Cancer and Leukemia Group B Gastrointestinal Cancer Committee

Richard M. Goldberg,1 Donna Niedzwiecki,2 Monica Bertagnolli,3 A. William Blackstock,4 Joel E. Tepper,5 and Robert J. Mayer3

Abstract

The Cancer and Leukemia Group B Gastrointestinal Cancer Committee was organized in the late 1970s under the leadership of Michael Perry and Philip Schein and began full-scale operations in the mid-1980s. Today, it is a multidisciplinary team of surgeons, radiation and medical oncologists, statisticians, quality-of-life experts, pharmacogeneticists, basic scientists, and community oncologists who design studies that are conducted across the United States. The Committee has done trials in patients with esophageal, gastric, pancreatic, colon, rectal, and anal cancers. New initiatives are under way in hepatocellular cancer, cholangiocarcinoma, and neuroendocrine tumors originating in the gastrointestinal tract. The Committee has increasingly concentrated on translational studies using tumor blocks, germ-line DNA, and plasma to evaluate biological correlates of tumor response and clinical outcomes. A broad program of pharmacogenomics has been incorporated for virtually all studies, including trials that prospectively use polymorphisms in drug-metabolizing genes to assign treatments. Future efforts aim to evolve new standards of care, evaluate new therapies, and answer relevant biological questions in gastrointestinal cancer.

The Committee's History

When the Cancer and Leukemia Group B (CALGB) was founded in 1956, treatment for gastrointestinal cancer was rudimentary and not a component of the Group's research agenda. During the early 1970s, the National Cancer Institute funded the Gastrointestinal Tumor Study Group to develop clinical trials in gastrointestinal cancers. Several founding institutional members of Gastrointestinal Tumor Study Group (i.e., Georgetown University, McGill University, Mt. Sinai Hospital, and Roswell Park Cancer Institute) were also active participants in the CALGB. During the late 1970s, under the leadership of Michael Perry and Philip Schein, CALGB launched a series of phase II to III trials in gastrointestinal cancer to address the research interests of investigators managing these common diseases, complementing the efforts of the Gastrointestinal Tumor Study Group. The nascent Committee also afforded CALGB members the opportunity to enroll patients in the gastrointestinal studies of other cooperative oncology groups. These efforts led to several publications (1–3). However, patient accrual lagged behind projections, and following a major reorganization of CALGB in 1980, research in gastrointestinal cancer was suspended.

The 1986 publication in New England Journal of Medicine of the results of the Gastrointestinal Tumor Study Group rectal adjuvant trial showed the value of postoperative chemoradiation therapy and the potential to realize meaningful advances in gastrointestinal cancer through randomized trials conducted by cooperative oncology groups (4). Shortly thereafter, preliminary data were presented, suggesting the benefit of adding leucovorin and/or levamisole to 5-fluorouracil (5-FU) in the advanced disease and adjuvant settings for patients with colorectal cancer (5, 6). In 1986, the CALGB Board of Directors discussed the potential for resuming investigative efforts in gastrointestinal cancer because of the success of other groups in accruing to large trials in gastrointestinal cancer, the high frequency of gastrointestinal cancers, and the interest expressed by CALGB surgeons and radiation oncologists to advance the field through clinical trials. By that time, the Gastrointestinal Tumor Study Group had disbanded and the CALGB members who had been active in that group lacked a platform for continued clinical investigation in gastrointestinal cancer treatments. In 1987, the Group Chairman, Emil Frei III, conveyed to the CALGB Board of Directors the National Cancer Institute's desire to ensure adequate accrual for selected high-priority randomized phase III trials, among them several colorectal cancer adjuvant protocols. Robert J. Mayer represented CALGB in developing an adjuvant colon cancer study to assess the efficacy of 5-FU and leucovorin at an organizational meeting convened by the National Cancer Institute with participants from the Eastern Cooperative Oncology Group, North Central Cancer Treatment Group, and Southwest Oncology Group. That spring, the plenary presentation of the CALGB meeting was devoted to a review of "the status of adjuvant therapy for colorectal cancer." The CALGB Board of Directors subsequently created a planning committee to develop clinical trials in gastrointestinal cancers. Dr. Mayer chaired this working group and was joined by Richard Schilsky, Glenn Steele, and Joel E. Tepper. In 1988, CALGB activated Intergroup adjuvant trials in colon cancer (CALGB 8896 and Intergroup 0089) and rectal cancer (CALGB 8894 and North Central Cancer Treatment Group 86-17-51).
The first meeting of the CALGB gastrointestinal working group in 1988 was attended by 55 members. Thirty-two CALGB surgeons convened in New York in January 1989 to stimulate surgical support for this initiative. By the time of the second gastrointestinal working group meeting that Spring, 44 patients had been registered onto the adjuvant colorectal cancer trials. In recognition of the obvious Group interest, the Board of Directors advanced the gastrointestinal working committee to full disease committee status, with Drs. Mayer and Tepper appointed chair and vice-chair, respectively. Their tenure as committee leaders continued until late 2004. Under their leadership, the Gastrointestinal Cancer Committee developed several phase II and III trials and participated in the design and accrual to many trials in which multiple oncology cooperative groups collaborated. The leadership of the Committee rotated in 2004 when Richard M. Goldberg (medical oncology), A. William Blackstock (radiation oncology), and Monica Bertagnolli (surgical oncology) were appointed chair and cochair, respectively. Statisticians Donna Niedzwiecki and Donna Hollis as well as other members of the statistical and administrative team provided continuity through the leadership transition. Throughout its existence, the Committee has been guided by the Gastrointestinal Cancer Committee members made up of leading gastrointestinal cancer researchers from multiple disciplines affiliated with numerous prominent cancer research centers across the country. The Committee’s studies pertain to cancers originating anywhere in the gastrointestinal tract. Highlights from selected research studies are included in this report.

