Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

August 2010 | A SPECIAL MEETING REVIEW EDITION | Volume 8, Issue 8, Supplement 15

Highlights in Colorectal Cancer Management From the American Society of Clinical Oncology (ASCO) Annual Meeting

June 4–8, 2010

Chicago, Illinois

Special Reporting on:

Management of Side Effects of the Treatment of Colorectal Cancer

Radiofrequency Ablation Combined With Chemotherapy for Unresectable Colorectal Liver Metastases

Treatment Outcome According to KRAS and BRAF Mutation Status in Metastatic Colorectal Cancer

PLUS Meeting Abstract Summaries

Management of Side Effects of the Treatment of Colorectal Cancer

In a session at the 2010 American Society of Clinical Oncology (ASCO) Annual Meeting chaired by Howard S. Hochster, MD, experts provided insight into the management of adverse events of colorectal cancer (CRC) treatments and reviewed efforts to reduce treatment toxicity. They focused on side effects from adjuvant management of rectal cancer, dermatologic toxicities of targeted therapy in CRC, and oxaliplatin-induced neurotoxicity.

ABSTRACT SUMMARY **Value of Plasma Carcinoembryonic Antigen Levels in Predicting Responses to Antiangiogenic Therapy in Metastatic Colorectal Cancer**

Carcinoembryonic antigen (CEA) is a glycosylated glycosylphosphatidylinositol -anchored cell surface protein used as a tumor marker in several cancer types. Dr. Kira Brämswig and coworkers analyzed the value of plasma CEA levels for predicting responses to antiangiogenic therapy with bevacizumab in patients with metastatic CRC (Abstract 3574). In this retrospective analysis, baseline CEA levels were correlated with response rate in 275 patients with metastatic CRC who received bevacizumab plus chemotherapy (149 patients); samples were analyzed from patients receiving cetuximab plus chemotherapy (126 patients) as a control. At baseline, CEA plasma levels were <5 ng/mL in 63 patients (22.9%), 6–30 ng/mL in 78 patients (28.4%), 31–100 ng/mL in 47 patients (17.1%), and >100 ng/mL in 87 patients (31.6%). The investigators reported a significant inverse correlation between baseline CEA plasma levels and therapeutic response in patients receiving bevacizumab (*P* value for trend <.001; odds ratio, 0.52; 95% CI, 0.36-0.74) but not cetuximab. Overall response rates ranged from 92.7% in patients with CEA levels <5 ng/mL to 80.4% with 6–30 ng/mL, 60.9% with 31–100 ng/mL, and 59.0% with >100 ng/mL. The researchers concluded that CEA may function as an angiogenesis-inducing protein in patients with cancer and that levels of CEA may predict efficacy of antiangiogenic therapy.

Managing Side Effects From Adjuvant Treatment of Rectal Cancer

Bruce D. Minsky, MD, began by discussing the side effects associated with adjuvant treatment for rectal cancer.[1] He explained that multiple variables influence the development of toxicity in patients undergoing pelvic radiation, including field size, treatment time, fraction size, energy, total dose, technique, sequence, and chemotherapy.

Most studies have shown a lower risk of side effects with preoperative versus postoperative therapy. In 2004, Sauer and colleagues showed that preoperative chemoradiotherapy, as compared with postoperative therapy, was associated with a lower risk of acute toxicity (27% vs 40%; *P*=.001) and chronic toxicity (14% vs 24%; *P*=.012).[2] However, the National Surgical Adjuvant Breast and Bowel Project trial R-03 of 254 patients showed a higher rate of grade 4 diarrhea with preoperative versus postoperative treatment (24% vs 13%).[3]

A recent retrospective review of patient-reported outcomes in 77 patients with rectal cancer showed that 30–77% of patients had adverse events of at least grade 3 in severity by week 5 of concurrent chemoradiation treatment.[4] Although these rates are higher than those generally reported in large trials, Dr. Minsky suggested that they better reflect what is seen in daily practice.

The type of chemotherapy and timing of treatment can affect toxicity. In the phase III ACCORD 12/0405 study, the addition of oxaliplatin to capecitabine for neoadjuvant chemoradiation provided no efficacy benefit but was associated with a significant increase in the risk of grade 3 or higher toxicity (25% vs 11%; *P*<.001).[5] The phase III STAR-01 (Studio Terapia Adiuvante Retto) trial, which evaluated preoperative chemoradiation with fluorouracil-based chemoradiation with or without oxaliplatin, confirmed this finding.[6]

In an attempt to reduce toxicity, Fernández-Martos and colleagues conducted a randomized phase II trial evaluating different sequences of treatment.[7] A total of 108 patients were randomly assigned to concomitant chemoradiotherapy followed by surgery and adjuvant chemotherapy or induction chemotherapy followed by concomitant chemoradiotherapy and surgery. Although induction chemotherapy was associated with a similar pathologic complete response rate as standard treatment (14% vs 13%), the rate of grade 3/4 toxicity was significantly lower (17% vs 51%; *P*=.00004), and significantly more patients were able to receive all 4 cycles (93% vs 51%; *P*=.0001).

New approaches being evaluated for reducing toxicity include intensity modulated radiation (IMRT) and radioprotectors. However, IMRT remains controversial and has technical challenges,[8] and randomized trials of radioprotectors have shown no benefit.

Dr. Minsky reviewed common treatments for patients who do develop side effects from pelvic radiation. For skin-related effects, a nongreasy, water-based ointment can be applied to the skin folds. For diarrhea, Dr. Minsky recommended loperamide as an initial treatment, with other options including diphenoxylate and atropine, and tincture of opium. For dysuria, Dr. Minsky recommended phenazopyridine, noting that bacterial and fungal infections should be ruled out. For proctitis, Dr. Minsky recommended initial treatment with acetaminophen, with alternatives including oxycodone and acetaminophen.

ABSTRACT SUMMARY **Skin Toxicity in Metastatic Colorectal Patients Taking FOLFOX4 With or Without Panitumumab**

Panitumumab is a fully human monoclonal antibody directed against EGFR. The agent is currently approved for use in patients with *KRAS* wild type metastatic CRC previously treated with chemotherapy. The PRIME (Panitumumab Randomized Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy) study was designed to evaluate the efficacy and safety of panitumumab added to FOLFOX4 in patients with previously untreated metastatic CRC. A total of 1,183 patients were randomized to panitumumab plus FOLFOX4 (n=593) or FOLFOX4 alone (n=590). Dr. Jean-Yves Douillard and colleagues analyzed data on panitumumab plus FOLFOX4 according to degree of skin toxicity (Abstract 3528). Overall, the incidence of panitumumab-associated grade 2–4 skin toxicity was 78% in patients with *KRAS* wild type tumors and 68% in patients with *KRAS*-mutated tumors. Compared with grade 0/1 skin toxicity, grade 2–4 skin toxicity was associated with significantly longer PFS and OS in patients with *KRAS*-wild type and KRAS-mutated tumors. Moreover, there was no significant difference in patient-reported outcomes in patients who developed grade 2/3/4 versus grade 0/1 skin toxicity.

Dermatologic Toxicities of Targeted Therapy in Colorectal Cancer

Mario E. Lacouture, MD, discussed dermatologic toxicities associated with targeted therapy in CRC.[9] He noted that dermatologic conditions in CRC patients can have multiple negative consequences, affecting patients psychosocially, financially, and physically, and sometimes resulting in treatment disruption.

Skin toxicities associated with epidermal growth factor receptor (EGFR) inhibitors include acneiform rash, paronychia, xerosis, pruritus, and hair alterations. Corneal erosion is also a potential effect of EGFR inhibitors, and, as such, ophthalmologic evaluation is appropriate for patients developing eye symptoms. EGFR inhibitor-induced rash consists of red papulopustules associated with pruritus and tenderness. Papulopustules can lead to the formation of crusted lesions; Dr. Lacouture said that clinicians should evaluate for the presence of infection in these patients.

Skin toxicity leads to dose modifications in 76% of patients and treatment discontinuation in 32%.[10] Dr. Lacouture noted that combining anti-EGFR agents with chemotherapeutic agents can increase the likelihood of grade 3/4 rash.[11] The addition of concurrent radiotherapy also increases the risk of EGFR inhibitor-associated dermatologic toxicities.[12]

Secondary infections are a concern in patients developing EGFR inhibitor-associated skin toxicity. In one retrospective analysis, 38% of patients receiving an EGFR inhibitor developed secondary infections, including bacterial, viral, and fungal infections.[13] Dr. Lacouture said that maintaining an integral barrier of skin can minimize the risk of secondary infections.

