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The Clinical Benefit of Bevacizumab in Metastatic Colorectal Cancer Is Independent of K-*ras* Mutation Status: Analysis of a Phase III Study of Bevacizumab with Chemotherapy in Previously Untreated Metastatic Colorectal Cancer

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Key Words. Bevacizumab • Vascular endothelial growth factor • Colorectal cancer • Survival • Fluorouracil • Angiogenesis inhibitors

Disclosures

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ABSTRACT

Purpose. **Mutations of the K-*ras* gene were identified as a prognostic marker in metastatic colorectal cancer (mCRC). In addition, emerging data suggest that K-*ras* mutations are a negative predictor of clinical benefit from anti–epidermal growth factor receptor treatment in mCRC. Previously reported data suggest that the longer overall survival (OS) observed with bevacizumab treatment in mCRC is independent of alterations in the Ras/Raf/Mek/Erk pathway. We conducted additional analyses to better describe the clinical benefit of bevacizumab treatment in mCRC relative to K-*ras* mutation status.**

Patients and Methods. **Additional statistical analyses were done with data from K-*ras* mutation analyses in 230 patients who were treated with irinotecan, fluorouracil, and leucovorin (IFL) in combination with either bevacizumab or placebo in a randomized phase III study. Following microdissection, tissue was subject to DNA sequencing to identify K-*ras* mutations in codons 12 and 13. Hazard ratios for the bevacizumab group relative to the control group were estimated from an unstratified Cox regression model. The median progression-free survival (PFS), OS times, and objective response rates were compared.**

Results. **K-*ras* status was assessed in 230 patients (28.3%). The median PFS was significantly longer in bevacizumab-treated patients with wild-type (wt)- (13.5 versus 7.4 months; hazard ratio 0.44, $p < .0001$) and mutant (m)-K-*ras* (9.3 versus 5.5 months; hazard ratio**

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0.41, $p = .0008$). A significantly higher response rate for IFL plus bevacizumab was observed only in wt-K-*ras* patients (60.0% versus 37.3%, $p = .006$) compared with 43.2% versus 41.2% in the m-K-*ras* group.

Conclusion. **Bevacizumab provides significant clinical benefit in patients with mCRC expressing either mutant or wild-type K-*ras*.** ***The Oncologist*** 2009;14:22–28

Introduction

Bevacizumab was shown to improve the overall survival (OS) time, progression-free survival (PFS) time, and objective response rate (RR) in a placebo-controlled phase III trial when added to irinotecan, fluorouracil, and leucovorin (IFL) chemotherapy in the first-line treatment of metastatic colorectal cancer (mCRC) [1]. An exploratory analysis of this study suggested that the OS benefit of the addition of bevacizumab was independent of the mutation status of K-*ras*, B-*raf*, or *p53* [2]. The selection of K-*ras* for these analyses was based upon evidence that K-*Ras* regulates vascular endothelial growth factor (VEGF) and other angiogenic factors [3, 4], as well as numerous reports that K-*ras* is a negative prognostic factor in patients with mCRC [5–8].

Mutations in K-*ras* strongly predict for a lack of response to anti–epidermal growth factor receptor (EGFR) antibodies [9–12]. For this reason, K-*ras* testing is required by the European Medical Authority for the use of panitumumab and cetuximab. The role of *ras* mutations in predicting response to traditional cytotoxic agents in advanced CRC has not been well studied.

The impact of *ras* mutations on OS was previously reported for the addition of bevacizumab to first-line IFL chemotherapy. To better describe the clinical benefit of bevacizumab according to K-*ras* mutation status in this patient population, we performed additional analyses of other measures of clinical benefit, including the PFS time and RR.

Methods

Patients and Study Design

The details of study AVF2107 (registered at http://www.ClinicalTrials.gov, ID number NCT00109070), including patient eligibility criteria, study design, treatment, and assessments, have been reported previously [1]. Only patients with sufficient tumor tissue for molecular assessment of K-*ras* were included in the exploratory analyses contained in this report.

Ethics

The institutional review boards of the investigative centers approved the study protocol, and the trial was conducted in accordance with the Declaration of Helsinki, U.S. Food and Drug Administration Good Clinical Practices, and local ethical and legal requirements. All patients provided written informed consent for their study participation.