Surgical Trials

Glenn Steele led an Intergroup study coordinated by CALGB that examined sphincter sparing surgery in patients with distal rectal adenocarcinomas (7). This study remains the only multi-institutional effort mounted to examine this management approach to our knowledge. The 59 patients with T1 tumors underwent local excision with no further treatment and that strategy resulted in one local recurrence. The 51 patients with T2 tumors received 5,400 cGy with bolus 5-FU after local excision. Of these patients, the 7 who recurred locally were all able to undergo abdominal perineal resection. The failure-free survival was 85% for the T1 and 78% for the T2 patients at a median of 6 years of follow-up. This trial provided evidence that sphincter function could safely be preserved in the majority of patients with T1 and T2 distal rectal cancers but also showed a surprisingly high local recurrence rate in patients with T2 lesions, particularly in the presence of perineural involvement.

CALGB surgeons also participated in the Intergroup trial of laparoscopic versus open colectomy led by Heidi Nelson from North Central Cancer Treatment Group. This study randomized 872 patients and showed that cancer-related outcomes were no different between these approaches (8). Laparoscopically resected patients had modestly shorter hospital stays, diminished parenteral and oral narcotic requirements, and smaller incisions, but their surgeries took more operative time. There was clear evidence that with experience operative times for laparoscopic surgery decreased to the point of mirroring those for open colectomy.

Selected Adjuvant Trials in Colon Cancer

CALGB 8896 was entitled “A prospectively randomized trial of low-dose levoucorin plus 5-FU, high-dose levoucorin plus 5-FU, levamisole plus 5-FU, or low-dose levoucorin plus 5-FU plus levamisole following curative resection in selected patients with Duke’s B or C colon cancer.” This study, designed in the late 1980s, was originally a comparison of two different dose schedules of adjuvant 5-FU and levoucorin compared with a nontreatment control arm. In September 1989, data showing the superiority of 5-FU and levoucorin to a nontreatment control arm led to revision of this study to substitute 5-FU and levoucorin as the control arm (9). A fourth arm was also added, combining 5-FU, leucovorin, and levamisole. By 1992, a total of 3,561 eligible patients had been registered, 936 (26%) by CALGB members.

Analysis showed that the four treatments produced similar disease-free and overall survival, but the toxicity patterns of the four treatment regimens varied greatly. In particular, the results of this trial directly comparing the 5-day “bolus” 5-FU/leucovorin program (“Mayo regimen”) with the weekly higher dose 5-FU/leucovorin program (“Roswell Park regimen”) showed the 5-day bolus schedule to produce a significantly higher rate of neutropenia and stomatitis than the weekly program, whereas the latter had a slightly higher rate of severe diarrhea. The study also showed conclusively that the addition of levamisole to 5-FU/leucovorin did not add benefit, leading to the replacement of levamisole by leucovorin as the preferred modulator of 5-FU. The final results of this study, with a median follow-up time in excess of 10 years, were recently published (10).

