KRAS Mutation in Stage III Colon Cancer and Clinical Outcome Following Intergroup Trial CALGB 89803

Shuji Ogino,1,2 Jeffrey A. Meyerhardt,1 Natsumi Irahara,1 Donna Niedzwiecki,5 Donna Hollis,5 Leonard B. Saltz,6 Robert J. Mayer,1 Paul Schaefer,7 Renaud Whittom,8 Alexander Hantel,9 Al B. Benson III,10 Richard M. Goldberg,11 Monica M. Bertagnolli,3 and Charles S. Fuchs1,4 for the Cancer and Leukemia Group B, North Central Cancer Treatment Group, Canadian Cancer Society Research Institute, Southwest Oncology Group

Abstract

Purpose: Alterations in the RAS and RAF pathway relate to epigenetic and epigenomic aberrations, and are important in colorectal carcinogenesis. KRAS mutation in metastatic colorectal cancer predicts resistance to anti–epidermal growth factor receptor (EGFR)-targeted therapy (cetuximab or panitumumab). It remains uncertain, however, whether KRAS mutation predicts prognosis or clinical outcome of colon cancer patients independent of anti-EGFR therapy.

Methods: We conducted a study of 508 cases identified among 1,264 patients with stage III colon cancer who enrolled in a randomized adjuvant chemotherapy trial (5-fluorouracil, leucovorin with or without irinotecan) in 1999-2001 (CALGB 89803). KRAS mutations were detected in 178 tumors (35%) by pyrosequencing. Kaplan-Meier and Cox proportional hazard models assessed the prognostic significance of KRAS mutation and adjusted for potential confounders including age, sex, tumor location, tumor/node stage, performance status, adjuvant chemotherapy arm, and microsatellite instability status.

Results: Compared with patients with KRAS-wild-type tumors, patients with KRAS-mutated tumors did not experience any difference in disease-free, recurrence-free, or overall survival. The 5-year disease-free, recurrence-free, and overall survival rates (KRAS-mutated versus KRAS-wild-type patients) were 62% versus 63% (log-rank \( P = 0.89 \)), 64% versus 66% \( (P = 0.84) \), and 75% versus 73% \( (P = 0.56) \), respectively. The effect of KRAS mutation on patient survival did not significantly differ according to clinical features, chemotherapy arm, or microsatellite instability status, and the effect of adjuvant chemotherapy assignment on outcome did not differ according to KRAS status.

Conclusions: In this large trial of chemotherapy in stage III colon cancer patients, KRAS mutational status was not associated with any significant influence on disease-free or overall survival. (Clin Cancer Res 2009;15(23):7322–9)

Authors’ Affiliations: 1Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, and Departments of 2Pathology, 3Surgery, and 4Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts; 5CALGB Statistical Center, Duke University Medical Center, Durham, North Carolina; 6Memorial Sloan-Kettering Cancer Center, New York, New York; 7Toledo Community Hospital Oncology Program, Toledo, Ohio; 8Hôpital du Sacré-Coeur de Montréal, Montréal, Canada; 9Loyola University Stritch School of Medicine, Maywood, Illinois; 10Northwestern University, Chicago, Illinois; and 11University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Received 6/18/09; revised 8/14/09; accepted 8/17/09; published OnlineFirst 11/24/09.

Grant support: The research for CALGB 89803 was supported, in part, by grants from the National Cancer Institute (CA31946) to the Cancer and Leukemia Group B (Richard L. Schilsky, MD, Chairman) and to the CALGB Statistical Center (Stephen George, PhD, CA33601), as well as support from Pharmacia & Upjohn Company, now Pfizer Oncology. Each author was supported as listed with affiliations. S. Ogino was supported in part by K07 award from the National Cancer Institute (K07 CA122826). S. Ogino, J.A. Meyerhardt, and C.S. Fuchs were supported in part by the SPORE grant (P50 CA127003). The sponsors did not participate in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

Requests for reprints: Shuji Ogino, Center for Molecular Oncologic Pathology, Dana-Farber Cancer Institute, Brigham and Women’s Hospital, Harvard Medical School, 44 Binney Streets, Room JF-215C, Boston, MA 02115. Phone: 1-617-632-3978; Fax: 1-617-277-9015; E-mail: shuji_ogino@dfci.harvard.edu.