Molecular Testing of Tumor Tissue

The details of the available tissue samples, laser capture microdissection, polymerase chain reaction (PCR) primers and conditions, and direct sequencing of PCR products have been described previously [2]. The selected primers covered codons 12 and 13.

Statistical Analyses

The efficacy analysis was based on randomized patients with known K-*ras* mutation status. The PFS time was defined as the time from randomization to disease progression or death resulting from any cause during first-line treatment. Median PFS times were estimated using the Kaplan–Meier method. An unstratified Cox regression model was used to estimate the hazard ratio (HR) for the bevacizumab group relative to the control group. A two-sided log-rank test ($\alpha = 0.05$) was used to compare the differences between the bevacizumab and the placebo group. Because of sample size considerations, this test was unstratified. The objective RR was defined as the rate of a complete or partial response determined on two consecutive occasions at least 4 weeks apart during first-line treatment. The χ^2 test was used to compare the objective RRs. Any differential effect of treatment between the K-*ras* mutation status groups was evaluated using a Cox model with K-*ras* mutation status, treatment, and the K-*ras*-by-treatment interaction term in the model.

Results

Tissue samples from 230 of 813 patients (28%) were available for molecular analysis of the selected K-*ras* codons. Of these 230 patients, 129 had been randomly assigned to receive IFL chemotherapy plus bevacizumab (IFL + BV) and 101 had been randomly assigned to receive IFL chemotherapy plus placebo (IFL + placebo). Demographic and baseline disease characteristics for the K-*ras* subgroup and for the overall phase III study population are summarized in Table 1. The median ages in the groups were 62.0 and 58.0 years, respectively. The demographic and baseline characteristics were similar in the subset of patients with available tumor tissue and the entire study population [1]. A higher incidence of patients with an Eastern Cooperative Oncol-

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Table 1. Baseline demographic and disease characteristics of randomized K-*ras* patients and overall phase III study population

Characteristic	K-*ras* subgroup		Overall	
	IFL + placebo (n = 101)	IFL + BV (n = 129)	IFL + placebo (n = 411)	IFL + BV (n = 402)
Age, yrs				
Mean (SD)	58.3 (10.8)	60.4 (10.9)	59.2 (11.5)	59.5 (11.3)
Median	58.0	62.0	60.0	60.0
Range	27–83	24–80	21–83	23–86
Sex				
Male	54 (53.5%)	75 (58.1%)	248 (60.3%)	237 (59.0%)
Female	47 (46.5%)	54 (41.9%)	163 (39.7%)	165 (41.0%)
ECOG performance status (baseline), n (%)				
0	62 (61.4%)	78 (60.5%)	227 (55.2%)	234 (58.4%)
1	39 (38.6%)	51 (39.5%)	182 (44.3%)	166 (41.4%)
2	0 (0.0%)	0 (0.0%)	2 (0.5%)	1 (0.2%)
Mean (SD) duration of disease, mos	12.4 (16.27)	13.2 (22.84)	16.1 (22.02)	15.2 (23.22)
Location of primary tumor				
Colon	83 (82.2%)	101 (78.3%)	334 (81.3%)	310 (77.1%)
Rectum	18 (17.8%)	28 (21.7%)	77 (18.7%)	92 (22.9%)
Mean (SD) serum albumin (baseline), g/dl	3.7 (0.51)	3.7 (0.53)	3.7 (0.54)	3.7 (0.53)
Mean (SD) serum alkaline phosphatase, U/l	172.6 (139.62)	181.0 (163.18)	163.1 (148.89)	165.6 (146.74)

Baseline ECOG performance status, weight, and laboratory test results are the last available values as reported on the case report form on or before the first day of treatment with study drug or chemotherapy.
Location of primary tumor obtained from interactive voice response system when not reported on case report form.
Abbreviations: BV, bevacizumab; ECOG, Eastern Cooperative Oncology Group; IFL, irinotecan, fluorouracil, and leucovorin; SD, standard deviation.

ogy Group performance status score of zero in the placebo arm (61.4% versus 55.2%) and a shorter mean time from diagnosis in both arms of the subpopulation (12.4 months for IFL + placebo and 13.2 months for IFL + BV in the tissue available subgroup versus 16.1 months for IFL + placebo and 15.2 months for IFL + BV in the study as a whole) were observed. Additional characteristics not included in Table 1, that is, gender, race/ethnicity, body weight and surface area, and serum lactate dehydrogenase, were comparable with those in the entire population. K-*ras* mutations were detected in 78 of the 230 patients (34%).