Because outcomes were identical among the four arms of this study, all patients could be pooled permitting a series of secondary analyses. Three of these secondary analyses were led by Jeffrey Meyerhardt from CALGB (11–13). Obese patients who received adjuvant chemotherapy were found to have a significant increase in overall mortality and a borderline significant increase in disease recurrence. Patients with diabetes mellitus who entered this trial were found to have a significantly higher rate of disease recurrence and mortality. Survival in this study was not associated with hospital volume for colon cancer as had been documented previously for rectal primary cancers. In an additional analysis led by Charles Fuchs of CALGB, the clinical benefits in African American and Caucasian patients were found to be similar as opposed to results suggested in other trials, and African Americans overall experienced less toxicity than did Caucasians (14).

Two additional Intergroup colon adjuvant trials that were initiated by CALGB have been thus far been reported in abstract form as their data continue to mature for article submission. Protocol 9581, led by Thomas Colacchio, randomized 1,738 stage II patients after resection of their primary tumors to monoclonal antibody 17-1A or to no postoperative therapy (15). There was little treatment-related toxicity but no discernable benefit associated with this treatment. CALGB 89803, led by Leonard Saltz, randomized 1,264 stage III patients to weekly bolus 5-FU with leucovorin alone or with irinotecan (IFL; ref. 16). In 2004, after a median follow-up time of 2 years, the CALGB Data and Safety Monitoring Board released the results due to futility. No difference in failure-free survival (P = 0.88) or overall survival (P = 0.92) was
discernable. A total of 18 patients randomized to the irinotecan/5-FU/leucovorin regimen died due to treatment-associated toxicity in comparison with 6 patients in the 5-FU/leucovorin cohort. The trial was important, as many oncologists had already begun to prescribe IFL as adjuvant chemotherapy for stage III colon cancer based on its superiority to 5-FU/leucovorin in the metastatic setting. The negative results of 89803, although surprising, spared many patients from the excessive toxicity of the IFL regimen.

Adjuvant Therapy of Rectal Cancer

CALGB 8894 was entitled “A phase III protocol for surgical adjuvant therapy of rectal cancer; a controlled evaluation of (a) protracted infusion of 5-FU as a radiation enhancer and (b) 5-FU plus methyl-CCNU chemotherapy.” This study enrolled 666 patients, 13% registered by CALGB, and showed the superiority of infusional compared with bolus 5-FU as a radiation sensitizer, setting a standard of care for management of rectal cancer in the postoperative setting that is current today. It also established that the addition of the potentially leukemogenic agent methyl-1-(2-chloroethyl)-3-cyclohexyl-L-nitrosourea to 5-FU added toxicity without augmenting efficacy (17).

Optimal chemotherapy for locally advanced rectal cancer was addressed in CALGB 9081/Intergroup 0114, which compared bolus 5-FU (standard of care) with 5-FU plus leucovorin, levamisole, or both. All 1,792 registered patients received two cycles of chemotherapy before and after 5-FU-based chemoradiation. With a median follow-up of 7.4 years, there was no difference in overall survival or disease-free survival between the four treatment groups (18). Retrospective subset analyses of these data resulted in several important observations. Thirty-four percent of patients with tumor recurrence or progression in a solitary site underwent resection (<0.001), underscoring the potential value of aggressive surgical resection for patients with limited metastatic disease. Another analysis showed that hospital surgical volume did not significantly affect cancer recurrence or survival, whereas sphincter-preserving surgery was more commonly done at high-volume centers (20).

The current Intergroup phase III trial is enrolling the role of adjuvant oxaliplatin/5-FU chemoradiation for the treatment of locally advanced rectal cancer. The preclinical rationale and phase I/II trial (CALGB 89901) in support of this important study originated, in part, from CALGB investigators (21).