The dermatologic side effects associated with EGFR inhibition are associated with better responses to therapy. The development of more severe rash is associated with longer median overall survival (OS) in

patients receiving cetuximab and panitumumab.[14,15]

Dr. Lacouture said that the toxicities develop over time, beginning with acne-like rash in the first few months and progressing to other toxicities. In regard to management, Scope and colleagues conducted a placebo-controlled, randomized, double-blind study evaluating tazarotene and minocycline for rash prevention in patients receiving cetuximab for treatment of CRC.[16] Whereas oral minocycline was associated with a trend toward a lower incidence of moderate to severe itch compared with placebo (20% vs 50%; *P*=.05), topical tazarotene had no clinical benefit. Dr. Lacouture noted that in this study, the rash developed early—in the first month of treatment—suggesting the importance of early intervention.

In 2010, Lacouture and colleagues reported results of a phase II, open-label study of preemptive treatment of skin toxicity versus reactive treatment in patients with metastatic CRC receiving panitumumab-containing therapy.[17] Patients randomly assigned to preemptive care used skin moisturizers, sunscreen, a topical steroid, and doxycycline 100 mg twice daily. The incidence of grade 2 or higher skin toxicity was 29% in these patients versus 62% in patients receiving reactive treatment. Quality of life and dose intensity were also improved with prophylactic treatment, and there was no negative impact of prophylactic treatment on overall response or progression-free survival (PFS). Interestingly, the incidence of multiple nondermatologic grade 3/4 toxicities was also reduced in patients receiving prophylactic skin treatment.

Hand-foot syndrome is an important side effect associated with antimetabolites and targeted agents. Studies evaluating treatments for hand-foot syndrome have focused on managing the inflammation associated with the condition. No approaches have demonstrated benefit in a controlled study. Extrapolating from dermatologic conditions, Dr. Lacouture recommended using high-potency topical corticosteroids or keratolytic agents such as urea 40% or salicylic acid creams. He concluded that an early, proactive approach toward skin toxicities is advisable.

Management of Oxaliplatin-induced Neurotoxicity

Howard S. Hochster, MD, ended the session by discussing the management of oxaliplatin-induced neurotoxicity, which is cumulative and dose-limiting.[18] In fact, this cumulative neurotoxicity precludes the attainment of the full benefit of biologic agents. In 2005, Green and colleagues reported that in the large intergroup trial N9741, 23% of patients discontinued treatment due to neurotoxicity.[19] The time to grade 2 or 3 symptoms depended on the duration of therapy and the cumulative dose of oxaliplatin, increasing from 33% at a cumulative dose of 800 mg/m^2 (approximately 9 cycles) to 61% at 1,020 mg/m^2 (12 cycles). Moreover, the median time to grade 2/3 toxicity was 6–7 months, but the median time to response was only 2.8 months.

Dr. Hochster explained that oxaliplatin-induced neurotoxicity includes acute neuropathy, which is transient and frequent but not dose-limiting; chronic neurotoxicity, which is cumulative and dose-limiting; and delayed neurotoxicity. The MOSAIC (Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer) trial demonstrated the reversibility of oxaliplatin-induced neurotoxicity.[20] One year after treatment, the incidences of grade 1, grade 2, and grade 3 neurotoxicity were 12.0%, 2.8%, and 0.7%, respectively. However, some patients still have grade 1/2 neurotoxicity 3–4 years after treatment.

Dr. Hochster reviewed several approaches to preventing oxaliplatin-associated neurotoxicity. One strategy to improve tolerability is the stop-and-go strategy developed by Aimery de Gramont, MD, in which patients stop

ABSTRACT SUMMARY **Genetic Markers Predictive for Response to Anti-EGFR Therapy in Metastatic Colorectal Cancer**

To investigate the predictive value of various potential biomarkers, Dr. Arjun Sood and coworkers performed a retrospective analysis of 119 tissue samples from 76 patients with metastatic CRC who had received cetuximab or panitumumab and had tissue available in a pharmacy database (Abstract 3567). The investigators used pyrosequencing to evaluate the presence of mutations in these samples at 15 hotspots in the EGFR pathway. The concordance between matched primary and metastatic tissue samples was 47%. Of the 44 patients evaluable for treatment efficacy, 4 patients (9%) had a partial response; all 4 patients tested PTEN-positive in the primary tumor. Lack of PTEN protein expression was significantly associated with lack of response to EGFR-targeted therapy (*P*=.04). In contrast, *PIK3CA* mutations had no significant predictive value. The truncating *PTEN* mutation R335X was significantly associated with lack of PTEN protein expression by immunohistochemistry. The investigators concluded that a lack of PTEN protein expression in the primary tumor may predict a lack of benefit from anti-EGFR therapy. The presence of both *KRAS* and *BRAF* mutations was predictive of a lack of clinical benefit in regard to median PFS (8.5 vs 23.3 weeks; HR, 2.12; *P*=.0085) and median OS (23.9 vs 46 weeks; HR, 2.178; *P*=.0055), confirming other studies.

Trials in Progress

The 2010 ASCO Meeting featured a Trials in Progress Poster Session designed to increase awareness of, and stimulate discussion about, ongoing phase I or phase II trials. Components of these posters could include the scientific background of the study, trial design, eligibility, assessments, statistical considerations, and current status. The posters were limited to trials that had not fully accrued. Thus, no outcomes data or study results were included.

Modified FOLFOX6 Plus Panitumumab or Bevacizumab in Metastatic Colorectal Cancer

Panitumumab was a treatment component in several of the presented trials in progress. PEAK (Panitumumab Efficacy in Combination with mFOLFOX6 Against Bevacizumab Plus mFOLFOX6 in mCRC Subjects With Wild-type KRAS Tumors) is a randomized phase II study comparing the efficacy of panitumumab plus modified FOLFOX6 versus bevacizumab plus modified FOLFOX6 in patients with previously untreated, unresectable, *KRAS* wild type metastatic CRC (TPS189). The primary endpoint is PFS; secondary endpoints include OS, objective response, duration of response, time to progression, time to response, resection rate, and safety. Exploratory objectives include a variety of protein, RNA, and gene biomarker analyses. The trial is limited to adults with unresectable metastatic disease with at least 1 measurable lesion, an ECOG performance status of 0 or 1, and adequate organ function. Exclusion criteria include prior systemic therapy for metastatic CRC, prior adjuvant therapy within the past year, radiotherapy within 2 weeks of randomization, unacceptable unresolved toxicities from prior therapies, history of other invasive primary cancer (with selected exceptions), clinically significant ascites, and cardiovascular or bleeding risk. The planned sample size is 280 patients, with 87 patients enrolled as of May 2010. The study is recruiting patients in North America and Europe.

FOLFIRI With Either Panitumumab or Bevacizumab in Metastatic Colorectal Cancer

Another ongoing trial comparing the treatment effects of panitumumab and bevacizumab is SPIRITT (Second-line Panitumumab-Irinotecan Treatment Trial), a multicenter, open-label, randomized, phase II trial comparing the efficacy of FOLFIRI plus panitumumab versus FOLFIRI plus bevacizumab in the second-line treatment of metastatic CRC (TPS195). The trial is enrolling patients with unresectable, *KRAS*-wild type, metastatic CRC whose disease progressed on prior first-line therapy with oxaliplatin-based chemotherapy plus bevacizumab. Patients must have at least 1 measurable lesion, an ECOG performance status of 0 or 1, and adequate organ function. Exclusion criteria include prior therapy for metastatic CRC, radiotherapy within 2 weeks of randomization, unacceptable unresolved toxicities from prior therapy, history of other invasive primary cancer (with selected exceptions), clinically significant ascites, and significant cardiovascular or bleeding risk. Patients are being randomly assigned to every-2-week FOLFIRI plus panitumumab 6 mg/kg or FOLFIRI plus bevacizumab, which could be administered at 5 mg/kg or 10 mg/kg, depending on physician choice and institutional standard of care. The primary objective is a PFS comparison, with secondary objectives including evaluations of objective response rate, duration of response, time to response, time to progression, disease control, and OS. Exploratory analyses will include patient-reported outcomes and biomarker analyses, including effects of tumor genetic variation in genes associated with signal transduction, drug targets, and genes known to be involved in cancer biology. The trial, which is being conducted at multiple centers in the United States, plans to enroll approximately 210 eligible patients. As of May 2010, 153 patients with *KRAS*-wild type metastatic CRC had enrolled.

oxaliplatin therapy after a predefined cumulative oxaliplatin dose or when neurotoxicity reaches a certain grade. Oxaliplatin is restarted when neurotoxicity has regressed or when oxaliplatin is required to stop tumor progression. In the OPTIMOX1 (A Randomized Study of FOLFOX4 or FOLFOX7 With Oxaliplatin in a Stop-and-Go Fashion in Advanced Colorectal Cancer) trial, the stop-and-go approach was associated with similar efficacy as conventional treatment but had lower rates of grade 3/4 neurotoxicity.[21] In OPTIMOX2, a chemotherapy-free interval was associated with a trend toward worse OS versus maintenance therapy (19 vs 26 months; P=.0549), showing that treatment is needed to maintain response.[22]