Measures of clinical benefit were generally comparable in the subgroup with available tissue and in the overall population. Comparing the subgroup with available tissue with the overall population, the HRs for OS were similar (HR, 0.60; 95% confidence interval [CI], 0.40–0.91; $p = .01$ versus HR, 0.66; 95% CI, 0.54–0.81; $p < .0001$, respectively), although a modest difference in the median OS time was noted (25.1 versus 17.5 months compared with 20.3 versus 15.6 months, respectively). Modest differences between the subgroup with available tissue and the overall population were noted for PFS (HR, 0.44; 95% CI, 0.32–0.61; $p < .0001$ versus HR, 0.54; 95% CI, 0.45–0.66; $p < .0001$; median, 11.3 months versus 6.3 months, compared with 10.6 months versus 6.2 months,

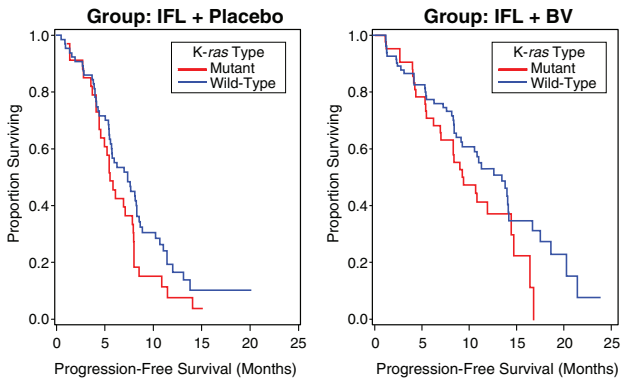

Figure 1. Progression-free survival by treatment for randomized patients with known K-*ras* status.
Abbreviations: BV, bevacizumab; IFL, irinotecan, fluorouracil, and leucovorin.

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Table 2. PFS, overall survival, and objective response rate for K-*ras* patients randomized to IFL + placebo or IFL + BV

	Wild-type			Mutant		
Efficacy variable	**IFL + placebo (n = 67)**	**IFL + BV (n = 85)**	***p*-value; HR (95% CI)[a]**	**IFL + placebo (n = 34)**	**IFL + BV (n = 44)**	***p*-value; HR (95% CI)[a]**
Median survival duration, mos[b]	17.6	27.7	p = .04; HR, 0.58 (0.3–1.0)	13.6	19.9	p = .26; HR, 0.69 (0.4–1.3)
Median PFS duration during first-line therapy, mos	7.4	13.5	p < .0001; HR, 0.44 (0.3–0.7)	5.5	9.3	p = .0008; HR, 0.41 (0.2–0.7)
Objective response, n (%)	25 (37.3%)	51 (60.0%)	p = .006	14 (41.2%)	19 (43.2%)	p = .86
Complete	2 (3.0%)	3 (3.5%)		0 (0.0%)	3 (6.8%)	
Partial	23 (34.3%)	48 (56.5%)		14 (41.2%)	16 (36.4%)	

[a]For survival and PFS, p-value is from an unstratified log-rank test; HR is relative to the placebo group and estimated by Cox regression. For objective response, p-value is from a Pearson χ^2 test.
[b]Previously reported by Ince et al. (2005) [2].
Abbreviations: BV, bevacizumab; CI, confidence interval; HR, hazard ratio; IFL, irinotecan, fluorouracil, and leucovorin; PFS, progression-free survival.

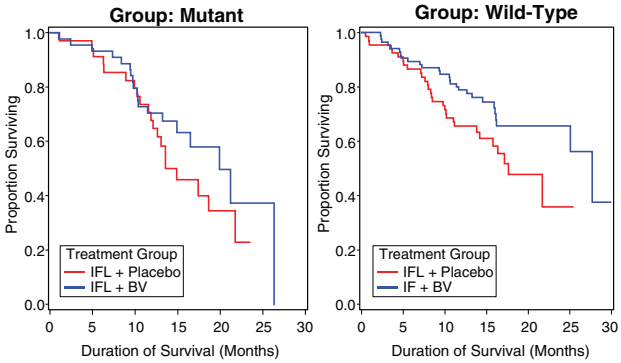

Figure 2. Duration of overall survival by K-*ras* status for randomized patients with known K-*ras* status.
Abbreviations: BV, bevacizumab; IFL, irinotecan, fluorouracil, and leucovorin.