Advanced Colorectal Cancer Studies

Nancy Kemeny led CALGB 9481, a trial that randomized 135 patients with unresectable metastatic colorectal cancer limited to the liver to i.v. 5-FU plus leucovorin or hepatic arterial infusion (HAI) of fluorodeoxyuridine (22). The patients receiving HAI had better survival (24 versus 20 months; \( P = 0.003 \)), a higher response rate (47% versus 24%; \( P = 0.01 \)), and longer time to hepatic progression (10 versus 7 months; \( P = 0.03 \)). The patients assigned to receive HAI also had less systemic toxicity and better physical functioning. Although CALGB 9481 unambiguously showed the value of HAI chemotherapy compared with systemic 5-FU/leucovorin for selected patients, it is uncertain if the results with HAI treatment are superior to those that can be achieved with contemporary systemic chemotherapeutic programs. CALGB is currently participating in the National Surgical Adjuvant Breast and Bowel Project C-09 study evaluating systemic capcitabine and oxaliplatin with or without HAI in patients with resected liver metastases, a research question that is at least in part an outgrowth of the research effort of Dr. Kemeny.

Intergroup study N9741 (CALGB 89804) randomized patients with advanced colorectal cancer to IFL, oxaliplatin plus infused 5-FU and leucovorin (FOLFOX), or irinotecan and oxaliplatin. Eventually, >1,700 patients enrolled through several trial modifications. As the study was accruing, CALGB Pharmacology and Experimental Therapeutics Committee Vice Chair Howard McLeod proposed that it would be an ideal vehicle through which to examine polymorphisms in candidate genes regulating drug metabolism. Because cohorts of patients were exposed to two of three chemotherapy drugs, comparisons correlating both toxicity and response with common polymorphisms among groups treated or not exposed to each agent were possible. Collection of germ-line DNA was optional on this trial; 520 patients donated blood for this purpose. This is the largest cohort of advanced colorectal cancer patients enrolled in a trial to date for which both clinical data and germ-line DNA are available and thus is among the largest populations currently available for correlation of genetic variables with cancer patient treatment outcomes. In addition, the study collected quality-of-life data using the validated European Organization for Research and Treatment of Cancer QLQ C30 questionnaire, customized questions to address neuropathy, and the Uniscale as a global assessment periodically.

The primary activity and toxicity data were reported on 795 patients (23). For patients randomized to FOLFOX, the median time to progression was 8.7 months, response rate was 45%, and median survival time was 19.5 months. These were significantly superior to results observed for the standard regimen of IFL for all cancer outcomes (6.9 months, 31%, and 15.0 months) and for irinotecan and oxaliplatin (6.5 months, 35%, and 17.4 months). The FOLFOX regimen had significantly lower rates of severe nausea, vomiting, diarrhea, febrile neutropenia, and dehydration but a higher rate of sensory neuropathy and neutropenia. Early in the trial, several arms delivered 5-FU as a bolus in combination with oxaliplatin or irinotecan, among them then standard IFL regimen (24). Each of these regimens was associated with significant toxicity, including early toxic deaths. These findings were a catalyst for the widespread adoption in North America of 5-FU infusion-based therapies, the preferred delivery platform used in most of Europe.

The study also contributed to the identification and subsequently sparked a better understanding of the severe toxicity, including early treatment-related deaths in a small minority of patients treated with irinotecan-based therapies. These observations have since been explained, mainly through the work of CALGB-associated investigator teams, by polymorphisms in the UGT1A1 gene that controls the metabolism of irinotecan (25).

In N9741, as in other trials, surgery was possible in all arms of the study but was more often possible with the oxaliplatin-containing regimens. The patients who underwent resection of metastases, 2% of those enrolled, enjoyed a prolonged median survival of 44 months (26). The achievement of a
complete remission in the absence of surgery also led to comparably long remissions in the 4% of patients classified in that category (27).

**Esophageal and Gastric Cancer Trials**

Until recently, the standard therapy for patients with locally advanced gastric/gastroesophageal cancer was surgical resection, a strategy leading to 20% to 30% survival. Neither adjuvant chemotherapy alone nor radiation alone improved this outcome. The Southwest Oncology Group initiated a trial (Intergroup 0116/CALGB 9195), which randomized 556 patients, of which 98 were contributed by CALGB members to receive either surgery or surgery followed by 5-FU/leucovorin and radiation therapy. The median relapse-free survival was 19 months in the surgery-only group versus 30 months in the chemoradiation group ($P < 0.001$; ref. 28). The median overall survival was 27 months for the surgery-only group versus 36 months for combination therapy ($P = 0.005$). There was also a reduction in the rate of local failure in the combined modality arm when compared with the surgery only (19% versus 29%). This combination therapy is now standard and serves as the control arm for CALGB 80101, an ongoing Intergroup phase III trial evaluating adjuvant epirubicin, cisplatin, and infusional 5-FU chemotherapy plus chemoradiation.