© 2009 American Association for Cancer Research.
doi:10.1158/1078-0432.CCR-09-1570


**Translational Relevance**

Activating mutations in the KRAS gene are important events during the colorectal carcinogenic process, and predict resistance to anti-epidermal growth factor receptor treatment for metastatic colorectal cancer. However, the literature data on the prognostic significance of KRAS mutation in colon cancer have been conflicting. We utilized the database of 508 stage III colon cancers in this adjuvant chemotherapy trial following surgical resection. Because data on pathologic stage, performance status, postoperative treatment, and follow-up were carefully captured in this trial, the simultaneous impact of disease characteristics and the use of adjuvant therapy could be assessed to be controlled for potential confounding. We found that KRAS mutation does not have a substantial prognostic or predictive role in stage III colon cancer treated with adjuvant chemotherapy.

KRAS, one of the first genes found to be mutated in human cancer, encodes a G-protein downstream of receptor tyrosine kinases, including epidermal growth factor receptor (EGFR; ref. 1–3). Population-based studies have shown that approximately 30% to 40% of colon cancers harbor mutations in codons 12 and 13 of KRAS (4–6). Retrospective observational studies (7–12) as well as randomized controlled trials (13–17) have consistently shown that KRAS mutation in stage IV colorectal cancer confers resistance to anti-EGFR targeted treatment (ce-tuximab or panitumumab). However, whether KRAS mutation in colorectal cancer has a prognostic role, independent of anti-EGFR therapy, has been controversial (18–21). Previous data have not been conclusive, even among several large studies (4, 6, 22–26). In addition, whether KRAS mutational status modifies the effect of irinotecan-based chemotherapy remains uncertain.

We therefore examined the influence of KRAS on cancer recurrence and survival in a large number (N = 508) of stage III colon cancer patients enrolled in a National Cancer Institute (NCI)-sponsored clinical trial of postoperative adjuvant chemotherapy (27). Within this trial (CALGB 89803), patients were randomized to either fluorouracil and leucovorin or fluorouracil, leucovorin, and irinotecan. Moreover, because data on pathologic stage, performance status, postoperative treatment, and follow-up were carefully captured in this trial, the simultaneous impact of disease characteristics and the use of adjuvant therapy could be assessed to be controlled for potential confounding.

**Materials and Methods**

**Study population.** Patients in this study were participants in the NCI-sponsored Cancer and Leukemia Group B (CALGB) adjuvant therapy trial for stage III colon cancer comparing therapy with the weekly Roswell Park regimen of 5-fluorouracil (FU) and leucovorin (FU/LV) with the weekly bolus regimen of irinotecan, FU, and leucovorin (IFL; CALGB 89803; ref. 27). From April 1999 to May 2001, 1,264 patients were enrolled in the treatment trial. Patients in the treatment trial (and thus this companion study) were eligible if they had undergone a complete surgical resection of the primary tumor within 56 d prior to study entry, and had regional lymph node metastases (stage III colon cancer) but no evidence of distant metastases. Moreover, patients were required to have a baseline Eastern Cooperative Oncology Group performance status of 0 to 2 (ambulatory; ref. 28) and have adequate bone marrow, renal, and hepatic function. The current analysis was limited to 508 patients for whom archived formalin-fixed paraffin-embedded tumor tissue was available and the KRAS gene was sequenced. All patients signed informed consent, approved by each site’s institutional review board.

We compared the baseline characteristics of the patients who were included in this study (with available KRAS data, n = 508) with those who were excluded from this study due to unavailability of tissue data (n = 756). We did not detect any significant or substantial difference between these two groups in terms of age, sex, body mass index, tumor location, T stage, N stage, performance status, bowel perforation, bowel obstruction, or treatment arm. In addition, tumor recurrence or mortality did not substantially differ between these two groups; multivariate hazard ratios (HR; KRAS data available versus unavailable) were 1.05 [95% confidence interval (95% CI), 0.87-1.27] for disease-free survival (DFS), 1.05 (95% CI, 0.86-1.28) for recurrence-free survival (RFS), and 1.06 (95% CI, 0.86-1.32) for overall survival (OS).

**Definitions of study end points.** In this study, the primary end point was DFS, defined as time from the study enrollment to tumor recurrence, occurrence of a new primary colon tumor, or death from any cause. In addition, we defined RFS as the time from the study enrollment to tumor recurrence or occurrence of a new primary colon tumor. For RFS, patients who withdrew without known tumor recurrence were censored at last documented evaluation by treatment provider. Finally, OS was defined as the time from the study enrollment to death from any cause.