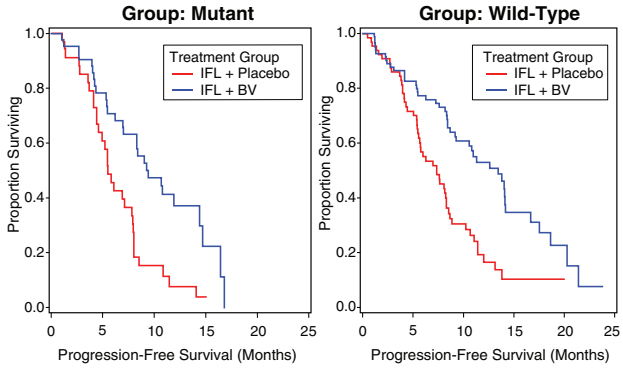

Figure 3. Duration of progression-free survival by K-*ras* status for randomized patients with known K-*ras* status.
Abbreviations: BV, bevacizumab; IFL, irinotecan, fluorouracil, and leucovorin.

respectively) and for RR (44.8% versus 34.8% compared with 54.3% versus 38.6%, respectively).

Prognostic Value of K-*ras* Mutations in mCRC

To assess the prognostic importance of K-*ras*, PFS was compared according to K-*ras* status for both the IFL + placebo and the IFL + BV groups (Fig. 1). For patients treated with IFL + placebo, the median PFS duration was 7.4 months for wild-type (wt)-K-*ras* patients and 5.5 months for mutant (m)-K-*ras* patients (HR, 0.69; 95% CI, 0.44–1.08; p = .11 for wt-K-*ras* versus m-K-*ras*). In patients treated with IFL + BV, the median PFS was 13.5 months for wt-K-*ras* patients and 9.3 months for m-K-*ras* patients (HR, 0.66; 95% CI, 0.41–1.08; p = .09 for wt-K-*ras* versus m-K-*ras*).

Predictive Value of K-*ras* Mutations for Treatment with Bevacizumab in mCRC

Results of the analyses of OS, PFS, and RR according to K-*ras* mutation status are listed in Table 2. Kaplan–Meier curves for OS and PFS are shown in Figure 2 and Figure 3, respectively. In both the wt-K-*ras* and m-K-*ras* groups, the addition of bevacizumab to IFL chemotherapy resulted in a statistically significant longer PFS time, with comparable HRs for progression. In the wt-K-*ras* group, the median PFS duration was 13.5 months for IFL + BV versus 7.4 months for IFL + placebo (HR, 0.44; 95% CI, 0.29–0.67; p < .0001). For the m-K-*ras* group, the median PFS duration was 9.3 months for IFL + BV versus 5.5 months for IFL + placebo (HR, 0.41; 95% CI, 0.24–0.70; p = .0008). As previously reported [2], comparable findings were noted for OS. In the wt-K-*ras* group, the median OS time was 27.7 months for IFL + BV versus 17.6 months for IFL + placebo (HR, 0.58; 95% CI, 0.34–0.99; p = .04). For the m-K-*ras* group, the median OS time was 19.9 months for IFL + BV versus 13.6 months for IFL + placebo (HR, 0.69; 95% CI, 0.37–1.31; p = .26). For PFS and OS, the point estimates for the interaction effect suggest that there is no dif-

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Table 3. *n* (%) of patients with selected adverse events during first-line therapy for treated patients with known K-*ras* status

	Wild-type		Mutant	
Adverse event	**IFL + placebo (*n* = 67)**	**IFL + BV (*n* = 85)**	**IFL + placebo (*n* = 34)**	**IFL + BV (*n* = 43)**
On-study death from any cause	5 (7.5)	2 (2.4)	0 (0)	1 (2.3)
Any adverse event, grade 3–4	50 (74.6)	78 (91.8)	25 (73.5)	39 (90.7)
Arterial thromboembolic event, any grade	1 (1.5)	1 (1.2)	0 (0)	1 (2.3)
GI perforation, grade 3–4[a]	0 (0)	1 (1.2)	0 (0)	3 (7.0)
Bleeding, grade 3–4[b]	3 (4.5)	2 (2.4)	1 (2.9)	3 (7.0)
Hypertension, grade 3–4	2 (3.0)	8 (9.4)	2 (5.9)	8 (18.6)
Proteinuria, grade 3–4	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea, grade 3–4	14 (20.9)	21 (24.7)	4 (11.8)	15 (34.9)