In regard to neuroprotectants, calcium and magnesium (CaMg) infusions have been evaluated in several studies. In a retrospective, post-hoc analysis, CaMg appeared to reduce the incidence of neurotoxicity-associated treatment discontinuations in patients receiving oxaliplatin-based chemotherapy and had no effects on treatment efficacy.[23] In the randomized, double-blind, placebo-controlled CONCEPT (Combined Oxaliplatin Neurotoxicity Prevention Trial) trial of FOLFOX plus bevacizumab in first-line metastatic CRC, investigators evaluated both stop-and-go oxaliplatin and CaMg for reducing neurotoxicity. The trial was stopped early after an independent data monitoring committee showed lower response rates in patients receiving CaMg; however, an independent radiologic review found no significant

effect of CaMg on response rate.[24] Intermittent oxaliplatin was more effective than continuous oxaliplatin in regard to median time to treatment failure (5.6 vs 4.2 months; hazard ratio [HR], 0.58; *P*=.0025) and PFS (12.0 vs 7.3 months; HR, 0.53; *P*=.048).[25]

A double-blind, phase III trial in patients receiving adjuvant treatment for colon cancer showed a significant reduction in grade 2 or higher neurotoxicity with CaMg versus placebo (22% vs 41%; *P*=.038).[26] Dr. Hochster concluded that CaMg appeared to be neuroprotective and could be considered a standard treatment due to its negligible toxicity, low cost, and lack of interference with chemotherapy. He also suggested that clinicians can use a stop-and-go or intermittent oxaliplatin approach, with 5-fluorouracil/leucovorin and bevacizumab continued, to optimize the benefit of oxaliplatin.

ABSTRACT SUMMARY **Effects of EGFR Positivity on Clinical Outcome in Metastatic Colorectal Cancer**

In an analysis of the PRIME study, Dr. Salvatore Siena and associates evaluated outcomes according to EGFR positivity, which was ascertained by immunohistochemistry on tumor tissue that had been sectioned within the past 2 months (Abstract 3566). EGFR staining results were not required for study entry but were available in 69% of all patients and 68% of patients with *KRAS* wild type tumors. Tissue section age exceeding 2 months was the most common reason for lack of an EGFR result. In a stratified, multivariate Cox model in patients with *KRAS*-wild type tumors, EGFR positivity had no treatment effect on PFS (*P*=.89) or OS (*P*=.43). The authors concluded that, in first-line therapy of mCRC, the addition of panitumumab to FOLFOX significantly improved PFS and was well tolerated in patients with *KRAS* wild type tumors. This effect of panitumumab on PFS and OS was seen in both EGFR-positive and EGFR-negative patients.

References

1. Minsky BD. Managing and reducing side effects of pelvic radiation. Paper presented at: 2010 Annual Meeting of the American Society of Clinical Oncology; June 4-8, 2010; Chicago, Illinois.
2. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004;351:1731-1740.
3. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *J Clin Oncol*. 2009;27:5124-5130.
4. Chen RC, Mamon HJ, Chen YH, et al. Patient-reported acute gastrointestinal symptoms during concurrent chemoradiation treatment for rectal cancer. *Cancer*. 2010;116:1879-1886.
5. Gérard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol*. 2010;28:1638-1644.
6. Aschele C, Pinto C, Cordio S, et al. Preoperative fluorouracil (FU)-based chemoradiation with and without weekly oxaliplatin in locally advanced rectal cancer: pathologic response analysis of the Studio Terapia Adiuvante Retto (STAR)-01 randomized phase III trial. *J Clin Oncol*. 2009;27. Abstract CRA4008.
7. Fernández-Martos C, Pericay, Aparicio J, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging–defined, locally advanced rectal cancer: Grupo Cáncer de Recto 3 Study. *J Clin Oncol*. 2010;28:859-865.
8. Kachnic LA, Winter KA, Myerson RJ, et al. RTOG 0529: a phase II study of dose-painted IMRT (DP-IMRT), 5-fluorouracil, and mitomycin-C for the reduction of acute morbidity in anal cancer. Presented at the 2010 Gastrointestinal Cancers Symposium. January 22-24, 2010; Orlando, Florida. Abstract 405.
9. Lacouture ME. Dermatologic toxicities of targeted therapy in CRC. Paper presented at: 2010 Annual Meeting of the American Society of Clinical Oncology; June 4-8, 2010; Chicago, Illinois.
10. Boone SL, Rademaker A, Liu D, Pfeiffer C, Mauro DJ, Lacouture ME. Impact and management of skin toxicity associated with anti-epidermal growth factor receptor therapy: survey results. *Oncology*. 2007;72:152-159.
11. Balagula Y, Wu S, Su X, Dusza SW, Lacouture ME. The effect of cytotoxic chemotherapy on the risk of high-grade acneiform rash with cetuximab in cancer patients: a meta-analysis. *J Clin Oncol*. 2010;28. Abstract 9072.
12. Budach W, Bölke E, Homey B. Severe cutaneous reaction during radiation therapy with concurrent cetuximab. *N Engl J Med*. 2007;357:514-515.
13. Eilers RE Jr, Gandhi M, Patel JD, et al. Dermatologic infections in cancer patients treated with epidermal growth factor receptor inhibitor therapy. *J Natl Cancer Inst*. 2010;102:47-53.
14. Saltz LB, Meropol NJ, Loehrer PJ Sr, Needle MN, Kopit J, Mayer RJ. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *J Clin Oncol*. 2004;22:1201-1208.
15. Hecht JR, Patnaik A, Berlin J, et al. Panitumumab monotherapy in patients with previously treated metastatic colorectal cancer. *Cancer*. 2007;110:980-988.
16. Scope A, Agero AL, Dusza SW, et al. Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. *J Clin Oncol*. 2007;25:5390-5396.
17. Lacouture ME, Mitchell EP, Piperdi B, et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. *J Clin Oncol*. 2010;28:1351-1357.
18. Hochster HS. Management of oxaliplatin-induced neurotoxicity. Paper presented at: 2010 Annual Meeting of the American Society of Clinical Oncology; June 4-8, 2010; Chicago, Illinois.
19. Green E, Sargent DJ, Goldberg RM, Grothey A. Detailed analysis of oxaliplatin-associated neurotoxicity in intergroup trial N9741. Presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium; January 27-29, 2005; Hollywood, Florida. Abstract 182.
20. De Gramont A, Boni C, Navarro M, et al. Oxaliplatin/5FU/LV in adjuvant colon cancer: updated efficacy results of the MOSAIC trial, including survival, with a median follow-up of six years. *J Clin Oncol*. 2007;25. Abstract 4007.
21. Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer—a GERCOR study. *J Clin Oncol*. 2006;24:394-400.
22. Maindrault-Goebel F, Lledo G, Chibaudel B, et al. Final results of OPTIMOX2, a large randomized phase II study of maintenance therapy or chemotherapy-free intervals (CFI) after FOLFOX in patients with metastatic colorectal cancer (MRC): a GERCOR study. *J Clin Oncol*. 2007;25. Abstract 4013.
23. Gamelin L, Boisdron-Celle M, Delva R, et al. Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-Fluorouracil and leucovorin for advanced colorectal cancer. *Clin Cancer Res*. 2004;10:4055-4061.
24. Hochster HS, Grothey A, Shpilisky A, Childs BH. Effect of intravenous (IV) calcium and magnesium (Ca/Mg) versus placebo on response to FOLFOX + bevacizumab (BEV) in the CONcePT trial. Presented at the 2008 Gastrointestinal Cancers Symposium; January 25-27, 2008; Orlando, Florida. Abstract 280.
25. Grothey A, Hart LL, Rowland KM, et al. Intermittent oxaliplatin (oxali) administration and time-to-treatment-failure (TTF) in metastatic colorectal cancer (mCRC): final results of the phase III CONcePT trial. *J Clin Oncol*. 2008;26. Abstract 4010.
26. Nikcevich DA, Grothey A, Sloan JA, et al. Effect of intravenous calcium and magnesium (IV CaMg) on oxaliplatin-induced sensory neurotoxicity (sNT) in adjuvant colon cancer: results of the phase III placebo-controlled, double-blind NCCTG trial N04C7. *J Clin Oncol*. 2008;26. Abstract 4009.