**DNA extraction from tumor, sequencing of KRAS, and microsatellite instability analysis.** DNA was extracted from paraffin-embedded tissue of colon cancer as previously described (29). We marked a tumor area on a H&E-stained slide, and dissected the tumor area from another tumor tissue section by a sterile needle for subsequent DNA extraction. PCR and pyrosequencing spanning KRAS codons 12 and 13 were done as previously described (29), and validated against Sanger sequencing method (29, 40). In our KRAS pyrosequencing assay, we routinely confirmed the presence of a mutation by two different sequencing primers and by the creation of frameshifted reading of a mutant sequence relative to a wild-type sequence in a pyrogram (29). Microsatellite instability (MSI) was assessed using 10 DNA mononucleotide and dinucleotide microsatellite markers as previously described (30). Tumors showing instability in ≥40% of the loci tested were classified as MSI-high. Tumors showing instability in no or <40% of the loci were classified as microsatellite stable (MSS)/MSI-low.

**Statistical analyses.** The goal of this correlative study was to determine whether tumoral KRAS mutational status influences clinical outcome of patients with stage III colon cancer. Patient registration and clinical data collection were managed by the CALGB Statistical Center, and analyses were conducted collaboratively between the CALGB Statistical Center and Dana-Farber Cancer Institute. All analyses were based on the study database frozen on March 7, 2008, except for the tumor KRAS data. All analyses used SAS version 9.1.3 (SAS Institute) and all P values were two-sided.

In the treatment trial (comparing two chemotherapy regimens), there was no statistical difference in either DFS or OS between the treatment arms (27). The Kaplan-Meier method was used to describe the distribution of survival time according to KRAS status, and the log-rank test was carried out. We used stage-matched (or stratified) Cox proportional hazard models to calculate the HR of events according to tumoral KRAS status, adjusted for age at study entry (as a continuous variable), gender, baseline body mass index (≥30 versus <30 kg/m²), baseline performance status (0 versus 1-2), presence of bowel perforation or obstruction at time of surgery, treatment arm, tumor location (proximal versus distal), and MSI status (high versus low/MSS). Tumor stage (IIIA, IIIB, IIIC, or III unspecified substage) was used as a matching...
Table 1. Baseline characteristics according to KRAS mutational status in stage III colon cancer

<table>
<thead>
<tr>
<th>Clinical or molecular feature</th>
<th>No. of cases</th>
<th>KRAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>508</td>
<td>330</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>276 (54%)</td>
<td>179 (54%)</td>
</tr>
<tr>
<td>Female</td>
<td>232 (46%)</td>
<td>151 (46%)</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>100 (20%)</td>
<td>62 (19%)</td>
</tr>
<tr>
<td>50-59</td>
<td>130 (26%)</td>
<td>82 (25%)</td>
</tr>
<tr>
<td>60-69</td>
<td>158 (31%)</td>
<td>102 (31%)</td>
</tr>
<tr>
<td>≥70</td>
<td>120 (24%)</td>
<td>84 (25%)</td>
</tr>
<tr>
<td>Mean age ± SD, y</td>
<td>59.8 ± 11.5</td>
<td>60.2 ± 11.6</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>163 (32%)</td>
<td>110 (34%)</td>
</tr>
<tr>
<td>25-29</td>
<td>182 (36%)</td>
<td>114 (35%)</td>
</tr>
<tr>
<td>≥30</td>
<td>157 (31%)</td>
<td>104 (32%)</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right (cecum to transverse colon)</td>
<td>291 (58%)</td>
<td>191 (58%)</td>
</tr>
<tr>
<td>Left (splenic flexure to sigmoid)</td>
<td>212 (42%)</td>
<td>136 (42%)</td>
</tr>
<tr>
<td>AJCC tumor stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>49 (9.7%)</td>
<td>34 (10%)</td>
</tr>
<tr>
<td>IIIB</td>
<td>270 (53%)</td>
<td>167 (51%)</td>
</tr>
<tr>
<td>IIIC</td>
<td>184 (36%)</td>
<td>125 (38%)</td>
</tr>
<tr>
<td>III, unknown substage</td>
<td>5 (1.0%)</td>
<td>4 (1.2%)</td>
</tr>
<tr>
<td>Performance status score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>384 (76%)</td>
<td>246 (75%)</td>
</tr>
<tr>
<td>1-2</td>
<td>120 (24%)</td>
<td>82 (25%)</td>
</tr>
<tr>
<td>Clinical bowel perforation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>477 (96%)</td>
<td>310 (96%)</td>
</tr>
<tr>
<td>+</td>
<td>22 (4.4%)</td>
<td>14 (4.3%)</td>
</tr>
<tr>
<td>Clinical bowel obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>393 (78%)</td>
<td>252 (77%)</td>
</tr>
<tr>
<td>+</td>
<td>112 (22%)</td>
<td>76 (23%)</td>
</tr>
<tr>
<td>MSI status*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSS/MSI-low</td>
<td>394 (82%)</td>
<td>247 (78%)</td>
</tr>
<tr>
<td>MSI-high</td>
<td>86 (18%)</td>
<td>68 (22%)</td>
</tr>
<tr>
<td>Treatment arm*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FU/LV</td>
<td>266 (52%)</td>
<td>157 (48%)</td>
</tr>
<tr>
<td>IFL</td>
<td>242 (48%)</td>
<td>173 (52%)</td>
</tr>
</tbody>
</table>

