

vascular consequences of dialysis are irreversible by this stage.

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Cetuximab for Metastatic Colorectal Cancer

TO THE EDITOR: As a gastroenterologist who claims to have been the first physician in Connecticut to give fluorouracil to a patient with colon cancer, I was delighted to read in the Conclusions of the Abstract of the article by Van Cutsem et al. (April 2 issue)¹ that “First-line treatment with cetuximab plus FOLFIRI [irinotecan, fluorouracil, and leucovorin], as compared with FOLFIRI alone, reduced the risk of progression of metastatic colorectal cancer.” My enthusiasm was tempered when I then read in the Results of the Abstract — and in the body of the article — that “There was no significant difference in the overall survival between the two treatment groups.”

That caveat might well have been required to appear in the Conclusions of the Abstract, lest the wrong overly sanguine impression appear in other publications.

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1. Van Cutsem E, Köhne C-H, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;360:1408-17.

TO THE EDITOR: In the study by Van Cutsem et al., the addition of cetuximab to FOLFIRI increased the median progression-free survival from 8.0 months to 8.9 months. This difference, even if it is statistically significant ($P < 0.05$), seems to us to be clinically irrelevant because the 95% confidence intervals of the separate estimations are overlapping. Furthermore, the emphasis given to the results of a retrospective subgroup analysis to investigate the influence of the tumor *KRAS* mutation status on outcome appears to be unjustified, not only because it was performed in 540 of 1198 patients who were not randomly selected (45%), but also because the interaction was not significant ($P = 0.07$); thus, the difference could have

been due to chance. Instead of considering this result as a hypothesis for a prospective randomized trial, the authors, as well as the National Cancer Comprehensive Network guidelines for colorectal cancer, a provisional clinical opinion of the American Society of Clinical Oncology,¹ and, even worse, the European Medicines Agency, which all have approved the use of cetuximab only in patients with *KRAS* wild-type tumors, seem to accept these results without criticism. We are afraid that this lack of criticism could contribute to acceleration of the process that is leading clinical studies away from the standards of scientific research.

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1. Allegra CJ, Jessup JM, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: testing for *KRAS* gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. *J Clin Oncol* 2009;27:2091-6.

TO THE EDITOR: The trial exploring the effect of first-line treatment with cetuximab plus chemotherapy and the association between the *KRAS* gene mutation and the clinical response to cetuximab provides the opportunity to speculate about the predictive and prognostic role of the *KRAS* mutation status of tumors. The results are consistent with those of studies showing that the benefit of cetuximab is limited to patients with *KRAS* wild-type tumors.^{1,2} *KRAS* mutation status seems not to be prognostic in patients receiving

cetuximab; this was already shown in the recent trial exploring the effect of cetuximab, as compared with supportive care, in patients who had already received treatment with chemotherapy for advanced disease.¹ These findings are in contrast to those in the randomized trial by Amado et al.,³ which tested the effect of panitumumab over supportive care and showed that the KRAS status had a prognostic effect on survival among the control group. This discordance raises the issue of the misinterpretation of data from retrospective analyses; indeed, this different behavior of KRAS status could be attributable to the tissue-sample selection, which allowed the recruitment of samples obtained from 68.9% of the patients in the trial reported on by Karapetis et al.¹ and 92.0% of the patients reported on by Amado et al.³

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1. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. *K-ras* mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008;359:1757-65.
2. 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;27:663-71.
3. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;26:1626-34.

TO THE EDITOR: In the retrospective analysis of the influence of the tumor KRAS mutation status on the response to cetuximab in metastatic colorectal cancer, the conclusion that the addition of cetuximab to FOLFIRI reduces the risk of progression, mainly in wild-type KRAS tumors, is questionable. The predictive effect of KRAS status on both progression-free survival and overall survival, which was previously emphasized at different congresses,^{1,2} is not supported by a statistically significant interaction test; therefore, we cannot exclude the possibility that the results based on subgroup analysis are biased toward a false positive effect.