Radiofrequency Ablation Combined With Chemotherapy for Unresectable Colorectal Liver Metastases

Although systemic therapy is the standard of care for the treatment of patients with unresectable colorectal liver metastases, radiofrequency ablation (RFA) is growing in popularity as a treatment modality for these patients. Prior to the current study, RFA had not been evaluated in a prospective, randomized trial. The European Organization for Research and Treatment of Cancer (EORTC) Intergroup trial 40004 (CLOCC [Chemotherapy + Local Ablation Versus Chemotherapy]) evaluated the safety and efficacy of adding RFA to systemic therapy in patients with unresectable colorectal liver metastases.[1] The study was initially designed as a randomized phase III trial but was modified to a randomized phase II design due to slow accrual.

A total of 119 patients were randomized to RFA plus systemic therapy (n=60) or systemic therapy alone (n=59). Upon downsizing, radical resection was allowed if feasible. RFA could be performed with resection (47%) or without resection (53%), and was performed via laparotomy (89.5%), laparoscopy (1.8%), or percutaneously (7.0%). The mean time in the hospital was 4.8 days. Systemic therapy in both arms consisted of oxaliplatin, leucovorin, and fluorouracil (FOLFOX4), with the addition of bevacizumab starting in 2006. Patients received 6 months of systemic therapy, with continued treatment based on the physician's discretion.

The study enrolled 119 patients between 2002 and 2007. Eligibility criteria included unresectable liver metastases, fewer than 10 metastatic deposits, a maximum diameter of 4 cm for lesions to be treated by RFA, and a performance status of 0–1. No extrahepatic disease was allowed; prior systemic therapy was permitted if disease progression did not occur on treatment.

The median age of enrolled patients was 64 years in the RFA-plus-chemotherapy arm and 61 years in the chemotherapy-alone arm; 61.7% and 71.2%, respectively, were male. Most patients had multiple liver metastases. The median number of liver lesions was 4.0 in the RFA-plus-chemotherapy arm and 5.0 in the chemotherapy-alone arm. The proportion of patients with 6–9 lesions was 26.6% and 38.9%, respectively; 61.7% and 52.5%, respectively, had metachronous liver metastases; 15.0% and 13.6%, respectively, had received prior chemotherapy for metastatic disease.

Most patients in the study received systemic treatment. FOLFOX was administered to 72% of patients in the RFA-plus-chemotherapy arm and 78% of patients in the chem-

ABSTRACT SUMMARY **Use of KRAS and BRAF Biomarker Status to Predict Treatment Outcome in Metastatic Colorectal Cancer**

Dr. Eric Van Cutsem and colleagues analyzed efficacy results from the CRYSTAL study according to *KRAS* and *BRAF* status (Abstract 3570). Of 1,198 patients randomized, 89% were evaluable for *KRAS* status and 83% were evaluated for *BRAF* status. Overall, 63% of patients had *KRAS* wild type tumors and 6% had *BRAF* mutations. After a median follow-up of approximately 46 months, the addition of cetuximab to FOLFIRI in patients with *KRAS* wild type tumors was associated with a significant improvement in median PFS (9.9 vs 8.4 months; HR, 0.696; 95% CI, 0.558–0.867; *P*=.0012). The addition of cetuximab to FOLFIRI was also associated with a significant improvement in OS (median OS, 23.5 vs 20.0 months; HR, 0.796; 95% CI, 0.670–0.946; *P*=.0093) and overall response rate (39.7% vs 57.3%; odds ratio, 2.069; *P*<.0001). Subgroup analyses showed a trend toward a greater benefit with cetuximab in younger versus older patients, in men versus women, in patients with an ECOG performance status of 0–1 versus 2, and in patients with metastases only in the liver. There was a significant interaction between treatment outcomes and *KRAS* mutation status for all efficacy variables, confirming the value of *KRAS* status for predicting responses to cetuximab plus FOLFIRI in first-line metastatic CRC. Conversely, *BRAF* status was not predictive of outcomes; patients with *BRAF* mutations had significantly worse outcomes regardless of the treatment arm, and there was no significant interaction between treatment outcomes and *BRAF* status. These findings suggest that *BRAF* mutations are a marker of poor prognosis in patients with previously untreated metastatic CRC.

ABSTRACT SUMMARY Impact of the Amount of Tumor Cells in Tissue Samples for Detection of KRAS Mutations in Colorectal Cancer

Accurate determination of *KRAS* status in CRC is essential, given that treatment of metastatic CRC is limited to patients with *KRAS* wild type tumors. Dr. Janick Selves and coauthors evaluated factors that may influence the detection of *KRAS* mutations in routine practice (Abstract 3571). Between October 2008 and June 2009, the investigators performed *KRAS* mutation analyses on 441 CRC samples that had been formalin-fixed and paraffin-embedded (89%) or cryopreserved (11%). The majority of the samples (75%) were obtained from surgery, with the remainder obtained from biopsies. Most samples (77%) were removed from primary tumors, with the remaining 13% removed from metastases. There was a significant correlation between the mutation detection rate and the percentage of tumor cells in the extracted sample. The frequency of *KRAS* mutations detected ranged from 41% in the samples containing at least 50% tumor cells (378 samples), to 27% in the samples with 20–50% tumor cells (44 samples), to 0% in the 5 samples with fewer than 20% tumor cells (*P*=.039). Thus, the investigators concluded that samples containing less than 50% tumor cells are at risk of false-negative results for detecting *KRAS* mutations. The investigators also noted that the mutation detection rate was higher in the 58 metastatic tumors than in the 344 primary tumors, with *KRAS* mutation rates of 48% and 38%, respectively. Conversely, the origin of the samples from biopsy or surgical specimen did not affect the detection rate.

otherapy-alone arm; 13% and 22% of patients, respectively, received FOLFOX plus bevacizumab. In the RFA arm, 10% of patients did not receive chemotherapy due to RFA or surgery complications (3 patients), disease progression (2 patients), or death (1 patient). Another 3 patients in the RFA arm (5%) received no treatment due to patient refusal, lack of treatment data, or presence of bone metastases at baseline. Seven patients in the chemotherapy-alone arm (12%) underwent resection after treatment.

Postoperative complications associated with RFA included wound infection or abscess (10.5%), cardiac complications (5.3%), hemorrhage (3.5%), and death (2%). Grade 3/4 toxicities associated with chemotherapy were neutropenia (27.5% and 20.3% in the RFA-plus-chemotherapy and chemotherapy-only arms, respectively), diarrhea (19.6% and 16.9%, respectively), grade 3 neuropathy (17.6% and 13.6%, respectively), and cardiotoxicity (9.8% and 1.7%, respectively).

After a median follow-up of 4.4 years, the 30-month OS was 63.8% in the RFA-plus-chemotherapy arm and 58.6% in the chemotherapy-alone arm. Thus, the study met its primary objective of attaining a 30-month OS above 38% with RFA plus chemotherapy. However, the control arm also met this endpoint. The study was not powered to detect a significant difference in survival at 30 months. Median OS was 3.78 years in the RFA-plus-chemotherapy arm and 3.38 years in the chemotherapy-alone arm. An analysis of survival curves showed similar survival rates in the first 3 years, with curves beginning to separate after 3 years. The proportion of patients alive at the end of follow-up was 48.3% in the RFA-plus-chemotherapy arm and 33.9% in the chemotherapy-alone arm. Causes of death included disease progression (46.7% and 62.7%, respectively), cardiovascular events (1.7% and 0%, respectively), and other causes (3.3% and 1.7%, respectively).

The addition of RFA to systemic therapy was associated with a significant PFS improvement, with a median PFS of 16.8 months in the RFA-plus-chemotherapy group and 9.9 months in the chemotherapy-alone group (HR, 0.63; 95% confidence interval [CI], 0.42–0.95; *P*=.025). At 3 years, the proportion of patients alive and progression-free was 27.7% and 10.7%, respectively.

The most common site of first disease progression was the liver in 64.3% of patients in the RFA-plus-chemotherapy arm and 84.9% of patients in the chemotherapy-alone arm. Among patients treated with RFA, the incidence of local recurrence at the RFA site was 11.5%.

Quality of life, as assessed by the EORTC QLQ-C30 scale of global health status, was lower in patients receiving RFA immediately around the time of the procedure, although it returned to baseline levels within approximately 6 weeks. The investigators concluded that RFA plus systemic therapy was associated with an acceptable safety profile and conferred a significant improvement in PFS.

Reference

1. Ruers T, Punt CJ, van Coevorden F, et al. Final results of the EORTC intergroup randomized study 40004 (CLOCC) evaluating the benefit of radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorectal liver metastases (CRC LM). *J Clin Oncol.* 2009;27. Abstract 3526.