NOTE: (%) indicates the proportion of tumors with a specific clinical feature in KRAS-wild-type tumors (or KRAS-mutated tumors). There were cases with missing value/status for some of the variables. Abbreviation: AJCC, American Joint Committee on Cancer. *Distributional differences are significant with P < 0.01.
compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, adverse events, tumor response, and outcome in a sample of protocols at each institution. Such on-site review of medical records was done for a subgroup of 328 patients (26%) of the 1,264 patients under this study.

Results

KRAS mutation and clinical outcome in stage III colon cancer. Study participants were drawn from a multicenter study of postoperative adjuvant chemotherapy in patients with stage III colon cancer who underwent a curative-intent surgical resection. We included 508 cases in this study based on availability of tumor tissue for KRAS sequencing, which detected a KRAS mutation in 178 (35%) patients. Identified KRAS mutations were as follows: 56 cases with codon 12 GGC > GAT (p.G12D, c.35G > A); 52 with codon 13 GGC > GAC (p.G13D, c.38G > A); 32 with codon 12 GGT > GTT (p.G12V, c.35G > T); 21 with codon 12 GGT > TGT (p.G12C, c.34G > T); 9 with codon 12 GGT > GCT (p.G12A, c.35G > C); and 8 with codon 12 GGT > AGT (p.G12S, c.34G > A). Table 1 summarizes the baseline characteristics of study subjects according to KRAS mutational status.

Patients with a mutation in KRAS were significantly less likely to possess MSI or receive IFL as compared with FU/LV. We assessed the influence of KRAS mutational status on clinical outcome in the 508 patients with stage III colon cancers. With median follow-up of 6.2 years among surviving participants, there were 196 events for DFS analysis, 180 events for RFS analysis, and 149 events for OS analysis. In Kaplan-Meier analysis, there were no significant differences in survival time distributions between patients with KRAS mutations and those with wild-type KRAS (log-rank P = 0.89 for DFS; Fig. 1; log-rank P = 0.84 for RFS; log-rank P = 0.56 for OS). DFS at 5 years was 62% for KRAS-mutated and 63% for KRAS-wild-type patients. RFS at 5 years was 64% for KRAS-mutated and 66% for KRAS-wild-type patients. Finally, OS at 5 years was 75% for KRAS-mutated and 73% for KRAS-wild-type patients.

In a univariate Cox regression analysis, when compared with KRAS-wild-type patients, KRAS-mutated patients did not experience a significant difference in DFS (HR, 0.98; 95% CI, 0.73-1.31), RFS (HR, 0.97; 95% CI, 0.71-1.32), or OS (HR, 0.90; 95% CI, 0.64-1.27).