Furthermore, although KRAS mutation seems to exclude the use of antibodies against the epidermal growth factor receptor (EGFR), the benefit of cetuximab in patients with KRAS wild-type

tumors is clinically modest, with an increase in median progression-free survival of less than 2 months and no effect on overall survival. Thus, the cost-benefit ratio of the use of the KRAS status of the tumor can be negative, increasing the burden of expenses for the public health system, with only a small, if any, benefit for patients. Prospective studies aimed at further refining the patient selection in this subgroup are warranted.

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1. Rougier P, Stroiakovski D, Köhne C, et al. Addition of cetuximab to FOLFIRI in first-line metastatic colorectal cancer (mCRC): updated survival data and influence of KRAS status on outcome in the CRYSTAL study. Presented at the American Society of Clinical Oncology 2009 Gastrointestinal Cancers Symposium, San Francisco, January 15-17, 2009. abstract.
2. Van Cutsem E, Lang I, D'haens G, et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: the CRYSTAL experience. *J Clin Oncol* 2008;26:Suppl:15S. abstract.

THE AUTHORS REPLY: The primary end point of our study was progression-free survival. The study was not powered to demonstrate significant differences in overall survival, because post-study therapy can confound the treatment effect. That the Conclusions section of the Abstract emphasizes the risk of progression is therefore entirely appropriate. Moreover, given the statistical design, conclusions should not be drawn from the consideration of single point estimates such as median values, as suggested by Roila et al., with the hazard ratio of 0.85 (95% confidence interval, 0.72 to 0.99) more appropriately illustrating the benefit in favor of the cetuximab-FOLFIRI combination.

As to whether KRAS tumor mutation status is prognostic in these patients, Bria and colleagues appear to have misinterpreted the data of Amado et al.¹ Although KRAS status was predictive of outcome in both study groups, among patients who did not cross over from best supportive care to receive panitumumab at disease progression, no difference in overall survival was observed between the groups with wild-type and mutant KRAS. Comparable data for cetuximab were reported by Karapetis et al.² Moreover, assessment of 1404 patients with stage II or III colon cancer

in the PETACC-3 (Pan-European Trials in Adjuvant Colon Cancer) study (Current Controlled Trials number, ISRCTN72194324) showed that KRAS status was not prognostic.³

An analysis of clinical outcome according to tumor KRAS mutation status was not planned. Consequently, there was no protocol-specified requirement in our study to obtain tissue specimens from patients. Anticipating that tumor samples would not be available from all patients, a number of steps were taken to minimize the potential for selection bias. The similarity of relevant baseline characteristics between the primary analysis and KRAS populations and the similarity of treatment effects between these populations both indicate that sampling bias was not an important confounding factor.

Interaction tests commonly lack power when they are not planned, as was the case for the KRAS analysis in our study. The associated P values should therefore be viewed only as descriptive measures. Evidence of KRAS as a predictive biomarker was initially provided by a series of small, single-group studies and is now confirmed in several randomized studies,^{1,2,4} each showing a

benefit associated with anti-EGFR antibody therapy in patients with metastatic colorectal cancer with wild-type but not mutant KRAS tumors.

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Moyamoya Disease and Moyamoya Syndrome

TO THE EDITOR: As the principal investigator of a National Institutes of Health (NIH)–funded natural-history study involving North American adults with moyamoya disease,¹ I read with interest the review article on this disease and moyamoya syndrome by Scott and Smith (March 19 issue).² There is one implicit, and, I believe, invalid, assumption in this otherwise thoughtful review: that the findings of the natural-history studies involving pediatric Asian populations are applicable to North American adults. I am writing to emphasize that the natural history of North American adults with this angiographic disorder is unknown. In addition, many adult patients in North America have a benign clinical course that is probably related to the development of sufficient collateral sources of blood flow in them. The phenotype of North American adult moyamoya disease is a woman in her fourth or fifth decade of life who presents with ischemic symptoms.³ This presentation differs from that reported in Asian studies.⁴ Finally, as noted by the au-

thors, the moyamoya vessels that are the hallmark of the disorder are simply a distinctive form of collateralization that develops in response to an underlying vasculopathy. The nature of the occlusive vasculopathy is unknown and probably multifactorial, particularly in North American adults.⁵

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3. Hallemeier CL, Rich KM, Grubb RL Jr, et al. Clinical features and outcome in North American adults with moyamoya phenomenon. *Stroke* 2006;37:1490-6.
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