Treatment Outcome According to *KRAS* and *BRAF* Mutation Status in Metastatic Colorectal Cancer

The anti-EGFR monoclonal antibody cetuximab is currently approved for use in patients with previously treated metastatic CRC.[1] Several large trials have evaluated the use of cetuximab in the first-line setting. The CRYSTAL (Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) trial was a multicenter, open-label, randomized phase III trial evaluating leucovorin, fluorouracil, and irinotecan (FOLFIRI) with or without cetuximab as first-line treatment in 1,198 patients with metastatic CRC expressing EGFR. In 2009, Van Cutsem and colleagues reported a significant PFS benefit with the addition of cetuximab to FOLFIRI in the subset of patients with *KRAS* wild type tumors (HR, 0.68; *P*=.02).[2] The OPUS (Oxaliplatin and Cetuximab in First-Line Treatment of mCRC) trial was a prospective, randomized phase II trial of FOLFOX4 with or without cetuximab as first-line treatment in 337 patients with EGFR-expressing metastatic CRC. In the subset of patients with *KRAS* wild type tumors, the addition of cetuximab to FOLFOX4 was associated with an increase in the likelihood of response (odds ratio, 2.54; *P*=.011), a reduction in the risk of disease progression (HR, 0.57; *P*=.0163), and a trend towards an improvement in OS.[3]

Subset analyses have shown that the benefit of cetuximab is limited to patients with *KRAS* wild type tumors, revealing *KRAS* status as an important predictive marker for cetuximab in the first-line treatment of metastatic CRC.[3,4] The serine/threonine kinase BRAF is a downstream effector of KRAS. *BRAF* mutations have been detected in approximately 8% of CRC tumors.[5] Evidence has suggested that *BRAF* mutations are predictive of responses to EGFR-targeted therapy in patients with previously treated metastatic CRC. In a study evaluating cetuximab plus irinotecan in chemotherapy-refractory patients, *BRAF* mutations were detected in 4.6% of patients (26 of 566 patients) and were associated with a lower response rate (8% vs 26%) and shorter PFS (8 vs 19 weeks).[6] Di Nicolantonio and colleagues reported that in patients with *KRAS* wild type tumors receiving panitumumab or cetuximab monotherapy or cetuximab plus chemotherapy, *BRAF* mutations were present in 9.7% of patients (11 of 79 patients) and were also associated with lower response rates (0% vs 32%) and shorter PFS.[7] However, these previous studies reporting poor outcomes and low response rates to EGFR-targeted therapy in patients with *BRAF* mutations have lacked a chemotherapy-only control arm. Thus, the value of *BRAF* mutations for specifically predicting responses to EGFR-targeted therapy, versus other therapies, has remained unknown.

To further assess the value of *KRAS* and *BRAF* status for predicting responses to first-line therapy with cetuximab plus chemotherapy, Bokemeyer and colleagues conducted a pooled analysis of the CRYSTAL and OPUS trials.[8] The investigators first evaluated outcomes according to *KRAS* status and next did so in patients with *KRAS* wild type tumors, according to tumor *BRAF* mutation status.

For the current analysis, *KRAS* mutation status was evaluable in 89% of tumor samples from the CRYSTAL study and 93% of samples from the OPUS study. This represents a substantial increase from previous reports from those studies, which included only 45% and 69% of samples, respectively.[2,3] In the *KRAS* wild type tumors, *BRAF* mutation status was evaluable in 94% of samples in the CRYSTAL study (625 of 666) and 98% of samples in the OPUS study (175 of 179). Overall, the baseline characteristics were well balanced between the chemotherapy-plus-cetuximab arm and the chemotherapy-alone arm. Approximately 60% of patients were male, the median age was 59–61 years, 95% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, metastases were detected in only the liver in 21–23% of patients, and 20–21% had received prior adjuvant chemotherapy.

Among the 800 evaluated patients with *KRAS* wild type tumors, *BRAF* mutations were detected in 8.8% of tumors (70 patients). Most baseline characteristics were balanced in this small subset of patients, although there was a higher proportion of patients with liver-only metastases in the chemotherapy-plus-cetuximab arm versus the chemotherapy-alone arm (31% vs 11%).

The pooled analysis confirmed the clinical efficacy of cetuximab added to chemotherapy in patients with *KRAS* wild type tumors. Compared with chemotherapy alone, cetuximab plus chemotherapy was associated with a significant improvement in median OS (23.5 vs 19.5 months; HR, 0.81; 95% CI, 0.69–0.94; *P*=.0062). Thus, this pooled analysis confirmed the survival improvement with cetuximab observed in the CRYSTAL study and

ABSTRACT SUMMARY Efficacy of Panitumumab According to Epidermal Growth Factor Receptor Staining by Immunohistochemistry

Dr. Marc Peeters and associates evaluated the efficacy of panitumumab according to EGFR staining by immunohistochemistry, with analyses by central review (Abstract 3565). Samples were evaluable for EGFR testing from 62% of patients overall and from 65% of patients with *KRAS* wild type tumors. Of the patients with *KRAS* wild type tumors, EGFR staining was positive in 74.7% of patients receiving panitumumab plus FOLFIRI and 76.2% of patients receiving FOLFIRI alone. The addition of panitumumab to FOLFIRI appeared to have a similar effect regardless of EGFR staining. In patients with EGFR-positive tumors, median PFS was 6.4 months with panitumumab plus FOLFIRI and 5.1 months with FOLFIRI alone (HR, 0.80; *P*=.09). In patients with EGFR-negative tumors, median PFS was 7.5 months and 5.5 months, respectively (HR, 0.81; *P*=.40). Median OS in patients with EGFR-positive tumors was 14.1 months with panitumumab plus FOLFIRI and 12.8 months with FOLFIRI alone (HR, 0.87; *P*=.32). Median OS in patients with EGFR-negative tumors was 14.5 months and 12.5 months, respectively (HR, 0.87; *P*=.58). The investigators concluded that EGFR expression did not appear to predict the efficacy of panitumumab and was not prognostic in patients receiving FOLFIRI.

the trend toward improved survival in the OPUS trial.

The addition of cetuximab to chemotherapy was also associated with a significant improvement in median PFS in the pooled analysis (9.6 vs 7.6 months; HR, 0.66; 95% CI, 0.55–0.80; *P*<.0001). In his presentation, Dr. Bokemeyer noted that the PFS curves with chemotherapy plus cetuximab versus chemotherapy alone separated at 3–4 months after the start of treatment and maintained that separation throughout the treatment period. The addition of cetuximab to chemotherapy was also associated with an approximate 20% improvement in overall response rate versus chemotherapy alone (57.3% vs 38.5%; odds ratio, 2.16; 95% CI, 1.64–2.86; *P*<.0001).

An analysis by *BRAF* status in the patients with *KRAS* wild type tumors showed that outcomes in the 91.2% of patients with *BRAF* wild type tumors were similar to those observed in the overall *KRAS* wild type population, with the addition of cetuximab conferring a significant efficacy benefit. However, in the 8.8% of patients with *BRAF*-mutated tumors, outcomes were significantly worse in both arms. Median OS with chemotherapy plus cetuximab versus chemotherapy alone was 14.1 months versus 9.9 months, compared with 24.8 months versus 21.1 months in the patients with *BRAF* wild type tumors. Median PFS was 7.1 in the cetuximab-plus-chemotherapy arm and 3.7 months in the chemotherapy-alone arm, compared with 10.9 months and 7.7 months, respectively, in patients with *BRAF* wild type tumors. The overall response rate was also lower in both arms, at 21.9% with cetuximab plus chemotherapy versus 13.2% with chemotherapy alone, compared with 60.7% versus 40.9%, respectively, in the patients with *BRAF* wild type tumors. Although the addition of cetuximab to chemotherapy did appear to confer some efficacy benefit in regard to each parameter assessed, none of the differences reached statistical significance. However, the number of patients with *BRAF* mutations was small.

Overall, this pooled analysis demonstrated a significant improvement in OS with chemotherapy plus cetuximab versus chemotherapy alone in the first-line treatment of patients with *KRAS* wild type metastatic CRC. The investigators concluded that the presence of *BRAF* mutations, detected in 8.8% of patients, appeared to be a marker of poor prognosis. However, the addition of cetuximab to chemotherapy appeared to provide some benefit to these patients.