CALGB initiated protocol 9781 in 1997 to definitively determine whether the administration of preoperative 5-FU/ cisplatin and radiation therapy improved the outcome over surgery alone in patients with esophageal cancer. The study closed due to slow accrual after enrolling only 59 patients. Nevertheless, a recent analysis indicates that patients treated with trimodality therapy had a median survival of 4.5 years compared with 1.8 years ($P = 0.02$) for those treated with surgery alone and 5-year overall survival of 39% versus 29% (29). This combination therapy is now standard and serves as the control arm for CALGB 80101, an ongoing Intergroup phase III trial evaluating adjuvant epirubicin, cisplatin, and infusional 5-FU chemotherapy plus chemoradiation.

Correlative Science in Gastrointestinal Malignancies

In the early 1990s, CALGB began correlative science studies in gastrointestinal cancers. The goal was to identify tumor- or patient-specific characteristics that predicted disease outcome or treatment toxicity. The challenge at that time was a lack of tissue specimens linked to clinical outcomes, as this was before collection of tumor blocks and peripheral blood samples from study participants had become a routine practice.

Defining Subtypes

The first CALGB gastrointestinal tissue resource linked to an ongoing clinical trial was developed from colorectal cancer patients treated on Intergroup protocol 0089, the previously described study of patients with stage II or III colon cancer treated with 5-FU with or without leucovorin/levamisole (11). An assessment of a cohort of 431 patients enrolled in this study showed that the presence of microsatellite instability (MSI) predicted for a higher probability of disease-free survival at 5 years (64% versus 49%; $P = 0.02$) but no difference in overall survival at 5 years (68% versus 56%; $P = 0.20$; ref. 30).

To extend this observation further, CALGB protocol 9865 collected tumor blocks from the CALGB patients enrolled on Intergroup 0089 to determine whether tumors with MSI exhibited unique molecular characteristics that would further distinguish them from tumors without this genetic pattern. Extracted DNA was analyzed to identify those tumors with MSI as well as those showing the alternative pathway to colon carcinogenesis of chromosomal instability. The study found that one third of sporadic colorectal cancers do not exhibit defining characteristics of either chromosomal instability or MSI, indicating that pathogenesis of colon cancer may not be fully defined by either chromosomal instability or MSI pathways (31). Additional studies of tumors with high levels of MSI showed that ~70% also had methylation leading to silencing or inactivation of the hMLH1 promoter. This finding suggests that this epigenetic event is a significant contributor to the MSI phenotype of sporadic colorectal cancer (32). Additional work showed that the tumor suppressor genes, PTEN, RUNX3, and APC, were frequently inactivated by promoter hypermethylation in sporadic colorectal cancer with high levels of MSI (33–35).

**Predicting Imatinib Response in Gastrointestinal Stromal Tumors**

Gastrointestinal stromal tumors (GIST) are rare sarcomas (~0.2% of all gastrointestinal malignancies; ref. 36). In 1998, Hirota et al. identified gain-of-function mutations of the KIT proto-oncogene in the majority of GIST (37). This enabled development of the first effective drug for GIST, the small-molecule inhibitor imatinib mesylate (imatinib). In 2002, it was reported that patients with metastatic GIST treated with imatinib had a 54% response rate, stable disease in 28%, and disease progression in 14% (38). Imatinib was approved for treatment of metastatic or unresectable GIST in February 2001 (39).

Intergroup study S0033 evaluated imatinib dose response (400 versus 800 mg) in metastatic or unresectable GIST. Correlative science studies for this trial coordinated by CALGB (protocol 150105) characterized the molecular and cytogenetic variables associated with KIT oncogene function to determine associations with response (40). The relationship between mutations in KIT or PDGFRA tyrosine kinases and drug response was examined in 324 patients with KIT-positive GIST. KIT mutations were present in 86% and PDGFRA mutations in 1% for a mutation frequency of 87%. Patients whose tumor expressed an exon 11 KIT mutant isoform were more likely to have a clinical response to imatinib (67%) than those with tumors expressing KIT exon 9 mutant isoforms (40%) or no kinase mutations (39%; $P = 0.0022$). There was a trend toward increased survival for patients with KIT exon 11 mutant GISTs compared with any other KIT mutation or wild-type GIST, but this difference was not statistically significant. The investigators concluded that activating mutations of KIT or PDGFRA are found in the vast majority of KIT-positive GISTs and that KIT exon 11 tumor genotype correlates with favorable response and time to progression. These results confirmed that KIT kinase genotype is prognostic of the likelihood and duration of response to imatinib therapy. In addition, this work indicated that new therapeutic strategies are needed for patients with GISTs not expressing an exon 11 mutant KIT isoform.