Grading of adverse events used National Cancer Institute–Common Toxicity Criteria.
[a]GI perforation was defined as GI abscess, perforation, or fistula.
[b]Reported adverse events included GI hemorrhage, hematuria, hemorrhage, hemothorax, melena, and rectal hemorrhage.
Abbreviations: BV, bevacizumab; GI, gastrointestinal; IFL, irinotecan, fluorouracil, and leucovorin.

ference in the treatment benefit between the K-*ras* subgroups (data not shown); however, wide CIs for these estimates indicate limited statistical power to detect a clinically meaningful differential effect. Regarding tumor response, the overall RRs for IFL + BV versus IFL + placebo were 60.0% versus 37.3% in the wt-K-*ras* group ($p = .006$) and 43.2% versus 41.2% in the m-K-*ras* group ($p = .86$), respectively.

The incidences of bevacizumab-associated adverse events and any grade 3 or 4 adverse events (based on the National Cancer Institute – Common Toxicity Criteria) were comparable for the two K-*ras* subgroups (Table 3), despite the longer time on treatment for the wt-K-*ras* subgroup compared with the m-K-*ras* subgroup (and for the bevacizumab group compared with the placebo group). Because of the limited size of the subgroup with tissue available for K-*ras* analysis and the low rates of most grade ≥3 adverse events and events of special interest regarding bevacizumab, small event rate differences between the m-K-*ras* and wt-K-*ras* groups cannot be excluded.

Discussion

A growing body of evidence suggests not only that mutations of the K-*ras* oncogene have prognostic significance in mCRC, but also that K-*ras* mutations may serve as predictive markers that can be used to guide the use of anti-EGFR therapy. Multiple phase II and III studies have demonstrated that patients with mCRC harboring mutations in K-*ras* do not appear to derive clinical benefit from anti-EGFR monoclonal antibody treatment, when used either as monotherapy or in combination with cytotoxic chemotherapy [9–16].

Several reports have indicated that K-*ras* mutations are negative prognostic markers and portend a poorer outcome in mCRC [7, 8, 17]. The retrospective analysis presented in this report appears to support the prognostic significance of K-*ras* mutations in mCRC. This finding is consistent with previously reported data involving cytotoxic chemotherapies that generally support the concept that K-*Ras* is not a predictive marker for benefit, or lack of benefit, from traditional cytotoxic chemotherapy [5–7]. More recent data [10–12], however, suggest that K-*ras* status is not generally prognostic and may have a modest but distinct predictive importance for oxaliplatin versus irinotecan regimens. Thus, the question of the prognostic significance of mutated K-*ras* in mCRC appears to remain open.

Independent of whether K-*ras* status is prognostic in mCRC, the data in the current report strongly suggest that K-*ras* status does not predict clinical benefit from the addition of bevacizumab to first-line IFL chemotherapy. The relative benefits in terms of PFS and OS associated with the addition of bevacizumab to IFL chemotherapy were comparable in the m-K-*ras* and wt-K-*ras* groups.

Whereas patients with wt-K-*ras* in this study appeared to have a greater RR with the addition of bevacizumab to IFL, no such benefit was found in patients with m-K-*ras*.

Multiple preclinical studies have demonstrated that K-*ras* mutations upregulate VEGF and numerous other angiogenic factors in tumor cells [3, 4, 18]. Given these potential mechanisms of resistance, the same clinical benefit from bevacizumab in patients with m-K-*ras* and wt-K-*ras* tumors supports the role of VEGF as the primary angiogenic factor in CRC.

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This analysis has several limitations. First, it is retrospective, so tissue was not available for the assessment of K-*ras* for a significant proportion of the study population; thus, an unintentional selection bias for the subset of patients included in this analysis is possible. However, the patient and tumor characteristics for the subgroup of patients with available tissue were comparable with those of the overall study population and the frequency and type of K-*ras* mutations in this study were similar to those from other reports [7–10, 17]. The relatively small sample size in this study also precludes a definitive assessment of the presence or absence of an interaction. A definitive study that could detect an HR of 0.6 in the wt-K-*ras* group and an HR of one in the m-K-*ras* group with 80% power would require 540 events and potentially >1,000 subjects.