References

1. Erbitux [package insert]. Branchburg, NJ: ImClone Systems Incorporated; Princeton, NJ: Bristol-Myers Squibb Company; 2010.
2. Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med.* 2009;360:1408-1417.
3. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol.* 2009;27:663-671.
4. Lièvre A, Bachet JB, Boige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. *J Clin Oncol.* 2008;26:374-379.
5. Roth AD, Tejpar S, Delorenzi M, et al. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. *J Clin Oncol.* 2010;28:466-474.
6. Lambrechts D, De Roock W, Prenen H, et al. The role of KRAS, BRAF, NRAS, and PIK3CA mutations as markers of resistance to cetuximab in chemorefractory metastatic colorectal cancer. *J Clin Oncol.* 2009;27. Abstract 4020.
7. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. *J Clin Oncol.* 2008;26:5705-5712.
8. Bokemeyer C, Kohne C, Rougier P, et al. Cetuximab with chemotherapy (CT) as first-line treatment for metastatic colorectal cancer (mCRC): analysis of the CRYSTAL and OPUS studies according to KRAS and BRAF mutation status. *J Clin Oncol.* 2010;28. Abstract 3506.

Vectibix® (panitumumab)
Injection for intravenous Infusion

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

Vectibix® (panitumumab)

WARNING: DERMATOLOGIC TOXICITY and INFUSION REACTIONS

Dermatologic Toxicity: Dermatologic toxicities occurred in 89% of patients and were severe (NCI-CTC grade 3 and higher) in 12% of patients receiving Vectibix monotherapy. ***[see Dosage and Administration, Warnings and Precautions, and Adverse Reactions].***

Infusion Reactions: Severe infusion reactions occurred in approximately 1% of patients. Fatal infusion reactions occurred in postmarketing experience ***[see Dosage and Administration, Warnings and Precautions, and Adverse Reactions].***

INDICATIONS AND USAGE

Vectibix is indicated as a single agent for the treatment of epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal carcinoma (mCRC) with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens *[see Clinical Studies (14) in Full Prescribing Information].*

The effectiveness of Vectibix as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma is based on progression-free survival *[see Clinical Studies (14) in Full Prescribing Information]*. Currently, no data demonstrate an improvement in disease-related symptoms or increased survival with Vectibix.

Retrospective subset analyses of metastatic colorectal cancer trials have not shown a treatment benefit for Vectibix in patients whose tumors had *KRAS* mutations in codon 12 or 13. Use of Vectibix is not recommended for the treatment of colorectal cancer with these mutations. *[see Clinical Studies (14) in Full Prescribing Information].*

DOSAGE AND ADMINISTRATION

Recommended Dose and Dose Modifications: The recommended dose of Vectibix is 6 mg/kg, administered as an intravenous infusion over 60 minutes, every 14 days. Doses higher than 1000 mg should be administered over 90 minutes *[see Dosage and Administration].*

Appropriate medical resources for the treatment of severe infusion reactions should be available during Vectibix infusions.

Dose Modifications for Infusion Reactions *[see Boxed Warning, Warnings and Precautions, and Adverse Reactions]*

- Reduce infusion rate by 50% in patients experiencing a mild or moderate (grade 1 or 2) infusion reaction for the duration of that infusion.

Terminate the infusion in patients experiencing severe infusion reactions. Depending on the severity and/or persistence of the reaction, permanently discontinue Vectibix.

Dose Modifications for Dermatologic Toxicity *[see Boxed Warning, Warnings and Precautions, and Adverse Reactions]*

- Withhold Vectibix for dermatologic toxicities that are grade 3 or higher or are considered intolerable. If toxicity does not improve to ≤ grade 2 within 1 month, permanently discontinue Vectibix.
- If dermatologic toxicity improves to ≤ grade 2, and the patient is symptomatically improved after withholding no more than two doses of Vectibix, treatment may be resumed at 50% of the original dose.
  - If toxicities recur, permanently discontinue Vectibix.
  - If toxicities do not recur, subsequent doses of Vectibix may be increased by increments of 25% of the original dose until the recommended dose of 6 mg/kg is reached.

Preparation and Administration: Do not administer Vectibix as an intravenous push or bolus.

Preparation

Prepare the solution for infusion, using aseptic technique, as follows:

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Although Vectibix should be colorless, the solution may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates (which will be removed by filtration; see below). Do not shake. Do not administer Vectibix if discoloration is observed.
- Withdraw the necessary amount of Vectibix for a dose of 6 mg/kg.
- Dilute to a total volume of 100 mL with 0.9% sodium chloride injection, USP. Doses higher than 1000 mg should be diluted to 150 mL with 0.9% sodium chloride injection, USP. Do not exceed a final concentration of 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.

Administration

- Administer using a low-protein-binding 0.2 µm or 0.22 µm in-line filter.
- Vectibix must be administered via infusion pump.
  - Flush line before and after Vectibix administration with 0.9% sodium chloride injection, USP, to avoid mixing with other drug products or intravenous solutions. Do not mix Vectibix with, or administer as an infusion with, other medicinal products. Do not add other medications to solutions containing panitumumab.
  - Infuse over 60 minutes through a peripheral intravenous line or indwelling intravenous catheter. Doses higher than 1000 mg should be infused over 90 minutes.

Use the diluted infusion solution of Vectibix within 6 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2° to 8°C (36° to 46°F). DO NOT FREEZE.

Discard any unused portion remaining in the vial.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Dermatologic Toxicity: In Study 1, dermatologic toxicities occurred in 90% of patients and were severe (NCI-CTC grade 3 and higher) in 16% of patients with mCRC receiving Vectibix. The clinical manifestations included, but were not limited to, dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures. Subsequent to the development of severe dermatologic toxicities, infectious complications, including sepsis, septic death, and abscesses requiring incisions and drainage were reported. Withhold Vectibix for severe or life-threatening dermatologic toxicity. *[see Boxed Warning, Adverse Reactions, and Dosage and Administration].*

Infusion Reactions: In Study 1, 4% of patients experienced infusion reactions and in 1% of patients, these reactions were graded as severe (NCI-CTC grade 3–4). Infusion reactions, manifesting as anaphylactoid reactions, bronchospasm, and hypotension, can occur following Vectibix administration *[see Boxed Warning, and Adverse Reactions]*. In clinical studies, severe infusion reactions occurred with the administration of Vectibix in approximately 1% of patients. Fatal infusion reactions occurred in postmarketing experience. Terminate the infusion for severe infusion reactions. *[see Dosage and Administration].*

Increased Toxicity With Combination Chemotherapy: Vectibix is not indicated for use in combination with chemotherapy. In an interim analysis of Study 2, the addition of Vectibix to the combination of bevacizumab and chemotherapy resulted in decreased overall survival and increased incidence of NCI-CTC grade 3–5 (87% vs 72%) adverse reactions *[see Clinical Studies (14) in Full Prescribing Information]*. NCI-CTC grade 3–4 adverse drug reactions occurring at a higher rate in Vectibix-treated patients included rash/dermatitis acneiform (26% vs 1%), diarrhea (23% vs 12%), dehydration (16% vs 5%), primarily occurring in patients with diarrhea, hypokalemia (10% vs 4%), stomatitis/mucositis (4% vs < 1%), and hypomagnesemia (4% vs 0). NCI-CTC grade 3–5 pulmonary embolism occurred at a higher rate in Vectibix-treated patients (7% vs 4%) and included fatal events in three (< 1%) Vectibix-treated patients.

As a result of the toxicities experienced, patients randomized to Vectibix, bevacizumab, and chemotherapy received a lower mean relative dose intensity of each chemotherapeutic agent (oxaliplatin, irinotecan, bolus 5-FU, and/or infusional 5-FU) over the first 24 weeks on study, compared with those randomized to bevacizumab and chemotherapy.

In a single-arm study of 19 patients receiving Vectibix in combination with IFL, the incidence of NCI-CTC grade 3–4 diarrhea was 58%; in addition, grade 5 diarrhea occurred in one patient. In a single-arm study of 24 patients receiving Vectibix plus FOLFIRI, the incidence of NCI-CTC grade 3 diarrhea was 25%.

Severe diarrhea and dehydration which may lead to acute renal failure and other complications have been observed in patients treated with Vectibix in combination with chemotherapy.

Pulmonary Fibrosis: Pulmonary fibrosis occurred in less than 1% (2/1467) of patients enrolled in clinical studies of Vectibix. Following the initial fatality described below, patients with a history of interstitial pneumonitis, pulmonary fibrosis, evidence of interstitial pneumonitis, or pulmonary fibrosis were excluded from clinical studies. Therefore, the estimated risk in a general population that may include such patients is uncertain.

One case occurred in a patient with underlying idiopathic pulmonary fibrosis who received Vectibix in combination with chemotherapy and resulted in death from worsening pulmonary fibrosis after four doses of Vectibix. The second case was characterized by cough and wheezing 8 days following the initial dose, exertional dyspnea on the day of the seventh dose, and persistent symptoms and CT evidence of pulmonary fibrosis following the 11th dose of Vectibix as monotherapy. An additional patient died with bilateral pulmonary infiltrates of uncertain etiology with hypoxia after 23 doses of Vectibix in combination with chemotherapy. Permanently discontinue Vectibix therapy in patients developing interstitial lung disease, pneumonitis, or lung infiltrates.