Table 2. KRAS mutational status and clinical outcome in stage III colon cancer

<table>
<thead>
<tr>
<th>KRAS</th>
<th>Total, n</th>
<th>Disease-free survival</th>
<th>Recurrence-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Univariate HR (95% CI)</td>
<td>Multivariate HR (95% CI)</td>
<td>Univariate HR (95% CI)</td>
</tr>
<tr>
<td>Wild-type</td>
<td>330 (65%)</td>
<td>1 (referent)</td>
<td>1 (referent)</td>
<td>117 (referent)</td>
</tr>
<tr>
<td>Mutant</td>
<td>178 (35%)</td>
<td>0.98 (0.73-1.31)</td>
<td>0.95 (0.70-1.28)</td>
<td>63 (0.71-1.32)</td>
</tr>
</tbody>
</table>

NOTE: The multivariate Cox regression model included age, sex, body mass index, tumor location, T and N stage, the presence or absence of perforation and/or obstruction at diagnosis, performance status, MSI status, and treatment arm.
These findings persisted in multivariate analysis that adjusted for clinical, pathologic, or molecular predictors of patient outcome, and no substantial confounding was identified.

**KRAS mutation and clinical outcome in strata of treatment arm.** We assessed whether the effect of KRAS mutational status on patient outcome was modified by adjuvant chemotherapy (Table 3). In both treatment arms (FU/LV and IFL), the presence of a mutation in KRAS was not associated with any significant difference in patient survival. Moreover, statistical tests for interaction failed to show any significant interaction between chemotherapy assignment and KRAS mutational status ($P$ for interaction = 0.64, 0.67, and 0.60 for DFS, RFS, and OS, respectively).

**Effect of irinotecan on clinical outcome in strata of KRAS status.** We also assessed whether the effect of adjuvant chemotherapy arm on patient survival was modified by KRAS mutational status (Table 4). In both KRAS-wild-type and KRAS-mutated cases, there were no significant differences in DFS, RFS, or OS between the two treatment arms. No significant modifying effect on the relation between KRAS and clinical outcome by any of the other covariates. Finally, we examined whether there was significant modifying effect on the relation between KRAS mutation and clinical outcome by any of the other covariates (age, sex, tumor location, T and N stage, the presence or absence of perforation and/or obstruction at diagnosis, performance status, and MSI status). There was no evidence of significant effect modification by any of the variables examined (all $P_{interaction} > 0.23$).

**Discussion**

In this study of 508 patients with stage III colon cancer treated with surgery and adjuvant chemotherapy, KRAS mutational status...
status was not associated with any significant influence on cancer recurrence or death. These results were not materially altered in multivariate analyses that adjusted for other predictors for patient outcome. Moreover, the effect of KRAS mutation on patient survival did not significantly differ according to clinical features, chemotherapy arm, or MSI status, and the effect of adjuvant chemotherapy arm did not differ according to KRAS status. In separate independent cohort studies (6, 33), we previously showed that KRAS mutation was not significantly associated with survival of colon cancer patients in univariate analysis as well as multivariate analysis that adjusted for tumor stage, MSI, BRAF mutation, and other related molecular features. Thus, together with our previous data, our current data do not support a substantial prognostic role of KRAS mutation in colon cancer.

Although KRAS mutation does not seem to be a significant prognostic marker in colon cancer, its importance in colorectal carcinogenesis has been well documented. KRAS is one of the most commonly mutated oncoproteins in human cancer. KRAS mutation activates the RAS-RAF pathway as well as the phosphoinositide 3-kinase-AKT pathway, leading to cellular growth and proliferation (2). Indeed, KRAS and PIK3CA mutations are associated with each other in colorectal cancer (34, 35), and KRAS and PIK3CA mutations seem to interact in survival analysis (33). Recently, a link between KRAS mutation and epigenomic aberrations in colorectal cancer has been suggested (31, 36–38). Specifically, KRAS mutation has been associated with low-level CpG island methylator phenotype (31, 36, 38, 39), and this relation has been shown in another independent dataset (22). In contrast to somatic mutations including those in KRAS, epigenomic aberrations are potentially reversible. Although a mechanistic link between epigenomics and KRAS mutation remains uncertain, analysis of KRAS mutation in colon cancer may shed light on epigenomic aberrations in cancer and provide targeted therapeutic opportunities.

Studying patient outcome has been an important area in cancer research. Accumulating evidence suggests KRAS mutational status is a critical biomarker to predict response or resistance to anti-EGFR targeted therapy in patients with metastatic colorectal cancer. Retrospective observational studies (7–12) as well as randomized controlled trials (13–17) have consistently shown that KRAS mutation in stage IV colorectal cancer confers resistance to cetuximab or panitumumab treatment. Thus, KRAS mutation testing is rapidly emerging as a routine clinical test for patients with metastatic colorectal cancers who are potential candidates for treatment with either cetuximab or panitumumab (1, 2, 40).