These data have implications for the appropriate management of patients with mCRC as well as the design and interpretation of clinical trials in this disease. Our analyses suggest that the clinical benefit from the anti-VEGF therapy bevacizumab, unlike EGFR-targeted antibodies, appears to be independent of K-*ras* status. At a practical level, K-*ras* testing is unnecessary to determine which patients should receive bevacizumab. These data also highlight the complexity of K-*ras* biology in mCRC. Clinical trial populations need to be defined regarding the selection, or lack of selection, for K-*ras* mutation status in order to allow for appropriate interpretation.

Lastly, these data also highlight the distinction between prognostic and predictive markers, a topic that has been extensively reviewed [19]. As diagnostics and therapeutics related to key oncogenes become available, these distinctions will take on even greater clinical significance.

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2. Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–2342.

3. Ince WL, Jubb AM, Holden SN et al. Association of k-ras, b-raf, and p53 status with the treatment effect of bevacizumab. J Natl Cancer Inst 2005;97:981–989.

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Provision of study materials: Herbert I. Hurwitz
Collection/assembly of data: William Ince, William F. Novotny, Oliver Rosen
Data analysis: Herbert I. Hurwitz, Jing Yi, William F. Novotny, Oliver Rosen
Manuscript writing: Herbert I. Hurwitz, Jing Yi, Oliver Rosen
Final approval of manuscript: Herbert I. Hurwitz, Jing Yi, William Ince, William F. Novotny, Oliver Rosen

The listed authors take full responsibility for the content of the paper, but wish to also thank Linda Phillips, Ph.D., from Genentech for her assistance in organizing the published literature and editing the manuscript.

References

1 Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–2342.

2 Ince WL, Jubb AM, Holden SN et al. Association of k-ras, b-raf, and p53 status with the treatment effect of bevacizumab. J Natl Cancer Inst 2005;97:981–989.

3 Rak J, Yu JL, Kerbel RS et al. What do oncogenic mutations have to do with angiogenesis/vascular dependence of tumors? Cancer Res 2002;62:1931–1934.

4 Mizukami Y, Kohgo Y, Chung DC. Hypoxia inducible factor-1 independent pathways in tumor angiogenesis. Clin Cancer Res 2007;13:5670–5674.

5 Ahnen DJ, Feigl P, Quan G et al. Ki-ras mutation and p53 overexpression predict the clinical behavior of colorectal cancer: A Southwest Oncology Group study. Cancer Res 1998;58:1149–1158.

6 Esteller M, González S, Risques RA et al. K-ras and p16 aberrations confer poor prognosis in human colorectal cancer. J Clin Oncol 2001;19:299–304.

7 Andreyev HJ, Norman AR, Cunningham D et al. Kirsten ras mutations in patients with colorectal cancer: The 'RASCAL II' study. Br J Cancer 2001;85:692–696.

8 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.

9 Amado RG, Wolf M, Peeters M et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:1626–1634.

10 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 5):2.

11 Bokemeyer C, Bondarenko I, Makhson A et al. Fluorouracil, leucovorin,

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and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2008; December 29 [Epub ahead of print], doi: 10.1200/JCO.2008.20.8397.

12 Punt CJ, Tol J, Rodenburg CJ et al. Randomized phase III study of capecitabine, oxaliplatin, and bevacizumab with or without cetuximab in advanced colorectal cancer (ACC), the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). J Clin Oncol 2008;26(suppl 15): LBA4011.

13 Lièvre A, Bachet JB, Le Corre D et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res 2006; 66:3992–3995.

14 Di Fiore F, Blanchard F, Charbonnier F et al. Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by cetuximab plus chemotherapy. Br J Cancer 2007;96:1166–1169.

15 Khambata-Ford S, Garrett CR, Meropol NJ et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol 2007;25:3230–3237.

16 De Roock W, Piessevaux H, De Schutter J et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol 2008;19: 508–515.

17 Benvenuti S, Sartore-Bianchi A, Di Nicolantonio F et al. Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. Cancer Res 2007;67:2643–2648.

18 Downward J. Targeting RAS signalling pathways in cancer therapy. Nat Rev Cancer 2003;3:11–22.

19 Sargent D, Allegra C. Issues in clinical trial design for tumor marker studies. Semin Oncol 2002;29:222–230.

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