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Developing Methods to Evaluate Micrometastatic Disease: Sentinel Lymph Node Studies in Colorectal Cancer

The resected lymph nodes in 35% to 45% of patients undergoing potentially curative surgery will be found to be tumor free (41). However, 12% to 25% of these stage II patients experience post-treatment recurrence, indicating that current histopathologic staging methods fail to identify those destined to manifest tumor progression. The application of better techniques to detect these high-risk cases would identify patients who may benefit from adjuvant chemotherapy.

The term, micrometastatic disease (MMD), broadly describes evidence of tumor metastases within regionally lymph nodes that are not scored “positive” by conventional histopathologic criteria. Examples of MMD include small foci of tumor cells visualized by H&E stain or individual tumor cells identified only after application of immunohistochemistry for tumor antigens.

Table 1. CALGB Gastrointestinal Cancer Committee portfolio: currently active trials (treatment and correlative science), protocols in development (approved by Ethics Committee), and concepts in development (trials endorsed by CALGB through the CancerTrials Support Unit)

<table>
<thead>
<tr>
<th>Trial number</th>
<th>Status</th>
<th>Description</th>
<th>Accrual current/target</th>
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<tbody>
<tr>
<td>Gastric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C80101</td>
<td>Active</td>
<td>Adjuvant chemoradiation postresection</td>
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<tr>
<td>C150205</td>
<td>Active (C80101)</td>
<td>Tumor: TS, ERCC-1, MSL, E-cadherin, epidermal growth factor receptor, p27, cyclo-oxygenase-2, c-erbB-2; serum: insulin-growth factor-I, insulin-growth factor-II, insulin-growth factor – binding protein-3</td>
<td>127/540</td>
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<tr>
<td>Advanced pancreatic</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C80303</td>
<td>Active</td>
<td>Gemcitabine + placebo vs gemcitabine + bevacizumab</td>
<td>533/590</td>
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<tr>
<td>C150405</td>
<td>Active (C80303)</td>
<td>Serum: vascular endothelial growth factor and related growth factors, markers of coagulation and endothelial cell activation; matrix-assisted laser desorption ionization-time of flight profiling</td>
<td>412/590</td>
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<tr>
<td>S0205*</td>
<td>Active</td>
<td>Gemcitabine ± cetuximab</td>
<td>702/704</td>
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<tr>
<td>C80401</td>
<td>In development</td>
<td>Chemotherapy/radiotherapy + biological, nonmetastatic</td>
<td>—/90</td>
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<tr>
<td>CALGB</td>
<td>Concept (letter of investigation under review)</td>
<td>Phase II gemcitabine, erlotinib and sunitinib; phase II sunitinib</td>
<td>—/53; —/—/64</td>
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<tr>
<td>GIST</td>
<td></td>
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<tr>
<td>Z9001*</td>
<td>Active</td>
<td>Adjuvant STI571 (Gleevec) vs placebo</td>
<td>549/732</td>
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<td>Colorectal</td>
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<tr>
<td>C80405</td>
<td>Active</td>
<td>Chemotherapy + bevacizumab vs chemotherapy + cetuximab vs chemotherapy + combination; metastatic colon</td>
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<td>C150506</td>
<td>Active (C80405)</td>
<td>Analysis of multiple potentially prognostic or predictive genetic and molecular markers</td>
<td>25/2,289</td>
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<td>C80402</td>
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<td>Phase II second-line liposome-encapsulated SN38 (metabolite of irinotecan) metastatic oxaliplatin failures</td>
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<tr>
<td>E5202*</td>
<td>Active</td>
<td>Adjuvant FOLFOX ± bevacizumab high-risk stage II</td>
<td>33/3,610</td>
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<tr>
<td>N0147*</td>
<td>Active</td>
<td>Adjuvant oxaliplatin + 5-FU ± cetuximab</td>
<td>564/2,300</td>
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<tr>
<td>C-08*</td>
<td>Active</td>
<td>FOLFOX6 ± bevacizumab resected stage II/III</td>
<td>1,650/2,632</td>
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<tr>
<td>R-04*</td>
<td>Active</td>
<td>Preoperative radiotherapy + capcitabine ± oxaliplatin vs preoperative radiotherapy + capcitabine + i.v. 5-FU ± oxaliplatin; operable rectal cancer</td>
<td>250/1,606</td>
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<td>C-09*</td>
<td>Active</td>
<td>Capcitabine/oxaliplatin ± HAI resected/ablated liver metastasis</td>
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<td>C80501</td>
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<td>Second-line AZD2171 + irinotecan; metastatic colon</td>
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<td>C80404</td>
<td>In development</td>
<td>Pharmacogenomics of high-dose irinotecan + cetuximab; metastatic colon</td>
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<td>ACCENT</td>
<td>Meta-analysis</td>
<td>Adjuvant outcomes for Caucasian vs African ancestry</td>
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<td>Meta-analysis</td>
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<td>Active</td>
<td>Multimodality for advanced</td>
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<tr>
<td>C80403</td>
<td>In development</td>
<td>Combinations with cetuximab for advanced</td>
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<td>Neuroendocrine</td>
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<tr>
<td>C80602</td>
<td>Concept (currently under review)</td>
<td>AMG706 ± bevacizumab</td>
<td>—/136</td>
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*Endorsed by CALGB through the CancerTrials Support Unit.
antigens, such as carcinoembryonic antigen or cytokeratins. For colon cancer, the clinical significance of regional MMD is unknown. Retrospective studies employing a variety of disease definitions do not consistently show a relationship between presence of MMD and tumor recurrence. Prospective studies of MMD are problematic due to the many subjects required, the substantial time and expense involved in the methodologies to identify micrometastases, and the lack of a clear definition of this entity.