In contrast to anti-EGFR targeted therapy, the role of KRAS mutation in predicting response to other therapies remains unclear. For example, a couple of previous studies have examined the relationship between KRAS mutation and response to bevacizumab, and have shown that KRAS mutation does not predict response or resistance to bevacizumab in colon cancer (25, 41).

Although the "predictive" role for KRAS mutational testing in defining sensitivity to anti-EGFR targeted therapy in stage IV colorectal cancer is now widely accepted, the "prognostic" role for KRAS as an independent predictor of survival in patients with colorectal cancer remains less conclusive (18–20). Previous meta-analyses (RASCAL and RASCAL II; refs. 42, 43) showed that KRAS mutation was associated with worse outcome in colorectal cancer. However, these meta-analyses substantially suffered from publication bias; especially as most studies used were relatively small (N <150 in most studies; N <290 in all included studies). Compared with small studies with significant results, small studies with null results were more likely unpublished, and thus more likely excluded from these meta-analyses. Larger studies (e.g., N >290) have tended to show no independent prognostic significance of KRAS mutation in colorectal cancer. A large population-based study of 569 colorectal cancer patients reported that KRAS mutation was independently associated with worse survival (22), whereas most other large studies found no independent prognostic role of KRAS mutation (4, 6, 23–25, 44), including a recent study on 1,379 stage II–III colon cancers (26). Our current findings were limited to only stage III colon cancers. Nonetheless, our results are consistent with most previous large studies on colon cancers including stage III and other stages (4, 6, 23–26, 44). Moreover, although one small study of 35 patients suggested that KRAS mutational status influenced irinotecan sensitivity (45), KRAS mutational status did not seem to modify the influence of irinotecan-based adjuvant therapy in our trial.

There are several advantages in examining associations of molecular markers with outcome of patients in a NCI-sponsored clinical trial of adjuvant chemotherapy. All patients had stage III colon cancer, thus reducing the impact of heterogeneity by disease stage. Moreover, treatment and follow-up care were all standardized within the clinical trial, and the date and nature of recurrence were prospectively recorded. In addition, detailed information on other prognostic variables was routinely collected at study entry.

We recognize that patients who enroll in randomized trials may differ from the population-at-large. To participate, patients must meet eligibility criteria, be selected as appropriate candidates, and be motivated to participate. In addition, patients were particularly selected for this study on the basis of availability of colon cancer tissue specimens. Nonetheless, the demographic data of the patients in this study did not suggest significant selection bias. Moreover, because the study included patients from both community and academic centers across North America, our findings should reflect the general population of stage III patients in North America. In addition, although data on KRAS mutational status were available on a subset of patients enrolled in the trial, baseline characteristics and patient survival did not differ for patients with and without available archived tumor tissue in this trial.

In conclusion, we found that KRAS mutational status did not significantly predict clinical outcome in this study of stage III colon cancer patients. Although KRAS mutational testing should be routinely utilized to assess for appropriate use of anti-EGFR therapy in advanced colorectal cancer, KRAS status is unlikely to meaningfully predict patient prognosis.

Disclosure of Potential Conflicts of Interest

L. Saltz has received research funding from Pfizer, Roche, Genentech, Bristol Myers Squibb, Imclone, and Amgen, and is a consultant to Pfizer, Roche, Genentech, Bristol Myers Squibb, Imclone, Amgen, Genzyme and Genomic Health; A. Benson has received research funding from Pfizer, Imclone, Bristol Myers Squibb, Amgen, and Sanofi Aventis and is a scientific advisor for Pfizer, Imclone, Bristol Myer Squibb, Amgen, and Sanofi Aventis.
Acknowledgments

We thank the CALGB Pathology Coordinating Office at the Ohio State University for banking and preparing the materials for the study. The following institutions participated in this study:

Baptist Cancer Institute CCOP, Memphis, TN - Lee S. Schwartzberg, M.D., supported by CA71323
Christiana Care Health Services, Inc. CCOP, Wilmington, DE - Stephen Grubbs, M.D., supported by CA45418
Dana-Farber Cancer Institute, Boston, MA - Eric P. Winer, M.D., supported by CA32291
Dartmouth Medical School - Norris Cotton Cancer Center, Lebanon, NH - Marc S. Ernstoff, M.D., supported by CA04326
Duke University Medical Center, Durham, NC - Jeffrey Crawford, M.D., supported by CA47577
Georgetown University Medical Center, Washington, DC - Minetta C. Liu, M.D., supported by CA77597
Cancer Centers of the Carolinas, Greenville, SC - Jeffrey K. Giguere, M.D., supported by CA29165
Hematology-Oncology Associates of Central New York CCOP, Syracuse, NY - Jeffrey Kirshner, M.D., supported by CA45389
Long Island Jewish Medical Center, Lake Success, NY - Kanti R. Rai, M.D., supported by CA11028
Massachusetts General Hospital, Boston, MA - Jeffrey W. Clark, M.D., supported by CA12449
Memorial Sloan-Kettering Cancer Center, New York, NY - Clifford A. Hudis, M.D., supported by CA77651
Missouri Baptist Medical Center, St. Louis, MO - Alan P. Lyss, M.D., supported by CA114558-02
Mount Sinai Medical Center, Miami, FL - Rogerio C. Lilienbaum, M.D., supported by CA45564
Mount Sinai School of Medicine, New York, NY - Lewis R. Silverman, M.D., supported by CA04457
Nevada Cancer Research Foundation CCOP, Las Vegas, NV - John A. Ellerton, M.D., supported by CA35421
North Shore-Long Island Jewish Health System, New Hyde Park, NY - Daniel Budman, M.D., supported by CA35279
Rhode Island Hospital, Providence, RI - William Sikov, M.D., supported by CA08025
Roswell Park Cancer Institute, Buffalo, NY - Ellis Levine, M.D., supported by CA02599
Southeast Cancer Control Consortium Inc. CCOP, Goldsboro, NC - James N. Atkins, M.D., supported by CA45808
State University of New York Upstate Medical University, Syracuse, NY - Stephen L. Graziano, M.D., supported by CA21060
The Ohio State University Medical Center, Columbus, OH - Clara D. Bloomfield, M.D., supported by CA77658
University of California at San Diego, San Diego, CA - Barbara A. Parker, M.D., supported by CA11789
University of California at San Francisco, San Francisco, CA - Alan P. Venook, M.D., supported by CA60138
University of Chicago, Chicago, IL - Gini Fleming, M.D., supported by CA41287
University of Illinois MBCOP, Chicago, IL - Lawrence E. Feldman, M.D., supported by CA74811
University of Iowa, Iowa City, IA - Daniel A. Vaena, M.D., supported by CA47642
University of Maryland Greenebaum Cancer Center, Baltimore, MD - Martin Edelman, M.D., supported by CA31983
University of Massachusetts Medical School, Worcester, MA - William V. Walsh, M.D., supported by CA37135
University of Minnesota, Minneapolis, MN - Bruce A. Peterson, M.D., supported by CA16450
University of Missouri/Ellis Fischel Cancer Center, Columbia, MO - Michael C. Perry, M.D., supported by CA12046
University of Nebraska Medical Center, Omaha, NE - Anne Kessinger, M.D., supported by CA77298
University of North Carolina at Chapel Hill, Chapel Hill, NC - Thomas C. Shea, M.D., supported by CA47559
University of Tennessee Memphis, Memphis, TN - Harvey B. Niell, M.D., supported by CA47555
University of Vermont, Burlington, VT - Hyman B. Mss, M.D., supported by CA77406
Wake Forest University School of Medicine, Winston-Salem, NC - David D Hurd, M.D., supported by CA03927
Walter Reed Army Medical Center, Washington, DC - Thomas Reid, M.D., supported by CA26806
Washington University School of Medicine, St. Louis, MO-Nancy Bartlett, M.D., supported by CA77440
Weill Medical College of Cornell University, New York, NY - John Leonard, M.D., supported by CA07968

References


Clinical Cancer Research

KRAS Mutation in Stage III Colon Cancer and Clinical Outcome Following Intergroup Trial CALGB 89803

Shuji Ogino, Jeffrey A. Meyerhardt, Natsumi Irahara, et al.


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-09-1570

Cited articles
This article cites 44 articles, 21 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/15/23/7322.full.html#ref-list-1

Citing articles
This article has been cited by 26 HighWire-hosted articles. Access the articles at:
/content/15/23/7322.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.