Electrolyte Depletion/Monitoring: In Study 1, median magnesium levels decreased by 0.1 mmol/L in the Vectibix arm; hypomagnesemia (NCI-CTC grade 3 or 4) requiring oral or intravenous electrolyte repletion occurred in 2% of patients. Hypomagnesemia occurred 6 weeks or longer after the initiation of Vectibix. In some patients, both hypomagnesemia and hypocalcemia occurred. Patients' electrolytes should be periodically monitored during and for 8 weeks after the completion of Vectibix therapy. Institute appropriate treatment, eg, oral or intravenous electrolyte repletion, as needed.

Photosensitivity: Exposure to sunlight can exacerbate dermatologic toxicity. Advise patients to wear sunscreen and hats and limit sun exposure while receiving Vectibix.

EGF Receptor Testing: Detection of EGFR protein expression is necessary for selection of patients appropriate for Vectibix therapy because these are the only patients studied and for whom benefit has been shown *[see Indications and Usage and Clinical Studies (14) in Full Prescribing Information]*. Patients with colorectal cancer enrolled in Study 1 were required to have immunohistochemical evidence of EGFR expression using the Dako EGFR pharmDx® test kit.

Assessment for EGFR expression should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specific reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. Refer to the package insert for the Dako EGFR pharmDx® test kit, or other test kits approved by FDA, for identification of patients eligible for treatment with Vectibix and for full instructions on assay performance.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Dermatologic Toxicity *[see Boxed Warning, Dosage and Administration, and Warnings and Precautions]*
- Infusion Reactions *[see Boxed Warning, Dosage and Administration, and Warnings and Precautions]*
- Increased Toxicity With Combination Chemotherapy *[see Warnings and Precautions]*
- Pulmonary Fibrosis *[see Warnings and Precautions]*
- Electrolyte Depletion/Monitoring *[see Warnings and Precautions]*
- Photosensitivity *[see Warnings and Precautions]*

The most common adverse events of Vectibix are skin rash with variable presentations, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea, and diarrhea, including diarrhea resulting in dehydration.

The most serious adverse events of Vectibix are pulmonary fibrosis, pulmonary embolism, severe dermatologic toxicity complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, and constipation. Adverse reactions requiring discontinuation of Vectibix were infusion reactions, severe skin toxicity, paronychia, and pulmonary fibrosis.

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Safety data are available from 15 clinical trials in which 1467 patients received Vectibix; of these, 1293 received Vectibix monotherapy and 174 received Vectibix in combination with chemotherapy *[see Warnings and Precautions].*

The data described in Table 1 and in other sections below, except where noted, reflect exposure to Vectibix administered as a single agent at the recommended dose and schedule (6 mg/kg every 2 weeks) in 229 patients with mCRC enrolled in Study 1, a randomized, controlled trial. The median number of doses was five (range: one to 26 doses), and 71% of patients received eight or fewer doses. The population had a median age of 62 years (range: 27 to 82 years), 63% were male, and 99% were white with < 1% black, < 1% Hispanic, and 0% other.

Table 1. Per-Patient Incidence of Adverse Reactions Occurring in ≥ 5% of Patients With a Between-Group Difference of ≥ 5% (Study 1)

		Patients Treated With Vectibix Plus BSC (n = 229)		Best Supportive Care (BSC) Alone (n = 234)	
		Grade*			
Body System		All Grades (%)	Grade 3–4 (%)	All Grades (%)	Grade 3–4 (%)
Body as a Whole	Fatigue	26	4	15	3
	General Deterioration	11	8	4	3
Digestive	Abdominal Pain	25	7	17	5
	Nausea	23	1	16	< 1
	Diarrhea	21	2	11	0
	Constipation	21	3	9	1
	Vomiting	19	2	12	1
	Stomatitis	7	0	1	0
	Mucosal Inflammation	6	< 1	1	0
Metabolic/Nutritional	Hypomagnesemia (Lab)	38	4	2	0
	Peripheral Edema	12	1	6	< 1
Respiratory	Cough	14	< 1	7	0
Skin/Appendages	All Skin/Integument Toxicity	90	16	9	0
	Skin	90	14	6	0
	Erythema	65	5	1	0
	Dermatitis Acneiform	57	7	1	0
	Pruritus	57	2	2	0
	Nail	29	2	0	0
	Paronychia	25	2	0	0
	Skin Exfoliation	25	2	0	0
	Rash	22	1	1	0
	Skin Fissures	20	1	< 1	0
	Eye	15	< 1	2	0
	Acne	13	1	0	0
	Dry Skin	10	0	0	0
	Other Nail Disorder	9	0	0	0
	Hair	9	0	1	0
	Growth of Eyelashes	6	0	0	0

*Version 2.0 of the NCI-CTC was used for grading toxicities. Skin toxicity was coded based on a modification of the NCI-CTCAE, version 3.0.

Dermatologic, Mucosal, and Ocular Toxicity: In Study 1, dermatologic toxicities occurred in 90% of patients receiving Vectibix. Skin toxicity was severe (NCI-CTC grade 3 and higher) in 16% of patients. Ocular toxicities occurred in 15% of patients and included, but were not limited to, conjunctivitis (4%), ocular hyperemia (3%), increased lacrimation (2%), and eye/eyelid irritation (1%). Stomatitis (7%) and oral mucositis (6%) were reported. One patient experienced an NCI-CTC grade 3 event of mucosal inflammation. The incidence of paronychia was 25% and was severe in 2% of patients. Nail disorders occurred in 9% of patients *[see Warnings and Precautions].*

Median time to the development of dermatologic, nail, or ocular toxicity was 14 days after the first dose of Vectibix; the median time to most severe skin/ocular toxicity was 15 days after the first dose of Vectibix; and the median time to resolution after the last dose of Vectibix was 84 days. Severe toxicity necessitated dose interruption in 11% of Vectibix-treated patients *[see Dosage and Administration].*

Subsequent to the development of severe dermatologic toxicities, infectious complications, including sepsis, septic death, and abscesses requiring incisions and drainage, were reported.

Infusion Reactions: Infusional toxicity was defined as any event within 24 hours of an infusion during the clinical study described as allergic reaction or anaphylactoid reaction, or any event occurring on the first day of dosing described as allergic reaction, anaphylactoid reaction, fever, chills, or dyspnea. Vital signs and temperature were measured within 30 minutes prior to initiation and upon completion of the Vectibix infusion. The use of premedication was not standardized in the clinical trials. Thus, the utility of premedication in preventing the first or subsequent episodes of infusional toxicity is unknown. Across several clinical trials of Vectibix monotherapy, 3% (43/1336) experienced infusion reactions of which approximately 1% (6/1336) were severe (NCI-CTC grade 3–4). In one patient, Vectibix was permanently discontinued for a serious infusion reaction *[see Dosage and Administration].*

Immunogenicity: As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of Vectibix has been evaluated using two different screening immunoassays for the detection of anti-panitumumab antibodies: an acid dissociation bridging enzyme-linked immunosorbent assay (ELISA) (detecting high-affinity antibodies) and a Biacore® biosensor immunoassay (detecting both high- and low-affinity antibodies). The incidence of binding antibodies to panitumumab (excluding predose and transient positive patients), as detected by the acid dissociation ELISA, was 3/613 (< 1%) and as detected by the Biacore® assay was 28/613 (4.6%).

For patients whose sera tested positive in screening immunoassays, an in vitro biological assay was performed to detect neutralizing antibodies. Excluding predose and transient positive patients, 10/613 patients (1.6%) with postdose samples and 3/356 (0.8%) of the patients with follow-up samples tested positive for neutralizing antibodies.

No evidence of altered pharmacokinetic profile or toxicity profile was found between patients who developed antibodies to panitumumab as detected by screening immunoassays and those who did not.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to panitumumab with the incidence of antibodies to other products may be misleading.

Postmarketing experience: The following adverse reaction has been identified during post-approval use of panitumumab. Because these reactions are reported in a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Angioedema *[see Boxed Warning, Dosage and Administration, and Warnings and Precautions]*
- Anaphylaxis *[see Boxed Warning, Dosage and Administration, and Warnings and Precautions]*

DRUG INTERACTIONS

No formal drug-drug interaction studies have been conducted with Vectibix.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C: There are no studies of Vectibix in pregnant women. Reproduction studies in cynomolgus monkeys treated with 1.25 to 5 times the recommended human dose of panitumumab resulted in significant embryolethality and abortions; however, no other evidence of teratogenesis was noted in offspring. *[see Reproductive and Developmental Toxicology]*. Vectibix should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Based on animal models, EGFR is involved in prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Human IgG is known to cross the placental barrier; therefore, panitumumab may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women.