CALGB 80001 aimed to determine whether sentinel lymph node sampling could identify a subset of lymph nodes that predicted the status of the nodal basin for resected colon cancer and therefore could be extensively studied for the presence of micrometastases. Patients enrolled underwent sentinel lymph node sampling following injection of 1% isosulfan blue, and both sentinel and nonsentinel nodes obtained during primary tumor resection were sectioned at multiple levels and stained using anti–carcinoembryonic antigen and anti-cytokeratin antibodies. Using standard histopathology, sentinel nodes failed to predict the presence of nodal disease in 13 of 24 (54%) of node-positive cases (42). Immunostains were done for cases with negative nodes by standard histopathology. Depending on the immunohistochemical criteria used to assign lymph node positivity, sentinel node exam resulted in either an unacceptable high false-positive rate (20%) or a low sensitivity for detection of MMD (40%; ref. 43). By examining both sentinel and nonsentinel nodes, this multi-institutional study showed that sentinel nodes from resectable colon cancers did not accurately predict the presence of either conventionally defined nodal metastases or MMD. As a result, sentinel lymph node sampling is not a useful technique for the study of MMD in patients with colon cancer.

Correlative Science Works in Progress

Because of the time required for building prospective outcome-linked tissue resources, most gastrointestinal correlative science studies initiated over the past 15 years are just now yielding data. Prospective correlative science studies were initiated for patients treated on stage II (CALGB 9581) and stage III (CALGB 89803) colorectal cancer trials. These databases are nearly mature, and the results of large, adequately powered correlative science studies examining p53 expression and genotype, thymidylate synthase expression, microvessel density, p27 expression, and MSI will be reported soon.

Additional correlative science studies in gastrointestinal tumors will examine predictive markers for response to adjuvant treatment of gastric cancer (CALGB 150205), the correlation of angiogenesis and inflammation markers with outcome in patients with advanced pancreatic cancer (CALGB 150405), and a broad panel of tumor- and serum-based markers of response to treatment with chemotherapy plus anti-vascular endothelial growth factor and anti–epidermal growth factor receptor therapy in advanced colorectal cancer (CALGB 150506).

References

arterial infusion (HAI) versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life (QOL), and molecular markers. J Clin Oncol 2006;24:1395–403.


