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

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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.

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. 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). 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%).

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. 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.

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.
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%; \( P \leq 0.001 \)). 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%; \( P = 0.0004 \)), and significantly more patients were able to receive all 4 cycles (93% vs 51%; \( P = 0.0001 \)).

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 acetaminophen, with alternatives including oxycodone and acetylsalicylic acid. For proctitis, Dr. Minsky recommended initial treatment with acetaminophen, with alternatives including oxycodone and acetylsalicylic acid.

**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. However, IMRT can increase the likelihood of infection in these patients. 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

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**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.
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 antineoplastics 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/m2 (approximately 9 cycles) to 61% at 1,020 mg/m2 (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...
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 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 significant 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. 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 Intermitent 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; \( P=0.0025 \)) and PFS (12.0 vs 7.3 months; HR, 0.53; \( P=0.048 \)).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%; \( P=0.038 \)).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.

References

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 (HR = 0.89) or OS (HR = 0.43). 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.
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-
S P E C I A L  M E E T I N G  R E V I E W  E D I T I O N

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=0.039). 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=0.025). 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
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. 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). 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 537 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. The serine/threonine kinase BRAF is a downstream effector of KRAS. BRAF mutations have been detected in approximately 8% of CRC tumors. 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). 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 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...
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

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.
Dose Modifications for Dermatologic Toxicity

VXTRX is not indicated for use in combination with chemotherapy. In an interim analysis of postmarketing experience, fatal infusion reactions occurred in patients receiving VXTRX. Terminate the infusion for severe infusion reactions.

- In patients receiving VXTRX who develop dermatologic toxicities that are grade 3 or higher, or are considered intolerable, withhold VXTRX for at least 5 days until the toxicities have resolved to grade 1 or lower. If the toxicities do not resolve within 5 days, permanently discontinue VXTRX.

- In patients receiving VXTRX who develop severe dermatologic toxicities, infectious complications, including sepsis, septic shock, and other serious infections, may occur. Withhold VXTRX for severe or life-threatening dermatologic toxicities. If toxicity does not improve to grade 1 or lower within 12 hours, permanently discontinue VXTRX.

- In patients receiving VXTRX who develop severe or life-threatening dermatologic toxicities, infectious complications, including sepsis, septic shock, and other serious infections, may occur. Withhold VXTRX for severe or life-threatening dermatologic toxicities. If toxicity does not improve to grade 1 or lower within 12 hours, permanently discontinue VXTRX.
The case for Vectibix®

- The recommended dose of Vectibix® is 6 mg/kg every 14 days
- Vectibix® is given by intravenous infusion over 60 minutes
- No loading dose is required
- Treatment benefit for Vectibix® in patients whose tumors had KRAS mutations in codons 12 or 13. Use of Vectibix® is not recommended for the treatment of colorectal cancer with these mutations.

Important Safety Information, including Boxed WARNINGS:

- 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, 6.2).)

In a single-arm study of 19 patients receiving Vectibix® in combination with IFL, the incidence of NCI-CTC grade 3-4 diarrhea was 88%, 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 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 3-4 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®.

Please see brief summary of Prescribing Information on next page.

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