Women who become pregnant during Vectibix treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-772-6436 (1-800-77-AMGEN) to enroll.

Nursing Mothers: It is not known whether panitumumab is excreted into human milk; however, human IgG is excreted into human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from Vectibix, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If nursing is interrupted, based on the mean half-life of panitumumab, nursing should not be resumed earlier than 2 months following the last dose of Vectibix *[see Clinical Pharmacology (12.3) in Full Prescribing Information].*

Pediatric Use: The safety and effectiveness of Vectibix have not been established in pediatric patients. The pharmacokinetic profile of Vectibix has not been studied in pediatric patients.

Geriatric Use: Of 229 patients with mCRC who received Vectibix in Study 1, 96 (42%) were ≥ age 65. Although the clinical study did not include a sufficient number of geriatric patients to determine whether they respond differently from younger patients, there were no apparent differences in safety and effectiveness of Vectibix between these patients and younger patients.

OVERDOSAGE

Doses up to approximately twice the recommended therapeutic dose (12 mg/kg) resulted in adverse reactions of skin toxicity, diarrhea, dehydration, and fatigue.

PATIENT COUNSELING INFORMATION

Advise patients to contact a healthcare professional for any of the following:

- Skin and ocular/visual changes *[see Boxed Warning and Warnings and Precautions],*
- Signs and symptoms of infusion reactions including fever, chills, or breathing problems *[see Boxed Warning, Dosage and Administration, Warnings and Precautions and Adverse Reactions],*
- Diarrhea and dehydration *[see Warnings and Precautions],*
- Persistent or recurrent coughing, wheezing, dyspnea, or new onset facial swelling *[see Warnings and Precautions, and Adverse Reactions],*
- Pregnancy or nursing *[see Use in Specific Populations].*

Advise patients of the need for:

- Periodic monitoring of electrolytes *[see Warnings and Precautions],*
- Limitation of sun exposure (use sunscreen, wear hats) while receiving Vectibix and for 2 months after the last dose of Vectibix therapy. *[see Warnings and Precautions],*
- Adequate contraception in both males and females while receiving Vectibix and for 6 months after the last dose of Vectibix therapy *[see Use in Specific Populations].*

This brief summary is based on the Vectibix® prescribing information v9, 5/2010

Rx Only This product, its production, and/or its use may be covered by one or more US Patents, including US Patent No. 6,235,883, as well as other patents or patents pending.

 MC46026-D

AMGEN®
Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
USA

The case for Vectibix®

Q2W dosing schedule[1]
- The recommended dose of Vectibix® is 6 mg/kg every 14 days

60-minute infusion[1]
- Vectibix® is given by intravenous infusion over 60 minutes
  - Doses greater than 1000 mg should be administered over 90 minutes

Premedication not standardized[1]
- The use of premedication was not standardized in the clinical trials
- The utility of premedication in preventing the first or subsequent episodes of infusional toxicity is unknown

No loading dose[1]
- No loading dose is required

1% severe infusion reactions reported[1]
- Across several clinical trials of Vectibix® monotherapy, 3% (43/1336) experienced infusion reactions of which approximately 1% (6/1336) were severe (NCI-CTC grade 3-4)
- Reduce infusion rate by 50% in patients experiencing a mild or moderate (grade 1 or 2) infusion reaction for the duration of that infusion
- Immediately and permanently discontinue Vectibix® infusion in patients experiencing severe (grade 3 or 4) infusion reactions
- Appropriate medical resources for the treatment of severe infusion reactions should be available during Vectibix® infusions

INDICATION: Vectibix® is indicated as a single agent for the treatment of epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal carcinoma (mCRC) with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

The effectiveness of Vectibix® as a single agent for the treatment of EGFR-expressing mCRC is based on progression-free survival. Currently, no data demonstrate an improvement in disease-related symptoms or increased survival with Vectibix®.

Retrospective subset analyses of metastatic colorectal cancer trials have not shown a treatment benefit for Vectibix® in patients whose tumors had *KRAS* mutations in codon 12 or 13. Use of Vectibix® is not recommended for the treatment of colorectal cancer with these mutations.

Important Safety Information, including **Boxed WARNINGS:**

WARNING: DERMATOLOGIC TOXICITY and INFUSION REACTIONS

Dermatologic Toxicity: Dermatologic toxicities occurred in 89% of patients and were severe (NCI-CTC grade 3 or higher) in 12% of patients receiving Vectibix® monotherapy. *[See Dosage and Administration (2.1), Warnings and Precautions (5.1), and Adverse Reactions (6.1)].*

Infusion Reactions: Severe infusion reactions occurred in approximately 1% of patients. Fatal infusion reactions occurred in postmarketing experience. *[See Dosage and Administration (2.1), Warnings and Precautions (5.2), and Adverse Reactions (6.1, 6.3)].*

In Study 1, dermatologic toxicities occurred in 90% of patients and were severe (NCI-CTC grade 3 and higher) in 16% of patients with mCRC receiving Vectibix®. Subsequent to the development of severe dermatologic toxicities, infectious complications, including sepsis, septic death, and abscesses requiring incisions and drainage were reported. Withhold or discontinue Vectibix® for severe or life-threatening dermatologic toxicity and monitor for inflammatory or infectious sequelae.

Terminate the infusion for severe infusion reactions.

Vectibix® is not indicated for use in combination with chemotherapy. In an interim analysis of a randomized clinical trial, the addition of Vectibix® to the combination of bevacizumab and chemotherapy resulted in decreased overall survival and increased incidence of NCI-CTC grade 3-5 (87% vs 72%) adverse reactions. NCI-CTC grade 3-4 adverse reactions occurring at a higher rate in patients treated with Vectibix® included rash/dermatitis/acneiform (26% vs 1%); diarrhea (23% vs 12%); dehydration (16% vs 5%), primarily occurring in patients with diarrhea; hypokalemia (10% vs 4%); stomatitis/mucositis (4% vs < 1%); and hypomagnesemia (4% vs 0%). NCI-CTC grade 3-5 pulmonary embolism occurred at a higher rate in patients treated with Vectibix® (7% vs 4%) and included fatal events in 3 (< 1%) patients treated with Vectibix®.

In a single-arm study of 19 patients receiving Vectibix® in combination with IFL, the incidence of NCI-CTC grade 3-4 diarrhea was 58%; in addition, grade 5 diarrhea occurred in 1 patient. In a single-arm study of 24 patients receiving Vectibix® plus FOLFIRI, the incidence of NCI-CTC grade 3 diarrhea was 25%.

Pulmonary fibrosis occurred in less than 1% (2/1467) of patients enrolled in clinical studies of Vectibix®. Of the 2 cases, 1 involved a patient with underlying idiopathic pulmonary fibrosis and resulted in death. The second patient had symptoms of pulmonary fibrosis, which was confirmed by CT. Additionally, a third patient died with bilateral pulmonary infiltrates of uncertain etiology with hypoxia. Permanently discontinue Vectibix® therapy in patients developing interstitial lung disease, pneumonitis, or lung infiltrates.

In a randomized, controlled clinical trial, median magnesium levels decreased by 0.1 mmol/L in the Vectibix® arm; hypomagnesemia (NCI-CTC grade 3 or 4) requiring oral or IV electrolyte repletion occurred in 2% of patients. Hypomagnesemia occurred 6 weeks or longer after the initiation of Vectibix®. In some patients, both hypomagnesemia and hypocalcemia occurred. Patients' electrolytes should be periodically monitored during and for 8 weeks after the completion of Vectibix® therapy. Institute appropriate treatment (eg, oral or intravenous electrolyte repletion) as needed.

Exposure to sunlight can exacerbate dermatologic toxicity. Advise patients to wear sunscreen and hats, and limit sun exposure while receiving Vectibix® and for 2 months after the last dose.

Adequate contraception in both males and females must be used while receiving Vectibix® and for 6 months after the last dose of Vectibix® therapy. Vectibix® may be transmitted from the mother to the developing fetus and has the potential to cause fetal harm when administered to pregnant women.

Discontinue nursing or discontinue drug, taking into account the importance of the drug to the mother. If nursing is interrupted, it should not be resumed earlier than 2 months following the last dose of Vectibix®.

The most common adverse events of Vectibix® are skin rash with variable presentations, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea, and diarrhea, including diarrhea resulting in dehydration.

The most serious adverse events of Vectibix® are pulmonary fibrosis, pulmonary embolism, severe dermatologic toxicity complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, and constipation.

Please see brief summary of Prescribing Information on next page.

Reference: 1. Vectibix® (panitumumab) prescribing information, Amgen.

AMGEN®

Amgen
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
www.amgen.com