 24:4954-4955, 2006